Catalytic Asymmetric Pictet-Spengler Reactions toward Tetrahydroisoquinolines

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“Nature has no mercy on the synthetic chemist.”
—K. C. Nicolaou

“Music has no effect on research work, but both are born of the same source and complement each other through the satisfaction they bestow.”
—A. Einstein

“Wäre, wäre, Hypersphäre.”
—B. Mitschke

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ABSTRACT

The Pictet-Spengler reaction of 2-arylethylamines with aldehydes is a powerful methodology for the redox-neutral synthesis of partly hydrogenated nitrogen heterocycles. Especially tetrahydro-*β*-carbolines and tetrahydroisoquinolines represent valuable synthetic targets due to the prevalence of the respective molecular frameworks in naturally occurring alkaloids. The work presented within this thesis describes the development of a catalytic asymmetric Pictet-Spengler reaction toward tetrahydroisoquinolines – a product class that had been largely inaccessible *via* this route. Furthermore, the utilization of the available products in the biomimetic formal or total synthesis of eleven distinct natural products from diverse alkaloid classes was accomplished. Key to the development of a general methodology was the design and synthesis of bespoke imidodiphosphorimidate catalysts featuring electron-rich substituents that offered unprecedentedly high reactivity and selectivity in the system under study. The mechanistic nuances of the reaction were studied experimentally through in-depth kinetic analyses. Our investigation thus provides insights into the overall reaction mechanism as well as specific interactions offered by the optimal catalysts. Finally, further studies were directed toward the development of a catalytic asymmetric Pictet-Spengler reaction of electronically unbiased phenethylamines.

KURZZUSAMMENFASSUNG

Die Pictet-Spengler Reaktion von 2-Arylethylaminen mit Aldehyden ist eine wirksame Methode zur redox-neutralen Synthese von teilweise hydrierten Stickstoff Heterozyklen. Insbesondere Tetrahydro-*β*-carboline und Tetrahydroisochinoline stellen aufgrund der weiten Verbreitung ihrer molekularen Strukturen in natürlich vorkommenden Alkaloiden wertvolle synthetische Zielmoleküle dar. Die hierin präsentierte Arbeit beschreibt die Entwicklung einer katalytischen, asymmetrischen Pictet-Spengler Synthese von Tetrahydroisochinolinen – eine Produktklasse welche über diese Route weitestgehend unzugänglich war. Des Weiteren wurden die erhaltenen Produkte für die formale oder Totalsynthese von elf verschiedenen Naturstoffen aus vielfältigen Klassen von Alkaloiden genutzt. Die Entwicklung einer generellen Methodik wurde ermöglicht durch das Design und die Synthese von angepassten Imidodiphosphorimidat Katalysatoren mit elektronenreichen Substituenten, welche außergewöhnlich hohe Reaktivität und Selektivität in dem untersuchten System ermöglichten. Die Mechanistischen Nuancen der Reaktion wurden durch detaillierte kinetische Analysen studiert. Unsere Untersuchungen liefern Einblicke in den übergeordneten Reaktionsmechanismus sowie spezifische Interaktionen durch den optimalen Katalysator. Abschließend wurden weitere Studien zur Entwicklung einer katalytischen asymmetrischen Pictet-Spengler Reaktion von elektronisch unaktivierten Phenethylaminen durchgeführt.

LIST OF ABBREVIATIONS

4-HDCA	4-hydroxyhydrocinnamaldehyde
4-HPAA	4-hydroxyphenylacetaldehyde
Ac	acyl
ACDC	asymmetric counteranion-directed catalysis
Alk	alkyl
Ar	aryl
aq.	aqueous
BALT	binaphthyl-allyl-tetrasulfone
BDD	boron-doped diamond
BIA	benzylisoquinoline alkaloid
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
brsm	based on recovered starting material
Bu	butyl
BSTFA	*N*,*O*-bis(trimethylsilyl)trifluoroacetamide
Bz	benzoyl
CCE	constant current electrolysis
CDI	carbonyldiimidazole
CPA	chiral phosphoric acid
Cy	cyclohexyl
DCE	1,2-dichloroethane
DCM	dichloromethane
DFT	density functional theory
DIBAL	diisobutylaluminum hydride
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
DSI	disulfonimide
d	doublet or day(s)
dr	diastereomeric ratio
ee	enantiomeric excess
EI	electron impact ionization
er	enantiomeric ratio

eq.	equivalents
ESI	electrospray ionization
et al.	*et alii/et aliae* – and others
EWG	electron withdrawing group
GC (GC-MS)	gas chromatography (gas chromatography coupled with mass spectrometry)
h	hour(s)
HBD	hydrogen bond donor
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
i	*iso*
IDP	imidodiphosphate
IDPi	imidodiphosphorimidate
iIDP	iminoimidodiphosphate
Int	intermediate
JINGLE	1,1'-binaphthyl-2,2'-bis(sulfuryl)imides
L	ligand
LB	Lewis base
LUMO	lowest unoccupied molecular orbital
m	multiplet
m	*meta*
M	molar
[M]	metal with ligand field
Me	methyl
min	minute(s)
MOM	methoxymethyl ether
Ms	methylsulfonyl
MS	mass spectrometry or molecular sieves
n	normal
NBA	*N*-bromoacetamide
NBS	*N*-bromosuccinimide
NCS	norcoclaurine synthase
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance (spectroscopy)
Nps	*o*-nitrophenylsulfenyl
NTPA	*N*-triflyl phosphoramide
[ox]	oxidation
o	*ortho*

p	*para*
P	phosphate
PADi	phosphoramidimidate
PES	potential energy surface
PG	protecting group
Ph	phenyl
PIFA	(bis(trifluoroacetoxy)iodo)benzene
PP	pyrophosphate
Pr	propyl
q	quartet
quant.	quantitative
RDS	rate-determining step
RT	room temperature
sat.	saturated
STR	strictosidine synthase
t	*tert*, tertiary
t	triplet or time
T	temperature
TADDOL	$\alpha,\alpha,\alpha',\alpha'$-tetraaryl-1,3-dioxolane-4,5-dimethanol
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
THBC	tetrahydro-β-carboline
THF	tetrahydrofuran
THIQ	tetrahydroisoquinoline
TLC	thin layer chromatography
TMS	trimethylsilyl
TPP	tetraphenylporphyrin
Tr	triphenylmethyl
TRIP	3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate
Troc	2,2,2-trichloroethoxycarbonyl
TS	transition state
TTP	tetratriflylpropene
via	by way of
VTNA	variable time normalization analysis
WT	wild type

1. INTRODUCTION

Chirality describes the fundamental property of an object that is non-superimposable with its mirror image. The emergence of homochirality, namely the uniform sense of chirality in the biochemistry on earth, is evidently intertwined with the existence of life. Nevertheless, its fundamental origin remains an unanswered chemical question to this day.[1] The significance of molecular chirality has been recognized by the chemical community since the groundbreaking discoveries by Louis Pasteur in 1848 and the deduction of the non-symmetrical tetrahedral carbon atom as the basis for chirality by Le Bel and van't Hoff in 1874.[2] When two enantiomers of a chiral molecule are located in a chiral environment like the enzymes of a living organism, dissimilar interactions with the host lead to the concept of chiral recognition. Consequently, chirality arguments dictate modern pharmaceutical sciences fundamentally. Today, it is widely appreciated that the administration of either enantiomer of a drug will show dissimilar behavior from both pharmacological and toxicological perspectives.[3]

The number and diversity of chiral and enantiopure compounds isolable from natural sources usually referred to as the "chiral pool" is seemingly unlimited. Somewhat contradictive yet, it is highly restricted by the narrow chemical space explored in biological systems. Providing general access to enantiopure compounds thus becomes a quest for synthetic organic chemistry. A traditional approach involves the production of a chiral but racemic molecule followed by resolution into the separate enantiomers e.g. *via* crystallization – a method that is severely limited to a maximum yield of 50% of the desired stereoisomer. The conceptually complementary strategy of asymmetric synthesis aims to control the handedness of a stereogenic element at the point of creation in the synthetic sequence. For the most part of the 20th century, diastereoselective reactions that take advantage of the chiral pool as either starting material or as chiral auxiliary have dominated the field of asymmetric synthesis.

As organic chemistry matured over the past 100 years, landmark total synthesis campaigns fostered the impression that no target molecule remains too complex to be synthesized, if only enough effort would be devoted. Approaching the end of the century however, scientists became increasingly aware of the never-ending quest for synthetic efficiency – a context by which the art of total synthesis was considered primitive at that time.[4] By the definition of Barry Trost, "*the ideal chemical reaction is not only selective but is also just a simple addition (…) in which any other reactant is required only in catalytic amounts.*"[5] In this context, the development of novel reaction systems that enable "perfect" chemical transformations is the cornerstone of a sustainable and resource-efficient future in synthetic organic chemistry. Catalysis must consequently be considered the key enabling technology for the realization of this goal.

The emergence of powerful catalytic hydrogenation strategies pioneered by Knowles[6] and Noyori[7] as well as the revolutionary studies on metal-catalyzed epoxidations by Sharpless[8]

paved the way for the invention of a novel chemical strategy – asymmetric catalysis. The field can be defined as the art of inducing enantiomeric enrichment over the course of a reaction by catalytic action of a chiral and enantiopure molecule or material. Chemists in the 1990s confined the research area into two fundamental concepts: transition metal catalysis and biocatalysis.[4] The invention and systematic development of asymmetric organocatalysis in the early 2000s by List[9] and MacMillan[10] has however established this field as the third pillar of asymmetric catalysis. The progression of the science ultimately culminated in the Nobel Prize in 2021 being awarded *"for the development of asymmetric organocatalysis"*.

The following chapter aims to provide a comprehensive literature overview in three distinct parts: First, the development of asymmetric organocatalysis will be covered with a particular focus on the advent of Brønsted acid catalysis. A section on isoquinoline alkaloids will then review the molecular diversity in this class of natural products as well as their biological and chemical synthesis. Finally, the Pictet-Spengler reaction will be introduced as a powerful synthetic access point to the isoquinoline skeleton and the literature on asymmetric variants of this reaction will be covered. The subsequent chapter will comprise my own work toward the realization of a general organocatalytic asymmetric Pictet-Spengler methodology.

2. BACKGROUND

2.1. Asymmetric Organocatalysis

2.1.1. Fundamentals of Asymmetric Catalysis

Any chemical reaction under thermal conditions proceeds toward the direction of minimal Gibbs free energy G. The change in free enthalpy ΔG between the starting materials and the products corresponds to the thermodynamic driving force of a transformation. Under reversible reaction conditions, ΔG is related to the chemical equilibrium K_{eq} according to:

$$\Delta G = -RT\ln(K_{eq}) \tag{2.1}$$

The rate by which a chemical transformation proceeds is not strictly related to the absolute ground-state energies of starting materials, high-energy intermediates, and products. Instead, the free enthalpy of activation $\Delta G^{\ddagger}$, which describes the free enthalpy difference between the starting material and the highest lying transition state (TS), determines the overall kinetics of a transformation (Figure 2.1). As a reaction proceeds, the reactants undergo geometrical changes along a multidimensional reaction coordinate (defined by the number of atoms and their degrees of freedom), which can be projected onto a potential energy surface (PES). The kinetically favored reaction pathway will proceed on the PES along the path with the lowest $\Delta G^{\ddagger}$.

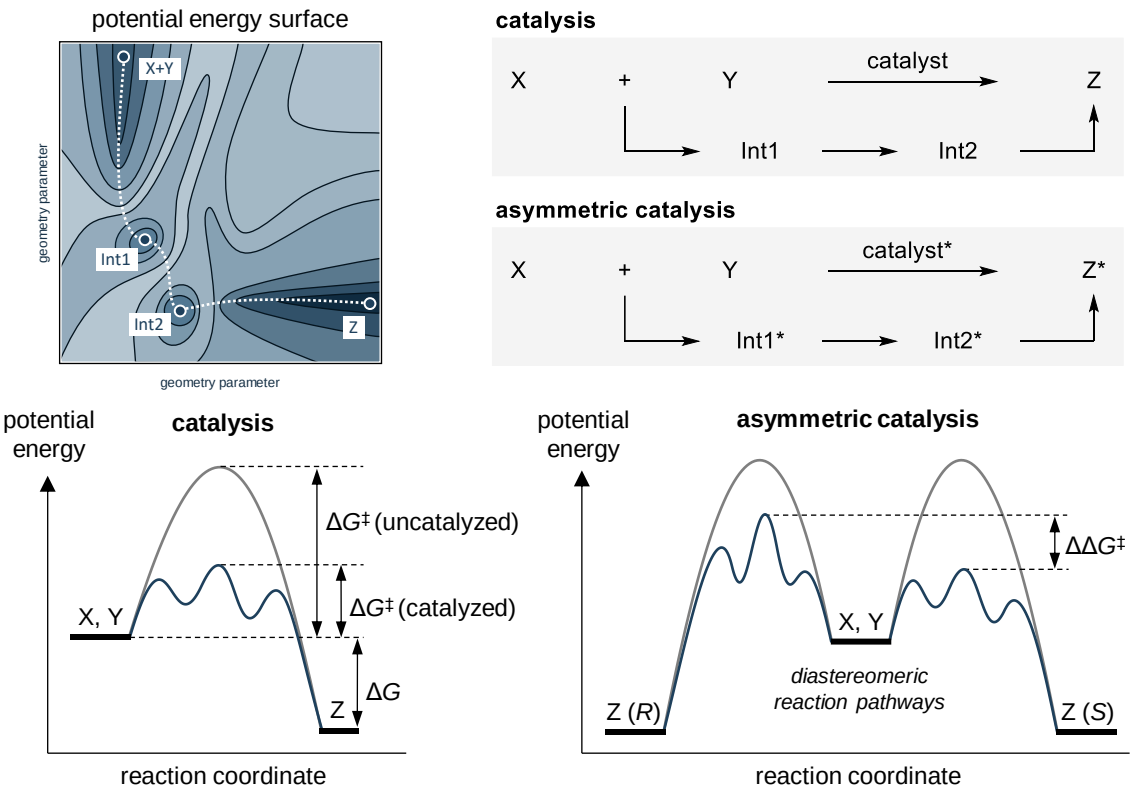


Figure 2.1 Hypothetical potential energy landscapes of catalytic stepwise reactions.

Catalysis is a kinetic phenomenon. The ground state energies of starting materials and products of a chemical reaction remain unaffected upon introduction of a sub-stoichiometric mediator. Instead, an energetically lower-lying pathway toward product formation is offered by the catalyst. In a hypothetical transformation of the type X + Y → Z, a catalyst might introduce a stepwise path including the formation of intermediates Int1 and Int2, which could be kinetically favored due to a lower overall $\Delta G^{\ddagger}$. Asymmetric catalysis however aims to control a more delicate obstacle: The two isolated enantiomeric products of a catalytic asymmetric transformation are identical in free enthalpy. If the system is allowed to reach thermodynamic equilibrium, the products will form a 1:1 mixture of enantiomers to reach the state of maximum entropy. A chiral catalyst therefore has to favor the kinetic formation of one enantiomeric product over the other. In a hypothetical reaction to a chiral product Z*, this is only possible *via* the involvement of diastereomeric transition states that are different in free enthalpy. Thus, the formation of chiral intermediates Int1* and Int2* are kinetically distinguishable by the difference in Gibbs free energy of activation, $\Delta\Delta G^{\ddagger}$.

The success of a catalytic asymmetric reaction is mostly determined by two factors: The overall yield of the product, and the relative distribution of the two possible enantiomers in the reaction mixture. As an accurate measure, the term *enantiomeric excess* (ee) is defined as the difference of molar fractions F_R and F_S of (*R*) and (*S*) enantiomers according to formula (2.2). The *enantiomeric ratio* (*er*) on the other hand is the ratio of F_R and F_S. The *er* has direct physical implications, as the product ratio is often directly dictated by the relative kinetic rate constants *k*. According to the Arrhenius equation (2.3), the $\Delta\Delta G^{\ddagger}$ in the rate-determining step is accountable for the enantioselectivity in a catalytic asymmetric reaction.[11]

$$ee = |F_R - F_S| \tag{2.2}$$

$$er = \frac{F_R}{F_S} = \frac{k_R}{k_S} = e^{-\frac{\Delta\Delta G^{\ddagger}}{RT}} \tag{2.3}$$

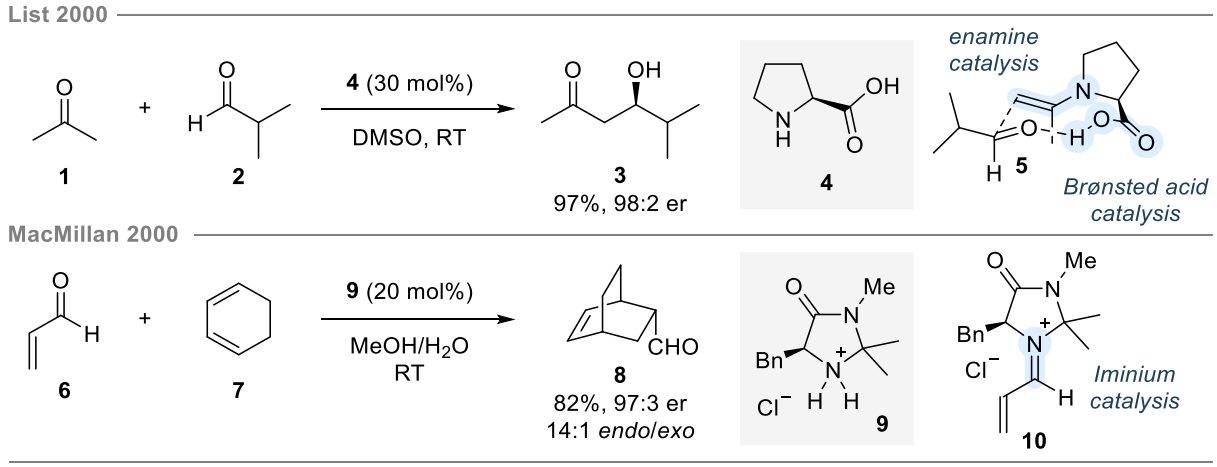
2.1.2. A Brief History of Asymmetric Organocatalysis

Organocatalysis can be comprehensively defined as a type of catalysis using small molecules, where an inorganic element is not part of the active principle.[12] By this broad characterization, the field is a remarkably old area of research. The first organocatalytic process, albeit not asymmetric, was reported in the year 1860 by Justus von Liebig.[13] In 1912, Bredig and Fiske reported the first asymmetric organocatalytic reaction.[14] The authors described the asymmetric hydrocyanation of benzaldehyde under the influence of the pseudo-enantiomeric alkaloids quinine and quinidine to give the cyanohydrine with low but reproducible enantiomeric excess (<10% ee). A related process using the same alkaloids as catalysts was disclosed by Pracejus in 1960.[15] In addition to the early experimental indication, the intellectual contributions of historic researchers in the field of asymmetric organocatalysis cannot be overstated. Already in the year 1900, Wilhelm

Ostwald predicted the existence of temperature-stable "*organic catalysts [translated]*".[16] The same terminology was used by German chemist Wolfgang Langenbeck in 1928 in an attempt to understand and classify the similarities between small molecules and enzymes.[17,18]

The scientific chemical literature of the 20th century furthermore contains scarce examples of asymmetric organocatalytic reactions. The independent discovery of the Hajos-Parrish-Eder-Sauer-Wiechert reaction by scientists at Hoffmann-La Roche and Schering in 1971 and 1974 probably stands out as the synthetically most significant contribution.[19,20] The enantioenriched products were important intermediates in syntheses of steroid hormones,[21] and the methodological potential was recognized by Woodward, who applied a stereoselective proline-catalyzed intramolecular aldol reaction in the total synthesis of Erythromycin.[22]

Perhaps due to a lack of understanding for the underlying reaction mechanism,[23] the full potential of the method was overlooked by the scientific community for almost 30 years. It was the eye-opening report from List, Lerner, and Barbas in the year 2000 that pointed toward the immense synthetic significance of proline-catalyzed aldol reactions.[9] The authors demonstrated the direct catalytic asymmetric intermolecular addition of acetone (**1**) to isobutyraldehyde (**2**) with high chemoselectivity and excellent enantioinduction by catalytic action of L-proline (**4**) (Scheme 2.1). In the same year, the group of David MacMillan reported the use of a phenylalanine-derived imidazolidinone catalyst **9** for the catalytic asymmetric Diels-Alder cycloaddition of enals **6** and unbiased dienes such as cyclohexadiene (**7**).[10] MacMillan furthermore coined the term "organocatalysis" to describe this new fundamental concept of enantioselective catalysis.



Scheme 2.1 Seminal contributions to the field of asymmetric organocatalysis by List and Macmillan.[9,10]

The realization that amino acids and simple derivatives thereof are competent chiral catalysts sparked the so-called "gold rush"[24,25] in asymmetric organocatalysis in the early 2000s. Especially the utilization of chiral amines dominated the research field in the following years. The seminal reports by List and MacMillan demonstrated two important catalytic activation modes

(Scheme 2.1). Firstly, *enamine catalysis* involves the formation of the enamine in TS **5**, which activates the nucleophile as a formal carbanion equivalent by raising the energy of the highest occupied molecular orbital (HOMO).[26] In proline-catalyzed aldol reactions, Brønsted acid activation of the electrophile is simultaneously achieved by the carboxylic acid of the amino acid. A single proline molecule thus is capable of efficiently mimicking the complex reaction mechanism of natural class I aldolases[27] and has consequently been described as a "micro-aldolase".[9] On the other hand, condensation of enal **6** toward intermediate iminium ion **10** lowers the energy of the lowest unoccupied molecular orbital (LUMO) in the electrophilic reaction partner by way of *iminium catalysis*.[28]

Creative catalyst and reaction design by research groups all over the world has enriched the field of asymmetric organocatalysis with an immense diversity of activation modes and catalytic intermediates. Therefore, an accurate formal taxonomy of the field seems necessary. The areas of research can theoretically be organized based on the mechanism in the catalytic cycle, the nature of the catalyst, or the principles of catalyst-substrate interactions. However, attempts to describe all subfields of asymmetric organocatalysis in a single "grand unified theory of organocatalysis" generally fall short of appreciating the characteristic nuances of discrete catalytic modes in an effort to define boundaries between the research areas. Nevertheless, classifications have been proposed in the literature, for example into areas of acid/base catalysis,[29] covalent and non-covalent interactions,[30] or specific reaction intermediates.[31] The following discussion will focus on a single but broadly defined activation mode in asymmetric organocatalysis, namely asymmetric Brønsted acid organocatalysis.

2.1.3. Asymmetric Brønsted Acid Organocatalysis

Identical chemical reactivity can be induced by conceptually dissimilar catalytic principles (Figure 2.2a). For example, the activation of an enal **11** for nucleophilic attack necessitates altering the electronic nature of the substrate in terms of LUMO lowering, which might be achieved by formation of an intermediate iminium ion, coordination to a metal-based Lewis acid, or protonation. While the activating principle does not necessarily imply the mode of stereoinduction, specific advantages can be associated with each approach. Iminium catalysis offers the opportunity to induce enantioselectivity from a covalently bound intermediate, thus ensuring close interactions with at least one of the reaction partners. Metal Lewis acid catalysis on the other hand involves the formation of a Lewis acid/base adduct, where the stereochemical information resides in the Ligand framework around the metal center. Variations of the metal ion allow the activation of diverse substrates due to particular affinity interactions such as π-Lewis acidity, resulting in the enormous variety within the field of asymmetric transition metal catalysis. Finally, protonation by a Brønsted acid catalyst is arguably the most elementary form of substrate activation, as it involves the transfer of the smallest positively charged chemical building block. Theoretically, the

generality of Brønsted acid catalysis is only limited by the Brønsted basicity of the reacting substrate. Hence, the concept is almost independent of functional handles for specific interactions with the catalyst, as opposed to iminium and metal Lewis acid catalysis.

The field of asymmetric Brønsted acid catalysis can be further subdivided into general and specific acid catalysis (not to be confused with the related but distinct nomenclature used to describe the acid/base mechanism of enzymes[32]). Based on the pK_a-difference between the catalyst H–X and the substrate, the activation toward the desired reactivity occurs either by hydrogen bonding, or by protonation (Figure 2.2b).[33] The distinction between the two activation modes is however not rigid.[34] It should additionally be noted that, even after formation of an ion-pair intermediate, the involvement of non-obvious hydrogen bonding (e.g. C–H–X) and other attractive or repulsive non-covalent forces is crucial for enantioinduction.[35]

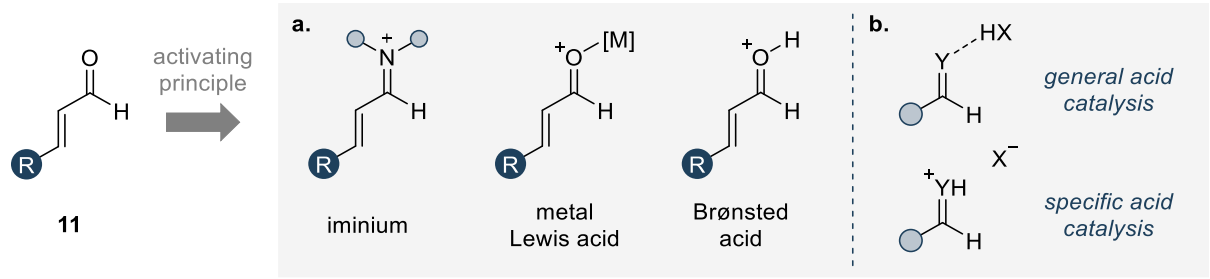


Figure 2.2 Comparison of selected activating principles in asymmetric catalysis; **a.** specific examples for the LUMO-lowering of enal **11**; **b.** Distinction between general and specific acid catalysis.

Despite the apparent universality of Brønsted acid catalysis, practical applications in the field of asymmetric catalysis were developed only in the past 25 years. In a pioneering study from 1998, Sigman and Jacobsen developed a library of peptide-derived urea and thiourea catalysts for an asymmetric Strecker reaction (Figure 2.3a).[36] The final catalyst structure **12** paved the way for the future development of hydrogen bond donors (HBDs) as chiral *general acid organocatalysts*.[37,38] The utilization of another HBD catalyst, TADDOL **13,** was first demonstrated by Rawal in 2003.[39]

Following seminal contributions on Lewis acid-enhanced Brønsted acid catalysis by Yamamoto,[40–42] the first powerful *specific acid organocatalysts* for asymmetric catalysis, chiral phosphoric acids (CPAs) **14** and **15**, were introduced independently by Terada and Akiyama in 2004 (Figure 2.3b).[43,44] These reports established several key catalyst design principles for advancing the research field as a whole. On the one hand, the axially chiral 1,1'-bi-2-naphthol (BINOL) backbone was found to provide a highly stable and rigid molecular structure. Furthermore, the introduction of 3,3'-substituents on the backbone efficiently induces enantioselectivity in the studied reactions and offers immense modularity for catalyst optimization and fine tuning. One of the most general CPA catalysts, **16** (commonly known as TRIP), was

reported by the List group in 2005[45] and still finds broad applications in asymmetric organocatalysis research to date.[46]

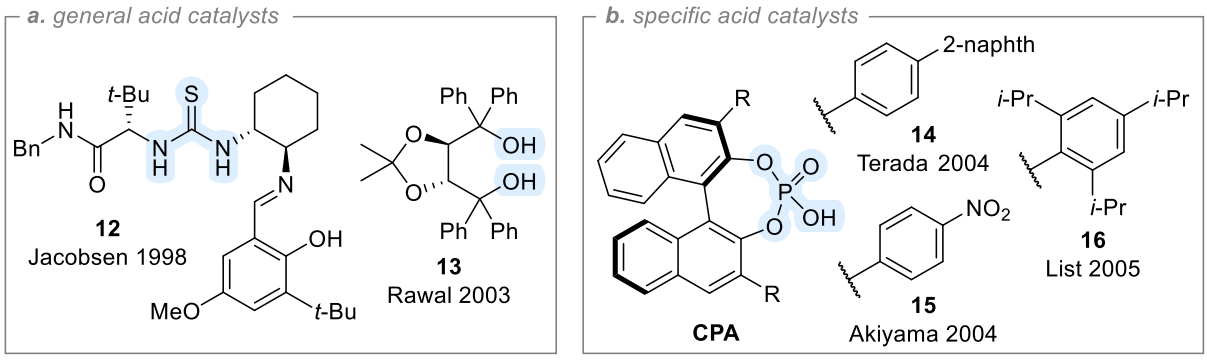


Figure 2.3 Early examples of general and specific chiral Brønsted acid organocatalysts.

Chiral Organic Superacids

A superacid has historically been characterized as an acidic medium with a Hammett acidity value H_0 lower than that of concentrated sulfuric acid (≤ -12).[47] In a complementary definition, considering an acidic species in a particular environment, a compound can be referred to as being superacidic if it has a higher equilibrium acidity than H_2SO_4.[48] The pioneering studies by George Olah during the second half of the 20th century established the immense potential of superacids for the generation and stabilization of high-energy cationic species, in particular carbenium and carbonium ions.[49]

Most strong organic Brønsted acids are comprised of an architecture that is built around a few central acidic functionalities such as phosphates (CPA **16** and NTPA **17**), sulfonates (DSI **18**), and sulfates (JINGLE **19**), by formal esterification or amidation. The development of strong C–H acids (BALT **20** and TTP **21**), albeit structurally highly intriguing, has remained a niche research area.[50–52] The acidity of the chiral catalysts can be conveniently compared if they are determined in the same solvent (Figure 2.4). It becomes apparent that CPAs ($pK_a > 13$ in CH_3CN) – though considerably more acidic than thioureas and related HBDs[53] – are poorly acidic compared to sulfuric acid ($pK_a = 7.6$). The development of more proficient Brønsted acid organocatalysts is thus undeniably linked with the quest for increasing their molecular acidity. To this end, the so-called *Yagupolskii principle* embodies a fundamental concept for enhancing the acidity of a compound by means of molecular design. The formal replacement of oxo groups (=O) with strongly electron withdrawing groups (EWGs) such as *N*-trifluoromethylsulfonyl (=NTf) imparts an immensely acidifying effect on an organic acid.[54] Exemplary, the single *Yagupolskii* modification of a CPA has been explored first by Yamamoto in 2006 and leads to the molecular structure of *N*-triflyl phosphoramides (NTPAs).[55] Ph-NTPA (**17**) displays a pK_a of 6.4 and is seven orders of magnitude more acidic than a CPA. Replacement of the second oxo group in

NTPAs was explored by List in 2016, and leads to extremely active Brønsted acid organocatalysts, phosphoramidimidates (PADis), the exact acidity of which has however not been reported yet.[56,57]

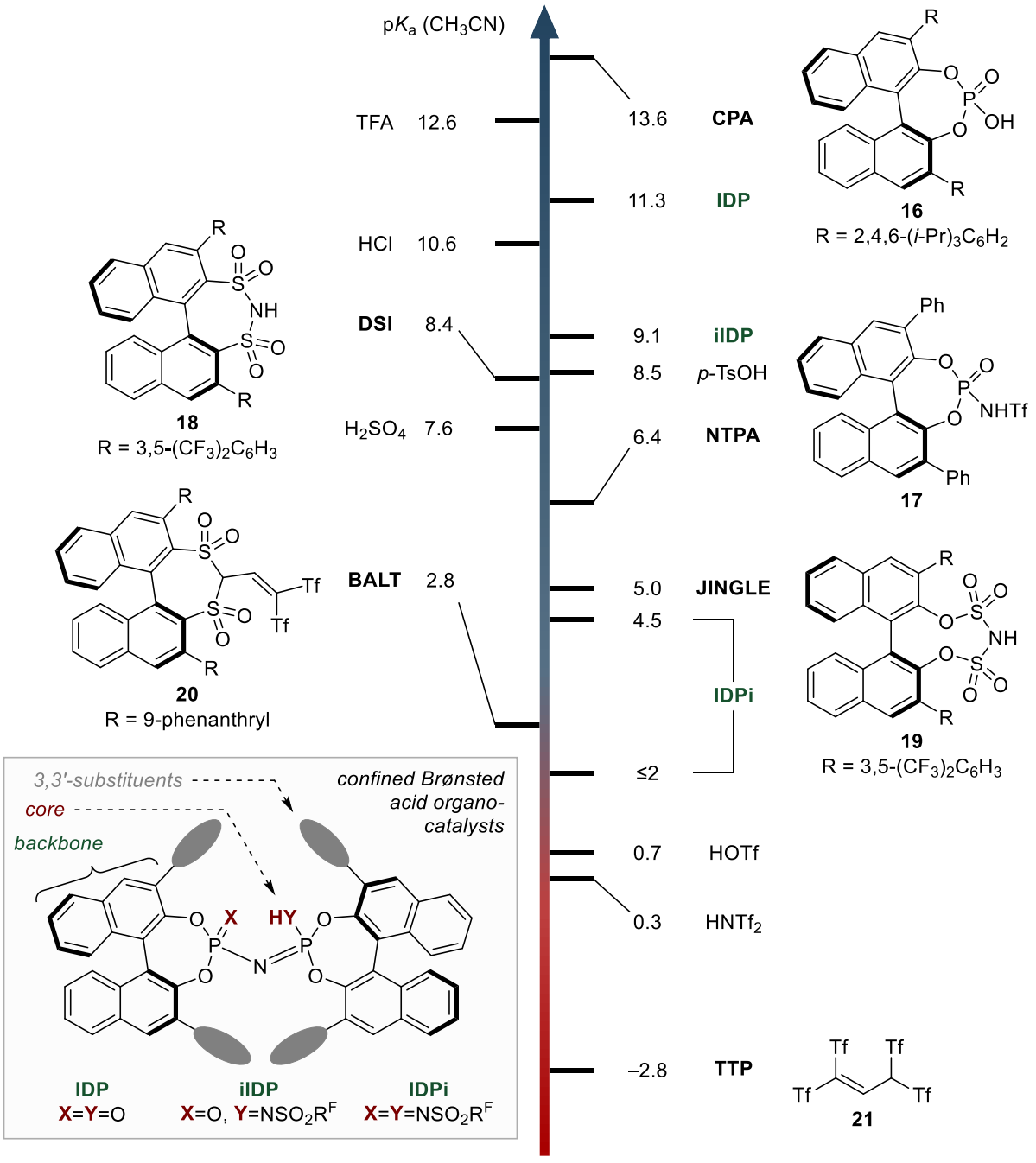


Figure 2.4 pK_a values in CH_3CN of selected Brønsted acid organocatalysts as well as simple mineral acids for comparison.[53,58] DSI = disulfonimide. NTPA = *N*-triflyl phosphoramide. BALT = binaphthyl-allyl-tetrasulfone. JINGLE = binaphthyl-2,2'-bis(sulfuryl)imides. TTP = tetratriflylpropene. IDP = imidodiphosphate. iIDP = imino-imidodiphosphate. IDPi = imidodiphosphorimidate.

Research by List and coworkers in the past decade has culminated in the design and synthesis of a novel class of dimeric chiral phosphoric acids that are commonly described as *confined Brønsted acid organocatalysts*.[58–61] As opposed to CPAs, disulfonimides (DSIs), and related

"exposed" structures, the dimeric nature of these molecules constructs a cavity for induction of unprecedented chemo-, regio-, and stereoselectivity onto small and unbiased substrates.[59,62] Within the dimeric architectural framework, *Yagupolskii*-type modifications were demonstrated to have a remarkable effect on acidity. From the parent imidodiphosphate (IDP, pK_a = 11.3), a single modulation leads to the iminoimidodiphosphate structure (iIDP, pK_a = 9.1). An even more pronounced increase in acidity is achieved upon installment of the second EWG toward the imidodiphosphorimidate structure (IDPi, pK_a = 4.5 to < 2). These catalysts reside completely in the superacid regime. Paired with the confinement induced by the structural framework, IDPis offer a highly modular catalyst platform for diverse reactivity even with unbiased and unreactive substrates.[58,63]

2.1.4. Asymmetric Counteranion-Directed Catalysis

The mode of choice for efficient enantioinduction depends on the interactions between catalyst and substrate in a specific transformation. Importantly, the majority of catalytic reactions that are accelerated *via* activation of an electrophilic reaction partner share a common property: They proceed through (partly) positively charged intermediates or transition states. This fact sufficiently offers the opportunity for transferring stereoinformation from a chiral and enantiopure counteranion onto a relevant transition state, a concept that has been coined asymmetric counteranion-directed catalysis (ACDC).[64]

The proof of principle for ACDC was reported by Mayer and List in 2006 in a study on asymmetric Hantzsch ester reductions of enals *via* iminium catalysis (Figure 2.5a).[35] The conventional organocatalytic approach for this reaction involves the formation of a chiral iminium ion through the use of MacMillans imidazolidinone catalysts.[65] However, the same mode of reactivity, iminium catalysis, can be achieved by using an achiral secondary amine (in this case morpholine). Utilization of TRIP as a counteranion leads to the formation of a chiral and enantiopure ion pair. The authors found that the transfer of stereochemical information from the counteranion onto the substrate was sufficient to generate the products in high stereoselectivity. A conceptual advantage of the ACDC approach is thus immediately obvious: The mode of enantioinduction can be rendered essentially independent from the mode of reactivity. This consequence can be clearly comprehended by examination of a seminal report of ACDC in the field of transition metal catalysis. Toste and coworkers reported the asymmetric intramolecular hydroetherification of enals under the influence of a Au^I-catalyst.[66] Conventional stereoinduction is usually attempted by design of a chiral phosphine or NHC ligand L* (Figure 2.5b). However, this approach has proven highly challenging in the field of homogeneous gold catalysis in general and has failed in the particular reaction under study. Stereoinduction *via* ACDC using (*R*)-TRIP as the counteranion was however successful in the developed methodology.

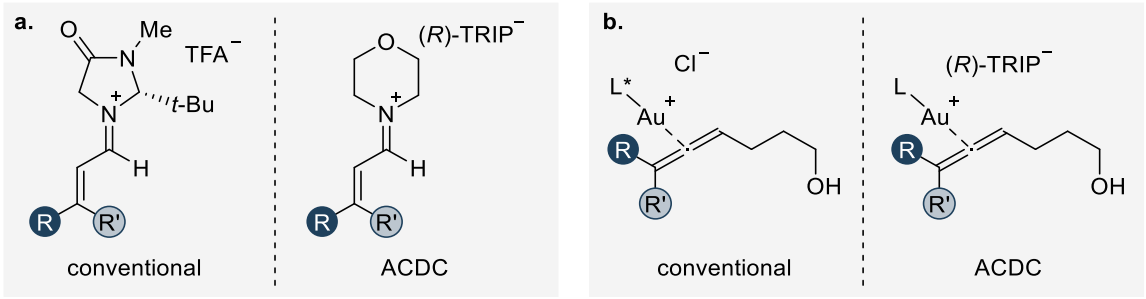


Figure 2.5 Comparison of conventional enantioinduction and ACDC approaches; **a.** Activation of enals by iminium formation;[35] **b.** Activation of allenes by cationic Au^{I}-complexes.[66]

ACDC is of immense relevance for organocatalytic processes. Essentially, strong organic Brønsted and Lewis acids catalyze reactions by formation of chiral ion pair intermediates.[67,68] Less acidic hydrogen bond donors like thioureas are competent catalysts within the conceptual framework of ACDC as well. Due to their capability to not only activate neutral Lewis basic substrates such as nitroolefins[69] or carbonyls[70,71] but also bind anionic species, they are accurately described as "anion binding catalysts".[37] In doing so, they become part of a supramolecular complex that effectively acts as a chiral and enantiopure counteranion.[64,72,73]

2.1.5. Summary and Outlook

Asymmetric organocatalysis has sometimes been described as a green alternative to transition metal catalysis and the nature of the catalysts—being robust, inexpensive, readily available, and non-toxic—were considered as main advantages of the field.[74] While simple amino acid derivatives are in fact inherently sustainable, contemporary asymmetric organocatalysis has escaped the need for such justifications. The research field has demonstrated the capability to facilitate reactivity and induce selectivity that is unprecedented with either transition metal or enzyme catalysis.[63,75] Thus, asymmetric organocatalysis is established at the forefront of asymmetric catalysis itself and the development of powerful chiral acids has shaped the field in recent years. In particular, ACDC has evolved into a dominating concept in all fields of asymmetric acid catalysis. In principle, the development of powerful chiral Brønsted acids suggests applications as chiral counteranions in related fields of asymmetric metal catalysis and the full potential of the concept is yet to be explored.

In the following section, the biological relevance of isoquinoline natural products will be introduced. The concluding section of the background will subsequently cover the Pictet-Spengler reaction as the privileged method for preparation of such natural alkaloids, with a particular focus on asymmetric organocatalytic methods.

2.2. Isoquinoline Natural Products

Plants produce a seemingly incomprehensible diversity of low molecular weight chemical compounds. Only a small number of these biochemicals, so-called "primary" metabolites, originates from metabolic pathways that are common to all organisms. On the other hand, over the course of evolution, different lineages of plants have gained the ability to generate "secondary" metabolites to address needs that are more specific in nature.[76] While not all purposes of these specialized metabolites are immediately obvious, many provide the producing organism with a clear evolutionary advantage. The generation of scents and pigments in plants for example can serve an interspecific communication purpose to increase fertilization by attraction of pollinators. The ability to produce toxic chemicals on the other hand can serve as a defense mechanism against pathogens or reduce growth of competing neighboring plants.[77]

The term "alkaloid" historically comprises all nitrogen-containing basic compounds of plant origin. In the 20th century, the term was broadened to include all nitrogen-containing natural products, also those from animals and microorganisms. While the alkaloids were originally classified based on their botanical source (e.g. *vinca* alkaloids or *papaver* alkaloids), modern chemical structure elucidation as well as investigations into biosynthetic conjunction allowed for systemization based on structural features (e.g. tropolone alkaloids or steroid alkaloids). The present scientific literature contains both classifications alongside of each other.[78]

Isoquinoline alkaloids are secondary metabolites produced by at least 40 different families of plants. They are – together with the monoterpene indoles – the overall largest family of alkaloids.[79,80] The chemically simple phenethylamine precursors as well as structurally more complex biochemicals can be found in varying quantities in families scattered throughout the plant kingdom. Chemotaxonomic analysis with regard to the skeletal structure of benzylisoquinoline alkaloids has revealed greater complexity and specialization along the biosynthetic path. In the case of *ranunculales* and *papaverales* plants, the increased molecular complexity furthermore appears to correlate with enhanced toxicity.[81] Due to the strong biological activity of some compounds – especially the alkaloids found in *papaver somniferum* ("opium poppy") – humankind has a long-lasting relationship with psychedelic plant alkaloids. In fact, systematic cultivation of poppy seeds can be archeologically traced back at least to the early Neolithic and cultural utilization for mind-altering purposes is evidenced for as long as 2500 years.[82] Maybe not surprisingly, the most active ingredient in opium, morphine, was also the single first alkaloid ever to be isolated in pure form by German pharmacist Friedrich Sertürner in 1806.[78,79] Ever since then, benzylisoquinoline alkaloids have proven both a *"boon and a curse"*[81] to humankind. While the natural product structures continue to serve chemists as inspiration for pharmaceutical applications and thus have shaped modern medicine, semisynthetic drugs such as heroin carry a strong potential for abuse. Members of the extended isoquinoline natural product family include

for example all opium alkaloids such as morphine and noscapine, the terpene alkaloid emetine, and the tropolone colchicine (Figure 2.6). In the following section, the structural diversity of isoquinoline alkaloids will be classified and the general biosynthesis of tetrahydroisoquinolines (THIQs) as well as that of selected examples will be discussed.

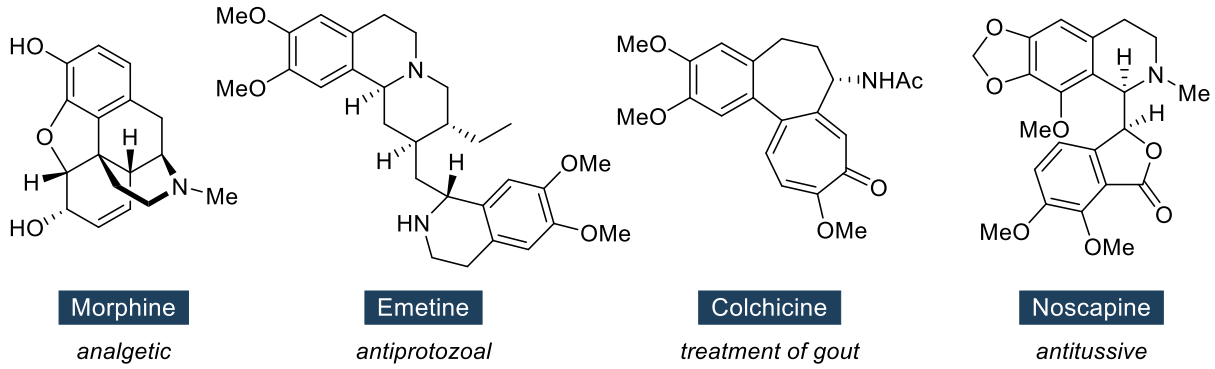


Figure 2.6 Selected members of the isoquinoline family of alkaloids and their general pharmaceutical utility.

2.2.1. Structural Network Analysis

Isoquinoline alkaloids are a large and diverse class of natural products with the parent compounds and related downstream secondary metabolites spanning many thousands of isolated structures. Members that occur in the same family of plants usually share a common biosynthesis. When grouping the alkaloids based on their molecular frameworks, the more primitive structures seem to occur widespread in all considered plant families, while particular molecular complexity appears infrequently and can be associated with higher specialization in an evolutionary sense.

Chemotaxonomy

In the following, a broad chemotaxonomic analysis will be presented (Figure 2.7). Connections between the classes are derived from their structural features as well as biosynthetic considerations. Importantly, a holistic breakdown of all known distinct skeletal types is not possible here, as more than 50 different varieties are described in the literature.[81] Focus was therefore laid on the most important classes. The chemically least complex members of the isoquinoline alkaloids are broadly grouped into the class of simple isoquinolines. On the other hand, the largest number of isolated compounds can be found in the benzylisoquinoline alkaloids (BIAs). They are mirrored by the homobenzylisoquinolines, which however enclose only a small number of compounds in comparison. Furthermore, the terpenoid and polyketide isoquinolines lie outside the scope of a more detailed discussion here.

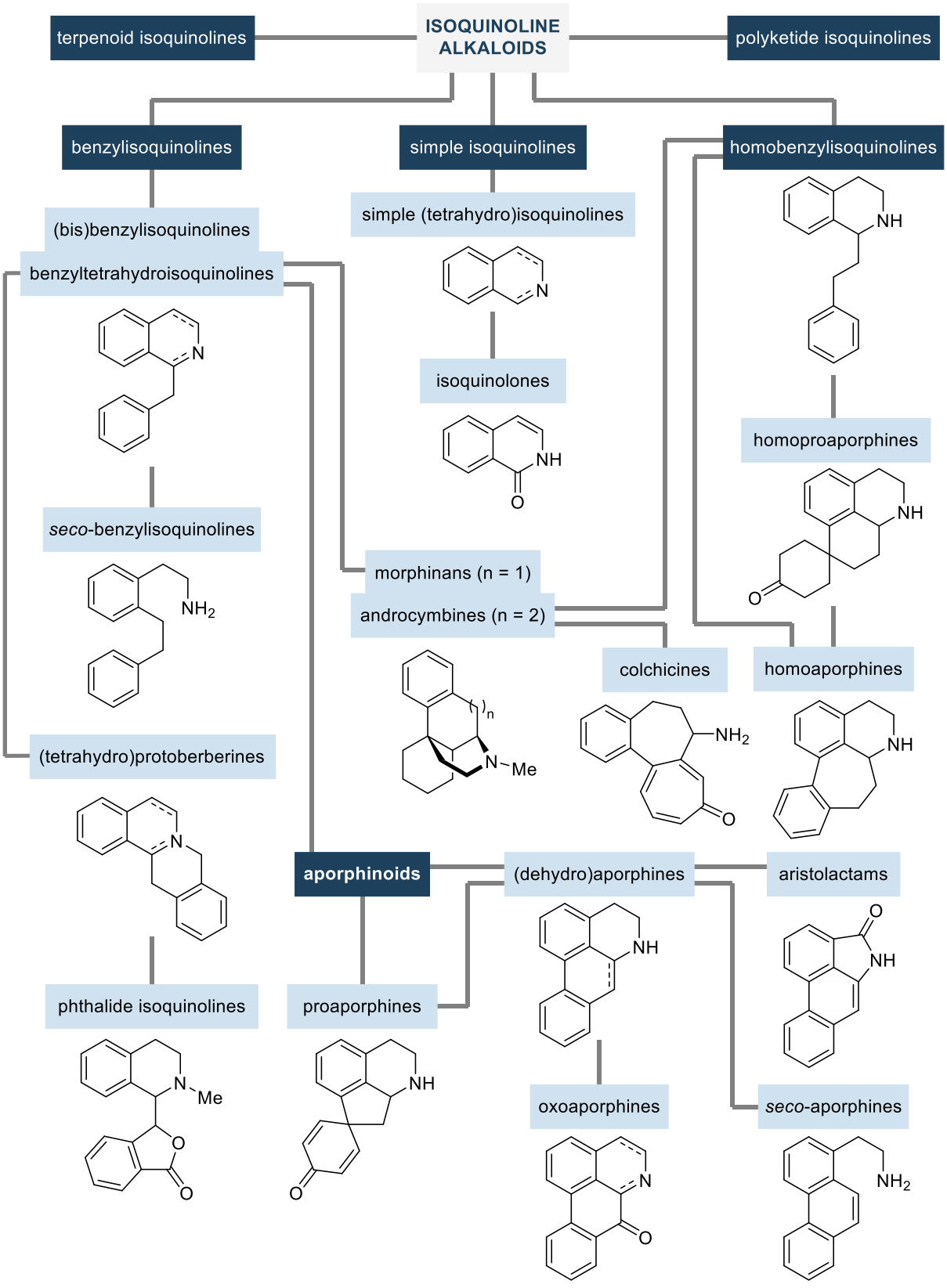


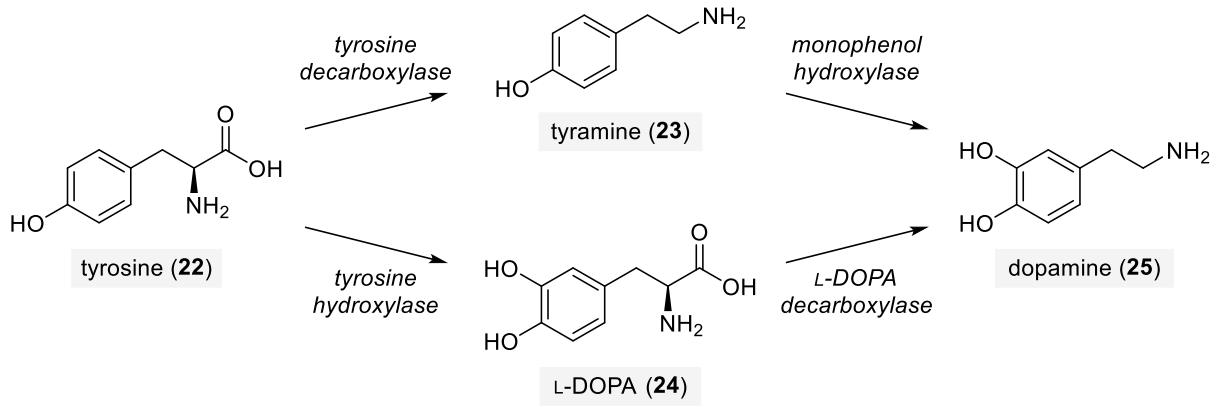
Figure 2.7 Chemotaxonomic classification of the most important Isoquinoline alkaloids into broadly defined classes and subclasses.

BIAs represent a major diversification point in the biosynthesis of more complex natural products, as different C–C bond-forming reactions in the parent compounds lead to structurally deviating alkaloid subclasses. Firstly, opening of the tetrahydroisoquinoline core gives rise to *seco*-benzylisoquinolines. If on the other hand an additional carbon atom is included in the structure to obtain another annulated tetrahydroisoquinoline, the subclass of berberines is reached. Even though chemically non-obvious, the berberines are biochemically connected to phthalide isoquinolines. By another C–C bond-formation from BIAs, dearomatization of the tetrahydroisoquinoline core leads to the morphinan structure. The subclass of aporphinoids arises by C–C bond-formation between the two arenes of BIAs and is subdivided into aporphines as well as proaporphines. The latter have been isolated as natural products but are also competent biosynthetic precursors to aporphines. Finally, the aristolactams, oxoaporphines, as well as *seco*-aporphines are derived by oxidation or deconstruction of the aporphine ring framework.

The homobenzylisoquinolines exist systematically in parallel to the BIAs, in the sense that they provide the subclasses of homoproaporphines as well as homoaporphines. In addition, a homologated morphinan skeleton is apparent in the androcymbines. Finally, further metabolic refinement gives rise to a more exotic subclass of compounds featuring a tropone substructure, the colchicines.

Biosynthesis of Isoquinoline Alkaloids

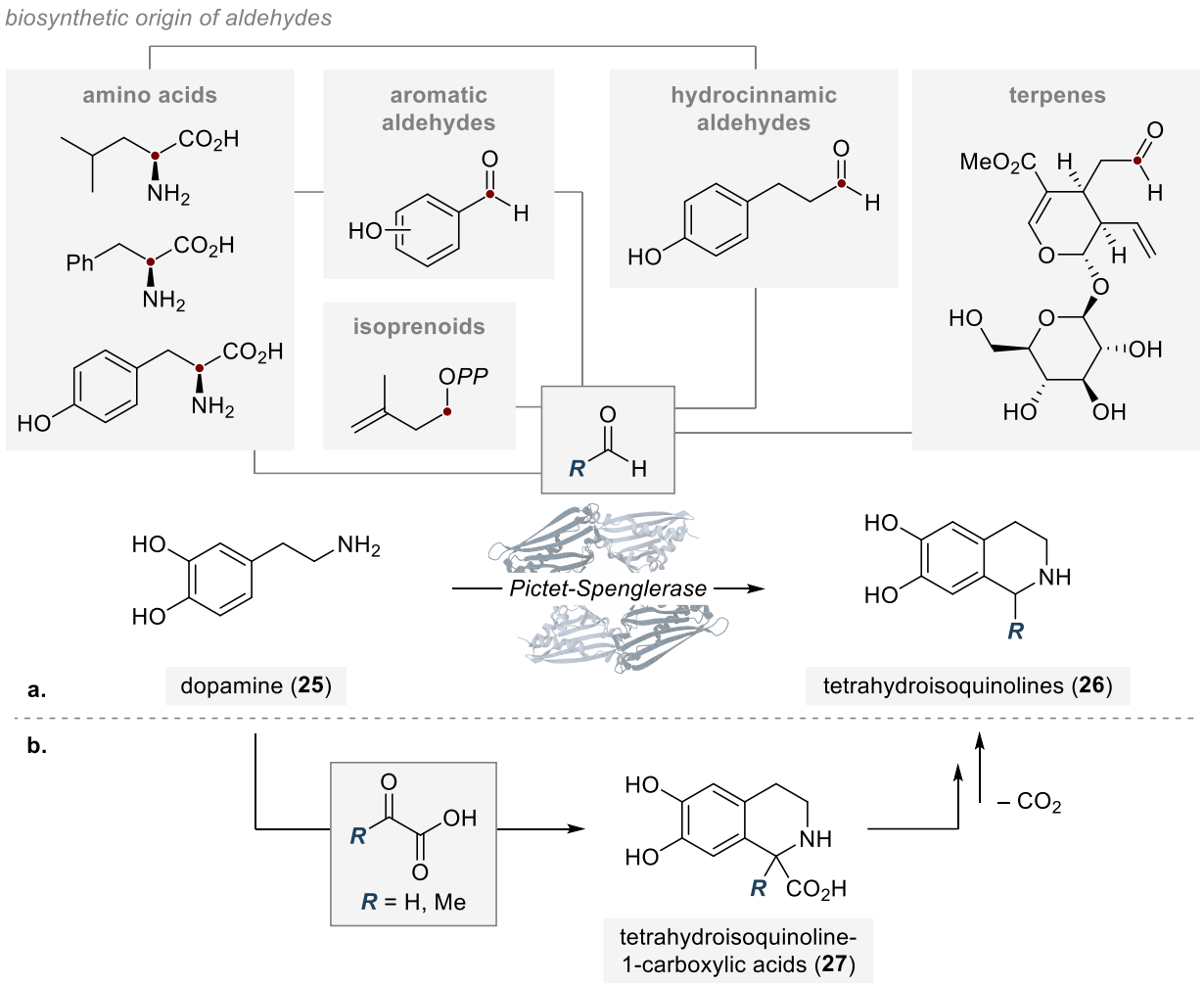
Isoquinoline biosynthesis in plants commences with the generation of biogenic amines from amino acids. Specifically, the conversion of tyrosine (**22**) to dopamine (**25**) can be considered as the first step in the biosynthesis of all isoquinoline alkaloids (Scheme 2.2).[83] The reaction sequence can proceed *via* either initial decarboxylation or hydroxylation of tyrosine to give tyramine (**23**) or L-DOPA (**24**), respectively. The more relevant pathway is specific to each plant species, but the latter route via L-DOPA seems to be dominant.[84] Dopamine is furthermore the precursor of important biogenic amines such as adrenaline and noradrenaline, or secondary metabolites such as the strong hallucinogen mescaline.[85]



Scheme 2.2 Biosynthetic origin of dopamine in plants.[84]

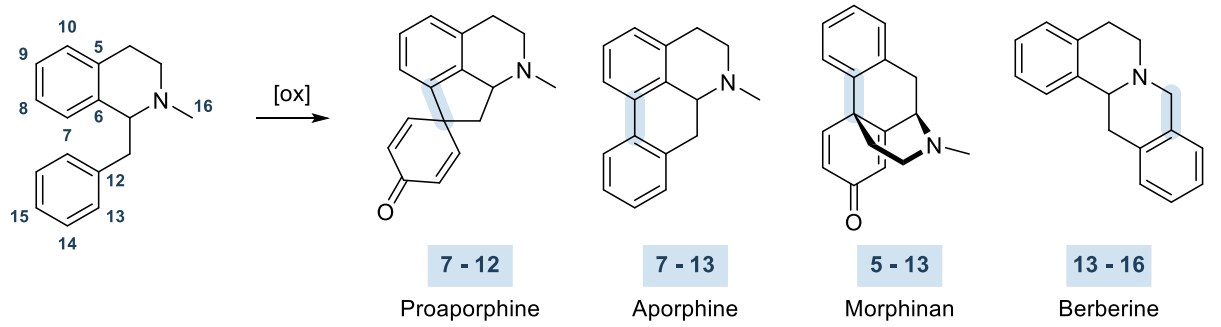
The origin of the C1-atom in isoquinoline alkaloids has been a long-standing matter of discussion.[86] It is now widely accepted that the biosyntheses of all isoquinoline alkaloids – with the polyketide isoquinolines being a notable exception[87] – include a Pictet-Spengler reaction as the key step.[88] The reaction of dopamine with an aldehyde furnishes the key tetrahydroisoquinoline skeleton through catalytic action of a Pictet-Spenglerase (Scheme 2.3a). While the enzymes are highly substrate specific for the use of dopamine-like phenethylamines, significant diversity in the alkaloid classes originates from the utilization of different aldehydes. Exemplary, aldehydes directly derived from aromatic amino acids *via* decarboxylative deamination are precursors to most of the benzylisoquinoline alkaloids. Alternatively, further metabolic processing of amino acids toward aromatic or hydrocinnamic aldehydes gives rise to a different subclass of isoquinoline alkaloids.[88] Finally, terpene-derived aldehydes furnish terpenoid tetrahydroisoquinolines. In recent years, a variety of different Pictet-Spenglerases that utilize aldehydes have been identified and characterized.[89] Their substrate scope was thoroughly investigated and found to be surprisingly broad. The Pictet-Spengler reaction and its relevance in chemistry and biology will be discussed in more detail in section 2.3.

An alternative biosynthetic pathway toward the key tetrahydroisoquinolines proceeds *via* the Pictet-Spengler cyclization of dopamine with α-oxoacids (Scheme 2.3b). The immediate products are tetrahydroisoquinoline-1-carboxylic acids, which can undergo further decarboxylation sequences toward THIQs. This pathway was hypothesized to be the biosynthetic pathway toward a variety of THIQs. However, current literature concludes that it is only operable in the reaction of very simple substrates like glyoxylic and pyruvic acid (R = H, Me), whereas more complex substituents (R = CH_2Ar, CH_2CH_2Ar) are incorporated *via* the corresponding aldehydes.[90] In fact, not a single biocatalyst has been identified that reacts dopamine with α-oxoacids naturally.[91,92] Finally, one should not discard the possibility of non-catalyzed Pictet-Spengler reactions under natural conditions. Certain THIQs were found to form spontaneously from dopamine in yeast strains[93] or in mammalian tissue[94] without the necessity of a biocatalyst.



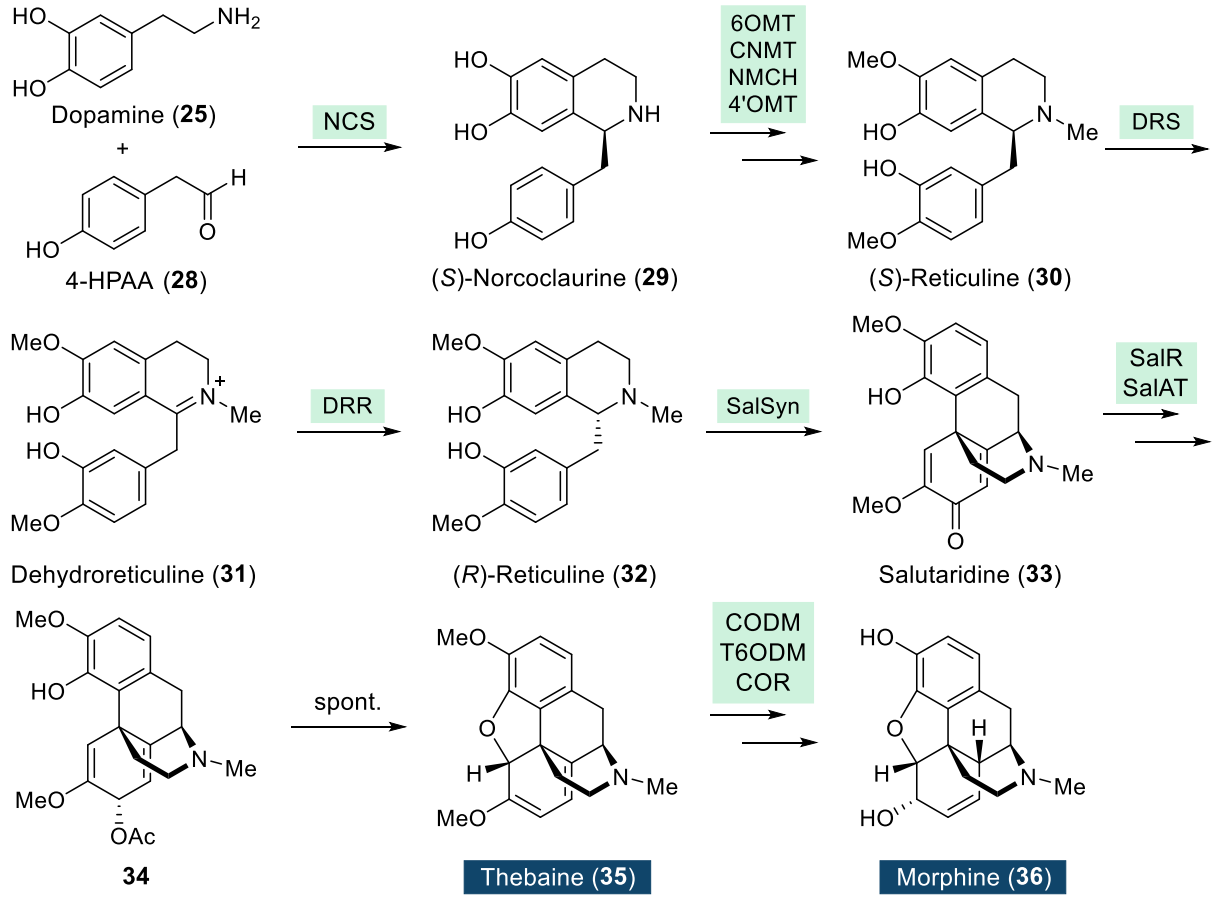
Scheme 2.3 Pictet-Spengler reactions of dopamine in the biosynthesis of THIQ alkaloids; **a.** Reactions involving aldehydes; **b.** Alternative reaction sequence involving α-ketoacids.

The biosynthesis of all benzylisoquinoline natural products includes the enzymatic Pictet-Spengler reaction of dopamine (**25**) with 4-hydroxyphenylacetaldehyde (4-HPAA, **28**) to furnish (*S*)-norcoclaurine (**29**), the biosynthetic precursor to an estimated number of more than 2000 BIAs.[95] Following formation of the THIQ skeleton, a series of individual hydroxylation and methylation reactions is common in the biosynthesis of most alkaloids. The next "key" reaction step, which represents a junction toward the specific subclasses of alkaloids, is an oxidative coupling reaction (Scheme 2.4). These reactions are regiodivergent with respect to the connections between the two arenes of the THIQ precursor. Importantly, all couplings require at least one free phenol in the substrate. The reactions regioselectivity with respect to the free OH (*ortho*- vs. *para*-selective coupling) thus furthermore determines the final oxygenation pattern in the natural alkaloids.



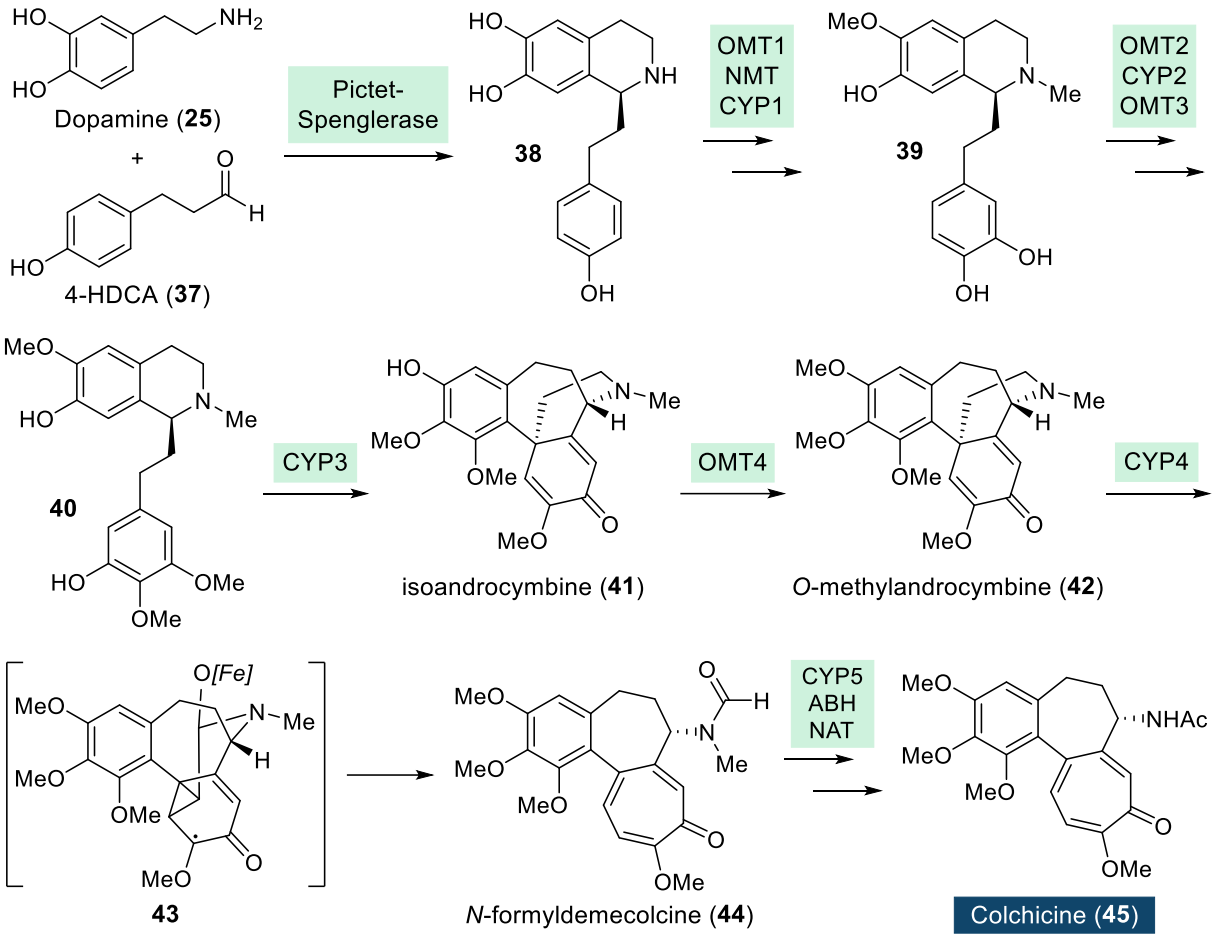
Scheme 2.4 The most important oxidative couplings in BIA biosynthesis.

The key steps in the biosynthetic sequence toward complex isoquinoline alkaloids can be best appreciated by examining specific examples. The complete biosynthesis of morphinan alkaloids in *papaver somniferum* has been elucidated (Scheme 2.5).[83,96–98] It commences with the Pictet-Spengler reaction of dopamine (**25**) and 4-HPAA (**28**) catalyzed by norcoclaurine synthase (NCS), followed by a sequence of oxidations and methylations toward (*S*)-reticuline (**30**). The following step is exclusively found in the synthesis of morphinan alkaloids: A biocatalytic stepwise epimerization converts (*S*)- to (*R*)-reticuline (**32**) *via* the intermediacy of a dehydroreticulinium ion (**31**). It has even been suggested that compartmentalization between different cell types in *Papaver* plants might play a critical role in regulating the selectivity for conversion of (*R*)-reticuline.[96] The key C-C bond-forming reaction is mediated by a cytochrome P450 (CYP) enzyme salutaridine synthase (SalSyn), which furnishes the morphinan skeleton **33** in an *ortho*-selective fashion. Subsequent functional group interconversions and cycloetherification deliver the family of alkaloids found in *papaver somniferum*, notably thebaine (**35**) and morphine (**36**). A related biosynthetic pathway also appears to be operative in human cells, generating endogenous morphinan alkaloids.[99]



Scheme 2.5 Biosynthesis of morphinan alkaloids in *Papaver somniferum*. NCS = norcoclaurine synthase. OMT = *O*-methyltransferase. CNMT = coclaurine *N*-methyltransferase. NMCH = *N*-methylcoclaurine 3′-hydroxylase. DRS = dehydroreticuline synthase. DRR = dehydroreticuline reductase. SalSyn = salutaridine synthase. SalR = salutaridine reductase. SalAT = salutaridinol 7-*O*-acetyltransferase. CODM = codeine *O*-demethylase. T6ODM = thebaine 6-*O*-demethylase. COR = codeinone reductase.

Colchicine (**45**) is a homobenzylisoquinoline alkaloid found in *Colchicum* and *Gloriosa* species (Scheme 2.6). The biosynthetic sequence is initiated likewise by a Pictet-Spengler reaction, in this case between dopamine (**25**) and 4-hydroxyhydrocinnamaldehyde (4-HPCA, **37**). After excessive oxidation and methylation toward THIQ **40**, the *para*-selective phenol coupling catalyzed by a CYP enzyme furnishes isoandrocymbine (**41**). However, the second and unique key step of the colchicine biosynthesis subsequently fully deconstructs the androcymbine framework. A proposed mechanistic intermediate **43** illustrates the fate of the original ring structure. C–H oxidation next to the tertiary amine leads to single-electron cyclopropanation to generate a stabilized radical intermediate, which ultimately dissects the initial 2-carbon bridge into a tropolone ring and a final *N*-formyl substituent on demecolcine (**44**). Colchicine (**45**) is lastly generated *via* oxidative demethylation, deformylation, and *N*-acetylation.[100,101]



Scheme 2.6 Biosynthesis of Colchicine in *gloriosa superba*. OMT = *O*-methyltransferase. NMT = *N*-methyltransferase. CYP = cytochrome P450. ABH = alpha/beta hydroxylase. NAT = *N*-acetyltransferase.

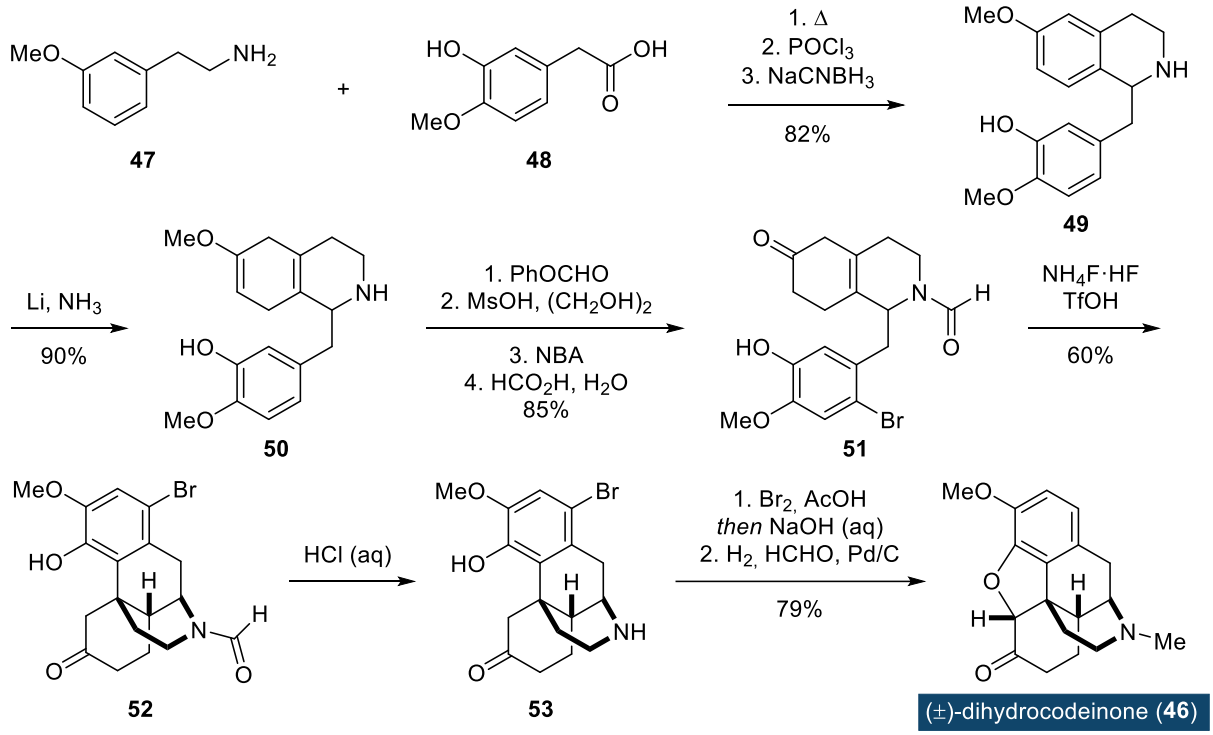
In summary, the biosynthesis of the majority of isoquinoline alkaloids proceeds *via* common steps, most notably a Pictet-Spengler cyclization toward tetrahydroisoquinolines. Subsequent divergence into alkaloid subclasses arises from unique chemo- and regio-selective oxidation reactions that can be evolutionary traced back to unique developments in specific plant families such as *Papaver* or *Berberis*. In the following section, some chemical synthesis efforts toward isoquinoline natural products will be highlighted, which utilize a biomimetic strategy.

2.2.2. Biomimetic Total Syntheses of Isoquinoline Alkaloids

The complex morphinan skeleton has posed a formidable challenge for chemical synthesis since its initial isolation by Sertürner. Until today, at least 40 discrete total synthesis campaigns toward morphine or direct derivatives thereof have been disclosed in the scientific literature.[102] The first total synthesis of morphine was accomplished by Gates in 1955 and simultaneously served as the unambiguous structural elucidation of the prominent alkaloid.[103] This initial synthetic campaign famously features a Diels-Alder reaction and is recognized as one of the first applications of this powerful methodology in total synthesis.[104] The first biomimetic synthetic approach toward the morphinan alkaloids however was published by Rice in 1980 (Scheme 2.7).[105] The newly

developed synthesis had proven more efficient and delivered the racemic morphinan skeleton of dihydrocodeinone (**46**) in 12 linear steps of which only six required isolation of the product, and an impressive overall yield of 29%. The synthesis can be considered biomimetic in the sense that the same key C-C bond connections are constructed in identical order as in the biosynthesis of morphinans. Nevertheless, Rice had to rely on several elaborate chemical maneuvers to accomplish the required selectivity.

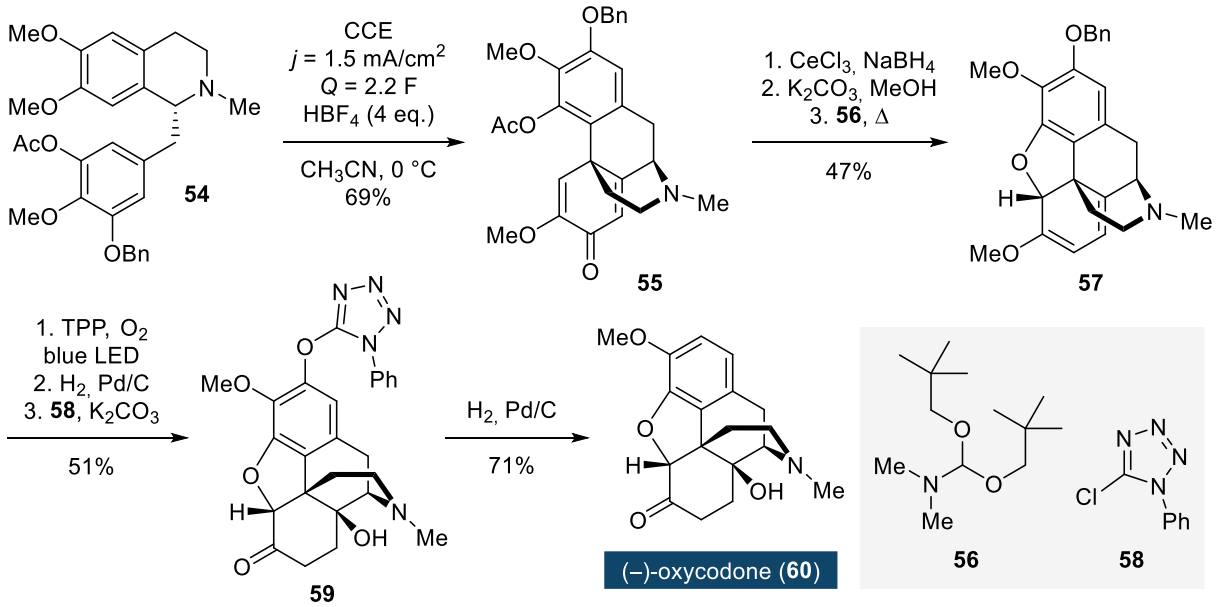
The synthesis commences with a Bischler-Napieralski cyclization of the amide obtained by condensation of arylethylamine **47** and carboxylic acid **48**. Subsequent reduction of the dihydroisoquinoline is followed by Birch reduction of THIQ **49** to give the dearomatized intermediate **50**. After *N*-formylation, conversion of the enol ether into an acetal serves as protection for the subsequent bromination with *N*-bromoacetamide (NBA), which is followed by hydrolysis toward ketone **51**. The acid-mediated cyclization, which furnishes the morphinan skeleton of **52**, deviates from the biochemical route in two significant ways: Firstly, the C–C bond formation occurs in a redox-neutral fashion between a nucleophilic aromatic ring and an electrophilic olefin, as opposed to an oxidative phenol coupling. Secondly, the aromatic ring is decorated with a bromine *para* to the free phenol. This maneuver proved crucial in order to override the natural *para* selectivity, which was previously shown by Grewe to be the sole cyclization product of the non-brominated substrate.[106] The total synthesis of dihydrocodeinone (**46**) was furthermore completed by traditional redox manipulations.



Scheme 2.7 Biomimetic synthesis of (±)-dihydrocodeinone (**46**) by Rice.[105]

A more recent study from 2014 by Opatz can be viewed as a modernization of the Rice synthesis.[107] The key disconnections maintained mostly unchanged, but the final natural products were obtained in an enantioenriched form due to an early asymmetric reduction of the dihydroisoquinoline intermediate. The selectivity problem in the morphinan skeleton construction could be circumvented by utilization of a symmetrically substituted nucleophilic arene. A truly biomimetic construction of the morphinan skeleton by selective phenol coupling however remains beyond reach of synthetic organic chemistry until today. Initial progress toward this goal was achieved by White in 1983, who demonstrated a direct phenol coupling with hypervalent iodine in the synthesis of codeine.[108] Nevertheless, the regioselectivity was still directed by a bromine substituent in the substrate.

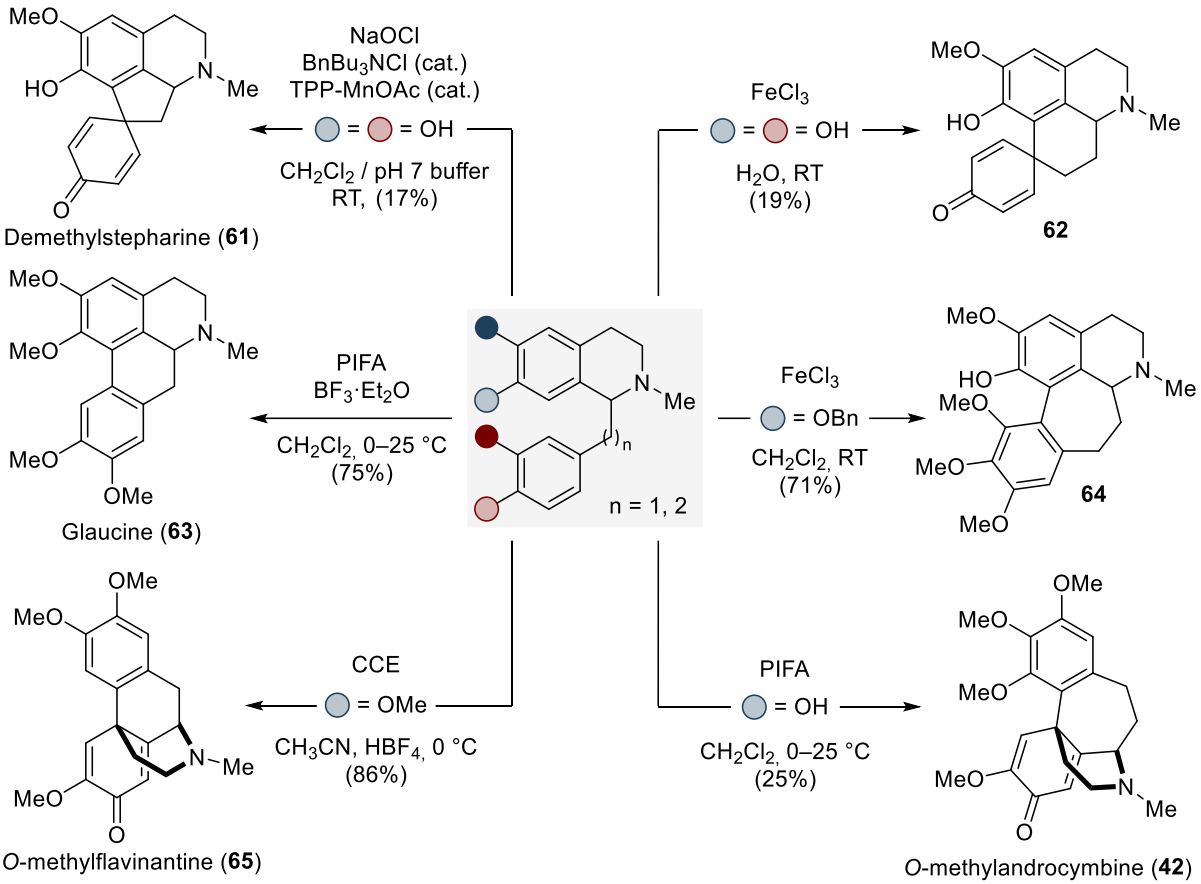
Further developments were published collaboratively by the groups of Opatz and Waldvogel in the time between 2016 and 2019. The authors demonstrated the synthetic potential of electrochemistry in the asymmetric synthesis of thebaine and oxycodone (**60**) *via* selective constant current electrolysis (CCE) (Scheme 2.8).[109–111] In an undivided electrochemical cell, the anodic oxidation of enantioenriched unsymmetrically protected THIQ **54** yields the morphinan skeleton of **55** in 69% isolated yield with complete regiocontrol. The coupling selectivity *para* to the OBn group of the nucleophilic arene is crucial, as this oxygen is further converted selectively to the tetrazole ether **59**, which allows for deoxygenation under hydrogenative conditions. Overall, the synthesis furnishes (–)-oxycodone (**60**) from THIQ **54** in 8 linear steps and 12% overall yield. However, the construction of the highly decorated and enantioenriched THIQ **54** requires another total of 14 steps from commercial starting materials, due to the need for excessive protecting group manipulations as well as the stepwise nature of a Bischler-Napieralski-type synthesis.



Scheme 2.8 Total synthesis of (–)-oxycodone (**60**) by Opatz and Waldvogel.[110] TPP = tetraphenylporphyrin.

In order to facilitate biomimetic access to all benzyl- and homobenzylisoquinoline alkaloids, regiodivergent intramolecular oxidative coupling reactions of THIQs toward the relevant frameworks have to be accomplished by means of chemical synthesis. Attempts in this direction utilize metal oxidants or, most notably, hypervalent iodine reagents. However, the selectivity is often governed by the inherent substrate reactivity, for example by installment of free hydroxyl groups as directing handles. Nonetheless, several relevant naturally occurring structures – (homo)proaporphines, (homo)aporphines, morphinans, and androcymbines – can be synthetically accessed directly from the corresponding THIQ precursor with varying efficiency (Scheme 2.9).

Oxidative coupling of THIQs toward (homo)proaporphines **61** and **62** generally proceeds in low yield, likely due to competing rearrangements to the aporphine skeleton.[112,113] Coupling of the two arenes toward (homo)aporphines on the other hand can be accomplished with high selectivity, as exemplified in the direct synthesis of Glaucine (**63**) and **64**.[114,115] Finally, oxidative dearomatization of the THIQ core toward morphinans (**65**) and androcymbines (**42**) is established by the use of traditional organic reagents e.g. based on hypervalent iodine,[116] optionally enhanced by addition of heteropoly acids,[117] or – as discussed in the total synthesis by Opatz – by electrochemical oxidation.



Scheme 2.9 Chemical oxidative conversion of benzyl- and homobenzyl-THIQs to relevant natural product frameworks. PIFA = (bis(trifluoroacetoxy)iodo)benzene.

2.2.3. Summary and Outlook

Synthetic organic chemistry has made significant progress toward the realization of general biomimetic syntheses of isoquinoline natural products. Most importantly, selective oxidations of THIQs toward relevant natural alkaloids pose a promising and efficient synthetic strategy. Until today, full regiocontrol over oxidative phenol coupling reactions by catalyst or reagent design and reliable and efficient access to the relevant enantiopure THIQ precursors remain unsolved problems in biomimetic syntheses of isoquinoline alkaloids. Due to the emergence of powerful catalytic asymmetric hydrogenation methods, the synthesis of enantioenriched THIQ *via* dehydration of amides and subsequent reduction of an intermediate dihydroisoquinoline remains a frequently employed approach to date.[118] Studies toward the realization of a more efficient catalytic asymmetric synthesis of THIQs have been conducted as part of this thesis and are presented in chapter 4.

2.3. Catalytic Asymmetric Pictet-Spengler Reactions

The Pictet-Spengler reaction is a powerful redox-neutral synthetic methodology for the construction of annulated saturated *N*-heterocycles from arylethylamines and aldehydes. Even though initially discovered in the context of synthetic organic chemistry, the reaction was later found to be prevalent in biological systems as well. The discovery of so-called Pictet-Spenglerase enzymes ultimately proved the value of this powerful transformation beyond applications in a chemical laboratory. The following chapter aims to give an overview on Pictet-Spengler reactions in chemistry as well as biology, with a particular focus on catalytic asymmetric transformations.

2.3.1. Discovery of the Pictet-Spengler Reaction

With the ascent of synthetic organic chemistry during the 19th century, a strong interest for the identification of novel methodologies for *N*-heterocycle formation had emerged in the scientific community. In fact, in the last 20 years of the century, a striking number of reactions was developed. Some discoveries were so significant that they remain in the common toolbox of modern synthetic chemists and are taught as named reactions in every undergraduate organic chemistry course (Figure 2.8). The Fischer indole synthesis or the Paal-Knorr reaction for the formation of pyrroles can be considered such groundbreaking discoveries.

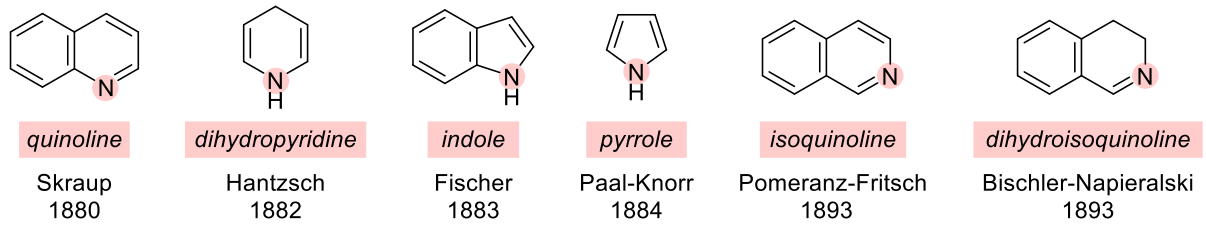


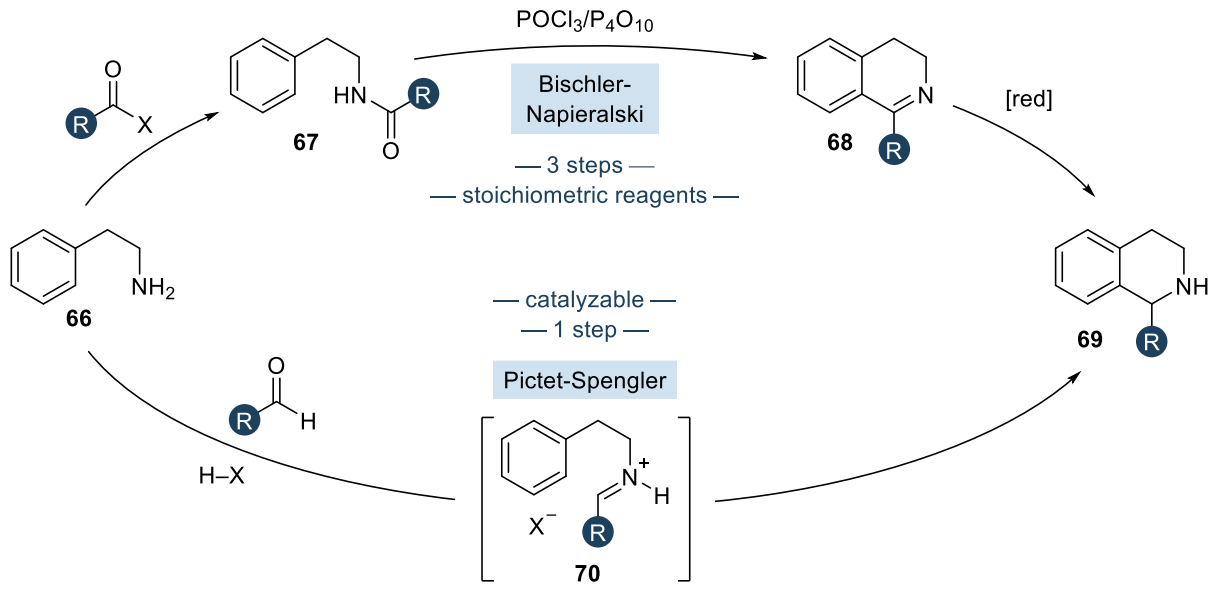
Figure 2.8 Selected traditional named reaction for the synthesis of *N*-heterocycles and the respective year of discovery (typical substitution patterns omitted for clarity).[119]

A number of synthetic approaches toward the isoquinoline skeleton were identified by the end of the 19th century, most notably by Pomeranz and Fritsch as well as Bischler and Napieralski. Both of these reactions deliver an isoquinoline framework, which is at least partly unsaturated. Swiss chemists Amé Pictet and Theodor Spengler recognized this as a disadvantage of the known approaches. In fact, they argued that a subsequent reduction step toward saturated heterocycles might be problematic. Pictet's and Spengler's intellectual contribution extends beyond the pure chemical method development. Already in the seminal work, they appreciated that the development of a novel method with a different redox nature would be particularly useful in the context of the chemical synthesis of plant alkaloids:[120]

"However, it is known that most naturally occurring alkaloids in this group are derivatives of an isoquinoline that is fully hydrogenated in the pyridine core. When applying abovementioned procedure for their synthetic production, it is necessary to hydrogenate the condensation product further, which in some cases (...) will likely be problematic."
[Translated from German].

A. Pictet, T. Spengler in *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030–2036.

The Pictet-Spengler reaction can be viewed as a redox neutral Bischler-Napieralski synthesis of THIQs (Scheme 2.10). While both sequences start from an arylethylamine of the type **66**, the latter utilizes a second component at the oxidation state of an acid to form amide **67**. The following cyclization toward dihydroisoquinoline **68** requires the use of stoichiometric dehydrating P(V)-reagent to furnish a highly electrophilic intermediate, capable of inducing electrophilic aromatic substitution. The Pictet-Spengler reaction however formally replaces the acid oxidation state with an aldehyde. Under acidic conditions, the intermediate iminium ion **70** can be rendered electrophilic enough for nucleophilic attack by the aromatic ring. The seminal publication by Pictet and Spengler describes the use of methylal as a formaldehyde equivalent (R = H). Overall, the THIQ products **69** can thus be obtained in a redox neutral fashion in a single step that does not necessarily require stoichiometric reagents. The Pictet-Spengler reaction is therefore fundamentally superior to the Bischler-Napieralski sequence toward THIQs in terms of step-,[121] atom-,[122] as well as redox-economic[123] perspectives.



Scheme 2.10 Comparison of synthetic sequences toward THIQs according to Bischler-Napieralski and Pictet-Spengler.

2.3.2. Modifications of the Original Pictet-Spengler Reactivity

The Pictet-Spengler reaction involves several key mechanistic steps that can be strongly affected by the applied reaction conditions. Fundamentally, the condensation reaction toward an intermediate imine requires assistance of an acid. Furthermore, the intramolecular electrophilic aromatic substitution step required for C–C bond formation is regulated by an interplay of nucleophilicity and electrophilicity parameters of the arene and the iminium ion, respectively. Consequently, the overall reactivity can be practically controlled by the applied reaction conditions with regard to the choice of solvent, acid, or temperature. Examination of the published procedures for Pictet-Spengler reactions offers a deeper understanding of the inherent requirements for the reaction to take place. Notably, several key modifications of the original procedure have been disclosed and are broadly summarized in the following.

The most important fundamentally distinct Pictet-Spengler reaction conditions are presented in Figure 2.9. The originally published procedure involves treatment of phenethylamine (**66**) and methylal in refluxing hydrochloric acid.[120] The reaction proceeds *via* the intermediacy of a protonated iminium ion and can therefore be classified as a *protic Pictet-Spengler* reaction. A discrete reaction design arises by utilization of *N*-alkylated or -arylated phenethylamines. The main difference is the lack of an intermediate neutral imine that could be further activated by the employed acid, as a fully substituted iminium ion is generated instead. This *N-alkyl/aryl Pictet-Spengler* reaction design has been especially successful in catalytic asymmetric Pictet-Spengler reactions of tryptamines (see section 2.3.4). The reaction modification with the highest impact on general reactivity is the *N-acyl Pictet-Spengler*. In this variant, the electronic properties of the iminium ion are altered significantly by substitution with an electron-withdrawing group (EWG).

The reaction can theoretically be conducted in two ways: Either by activation of a pre-formed imine with a suitable reagent, or by acid-mediated conversion of an *N*-acyl phenethylamine precursor into the activated iminium ion. Notable modularity of the *N-acyl Pictet-Spengler* reaction arises by modification of the EWG (e.g. –COR, –CO_2R, –$CONR_2$, –SO_2R, –$PO(OR)_2$).

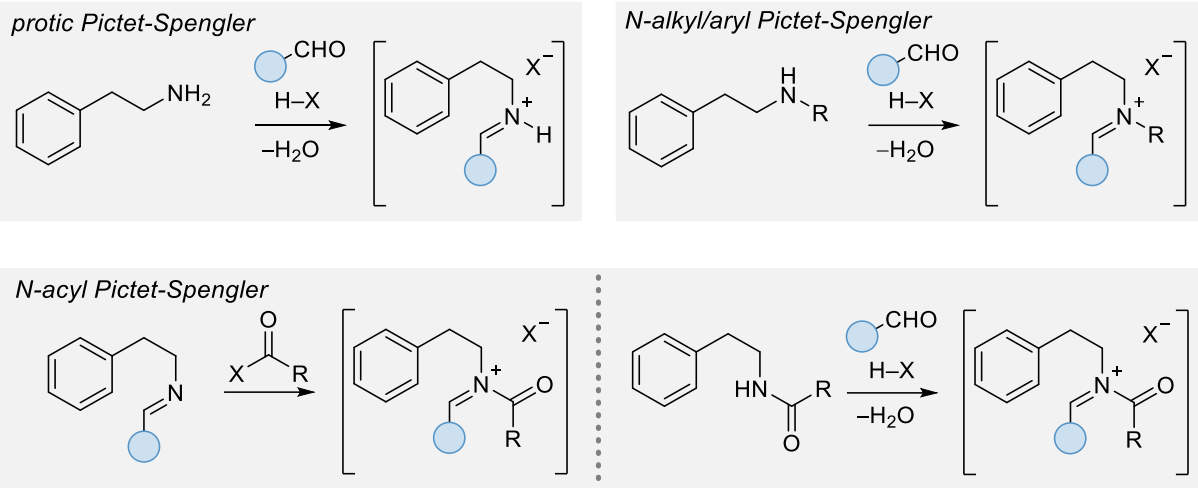
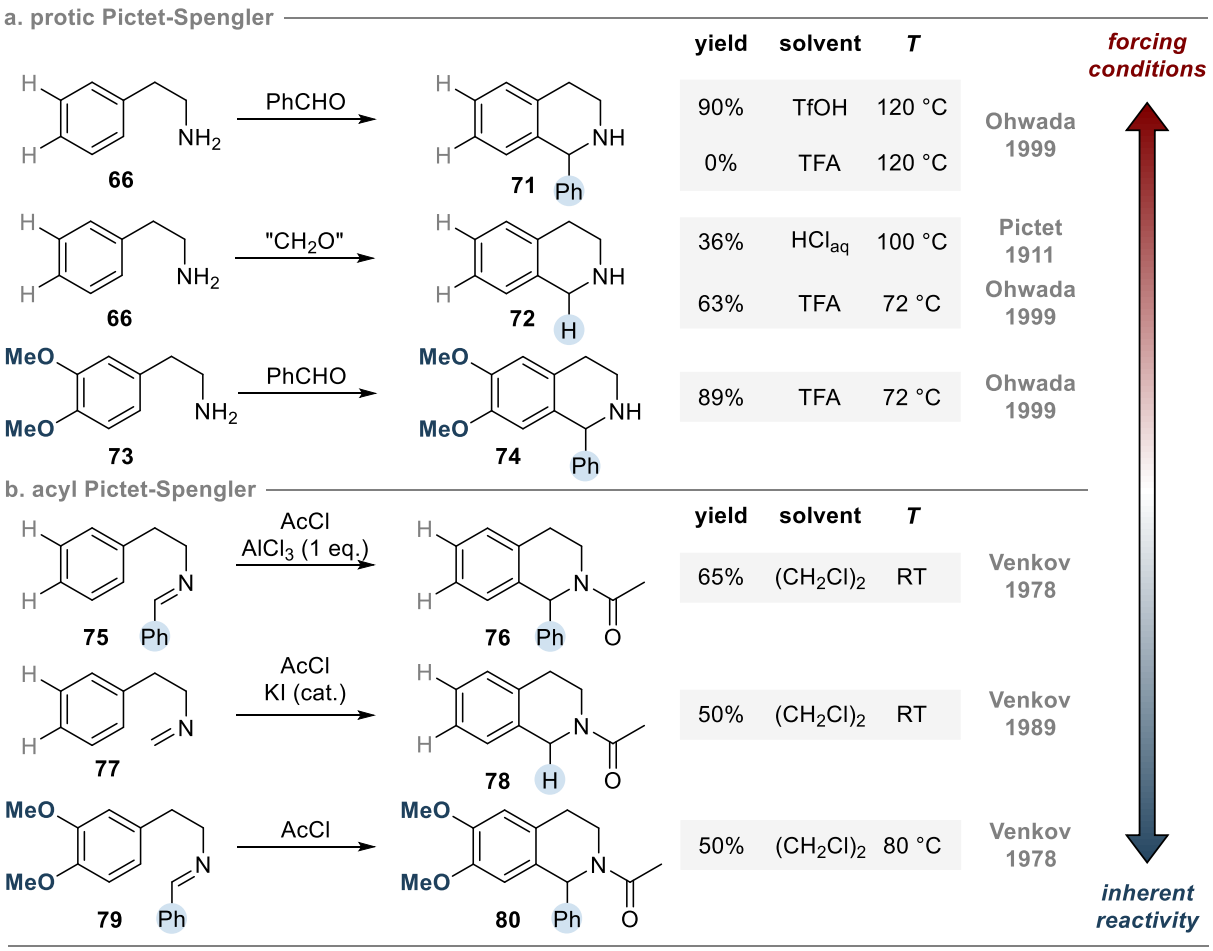


Figure 2.9 Relevant activation modes in Pictet-Spengler reactions.

The dramatic reactivity enhancement from protic to *N*-acyl Pictet-Spengler reactions becomes most obvious by comparison of the reaction conditions for poorly reactive substrates (Scheme 2.11). Three "prototype" Pictet-Spengler reactions are displayed under either protic or *N*-acyl conditions.[120,124–126] The least reactive example in the series is the combination of unsubstituted phenethylamine (**66**) with benzaldehyde toward THIQ **71**. This reaction requires the use of a superacid, trifluoromethanesulfonic acid (TfOH), as the solvent under refluxing conditions. The authors of the study suggested that this particular substrate might even require a dicationic intermediate to undergo cyclization. The reaction with formaldehyde toward THIQ **72** can be realized at slightly lower temperatures in trifluoroacetic acid (TFA), or in refluxing concentrated hydrochloric acid. Similarly, when benzaldehyde is reacted with electron rich homoveratrylamine (**73**) the cyclization toward **74** proceeds smoothly in refluxing TFA. The *N*-acyl modifications of these reactions on the other hand require less forcing conditions due to the increased substrate-inherent reactivity. The imine of phenethylamine and benzaldehyde, **75**, undergoes cyclization upon treatment with acetyl chloride (AcCl) and stoichiometric $AlCl_3$, which facilitates chloride abstraction and formation of the active iminium ion. Notably, the reaction proceeds in non-polar solvent (1,2-dichloroethane, DCE) at ambient temperature. Even milder conditions have been developed for the reaction of formaldehyde-derived imine **77**, where catalytic quantities of potassium iodide are sufficient to induce acetylation and cyclization to **78**. Finally, the electron-rich arene in imine **79** can be transformed to **80** by treatment with AcCl under thermal conditions without the requirement of further catalytic activation.

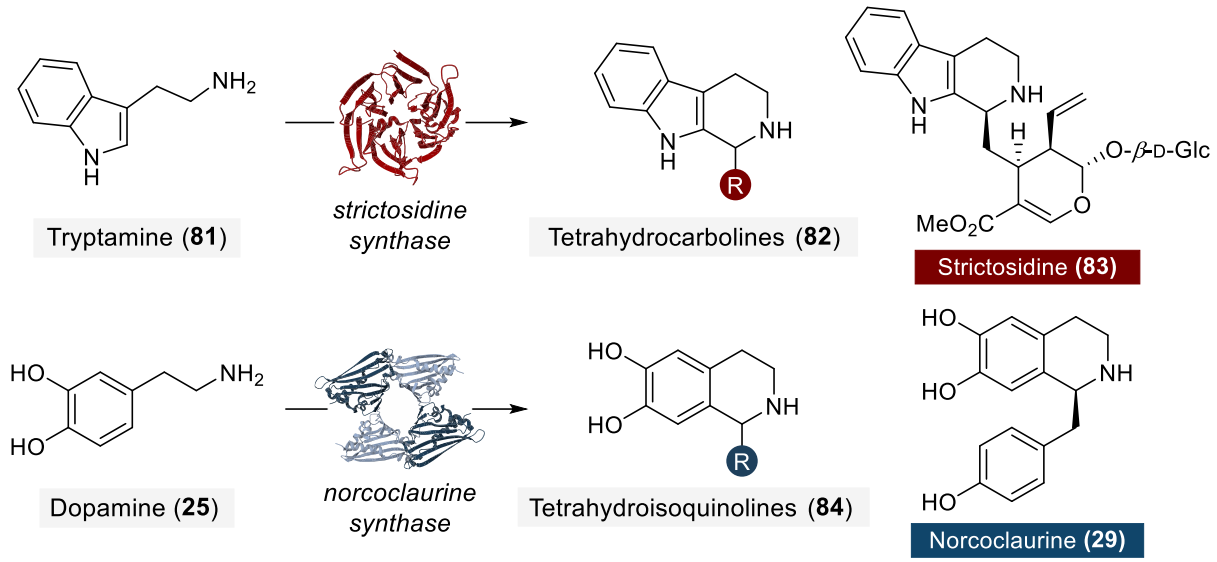


Scheme 2.11 Reactivity comparison of three prototype Pictet-Spengler reactions;[120,124–126] **a.** Protic conditions; **b.** *N*-acyl Pictet-Spengler conditions.

2.3.3. Pictet-Spengler Reactions in Biology

The Pictet-Spengler reaction was developed in the field of traditional synthetic organic chemistry, but was later found to be a widespread phenomenon in biology as well. However, it took more than six decades from the initial chemical discovery, until the first Pictet-Spenglerase enzyme was identified. Significant discoveries can be attributed to German chemist Meinhart Zenk, who made groundbreaking contributions to the study of biosyntheses and metabolisms. He revealed that strictosidine synthase (STR) catalyzes the condensation of tryptamine (**81**) and the terpenoid secologanine toward the tetrahydro-β-carboline (THBC) strictosidine (**83**) with complete stereocontrol at C3 (Scheme 2.12).[127] The great biochemical relevance of this discovery became evermore apparent with the realization that strictosidine is the sole biosynthetic precursor to likely more than 2000 monoterpene indole alkaloids.[83,91,128] Only a short time after the discovery of STR, Zenk *et al.* revealed another important enzymatic Pictet-Spengler reaction: Norcoclaurine synthase (NCS) catalyzes the reaction of dopamine (**25**) with 4-hydroxyphenylacetaldehyde (4-HPAA) to norcoclaurine (**29**).[129] Similarly to strictosidine,

norcoclaurine was subsequently found to be the biosynthetic precursor to more than 2500 benzylisoquinoline alkaloids.[91,95]



Scheme 2.12 Pictet-Spenglerase enzymes in the biocatalytic production of THBCs and THIQs.

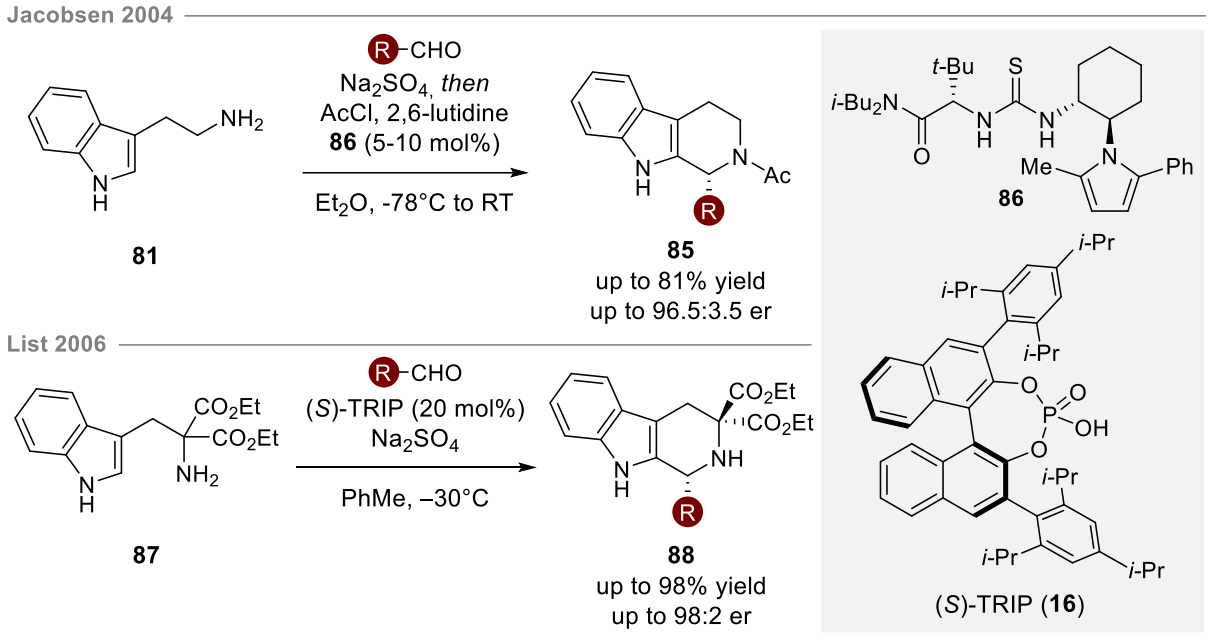
Pictet-Spenglerases belong to the class of lyases, but no further specification is dedicated to the family of enzymes. The scope of amenable substrates for the production of THIQs by NCS enzymes from different plant sources has been studied extensively.[89] In particular, the enzymes seem to accept a variety of different aldehyde reaction partners and in some cases even ketones or α-ketoacids. It can therefore be expected that the biosynthesis of alkaloids closely related to (*S*)-norcoclaurine, such as homobenzyl, isoprenoid, or aromatic THIQs, will likely involve Pictet-Spenglerases that belong to the same family of NCS enzymes. In addition to the two most important types of Pictet-Spenglerases, STR and NCS, a variety of other enzymes capable of catalyzing similar reactions are expected to exist in biology.[89] Most notably, the biosynthetic production of monoterpenoid THIQs requires a Pictet-Spenglerase for the reaction of dopamine with secologanine and two candidate enzymes have been identified.[91] Furthermore, the Pictet-Spengler reaction of histidine with α-ketoacids has been observed in plant tumor cells, but the responsible, likely bacterial enzyme, could not be isolated yet. Finally, a mammalian Pictet-Spenglerase has been isolated from rat brain tissue and revealed catalytic activity for the production of salsolinol from dopamine and acetaldehyde.[130] The process has gained significant attention, as salsolinol is suspected to be involved in human brain processes linked to Parkinson's disease and alcoholism.[94,131,132]

With the advances in modern asymmetric synthesis, chemists sought to develop chemical methods for the synthesis of enantiomerically enriched naturally occurring THBCs and THIQs. The following sections will focus exclusively on catalyst controlled asymmetric Pictet-Spengler

reactions. Substrate- and auxiliary-controlled diastereoselective approaches have been extensively reviewed and are beyond the scope of this analysis.[91,133–135]

2.3.4. Catalytic Asymmetric Pictet-Spengler Reactions toward Tetrahydro-*β*-carbolines

Even though the field was still young and rapidly growing in the early 2000s, asymmetric organocatalysis proved to be particularly suited for the development of catalytic asymmetric Pictet-Spengler reactions. Early work focused solely on tryptamine-related substrates and selected important developments will be covered in this section. Seminal contributions were made by Jacobsen and List in 2004 and 2006, respectively (Scheme 2.13).[136,137] The Jacobsen group contributed a stepwise acyl Pictet-Spengler reaction of tryptamine (**81**) and aliphatic aldehydes. After preformation of the imine, activation with acetyl chloride is accelerated by the use of thiourea **86** as anion binding catalyst to generate the reactive *N*-acyl iminium ion in proximity to a chiral counteranion (ACDC). The List group on the other hand developed the first catalytic asymmetric protic Pictet-Spengler reaction of tryptamine derivatives **87**. The utilization of (*S*)-TRIP as Brønsted-acidic organocatalyst in combination with dehydrating salts successfully furnished the THBCs **88** in high yield and enantioselectivity, however relying on Thorpe-Ingold activation of the substrates.



Scheme 2.13 Organocatalytic asymmetric Pictet-Spengler reactions by Jacobsen and List.[136,137]

Following the seminal reports by Jacobsen and List, a large number of asymmetric organocatalytic Pictet-Spengler reactions of tryptamine-related substrates has been developed (Figure 2.10). The use of HBD catalysts has proven to be one of the most successful catalytic systems for these reactions. The catalysts could directly activate the substrate through weak Brønsted acidic interactions or alternatively serve as anion binders either in acyl Pictet-Spengler

reactions or through the interaction with an additional achiral Brønsted acid. Thus, almost all imaginable iminium ion intermediates could be engaged in asymmetric cyclizations controlled by (thio)urea or squaramide catalysts in the past 20 years. Substrate classes ranging from simple aliphatic and aromatic aldehydes and ketones, over cyclic *N*-acyl iminium ions, 1,2-diketones and α-keto amides, to even heteroaromatic aldehydes are reported in the literature.[138]

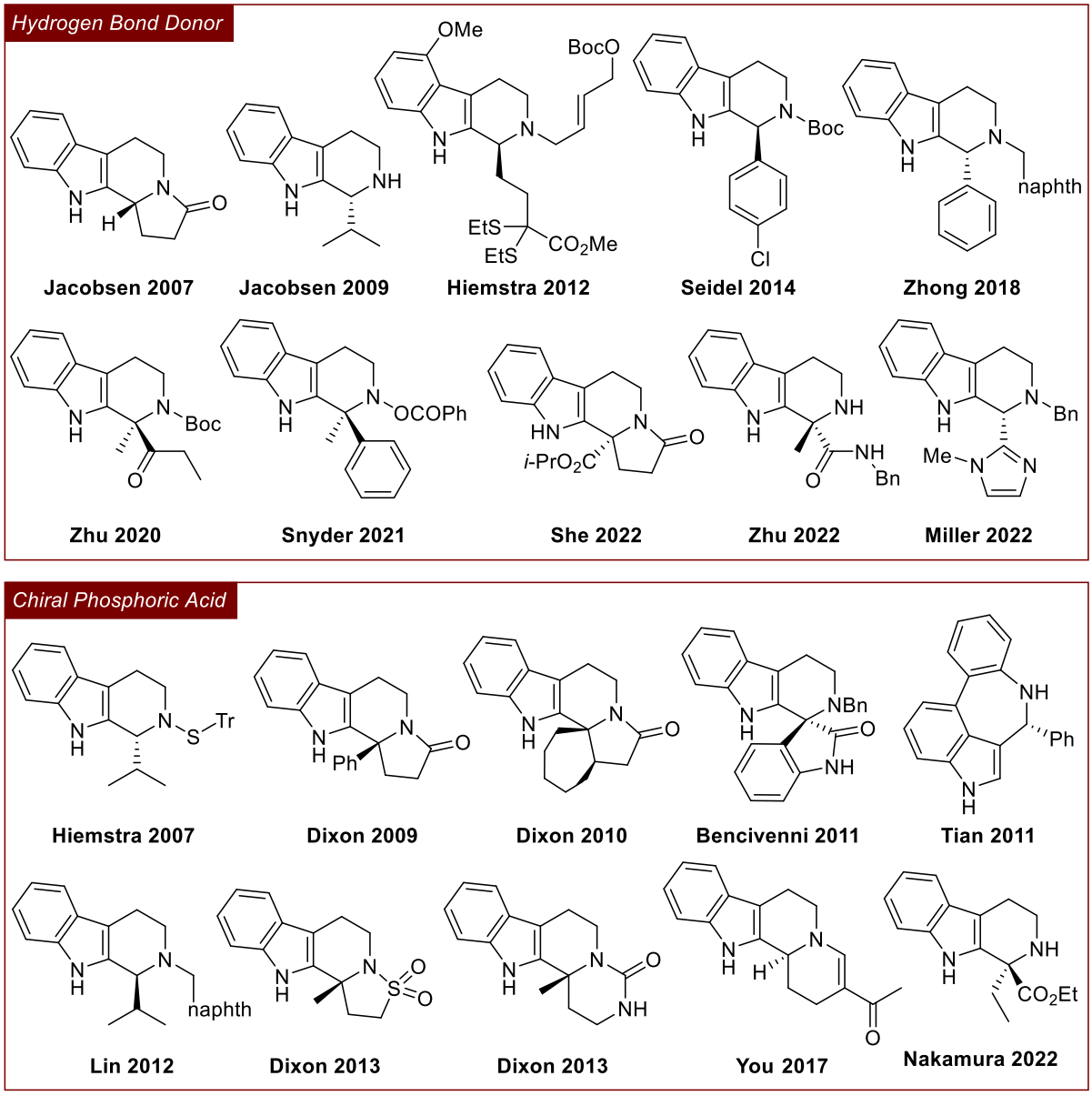


Figure 2.10 Representative products formed by organocatalytic asymmetric Pictet-Spengler reactions of tryptamine-related substrates *via* either HBD or CPA catalysis.[138]

Chiral phosphoric acid (CPA) catalysts have been similarly successful in asymmetric Pictet-Spengler reaction of tryptamines. Especially cyclic *N*-acyl iminium ions such as lactams, ureas, and sulfonamides seem to be privileged scaffolds for the interaction with CPA counteranions. In total, at least 20 different methodologies for Pictet-Spengler reactions of tryptamine-related substrates have been disclosed since 2004. It is for this reason that one might consider the catalytic

asymmetric synthesis of THBCs as one of the most successful reaction developments in the field of asymmetric catalysis in general, with almost no room for further improvements.[138]

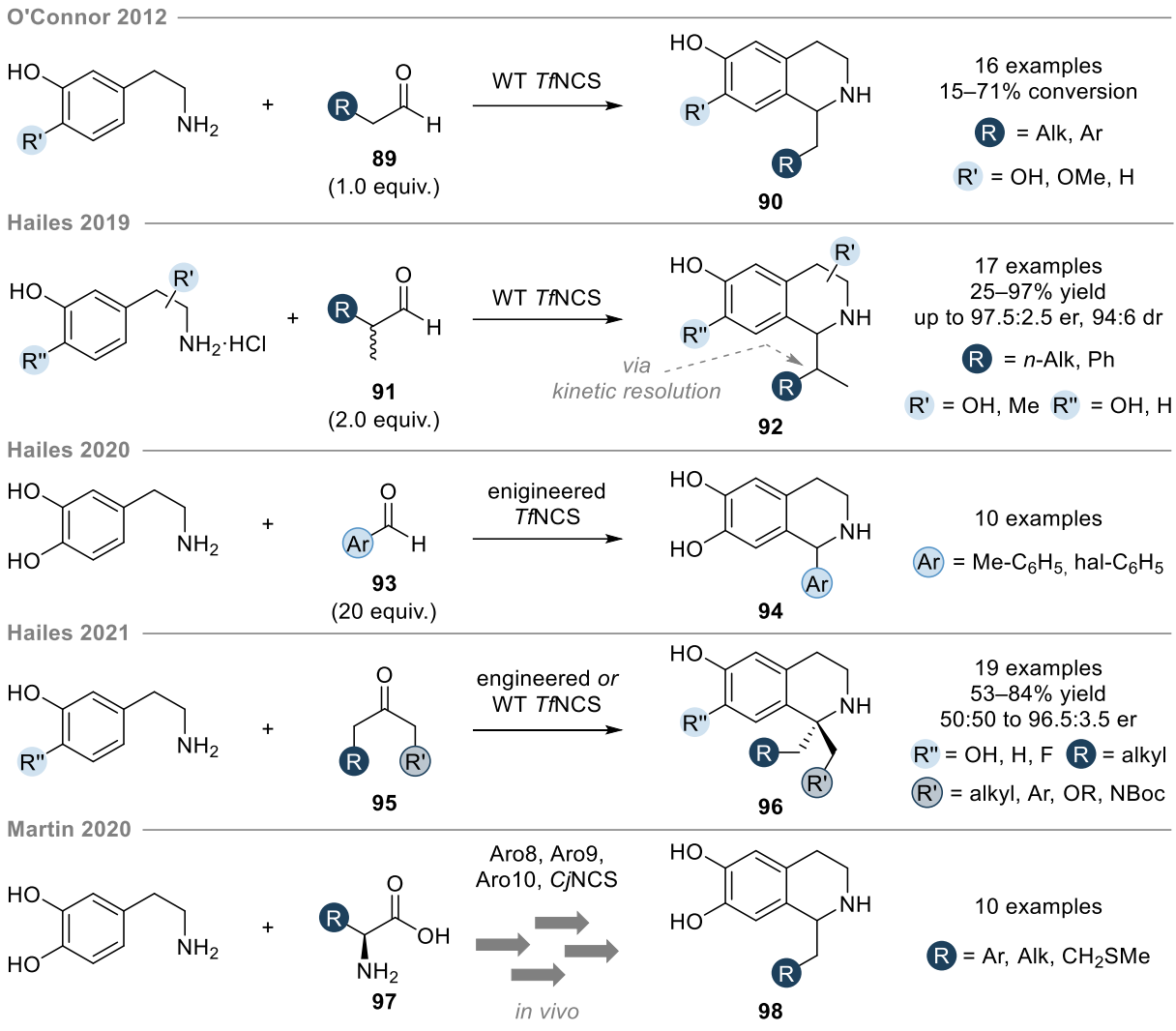
2.3.5. Catalytic Asymmetric Pictet-Spengler Reactions toward Tetrahydroisoquinolines

The catalytic asymmetric synthesis of THIQs is significantly underdeveloped in comparison to the related THBC substrates. Recent success in the scientific literature, most importantly by utilization of engineered or wild type biocatalysts, or through Brønsted acid organocatalysis, highlights the potential for further developments.

Biocatalytic Approaches

Significant research effort has been devoted to elucidation of the structure and catalytic function of norcoclaurine synthase (NCS). Through systematic investigation of the enzyme's substrate specificity and the emergence of powerful enzyme engineering techniques, major success in terms of chemoenzymatic method development has been disclosed in the past decade (Scheme 2.14). The catalytic potential of NCS was systematically explored for the first time independently by O'Connor[139] and Hailes[140] in 2012. The authors found that NCS is surprisingly tolerant for modifications of the aldehyde **89** away from native 4-hydroxyphenylacetaldehyde. Electronically altered as well as substituted phenylacetaldehydes were reacted by the enzyme, as well as *α*-unsubstituted aliphatic aldehydes. However, no THIQ could be detected in the reaction of benzaldehyde, acetaldehyde, or *α*-methyl substituted naphthylacetaldehyde. Moreover, while the aldehyde scope of NCS was found to be broad, the range of acceptable phenethylamines is highly limited. A single free hydroxyl group in the *m*-position to the alkyl chain is crucial for turnover. The second hydroxyl group could however be altered to a methoxy substituent or removed completely. NCS moreover does not accept tryptamine, the native substrate of the second prominent Pictet-Spenglerase, strictosidine synthase.

Further studies on NCS-catalyzed THIQ synthesis focused largely on expanding the scope of amenable aldehydes.[141–144] Despite initial negative results reported by O'Connor, Hailes *et al.* successfully realized the reaction of *α*-methyl substituted aldehydes **91** with wild type NCS by optimizing the reaction conditions.[145] Notably, by employing an excess of the racemic aldehyde, the exocyclic stereocenter in **92** could be controlled with high diastereoselectivity *via* a kinetic resolution process. Furthermore, the acceptance of methyl substituted or halogenated aromatic aldehydes **93** toward 1-aryl THIQs **94** was accomplished by the same author through utilization of an engineered NCS.[146] In the most recent study by Hailes *et al.*, the synthesis of 1,1-disubstituted THIQs was realized by reacting dopamine analogs with a variety of *α*-unsubstituted ketones **95**.[147,148] Thus, aliphatic, aromatic, and spirocyclic products **96** were obtained with high efficiency.



Scheme 2.14 Examples of biocatalytic Pictet-Spengler reactions toward THIQs. WT = wild type. *Tf*NCS = NCS from *Thalictrum flavum*. *Cj*NCS = NCS from *Coptis japonica*.

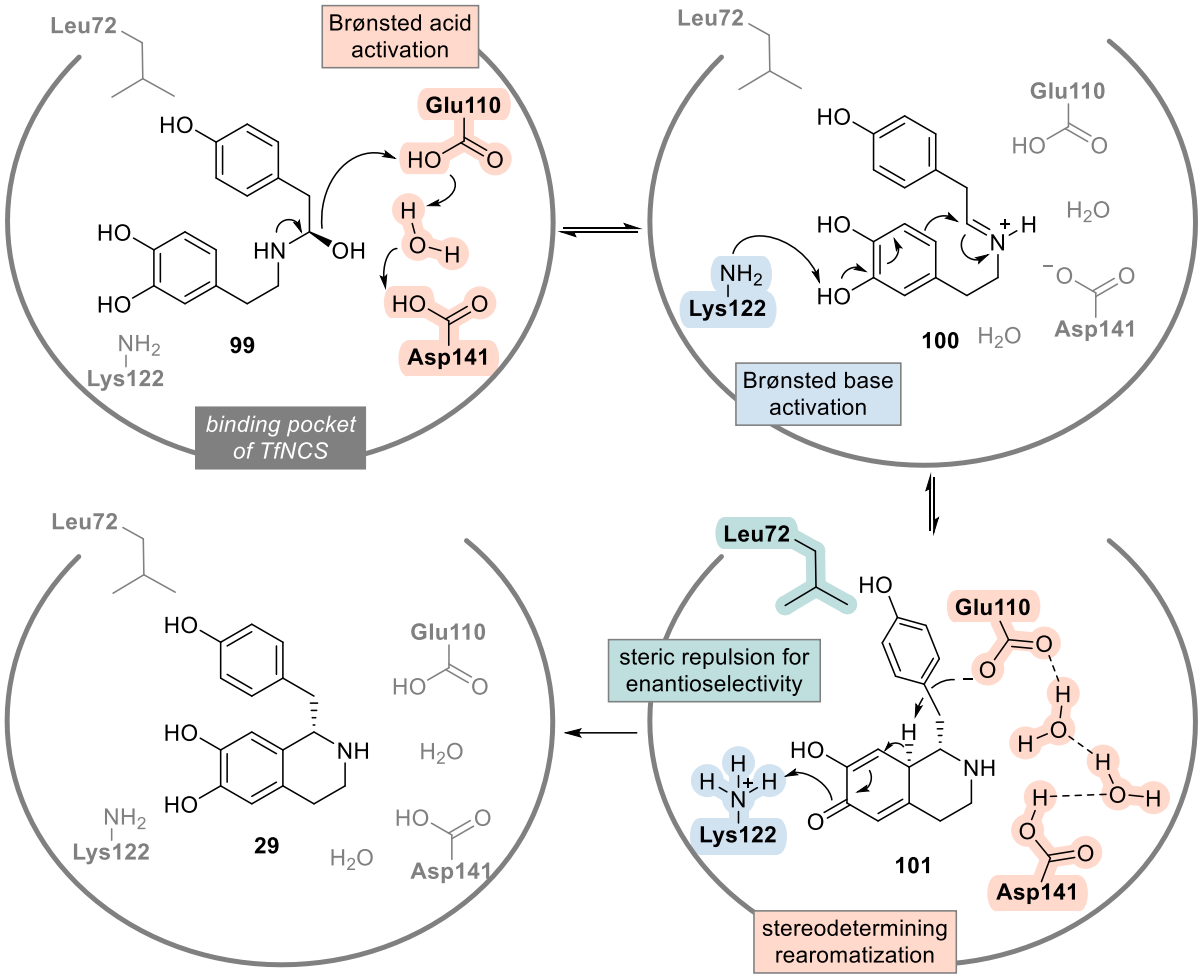
Biocatalysis has thus been able to achieve significant progress in the synthesis of THIQs. However, the enantioselectivity of the products was not rigorously determined in all reports. In the case of the reactions with ketones, the stereoinduction was found to be unsatisfactory in most examples. Nevertheless, the arguably largest advantage of biocatalysis over traditional chemical synthesis arises from the possibility to conduct multi-step reaction sequences from feedstock biochemicals *in vivo*. Several reports have demonstrated the capability of NCS to be incorporated in such processes.[149–152] In an impressive example from 2020, Martin *et al.* reported the engineering of a yeast strain for production of THIQs **98** directly from the amino acid precursors **97**, which were supplemented as major source of nitrogen in each synthesis. The THIQ products of natural or unnatural amino acids were produced with appreciable efficiency.[93]

Due to the success of biocatalytic methods for THIQ production using NCS, efforts have been devoted to understanding the detailed reaction mechanism of this important Pictet-Spenglerase.

Notably, two different modes of substrate activation were proposed in the literature. As the two native substrates of NCS, dopamine and 4-HPAA, are very similar in size, they could theoretically occupy similar regions in the active site of the enzyme. Consequently, the substrate that binds to the enzyme first would be buried deeper inside the pocket. Based on product inhibition patterns as well as crystal structure analysis of enzyme-ligand complexes utilizing unproductive substrate analogs, the so-called "HPAA-first" mechanism has been suggested to be operative.[153,154] However, this binding mode is in disagreement with the observed promiscuity of NCS with regard to the acceptance of diverse carbonyl reaction partners.

In 2017, a crystal structure of the enzyme ligated with a mimic of the intermediate iminium ion has been resolved.[155] Computational docking studies[142] as well as quantum chemical calculations based on this structure[156] have substantiated the "dopamine first" mechanism to be likely operative. Specifically, dopamine is buried deep in the enzymes pocket, which contains an extensive hydrogen-bonding network to bind the polar substrates. Interesting from a chemical perspective is the cooperative acid-base mechanism presented in Scheme 2.15. Brønsted acid activation of the intermediate hemiaminal **99** leads to the formation of iminium ion **100**. Subsequently, base-assisted cyclization toward a neutral cyclohexadienone **101** occurs. This step explains the necessity of a free hydroxyl group in the phenethylamine component in all biocatalytic Pictet-Spengler reactions (see Scheme 2.14). However, the barrier for cyclization seems to be low in comparison to the rearomatization step, which was found to be rate limiting. The stereoselectivity inside the pocket of NCS is thus determined in the final deprotonation by a carboxylate, dictated through the steric repulsion induced by a leucine residue in close proximity.

Overall, biocatalysis constitutes a highly promising approach to the streamlined synthesis of isoquinoline alkaloids. Further advances utilizing deliberately engineered NCS enzymes based on a detailed understanding of the underlying reaction mechanism can be expected in the future. Nevertheless, current limitations in the scope of chemoenzymatic THIQ syntheses include the strict dependency on a free hydroxy group in the phenethylamine substrate, the restricted acceptance of unbiased aldehydes or unnatural substrates such as terpenes, and widespread enantioselectivity concerns in the reported processes. Furthermore, biocatalysts are generally only capable of generating one stereoisomer of the desired product, and purposely switching the selectivity through directed evolution is rarely accomplished.[157] All of these limitations in theory might be overcome by the utilization of modular small molecule chiral catalysts. Initial success has been reported in the literature and will be presented in the following section.



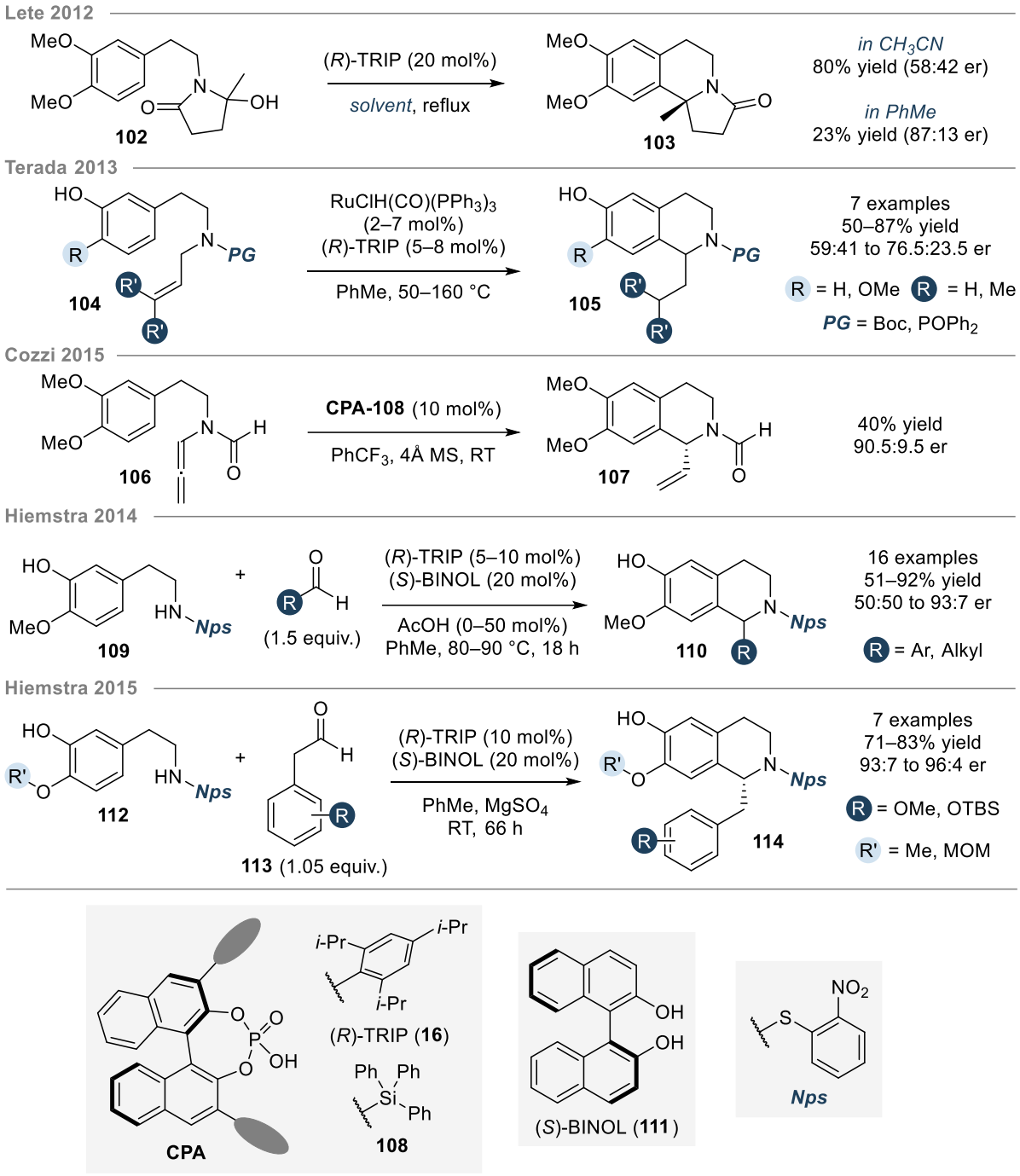
Scheme 2.15 Crucial steps of the computed "dopamine first" mechanism in the pocket of norcoclaurine synthase from *Thalictrum flavum*.[156]

Chemical Approaches

The asymmetric Pictet-Spengler synthesis of THIQs is largely dominated by biocatalytic methodologies. Nevertheless, a few organocatalytic examples relying on the use of CPAs have been disclosed in the literature (Scheme 2.16). In a seminal contribution from 2012, Lete *et al.* developed an asymmetric Pictet-Spengler reaction of racemic hemiaminals **102** toward THIQ lactam **103** through catalytic action of (*R*)-TRIP.[158] The synthetic procedure required high catalyst loadings of 20 mol% and refluxing conditions, which are presumably essential for generation of a highly reactive *N*-acyl iminium ion. Furthermore, while high yields of the product could be obtained in acetonitrile, the reaction in toluene furnished the desired product in only 23% yield, albeit with promising enantioselectivity (87:13 er). A succeeding contribution from the Terada group in 2013 demonstrated Pictet-Spengler-type reactivity of *N*-allyl phenethylamines **104**.[159] In a co-catalytic fashion, a ruthenium hydride complex was utilized for catalytic double-bond migration toward an intermediate enamine, which could be re-protonated by (*R*)-TRIP toward an *N*-acyl iminium ion to induce cyclization and furnish THIQs of the type **105**. The

developed method proceeds in high yields, but provided the products with insufficient enantioselectivities. Furthermore, the reaction is strictly limited to *N*-alkyl substrates containing a π-system for isomerization and is consequently deprived of the valuable aldehyde modularity in a traditional Pictet-Spengler reaction. A conceptually related reaction was developed Cozzi and co-workers in 2015.[160] Pre-formed allenamides **106** were protonated by catalytic action of CPA **108** to induce cyclization toward **107** from the intermediate *N*-acyliminium ion. Notably, unprecedented enantioselectivity without the necessity of a free hydroxy group in the aromatic ring was observed by utilization of an *N*-formyl protecting group, proposedly directed *via* non-obvious hydrogen bonding from the chiral counteranion to the *N*-formyl C–H bond.

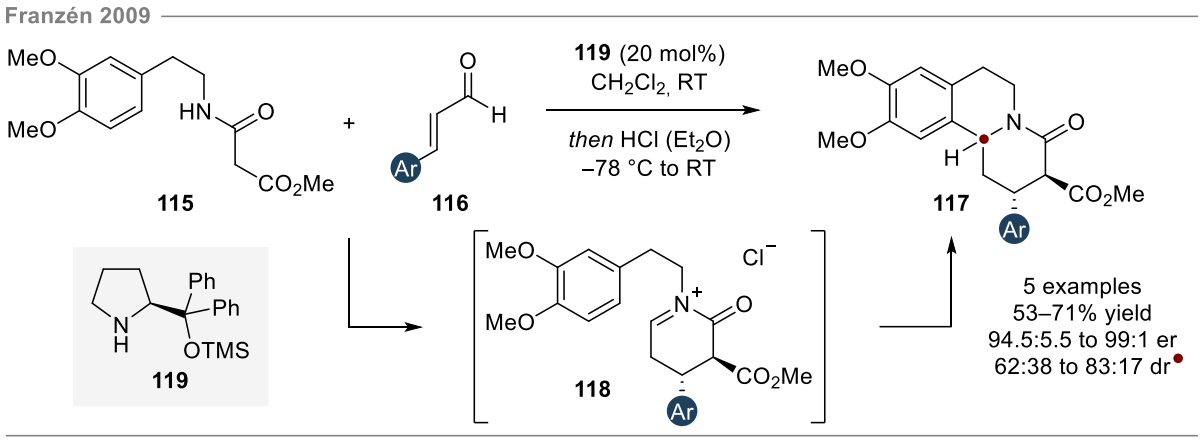
The first intermolecular catalytic asymmetric Pictet-Spengler reaction toward THIQs was ultimately published by the group of Hiemstra in 2014.[161] The reaction design features an *N*-sulfenyl protecting group, *o*-nitrophenylsulfenyl (Nps), the type of which had previously been successfully applied in asymmetric Pictet-Spengler reactions of tryptamines.[162] This class of protecting groups allegedly shows moderate electron withdrawing properties, following an approximate order of increasing electrophilicity according to *N*–alkyl < *N*–sulfenyl < *N*–acyl. Substrate **109** includes a free hydroxy group in the *meta* position that was found to be indispensable for reactivity purposes. The catalyst system is composed of (*R*)-TRIP as Brønsted acid catalyst, as well as additional unsubstituted (*S*)-BINOL (**111**) as a hydrogen bonding co-catalyst for a slight increase in enantioselectivity. Despite significant engineering of the substrate and catalyst system, the reaction still requires elevated temperatures to promote the cyclization. Nevertheless, aliphatic as well as aromatic aldehydes could be converted to THIQs **110** with high efficiency. However, enantioinduction was found to fluctuate significantly even between similar aldehydes and was overall insufficient in most cases. The same group therefore developed an improved reaction protocol for a specific subclass of substrates in 2015.[163] The authors discovered that arylacetaldehydes **113** could be smoothly reacted at room temperature with the same catalyst system, when $MgSO_4$ was added as drying agent to the reaction mixture. Under these conditions, relevant benzyltetrahydroisoquinolines **114** could be accessed in high stereoselectivity. Furthermore, the Nps protecting group facilitated efficient crystallization of products **114** to increase their enantiopurity further. Additionally, the products could be converted to 13 different naturally occurring benzyl isoquinoline alkaloids by simple protecting group manipulations. Subsequently, Hiemstra and coworkers demonstrated the potential of the developed catalytic asymmetric Pictet-Spengler reaction in the context of natural product synthesis in a practical application toward tetrahydroprotoberberine alkaloids.[164]



Scheme 2.16 Catalytic asymmetric Pictet-Spengler reactions toward THIQs.

An alternative catalytic asymmetric approach toward THIQs was pioneered by Franzén and Fisher in 2009 (Scheme 2.17).[165] The conjugate addition of malonate monoamide **115** to cinnamaldehydes **116** could be catalyzed by a Hayashi-Jørgensen prolinol catalyst **119** with high efficiency and stereoinduction. From the resulting 1,4-adduct, acid-mediated formation of *N*-acyliminium ion **118** induces the subsequent Pictet-Spengler cyclization. Products **117** were thus furnished with excellent enantioselectivity. The process should however be cautiously recognized as a substrate-directed diastereoselective Pictet-Spengler reaction, as the selectivity of

the cyclization step is not dictated by a chiral catalyst. Upon closer examination, the limitations in terms of stereochemical control become ever more apparent. The observed poor diastereoselectivity of products **117** is determined with regard to the newly created stereocenter in the THIQ core (marked red), revealing that the Pictet-Spengler step of the synthesis proceeds with poor stereocontrol. Nevertheless, the reaction could be further developed to provide a variety of different Pictet-Spengler type products, including less nucleophilic aromatic systems.[166] Furthermore, products obtained *via* a similar process proved to be valuable intermediates in the synthesis of monoterpene THIQ alkaloid emetine.[167]



Scheme 2.17 Catalytic asymmetric Michael addition Pictet-Spengler sequence.[165]

2.3.6. Summary and Outlook

More than a century has passed since the initial discovery of the Pictet-Spengler reaction. The chemistry and biology of this important reaction has experienced tremendous advancements and reinventions, driven by a continuously deepened understanding of the underlying reaction mechanisms as well as the unexpected prevalence of Pictet-Spenglerases in natural product biosynthesis and biology in general. The ascent of asymmetric organocatalysis in the early 2000s facilitated innovation in the modern era of Pictet-Spengler chemistry and ultimately established the catalytic asymmetric synthesis of tetrahydro-β-carbolines (THBCs) as a shining example in contemporary asymmetric catalysis in general. The Pictet-Spengler universe comprises two major product classes, THBCs and tetrahydroisoquinolines (THIQs), both of which are equally widespread structural motifs in naturally occurring alkaloids. A thorough analysis of the present scientific literature reveals a pronounced substrate bias in the field of asymmetric catalysis, with more than 20 distinct methods published for the Pictet-Spengler reaction of tryptamine derivatives with high efficiency and stereoselectivity. The related cyclization of dopamine-related substrates is essentially undeveloped and embodies a substantial gap in the scientific literature (Figure 2.11). Research concerning the realization of a general catalytic asymmetric Pictet-Spengler reaction toward THIQs has been conducted as part of this thesis and will be presented in chapter 4.

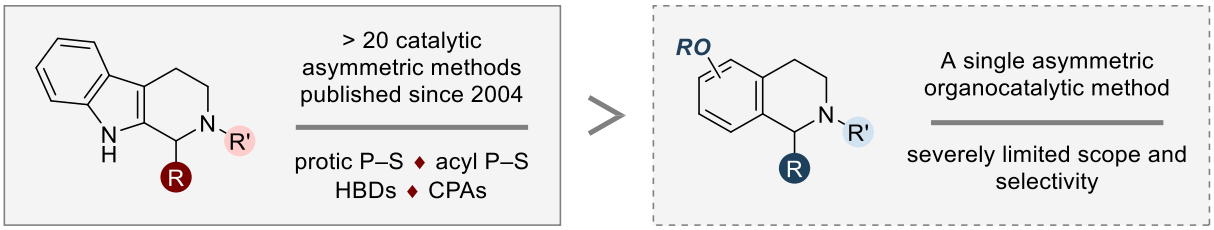
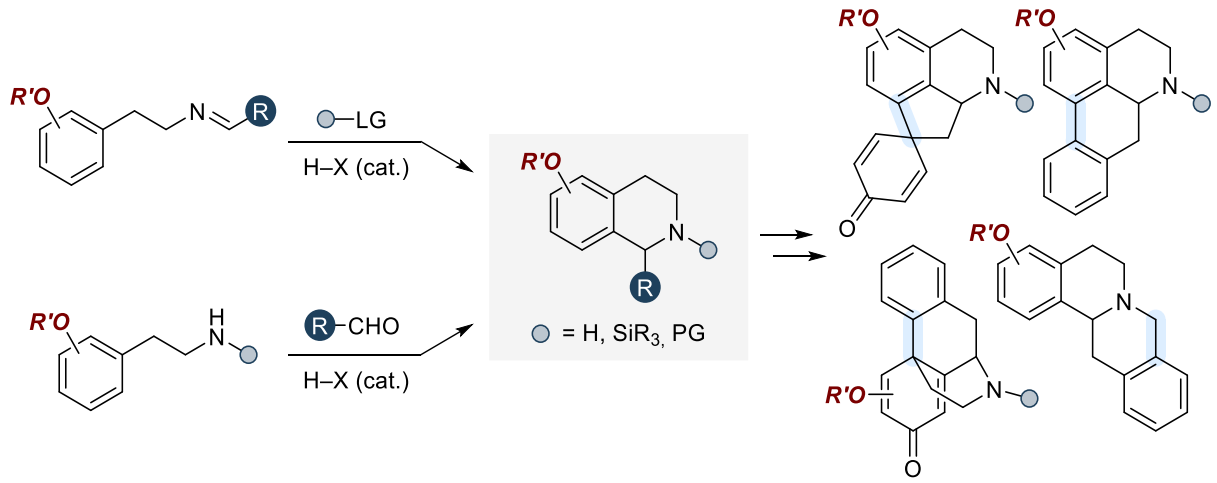


Figure 2.11 Summary of catalytic asymmetric chemical methods toward THBCs and THIQs.

3. OBJECTIVES

As outlined in chapter 2, the catalytic asymmetric Pictet-Spengler reaction is the key methodology for an efficient synthesis of isoquinoline natural products. While many methods are available for the reaction of tryptamine derivatives toward tetrahydro-β-carbolines (THBCs), the equally important catalytic asymmetric synthesis of tetrahydroisoquinolines (THIQs) from dopamine derivatives is significantly underdeveloped. From a total synthesis perspective with an emphasis of synthetic ideality,[5] the state-of-the-art asymmetric access to THIQs involves an imperfect stepwise Bischler-Napieralski sequence.

Based on abundant literature precedents,[138,161,163] we anticipated that organocatalysis would be a particularly well-suited technology for the development of a general catalytic asymmetric Pictet-Spengler synthesis of THIQs. More specifically, Brønsted acid catalysis has dominated the field of asymmetric Pictet-Spengler reactions toward THBCs. We hypothesized that a strongly acidic catalyst might be able to impart stereocontrol over an essential highly reactive intermediate iminium ion by means of asymmetric counteranion-directed catalysis. In order to unlock this unprecedented reactivity, a protic or an acyl Pictet-Spengler reaction starting from either a pre-formed imine or the respective phenethylamine can be envisioned (Scheme 3.1). The catalytic reaction might be accomplished with a strong Brønsted or Lewis acid. As the primary motivation for this project stems from the importance of the natural products, the synthesis of diverse alkaloid structural frameworks from the THIQ intermediates should be explored.



Scheme 3.1 Proposed synthetic approaches toward enantioenriched tetrahydroisoquinolines as key intermediates in the synthesis of naturally occurring alkaloids.

Naturally occurring alkaloids possess a strong structural bias due to the reactivity realm that enzymes are capable of controlling. However, specifically designed highly acidic catalysts might be able to surpass the electronic activation found in natural pathways and provide access to THIQs from “unactivated” precursors (Figure 3.1). To this end, novel reaction designs should be examined that alter the underlying reactivity paradigm and potentially provide a significant advancement in the reactivity landscape of catalytic asymmetric Pictet-Spengler reactions.

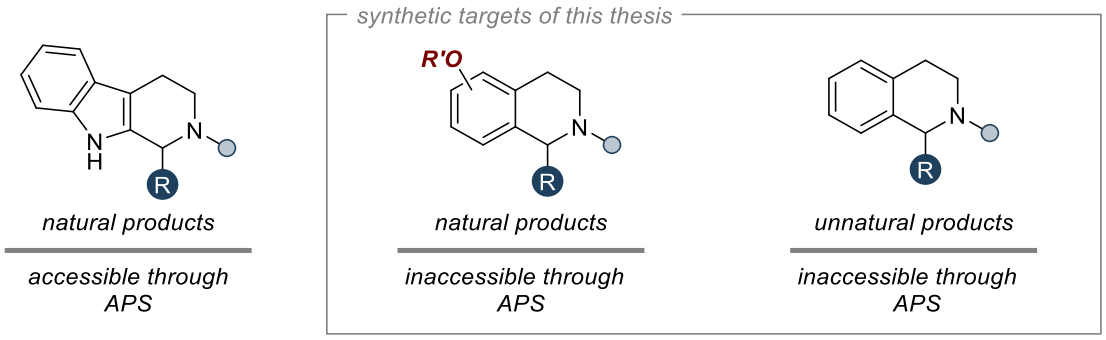


Figure 3.1 Synthetic targets of this thesis. Nucleophilicity of the reacting aromatic ring decreases from left to right. APS = Asymmetric Pictet-Spengler reaction.

4. RESULTS AND DISCUSSION

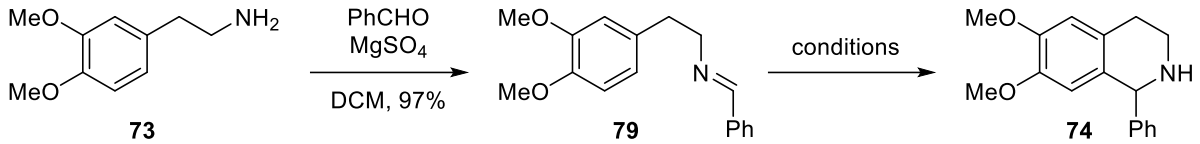
The experimental studies conducted as part of this thesis will be presented in three separate sections: The first part will focus on studies toward the realization of a general catalytic asymmetric Pictet-Spengler reaction for the synthesis of natural products. These relevant substrates possess an inherent electronic and structural bias that strongly influenced the reaction development. A second part will then cover mechanistic considerations for the methodology presented in the first part. A third section will conclude with experimental studies toward a Pictet-Spengler reaction of electron-neutral phenethylamines.

4.1. Catalytic Asymmetric Pictet-Spengler Reactions for the Synthesis of THIQ Natural Products

4.1.1. Reaction Discovery and Initial Optimization Studies

We commenced our studies by examining the general reactivity profile of suitable phenethylamines under acidic conditions. We chose homoveratrylamine (**73**) as a model substrate for two reasons: (1) The methoxylation pattern is representative for many naturally occurring alkaloids derived from dopamine and (2) it lacks the free hydroxy group of dopamine, which was indispensable in previous catalytic Pictet-Spengler reactions.[161] The substrate therefore seemed a reasonable model for the development of a general synthetic method within the chemical space of biologically relevant THIQs. After condensation of **73** with benzaldehyde toward imine **79**, several Brønsted and Lewis acidic reaction conditions were tested for the cyclization reaction to THIQ **74** (Table 4.1). The literature conditions by Ohwada reportedly deliver the desired product in 89% yield after refluxing in TFA (entry 1). However, when the reaction was attempted in chloroform, neither strongly Brønsted acidic (entry 2) nor Lewis acidic (entry 3–4) mediators were capable of facilitating the desired transformation, even at elevated temperatures. Due to these severe reactivity limitations, we shifted our focus toward the development of *N*-acyl Pictet-Spengler reactions.

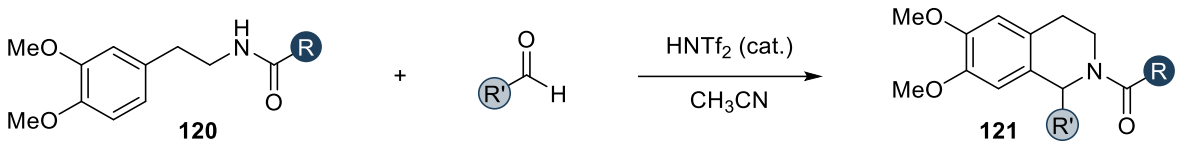
Table 4.1 Initial studies on the Pictet-Spengler reaction of homoveratrylamine (**73**) and benzaldehyde under Brønsted and Lewis acidic conditions. TFA = trifluoroacetic acid. TMS = trimethylsilyl.



entry	Brønsted/Lewis acid	solvent	*T*	yield
1	TFA	-	72 °C	89 %[124]
2	$HNTf_2$ (50 mol%)	$CDCl_3$	RT	no conv.
3	$HNTf_2$ (15 mol%) + allyl-TMS (2 eq.)	$CHCl_3$	RT	no conv.
4	TMSOTf (1.2 eq.)	$CDCl_3$	RT to 50 °C	no conv.

The *N*-acyl variation of a Pictet-Spengler reaction using pre-activated amines is a highly practical approach due to the moisture and air stability of suitably protected primary amines, as well as their ease of handling. We therefore chose to explore the reactivity of derivatized homoveratrylamines **120** in a direct reaction with aldehydes under the catalytic action of a strong Brønsted acid (Table 4.2). Using catalytic amounts of $HNTf_2$ in acetonitrile as solvent, the desired reaction of *N*-acetyl and *N*-formyl homoveratrylamine could not be observed (entries 1–2), whereas common benzyl and methyl carbamates readily reacted under identical conditions (entries 3–5). Only the *N*-Boc substrate was unreactive, potentially due to the protecting group's instability under acidic conditions, which leads to liberation of the basic amine and deactivation of the catalyst (entry 6). Notably, conducting the reaction under Lewis acidic conditions would require stoichiometric amounts of a dehydrating reagent to prevent hydrolysis of the Lewis acid toward the Brønsted acid state. Nevertheless, the Pictet-Spengler reaction with carbamates can readily be promoted by using superstoichiometric amounts of TMSOTf in CH_3CN. From this preliminary reactivity assessment, we chose carbamates as suitable model substrates for further optimization studies.

Table 4.2 Racemic synthesis of tetrahydroisoquinolines **121** from **120** with benzaldehyde or phenylacetaldehyde and general reactivity assessment under Brønsted-acidic conditions.



entry	R	R'	yield
1	Me	Bn	0%
2	H	Bn	0%
3	OBn	Bn	96%
4	OMe	Ph	>99%
5	OMe	Bn	55%
6	O*t*-Bu	Bn	0%

We specifically selected phenyl carbamate **120a** as model substrate to prevent possible catalyst alkylation from alkyl carbamates under strongly acidic conditions. As a first step of reaction development, we tested different general classes of Brønsted acid catalysts (Figure 4.1). Even though higher catalyst reactivity can be expected in polar solvents such as acetonitrile, we decided to develop the reaction in non-polar chloroform to ensure strong substrate-catalyst interactions within the concept of ACDC, while simultaneously enabling homogenous reaction conditions. We observed a strong correlation between acidity and reactivity in all examined catalytic systems. Common chiral Brønsted acids such as CPAs (**124**, **125**) and DSIs (**18**) failed to show any product formation at ambient temperature, even when an acidifying 3,5-$(CF_3)_2$-C_6H_3 substituent was introduced into the catalyst structure. Similarly, moderately acidic dimeric catalysts, IDPs (**126**, **127**) and iIDPs (**128**, **129**), were inactive under these conditions. Product formation was observed only when catalysts in the so-called superacid regime were tested. NTPA **17** (pK_a = 6.4 in CH_3CN) showed low but measurable activity and gave racemic product in 10% yield. The exceptionally acidic phosphoramidimidate (PADi **131**) was significantly more reactive, but similarly delivered the product only with insignificant enantioenrichment. When IDPi **130a** was tested under the reaction conditions, the product was obtained in appreciable yields (45%) and low but reproducible enantiomeric ratio (59:41 er). We therefore chose IDPis as the appropriate catalyst platform for further optimization studies due to their unique combination of high acidity and confinement.

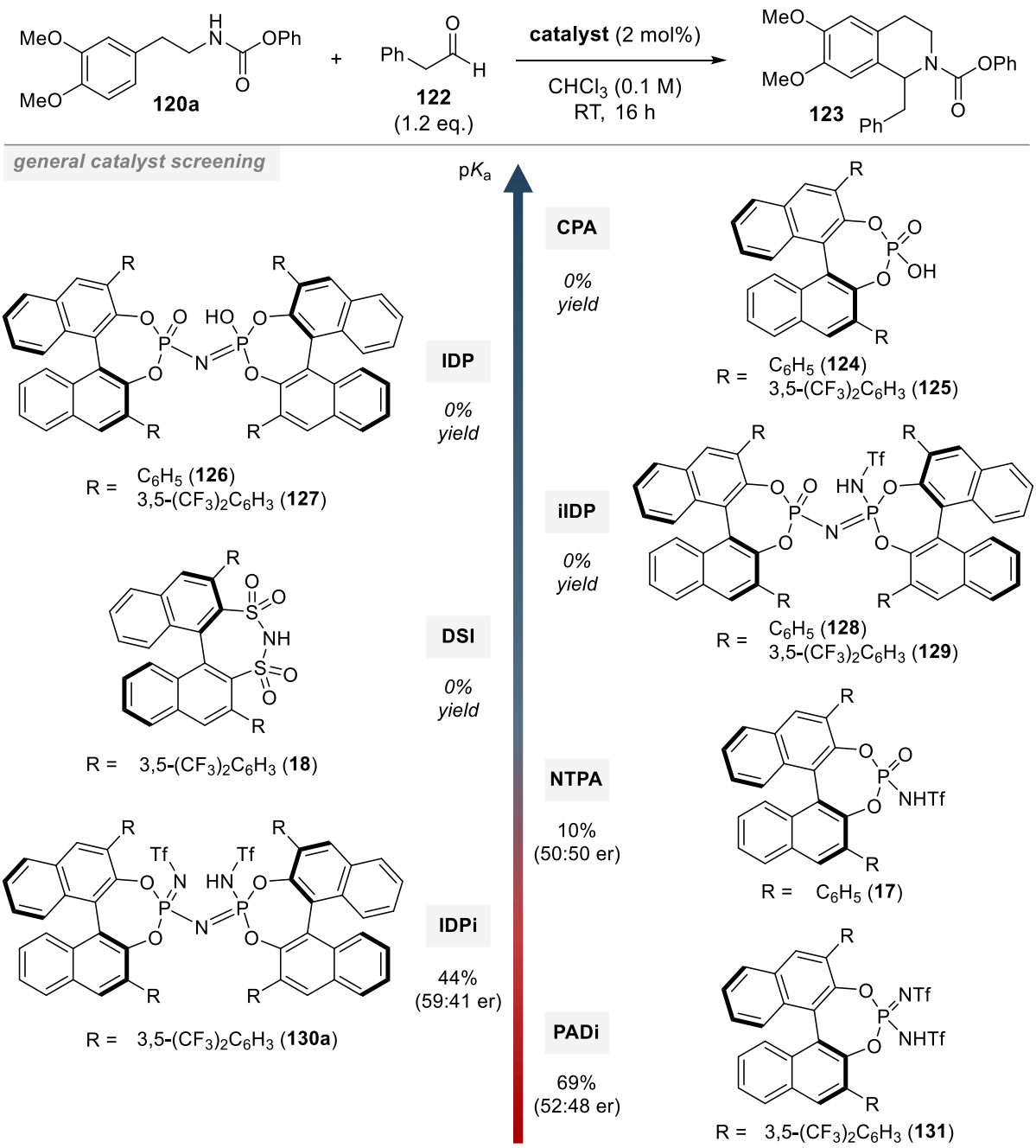


Figure 4.1 Screening of general catalyst motifs in the asymmetric Pictet-Spengler reaction of **120a** with phenylacetaldehyde (**122**). All reactions were performed on a 0.025 mmol scale. Yields were determined by ^{1}H-NMR of the crude reaction mixture using Ph_3CH as internal standard. Enantiomeric ratios were determined by HPLC after purification by preparative TLC. All screening reactions presented in this thesis have been conducted analogously. See the experimental section for further details. PADi = phosphoramidimidate.

In an initial IDPi catalyst screening under identical reaction conditions, we recognized that only highly acidic catalysts that possess electron poor arenes as 3,3'-substituents were capable of delivering the products in notable yields required for accurate HPLC analyses. Fortunately, more concentrated reaction conditions (0.1 M → 0.4 M) allowed us to test diverse catalysts in the model Pictet-Spengler reaction (Table 4.3). Again, within the catalyst class of IDPis, we saw a pronounced effect of catalyst acidity. The 3,5-$(CF_3)_2C_6H_3$-substituted catalysts **130a** and **130b** (entries 2–3) showed superior reactivity compared to all electronically neutral (poly)aromatic catalysts (entries 1–14). A significant drop in reactivity was also detected when the catalyst core was altered from a CF_3 (**a**) to a C_6F_5 group (**b**). The highest enantioselectivity was observed with polyaromatic catalysts **134b** and **138a** (entries 5 and 10).

While the *acidity ~ reactivity* paradigm might be useful for guiding the choice of general catalyst motifs in method development (see Figure 4.1), the correlation is not necessarily strictly valid within a specific class of Brønsted acids (e.g. IDPis). We therefore chose to explore electron-rich IDPi catalysts that would not be expected to be more acidic based on their electronic properties (Figure 4.2). Instead, we hypothesized that stabilizing cation-π interactions between the 3,3'-substituents of the catalyst and the cationic reaction intermediates could potentially accelerate the overall reaction rate. Gratifyingly, when we tested benzofuranyl and benzothiophenyl catalysts **143a** and **144a**, we observed a significant reactivity enhancement in comparison to all previously examined catalysts (entries 15–16). The product was formed in up to 61% yield and with appreciable enantioselectivity of approximately 30% ee.

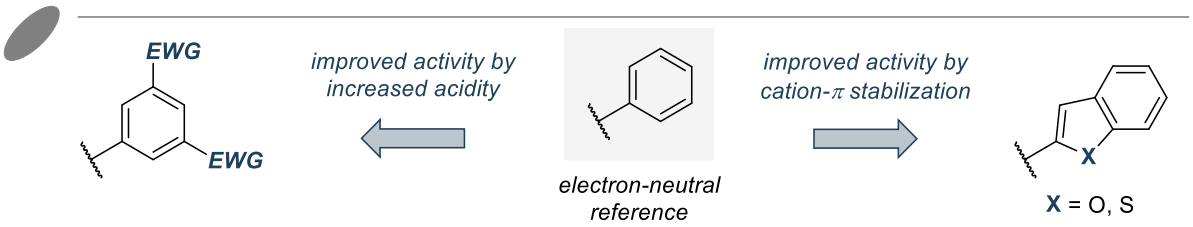
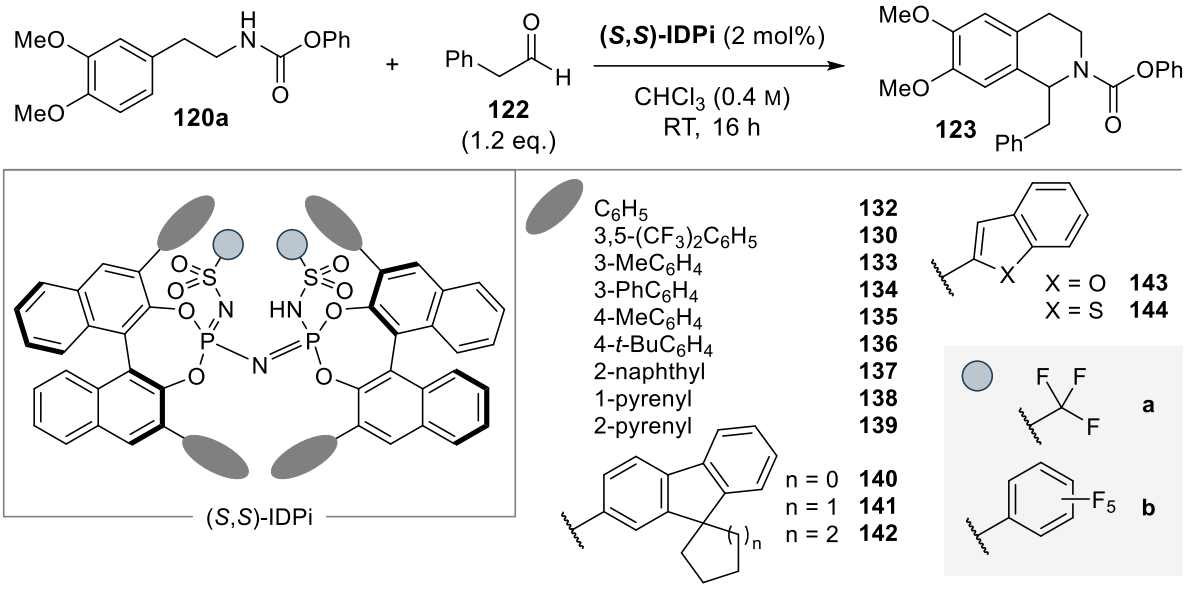


Figure 4.2 Rationale for the development of IDPi catalysts with electron-rich heteroaromatic 3,3'-substituents.

Table 4.3 IDPi catalyst screening at high reaction concentrations. All catalysts except **143a** and **144a** were generously provided by technicians and (former) group members from the List group. n.d. = not determined.



entry	(*S*,*S*)-IDPi	yield	er	entry	(*S*,*S*)-IDPi	yield	er
1	**132a**	27%	45:55	9	**137b**	5%	60:40
2	**130a**	49%	59:41	10	**138a**	17%	75:25
3	**130b**	32%	64:36	11	**139a**	17%	63:37
4	**133a**	17%	38:62	12	**140a**	17%	63:37
5	**134b**	7%	74:26	13	**141a**	15%	59:41
6	**135a**	13%	49:51	14	**142a**	8%	60:40
7	**136b**	0%	n.d.	15	**143a**	61%	34:66
8	**137a**	28%	59:41	16	**144a**	52%	35:65

Due to the peculiarly high reactivity with benzofuran-substituted catalyst **143a**, we were motivated to explore the generality of the rate-enhancement in Pictet-Spengler reactions of three different carbamates **120** with three aldehydes **145** (Figure 4.3). The catalytic activities of three prototypical IDPi catalysts bearing either an electron-neutral phenyl substituent (**132a**), an electron-withdrawing 3,5-$(CF_3)_2C_6H_3$ group (**130a**), or a benzofuran substituent (**143a**) were compared under identical reaction conditions. Using phenylacetaldehyde (R' = Bn), benzofuran-substituted catalyst **143a** offered a general reactivity enhancement in comparison to the electron neutral IDPi **132a**. The effect was most pronounced in the reaction of phenyl-carbamate **120a**, where catalyst **143a** generated significantly more product than the electron-poor IDPi **130a**. When the aldehyde was altered to acetaldehyde, only electron-neutral IDPi **132a** did not lead to quantitative product formation. Similarly, IDPi **132a** was completely ineffective in the reaction of benzaldehyde, where benzofuran catalyst **143a** produced significantly more product than IDPi **130a**. These observations lead to the conclusion that the reactivity enhancement offered by IDPi

143a is a general phenomenon in the Pictet-Spengler reaction under study, independent of the specific aldehyde and carbamate substituents R and R'.

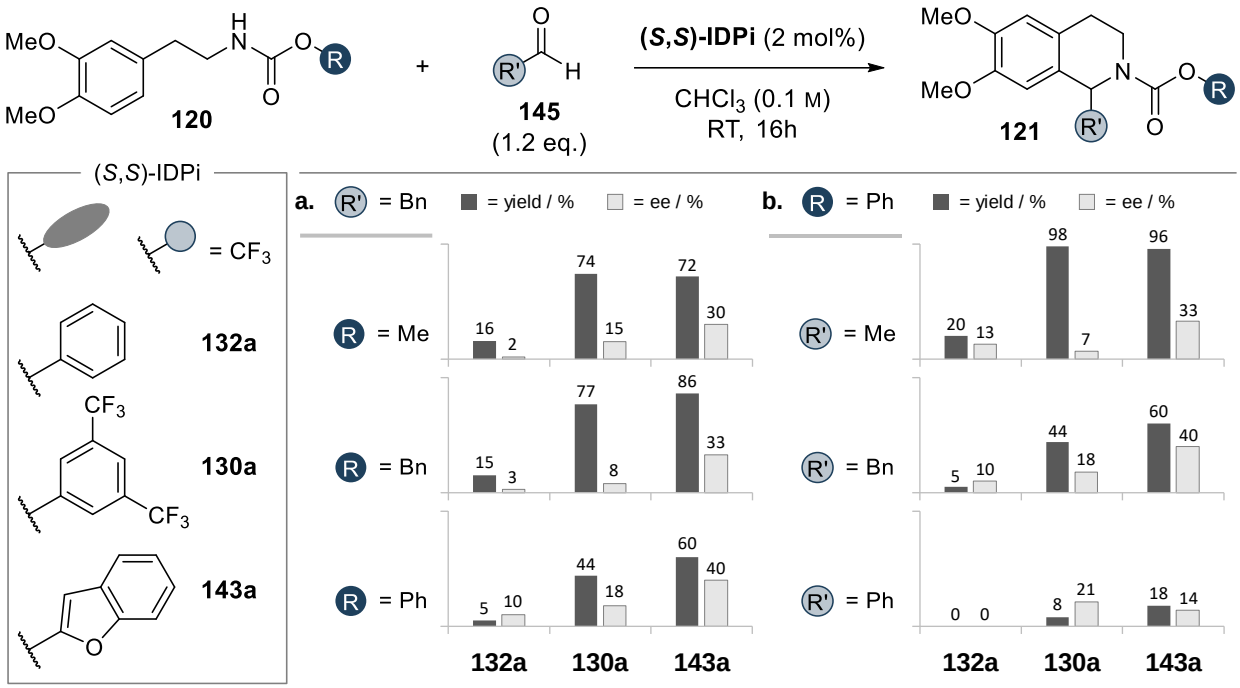


Figure 4.3 Reactivity and selectivity in asymmetric Pictet-Spengler reactions under the influence of three prototypical IDPi catalysts. **a.** comparison of Me-, Bn-, and Ph-carbamates **120** (R). **b.** comparison of Me-, Bn-, and Ph-substituted aldehydes **145** (R').

4.1.2. Synthesis of an Electron-Rich Heteroaromatic IDPi Catalyst Library

The unique synergy of reactivity and selectivity observed with catalyst **143a** inspired us to explore the chemical space of electron-rich heteroaromatic IDPi catalysts. We recognized the benzofuran-2-yl and benzothiophen-2-yl IDPis as parent lead structures and chose to synthesize related catalysts. We designed a library of synthetically accessible motifs that follows four basic design principles (Figure 4.4):

(1) Alkyl- and aryl-substituents in different positions of heterocycles, to explore specific steric requirements for induction of enantioselectivity;

(2) Benzannulations of an electron-rich aromatic ring to explore the effect of an extended π-surface;

(3) Further annulation with electron-rich heteroaromatic rings to explore the effect on reactivity and selectivity;

(4) The connectivity of electron-rich substituents to the 3,3'-position of the IDPi, to determine the optimal geometric location of the heterocycle.

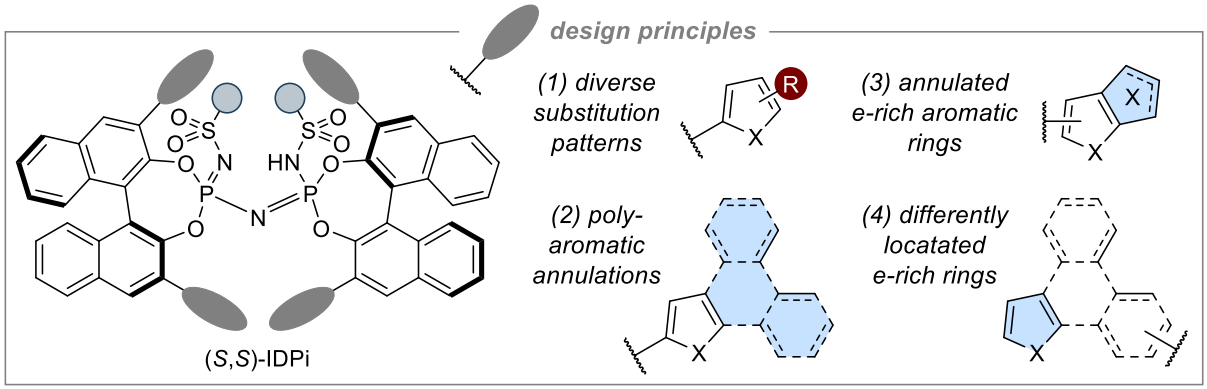


Figure 4.4 Design principles for the conception of an IDPi catalyst library comprised of electron-rich heteroaromatic 3,3'-substituents.

As the established synthetic route to IDPi catalysts involves dimerization of a suitably substituted (*S*)-BINOL precursor, the primary synthetic task for the realization of a novel catalyst library is gaining access to the heteraromatic 3,3'-substituents, which can conveniently be attached to the BINOL *via* Pd-catalyzed cross-coupling reactions. A number of structurally diverse heterocyclic bromides (**146**–**154**) are commercially available (Figure 4.5). As for design-principle 1, we were eager to determine the optimal site for the introduction of an alkyl-substituent on a benzofuran systematically. We therefore synthesized alkyl-substituted benzofurans **156**–**160** *via* a reliable four step reaction sequence developed by the Lautens group (Figure 4.5).[168] Starting from commercially available salicylaldehydes **155**, the introduction of a dibromoolefin through a Ramirez reaction gave rise to *gem*-dibromides, which could be cyclized to 2-bromobenzofurans using copper catalysis after liberation of the free phenol. Naphthofurans **161** and **162** were accessed by the same sequence. Phenanthrofuran **165** and phenanthrothiophene **166** were accessible through a Pd-catalyzed decarboxylative coupling reaction using iodonium salt **163**.[169] A single-step benzannulation of bromothienothiophene **167** using 2,5-dimethoxytetrahydrofuran (**168**) provided benzothienothiophene **169**.[170] To explore the effect of rotationally flexible π-systems in the catalyst wing, we synthesized biaryls **170**–**173**. Finally, the introduction of an iodide or bromide in the 2-position of the relevant heterocycles could be accomplished readily either by deprotonation with *n*-BuLi and interception of the organolithium species with elemental iodine (**174**–**178**), or by electrophilic aromatic substitution with *N*-bromosuccinimide (NBS) (**179**–**184**).

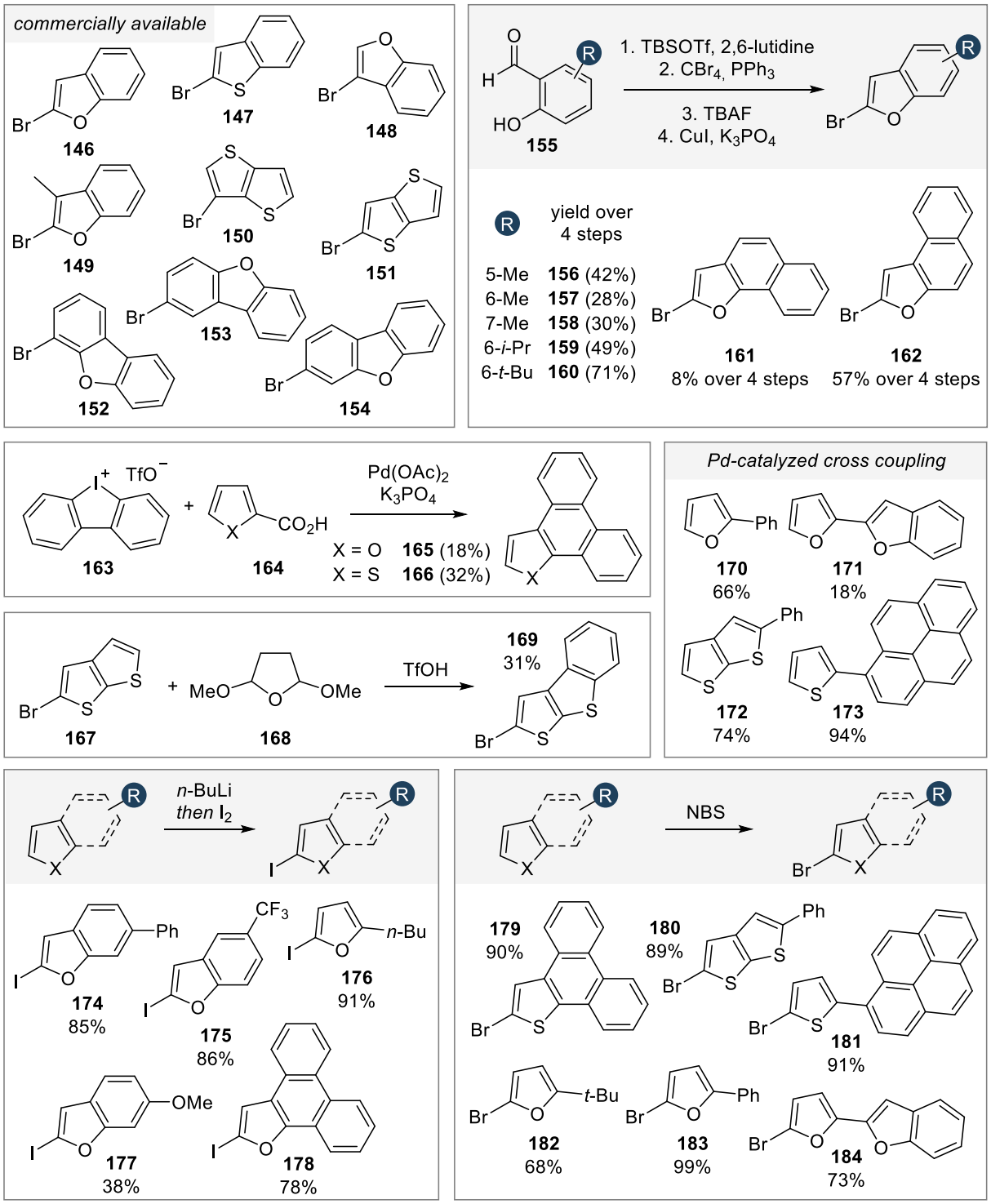


Figure 4.5 Synthesis of heteroaromatic bromides and iodides for installment as 3,3'-substituents in IDPi catalysts. NBS = *N*-bromosuccinimide.

One of the advantages of the IDPi motif is the structural modularity of the catalyst. We were therefore intrigued to explore the catalytic activity of the various 3,3'-substituents in combination with diverse catalyst cores. Figure 4.6 summarizes our newly synthesized catalyst library. All catalyst core structures (**a**–**l**) were synthesized in combination with the parent benzofuran substituent (**143**), and selected cores were combined with lead substituent structures. Moreover,

the acidifying effect of 6,6'-perfluoroisopropyl groups was explored in selected catalyst structures. It is worth mentioning that the catalyst library was established in parallel to the optimization studies and does therefore not cover all conceivable catalyst variations.

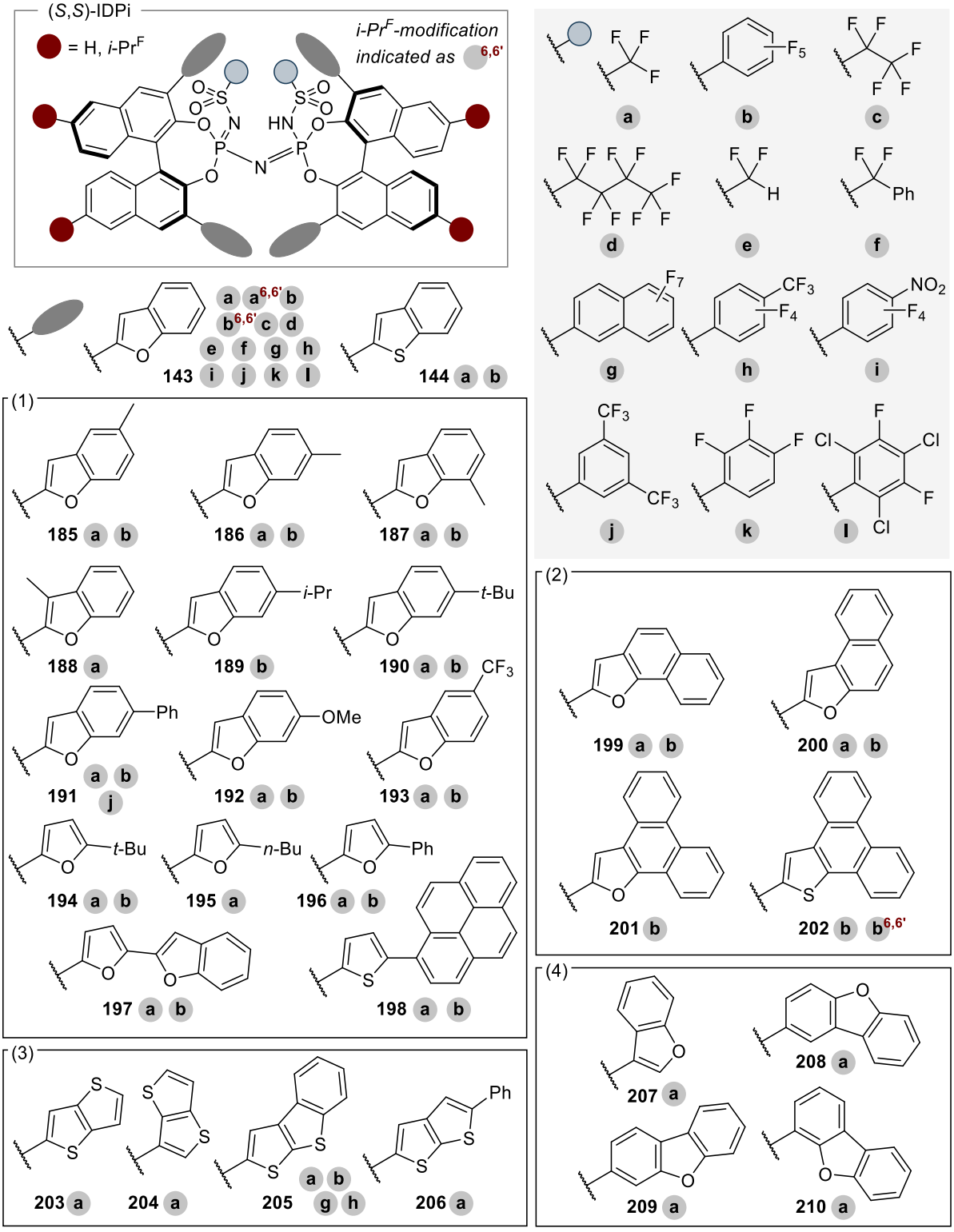


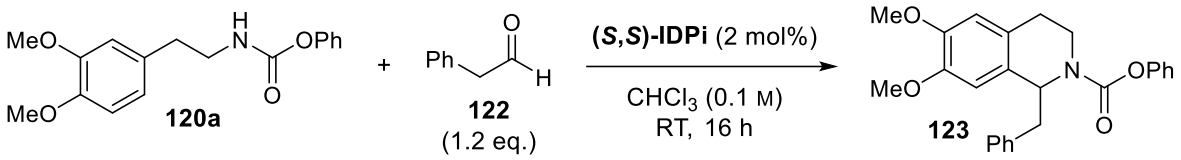
Figure 4.6 Newly synthesized IDPi catalyst library. Structures are grouped according to design principles (1)–(4).

4.1.3. Optimization Studies with Electron-Rich IDPi Catalysts

In the initial evaluation of the reactivity enhancement with benzofuran catalyst **143a** (Figure 4.3), we established that Ph-carbamate **120a** was the optimal substrate for enantioinduction. Before testing the newly synthesized catalysts, the reaction conditions regarding solvent and concentration were reevaluated. Chloroform stood out as the optimal solvent under dilute conditions (0.1 M) at ambient temperature. When our new catalysts were tested in the model reaction, we were able to identify multiple lead structures (Table 4.4). First, we explored variations of the 3,3'-substituents with a Tf-core. According to design principle 1, a 3-Me substituents leads to highly reduced activity (entry 7). On the other hand, alkylation in alternative positions of the benzofuran ring generally preserves the activity, while a significant increase in selectivity is observed for the 6 and 7 position (entries 4–6). This selectivity effect is most pronounced in the 6-*t*-Bu and 6-Ph substituted benzofuran catalysts (entries 8–9). Non-benzannulated catalysts were generally less reactive and selective (entries 11–15). On the contrary, additional benzannulation according to design principle 2 (Figure 4.4) gave reactive and selective catalysts (entries 16–17). Similar trends were observed in the exploration of design principle 3. Simple thienothiophenes as 3,3'-substituents provided poorly reactive and unselective catalysts (entries 18–19), while their benzannulated and Ph-substituted counterparts restored the high reactivity and simultaneously provided promising enantioselectivity (entries 20–21). Finally, attachment of electron-rich rings in different positions according to design principle 4 did not provide new lead structures. While the activity was preserved with 3-substituted benzofuran (entry 22), the reactivity dropped significantly, when dibenzofuran-substituted catalysts were employed (entries 23–25). We can therefore conclude, that the electron-rich ring should be directly attached to the 3,3'-position of the BINOL backbone. Further annulations on the substituent seem to be well tolerated, as well as alkylation in various positions.

Next, we tested the effect of core structures on the parent benzofuran catalyst. Elongation of the perfluoroalkyl sulfonyl group leads to increased reactivity paired with reduced selectivity (entries 27–28). Furthermore, replacing a single fluorine atom with either a hydrogen or a Ph-ring had only detrimental effects (entries 29–30). On the other hand, variation of the CF_3-group in the core to a perfluorophenyl ring lead to a significant rise in selectivity (entry 26). When various aromatic catalyst cores were explored, we saw no further improvement in reactivity or selectivity (entries 31–36). We can thus conclude that aromatic core catalysts facilitate enantioinduction. Nevertheless, proposedly due to their reduced acidity in comparison to perfluoroalkyl cores, a severe decrease in reactivity was observed.

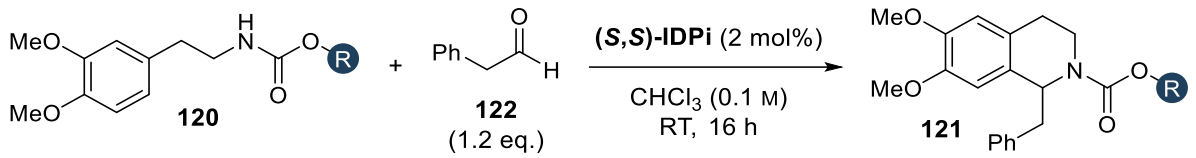
Table 4.4 Screening of newly synthesized IDPi catalysts in the model Pictet-Spengler reaction. Effect of the 3,3'-substituent (entries 1–25) and of the catalyst core (entries 26–36). Lead structures are highlighted in grey.



entry	(*S*,*S*)-IDPi	yield	er	entry	(*S*,*S*)-IDPi	yield	er
1	**143a**	60%	30:70	19	**204a**	20%	56:44
2	**143a**[6,6']	73%	37:63	20	**205a**	50%	23:77
3	**144a**	40%	32:68	21	**206a**	57%	27:73
4	**185a**	61%	34:66	22	**207a**	63%	45:55
5	**186a**	64%	26:74	23	**208a**	23%	73:27
6	**187a**	62%	26:74	24	**209a**	18%	56:44
7	**188a**	3%	43:57	25	**210a**	7%	56:44
8	**190a**	63%	24:76	26	**143b**	12%	15:85
9	**191a**	72%	23:77	27	**143c**	69%	34:66
10	**192a**	50%	27:73	28	**143d**	71%	32:68
11	**194a**	20%	39:61	29	**143e**	17%	33:67
12	**195a**	18%	46:54	30	**143f**	2%	31:69
13	**196a**	41%	43:57	31	**143g**	18%	16:84
14	**197a**	35%	49:51	32	**143h**	34%	15:85
15	**198a**	32%	55:45	33	**143i**	12%	20:80
16	**199a**	64%	23:77	34	**143j**	1%	12:88
17	**200a**	61%	26:74	35	**143k**	2%	14:85
18	**203a**	19%	53:47	36	**143l**	3%	21:79

It is worth noting that IDPis with aromatic and aliphatic cores can behave as entirely different catalysts in a reaction under study, even if they possess identical 3,3'-substituents. It therefore seemed necessary to reevaluate our model Pictet-Spengler reaction using perfluorophenyl-substituted catalyst **143b**. When testing different solvents, we found that $CHCl_3$ remains optimal for stereoselectivity and reactivity, possibly due to the relatively low polarity combined with the high solubilizing properties. Next, we reexamined different carbamate protecting groups (Table 4.5). As was previously established, catalyst **143a** provides optimal enantioselectivity with the Ph-substituted carbamate (entries 1–3). On the contrary, we saw a dramatic increase in reactivity and selectivity with catalyst **143b** when switching from phenyl to alkyl carbamates (entries 4–6). Strikingly, when a simple Me-carbamate was employed, the product could be obtained in synthetically useful yields (68%) and unprecedented selectivity (5:95 er). The *t*-Bu carbamate was again not reactive under the applied conditions (entry 7).

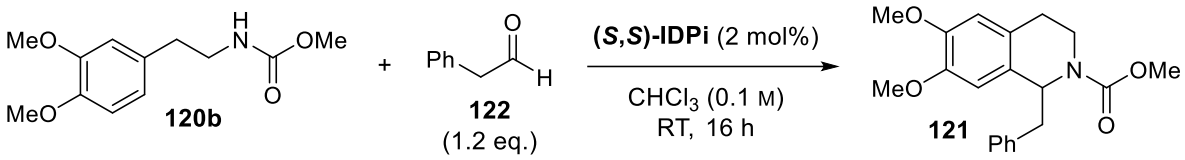
Table 4.5 Reoptimization of the carbamate substituent using IDPi catalysts **143a** and **143b**. Optimal reaction conditions highlighted in grey. n.d. = not determined.



entry	(*S*,*S*)-IDPi	R	yield	er
1	**143a**	Ph	60%	70:30
2	**143a**	Bn	86%	67:33
3	**143a**	Me	72%	65:35
4	**143b**	Ph	12%	15:85
5	**143b**	Bn	62%	13:87
6	**143b**	Me	68%	5:95
7	**143b**	*t*-Bu	0%	n.d.

After having established ideal reaction conditions with prototypical catalyst **143b**, we went on to test our catalyst library of IDPis with aromatic cores in the Pictet-Spengler reaction of methyl carbamate **120b** (Table 4.6). Again, we saw no significant positive effect of the core structure on enantioselectivity (entries 1–6). High selectivity was observed with benzothiophenes as well as substituted benzofurans (entries 7–13). The strongest positive effect stems from a 6-*t*-Bu-substituted benzofuran catalyst (entry 9). Furthermore, substituted furans and thiophenes were less effective (entries 14–17). When benzannulated catalysts were explored, only phenantrothiophene catalyst **202b** stood out as a lead structure (entries 18–21). Finally, benzothienothiophene catalysts also provided high enantioselectivity (entries 22–24).

Table 4.6 Screening of newly synthesized IDPi catalysts in the model Pictet-Spengler reaction using methyl carbamates **120b**. Effect of the catalyst core and the 3,3'-substituent. Lead structures are highlighted in grey.



entry	(*S*,*S*)-IDPi	yield	er	entry	(*S*,*S*)-IDPi	yield	er
1	**143b**	68%	5:95	13	**193b**	85%	16:84
2	**143g**	71%	5:95	14	**194b**	29%	41:59
3	**143h**	83%	6.5:93.5	15	**196b**	53%	37:63
4	**143j**	9%	9:91	16	**197b**	62%	41:59
5	**143k**	27%	5:95	17	**198b**	40%	17:83
6	**143l**	31%	14:86	18	**199b**	63%	11:89
7	**144b**	44%	5.5:94.5	19	**200b**	68%	9.5:90.5
8	**186b**	63%	5:95	20	**201b**	84%	31:69
9	**190b**	60%	4:96	21	**202b**	51%	5.5:94.5
10	**191b**	74%	5.5:94.5	22	**205b**	65%	5:95
11	**191j**	14%	10:90	23	**205g**	47%	5:95
12	**192b**	60%	5:95	24	**205h**	73%	7.5:92.5

The absence of positive effects on stereoselectivity upon introduction of sterically demanding aromatic core structure can be rationalized by examination of the X-ray crystal structure of IDPi **143b** (Figure 4.7). Viewing the structure from the side (**a.**) reveals significant π-π stacking interactions between the BINOL backbone and both perfluorinated cores. The front view (**b.**) signifies how the benzofuran substituents shape the active site of the catalyst. It seems reasonable to conclude that the catalyst core is creating an organized confined pocket by non-covalent interactions with the backbone. Introduction of extended core substituents (as in IDPis **143h–l**) disrupts these interactions, leading to a less organized catalyst and overall deterioration of enantioselectivity. Importantly, the proposed interactions are unavailable in catalysts with perfluoroalkyl cores, thus explaining their inferior enantioinduction. Nevertheless, the solution structure and dynamic interactions between catalyst and substrates cannot be explicitly derived from the crystal structure.

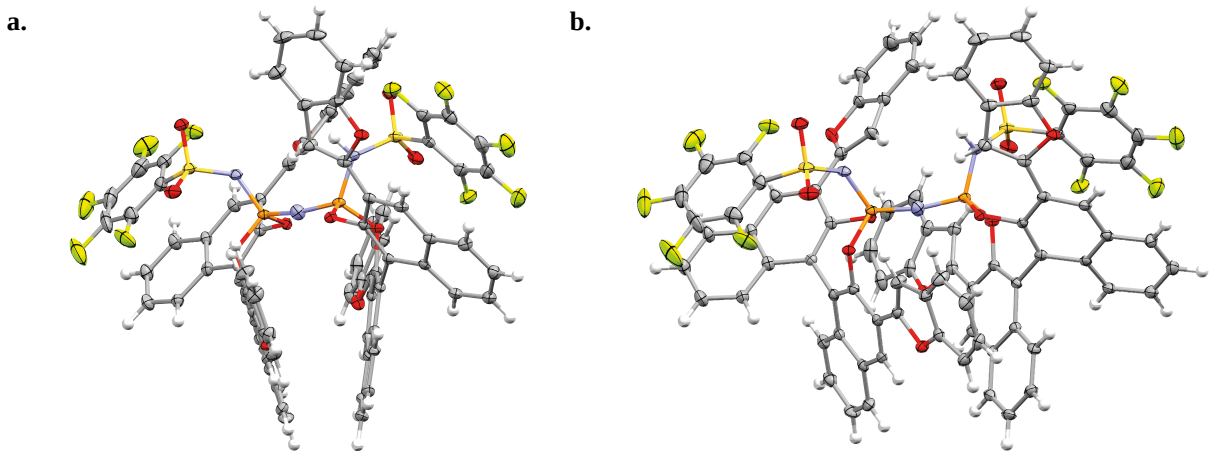


Figure 4.7 X-ray crystal structure of catalyst **143b**. **a.** side view. **b.** front view.

To summarize, we were able to optimize the Pictet-Spengler reaction of *N*-carbamoyl homoveratrylamines **120** with phenylacetaldehyde (**122**), a model for many naturally occurring benzylisoquinoline alkaloids. Our search for an optimal catalyst systematically lead us to electron-rich IDPis with aromatic cores. To this end, three lead structures were identified that possess either a *t*-Bu-substituted benzofuran (**190b**), a phenanthrothiophene (**202b**), or a benzothienothiophene (**205b**). All of these IDPi catalysts were able to produce the product in useful yields (up to 65%) and high enantioselectivities (up to 96:4 er).

As the next step of the reaction development, it seemed necessary to test the generality of the lead catalyst structures in the production of diverse THIQ products. We therefore selected four prototypical Pictet-Spengler products that a highly general catalyst should ideally be able to handle (Figure 4.8). Substrate **211** is representative for purely aliphatic aldehydes, whereas substrate **212** is a model for aromatic aldehydes. Substrate **213** possesses the dioxole annulation that is present in many natural products, while substrate **214** is a formidable challenge to test the catalysts independence from strong hydrogen-bond donors in the substrate.

Aliphatic substrate **211** could be handled best by polyaromatic IDPi **202b**. The same catalyst was also optimal in terms of enantioselectivity for the reaction of aromatic substrate **212** (2:98 er). However, only traces of the desired product were formed with all lead catalysts. This reactivity obstacle of aromatic aldehydes will be discussed in more detail in section 4.1.8 of this thesis. A dramatic decrease in enantioselectivity was observed in the reaction toward dioxole THIQ **213** with all catalysts. Uniquely, *t*-Bu-substituted catalyst **190b** gave promising enantioselectivity (17:83 er). The same catalyst was also the only lead structure that was able to facilitate the formation of free hydroxy product **214** with high stereoselectivity. We therefore concluded that catalysts with a 6-substituted benzofuran represent a promising structural blueprint for the development of a truly "general"[171] asymmetric catalyst. Especially steric alterations in the methoxylation pattern of the substrate proved challenging to the IDPis developed to this stage.

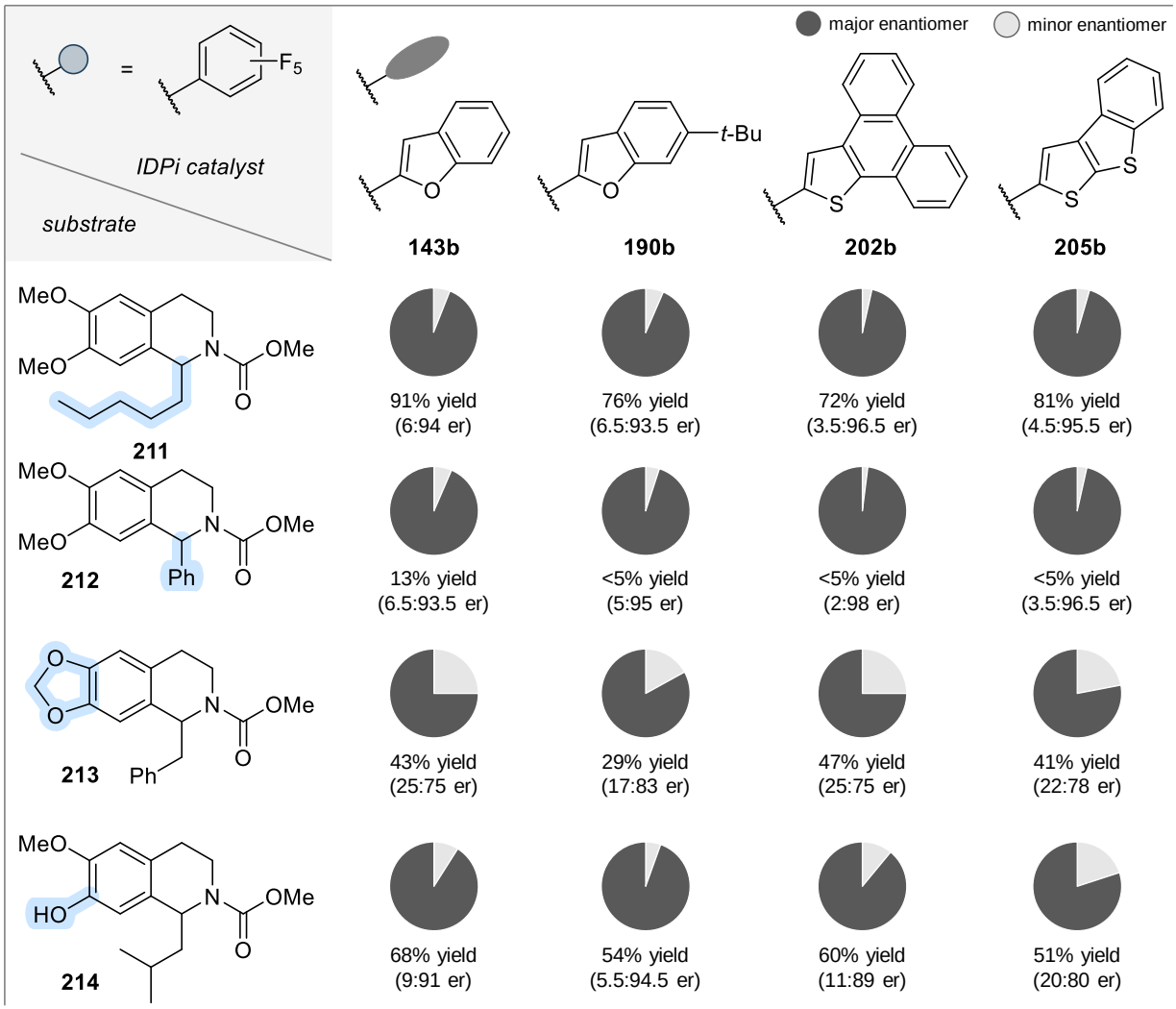


Figure 4.8 Initial screening of diverse scope examples **211**, **212**, **213**, and **214** with parent benzofuran catalyst **143b**, as well as the three lead catalyst structures. Reaction conditions are the same as in previous screenings (see Table 4.6).

In order to leverage the potential of 6-substituted benzofurans as substituents in IDPi catalysts, we were interested in understanding and extending the lead catalyst structure of **190b**. As a *t*-Bu-substituent is known to be not only sterically demanding, but also highly dispersive in nature,[172,173] we envisioned large alkyl substituents as promising structures for more efficient enantioinduction. To this end, commercially available 6-bromobenzofuran (**215**) allowed us to gain access to 6-alkyl benzofurans by adapting methylation chemistry developed by the Reetz group for our purpose (Figure 4.9).[174,175]

After lithiation of **215** with *n*BuLi, nucleophilic addition to a ketone gives rise to a tertiary lithium alkoxide, which could be exchanged to a methyl group by treatment with $Me_2Zn/TiCl_4$ in a one-pot procedure. By this addition/methylation sequence, methyl-adamantyl (**216**) and methyl-dipropyl groups (**217**) were installed successfully. On the other hand, after treatment of lithiated **215** or the corresponding Grignard reagent with an acid chloride, the resultant ketone could be *gem*-dimethylated with $Me_2Zn/TiCl_4$ to give dimethyl-*tert*-butyl (**218**) and dimethyl-adamantyl

benzofuran (**219**). The four newly synthesized benzofurans were subsequently iodinated and transformed into the corresponding IDPi catalysts with a C_6F_5 (**b**) core.

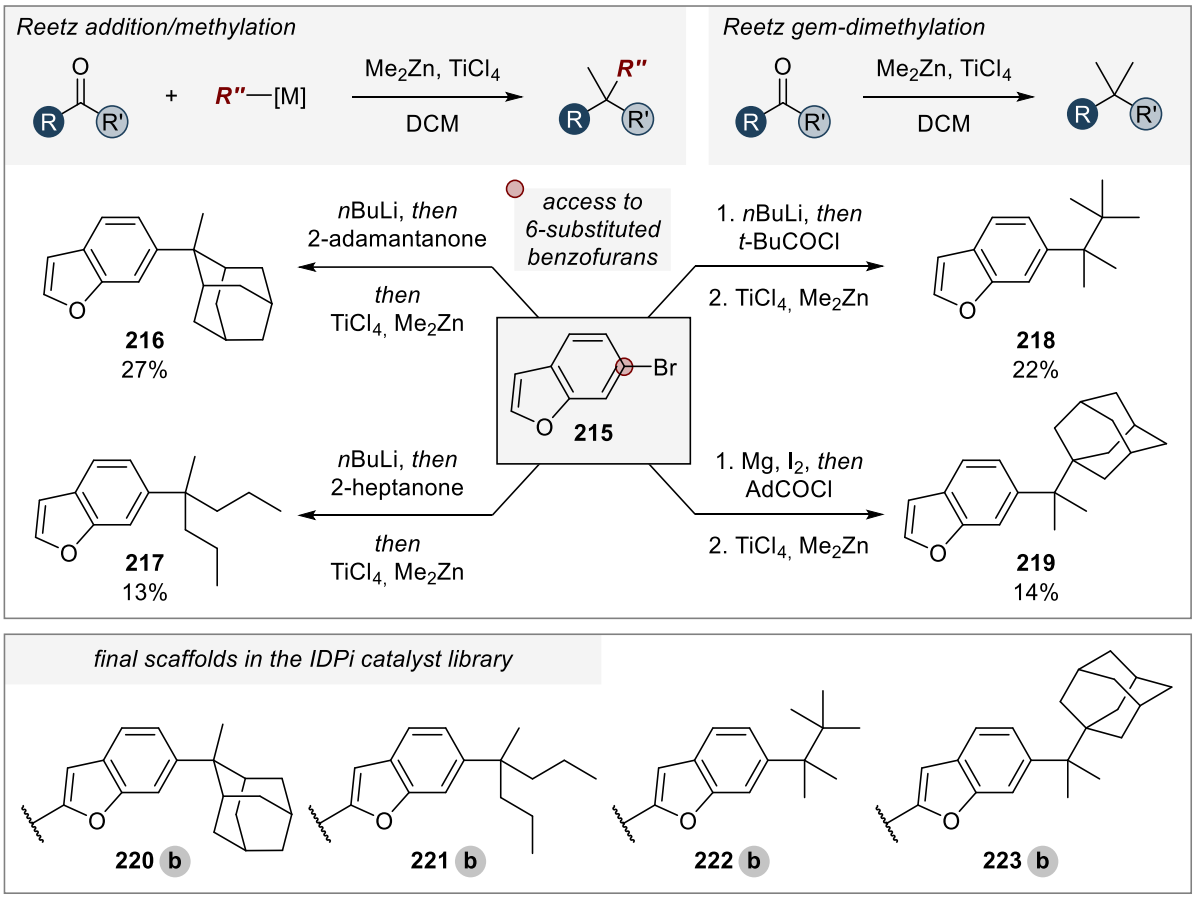


Figure 4.9 Synthesis of 6-substituted benzofurans **216**–**219** *via* Reetz methylation reactions[174,175] and the final scaffolds in the IDPi catalyst library.

We directly compared all of our 6-alkyl benzofuran IDPi catalysts in the reaction toward the most challenging dioxole substrate **213** (Figure 4.10). With increasing size of the substituent, a substantial increase in enantioselectivity became apparent. In the series of Me, *i*-Pr, and *t*-Bu, the latter is the most selective catalyst. Gratifyingly, a further improvement in enantioselectivity was observed with all four newly synthesized catalysts (**220b**–**223b**). Of these IDPis, the 2-methyladamantane substituent (catalyst **220b**) stood out as the most selective, providing the product with almost sufficient enantioselectivity (81% ee). Fascinatingly, the introduction of sterically more demanding alkyl groups in the new catalysts did not lead to reduced catalytic activity. This observation might suggest that attractive London-dispersive interactions play a significant role in accelerating the formation of the major stereoisomer, rather than Pauli-repulsive steric interactions hampering the formation of the minor enantiomer. With the identification of catalyst **220b**, our search for the optimal IDPi catalyst for the Pictet-Spengler reaction was completed. We therefore turned our attention to the investigation of the substrate scope with regard to the carbamate as well as aldehyde reaction partner.

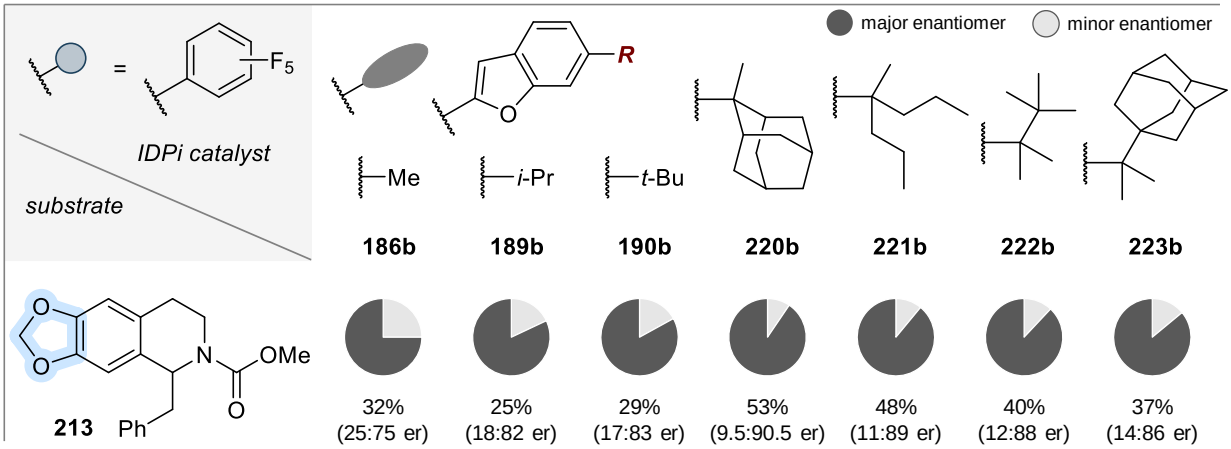


Figure 4.10 Comparison of 6-alkyl benzofuran IDPis as catalysts in the formation of dioxole substrate **213**. Reaction conditions are the same as in previous screenings (see Table 4.6).

4.1.4. Aldehyde Scope

As the primary objective of this project was the synthesis of naturally occurring alkaloids, we designed the substrate scope of the developed method to be representative of natural structures or direct precursors thereof. This section is therefore divided into subsections of structurally distinct product classes, as well as specific examples that required substantial re-optimization of the reaction conditions.

(Homo)benzyl Tetrahydroisoquinolines

Benzylisoquinolines are the largest subclass of isoquinoline alkaloids. We were therefore interested to test our method on synthetically relevant substituted phenylacetaldehydes **224** (Figure 4.11). We observed that, in addition to unsubstituted substrate **226a**, (poly)oxygenated THIQs **226b-g** were formed in generally high yields and with excellent enantioselectivities. Even though protodesilylation of substrates **226d** and **226e** was observed in the racemate synthesis using Tf_2NH, it was gratifyingly not a problem under optimized conditions. The tolerance toward silyl protecting groups is instrumental for the synthesis of natural products with free hydroxyl groups. Furthermore, bromine-containing substrates **226h** and **226i** were produced with high efficiency. The halides might represent reactivity handles for the synthesis of complex bisbenzylisoquinoline natural products *via* cross-coupling approaches. Substrate **226i** additionally allowed for unambiguous determination of the absolute configuration by single crystal X-ray diffractometry. When substituted hydrocinnamic aldehydes **225** were employed, homobenzyl THIQs **226j-m** were formed in high yields and with excellent enantioselectivities. Again, relevant polyalkoxylation of the aromatic ring was well tolerated by the optimal catalyst.

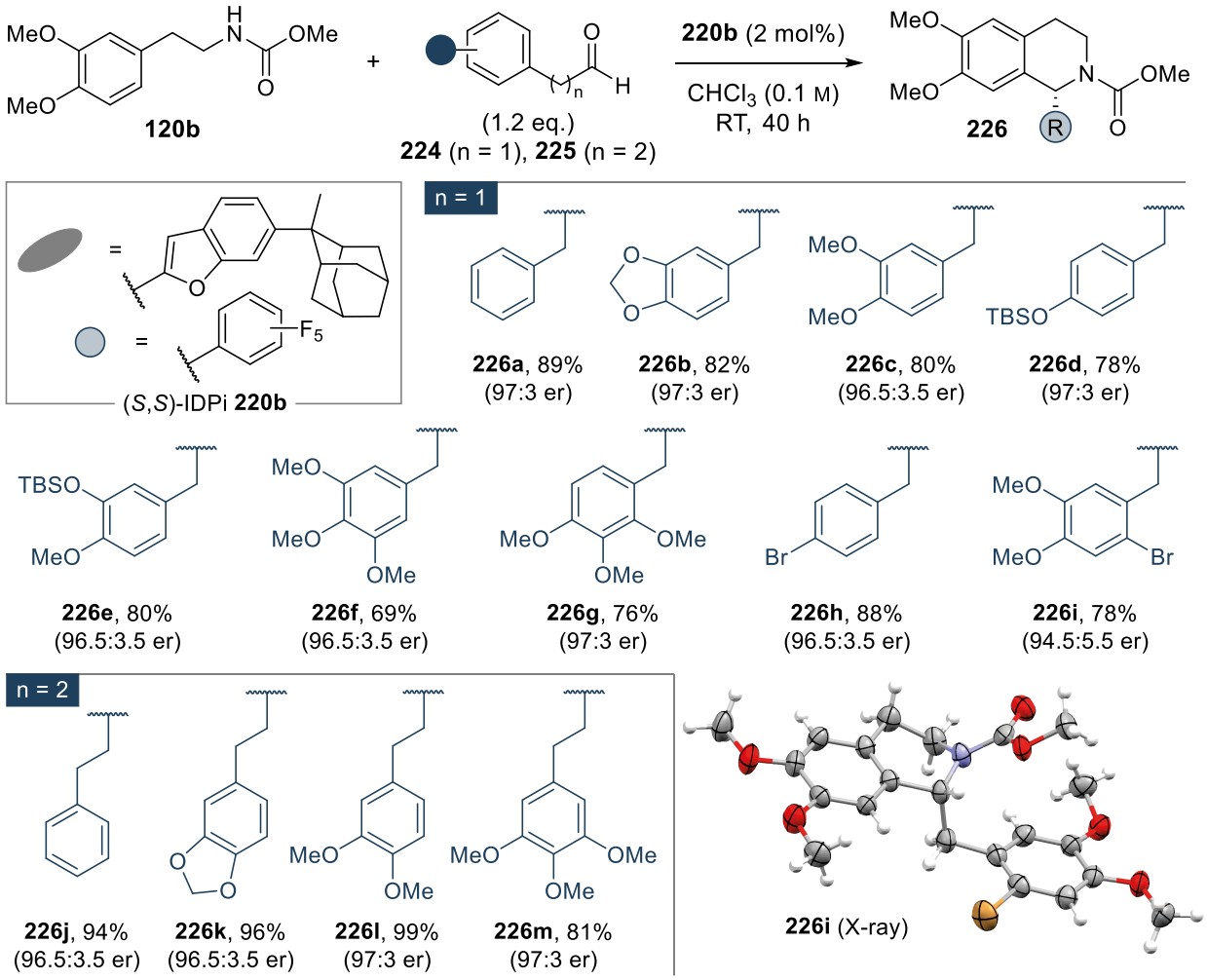


Figure 4.11 Catalytic asymmetric Pictet-Spengler reactions toward benzyl and homobenzyl THIQs **226a**–**m**. All reactions were conducted on a 0.10 mmol scale. Yields are reported as isolated yields after column chromatography.

Non-Aromatic aldehydes

Next, we were interested in exploring the Pictet-Spengler reaction of simple non-aromatic aldehydes (Figure 4.12). Linear aliphatic as well as *β*- and *α*-branched aldehydes were well tolerated to furnish products **226n**–**p**, although slightly reduced reactivity was observed with cyclopentanecarbaldehyde. We were particularly interested in the reaction of acetaldehyde toward product **226q**, because 1-methyl substituted THIQs represent a prominent group of naturally occurring alkaloids. However, the extraordinarily high reactivity of acetaldehyde impaired with its insignificant steric bias renders this substrate notoriously difficult to control in asymmetric catalysis. We were therefore pleased to observe sufficiently high reactivity at reduced reaction temperatures (−40 °C), where product **226q** was formed in quantitative yield and with excellent stereoselectivity (98.5:1.5 er). Furthermore, introduction of a benzyloxy substituent or a methyl ester in the aliphatic chain was well tolerated by the optimal IDPi catalyst, giving THIQs **226r** and **226s**.

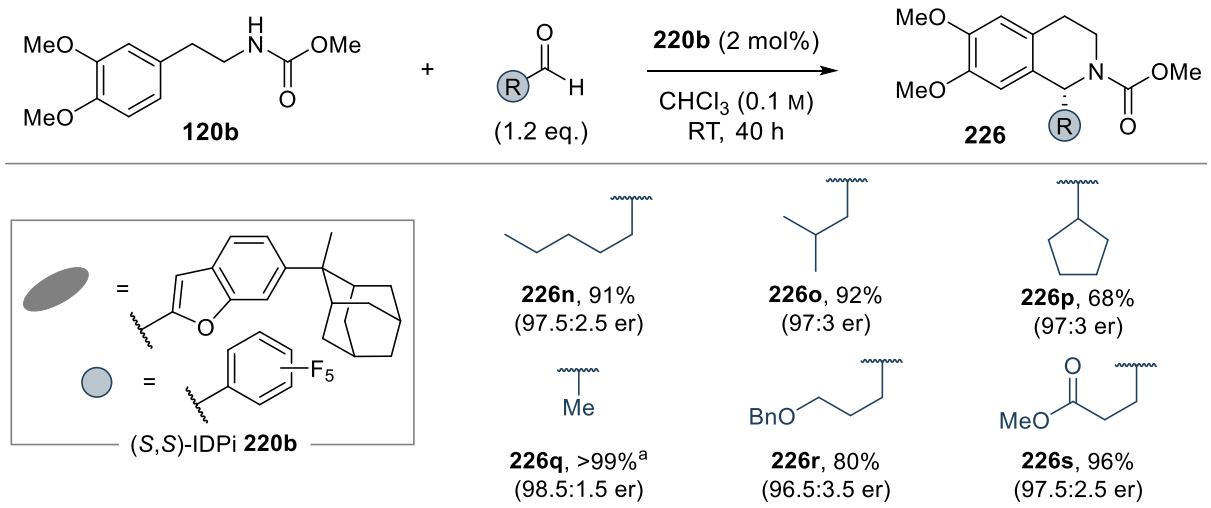


Figure 4.12 Catalytic asymmetric Pictet-Spengler reactions toward THIQs **226n**–**s** using non-aromatic aldehydes. All reactions were conducted on a 0.10 mmol scale. Yields are reported as isolated yields after column chromatography. [a]Reaction was performed at −40 °C with 3.0 eq. of acetaldehyde.

Studies toward a Suitable Precursor of Calycotomine

We identified calycotomine (**227**) as an interesting molecular target for our Pictet-Spengler methodology and devised two possible retrosynthetic approaches toward this oxygenated natural product (Figure 4.13). Concept **a** relies on the use of a single carbamate as protecting group for both the primary alcohol and the amine. The suitable reaction precursor **228** could then furnish the cyclic THIQ carbamate **229** *via* an intramolecular Pictet-Spengler cyclization. Approach **b** on the other hand relies on the use of a protected or unprotected glycolaldehyde reaction partner to give rise to THIQ products **230**, which would need to be globally deprotected toward the natural product.

Bn- (**231**) as well as TBS-protected (**232**) glycol aldehydes were commercially available, as was the cyclic dimer **234**, which serves as surrogate for unprotected glycolaldehyde (**233**). Benzoate **236** was available in two steps from bromo-acetal **235**. 2,2,2-trichloroethoxycarbonyl (Troc)-protected aldehyde **238** on the other hand was obtained by mono-protection of ethylene glycol (**237**) and subsequent oxidation. *Tert*-butyl-protected substrate **240** was obtained in the same way. Contrarily, acetoxy and trifluoroacetoxy substrates **242** and **243** were synthesized by ozonolysis of the respective olefins **241**. Finally, the starting material for approach **a** was accessible in a multi-step procedure. First, glycolaldehyde dimethylacetal (**244**) was reacted with carbonyldiimidazole (CDI) to give rise to carbamate **245**. After *in situ N*-methylation with methyl iodide toward an imidazolium intermediate, substitution with homoveratrylamine (**73**) furnished **228** in high yield.

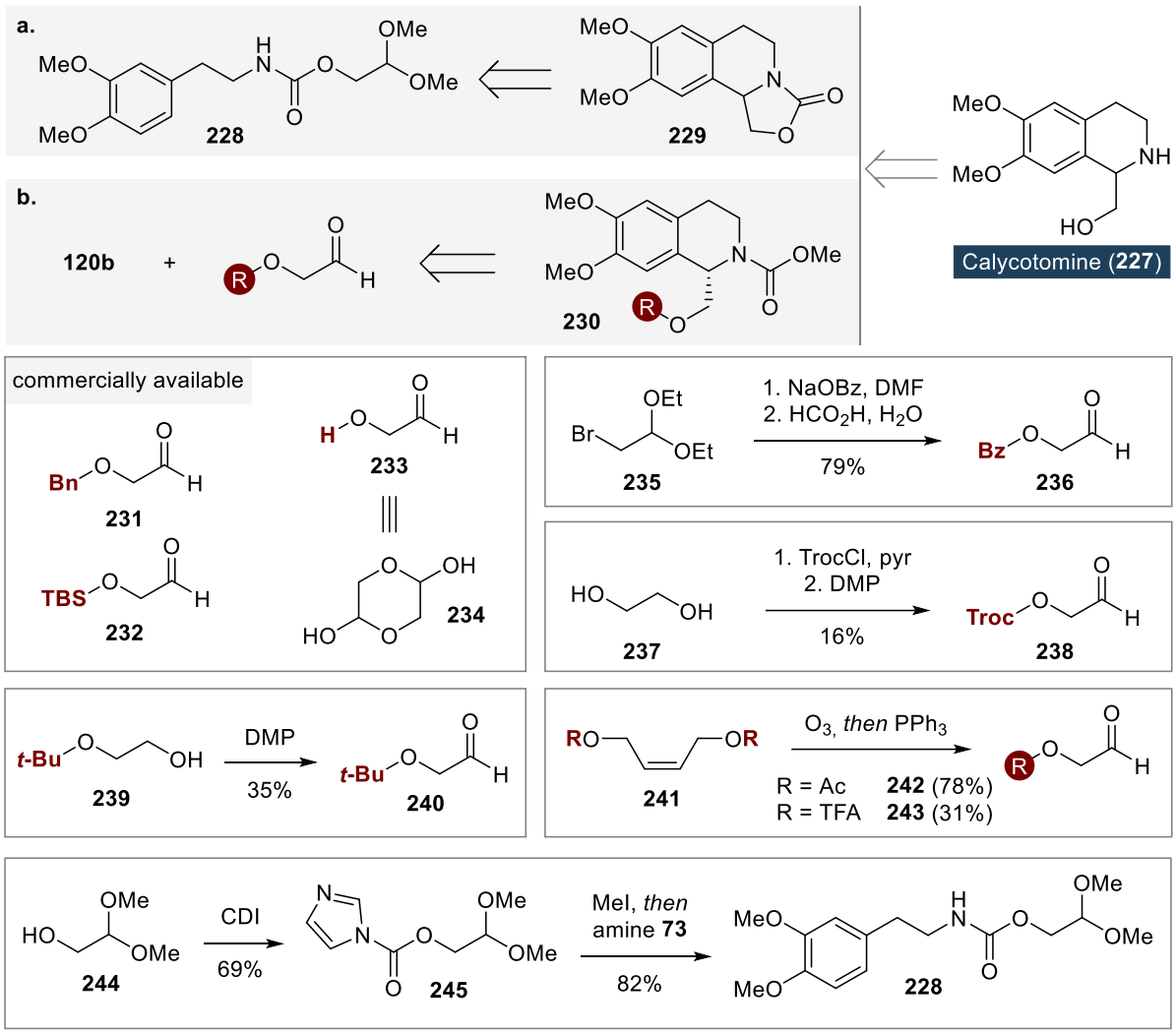
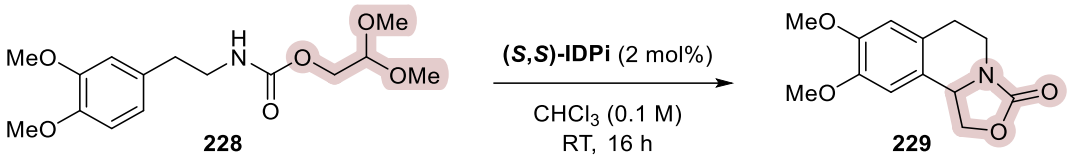


Figure 4.13 Retrosynthetic considerations toward calycotomine (**227**): **a.** Design of an intramolecular carbamate protection. **b.** Implementation of protected or unprotected glycolaldehyde (**233**). Synthetic efforts toward the relevant starting materials for the synthesis of calycotomine. Troc = 2,2,2-trichloroethoxycarbonyl. CDI = carbonyldiimidazole.

When we tested carbamate **228** for an intramolecular Pictet-Spengler reaction, we saw formation of the desired product. However, the reaction was both slow and unselective. Especially in the racemate synthesis (catalytic amounts of $HNTf_2$ in CH_3CN), the formation of multiple side products was observed, possibly due to oligomerization. When we tested IDPi catalysts, the reaction could be tamed in a sense that the desired product was formed as the major species, however with low conversion of the starting material (Table 4.7). Prototypical catalysts **143b**, **190b**, and **220b** provided the product in a maximum of 11% yield and insufficient enantioselectivities of around 50% ee (entries 1–3). When we tested additional *N*,*O*-bis-(trimethylsilyl)trifluoroacetamide as silylating agent, the reactivity was lost entirely (entry 4). This approach toward calycotomine (**227**) was therefore abandoned.

Table 4.7 Screening of IDPi catalysts for the intramolecular Pictet-Spengler reaction toward possible calycotomine precursor **229**. BSTFA = *N*,*O*-bis(trimethylsilyl)trifluoroacetamide.



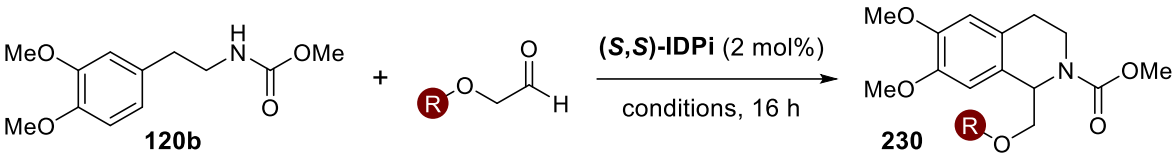
entry	(*S*,*S*)-IDPi	additive	yield	er
1	**143b**	–	11%	76:24
2	**190b**	–	4%	75:25
3	**220b**	–	7%	77:23
4	**143b**	BSTFA	0%	n.d.

We tested approach **b** with glycolaldehyde dimer **234** and prototypical IDPi **143b** (Table 4.8, entry 1). The product was obtained in poor yield and with insufficient enantioselectivity. As a general screening of non-heteroaromatic IDPi catalysts did not result in the identification of a new lead structure, we focused our efforts on the use of *O*-protected glycolaldehydes with catalysts **143b**, **190b**, and **220b**. TBS-protection resulted in poor activity and selectivity, presumably due to the large steric demand of the silyl group (entries 2–4). On the other hand, *O*-benzyl glycolaldehyde (**231**) was highly reactive and showed promising enantioselectivities (entries 5–7). In our experience with ion-pairing catalysis, selectivity can often be improved by employing non-polar hydrocarbon solvents that permit and amplify weak non-covalent interactions in the ion-pair. When we tested the reaction in cyclohexane, we however saw a large drop in enantioselectivity (entry 8). We attribute this effect to the Lewis-basicity of the benzyloxy substituent, which likely interferes with the interactions between catalyst and substrate in the relevant transition state. We thus hypothesized that a reduction of electron density on the α-oxygen of the aldehyde by installment of electron withdrawing protecting groups could lead to increased stereoinduction. When we tested α-acetoxy acetaldehyde (**242**), we indeed saw improved selectivity with respect to the benzyloxy substrate (entries 9–11). For the reason that the enantioselectivity was promising, we screened our complete library of electron-rich IDPi catalysts with a C_6F_5-core under identical conditions (not shown). Nevertheless, none of the catalysts was superior to IDPi **190b**. A change of solvents did not improve the outcome of this reaction either. Benzoate **236** gave similar results to the acetate, however with slightly reduced selectivity (entries 12–14). The electron-poor *O*-Troc and *O*-TFA glycolaldehydes **238** and **243** were inferior to all other tested protecting groups in terms of both reactivity and selectivity (entries 15–20).

Finally, when we tested *tert*-butyl-protected aldehyde **240**, we saw high reactivity similar to the benzyloxy substrate, combined with promising enantioinduction (entries 21–23). In an effort to optimize the reaction further, we reduced the reaction temperature but found a decrease in selectivity (entry 24). However, switching to hydrocarbon solvents provided an enhancement of

stereoinduction, with *n*-pentane being optimal compared to *n*-hexane, *n*-heptane, and cyclohexane (entry 25). Finally, due to the extraordinarily high reactivity of aldehyde **240**, we were able to perform the reaction under significantly diluted conditions, which provided a final increase in enantioselectivity. We were thus able to isolate the product on a 0.1 mmol scale in quantitative yield and with high enantioselectivity (91.5:8.5 er, entry 26).

Table 4.8 Screening of IDPi catalysts for the Pictet-Spengler reaction of diverse protected glycolaldehydes and optimization of the reaction conditions with the optimal substituent (R = *t*-Bu). [a]1,4-dioxane-2,5-diol (**234**) was utilized as aldehyde reaction partner. [b]Products were isolated as free OH after preparative TLC. [c]Isolated yield after 40 h reaction time on 0.1 mmol scale.



entry	R	(*S*,*S*)-IDPi	solvent (conc.)	*T*	yield	er
1	**H**	**143b**	$CHCl_3$ (0.1 M)	RT	<5%	36:64
2		**143b**	$CHCl_3$ (0.1 M)	RT	43%	25:75
3	**TBS**	**190b**	$CHCl_3$ (0.1 M)	RT	40%	20:80
4		**220b**	$CHCl_3$ (0.1 M)	RT	42%	21:79
5		**143b**	$CHCl_3$ (0.1 M)	RT	95%	21:79
6	**Bn**	**190b**	$CHCl_3$ (0.1 M)	RT	88%	18:82
7		**220b**	$CHCl_3$ (0.1 M)	RT	91%	18:82
8		**143b**	CyH (0.1 M)	RT	58%	39:61
9		**143b**	$CHCl_3$ (0.1 M)	RT	49%	13:87
10	**Ac**	**190b**	$CHCl_3$ (0.1 M)	RT	30%	11:89
11		**220b**	$CHCl_3$ (0.1 M)	RT	43%	13:87
12		**143b**	$CHCl_3$ (0.1 M)	RT	69%	15:85
13	**Bz**	**190b**	$CHCl_3$ (0.1 M)	RT	60%	15:85
14		**220b**	$CHCl_3$ (0.1 M)	RT	59%	16:84
15		**143b**	$CHCl_3$ (0.1 M)	RT	35%	50:50
16	**Troc**	**190b**	$CHCl_3$ (0.1 M)	RT	17%	50:50
17		**220b**	$CHCl_3$ (0.1 M)	RT	20%	50:50
18		**143b**	$CHCl_3$ (0.1 M)	RT	22%	55:45
19	**TFA**[b]	**190b**	$CHCl_3$ (0.1 M)	RT	13%	55:45
20		**220b**	$CHCl_3$ (0.1 M)	RT	18%	56:44
21		**143b**	$CHCl_3$ (0.1 M)	RT	76%	16:84
22		**190b**	$CHCl_3$ (0.1 M)	RT	82%	14:86
23	***t*-Bu**	**220b**	$CHCl_3$ (0.1 M)	RT	82%	14:86
24		**220b**	$CHCl_3$ (0.1 M)	0 °C	86%	15:85
25		**220b**	*n*-pentane (0.1 M)	RT	62%	11:89
26	***t*-Bu**[c]	**220b**	*n*-pentane (0.025 M)	RT	99%	8.5:91.5

4.1.5. Carbamate Scope

We were eager to explore synthetically relevant oxygenation patterns in the aromatic component of the carbamate (Figure 4.14). As was previously assessed, the dioxole annulation of product **213** resulted in highly reduced enantioselectivities with all IDPi catalysts (see Figure 4.8 and Figure 4.10). While IDPi **220b** was the ideal catalyst from our library, the conditions had to be slightly refined for sufficient stereoinduction. Thus, product **213** could be formed in excellent yield and high selectivity, when the reaction was conducted in CyH as solvent. The same conditions were however not successful for substrate **246**, due to low solubility of all reaction partners. Instead, a non-polar solvent mixture of CyH/$CHCl_3$ 10:1 at higher dilution (0.05 M) allowed for sufficient reactivity and enantioinduction.

Substrate **247** was chosen as a test to the electronic properties of the aromatic ring. Removal of one of the methoxy substituent was well tolerated by the catalyst, giving the product in excellent yield and enantioselectivity. Furthermore, liberation of a free phenol in substrates **248** and **249** had no detrimental effects on enantioselectivity. Importantly, these substrates are relevant intermediates in the synthesis of natural alkaloids. Finally, decorating the aromatic ring with another bromine resulted in slightly reduced reactivity. Nevertheless, the enantioselectivity toward **250** remained excellent.

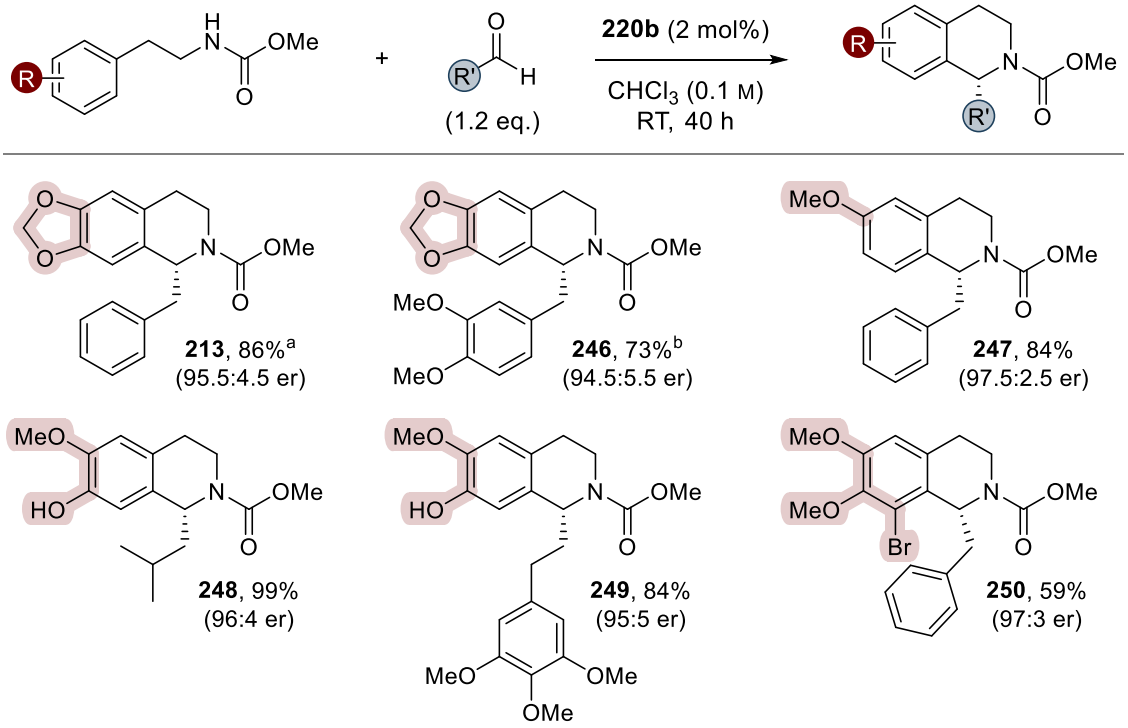


Figure 4.14 Substrate scope regarding variations of the substituents on the carbamate. All reactions were conducted on a 0.10 mmol scale. Yields are reported as isolated yields after column chromatography. [a]Reaction was performed in CyH instead of $CHCl_3$. [b]Reaction was performed in CyH/$CHCl_3$ (10:1, 0.05 M) instead of $CHCl_3$.

4.1.6. Scope Limitations

We encountered a number of theoretical reaction products that could either not be formed in sufficient yield under the reaction conditions, or were produced with low enantioinduction (Figure 4.15). In particular, certain variations of the aldehyde were not tolerated by the optimal catalysts. The formation of product **266** by the reaction with crotonaldehyde was not observed under standard reaction conditions. Chlorinated and brominated products **267** and **268** could indeed be accessed from their respective dimethyl acetals, which were employed instead of the aldehyde due to their higher stability and ease of handling. However, the enantioselectivity was insufficient in both cases.

Liberation of one of the phenols in the carbamate's arene was well tolerated by our optimized catalyst system (see Figure 4.14). However, when the methoxy substituent in the *meta* position was altered to the free phenol, the reaction toward product **269** proceeded with reduced enantioselectivity. This can be rationalized by appreciating that this particular hydroxy group is actively involved in the cyclization step of the reaction mechanism by means of electron donation. Thus, the hydrogen bonding capabilities of the OH in the relevant transition states are likely to be prominent due to the strong polarization. Interference with the enantiodetermining non-covalent interactions with the catalyst counteranion are therefore likely responsible for the reduced enantioinduction.

Somewhat surprisingly, substrate **270**, which possesses another methoxy substituent in the aromatic ring *ortho* to the alkyl chain, could not be formed under our reaction conditions. As the racemic reaction with catalytic amounts of $HNTf_2$ proceeded smoothly, it seems legitimate to invoke confinement effects in the IDPi catalyst as justification for the loss of reactivity.

Substrate **212**, which is formed by the reaction of benzaldehyde, can be produced with high enantioselectivity under our optimized reaction conditions. Nevertheless, the reactivity is highly diminished. Reoptimization studies with regard to the tolerance toward aromatic aldehydes will be presented in section 4.1.8.

Finally, the reactivity of the arene component is highly restricted. While naphthalene-derived product **271** was formed in traces with promising enantioselectivity, the less nucleophilic arenes in **272** and **273** were not tolerated by our catalyst system. Attempts to develop alternative approaches for electron-neutral arenes will be presented in chapter 4.3**.**

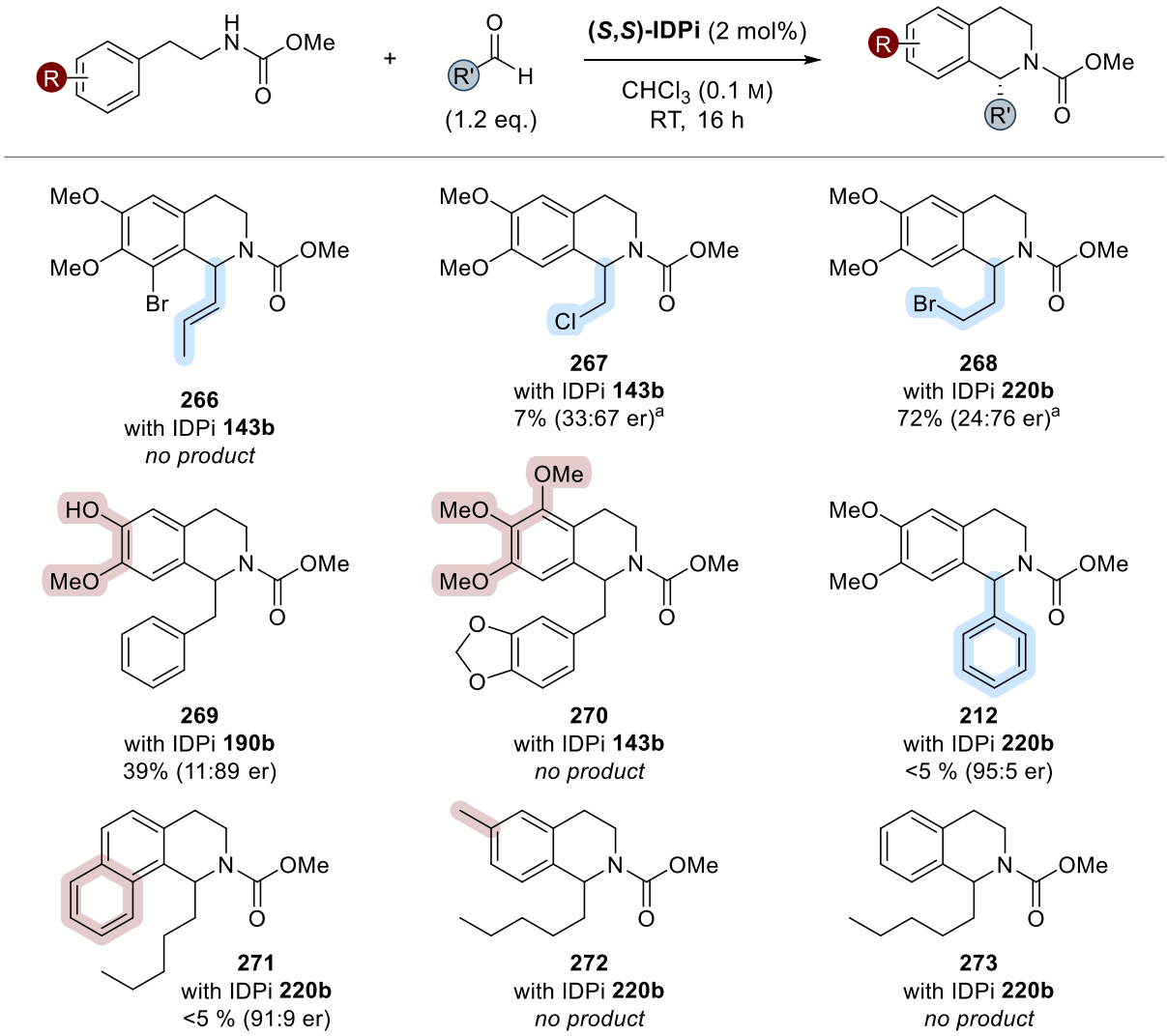
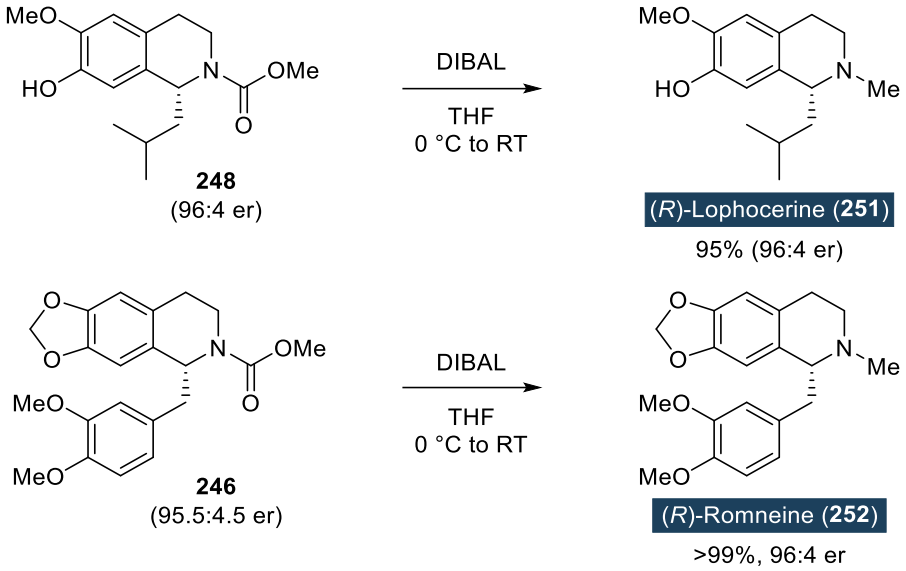


Figure 4.15 Limitations of the substrate scope. Examples that showed either low reactivity or insufficient enantioinduction under the standard reaction conditions with prototypical benzofuran IDPi catalysts. [a]The dimethyl acetal of the corresponding aldehyde was used in the reaction.

4.1.7. Synthesis of Natural Products

Having established the reaction scope, we turned our attention to the synthesis of naturally occurring alkaloids. First, we focused on the reduction of the methyl carbamate toward the corresponding tertiary methylamine. The possibility to access the *N*-methyl alkaloids directly embodies a major advantage of carbamates over previously utilized protecting groups, which require additional reaction steps and stoichiometric reagents for deprotection and *N*-methylation.[161,163] We however noticed chemoselectivity issues, when methyl carbamates were treated with strong reductants such as $LiAlH_4$ or Red-Al. In particular, unselective demethylation of the electron rich arenes was observed even at ambient temperature, leading to both purification as well as reproducibility complications. To our delight, high chemoselectivity and clean reaction profiles were observed, when diisobutylaluminum hydride (DIBAL) was employed as reductant

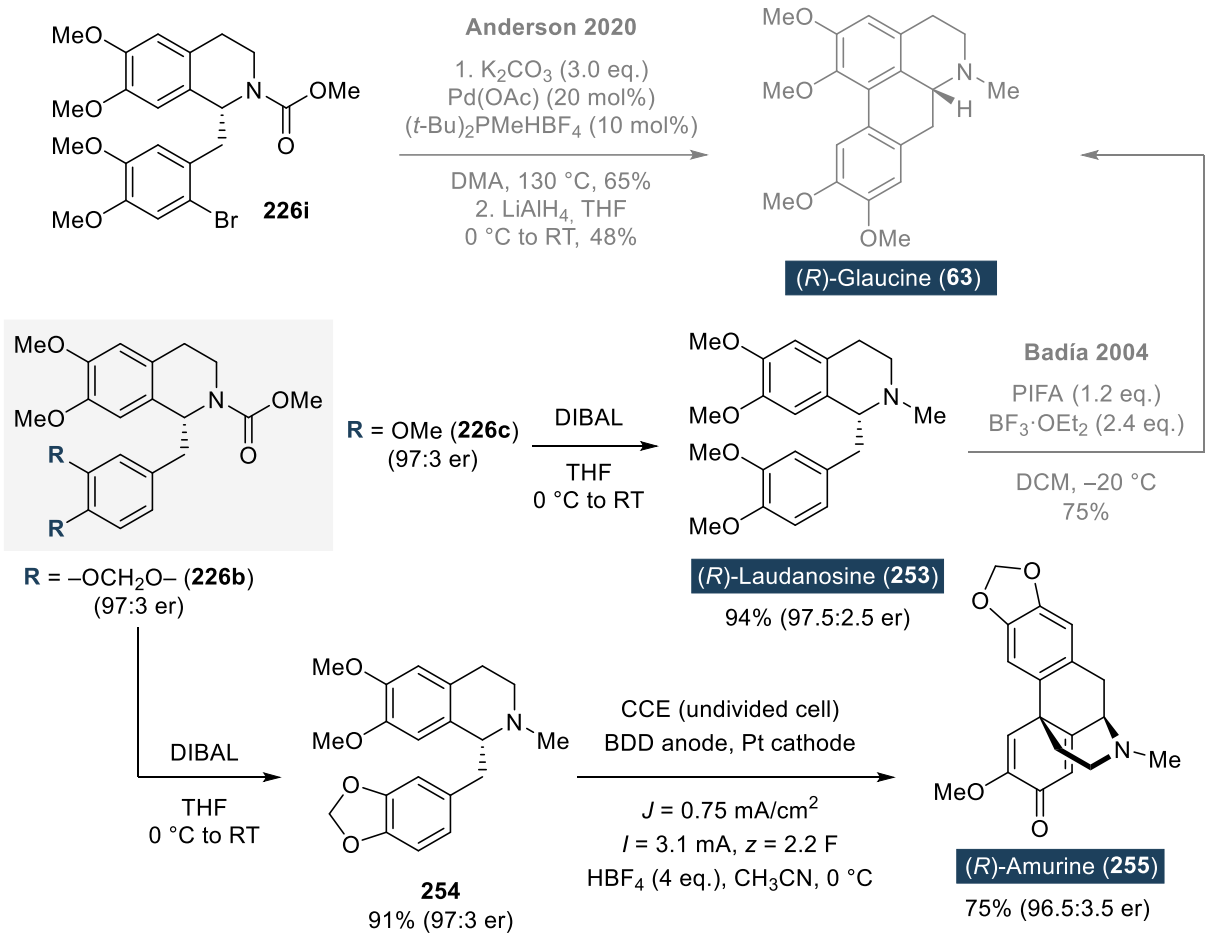
(Scheme 4.1). Thus, (*R*)-lophocerine (**251**) and (*R*)-romneine (**252**) were accessible in a single step from Pictet-Spengler products **248** and **246** respectively in excellent yields.



Scheme 4.1 Total synthesis of (*R*)-lophocerine (**251**) and (*R*)-romneine (**252**). DIBAL = diisobutylaluminum hydride.

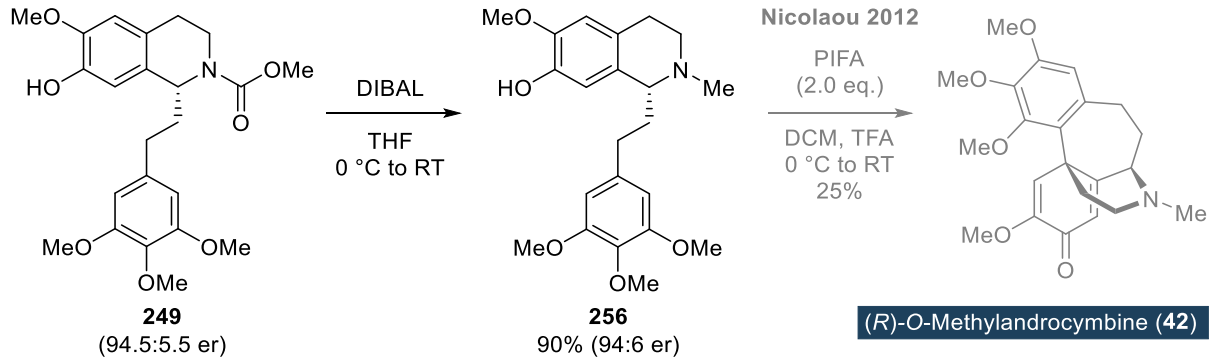
(*R*)-laudanosine (**253**) was accessible in an identical way from Pictet-Spengler product **226c** (Scheme 4.2). This natural product is an established synthetic intermediate toward aporphine alkaloid (*R*)-glaucine (**63**) *via* a direct aryl-aryl coupling reaction using a combination of hypervalent iodine (PIFA) and strong Lewis acid ($BF_3 \cdot Et_2O$).[115] The same product can formally also be synthesized from brominated Pictet-Spengler product **226i**. A palladium-catalyzed intramolecular C–H-arylation constructs the desired aporphine skeleton and a subsequent reduction delivers the natural alkaloid.[176]

Having established formal access to the aporphine skeleton, we were keen to approach the morphinan alkaloid family synthetically. Again, simple reduction of dioxole-containing THIQ product **226b** delivers tertiary amine **254**. For the required selective oxidative aryl-aryl coupling reaction, we adapted the electrochemical approach from Opatz and Waldvogel.[110] Key to the success of this reaction is the utilization of superstoichiometric amounts of HBF_4 to protonate the basic amine and thus prevent its electrochemical oxidation. After some fine-tuning of the reaction conditions with regard to current density, we were pleased to observe clean formation of (*R*)-amurine (**255**) *via* constant current electrolysis (CCE) in an undivided cell with a boron-doped diamond (BDD) anode and a platinum cathode.



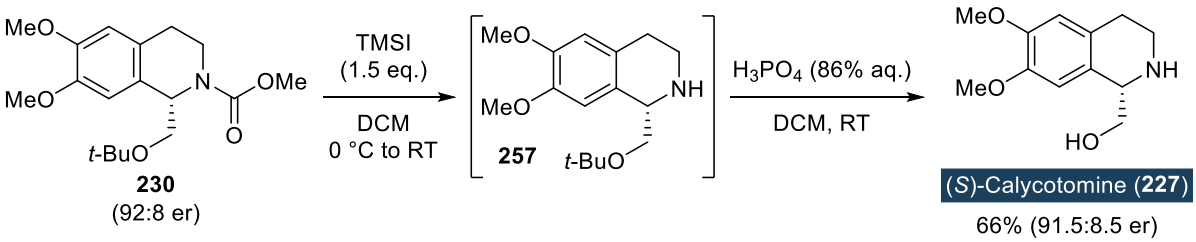
Scheme 4.2 Total synthesis of (*R*)-laudanosine (**253**) by reduction, and formal syntheses of (*R*)-glaucine (**63**) from laudanosine (**253**)[115] or **226i**.[176] Total synthesis of (*R*)-amurine (**255**) by reduction of **226b** to **254** and subsequent anodic oxidation. DMA = dimethylacetamide. CCE = constant current electrolysis. BDD = boron-doped diamond.

Due to its similarity to the morphinan skeleton, we were also interested in the synthesis of androcymbines (Scheme 4.3). Reduction of THIQ **249** delivers the established synthetic intermediate **256** toward *O*-methylandrocymbine (**42**).[116] The natural product could be formally obtained by treatment with PIFA, while the selectivity is governed by the free hydroxy group in the starting material. Importantly, *O*-methylandrocymine is a late biosynthetic intermediate toward the toxic natural product colchicine[101] and our route delivers the alkaloid in only 6 linear steps with high enantiopurity.



Scheme 4.3 Synthesis of **256** by reduction and formal synthesis of *O*-methylandrocymbine (**42**).[116]

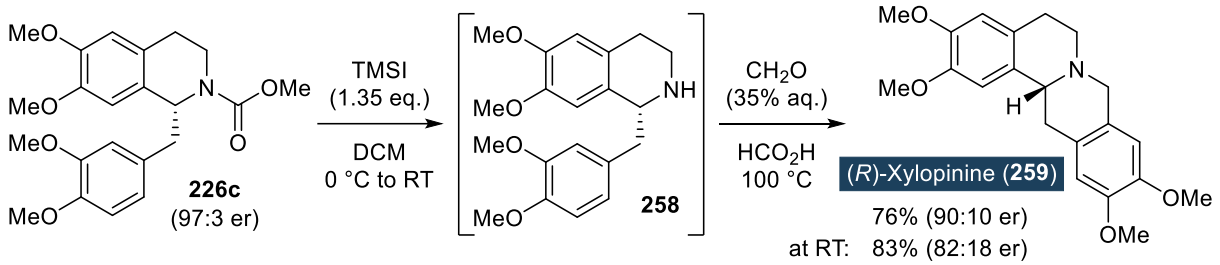
In an effort to obtain the unprotected secondary amine products, we found that removal of the methyl carbamate is not as facile and selective as the deprotection of related *t*-Bu- or Bn-carbamates. For the THIQ products under study, treatment with trimethylsilyl iodide (TMSI) results in facile liberation of the secondary amine. Nevertheless, we found competitive demethylation of the aromatic methoxy groups to be problematic, especially in highly electron-rich systems. We therefore applied only a slight excess of the reagent, which ensured a clean reaction profile, but simultaneously resulted in incomplete conversion of the starting materials. When we treated oxygenated THIQ **230** with TMSI in DCM, we achieved deprotection to the secondary amine **257** (Scheme 4.4). Further removal of the *t*-Bu group was conducted on the crude reaction material by treatment with aqueous H_3PO_4. While silica gel column chromatography on the highly polar product proved challenging, simple acid-base extraction allowed isolation of (*S*)-calycotomine (**227**) in 66% yield over two steps.



Scheme 4.4 Total synthesis of (*S*)-calycotomine (**227**) by global deprotection of **230**.

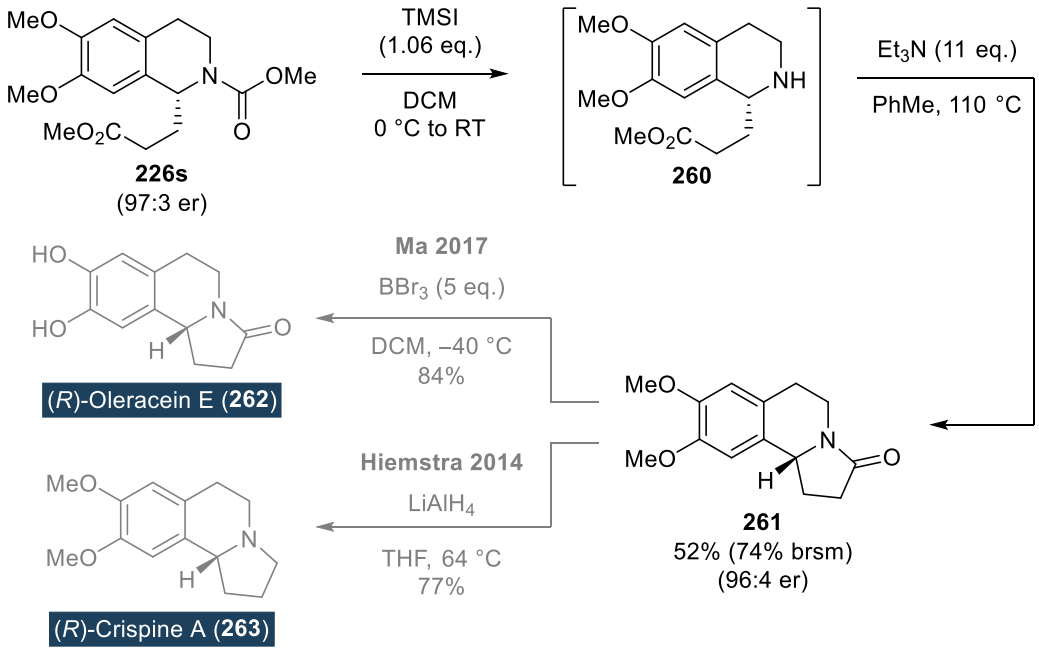
In a similar fashion, deprotection of benzyl THIQ **226c** gave secondary amine **258** (Scheme 4.5). This material could be engaged in a subsequent Pictet-Spengler reaction with aqueous formaldehyde and formic acid toward the tetrahydroprotoberberine alkaloid (*R*)-xylopinine (**259**). However, the reaction required strongly acidic conditions, which resulted in a slight reduction of enantiomeric enrichment in the product (90:10 er). This might be rationalized by invoking the intermediacy of a stabilized achiral benzylic carbocation from either the protonated tertiary amine, or the methylene iminium ion. In an attempt to prevent this racemization, we tested the reaction at ambient temperature. Conversely, the enantiopurity was further reduced (82:18 er), suggesting that

the increased lifetime of the iminium ion before cyclization at reduced temperatures allows for facile racemization.



Scheme 4.5 Total synthesis of (*R*)-xylopinine (**259**) by deprotection of **226c** and subsequent Pictet-Spengler reaction of **258** with formaldehyde.

Chemoselective deprotection of the methyl carbamate was a particularly challenging quest for THIQ **226s**, which is why only a slight excess of TMSI was employed (Scheme 4.6). Nevertheless, the product amine **260** could be obtained in pure form and simple treatment of the crude product mixture with Et_3N at elevated temperatures resulted in cyclization toward THIQ lactam **261**, after which unreacted starting material could be re-isolated. The two natural products, (*R*)-oleracein E (**262**) and (*R*)-crispine A (**263**) are formally accessible from this common intermediate *via* either demethylation using BBr_3,[177] or by reduction with $LiAlH_4$.[161]



Scheme 4.6 Formal synthesis of (*R*)-oleracein E (**262**)[177] and (*R*)-crispine A (**263**)[161] by deprotection of **226s** and subsequent lactamization of **260** toward common intermediate **261**.

As a final test to our methodology, we pursued the total synthesis of (*R*)-salsolidine (**264**) on a gram scale (Figure 4.16a). The Pictet-Spengler reaction of 5.0 mmol of carbamate **120b** with acetaldehyde could be catalyzed by IDPi **220b** at reduced catalyst loadings of 0.5 mol% at –40 °C.

The desired THIQ **226q** was formed in quantitative yield, and HPLC-analysis of the crude reaction mixture after removal of the excess aldehyde under reduced pressure revealed >99% purity and excellent enantioselectivity of 99:1 er (Figure 4.16b). The mixture was treated with TMSI to furnish the secondary amine **264**, which could be separated from all non-basic organic components by acid base extraction. Column chromatography of the remaining material allowed for recovery of non-deprotected Pictet-Spengler product **226q** (16%) as well as IDPi catalyst **220b** (98%). The desired (*R*)-salsolidine could be efficiently isolated as the hydrochloride salt **265** by treatment of amine **264** with non-aqueous HCl in ethereal solvents, which precipitated a white solid with >95% purity as determined by ^{1}H-NMR. Furthermore, the product could be crystallized from THF/H_2O, which allowed for determination of the absolute configuration by X-ray crystallography (Figure 4.16c). Overall, (*R*)-salsolidine hydrochloride (**265**) could be obtained in 70% yield from carbamate **120b**, resulting in an overall two-step catalytic and asymmetric total synthesis of the natural alkaloid.

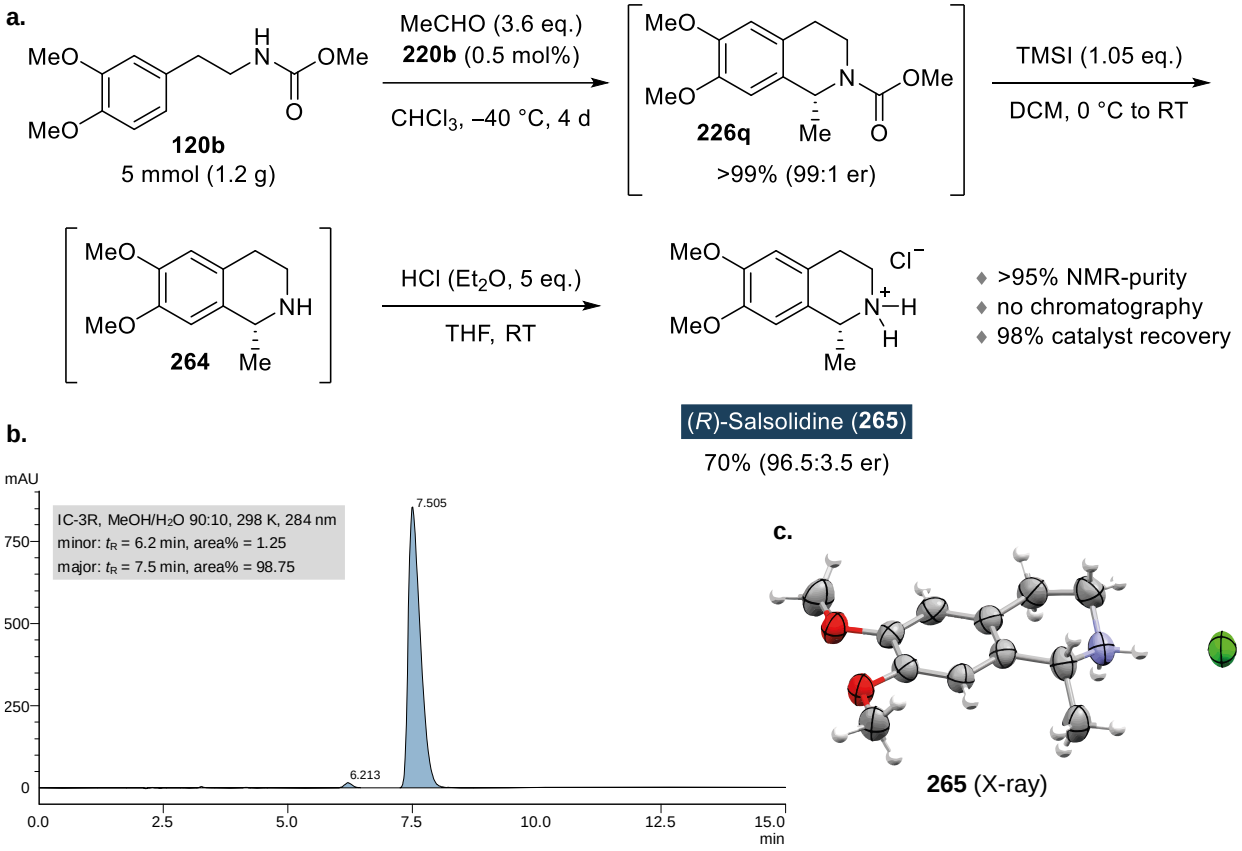


Figure 4.16 a. Gram-scale total synthesis of (*R*)-salsolidine hydrochloride (**265**) from carbamate **120b**. **b.** HPLC-trace of the crude reaction mixture of THIQ product **226q**. **c.** X-ray crystal structure of (*R*)-salsolidine hydrochloride (**265**).

4.1.8. Reaction Optimization and Scope of 1-Aryl Tetrahydroisoquinolines

Parts of the results presented in section 4.1.8 have been obtained in collaboration with Tram-Anh Bui.

We previously faced the problem of diminished reactivity with benzaldehyde under standard reaction conditions (see Figure 4.15), although the enantioinduction was excellent. It was thus required to re-optimize the method in order to obtain 1-aryl THIQs in synthetically useful yields. Theoretically, the change in reactivity by employing aromatic aldehydes might be rationalized in different ways. On the one hand, aromatic aldehydes are less electrophilic than their aliphatic counterparts due to the electron delocalization over the extended π-system. This characteristic would decrease both the rate of nucleophilic attack of the carbamate onto the aldehyde, as well as the cyclization of the aromatic ring onto the less electrophilic intermediate iminium ion. On the other hand, the mesomeric effect would stabilize said iminium ion and thus increase its rate of formation from the corresponding *N*,*O*-acetal precursor.

We hypothesized that we could effectively increase the rate of nucleophilic attack of the carbamate onto the aldehyde by switching to dimethyl acetals as electrophilic reaction partners. The generation of a high-energy *O*-methyl oxocarbenium ion would theoretically facilitate formation of the *N*,*O*-acetal and furthermore render it irreversible. Additionally, the extrusion of two molecules of MeOH instead of one molecule of H_2O may facilitate the entropically favorable condensation. Importantly, these effects are pronounced to varying extends, depending on the electronic properties of the aromatic aldehyde itself. In order to explore the reactivity of electron-rich and electron-poor aromatic aldehydes, we therefore tested a range of *para*-substituted benzaldehydes, spanning diverse electronic characteristics as defined by their respective Hammett constants σ_p (Figure 4.17).[178] We recognized a maximum reactivity for electron-neutral and slightly electron-poor benzaldehydes (R = H, F, Cl, Br), although on a low-yielding plateau ($\leq$ 7%).

When we switched to the corresponding dimethyl acetals, we were pleased to observe a sharp increase in product yield. The reactivity enhancement was especially evident for electron-rich arenes (R = OMe, Me). This observation underpins our hypothesis that the electrophilicity of the aldehyde must be enhanced in order to facilitate reaction progress. However, the electronic bias of the arene was still noticeable, as highly electron-poor acetals (R = CF_3, CN) did not show any reactivity increase.

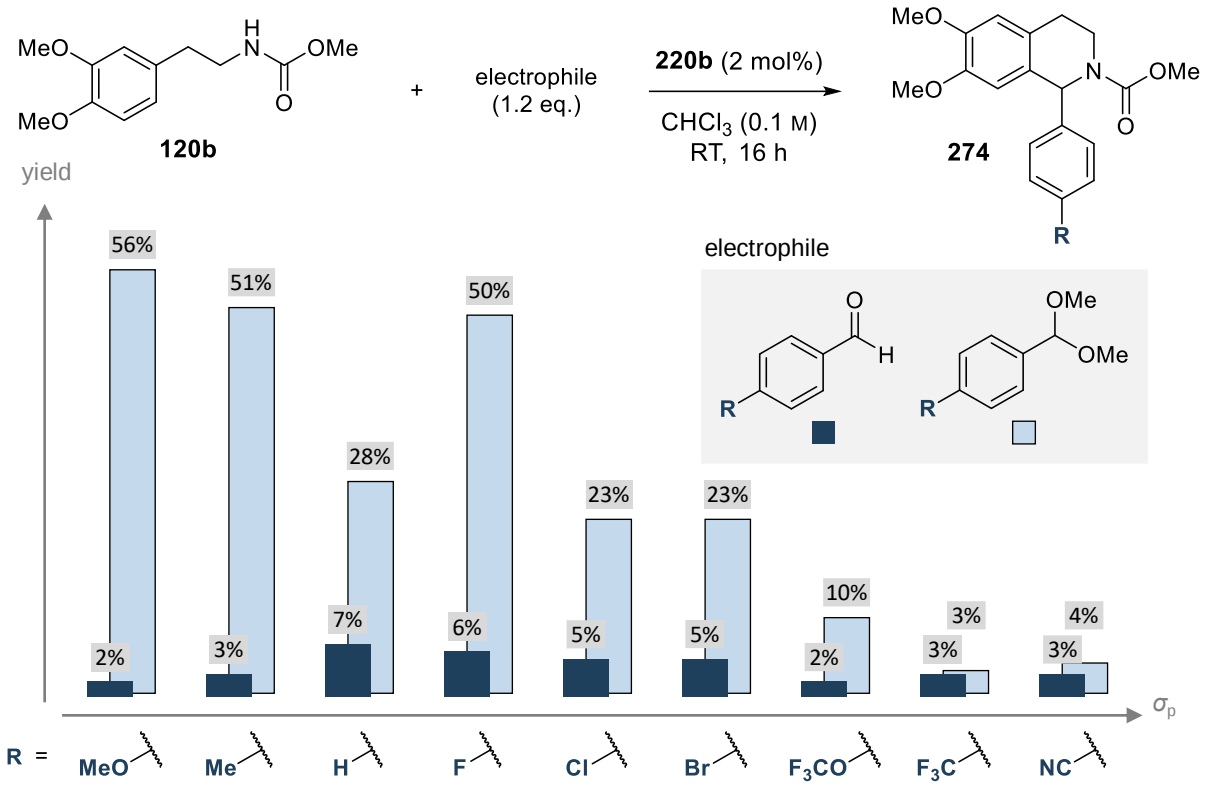
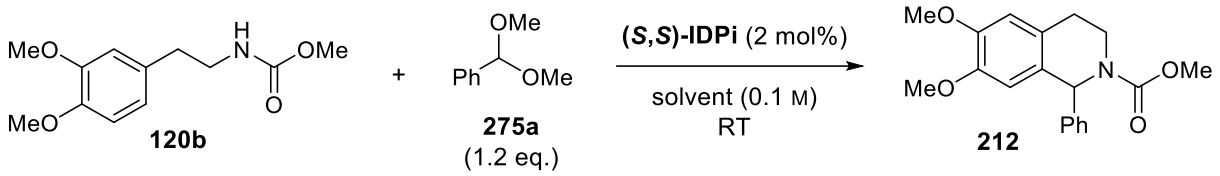


Figure 4.17 Reactivity assessment in the Pictet-Spengler reaction toward 1-aryl THIQs **274** by employing aldehydes and dimethyl acetals as electrophiles. Comparison of *para*-substituted electrophiles with diverse electronic properties according to their respective Hammett coefficient σ_p.[178]

Having established the scope and extend of the reactivity enhancement with aromatic acetals, we saw room for further improvements of the reaction conditions (Table 4.9). First, we compared four lead IDPi catalysts and concluded that catalyst **220b** remains optimal (entries 1–4), even though catalyst **202b** previously showed extraordinarily high selectivity in the reaction with benzaldehyde (98:2 er, see Figure 4.8). We then proceeded to test different solvents in the reaction with IDPi **220b** (entries 5–10). We were surprised to see another sharp increase in reactivity, when Et_2O was employed (79% yield). On the other hand, CyH allowed a significant increase in enantioselectivity. In order to combine both effects, we tested solvent mixtures (entries 11–15) and identified CyH/Et_2O in an optimal ratio of 4:1 to deliver the product in good yields as well as high enantiopurity (entry 14).

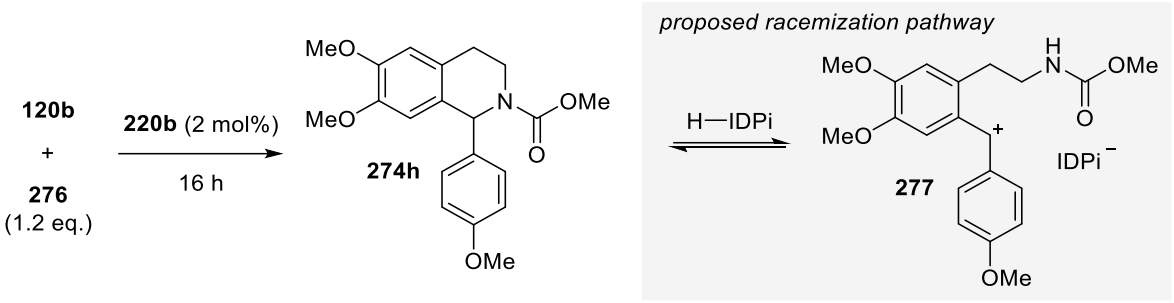
Table 4.9 Optimization of the reaction conditions for the Pictet-Spengler reaction of **120b** and acetal **275a** as model reaction for 1-aryl THIQs.



entry	(*S*,*S*)-IDPi	solvent	time	yield	er
1	**143b**	$CHCl_3$	40 h	51%	90:10
2	**190b**	$CHCl_3$	40 h	42%	94.5:5.5
3	**202b**	$CHCl_3$	40 h	49%	93.5:6.5
4	**220b**	$CHCl_3$	40 h	49%	95:5
5	**220b**	$CHCl_3$	16 h	26%	94.5:5.5
6	**220b**	CH_2Cl_2	16 h	36%	83:17
7	**220b**	PhMe	16 h	40%	96:4
8	**220b**	Et_2O	16 h	79%	93.5:6.5
9	**220b**	THF	16 h	26%	89:11
10	**220b**	CyH	16 h	36%	97.5:2.5
11	**220b**	Et_2O/CyH 9:1	16 h	82%	94.5:5.5
12	**220b**	Et_2O/CyH 4:1	16 h	78%	95:5
13	**220b**	Et_2O/CyH 1:1	16 h	73%	96:4
14	**220b**	Et_2O/CyH 1:4	16 h	63%	97:3
15	**220b**	Et_2O/CyH 1:9	16 h	49%	97.5:2.5

1-Aryl THIQs are rarely found in naturally occurring alkaloids. However, some natural products were isolated from the *cryptostylis fulva* and *cryptostylis erythroglossa* orchids.[179,180] These so-called cryptostyline alkaloids feature an electron-rich oxygenated 1-aryl THIQ. When relevant electrophiles such as anisaldehyde dimethylacetal (**276**) were employed, we however encountered an unexpected problem of product racemization (Table 4.10). A likely mechanism involves acid-mediated ring opening of the THIQ core in **274h** toward the highly stabilized and achiral bis-benzylic carbocation **277**. Deterioration of enantiopurity from the products could indeed be confirmed by treating enantioenriched THIQs with catalytic amounts of $HNTf_2$. Nevertheless, the rate of racemization could by suppressed by optimizing solvents and reaction temperature. At ambient temperature, product **274h** was formed with poor enantiopurity (entries 1–2). At 0 °C however, racemization could be reduced while still allowing for significant product formation (entries 3–6).

Table 4.10 Proposed racemization pathway for electron rich THIQs and re-optimization of the reaction conditions for substrate **277**.



entry	solvent	*T*	yield	er
1	$CHCl_3$	RT	56%	63:37
2	CyH	RT	65%	77:23
3	$CHCl_3$	0 °C	23%	95:5
4	CyH	0 °C	4%	94:6
5	Et_2O	0 °C	52%	72:28
6	Et_2O/CyH 1:4	0 °C	30%	93.5:6.5

With suitable reaction conditions in hand, we explored the scope of 1-aryl THIQs **274** that are accessible *via* this route (Figure 4.1). Apart from the parent benzaldehyde-derived substrate **274a**, methylation in the *ortho*-, *meta*-, and *para*-position was tolerated to give THIQs **274b**, **274c**, and **274d** in excellent yields and high enantioselectivities. Furthermore, substituting the *para*-position with a halide was equally well tolerated toward **274e**, **274f**, and **274g**. Only *p*-Cl compound **274f** was produced in slightly reduced yield (50%). When we applied the re-optimized conditions for electron-rich THIQs **274h**, **274i**, and **274j**, the products were formed with high enantiopurity and reasonable yields after prolonged reaction time (72 h). To complete the substrate scope, we explored larger arene substituents. Exemplary, a 2-naphthyl ring could be installed to give **274k**, and a 3-benzothiophenyl substituent gave rise to product **274l**.

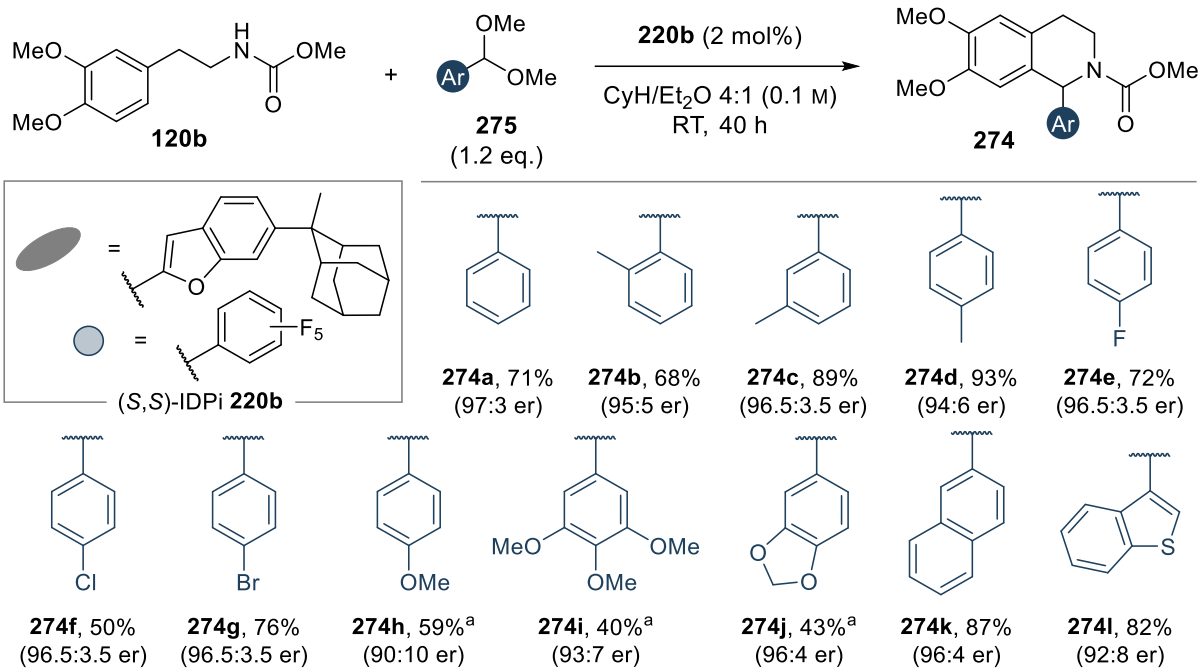
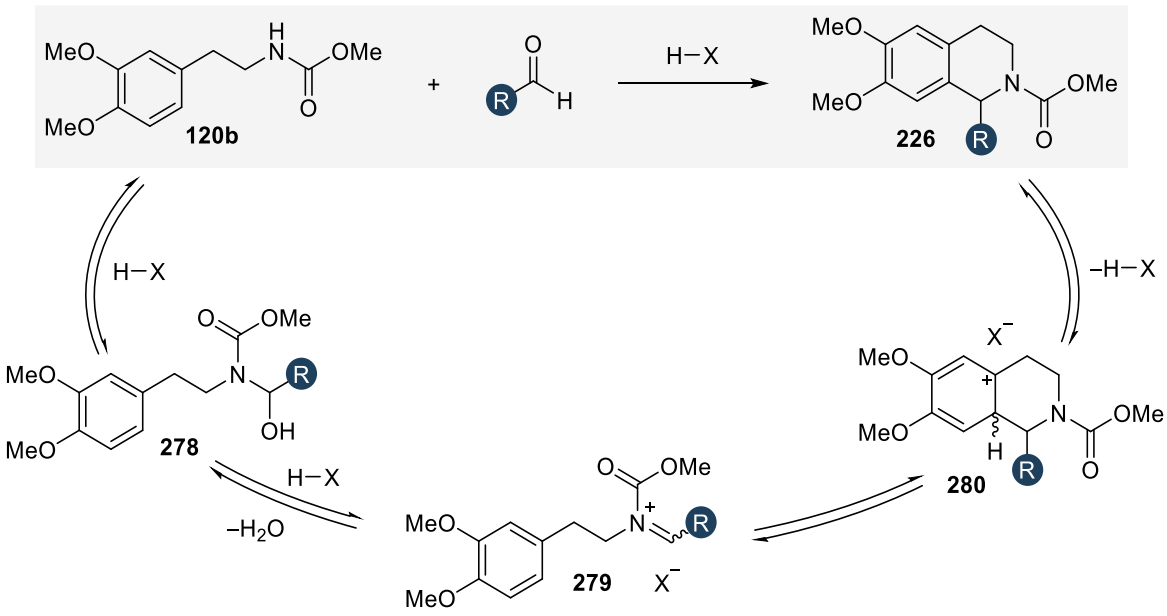


Figure 4.18 Catalytic asymmetric Pictet-Spengler reactions toward 1-aryl THIQs **274** using aromatic dimethyl acetals **275**. All reactions were conducted on a 0.10 mmol scale. Yields are reported as isolated yields after column chromatography. [a]Reaction was conducted at 0 °C for 72 h.

4.2. Experimental Studies on the Mechanism of the Catalytic Asymmetric Pictet-Spengler Reaction

The NMR-spectroscopic data presented in section 4.1.8 has been measured in collaboration with Dr. Markus Leutzsch.

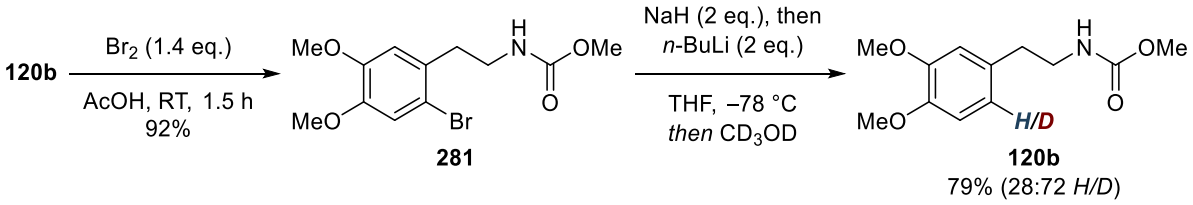
With the aim to understand the nature of our developed methodology on a molecular level, it seemed necessary to examine the underlying reaction mechanism. Especially the origin of rate enhancement by employing electron-rich IDPi catalysts was at the center of our attention. A general mechanistic hypothesis for our acid-catalyzed Pictet-Spengler reaction is shown in Scheme 4.7. It is worth noting that the catalyst is involved in several mechanistic key steps, all of which could theoretically be rate-determining and, in the case of a chiral catalyst, enantiodetermining. First, nucleophilic attack of the carbamate onto the aldehyde furnishes *N*,*O*-acetal **278**, which could be classified as a "*fleeting chiral intermediate*".[181] The next step involves extrusion of H_2O to generate an achiral *N*-acyliminium ion **279**, paired with the anion of the acid catalyst. Nucleophilic attack of the aromatic ring then generates the dearomatized arenium ion pair **280**. Deprotonation by the acid counteranion furnishes THIQ **226**. Again, Wheland intermediate **280** can be formed as two diastereomers. While the relative configuration might be inconsequential for the product formation, the stability and reactivity of the isomers in proximity to a chiral counteranion might have a significant impact on the stereochemical outcome in an asymmetric catalytic reaction.



Scheme 4.7 General mechanistic hypothesis for an acid-catalyzed Pictet-Spengler reaction of *N*-carbamoyl homoveratrylamine **120b**.

4.2.1. Kinetic Isotope Effects

In order to probe the reaction for a deuterium kinetic isotope effect, we synthesized isotopically labelled substrate **120b-D** in two steps from carbamate **120b** (Scheme 4.8). First, bromination at the most nucleophilic position of the arene was achieved by treatment with bromine in AcOH. The transformation of bromide **281** was achieved by first masking the acidic N–H group by deprotonation with NaH, followed by lithium halogen exchange with *n*BuLi at low temperatures. The lithium organyl was subsequently trapped with deuterated methanol to give isotopically enriched carbamate **120b**. The incomplete deuteration (72% D) can likely be attributed to a partial proton/deuterium exchange in the employed CD_3OD.



Scheme 4.8 Synthesis of deuterated substrate **120b** *via* lithiation of brominated arene **281**.

We subjected a mixture of deuterated and non-deuterated carbamate **120b** to the reaction conditions with general benzofuran catalyst **143b**. In the resulting competition KIE experiment, the absolute concentrations of both substrates could be followed by ^{1}H-NMR at each point of the reaction progress (Figure 4.19). By examination of the concentration profiles, it becomes apparent that the deuterated substrate is converted slower, which qualitatively translates into a significant primary KIE. The magnitude of the effect can be quantified by employing formula (4.1)[182,183],

where F_H is the fractional conversion of the protonated starting material, R is the proportion of the deuterated component in the starting material (X_D/X_H) at the time of observation, and R_0 is the initial proportion at the start of the reaction.

$$\mathrm{KIE} = \frac{\ln(1 - F_H)}{\ln\left[(1 - F_H)\frac{R}{R_0}\right]} \tag{4.1}$$

A typical literature procedure for the determination of KIEs involves running an experiment to approximately 50% conversion and measuring the deuterium incorporation in the recovered starting material. Formula (4.1) is then applied to calculate a single data point, which is usually obtained in duplicates or triplicates to reduce the experimental error.[183] Following the reaction progress by ^{1}H-NMR allowed us to determine the KIE at every single point of measurement. However, the error of the calculation is magnified at low conversions. We therefore averaged the calculated values at fractional conversions $F_H > 0.25$ and obtained a KIE of 2.00 (± 0.13).

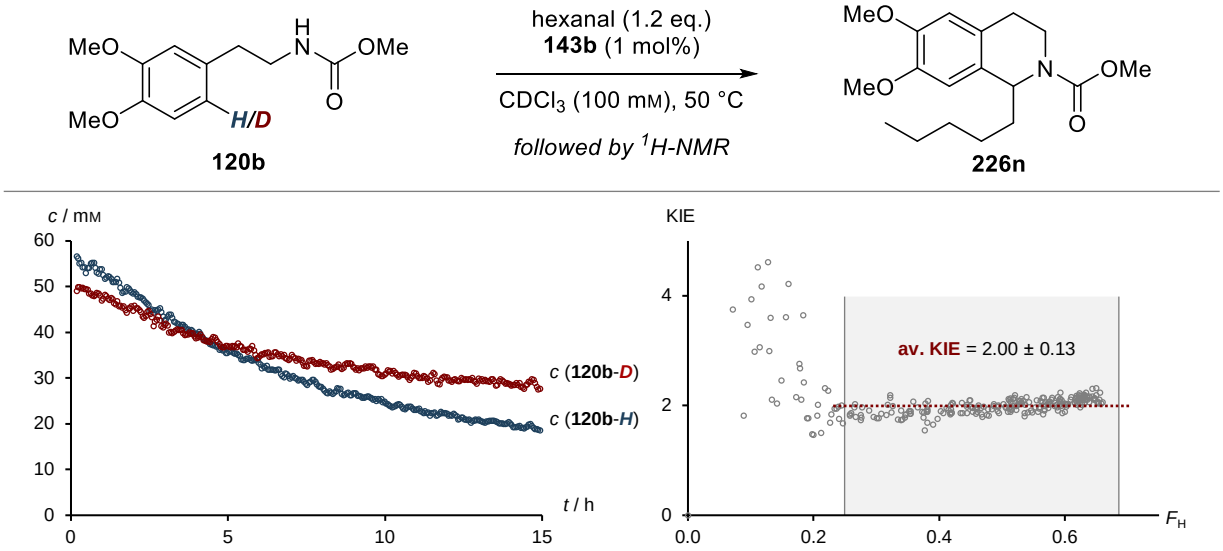


Figure 4.19 Competition kinetic isotope effect (KIE) experiment with hexanal. The average KIE was determined at fractional conversion of the protonated starting material $F_H > 0.25$. The error is given as the standard deviation.

The measured primary kinetic isotope effect mechanistically originates from the relative rates of deprotonation of Wheland intermediate **280**. The magnitude of the KIE suggests that this step is contributing significantly to the overall reaction rate. In fact, a similar KIE has been measured in the enzymatic conversion of dopamine to norcoclaurine (**29**)[184], and was subsequently supported by computations.[156] Jacobsen *et al.* detected a significantly stronger primary KIE in the conversion of tryptamine derivatives to THBC **282**. This observation is consistent with the higher nucleophilicity of the indole ring, which accelerates the reaction steps prior to the rearomatization and thus provides a more pronounced contribution to the overall rate (Figure 4.20).

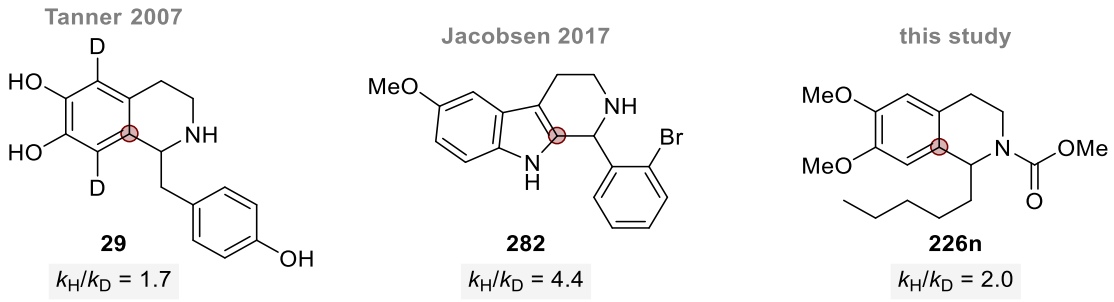


Figure 4.20 Comparison of experimental KIEs in catalytic Pictet-Spengler reactions.[183,184]

4.2.2. Hammett Studies

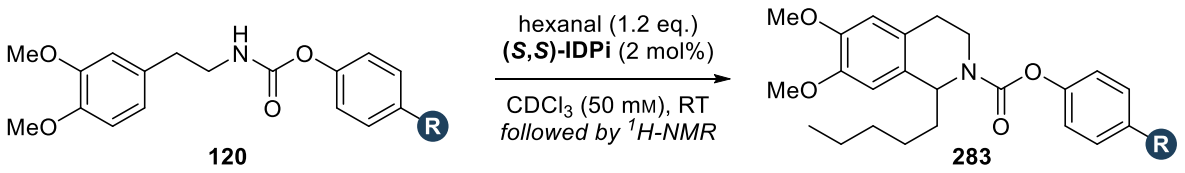
Hammett plots can offer valuable insights into reaction mechanisms and the electronic nature of key intermediates. According to Hammett equation (4.2), the relative reaction rates k of substituted substrates can be parametrized in a linear free energy relationship (LFER), where the Hammett parameter σ_p describes the electronic properties of the substituent in a benchmark reaction, and the obtained slope ρ allows for deduction of the electronic nature of the transition states in the reaction under study.

$$\log\left(\frac{k}{k_H}\right) = \rho\sigma_p \tag{4.2}$$

Often, the Hammett substituents are positioned in the substrate such that the reactive center resides at the benzylic position *para* to the substituent. In the Pictet-Spengler reaction under study, the electronic properties of the substrates are however highly restricted with regard to the nucleophilic aromatic ring and do not allow the variation required for a Hammett plot. We therefore focused on *para*-substituted phenyl carbamates **120**, where the Hammett substituent R resides relatively distant from the reacting carbons, but could still influence the early steps of the mechanism. We followed the individual reactions by ^{1}H-NMR at room temperature using prototypical IDPi catalysts **130a** and **143a** (Figure 4.21). Due to the observed linearity of the reaction profile at < 30% conversion, we were able to extract early rates r by linear regression of the concentration over time. Notably, benzofuran IDPi **143a** is approximately twice as active as the electron-poor catalyst **130a** in almost all experiments. Only the *para* chloro-substituted substrate showed unusual low reactivity with catalyst **143a**.

Plotting $\log(r/r_H)$ against the Hammett constants σ_p corresponds to a linearization according to Hammett equation (4.2).[178] We obtained two similar linear regressions for IDPis **130a** and **143a** with the corresponding slopes ρ(**130a**) = −(1.07 ± 0.07) and ρ(**143a**) = −(1.20 ± 0.18). These large negative correlations corroborate the build-up of positive charge in the transition state of the reaction. Interestingly, a strong electronic influence on the stability of Wheland intermediate **280** would not be expected from substituents R. The deprotonation step was however shown to have a

pronounced influence on the overall rate in the KIE experiments. In order to combine these results, the presented Hammett plot must therefore be interpreted in terms of more subtle effects on the rate constants prior to the rate-determining step (RDS). For example, the rate of *N*-acyliminium formation should be positively influenced by electron-donating groups, which results in a higher concentration or longer lifetime of the iminium ion. The Hammett slope therefore suggests that the cyclization from the aromatic ring is fast in comparison, which translates into a higher concentration of the Wheland intermediate, the deprotonation of which determines the overall rate.



R	OMe	Me	H	F	Cl	NO_2
σ_p	−0.27	−0.17	0	0.06	0.23	0.78
r (**130a**) / mol L^{-1} s^{-1}	(16 ± 0.6)×10^{-7}	(10 ± 0.3)×10^{-7}	(8.5 ± 0.2)×10^{-7}	(5.6 ± 0.05)×10^{-7}	(4.7 ± 0.05)×10^{-7}	(1.1 ± 0.006)×10^{-7}
r (**143a**) / mol L^{-1} s^{-1}	(35 ± 1.5)×10^{-7}	(23 ± 0.6)×10^{-7}	(18 ± 0.3)×10^{-7}	(13 ± 0.2)×10^{-7}	(4.2 ± 0.1)×10^{-7}	(2.1 ± 0.01)×10^{-7}

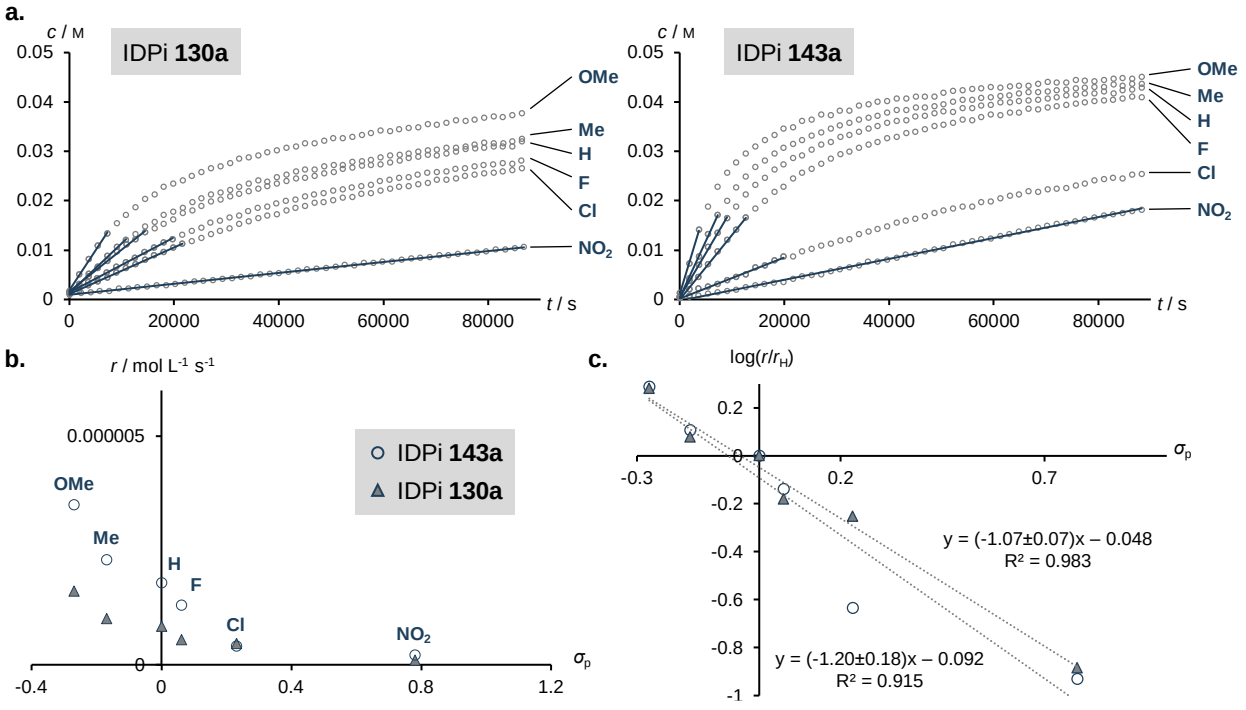


Figure 4.21 a. concentration profiles of products **283** with *para*-substituted phenyl carbamates using IDPi catalyst **130a** and **143a**. **b.** Reaction rates, as determined by linearization of the early rate (< 30%) in individual kinetic measurements. **c.** Hammett Plots for both catalytic systems. Uncertainties are given as the regression error using the LINEST function in Microsoft excel.

4.2.3. Determination of the Reaction Order in Catalyst and Substrates

We chose the variable time normalization analysis (VTNA) method developed by Jordi Burés to examine the apparent order of substrates and catalyst in our reaction (Figure 4.22).[185–187] We

followed the concentration profile of product formation at ambient temperature under varied starting concentrations of carbamate **120b**, aldehyde **284**, and IDPi catalyst **143b**. After graphical normalization of the time axis, we found an order of 0.93 for the carbamate, 1.00 for the aldehyde, as well as 1.00 for the catalyst. All of these values are well within the expected magnitude. The slight deviation from 1 for the starting carbamate may be explained by considering product inhibition and competitive binding pathways.

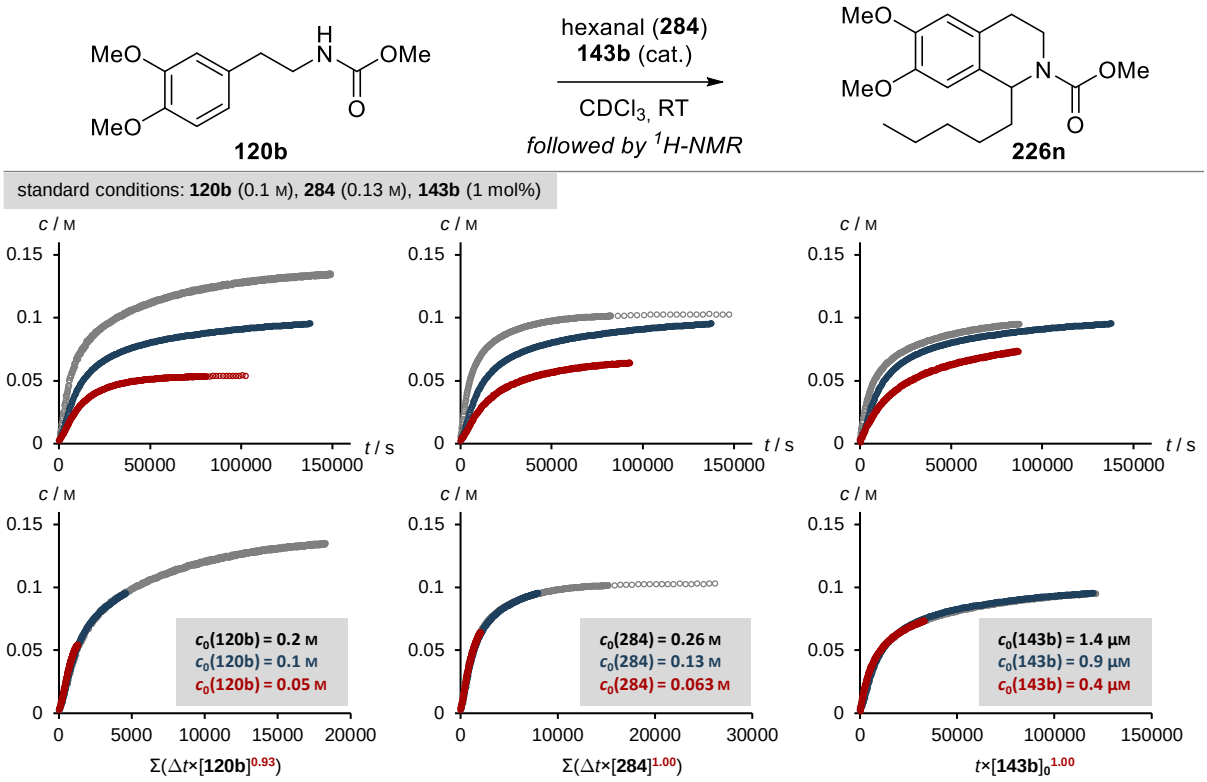


Figure 4.22 Variable time normalization analysis (VTNA) of the catalytic asymmetric Pictet-Spengler reaction. Product concentrations were followed over time in separate experiments with variable initial concentrations of the substrates and the catalyst. Normalization of the time axis was visually optimized by varying the relevant order.

4.2.4. Catalyst Stability

We were previously able to re-isolate the IDPi catalyst quantitatively in the synthesis of salsolidine, where the reaction was conducted at −40 °C (see Figure 4.16). Following the catalytic reactions at elevated temperatures allowed us to monitor the catalyst stability simultaneously over time (Figure 4.23). Even though the integration of the relevant signals in the ^{1}H-NMR is not quantitative and is overlaid with significant baseline noise, a qualitative stability assessment still seems reasonable. As for benzofuran catalyst **143b**, we saw slight decomposition even at 10 °C, which became greatly enhanced at elevated reaction temperatures. At 60 °C, only approximately 25% of the initial catalyst remained in solution after 20 h. The decomposition pathway could be confirmed as hydrolysis to the corresponding iIDP and IDP catalysts by examination of the ^{31}P-NMR after addition of Et_3N. The possibility for significant hydrolysis of IDPis under the reaction

conditions is not entirely surprising, as it can also be observed when concentrating an aqueous solution after reversed phase chromatography as part of the catalyst synthesis. The corresponding Tf-core IDPis in our experience generally tend to be more resilient toward hydrolysis. In fact, no decomposition of IDPi catalyst **130a** could be observed under our reaction conditions, even at 60 °C.

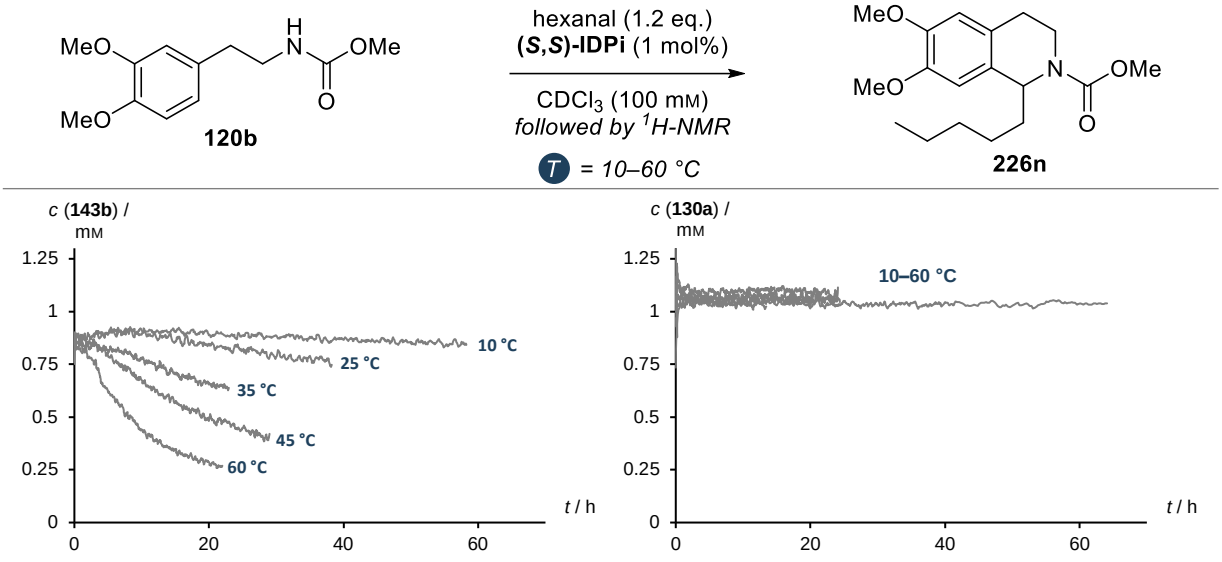


Figure 4.23 Catalyst stability at different reaction temperatures using IDPis **143b** and **130a**.

4.2.5. Eyring Studies

The thermodynamic nature of a transition state can be elucidated by employing Eyring equation (4.3), which is an Arrhenius-like correlation of a reaction rate constant k to the free enthalpy of activation $\Delta G^{\ddagger}$. A so-called transmission-coefficient κ furthermore represents the microscopic reversibility of the product-forming vibrational mode and is experimentally assumed equal to 1. The Eyring equation can be further modified by taking into account the enthalpic and entropic contributions to the Gibbs free energy of activation. The formula can then be rewritten in a linearized form (4.4). Due to the temperature dependency of the entropic term, measurement of rate constants k at different temperatures T thus allows for experimental determination of the overall activation enthalpy and entropy.

$$k = \frac{\kappa k_B T}{h} e^{-\frac{\Delta G^{\ddagger}}{RT}} \tag{4.3}$$

$$\ln\left(\frac{kh}{\kappa k_B T}\right) = \frac{-\Delta H^{\ddagger}}{R} \cdot \frac{1}{T} + \frac{\Delta S^{\ddagger}}{R} \tag{4.4}$$

For a second-order reaction, the rate equation has the general form of $r = k \cdot [\mathbf{A}]^{\alpha}[\mathbf{B}]^{\beta}[\mathrm{cat}]^{\gamma}$, where α, β, and γ are the respective orders in substrates and catalyst and were confirmed to equal 1 in first approximation (see Figure 4.22). The integrated rate equation can then be rearranged to

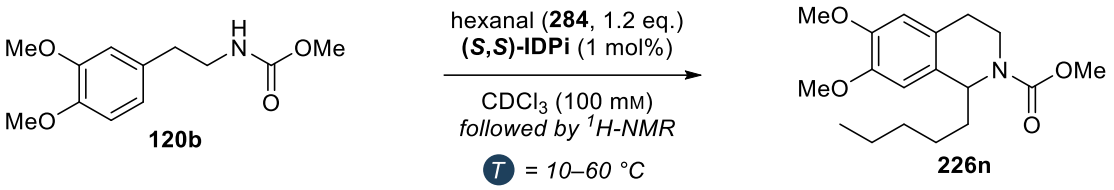
formula (4.5), which allows for graphical linearization.[188] A simple plot against the time scale normalized by the active catalyst concentration permits extraction of the overall kinetic rate constant *k*.

$$\frac{\ln\left(\frac{[\mathbf{A}][\mathbf{B}]_0}{[\mathbf{B}][\mathbf{A}]_0}\right)}{[\mathbf{A}]_0 - [\mathbf{B}]_0} = [\mathrm{cat}] \cdot kt \tag{4.5}$$

We conducted separate rate experiments at temperatures between 10–60 °C using IDPi catalysts **143b** and **130a** (Figure 4.24). The concentration profiles of product formation (**a**) visually show a strongly pronounced temperature dependency on the rate with catalyst **130a**, while benzofuran catalyst **143b** is less affected. This trend also becomes apparent, when the early rates *r* are extracted by linearization of the concentration curves at low conversion (< 30%). While the linear fits are reasonable for the benzofuran catalyst **143b**, the reaction profiles with catalyst **130a** show a significant curvature even at low conversions, which renders linearization and early rate analysis impractical.

We plotted the reaction profiles according to the integrated second order rate law (Figure 4.24b). As demonstrated in section 4.2.4, IDPi catalyst **143b** decomposes significantly at elevated reaction temperatures. It is therefore essential to normalize the time axis with the active catalyst concentration at each time point for determination of the rate constant. The relevant values could be extracted from the ^{1}H-NMR spectra and were averaged over five data points to reduce spectral noise. The resultant plots were linear for both catalysts and all temperatures under study and allowed linear regression over the complete reaction profile. The linear slopes provided the rate constants *k*, which were plotted according to the Eyring equation (Figure 4.24c). Linearization of the data allowed for extraction of the thermodynamic activation barriers for both catalysts under study.

Interestingly, a sharp difference in enthalpic and entropic contributions to the reaction barriers with catalysts **130a** and **143b** was determined. The overall $\Delta G^{\ddagger}$ at room temperature was almost identical in both catalytic systems (18 kcal·mol^{-1}), which correlates well with their comparable reaction rates. However, benzofuran catalyst **143b** shows a much smaller enthalpic reaction barrier ($\Delta H^{\ddagger}$ = 7.8 ± 0.3 kcal·mol^{-1}) than IDPi **130a** ($\Delta H^{\ddagger}$ = 14 ± 1.4 kcal·mol^{-1}). On the other hand, the entropic contribution is enhanced with catalyst **143b** ($-T\Delta S^{\ddagger}_{298\,\mathrm{K}}$ = 10 ± 0.3 kcal·mol^{-1}) with respect to IDPi **130a** ($-T\Delta S^{\ddagger}$ = 4.7 ± 1.4 kcal·mol^{-1}). These thermodynamic contributors translate into a larger temperature dependency of the overall rate with catalyst **130a**, as the smaller temperature-dependent entropic term can effectively be compensated by increasing the average kinetic energy of the reacting molecules.



	10 °C	25 °C	35 °C	45 °C	60 °C
r (**143b**) / mol L^{-1} s^{-1}	(4.54 ± 0.08)×10^{-6}	(4.53 ± 0.06)×10^{-6}	(4.90 ± 0.07)×10^{-6}	(5.42 ± 0.07)×10^{-6}	(6.09 ± 0.09)×10^{-6}
r (**130a**) / mol L^{-1} s^{-1}	(2.18 ± 0.10)×10^{-6}	(8.58 ± 0.41)×10^{-6}	(12.8 ± 0.63)×10^{-6}	(16.7 ± 0.63)×10^{-6}	(20.6 ± 0.44)×10^{-6}
k (**143b**) / L mol^{-1} s^{-1}	0.14 ± 0.00041	0.31 ± 0.0013	0.52 ± 0.0011	0.71 ± 0.0010	1.4 ± 0.0069
k (**130a**) / L mol^{-1} s^{-1}	0.040 ± 0.00048	0.18 ± 0.0014	0.43 ± 0.0010	1.1 ± 0.0015	1.6 ± 0.0025

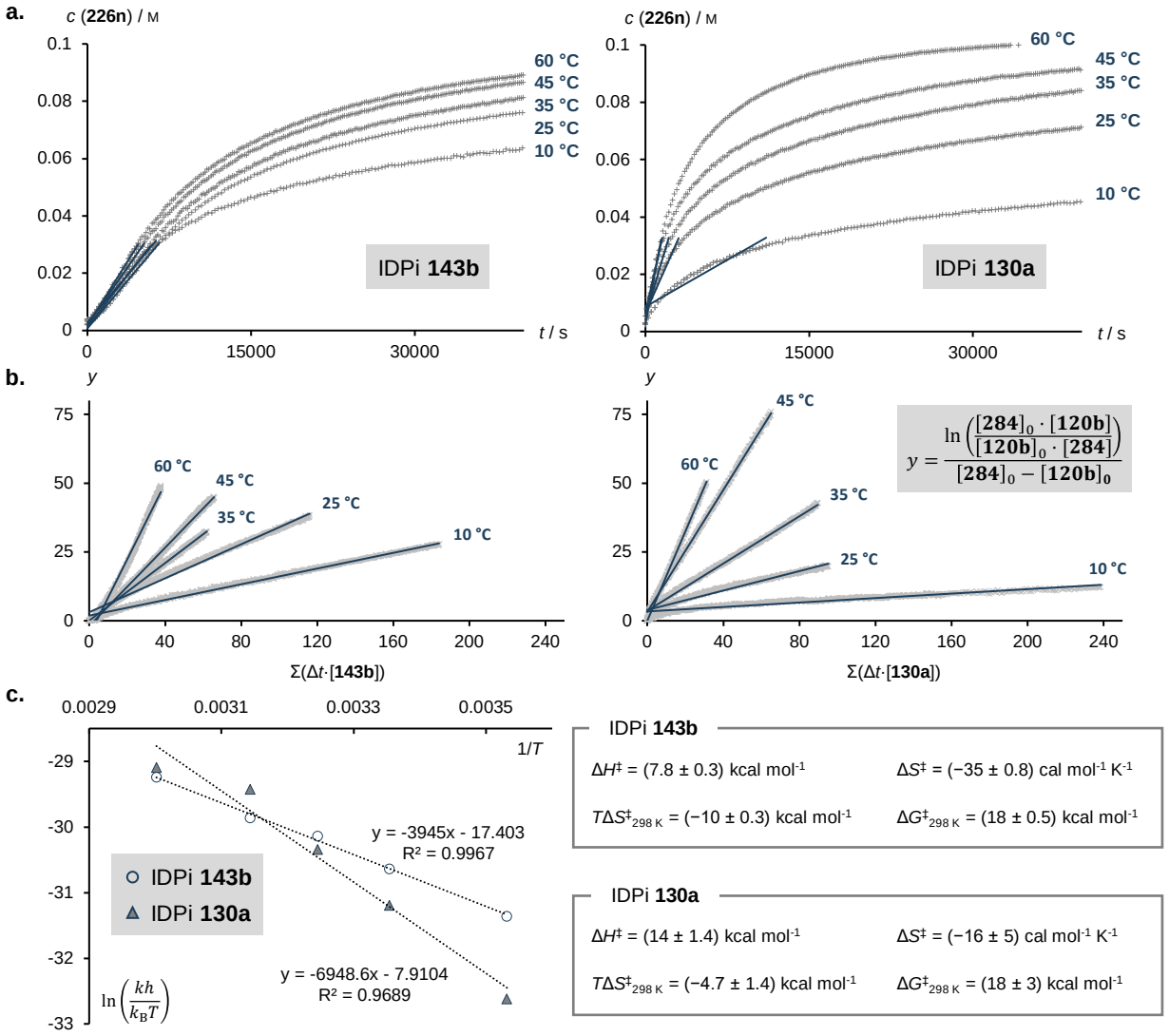
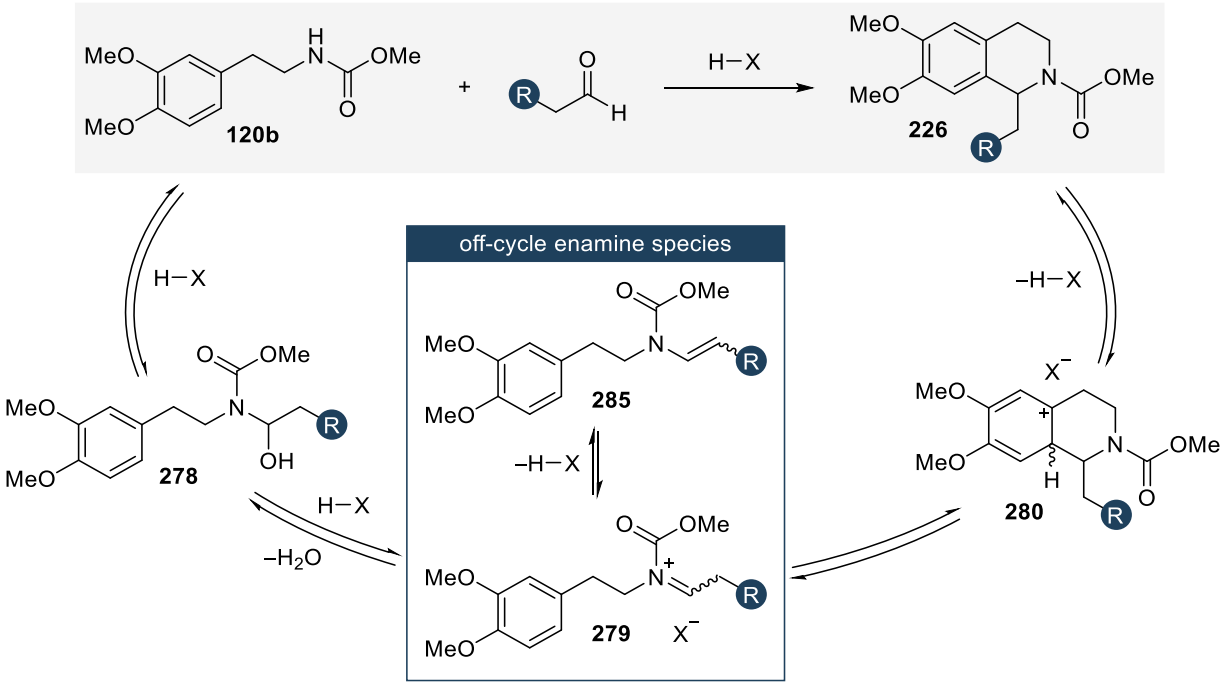


Figure 4.24 Catalytic Pictet-Spengler reactions of **120b** with hexanal (**284**) using either IDPi **143b** or **130a** at varied temperatures. **a.** Concentration profiles of product **226n** and early rates by linearization < 30% conversion. **b.** Extraction of overall rate constants *k* by linearization of the integrated second order rate law (4.5). **c.** Eyring plot according to equation (4.4) and the extracted thermodynamic barriers of activation. Uncertainties are given as the regression error using the LINEST function in Microsoft excel.

The small enthalpy of activation with catalyst **143b** can be interpreted in terms of highly ordered transition states. On the molecular level, the electron-rich benzofuran substituents of the catalyst might engage in cation-π interactions with cationic reaction intermediates. The resulting enthalpic stabilization of the transition states however results in an enhanced entropy of activation, as the ion pairs possess less degrees of rotational and vibrational freedom due to attractive non-covalent interactions. Catalyst **130a** on the other hand is allegedly highly acidic,[58] which renders the corresponding counteranion relatively stable. It can therefore be reasoned that the ion pair intermediates and transition states of the reaction with catalyst **130a** are more dissociated and rely less on stabilizing non-covalent forces. The experimental differences between catalyst **143b** and **130a** with respect to their thermodynamic reaction barriers corroborate this interpretation of the microscopic nature of the reaction.

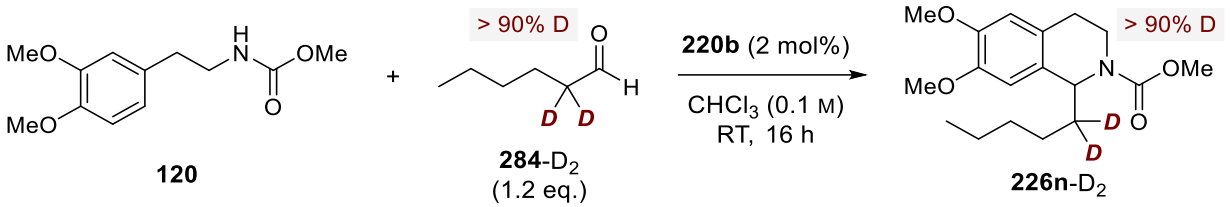
4.2.6. On the Relevance of an Off-Cycle Enamine Species

Another mechanistic hypothesis that can be experimentally probed is the existence of an off-cycle enamine (Scheme 4.9). More precisely, **285** could be formed by deprotonation of *N*-acyliminium ion **279**, if an enolizable aldehyde is employed in the reaction. As enamine **285** is a neutral species, dissociation from the chiral acid could lead to enrichment under catalytic conditions, which would render coordination and re-protonation toward iminium ion **279** a significant contributor to the overall reaction rate.



Scheme 4.9 Mechanistic possibility of an off-cycle enamine intermediate **285** in the Pictet-Spengler reaction of enolizable aldehydes formed by deprotonation of *N*-acyliminium ion **279**.

We chose to probe the existence of an enamine intermediate experimentally (Scheme 4.10). The equilibrium between iminium ion **279** and enamine **285** would involve deprotonation, possible dissociation, and re-protonation. By employing α-deuterated hexanal (**284**-D_2) in the reaction conditions, we therefore expected significant isotopic scrambling in the THIQ product **226n**. The water that is necessarily formed under the reaction conditions would serve as the proton source. We however saw no significant deterioration of isotopic labelling by ^{1}H-NMR or mass spectrometry. It thus seems unlikely that enamine intermediates of the type **285** are formed to a significant extend under our optimal reaction conditions, even though their existence cannot be completely ruled out in the case of more α-acidic aldehydes.



Scheme 4.10 Isotope scrambling experiment using α-deuterated hexanal (**284**-D_2).

4.2.7. Mechanistic Considerations with Aromatic Dimethyl Acetals

We utilized dimethyl acetals for the synthesis of 1-aryl THIQs because we hypothesized that the reduced electrophilicity of aromatic aldehydes could be overcome by the catalytic generation of oxocarbenium ions. In line with this hypothesis, we can expect a change in the relative rate constants in the reaction mechanism. Specifically, the formation of the high-energy oxocarbenium ion is expected to contribute to the overall rate of the reaction. In order to probe this effect, we conducted a competition KIE experiment with deuterated carbamate **120** and benzaldehyde dimethylacetal (**275a**) (Figure 4.25). In sharp contrast to the reaction with hexanal (see Figure 4.19), we observed no significant difference in the rate of consumption of deuterated and non-deuterated substrate. The parallel concentration profiles are reflected in an average calculated KIE of 0.98 ± 0.05, as determined according to formula (4.1) at fractional conversions $F_H > 0.25$. Based on this experiment as well as the qualitative reactivity difference of electronically divers aldehydes and acetals (see Figure 4.17), we conclude that the rate-determining step in the reaction of aromatic dimethylacetals is indeed the formation of the oxocarbenium ion pair by extrusion of methanol.

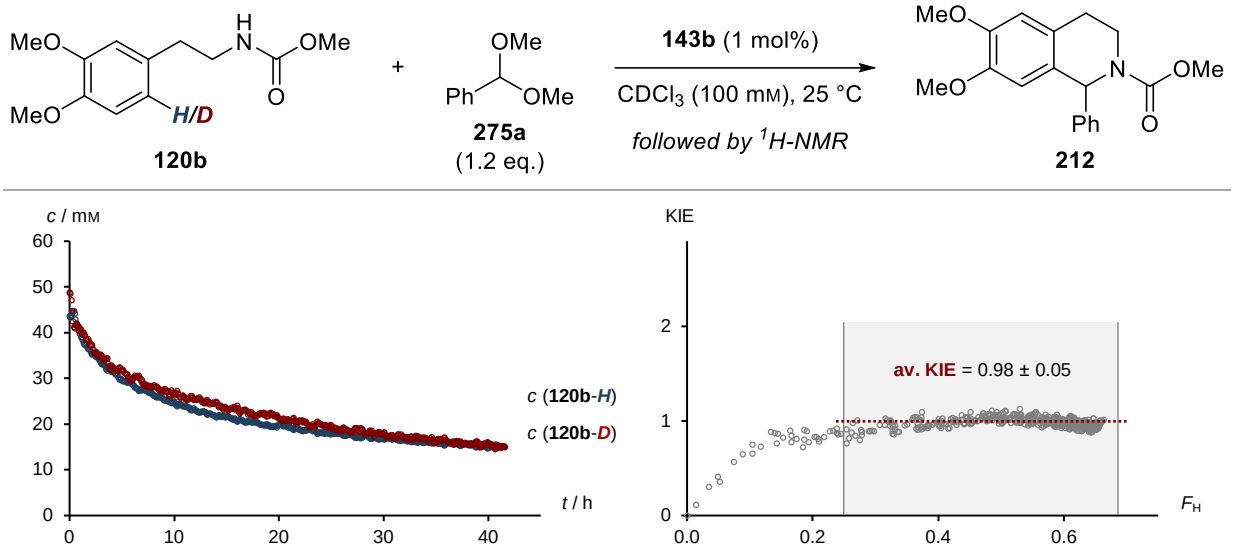


Figure 4.25 Competition kinetic isotope effect (KIE) experiment with benzaldehyde dimethylacetal (**275a**). Average KIE was determined at fractional conversion of the protonated starting material $F_H > 0.25$. The error is given as the standard deviation.

4.2.8. Proposed Mechanism

Based on our experimental studies as well as literature precedence for biocatalytic and organocatalytic Pictet-Spengler reactions, we propose a mechanistic scenario as depicted in Figure 4.26. The Brønsted acid catalyst H–X will likely exist as a complex with a Lewis basic component (LB) of the reaction mixture, which may be carbamate **120**, the employed aldehyde (or acetal), or the product THIQ **226**. The first productive step of the catalytic cycle is the activation of the electrophile. For alkyl aldehydes, this is achieved by protonation toward **286**, whereas in the case of aromatic dimethylacetals, the extrusion of MeOH leads to the formation of ion pair **287**. This step is likely rate limiting for aromatic substrates, as discussed in section 4.2.7. The activated electrophile is subsequently attacked by the nucleophilic carbamate reaction partner to form *N*,*O*-acetal **278**, which proposedly remains in close proximity to the Brønsted acid catalyst, as we were unable to detect any enrichment of this compound when following the reaction progress by ^{1}H-NMR. From acetal **278**, extrusion of H_2O or MeOH leads to the formation of iminium ion **279**. Overall, the conducted Hammett studies (Figure 4.21) fostered our understanding that the formation of ion pair **279** is a slow mechanistic step. Whether the limiting step is the attack of carbamate **120** onto the activated electrophile or the subsequent activation of **278** could however not be distinguished. From a purely kinetic perspective, the cyclization of the aromatic ring onto iminium ion **279** is a fast step in comparison to both the preceding as well as the following step. Based on our KIE studies (Figure 4.19), the deprotonation of Wheland intermediate **280** toward THIQ product **226** is slow and overall rate limiting in the case of alkyl aldehydes.

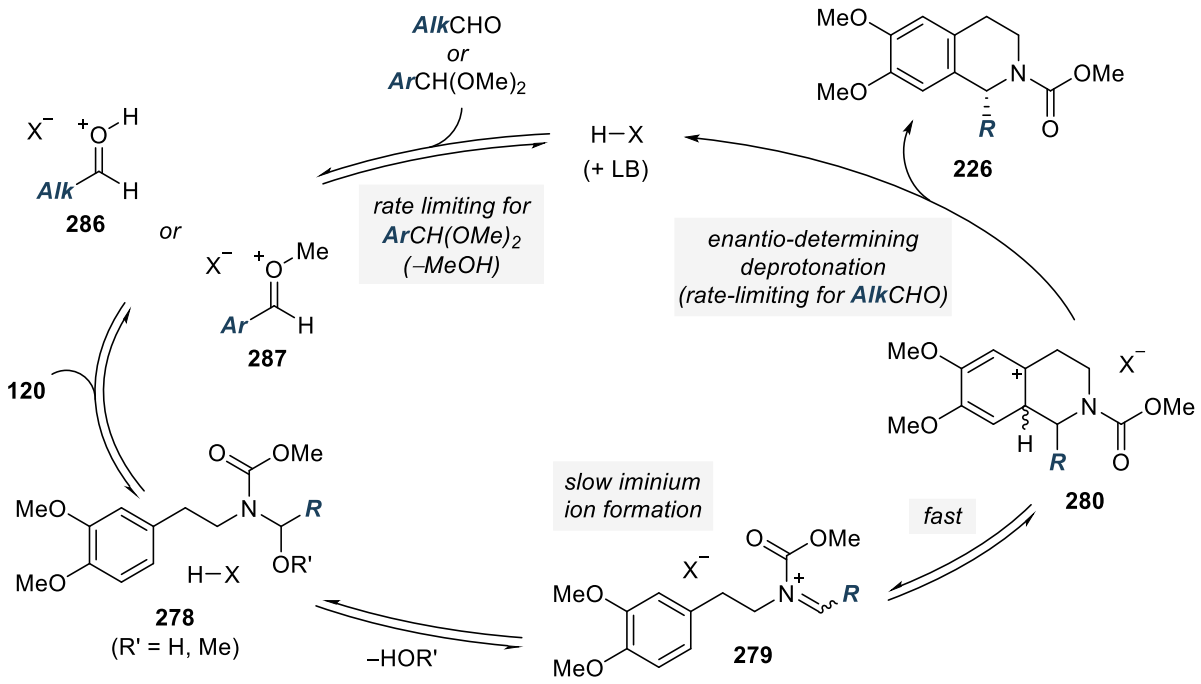


Figure 4.26 Overall kinetic considerations and proposed catalytic cycle based on the experimental studies.

The above outlined kinetic considerations of the catalytic cycle have profound impacts for rationalizing the stereochemical outcome of the reaction. Wheland intermediate **280** can theoretically exist as four different stereoisomers, the absolute and relative configuration of which are defined in the C–C bond-forming cyclization step (Figure 4.27). We propose that chair-like transition states are likely involved in the formation of **280**. This view is in line with previous computational studies on related systems.[156,183] Consequently, the cyclization step would be diastereospecific with regard to the iminium ion geometry, with the (*Z*)-iminium ions leading to anti-configured products, and the (*E*) isomers providing syn products. Based on the concept of microscopic reversibility, a fast cyclization reaction also necessarily allows for a facile backwards reaction. Accordingly, we propose that different stereoisomers of Wheland intermediate **280** are formed in an equilibrium, governed by their relative ground-state stability in proximity to a chiral counteranion, rather than their respective kinetic rate of formation. This perception necessarily renders the deprotonation of **280** enantio-determining. In previous studies, anti-configured Wheland intermediates were found to be the more stable isomers. Nevertheless, both an anti and a syn isomer must be considered as potential intermediates leading to the major (*R*)-product under optimized reaction conditions (highlighted in grey).

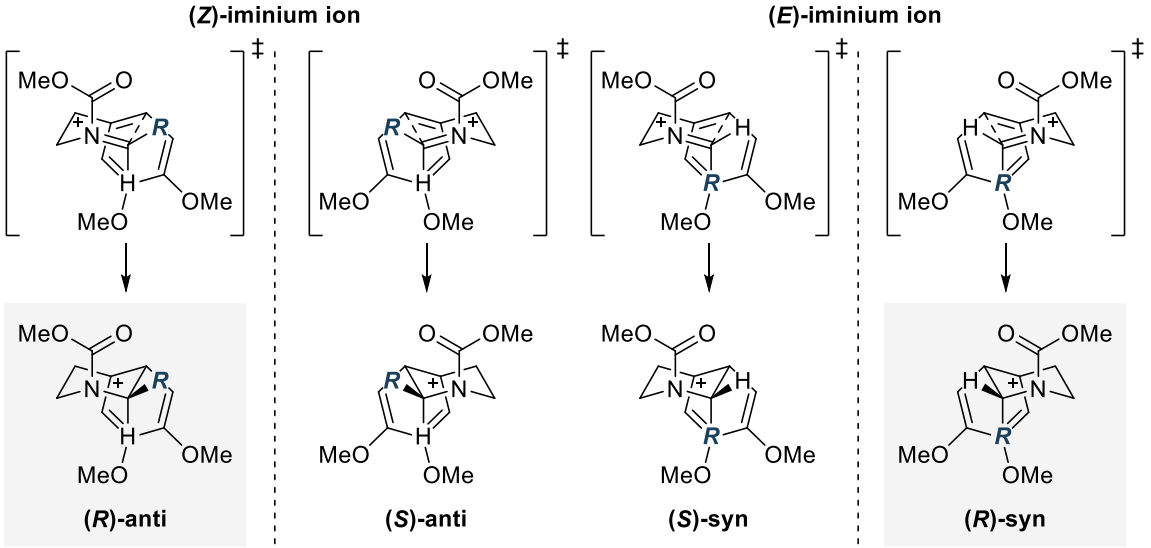


Figure 4.27 Proposed transition states leading to the four possible diastereomeric Wheland intermediates **280**.

In line with our experimental studies, we propose that benzofuran-substituted catalysts engage in stabilizing interactions with the cationic reaction intermediates – namely *N*-acyliminium ion **279** and Wheland intermediate **280**. The optimal catalysts therefore allows for facile formation and equilibration of diastereomeric intermediates. In order to shed light on the specific interactions offered by the optimal catalyst in the enantio-determining deprotonation, we turned to density functional theory (DFT) calculations. The optimized geometry of the TS leading to the major (*R*)-configured product displays multiple key elements (Figure 4.28). First, the lowest-lying TS was found in the deprotonation of (*R*)-syn-configured intermediate **280**. This result stands in contrast to both the mechanism of NCS,[156] as well as the computed mechanism of HBD-catalyzed Pictet-Spengler reactions of tryptamine.[183] Furthermore in line with our hypothesis, one benzofuran substituent of the counteranion is in close face-to-face contact (3.31 Å) to the reacting aromatic ring. The shortest distance was found to the *meta*-methoxy group, which contributes largely to the positive charge by electron donation and is thus predestined for cation-π stabilization. The measured distance is furthermore in good agreement with typical cation-π interactions found in structural biology and asymmetric catalysis.[189,190] The final deprotonation occurs by a basic sulfonate residue of the catalyst core (1.28 Å O–H distance). As previously hypothesized by analysis of the catalyst's crystal structure (see Figure 4.7), the perfluorinated arenes of the core engage in π-π stacking with the BINOL backbone. Importantly, these interactions influence the geometry of the basic sulfonate residue and are thus instrumental to the deprotonation and consequently the stereochemical outcome of the reaction.

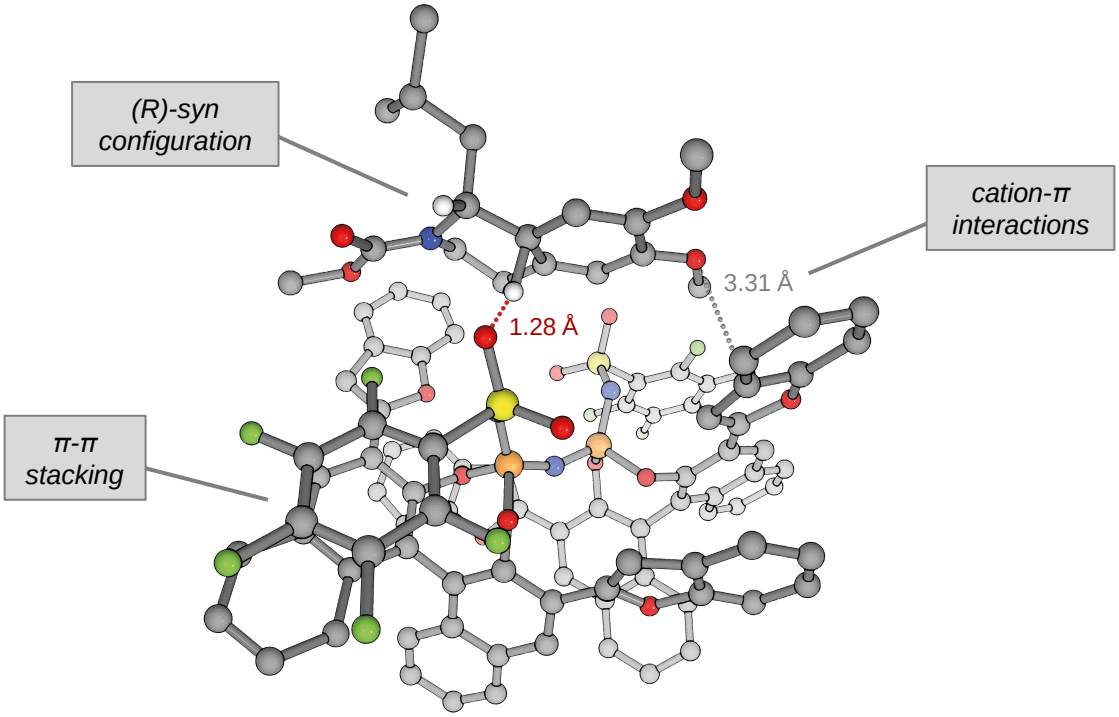


Figure 4.28 DFT-optimized TS structure of the deprotonation of (*R*)-syn-configured Wheland intermediate **280** by IDPi **143b**. Isovaleraldehyde was chosen as a model aldehyde. Only the relevant two hydrogen atoms are shown for clarity. Geometry optimization was performed at the r2SCAN-3c level of theory by Dr. Nobuya Tsuji.

4.3. Studies toward a Pictet-Spengler Reaction of Electron-Neutral Phenethylamines

Over the course of our studies on asymmetric Pictet-Spengler reactions, we became increasingly aware of the reactivity limitations imparted by the substrate-inherent electronic properties. Specifically, the nucleophilicity of the cyclizing aromatic ring can be estimated by analysis of Mayr's nucleophilicity parameter *N* of the reacting fragment (Figure 4.29).[191,192] We directly compared four substrates bearing either no activating substituent (**273**), a methyl group (**272**), a benzannulation (**271**), or a methoxy substituent (**288**) under catalytic reaction conditions. On the one hand, the strong acid $HNTf_2$ was chosen as catalyst for the reaction in MeCN (conditions **a**). These conditions enable reactivity that is thus far unparalleled in asymmetric Brønsted acid catalysis, as exemplified by comparison with our previously optimized reaction (conditions **b**). For the most nucleophilic substrate **288**, both conditions delivered the product in high yields. For the slightly less reactive naphthalene substrate **271**, only $HNTf_2$ was able to produce the product in high yield, even though IDPi catalyst **220b** still shows trace activity. However, the same is not true for the least activated substrates **272** and **273**, where the catalytic IDPi conditions **b** fail to show any reactivity. Even the most forcing catalytic conditions **a** delivered the products in highly diminished yields.

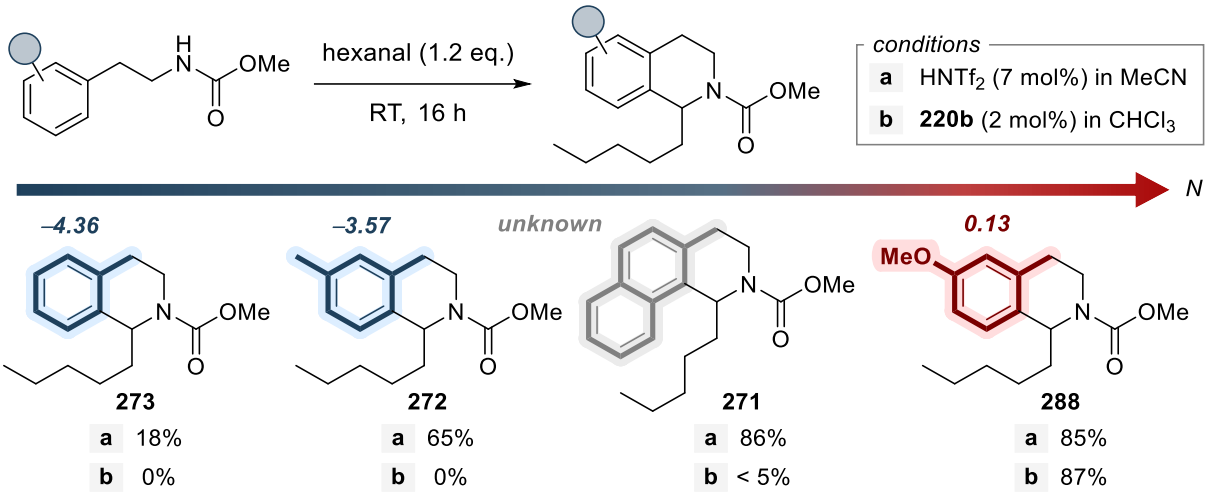
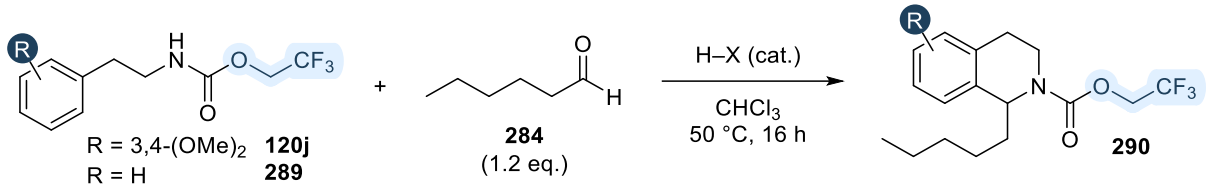


Figure 4.29 Pictet-Spengler reactivity comparison of increasingly nucleophilic arenes under catalytic conditions. **a.** $HNTf_2$ (7 mol%) in CH_3CN (isolated yields). **b.** IDPi **220b** (2 mol%) in $CHCl_3$ (NMR yields). *N* = nucleophilicity parameter of the highlighted fragment according to Mayr et al.[191,192]

Essentially, two design principles for increasing the reactivity in Pictet-Spengler reactions of poorly nucleophilic aromatic systems can be conceived: (1) Increasing the lifetime and reactivity of the intermediate *N*-acyliminium ion by application of a stronger acid, or (2) Rendering the iminium ion more electrophilic by application of electron withdrawing groups on the protecting group. Importantly, both concepts are connected to each other, as the generation of highly reactive catalytic intermediates usually necessitates the application of a more reactive catalyst.

Our Hammett studies (see Figure 4.21) exposed that electron-donating carbamate groups overall accelerate the Pictet-Spengler reaction. Nevertheless, we hypothesized that electron-poor carbamates might facilitate the reaction of poorly nucleophilic phenethylamines *via* the formation of a more electrophilic iminium ion intermediate, the generation of which would require highly acidic catalysts and possibly elevated reaction temperatures. We therefore synthesized trifluoroethyl carbamates **120j** and **289** and examined their reactivity with hexanal (**284**) (Table 4.11). The reaction of an electron-rich phenethylamine (R = 3,4-$(OMe)_2$) proceeded smoothly at 50 °C. With $HNTf_2$, the product was formed in quantitative yield (entry 1). Electron-poor IDPi **130a** was less reactive (entry 2) than benzofuran-substituted catalysts **143a** and **143a**[6,6'] (entries 3–4). When the same conditions were applied to unsubstituted phenethylamine (R = H), none of the acids were able to facilitate product formation (entries 5–8). We thus conclude that the desired reaction of unsubstituted phenethylamines would require the use of even stronger electron withdrawing pre-formed carbamates.

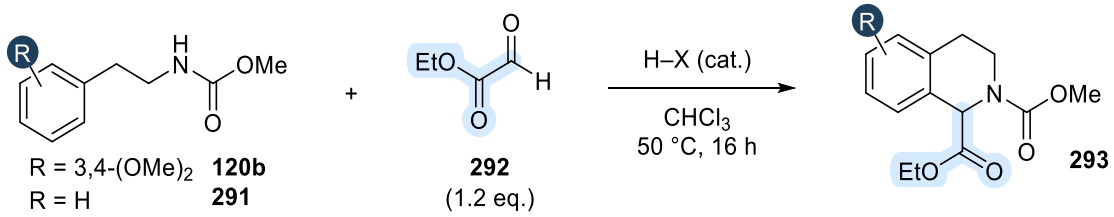
Table 4.11 Reactivity of electron-poor carbamates **120e** and **289** with hexanal (**284**) under the influence of highly reactive Brønsted acid catalysts at elevated temperatures.



entry	H–X	R	yield	er
1	$HNTf_2$	3,4-$(OMe)_2$	99%	–
2	**130a**	3,4-$(OMe)_2$	66%	59:41
3	**143a**	3,4-$(OMe)_2$	82%	47:53
4	**143a**$^{6,6'}$	3,4-$(OMe)_2$	96%	51:49
5	$HNTf_2$	H	0%	–
6	**130a**	H	0%	n.d.
7	**143a**	H	0%	n.d.
8	**143a**$^{6,6'}$	H	0%	n.d.

As an alternative mode for the generation of a highly electrophilic iminium ion, we examined the reaction of methyl carbamates **120b** and **291** with ethyl glyoxylate (**292**) (Table 4.12). As expected, the reactivity was diminished in comparison to simple aliphatic aldehydes, purportedly due to the slow formation of the high-energy iminium ion. Nevertheless, the reaction of electron rich phenethylamines (R = 3,4-$(OMe)_2$) could be efficiently catalyzed by $HNTf_2$ (entry 1). Of the selected IDPi catalysts (entries 2–4), the 6,6'-modified benzofuran catalyst **143a**$^{6,6'}$ was the most reactive, producing the product in 44% yield and with 45:55 er. Interestingly, the reaction of unsubstituted phenethylamines (R = H) could be catalyzed not only by $HNTf_2$ (entry 5), but also by the benzofuran-substituted catalysts (entries 7–8). Traces of the desired product could be detected by ^{1}H-NMR and low enantiomeric enrichment could be measured. These results clearly point toward the promise of unlocking new reactivity by application of evermore-acidic catalysts. However, the studied reaction with glyoxylates seems just beyond the capability of the currently most active catalysts described in this thesis.

Table 4.12 Reactivity of methyl carbamates **120b** and **291** with ethyl glyoxylate (**292**) under the influence of highly reactive Brønsted acid catalysts at elevated temperatures.



entry	H–X	R	yield	er
1	$HNTf_2$	3,4-$(OMe)_2$	70%	–
2	**130a**	3,4-$(OMe)_2$	18%	51:49
3	**143a**	3,4-$(OMe)_2$	25%	47:53
4	**143a**[6,6']	3,4-$(OMe)_2$	44%	45:55
5	$HNTf_2$	H	56%	–
6	**130a**	H	0%	n.d.
7	**143a**	H	traces	49:51
8	**143a**[6,6']	H	traces	45:55

We rationalize that the application of even stronger EWGs on either phenethylamines **294** or the applied aldehyde reaction partner cannot further increase the desired reactivity, allegedly due to a multitude of slow mechanistic steps. As the nucleophilic cyclization is accelerated by a strong EWG, the condensation steps are decelerated. Nevertheless, by enhancing the acidity of an applied Brønsted acid catalyst through co-catalytic additives, a potential increase in reactivity can be envisioned (Figure 4.30). On the other hand, a possible advantage arises from the application of pre-formed imines **295**. These substrates are inherently Lewis basic and typically undergo nucleophilic addition or substitution with an electrophilic reaction partner. The arising "electronic match" hypothetically allows for introduction of highly electron-withdrawing groups as reaction partners. For the reason that the condensation step is not part of the catalytic cycle, formation of the reactive iminium ion could potentially be facilitated.

In the following sections, two distinct reaction designs for enhanced Pictet-Spengler reactivity will be presented: First, the effect of anion binding co-catalysts on chiral Brønsted acids will be covered (principle 1). Subsequently, the design and proof of principle of a silyl acyl Pictet-Spengler reaction from pre-formed imine precursors will be discussed (principle 2).

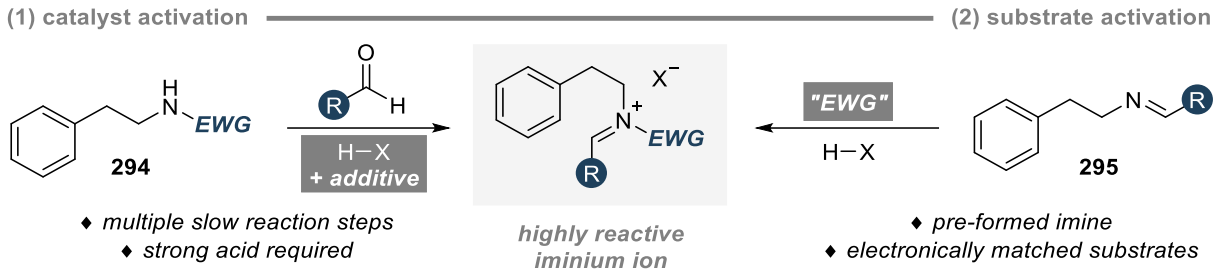


Figure 4.30 Generation of highly electrophilic iminium ions from **294** by activation of the catalyst (1), or from pre-formed imines **295** (2).

4.3.1. Enhancing Catalytic Activity by Anion Binding Co-Catalysis

Research in the field of hydrogen bond donor (HBD) catalysis in the past decade has established the concept of anion binding as a crucial activation mode. Most often, one of the reacting substrates is activated or guided by catalyst binding or abstraction of an anion. A complementary catalytic mode arises by binding the counteranion of an acid co-catalyst, thus enhancing the overall acid activity.[193,194] Furthermore, the specific anion affinity of neutral HBDs dictates the choice of catalyst/co-catalyst in such a catalytic reaction.[195] Specifically, Jacobsen et al. have utilized chiral thiourea catalysts in combination with carboxylic acids[196] and hydrochlorid acid,[197] or a chiral squaramide catalyst in combination with triethylsilyl triflate to purportedly generate a strong and chiral supramolecular silylium Lewis acid.[73] However, the established approaches rely on the combination of a chiral and enantiopure anion binding catalyst with a strong achiral acid. The reverse reaction design proposed herein might be summarized as enhancing catalytic activity of chiral Brønsted acids *via* HBD co-catalytic stabilization of the counteranion.

Prototypical achiral anion binding catalysts include thiourea **296** introduced by the Schreiner group,[70] or the related squaramide **297**.[198] In 2013, the group of Nagorny furthermore introduced thiophosphoramide **298** as a powerful sulfonate anion binder.[199] However, the catalyst has been significantly underexplored in homogenous catalysis, apart from few examples in selective polymerization reactions.[200,201] Phosphoramide **298** seems particularly fit for combination with the strong Brønsted acids from the List group, due to the specific anion-binding interactions. Nagorny *et al.* propose a highly stable tricoordinate binding mode of **298** to sulfonate anions, thus allowing an impressive rate enhancement upon co-catalytic employment of *p*-toluene sulfonic acid (Figure 4.31). We thus hypothesized that a similar interaction between an HBD catalyst and the strong phosphonimide-based Brønsted acids from the List group might be feasible. Importantly, the interaction with exposed catalyst structures such as PADis could theoretically create a confined supramolecular complex, which could influence not only reactivity but also selectivity.

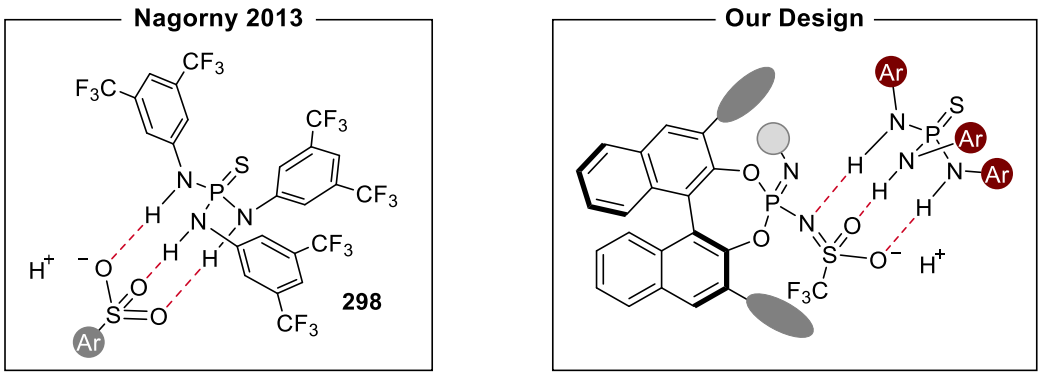


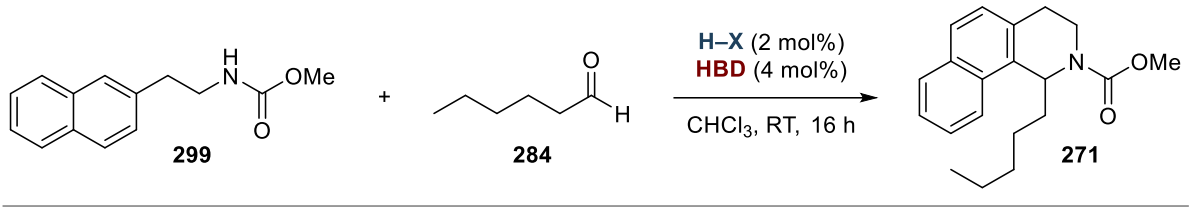
Figure 4.31 Anion binding mode of thiophosphoramide **298** as proposed by Nagorny[199] and our design to enhance the acidity of *N*-sulfonyl phosphonimides.

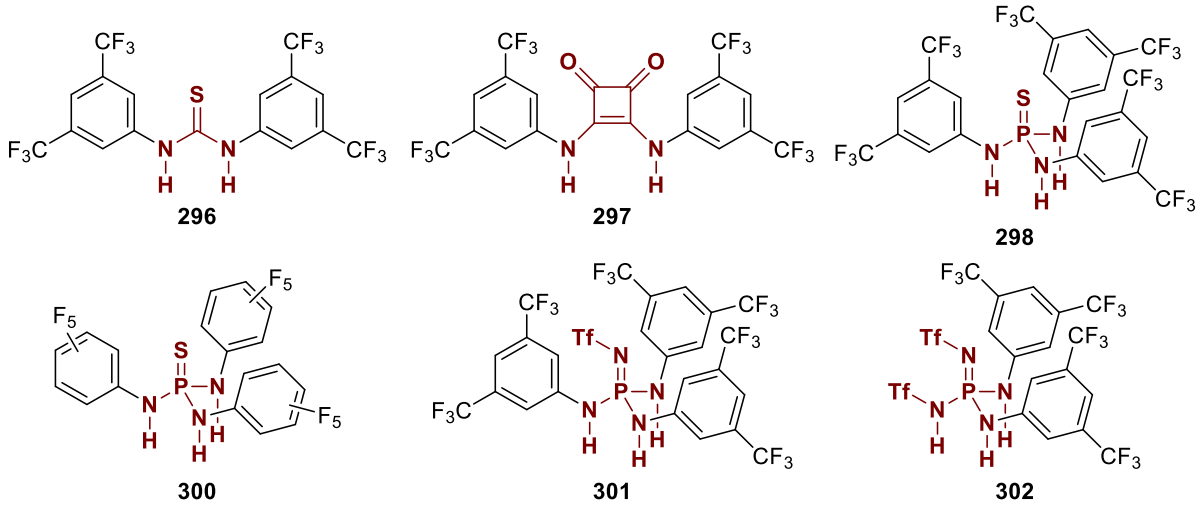
To put our reaction design to test, we chose the Pictet-Spengler reaction of a poorly reactive substrate as suitable model. Naphthalene carbamate **299** provides an ideal level of natural reactivity with strong Brønsted acids and chiral catalysts, in order to examine the effect of HBD co-catalysts on reactivity and selectivity. We were interested in exploring the literature-known thiourea **296**, squareamide **297**, and thiophosphoramide **298**. Additionally, in order to enhance the anion binding capabilities of the HBDs, we synthesized the novel phosphoramide **300**, and the mono- and bis-triflated catalysts **301** and **302** *via* Yagupolskii-type modifications.

We selected several highly active Brønsted acid catalysts to test in combination with the aforementioned HBDs. In addition to achiral TfOH and Tf_2NH, we were eager to test 3,3'-phenyl-substituted PADi **303**, which possesses a sterically open active site, highly acidic IDPi **130a**, as well as prototypical benzofuran IDPi **143b**. As a first experiment, we tested the "native" activity of the Brønsted acids. Both TfOH and Tf_2NH provide significant amounts of the product. PADi **303** was still the most reactive catalyst in the series of chiral acids. Highly acidic IDPi **130a** provided only traces of the product, and benzofuran IDPi **143b** gave the THIQ in 3% yield.

Under co-catalytic conditions using the synthesized HBDs, only two anion binders showed a promising effect on activity and selectivity. Thiourea **296** was able to enhance the catalytic activity of TfOH, Tf_2NH, PADi **303**, and IDPi **130a** significantly. The enantioselectivities with the chiral acids where however not effected, or even diminished in the case of IDPi **143b**. Thiophosphoramide **298** was able to enhance the catalytic activity of all acids except for IDPi **130a**. Fascinatingly, this HBD was even able to induce enantioselectivity (46:54 er) in the reaction with PADi **303**, thus corroborating the hypothesis that a more confined anionic supramolecular complex is created. Surprisingly, an activity-enhancing effect with benzofuran catalyst **143b** came impaired with a striking reverse in stereoinduction (69:31 er). Finally, HBD **302** showed significant background reactivity, probably due to strongly acidifying effect of the two *N*-Tf substituents.

Table 4.13 Reactivity and selectivity of asymmetric Pictet-Spengler reactions with poorly reactive naphthalene substrate **299** under hydrogen bond donor (HBD)-assisted Brønsted acid catalysis. n.d. = not determined.





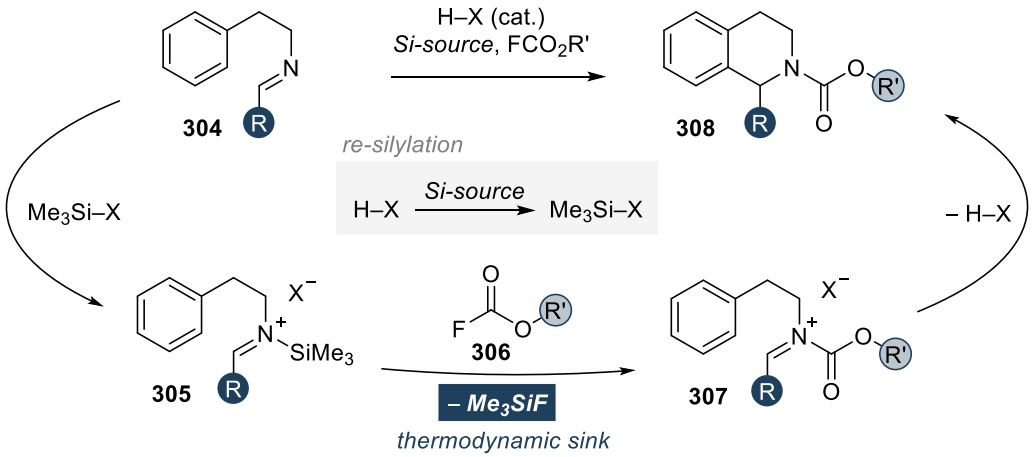
	–	296	297	298	300	301	302
TfOH	22%	38%	21%	39%	23%	35%	50%
Tf_2NH	39%	57%	39%	50%	40%	41%	50%
PADi **303**	6% (50:50 er)	19% (50:50 er)	7% (50:50 er)	21% (46:54 er)	5% (50:50 er)	7% (49:51 er)	36% (50:50 er)
IDPi **130a**	< 1% (56:44 er)	3% (55:45 er)	< 1% (56:44 er)	< 1% (54:46 er)	< 1% (55:45 er)	< 1% (52:48 er)	35% (50:50 er)
IDPi **143b**	3% (21:79 er)	4% (31:69 er)	3% (22:78 er)	7% (69:31 er)	3% (22:78 er)	2% (28:72 er)	n.d.
–	n.d.	0%	0%	0%	0%	0%	36%

To summarize, the anion recognition characteristics of HBD **298** are a sufficient fit to the general molecular structures of PADis and IDPis. Especially the induction of enantioselectivity in the reaction with PADis stands out, as it promises a novel design platform for highly reactive Brønsted acid catalysis. However, the general acidifying effects observed under HBD co-catalysis did not reach the necessary levels to provide a reactivity breakthrough for activation of simple phenethylamines in the Pictet-Spengler reactions under study.

4.3.2. Silyl Acyl Pictet-Spengler Reactions

We were interested in the design of a Pictet-Spengler reaction that would combine the advantageous modularity and confinement of the acids developed in the List group with the reactivity of Acyl Pictet-Spengler reactions starting from pre-formed imines. The traditional

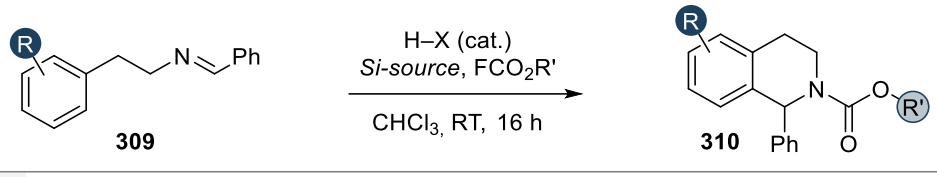
design utilizes an acyl chloride and a chloride-specific anion binding catalyst to produce an intermediate chiral ion pair.[136] Strong Brønsted acids can be transformed into their respective silylium Lewis acid form under established silylation conditions.[67,202,203] The silylated acid could form a stable Lewis acid/base adduct **305** with imine **304** (Scheme 4.11). As source for the electronically activating carbamate group, we envisioned fluoroformates **306**. The fluoride abstraction by the silylated acid would create a thermodynamic driving force, which could facilitate the formation of a high-energy iminium ion **307**. By utilization of electron-poor substituents R', the cyclization toward THIQ **308** might be enabled even with moderately nucleophilic aromatic systems. The resultant Brønsted acid after product formation would be re-silylated by a stoichiometric silicon source.



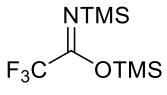
Scheme 4.11 Reaction design for a catalytic silyl acyl Pictet-Spengler reaction.

We tested our reaction design with benzaldehyde-derived imines **309**, where we focused first on the 3,4-$(OMe)_2$-substituted imine to probe the overall feasibility (Table 4.14). Bis(trimethylsilyl)trifluorosulfonamide (BSTFA) serves as a commercial non-nucleophilic silicon source. We could indeed observe the desired Pictet-Spengler reactivity by employing phenyl fluoroformate, however with poor reactivity with IDPi **130a** (entries 1–2). When we switched to ethyl fluoroformate, the reactivity was lost altogether (entries 3–5). We were however pleased to observe high reactivity in the reaction of trichloroethyl fluoroformate with catalytic amounts of Tf_2NH (entry 6). We hypothesized that the silicon source might be able to intercept the formed iminium intermediate nucleophilically. We therefore tested other, hypothetically less nucleophilic sources of silicon, and did indeed see a fluctuation in the reactivity profile (entries 7–9). When we tested IDPis **130a** and **143a**, bis(trimethylsilyl)trifluorosulfonamide (BSTFS) gave the best yield of the product, albeit in poor selectivity (entries 10–17). Finally, having established the general feasibility of the reaction design, we tested unsubstituted phenethylamine-derived imine **309** (R = H) under the most reactive reaction conditions with Tf_2NH as catalyst. However, even at elevated temperatures, the desired product could not be detected (entries 18–20).

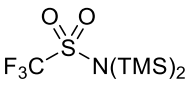
Table 4.14 Screening of reaction conditions for catalytic silyl acyl Pictet-Spengler reactions. BSTFA = *N,O*-bis(trimethylsilyl)trifluoroacetamide. BSTFS = bis(trimethylsilyl)trifluorosulfonamide. [a]Reaction was conducted in PhMe at 80 °C.



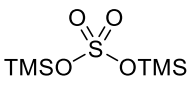
Si-source



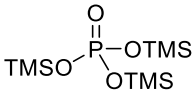
BSTFA



BSTFS



TMS_2SO_4



TMS_3PO_4

entry	H–X	*Si-source*	R	R'	yield	er
1	Tf_2NH	BSTFA	3,4-$(OMe)_2$	Ph	83%	–
2	**130a**	BSTFA	3,4-$(OMe)_2$	Ph	7%	63:37
3	Tf_2NH	BSTFA	3,4-$(OMe)_2$	Et	0%	–
4	**130a**	BSTFA	3,4-$(OMe)_2$	Et	0%	n.d.
5	**143a**[6,6']	BSTFA	3,4-$(OMe)_2$	Et	0%	n.d
6	Tf_2NH	BSTFA	3,4-$(OMe)_2$	CH_2CCl_3	88%	–
7	Tf_2NH	BSTFS	3,4-$(OMe)_2$	CH_2CCl_3	94%	–
8	Tf_2NH	TMS_2SO_4	3,4-$(OMe)_2$	CH_2CCl_3	18%	–
9	Tf_2NH	TMS_3PO_4	3,4-$(OMe)_2$	CH_2CCl_3	28%	–
10	**130a**	BSTFA	3,4-$(OMe)_2$	CH_2CCl_3	0%	n.d.
11	**130a**	BSTFS	3,4-$(OMe)_2$	CH_2CCl_3	68%	48:52
12	**130a**	TMS_2SO_4	3,4-$(OMe)_2$	CH_2CCl_3	20%	50:50
13	**130a**	TMS_3PO_4	3,4-$(OMe)_2$	CH_2CCl_3	7%	46:54
14	**143a**	BSTFA	3,4-$(OMe)_2$	CH_2CCl_3	0%	n.d.
15	**143a**	BSTFS	3,4-$(OMe)_2$	CH_2CCl_3	28%	54:46
16	**143a**	TMS_2SO_4	3,4-$(OMe)_2$	CH_2CCl_3	18%	50:50
17	**143a**	TMS_3PO_4	3,4-$(OMe)_2$	CH_2CCl_3	6%	52:48
18	Tf_2NH	BSTFA	H	CH_2CCl_3	0%	–
19[a]	Tf_2NH	BSTFA	H	CH_2CCl_3	0%	–
20[a]	Tf_2NH	BSTFS	H	CH_2CCl_3	0%	–

In summary, we were able to conceive a new silyl acyl Pictet-Spengler reaction with strong and confined acids. The reactivity profile appears promising for activated nucleophilic arenes. The design could however not be extended to the desired unsubstituted phenethylamines. We therefore conclude that the catalytically generated *N*-acyliminium ions are still not sufficiently electrophilic to induce cyclization from poorly nucleophilic arenes.

5. SUMMARY

Our interest in catalytic asymmetric Pictet-Spengler reactions for the synthesis of isoquinoline alkaloids led us down a research path shaped by the interplay of reactivity and selectivity in the realm of Brønsted acid catalysis. Specifically, the reduced nucleophilicity of the reacting arene in the reaction toward THIQs as opposed to THBCs required the development of an *N*-acyl Pictet-Spengler reaction. The recognition that high-energy *N*-carbamoyl iminium ions are competent intermediates for the desired reactivity was promptly countered by the understanding that their generation and control requires thus far unprecedentedly active catalysts. We were able to tackle this specific methodological problem by means of novel catalyst design. In particular, we postulated that non-obvious cation-π interactions between a catalysts counteranion and the cationic reaction intermediates might facilitate reactivity and selectivity. In this regard, we recognized that electron-rich heterocyclic IDPi catalysts – a previously unexplored class of IDPis – represented a rewarding chemical space for catalyst development. After systematic investigation and synthesis of more than 60 new confined Brønsted acids, we were able to identify a single IDPi to enable the desired asymmetric reaction. The structure comprises a 2-benzofuranyl substituent, which is primarily accountable for high catalyst activity. A sterically demanding as well as highly dispersive 2-methyladamantyl substituent was furthermore introduced to ensure high selectivity in a general range of substrates (Figure 5.1).

During the exploration of the reaction scope, we found that discrete conditions were required for aliphatic and aromatic targets. Aliphatic aldehydes could be reacted in an extraordinarily general fashion, enabling access to a total of 26 different products, including benzyl, homobenzyl, hydrocarbon, or oxygenated THIQs. Even small and unbiased substrates such as acetaldehyde were controlled with high stereochemical precision. Aromatic aldehydes on the other hand remained almost unreactive and had to be converted to the corresponding dimethyl acetals for enhanced reactivity. Nevertheless, the identical IDPi catalyst imparts excellent enantiocontrol onto 1-aryl THIQs, as demonstrated in the synthesis of 12 aromatic products.

Finally, we were able to illustrate the synthetic utility of the obtained enantioenriched THIQ products in the total or formal synthesis of 11 natural products. Importantly, the accessible molecular structures encompass not only the parent THIQs and simple derivatives thereof, but also protoberberines, morphinans, androcymbines, and aporphines. Key to the success of the respective syntheses was the facile cleavage or reduction of the carbamate protecting group. Subsequent selective ring-forming reactions, either in a redox-neutral or an oxidative fashion, gave rise to a range of natural products, featuring the intermediate tetrahydroisoquinolines as a key diversification point in the biomimetic total synthesis of naturally occurring isoquinoline alkaloids.

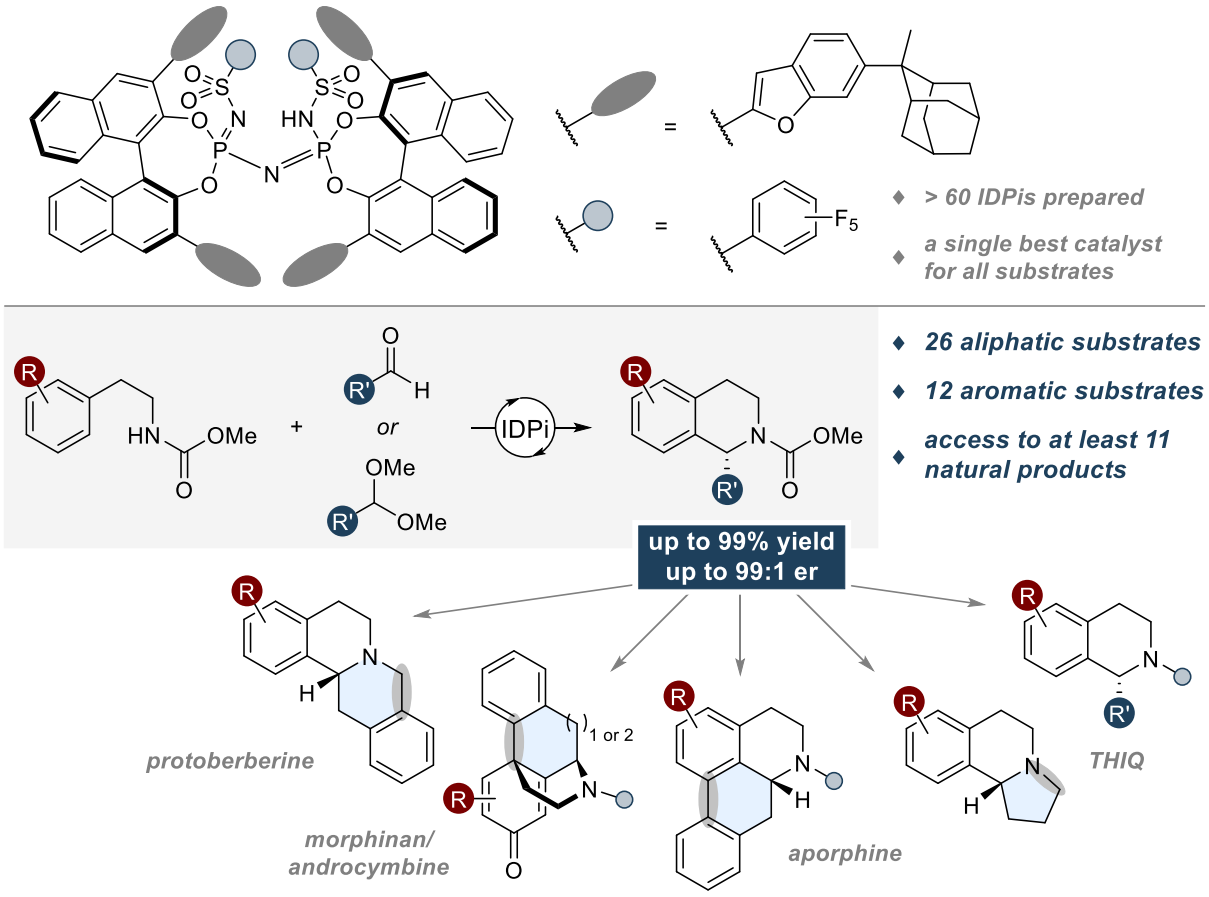


Figure 5.1 Summary of the developed catalytic asymmetric Pictet-Spengler reaction as well as the completed formal and total synthesis of naturally occurring alkaloid classes.

We conducted extensive experimental studies to elucidate the mechanism of the newly developed catalytic asymmetric Pictet-Spengler reaction (Figure 5.2). Our investigation included the successful determination of the order in substrates and catalyst, a Hammett study, measurement of kinetic isotope effects, variable temperature experiments combined with catalyst stability studies and Eyring plots, as well as an isotopic scrambling control experiment. Overall, we were thus able to shed light on the nature of the catalytic methodology on a molecular level. While the KIE studies substantiate that the final deprotonation/rearomatization step is partially rate-limiting in the reaction of aliphatic aldehydes, our Hammett plot proved that the formation of the intermediate *N*-acyliminium ion contributes to the overall rate as well. Under the studied conditions, it thus seems reasonable to conclude that the nucleophilic attack of the aromatic ring with formation of the Wheland intermediate is fast in comparison to both the preceding and following reaction steps. The final deprotonation must consequently be the enantiodetermining step. The resultant short lifetime of the iminium ion is reflected in the non-observability of an off-cycle enamine species. In the case of aromatic dimethylacetals, the rate-limiting step is altered to the formation of the reactive oxocarbenium ion from the acetal.

Our Eyring studies corroborate a strong dissimilarity between our newly developed electron-rich IDPi catalysts and the similarly reactive electron-poor catalysts. In line with the extracted thermodynamic data on the nature of the transition states, benzofuran-containing catalysts purportedly allow for enthalpic stabilization of positively charged intermediates through cation-π interactions or other attractive non-covalent forces. The resultant highly organized transition states are entropically disfavored. The observed rate-enhancement in comparison to commonly employed IDPi catalysts could thus be accounted for, as this stabilization is proposedly diminished in electronically neutral and electron-poor catalysts. Furthermore, preliminary DFT calculations on the transition state of the enantio-determining deprotonation step support our view on the relevance of stabilizing cation-π interactions offered by the ideal catalysts.

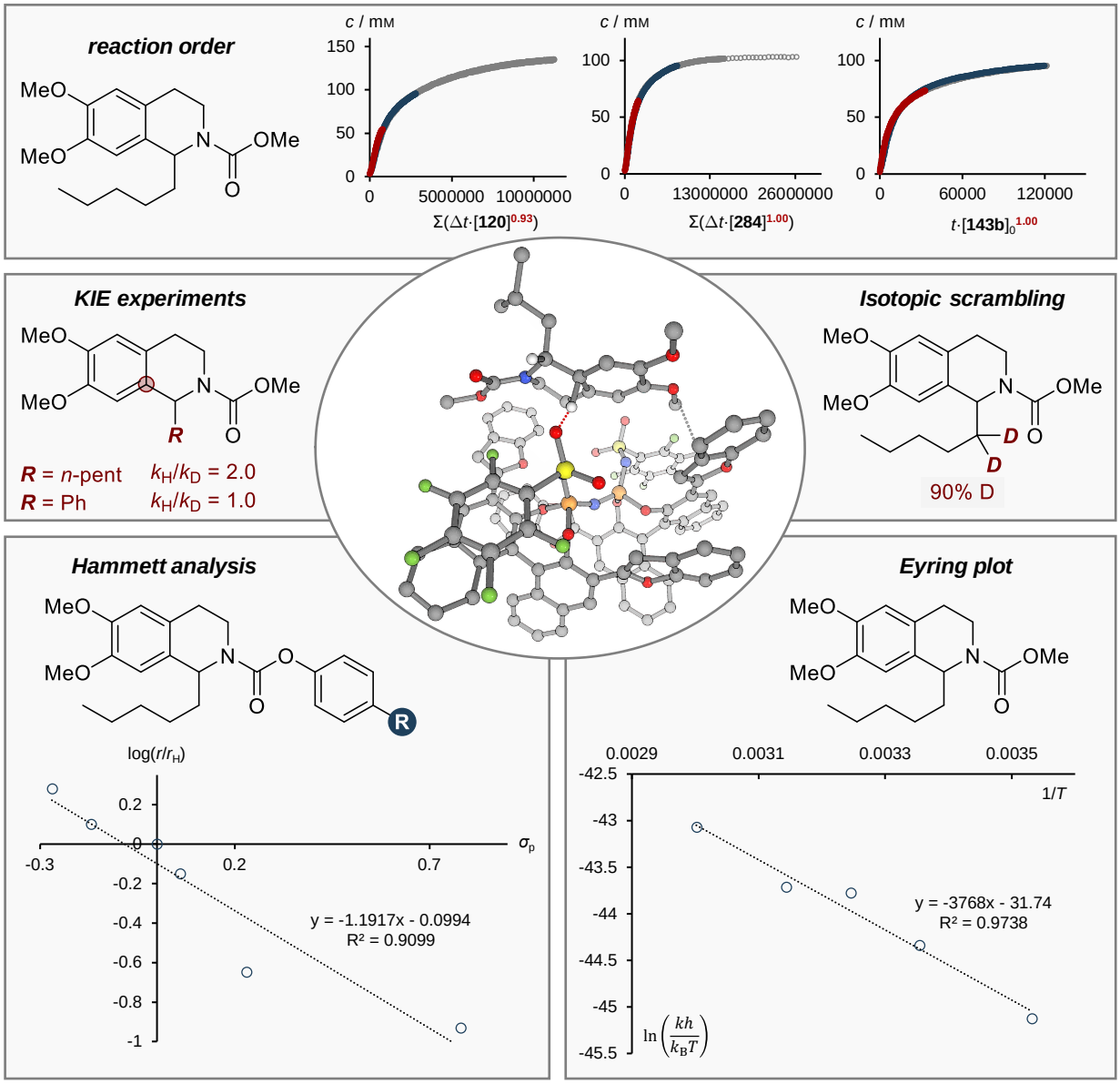


Figure 5.2 Summary of experimental and computational studies on the mechanism of the catalytic asymmetric Pictet-Spengler reaction.

Finally, we explored the general reactivity profile of unsubstituted phenethylamines under reformed reaction conditions. While we were unable to unlock catalytic activity by application of electron-poor carbamates, we recognized that highly electrophilic glyoxylate-derived iminium ions undergo cyclization toward the Pictet-Spengler product, if highly acidic Brønsted acid catalysts are employed. However, even with the most active IDPi catalysts, only trace reactivity could be observed. We therefore chose to explore novel reaction designs with the goal to unlock catalytic reactivity in poorly nucleophilic phenethylamines (Figure 5.3). To this end, we have developed and tested two novel approaches for catalytic Pictet-Spengler reactions. While the application of HBDs as co-catalysts for asymmetric Brønsted acid catalysis does offer an improvement in activity, the effect was not pronounced enough to unlock new substrate classes. The significant effects on enantioselectivity in some reactions served as an indirect proof for the general viability of our reaction design and the proposed supramolecular interactions of the catalysts. Similarly, the silyl acyl Pictet-Spengler reaction did provide the desired THIQ products in good to excellent yields for the activated substrate (R = 3,4-$(OMe)_2$). However, the necessary reactivity boost for truly unactivated phenethylamines (R = H) was not observed in any reaction under study.

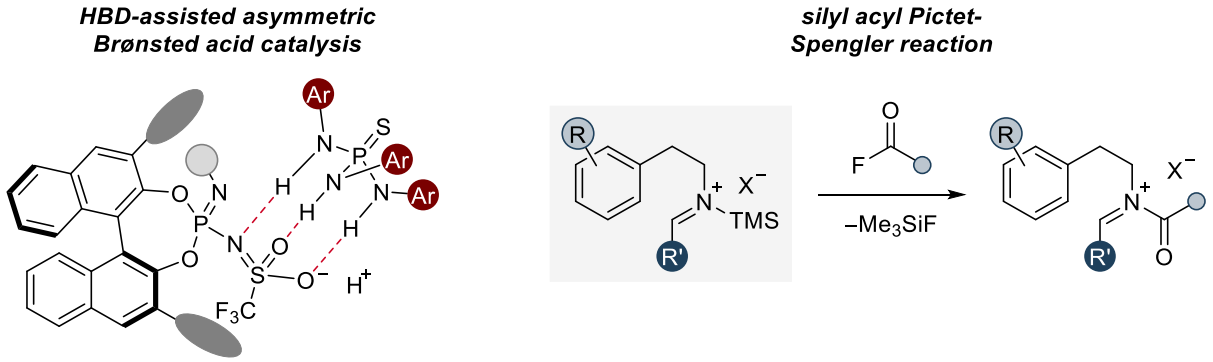


Figure 5.3 Conceptually novel reaction designs for enhancing catalytic Pictet-Spengler reactivity.

6. OUTLOOK

We were able to elucidate mechanistic details of the developed Pictet-Spengler methodology through exhaustive experimental studies. Nevertheless, a necessity for further studies on the catalytic system remains. Primarily, the acidity of benzofuran-substituted IDPi catalysts could not be confirmed yet, but can be expected to contribute significantly to the observed reaction rate. Especially a comparison to similar catalyst structures in a rate/acidity plot would offer valuable insights into the mechanistic nuances beyond molecular acidity. Further computational studies could be conducted to prove the experimentally suggested cation-π interactions and additional stabilization energies *in silico*.

Future innovations in the field of asymmetric Brønsted acid catalysis will be without a doubt connected to the quest for increasing the molecular acidity of chiral catalysts. With regard to catalytic asymmetric Pictet-Spengler reactions, we were able to demonstrate promising reactivity in the transformation of *N*-carbamoyl phenethylamines with glyoxylates. However, the success of this reaction relies on the high electrophilicity of a specific aldehyde class. The system is thus deprived of the valuable generality of Pictet-Spengler reactions. Nevertheless, similarly reactive iminium ions might be generated from a scope of aliphatic and aromatic aldehydes by application of highly electron-withdrawing activating groups such as *N*-Ts or *N*-Tf. In this regard, novel catalysts with significantly increased molecular acidity might hold promise for future discoveries.

The presented Pictet-Spengler reaction of oxygenated phenethylamines has proven highly general for a broad scope of aliphatic and aromatic substrates. We were able to demonstrate singular natural product synthesis examples for different families of alkaloids. All of the synthetically accessible products were obtained *via* a small number of conventional chemical transformations. Our methodology might however also find application in total synthesis campaigns targeting highly complex molecular structures (Figure 6.1). The implementation of a catalytic asymmetric Pictet-Spengler reaction might potentially enable access to fascinating targets such as the bis-benzylisoquinoline dauricine (**311**), the C_2-symmetric isoquinoline argemonine (**312**), or the unusual *stephania excentrica* alkaloid excentricine (**313**).[204]

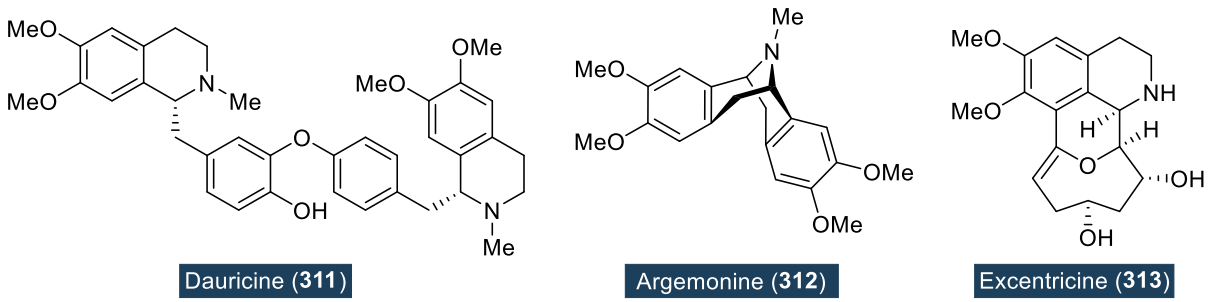


Figure 6.1 Complex natural products that are potentially accessible through the developed catalytic asymmetric Pictet-Spengler reaction.

The main body of this thesis focused on accessing naturally occurring alkaloid structures in a catalytic fashion. In particular, the asymmetric synthesis of the THIQ core was found to be a bottleneck of all previous total synthesis campaigns, which usually rely on a stepwise Bischler-Napieralski sequence. Nevertheless, the downstream elaboration of benzyl tetrahydroisoquinolines into complex structures such as aporphines, morphinans, or berberines also suffers from severe selectivity problems. As exemplified in the landmark morphinan total syntheses by Rice,[105] or the modern approach by Opatz and Waldvogel[110], the inherent *para*-selectivity in oxidative phenol couplings is *de facto* overcome by means of substrate engineering. Consequently, the overall synthetic efficiency is diminished, due to the requirement for additional steps and reagents for installing and removing functional handles. This synthetic problem might theoretically be embarked upon by employing confined organic Brønsted acids (Figure 6.2). Regioselective transformations of benzylisoquinoline alkaloids **314** could theoretically be achieved by designing and modular tuning of active catalytic sites, thus enabling an "ideal" catalytic and asymmetric synthesis of natural isoquinoline alkaloids.

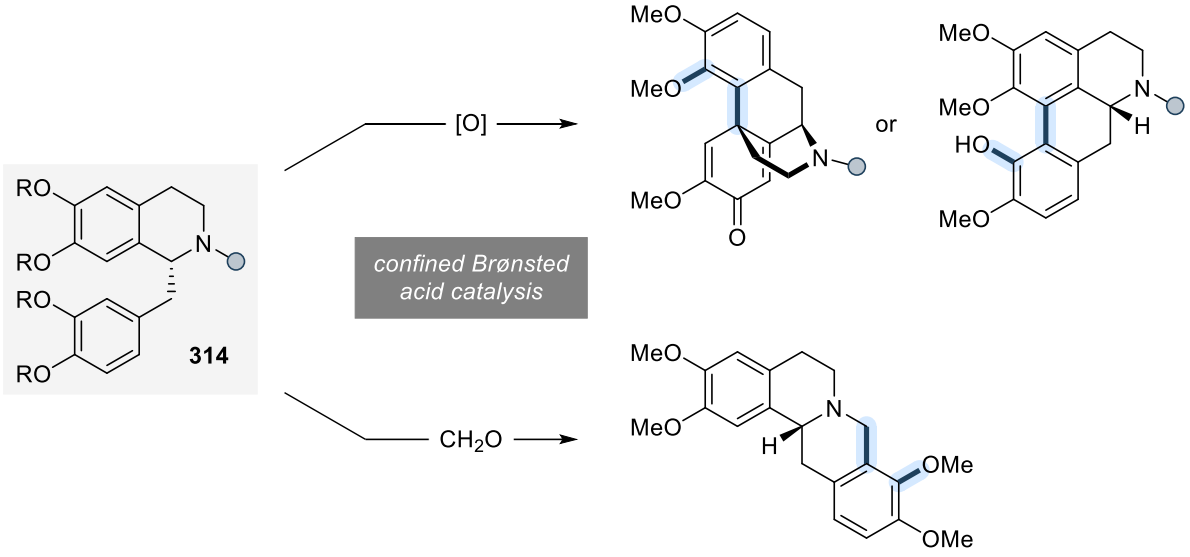
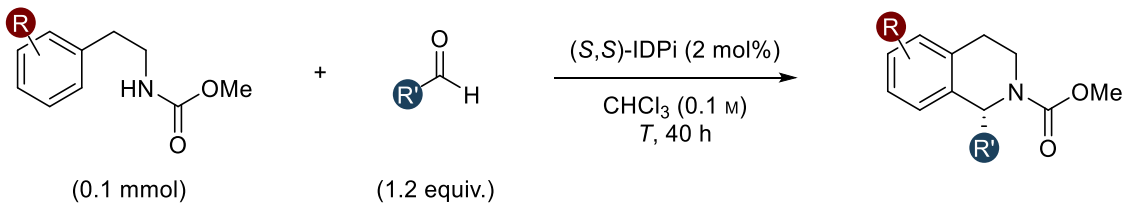


Figure 6.2 Proposed catalyst-controlled regioselective transformations of benzyl tetrahydroisoquinolines **314** toward naturally occurring alkaloids.

7. EXPERIMENTAL SECTION

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. All solvents used in the reactions were distilled from appropriate drying agents prior to use. Reactions were monitored by thin layer chromatography (TLC) on silica gel pre-coated glass (0.2 mm, Macherey-Nagel). Visualization was accomplished by irradiation with UV light at 254 nm and/or cerium ammonium molybdate (CAM) stain and/or $KMnO_4$ stain. Column chromatography was carried out using Merck (60 Å, 230−400 mesh, particle size 0.040−0.063 mm) or VWR (40−63 μm) silica gel, using technical grade solvents. Automated reversed phase column chromatography was conducted on a Biotage Isolera Spektra Four system, using SNAP Ultra C18 HP-Sphere 25 μm reversed phase cartridges. All reported yields refer to chromatographically and spectroscopically pure compounds. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-600, AV-500, AV-400, or AV-300 spectrometer in deuterated solvents. ^{1}H chemical shifts (δ) are reported in ppm relative to residual protonated solvent resonance employed as the internal standard ($CDCl_3$ δ = 7.26, CD_2Cl_2 δ = 5.32, DMSO δ = 2.50, CD_3OD δ = 3.31 ppm, CD_3CN δ = 1.94 ppm, C_6D_6 δ = 7.16 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, s = sextet, hept = heptet, m = multiplet, br = broad), coupling constants (Hz), and integration. ^{13}C chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$ δ = 77.16, CD_2Cl_2 δ = 54.00, DMSO δ = 39.52, CD_3OD δ = 49.00 ppm, CD_3CN δ = 1.32 ppm, C_6D_6 δ = 128.06 ppm). High resolution mass spectra were determined on a Bruker APEX III FTMS (7 T magnet). Optical rotations were determined with an Autopol IV polarimeter (Rudolph Research Analytical) at 589 nm and 25 °C. Data are reported as follows: α_λ^T, concentration *c* (g/100 mL), and solvent. Enantiomeric ratios (er) were determined by HPLC analysis employing a chiral stationary phase column specified in the individual experiment, by comparing the samples with the corresponding racemic mixtures. Electrochemical transformations were performed using an IKA ElectraSyn 2.0 System in an undivided cell with Electrodes purchased from IKA.

7.1. Asymmetric Pictet-Spengler Reactions



General procedure for reaction optimization

An oven-dried GC vial equipped with a magnetic stir bar was charged with the catalyst (2 mol%) and placed under argon. Substrate (0.025 mmol) and aldehyde (1.2 eq.) were dissolved

separately in the reaction solvent and sequentially added to the catalyst. The mixture was then stirred at the appropriate temperature for 16 h (for reactions at reduced *T*, the reaction was started at –78 °C and then warmed to the reaction temperature). The reaction was quenched by addition of Et_3N (10 µL) followed by addition of Ph_3CH as internal standard (1.0 M in PhMe, 25 µL, 1.0 eq.). $CDCl_3$ (0.5 mL) was added to the mixture, and 0.5 mL were analyzed by ^{1}H-NMR to determine the product yield. The remaining solution was purified by preparative thin layer chromatography to give the enantiomeric ratio after HPLC analysis.

General procedure a (liquid aliphatic aldehydes)

Carbamate (0.10 mmol) and (*S*,*S*)-IDPi catalyst **220b** (4.39 mg, 0.002 mmol, 2 mol%) were weighed into a septum-capped 4 mL vial equipped with a magnetic stir bar, placed under argon, and dissolved in dry $CHCl_3$ (1.0 mL). The corresponding aldehyde (0.12 mmol, 1.2 eq.) was subsequently added *via* Hamilton syringe, the vial was sealed with Parafilm©, and the mixture was stirred at RT for 40 h. The reaction was quenched by addition of 5 drops of Et_3N and concentrated on silica. The product was isolated by silica gel flash column chromatography. **for deviations from the general procedure, see the corresponding entries.*

General procedure b (solid aliphatic aldehydes)

Carbamate (0.10 mmol) and (*S*,*S*)-IDPi catalyst **220b** (4.39 mg, 0.002 mmol, 2 mol%) were weighed into a septum-capped 4 mL vial equipped with a magnetic stir bar and placed under argon. The corresponding aldehyde (0.132 mmol, 1.32 eq.) was placed in an oven-dried GC-vial, argonated, and dissolved in dry $CHCl_3$ (1.1 mL). Of the thus prepared aldehyde stock solution, 1.0 mL (0.12 mmol, 1.2 eq.) were added to the substrate and catalyst under argon, the vial was sealed with Parafilm©, and the mixture was stirred at RT for 40 h. The reaction was quenched by addition of 5 drops of Et_3N and concentrated on silica. The product was isolated by silica gel flash column chromatography. **for deviations from the general procedure, see the corresponding entries.*

General procedure c (liquid aromatic dimethylacetals)

Carbamate (0.10 mmol) and (*S*,*S*)-IDPi catalyst **220b** (4.39 mg, 0.002 mmol, 2 mol%) were weighed into a septum-capped 4 mL vial equipped with a magnetic stir bar, placed under argon, and dissolved in dry CyH (0.8 mL) and Et_2O (0.2 mL). The corresponding acetal (0.12 mmol, 1.2 eq.) was subsequently added *via* Hamilton syringe, the vial was sealed with Parafilm©, and the mixture was stirred at RT for 40 h. The reaction was quenched by addition of 5 drops of Et_3N and concentrated on silica. The product was isolated by silica gel flash column chromatography. **for deviations from the general procedure, see the corresponding entries.*

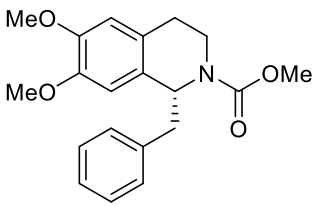
General procedure d (solid aromatic dimethylacetals)

Carbamate (0.10 mmol) and (*S*,*S*)-IDPi catalyst **220b** (4.39 mg, 0.002 mmol, 2 mol%) were weighed into a septum-capped 4 mL vial equipped with a magnetic stir bar, placed under argon, and suspended in dry CyH (0.8 mL). The corresponding acetal (0.18 mmol, 1.8 eq.) was placed in an oven-dried GC-vial, argonated, and dissolved in dry Et_2O (0.3 mL). Of the thus prepared acetal stock solution, 0.2 mL (0.12 mmol, 1.2 eq.) were added to the substrate and catalyst under argon, the vial was sealed with Parafilm©, and the mixture was stirred at RT for 40 h. The reaction was quenched by addition of 5 drops of Et_3N and concentrated on silica. The product was isolated by silica gel flash column chromatography. **for deviations from the general procedure, see the corresponding entries.*

Racemate synthesis

The corresponding racemates for determination of the enantiomeric access by HPLC-analysis were synthesized by reacting carbamate (0.1 mmol) with aldehyde (1.2 mmol) and catalytic amounts of Tf_2NH (7.5 mol%) in dry CH_3CN (1.0 mL) for 16 h. For acid sensitive TBS-protected products **226d** and **226e**, $CHCl_3$ was used instead of CH_3CN.

methyl (*R*)-1-benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (226a)



The reaction was performed according to **general procedure a** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and phenylacetaldehyde (14 µL, 0.12 mmol, 1.2 eq.). Purification by silica gel flash column chromatography (hex/EtOAc 2:1) afforded the product as a colorless oil (30.4 mg, 89 µmol, 89%).

R_F (hex/EtOAc 2:1) = 0.38.

^{1}H-NMR (501 MHz, $CDCl_3$): Mixture of two rotamers with a ratio ≈ 55:45. δ = 7.30–7.16 (m, $3H_{all}$), 7.13–7.06 (m, $2H_{all}$), 6.60 (s, $1H_{maj}$), 6.57 (s, $1H_{min}$), 6.26 (s, $1H_{maj}$), 6.09 (s, $1H_{min}$), 5.26 (dd, J = 8.1, 5.7 Hz, $1H_{min}$), 5.15 (t, J = 7.0 Hz, $1H_{maj}$), 4.17 (ddd, J = 13.1, 5.9, 3.6 Hz, $1H_{maj}$), 3.88–3.80 (m, $3H_{all}$ + $1H_{min}$), 3.71 (s, $3H_{min}$), 3.67 (s, $3H_{maj}$), 3.56 (s, $3H_{min}$), 3.49 (s, $3H_{maj}$), 3.42–3.29 (m, $1H_{all}$), 3.18 (dd, J = 13.1, 5.6 Hz, H_{min}), 3.09 (dd, J = 13.4, 7.4 Hz, $1H_{maj}$), 2.97 (ddd, J = 13.0, 9.9, 7.3 Hz, $1H_{all}$), 2.86 (ddd, J = 16.3, 10.5, 5.9 Hz, $1H_{maj}$), 2.77 (ddd, J = 15.2, 9.2, 5.6 Hz, $1H_{min}$), 2.61 (ddt, J = 26.4, 15.8, 4.5 Hz, $1H_{all}$).

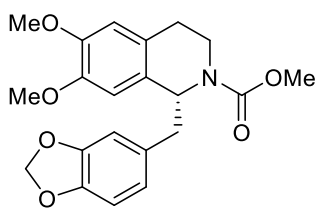
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.12, 156.07, 147.91, 147.73, 147.09, 146.86, 138.39, 130.03, 129.81, 128.35, 128.30, 128.23, 126.54, 126.47, 126.40, 126.15, 111.48, 111.14, 110.73, 110.35, 56.40, 56.37, 55.97, 55.95, 55.87, 55.71, 52.69, 52.49, 43.22, 42.82, 39.34, 38.18, 28.23, 28.13.

CI-HRMS: calculated for $C_{20}H_{24}N_1O_4$ ($[M+H]^+$): 342.169983, found: 342.170590.

HPLC (OD-3, *n*-heptane/*i*-PrOH 95:5, 298 K, 283 nm): t_R (minor) = 9.4 min, t_R (major) = 10.7 min, er = 97:3 (94% ee).

$[\alpha]_D^{25}$ = −69.6 (*c* = 0.23, $CHCl_3$).

methyl (*R*)-1-(benzo[*d*][1,3]dioxol-5-ylmethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (226b)



The reaction was performed according to **general procedure b** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and 2-(benzo[*d*][1,3]dioxol-5-yl)acetaldehyde (**224b**, 21.7 mg, 0.132 mmol, 1.32 eq.). Purification by silica gel flash column chromatography (DCM/EtOAc 19:1 to 9:1) afforded the product as a white foam (31.5 mg, 82 µmol, 82%).

R_F (DCM/EtOAc 9:1) = 0.62.

^{1}H-NMR (501 MHz, $CDCl_3$): Mixture of two rotamers with a ratio ≈ 55:45. δ = 6.71 (d, J = 7.9 Hz, $1H_{maj}$), 6.68 (d, J = 7.9 Hz, $1H_{min}$), 6.63–6.56 (m, $2H_{all}$), 6.55–6.48 (m, $1H_{all}$), 6.31 (s, $1H_{maj}$), 6.22 (s, $1H_{min}$), 5.94–5.86 (m, $2H_{all}$), 5.20 (t, J = 6.7 Hz, $1H_{min}$), 5.10 (t, J = 6.9 Hz, $1H_{maj}$), 4.14 (ddd, J = 13.2, 6.0, 3.7 Hz, $1H_{maj}$), 3.85 (s, $3H_{maj}$), 3.86–3.79 (m, $3H_{min}$ + $1H_{min}$), 3.72 (s, $3H_{maj}$), 3.71 (s, $3H_{min}$), 3.66 (s, $3H_{min}$), 3.57 (s, $3H_{maj}$), 3.34 (ddd, J = 13.4, 9.2, 4.6 Hz, $1H_{min}$), 3.27 (ddd, J = 13.2, 10.5, 4.4 Hz, $1H_{maj}$), 3.07 (dd, J = 13.4, 5.8 Hz, $1H_{min}$), 3.00 (dd, J = 13.6, 7.3 Hz, $1H_{maj}$), 2.94–2.81 (m, $1H_{all}$ + $1H_{maj}$), 2.76 (ddd, J = 15.2, 9.2, 5.6 Hz, $1H_{min}$), 2.60 (ddt, J = 25.7, 15.8, 4.5 Hz, $1H_{all}$).

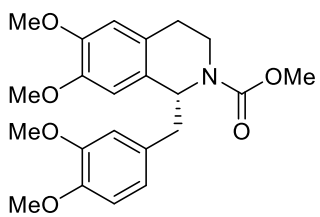
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.14, 156.08, 147.96, 147.81, 147.58, 147.52, 147.15, 147.02, 146.22, 146.21, 132.14, 128.37, 128.18, 126.47, 126.26, 122.92, 122.83, 111.54, 111.22, 110.73, 110.36, 110.12, 108.16, 108.11, 100.93, 100.88, 56.43, 56.34, 55.98, 55.88, 52.72, 52.60, 42.94, 42.48, 39.33, 38.27, 28.27, 28.10.

ESI-HRMS: calculated for $C_{21}H_{23}N_1O_6Na_1$ ($[M+Na]^+$): 408.141758, found: 408.141780.

HPLC (OD-3, *n*-heptane/*i*-PrOH 90:10, 298 K, 287 nm): t_R (minor) = 9.0 min, t_R (major) = 11.0 min, er = 97:3 (94% ee).

$[\alpha]_D^{25}$ = −72.9 (*c* = 0.13, $CHCl_3$).

methyl (*R*)-1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (226c)



The reaction was performed according to **general procedure b** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and 2-(3,4-dimethoxyphenyl)acetaldehyde (**224c**, 23.8 mg, 0.132 mmol, 1.32 eq.). Purification by silica gel flash column chromatography (hex/EtOAc 1:1) afforded the product as a colorless oil (32.0 mg, 80 µmol, 80%).

R_F (hex/EtOAc 1:1) = 0.30.

^{1}H-NMR (501 MHz, $CDCl_3$): Mixture of two rotamers with a ratio ≈ 1:1. δ = 6.75 (dd, J = 19.0, 8.1 Hz, $1H_{all}$), 6.66–6.53 (m, $3H_{all}$), 6.34 (s, 1H), 6.18 (s, 1H), 5.23 (dd, J = 7.9, 5.4 Hz, 1H), 5.12

(t, J = 6.9 Hz, 1H), 4.13 (ddd, J = 13.3, 6.0, 3.8 Hz, 1H), 3.84 (s, $3H_{all}$), 3.83 (s, $3H_{all}$), 3.80 (s, 3H), 3.77 (s, 3H), 3.72 (s, $3H_{all}$), 3.62 (s, 3H), 3.54 (s, 3H), 3.32 (ddd, J = 13.3, 9.1, 4.7 Hz, 1H), 3.24 (ddd, J = 13.1, 10.5, 4.4 Hz, 1H), 3.10 (dd, J = 13.3, 5.4 Hz, 1H), 3.02 (dd, J = 13.6, 7.1 Hz, 1H), 2.94 (dd, J = 13.5, 7.2 Hz, $1H_{all}$), 2.83 (ddd, J = 16.2, 10.4, 5.9 Hz, 1H), 2.74 (ddd, J = 15.3, 9.0, 5.6 Hz, 1H), 2.55 (ddt, J = 25.7, 15.8, 4.6 Hz, $1H_{all}$).

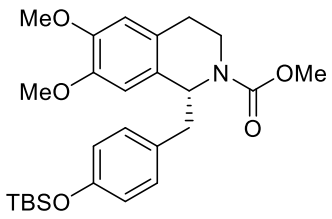
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.17, 156.11, 148.78, 148.72, 147.93, 147.84, 147.76, 147.74, 147.17, 146.94, 130.86, 128.41, 128.26, 126.57, 126.33, 122.12, 121.98, 112.97, 111.51, 111.17, 111.02, 110.80, 110.39, 56.27, 56.05, 55.98, 55.90, 55.85, 52.70, 52.60, 42.76, 42.31, 39.41, 38.27, 28.21, 28.09.

ESI-HRMS: calculated for $C_{22}H_{27}N_1O_6Na_1$ ($[M+Na]^+$): 424.173058, found: 424.173050.

HPLC (OD-3, *n*-heptane/*i*-PrOH 90:10, 298 K, 282 nm): t_R (minor) = 13.9 min, t_R (major) = 15.8 min, er = 96.5:3.5 (93% ee).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = −51.7 (*c* = 0.14, $CHCl_3$).

methyl (*R*)-1-(4-((*tert*-butyldimethylsilyl)oxy)benzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (226d)



The reaction was performed according to **general procedure b** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and 2-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)acetaldehyde (**224d**, 33.1 mg, 0.132 mmol, 1.32 eq.). Purification by silica gel flash column chromatography (hex/EtOAc 2:1) afforded the product as a colorless oil (36.7 mg, 78 µmol, 78%).

$\boldsymbol{R_F}$ (hex/EtOAc 2:1) = 0.64.

^{1}H-NMR (501 MHz, $CDCl_3$): Mixture of two rotamers with a ratio ≈ 55:45. δ = 6.93 (dd, J = 12.1, 8.0 Hz, $2H_{all}$), 6.72 (dd, J = 16.0, 8.0 Hz, $2H_{all}$), 6.59 (s, $1H_{maj}$), 6.57 (s, $1H_{min}$), 6.32 (s, $1H_{maj}$), 6.19 (s, $1H_{min}$), 5.21 (dd, J = 7.9, 5.4 Hz, $1H_{min}$), 5.10 (t, J = 6.8 Hz, $1H_{maj}$), 4.14 (ddd, J = 13.2, 5.9, 3.7 Hz, $1H_{maj}$), 3.87–3.76 (m, $3H_{all}$ + $1H_{min}$), 3.71 (d, J = 2.1 Hz, $3H_{all}$), 3.63 (s, $3H_{min}$), 3.53 (s, $3H_{maj}$), 3.38–3.25 (m, $1H_{all}$), 3.08 (dd, J = 13.3, 5.4 Hz, $1H_{min}$), 3.01 (dd, J = 13.6, 7.3 Hz, $1H_{maj}$), 2.96–2.88 (m, $1H_{all}$), 2.84 (ddd, J = 16.3, 10.5, 5.9 Hz, $1H_{maj}$), 2.74 (ddd, J = 15.1, 9.1, 5.6 Hz, $1H_{min}$), 2.61 (dt, J = 16.0, 4.1 Hz, $1H_{maj}$), 2.54 (dt, J = 15.8, 5.0 Hz, $1H_{min}$), 0.97 (s, $9H_{maj}$), 0.97 (s, $9H_{min}$), 0.17 (s, $6H_{maj}$), 0.16 (s, $6H_{min}$).

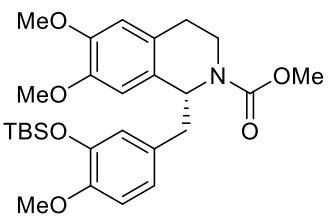
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.11, 154.42, 154.37, 147.89, 147.71, 147.13, 146.93, 131.09, 131.06, 130.93, 130.72, 128.54, 128.41, 126.47, 126.25, 119.94, 119.87, 111.49, 111.15, 110.76, 110.38, 56.45, 55.98, 55.95, 55.82, 52.67, 52.55, 42.47, 42.08, 39.40, 38.24, 28.25, 28.14, 25.82, 18.34, -4.30.

ESI-HRMS: calculated for $C_{26}H_{37}N_1Na_1O_5Si_1$ ($[M+Na]^+$): 494.23332, found: 494.23359.

HPLC (OD-3, *n*-heptane/*i*-PrOH 90:10, 298 K, 282 nm): t_R (minor) = 5.6 min, t_R (major) = 6.8 min, er = 97:3 (94% ee).

$[\alpha]_D^{25}$ = −59.4 (*c* = 0.36, $CHCl_3$).

methyl (*R*)-1-(3-((*tert*-butyldimethylsilyl)oxy)-4-methoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (226e)



The reaction was performed according to general procedure **b** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and 2-(4-((*tert*-butyldimethylsilyl)oxy)-3-methoxyphenyl)acetaldehyde (224e, 37.0 mg, 0.132 mmol, 1.32 eq.). Purification by silica gel flash column chromatography (hex/EtOAc 2:1) afforded the product as a colorless oil (40.1 mg, 80 µmol, 80%).

R_F (hex/EtOAc 2:1) = 0.42.

^{1}H-NMR (501 MHz, $CDCl_3$): Mixture of two rotamers with a ratio ≈ 55:45. δ = 6.73 (d, J = 8.2 Hz, $1H_{maj}$), 6.70 (d, J = 8.6 Hz, $1H_{min}$), 6.63 (d, J = 2.2 Hz, $1H_{maj}$), 6.60–6.53 (m, $2H_{all}$ + $1H_{min}$), 6.29 (s, $1H_{maj}$), 6.26 (s, $1H_{min}$), 5.22 (dd, J = 7.6, 5.4 Hz, $1H_{min}$), 5.10 (t, J = 6.7 Hz, $1H_{maj}$), 4.11 (ddd, J = 13.3, 5.8, 3.5 Hz, $1H_{maj}$), 3.89–3.78 (m, $3H_{all}$ + $1H_{min}$), 3.76 (s, $3H_{maj}$), 3.75 (s, $3H_{min}$), 3.71 (s, $3H_{min}$), 3.70 (s, $3H_{maj}$), 3.66 (s, $3H_{min}$), 3.59 (s, $3H_{maj}$), 3.22 (ddt, J = 12.9, 10.2, 3.2 Hz, $1H_{all}$), 3.08–2.80 (m, $2H_{all}$ + $1H_{maj}$), 2.72 (ddd, J = 15.3, 9.3, 5.6 Hz, $1H_{min}$), 2.60 (dt, J = 15.9, 4.1 Hz, $1H_{maj}$), 2.50 (dt, J = 15.8, 4.8 Hz, $1H_{min}$), 0.98 (s, $9H_{maj}$), 0.96 (s, $9H_{min}$), 0.13 (s, $3H_{maj}$), 0.11 (s, $3H_{maj}$), 0.09 (s, $3H_{min}$), 0.09 (s, $3H_{min}$).

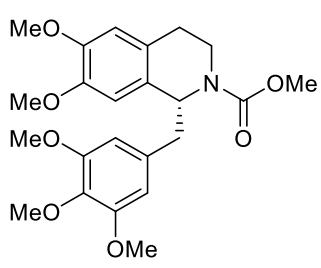
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.10, 149.83, 149.78, 147.88, 147.73, 147.12, 147.06, 144.97, 144.78, 130.95, 130.82, 128.46, 128.36, 126.46, 126.37, 123.20, 123.10, 122.66, 122.34, 111.99, 111.49, 111.16, 110.70, 110.37, 56.32, 56.20, 55.94, 55.90, 55.72, 55.68, 52.63, 42.49, 41.70, 39.40, 38.41, 28.26, 28.12, 25.84, 18.55, 18.53, -4.55, -4.61, -4.64.

ESI-HRMS: calculated for $C_{27}H_{39}N_1Na_1O_6Si_1$ ($[M+Na]^+$): 524.24389, found: 524.24435.

HPLC (OD-3, *n*-heptane/*i*-PrOH 97:3, 298 K, 282 nm): t_R (minor) = 8.2 min, t_R (major) = 9.6 min, er = 96.5:3.5 (93% ee).

$[\alpha]_D^{25}$ = −44.8 (*c* = 0.22, $CHCl_3$).

methyl (*R*)-6,7-dimethoxy-1-(3,4,5-trimethoxybenzyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (226f)



The reaction was performed according to **general procedure b** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and 2-(3,4,5-trimethoxyphenyl)acetaldehyde (**224f**, 27.7 mg, 0.132 mmol, 1.32 eq.). Purification by silica gel flash column chromatography (hex/EtOAc 1:1) afforded the product as a colorless oil (29.8 mg, 69 µmol, 69%).

R_F (hex/EtOAc 1:1) = 0.21.

^{1}H-NMR (501 MHz, $CDCl_3$): Mixture of two rotamers with a ratio ≈ 55:45. δ = 6.60 (s, $1H_{min}$), 6.59 (s, $1H_{maj}$), 6.33 (s, $1H_{min}$), 6.29 (s, $2H_{min}$), 6.27 (s, $2H_{maj}$), 6.14 (s, $1H_{maj}$), 5.24 (dd, J = 8.3,

5.2 Hz, $1H_{maj}$), 5.13 (t, J = 6.8 Hz, $1H_{min}$), 4.19–4.13 (m, $1H_{min}$), 3.88–3.82 (m, $3H_{all}$ + $1H_{maj}$), 3.83–3.77 (m, $6H_{all}$), 3.75 (s, $3H_{all}$), 3.73 (s, $3H_{min}$), 3.72 (s, $3H_{maj}$), 3.61 (s, $3H_{maj}$), 3.56 (s, $3H_{min}$), 3.36 (ddd, J = 13.2, 8.9, 4.6 Hz, $1H_{maj}$), 3.27 (ddd, J = 13.4, 10.7, 4.4 Hz, $1H_{min}$), 3.12 (dd, J = 13.2, 5.2 Hz, $1H_{maj}$), 3.02 (dd, J = 13.5, 7.1 Hz, $1H_{min}$), 2.95–2.82 (m, $1H_{all}$ + $1H_{min}$), 2.77 (ddd, J = 15.1, 8.9, 5.5 Hz, $1H_{maj}$), 2.60 (ddd, J = 19.6, 11.8, 7.4 Hz, $1H_{all}$).

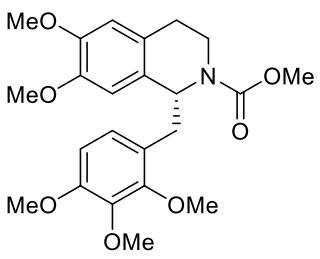
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.19, 156.07, 153.12, 153.04, 148.01, 147.84, 147.19, 146.93, 136.85, 136.70, 134.08, 134.00, 128.27, 128.17, 126.55, 126.32, 111.56, 111.22, 110.91, 110.44, 106.89, 106.82, 60.97, 56.28, 56.25, 56.20, 56.03, 56.01, 55.83, 52.74, 52.64, 43.54, 43.10, 39.50, 38.26, 28.23, 28.10.

ESI-HRMS: calculated for $C_{23}H_{29}N_1O_7Na_1$ ($[M+Na]^+$): 454.183623, found: 454.183800.

HPLC (OD-3, *n*-heptane/*i*-PrOH 90:10, 298 K, 282 nm): t_R (minor) = 12.7 min, t_R (major) = 15.2 min, er = 96.5:3.5 (93% ee).

$[\alpha]_D^{25}$ = −54.4 (*c* = 0.21, $CHCl_3$).

methyl (*R*)-6,7-dimethoxy-1-(2,3,4-trimethoxybenzyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (226g)



The reaction was performed according to **general procedure b** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and 2-(2,3,4-trimethoxyphenyl)acetaldehyde (**224g**, 22.7 mg, 0.132 mmol, 1.32 eq.). Purification by silica gel flash column chromatography (DCM/EtOAc 19:1 to 4:1) afforded the product as a colorless oil (33.0 mg, 76 µmol, 76%).

R_F (DCM/EtOAc 9:1) = 0.31.

^{1}H-NMR (501 MHz, $CDCl_3$): Mixture of two rotamers with a ratio ≈ 65:35. δ = 6.76 (d, J = 8.5 Hz, $1H_{min}$), 6.65 (d, J = 8.5 Hz, $1H_{maj}$), 6.60 (s, $1H_{maj}$), 6.58–6.54 (m, $1H_{all}$ + $1H_{min}$), 6.46 (s, $1H_{maj}$), 6.25 (s, $1H_{min}$), 5.31 (t, J = 7.3 Hz, $1H_{min}$), 5.19 (dd, J = 9.1, 5.1 Hz, $1H_{maj}$), 4.26 (ddd, J = 13.2, 6.1, 2.8 Hz, $1H_{maj}$), 3.99–3.89 (m, $3H_{maj}$ + $1H_{min}$), 3.87 (s, $3H_{maj}$), 3.84 (s, $3H_{maj}$), 3.84–3.81 (m, 5.10H), 3.77 (s, $3H_{min}$), 3.76 (s, $3H_{maj}$), 3.65 (s, $3H_{min}$), 3.64 (s, $3H_{min}$), 3.45 (ddd, J = 13.7, 9.9, 4.6 Hz, $1H_{min}$), 3.41–3.31 (m, $3H_{maj}$ + $1H_{maj}$), 3.09–2.98 (m, $1H_{all}$ + $1H_{min}$), 2.93–2.76 (m, $1H_{all}$ + $1H_{maj}$), 2.66 (ddt, J = 15.9, 8.8, 4.1 Hz, $1H_{all}$).

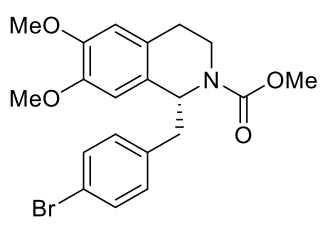
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.12, 156.04, 152.75, 152.59, 152.27, 147.88, 147.71, 147.26, 146.98, 142.17, 142.14, 129.08, 128.89, 126.31, 126.15, 125.31, 124.60, 124.41, 111.49, 111.26, 110.67, 110.30, 106.99, 106.93, 60.87, 60.84, 60.74, 56.15, 56.12, 55.99, 55.93, 55.79, 55.46, 55.27, 52.60, 52.33, 38.77, 37.52, 37.15, 35.94, 28.24, 28.20.

ESI-HRMS: calculated for $C_{23}H_{29}N_1Na_1O_7$ ($[M+Na]^+$): 454.18362, found: 454.18378.

HPLC (OD-3, *n*-heptane/*i*-PrOH 95:5, 298 K, 282 nm): t_R (minor) = 16.6 min, t_R (major) = 20.0 min, er = 97:3 (94% ee).

$[\alpha]_D^{25}$ = −69.7 (*c* = 0.37, $CHCl_3$).

methyl (*R*)-1-(4-bromobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (226h)



The reaction was performed according to **general procedure b** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and 2-(4-bromophenyl)acetaldehyde (**224h**, 26.3 mg, 0.132 mmol, 1.32 eq.). Purification by silica gel flash column chromatography (hex/EtOAc 2:1) afforded the product as a colorless oil (36.9 mg, 88 µmol, 88%).

R_F (hex/EtOAc 2:1) = 0.36.

^{1}H-NMR (501 MHz, $CDCl_3$): Mixture of two rotamers with a ratio ≈ 1:1. δ = 7.37 (dd, J = 17.0, 7.9 Hz, $2H_{all}$), 6.95 (dd, J = 10.2, 7.9 Hz, $2H_{all}$), 6.60 (s, 1H), 6.57 (s, 1H), 6.30 (s, 1H), 6.15 (s, 1H), 5.22 (t, J = 6.7 Hz, 1H), 5.12 (t, J = 6.9 Hz, 1H), 4.14 (ddd, J = 13.2, 5.9, 3.7 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.79 (dt, J = 12.8, 5.5 Hz, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.64 (s, 3H), 3.50 (s, 3H), 3.34 (ddd, J = 13.2, 8.9, 4.7 Hz, 1H), 3.27 (ddd, J = 13.0, 10.4, 4.4 Hz, 1H), 3.11 (dd, J = 13.3, 5.9 Hz, 1H), 3.03 (dd, J = 13.5, 7.7 Hz, 1H), 2.95 (dt, J = 12.6, 6.4 Hz, $1H_{all}$), 2.84 (ddd, J = 16.2, 10.4, 5.9 Hz, 1H), 2.75 (ddd, J = 15.0, 8.9, 5.5 Hz, 1H), 2.58 (ddt, J = 29.0, 15.8, 4.7 Hz, $1H_{all}$).

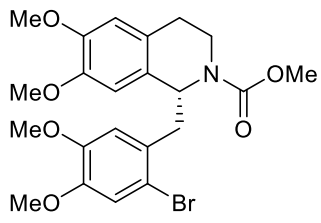
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.18, 155.98, 148.05, 147.88, 147.25, 147.06, 137.34, 131.71, 131.53, 131.38, 131.33, 128.00, 127.85, 126.54, 126.32, 120.47, 120.43, 111.56, 111.23, 110.54, 110.20, 56.20, 56.12, 55.98, 55.96, 55.82, 52.77, 52.55, 42.55, 42.19, 39.44, 38.26, 28.18, 28.06.

ESI-HRMS: calculated for $C_{20}H_{22}Br_1N_1Na_1O_4$ ($[M+Na]^+$): 442.06244, found: 442.06243.

HPLC (OD-3, *n*-heptane/*i*-PrOH 90:10, 298 K, 283 nm): t_R (minor) = 6.5 min, t_R (major) = 8.1 min, er = 96.5:3.5 (93% ee).

$[\alpha]_D^{25}$ = −59.7 (*c* = 0.21, $CHCl_3$).

methyl (*R*)-1-(2-bromo-4,5-dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (226i)



The reaction was performed according to **general procedure b** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and 2-(2-bromo-4,5-dimethoxyphenyl)acetaldehyde (**224i**, 34.2 mg, 0.132 mmol, 1.32 eq.). Purification by silica gel flash column chromatography (hex/MTBE 1:3) and another silica gel flash column chromatography (hex/EtOAc 1:1) afforded the product as a white solid (37.4 mg, 78 µmol, 78%).

A crystalline sample for x-ray single crystal structure analysis was obtained by dissolving an aliquot of the product in a small amount of DCM and layering with *n*-pentane.

R_F (hex/EtOAc 1:1) = 0.25.

^{1}H-NMR (501 MHz, $CDCl_3$): Mixture of two rotamers with a ratio ≈ 55:45. δ = 7.02 (s, $1H_{maj}$), 6.96 (s, $1H_{min}$), 6.62 (s, $1H_{min}$), 6.60 (s, $1H_{maj}$), 6.58 (s, $1H_{maj}$), 6.57 (s, $1H_{min}$), 6.48 (s, $1H_{maj}$), 6.35 (s, $1H_{min}$), 5.36 (t, J = 7.0 Hz, $1H_{min}$), 5.28 (dd, J = 9.0, 4.8 Hz, $1H_{maj}$), 4.25 (ddd, J = 13.3, 6.0, 3.1 Hz, $1H_{maj}$), 3.90 (dt, J = 13.3, 5.4 Hz, $1H_{min}$), 3.87–3.81 (m, $6H_{all}$), 3.79 (s, $3H_{maj}$), 3.78–3.75 (m, $3H_{all}$), 3.69 (s, $3H_{min}$), 3.66 (s, $3H_{min}$), 3.46–3.29 (m, $3H_{maj}$ + $1H_{all}$), 3.21 (dt, J = 13.8, 5.5 Hz, $1H_{all}$), 3.09 (dd, J = 13.8, 7.5 Hz, $1H_{min}$), 2.99 (dd, J = 13.8, 9.1 Hz, $1H_{maj}$), 2.87 (ddd, J = 16.5, 10.9, 5.9 Hz, $1H_{maj}$), 2.79 (ddd, J = 15.5, 9.5, 5.7 Hz, $1H_{min}$), 2.63 (tt, J = 16.4, 4.3 Hz, $1H_{all}$).

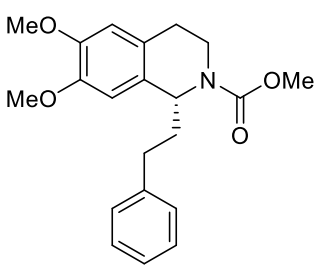
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.12, 156.03, 148.42, 148.28, 148.25, 148.19, 148.07, 147.99, 147.47, 147.31, 129.93, 129.77, 128.26, 126.54, 126.45, 115.46, 115.31, 115.04, 114.33, 113.99, 111.52, 111.26, 110.48, 110.22, 56.35, 56.23, 56.17, 56.14, 56.06, 56.01, 55.97, 55.00, 54.50, 52.72, 52.42, 42.29, 41.40, 39.03, 37.84, 28.19, 28.17.

ESI-HRMS: calculated for $C_{22}H_{26}Br_1N_1Na_1O_6$ ($[M+Na]^+$): 502.08357, found: 502.08375.

HPLC (OD-3, *n*-heptane/*i*-PrOH 80:20, 298 K, 286 nm): t_R (minor) = 7.9 min, t_R (major) = 9.9 min, er = 94.5:5.5 (89% ee).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = −62.5 (*c* = 0.22, $CHCl_3$).

methyl (*R*)-6,7-dimethoxy-1-phenethyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (226j)



The reaction was performed according to **general procedure a** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and 3-phenylpropanal (**225j**, 16 µL, 0.12 mmol, 1.2 eq.). Purification by silica gel flash column chromatography (hex/EtOAc 70:30) afforded the product as a colorless oil (33.4 mg, 94 µmol, 94%).

$\boldsymbol{R_F}$ (hex/EtOAc 2:1) = 0.39.

^{1}H-NMR (501 MHz, $CDCl_3$): Mixture of two rotamers with a ratio ≈ 1:1. δ = 7.28 (d, J = 6.8 Hz, $2H_{all}$), 7.24–7.12 (m, $3H_{all}$), 6.63–6.56 (m, $2H_{all}$), 6.55 (s, 1H), 6.52 (s, 1H), 5.22 (dd, J = 10.1, 4.8 Hz, 1H), 5.05 (dd, J = 9.6, 4.5 Hz, 1H), 4.34–4.20 (m, 1H), 4.03 (d, J = 13.4 Hz, 1H), 3.84 (s, $3H_{all}$), 3.83 (s, $3H_{all}$), 3.75 (s, 3H), 3.73 (s, 3H), 3.29 (dt, J = 25.6, 11.8 Hz, $1H_{all}$), 3.00–2.68 (m, $3H_{all}$), 2.65 (ddd, J = 16.0, 4.3, 3.0 Hz, $1H_{all}$), 2.18–1.99 (m, $2H_{all}$).

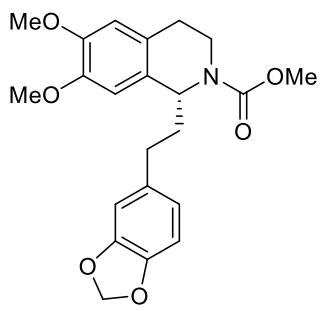
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.48, 156.38, 147.87, 147.79, 147.54, 142.07, 141.80, 129.88, 129.52, 128.47, 128.43, 126.18, 126.02, 125.91, 125.85, 111.72, 111.54, 110.20, 109.92, 56.13, 56.00, 54.55, 54.32, 52.77, 52.69, 38.59, 38.42, 38.20, 37.64, 32.87, 32.82, 28.16, 27.80.

CI-HRMS: calculated for $C_{21}H_{26}N_1O_4$ ($[M+H]^+$): 356.185634, found: 356.186280.

HPLC (OD-3, *n*-heptane/*i*-PrOH 90:10, 298 K, 282 nm): t_R (minor) = 6.7 min, t_R (major) = 9.5 min, er = 97:3 (94% ee).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = −88.3 (*c* = 0.36, $CHCl_3$).

methyl (*R*)-1-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (226k)



The reaction was performed according to **general procedure b** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and 3-(benzo[*d*][1,3]dioxol-5-yl)propanal (**225k**, 23.5 mg, 0.132 mmol, 1.32 eq.). Purification by silica gel flash column chromatography (hex/EtOAc 70:30) afforded the product as a colorless oil (38.3 mg, 96 µmol, 96%).

$\boldsymbol{R_F}$ (hex/EtOAc 2:1) = 0.30.

^{1}H-NMR (501 MHz, $CDCl_3$): Mixture of two rotamers with a ratio ≈ 1:1. δ = 6.79–6.61 (m, $3H_{all}$), 6.61–6.56 (m, $1H_{all}$), 6.54 (s, 1H), 6.51 (s, 1H), 5.94–5.85 (m, $2H_{all}$), 5.23–5.12 (m, 1H), 5.02 (dd, J = 9.2, 4.4 Hz, 1H), 4.25 (d, J = 13.3 Hz, 1H), 4.10–3.97 (m, 1H), 3.84 (s, $3H_{all}$), 3.83 (s, $3H_{all}$), 3.74 (s, $3H_{all}$), 3.26 (dd, J = 25.4, 13.3 Hz, $1H_{all}$), 2.98–2.78 (m, $1H_{all}$), 2.75–2.50 (m, $3H_{all}$), 2.12–1.90 (m, $2H_{all}$).

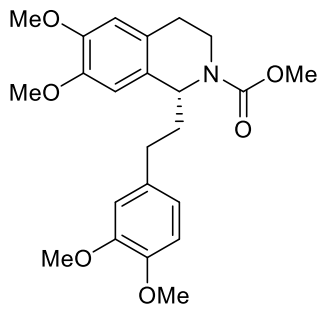
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.47, 156.37, 147.88, 147.79, 147.67, 147.55, 145.77, 145.68, 135.93, 135.62, 129.84, 129.48, 126.17, 125.84, 121.13, 111.72, 111.55, 110.18, 109.90, 108.91, 108.24, 100.86, 56.13, 56.00, 54.44, 54.21, 52.76, 52.71, 38.88, 38.75, 38.18, 37.66, 32.62, 32.53, 28.15, 27.78.

ESI-HRMS: calculated for $C_{22}H_{25}N_1O_6Na_1$ ($[M+Na]^+$): 422.157408, found: 422.157530.

HPLC (OD-3, *n*-heptane/*i*-PrOH 70:30, 298 K, 286 nm): t_R (minor) = 4.6 min, t_R (major) = 6.3 min, er = 96.5:3.5 (93% ee).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = −79.7 (*c* = 0.15, $CHCl_3$).

methyl (*R*)-1-(3,4-dimethoxyphenethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (226l)



The reaction was performed according to **general procedure b** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and 3-(3,4-dimethoxyphenyl)propanal (**225l**, 25.6 mg, 0.132 mmol, 1.32 eq.). Purification by silica gel flash column chromatography (hex/EtOAc 1:1) afforded the product as a colorless oil (38.3 mg, 96 µmol, 96%).

$\boldsymbol{R_F}$ (hex/EtOAc 1:1) = 0.31.

^{1}H-NMR (501 MHz, $CDCl_3$): Mixture of two rotamers with a ratio ≈ 1:1. δ = 6.83–6.66 (m, $3H_{all}$), 6.62–6.56 (m, $1H_{all}$), 6.54 (s, 1H), 6.53 (s, 1H), 5.21 (dd, J = 9.9, 4.8 Hz, 1H), 5.05 (dd, J = 9.3, 4.5 Hz, 1H), 4.27 (dd, J = 13.8, 5.9 Hz, 1H), 4.02 (d, J = 12.9 Hz, 1H), 3.86 (s, $3H_{all}$), 3.86–3.83 (m, $6H_{all}$), 3.82 (s, $3H_{all}$), 3.74 (s, $3H_{all}$), 3.35–3.20 (m, $1H_{all}$), 2.99–2.79 (m, $1H_{all}$), 2.79–2.57 (m, $3H_{all}$), 2.19–1.94 (m, $2H_{all}$).

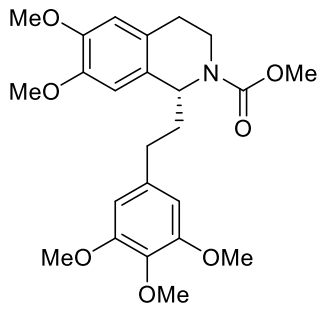
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.48, 156.40, 148.95, 147.90, 147.80, 147.53, 147.36, 147.26, 134.68, 134.45, 129.88, 129.51, 126.18, 125.87, 120.16, 111.88, 111.72, 111.54, 111.39, 110.24, 109.94, 56.14, 56.03, 55.99, 55.96, 54.48, 54.33, 52.74, 38.74, 38.42, 38.24, 37.64, 32.37, 28.15, 27.79.

ESI-HRMS: calculated for $C_{23}H_{29}N_1O_6Na_1$ ([M+Na]$^+$): 438.188708, found: 438.188930.

HPLC (OD-3, *n*-heptane/*i*-PrOH 70:30, 298 K, 281 nm): t_R (minor) = 6.5 min, t_R (major) = 8.6 min, er = 97:3 (94% ee).

$[\alpha]_D^{25}$ = −72.1 (*c* = 0.32, $CHCl_3$).

methyl (*R*)-6,7-dimethoxy-1-(3,4,5-trimethoxyphenethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (226m)



The reaction was performed according to **general procedure b** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and 3-(3,4,5-trimethoxyphenyl)propanal (**225m**, 29.6 mg, 0.132 mmol, 1.32 eq.). Purification by silica gel flash column chromatography (hex/EtOAc 3:2 to 1:1) afforded the product as a colorless oil (36.3 mg, 81 µmol, 81%).

R_F (hex/EtOAc 1:1) = 0.29.

^{1}H-NMR (501 MHz, $CDCl_3$): Mixture of two rotamers with a ratio ≈ 1:1. δ = 6.59 (s, 1H$_{all}$), 6.57–6.52 (m, 1H$_{all}$), 6.46–6.37 (m, 2H$_{all}$), 5.21 (dd, J = 9.9, 4.9 Hz, 1H), 5.10–5.03 (m, 1H), 4.28 (dd, J = 13.6, 5.9 Hz, 1H), 4.02 (d, J = 13.1 Hz, 1H), 3.87–3.82 (m, 12H$_{all}$), 3.81 (s, 3H$_{all}$), 3.74 (s, 3H$_{all}$), 3.36–3.20 (m, 1H$_{all}$), 2.99–2.79 (m, 1H$_{all}$), 2.79–2.57 (m, 3H$_{all}$), 2.21–1.94 (m, 2H$_{all}$).

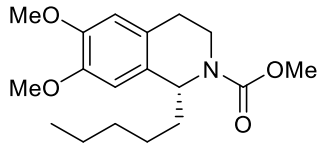
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.50, 156.40, 153.28, 153.22, 147.97, 147.86, 147.57, 137.80, 137.61, 136.36, 136.21, 129.78, 129.40, 126.21, 125.92, 111.75, 111.57, 110.28, 109.97, 105.36, 60.95, 56.22, 56.18, 56.01, 54.51, 54.37, 52.78, 38.56, 38.30, 38.16, 37.67, 33.20, 28.16, 27.80.

ESI-HRMS: calculated for $C_{24}H_{31}N_1O_7Na_1$ ([M+Na]$^+$): 468.199273, found: 468.198940.

HPLC (OD-3, *n*-heptane/*i*-PrOH 70:30, 298 K, 282 nm): t_R (minor) = 6.2 min, t_R (major) = 8.6 min, er = 97:3 (94% ee).

$[\alpha]_D^{25}$ = −66.1 (*c* = 0.35, $CHCl_3$).

methyl (*R*)-6,7-dimethoxy-1-pentyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (226n)



The reaction was performed according to **general procedure a** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and hexanal (15 µL, 0.12 mmol, 1.2 eq.). Purification by silica gel flash column chromatography (hex/EtOAc 70:30) afforded the product as a colorless oil (29.2 mg, 91 µmol, 91%).

R_F (hex/EtOAc 2:1) = 0.64.

^{1}H-NMR (501 MHz, $CDCl_3$): Mixture of two rotamers with a ratio ≈ 1:1. δ = 6.61–6.53 (m, $2H_{all}$), 5.09 (dd, J = 9.7, 5.1 Hz, 1H), 4.97 (dd, J = 10.1, 4.4 Hz, 1H), 4.28–4.19 (m, 1H), 4.04–3.96 (m, 1H), 3.85 (s, $3H_{all}$), 3.84 (s, $3H_{all}$), 3.71 (s, $3H_{all}$), 3.33–3.24 (m, 1H), 3.19 (ddd, J = 15.5, 11.9, 4.2 Hz, 1H), 2.86 (dddd, J = 32.5, 16.3, 11.0, 6.1 Hz, $1H_{all}$), 2.62 (dt, J = 16.2, 3.7 Hz, $1H_{all}$), 1.84–1.61 (m, $2H_{all}$), 1.50–1.21 (m, $6H_{all}$), 0.93–0.84 (m, $3H_{all}$).

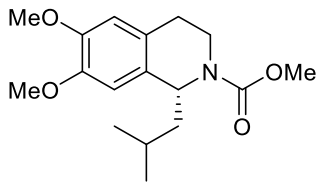
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.43, 147.80, 147.70, 147.49, 130.45, 130.07, 126.14, 125.82, 111.72, 111.54, 110.31, 110.01, 56.16, 56.02, 54.65, 54.52, 52.69, 52.63, 38.09, 37.42, 36.98, 36.81, 31.91, 31.78, 28.20, 27.89, 26.17, 26.11, 22.74, 14.19.

EI-HRMS: calculated for $C_{18}H_{27}N_1O_4$ ($[M]^+$): 321.193459, found: 321.193110.

HPLC (OD-3, *n*-heptane/*i*-PrOH 97:3, 298 K, 282 nm): t_R (minor) = 7.0 min, t_R (major) = 8.4 min, er = 97.5:2.5 (95% ee).

$[\alpha]_D^{25}$ = −89.2 (*c* = 0.21, $CHCl_3$).

methyl (*R*)-1-isobutyl-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (226o)



The reaction was performed according to **general procedure a** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and isovaleraldehyde (13 µL, 0.12 mmol, 1.2 eq.). Purification by silica gel flash column chromatography (hex/EtOAc 4:1) afforded the product as a colorless oil (28.3 mg, 92 µmol, 92%).

R_F (hex/EtOAc 2:1) = 0.59.

^{1}H-NMR (501 MHz, $CDCl_3$): Mixture of two rotamers with a ratio ≈ 1:1. δ = 6.58 (s, 1H), 6.55 (s, 1H), 6.54 (s, 1H), 6.50 (s, 1H), 5.20 (dd, J = 10.7, 4.2 Hz, 1H), 5.05 (dd, J = 10.8, 3.9 Hz, 1H), 4.23 (ddd, J = 13.5, 6.3, 2.2 Hz, 1H), 4.02 (ddd, J = 13.5, 6.1, 2.7 Hz, 1H), 3.85 (d, J = 2.7 Hz, $3H_{all}$), 3.83 (d, J = 2.4 Hz, $3H_{all}$), 3.71 (d, J = 2.7 Hz, $3H_{all}$), 3.26 (ddd, J = 13.5, 11.3, 4.4 Hz, 1H), 3.19 (td, J = 12.6, 4.3 Hz, 1H), 2.88 (dddd, J = 33.7, 16.8, 11.4, 6.2 Hz, $1H_{all}$), 2.60 (ddd, J = 16.1, 4.4, 2.5 Hz, $1H_{all}$), 1.78 (ddt, J = 14.3, 10.6, 3.6 Hz, $1H_{all}$), 1.72–1.58 (m, $1H_{all}$), 1.48–1.35 (m, $1H_{all}$), 1.08 (d, J = 6.4 Hz, 3H), 1.04 (d, J = 6.5 Hz, 3H), 0.96–0.91 (m, $3H_{all}$).

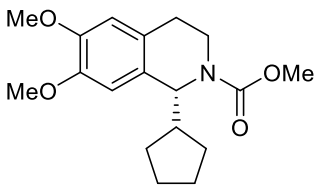
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.44, 156.37, 147.82, 147.69, 147.51, 130.81, 130.38, 126.13, 125.76, 111.80, 111.62, 110.24, 109.97, 56.20, 56.18, 56.02, 52.88, 52.85, 52.72, 52.61, 46.44, 46.14, 37.72, 37.15, 28.07, 27.71, 25.21, 25.06, 23.72, 23.64, 22.33, 21.91.

ESI-HRMS: calculated for $C_{17}H_{25}N_1O_4Na_1$ ($[M+Na]^+$): 330.167578, found: 330.167580.

HPLC (OD-3, *n*-heptane/*i*-PrOH 97:3, 298 K, 282 nm): t_R (minor) = 6.4 min, t_R (major) = 8.2 min, er = 97:3 (94% ee).

$[\alpha]_D^{25}$ = −82.2 (*c* = 0.24, $CHCl_3$).

methyl (*R*)-1-cyclopentyl-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (226p)



The reaction was performed according to **general procedure a** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and cyclopentanecarbaldehyde (13 µL, 0.12 mmol, 1.2 eq.). Purification by silica gel flash column chromatography (hex/EtOAc 4:1) afforded the product as a colorless oil (21.7 mg, 68 µmol, 68%).

R_F (hex/EtOAc 2:1) = 0.48.

^{1}H-NMR (501 MHz, $CDCl_3$): Mixture of two rotamers with a ratio ≈ 1:1. δ = 6.66 (s, 1H), 6.63 (s, 1H), 6.60 (s, 1H), 6.59 (s, 1H), 4.90 (d, J = 9.8 Hz, 1H), 4.75 (d, J = 9.7 Hz, 1H), 4.18 (ddd, J = 13.4, 7.0, 3.4 Hz, 1H), 3.94 (ddd, J = 13.2, 6.6, 4.7 Hz, 1H), 3.87 – 3.81 (m, $6H_{all}$), 3.70 (s, $3H_{all}$), 3.43 (ddd, J = 13.4, 9.2, 5.6 Hz, 1H), 3.34 (ddd, J = 13.3, 10.2, 5.4 Hz, 1H), 2.92 (ddd, J = 16.9, 10.2, 7.0 Hz, 1H), 2.84 (ddd, J = 15.9, 9.2, 6.6 Hz, 1H), 2.78–2.68 (m, $1H_{all}$), 2.15 (dtd, J = 10.1, 6.8, 2.9 Hz, $1H_{all}$), 1.83–1.61 (m, $4H_{all}$), 1.59–1.33 (m, $4H_{all}$).

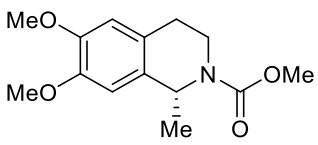
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.59, 156.20, 147.97, 147.84, 146.93, 146.87, 130.39, 129.92, 126.10, 125.82, 111.81, 111.57, 111.05, 110.77, 58.97, 58.94, 56.17, 56.13, 52.70, 52.62, 47.02, 46.89, 38.89, 38.21, 31.42, 31.33, 30.01, 29.96, 27.81, 27.51, 25.41, 25.32, 24.38, 24.25.

ESI-HRMS: calculated for $C_{18}H_{25}N_1O_4Na_1$ ($[M+Na]^+$): 342.167578, found: 342.167800.

HPLC (OJ-3R, MeOH/H_2O 90:10, 298 K, 283 nm): t_R (minor) = 4.5 min, t_R (major) = 6.6 min, er = 97:3 (94% ee).

$[\alpha]_D^{25}$ = −60.2 (*c* = 0.22, $CHCl_3$).

methyl (*R*)-6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (226q)



The reaction was performed according to **general procedure a** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and acetaldehyde (17 µL, 0.30 mmol, 3.0 eq.) at −40 °C. Purification by silica gel flash column chromatography (hex/EtOAc 4:1) afforded the product as a colorless oil (26.5 mg, 100 µmol, >99%).

R_F (hex/EtOAc 2:1) = 0.32.

^{1}H-NMR (501 MHz, $CDCl_3$): Mixture of two rotamers with a ratio ≈ 1:1. δ = 6.62–6.51 (m, $2H_{all}$), 5.27–5.01 (m, $1H_{all}$), 4.31–4.16 (m, 1H), 4.11–3.99 (m, 1H), 3.85 (s, $3H_{all}$), 3.84 (s, $3H_{all}$), 3.73 (s, $3H_{all}$), 3.33–3.13 (m, $1H_{all}$), 2.94–2.77 (m, $1H_{all}$), 2.63 (dt, J = 15.9, 3.4 Hz, $1H_{all}$), 1.43 (d, J = 6.8 Hz, $3H_{all}$).

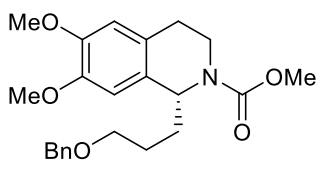
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 147.74, 130.72, 130.26, 126.12, 125.76, 111.54, 109.84, 56.14, 56.03, 52.69, 50.20, 37.85, 37.43, 28.63, 28.49, 22.26, 21.83.

EI-HRMS: calculated for $C_{14}H_{19}N_1O_4$ ($[M]^+$): 265.130858, found: 265.130920.

HPLC (IC-3R, MeOH/H_2O 90:10, 298 K, 284 nm): t_R (minor) = 6.3 min, t_R (major) = 7.9 min, er = 98.5:1.5 (97% ee).

$[\alpha]_D^{25}$ = −119.4 (*c* = 0.28, $CHCl_3$).

methyl (*R*)-1-(3-(benzyloxy)propyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (226r)



The reaction was performed according to **general procedure b** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and 4-(benzyloxy)butanal (23.5 mg, 0.132 mmol, 1.32 eq.). Purification by silica gel flash column chromatography (DCM/acetone 19:1) and another silica gel flash column chromatography (hex/acetone 4:1) afforded the product as a colorless oil (31.9 mg, 80 µmol, 80%) as well as unreacted starting material **120b** (4.8 mg, 20 µmol, 20%).

R_F (hex/EtOAc 2:1) = 0.33.

^{1}H-NMR (501 MHz, $CDCl_3$): Mixture of two rotamers with a ratio ≈ 1:1. δ = 7.38–7.23 (m, $5H_{all}$), 6.63–6.52 (m, $2H_{all}$), 5.19–5.08 (m, 1H), 5.05–4.94 (m, 1H), 4.50 (s, $2H_{all}$), 4.23 (dd, J = 13.9, 5.9 Hz, 1H), 4.01 (d, J = 13.6 Hz, 1H), 3.84 (s, $3H_{all}$), 3.83–3.80 (m, $3H_{all}$), 3.71 (s, 3H), 3.69 (s, 3H), 3.60–3.45 (m, $2H_{all}$), 3.27 (t, J = 12.1 Hz, 1H), 3.19 (td, J = 12.7, 4.1 Hz, 1H), 2.94–2.79 (m, $1H_{all}$), 2.65–2.57 (m, $1H_{all}$), 1.95–1.66 (m, $4H_{all}$).

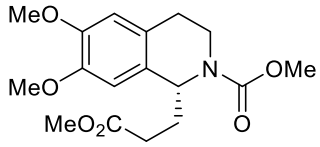
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.47, 156.38, 147.85, 147.75, 147.55, 138.74, 138.64, 130.15, 129.78, 128.50, 127.76, 127.71, 127.64, 126.14, 125.83, 111.71, 111.53, 110.26, 109.99, 73.12, 73.06, 70.12, 70.05, 56.14, 56.03, 54.30, 54.27, 52.72, 38.06, 37.45, 33.48, 33.29, 28.20, 27.83, 26.76.

ESI-HRMS: calculated for $C_{23}H_{29}N_1O_5Na_1$ ($[M+Na]^+$): 422.193793, found: 422.194220.

HPLC (OD-3, *n*-heptane/*i*-PrOH 80:20, 298 K, 282 nm): t_R (minor) = 4.9 min, t_R (major) = 6.7 min, er = 96.5:3.5 (93% ee).

$[\alpha]_D^{25}$ = −62.4 (*c* = 0.26, $CHCl_3$).

methyl (*R*)-6,7-dimethoxy-1-(3-methoxy-3-oxopropyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (226s)



The reaction was performed according to **general procedure b** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and methyl 4-oxobutanoate (15.3 mg, 0.132 mmol, 1.32 eq.). Purification by silica gel flash column chromatography (DCM/Et_2O 9:1) afforded the product as a colorless oil (32.4 mg, 96 µmol, 96%).

R_F (DCM/Et_2O 9:1) = 0.22.

^{1}H-NMR (501 MHz, $CDCl_3$): Mixture of two rotamers with a ratio ≈ 55:45. δ = 6.63 (s, $1H_{min}$), 6.62 (s, $1H_{maj}$), 6.58 (s, $1H_{maj}$), 6.56 (s, $1H_{min}$), 5.14 (dd, J = 10.5, 4.5 Hz, $1H_{min}$), 5.04 (dd, J = 11.0, 3.6 Hz, $1H_{maj}$), 4.23 (ddd, J = 13.4, 6.1, 2.2 Hz, $1H_{maj}$), 4.00 (ddd, J = 13.6, 5.9, 2.9 Hz, $1H_{min}$), 3.86 (s, $3H_{maj}$), 3.86 (s, $3H_{min}$), 3.85 (s, $3H_{min}$), 3.84 (s, $3H_{maj}$), 3.71 (s, $3H_{min}$), 3.70 (s,

$3H_{maj}$), 3.68 (s, $3H_{maj}$), 3.67 (s, $3H_{min}$), 3.23 (ddd, J = 13.5, 11.2, 4.2 Hz, $1H_{min}$), 3.13 (ddd, J = 13.3, 11.7, 4.1 Hz, $1H_{maj}$), 2.85 (dddd, J = 32.4, 16.6, 11.5, 5.9 Hz, $1H_{all}$), 2.61 (ddt, J = 16.3, 4.5, 2.4 Hz, $1H_{all}$), 2.56–2.36 (m, $2H_{all}$), 2.20–1.95 (m, $2H_{all}$).

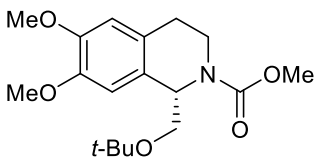
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 173.95, 173.78, 156.58, 156.25, 147.99, 147.92, 147.69, 129.30, 128.96, 126.19, 125.93, 111.66, 111.54, 110.13, 109.89, 56.15, 56.03, 54.04, 53.76, 52.84, 52.71, 51.77, 38.16, 37.46, 31.51, 31.41, 31.19, 30.86, 28.15, 27.83.

EI-HRMS: calculated for $C_{17}H_{23}N_1O_6$ ($[M]^+$): 337.151989, found: 337.152020.

HPLC (OJ-3, *n*-heptane/*i*-PrOH 80:20, 298 K, 300 nm): t_R (minor) = 9.0 min, t_R (major) = 11.9 min, er = 97.5:2.5 (95% ee).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25}}$ = −78.1 (*c* = 0.21, $CHCl_3$).

methyl (*R*)-1-(*tert*-butoxymethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (226t)



The reaction was performed according to **general procedure b** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and 2-(*tert*-butoxy)acetaldehyde (**240**, 58 wt% in DCM, 26.5 mg, 0.132 mmol, 1.32 eq.) in *n*-pentane (4.4 mL). Purification by silica gel flash column chromatography (hex/EtOAc 40%) afforded the product as a colorless oil (33.5 mg, 99 µmol, 99%).

$\boldsymbol{R_F}$ (hex/EtOAc 2:1) = 0.37.

^{1}H-NMR (501 MHz, $CDCl_3$): Mixture of two rotamers with a ratio ≈ 60:40. δ = δ 6.79 (s, $1H_{min}$), 6.74 (s, $1H_{maj}$), 6.62–6.53 (m, $1H_{all}$), 5.13–5.01 (m, $1H_{all}$), 4.27–4.16 (m, $1H_{maj}$), 3.97–3.90 (m, $1H_{min}$), 3.84 (s, $6H_{all}$), 3.72 (s, $3H_{all}$), 3.66–3.60 (m, $1H_{min}$), 3.57 (t, J = 8.2 Hz, $1H_{all}$), 3.54–3.48 (m, $1H_{maj}$), 3.48–3.39 (m, $1H_{min}$), 3.26 (td, J = 12.2, 4.1 Hz, $1H_{maj}$), 2.93–2.73 (m, $1H_{all}$), 2.73–2.59 (m, $1H_{all}$), 1.12 (s, $9H_{maj}$), 1.10 (s, $9H_{min}$).

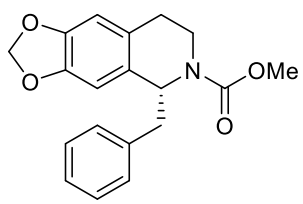
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.64, 156.23, 148.03, 147.80, 147.22, 127.21, 126.94, 126.87, 126.36, 111.46, 111.14, 111.05, 110.80, 73.36, 73.25, 64.97, 64.93, 56.04, 55.96, 54.82, 54.68, 52.64, 39.74, 38.35, 28.56, 28.25, 27.54.

ESI-HRMS: calculated for $C_{18}H_{27}N_1O_5Na_1$ ($[M+Na]^+$): 360.178143, found: 360.178030.

HPLC (OD-3, *n*-heptane/*i*-PrOH 98:2, 298 K, 282 nm): t_R (minor) = 9.4 min, t_R (major) = 10.2 min, er = 91.5:8.5 (83% ee).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25}}$ = −70.0 (*c* = 0.22, $CHCl_3$).

methyl (*R*)-5-benzyl-7,8-dihydro-[1,3]dioxolo[4,5-*g*]isoquinoline-6(5*H*)-carboxylate (213)



The reaction was performed according to **general procedure a** with carbamate **315** (22.3 mg, 0.10 mmol, 1.00 eq.) and phenylacetaldehyde (14 µL, 0.12 mmol, 1.2 eq.) in CyH. Purification by silica gel flash column chromatography (hex/EtOAc 3:1) afforded the product as a colorless oil (27.9 mg, 86 µmol, 86%).

R_F (hex/EtOAc 2:1) = 0.61.

^{1}H-NMR (501 MHz, $CDCl_3$): Mixture of two rotamers with a ratio ≈ 55:45. δ = 7.30–7.17 (m, $3H_{all}$), 7.12–7.03 (m, $2H_{all}$), 6.58 (s, $1H_{maj}$), 6.55 (s, $1H_{min}$), 6.47 (s, $1H_{maj}$), 6.32 (s, $1H_{min}$), 5.95–5.85 (m, $2H_{all}$), 5.26 (t, J = 6.6 Hz, $1H_{min}$), 5.13 (t, J = 6.8 Hz, $1H_{maj}$), 4.12 (ddd, J = 13.1, 6.0, 4.0 Hz, $1H_{maj}$), 3.73 (dt, J = 12.1, 5.6 Hz, $1H_{min}$), 3.68 (s, $3H_{min}$), 3.39 (s, $3H_{maj}$), 3.35–3.23 (m, $1H_{all}$), 3.13–2.96 (m, $2H_{all}$), 2.81 (ddd, J = 16.2, 10.4, 5.9 Hz, $1H_{maj}$), 2.69 (ddd, J = 14.9, 8.7, 5.5 Hz, $1H_{min}$), 2.58 (dt, J = 16.1, 4.2 Hz, $1H_{maj}$), 2.46 (dt, J = 15.9, 5.3 Hz, $1H_{min}$).

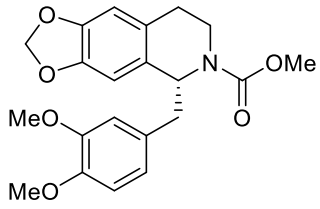
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.14, 156.04, 146.54, 146.40, 146.06, 145.88, 138.23, 138.08, 129.82, 129.78, 129.64, 128.33, 128.26, 127.76, 127.73, 126.59, 126.56, 108.72, 108.36, 107.67, 107.20, 101.01, 100.92, 56.70, 52.70, 52.39, 43.24, 42.84, 39.42, 38.06, 28.57, 28.54.

CI-HRMS: calculated for $C_{19}H_{20}N_1O_4$ ($[M+H]^+$): 326.138684, found: 326.139160.

HPLC (OD-3, *n*-heptane/*i*-PrOH 98:2, 298 K, 290 nm): t_R (minor) = 11.0 min, t_R (major) = 12.1 min, er = 95.5:4.5 (91% ee).

$[\alpha]_D^{25}$ = −48.0 (*c* = 0.17, $CHCl_3$).

methyl (*R*)-5-(3,4-dimethoxybenzyl)-7,8-dihydro-[1,3]dioxolo[4,5-*g*]isoquinoline-6(5*H*)-carboxylate (246)



The reaction was performed according to **general procedure b** with carbamate **315** (22.3 mg, 0.10 mmol, 1.00 eq.) and 2-(3,4-dimethoxyphenyl)acetaldehyde (**224c**, 22.3 mg, 0.132 mmol, 1.32 eq.) in CyH/$CHCl_3$ 10:1 (2.2 mL). Purification by silica gel flash column chromatography (hex/EtOAc 3:1) afforded the product as a white solid (27.9 mg, 86 µmol, 86%).

R_F (DCM/EtOAc 9:1) = 0.47.

^{1}H-NMR (501 MHz, $CDCl_3$): Mixture of two rotamers with a ratio ≈ 50:50. δ = 6.77 (d, J = 8.1 Hz, 1H), 6.73 (d, J = 8.1 Hz, 1H), 6.62 (dd, J = 8.1, 1.9 Hz, 1H), 6.60–6.52 (m, $2H_{all}$ + 1H), 6.48 (s, 1H), 6.34 (s, 1H), 5.90 (d, J = 4.8 Hz, 2H), 5.88 (d, J = 8.3 Hz, 2H), 5.23 (t, J = 6.5 Hz, 1H), 5.10 (t, J = 6.6 Hz, 1H), 4.07 (ddd, J = 13.1, 5.9, 4.0 Hz, 1H), 3.86–3.84 (m, $3H_{all}$), 3.81 (s, 3H), 3.77 (s, 3H), 3.73–3.61 (m, 3H + 1H), 3.48 (s, 3H), 3.25 (dddd, J = 27.6, 13.6, 9.3, 4.6 Hz, $1H_{all}$), 3.00 (dtd, J = 31.7, 13.3, 6.9 Hz, $2H_{all}$), 2.79 (ddd, J = 16.1, 10.2, 5.9 Hz, 1H), 2.68 (ddd, J = 14.6, 8.4, 5.4 Hz, 1H), 2.54 (dt, J = 16.1, 4.3 Hz, 1H), 2.45 (dt, J = 15.9, 5.4 Hz, 1H).

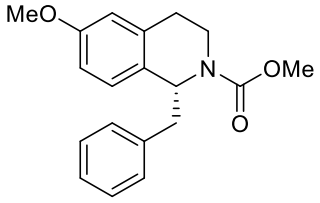
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.18, 156.10, 148.77, 148.65, 147.85, 147.77, 146.51, 146.38, 146.04, 145.86, 130.73, 130.57, 129.79, 129.63, 127.85, 127.82, 121.91, 121.82, 112.91, 112.83, 111.15, 111.01, 108.70, 108.35, 107.80, 107.27, 101.00, 100.91, 56.64, 56.62, 56.03, 55.98, 55.94, 55.88, 52.71, 52.55, 42.80, 42.34, 39.56, 38.24, 28.58, 28.51.

ESI-HRMS: calculated for $C_{21}H_{23}N_1O_6Na_1$ ($[M+Na]^+$): 408.141758, found: 408.141880.

HPLC (OJ-3, *n*-heptane/*i*-PrOH 70:30, 298 K, 287 nm): t_R (minor) = 8.8 min, t_R (major) = 12.7 min, er = 94.5:5.5 (89% ee).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = −43.4 (*c* = 0.27, $CHCl_3$).

methyl (*R*)-1-benzyl-6-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (247)



The reaction was performed according to **general procedure a** with carbamate **316** (20.9 mg, 0.10 mmol, 1.00 eq.) and phenylacetaldehyde (14 µL, 0.12 mmol, 1.2 eq.). Purification by silica gel flash column chromatography (hex/EtOAc 4:1) and another silica gel flash column chromatography (DCM/EtOAc 3%) afforded the product as a colorless oil (26.3 mg, 84 µmol, 84%).

$\boldsymbol{R}_\mathbf{F}$ (hex/EtOAc 2:1) = 0.54.

^{1}H-NMR (501 MHz, $CDCl_3$): Mixture of two rotamers with a ratio ≈ 60:40. δ = 7.29–7.17 (m, $3H_{all}$), 7.09 (d, J = 7.0 Hz, $2H_{maj}$), 7.05 (d, J = 7.1 Hz, $2H_{min}$), 6.90 (d, J = 8.5 Hz, $1H_{maj}$), 6.76–6.70 (m, $1H_{all}$), 6.68–6.61 (m, $1H_{all}$ + $1H_{min}$), 5.32 (t, J = 6.7 Hz, $1H_{min}$), 5.20 (dd, J = 8.1, 5.7 Hz, $1H_{maj}$), 4.14 (ddt, J = 11.6, 5.5, 2.8 Hz, $1H_{maj}$), 3.79 (s, $3H_{maj}$), 3.78 (s, $3H_{min}$), 3.77–3.72 (m, $1H_{min}$), 3.69 (s, $3H_{min}$), 3.41 (s, $3H_{maj}$), 3.39–3.28 (m, $1H_{all}$), 3.13 (dd, J = 13.3, 6.1 Hz, $1H_{min}$), 3.09–2.97 (m, $1H_{all}$ + $1H_{maj}$), 2.89 (ddd, J = 16.3, 10.4, 5.9 Hz, $1H_{maj}$), 2.76 (ddd, J = 14.8, 8.5, 5.5 Hz, $1H_{min}$), 2.67 (dt, J = 16.2, 4.2 Hz, $1H_{maj}$), 2.57 (dt, J = 15.9, 5.3 Hz, $1H_{min}$).

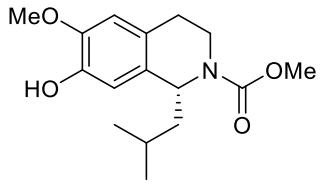
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 158.33, 158.28, 156.18, 138.38, 138.25, 135.83, 135.75, 129.90, 129.69, 128.86, 128.67, 128.32, 128.29, 128.20, 126.50, 126.44, 113.49, 113.31, 112.47, 111.99, 56.30, 56.27, 55.37, 55.33, 52.68, 52.38, 43.40, 43.00, 39.40, 38.00, 28.92, 28.89.

ESI-HRMS: calculated for $C_{19}H_{21}N_1O_3Na_1$ ($[M+Na]^+$): 334.141363, found: 334.141270.

HPLC (OJ-3R, CH_3CN/H_2O 70:30, 298 K, 278 nm): t_R (minor) = 3.5 min, t_R (major) = 4.9 min, er = 97.5:2.5 (95% ee).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = −48.6 (*c* = 0.22, $CHCl_3$).

methyl (*R*)-7-hydroxy-1-isobutyl-6-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (248)



The reaction was performed according to **general procedure a** with carbamate **317** (22.5 mg, 0.10 mmol, 1.00 eq.) and isovaleraldehyde (13 µL, 0.12 mmol, 1.2 eq.). Purification by silica gel flash column chromatography (hex/EtOAc 2:1) afforded the product as a colorless oil (29.0 mg, 89 µmol, 84%).

R_F (hex/EtOAc 2:1) = 0.49.

^{1}H-NMR (501 MHz, $CDCl_3$): Mixture of two rotamers with a ratio ≈ 55:45. δ = 6.64 (s, $1H_{min}$), 6.61 (s, $1H_{maj}$), 6.56 (s, $1H_{maj}$), 6.54 (s, $1H_{min}$), 5.53 (s, $1H_{all}$), 5.16 (dd, J = 10.4, 4.4 Hz, $1H_{min}$), 5.02 (dd, J = 10.5, 4.0 Hz, $1H_{maj}$), 4.20 (ddd, J = 13.4, 6.2, 2.4 Hz, $1H_{maj}$), 3.99 (ddd, J = 13.5, 6.0, 3.0 Hz, $1H_{min}$), 3.86–3.83 (m, $3H_{all}$), 3.71 (s, $3H_{min}$), 3.70 (s, $3H_{maj}$), 3.26 (ddd, J = 13.3, 11.1, 4.3 Hz, $1H_{min}$), 3.19 (ddd, J = 13.3, 11.5, 4.4 Hz, $1H_{maj}$), 2.86 (dddd, J = 34.5, 16.6, 11.3, 6.1 Hz, $1H_{all}$), 2.60 (ddd, J = 16.0, 4.3, 2.7 Hz, $1H_{all}$), 1.75 (ddt, J = 13.3, 10.4, 2.8 Hz, $1H_{all}$), 1.71–1.57 (m, $1H_{all}$), 1.40 (tdd, J = 14.0, 9.1, 4.2 Hz, $1H_{all}$), 1.05 (d, J = 6.5 Hz, $3H_{min}$), 1.01 (d, J = 6.5 Hz, $3H_{maj}$), 0.93 (d, J = 6.7 Hz, $3H_{min}$), 0.92 (d, J = 6.6 Hz, $3H_{maj}$).

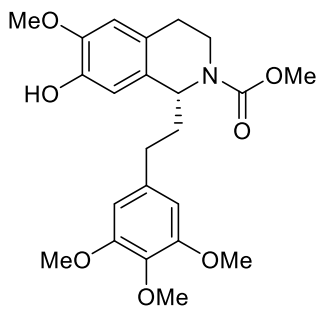
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.44, 156.41, 145.38, 145.29, 143.99, 131.52, 131.15, 125.45, 125.17, 113.09, 112.73, 111.05, 110.86, 56.08, 52.80, 52.75, 52.71, 52.61, 46.53, 46.29, 37.91, 37.33, 28.25, 27.84, 25.17, 25.03, 23.65, 23.56, 22.35, 21.90.

CI-HRMS: calculated for $C_{16}H_{23}N_1O_4Na_1$ ($[M+Na]^+$): 316.151928, found: 316.151620.

HPLC (OD-3, *n*-heptane/*i*-PrOH 95:5, 298 K, 285 nm): t_R (minor) = 7.5 min, t_R (major) = 9.0 min, er = 96:4 (92% ee).

$[\alpha]_D^{25}$ = −55.3 (*c* = 0.25, $CHCl_3$).

methyl (*R*)-7-hydroxy-6-methoxy-1-(3,4,5-trimethoxyphenethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (249)



The reaction was performed according to **general procedure b** with carbamate **317** (22.5 mg, 0.10 mmol, 1.00 eq.) and 3-(3,4,5-trimethoxyphenyl)propanal (**225m**, 29.6 mg, 0.132 mmol, 1.32 eq.). Purification by silica gel flash column chromatography (hex/EtOAc 40–50%) afforded the product as a white foam (36.1 mg, 84 µmol, 84%).

R_F (hex/EtOAc 1:1) = 0.26.

^{1}H-NMR (501 MHz, $CDCl_3$): Mixture of two rotamers with a ratio ≈ 1:1. δ = 6.66 (s, $1H_{all}$), 6.57 (s, $1H_{all}$), 6.43–6.38 (m, $2H_{all}$), 5.55 (s, $1H_{all}$), 5.17 (s, 1H), 5.03 (s, 1H), 4.25 (d, J = 13.0 Hz, 1H), 4.00 (t, J = 8.4 Hz, 1H), 3.86–3.83 (m, $9H_{all}$), 3.81 (s, $3H_{all}$), 3.73 (s, $3H_{all}$), 3.36–3.17 (m, $1H_{all}$), 2.99–2.78 (m, $1H_{all}$), 2.64 (dt, J = 16.0, 3.8 Hz, $1H_{all}$), 2.05 (s, $2H_{all}$).

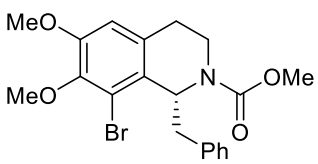
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.49, 153.22, 145.50, 144.08, 137.86, 137.62, 136.28, 136.17, 130.50, 130.18, 125.53, 125.35, 113.14, 112.71, 111.02, 110.84, 105.33, 60.97, 56.22, 56.08, 54.50, 54.33, 52.77, 38.47, 38.22, 37.81, 33.18, 28.33, 27.94.

CI-HRMS: calculated for $C_{23}H_{29}N_1O_7Na_1$ ($[M+Na]^+$): 454.183623, found: 454.183480.

HPLC (IC-3R, MeOH/H_2O 90:10, 298 K, 284 nm): t_R (minor) = 10.6 min, t_R (major) = 13.2 min, er = 95:5 (90% ee).

$[\alpha]_D^{25}$ = −48.9 (*c* = 0.38, $CHCl_3$).

methyl (*R*)-1-benzyl-8-bromo-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (250)



The reaction was performed according to **general procedure a** with carbamate **318** (31.8 mg, 0.10 mmol, 1.00 eq.) and phenylacetaldehyde (14 µL, 0.12 mmol, 1.2 eq.). Purification by silica gel flash column chromatography (DCM/EtOAc 19:1) afforded the product as a colorless oil (24.9 mg, 59 µmol, 59%).

R_F (hex/EtOAc 2:1) = 0.29.

^{1}H-NMR (501 MHz, $CDCl_3$): Mixture of two rotamers with a ratio ≈ 70:30. δ = 7.32–7.10 (m, $5H_{all}$), 6.66 (s, $1H_{maj}$), 6.60 (s, $1H_{min}$), 5.69 (dd, J = 8.9, 4.4 Hz, $1H_{min}$), 5.46 (dd, J = 10.3, 3.3 Hz, $1H_{maj}$), 4.17 (ddd, J = 13.3, 6.7, 3.7 Hz, $1H_{maj}$), 3.87 (s, $3H_{maj}$), 3.86 (s, $3H_{maj}$), 3.85 (s, $3H_{min}$), 3.83 (s, $3H_{min}$), 3.76 (dt, J = 12.3, 5.8 Hz, $1H_{min}$), 3.60 (s, $3H_{min}$), 3.57–3.46 (m, $1H_{all}$), 3.37 (dd, J = 14.1, 4.4 Hz, $1H_{min}$), 3.30 (dd, J = 14.0, 3.4 Hz, $1H_{maj}$), 3.26 (s, $3H_{maj}$), 2.94–2.84 (m, $1H_{all}$), 2.80 (dd, J = 13.9, 10.3 Hz, $1H_{maj}$), 2.76–2.65 (m, $1H_{all}$), 2.41 (dt, J = 16.2, 5.4 Hz, $1H_{min}$).

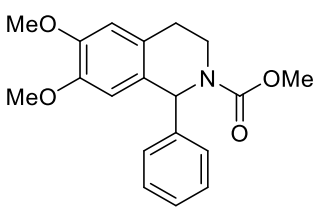
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.13, 152.29, 152.19, 145.20, 138.51, 138.19, 131.91, 131.77, 129.60, 129.47, 129.39, 129.09, 128.27, 128.20, 126.58, 126.54, 118.77, 118.41, 112.15, 111.79, 60.70, 60.66, 56.47, 56.21, 55.93, 52.74, 52.37, 39.51, 39.44, 38.51, 37.22, 28.37.

ESI-HRMS: calculated for $C_{20}H_{22}N_1O_4Br_1Na_1$ ($[M+Na]^+$): 442.062453, found: 442.062560.

HPLC (OD-3, *n*-heptane/*i*-PrOH 97:3, 298 K, 287 nm): t_R (minor) = 9.4 min, t_R (major) = 10.4 min, er = 97:3 (94% ee).

$[\alpha]_D^{25}$ = −33.2 (*c* = 0.25, $CHCl_3$).

methyl 6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (274a)



The reaction was performed according to **general procedure c** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and benzaldehyde dimethylacetal (**275a**, 18 µL, 0.12 mmol, 1.2 eq.). Purification by silica gel flash column chromatography (DCM/EtOAc 3–7.5%) afforded the product as a white foam (23.3 mg, 71 µmol, 71%).

R_F (DCM/EtOAc 19:1) = 0.44.

^{1}H-NMR (501 MHz, CD_3CN): δ = 7.33–7.28 (m, 2H), 7.28–7.20 (m, 3H), 6.77 (s, 1H), 6.63 (s, 1H), 6.24 (s, 1H), 3.89 (s, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 3.66 (s, 3H), 3.21 (s, 1H), 2.84 (ddd, J = 16.2, 10.3, 5.9 Hz, 1H), 2.68 (dt, J = 16.1, 4.3 Hz, 1H).

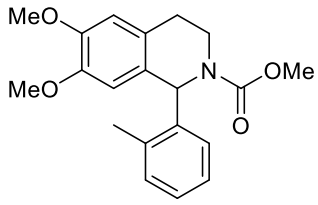
^{13}C-NMR (126 MHz, CD_3CN): δ = 156.87, 149.36, 148.68, 144.13, 129.24, 129.00, 128.28, 128.22, 128.11, 112.80, 112.46, 58.25, 56.41, 56.37, 53.18, 39.19, 28.42.

EI-HRMS: calculated for $C_{19}H_{21}N_1O_4$ ($[M]^+$): 327.146509, found: 327.146690.

HPLC (IA-3, *n*-heptane/*i*-PrOH 80:20, 298 K, 283 nm): t_R (major) = 9.1 min, t_R (minor) = 11.7 min, er = 97:3 (94% ee).

$[\alpha]_D^{25}$ = −168.8 (*c* = 0.25, $CHCl_3$).

methyl 6,7-dimethoxy-1-(*o*-tolyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (274b)



The reaction was performed according to **general procedure c** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and 2-methylbenzaldehyde dimethylacetal (**275b**, 20 µL, 0.12 mmol, 1.2 eq.). Purification by silica gel flash column chromatography (DCM/EtOAc 10%) afforded the product as a white foam (23.1 mg, 68 µmol, 68%).

R_F (hex/EtOAc 2:1) = 0.43.

^{1}H-NMR (501 MHz, CD_3CN): δ = 7.23 (d, J = 7.4 Hz, 1H), 7.16 (td, J = 7.4, 1.4 Hz, 1H), 7.07–7.01 (m, 1H), 6.76 (s, 1H), 6.72 (d, J = 7.8 Hz, 1H), 6.45 (s, 1H), 6.39 (s, 1H), 3.95 (s, 1H), 3.79 (s, 3H), 3.66 (s, 3H), 3.61 (s, 3H), 3.11 (ddd, J = 13.6, 12.1, 4.4 Hz, 1H), 2.92 (ddd, J = 18.0, 12.1, 6.2 Hz, 1H), 2.72–2.62 (m, 1H), 2.51 (s, 3H).

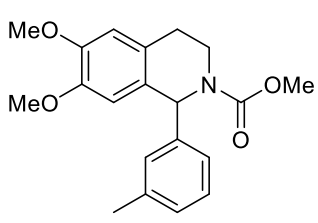
^{13}C-NMR (126 MHz, CD_3CN): δ = 157.10, 149.32, 148.74, 141.96, 138.47, 131.54, 130.52, 128.83, 128.41, 128.18, 126.42, 112.99, 112.00, 56.36, 56.32, 55.97, 53.25, 38.72, 28.04, 19.87.

EI-HRMS: calculated for $C_{20}H_{23}N_1O_4$ ($[M]^+$): 341.162159, found: 341.162460.

HPLC (IA-3, *n*-heptane/*i*-PrOH 80:20, 298 K, 283 nm): t_R (major) = 7.0 min, t_R (minor) = 8.3 min, er = 95:5 (90% ee).

$[\alpha]_D^{25}$ = −225.5 (*c* = 0.33, $CHCl_3$).

methyl 6,7-dimethoxy-1-(*m*-tolyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (274c)

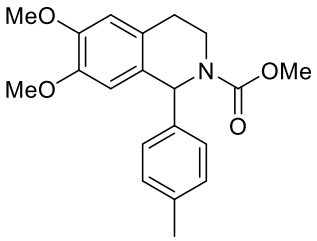


The reaction was performed according to **general procedure c** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and 3-methylbenzaldehyde dimethylacetal (**275c**, 20 µL, 0.12 mmol, 1.2 eq.). Purification by silica gel flash column chromatography (DCM/EtOAc 10%) afforded the product as a white foam (30.4 mg, 89 µmol, 89%).

R_F (hex/EtOAc 2:1) = 0.39.

^{1}H-NMR (501 MHz, CD_3CN): δ = 7.18 (t, J = 7.6 Hz, 1H), 7.10–7.03 (m, 2H), 7.00 (d, J = 7.6 Hz, 1H), 6.76 (s, 1H), 6.61 (s, 1H), 6.20 (s, 1H), 3.89 (s, 1H), 3.78 (s, 3H), 3.69 (s, 3H), 3.66 (s, 3H), 3.27–3.17 (m, 1H), 2.84 (ddd, J = 16.2, 10.4, 5.9 Hz, 1H), 2.74–2.64 (m, 1H), 2.28 (s, 3H).
^{13}C-NMR (126 MHz, CD_3CN): δ = 156.79, 149.34, 148.66, 144.12, 138.95, 129.59, 129.14, 128.97, 128.21, 128.19, 126.13, 112.77, 112.46, 58.25, 56.41, 56.36, 53.17, 39.18, 28.43, 21.51.
EI-HRMS: calculated for $C_{20}H_{23}N_1O_4$ ($[M]^+$): 341.162159, found: 341.162530.
HPLC (IA-3, *n*-heptane/*i*-PrOH 80:20, 298 K, 283 nm): t_R (major) = 8.0 min, t_R (minor) = 10.3 min, er = 96.5:3.5 (93% ee).
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = −172.0 (*c* = 0.34, $CHCl_3$).

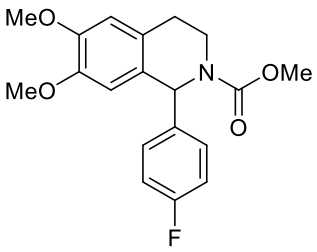
methyl 6,7-dimethoxy-1-(*p*-tolyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (274d)



The reaction was performed according to **general procedure c** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and 4-methylbenzaldehyde dimethylacetal (**275d**, 20 µL, 0.12 mmol, 1.2 eq.). Purification by silica gel flash column chromatography (DCM/EtOAc 5–10%) afforded the product as a white foam (31.9 mg, 93 µmol, 93%).

$\boldsymbol{R_F}$ (hex/EtOAc 2:1) = 0.39.
^{1}H-NMR (501 MHz, CD_3CN): δ = 7.14–7.06 (m, 4H), 6.76 (s, 1H), 6.60 (s, 1H), 6.20 (s, 1H), 3.89 (s, 1H), 3.78 (s, 3H), 3.68 (s, 3H), 3.65 (s, 3H), 3.25–3.10 (m, 1H), 2.83 (ddd, J = 16.3, 10.5, 5.9 Hz, 1H), 2.67 (dt, J = 16.1, 4.1 Hz, 1H), 2.28 (s, 3H).
^{13}C-NMR (126 MHz, CD_3CN): δ = 156.75, 149.31, 148.65, 141.16, 138.03, 129.83, 129.00, 128.25, 128.16, 112.78, 112.43, 57.97, 56.40, 56.36, 53.14, 39.00, 28.45, 21.07.
EI-HRMS: calculated for $C_{20}H_{23}N_1O_4$ ($[M]^+$): 341.162159, found: 341.162470.
HPLC (IA-3, *n*-heptane/*i*-PrOH 80:20, 298 K, 283 nm): t_R (major) = 9.1 min, t_R (minor) = 10.7 min, er = 94:6 (88% ee).
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = −163.2 (*c* = 0.44, $CHCl_3$).

methyl 1-(4-fluorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (274e)



The reaction was performed according to **general procedure c** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and 4-fluorobenzaldehyde dimethylacetal (**275e**, 19 µL, 0.12 mmol, 1.2 eq.). Purification by silica gel flash column chromatography (DCM/EtOAc 10%) afforded the product as a white foam (24.9 mg, 72 µmol, 72%).
$\boldsymbol{R_F}$ (hex/EtOAc 2:1) = 0.31.

^{1}H-NMR (501 MHz, CD_3CN): δ = 7.23 (dd, J = 8.6, 5.7 Hz, 2H), 7.07–6.99 (m, 2H), 6.77 (s, 1H), 6.60 (s, 1H), 6.23 (s, 1H), 3.90 (s, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 3.66 (s, 3H), 3.27–3.08 (m, 1H), 2.84 (ddd, J = 16.3, 10.5, 5.9 Hz, 1H), 2.67 (dt, J = 16.1, 4.2 Hz, 1H).

^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -114.96, -115.10.

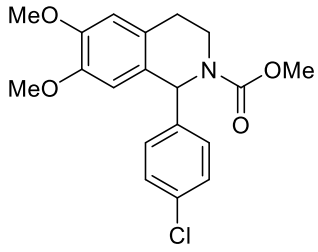
^{13}C-NMR (126 MHz, CD_3CN): δ = 163.87, 161.94, 156.80, 149.42, 148.73, 140.30, 140.28, 131.02, 130.95, 128.21, 127.86, 115.89, 115.72, 112.80, 112.39, 57.53, 56.40, 56.36, 53.21, 39.00, 28.41.

EI-HRMS: calculated for $C_{19}H_{20}N_1O_4F_1$ ($[M]^+$): 345.137087, found: 345.137460.

HPLC (IA-3, *n*-heptane/*i*-PrOH 80:20, 298 K, 283 nm): t_R (major) = 9.6 min, t_R (minor) = 12.1 min, er = 96.5:3.5 (93% ee).

$[\alpha]_D^{25}$ = −73.8 (*c* = 0.44, $CHCl_3$).

methyl 1-(4-chlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (274f)



The reaction was performed according to **general procedure c** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and 4-chlorobenzaldehyde dimethylacetal (**275f**, 20 µL, 0.12 mmol, 1.2 eq.). Purification by silica gel flash column chromatography (DCM/EtOAc 10%) afforded the product as a white foam (18.0 mg, 50 µmol, 50%).

R_F (hex/EtOAc 2:1) = 0.40.

^{1}H-NMR (501 MHz, CD_3CN): δ = 7.33–7.28 (m, 2H), 7.25–7.17 (m, 2H), 6.77 (s, 1H), 6.61 (s, 1H), 6.21 (s, 1H), 3.89 (s, 1H), 3.78 (s, 3H), 3.69 (s, 3H), 3.66 (s, 3H), 3.22–3.13 (m, 1H), 2.84 (ddd, J = 16.1, 10.3, 5.8 Hz, 1H), 2.67 (dt, J = 16.1, 4.3 Hz, 1H).

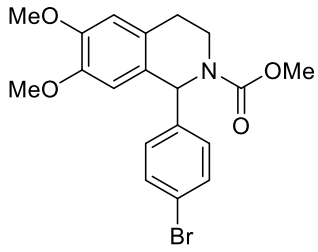
^{13}C-NMR (126 MHz, CD_3CN): δ = 156.93, 149.46, 148.74, 143.05, 133.54, 130.73, 129.20, 128.25, 127.58, 112.81, 112.37, 57.62, 56.41, 56.36, 53.25, 39.20, 28.38.

EI-HRMS: calculated for $C_{19}H_{20}N_1O_4Cl_1$ ($[M]^+$): 361.107537, found: 361.107910.

HPLC (IA-3, *n*-heptane/*i*-PrOH 90:10, 298 K, 284 nm): t_R (major) = 16.3 min, t_R (minor) = 19.5 min, er = 96.5:3.5 (93% ee).

$[\alpha]_D^{25}$ = −164.0 (*c* = 0.27, $CHCl_3$).

methyl 1-(4-bromophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (274g)



The reaction was performed according to **general procedure c** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and 4-bromobenzaldehyde dimethylacetal (**275g**, 20 µL, 0.12 mmol, 1.2 eq.). Purification by silica gel flash column chromatography (DCM/EtOAc 10%) afforded the product as a white foam (30.8 mg, 76 µmol, 76%).

R_F (hex/EtOAc 2:1) = 0.38.

^{1}H-NMR (501 MHz, CD_3CN): δ = 7.47–7.41 (m, 2H), 7.18–7.11 (m, 2H), 6.76 (s, 1H), 6.61 (s, 1H), 6.20 (s, 1H), 3.89 (s, 1H), 3.78 (s, 3H), 3.68 (s, 3H), 3.66 (s, 3H), 3.24–3.09 (m, 1H), 2.83 (ddd, J = 16.2, 10.3, 5.8 Hz, 1H), 2.66 (dt, J = 16.1, 4.3 Hz, 1H).

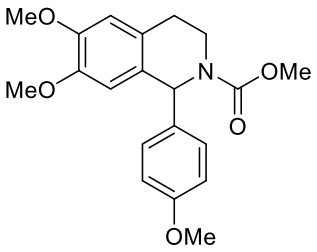
^{13}C-NMR (126 MHz, CD_3CN): δ = 156.89, 149.46, 148.74, 143.51, 132.20, 131.07, 128.24, 127.49, 121.68, 112.80, 112.36, 57.68, 56.41, 56.36, 53.25, 39.21, 28.37.

ESI-HRMS: calculated for $C_{19}H_{20}Br_1N_1Na_1O_4$ ($[M+Na]^+$): 428.04679, found: 428.04678.

HPLC (IA-3, *n*-heptane/*i*-PrOH 90:10, 298 K, 284 nm): t_R (major) = 16.3 min, t_R (minor) = 19.5 min, er = 96.5:3.5 (93% ee).

$[\alpha]_D^{25}$ = −150.2 (*c* = 0.27, $CHCl_3$).

methyl 6,7-dimethoxy-1-(4-methoxyphenyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (274h)



The reaction was performed according to **general procedure c** at 0 °C for 72 h with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and 4-methoxybenzaldehyde dimethylacetal (**275h**, 20.5 µL, 0.12 mmol, 1.2 eq.). Purification by silica gel flash column chromatography (DCM/EtOAc 10%) afforded the product as a white foam (21.2 mg, 59 µmol, 59%).

R_F (hex/EtOAc 1:1) = 0.51.

^{1}H-NMR (501 MHz, CD_3CN): δ = 7.15–7.09 (m, 2H), 6.88–6.80 (m, 2H), 6.76 (s, 1H), 6.58 (s, 1H), 6.19 (s, 1H), 3.91 (s, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.68 (s, 3H), 3.65 (s, 3H), 3.22–3.07 (m, 1H), 2.83 (ddd, J = 16.5, 10.8, 6.0 Hz, 1H), 2.67 (dt, J = 16.1, 4.0 Hz, 1H).

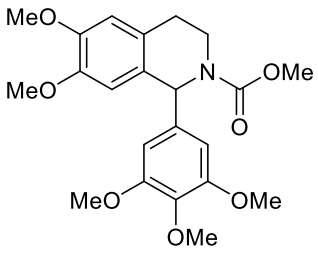
^{13}C-NMR (126 MHz, CD_3CN): δ = 159.93, 156.82, 149.29, 148.65, 136.22, 130.32, 128.34, 128.14, 114.48, 112.78, 112.41, 57.62, 56.39, 56.36, 55.87, 53.13, 38.77, 28.46.

EI-HRMS: calculated for $C_{20}H_{23}N_1O_5$ ($[M]^+$): 357.157074, found: 357.157540.

HPLC (IA-3, *n*-heptane/*i*-PrOH 70:30, 298 K, 283 nm): t_R (major) = 8.9 min, t_R (minor) = 10.3 min, er = 90:10 (80% ee).

$[\alpha]_D^{25}$ = −150.5 (*c* = 0.30, $CHCl_3$).

methyl 6,7-dimethoxy-1-(3,4,5-trimethoxyphenyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (274i)



The reaction was performed according to **general procedure d** at 0 °C for 72 h with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and 3,4,5-trimethoxybenzaldehyde dimethylacetal (**275i**, 45.9 mg, 0.18 mmol, 1.8 eq.). Purification by silica gel flash column chromatography (hex/EtOAc 1:1) and preparative silica gel thin layer chromatography (hex/EtOAc 60:40) afforded the product as a white foam (16.7 mg, 40 µmol, 40%).

R_F (hex/EtOAc 1:1) = 0.27.

^{1}H-NMR (501 MHz, CD_3CN): δ = 6.76 (s, 1H), 6.65 (s, 1H), 6.49 (s, 2H), 6.15 (s, 1H), 3.90 (s, 1H), 3.79 (s, 3H), 3.71 (s, 6H), 3.70 (s, 3H), 3.69 (s, 6H), 3.29 (q, J = 8.2 Hz, 1H), 2.84 (ddd, J = 16.0, 10.2, 5.8 Hz, 1H), 2.72 (dt, J = 16.1, 4.3 Hz, 1H).

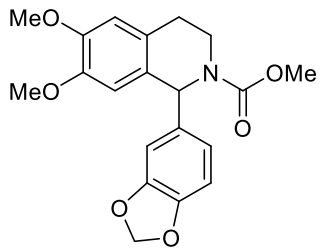
^{13}C-NMR (126 MHz, CD_3CN): δ = 154.09, 149.37, 148.67, 139.99, 138.22, 128.28, 127.99, 112.72, 112.47, 106.50, 60.79, 58.43, 56.65, 56.46, 56.34, 53.20, 39.43, 28.49.

ESI-HRMS: calculated for $C_{22}H_{27}N_1Na_1O_7$ ($[M+Na]^+$): 440.16797, found: 440.16812.

HPLC (IA-3, *n*-heptane/*i*-PrOH 60:40, 298 K, 282 nm): t_R (minor) = 10.4 min, t_R (major) = 19.6 min, er = 93:7 (86% ee).

$[\alpha]_D^{25}$ = −118.1 (*c* = 0.19, $CHCl_3$).

methyl 1-(benzo[*d*][1,3]dioxol-5-yl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (274j)



The reaction was performed according to **general procedure d** at 0 °C for 72 h with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and benzo[*d*][1,3]dioxole-5-carbaldehyde dimethylacetal (**275j**, 37.2 mg, 0.18 mmol, 1.8 eq.). Purification by silica gel flash column chromatography (DCM/EtOAc 9:1) afforded the product as a white foam (16.0 mg, 43 µmol, 43%).

R_F (hex/EtOAc 2:1) = 0.53.

^{1}H-NMR (501 MHz, CD_3CN): δ = 6.76–6.72 (m, 3H), 6.70–6.64 (m, 1H), 6.59 (s, 1H), 6.15 (s, 1H), 5.92 (q, J = 1.1 Hz, 2H), 3.91 (s, 1H), 3.78 (s, 3H), 3.68 (s, 3H), 3.66 (s, 3H), 3.26–3.12 (m, 1H), 2.82 (ddd, J = 16.5, 10.7, 6.0 Hz, 1H), 2.67 (dt, J = 16.2, 4.0 Hz, 1H).

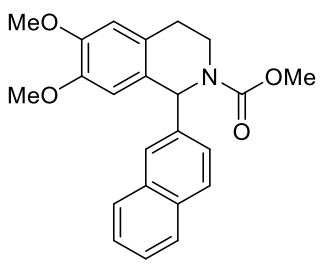
^{13}C-NMR (126 MHz, CD_3CN): δ = 148.36, 147.68, 147.65, 146.81, 137.19, 127.15, 127.12, 121.61, 111.76, 111.40, 108.47, 107.59, 101.36, 56.92, 55.39, 55.36, 52.16, 37.83, 27.42.

EI-HRMS: calculated for $C_{20}H_{21}N_1O_6$ ($[M]^+$): 371.136339, found: 371.136810.

HPLC (IA-3, *n*-heptane/*i*-PrOH 60:40, 298 K, 283 nm): t_R (major) = 9.0 min, t_R (minor) = 10.5 min, er = 96:4 (92% ee).

$[\alpha]_D^{25}$ = −172.6 (*c* = 0.12, $CHCl_3$).

methyl 6,7-dimethoxy-1-(naphthalen-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (274k)



The reaction was performed according to **general procedure c** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and 2-naphthaldehyde dimethylacetal (**275k**, 22 µL, 0.12 mmol, 1.2 eq.). Purification by silica gel flash column chromatography (DCM/EtOAc 10%) afforded the product as a white foam (32.7 mg, 87 µmol, 87%).

R_F (hex/EtOAc 2:1) = 0.35.

^{1}H-NMR (501 MHz, CD_3CN): δ = 7.82 (dd, J = 9.0, 6.1 Hz, 2H), 7.79–7.74 (m, 1H), 7.57 (d, J = 1.8 Hz, 1H), 7.51–7.42 (m, 3H), 6.80 (s, 1H), 6.69 (s, 1H), 6.40 (s, 1H), 3.92 (s, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 3.65 (s, 3H), 3.24 (ddd, J = 14.1, 10.6, 4.5 Hz, 1H), 2.87 (ddd, J = 16.3, 10.5, 5.9 Hz, 1H), 2.70 (dt, J = 16.2, 4.1 Hz, 1H).

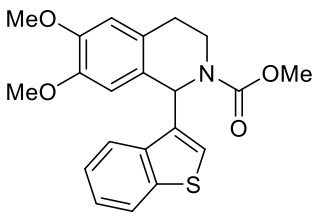
^{13}C-NMR (126 MHz, CD_3CN): δ = 157.03, 149.45, 148.71, 141.64, 134.00, 133.62, 129.00, 128.96, 128.44, 128.36, 127.88, 127.80, 127.31, 127.20, 127.03, 112.86, 112.57, 58.40, 56.39, 56.37, 53.25, 39.19, 28.45.

EI-HRMS: calculated for $C_{23}H_{23}N_1O_4$ ($[M]^+$): 377.162159, found: 377.162620.

HPLC (IA-3, *n*-heptane/*i*-PrOH 90:10, 298 K, 277 nm): t_R (major) = 20.2 min, t_R (minor) = 22.7 min, er = 96:4 (92% ee).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = −155.0 (*c* = 0.35, $CHCl_3$).

Methyl 1-(benzo[*b*]thiophen-3-yl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (274l)



The reaction was performed according to **general procedure c** with carbamate **120b** (23.9 mg, 0.10 mmol, 1.00 eq.) and benzo[*b*]thiophene-3-carbaldehyde dimethylacetal (**275l**, 21 µL, 0.12 mmol, 1.2 eq.). Purification by silica gel flash column chromatography (DCM/EtOAc 10%) afforded the product as a white foam (31.4 mg, 82 µmol, 82%).

$\boldsymbol{R}_\mathbf{F}$ (hex/EtOAc 2:1) = 0.39.

^{1}H-NMR (501 MHz, CD_3CN): δ = 8.16 (s, 1H), 7.90 (dt, J = 7.9, 1.0 Hz, 1H), 7.43 (ddd, J = 8.1, 7.1, 1.2 Hz, 1H), 7.38 (ddd, J = 8.2, 7.0, 1.3 Hz, 1H), 6.82 (s, 1H), 6.77 (s, 1H), 6.71–6.62 (m, 2H), 3.93 (s, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.64 (s, 3H), 3.11–3.00 (m, 1H), 2.92 (ddd, J = 16.4, 12.4, 6.1 Hz, 1H), 2.65 (ddd, J = 16.4, 4.3, 1.5 Hz, 1H).

^{13}C-NMR (126 MHz, CD_3CN): δ = 156.91, 149.53, 148.62, 141.38, 139.34, 139.21, 128.25, 128.04, 127.74, 125.65, 125.35, 123.79, 123.56, 112.96, 112.25, 56.35, 53.44, 38.46, 28.03.

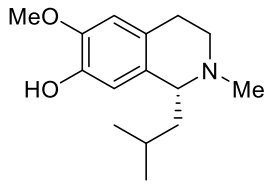
EI-HRMS: calculated for $C_{21}H_{21}N_1O_4S_1$ ($[M]^+$): 383.118581, found: 383.119240.

HPLC (IA-3, *n*-heptane/*i*-PrOH 80:20, 298 K, 282 nm): t_R (major) = 8.8 min, t_R (minor) = 11.7 min, er = 92:8 (84% ee).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = −150.0 (*c* = 0.34, $CHCl_3$).

7.2. Synthesis of Natural Products

(*R*)-Lophocerine (251)



A flame-dried 25 mL flask under argon was charged with Pictet-Spengler product **248** (24.4 mg, 0.0832 mmol, 1.00 eq.) and dry THF (5.0 mL). The solution was cooled to 0 °C and diisobutylaluminum hydride (1.0 M in PhMe, 1.3 mL, 1.3 mmol, 16 eq.) was added slowly. The mixture was then warmed to RT and stirred for 1 h, when full conversion of the starting material was observed by TLC. The reaction was quenched by addition of sat. aq. sodium potassium tartrate (15 mL) and stirred for another 30 min. The phases were separated and the aqueous layer was extracted with DCM (3x). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel flash column chromatography (DCM/MeOH 8–10%) gave Lophocerine (**251**, 19.7 mg, 0.079 mmol, 95%) as a yellow oil.

$\boldsymbol{R_F}$ (DCM/MeOH 9:1) = 0.26.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 6.61 (s, 1H), 6.54 (s, 1H), 3.85 (s, 3H), 3.46 (dd, J = 8.1, 5.2 Hz, 1H), 3.20 (ddd, J = 12.9, 8.9, 5.3 Hz, 1H), 2.90–2.76 (m, 2H), 2.57–2.47 (m, 1H), 2.45 (s, 3H), 1.85 (ddt, J = 15.0, 13.1, 6.6 Hz, 1H), 1.69 (ddd, J = 13.9, 8.1, 5.7 Hz, 1H), 1.39 (ddd, J = 13.9, 8.3, 5.2 Hz, 1H), 0.97 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.7 Hz, 3H).

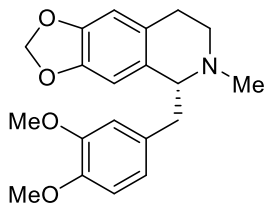
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 145.17, 143.89, 131.34, 124.80, 113.52, 110.87, 60.83, 56.01, 45.79, 45.49, 41.86, 25.29, 23.43, 23.37, 22.57.

ESI-HRMS: calculated for $C_{15}H_{24}N_1O_2$ ($[M+H]^+$): 250.180154, found: 250.180370.

HPLC (IC-3, (*n*-heptane + 0.1% Et_3N)/*i*-PrOH 70:30, 298 K, 286 nm): t_R (minor) = 3.0 min, t_R (major) = 7.5 min, er = 96:4 (92% ee).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25}}$ = −12.0 (*c* = 0.12, $CHCl_3$).

(*R*)-Romneine (252)



A flame-dried 25 mL flask under argon was charged with Pictet-Spengler product **246** (27.5 mg, 0.0714 mmol, 1.00 eq.) and dry THF (5.0 mL). The solution was cooled to 0 °C and diisobutylaluminum hydride (1.0 M in PhMe, 1.1 mL, 1.1 mmol, 15 eq.) was added slowly. The mixture was then warmed to RT and stirred for 1 h, when full conversion of the starting material was observed by TLC. The reaction was quenched by addition of sat. aq. sodium potassium tartrate (15 mL) and stirred for another 30 min. The phases were separated and the aqueous layer was extracted with DCM (3x). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel flash column chromatography (DCM/MeOH 9:1) gave romneine (**252**, 24.3 mg, 0.071 mmol, >99%) as a colorless oil. The NMR-spectroscopic data was in agreement with the literature.[205]

$\boldsymbol{R_F}$ (DCM/MeOH 9:1) = 0.42.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 6.76 (d, J = 8.2 Hz, 1H), 6.68 (dd, J = 8.2, 2.0 Hz, 1H), 6.61 (d, J = 2.0 Hz, 1H), 6.53 (s, 1H), 6.26 (s, 1H), 5.88–5.83 (m, 2H), 3.85 (s, 3H), 3.79 (s, 3H), 3.68 (t, J = 6.0 Hz, 1H), 3.17–3.10 (m, 1H), 3.06 (dd, J = 14.0, 5.7 Hz, 1H), 2.86–2.68 (m, 3H), 2.53 (dt, J = 15.4, 4.7 Hz, 1H), 2.49 (s, 3H).

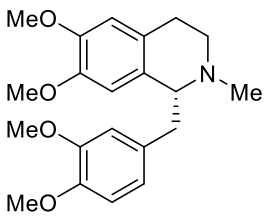
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 148.64, 147.48, 146.01, 145.50, 132.31, 130.49, 127.39, 121.72, 113.01, 111.10, 108.48, 108.04, 100.67, 65.28, 55.97, 55.91, 46.96, 42.69, 41.24, 25.86.

ESI-HRMS: calculated for $C_{20}H_{24}N_1O_4$ ($[M+H]^+$): 342.16998, found: 342.16992.

HPLC (OJ-3, (*n*-heptane + 0.1% Et_3N)/*i*-PrOH 70:30, 298 K, 287 nm): t_R (minor) = 7.0 min, t_R (major) = 8.2 min, er = 96:4 (92% ee).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25}}$ = −17.9 (*c* = 0.12, $CHCl_3$).

(*R*)-Laudanosine (253)



A flame-dried 25 mL flask under argon was charged with Pictet-Spengler product **226c** (37.3 mg, 0.0929 mmol, 1.00 eq.) and dry THF (5.0 mL). The solution was cooled to 0 °C and diisobutylaluminum hydride (1.0 M in PhMe, 1.4 mL, 1.4 mmol, 15 eq.) was added slowly. The mixture was then warmed to RT and stirred for 1 h, when full conversion of the starting material was observed by TLC. The reaction was quenched by addition of sat. aq. sodium potassium tartrate (15 mL) and stirred for another 30 min. The phases were separated and the aqueous layer was extracted with DCM (3x). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel flash column chromatography (DCM/MeOH 9:1) gave laudanosine (**253**, 31.2 mg, 0.087 mmol, 94%) as a white solid. The NMR-spectroscopic data was in agreement with the literature.[206]

$\boldsymbol{R_F}$ (DCM/MeOH 9:1) = 0.37.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 6.76 (d, J = 8.1 Hz, 1H), 6.63 (dd, J = 8.1, 2.0 Hz, 1H), 6.59 (d, J = 2.0 Hz, 1H), 6.55 (s, 1H), 6.05 (s, 1H), 3.83 (s, 3H), 3.83 (s, 3H), 3.78 (s, 3H), 3.70 (dd, J = 7.9, 4.8 Hz, 1H), 3.56 (s, 3H), 3.21–3.11 (m, 2H), 2.87–2.73 (m, 3H), 2.58 (dt, J = 15.6, 4.7 Hz, 1H), 2.54 (s, 3H).

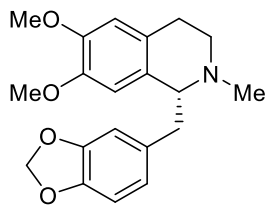
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 148.69, 147.47, 147.43, 146.47, 132.53, 129.20, 126.04, 121.99, 113.16, 111.32, 111.23, 111.15, 64.97, 56.03, 55.93, 55.88, 55.67, 47.05, 42.73, 40.97, 25.58.

ESI-HRMS: calculated for $C_{21}H_{28}N_1O_4$ ($[M+H]^+$): 358.20128, found: 358.20111.

HPLC (AD-3, (*n*-heptane + 0.1% Et_3N)/*i*-PrOH 80:20, 298 K, 282 nm): t_R (minor) = 5.9 min, t_R (major) = 6.5 min, er = 97.5:2.5 (95% ee).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25}}$ = −46.5 (*c* = 0.20, $CHCl_3$).

(*R*)-1-(benzo[*d*][1,3]dioxol-5-ylmethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (254)



A flame-dried 50 mL flask under argon was charged with Pictet-Spengler product **226b** (99.0 mg, 0.257 mmol, 1.00 eq.) and dry THF (15 mL). The solution was cooled to 0 °C and diisobutylaluminum hydride (1.0 M in PhMe, 3.8 mL, 3.8 mmol, 15 eq.) was added slowly. The mixture was then warmed to RT and stirred for 1 h, when full conversion of the starting material was observed by TLC. The reaction was quenched by addition of sat. aq. sodium potassium tartrate (20 mL) and stirred for another 30 min. The phases were separated and the aqueous layer was extracted with DCM (3x). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel flash column chromatography (DCM/MeOH 9:1) gave the desired product (80.2 mg, 0.235 mmol, 91%) as a white solid. The NMR-spectroscopic data was in agreement with the literature.[207]

$\boldsymbol{R_F}$ (DCM/MeOH 9:1) = 0.49.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 6.70 (d, J = 7.9 Hz, 1H), 6.64 (d, J = 1.7 Hz, 1H), 6.57–6.53 (m, 2H), 6.11 (s, 1H), 5.92–5.88 (m, 2H), 3.84 (s, 3H), 3.66 (dd, J = 7.4, 5.4 Hz, 1H), 3.62 (s, 3H), 3.17 (ddd, J = 12.5, 8.9, 5.1 Hz, 1H), 3.09 (dd, J = 13.8, 5.4 Hz, 1H), 2.83 (ddd, J = 15.1, 8.9, 5.7 Hz, 1H), 2.79–2.71 (m, 2H), 2.59 (dt, J = 15.8, 4.6 Hz, 1H), 2.51 (s, 3H).

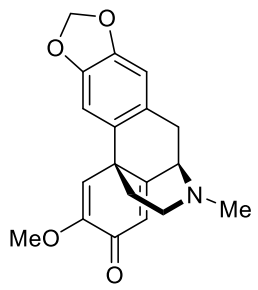
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 147.49, 147.45, 146.57, 145.85, 133.93, 129.30, 126.08, 122.75, 111.36, 111.14, 110.26, 108.07, 100.85, 65.02, 55.89, 55.73, 46.93, 42.74, 41.17, 25.44.

ESI-HRMS: calculated for $C_{20}H_{24}N_1O_4$ ($[M+H]^+$): 342.16998, found: 342.17006.

HPLC (AD-3, (*n*-heptane + 0.1% Et_3N)/*i*-PrOH 80:20, 298 K, 282 nm): t_R (minor) = 6.1 min, t_R (major) = 5.4 min, er = 97:3 (94% ee).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = −67.1 (*c* = 0.29, $CHCl_3$).

(*R*)-Amurine (255)



A 10 mL IKA ElectraSyn vial was charged with 1-(benzo[*d*][1,3]dioxol-5-ylmethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**254**, 34.1 mg, 0.10 mmol, 1.0 eq.), HPLC grade CH_3CN (10.0 mL), and HBF_4 (48 wt% in H_2O, 52 µL, 0.40 mmol, 4.0 eq.). The mixture was mounted on an ElectraSyn GOGO module equipped with a BDD anode (approx. 4.2 cm^2 submerged area) and a Pt cathode. The reaction was cooled to 0 °C and constant current electrolysis was performed (J = 0.75 mA/cm^2, I = 3.1 mA, z = 2.2 F). After complete reaction, the mixture was diluted with EtOAc (50 mL) and quenched with sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc (3x), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel flash column chromatography (EtOAc/Et_3N 4:1) gave amurine (**255**,

24.5 mg, 0.075 mmol, 75%) as a yellow foam. The NMR-spectroscopic data was in agreement with the literature.[117]

$\boldsymbol{R_F}$ (EtOAc/Et_3N 4:1) = 0.35.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 6.82 (s, 1H), 6.59 (s, 1H), 6.30 (s, 1H), 6.28 (s, 1H), 5.93 (d, J = 1.4 Hz, 1H), 5.90 (d, J = 1.4 Hz, 1H), 3.78 (s, 3H), 3.65 (d, J = 6.1 Hz, 1H), 3.29 (d, J = 17.9 Hz, 1H), 2.98 (dd, J = 17.9, 6.2 Hz, 1H), 2.61–2.52 (m, 2H), 2.44 (s, 3H), 1.91 (ddd, J = 12.7, 10.8, 6.5 Hz, 1H), 1.80 (dt, J = 12.5, 2.6 Hz, 1H).

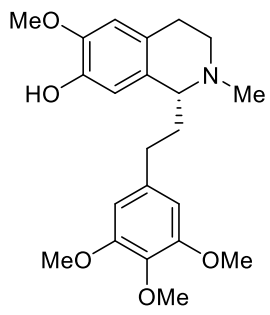
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 181.03, 161.44, 151.49, 147.01, 146.89, 131.11, 129.69, 122.31, 118.87, 107.63, 105.24, 101.31, 60.83, 55.17, 45.77, 42.55, 41.82, 41.35, 33.04.

ESI-HRMS: calculated for $C_{19}H_{20}N_1O_4$ ($[M+H]^+$): 326.13868, found: 326.13901.

HPLC (IE-3, (*n*-heptane + 0.1% Et_3N)/*i*-PrOH 50:50, 298 K, 290 nm): t_R (minor) = 19.1 min, t_R (major) = 11.9 min, er = 96.5:3.5 (93% ee).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25}}$ = +5.5 (*c* = 0.18, $CHCl_3$).

(*R*)-6-methoxy-2-methyl-1-(3,4,5-trimethoxyphenethyl)-1,2,3,4-tetrahydroisoquinolin-7-ol (256)



A flame-dried 25 mL flask under argon was charged with Pictet-Spengler product **249** (40.3 mg, 0.0934 mmol, 1.00 eq.) and dry THF (5.0 mL). The solution was cooled to 0 °C and diisobutylaluminum hydride (1.0 M in PhMe, 1.4 mL, 1.4 mmol, 15 eq.) was added slowly. The mixture was then warmed to RT and stirred for 1 h, when full conversion of the starting material was observed by TLC. The reaction was quenched by addition of sat. aq. sodium potassium tartrate (15 mL) and stirred for another 30 min. The phases were separated and the aqueous layer was extracted with DCM (3x). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel flash column chromatography (DCM/MeOH 9:1) gave the desired product (31.2 mg, 0.087 mmol, 94%) as a colorless oil. The NMR-spectroscopic data was in agreement with the literature.[116]

$\boldsymbol{R_F}$ (DCM/MeOH 9:1) = 0.34.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 6.67 (s, 1H), 6.55 (s, 1H), 6.40 (s, 2H), 3.85 (s, 3H), 3.83 (s, 6H), 3.81 (s, 3H), 3.41 (t, J = 5.4 Hz, 1H), 3.20–3.09 (m, 1H), 2.80–2.63 (m, 4H), 2.55–2.48 (m, 1H), 2.47 (s, 3H), 2.10–1.98 (m, 2H).

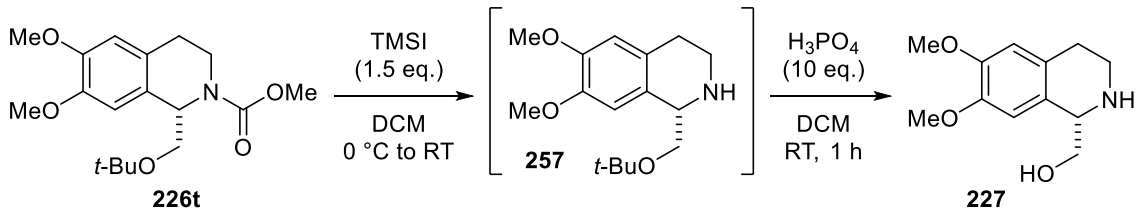
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 153.16, 145.12, 143.99, 138.75, 136.05, 130.43, 126.07, 112.97, 110.74, 105.47, 62.78, 60.95, 56.19, 55.99, 48.44, 42.80, 36.72, 32.02, 25.67.

ESI-HRMS: calculated for $C_{22}H_{30}N_1O_5$ ($[M+H]^+$): 388.21185, found: 388.21188.

HPLC (OJ-3, (*n*-heptane + 0.1% Et_3N)/*i*-PrOH 70:30, 298 K, 286 nm): t_R (minor) = 6.9 min, t_R (major) = 9.0 min, er = 94:6 (88% ee).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25}}$ = −10.9 (*c* = 0.11, $CHCl_3$).

(*S*)-Calycotomine (227)



A flame-dried Schlenk under argon was charged with Pictet–Spengler product **226t** (95.1 mg, 0.282 mmol, 1.00 eq.) and dry DCM (5.5 mL). The mixture was cooled to 0 °C and TMSI (60 µL, 0.42 mmol, 1.5 eq.) was added. The reaction vessel was covered in Al-foil and the mixture was stirred overnight while slowly warming to RT. The reaction was quenched by addition of sat. aq. $NaHCO_3$, the aqueous layer was extracted with EtOAc (3x), the combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure.

The crude material was redissolved in DCM (5.5 mL) in a 10 mL vial, aq. H_3PO_4 (85 wt%, 0.2 mL, 3.0 mmol, 10 eq.) was added, and the mixture was stirred vigorously at RT for 1 h. The reaction was quenched by addition of sat. aq. Na_2CO_3 and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude material was redissolved in DCM (25 mL) and extracted with aq. HCl (10 w%, 3x). The combined HCl-layers were washed with DCM, basified with solid NaOH, and reextracted with DCM (3x). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give calycotomine (**227**, 41.7 mg, 0.187 mmol, 66%) as a white solid.

^{1}H-NMR (501 MHz, CD_3OD): δ = 6.75 (s, 1H), 6.68 (s, 1H), 3.92 (dd, J = 8.4, 4.0 Hz, 1H), 3.80 (dd, J = 11.2, 4.1 Hz, 1H), 3.78 (s, 2H), 3.78 (s, 3H), 3.72 (dd, J = 11.1, 8.4 Hz, 1H), 3.17 (ddd, J = 12.3, 7.2, 5.2 Hz, 1H), 2.92 (dt, J = 11.8, 5.6 Hz, 1H), 2.81–2.67 (m, 2H).

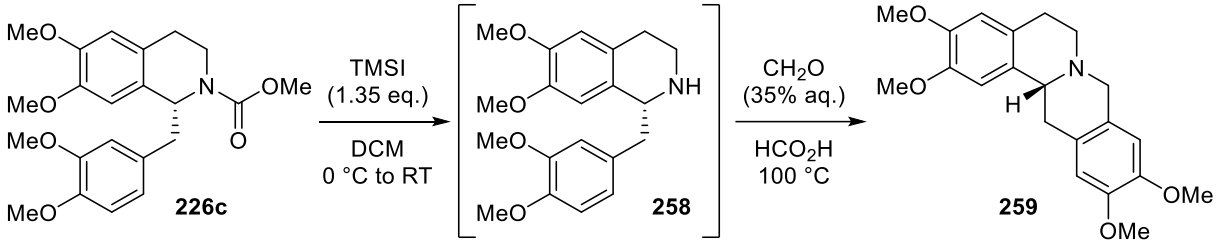
^{13}C-NMR (126 MHz, CD_3OD): δ = 149.35, 148.79, 129.06, 128.16, 113.51, 111.42, 65.16, 57.99, 56.58, 56.40, 40.35, 29.49.

ESI-HRMS: calculated for $C_{12}H_{18}N_1O_3$ ($[M+H]^+$): 224.12812, found: 224.12816.

HPLC was measured after derivatization to the *N*-Boc protected amine according to a literature procedure[208] (IA-3, *n*-heptane/*i*-PrOH 70:30, 298 K, 282 nm): t_R (minor) = 6.2 min, t_R (major) = 5.2 min, er = 91.5:8.5 (83% ee).

$[\alpha]_D^{25}$ = −9.8 (*c* = 0.16, $CHCl_3$); Lit.:[209] $[\alpha]_D^{25}$ = −15.0 (*c* = 0.18, $CHCl_3$).

(*R*)-Xylopinine (259)



A flame-dried Schlenk under argon was charged with Pictet–Spengler product **226c** (67.0 mg, 0.167 mmol, 1.00 eq.) and dry DCM (3.5 mL). The mixture was cooled to 0 °C and TMSI (32 µL, 0.22 mmol, 1.4 eq.) was added. The reaction vessel was covered in Al-foil and the mixture was stirred overnight while slowly warming to RT. The reaction was quenched by addition of sat. aq. $NaHCO_3$, the aqueous layer was extracted with EtOAc (3x), the combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure.

The crude material was redissolved in formic acid (98%, 0.75 mL) in a 5 mL vial, aq. CH_2O (35 wt%, 0.42 mL, 5.3 mmol, 32 eq.) was added, and the mixture was heated to 100 °C for 1 h. After cooling to RT, the reaction was quenched by addition of sat. aq. $NaHCO_3$ and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel flash column chromatography (EtOAc/Et_3N 99:1) gave (*R*)-xylopinine (**259**, 45.1 mg, 0.127 mmol, 76%) as a white solid. The NMR-spectroscopic data was in agreement with the literature.[210]

$\boldsymbol{R_F}$ (EtOAc/Et_3N 99:1) = 0.43.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 6.74 (s, 1H), 6.66 (s, 1H), 6.61 (s, 1H), 6.57 (s, 1H), 3.94 (d, J = 14.5 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.85 (s, 4H), 3.84 (s, 3H), 3.67 (d, J = 14.5 Hz, 1H), 3.58 (dd, J = 11.3, 3.9 Hz, 1H), 3.24 (dd, J = 15.9, 4.0 Hz, 1H), 3.18–3.09 (m, 2H), 2.83 (dd, J = 15.5, 11.5 Hz, 1H), 2.69–2.57 (m, 2H).

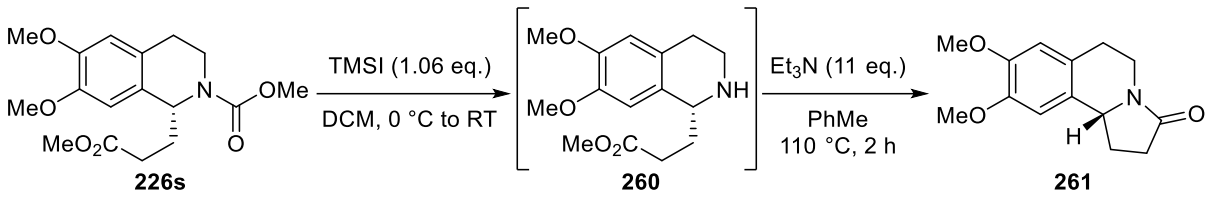
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 147.73, 147.59, 147.54, 147.50, 129.89, 126.85, 126.46, 126.40, 111.49, 111.46, 109.13, 108.65, 59.70, 58.35, 56.15, 56.05, 56.01, 55.94, 51.47, 36.52, 29.16.

EI-HRMS: calculated for $C_{21}H_{25}N_1O_4$ ($[M]^+$): 355.177809, found: 355.178410.

HPLC (AD-3, (*n*-heptane + 0.1% Et_3N)/*i*-PrOH 60:40, 298 K, 283 nm): t_R (minor) = 19.8 min, t_R (major) = 6.3 min, er = 90:10 (80% ee).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25}}$ = +159.4 (*c* = 0.35, $CHCl_3$); Lit. (for the opposite enantiomer):[211] $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25}}$ = −280 (*c* = 0.1, $CHCl_3$).

(*R*)-8,9-dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (261)



A flame-dried Schlenk under argon was charged with Pictet–Spengler product **226s** (78 mg, 0.23 mmol, 1.0 eq.) and dry DCM (2.5 mL). The solution was cooled to 0 °C and TMSI (35 µL, 0.25 mmol, 1.06 eq.) was added. The reaction vessel was covered in Al-foil and the mixture was stirred overnight while slowly warming to RT. The reaction was quenched by addition of sat. aq. $NaHCO_3$, the aqueous layer was extracted with EtOAc (3x), the combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure.

The crude material was redissolved in dry PhMe (5 mL) in a 25 mL flask equipped with a reflux condenser, Et_3N (0.35mL) was added, and the mixture was heated to reflux for 2 h. After cooling to RT, the reaction was quenched by addition of sat. aq. $NaHCO_3$, the aqueous layer was extracted with EtOAc (3x), the combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (DCM/acetone 10–40%) gave unreacted starting material **226s** (23.9 mg, 0.071 mmol, 31%) as well as 8,9-dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3(2H)-one (**261**, 29.5 mg, 0.119 mmol, 52%, 74% brsm) as a yellow oil. The NMR-spectroscopic data was in agreement with the literature.[212]

$\boldsymbol{R_F}$ (DCM/acetone 1:1) = 0.47.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 6.61 (s, 1H), 6.56 (s, 1H), 4.71 (t, J = 7.9 Hz, 1H), 4.30 (ddd, J = 12.8, 6.1, 2.0 Hz, 1H), 3.86 (s, 4H), 3.85 (s, 3H), 3.06–2.94 (m, 1H), 2.87 (ddd, J = 17.2, 11.4, 6.1 Hz, 1H), 2.70–2.65 (m, 1H), 2.65–2.60 (m, 1H), 2.60–2.51 (m, 1H), 2.50–2.40 (m, 1H), 1.89–1.76 (m, 1H).

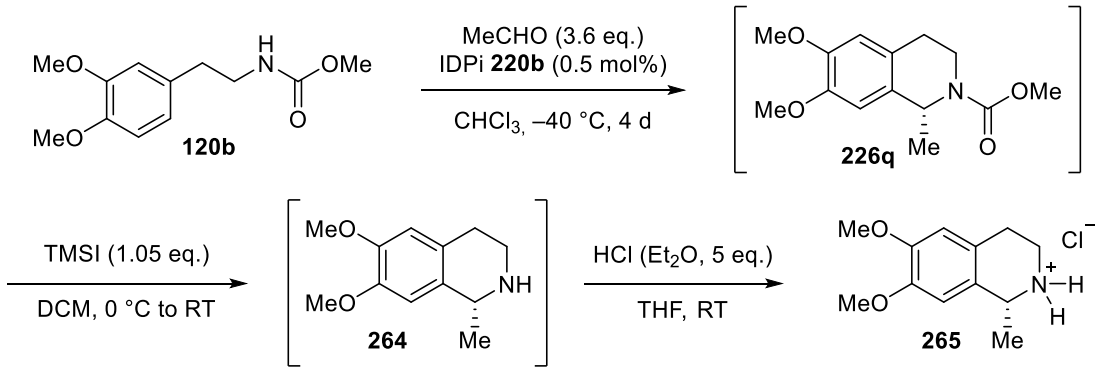
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 173.25, 148.26, 148.07, 129.49, 125.68, 111.83, 107.80, 56.68, 56.19, 56.04, 37.18, 31.91, 28.22, 27.89.

EI-HRMS: calculated for $C_{14}H_{17}N_1O_3$ ($[M]^+$): 247.120294, found: 247.120490.

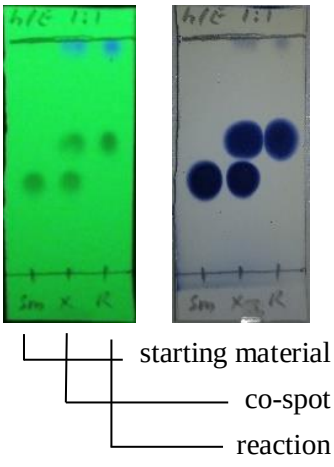
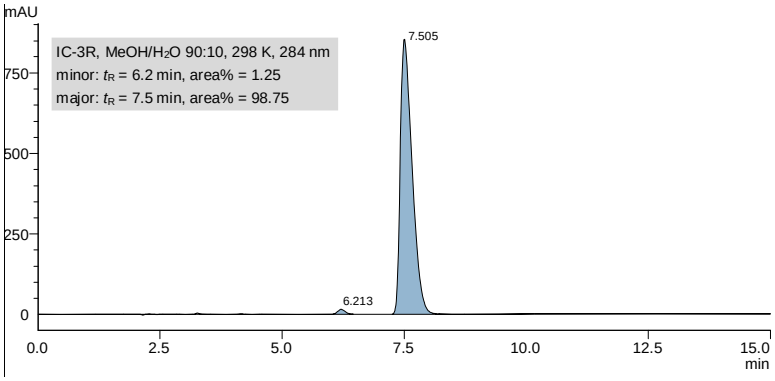
HPLC (OJ-3, *n*-heptane/*i*-PrOH 60:40, 298 K, 283 nm): t_R (minor) = 5.8 min, t_R (major) = 7.1 min, er = 96:4 (92% ee).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25}}$ = +124.6 (*c* = 0.18, $CHCl_3$); Lit.:[213] $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25}}$ = +175.8 (*c* = 3.09, $CHCl_3$).

(*R*)-Salsolidine hydrochloride (265)



A flame-dried 100 mL Young Schlenk under argon was charged with carbamate **120b** (1.20 g, 5.00 mmol, 1.00 eq.) and IDPi catalyst **220b** (54.8 mg, 0.025 mmol, 0.5 mol%). Dry $CHCl_3$ (50 mL) was added and the solution was cooled to –78 °C. Acetaldehyde (1.0 mL, 18 mmol, 3.6 eq.) was added to the reaction, the Schlenk was closed, and the mixture was stirred in a Dewar filled with EtOH maintained at –40 °C by the aid of a cryostat. After 4 d reaction time, the mixture was warmed to RT and stirred for another 2 h. The reaction was then quenched by addition of sat. aq. $NaHCO_3$ (100 mL), the aqueous layer was extracted with DCM (5x), the combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and azeotroped from PhMe (3x). An aliquot of the crude material was analyzed by ^{1}H-NMR to confirm quantitative formation of the Pictet-Spengler product. A small sample was taken for determination of the enantiomeric excess by HPLC.

TLC of the crude reaction mixture (hex/EtOAc 1:1). UV (left), CAM-stain (right)	HPLC-trace of the crude reaction mixture (IC-3R, MeOH/H_2O 90:10, 298 K, 284 nm): t_R (minor) = 6.3 min, t_R (major) = 7.9 min, er = 99:1 (98% ee).
	

The crude material was dissolved in dry DCM (50 mL) in a flame-dried Schlenk under argon and cooled to 0 °C. TMSI (0.75 mL, 5.3 mmol, 1.05 eq.) was added slowly and the mixture was

allowed to warm to RT over the course of 16 h. The reaction was quenched by addition sat. aq. $NaHCO_3$ (50 mL) and the aqueous layer was extracted with DCM (5x). The combined organic layers were extracted with aqueous HCl (1.2 M, 5x), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (DCM/EtOAc 100:0 to 19:1) gave remaining Pictet-Spengler product **226q** (216 mg, 0.815 mmol, 16%) as well as, after filtration over DOWEX, recovered IDPi catalyst **220b** (53.7 mg, 0.024 mmol, 98%). The combined HCl-layers were basified by addition of solid NaOH and extracted with MTBE (5x). The combined MTBE layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, to give 1.17 g of crude material.

The crude material was dissolved in dry THF (25 mL) and HCl (2.0 M in Et_2O, 12.5 mL, 25 mmol, 5 eq.) was added under vigorous stirring. A white precipitate formed immediately and the flask was placed in the freezer at –20 °C overnight. After warming to RT, the solid was collected by filtration (under gentle stream of argon to prevent product solubilizing in condensed water) and washed with Et_2O to give salsolidine hydrochloride (**265**, 852 mg, 3.49 mmol, 70%) as a white solid. The NMR-spectroscopic data was in agreement with the literature.[214]

A crystalline sample for x-ray single crystal structure analysis was obtained by dissolving an aliquot of the product in a small amount of water and layering with THF.

^{1}H-NMR (501 MHz, DMSO-d_6): δ = 9.80 (s, 1H), 9.31 (s, 1H), 6.83 (s, 1H), 6.77 (s, 1H), 4.42 (q, J = 7.0 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.41–3.34 (m, 1H), 3.27–3.17 (m, 1H), 2.97 (dt, J = 17.0, 6.4 Hz, 1H), 2.87 (dt, J = 16.9, 5.9 Hz, 1H), 1.58 (d, J = 6.8 Hz, 3H).

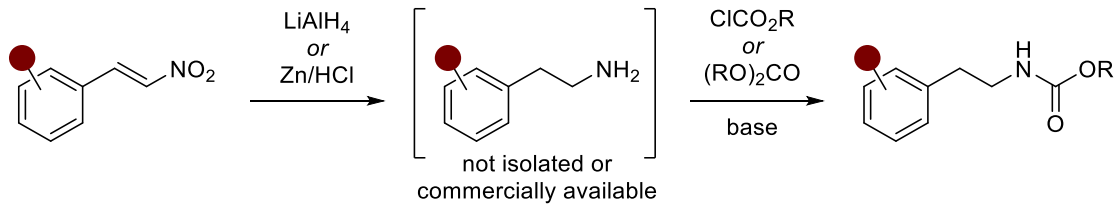
^{13}C-NMR (126 MHz, DMSO-d_6): δ = 148.14, 147.70, 125.82, 123.64, 111.68, 109.56, 55.72, 55.52, 49.87, 38.19, 24.58, 19.18.

ESI-HRMS: calculated for $C_{12}H_{18}N_1O_2$ ($[M\text{-}Cl]^+$): 208.133204, found: 208.133230.

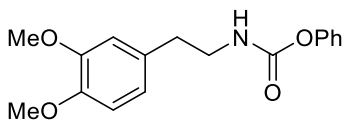
HPLC was measured after derivatization to methyl carbamate **226q** (IC-3R, MeOH/H_2O 90:10, 298 K, 284 nm): t_R (minor) = 6.1 min, t_R (major) = 7.6 min, er = 96.5:3.5 (93% ee).

$[\alpha]_D^{25}$ = +22.7 (*c* = 1.21, H_2O); Lit.:[215] $[\alpha]_D^{25}$ = +24.1 (*c* = 1.8, H_2O).

7.3. Synthesis of Protected *β*-arylethylamines



phenyl (3,4-dimethoxyphenethyl)carbamate (120a)



A 100 mL flask equipped with a stir bar was charged with diphenyl carbonate (4.3 g, 20 mmol, 1.0 eq.), H_2O (36 mL) and THF (5 mL). Homoveratrylamine (**73**, 3.4 mL, 20 mmol, 1.0 eq.) was added

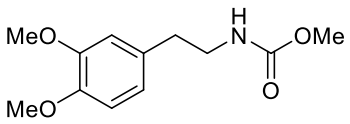
dropwise and the mixture was stirred at RT for 16 h. The aqueous layer was extracted with EtOAc (3x50 mL). The combined organic layers were washed with NaOH (2 M) and brine, dried over anhydrous Na_2SO_4, and concentrated. Purification by silica gel flash column chromatography (hex/EtOAc 2:1 to 1:1) and crystallization from hex/EtOAc yielded the desired product as a white crystalline solid (5.0 g, 17 mmol, 82%).

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.35 (t, J = 8.0 Hz, 2H), 7.19 (t, J = 6.9 Hz, 1H), 7.10 (d, J = 7.4 Hz, 2H), 6.84 (d, J = 8.1 Hz, 1H), 6.79–6.73 (m, 2H), 5.04 (bs, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.51 (q, J = 6.7 Hz, 2H), 2.84 (t, J = 7.0 Hz, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 154.70, 151.15, 149.28, 147.97, 131.18, 129.42, 125.43, 121.69, 120.86, 112.12, 111.62, 56.10, 56.04, 42.61, 35.65.

EI-HRMS: calculated for $C_{17}H_{19}N_1O_4$ ($[M]^+$): 301.130859, found: 301.130390.

methyl (3,4-dimethoxyphenethyl)carbamate (120b)



A 500 mL round-bottom flask equipped with a stir bar was charged with 3,4-dimethoxyphenethylamine (**73**, 8.5 mL, 50 mmol, 1.0 eq.), Na_2CO_3 (13.3 g, 126 mmol, 2.5 eq.), THF (100 mL), and water (100 mL). Methyl chloroformate (4.6 mL, 60 mmol, 1.2 eq.) was added dropwise, and the mixture was vigorously stirred at RT for 16 h. The reaction was quenched by addition of aqueous HCl (1.2 M, 100 mL) and EtOAc (50 mL). The phases were separated and the organic layer was washed with aqueous HCl (1.2 M, 3x) and brine, dried over anhydrous Na_2SO_4, and concentrated. Purification by silica gel flash column chromatography (hex/EtOAc 20–40%) yielded the desired product as a slowly solidifying colorless oil (9.93 g, 41.5 mmol, 82%).

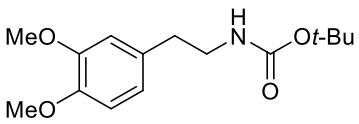
$\boldsymbol{R_F}$ (hex/EtOAc 2:1) = 0.19.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 6.81 (d, J = 8.0 Hz, 1H), 6.73 (dd, J = 8.2, 2.0 Hz, 1H), 6.71–6.69 (m, 1H), 4.68 (bs, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.66 (bs, 3H), 3.42 (q, J = 6.7 Hz, 2H), 2.75 (t, J = 7.0 Hz, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 157.12, 149.21, 147.87, 131.40, 120.83, 112.09, 111.55, 56.08, 56.01, 52.19, 42.46, 35.88.

EI-HRMS: calculated for $C_{12}H_{17}N_1O_4$ ($[M]^+$): 239.115209, found: 239.115470.

***tert*-butyl (3,4-dimethoxyphenethyl)carbamate (120c)**



A flame-dried 100 mL two-necked flask under argon equipped with a stir bar was charged with di-*tert*-butyl dicarbonate (7.8 mL, 34 mmol, 1.0 eq.) and THF (50 mL). 3,4-dimethoxyphenethylamine (**73**, 8.6 mL, 51 mmol, 1.5 eq.) was added dropwise and the mixture was allowed to reach RT while stirring for 6 h. The reaction was quenched by addition of sat. aq. $NaHCO_3$ (100 mL) and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with aqueous HCl (1.2 M, 3x), saturated $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, and

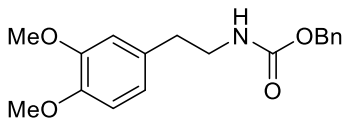
concentrated. Crystallization from hex/EtOAc yielded the desired product as a white solid (6.8 g, 24 mmol, 71%).

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 6.80 (d, J = 8.5 Hz, 1H), 6.75–6.70 (m, 2H), 4.61 (bs, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.31 (q, J = 6.8 Hz, 2H), 2.71 (t, J = 7.1 Hz, 2H), 1.41 (s, 9H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 156.09, 149.61, 148.24, 132.18, 121.06, 112.77, 112.11, 79.16, 56.24, 56.12, 42.30, 36.08, 28.53.

EI-HRMS: calculated for $C_{15}H_{23}N_1O_4$ ($[M]^+$): 281.162159, found: 281.162240.

benzyl (3,4-dimethoxyphenethyl)carbamate (120d)



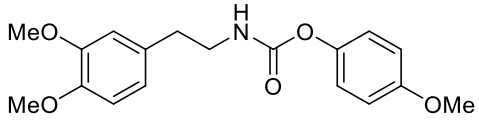
A 250 mL flask equipped with a stir bar was charged with dimethoxyphenethylamine (**73**, 1.7 mL, 10 mmol, 1.0 eq.), K_2CO_3 (1.66 g, 12 mmol, 1.2 eq.) and THF (50 mL). Benzyl chloroformate (1.6 mL, 11 mmol, 1.1 eq.) was added dropwise and the mixture was stirred at RT for 1 h. The reaction was then filtered and concentrated. Crystallization from hex/THF yielded the desired product as a white solid (1.0 g, 3.2 mmol, 32%).

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 5H), 6.79 (d, J = 8.0 Hz, 1H), 6.74–6.62 (m, 2H), 5.10 (s, 2H), 4.77 (bs, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.44 (q, J = 6.8 Hz, 2H), 2.76 (t, J = 7.0 Hz, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.45, 149.19, 147.86, 136.72, 131.33, 128.66, 128.25, 120.82, 112.08, 111.55, 66.77, 56.07, 55.97, 42.46, 35.80.

EI-HRMS: calculated for $C_{18}H_{21}N_1O_4$ ($[M]^+$): 315.146509, found: 315.146420.

4-methoxyphenyl (3,4-dimethoxyphenethyl)carbamate (120e)



A 100 mL flask equipped with a stir bar was charged with bis(4-methoxyphenyl) carbonate (1.5 g, 5.3 mmol, 1.0 eq.), H_2O (10 mL) and THF (1.3 mL). Homoveratrylamine (**73**, 0.9 mL, 5.3 mmol, 1.0 eq.) was added dropwise and the mixture was stirred at RT for 16 h. The aqueous layer was extracted with EtOAc (3x50 mL). The combined organic layers were washed with NaOH (1 M) and brine, dried over anhydrous Na_2SO_4, and concentrated. Purification by silica gel flash column chromatography (hex/EtOAc 2:1) yielded the desired product as a white solid (1.6 g, 4.7 mmol, 88%).

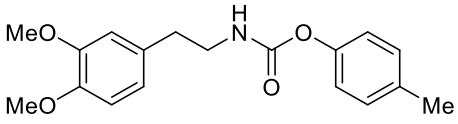
$\boldsymbol{R_F}$ (hex/EtOAc 2:1) = 0.20.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.20–7.15 (m, 1H), 7.08 (dd, J = 7.9, 1.7 Hz, 1H), 6.98–6.91 (m, 2H), 6.83 (d, J = 8.0 Hz, 1H), 6.81–6.75 (m, 2H), 5.10 (s, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 3.51 (q, J = 6.7 Hz, 2H), 2.84 (t, J = 7.0 Hz, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 154.51, 151.84, 149.25, 147.93, 140.09, 131.29, 126.64, 123.41, 120.92, 120.90, 112.55, 112.16, 111.59, 56.11, 56.06, 56.03, 42.77, 35.66.

ESI-HRMS: calculated for $C_{18}H_{21}N_1O_5Na_1$ ($[M+Na]^+$): 354.131192, found: 354.131110.

_p_-tolyl (3,4-dimethoxyphenethyl)carbamate (120f)



A 100 mL flask equipped with a stir bar was charged with homoveratrylamine (**73**, 1.5 mL, 8.9 mmol, 1.0 eq.), THF (40 mL), and K_2CO_3 (1.5 g, 11 mmol, 1.2 eq.). 4-methylphenyl chloroformate (1.5 mL, 10.1 mmol, 1.1 eq.) was added and the mixture was stirred at RT for 16 h. The reaction was quenched by addition of HCl (1.2 M) and the aqueous layer was extracted with EtOAc (3x50 mL). The combined organic layers were washed with HCl (1.2 M) and brine, dried over anhydrous Na_2SO_4, and concentrated. Purification by silica gel flash column chromatography (hex/EtOAc 4:1 to 3:1) yielded the desired product as a white solid (1.52 g, 4.82 mmol, 54%).

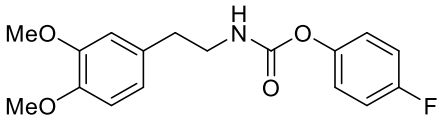
$\boldsymbol{R_F}$ (hex/EtOAc 2:1) = 0.31.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 7.14 (d, J = 8.1 Hz, 2H), 6.98 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.1 Hz, 1H), 6.77 (dd, J = 8.1, 2.0 Hz, 1H), 6.75 (d, J = 1.9 Hz, 1H), 5.00 (t, J = 6.0 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.51 (q, J = 6.7 Hz, 2H), 2.83 (t, J = 7.0 Hz, 2H), 2.33 (s, 3H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 154.93, 149.26, 148.90, 147.95, 135.04, 131.21, 129.93, 121.41, 120.86, 112.11, 111.60, 56.10, 56.03, 42.60, 35.66, 20.96.

ESI-HRMS: calculated for $C_{18}H_{21}N_1O_4Na_1$ ($[M+Na]^+$): 338.136278, found: 338.135940.

4-fluorophenyl (3,4-dimethoxyphenethyl)carbamate (120g)



A 100 mL flask equipped with a stir bar was charged with homoveratrylamine (**73**, 0.9 mL, 5.3 mmol, 1.0 eq.), THF (25 mL), and K_2CO_3 (0.88 g, 6.4 mmol, 1.2 eq.). 4-fluorophenyl chloroformate (0.77 mL, 5.9 mmol, 1.1 eq.) was added and the mixture was stirred at RT for 1.5 h. The reaction was quenched by addition of HCl (1.2 M) and the aqueous layer was extracted with EtOAc (3x50 mL). The combined organic layers were washed with HCl (1.2 M) and brine, dried over anhydrous Na_2SO_4, and concentrated. Purification by silica gel flash column chromatography (hex/EtOAc 3:1 to 2:1) yielded the desired product as a white solid (0.84 g, 2.6 mmol, 49%).

$\boldsymbol{R_F}$ (hex/EtOAc 2:1) = 0.38.

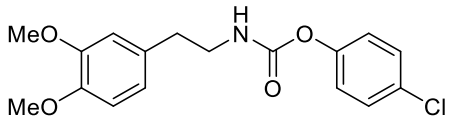
^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 7.11–7.00 (m, 4H), 6.83 (d, J = 7.9 Hz, 1H), 6.80–6.73 (m, 2H), 5.11 (s, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.47 (q, J = 6.7 Hz, 2H), 2.81 (t, J = 7.0 Hz, 2H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 154.76, 149.72, 148.42, 147.54, 131.58, 123.52, 123.45, 121.11, 116.18, 115.99, 112.73, 112.15, 56.25, 56.18, 42.88, 35.80.

^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -118.67.

ESI-HRMS: calculated for $C_{17}H_{18}N_1O_4F_1Na_1$ ($[M+Na]^+$): 342.111206, found: 342.111060.

4-chlorophenyl (3,4-dimethoxyphenethyl)carbamate (120h)



A 100 mL flask equipped with a stir bar was charged with homoveratrylamine (**73**, 1.5 mL, 8.9 mmol, 1.0 eq.), THF (40 mL), and K_2CO_3 (1.5 g, 11 mmol, 1.2 eq.). 4-chlorophenyl chloroformate (1.4 mL, 9.8 mmol, 1.1 eq.) was added and the mixture was stirred at RT for 16 h. The reaction was quenched by addition of HCl (1.2 M) and the aqueous layer was extracted with EtOAc (3x50 mL). The combined organic layers were washed with HCl (1.2 M) and brine, dried over anhydrous Na_2SO_4, and concentrated. Purification by silica gel flash column chromatography (hex/EtOAc 4:1 to 3:1) yielded the desired product as a white solid (1.56 g, 4.67 mmol, 52%).

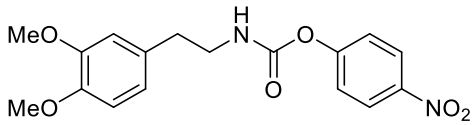
$\boldsymbol{R_F}$ (hex/EtOAc 2:1) = 0.35.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = δ 7.36–7.29 (m, 2H), 7.08–7.03 (m, 2H), 6.83 (d, J = 7.9 Hz, 1H), 6.80–6.73 (m, 2H), 5.12 (s, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.48 (q, J = 6.7 Hz, 2H), 2.81 (t, J = 7.0 Hz, 2H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 154.43, 150.21, 149.73, 148.43, 131.53, 130.72, 129.58, 123.44, 121.11, 112.72, 112.15, 56.25, 56.18, 42.88, 35.78.

ESI-HRMS: calculated for $C_{17}H_{18}Cl_1N_1O_4Na_1$ ($[M+Na]^+$): 358.081656, found: 358.081410.

4-nitrophenyl (3,4-dimethoxyphenethyl)carbamate (120i)



A 100 mL flask equipped with a stir bar was charged with bis(4-nitrophenyl) carbonate (1.6 g, 5.3 mmol, 1.0 eq.), H_2O (10 mL) and THF (1.3 mL). Homoveratrylamine (**73**, 0.9 mL, 5.3 mmol, 1.0 eq.) was added dropwise and the mixture was stirred at RT for 16 h. The aqueous layer was extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Purification by silica gel flash column chromatography (hex/EtOAc 3:1 to 2:1) yielded the desired product as a white solid (1.0 g, 2.9 mmol, 54%).

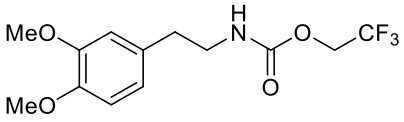
$\boldsymbol{R_F}$ (hex/EtOAc 2:1) = 0.20.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 8.27–8.20 (m, 2H), 7.32–7.27 (m, 2H), 6.84 (d, J = 8.1 Hz, 1H), 6.77 (dd, J = 8.1, 2.0 Hz, 1H), 6.74 (d, J = 2.0 Hz, 1H), 5.14 (t, J = 6.3 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.54 (q, J = 6.7 Hz, 2H), 2.85 (t, J = 7.0 Hz, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.03, 153.17, 149.34, 148.09, 144.89, 130.74, 125.25, 122.04, 120.86, 112.06, 111.63, 56.10, 56.06, 42.64, 35.49.

ESI-HRMS: calculated for $C_{17}H_{18}N_2O_6Na_1$ ($[M+Na]^+$): 369.105706, found: 369.105520.

2,2,2-trifluoroethyl (3,4-dimethoxyphenethyl)carbamate (120j)



A 50 mL flask equipped with a stir bar was charged with bis-(2,2,2-trifluorethyl) carbonate (1.2 g, 5.3 mmol, 1.0 eq.), H_2O (10 mL) and THF (1.3 mL). Homoveratrylamine (**73**, 0.9 mL, 5.3 mmol, 1.0 eq.) was added dropwise and the mixture was stirred at RT for 16 h. The aqueous layer was extracted with EtOAc (3x50 mL). The combined organic layers were washed with NaOH (1 M) and brine, dried over anhydrous Na_2SO_4, and concentrated. Purification by silica gel flash column chromatography (hex/EtOAc 9:1 to 4:1) yielded the desired product as a white solid (1.53 g, 4.99 mmol, 94%).

$\boldsymbol{R_F}$ (hex/EtOAc 4:1) = 0.20.

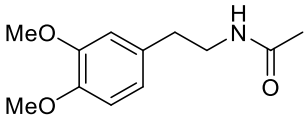
^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 6.81 (d, J = 8.0 Hz, 1H), 6.75–6.69 (m, 2H), 4.99 (s, 1H), 4.46 (q, J = 8.6 Hz, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.42 (q, J = 6.7 Hz, 2H), 2.76 (t, J = 7.0 Hz, 2H).

^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -74.79.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 154.65, 149.70, 148.41, 131.46, 123.77 (q, J = 277.5 Hz), 121.06, 112.67, 112.15, 61.03 (q, J = 36.1 Hz), 56.23, 56.12, 42.98, 35.75.

CI-HRMS: calculated for $C_{13}H_{17}N_1O_4F_3$ ($[M+H]^+$): 308.110419, found: 308.110580.

***N*-(3,4-dimethoxyphenethyl)acetamide (120k)**

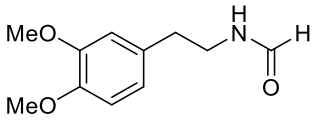


A 100 mL flask equipped with a stir bar was charged with acetyl chloride (0.72 mL, 10 mmol, 1.0 eq.), DCM (20 mL), Et_3N (1.4 mL, 10 mmol, 1.0 eq.) and homoveratrylamine (**73**, 1.7 mL, 10 mmol, 1.0 eq.). The mixture was stirred at RT for 3 h. Water (100 mL) was added and the aqueous layer was extracted with EtOAc (3x50 mL). The combined organic layers were washed with NaOH (1 M) and brine, dried over anhydrous Na_2SO_4, and concentrated. Purification by silica gel flash column chromatography (DCM/MeOH 2–3%) yielded the desired product as a white solid (791 mg, 3.55 mmol, 35%). The NMR-spectroscopic data was in agreement with the literature.[216]

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 6.81 (d, J = 7.9 Hz, 1H), 6.77–6.69 (m, 2H), 5.52 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.49 (q, J = 6.6 Hz, 2H), 2.76 (t, J = 7.0 Hz, 2H), 1.95 (s, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 6.82, 6.80, 6.74, 6.73, 6.72, 6.72, 6.71, 6.71, 5.52, 3.87, 3.86, 3.51, 3.50, 3.49, 3.47, 2.78, 2.76, 2.75, 1.95.

***N*-(3,4-dimethoxyphenethyl)formamide (120l)**



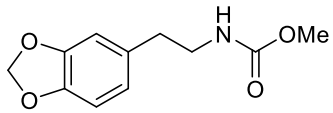
A 25 mL flask equipped with a stir bar and a reflux condenser was charged with ethyl formate (3.7 mL, 46 mmol, 2.5 eq.) and homoveratrylamine (**73**, 3.1 mL, 18 mmol, 1.0 eq.). The mixture was refluxed for 16 h. After cooling to RT, the mixture was concentrated under reduced pressure. Purification by silica gel flash column chromatography (DCM/MeOH 3–5%) yielded the desired

product as a colorless oil (3.7 g, 18 mmol, 97%). The NMR-spectroscopic data was in agreement with the literature.[217]

^{1}H-NMR (501 MHz, CD_2Cl_2): Mixture of two rotamers with a ratio ≈ 80:20. δ = 8.14 (d, J = 1.6 Hz, $1H_{maj}$), 7.95 (d, J = 12.0 Hz, $1H_{min}$), 6.83–6.80 (m, $1H_{all}$), 6.76–6.66 (m, $2H_{all}$), 5.53 (s, $1H_{all}$), 3.87 (s, $3H_{all}$), 3.86 (s, $3H_{all}$), 3.56 (q, J = 6.7 Hz, $2H_{maj}$), 3.46 (q, J = 6.6 Hz, $2H_{min}$), 2.79 (t, J = 7.0 Hz, $2H_{maj}$), 2.76 (t, J = 6.7 Hz, $2H_{min}$).

EI-HRMS: calculated for $C_{11}H_{15}N_1O_3$ ($[M+H]^+$): 209.104644, found: 209.104650.

methyl (2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)carbamate (315)



A 100 mL round-bottom flask equipped with a stir bar was charged with 3,4-methylenedioxyphenethylamine hydrochloride (2.0 g, 9.9 mmol, 1.0 eq.), THF (50 mL), and Et_3N (5.5 mL, 39 mmol, 4.0 eq.). Methyl chloroformate (0.85 mL, 11 mmol, 1.1 eq.) was added dropwise, and the mixture was stirred at RT for 2 h. The reaction was quenched by addition of aqueous HCl (1.2 M, 50 mL) and EtOAc (50 mL). The phases were separated and the organic layer was washed with aqueous HCl (1.2 M, 3x) and brine, dried over anhydrous Na_2SO_4, and concentrated. Purification by silica gel flash column chromatography (pentane/EtOAc 30–40%) yielded the desired product as a white solid (1.0 g, 4.7 mmol, 47%).

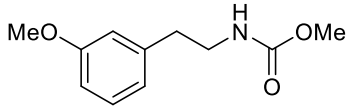
***R*$_F$** (hex/EtOAc 2:1) = 0.39.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 6.74 (d, J = 7.9 Hz, 1H), 6.69 (d, J = 1.7 Hz, 1H), 6.64 (dd, J = 7.9, 1.7 Hz, 1H), 5.92 (s, 2H), 4.73 (bs, 1H), 3.61 (s, 3H), 3.34 (q, J = 6.7 Hz, 2H), 2.70 (t, J = 7.0 Hz, 2H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 157.17, 148.22, 146.59, 133.19, 122.06, 109.41, 108.57, 101.48, 52.23, 42.79, 36.21.

EI-HRMS: calculated for $C_{11}H_{13}N_1O_4$ ($[M]^+$): 223.083909, found: 223.083930.

methyl (3-methoxyphenethyl)carbamate (316)

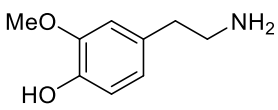


A 250 mL round-bottom flask equipped with a stir bar was charged with 3-methoxyphenethylamine (3.0 mL, 21 mmol, 1.0 eq.), THF (100 mL), and Et_3N (8.6 mL, 62 mmol, 3.0 eq.). Methyl chloroformate (1.8 mL, 23 mmol, 1.1 eq.) was added dropwise, and the mixture was stirred at RT for 16 h. The reaction was quenched by addition of aqueous HCl (1.2 M, 100 mL) and EtOAc (50 mL). The phases were separated and the organic layer was washed with aqueous HCl (1.2 M, 3x) and brine, dried over anhydrous Na_2SO_4, and concentrated. Purification by silica gel flash column chromatography (hex/EtOAc 4:1) yielded the desired product as a colorless oil (3.51 g, 16.8 mmol, 82%).

***R*$_F$** (hex/EtOAc 4:1) = 0.20.

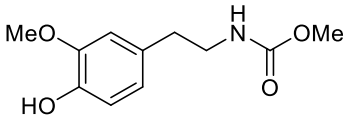
^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 7.21 (t, J = 7.8 Hz, 1H), 6.81–6.71 (m, 3H), 4.79 (bs, 1H), 3.78 (s, 3H), 3.61 (s, 3H), 3.40 (q, J = 6.8 Hz, 2H), 2.77 (t, J = 7.1 Hz, 2H).
^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 160.28, 157.19, 141.04, 129.88, 121.42, 114.84, 112.10, 55.50, 52.21, 42.51, 36.53.
EI-HRMS: calculated for $C_{11}H_{15}N_1O_3$ ($[M]^+$): 209.104643, found: 209.104900.

4-(2-aminoethyl)-2-methoxyphenol (319)



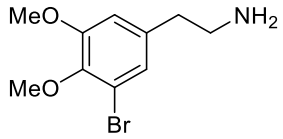
A flame-dried 250 mL round-bottom flask under argon equipped with a stir bar and a reflux condenser was charged with $LiAlH_4$ (1.0 M in THF, 55 mL, 55 mmol, 4.0 eq.) and cooled to 0 °C. (*E*)-2-methoxy-4-(2-nitrovinyl)phenol[218] (2.7 g, 14 mmol, 1.0 eq.) was dissolved in dry THF (25 mL) and added slowly to the reaction mixture. After complete addition, the mixture was heated to reflux for 3 h. The reaction was cooled to 0 °C and quenched by careful addition of water (25 mL). Sat. aq. potassium sodium tartrate (100 mL) was added and the aqueous layer was extracted with EtOAc (5x). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to yield a brown oil that was used for the next step without further purification.

methyl (4-hydroxy-3-methoxyphenethyl)carbamate (317)



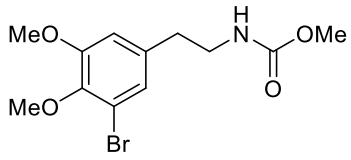
A 250 mL round-bottom flask equipped with a stir bar was charged with crude 4-(2-aminoethyl)-2-methoxyphenol (**319**, 14 mmol, 1.0 eq.), Et_2O (25 mL), water (25 mL), and Na_2CO_3 (4.5 g, 42 mmol, 3.1 eq.). Methyl chloroformate (1.1 mL, 14 mmol, 1.0 eq.) was added dropwise, and the mixture was stirred at RT for 3 h. The reaction was diluted with EtOAc (100 mL) and quenched by addition of aqueous HCl (1.2 M, 100 mL). The phases were separated and the organic layer was washed with aqueous HCl (1.2 M, 3x) and brine, dried over anhydrous Na_2SO_4, and concentrated. Purification by silica gel flash column chromatography (hex/EtOAc 30–50%) and automated reversed phase column chromatography ($MeOH/H_2O$ 60:40 to 100:0) yielded the desired product as a white solid (598 mg, 2.65 mmol, 19% over two steps). The NMR-spectroscopic data was in agreement with the literature.[219]
^{1}H-NMR (501 MHz, $CDCl_3$): δ = 6.85 (d, J = 8.1 Hz, 1H), 6.71–6.66 (m, 2H), 5.51 (s, 1H), 4.67 (s, 1H), 3.88 (s, 3H), 3.66 (s, 3H), 3.41 (q, J = 6.7 Hz, 2H), 2.74 (t, J = 7.0 Hz, 2H).
^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 157.22, 147.09, 144.68, 131.23, 121.69, 114.57, 111.80, 56.33, 52.21, 42.79, 36.15.
EI-HRMS: calculated for $C_{11}H_{15}N_1O_4$ ($[M]^+$): 225.099559, found: 225.099420.

2-(3-bromo-4,5-dimethoxyphenyl)ethan-1-amine (320)



The reaction was performed according to a literature procedure.[220] A 500 mL round-bottom flask equipped with a stir bar was charged with MeOH (42 mL), and cooled to –10 °C (acetone/ice). (*E*)-1-bromo-2,3-dimethoxy-5-(2-nitrovinyl)benzene[220] (5.7 g, 20 mmol, 1.0 eq.), zinc powder (22.8 g, 349 mmol, 17.6 eq.), and conc. aq. HCl (58 mL) were added in alternating small portions over the course of 30 min. The reaction was warmed to 0 °C after 15 min and then stirred for a total of 8 h. The mixture was subsequently filtered through filter paper while cooling the receiving flask to 0 °C. The liquid was basified with solid NaOH, dried over anhydrous Na_2SO_4, and concentrated to yield the desired product as a yellow oil (4.66 g). The crude material was used for the next step without further purification.

methyl (3-bromo-4,5-dimethoxyphenethyl)carbamate (318)



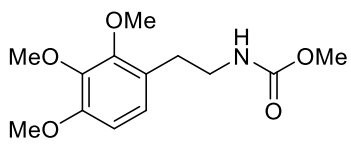
A 250 mL round-bottom flask equipped with a stir bar was charged with crude 2-(3-bromo-4,5-dimethoxyphenyl)ethan-1-amine (**320**, 4.66 g, 17.9 mmol, 1.0 eq.), THF (100 mL), and Et_3N (11 mL, 79 mmol, 4.4 eq.). Methyl chloroformate (2.2 mL, 29 mmol, 1.6 eq.) was added dropwise, and the mixture was stirred at RT for 16 h. The reaction was quenched by addition of aqueous HCl (1.2 M, 50 mL) and EtOAc (50 mL). The phases were separated and the organic layer was washed with aqueous HCl (1.2 M, 3x) and brine, dried over anhydrous Na_2SO_4, and concentrated. Purification by silica gel flash column chromatography (hex/EtOAc 3:1 to 2:1) and another silica gel flash column chromatography (DCM/EtOAc 2.5-10%) yielded the desired product as a yellow solid (3.44 g, 10.8 mmol, 55% over two steps). The NMR-spectroscopic data was in agreement with the literature.[221]

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 6.95 (d, J = 1.9 Hz, 1H), 6.69–6.65 (m, 1H), 4.74 (s, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.66 (s, 3H), 3.40 (q, J = 6.8 Hz, 2H), 2.73 (t, J = 7.0 Hz, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 157.08, 153.80, 145.21, 136.12, 124.78, 117.76, 112.40, 60.68, 56.23, 52.23, 42.17, 35.87.

ESI-HRMS: calculated for $C_{12}H_{17}N_1O_4Br_1$ ($[M+H]^+$): 318.033559, found: 318.033500.

methyl (2,3,4-trimethoxyphenethyl)carbamate (321)



A 100 mL flask equipped with a stir bar was charged with 2-(2,3,4-trimethoxyphenyl)ethylamine (2.8 g, 13 mmol, 1.0 eq.), THF (50 mL), Et_3N (5.0 mL, 36 mmol, 2.7 eq.) and methyl chloroformate (1.3 mL, 17 mmol, 1.5 eq.). The mixture was stirred at RT for 16 h. Aqueous HCl (1.2 M) and EtOAc (50 mL) were added and the organic layer was washed with HCl (1.2 M, 3x) and brine. The combined organic layer was dried over anhydrous Na_2SO_4 and

concentrated. Purification by silica gel flash column chromatography (hex/EtOAc 4:1) yielded the desired product as a yellow oil (2.0 g, 7.4 mmol, 55%).

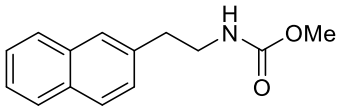
R_F (hex/EtOAc 2:1) = 0.27.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 6.81 (d, J = 8.5 Hz, 1H), 6.60 (d, J = 8.5 Hz, 1H), 4.90 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.63 (s, 2H), 3.37 (q, J = 6.6 Hz, 2H), 2.74 (t, J = 6.8 Hz, 2H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 157.18, 152.74, 152.13, 142.41, 124.84, 124.54, 107.48, 61.06, 60.85, 56.13, 52.07, 42.07, 30.29.

ESI-HRMS: calculated for $C_{13}H_{19}N_1O_5Na_1$ ($[M+Na]^+$): 292.115543, found: 292.115690.

methyl (2-(naphthalen-2-yl)ethyl)carbamate (299)



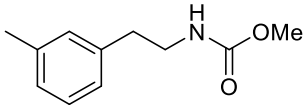
A 100 mL flask equipped with a stir bar was charged with 2-(2-naphthyl)ethylamine (2.0 g, 12 mmol, 1.0 eq.), THF (50 mL), Et_3N (5.0 mL, 36 mmol, 3.1 eq.) and methyl chloroformate (1.0 mL, 13 mmol, 1.1 eq.). The mixture was stirred at RT for 2 h. Aqueous HCl (1.2 M) and EtOAc (50 mL) were added and the organic layer was washed with HCl (1.2 M, 3x) and brine. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. Purification by silica gel flash column chromatography (hex/EtOAc 4:1) yielded the desired product as a white solid (2.1 g, 9.0 mmol, 77%).

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 7.86–7.77 (m, 3H), 7.50–7.42 (m, 2H), 7.35 (dd, J = 8.5, 1.8 Hz, 1H), 4.77 (s, 1H), 3.61 (s, 3H), 3.50 (q, J = 6.7 Hz, 2H), 2.97 (t, J = 7.0 Hz, 2H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 157.22, 137.00, 134.01, 132.68, 128.52, 127.96, 127.82, 127.64, 127.52, 126.47, 125.85, 52.24, 42.49, 36.67.

CI-HRMS: calculated for $C_{14}H_{16}N_1O_2$ ($[M+H]^+$): 230.117554, found: 230.117270.

methyl (3-methylphenethyl)carbamate (322)



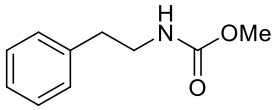
A 100 mL flask equipped with a stir bar was charged with 3-methylphenethylamine (1.5 mL, 10 mmol, 1.0 eq.), THF (50 mL), Et_3N (4.4 mL, 32 mmol, 3.0 eq.) and methyl chloroformate (0.9 mL, 12 mmol, 1.1 eq.). The mixture was stirred at RT for 16 h. Aqueous HCl (1.2 M) and EtOAc (50 mL) were added and the organic layer was washed with HCl (1.2 M, 3x) and brine. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. Purification by silica gel flash column chromatography (hex/EtOAc) yielded the desired product as a colorless oil (2.1 g, 9.0 mmol, 77%).

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 7.18 (t, J = 7.5 Hz, 1H), 7.05–6.96 (m, 3H), 4.74 (s, 1H), 3.61 (s, 3H), 3.38 (q, J = 6.7 Hz, 2H), 2.75 (t, J = 7.1 Hz, 2H), 2.32 (s, 3H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 157.18, 139.31, 138.64, 129.93, 128.77, 127.49, 126.13, 52.21, 42.65, 36.43, 21.48.

CI-HRMS: calculated for $C_{11}H_{16}N_1O_2$ ($[M+H]^+$): 194.117553, found: 194.117790.

methyl phenethylcarbamate (291)



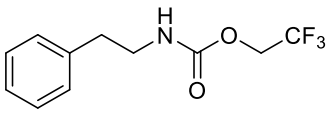
A 250 mL flask equipped with a stir bar was charged with phenethylamine (3.0 mL, 24 mmol, 1.0 eq.), THF (100 mL), Et_3N (10 mL, 72 mmol, 3.0 eq.) and methyl chloroformate (2.0 mL, 26 mmol, 1.1 eq.). The mixture was stirred at RT for 16 h. Aqueous HCl (1.2 M) and EtOAc (50 mL) were added and the organic layer was washed with HCl (1.2 M, 3x) and brine. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. Purification by silica gel flash column chromatography (hex/EtOAc 9:1 to 4:1) yielded the desired product as a colorless oil (3.5 g, 19 mmol, 81%).

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 7.34–7.27 (m, 2H), 7.24–7.18 (m, 3H), 4.76 (s, 1H), 3.61 (s, 3H), 3.40 (q, J = 6.7 Hz, 2H), 2.79 (t, J = 7.1 Hz, 2H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 157.19, 139.47, 129.17, 128.91, 126.77, 52.22, 42.64, 36.51.

CI-HRMS: calculated for $C_{10}H_{14}N_1O_2$ ($[M+H]^+$): 180.101903, found: 180.101800.

2,2,2-trifluoroethyl phenethylcarbamate (289)



A 50 mL flask equipped with a stir bar was charged with bis-(2,2,2-trifluorethyl) carbonate (1.8 g, 7.9 mmol, 1.0 eq.), H_2O (14 mL) and THF (2 mL). Phenethylamine (1.0 mL, 7.9 mmol, 1.0 eq.) was added dropwise and the mixture was stirred at RT for 16 h. The aqueous layer was extracted with EtOAc (3x50 mL). The combined organic layers were washed with NaOH (1 M) and brine, dried over anhydrous Na_2SO_4, and concentrated. Purification by silica gel flash column chromatography (hex/EtOAc) yielded the desired product as a white solid (1.9 g, 7.7 mmol, 97%).

***R*$_F$** (hex/EtOAc 9:1) = 0.22.

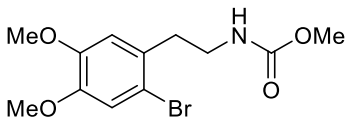
^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.36–7.30 (m, 2H), 7.27–7.23 (m, 1H), 7.22–7.16 (m, 2H), 4.92 (s, 1H), 4.45 (q, J = 8.5 Hz, 2H), 3.48 (q, J = 6.7 Hz, 2H), 2.84 (t, J = 6.9 Hz, 2H).

^{19}F-NMR (471 MHz, $CDCl_3$): δ = -74.29.

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 154.48, 138.44, 128.89, 128.88, 126.84, 123.25 (q, J = 277.5 Hz), 60.97 (q, J = 36.3 Hz), 42.58, 35.99.

EI-HRMS: calculated for $C_{11}H_{12}N_1O_2F_3$ ($[M]^+$): 247.081464, found: 247.081750.

methyl (2-bromo-4,5-dimethoxyphenethyl)carbamate (281)



A 50 mL round-bottom flask equipped with a stir bar was charged with carbamate **120b** (1.0 g, 4.2 mmol, 1.0 eq.) and AcOH (15 mL). Bromine was added and the reaction was stirred at RT for 90 min. The mixture was poured onto ice water and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with sat. aq. $NaHCO_3$, H_2O, sat. aq. Na_2SO_3, and brine, dried over anhydrous Na_2SO_4, and concentrated. Purification by silica gel flash column

chromatography (hex/EtOAc 60:40) yielded the desired product as a white solid (1.2 g, 3.9 mmol, 92%).

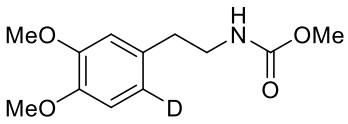
R_F (hex/EtOAc 1:1) = 0.41.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.00 (s, 1H), 6.72 (s, 1H), 4.74 (s, 1H), 3.85 (s, 6H), 3.67 (s, 3H), 3.42 (q, J = 6.8 Hz, 2H), 2.88 (d, J = 7.2 Hz, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 157.19, 148.63, 148.48, 130.16, 115.80, 114.40, 113.58, 56.32, 56.24, 52.23, 41.10, 36.09.

EI-HRMS: calculated for $C_{12}H_{16}N_1O_4Br_1$ ([M]$^+$): 317.025734, found: 317.025210.

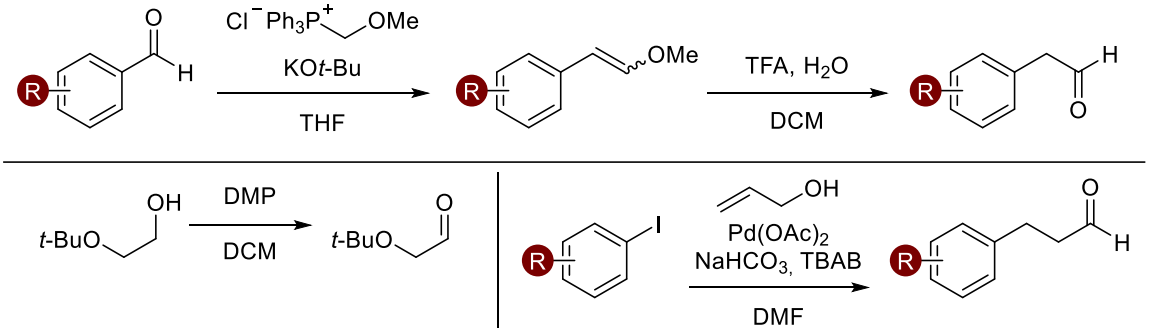
methyl (dimethoxyphenethyl)carbamate (120b-*D*)



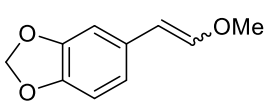
A flame-dried 50 mL Schlenk under argon was charged with carbamate **281** (499 mg, 1.6 mmol, 1.0 eq.) and THF (16 mL). The mixture was cooled to 0 °C, NaH (60 wt%, 125 mg, 31 mmol, 2.0 eq.) was added in one portion, and the reaction was stirred for 45 min. The mixture was cooled to −78 °C, *n*-BuLi (2.5 M in hexane, 1.3 mL, 3.3 mmol, 2.1 eq.) was added carefully, and the reaction aws stirred for 2 h at −78 °C. CD_3OD (0.65 mL, 16 mmol, 10 eq.) was added carefully and the mixture was stirred for another 15 min, before warming to RT. Sat. Aq. NH_4Cl was added, and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with sat. aq. $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated. Purification by silica gel flash column chromatography (hex/EtOAc 2:1 to 3:2) yielded the desired product as a white solid (298 mg, 1.2 mmol, 79%, 72% deuterium incorporation by ^{1}H-NMR).

EI-HRMS: calculated for $C_{12}H_{16}N_1O_4D_1$ ([M]$^+$): 240.121486, found: 240.121450.

7.4. Synthesis of Aldehydes and Acetals



5-(2-methoxyvinyl)benzo[*d*][1,3]dioxole (323)



A flame-dried 250 mL three-necked flask under argon was charged with piperonal (1.50 g, 10 mmol, 1.0 eq.), (methoxymethyl)triphenyl-phosphonium chloride (4.1 g, 12 mmol, 1.2 eq.) and dry THF (50 mL). The suspension was cooled to –10 °C (acetone/ice) and KO*t*-Bu (1.35 g, 12.0 mmol, 1.20 eq.) was added in one portion. The mixture was warmed to RT and stirred for 16 h. The reaction was

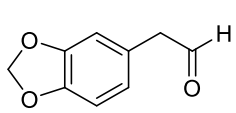
quenched by addition of sat. aq. NH_4Cl and the aqueous layer was extracted with MTBE (3x). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/MTBE 19:1 to 9:1) yielded the product (1.33 g, 7.47 mmol, 75%, $E/Z \approx 55:45$) as a yellow oil. The NMR-spectroscopic data was in agreement with the literature.[222]

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 7.25 (d, J = 1.6 Hz, $1H_{min}$), 6.92 (d, J = 13.0 Hz, $1H_{maj}$), 6.91 (dd, J = 8.1, 1.7 Hz, $1H_{min}$), 6.76 (d, J = 1.7 Hz, $1H_{maj}$), 6.73 (d, J = 4.6 Hz, $1H_{min}$), 6.71 (d, J = 4.5 Hz, $1H_{maj}$), 6.66 (dd, J = 8.0, 1.7 Hz, $1H_{maj}$), 6.07 (d, J = 7.0 Hz, $1H_{min}$), 5.91 (s, $2H_{min}$), 5.91 (s, $2H_{maj}$), 5.75 (d, J = 12.9 Hz, $1H_{maj}$), 5.14 (d, J = 7.0 Hz, $1H_{min}$), 3.75 (s, $3H_{min}$), 3.64 (s, $3H_{maj}$).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 148.42, 148.32, 147.84, 147.13, 146.15, 145.84, 131.07, 130.80, 122.08, 119.24, 108.81, 108.71, 108.28, 105.51, 105.22, 105.12, 101.44, 101.34, 60.92, 56.93.

EI-HRMS: calculated for $C_{10}H_{10}O_3$ ($[M]^+$): 178.062445, found: 178.062710.

2-(benzo[*d*][1,3]dioxol-5-yl)acetaldehyde (224b)



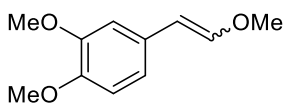
A 250 mL flask was charged with 5-(2-methoxyvinyl)benzo[*d*][1,3]dioxole (**323**, 1.33 g, 7.47 mmol, 1.00 eq.), DCM (110 mL) and water (2.3 mL, 130 mmol, 17 eq.). The mixture was cooled to 0 °C and trifluoroacetic acid (2.3 mL, 30 mmol, 4.0 eq.) was added. The mixture was subsequently warmed to RT and stirred for 16 h. The reaction was quenched by addition of sat. aq. Na_2CO_3 and the aqueous layer was extracted with DCM (3x). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/MTBE 19:1 to 9:1) yielded the product (510 mg, 2.95 mmol, 40%) as a colorless oil. The NMR-spectroscopic data was in agreement with the literature.[222]

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 9.69 (t, J = 2.2 Hz, 1H), 6.80 (d, J = 7.9 Hz, 1H), 6.69 (d, J = 1.7 Hz, 1H), 6.67 (dd, J = 7.9, 1.8 Hz, 1H), 5.96 (s, 2H), 3.59 (d, J = 2.2 Hz, 2H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 199.59, 148.54, 147.36, 126.10, 123.17, 110.24, 108.89, 101.74, 50.46.

EI-HRMS: calculated for $C_9H_8O_3$ ($[M]^+$): 164.046795, found: 164.046910.

1,2-dimethoxy-4-(2-methoxyvinyl)benzene (324)



A flame-dried 500 mL three-necked flask under argon was charged with 3,4-dimethoxybenzaldehyde (5.82 g, 35 mmol, 1.0 eq.), (methoxymethyl)-triphenylphosphonium chloride (14 g, 42 mmol, 1.2 eq.) and dry THF (175 mL). The suspension was cooled to –10 °C (acetone/ice) and KO*t*-Bu (4.7 g, 42 mmol, 1.2 eq.) was added in one portion. The mixture was warmed to RT and stirred for 16 h. The reaction was quenched by addition of sat. aq. NH_4Cl and the aqueous layer was extracted with MTBE (3x). The combined organic layers were washed with brine, dried over anhydrous

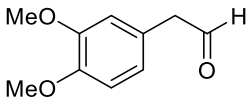
Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/EtOAc 15–20%) yielded the product (4.64 g, 23.9 mmol, 68%, *E*/*Z* ≈ 55:45) as a colorless oil. The NMR-spectroscopic data was in agreement with the literature.[222]

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.24 (d, J = 2.0 Hz, $1H_{min}$), 7.07 (dd, J = 8.3, 2.0 Hz, $1H_{min}$), 6.94 (d, J = 12.9 Hz, $1H_{maj}$), 6.80 (d, J = 8.4 Hz, $1H_{min}$), 6.79–6.76 (m, $3H_{maj}$), 6.07 (d, J = 7.0 Hz, $1H_{min}$), 5.78 (d, J = 12.9 Hz, $1H_{maj}$), 5.17 (d, J = 7.0 Hz, $1H_{min}$), 3.88 (s, $3H_{maj}$ + $3H_{min}$), 3.87 (s, $3H_{min}$), 3.86 (s, $3H_{maj}$), 3.77 (s, $3H_{min}$), 3.67 (s, $3H_{maj}$).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 149.75, 149.13, 148.15, 148.00, 147.80, 147.03, 129.80, 129.62, 121.14, 117.92, 112.33, 112.30, 111.70, 108.90, 105.57, 105.17, 60.92, 56.89, 56.25, 56.13, 56.09, 56.03.

EI-HRMS: calculated for $C_{11}H_{14}O_3$ ($[M]^+$): 194.093745, found: 194.093990.

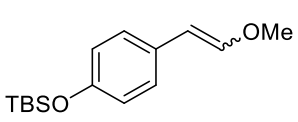
2-(3,4-dimethoxyphenyl)acetaldehyde (224c)



A 500 mL flask was charged with 1,2-dimethoxy-4-(2-methoxyvinyl)benzene (**324**, 3.56 g, 18.3 mmol, 1.00 eq.), DCM (270 mL) and water (6.0 mL, 330 mmol, 18 eq.). The mixture was cooled to 0 °C and trifluoroacetic acid (6.0 mL, 78 mmol, 4.3 eq.) was added. The mixture was subsequently warmed to RT and stirred for 16 h. The reaction was quenched by addition of sat. aq. Na_2CO_3 and the aqueous layer was extracted with DCM (3x). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/MTBE 10–40%) yielded the product (1.19 g, 6.27 mmol, 34%) as a colorless oil. The NMR-spectroscopic data was in agreement with the literature.[222]

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 9.73 (t, J = 2.4 Hz, 1H), 6.87 (d, J = 8.1 Hz, 1H), 6.77 (dd, J = 8.1, 2.0 Hz, 1H), 6.70 (d, J = 2.0 Hz, 1H), 3.88 (s, 6H), 3.62 (d, J = 2.5 Hz, 2H).

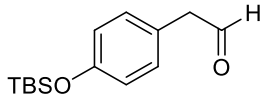
***tert*-butyl(4-(2-methoxyvinyl)phenoxy)dimethylsilane (325)**



A flame-dried 500 mL three-necked flask under argon was charged with 4-((*tert*-butyldimethylsilyl)oxy)benzaldehyde (5.9 g, 25 mmol, 1.0 eq.), (methoxy-methyl)triphenylphosphonium chloride (14.6 g, 42.6 mmol, 1.70 eq.) and dry THF (175 mL). The suspension was cooled to –10 °C (acetone/ice) and KO*t*-Bu (4.78 g, 42.6 mmol, 1.70 eq.) was added in one portion. The mixture was warmed to RT and stirred for 16 h. The reaction was quenched by addition of sat. aq. NH_4Cl and the aqueous layer was extracted with MTBE (3x). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/EtOAc 2.5%) and another silica gel flash column chromatography (hex/MTBE 2.5%) yielded the product (4.64 g, 17.5 mmol, 70%, *E*/*Z* ≈ 1:1) as a colorless oil. The NMR-spectroscopic data was in agreement with the literature.[163]

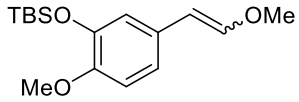
^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.47–7.42 (m, 2H), 7.11–7.07 (m, 2H), 6.93 (d, J = 13.0 Hz, 1H), 6.78–6.73 (m, 4H), 6.05 (d, J = 7.0 Hz, 1H), 5.77 (d, J = 13.0 Hz, 1H), 5.17 (d, J = 7.0 Hz, 1H), 3.75 (s, 3H), 3.66 (s, 3H), 0.98 (d, J = 0.9 Hz, 18H), 0.18 (d, J = 1.2 Hz, 12H).
EI-HRMS: calculated for $C_{15}H_{24}O_2Si_1$ ($[M]^+$): 264.154008, found: 264.154080.

2-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)acetaldehyde (224d)



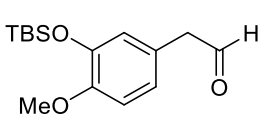
A 500 mL flask was charged with *tert*-butyl(4-(2-methoxyvinyl)phenoxy)-dimethylsilane (**325**, 3.42 g, 13.0 mmol, 1.00 eq.), DCM (190 mL) and water (4.0 mL, 220 mmol, 17 eq.). The mixture was cooled to 0 °C and trifluoroacetic acid (4.0 mL, 52 mmol, 4.0 eq.) was added. The mixture was subsequently warmed to RT and stirred for 16 h. The reaction was quenched by addition of sat. aq. Na_2CO_3 and the aqueous layer was extracted with DCM (3x). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/MTBE 2.5%) yielded the product (245 mg, 0.931 mmol, 7%) as a colorless oil. The NMR-spectroscopic data was in agreement with the literature.[163]
^{1}H-NMR (501 MHz, $CDCl_3$): δ = 9.72 (t, J = 2.5 Hz, 1H), 7.09–7.05 (m, 2H), 6.85–6.81 (m, 2H), 3.61 (d, J = 2.5 Hz, 2H), 0.98 (s, 9H), 0.20 (s, 6H).
EI-HRMS: calculated for $C_{14}H_{22}O_2Si_1$ ($[M]^+$): 250.138359, found: 250.138040.

***tert*-butyl(2-methoxy-5-(2-methoxyvinyl)phenoxy)dimethylsilane (326)**



A flame-dried 250 mL three-necked flask under argon was charged with 3-((*tert*-butyldimethylsilyl)oxy)-4-methoxybenzaldehyde (7.2 g, 27 mmol, 1.0 eq.), (methoxy-methyl)triphenylphosphonium chloride (11.1 g, 32.4 mmol, 1.20 eq.) and dry THF (135 mL). The suspension was cooled to 0 °C and KO*t*-Bu (3.65 g, 32.5 mmol, 1.20 eq.) was added in one portion. The mixture was warmed to RT and stirred for 4 h. The reaction was quenched by addition of sat. aq. NH_4Cl and the aqueous layer was extracted with MTBE (3x). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/EtOAc 19:1 to 9:1) yielded the product (6.05 g, 20.6 mmol, 76%, *E*/*Z* ≈ 55:45) as a colorless oil. The NMR-spectroscopic data was in agreement with the literature.[163]
^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 7.17 (d, J = 2.1 Hz, 1H), 7.06 (dd, J = 8.4, 2.1 Hz, 1H), 6.91 (d, J = 12.9 Hz, 1H), 6.79–6.73 (m, 4H), 6.05 (d, J = 7.0 Hz, 1H), 5.71 (d, J = 12.9 Hz, 1H), 5.10 (d, J = 7.0 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.74 (s, 3H), 3.64 (s, 3H), 0.99 (s, 18H), 0.15 (s, 6H), 0.15 (s, 6H).

2-(3-((*tert*-butyldimethylsilyl)oxy)-4-methoxyphenyl)acetaldehyde (224e)



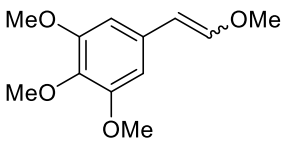
A 500 mL flask was charged with *tert*-butyl(2-methoxy-5-(2-methoxyvinyl)-phenoxy)dimethylsilane (**326**, 6.05 g, 20.6 mmol, 1.00 eq.), DCM (360 mL) and water (6.3 mL, 350 mmol, 17 eq.). Trifluoroacetic acid (6.3 mL, 82 mmol, 4.0 eq.) was added and the mixture was stirred at RT for 20 h. The reaction was quenched by addition of sat. aq. Na_2CO_3 and the aqueous layer was extracted with DCM (3x). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/EtOAc 2–3%), automated reversed phase column chromatography (CH_3CN/H_2O 60:40 to 100:0) and another silica gel flash column chromatography (hex/MTBE 95:5) yielded the product (2.15 g, 7.68 mmol, 37%) as a colorless oil. The NMR-spectroscopic data was in agreement with the literature.[163]

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 9.69 (t, J = 2.5 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.75 (dd, J = 8.1, 2.2 Hz, 1H), 6.71 (d, J = 2.2 Hz, 1H), 3.80 (s, 3H), 3.55 (d, J = 2.6 Hz, 2H), 0.99 (s, 9H), 0.15 (s, 6H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 199.90, 150.77, 145.69, 124.93, 123.20, 122.65, 112.80, 55.81, 50.09, 25.88, 18.74, -4.54.

ESI-HRMS: calculated for $C_{15}H_{24}O_3Si_1Na_1$ ($[M+Na]^+$): 303.138693, found: 303.138490.

1,2,3-trimethoxy-5-(2-methoxyvinyl)benzene (327)

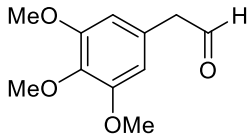


A flame-dried 250 mL three-necked flask under argon was charged with 3,4,5-trimethoxybenzaldehyde (5.9 g, 30 mmol, 1.0 eq.), (methoxymethyl)-triphenylphosphonium chloride (12.0 g, 35.0 mmol, 1.20 eq.) and dry THF (150 mL). The suspension was cooled to 0 °C and KO*t*-Bu (3.93 g, 35.0 mmol, 1.20 eq.) was added in one portion. The mixture was warmed to RT and stirred for 4 h. The reaction was quenched by addition of sat. aq. NH_4Cl and the aqueous layer was extracted with MTBE (3x). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/EtOAc 17.5–20%) yielded the product (3.66 g, 16.3 mmol, 54%, *E*/*Z* ≈ 55:45) as a colorless oil. The NMR-spectroscopic data was in agreement with the literature.[163]

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 7.00 (d, J = 12.9 Hz, $1H_{maj}$), 6.83 (s, $2H_{min}$), 6.45 (s, $2H_{maj}$), 6.12 (d, J = 7.0 Hz, $1H_{min}$), 5.75 (d, J = 12.9 Hz, $1H_{maj}$), 5.13 (d, J = 7.0 Hz, $1H_{min}$), 3.82 (s, $6H_{maj}$), 3.81 (s, $6H_{min}$), 3.78 (s, $3H_{min}$), 3.74 (s, $3H_{min}$), 3.73 (s, $3H_{maj}$), 3.67 (s, $3H_{maj}$).

EI-HRMS: calculated for $C_{12}H_{16}O_4$ ($[M]^+$): 224.104310, found: 224.104390.

2-(3,4,5-trimethoxyphenyl)acetaldehyde (224f)



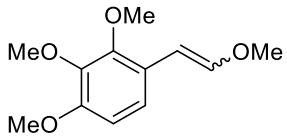
A 500 mL flask was charged with 1,2,3-trimethoxy-5-(2-methoxyvinyl)benzene (**327**, 3.63 g, 16.2 mmol, 1.00 eq.), DCM (250 mL) and water (5.0 mL, 280 mmol, 17 eq.). Trifluoroacetic acid (5.0 mL, 65 mmol, 4.0 eq.) was added and the mixture was stirred at RT for 20 h. The reaction was quenched by addition of sat. aq. Na_2CO_3 and the aqueous layer was extracted with DCM (3x). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/EtOAc 4:1 to 2:1), another silica gel flash column chromatography (DCM/acetone 2–3%), and automated reversed phase column chromatography (CH_3CN/H_2O 50:50 to 100:0) yielded the product (1.93 g, 9.17 mmol, 57%) as a yellow oil. The NMR-spectroscopic data was in agreement with the literature.[163]

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 9.71 (t, J = 2.3 Hz, 1H), 6.42 (s, 2H), 3.82 (s, 6H), 3.76 (s, 3H), 3.60 (d, J = 2.3 Hz, 2H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 199.50, 154.09, 137.74, 128.07, 107.07, 60.81, 56.44, 51.12.

EI-HRMS: calculated for $C_{11}H_{14}O_4$ ($[M]^+$): 210.088660, found: 210.088800.

1,2,3-trimethoxy-4-(2-methoxyvinyl)benzene (328)



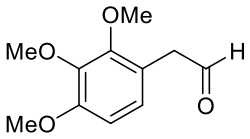
A flame-dried 250 mL three-necked flask under argon was charged with 2,3,4-trimethoxybenzaldehyde (3.0 g, 15 mmol, 1.0 eq.), (methoxymethyl)-triphenylphosphonium chloride (6.1 g, 18 mmol, 1.2 eq.) and dry THF (75 mL). The suspension was cooled to 0 °C and KO*t*-Bu (2.0 g, 18 mmol, 1.2 eq.) was added in one portion. The mixture was warmed to RT and stirred for 16 h. The reaction was quenched by addition of sat. aq. NH_4Cl and the aqueous layer was extracted with MTBE (3x). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/EtOAc 15–20%) yielded the product (2.23 g, 9.94 mmol, 65%, *E*/*Z* ≈ 55:45) as a colorless oil.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 7.69 (d, J = 8.8 Hz, $1H_{min}$), 7.02 (d, J = 13.0 Hz, $1H_{maj}$), 6.94 (d, J = 8.7 Hz, $1H_{maj}$), 6.64 (d, J = 8.8 Hz, $1H_{min}$), 6.62 (d, J = 8.8 Hz, $1H_{maj}$), 6.13 (d, J = 7.2 Hz, $1H_{min}$), 5.91 (d, J = 13.0 Hz, $1H_{maj}$), 5.46 (d, J = 7.2 Hz, $1H_{min}$), 3.82 (s, $3H_{maj}$), 3.82 (s, $3H_{maj}$), 3.81 (s, $3H_{maj}$ + $3H_{min}$), 3.81 (s, $3H_{min}$), 3.80 (s, $3H_{min}$), 3.74 (s, $3H_{min}$), 3.67 (s, $3H_{maj}$).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 152.31, 152.24, 150.90, 149.03, 147.60, 143.16, 142.64, 124.48, 123.61, 123.16, 120.07, 108.40, 107.85, 100.33, 98.80, 61.35, 61.01, 60.99, 60.92, 60.83, 56.82, 56.38, 56.30.

EI-HRMS: calculated for $C_{12}H_{16}O_4$ ($[M]^+$): 224.104310, found: 224.104590.

2-(2,3,4-trimethoxyphenyl)acetaldehyde (224g)



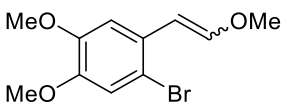
A 500 mL flask was charged with 1,2,3-trimethoxy-4-(2-methoxyvinyl)benzene (**328**, 2.19 g, 9.78 mmol, 1.00 eq.), DCM (150 mL) and water (3.0 mL, 170 mmol, 17 eq.). Trifluoroacetic acid (3.0 mL, 39 mmol, 4.0 eq.) was added and the mixture was stirred at RT for 20 h. The reaction was quenched by addition of sat. aq. Na_2CO_3 and the aqueous layer was extracted with DCM (3x). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/EtOAc 9:1 to 4:1) yielded the product (1.42 g, 6.73 mmol, 69%) as a colorless oil.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 9.67 (t, J = 2.0 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.66 (d, J = 8.5 Hz, 1H), 3.84 (s, 6H), 3.83 (s, 3H), 3.58 (d, J = 1.9 Hz, 2H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 200.09, 154.00, 152.56, 142.77, 125.47, 119.12, 107.86, 61.11, 60.92, 56.35, 45.45.

EI-HRMS: calculated for $C_{11}H_{14}O_4$ ($[M]^+$): 210.088660, found: 210.088780.

1-bromo-4,5-dimethoxy-2-(2-methoxyvinyl)benzene (329)



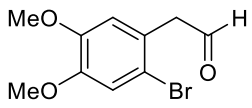
A flame-dried 250 mL three-necked flask under argon was charged with 6-bromoveratraldehyde (2.46 g, 10.0 mmol, 1.00 eq.), (methoxymethyl)triphenyl-phosphonium chloride (4.1 g, 12 mmol, 1.2 eq.) and dry THF (50 mL). The suspension was cooled to –10 °C (acetone/ice) and KO*t*-Bu (1.35 g, 12.0 mmol, 1.20 eq.) was added in one portion. The mixture was warmed to RT and stirred for 6.5 h. The reaction was quenched by addition of sat. aq. NH_4Cl and the aqueous layer was extracted with MTBE (3x). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (*n*-pentane/MTBE 9:1 to 4:1) yielded the product (1.94 g, 7.09 mmol, 71%, *E*/*Z* ≈ 65:35) as a colorless oil.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 7.68 (s, $1H_{min}$), 7.01 (s, $1H_{maj}$), 7.00 (s, $1H_{min}$), 6.92 (d, J = 12.8 Hz, $1H_{maj}$), 6.84 (s, $1H_{maj}$), 6.20 (d, J = 7.2 Hz, $1H_{min}$), 6.00 (d, J = 12.9 Hz, $1H_{maj}$), 5.48 (d, J = 7.2 Hz, $1H_{min}$), 3.82 (s, $3H_{maj}$), 3.81 (s, $3H_{min}$), 3.80–3.79 (m, $3H_{maj}$ + $3H_{min}$), 3.78 (s, $3H_{min}$), 3.70 (s, $3H_{maj}$).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 149.96, 149.25, 148.68, 148.55, 148.43, 148.22, 128.79, 128.11, 116.20, 115.75, 113.42, 113.12, 113.04, 109.00, 104.66, 103.80, 61.18, 57.05, 56.49, 56.37, 56.34, 56.18.

EI-HRMS: calculated for $C_{11}H_{13}O_3Br_1$ ($[M]^+$): 272.004270, found: 272.004750.

2-(2-bromo-4,5-dimethoxyphenyl)acetaldehyde (224i)



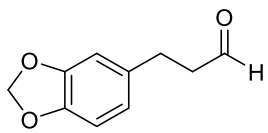
A 250 mL flask was charged with 1-bromo-4,5-dimethoxy-2-(2-methoxyvinyl)benzene (**329**, 1.94 g, 7.09 mmol, 1.00 eq.), DCM (100 mL) and water (2.2 mL, 120 mmol, 17 eq.). Trifluoroacetic acid (2.2 mL, 29 mmol, 4.1 eq.) was added and the mixture was stirred at RT for 20 h. The reaction was quenched by addition of sat. aq. Na_2CO_3 and the aqueous layer was extracted with DCM (3x). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/MTBE 4:1 to 2:1) yielded the product (1.36 g, 5.27 mmol, 74%) as a white solid.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 9.71 (t, J = 1.7 Hz, 1H), 7.08 (s, 1H), 6.72 (s, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.77 (d, J = 1.7 Hz, 2H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 198.78, 149.72, 149.32, 124.90, 116.19, 115.20, 114.79, 56.54, 56.43, 50.56.

EI-HRMS: calculated for $C_{10}H_{11}O_3Br_1$ ($[M]^+$): 257.988620, found: 257.988810.

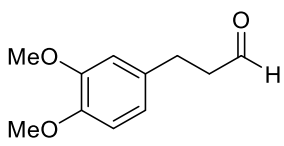
3-(benzo[*d*][1,3]dioxol-5-yl)propanal (225k)



The reaction was performed according to a literature procedure.[223] A flame-dried Schlenk under argon was charged with $NaHCO_3$ (1.68 g, 20.0 mmol, 2.00 eq.), tetrabutylammonium bromide (1.61 g, 5.00 mmol, 0.5 eq.), $Pd(OAc)_2$ (112 mg, 0.500 mmol, 0.05 eq.), and dry DMF (8.5 mL) and the mixture was sparged with argon for 30 seconds. Allyl alcohol (1.0 mL, 15 mmol, 1.5 eq.) and 5-iodobenzo[*d*][1,3]dioxole (2.48 g, 10.0 mmol, 1.00 eq.) were added, the flask was closed, and the mixture was heated to 80 °C for 4.5 h. After cooling to RT, the reaction was diluted with MTBE and subsequently washed with H_2O (3x) and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel flash column chromatography (*n*-pentane/MTBE 19:1 to 9:1) yielded the product (1.34 g, 7.49 mmol, 75%) as a colorless oil. The NMR-spectroscopic data was in agreement with the literature.[223]

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 9.80 (t, J = 1.4 Hz, 1H), 6.73 (d, J = 7.9 Hz, 1H), 6.68 (d, J = 1.7 Hz, 1H), 6.63 (dd, J = 7.9, 1.7 Hz, 1H), 5.92 (s, 2H), 2.88 (t, J = 7.5 Hz, 2H), 2.73 (ddd, J = 8.9, 7.4, 1.3 Hz, 2H).

3-(3,4-dimethoxyphenyl)propanal (225l)



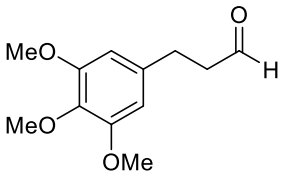
The reaction was performed according to a literature procedure.[223] A flame-dried Schlenk under argon was charged with $NaHCO_3$ (1.68 g, 20.0 mmol, 2.00 eq.), tetrabutylammonium bromide (1.61 g, 5.00 mmol, 0.5 eq.), $Pd(OAc)_2$ (112 mg, 0.500 mmol, 0.05 eq.), and dry DMF (8.5 mL) and the mixture was sparged with argon for 30 seconds. Allyl alcohol (1.0 mL, 15 mmol, 1.5 eq.) and 4-iodo-1,2-dimethoxybenzene (2.64 g, 10.0 mmol, 1.00 eq.) were added, the flask was

closed, and the mixture was heated to 80 °C for 4.5 h. After cooling to RT, the reaction was diluted with MTBE and subsequently washed with H_2O (3x) and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/MTBE 9:1 to 4:1) yielded the product (1.20 g, 6.18 mmol, 62%) as a colorless oil. The NMR-spectroscopic data was in agreement with the literature.[224]

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 9.82 (t, J = 1.6 Hz, 1H), 6.79 (d, J = 7.9 Hz, 1H), 6.74–6.70 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.91 (t, J = 7.5 Hz, 2H), 2.78–2.74 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 201.83, 149.13, 147.69, 133.06, 120.23, 111.83, 111.53, 56.07, 55.98, 45.64, 27.89.

3-(3,4,5-trimethoxyphenyl)propanal (225m)

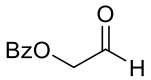


The reaction was performed according to a literature procedure.[223] A flame-dried Schlenk under argon was charged with $NaHCO_3$ (1.68 g, 20.0 mmol, 2.00 eq.), tetrabutylammonium bromide (1.61 g, 5.00 mmol, 0.5 eq.), $Pd(OAc)_2$ (112 mg, 0.500 mmol, 0.05 eq.), and dry DMF (8.5 mL) and the mixture was sparged with argon for 30 seconds. Allyl alcohol (1.0 mL, 15 mmol, 1.5 eq.) and 5-iodo-1,2,3-trimethoxybenzene (2.94 g, 10.0 mmol, 1.00 eq.) were added, the flask was closed, and the mixture was heated to 80 °C for 5 h. After cooling to RT, the reaction was diluted with MTBE and subsequently washed with H_2O (3x) and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/MTBE 10–40%) yielded the product (1.28 g, 5.69 mmol, 57%) as a colorless oil. The NMR-spectroscopic data was in agreement with the literature.[225]

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 9.82 (p, J = 1.2 Hz, 1H), 6.40 (s, 2H), 3.84 (q, J = 1.0 Hz, 6H), 3.81 (q, J = 0.9 Hz, 3H), 2.90 (t, J = 7.5 Hz, 2H), 2.79–2.72 (m, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 201.56, 153.40, 136.61, 136.25, 105.40, 60.96, 56.21, 45.51, 28.60.

2-oxoethyl benzoate (236)



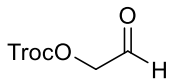
A flame-dried 100 mL two-necked flask equipped with a reflux condenser was charged with bromacetaldehyd diethylacetal (3.0 mL, 19 mmol, 1.0 eq.), sodium benzoate (3.2 g, 22 mmol, 1.1 eq.) and DMF (30 mL) and the mixture was heated to reflux for 16 h. The reaction was quenched by addition of H_2O, the aqueous layer was extracted with MTBE (3x), washed with H_2O (2x) and brine (2x), dried over dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/EtOAc 9:1) yielded 2,2-diethoxyethyl benzoate (3.7 g, 15 mmol, 79%). The material was stirred with H_2O (8 mL) and formic acid (98%, 30 mL) at room temperature for 16 h. The mixture was concentrated under reduced pressure and dried by azeotroping from PhMe (2x) to give the

desired product (2.5 g, 15 mmol, 79% over two steps) as a colorless oil. The NMR-spectroscopic data was in agreement with the literature.[226]

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 9.73 (s, 1H), 8.14–8.08 (m, 2H), 7.64–7.59 (m, 1H), 7.51 – 7.46 (m, 2H), 4.90 (d, J = 0.6 Hz, 2H).

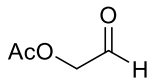
CI-HRMS: calculated for $C_9H_9O_3$ ($[M+H]^+$): 165.054620, found: 165.054790.

2-oxoethyl (2,2,2-trichloroethyl) carbonate (238)



The compound was prepared according to a literature procedure.[227] A flame-dried 250 mL two-necked flask under argon was charged with ethyleneglycol (11.5 mL, 206 mmol, 10.1 eq.), pyridine (1.8 mL), and DCM (50 mL) and cooled to 0 °C. 2,2,2-trichloroethoxycarbonyl chloride (2.8 mL, 20 mmol, 1.0 eq.) was added slowly, and the mixture was stirred at RT for 2 h. The reaction was diluted with DCM (50 mL), washed with HCl (10%), H_2O, and brine, and the combined organic layers were dried over dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/EtOAc 3:1 to 1:1) yielded the mono-protected alcohol (799 mg, 3.4 mmol, 17%). The material was redissolved in DCM (8 mL) and Dess-Martin periodinane (1.6 g, 3.7 mmol, 1.1 eq.) was added. After stirring at room temperature for 45 min, the reaction was diluted with MTBE and filtered over celite. Purification by silica gel flash column chromatography (*n*-pentane/Et2O 1:1) yielded the desired product (759 mg, 3.2 mmol, 16% over two steps) as a colorless oil.

2-oxoethyl acetate (242)

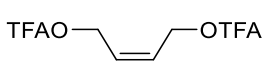


A flame-dried 250 mL two-necked flask under argon was charged with 1,4-diacetoxy-2-butene (**241a**, 2.0 g, 12 mmol, 1.0 eq.) and dry DCM (100 mL). The mixture was cooled to −78 °C and a stream of ozone was directed into the reaction solution until a blue color was observed (1 h reaction time). The ozone stream was stopped and exchanged for argon, until complete decolorization was observed (2 h). Triphenylphosphine (3.75 g, 14.3 mmol, 1.2 eq.) was added, and the reaction was allowed to slowly warm to room temperature over night. The mixture was concentrated and purified by silica gel flash column chromatography (*n*-pentane/Et_2O 9:1 to 4:1) to give the desired product (1.9 g, 19 mmol, 78%) as a colorless oil. The NMR-spectroscopic data was in agreement with the literature.[228]

$\boldsymbol{R_F}$ (hex/EtOAc 2:1) = 0.20 ($KMnO_4$ stain).

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 9.60 (s, 1H), 4.66 (s, 2H), 2.18 (s, 3H).

(*Z*)-but-2-ene-1,4-diyl bis(2,2,2-trifluoroacetate) (241b)



A flame-dried 250 mL flask under argon was charged with 2-butene-1,4-diol (4.0 mL, 49 mmol, 1.0 eq.), Et_3N (20 mL, 140 mmol, 2.9 eq.), DMAP (600 mg, 5 mmol, 0.1 eq.), and dry DCM (100 mL). The reaction was cooled to 0 °C, TFAA

(16 mL, 115 mmol, 2.4 eq.) was added slowly, and the mixture was allowed to warm to room temperature over night. The reaction was quenched by addition of sat. aq. $NaHCO_3$, the aqueous layer was extracted with DCM (3x), and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The mixture was purified by silica gel flash column chromatography (hex/EtOAc 9:1) to give the desired product (11.1 g, 39.6 mmol, 81%) as a colorless oil.

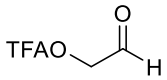
^{1}H-NMR (501 MHz, $CDCl_3$): δ = 5.93 (ddd, J = 5.4, 4.2, 1.3 Hz, 2H), 5.01–4.94 (m, 4H).

^{19}F-NMR (471 MHz, $CDCl_3$): δ = -74.97.

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 157.36 (q, J = 42.8 Hz), 127.89, 114.54 (q, J = 285.0 Hz), 62.82.

ESI-HRMS: calculated for $C_8H_6O_4F_6Na_1$ ($[M+Na]^+$): 303.006250, found: 303.006160.

2-oxoethyl 2,2,2-trifluoroacetate (243)



A flame-dried 250 mL two-necked flask under argon was charged with (*Z*)-but-2-ene-1,4-diyl bis(2,2,2-trifluoroacetate) (**241b**, 1.7 g, 6.2 mmol, 1.0 eq.) and dry DCM (100 mL). The mixture was cooled to −78 °C and a stream of ozone was directed into the reaction solution until a blue color was observed (30 min reaction time). The ozone stream was stopped and exchanged for argon, until complete decolorization was observed (1 h). Triphenylphosphine (1.9 g, 7.4 mmol, 1.2 eq.) was added, and the reaction was allowed to slowly warm to room temperature over night. All volatile components were collected in a cooling trap cooled with liquid nitrogen. The resultant product mixture was carefully concentrated (30 °C and 400 mbar) to give the desired product (77 wt% in DCM, 773 mg, 3.85 mmol, 31%) as a colorless oil.

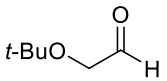
^{1}H-NMR (501 MHz, $CDCl_3$): δ = 9.64 (s, 1H), 4.96 (s, 2H).

^{19}F-NMR (471 MHz, $CDCl_3$): δ = -74.57.

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 191.69, 157.01 (q, J = 43.7 Hz), 114.50 (d, J = 285.0 Hz), 70.50.

CI-HRMS: calculated for $C_4H_4O_3F_3$ ($[M+H]^+$): 157.010706, found: 157.010830.

2-(*tert*-butoxy)acetaldehyde (240)



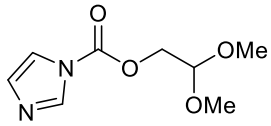
A flame-dried 250 mL two-necked flask under argon was charged with 2-*tert*-butoxyethanol (2.0 g, 17 mmol, 1.0 eq.) and dry DCM (80 mL) and cooled to 0 °C. Dess-Martin periodinane (7.96 g, 18.8 mmol, 1.11 eq.) was added, and the mixture was stirred at RT for 2.5 h. The reaction was quenched by addition of sat. aq. $NaHCO_3$, the aqueous layer was extracted with DCM (3x), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel flash column chromatography (*n*-pentane/Et_2O 3:1) yielded the product (1.17 g, 5.84 mmol, 35%) as a colorless 58 wt% solution in DCM.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 9.72 (t, J = 1.2 Hz, 1H), 3.98 (d, J = 1.1 Hz, 2H), 1.24 (s, 9H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 202.56, 74.51, 68.77, 27.51.

EI-HRMS: calculated for $C_6H_{13}O_2$ ($[M+H]^+$): 117.091005, found: 117.091200.

2,2-dimethoxyethyl 1*H*-imidazole-1-carboxylate (245)



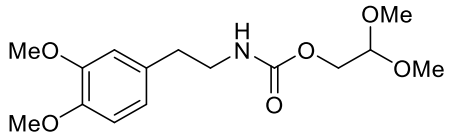
Synthesized according to a literature procedure for related compounds.[229] A flame-dried 100 mL three-necked flask under argon was charged with glycolaldehyde dimethyl acetal (1.0 g, 9.7 mmol, 1.0 eq.) and dry THF (20 mL). Carbonyl diimidazole (1.9 g, 12 mmol, 1.2 eq.) was added, and the mixture was stirred at RT for 16 h. The reaction was quenched by addition of H_2O (100 mL), the aqueous layer was extracted with MTBE (3x), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material (1.34 g, 6.70 mmol, 69%) was used for the next step without further purification.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 8.16–8.12 (m, 1H), 7.42 (q, J = 1.2 Hz, 1H), 7.06 (dt, J = 1.6, 0.8 Hz, 1H), 4.69 (t, J = 5.3 Hz, 1H), 4.39 (dd, J = 5.3, 0.8 Hz, 2H), 3.43 (d, J = 0.8 Hz, 6H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 148.56, 137.30, 130.91, 117.30, 100.73, 65.92, 54.28.

CI-HRMS: calculated for $C_8H_{13}N_2O_4$ ($[M+H]^+$): 201.086982, found: 201.087000.

2,2-dimethoxyethyl (3,4-dimethoxyphenethyl)carbamate (228)



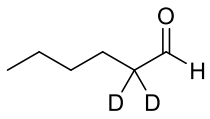
Synthesized according to a literature procedure for related compounds.[229] A 50 mL flask was charged with acetal **245** (1.3 g, 6.5 mmol, 1.0 eq.) and CH_3CN (15 mL). Methyl iodide (1.4 mL, 22 mmol, 3.4 eq.) was added, and the reaction was stirred at room temperature for 16 h. The mixture was concentrated under reduced pressure and redissolved in CH_3CN (30 mL). Homoveratrylamine (**73**, 1.2 mL, 7.1 mmol, 1.1 eq.) was added and the mixture was stirred at room temperature for 16 h. The reaction was quenched by addition of H_2O (100 mL), the aqueous layer was extracted with DCM (3x), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/EtOAc 40–50%) yielded the desired product (1.7 g, 5.4 mmol, 82%) as a yellow oil.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 6.79 (d, J = 8.1 Hz, 1H), 6.74–6.67 (m, 2H), 4.83 (t, J = 5.9 Hz, 1H), 4.51 (t, J = 5.3 Hz, 1H), 4.07 (d, J = 5.3 Hz, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.41 (q, J = 7.3 Hz, 2H), 3.37 (s, 6H), 2.74 (t, J = 7.1 Hz, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.06, 149.15, 147.83, 131.22, 120.77, 112.03, 111.51, 101.64, 63.24, 56.03, 55.94, 53.97, 42.43, 35.69.

ESI-HRMS: calculated for $C_{15}H_{23}N_1O_6Na_1$ ($[M+Na]^+$): 336.141757, found: 336.141850.

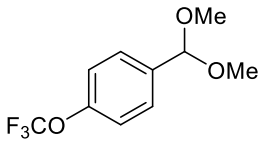
hexanal-2,2-D_2 (284-D_2)



A 5 mL microwave vial was charged with hexanal (1.0 mL, 8.1 mmol, 1.0 eq.), deuterium oxide (2.0 mL, 110 mmol, 13.6 eq.), and 4-DMAP (13 mg,

0.11 mmol, 1 mol%). The vial was capped, and the mixture was heated to 100 °C for 24 h. After cooling to RT, the reaction was diluted with Et_2O, and washed with HCl (1.2 M), saturated aqueous $NaHCO_3$, and brine. The organic layers were dried over Na_2SO_4 and concentrated to give the desired product, which was used without further purification (370 mg, 3.6 mmol, 44%, >90% *d*).
^{1}H-NMR (501 MHz, $CDCl_3$): δ = 9.76 (s, 1H), 1.61 (t, J = 7.1 Hz, 2H), 1.32 (dtt, J = 11.9, 8.2, 4.4 Hz, 4H), 0.98–0.83 (m, 3H).
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 203.27, 43.44 (dt, J = 47.6, 19.3 Hz), 31.39, 22.54, 21.78, 13.98.
EI-HRMS: calculated for $C_6H_{10}D_2O_1$ ($[M]^+$): 102.100819, found: 102.100840.

1-(dimethoxymethyl)-4-(trifluoromethoxy)benzene (330)

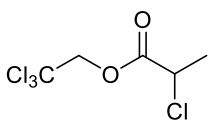


A 25 mL flask equipped with a reflux condenser was charged with 4-(trifluoromethoxy)benzaldehyde (0.75 mL, 5.3 mmol, 1.0 eq.), MeOH (5 mL), and trimethyl orthoformate (3.0 mL, 27 mmol, 5.2 eq.). para-toluenesulfonic acid monohydrate (90 mg, 0.5 mmol, 9 mol%) was added lastly, and the mixture was heated to 70 °C for 16 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$, the aqueous layer was extracted with Et_2O (3x), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by distillation (80 °C, 19 mbar) yielded the desired product (556 mg, 2.4 mmol, 45%) as a colorless oil.
^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.52–7.46 (m, 2H), 7.24–7.19 (m, 2H), 5.39 (s, 1H), 3.33 (s, 6H).
^{19}F-NMR (471 MHz, $CDCl_3$): δ = -57.85.
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 149.39, 136.98, 128.42, 120.77, 120.61 (q, J = 257.3 Hz), 102.43, 52.84.
CI-HRMS: calculated for $C_{10}H_{10}O_3F_3$ ($[M-H]^-$): 235.057655, found: 235.057260.

7.5. Synthesis of Fluoroformates

Phenyl fluoroformate and ethyl fluoroformate were prepared according to established literature procedures from the corresponding chloroformates.

2,2,2-trichloroethyl 2-chloropropanoate (331)



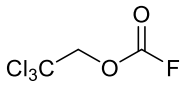
Adapted from a literature procedure.[230] A flame-dried 250 mL two-necked flask under argon was charged with 2,2,2-trichloroethanol (5.5 mL, 57 mmol, 1.0 eq.), 1-chloroethyl chloroformate (6.5 mL, 60 mmol, 1.05 eq.) and DCM (50 mL). The solution was cooled to 0 °C and pyridine (5.4 mL, 67 mmol, 1.2 eq.) was added carefully. The reaction was stirred for 16 h while slowly reaching room temperature. The mixture was filtered over celite (eluted with DCM) and concentrated under reduced pressure. Distillation (115 °C, 18 mbar) afforded the desired product (13.8 g, 54.0 mmol, 94%) as a colorless oil.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 6.46 (q, J = 5.8 Hz, 1H), 4.84 (d, J = 11.8 Hz, 1H), 4.80 (d, J = 11.8 Hz, 1H), 1.88 (d, J = 5.8 Hz, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 152.09, 94.01, 85.31, 77.26, 25.27.

CI-HRMS: calculated for $C_5H_7O_3Cl_4$ ($[M+H]^+$): 254.914382, found: 254.914340.

2,2,2-trichloroethyl carbonofluoridate (306c)



Adapted from a literature procedure.[230] A flame-dried 50 mL two-necked flask under argon was charged with **331** (13.8 g, 54 mmol, 1.0 eq.), dry potassium fluoride (7.8 g, 134 mmol, 2.5 eq.), and 18-crown-6 (1.0 g, 3.8 mmol, 7 mol%). A second flame-dried flask was attached to the reaction vessel *via* a glass bridge. The receiving flask was cooled to −78 °C, and the pressure was reduced to 30 mbar. The reaction flask was heated to 70 °C for 16 h and subsequently to 90 °C for 24 h. The material that was collected by condensation in the receiving flask was distilled (45 °C, 25 mbar) to yield the desired product as a colorless oil.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 4.86 (s, 2H).

^{19}F-NMR (471 MHz, $CDCl_3$): δ = -17.91.

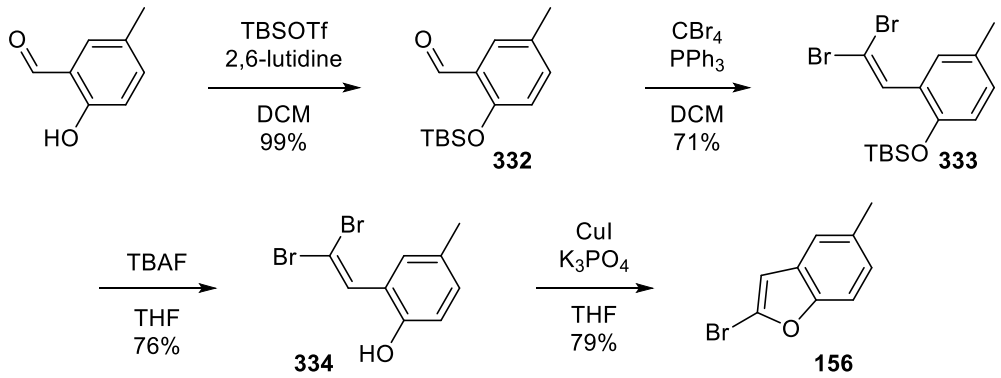
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 144.70 (d, J = 286.8 Hz), 92.95, 78.92.

Detection of the product by high resolution mass spectrometry has thus far proven unsuccessful.

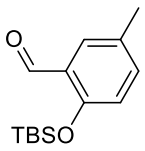
7.6. Catalyst Synthesis

7.6.1. Synthesis of 3,3'-substituents

2-bromo-5-methylbenzofuran (156)



2-((*tert*-butyldimethylsilyl)oxy)-5-methylbenzaldehyde (332)



A flame-dried 100 mL Schlenk flask under argon was charged with 5-methylsalicylaldehyde (2.0 g, 15 mmol, 1.00 eq.), DCM (30 mL), and 2,6-lutidine (5.5 mL, 47 mmol, 3.1 eq.). The mixture was cooled to 0 °C, TBSOTf (5.25 mL, 22.9 mmol, 1.52 eq.) was added slowly, and the mixture was allowed to slowly warm to RT over night. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ and extracted with DCM (3x). The combined organic layers were washed with brine, dried over

Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/EtOAc 100:0 to 99.4:0.6) gave the desired product as a yellow oil (3.7 g, 14.8 mmol, 99%).

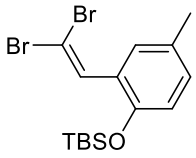
$\boldsymbol{R_F}$ (hex/EtOAc 9:1) = 0.62.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 10.43 (s, 1H), 7.60 (d, J = 2.4 Hz, 1H), 7.29–7.24 (m, 1H), 6.78 (d, J = 8.3 Hz, 1H), 2.30 (s, 3H), 1.02 (s, 9H), 0.26 (s, 6H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 190.48, 157.01, 136.68, 131.06, 128.32, 126.98, 120.28, 25.83, 20.51, 18.50, -4.18.

CI-HRMS: calculated for $C_{14}H_{23}O_2Si_1^+$ ($[M+H]^+$): 251.146183, found: 251.146080.

***tert*-butyl(2-(2,2-dibromovinyl)-4-methylphenoxy)dimethylsilane (333)**



A flame-dried 100 mL Schlenk under argon was charged with 2-((*tert*-butyldimethylsilyl)oxy)-5-methylbenzaldehyde (**332**, 3.69 g, 14.7 mmol, 1.00 eq.) and DCM (45 mL) and cooled to 0 °C. Triphenylphosphine (11.6 g, 44.2 mmol, 3.01 eq.) and tetrabromomethane (7.3 g, 22.0 mmol, 1.50 eq.) were added simultaneously and the mixture was allowed to slowly warm to RT over night. The reaction was quenched by addition of saturated aqueous Na_2SO_3 and the aqueous layer was extracted with DCM (3x). The combined organic phases were washed with saturated aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/EtOAc 100:0 to 99.5:0.5) yielded the product as a colorless oil (4.22 g, 10.4 mmol, 71%).

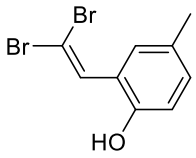
$\boldsymbol{R_F}$ (hex/EtOAc 19:1) = 0.76.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.54 (s, 1H), 7.44 (d, J = 2.3 Hz, 1H), 7.02 (dd, J = 8.2, 2.3 Hz, 1H), 6.70 (d, J = 8.2 Hz, 1H), 2.30 (s, 3H), 1.02 (s, 9H), 0.19 (s, 6H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 150.89, 134.32, 130.46, 130.44, 129.64, 127.08, 119.42, 89.63, 25.87, 20.83, 18.37, -4.27.

CI-HRMS: calculated for $C_{15}H_{23}O_1Si_1Br_2^+$ ($[M+H]^+$): 404.987969, found: 404.987920.

2-(2,2-dibromovinyl)-4-methylphenol (334)



A flame-dried Schlenk under argon was charged with *tert*-butyl(2-(2,2-dibromovinyl)-4-methylphenoxy)dimethylsilane (**333**, 4.18 g, 10.3 mmol, 1.00 eq.) and THF (50 mL) and cooled to 0 °C. TBAF (1.0 M in THF, 15 mL, 15 mmol, 1.5 eq.) was added and the mixture was allowed to slowly warm to RT over night. The reaction was quenched by addition of H_2O (100 mL) and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (pentane/Et_2O 19:1 to 9:1) yielded the product as a yellow oil (2.28 g, 7.82 mmol, 76%).

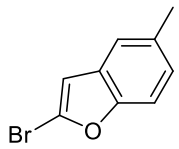
R_F (hex/EtOAc 9:1) = 0.26.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.53 (s, 1H), 7.32 (d, J = 2.2 Hz, 1H), 7.03 (dd, J = 8.3, 2.2 Hz, 1H), 6.73 (d, J = 8.2 Hz, 1H), 2.30 (s, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 150.39, 132.71, 130.74, 130.08, 129.50, 122.69, 115.76, 91.97, 20.68.

EI-HRMS: calculated for $C_9H_8O_1Br_2^+$ ($[M]^+$): 289.893665, found: 289.893540.

2-bromo-5-methylbenzofuran (156)



The reaction was conducted according to a literature procedure.[168] An oven-dried 20 mL microwave vial under argon was charged with K_3PO_4 (1.5 g, 7.1 mmol, 2.0 eq.) and CuI (33 mg, 0.17 mmol, 5 mol%). 2-(2,2-dibromovinyl)-4-methylphenol (**334**, 1.02 g, 3.5 mmol, 1.00 eq.) was added in THF (15 mL), the flask was capped, covered in aluminum foil, and heated to 80 °C for 15 h. After cooling to RT, the mixture was filtered over silica gel (eluted with Et_2O), and concentrated under reduced pressure. Purification by silica gel flash column chromatography (100% hex) yielded the product as a colorless oil (587 mg, 2.78 mmol, 79%).

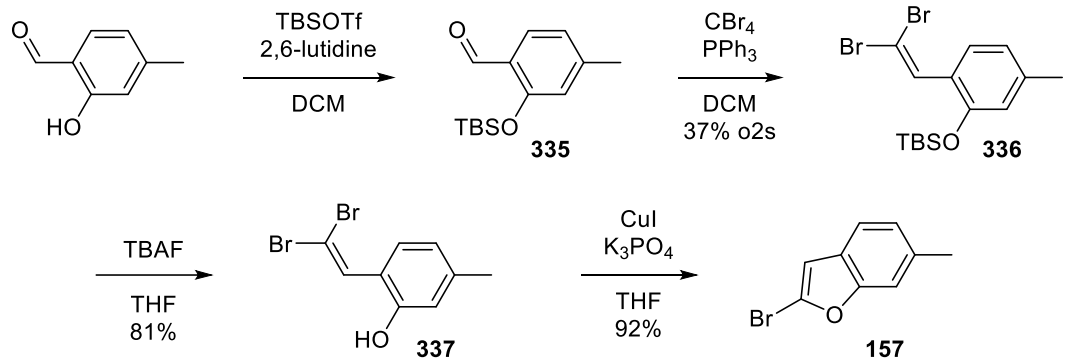
R_F (100% hex) = 0.66.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.32 (d, J = 8.5 Hz, 1H), 7.30–7.28 (m, 1H), 7.07 (dd, J = 8.4, 1.8 Hz, 1H), 6.65 (d, J = 0.9 Hz, 1H), 2.43 (s, 3H).

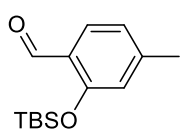
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 154.38, 133.04, 128.89, 128.17, 125.54, 120.00, 110.53, 108.15, 21.44.

EI-HRMS: calculated for $C_9H_7O_1Br_1^+$ ($[M]^+$): 209.967490, found: 209.967500.

2-bromo-6-methylbenzofuran (157)



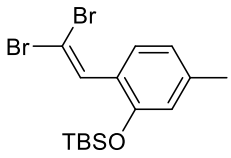
2-((*tert*-butyldimethylsilyl)oxy)-4-methylbenzaldehyde (335)



A flame-dried 100 mL Schlenk flask under argon was charged with 4-methylsalicylaldehyde (2.04 g, 15.0 mmol, 1.00 eq.), DCM (30 mL), and 2,6-lutidine (5.5 mL, 46.7 mmol, 3.12 eq.). The mixture was cooled to 0 °C, TBSOTf (5.25 mL, 22.9 mmol, 1.52 eq.) was added slowly, and the mixture was allowed to slowly warm

to RT over night. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ and extracted with DCM (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/EtOAc 100:0 to 99:1) gave the desired product together with an inseparable impurity in a ratio of 63:37 (4.24 g). The mixture was used for the next step without further purification.

tert-butyl(2-(2,2-dibromovinyl)-5-methylphenoxy)dimethylsilane (336)



A flame-dried 100 mL Schlenk under argon was charged with impure 2-((*tert*-butyldimethylsilyl)oxy)-4-methylbenzaldehyde (**335**, 4.24 g) and DCM (45 mL) and cooled to 0 °C. Triphenylphosphine (13.3 g, 50.7 mmol, 3.38 eq.) and tetrabromomethane (8.4 g, 25.3 mmol, 1.69 eq.) were added simultaneously and the mixture was allowed to slowly warm to RT over night. The reaction was quenched by addition of saturated aqueous Na_2SO_3 and the aqueous layer was extracted with DCM (3x). The combined organic phases were washed with saturated aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/EtOAc 100:0 to 99.5:0.5) yielded the product as a colorless oil (2.27 g, 5.59 mmol, 37% over 2 steps).

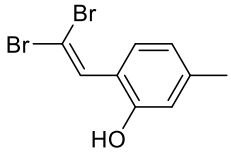
$\boldsymbol{R_F}$ (hex/EtOAc 19:1) = 0.59.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.55 (d, J = 8.1 Hz, 1H), 7.54 (s, 1H), 6.81–6.77 (m, 1H), 6.62 (t, J = 1.2 Hz, 1H), 2.29 (s, 3H), 1.02 (s, 9H), 0.20 (s, 6H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 153.08, 140.32, 134.08, 128.96, 124.55, 122.07, 120.34, 89.02, 25.86, 21.64, 18.38, -4.22.

EI-HRMS: calculated for $C_{15}H_{22}O_1Si_1Br_2^+$ ($[M]^+$): 403.980144, found: 403.979910.

2-(2,2-dibromovinyl)-5-methylphenol (337)



A flame-dried Schlenk under argon was charged with *tert*-butyl(2-(2,2-dibromovinyl)-5-methylphenoxy)dimethylsilane (**336**, 2.22 g, 5.48 mmol, 1.00 eq.) and THF (25 mL) and cooled to 0 °C. TBAF (1.0 M in THF, 8.5 mL, 8.5 mmol, 1.55 eq.) was added and the mixture was allowed to slowly warm to RT over night. The reaction was quenched by addition of H_2O (100 mL) and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/EtOAc 95:5) yielded the product as a yellow oil (1.29 g, 4.42 mmol, 81%).

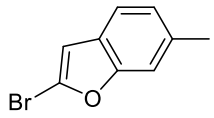
$\boldsymbol{R_F}$ (hex/EtOAc 9:1) = 0.29.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.53 (s, 1H), 7.44 (d, J = 7.9 Hz, 1H), 6.77 (dd, J = 7.9, 1.6 Hz, 1H), 6.64 (d, J = 1.6 Hz, 1H), 2.30 (s, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 152.46, 140.77, 132.41, 129.04, 121.74, 120.12, 116.48, 91.41, 21.48.

EI-HRMS: calculated for $C_9H_8O_1Br_2^+$ ([M]$^+$): 289.893666, found: 289.893820.

2-bromo-6-methylbenzofuran (157)



The reaction was conducted according to a literature procedure.[168] An oven-dried 20 mL microwave vial under argon was charged with K_3PO_4 (1.49 g, 7.00 mmol, 2.00 eq.) and CuI (33 mg, 0.17 mmol, 5 mol%). 2-(2,2-dibromovinyl)-5-methylphenol (**337**, 1.02 g, 3.5 mmol, 1.00 eq.) was added in THF (15 mL), the flask was capped, covered in aluminum foil, and heated to 80 °C for 15 h. After cooling to RT, the mixture was filtered over silica gel (eluted with Et_2O), and concentrated under reduced pressure. Purification by silica gel flash column chromatography (100% hex) yielded the product as a colorless oil (680 mg, 3.22 mmol, 92%).

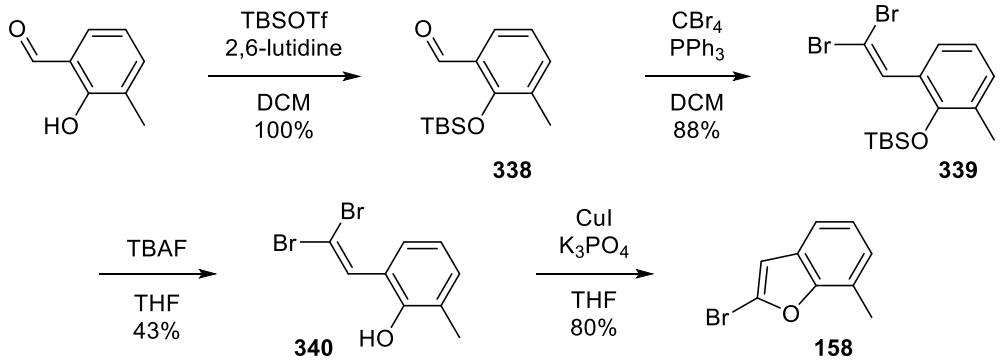
$\boldsymbol{R_F}$ (100% hex) = 0.62.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.37 (d, J = 7.9 Hz, 1H), 7.27–7.25 (m, 3H), 7.06 (dd, J = 7.9, 1.5 Hz, 1H), 6.67 (d, J = 0.9 Hz, 1H), 2.46 (s, 3H).

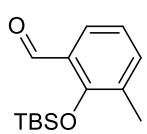
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.30, 134.68, 127.31, 126.30, 124.87, 119.62, 111.25, 108.21, 21.77.

EI-HRMS: calculated for $C_9H_7O_1Br_1^+$ ([M]$^+$): 209.967490, found: 209.967680.

2-bromo-7-methylbenzofuran (158)



2-((*tert*-butyldimethylsilyl)oxy)-3-methylbenzaldehyde (338)



A flame-dried 100 mL Schlenk flask under argon was charged with 3-methylsalicylaldehyde (1.8 mL, 15 mmol, 1.00 eq.), DCM (30 mL), and 2,6-lutidine (5.25 mL, 44.6 mmol, 3.00 eq.). The mixture was cooled to 0 °C, TBSOTf (5.25 mL, 22.9 mmol, 1.54 eq.) was added slowly, and the mixture was allowed to slowly warm to RT over night. More TBSOTf (0.50 mL, 2.18 mmol, 0.15 eq.) was added and the reaction was stirred for another 2 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ and extracted with DCM (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, and

concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/EtOAc 100:0 to 99:1) gave the desired product as a yellow oil (3.7 g, 15 mmol, 100%).

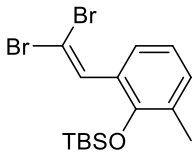
R_F (hex/EtOAc 9:1) = 0.59.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 10.32 (d, J = 0.8 Hz, 1H), 7.65 (dd, J = 7.7, 1.8 Hz, 1H), 7.39 (ddd, J = 7.3, 1.9, 0.9 Hz, 1H), 6.99 (t, J = 7.5 Hz, 1H), 2.26 (s, 3H), 1.06 (s, 9H), 0.17 (s, 6H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 190.61, 157.06, 137.56, 130.75, 128.20, 126.12, 122.03, 25.98, 18.73, 16.96, -3.67.

CI-HRMS: calculated for $C_{14}H_{23}O_2Si_1^+$ ($[M+H]^+$): 251.146184, found: 251.146050.

tert-butyl(2-(2,2-dibromovinyl)-6-methylphenoxy)dimethylsilane (339)



A flame-dried 100 mL Schlenk under argon was charged with 2-((*tert*-butyldimethylsilyl)oxy)-3-methylbenzaldehyde (**338**, 3.72 g, 14.9 mmol, 1.00 eq.) and DCM (45 mL) and cooled to 0 °C. Triphenylphosphine (11.7 g, 44.6 mmol, 3.00 eq.) and tetrabromomethane (7.4 g, 22.3 mmol, 1.50 eq.) were added simultaneously and the mixture was allowed to slowly warm to RT over night. The reaction was quenched by addition of saturated aqueous Na_2SO_3 and the aqueous layer was extracted with DCM (3x). The combined organic phases were washed with saturated aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/EtOAc 100:0 to 99.5:0.5) yielded the product as a white solid (5.34 g, 13.1 mmol, 88%).

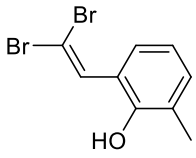
R_F (hex/EtOAc 19:1) = 0.75.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.49–7.44 (m, 2H), 7.18–7.11 (m, 1H), 6.91 (t, J = 7.6 Hz, 1H), 2.23 (s, 3H), 1.05 (s, 8H), 0.19 (s, 6H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 151.44, 135.44, 131.86, 129.44, 127.56, 127.19, 121.33, 90.34, 26.16, 18.78, 17.57, -3.26.

CI-HRMS: calculated for $C_{15}H_{23}O_1Si_1Br_2^+$ ($[M+H]^+$): 404.987969, found: 404.987920.

2-(2,2-dibromovinyl)-6-methylphenol (340)



A flame-dried Schlenk under argon was charged with *tert*-butyl(2-(2,2-dibromovinyl)-6-methylphenoxy)dimethylsilane (**339**, 5.30 g, 13.1 mmol, 1.00 eq.) and THF (50 mL) and cooled to 0 °C. TBAF (1.0 M in THF, 20 mL, 20 mmol, 1.5 eq.) was added and the mixture was allowed to slowly warm to RT over night. The reaction was quenched by addition of H_2O (100 mL) and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/EtOAc 95:5) yielded the product as a brown oil (1.65 g, 5.66 mmol, 43%).

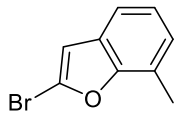
R_F (hex/EtOAc 9:1) = 0.34.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.54 (s, 1H), 7.34–7.31 (m, 1H), 7.16–7.11 (m, 1H), 6.87 (t, J = 7.6 Hz, 1H), 2.27 (s, 3H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 150.90, 132.93, 131.46, 127.03, 124.00, 122.64, 120.41, 92.75, 15.95.

EI-HRMS: calculated for $C_9H_8O_1Br_2^+$ ($[M]^+$): 289.893666, found: 289.893750.

2-bromo-7-methylbenzofuran (158)



The reaction was conducted according to a literature procedure.[168] An oven-dried 20 mL microwave vial under argon was charged with K_3PO_4 (1.5 g, 7.1 mmol, 2.0 eq.) and CuI (33 mg, 0.17 mmol, 5 mol%). 2-(2,2-dibromovinyl)-6-methylphenol (**340**, 1.02 g, 3.5 mmol, 1.00 eq.) was added in THF (15 mL), the flask was capped, covered in aluminum foil, and heated to 80 °C for 15 h. After cooling to RT, the mixture was filtered over silica gel (eluted with Et_2O), and concentrated under reduced pressure. Purification by silica gel flash column chromatography (100% hex) yielded the product as a colorless oil (588 mg, 2.79 mmol, 80%).

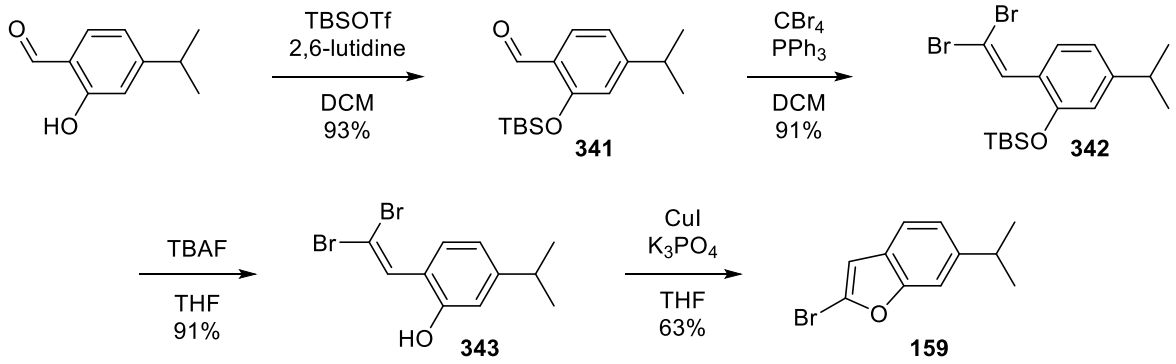
$\boldsymbol{R_F}$ (100% hex) = 0.73.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.34–7.31 (m, 1H), 7.13 (t, J = 7.5 Hz, 1H), 7.08–7.04 (m, 1H), 6.71 (s, 1H), 2.51 (s, 3H).

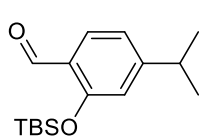
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 155.11, 128.37, 127.96, 125.32, 123.53, 121.35, 117.61, 108.64, 15.06.

EI-HRMS: calculated for $C_9H_7O_1Br_1^+$ ($[M]^+$): 209.967490, found: 209.967470.

2-bromo-6-isopropylbenzofuran (159)



2-((*tert*-butyldimethylsilyl)oxy)-4-isopropylbenzaldehyde (341)



A flame-dried 100 mL Schlenk flask under argon was charged with 4-isopropylsalicylaldehyde (1.05 g, 6.41 mmol, 1.00 eq.), DCM (14 mL), and 2,6-lutidine (2.25 mL, 19.1 mmol, 2.99 eq.). The mixture was cooled to 0 °C and TBSOTf (3.0 mL, 13 mmol, 2.0 eq.) was added slowly and the mixture was allowed to warm to RT over night. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ and extracted

with DCM (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/EtOAc 100:0 to 98:2) yielded the product as a yellow oil (1.66 g, 5.95 mmol, 93%).

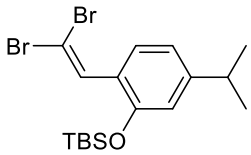
$\boldsymbol{R_F}$ (hex/EtOAc 9:1) = 0.40.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 10.39 (d, J = 0.8 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 6.93–6.89 (m, 1H), 6.72 (d, J = 1.6 Hz, 1H), 2.89 (hept, J = 6.9 Hz, 1H), 1.24 (d, J = 6.9 Hz, 6H), 1.02 (s, 9H), 0.28 (s, 6H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 189.92, 159.24, 158.03, 128.46, 125.43, 120.25, 118.21, 34.54, 25.84, 23.62, 18.51, -4.10.

ESI-HRMS: calculated for $C_{16}H_{27}O_2Si_1^+$ ($[M+H]^+$): 279.177484, found: 279.177470.

***tert*-butyl(2-(2,2-dibromovinyl)-5-isopropylphenoxy)dimethylsilane (342)**



A flame-dried 100 mL three-necked flask under argon was charged with 2-((*tert*-butyldimethylsilyl)oxy)-4-isopropylbenzaldehyde (**341**, 1.64 g, 5.89 mmol, 1.00 eq.) and DCM (30 mL) and cooled to 0 °C. Triphenylphosphine (4.7 g, 18 mmol, 3.0 eq.) and tetrabromomethane (3.0 g, 9.0 mmol, 1.5 eq.) were added simultaneously and the mixture was allowed to slowly warm to RT over night. The reaction was quenched by addition of saturated aqueous Na_2SO_3 and the aqueous layer was extracted with DCM (3x). The combined organic phases were washed with saturated aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (100% hex) yielded the product as a colorless oil (2.33 g, 5.36 mmol, 91%).

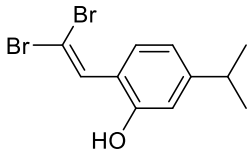
$\boldsymbol{R_F}$ (100% hex) = 0.59.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.61 (d, J = 8.0 Hz, 1H), 7.55 (s, 1H), 6.85 (dd, J = 8.0, 1.9 Hz, 1H), 6.67 (d, J = 1.7 Hz, 1H), 2.84 (hept, J = 6.9 Hz, 1H), 1.23 (d, J = 6.9 Hz, 6H), 1.03 (s, 9H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 153.17, 151.32, 133.98, 128.93, 124.74, 119.42, 117.66, 88.83, 34.07, 25.88, 23.86, 18.39, -4.19.

ESI-HRMS: calculated for $C_{17}H_{27}Br_2O_1Si_1^+$ ($[M+H]^+$): 433.019269, found: 433.019130.

2-(2,2-dibromovinyl)-5-isopropylphenol (343)



A flame-dried 50 mL three-necked flask under argon was charged with *tert*-butyl(2-(2,2-dibromovinyl)-5-isopropylphenoxy)dimethylsilane (**342**, 2.3 g, 5.3 mmol, 1.0 eq.) and THF (25 mL) and cooled to 0 °C. TBAF (1.0 M in THF, 8.0 mL, 8.0 mmol, 1.5 eq.) was added and the mixture was allowed to slowly warm to RT over night. The reaction was quenched by addition of H_2O (50 mL) and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, and concentrated under reduced pressure.

Purification by silica gel flash column chromatography (hex/EtOAc 95:5) yielded the desired product (1.54 g, 4.81 mmol, 91%).

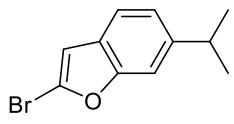
***R*$_F$** (hex/EtOAc 9:1) = 0.29.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.54 (s, 1H), 7.51 (dd, J = 8.1, 1.4 Hz, 1H), 6.82 (dd, J = 8.0, 1.7 Hz, 1H), 6.69 (d, J = 1.7 Hz, 1H), 2.84 (hept, J = 6.9 Hz, 1H), 1.23 (d, J = 6.9 Hz, 7H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 152.75, 151.74, 132.45, 129.04, 120.38, 119.02, 113.82, 90.96, 34.07, 23.81.

ESI-HRMS: calculated for $C_{11}H_{11}Br_2O_1^-$ ($[M-H]^-$): 316.918240, found: 316.917980.

2-bromo-6-isopropylbenzofuran (159)



The reaction was conducted according to a literature procedure.[168] A flame-dried 20 mL microwave vial under argon was charged with K_3PO_4 (2.0 g, 9.5 mmol, 2.0 eq.), CuI (74 mg, 0.39 mmol, 8 mol%), 2-(2,2-dibromovinyl)-5-isopropylphenol (**343**, 1.52 g, 4.75 mmol, 1.00 eq.), and THF (15 mL). The vial was capped and covered in aluminum foil, and the mixture was heated to 80 °C for 17 h. After cooling to RT, the mixture was filtered over celite (eluted with MTBE), and concentrated under reduced pressure. Purification by silica gel flash column chromatography (100% pentane) yielded the product as a colorless oil (712 mg, 2.98 mmol, 63%).

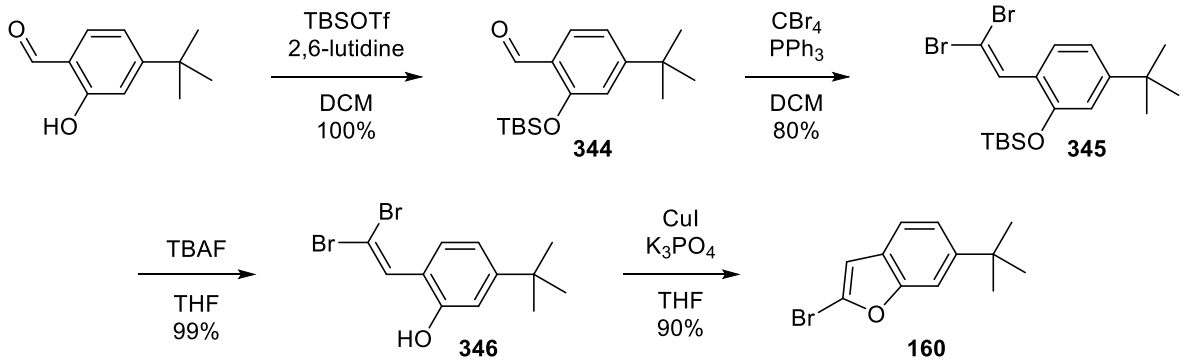
***R*$_F$** (100% pentane) = 0.74.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.40 (d, J = 8.0 Hz, 1H), 7.33–7.29 (m, 1H), 7.12 (dd, J = 8.0, 1.5 Hz, 1H), 6.67 (d, J = 0.9 Hz, 1H), 3.01 (hept, J = 6.9 Hz, 1H), 1.29 (d, J = 6.9 Hz, 6H).

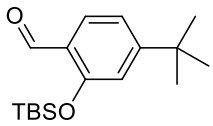
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.38, 146.08, 127.48, 126.65, 122.52, 119.75, 108.56, 108.18, 34.43, 24.39.

EI-HRMS: calculated for $C_{11}H_{11}O_1Br_1^+$ ($[M]^+$): 237.998790, found: 237.999210.

2-bromo-6-(*tert*-butyl)benzofuran (160)



4-(*tert*-butyl)-2-((*tert*-butyldimethylsilyl)oxy)benzaldehyde (344)



A flame-dried 100 mL Schlenk flask under argon was charged with 4-*tert*-butylsalicylaldehyde (5.24 g, 29.4 mmol, 1.00 eq.), DCM (60 mL), and 2,6-lutidine (10.5 mL, 89.2 mmol, 3.04 eq.). The mixture was cooled to 0 °C and TBSOTf (10.0 mL, 43.5 mmol, 1.48 eq.) was added slowly. The mixture was warmed to RT and stirred for 24 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ and extracted with DCM (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/EtOAc 100:0 to 99:1) yielded the product as a yellow oil (8.60 g, 29.4 mmol, 100%).

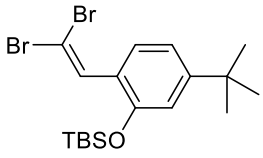
$\boldsymbol{R_F}$ (hex/EtOAc 9:1) = 0.57.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 10.40 (d, J = 0.9 Hz, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.07 (ddd, J = 8.3, 1.8, 0.9 Hz, 1H), 6.88 (d, J = 1.7 Hz, 1H), 1.31 (s, 9H), 1.03 (s, 9H), 0.28 (s, 6H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 189.93, 160.29, 158.97, 128.09, 124.93, 119.07, 117.46, 35.38, 31.06, 25.86, 18.53, -4.09.

CI-HRMS: calculated for $C_{17}H_{29}O_2Si_1^+$ ($[M+H]^+$): 293.193134, found: 293.193110.

***tert*-butyl(5-(*tert*-butyl)-2-(2,2-dibromovinyl)phenoxy)dimethylsilane (345)**



A flame-dried 500 mL three-necked flask under argon was charged with 4-(*tert*-butyl)-2-((*tert*-butyldimethylsilyl)oxy)benzaldehyde (**344**, 8.60 g, 29.4 mmol, 1.00 eq.) and DCM (140 mL) and cooled to 0 °C. Triphenylphosphine (23.1 g, 88.1 mmol, 3.00 eq.) and tetrabromomethane (14.6 g, 44.0 mmol, 1.50 eq.) were added simultaneously and the mixture was allowed to slowly warm to RT over night. The reaction was quenched by addition of Na_2SO_3 (75 g in 500 mL H_2O) and the aqueous layer was extracted with DCM (3x). The combined organic phases were washed with saturated aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/EtOAc 100:0 to 98:2) yielded the product as a yellow oil (10.5 g, 23.4 mmol, 80%).

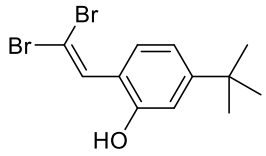
R_F (hex/EtOAc 19:1) = 0.76.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.63 (d, J = 8.2 Hz, 1H), 7.56 (s, 1H), 7.00 (dd, J = 8.2, 1.9 Hz, 1H), 6.83 (d, J = 1.9 Hz, 1H), 1.29 (s, 9H), 1.03 (s, 9H), 0.21 (s, 6H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 153.63, 152.94, 133.83, 128.57, 124.31, 118.21, 116.92, 88.81, 34.83, 31.26, 25.89, 18.41, -4.18.

EI-HRMS: calculated for $C_{18}H_{28}O_1Si_1Br_2^+$ ($[M]^+$): 446.027094, found: 446.026650.

5-(*tert*-butyl)-2-(2,2-dibromovinyl)phenol (346)



A flame-dried 250 mL three-necked flask under argon was charged with *tert*-butyl (5-(*tert*-butyl)-2-(2,2-dibromovinyl)phenoxy)dimethylsilane (**345**, 10.5 g, 23.4 mmol, 1.00 eq.) and THF (120 mL) and cooled to 0 °C. TBAF (1.0 M in THF, 30 mL, 30 mmol, 1.28 eq.) was added and the mixture was allowed to slowly warm to RT over night. The reaction was quenched by addition of H_2O (100 mL) and the aqueous layer was extracted with MTBE (3x). The combined organic phases were washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/EtOAc 100:0 to 95:5) yielded the product as a colorless oil (7.73 g, 23.1 mmol, 99%).

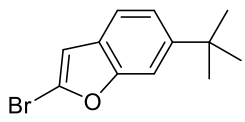
R_F (hex/EtOAc 9:1) = 0.33.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.54 (s, 1H), 7.51 (dd, J = 8.2, 0.7 Hz, 1H), 6.98 (dd, J = 8.2, 1.9 Hz, 1H), 6.84 (d, J = 1.9 Hz, 1H), 4.93 (s, 1H), 1.30 (s, 9H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 154.14, 152.38, 132.35, 128.75, 120.01, 118.00, 113.06, 91.18, 34.90, 31.24.

EI-HRMS: calculated for $C_{12}H_{14}O_1Br_2^+$ ($[M]^+$): 331.940616, found: 331.940700.

2-bromo-6-(*tert*-butyl)benzofuran (160)



The reaction was conducted according to a literature procedure.[168] A flame-dried 250 mL Young Schlenk under argon was charged with K_3PO_4 (9.6 g, 45 mmol, 2.0 eq.) and CuI (216 mg, 1.13 mmol, 5 mol%). 5-(*tert*-butyl)-2-(2,2-dibromovinyl)phenol (**346**, 7.57 g, 22.7 mmol, 1.00 eq.) was added in THF (110 mL), the flask was closed and covered in aluminum foil, and the mixture was heated to 80 °C for 20 h. After cooling to RT, the mixture was filtered over celite (eluted with MTBE), and concentrated under reduced pressure. Purification by silica gel flash column chromatography (100% hex) yielded the product as a colorless oil (5.15 g, 20.4 mmol, 90%).

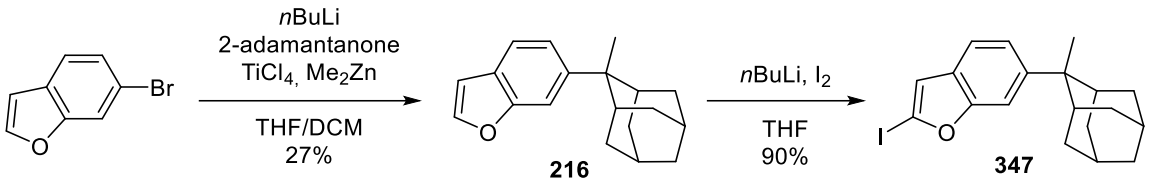
R_F (100% hex) = 0.68.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.47 (dt, J = 1.6, 0.8 Hz, 1H), 7.42 (dd, J = 8.2, 0.6 Hz, 1H), 7.30 (dd, J = 8.2, 1.6 Hz, 1H), 6.67 (d, J = 0.9 Hz, 1H), 1.36 (s, 9H).

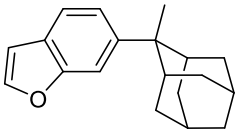
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 148.41, 127.63, 126.19, 121.29, 119.43, 108.06, 107.76, 35.10, 31.74.

EI-HRMS: calculated for $C_{12}H_{13}O_1Br_1^+$ ([M]$^+$): 252.014440, found: 252.014680.

2-iodo-6-(2-methyladamantan-2-yl)benzofuran (347)



6-(2-methyladamantan-2-yl)benzofuran (216)



A flame-dried 100 mL Schlenk flask under argon was charged with 6-bromobenzofuran (2.48 g, 12.6 mmol, 1.00 eq.) and THF (50 mL). The mixture was cooled to –78 °C, *n*BuLi (2.40 M in *n*-hexane, 5.50 mL, 13.2 mmol, 1.05 eq.) was added slowly, and the reaction was stirred for 2 h at –78 °C (formation of a white precipitate was observed). 2-adamantanone (2.08 g, 13.9 mmol, 1.10 eq.) was added in one portion, and the reaction was allowed to slowly warm to RT over night. The solvent was removed under reduced pressure and a white powder was obtained that was further dried on high vacuum for 30 min. The solid was redissolved in DCM (60 mL) and cooled to –40 °C. $TiCl_4$ (5.5 mL, 50 mmol, 4.0 eq.) and Me_2Zn (5.92 M in DCM, 8.5 mL, 50 mmol, 4.0 eq.) were added simultaneously and the reaction was stirred at –40 °C for 1h, and at –10 °C for another 2 h. The mixture was poured onto ice water and the aqueous layer was extracted with DCM (3x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (100% pentane) to give the product as a colorless oil (907 mg, 3.40 mmol, 27%).

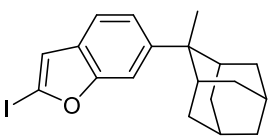
$\boldsymbol{R_F}$ (pentane) = 0.51.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 7.60 (d, J = 2.2 Hz, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.51–7.50 (m, 1H), 7.28 (dd, J = 8.3, 1.7 Hz, 1H), 6.74 (dd, J = 2.3, 1.0 Hz, 1H), 2.40 (t, J = 3.2 Hz, 2H), 2.29 (dd, J = 12.8, 3.2 Hz, 2H), 1.97–1.87 (m, 3H), 1.80 (dtt, J = 12.0, 2.7, 1.6 Hz, 2H), 1.76–1.66 (m, 3H), 1.63–1.55 (m, 2H), 1.26 (s, 3H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 156.26, 148.47, 145.05, 124.72, 121.00, 120.89, 108.86, 106.59, 44.09, 39.18, 35.18, 34.40, 33.52, 30.99, 28.53, 28.20.

EI-HRMS: calculated for $C_{19}H_{22}O_1^+$ ([M]$^+$): 266.166515, found: 266.166970.

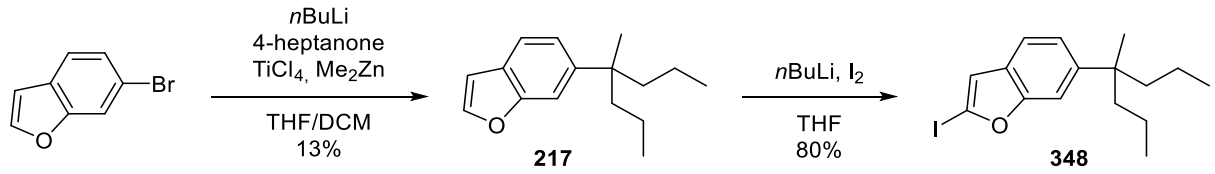
2-iodo-6-(2-methyladamantan-2-yl)benzofuran (347)



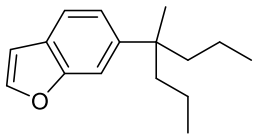
A flame-dried 50 mL Schlenk flask under argon was charged with 6-(2-methyladamantan-2-yl)benzofuran (**216**, 868 mg, 3.26 mmol, 1.00 eq.) and THF (10 mL). The mixture was cooled to –78 °C and *n*BuLi (2.50 M in *n*-hexane, 1.70 mL, 4.25 mmol, 1.30 eq.) was added slowly. The reaction was warmed to 0 °C, stirred for 2 h, and cooled to –78 °C again. Iodine (1.34 g,

5.28 mmol, 1.62 eq.) was dissolved in THF (2 mL) and slowly added to the reaction mixture, which was allowed to slowly warm to RT over night. The reaction was quenched by addition of H_2O (100 mL) and the aqueous layer was extracted with MTBE (3x). The combined organic phases were washed with saturated aqueous Na_2SO_3 and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (100% pentane) to yield the product as a white foam (1.15 g, 2.93 mmol, 90%).
$\boldsymbol{R_F}$ (pentane) = 0.56.
^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.48–7.46 (m, 1H), 7.43 (d, J = 8.2 Hz, 1H), 7.23 (dd, J = 8.3, 1.6 Hz, 1H), 6.90 (d, J = 0.9 Hz, 1H), 2.36 (d, J = 4.0 Hz, 2H), 2.26 (dd, J = 13.1, 3.3 Hz, 2H), 1.93 (s, 1H), 1.87 (d, J = 12.7 Hz, 2H), 1.82–1.74 (m, 2H), 1.70 (s, 3H), 1.57 (dd, J = 12.4, 2.9 Hz, 2H), 1.25 (s, 3H).
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 159.24, 148.23, 126.36, 120.89, 119.32, 117.05, 108.16, 94.85, 43.82, 38.88, 34.82, 34.08, 33.27, 30.89, 28.05, 27.71.
EI-HRMS: calculated for $C_{19}H_{21}O_1I_1^+$ ([M]$^+$): 392.063162, found: 392.063900.

2-iodo-6-(4-methylheptan-4-yl)benzofuran (348)



6-(4-methylheptan-4-yl)benzofuran (217)



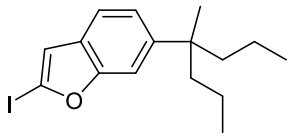
A flame-dried 50 mL Schlenk flask under argon was charged with 6-bromobenzofuran (514 mg, 2.61 mmol, 1.00 eq.) and THF (10 mL). The mixture was cooled to –78 °C, *n*BuLi (2.88 M in *n*-hexane, 1.00 mL, 2.88 mmol, 1.10 eq.) was added slowly, and the reaction was stirred for 2 h at –78 °C (formation of a white precipitate was observed). Freshly distilled 4-heptanone (0.74 mL, 5.25 mmol, 2.01 eq.) was added and the reaction was allowed to slowly warm to RT over night. The solvent was removed under reduced pressure, the residue was redissolved in DCM (10 mL) and cooled to –40 °C. $TiCl_4$ (2.3 mL, 21 mmol, 8.0 eq.) and Me_2Zn (6.20 M in DCM, 3.4 mL, 21 mmol, 8.1 eq.) were added simultaneously and the reaction was allowed to slowly reach RT over the 3 h. The mixture was poured onto ice water and the aqueous layer was extracted with DCM (3x). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (100% pentane) to give the product as a colorless oil (77.7 mg, 0.34 mmol, 13%).
$\boldsymbol{R_F}$ (pentane) = 0.61.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.60 (d, J = 2.2 Hz, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.48–7.44 (m, 1H), 7.24 (dd, J = 8.2, 1.6 Hz, 1H), 6.74 (dd, J = 2.2, 1.0 Hz, 1H), 1.74 (td, J = 13.0, 4.3 Hz, 2H), 1.58 (ddd, J = 13.6, 12.2, 4.6 Hz, 2H), 1.36 (s, 3H), 1.27–1.15 (m, 2H), 1.07–0.95 (m, 2H), 0.85 (t, J = 7.3 Hz, 7H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 155.64, 145.62, 144.62, 124.61, 121.54, 120.34, 109.49, 106.37, 46.42, 41.36, 24.44, 17.61, 14.97.

EI-HRMS: calculated for $C_{16}H_{23}O_1^+$ ($[M+H]^+$): 231.174340, found: 231.174520.

2-iodo-6-(4-methylheptan-4-yl)benzofuran (348)



A flame-dried 20 mL Schlenk flask under argon was charged with 6-(4-methylheptan-4-yl)benzofuran (**217**, 77 mg, 0.33 mmol, 1.00 eq.) and THF (3 mL). The mixture was cooled to –78 °C and *n*BuLi (2.50 M in *n*-hexane, 0.20 mL, 0.50 mmol, 1.5 eq.) was added slowly. The reaction was warmed to 0 °C, stirred for 15 min, and cooled to –78 °C again. Iodine (170 mg, 0.67 mmol, 2.0 eq.) was dissolved in THF (0.5 mL) and slowly added to the reaction mixture, which was allowed to slowly warm to RT over 2 h. The reaction was quenched by addition of H_2O (50 mL) and the aqueous layer was extracted with MTBE (3x). The combined organic phases were washed with saturated aqueous Na_2SO_3 and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (100% pentane) to yield the product as a colorless oil (100 mg, 0.28 mmol, 80%).

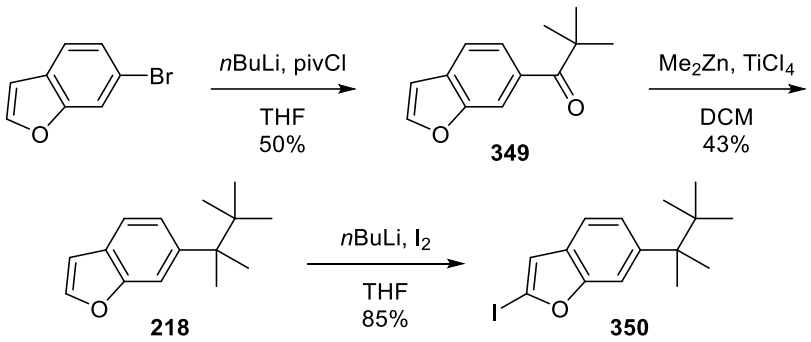
$\boldsymbol{R}_{\mathbf{F}}$ (pentane) = 0.69.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.41 (d, J = 8.3 Hz, 1H), 7.39–7.38 (m, 1H), 7.16 (dd, J = 8.2, 1.6 Hz, 1H), 6.89 (d, J = 0.9 Hz, 1H), 1.68 (td, J = 13.0, 4.3 Hz, 2H), 1.56–1.48 (m, 4H), 1.31 (s, 3H), 1.23–1.09 (m, 2H), 1.00–0.86 (m, 2H), 0.80 (t, J = 7.3 Hz, 6H).

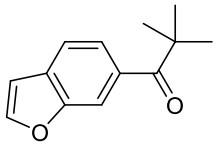
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 158.90, 145.73, 126.52, 121.87, 118.88, 117.04, 108.95, 94.86, 46.38, 41.37, 24.34, 17.58, 14.93.

EI-HRMS: calculated for $C_{16}H_{21}O_1I_1^+$ ($[M]^+$): 356.063162, found: 356.063120.

2-iodo-6-(2,3,3-trimethylbutan-2-yl)benzofuran (350)



1-(benzofuran-6-yl)-2,2-dimethylpropan-1-one (349)



A flame-dried 20 mL Schlenk flask under argon was charged with 6-bromobenzofuran (385 mg, 1.96 mmol, 1.00 eq.) and THF (8 mL). The mixture was cooled to –78 °C, *n*BuLi (2.80 M in *n*-hexane, 0.77 mL, 2.16 mmol, 1.10 eq.) was added slowly, and the reaction was stirred for 1 h at –78 °C (formation of a white precipitate was observed). Pivaloyl chloride (0.50 mL, 4.06 mmol, 2.08 eq.) was added and the reaction was allowed to reach RT over 90 min. The reaction was quenched by addition of HCl (1.2 M, 50 mL) and the aqueous layer was extracted with MTBE (3x). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (hex/EtOAc 97:3) and another silica gel flash column chromatography (hex/acetone 97:3) to give the product as a colorless oil (199 mg, 0.99 mmol, 50%).

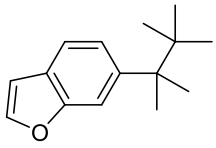
$\boldsymbol{R_F}$ (hex/EtOAc 9:1) = 0.47.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.95 (dt, J = 1.6, 0.8 Hz, 1H), 7.73 (d, J = 2.2 Hz, 1H), 7.69 (dd, J = 8.2, 1.5 Hz, 1H), 7.61 (d, J = 8.2 Hz, 1H), 6.80 (dd, J = 2.2, 1.0 Hz, 1H), 1.41 (s, 9H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 208.15, 154.35, 147.55, 134.44, 130.10, 123.37, 120.74, 111.92, 106.77, 44.39, 28.50.

EI-HRMS: calculated for $C_{13}H_{14}O_2^+$ ($[M]^+$): 202.098830, found: 202.098870.

6-(2,3,3-trimethylbutan-2-yl)benzofuran (218)



A flame-dried 20 mL Schlenk flask under argon was charged with DCM (4 mL) and $TiCl_4$ (0.28 mL, 2.6 mmol, 2.6 eq.). The mixture was cooled to –30 °C, Me_2Zn (6.20 M in DCM, 0.41 mL, 2.5 mmol, 2.6 eq.) was added slowly, and the reaction was stirred for 10 min to give a yellow suspension and subsequently cooled to –78 °C. 1-(benzofuran-6-yl)-2,2-dimethylpropan-1-one (**349**, 198 mg, 0.98 mmol, 1.0 eq.) was dissolved in DCM (2 mL) and added slowly to the reaction. The mixture was allowed to slowly warm to RT over night. The reaction was quenched by pouring onto ice

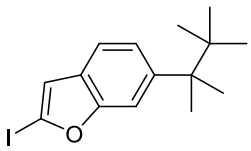
water and the aqueous layer was extracted with DCM (3x). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (100% pentane) to give the product as a colorless oil (86.6 mg, 0.40 mmol, 43%).

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.58 (d, J = 2.2 Hz, 1H), 7.53 (dt, J = 1.6, 0.8 Hz, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.29 (dd, J = 8.3, 1.7 Hz, 1H), 6.72 (dd, J = 2.2, 1.0 Hz, 1H), 1.42 (s, 6H), 0.88 (s, 9H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 155.00, 144.86, 144.83, 129.19, 128.38, 125.45, 124.65, 123.68, 118.99, 111.38, 106.28, 43.32, 36.27, 26.59, 25.01.

EI-HRMS: calculated for $C_{15}H_{20}O_1^+$ ($[M]^+$): 216.150865, found: 216.150520.

2-iodo-6-(2,3,3-trimethylbutan-2-yl)benzofuran (350)



A flame-dried Schlenk flask under argon was charged with 6-(2,3,3-trimethylbutan-2-yl)benzofuran (**218**, 55.2 mg, 0.26 mmol, 1.00 eq.) and THF (2 mL). The mixture was cooled to –78 °C and *n*BuLi (2.5 M in *n*-hexane, 0.13 mL, 0.33 mmol, 1.3 eq.) was added slowly. The reaction was warmed to 0 °C, stirred for 15 min, and cooled to -78 °C again. Iodine (110 mg, 0.43 mmol, 2.0 eq.) was dissolved in THF (0.4 mL) and slowly added to the reaction mixture, which was then warmed to 0 °C and stirred for 2 h. The reaction was quenched by addition of H_2O (50 mL) and the aqueous layer was extracted with MTBE (3x). The combined organic phases were washed with saturated aqueous Na_2SO_3 and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (100% pentane) to yield the product as a slowly solidifying colorless oil (79.9 mg, 0.22 mmol, 85%).

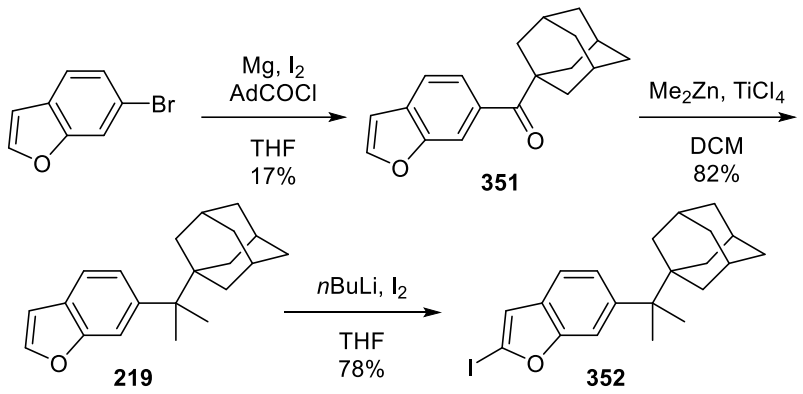
$\boldsymbol{R_F}$ (pentane) = 0.70.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.50 (dd, J = 1.8, 0.9 Hz, 1H), 7.38 (d, J = 8.3 Hz, 1H), 7.26 (dd, J = 8.3, 1.7 Hz, 1H), 6.91 (d, J = 0.9 Hz, 1H), 1.40 (s, 6H), 0.87 (s, 9H).

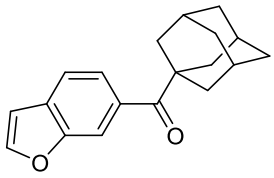
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 158.26, 144.93, 126.56, 123.93, 117.54, 116.96, 110.79, 95.15, 43.30, 36.28, 26.53, 24.92.

EI-HRMS: calculated for $C_{15}H_{19}O_1I_1^+$ ($[M]^+$): 342.047513, found: 342.047400.

2-iodo-6-(2-(adamantan-1-yl)propan-2-yl)-benzofuran (219)



(adamantan-1-yl)(benzofuran-6-yl)methanone (351)



A flame-dried 50 mL three-necked flask equipped with a reflux condenser under argon was charged with Magnesium turnings (93 mg, 3.8 mmol, 1.5 eq.). A small piece of iodine was added and the flask was gently heated with a heat gun while vigorously stirring for 5 min. THF (10 mL) and 6-bromobenzofuran (500 mg, 2.54 mmol, 1.00 eq.) were added and the mixture was heated to reflux for 45 min, after which ^{1}H-NMR-analysis (aliquot quenched with d_4-methanol) revealed full starting material conversion. The mixture was cooled to 0 °C, and 1-adamantanecarboxylic acid chloride (655 mg, 3.30 mmol, 1.30 eq.) was added and the reaction was allowed to slowly warm to RT over night. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (50 mL) and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (hex/EtOAc 49:1) and another silica gel flash column chromatography (hex/MTBE 19:1) to give the product as a colorless oil (120.5 mg, 0.43 mmol, 17%).

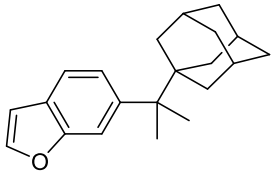
$\boldsymbol{R_F}$ (hex/EtOAc 9:1) = 0.50.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.82 (d, J = 1.3 Hz, 1H), 7.72 (d, J = 2.2 Hz, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.54 (dd, J = 8.1, 1.4 Hz, 1H), 6.80 (dd, J = 2.2, 1.0 Hz, 1H), 2.15–2.03 (m, 9H), 1.82–1.68 (m, 6H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 209.13, 154.25, 147.16, 135.51, 129.48, 122.72, 120.76, 111.17, 106.75, 47.25, 39.56, 36.74, 28.39.

ESI-HRMS: calculated for $C_{19}H_{21}O_2^+$ ($[M+H]^+$): 281.153605, found: 281.153680.

6-(2-(adamantan-1-yl)propan-2-yl)benzofuran (219)



A flame-dried 20 mL Schlenk flask under argon was charged with DCM (5 mL) and $TiCl_4$ (0.20 mL, 1.8 mmol, 4.3 eq.). The mixture was cooled to –30 °C, Me_2Zn (6.20 M in DCM, 0.30 mL, 1.9 mmol, 4.3 eq.) was added slowly, the reaction was stirred for 10 min to give a yellow suspension and subsequently cooled to –78 °C. (adamantan-1-yl)(benzofuran-6-yl)methanone (**351**, 120 mg, 0.43 mmol, 1.0 eq.) was dissolved in DCM (2 mL) and added slowly to the reaction. The mixture was allowed to slowly warm to RT over night. The reaction was quenched by pouring onto ice water and the aqueous layer was extracted with MTBE (3x). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (100% pentane) to give the product as colorless crystalline solid (103.3 mg, 0.43 mmol, 82%).

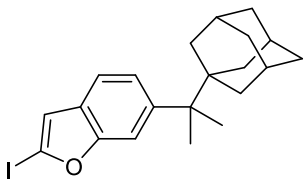
$\boldsymbol{R_F}$ (100% pentane) = 0.59.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.59 (d, J = 2.2 Hz, 1H), 7.49–7.44 (m, 2H), 7.22 (dd, J = 8.3, 1.6 Hz, 1H), 6.73 (dd, J = 2.2, 0.9 Hz, 1H), 1.94–1.88 (m, 3H), 1.63–1.45 (m, 12H), 1.36 (s, 6H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 154.96, 144.76, 144.20, 124.58, 123.98, 118.81, 111.66, 106.32, 43.83, 37.28, 37.14, 37.03, 29.05, 23.71.

ESI-HRMS: calculated for $C_{21}H_{27}O_1$ ($[M+H]^+$): 295.205640, found: 295.205350.

2-iodo-6-(2-(adamantan-1-yl)propan-2-yl)-benzofuran (352)



A flame-dried 20 mL Schlenk flask under argon was charged with 6-(2-(adamantan-1-yl)propan-2-yl)benzofuran (**219**, 103 mg, 0.35 mmol, 1.00 eq.) and THF (3 mL). The mixture was cooled to –78 °C and *n*BuLi (2.5 M in *n*-hexane, 0.20 mL, 0.50 mmol, 1.4 eq.) was added slowly. The reaction was warmed to 0 °C, stirred for 15 min, and cooled to -78 °C again. Iodine (150 mg, 0.59 mmol, 1.7 eq.) was dissolved in THF (0.5 mL) and slowly added to the reaction mixture, which was then warmed to 0 °C and stirred for 2 h while warming to RT. The reaction was quenched by addition of H_2O (50 mL) and the aqueous layer was extracted with MTBE (3x). The combined organic phases were washed with saturated aqueous Na_2SO_3 and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (100% pentane) to yield the product as a white solid (124.1 mg, 0.28 mmol, 78%).

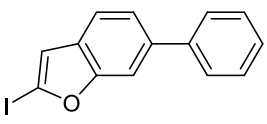
$\boldsymbol{R_F}$ (pentane) = 0.55.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.45–7.41 (m, 1H), 7.37 (d, J = 8.2 Hz, 1H), 7.18 (dd, J = 8.3, 1.7 Hz, 1H), 6.90 (d, J = 0.9 Hz, 1H), 1.93–1.88 (m, 3H), 1.62–1.43 (m, 12H), 1.34 (s, 6H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 158.24, 144.30, 126.50, 124.24, 117.36, 116.99, 111.09, 95.06, 53.57, 43.84, 37.30, 37.11, 37.00, 29.02, 23.62.

ESI-HRMS: calculated for $C_{21}H_{26}I_1O_1^+$ ([M]$^+$): 421.102287, found: 421.101860.

2-iodo-6-phenylbenzofuran (174)



A flame-dried 100 mL Schlenk flask under argon was charged with 6-phenylbenzofuran (979.4 mg, 5.04 mmol, 1.00 eq.) and THF (20 mL). The mixture was cooled to –78 °C and *n*BuLi (2.5 M in *n*-hexane, 2.6 mL, 6.5 mmol, 1.3 eq.) was added slowly. The reaction was warmed to 0 °C, stirred for 15 min, and cooled to -78 °C again. Iodine (1.66 g, 6.54 mmol, 1.30 eq.) was dissolved in THF (4 mL) and slowly added to the reaction mixture, which was then warmed to 0 °C and stirred for 1 h. The reaction was quenched by addition of H_2O (100 mL) and the aqueous layer was extracted with Et_2O (3x). The combined organic phases were washed with saturated aqueous Na_2SO_3 and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (100% pentane) to yield the desired product (1.47 g, 4.28 mmol, 85%).

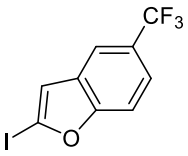
$\boldsymbol{R_F}$ (pentane) = 0.42.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 7.71 (d, J = 1.5 Hz, 1H), 7.68–7.61 (m, 2H), 7.59 (d, J = 8.1 Hz, 1H), 7.50 (dd, J = 8.1, 1.6 Hz, 1H), 7.48–7.43 (m, 2H), 7.40–7.32 (m, 1H), 7.02 (d, J = 1.0 Hz, 1H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 159.24, 141.13, 138.33, 129.28, 128.80, 127.79, 127.67, 123.08, 120.21, 117.63, 109.46, 96.62.

EI-HRMS: calculated for $C_{14}H_9O_1I_1^+$ ([M]$^+$): 319.969262, found: 319.969710.

2-iodo-5-(trifluoromethyl)benzofuran (175)



A flame-dried 100 mL Schlenk flask under argon was charged with 5-(trifluoromethyl)benzofuran (485.6 mg, 2.61 mmol, 1.00 eq.) and THF (10 mL). The mixture was cooled to –78 °C and *n*BuLi (2.8 M in *n*-hexane, 1.20 mL, 3.36 mmol, 1.29 eq.) was added slowly. The reaction was warmed to 0 °C, stirred for 15 min, and cooled to -78 °C again. Iodine (860 mg, 3.4 mmol, 1.3 eq.) was dissolved in THF (4 mL) and slowly added to the reaction mixture, which was warmed to 0 °C and stirred for 2 h. The reaction was quenched by addition of H_2O (100 mL) and the aqueous layer was extracted with Et_2O (3x). The combined organic phases were washed with saturated aqueous Na_2SO_3 and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (100% pentane) to yield the desired product (755 mg, 2.25 mmol, 86%).

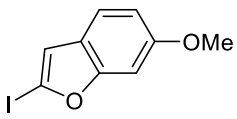
$\boldsymbol{R_F}$ (pentane) = 0.62.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 7.84 (dt, J = 1.8, 0.9 Hz, 1H), 7.59 (dq, J = 8.7, 0.8 Hz, 1H), 7.51 (dd, J = 8.6, 1.9 Hz, 1H), 7.08 (d, J = 0.9 Hz, 1H).

^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -61.34.

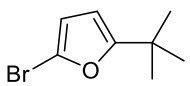
^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 159.85, 129.70, 126.08 (q, *J* = 32.3 Hz), 124.94 (q, *J* = 272.1 Hz), 121.75 (q, *J* = 3.7 Hz), 117.97, 117.81 (q, *J* = 4.1 Hz), 111.66, 98.85.
EI-HRMS: calculated for $C_9H_7O_2I_1^+$ ([M]$^+$): 273.948527, found: 273.948810.

2-iodo-6-methoxybenzofuran (177)



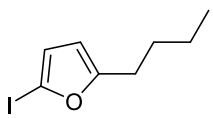
A flame-dried 100 mL Schlenk flask under argon was charged with 6-methoxybenzofuran (1.34 g, 9.02 mmol, 1.00 eq.) and THF (35 mL). The mixture was cooled to –78 °C and *n*BuLi (2.5 M in *n*-hexane, 4.75 mL, 11.9 mmol, 1.32 eq.) was added slowly. The reaction was warmed to 0 °C, stirred for 15 min, and cooled to -78 °C again. Iodine (3.0 g, 12 mmol, 1.3 eq.) was dissolved in THF (7.5 mL) and slowly added to the reaction mixture, which was allowed to slowly warm to RT over night. The reaction was quenched by addition of H_2O (100 mL) and the aqueous layer was extracted with Et_2O (3x). The combined organic phases were washed with saturated aqueous Na_2SO_3 and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (100% pentane) to yield the product as a white solid (1.01 g, 3.42 mmol, 38%).
^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 7.38 (d, J = 8.7 Hz, 1H), 7.04–7.00 (m, 1H), 6.90 (d, J = 0.9 Hz, 1H), 6.84 (dd, J = 8.6, 2.3 Hz, 1H), 3.83 (s, 3H).
^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 159.44, 158.42, 122.95, 120.16, 117.43, 112.51, 95.81, 93.26, 56.09.
EI-HRMS: calculated for $C_9H_7O_2I_1^+$ ([M]$^+$): 273.948527, found: 273.948810.

2-bromo-5-(*tert*-butyl)furan (182)



A 50 mL round bottom flask under air was charged with 2-(*tert*-butyl)furan (500 mg, 4.03 mmol, 1.00 eq.) and $CHCl_3$ (20 mL). *N*-bromosuccinimide (752 mg, 4.23 mmol, 1.05 eq.) was added in one portion and the mixture was stirred at RT for 2.5 h. The reaction was quenched by addition of saturated aqueous Na_2SO_3 (50 mL) and the aqueous layer was extracted with DCM (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (100% pentane) to yield the desired product as a colorless oil (558 mg, 2.75 mmol, 68%).
^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 6.18 (d, J = 3.3 Hz, 1H), 5.96 (d, J = 3.2 Hz, 1H), 1.26 (s, 9H).
^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 166.94, 119.20, 111.79, 105.18, 33.21, 28.98.
EI-HRMS: calculated for $C_8H_{11}O_1Br_1^+$ ([M]$^+$): 201.998790, found: 201.998920.

2-iodo-5-butylfuran (176)



A flame-dried 100 mL Schlenk flask under argon was charged with 2-butylfuran (1.0 g, 8.1 mmol, 1.0 eq.) and THF (32 mL). The mixture was cooled

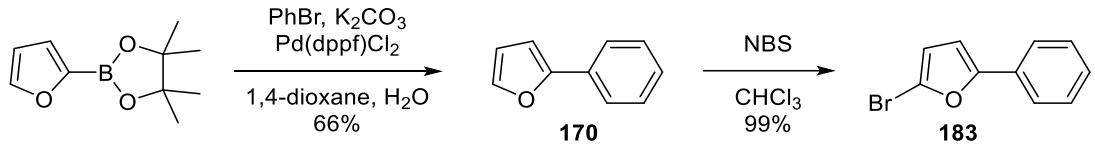
to –78 °C and *n*BuLi (2.5 M in *n*-hexane, 4.2 mL, 10.5 mmol, 1.31 eq.) was added slowly. The reaction was warmed to 0 °C, stirred for 15 min, and cooled to -78 °C again. Iodine (2.74 g, 10.8 mmol, 1.34 eq.) was dissolved in THF (6.5 mL) and slowly added to the reaction mixture, which was warmed to 0 °C and stirred for 2 h. The reaction was quenched by addition of H_2O (100 mL) and the aqueous layer was extracted with Et_2O (3x). The combined organic phases were washed with saturated aqueous Na_2SO_3 and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (100% pentane) to yield the desired product (1.83 g, 7.54 mmol, 91%).

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 6.43 (d, J = 3.2 Hz, 1H), 5.94 (dt, J = 3.3, 1.0 Hz, 1H), 2.68–2.62 (m, 2H), 1.64–1.56 (m, 2H), 1.40–1.32 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H).

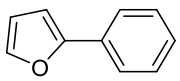
^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 162.93, 121.15, 108.40, 84.43, 30.48, 28.25, 22.55, 13.93.

EI-HRMS: calculated for $C_8H_{11}O_1I_1^+$ ($[M]^+$): 249.984913, found: 249.985150.

2-bromo-5-phenylfuran (183)



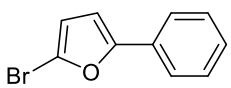
2-phenylfuran (170)



A 500 mL three-necked flask equipped with a reflux condenser under argon was charged with K_2CO_3 (8.8 g, 64 mmol, 3.2 eq.), 1,4-dioxane (150 mL), and H_2O (30 mL) and the mixture was sparged with argon for 30 min. Furan-2-boronic acid pinacol ester (3.88 g, 20 mmol, 1.00 eq.), bromobenzene (3.4 mL, 32 mmol, 1.6 eq.), and $Pd(dppf)Cl_2$ (700 mg, 1.0 mmol, 5 mol%) were added and the reaction was heated to reflux for 16 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous phase was extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered through a plug of silica and florisil®, and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (100% pentane) to yield the desired product as a yellow oil (2.13 g, 13.3 mmol, 66%). The NMR-spectroscopic data was in agreement with the literature.[231]

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.72–7.66 (m, 2H), 7.50–7.46 (m, 1H), 7.39 (dd, J = 8.5, 7.2 Hz, 2H), 7.30–7.23 (m, 1H), 6.66 (dd, J = 3.3, 0.8 Hz, 1H), 6.48 (dd, J = 3.4, 1.8 Hz, 1H).

2-bromo-5-phenylfuran (183)



A 50 mL round bottom flask under air was charged with 2-phenylfuran (**170**, 351 mg, 1.81 mmol, 1.00 eq.) and $CHCl_3$ (9 mL). *N*-bromosuccinimide (338 mg, 1.89 mmol, 1.05 eq.) was added in one portion and the mixture was stirred at RT for 5 h. The reaction was quenched by addition of H_2O (50 mL) and the aqueous layer was extracted

with DCM (3x). The combined organic layers were washed with saturated aqueous Na_2SO_3 and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (100% pentane) to yield the desired product as a colorless oil (400 mg, 1.79 mmol, 99%).

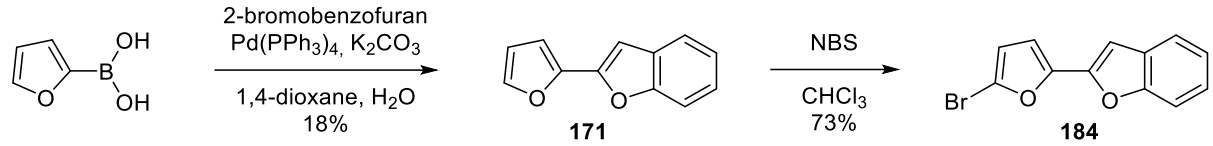
R_F (100% pentane) = 0.67.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 7.67–7.60 (m, 2H), 7.40 (dd, J = 8.5, 7.1 Hz, 2H), 7.34–7.26 (m, 1H), 6.65 (d, J = 3.4 Hz, 1H) 6.43 (d, *J* = 3.4 Hz, 1H).

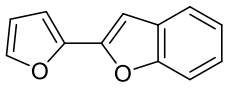
^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 156.35, 130.29, 129.18, 128.21, 123.80, 121.77, 113.87, 107.83.

EI-HRMS: calculated for $C_{10}H_7O_1Br_1^+$ ($[M]^+$): 221.967490, found: 221.967850.

2-(5-bromofuran-2-yl)benzofuran (184)



2-(furan-2-yl)benzofuran (171)

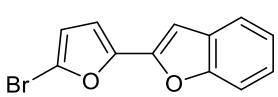


A 70 mL pressure vial was charged with furan-2-ylboronic acid (1.0 g, 8.9 mmol, 1.0 eq.), 2-bromobenzofuran (2.1 g, 11 mmol, 1.2 eq.), K_2CO_3 (2.0 M in H_2O, 13.4 mL, 27 mmol, 3.0 eq.), and 1,4-dioxane (30 mL) and the mixture was sparged with argon for 15 min. $Pd(PPh_3)_4$ (103 mg, 0.09 mmol, 1 mol%) was added, the vial was capped, and the mixture was heated to 120 °C for 16 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous phase was extracted with EtOAc (2x). The combined organic layers were washed with saturated aqueous Na_2CO_3 and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (100% pentane) to yield the product as a white solid (301 mg, 8.93 mmol, 18%). The NMR-spectroscopic data was in agreement with the literature.[232]

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 7.59 (dd, J = 7.7, 1.4 Hz, 1H), 7.55 (d, J = 1.8 Hz, 1H), 7.50 (dd, J = 8.0, 1.0 Hz, 1H), 7.29 (ddd, J = 8.2, 7.2, 1.5 Hz, 1H), 7.24 (td, J = 7.5, 1.1 Hz, 1H), 6.93 (d, J = 0.9 Hz, 1H), 6.82 (d, J = 3.4 Hz, 1H), 6.56 (dd, J = 3.4, 1.8 Hz, 1H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 155.00, 148.53, 146.58, 143.62, 129.14, 124.87, 123.61, 121.43, 112.12, 111.40, 108.09, 101.42.

2-(5-bromofuran-2-yl)benzofuran (184)



A 50 mL round bottom flask under air was charged with 2-(furan-2-yl)benzofuran (**171**, 281 mg, 1.53 mmol, 1.00 eq.) and $CHCl_3$ (7.6 mL). *N*-bromosuccinimide (285 mg, 1.60 mmol, 1.05 eq.) was added in one

portion and the mixture was stirred at RT for 5 h. The reaction was quenched by addition of H_2O (50 mL) and the aqueous layer was extracted with DCM (3x). The combined organic layers were washed with saturated aqueous Na_2SO_3 and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (100% pentane) and automated reversed phase silica gel column chromatography (100% CH_3CN) to yield the product as a white solid (292 mg, 1.11 mmol, 73%).

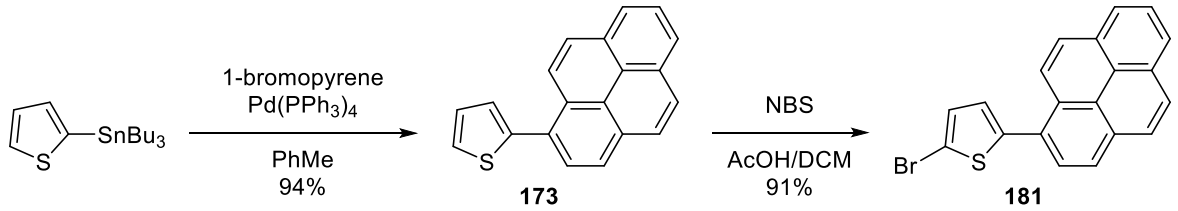
$\boldsymbol{R_F}$ (100% pentane) = 0.55.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 7.60 (ddd, J = 7.6, 1.4, 0.7 Hz, 1H), 7.49 (dq, J = 8.2, 0.9 Hz, 1H), 7.31 (ddd, J = 8.2, 7.3, 1.4 Hz, 1H), 7.25 (td, J = 7.5, 1.1 Hz, 1H), 6.95 (d, J = 1.0 Hz, 1H), 6.77 (d, J = 3.5 Hz, 1H), 6.49 (d, J = 3.5 Hz, 1H).

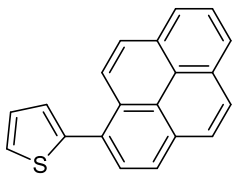
^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 154.99, 148.41, 147.28, 128.93, 125.20, 123.75, 123.28, 121.59, 114.02, 111.44, 110.29, 102.00.

EI-HRMS: calculated for $C_{12}H_7O_2Br_1^+$ ($[M]^+$): 261.962405, found: 261.962900.

2-bromo-5-(pyren-1-yl)thiophene (181)



2-(pyren-1-yl)thiophene (173)



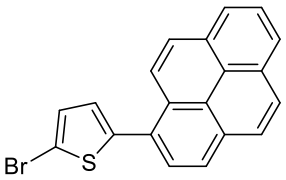
A flame-dried 100 mL Young Schlenk under argon was charged with degassed toluene (18 mL), 2-(tributylstannyl)thiophene (1.5 mL, 4.7 mmol, 1.3 eq.), 2-bromopyrene (1.0 g, 3.6 mmol, 1.0 eq.), and $Pd(PPh_3)_4$ (205 mg, 0.18 mmol, 5 mol%). The flask was closed and the mixture was heated to 115 °C for 23 h. After cooling to RT, the reaction was quenched by addition of NaOH (1 M, 50 mL) and the aqueous phase was extracted with DCM (3x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (100% hex) to yield the product as a yellow solid (952 mg, 3.36 mmol, 94%). The NMR-spectroscopic data was in agreement with the literature.[233]

$\boldsymbol{R_F}$ (100% pentane) = 0.26.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 8.50 (d, J = 9.2 Hz, 1H), 8.23–8.17 (m, 3H), 8.14–8.06 (m, 4H), 8.03 (t, J = 7.6 Hz, 1H), 7.52 (dd, J = 5.2, 1.2 Hz, 1H), 7.39 (dd, J = 3.5, 1.2 Hz, 1H), 7.27 (dd, J = 5.2, 3.5 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 142.66, 131.62, 131.16, 131.11, 129.96, 129.28, 128.62, 128.09, 128.06, 127.93, 127.62, 127.51, 126.35, 126.29, 125.48, 125.19, 125.18, 125.16, 124.93, 124.71.

2-bromo-5-(pyren-1-yl)thiophene (181)



A 25 mL round bottom flask under air was charged with 2-(pyren-1-yl)thiophene (**173**, 924 mg, 3.25 mmol, 1.00 eq.), DCM (5 mL), and glacial acetic acid (5 mL). *N*-bromosuccinimide (580 mg, 3.26 mmol, 1.00 eq.) was added in one portion, the flask was wrapped in aluminum foil, and the mixture was stirred at RT for 3 h. The reaction was quenched by addition of NaOH (1 M, 50 mL) and the aqueous layer was extracted with Et_2O (3x). The combined organic layers were washed with NaOH (1 M, 2x), H_2O, and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (100% hex) to yield the product as a yellow solid (1.08 g, 2.96 mmol, 91%).

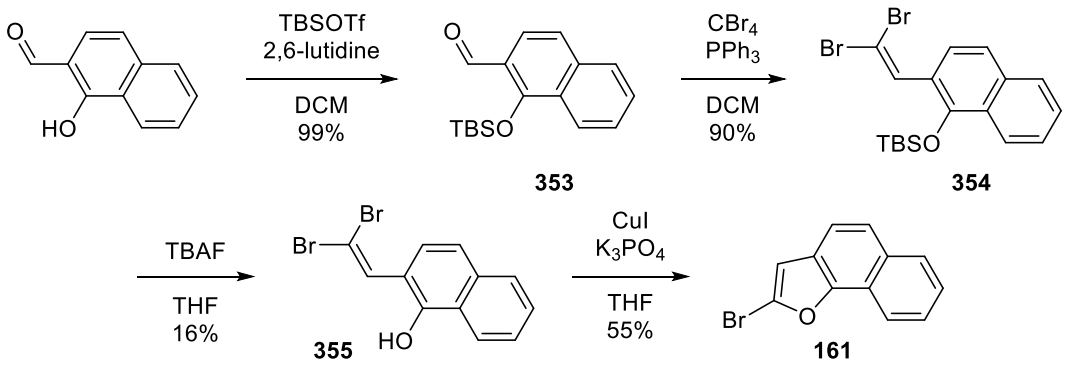
$\boldsymbol{R_F}$ (100% hex) = 0.34.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 8.45 (d, J = 9.2 Hz, 1H), 8.24–8.17 (m, 2H), 8.17 (d, J = 7.9 Hz, 1H), 8.14–8.00 (m, 5H), 7.21 (d, J = 3.7 Hz, 1H), 7.12 (d, J = 3.8 Hz, 1H).

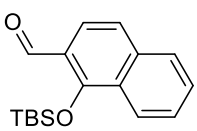
^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 144.30, 131.55, 131.46, 131.01, 130.49, 129.25, 128.82, 128.36, 128.33, 128.21, 127.42, 126.39, 125.69, 125.39, 125.12, 124.82, 124.71, 124.70, 112.67. Other peaks could not be observed.

EI-HRMS: calculated for $C_{20}H_{11}Br_1S_1^+$ ($[M]^+$): 361.976498, found: 361.977127.

2-bromonaphtho[1,2-*b*]furan (161)



1-((*tert*-butyldimethylsilyl)oxy)-2-naphthaldehyde (353)



A flame-dried 100 mL Schlenk flask under argon was charged with 1-hydroxy-2-naphthaldehyde (1.13 g, 6.54 mmol, 1.00 eq.), DCM (13 mL), and 2,6-lutidine (2.3 mL, 20 mmol, 3.0 eq.). The mixture was cooled to 0 °C, TBSOTf (2.25 mL, 9.80 mmol, 1.50 eq.) was added slowly, and the mixture was allowed to slowly warm to RT over night. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ and extracted with DCM (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/EtOAc 100:0 to 99:1) gave the desired product as a yellow oil (1.8 g, 6.4 mmol, 99%).

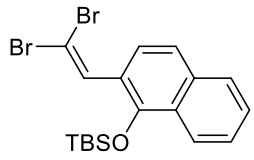
$\boldsymbol{R_F}$ (hex/EtOAc 9:1) = 0.57.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 10.51 (d, J = 0.9 Hz, 1H), 8.20 (dd, J = 8.5, 1.1 Hz, 1H), 7.83 (t, J = 8.7 Hz, 2H), 7.61 (ddd, J = 8.1, 6.8, 1.3 Hz, 1H), 7.52 (td, J = 8.6, 1.7 Hz, 2H), 1.17 (s, 9H), 0.18 (s, 6H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 189.86, 157.86, 138.22, 129.42, 128.41, 128.20, 126.03, 124.23, 123.19, 122.85, 122.43, 26.03, 18.83, -3.75.

CI-HRMS: calculated for $C_{17}H_{23}O_2Si_1^+$ ($[M+H]^+$): 287.146184, found: 287.146160.

tert-butyl((2-(2,2-dibromovinyl)naphthalen-1-yl)oxy)dimethylsilane (354)



A flame-dried 100 mL Schlenk under argon was charged with 1-((*tert*-butyldimethylsilyl)oxy)-2-naphthaldehyde (**353**, 1.83 g, 6.37 mmol, 1.00 eq.) and DCM (30 mL) and cooled to 0 °C. Triphenylphosphine (5.0 g, 19 mmol, 3.0 eq.) and tetrabromomethane (3.2 g, 9.6 mmol, 1.5 eq.) were added simultaneously and the mixture was allowed to slowly warm to RT over night. The reaction was quenched by addition of saturated aqueous Na_2SO_3 and the aqueous layer was extracted with DCM (3x). The combined organic phases were washed with saturated aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/EtOAc 100:0 to 99.5:0.5) yielded the product as a colorless oil (2.52 g, 5.71 mmol, 90%).

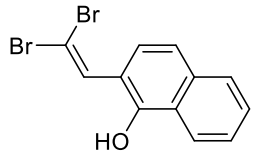
$\boldsymbol{R_F}$ (hex/EtOAc 19:1) = 0.77.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 8.12–8.07 (m, 1H), 7.78 (dd, J = 7.7, 1.6 Hz, 1H), 7.75 (d, J = 8.6 Hz, 1H), 7.69 (s, 1H), 7.52–7.42 (m, 3H), 1.14 (s, 9H), 0.20 (s, 6H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 149.42, 135.30, 134.96, 128.03, 127.89, 126.90, 125.99, 125.56, 123.37, 122.17, 121.44, 90.55, 26.21, 18.86, -3.38.

EI-HRMS: calculated for $C_{18}H_{22}O_1Si_1Br_2^+$ ($[M]^+$): 439.980144, found: 439.979820.

2-(2,2-dibromovinyl)naphthalen-1-ol (355)



A flame-dried Schlenk under argon was charged with *tert*-butyl((2-(2,2-dibromovinyl)naphthalen-1-yl)oxy)dimethylsilane (**354**, 2.47 g, 5.59 mmol, 1.00 eq.) and THF (30 mL) and cooled to 0 °C. TBAF (1.0 M in THF, 8.5 mL, 8.5 mmol, 1.5 eq.) was added and the mixture was allowed to slowly warm to RT over night. The reaction was quenched by addition of H_2O (50 mL) and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/EtOAc 19:1) yielded the product as a yellow oil (290 mg, 0.885 mmol, 16%).

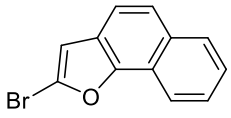
$\boldsymbol{R_F}$ (hex/EtOAc 9:1) = 0.39.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 8.22–8.17 (m, 1H), 7.82–7.77 (m, 1H), 7.66 (s, 1H), 7.55–7.49 (m, 2H), 7.42 (q, J = 8.6 Hz, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 148.18, 134.63, 133.07, 127.92, 127.24, 126.00, 125.64, 124.45, 121.93, 120.58, 116.68, 94.45.

EI-HRMS: calculated for $C_{12}H_8O_1Br_2^+$ ([M]$^+$): 325.893665, found: 325.893680.

2-bromonaphtho[1,2-*b*]furan (161)



An oven-dried 20 mL microwave vial under argon was charged with K_3PO_4 (347 mg, 1.63 mmol, 2.0 eq.), CuI (7.8 mg, 0.041 mmol, 5 mol%), 2-(2,2-dibromovinyl)naphthalen-1-ol (**355**, 268 mg, 0.82 mmol, 1.00 eq.) and THF (5 mL). The flask was capped, covered in aluminum foil, and heated to 80 °C for 15 h. After cooling to RT, the mixture was filtered over silica gel (eluted with Et_2O), and concentrated under reduced pressure. Purification by silica gel flash column chromatography (100% hex) yielded the product as a white solid (110.5 mg, 0.45 mmol, 55%).

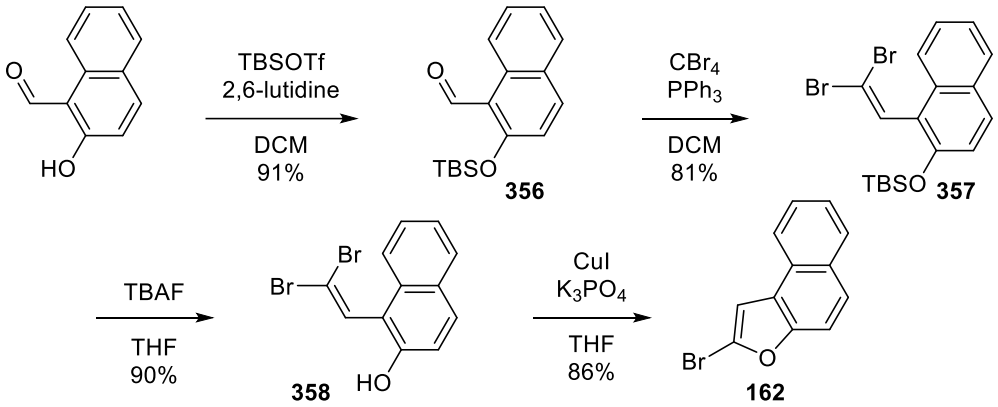
$\boldsymbol{R_F}$ (100% hex) = 0.56.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 8.05 (dd, J = 8.3, 1.1 Hz, 1H), 7.94 (dd, J = 8.1, 1.1 Hz, 1H), 7.70 (d, J = 8.9 Hz, 1H), 7.61 (dd, J = 9.0, 0.9 Hz, 1H), 7.59 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 7.51 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 7.21 (d, J = 0.9 Hz, 1H).

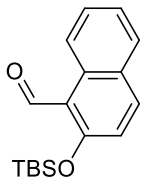
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 153.60, 130.51, 128.90, 126.81, 126.74, 126.46, 125.27, 125.09, 124.34, 123.46, 111.89, 107.63.

EI-HRMS: calculated for $C_{12}H_7O_1Br_1^+$ ([M]$^+$): 245.967490, found: 245.967890.

2-bromonaphtho[2,1-*b*]furan (162)



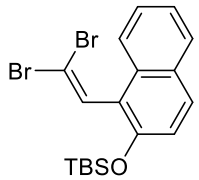
2-((*tert*-butyldimethylsilyl)oxy)-1-naphthaldehyde (356)



A flame-dried 100 mL Schlenk flask under argon was charged with 2-hydroxy-1-naphthaldehyde (2.6 g, 15 mmol, 1.00 eq.), DCM (30 mL), and 2,6-lutidine (5.5 mL, 47 mmol, 3.1 eq.). The mixture was cooled to 0 °C, TBSOTf (5.25 mL, 22.9 mmol, 1.52 eq.) was added slowly, and the mixture was allowed to slowly warm to RT over night. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ and extracted with DCM (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, and

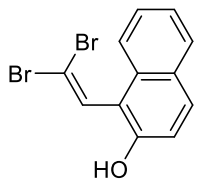
concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/EtOAc 100:0 to 99.4:0.6) gave the desired product as a yellow oil (3.9 g, 13.6 mmol, 91%).
R_F (hex/EtOAc 9:1) = 0.59.
^{1}H-NMR (501 MHz, $CDCl_3$): δ = 10.87 (s, 1H), 9.28 (dq, J = 8.5, 0.8 Hz, 1H), 7.96 (d, J = 8.9 Hz, 1H), 7.76 (dt, J = 8.2, 0.9 Hz, 1H), 7.62 (ddd, J = 8.5, 6.8, 1.4 Hz, 1H), 7.43 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 7.06 (d, J = 9.0 Hz, 1H), 1.06 (s, 9H), 0.33 (s, 6H).
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 192.55, 161.72, 137.28, 131.92, 129.74, 129.20, 128.30, 125.14, 125.12, 120.83, 119.31, 25.86, 18.61, -3.89.
CI-HRMS: calculated for $C_{17}H_{23}O_2Si_1^+$ ($[M+H]^+$): 287.146184, found: 287.146060.

***tert*-butyl((1-(2,2-dibromovinyl)naphthalen-2-yl)oxy)dimethylsilane (357)**



A flame-dried 100 mL Schlenk under argon was charged with 2-((*tert*-butyldimethylsilyl)oxy)-1-naphthaldehyde (**356**, 3.95 g, 13.8 mmol, 1.00 eq.) and DCM (70 mL) and cooled to 0 °C. Triphenylphosphine (10.9 g, 41.6 mmol, 3.01 eq.) and tetrabromomethane (6.9 g, 20.7 mmol, 1.50 eq.) were added simultaneously and the mixture was allowed to slowly warm to RT over night. The reaction was quenched by addition of saturated aqueous Na_2SO_3 and the aqueous layer was extracted with DCM (3x). The combined organic phases were washed with saturated aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (hex/EtOAc 100:0 to 99.5:0.5) yielded the product as a white solid (4.95 g, 11.2 mmol, 81%).
R_F (hex/EtOAc 19:1) = 0.72.
^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.82–7.74 (m, 3H), 7.62 (s, 1H), 7.50 (ddd, J = 8.3, 6.8, 1.3 Hz, 1H), 7.37 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H), 7.08 (d, J = 8.8 Hz, 1H), 1.07 (s, 10H), 0.25 (s, 6H).
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 150.54, 134.19, 131.66, 130.10, 129.29, 128.36, 126.85, 124.64, 124.14, 121.92, 121.05, 94.52, 25.86, 18.34, -3.93.
EI-HRMS: calculated for $C_{18}H_{22}O_1Si_1Br_2^+$ ($[M]^+$): 439.980144, found: 439.979900.

1-(2,2-dibromovinyl)naphthalen-2-ol (358)



A flame-dried Schlenk under argon was charged with *tert*-butyl((1-(2,2-dibromovinyl)naphthalen-2-yl)oxy)dimethylsilane (**357**, 4.93 g, 11.2 mmol, 1.00 eq.) and THF (50 mL) and cooled to 0 °C. TBAF (1.0 M in THF, 17 mL, 17 mmol, 1.5 eq.) was added and the mixture was allowed to slowly warm to RT over night. The reaction was quenched by addition of H_2O (100 mL) and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (pentane/Et_2O 19:1 to 9:1) yielded the product as a brown solid (3.3 g, 10.0 mmol, 90%).

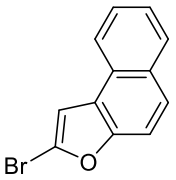
R_F (hex/EtOAc 9:1) = 0.23.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.80 (dd, J = 8.5, 1.8 Hz, 2H), 7.70 (dt, J = 8.4, 1.0 Hz, 1H), 7.67 (s, 1H), 7.51 (ddd, J = 8.2, 6.8, 1.3 Hz, 1H), 7.38 (ddd, J = 8.0, 6.9, 1.2 Hz, 1H), 7.18 (d, J = 8.9 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 150.04, 132.33, 131.58, 130.92, 128.95, 128.54, 127.29, 124.10, 123.71, 117.98, 115.63, 97.16.

EI-HRMS: calculated for $C_{12}H_8O_1Br_2^+$ ($[M]^+$): 325.893666, found: 325.894120.

2-bromonaphtho[2,1-*b*]furan (162)



An oven-dried 20 mL microwave vial under argon was charged with K_3PO_4 (1.5 g, 7.1 mmol, 2.0 eq.), CuI (33 mg, 0.17 mmol, 5 mol%), 1-(2,2-dibromovinyl)naphthalen-2-ol (**358**, 1.02 g, 3.5 mmol, 1.00 eq.) and THF (15 mL). The flask was capped, covered in aluminum foil, and heated to 80 °C for 15 h. After cooling to RT, the mixture was filtered over silica gel (eluted with Et_2O), and concentrated under reduced pressure. Purification by silica gel flash column chromatography (100% hex) yielded the product as a colorless oil (743 mg, 3.01 mmol, 86%).

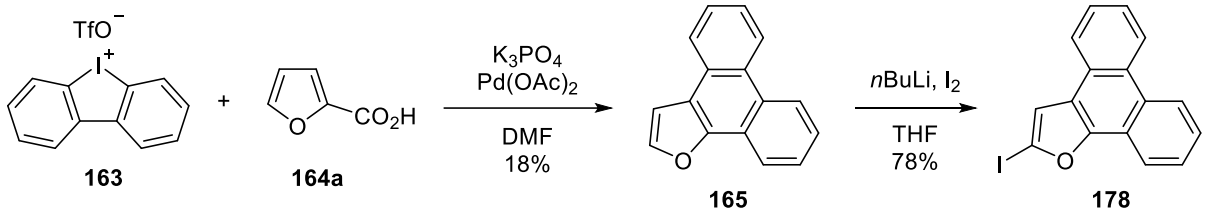
R_F (100% hex) = 0.49.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 8.27 (dd, J = 8.1, 1.2 Hz, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.63–7.54 (m, 2H), 7.50 (ddd, J = 8.2, 6.8, 1.3 Hz, 1H), 6.85 (s, 1H).

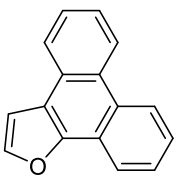
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 151.71, 131.26, 128.48, 126.86, 126.31, 125.52, 124.64, 124.20, 120.90, 119.94, 118.64, 109.53.

EI-HRMS: calculated for $C_{12}H_7O_1Br_1^+$ ($[M]^+$): 245.967490, found: 245.967870.

2-iodophenanthro[9,10-*b*]furan (178)



phenanthro[9,10-b]furan (165)



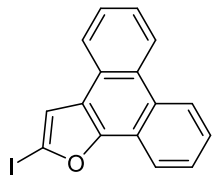
The reaction was conducted according to a literature procedure.[169] A flame-dried 20 mL microwave vial under argon was charged with diphenyleniodonium trifluoromethanesulfonate[234] (**163**, 2.1 g, 4.9 mmol, 1.0 eq.), 2-furancarboxylic acid (**164a**, 1.1 g, 9.8 mmol, 2.0 eq.), K_3PO_4 (2.1 g, 9.8 mmol, 2.0 eq.), $Pd(OAc)_2$ (110 mg, 0.49 mmol, 10 mol%) and DMF (10 mL). The vial was capped and heated to 145 °C for 16 h. After cooling to RT, the mixture was filtered over cotton (eluted with EtOAc), washed with H_2O (2x) and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude

mixture was purified by silica gel flash column chromatography (100% hex) to yield the product as a white solid (190 mg, 0.87 mmol, 18%). The NMR-spectroscopic data was in agreement with the literature.

R_F (100% hex) = 0.23.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 8.72 (d, J = 8.1 Hz, 2H), 8.36 (dd, J = 7.7, 1.6 Hz, 1H), 8.15 (dd, J = 7.6, 1.6 Hz, 1H), 7.82 (d, J = 2.0 Hz, 1H), 7.72–7.60 (m, 4H), 7.28 (d, J = 2.0 Hz, 1H).

2-iodophenanthro[9,10-*b*]furan (178)



A flame-dried 20 mL Schlenk flask under argon was charged with phenanthro[9,10-b]furan (**165**, 138.5 mg, 0.635 mmol, 1.00 eq.) and THF (2.5 mL). The mixture was cooled to –78 °C and *n*BuLi (2.8 M in *n*-hexane, 0.30 mL, 0.84 mmol, 1.32 eq.) was added slowly. The reaction was warmed to 0 °C, stirred for 15 min, and cooled to -78 °C again. Iodine (248 mg, 0.98 mmol, 1.54 eq.) was dissolved in THF (1.0 mL) and slowly added to the reaction mixture, which was warmed to 0 °C and stirred for 2 h. The reaction was quenched by addition of H_2O (100 mL) and the aqueous layer was extracted with MTBE (3x). The combined organic phases were washed with saturated aqueous Na_2SO_3 and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (100% hex) to yield the desired product (183 mg, 0.50 mmol, 78%).

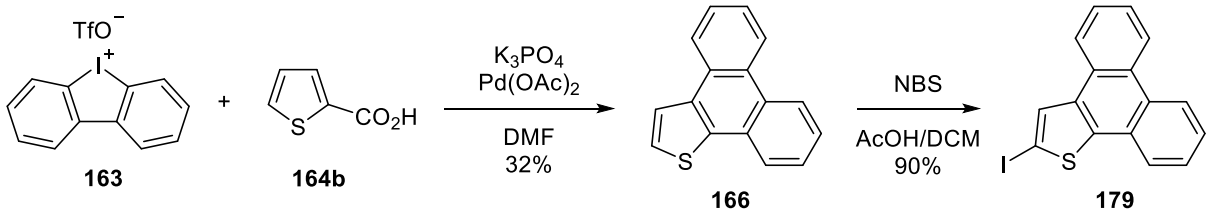
R_F (100% hex) = 0.26.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.73 (d, J = 1.5 Hz, 1H), 8.71 (d, J = 1.5 Hz, 1H), 8.32–8.26 (m, 1H), 8.13–8.06 (m, 1H), 7.73–7.62 (m, 4H), 7.48 (s, 1H).

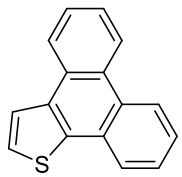
^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 153.70, 129.07, 128.71, 127.72, 127.68, 126.76, 126.47, 126.12, 124.37, 123.98, 123.83, 122.73, 121.95, 120.84, 117.47, 92.24.

EI-HRMS: calculated for $C_{16}H_9O_1I_1^+$ ([M]$^+$): 343.969262, found: 343.969360.

2-bromophenanthro[9,10-*b*]thiophene (179)



phenanthro[9,10-*b*]thiophene (166)



The reaction was conducted according to a literature procedure.[169] A flame-dried 100 mL three-necked flask equipped with a reflux condenser under argon was charged with diphenyleniodonium trifluoromethanesulfonate[234] (**163**, 10.0 g, 23.4 mmol, 1.00 eq.), 2-thiophenecarboxylic acid (**164b**, 6.0 g, 47 mmol, 2.0 eq.),

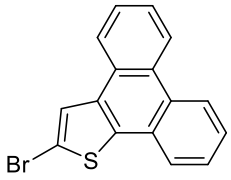
K_3PO_4 (10 g, 47 mmol, 2.0 eq.), $Pd(OAc)_2$ (500 mg, 2.23 mmol, 9.5 mol%) and DMF (47 mL), and the mixture was heated to reflux for 16 h. After cooling to RT, the mixture was filtered over cotton (eluted with EtOAc), washed with H_2O (2x) and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (100% hex) to yield the product as a white solid (1.74 g, 7.41 mmol, 32%). The NMR-spectroscopic data is in agreement with the literature.

$\boldsymbol{R_F}$ (100% hex) = 0.26.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.75–8.69 (m, 2H), 8.38–8.34 (m, 1H), 8.20–8.13 (m, 1H), 8.01 (d, J = 5.3 Hz, 1H), 7.72–7.63 (m, 4H), 7.62 (d, J = 5.3 Hz, 1H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 136.96, 135.47, 129.41, 129.20, 128.97, 128.68, 127.73, 127.61, 126.84, 126.53, 125.54, 124.70, 124.62, 124.05, 123.90, 123.66.

2-bromophenanthro[9,10-*b*]thiophene (179)



A 250 mL round bottom flask under air was charged with phenanthro[9,10-b]thiophene (**166**, 1.73 g, 7.37 mmol, 1.00 eq.), DCM (30 mL), and glacial acetic acid (30 mL). *N*-bromosuccinimide (1.38 g, 7.74 mmol, 1.05 eq.) was added in one portion, the flask was wrapped in aluminum foil, and the mixture was stirred at RT for 16 h. The reaction was quenched by addition of NaOH (1 M, 200 mL) and the aqueous layer was extracted with MTBE (3x). The combined organic layers were washed with NaOH (1 M), saturated aqueous Na_2SO_3, and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (100% hex) to yield the product as a white solid (2.07 g, 6.61 mmol, 90%).

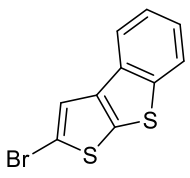
$\boldsymbol{R_F}$ (100% hex) = 0.39.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 8.75–8.65 (m, 2H), 8.25–8.18 (m, 1H), 8.02–7.98 (m, 1H), 7.97 (s, 1H), 7.72–7.60 (m, 4H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 137.74, 135.12, 128.92, 128.46, 127.69, 127.48, 127.36, 127.31, 126.71, 126.49, 126.37, 124.16, 123.92, 123.65, 123.48, 113.31.

EI-HRMS: calculated for $C_{16}H_9S_1Br_1^+$ ($[M]^+$): 311.960298, found: 311.960790.

2-bromobenzo[*b*]thieno[3,2-*d*]thiophene (169)



A flame-dried 500 mL two-necked flask under argon was charged with 2-bromothieno[2,3-b]thiophene (**167**, 3.59 g, 16.4 mmol, 1.00 eq.), DCM (325 mL), and 2,5-dimethoxytetrahydrofuran (**168**, 4.8 mL, 37 mmol, 2.3 eq.) and cooled to 0 °C. Triflic acid (1.5 mL, 17 mmol, 1.0 eq.) was added dropwise, the mixture was stirred at 0 °C for 15 min, and subsequently warmed to RT and stirred for another 2 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (200 mL) and the aqueous layer was extracted with DCM (3x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by silica gel flash

column chromatography (100% hex) to yield the product as a white solid (1.38 g, 5.12 mmol, 31%).

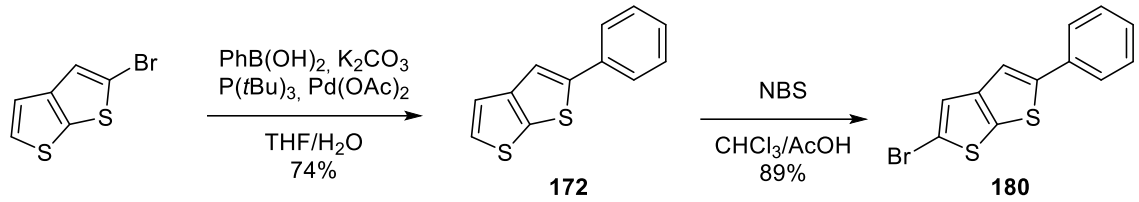
R_F (100% hex) = 0.60.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 7.90 (dt, J = 7.9, 1.0 Hz, 1H), 7.85 (dd, J = 8.1, 1.0 Hz, 1H), 7.61–7.55 (m, 1H), 7.44 (ddd, J = 8.0, 7.2, 1.1 Hz, 1H), 7.38 (ddd, J = 8.4, 7.2, 1.3 Hz, 1H).

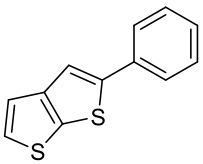
^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 143.19, 141.34, 137.32, 132.49, 125.24, 125.04, 123.53, 122.91, 121.87, 112.91.

APPI-HRMS: calculated for $C_{10}H_5Br_1S_2^+$ ($[M]^+$): 267.901071, found: 267.901040.

2-bromo-5-phenylthieno[2,3-*b*]thiophene (180)



2-phenylthieno[2,3-*b*]thiophene (172)



A 20 mL microwave vial under argon was charged with bromothieno[2,3-b]thiophene (**167**, 500 mL, 2.28 mmol, 1.00 eq.), K_2CO_3 (946 mg, 6.85 mmol, 3.00 eq.), phenylboronic acid (417 mg, 3.42 mmol, 1.50 eq.), and $Pd(OAc)_2$ (51 mg, 0.23 mmol, 10 mol%). THF (8 mL) and H_2O (2 mL) were added and the mixture was sparged with argon for 10 min. P(*t*Bu)$_3$ (1 M in PhMe, 228 µL, 0.228 mmol, 10 mol%) was added quickly, the vial was capped, and the reaction was heated to 80 °C for 3 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous phase was extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (100% hex) to yield the desired product as a white solid (365 mg, 1.69 mmol, 74%).

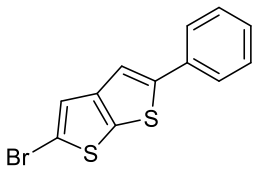
R_F (100% hex) = 0.41.

^{1}H-NMR (600 MHz, CD_2Cl_2): δ = 7.65–7.62 (m, 2H), 7.49 (s, 1H), 7.43–7.39 (m, 2H), 7.38 (d, J = 5.2 Hz, 1H), 7.33–7.30 (m, 1H), 7.25 (d, J = 5.2 Hz, 1H).

^{13}C-NMR (151 MHz, CD_2Cl_2): δ = 147.88, 147.67, 136.85, 135.17, 129.39, 128.33, 128.18, 126.12, 120.53, 116.14.

APPI-HRMS: calculated for $C_{12}H_8S_2^+$ ($[M]^+$): 216.006195, found: 216.006360.

2-bromo-5-phenylthieno[2,3-*b*]thiophene (180)



A 50 mL round bottom flask under air was charged with 2-phenylthieno[2,3-b]thiophene (**172**, 364 mg, 1.68 mmol, 1.00 eq.) and $CHCl_3$ (10 mL). *N*-bromosuccinimide (315 mg, 1.77 mmol, 1.05 eq.) was added, the flask was wrapped in aluminum foil, and the reaction was stirred at RT over night. AcOH (5 mL) was added and the mixture was stirred for another 5 h. stirred at 0 °C for 15 min, and subsequently warmed to RT and stirred for another 2 h. The reaction was quenched by addition of NaOH (1 M, 50 mL) and the aqueous layer was extracted with DCM (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by silica gel flash column chromatography (100% hex) to yield the desired product (443 mg, 1.50 mmol, 89%).

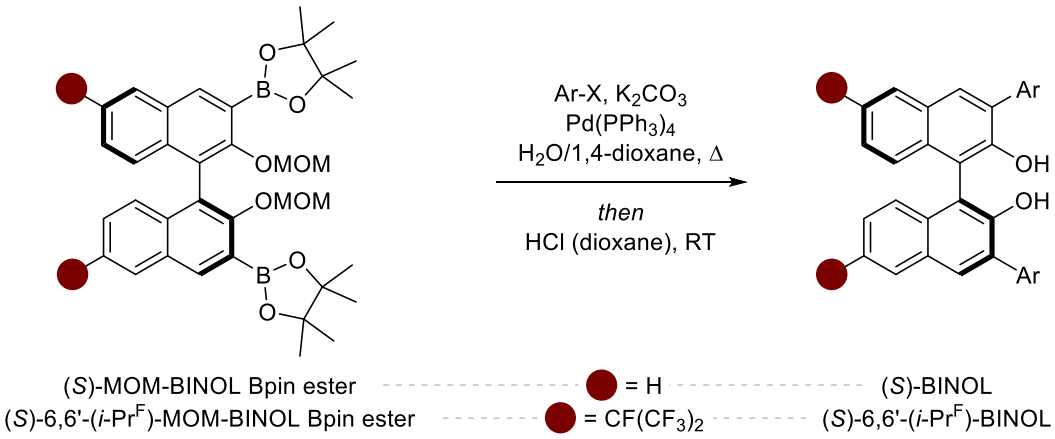
$\boldsymbol{R_F}$ (100% hex) = 0.47.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 7.63–7.59 (m, 2H), 7.44–7.39 (m, 3H), 7.35–7.30 (m, 1H), 7.27 (s, 1H).

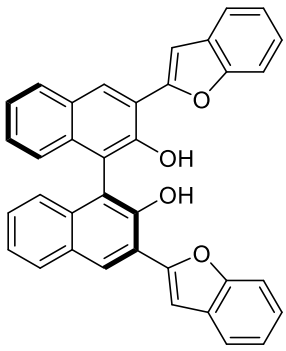
^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 147.33, 146.67, 136.22, 134.64, 129.45, 128.43, 126.19, 123.69, 115.71, 113.32.

APPI-HRMS: calculated for $C_{12}H_7Br_1S_2^+$ ($[M]^+$): 293.916720, found: 293.916720.

7.6.2. Synthesis of (*S*)-BINOLs



(*S*)-3,3'-bis(benzofuran-2-yl)-BINOL (359)



A 100 mL three-necked flask equipped with a reflux condenser was charged with (*S*)-MOM-BINOL Bpin ester (2.24 g, 3.58 mmol, 1.00 eq.) and 2-bromobenzofuran (1.90 g, 9.64 mmol, 2.70 eq.) and argonated (3x). 1,4-dioxane (30 mL) and K_2CO_3 (2.0 M in H_2O, 10 mL, 20 mmol, 5.6 eq.) were added and the solution was sparged with argon for 20 min. Subsequently, $Pd(PPh_3)_4$ (185 mg, 0.160 mmol, 0.045 eq.) was added and the reaction was heated to reflux for 5 h. After cooling to RT, the reaction

was quenched by addition of saturated aqueous NH_4Cl (50 mL) and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (25 mL) in a 100 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 16 mL, 64 mmol, 18 eq.) was added and the reaction was stirred at RT for 16 h, after which full conversion was apparent by TLC (hex/EtOAc 9:1). The mixture was diluted with EtOAc (50 mL) and quenched by addition of HCl (1.2 M, 100 mL). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 19:1 to 9:1) to give the product as an off-white solid (1.85 g, 3.57 mmol, 99%).

$\boldsymbol{R_F}$ (hex/EtOAc 9:1) = 0.28.

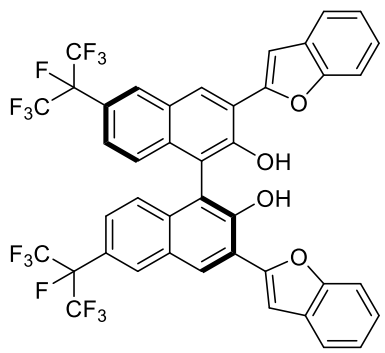
^{1}H-NMR (501 MHz, $CDCl_3$): δ = 8.78 (s, 2H), 8.05 (d, J = 8.1 Hz, 2H), 7.61 (td, J = 7.8, 1.1 Hz, 4H), 7.49 (d, J = 1.0 Hz, 2H), 7.44 (ddd, J = 8.0, 6.7, 1.2 Hz, 2H), 7.34 (dddd, J = 15.2, 8.2, 7.0, 1.3 Hz, 4H), 7.25 (td, J = 7.4, 1.0 Hz, 2H), 7.18 (dd, J = 8.5, 1.1 Hz, 2H), 5.88 (s, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 154.41, 151.78, 149.98, 133.00, 129.69, 129.42, 129.19, 128.51, 128.23, 124.97, 124.22, 123.13, 121.61, 119.53, 111.95, 111.07, 107.86.

ESI-HRMS: calculated for $C_{36}H_{21}O_4^-$ ([M-H]$^-$): 517.144535, found: 517.144550.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +91.9 (*c* = 0.21, $CHCl_3$).

(*S*)-3,3'-bis(benzofuran-2-yl)-6,6'-bis(perfluoropropan-2-yl)-BINOL (360)



A 5 mL microwave vial was charged with (*S*)-6,6'-(*i*-Pr^F)-MOM-BINOL Bpin ester (147 mg, 0.152 mmol, 1.00 eq.), 2-bromobenzofuran (107 mg, 0.543 mmol, 3.57 eq.), 1,4-dioxane (1.5 mL), and K_2CO_3 (2.0 M in H_2O, 0.5 mL, 1.0 mmol, 6.6 eq.), and the solution was sparged with argon for 15 min. $Pd(PPh_3)_4$ (18 mg, 0.015 mmol, 10 mol%) was added lastly, the vial was capped, and the reaction was heated in a microwave to 140 °C for 1 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (1.5 mL) in a 10 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 0.75 mL, 3.0 mmol, 20 eq.) was added and the reaction was stirred at RT for 6 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc

49:1) and another silica gel flash column chromatography (hex/DCM 4:1) to yield the desired product as a white solid (93 mg, 0.11 mmol, 71%).

R_F (hex/EtOAc 9:1) = 0.50.

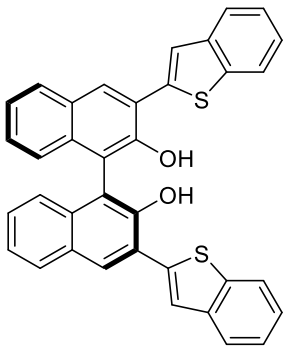
^{1}H-NMR (600 MHz, CD_2Cl_2): δ = 8.89 (t, J = 0.7 Hz, 2H), 8.39–8.36 (m, 2H), 7.66 (ddd, J = 7.7, 1.3, 0.7 Hz, 2H), 7.64–7.62 (m, 2H), 7.58 (d, J = 1.0 Hz, 2H), 7.53–7.48 (m, 2H), 7.39 (ddd, J = 8.4, 7.2, 1.3 Hz, 2H), 7.33–7.26 (m, 4H), 6.32 (d, J = 0.6 Hz, 2H).

^{19}F-NMR (565 MHz, CD_2Cl_2) δ = -73.86 (dq, J = 7.4, 3.9 Hz, 12F), -180.16 (hept, J = 7.5 Hz, 2F).

^{13}C-NMR (151 MHz, CD_2Cl_2): δ = 154.83, 152.09, 151.50, 134.23, 129.61 (d, J = 2.2 Hz), 128.92 (d, J = 2.2 Hz), 127.95 (d, J = 11.7 Hz), 125.77, 125.47 (d, J = 2.2 Hz), 124.06 (d, J = 9.4 Hz), 123.71, 123.29 (d, J = 20.6 Hz), 122.05, 121.27, 121.13 (qd, J = 287.3, 28.1 Hz), 112.22, 111.41, 108.63, 92.10 (dhept, J = 202.0, 32.8 Hz).

ESI-HRMS: calculated for $C_{42}H_{19}F_{14}O_4^-$ ([M-H]$^-$): 853.106534, found: 853.106860.

(*S*)-3,3'-bis(benzothiophen-2-yl)-BINOL (361)



A 20 mL microwave vial was charged with (*S*)-MOM-BINOL Bpin ester (495 mg, 0.790 mmol, 1.00 eq.) and 2-bromobenzothiophene (356 mg, 1.67 mmol, 2.11 eq.). 1,4-dioxane (8 mL) and K_2CO_3 (2.0 M in H_2O, 2.4 mL, 4.8 mmol, 6.1 eq.) were added and the solution was sparged with argon for 10 min. Subsequently, $Pd(PPh_3)_4$ (45 mg, 0.039 mmol, 0.05 eq.) was added and the reaction was heated to 120 °C in a microwave for 1 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (15 mL) in a 50 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 4 mL, 16 mmol, 20 eq.) was added and the reaction was stirred at RT for 16 h, after which full conversion was apparent by TLC (hex/EtOAc 9:1). The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 49:1 to 19:1) and a second column chromatography (hex/DCM 20–40%) to give the product as a white solid (298 mg, 0.541 mmol, 69%).

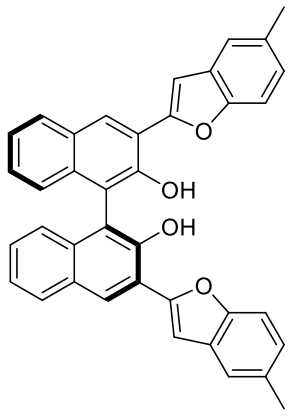
R_F (hex/EtOAc 9:1) = 0.22.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.43 (s, 2H), 8.04–7.98 (m, 4H), 7.95–7.87 (m, 2H), 7.87–7.80 (m, 2H), 7.48–7.41 (m, 2H), 7.41–7.32 (m, 6H), 7.18 (dt, J = 8.6, 1.0 Hz, 2H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 150.56, 140.96, 140.11, 139.65, 133.43, 131.36, 129.84, 129.11, 128.37, 125.24, 125.11, 124.92, 124.77, 124.43, 124.30, 123.85, 122.35, 112.74.

ESI-HRMS: calculated for $C_{36}H_{21}O_2S_2^-$ ([M-H]$^-$): 549.098850, found: 549.098890.

(*S*)-3,3'-bis(5-methylbenzofuran-2-yl)-BINOL (362)



A 5 mL microwave vial was charged with (*S*)-MOM-BINOL Bpin ester (250 mg, 0.399 mmol, 1.00 eq.), 2-bromo-5-methylbenzofuran (**156**, 211 mg, 1.00 mmol, 2.50 eq.) and K_2CO_3 (331 mg, 2.40 mmol, 6.00 eq.) under argon. Degassed 1,4-dioxane (3.5 mL) and H_2O (1.0 mL) were added and lastly $Pd(PPh_3)_4$ (46 mg, 0.040 mmol, 10 mol%). The vial was capped and heated to 140 °C in a microwave for 1 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with Et_2O (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in MeOH (3 mL) in a 25 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 2.0 mL, 8.0 mmol, 20 eq.) was added and the reaction was stirred at RT for 16 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/acetone 49:1 to 19:1) and a second silica gel flash column chromatography (hex/PhMe 2:1). The obtained solid was further purified by trituration (3 mL hex/EtOAc 9:1) to give the product as a white solid (214 mg, 0.39 mmol, 98%).

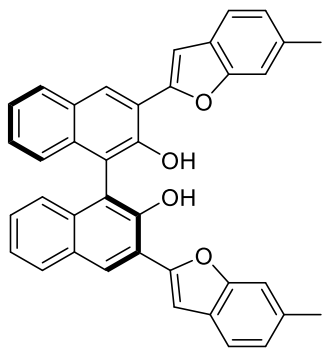
$\boldsymbol{R_F}$ (hex/EtOAc 9:1) = 0.41.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 8.75 (s, 2H), 8.03 (d, J = 8.1 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.46–7.41 (m, 4H), 7.41–7.39 (m, 2H), 7.34–7.30 (m, 2H), 7.19–7.13 (m, 4H), 5.91 (s, 1H), 2.46 (s, 6H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 152.88, 151.92, 149.95, 132.99, 132.57, 129.78, 129.44, 129.15, 128.37, 128.15, 126.28, 124.93, 124.26, 121.41, 119.65, 112.03, 110.56, 107.64, 21.49.

ESI-HRMS: calculated for $C_{38}H_{25}O_4^-$ ([M-H]$^-$): 545.175835, found: 545.176420.

(*S*)-3,3'-bis(6-methylbenzofuran-2-yl)-BINOL (363)



A 5 mL microwave vial was charged with (*S*)-MOM-BINOL Bpin ester (418 mg, 0.67 mmol, 1.00 eq.), 2-bromo-6-methylbenzofuran (**157**, 412.5 mg, 1.67 mmol, 2.50 eq.), 1,4-dioxane (3.0 mL), and K_2CO_3 (2.0 M in H_2O, 2.0 mL, 4.0 mmol, 6.0 eq.), and the solution was sparged with argon for 10 min. $Pd(PPh_3)_4$ (60 mg, 0.052 mmol, 7.8 mol%) was added lastly, the vial was capped, and heated to 120 °C in a microwave for 1.5 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried

over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (5.5 mL) in a 25 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 3.3 mL, 13 mmol, 20 eq.) was added and the reaction was stirred at RT for 16 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/DCM 70:30) to yield the product as a white solid (305 mg, 0.56 mmol, 84%).

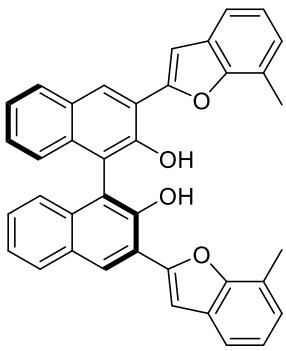
$\boldsymbol{R_F}$ (hex/DCM 2:1) = 0.32.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 8.74 (s, 2H), 8.04 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 7.9 Hz, 2H), 7.47 (d, J = 1.0 Hz, 2H), 7.45–7.40 (m, 4H), 7.32 (ddd, J = 8.2, 6.8, 1.3 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 7.08 (dd, J = 7.7, 1.3 Hz, 2H), 5.89 (s, 2H), 2.53 (s, 6H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 154.88, 151.29, 149.92, 135.37, 132.90, 129.46, 129.12, 128.17, 128.08, 127.18, 124.92, 124.61, 124.26, 121.07, 119.71, 112.00, 111.34, 107.77, 22.02.

ESI-HRMS: calculated for $C_{38}H_{25}O_4^-$ ([M-H]$^-$): 545.175835, found: 545.175860.

(*S*)-3,3'-bis(7-methylbenzofuran-2-yl)-BINOL (364)



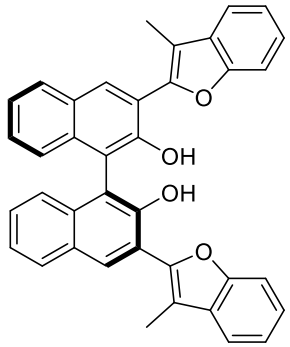
A 5 mL microwave vial was charged with (*S*)-MOM-BINOL Bpin ester (250 mg, 0.399 mmol, 1.00 eq.), 2-bromo-7-methylbenzofuran (**158**, 211 mg, 1.00 mmol, 2.50 eq.) and K_2CO_3 (331 mg, 2.40 mmol, 6.00 eq.) under argon. Degassed 1,4-dioxane (3.5 mL) and H_2O (1.0 mL) were added and lastly $Pd(PPh_3)_4$ (46 mg, 0.040 mmol, 10 mol%). The vial was capped and heated to 140 °C in a microwave for 1 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with Et_2O (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in MeOH (3 mL) in a 25 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 2.0 mL, 8.0 mmol, 20 eq.) was added and the reaction was stirred at RT for 16 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/acetone 49:1 to 19:1) and a second silica gel flash column chromatography (hex/PhMe 9:1 to 2:1). The obtained solid was further purified by trituration (3 mL hex/EtOAc 9:1) to give the product as a white solid (179 mg, 0.33 mmol, 82%).

$\boldsymbol{R_F}$ (hex/EtOAc 9:1) = 0.47.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 8.76 (s, 2H), 8.09–8.01 (m, 2H), 7.50 (s, 2H), 7.48–7.41 (m, 4H), 7.33 (ddd, J = 8.1, 6.7, 1.2 Hz, 2H), 7.21–7.12 (m, 6H), 2.69 (s, 6H).

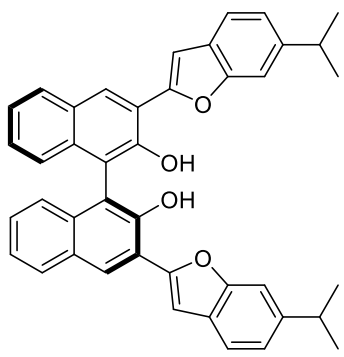
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 153.49, 151.55, 149.98, 133.05, 129.42, 129.14, 129.09, 128.31, 128.15, 125.94, 124.93, 124.30, 123.22, 121.34, 119.69, 119.06, 112.24, 108.07, 15.40.
ESI-HRMS: calculated for $C_{38}H_{25}O_4^-$ ([M-H]$^-$): 545.175835, found: 545.176450.

(*S*)-3,3'-bis(3-methylbenzofuran-2-yl)-BINOL (365)



A 20 mL microwave vial was charged with (*S*)-MOM-BINOL Bpin ester (500 mg, 0.80 mmol, 1.00 eq.), 2-bromo-3-methylbenzofuran (**149**, 425 mg, 2.01 mmol, 2.52 eq.), 1,4-dioxane (8.0 mL), and K_2CO_3 (2.0 M in H_2O, 2.4 mL, 4.8 mmol, 6.0 eq.), and the solution was sparged with argon for 15 min. $Pd(PPh_3)_4$ (92 mg, 0.080 mmol, 10 mol%) was added lastly, the vial was capped, and heated to 120 °C for 16 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (6 mL) in a 25 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 4.0 mL, 16 mmol, 20 eq.) was added and the reaction was stirred at RT for 6 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 19:1) to yield the desired product (435 mg, 0.80 mmol, 99%).
R_F (hex/EtOAc 9:1) = 0.30.
^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.22 (s, 2H), 8.02–7.96 (m, 2H), 7.69–7.61 (m, 2H), 7.54–7.47 (m, 2H), 7.42 (ddd, J = 8.1, 6.8, 1.3 Hz, 2H), 7.40–7.30 (m, 7H), 7.25 (dd, J = 8.4, 1.1 Hz, 2H), 6.59 (s, 2H), 2.51 (s, 6H).
^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 154.41, 150.42, 149.00, 134.41, 131.38, 130.79, 129.19, 129.02, 128.08, 125.22, 124.90, 124.71, 123.27, 120.11, 119.76, 115.63, 115.01, 111.38, 9.72.
ESI-HRMS: calculated for $C_{38}H_{25}O_4^-$ ([M-H]$^-$): 545.175835, found: 545.176570.

(*S*)-3,3'-bis(6-isopropylbenzofuran-2-yl)-BINOL (366)



A 20 mL microwave vial was charged with (*S*)-MOM-BINOL Bpin ester (350 mg, 0.559 mmol, 1.00 eq.), 2-bromo-6-isopropylbenzofuran (**159**, 334 mg, 1.40 mmol, 2.50 eq.), 1,4-dioxane (6.0 mL), and K_2CO_3 (2.0 M in H_2O, 1.7 mL, 3.4 mmol, 6.1 eq.), and the solution was sparged with argon for 10 min. $Pd(PPh_3)_4$ (65 mg, 0.060 mmol, 10 mol%) was added lastly, the vial was capped, and the mixture was heated to 120 °C in a microwave for 90 min. After cooling to RT, the reaction was quenched by addition

of saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (20 mL) in a 50 mL round bottom flask under air. HCl (2.0 M in Et_2O, 5.5 mL, 11 mmol, 20 eq.) was added and the reaction was stirred at RT for 16 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 98:2) to give a mixture of inseparable partly MOM-protected products. The material was re-dissolved in THF (10 mL) in a 50 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 2.8 mL, 11 mmol, 20 eq.) was added and the reaction was stirred at RT for another 4 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 95:5) to give the product as a white solid (319 mg, 0.56 mmol, 95%).

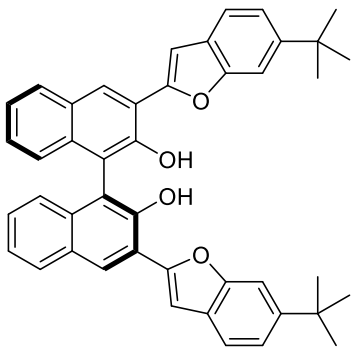
$\boldsymbol{R_F}$ (hex/EtOAc 9:1) = 0.45.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 8.74 (s, 2H), 8.06–8.01 (m, 2H), 7.52 (d, J = 7.9 Hz, 2H), 7.48 (s, 2H), 7.47 (d, J = 1.0 Hz, 2H), 7.43 (ddd, J = 8.1, 6.8, 1.2 Hz, 2H), 7.32 (ddd, J = 8.2, 6.8, 1.3 Hz, 2H), 7.19–7.16 (m, 2H), 7.15 (dd, J = 8.0, 1.6 Hz, 2H), 5.91 (s, 2H), 3.08 (hept, J = 6.9 Hz, 2H), 1.35 (d, J = 6.9 Hz, 12H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 154.92, 151.45, 149.96, 146.79, 132.92, 129.46, 129.10, 128.15, 128.08, 127.53, 124.91, 124.28, 122.30, 121.17, 119.76, 112.01, 108.55, 107.77, 34.59, 24.48.

ESI-HRMS: calculated for $C_{42}H_{33}O_4^-$ ([M-H]$^-$): 601.238435, found: 601.238910.

(*S*)-3,3'-bis(6-(*tert*-butyl)benzofuran-2-yl)-BINOL (367)



A 100 mL three-necked flask equipped with a reflux condenser under argon was charged with (*S*)-MOM-BINOL Bpin ester (1.70 g, 2.70 mmol, 1.00 eq.), 2-bromo-6-(*tert*-butyl)benzofuran (**160**, 1.68 g, 2.50 mmol, 2.50 eq.), 1,4-dioxane (25 mL), and K_2CO_3 (2.0 M in H_2O, 8.5 mL, 17 mmol, 6.3 eq.), and the solution was sparged with argon for 15 min. $Pd(PPh_3)_4$ (157 mg, 0.14 mmol, 5 mol%) was added lastly and the mixture was heated to reflux for 16 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (20 mL) in a 100 mL round bottom flask under air. HCl (4.0

M in 1,4-dioxane, 14 mL, 56 mmol, 21 eq.) was added and the reaction was stirred at RT for 16 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed saturated aqueous $NaHCO_3$ and with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 19:1 to 9:1) and another silica gel flash column chromatography (hex/DCM 20-30%) to yield the product as a white solid (1.59 g, 2.53 mmol, 79%).

$\boldsymbol{R_F}$ (hex/EtOAc 9:1) = 0.50.

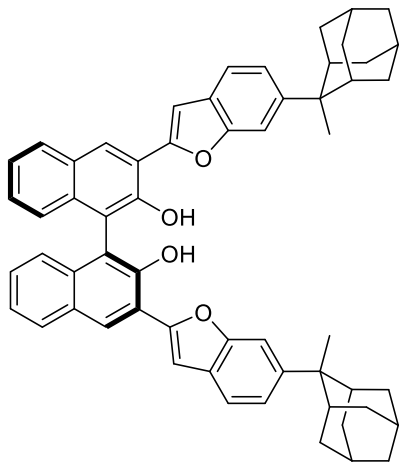
^{1}H-NMR (501 MHz, $CDCl_3$): δ = 8.75 (s, 2H), 8.03 (d, J = 8.1 Hz, 2H), 7.65 (d, J = 1.6 Hz, 2H), 7.53 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 1.0 Hz, 2H), 7.43 (ddd, J = 8.1, 6.8, 1.2 Hz, 2H), 7.36–7.29 (m, 4H), 7.17 (dd, J = 8.4, 1.1 Hz, 2H), 5.89 (s, 2H), 1.43 (s, 18H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 154.85, 151.60, 149.96, 149.10, 132.92, 129.47, 129.11, 128.17, 128.08, 127.05, 124.92, 124.28, 121.03, 120.86, 119.78, 111.98, 107.78, 107.65, 35.25, 31.85.

ESI-HRMS: calculated for $C_{44}H_{37}O_4^-$ ([M-H]$^-$): 629.269735, found: 629.270020.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25}}$ = +90.1 (*c* = 0.30, $CHCl_3$).

(*S*)-3,3'-bis(6-(2-methyladamantan-2-yl)benzofuran)-BINOL (368)



A 50 mL three-necked flask equipped with a reflux condenser under argon was charged with (*S*)-MOM-BINOL Bpin ester (1.27 g, 2.02 mmol, 1.00 eq.), 2-iodo-6-(2-methyladamantan-2-yl)benzofuran (**347**, 1.13 g, 4.56 mmol, 2.26 eq.), 1,4-dioxane (20 mL), and K_2CO_3 (2.0 M in H_2O, 6.0 mL, 12 mmol, 5.9 eq.), and the solution was sparged with argon for 15 min. $Pd(PPh_3)_4$ (117 mg, 0.10 mmol, 5 mol%) was added lastly and the mixture was heated to reflux for 16 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (20 mL) in a 100 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 10 mL, 40 mmol, 20 eq.) was added and the reaction was stirred at RT for 16 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/DCM 15-20%) to yield the product as a white solid (790 mg, 0.969 mmol, 48%).

$\boldsymbol{R_F}$ (hex/EtOAc 19:1) = 0.27.

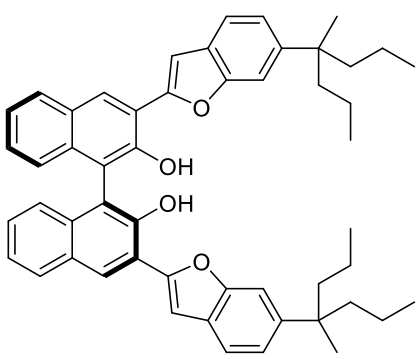
^{1}H-NMR (501 MHz, $CDCl_3$): δ = 8.74 (s, 2H), 8.02 (d, J = 8.2 Hz, 2H), 7.61 (s, 2H), 7.54 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 0.9 Hz, 2H), 7.43 (ddd, J = 8.1, 6.7, 1.2 Hz, 2H), 7.32 (ddd, J = 8.2, 6.8, 1.3 Hz, 2H), 7.29 (dd, J = 8.3, 1.5 Hz, 2H), 7.17 (dd, J = 8.4, 1.1 Hz, 2H), 5.91 (s, 2H), 2.44 (d, J = 3.7 Hz, 4H), 2.30 (dd, J = 12.6, 3.3 Hz, 4H), 2.02–1.93 (m, 6H), 1.87–1.78 (m, 4H), 1.78–1.70 (m, 6H), 1.66–1.58 (m, 4H), 1.32 (s, 6H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 155.34, 151.50, 149.97, 148.97, 132.90, 129.48, 129.09, 128.11, 128.04, 126.66, 124.90, 124.29, 121.13, 120.87, 119.83, 112.03, 108.24, 107.70, 44.02, 38.96, 34.93, 34.22, 33.36, 30.91, 28.12, 27.79.

ESI-HRMS: calculated for $C_{58}H_{53}O_4^-$ ([M-H]$^-$): 813.394935, found: 813.394950.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +53.1 (*c* = 0.38, $CHCl_3$).

(*S*)-3,3'-bis(6-(4-methylheptan-4-yl)benzofuran-2-yl)-BINOL (369)



A 5 mL microwave vial was charged with (*S*)-MOM-BINOL Bpin ester (70.0 mg, 0.112 mmol, 1.00 eq.), 2-iodo-6-(4-methylheptan-4-yl)benzofuran (**348**, 97.7 mg, 0.274 mmol, 2.45 eq.), 1,4-dioxane (2.0 mL), and K_2CO_3 (2.0 M in H_2O, 0.40 mL, 0.80 mmol, 7.2 eq.), and the solution was sparged with argon for 15 min. $Pd(PPh_3)_4$ (15 mg, 13 µmol, 12 mol%) was added lastly, the vial was capped, and the mixture was heated in a microwave for 3 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (5 mL) in a 25 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 0.60 mL, 2.4 mmol, 21 eq.) was added and the reaction was stirred at RT for 16 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed saturated aqueous $NaHCO_3$ and with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Analysis by ^{1}H-NMR revealed incomplete deprotection. The mixture was redissolved in THF (5 mL) in a 25 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 0.60 mL, 2.4 mmol, 21 eq.) was added and the reaction was stirred at RT for 16 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed saturated aqueous $NaHCO_3$ and with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 99:1), and another silica gel flash column chromatography (hex/DCM 9:1 to 4:1) to yield the product as a white solid (26.6 mg, 112 µmol, 32%).

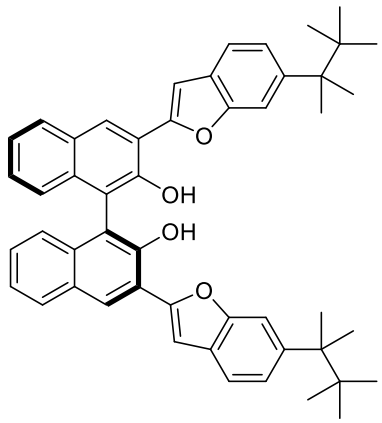
$\boldsymbol{R_F}$ (hex/EtOAc 19:1) = 0.27

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 8.75 (s, 2H), 8.03 (d, J = 8.2 Hz, 2H), 7.55 (s, 2H), 7.51 (d, J = 8.1 Hz, 2H), 7.46–7.40 (m, 4H), 7.31 (ddd, J = 8.3, 6.8, 1.3 Hz, 2H), 7.22 (dd, J = 8.2, 1.6 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 5.89 (s, 2H), 1.76 (td, J = 13.0, 4.3 Hz, 4H), 1.64–1.54 (m, 4H), 1.38 (s, 6H), 1.23 (ddt, J = 19.7, 12.3, 3.7 Hz, 4H), 1.03 (ddd, J = 19.7, 9.8, 6.0 Hz, 4H), 0.85 (t, J = 7.3 Hz, 12H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 154.97, 151.41, 149.96, 146.46, 132.89, 129.47, 129.09, 128.12, 128.04, 126.82, 124.90, 124.26, 121.85, 120.70, 119.82, 111.98, 109.07, 107.70, 46.46, 41.56, 24.46, 17.66, 15.01.

ESI-HRMS: calculated for $C_{52}H_{53}O_4^-$ ([M-H]$^-$): 741.394935, found: 741.395690.

(*S*)-3,3'-bis(6-(2,3,3-trimethylbutan-2-yl)benzofuran-2-yl)-BINOL (370)



A 2 mL microwave vial was charged with (*S*)-MOM-BINOL Bpin ester (58.5 mg, 93.4 µmol, 1.00 eq.), 2-iodo-6-(2,3,3-trimethylbutan-2-yl)benzofuran (**350**, 76.6 mg, 0.208 mmol, 2.23 eq.), 1,4-dioxane (2.0 mL), and K_2CO_3 (2.0 M in H_2O, 0.28 mL, 0.56 mmol, 6.0 eq.), and the solution was sparged with argon for 15 min. $Pd(PPh_3)_4$ (28 mg, 24 µmol, 25 mol%) was added lastly, the vial was capped, and the mixture was heated in a microwave for 2 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (5 mL) in a 10 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 0.50 mL, 2.0 mmol, 21 eq.) was added and the reaction was stirred at RT for 16 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed saturated aqueous $NaHCO_3$ and with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 98:2) and another silica gel flash column chromatography (hex/DCM 19:1 to 4:1) to yield the product as a white solid (37.5 mg, 93.4 µmol, 56%).

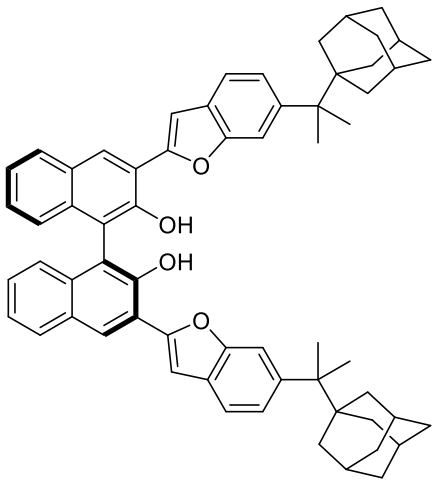
***R*$_F$** (hex/EtOAc 9:1) = 0.57.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 8.75 (s, 2H), 8.03 (d, J = 8.1 Hz, 2H), 7.64 (s, 2H), 7.48 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 0.9 Hz, 2H), 7.43 (ddd, J = 8.1, 6.8, 1.2 Hz, 2H), 7.34–7.28 (m, 4H), 7.17 (dd, J = 8.4, 1.1 Hz, 2H), 5.93 (s, 2H), 1.46 (s, 12H), 0.92 (s, 18H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 154.33, 151.59, 149.99, 145.67, 132.93, 129.46, 129.09, 128.18, 128.06, 126.87, 124.91, 124.27, 123.95, 119.81, 119.35, 112.02, 110.97, 107.59, 43.49, 36.40, 26.64, 24.99.

ESI-HRMS: calculated for $C_{50}H_{49}O_4^-$ ([M-H]$^-$): 713.363635, found: 713.364290.

(*S*)-3,3'-bis(6-(2-(adamantan-1-yl)propan-2-yl)benzofuran-2-yl)-BINOL (371)



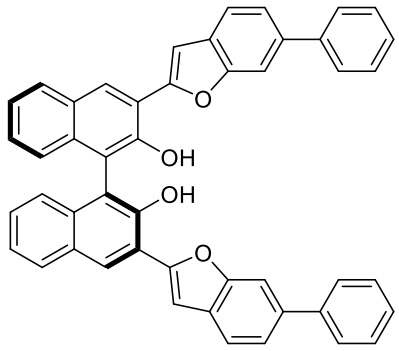
A 5 mL microwave vial was charged with (*S*)-MOM-BINOL Bpin ester (75.0 mg, 0.120 mmol, 1.00 eq.), 2-iodo-6-(2-(adamantan-1-yl)propan-2-yl)benzofuran (**352**, 128 mg, 0.282 mmol, 2.36 eq.), 1,4-dioxane (2.5 mL), and K_2CO_3 (2.0 M in H_2O, 0.36 mL, 0.72 mmol, 6.0 eq.), and the solution was sparged with argon for 15 min. $Pd(PPh_3)_4$ (28 mg, 24 µmol, 20 mol%) was added lastly, the vial was capped, and the mixture was heated in a microwave for 3 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (5.5 mL) in a 25 mL round bottom flask under air. HCl (2.0 M in Et_2O, 1.2 mL, 2.4 mmol, 20 eq.) was added and the reaction was stirred at RT for 16 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed saturated aqueous $NaHCO_3$ and with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 98:2), another silica gel flash column chromatography (hex/DCM 19:1 to 4:1), and another silica gel flash column chromatography (hex/PhMe 9:1 to 4:1) to yield the product as a white solid (37.5 mg, 93.4 µmol, 56%).

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 8.76 (s, 2H), 8.05–7.98 (m, 2H), 7.58 (s, 2H), 7.50–7.47 (m, 4H), 7.43 (ddd, J = 8.1, 6.8, 1.2 Hz, 2H), 7.32 (ddd, J = 8.2, 6.8, 1.3 Hz, 2H), 7.24 (dd, J = 8.3, 1.6 Hz, 2H), 7.17 (dd, J = 8.5, 1.1 Hz, 2H), 5.91 (s, 2H), 1.94 (s, 6H), 1.64–1.48 (m, 24H), 1.41 (s, 12H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 154.26, 151.49, 149.95, 144.98, 132.89, 129.43, 129.08, 128.14, 128.01, 126.80, 124.87, 124.23, 124.21, 119.78, 119.18, 111.96, 111.24, 107.61, 43.99, 37.41, 37.16, 37.10, 29.08, 23.66.

ESI-HRMS: calculated for $C_{62}H_{61}O_4^-$ ([M-H]$^-$): 869.457535, found: 869.457520.

(*S*)-3,3'-bis(6-phenylbenzofuran-2-yl)-BINOL (372)



A 20 mL microwave vial was charged with (*S*)-MOM-BINOL Bpin ester (500 mg, 0.8 mmol, 1.00 eq.) and 2-iodo-6-phenylbenzofuran (**174**, 605 mg, 1.76 mmol, 2.20 eq.). 1,4-dioxane (8.4 mL) and K_2CO_3 (2.0 M in H_2O, 2.4 mL, 4.8 mmol, 6.0 eq.) were added and the solution was sparged with argon for 10 min. Subsequently, $Pd(PPh_3)_4$ (92 mg, 0.080 mmol, 10 mol%) was added and the reaction was heated to 120 °C in a microwave for 90 min. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (8 mL) in a 25 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 4 mL, 16 mmol, 20 eq.) was added and the reaction was stirred at RT for 16 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 49:1 to 4:1) and reversed phase automated column chromatography (CH_3CN/H_2O 60:40 to 100:0) to give the product as a white solid (478 mg, 0.798 mmol, 89%).

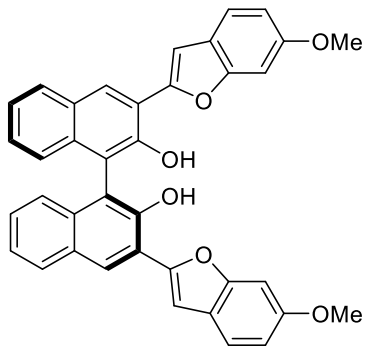
$\boldsymbol{R_F}$ (hex/EtOAc 9:1) = 0.32.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.83 (s, 2H), 8.10 (d, J = 8.2 Hz, 2H), 7.87 (d, J = 1.3 Hz, 2H), 7.76–7.67 (m, 6H), 7.57 (d, J = 1.0 Hz, 2H), 7.55 (dd, J = 8.0, 1.6 Hz, 2H), 7.53–7.45 (m, 6H), 7.41–7.33 (m, 4H), 7.18 (dd, J = 8.4, 1.0 Hz, 2H), 6.03 (s, 2H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 155.42, 152.87, 150.39, 141.60, 138.89, 133.49, 129.83, 129.50, 129.31, 129.23, 128.75, 128.50, 127.70, 127.67, 125.28, 124.42, 123.06, 121.96, 119.78, 112.49, 109.67, 107.87.

ESI-HRMS: calculated for $C_{48}H_{29}O_4^-$ ($[M-H]^-$): 669.207135, found: 669.207870.

(*S*)-3,3'-bis(6-methoxybenzofuran-2-yl)-BINOL (373)



A 5 mL microwave vial was charged with (*S*)-MOM-BINOL Bpin ester (250 mg, 0.40 mmol, 1.00 eq.) and 2-iodo-6-methoxybenzofuran (**177**, 294 mg, 1.00 mmol, 2.50 eq.). 1,4-dioxane (3.5 mL) and K_2CO_3 (2.0 M in H_2O, 1.2 mL, 2.4 mmol, 6.0 eq.) were added and the solution was sparged with argon for 10 min. Subsequently, $Pd(PPh_3)_4$ (46 mg, 0.040 mmol, 10 mol%) was added and the reaction was heated to 120 °C in a microwave for 90 min. After cooling to RT, the reaction was quenched by addition

of saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (3.5 mL) in a 25 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 2.0 mL, 8.0 mmol, 20 eq.) was added and the reaction was stirred at RT for 16 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 19:1) to give the product as a white solid (230 mg, 0.399 mmol, >99%).

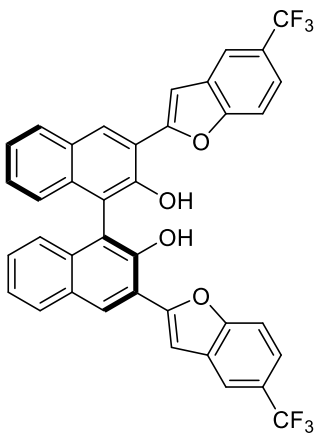
$\boldsymbol{R_F}$ (hex/EtOAc 9:1) = 0.13

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.72 (s, 2H), 8.08–8.02 (m, 2H), 7.49 (d, J = 8.5 Hz, 2H), 7.47–7.41 (m, 4H), 7.32 (ddd, J = 8.2, 6.8, 1.3 Hz, 2H), 7.17 (dd, J = 2.3, 0.9 Hz, 2H), 7.14 (dd, J = 8.5, 1.1 Hz, 2H), 6.89 (dd, J = 8.5, 2.3 Hz, 2H), 5.98 (s, 2H), 3.90 (s, 6H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 159.13, 155.82, 151.44, 150.14, 133.17, 129.84, 129.31, 128.15, 127.93, 125.15, 124.39, 123.20, 121.97, 120.03, 112.45, 112.41, 107.90, 95.97, 56.15.

ESI-HRMS: calculated for $C_{38}H_{25}O_6^-$ ([M-H]$^-$): 577.165665, found: 577.165920.

(*S*)-3,3'-bis(5-(trifluoromethyl)benzofuran-2-yl)-BINOL (374)



A 20 mL microwave vial was charged with (*S*)-MOM-BINOL Bpin ester (350 mg, 0.56 mmol, 1.00 eq.) and 2-iodo-5-(trifluoromethyl)benzofuran (**175**, 417 mg, 1.24 mmol, 2.22 eq.). 1,4-dioxane (5.5 mL) and K_2CO_3 (2.0 M in H_2O, 1.7 mL, 3.4 mmol, 6.1 eq.) were added and the solution was sparged with argon for 10 min. Subsequently, $Pd(PPh_3)_4$ (32 mg, 0.028 mmol, 5 mol%) was added and the reaction was heated to 120 °C in a microwave for 1 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (5.5 mL) in a 50 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 2.8 mL, 11 mmol, 20 eq.) was added and the reaction was stirred at RT for 16 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 99:1 to 98:2) to give the product as a white solid (363 mg, 0.559 mmol, 99%).

$\boldsymbol{R_F}$ (hex/EtOAc 9:1) = 0.36

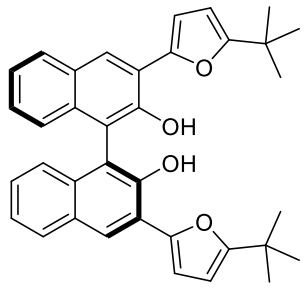
^{1}H-NMR (600 MHz, CD_2Cl_2): δ = 8.84 (s, 2H), 8.09 (ddd, J = 8.6, 1.2, 0.6 Hz, 2H), 7.93 (dq, J = 1.6, 0.7 Hz, 2H), 7.74 (dp, J = 8.7, 0.7 Hz, 2H), 7.63 (ddd, J = 8.6, 1.9, 0.6 Hz, 2H), 7.60 (d, J = 1.0 Hz, 2H), 7.48 (ddd, J = 8.1, 6.8, 1.2 Hz, 2H), 7.37 (ddd, J = 8.2, 6.7, 1.3 Hz, 2H), 7.16 (dq, J = 8.5, 0.9 Hz, 2H), 5.96 (d, J = 0.6 Hz, 2H).

^{13}C-NMR (151 MHz, CD_2Cl_2): δ = 156.04 (q, J = 1.4 Hz), 154.06, 150.41, 133.66, 130.14, 129.72, 129.64, 129.28, 128.86, 125.87 (q, J = 32.0 Hz), 125.43, 125.20 (q, J = 271.9 Hz), 124.34, 122.20 (q, J = 3.7 Hz), 119.44 (q, J = 4.1 Hz), 119.20, 112.26, 111.79, 10f7.90.

^{19}F-NMR (565 MHz, CD_2Cl_2): δ = -61.23.

ESI-HRMS: calculated for $C_{38}H_{19}O_4F_6^-$ ([M-H]$^-$): 653.119306, found: 653.119540.

(*S*)-3,3'-bis(5-(*tert*-butyl)furan-2-yl)-BINOL (375)



A 5 mL microwave vial was charged with (*S*)-MOM-BINOL Bpin ester (250 mg, 0.40 mmol, 1.00 eq.) and 2-bromo-5-(*tert*-butyl)furan (**182**, 203 mg, 1.00 mmol, 2.50 eq.). 1,4-dioxane (3.5 mL) and K_2CO_3 (2.0 M in H_2O, 1.2 mL, 2.4 mmol, 6.0 eq.) were added and the solution was sparged with argon for 15 min. Subsequently, $Pd(PPh_3)_4$ (46 mg, 0.040 mmol, 10 mol%) was added, the vial was capped, and the reaction was heated to 140 °C in a microwave for 1 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (3.5 mL) in a 25 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 2.0 mL, 8.0 mmol, 20 eq.) was added and the reaction was stirred at RT for 16 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 99:1) to give the product as a white solid (200 mg, 0.378 mmol, 95%).

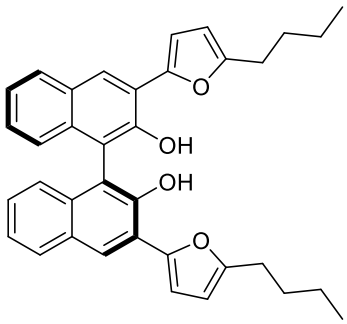
***R*$_F$** (hex/EtOAc 19:1) = 0.39.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.43 (s, 2H), 7.97 (dt, J = 8.3, 0.9 Hz, 2H), 7.38 (ddd, J = 8.1, 6.8, 1.2 Hz, 2H), 7.25 (ddd, J = 8.2, 6.8, 1.3 Hz, 2H), 7.07 (dq, J = 8.5, 0.9 Hz, 2H), 6.96 (d, J = 3.3 Hz, 2H), 6.16 (d, J = 3.3 Hz, 2H), 6.02 (s, 2H), 1.41 (s, 18H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 164.70, 149.56, 148.67, 132.71, 129.80, 128.86, 127.35, 125.97, 124.81, 124.44, 120.41, 112.97, 111.89, 105.02, 33.20, 29.34.

ESI-HRMS: calculated for $C_{36}H_{33}O_4^-$ ([M-H]$^-$): 529.238435, found: 529.238490.

(*S*)-3,3'-bis(5-butylfuran-2-yl)-BINOL (376)



A 5 mL microwave vial was charged with (*S*)-MOM-BINOL Bpin ester (250 mg, 0.40 mmol, 1.00 eq.) and 2-iodo-5-butylfuran (**176**, 268 mg, 1.00 mmol, 2.50 eq.). 1,4-dioxane (3.5 mL) and K_2CO_3 (2.0 M in H_2O, 1.2 mL, 2.4 mmol, 6.0 eq.) were added and the solution was sparged with argon for 15 min. Subsequently, $Pd(PPh_3)_4$ (46 mg, 0.040 mmol, 10 mol%) was added, the vial was capped, and the reaction was heated to 140 °C in a microwave for 1 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (3.5 mL) in a 25 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 2.0 mL, 8.0 mmol, 20 eq.) was added and the reaction was stirred at RT for 16 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 99:1) to give the product as an off-white solid (108 mg, 0.204 mmol, 51%).

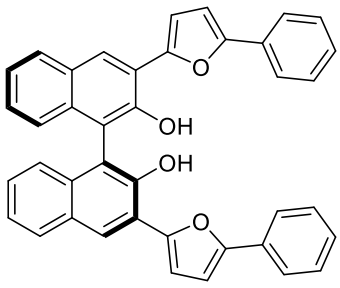
$\boldsymbol{R_F}$ (hex/EtOAc 19:1) = 0.31.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.43 (s, 2H), 7.96 (d, J = 8.0 Hz, 2H), 7.38 (ddd, J = 8.0, 6.8, 1.2 Hz, 2H), 7.25 (ddd, J = 8.2, 6.8, 1.3 Hz, 2H), 7.07 (dd, J = 8.4, 1.1 Hz, 2H), 6.98 (d, J = 3.2 Hz, 2H), 6.17 (dd, J = 3.2, 0.9 Hz, 2H), 5.99 (s, 2H), 2.78 (t, J = 7.6 Hz, 4H), 1.75 (p, J = 7.5 Hz, 4H), 1.51–1.41 (m, 4H), 0.98 (t, J = 7.4 Hz, 6H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 157.18, 149.53, 148.83, 132.66, 129.82, 128.87, 127.35, 125.99, 124.80, 124.41, 120.36, 112.88, 112.16, 107.77, 30.70, 28.27, 22.75, 14.03.

ESI-HRMS: calculated for $C_{36}H_{33}O_4^-$ ([M-H]$^-$): 529.238435, found: 529.238560.

(*S*)-3,3'-bis(5-phenylfuran-2-yl)-BINOL (377)



A 5 mL microwave vial was charged with (*S*)-MOM-BINOL Bpin ester (250 mg, 0.40 mmol, 1.00 eq.) and 2-bromo-5-phenylfuran (**183**, 223 mg, 1.00 mmol, 2.50 eq.). 1,4-dioxane (4.2 mL) and K_2CO_3 (2.0 M in H_2O, 1.2 mL, 2.4 mmol, 6.0 eq.) were added and the solution was sparged with argon for 15 min. Subsequently, $Pd(PPh_3)_4$ (46 mg, 0.040 mmol, 10 mol%) was added, the vial was capped, and the reaction was heated to 140 °C in a microwave for 1 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with

brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (3 mL) in a 25 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 2.0 mL, 8.0 mmol, 20 eq.) was added and the reaction was stirred at RT for 16 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 19:1) to give the product as a faint yellow solid (209 mg, 0.365 mmol, 92%).

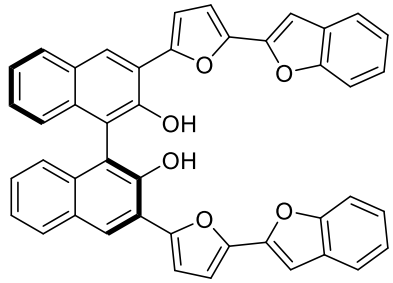
$\boldsymbol{R_F}$ (hex/EtOAc 9:1) = 0.27.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.66 (s, 2H), 8.08–8.02 (m, 2H), 7.90–7.85 (m, 4H), 7.51–7.46 (m, 4H), 7.43 (ddd, J = 8.0, 6.8, 1.2 Hz, 2H), 7.38–7.28 (m, 4H), 7.21 (d, J = 3.5 Hz, 2H), 7.13 (dq, J = 8.3, 0.9 Hz, 2H), 6.87 (d, J = 3.5 Hz, 2H), 5.90 (s, 2H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 153.34, 149.53, 149.38, 132.42, 130.54, 129.49, 128.81, 128.69, 127.67, 127.38, 126.33, 124.66, 123.97, 123.89, 119.66, 113.53, 111.99, 107.71.

ESI-HRMS: calculated for $C_{40}H_{25}O_4^-$ ([M-H]$^-$): 569.175835, found: 569.176210.

(*S*)-3,3'-bis(5-(benzofuran-2-yl)-furan-2-yl)-BINOL (378)



A 5 mL microwave vial was charged with (*S*)-MOM-BINOL Bpin ester (250 mg, 0.40 mmol, 1.00 eq.) and 2-bromo-5-(benzofuran-2-yl)furan (**184**, 263 mg, 1.00 mmol, 2.50 eq.). 1,4-dioxane (4.2 mL) and K_2CO_3 (2.0 M in H_2O, 1.2 mL, 2.4 mmol, 6.0 eq.) were added and the solution was sparged with argon for 15 min. Subsequently, $Pd(PPh_3)_4$ (46 mg, 0.040 mmol, 10 mol%) was added, the vial was capped, and the reaction was heated to 140 °C in a microwave for 1 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (3 mL) in a 25 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 2.0 mL, 8.0 mmol, 20 eq.) was added and the reaction was stirred at RT for 16 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/PhMe 2:1) and automated reversed phase column chromatography (CH_3CN/H_2O 80:20 to 100:0) to give the product as a faint yellow solid (215 mg, 0.330 mmol, 83%).

$\boldsymbol{R_F}$ (hex/EtOAc 9:1) = 0.26.

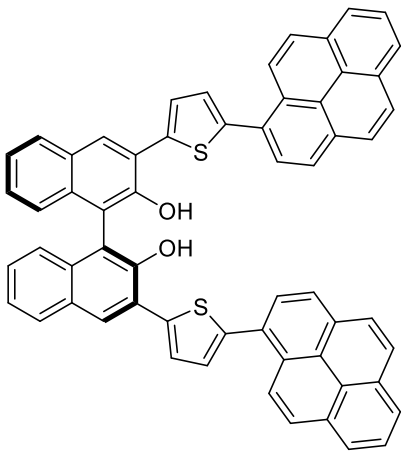
^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.70 (s, 2H), 8.08 (dt, J = 8.4, 0.9 Hz, 2H), 7.70 – 7.64 (m, 2H), 7.56 (dq, J = 8.1, 0.9 Hz, 2H), 7.46 (ddd, J = 8.1, 6.8, 1.2 Hz, 2H), 7.36 – 7.29 (m, 7H), 7.27 (d, J

= 3.6 Hz, 2H), 7.20 (d, J = 1.0 Hz, 2H), 7.14 (dq, J = 8.3, 0.9 Hz, 2H), 6.99 (d, J = 3.5 Hz, 2H), 5.88 (s, 2H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 155.24, 151.00, 149.85, 148.37, 145.85, 133.04, 129.89, 129.27, 128.12, 127.22, 125.23, 125.08, 124.38, 123.74, 121.52, 119.68, 113.82, 112.33, 111.46, 110.69, 102.06.

ESI-HRMS: calculated for $C_{44}H_{25}O_6^-$ ([M-H]$^-$): 649.165665, found: 649.166150.

(*S*)-3,3'-bis(5-(pyren-1-yl)thiophen-2-yl)-BINOL (379)



A 20 mL microwave vial was charged with (*S*)-MOM-BINOL Bpin ester (500 mg, 0.80 mmol, 1.00 eq.), 2-bromo-5-(pyren-1-yl)thiophene (**181**, 725 mg, 2.00 mmol, 2.50 eq.), and K_2CO_3 (662 mg, 4.79 mmol, 6.00 eq.) under argon. Degassed 1,4-dioxane (7.0 mL) and H_2O (2.0 mL), and lastly $Pd(PPh_3)_4$ (92 mg, 0.080 mmol, 10 mol%) were added, the vial was capped, and the reaction was heated to 140 °C for 16 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (6.0 mL) in a 50 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 4.0 mL, 16 mmol, 20 eq.) was added and the reaction was stirred at RT for 16 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 19:1 to 4:1) and another silica gel flash column chromatography (100% PhMe) to give the product as a yellow solid (266 mg, 0.312 mmol, 39%).

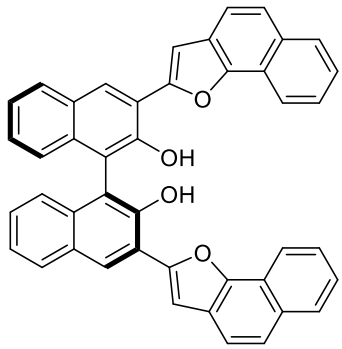
R_F (hex/EtOAc 4:1) = 0.35.

^{1}H-NMR (600 MHz, CD_2Cl_2): δ = 8.67 (d, J = 9.3 Hz, 2H), 8.49 (s, 2H), 8.27–8.18 (m, 8H), 8.16 (d, J = 9.2 Hz, 2H), 8.14–8.11 (m, 4H), 8.08–8.01 (m, 4H), 7.92 (d, J = 3.7 Hz, 2H), 7.49 (d, J = 3.7 Hz, 2H), 7.46 (ddd, J = 8.1, 6.8, 1.2 Hz, 2H), 7.37 (ddd, J = 8.2, 6.8, 1.3 Hz, 2H), 7.25–7.20 (m, 2H), 5.87 (d, J = 0.6 Hz, 2H).

^{13}C-NMR (151 MHz, CD_2Cl_2): δ = 150.25, 143.61, 140.27, 133.14, 131.91, 131.49, 131.39, 130.04, 130.01, 129.89, 129.35, 129.06, 128.99, 128.73, 128.41, 128.23, 128.12, 128.03, 127.74, 126.68, 125.83, 125.51, 125.44, 125.35, 125.18, 125.11, 125.10, 124.45, 123.91, 112.72.

ESI-HRMS: calculated for $C_{60}H_{33}O_2S_2^-$ ([M-H]$^-$): 849.192750, found: 849.193590.

(*S*)-3,3'-bis(naphtho[1,2-*b*]furan-2-yl)-BINOL (380)



A 5 mL microwave vial was charged with (*S*)-MOM-BINOL Bpin ester (116 mg, 0.19 mmol, 1.00 eq.), 2-bromonaphtho[1,2-*b*]furan (**161**, 101 mg, 0.408 mmol, 2.20 eq.), and K_2CO_3 (154 mg, 1.11 mmol, 6.00 eq.) under argon. Degassed 1,4-dioxane (1.7 mL) and H_2O (0.5 mL), and lastly $Pd(PPh_3)_4$ (46 mg, 0.040 mmol, 21 mol%) were added, the vial was capped, and the reaction was heated to 140 °C in an oil bath for 16 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (1.4 mL) in a 25 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 0.93 mL, 3.7 mmol, 20 eq.) was added and the reaction was stirred at RT for 16 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 19:1) and another silica gel flash column chromatography (hex/PhMe 2:1) to give the product as an off-white solid (101.5 mg, 0.186 mmol, 88%).

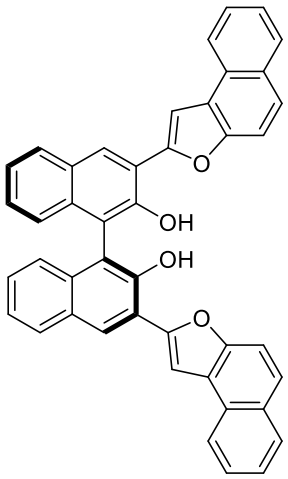
$\boldsymbol{R_F}$ (hex/EtOAc 9:1) = 0.32.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.96 (s, 2H), 8.56 (d, J = 8.1 Hz, 2H), 8.14 (d, J = 8.1 Hz, 2H), 7.99 (dt, J = 8.2, 1.1 Hz, 3H), 7.73–7.67 (m, 8H), 7.56 (ddd, J = 8.2, 6.9, 1.3 Hz, 2H), 7.49 (ddd, J = 8.1, 6.7, 1.2 Hz, 2H), 7.36 (ddd, J = 8.2, 6.8, 1.3 Hz, 2H), 7.21 (dd, J = 8.5, 1.0 Hz, 2H), 6.05 (s, 2H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 151.76, 150.27, 133.33, 132.29, 129.91, 129.41, 128.92, 128.31, 128.27, 126.94, 125.78, 125.63, 125.26, 124.46, 124.13, 121.56, 120.50, 120.33, 120.10, 112.51, 109.17.

ESI-HRMS: calculated for $C_{44}H_{25}O_4^-$ ($[M-H]^-$): 617.175835, found: 617.176310.

(*S*)-3,3'-bis(naphtho[2,1-*b*]furan-2-yl)-BINOL (381)



A 5 mL microwave vial was charged with (*S*)-MOM-BINOL Bpin ester (250 mg, 0.40 mmol, 1.00 eq.), 2-bromonaphtho[2,1-*b*]furan (**162**, 247 mg, 1.00 mmol, 2.50 eq.), and K_2CO_3 (331 mg, 2.39 mmol, 6.00 eq.) under argon. Degassed 1,4-dioxane (3.5 mL) and H_2O (1.0 mL), and lastly $Pd(PPh_3)_4$ (46 mg, 0.040 mmol, 10 mol%) were added, the vial was capped, and the reaction was heated to 140 °C in an oil bath for 16 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (3.0 mL) in a 25 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 2.0 mL, 8.0 mmol, 20 eq.) was added and the reaction was stirred at RT for 16 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 49:1 to 19:1) and another silica gel flash column chromatography (hex/PhMe 2:1) to give the product as an off-white solid (246 mg, 0.399 mmol, >99%).

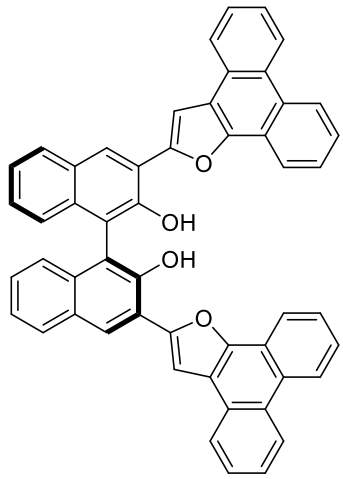
$\boldsymbol{R_F}$ (hex/EtOAc 9:1) = 0.27.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.86 (s, 2H), 8.20 (dd, J = 8.2, 1.3 Hz, 2H), 8.10 (d, J = 8.2 Hz, 2H), 8.06 (s, 2H), 7.99 (dt, J = 8.0, 1.0 Hz, 2H), 7.82 (s, 4H), 7.59 (ddd, J = 8.1, 6.8, 1.3 Hz, 2H), 7.51 (ddd, J = 8.2, 6.8, 1.3 Hz, 2H), 7.47 (ddd, J = 8.1, 6.8, 1.2 Hz, 2H), 7.36 (ddd, J = 8.2, 6.8, 1.3 Hz, 2H), 7.21 (dd, J = 8.4, 1.1 Hz, 2H), 6.10 (s, 2H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 152.35, 151.83, 150.25, 133.32, 130.93, 129.91, 129.43, 129.17, 128.34, 128.29, 128.22, 126.88, 126.28, 125.26, 125.18, 125.11, 124.43, 123.90, 120.01, 112.54, 112.45, 107.04.

ESI-HRMS: calculated for $C_{44}H_{25}O_4^-$ ($[M-H]^-$): 617.175835, found: 617.176370.

(*S*)-3,3'-bis(phenanthro[9,10-*b*]furan-2-yl)-BINOL (382)



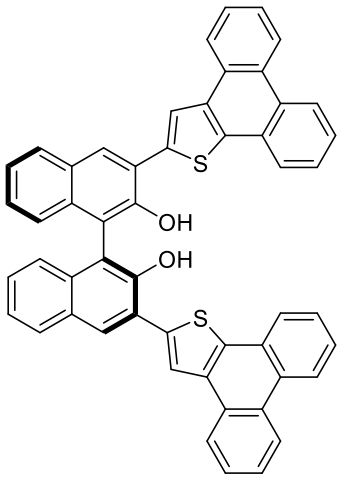
A 5 mL microwave vial was charged with (*S*)-MOM-BINOL Bpin ester (137 mg, 0.22 mmol, 1.00 eq.) and 2-iodophenanthro[9,10-*b*]furan (**165**, 166 mg, 0.45 mmol, 2.05 eq.). 1,4-dioxane (2.0 mL) and K_2CO_3 (2.0 M in H_2O, 0.67 mL, 1.34 mmol, 6.1 eq.) were added and the solution was sparged with argon for 10 min. Subsequently, $Pd(PPh_3)_4$ (21.1 mg, 0.018 mmol, 8 mol%) was added and the reaction was heated to 120 °C in a microwave for 1 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (4.0 mL) in a 25 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 1.1 mL, 4.4 mmol, 20 eq.) was added and the reaction was stirred at RT for 16 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/acetone 9:1) and reversed phase automated flash column chromatography (CH_3CN/H_2O 80:20 to 100:0) to give the product as an off-white solid (31.1 mg, 0.043 mmol, 20%). Due to poor solubility of the product, NMR-analysis could only be conducted in DMSO-d_6.

^{1}H-NMR (600 MHz, DMSO-d_6): δ = 9.31 (s, 2H), 8.97–8.94 (m, 4H), 8.94–8.91 (m, 2H), 8.66 (ddd, J = 7.9, 1.4, 0.6 Hz, 2H), 8.36–8.28 (m, 2H), 8.20–8.12 (m, 4H), 7.88 (ddd, J = 8.0, 7.1, 1.1 Hz, 2H), 7.77 (ddd, J = 8.4, 7.1, 1.4 Hz, 2H), 7.74 (ddd, J = 8.1, 6.9, 1.3 Hz, 2H), 7.70 (ddd, J = 8.3, 6.9, 1.5 Hz, 2H), 7.39 (t, J = 7.4 Hz, 2H), 7.32–7.25 (m, 2H), 6.99 (dq, J = 8.5, 0.9 Hz, 2H).

^{13}C-NMR (151 MHz, DMSO-d_6): δ = 152.32, 147.23, 133.75, 128.68, 128.66, 128.52, 127.67, 127.59, 127.53, 126.81, 126.79, 126.42, 126.40, 125.72, 124.10, 124.02, 123.99, 123.45, 121.88, 121.42, 120.50, 120.36, 114.84, 106.90. Other peaks could not be observed.

ESI-HRMS: calculated for $C_{52}H_{29}O_4^-$ ([M-H]$^-$): 717.207135, found: 717.207140.

(*S*)-3,3'-bis(phenanthro[9,10-*b*]thiophene-2-yl)-BINOL (383)



A 50 mL 3-necked flask under argon equipped with a reflux condenser was charged with (*S*)-MOM-BINOL Bpin ester (992 mg, 1.59 mmol, 1.00 eq.) and 2-bromophenanthro[9,10-*b*]thiophene (**166**, 1.06 g, 3.37 mmol, 2.12 eq.). 1,4-dioxane (15 mL) and K_2CO_3 (2.0 M in H_2O, 5.0 mL, 10 mmol, 6.3 eq.) were added and the solution was sparged with argon for 15 min. Subsequently, $Pd(PPh_3)_4$ (92 mg, 0.080 mmol, 0.05 eq.) was added and the reaction was heated to 120 °C for 16 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over Na_2SO_4 (rewashed with DCM), and concentrated under reduced pressure. The crude material was dissolved in THF (30 mL) in a 100 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 8 mL, 32 mmol, 20 eq.) was added and the reaction was stirred at RT for 16 h, after which full conversion was apparent by TLC (hex/EtOAc 9:1). The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (PhMe/*n*-pentane 1:1 to 100:0, then washed with 100% DCM). Further purification via trituration from hot PhMe (80 °C) gave the desired product as an off-white solid (949 mg, 1.26 mmol, 79%).

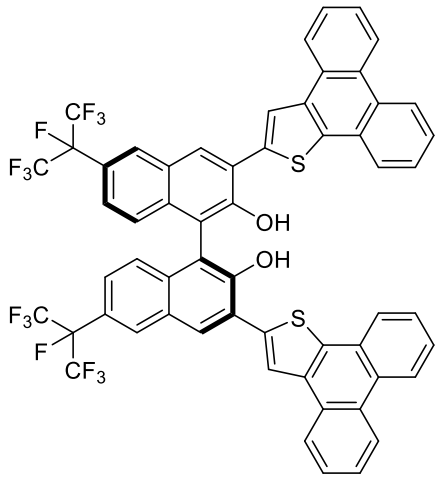
$\boldsymbol{R_F}$ (hex/EtOAc 9:1) = 0.12.

^{1}H-NMR (500 MHz, CD_2Cl_2): δ = 8.74 (ddd, J = 6.4, 4.1, 2.4 Hz, 4H), 8.68 (s, 2H), 8.60 (s, 2H), 8.43–8.40 (m, 2H), 8.26–8.19 (m, 2H), 8.08 (d, J = 8.2 Hz, 2H), 7.74–7.65 (m, 8H), 7.49 (ddd, J = 8.0, 6.7, 1.2 Hz, 2H), 7.39 (ddd, J = 8.2, 6.8, 1.3 Hz, 2H), 7.26 (dq, J = 8.5, 0.9 Hz, 2H), 5.96 (s, 2H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 150.50, 138.83, 137.14, 136.01, 133.38, 130.85, 129.99, 129.13, 129.11, 128.41, 128.35, 127.82, 127.69, 127.01, 126.62, 125.32, 124.69, 124.67, 124.48, 124.10, 123.94, 123.90, 123.71, 112.78, 100.41.

ESI-HRMS: calculated for $C_{52}H_{29}O_2S_2^-$ ([M-H]$^-$): 749.161450, found: 749.160650.

(*S*)-3,3'-bis(benzofuran-2-yl)-6,6'-bis(perfluoropropan-2-yl)-BINOL (384)



A 20 mL microwave vial was charged with (*S*)-6,6'-(*i*-Pr^F)-MOM-BINOL Bpin ester (501 mg, 0.520 mmol, 1.00 eq.), 2-bromophenanthro[9,10-*b*]thiophene (**166**, 361 mg, 1.15 mmol, 2.22 eq.), 1,4-dioxane (5 mL), and K_2CO_3 (2.0 M in H_2O, 1.6 mL, 3.2 mmol, 6.1 eq.), and the solution was sparged with argon for 15 min. $Pd(PPh_3)_4$ (18 mg, 0.015 mmol, 10 mol%) was added lastly, the vial was capped, and the reaction was heated in a microwave to 120 °C for 90 min. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (10 mL) in a 25 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 2.6 mL, 10.4 mmol, 20 eq.) was added and the reaction was stirred at RT for 16 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/acetone 10-15%), automated reversed phase column chromatography (MeOH/H_2O 97:3 to 100:0), and another silica gel flash column chromatography (100% PhMe) to yield the desired product as a white solid (282 mg, 0.26 mmol, 50%).

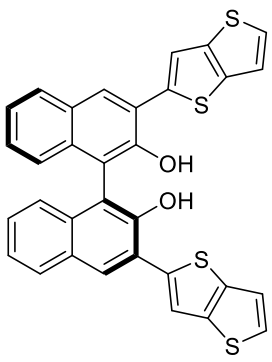
^{1}H-NMR (600 MHz, DMSO): δ = 10.11 (s, 2H), 9.15 (s, 2H), 9.07 (s, 2H), 8.93–8.87 (m, 4H), 8.67 (dd, J = 8.1, 1.4 Hz, 2H), 8.48 (d, J = 2.1 Hz, 2H), 8.20–8.14 (m, 2H), 7.81 (ddd, J = 8.1, 7.0, 1.2 Hz, 2H), 7.74 (ddd, J = 8.2, 7.0, 1.3 Hz, 2H), 7.73–7.69 (m, 4H), 7.53 (d, J = 9.1 Hz, 2H), 7.26–7.22 (m, 2H).

^{19}F-NMR (565 MHz, DMSO) δ = (-72.81)–(-73.03) (m, 12F), -178.96 (hept, J = 7.6 Hz, 2F).

^{13}C-NMR (151 MHz, DMSO): δ = 153.19, 138.55, 136.59, 134.56, 134.42, 129.55, 128.56, 128.13, 128.11, 127.91, 127.86, 127.60, 127.46, 126.83, 126.74 (d, J = 11.0 Hz), 126.56, 125.84, 125.27, 124.44, 124.20, 123.94, 123.66, 122.63, 122.17 (d, J = 9.5 Hz), 120.50 (qd, J = 287.0, 27.9 Hz), 119.81 (d, J = 20.4 Hz), 114.31, 91.54 (dhept, J = 200.4, 32.7 Hz).

ESI-HRMS: calculated for $C_{58}H_{27}O_2S_2F_{14}^-$ ($[M-H]^-$): 1085.123449, found: 1085.123530.

(*S*)-3,3'-bis(thieno[3,2-*b*]thiophene-2-yl)-BINOL (385)



A 5 mL microwave vial was charged with (*S*)-MOM-BINOL Bpin ester (250 mg, 0.40 mmol, 1.00 eq.), 2-bromothieno[3,2-*b*]thiophene (**151**, 219 mg, 1.00 mmol, 2.50 eq.), and K_2CO_3 (331 mg, 2.39 mmol, 6.00 eq.) under argon. Degassed 1,4-dioxane (3.5 mL) and H_2O (1.0 mL) were added, then $Pd(PPh_3)_4$ (46 mg, 0.040 mmol, 0.10 eq.), the vial was capped, and the reaction was heated in a microwave to 140 °C for 1 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (3 mL) in a 25 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 4 mL, 16 mmol, 40 eq.) was added and the reaction was stirred at RT for 16 h, after which full conversion was apparent by TLC (hex/EtOAc 9:1). The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 19:1), another silica gel flash column chromatography (hex/EtOAc 9:1 to 2:1), another silica gel flash column chromatography (100% PhMe), automated reversed phase column chromatography (CH_3CN/H_2O 60:40 to 100:0), and another silica gel flash column chromatography (100% PhMe) to give the product as a white solid (40.2 mg, 0.071 mmol, 18%).

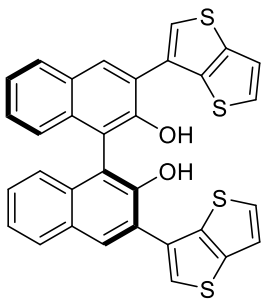
$\boldsymbol{R_F}$ (hex/EtOAc 9:1) = 0.21.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.36 (s, 2H), 7.98 (d, J = 8.2 Hz, 2H), 7.96 (s, 2H), 7.47–7.41 (m, 4H), 7.36–7.29 (m, 4H), 7.18–7.12 (m, 2H), 5.75 (s, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 149.88, 141.06, 140.12, 139.46, 132.66, 129.95, 129.56, 128.71, 128.00, 127.68, 125.01, 124.24, 124.03, 120.11, 119.65, 112.14.

ESI-HRMS: calculated for $C_{32}H_{17}O_2S_4^-$ ($[M-H]^-$): 561.011695, found: 561.012250.

(*S*)-3,3'-bis(thieno[3,2-*b*]thiophene-3-yl)-BINOL (386)



A 5 mL microwave vial was charged with (*S*)-MOM-BINOL Bpin ester (250 mg, 0.40 mmol, 1.00 eq.), 3-bromothieno[3,2-*b*]thiophene (**150**, 367 mg, 1.67 mmol, 4.20 eq.), and K_2CO_3 (331 mg, 2.40 mmol, 6.00 eq.) under argon. Degassed 1,4-dioxane (4.0 mL) and H_2O (1.2 mL) were added, then $Pd(PPh_3)_4$ (46 mg, 0.040 mmol, 0.10 eq.), the vial was capped, and the reaction was heated in a microwave to 140 °C for 1 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed

with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (3 mL) in a 25 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 2 mL, 8 mmol, 20 eq.) was added and the reaction was stirred at RT for 16 h, after which full conversion was apparent by TLC (hex/EtOAc 9:1). The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 19:1 to 1:1), and another silica gel flash column chromatography (hex/PhMe 1:1 to 3:7) to give the product as a yellow solid (219 mg, 0.389 mmol, 97%).

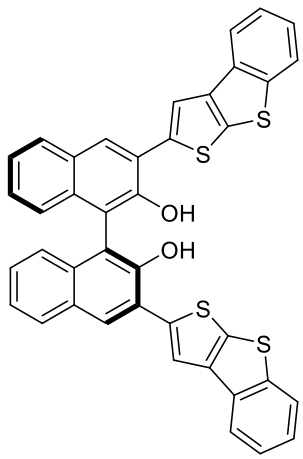
$\boldsymbol{R_F}$ (hex/EtOAc 9:1) = 0.23.

^{1}H-NMR (600 MHz, CD_2Cl_2): δ = 8.47–8.43 (m, 2H), 8.01 (dddd, J = 8.2, 1.3, 0.7, 0.4 Hz, 2H), 7.93 (d, J = 1.6 Hz, 2H), 7.51 (dd, J = 5.3, 1.6 Hz, 2H), 7.45 (ddd, J = 8.1, 6.8, 1.2 Hz, 2H), 7.40–7.34 (m, 4H), 7.23 (ddt, J = 8.5, 1.2, 0.7 Hz, 2H), 5.69 (q, J = 0.5 Hz, 2H).

^{13}C-NMR (151 MHz, CD_2Cl_2): δ = 150.79, 140.00, 139.34, 133.29, 130.59, 130.24, 129.84, 128.97, 128.09, 127.94, 127.18, 125.02, 124.47, 124.44, 120.11, 112.83.

ESI-HRMS: calculated for $C_{32}H_{17}O_2S_4^-$ ([M-H]$^-$): 561.011695, found: 561.011970.

(*S*)-3,3'-bis(benzo[*b*]thieno[3,2-*d*]thiophene-2-yl)-BINOL (387)



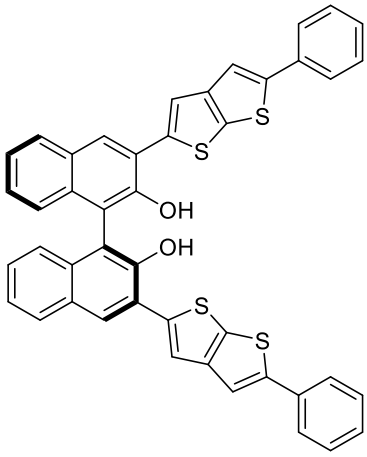
A 20 mL microwave vial was charged with (*S*)-MOM-BINOL Bpin ester (511 mg, 0.817 mmol, 1.00 eq.) and 2-bromobenzo[*b*]thieno[3,2-*d*]thiophene (**169**, 457 mg, 1.85 mmol, 2.26 eq.). 1,4-dioxane (8.5 mL) and K_2CO_3 (2.0 M in H_2O, 2.5 mL, 5.0 mmol, 6.1 eq.) were added and the solution was sparged with argon for 15 min. Subsequently, $Pd(PPh_3)_4$ (45.5 mg, 0.040 mmol, 0.05 eq.) was added and the reaction was heated in a microwave to 120 °C for 2 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (6 mL) in a 25 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 4 mL, 16 mmol, 20 eq.) was added and the reaction was stirred at RT for 16 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (PhMe/hex 1:1, then washed with 100% DCM), and automated reversed phase column chromatography (CH_3CN/H_2O 60:40 to 100:0, then 100% MTBE). Further purification via trituration from refluxing PhMe gave the desired product as a white solid (380 mg, 0.573 mmol, 72%).

^{1}H-NMR (600 MHz, CD_2Cl_2): δ = 8.45–8.42 (m, 2H), 8.23 (s, 2H), 8.01 (dddd, J = 9.6, 7.9, 1.3, 0.7 Hz, 4H), 7.88 (ddd, J = 8.0, 1.1, 0.7 Hz, 2H), 7.48 – 7.43 (m, 4H), 7.41–7.32 (m, 4H), 7.19 (ddt, J = 8.5, 1.2, 0.8 Hz, 2H), 5.82 (s, 2H).

^{13}C-NMR (151 MHz, CD_2Cl_2): δ = 150.05, 143.97, 142.58, 142.00, 138.75, 133.34, 133.10, 129.95, 129.92, 128.99, 128.16, 125.28, 125.16, 124.86, 124.41, 124.13, 123.61, 121.96, 119.50, 112.64.

ESI-HRMS: calculated for $C_{40}H_{21}O_2S_4^-$ ([M-H]$^-$): 661.042996, found: 661.043760.

(*S*)-3,3'-bis(5-phenylthieno[2,3-*b*]thiophen-2-yl)-BINOL (388)



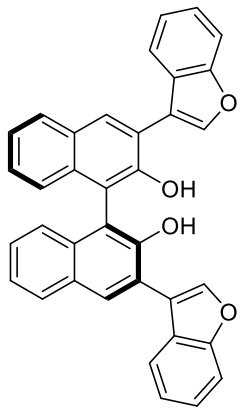
A 5 mL microwave vial was charged with (*S*)-MOM-BINOL Bpin ester (250 mg, 0.817 mmol, 1.00 eq.) and 2-bromo-5-phenylthieno[2,3-*b*]thiophene (**180**, 295 mg, 1.00 mmol, 2.50 eq.). 1,4-dioxane (4.2 mL) and K_2CO_3 (2.0 M in H_2O, 1.2 mL, 2.4 mmol, 6.0 eq.) were added and the solution was sparged with argon for 15 min. Subsequently, $Pd(PPh_3)_4$ (46 mg, 0.040 mmol, 0.10 eq.) was added and the reaction was heated to 130 °C for 16 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with Et_2O (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (3 mL) in a 25 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 2 mL, 8 mmol, 20 eq.) was added and the reaction was stirred at RT for 4 h after which full conversion was apparent by TLC (hex/EtOAc 9:1). The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/PhMe 70:30 to 0:100), then washed with 100% DCM) and automated reversed phase column chromatography (CH_3CN/H_2O 60:40 to 100:0) to give the product as an off-white solid (145 mg, 0.203 mmol, 51%).

^{1}H-NMR (600 MHz, CD_2Cl_2): δ = 8.37 (d, J = 0.7 Hz, 2H), 8.05–7.97 (m, 2H), 7.89 (s, 2H), 7.69–7.64 (m, 4H), 7.53 (s, 2H), 7.46–7.40 (m, 6H), 7.36–7.31 (m, 4H), 7.19–7.14 (m, 2H), 5.77 (s, 2H).

^{13}C-NMR (151 MHz, CD_2Cl_2): δ = 150.09, 148.11, 147.36, 142.00, 137.67, 135.01, 133.13, 130.09, 129.89, 129.42, 128.96, 128.24, 128.13, 126.14, 125.22, 124.42, 124.13, 120.61, 116.46, 112.68.

ESI-HRMS: calculated for $C_{44}H_{25}O_2S_4^-$ ([M-H]$^-$): 713.074295, found: 713.075260.

(*S*)-3,3'-bis(benzofuran-3-yl)-BINOL (389)



A 5 mL microwave vial was charged with (*S*)-MOM-BINOL Bpin ester (250 mg, 0.40 mmol, 1.00 eq.), 3-bromobenzofuran (**148**, 197 mg, 1.00 mmol, 2.50 eq.), and K_2CO_3 (331 mg, 2.39 mmol, 6.00 eq.) under argon. Degassed 1,4-dioxane (4.0 mL) and H_2O (1.2 mL), and lastly $Pd(PPh_3)_4$ (46 mg, 0.040 mmol, 10 mol%) were added, the vial was capped, and the reaction was heated in a microwave to 140 °C for 1 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (3.0 mL) in a 25 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 2.0 mL, 8.0 mmol, 20 eq.) was added and the reaction was stirred at RT for 16 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 19:1) and reversed phase automated flash column chromatography (CH_3CN/H_2O 60:40 to 100:0) to give the product as a white solid (150.2 mg, 0.290 mmol, 73%).

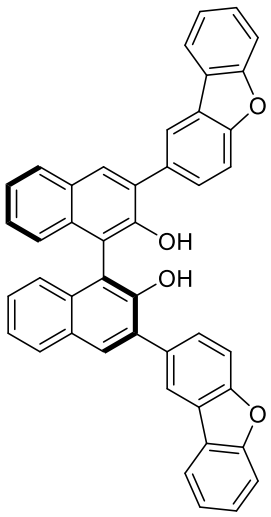
$\boldsymbol{R_F}$ (hex/EtOAc 9:1) = 0.32.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.41 (s, 2H), 8.18 (s, 2H), 8.02 (dt, J = 8.3, 0.9 Hz, 2H), 7.99–7.95 (m, 2H), 7.64–7.59 (m, 2H), 7.47–7.43 (m, 2H), 7.41 (td, J = 7.7, 1.7 Hz, 2H), 7.39–7.34 (m, 4H), 7.24 (dd, J = 8.4, 1.1 Hz, 2H), 5.60 (s, 2H).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 155.78, 150.98, 145.06, 133.21, 131.09, 129.94, 128.86, 127.91, 127.28, 125.09, 124.94, 124.47, 123.50, 121.53, 121.42, 117.35, 112.72, 112.10.

ESI-HRMS: calculated for $C_{36}H_{21}O_4^-$ ($[M-H]^-$): 517.144535, found: 517.144600.

(*S*)-3,3'-bis(dibenzofuran-2-yl)-BINOL (390)



A 5 mL microwave vial was charged with (*S*)-MOM-BINOL Bpin ester (250 mg, 0.40 mmol, 1.00 eq.), 2-bromodibenzofuran (**153**, 247 mg, 1.00 mmol, 2.50 eq.), and K_2CO_3 (331 mg, 2.39 mmol, 6.00 eq.) under argon. Degassed 1,4-dioxane (3.5 mL) and H_2O (1.0 mL), and lastly $Pd(PPh_3)_4$ (46 mg, 0.040 mmol, 10 mol%) were added, the vial was capped, and the reaction was heated to 140 °C in a microwave for 1 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with Et_2O (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (3.0 mL) in a 25 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 2.0 mL, 8.0 mmol, 20 eq.) was added and the reaction was stirred at RT for 16 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/PhMe/acetone 50:50:1 to 100% PhMe), but no separation could be achieved due to low solubility. Further purification by crystallization from $CHCl_3$ layered with *n*-pentane and subsequent trituration from hot PhMe gave the product as a white solid (103.1 mg, 0.167 mmol, 42%).

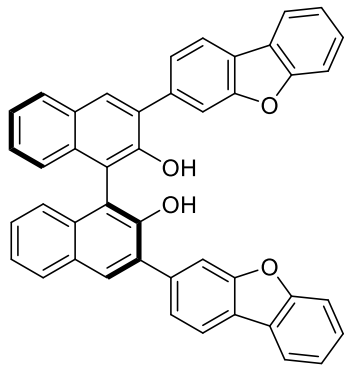
$\boldsymbol{R_F}$ (hex/EtOAc 9:1) = 0.24.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 8.33 (d, J = 1.8 Hz, 2H), 8.12 (s, 2H), 8.00 (dd, J = 8.2, 1.7 Hz, 2H), 7.97 (d, J = 8.4 Hz, 2H), 7.84 (dd, J = 8.5, 1.9 Hz, 2H), 7.69 (d, J = 8.5 Hz, 2H), 7.61 (d, J = 8.2 Hz, 2H), 7.49 (ddd, J = 8.4, 7.3, 1.4 Hz, 2H), 7.43 (ddd, J = 8.1, 6.8, 1.3 Hz, 2H), 7.37 (tdd, J = 7.5, 2.8, 1.1 Hz, 4H), 7.30 (d, J = 8.4 Hz, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.81, 156.00, 150.39, 133.12, 132.33, 131.83, 130.81, 129.70, 129.08, 128.62, 127.55, 127.51, 124.69, 124.61, 124.49, 124.34, 123.02, 122.02, 120.94, 112.65, 111.93, 111.77.

ESI-HRMS: calculated for $C_{44}H_{25}O_4^-$ ($[M-H]^-$): 617.175835, found: 617.176620.

(*S*)-3,3'-bis(dibenzofuran-3-yl)-BINOL (391)



A 5 mL microwave vial was charged with (*S*)-MOM-BINOL Bpin ester (250 mg, 0.40 mmol, 1.00 eq.), 3-bromodibenzofuran (**154**, 247 mg, 1.00 mmol, 2.50 eq.), and K_2CO_3 (331 mg, 2.39 mmol, 6.00 eq.) under argon. Degassed 1,4-dioxane (3.5 mL) and H_2O (1.0 mL), and lastly $Pd(PPh_3)_4$ (46 mg, 0.040 mmol, 10 mol%) were added, the vial was capped, and the reaction was heated to 140 °C in a microwave for 1 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with Et_2O (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (3.0 mL) in a 25 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 2.0 mL, 8.0 mmol, 20 eq.) was added and the reaction was stirred at RT for 16 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (100% PhMe). Further purification by crystallization from $CHCl_3$ layered with hexanes gave the product as a white solid (176 mg, 0.284 mmol, 71%).

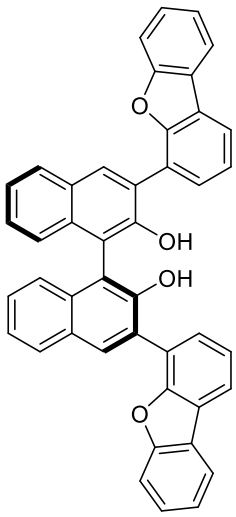
$\boldsymbol{R_F}$ (hex/EtOAc 9:1) = 0.16.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 8.14 (s, 2H), 8.06 (d, J = 8.0 Hz, 2H), 8.03–7.95 (m, 6H), 7.75 (dd, J = 8.0, 1.4 Hz, 2H), 7.60 (dt, J = 8.3, 0.8 Hz, 2H), 7.48 (ddd, J = 8.4, 7.3, 1.4 Hz, 2H), 7.43 (ddd, J = 8.1, 6.8, 1.3 Hz, 2H), 7.37 (tdd, J = 6.9, 2.4, 1.2 Hz, 4H), 7.29 (dd, J = 8.4, 1.1 Hz, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.85, 156.54, 150.35, 136.82, 133.16, 131.98, 130.64, 129.66, 128.72, 127.74, 127.43, 124.67, 124.61, 124.44, 124.19, 123.91, 122.98, 120.91, 120.59, 113.05, 112.60, 111.91.

ESI-HRMS: calculated for $C_{44}H_{25}O_4^-$ ([M-H]$^-$): 617.175835, found: 617.176540.

(*S*)-3,3'-bis(dibenzofuran-4-yl)-BINOL (392)



A 5 mL microwave vial was charged with (*S*)-MOM-BINOL Bpin ester (250 mg, 0.40 mmol, 1.00 eq.), 4-bromodibenzofuran (**152**, 247 mg, 1.00 mmol, 2.50 eq.), and K_2CO_3 (331 mg, 2.39 mmol, 6.00 eq.) under argon. Degassed 1,4-dioxane (3.5 mL) and H_2O (1.0 mL), and lastly $Pd(PPh_3)_4$ (46 mg, 0.040 mmol, 10 mol%) were added, the vial was capped, and the reaction was heated to 140 °C in a microwave for 1 h. After cooling to RT, the reaction was quenched by addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with Et_2O (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was dissolved in THF (3.0 mL) in a 25 mL round bottom flask under air. HCl (4.0 M in 1,4-dioxane, 2.0 mL, 8.0 mmol, 20 eq.) was added and the reaction was stirred at RT for 16 h. The mixture was diluted with EtOAc and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with EtOAc (3x), the combined organic phases were washed with aqueous saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (100% PhMe). Further purification by precipitation with *n*-pentane from $CHCl_3$ gave the product as a white solid (110 mg, 0.178 mmol, 45%).

$\boldsymbol{R_F}$ (hex/EtOAc 9:1) = 0.19.

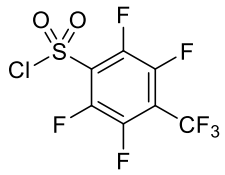
^{1}H-NMR (501 MHz, $CDCl_3$): δ = 8.29 (s, 2H), 8.05–7.97 (m, 6H), 7.77 (dd, J = 7.5, 1.2 Hz, 2H), 7.53 (d, J = 8.2 Hz, 2H), 7.49 (t, J = 7.6 Hz, 2H), 7.47–7.39 (m, 7H), 7.36 (t, J = 7.4 Hz, 2H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 156.31, 154.12, 150.73, 133.54, 132.73, 129.48, 129.01, 128.80, 127.72, 127.39, 125.78, 124.85, 124.72, 124.50, 124.46, 123.03, 122.96, 122.24, 120.87, 120.50, 112.93, 112.04.

ESI-HRMS: calculated for $C_{44}H_{25}O_4^-$ ([M-H]$^-$): 617.175835, found: 617.176400.

7.6.3. Synthesis of Phosphazene Reagents

2,3,5,6-tetrafluoro-4-(trifluoromethyl)benzenesulfonyl chloride (393)



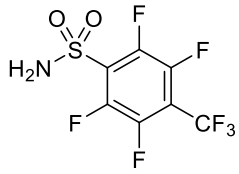
In a 100 mL round bottom flask, *N*-chlorosuccinimide (6.4 g, 48 mmol, 4.0 eq.) was suspended in aqueous HCl (2 M, 4 mL) and CH_3CN (20 mL) and the mixture was cooled to 0 °C. 2,3,5,6-tetrafluoro-4-(trifluoromethyl)benzenethiol (3.0 g, 12 mmol, 1.0 eq.) was added dropwise via pipette and a small amount of CH_3CN was used to transfer all material into the reaction flask. The mixture was stirred for 30 min at 0 °C, and another 30 min at RT, after which full conversion of the starting material was apparent by TLC (hex/EtOAc 9:1). The mixture was diluted with EtOAc, the layers were separated, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The material was redissolved in MTBE, washed with H_2O (2x) and brine (2x), dried over Na_2SO_4, and concentrated under reduced pressure to give the product as a yellow oil (3.35 g, 10.6 mmol, 88%). The crude material was used for the next step without further purification.

^{19}F-NMR (471 MHz, $CDCl_3$): δ = -56.89 (t, J = 22.2 Hz, 3F), (-132.04)–(-132.35) (m, 2F), (-134.45)–(-134.95) (m, 2F).

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 146.52–146.03 (m), 145.66–145.12 (m), 144.57–143.92 (m), 143.41–143.09 (m), 126.56 (t, J = 13.0 Hz), 120.36 (d, J = 276.8 Hz), 116.78–116.16 (m).

EI-HRMS: calculated for $C_7O_2S_1F_7Cl_1^+$ ($[M]^+$): 315.919030, found: 315.919200.

2,3,5,6-tetrafluoro-4-(trifluoromethyl)benzenesulfonamide (394)



A flame-dried 250 mL round bottom flask under argon was charged with 2,3,5,6-tetrafluoro-4-(trifluoromethyl)benzenesulfonyl chloride (**393**, 3.26 g, 10.3 mmol, 1.00 eq.). The material was dissolved in dry THF (95 mL) and cooled to below -40 °C. Ammonia (0.5 M in 1,4-dioxane) was added via syringe pump (0.4 mL min^{-1}) and the reaction was followed by ^{19}F-NMR. Full conversion of the starting material was reached after addition of 2 eq. NH_3, after which the reaction was quenched by addition of HCl (1.2 M, 100 mL) and warmed to RT. The aqueous layer was extracted with EtOAc (3x), and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 3:1) to give the product as a white solid (2.57 g, 8.64 mmol, 84%).

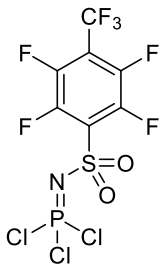
^{1}H-NMR (501 MHz, DMSO): δ = 8.64 (s, 2H).

^{19}F-NMR (471 MHz, DMSO): δ = -56.16 (t, J = 21.6 Hz, 3F), (-137.10)–(-137.27) (m, 2F), -139.67 (qq, J = 23.0, 12.9 Hz, 2F).

^{13}C-NMR (126 MHz, DMSO): δ = 144.05 (dd, J = 260.2, 17.5 Hz), 143.02 (dd, J = 255.6, 14.8 Hz), 127.07 (t, J = 15.3 Hz), 120.35 (q, J = 274.4 Hz), 111.10–110.25 (m).

ESI-HRMS: calculated for $C_7H_1F_7N_1O_2S_1^-$ ($[M-H]^-$): 295.962176, found: 295.962290.

((2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)sulfonyl)phosphorimidoyl trichloride (395)



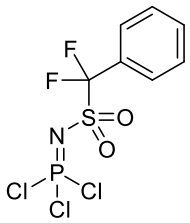
A flame-dried Schlenk under argon was charged with 2,3,5,6-tetrafluoro-4-(trifluoromethyl)benzenesulfonamide **394** (533 mg, 1.79 mmol, 1.00 eq.), PCl_5 (560 mg, 2.69 mmol, 1.50 eq.) and dry PhMe (5 mL). The reaction was heated to 110 °C for 2 h after which no full conversion was apparent by ^{19}F-NMR. The solvent was removed under reduced pressure, an excess of PCl_5 was added, and heating to 100°C was continued under a stream of argon for 2 h. A finger condenser was attached to the flask and the mixture was heated to 130 °C to remove excess PCl_5 and $POCl_3$ by sublimation. After cooling to RT and removal of any remaining volatiles under reduced pressure, the product was obtained as a colorless solid (775 mg, 1.79 mmol, quant.) and used for the IDPi synthesis without further purification.

^{19}F-NMR (471 MHz, $CDCl_3$): δ = -56.74 (t, J = 21.8 Hz, 3F), (-134.26)–(-134.45) (m, 2F), -137.20 (dddd, J = 29.9, 21.4, 12.8, 7.9 Hz, 2F).

^{31}P-NMR (203 MHz, $CDCl_3$): δ = 9.91.

EI-HRMS: calculated for $C_7N_1O_2P_1S_1F_7Cl_3^+$ ($[M]^+$): 430.833574, found: 430.833370.

((difluoro(phenyl)methyl)sulfonyl)phosphorimidoyl trichloride (396)



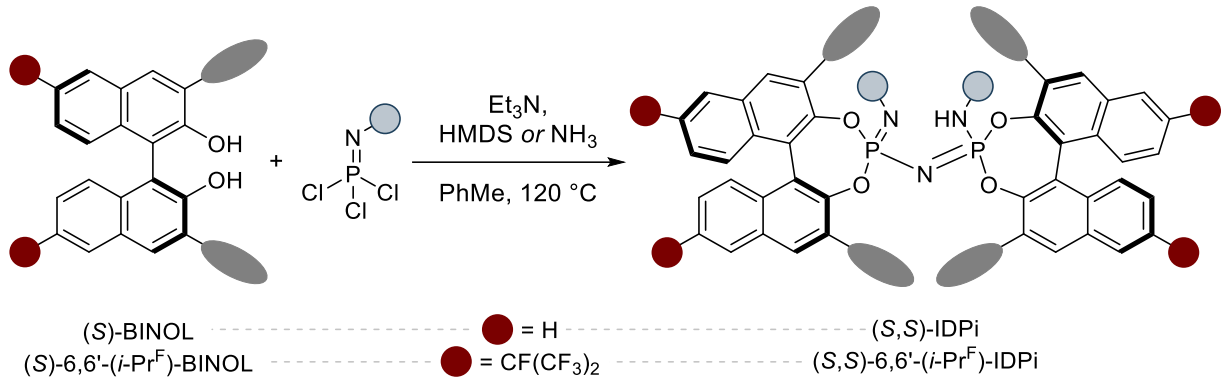
A flame-dried Schlenk under argon was charged with 1,1-difluoro-1-phenylmethanesulfonamide[235] (200 mg, 0.965 mmol, 1.00 eq.) and PCl_5 (331.8 mg, 1.59 mmol, 1.65 eq.). The reaction was heated to 80 °C, upon which a homogeneous liquid phase was obtained. Heating was continued under a continuous stream of argon for 4 h, after which full conversion of the starting material was apparent by ^{19}F-NMR. A finger condenser was attached to the flask and the mixture was heated to 130 °C to remove excess PCl_5 and $POCl_3$ by sublimation. After cooling to RT and removal of any remaining volatiles under reduced pressure, the product was obtained as a light brown solid (287 mg, 0.838 mmol, 87%) and used for the IDPi synthesis without further purification.

^{1}H-NMR (501 MHz, $CDCl_3$): δ = 7.73 (dd, J = 7.6, 1.7 Hz, 2H), 7.60–7.54 (m, 1H), 7.50 (t, J = 7.4 Hz, 2H).

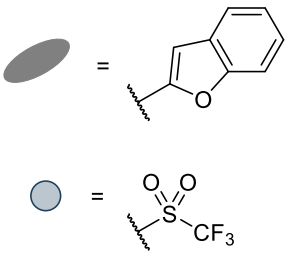
^{19}F-NMR (471 MHz, $CDCl_3$): δ = -101.89 (d, J = 3.4 Hz).

^{31}P-NMR (203 MHz, $CDCl_3$): δ = 10.46.

7.6.4. Synthesis of (*S*,*S*)-IDPi Catalysts



IDPi 143a



(*S*)-BINOL **359** (75.0 mg, 0.145 mmol, 2.01 eq.) was placed in a flame-dried Young-Schlenk under Argon and dissolved in toluene (1.5 mL). $P(NTf)Cl_3$ (23.0 µL, 0.144 mmol, 2.00 eq.) and subsequently Et_3N (80.0 µL, 0.574 mmol, 7.99 eq.) were added to the reaction. The mixture was stirred at room temperature for 30 min. HMDS (15.0 µL, 0.072 mmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 15 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 2:1) and another silica gel flash column chromatography (DCM/EtOAc 19:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as a beige solid (85.0 mg, 0.061 mmol, 84%).

R_F (hex/EtOAc 2:1) = 0.28.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.64 (s, 2H), 8.12–8.06 (m, 2H), 8.06–8.00 (m, 2H), 7.88 (ddd, J = 8.0, 6.7, 1.1 Hz, 2H), 7.70–7.62 (m, 6H), 7.57 (ddd, J = 8.1, 6.7, 1.1 Hz, 2H), 7.48–7.40 (m, 4H), 7.39–7.29 (m, 4H), 7.29–7.16 (m, 6H), 7.16–7.11 (m, 2H), 6.91 (d, J = 15.1 Hz, 4H), 6.84 (ddd, J = 8.4, 7.1, 1.2 Hz, 2H), 6.80 (s, 2H), 6.63 (td, J = 7.4, 1.1 Hz, 2H).

^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -78.30.

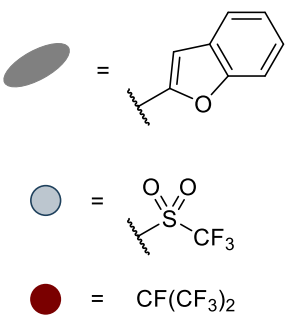
^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -16.89.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 155.04, 154.44, 148.89, 148.60, 144.18, 143.40, 132.70, 132.40, 131.34, 130.06, 129.39, 129.13, 128.88, 128.83, 128.32, 128.23, 128.00, 127.69, 127.60, 126.66, 126.23, 125.85, 125.78, 125.69, 123.92, 123.75, 123.61, 123.31, 123.17, 122.07, 122.00, 121.52, 111.52, 110.90, 109.35, 109.10.

ESI-HRMS: calculated for $C_{74}H_{40}N_3O_{12}P_2S_2F_6^-$ ($[M-H]^-$): 1402.143846, found: 1402.145400.

$[\alpha]_D^{25}$ = +573.4 (*c* = 0.22, $CHCl_3$).

IDPi 143a[6,6']



(*S*)-6,6'-(*i*-Pr^F)-BINOL **360** (30 mg, 0.035 mmol, 2.0 eq.) was placed in a flame-dried Young-Schlenk under Argon and dissolved in toluene (0.5 mL). P(NTf)Cl_3 (5.6 µL, 0.035 mmol, 2.0 eq.) and subsequently Et_3N (20 µL, 0.14 mmol, 8.1 eq.) were added to the reaction. The mixture was stirred at room temperature for 30 min. HMDS (3.7 µL, 0.018 mmol, 1.0 eq.) was added, the mixture was stirred at room temperature for 15 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 9:1 to 4:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as a white solid (33.8 mg, 0.016 mmol, 92%).

***R*$_F$** (hex/EtOAc 2:1) = 0.13.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.76 (s, 2H), 8.46 (d, J = 2.0 Hz, 2H), 8.40 (d, J = 2.0 Hz, 2H), 7.89 (d, J = 9.0 Hz, 2H), 7.67 (t, J = 8.3 Hz, 4H), 7.54 (d, J = 9.1 Hz, 2H), 7.51 (s, 2H), 7.49–7.42 (m, 4H), 7.39–7.31 (m, 4H), 7.16 (d, J = 7.7 Hz, 2H), 7.11 (s, 2H), 7.02 (s, 2H), 6.91 (t, J = 7.7 Hz, 2H), 6.86 (d, J = 8.2 Hz, 2H), 6.69 (t, J = 7.4 Hz, 2H).

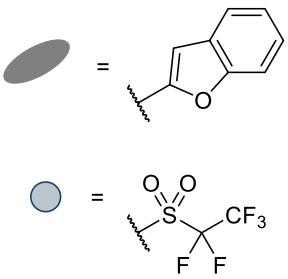
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = (-75.21)–(-75.44) (m, 12F), (-75.47)–(-75.59) (m, 6F), (-75.59)–(-75.69) (m, 6F), -78.46 (s, 6F), -182.10 (h, J = 7.2 Hz, 2F), -182.17 (s, 2F).

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -16.07.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 154.79, 154.57, 149.98, 149.65, 142.71 (t, J = 5.2 Hz), 141.58(t, J = 5.3 Hz), 132.21, 132.03, 131.96, 131.93, 129.92, 129.70, 129.50, 129.08, 129.03, 128.94, 128.15, 127.88, 127.88, 127.45, 127.27, 127.25, 125.65, 125.08, 123.65, 123.30, 122.97, 122.05, 122.03, 121.94, 121.86, 121.68, 119.86 (qt, J = 320.4, 2.6 Hz), 111.35, 110.82, 108.36, 107.67.

ESI-HRMS: calculated for $C_{74}H_{40}N_3O_{12}P_2S_2F_6^-$ ([M-H]$^-$): 1402.143846, found: 1402.145400.

IDPi 143c



(*S*)-BINOL **359** (76.4 mg, 0.147 mmol, 2.05 eq.) was placed in a flame-dried Young-Schlenk under Argon and dissolved in toluene (0.75 mL). P($NSO_2C_2F_5$)Cl_3 (26.0 µL, 0.144 mmol, 2.00 eq.) and subsequently Et_3N (80.0 µL, 0.574 mmol, 7.99 eq.) were added to the reaction. The mixture was stirred at room temperature for 30 min. HMDS (15.0 µL, 0.072 mmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 15 min and subsequently heated to 120 °C for 3 d. After cooling to room

temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (toluene/EtOAc 19:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as a beige solid (92.6 mg, 0.062 mmol, 86%).

$\boldsymbol{R_F}$ (hex/EtOAc 2:1) = 0.24.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.65 (s, 2H), 8.08 (d, J = 8.3 Hz, 2H), 7.97 (d, J = 8.2 Hz, 2H), 7.86 (t, J = 7.4 Hz, 2H), 7.66 (t, J = 7.8 Hz, 6H), 7.55 (t, J = 7.6 Hz, 2H), 7.48 (d, J = 8.6 Hz, 2H), 7.44 (t, J = 7.7 Hz, 2H), 7.36 (t, J = 7.4 Hz, 2H), 7.28 (q, J = 5.9, 3.9 Hz, 2H), 7.20–7.12 (m, 6H), 6.94 (s, 2H), 6.87 (dt, J = 15.3, 8.1 Hz, 4H), 6.72 (s, 2H), 6.63 (t, J = 7.4 Hz, 2H).

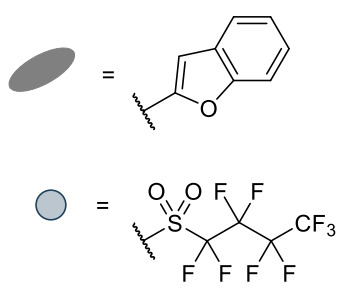
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -78.68 (s, 6F), -116.13 (s, 4F).

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -17.24.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 154.77, 154.61, 150.04, 149.49, 142.81 (t, J = 5.3 Hz), 141.48 (t, J = 5.0 Hz), 132.20, 132.03, 131.90, 130.07, 129.72, 129.49, 129.11, 129.05, 129.00, 128.15, 127.89, 127.85, 127.37, 127.28, 127.27, 125.62, 125.17, 123.61, 123.31, 123.04, 122.05, 121.97, 121.91, 121.82, 121.74, 111.32, 110.77, 108.39, 107.66.

ESI-HRMS: calculated for $C_{86}H_{36}N_3O_{12}S_2F_{34}P_2^-$ ([M-H]$^-$): 2074.067844, found: 2074.067820.

IDPi 143d



(*S*)-BINOL **359** (76.4 mg, 0.147 mmol, 2.05 eq.) was placed in a flame-dried Young-Schlenk under Argon and dissolved in toluene (0.75 mL). $P(NSO_2C_4F_9)Cl_3$ (34.0 µL, 0.146 mmol, 2.04 eq.) and subsequently Et_3N (80.0 µL, 0.574 mmol, 7.99 eq.) were added to the reaction. The mixture was stirred at room temperature for 30 min. HMDS (15.0 µL, 0.072 mmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 15 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (toluene/EtOAc 19:1), another silica gel flash column chromatography (DCM/MeOH 119:1 to 99:1), another silica gel flash column chromatography (hex/acetone 3:1 to 2:1), and a final automated reversed phase silica gel chromatography (C18, CH_3CN/H_2O 60:40 to 100:0). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as a beige solid (33.7 mg, 0.020 mmol, 28%).

$\boldsymbol{R_F}$ (hex/EtOAc 2:1) = 0.21.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.62 (s, 2H), 8.09 (d, J = 8.3 Hz, 2H), 8.02 (d, J = 8.2 Hz, 2H), 7.90 (dd, J = 8.1, 6.8 Hz, 2H), 7.72–7.66 (m, 2H), 7.62 (d, J = 8.3 Hz, 2H), 7.58 (t, J = 7.2 Hz,

4H), 7.47 (d, J = 8.6 Hz, 2H), 7.39 (ddd, J = 8.4, 7.2, 1.3 Hz, 2H), 7.35–7.26 (m, 4H), 7.26–7.17 (m, 4H), 7.09 (d, J = 7.6 Hz, 2H), 6.97 (s, 2H), 6.86 (d, J = 8.2 Hz, 2H), 6.84–6.80 (m, 2H), 6.74 (s, 2H), 6.59 (td, J = 7.4, 1.2 Hz, 2H).

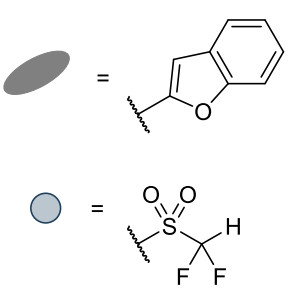
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -81.01 (t, J = 9.9 Hz, 6F), -111.98 (s, 4F), -121.02 (s, 4F), -125.96 (t, J = 15.5 Hz, 4F).

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -16.92.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 154.70, 154.55, 150.02, 149.52, 142.85 (t, J = 5.3 Hz), 141.69 (t, J = 5.6 Hz), 132.22, 132.03, 131.96, 131.92, 130.07, 129.69, 129.51, 129.15, 128.99, 128.90, 128.10, 127.93, 127.79, 127.35, 127.32, 127.22, 125.55, 125.07, 123.48, 123.33, 122.97, 122.08, 122.06, 121.78, 121.63, 111.26, 110.71, 108.43, 107.71.

ESI-HRMS: calculated for $C_{80}H_{40}F_{18}N_3O_{12}P_2S_2^-$ ([M-H]$^-$): 1702.124688, found: 1702.125780.

IDPi 143e



(*S*)-BINOL **359** (76.4 mg, 0.147 mmol, 2.05 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2CF_2H)Cl_3$ (20.6 mg, 0.0771 mmol, 2.00 eq.) and toluene (0.50 mL) under Argon. Et_3N (80.0 µL, 0.574 mmol, 7.99 eq.) was added and the mixture was stirred at room temperature for 30 min. HMDS (15.0 µL, 0.072 mmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 15 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 2:1), and another silica gel flash column chromatography (DCM/EtOAc 19:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as a beige solid (36.0 mg, 0.026 mmol, 68%).

***R*$_F$** (hex/EtOAc 1:1) = 0.23.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.62 (s, 2H), 8.07 (dd, J = 8.3, 5.8 Hz, 4H), 7.89 (t, J = 7.5 Hz, 2H), 7.70–7.62 (m, 6H), 7.59–7.53 (m, 2H), 7.44–7.38 (m, 4H), 7.35–7.28 (m, 6H), 7.21 (d, J = 8.5 Hz, 2H), 7.09 (d, J = 7.6 Hz, 2H), 6.93–6.86 (m, 6H), 6.83–6.76 (m, 2H), 6.59 (t, J = 7.5 Hz, 2H), 6.19 (t, J = 53.9 Hz, 2H).

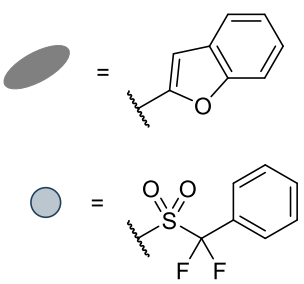
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -120.80 (d, J = 265.4 Hz, 2F), -122.62 (d, J = 265.1 Hz, 2F).

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -15.98.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 154.73, 154.54, 150.10, 149.61, 142.88 (t, J = 5.0 Hz), 141.75 (t, J = 5.1 Hz), 132.22, 131.95, 131.93, 129.85, 129.47, 129.09, 128.84, 128.68, 128.06, 127.86, 127.75, 127.38, 127.21, 127.13, 125.55, 124.98, 123.57, 123.37, 122.85, 122.19, 122.04, 121.71, 113.75 (t, J = 281.4 Hz), 111.27, 110.78, 108.70, 107.77.

ESI-HRMS: calculated for $C_{74}H_{42}N_3O_{12}S_2F_4P_2^-$ ([M-H]$^-$): 1366.162689, found: 1366.162670.

IDPi 143f



(*S*)-BINOL **359** (121 mg, 0.234 mmol, 1.99 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2CF_2Ph)Cl_3$ (**396**, 80.0 mg, 0.234 mmol, 2.00 eq.) and toluene (3.60 mL) under Argon. Et_3N (130 µL, 0.933 mmol, 7.95 eq.) was added and the mixture was stirred at room temperature for 30 min. HMDS (15.0 µL, 0.072 mmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 15 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 9:1 to 1:1), and another silica gel flash column chromatography (DCM/EtOAc 19:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as a beige solid (68.3 mg, 0.045 mmol, 38%).

R_F (DCM/EtOAc 9:1) = 0.56.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.60 (s, 2H), 8.05 (t, J = 8.4 Hz, 4H), 7.88 (t, J = 7.5 Hz, 2H), 7.66 (t, J = 7.7 Hz, 2H), 7.60 (d, J = 8.3 Hz, 2H), 7.58–7.50 (m, 8H), 7.48–7.40 (m, 4H), 7.35 (t, J = 7.7 Hz, 2H), 7.32–7.27 (m, 6H), 7.26 (s, 2H), 7.23–7.12 (m, 8H), 6.99 (s, 2H), 6.92 (d, J = 8.3 Hz, 2H), 6.82 (t, J = 7.7 Hz, 2H), 6.57 (t, J = 7.5 Hz, 2H).

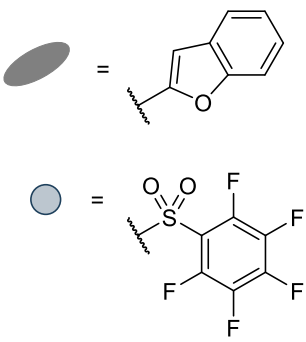
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -100.61 (d, J = 226.6 Hz, 2F), -101.84 (d, J = 226.4 Hz, 2F).

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -14.92.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 154.64, 154.50, 150.21, 149.56, 143.25, 141.97, 132.43, 132.24, 131.93, 131.90, 131.86, 129.98, 129.94, 129.44, 129.31, 128.79, 128.67, 128.39, 127.94, 127.88, 127.83, 127.78, 127.53, 127.30, 127.16, 126.95, 125.35, 124.92, 123.38, 123.32, 122.75, 122.36, 122.26, 122.23, 122.01, 121.83, 121.48 (t, 283.0 Hz), 111.08, 110.75, 108.98, 107.89, 107.87.

ESI-HRMS: calculated for $C_{86}H_{50}N_3O_{12}S_2F_4P_2^-$ ($[M-H]^-$): 1518.225289, found: 1518.226560.

IDPi 143b



(*S*)-BINOL **359** (1.06 g, 2.05 mmol, 2.03 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2C_6F_5)Cl_3$ (782 mg, 2.04 mmol, 2.03 eq.) and the solids were gently heated to 50 °C with a heat gun under high vacuum for 10 min. The mixture was placed under argon and suspended in dry toluene (20 mL). Et_3N (1.2 mL, 8.6 mmol, 8.6 eq.) was added and the mixture was stirred at room temperature for 1 h. HMDS (210 µL, 1.01 mmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to

120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (100% DCM). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (825 mg, 0.516 mmol, 51%).

$\boldsymbol{R_F}$ (hex/EtOAc 2:1) = 0.17.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.55 (s, 2H), 8.12 (d, J = 8.1 Hz, 2H), 8.07 (d, J = 8.3 Hz, 2H), 7.87 (ddd, J = 8.1, 6.7, 1.1 Hz, 2H), 7.73 (d, J = 7.4 Hz, 2H), 7.63–7.55 (m, 6H), 7.52 (s, 2H), 7.40 (ddd, J = 8.4, 7.1, 1.3 Hz, 2H), 7.31 (dddd, J = 15.9, 8.2, 7.1, 1.1 Hz, 4H), 7.23 (d, J = 8.6 Hz, 2H), 7.19 (d, J = 8.5 Hz, 2H), 7.12–7.06 (m, 6H), 6.83–6.77 (m, 4H), 6.61–6.54 (m, 2H).

^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -136.71 (d, J = 21.3 Hz, 4F), -145.73 (t, J = 21.5 Hz, 2F), -159.61 (t, J = 20.7 Hz, 4F).

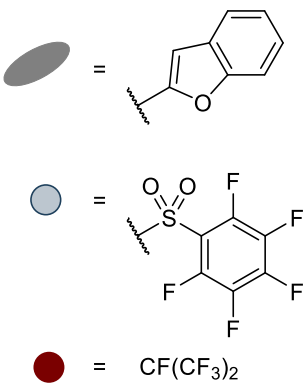
^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -16.65.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 154.49, 154.32, 149.80, 149.43, 142.45 (t, J = 5.4 Hz), 141.72 (t, J = 5.0 Hz), 132.02, 132.01, 131.82, 131.80, 129.67, 129.58, 129.31, 129.18, 128.78, 128.03, 128.00, 127.89, 127.73, 127.43, 127.36, 127.09, 125.77, 124.87, 123.65, 123.16 (t, J = 1.6 Hz), 122.73, 122.35, 122.07 (t, J = 1.5 Hz), 121.77 (t, J = 1.8 Hz), 121.72, 111.03, 110.80, 108.90, 107.99.

ESI-HRMS: calculated for $C_{84}H_{40}N_3O_{12}S_2P_2F_{10}^-$ ([M-H]$^-$): 1598.137460, found: 1598.136910.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{25}}$ = +492.8 (*c* = 0.39, $CHCl_3$).

IDPi 143b$^{6,6'}$



(*S*)-6,6'-(*i*-Pr^F)-BINOL **360** (37.3 mg, 0.044 mmol, 2.00 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2C_6F_5)Cl_3$ (16.7 mg, 0.044 mmol, 2.00 eq.). The mixture was placed under argon and suspended in dry toluene (0.5 mL). Et_3N (24.5 µL, 0.18 mmol, 8.0 eq.) was added and the mixture was stirred at room temperature for 30 min. NH_3 (0.34 M in 1,4-dioxane, 63.5 µL, 0.022 mmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 9:1 to 2:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (25.1 mg, 0.011 mmol, 51%).

$\boldsymbol{R_F}$ (hex/EtOAc 1:1) = 0.17.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.67 (s, 2H), 8.45 (d, J = 2.0 Hz, 2H), 8.39 (d, J = 2.0 Hz, 2H), 7.83 (d, J = 9.1 Hz, 2H), 7.76 (d, J = 7.7 Hz, 2H), 7.66–7.59 (m, 4H), 7.54 (dd, J = 8.9, 1.9 Hz, 2H), 7.46–7.41 (m, 2H), 7.37–7.19 (m, 10H), 7.14 (d, J = 7.7 Hz, 2H), 6.91–6.86 (m, 2H), 6.79 (d, J = 8.3 Hz, 2H), 6.65 (t, J = 7.4 Hz, 2H).

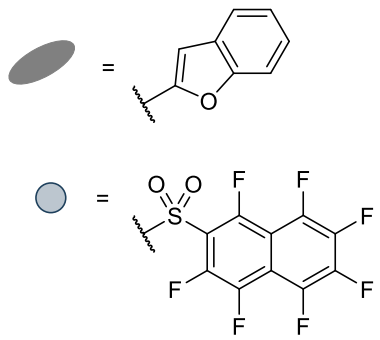
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = (-75.26)–(-75.48) (m, 12F), (-75.49)–(-75.61) (m, 6F), (-75.62)–(-75.74) (m, 6F), (-135.84)–(-137.52) (m, 4F), -145.36 (s, 2F), -159.29 (s, 4F), -182.02 (h, J = 7.6 Hz, 2F), (-182.07)–(-182.18) (m, 2F).

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -16.45.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 154.71, 154.30, 148.57, 144.01, 132.51, 132.28, 131.35, 131.14, 129.28, 129.16, 128.98, 128.93, 128.69, 128.17, 128.08, 127.84, 127.66, 127.59, 126.39, 125.96, 125.80, 125.66, 124.03, 123.96, 123.84, 123.27, 123.15, 123.01, 122.59, 122.06, 121.71, 111.20, 110.81, 109.89, 109.35.

ESI-HRMS: calculated for $C_{96}H_{36}N_3O_{12}S_2F_{38}P_2^-$ ([M-H]$^-$): 2270.061458, found: 2270.060790.

IDPi 143g



(*S*)-BINOL **359** (59.2 mg, 0.114 mmol, 2.01 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2C_{10}F_7)Cl_3$ (53.3 mg, 0.113 mmol, 2.00 eq.) and toluene (0.60 mL) under Argon. Et_3N (63.0 µL, 0.452 mmol, 7.96 eq.) was added and the mixture was stirred at room temperature for 20 min. NH_3 (0.344 M in 1,4-dioxane, 165 µL, 56.8 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 20 h. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 9:1 to 4:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as a white solid (24.8 mg, 0.014 mmol, 25%).

R_F (hex/EtOAc 2:1) = 0.14.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.48 (s, 1H), 8.11 (d, J = 8.2 Hz, 1H), 7.99 (d, J = 8.3 Hz, 1H), 7.83 (t, J = 7.5 Hz, 1H), 7.66 (d, J = 7.7 Hz, 1H), 7.57–7.47 (m, 4H), 7.44 (d, J = 8.3 Hz, 1H), 7.30–7.22 (m, 2H), 7.19–7.08 (m, 4H), 7.00 (d, J = 7.7 Hz, 1H), 6.80–6.72 (m, 2H), 6.52 (ddd, J = 7.9, 4.9, 3.3 Hz, 1H).

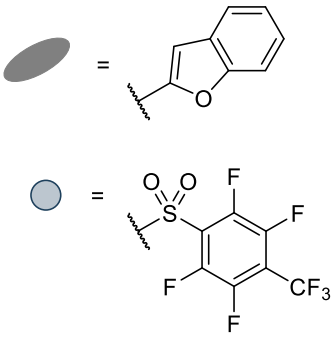
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -109.74 (d, J = 76.9 Hz, 1F), -134.14 (1F), -139.27 (d, J = 77.3 Hz, 1F), -143.33 (d, J = 57.8 Hz, 1F), -144.71 (d, J = 59.1 Hz, 1F), -147.76 (1F), -152.54 (1F).

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -15.02.

^{13}C-NMR (151 MHz, CD_2Cl_2): δ = 154.22, 149.76, 149.48, 142.48, 141.73, 131.95, 131.88, 131.77, 129.57, 129.21, 129.13, 128.83, 127.96, 127.76, 127.63, 127.38, 127.14, 125.48, 124.79, 123.37, 123.04, 122.62, 122.42, 122.30, 122.02, 121.61, 110.73, 110.63, 108.68, 107.95, 107.69. *Other signals could not be observed due to significant peak broadening.*

ESI-HRMS: calculated for $C_{92}H_{40}F_{14}N_3O_{12}P_2S_2^-$ ([M-H]$^-$): 1770.131074, found: 1770.132240.

IDPi 143h



(*S*)-BINOL **359** (139 mg, 0.268 mmol, 2.00 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2(4\text{-}CF_3\text{-}C_6F_4))Cl_3$ (**395**, 116 mg, 0.268 mmol, 2.00 eq.) and toluene (2.00 mL) under Argon. Et_3N (150 µL, 1.08 mmol, 8.02 eq.) was added and the mixture was stirred at room temperature for 20 min. HMDS (28.0 µL, 134 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 15 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 2:1 to 1:1) and a second silica gel flash column chromatography (DCM/MeOH 99:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as a white solid (173 mg, 0.102 mmol, 76%).

$\boldsymbol{R_F}$ (hex/EtOAc 1:1) = 0.27.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.56 (s, 2H), 8.08 (t, J = 8.0 Hz, 4H), 7.83 (dd, J = 9.9, 7.2 Hz, 4H), 7.65 (d, J = 8.3 Hz, 2H), 7.57 (dt, J = 12.4, 7.5 Hz, 4H), 7.48 (s, 2H), 7.43 (t, J = 7.7 Hz, 2H), 7.33 (dt, J = 15.2, 7.4 Hz, 4H), 7.26 (d, J = 8.7 Hz, 2H), 7.19 (q, J = 6.0, 4.5 Hz, 4H), 7.14 (d, J = 7.7 Hz, 2H), 7.08 (s, 2H), 6.84 (d, J = 4.1 Hz, 4H), 6.62 (dp, J = 8.9, 4.9 Hz, 2H).

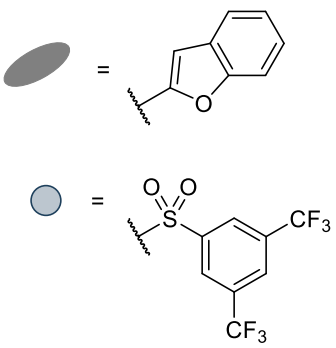
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -56.77 (t, J = 21.6 Hz, 6F), -134.99 (dd, J = 23.0, 12.5 Hz, 4F), -137.74 (s, 4F).

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -17.05.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 154.54, 154.35, 149.82, 149.55, 145.21 (dd, J = 60.3, 15.9 Hz), 143.12 (dd, J = 58.4, 15.8 Hz), 142.55 (t, J = 5.0 Hz), 141.71 (t, J = 4.8 Hz), 132.04, 131.98, 131.91, 131.81, 129.67, 129.61, 129.36, 129.17, 128.84, 128.22, 128.04, 127.97, 127.73, 127.44, 127.34, 127.17, 125.86, 124.95, 123.76, 123.20, 122.82, 122.33, 121.98, 121.73, 120.50 (q, J = 276.6 Hz), 111.17, 110.84, 108.87, 107.92.

ESI-HRMS: calculated for $C_{86}H_{40}N_3O_{12}P_2S_2F_{14}^-$ ([M-H]$^-$): 1698.131074, found: 1698.131820.

IDPi 143j



(*S*)-BINOL **359** (89.0 mg, 0.172 mmol, 2.05 eq.) was added to a flame-dried Young-Schlenk charged with P(NSO_2(3,5-(CF_3)$_2$-C_6H_3))Cl_3 (73.5 mg, 0.172 mmol, 2.00 eq.) and toluene (1.80 mL) under Argon. Et_3N (95.0 µL, 0.682 mmol, 8.13 eq.) was added and the mixture was stirred at room temperature for 20 min. HMDS (17.5 µL, 83.8 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 4 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 49:1 to 4:1), a second silica gel flash column chromatography (toluene/EtOAc 19:1) and another silica gel flash column chromatography (DCM/EtOAc 100:0 to 19:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as a white solid (24.4 mg, 0.014 mmol, 17%).

$\boldsymbol{R_F}$ (hex/EtOAc 2:1) = 0.53.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.57 (s, 2H), 8.15 (d, J = 8.1 Hz, 2H), 8.07 (d, J = 8.3 Hz, 2H), 7.99 (s, 4H), 7.88 (t, J = 7.5 Hz, 2H), 7.65–7.53 (m, 10H), 7.48 (d, J = 8.3 Hz, 2H), 7.36–7.29 (m, 4H), 7.28–7.17 (m, 6H), 7.07 (d, J = 19.5 Hz, 4H), 6.99 (d, J = 7.7 Hz, 2H), 6.83–6.73 (m, 4H), 6.57–6.49 (m, 2H).

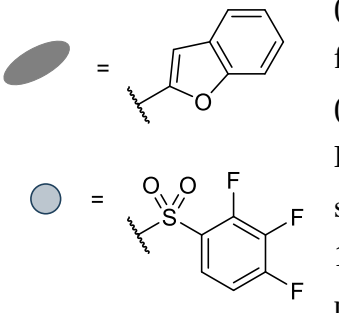
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -63.19.

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -14.80.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 154.28, 154.19, 149.87, 149.14, 144.15, 142.86, 141.86, 132.37, 132.10, 132.05, 132.03, 131.92, 131.82, 129.64, 129.49, 129.44, 129.14, 128.64, 128.10, 127.95, 127.80, 127.40, 127.22, 127.12, 126.60, 125.99, 125.55, 124.79, 123.80, 123.50, 123.27, 122.61, 122.36, 122.22, 122.15, 121.74, 121.67, 121.63, 119.46, 111.06, 110.83, 109.23, 107.98.

ESI-HRMS: calculated for $C_{88}H_{46}N_3O_{12}S_2F_{12}P_2^-$ ([M-H]$^-$): 1690.181217, found: 1690.181740.

IDPi 143k



(*S*)-BINOL **359** (40.0 mg, 0.0771 mmol, 2.01 eq.) was added to a flame-dried Young-Schlenk charged with P(NSO_2(2,3,4-F_3-C_6H_2))Cl_3 (27.1 mg, 0.0782 mmol, 2.04 eq.) and toluene (0.50 mL) under Argon. Et_3N (43.0 µL, 0.309 mmol, 8.05 eq.) was added and the mixture was stirred at room temperature for 30 min. HMDS (8.00 µL, 38.3 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 15 min and subsequently heated to 120 °C for 4 d. After cooling to room

temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 19:1 to 4:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (42.4 mg, 0.028 mmol, 72%).

R_F (hex/EtOAc 2:1) = 0.26.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.56 (s, 2H), 8.10 (d, J = 8.2 Hz, 2H), 8.06 (d, J = 8.3 Hz, 2H), 7.85 (t, J = 7.4 Hz, 2H), 7.76 (d, J = 7.6 Hz, 2H), 7.62 (d, J = 8.3 Hz, 2H), 7.60 – 7.52 (m, 4H), 7.47 (s, 2H), 7.39 (ddd, J = 8.4, 7.1, 1.4 Hz, 2H), 7.33–7.26 (m, 4H), 7.20 (dt, J = 29.5, 8.6 Hz, 8H), 7.09 (d, J = 7.7 Hz, 2H), 6.99 (s, 2H), 6.81 (d, J = 3.9 Hz, 4H), 6.63–6.55 (m, 2H), 6.53–6.40 (m, 4H).

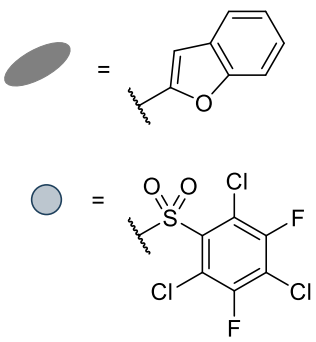
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -125.06 (t, J = 16.4 Hz, 2F), -130.01 (t, J = 16.5 Hz, 2F), -157.19 (t, J = 20.7 Hz, 2F).

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -15.53.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 154.59, 154.25, 149.83, 149.43, 142.86, 141.81, 132.02, 131.93, 131.83, 131.78, 129.92, 129.67, 129.32, 129.22, 128.52, 128.08, 127.86, 127.77, 127.64, 127.27, 127.16, 127.08, 125.56, 124.79, 123.79, 123.76, 123.72, 123.69, 123.51, 123.26, 122.70, 122.56, 122.14, 122.05, 121.71, 112.14, 111.99, 111.05, 110.78, 109.25, 107.95.

ESI-HRMS: calculated for $C_{84}H_{44}N_3O_{12}P_2S_2F_6^-$ ([M-H]$^-$): 1526.175146, found: 1526.174790.

IDPi 143l



(*S*)-BINOL **359** (40.0 mg, 0.0771 mmol, 2.01 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2(2,4,6\text{-}Cl_3\text{-}C_6F_2))Cl_3$ (34.4 mg, 0.0797 mmol, 2.08 eq.) and toluene (0.50 mL) under Argon. Et_3N (43.0 µL, 0.309 mmol, 8.05 eq.) was added and the mixture was stirred at room temperature for 30 min. HMDS (8.00 µL, 38.3 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 15 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 9:1 to 4:1) and a second silica gel flash column chromatography (DCM/EtOAc 49:1 to 19:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (40.4 mg, 0.024 mmol, 62%).

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.46 (s, 2H), 8.11 (d, J = 8.2 Hz, 2H), 8.04 (d, J = 8.3 Hz, 2H), 7.85 (t, J = 7.5 Hz, 2H), 7.78 (d, J = 7.6 Hz, 2H), 7.61–7.53 (m, 6H), 7.47 (s, 2H), 7.40 (ddd, J =

8.3, 7.0, 1.3 Hz, 2H), 7.35–7.26 (m, 4H), 7.22 (d, J = 8.7 Hz, 2H), 7.16 (d, J = 8.5 Hz, 2H), 7.13 (s, 2H), 7.08 (d, J = 8.5 Hz, 4H), 6.85–6.76 (m, 4H).

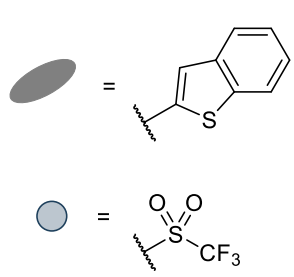
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -106.79.

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -17.19.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 154.86 (d, *J* = 2.6 Hz), 154.47, 154.27, 152.86 (d, *J* = 2.8 Hz), 149.81, 149.28, 142.55 (t, *J* = 5.0 Hz), 141.71 (t, *J* = 5.3 Hz), 136.83, 132.04, 131.94, 131.86, 131.76, 129.66, 129.63, 129.31, 129.16, 128.64, 127.92, 127.79, 127.76, 127.34, 127.28, 127.16, 125.82, 124.85, 123.58, 123.14, 122.69, 122.50, 122.27, 121.97, 121.84, 121.75, 110.99, 110.76, 109.18, 107.98.

ESI-HRMS: calculated for $C_{84}H_{40}N_3O_{12}P_2S_2F_4Cl_6^-$ ([M-H]$^-$): 1693.960157, found: 1693.960750.

IDPi 144a



(*S*)-BINOL **361** (80.0 mg, 0.145 mmol, 2.02 eq.) was placed in a flame-dried Young-Schlenk under Argon and dissolved in toluene (0.75 mL). $P(NTf)Cl_3$ (23.0 µL, 0.144 mmol, 2.00 eq.) and subsequently Et_3N (80 µL, 0.57 mmol, 7.99 eq.) were added to the reaction. The mixture was stirred at room temperature for 30 min. HMDS (15.0 µL, 71.9 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 15 min and subsequently heated to 120 °C for 4 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (DCM/MeOH 500:1), and another silica gel flash column chromatography (toluene/EtOAc 50:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (103.7 mg, 0.071 mmol, 98%).

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.26 (s, 2H), 8.01 (d, J = 8.3 Hz, 2H), 7.97 (d, J = 8.2 Hz, 2H), 7.81 (t, J = 7.5 Hz, 2H), 7.70 (t, J = 7.9 Hz, 4H), 7.62 (t, J = 7.7 Hz, 2H), 7.58–7.50 (m, 4H), 7.44 (d, J = 7.4 Hz, 2H), 7.34–7.23 (m, 12H), 7.12 (bs, 2H), 6.95–6.74 (m, 6H).

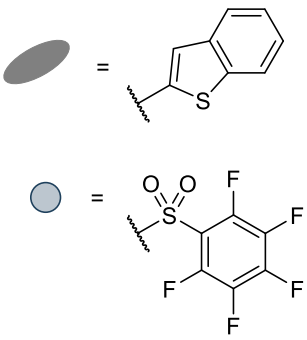
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -78.36.

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -14.46.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 143.49, 142.64, 140.51, 139.92, 139.87, 139.38, 136.92, 131.97, 131.69, 131.62, 131.59, 130.67, 129.74, 129.15, 128.81, 128.39, 127.70, 127.49, 127.25, 127.11, 126.84, 126.70, 126.43, 126.07, 124.98, 124.81, 124.77, 124.68, 124.45, 124.37, 124.33, 123.68, 123.64, 122.29, 121.68, 121.52.

ESI-HRMS: calculated for $C_{74}H_{40}N_3O_8P_2S_6F_6^-$ ([M-H]$^-$): 1466.052477, found: 1466.053980.

IDPi 144b



(*S*)-BINOL **361** (126.5 mg, 0.230 mmol, 2.00 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2C_6F_5)Cl_3$ (87.8 mg, 0.230 mmol, 2.00 eq.) and dry toluene (2.5 mL). Et_3N (130 µL, 0.93 mmol, 8.1 eq.) was added and the mixture was stirred at room temperature for 30 min. HMDS (24 µL, 0.12 µmol, 1.0 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 30–40%) and another silica gel flash column chromatography (DCM/EtOAc 2–4%). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as a white solid (139 mg, 84 µmol, 73%).

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.28 (s, 2H), 8.04 (d, J = 8.3 Hz, 2H), 7.96 (d, J = 8.2 Hz, 2H), 7.92–7.86 (m, 2H), 7.83–7.79 (m, 2H), 7.76 (ddd, J = 8.1, 6.6, 1.1 Hz, 2H), 7.58 (ddd, J = 8.1, 6.7, 1.1 Hz, 2H), 7.53 (ddd, J = 8.2, 6.7, 1.2 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H), 7.41–7.30 (m, 6H), 7.30–7.22 (m, 6H), 7.17 (d, J = 8.5 Hz, 2H), 7.11 (s, 2H), 6.81–6.70 (m, 6H).

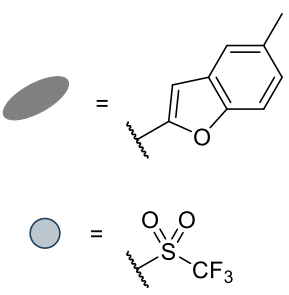
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -136.56 (d, J = 21.3 Hz, 4F), -146.01 (t, J = 21.3 Hz, 2F), 159.54 (t, J = 21.1 Hz, 4F).

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -17.17.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 145.49, 144.91, 143.43, 142.43, 140.88, 140.49, 139.80, 139.15, 138.67, 136.94, 136.91, 136.65, 132.34, 132.13, 131.92, 131.82, 130.18, 130.06, 129.39, 128.97, 128.11, 127.80, 127.59, 127.52, 127.33, 127.05, 126.44, 125.83, 125.42, 125.25, 124.96, 124.93, 124.88, 124.77, 124.55, 123.87, 123.80, 122.54, 121.81, 121.70, 117.68.

ESI-HRMS: calculated for $C_{84}H_{40}F_{10}N_3O_8P_2S_6^-$ ($[M-H]^-$): 1662.04607, found: 1662.04716.

IDPi 185a



(*S*)-BINOL **362** (96.6 mg, 0.177 mmol, 2.05 eq.) was placed in a flame-dried Young-Schlenk under Argon and suspended in toluene (1.9 mL). $P(NTf)Cl_3$ (28.0 µL, 0.175 mmol, 2.03 eq.) and subsequently Et_3N (96.0 µL, 0.689 mmol, 7.99 eq.) were added to the reaction. The mixture was stirred at room temperature for 45 min. HMDS (18.0 µL, 86.2 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 15 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The

aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (toluene/EtOAc 49:1 to 19:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as a white solid (78.3 mg, 0.054 mmol, 62%).

R_F (hex/EtOAc 1:1) = 0.34.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.66 (s, 2H), 8.09 (d, J = 8.3 Hz, 2H), 7.96 (d, J = 8.1 Hz, 2H), 7.90 – 7.83 (m, 2H), 7.66 (ddd, J = 8.2, 6.7, 1.3 Hz, 2H), 7.57 (ddd, J = 8.2, 6.7, 1.1 Hz, 2H), 7.52 (dd, J = 11.0, 8.5 Hz, 4H), 7.45 (s, 2H), 7.31 (ddd, J = 8.3, 6.8, 1.3 Hz, 2H), 7.25 (dd, J = 8.6, 1.7 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 7.12 (s, 2H), 6.93 (s, 2H), 6.88 (s, 2H), 6.72 (d, J = 8.4 Hz, 2H), 6.67 (s, 2H), 6.61 (dd, J = 8.5, 1.7 Hz, 2H), 2.54 (s, 6H), 1.73 (s, 6H).

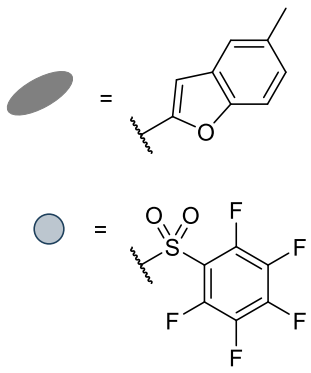
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -78.18.

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -17.50.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 153.20, 153.05, 150.00, 149.59, 142.74 (t, J = 5.3 Hz), 141.51 (t, J = 5.0 Hz), 133.24, 132.84, 132.16, 132.05, 131.97, 131.85, 130.05, 129.73, 129.48, 129.23, 128.85, 128.46, 128.02, 127.92, 127.74, 127.29, 127.21, 127.03, 126.29, 123.28, 122.15, 122.13, 121.98, 121.69, 121.58, 119.90 (q, *J* = 320.4 Hz), 110.81, 110.20, 108.21, 107.56, 21.58, 20.61.

ESI-HRMS: calculated for $C_{78}H_{48}N_3O_{12}P_2S_2F_6^-$ ([M-H]$^-$): 1458.206446, found: 1458.208420.

IDPi 185b



(*S*)-BINOL **362** (55.5 mg, 0.102 mmol, 2.02 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2C_6F_5)Cl_3$ (38.1 mg, 0.100 mmol, 1.98 eq.), dry toluene (1.0 mL). Et_3N (57 µL, 0.41 mmol, 8.1 eq.) was added and the mixture was stirred at room temperature for 45 min. HMDS (6.5 µL, 31 µmol, 1.0 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/acetone 70:30 to 2:1), and another silica gel flash column chromatography (DCM/EtOAc 1-4%). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (48.8 mg, 29 µmol, 59%).

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.55 (s, 2H), 8.07 (d, J = 8.3 Hz, 2H), 8.01 (d, J = 8.1 Hz, 2H), 7.84 (t, J = 7.4 Hz, 2H), 7.64–7.55 (m, 4H), 7.50 (s, 2H), 7.48 (d, J = 8.6 Hz, 2H), 7.36 (d, J = 8.6 Hz, 2H), 7.32 (ddd, J = 8.3, 6.7, 1.3 Hz, 2H), 7.25 (s, 2H), 7.22 (dd, J = 8.5, 1.8 Hz, 2H), 7.19 (d,

J = 8.5 Hz, 2H), 7.02 (s, 2H), 6.89 (s, 2H), 6.85 (s, 2H), 6.65 (d, J = 8.3 Hz, 2H), 6.57 (dd, J = 8.4, 1.8 Hz, 2H), 2.51 (s, 6H), 1.68 (s, 6H).

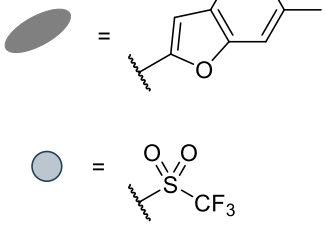
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -136.81 (d, J = 21.4 Hz, 4F), -145.99 (d, J = 22.9 Hz, 2F), -159.81 (t, J = 20.9 Hz, 4F).

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -17.80.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 152.88, 152.85, 149.96, 149.42, 142.55 (t, J = 5.3 Hz), 141.75 (t, J = 5.1 Hz), 133.35, 132.54, 132.04, 131.98, 131.83, 131.78, 129.83, 129.57, 129.39, 129.29, 128.58, 127.83, 127.75, 127.61, 127.25, 127.21, 127.16, 127.14, 126.04, 123.17, 122.28, 121.88, 121.85, 110.51, 110.10, 108.64, 107.82, 21.44, 20.56.

ESI-HRMS: calculated for $C_{88}H_{48}N_3O_{12}P_2S_2F_{10}^-$ ([M-H]$^-$): 1654.200060, found: 1654.202370.

IDPi 186a



(*S*)-BINOL **363** (96.6 mg, 0.177 mmol, 2.05 eq.) was placed in a flame-dried Young-Schlenk under Argon and dissolved in toluene (0.90 mL). $P(NTf)Cl_3$ (28.0 µL, 0.175 mmol, 2.03 eq.) and subsequently Et_3N (96.0 µL, 0.689 mmol, 7.99 eq.) were added to the reaction. The mixture was stirred at room temperature for 45 min. HMDS (18.0 µL, 86.2 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 15 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (toluene/EtOAc 49:1 to 24:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as a white solid (68.8 mg, 0.047 mmol, 55%).

***R*$_F$** (hex/EtOAc 1:1) = 0.50.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.64 (s, 2H), 8.10 (d, J = 8.3 Hz, 2H), 7.96 (d, J = 8.2 Hz, 2H), 7.86 (t, J = 7.4 Hz, 2H), 7.69–7.62 (m, 2H), 7.57 (t, J = 7.5 Hz, 2H), 7.50 (dd, J = 8.2, 2.9 Hz, 4H), 7.46 (s, 2H), 7.35–7.28 (m, 2H), 7.22 (d, J = 8.6 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 7.14 (s, 2H), 6.95 (d, J = 7.9 Hz, 2H), 6.78 (s, 2H), 6.65 (d, J = 15.4 Hz, 4H), 6.39 (d, J = 8.1 Hz, 2H), 2.57 (s, 6H), 2.08 (s, 6H).

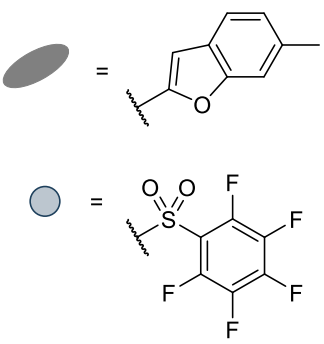
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -78.29.

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -16.93

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 155.17, 155.16, 149.51, 148.97, 142.85 (t, J = 5.0 Hz), 141.69 (t, J = 5.0 Hz), 136.16, 135.58, 132.12, 132.06, 131.97, 131.84, 130.03, 129.42, 128.83, 128.22, 127.92, 127.86, 127.64, 127.33, 127.31, 127.18, 126.61, 125.10, 124.38, 123.33, 122.40, 122.36, 122.08, 121.36, 121.09, 119.90 (q, J = 320.5 Hz), 111.46, 110.98, 108.32, 107.63, 22.05, 21.56.

ESI-HRMS: calculated for $C_{78}H_{48}N_3O_{12}P_2S_2F_6^-$ ([M-H]$^-$): 1458.206446, found: 1458.208090.

IDPi 186b



(*S*)-BINOL **363** (194 mg, 0.355 mmol, 2.00 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2C_6F_5)Cl_3$ (136 mg, 0.355 mmol, 2.00 eq.) and dry toluene (4.0 mL). Et_3N (200 µL, 1.43 mmol, 8.10 eq.) was added and the mixture was stirred at room temperature for 30 min. HMDS (37 µL, 0.18 mmol, 1.0 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (DCM/EtOAc 1-4%), and another silica gel flash column chromatography (hex/acetone 2:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (236 mg, 143 µmol, 78%).

$\boldsymbol{R_F}$ (hex/acetone 1:1) = 0.36.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.50 (s, 2H), 8.04 (d, J = 8.4 Hz, 2H), 8.01 (d, J = 8.3 Hz, 2H), 7.78 (ddd, J = 8.0, 6.7, 1.1 Hz, 2H), 7.59 (d, J = 7.9 Hz, 2H), 7.57–7.49 (m, 4H), 7.43 (s, 2H), 7.38 (s, 2H), 7.29 (ddd, J = 8.3, 6.8, 1.3 Hz, 2H), 7.23 (d, J = 8.5 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 7.08 (dd, J = 7.7, 1.2 Hz, 2H), 7.05 (s, 2H), 6.99 (s, 2H), 6.93 (d, J = 7.8 Hz, 2H), 6.47 (s, 2H), 6.34 (dd, J = 7.9, 1.4 Hz, 2H), 2.55 (s, 6H), 2.05 (s, 6H).

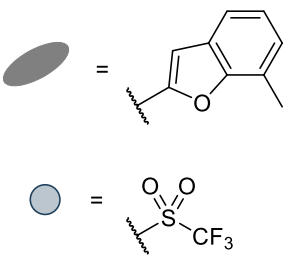
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -135.95 (d, J = 21.5 Hz, 4F), -145.91 (t, J = 21.6 Hz, 2F), -159.33 (t, J = 20.1 Hz, 4F).

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -16.14.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 154.56, 148.92, 148.39, 142.33 (t, J = 5.3 Hz), 141.63 (t, J = 5.5 Hz), 135.98, 134.76, 131.69, 131.56, 131.47, 131.38, 129.38, 128.88, 128.12, 127.46, 127.30, 127.22, 127.03, 126.98, 126.93, 126.88, 126.67, 126.48, 124.83, 123.87, 122.88, 122.38, 122.06, 121.93, 121.80, 121.01, 110.84, 110.64, 108.70, 107.91, 22.02, 21.60.

ESI-HRMS: calculated for $C_{88}H_{48}N_3O_{12}P_2S_2F_{10}^-$ ($[M-H]^-$): 1654.200060, found: 1654.199820.

IDPi 187a



(*S*)-BINOL **364** (96.6 mg, 0.177 mmol, 2.05 eq.) was placed in a flame-dried Young-Schlenk under Argon and suspended in toluene (0.90 mL). $P(NTf)Cl_3$ (28.0 µL, 0.175 mmol, 2.03 eq.) and subsequently Et_3N (96.0 µL, 0.689 mmol, 7.99 eq.) were added to the reaction. The mixture was stirred at room temperature for 45 min. HMDS (18.0 µL, 86.2 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 15

min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 4:1 to 7:3) and a second silica gel flash column chromatography (toluene/EtOAc 49:1 to 9:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as a white solid (79.6 mg, 0.055 mmol, 63%).

R_F (hex/EtOAc 1:1) = 0.56.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.74 (s, 2H), 8.14 (d, J = 8.3 Hz, 2H), 7.80 (t, J = 7.4 Hz, 2H), 7.71 (d, J = 8.1 Hz, 2H), 7.59 (q, J = 7.5 Hz, 4H), 7.46 (d, J = 8.6 Hz, 2H), 7.42 (dd, J = 6.0, 2.9 Hz, 2H), 7.30 (ddd, J = 8.2, 6.8, 1.2 Hz, 2H), 7.26–7.21 (m, 6H), 7.17 (d, J = 8.6 Hz, 2H), 7.03 (d, J = 7.9 Hz, 2H), 7.01 (s, 2H), 6.65 (d, J = 7.3 Hz, 2H), 6.54 (s, 2H), 6.39 (t, J = 7.5 Hz, 2H), 2.73 (s, 6H), 2.03 (s, 6H).

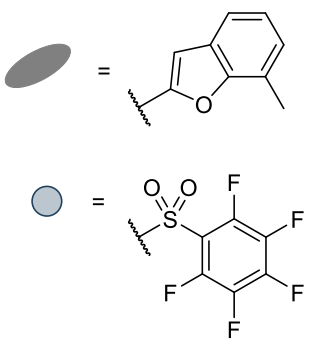
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -78.34.

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -17.05.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 153.69, 153.64, 149.88, 148.77, 143.06 (t, J = 5.3 Hz), 141.64 (t, J = 5.3 Hz), 132.13, 131.90, 131.85, 131.69, 130.74, 129.44, 128.72, 128.71, 128.60, 127.98, 127.70, 127.45, 127.34, 127.27, 127.02, 126.43, 126.24, 123.54, 123.23, 123.21, 122.43, 122.42, 122.14, 121.52, 120.98, 119.83 (q, J = 320.5 Hz), 119.45, 119.24, 108.66, 108.23, 15.35, 14.98.

ESI-HRMS: calculated for $C_{78}H_{48}N_3O_{12}P_2S_2F_6^-$ ([M-H]$^-$): 1458.206446, found: 1458.208500.

IDPi 187b



(*S*)-BINOL **364** (34.5 mg, 0.063 mmol, 2.03 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2C_6F_5)Cl_3$ (23.7 mg, 0.062 mmol, 1.99 eq.) and dry toluene (1.0 mL). Et_3N (35 µL, 0.25 mmol, 8.1 eq.) was added and the mixture was stirred at room temperature for 45 min. HMDS (6.5 µL, 31 µmol, 1.0 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/acetone 70:30 to 2:1), and another silica gel flash column chromatography (DCM/EtOAc 1-4%). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (32.2 mg, 19 µmol, 62%).

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.62 (s, 2H), 8.11 (d, J = 8.4 Hz, 2H), 7.89 (d, J = 8.1 Hz, 2H), 7.78 (t, J = 7.5 Hz, 2H), 7.58 (t, J = 7.6 Hz, 2H), 7.51–7.44 (m, 6H), 7.33–7.27 (m, 2H), 7.22–7.09

(m, 8H), 6.90 (d, J = 7.7 Hz, 2H), 6.87 (s, 2H), 6.82 (s, 2H), 6.61 (d, J = 7.2 Hz, 2H), 6.43 (t, J = 7.5 Hz, 2H), 2.70 (s, 6H), 2.14 (s, 6H).

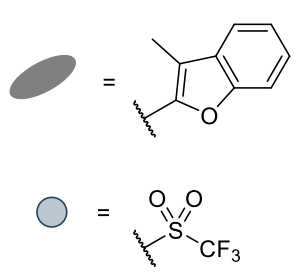
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -136.82 (d, J = 21.0 Hz, 4F), -146.13 (s, 2F), -159.73 (t, J = 20.4 Hz, 4F).

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -17.10.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 153.73, 153.30, 149.92, 148.82, 142.78 (t, J = 5.5 Hz), 141.84, 131.95, 131.86, 131.84, 131.75, 130.02, 129.27, 129.12, 128.47, 128.45, 127.90, 127.88, 127.75, 127.32, 127.27, 127.19, 127.07, 126.59, 126.11, 123.63, 123.22, 123.00, 122.48, 122.43, 122.05, 121.38, 121.08, 119.82, 118.99, 108.98, 107.94, 15.13, 15.12.

ESI-HRMS: calculated for $C_{88}H_{48}N_3O_{12}P_2S_2F_{10}^-$ ([M-H]$^-$): 1654.200060, found: 1654.202380.

IDPi 188a



(*S*)-BINOL **365** (268.4 mg, 0.491 mmol, 2.05 eq.) was placed in a flame-dried Young-Schlenk under Argon and dissolved in toluene (2.6 mL). $P(NTf)Cl_3$ (77.0 µL, 0.482 mmol, 2.01 eq.) and subsequently Et_3N (0.27 mL, 1.94 mmol, 8.09 eq.) were added to the reaction. The mixture was stirred at room temperature for 30 min. HMDS (50.0 µL, 240 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 19:1 to 2:1), another silica gel flash column chromatography (toluene/EtOAc 19:1 to 9:1), a third silica gel column chromatography (mesh size 0.1-0.2 mm, DCM/EtOAc 49:1 to 19:1), and automated reversed phase silica gel column chromatography (CH_3CN/H_2O 3:2 to 100:0). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (40.5 mg, 0.028 mmol, 12%).

***R*$_F$** (hex/EtOAc 1:1) = 0.70.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.24 (s, 2H), 8.06 (d, J = 8.2 Hz, 2H), 8.01 (d, J = 8.2 Hz, 2H), 7.79–7.71 (m, 2H), 7.61–7.53 (m, 4H), 7.40 (ddd, J = 8.3, 6.8, 1.2 Hz, 2H), 7.38–7.35 (m, 2H), 7.34–7.25 (m, 12H), 7.20 (d, J = 8.6 Hz, 2H), 7.00 (ddd, J = 7.7, 6.5, 1.8 Hz, 2H), 6.98–6.91 (m, 4H), 2.23 (s, 6H), 1.95 (s, 6H).

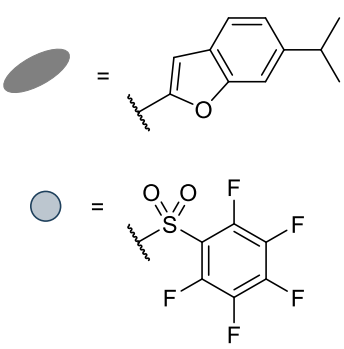
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -78.83.

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -14.83.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 155.00, 154.57, 146.95, 146.06, 144.51 (t, J = 5.0 Hz), 142.38 (t, J = 5.0 Hz), 132.99, 132.50, 132.29, 131.92, 131.80, 131.47, 130.50, 130.46, 129.24, 129.23, 127.85, 127.80, 127.73, 127.23, 127.05, 127.03, 125.02, 124.75, 123.33, 123.23, 122.61, 122.60, 122.38, 119.76, 119.38 (q, J = 320.8 Hz), 115.94, 115.25, 111.99, 111.13, 9.47, 9.42.

ESI-HRMS: calculated for $C_{78}H_{48}F_6N_3O_{12}P_2S_2^-$ ([M-H]$^-$): 1458.206446, found: 1458.206630.

IDPi 189b



(*S*)-BINOL **366** (153 mg, 0.254 mmol, 2.00 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2C_6F_5)Cl_3$ (96.9 mg, 0.253 mmol, 2.00 eq.) and dry toluene (3 mL) was added. Et_3N (140 µL, 1.00 mmol, 7.93 eq.) was added to the reaction and the mixture was stirred at room temperature for 1 h. HMDS (26.5 µL, 0.127 mmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 4:1), another silica gel flash column chromatography (DCM/MTBE 1-5%), and another silica gel flash column chromatography (hex/acetone 4:1 to 2:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (61.2 mg, 35 µmol, 27%).

R_F (hex/EtOAc 4:1) = 0.18.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.49 (s, 2H), 8.13 (d, J = 8.2 Hz, 2H), 8.03 (d, J = 8.3 Hz, 2H), 7.82 (ddd, J = 8.0, 6.7, 1.1 Hz, 2H), 7.68 (d, J = 8.0 Hz, 2H), 7.59 (s, 2H), 7.55 (dtd, J = 8.4, 7.0, 1.2 Hz, 4H), 7.49 (s, 2H), 7.31 (ddd, J = 8.2, 6.8, 1.3 Hz, 2H), 7.28 (s, 2H), 7.23–7.17 (m, 8H), 7.01 (d, J = 8.0 Hz, 2H), 6.59 (s, 2H), 6.47 (dd, J = 7.9, 1.5 Hz, 2H), 3.12 (hept, J = 6.8 Hz, 2H), 2.62 (hept, J = 6.6 Hz, 2H), 1.39 (dd, J = 6.9, 1.8 Hz, 12H), 0.96 (d, J = 6.9 Hz, 6H), 0.89 (d, J = 7.0 Hz, 6H).

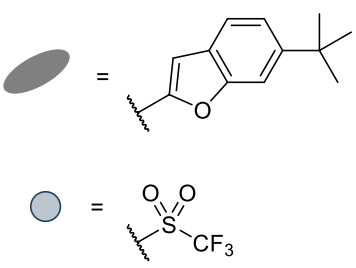
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -137.44 (d, J = 22.0 Hz, 4F), -147.57 (s, 2F), -160.37 (t, J = 20.5 Hz, 4F).

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -13.91

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 155.01, 154.71, 149.62, 149.55, 147.73, 146.29, 142.65, 142.40, 132.07, 131.79, 131.64, 131.61, 129.55, 129.08, 128.23, 127.68, 127.55, 127.48, 127.43, 127.28, 127.26, 127.13, 127.06, 126.98, 123.09, 122.86, 122.69, 122.61, 122.12, 121.91, 121.61, 121.47, 108.85, 108.60, 108.35, 108.19, 34.92, 34.44, 24.46, 24.41, 24.25, 24.06.

ESI-HRMS: calculated for $C_{96}H_{64}N_3O_{12}S_2F_{10}P_2^-$ ([M-H]$^-$): 1766.325260, found: 1766.326900.

IDPi 190a



(*S*)-BINOL **367** (111.5 mg, 0.177 mmol, 2.05 eq.) was placed in a flame-dried Young-Schlenk under Argon and suspended in toluene (1.9 mL). $P(NTf)Cl_3$ (28.0 µL, 0.175 mmol, 2.03 eq.) and subsequently Et_3N (96.0 µL, 0.689 mmol, 7.99 eq.) were added to the reaction. The mixture was stirred at room temperature for 45 min. HMDS (18.0 µL, 86.2 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 15 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (toluene/EtOAc 100:0 to 49:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM/toluene) and obtained as a white solid (102.7 mg, 0.063 mmol, 73%).

R_F (hex/EtOAc 2:1) = 0.50.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.62 (s, 2H), 8.07 (d, J = 8.7 Hz, 4H), 7.91 (t, J = 7.7 Hz, 2H), 7.75–7.68 (m, 4H), 7.61–7.55 (m, 4H), 7.51 (d, J = 8.6 Hz, 2H), 7.46 (dd, J = 8.2, 1.6 Hz, 2H), 7.33 (ddd, J = 8.2, 6.7, 1.3 Hz, 2H), 7.28–7.24 (m, 4H), 7.09 (d, J = 8.1 Hz, 2H), 7.03 (s, 2H), 6.86 (s, 2H), 6.75 (s, 2H), 6.71 (dd, J = 8.2, 1.6 Hz, 2H), 1.51 (s, 18H), 1.06 (s, 18H).

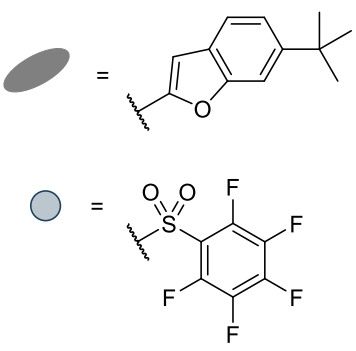
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -78.20.

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -17.24.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 155.19, 154.85, 149.90, 149.47, 149.21, 149.12, 142.66 (t, J = 5.3 Hz), 141.58 (t, J = 5.0 Hz), 132.15, 132.05, 131.99, 131.77, 129.97, 129.35, 128.81, 128.58, 128.04, 127.84, 127.71, 127.44, 127.29, 127.10, 126.55, 123.24, 122.29, 122.21, 122.02, 121.65, 121.26, 121.14, 120.95, 119.91 (q, J = 320.5 Hz), 108.45, 108.00, 107.71, 107.28, 35.51, 34.96, 31.92, 31.47.

ESI-HRMS: calculated for $C_{90}H_{72}N_3O_{12}P_2S_2F_6^-$ ($[M-H]^-$): 1626.394246, found: 1626.395810.

IDPi 190b



(*S*)-BINOL **367** (1.02 g, 1.62 mmol, 2.05 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2C_6F_5)Cl_3$ (620 mg, 1.62 mmol, 2.05 eq.) and the solids were gently heated to 50 °C with a heat gun under high vacuum for 10 min. The mixture was placed under argon and dissolved in dry toluene (15 mL). Et_3N (0.89 mL, 6.39 mmol, 8.08 eq.) was added to the reaction and the mixture was stirred at room temperature for 15 min (formation of a white precipitate was observed). HMDS (165 µL, 0.79 mmol, 1.00 eq.)

was added, the mixture was stirred at room temperature for 15 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (100% DCM). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (1.32 g, 0.724 mmol, 92%).

R_F (hex/EtOAc 4:1) = 0.22.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.48 (s, 2H), 8.13 (d, J = 8.1 Hz, 2H), 8.04 (d, J = 7.9 Hz, 2H), 7.89 (ddd, J = 8.0, 6.8, 1.1 Hz, 2H), 7.68–7.53 (m, 8H), 7.42 (s, 2H), 7.38 (dd, J = 8.3, 1.6 Hz, 2H), 7.33 (ddd, J = 8.2, 6.7, 1.2 Hz, 4H), 7.23 (d, J = 8.5 Hz, 2H), 7.13 (s, 2H), 7.03 (d, J = 8.2 Hz, 2H), 6.93 (s, 2H), 6.79–6.75 (m, 2H), 6.63 (dd, J = 8.2, 1.7 Hz, 2H), 1.47 (s, 18H), 0.99 (s, 18H).

^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -136.71 (d, J = 21.2 Hz, 4F), -145.82 (t, J = 22.0 Hz, 2F), -159.70 (t, J = 19.7 Hz, 4F).

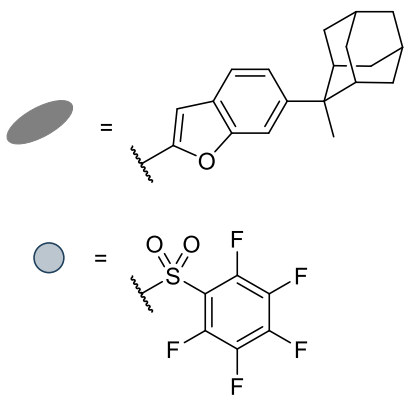
^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -17.44.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 154.85, 154.66, 150.09, 149.41, 149.00, 148.83, 142.43 (t, J = 5.3 Hz), 141.74 (t, J = 5.3 Hz), 132.17, 131.89, 131.78, 131.64, 129.71, 129.14, 128.55, 127.92, 127.68, 127.63, 127.60, 127.39, 127.32, 127.12, 126.82, 126.59, 123.12, 122.44, 122.24, 121.93, 121.66, 121.49, 121.29, 120.72, 108.84, 107.93, 107.63, 107.25, 35.48, 34.89, 31.80, 31.41.

ESI-HRMS: calculated for $C_{100}H_{72}N_3O_{12}S_2F_{10}P_2^-$ ([M-H]$^-$): 1822.387860, found: 1822.388580.

$[\alpha]_D^{25}$ = +450.9 (*c* = 0.50, $CHCl_3$).

IDPi 220b



(*S*)-BINOL **368** (700 mg, 0.859 mmol, 2.01 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2C_6F_5)Cl_3$ (328 mg, 0.858 mmol, 2.01 eq.) and the solids were gently heated to 50 °C with a heat gun under high vacuum for 10 min. The mixture was placed under argon and suspended in dry toluene (20 mL). Et_3N (0.50 mL, 3.59 mmol, 8.44 eq.) was added to the reaction and the mixture was stirred at room temperature for 1 h. HMDS (89 µL, 0.43 mmol, 1.0 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 4 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (100% DCM) and a second silica gel flash column chromatography (hex/EtOAc 9:1 to 4:1). The

product was acidified by filtration over a plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as a white solid (696 mg, 0.317 mmol, 75%).

R_F (hex/EtOAc 4:1) = 0.40.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.41 (s, 2H), 8.17 (d, J = 8.2 Hz, 2H), 7.96 (d, J = 8.3 Hz, 2H), 7.90 (t, J = 7.5 Hz, 2H), 7.69 (dd, J = 8.4, 2.1 Hz, 2H), 7.62 (ddd, J = 8.4, 6.9, 1.3 Hz, 2H), 7.59 (s, 2H), 7.53 (ddd, J = 8.1, 6.7, 1.1 Hz, 2H), 7.46 (s, 2H), 7.36 (dd, J = 8.4, 1.7 Hz, 2H), 7.33–7.25 (m, 4H), 7.17 (d, J = 8.6 Hz, 2H), 7.14 (s, 2H), 7.07 (d, J = 8.0 Hz, 2H), 6.81 (s, 2H), 6.62 (dd, J = 8.3, 1.6 Hz, 2H), 2.49 (s, 4H), 2.38–2.32 (m, 4H), 2.17–1.94 (m, 14H), 1.91–1.81 (m, 6H), 1.77 (s, 6H), 1.72–1.48 (m, 14H), 1.404–1.36 (m, 10H), 0.99–0.84 (m, 10H).

^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -136.48 (d, J = 21.9 Hz, 4F), -146.02 (s, 2F), -159.61 (t, J = 20.4 Hz, 4F).

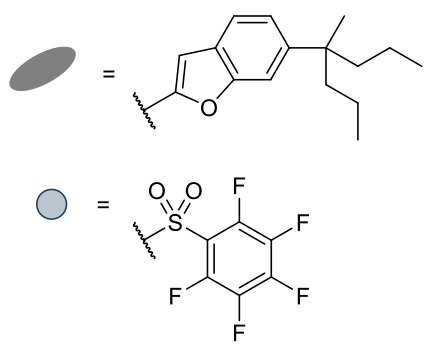
^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -17.14.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 155.51, 154.98, 149.82, 149.24, 148.89, 148.82, 142.19 (t, J = 5.1 Hz), 141.60 (t, J = 4.9 Hz), 132.21, 131.84, 131.76, 131.48, 129.56, 129.02, 128.11, 127.88, 127.58, 127.54, 127.52, 127.48, 127.22, 126.95, 126.64, 126.43, 123.12, 122.21, 121.82, 121.60, 121.45, 120.36, 108.93, 108.27, 108.14, 107.65, 44.36, 43.92, 39.27, 39.02, 35.32, 35.27, 35.08, 34.80, 34.46, 34.41, 34.06, 33.84, 33.61, 33.37, 33.24, 30.78, 30.74, 28.64, 28.29, 28.28, 28.02.

ESI-HRMS: calculated for $C_{128}H_{104}F_{10}N_3O_{12}P_2S_2^-$ ([M-H]$^-$): 2190.638260, found: 2190.639340.

$[\alpha]_D^{25}$ = +350.5 (*c* = 0.33, $CHCl_3$).

IDPi 221b



(*S*)-BINOL **369** (29 mg, 0.40 mmol, 2.1 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2C_6F_5)Cl_3$ (15 mg, 0.040 mmol, 2.1 eq.) and dry toluene (1.0 mL). Et_3N (22 µL, 0.16 mmol, 8.2 eq.) was added and the mixture was stirred at room temperature for 30 min. HMDS (4.0 µL, 0.019 mmol, 1.0 eq.) was added, the mixture was stirred at room temperature for 15 min, and subsequently heated to 120 °C for 4 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (100% DCM). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (29 mg, 14 µmol, 74%).

R_F (hex/EtOAc 4:1) = 0.44.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.48 (s, 2H), 8.17 (d, J = 8.1 Hz, 2H), 8.01 (d, J = 8.3 Hz, 2H), 7.90 (t, J = 7.5 Hz, 2H), 7.66 (d, J = 8.2 Hz, 2H), 7.60 (t, J = 7.7 Hz, 2H), 7.57–7.52 (m, 4H), 7.50 (s, 2H), 7.34–7.26 (m, 4H), 7.26–7.21 (m, 2H), 7.18–7.11 (m, 6H), 7.02 (d, J = 8.2 Hz, 2H), 6.70

(s, 2H), 6.52 (dd, J = 8.2, 1.5 Hz, 2H), 1.85–1.76 (m, 4H), 1.64 (td, J = 12.7, 4.1 Hz, 4H), 1.42 (s, 6H), 1.40–1.19 (m, 12H), 1.17–1.05 (m, 4H), 0.99 (s, 6H), 0.95–0.73 (m, 16H), 0.68 (t, J = 6.9 Hz, 6H), 0.65–0.46 (m, 10H).

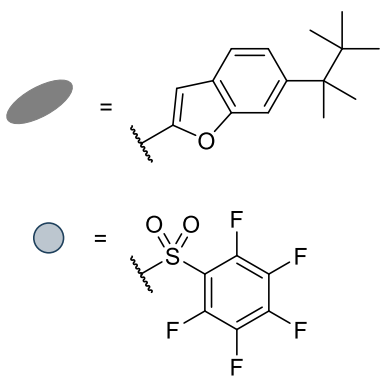
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -136.53 (s, 4F), -145.94 (s, 4F), -159.63 (s, 4F).

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -17.12.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 155.13, 154.60, 149.13, 147.46, 146.34, 142.29, 132.15, 131.81, 131.75, 131.53, 129.56, 129.21, 128.17, 127.72, 127.63, 127.42, 127.25, 126.97, 126.44, 123.13, 122.42, 122.25, 121.96, 121.46, 121.41, 121.03, 109.08, 108.98, 108.71, 108.16, 46.49, 46.44, 46.04, 45.95, 41.81, 41.17, 24.77, 24.69, 17.91, 17.69, 17.57, 15.05, 14.97, 14.82.

ESI-HRMS: calculated for $C_{116}H_{104}N_3O_{12}S_2F_{10}P_2^-$ ([M-H]$^-$): 2046.638260, found: 2046.639080.

IDPi 222b



(*S*)-BINOL **370** (38 mg, 0.53 mmol, 2.0 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2C_6F_5)Cl_3$ (20 mg, 0.053 mmol, 2.0 eq.) and dry toluene (1.5 mL). Et_3N (30 µL, 0.22 mmol, 8.2 eq.) was added and the mixture was stirred at room temperature for 45 min. HMDS (5.5 µL, 0.026 mmol, 1.0 eq.) was added, the mixture was stirred at room temperature for 10 min, and subsequently heated to 120 °C for 7 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 9:1 to 4:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (34 mg, 17 µmol, 65%).

***R*$_F$** (hex/EtOAc 4:1) = 0.23.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.45 (s, 2H), 8.13 (d, J = 8.1 Hz, 2H), 8.01 (d, J = 8.3 Hz, 2H), 7.90 (t, J = 7.5 Hz, 2H), 7.67–7.58 (m, 6H), 7.55 (t, J = 7.5 Hz, 2H), 7.42–7.35 (m, 4H), 7.30 (ddd, J = 10.8, 6.7, 2.6 Hz, 4H), 7.22 (s, 2H), 7.18 (d, J = 8.5 Hz, 2H), 7.04 (s, 2H), 6.96 (d, J = 8.1 Hz, 2H), 6.81 (s, 2H), 6.59 (dd, J = 8.2, 1.7 Hz, 2H), 1.51 (s, 12H), 1.13 (s, 6H), 0.97 (s, 6H), 0.96 (s, 18H), 0.53 (s, 18H).

^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -136.64 (d, J = 21.6 Hz, 4F), -145.85 (s, 2F), -159.62 (d, J = 25.7 Hz, 4F).

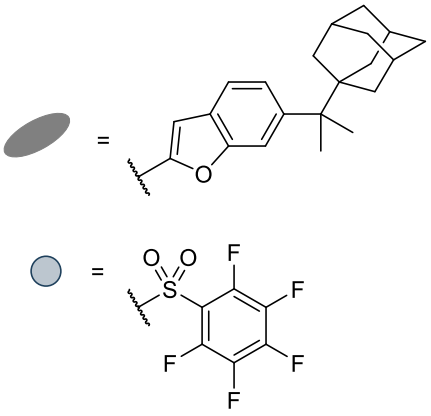
^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -17.37.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 154.43, 154.04, 149.43, 148.92, 146.58, 145.49, 143.35, 142.31, 141.69, 132.12, 131.89, 131.85, 131.58, 129.68, 129.14, 128.22, 127.80, 127.63, 127.48, 127.38, 127.27, 127.02, 126.84, 126.52, 124.50, 123.60, 123.10, 122.26, 122.22, 121.88, 119.99,

119.80, 110.91, 110.48, 108.79, 107.95, 43.79, 43.28, 36.59, 36.17, 26.65, 26.28, 24.98, 24.60, 24.57.

ESI-HRMS: calculated for $C_{112}H_{96}F_{10}N_3O_{12}P_2S_2^-$ ([M-H]$^-$): 1990.575660, found: 1990.578680.

IDPi 223b



(*S*)-BINOL **371** (45 mg, 0.52 mmol, 2.0 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2C_6F_5)Cl_3$ (20 mg, 0.052 mmol, 2.0 eq.) and dry toluene (1.5 mL). Et_3N (29 µL, 0.21 mmol, 7.9 eq.) was added and the mixture was stirred at room temperature for 45 min. HMDS (5.5 µL, 0.026 mmol, 1.0 eq.) was added, the mixture was stirred at room temperature for 10 min, and subsequently heated to 120 °C for 7 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 9:1) and another silica gel flash column chromatography (hex/acetone 4:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (26 mg, 11 µmol, 43%).

R_F (hex/EtOAc 4:1) = 0.27.

^{1}H-NMR (600 MHz, CD_2Cl_2): δ = 8.49 (s, 2H), 8.07 (dd, J = 8.2, 1.2 Hz, 2H), 8.01 (d, J = 8.6 Hz, 2H), 7.87 (t, J = 7.4 Hz, 2H), 7.63–7.50 (m, 8H), 7.36 (s, 2H), 7.33–7.27 (m, 4H), 7.23 (d, J = 8.6 Hz, 2H), 7.16 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.1 Hz, 2H), 6.72 (s, 2H), 6.47 (dd, J = 8.2, 1.6 Hz, 2H), 1.99–1.95 (m, 6H), 1.78–1.73 (m, 6H), 1.70–1.62 (m, 18H), 1.58 (d, J = 11.6 Hz, 6H), 1.52–1.48 (m, 6H), 1.46 (d, J = 3.1 Hz, 12H), 1.32 (q, J = 12.7 Hz, 18H), 1.07 (s, 6H), 0.85 (s, 6H).

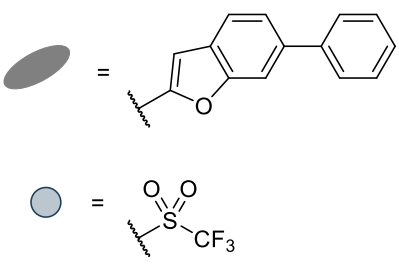
^{19}F-NMR (565 MHz, CD_2Cl_2): δ = -136.78 (s, 4F), -145.90 (s, 2F), -159.69 (s, 4F).

^{31}P-NMR (243 MHz, CD_2Cl_2): δ = -17.55.

^{13}C-NMR (151 MHz, CD_2Cl_2): δ = 154.28, 154.06, 149.31, 148.84, 145.79, 145.19, 144.74, 143.48, 142.41, 141.82, 138.54, 136.85, 132.03, 131.85, 131.71, 131.61, 129.70, 129.11, 128.16, 127.60, 127.49, 127.22, 126.98, 126.41, 124.78, 123.87, 123.09, 123.08, 123.07, 122.36, 122.26, 121.98, 119.81, 119.48, 111.18, 110.61, 108.79, 108.01, 44.26, 43.71, 37.76, 37.46, 37.38, 37.33, 37.28, 37.10, 29.60, 29.33, 23.63, 23.60, 23.31, 23.13, 14.29, 1.18.

ESI-HRMS: calculated for $C_{136}H_{120}N_3O_{12}S_2F_{10}P_2^-$ ([M-H]$^-$): 2302.763460, found: 2302.766500.

IDPi 191a



(*S*)-BINOL **372** (53.6 mg, 0.0799 mmol, 2.01 eq.) was placed in a flame-dried Young-Schlenk under Argon and dissolved in toluene (0.45 mL). $P(NTf)Cl_3$ (12.75 µL, 0.0798 mmol, 2.01 eq.) and subsequently Et_3N (45.0 µL, 0.323 mmol, 8.12 eq.) were added to the reaction. The mixture was stirred at room temperature for 30 min. HMDS (8.3 µL, 40.0 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 15 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 9:1 to 3:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (58.1 mg, 0.034 mmol, 86%).

$\boldsymbol{R_F}$ (hex/EtOAc 2:1) = 0.26.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.49 (s, 2H), 8.02 (d, J = 8.2 Hz, 4H), 7.88 (t, J = 7.4 Hz, 2H), 7.81 (s, 2H), 7.76 (d, J = 1.4 Hz, 2H), 7.74 (s, 2H), 7.69–7.62 (m, 4H), 7.61–7.48 (m, 10H), 7.43–7.31 (m, 10H), 7.26 (d, J = 7.8 Hz, 4H), 7.20–7.13 (m, 6H), 7.02 (d, J = 7.7 Hz, 4H), 6.89 (s, 2H), 6.87–6.83 (m, 2H).

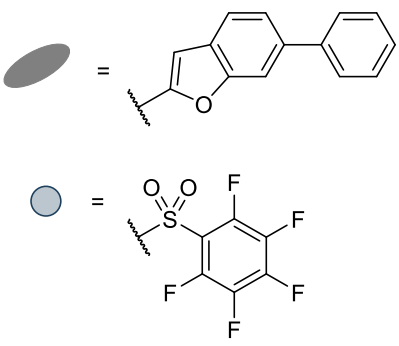
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -78.45.

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -15.81.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 155.27, 150.72, 150.22, 142.95 (t, J = 5.2 Hz), 141.98 (t, J = 5.2 Hz, 141.63, 141.34, 139.12, 138.63, 132.25, 131.99, 131.97, 131.91, 130.15, 129.43, 129.29, 129.11, 129.00, 128.98, 128.71, 128.54, 128.09, 127.85, 127.82, 127.72, 127.68, 127.45, 127.34, 127.26, 127.22, 123.35, 123.23, 122.47, 122.22, 122.13, 121.92, 121.90, 121.85, 119.94 (q, J = 320.4 Hz), 109.59, 109.09, 108.34, 107.74.

ESI-HRMS: calculated for $C_{98}H_{56}F_6N_3O_{12}P_2S_2^-$ ($[M-H]^-$): 1706.269046, found: 1706.269830.

IDPi 191b



(*S*)-BINOL **372** (108 mg, 0.161 mmol, 2.01 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2C_6F_5)Cl_3$ (61.3 mg, 0.160 mmol, 2.00 eq.) and dry toluene (0.85 mL). Et_3N (89 µL, 0.64 mmol, 8.0 eq.) was added and the mixture was stirred at room temperature for 30 min. NH_3 (0.344 mol L^{-1} in 1,4-dioxane, 233 µL, 80.2 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 3 d. After cooling to room

temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 9:1 to 3:1) and another silica gel flash column chromatography (DCM/EtOAc 19:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (75.4 mg, 40 µmol, 49%).

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.46 (s, 2H), 8.09 (d, J = 8.2 Hz, 2H), 8.03 (d, J = 8.3 Hz, 2H), 7.89–7.82 (m, 4H), 7.81–7.75 (m, 6H), 7.64–7.56 (m, 6H), 7.53 (t, J = 7.7 Hz, 4H), 7.46 (s, 2H), 7.44–7.29 (m, 12H), 7.26 (d, J = 8.5 Hz, 2H), 7.21–7.14 (m, 6H), 7.10 (s, 2H), 7.07 (s, 2H), 6.99 (s, 2H), 6.88 (dd, J = 8.0, 1.5 Hz, 2H).

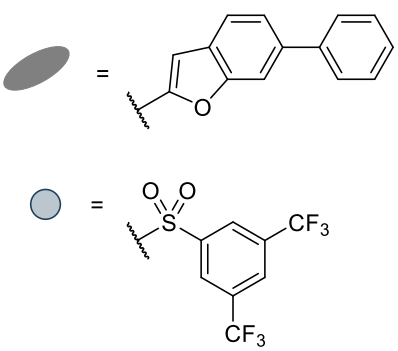
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -136.56 (d, J = 21.6 Hz, 4F), -145.72 (t, J = 21.7 Hz, 2F), -159.48 (t, J = 20.5 Hz, 4F).

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -16.50.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 155.19, 155.13, 150.63, 149.97, 142.58 (t, J = 5.3 Hz), 141.86 (t, J = 5.3 Hz), 141.65, 141.35, 139.44, 138.57, 132.10, 132.07, 131.84, 131.80, 129.93, 129.29, 129.04, 128.97, 128.79, 128.54, 128.15, 128.07, 127.98, 127.75, 127.72, 127.69, 127.47, 127.43, 127.41, 127.34, 127.16, 123.28, 123.26, 122.43, 122.40, 122.32, 122.28, 121.90, 121.65, 109.43, 109.16, 108.75, 107.89.

ESI-HRMS: calculated for $C_{108}H_{56}F_{10}N_3O_{12}P_2S_2^-$ ([M-H]$^-$): 1902.26265, found: 1902.26279.

IDPi 191j



(*S*)-BINOL **372** (73.4 mg, 0.109 mmol, 1.99 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2(3,5\text{-}(CF_3)_2\text{-}C_6H_3))Cl_3$ (46.9 mg, 0.110 mmol, 1.99 eq.) and dry toluene (0.6 mL). Et_3N (61 µL, 0.44 mmol, 7.9 eq.) was added and the mixture was stirred at room temperature for 30 min. HMDS (11.5 µL, 55.1 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 9:1 to 4:1) and another silica gel flash column chromatography (DCM/EtOAc 100:0 to 99:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (17.1 mg, 9 µmol, 16%).

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.49 (s, 2H), 8.13 (d, J = 8.2 Hz, 2H), 8.06–7.98 (m, 6H), 7.90–7.83 (m, 2H), 7.76–7.66 (m, 6H), 7.63–7.53 (m, 10H), 7.51 (t, J = 7.6 Hz, 4H), 7.44 (d, J = 8.1 Hz,

2H), 7.42–7.34 (m, 6H), 7.34–7.25 (m, 8H), 7.17–7.11 (m, 4H), 7.05 (d, J = 8.0 Hz, 4H), 7.00 (d, J = 13.5 Hz, 4H), 6.81 (d, J = 8.0 Hz, 2H).

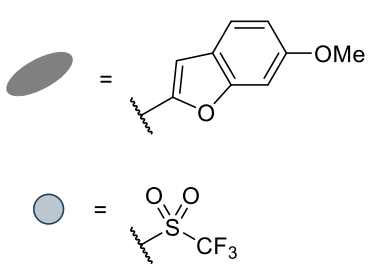
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -63.15.

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -14.56.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 155.15, 154.82, 150.71, 149.63, 144.19, 142.96, 141.70, 141.35, 139.12, 138.52, 132.45, 132.14, 132.10, 131.93, 131.81, 129.87, 129.42, 129.26, 128.94, 128.88, 128.46, 128.18, 127.99, 127.88, 127.75, 127.67, 127.38, 127.36, 127.27, 127.22, 126.63, 125.97, 123.79, 123.36, 123.11, 122.42, 122.36, 122.27, 122.20, 121.83, 121.62, 109.40, 109.20, 109.13, 107.82.

ESI-HRMS: calculated for $C_{112}H_{62}F_{12}N_3O_{12}P_2S_2^-$ ([M-H]$^-$): 1994.30640, found: 1994.30923.

IDPi 192a



(*S*)-BINOL **373** (79.0 mg, 0.137 mmol, 1.97 eq.) was placed in a flame-dried Young-Schlenk under Argon and dissolved in toluene (1.5 mL). $P(NTf)Cl_3$ (22.0 µL, 0.138 mmol, 1.98 eq.) and subsequently Et_3N (80.0 µL, 0.574 mmol, 8.26 eq.) were added to the reaction. The mixture was stirred at room temperature for 30 min. HMDS (14.5 µL, 69.5 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 3:1 to 1:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (65.8 mg, 0.043 mmol, 62%).

R_F (hex/EtOAc 1:1) = 0.28.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.60 (s, 2H), 8.10–8.05 (m, 2H), 7.98 (d, J = 8.2 Hz, 2H), 7.85 (t, J = 7.5 Hz, 2H), 7.63 (t, J = 7.7 Hz, 2H), 7.56 (t, J = 7.0 Hz, 2H), 7.53–7.43 (m, 4H), 7.42–7.09 (m, 6H), 7.16 (s, 2H), 7.02–6.93 (m, 4H), 6.80 (s, 2H), 6.72 (s, 2H), 6.37 (d, J = 2.3 Hz, 2H), 6.24 (dd, J = 8.5, 2.3 Hz, 2H), 3.94 (s, 6H), 3.49 (s, 6H).

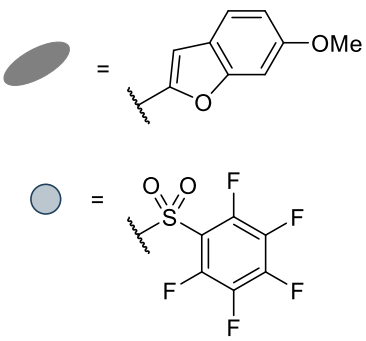
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -78.28.

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -16.91.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 159.43, 158.73, 155.89, 155.74, 149.23, 148.80, 142.63 (t, J = 5.0 Hz), 141.52 (t, J = 5.3f Hz), 132.08, 132.03, 131.93, 131.68, 129.97, 129.32, 128.48, 127.95, 127.83, 127.72, 127.59, 127.32, 127.26, 123.24, 123.05, 122.56, 122.32, 122.29, 122.08, 122.00, 121.83, 119.86 (q, J = 320.5 Hz), 112.77, 111.66, 108.43, 107.63, 95.91, 95.67, 56.14, 55.78.

ESI-HRMS: calculated for $C_{78}H_{48}N_3O_{16}S_2F_6P_2^-$ ([M-H]$^-$): 1522.186106, found: 1522.188310.

IDPi 192b



(*S*)-BINOL **373** (67.8 mg, 0.117 mmol, 2.00 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2C_6F_5)Cl_3$ (44.8 mg, 0.117 mmol, 2.00 eq.) and dry toluene (0.6 mL). Et_3N (65 µL, 0.47 mmol, 8.0 eq.) was added and the mixture was stirred at room temperature for 30 min. NH_3 (0.344 mol L^{-1} in 1,4-dioxane, 170 µL, 58.5 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 4 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 4:1 to 2:1), and another silica gel flash column chromatography (DCM/EtOAc 19:1 to 9:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (12.9 mg, 7 µmol, 13%).

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.50 (s, 2H), 8.06 (dd, J = 8.4, 4.8 Hz, 4H), 7.82 (t, J = 7.6 Hz, 2H), 7.61–7.50 (m, 6H), 7.44 (s, 2H), 7.31 (t, J = 7.7 Hz, 2H), 7.26–7.11 (m, 8H), 7.08–6.94 (m, 2H), 6.91 (s, 2H), 6.90 (s, 2H), 6.30 (s, 2H), 6.21 (dd, J = 8.4, 2.2 Hz, 2H), 3.93 (s, 6H), 3.48 (s, 6H).

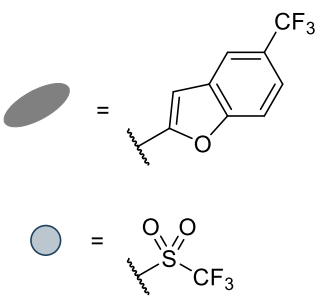
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -136.75 (s, 4F), -146.15 (s, 2F), -159.73 (s, 4F).

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -17.07.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 159.57, 158.53, 155.66, 155.48, 149.10, 148.81, 132.07, 131.86, 131.72, 131.57, 129.65, 129.38, 129.13, 128.57, 128.14, 127.60, 127.59, 127.51, 127.32, 127.19, 127.12, 127.07, 123.09, 122.88, 122.68, 122.54, 122.43, 121.82, 112.77, 111.61, 108.82, 108.01, 95.59, 56.17, 55.78.

ESI-HRMS: calculated for $C_{88}H_{48}F_{10}N_3O_{16}P_2S_2^-$ ($[M-H]^-$): 1718.17970, found: 1718.18017.

IDPi 193a



(*S*)-BINOL **374** (103.5 mg, 0.158 mmol, 2.00 eq.) was placed in a flame-dried Young-Schlenk under Argon and dissolved in toluene (1.6 mL). $P(NTf)Cl_3$ (25.5 µL, 0.160 mmol, 2.02 eq.) and subsequently Et_3N (88.0 µL, 0.631 mmol, 7.99 eq.) were added to the reaction. The mixture was stirred at room temperature for 30 min. HMDS (16.5 µL, 97.1 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 2 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases

were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 7:3) and another silica gel flash column chromatography (DCM/EtOAc 49:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (132.5 mg, 0.049 mmol, 62%).

R_F (hex/EtOAc 2:1) = 0.23.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.66 (s, 2H), 8.10 (d, J = 8.4 Hz, 2H), 8.08 (d, J = 8.2 Hz, 2H), 7.96–7.89 (m, 4H), 7.75–7.69 (m, 4H), 7.67 (dd, J = 8.8, 1.8 Hz, 2H), 7.59 (ddd, J = 8.1, 6.7, 1.1 Hz, 2H), 7.48–7.42 (m, 4H), 7.36 (ddd, J = 8.2, 6.7, 1.3 Hz, 2H), 7.29 (s, 2H), 7.23 (d, J = 8.5 Hz, 2H), 7.06 (dd, J = 8.5, 1.9 Hz, 2H), 6.99–6.93 (m, 4H), 6.89 (s, 2H).

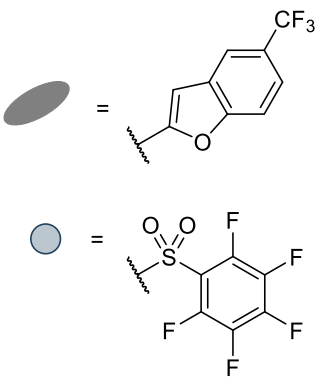
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -61.38 (s, 3F), -62.01 (s, 3F), -78.59 (s, 3F).

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -15.79.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 156.21, 155.81, 152.19, 151.61, 142.58 (t, J = 5.0 Hz), 141.74 (t, J = 5.3 Hz), 132.45, 132.21, 131.98, 131.88, 130.12, 129.74, 129.57, 129.52, 129.16, 128.71, 128.41, 127.75, 127.72, 127.56, 127.23, 126.56, 126.31, 126.28, 126.05, 125.94, 125.80, 125.68, 125.55, 125.43, 125.17, 124.12, 123.62, 123.40, 123.37 (t, J = 1.6 Hz), 122.72 (q, J = 3.4 Hz), 122.12 (t, J = 1.2 Hz), 121.98 (q, J = 3.3 Hz), 121.34 (t, J = 1.5 Hz), 121.23, 121.06 (t, J = 2.0 Hz), 119.28, 119.24, 119.21, 119.18, 119.15, 118.54, 112.06, 111.52, 107.90, 107.57.

ESI-HRMS: calculated for $C_{78}H_{36}N_3O_{12}S_2F_{18}P_2^-$ ([M-H]$^-$): 1674.093388, found: 1674.094560.

IDPi 193b



(*S*)-BINOL **374** (103.5 mg, 0.158 mmol, 2.00 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2C_6F_5)Cl_3$ (60.3 mg, 0.158 mmol, 1.99 eq.) and dry toluene (0.8 mL). Et_3N (88 µL, 0.63 mmol, 8.0 eq.) was added and the mixture was stirred at room temperature for 60 min. HMDS (16,5 µL, 0.79 mmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 15 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 30–70%), another silica gel flash column chromatography (DCM/EtOAc 19:1), another silica gel flash column chromatography (PhMe/EtOAc 19:1), and another silica gel flash column chromatography (DCM/MeOH 99:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as a white solid (33.4 mg, 18 µmol, 23%).

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.62 (s, 2H), 8.15 (d, J = 8.2 Hz, 2H), 8.11 (d, J = 8.3 Hz, 2H), 8.03 (s, 2H), 7.90 (t, J = 7.5 Hz, 2H), 7.74 (d, J = 8.7 Hz, 2H), 7.68–7.55 (m, 8H), 7.43 (s, 2H), 7.38 (ddd, J = 8.2, 6.8, 1.3 Hz, 2H), 7.29–7.20 (m, 6H), 7.20–7.11 (m, 2H), 7.06–7.00 (m, 2H), 6.88 (d, J = 8.6 Hz, 2H).

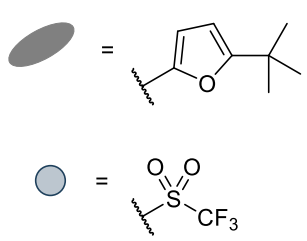
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -61.42 (s, 6F), -62.10 (s, 6F), (-135.38)–(-137.40) (m, 4F), -145.47 (s, 2F), -159.62 (s, 4F).

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -14.46.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 156.04, 155.64, 151.99, 151.21, 142.30 (t, J = 5.2 Hz), 141.85, 132.19, 132.02, 131.95, 131.75, 129.94, 129.52, 129.45, 129.35, 129.31, 128.66, 128.59, 128.47, 127.76, 127.55, 127.00, 126.30, 126.23, 126.04, 125.56, 125.42, 125.17, 124.08, 123.40, 123.22, 122.80 (q, J = 3.3 Hz), 122.35, 121.85 (q, J = 3.1 Hz), 121.59, 120.98, 119.89 (q, J = 3.9 Hz), 119.32 (q, J = 4.0 Hz), 111.81, 111.48, 108.66, 108.07.

ESI-HRMS: calculated for $C_{88}H_{36}N_3O_{12}S_2F_{22}P_2^-$ ([M-H]$^-$): 1870.087002, found: 1870.088450.

IDPi 194a



(*S*)-BINOL **375** (102.5 mg, 0.193 mmol, 2.02 eq.) was placed in a flame-dried Young-Schlenk under Argon and dissolved in toluene (1.0 mL). $P(NTf)Cl_3$ (31.0 µL, 0.194 mmol, 2.02 eq.) and subsequently Et_3N (107 µL, 0.768 mmol, 8.01 eq.) were added to the reaction. The mixture was stirred at room temperature for 20 min. HMDS (20.0 µL, 95.8 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (toluene/EtOAc 19:1 to 9:1), automated reversed phase silica gel chromatography (CH_3CN/H_2O 60:40 to 100:0), and another silica gel column chromatography (hex/acetone 9:1 to 4:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (60.9 mg, 0.043 mmol, 45%).

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.50 (s, 2H), 8.03 (d, J = 8.4 Hz, 2H), 7.66 (t, J = 7.5 Hz, 2H), 7.54–7.47 (m, 4H), 7.44 (t, J = 7.6 Hz, 2H), 7.20 (dd, J = 17.9, 8.3 Hz, 4H), 7.07 (s, 2H), 7.02 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 3.5 Hz, 2H), 6.78 (d, J = 3.4 Hz, 2H), 6.28 (d, J = 3.5 Hz, 2H), 5.87 (d, J = 3.4 Hz, 2H), 1.48 (s, 18H), 0.92 (s, 18H).

^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -78.59.

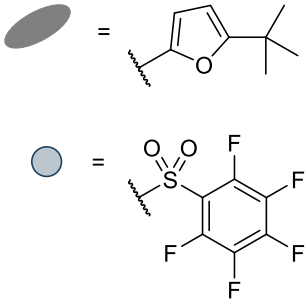
^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -17.96.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 165.68, 164.51, 146.29, 145.97, 142.57 (t, J = 5.0 Hz), 140.89 (t, J = 5.2 Hz), 132.30, 131.96, 131.13, 130.52, 130.40, 129.02, 127.45, 127.21, 126.90, 126.84,

126.79, 126.55, 126.39, 125.20, 123.30, 122.71, 122.38, 122.07, 119.79 (d, J = 320.0 Hz), 113.77, 112.34, 105.79, 105.13, 33.32, 32.79, 29.40, 28.94.

ESI-HRMS: calculated for $C_{74}H_{64}F_6N_3O_{12}P_2S_2^-$ ([M-H]$^-$): 1426.33163, found: 1426.33324.

IDPi 194b



(*S*)-BINOL **375** (60.0 mg, 0.113 mmol, 2.01 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2C_6F_5)Cl_3$ (43.0 mg, 0.112 mmol, 2.00 eq.) and dry toluene (2.0 mL). Et_3N (65 µL, 0.47 mmol, 8.3 eq.) was added and the mixture was stirred at room temperature for 30 min. HMDS (11.75 µL, 56.3 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 15 min and subsequently heated to 120 °C for 2 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 30–70%), another silica gel flash column chromatography (DCM/EtOAc 49:1), and another silica gel flash column chromatography (hex/EtOAc 4:1 to 2:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as a white solid (29.5 mg, 18 µmol, 23%).

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.39 (s, 2H), 7.99 (d, J = 8.3 Hz, 2H), 7.61 (t, J = 7.4 Hz, 2H), 7.52–7.45 (m, 4H), 7.36 (ddd, J = 8.2, 6.7, 1.3 Hz, 2H), 7.18 (ddd, J = 8.3, 6.8, 1.3 Hz, 2H), 7.11–7.06 (m, 4H), 6.97 (d, J = 8.5 Hz, 2H), 6.93 (d, J = 3.5 Hz, 2H), 6.77 (d, J = 3.3 Hz, 2H), 6.26 (d, J = 3.5 Hz, 2H), 5.75 (d, J = 3.3 Hz, 2H), 1.46 (s, 18H), 0.87 (s, 18H).

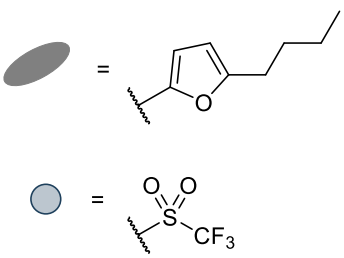
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -136.28 (d, J = 21.5 Hz, 4F), -146.74 (s, 2F), -159.84 (t, J = 20.0 Hz, 4F).

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -17.80.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 165.47, 164.23, 146.32, 145.87, 142.29 (t, J = 5.0 Hz), 141.05, 131.98, 131.91, 131.02, 130.47, 130.22, 128.73, 127.23, 127.10, 126.98, 126.85, 126.61, 126.36, 125.55, 124.98, 122.95, 122.58, 122.53, 122.34, 114.03, 112.53, 105.72, 105.17, 33.27, 32.71, 29.35, 28.88.

ESI-HRMS: calculated for $C_{84}H_{64}N_3O_{12}S_2F_{10}P_2^-$ ([M-H]$^-$): 1622.325260, found: 1622.327250.

IDPi 195a



(*S*)-BINOL **376** (87.0 mg, 0.164 mmol, 2.01 eq.) was placed in a flame-dried Young-Schlenk under Argon and dissolved in toluene (0.87 mL). $P(NTf)Cl_3$ (26.0 µL, 0.163 mmol, 2.00 eq.) and subsequently Et_3N (90.0 µL, 0.646 mmol, 7.93 eq.) were added to the reaction. The mixture was stirred at room temperature for 20 min. HMDS (17.0 µL, 81.4 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/acetone 9:1 to 4:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (63.7 mg, 0.045 mmol, 55%).

R_F (hex/acetone 2:1) = 0.10.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.51 (s, 2H), 8.04 (d, J = 8.3 Hz, 2H), 7.80 (d, J = 8.1 Hz, 2H), 7.75 (t, J = 7.4 Hz, 2H), 7.51 (t, J = 7.6 Hz, 2H), 7.47 (ddd, J = 8.2, 6.6, 1.4 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 7.24 (t, J = 7.6 Hz, 2H), 7.13 (d, J = 8.5 Hz, 2H), 6.91 (s, 2H), 6.84 (d, J = 3.4 Hz, 2H), 6.55 (d, J = 3.3 Hz, 2H), 6.26 (d, J = 3.4 Hz, 2H), 5.82 (d, J = 3.3 Hz, 2H), 2.85 (t, J = 7.6 Hz, 4H), 2.16–1.97 (m, 4H), 1.82 (p, J = 7.6 Hz, 4H), 1.52 (h, J = 7.4 Hz, 4H), 1.38–1.05 (m, 12H), 1.03 (t, J = 7.4 Hz, 6H), 0.73 (t, J = 7.3 Hz, 6H).

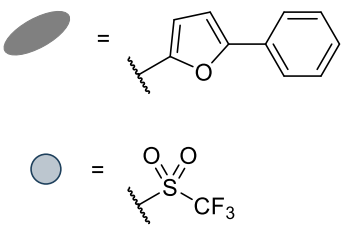
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -78.62.

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -17.74.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 158.22, 157.35, 146.53, 146.33, 142.53 (t, J = 5.3 Hz), 141.07 (t, J = 5.0 Hz), 132.34, 132.07, 131.22, 131.00, 129.78, 129.07, 127.53, 127.26, 126.98, 126.93, 126.88, 126.73, 126.61, 126.27, 123.14, 122.92, 122.51, 122.13, 119.78 (q, J = 320.0 Hz), 113.55, 112.22, 107.86, 107.82, 30.65, 29.70, 28.31, 27.75, 22.77, 22.61, 14.08, 13.88.

ESI-HRMS: calculated for $C_{74}H_{64}F_6N_3O_{12}P_2S_2^-$ ($[M-H]^-$): 1426.33163, found: 1426.33303.

IDPi 196a



(*S*)-BINOL **377** (111.3 mg, 0.195 mmol, 2.04 eq.) was placed in a flame-dried Young-Schlenk under Argon and dissolved in toluene (1.0 mL). $P(NTf)Cl_3$ (31.0 µL, 0.194 mmol, 2.02 eq.) and subsequently Et_3N (107 µL, 0.768 mmol, 8.01 eq.) were added to the reaction. The mixture was stirred at room temperature for 20 min. HMDS (20.0 µL, 95.8 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture

was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (toluene/EtOAc 19:1 to 9:1), another silica gel column chromatography (DCM/EtOAc 49:1 to 19:1), another silica gel column chromatography (hex/acetone 9:1 to 4:1), and another silica gel column chromatography (hex/EtOAc 4:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (27.9 mg, 0.018 mmol, 19%).

$\boldsymbol{R_F}$ (toluene/EtOAc 4:1) = 0.33.

^{1}H-NMR (600 MHz, C_6D_6): δ = 8.38 (s, 2H), 7.83–7.78 (m, 4H), 7.58–7.54 (m, 4H), 7.51–7.46 (m, 2H), 7.35–7.30 (m, 4H), 7.27 (t, J = 7.8 Hz, 4H), 7.24–7.20 (m, 6H), 7.18–7.09 (m, 8H), 7.05 (ddd, J = 8.1, 6.7, 1.1 Hz, 2H), 6.96–6.87 (m, 8H), 6.79 (ddd, J = 8.2, 6.7, 1.3 Hz, 2H), 6.39 (d, J = 3.4 Hz, 2H).

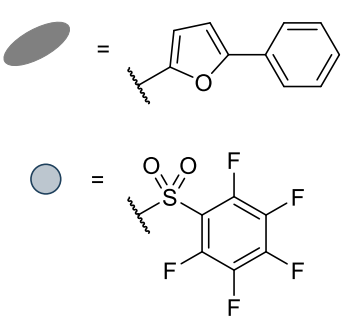
^{19}F-NMR (565 MHz, C_6D_6): δ = -78.38.

^{31}P-NMR (243 MHz, C_6D_6): δ = -15.34.

^{13}C-NMR (151 MHz, C_6D_6): δ = 154.45, 154.07, 148.08, 147.83, 143.04 (t, J = 5.1 Hz), 141.91, 131.94, 131.91, 131.43, 131.25, 131.09, 130.32, 129.80, 129.09, 128.95, 128.35, 128.14, 127.98, 127.71, 127.51, 127.22, 126.83, 126.78, 126.53, 126.48, 126.30, 124.69, 124.40, 123.48, 122.84, 122.65, 121.99, 120.26 (q, J = 320.8 Hz), 115.19, 114.24, 108.71, 108.54.

ESI-HRMS: calculated for $C_{82}H_{48}F_6N_3O_{12}P_2S_2^-$ ([M-H]$^-$): 1506.20643, found: 1506.20731.

IDPi 196b



(*S*)-BINOL **377** (70.4 mg, 0.123 mmol, 2.02 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2C_6F_5)Cl_3$ (47.2 mg, 0.123 mmol, 2.02 eq.) and dry toluene (2.0 mL). Et_3N (70 µL, 0.50 mmol, 8.2 eq.) was added and the mixture was stirred at room temperature for 30 min. HMDS (12.75 µL, 61.1 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 2 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 30–70%), another silica gel flash column chromatography (DCM/EtOAc 49:1 to 19:1), automated reversed phase column chromatography (CH_3CN/H_2O 60:40 to 100:0), and another silica gel flash column chromatography (hex/EtOAc 2:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as a white solid (35.6 mg, 21 µmol, 34%).

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.29 (s, 2H), 7.95 (d, J = 8.3 Hz, 2H), 7.92 (s, 4H), 7.91 (s, 2H), 7.77–7.68 (m, 4H), 7.56 (t, J = 7.7 Hz, 4H), 7.50 (t, J = 7.6 Hz, 2H), 7.46–7.39 (m, 4H), 7.21 (ddd, J = 8.3, 6.8, 1.3 Hz, 2H), 7.19–7.14 (m, 6H), 7.14–7.09 (m, 6H), 7.09–7.03 (m, 6H), 6.87 (d, J = 3.6 Hz, 2H), 6.81 (d, J = 3.5 Hz, 2H), 6.45 (d, J = 3.5 Hz, 2H).

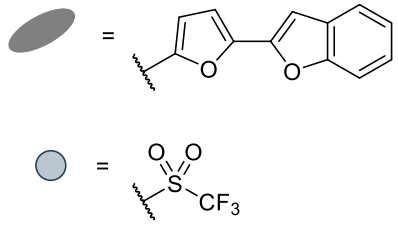
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -136.44 (d, J = 21.6 Hz, 4F), -146.53 (s, 2F), -159.75 (t, J = 20.2 Hz, 4F).

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -17.55.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 154.17, 153.92, 147.89, 147.53, 142.30 (t, J = 5.1 Hz), 141.34 (t, J = 4.8 Hz), 131.96, 131.75, 131.21, 131.05, 130.66, 130.16, 129.98, 129.32, 128.80, 128.42, 128.37, 127.69, 127.43, 127.22, 127.11, 127.08, 127.05, 126.78, 126.51, 126.29, 124.37, 124.31, 122.99, 122.33, 122.15, 121.87, 115.02, 113.65, 108.54, 108.04.

ESI-HRMS: calculated for $C_{92}H_{48}N_3O_{12}S_2P_2F_{10}^-$ ([M-H]$^-$): 1702.200060, found: 1702.200630.

IDPi 197a



(*S*)-BINOL **378** (125.5 mg, 0.193 mmol, 2.01 eq.) was placed in a flame-dried Young-Schlenk under Argon and dissolved in toluene (1.0 mL). P(NTf)Cl_3 (31.0 µL, 0.194 mmol, 2.02 eq.) and subsequently Et_3N (107 µL, 0.768 mmol, 8.01 eq.) were added to the reaction. The mixture was stirred at room temperature for 20 min. HMDS (20.0 µL, 95.8 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (toluene/EtOAc 19:1 to 9:1), automated reversed phase silica gel chromatography (CH_3CN/H_2O 60:40 to 100:0), another silica gel column chromatography (DCM/EtOAc 49:1 to 19:1), and another silica gel column chromatography (hex/EtOAc 9:1 to 4:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (80.1 mg, 0.048 mmol, 50%).

***R*$_F$** (hex/EtOAc 1:1) = 0.41.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.06 (s, 2H), 7.75 (d, J = 7.8 Hz, 4H), 7.71 (d, J = 8.5 Hz, 2H), 7.64 (t, J = 7.4 Hz, 4H), 7.59 (t, J = 7.7 Hz, 2H), 7.50 (d, J = 8.6 Hz, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.40 (q, J = 7.5, 5.3 Hz, 4H), 7.35 (t, J = 7.4 Hz, 2H), 7.31–7.14 (m, 10H), 7.13–7.05 (m, 4H), 7.03–6.96 (m, 4H), 6.78 (d, J = 3.5 Hz, 2H), 6.66 (d, J = 3.6 Hz, 2H), 6.44 (s, 2H).

^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -78.39.

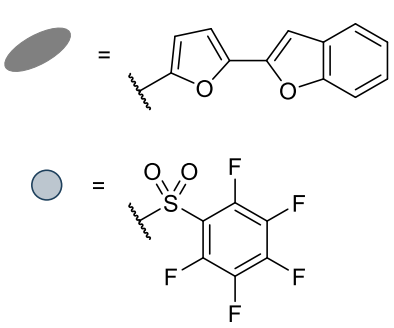
^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -17.18.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 155.34, 154.82, 148.93, 148.78, 148.24, 147.37, 146.40, 146.25, 142.58 (t, J = 5.7 Hz), 141.18 (t, J = 4.9 Hz), 131.96, 131.89, 131.45, 131.42, 130.52,

129.29, 129.25, 128.78, 127.58, 127.55, 127.53, 127.30, 127.27, 127.10, 127.06, 126.91, 125.20, 125.02, 123.78, 123.57, 123.17, 121.79, 121.66, 121.62, 121.43, 121.22, 119.76 (q, J = 320.3 Hz), 114.03, 113.18, 111.57, 111.29, 111.13, 110.49, 102.47, 102.19.

ESI-HRMS: calculated for $C_{90}H_{48}F_6N_3O_{16}P_2S_2^-$ ([M-H]$^-$): 1666.186106, found: 1666.187040.

IDPi 197b



(*S*)-BINOL **378** (68.0 mg, 0.104 mmol, 1.98 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2C_6F_5)Cl_3$ (40.0 mg, 0.105 mmol, 1.98 eq.) and dry toluene (2.0 mL). Et_3N (60 µL, 0.43 mmol, 8.2 eq.) was added and the mixture was stirred at room temperature for 30 min. HMDS (11 µL, 53 µmol, 1.0 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 2 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 30–70%), another silica gel flash column chromatography (DCM/EtOAc 49:1 to 19:1), automated reversed phase column chromatography (CH_3CN/H_2O 60:40 to 100:0), and another silica gel flash column chromatography (hex/EtOAc 2:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as a white solid (24.7 mg, 13 µmol, 25%).

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 7.96 (s, 2H), 7.77–7.67 (m, 6H), 7.67–7.60 (m, 4H), 7.53 (t, J = 7.6 Hz, 2H), 7.47 (t, J = 7.5 Hz, 2H), 7.43–7.36 (m, 6H), 7.34 (t, J = 7.2 Hz, 2H), 7.29–7.20 (m, 6H), 7.20–7.15 (m, 6H), 7.08–7.03 (m, 4H), 6.91 (d, J = 3.7 Hz, 2H), 6.76 (d, J = 3.4 Hz, 2H), 6.57 (d, J = 3.6 Hz, 2H), 6.47 (s, 2H).

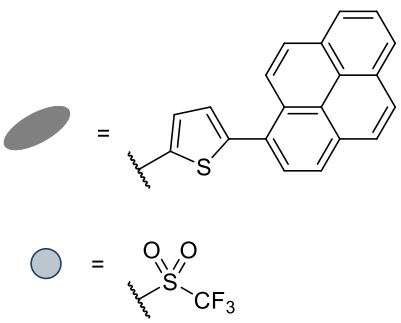
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -136.51 (d, J = 21.5 Hz, 4F), -146.43 (s, 2F), -159.68 (t, J = 20.7 Hz, 4F).

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -17.07.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 155.37, 154.82, 149.08, 148.63, 148.06, 147.53, 146.23, 146.05, 142.37 (t, J = 5.6 Hz), 141.40, 131.92, 131.67, 131.37, 130.36, 129.25, 129.02, 128.87, 127.40, 127.38, 127.17, 127.03, 126.88, 126.65, 125.22, 124.93, 124.09, 123.76, 123.53, 123.09, 122.13, 121.95, 121.64, 121.60, 121.21, 114.46, 113.33, 111.58, 111.30, 111.10, 110.53, 102.44, 102.04.

ESI-HRMS: calculated for $C_{100}H_{48}N_3O_{16}S_2F_{10}P_2^-$ ([M-H]$^-$): 1862.179720, found: 1862.179450.

IDPi 198a



(*S*)-BINOL **379** (92 mg, 0.11 mmol, 2.05 eq.) was placed in a flame-dried Young-Schlenk under Argon and dissolved in toluene (0.6 mL). $P(NTf)Cl_3$ (17 µL, 0.11 mmol, 2.02 eq.) and subsequently Et_3N (60 µL, 0.43 mmol, 8.2 eq.) were added to the reaction. The mixture was stirred at room temperature for 20 min. HMDS (11 µL, 53 µmol, 1.0 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 4 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 2:1 to 3:2), another silica gel column chromatography (PhMe/EtOAc 2–3%), and another silica gel column chromatography (hex/EtOAc 2:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (86.4 mg, 0.042 mmol, 79%).

$\boldsymbol{R_F}$ (hex/EtOAc 1:1) = 0.44.

^{1}H-NMR (600 MHz, CD_2Cl_2): δ = 8.34 (s, 2H), 8.32 (s, 2H), 8.27–8.21 (m, 2H), 8.21–8.10 (m, 6H), 8.10–8.05 (m, 4H), 8.05–7.97 (m, 12H), 7.97–7.91 (m, 2H), 7.89 (s, 2H), 7.87 (s, 2H), 7.86–7.82 (m, 4H), 7.79–7.68 (m, 8H), 7.56–7.51 (m, 2H), 7.49 (s, 2H), 7.45 (s, 2H), 7.36 (d, J = 8.5 Hz, 2H), 7.31–7.21 (m, 6H), 7.19–7.13 (m, 2H), 7.04–6.95 (m, 2H), 6.90 (s, 2H).

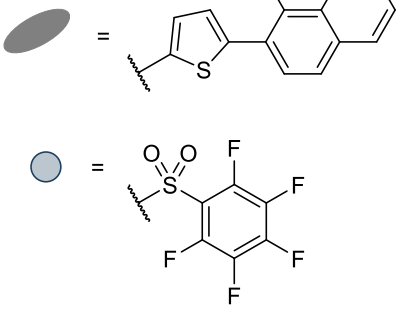
^{19}F-NMR (565 MHz, CD_2Cl_2): δ = -78.20.

^{31}P-NMR (243 MHz, CD_2Cl_2): δ = -16.74.

^{13}C-NMR (151 MHz, CD_2Cl_2): δ = 144.27, 144.08, 143.52, 142.30, 138.04, 137.82, 132.49, 132.32, 132.04, 131.81, 131.73, 131.35, 131.28, 131.16, 130.18, 129.33, 129.15, 128.98, 128.75, 128.64, 128.46, 128.22, 128.08, 127.84, 127.68, 127.58, 127.42, 127.28, 127.16, 126.71, 126.57, 126.41, 125.96, 125.79, 125.35, 125.28, 125.14, 124.99, 124.91, 124.86, 124.79, 123.81, 122.80, 120.67, 118.54, 116.41.

ESI-HRMS: calculated for $C_{122}H_{64}N_3O_8P_2S_6F_6^-$ ($[M-H]^-$): 2066.240277, found: 2066.243510.

IDPi 198b



(*S*)-BINOL **379** (108 mg, 0.13 mmol, 2.0 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2C_6F_5)Cl_3$ (48.5 mg, 0.13 mmol, 2.0 eq.) and dry toluene (1.3 mL). Et_3N (70 µL, 0.50 mmol, 8.1 eq.) was added and the mixture was stirred at room temperature for 30 min. HMDS (13 µL, 62 µmol, 1.0 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 2 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 4:1 to 1:1), another silica gel flash column chromatography (100% DCM), automated reversed phase column chromatography (CH_3CN/H_2O 80:20 to 100:0), and another silica gel flash column chromatography (*n*-pentane/acetone 20–30%). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as a green solid (70.7 mg, 31 µmol, 71%).

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.52 (d, J = 9.3 Hz, 2H), 8.42 (s, 2H), 8.26 (d, J = 9.2 Hz, 2H), 8.17 (d, J = 7.6 Hz, 4H), 8.12–8.07 (m, 6H), 8.06 (s, 2H), 8.05–8.01 (m, 8H), 8.01–7.98 (m, 2H), 7.98–7.95 (m, 2H), 7.95–7.91 (m, 6H), 7.83 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 3.7 Hz, 2H), 7.78 (s, 2H), 7.71 (d, J = 9.3 Hz, 2H), 7.64 (d, J = 7.8 Hz, 2H), 7.51 (t, J = 7.6 Hz, 2H), 7.44 (t, J = 7.5 Hz, 2H), 7.30 (d, J = 3.8 Hz, 2H), 7.20 (q, J = 6.2 Hz, 4H), 7.13 (d, J = 8.6 Hz, 2H), 7.10 (d, J = 3.7 Hz, 2H), 6.66 (d, J = 8.6 Hz, 2H), 6.45 (t, J = 7.7 Hz, 2H).

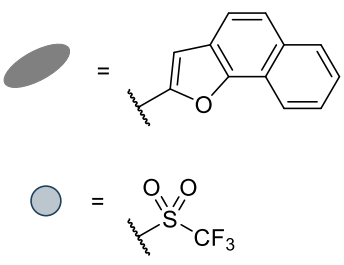
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -135.33 (d, J = 22.1 Hz, 4F), -146.58 (s, 2F), -159.97 (t, J = 21.5 Hz, 4F).

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -14.04.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 144.18, 143.64, 143.52, 142.70, 138.20, 132.51, 132.15, 131.81, 131.74, 131.54, 131.28, 131.18, 131.13, 129.82, 129.61, 129.57, 129.45, 129.29, 129.13, 128.80, 128.77, 128.73, 128.69, 128.48, 128.20, 128.04, 128.00, 127.87, 127.65, 127.63, 127.39, 127.33, 127.12, 126.98, 126.90, 126.52, 126.48, 126.40, 125.66, 125.64, 125.55, 125.43, 125.30, 125.28, 125.12, 124.99, 124.93, 124.90, 124.84, 124.76, 123.67, 123.30.

ESI-HRMS: calculated for $C_{132}H_{64}N_3O_8S_6P_2F_{10}^-$ ([M-H]$^-$): 2262.233890, found: 2262.232950.

IDPi 199a



(*S*)-BINOL **380** (66.8 mg, 0.108 mmol, 2.05 eq.) was placed in a flame-dried Young-Schlenk under Argon and dissolved in toluene (0.60 mL). $P(NTf)Cl_3$ (17.0 µL, 0.106 mmol, 2.02 eq.) and subsequently Et_3N (60.0 µL, 0.431 mmol, 8.17 eq.) were added to the reaction. The mixture was stirred at room temperature for 30 min. HMDS (11.0 µL, 52.7 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 15 min and subsequently heated to 120 °C for 4 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 4:1 to 1:1) and a second silica gel flash column chromatography (toluene/EtOAc 9:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (65.9 mg, 0.041 mmol, 78%).

$\boldsymbol{R_F}$ (hex/EtOAc 1:1) = 0.24.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.53 (d, J = 8.2 Hz, 2H), 8.47 (s, 2H), 8.04 (dd, J = 8.3, 5.2 Hz, 2H), 7.93–7.77 (m, 4H), 7.77–7.69 (m, 4H), 7.64–7.59 (m, 4H), 7.56 (t, J = 7.6 Hz, 2H), 7.55–7.45 (m, 2H), 7.42 (d, J = 8.1 Hz, 4H), 7.36–7.24 (m, 8H), 7.18 (d, J = 8.3 Hz, 6H), 7.08 (s, 2H), 6.79 (d, J = 8.4 Hz, 2H), 6.61 (s, 2H).

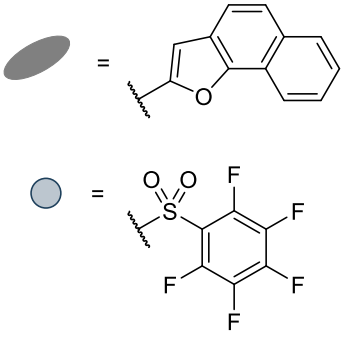
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -78.25.

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -16.85.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 150.46, 150.03, 149.67, 148.55, 142.72 (t, J = 5.3 Hz), 141.62, 132.47, 132.09, 132.02, 131.99, 131.70, 131.68, 130.46, 129.30, 128.97, 128.67, 128.60, 128.21, 128.04, 127.53, 127.27, 127.24, 127.16, 126.85, 126.22, 125.84, 125.63, 125.39, 124.96, 124.15, 124.01, 123.32, 122.46, 121.86, 121.47, 120.96, 120.55, 120.43, 119.87, 119.82 (q, J = 320.6 Hz), 119.66, 109.03, 108.97.

ESI-HRMS: calculated for $C_{90}H_{48}N_3O_{12}S_2P_2F_6^-$ ($[M-H]^-$): 1602.206446, found: 1602.207590.

IDPi 199b



(*S*)-BINOL **380** (22.3 mg, 0.036 mmol, 2.02 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2C_6F_5)Cl_3$ (13.8 mg, 0.036 mmol, 2.02 eq.) and dry toluene (0.5 mL). DIPEA (25 µL, 0.14 mmol, 8.0 eq.) was added and the mixture was stirred at room temperature for 30 min. NH_3 (0.344 mol L^{-1} in 1,4-dioxane, 52 µL, 17.9 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for

3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/acetone 9:1 to 2:1), another silica gel flash column chromatography (PhMe/EtOAc 19:1), and another silica gel flash column chromatography (hex/EtOAc 9:1 to 2:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (11 mg, 18 µmol, 34%).

$\boldsymbol{R_F}$ (hex/EtOAc 1:1) = 0.18.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.53–8.48 (m, 4H), 8.05 (d, J = 8.3 Hz, 2H), 8.02–7.92 (m, 6H), 7.78–7.68 (m, 6H), 7.68–7.54 (m, 8H), 7.48 (d, J = 8.0 Hz, 2H), 7.37 (t, J = 7.6 Hz, 2H), 7.28 (p, J = 6.9 Hz, 6H), 7.17–7.02 (m, 10H), 6.90 (d, J = 8.4 Hz, 2H).

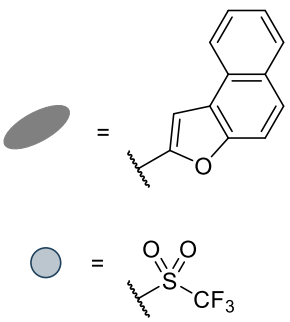
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -136.64 (d, J = 21.3 Hz, 4F), -146.40 (s, 2F), -159.77 (s, 4F).

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -15.98.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 150.34, 149.94, 149.58, 148.69, 142.45, 132.52, 132.05, 131.94, 131.86, 131.60, 129.75, 129.11, 128.98, 128.45, 128.22, 127.79, 127.60, 127.42, 127.30, 127.11, 126.90, 126.28, 125.91, 125.56, 125.41, 124.89, 124.07, 123.69, 123.20, 122.42, 121.26, 121.00, 120.85, 120.44, 120.37, 119.73, 109.75, 109.00.

ESI-HRMS: calculated for $C_{100}H_{48}N_3O_{12}S_2P_2F_{10}^-$ ([M-H]$^-$): 1798.200060, found: 1798.201070.

IDPi 200a



(*S*)-BINOL **381** (66.8 mg, 0.108 mmol, 2.05 eq.) was placed in a flame-dried Young-Schlenk under Argon and dissolved in toluene (0.60 mL). $P(NTf)Cl_3$ (17.0 µL, 0.106 mmol, 2.02 eq.) and subsequently Et_3N (60.0 µL, 0.431 mmol, 8.17 eq.) were added to the reaction. The mixture was stirred at room temperature for 30 min. HMDS (11.0 µL, 52.7 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 15 min and subsequently heated to 120 °C for 4 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (toluene/EtOAc 19:1) and a second silica gel flash column chromatography (hex/EtOAc 2:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (58.3 mg, 0.036 mmol, 69%).

$\boldsymbol{R_F}$ (hex/EtOAc 1:1) = 0.25.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.53 (s, 2H), 8.06 (d, J = 8.4 Hz, 4H), 7.97 (d, J = 8.0 Hz, 2H), 7.79 (dt, J = 23.4, 8.5 Hz, 6H), 7.67–7.49 (m, 14H), 7.43 (s, 2H), 7.30 (d, J = 8.2 Hz, 2H), 7.25 (t,

J = 7.5 Hz, 2H), 7.17 (d, J = 8.9 Hz, 2H), 7.12 (d, J = 8.5 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 6.93 (s, 2H), 6.85 (s, 2H), 6.62 (t, J = 7.5 Hz, 2H), 6.40 (t, J = 7.4 Hz, 2H).

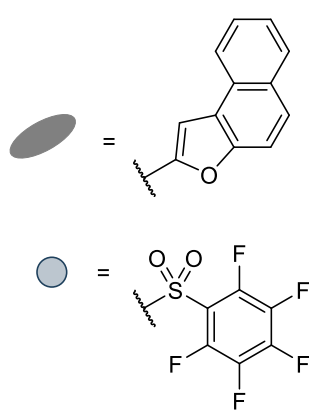
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -78.41

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -16.89.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 152.40, 152.08, 149.65, 148.28, 143.03 (t, J = 4.9 Hz), 141.50 (t, J = 5.0 Hz), 132.08, 131.95, 131.92, 131.75, 130.75, 130.48, 130.18, 129.26, 128.77, 128.67, 128.61, 128.30, 128.04, 127.89, 127.79, 127.75, 127.52, 127.44, 127.15, 126.99, 126.52, 126.36, 126.28, 126.17, 124.85, 124.66, 124.63, 124.50, 124.20, 123.38, 122.83, 122.21, 121.89, 119.72 (q, J = 320.1 Hz), 112.19, 111.27, 106.65, 106.60.

ESI-HRMS: calculated for $C_{90}H_{48}N_3O_{12}S_2P_2F_6^-$ ([M-H]$^-$): 1602.206446, found: 1602.207590.

IDPi 200b



(*S*)-BINOL **381** (62 mg, 0.10 mmol, 2.0 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2C_6F_5)Cl_3$ (38 mg, 0.10 mmol, 2.0 eq.) and dry toluene (1.0 mL). DIPEA (70 µL, 0.40 mmol, 8.1 eq.) was added and the mixture was stirred at room temperature for 30 min. NH_3 (0.344 mol L^{-1} in 1,4-dioxane, 145 µL, 49.9 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/acetone 9:1 to 2:1) and another silica gel flash column chromatography (PhMe/EtOAc 98:2). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (21 mg, 12 µmol, 23%).

***R*$_F$** (hex/EtOAc 1:1) = 0.09.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.51 (s, 2H), 8.21 (d, J = 8.2 Hz, 2H), 8.15–8.05 (m, 4H), 7.94–7.86 (m, 4H), 7.80 (s, 2H), 7.78–7.72 (m, 4H), 7.72–7.67 (m, 2H), 7.66–7.60 (m, 4H), 7.56 (d, J = 9.4 Hz, 2H), 7.50 (t, J = 7.5 Hz, 2H), 7.45 (t, J = 7.3 Hz, 2H), 7.38 (t, J = 7.7 Hz, 2H), 7.29 (d, J = 8.5 Hz, 2H), 7.25–7.15 (m, 4H), 7.10 (d, J = 8.8 Hz, 2H), 6.96–6.89 (m, 4H), 6.43 (s, 2H), 6.12 (t, J = 7.3 Hz, 2H).

^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -136.30 (d, J = 21.0 Hz, 4F), -146.04 (s, 2F), -159.96 (t, J = 19.5 Hz, 4F).

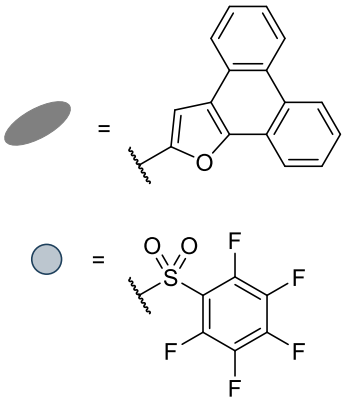
^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -17.29.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 152.32, 151.63, 149.67, 147.66, 132.18, 132.11, 131.88, 131.61, 130.54, 130.07, 130.02, 129.23, 128.64, 128.51, 128.20, 127.97, 127.89, 127.81, 127.70,

127.42, 127.29, 126.99, 126.72, 126.60, 126.45, 125.78, 125.28, 124.99, 124.34, 123.87, 123.38, 122.75, 122.44, 121.71, 111.52, 111.36, 107.38, 107.21.

ESI-HRMS: calculated for $C_{100}H_{48}N_3O_{12}S_2P_2F_{10}^-$ ([M-H]$^-$): 1798.200060, found: 1798.201570.

IDPi 201b



(*S*)-BINOL **382** (26 mg, 0.036 mmol, 2.0 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2C_6F_5)Cl_3$ (13.8 mg, 0.036 mmol, 1.99 eq.) and dry toluene (0.5 mL). Et_3N (20 µL, 0.14 mmol, 7.9 eq.) was added and the mixture was stirred at room temperature for 45 min. HMDS (3.8 µL, 18 µmol, 1.0 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/acetone 30-40%), and another silica gel flash column chromatography (DCM/acetone 4:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (18.1 mg, 9 µmol, 50%).

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = δ 8.80–8.67 (m, 2H), 8.61–8.49 (m, 2H), 8.45 (s, 2H), 8.25–8.15 (m, 2H), 8.15–7.96 (m, 4H), 7.92–7.44 (m, 24H), 7.44–7.00 (m, 14H), 6.85 (s, 2H), 6.48–6.39 (m, 4H).

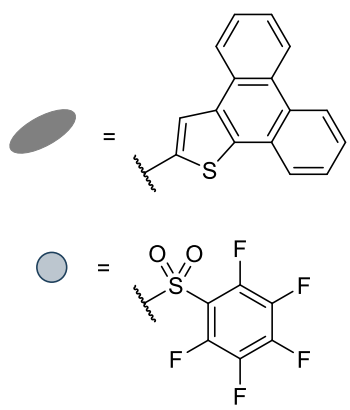
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -136.26 (d, J = 21.2 Hz, 4F), -146.98 (s, 2F), -160.17 (s, 4F).

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -17.02

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 149.81, 149.08, 147.68, 147.36, 142.53, 141.87, 131.98, 131.63, 131.39, 130.79, 129.95, 129.34, 129.01, 128.23, 127.74, 127.52, 127.36, 127.16, 127.02, 126.79, 126.57, 126.43, 125.75, 125.55, 125.40, 124.58, 123.77, 123.63, 123.34, 123.20, 122.91, 122.48, 122.26, 121.83, 121.66, 120.77, 120.20, 107.83, 107.36.

ESI-HRMS: calculated for $C_{116}H_{56}N_3O_{12}F_{10}P_2S_2^-$ ([M-H]$^-$): 1998.262660, found: 1998.263770.

IDPi 202b



(*S*)-BINOL **383** (442 mg, 0.589 mmol, 2.00 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2C_6F_5)Cl_3$ (225 mg, 0.588 mmol, 2.00 eq.) and dry toluene (6.0 mL). Et_3N (328 µL, 2.35 mmol, 8.00 eq.) was added and the mixture was stirred at room temperature for 30 min. HMDS (61.5 µL, 0.295 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (MTBE/hex 2:1 to 4:1), another silica gel flash column chromatography (PhMe/EtOAc 49:1), and another silica gel flash column chromatography (hex/acetone 2:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (297 mg, 144 µmol, 49%).

^{1}H-NMR (600 MHz, CD_2Cl_2): δ = 8.64 (d, J = 8.0 Hz, 2H), 8.62–8.58 (m, 2H), 8.12 (s, 2H), 8.11–8.04 (m, 4H), 7.89 (d, J = 8.1 Hz, 4H), 7.85 (s, 2H), 7.82–7.73 (m, 10H), 7.67 (dd, J = 9.0, 6.2 Hz, 4H), 7.64–7.53 (m, 4H), 7.51 (t, J = 7.6 Hz, 2H), 7.47 (s, 2H), 7.40 (t, J = 7.5 Hz, 2H), 7.28 (t, J = 8.9 Hz, 4H), 7.08 (s, 2H), 6.95 (s, 2H), 6.87 (s, 2H), 6.81 (t, J = 7.4 Hz, 4H).

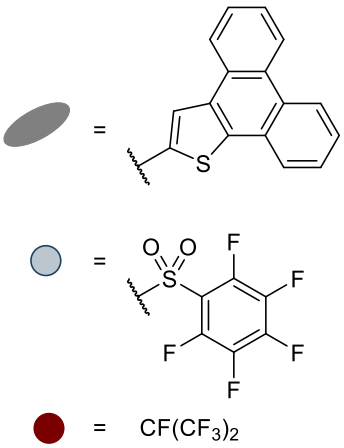
^{19}F-NMR (565 MHz, CD_2Cl_2): δ = -135.78 (s, 4F), -147.84 (s, 2F), -160.29 (s, 4F).

^{31}P-NMR (243 MHz, CD_2Cl_2): δ = -20.46.

^{13}C-NMR (151 MHz, CD_2Cl_2): δ = 144.76, 143.25, 143.03, 142.71, 137.89, 136.66, 136.56, 136.27, 135.94, 134.52, 134.07, 132.19, 131.91, 131.81, 131.75, 130.59, 130.26, 129.43, 129.02, 128.92, 128.79, 128.54, 128.43, 128.22, 128.10, 128.03, 127.75, 127.61, 127.52, 127.38, 127.36, 127.31, 127.26, 126.96, 126.92, 126.83, 126.79, 126.44, 126.38, 126.09, 125.61, 125.25, 124.81, 124.61, 124.47, 124.32, 123.78, 123.76, 123.49, 123.38, 122.95, 122.73, 122.45, 120.90.

ESI-HRMS: calculated for $C_{116}H_{57}N_3O_8P_2S_6F_{10}^-$ ([M-H]$^-$): 2062.171291, found: 2062.173220.

IDPi 202b[6,6']



(*S*)-6,6'-(*i*-Pr^F)-BINOL **384** (207 mg, 0.19 mmol, 2.0 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2C_6F_5)Cl_3$ (72.6 mg, 0.19 mmol, 2.0 eq.) and dry toluene (2.0 mL). Et_3N (110 µL, 0.79 mmol, 8.2 eq.) was added and the mixture was stirred at room temperature for 30 min. HMDS (20 µL, 0.96 µmol, 1.0 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 4 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/acetone 20–30%), and another silica gel flash column chromatography (100% DCM). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as a yellow solid (146 mg, 53 µmol, 56%).

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.70 (d, J = 8.1 Hz, 2H), 8.60 (d, J = 8.1 Hz, 2H), 8.41 (s, 2H), 8.26 (s, 2H), 8.24 (d, J = 1.9 Hz, 2H), 8.16 (d, J = 8.0 Hz, 2H), 8.07 (s, 2H), 8.01 (d, J = 9.2 Hz, 2H), 7.92 (d, J = 9.3 Hz, 2H), 7.85–7.78 (m, 6H), 7.77–7.69 (m, 4H), 7.70–7.63 (m, 2H), 7.63–7.52 (m, 6H), 7.46 (t, J = 7.6 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 7.27 (s, 2H), 7.23–7.17 (m, 4H), 6.94 (t, J = 7.4 Hz, 2H), 6.66 (t, J = 7.4 Hz, 2H), 6.61 (d, J = 8.0 Hz, 2H).

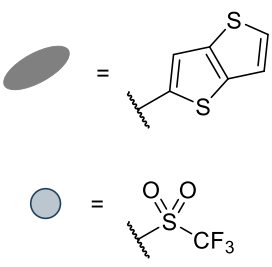
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = (-74.77)–(-75.03) (m, 6F), (-75.29)–(-75.49) (m, 6F), (-75.50)–(-75.78) (m, 12F), -135.74 (s, 4F), -147.18 (s, 2F), -159.97 (t, J = 21.1 Hz, 4F), -182.10 (s, 2F), -183.31 (s, 2F).

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -19.75.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 144.86, 144.41, 144.20, 142.81, 138.07, 137.72, 137.50, 136.46, 136.05, 134.83, 133.56, 132.48, 132.14, 131.55, 130.80, 130.49, 129.53, 128.97, 128.85, 128.66, 128.56, 128.48, 128.23, 128.12, 127.95, 127.72, 127.55, 127.47, 127.29, 127.16, 126.96, 126.86, 126.65, 126.53, 126.42, 125.97, 125.81, 125.68, 125.50, 125.43, 124.28, 123.89, 123.66, 123.58, 123.44, 123.25, 122.23, 122.01, 121.34, 119.80, 117.02.

ESI-HRMS: calculated for $C_{128}H_{53}N_3O_8P_2S_6F_{38}^-$ ([M-H]$^-$): 2734.095289, found: 2734.096680.

IDPi 203a



(*S*)-BINOL **385** (36.7 mg, 0.065 mmol, 2.06 eq.) was placed in a flame-dried Young-Schlenk under Argon and dissolved in toluene (0.75 mL). $P(NTf)Cl_3$ (10 µL, 0.063 mmol, 2.0 eq.) and subsequently Et_3N (36 µL, 0.26 mmol, 8.2 eq.) were added to the reaction. The mixture was stirred at room temperature for 30 min. HMDS (6.6 µL, 32 µmol, 1.0 eq.) was

added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (PhMe/EtOAc 9:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (28.6 mg, 0.019 mmol, 61%).

R_F (hex/EtOAc 1:1) = 0.47.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.30 (s, 2H), 8.03 (d, J = 8.3 Hz, 2H), 8.00 (d, J = 8.2 Hz, 2H), 7.86 (t, J = 7.5 Hz, 2H), 7.65 (t, J = 7.7 Hz, 2H), 7.60–7.53 (m, 4H), 7.45 (d, J = 5.2 Hz, 2H), 7.33 (ddd, J = 8.2, 6.7, 1.3 Hz, 2H), 7.30–7.22 (m, 6H), 7.03 (d, J = 5.2 Hz, 2H), 6.95 (s, 2H), 6.86 (d, J = 5.2 Hz, 2H), 6.48 (s, 2H).

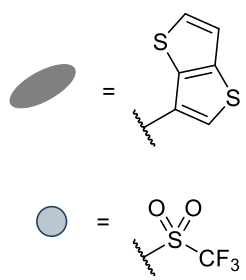
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -78.23.

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -17.09.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 143.16, 142.15, 140.91, 140.44, 139.99, 139.51, 138.92, 138.79, 132.31, 132.24, 132.12, 131.69, 130.07, 129.42, 129.05, 128.53, 128.48, 128.05, 127.85, 127.66, 127.51, 127.27, 127.19, 126.80, 126.72, 123.88, 122.43, 120.64, 120.03, 119.64, 119.60.

ESI-HRMS: calculated for $C_{66}H_{32}F_6N_3O_8P_2S_{10}^-$ ([M-H]$^-$): 1489.878167, found: 1489.879200.

IDPi 204a



(*S*)-BINOL **386** (60.8 mg, 0.108 mmol, 2.05 eq.) was placed in a flame-dried Young-Schlenk under Argon and dissolved in toluene (0.6 mL). $P(NTf)Cl_3$ (17 µL, 0.11 mmol, 2.0 eq.) and subsequently Et_3N (60 µL, 0.43 mmol, 8.2 eq.) were added to the reaction. The mixture was stirred at room temperature for 30 min. HMDS (11 µL, 53 µmol, 1.0 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 4:1 to 3:1) and another silica gel flash column chromatography (PhMe/EtOAc 4:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (49.9 mg, 0.033 mmol, 63%).

R_F (hex/EtOAc 1:1) = 0.34.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.61 (s, 2H), 8.11 (d, J = 8.3 Hz, 2H), 7.94 (d, J = 7.8 Hz, 2H), 7.76–7.69 (m, 4H), 7.61 (td, J = 6.1, 3.0 Hz, 2H), 7.55 (ddd, J = 8.2, 6.7, 1.3 Hz, 2H), 7.53–7.47 (m, 4H), 7.40–7.33 (m, 6H), 7.10–7.04 (m, 4H), 6.95 (s, 1H), 6.94 (s, 1H), 6.64 (d, J = 1.6 Hz, 2H).

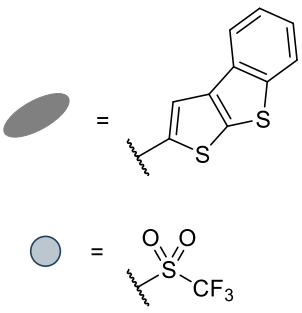
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -78.62.

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -14.22.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 143.63 (t, J = 5.0 Hz), 143.17 (t, J = 5.3 Hz), 139.73, 139.39, 139.38, 139.13, 132.36, 132.26, 132.20, 131.80, 130.45, 130.02, 129.26, 129.08, 128.69, 128.49, 127.99, 127.90, 127.73, 127.67, 127.54, 127.51, 127.47, 127.45, 127.28, 127.25, 127.07, 126.85, 123.60, 123.00, 120.18, 119.68.

ESI-HRMS: calculated for $C_{66}H_{32}N_3O_8P_2S_{10}F_6^-$ ([M-H]$^-$): 1489.878167, found: 1489.879430.

IDPi 205a



(*S*)-BINOL **387** (71.6 mg, 0.108 mmol, 2.05 eq.) was placed in a flame-dried Young-Schlenk under Argon and dissolved in toluene (0.6 mL). $P(NTf)Cl_3$ (17 µL, 0.11 mmol, 2.0 eq.) and subsequently Et_3N (60 µL, 0.43 mmol, 8.2 eq.) were added to the reaction. The mixture was stirred at room temperature for 30 min. HMDS (11 µL, 53 µmol, 1.0 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (PhMe/MTBE 0–3%) and another silica gel flash column chromatography (hex/EtOAc 4:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (52.4 mg, 0.031 mmol, 59%).

R_F (hex/EtOAc 2:1) = 0.20.

^{1}H-NMR (501 MHz, C_6D_6): δ = 8.09 (s, 2H), 7.86 (s, 2H), 7.73–7.56 (m, 8H), 7.52 (d, J = 8.2 Hz, 4H), 7.43–7.30 (m, 4H), 7.30–7.09 (m, 6H), 7.07–6.96 (m, 8H), 6.96–6.84 (m, 4H), 6.69 (t, J = 7.6 Hz, 2H).

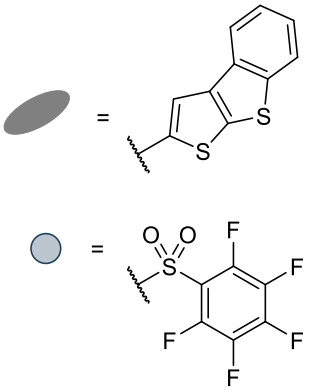
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -78.20.

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -16.84.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 143.82, 142.64, 142.14, 139.65, 139.22, 132.83, 132.23, 131.79, 130.06, 129.87, 128.11, 127.77, 127.33, 126.61, 124.93, 124.61, 123.83, 123.32, 123.07, 122.19, 121.27, 120.88, 120.30, 118.34.

ESI-HRMS: calculated for $C_{82}H_{40}N_3O_8P_2S_{10}F_6^-$ ([M-H]$^-$): 1689.940767, found: 1689.942720.

IDPi 205b



(*S*)-BINOL **387** (60 mg, 0.091 mmol, 2.0 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2C_6F_5)Cl_3$ (34.6 mg, 0.091 mmol, 2.0 eq.) and dry toluene (0.5 mL). Et_3N (50 µL, 0.36 mmol, 7.9 eq.) was added and the mixture was stirred at room temperature for 30 min. NH_3 (0.344 M in 1,4-dioxane, 130 µL, 0.045 µmol, 1.0 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 9:1 to 4:1), and another silica gel flash column chromatography (DCM/EtOAc 100:0 to 99:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (19.4 mg, 10 µmol, 23%).

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.16 (s, 2H), 8.03 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 7.9 Hz, 2H), 7.88 (d, J = 8.1 Hz, 2H), 7.83–7.77 (m, 4H), 7.60 (ddd, J = 8.2, 6.8, 1.1 Hz, 4H), 7.52 (d, J = 8.6 Hz, 2H), 7.49 (s, 2H), 7.42–7.30 (m, 10H), 7.28 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.5 Hz, 2H), 7.17 (s, 2H), 6.91–6.81 (m, 2H), 6.68 (t, J = 7.5 Hz, 2H).

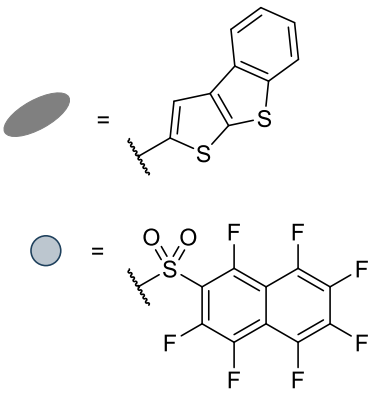
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -136.12 (d, J = 21.4 Hz, 4F), -146.44 (s, 2F), -159.81 (s, 4F).

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -17.12.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 143.54, 143.49, 142.98, 142.65, 142.50, 139.62, 139.59, 139.11, 138.34, 133.02, 132.76, 132.36, 131.95, 131.86, 131.51, 129.89, 129.46, 128.76, 128.18, 127.94, 127.52, 127.45, 127.23, 127.13, 126.86, 125.86, 125.13, 124.82, 124.50, 124.21, 123.71, 123.12, 122.94, 122.74, 122.60, 121.49, 120.47, 118.81.

ESI-HRMS: calculated for $C_{92}H_{41}F_{10}N_3O_8P_2S_{10}^-$ ($[M-H]^-$): 1885.93435, found: 1885.933394.

IDPi 205g



(*S*)-BINOL **387** (77.8 mg, 0.117 mmol, 1.96 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2C_{10}F_7)Cl_3$ (55.4 mg, 0.118 mmol, 1.97 eq.) and dry toluene (2.0 mL). Et_3N (66 µL, 0.47 mmol, 7.9 eq.) was added and the mixture was stirred at room temperature for 30 min. HMDS (12.5 µL, 0.060 µmol, 1.0 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 2 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was

extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 9:1 to 4:1), and another silica gel flash column chromatography (DCM/EtOAc 99:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (39.8 mg, 19 µmol, 32%).

^{1}H-NMR (600 MHz, CD_6Cl_6/DMSO-d_6 5:1): δ = 8.22 (s, 2H), 8.15 (s, 2H), 8.14–8.11 (m, 2H), 7.73 (dt, J = 8.5, 0.9 Hz, 2H), 7.65 (d, J = 10.0 Hz, 4H), 7.54 (d, J = 8.3 Hz, 2H), 7.48–7.43 (m, 2H), 7.30 (ddt, J = 7.0, 5.2, 2.7 Hz, 2H), 7.15–7.12 (m, 4H), 6.99 (ddd, J = 8.0, 6.7, 1.1 Hz, 2H), 6.97–6.92 (m, 4H), 6.78–6.74 (m, 2H), 6.60 (ddd, J = 8.2, 6.7, 1.3 Hz, 2H), 6.55 (ddd, J = 8.1, 7.0, 1.4 Hz, 2H), 6.50 (ddd, J = 8.0, 7.0, 1.1 Hz, 2H).

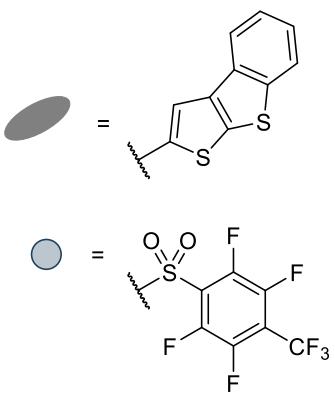
^{19}F-NMR (565 MHz, CD_6Cl_6/DMSO-d_6 5:1): δ = -112.14 (dd, J = 76.2, 17.9 Hz, 2F), -132.98 (d, J = 18.2 Hz, 2F), -143.09 (dt, J = 75.3, 17.5 Hz, 2F), -146.17 (dt, J = 57.3, 17.3 Hz, 2F), -149.00 (dt, J = 57.4, 19.0 Hz, 2F), -153.65 (t, J = 19.9 Hz, 2F), (-156.64)–(-157.28) (m, 2F).

^{31}P-NMR (243 MHz, CD_6Cl_6/DMSO-d_6 5:1): δ = -8.68.

^{13}C-NMR (126 MHz, CD_6Cl_6/DMSO-d_6 5:1): δ = 144.11, 144.01 (t, J = 6.2 Hz), 143.41 (t, J = 4.8 Hz), 143.41, 142.91, 142.35, 141.12, 140.01, 139.46, 136.65, 133.66, 133.65, 132.27, 132.02, 131.05, 130.94, 128.86, 128.56, 127.98, 127.33, 127.14, 126.89, 126.76, 126.58, 126.37, 126.32, 125.94, 125.85, 125.03, 124.46, 124.18, 123.70, 123.51, 123.44, 123.38, 123.17, 122.75, 122.67, 122.26, 119.11.

ESI-HRMS: calculated for $C_{100}H_{40}F_{14}N_3O_8P_2S_{10}^-$ ($[M-H]^-$): 2057.927995, found: 2057.931580.

IDPi 205h



(*S*)-BINOL **387** (72.2 mg, 0.109 mmol, 1.98 eq.) was added to a flame-dried Young-Schlenk charged with $P(NSO_2(4\text{-}CF_3\text{-}C_6F_4))Cl_3$ (47 mg, 0.11 mmol, 2.0 eq.) and dry toluene (2.0 mL). Et_3N (60 µL, 0.43 mmol, 7.8 eq.) was added and the mixture was stirred at room temperature for 30 min. HMDS (11.5 µL, 0.055 µmol, 1.0 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 4:1 to 3:1), and another silica gel flash column chromatography (DCM/EtOAc 99:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (72.1 mg, 36 µmol, 66%).

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.13 (s, 2H), 8.02 (d, J = 8.4 Hz, 2H), 8.00–7.96 (m, 2H), 7.84–7.75 (m, 6H), 7.64–7.58 (m, 4H), 7.55 (d, J = 8.6 Hz, 2H), 7.43–7.38 (m, 2H), 7.38–7.31 (m, 7H),

7.29 (d, J = 7.7 Hz, 2H), 7.26 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 8.5 Hz, 2H), 7.07 (s, 3H), 6.88 (ddd, J = 8.2, 7.2, 1.2 Hz, 2H), 6.73–6.67 (m, 2H).

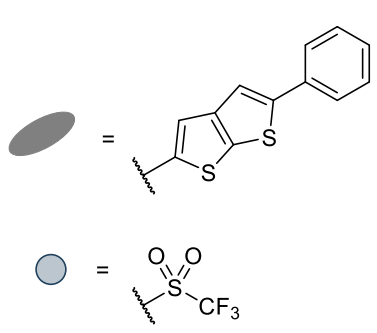
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -56.96 (t, J = 21.7 Hz, 6F), (-134.14)–(-134.45) (m, 4F), -138.12 (dq, J = 25.2, 13.7 Hz, 4F).

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -17.74.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 143.68, 143.55, 142.96, 142.48, 142.43, 142.25, 139.50, 139.41, 139.25, 138.39, 132.94, 132.61, 132.30, 131.93, 131.81, 131.54, 129.97, 129.44, 128.83, 128.10, 128.02, 127.57, 127.41, 127.37, 127.25, 127.20, 126.68, 125.60, 125.09, 124.86, 124.46, 124.27, 123.63, 123.21, 122.81, 122.65, 122.52, 121.30, 120.23, 118.67.

ESI-HRMS: calculated for $C_{94}H_{40}N_3O_8S_{10}F_{14}P_2^-$ ([M-H]$^-$): 1985.927995, found: 1985.930780.

IDPi 206a



(*S*)-BINOL **388** (77 mg, 0.11 mmol, 2.04 eq.) was placed in a flame-dried Young-Schlenk under Argon and dissolved in toluene (0.6 mL). $P(NTf)Cl_3$ (17 µL, 0.11 mmol, 2.0 eq.) and subsequently Et_3N (60 µL, 0.43 mmol, 8.2 eq.) were added to the reaction. The mixture was stirred at room temperature for 30 min. HMDS (11 µL, 53 µmol, 1.0 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 4:1 to 3:1), another silica gel flash column chromatography (PhMe/EtOAc 19:1), another silica gel flash column chromatography (PhMe/MTBE 49:1), and another silica gel flash column chromatography (hex/EtOAc 9:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (27.3 mg, 0.015 mmol, 29%).

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.32 (s, 2H), 8.04 (d, J = 8.3 Hz, 2H), 7.89 (d, J = 8.1 Hz, 2H), 7.83 (t, J = 7.4 Hz, 2H), 7.65 (t, J = 7.7 Hz, 2H), 7.61–7.55 (m, 4H), 7.55–7.52 (m, 4H), 7.39 (t, J = 7.6 Hz, 4H), 7.37–7.24 (m, 6H), 7.23 (s, 2H), 7.21–7.00 (m, 18H).

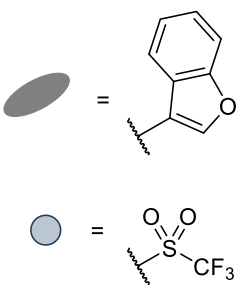
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -78.16.

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -17.11.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 148.15, 148.07, 147.94, 147.23, 143.13, 142.27, 139.69, 139.45, 137.77, 135.07, 134.54, 132.28, 132.00, 131.64, 129.66, 129.57, 129.28, 129.19, 129.04, 129.00, 128.05, 127.98, 127.88, 127.47, 127.44, 127.30, 127.24, 126.64, 126.39, 126.20, 125.96, 123.91, 122.56, 121.36, 121.02, 116.55, 116.02.

ESI-HRMS: calculated for $C_{90}H_{48}N_3O_8P_2S_{10}F_6^-$ ([M-H]$^-$): 1794.003367, found: 1794.005630.

IDPi 207a



(*S*)-BINOL **389** (56 mg, 0.11 mmol, 2.0 eq.) was placed in a flame-dried Young-Schlenk under Argon and dissolved in toluene (0.6 mL). $P(NTf)Cl_3$ (17 µL, 0.11 mmol, 2.0 eq.) and subsequently Et_3N (59 µL, 0.42 mmol, 8.0 eq.) were added to the reaction. The mixture was stirred at room temperature for 30 min. HMDS (11 µL, 53 µmol, 1.0 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 4:1 to 3:1), another silica gel flash column chromatography (PhMe/EtOAc 9:1), and another silica gel flash column chromatography (mesh size 70–140 µm, DCM/EtOAc 99:1 to 9:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (33.4 mg, 0.024 mmol, 33%).

$\boldsymbol{R_F}$ (hex/EtOAc 1:1) = 0.53.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.47 (s, 2H), 8.12 (d, J = 8.3 Hz, 2H), 8.00 (d, J = 8.2 Hz, 2H), 7.83 – 7.76 (m, 4H), 7.65 – 7.56 (m, 8H), 7.54 (d, J = 8.2 Hz, 2H), 7.42 – 7.38 (m, 3H), 7.38 – 7.33 (m, 2H), 7.28 (t, J = 7.8 Hz, 2H), 7.26 (s, 2H), 7.16 (d, J = 8.3 Hz, 2H), 7.07 (d, J = 7.9 Hz, 2H), 7.05 – 6.97 (m, 4H), 6.75 (t, J = 7.5 Hz, 2H).

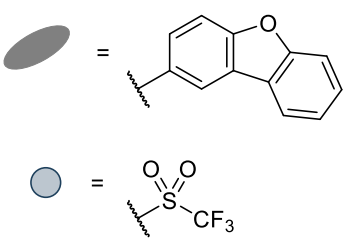
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -79.19.

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -13.76.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 155.80, 155.31, 145.22, 144.23, 143.72 (t, J = 5.2 Hz), 143.57 (t, J = 5.3 Hz), 132.53, 132.27, 131.99, 131.73, 131.37, 130.88, 129.21, 129.01, 127.90, 127.82, 127.52, 127.48, 127.29, 127.26, 126.77, 126.38, 125.06, 124.92, 124.18, 123.98, 123.45, 123.37, 123.33, 122.71, 120.88, 120.85, 116.67, 115.40, 111.93, 111.64.

ESI-HRMS: calculated for $C_{74}H_{40}N_3O_{12}P_2S_2F_6^-$ ($[M-H]^-$): 1402.143846, found: 1402.144600.

IDPi 208a



(*S*)-BINOL **390** (91.1 mg, 0.147 mmol, 2.05 eq.) was placed in a flame-dried Young-Schlenk under Argon and dissolved in toluene (0.75 mL). $P(NTf)Cl_3$ (23.0 µL, 0.144 mmol, 2.00 eq.) and subsequently Et_3N (80 µL, 0.57 mmol, 7.99 eq.) were added to the reaction. The mixture was stirred at room temperature for 30 min. HMDS (15.0 µL, 71.9 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 4 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M).

The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (toluene/EtOAc 99:1 to 49:1), silica gel column chromatography (hex/EtOAc 9:1 to 2:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (41.2 mg, 0.026 mmol, 36%).

R_F (hex/EtOAc 2:1) = 0.26.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.20 (d, J = 8.2 Hz, 2H), 8.06 (m, 6H), 7.89 (dd, J = 8.1, 5.7 Hz, 6H), 7.85–7.78 (m, 2H), 7.74 (t, J = 7.7 Hz, 2H), 7.62 (dd, J = 7.9, 5.3 Hz, 4H), 7.58–7.48 (m, 8H), 7.44 (tt, J = 6.2, 3.3 Hz, 4H), 7.37 (d, J = 8.3 Hz, 2H), 7.28 (t, J = 7.8 Hz, 2H), 7.11 (t, J = 7.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 6.11 (dd, J = 8.5, 1.8 Hz, 2H), 5.88 (d, J = 8.6 Hz, 2H), 5.59 (dd, J = 8.4, 1.9 Hz, 2H).

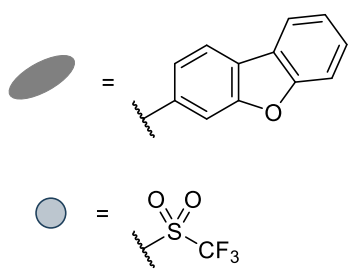
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -78.71.

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -16.07.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ 156.74, 156.38, 155.63, 143.64 (t, J = 5.0 Hz), 143.17 (t, J = 5.2 Hz), 134.31, 133.67, 132.54, 132.21, 132.17, 132.12, 131.75, 131.13, 130.17, 128.88, 128.85, 128.35, 128.29, 127.90, 127.68, 127.37, 127.34, 127.11, 127.04, 126.98, 126.77, 124.28, 124.22, 124.20, 124.08, 123.82, 123.48, 122.71, 122.50, 122.03, 121.97, 120.99, 120.86, 118.75 (q, J = 321.4 Hz), 112.13, 111.42, 111.04, 110.37.

ESI-HRMS: calculated for $C_{90}H_{48}N_3O_{12}S_2P_2F_6^-$ ($[M-H]^-$): 1602.206446, found: 1602.206520.

IDPi 209a



(*S*)-BINOL **391** (91.1 mg, 0.147 mmol, 2.05 eq.) was placed in a flame-dried Young-Schlenk under Argon and dissolved in toluene (0.75 mL). $P(NTf)Cl_3$ (23.0 µL, 0.144 mmol, 2.00 eq.) and subsequently Et_3N (80 µL, 0.57 mmol, 7.99 eq.) were added to the reaction. The mixture was stirred at room temperature for 30 min. HMDS (15.0 µL, 71.9 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 4 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (toluene/EtOAc 2% to 4%). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (46.1 mg, 0.029 mmol, 40%).

R_F (hex/EtOAc 2:1) = 0.24.

^{1}H-NMR (501 MHz, CD_2Cl_2): δ = 8.22 (d, J = 8.3 Hz, 2H), 8.08 (d, J = 8.3 Hz, 2H), 8.05 (s, 2H), 7.97 (d, J = 8.6 Hz, 2H), 7.94 (ddd, J = 8.1, 6.8, 1.1 Hz, 2H), 7.86–7.78 (m, 6H), 7.67 (d, J = 8.1

Hz, 2H), 7.64 (ddd, J = 8.1, 6.7, 1.2 Hz, 2H), 7.53 (d, J = 8.5 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 7.48–7.43 (m, 8H), 7.41 (ddd, J = 8.4, 7.3, 1.3 Hz, 2H), 7.31 (ddd, J = 8.6, 7.4, 1.4 Hz, 2H), 7.27 (td, J = 7.6, 1.0 Hz, 2H), 7.14 (t, J = 7.5 Hz, 2H), 7.02 (d, J = 1.5 Hz, 2H), 6.86 (d, J = 1.5 Hz, 2H), 6.69 (dd, J = 8.0, 1.6 Hz, 2H), 6.53 (dd, J = 8.2, 1.5 Hz, 2H).

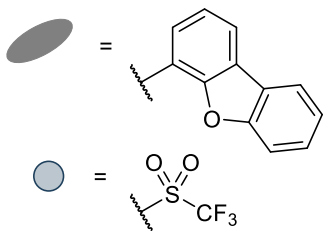
^{19}F-NMR (471 MHz, CD_2Cl_2): δ = -79.24.

^{31}P-NMR (203 MHz, CD_2Cl_2): δ = -16.74.

^{13}C-NMR (126 MHz, CD_2Cl_2): δ = 157.26, 156.97, 156.41, 156.05, 143.68 (t, J = 5.0 Hz), 143.10 (t, J = 5.0 Hz), 134.80, 134.48, 133.61, 133.50, 132.53, 132.50, 132.42, 132.39, 132.15, 131.66, 129.29, 129.23, 128.21, 128.05, 127.80, 127.69, 127.48, 127.26, 127.08, 124.73, 124.45, 124.38, 124.13, 124.04, 123.95, 123.84, 123.18, 122.90, 122.45, 121.09, 120.94, 120.23, 120.06, 119.07 (q, J = 321.4 Hz), 113.27, 112.88, 111.92, 111.76.

ESI-HRMS: calculated for $C_{90}H_{48}N_3O_{12}S_2P_2F_6^-$ ([M-H]$^-$): 1602.206446, found: 1602.207750.

IDPi 210a



(*S*)-BINOL **392** (91.1 mg, 0.147 mmol, 2.05 eq.) was placed in a flame-dried Young-Schlenk under Argon and dissolved in toluene (0.75 mL). $P(NTf)Cl_3$ (23.0 µL, 0.144 mmol, 2.00 eq.) and subsequently Et_3N (80 µL, 0.57 mmol, 7.99 eq.) were added to the reaction. The mixture was stirred at room temperature for 30 min. HMDS (15.0 µL, 71.9 µmol, 1.00 eq.) was added, the mixture was stirred at room temperature for 10 min and subsequently heated to 120 °C for 4 d. After cooling to room temperature, the mixture was diluted with DCM and quenched by addition of HCl (1.2 M). The aqueous layer was extracted with DCM (3x), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 9:1 to 4:1), another silica gel flash column chromatography (toluene/EtOAc 19:1), and another silica gel flash column chromatography (hex/EtOAc 4:1 to 2:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM) and obtained as an off-white solid (46.1 mg, 0.029 mmol, 40%).

***R*$_F$** (hex/EtOAc 2:1) = 0.16.

^{1}H-NMR (600 MHz, CD_2Cl_2): δ = 8.55 (s, 2H), 8.19 (s, 4H), 7.96–7.47 (m, 8H), 7.43 (ddd, J = 8.4, 7.3, 1.3 Hz, 2H), 7.38–7.26 (m, 8H), 7.05 (d, J = 6.7 Hz, 2H), 6.66 (d, J = 7.7 Hz, 4H), 5.56 (d, J = 6.8 Hz, 2H). *Significant peak-broadening due to rotameric structures.*

^{19}F-NMR (565 MHz, CD_2Cl_2): δ = -79.70.

^{31}P-NMR (243 MHz, CD_2Cl_2): δ = -15.51.

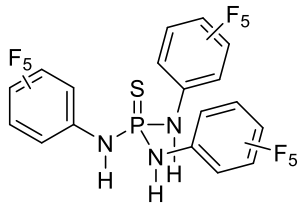
^{13}C-NMR (151 MHz, CD_2Cl_2): δ = 156.63, 156.58, 154.02, 153.69, 144.03, 143.71, 134.02, 132.88, 132.52, 132.46, 132.17, 129.86, 129.76, 129.38, 129.27, 128.63, 128.34, 127.85, 127.58,

127.50, 127.47, 127.43, 127.20, 126.40, 125.15, 124.63, 124.10, 123.24, 123.05, 122.99, 122.71, 122.59, 122.52, 121.03, 120.92, 120.73, 120.68, 120.52, 119.57, 117.40, 112.19, 112.05.

ESI-HRMS: calculated for $C_{90}H_{48}N_3O_{12}S_2P_2F_6^-$ ([M-H]$^-$): 1602.206446, found: 1602.206910.

Synthesis of Hydrogen Bond Donor Catalysts

HBD 300



A flame-dried Young schlenk under argon was charged with 2,3,4,5,6-pentafluoroaniline (1.0 mL, 3.9 mmol, 3.3 eq.) and Et_3N (2.5 mL, 18 mmol, 15 eq.). The mixture was cooled to 0 °C and thiophosphoryl chloride (120 µL, 1.2 mmol, 1.0 eq.) was added carefully. The mixture was subsequently heated to 100 °C for 16 h. After cooling to room temperature, the reaction was quenched by addition of HCl (1.2 M) and the aqueous layer was extracted with DCM (3x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 95:5 to 2:1) to give the desired product (94.8 mg, 0.16 mmol, 13%) as a white solid.

^{1}H-NMR (600 MHz, DMSO): δ = 7.89 (d, J = 7.5 Hz, 3H).

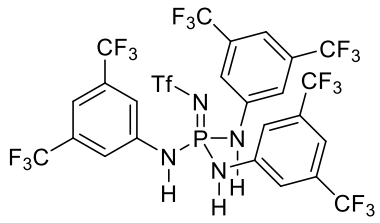
^{19}F-NMR (565 MHz, DMSO): δ = -144.59 (d, J = 22.0 Hz, 6F), -160.11 (t, J = 22.6 Hz, 3F), -164.66 (t, J = 22.6 Hz, 6F).

^{31}P-NMR (243 MHz, DMSO): δ = 54.53.

^{13}C-NMR (151 MHz, DMSO): δ = 143.73 (d, J = 242.4 Hz), 137.95 (dt, J = 248.8, 13.6 Hz), 136.99 (dt, J = 248.9, 13.0 Hz), 115.75 (t, J = 13.5 Hz).

ESI-HRMS: calculated for $C_{18}H_2F_{15}N_3P_1S_1$ ([M-H]$^-$): 607.94620, found: 607.94765.

HBD 301



A flame-dried Young schlenk under argon was charged with 3,5-bis(trifluoromethyl)aniline (160 µL, 1.0 mmol, 3.3 eq.), Et_3N (0.25 mL, 1.8 mmol, 5.7 eq.), and PhMe (3.5 mL). $P(NTf)Cl_3$ (50 µL, 0.31 mmol, 1.0 eq.) was added, the mixture was stirred for 30 min, and subsequently heated to 120 °C for 3 d. After cooling to room temperature, the reaction was quenched by addition of HCl (1.2 M) and the aqueous layer was extracted with DCM (3x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (hex/EtOAc 9:1 to 2:1), and another silica gel flash column chromatography (hex/acetone 4:1 to 2:1). The product was acidified by filtration over a short plug of DOWEX 50WX8 (H-form, eluted with DCM and MeOH) and obtained as a white solid (160 mg, 0.19 mmol, 59%).

^{1}H-NMR (600 MHz, DMSO): δ = 10.10 (d, J = 10.8 Hz, 3H), 7.74–7.68 (m, 9H).

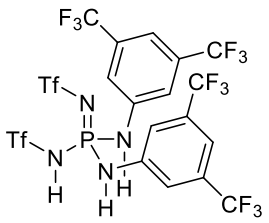
^{19}F-NMR (565 MHz, DMSO): δ = -61.96 (s, 18F), -79.68 (s, 3F).

^{31}P-NMR (243 MHz, DMSO): δ = -5.81.

^{13}C-NMR (151 MHz, DMSO): δ = 140.62, 131.20 (q, J = 33.0 Hz), 122.92 (q, J = 272.8 Hz), 119.52, 119.45 (qd, J = 320.5, 9.7 Hz), 116.06.

ESI-HRMS: calculated for $C_{25}H_{11}F_{21}N_4O_2P_1S_1$ ([M-H]$^-$): 861.00105, found: 861.00135.

HBD 302



A flame-dried Young schlenk under argon was charged with trifluoromethane sulfonamide (50 mg, 0.34 mmol, 1.1 eq.) and Et_3N (2.0 mL, 14 mmol, 46 eq.). $P(NTf)Cl_3$ (50 µL, 0.31 mmol, 1.0 eq.) was added carefully and the mixture was cooled heated to 120 °C for 1 h. 3,5-bis(trifluoromethyl)aniline (150 µL, 0.96 mmol, 3.1 eq.) was added, and the reaction was heated to 120 °C for 16 h. After cooling to room temperature, the reaction was quenched by addition of HCl (1.2 M) and the aqueous layer was extracted with DCM (3x). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by automated reversed phase silica gel flash column chromatography (CH_3CN/H_2O 40:60 to 100:0) and silica gel flash column chromatography (EtOAc/AcOH 19:1). The mixture was acidified by dissolving the mixture in DCM (20 mL) and stirring vigurously with HCl (6 M, 30 mL). The product was dried by azeotroping from PhMe (3x) and obtained as a beige solid (61.6 mg, 0.079 mmol, 25%).

^{1}H-NMR (600 MHz, DMSO): δ = 9.34 (d, J = 10.2 Hz, 3H), 7.63 (s, 6H), 7.43 (s, 3H).

^{19}F-NMR (565 MHz, DMSO): δ = -62.00 (s, 12F), -79.19 (s, 6F).

^{31}P-NMR (243 MHz, DMSO): δ = -13.76.

^{13}C-NMR (151 MHz, DMSO): δ = 142.45 (d, J = 4.0 Hz), 130.49 (q, J = 32.6 Hz), 123.14 (q, J = 272.6 Hz), 119.85 (qd, J = 322.3, 5.6 Hz), 117.85 (dd, J = 8.2, 4.2 Hz), 113.40 (dt, J = 7.9, 3.7 Hz).

ESI-HRMS: calculated for $C_{18}H_8N_4O_4F_{18}S_2P_1$ ([M-H]$^-$): 780.944277, found: 780.945250.

7.7. Supplementary Data

7.7.1. Cartesian Coordinates of Optimized Geometries

Table 7.1 Lowest-Lying Enantio-Determining Transition State for the Deprotonation of Wheland Intermediate **280** by IDPi **143b**.

Atom	X	Y	Z
O	0.792476059	2.549621116	-2.388004702
O	-1.151195912	1.78068566	-0.944365346
O	0.52352804	-2.086130212	-0.291762666
O	2.143672266	-1.696297329	-2.209793192
N	-1.258804701	1.419566144	-3.552670253
S	-1.426228283	-3.440046053	-2.083524037

S	-0.813948543	2.083619603	-4.95563215
O	-2.360108993	-2.869387639	-1.108585348
O	-2.096488236	-4.183849045	-3.233293583
O	0.566581851	1.762660375	-5.355159877
O	-1.878748449	1.825821851	-5.937712205
N	-0.350520498	-2.461221233	-2.705675375
H	-3.761358696	-3.9541122	-8.019563081
P	0.590901767	-1.494947884	-1.81174354
N	0.40209403	0.039272704	-1.836966828
P	-0.309497006	1.358860318	-2.270394382
C	-1.58484216	3.097912299	-0.886665693
C	1.435060877	2.894003036	-1.20125591
C	1.511794398	-1.596707094	0.565195358
C	2.756092223	-2.901488775	-1.907421408
C	-2.972482517	3.348997347	-1.048357966
C	3.130562687	-3.766015325	-2.972050118
C	2.736596757	2.380970483	-0.965312214
C	1.165957319	-0.56547176	1.475627859
C	-0.601155594	7.818854171	-0.647843063
C	-0.158861075	6.519051348	-0.584971772
C	-1.071560147	5.44124971	-0.665404607
C	-2.461958665	5.725877159	-0.849019085
C	-2.883679975	7.078800454	-0.888703066
C	-1.976032658	8.102396923	-0.786602754
H	0.114348521	8.634308011	-0.600800143
H	0.900827133	6.305542633	-0.48503065
C	-0.652391707	4.079532092	-0.622380477
C	-3.383103563	4.671445934	-1.008016697
H	-3.941027955	7.289069416	-1.025463083
H	-4.436113474	4.906788444	-1.119637058
C	2.616074224	4.477245098	3.420677073
C	3.277068455	3.7589099	2.456241014
C	2.666991209	3.479815837	1.208062096
C	1.354228791	3.986201546	0.946380654
C	0.697264351	4.713089537	1.966157823
C	1.311094782	4.949940634	3.173380672
H	4.316640472	2.303495492	0.468509118
H	4.282981488	3.386231886	2.632874601
C	3.328199017	2.693256864	0.244656762
C	0.743473583	3.68194665	-0.30929007
H	-0.305272325	5.085956091	1.787349169
H	0.786218678	5.50804479	3.943318966
C	6.169360111	-1.334681334	1.832410072
C	5.183409048	-1.945082552	1.093768384
C	3.832253182	-1.546922715	1.217532004
C	3.51498831	-0.478801161	2.114909376

C	4.553370675	0.116599902	2.872517111
C	5.853770858	-0.299730629	2.736021496
H	7.201728231	-1.65244639	1.718101627
H	5.440455431	-2.737376355	0.399282851
C	2.778984763	-2.116396138	0.43694135
C	2.187764274	-0.022199852	2.231591453
H	4.29464522	0.914606153	3.563742277
H	1.965785702	0.786921023	2.920899151
C	4.640357157	-6.971631975	0.365541857
C	4.49094044	-6.599205664	-0.9457284
C	3.947472001	-5.333427177	-1.28303285
C	3.584652542	-4.432854222	-0.232680878
C	3.734715059	-4.855079684	1.10975177
C	4.245129268	-6.097252068	1.40056145
H	4.019349266	-5.666091533	-3.399872831
H	4.768228089	-7.277934332	-1.748030212
H	3.430890261	-4.186940742	1.909482122
H	4.339474393	-6.412119681	2.435436124
C	3.730461116	-4.965225177	-2.622496821
C	3.041507927	-3.163744027	-0.580796912
H	-2.310945554	9.134126595	-0.835432316
H	3.093346982	4.681857395	4.374527477
H	6.641984284	0.166844508	3.319497315
H	5.043427224	-7.949414383	0.61143621
C	2.962657667	-3.432731245	-4.375224366
C	3.471417006	-4.033948649	-5.4948463
O	2.2255217	-2.32177495	-4.713255373
C	3.03662804	-3.261285692	-6.612387777
H	4.112271372	-4.902742648	-5.516651873
C	2.285551674	-2.205687329	-6.069087197
C	2.62749403	-2.322088625	-8.774519124
H	2.744544831	-2.347506834	-9.853804456
C	1.909503212	-1.263874301	-8.190665959
H	1.495911871	-0.485252553	-8.824418543
C	3.202591972	-3.321189341	-8.00259208
H	3.771982299	-4.122605317	-8.464688934
C	1.726995997	-1.181898168	-6.81393036
H	1.199547835	-0.35583048	-6.345595928
C	-3.924344827	2.266346747	-1.183372931
C	-3.833676065	0.901271665	-1.192009101
O	-5.254105975	2.664406504	-1.230910411
C	-5.167411941	0.397026336	-1.213020702
H	-2.935786035	0.310426483	-1.139254816
C	-6.003923227	1.522874841	-1.238119691
C	-5.739012564	-0.879473519	-1.167816842
C	-7.384894771	1.453114279	-1.247231698

C	-7.122846829	-0.9706741	-1.156776199
H	-5.109160198	-1.764840146	-1.140598809
C	-7.933618758	0.173781622	-1.204710247
H	-8.002178039	2.345045544	-1.271733911
H	-7.594534434	-1.947958889	-1.114780587
H	-9.013645221	0.062158866	-1.201226056
C	3.405275443	1.528968211	-1.927162885
C	3.301872945	1.358245678	-3.277612125
O	4.394462338	0.714615504	-1.395277107
C	4.27632437	0.377060009	-3.637974687
H	2.608204563	1.859770048	-3.935662646
C	4.91158669	0.006665999	-2.441548878
C	4.673414738	-0.235401249	-4.832500433
C	5.906443115	-0.951423912	-2.362268065
C	5.664432892	-1.204635813	-4.77589077
H	4.206940772	0.031972371	-5.775688996
C	6.270542686	-1.560651197	-3.560187541
H	6.374512112	-1.202162701	-1.416709119
H	5.976877649	-1.70135177	-5.689748231
H	7.045378078	-2.321569618	-3.553874446
C	-0.196744047	-0.095763354	1.616182789
C	-1.416187515	-0.676346118	1.416652694
O	-0.330298808	1.175031607	2.148417023
C	-2.393347074	0.27127923	1.853661032
H	-1.595292491	-1.661138186	1.012999279
C	-1.671486334	1.39946884	2.276206032
C	-3.790913734	0.296539339	1.924797338
C	-2.262052362	2.56121969	2.739781653
C	-4.405031719	1.451954551	2.384102294
H	-4.379893718	-0.55691705	1.602938619
C	-3.65363215	2.56955075	2.780742488
H	-1.66715668	3.410939724	3.055685127
H	-5.489141643	1.498357847	2.428511387
H	-4.167318213	3.459369141	3.131981742
C	-3.49911412	-1.017267722	-5.245025509
C	-2.833949332	-2.18841463	-5.580835424
C	-3.449575235	-3.449387376	-5.3333699
C	-4.808648988	-3.465111203	-4.868401154
C	-5.482676206	-2.306862212	-4.590842795
C	-4.813949592	-1.052147454	-4.778751173
H	-2.992581009	-0.066703189	-5.378436761
H	-2.7602194	-3.646546789	-4.187700773
H	-5.282032486	-4.430343517	-4.720705361
C	-1.423234799	-2.152519686	-6.085260203
H	-1.239003334	-1.20393053	-6.600450066
H	-0.748237386	-2.178281921	-5.216545082

C	-1.101497681	-3.332860633	-7.003681443
H	-1.596440483	-3.194639339	-7.976780067
H	-0.029003514	-3.386794054	-7.187449669
N	-1.556616036	-4.581463798	-6.397104083
C	-0.779025974	-5.68846056	-6.207437507
O	-1.173159716	-6.750421987	-5.754413679
O	0.504187509	-5.476123354	-6.603792461
C	1.360850982	-6.619847703	-6.455816749
H	0.936912209	-7.488085706	-6.968008698
H	2.306717773	-6.326667765	-6.913212949
H	1.503788237	-6.859583195	-5.397821395
C	-2.982710261	-4.685876048	-6.120469734
H	-3.113499518	-5.577752393	-5.496594218
C	-3.835567599	-4.857012944	-7.39548606
H	-4.880523778	-4.899967468	-7.063663574
C	-3.524761838	-6.111003927	-8.234412401
H	-3.216158206	-6.910902063	-7.546353277
C	-4.79021522	-6.565577027	-8.969120617
H	-4.593506349	-7.450606903	-9.58374664
H	-5.593079944	-6.814003943	-8.266354325
H	-5.157517017	-5.772866441	-9.63334925
C	-2.398127471	-5.884226852	-9.247570767
H	-2.67992618	-5.09831226	-9.960186873
H	-1.45746564	-5.589481658	-8.77547672
H	-2.20843538	-6.798225167	-9.820753403
O	-6.759768387	-2.21299013	-4.156056762
O	-5.537868151	0.019393981	-4.481935258
C	-7.456356011	-3.432746411	-3.927211026
H	-7.550794671	-4.017877592	-4.852403296
H	-6.954885554	-4.03800461	-3.159503385
H	-8.448676194	-3.145715231	-3.576780022
C	-4.908903625	1.314178413	-4.593770692
H	-4.639842767	1.523847059	-5.633702043
H	-5.656944735	2.024037927	-4.2407027
H	-4.015143138	1.36023214	-3.965252131
C	-0.877084491	3.885203596	-4.62825199
C	0.255066668	4.69845584	-4.570973358
C	-2.117059473	4.48719755	-4.410046131
C	0.146019649	6.064022147	-4.32608828
C	-2.239402841	5.849645806	-4.182837556
C	-1.101236384	6.644042657	-4.147484987
F	1.485773374	4.221178198	-4.744120788
F	1.241211276	6.826285564	-4.275693754
F	-1.205063483	7.955980059	-3.949957596
F	-3.443717946	6.399433814	-4.005668639
F	-3.242535172	3.767632565	-4.408080754

C	-0.510972023	-4.806511305	-1.318020446
C	-0.543512003	-5.07230843	0.050551754
C	0.277624338	-5.62196711	-2.133819126
C	0.168585029	-6.141419365	0.583129956
F	-1.245576873	-4.326866826	0.900126632
C	0.969495956	-6.704457932	-1.612935368
F	0.396191813	-5.380250136	-3.436315198
C	0.910517602	-6.967641137	-0.249873984
F	0.133334774	-6.384428614	1.893851182
F	1.69402695	-7.48935953	-2.412497572
F	1.56072065	-8.009227317	0.25803329

7.7.2. Crystallographic Data

X-ray data for compound 226i

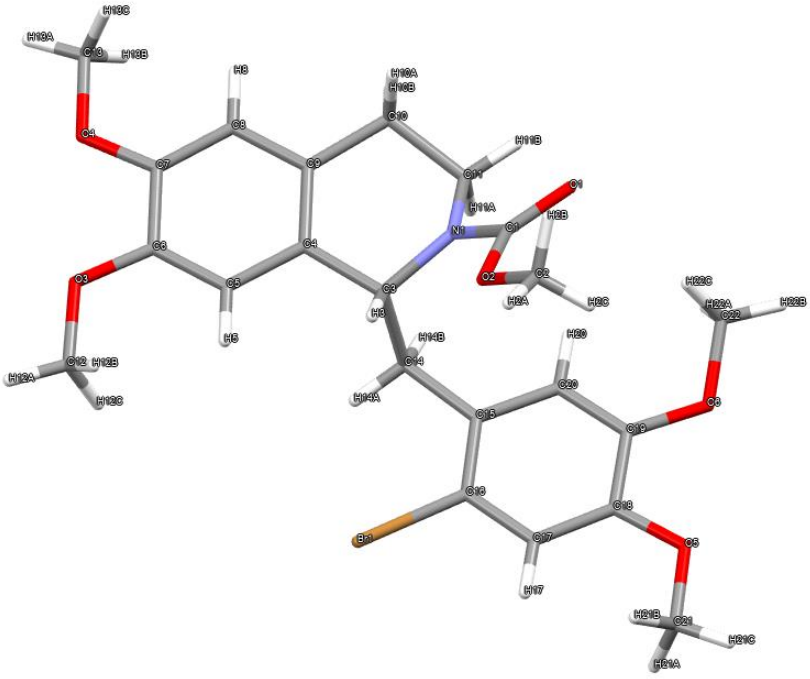


Figure 7.1 X-ray structure of **226i**.

Table 7.2 Crystal data and structure refinement.

Identification code	14467	
Empirical formula	$C_{22}H_{26}BrNO_6$	
Color	colourless	
Formula weight	480.35 g · mol-1	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	MONOCLINIC	
Space group	**$P2_1$, (no. 4)**	
Unit cell dimensions	a = 9.7395(4) Å	α = 90°.
	b = 6.1243(2) Å	β = 91.348(2)°.
	c = 17.5601(7) Å	γ = 90°.

Volume	1047.13(7) $Å^3$
Z	2
Density (calculated)	1.523 $Mg \cdot m^{-3}$
Absorption coefficient	2.002 mm^{-1}
F(000)	496 e
Crystal size	0.121 x 0.051 x 0.032 mm^3
θ range for data collection	1.160 to 34.925°.
Index ranges	$-15 \leq h \leq 15, -9 \leq k \leq 9, -28 \leq l \leq 28$
Reflections collected	34114
Independent reflections	9085 [R_{int} = 0.0327]
Reflections with I>2σ(I)	7802
Completeness to θ = 25.242°	100.0 %
Absorption correction	Gaussian
Max. and min. transmission	0.95 and 0.85
Refinement method	Full-matrix least-squares on F2
Data/restraints/parameters	9085/1/280
Goodness-of-fit on F^2	1.020
Final R indices [I>2σ(I)]	R_1 = 0.0319 wR^2 = 0.0630
R indices (all data)	R_1 = 0.0439 wR^2 = 0.0667
Absolute structure parameter	-0.011(3)
Largest diff. peak and hole	0.4 and -0.5 e $\cdot Å^{-3}$

Table 7.3 Bond lengths [Å] and angles [°].

Br1-C16	1.906(2)	C9-C10	1.507(3)
O1-C1	1.216(2)	C10-H10A	0.990
O2-C1	1.346(2)	C10-H10B	0.990
O2-C2	1.448(2)	C10-C11	1.529(3)
O3-C6	1.365(2)	C11-H11A	0.990
O3-C12	1.417(3)	C11-H11B	0.990
O4-C7	1.360(2)	C12-H12A	0.980
O4-C13	1.433(3)	C12-H12B	0.980
O5-C18	1.363(2)	C12-H12C	0.980
O5-C21	1.432(3)	C13-H13A	0.980
O6-C19	1.360(2)	C13-H13B	0.980
O6-C22	1.436(2)	C13-H13C	0.980
N1-C1	1.358(2)	C14-H14A	0.990
N1-C3	1.462(3)	C14-H14B	0.990
N1-C11	1.458(3)	C14-C15	1.510(3)
C2-H2A	0.980	C15-C16	1.384(3)
C2-H2B	0.980	C15-C20	1.404(3)
C2-H2C	0.980	C16-C17	1.399(3)
C3-C4	1.519(3)	C17-H17	0.950
C3-C14	1.551(3)	C17-C18	1.382(3)
C3-H3	1.01(2)	C18-C19	1.406(3)
C4-C5	1.406(3)	C19-C20	1.386(3)
C4-C9	1.382(3)	C20-H20	0.950
C5-H5	0.950	C21-H21A	0.980
C5-C6	1.383(3)	C21-H21B	0.980
C6-C7	1.415(3)	C21-H21C	0.980
C7-C8	1.378(3)	C22-H22A	0.980

C8-H8	0.950	C22-H22B	0.980
C8-C9	1.410(2)	C22-H22C	0.980
C1-O2-C2	114.7(1)	C10-C11-H11B	109.9
C6-O3-C12	117.5(2)	H11A-C11-H11B	108.3
C7-O4-C13	116.1(2)	O3-C12-H12A	109.5
C18-O5-C21	117.0(2)	O3-C12-H12B	109.5
C19-O6-C22	116.8(1)	O3-C12-H12C	109.5
C1-N1-C3	124.5(2)	H12A-C12-H12B	109.5
C1-N1-C11	119.6(2)	H12A-C12-H12C	109.5
C3-N1-C11	115.8(2)	H12B-C12-H12C	109.5
O1-C1-O2	123.5(2)	O4-C13-H13A	109.5
O1-C1-N1	124.1(2)	O4-C13-H13B	109.5
O2-C1-N1	112.3(2)	O4-C13-H13C	109.5
O2-C2-H2A	109.5	H13A-C13-H13B	109.5
O2-C2-H2B	109.5	H13A-C13-H13C	109.5
O2-C2-H2C	109.5	H13B-C13-H13C	109.5
H2A-C2-H2B	109.4	C3-C14-H14A	109.1
H2A-C2-H2C	109.5	C3-C14-H14B	109.1
H2B-C2-H2C	109.5	C3-C14-C15	112.5(2)
N1-C3-C4	109.9(2)	H14A-C14-H14B	107.8
N1-C3-C14	110.7(2)	H14A-C14-C15	109.1
N1-C3-H3	108(1)	H14B-C14-C15	109.1
C4-C3-C14	111.2(2)	C14-C15-C16	123.8(2)
C4-C3-H3	108(1)	C14-C15-C20	119.3(2)
C14-C3-H3	109(1)	C16-C15-C20	116.8(2)
C3-C4-C5	118.2(2)	Br1-C16-C15	120.6(1)
C3-C4-C9	121.8(2)	Br1-C16-C17	116.9(1)
C5-C4-C9	119.9(2)	C15-C16-C17	122.5(2)
C4-C5-H5	119.5	C16-C17-H17	120.2
C4-C5-C6	121.0(2)	C16-C17-C18	119.5(2)
H5-C5-C6	119.5	H17-C17-C18	120.2
O3-C6-C5	125.6(2)	O5-C18-C17	125.4(2)
O3-C6-C7	115.2(2)	O5-C18-C19	115.0(2)
C5-C6-C7	119.2(2)	C17-C18-C19	119.6(2)
O4-C7-C6	115.2(2)	O6-C19-C18	115.8(2)
O4-C7-C8	125.3(2)	O6-C19-C20	124.8(2)
C6-C7-C8	119.5(2)	C18-C19-C20	119.4(2)
C7-C8-H8	119.4	C15-C20-C19	122.2(2)
C7-C8-C9	121.2(2)	C15-C20-H20	118.9
H8-C8-C9	119.4	C19-C20-H20	118.9
C4-C9-C8	119.1(2)	O5-C21-H21A	109.5
C4-C9-C10	122.2(2)	O5-C21-H21B	109.5
C8-C9-C10	118.7(2)	O5-C21-H21C	109.5
C9-C10-H10A	109.3	H21A-C21-H21B	109.5
C9-C10-H10B	109.3	H21A-C21-H21C	109.5
C9-C10-C11	111.6(2)	H21B-C21-H21C	109.5
H10A-C10-H10B	108.0	O6-C22-H22A	109.5
H10A-C10-C11	109.3	O6-C22-H22B	109.5
H10B-C10-C11	109.3	O6-C22-H22C	109.5
N1-C11-C10	108.8(2)	H22A-C22-H22B	109.5

N1-C11-H11A	109.9	H22A-C22-H22C	109.4
N1-C11-H11B	109.9	H22B-C22-H22C	109.5
C10-C11-H11A	109.9		

X-Ray data for compound 265

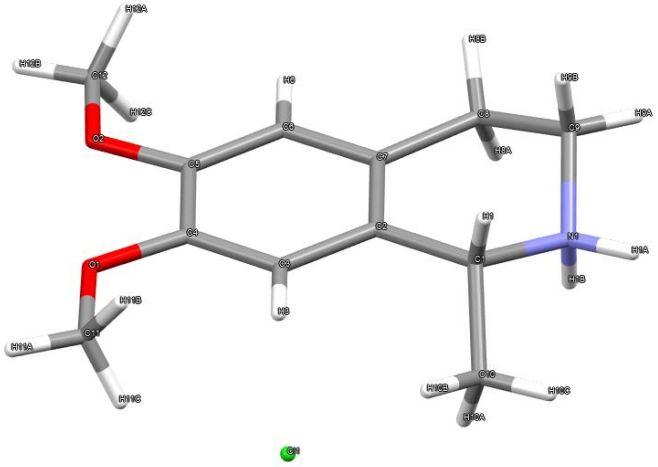


Figure 7.2 X-ray structure of salsolidine hydrochloride (**265**).

Table 7.4 Crystal data and structure refinement.

Identification code	14446
Empirical formula	$C_{12}H_{22}ClNO_4$
Color	colourless
Formula weight	279.75 g · mol^{-1}
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	ORTHORHOMBIC
Space group	**$P2_12_12_1$, (no. 19)**
Unit cell dimensions	a = 7.1714(8) Å α = 90°. b = 12.5370(19) Å β = 90°. c = 15.6182(15) Å γ = 90°.
Volume	1404.2(3) Å^3
Z	4
Density (calculated)	1.323 Mg · m^{-3}
Absorption coefficient	0.279 mm^{-1}
F(000)	600 e
Crystal size	0.25 x 0.09 x 0.07 mm^3
θ range for data collection	3.073 to 33.164°.
Index ranges	$-10 \le h \le 11$, $-19 \le k \le 19$, $-24 \le l \le 24$
Reflections collected	38264
Independent reflections	5356 [R_{int} = 0.0530]
Reflections with I>2σ(I)	4574
Completeness to θ = 25.242°	99.7 %
Absorption correction	Gaussian
Max. and min. transmission	0.98 and 0.95
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5356/0/194

Goodness-of-fit on F^2	1.042
Final R indices [I>2σ(I)]	R_1 = 0.0306 wR^2 = 0.0713
R indices (all data)	R_1 = 0.0435 wR^2 = 0.0753
Absolute structure parameter	-0.015(19)
Largest diff. peak and hole	0.3 and -0.3 e · $Å^{-3}$

Table 7.5 Bond lengths [Å] and angles [°].

O1-C4	1.376(2)	C6-H6	0.950
O1-C11	1.428(2)	C6-C7	1.403(2)
O2-C5	1.367(2)	C7-C8	1.515(2)
O2-C12	1.436(2)	C8-H8A	0.990
N1-H1A	0.96(2)	C8-H8B	0.990
N1-H1B	0.86(2)	C8-C9	1.514(2)
N1-C1	1.507(2)	C9-H9A	0.990
N1-C9	1.490(2)	C9-H9B	0.990
C1-H1	0.98(2)	C10-H10A	0.980
C1-C2	1.517(2)	C10-H10B	0.980
C1-C10	1.526(2)	C10-H10C	0.980
C2-C3	1.407(2)	C11-H11A	0.980
C2-C7	1.392(2)	C11-H11B	0.980
C3-H3	0.950	C11-H11C	0.980
C3-C4	1.380(2)	C12-H12A	0.980
C4-C5	1.409(2)	C12-H12B	0.980
C5-C6	1.382(2)	C12-H12C	0.980
C4-O1-C11	116.6(1)	C7-C8-H8A	109.2
C5-O2-C12	116.3(1)	C7-C8-H8B	109.2
H1A-N1-H1B	104(2)	C7-C8-C9	112.2(1)
H1A-N1-C1	111(1)	H8A-C8-H8B	107.9
H1A-N1-C9	110(1)	H8A-C8-C9	109.2
H1B-N1-C1	110(1)	H8B-C8-C9	109.2
H1B-N1-C9	109(1)	N1-C9-C8	108.9(1)
C1-N1-C9	112.6(1)	N1-C9-H9A	109.9
N1-C1-H1	106(1)	N1-C9-H9B	109.9
N1-C1-C2	109.7(1)	C8-C9-H9A	109.9
N1-C1-C10	107.4(1)	C8-C9-H9B	109.9
H1-C1-C2	110(1)	H9A-C9-H9B	108.3
H1-C1-C10	109(1)	C1-C10-H10A	109.5
C2-C1-C10	114.6(1)	C1-C10-H10B	109.5
C1-C2-C3	118.4(1)	C1-C10-H10C	109.5
C1-C2-C7	122.1(1)	H10A-C10-H10B	109.5
C3-C2-C7	119.5(1)	H10A-C10-H10C	109.5
C2-C3-H3	119.7	H10B-C10-H10C	109.5
C2-C3-C4	120.6(1)	O1-C11-H11A	109.5
H3-C3-C4	119.7	O1-C11-H11B	109.5
O1-C4-C3	124.9(1)	O1-C11-H11C	109.5
O1-C4-C5	115.1(1)	H11A-C11-H11B	109.5
C3-C4-C5	120.0(1)	H11A-C11-H11C	109.4
O2-C5-C4	115.1(1)	H11B-C11-H11C	109.5
O2-C5-C6	125.4(1)	O2-C12-H12A	109.5
C4-C5-C6	119.4(1)	O2-C12-H12B	109.5

C5-C6-H6	119.6	O2-C12-H12C	109.5
C5-C6-C7	120.9(1)	H12A-C12-H12B	109.5
H6-C6-C7	119.6	H12A-C12-H12C	109.5
C2-C7-C6	119.6(1)	H12B-C12-H12C	109.4
C2-C7-C8	121.8(1)	H3A-O3-H3B	101(3)
C6-C7-C8	118.6(1)	H4A-O4-H4B	109(3)

X-Ray data for IDPi 143b

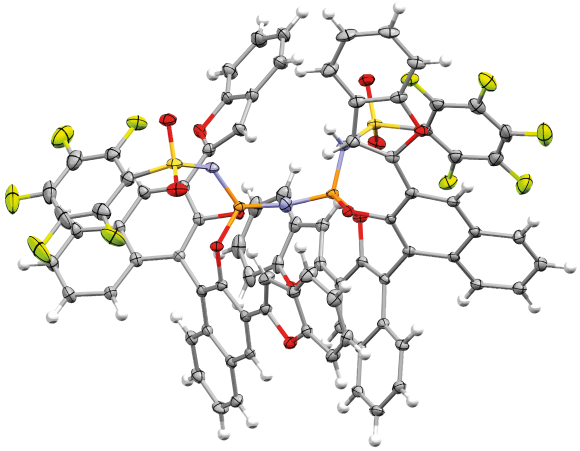


Figure 7.3 X-Ray structure of IDPi **143b**.

Table 7.6 Crystal data and structure refinement.

Identification code	13668
Empirical formula	$C_{252.50}H_{124}ClF_{30}N_9O_{36}P_6S_6$
Color	colorless
Formula weight	4843.23 g · mol-1
Temperature	100.15 K
Wavelength	0.71073 Å
Crystal system	ORTHORHOMBIC
Space group	**$P2_12_12_1$, (no. 19)**
Unit cell dimensions	a = 19.5110(7) Å α = 90°. b = 30.3940(13) Å β = 90°. c = 36.8917(15) Å γ = 90°.
Volume	21877.4(15) $Å^3$
Z	4
Density (calculated)	1.470 Mg · m^{-3}
Absorption coefficient	0.223 mm^{-1}
F(000)	9852 e
Crystal size	0.248 x 0.060 x 0.051 mm3
θ range for data collection	0.868 to 27.046°.
Index ranges	$-24 \leq h \leq 24$, $-38 \leq k \leq 38$, $-46 \leq l \leq 46$
Reflections collected	593818
Independent reflections	47171 [R_{int} = 0.0681]
Reflections with I>2σ(I)	39626
Completeness to θ = 25.242°	100.0 %
Absorption correction	Gaussian
Max. and min. transmission	0.99 and 0.98

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	47171 / 0 / 3061
Goodness-of-fit on F2	1.043
Final R indices [I>2σ(I)]	R_1 = 0.0419 wR^2 = 0.0955
R indices (all data)	R_1 = 0.0581 wR^2 = 0.1029
Absolute structure parameter	0.004(10)
Remarks	"Use solvent mask" was applied
Largest diff. peak and hole	0.6 and -0.5e·$Å^{-3}$

Table 7.7 Bond lengths [Å] and angles [°].

Cl(1)-C(100)	1.743(9)	Cl(2)-C(100)	1.771(8)
C(100)-H(10A)	0.99	C(100)-H(10B)	0.99
S(1A)-O(5A)	1.433(3)	S(1A)-O(6A)	1.435(3)
S(1A)-N(1A)	1.565(3)	S(1A)-C(37A)	1.779(4)
S(1B)-O(5B)	1.445(3)	S(1B)-O(6B)	1.435(3)
S(1B)-N(1B)	1.537(3)	S(1B)-C(37B)	1.782(4)
S(2B)-O(11B)	1.435(3)	S(2B)-O(12B)	1.437(3)
S(2B)-N(2B)	1.556(3)	S(2B)-C(87B)	1.790(5)
P(1B)-O(1B)	1.589(3)	P(1B)-O(2B)	1.584(3)
P(1B)-N(1B)	1.576(3)	P(1B)-N(3B)	1.546(3)
P(2B)-O(7B)	1.587(3)	P(2B)-O(8B)	1.596(3)
P(2B)-N(2B)	1.582(3)	P(2B)-N(3B)	1.538(3)
F(1B)-C(38B)	1.331(5)	F(2B)-C(39B)	1.330(6)
F(3B)-C(40B)	1.339(6)	F(4B)-C(41B)	1.341(6)
F(5B)-C(42B)	1.342(6)	F(6B)-C(88B)	1.323(5)
F(7B)-C(89B)	1.342(6)	F(8B)-C(90B)	1.338(6)
F(9B)-C(91B)	1.324(6)	F(10B)-C(92B)	1.353(6)
O(1B)-C(1B)	1.402(5)	O(2B)-C(11B)	1.404(4)
O(3B)-C(21B)	1.406(5)	O(3B)-C(28B)	1.368(5)
O(4B)-C(29B)	1.389(5)	O(4B)-C(36B)	1.377(5)
O(7B)-C(51B)	1.407(5)	O(8B)-C(61B)	1.401(5)
O(9B)-C(71B)	1.379(6)	O(9B)-C(78E)	1.550(11)
O(9B)-C(78D)	1.300(5)	O(10B)-C(79B)	1.401(5)
O(10B)-C(86B)	1.372(5)	N(1B)-H(1B)	0.88
C(1B)-C(2B)	1.422(6)	C(1B)-C(10B)	1.380(6)
C(2B)-C(3B)	1.379(6)	C(2B)-C(21B)	1.459(6)
C(3B)-H(3B)	0.95	C(3B)-C(4B)	1.405(6)
C(4B)-C(5B)	1.416(6)	C(4B)-C(9B)	1.412(6)
C(5B)-H(5B)	0.95	C(5B)-C(6B)	1.366(7)

C(6B)-H(6B)	0.95	C(6B)-C(7B)	1.402(7)
C(7B)-H(7B)	0.95	C(7B)-C(8B)	1.360(6)
C(8B)-H(8B)	0.95	C(8B)-C(9B)	1.418(6)
C(9B)-C(10B)	1.435(6)	C(10B)-C(20B)	1.508(6)
C(11B)-C(12B)	1.409(5)	C(11B)-C(20B)	1.369(5)
C(12B)-C(13B)	1.372(5)	C(12B)-C(29B)	1.464(5)
C(13B)-H(13B)	0.95	C(13B)-C(14B)	1.410(6)
C(14B)-C(15B)	1.415(6)	C(14B)-C(19B)	1.421(6)
C(15B)-H(15B)	0.95	C(15B)-C(16B)	1.366(7)
C(16B)-H(16B)	0.95	C(16B)-C(17B)	1.401(8)
C(17B)-H(17B)	0.95	C(17B)-C(18B)	1.362(7)
C(18B)-H(18B)	0.95	C(18B)-C(19B)	1.424(6)
C(19B)-C(20B)	1.433(6)	C(21B)-C(22B)	1.332(6)
C(22B)-H(22B)	0.95	C(22B)-C(23B)	1.441(6)
C(23B)-C(24B)	1.398(7)	C(23B)-C(28B)	1.383(7)
C(24B)-H(24B)	0.95	C(24B)-C(25B)	1.401(8)
C(25B)-H(25B)	0.95	C(25B)-C(26B)	1.379(9)
C(26B)-H(26B)	0.95	C(26B)-C(27B)	1.381(8)
C(27B)-H(27B)	0.95	C(27B)-C(28B)	1.382(7)
C(29B)-C(30B)	1.328(6)	C(30B)-H(30B)	0.95
C(30B)-C(31B)	1.430(6)	C(31B)-C(32B)	1.401(6)
C(31B)-C(36B)	1.395(6)	C(32B)-H(32B)	0.95
C(32B)-C(33B)	1.375(6)	C(33B)-H(33B)	0.95
C(33B)-C(34B)	1.384(7)	C(34B)-H(34B)	0.95
C(34B)-C(35B)	1.370(6)	C(35B)-H(35B)	0.95
C(35B)-C(36B)	1.377(6)	C(37B)-C(38B)	1.386(6)
C(37B)-C(42B)	1.387(6)	C(38B)-C(39B)	1.386(7)
C(39B)-C(40B)	1.373(8)	C(40B)-C(41B)	1.365(8)
C(41B)-C(42B)	1.380(7)	C(51B)-C(52B)	1.411(6)
C(51B)-C(60B)	1.377(6)	C(52B)-C(53B)	1.375(6)
C(52B)-C(71B)	1.459(6)	C(53B)-H(53B)	0.95
C(53B)-C(54B)	1.405(6)	C(54B)-C(55B)	1.426(6)
C(54B)-C(59B)	1.420(6)	C(55B)-H(55B)	0.95
C(55B)-C(56B)	1.360(7)	C(56B)-H(56B)	0.95
C(56B)-C(57B)	1.405(7)	C(57B)-H(57B)	0.95
C(57B)-C(58B)	1.374(6)	C(58B)-H(58B)	0.95
C(58B)-C(59B)	1.413(6)	C(59B)-C(60B)	1.430(6)

C(60B)-C(70B)	1.490(6)	C(61B)-C(62B)	1.425(6)
C(61B)-C(70B)	1.358(6)	C(62B)-C(63B)	1.388(6)
C(62B)-C(79B)	1.451(6)	C(63B)-H(63B)	0.95
C(63B)-C(64B)	1.408(6)	C(64B)-C(65B)	1.413(6)
C(64B)-C(69B)	1.416(6)	C(65B)-H(65B)	0.95
C(65B)-C(66B)	1.360(7)	C(66B)-H(66B)	0.95
C(66B)-C(67B)	1.406(7)	C(67B)-H(67B)	0.95
C(67B)-C(68B)	1.374(7)	C(68B)-H(68B)	0.95
C(68B)-C(69B)	1.412(6)	C(69B)-C(70B)	1.440(6)
C(71B)-C(72B)	1.330(7)	C(72B)-H(72B)	0.95
C(72B)-C(73E)	1.152(12)	C(72B)-C(78E)	2.037(12)
C(72B)-C(73D)	1.650(7)	C(73E)-C(74E)	1.422(19)
C(73E)-C(78E)	1.375(16)	C(74E)-H(74E)	0.95
C(74E)-C(75E)	1.45(2)	C(75E)-H(75E)	0.95
C(75E)-C(76E)	1.25(2)	C(76E)-H(76E)	0.95
C(76E)-C(77E)	1.33(2)	C(77E)-H(77E)	0.95
C(77E)-C(78E)	1.344(17)	C(79B)-C(80B)	1.347(6)
C(80B)-H(80B)	0.95	C(80B)-C(81B)	1.444(6)
C(81B)-C(82B)	1.397(7)	C(81B)-C(86B)	1.385(7)
C(82B)-H(82B)	0.95	C(82B)-C(83B)	1.382(8)
C(83B)-H(83B)	0.95	C(83B)-C(84B)	1.392(9)
C(84B)-H(84B)	0.95	C(84B)-C(85B)	1.386(8)
C(85B)-H(85B)	0.95	C(85B)-C(86B)	1.379(7)
C(87B)-C(88B)	1.399(7)	C(87B)-C(92B)	1.390(6)
C(88B)-C(89B)	1.362(7)	C(89B)-C(90B)	1.377(8)
C(90B)-C(91B)	1.380(9)	C(91B)-C(92B)	1.357(8)
S(1C)-O(5C)	1.438(3)	S(1C)-O(6C)	1.449(3)
S(1C)-N(1C)	1.545(3)	S(1C)-C(37C)	1.794(4)
S(2C)-O(11C)	1.436(3)	S(2C)-O(12C)	1.432(3)
S(2C)-N(2C)	1.559(3)	S(2C)-C(87C)	1.794(4)
P(1C)-O(1C)	1.581(3)	P(1C)-O(2C)	1.585(3)
P(1C)-N(1C)	1.586(3)	P(1C)-N(3C)	1.537(3)
P(2C)-O(7C)	1.580(3)	P(2C)-O(8C)	1.587(3)
P(2C)-N(2C)	1.588(3)	P(2C)-N(3C)	1.536(3)
F(1C)-C(38C)	1.334(6)	F(2C)-C(39C)	1.340(6)
F(3C)-C(40C)	1.329(6)	F(4C)-C(41C)	1.324(6)
F(5C)-C(42C)	1.347(5)	F(6C)-C(88C)	1.330(5)

F(7C)-C(89C)	1.341(5)	F(8C)-C(90C)	1.344(5)
F(9C)-C(91C)	1.343(5)	F(10C)-C(92C)	1.330(5)
O(1C)-C(1C)	1.402(4)	O(2C)-C(11C)	1.412(4)
O(3C)-C(21C)	1.395(4)	O(3C)-C(28C)	1.360(4)
O(4C)-C(29C)	1.380(4)	O(4C)-C(36C)	1.371(4)
O(7C)-C(51C)	1.412(4)	O(8C)-C(61C)	1.399(4)
O(9C)-C(71C)	1.392(4)	O(9C)-C(78C)	1.375(5)
O(10C)-C(79C)	1.390(4)	O(10C)-C(86C)	1.368(5)
N(2C)-H(2C)	0.88	C(1C)-C(2C)	1.413(5)
C(1C)-C(10C)	1.374(5)	C(2C)-C(3C)	1.371(5)
C(2C)-C(21C)	1.461(5)	C(3C)-H(3C)	0.95
C(3C)-C(4C)	1.409(5)	C(4C)-C(5C)	1.423(5)
C(4C)-C(9C)	1.417(5)	C(5C)-H(5C)	0.95
C(5C)-C(6C)	1.361(6)	C(6C)-H(6C)	0.95
C(6C)-C(7C)	1.409(6)	C(7C)-H(7C)	0.95
C(7C)-C(8C)	1.357(5)	C(8C)-H(8C)	0.95
C(8C)-C(9C)	1.412(5)	C(9C)-C(10C)	1.437(5)
C(10C)-C(20C)	1.490(5)	C(11C)-C(12C)	1.417(5)
C(11C)-C(20C)	1.357(5)	C(12C)-C(13C)	1.381(5)
C(12C)-C(29C)	1.462(5)	C(13C)-H(13C)	0.95
C(13C)-C(14C)	1.418(5)	C(14C)-C(15C)	1.425(5)
C(14C)-C(19C)	1.419(5)	C(15C)-H(15C)	0.95
C(15C)-C(16C)	1.365(6)	C(16C)-H(16C)	0.95
C(16C)-C(17C)	1.409(6)	C(17C)-H(17C)	0.95
C(17C)-C(18C)	1.377(6)	C(18C)-H(18C)	0.95
C(18C)-C(19C)	1.412(5)	C(19C)-C(20C)	1.438(5)
C(21C)-C(22C)	1.337(5)	C(22C)-H(22C)	0.95
C(22C)-C(23C)	1.437(5)	C(23C)-C(24C)	1.395(6)
C(23C)-C(28C)	1.384(5)	C(24C)-H(24C)	0.95
C(24C)-C(25C)	1.370(6)	C(25C)-H(25C)	0.95
C(25C)-C(26C)	1.394(6)	C(26C)-H(26C)	0.95
C(26C)-C(27C)	1.369(6)	C(27C)-H(27C)	0.95
C(27C)-C(28C)	1.382(5)	C(29C)-C(30C)	1.343(5)
C(30C)-H(30C)	0.95	C(30C)-C(31C)	1.428(5)
C(31C)-C(32C)	1.401(6)	C(31C)-C(36C)	1.387(6)
C(32C)-H(32C)	0.95	C(32C)-C(33C)	1.371(6)
C(33C)-H(33C)	0.95	C(33C)-C(34C)	1.402(7)

C(34C)-H(34C)	0.95	C(34C)-C(35C)	1.388(6)
C(35C)-H(35C)	0.95	C(35C)-C(36C)	1.375(6)
C(37C)-C(38C)	1.401(6)	C(37C)-C(42C)	1.377(6)
C(38C)-C(39C)	1.375(7)	C(39C)-C(40C)	1.355(8)
C(40C)-C(41C)	1.382(8)	C(41C)-C(42C)	1.368(7)
C(51C)-C(52C)	1.420(5)	C(51C)-C(60C)	1.363(5)
C(52C)-C(53C)	1.377(5)	C(52C)-C(71C)	1.458(5)
C(53C)-H(53C)	0.95	C(53C)-C(54C)	1.404(5)
C(54C)-C(55C)	1.421(5)	C(54C)-C(59C)	1.427(5)
C(55C)-H(55C)	0.95	C(55C)-C(56C)	1.372(6)
C(56C)-H(56C)	0.95	C(56C)-C(57C)	1.404(6)
C(57C)-H(57C)	0.95	C(57C)-C(58C)	1.359(5)
C(58C)-H(58C)	0.95	C(58C)-C(59C)	1.410(5)
C(59C)-C(60C)	1.431(5)	C(60C)-C(70C)	1.495(5)
C(61C)-C(62C)	1.417(5)	C(61C)-C(70C)	1.373(5)
C(62C)-C(63C)	1.370(5)	C(62C)-C(79C)	1.467(5)
C(63C)-H(63C)	0.95	C(63C)-C(64C)	1.411(5)
C(64C)-C(65C)	1.417(5)	C(64C)-C(69C)	1.424(5)
C(65C)-H(65C)	0.95	C(65C)-C(66C)	1.353(6)
C(66C)-H(66C)	0.95	C(66C)-C(67C)	1.417(6)
C(67C)-H(67C)	0.95	C(67C)-C(68C)	1.364(6)
C(68C)-H(68C)	0.95	C(68C)-C(69C)	1.405(5)
C(69C)-C(70C)	1.448(5)	C(71C)-C(72C)	1.344(5)
C(72C)-H(72C)	0.95	C(72C)-C(73C)	1.433(5)
C(73C)-C(74C)	1.411(6)	C(73C)-C(78C)	1.385(6)
C(74C)-H(74C)	0.95	C(74C)-C(75C)	1.379(6)
C(75C)-H(75C)	0.95	C(75C)-C(76C)	1.380(7)
C(76C)-H(76C)	0.95	C(76C)-C(77C)	1.387(7)
C(77C)-H(77C)	0.95	C(77C)-C(78C)	1.381(6)
C(79C)-C(80C)	1.352(6)	C(80C)-H(80C)	0.95
C(80C)-C(81C)	1.441(5)	C(81C)-C(82C)	1.400(6)
C(81C)-C(86C)	1.372(6)	C(82C)-H(82C)	0.95
C(82C)-C(83C)	1.379(6)	C(83C)-H(83C)	0.95
C(83C)-C(84C)	1.382(7)	C(84C)-H(84C)	0.95
C(84C)-C(85C)	1.369(6)	C(85C)-H(85C)	0.95
C(85C)-C(86C)	1.392(6)	C(87C)-C(88C)	1.395(6)
C(87C)-C(92C)	1.380(6)	C(88C)-C(89C)	1.372(6)

C(89C)-C(90C)	1.377(7)	C(90C)-C(91C)	1.367(7)
C(91C)-C(92C)	1.382(6)	S(2A)-O(11A)	1.446(3)
S(2A)-O(12A)	1.442(3)	S(2A)-N(2A)	1.537(3)
S(2A)-C(87A)	1.781(5)	P(1A)-O(1A)	1.583(2)
P(1A)-O(2A)	1.581(3)	P(1A)-N(1A)	1.598(3)
P(1A)-N(3A)	1.539(3)	P(2A)-O(7A)	1.580(2)
P(2A)-O(8A)	1.584(3)	P(2A)-N(2A)	1.584(3)
P(2A)-N(3A)	1.535(3)	F(1A)-C(38A)	1.333(5)
F(2A)-C(39A)	1.332(5)	F(3A)-C(40A)	1.334(5)
F(4A)-C(41A)	1.338(5)	F(5A)-C(42A)	1.332(4)
F(6A)-C(92A)	1.334(7)	F(7A)-C(91A)	1.345(8)
F(8A)-C(90A)	1.342(6)	F(9A)-C(89A)	1.328(8)
F(10A)-C(88A)	1.342(6)	O(1A)-C(1A)	1.408(4)
O(2A)-C(11A)	1.399(4)	O(3A)-C(21A)	1.392(4)
O(3A)-C(28A)	1.364(5)	O(4A)-C(29A)	1.395(5)
O(4A)-C(36A)	1.372(5)	O(7A)-C(51A)	1.409(4)
O(8A)-C(61A)	1.409(4)	O(9A)-C(71A)	1.383(4)
O(9A)-C(78A)	1.382(5)	O(10A)-C(79A)	1.360(5)
O(10A)-C(86A)	1.402(5)	N(2A)-H(2A)	0.88
C(1A)-C(2A)	1.425(5)	C(1A)-C(10A)	1.365(5)
C(2A)-C(3A)	1.374(5)	C(2A)-C(21A)	1.451(5)
C(3A)-H(3A)	0.95	C(3A)-C(4A)	1.422(5)
C(4A)-C(5A)	1.420(5)	C(4A)-C(9A)	1.427(5)
C(5A)-H(5A)	0.95	C(5A)-C(6A)	1.356(6)
C(6A)-H(6A)	0.95	C(6A)-C(7A)	1.401(6)
C(7A)-H(7A)	0.95	C(7A)-C(8A)	1.366(5)
C(8A)-H(8A)	0.95	C(8A)-C(9A)	1.419(5)
C(9A)-C(10A)	1.429(5)	C(10A)-C(20A)	1.496(5)
C(11A)-C(12A)	1.424(5)	C(11A)-C(20A)	1.368(5)
C(12A)-C(13A)	1.373(5)	C(12A)-C(29A)	1.458(5)
C(13A)-H(13A)	0.95	C(13A)-C(14A)	1.419(6)
C(14A)-C(15A)	1.408(6)	C(14A)-C(19A)	1.414(5)
C(15A)-H(15A)	0.95	C(15A)-C(16A)	1.358(6)
C(16A)-H(16A)	0.95	C(16A)-C(17A)	1.398(6)
C(17A)-H(17A)	0.95	C(17A)-C(18A)	1.370(6)
C(18A)-H(18A)	0.95	C(18A)-C(19A)	1.405(5)
C(19A)-C(20A)	1.440(5)	C(21A)-C(22A)	1.360(5)

C(22A)-H(22A)	0.95	C(22A)-C(23A)	1.427(5)
C(23A)-C(24A)	1.414(6)	C(23A)-C(28A)	1.379(6)
C(24A)-H(24A)	0.95	C(24A)-C(25A)	1.380(7)
C(25A)-H(25A)	0.95	C(25A)-C(26A)	1.380(7)
C(26A)-H(26A)	0.95	C(26A)-C(27A)	1.393(7)
C(27A)-H(27A)	0.95	C(27A)-C(28A)	1.400(6)
C(29A)-C(30A)	1.352(6)	C(30A)-H(30A)	0.95
C(30A)-C(31A)	1.441(6)	C(31A)-C(32A)	1.388(6)
C(31A)-C(36A)	1.379(7)	C(32A)-H(32A)	0.95
C(32A)-C(33A)	1.378(7)	C(33A)-H(33A)	0.95
C(33A)-C(34A)	1.394(8)	C(34A)-H(34A)	0.95
C(34A)-C(35A)	1.377(7)	C(35A)-H(35A)	0.95
C(35A)-C(36A)	1.393(6)	C(37A)-C(38A)	1.395(6)
C(37A)-C(42A)	1.389(6)	C(38A)-C(39A)	1.380(6)
C(39A)-C(40A)	1.379(7)	C(40A)-C(41A)	1.374(6)
C(41A)-C(42A)	1.378(6)	C(51A)-C(52A)	1.416(5)
C(51A)-C(60A)	1.378(5)	C(52A)-C(53A)	1.373(5)
C(52A)-C(71A)	1.459(5)	C(53A)-H(53A)	0.95
C(53A)-C(54A)	1.410(6)	C(54A)-C(55A)	1.423(6)
C(54A)-C(59A)	1.418(5)	C(55A)-H(55A)	0.95
C(55A)-C(56A)	1.360(6)	C(56A)-H(56A)	0.95
C(56A)-C(57A)	1.395(6)	C(57A)-H(57A)	0.95
C(57A)-C(58A)	1.377(6)	C(58A)-H(58A)	0.95
C(58A)-C(59A)	1.414(5)	C(59A)-C(60A)	1.431(5)
C(60A)-C(70A)	1.487(5)	C(61A)-C(62A)	1.413(5)
C(61A)-C(70A)	1.373(5)	C(62A)-C(63A)	1.369(5)
C(62A)-C(79A)	1.464(6)	C(63A)-H(63A)	0.95
C(63A)-C(64A)	1.415(6)	C(64A)-C(65A)	1.411(5)
C(64A)-C(69A)	1.424(6)	C(65A)-H(65A)	0.95
C(65A)-C(66A)	1.364(7)	C(66A)-H(66A)	0.95
C(66A)-C(67A)	1.398(7)	C(67A)-H(67A)	0.95
C(67A)-C(68A)	1.365(6)	C(68A)-H(68A)	0.95
C(68A)-C(69A)	1.431(6)	C(69A)-C(70A)	1.427(5)
C(71A)-C(72A)	1.357(5)	C(72A)-H(72A)	0.95
C(72A)-C(73A)	1.436(5)	C(73A)-C(74A)	1.388(6)
C(73A)-C(78A)	1.383(6)	C(74A)-H(74A)	0.95
C(74A)-C(75A)	1.381(6)	C(75A)-H(75A)	0.95

C(75A)-C(76A)	1.385(7)	C(76A)-H(76A)	0.95
C(76A)-C(77A)	1.383(6)	C(77A)-H(77A)	0.95
C(77A)-C(78A)	1.381(6)	C(78D)-C(77D)	13.900
C(78D)-C(73D)	13.900	C(77D)-H(77D)	0.95
C(77D)-C(76D)	13.900	C(76D)-H(76D)	0.95
C(76D)-C(75D)	13.900	C(75D)-H(75D)	0.95
C(75D)-C(74D)	13.900	C(74D)-H(74D)	0.95
C(74D)-C(73D)	13.900	C(79A)-C(80A)	1.310(6)
C(80A)-H(80A)	0.95	C(80A)-C(81A)	1.405(6)
C(81A)-C(82A)	1.400(7)	C(81A)-C(86A)	1.375(7)
C(82A)-H(82A)	0.95	C(82A)-C(83A)	1.351(8)
C(83A)-H(83A)	0.95	C(83A)-C(84A)	1.369(8)
C(84A)-H(84A)	0.95	C(84A)-C(85A)	1.378(8)
C(85A)-H(85A)	0.95	C(85A)-C(86A)	1.377(6)
C(87A)-C(88A)	1.380(7)	C(87A)-C(92A)	1.415(7)
C(88A)-C(89A)	1.381(7)	C(89A)-C(90A)	1.380(10)
C(90A)-C(91A)	1.359(10)	C(91A)-C(92A)	1.347(8)
Cl(1)-C(100)-Cl(2)	110.7(5)	Cl(1)-C(100)-H(10A)	109.5
Cl(1)-C(100)-H(10B)	109.5	Cl(2)-C(100)-H(10A)	109.5
Cl(2)-C(100)-H(10B)	109.5	H(10A)-C(100)-H(10B)	108.1
O(5A)-S(1A)-O(6A)	115.53(17)	O(5A)-S(1A)-N(1A)	107.96(17)
O(5A)-S(1A)-C(37A)	105.40(17)	O(6A)-S(1A)-N(1A)	113.73(16)
O(6A)-S(1A)-C(37A)	107.27(18)	N(1A)-S(1A)-C(37A)	106.23(17)
O(5B)-S(1B)-N(1B)	114.34(18)	O(5B)-S(1B)-C(37B)	104.99(19)
O(6B)-S(1B)-O(5B)	115.19(17)	O(6B)-S(1B)-N(1B)	109.05(18)
O(6B)-S(1B)-C(37B)	106.50(19)	N(1B)-S(1B)-C(37B)	105.96(19)
O(11B)-S(2B)-O(12B)	115.6(2)	O(11B)-S(2B)-N(2B)	114.17(19)
O(11B)-S(2B)-C(87B)	106.2(2)	O(12B)-S(2B)-N(2B)	108.59(19)
O(12B)-S(2B)-C(87B)	106.0(2)	N(2B)-S(2B)-C(87B)	105.5(2)
O(2B)-P(1B)-O(1B)	103.06(14)	N(1B)-P(1B)-O(1B)	111.48(17)
N(1B)-P(1B)-O(2B)	108.19(16)	N(3B)-P(1B)-O(1B)	105.84(16)
N(3B)-P(1B)-O(2B)	110.78(16)	N(3B)-P(1B)-N(1B)	116.66(18)
O(7B)-P(2B)-O(8B)	102.98(15)	N(2B)-P(2B)-O(7B)	108.37(16)
N(2B)-P(2B)-O(8B)	111.26(17)	N(3B)-P(2B)-O(7B)	112.36(17)
N(3B)-P(2B)-O(8B)	104.83(16)	N(3B)-P(2B)-N(2B)	116.22(19)
C(1B)-O(1B)-P(1B)	119.9(2)	C(11B)-O(2B)-P(1B)	114.6(2)
C(28B)-O(3B)-C(21B)	106.0(4)	C(36B)-O(4B)-C(29B)	105.6(3)

C(51B)-O(7B)-P(2B)	114.8(2)	C(61B)-O(8B)-P(2B)	120.1(2)
C(71B)-O(9B)-C(78E)	93.5(5)	C(78D)-O(9B)-C(71B)	113.7(4)
C(86B)-O(10B)-C(79B)	106.2(3)	S(1B)-N(1B)-P(1B)	132.9(2)
S(1B)-N(1B)-H(1B)	113.5	P(1B)-N(1B)-H(1B)	113.5
S(2B)-N(2B)-P(2B)	131.0(2)	P(2B)-N(3B)-P(1B)	146.7(2)
O(1B)-C(1B)-C(2B)	117.3(4)	C(10B)-C(1B)-O(1B)	118.8(4)
C(10B)-C(1B)-C(2B)	123.9(4)	C(1B)-C(2B)-C(21B)	122.8(4)
C(3B)-C(2B)-C(1B)	116.6(4)	C(3B)-C(2B)-C(21B)	120.5(4)
C(2B)-C(3B)-H(3B)	118.9	C(2B)-C(3B)-C(4B)	122.3(4)
C(4B)-C(3B)-H(3B)	118.9	C(3B)-C(4B)-C(5B)	119.9(4)
C(3B)-C(4B)-C(9B)	120.0(4)	C(9B)-C(4B)-C(5B)	120.0(4)
C(4B)-C(5B)-H(5B)	119.9	C(6B)-C(5B)-C(4B)	120.2(4)
C(6B)-C(5B)-H(5B)	119.9	C(5B)-C(6B)-H(6B)	120.1
C(5B)-C(6B)-C(7B)	119.9(4)	C(7B)-C(6B)-H(6B)	120.1
C(6B)-C(7B)-H(7B)	119.5	C(8B)-C(7B)-C(6B)	121.1(4)
C(8B)-C(7B)-H(7B)	119.5	C(7B)-C(8B)-H(8B)	119.6
C(7B)-C(8B)-C(9B)	120.8(4)	C(9B)-C(8B)-H(8B)	119.6
C(4B)-C(9B)-C(8B)	118.0(4)	C(4B)-C(9B)-C(10B)	118.8(4)
C(8B)-C(9B)-C(10B)	123.2(4)	C(1B)-C(10B)-C(9B)	118.0(4)
C(1B)-C(10B)-C(20B)	120.6(4)	C(9B)-C(10B)-C(20B)	121.3(3)
O(2B)-C(11B)-C(12B)	116.9(3)	C(20B)-C(11B)-O(2B)	117.8(3)
C(20B)-C(11B)-C(12B)	125.2(4)	C(11B)-C(12B)-C(29B)	120.4(3)
C(13B)-C(12B)-C(11B)	116.7(4)	C(13B)-C(12B)-C(29B)	122.9(4)
C(12B)-C(13B)-H(13B)	119.2	C(12B)-C(13B)-C(14B)	121.5(4)
C(14B)-C(13B)-H(13B)	119.2	C(13B)-C(14B)-C(15B)	119.8(4)
C(13B)-C(14B)-C(19B)	120.5(4)	C(15B)-C(14B)-C(19B)	119.7(4)
C(14B)-C(15B)-H(15B)	119.9	C(16B)-C(15B)-C(14B)	120.2(5)
C(16B)-C(15B)-H(15B)	119.9	C(15B)-C(16B)-H(16B)	119.9
C(15B)-C(16B)-C(17B)	120.3(4)	C(17B)-C(16B)-H(16B)	119.9
C(16B)-C(17B)-H(17B)	119.4	C(18B)-C(17B)-C(16B)	121.2(4)
C(18B)-C(17B)-H(17B)	119.4	C(17B)-C(18B)-H(18B)	119.9
C(17B)-C(18B)-C(19B)	120.3(5)	C(19B)-C(18B)-H(18B)	119.9
C(14B)-C(19B)-C(18B)	118.3(4)	C(14B)-C(19B)-C(20B)	118.3(4)
C(18B)-C(19B)-C(20B)	123.4(4)	C(11B)-C(20B)-C(10B)	119.1(3)
C(11B)-C(20B)-C(19B)	117.7(4)	C(19B)-C(20B)-C(10B)	123.1(4)
O(3B)-C(21B)-C(2B)	112.6(4)	C(22B)-C(21B)-O(3B)	110.5(4)
C(22B)-C(21B)-C(2B)	136.7(4)	C(21B)-C(22B)-H(22B)	126.3

C(21B)-C(22B)-C(23B)	107.5(4)	C(23B)-C(22B)-H(22B)	126.3
C(24B)-C(23B)-C(22B)	135.0(5)	C(28B)-C(23B)-C(22B)	105.6(4)
C(28B)-C(23B)-C(24B)	119.3(5)	C(23B)-C(24B)-H(24B)	121.6
C(23B)-C(24B)-C(25B)	116.8(5)	C(25B)-C(24B)-H(24B)	121.6
C(24B)-C(25B)-H(25B)	118.9	C(26B)-C(25B)-C(24B)	122.2(5)
C(26B)-C(25B)-H(25B)	118.9	C(25B)-C(26B)-H(26B)	119.3
C(25B)-C(26B)-C(27B)	121.5(5)	C(27B)-C(26B)-H(26B)	119.3
C(26B)-C(27B)-H(27B)	122	C(26B)-C(27B)-C(28B)	115.9(5)
C(28B)-C(27B)-H(27B)	122	O(3B)-C(28B)-C(23B)	110.4(4)
O(3B)-C(28B)-C(27B)	125.3(5)	C(27B)-C(28B)-C(23B)	124.3(4)
O(4B)-C(29B)-C(12B)	114.4(3)	C(30B)-C(29B)-O(4B)	111.7(3)
C(30B)-C(29B)-C(12B)	133.9(4)	C(29B)-C(30B)-H(30B)	126.4
C(29B)-C(30B)-C(31B)	107.2(4)	C(31B)-C(30B)-H(30B)	126.4
C(32B)-C(31B)-C(30B)	135.9(4)	C(36B)-C(31B)-C(30B)	105.8(3)
C(36B)-C(31B)-C(32B)	118.3(4)	C(31B)-C(32B)-H(32B)	121
C(33B)-C(32B)-C(31B)	118.1(4)	C(33B)-C(32B)-H(32B)	121
C(32B)-C(33B)-H(33B)	119.2	C(32B)-C(33B)-C(34B)	121.6(4)
C(34B)-C(33B)-H(33B)	119.2	C(33B)-C(34B)-H(34B)	119
C(35B)-C(34B)-C(33B)	121.9(4)	C(35B)-C(34B)-H(34B)	119
C(34B)-C(35B)-H(35B)	121.9	C(34B)-C(35B)-C(36B)	116.1(4)
C(36B)-C(35B)-H(35B)	121.9	O(4B)-C(36B)-C(31B)	109.7(3)
O(4B)-C(36B)-C(35B)	126.3(4)	C(35B)-C(36B)-C(31B)	124.0(4)
C(38B)-C(37B)-S(1B)	122.1(3)	C(38B)-C(37B)-C(42B)	116.8(4)
C(42B)-C(37B)-S(1B)	121.1(4)	F(1B)-C(38B)-C(37B)	120.9(4)
F(1B)-C(38B)-C(39B)	117.5(4)	C(37B)-C(38B)-C(39B)	121.7(4)
F(2B)-C(39B)-C(38B)	120.2(5)	F(2B)-C(39B)-C(40B)	120.4(5)
C(40B)-C(39B)-C(38B)	119.4(5)	F(3B)-C(40B)-C(39B)	119.1(6)
F(3B)-C(40B)-C(41B)	120.4(5)	C(41B)-C(40B)-C(39B)	120.6(5)
F(4B)-C(41B)-C(40B)	120.5(5)	F(4B)-C(41B)-C(42B)	120.2(5)
C(40B)-C(41B)-C(42B)	119.3(5)	F(5B)-C(42B)-C(37B)	121.7(4)
F(5B)-C(42B)-C(41B)	116.1(4)	C(41B)-C(42B)-C(37B)	122.2(5)
O(7B)-C(51B)-C(52B)	117.9(4)	C(60B)-C(51B)-O(7B)	117.3(4)
C(60B)-C(51B)-C(52B)	124.7(4)	C(51B)-C(52B)-C(71B)	122.6(4)
C(53B)-C(52B)-C(51B)	116.5(4)	C(53B)-C(52B)-C(71B)	120.9(4)
C(52B)-C(53B)-H(53B)	118.9	C(52B)-C(53B)-C(54B)	122.2(4)
C(54B)-C(53B)-H(53B)	118.9	C(53B)-C(54B)-C(55B)	120.4(4)
C(53B)-C(54B)-C(59B)	120.0(4)	C(59B)-C(54B)-C(55B)	119.6(4)

C(54B)-C(55B)-H(55B)	119.7	C(56B)-C(55B)-C(54B)	120.6(4)
C(56B)-C(55B)-H(55B)	119.7	C(55B)-C(56B)-H(56B)	120
C(55B)-C(56B)-C(57B)	120.0(4)	C(57B)-C(56B)-H(56B)	120
C(56B)-C(57B)-H(57B)	119.6	C(58B)-C(57B)-C(56B)	120.8(5)
C(58B)-C(57B)-H(57B)	119.6	C(57B)-C(58B)-H(58B)	119.5
C(57B)-C(58B)-C(59B)	121.0(4)	C(59B)-C(58B)-H(58B)	119.5
C(54B)-C(59B)-C(60B)	118.8(4)	C(58B)-C(59B)-C(54B)	118.0(4)
C(58B)-C(59B)-C(60B)	123.1(4)	C(51B)-C(60B)-C(59B)	117.7(4)
C(51B)-C(60B)-C(70B)	118.8(4)	C(59B)-C(60B)-C(70B)	123.5(4)
O(8B)-C(61B)-C(62B)	116.4(3)	C(70B)-C(61B)-O(8B)	119.4(4)
C(70B)-C(61B)-C(62B)	124.1(4)	C(61B)-C(62B)-C(79B)	122.9(4)
C(63B)-C(62B)-C(61B)	116.2(4)	C(63B)-C(62B)-C(79B)	120.8(4)
C(62B)-C(63B)-H(63B)	118.8	C(62B)-C(63B)-C(64B)	122.4(4)
C(64B)-C(63B)-H(63B)	118.8	C(63B)-C(64B)-C(65B)	121.0(4)
C(63B)-C(64B)-C(69B)	119.7(4)	C(65B)-C(64B)-C(69B)	119.3(4)
C(64B)-C(65B)-H(65B)	119.4	C(66B)-C(65B)-C(64B)	121.3(5)
C(66B)-C(65B)-H(65B)	119.4	C(65B)-C(66B)-H(66B)	120
C(65B)-C(66B)-C(67B)	119.9(5)	C(67B)-C(66B)-H(66B)	120
C(66B)-C(67B)-H(67B)	120.1	C(68B)-C(67B)-C(66B)	119.9(5)
C(68B)-C(67B)-H(67B)	120.1	C(67B)-C(68B)-H(68B)	119.2
C(67B)-C(68B)-C(69B)	121.6(5)	C(69B)-C(68B)-H(68B)	119.2
C(64B)-C(69B)-C(70B)	118.6(4)	C(68B)-C(69B)-C(64B)	117.8(4)
C(68B)-C(69B)-C(70B)	123.5(4)	C(61B)-C(70B)-C(60B)	120.5(4)
C(61B)-C(70B)-C(69B)	118.8(4)	C(69B)-C(70B)-C(60B)	120.7(4)
O(9B)-C(71B)-C(52B)	118.0(4)	C(72B)-C(71B)-O(9B)	113.7(4)
C(72B)-C(71B)-C(52B)	128.3(5)	C(71B)-C(72B)-H(72B)	130.7
C(71B)-C(72B)-C(78E)	75.5(5)	C(71B)-C(72B)-C(73D)	98.7(5)
C(73E)-C(72B)-C(71B)	115.5(7)	C(73E)-C(72B)-C(78E)	40.2(6)
C(73D)-C(72B)-H(72B)	130.7	C(72B)-C(73E)-C(74E)	135.9(12)
C(72B)-C(73E)-C(78E)	107.1(9)	C(78E)-C(73E)-C(74E)	116.3(12)
C(73E)-C(74E)-H(74E)	125.6	C(73E)-C(74E)-C(75E)	108.9(14)
C(75E)-C(74E)-H(74E)	125.6	C(74E)-C(75E)-H(75E)	113.3
C(76E)-C(75E)-C(74E)	133.5(19)	C(76E)-C(75E)-H(75E)	113.3
C(75E)-C(76E)-H(76E)	122.1	C(75E)-C(76E)-C(77E)	115.8(18)
C(77E)-C(76E)-H(76E)	122.1	C(76E)-C(77E)-H(77E)	121.1
C(76E)-C(77E)-C(78E)	117.7(15)	C(78E)-C(77E)-H(77E)	121.1
O(9B)-C(78E)-C(72B)	77.1(4)	C(73E)-C(78E)-O(9B)	109.5(8)

C(73E)-C(78E)-C(72B)	32.7(5)	C(77E)-C(78E)-O(9B)	122.8(11)
C(77E)-C(78E)-C(72B)	159.9(11)	C(77E)-C(78E)-C(73E)	127.7(12)
O(10B)-C(79B)-C(62B)	113.3(4)	C(80B)-C(79B)-O(10B)	110.5(4)
C(80B)-C(79B)-C(62B)	136.2(4)	C(79B)-C(80B)-H(80B)	126.5
C(79B)-C(80B)-C(81B)	107.1(4)	C(81B)-C(80B)-H(80B)	126.5
C(82B)-C(81B)-C(80B)	135.0(5)	C(86B)-C(81B)-C(80B)	105.8(4)
C(86B)-C(81B)-C(82B)	119.2(5)	C(81B)-C(82B)-H(82B)	120.9
C(83B)-C(82B)-C(81B)	118.1(6)	C(83B)-C(82B)-H(82B)	120.9
C(82B)-C(83B)-H(83B)	119.5	C(82B)-C(83B)-C(84B)	121.0(5)
C(84B)-C(83B)-H(83B)	119.5	C(83B)-C(84B)-H(84B)	119.1
C(85B)-C(84B)-C(83B)	121.9(5)	C(85B)-C(84B)-H(84B)	119.1
C(84B)-C(85B)-H(85B)	122.1	C(86B)-C(85B)-C(84B)	115.9(6)
C(86B)-C(85B)-H(85B)	122.1	O(10B)-C(86B)-C(81B)	110.4(4)
O(10B)-C(86B)-C(85B)	125.7(5)	C(85B)-C(86B)-C(81B)	123.9(5)
C(88B)-C(87B)-S(2B)	120.8(3)	C(92B)-C(87B)-S(2B)	123.0(4)
C(92B)-C(87B)-C(88B)	116.2(5)	F(6B)-C(88B)-C(87B)	120.9(4)
F(6B)-C(88B)-C(89B)	117.5(4)	C(89B)-C(88B)-C(87B)	121.6(4)
F(7B)-C(89B)-C(88B)	120.3(5)	F(7B)-C(89B)-C(90B)	119.8(5)
C(88B)-C(89B)-C(90B)	119.9(5)	F(8B)-C(90B)-C(89B)	120.1(6)
F(8B)-C(90B)-C(91B)	119.4(5)	C(89B)-C(90B)-C(91B)	120.4(5)
F(9B)-C(91B)-C(90B)	119.8(5)	F(9B)-C(91B)-C(92B)	121.6(6)
C(92B)-C(91B)-C(90B)	118.6(5)	F(10B)-C(92B)-C(87B)	120.9(5)
F(10B)-C(92B)-C(91B)	115.7(5)	C(91B)-C(92B)-C(87B)	123.3(5)
O(5C)-S(1C)-O(6C)	114.27(17)	O(5C)-S(1C)-N(1C)	115.23(18)
O(5C)-S(1C)-C(37C)	106.3(2)	O(6C)-S(1C)-N(1C)	107.85(17)
O(6C)-S(1C)-C(37C)	103.02(19)	N(1C)-S(1C)-C(37C)	109.35(18)
O(11C)-S(2C)-N(2C)	107.95(17)	O(11C)-S(2C)-C(87C)	104.94(17)
O(12C)-S(2C)-O(11C)	115.85(17)	O(12C)-S(2C)-N(2C)	113.96(17)
O(12C)-S(2C)-C(87C)	106.42(18)	N(2C)-S(2C)-C(87C)	106.97(17)
O(1C)-P(1C)-O(2C)	105.15(13)	O(1C)-P(1C)-N(1C)	106.63(15)
O(2C)-P(1C)-N(1C)	110.26(15)	N(3C)-P(1C)-O(1C)	112.32(16)
N(3C)-P(1C)-O(2C)	106.30(16)	N(3C)-P(1C)-N(1C)	115.71(18)
O(7C)-P(2C)-O(8C)	104.98(13)	O(7C)-P(2C)-N(2C)	105.33(15)
O(8C)-P(2C)-N(2C)	111.70(15)	N(3C)-P(2C)-O(7C)	116.54(16)
N(3C)-P(2C)-O(8C)	102.01(16)	N(3C)-P(2C)-N(2C)	115.85(18)
C(1C)-O(1C)-P(1C)	119.4(2)	C(11C)-O(2C)-P(1C)	115.3(2)
C(28C)-O(3C)-C(21C)	106.0(3)	C(36C)-O(4C)-C(29C)	106.1(3)

C(51C)-O(7C)-P(2C)	118.0(2)	C(61C)-O(8C)-P(2C)	119.7(2)
C(78C)-O(9C)-C(71C)	105.6(3)	C(86C)-O(10C)-C(79C)	106.0(3)
S(1C)-N(1C)-P(1C)	130.5(2)	S(2C)-N(2C)-P(2C)	130.2(2)
S(2C)-N(2C)-H(2C)	114.9	P(2C)-N(2C)-H(2C)	114.9
P(2C)-N(3C)-P(1C)	160.6(2)	O(1C)-C(1C)-C(2C)	118.2(3)
C(10C)-C(1C)-O(1C)	117.9(3)	C(10C)-C(1C)-C(2C)	123.9(3)
C(1C)-C(2C)-C(21C)	122.3(3)	C(3C)-C(2C)-C(1C)	117.0(3)
C(3C)-C(2C)-C(21C)	120.7(3)	C(2C)-C(3C)-H(3C)	119
C(2C)-C(3C)-C(4C)	122.0(3)	C(4C)-C(3C)-H(3C)	119
C(3C)-C(4C)-C(5C)	120.9(3)	C(3C)-C(4C)-C(9C)	120.3(3)
C(9C)-C(4C)-C(5C)	118.7(3)	C(4C)-C(5C)-H(5C)	119.5
C(6C)-C(5C)-C(4C)	120.9(4)	C(6C)-C(5C)-H(5C)	119.5
C(5C)-C(6C)-H(6C)	120.2	C(5C)-C(6C)-C(7C)	119.7(4)
C(7C)-C(6C)-H(6C)	120.2	C(6C)-C(7C)-H(7C)	119.5
C(8C)-C(7C)-C(6C)	120.9(4)	C(8C)-C(7C)-H(7C)	119.5
C(7C)-C(8C)-H(8C)	119.6	C(7C)-C(8C)-C(9C)	120.9(4)
C(9C)-C(8C)-H(8C)	119.6	C(4C)-C(9C)-C(10C)	118.0(3)
C(8C)-C(9C)-C(4C)	118.8(3)	C(8C)-C(9C)-C(10C)	123.2(3)
C(1C)-C(10C)-C(9C)	118.6(3)	C(1C)-C(10C)-C(20C)	120.4(3)
C(9C)-C(10C)-C(20C)	120.7(3)	O(2C)-C(11C)-C(12C)	116.9(3)
C(20C)-C(11C)-O(2C)	118.0(3)	C(20C)-C(11C)-C(12C)	125.1(3)
C(11C)-C(12C)-C(29C)	121.2(3)	C(13C)-C(12C)-C(11C)	116.6(3)
C(13C)-C(12C)-C(29C)	122.2(3)	C(12C)-C(13C)-H(13C)	119.5
C(12C)-C(13C)-C(14C)	121.0(4)	C(14C)-C(13C)-H(13C)	119.5
C(13C)-C(14C)-C(15C)	121.1(4)	C(13C)-C(14C)-C(19C)	120.4(3)
C(19C)-C(14C)-C(15C)	118.4(3)	C(14C)-C(15C)-H(15C)	119.5
C(16C)-C(15C)-C(14C)	121.1(4)	C(16C)-C(15C)-H(15C)	119.5
C(15C)-C(16C)-H(16C)	119.9	C(15C)-C(16C)-C(17C)	120.1(4)
C(17C)-C(16C)-H(16C)	119.9	C(16C)-C(17C)-H(17C)	119.8
C(18C)-C(17C)-C(16C)	120.5(4)	C(18C)-C(17C)-H(17C)	119.8
C(17C)-C(18C)-H(18C)	119.8	C(17C)-C(18C)-C(19C)	120.4(4)
C(19C)-C(18C)-H(18C)	119.8	C(14C)-C(19C)-C(20C)	118.3(3)
C(18C)-C(19C)-C(14C)	119.5(3)	C(18C)-C(19C)-C(20C)	122.2(3)
C(11C)-C(20C)-C(10C)	120.1(3)	C(11C)-C(20C)-C(19C)	117.6(3)
C(19C)-C(20C)-C(10C)	122.2(3)	O(3C)-C(21C)-C(2C)	113.0(3)
C(22C)-C(21C)-O(3C)	110.7(3)	C(22C)-C(21C)-C(2C)	136.4(3)
C(21C)-C(22C)-H(22C)	126.4	C(21C)-C(22C)-C(23C)	107.3(3)

C(23C)-C(22C)-H(22C)	126.4	C(24C)-C(23C)-C(22C)	136.3(4)
C(28C)-C(23C)-C(22C)	105.3(3)	C(28C)-C(23C)-C(24C)	118.4(4)
C(23C)-C(24C)-H(24C)	120.7	C(25C)-C(24C)-C(23C)	118.6(4)
C(25C)-C(24C)-H(24C)	120.7	C(24C)-C(25C)-H(25C)	119.2
C(24C)-C(25C)-C(26C)	121.5(4)	C(26C)-C(25C)-H(25C)	119.2
C(25C)-C(26C)-H(26C)	119.5	C(27C)-C(26C)-C(25C)	121.0(4)
C(27C)-C(26C)-H(26C)	119.5	C(26C)-C(27C)-H(27C)	121.6
C(26C)-C(27C)-C(28C)	116.7(4)	C(28C)-C(27C)-H(27C)	121.6
O(3C)-C(28C)-C(23C)	110.7(3)	O(3C)-C(28C)-C(27C)	125.6(3)
C(27C)-C(28C)-C(23C)	123.7(4)	O(4C)-C(29C)-C(12C)	114.8(3)
C(30C)-C(29C)-O(4C)	110.8(3)	C(30C)-C(29C)-C(12C)	134.3(4)
C(29C)-C(30C)-H(30C)	126.3	C(29C)-C(30C)-C(31C)	107.4(3)
C(31C)-C(30C)-H(30C)	126.3	C(32C)-C(31C)-C(30C)	135.3(4)
C(36C)-C(31C)-C(30C)	105.5(3)	C(36C)-C(31C)-C(32C)	119.2(4)
C(31C)-C(32C)-H(32C)	121.1	C(33C)-C(32C)-C(31C)	117.7(4)
C(33C)-C(32C)-H(32C)	121.1	C(32C)-C(33C)-H(33C)	119.1
C(32C)-C(33C)-C(34C)	121.9(4)	C(34C)-C(33C)-H(33C)	119.1
C(33C)-C(34C)-H(34C)	119.6	C(35C)-C(34C)-C(33C)	120.9(4)
C(35C)-C(34C)-H(34C)	119.6	C(34C)-C(35C)-H(35C)	121.9
C(36C)-C(35C)-C(34C)	116.2(4)	C(36C)-C(35C)-H(35C)	121.9
O(4C)-C(36C)-C(31C)	110.2(3)	O(4C)-C(36C)-C(35C)	125.8(4)
C(35C)-C(36C)-C(31C)	124.0(4)	C(38C)-C(37C)-S(1C)	123.9(4)
C(42C)-C(37C)-S(1C)	119.5(3)	C(42C)-C(37C)-C(38C)	116.2(4)
F(1C)-C(38C)-C(37C)	120.8(5)	F(1C)-C(38C)-C(39C)	118.5(5)
C(39C)-C(38C)-C(37C)	120.6(5)	F(2C)-C(39C)-C(38C)	118.9(6)
F(2C)-C(39C)-C(40C)	119.7(5)	C(40C)-C(39C)-C(38C)	121.3(5)
F(3C)-C(40C)-C(39C)	120.1(5)	F(3C)-C(40C)-C(41C)	120.3(6)
C(39C)-C(40C)-C(41C)	119.6(5)	F(4C)-C(41C)-C(40C)	120.3(5)
F(4C)-C(41C)-C(42C)	120.9(5)	C(42C)-C(41C)-C(40C)	118.8(5)
F(5C)-C(42C)-C(37C)	118.6(4)	F(5C)-C(42C)-C(41C)	117.9(4)
C(41C)-C(42C)-C(37C)	123.5(4)	O(7C)-C(51C)-C(52C)	116.6(3)
C(60C)-C(51C)-O(7C)	118.1(3)	C(60C)-C(51C)-C(52C)	125.3(3)
C(51C)-C(52C)-C(71C)	122.5(3)	C(53C)-C(52C)-C(51C)	116.1(3)
C(53C)-C(52C)-C(71C)	121.4(3)	C(52C)-C(53C)-H(53C)	119.1
C(52C)-C(53C)-C(54C)	121.7(3)	C(54C)-C(53C)-H(53C)	119.1
C(53C)-C(54C)-C(55C)	120.3(3)	C(53C)-C(54C)-C(59C)	120.6(3)
C(55C)-C(54C)-C(59C)	119.1(3)	C(54C)-C(55C)-H(55C)	119.7

C(56C)-C(55C)-C(54C)	120.6(4)	C(56C)-C(55C)-H(55C)	119.7
C(55C)-C(56C)-H(56C)	120.2	C(55C)-C(56C)-C(57C)	119.5(3)
C(57C)-C(56C)-H(56C)	120.2	C(56C)-C(57C)-H(57C)	119.3
C(58C)-C(57C)-C(56C)	121.4(4)	C(58C)-C(57C)-H(57C)	119.3
C(57C)-C(58C)-H(58C)	119.6	C(57C)-C(58C)-C(59C)	120.9(4)
C(59C)-C(58C)-H(58C)	119.6	C(54C)-C(59C)-C(60C)	118.2(3)
C(58C)-C(59C)-C(54C)	118.4(3)	C(58C)-C(59C)-C(60C)	123.3(3)
C(51C)-C(60C)-C(59C)	117.8(3)	C(51C)-C(60C)-C(70C)	119.5(3)
C(59C)-C(60C)-C(70C)	122.8(3)	O(8C)-C(61C)-C(62C)	117.2(3)
C(70C)-C(61C)-O(8C)	118.8(3)	C(70C)-C(61C)-C(62C)	124.0(3)
C(61C)-C(62C)-C(79C)	123.0(3)	C(63C)-C(62C)-C(61C)	117.3(3)
C(63C)-C(62C)-C(79C)	119.6(3)	C(62C)-C(63C)-H(63C)	118.9
C(62C)-C(63C)-C(64C)	122.1(3)	C(64C)-C(63C)-H(63C)	118.9
C(63C)-C(64C)-C(65C)	121.2(3)	C(63C)-C(64C)-C(69C)	119.7(3)
C(65C)-C(64C)-C(69C)	119.1(3)	C(64C)-C(65C)-H(65C)	119.4
C(66C)-C(65C)-C(64C)	121.1(4)	C(66C)-C(65C)-H(65C)	119.4
C(65C)-C(66C)-H(66C)	120.2	C(65C)-C(66C)-C(67C)	119.6(4)
C(67C)-C(66C)-H(66C)	120.2	C(66C)-C(67C)-H(67C)	119.6
C(68C)-C(67C)-C(66C)	120.8(4)	C(68C)-C(67C)-H(67C)	119.6
C(67C)-C(68C)-H(68C)	119.6	C(67C)-C(68C)-C(69C)	120.8(4)
C(69C)-C(68C)-H(68C)	119.6	C(64C)-C(69C)-C(70C)	118.5(3)
C(68C)-C(69C)-C(64C)	118.5(3)	C(68C)-C(69C)-C(70C)	122.9(3)
C(61C)-C(70C)-C(60C)	121.5(3)	C(61C)-C(70C)-C(69C)	117.9(3)
C(69C)-C(70C)-C(60C)	120.5(3)	O(9C)-C(71C)-C(52C)	114.6(3)
C(72C)-C(71C)-O(9C)	111.0(3)	C(72C)-C(71C)-C(52C)	134.4(3)
C(71C)-C(72C)-H(72C)	126.4	C(71C)-C(72C)-C(73C)	107.2(3)
C(73C)-C(72C)-H(72C)	126.4	C(74C)-C(73C)-C(72C)	135.3(4)
C(78C)-C(73C)-C(72C)	105.6(3)	C(78C)-C(73C)-C(74C)	119.0(4)
C(73C)-C(74C)-H(74C)	121.3	C(75C)-C(74C)-C(73C)	117.4(4)
C(75C)-C(74C)-H(74C)	121.3	C(74C)-C(75C)-H(75C)	118.8
C(74C)-C(75C)-C(76C)	122.3(4)	C(76C)-C(75C)-H(75C)	118.8
C(75C)-C(76C)-H(76C)	119.4	C(75C)-C(76C)-C(77C)	121.3(4)
C(77C)-C(76C)-H(76C)	119.4	C(76C)-C(77C)-H(77C)	121.8
C(78C)-C(77C)-C(76C)	116.3(4)	C(78C)-C(77C)-H(77C)	121.8
O(9C)-C(78C)-C(73C)	110.5(3)	O(9C)-C(78C)-C(77C)	125.8(4)
C(77C)-C(78C)-C(73C)	123.7(4)	O(10C)-C(79C)-C(62C)	112.6(3)
C(80C)-C(79C)-O(10C)	110.6(3)	C(80C)-C(79C)-C(62C)	136.6(3)

C(79C)-C(80C)-H(80C)	126.7	C(79C)-C(80C)-C(81C)	106.7(4)
C(81C)-C(80C)-H(80C)	126.7	C(82C)-C(81C)-C(80C)	135.7(4)
C(86C)-C(81C)-C(80C)	105.7(3)	C(86C)-C(81C)-C(82C)	118.6(4)
C(81C)-C(82C)-H(82C)	121.2	C(83C)-C(82C)-C(81C)	117.7(4)
C(83C)-C(82C)-H(82C)	121.2	C(82C)-C(83C)-H(83C)	118.9
C(82C)-C(83C)-C(84C)	122.1(4)	C(84C)-C(83C)-H(83C)	118.9
C(83C)-C(84C)-H(84C)	119.3	C(85C)-C(84C)-C(83C)	121.4(4)
C(85C)-C(84C)-H(84C)	119.3	C(84C)-C(85C)-H(85C)	122.1
C(84C)-C(85C)-C(86C)	115.8(4)	C(86C)-C(85C)-H(85C)	122.1
O(10C)-C(86C)-C(81C)	111.0(3)	O(10C)-C(86C)-C(85C)	124.6(4)
C(81C)-C(86C)-C(85C)	124.4(4)	C(88C)-C(87C)-S(2C)	119.5(3)
C(92C)-C(87C)-S(2C)	122.8(3)	C(92C)-C(87C)-C(88C)	117.6(4)
F(6C)-C(88C)-C(87C)	120.5(4)	F(6C)-C(88C)-C(89C)	117.8(4)
C(89C)-C(88C)-C(87C)	121.6(4)	F(7C)-C(89C)-C(88C)	120.8(4)
F(7C)-C(89C)-C(90C)	119.9(4)	C(88C)-C(89C)-C(90C)	119.3(4)
F(8C)-C(90C)-C(89C)	119.4(4)	F(8C)-C(90C)-C(91C)	120.2(4)
C(91C)-C(90C)-C(89C)	120.4(4)	F(9C)-C(91C)-C(90C)	119.9(4)
F(9C)-C(91C)-C(92C)	120.0(4)	C(90C)-C(91C)-C(92C)	120.0(4)
F(10C)-C(92C)-C(87C)	122.6(4)	F(10C)-C(92C)-C(91C)	116.4(4)
C(87C)-C(92C)-C(91C)	121.0(4)	O(11A)-S(2A)-N(2A)	110.06(18)
O(11A)-S(2A)-C(87A)	104.34(19)	O(12A)-S(2A)-O(11A)	115.62(19)
O(12A)-S(2A)-N(2A)	112.85(19)	O(12A)-S(2A)-C(87A)	107.5(2)
N(2A)-S(2A)-C(87A)	105.59(19)	O(1A)-P(1A)-N(1A)	105.81(15)
O(2A)-P(1A)-O(1A)	105.15(13)	O(2A)-P(1A)-N(1A)	111.08(15)
N(3A)-P(1A)-O(1A)	114.22(15)	N(3A)-P(1A)-O(2A)	103.28(15)
N(3A)-P(1A)-N(1A)	116.77(17)	O(7A)-P(2A)-O(8A)	104.15(13)
O(7A)-P(2A)-N(2A)	108.83(16)	O(8A)-P(2A)-N(2A)	106.66(15)
N(3A)-P(2A)-O(7A)	106.13(15)	N(3A)-P(2A)-O(8A)	110.89(16)
N(3A)-P(2A)-N(2A)	119.19(17)	C(1A)-O(1A)-P(1A)	116.5(2)
C(11A)-O(2A)-P(1A)	122.0(2)	C(28A)-O(3A)-C(21A)	105.8(3)
C(36A)-O(4A)-C(29A)	105.8(3)	C(51A)-O(7A)-P(2A)	117.6(2)
C(61A)-O(8A)-P(2A)	115.3(2)	C(78A)-O(9A)-C(71A)	106.3(3)
C(79A)-O(10A)-C(86A)	106.3(4)	S(1A)-N(1A)-P(1A)	126.9(2)
S(2A)-N(2A)-P(2A)	126.7(2)	S(2A)-N(2A)-H(2A)	116.6
P(2A)-N(2A)-H(2A)	116.6	P(2A)-N(3A)-P(1A)	152.8(2)
O(1A)-C(1A)-C(2A)	117.2(3)	C(10A)-C(1A)-O(1A)	118.1(3)
C(10A)-C(1A)-C(2A)	124.7(3)	C(1A)-C(2A)-C(21A)	122.5(3)

C(3A)-C(2A)-C(1A)	116.7(3)	C(3A)-C(2A)-C(21A)	120.9(3)
C(2A)-C(3A)-H(3A)	119.1	C(2A)-C(3A)-C(4A)	121.7(3)
C(4A)-C(3A)-H(3A)	119.1	C(3A)-C(4A)-C(9A)	119.7(3)
C(5A)-C(4A)-C(3A)	120.9(3)	C(5A)-C(4A)-C(9A)	119.4(3)
C(4A)-C(5A)-H(5A)	119.7	C(6A)-C(5A)-C(4A)	120.6(4)
C(6A)-C(5A)-H(5A)	119.7	C(5A)-C(6A)-H(6A)	120
C(5A)-C(6A)-C(7A)	120.0(4)	C(7A)-C(6A)-H(6A)	120
C(6A)-C(7A)-H(7A)	119.3	C(8A)-C(7A)-C(6A)	121.4(4)
C(8A)-C(7A)-H(7A)	119.3	C(7A)-C(8A)-H(8A)	119.8
C(7A)-C(8A)-C(9A)	120.5(4)	C(9A)-C(8A)-H(8A)	119.8
C(4A)-C(9A)-C(10A)	118.9(3)	C(8A)-C(9A)-C(4A)	117.9(3)
C(8A)-C(9A)-C(10A)	123.1(3)	C(1A)-C(10A)-C(9A)	118.0(3)
C(1A)-C(10A)-C(20A)	119.5(3)	C(9A)-C(10A)-C(20A)	122.4(3)
O(2A)-C(11A)-C(12A)	117.1(3)	C(20A)-C(11A)-O(2A)	119.2(3)
C(20A)-C(11A)-C(12A)	123.7(3)	C(11A)-C(12A)-C(29A)	123.0(3)
C(13A)-C(12A)-C(11A)	117.3(3)	C(13A)-C(12A)-C(29A)	119.7(3)
C(12A)-C(13A)-H(13A)	119.1	C(12A)-C(13A)-C(14A)	121.7(3)
C(14A)-C(13A)-H(13A)	119.1	C(15A)-C(14A)-C(13A)	120.7(4)
C(15A)-C(14A)-C(19A)	119.5(4)	C(19A)-C(14A)-C(13A)	119.7(4)
C(14A)-C(15A)-H(15A)	119.6	C(16A)-C(15A)-C(14A)	120.8(4)
C(16A)-C(15A)-H(15A)	119.6	C(15A)-C(16A)-H(16A)	120
C(15A)-C(16A)-C(17A)	119.9(4)	C(17A)-C(16A)-H(16A)	120
C(16A)-C(17A)-H(17A)	119.7	C(18A)-C(17A)-C(16A)	120.6(4)
C(18A)-C(17A)-H(17A)	119.7	C(17A)-C(18A)-H(18A)	119.6
C(17A)-C(18A)-C(19A)	120.9(4)	C(19A)-C(18A)-H(18A)	119.6
C(14A)-C(19A)-C(20A)	118.8(3)	C(18A)-C(19A)-C(14A)	118.2(4)
C(18A)-C(19A)-C(20A)	122.9(3)	C(11A)-C(20A)-C(10A)	121.7(3)
C(11A)-C(20A)-C(19A)	118.2(3)	C(19A)-C(20A)-C(10A)	120.1(3)
O(3A)-C(21A)-C(2A)	114.9(3)	C(22A)-C(21A)-O(3A)	110.7(3)
C(22A)-C(21A)-C(2A)	134.4(3)	C(21A)-C(22A)-H(22A)	126.7
C(21A)-C(22A)-C(23A)	106.5(3)	C(23A)-C(22A)-H(22A)	126.7
C(24A)-C(23A)-C(22A)	134.6(4)	C(28A)-C(23A)-C(22A)	106.2(3)
C(28A)-C(23A)-C(24A)	119.2(4)	C(23A)-C(24A)-H(24A)	121.3
C(25A)-C(24A)-C(23A)	117.4(5)	C(25A)-C(24A)-H(24A)	121.3
C(24A)-C(25A)-H(25A)	119	C(26A)-C(25A)-C(24A)	121.9(4)
C(26A)-C(25A)-H(25A)	119	C(25A)-C(26A)-H(26A)	118.8
C(25A)-C(26A)-C(27A)	122.5(4)	C(27A)-C(26A)-H(26A)	118.8

C(26A)-C(27A)-H(27A)	122.6	C(26A)-C(27A)-C(28A)	114.7(4)
C(28A)-C(27A)-H(27A)	122.6	O(3A)-C(28A)-C(23A)	110.8(3)
O(3A)-C(28A)-C(27A)	124.9(4)	C(23A)-C(28A)-C(27A)	124.3(4)
O(4A)-C(29A)-C(12A)	112.8(3)	C(30A)-C(29A)-O(4A)	110.6(3)
C(30A)-C(29A)-C(12A)	136.6(4)	C(29A)-C(30A)-H(30A)	126.4
C(29A)-C(30A)-C(31A)	107.1(4)	C(31A)-C(30A)-H(30A)	126.4
C(32A)-C(31A)-C(30A)	135.7(5)	C(36A)-C(31A)-C(30A)	105.5(4)
C(36A)-C(31A)-C(32A)	118.8(4)	C(31A)-C(32A)-H(32A)	120.7
C(33A)-C(32A)-C(31A)	118.6(5)	C(33A)-C(32A)-H(32A)	120.7
C(32A)-C(33A)-H(33A)	119.4	C(32A)-C(33A)-C(34A)	121.2(5)
C(34A)-C(33A)-H(33A)	119.4	C(33A)-C(34A)-H(34A)	119.3
C(35A)-C(34A)-C(33A)	121.5(4)	C(35A)-C(34A)-H(34A)	119.3
C(34A)-C(35A)-H(35A)	122.1	C(34A)-C(35A)-C(36A)	115.9(5)
C(36A)-C(35A)-H(35A)	122.1	O(4A)-C(36A)-C(31A)	111.0(3)
O(4A)-C(36A)-C(35A)	125.0(4)	C(31A)-C(36A)-C(35A)	123.9(4)
C(38A)-C(37A)-S(1A)	123.4(3)	C(42A)-C(37A)-S(1A)	119.3(3)
C(42A)-C(37A)-C(38A)	117.3(4)	F(1A)-C(38A)-C(37A)	121.6(4)
F(1A)-C(38A)-C(39A)	117.0(4)	C(39A)-C(38A)-C(37A)	121.4(4)
F(2A)-C(39A)-C(38A)	120.8(4)	F(2A)-C(39A)-C(40A)	119.5(4)
C(40A)-C(39A)-C(38A)	119.7(4)	F(3A)-C(40A)-C(39A)	119.7(4)
F(3A)-C(40A)-C(41A)	120.1(4)	C(41A)-C(40A)-C(39A)	120.2(4)
F(4A)-C(41A)-C(40A)	120.4(4)	F(4A)-C(41A)-C(42A)	119.9(4)
C(40A)-C(41A)-C(42A)	119.7(4)	F(5A)-C(42A)-C(37A)	120.5(3)
F(5A)-C(42A)-C(41A)	117.7(4)	C(41A)-C(42A)-C(37A)	121.7(4)
O(7A)-C(51A)-C(52A)	117.4(3)	C(60A)-C(51A)-O(7A)	118.2(3)
C(60A)-C(51A)-C(52A)	124.3(3)	C(51A)-C(52A)-C(71A)	121.6(3)
C(53A)-C(52A)-C(51A)	116.7(3)	C(53A)-C(52A)-C(71A)	121.6(3)
C(52A)-C(53A)-H(53A)	119.1	C(52A)-C(53A)-C(54A)	121.8(4)
C(54A)-C(53A)-H(53A)	119.1	C(53A)-C(54A)-C(55A)	121.3(4)
C(53A)-C(54A)-C(59A)	120.3(3)	C(59A)-C(54A)-C(55A)	118.4(4)
C(54A)-C(55A)-H(55A)	119.6	C(56A)-C(55A)-C(54A)	120.8(4)
C(56A)-C(55A)-H(55A)	119.6	C(55A)-C(56A)-H(56A)	119.7
C(55A)-C(56A)-C(57A)	120.6(4)	C(57A)-C(56A)-H(56A)	119.7
C(56A)-C(57A)-H(57A)	119.6	C(58A)-C(57A)-C(56A)	120.9(4)
C(58A)-C(57A)-H(57A)	119.6	C(57A)-C(58A)-H(58A)	120.1
C(57A)-C(58A)-C(59A)	119.8(4)	C(59A)-C(58A)-H(58A)	120.1
C(54A)-C(59A)-C(60A)	118.6(3)	C(58A)-C(59A)-C(54A)	119.6(4)

C(58A)-C(59A)-C(60A)	121.8(3)	C(51A)-C(60A)-C(59A)	117.7(3)
C(51A)-C(60A)-C(70A)	119.6(3)	C(59A)-C(60A)-C(70A)	122.7(3)
O(8A)-C(61A)-C(62A)	118.7(3)	C(70A)-C(61A)-O(8A)	116.9(3)
C(70A)-C(61A)-C(62A)	124.3(3)	C(61A)-C(62A)-C(79A)	120.8(4)
C(63A)-C(62A)-C(61A)	117.1(3)	C(63A)-C(62A)-C(79A)	122.1(4)
C(62A)-C(63A)-H(63A)	118.9	C(62A)-C(63A)-C(64A)	122.2(4)
C(64A)-C(63A)-H(63A)	118.9	C(63A)-C(64A)-C(69A)	119.1(3)
C(65A)-C(64A)-C(63A)	120.7(4)	C(65A)-C(64A)-C(69A)	120.2(4)
C(64A)-C(65A)-H(65A)	119.9	C(66A)-C(65A)-C(64A)	120.2(4)
C(66A)-C(65A)-H(65A)	119.9	C(65A)-C(66A)-H(66A)	119.9
C(65A)-C(66A)-C(67A)	120.2(4)	C(67A)-C(66A)-H(66A)	119.9
C(66A)-C(67A)-H(67A)	119.2	C(68A)-C(67A)-C(66A)	121.6(4)
C(68A)-C(67A)-H(67A)	119.2	C(67A)-C(68A)-H(68A)	120
C(67A)-C(68A)-C(69A)	120.1(4)	C(69A)-C(68A)-H(68A)	120
C(64A)-C(69A)-C(68A)	117.7(3)	C(64A)-C(69A)-C(70A)	119.4(3)
C(70A)-C(69A)-C(68A)	122.9(4)	C(61A)-C(70A)-C(60A)	119.4(3)
C(61A)-C(70A)-C(69A)	117.9(3)	C(69A)-C(70A)-C(60A)	122.4(3)
O(9A)-C(71A)-C(52A)	114.6(3)	C(72A)-C(71A)-O(9A)	110.4(3)
C(72A)-C(71A)-C(52A)	134.9(3)	C(71A)-C(72A)-H(72A)	126.3
C(71A)-C(72A)-C(73A)	107.3(4)	C(73A)-C(72A)-H(72A)	126.3
C(74A)-C(73A)-C(72A)	134.7(4)	C(78A)-C(73A)-C(72A)	105.6(3)
C(78A)-C(73A)-C(74A)	119.6(4)	C(73A)-C(74A)-H(74A)	120.9
C(75A)-C(74A)-C(73A)	118.2(4)	C(75A)-C(74A)-H(74A)	120.9
C(74A)-C(75A)-H(75A)	119.7	C(74A)-C(75A)-C(76A)	120.6(4)
C(76A)-C(75A)-H(75A)	119.7	C(75A)-C(76A)-H(76A)	118.7
C(77A)-C(76A)-C(75A)	122.5(4)	C(77A)-C(76A)-H(76A)	118.7
C(76A)-C(77A)-H(77A)	122.3	C(78A)-C(77A)-C(76A)	115.5(4)
C(78A)-C(77A)-H(77A)	122.3	O(9A)-C(78A)-C(73A)	110.3(3)
C(77A)-C(78A)-O(9A)	126.2(4)	C(77A)-C(78A)-C(73A)	123.6(4)
O(9B)-C(78D)-C(77D)	132.3(4)	O(9B)-C(78D)-C(73D)	107.3(4)
C(77D)-C(78D)-C(73D)	120	C(78D)-C(77D)-H(77D)	120
C(78D)-C(77D)-C(76D)	120	C(76D)-C(77D)-H(77D)	120
C(77D)-C(76D)-H(76D)	120	C(75D)-C(76D)-C(77D)	120
C(75D)-C(76D)-H(76D)	120	C(76D)-C(75D)-H(75D)	120
C(76D)-C(75D)-C(74D)	120	C(74D)-C(75D)-H(75D)	120
C(75D)-C(74D)-H(74D)	120	C(75D)-C(74D)-C(73D)	120
C(73D)-C(74D)-H(74D)	120	C(78D)-C(73D)-C(72B)	106.2(4)

C(74D)-C(73D)-C(72B)	133.8(4)	C(74D)-C(73D)-C(78D)	120
O(10A)-C(79A)-C(62A)	119.6(4)	C(80A)-C(79A)-O(10A)	110.8(4)
C(80A)-C(79A)-C(62A)	129.4(4)	C(79A)-C(80A)-H(80A)	125.6
C(79A)-C(80A)-C(81A)	108.8(4)	C(81A)-C(80A)-H(80A)	125.6
C(82A)-C(81A)-C(80A)	133.7(5)	C(86A)-C(81A)-C(80A)	106.1(4)
C(86A)-C(81A)-C(82A)	120.1(4)	C(81A)-C(82A)-H(82A)	121.5
C(83A)-C(82A)-C(81A)	117.0(5)	C(83A)-C(82A)-H(82A)	121.5
C(82A)-C(83A)-H(83A)	118.7	C(82A)-C(83A)-C(84A)	122.6(5)
C(84A)-C(83A)-H(83A)	118.7	C(83A)-C(84A)-H(84A)	119.2
C(83A)-C(84A)-C(85A)	121.5(5)	C(85A)-C(84A)-H(84A)	119.2
C(84A)-C(85A)-H(85A)	121.8	C(86A)-C(85A)-C(84A)	116.3(5)
C(86A)-C(85A)-H(85A)	121.8	C(81A)-C(86A)-O(10A)	108.0(4)
C(81A)-C(86A)-C(85A)	122.4(5)	C(85A)-C(86A)-O(10A)	129.5(5)
C(88A)-C(87A)-S(2A)	119.6(4)	C(88A)-C(87A)-C(92A)	116.9(5)
C(92A)-C(87A)-S(2A)	123.4(4)	F(10A)-C(88A)-C(87A)	119.7(4)
F(10A)-C(88A)-C(89A)	118.3(5)	C(87A)-C(88A)-C(89A)	122.0(5)
F(9A)-C(89A)-C(88A)	120.0(6)	F(9A)-C(89A)-C(90A)	121.3(6)
C(90A)-C(89A)-C(88A)	118.6(6)	F(8A)-C(90A)-C(89A)	118.5(7)
F(8A)-C(90A)-C(91A)	121.0(6)	C(91A)-C(90A)-C(89A)	120.5(5)
F(7A)-C(91A)-C(90A)	119.0(6)	F(7A)-C(91A)-C(92A)	119.9(7)
C(92A)-C(91A)-C(90A)	121.0(6)	F(6A)-C(92A)-C(87A)	120.7(5)
F(6A)-C(92A)-C(91A)	118.4(6)	C(91A)-C(92A)-C(87A)	120.8(6)

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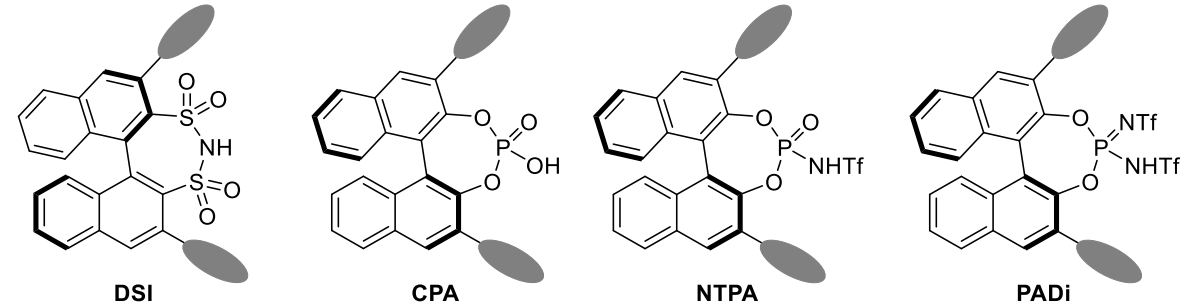
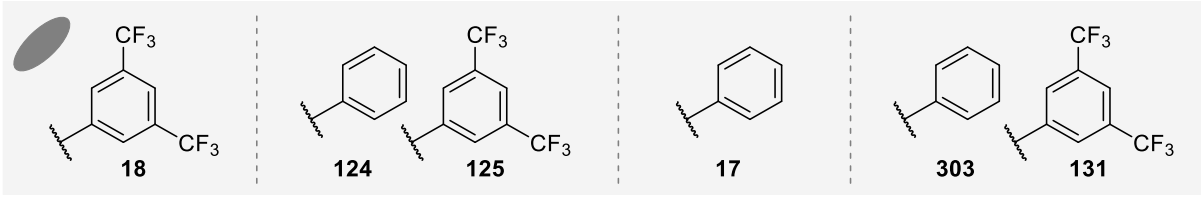
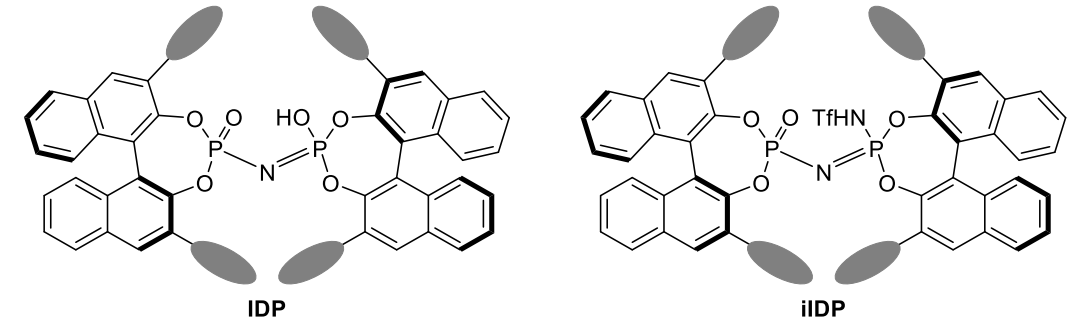
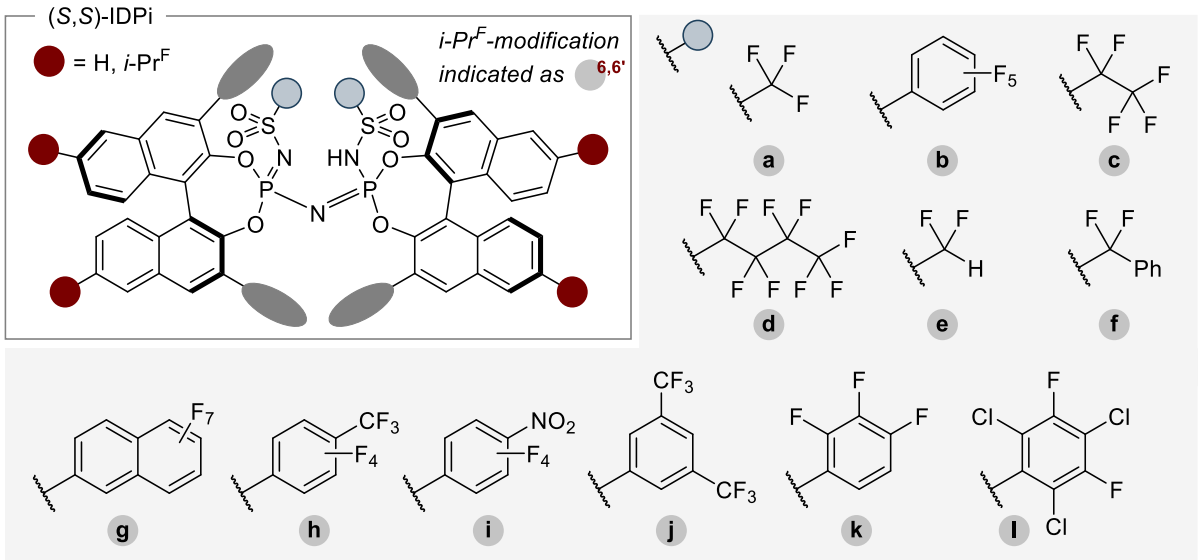
9. APPENDIX

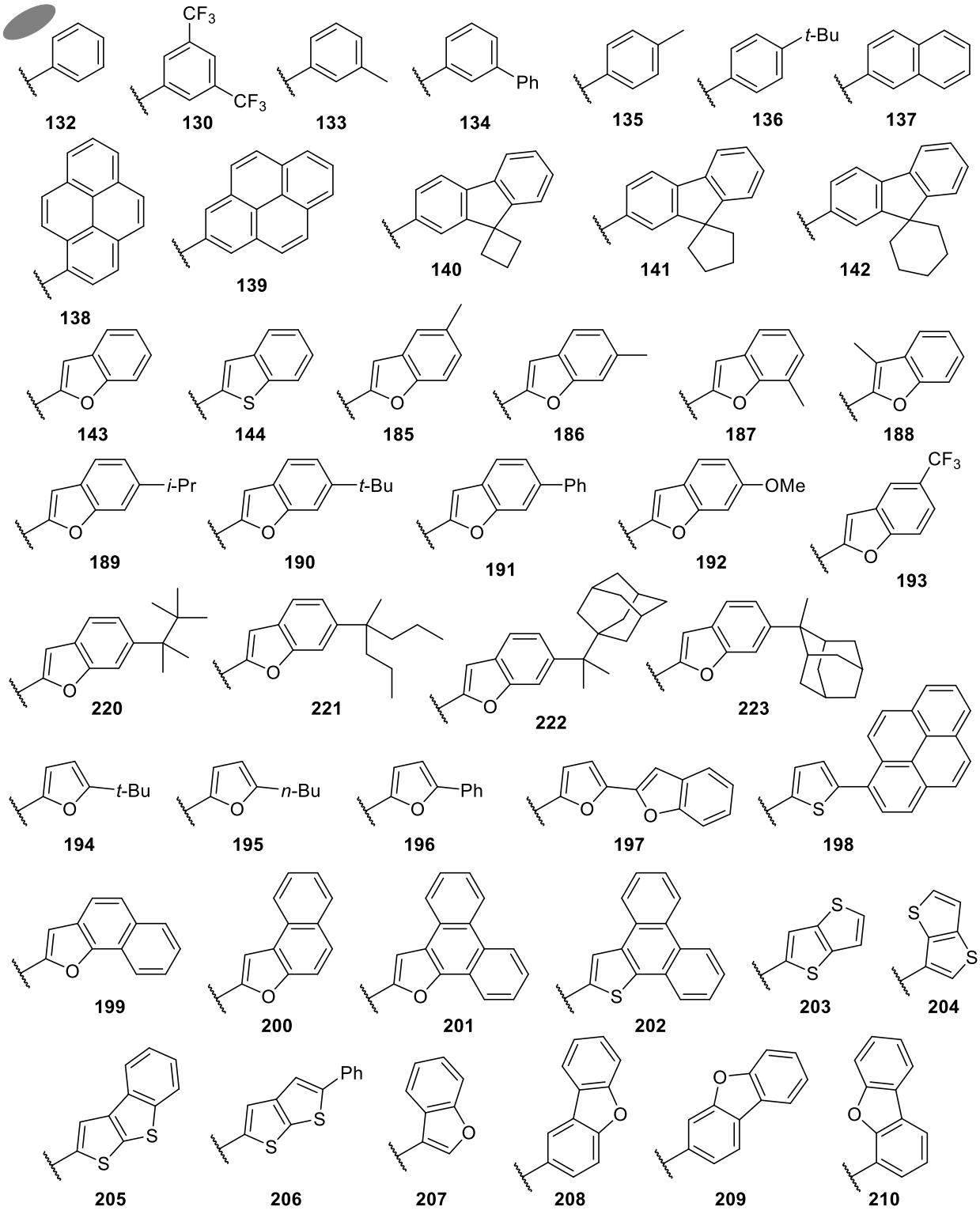
9.1. Reoccurring Catalyst Structures in this Thesis







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(Manuel J. Scharf)

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(1) “Catalytic Asymmetric Hydroalkoxylation of C–C Multiple Bonds“: J. L. Kennemur, R. Maji, M. J. Scharf, B. List, *Chem. Rev.* **2021**, *121*, 14649–14681.

(2) “A Catalytic Asymmetric Pictet–Spengler Platform as a Biomimetic Diversification Strategy toward Naturally Occurring Alkaloids”: M. J. Scharf, B. List, *J. Am. Chem. Soc.* **2022**, *144*, 15451–15456.

(3) “A leap forward in the quest for general catalysts“: M. J. Scharf, B. List, *Nature* **2022**, *610*, 632–633.