Asymmetric Organocatalysis with

_bis-_Silyl Ketene Acetals

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Francesca Mandrelli

aus Sansepolcro (Italien)

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Berichterstatter: Prof. Dr. Benjamin List
Prof. Dr. Hans-Günther Schmalz

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“Most people say that it is intellect which makes a great scientist. They are wrong: it is character”

Albert Einstein
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Abstract

Enantiomerically pure α-stereogenic carboxylic acids are encountered in a variety of natural products and pharmaceuticals and are useful substrates for various transformations. The direct synthesis of such motifs via catalytic asymmetric α-functionalization remains challenging in both metal- and organocatalysis. A general approach toward α-functionalization can be envisioned via formation of bis-silyl ketene acetal intermediates followed by functionalization with an electrophilic counterpart. This thesis focuses on the development of enantioselective transformations with bis-silyl ketene acetals, exploring the generality of this strategy within Brønsted and Lewis acid catalysis for a variety of enantioselective C–H and C–C bond forming reactions, using simple and unactivated substrates. This strategy was successfully applied to the deracemization of α-branched aryl carboxylic acids via catalytic asymmetric protonation of bis-silyl ketene acetals with water or methanol as a proton source, delivering valuable products with high enantiomeric purity and high yields, including non-steroidal anti-inflammatory arylpropionic acids, such as Ibuprofen. Furthermore, this strategy showed great potential under Lewis acidic conditions for a direct aminomethylation, allowing the first asymmetric organocatalytic synthesis of β2-amino acids from aliphatic and aromatic unactivated substrates, in very good enantioselectivities and excellent yields. This work opens the field of catalytic asymmetric transformations with bis-silyl ketene acetals for the direct access of enantioenriched α-branched carboxylic acids.
KURZZUSAMMENFASSUNG

List of Abbreviations

* designating chiral element
ACDC asymmetric counteranion-directed catalysis
Alk alkyl
Ar aryl
aq. aqueous
BINOL 1,1′-bi-2-naphthol
Boc tert-butyloxycarbonyl
cat. catalyst or catalytic
conv. conversion
DBU 1,8-diazabicyclo[5.4.0]undec-7-ene
DCE 1,2-dichloroethane
DCM dichloromethane
DMF dimethylformamide
DMSO dimethylsulfoxide
dr diastereomeric ratio
DSI disulfonimide
E electrophile
EDG electron donating group
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>er</td>
<td>enantiomeric ratio</td>
</tr>
<tr>
<td>equiv.</td>
<td>equivalents</td>
</tr>
<tr>
<td>et al.</td>
<td><em>et alii / et aliae</em> – and others</td>
</tr>
<tr>
<td>EWG</td>
<td>electron withdrawing group</td>
</tr>
<tr>
<td>Fmoc</td>
<td>fluorenylmethyloxycarbonyl</td>
</tr>
<tr>
<td>h</td>
<td>hours</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
</tr>
<tr>
<td>i</td>
<td>iso</td>
</tr>
<tr>
<td>IDP</td>
<td>imidodiphosphate</td>
</tr>
<tr>
<td>IDPi</td>
<td>imidodiphosphorimidate</td>
</tr>
<tr>
<td>iIDP</td>
<td>imino-imidodiphosphate</td>
</tr>
<tr>
<td>m</td>
<td>meta</td>
</tr>
<tr>
<td>M</td>
<td>molar</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry or molecular sieves</td>
</tr>
<tr>
<td>MTBE</td>
<td>methyl tert-butyl ether</td>
</tr>
<tr>
<td>MW</td>
<td>molecular weight</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance (spectroscopy)</td>
</tr>
<tr>
<td>Nu/NuH</td>
<td>nucleophile</td>
</tr>
<tr>
<td>o</td>
<td>ortho</td>
</tr>
<tr>
<td>P</td>
<td>product</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>$p$</td>
<td>para</td>
</tr>
<tr>
<td>quant.</td>
<td>quantitative</td>
</tr>
<tr>
<td>$rac$</td>
<td>racemic</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>SKA</td>
<td>silyl ketene acetal</td>
</tr>
<tr>
<td>$t$</td>
<td>tert, tertiary</td>
</tr>
<tr>
<td>T</td>
<td>temperature</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethylsulfonyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TRIP</td>
<td>3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl-hydrogen phosphate</td>
</tr>
<tr>
<td>TsOH</td>
<td>para-toluenesulfonic acid</td>
</tr>
</tbody>
</table>
Introduction
1 Introduction

1.1 Carboxylic Acids in Organic Synthesis

Carboxylic acids are ubiquitous structural motifs in biologically active compounds and are among the most common functionalities in organic chemistry.\[1\] For organic synthesis, carboxylic acids are convenient raw materials and intermediates, as they are commercially available in a wide structural variety, easy to store and to handle, and preparatively accessible by a variety of established routes.\[2\] The reactivity of the carboxylic group depends on its protonation state: (a) the protonated form as carboxonium ion, (b) neutral, in the acid form, (c) anionic, in the carboxylate form, and (d) di-anionic, in the form of the enediolate (Scheme 1.1). Addition of a nucleophile (NuH) at the partially positively charged carbon of the acid allows a variety of functional group modifications upon condensation, giving access to acyl chlorides, anhydrides, esters and amides (mode A). The same functional group modification can be envisioned via the initial formation of the carboxonium ion, followed by addition of a nucleophile, condensation and, ultimately, deprotonation to the corresponding acyl derivative. Carboxylates can be activated in a very similar way, however having a carboxylate–catalyst complex as the reactive intermediate. This can either still react as a carboxyl O-nucleophile, giving ester derivatives, or, on the other hand, it can undergo decarboxylation forming a highly nucleophilic organometallic intermediate; this latter reactive intermediate readily reacts with available electrophiles\[3\] or with radicals\[4\] (mode B). Lastly, the di-anionic form, accessed using an excess of a strong base, can react with a large variety of electrophiles, allowing the direct functionalization at the α-carbon (mode C).\[5\] Noteworthy, the α–functionalization erases the stereochemical information of the starting carboxylic acid; hence the stereogenic information of the obtained product depends only on the nucleophilic attack onto the electrophile.
Despite the importance and the versatility of carboxylic acids as synthetic intermediates, their application in catalytic transformations is rather limited. In recent years, progress in metal-catalysis has allowed the functionalization of unbiased and unprotected carboxylic acids.\(^3\) However, enantioselective transformations remain scarce and, more surprisingly, the direct and enantioselective α-functionalization is still elusive.

1.1.1 Asymmetric α-Functionalization of Carboxylic Acids

The most applied and reliable strategy to access α-functionalized carboxylic acids consists of multi-step procedures, taking advantage of chiral auxiliaries (Scheme 1.2). In such a sequence, the acid is first derivatized with an enantiopure auxiliary (step 1), followed by the desired, strong base-mediated functionalization in a diastereoselective fashion (step 2), and finally deprotected to furnish the desired enantioenriched product (step 3).\(^6\) The auxiliary can be recovered; however, this requires an additional purification step.
Scheme 1.2 Multi-step asymmetric α-functionalization using a chiral auxiliary.

A possible direct α-functionalization, in an ideal case, would require a catalyst which is able to deprotonate the carboxylic acid twice, at the OH group and at its α-position, to afford the bis–enolate. Simultaneously, the catalyst would provide a chiral environment to control the enantioselectivity of the nucleophilic attack onto a given electrophile (Scheme 1.3). Such a transformation has not been reported so far, however a patent exists claiming the benzylolation of glycine using (R)-2-amino-2'-hydroxy-1,1'-binaphthyl (NOBIN) as the catalyst.\[7\]

Scheme 1.3 Direct asymmetric α-functionalization with a chiral catalyst.

In pioneering studies by Shioiri\[8\] and Koga,\[9\] and more recently further developed by Zakarian,\[10\] the authors described an alternative solution to this challenge by using stoichiometric C₂–symmetric diamine reagents as chiral ligands (Scheme 1.4). This strategy is based on the in situ coordination of the bis-lithium enolate to the chiral amine; this complex directly enables the enantioselective functionalization, furnishing the targeted free carboxylic acid upon acidic workup. Moreover, the
stoichiometric chiral amine as the non-covalent auxiliary can be quantitatively recovered upon extraction. Furthermore, the whole sequence does not require the isolation of covalently bonded chiral intermediates or subsequent deprotection steps.

![Scheme 1.4 α-Functionalization with a traceless stoichiometric auxiliary.](image)

The *in situ* formation of the bis-lithium enolate from the carboxylic acid requires at least two equivalents of a strong base (pK$_a$ > 30) (Note: pK$_a$ values of bases refer to the corresponding conjugate acid). Therefore, lithium diisopropylamide (pK$_a$ ≃ 35) or n-butyl lithium (pK$_a$ ≃ 50) are the most commonly used reagents. The highly reactive bis-lithium enolates have several disadvantages as they can undergo decomposition and cannot be isolated as stable intermediates. Furthermore, these harsh conditions are incompatible with a large variety of functional groups. Therefore, in order to develop a general asymmetric and catalytic strategy, a less reactive and more stable enediolate equivalent is required.

### 1.2 Bis-Silyl Ketene Acetals as Carboxylic Acid Equivalents

Silicon-based protecting groups are among the most frequently employed of all protecting groups.[11] Furthermore, silyl enol ethers, silyl ketene acetals (SKAs), and *bis*-silyl ketene acetals (*bis*-SKAs) are the protagonists in a large variety of transformations since they represent stable and accessible enol and enolate equivalents of ketones, esters and carboxylic acids respectively (Figure 1.1). While a wide selection of catalytic asymmetric transformations has been developed using silyl enol ethers and SKAs,[12] enantioselective transformations using *bis*-SKAs are
Introduction

rare.\textsuperscript{[13]} The main advantage of bis-SKAs is that they allow direct access to carboxylic acids upon simple hydrolysis and, due to the absence of E/Z-diastereomers, their synthesis and purification is more facile compared to SKAs. However, bis-SKAs are challenging substrates as they are highly prone to hydrolysis and, in order to achieve high enantioselectivities, a chiral catalyst would have to differentiate the two relatively similar enantiotopic faces (Figure 1.1). Despite their challenges, bis-SKAs would be ideal substrates for accessing functionalized \(\alpha\)-branched carboxylic acids.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Stereochemical considerations of enolate equivalents and selected examples of silicon-based protecting groups.}
\end{figure}

In the following chapters, an overview of asymmetric catalytic reactions is presented, with particular focus on organocatalytic transformations under Brønsted and Lewis acidic conditions, followed by the discussion of the investigation conducted during these doctoral studies on the asymmetric transformations toward \(\alpha\)-branched carboxylic acids.
Background
2 Background

2.1 Asymmetric Catalysis

A catalyst is a component of the reaction mixture which is not consumed during the reaction and is able to increase the reaction rate by lowering the activation energy of a chemical transformation. It does not modify the energy of the reagents or products, but interacts with reagents and reaction intermediates, allowing the same reaction to occur via a different and less energetic pathway (Figure 2.1). In the case of enantioselective transformations, stereogenic elements may assemble in a selective fashion through the action of a chiral catalyst and the two enantiomers are obtained through energetically non-equivalent diastereomeric reaction pathways.

![General energy diagram of non–catalyzed and catalyzed reactions.](image)

**Figure 2.1** General energy diagram of non–catalyzed and catalyzed reactions.

The field of asymmetric transition metal catalysis was opened with the independent work of Horner,[14] Knowles,[15] Kagan,[16] Noyori[17] and Sharpless,[18] in which the authors disclosed (transition) metal–catalyzed transformations in the presence of chiral ligands (Scheme 2.1). Despite the poor enantioselectivities achieved, these seminal discoveries were recognized by the scientific community as milestones for catalytic enantioselective synthesis and thus were awarded with the Nobel Prize in Chemistry in 2001. Soon after these first reports, chemical industries
implemented the use of enantiopure ligands in catalytic processes underlining their importance.\cite{19}

**Scheme 2.1** Knowles and Noyori´s pioneering achievements in asymmetric catalysis.

In the 1960s, bioengineering emerged as a parallel approach to overcome the challenge of controlling chemo- and enantioselectivity in chemical transformations.\cite{20} Today, the use of enzymes or even whole cells finds wide application across the chemical industries.\cite{21} Hence, by the beginning of the 21st century, the field of catalytic transformations was dominated by two independent approaches: metal- and biocatalysis.

However, few isolated examples were not fitting in either one of the two categories and have been considered for a long time as mere curiosities. Those examples had a small organic chiral molecule acting as the catalyst, inducing low\cite{22} to moderate enantioselectivities.\cite{23} For example, in 1960 Pracejus showed that O–acetylquinine 1 catalyzed the addition of methanol to ketenes and enabled chirality transfer in the protonation step, giving the targeted esters in moderate enantioselectivities (Scheme 2.2).\cite{23}
Background

Scheme 2.2 Pracejus’ pioneering achievement in asymmetric organocatalysis.

Another remarkable example was reported by Hajos and Parrish\textsuperscript{[24]} at Hoffmann-La Roche and Eder, Sauer, and Wiechert\textsuperscript{[25]} at Schering. In this case, using (S)-proline (2) as catalyst, the reported intramolecular aldol reaction afforded the cyclization products in good to excellent yields with moderate to very high enantioselectivities (Scheme 2.3).

Scheme 2.3 The Hajos–Parrish–Eder–Sauer–Wiechert reaction.

Only in the early 2000s, the rationalization of the basic concepts of organocatalysis allowed the establishment of this new research field (Figure 2.2). Nowadays, organocatalysis is widely accepted as the third pillar of catalysis, complementing metal- and biocatalysis.\textsuperscript{[26]} In fact, in terms of numbers of papers, organocatalysis is number one in asymmetric synthesis.
2.2 Asymmetric Organocatalysis

2.2.1 Introduction

The groundbreaking simultaneous reports of List \cite{27} and MacMillan \cite{28} opened the field of organocatalysis. They independently showed that small organic molecules without any metal in their active site are potent and general catalysts for asymmetric transformations. In particular, the former described the proline-catalyzed aldol reaction of acetone with different aldehydes via enamine catalysis (remarkably, elimination to the corresponding enone did not take place under these reaction conditions), \cite{29} while the latter reported an asymmetric Diels–Alder reaction of cyclopentadiene and unsaturated aldehydes via iminium ion catalysis (Scheme 2.4).
Background

Scheme 2.4 Pioneering reports on secondary amine-catalyzed enantioselective reactions.

In the following years, the field was rationalized by well-defined interactions (covalent or non-covalent) and specific modes of action,[30] thus allowing rational reaction design. A comprehensive classification was reported by Seayad and List,[31] organizing the field based on the role of the catalyst and its mode of action: Brønsted acid, Brønsted base, Lewis acid and Lewis base (Figure 2.3).

Figure 2.3 Classification of organocatalytic transformations based on the role of the catalyst.

Lewis base catalysis covers the majority of the reported transformations. Here, the catalyst promotes the reaction by donating one (or more) electrons to a substrate. Indeed, enamine[32] and iminium ion catalysis,[33] SOMO[34] and carbene catalysis[35] operate through this type of mechanism.
This classification should be considered flexible, as many of the reported catalysts exploit multiple activation modes. Those catalysts are defined as “bifunctional”, as their activation modes depend on different functionalities. For example, the above-mentioned proline-catalyzed aldol reaction is promoted both by a Lewis base (secondary amine) for the enamine formation and simultaneously by a Brønsted acid (carboxylic acid) for the activation of the aldehyde.

2.2.2 Chiral Acids for Asymmetric Synthesis

In 1923 Brønsted\textsuperscript{[36]} and Lowry\textsuperscript{[37]} independently published a theory in which bases are defined as proton acceptors and acids as proton donors. Accordingly, a Brønsted acid (HA) reacts by releasing a proton (H\(^+\)), thereby generating the corresponding anion, defined as the conjugated base (A\(^-\)). In the same year, Lewis gave a broader definition:

“It seems to me that with complete generality we may say that a basic substance is one which has a lone pair of electrons which may be used to complete the stable group of another atom, and that an acid substance is one which can employ a lone pair from another molecule in completing the stable group of one of its own atoms. In other words, the basic substance furnishes a pair of electrons for a chemical bond, the acid substance accepts such a pair.”\textsuperscript{[38]}

In contrast to the Brønsted–Lowry definition, the Lewis definition covers acid-base reactions in which no proton transfer is involved, and it concludes that a proton is the smallest possible Lewis acid.

In the context of asymmetric transformations, a close similarity can be envisioned between enantioselective Lewis- and Brønsted-acid activation. On one hand, Lewis acidic metals or metalloid centered atoms (M) are coordinated to enantiopure ligands (L\(^*\)) guiding asymmetric transformations; on the other hand, in the Brønsted acid activation, the proton can be envisioned as the smallest centered element and the backbone of an organic catalyst (X\(^*\)) may be the effective source of stereoselectivity (Scheme 2.5).
**Background**

**Scheme 2.5** Lewis acid and Brønsted acid electrophile activation.

Depending on the acidity of the Brønsted acid, a more specific differentiation can be made: general and specific catalysis. In the first case, the neutral or weakly acidic functionality activates the substrate by weak interactions. This category includes (thio)ureas, alcohols and phenols, and those functionalities are also referred to as hydrogen-bond donors. In the second case, the stronger acidic functionalities activate the substrate by direct protonation of the substrate. This class includes phosphoric acids and derivatives, carboxylic acids, sulfonamides, sulfonic acids, C–H acids, and phosphorimidate derivatives, which are generally referred to as Brønsted acid catalysts (Figure 2.4).

**Figure 2.4** General and specific Brønsted acid catalysts.

The first application of chiral hydrogen bond donors as catalysts in an enantioselective transformation was serendipitously discovered by Sigman and Jacobsen while investigating a combinatorial approach to an enantioselective Strecker reaction.\(^{[39]}\) Surprisingly, among the many ligand-metal combinations tested, the control experiments using “ligand” 4 in absence of a transition-metal gave the highest enantioselectivity. Key interactions were identified in the hydrogen bonding...
ability of the thiourea moiety. A few years later, Rawal and co-workers identified chiral TADDOL-derived diols 5 as effective catalysts for an asymmetric hetero-Diels–Alder reaction\cite{40}, proving that small molecules can control enantioselectivity solely by having hydrogen bond interactions with the corresponding substrate (Scheme 2.6).

Scheme 2.6 Strecker reaction catalyzed by chiral thiourea\cite{39} and hetero–Diels–Alder reaction catalyzed by chiral TADDOL\cite{40}.

Following these seminal works, the incorporation of various acidic functionalities (Figure 2.4) within different chiral scaffolds allowed the rapid development of enantioselective organocatalytic transformations.

Among the many possible sources of chirality, axially chiral molecules, for instance the binaphthyl structure b1, appear to be a privileged scaffold for organocatalysts. Many modifications have been explored on the naphthyl moiety, such as (a) modification of the 6,6'-position\cite{41} (b) partial saturation of the backbone (b2)\cite{42} (c) addition and/or removal of benzene rings in either direction (b3 and b4)\cite{43} or (d) formation of analogs such as 1,1'-spirobiindane (b5)\cite{44}. The most recent development in this field includes the linkage of two binaphthyl units\cite{45} in particular using highly acidic “linkers” (Figure 2.5)\cite{12a,46}. 

\_Background\_
Figure 2.5 Examples of modifications of the chiral binaphthyl backbone.

An overview of the development of chiral Brønsted- and Lewis-acids for organocatalytic transformations is presented in the following sections, alongside with the discovery and the application of the concept of “asymmetric counteranion-directed catalysis” (ACDC).
2.2.3 Asymmetric Counteranion-Directed Catalysis (ACDC)

In general, the majority of asymmetric reactions proceed through partially charged or completely ionic intermediates. This feature is exploited and widely applied in the field of phase transfer catalysis (PTC), in which a negatively charged intermediate undertakes coulombic interaction with an enantiopure cationic catalyst.\textsuperscript{[47]} These ionic interactions are sufficient to create a chiral environment for the desired transformation. Asymmetric induction upon ion-pair formation may also proceed with a corresponding chiral anionic partner. In the concept of asymmetric counteranion-directed catalysis (ACDC), a cationic species, including but not being limited to a protonated intermediate from Brønsted acid activation, forms an ion pair with a chiral anion, determining the enantiodifferentiation of the desired transformation (Figure 2.6).\textsuperscript{[48]}

![Figure 2.6](image_url)

**Figure 2.6** Schematic representation of PTC and ACDC. (\(S = \text{substrate; } X^- = \text{anion; } X^{*+} = \text{chiral anion; } NR_4^* = \text{chiral ammonium ion; } R = \text{reactant; } P^* = \text{chiral product; } E^+ = \text{achiral cation} \))

The term itself was introduced by Mayer and List, giving the proof of concept by developing the enantioselective amino-catalyzed transfer-hydrogenation of enals, using a Hantzsch ester as the reductant (Scheme 2.7).\textsuperscript{[49]} A general definition was given as:

“\textit{Asymmetric counteranion-directed catalysis refers to the induction of enantioselectivity in a reaction proceeding through a cationic intermediate by means of ion pairing with a chiral, enantiomerically pure anion provided by the catalyst.}”\textsuperscript{[48]}
The authors showed the generality of this concept by employing the morpholinium salt of tri-isopropylphenyl phosphoric acid (TRIP) 6. The BINOL-based phosphate anion was the only given source of chirality and, upon proposed coulombic interactions with the cationic iminium ion intermediate 8, it directed the approach of the hydride source 7 with excellent stereoinduction. The absence of additional “coordination” sites besides coulombic interactions, or assisting obvious hydrogen-bonding in the substrate, renders this example as a clear showcase of ACDC (Scheme 2.8).

Scheme 2.7 Proof of concept of asymmetric counteranion-directed catalysis.\[49\]

Since this groundbreaking publication, this concept has been extensively explored in context of chiral Lewis- and Brønsted-acid organocatalysis, as well as in metal-catalyzed transformations.\[50\]

### 2.2.4 Chiral Brønsted Acids

In 2004, two groups independently reported the synthesis and application of axially chiral phosphoric acids derived from enantiopure 1,1ʹ-bi-2-naphthol (BINOL) as chiral Brønsted acid catalysts. Akiyama and co-workers developed an enantioselective Mannich-type reaction of SKAs with imines,\[51\] while Terada and co-workers reported an enantioselective addition of acetylacetone to imines\[52\] (Scheme 2.8). However, Ishihara group later showed that the catalytic species in Terada’s report was not the free acid, but the corresponding calcium salt formed during purification.\[53\]
Scheme 2.8 Initial reports using BINOL-based Brønsted acid catalysts.\cite{51-52}

In the following years, several research groups focused their endeavors on the development of chiral phosphoric acid catalysts.\cite{54} The most prominent approach is the variation of the substituents at the 3,3\textsuperscript{\textquoteleft}'-positions of the binaphthyl backbone. These substituents create steric bulk around the active site and additionally, depending on their electron-donating or -withdrawing behavior, influence the electron density of the entire catalyst. The choice of the substituent has to be optimized for each individual enantioselective transformation. To date, the most successfully applied catalyst is the 2,4,6-trisopropylphenyl substituted phosphoric acid (TRIP) initially developed by List and co-workers.\cite{55}

Despite the success and generality of BINOL-derived phosphoric acids, two major challenges have to be considered: (a) the requirement for relatively (Lewis-)basic substrates to provide sufficient activation, and (b) the low stereoinduction with small, unbiased substrates. In order to tackle these challenges, efforts within the scientific community have been devoted to develop (a) more acidic catalysts, able to protonate less reactive substrates and (b) catalysts able to provide a more confined chiral environment around the active site.
2.2.4.1 Toward More Acidic Catalysts

The acidity of BINOL-derived acids can be tuned by three individual approaches: (a) changing the electronics of the 3,3’-substituents, (b) introducing electron-withdrawing groups (EWGs) in the BINOL-backbone and (c), the most effective, changing the acidic functionality in the active site.\[56\] Considering that high acidity implies particularly mild conjugated bases, improved charge delocalization in the conjugate base is expected to have the largest impact on acidity. Yagupolskii et al. showed that the substitution of oxygen atoms with N(H)Tf (trifluoromethylsulfonyl) in benzoic acid increases the acidity by several orders of magnitude (Figure 2.7).\[57\]

![Figure 2.7 Yagupolskii’s principle to increase acidity by substituting O with N(H)Tf.](image)

Yamamoto and co-workers reported the expansion of this concept to BINOL-derived phosphates, introducing phosphoramidate 11. The increased acidity allowed the development of a catalytic enantioselective Diels–Alder reaction of α,β-unsaturated ketones with silyloxydienes (Scheme 2.9, Eq. a).\[56c\] The same authors could further increase the acidity by introduction of a sulfur atom, resulting in thiophosphoramidate catalyst 12. This catalyst enabled the first organocatalytic enantioselective protonation of silyl enol ethers (Scheme 2.9, Eq. b). At the same time, List and co-workers reported several examples with BINOL-based thiophosphoramide-derivatives.\[58\] Almost a decade later, Kaib and List further expanded the application of Yagupolskii’s principle to chiral phosphates, reporting the synthesis and synthetic application of highly acidic phosphoramidimidate 13. The
superior acidity enables more challenging reactions, such as the Friedel-Crafts alkylation of isophytol 15 and hydroquinone 14, giving α-tocopherol (16).\textsuperscript{[59]} The outstanding acidity was not complemented by sufficient diastereodifferentiation, achieving only moderate diasteromeric ratios (Scheme 2.9, Eq. c).

**Scheme 2.9** Synthetic application of BINOL-phosphoric acid derivatives with increased acidity achieved by applying Yagupolskii’s principle.

An alternative approach to increase the acidity by changing the active site of the catalysts was reported by List.\textsuperscript{[60]} In these reports, a strong increase of acidity was achieved by substituting the phosphate moiety to the significantly more acidic disulfonimide (DSI). The main field of application of these structures is as highly potent precatalysts for silicon Lewis acid catalysis (vide infra). However, some reports exploiting their application as strong Brønsted acids also exist. In particular, Lee and co-workers applied DSI 17a to the aminoalkylation of indoles.\textsuperscript{[61]} More recently, List and co-workers reported an asymmetric Torgov cyclization and applied
the method to the so far shortest reported total synthesis of (+)-estrone.\textsuperscript{[62]} In this case, an additional increase in acidity was achieved by introduction of strong EWGs on the 3,3’-substituents (SF\textsubscript{5} groups) and on the 5,5’-positions of the binaphthyl scaffold (NO\textsubscript{2} groups) (18) (Scheme 2.10).

**Scheme 2.10** Application of chiral DSI as Brønsted acid catalysts.

Even higher acidities have been achieved when the disulfonimide unit was substituted with bis(sulfonyl)imides (JINGLE), introduced by Berkessel et al.,\textsuperscript{[63]} or with disulfonic acid (BINSAs), introduced by List et al.\textsuperscript{[64]} BINSAs could only be successfully applied in asymmetric transformations as either the pyridinium salt as reported by Ishihara et al.\textsuperscript{[65]} or as ligands in the presence of Lewis acidic metals.\textsuperscript{[66]} However, the most acidic catalysts in this series have not found application in highly enantioselective catalysis,\textsuperscript{[12b]} as presumably the space around the active site is not confined enough to allow efficient enantiodifferentiation.
2.2.4.2 Toward More Confined Catalysts

In 2012, Čorić and List reported an innovative solution to increase the confinement around the catalytically active site.\cite{46a} The catalyst design included the expansion of the anion delocalization, by introducing the imidodiphosphate anion, and the restriction of the rotational freedom around the P–N bond, by introducing an additional BINOL unit. The combination of two identical BINOLs bearing 3,3'-substituents, which are large enough to block the rotation of the imidodiphosphate unit, maintains the C$_2$-symmetry. This leads to a reduced amount of catalytically active conformations, which can stabilize only few and selected transition states, therefore resulting in higher selectivity (Figure 2.8).

![Design of conformationally locked imidodiphosphates with C$_2$-symmetry.](image)

These newly designed confined imidodiphosphates (IDPs) allowed the spiroacetalization of electronically and sterically unbiased substrates, in high yields and very high enantioselectivities.\cite{46a} The power of the IDP scaffold can be highlighted by a direct comparison with the subsequently reported example of enantioselective spiroacetalization by Nagorny et al.\cite{67} In this case, specific modifications had to be added to the substrate in order to apply (S)-TRIP (20) as the chiral catalyst. In particular, the addition of two germinal phenyl groups (highlighted in red) were required in order to achieve good reactivity (Thorpe–Ingold effect) and high enantioselectivity (Scheme 2.11).
Scheme 2.11 Comparison of IDP 19a and TRIP (20) as chiral catalysts for the enantioselective spiroacetalization.

Furthermore, IDPs proved to be very efficient catalysts for a large selection of reactions (Scheme 2.12) and showed outstanding results also for unbiased, namely aliphatic, substrates. The main limitation of IDPs is their acidity (pKₐ ≈ 11), which is far lower than the phosphoramidates and dwells between phosphoric acids and DSIs.

Scheme 2.12 Initial reports using chiral IDPs as catalysts.
2.2.4.3 Toward More Acidic and Confined Catalysts

A higher acidity in the confined pocket of the IDPs was needed to activate and functionalize less reactive substrates. Increased reactivity was initially achieved by the incorporation of EWGs in the BINOL backbone,[69] however the key to success was again the application of Yagupolskii’s principle (Figure 2.7): the substitution of the P=O unit with P=NTf (iIDP and IDPI).[12a] These new classes of catalysts have complementary activation modes; iIDPs have moderate acidities (pK_a in CH_3CN ≈ 7–9) and maintain a bifunctional character (whereas P=O is the basic site, and P=NTf is the acidic site), while IDPIs are exclusively strongly acidic (pK_a in CH_3CN ≈ 2–5) (Figure 2.9).

![Figure 2.9](image)

**Figure 2.9** Evolution of the active site of the IDP, iIDP and IDPI reported by List et al.

The significantly increased acidities attained with the IDPIs allowed the activation of unbiased and highly unreactive functionalities. Excellent enantioselectivities have been already shown in the hetero-Diels–Alder reactions,[70] vinylogous Prins cyclizations[71] and Nazarov cyclizations.[72] Furthermore, the frontiers of asymmetric Brønsted acid catalysis have been expanded to the activation of simple and unbiased olefins[73] (Scheme 2.13).
Scheme 2.13 Transformations with IDPis as Brønsted acids.

Figure 2.10 gives a general overview of the historic development of the BINOL-based Brønsted-acid organocatalysts alongside with the experimental pKa values (TTP = 1,1,3,3-Tetratriflylpropene).

Figure 2.10 Development of BINOL-based Brønsted-acid organocatalysts and corresponding pKa values (TTP = 1,1,3,3-Tetratriflylpropene).
2.2.5 Chiral Lewis Acids

Strong Brønsted acids can be converted into potent organic silylium Lewis acids\cite{74} upon treatment with a suitable silylating agent.\cite{75} The silylated forms of triflic acid (trimethylsilyl triflate, TMSOTf)\cite{76} and triflimide (trimethylsilyl bis-triflimide, TMSNTf$_2$)\cite{77}, for instance, are well established highly reactive Lewis acid catalysts.\cite{78} Regarding asymmetric transformations involving silicon-protected enol equivalents, (transition-)metal-derived Lewis acid catalysts strongly suffer from the competition between the anticipated chiral Lewis acid itself and “silylium” background catalysis, a non-enantioselective off-cycle pathway.\cite{79}

2.2.5.1 Disulfonimides as Lewis Acid Catalysts

The silylation of a suitable enantiopure strong organic Brønsted acid allows an asymmetric transformation through ACDC. Taking advantage of the silylium background catalysis, List and coworkers reported the first example of a catalytic enantioselective transformation exploiting “silylium” ions as potent Lewis acids in 2009. DSI 17 served as the precatalyst and, upon silylation, acted as the Lewis acid catalyst in the Mukaiyama–aldol reaction of aromatic aldehydes and SKAs (Scheme 2.14).\cite{60a}

\[
\begin{align*}
\text{List 2009} & \\
\text{Ar}^+\text{H} + \text{R}_1^1\text{OR}_1^2\text{OR}_1^3 & \xrightarrow{(S)\text{-17a (0.01–5 mol%)}} \text{Ar}^+\text{R}_1^1\text{CO}_{\text{OR}_3}^3 \\
\text{Et}_2\text{O}, –78 °C & \text{up to 93% yield} \\
& \text{up to 97:3 er}
\end{align*}
\]

**Scheme 2.14** Chiral DSI-catalyzed Mukaiyama–aldol reaction.
**Background**

A generalized mechanism for disulfonimide-catalyzed reactions is depicted in Scheme 2.15. Initially, a Brønsted acid catalyst (pKₐ usually < 11) is activated by a silylating agent to give the active Lewis acid catalyst. In case of residual water in the reaction mixture, the active catalyst is hydrolyzed and re-silylated until all the water is converted into the corresponding silyl ether (or hexamethyldisiloxane); even R₃SiOH substrates would still desilylate the catalyst, so that ultimately only (R₃Si)₂O is formed. The ability of the catalyst to regenerate is referred to as self-healing. As no catalytic activity can be observed until the reaction solution is anhydrous, this period is referred to as the dormant period. The first step of the catalytic cycle consists of silylation of the electrophilic substrate (E), presumably forming a tight ion pair between the enantiopure anion (catalyst) and the cationic electrophile. In this induced asymmetric environment, the nucleophile (Nu) attacks onto the electrophile giving the silylated product. Finally, the lower affinity of the product (P) for the catalyst leads to silicon transfer back onto the catalyst releasing the desired product and completing the catalytic cycle (Scheme 2.15).

![Scheme 2.15 General catalytic cycle for disulfonimide ACDC in silylium Lewis acid catalysis using SKAs.](image)

Exploring the concept of ACDC, chiral DSIs were successfully applied as catalysts in numerous enantioselective transformations. Aromatic aldehydes and imines were preferred substrates reacting with a variety of silylated nucleophiles. In
analogy to the Mukaiyama–aldol reaction (Scheme 2.14), the vinylogous,[80] bis-
vinylogous[80] and alkyynylogous[81] variants were reported. Other examples include:
the hetero-Diels–Alder reaction using Danishefsky-type dienes and their
alkynylogous analogs,[82] the Mukaiyama–Mannich reaction with SKA[83] and its
vinylogous variant to access α-amino-β-ketoesters in the presence of
silyloxydienes,[84] the cyanosilylation with TMSCN in the presence of 0.005 mol% (50
ppm) of catalyst,[85] and the Abramov reaction with silylated phosphites to access α-
hydroxy phosphonates.[86] The asymmetric Hosomi–Sakurai allylation was
achieved[87] with highly nucleophilic (2-methylallyl)trimethylsilanes (N = 4.41),[88]
however, the use of allyltrimethylsilane (N = 1.68)[89] proved to be challenging. This
limitation was overcome using the in situ generated N-fluorenlymethoxycarbonyl
(Fmoc) imines as electrophiles (Scheme 2.16).[90]

Scheme 2.16 Overview of DSI-catalyzed asymmetric transformations using aromatic
aldehydes and imines reported so far.
In summary, the high acidity of the DSI motif enables a variety of enantioselective silylium-catalyzed transformations via ACDC. However, in order to achieve high levels of enantioinduction, the reported systems were limited to aromatic starting materials, presumably due to π/π–stacking between the 3,3'-substituents of the catalyst and the substrate. Therefore, the design of a more confined active site would be the next step toward generalizing silylium ACDC.

2.2.5.2 IDPis as Lewis Acid Catalysts

The transformation of small, unbiased aliphatic substrates is a major challenge in asymmetric Lewis acid organocatalysis, as a highly acidic functionality in a well-defined and confined environment is required. BINOL-based imidodiphosphates (IDPs) ensure a confined pocket; however, their reduced acidity ($pK_a \approx 11.5$) as compared to DSIs ($pK_a \approx 8.5$) renders them incompatible with "silylium" Lewis acid catalysis. The profoundly enhanced acidity of the IDPis ($pK_a < 4.5$) encapsulated inside the $C_2$-symmetric BINOL dimer makes them promising candidates for the exploration of new reactivities in Lewis acid catalysis.

In 2016 the List group reported the development and application of IDPis in organic Lewis acid catalysis. A general Hosomi–Sakurai allylation of aromatic and aliphatic aldehydes with excellent enantioselectivities and yields was presented (Scheme 2.17).\cite{46b} Noteworthy, at even low catalyst loadings (down to 0.5 mol%) the less reactive allyltrimethylsilane ($N = 1.68$) readily reacted.
Scheme 2.17 Silylium Lewis acid-catalyzed Hosomi–Sakurai allylations using allyltrimethylsilane derivatives.

Following this groundbreaking work, the power of IDPi catalysts for the activation of small and unbiased substrates with high selectivity has been shown in several reports. Namely, the Mukaiyama–aldol reaction was made possible with catalyst loadings approaching the ppb levels,[91] both the Mukaiyama–Michael reaction[92] and the Diels–Alder reaction[93] were performed exploiting a wide substrate scope. The latter allowed access to previously inaccessible cycloaddition products via Lewis acid catalysis. Furthermore, the synthesis and functionalization of the tetrahydrofuran moiety through stereoselective control of the corresponding oxocarbenium ion was reported.[94] Last, the single addition of acetaldehyde derived silyl enol ethers to aldehydes[95] proved that the chiral Lewis acid controls the chemo- and the enantioselectivity of the transformation, avoiding engineered substrates and undesired polymerization products (Scheme 2.18).
Scheme 2.18 Overview on applications of “silylium” IDPi-catalyzed asymmetric transformations.

The wide success of the IDPi scaffold can be attributed not only to the high acidity and the confinement of the catalytic active site, but also to the many structural diversifications achievable upon modification of the 3,3′-substituents (Ar) and the sulfonimidic residue (R). Indeed, in comparison the DSI motif offers limited possibilities of structural modifications; the explored ones are different 3,3′-substituents (electron-rich or electron-poor, aromatic and aliphatic substituents) which affect the enantioselectivity with its close proximity to the active site, or different positions in the backbone, with the introduction of EWG (e.g. nitro groups) or EDG (alkyl chains), usually influencing mainly the reactivity of the catalyst. IDPiS, on the other hand, in addition to all the above mentioned modifications, can be further modified in proximity to the catalytic active site, upon variation of the sulfonimidic residue (R) (Figure 2.11).
Figure 2.11 Structural diversity of DSI vs IDPi.
2.3 **Bis-Silyl Ketene Acetals**

The first reports on the synthesis and characterization of bis-SKAs appeared in the early 1970s.\[^{96}\] Bis-SKAs and silyl enol ethers differ both on electronic and structural properties. Moving from silyl enol ethers to SKAs, the nucleophilicity $N$ at the $\alpha$-position increases by several orders of magnitude.\[^{88}\] The presence of a second silicon group shifts $N$ further toward higher nucleophilicity, implying a more facile reaction with an electrophilic partner.\[^{97}\] Structurally, bis-SKAs bearing the identical silyl groups do not exhibit $E/Z$ stereoisomer isoforms; this reduces the amount of diastereomeric transition states when reacting with an electrophile in the presence of a chiral catalyst (Figure 2.12). Furthermore, the absence of $E/Z$ stereoisomers enables facile synthesis and purification of the starting material.

![Figure 2.12](Image)

**Figure 2.12** Comparison of electronic and structural properties of silyl enol ethers/SKAs and bis-SKAs.
2.3.1 Bis-SKAs in the Synthesis of α-Functionalized Carboxylic Acids

Significant attention has been devoted towards the exploration of the synthetic potential of bis-SKAs as surrogates of α-enolizable carboxylic acids. In this section, the different transformations so far developed with bis-SKAs are presented. Initial studies were performed with highly electrophilic reagents, such as trifluoromethyl hypofluorite,[98] fluorine[99] and nitrosobenzene[100] or oxidants such as m-chloroperbenzoic acid.[101] These reagents enabled the direct formation of C–F, C–N and C–O bonds, respectively, providing a formal α-functionalization of carboxylic acids (Scheme 2.19).

Scheme 2.19 Bis-SKAs in C–heteroatom bond forming reactions.

The pioneering work of Reetz et al. paved the way for several C–C bond forming reactions under Lewis acidic conditions.[102] In this first example, an α-alkylation in the presence of catalytic ZnCl$_2$ and tertiary haloalkanes or tertiary acetates was reported. Recently, Baba et al. reported that InBr$_3$ was a competent Lewis acid for the α-alkylation of bis-SKAs in the presence of benzyl chloride.[103] The first α-aminomethylation was reported by Morimoto et al. in 1985, where TMSOTf was chosen to catalyze the in situ formation of a reactive iminium ion, which is quantitatively trapped by the bis-SKA to afford the tris-silylated β$_2$-amino ester. Upon protic workup, the free β$_2$-amino acid is formed.[100] An extension of this work was reported by Karoyan in 2007, in which various preformed iminium salts bearing
different protecting groups were used as reagents for the α-aminomethylation of \textit{bis-}SKAs\cite{104} (Scheme 2.20).

**Scheme 2.20** C–C bond forming reactions: α-alkylation and α-aminomethylation of \textit{bis-}SKAs.

One of the most explored reactions for this class of substrates is the Mukaiyama–aldol reaction in the presence of a Lewis acid. Wissner reported the first example in 1979 in the presence of SnCl$_4$ and O-trimethylsilyl \textit{bis-}SKA affording 2,3-dihydroxy carboxylic acid.\cite{105} Dubois \textit{et al.} showed a moderately diastereoselective example in the presence of α-monosubstituted \textit{bis-}SKA and a catalytic amount of TiCl$_4$.\cite{106} Skarek \textit{et al.} used N-methyl-N- trimethylsilyl \textit{bis-}SKA as a glycine surrogate and TMSOTf as the Lewis acidic catalyst, to obtain the α-functionalized β-hydroxy-α- amino acid, albeit with poor diastereoselectivities.\cite{107} More recently, Bellassoued showed that, when the \textit{bis-}SKA has a TMS group in the α-position, the Mukaiyama-aldol product eliminates and selectively forms the (E)-cinnamic acid derivative (Scheme 2.21).\cite{108}
Background

Scheme 2.21 Mukaiyama-aldol reactions with bis-SKA nucleophiles.

Rudle et al. reported several examples of α-arylations of bis-SKAs, catalyzed by Pd(PPh₃)₄. Successful coupling partners were tricarboxylchromium complexes of aryl ethers,[109] tungsten(0) alkylidene complexes stabilized as pyridinium ylides[110] and allylic acetates, albeit with poor regioselectivity. Recently, Hartwig et al. reported a general arylation of carboxylic acids and amides via the in situ formation of bis-SKA with a stoichiometric base (LiHMDS) and a catalytic amount of Pd(dba)₂ and 1Bu₃P (Scheme 2.22).[111]

Scheme 2.22 Cross-coupling reactions with bis-SKAs.
Background

The transformations shown above are summarized in the following timeline, giving a general overview for the transformations achieved so far with bis-SKAs as substrates for the α-functionalization of carboxylic acids (Figure 2.13). Until today, the only reported enantioselective transformation using bis-SKAs is their enantioselective protonation using stoichiometric quantities of an enantiopure BINOL–Sn complex, reported by Yamamoto et al.\textsuperscript{[112]} Recently, Ooi and co-workers expanded the portfolio of this reaction, reporting two catalytic examples using asymmetric phase-transfer catalysts.\textsuperscript{[13b, 13c]} A comprehensive overview on enantioselective protonation of bis-SKA is presented in the following section.

![Figure 2.13 General overview of the transformations reported with bis-SKAs.](image-url)
Background
2.4 Enantioselective Protonation of \textit{bis}-SKAs

2.4.1 Introduction

The abundance of tertiary carbon centers at the \(\alpha\)-position of carbonyl compounds in biological and natural products encouraged many scientists to investigate enantioselective transformations to access the enantiopure \(\alpha\)-chiral carbonyl motif in an efficient and highly selective manner. The asymmetric protonation of preformed or catalytically generated transient enol equivalents enables straightforward access to these valuable scaffolds (Scheme 2.23). As the high reactivity of the proton and the basicity of the enolate result in a fast reaction, control of the enantioselectivity is very challenging. Inhibition of the background reactivity is usually overcome by performing the reactions under cryogenic conditions, with slow addition of either reagent, and using bulky PSs as for instance DMP.\cite{113} The enantiocontrol of the proton transfer highly depends on the enolate geometry; therefore, many examples are reported using cyclic substrates, in which the geometry of the enolate is restricted to the \(E\)-form. In the case of metal-derived Lewis acid-catalyzed transformations, the stability of the catalyst can be affected by simple proton sources, such as water or methanol, due to their mild Lewis basic character (Scheme 2.23).

\textbf{Scheme 2.23} Catalytic asymmetric protonation strategies and challenges.
The previously mentioned report from Pracejus (Scheme 2.2) represents an early example of a catalytic asymmetric protonation.[23] Indeed, upon the nucleophilic addition of methanol to the ketene, the transient enolate is protonated to afford the corresponding enantioenriched ester. Despite this successful pioneering work, it was not until the late 1980s that significant developments for asymmetric protonation of metal enolates with the aid of stoichiometric chiral Brønsted acids began to emerge.[114] Catalytic approaches started appearing in the early 1990s employing chiral catalysts for the protonation of lithium enolates by slow addition of an achiral PS.[115] Since then, an increased interest in asymmetric protonation led to successful reports starting from silyl enolates,[56d, 116] β-keto acids,[117] ketenes,[118] α,β-unsaturated carbonyl compounds,[119] and many others.[120] Furthermore, enzymes have also been employed in biocatalytic processes, including esterases[121] and decarboxylases,[122] for the protonation of enol esters or the decarboxylative protonation of malonic acid derivatives.

### 2.4.2 Catalytic Asymmetric Protonation of Enolate Derivatives

The first catalytic enantioselective protonation of silyl enolates was developed by Yamamoto et al., exploiting Lewis acid-assisted Brønsted acid (LBA) catalysis.[123] This concept is based on the association of an enantiopure BINOL-based Brønsted acid ((R)-Me-BINOL) and an achiral Lewis acid (e.g. SnCl₄), leading to an increased acidity of the BINOL proton.[13a, 124] The transformation afforded the products in very high yields and enantioselectivities, however, a bulky PS (e.g. 2,6-dimethylphenol 23, DMP) and very low temperatures (e.g. –80 °C) were required. Thus, the major drawbacks of LBA catalysis are the poor stability of the catalyst towards moisture and mild Lewis bases (e.g. simple alcohols), requiring strictly anhydrous conditions in order to perform efficiently.[113a] The same author reported an improved LBA catalyst (25), which was formed by complexation of La(OTf)₃ with an (S)-HOP (2-hydroxy-2'-diphenylphosphino-1,1'-binaphthyl) scaffold, allowing methanol to be used as the stoichiometric achiral PS at room temperature, without the need of slow addition of
either reagent. Only cyclic substrates were tolerated attaining moderate enantioselectivities, thus, not exceeding the first generation of LBAs\textsuperscript{[125]} (Scheme 2.24).

Scheme 2.24 Development of LBA catalysis to Lewis base tolerant systems.

A major advance in the field of catalytic enantioselective protonation of silyl enol ethers and SKAs was achieved by Toste and co-workers, who further exploited the LBA catalysis concept\textsuperscript{[113b]} The cationic \( (R)\)-BINAP (2,2’–bis-(diphenylphosphino)–1,1’–binaphthyl) gold(I) complex, combined with equimolar amount of AgBF\(_4\), tolerates an excess of EtOH at room temperature, enabling very high enantioselectivities for a wide selection of cyclic and acyclic silyl enolates. The highlight of this system is the ability of the LBA catalyst to discriminate between the \( Z \) - and \( E \)-diastereomers approaching the silyl enol ether from the same enantiotopic face. This leads to a stereoconvergent asymmetric protonation, erasing the challenge of selective \( Z \) or \( E \) synthesis of the starting material (Scheme 2.25).
Background

\[
\begin{align*}
\text{Scheme 2.25 Gold(I) LBA catalysis for asymmetric protonation of acyclic silyl enolates.}
\end{align*}
\]

Many organometallic catalysts have been reported, providing excellent levels of enantioselectivity with wide substrate scopes. Metal-free solutions began to appear in 2007, with the first report from Levacher, in the presence of a chiral tertiary amine and a stoichiometric PS (XH).\[^{116a}\] In those systems, the Lewis basic anion (X:\(^-\)) activates the silyl enol ether towards enantioselective protonation by the chiral ammonium salt (see TS, Scheme 2.26). Initially, only a limited substrate scope was reported, however, further developments included different PSs (bulky, highly acidic or generated \textit{in situ}) and a variety of chiral bases (Scheme 2.26).\[^{116c}\]

\[
\begin{align*}
\text{Scheme 2.26 Chiral ammonium salts for enantioselective protonation of silyl enol ethers.}
\end{align*}
\]

The first organocatalytic Brønsted acid-catalyzed example was reported by Cheon and Yamamoto in 2008, using BINOL-based \(N\)-triflyl thiophosphoramide 12 in the
Background

presence of phenol as the achiral PS (Scheme 2.27). This report represents an important achievement in the field of organocatalytic asymmetric protonations, even though only cyclic substrates with aromatic substituents were successfully employed. Recently, Li and co-workers aimed to use the simplest PS available, H$_2$O, in combination with pentacarboxycyclopentadiene (PCCP) as the chiral acid. Only cyclic substrates have been reported and only moderate enantioselectivities were achieved, thus showing the challenges associated with using water as the PS (Scheme 2.27).

Scheme 2.27 Organocatalytic protonation of cyclic silyl enol ether with PhOH and H$_2$O.

Additional examples of enantioselective organocatalytic protonations, enabled by chiral Brønsted acids, have been reported in the context of deracemization sequences of $\alpha$-alkyl-$\alpha$-aryl nitrites (26) and $\alpha$-aryl-substituted hydrocoumarins (28). In the first case, the protonation of silyl ketene imines occurred in the presence of MeOH and (R)-TRIP (20) as the catalyst, while in the second case, the enantioselective protonation of the intermediate ketene dithioacetals occurred with phosphoric acid 30 (Scheme 2.28). Both examples highlight the importance of this transformation, particularly when included in a deracemization sequence. Indeed, the racemic starting material was almost exclusively converted to a single enantiomer.
Background

without tedious purification of the intermediates. Stoichiometric reagents enabled the initial planarization of the stereogenic center to the protected ketene intermediates (27 and 29). A catalytic amount of chiral acid was sufficient to protonate the intermediate from only one enantiopatic face, reforming the sp³-configured carbon in high enantioselectivity.

Scheme 2.28 Examples of deracemization sequences via asymmetric protonation of the corresponding ketene intermediate.
2.4.3 Catalytic Asymmetric Protonation of bis-Silyl Ketene Acetals

The deracemization strategy of carboxylic acids via an intermediate (or catalytically formed) enolate has already been mentioned in the context of direct α-functionalizations (Chapter 1, Scheme 1.3). This strategy involves the transformation of racemic carboxylic acids into their corresponding enediolates. Subsequent asymmetric protonation can then afford the starting carboxylic acid as a single enantiomer. A similar sequence can be envisioned by stabilizing the intermediate enediolate with two silicon groups (Scheme 2.29).

Scheme 2.29 Deracemization of carboxylic acids via a sequence of bis-SKA generation and subsequent enantioselective protonation.

Despite the similarity compared to SKAs, different considerations must be taken into account while envisioning catalytic enantioselective protonations of bis-SKAs. The higher nucleophilicity generally associated with bis-SKAs leads to faster background reactions with the achiral PS. Hence, the catalyst, in order to avoid high catalyst loadings, should be acidic enough to protonate the substrate faster than the stoichiometric reagent. Furthermore, the catalyst must deliver the proton with high selectivity, discriminating the two enantiotopic faces of the bis-SKA.
2.4.3.1 Stoichiometric Reagents

Significant effort has been dedicated to address the challenges encountered with the enantioselective protonation of bis-SKAs. The first example was reported in 1994 by Yamamoto et al. using stoichiometric amounts of a chiral complex generated in situ by reacting equimolar amounts of enantiopure BINOL and SnCl$_4$. Noteworthy, the acidity of the Brønsted acid was enhanced by the combination with a Lewis acid, thus named Lewis acid-assisted Brønsted acid (LBA). Although high levels of enantioselectivity were observed, the selection of substrates was limited only to $\beta$-methyl-$\beta$-aryl substituted bis-SKAs, as any alkyl group (R) other than methyl group resulted in low or moderate enantioselectivities. The authors derived a stereochemical model for the proposed transition state (Scheme 2.30), explaining the limitations in the substrate scope.$^{[112]}$ Different ligands have been designed for the same transformation,$^{[130]}$ however the limitations on the substrates scope tolerance remained.

Scheme 2.30 Enantioselective protonation with a stoichiometric chiral reagent.
2.4.3.2 Catalytic Asymmetric Protonation

A proposed mechanism for the reaction described in the previous section is depicted in Scheme 2.31 (route 1) in which the chiral PS (HOAr*), upon enantioselective protonation, is ultimately silylated (Me₃SiOAr*) and the Lewis acid (e.g. SnCl₄) is regenerated. A catalytic version requires that HOAr* is regenerated from an achiral PS (HOAr). In this case, the SnCl₄ needs to be preferentially coordinated to HOAr* and the reactivity of HOAr*•SnCl₄ has to be greater than of HOAr•SnCl₄ in order to avoid the background reaction (Scheme 2.31). In fact, HOAr can react with two nucleophiles, the anion OAr* and the bis-SKA, leading to the completion of the catalytic cycle (route 2) or to the undesired background reaction (route 3). A common strategy to minimize route 3 consists of keeping the ratio between the chiral and the achiral PS (HOAr*/HOAr) as high as possible. This can be realized by slow addition of HOAr or by using biphasic systems (e.g. liquid/liquid or solid-liquid). Another strategy consists of designing an achiral PS which is less associated to the substrate, for example by reducing the accessibility of the transferred proton, as for example in the more strically hindered 2,6-dimethylphenol (DMP).

Scheme 2.31 Stoichiometric vs catalytic enantioselective protonation of bis-SKAs.
In summary, careful control of the reaction conditions is needed to avoid background reactivity, including a strictly inert atmosphere, very low temperatures and slow addition of the PS. Furthermore, tailored design of the PS is particularly crucial to avoid the undesired pathways. DMP appears to be particularly suitable to suppress background reactivity. In fact, the steric bulk of the methyl groups ortho to the phenol functionality disfavored both the formation of achiral Lewis acids and the direct protonation of silyl enol ether.

Yamamoto and co-workers showed that using (R)-Me-BINOL as the ligand, the above-mentioned transformation can be performed in the presence of a catalytic amount of Lewis acid (SnCl₄), maintaining the same high enantioselectivity (Scheme 2.32). Unfortunately, the limitations of the system remained unsolved, such as slow addition of the bis-SKA, and the requirement for a sterically hindered PS (23) as well as strictly anhydrous conditions. Furthermore, only substrate 31a was reported as single example.

**Scheme 2.32** First catalytic asymmetric protonation of bis-SKA via LBA catalysis.

Ooi *et al.* reported two remarkable examples of catalytic enantioselective protonation of bis-SKA derivatives. The axially chiral Brønsted acid catalyst, *P*-spiro diaminodioxaphosphonium barfate 33, showed high levels of enantioinduction for the protonation of α-amino acid-derived[13b] and for α-halo and α-alkoxy acid-derived bis-SKAs.[13c] However, it still required a bulky PS in order to inhibit both the background reaction with the substrate and the decomplexation of the catalytic system, leading to the formation of HBArF, which is itself a highly reactive achiral PS. This was prevented by addition of a scavenger (34) neutralizing this side reaction (Scheme 2.33). In this system, the enantiofacial discrimination depended predominantly on the
Background

electronic bias of the substrate and was independent on the steric features of the substituents.

Scheme 2.33 Catalytic asymmetric protonation of bis-SKA via organic LBA catalysis; BARF = Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

To date, a catalytic asymmetric protonation of bis-SKAs from electronically unbiased carboxylic acids in the presence of water as the simplest PS has not been reported.
2.5 Enantioselective $\alpha$-Aminomethylation

2.5.1 Introduction

Over the last decades, catalytic and enantioselective C–C bond forming reactions at the $\alpha$-position of carbonyl compounds have been an ambitious target, approached by many scientific groups. However, the direct, enantioselective $\alpha$-functionalization of carboxylic acids still remains an unsolved challenge. The following chapter will give a concise overview of asymmetric $\alpha$-functionalization reactions of carbonyl compounds in the context of direct aminomethylation reactions.

The high abundance of $\beta$-amino carbonyl compounds in biological and natural products (Scheme 2.34) drove the interest toward the investigation of enantioselective transformations to efficiently access this motif\textsuperscript{132} $\beta$-Amino acids are naturally present in important co-factors, such as panthotenic acid (vitamin B$_5$), and $\beta$-lactam antibiotics. The key feature of this scaffold relies on the close structural similarity to the corresponding $\alpha$-amino acid, maintaining their main functionality but increasing their metabolic stability by several orders of magnitude\textsuperscript{133}.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme_2_34.png}
\caption{Examples of biologically active compounds containing $\beta$-amino acid-derived functionalities.}
\end{figure}

\textsuperscript{132} Pantothenic acid
\textsuperscript{133} $\beta$-lactam antibiotic
Peptide-containing molecules are highly unstable in the presence of proteases, which are ubiquitous enzymes designated for the digestion of proteins by hydrolyzing the peptide bond. The binding selectivity of the β-amino acid substrate to the active site of the proteases remains, but the catalytic activity is inhibited, rendering those substrates as metabolically stable (Scheme 2.35, a). The success of the β-amino acid functionality is also attributable to the ability of β-peptides (short sequence β-amino acids) to self-assemble into secondary structures such as α-helices or β-sheets, in close relationship to the analogous natural α-peptides (Scheme 2.35, b).

**Scheme 2.35** a) Schematic representation of the binding of an α-peptide and a β-amino acid-containing peptide to the active site of a protease; b) structural similarity of a β-turn in natural occurring α-peptides and unnatural β-peptides.

The introduction of an aminomethyl group into small organic molecules has recently attracted a great deal of attention, particularly toward the synthesis of β-amino acids (Scheme 2.36). β3-Amino acids can be obtained by enantiospecific homologation of the natural α-amino acids, and the catalytic asymmetric synthesis of β3-amino acids, although not discussed in this section, has delivered remarkable progress in the last years. Few diastereoselective syntheses of β2,3-amino acids...
Background

Acid derivatives have recently been reported,[52,137] however, only in the presence of directing protecting groups or activated substrates. On the other side, β2-amino acids cannot be obtained through enantiospecific transformations of the corresponding α-amino acids; currently, the use of chiral auxiliaries for a diastereoselective α-aminomethylation of the carboxylic acid derivative is a common and reliable synthetic alternative. The catalytic enantioselective synthesis of β2-amino acids via aminomethylation remains a challenge,[138] particularly in protecting group-free approaches and using unbiased substrates.

Scheme 2.36 Retrosynthetic analysis of β-amino acids from the parent α-amino acid or via aminomethylation reaction.
2.5.2 Asymmetric Synthesis of $\beta^{2,3}$-Amino Acids

Organocatalytic asymmetric syntheses of $\beta^{2,3}$-amino acids have been reported both in the field of Lewis base and Brønsted acid catalysis. Inspired by the pioneering discovery of a proline-catalyzed direct Mannich reaction by List in 2000, the combination of an enolizable aldehyde and an aromatic imine, bearing aromatic protecting groups, was reported by Barbas et al. in 2002 to give syn $\beta^{2,3}$-amino aldehydes and, in 2006, to give anti-$\beta^{2,3}$-amino aldehydes. In 2007, List et al. reported the Mannich reaction of simple alkyl aldehydes with $N$-Boc-protected aryl imines catalyzed by ($S$)-proline. The corresponding syn-$\beta^{2,3}$-amino aldehydes were obtained in high yields as well as enantio- and diastereoselectivities. Finally, an additional oxidation step provided access to the desired enantioenriched $\beta$-amino acids (Scheme 2.37).

Scheme 2.37 Enantioselective synthesis of $\beta^{2,3}$-amino aldehydes with ($S$)-Proline as catalyst.

An asymmetric synthesis of $\beta^{2,3}$-amino acids in the field of Brønsted acid catalysis has been already mentioned in chapter 2.2.4 (Scheme 2.8): Akiyama et al. reported a Mannich-type reaction of SKAs with $N$-(2-hydroxyphenyl)-arylimines, affording the corresponding syn-$\beta$-amino esters in high yields, diastereo- and enantioselectivities. The 2-hydroxyphenyl substituent is crucial, as the $H$-bonding to the catalyst is a pre-requisite for the high selectivity of the reaction. However, the protecting group limits the utility of the transformation. Recently, Zhou, Yamamoto et al. reported an expansion of the substrate scope by applying the more acidic phosphoramide 35 as the catalyst. The wider scope includes disubstituted SKAs and aliphatic imines, having either the same protecting group (2-hydroxyphenyl) or
Background

simply a phenyl group. However, additional steps are required to obtain the desired β-amino acids (Scheme 2.38).

**Scheme 2.38** Asymmetric synthesis of β^{2,3}-amino esters via Brønsted acid catalysis.
2.5.3 Asymmetric Synthesis of $\beta^2$-Amino Acids

Several synthetically equivalent transformations can be envisioned for the synthesis of $\beta^2$-amino acids, in which the NH$_2$–CH$_2$ synthon can act as electrophile,$^{138}$ nucleophile$^{143}$ or carbenophile.$^{144}$ Among those, Mannich-type reactions are the most explored ones (Scheme 2.39).

Scheme 2.39 Retrosynthetic analysis for the highlighted disconnection of $\beta^2$-amino acids.

More than one century ago,$^{145}$ Mannich found that $\beta$-amino acids could be formed by combining enolizable carboxylic acid derivatives, formaldehyde and ammonia.$^{146}$ Despite the availability of these starting materials, asymmetric variants of this transformation have been developed only with more reactive substrates, such as enolizable aliphatic aldehydes,$^{144}$ or preformed enolates,$^{83, 147}$ such as SKAs. In the case of $\beta^2$-amino acid derivatives, the three-component one-pot procedure would require formaldehyde, ammonia and an enolizable carboxylic acid derivative. The first two reagents are difficult to handle themselves, as they irreversibly form urotropine, the tetramer of the highly reactive unsubstituted iminium ion.

Therefore, this iminium ion can only be applied in protected form: A common precursor is bis-benzyl protected tertiary amine having a leaving group in the $\alpha$-position.$^{148}$ The protected methylene iminium ion is then liberated in situ under the
reaction conditions (Scheme 2.40). Protecting groups (e.g. benzyl groups) and activated substrates (aldehydes or SKAs) facilitate the design of asymmetric transformations; however, they imply additional steps (deprotection and functional group manipulation) before achieving the desired target $\beta^2$-amino acid.

Scheme 2.40 Mannich reaction for the synthesis of $\beta^2$-amino acids.

In 2006, Gellman et al. reported a remarkable example of a catalytic enantioselective transformation toward $\beta^2$-amino acid precursors.$^{[138]}$ In this case, the authors combined aliphatic aldehydes with $N,N$-dibenzyl-1-methoxymethanamine (36) as the iminium ion precursor and the Jørgensen–Hayashi catalyst (37). The hindered silyl ether prevents any hydrogen-bonding or ion-pairing interactions and, thus, directs the nucleophilic attack from the opposite face compared to (S)-Proline, however, the role of the additives remained unclear. The intermediate $\beta^2$-amino aldehydes were immediately reduced to avoid epimerization. From the obtained enantioenriched $\beta$-amino alcohols, a recrystallization and three additional steps where required to obtain $N$-Boc-$\beta^2$-homonorvaline (38) (Scheme 2.41).
**Background**

**Scheme 2.41** Enantioselective synthesis of \( \beta^2 \)-amino acids by Gellman.

Enantioselective transformations directly affording the unprotected amino acids, hence containing the unprotected amine and acid functionalities, have not been reported to date. However, in 1985 Morimoto et al. demonstrated the principal feasibility of this transformation in a non-asymmetric fashion.\(^{[100]}\) Pre-activating a carboxylic acid as the corresponding bis-SKA in combination with the iminium ion precursor 38, and a catalytic amount of Lewis acid yielded the targeted unprotected \( \beta^2 \)-amino acids, upon exposure to protic conditions (Scheme 2.42).

**Scheme 2.42** Direct non-enantioselective synthesis of \( \beta^2 \)-amino acids.

Noteworthy, an enantioselective aminomethylation reaction exploiting a similar strategy was recently reported by Xu, Hu et al.\(^{[127]}\) The transformation was enabled by asymmetric counteranion-directed catalysis in the presence of a \([\text{PdCl} \left( \eta^3-\text{C}_3\text{H}_5 \right) \text{]}_2\) catalyst and pentacarboxy(cyclopentadiene (PCCP) acid as the chiral counteranion. The metal-based catalyst promotes the *in situ* formation of reactive enolate 42 from
Background

diazo compound 40 and an alcohol. PCCP activates the aminomethylating reagent 36, forming the iminium ion 41, and provides the chiral environment for the asymmetric Mannich-type reaction (Scheme 2.43). Despite the relevance of this transformation, the authors did not report a synthesis of $\beta^2$-amino acids from the obtained $\beta^{2,2}$-amino acids.

Scheme 2.43 Asymmetric Counter-Anion-Directed Aminomethylation to $\alpha$-alkoxy-$\beta$-amino esters.
3 Objectives

A direct enantioselective α-functionalization of carboxylic acids still remains elusive, both in metal-, bio- and organocatalysis. Only a few systems using in situ generated enediolates taking advantage of chiral auxiliaries have been reported.\textsuperscript{10a, 10d, 14g} A highly attractive alternative for a versatile catalytic approach to the α-functionalization of carboxylic acids, circumventing the use of moisture-labile and highly reactive enediolates, could rely on the formation of bis-SKA intermediates followed by functionalization with an electrophilic partner (Figure 3.1).

**Figure 3.1** α-Functionalization of carboxylic acids via activation to the bis-SKA intermediate.

Despite the potential of this transformation, exclusively the catalytic asymmetric protonation of bis-SKAs has been reported so far, affording enantioenriched α-branched carboxylic acids by employing (Lewis acid-assisted) Brønsted acid catalysts. In order to achieve high enantioselectivities, the systems were limited to bulky proton sources\textsuperscript{113a} and electronically-biased bis-SKAs.\textsuperscript{13b, 13c} Furthermore, cryogenic conditions, inert atmosphere and slow addition of the reagents were needed, rendering these methods less practical. In this context we speculated if we could find a general solution for electronically-unbiased substrates, using a simple proton source, such as water (Figure 3.2). Furthermore, we envisioned the application of this method in a one-pot deracemization sequence of α-branched carboxylic acids-containing drugs, such as Ibuprofen®.
**Figure 3.2** Envisioned enantioselective protonation of electronically-unbiased *bis*-SKAs using water as the proton source.

A catalytic enantioselective C–C bond formation for the α-functionalization of *bis*-SKAs has not been reported so far. Several reports have focused on the utilization of SKAs for the functionalization of various electrophilic species; in those systems, an enantiopure catalyst enables the nucleophilic attack selectively onto one of the enantiotropic faces of the electrophile, forming the stereogenic center in the β-position of the acid derivative.\[^{12b, 51}\] In this thesis, we aimed to reverse the roles: The employed catalyst should discriminate the enantiotropic faces of the nucleophile and install selectively the stereogenic center in the α-position of the carboxylic acid. With this aim in mind, we selected the α-aminomethylation of *bis*-SKAs as the targeted reaction, as this would lead to synthetically-valuable unprotected β^2^-amino acids, since those valuable motifs are not accessible via straightforward catalytic asymmetric transformations yet. This reaction was reported by Morimoto *et al.* under Lewis acidic conditions, using TMSOTf as the catalyst.\[^{100}\] We envisioned that we could exploit the ACDC concept and, after the *in situ* formation of the iminium ion, control the enantiotopic discrimination on the *bis*-SKA (Figure 3.3).

**Figure 3.3** Proposed enantioselective aminomethylation of *bis*-SKAs via ACDC.
In summary, the goal of this thesis is to explore the use of *bis*-SKAs as potent starting materials for the catalytic enantioselective synthesis of $\alpha$-functionalized carboxylic acids under Brønsted or Lewis acidic conditions by developing conditions for an $\alpha$-protonation and $\alpha$-aminomethylation.
Objectives
4 Results and discussion

4.1 Asymmetric $\alpha$-Protonation with $\text{H}_2\text{O}$ and $\alpha$-Deuteration with $\text{D}_2\text{O}$

The work presented in this section was performed in cooperation with Dr. Thomas James, Dr. Aurélie Blond and Dr. Hyejin Kim.

4.1.1.1 Synthesis and Handling of bis-SKAs

The purity of the employed bis-SKA, which has to be $>99\%$ as determined by $^1\text{H}$ NMR, is a crucial factor for the success of the targeted $\alpha$-functionalizations. Traces of water are potent enough to protonate the starting material in the absence of an appropriate catalyst resulting in racemic product. Furthermore, after the protonation, one molecule of silanol ($\text{R}_3\text{SiOH}$) is released, which is itself a potent proton source reacting with the employed bis-SKA ultimately forming ($\text{R}_3\text{Si}$)$_2\text{O}$. Therefore, full conversion of the bis-SKA has to be ensured in order to determine the performance of a chiral catalyst, as partial conversion leads to background reactivity upon quench or exposure to the atmosphere. An additional crucial factor is the absence of bases, as they would react with the acidic catalyst forming very stable and unproductive salts. Moreover, low catalyst loadings (1 mol\% or lower) are a crucial goal for the relevance of any catalytic transformation, thus the starting material has to be base-free (at least within the sensitivity of $^1\text{H}$ NMR). Due to these requirements, particular attention and effort had to be dedicated to synthesis, purification and storage of the bis-SKAs.

Commonly, bis-SKAs are synthesized by the original procedure reported by Ainsworth et al. in which the carboxylic acid is first reacted with base (usually NaH or pyridine) and TMSCl to the corresponding silyl ester. This is then subsequently treated with an additional base (e. g. LDA) and more TMSCl to give the desired products (Scheme 4.1).$^{[96]}$ The speed of addition of the reagents is a crucial and tedious step influencing the yield of the reaction and consequently the efficiency of
the purification, particularly in the case of mono-substituted bis-SKAs \((R^2 = H)\). However, during our studies we discovered a more facile and higher yielding single step procedure using an excess of LDA (2.1 equiv.) and TMSCl (2.2 equiv.). By premixing the carboxylic acid and the TMSCl at low temperatures, a faster addition of the base was the key to a cleaner reaction profile. This observation can be explained by the competition between kinetic and thermodynamic product: the O,O-bis-silylated ketene acetal \((\text{bis-SKA 31b})\) is the kinetic product while the C-silylated trimethylsilyl ester \(44\) is the thermodynamic product and the main side reaction observed for mono-substituted bis-SKAs. The rapid “internal quench” of the bis-Li enolate by the constant high excess of TMSCl favored the kinetic product and thus resulted in a cleaner reaction profile and higher yield. A similar strategy was adopted by Corey et al. while developing \(E\)- or \(Z\)-selective synthesis of silyl enol ethers of SKAs.\[150\]

Interestingly, the migration of the TMS group from oxygen to carbon could be observed upon storage of bis-SKAs at ambient temperature. Noteworthy, additional precautions were required including the use of freshly distilled diisopropylamine, accurate butyl lithium titration, strict inert conditions and very low pressures for the purification via distillation.

**Scheme 4.1** Original and improved procedure for the preparation of bis-SKAs.
4.1.2 Reaction Design and Optimization Studies

In an initial experiment, bis-SKA 31a was added to a stoichiometric amount of methanol in dichloromethane with (S)-DSI (17a) as the catalyst. Gratifyingly, the desired product was obtained after full conversion in 82:18 er (Scheme 4.2) (Note: Conversion was monitored via $^1$H NMR of the crude reaction mixture prior to treatment with SiO$_2$). Compared with previous results by Yamamoto et al. (95:5 er using 2,6-DMP as the PS),\textsuperscript{[113a]} this result indicated promising enantioselectivity in the presence of a non-bulky PS.

Scheme 4.2 Initial result for the asymmetric protonation of bis-SKA in the presence of methanol.

These results prompted us to evaluate the catalytic ability of different Brønsted acid catalysts, exploring different ranges of acidities and confinements (Scheme 4.3). Catalysts with lower acidities, such as (S)-TRIP 20 ($p$K$_a$ in CH$_3$CN = 13.6), (S,S)-IDP 19b ($p$K$_a$ in CH$_3$CN = 11.3) and (S,S)-iDP 46 ($p$K$_a$ in CH$_3$CN = 9.1), catalyzed the reaction with very low enantioselectivity (52:48 er; 51:49 er and 51:49 er respectively). Catalysts with higher acidities, such as the BALT catalysts 45a and 45b ($p$K$_a$ in CH$_3$CN = ~2.8), did not show any level of enantioselectivity (both 50:50 er). The combination of great acidity and confined active site as in IDPi 47a ($p$K$_a$ in CH$_3$CN = 4.5) also did not show any level of enantioselectivity (51:49 er), presumably because bis-SKA (31a) may be too sterically congested and therefore not able to interact/to intercept the acidic proton of the IDPi. Exclusively, the intermediate
Results and Discussion

Acidities of the DSIs 17a (pKₐ = 8.5) and 17b, which have more open active sites, gave the desired products in improved enantioselectivities (82:18 er and 85:15 er respectively) (Scheme 4.3).

![Scheme 4.3 Screening of catalysts.](image)

As DSIs were identified as the ideal class of Brønsted acids for this transformation, initial screenings were performed using catalyst 17a. Remarkably, the use of different PSs had no influence on the enantioselectivity of the transformation (Table 4.1). From the bulkiest PS in the series (Entry 5) to the smallest one (Entry 1), the enantioselectivity remained unchanged. These results indicate that the background reactivity is not a major concern under this condition and the catalyst is the exclusive proton source.
Table 4.1 Effect of the PS. \(^{a}\)Time required to reach full conversion

<table>
<thead>
<tr>
<th>Entry</th>
<th>PS</th>
<th>time(^{a})</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H(_2)O</td>
<td>1 h</td>
<td>82:18</td>
</tr>
<tr>
<td>2</td>
<td>MeOH</td>
<td>1 h</td>
<td>82:18</td>
</tr>
<tr>
<td>3</td>
<td>(i)-PrOH</td>
<td>1 h</td>
<td>82:18</td>
</tr>
<tr>
<td>4</td>
<td>(t)-BuOH</td>
<td>1 h</td>
<td>82:18</td>
</tr>
<tr>
<td>5</td>
<td>DMP</td>
<td>4 h</td>
<td>82:18</td>
</tr>
</tbody>
</table>

Lowering the temperature to 0 °C did not improve the enantioselectivity and, interestingly, lower temperatures such as –20 °C and –40 °C were even detrimental. This result suggests that the activity of the catalyst is reduced, making the background reaction predominant (Table 4.2).

Table 4.2 Effect of temperature. \(^{a}\)Time required to reach full conversion

<table>
<thead>
<tr>
<th>Entry</th>
<th>T/°C</th>
<th>time(^{a})</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rt</td>
<td>1 h</td>
<td>82:18</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>2 h</td>
<td>78:22</td>
</tr>
<tr>
<td>3</td>
<td>–20</td>
<td>16 h</td>
<td>51:49</td>
</tr>
<tr>
<td>4</td>
<td>–40</td>
<td>16 h</td>
<td>51:49</td>
</tr>
</tbody>
</table>

A solvent screening revealed that choice of solvent mainly affected the enantioselectivity, whereas reactivity remained similar (Table 4.3). Due to higher
enantioinduction obtained with it, dichloromethane was used as solvent for further studies.

**Table 4.3** Effect of solvent. Superscript: Time required to reach full conversion

<table>
<thead>
<tr>
<th>Entry</th>
<th>solvent</th>
<th>time&lt;sup&gt;a&lt;/sup&gt;</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1 h</td>
<td>82:18</td>
</tr>
<tr>
<td>2</td>
<td>PhMe</td>
<td>2 h</td>
<td>66:34</td>
</tr>
<tr>
<td>3</td>
<td>Et&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>2 h</td>
<td>78:22</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>2 h</td>
<td>56:44</td>
</tr>
<tr>
<td>5</td>
<td>n-pentane</td>
<td>1 h</td>
<td>78:22</td>
</tr>
<tr>
<td>6</td>
<td>MeOH</td>
<td>1 h</td>
<td>54:46</td>
</tr>
</tbody>
</table>

The optimal concentration was identified to be at 0.2 M (Table 4.5, Entry 3), since lower concentrations did not improve the enantiosel ectivity (Entries 1 and 2) and higher concentrations were detrimental (Entries 4 and 5).

**Table 4.4** Effect of the molarity on the DSI-catalyzed protonation of *bis*-SKA

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conc. (M)</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.05</td>
<td>82:18</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>82:18</td>
</tr>
<tr>
<td>3</td>
<td>0.2</td>
<td>82:18</td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>76:14</td>
</tr>
<tr>
<td>5</td>
<td>neat</td>
<td>70:30</td>
</tr>
</tbody>
</table>
Results and Discussion

Using these optimized conditions, the catalyst loading could be reduced to 1 mol%, without deteriorating yield or enantioselectivity (Entries 1 and 2). Lower catalyst loadings however, gave worse and less reproducible results (Entries 4 and 5).

Table 4.5 Effect of the catalyst loading

<table>
<thead>
<tr>
<th>Entry</th>
<th>mol% b</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>82:18</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>82:18</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>82:18</td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>77:23</td>
</tr>
<tr>
<td>5</td>
<td>0.1</td>
<td>75:25</td>
</tr>
</tbody>
</table>

Taking the best reaction conditions, the catalytic activities of various DSI catalysts bearing different 3,3′-substituents were evaluated (Scheme 4.4). Modifications of the substituents in the meta-position slightly improved the enantioselectivity (17b 85:15 er and 17c 87:13 er), however not to sufficient levels. The expansion of the aromatic surface to a naphthalene moiety was not sufficient (17e 78:22 er and 17f 65:35 er). However, high enantioselectivity was achieved with the catalyst containing the phenanthrene (17g) and anthracene substituents (17h), which gave 89:11 er and 95:5 er respectively.
Results and Discussion

Scheme 4.4 Effect of the 3,3′-substituents of the DSI catalyst.

4.1.3 Preliminary Substrate Scope

Despite the promising result, a preliminary substrate scope showed that, in the presence of 17h as the catalyst, the reaction scope lacked generality (Scheme 4.5). Whereas the model substrate 32a could be obtained with very good enantioselectivities (95:5 er), modifications of the R1 group from methyl to isopropyl (32c) or benzyl groups (32d) were detrimental for the enantioselectivity (72:28 er and 75:25 er). In particular, ortho-substituents at the aromatic group (32e and 32h) of the substrate led to racemic products (both 50:50 er), and meta- (32f 88:12 er; 32i 94:6 er) and para-substituents (32g 94:6 er) gave high but overall not sufficient enantioselectivities.
Results and Discussion

Scheme 4.5 Preliminary substrate scope.

4.1.4 Fine-Tuning of the Catalyst Design

In order to achieve a more general system, further catalyst development was required. Therefore, the synthetic focus on the catalysts structures was divided into two branches. Firstly, maintaining the anthracene unit and functionalizing possible positions (17i-17k), and secondly, reinvestigating the second best catalyst (17g) and modifying the present phenanthrene group (17l-17p) (Figure 4.1).
Results and Discussion

In the 17i-17k series, the particular challenge was the functionalization of position 6 with a suitable boron reagent (acid or ester) in order to enable Suzuki cross coupling reactions with the corresponding 3,3′-l2-DSI (48). Neither the envisioned boronic acids nor the corresponding bromides (54a-c) are commercially available or reported in literature, therefore a suitable synthetic sequence was designed (Scheme 4.6). The sequence consisted of an initial Diels–Alder reaction between an in situ formed benzyne and furane, followed by metal-catalyzed deoxygenation using TiCl4 and Zn.[151] After conversion of 50 to the bromo-aldehyde 51 with iPrMgCl•LiCl (turbo Grignard)[152] and DMF,[153] the Suzuki coupling with three different boronic acids afforded intermediates 54a, 54b and 54c. The formyl group was used as a handle to install the required alkyne 53, which was achieved by a Corey–Fuchs reaction.[154] The newly introduced aryl group and the ortho-alkyne functionality underwent an Au(l)-catalyzed cycloisomerization in which a 1,2-halide shift occurred. This can be explained by assuming a metal vinlyidene species as the reactive intermediate.[155] Unfortunately, the desired boronic acids could not be synthetized, as intermediates 54a and 54b were extremely insoluble and additionally highly unstable in the presence of oxygen or light. Intermediate 54c was not formed, as the Au(l)-catalyzed cyclization does not tolerate electron deficient ring systems.
Scheme 4.6 Synthetic sequence toward tetraphene derivatives 54a, 54b and 54c.

Further efforts were therefore dedicated toward the preparation of functionalized phenanthrene derivatives (Scheme 4.7). In this case, the same synthetic strategy was applied starting from the commercially available 2-bromo-arylaldehydes (55, 57, 58) in combination with different boronic acids (56, 59, 60). Finally, the obtained boronic acid intermediates (65a–65e) were reacted with 48 via a Suzuki cross-coupling reaction, affording the desired DSI catalysts (17l–17p).
Scheme 4.7 Synthesis of phenanthrene boronic acid derivatives 65a–65e.

To our delight, the newly designed catalysts led to higher enantioselectivities when compared to the parent catalyst 17g in the asymmetric protonation of the model substrate 31a (Scheme 4.8). In particular, a significant increase of enantioselectivity was achieved when position 1, 3 and 6 were substituted with a methyl group (17o and 17p, 96:4 er).
Results and Discussion

Scheme 4.8 Evaluation of differently substituted phenantrenes in the 3,3’-positions of the DSI.

4.1.5 Substrate Scope

Encouraged by these promising results, we explored a variety of differentially-substituted bis-SKAs (Scheme 4.9). Various alkyl substituents were well tolerated in the asymmetric protonation, including a longer alkyl chain (32b, 96:4 er) and a benzyl group (32d, 95:5 er). However, substitution of the alkyl unit with an isopropyl group (32c) resulted in diminished enantioselectivity (70.5:29.5 er), suggesting that the enantioinduction of this catalytic system is extremely sensitive to the size of R1 and R2. Ortho- (32e, 97:3 er, and 32h, 95:5 er) and para-substitution (32g, 95:5 er) on the aromatic unit proved to be superior to meta-substitution (32f, 92:8 er). Both electron-rich (32e-32g) and electron-deficient (32h-32j) aromatic substituents displayed a similar position-dependent selectivity pattern. Non-steroidal anti-inflammatory drugs (NSAIDs)-derived bis-SKAs showed an analogous trend, where para-substituted starting materials (32o and 32p) gave slightly higher enantioselectivities than meta-substituted ones (32l and 32n). As observed in previous DSI-catalyzed transformations, the enantioselectivity of this method is dependent on an α-aromatic-α-alkyl substitution pattern, as α,α-dialkyl substrates, such as carboxylic acid 32k, were obtained in essentially racemic form.\cite{12b}
Results and Discussion

Scheme 4.9 Substrate scope of the enantioselective protonation of bis-SKAs.

As already mentioned in Table 4.1, consistent results were also obtained when using water as a PS (3a, 95:5 er, and 3m, 95.5:4.5 er) (Table 4.6). However, initial results were non reproducible because the addition of 0.55 equiv. of water (6 µL, in a 0.2 mmol scale of 31a) in CH₂Cl₂ (1 mL) in a single portion resulted to a heterogeneous system (liquid/liquid). Therefore, the 0.55 equiv. of water were initially dissolved in CH₂Cl₂ reaching a saturated solution. The stock solution of water in CH₂Cl₂ was then added via syring pump to the reaction mixture. Reproducible and consistent results could be obtained with this setup.
**Results and Discussion**

**Table 4.6** Enantioselective protonation of *bis*-SKAs using water as the PS.

![Chemical reaction image](image)

**Mechanistic Investigations**

4.1.6 To gain insight into the reaction mechanism, we studied the effect of the PS on the conversion and stereochemical outcome (Table 4.7). In the absence of a PS, a conversion equal to the catalyst loading was observed (Entries 1 and 2), suggesting that the substrate is only protonated by the catalyst. Turnover was only observed upon adding a stoichiometric amount of PS (Entries 3 and 4). Notably, enantioselectivities consistently proved to be independent of the PS (Entries 4-6), suggesting that the stoichiometric PS is not involved in the enantiodetermining step. Furthermore, a sub-stoichiometric amount of water also enabled full conversion (Entry 7), as the 0.5 equiv. of silanol, formed during the protodesilylation of the SKA, acts as an efficient PS, ultimately generating hexamethyldisiloxane.
Table 4.7 Reaction mechanism investigation

<table>
<thead>
<tr>
<th>Entry</th>
<th>PS (equiv.)</th>
<th>mol% D</th>
<th>conv.</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–</td>
<td>50</td>
<td>~50%</td>
<td>nd</td>
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<tr>
<td>2</td>
<td>–</td>
<td>100</td>
<td>full</td>
<td>95.5:4.5</td>
</tr>
<tr>
<td>3</td>
<td>MeOH (1.0)</td>
<td>50</td>
<td>full</td>
<td>95.5:4.5</td>
</tr>
<tr>
<td>4</td>
<td>MeOH (1.1)</td>
<td>1</td>
<td>full</td>
<td>95.5:4.5</td>
</tr>
<tr>
<td>5</td>
<td>DMP (1.1)</td>
<td>1</td>
<td>full</td>
<td>95.5:4.5</td>
</tr>
<tr>
<td>6</td>
<td>H$_2$O (1.1)</td>
<td>1</td>
<td>full</td>
<td>95:5</td>
</tr>
<tr>
<td>7</td>
<td>H$_2$O (0.55)</td>
<td>1</td>
<td>full</td>
<td>95:5</td>
</tr>
</tbody>
</table>

We speculate that the high efficiency of our catalytic system, compared to that of the racemic background reaction, is a result of a relatively fast protodesilylation event depicted in the proposed transition state (TS) (Scheme 4.10), which likely exploits the bifunctionality of the DSI with its high N–H acidity and concomitant Lewis basicity of the S=O bond, in combination with the oxophilicity of the silicon group. An analogous protodesilylation event can be envisioned for the re-protonation of 66 by the achiral PS, overall resulting in a fast and efficient enantioselective protonation. In this scenario, the background reaction between 31a and the achiral PS is avoided by the high efficiency of the catalytic system without the need of a bulky PS, thereby improving the atom economy of the protonation step.
4.1.7 Enantioselective Deuteration of bis-SKAs

The robustness of this catalytic system to any PS also provided direct access also to the corresponding deuterated products (67a, 95.5:4.5 er, and 67b, 95.5:4.5 er), achieving the first organocatalytic enantioselective deuteration of bis-SKAs with D$_2$O or CD$_3$OD (Scheme 4.11). Moderate enantioselectivity was obtained with a monosubstituted bis-SKA, furnishing enantioenriched α-deuterated phenylacetic acid 67c with an er of 81:19.
Results and Discussion

**Scheme 4.11** Enantioselective deuteration of bis-SKAs.

### 4.1.8 Deracemization Sequence

To illustrate the practicality of our method, a late stage deracemization of Ibuprofen® (32o) was performed on a multigram scale (Scheme 4.12). Starting from 5 g of (±)-32o, stoichiometric amounts of TMSCl and LDA were added. The resulting suspension was concentrated and LiCl was filtered, furnishing ketene acetal 31o in >95% purity (determined by $^1$H NMR), which was used without further purification. Subsequently, solvent and catalyst (1 mol%) were directly added to bis-SKA 31o and 1.1 equiv. of MeOH was added over 30 min. Upon extraction, the final product was isolated in 95% yield and 95:5 er; furthermore, the catalyst could also be recycled upon extraction, followed by acidification, in quantitative yield.

**Scheme 4.12** Chromatography-free preparative deracemization of (±)-Ibuprofen® (32o).
4.1.9 Conclusions

In summary, we have developed a deracemization of α-branched aryl carboxylic acids based on the asymmetric Brønsted acid-catalyzed protonation of the corresponding bis-SKAs in the presence of methanol or water. The operationally simple protocol allows a facile transformation under mild reaction conditions and exclusively furnishes the enantioenriched products in almost quantitative yields starting from the corresponding racemic acids without the need for additional purification. We suggest that the bifunctional activation mode of the DSI catalyst enables a highly efficient catalytic cycle that in turn circumvents racemic background reactivity with the achiral, stoichiometric PS. The late stage deracemization of NSAIDs on gram scale and the simple direct enantioselective deuteration of bis-SKAs using CD$_3$OD or D$_2$O as deuterium source demonstrate the applicability of the developed system.
Results and Discussion
4.2 Asymmetric α-Aminomethylation for the Direct Synthesis of Unprotected β-Amino Acids

The work presented in this section was performed in collaboration with Dr. Chendan Zhu.

4.2.1 Reaction Design and Optimization

Inspired by the work of Morimoto et al.,[100] an initial experiment was conducted using bis-SKA 31q and bis-silylated hemiaminal 38 in the presence of a catalytic amount of (S)-DSI 17a as the pre-catalyst. An apolar solvent (toluene) was chosen to enable the formation of a tight ion pair between the iminium ion formed in situ and the chiral counteranion, as proposed in an ACDC scenario. A small excess of the bis-SKA (1.2 equiv.) was added to a solution containing the catalyst 17a, in order to (a) ensure the full activation of the catalyst by silylation and (b) convert each available source of protons to TMS$_2$O according to the self-healing cycle (see section 2.2.5.1). Subsequently, the electrophilic aminomethylating reagent was added. The targeted reaction (Scheme 4.13) proceeded within 1 hour in quantitative yield (Note: yield was determined by $^1$H NMR analysis of the crude reaction mixture using mesitylene as an internal standard) and moderate yet promising enantioselectivity (61:39 er).

Scheme 4.13 Initial result for the asymmetric aminomethylation of bis-SKA 31q; $^a$ NMR yield measured with mesitylene as internal standard. $^b$ The enantiomeric ratio of the product was determined by chiral phase HPLC analysis, without further derivatization using Chirobiotic T2 (for further details, see Experimental Part).
These results motivated us to explore the catalytic ability of different Brønsted acid pre-catalysts (Scheme 4.14). In the case of (S)-TRIP 20 (pKₐ in CH₃CN = 13.6), IDP 19b (pKₐ in CH₃CN = 11.3) and iIDP 46 (pKₐ in CH₃CN = 9.1) no reaction occurred, as due to their low acidity presumably an irreversible silylation of the corresponding catalysts takes place. BALT catalysts 45a and 45b (pKₐ in CH₃CN = -2.8) and IDPi 47a (pKₐ in CH₃CN = 4.5) catalyzed the targeted reaction, however without any induction of enantioselectivity. Gratifyingly, DSIs 17a (pKₐ = 8.5) and 17g gave the desired products in moderate enantioselectivities (61:39 er and 59:41 er respectively). We therefore decided to continue our investigations with the DSI motif (17a).

![Scheme 4.14 Initial screening for the most suitable catalyst motif.](image)

### 4.2.1.1 Exploration of DSI Catalysts

The initial screening of solvents and temperatures showed that apolar solvents were required and lowering the temperature down to -60 °C improved the enantioselectivity of the transformation. In particular, the targeted product was obtained in an enantioselectivity up to 78.5:21.5 er, in toluene at -60 °C. Using n-
hexane as the solvent resulted in comparable 76.5:23.5 er at –40 °C. However, at –60 °C, the enantioselectivity decreased to 69:31 er, probably due to the lower solubility and hence lower reactivity of the catalyst under these conditions (Table 4.8). In each case, the reaction profile was very clean and the substrates converted exclusively to the desired product. Therefore, yields will not be reported for all the initial screenings, unless they do not match with the conversion.

**Table 4.8** Effect of temperature and solvent.

```
<table>
<thead>
<tr>
<th>er</th>
<th>CH₂Cl₂</th>
<th>EtOAc</th>
<th>Et₂O</th>
<th>PhMe</th>
<th>n-hexane</th>
</tr>
</thead>
<tbody>
<tr>
<td>–40 °C</td>
<td>53:47</td>
<td>67:33</td>
<td>71:29</td>
<td>76:24</td>
<td>76.5:23.5</td>
</tr>
</tbody>
</table>
```

Additional parameters were tested, including molarity (0.01, 0.05, 0.1, 0.5 and 1 M) (Table 4.9), catalyst loading (0.1, 0.5, 1, 2 and 5 mol%) (Table 4.10) and different stoichiometries of 31q (2, 5 and 10 equivalents) (Table 4.11). However, these parameters had no particular effect on the enantioselectivity of the reaction.
### Table 4.9 Effect of molarity in toluene. \[^{[a]}\] NMR yield measured with mesitylene as internal standard.

$$\text{Ph} \quad \text{OTMS} \quad \text{+ TMS} \quad \text{N} \quad \text{OMe} \quad 17a (1 \text{ mol}) \quad \text{PhMe (xx M)} \quad \text{NMR yield measured with mesitylene as internal standard.}$$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conc. (M)</th>
<th>yield (%)[^{[a]}]</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.01</td>
<td>73</td>
<td>77:23</td>
</tr>
<tr>
<td>2</td>
<td>0.05</td>
<td>&gt;95</td>
<td>76:24</td>
</tr>
<tr>
<td>3</td>
<td>0.1</td>
<td>&gt;95</td>
<td>76:24</td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>93</td>
<td>75:25</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>81</td>
<td>74:26</td>
</tr>
</tbody>
</table>

### Table 4.10 Effect of the catalyst loading. \[^{[a]}\] NMR yield measured with mesitylene as internal standard.

$$\text{Ph} \quad \text{OTMS} \quad \text{+ TMS} \quad \text{N} \quad \text{OMe} \quad xx (xx \text{ mol}) \quad \text{PhMe (0.2 M)} \quad \text{NMR yield measured with mesitylene as internal standard.}$$

<table>
<thead>
<tr>
<th>Entry</th>
<th>xx (mol %)</th>
<th>yield (%)[^{[a]}]</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>6</td>
<td>70:30</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>30</td>
<td>75:25</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>&gt;95</td>
<td>76:24</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>&gt;95</td>
<td>76:24</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>86</td>
<td>76:24</td>
</tr>
</tbody>
</table>
Results and Discussion

Table 4.11 Effect of the stoichiometry of the bis-SKA. [a] NMR yield measured with mesitylene as internal standard.

<table>
<thead>
<tr>
<th>Entry</th>
<th>xx (equiv.)</th>
<th>yield (%)[a]</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2</td>
<td>95</td>
<td>76:24</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>&gt;95</td>
<td>76:24</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>&gt;95</td>
<td>76:24</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>&gt;95</td>
<td>76:24</td>
</tr>
</tbody>
</table>

Thus, the same reaction conditions were maintained to evaluate the effects of the substituents in the 3,3'-positions of the DSI catalyst (Scheme 4.15). Modifications of the substituents in the meta-positions decreased the enantioselectivity (17c 71:29 er and 17q 62:38 er) and any substituent in para-position resulted in either low enantioselectivity (17r 58:42 er) or racemic products (17s 51:49 er). Catalysts with lower acidities, such as the ones with extended aromatic substituents, gave lower enantioselectivities (17g 70:30 er, 17h 68:32 er and 17t 69:31 er) and yields (usually in the range of 10–15% NMR yield). In these cases the aminomethylating reagent was fully decomposed forming the tris-silylated 1,3,5-triazine 70 and unreacted bis-SKA 31q remained in the reaction mixture. A possible explanation for the observed side-reaction could be that the nucleophilic attack of the bis-SKA is slowed down due to the decreased Lewis acidity, giving the in situ generated iminium ion 69 more time to react with itself. In agreement with this explanation, the presence of EWGs (17b) increased the acidity of the catalysts and resulted in quantitative yields, however without improving the enantioselectivity (71:29 er).
**Results and Discussion**

Scheme 4.15 Effects of the substituents in the 3,3'-positions of the DSI catalysts. NMR yield measured with mesitylene as internal standard.

The observed levels of enantioselectivity were only moderate to good at this point and there was no clear direction on how to improve them. On the other hand, the results were encouraging as the model substrate was aliphatic, and DSI catalysts have typically been only successful with aromatic substrates (as mentioned in section 2.2.5.1). However, when aromatic substrate 31r was tested, lower reactivity but similar enantioselectivity was observed. The lower reactivity could be explained by the decreased nucleophilicity of the substrate, as the HOMO of 31r is stabilized by conjugation. Higher temperatures were required as no conversion of the starting material could be observed below –20 °C. Regarding the substituents on the catalyst,
a similar trend as for the previous substrate was observed: Whereas different meta-substituted aryl groups gave similar or lower enantioselectivities (17c 60:40 er and 17q 58:42 er), para-substituted ones afforded only racemic product (17r and 17s). The moderate enantioselectivity of 17g was accompanied by mainly decomposition of 38 and thus low yield. Similar behavior could be observed for 17h and 17t. The best result is this series was obtained using 17b (quantitative yield, 63:37 er), however, this result could not be improved by further optimizations (Scheme 4.16).

Scheme 4.16 Effect of substituents in the 3,3'-positions of the DSI catalysts. \[a\] NMR yield measured with mesitylene as internal standard.

As already pointed out in section 2.2.5.2, the DSI motif has structural limitations compared to the IDPis. Indeed, DSI can bear different 3,3'-substituents and modifications on 5,5'- and 6,6'-positions have been reported. In addition to all the previously mentioned possibilities of modification, IDPis can be further modified in proximity to the catalytically active site, by variation of the sulfonimidic residue in the core of the catalyst. Based on our initial results, we concluded that IDPis were
sterically too confined to incorporate the intermediate iminium-ion thus resulting in low or no enantioinduction in the targeted reaction. Reaching this point in our investigations, we questioned whether we discarded the IDP\textsubscript{i} motif too early, as it offers an additional possibility for modifications at the catalyst’s core, allowing a more accurate design of the required key chiral counteranion. We therefore decided to reinvestigate and further explore the catalytic abilities of the IDP\textsubscript{i} motif by testing different combinations of substituents in the 3,3’-positions and sulfonimidic residues.

### 4.2.2 Examination of IDP\textsubscript{i} Catalysts

We began our investigations by comparing the reactivity of IDP\textsubscript{i} 47\textit{f} and DSI 17\textit{a} using 31\textit{r} as the starting material. A series of reaction parameters (e.g. solvent polarity, concentration, catalyst loading and reaction time) were evaluated for both catalysts in parallel (Table 4.12). When performed in toluene (0.5 M) at room temperature, a clean reaction profile was observed using 2 mol\% of DSI 17\textit{a}, giving the targeted product in 91\% yield and 60:40 er (Entry 1). Using IDP\textsubscript{i} 47\textit{f} under the same reaction conditions resulted in significant formation of by-products, mainly due to Claisen condensation. The desired product could be obtained in 75\% yield, however in racemic form. Decreasing the temperature had different impact on the two catalytic systems: With 17\textit{a} no significant change in enantioselectivity was observed, however the reactivity decreased until no reaction could be obtained below –40 °C (Entries 2–4). Gratifyingly, with 47\textit{f}, the lower temperatures decreased the amount of side products, resulting in a cleaner reaction profile and the enantioselectivity increased to 60:40 er (Entries 3 and 4). Further modifications of the reaction parameters for DSI 17\textit{a}, such as the catalyst loading, molarity or solvent polarity did not improve the enantioselectivity (Entries 5–9). With IDP\textsubscript{i} 47\textit{f} on the other hand, increased catalyst loading lead to by-product formation (Entry 5, 93\% yield instead of 99\% yield of Entry 4), a higher concentration decreased the enantioselectivity (Entry 6, 56:44 er) and a lower concentration slowed down the reaction rate, yet with a cleaner reaction profile (Entry 7, 41\% yield at 42\%
conversion, 62:48 er). As already previously shown, the choice of the solvent was not a determining parameter for the enantioselectivity (Entries 4, 8 and 9).

**Table 4.12** Parallel screening of reaction conditions using DSI 17a and IDPi 47f; [a] NMR yield measured with mesitylene as internal standard.

<table>
<thead>
<tr>
<th>Entry</th>
<th>mol%</th>
<th>Conc. (M)</th>
<th>solvent</th>
<th>T (°C)</th>
<th>yield (%)</th>
<th>er</th>
<th>T (°C)</th>
<th>yield (%)</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>0.5</td>
<td>PhMe</td>
<td>rt</td>
<td>91</td>
<td>60:40</td>
<td>rt</td>
<td>75</td>
<td>50:50</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>0.5</td>
<td>PhMe</td>
<td>0</td>
<td>69</td>
<td>60:40</td>
<td>0</td>
<td>86</td>
<td>50:50</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>0.5</td>
<td>PhMe</td>
<td>−20 °C</td>
<td>13</td>
<td>61:39</td>
<td>−20 °C</td>
<td>99</td>
<td>60:40</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
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<td>PhMe</td>
<td>−40 °C</td>
<td>nd</td>
<td>nd</td>
<td>−40 °C</td>
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</tr>
<tr>
<td>5</td>
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<td>0.5</td>
<td>PhMe</td>
<td>rt</td>
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<td>−40 °C</td>
<td>93</td>
<td>61:39</td>
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<tr>
<td>6</td>
<td>2</td>
<td>1</td>
<td>PhMe</td>
<td>rt</td>
<td>64</td>
<td>58:42</td>
<td>−40 °C</td>
<td>99</td>
<td>56:44</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>0.05</td>
<td>PhMe</td>
<td>rt</td>
<td>26</td>
<td>61:39</td>
<td>−40 °C</td>
<td>41</td>
<td>62:38</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>0.5</td>
<td>CHCl₃</td>
<td>rt</td>
<td>90</td>
<td>60:40</td>
<td>−40 °C</td>
<td>99</td>
<td>62:38</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>0.5</td>
<td>Et₂O</td>
<td>rt</td>
<td>86</td>
<td>60:40</td>
<td>−40 °C</td>
<td>86</td>
<td>62:38</td>
</tr>
</tbody>
</table>

With these reaction conditions in hand, a screening of IDPi catalysts employing a variety of aryl-substituents in the 3,3′-positions (Ar) and sulfonimidic residues in the core of the catalyst (R) (Scheme 4.17) was performed. In order to obtain a comprehensive overview of the electronic and steric effects of the substituents in the 3,3′-positions of the catalyst, aryl-groups having ortho, meta- (47b and 47g), mono-meta- (47c), para-EDGs (47d and 47h), and para-(47e) or meta, meta-EWGs (47f and 47i) were tested in combination with CF₃- or C₆F₅- groups in the catalyst core. It could be shown that catalysts containing aromatic sulfonamide-derived cores afforded either lower yields (47g, 19% yield, full degradation of 38 to undefined
polymers according to $^1$H NMR analysis of the crude reaction mixture) or lower enantioselectivity (47i, 50:50 er).

Scheme 4.17 Evaluation of different aromatic substituents in the 3,3'-positions (Ar) and cores (R). \textsuperscript{[a]}Reactions quenched with Et$_3$N after 16 hours; \textsuperscript{[b]}Reactions quenched with Et$_3$N after 3 days.

As no clear lead could not be identified due to the generally low obtained enantioselectivities, systematic investigations of each individual structural and electronic parameter were performed. Catalysts having electron-withdrawing para-substituents (47e), meta,meta-substituents (47f) and electron-donating para-substituents (47d) at the aryl-groups in the 3,3'-positions were combined with a variety of sulfonimidic substituents. Due to the high acidity and therefore increased
reactivity of the resulting IDPis, they were tested at –60 °C, in contrast to catalysts (47s–47v) equipped with aromatic cores, which were tested at room temperature (Scheme 4.18). Changing the p-CF₃-substituent to a p-SF₅-group had no impact on the enantioselectivity (47l, 62:38 er). To our delight, modifications of the catalyst’s core to a longer perfluorinated alkyl chain (47m, 69:31 er), to an electron-poor aryl group (47n, 76:24 er) or to an electron-poor terphenyl group (47o, 79:21 er) increased the enantiomeric excess of the desired product. Similar modifications of 47f did not influence the enantioselectivity in the same amount (47p, 53:47 er and 47r, 61:39 er), thus further catalysts in this series were not tested. The combination of para-tert-butyl-substituted aryl-groups in the 3,3′-positions and aromatic cores diminished the reactivity, however the enantioselectivity was increased (47s, 20% conv. and 64.5:35.5 er, 47t, 1% conv. and 78:22 er, 47u, 20% conv. and 61:39 er). Due to the low reactivity of the latter catalysts, the temperature had to be raised to room temperature in order to obtain some conversion of the starting material. IDP/47s in particular showed the same level of enantioselectivity under these reaction conditions as 47t at –60 °C, yet only with 1% yield. We therefore concluded that the catalyst should include electron-rich 3,3′-substituents; therefore, acidity and reactivity should be adjusted by suitable modification of the core. We envisioned that ideally we could identify a catalyst which would be reactive enough to allow us to improve enantioselectivity by decreasing the temperature.
Results and Discussion

We identified 2-fluorenyl as a promising substituent at the 3,3'-positions of the IDPi catalyst (a selection of the tested catalysts is shown in Scheme 4.19). A library of catalysts consisting of (a) various perfluorinated alkyl-chains in the core and (b) fluorenyl-derived spiro-substituents were prepared and evaluated using bis-SKA 31r as the starting material. Based on the obtained results, we concluded that an increased length of the perfluorinated alkyl chain leads to a slight increase in enantiomeric excess. When comparing different fluorenyl-substituents, the 5-membered ring-containing motif was consistently more selective than the other ones tested. Moreover, the majority of the catalysts afforded full conversion and quantitative yields within 3 days. The only catalysts that showed lower conversions were those containing a perfluorinated aromatic ring in the core (48f, 49f and 50f).
The best result within this series was obtained using the catalyst with the fluorenlyl-3,3′-substituents 49 and \( n-C_8F_{17} \) as perfluorinated alkyl chain in the core (49e), giving the desired product in 92% yield and 82:12 er.

Scheme 4.19 Screening of the fluorenlyl-based IDPi library. NMR yield measured with mesitylene as internal standard given.

A similar series of screenings were performed using the aliphatic substrate 31q (Scheme 4.20). To our delight, enantioselectivities obtained with this substrate were overall higher when compared with the aromatic bis-SKA 31a. Nevertheless, this system follows the same trends as previously observed: Increased enantioselectivity was achieved upon elongation of the perfluorinated alkyl chain, reaching a maximum using \( n-C_6F_{13} \) and \( n-C_8F_{17} \) (88:12 er for both, 71i and 71j).
Results and Discussion

Scheme 4.20 Screening of 5-membered ring containing fluorenyl-derived IDPi catalysts with substrate 31q. NMR yield measured with mesitylene as internal standard.

As the best catalyst (71j) strongly differs by means of sterics and electronics from the catalyst (47f) used for the initial optimization, we decided to reevaluate the reaction conditions by rescreening some crucial reaction parameters (Table 4.13). To our delight, using n-pentane (Entry 4) and n-hexane (Entry 5), the desired product was obtained in quantitative yield and improved enantioselectivity (93:7 er and 93.5:6.5 er respectively).
Table 4.13 Optimization of the reaction conditions using 71j. \[^{[a]}\] NMR yield measured with mesitylene as internal standard.

<table>
<thead>
<tr>
<th>Entry</th>
<th>solvent</th>
<th>yield (%[^{[\text{dil}}]</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe</td>
<td>83</td>
<td>87:13</td>
</tr>
<tr>
<td>2</td>
<td>CyH</td>
<td>90</td>
<td>91.5:9.5</td>
</tr>
<tr>
<td>3</td>
<td>MeCy</td>
<td>99</td>
<td>93:7</td>
</tr>
<tr>
<td>4</td>
<td>(n)-pentane</td>
<td>99</td>
<td>93:7</td>
</tr>
<tr>
<td>5</td>
<td>(n)-hexane</td>
<td>90</td>
<td>93.5:6.5</td>
</tr>
<tr>
<td>6</td>
<td>(n)-heptane</td>
<td>97</td>
<td>93:7</td>
</tr>
</tbody>
</table>

Regarding concentration and catalyst loading, we could confirm our previous findings with the catalytic system having an optimum at 0.2 \(\text{M}\) and 1 \(\text{mol}\%\) of 71j (Table 4.14, Entry 2). The use of lower catalyst loadings was possible without deterioration of the enantioselectivity; however, the reaction rate was reduced (Entry 6).
Table 4.14 Optimization of the reaction conditions using 71j. \(^{[a]}\) NMR yield measured with mesitylene as internal standard.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conc. (M)</th>
<th>mol% 71j</th>
<th>yield (%)(^{[a]})</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>1</td>
<td>95</td>
<td>93:7</td>
</tr>
<tr>
<td>2</td>
<td>0.2</td>
<td>1</td>
<td>90</td>
<td>93.5:6.5</td>
</tr>
<tr>
<td>3</td>
<td>0.1</td>
<td>1</td>
<td>86</td>
<td>93.5:6.5</td>
</tr>
<tr>
<td>4</td>
<td>0.05</td>
<td>1</td>
<td>83</td>
<td>94:6</td>
</tr>
<tr>
<td>5</td>
<td>0.2</td>
<td>5</td>
<td>90</td>
<td>92:8</td>
</tr>
<tr>
<td>6</td>
<td>0.2</td>
<td>0.2</td>
<td>71</td>
<td>93.5:6.5</td>
</tr>
</tbody>
</table>

As the target level of enantioselectivity (> 95:5 er) could not be achieved by further optimization of the reaction conditions, we focused our attention back on optimizing the catalysts structure by further modification of core and/or the 3,3’-substituents. An easily accessible modification of the core was the extension of the length of the alkyl chain to n-C\(_{10}\)F\(_{21}\) (Scheme 4.21). The required sulfonamide 75 was synthesized starting from the commercially available iodide 72 by first transforming it into the corresponding sulfonic acid 73. Oxidation in the presence of an electrophilic fluorine source and subsequent treatment with ammonia gave 75. Finally, catalyst 71r could then be obtained using the established lDPi synthesis, by the reaction of phosphazene reagent 76, resulting from the reaction of 75 and PCl\(_5\), and BINOL-derivative 77.
Results and Discussion

Scheme 4.21 Synthesis of C_{10}F_{21} core-containing catalyst (71r).

Unfortunately, the newly designed core did not improve the enantioselctivity of the reaction (Table 4.15).

**Table 4.15** Asymmetric aminomethylation using 71j. [a] NMR yield measured with mesitylene as internal standard.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>pentane</td>
<td>&gt;90</td>
<td>94:6</td>
</tr>
<tr>
<td>2</td>
<td>hexane</td>
<td>&gt;90</td>
<td>93.5:6.5</td>
</tr>
</tbody>
</table>

Due to low commercial availability of alternative precursors for synthetizing perfluorinated alkyl chains, we decided to focus on the modification of the fluorenyl substituents. However, before investing additional tedious efforts into multi-step synthesis of new catalysts, we initiated preliminary investigations of the reaction mechanism, aiming to identify strategic positions for modification.
4.2.3 Mechanistic Insights Lead to a New Catalyst Design

A proposed catalytic cycle is depicted in Figure 4.2, including a schematic representation of the catalyst in which the 3,3'-fluorenyl substituents are highlighted in black and the perfluoroalkyl chain on the sulfonimidic residue in purple. After the initial drying/self-healing cycle (introduced in Section 2.2.5.1), the key steps are (a) the activation of the electrophilic substrate (38), forming a tight ion pair between the anionic catalyst (49f) and the cationic electrophile (iminium ion 69) and (b) the enantiodetermining step in which the bis-SKA 31q attacks onto the electrophile, giving the silylated product (79) and the silylated catalyst (78).

**Figure 4.2** Proposed catalytic cycle.
Results and Discussion

In the first step, the silylium ion in the active site of the catalyst is attacked by the oxygen of the electrophile, and TMSOMe is liberated, leaving the bis-silylium iminium ion coordinated to the IDPi. In support of this mechanism, an additional aminomethylating reagent (80) was prepared and subjected to the reaction conditions. Following the proposed reaction mechanism, after the initial activation of 38 or 80, the formed iminium ion (69) and the derived ion pair should be the same, and the enantioselectivity of the reaction should not be affected. Indeed, the use of 38 (R = Me) or 80 (R = Bn) afforded very similar enantioselectivities (93:7 er and 92:8 er, respectively) (Scheme 4.22).

Scheme 4.22 Preliminary mechanistic studies: use of 38 or 80 as aminomethylating reagent. NMR yields measured with mesitylene as internal standard given.

The proposed stereochemical model depicted in Figure 4.3 supports the observed trends in catalyst design, namely (a) a clear influence of the size of the spiro-cycle in the fluorenyl substituent (4, 5 or 6 membered ring) and (b) the influence of the perfluoroalkyl chain up to a certain length of the residue. Based on this model, we reasoned that introducing an additional EDG substituent in 7-position of the fluorenyl group might influence the enantioselectivity for two reasons: (1) an electron-rich aromatic unit could favor the stabilization of cation in the crucial ion pair, and (2) the additional steric bulk may remotely influence the access to the active site or the rearrangement of the neighboring groups.
In influencing parameters for enantioselectivity:
- size of the spiro-cyclo ring
- length of the perfluoroalkyl chain
- Potential influencing positions
- introduce EDGs (e.g., Alk) or aryl groups

Figure 4.3 Proposed stereochemical model.

4.2.4 Final Catalyst Optimization

In order to validate these assumptions, a series of catalysts were prepared in which the fluorenyl-substituents were additionally substituted in either the 6- or 7-positions. C$_8$F$_{17}$ were chosen as the substituents in the core (Scheme 4.23). To our delight, all the modifications performed in position 7 increased the enantioselectivity. A methyl group (71s) influenced the steric properties and the electron-density of the system enough giving the desired product in 96:4 er. The bulkier tert-butyl-substituted analogue resulted in the same enantiomeric excess (71t, 96:4 er) and a longer alkyl chain (71v) or a phenyl group (71w) did not afford the desired enantioselectivity (>95:5 er). Moreover, substitution in position 6 with a tert-butyl group even decreased the enantioselectivity to 90.5:9.5 er (71u).
Scheme 4.23 Screening of 6- and 7-substituted fluorenyl derivatives.
4.2.5 Substrate Scope

Finally, with this set of catalysts in hand, we set out to explore the scope of this transformation. As this is currently under investigation in our laboratory, only preliminary results using IDPis 71s and 71t are depicted in Scheme 4.24. Both catalysts delivered the desired products in high yields (>90%), however their performances differ in selectivity. Whereas the tert-butyl-substituted catalyst 71t delivered aliphatic substrates (R=Alk) in slightly higher enantioselectivities, the Me-substituted catalyst 71s was better with the single tested aryl-substituted substrate 31a (R=Ph).

Preliminary substrate scope. NMR yields measured with mesitylene as internal standard given.

While this thesis is being written, experiments to fully investigate the discovered process are ongoing and are expected to lead to a successful completion of the project in due course.
Outlook and Conclusion

In summary, we have developed the first asymmetric organocatalytic α-aminomethylation of bis-SKAs, enabling direct access to unprotected β²-amino acids under Lewis acidic conditions. The newly designed catalyst, upon activation of the aminomethylating reagent, forms a tight ion pair with the bis-silylated iminium ion, formed \textit{in situ}, and controls the enantiotopic differentiation of the nucleophilic bis-SKA. The enantioenriched silylated products are formed in quantitative yields and a mild acidic workup, or simply protic conditions, liberates the unprotected β²-amino acid. The final compounds can be isolated quantitatively upon precipitation and filtration, without additional purification steps. Currently, investigation of the generality of the developed method is under examination; the developed methodology will be applied in the synthesis of biologically active compounds, such as Alvimopan\textsuperscript{®} and Rhopressa\textsuperscript{®} (Figure 4.4).

\textbf{Figure 4.4} Candidates for the application of the developed enantioselective aminomethylation.
Summary
5 Summary

Strong Brønsted acids can be converted in strong Lewis acids upon silylation with a suitable reagent. This ambivalent feature was fully exploited in this thesis (Scheme 5.1).

Scheme 5.1 Enantioselective protonation and enantioselective aminomethylation of bis-SKAs.

5.1 Catalytic Asymmetric α-Protonation with Water and α-Deuteration with D₂O

In the first part of this thesis, we exploited this cycle to protonate enantioselectively bis-SKAs using simple PSs (e.g. water). We showed that Brønsted acid DSI 17o enabled the facial recognition of the bis-SKA and afforded the corresponding carboxylic acids in high yields and enantioselectivities (Scheme 5.2).
Summary

Scheme 5.2 Catalytic Asymmetric $\alpha$-Protonation with a simple PS.

The application of this method in the late stage deracemization of Ibuprofen proved the potential and utility of this strategy (Scheme 5.3).

Scheme 5.3 Late stage deracemization of NSAIDs with DSI.

The greater advantage of this methodology relies on the possibility to use any PS; this enabled the use of D$_2$O or CD$_3$OD for the enantioselective deuteration of bis-SKAs and allowed an easier access to enantioenriched $\alpha$-deuterated carboxylic acids. A particularly interesting substrate was 67c, in which we introduced a stereogenic center upon deuteration (Figure 5.1). Further development of a highly enantioselective deuteration could open the access to this class of compounds, which is not particularly explored yet.

Figure 5.1 Enantioselective deuteration of bis-SKAs with CD$_3$OD.
5.2 Catalytic Asymmetric $\alpha$-Aminomethylation

In the second part of this thesis, we exploited the Lewis acidity of the silylated IDPi $71s$ for the *in situ* formation of a highly reactive protected iminium ion and subsequent reaction with a *bis*-SKA, affording unprotected $\beta^2$-amino acids in an enantioselective fashion.

Until now, ACDC was widely applied in enantioselective transformations in which the activated electrophile would initially interact in a tight ion pair with the catalyst providing a chiral environment. Subsequently, the nucleophile preferentially attacks from one side onto the catalyst-electrophile complex, generating a stereogenic center on the former electrophile. However, this differs in the reported aminomethylation. While the activation of the electrophile follows the same logic, the stereogenic center formed by the attack of the nucleophile is located on the nucleophile itself (Figure 5.2). The targeted $\alpha$-aminomethylation of *bis*-SKAs was achieved by using $71s$ or $71t$ as the Lewis acid catalyst. The unprotected $\beta^2$-amino acids were obtained in quantitative yields and high enantioselectivities.

![Figure 5.2 Enantioselective $\alpha$-aminomethylation of *bis*-SKAs.](image)

Summary

In the second part of this thesis, we exploited the Lewis acidity of the silylated IDPi $71s$ for the *in situ* formation of a highly reactive protected iminium ion and subsequent reaction with a *bis*-SKA, affording unprotected $\beta^2$-amino acids in an enantioselective fashion.

Until now, ACDC was widely applied in enantioselective transformations in which the activated electrophile would initially interact in a tight ion pair with the catalyst providing a chiral environment. Subsequently, the nucleophile preferentially attacks from one side onto the catalyst-electrophile complex, generating a stereogenic center on the former electrophile. However, this differs in the reported aminomethylation. While the activation of the electrophile follows the same logic, the stereogenic center formed by the attack of the nucleophile is located on the nucleophile itself (Figure 5.2). The targeted $\alpha$-aminomethylation of *bis*-SKAs was achieved by using $71s$ or $71t$ as the Lewis acid catalyst. The unprotected $\beta^2$-amino acids were obtained in quantitative yields and high enantioselectivities.
6 Outlook

We have demonstrated that *bis*-SKAs are valuable intermediates for the enantioselective $\alpha$-functionalization of carboxylic acids. As mentioned in section 2.3.1, a wide selection of transformations have been reported in a non-asymmetric fashion. We believe that ACDC is a powerful concept that could enable access to their enantioselective equivalents. Among the many possible functionalizations, we envisioned a few interesting, yet very challenging, transformations:

(1) The $\alpha$-amination of *bis*-SKAs, to access $\alpha$-amino acids directly from the corresponding carboxylic acid. Unfortunately, a successful catalytic system has not been identified yet, since the selection of the electrophilic nitrogen source is crucial for the turnover of the catalyst. Particularly, under Lewis acidic conditions, any Lewis basic functionality (such as amines) forms stable salts with the catalyst and inhibits its reactivity.

(2) The $\alpha$-trifluoromethylation of *bis*-SKAs, to directly access the enantioenriched $\alpha$-trifluoromethylated carboxylic acids. In initial experiments we found that this transformation is possible under catalytic Lewis acidic conditions, however, only low enantioselectivity was observed. A highly Lewis acidic catalyst is required in order to outcompete the radical mechanism. Furthermore, the nature of the electrophilic trifluoromethylating reagent highly influences the reactivity and feasibility of the transformation.

This thesis opens the field of enantioselective Lewis acid-catalyzed $\alpha$-functionalizations of carboxylic acids *via* the formation of *bis*-SKAs intermediates. Ideally, an enantioselective catalytic system could be envisioned for each of the transformations previously reported in Section 2.3.1, exploiting the ACDC concept (Figure 6.1), in which the enantiopure Lewis acidic catalyst could control the formation of the positively charged electrophilic reagent and the nucleophilic attack by the *bis*-SKA.
Outlook

Figure 6.1 Potentially-accessible compounds from bis-SKAs upon asymmetric transformations.
7 Experimental Section

7.1 General Information and Instrumentation

Chemicals

Chemicals (Abcr, Acros, Aldrich, Gelest, Fluka, Fluorochem, Strem, TCI) were purchased as reagent grade and used without further purification unless indicated otherwise. Commercially available carboxylic acids were purchased from Sigma-Aldrich, Alfa Aesar, Acros Organics, AK Scientific, Apollo Scientific, Key Organics and Aronis. n-Butyllithium was purchased from Sigma-Aldrich (2.5 M solution in hexanes) and used directly as received. The reagent was titrated before use.

Solvents

Solvents (CH$_2$Cl$_2$, CHCl$_3$, Et$_2$O, THF, PhMe) were dried by distillation from an appropriate drying agent in the technical department of the Max-Planck-Institut für Kohlenforschung and received in Schlenk flasks under argon. Other solvents (acetone, benzene, cyclohexane, chlorobenzene, 1,4-dioxane, DME, DMF, DMSO, EtOAc, EtOH, MeCN, MeOH, MTBE, NMP, n-Bu$_2$O, n-hexane, n-octane, n-pentane, pyridine, xylenes) were purchased from commercial suppliers and dried over molecular sieves.

Inert Gas

Dry argon was purchased from Air Liquide with >99.5% purity.

Glassware

All non-aqueous reactions were performed in oven-dried (85 °C) or flame-dried glassware under Argon. Solvents were removed under reduced pressure at 40 °C using a rotary evaporator and drying under high vacuum (10$^{-3}$ mbar).
Thin Layer Chromatography

Thin layer chromatography (TLC) was performed using silica gel pre-coated plastic sheets (Polygram SIL G/UV254, 0.2 mm, with fluorescent indicator; Macherey-Nagel), which were visualized with a UV lamp (254 or 366 nm) and phosphomolybdic acid (PMA). PMA stain: PMA (20 g) in EtOH (200 mL). Preparative thin-layer chromatography was performed on silica gel pre-coated glass plates SIL G-25 UV254 and SIL G-100 UV254, with 0.25 mm and 1.0 mm SiO$_2$ layers, respectively (Macherey-Nagel).

Flash Column Chromatography

Flash column chromatography (FCC) was carried out using Merck silica gel (60 Å, 230−400 mesh, particle size 0.040−0.063 mm) using technical grade solvents. Elution was accelerated using compressed air. All reported yields, unless otherwise specified, refer to spectroscopically and chromatographically pure compounds.

Nomenclature

Nomenclature follows the suggestions proposed by the computer program ChemBioDraw (15.0.0.106) of CBD/Cambridgesoft.

Nuclear Magnetic Resonance Spectroscopy

$^1$H, $^{13}$C, $^{19}$F, $^{31}$P nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AV-500, AV-400 or DPX-300 spectrometer in a suitable deuterated solvent. The employed solvent and respective measuring frequencies are indicated for each experiment. Chemical shifts are reported with tetramethylsilane (TMS) serving as a universal reference of all nuclides and with two or one digits after the marker. The resonance multiplicity is described as s (singlet), d (doublet), t (triplet), q (quadruplet), p (pentet), hept (heptet), m (multiplet), and br (broad). All spectra were recorded at 298 K unless otherwise noted, processed with Bruker TOPSPIN 2.1 or MestReNova 11.0.2 suite of programs, and coupling constants are reported as observed. The
residual deuterated solvent signals relative to tetramethylsilane were used as the internal reference in $^1$H NMR spectra (e.g. CDCl$_3$ = 7.26 ppm), and are reported as follows: chemical shift $\delta$ in ppm (multiplicity, coupling constant $J$ in Hz, number of protons). $^{13}$C, $^{19}$F, $^{31}$P NMR spectra were referenced according to $\Xi$-values (IUPAC recommendations 2008) relative to the internal references set in $^1$H NMR spectra (e.g. $^{13}$C: Me$_4$Si, $^{19}$F: CCl$_3$F, $^{31}$P: H$_3$PO$_4$; each 0.00 ppm). All spectra are broadband decoupled unless otherwise noted.

**Mass Spectrometry**

Electron impact (EI) mass spectrometry (MS) was performed on a Finnigan MAT 8200 (70 eV) or MAT 8400 (70 eV) spectrometer. Electrospray ionization (ESI) mass spectrometry was conducted on a Bruker ESQ 3000 spectrometer. High resolution mass spectrometry (HRMS) was performed on a Finnigan MAT 95 (EI) or Bruker APEX III FTMS (7T magnet, ESI). The ionization method and mode of detection employed is indicated for the respective experiment and all masses are reported in atomic units per elementary charge ($m/z$) with an intensity normalized to the most intense peak.

**Specific Rotations**

Specific rotations were measured with a Rudolph RA Autopol IV Automatic Polarimeter at the indicated temperature with a sodium lamp (sodium D line, $\lambda$ = 589 nm). Measurements were performed in an acid-resistant 1 mL cell (50 mm length) with concentrations (g/(100 mL)) reported in the corresponding solvent.

**High Performance Liquid Chromatography**

High performance liquid chromatography (HPLC) was performed on Shimadzu LC-20AD liquid chromatograph (SIL-20AC auto sampler, CMB-20A communication bus module, DGU-20A5 degasser, CTO-20AC column oven, SPD-M20A diode array detector), Shimadzu LC-20AB liquid chromatograph (SIL-20ACHT auto sampler, DGU-20A5 degasser, CTO-20AC column oven, SPD-M20A diode array detector), or
Shimadzu LC-20AB liquid chromatograph (reverse phase, SIL-20ACHT autosampler, CTO-20AC column oven, SPD-M20A diode array detector) using Daicel columns with a chiral stationary phase. All solvents used were HPLC-grade solvents purchased from Sigma-Aldrich. The column employed and respective solvent mixtures are indicated for each experiment.

**Preparative High Performance Liquid Chromatography**

Preparative high performance liquid chromatography (Prep-HPLC) was performed on a Shimadzu LC-8A/10A liquid chromatograph (FRC-10A fraction collector, SPD-10-AVP diode array detector). All solvents used were HPLC-grade solvents purchased from Sigma-Aldrich. The column employed and respective solvent mixtures are indicated for each experiment.

**Gas Chromatography**

Gas chromatography (GC) analyses on a chiral stationary phase were performed on HP 6890 and 5890 series instruments (split-mode capillary injection system, flame ionization detector (FID), hydrogen carrier gas). All the analyses were conducted in the GC department of the Max-Planck-Institut für Kohlenforschung. The conditions employed are described in detail in the individual experiments.

**Gas Chromatography Mass Spectroscopy**

Gas chromatography-mass spectrometry (GC-MS) analyses were recorded on an Agilent Technologies 6890N Network GC System equipped with a 5973 Mass Selective Detector, Gerstel Multi-Purpose Sampler MPS2, and a Macherey-Nagel Optima 5 column (30 m length, 0.25 mm i. D.), and an Agilent Technologies 7890A GC System equipped with a 5975C VL MSD mass selective detector, Gerstel Multi-Purpose Sampler MPS2, and a Macherey-Nagel Optima 5 column (30 m length, 0.25 mm i.D.).
Liquid Chromatography Mass Spectrometry

Liquid chromatography-mass spectrometry (LC-MS) was performed on a Shimadzu LC-MS 2020 liquid chromatograph. All solvents used were HPLC-grade solvents purchased from Sigma-Aldrich. The column employed, the respective solvent mixture, and the MS parameters are indicated for each experiment.
Experimental Section
7.2 Asymmetric α-Protonation with H$_2$O and α-Deuteration with D$_2$O

7.2.1 Synthesis and Characterization of Racemic Carboxylic Acids

Non-commercially available carboxylic acids where prepared following a reported procedure.$^{[10a]}$

**General Procedure A**

\[
\begin{align*}
\text{R}^\text{BuLi} & (2.1 \text{ equiv.}) \\
\text{Mel} & (1 \text{ equiv.}) \\
\text{THF, } -78 \degree \text{C to rt} \\
\end{align*}
\]

$n$-BuLi (2.54 M in hexanes, 2.1 equiv.) was added dropwise to a solution of acid (1.0 equiv.) in THF (0.2 M) at $-78 \degree \text{C}$ and the reaction mixture was allowed to stir at this temperature for 15 min. Methyl iodide (1.0 equiv., neat) was added to the reaction mixture dropwise over 10 min. The reaction was allowed to stir and warm to room temperature overnight. The reaction was quenched with sat. NH$_4$Cl$_{(aq)}$ solution. After 5 min, the reaction mixture was diluted with diethyl ether. The aqueous layer was extracted with diethyl ether (x3). The combined organic layers were washed with sat. Na$_2$S$_2$O$_3$_{(aq)}$ solution until the organic phase turns to transparent, then washed with brine, dried with magnesium sulfate, concentrated under reduced pressure, and the solid residue was purified by flash column chromatography (SiO$_2$, dichloromethane/methanol = 95:5).

**2-(2-methylphenyl)propanoic acid (32e)**

Prepared according to general procedure A using o-Tolylacetic acid (4.8 g, 32 mmol) and obtained as a colorless solid (4.95 g, 30.1 mmol, 93% yield).
**Experimental Section**

\[^1\text{H NMR}\] (501 MHz, CDCl\(_3\)) \(\delta = 7.29\) (d, \(J = 7.2\) Hz, 1H), 7.23–7.15 (m, 3H), 3.99 (q, \(J = 7.1\) Hz, 1H), 2.38 (s, 3H), 1.50 ppm (d, \(J = 7.1\) Hz, 3H), [acid proton not visible due to fast exchange].

\[^{13}\text{C NMR}\] (126 MHz, CDCl\(_3\)) \(\delta = 179.69, 138.33, 135.89, 130.56, 127.21, 126.55, 126.47, 40.96, 19.63, 17.56\) ppm.

**HRMS (GC–EI) m/z calculated for C\(_{10}\)H\(_{12}\)O\(_2\) [M–H]: 164.0832; found 164.0837.**

\(2\text{-}(3\text{-methylphenyl})\text{propanoic acid (32f)}\)

Prepared according to general procedure A using \(m\)-Tolylacetic acid (4.8 g, 32 mmol) and obtained as a colorless solid (4.75 g, 28.9 mmol, 89% yield).

\[^1\text{H NMR}\] (501 MHz, CDCl\(_3\)) \(\delta = 7.26–7.14\) (m, 1H), 7.16–7.02 (m, 3H), 3.71 (q, \(J = 7.2\) Hz, 1H), 2.35 (s, 3H), 1.50 ppm (s, 3H), [acid proton not visible due to fast exchange].

\[^{13}\text{C NMR}\] (126 MHz, CDCl\(_3\)) \(\delta = 167.33, 139.72, 138.38, 128.59, 128.28, 128.16, 124.58, 45.05, 21.41, 18.16\) ppm.

**HRMS (GC–EI) m/z calculated for C\(_{10}\)H\(_{12}\)O\(_2\) [M–H]: 164.0832; found 164.0837.**

\(2\text{-}(2\text{-methoxyphenyl})\text{propanoic acid (32m)}\)

Prepared according to general procedure A from 2-methoxyphenylacetic acid (5.39 g, 32.4 mmol) and obtained as a colorless solid (5.31 g, 29.5 mmol, 90% yield).

\[^1\text{H NMR}\] (501 MHz, CDCl\(_3\)) \(\delta = 7.37–7.15\) (m, 2H), 6.96 (td, \(J = 7.5, 1.1\) Hz, 1H), 6.89 (dd, \(J = 8.7, 1.1\) Hz, 1H), 4.09 (q, \(J = 7.2\) Hz, 1H), 3.84 (s, 3H), 1.49 ppm (d, \(J = 7.2\) Hz, 3H), [acid proton not visible due to fast exchange].

\[^{13}\text{C NMR}\] (126 MHz, CDCl\(_3\)) \(\delta = 156.78, 128.54, 128.16, 121.04, 110.92, 77.41, 76.91, 55.68, 39.10, 16.94\) ppm.

**HRMS (GC–EI) m/z calculated for C\(_{10}\)H\(_{12}\)O\(_3\) [M–H]: 180.0781; found 180.0781.**
Experimental Section

2-(m-chlorophenyl)propanoic acid (32i)

Prepared according to general procedure A using 4-Chlorophenylacetic acid (5.0 g, 29.3 mmol) and obtained as a colorless solid (3.54 g, 19.2 mmol, 65% yield).

$^1$H NMR (501 MHz, CDCl$_3$) $\delta$ = 7.32 (s, 1H), 7.28–7.24 (m, 3H), 7.23–7.18 (m, 1H), 3.72 (q, $J$ = 7.2 Hz, 1H), 1.52 ppm (d, $J$ = 7.2 Hz, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ = 179.00, 141.57, 134.50, 129.92, 127.85, 127.65, 125.87, 44.89, 18.05 ppm.

HRMS (GC–EI) $m/z$ calculated for C$_9$H$_9$O$_2$ClNa [M–Na]: 207.0183; found 207.0183.

7.2.2 Synthesis and Characterization of bis-Silyl Ketene Acetals

Preparation of lithium diisopropyl amine (LDA) solution: To a stirring solution of freshly distilled diisopropyl amine (DPA; 50 mmol, 7.0 mL, 1.0 equiv.) in THF (21 mL, 1 M) under an atmosphere of argon, n-BuLi (2.45 M solution in hexane, 52.5 mmol, 24.5 mL, 1.05 equiv.) was added dropwise at –78 °C and the resulting reaction mixture was stirred for additional 30 min at this temperature.

Note. n-BuLi was freshly titrated.

General Procedure B

A stirring solution of acid (30.0 mmol, 1.0 equiv.) and Me$_3$SiCl (4.6 mL, 33.0 mmol, 2.2 equiv.) in THF (12 mL) under an atmosphere of argon was cooled to –78 °C. The LDA solution (2.1 equiv.) was added via cannula. The cooling bath was removed after complete addition and the reaction solution was stirred for 1 hour at room temperature. The reaction mixture was concentrated in vacuo, and then hexane (50 mL) was added to the residue and was filtered under an atmosphere of argon. After concentration under reduced pressure, the crude product was purified by
distillation under reduced pressure to afford the disilyl ketene acetal as colorless liquids, which were stored in Schlenk flasks under an atmosphere of argon at 4 °C.

2-Methyl-2-phenyl-1,1-bis(trimethylsilyloxy)ethane (31a)

Prepared according to general procedure B using 2-phenylpropionic acid (6.0 g, 40.0 mmol) and obtained after distillation (bp = 65 °C at 5x10^{-2} mbar) as colorless liquid (8.6 g, 29.0 mmol, 73% yield).

\[ \text{H NMR (501 MHz, CD}_2\text{Cl}_2 \delta = 7.39–7.34 (m, 2H), 7.26–7.19 (m, 2H), 7.11–7.03 (m, 1H), 1.89 (s, 3H), 0.27 (s, 9H), –0.05 ppm (s, 9H).} \]

\[ \text{C NMR (126 MHz, CD}_2\text{Cl}_2 \delta = 148.17, 142.51, 129.34, 129.34, 128.27, 128.27, 125.44, 95.09, 17.13, 0.90, 0.53 ppm.} \]

HRMS (ESI) m/z calculated for C_{15}H_{26}O_{2}Si_2 [M+H]^+: 295.1544; found 295.1544.

3-Ethyl-2-phenyl-1,1-bis(trimethylsilyloxy)ethane (31b)

Prepared according to general procedure B using 2-phenylbutanonic acid (5.0 g, 30.5 mmol) and obtained after distillation (bp = 71 °C at 5x10^{-2} mbar) as a colorless liquid (7.2 g, 23.0 mmol, 76% yield).

\[ \text{H NMR (501 MHz, CD}_2\text{Cl}_2 \delta = 7.34–7.26 (m, 2H), 7.23 (dd, J = 8.5, 6.9 Hz, 2H), 7.13–7.05 (m, 1H), 2.37 (q, J = 7.5 Hz, 2H), 0.90 (t, J = 7.4 Hz, 3H), 0.28 (s, 9H), –0.09 ppm (s, 9H).} \]

\[ \text{C NMR (126 MHz, CD}_2\text{Cl}_2 \delta = 147.20, 140.78, 129.71, 129.71 127.81, 127.81, 125.14, 101.66, 23.85, 13.59, 0.15, –0.04 ppm.} \]

HRMS (ESIpos) m/z calculated for C_{16}H_{28}O_{2}Si_2 [M+H]^+: 309.1701; found 309.1702.
3-Isopropyl-2-phenyl-1,1-bis(trimethylsilyloxy)ethane (31c)

Prepared according to general procedure B using 3-methyl-2-phenylbutyric acid (4.0 g, 22.4 mmol) and obtained after distillation \( \text{bp} = 86 \degree \text{C at 5 x}10^{-2} \text{ mbar} \) as a colorless liquid (5.0 g, 15.5 mmol, 69% yield).

\(^1\text{H NMR} (501 \text{ MHz, CD}_2\text{Cl}_2) \delta = 7.27–7.21 \text{ (m, 2H), 7.21–7.10 \text{ (m, 3H), 2.91 \text{ (hept, J = 7.0 Hz, 1H), 0.94 \text{ (d, J = 7.0 Hz, 6H), 0.27 \text{ (s, 9H), –0.15 ppm (s, 9H).}}}}\)

\(^{13}\text{C NMR} (126 \text{ MHz, CD}_2\text{Cl}_2) \delta = 146.68, 139.45, 132.08, 127.90, 127.90, 126.13, 106.27, 29.28, 22.32, 22.32, 0.64, 0.16 \text{ ppm.} \)

HRMS (ESI) \( m/z \) calculated for C\(_{17}\)H\(_{30}\)O\(_2\)Si\(_2\) [M+H]\(^+\): 323.1857; found 323.1857.

3-Benzyl-2-phenyl-1,1-bis(trimethylsilyloxy)ethane (31d)

Prepared according to general procedure B using 2,3-diphenylpropionic acid (4.0 g, 17.7 mmol) and obtained after distillation \( \text{bp} = 110 \degree \text{C at 5 x}10^{-2} \text{ mbar} \) as a colorless liquid (5.3 g, 14.3 mmol, 43% yield).

\(^1\text{H NMR} (501 \text{ MHz, CD}_2\text{Cl}_2) \delta = 7.30–7.25 \text{ (m, 2H), 7.23–7.14 \text{ (m, 6H), 7.13–7.07 \text{ (m, 1H), 7.07–7.01 \text{ (m, 1H), 3.72 \text{ (s, 2H), 0.24 \text{ (s, 9H), –0.04 \text{ (s, 9H) ppm.}}}}}}\)

\(^{13}\text{C NMR} (126 \text{ MHz, CD}_2\text{Cl}_2) \delta = 149.60, 142.62, 141.18, 129.85, 129.85, 128.95, 128.95, 128.52, 128.52, 128.09, 128.09, 125.93, 125.46, 98.65, 37.09, 0.75, 0.38 \text{ ppm.} \)

HRMS (ESI) \( m/z \) calculated for C\(_{21}\)H\(_{30}\)O\(_2\)Si\(_2\) [M+H]\(^+\): 371.1857; found 371.1858.

2-(2-methylphenyl)-2-methyl-1,1-bis(trimethylsilyloxy)ethane (31e)

Prepared according to general procedure B using 2-((o-tolyl)propanoic acid (1.8 g, 10.7 mmol) and obtained after distillation \( \text{bp} = 68 \degree \text{C at 5 x}10^{-2} \text{ mbar} \) as a colorless liquid (2.2 g, 7.1 mmol, 67% yield).
Experimental Section

$^{1}$H NMR (501 MHz, CD$_2$Cl$_2$) $\delta$ = 7.21–6.98 (m, 4H), 2.24 (s, 3H), 1.80 (s, 3H), 0.27 (s, 9H), 0.16 (s, 9H) ppm.

$^{13}$C NMR (126 MHz, CD$_2$Cl$_2$) $\delta$ = 146.54, 141.69, 137.60, 130.69, 130.19, 126.35, 125.60, 94.00, 20.30, 18.02, 0.80, 0.13 ppm.

HRMS (GC–Cl) $m/z$ calculated for C$_{16}$H$_{28}$O$_2$Si$_2$[M]: 308.1622; found 308.1619.

2-<em>m</em>-Tolyl-2-methyl-1,1-bis(trimethylsilyloxy)ethane (31f)

Prepared according to general procedure B using 2-<em>m</em>-tolylpropanoic acid (1.3 g, 7.6 mmol) and obtained after distillation (bp = 65 °C at 5 x 10$^{-2}$ mbar) as a colorless liquid (1.5 g, 4.8 mmol, 64% yield).

$^{1}$H NMR (501 MHz, CD$_2$Cl$_2$) $\delta$ = 7.21 (d, $J$ = 1.8, 1H), 7.18–7.06 (m, 2H), 6.94–6.81 (m, 1H), 2.30 (s, 3H), 1.87 (s, 3H), 0.27 (s, 9H), −0.04 (s, 9H) ppm.

$^{13}$C NMR (126 MHz, CD$_2$Cl$_2$) $\delta$ = 147.56, 141.80, 137.11, 129.62, 127.65, 125.74, 125.64, 94.53, 21.47, 16.66 ppm.

HRMS (GC–Cl) $m/z$ calculated for C$_{16}$H$_{28}$O$_2$Si$_2$ [M]: 308.1622; found 308.1620.

2-<em>p</em>-Tolyl-2-methyl-1,1-bis(trimethylsilyloxy)ethane (31g)

Prepared according to general procedure B using 2-<em>p</em>-tolylpropanoic acid (1.5 g, 9.4 mmol) and obtained after distillation (bp = 67 °C at 5 x 10$^{-2}$ mbar) as a colorless liquid (2.0 g, 6.5 mmol, 68% yield).

$^{1}$H NMR (501 MHz, CD$_2$Cl$_2$) $\delta$ = 7.28–7.22 (m, 2H), 7.09–7.02 (m, 2H), 2.29 (s, 3H), 1.86 (s, 3H), 0.27 (s, 9H), −0.07 (s, 9H) ppm.

$^{13}$C NMR (126 MHz, CD$_2$Cl$_2$) $\delta$ = 147.63, 139.13, 134.67, 128.87, 128.70, 128.70, 94.63, 21.28, 16.93, 0.66, 0.34 ppm.

HRMS (GC–Cl) $m/z$ calculated for C$_{16}$H$_{28}$O$_2$Si$_2$ [M]: 308.1622; found 308.1619.
Experimental Section

2-o-Methoxyphenyl-2-methyl-1,1-bis(trimethylsilyloxy)ethane (31m)

Prepared according to general procedure B using 2-(o-methoxyphenyl)propanoic acid (1.7 g, 10.6 mmol) and obtained after distillation (bp = 98 °C at 5 x 10⁻² mbar) as a colorless liquid (1.5 g, 4.6 mmol, 43% yield).

¹H NMR (501 MHz, CD₂Cl₂) δ = 7.17–7.09 (m, 2H), 6.87–6.81 (m, 2H), 3.77 (s, 3 H), 1.77 (s, 3H), 0.27 (s, 9H), –0.14 ppm (s, 9H).

¹³C NMR (126 MHz, CD₂Cl₂) δ = 158.50, 147.40, 132.69, 127.87, 120.80, 111.52, 92.84, 55.95, 17.20, 0.90, 0.35 ppm.

HRMS (GC–Cl) m/z calculated for C₁₆H₂₈O₃Si₂ [M]: 324.1566; found 324.1572.

2-o-Chlorophenyl-2-methyl-1,1-bis(trimethylsilyloxy)ethane (31h)

Prepared according to general procedure B using 2-(2-chlorophenyl)propanoic acid (2.1 g, 11.3 mmol) and obtained after distillation (bp = 91 °C at 5 x 10⁻² mbar) as a colorless liquid (1.2 g, 3.6 mmol, 33% yield).

¹H NMR (501 MHz, CD₂Cl₂) δ = 7.34 (dd, J = 7.9, 1.4 Hz, 1H), 7.24 (dd, J = 7.5, 1.9 Hz, 1H), 7.19 (td, J = 7.4, 1.4 Hz, 1H), 7.13 (ddd, J = 7.8, 7.2, 1.9 Hz, 1H), 1.83 (s, 3H), 0.30 (s, 9H), –0.09 ppm (s, 9H).

¹³C NMR (126 MHz, CD₂Cl₂) δ = 141.86, 135.68, 133.75, 130.51, 128.55, 127.56, 125.25, 94.18, 17.74, 1.48, 0.90 ppm.

HRMS (GC–Cl) m/z calculated for C₁₅H₂₅O₂ClSi₂ [M]: 328.1076; found 328.1079.

2-m-Chlorophenyl-2-methyl-1,1-bis(trimethylsilyloxy)ethane (31i)

Prepared according to general procedure B using 2-(3-chlorophenyl)propanoic acid (1.5 g, 7.9 mmol) and obtained after distillation (bp = 82 °C at 5 x 10⁻² mbar) as a colorless liquid (1.2 g, 3.6 mmol, 46% yield).
Experimental Section

$^1$H NMR (501 MHz, CD$_2$Cl$_2$) $\delta$ = 7.44 (t, $J$ = 1.9 Hz, 1H), 7.27 (ddd, $J$ = 7.9, 1.7, 1.1 Hz, 1H), 7.18 (m, 1H), 7.05 (ddd, $J$ = 8.0, 2.2, 1.1 Hz, 1H), 1.88 (s, 3H), 0.28 (s, 9H), 0.00 ppm (s, 9H).

$^{13}$C NMR (126 MHz, CD$_2$Cl$_2$) $\delta$ = 149.38, 144.84, 134.30, 129.91, 129.60, 127.50, 125.51, 94.45, 17.05, 1.23, 0.90 ppm.

HRMS (GC–Cl) m/z calculated for C$_{15}$H$_{25}$O$_2$Cl$_1$Si$_2$ [M]: 328.1076; found 328.1072.

2-p-Chlorophenyl-2-methyl-1,1-bis(trimethylsilyloxy)ethane (31j)

Prepared according to general procedure B using 2-(2-chlorophenyl)propanoic acid (3.5 g, 19.2 mmol) and obtained after distillation (bp 86 °C at 5 x10$^{-2}$ mbar) as a colorless liquid (3.9 g, 11.9 mmol, 62%).

$^1$H NMR (501 MHz, CD$_2$Cl$_2$) $\delta$ = 7.37–7.29 (m, 2H), 7.24–7.14 (m, 2H), 1.87 (s, 3 H), 0.27 (s, 9H), $-$0.02 ppm (s, 9H).

$^{13}$C NMR (126 MHz, CD$_2$Cl$_2$) $\delta$ = 148.97, 141.45, 130.94, 130.89, 129.05, 128.61, 128.46, 94.46, 17.18, 1.21, 0.90 ppm.

HRMS (GC–Cl) m/z calculated for C$_{15}$H$_{25}$O$_2$Cl$_1$Si$_2$ [M]: 328.1076; found 328.1072.

3-Benzyl-2-methyl-1,1-bis(trimethylsilyloxy)ethane (31k)

Prepared according to general procedure B using 2-methyl-3-phenylpropionic acid (5.0 g, 30.5 mmol) and obtained after distillation (bp = 72 °C at 5 x10$^{-2}$ mbar) as a colorless liquid (4.5 g, 14.6 mmol, 48% yield).

$^1$H NMR (501 MHz, CD$_2$Cl$_2$) $\delta$ = 7.30–7.20 (m, 2H), 7.19–7.10 (m, 3H), 3.27 (s, 2 H), 1.40 (s, 3H), 0.20 ppm (d, $J$ = 1.4 Hz, 18H).

$^{13}$C NMR (126 MHz, CD$_2$Cl$_2$) $\delta$ = 146.89, 142.45, 129.08, 129.08, 128.57, 128.57, 126.00, 92.02, 37.81, 15.14, 0.90, 0.88 ppm.

HRMS (ESI) m/z calculated for C$_{16}$H$_{28}$O$_2$ [M+H]$^+$: 309.1701; found 309.1701.
Experimental Section

2-p-isobutylphenyl-2-methyl-1,1-bis(trimethylsilyloxy)ethane (31o)
Prepared according to general procedure B using 2-(4-isobutylphenyl)propanoic acid (5.0 g, 24.2 mmol) and obtained after distillation (bp = 105 °C at 5 x 10⁻² mbar) as a colorless liquid (6.5 g, 18.5 mmol, 77% yield).

\[ \text{1H NMR (501 MHz, CD}_2\text{Cl}_2 \] \[ \delta = 7.28–7.23 \text{ (m, 2H), 7.04–6.99 \text{ (m, 2H), 2.42 \text{ (d, J = 7.2 Hz, 2H), 1.87 \text{ (s, 3H), 1.84–1.77 \text{ (m, 1H), 0.88 \text{ (d, J = 6.6 Hz, 6H), 0.26 \text{ (s, 9H), –0.06 ppm (s, 9H).}}}} \]

\[ \text{13C NMR (126 MHz, CD}_2\text{Cl}_2 \] \[ \delta = 147.89, 139.70, 138.92, 129.06, 129.06, 129.02, 129.02, 94.98, 45.80, 31.15, 22.88, 17.17, 0.90, 0.56 ppm. \]

\[ \text{HRMS (ESI) m/z calculated for C}_{19}\text{H}_{35}\text{O}_2\text{Si}_2 \text{ [M+H]^+}: 351.2171; found 351.2170.} \]

2-(6-methoxynaphthalen-2-yl)-2-methyl-1,1-bis(trimethylsilyloxy)ethane (31l)
Prepared according to general procedure B using 2-(6-methoxynaphthalen-2-yl)-propanoic acid (4.0 g, 17.4 mmol) and obtained after sublimation (sp = 150 °C at 5 x 10⁻² mbar) as a colorless solid (4.0 g, 10.8 mmol, 62% yield).

\[ \text{1H NMR (501 MHz, CD}_2\text{Cl}_2 \] \[ \delta = 7.70–7.69 \text{ (m, 1H), 7.67–7.64 \text{ (m, 1H), 7.63–7.56 \text{ (m, 2H), 7.10 \text{ (d, J = 2.6 Hz, 1H), 7.07 \text{ (dd, J = 8.8, 2.6 Hz, 1H), 3.90 \text{ (s, 3H), 1.98 \text{ (s, 3H), 0.30 \text{ (s, 9H), –0.06 ppm (s, 9H).}}}}}} \]

\[ \text{13C NMR (126 MHz, CD}_2\text{Cl}_2 \] \[ \delta = 137.60, 132.88, 129.53, 129.53, 128.90, 126.64, 126.03, 118.74, 118.74, 106.02, 106.02, 94.76, 55.77, 16.92, 0.69, 0.34 ppm. \]

\[ \text{HRMS (ESI) m/z calculated for C}_{20}\text{H}_{30}\text{O}_3\text{Si}_2\text{Na [M+Na]^+}: 397.1629; found 397.1626.} \]

2-(3-fluoro-4-phenyl-phenyl)-2-methyl-1,1-bis(trimethylsilyloxy)ethane (31p)
Prepared according to general procedure B using 2-(3-fluoro-4-phenyl-phenyl)-propanoic acid (4.0 g, 16.4 mmol) and obtained after distillation (bp = 145 °C at 5 x 10⁻² mbar)
as a colorless liquid (4.0 g, 10.3 mmol, 63% yield).

\(^1\)H NMR (501 MHz, CD\(_2\)Cl\(_2\)) \(\delta = 7.58–7.54\) (m, 2H), 7.46–7.40 (m, 2H), 7.37–7.31 (m, 2H), 7.30–7.25 (m, 2H), 1.92 (s, 3H), 0.29 (d, \(J = 1.0\) Hz, 9H), 0.06 ppm (s, 9H).

\(^{13}\)C NMR (75 MHz, CD\(_2\)Cl\(_2\)) \(\delta = 160.43\) (d, \(J = 244.6\) Hz), 149.12, 143.73 (d, \(J = 8.6\) Hz), 136.74, 130.00 (d, \(J = 4.3\) Hz), 129.41 (d, \(J = 3.2\) Hz), 128.94, 127.81, 124.73 (d, \(J = 3.0\) Hz), 116.07 (d, \(J = 23.7\) Hz), 93.87, 16.43, 0.72, 0.45 ppm.

HRMS (ESI) \(m/z\) calculated for C\(_{21}\)H\(_{30}\)O\(_2\)F\(_1\)Si\(_2\) [M+H]\(^+\): 389.1764; found 389.1763.

2\(-m\)-phenoxyphenyl-2-methyl-1,1-bis(trimethylsilyloxy)ethane (31n)

Prepared according to general procedure B using 2-(3-phenoxyphenyl)propanoic acid (2.0 g, 8.3 mmol) and obtained after distillation (bp = 135 °C at 5 x10\(^{-2}\) mbar) as a colorless liquid (1.3 g, 3.4 mmol, 41% yield).

\(^1\)H NMR (501 MHz, CD\(_2\)Cl\(_2\)) \(\delta = 7.35–7.29\) (m, 2H), 7.25–7.20 (m, 1H), 7.17 (d, \(J = 7.8, 1\) Hz), 7.11 (dd, \(J = 2.5, 1.7\) Hz, 1H), 7.07 (tt, \(J = 7.4, 1.1\) Hz, 1H), 7.01–6.96 (m, 2H), 6.73 (ddd, \(J = 7.9, 2.5, 1.2\) Hz, 1H), 1.88 (s, 3H), 0.27 (s, 9H), 0.00 ppm (s, 9H).

\(^{13}\)C NMR (126 MHz, CD\(_2\)Cl\(_2\)) \(\delta = 158.51, 156.85, 148.37, 144.34, 130.15, 129.18, 124.44, 123.19, 120.17, 118.76, 116.05, 94.39, 16.76, 0.64, 0.36 ppm.

HRMS (ESI) \(m/z\) calculated for C\(_{21}\)H\(_{31}\)O\(_2\)Si\(_2\) [M+H]\(^+\): 387.1807; found 387.1806.

4-benzylidene-2,2,6,6-tetramethyl-3,5-dioxa-2,6-disilaheptane (31r)

Prepared according to general procedure B using phenylacetic acid (5.0 g, 36.7 mmol) and obtained after distillation (bp = 59 °C at 5 x10\(^{-2}\) mbar) as a colorless liquid (7.6 g, 27.0 mmol, 74%) yield.

\(^1\)H NMR (501 MHz, CD\(_2\)Cl\(_2\)) \(\delta = 7.40–7.34\) (m, 2H), 7.22–7.16 (m, 2H), 6.98 (tt, \(J = 7.1, 1.3\) Hz, 1H), 4.61 (s, 1H), 0.33 (s, 9H), 0.30 ppm (s, 9H).

\(^{13}\)C NMR (126 MHz, CD\(_2\)Cl\(_2\)) \(\delta = 152.73, 138.11, 128.52, 128.52, 126.74, 126.74, 123.92, 85.58, 0.84, 0.16 ppm.

HRMS (GC–Cl) \(m/z\) calculated for C\(_{14}\)H\(_{24}\)O\(_2\)Si\(_2\) [M]: 280.13053; found 280.13094.
7.2.3 General procedure for the asymmetric protonation of bis-SKAs

An oven dry 2 ml vial was charged with disulfonamide 17o (4.0 µmol, 3.2 mg, 2 mol%), a magnetic stir bar and, under argon atmosphere, dry CH₂Cl₂ (0.5 mL) and bis-silyl ketene acetal 31 (0.2 mmol, 1.0 equiv.) were added. Then MeOH (9.0 µL, 1.1 equiv.) in CH₂Cl₂ (2% solution, v%) was added over 15 min via Hamilton syringe using a syringe pump (33 µL/min). Afterwards, the reaction mixture was diluted with water, stirred for 5 min and the organic phase was extracted with aq. NaOH (1M). The organic phase was acidified with HCl (6M) for 5 min, extracted with CH₂Cl₂ (3x5 mL), and the solvent was removed under reduced pressure to fully recycle catalyst 17o. The aqueous phase was acidified with HCl (1M) and extracted with Et₂O (3x3 mL). The combined organic phase was dried over MgSO₄ and the solvent was removed under reduced pressure to yield the targeted product 32 as a colorless solid in >99% purity (analyzed by ¹H-NMR). The obtained product was dissolved in HPLC grade Heptane:iPrOH (1:1, v/v) and directly used for the determination of the enantiomeric ratio.

(S)-2-phenylpropanoic acid (32a)

Prepared according to the general procedure using 2-methyl-2-phenyl-1,1-bis(trimethylsilyloxy)ethane (31a) (59 mg, 59 µL, 0.2 mmol) and obtained after extraction as a colorless liquid (22 mg, 0.15 mmol, 73% yield, 95.5:4.5 er).
**Experimental Section**

$^1$H NMR (501 MHz, CDCl$_3$) $\delta = 7.38–7.30$ (m, 4H), 7.28 (ddd, $J = 6.3$, 3.1, 1.8 Hz, 1H), 3.74 (q, $J = 7.1$ Hz, 1H), 1.52 ppm (d, $J = 7.2$ Hz, 3H), [acid proton not visible due to fast exchange].

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta = 180.36$, 139.75, 128.69, 127.60, 127.40, 45.31, 18.11 ppm.

HRMS (GC–EI) $m/z$ calculated for C$_9$H$_{10}$O$_2$ [M]: 150.0678; found 150.0675.

The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak OD-3, n-Heptane/iPrOH/TFA = 97.9:2:0.1 (v/v/v), flow rate = 1 mL/min, 25 °C, $\lambda = 210$ nm, $t_R = 6.57$ min (minor) and $t_R = 7.62$ min (major).

$[\alpha]_D^{25} = 69.2$ (c 1.0, CHCl$_3$). Lit $[\alpha]_D^{20} = 75.0$ (c 1.6, CHCl$_3$). (obtained from Sigma-Aldrich)

**(S)-2-phenylbutanoic acid (32b)**

Prepared according to general procedure using 3-Ethyl-2-phenyl-1,1-bis(trimethylsilyloxy)ethane (31b) (62 mg, 60 $\mu$L, 0.2 mmol) and obtained after extraction as a colorless solid (26 mg, 0.16 mmol, 82% yield, 95:5 er).

$^1$H NMR (501 MHz, CDCl$_3$) $\delta = 7.36–7.26$ (m, 5H), 3.47 (t, $J = 7.7$ Hz, 1H), 2.11 (m, 1H), 1.82 (m, 1H), 0.92 ppm (t, $J = 7.4$ Hz, 3H), [acid proton not visible due to fast exchange].

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta = 180.00$, 138.38, 128.63, 128.07, 127.43, 53.18, 26.31, 12.09 ppm.

HRMS (GC–EI) $m/z$ calculated for C$_{10}$H$_{12}$O$_2$ [M]: 164.0834; found 164.0832.

The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak OD-3, n-Heptane/iPrOH/TFA = 97.9:2:0.1 (v/v/v), flow rate = 1 mL/min, 25 °C, $\lambda = 210$ nm, $t_R = 5.68$ min (minor) and $t_R = 7.54$ min (major).

$[\alpha]_D^{20} = 32.5$ (c 1.1, CHCl$_3$). Lit$^{[10a]}$
**Experimental Section**

**(S)-3-methyl-2-phenylbutanoic acid (32c)**

Prepared according to general procedure using 3-isopropyl-2-phenyl-1,1-bis(trimethylsilyloxy)ethane (31c) (65 mg, 59 µL, 0.2 mmol) and obtained after extraction as a colorless solid (32 mg, 0.18 mmol, 89% yield, 70.5:29.5 er).

\[\text{\textsuperscript{1}H NMR} \left(501 \text{ MHz, CDCl}_3\right) \delta = 7.35–7.29 (m, 4H), 7.30–7.23 (m, 1H), 3.15 (d, J = 10.5 Hz, 1H), 2.33 (dp, J = 10.6, 6.6 Hz, 1H), 1.08 (d, J = 6.5 Hz, 3H), 0.71 ppm (d, J = 6.7 Hz, 3H), [acid proton not visible due to fast exchange].

\[\text{\textsuperscript{13}C NMR} \left(126 \text{ MHz, CDCl}_3\right) \delta = 179.85, 137.73, 128.59, 128.54, 127.46, 59.95, 59.91, 31.56, 21.47, 20.11 \text{ ppm.}

**HRMS** (GC–EI) m/z calculated for C\textsubscript{11}H\textsubscript{14}O\textsubscript{2} [M]: 178.0990; found 178.0988.

The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak OD-3, n-Heptane/iPrOH/TFA = 97.9:2:0.1 (v/v/v), flow rate = 1 mL/min, 25 °C, \(\lambda = 210 \text{ nm, } t_R = 5.09 \text{ min (minor) and } t_R = 6.88 \text{ min (major).}

\[\alpha\]\textsubscript{D}\textsuperscript{25} = 23.4 (c 0.95, CHCl\textsubscript{3}). Lit\textsuperscript{[156]}

**(S)-2,3-diphenylpropanoic acid (31d)**

Prepared according to general procedure using 3-benzyl-2-phenyl-1,1-bis(trimethylsilyloxy)ethane (32d) (74 mg, 68 µL, 0.2 mmol) and obtained after extraction as a colorless solid (43 mg, 0.19 mmol, 96% yield, 95:5 er).

\[\text{\textsuperscript{1}H NMR} \left(501 \text{ MHz, CDCl}_3\right) \delta = 7.42–7.15 (m, 8H), 7.14–7.08 (m, 2H), 3.87 (dd, J = 8.4, 7.0 Hz, 1H), 3.42 (dd, J = 13.8, 8.4 Hz, 1H), 3.05 ppm (dd, J = 13.8, 7.0 Hz, 1H), [acid proton not visible due to fast exchange].

\[\text{\textsuperscript{13}C NMR} \left(126 \text{ MHz, CDCl}_3\right) \delta = 178.77, 138.80, 138.05, 129.05, 128.85, 128.51, 128.23, 127.77, 126.61, 53.52, 39.42 \text{ ppm.}

**HRMS** (GC–EI) m/z calculated for C\textsubscript{15}H\textsubscript{14}O\textsubscript{2} [M]: 226.0990; found 226.0988.
Experimental Section

The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak OD-3, n-Heptane/iPrOH/TFA = 97.9:2:0.1 (v/v/v), flow rate = 1 mL/min, 25 °C, λ = 210 nm, t<sub>R</sub> = 8.08 min (minor) and t<sub>R</sub> = 9.97 min (major).

[α]<sup>D</sup><sub>25</sub> = 56.0 (c 1.1, CHCl<sub>3</sub>). Lit[156]

(S)-2-(o-tolyl)propanoic acid (32e)

Prepared according to general procedure using 2-o-tolyl-2-methyl-1,1-bis(trimethylsilyloxy)ethane (31e) (62 mg, 56 µL, 0.2 mmol) and obtained after extraction as a colorless solid (3 mg, 0.18 mmol, 91% yield, 96.5:3.5 er).

<sup>1</sup>H NMR (501 MHz, CDCl<sub>3</sub>) δ = 7.29 (d, J = 7.2 Hz, 1H), 7.23–7.14 (m, 3H), 3.99 (q, J = 7.1 Hz, 1H), 2.38 (s, 3H), 1.50 ppm (d, J = 7.1 Hz, 3H), [acid proton not visible due to fast exchange].

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 179.59, 138.33, 135.88, 130.56, 127.21, 126.55, 126.47, 40.95, 19.63, 17.56 ppm.

HRMS (GC–EI) m/z calculated for C<sub>10</sub>H<sub>12</sub>O<sub>2</sub> [M]: 164.0834; found 164.0832.

The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak OD-3, n-Heptane/iPrOH/TFA = 97.9:2:0.1 (v/v/v), flow rate = 1 mL/min, 25 °C, λ = 210 nm, t<sub>R</sub> = 7.05 min (minor) and t<sub>R</sub> = 8.06 min (major).

[α]<sup>D</sup><sub>25</sub> = 50.9 (c 1.05, CHCl<sub>3</sub>). Lit[157]

(S)-3-(o-tolyl)propanoic acid (32f)

Prepared according to general procedure using 2-m-tolyl-2-methyl-1,1-bis(trimethylsilyloxy)ethane (31f) (62 mg, 57 µL, 0.2 mmol) and obtained after extraction as a colorless solid (29 mg, 0.19 mmol, 97% yield, 92.5:7.5 er).

<sup>1</sup>H NMR (501 MHz, CDCl<sub>3</sub>) δ = 7.25–7.19 (m, 1H), 7.16–7.03 (m, 3H), 3.72 (q, J = 7.2 Hz, 1H), 2.35 (s, 3H), 1.51 ppm (d, J = 7.2 Hz, 3H), [acid proton not visible due to fast exchange].
**Experimental Section**

**13C NMR** (126 MHz, CDCl₃) δ = 167.33, 139.72, 138.38, 128.59, 128.28, 128.16, 124.58, 45.05, 21.41, 18.16 ppm.

**HRMS** (GC–EI) m/z calculated for C₁₀H₁₂O₂ [M]: 164.0834; found 164.0832. The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak OD-3, n-Heptane/iPrOH/TFA = 97.9:2:0.1 (v/v/v), flow rate = 1 mL/min, 25 °C, λ = 210 nm, tᵣ = 6.0 min (minor) and tᵣ = 7.64 min (major).

[α]₀° twenty-five = 33.3 (c 0.75, CHCl₃). Lit[^157]

**(S)-2-(p-Tolyl)propanoic acid (32g)**

![Image](https://via.placeholder.com/150)

Prepared according to general procedure using 2-p-Tolyl-2-methyl-1,1-bis(trimethylsilyloxy)ethane (31g) (63 mg, 60 µL, 0.2 mmol) and obtained after extraction as a colorless solid (29 mg, 0.18 mmol, 88% yield, 95.5:4.5 er).

**¹H NMR** (501 MHz, CDCl₃) δ = 11.38 (s, 1H), 7.20 (d, J = 8.1, 2H), 7.13 (d, J = 8.1, 2H), 3.68 (q, J = 7.1, 1H), 1.47 ppm (d, J = 7.1, 3H).

**13C NMR** (126 MHz, CDCl₃) δ = 181.14, 137.04, 136.75, 129.33, 127.43, 44.94, 21.01, 18.05 ppm.

**HRMS** (GC–EI) m/z calculated for C₁₀H₁₂O₂ [M]: 164.0835; found 164.0832. The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak OD-3, n-Heptane/iPrOH/TFA = 97.9:2:0.1 (v/v/v), flow rate = 1 mL/min, 25 °C, λ = 210 nm, tᵣ = 6.25 min (minor) and tᵣ = 9.95 min (major).

[α]₀° twenty-five = 42.3 (c 0.6, CHCl₃).

**(S)-2-(2-methoxyphenyl)propanoic acid (32m)**

![Image](https://via.placeholder.com/150)

Prepared according to general procedure using 2-o-methoxyphenyl-2-methyl-1,1-bis(trimethylsilyloxy)ethane (31m) (73 mg, 65 µL, 0.2 mmol) and obtained after extraction as a colorless solid (33 g, 0.18 mmol, 92% yield, 95:5 er).
**Experimental Section**

\( ^{1} \text{H NMR} \) (501 MHz, CDCl\(_3\)) \( \delta = 7.29–7.22 \text{ (m, } 2\text{H}), \) 6.96 (dt \( J = 7.5, 1.1 \text{ Hz}, 1\text{H}), 6.89 \text{ (dd}, \ J = 8.7, 1.1 \text{ Hz}, 1\text{H}), 4.09 \text{ (q}, \ J = 7.2 \text{ Hz}, 1\text{H}), 3.84 \text{ (s}, 3\text{H}), 1.49 \text{ ppm (d}, \ J = 7.2 \text{ Hz}, 3\text{H}), [\text{acid proton not visible due to fast exchange}].

\( ^{13} \text{C NMR} \) (126 MHz, CDCl\(_3\)) \( \delta = 156.63, 128.65, 128.65, 128.39, 128.01, 120.89, 110.77, 55.53, 38.95, 16.79 \text{ ppm}.

**HRMS** (GC–EI) \( m/z \) calculated for C\(_{10}\)H\(_{12}\)O\(_3\) [M]: 180.0781; found 180.0781.

The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak OD-3, \( n\)-Heptane/iPrOH/TFA = 97.9:2:0.1 (v/v/v), flow rate = 1 mL/min, 25 °C, \( \lambda = 210 \) nm, \( t_R = 15.3 \text{ min (minor) and } t_R = 16.5 \text{ min (major).} \]

\[ [\alpha]_D^{25} = 69.5 \text{ (c 1.1, CHCl}_3\text{). Lit}^{[158]} \]

\((S)-2-(2\text{-chlorophenyl})\text{propanoic acid (32h)}\)

\[
\begin{array}{c}
\text{Cl} \quad \text{O} \\
\text{H} \quad \text{C}
\end{array}
\]

Prepared according to general procedure using 2-\( o\)-chlorophenyl-2-methyl-1,1-\( \text{bis}(\text{trimethylsilyloxy})\text{ethane (31h)}\) (73 mg, 70 \( \mu \)L, 0.2 mmol) and obtained after extraction as a colorless solid (35 mg, 0.19 mmol, 95% yield, 95:5 er).

\( ^{1} \text{H NMR} \) (501 MHz, CDCl\(_3\)) \( \delta = 7.37 \text{ (ddd}, \ J = 17.1, 7.8, 1.6 \text{ Hz}, 2\text{H}), 7.26 \text{ (td}, \ J = 7.6, 1.5 \text{ Hz}, 1\text{H}), 7.21 \text{ (td}, \ J = 7.6, 1.8 \text{ Hz}, 1\text{H}), 4.28 \text{ (q}, \ J = 7.2 \text{ Hz}, 1\text{H}), 1.53 \text{ ppm (d}, \ J = 7.3 \text{ Hz}, 3\text{H}), [\text{acid proton not visible due to fast exchange}].

\( ^{13} \text{C NMR} \) (126 MHz, CDCl\(_3\)) \( \delta = 178.76, 137.66, 129.70, 128.53, 128.45, 127.20, 41.80, 17.31 \text{ ppm}.

**HRMS** (ESI) \( m/z \) calculated for C\(_9\)H\(_8\)ClO\(_2\) [M–H]\(^{-}\): 183.0218; found 183.0218.

The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak OJ-3, \( n\)-Heptane/iPrOH/TFA = 97.9:2:0.1 (v/v/v), flow rate = 1 mL/min, 25 °C, \( \lambda = 210 \) nm, \( t_R = 32.2 \text{ min (minor) and } t_R = 35.1 \text{ min (major).} \]

\[ [\alpha]_D^{25} = 46.2 \text{ (c 0.6, CHCl}_3\text{). Lit}^{[158]} \]

\((S)-2-(3\text{-chlorophenyl})\text{propanoic acid (32i)}\)

\[
\begin{array}{c}
\text{Cl} \quad \text{O} \\
\text{H} \quad \text{C}
\end{array}
\]

Prepared according to general procedure using 2-\( m\)-chlorophenyl-2-methyl-1,1-\( \text{bis}(\text{trimethylsilyloxy})\text{ethane (31i)}\) (73
mg, 69 µL, 0.2 mmol) and obtained after extraction as a colorless solid (32 mg, 0.17 mmol, 87% yield, 93:7 er).

$^1$H NMR (501 MHz, CDCl$_3$) $\delta$ = 7.32 (bs, 1H), 7.30–7.22 (m, 2H), 7.23–7.18 (m, 1H), 3.72 (q, J = 7.2 Hz, 1H), 1.52 ppm (d, J = 7.2 Hz, 3H), [acid proton not visible due to fast exchange].

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ = 179.00, 141.57, 134.50, 129.92, 127.85, 127.65, 125.87, 44.89, 18.05 ppm.

HRMS (ESI) m/z calculated for C$_9$H$_8$ClO$_2$Na$_1$ [M+Na]$^+$: 207.0183; found 207.0183.

The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak OJ-3, n-Heptane/iPrOH/TFA = 97.9:2:0.1 (v/v/v), flow rate = 1 mL/min, 25 °C, $\lambda$ = 210 nm, $t_R$ = 27.3 min (minor) and $t_R$ = 31.5 min (major).

[$\alpha$]$^D_{25}$ = 32.9 (c 0.85, CHCl$_3$). Lit$^{[158]}$

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(S)-2-(4-chlorophenyl)propanoic acid (32j)

Prepared according to general procedure using 2-$p$-chlorophenyl-2-methyl-1,1-bis(trimethylsilyloxy)ethane (31j) (73 mg, 70 µL, 0.2 mmol) and obtained after extraction as a colorless solid (29 mg, 0.16 mmol, 79% yield, 95:5 er).

$^1$H NMR (501 MHz, CDCl$_3$) $\delta$ = 7.30 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 8.3 Hz, 2H), 3.71 (q, J = 6.6 Hz, 1H), 1.49 ppm (d, J = 7.2 Hz, 3H), [acid proton not visible due to fast exchange].

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ = 180.14, 138.58, 133.18, 129.29, 129.29, 129.05, 129.05, 45.09, 18.49 ppm.

HRMS (ESI) m/z calculated for C$_9$H$_8$ClO$_2$Na$_1$ [M+Na]$^+$: 207.0183; found 207.0183.

The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak OD-3, n-Heptane/iPrOH/TFA = 97.9:2:0.1 (v/v/v), flow rate = 1 mL/min, 25 °C, $\lambda$ = 210 nm, $t_R$ = 13.8 min (minor) and $t_R$ = 16.38 min (major).

[$\alpha$]$^D_{25}$ = 36.2 (c 0.80, CHCl$_3$). Lit$^{[158]}$. 

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(S)-2-methyl-3-phenylpropanoic acid (32k)
Prepared according to general procedure using 3-benzyl-2-methyl-1,1-bis(trimethylsilyloxy)ethane (31k) (62 mg, 60 μL, 0.2 mmol) and obtained after extraction as a colorless solid (29 mg, 0.18 mmol, 89% yield, 51:49 er).

$^1$H NMR (501 MHz, CDCl$_3$) δ = 7.30–7.26 (m, 2H), 7.23–7.17 (m, 3H), 3.08 (dd, $J = 13.8, 6.6$ Hz, 1H), 2.80–2.73 (m, 1H), 2.67 (dd, $J = 13.8, 8.4$ Hz, 1H), 1.17 ppm (d, $J = 7.2$ Hz, 3H), [acid proton not visible due to fast exchange].

$^{13}$C NMR (126 MHz, CDCl$_3$) δ = 182.2, 139.2, 129.1, 128.5, 126.5, 41.3, 39.4, 16.6 ppm.

HRMS (GC-EI) m/z calculated for C$_{10}$H$_{12}$O$_2$ [M]: 164.0835; found 164.0832.

The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak OJ-3, n-Heptane/iPrOH/TFA = 97.9:2:0.1 (v/v/v), flow rate = 1 mL/min, 25 °C, $\lambda$ = 210 nm, $t_R$ = 7.58 min (minor) and $t_R$ = 8.55 min (major).

[$\alpha$]$_{D}^{25}$ = −0.0 (c 0.75, CHCl$_3$).

(S)-Ibuprofen (32o)
Prepared according to general procedure using 2-p-isobutylphenyl-2-methyl-1,1-bis(trimethylsilyloxy)ethane (31o) (70 mg, 62 μL, 0.2 mmol) and obtained after extraction as a colorless solid (38 mg, 0.18 mmol, 92% yield, 96.5:3.5 er).

$^1$H NMR (501 MHz, CDCl$_3$) δ = 7.24–7.18 (m, 2H), 7.14–7.06 (m, 2H), 3.71 (q, $J = 7.2$ Hz, 1H), 2.45 (d, $J = 7.2$ Hz, 2H), 1.84–1.77 (m, 1H), 1.50 (d, $J = 7.2$ Hz, 3H), 0.90 ppm (d, $J = 6.6$ Hz, 6H), [acid proton not visible due to fast exchange].

$^{13}$C NMR (126 MHz, CDCl$_3$) δ = 180.79, 140.86, 136.96, 129.39, 127.27, 45.05, 44.94, 30.17, 22.40, 18.11 ppm.

HRMS (GC-EI) m/z calculated for C$_{13}$H$_{18}$O$_2$ [M]: 206.1307; found 206.1309.

The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak OD-3, n-Heptane/iPrOH/TFA = 97.9:2:0.1 (v/v/v), flow rate = 1 mL/min, 25 °C, $\lambda$ = 210 nm, $t_R$ = 5.37 min (minor) and $t_R$ = 6.11 min (major).
Experimental Section

\[ [\alpha]_D^{25} = 39.1 \ (c\ 1.0, \ CHCl_3) \ \text{Lit}^{[158]} \]

**S)-Naproxen (32I)**

Prepared according to general procedure using 2-(6-methoxynaphthalen-2-yl)-2-methyl-1,1-bis(trimethylsilyloxy)ethane (31I) (75 mg, 0.2 mmol) and obtained after extraction as a colorless solid (41 mg, 0.18 mmol, 90% yield, 93:7).

1H NMR (501 MHz, CDCl3) \( \delta = 7.74–7.64 \) (m, 3H), 7.41 (dd, \( J = 8.5, 1.9 \) Hz, 1H), 7.18–7.07 (m, 2H), 3.91 (s, 3H), 3.87 (q, \( J = 7.3 \) Hz, 1H), 1.59 ppm (d, \( J = 7.2 \) Hz, 3H), [acid proton not visible due to fast exchange].

13C NMR (126 MHz, CDCl3) \( \delta = 179.66, 157.72, 134.87, 133.82, 129.30, 128.89, 127.24, 126.13, 119.05, 105.60, 55.31, 45.12, 18.17 \) ppm.

HRMS (GC-EI) m/z calculated for C14H14O2 [M]: 230.0930; found 230.0928.

The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak OD-3, n-Heptane/iPrOH/TFA = 97.9:2:0.1 (v/v/v), flow rate = 1 mL/min, 25 °C, \( \lambda = 210 \) nm, \( t_R = 14.9 \) min (minor) and \( t_R = 17.8 \) min (major).

\[ [\alpha]_D^{25} = 41.2 \ (c\ 0.90, \ CHCl_3) \ \text{Lit}^{[158]} \]

**S)-Flurbiprofen (32p)**

Prepared according to general procedure using 2-(3-fluoro-4-phenyl-phenyl)-2-methyl-1,1-bis(trimethylsilyloxy)ethane (31p) (70 mg, 0.2 mmol) and obtained after extraction as a colorless solid (43 mg, 0.18 mmol, 89% yield, 95:5 er).

1H NMR (501 MHz, CDCl3) \( \delta = 7.53 \) (m, 2H), 7.48–7.31 (m, 4H), 7.22–7.11 (m, 2 H), 3.80 (q, \( J = 7.2 \) Hz, 1H), 1.57 ppm (d, \( J = 7.2 \) Hz, 3H), [acid proton not visible due to fast exchange].

13C NMR (126 MHz, CDCl3) \( \delta = 178.71, 159.69 \) (d, \( J = 248.5 \) Hz), 140.95 (d, \( J = 7.6 \) Hz), 135.40, 130.91 (d, \( J = 4.1 \) Hz), 128.96, 128.94, 128.45, 128.45, 128.21(d, \( J = 13.5 \) Hz), 127.71, 123.66 (d, \( J = 3.6 \) Hz), 115.46 (d, \( J = 23.6 \) Hz), 44.64, 18.06 ppm.

19F NMR (471 MHz, CDCl3) \( \delta = -117.39 \).

HRMS (GC-EI) m/z calculated for C15H13FO2 [M]: 244.0900; found 244.0895.
The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak OD-3, n-Heptane/iPrOH/TFA = 97.9:2:0.1 (v/v/v), flow rate = 1 mL/min, 25 °C, λ = 210 nm, t<sub>R</sub> = 8.46 min (minor) and t<sub>R</sub> = 9.47 min (major).

[α]<sup>25</sup><sub>0</sub> = 29.2 (c 0.95, CHCl<sub>3</sub>). Lit<sup>158</sup>

(S)-Fenoprofen (32n)

Prepared according to general procedure using 2-m-phenoxyphenyl-2-methyl-1,1-bis(trimethylsilyloxy)ethane (31n) (68 mg, 59 µL, 0.2 mmol) and obtained after extraction as a colorless solid (35 mg, 0.16 mmol, 76%, 92:8 er).

<sup>1</sup>H NMR (501 MHz, CDCl<sub>3</sub>) δ = 7.36–7.30 (m, 2H), 7.30–7.26 (m, 1H), 7.13–7.08 (m, 1H), 7.08–7.04 (m, 1H), 7.03–6.97 (m, 3H), 6.88 (ddd, J = 8.1, 2.5, 0.9 Hz, 1H), 3.71 (q, J = 7.2 Hz, 1H), 1.50 ppm (d, J = 7.2 Hz, 3H), [acid proton not visible due to fast exchange].

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ = 179.56, 157.49, 156.92, 141.68, 129.88, 129.76, 123.38, 122.35, 118.98, 118.98, 118.22, 117.50, 77.27, 77.01, 76.76, 45.09, 18.09 ppm.

HRMS (GC-EI) m/z calculated for C<sub>15</sub>H<sub>14</sub>O<sub>3</sub> [M]: 242.0943; found 242.0946.

The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak OD-3, n-Heptane/iPrOH/TFA = 97.9:2:0.1 (v/v/v), flow rate = 1 mL/min, 25 °C, λ = 210 nm, t<sub>R</sub> = 15 min (minor) and t<sub>R</sub> = 17.8 min (major).

[α]<sup>25</sup><sub>0</sub> = 39.1 (c 1.05, CHCl<sub>3</sub>). Lit<sup>158</sup>

(S)-2-phenylpropanoic acid (32a)

Prepared according to the general procedure using water as the proton source (6 µL, 0.11 mmol, 0.55 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (2% solution, v%) and 2-methyl-2-phenyl-1,1-bis(trimethylsilyloxy)ethane (31a) (59 mg, 59 µL, 0.2 mmol). The product was obtained after extraction as a colorless liquid (27 mg, 0.18 mmol, 82% yield, 95:5 er).

Analytics matched compound 31a.
(S)-Ibuprofen (32o)

Prepared according to the general procedure using water as the proton source (6 µL, 0.11 mmol, 0.55 equiv.) in CH₂Cl₂ (2% solution, v%) and 2-p-isobutylphenyl-2-methyl-1,1-bis(trimethylsilyloxy)ethane (31o) (70 mg, 62 µL, 0.2 mmol) and obtained after extraction as a colorless solid (33 mg, 0.17 mmol, 82% yield, 95.5:4.5 er). Analytics matched compound 31o.

7.2.4 General Procedure for the Asymmetric Deuteration of Bis-SKAs

An oven dried 2 mL vial was charged with disulfonamide 17o (4.0 µmol, 3.2 mg, 2 mol%), a magnetic stir bar and, under argon atmosphere, dry CH₂Cl₂ (0.5 mL) and bis-silyl ketene acetal 31 (0.2 mmol, 1 equiv.) were added. Then CD₃OD (9 µL, 0.22 mmol, 1.1 equiv.) in CH₂Cl₂ (2% solution, v%) was added over 15 min via Hamilton syringe using a syringe pump (33 µL/min). Afterwards, the reaction mixture was acidified with HCl (1M) and extracted with Et₂O (3x3 mL), and the combined organic phase was dried over MgSO₄ and purified by column chromatography (CH₂Cl₂:MeOH, 98:2, v/v). The obtained product (67) was dissolved in HPLC grade Hept:iPrOH (1:1, v/v) and directly used for the determination of the enantiomeric ratio.
Experimental Section

**(S)-2-phenylpropanoic acid (67a)**

Prepared according to general procedure using 2-methyl-2-phenyl-1,1-bis(trimethylsilyloxy)ethane (31a) (59 mg, 59 µL, 0.2 mmol) and obtained after extraction as a colorless liquid (25 mg, 0.16 mmol, 77% yield, 95.5:4.5 er).

$^1$H NMR (501 MHz, CDCl$_3$) δ = 7.41–7.28 (m, 4H), 7.27–7.21 (m, 1H), 1.50 ppm (s, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ = 180.68, 139.77, 139.72, 128.68, 127.61, 127.59, 127.39, 45.00 ($J = 19.2$ Hz), 18.01 ppm.

HRMS (GC-CI) m/z calculated for C$_9$H$_9$DO$_2$: 151.07436; found 151.07435.

The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak OD-3, n-Heptane/iPrOH/TFA = 97.9:2:0.1 (v/v/v), flow rate = 1 mL/min, 25 °C, λ = 210 nm, $t_R = 6.57$ min (minor) and $t_R = 7.62$ min (major)

$[^{[\alpha]}]D_{25} = 35.1$ (c 1.05, CHCl$_3$). Lit$^{[159]}$

**(S)-Ibuprofen-d (67b)**

Prepared according to general procedure using 2-p-isobutylphenyl-2-methyl-1,1-bis(trimethylsilyloxy)ethane (31o) (70 mg, 62 µL, 0.2 mmol) and obtained after extraction as a colorless solid (40 mg, 0.19 mmol, 94% yield, 95:5 er).

$^1$H NMR (501 MHz, CD$_2$Cl$_2$) δ = 7.29–7.17 (m, 2H), 7.15–7.05 (m, 2H), 2.45 (d, $J = 7.2$ Hz, 2H), 1.85 (dhept, $J = 13.6, 6.8$ Hz, 1H), 1.46 (s, 3H), 0.90 ppm (d, $J = 6.6$ Hz, 6H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ = 178.25, 141.28, 138.43, 129.86, 129.86, 127.77, 127.77, 49.77 (t [1:1:1], $J = 19.9$ Hz), 45.50, 30.81, 22.67, 22.67, 18.67 ppm.

HRMS (GC-CI) m/z calculated for C$_{13}$H$_{17}$DO$_2$: 207.1367; found 207.1368.

The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak OD-3, n-Heptane/iPrOH/TFA = 97.9:2:0.1 (v/v/v), flow rate = 1 mL/min, 25 °C, λ = 210 nm, $t_R = 5.37$ min (minor) and $t_R = 6.11$ min (major)

$[^{[\alpha]}]D_{25} = 37.9$ (c 0.95, CHCl$_3$). Lit$^{[158]}$
Experimental Section

(R)-2-phenylacetic-2-d acid (67c)
Prepared according to general procedure using 2-(3-fluoro-4-phenyl-phenyl)-2-methyl-1,1-bis(trimethylsilyloxy)ethane (31r) (70 mg, 79 μL, 0.2 mmol) and obtained after extraction as a clear liquid (43 mg, 0.18 mmol, 89% yield, 81:19 er).

\[ \text{HRMS (GC-Cl) } m/z \text{ calculated for C}_9\text{H}_7\text{DO}_2: 137.0587; \text{ found 137.0586.} \]

The enantiomeric ratio was determined by \( ^1\text{H} \) NMR analysis upon derivatization to the corresponding Mosher ester (Scheme 1), following the reported procedure for the derivatization and the diastereomeric ratio determination.\[^{122}\]

\[ [\alpha]_D^{25} = 0.6 \text{ (c 0.60, CHCl}_3). \text{ Lit}^{[^{158}]}

\[ \text{Scheme 1. Derivatization sequence for the determination of the enantiomeric ratio.} \]

(R)-2-phenylethanol-2-d-1-ol (4u)

\[ \text{\( ^1\text{H} \) NMR (501 MHz, CDCl}_3) \delta = 7.36–7.28 \text{ (m, 2H), 7.28–7.20 \text{ (m, 3H), 3.87 (dt, J = 6.6, 0.9 Hz, 2H), 2.86 (ddt, J = 6.6, 4.1, 2.1 Hz, 1H), 1.43 ppm (bs, 1 H).} \]

(R)-2-phenylethyl-2-d (R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (5u)

\[ \text{\( ^1\text{H} \) NMR (500 MHz, CD}_2\text{Cl}_2) \delta = 7.44–7.39 \text{ (m, 3H), 7.39–7.34 \text{ (m, 2H), 7.31–7.25 \text{ (m, 2H), 7.25–7.20 \text{ (m, 1H), 7.20–7.16 \text{ (m, 2H), 4.61–4.44 \text{ (m, 2H), 3.44 (s, 3H), 2.99 ppm (dtt, J = 13.9, 7.1, 1.9 Hz, 1H).} \]

\[ \text{145} \]
Gram Scale Reaction

A stirring solution of acid rac-32o (5.2 g, 24.7 mmol, 1.0 equiv.) and Me₃SiCl (6.9 mL, 54.3 mmol, 2.2 equiv.) in THF (200 mL) under an atmosphere of dry argon was cooled to −78 °C. The freshly prepared LDA solution (54.3 mmol, 1 M, 55 mL 2.2 equiv.) was added dropwise at −78 °C via canula. The ice bath was removed upon complete addition and the reaction solution was stirred for 1 hour at room temperature. The reaction mixture was concentrated in vacuo. Hexane (50 mL) was added to the residue and the organic layer was filtered under argon. After concentration under reduced pressure, the crude product (31o) was dissolved in dry CH₂Cl₂ (60 mL) and a solution of catalyst 17o (200 mg, 1 mol%) in CH₂Cl₂ (40 mL) was added at room temperature. A solution of MeOH (1.1 mL, 32 mmol, 1.1 equiv.) in CH₂Cl₂ (19 mL) was added via syringe pump (0.66 mL/min) in 30 min. The reaction mixture was diluted with HCl (1 M, 2 mL), stirred for 5 min, and the organic phase was concentrated in vacuo and diluted with Et₂O (50 mL). The crude mixture was extracted with aq. NaOH (1 M, 3x30 mL). The organic phase was acidified HCl (6 M) for 5 min, extracted with CH₂Cl₂ (3x50 mL), and the solvent was removed under reduced pressure to fully recycle catalyst 17o. The aqueous phase was acidified with HCl (1 M, 50 mL) and extracted with Et₂O (3x50 mL). The combined organic phase was dried over MgSO₄ and the solvent was removed under reduced pressure to yield the desired product 32o as a colorless solid (4.81 g, 23.3 mmol, 95% yield, 95:5 er).
7.2.6 Synthesis and Characterization of DSI Catalysts

Compound 48 and 17g were synthetized following the reported procedure $^{[160]}$

2,6-di(phenanthren-9-yl)-4H-dinaphtho[2,1-d:1’,2’-f][1,3,2]dithiazepine 3,3,5,5-tetraoxide (17g)

In an oven dried microwave vial (5 mL) (S)-3,3′-diiododisulfonimide (48, 100 mg, 0.15 mmol, 1 equiv.), 9-phenanthracenyl boronic acid (137 mg, 0.45 mmol, 3 equiv.), K$_2$CO$_3$ (85 mg, 0.6 mmol, 4 equiv.), Palladium(II)-acetate (3.5 mg, 0.015 mmol, 10 mol%) were suspended in THF/water (4 mL, 1:1, v/v) under an atmosphere of dry argon. Tri-tert-butylphosphine (1 M, dioxane solution) (0.1 mL, 81 mg, 0.1 mmol) was added and the vial was sealed and heated for 30 min at 120 °C in a microwave reactor. The reaction was poured into HCl (1 N, 5 mL) and extracted with CH$_2$Cl$_2$ (3x10mL), and the combined organic layers were washed with water (10 mL) and brine (2x10 mL). The organic layer was dried over MgSO$_4$, and the product was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH = 100:0 to 98:2). The purified product was dissolved in CH$_2$Cl$_2$ (30 mL), acidified with HCl (6 M, 20 mL) and the solvent was removed in vacuo to obtain the targeted product 17g as pale yellow solid (96 mg, 84% yield).

Note: Upon acidification, catalyst 17g equilibrates to an unseparable mixture of 3 rotamers
**Experimental Section**

**1H NMR** (501 MHz, CDCl₃) δ = 8.87–8.71 (m, 4H), 8.34–8.17 (m, 2H), 8.17–8.02 (m, 2H), 8.02–7.92 (m, 2H), 7.92−7.85 (m, 2H), 7.85–7.76 (m, 2H), 7.76–7.35 (m, 14H), 1.53 ppm (bs, 1H).

**13C NMR** (126 MHz, CDCl₃) δ = 138.30, 138.25, 138.06, 136.04, 135.48, 135.35, 135.27, 135.11, 134.88, 134.86, 134.77, 134.75, 134.29, 134.24, 133.91, 133.75, 133.47, 133.04, 132.98, 132.44, 132.42, 132.28, 132.22, 132.16, 132.07, 131.34, 131.29, 131.17, 131.13, 130.41, 130.39, 130.36, 130.34, 129.93, 129.81, 129.79, 128.85, 128.74, 128.68, 128.61, 128.53, 128.48, 128.40, 128.26, 128.24, 127.92, 127.45, 127.43, 127.14, 127.03, 126.98, 126.94, 126.92, 126.90, 126.88, 126.81, 126.78, 126.53, 126.50, 126.46, 126.09, 126.01, 123.11, 122.90, 122.87, 122.72, 122.69 ppm.

**2-(anthracen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (81)**

![Reaction Scheme](image)

In a vial with stir bar was charged with 1-chloro-anthracene (500 mg, 2.4 mmol, 1.0 equiv.), anhydrous NaOAc (385 mg, 4.7 mmol, 2.0 equiv.), B₂Pin₂ (627 mg, 2.5 mmol, 1.05 equiv.), Pd(dbach₂ (13.5 mg, 0.02 mmol, 1 mol%), XPhos (11.2 mg, 0.02 mmol, 1 mol%). The vial was transferred to a preheated oil bath (110 °C). After 16 h, the reaction mixture was cooled, dissolved in CH₂Cl₂−H₂O mixture (1:1, v/v), the organic phase separated, the solvent evaporated under vacuum and the product isolated by flash chromatography on silica gel by elution with hexanes/CH₂Cl₂ (9:1 to 7:3), to obtain 81 (535 mg, 1.8 mmol, 76% yield).

**1H NMR** (501 MHz, CDCl₃) δ = 9.35 (s, 1H), 8.42 (s, 1H), 8.17−8.05 (m, 3H), 8.04−7.94 (m, 1H), 7.56−7.36 (m, 3H), 1.48 ppm (s, 12H).
Experimental Section

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ = 135.98, 134.31, 132.02, 131.98, 131.98, 131.58, 131.24, 128.97, 127.87, 127.30, 126.61, 125.30, 125.10, 124.54, 83.82, 83.82, 25.04, 25.04, 25.04, 25.04 ppm.

HRMS (EI) $m/z$ calculated for C$_{20}$H$_{21}$O$_2$B$_1$ [M]: 304.1635; found 304.1637.

2,6-di(anthracen-1-yl)-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine 3,3,5,5-tetraoxide (17h)

In a 25 mL Schlenk flask were placed (S)-48 (387 mg, 0.6 mmol, 1 equiv.), aryl boronic ester 81 (545 mg, 1.8 mmol, 3 equiv.), Pd(OAc)$_2$ (10.5 mg, 0.05 mmol, 8 mol%), 6 mL of THF and 2 M aqueous K$_2$CO$_3$ (6 mL). The reaction flask was evacuated and filled with Ar for three times with stirring. P(Ph)$_3$ (94 $\mu$L, 0.09 mmol, 15 mol%) was then added. The reaction mixture was heated at 80 °C until the consumption of the starting material (16 h). After the reaction was completed, the resulting mixture was acidified with 1 N HCl and extracted with CHCl$_3$ for three times. The combined organic phase was dried over MgSO$_4$ followed by filtration and evaporation. The crude product was purified by column chromatography (DCM:MeOH, 98:2) to give the coupled compound 17h as a solid.
Experimental Section

$^1$H NMR (501 MHz, CDCl$_3$) δ = 8.42 (s, 1H), 8.23 (d, J = 0.8 Hz, 1H), 8.10–8.00 (m, 3H), 7.93–7.88 (m, 1H), 7.76 (ddd, J = 8.2, 6.8, 1.2 Hz, 1H), 7.69–7.62 (m, 2H), 7.57 (dd, J = 8.5, 6.7 Hz, 1H), 7.52 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 7.44 (dq, J = 8.7, 0.9 Hz, 1H), 7.32 (ddd, J = 8.3, 6.5, 1.2 Hz, 1H), 7.17 ppm (ddd, J = 8.1, 6.5, 1.2 Hz, 1H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ = 138.49, 136.99, 135.64, 134.97, 134.13, 133.59, 132.09, 131.83, 131.75, 131.48, 131.09, 130.00, 128.69, 128.64, 128.61, 128.37, 128.36, 127.70, 126.47, 125.87, 125.59, 125.50, 125.14, 124.42 ppm.

HRMS (ESI) m/z calculated for C$_{48}$H$_{28}$N$_{4}$O$_{3}$S$_{2}$ [M–H]: 746.1465; found 746.1470.

Synthesis of Tetrathene Derivatives
Experimental Section

**6,7-dibromo-1,4,4a,8a-tetrahydro-1,4-epoxynaphthalene (49)**

![Chemical Structure](image)

Under inert conditions 1,2,4,5-tetrabromobenzene (8.0 g, 20.5 mmol, 1.0 equiv.) was dissolved in dry toluene (200 mL). Dry furan (10 mL, 137 mmol, 6.8 equiv.) was added and the solution was cooled down to $-30$ °C, which led to the precipitation of starting compound. $n$-Butyl lithium (9 mL, 2.4M in hexane, 22.6 mmol) was added dropwise during 20 minutes. Following an additional 15 min stirring at $-30$ °C, the mixture was warmed to 25 °C and MeOH (1 mL) was added. The solution was washed with water (30 mL) and brine (30 mL), the organic layer was dried with MgSO$_4$ and all solvents were evaporated under vacuum. The brownish raw product was applied onto silica gel via dichloromethane and subjected to column chromatography (hexanes/EtOAc, 10:1) to yield a yellowish oil, which upon cooling crystallized to give a colourless solid (4.1 g, 66%).

$^1$H NMR (501 MHz, CDCl$_3$) $\delta = 7.48$ (s, 2H), 7.03–6.97 (m, 2H), 5.68–5.65 ppm (m, 2H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta = 150.2, 150.2, 142.7, 142.7, 125.5, 125.5, 120.7, 120.7, 81.8$ 81.8 ppm.

**2,3-dibromonaphthalene (50)**

![Chemical Structure](image)

TiCl$_4$ (8.5 mL, 75 mmol) was added dropwise to a stirred suspension of Zn-dust (8.5 g, 125 mmol) in THF (150 mL) at 0 °C under Ar carefully. (Caution: Violent reaction)
The resulting mixture was heated to reflux for 5 min then cooled to 0 °C again. Compound 49 (4 g, 13.2 mmol, 1 equiv.) was added in THF solution (15 mL) and the mixture was heated at reflux for an additional 3 h. After cooling to 25 °C, it was poured on ice cold aqueous HCl (0.1 M, 300 mL), followed by extraction with CH₂Cl₂. The organic phase was washed with water (30 mL) and brine (30 mL), dried, MgSO₄ and filtered. After removal of the solvent under reduced pressure, purification by column chromatography (hexanes) gave 50 as white crystals (3.5 g, 92% yield).

**1H NMR** (500 MHz, CDCl₃) δ = 8.14 (s, 2H), 7.73 (dd, J = 6.2, 3.2, 2H), 7.51 ppm (dd, J = 6.3, 3.2, 2H).

**13C NMR** (125 MHz, CDCl₃) δ = 133.0, 132.2, 132.2, 127.2, 127.2, 126.9, 126.9, 122.0, 122.0 ppm.

In agreement with literature data.¹⁶¹

3-bromo-2-naphthaldehyde (51)

![](image)

*iPrMgCl-LiCl (1.3M in THF, 5.0 mL, 6.8 mmol, 1.0 equiv.) was added dropwise to a solution of compound 50 (1.86 g, 1.75 mmol) in THF (50 mL) at 0 °C under Ar in 10 min. After stirring for 90 min at 0 °C, DMF (3 mL, 38.7 mmol, 6 equiv.) was added and the mixture stirred for an additional 15 min at 0 °C. The mixture was treated with water (100 mL) and the aqueous mixture extracted with EtOAc. The organic phase was washed with water (50 mL) and brine (30 mL), dried over MgSO₄ and filtered. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (hexanes/EtOAc, 20:1) giving 51 as a colorless solid (692 mg, 45% yield).
Experimental Section

$^1$H NMR (500 MHz, CDCl$_3$) $\delta =$ 10.51 (s, 1H), 8.47 (s, 1H), 8.13 (s, 1H), 8.00–7.94 (m, 2H), 7.82–7.78 (m, 1H), 7.64 (ddd, $J =$ 8.2, 6.8, 1.3 Hz, 1H), 7.58 ppm (ddd, $J =$ 8.2, 6.8, 1.3 Hz, 1H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta =$ 192.1, 137.1, 132.7, 132.1, 131.7, 130.7, 130.2, 130.1, 127.6, 127.6, 127.1, 120.7 ppm.

In agreement with literature data.$^{[162]}$

Synthesis of 3-Aryl-2-naphthaldehyde Derivatives (52a–52c)

In an oven dried microwave vial (5 mL) 51 (1 equiv.), boronic acid (1.2 equiv.), CsF (2.8 equiv.), tetrakis(triphenylphosphine) palladium(0) (5 mol%) were suspended in DME (0.5 M) under an atmosphere of dry argon. The vial was sealed and heated for 1 h at 120 °C in a microwave reactor. The reaction was poured into water (5 mL) and extracted with EtOAc (3x10mL), and the combined organic layers were washed with brine (2x10 mL). The organic layer was dried over MgSO$_4$, and the product was purified by flash column chromatography (hexanes/EtOAc = 100:0 to 80:20). The targeted product as a colorless solid.

3-phenyl-2-naphthaldehyde (52a)

Prepared according to general procedure for 3-aryl-2-naphthaldehyde derivatives using 3-bromo-2-naphthaldehyde (51) (70 mg, 0.3 mmol) and obtained after extraction as a colorless solid (63 mg, 0.28 mmol, 96% yield).
1H NMR (500 MHz, CDCl$_3$) $\delta = 10.13$ (s, 1H), 8.58 (s, 1H), 8.07–8.01 (m, 1H), 7.93–7.89 (m, 1H), 7.88 (s, 1H), 7.65 (ddd, $J = 8.1$, 6.8, 1.3 Hz, 1H), 7.58 (ddd, $J = 8.2$, 6.9, 1.3 Hz, 1H), 7.54–7.43 ppm (m, 6H).

3-(3,4-dimethylphenyl)-2-naphthaldehyde (52b)

Prepared according to general procedure for 3-aryl-2-naphthaldehyde derivatives using 3-bromo-2-naphthaldehyde (51) (70 mg, 0.3 mmol) and obtained after extraction as a colorless solid (70 mg, 0.28 mmol, 90% yield).

1H NMR (501 MHz, CDCl$_3$) $\delta = 10.07$ (s, 1H), 8.49 (s, 1H), 7.96 (dd, $J = 8.2$, 1.1 Hz, 1H), 7.82 (dd, $J = 8.4$, 1.0 Hz, 1H), 7.79 (s, 1H), 7.56 (ddd, $J = 8.2$, 6.9, 1.3 Hz, 1H), 7.49 (ddd, $J = 8.2$, 6.9, 1.3 Hz, 1H), 7.42–7.37 (m, 1H), 7.22–7.16 (m, 1H), 7.13 (dd, $J = 7.7$, 2.1 Hz, 1H), 2.32–2.27 ppm (m, 6H).

3-(3,5-bis(trifluoromethyl)phenyl)-2-naphthaldehyde (52c)

Prepared according to general procedure for 3-aryl-2-naphthaldehyde derivatives using 3-bromo-2-naphthaldehyde (51) (70 mg, 0.3 mmol) and obtained after extraction as a colorless solid (76 mg, 0.20 mmol, 69% yield).

1H NMR (501 MHz, CDCl$_3$) $\delta = 10.10$ (s, 1H), 8.57 (s, 1H), 8.14–8.05 (m, 1H), 7.98–7.92 (m, 2H), 7.90 (d, $J = 1.6$ Hz, 2H), 7.84 (s, 1H), 7.72 (ddd, $J = 8.2$, 6.9, 1.3 Hz, 1H), 7.67 ppm (ddd, $J = 8.1$, 6.9, 1.3 Hz, 1H).
**Experimental Section**

**Synthesis of 2-(Bromoethynyl)-3-arylnaphthalene Derivatives (53a–53c)**

![Chemical Structures]

**Step 1:** CBr₄ (2.5 equiv.) was added to a solution of PPh₃ (5 equiv.) in DCM (6 ml) and the resulting mixture was stirred for 10 min at 0°C. A solution of 3-aryl-2-naphthaldehydes (52a–52c) (1 equiv.) in DCM (4 ml) was slowly introduced and stirring was continued for 1 h at 0°C. The reaction was then quenched with brine (20 mL), the aqueous layer was repeatedly extracted with DCM (3x 20 mL), and the combined organic layer were dried with MgSO₄ and evaporated. The residue was purified with chromatography (hexanes/EtOAc, 95:5). The intermediate dibromocompound (A–C) was directly subjected to the following synthetic step.

**Step 2:** A solution of DBU (58 µl) in DMSO (2 ml) was added to a cooled solution of dibromide (A–C) (50 mg) in DMSO (20 ml) at such rate to maintain the internal temperature below 15 °C. The resulting mixture was stirred for 1 h before the reaction was quenched with aq HCl at 0°C.

**2-(bromoethynyl)-3-phenynaphthalene (53a)**

Prepared according to general procedure for 2-(bromoethynyl)-3-arylnaphthalene derivatives using 3-phenyl-2-naphthaldehyde (52a) (38 mg, 0.16 mmol) and obtained after two steps as a pale yellow solid (38 mg, 0.12 mmol, 75% yield).

**Intermediate A:** ¹H NMR (501 MHz, CDCl₃) δ = 8.16 (s, 1H), 7.93 – 7.88 (m, 1H), 7.88 – 7.83 (m, 1H), 7.82 (s, 1H), 7.56 – 7.39 (m, 6H), 7.31 ppm (d, J = 1.0 Hz, 1H).
Experimental Section

\(^1\)H NMR (501 MHz, CDCl\(_3\)) \(\delta = 8.11\) (s, 1H), 7.85 – 7.77 (m, 3H), 7.69 – 7.61 (m, 2H), 7.54–7.43 (m, 4H), 7.44–7.37 ppm (m, 1H).

2-(bromoethynyl)-3-(3,4-dimethylphenyl)naphthalene (53b)

Prepared according to general procedure for 2-(bromoethynyl)-3-arylnaphthalene derivatives using 3-(3,4-dimethylphenyl)-2-naphthaldehyde (52b) (26 mg, 0.10 mmol) and obtained after two steps as a pale yellow solid (38 mg, 0.07 mmol, 75% yield).

\(^1\)H NMR (501 MHz, CDCl\(_3\)) \(\delta = 8.10\) (d, \(J = 0.8\) Hz, 1H), 7.85–7.77 (m, 3H), 7.52–7.43 (m, 3H), 7.41 (dd, \(J = 7.7, 2.0\) Hz, 1H), 7.23 (d, \(J = 7.7\) Hz, 1H), 2.36 (s, 3H), 2.34 ppm (s, 3H).

2-(3,5-bis(trifluoromethyl)phenyl)-3-(bromoethynyl)naphthalene (53c)

Prepared according to general procedure for 2-(bromoethynyl)-3-arylnaphthalene derivatives using 3-(3,5-bis(trifluoromethyl)phenyl)-2-naphthaldehyde (52c) (36 mg, 0.10 mmol) and obtained after two steps as a pale yellow solid (38 mg, 0.12 mmol, 69% yield).

\(^1\)H NMR (501 MHz, CDCl\(_3\)) \(\delta = 8.17–8.15\) (m, 1H), 8.15–8.12 (m, 2H), 7.94–7.90 (m, 1H), 7.90–7.83 (m, 3H), 7.61–7.53 ppm (m, 2H).
Synthesis of 6-Bromo-tetraphene Derivatives (54a–54c)

In an oven dried microwave vial (5 mL) 2-(bromoethynyl)-3-arylnaphthalene derivatives (53a–52c) (1 equiv.) and AuCl (20 mol%) were dissolved in toluene (0.5 M) under an atmosphere of dry argon. The vial was sealed and heated for 1 h at 120 °C in a microwave reactor. The reaction was directly concentrated under reduced pressure and the crude reaction mixture was purified by flash column chromatography (hexanes/EtOAc = 100:0 to 95:5). The targeted product as pale yellow solid.

6-bromo-tetraphene (54a)

Prepared according to general procedure for 6-bromo-tetraphene derivatives (54a–54c) using 2-(bromoethynyl)-3-phenynaphthalene (53a) (31 mg, 0.10 mmol) and obtained after column chromatography as a pale yellow solid (20 mg, 0.1 mmol, 65% yield).

$^1$H NMR (501 MHz, CDCl$_3$) δ = 9.18 (s, 1H), 8.86 (s, 1H), 8.81 (d, $J = 8.2$ Hz, 1H), 8.19–8.11 (m, 2H), 8.04 (s, 1H), 7.79–7.74 (m, 1H), 7.71 (ddd, $J = 8.4$, 7.1, 1.4 Hz, 1H), 7.66–7.58 ppm (m, 3H).

6-bromo-2,3-bis-methyl-tetraphene and 6-bromo-3,4-dimethyl-tetraphene (54b)

Prepared according to general procedure for 6-bromo-tetraphene derivatives (54a–54c) using 2-(bromoethynyl)-3-(3,4-dimethylphenyl)naphthalene (53b) (32 mg, 0.10 mmol). The desired regioisomers could not be separated by column chromatography.
After repeated attempts to purify the compounds, the final products could not be recovered as they fully decomposed (the compounds are unstable in the presence of oxygen and light).

2,4-bis-trifluoromethyl-6-bromo-tetraphene (54c)

The desired product was not formed and only starting material was recovered. Increasing the AuCl catalyst loading, the reaction time or the temperature led to decomposition to undefined by-products.

Boronic acid 82

A two-necked 25 mL flask was charged with 6-bromo-tetraphene (54a) (20 mg, 0.1 mmol) under argon. Dry THF (3 mL) was added, and the solution was cooled to 78 °C. To this solution was added n-butyllithium (40 µL, 2.5 M, 0.1 mmol) dropwise. The solution was stirred at -78 °C for 2 h whereupon trimethyl borate (16 µg, 0.15 mmol) dissolved in 1 mL of dry THF was added dropwise through the second dropping funnel. The solution was allowed to warm to room temperature overnight. The crude reaction was checked via 1H-NMR, however the desired compound was not identified and exclusively highly unsoluble solids were obtained.
Experimental Section

Synthesis of DSI 17o

Compound 64d was synthesized following a modification of the reported procedure.\textsuperscript{163}

2-(3,5-dimethylphenyl)benzaldehyde (61d)

In a oven dried 20 mL microwave vial under an atmosphere of dry argon 2-bromobenzaldehyde 58 (1.0 g, 5.4 mmol, 1 equiv.), 3,5-dimethylphenyl boronic acid 60 (0.97 g, 6.5 mmol, 1.2 equiv.), cesium fluoride (2.3 g, 15.1 mmol, 2.8 equiv.) and
tetrakis(triphenylphosphine)palladium(0) (0.313 g, 0.27 mmol, 5 mol%) were added and suspended in degassed 1,2-DME (10 mL). The vial was sealed and heated at 120 °C for 1 hour in a microwave reactor. The reaction mixture was diluted with EtOAc (30 mL) and water (30 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were dried over MgSO₄, concentrated under reduced pressure and the crude product was purified by flash column chromatography (Hexanes/EtOAc = 100:0 to 95:5) to obtain **61d** as a colorless solid (1.06 g, 5.0 mmol, 93% yield).

**1H NMR** (501 MHz, CDCl₃) δ = 9.99 (d, J = 0.8 Hz, 1H), 8.01 (dd, J = 7.8, 1.5 Hz, 1H), 7.62 (td, J = 7.5, 1.5 Hz, 1H), 7.47 (tt, J = 7.6, 1.1 Hz, 1H), 7.44 (dd, J = 7.7, 1.2 Hz, 1H), 7.08 (s, 1H), 7.00 (s, 2H), 2.46–2.31 ppm (m, 6H).

**13C NMR** (126 MHz, CDCl₃) δ 192.89, 146.49, 138.16, 137.80, 133.90, 133.59, 130.83, 129.86, 128.19, 127.68, 127.51, 21.45 ppm.

**HRMS** (GC–EI) m/z calculated for C₁₅H₁₄O [M]: 210.1041; found 210.1039.

**2-(2,2-dibromovinyl)-3',5'-dimethyl-1,1'-biphenyl (62d)**

CB₄ (4.20 g, 12.6 mmol, 2.5 equiv.) was added portion wise to a solution of PPh₃ (6.7 g, 25.0 mmol, 5.0 equiv.) in CH₂Cl₂ (20 mL) and the resulting yellow mixture was stirred for 10 min at 0 °C. A solution of 2-(3,5-dimethylphenyl)benzaldehyde (**61d**; 1.06 g, 5.0 mmol, 1.0 equiv.) in CH₂Cl₂ (20 mL) was added dropwise and stirring was continued for an additional 1 h at 0 °C. The reaction was then quenched with brine and the aqueous layer was extracted with CH₂Cl₂ (3×20 mL). The combined organic layers were dried over MgSO₄, concentrated under reduced pressure and the crude product was purified by flash column chromatography (Hexanes/EtOAc = 100:0 to 95:5) to obtain **62d** as a colorless solid (1.60 g, 88% yield)

**1H NMR** (501 MHz, CDCl₃) δ = 7.73–7.65 (m, 1H), 7.43–7.32 (m, 3H), 7.23 (s, 1H), 7.02 (s, 1H), 6.95 (s, 2H), 2.38 ppm (s, 6H).
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$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta =$ 141.17, 139.87, 137.62, 137.59, 132.86, 132.03, 131.80, 129.62, 129.04, 128.97, 128.43, 128.33, 127.29, 126.78, 90.23, 21.25 ppm.

**HRMS** (GC–EI) $m/z$ calculated for C$_{16}$H$_{14}$Br$_2$ [M]: 363.9460; found 363.9457.

**2-(bromoethynyl)-3',5'-dimethyl-1,1'-biphenyl (63d)**

A solution of DBU (1.4 mL, 9.8 mmol, 3.0 equiv.) in DMSO (20 mL) was added to a cooled solution of 62d (1.2 g, 3.3 mmol, 1.0 equiv.) in DMSO (30 ml) at such rate to maintain the internal temperature below 15 °C. The resulting mixture was stirred at 15 °C for 1 h before the reaction was quenched with aq. HCl (1M) at 0°C. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 20 mL) and the combined organic layers were washed with sat. aq. NaHCO$_3$ solution (20 mL), water (10 mL) and brine (2x10 mL). Afterwards, the organic layer was dried over MgSO$_4$, the solvent was removed under reduced pressure to obtain 63d as a colorless solid (703 mg, 75% yield) without further purification.

$^1$H NMR (501 MHz, CDCl$_3$) $\delta =$ 7.55 (dt, $J =$ 7.6, 1.0 Hz, 1H), 7.38 (dd, $J =$ 3.9, 0.9 Hz, 2H), 7.31–7.23 (m, 1H), 7.23–7.18 (m, 2H), 7.02 (m, 1H), 2.41–2.35 ppm (m, 6H).

**HRMS** (GC–EI) $m/z$ calculated for C$_{15}$H$_{13}$Br [M]: 284.0197; found 284.0195.

**9-Bromo-1,3-dimethyl-phenanthrene (64d)**

In an oven-dried 5 mL microwave vial under an atmosphere of dry argon, AuCl (102 mg, 0.44 mmol, 20 mol%) and 63d (630 mg, 2.2 mmol, 1.0 equiv.) in toluene (3 mL) were heated at 100°C for 1 h. The mixture was then adsorbed on silica gel and purified by flash chromatography (Hexanes/EtOAc = 9:1 to 8:2) to obtain 64d as a colorless solid (576 mg, 91% yield).
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$^1$H NMR (501 MHz, CDCl$_3$) $\delta$ = 8.73–8.64 (m, 1H), 8.39–8.29 (m, 2H), 8.26 (s, 1H), 7.73–7.62 (m, 2H), 7.29 (s, 1H), 2.69 (s, 3H), 2.57 ppm (s, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ = 136.41, 134.03, 131.40, 130.22, 130.17, 130.05, 129.17, 127.97, 127.23, 127.16, 126.85, 123.10, 120.75, 120.62, 22.10, 19.69 ppm.

HRMS (GC–EI) $m/z$ calculated for C$_{16}$H$_{13}$Br [M]: 284.0201; found 284.0195.

1,3-dimethyl-phenanthren-9-yl boronic acid (65d)

An oven dried two-necked 100 mL flask was charged with 64d (570 mg, 2.0 mmol, 1.0 equiv.) under an atmosphere of dry argon. Dry THF (20 mL) was added and the resulting solution was cooled to $-78 \degree$C and n-butyllithium (0.8 mL, 2.6 M in hexane, 2 mmol, 1.0 equiv.) was added dropwise. The reaction mixture was stirred at $-78 \degree$C for 1 h and a solution of trimethyl borate (0.34 mL, 312 mg, 3 mmol, 1.5 equiv.) in dry THF (10 mL) was added dropwise. The solution was allowed to warm to room temperature overnight. The reaction was quenched with aq. HCl (1 M, 5 mL), concentrated under reduced pressure to 50% of its original volume and poured into H$_2$O. The resulted biphasic solution was extracted with Et$_2$O (2 x 50 mL). The ethereal solution was washed twice with H$_2$O and concentrated under reduced pressure. The targeted product 65d was obtained after filtration as a colorless solid (375 mg, 76% yield).

$^1$H NMR (501 MHz, d$_8$-THF) $\delta$ = 8.64 (ddd, $J$ = 19.4, 8.2, 1.5 Hz, 2H), 8.34 (m, 2H), 7.47 (m, 2H), 7.22 (s, 1H), 2.68 (s, 3H), 2.49 ppm (s, 3H), [acid proton not visible due to fast exchange].

$^{13}$C NMR (126 MHz, d$_8$-THF) $\delta$ = 135.98, 134.86, 134.40, 131.35, 130.20, 129.97, 129.48, 129.07, 127.88, 125.56, 125.35, 122.52, 120.11, 21.19, 18.94 ppm.

HRMS (ESI) $m/z$ calculated for C$_{16}$H$_{14}$BO$_2$ [M–H]$^-$: 249.1092; found 249.1096.
2,6-bis(1,3-dimethylphenanthren-9-yl)4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine 3,3,5,5-tetraoxide (17o)

In an oven dried microwave vial (5 mL) (S)-3,3'-diiododisulfonimide 48 (320 mg, 0.5 mmol, 1 equiv.), 65d (330 mg, 1.5 mmol, 3 equiv.), K₂CO₃ (273 mg, 2.0 mmol, 4 equiv.), Palladium(II)-acetate (11 mg, 0.05 mmol, 0.1 equiv, 10 mol%). were suspended in THF/water (4 mL, 1:1, v/v) under an atmosphere of dry argon. Tri-tert-butylphosphine (1M, dioxane solution) (0.1 mL, 81 mg, 0.1 mmol) was added and the vial was sealed and heated for 30 min at 120 °C in a microwave reactor. The reaction was poured into HCl (1N, 5 mL) and extracted with CH₂Cl₂ (3 x 10mL), and the combined organic layers were washed with water (10 mL) and brine (2x10 mL). The organic layer was dried over MgSO₄, and the product was purified by flash column chromatography (CH₂Cl₂/MeOH = 100:0 to 98:2). The purified product was dissolved in CH₂Cl₂ (30 mL), acidified with HCl (6 M, 20 mL) and the solvent removed in vacuo to obtain the targeted product as pale yellow solid (365 mg, 91% yield).

Note: Upon acidification, catalyst 17o equilibrates to an unseperable mixture of 3 rotamers (1.7:49:3.4).

¹H NMR (501 MHz, CDCl₃) δ = 8.82–8.72 (m, 2H), 8.41 (d, J = 4.4 Hz, 2H), 8.28–8.17 (m, 2H), 8.10–7.98 (m, 4H), 7.80–7.69 (m, 2H), 7.69–7.46 (m, 8H), 7.46–7.28 (m, 6H), 2.80–2.68 (m, 6H), 2.64–2.54 ppm (m, 6H).

¹³C NMR (126 MHz, CDCl₃) δ 138.28, 138.25, 138.04, 137.98, 136.21, 136.06, 136.04, 135.98, 135.87, 135.45, 135.40, 135.12, 135.08, 135.00, 134.81, 134.76, 134.74, 134.39, 134.37, 134.35, 134.32, 134.21, 134.06, 133.87, 133.54, 133.34, 132.71, 132.62, 132.23, 132.17, 132.13, 132.01, 130.62, 130.59, 130.55, 130.01, 129.98, 129.95, 129.90, 129.86, 129.83, 129.81, 128.61, 128.59, 128.56, 128.53, 128.51, 128.39, 128.30, 128.24, 128.22, 128.12, 128.08, 127.94, 127.91, 126.95, 126.68, 126.66, 126.49, 126.44, 126.25, 126.21, 126.16, 125.84, 125.70, 123.88,
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123.86, 123.58, 123.50, 123.39, 123.37, 123.14, 123.11, 120.61, 120.58, 22.12, 22.11, 19.94, 19.91 ppm.

HRMS (ESI) m/z calculated for C₅₂H₃₆N₁O₄S₂ [M–H]: 802.2102; found 802.2091.

**Synthesis of DSI-17p**

\[
\begin{align*}
\text{Br} & \rightarrow \text{60} \quad \text{(Pd(OAc)}_2\text{ (5 mol%)} \\
\text{Br} & \rightarrow \text{60} \quad \text{(CsF (2.8 equiv.))} \\
\text{DME, 120°C, mw} & \rightarrow \text{61e} \\
\text{CBr₄ (2.5 equiv.)} & \rightarrow \text{62e} \\
\text{CH₂Cl₂, 0°C, 3 h} & \rightarrow \text{62e} \\
\text{DBU (3 equiv.)} & \rightarrow \text{65e} \\
\text{DMSO, 15°C, 1 h} & \rightarrow \text{65e} \\
\end{align*}
\]

**2-(3,5-dimethylphenyl)-4-methylbenzaldehyde (61e)**

In a oven dried 20 mL microwave vial under an atmosphere of dry argon 2-bromo-4-methylbenzaldehyde 57 (1.0 g, 5.4 mmol, 1 equiv.), 3,5-dimethylphenyl boronic acid 60 (0.97 g, 6.5 mmol, 1.2 equiv.),
Experimental Section

cesium fluoride (2.3 g, 15.1 mmol, 2.8 equiv.) and tetrakis(triphenylphosphine)palladium(0) (0.313 g, 0.27 mmol, 5 mol%) were added and suspended in degassed 1,2-DME (10 mL). The vial was sealed and heated at 120 °C for 1 hour in a microwave reactor. The reaction mixture was diluted with EtOAc (30 mL) and water (30 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were dried over MgSO₄, concentrated under reduced pressure and the crude product was purified by flash column chromatography (Hexanes/EtOAc = 100:0 to 95:5) to obtain 61e as a colorless solid (1.13 g, 5.0 mmol, 93% yield).

\[ ^1H \text{ NMR} \ (501 \text{ MHz, CDCl}_3) \delta = 9.96 \ (s, 1H), 7.95 \ (d, J = 7.9 \text{ Hz, 1H}), 7.33–7.22 \ (m, 3H), 7.09 \ (s, 1H), 7.01 \ (s, 2H), 2.47 \ (s, 3H), 2.40 \text{ ppm (s, 6H).} \]

\[ ^{13}C \text{ NMR} \ (126 \text{ MHz, CDCl}_3) \delta = 192.43, 144.40, 137.93, 133.29, 131.27, 129.61, 128.45, 127.97, 127.97, 127.49, 77.27, 77.01, 76.76, 21.82, 21.35, 21.30 \text{ ppm.} \]

\[ \text{HRMS (GC–EI) } m/z \text{ calculated for C}_{15}H_{14}O \ [M]: 224.1201; \text{ found 224.1203.} \]

2-(2,2-dibromovinyl)-3',5,5'-trimethyl-1,1'-biphenyl (62e)

CBr₄ (4.18 g, 12.6 mmol, 2.5 equiv.) was added portion wise to a solution of PPh₃ (6.7 g, 25.0 mmol, 5.0 equiv.) in CH₂Cl₂ (20 mL) and the resulting yellow mixture was stirred for 10 min at 0 °C. A solution of 2-(3,5-dimethylphenyl)-4-methylbenzaldehyde (61e; 1.06 g, 5.0 mmol, 1.0 equiv.) in CH₂Cl₂ (20 mL) was added dropwise and stirring was continued for an additional 1 h at 0 °C. The reaction was then quenched with brine and the aqueous layer was extracted with CH₂Cl₂ (3x20 mL). The combined organic layers were dried over MgSO₄, concentrated under reduced pressure and the crude product was purified by flash column chromatography (Hexanes/EtOAc = 100:0 to 95:5) to obtain 62e as a colorless solid (1.83 g, 95% yield).

\[ ^1H \text{ NMR} \ (501 \text{ MHz, CDCl}_3) \delta = 7.63 – 7.57 \ (m, 1H), 7.22 – 7.13 \ (m, 3H), 7.01 \ (s, 1H), 6.94 \ (s, 2H), 2.38 \ (s, 3H), 2.37 \text{ ppm (s, 6H).} \]

\[ ^{13}C \text{ NMR} \ (126 \text{ MHz, CDCl}_3) \delta = 141.17, 139.87, 137.62, 137.59, 132.86, 132.03, 131.80, 129.62, 129.04, 128.97, 128.43, 128.33, 127.29, 126.78, 90.23, 21.25 \text{ ppm.} \]
Experimental Section

2-(bromoethynyl)-3',5,5'-trimethyl-1,1'-biphenyl (63e)

A solution of DBU (1.0 mL, 14.4 mmol, 3.0 equiv.) in DMSO (30 mL) was added to a cooled solution of 62e (1.8 g, 3.3 mmol, 4.8 equiv.) in DMSO (30 ml) at such rate to maintain the internal temperature below 15 °C. The resulting mixture was stirred at 15 °C for 1 h before the reaction was quenched with aq. HCl (1M) at 0°C. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 20 mL) and the combined organic layers were washed with sat. aq. NaHCO$_3$ solution (20 mL), water (10 mL) and brine (2x10 mL). Afterwards, the organic layer was dried over MgSO$_4$, the solvent was removed under reduced pressure to obtain 63e as a colorless solid (850 mg, 59% yield) without further purification.

$^1$H NMR (501 MHz, CDCl$_3$) $\delta = 7.44$ (d, $J = 7.8$ Hz, 1H), 7.21–7.18 (m, 3H), 7.08 (ddd, $J = 7.9$, 1.8, 0.8 Hz, 1H), 7.03–6.99 (m, 1H), 2.61 (s, 3H), 2.38 ppm (s, 6H).

9-Bromo-1,3,6_trimethyl_phenanthrene (64e)

In an oven-dried 5 mL microwave vial under an atmosphere of dry argon, AuCl (217 mg, 0.94 mmol, 20 mol%) and 63e (1400 mg, 4.7 mmol, 1.0 equiv.) in toluene (5 mL) were heated at 100°C for 1 h. The mixture was then adsorbed on silica gel and purified by flash chromatography (Hexanes/EtOAc = 9:1 to 8:2) to obtain 64e as a colorless solid (600 mg, 43% yield).

$^1$H NMR (501 MHz, CDCl$_3$) $\delta = 8.47$ (s, 1H), 8.33–8.30 (m, 1H), 8.23 (d, $J = 8.4$ Hz, 1H), 8.18 (d, $J = 0.8$ Hz, 1H), 7.52–7.48 (m, 1H), 7.28 (s, 1H), 2.68 (s, 3H), 2.64 (s, 3H), 2.56 ppm (s, 3H).
**Experimental Section**

**1,3,6-trimethyl-phenanthren-9-yl boronic acid (65e)**

An oven dried two-necked 100 mL flask was charged with 64e (500 mg, 1.7 mmol, 1.0 equiv.) under an atmosphere of dry argon. Dry THF (20 mL) was added and the resulting solution was cooled to –78 °C and n-butyllithium (0.7 mL, 2.4 M in hexane, 1.7 mmol, 1.0 equiv.) was added dropwise. The reaction mixture was stirred at –78 °C for 1 h and a solution of trimethyl borate (0.28 mL, 260 mg, 2.5 mmol, 1.5 equiv.) in dry THF (10 mL) was added dropwise. The solution was allowed to warm to room temperature overnight. The reaction was quenched with aq. HCl (1 M, 5 mL), concentrated under reduced pressure to 50% of its original volume and poured into H₂O. The resulted biphasic solution was extracted with Et₂O (2 x 50 mL). The ethereal solution was washed twice with H₂O and concentrated under reduced pressure. The targeted product 65e was obtained after filtration as a colorless solid (320 mg, 75% yield).

\[ ^1H \text{ NMR} \ (501 \text{ MHz, CDCl}_3) \delta = 8.56–8.48 \ (m, 1H), 8.42–8.31 \ (m, 1H), 8.28 – 8.18 \ (m, 1H), 7.72 – 7.62 \ (m, 1H), 7.52–7.41 \ (m, 1H), 7.36–7.28 \ (m, 1H), 7.18 \ (d, J = 11.1 \text{ Hz}, 1H), 2.78–2.67 \ (m, 3H), 2.67–2.51 \ (m, 6H). \]

The product is highly unsoluble in CHCl₃, therefore \(^{13}\text{C-NMR}\) spectra was not informative.

**2,6-bis(1,3,6-trimethylphenanthren-9-yl)-4H-dinaphtho[2,1-d:1',2'-f][1,3,2]dithiazepine 3,3,5,5-tetraoxide (17p)**

In an oven dried microwave vial (5 mL) (S)-3,3'-diiododisulfonimide 48 (69 mg, 0.1 mmol, 1 equiv.), 65e (112 mg, 0.4 mmol, 3 equiv.), K₂CO₃ (58 mg, 0.4 mmol, 4 equiv.), Palladium(II)-acetate (2.4 mg, 0.01 mmol, 0.1 equiv, 10 mol%) were suspended in THF/water (4 mL, 1:1, v/v) under an atmosphere of dry argon. Tri-tert-butylphosphine (1M, dioxane solution) (0.02 mL, 21 mg, 0.1 mmol) was added and the vial...
was sealed and heated for 30 min at 120 °C in a microwave reactor. The reaction was poured into HCl (1N, 5 mL) and extracted with CH₂Cl₂ (3 x 10mL), and the combined organic layers were washed with water (10 mL) and brine (2x10 mL). The organic layer was dried over MgSO₄, and the product was purified by flash column chromatography (CH₂Cl₂/MeOH = 100:0 to 98:2). The purified product was dissolved in CH₂Cl₂ (30 mL), acidified with HCl (6 M, 20 mL) and the solvent removed in vacuo to obtain the targeted product as pale yellow solid (69 mg, 78% yield).

**Note:** Upon acidification, catalyst 17p equilibrates to an unseparable mixture of 3 rotamers.

**¹H NMR** (501 MHz, CDCl₃) δ = 8.58–8.50 (m, 2H), 8.39 (d, J = 5.5 Hz, 2H), 8.24 (d, J = 7.7 Hz, 2H), 8.18 (d, J = 2.2 Hz, 2H), 8.06 (d, J = 8.1 Hz, 2H), 8.05–8.00 (m, 2H), 7.97–7.90 (m, 2H), 7.80–7.68 (m, 2H), 7.59–7.45 (m, 4H), 7.40 (q, J = 7.7, 6.9 Hz, 3H), 7.35–7.27 (m, 3H), 7.23–7.18 (m, 1H), 2.79–2.64 (m, 6H), 2.66–2.47 (m, 12H).
7.3 Asymmetric α-Aminomethylation for the Direct Synthesis of Unprotected β-Amino Acids

7.3.1 Synthesis of Aminomethylating Reagents

*N-(methoxymethyl)-1,1,1-trimethyl-\(N\)-(trimethylsilyl)silanamine (38)*

\[
\begin{align*}
\text{TMS-} & \text{CH}_2\text{Si-} \text{N} \quad \text{THF, 0 °C} \\
\text{Cl-} & \text{OMe} + \text{NaH (1 equiv.)} \\
\text{TMS-} & \text{CH}_2\text{Si-} \text{N} \quad \text{THF, 0 °C} \\
\text{OMe} & \quad \text{TMS-} \\
\end{align*}
\]

A solution of \(n\)-BuLi (4.8 mL, 2.2 M, 10.5 mmol, 1.05 equiv.) was added dropwise at 0 °C to a stirred solution of hexamethyldisilazane (2.1 mL, 10 mmol, 1.0 equiv.) in THF (200 mL) under argon atmosphere and the mixture was stirred for 30 min. Chloromethyl methyl ether (0.8 mL, 10 mmol, 1 equiv.) was added dropwise to the cooled and stirred mixture, and stirring was continued for 2 h at 0 °C. The solvent was removed by evaporation and the resulting residue was filtered to remove the lithium chloride, which was rinsed by \(n\)-hexane. After removal of the solvent, distillation of the liquid residue gave pure 38 (1.8 g, 8.6 mmol, 89% yield), bp 67-68 °C (50 mBar).

\(^1\text{H NMR} \quad (501 \text{ MHz, CD}_2\text{Cl}_2) \delta = 4.27 \text{ (s, 2H), 3.14 \text{ (s, 3H), 0.13 ppm (s, 18H).} \)

\(^{13}\text{C NMR} \quad (126 \text{ MHz, CD}_2\text{Cl}_2) \delta = 81.23, 53.77, \text{ (6x) 2.08 ppm.} \)

*N-((benzyloxy)methyl)-1,1,1-trimethyl-\(N\)-(trimethylsilyl)silanamine (80)*

\[
\begin{align*}
\text{TMS-} & \text{CH}_2\text{Si-} \text{N} \quad \text{THF, 0 °C} \\
\text{Cl-} & \text{O-} \text{C-} \text{C} \text{H}_3 + \text{NaH (1 equiv.)} \\
\text{TMS-} & \text{CH}_2\text{Si-} \text{N} \quad \text{THF, 0 °C} \\
\text{N} & \quad \text{TMS-} \\
\end{align*}
\]

A solution of \(n\)-BuLi (4.8 mL, 2.2 M, 10.5 mmol, 1.05 equiv.) was added dropwise at 0 °C to a stirred solution of hexamethyldisilazane (2.1 mL, 10 mmol, 1.0 equiv.) in
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THF (200 mL) under argon atmosphere and the mixture was stirred for 30 min. Chloromethyl benzyl ether (10 mmol, 1 equiv.) was added dropwise to the cooled and stirred mixture, and stirring was continued for 2 h at 0 °C. The solvent was removed by evaporation and the resulting residue was filtered to remove the lithium chloride, which was rinsed by n-hexane. After removal of the solvent, distillation of the liquid residue gave pure 80, bp 39–42 °C (4.5 x 10^{-2} mBar).

^1H NMR (501 MHz, CD_2Cl_2) δ = 7.29–7.23 (m, 2H), 7.17–7.12 (m, 2H), 7.08–7.03 (m, 1H), 4.33 (s, 2H), 4.24 (s, 2H), 0.19 ppm (s, 18H).

^13C NMR (126 MHz, CD_2Cl_2) δ = 139.42, 129.15, 128.42, 128.22, 127.58, 127.40, 79.54, 68.57, (6x) 2.00 ppm.

7.3.2 Synthesis and Characterization of bis-Silyl Ketene Acetals

General Procedure B:

A stirring solution of acid (1.0 equiv.) and Me_3SiCl (2.1 equiv.) in THF (0.5 M) under an atmosphere of argon was cooled to –78 °C. The LDA solution (2.2) was added via cannula. The cooling bath was removed after complete addition and the reaction solution was stirred for 1 hour at room temperature. The reaction mixture was concentrated in vacuo, and then hexane (50 mL) was added to the residue and was filtered under an atmosphere of argon. After concentration under reduced pressure, the crude product was purified by distillation under reduced pressure to afford the bis-silyl ketene acetals as colorless liquids, which were stored in Schlenk flasks under an atmosphere of argon at 4 °C.
Experimental Section

2,2,6,6-tetramethyl-4-(2-phenylethylidene)-3,5-dioxa-2,6-disilaheptane (31q)

Prepared according to general procedure B using 3-phenylpropanoic acid (1.5 g, 10 mmol) and obtained after distillation (bp = 69–70 °C at 1.0 x 10⁻² mBar) as colorless liquid (1.5 g, 5.0 mmol, 50 % yield).

\[ ^1H \text{NMR} \ (501 \text{ MHz, CD}_2\text{Cl}_2) \delta = 7.28–7.22 (m, 2H), 7.22–7.17 (m, 2H), 7.17–7.10 (m, 1H), 3.76 (t, J = 7.3 Hz, 1H), 3.27 (d, J = 7.3 Hz, 2H), 0.23 (s, 9H), 0.20 (s, 9H). \]

\[ ^13C \text{NMR} \ (126 \text{ MHz, CD}_2\text{Cl}_2) \delta = 151.92, 143.94, 129.03, 128.67, 128.66, 128.37, 125.93, 82.32, 31.92, 0.75, 0.14 \text{ ppm}. \]

2,2,6,6-tetramethyl-4-(3-phenylpropylidene)-3,5-dioxa-2,6-disilaheptane (31s)

Prepared according to general procedure B using 4-phenylbutanoic acid (3.9 g, 20.0 mmol) and obtained after distillation (bp = 86–88 °C at 7.8 x 10⁻² mbar) as colorless liquid.

\[ ^1H \text{NMR} \ (501 \text{ MHz, CD}_2\text{Cl}_2) \delta = 7.15–7.04 (m, 2H), 7.04–6.92 (m, 3H), 3.38 (t, J = 7.1 Hz, 1H), 2.49–2.31 (m, 2H), 2.10–1.95 (m, 2H), 0.02 (s, 9H), 0.00 (s, 9H). \]

2,2,6,6-tetramethyl-4-pentylidene-3,5-dioxa-2,6-disilaheptane (31t)

Prepared according to general procedure B using hexanoic acid (2.3 g, 20.0 mmol) and obtained after distillation (bp = 41–42 °C at 5.7 x 10⁻² mbar) as colorless liquid.

\[ ^1H \text{NMR} \ (501 \text{ MHz, CD}_2\text{Cl}_2) \delta = 3.53 (t, J = 7.1 Hz, 1H), 1.89 (q, J = 7.1 Hz, 2H), 1.36–1.17 (m, 4H), 0.95–0.84 (m, 3H), 0.21 (s, 9H), 0.18 \text{ ppm (s, 9H).} \]

\[ ^13C \text{NMR} \ (126 \text{ MHz, CD}_2\text{Cl}_2) \delta = 150.83, 83.87, 33.45, 25.24, 22.78, 14.35, 0.66, 0.06 \text{ ppm.} \]
Experimental Section

4-ethylidene-2,2,6,6-tetramethyl-3,5-dioxa-2,6-disilaheptane (31u)

Prepared according to general procedure B using propanoic acid (1.0 g, 13.5 mmol) and obtained after distillation (bp = 65-68 °C at 20 mBar) as colorless liquid (2.3 g, 13.4 mmol, 79 % yield).

\(^1\)H NMR (501 MHz, CD\(_2\)Cl\(_2\)) \(\delta = 3.36 \ (q, \ J = 6.5 \ Hz, \ 1H), \ 1.25 \ (d, \ J = 6.5 \ Hz, \ 3H), \ 0.02 \ (s, \ 9H), \ 0.00 \ (s, \ 9H)\).

\(^{13}\)C NMR (126 MHz, CD\(_2\)Cl\(_2\)) \(\delta = 151.33, \ 77.42, \ 10.38, \ 0.69, \ 0.08 \ ppm.\)

4-(2-(4-methoxyphenyl)ethylidene)-2,2,6,6-tetramethyl-3,5-dioxa-2,6-disilaheptane (31v)

Prepared according to general procedure B using 3-(4-methoxyphenyl)propanoic acid (3.6 g, 20 mmol) and obtained after distillation (bp = 108–110 °C at 4.8 *10\(^{-2}\) mBar) as colorless liquid.

\(^1\)H NMR (501 MHz, CD\(_2\)Cl\(_2\)) \(\delta = 7.20–7.03 \ (m, \ 2H), \ 6.86–6.75 \ (m, \ 2H), \ 3.83–3.70 \ (m, \ 4H), \ 3.20 \ (d, \ J = 7.3 \ Hz, \ 2H), \ 0.23 \ (s, \ 9H), \ 0.21 \ (s, \ 9H)\).
Experimental Section

7.3.3 General procedure for the α-Aminomethylation of bis-SKAs

General Procedure C

An oven dry 2 ml vial was charged with imidodiphosphate 71s or 71t as the catalyst (0.2 μmol, 0.5 mg, 1 mol%), a magnetic stir bar and, under argon atmosphere, dry pentane (0.1 mL) and bis-silyl ketene acetal 31 (0.024 mmol, 1.2 equiv.) were added. The reaction mixture was cooled down to the desired temperature, and then N-(methoxymethyl)-1,1,1-trimethyl-N-(trimethylsilyl)silanamine 38 (0.02 μL, 1.0 equiv.) was added. After 3 days, the targeted product 68 was precipitated with water (0.1 mL) and directly dissolved with water/MeOH (0.5 mL, 1:1, v/v). The aqueous phase was extracted with Et₂O (2x 1 mL) in order to remove the catalyst. The water was evaporated under reduced pressure to obtain the desired product as a colorless solid in >99% purity (analyzed by ¹H-NMR). The obtained product was dissolved in HPLC grade water:MeCN (1:1, v/v) and directly used for the determination of the enantiomeric ratio.

3-amino-2-phenylpropanoic acid (68r)

Prepared according to general procedure C using 2,2,6,6-tetramethyl-4-(2-phenylethylidene)-3,5-dioxa-2,6-disilaheptane (31r) (5.5 mg, 0.02 mmol) using catalyst 71s and obtained after extraction as a colorless solid (91% yield, 91:9 er).

¹H NMR (501 MHz, CDCl₃) δ = 7.26–7.15 (m, 3H), 7.14–7.10 (m, 2H), 3.86 (t, J = 7.5 Hz, 1H), 3.37 (dd, J = 13.1, 7.6 Hz, 1H), 3.13 ppm (dd, J = 13.1, 7.4 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃) δ = 174.6, 134.3, 129.6, 128.9, 128.9, 128.3, 128.3, 48.5, 41.1 ppm.
The enantiomeric ratio was determined by HPLC analysis using Daicel Chirobiotic T2, water:methanol = 50:50 (v/v), flow rate = 1 mL/min, 25 °C, λ = 210 nm, t_R = 11.1 min (minor) and t_R = 17.1 min (major).

3-amino-2-benzylpropanoic acid (68q)

Prepared according to the general procedure using 2,2,6,6-tetramethyl-4-(2-phenylethylidene)-3,5-dioxa-2,6-disilaheptane (31q) (5.6 mg, 0.02 mmol) using catalyst 71s and obtained after precipitation as a colorless solid (5.0 mg, 0.019 mmol, 95 % yield, 96:4 er).

^1H NMR (501 MHz, D_2O) δ = 7.45 – 7.34 (m, 2H), 7.35 – 7.27 (m, 3H), 3.16 – 3.06 (m, 1H), 3.06 – 2.98 (m, 2H), 2.94 – 2.80 (m, 2H).

^13C NMR (126 MHz, D_2O) δ = 179.52, 138.48, 128.96, 128.96, 128.69, 128.69, 126.75, 46.90, 40.63, 36.15 ppm.

The enantiomeric ratio was determined by HPLC analysis using Daicel Chirobiotic T2, water:methanol = 50:50 (v/v), flow rate = 1 mL/min, 25 °C, λ = 210 nm, t_R = 6.3 min (minor) and t_R = 7.9 min (major)

3-amino-2-phenylpropanoic acid (68w)

Prepared according to the general procedure using 4-ethylidene-2,2,6,6-tetramethyl-3,5-dioxa-2,6-disilaheptane (31w) (4.1 mg, 0.02 mmol) using catalyst 71t and obtained after precipitation as a colorless solid (95% NMR yield, 82.5:17.5 er).

^1H NMR (501 MHz, D_2O) δ = 3.17 (ddd, J = 14.0, 6.9, 1.1 Hz, 1H), 2.66 (dd, J = 14.0, 7.6 Hz, 1H), 2.40 (h, J = 7.3 Hz, 1H), 0.9 ppm (d, J = 7.1 Hz, 3H).

^13C NMR (126 MHz, D_2O) δ = 181.67, 42.37, 39.25, 15.13 ppm.

The enantiomeric ratio was determined by HPLC analysis after derivatization of the obtained product to the corresponding HPLC analysis using Chiralpak ID-3, n-heptane:i-PrOH = 80:20 (v/v), flow rate = 1 mL/min, 25 °C, λ = 210 nm, t_R = 4.5 min (major) and t_R = 4.9 min (minor)
3-amino-2-phenylpropanoic acid (68s)

Prepared according to the general procedure using 2,2,6,6-tetramethyl-4-(3-phenylpropylidene)-3,5-dioxa-2,6-disilaheptane (31s) (6.1 mg, 0.02 mmol) using catalyst 71s and obtained after extraction as a colorless solid (91% NMR yield, 95.5:4.5 er).

$^1$H NMR (501 MHz, CDCl$_3$) $\delta$ = 7.35–7.27 (m, 2H), 7.27–7.19 (m, 3H), 3.14–3.05 (m, 1H), 3.05–2.96 (m, 1H), 2.67–2.52 (m, 2H), 2.52–2.44 (m, 1H), 1.92–1.81 (m, 1H), 1.80–1.70 ppm (m, 1H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ = 180.47, 141.87, 128.69, 128.51, 126.21, 45.03, 41.07, 32.50, 31.89 ppm.

The enantiomeric ratio was determined by HPLC analysis using Daicel Chirobiotic T2, water:methanol = 50:50 (v/v), flow rate = 1 mL/min, 25 °C, $\lambda$ = 210 nm, $t_R = 8.0$ min (minor) and $t_R = 10.2$ min (major).
7.3.4 Synthesis and Characterization of IDP$^i$ Catalysts

7.3.4.1 Procedure for derivatization of 2,7-dibromo-9H-fluorene

2',7'-dibromospiro[cyclopentane-1,9'-fluorene] (83)

Aq. NaOH (50%, 110 mmol, 5.5 equiv.) was added dropwise to the mixture of 2,7-dibromo-9H-fluorene (6.5 g, 20 mmol, 1.0 equiv.) and benzyltriethylammonium chloride (91.1 mg, 0.4 mmol, 2 mol%) in DMSO (10 mL) under argon at rt (NOTE:
rapid color change from yellow to red). After the subsequent addition of 1,4-dibromobutane (2.4 mL, 20 mmol, 1.0 equiv.) (NOTE: color change from red to beige), the reaction was stirred for 5 hours at rt. Then, water (30 mL) and toluene (30 mL) were added and the organic layer was separated, dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography (hexanes) to yield 2',7'-dibromospiro[cyclopentane-1,9'-fluorene] 83 as a light yellow solid (5.4 g, 14.2 mmol, 71%).

^{1}H NMR (501 MHz, CDCl₃) δ = 7.55–7.50 (m, 4H), 7.44 (dd, J = 8.1, 1.8 Hz, 2H), 2.18–2.10 (m, 4H), 2.10–2.00 ppm (m, 4H).
^{13}C NMR (126 MHz, CDCl₃) δ = 156.01, 156.01, 137.44, 137.44, 130.01, 130.01, 126.31, 126.31, 121.57, 121.57, 120.99, 120.99, 57.90, 39.65, 39.65, 26.92, 26.92 ppm.

7.3.4.1 Derivatization of 2',7'-Dibromospiro[cyclopentane-1,9'-fluorene]

Procedure D

2'-bromo-7'-methylspiro[cyclopentane-1,9'-fluorene] (84a)

\[ \text{n-BuLi} \rightarrow \text{MeI} \]  
\[ \text{THF} \]

\( n\text{-BuLi} \) (2.54 M in hexanes, 2.1 equiv.) was added dropwise to a solution of 2',7'-dibromospiro[cyclopentane-1,9'-fluorene] 83 (1.0 equiv.) in THF (0.2 M) at −78 °C and the reaction mixture was allowed to stir at this temperature for 15 min. Methyl iodide (1.0 equiv., neat) was added to the reaction mixture dropwise over 10 min. The reaction was allowed to stir and warm to room temperature overnight. The reaction was quenched with sat. NH₄Cl(aq) solution. After 5 min, the reaction mixture
Experimental Section

was diluted with diethyl ether. The aqueous layer was extracted with diethyl ether (x3). The combined organic layers were washed with sat. Na$_2$S$_2$O$_4$(aq) solution until the organic phase turn to transparent, then washed with brine, dried with magnesium sulfate, concentrated under reduced pressure, and the solid residue was purified by flash column chromatography (SiO$_2$, dichloromethane/methanol = 95:5).

$^1$H NMR (501 MHz, CDCl$_3$) $\delta$ = 7.57–7.48 (m, 3H), 7.42 (dd, $J$ = 8.0, 1.8 Hz, 1H), 7.24–7.20 (m, 1H), 7.17–7.11 (m, 1H), 2.42 (s, 3H), 2.25–1.91 ppm (m, 8H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ = 156.51, 154.34, 138.73, 137.97, 135.96, 129.81, 127.87, 126.34, 123.74, 120.72, 120.67, 119.53, 57.77, 39.91, 27.11, 22.00 ppm.

Procedure E

2'-bromo-7'-butylspiro[cyclopentane-1,9'-fluorene] (84b)

![](image)

$n$-BuLi (2.54 M in hexanes, 2.1 equiv.) was added dropwise to a solution of acid (1.0 equiv.) in THF (0.2 M) at −78 °C and the reaction mixture was allowed to stir at room temperature overnight. The reaction was quenched with sat. NH$_4$Cl(aq) solution. After 5 min, the reaction mixture was diluted with diethyl ether. The aqueous layer was extracted with diethyl ether (x3). The combined organic layers were washed with sat. Na$_2$S$_2$O$_4$(aq) solution until the organic phase turn to transparent, then washed with brine, dried with magnesium sulfate, concentrated under reduced pressure, and the solid residue was purified by flash column chromatography (SiO$_2$, dichloromethane/methanol = 95:5).

$^1$H NMR (501 MHz, CDCl$_3$) $\delta$ = 7.67–7.46 (m, 3H), 7.41 (dd, $J$ = 7.8, 1.8 Hz, 1H), 7.21 (d, $J$ = 1.5 Hz, 1H), 7.14 (dd, $J$ = 7.7, 1.5 Hz, 1H), 2.66 (td, $J$ = 8.0, 3.1 Hz, 2H),
Experimental Section

2.19–2.01 (m, 8H), 1.70–1.58 (m, 2H), 1.44–1.34 (m, 2H), 0.95 ppm (t, \( J = 7.3 \) Hz, 3H).

**Procedure D**

2'-bromo-7'-(tert-butyl)spiro[cyclopentane-1,9'-fluorene] (84c)

\[
\begin{align*}
\text{Br} & \quad \text{Br} \\
\text{83} & \quad \text{THF} \\
\end{align*}
\]

\( n\text{-BuLi} \) (2.54 M in hexanes, 2.1 equiv.) was added dropwise to a solution of acid (1.0 equiv.) in THF (0.2 M) at –78 °C and the reaction mixture was allowed to stir at this temperature for 15 min. \textit{t}-Butyl iodide (1.0 equiv., neat) was added to the reaction mixture dropwise over 10 min. The reaction was allowed to stir and warm to room temperature overnight. The reaction was quenched with sat. \( \text{NH}_4\text{Cl(aq)} \) solution. After 5 min, the reaction mixture was diluted with diethyl ether. The aqueous layer was extracted with diethyl ether (x3). The combined organic layers were washed with sat. \( \text{Na}_2\text{S}_2\text{O}_4(aq) \) solution until the organic phase turn to transparent, then washed with brine, dried with magnesium sulfate, concentrated under reduced pressure, and the solid residue was purified by flash column chromatography (SiO\(_2\), dichloromethane/methanol = 95:5).

\(^1\text{H NMR} \) (501 MHz, CDCl\(_3\)) \( \delta = 7.51 \) (d, \( J = 7.9 \) Hz, 1H), 7.46–7.42 (m, 2H), 7.37–7.32 (m, 2H), 7.30 (dd, \( J = 8.0, 1.8 \) Hz, 1H), 2.13–1.92 (m, 8H), 1.30 ppm (s, 9H).

\(^{13}\text{C NMR} \) (126 MHz, CDCl\(_3\)) \( \delta = 156.61, 153.66, 151.33, 138.49, 135.86, 129.64, 126.18, 124.10, 120.63, 120.54, 119.53, 119.09, 64.39, 57.84, 39.78, 26.91, 25.35, 14.19, 14.19, 14.19 \) ppm.
Experimental Section

7.3.4.2  Suzukii Coupling of 2-Bromo-7-alkyl-9H-fluorene and MOM-protected (S,S)-BINOL

\[
\begin{align*}
\text{OMOM} & \quad \text{OMOM} \\
\text{Br} & \quad \text{Br} \\
\text{OMOM} & \quad \text{OMOM}
\end{align*}
\]

To a flame dried two-neck round-bottom flask with a condenser was added (S)-
2,2'-(2,2'-bis(methoxymethoxy)-1,1'binaphthyl-3,3'-diyl)bis(4,4,5,5-tetramethyl-1,3,2-
dioxaborolane) 86 (0.5 mmol, 1.0 equiv), 2-bromo fluorenyl derivative 84a–e (1.1
mmol, 2.2 equiv) and tetrakis(triphenylphosphine)palladium (0.05 mmol, 0.1 equiv).
After degassing the reaction mixture with argon for 20 min, toluene/ethanol/methanol
(3:2:1, v/v/v, 0.15 M) and K₂CO₃ (3 mmol, 6 equiv.) were sequentially added. The
mixture was then heated to 110 °C and stirred at that temperature for 16 h. After
cooling the reaction to room temperature, the reaction mixture was extracted with
EtOAc (3x), the combined organic phase was dried over MgSO₄ and concentrated
under reduced pressure. Subsequently, the solid was dissolved in dioxane and HCl
in dioxane was added. This mixture was stirred at room temperature until the starting
material was consumed (as monitored by TLC analysis). The reaction was then
evaporated under reduced pressure. The resulting residue was purified by column
chromatography (EtOAc:hexanes = 1:5) to afford the targeted compound 85a–e as a
colorless solid.
(S)-3,3'-bis(2'-methylspiro[cyclopentane-1,9'-fluoren]-7'-yl)-[1,1'-binaphthalene]-2,2'-dial (85a)

Prepared according to the representative procedure on a 0.5 mmol scale for (S)-2,2'-(2,2'-bis(methoxymethoxy)-1,1'binaphthyl-3,3'-diyl)bis(4,4',5,5-tetramethyl-1,3,2-dioxaborolane) 86 with 2'-bromo-7'-methylspiro[cyclopentane-1,9'-fluorene] (84a) (345.0 mg, 1.1 mmol) to give the title compound 85a as an off-white solid.

$^1$H NMR (501 MHz, CDCl$_3$) $\delta$ = 8.08 (s, 2H), 7.98–7.93 (m, 2H), 7.81–7.75 (m, 4H), 7.69 (dd, $J$ = 7.8, 1.6 Hz, 2H), 7.63 (d, $J$ = 7.6 Hz, 2H), 7.41 (ddd, $J$ = 8.1, 6.7, 1.4 Hz, 2H), 7.34 (ddd, $J$ = 8.1, 6.7, 1.3 Hz, 2H), 7.30–7.27 (m, 1H), 7.20–7.13 (m, 2H), 2.45 (s, 6H), 2.24–2.05 (m, 16H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ = 154.94, 154.94, 154.52, 154.52, 150.16, 150.16, 139.35, 139.35, 137.52, 137.52, 136.48, 136.48, 135.97, 135.97, 132.97, 132.97, 131.16, 131.16, 131.13, 131.13, 129.52, 129.52, 128.40, 128.40, 128.23, 128.23, 127.62, 127.62, 127.19, 127.19, 124.42, 124.42, 124.28, 124.28, 124.14, 124.14, 123.67, 123.67, 119.52, 119.52, 119.29, 119.29, 112.71, 112.71, 57.64, 57.64, 39.92, 39.92, 39.87, 39.87, 27.03, 27.03, 27.03, 27.03, 21.88, 21.88 ppm.

((Perfluoro-n-decyl)sulfonyl)phosphorimidoyl trichloride (76)

In a Schlenk flask under Argon equipped with a magnetic stirring bar connected to a two-neck flask containing NaOH pellets and a vacuum pump in this order, a mixture of sulfonamide 75 (600.0 mg, 1 mmol, 1.0 equiv) and PCl$_5$ (270.0 mg, 1.3 mmol, 1.3 equiv) was heated to 140 °C under Argon for 2 h. The reaction was monitored by $^1$H,
**Experimental Section**

$^{19}$F, and $^{31}$P NMR to ensure full consumption of sulfonamide. Removal of the excess amount of PCl$_5$ by prolonged evacuation in vacuum afforded the title compound 76 in quantitative yield as colorless solid, which was stored in a Schlenk flask under argon.

$^{19}$F NMR (471 MHz, CD$_2$Cl$_2$) $\delta$ = -81.10, -112.32, -120.23, -121.65, -121.82, -121.82, -121.82, -122.04, -122.86, -126.30 ppm.

$^{31}$P NMR (203 MHz, CD$_2$Cl$_2$) $\delta$ = 16.89 ppm.
7.3.4.3 General Procedure for IDPi synthesis

In a Schlenk tube under argon, a suspension of 3,3′-substituted (S,S)-BINOL (1.05 mmol, 2.1 equiv.) in toluene (2.5 mL) was treated with phosphorimidoyl trichloride \(87\) (1.05 mmol, 2.1 equiv.) and then \(\text{NEt}_3\) (1.12 mL, 8.0 mmol, 16 equiv.). The reaction mixture was stirred for 15 min at r.t., until neat hexamethyldisilazane (HMDS, 104 µL, 0.5 mmol, 1 equiv.) was added dropwise. The reaction mixture was stirred for additional 15 min at r.t., the Schlenk tube was subsequently sealed and heated to 120 °C for 3 days. After cooling to r.t., aq. HCl (10%) was added and the mixture was extracted with DCM or EtO. The combined organic layers were washed with brine, dried over MgSO\(_4\) and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (hexane/MTBE 90:10→80:20→70:30→60:40→50:50 and/or 0.5–5% EtOAc in DCM) to afford the desired product as a salt. The corresponding IDPi Brønsted acids (S,S)-\(71s–w\) were obtained after acidification in DCM or EtO with aq. HCl (6 M) and evaporation of the solvent followed by drying under high vacuum as typically off-white solids.

\((S,S)-(71s)\)

Prepared according to the general procedure on a 0.1 mmol scale (with respect to HMDS) and purified by column chromatography (hexane/EtOAc, 95:5). Colorless solid.
**Experimental Section**

**$^1$H NMR** (501 MHz, CDCl$_3$) $\delta = 8.02$ (d, $J = 7.9$ Hz, 4H), 7.95 (d, $J = 8.3$ Hz, 2H), 7.85 – 7.79 (m, 2H), 7.76 (d, $J = 8.5$ Hz, 2H), 7.67 – 7.61 (m, 2H), 7.58 – 7.52 (m, 2H), 7.49 – 7.46 (m, 2H), 7.40 (d, $J = 7.8$ Hz, 2H), 7.37 – 7.29 (m, 6H), 7.22 – 7.15 (m, 6H), 7.10 (s, 2H), 7.00 – 6.93 (m, 6H), 6.58 (d, $J = 8.1$ Hz, 2H), 6.53 (d, $J = 8.0$ Hz, 2H), 6.42 (dd, $J = 8.1$, 1.6 Hz, 2H), 2.33 (d, $J = 3.0$ Hz, 12H), 2.23 – 1.86 (m, 22H), 1.77 (dd, $J = 12.8$, 6.9 Hz, 2H), 1.35 – 1.14 ppm (m, 12H).

**$^{19}$F NMR** (471 MHz, CDCl$_3$) $\delta = -80.78$, -110.28 – -112.60 (m), -120.00 (d, $J = 53.4$ Hz), -121.48, -122.01 (d, $J = 58.6$ Hz), -122.79 (d, $J = 17.9$ Hz), -126.18 ppm (d, $J = 15.4$ Hz).

**$^{31}$P NMR** (203 MHz, CDCl$_3$) $\delta = -16.67$ ppm.

(S,S)-(71v)

Prepared according to the general procedure on a 0.1 mmol scale (with respect to HMDS) and purified by column chromatography (hexane/EtOAc, 95:5). Colorless solid.

**$^1$H NMR** (501 MHz, CDCl$_3$) $\delta = 7.93$ (s, 2H), 7.89 – 7.79 (m, 1H), 7.76 – 7.61 (m, 2H), 7.59 – 7.50 (m, 1H), 7.46 (dd, $J = 8.1$, 3.6 Hz, 2H), 7.41 (d, $J = 1.6$ Hz, 1H), 7.34 (d, $J = 7.8$ Hz, 2H), 7.32 – 7.28 (m, 3H), 7.26 – 7.20 (m, 6H), 7.17 – 7.11 (m, 6H), 7.09 (s, 2H), 7.02 (d, $J = 1.6$ Hz, 2H), 6.93 – 6.82 (m, 6H), 6.39 (d, $J = 7.9$ Hz, 2H), 2.50 (td, $J = 7.5$, 5.5 Hz, 8H), 2.27 – 1.75 (m, 22H), 1.63 – 1.39 (m, 16H), 1.31 – 1.14 (m, 12H), 0.83 (t, $J = 7.3$ Hz, 6H), 0.77 ppm (t, $J = 7.3$ Hz, 6H).

**$^{19}$F NMR** (471 MHz, CDCl$_3$) $\delta = -80.79$, -109.52 – -112.99 (m), -119.95 (dt, $J = 31.1$, 13.7 Hz), -121.39, -121.94 (d, $J = 33.4$ Hz), -122.72, -126.15 ppm (d, $J = 14.4$ Hz).

**$^{31}$P NMR** (203 MHz, CDCl$_3$) $\delta = -16.65$ ppm.
(S,S)-(71t)

Prepared according to the general procedure on a 0.1 mmol scale (with respect to HMDS) and purified by column chromatography (hexane/EtOAc, 95:5). Colorless solid.

$^1$H NMR (501 MHz, CDCl$_3$) $\delta = 8.08$–$7.99$ (m, 4H), $7.96$ (d, $J = 8.3$ Hz, 2H), $7.85$–$7.79$ (m, 2H), $7.76$ (d, $J = 8.5$ Hz, 2H), $7.64$ (ddd, $J = 8.5$, 6.7, 1.4 Hz, 2H), $7.55$ (ddd, $J = 8.2$, 5.8, 2.2 Hz, 2H), $7.49$ (d, $J = 1.6$ Hz, 2H), $7.46$–$7.38$ (m, 3H), $7.37$–$7.29$ (m, 8H), $7.23$–$7.13$ (m, 8H), $6.97$ (s, 2H), $6.62$ (d, $J = 8.0$ Hz, 1H), $6.54$–$6.44$ (m, 3H), $2.25$–$2.01$ (m, 22H), $1.83$–$1.58$ (m, 4H), $1.29$ ppm (d, $J = 1.3$ Hz, 36H).

$^{19}$F NMR (471 MHz, CDCl$_3$) $\delta = -80.79$, $-109.52$ – $-112.99$ (m), $-119.95$ (dt, $J = 31.1$, 13.7 Hz), $-121.39$, $-121.94$ (d, $J = 33.4$ Hz), $-122.72$, $-126.15$ ppm (d, $J = 14.4$ Hz).

$^{31}$P NMR (203 MHz, CDCl$_3$) $\delta = -16.69$ ppm.

(S,S)-(71w)

Prepared according to the general procedure on a 0.1 mmol scale (with respect to HMDS) and purified by column chromatography (hexane/EtOAc, 95:5). Colorless solid.

$^1$H NMR (501 MHz, CDCl$_3$) $\delta = 8.04$ (d, $J = 9.3$ Hz, 4H), $7.98$ (d, $J = 8.2$ Hz, 2H), $7.87$–$7.82$ (m, 2H), $7.80$ (d, $J = 8.5$ Hz, 2H), $7.71$–$7.65$ (m, 2H), $7.64$ – $7.50$ (m, 18H), $7.50$–$7.27$ (m, 28H), $7.01$ (s, 2H), $6.72$ (d, $J = 8.0$ Hz, 2H), $6.63$ (d, $J = 7.9$ Hz, 2H), $6.53$ (dd, $J = 7.9$, 1.5 Hz, 2H), $2.23$ (dd, $J = 12.6$, 6.0 Hz, 2H), $2.19$ – $1.92$ (m, 22H), $1.88$ – $1.74$ (m, 6H).
19F NMR (471 MHz, CDCl3) δ = -80.81 (t, J = 9.9 Hz), -110.41 – -112.49 (m), -119.95 (d, J = 56.1 Hz), -121.44, -121.96 (d, J = 56.1 Hz), -122.74, -126.18 ppm (d, J = 15.3 Hz).

31P NMR (203 MHz, CDCl3) δ = -16.46 ppm.
8 Bibliography

Appendix


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Appendix


Appendix


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Appendix


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9 Appendix

9.1 Erklärung/Declaration


Mülheim an der Ruhr, November 2019

Bisher ist folgende Teilpublikation veröffentlicht worden:

9.2 Lebenslauf/CV

Francesca Mandrelli

Geboren am 11. März 1990 in Sansepolcro/Italien

Staatsangehörigkeit: Italienisch

Akademischer Werdegang

Promotion
01.2016–11.2019
Dissertation im Arbeitskreis von Prof. Dr. Benjamin List
Max-Planck-Institut für Kohlenforschung, Mülheim an der Ruhr
Title: "Organocatalytic Asymmetric α-Functionalization of bis-Silyl Ketene Acetals"

Hochschulstudium
09.2009–02.2015
M.Sc. im Arbeitskreis von Dr. Francesco Venturoni, Dr. Antimo Gioiello
Chimica e Tecnologia Farmaceutiche, Università degli studi di Perugia
Title: “Development of Thiourea Organocatalysts as Enabling Tools for Asymmetric Michael Addition”

Schulbildung
Liceo Piero della Francesca, naturwissenschaftliches Gymnasium, Sansepolcro, Italien
09.2001–07.2004
Leonardo da Vinci, Sekundarschule, Selci–Lama, Italien
09.1996–07.2001
Don Lorenzo Milani, Grundschule, Lama, Italien