BRØNSTED ACID CATALYZED ASYMMETRIC ACETALIZATIONS

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ABSTRACT

This work describes the development of Brønsted acid catalyzed asymmetric acetalization of aldehydes and its application to kinetic resolution of chiral diols.

In the first part, the first asymmetric version of the direct *O,O*-acetalization of aldehydes with 1,2- and 1,3-diols is presented. The reaction is catalyzed by chiral confined Brønsted acids, which are based on an imidodiphosphoric acid moiety and can provide structurally versatile confined chiral microenvironments. A new confined catalyst significantly outperformed previously established phosphoric acids and their derivatives, giving highly enantioenriched acetal products. The catalyst is readily prepared from the natural product thymol, possessing isopropyl and methyl substituents in the 2- and 5-position, respectively, on the aryl group providing a more rigid catalyst structure. A highly enantioselective reaction can be performed delivering acetals with excellent enantioselectivity (er up to 99.8:0.2) and excellent yields. The method tolerates both aliphatic and aromatic aldehydes delivering the corresponding acetal products with high enantioselectivities.

The second part of this thesis describes a highly enantioselective kinetic resolution of chiral racemic diols through acetal formation employing the thymol derived imidodiphosphoric acid catalyst and an even bulkier catalyst which possesses a cyclohexyl substituent instead of the isopropyl substituent in the 2-position on the aryl group. The reaction is highly efficient for the resolution of diols with tertiary alcohol stereocenters, giving selectivity factors of up to 389. Remarkably, in cases where the selectivity factors are only moderate, highly enantioenriched diols can still be obtained via a stereodivergent resolution to diastereomeric acetals. This approach can be used for resolution of 1,2-diols possessing similar aliphatic substituents at the tertiary alcohol stereocenter.

Initial studies regarding the development of related asymmetric *S,O*- and *S,S*-acetalizations are also presented in this thesis.

KURZZUSAMMENFASSUNG

Diese Arbeit beschreibt die Entwicklung einer Brønstedsäure-katalysierten asymmetrischen Acetalisierung von Aldehyden und deren Anwendung in der kinetischen Racematspaltung von chiralen Diolen.

Im ersten Teil dieser Arbeit wird die erste asymmetrische direkte *O*,*O*-Acetalisierung von Aldehyden mit 1,2- und 1,3-Diolen vorgestellt. Die Reaktion wird durch chirale sterisch anspruchsvolle Brønstedsäuren katalysiert, die eine Imidodiphosphorsäure-Einheit enthalten und eine Vielzahl chiraler Mikroumgebungen ermöglichen.

Ein neuer sterisch anspruchsvoller Katalysator lieferte deutlich bessere Ergebnisse als bisher etablierte Phosphorsäuren und deren Derivate und ermöglichte die Synthese hoch enantiomerenreiner Acetale als Produkte. Der Katalysator ist leicht zugänglich und kann ausgehend vom Naturstoff Thymol synthetisiert werden, welcher einen Isopropyl- und Methyl-Substituenten in der 2- und 5-Position besitzt und so eine starre Katalysatorstruktur aufweist. Dies ermöglicht die Synthese von Acetalen mit exzellenter Enantioselektivität (er bis zu 99.8:0.2) und hoher Ausbeute. Die Methode toleriert sowohl aliphatische als auch aromatische Aldehyde und liefert die entsprechenden Acetale in hohen Enantioselektivitäten.

Der zweite Teil dieser Arbeit beschreibt eine hochselektive kinetische Racematspaltung von racemischen Diolen durch Acetalbildung. Hierfür wurde eine sterisch anspruchsvollere Imidodiphosphorsäure mit Cyclohexyl- und Methyl-Substituenten in der 2-und 5-Position der Aryl-Gruppe verwendet. Die Reaktion ist sehr effizient für die Auftrennung von Diolen mit tertiären Alkohol-Stereozentren und liefert Selektivitätsfaktoren von bis zu 389. In Fällen, in denen der Selektivitätsfaktor geringer ist, können trotzdem enantiomerenreine Diole durch eine stereodivergente Racematspaltung zu diastereomeren Acetalen erhalten werden. Diese Methode kann zur Racematspaltung von 1,2-Diolen mit ähnlichen Substituenten am tertiären Stereozentrum angewandt werden.

Erste Untersuchungen zur Entwicklung von asymmetrischen *S*,*O*- und *S*,*S*-Acetalisierungen werden ebenfalls in dieser Arbeit vorgestellt.

LIST OF SIMBOLS AND ABBREVIATIONS

*	designating chiral moiety
Ac	acetyl
acac	acetylacetonate
AIBN	azobis(isobutyronitrile)
Alk	alkyl
Ar	aryl, aromatic
aq.	aqueous
Boc	*tert*-butyloxycarbonyl
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Bu	butyl
Bz	benzoyl
cat.	catalyst/catalytic
conv.	conversion
d	doublet
dba	(*E*,*E*)-dibenzylideneacetone
DCE	1,2-dichloroethane
DCM	dichloromethane
$(DHQ)_2$-PHAL	1,4-bis(dihydroquininyl)phthalazine
$(DHQD)_2$-PHAL	1,4-bis(dihydroquinidinyl)phthalazine
DIOP	2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
EI	electron impact
ent	enantiomer(ic)
equiv	equivalent(s)
er	enantiomeric ratio

Et	ethyl
ESI	electrospray ionization
GC (GC-MS)	gas chromatography (gas chromatography coupled with mass detection)
H_8-BINOL	5,5',6,6',7,7',8,8'-octahydro-1,1'-bi-2-naphtol
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HX*	designating chiral Brønsted acids, e.g. chiral phosphoric acid diesters
L	ligand (abbreviation used in schemes)
LUMO	lowest unoccupied molecular orbital
m	*meta*
m	multiplet
M	metal (abbreviation used in schemes)
M	molar (concentration)
Me	methyl
MS	mass spectrometry, molecular sieves
MTBE	methyl *tert*-butyl ether
MW	molecular weight
m/*z*	atomic mass units per charge
N	normal (concentration)
nbd	norbornadiene
NMR	nuclear magnetic resonance spectroscopy
NOE(SY)	nuclear Overhauser effect (spectroscopy)
NuH/Nu	nucleophile
o	*ortho*
p	*para*
PG	protecting group
Ph	phenyl
PMP	*para*-methoxyphenyl
Pr	propyl
PTSA	*para*-toluenesulfonic acid
Py	pyridine

quint	quintet
rac.	racemic
r.t.	room temperature
sept	septet
sext	sextet
SPINOL	1,1’-spirobiindane-7,7’-diol
t	*tert, tertiary*
t	triplet
TADDOL	α,α,α’,α’-tetraaryl-1,3-dioxolan-4,5-dimethanol
TBS	*tert*-butyl-dimethylsilyl
TES	$-SiEt_3$
Tf	$-SO_2CF_3$
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMS	trimethylsilyl
TRIP	3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate
VAPOL	2,2´-Diphenyl-(4-biphenanthrol)

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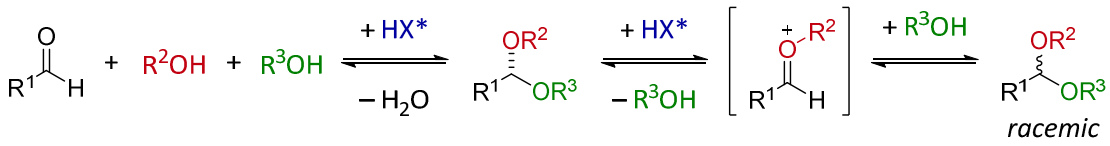
1. INTRODUCTION

1.1. Catalytic asymmetric synthesis of acetals

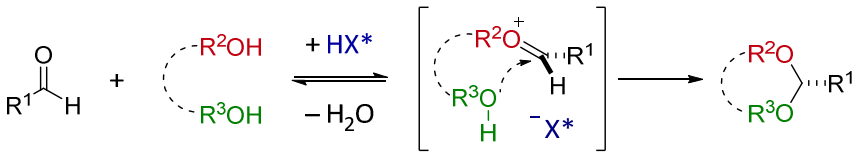
The acetalization of aldehydes with alcohols is one of the most common transformations in organic synthesis. Moreover, enantiopure acetals represent a class of important motives in many natural products and bioactive compounds.[1-6] Approaches to the synthesis of chiral acetals have been investigated over the past decades, nevertheless, these methods are usually based on the use of enantioenriched starting materials or reagents.

The formation of acetals is commonly performed by treating carbonyl compounds with an alcohol or a diol in the presence of relatively strong Brønsted acids. The reaction proceeds through the formation of oxocarbenium ion intermediates. Strong Brønsted acids are used not only for the formation of acetals, but also for cleavage of acetals. The sensitivity of the acetal product under acidic conditions makes performing an asymmetric acetalization with enantiopure acids challenging. Thus, even if high enantioselectivity is initially induced in an asymmetric acetalization reaction, the product may also be activated by the catalysts, reversibly forming the oxocarbenium ion intermediate and thus leading to racemization of the product (Scheme 1.1).



Scheme 1.1. Reversibility and racemization issues in acetalization reactions.

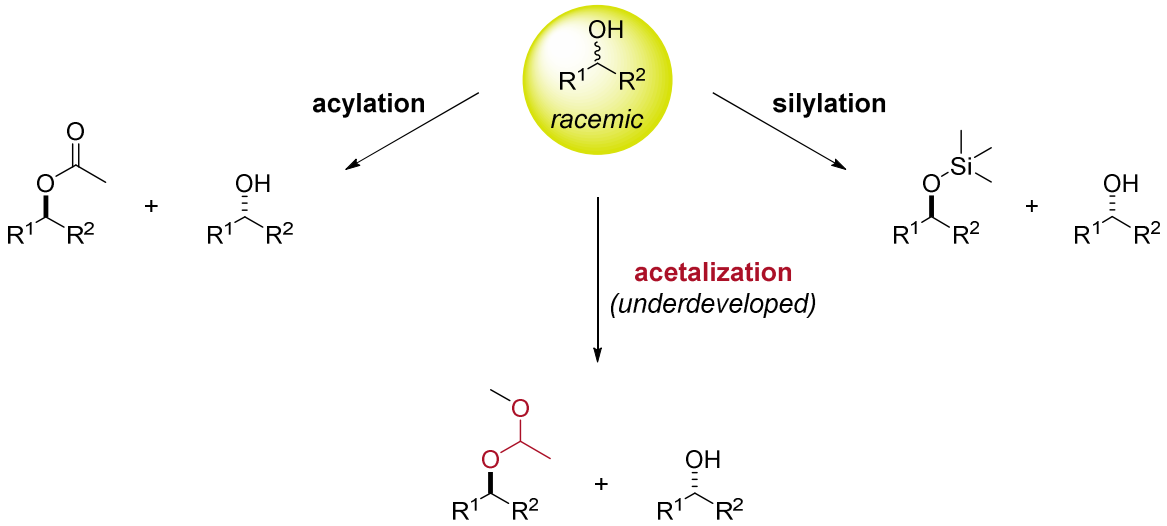
To avoid these issues, the acetalization reaction can be run under milder reaction conditions, and/or to give cyclic acetals that are usually more stable than acyclic acetals under acidic conditions. The racemic version of Brønsted acid catalyzed acetalization of aldehydes with diols to give cyclic *O,O*-acetals has been performed numerous times, however, its asymmetric version was entirely unknown prior to the work described in this thesis (Scheme 1.2). We have found that a new member of our recently developed class of chiral confined Brønsted acids finally enables this elusive transformation with high enantioselectivity.



Scheme 1.2. Brønsted acid catalyzed acetalization of aldehydes with diols.

1.2. Kinetic resolution of diols via acetal formation

Next to ester and silyl groups, acetals are one of the most common protecting groups for alcohols. They possess complimentary stability properties to ester and silyl groups during further synthetic steps, and also alternative deprotection conditions. The acetal moiety is resistant to hydrolysis under mildly acidic conditions and is stable in a range of basic and nucleophilic conditions. Acetals are stable in the presence of the fluoride anion, which is commonly used to remove silyl groups. Due to usually simple access to racemic alcohols, kinetic resolutions present a popular strategy for the preparation of enantioenriched compounds (Scheme 1.3). Most practical methods involve reactions that enantioselectively introduce a common alcohol protecting group, which can be of use in further synthetic steps. Numerous enzymatic and nonenzymatic methods for asymmetric acylation, and more recently silylation have been developed providing esters and silyl ethers respectively. However, the processes for the kinetic resolution of alcohols via acetal formation were reported only recently.[7-8] Kinetic resolutions of diols through the formation of an acetal have not been described prior to our work. We have applied our newly developed asymmetric acetalization reaction to the kinetic resolution of diols, giving highly enantioenriched diols and acetal products.



Scheme 1.3. Kinetic resolution of alcohols by placing common protecting groups.

1.3. Brønsted acid catalysis with challenging substrates

Asymmetric Brønsted acid catalysis, in particular with chiral phosphoric acid type catalysts, has acquired wide popularity and importance in the field of organocatalysis.[9-10] However, substrates are usually required to possess relatively high basicity, sterically demanding protecting groups, large aromatic/planar surfaces, and/or bulky substituents to have sufficient steric interaction with the catalyst for high asymmetric induction (Figure 1.1).[11] Either strong covalent or hydrogen bond interactions between the catalyst and substrates result in high asymmetric induction, as successfully demonstrated with, for example, iminium ions. Opposed to reactions involving large substrates or possessing a strong interaction between the catalyst and substrates, reactions involving small substrates which cannot have sufficient steric interaction with the catalyst or possessing weak interactions between the catalyst and substrates result in low asymmetric induction. Therefore, for example, successful asymmetric addition reactions of nucleophiles to oxocarbenium ions have very rarely been reported.[12-14]

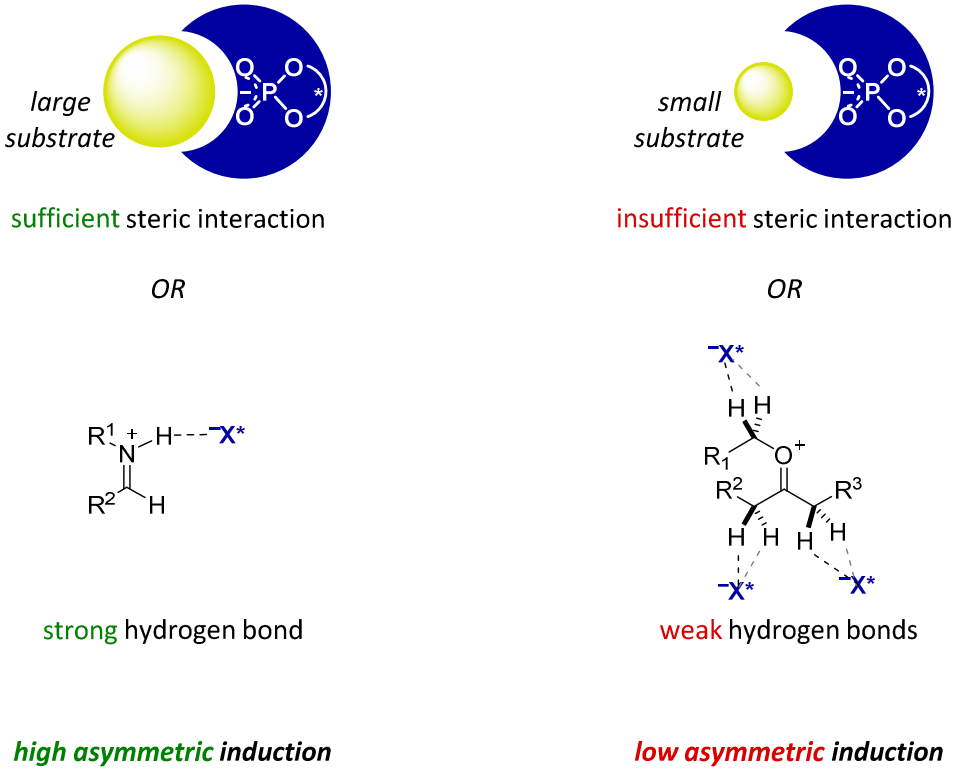


Figure 1.1. Asymmetric induction of phosphoric acid type catalysts.

Recently, the List group designed and reported confined Brønsted acid catalysts that possess an extremely sterically demanding chiral microenvironment.[15] We demonstrate the utility of

this catalyst class in asymmetric acetalization reactions that involve small and functionally unbiased substrates and proceed through oxocarbenium ions intermediates.

2. BACKGROUND

2.1. Asymmetric catalysis

A structure which is not superimposable with its mirror image is chiral.[3] Chirality results from the absence of certain symmetry elements. A chiral element is usually found in molecules which contain a tetrahedral carbon atom (stereogenic or chiral center) possessing four different substituents. The chirality of molecules can alternatively originate from the presence of an axial chirality, a planar chirality or others (Figure 2.1).[16] The two mirror images of a chiral compound are therefore not identical and are called enantiomers.

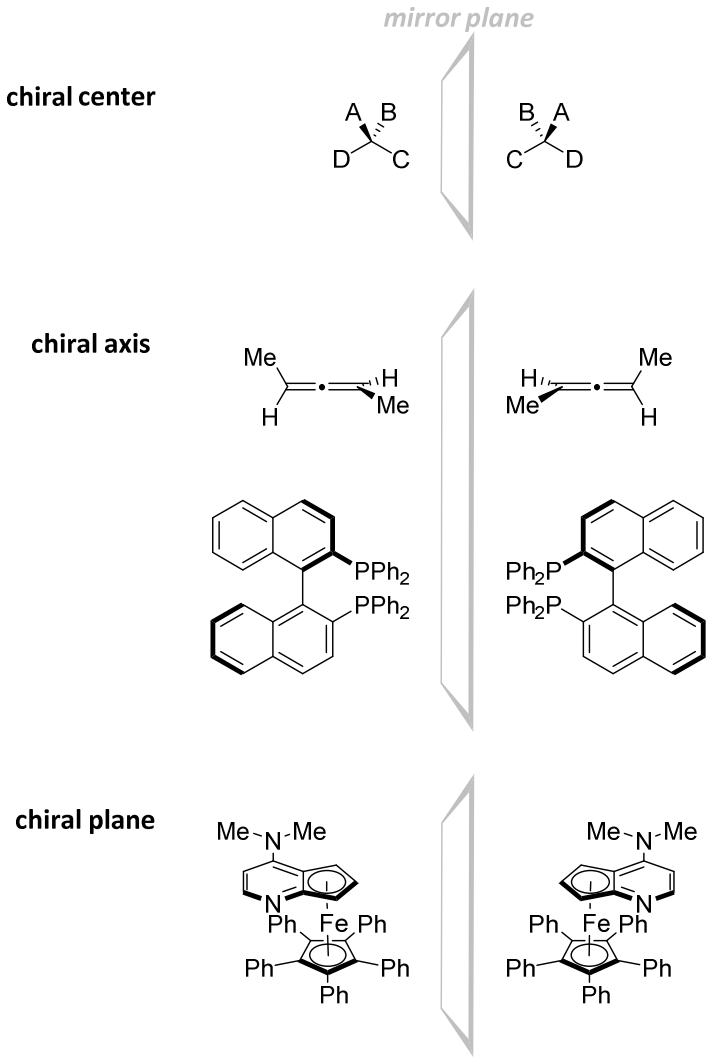


Figure 2.1. Examples of chiral molecules.

Most molecules in nature are chiral, and living organisms tend to produce only a single enantiomer.[17] Enantiomers of a chiral compound are identical in terms of usual physical

properties such as boiling point and density. However, enantiomers can behave dramatically different in chiral environments that are sensitive to changes in spatial orientation of a single functional group. For example, enantiomers of Carvone smell differently, each having its own characteristic odor. The tragic case of Thalidomide demonstrated that using chiral drugs as racemic mixtures can cause disastrous outcomes, since one enantiomer has sedative properties while the other one is teratogenic and induces fetal malformations (Figure 2.2).[3]

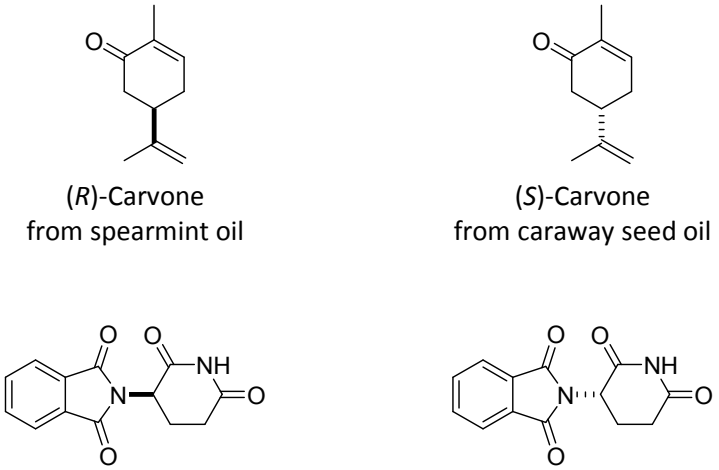


Figure 2.2. Enantiomers with different biological properties.

These are just two examples where biological systems react differently to one enantiomeric form of a certain molecule. Therefore, developing synthesis of chiral molecules in enantiomerically pure form by controlling the stereochemistry of chemical reactions is highly important.

There are basically two options to access single enantiomers, either the racemic mixture of a molecule is resolved into separate enantiomers, or the enantioenriched compound is produced by asymmetric synthesis. The latter is a more attractive approach, because it minimizes the waste of the undesired enantiomer, which is a general drawback of resolution strategies. Regarding asymmetric synthesis, the use of starting materials from the chiral pool or of chiral auxiliaries are basic approaches which are well established in industrial processes. An external chiral auxiliary, which can be recoverable and recyclable, can induce the asymmetry in the target molecule. Natural products often are the source of chirality in these auxiliaries.[17]

A catalyst is a substance which can participate in chemical reactions, accelerating the rate of the reaction, without being consumed. Catalysts can be employed to reaction processes to promote a different reaction pathway that involves a lower energy transition state, compared to uncatalyzed reactions that proceed through higher energy transition states.

In asymmetric catalysis which is a fundamental part of asymmetric synthesis, the catalyst not only accelerates the reaction but also produces the compounds favoring the formation of a specific enantiomer or diastereomer. A small quantity of a chiral, enantiopure catalyst can transform a large amount of chiral/achiral starting material into enantiomerically pure products.

Developments of asymmetric catalysis are divided in three main fields: biocatalysis, metal catalysis, and organocatalysis.[18] Biocatalysis is based on the use of enzymes and is the oldest known synthetic method for asymmetric catalysis. In the field of asymmetric metal catalysis, the pioneering contributions were recognized with the 2001 chemistry Nobel Prize to William Knowles and Ryoji Noyori for catalytic asymmetric reduction reactions, and to K. Barry Sharpless for enantioselective oxidations.

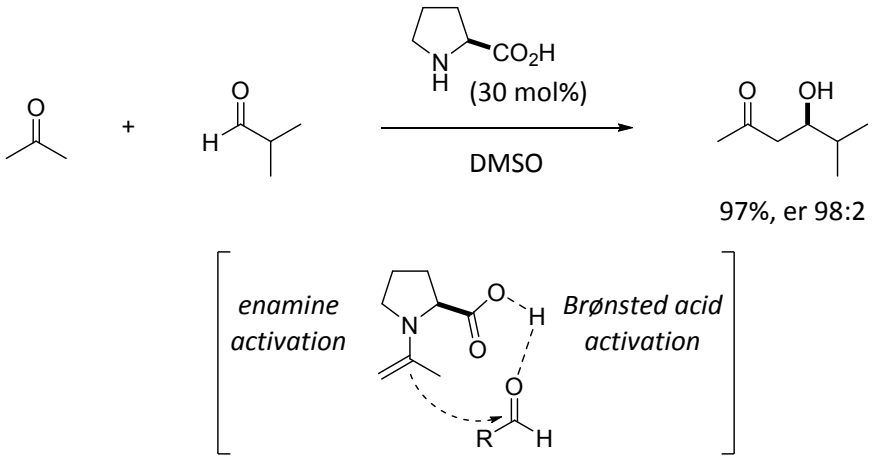
Next to bio- and metal catalysis, the interest in organocatalysis has increased significantly in the last few years.[18-19] Although metal catalysts and biocatalysts have been used for a large variety of reactions, organocatalysts seem to be attractive alternatives to a number of known metal-catalyzed reactions. Also, organocatalysis enables reactions that are not possible with metals or enzymes. Numerous reactions in the field of organocatalysis have been developed even overcoming drawbacks from the reactions with metal- and biocatalysis.

2.2. Asymmetric organocatalysis

Organocatalysts have recently emerged as a third class of powerful asymmetric catalysts. Organocatalysts are purely organic and metal free small molecules which mainly consist of carbon, nitrogen, sulfur, phosphorous, and hydrogen. They can readily be designed and synthesized and are generally stable toward oxygen and moisture. Thus organocatalyzed reactions usually do not require inert atmosphere and high purity solvents which are often used in metal catalysis.[20]

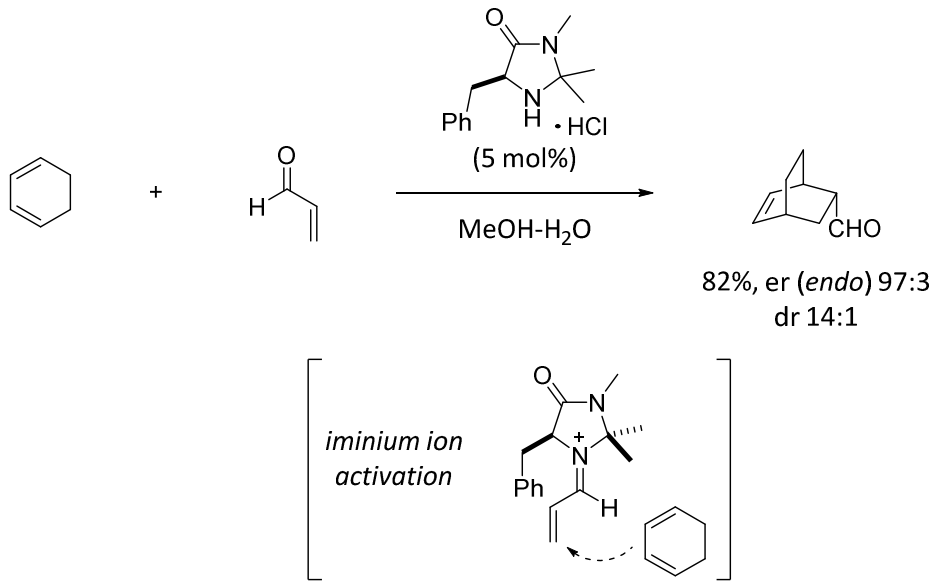
In early studies of asymmetric reactions employing small organic molecules, Bredig and Fiske reported a hydrogen cyanide addition to benzaldehyde catalyzed by cinchona alkaloid in 1912.[21-22] In 1960 Pracejus developed a cinchona alkaloid promoted asymmetric addition of methanol to ketenes.[23] In the early 1970's a proline catalyzed intramolecular aldol reaction has been disclosed by Hajos and Parrish[24-25] and by Eder, Sauer, and Wiechert.[26-27]

Although organocatalytic reactions have a long history, the full potential of organocatalysis was exposed with initial reports by List and MacMillan. Their independent reports showed that aldehydes or ketones can be activated by the use of nonmetallic small molecules as catalysts for asymmetric reactions. List described that amino acid L-proline catalyzed the direct intermolecular asymmetric aldol reactions by activating acetone as an enamine (Scheme 2.1).[28] Enamines are better nucleophiles than the corresponding enols having a higher HOMO (highest occupied molecular orbital) energy. The carboxylic acid moiety of proline can simultaneously activate the aldehyde electrophile further promoting the reactions and fixing the relative special orientation of the substrates required for high enantioselectivities.



Scheme 2.1. Proline catalyzed aldol reaction.

MacMillan reported that a chiral imidazolidinone catalyst can activate enals to form iminium ions promoting a Diels-Alder reaction with dienes (Scheme 2.2).[29] Iminium ions are better electrophiles than the corresponding enals (or aldehydes) having a lower LUMO (lowest unoccupied molecular orbital) energy. The stereochemistry of the products is explained with benzyl group on the catalyst shielding one of the faces of the dienophile leaving the other face exposed to cycloaddition.



Scheme 2.2. Imidazolidinone catalyzed Diels-Alder reaction.

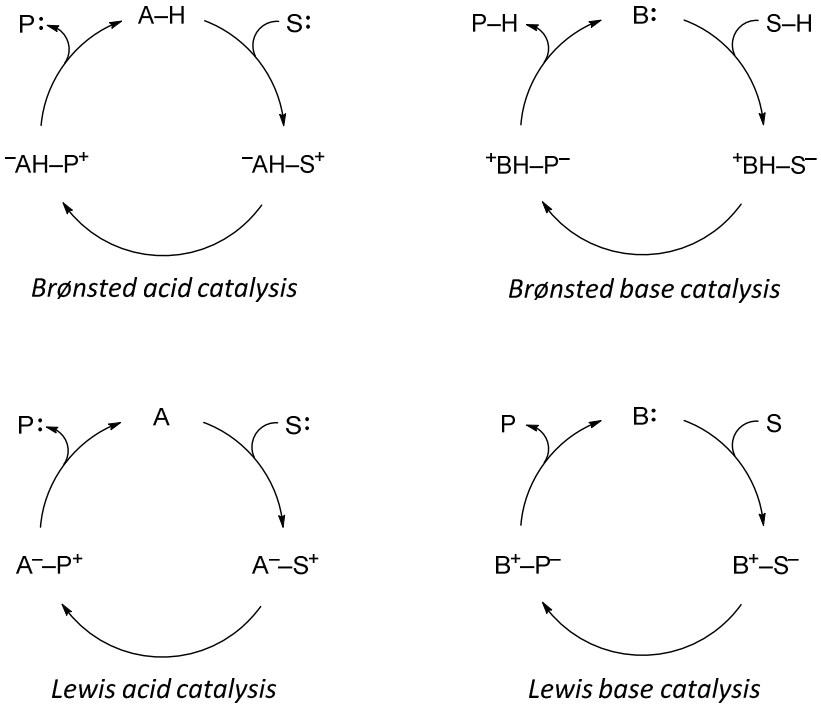
These achievements with well-defined modes of activation have triggered and accelerated the development of numerous new activation modes with small organic catalysts.

Classification of modern organocatalysis

According to the report by Seayad and List in 2004, most organocatalysts can be classified as Lewis bases, Lewis acids, Brønsted bases and Brønsted acids.[30] They introduced a classification system for organocatalysts based on Brønsted acid/base and Lewis acid/base theories (Scheme 2.3). Based on their interaction with substrates, organocatalysts can be classified as proton donors (Brønsted acid), proton acceptors (Brønsted base), electron acceptor (Lewis acid), and electron donors (Lewis base).

In Brønsted acid catalysis, the catalyst initiates the catalytic cycle by protonation of substrates. The resulting complex proceeds to undergo a reaction, then product and the catalyst are

liberated to enable repetition of the catalytic cycle. The Brønsted base catalytic cycle is initiated by deprotonation of the substrates. Lewis acid catalysis and Lewis base catalysis are conceptually related catalytic modes which involve catalysts that accept or donate electrons, respectively, to activate the substrate.



Scheme 2.3. Schematic organocatalytic cycles (A = acid, B = base, S = substrate, P = product).

Notwithstanding the efforts for classification of organocatalysts, organocatalysts usually facilitate these modes concurrently in the reactions. For example, proline's amino group acts as a Lewis base donating its pair of electrons to form a corresponding enamine with aldehydes or ketones and simultaneously its carboxylic acid moiety acts as Brønsted acid by activating the electrophile utilizing hydrogen bonding and protonation (Figure 2.3).[28]

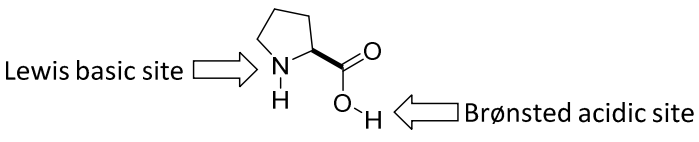


Figure 2.3. Dual activation mode of proline.

2.3. Asymmetric Brønsted acid catalysis

The use of metal based Lewis acid catalysts has been recognized as efficient approach to activate electrophiles, particularly carbonyl groups. Lewis acid catalysts lower the electron density of the substrate by accepting a pair of electrons of the substrate and consequently inducing nucleophilic attack to the electrophile (Figure 2.4). Chiral Lewis acid catalysts which are composed of metal based Lewis acid and a chiral ligand have been employed in numerous asymmetric reactions.

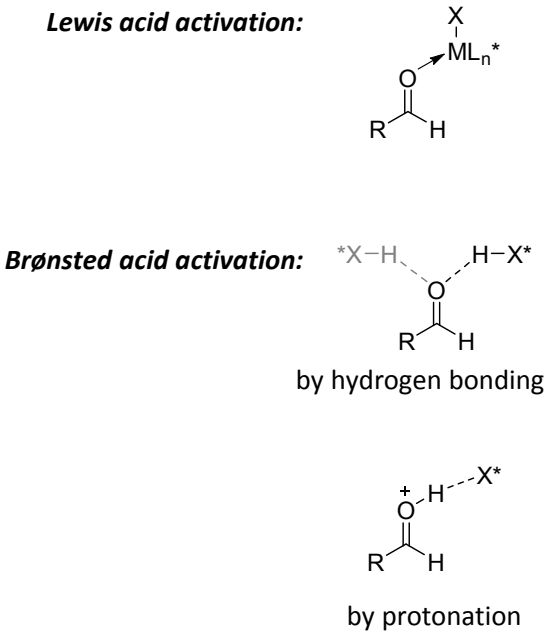
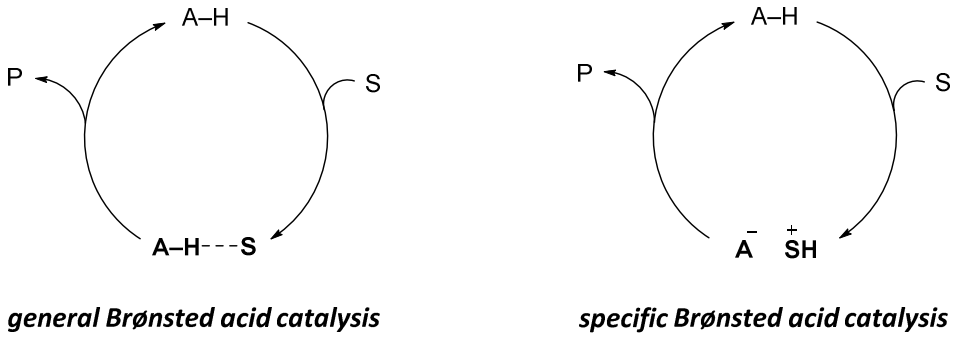


Figure 2.4. Activation modes of aldehydes by acids.

On the other hand, asymmetric Brønsted acid catalysis has been growing significantly in the field of organocatalysis enabling the activation of a wide range of functional groups.[31] Brønsted acid catalysts are often stable to oxygen and moisture and are easier to handle than Lewis acids. The use of metal catalysts can result in traces of toxic metal impurities in the final products, which is especially relevant in the pharmaceutical industry. This can be avoided by using Brønsted acid catalysts which are metal-free molecules. The activation mode of Brønsted acid catalysts involves protonation/deprotonation, and the fact that Brønsted acids can activate various organic substrates is well known. However, asymmetric Brønsted acid catalysis has been considered difficult because a proton cannot possess substituents which could be made chiral. However, since 2004 it has been demonstrated in numerous reactions that the

respective counteranion can impart enantioselectivity during the reaction, by hydrogen bonding with a protonated substrate.[32-33]

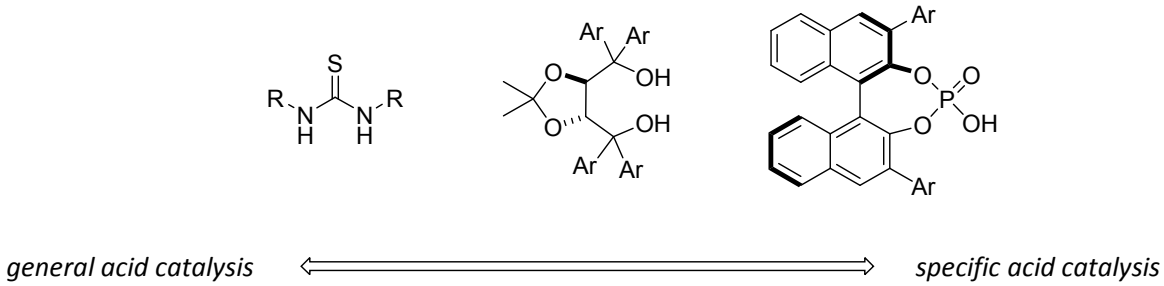
Chiral Brønsted acid catalysis is generally classified into two categories, general Brønsted acid catalysis and specific Brønsted acid catalysis (Scheme 2.4).[34] General Brønsted acid catalysis operates when the catalyst activates the substrate by hydrogen bonding and the proton transfer occurs to the transition state of the rate determining step. A specific Brønsted acid catalysis is the case when the proton is completely dissociated from the catalyst therefore the substrate is fully protonated for further transformation.



general Brønsted acid catalysis ***specific Brønsted acid catalysis***

Scheme 2.4. Simplified catalytic cycles of general and specific Brønsted acid catalysis.

A given reaction can be categorized to either of these classes depending on the substrate and the reaction type. However, it is not always straightforward to classify by these two mechanisms. Nonetheless, the nature of the catalyst can be suggested from the pK_a value of the Brønsted acid (Figure 2.5).[31]



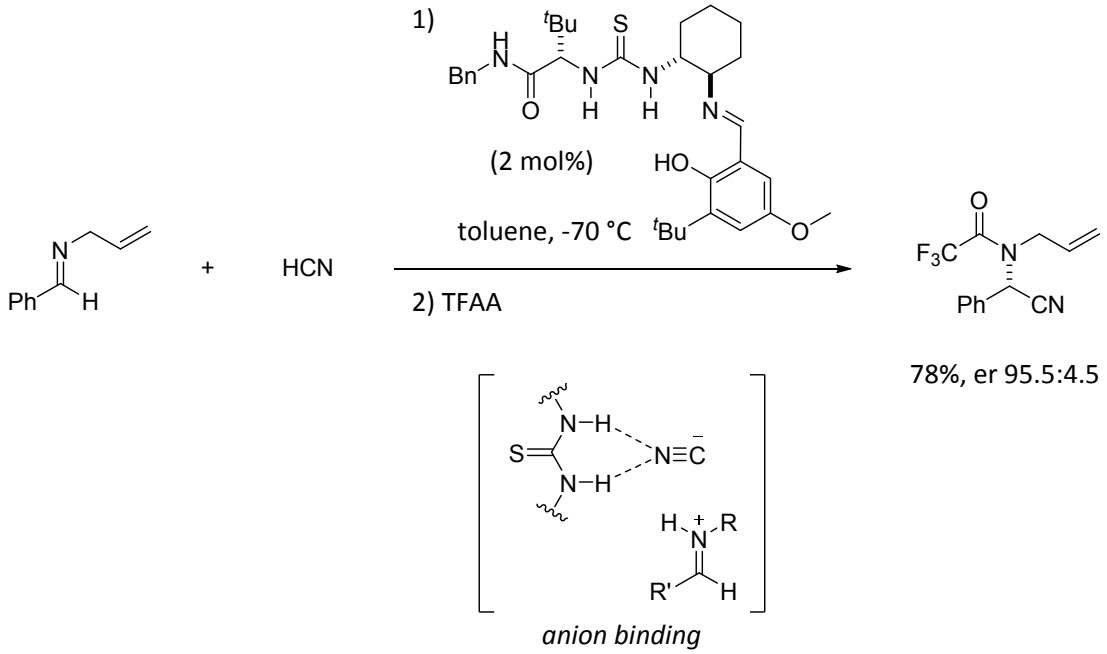
general acid catalysis ⟺ *specific acid catalysis*

Figure 2.5. Types of chiral Brønsted acids.

2.3.1. General Brønsted acid catalysis

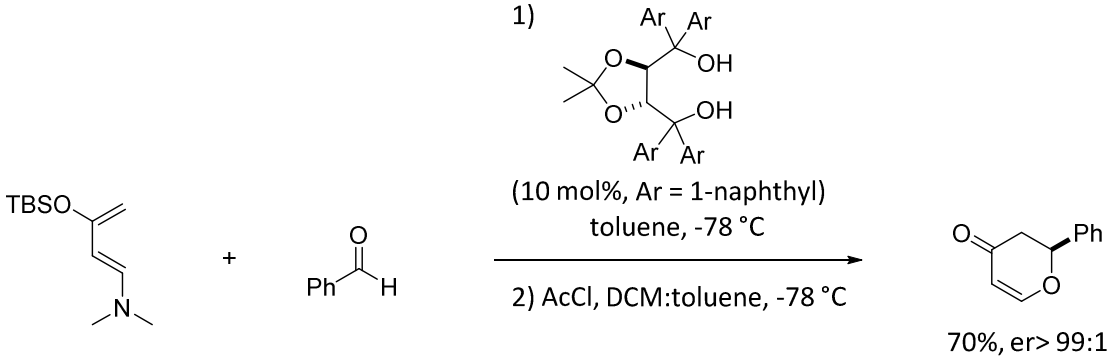
Hydrogen bonding catalysts which can be classified as general acid catalysts are weak Brønsted acids. Due to their weak acidity, the proton cannot be fully transferred to the substrate but it

activates the substrate by hydrogen bonding interaction. Nature has employed general Brønsted acid catalysis in enzyme mediated enantioselective synthesis of organic molecules where hydrogen bonding to a transition state occurs. However, highly enantioselective catalysis based on this type of activation mode was introduced only very recently. Among others, chiral thioureas and the chiral diol TADDOL are the most prominent examples. In 1998, Sigman and Jacobsen found that chiral urea and thiourea derivatives can catalyze enantioselective hydrocyanation reactions of imines known as Strecker reaction, suggesting that the imine substrate interacts with the catalyst through a dual hydrogen bond interaction to the urea protons.[35-36] Later, they revised the mechanism of this reaction proposing catalyst promoted proton transfer from hydrogen isocyanide to imine and anion binding, rather than the direct activation of neutral imine electrophiles by hydrogen bonding (Scheme 2.5).[37-38]



Scheme 2.5. Thiourea catalyzed asymmetric Strecker reaction.

The Rawal group reported a highly enantioselective hetero Diels-Alder reaction between diene and benzaldehyde catalyzed by a chiral diol TADDOL (Scheme 2.6).[39]

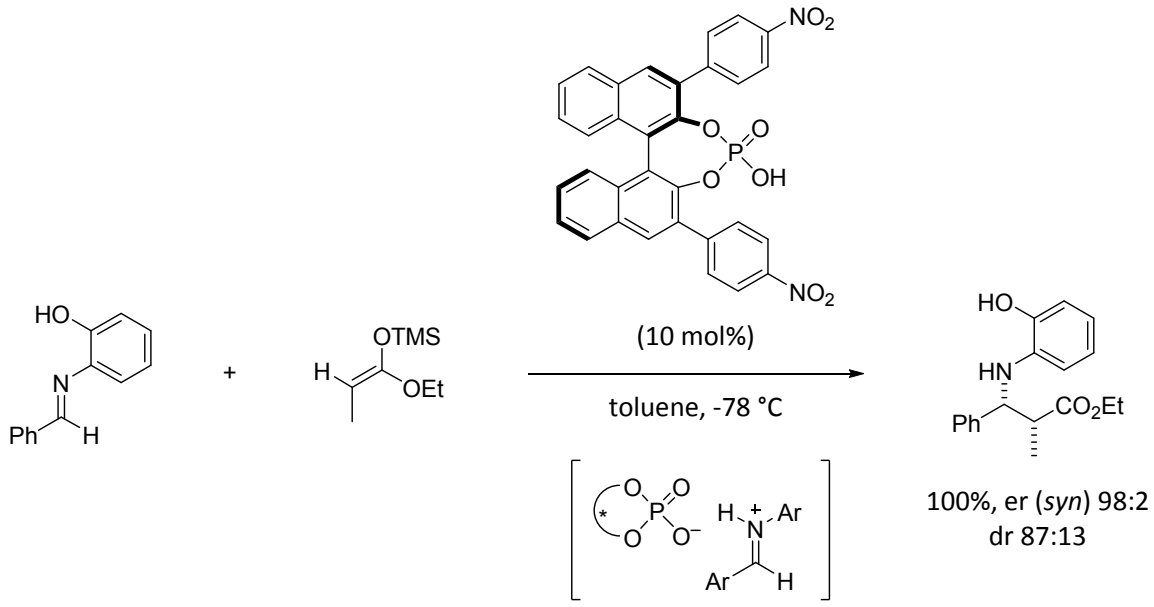


Scheme 2.6. TADDOL catalyzed hetero Diels-Alder reaction.

These examples are just the tip of the iceberg in this field, and numerous other reactions and catalysts have been studied that employ hydrogen bonding catalysis for the activation of electrophiles.[36, 40]

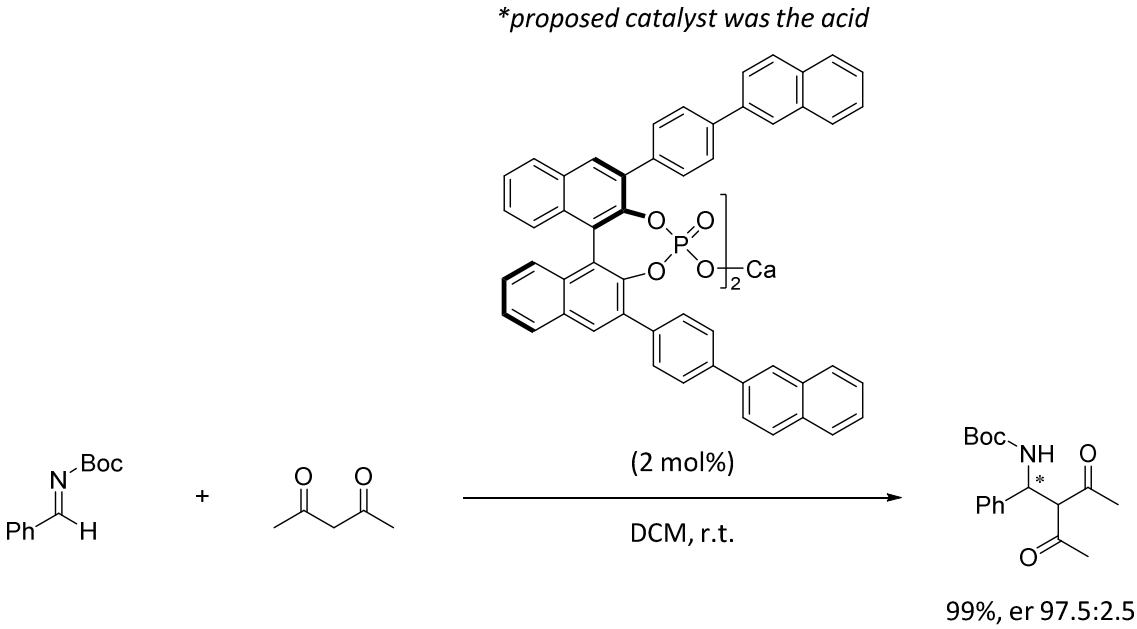
2.3.2. Specific Brønsted acid catalysis

Compared to general Brønsted acid catalysts, relatively stronger Brønsted acid catalysts that activate the substrate by fully protonating it can be classified as specific Brønsted acid catalysts. The field of asymmetric catalysis with strong Brønsted acids exploded since the reports from the Akiyama and Terada groups. The Akiyama group reported a highly enantioselective Mannich reaction using a chiral BINOL-derived phosphoric acid as a catalyst (Scheme 2.7).[33]



Scheme 2.7. Chiral phosphoric acid catalyzed Mannich reaction by Akiyama *et al*.

The Terada group simultaneously reported an asymmetric Mannich reaction catalyzed by a similar chiral BINOL-derived phosphoric acid (Scheme 2.8).[32] Later, however, the Ishihara group found that the actual catalyst in this reaction was not the phosphoric acid, but rather its calcium salt which was formed during purification on silica gel.[41]



Scheme 2.8. Chiral phosphate catalyzed Mannich reaction by Terada *et al*.

After these reports, chiral phosphoric acid catalysis attracted much attention being successfully applied to numerous asymmetric reactions.[9-10, 34, 38, 42-43] Chiral phosphoric acids generally possess bulky substituents which play a crucial role in enantiofacial discrimination of substrates. Furthermore, they enable bifunctional activation modes in which a Brønsted acidic site and a basic site simultaneously activate the electrophile and the nucleophile, respectively (Figure 2.6).[9]

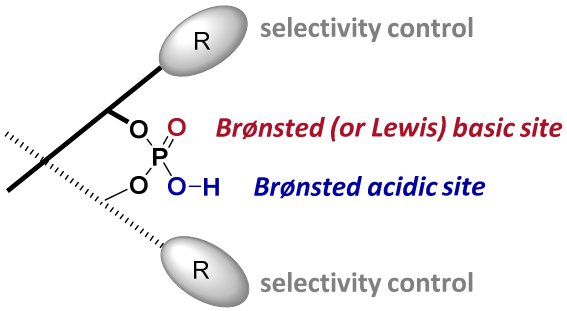
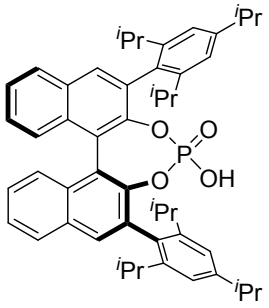


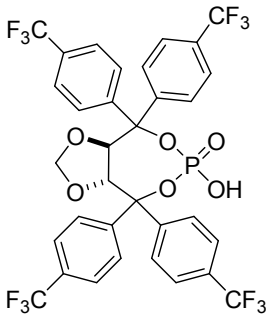
Figure 2.6. Bifunctionality in chiral phosphoric acids.

Phosphoric acids and derivatives

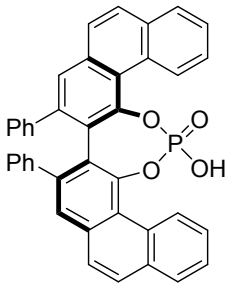
One of the most successful chiral phosphoric acids is the TRIP catalyst which was initially reported by the List group (Figure 2.7).[44-46] TRIP possesses bulky substituents (2,4,6-$^{i}Pr_3C_6H_2$) near the active site and was initially applied to the highly enantioselective asymmetric transfer hydrogenation of imines.[44-45] Moreover, the TRIP anion can be employed as the counteranion in asymmetric counteranion-directed catalysis (ACDC) which was introduced by Mayer and List.[47-48] Later this principle has been applied in metal catalysis as well.[49-50] Along with the success of BINOL based phosphoric acids, some other chiral scaffolds have been designed and investigated aiming at modified geometrical parameters of the active site. The Akiyama group introduced a new chiral phosphoric acid catalyst which is derived from TADDOL for Mannich type reactions,[51] and the Antilla group developed the VAPOL phosphoric acid for imine amidation reactions (Figure 2.7).[52] The Gong group reported the high enantioselective Biginelli reaction catalyzed by H_8-BINOL-based phosphoric acids which are superior to BINOL based analogs in certain cases,[53] and a bis-BINOL-derived phosphoric acid was designed by the Du group for the transfer hydrogenation of quinolines (Figure 2.7).[54] In 2010, Lin, Wang and coworkers introduced the naphthyl-substituted SPINOL backbone phosphoric acids which are based on spirobiindane scaffold and were employed to catalyze the asymmetric Friedel-Crafts reaction of indoles with imines (Figure 2.7).[55] The List group reported independently and, simultaneously, a kinetic resolution of alcohols via asymmetric transacetalization using the 2,4,6-$^{i}Pr_3C_6H_2$-substituted SPINOL-derived phosphoric acid (STRIP) as an efficient catalyst (Figure 2.7).[56] The Akiyama group developed biphenol-derived phosphoric acids for asymmetric C-H bond functionalization via a hydride shift/cyclization reaction (Figure 2.7).[57] Two independent reports by Gong and coworkers, and Momiyama and Terada *et al*. presented the development of bisphosphoric acids which were applied to a three component 1,3-dipolar cycloaddition reaction, and Diels-Alder reaction of α,β-unsaturated aldehydes with amidodienes, respectively (Figure 2.8).[58-59]



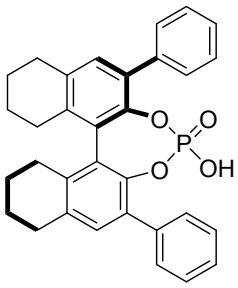
TRIP
List *et al*. (2005)



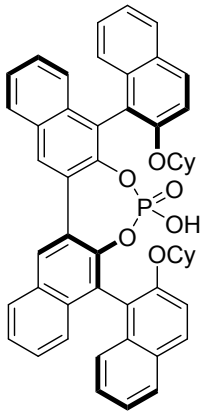
TADDOL-derivative
Akiyama *et al*. (2005)



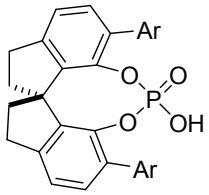
VAPOL
Antilla *et al*. (2005)



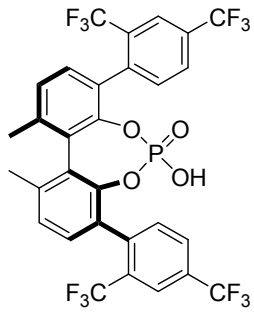
H_8-BINOL-derivative
Gong *et al*. (2006)



bis-BINOL-derivative
Du *et al*. (2008)

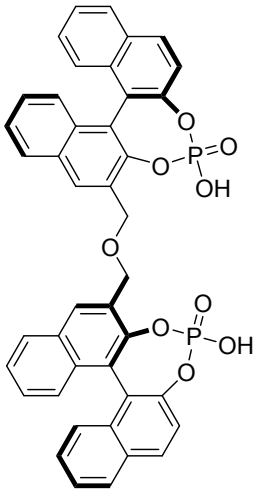


SPINOL-derivative (2010)
Lin, Wang *et al*. (Ar = 1-naphthyl)
List *et al*. (Ar = 2,4,6-$^{i}Pr_3C_6H_2$)

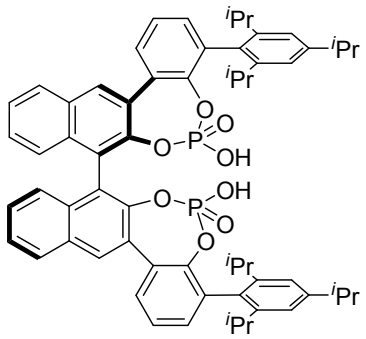


biphenol-derivative
Akiyama *et al*. (2011)

Figure 2.7. Chiral phosphoric acids and derivatives.



Gong *et al*. (2008)

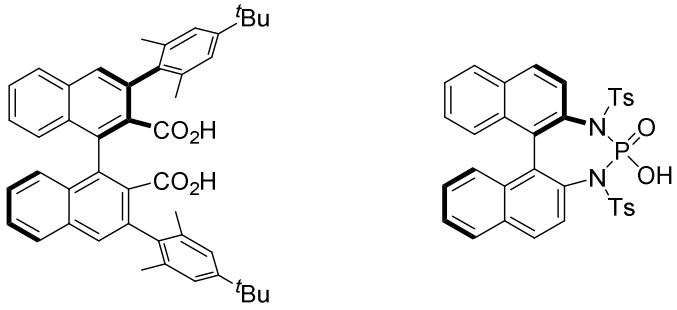


Momiyama, Terada *et al*. (2011)

Figure 2.8. Bisphosphoric acids.

Other than phosphoric acids, a binaphthyl derived dicarboxylic acids were used by the Maruoka group to achieve an enantioselective Mannich reaction of *N*-Boc-imines with diazo

compounds,[60] and a phosphordiamidic acid was designed by the Terada group for the direct Mannich reaction of *N*-acyl-imines with 1,3-dicarbonyl compounds (Figure 2.9).[61]



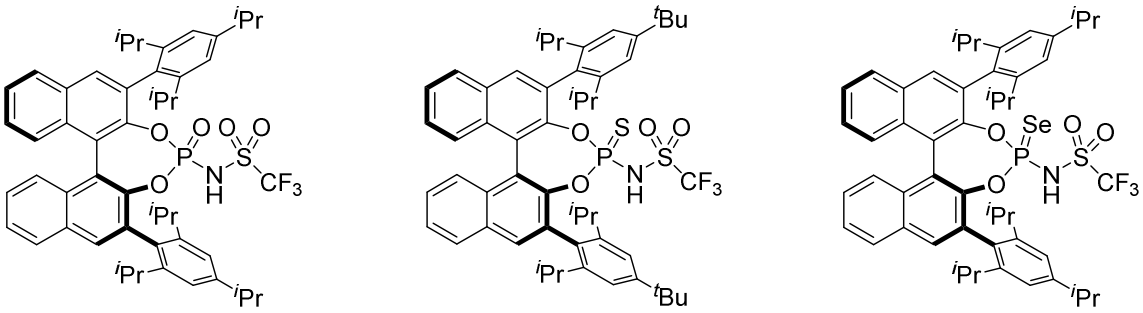
Maruoka *et al*. (2007) **Terada** *et al*. (2006)

Figure 2.9. Other strong chiral Brønsted acids.

Phosphoramides and derivatives

Although those seminal reports demonstrated that chiral phosphoric acids are highly potent catalysts for development of novel asymmetric processes, their usage has been limited to the transformations which involve more basic nitrogen-based electrophiles, because of their relatively low acidity.[9]

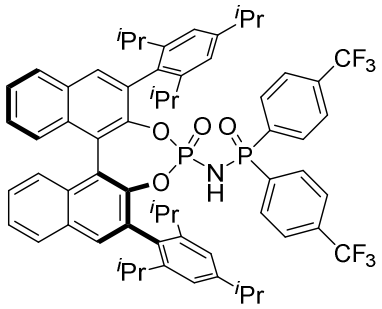
Towards the development of stronger Brønsted acids that are more reactive and acidic than phosphoric acids, various derivatives have been studied by the Yamamoto group. The chiral *N*-triflyl phosphoramide was suggested as a sufficiently strong chiral Brønsted acid catalyst to catalyze the asymmetric Diels-Alder reaction of α,β-unsaturated ketones with siloxydienes (Figure 2.10).[62] Later they reported *N*-triflyl thio- and seleno-derivatives for the protonation reactions of silyl enol ethers (Figure 2.10).[63]



N-triflyl phosphoramide *N*-triflyl thiophosphoramide *N*-triflyl selenophosphoramide

Figure 2.10. *N*-triflyl phosphoramides and derivatives.

In 2010, the List group reported the direct asymmetric *N,O*-acetalization of aldehydes catalyzed by *N*-phosphinyl phosphoramides. This is a novel class of stronger Brønsted acids possessing the phosphinyl electron-withdrawing group instead of the triflyl group in Yamamoto's catalyst (Figure 2.11).[64]



List *et al.* (2010)

Figure 2.11. *N*-phosphinyl phosphoramides.

2.3.3. Confined Brønsted acids

In the field of asymmetric Brønsted acid catalysis, chiral phosphoric acids were successfully employed in a wide range of asymmetric transformations.[9-10, 65] However, substrates have often been electronically or sterically biased to achieve high asymmetric induction. BINOL backbone chiral phosphoric acids and derivatives have been rationalized as successful catalysts in numerous enantioselective reactions due to a strong hydrogen bond between the protonated imine substrate and the chiral anion, N^{+}–H···^{-}X* (Figure 2.12).[11] The strong hydrogen bond furnishes a structurally organized chiral ion pair, promoting enantioselective addition of nucleophiles to imines. A strong covalent or hydrogen bonding interaction between the catalyst and the substrates can lead to a well-organized transition state which can result in high enantioselectivity.

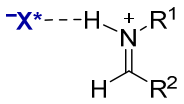


Figure 2.12. Strong binding of iminium ion with a chiral counteranion.

On the other hand, substrates or intermediates which possess only very weakly acidic *C*–*H* bonds, such as oxocarbenium ions, are very rarely found to give high enantioselectivity in

asymmetric reactions (Figure 2.13).[12-14] The presence of several weak anion binding sites does not enable strong and geometrically restricted interaction with the chiral anion resulting in low enantioselectivity.[1, 11]

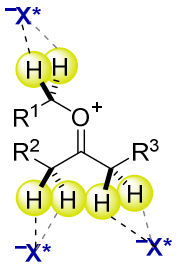


Figure 2.13. Multiple binding sites of oxocarbenium ion with a chiral counteranion.

Phosphoric acid type catalysts have imparted selectivity to large substrates which possess sterically demanding protecting groups, large aromatic/planar surfaces, or bulky substituents being placed in a sterically demanding environment of the catalyst. This sufficient steric interaction with the catalyst's active site is able to accommodate one of the two enantiomeric transition states leading to good reactivity and selectivity (Figure 2.14). However, phosphoric acid type catalysts are rarely efficient in enabling asymmetric reactions of small aliphatic substrates, because of the lack of sterically well defined interactions with the active site of the catalyst (Figure 2.14).[11, 15]

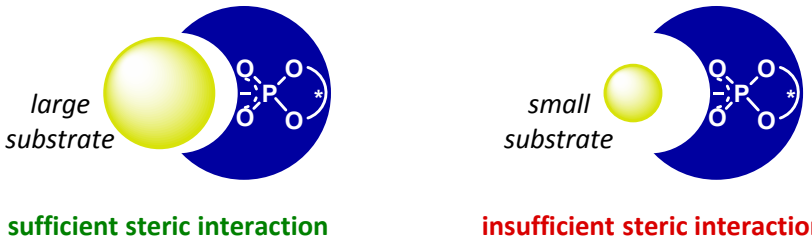


Figure 2.14. Schematic steric interaction of the phosphoric acid type catalysts.

To solve the inability of current synthetic Brønsted acid catalysts, in 2012, Čorić and List designed and synthesized novel confined Brønsted acid catalysts based on a C_2-symmetric imidodiphosphoric acids which are able to provide an extremely sterically demanding chiral microenvironment (Figure 2.15).[1, 11, 15]

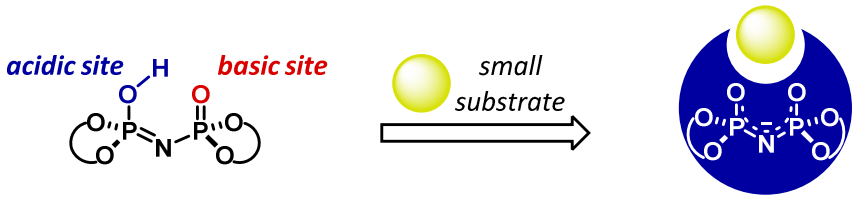
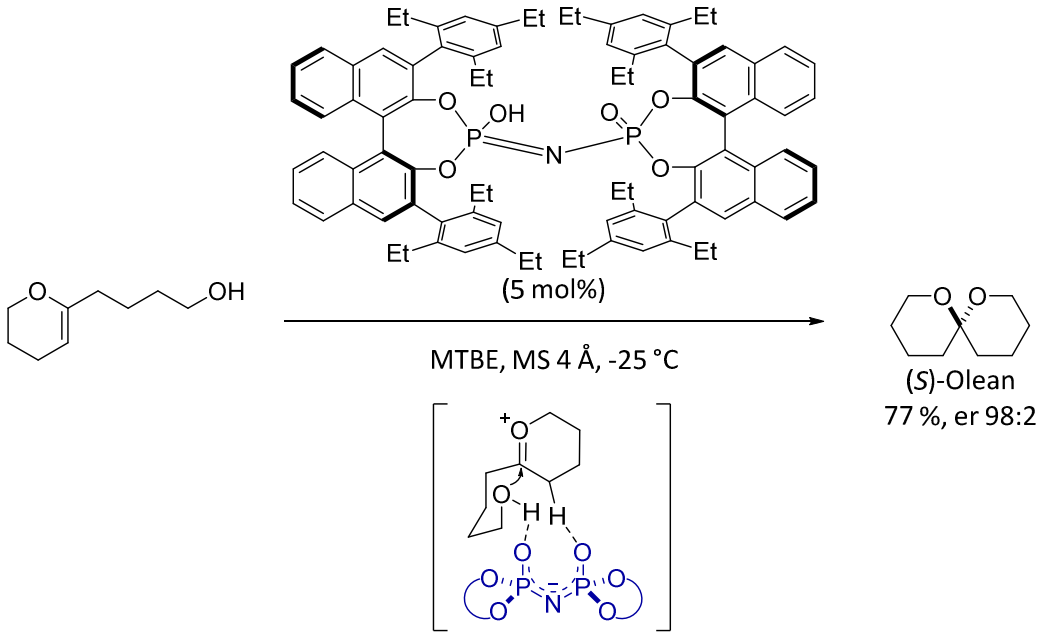


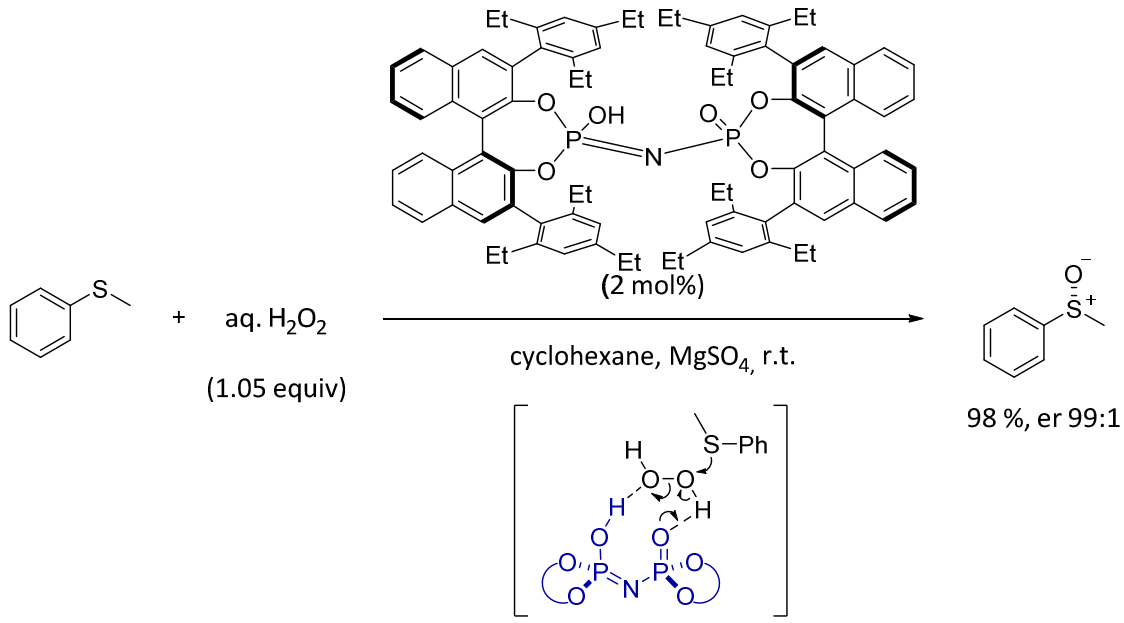
Figure 2.15. C_2-symmetric imidodiphosphoric acid with small substrate.

The C_2-symmetric imidodiphosphoric acids possess compact chiral environments and induce enantioselectivity in reactions involving small molecules/intermediates and featuring less organized transition states that for example do not possess strong hydrogen bonding interactions between the catalyst and the nucleophile or electrophile. The imidodiphosphoric acid which possesses 2,4,6-$Et_3C_6H_2$ substituents efficiently catalyzed the asymmetric conversion of small and further unfunctionalized hydroxyl enolether substrates providing various spiroacetals with high enantioselectivity (Scheme 2.9).[15]



Scheme 2.9. Catalytic asymmetric spiroacetalization.

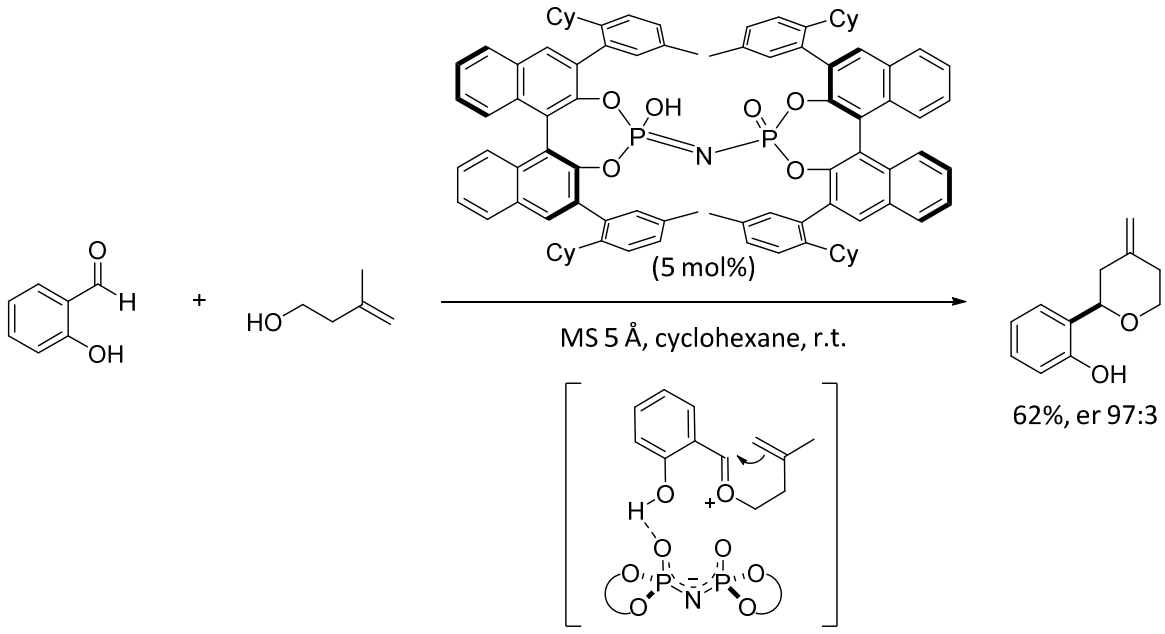
These confined chiral Brønsted acids were also demonstrated as superior catalysts for the asymmetric oxidation of sulfides to sulfoxides with hydrogen peroxide, which is presumably bound by the catalyst inside its chiral cavity (Scheme 2.10).[66]



Scheme 2.10. Enantioselective organocatalytic sulfoxidation.

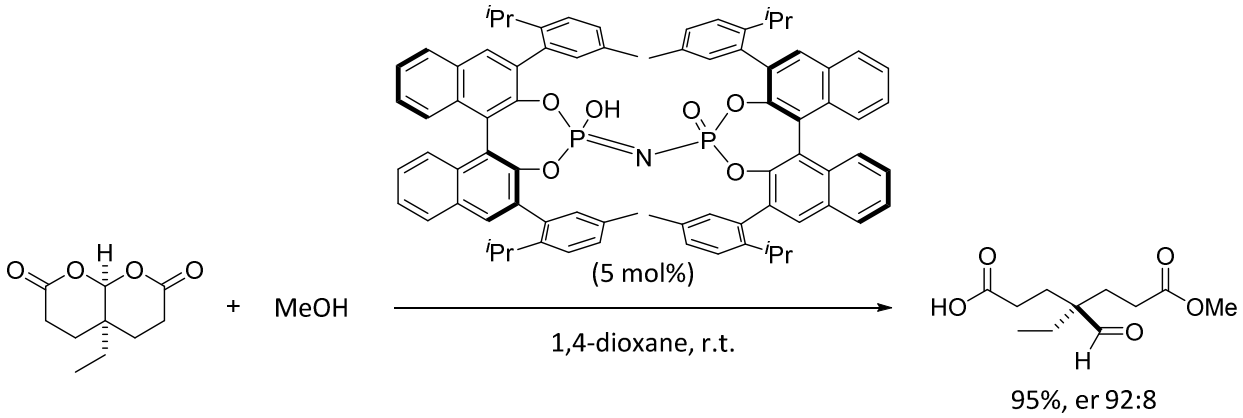
Following these reports, the direct asymmetric acetalization of aldehydes with diols catalyzed by chiral imidodiphosphoric acid, which is the topic of this thesis, was developed (chapter 4.1).[67]

Recently, the List group reported an asymmetric Prins cyclization of salicylaldehydes with homoallylic alcohols catalyzed by cyclohexyl, methyl-substituted imidodiphosphoric acid, which was developed during our acetalization studies[68] (Scheme 2.11).[69]



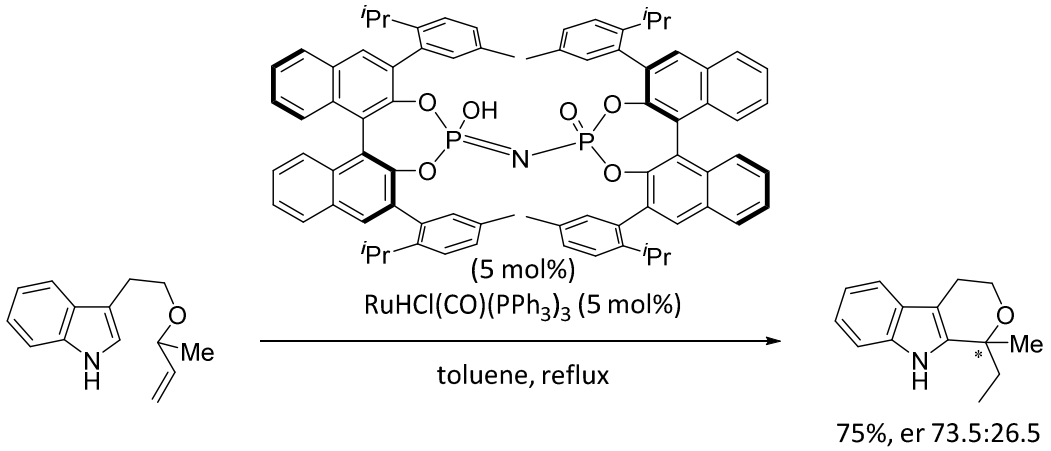
Scheme 2.11. Asymmetric Prins cyclization of salicylaldehydes.

The Zhu group showed that the imidodiphosphoric acid which we had earlier introduced for the asymmetric acetalization,[11, 67] can promote the enantioselective desymmetrization of bicyclic bislactones with alcohols and the products can be utilized as chiral building blocks in natural product synthesis (Scheme 2.12).[70]



Scheme 2.12. Enantioselective desymmetrization of bicyclic bislactones.

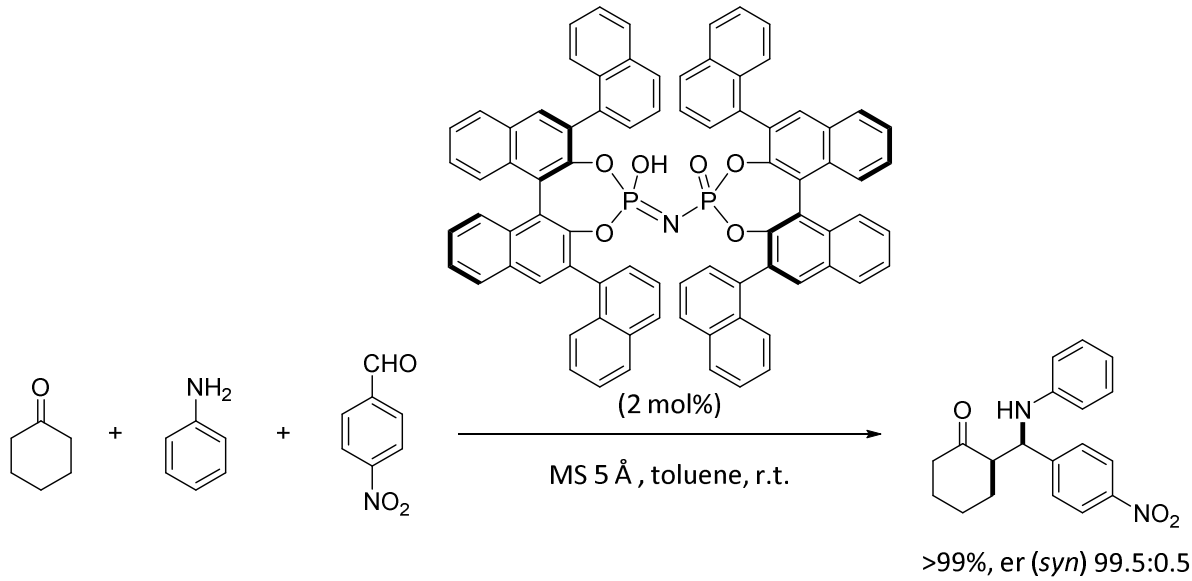
The Nielsen group reported that the use of the same imidodiphosphoric acid as a co-catalyst promotes an enantioselective oxa-Pictet-Spengler reaction (Scheme 2.13).[71] Allylic ethers undergo sequential isomerization to enol ethers catalyzed by ruthenium, and then the imidodiphosphoric acid catalyzes the formation of an oxocarbenium ion followed by enantioselective endo cyclization.



Scheme 2.13. Dual ruthenium hydride/Brønsted acid catalyzed tandem sequence.

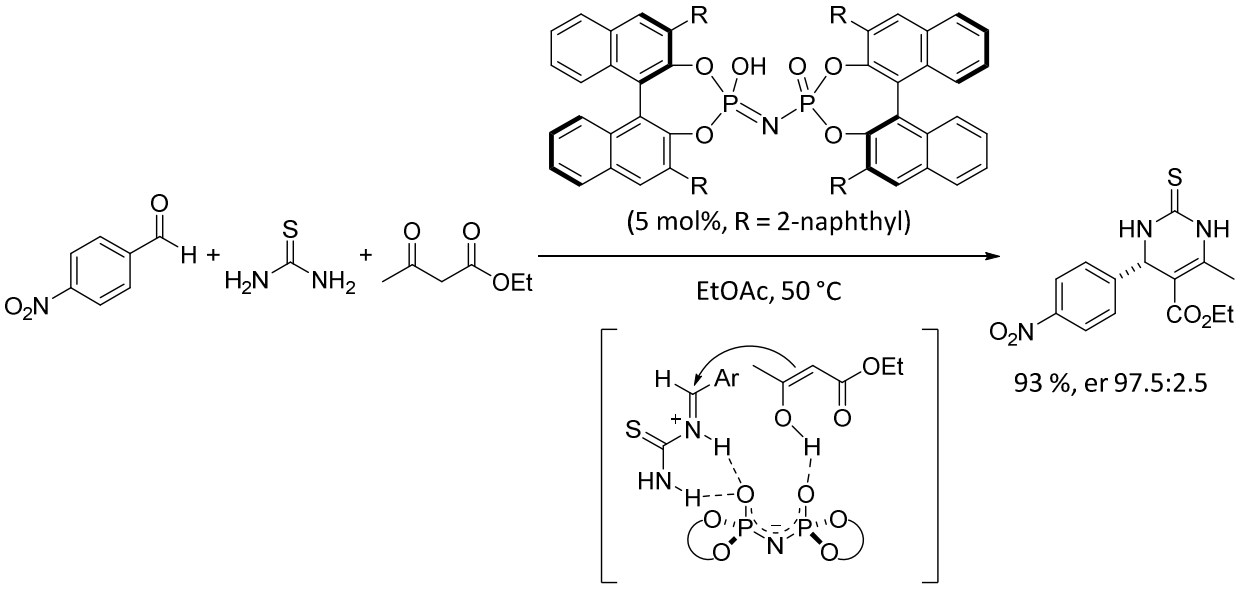
Other imidodiphosphoric acids were reported and applied to various transformations. The Zheng and Zhang group reported asymmetric three-component Mannich reactions catalyzed

by the less bulky 1-naphthly substituted imidodiphosphoric acid to give *syn*-β-amino ketones with high enantioselectivity (Scheme 2.14).[72]



Scheme 2.14. Asymmetric three-component Mannich reactions.

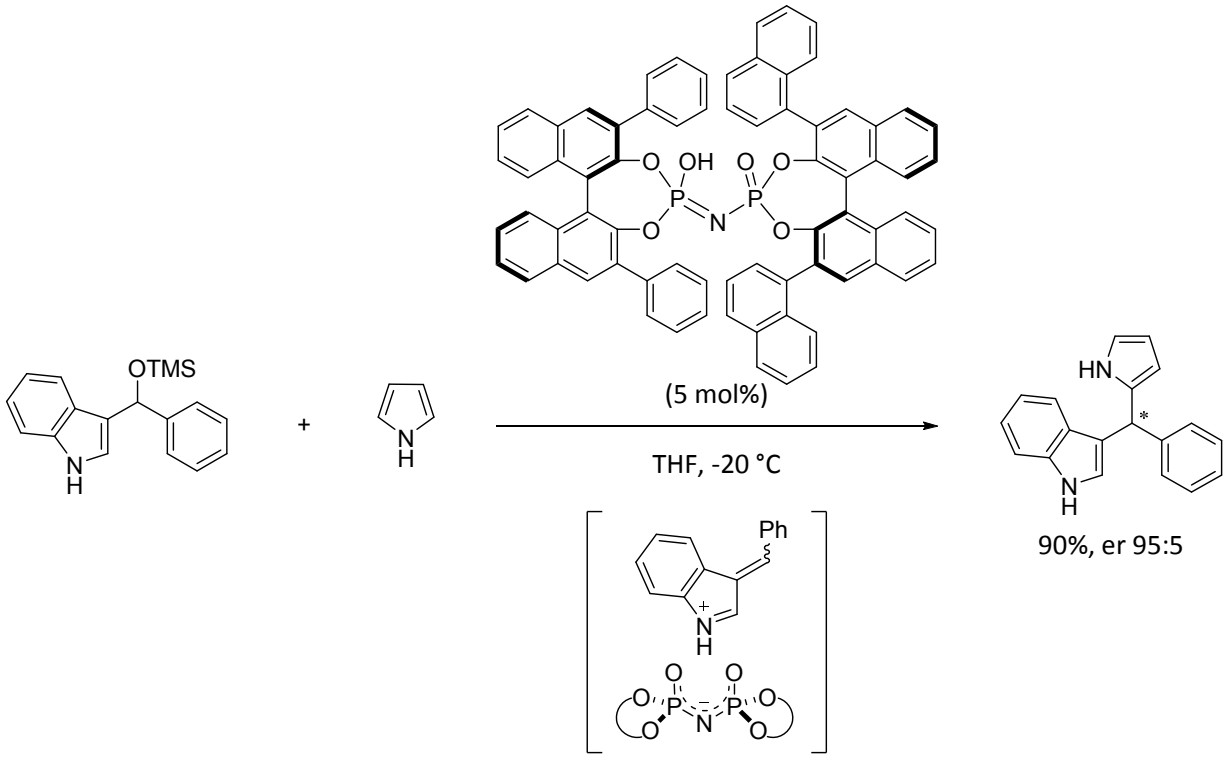
2-Naphthyl imidodiphosphoric acid catalyzed enantioselective Biginelli reactions of aromatic aldheydes, thiourea, and ethyl acetoacetate to give dihydropyrimidinethiones were reported by the same group (Scheme 2.15).[73]



Scheme 2.15. Enantioselective Biginelli reaction.

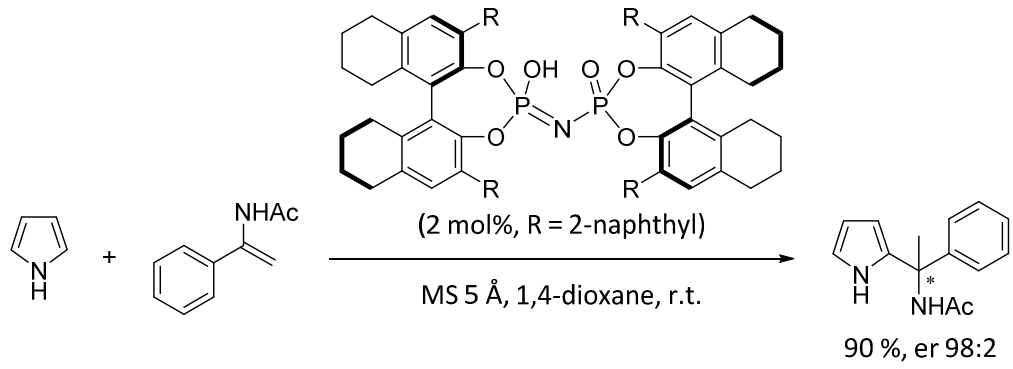
Imidodiphosphoric acids are readily accessible requiring only a single additional synthetic step compared to the corresponding phosphoric acids. Thus, catalysts can be derived from various

BINOL frameworks with different 3,3'-substituents on two BINOL backbones. The Jiang and Zhang group reported enantioselective Friedel-Crafts reactions of pyrrole with trimethylsilyl protected 3-arylindolylmethanols catalyzed by imidodiphosphoric acid bearing phenyl and naphthyl-substituents respectively on the two BINOL frameworks (Scheme 2.16).[74]



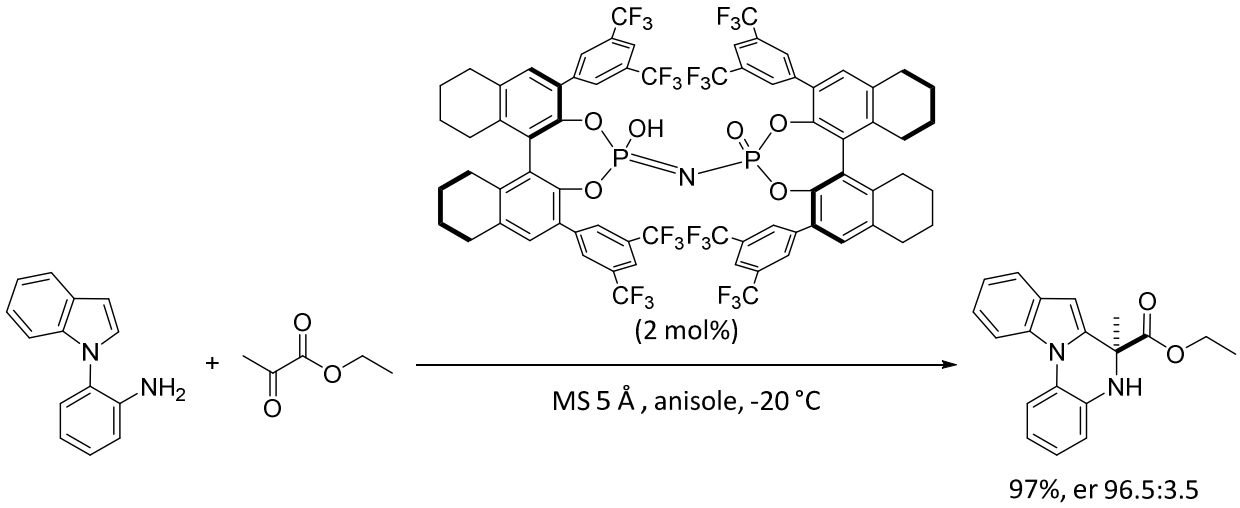
Scheme 2.16. Enantioselective Friedel-Crafts-type alkylations.

A H_8-BINOL derived imidodiphosphoric acid was prepared by the same group to catalyze enantioselective aza-Friedel-Crafts reactions of pyrroles and enamides/imines (Scheme 2.17).[75]



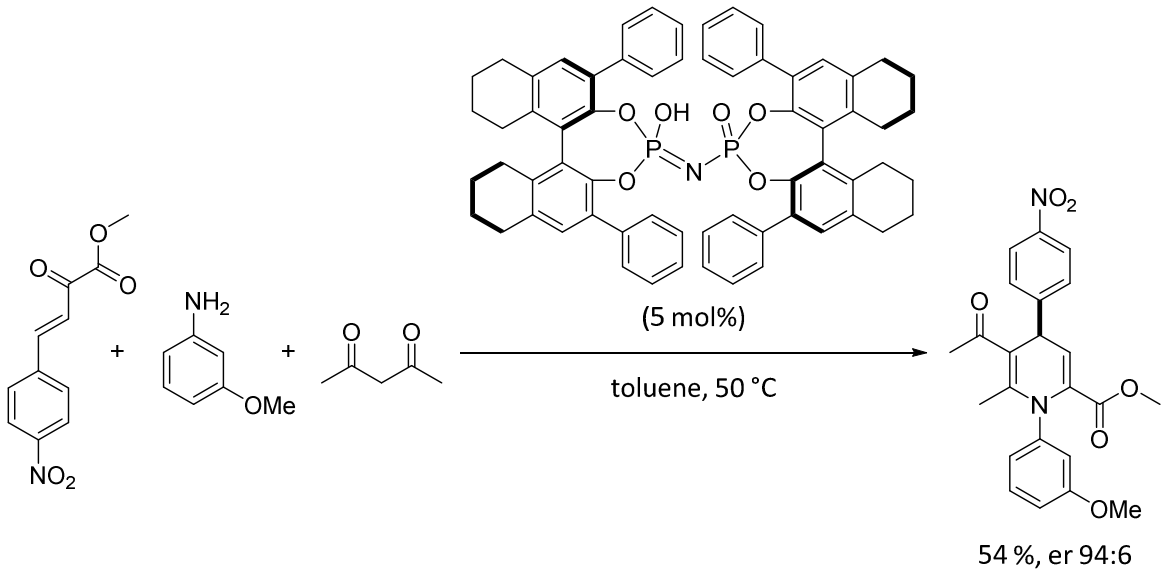
Scheme 2.17. Enantioselective aza-Friedel-Crafts reaction.

This H_8-BINOL derived imidodiphosphoric acid enables asymmetric Pictet-Spengler-type reactions of indolyl anilines with ketones (Scheme 2.18). The utility of this method was demonstrated with the synthesis of a HIV-1 inhibitor.[76]



Scheme 2.18. Asymmetric Pictet-Spengler-type reaction.

Very recently, H_8-BINOL derived imidodiphosphoric acid catalyzed enantioselective cyclization reactions of β,γ-unsaturated α-ketoesters, arylamines and acetylacetone to give penta-substituted 1,4-dihydropyridines with high enantioselectivity were reported (Scheme 2.19).[77]



Scheme 2.19. Catalytic asymmetric synthesis of penta-substituted 1,4-dihydropyridines.

2.4. Chiral acetals

Acetals are one of the most common stereogenic centers in nature. Stereogenic acetals are widely found in natural products, in small insect pheromones such as olean and also in complex spiroketal polyketides (Figure 2.16).[4-6]

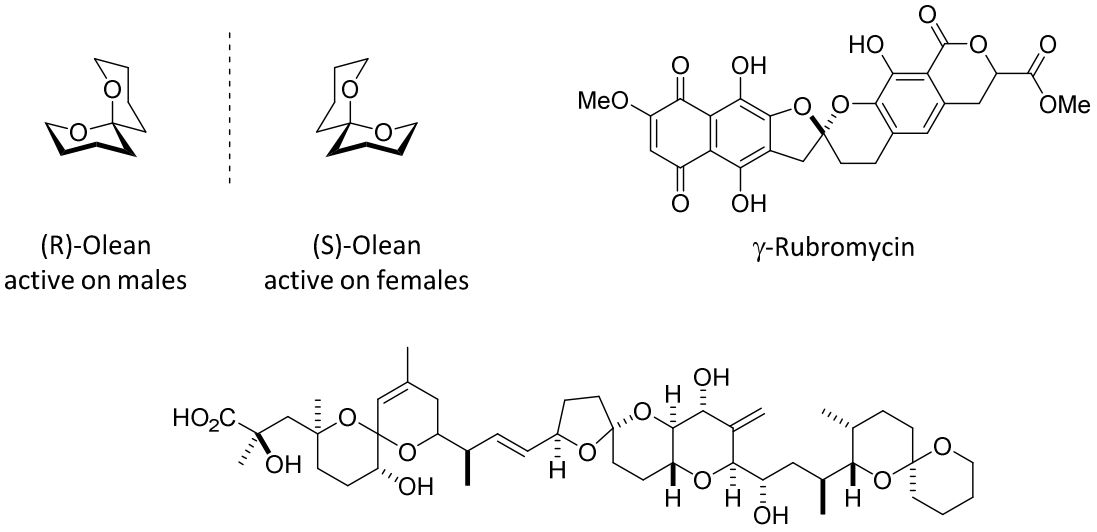


Figure 2.16. Stereogenic acetals in nature.

Acetals form glycosidic bonds that form carbohydrates which are the most abundant class of natural organic compounds, including cellulose and starch (Figure 2.17).[3] The configuration of the anomeric acetal stereocenter in starch differs from the one in cellulose. This highlights the importance of controlling the relative and absolute configuration of acetal stereocenters.[11]

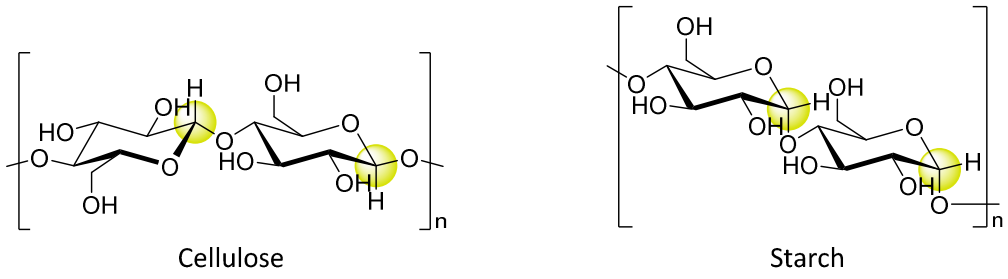


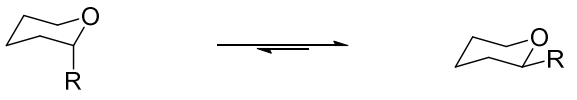
Figure 2.17. Cellulose and starch.

Spiroacetals are one subgroup of acetals and are structurally particularly distinctive compounds in which two oxygen-carbon single bonds of two rings are connected at a single carbon atom (Figure 2.16).[15] Their absolute configuration can result in nonanomeric or

anomeric configuration, which is often thermodynamically favored as a consequence of the anomeric effect. The term anomeric effect is used to describe the observation that electronegative (O, N, or S usually) substituents of tetrahydropyrans in the 2-position stabilize axial orientation of the substituent (Scheme 2.20).[78] The relative amount of axial isomer is then increased compared to equatorial isomer, and can sometimes become preferred (Scheme 2.20b). This effect is often attributed to the presence of n–σ* stabilizing interaction that involves the donation of oxygen lone pair into C–heteroatom antibonding orbital of the 2-substituent (Scheme 2.20c).[79] The anomeric carbon of glucose, which is the most abundant natural sugar, prefers equatorial configuration but only with 2:1 ratio, as a result of anomeric stabilization of the axial diastereomer (Scheme 2.20d). A more electronegative substituent at anomeric carbon prefers more to be axial rather than equatorial. The anomeric effect is observed also in spiroacetals resulting often in the axial preference (Scheme 2.20e).[4] Spiroacetals feature as a core motif in a variety of natural products and thus controlling the configuration of spiroacetals is very important.[11] Although many synthetic methods have been developed, access to spiroacetals with chiral catalyst control in a highly enantioselective manner was reported only recently.[15, 80]

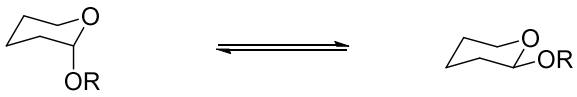
The importance of chiral acetals is also demonstrated by their presence in sugars, alkaloids and several chiral pharmaceuticals.[11, 81-82] Furthermore, they can be used as diastereocontrolling elements in organic synthesis.[2, 83-85] However, methods for enantioselective synthesis of stereogenic acetals are underdeveloped and mainly rely on chiral starting materials or reagents to induce the enantioselective formation of acetal stereocenters.[86-91]

a. Orientation of tetrahydropyrans bearing an alkyl substituent in the 2-position



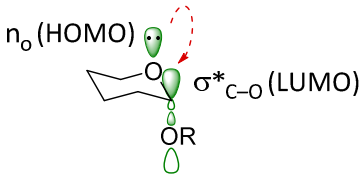
axial — *equatorial* preference

b. Orientation of tetrahydropyrans bearing an electronegative substituent in the 2-position

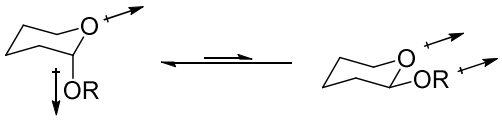


axial higher amount then expected from steric argument — *equatorial*

c. Explanations for anomeric effect

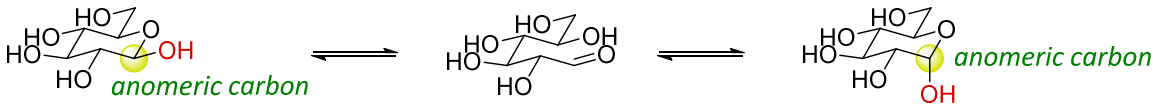


parellal orbital stablization
: lone pair donates into C–O σ*



dipole minimization
: axial configuration has opposed dipole

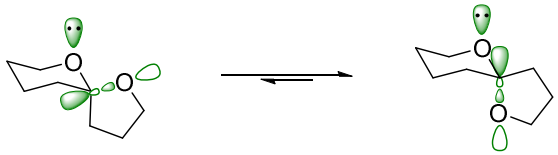
d. The anomeric effect in glucose derivatives



64% *equatorial* OH — <1% — 35% *axial* OH

33% — 67% *axial* — 14% — 86% *axial*

e. The anomeric effect in spiroacetals



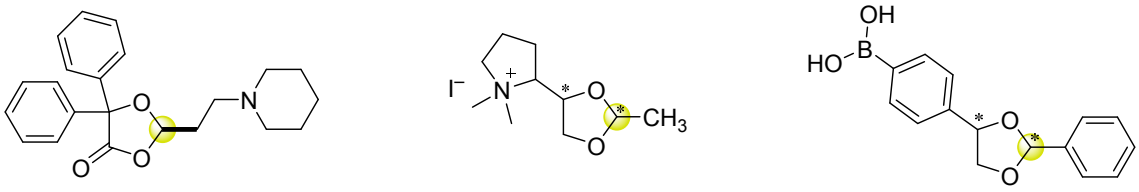
equatorial C–O bond
: nonanomeric configuration

axial C–O bond
: anomeric configuration

Scheme 2.20. The anomeric effect.

Dioxolanes and dioxanes

Due to their relative stability in mildly acidic conditions and the convenience of preparation, the synthesis of cyclic acetals has been a common transformation in organic synthesis. Reaction of a single molecule of a diol, which contains two hydroxyl groups, with carbonyl groups of ketones or aldehydes forms cyclic acetals. When 1,2-diol is used it provides a five-membered 1,3-dioxolane ring, and 1,3-diol provides a six-memebered 1,3-dioxane ring. One important use of cyclic acetals is as protecting groups for carbonyl groups. They are readily introduced and cleaved in high yields and are among the most useful protecting groups.[92] Moreover, synthesis of chiral cyclic acetals with control of their relative and absolute configuration is important as they can be common structural subunits in natural products and bioactive compounds.[1] Molecules with stereogenic acetal can be employed to relief muscle spasms, as anti-infective agents, as cardiovascular and immune agents (Figure 2.18).[93]



Pipoxolan

Cardiovascular and anti-infective agent

Anti-infective and immune agent

Figure 2.18. Biological and pharmacological activity of cyclic acetals.

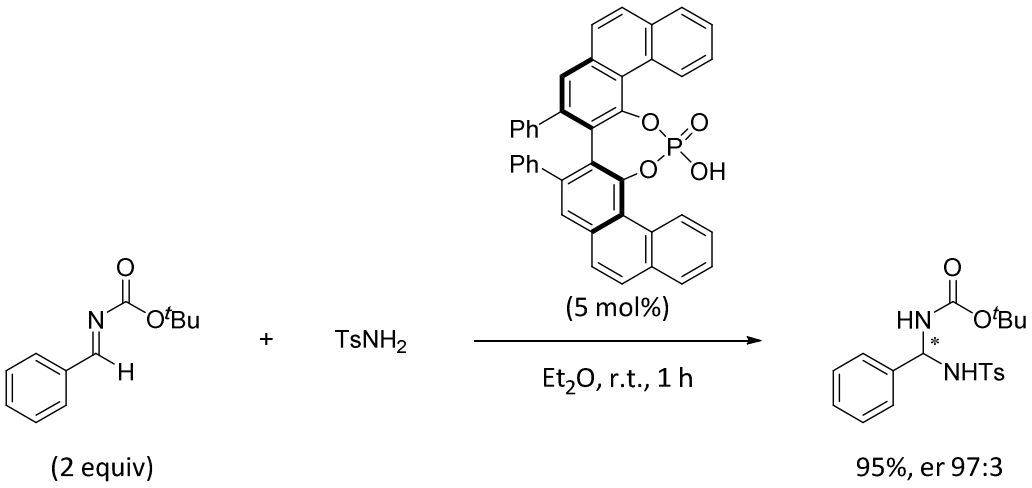
Although several asymmetric syntheses for stereoselective formation of *O,O*-acetals have been published, these synthetic methods rely on the use of enantioenriched staring materials or reagents. There are few recent examples of catalytic asymmetric reactions that form highly enantioenriched acetals, but direct acetalization of aldehydes with diols to give 1,3-dioxolanes or 1,3-dioxanes was unknown prior to our work described in this thesis.[67]

2.4.1. Organocatalytic asymmetric acetalizations via iminium intermediates.

Meanwhile, *N,X*-acetalizations that involve iminium intermediates in the reaction have been developed. Chiral *N,N*-, *N,O*-, and *N,S*-acetals are common motives in pharmaceuticals and are

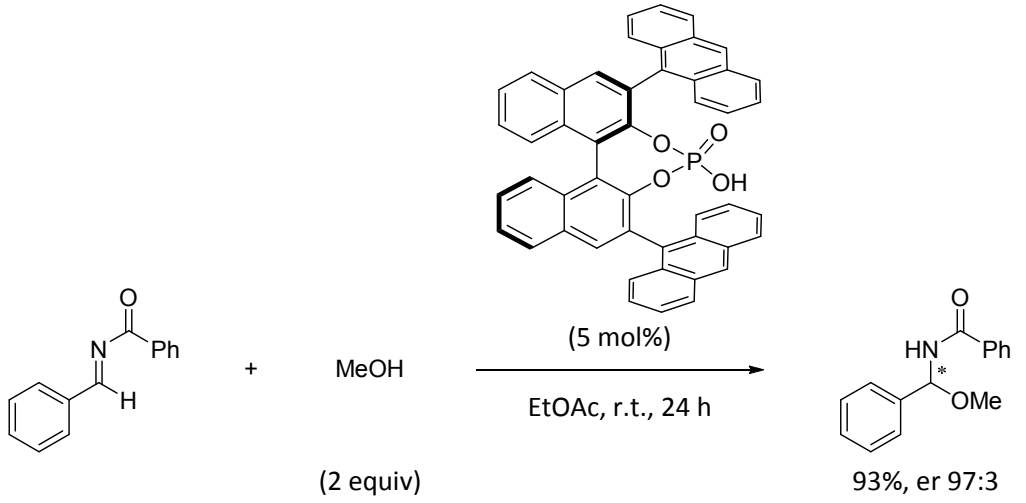
present in natural products. Consequently, their catalytic asymmetric syntheses have been studied over the years.

The initial study of asymmetric *N*,*N*-acetalization that includes addition of nitrogen nucleophiles to imines using a chiral Brønsted acid has been reported by the Antilla group in 2005 (Scheme 2.21).[52, 94]



Scheme 2.21. Catalytic asymmetric *N*,*N*-acetalization.

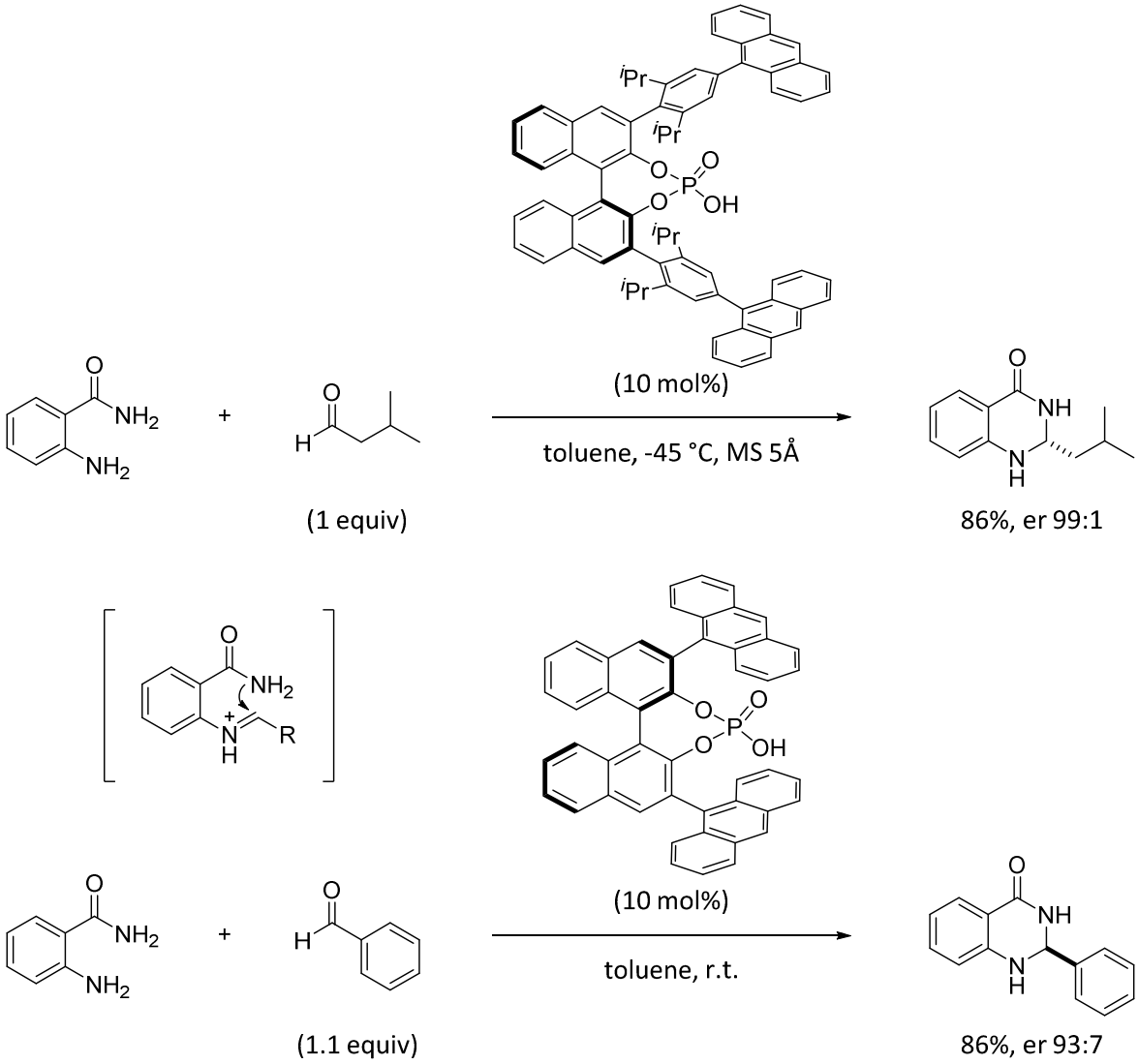
In 2008, the Antilla group also reported a catalytic asymmetric addition of alcohols to imines providing chiral *N*,*O*-acetals with high enantioselectivity (Scheme 2.22).[95]



Scheme 2.22. Catalytic asymmetric *N*,*O*-acetalization.

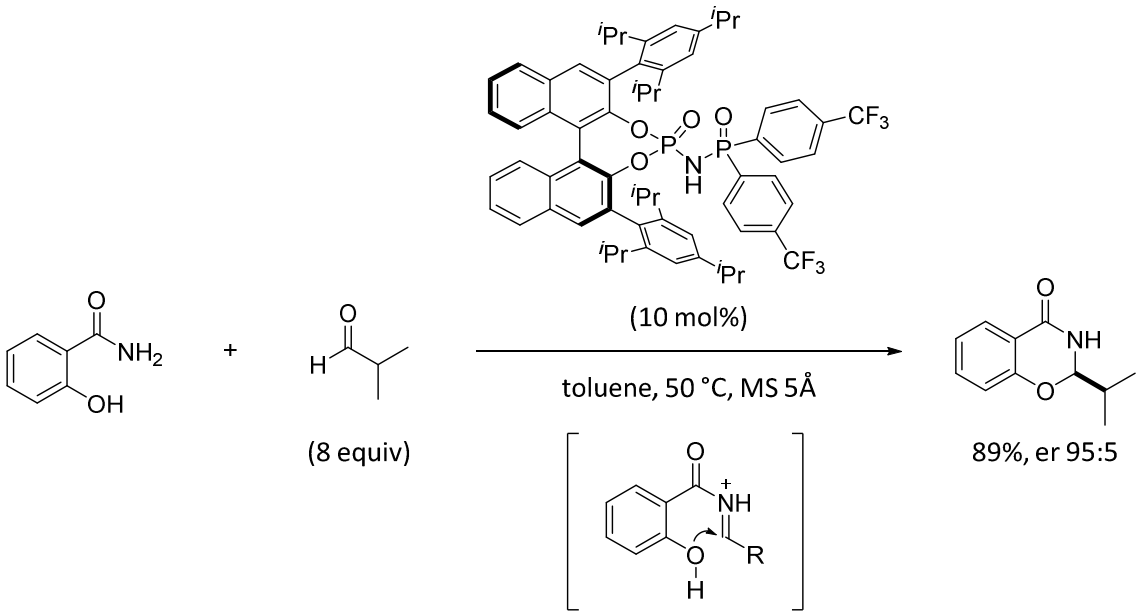
Independently, a direct asymmetric *N*,*N*-acetalization of aldehydes has been developed by the List group, and the Rueping group subsequently reported the same reaction using various aromatic aldehydes (Scheme 2.23).[96-97] The reactions proceed through imine formation,

followed by intramolecular amidation giving cyclic *N*,*N*-acetals which are often found in diverse commercial pharmaceuticals.



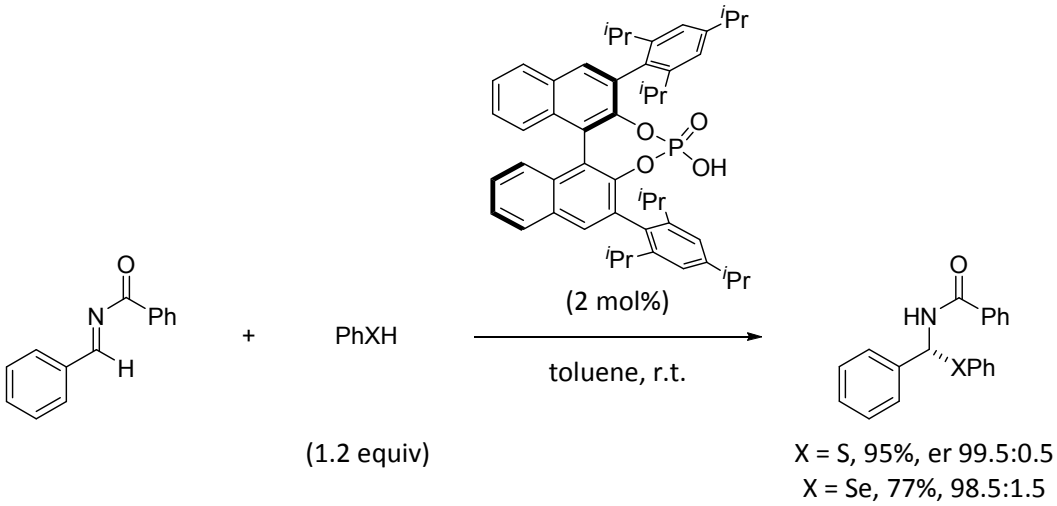
Scheme 2.23. Direct catalytic asymmetric *N*,*N*-acetalization of aldehydes.

Subsequently, the direct synthesis of cyclic *N*,*O*-acetals from aldehydes and hydroxyl amides catalyzed by chiral *N*-phosphinyl phosphoramides was reported by the List group (Scheme 2.24).[64]



Scheme 2.24. Direct catalytic asymmetric *N*,*O*-acetalization of aldehydes.

Afterwards, the Antilla group reported the preparation of enantioenriched *N*,*S*- and *N*,*Se*-acetals via an asymmetric addition of thiols and seleophenol to imines (Scheme 2.25).[98]



Scheme 2.25. Catalytic asymmetric *N*,*S*- and *N*,*Se*-acetalizations.

All of these reported acetalization reactions are based on the enantioselective addition to an iminium ion intermediate catalyzed by phosphoric acid derivatives. To achieve a successful asymmetric reaction, a well organized transition state is required having a strong covalent or hydrogen bonding interaction between the catalyst and the substrates. Imines are easily activated by Brønsted acids because of their basicity and in the subsequent iminium salts a

strong hydrogen bonding to the chiral anion of the Brønsted acid enables the formation of a well organized transition state which results in high enantioselectivity (Figure 2.19).

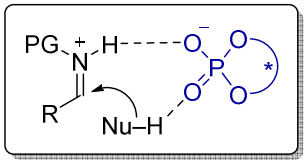


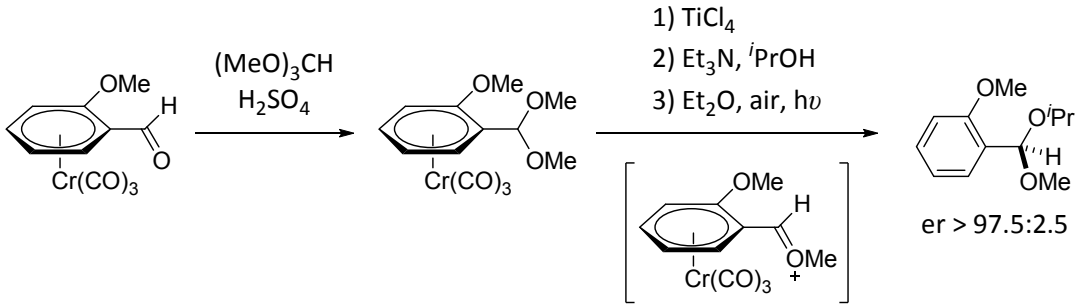
Figure 2.19. Hydrogen bonds between iminium ion and chiral phosphate anion.

2.4.2. Approaches to the synthesis of enantioenriched *O*,*O*-acetals

Although *O*,*O*-acetals are much more common motives in natural products and organic synthesis than the analogous *N*,*N*-, *N*,*O*-, or *N*,*S*-acetals, synthetic methods for their asymmetric synthesis are mostly based on enantiopure/enantioenriched starting materials or reagents.

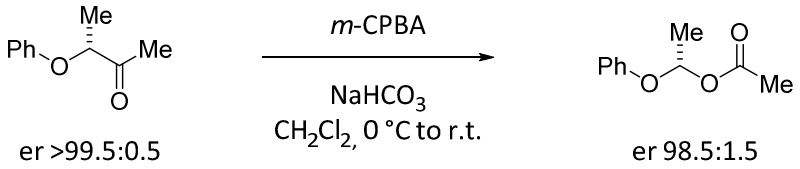
Using enantiopure/enantioenriched starting materials or reagents

The Davies group reported stereoselective reactions of an enantiopure *ortho*-substituted benzaldehyde chromium tricarbonyl complex to obtain enantioenriched *o*-anisaldehyde methyl isopropyl acetal (Scheme 2.26).[86] The enantiopure aldehyde chromium complex can be prepared by chromatographic separation of diastereomeric valinol imine derivatives.[99]



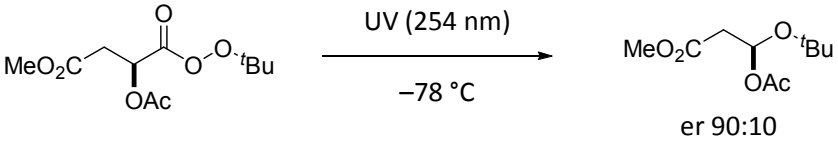
Scheme 2.26. Using enantiopure metal complex as a starting material.

Enantioenriched acyl alkyl acetals can be obtained via a Baeyer-Villiger oxidation using optically active α-alkoxyalkyl ketones as starting materials (Scheme 2.27).[87]



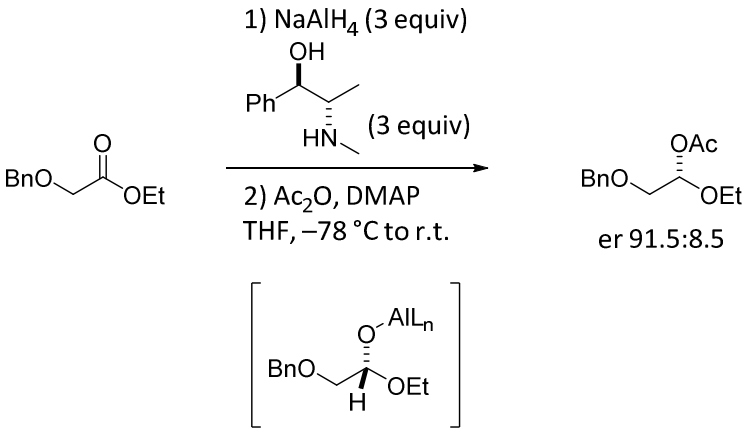
Scheme 2.27. Baeyer-Villiger oxidation of enantioenriched α-alkoxy ketones.

Enantiopure α-alkoxy peresters undergo photolytic decarboxylation to give enantioenriched acyl alkyl acetals with retention of stereochemistry (Scheme 2.28).[89]



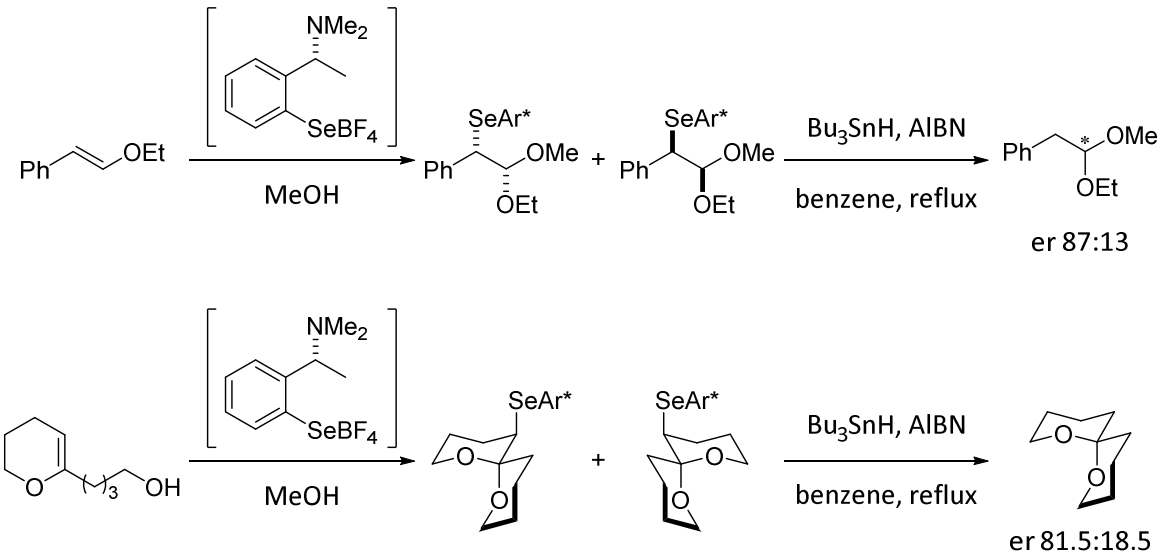
Scheme 2.28. Photolytic decarboxylation of enantiopure α-alkoxy peresters.

The reduction of achiral esters using a chiral reagent formed by combining $NaAlH_4$ and ephedrine, followed by in situ acetylation of the enantioenriched alkoxy aluminium intermediate, provides enantioenriched acyl alkyl acetals (Scheme 2.29).[88]



Scheme 2.29. Enantioselective reduction of esters using chiral aluminium reagent.

An asymmetric selenenylation of vinyl ethers employing an enantioenriched selenium reagent was developed by the Uchiyama group (Scheme 2.30). The selenium group can be removed to give the corresponding acetals with moderate to good enantioselectivity.[90-91]



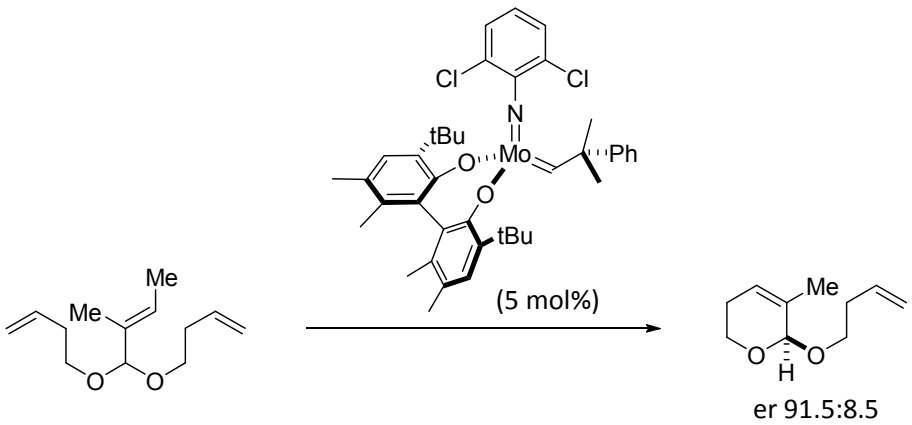
Scheme 2.30. Asymmetric selenenylation of vinyl ethers.

These methods that are based on enantiopure/enantioenriched starting materials or reagents are very substrate specific and often do not result in high enantioselectivity.

Catalytic asymmetric approaches: metal catalysis

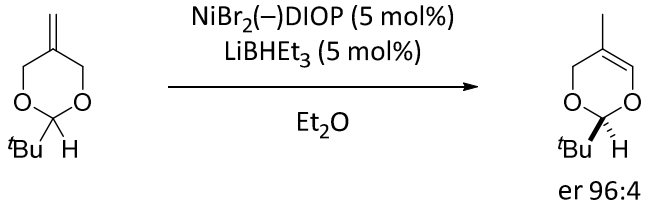
Catalytic asymmetric synthesis is the most practical and straightforward strategy for the preparation of enantioenriched compounds. However, there are only few examples of the catalytic asymmetric synthesis of *O,O*-acetals. Among these methods, catalytic asymmetric approaches to the synthesis of *O,O*-acetals with the acetal center as the only stereogenic element have been developed employing metal catalysts.

A chiral molybdenum catalyst can promote asymmetric ring closing metathesis of achiral triene acetals to give enantioenriched cyclic acetals with good enantioselectivity (Scheme 2.31).[100-101]



Scheme 2.31. Molybdenum catalyzed ring closing metathesis reaction.

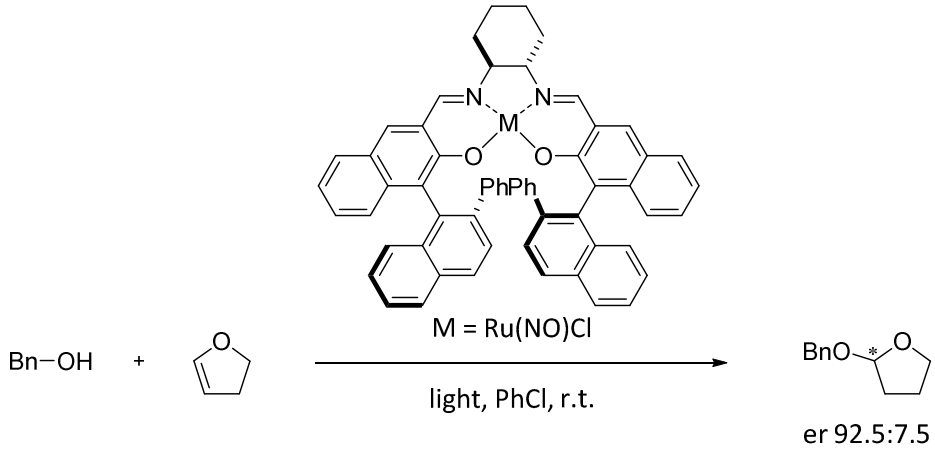
An asymmetric isomerization of exocyclic double bond using a chiral nickel catalyst can provide cyclic allyl acetals having a more stable endocyclic double bond with high enantioselectivity (Scheme 2.32).[102-103]



Scheme 2.32. Ni-catalyzed asymmetric isomerization of double bond.

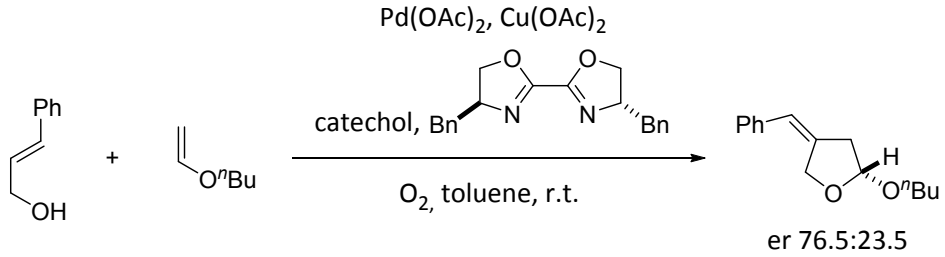
However, these desymmetrization reactions are transformations, in which the acetal carbon is not the reaction center. Transformations towards catalytic asymmetric *O,O*-acetalization that involve the acetal carbon as the reaction center have been reported only recently.

The first catalytic asymmetric acetalization reaction using a metal-catalyst was reported by Nagano and Katsuki.[104] A chiral salen-ruthenium complex catalyzes the hydroetherification of enol ethers to obtain enantioenriched acetal products, although the exact mechanism is unkown (Scheme 2.33).



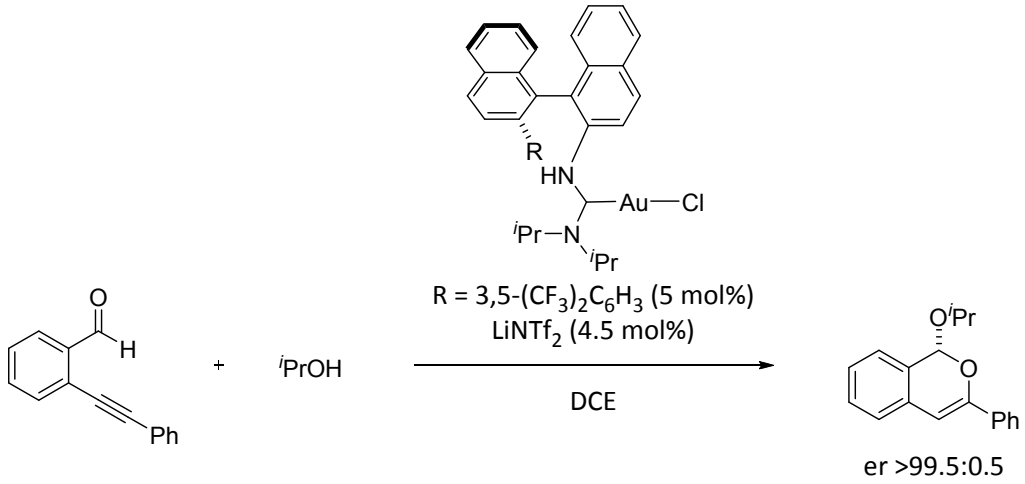
Scheme 2.33. First catalytic asymmetric acetalization.

The use of a chiral metal complex under O_2 induces the asymmetric coupling of cinnamyl alcohols and vinyl ethers to give acetal products with low to moderate enantioselectivity (Scheme 2.34).[105]



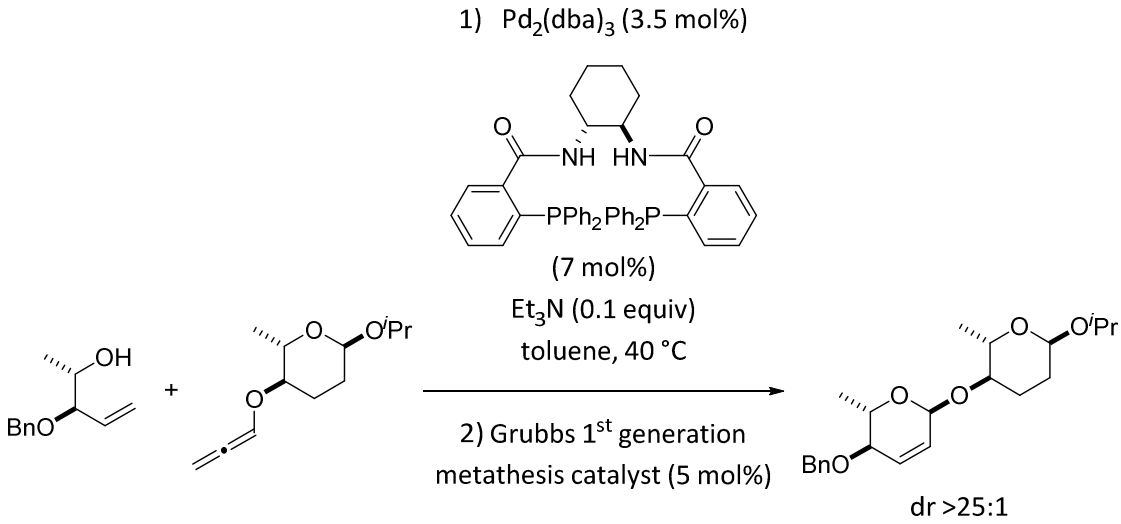
Scheme 2.34. Asymmetric coupling of allylic alcohols and vinyl ethers.

After the catalytic asymmetric acetalization studies by our group,[11, 15, 56, 106] Handa and Slaughter employed a chiral gold(I) diaminocarbene complex as catalyst for enantioselective alkynylbenzaldehyde cyclizations obtaining highly enantioenriched acetal products (Scheme 2.35).[107]



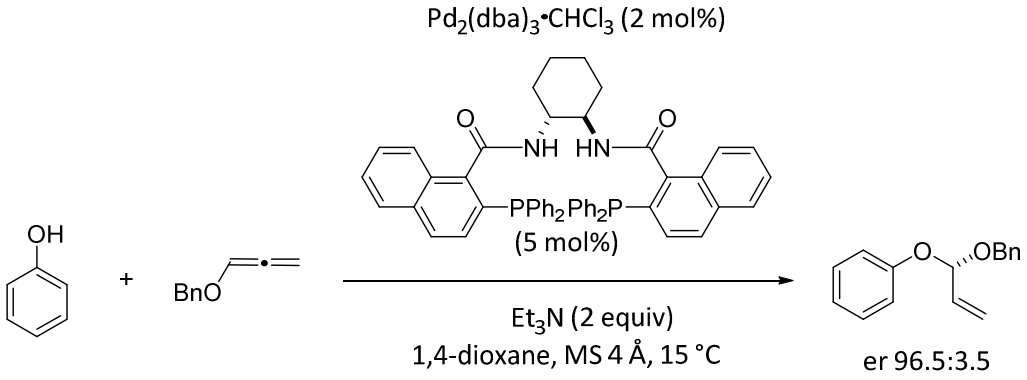
Scheme 2.35. Gold catalyzed asymmetric synthesis of acetals.

Recently, the Rhee group reported the palladium catalyzed asymmetric intermolecular hydroalkoxylation of alkoxyallenes with alcohols and subsequent ring-closing-metathesis to give acetals with high diastereocontrol (Scheme 2.36).[108] The method can be utilized to give various mono- and disaccharides.



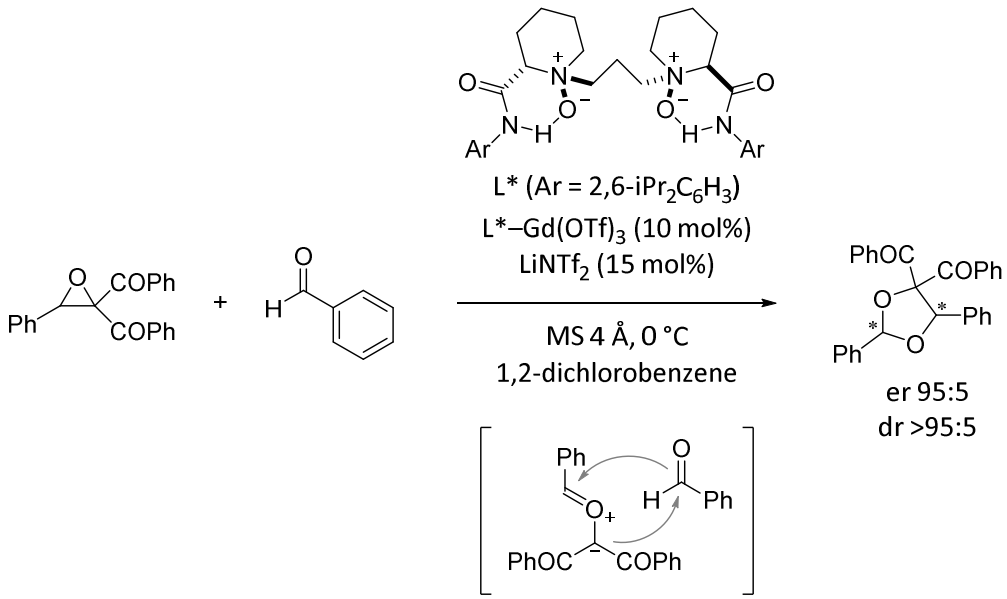
Scheme 2.36. Pd-catalyzed asymmetric hydroalkoxylation of alkoxyallenes with alcohols.

Later, a palladium catalyzed enantioselective hydroalkoxylation of alkoxyallens using phenols as pronucleophiles to obtain acyclic acetals was described (Scheme 2.37).[109]



Scheme 2.37. Enantioselective hydroalkoxylation of alkoxyallens with phenols.

Very recently, a chiral Gd complex catalyzed enantioselective [3+2] cycloaddition of aryl oxiranyl diketones and aromatic aldehydes was reported (Scheme 2.38).[93] The reaction proceeds through C–C bond cleavage of oxiranes to form a carbonyl ylide and subsequent cyclization with aldehydes providing chiral 1,3-dioxolanes with high enantioselectivities and diastereoselectivities.

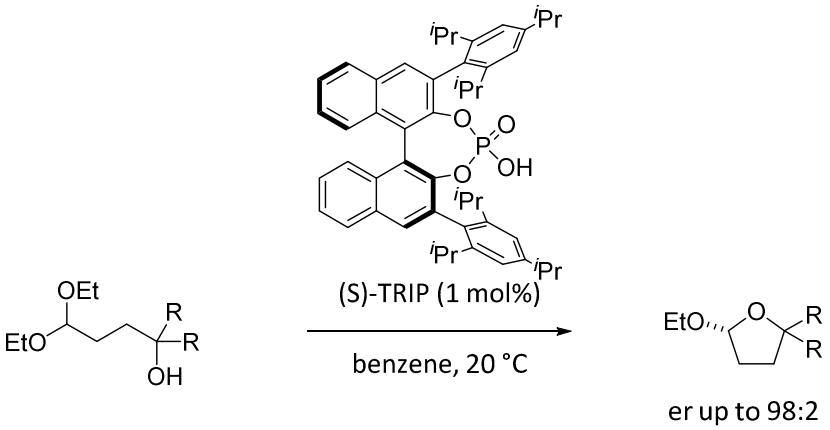


Scheme 2.38. Catalytic asymmetric [3+2] cycloaddition of aldehydes with oxiranes.

Catalytic asymmetric approaches: Brønsted acid catalysis

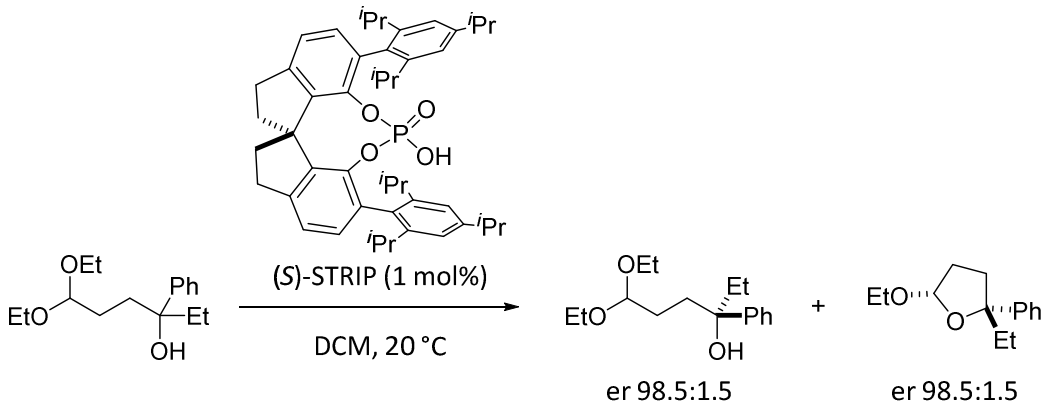
The first example of an enantioselective Brønsted acid catalyzed acetal synthesis was reported by the List group, employing an asymmetric transacetalization reaction (Scheme 2.39).[106] Although Brønsted acids are the most common catalysts for transacetalization reactions,

functional similarity of the starting material and the product can lead to reversibility and racemization under the acidic conditions. By developing an intramolecular variant of the transacetalization reaction this issue could be avoided to give highly enantioenriched acetal products. Afterwards several Brønsted acid catalyzed asymmetric reactions to form enantioenriched acetal products have been developed.



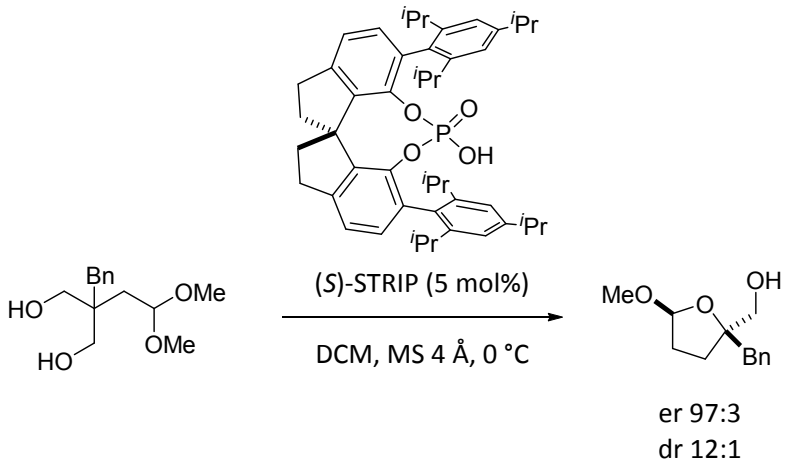
Scheme 2.39. Catalytic asymmetric transacetalization.

The asymmetric transacetalization reaction can be applied to the kinetic resolution of alcohols to give access to enantioenriched acetal protected homoaldols compounds (Scheme 2.40).[56]



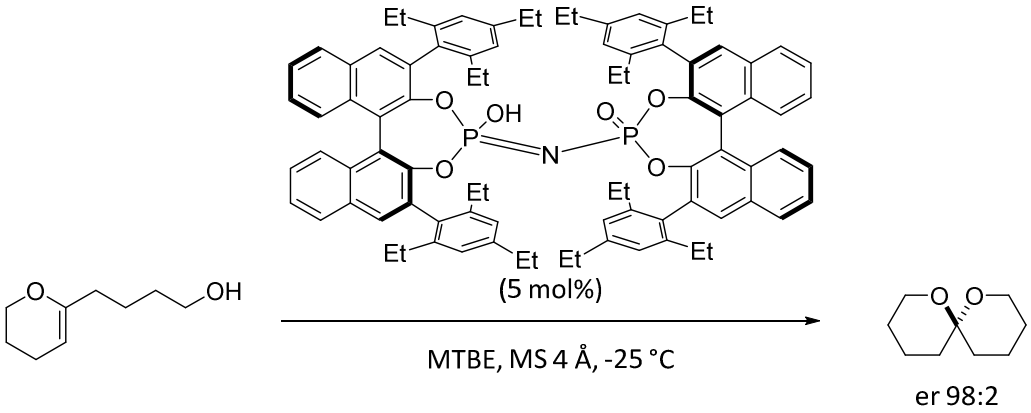
Scheme 2.40. Kinetic resolution of alcohols via catalytic asymmetric transacetalization.

Using the transacetalization reaction reported by the List group, it was later shown that asymmetric desymmetrization of prochiral *meso* 1,3-diols through mono-transacetalization can be achieved (Scheme 2.41).[110]



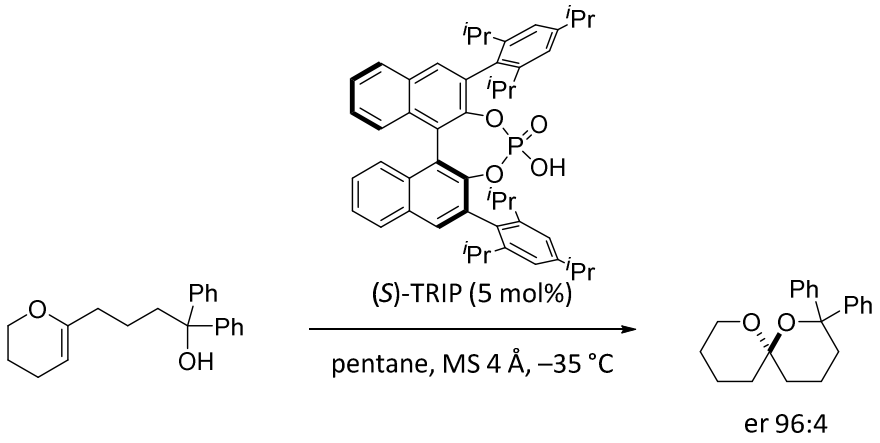
Scheme 2.41. Asymmetric desymmetrization of *meso* 1,3-diols via transacetalization.

The first catalytic asymmetric spiroacetalization reaction was disclosed recently by the List group. By employing confined imidodiphosphoric acids, small unfunctionalized spiroacetals can be obtained with high enantioselectivity (Scheme 2.42).[15]



Scheme 2.42. Imidodiphosphoric acid catalyzed spiroacetalizations.

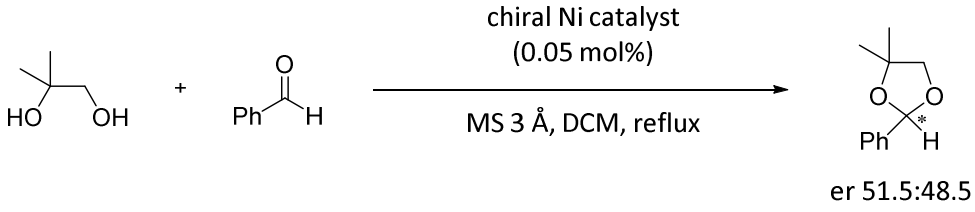
Subsequent to the publication of this work, the Nagorny group reported the asymmetric spiroacetalization of hydroxyenol ethers catalyzed by the chiral phosphoric acid TRIP (Scheme 2.43).[80] This report, compared to the reaction in Scheme 2.42 demonstrated that less sterically demanding phosphoric acid catalysts could tackle larger, decorated substrates.



Scheme 2.43. Chiral phosphoric acid catalyzed spiroacetalizations.

Attempt towards direct *O,O*-acetalization of aldehydes

An attempt at a direct catalytic asymmetric *O,O*-acetalization of an aldehyde with a diol using a chiral metal catalyst was reported in 1999 by P. Barbaro *et al*. (Scheme 2.44).[111] However, the acetalization reaction proceeded without significant enantioselectivity, even when different reaction conditions were employed, such as using different metal catalysts, solvents, and substrates.



Scheme 2.44. Catalytic acetalization using chiral metal complex.

2.5. Asymmetric synthesis of diols

Diols are common motives in natural products and bioactive compounds, and are also valuable synthetic building blocks (Figure 2.20).[112-114] Consequently, access to enantiomerically pure diols has attracted much attention, and it is still an important synthetic task.

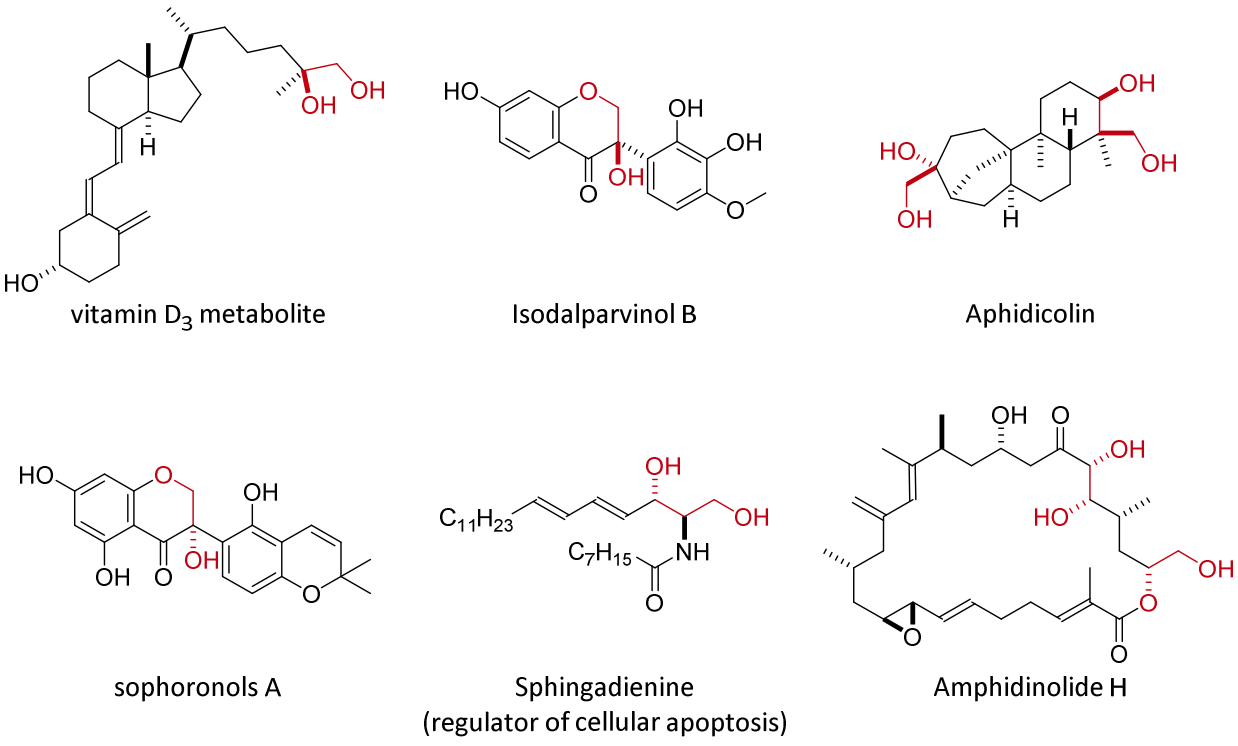
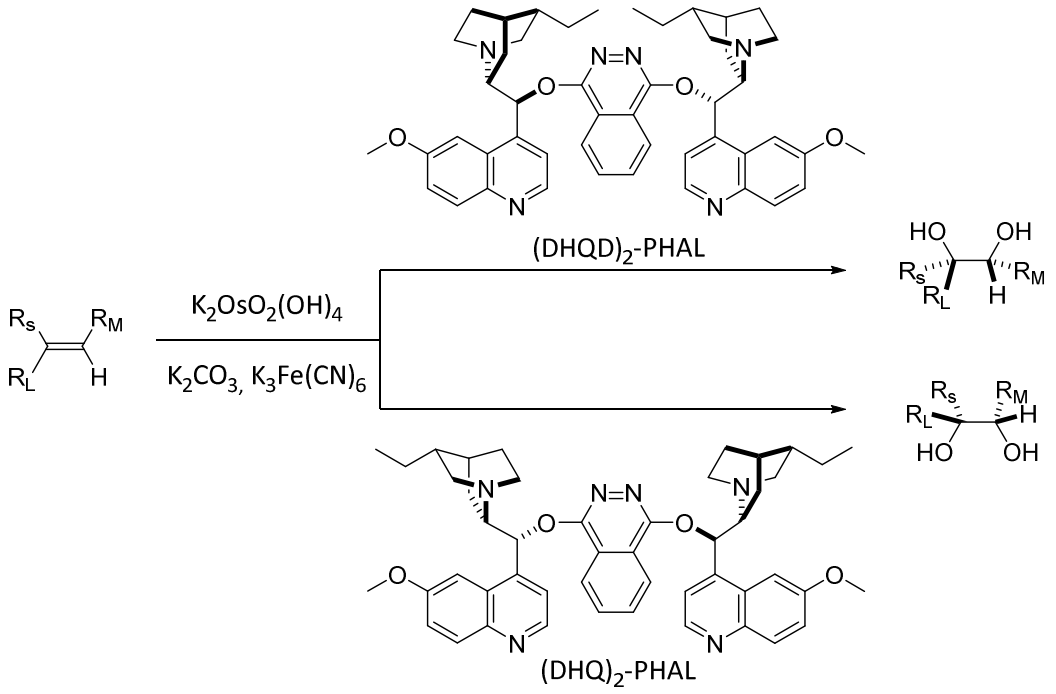


Figure 2.20. Diols in nature and bioactive compounds.

2.5.1. Synthetic approaches to enantioenriched diols

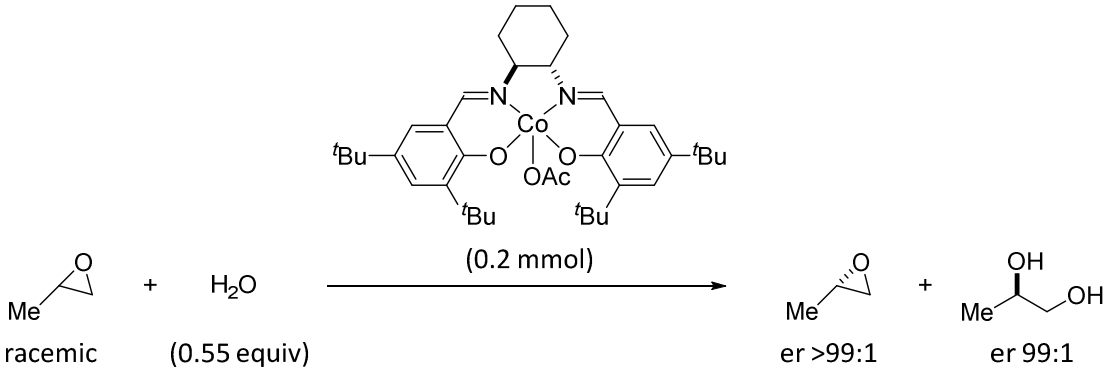
Diols with *secondary* alcohol stereocenter

Numerous synthetic methods to access to enantiomerically pure diols have been studied. One of the most well-known approaches to the enantioselective synthesis of 1,2-diols is the Sharpless asymmetric dihydroxylation reaction (Scheme 2.45).[115-120] Enantioenriched 1,2-diols can be obtained from olefins using an osmium catalyst with chiral ligands $(DHQD)_2$-PHAL or $(DHQ)_2$-PHAL.



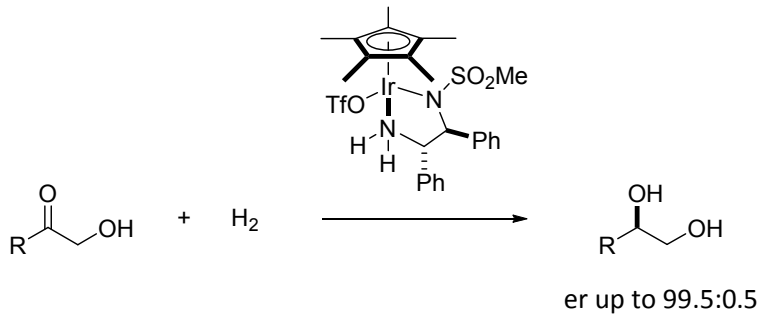
Scheme 2.45. Sharpless dihydroxylation reaction.

Next to the Sharpless dihydroxylation of olefins, numerous other methods have been developed such as opening of epoxides,[121-126] asymmetric hydrogenation of α-hydroxyketones,[127-129] α-oxyamination/reduction of carbonyls,[130-132] diboration/oxidation of alkenes.[133-134] The Jacobsen group reported a hydrolytic kinetic resolution reaction of terminal epoxides catalyzed by a cobalt-salen complex to give 1,2-diol products in high enantiomeric excess and recovering enantioenriched epoxides (Scheme 2.46).[124]



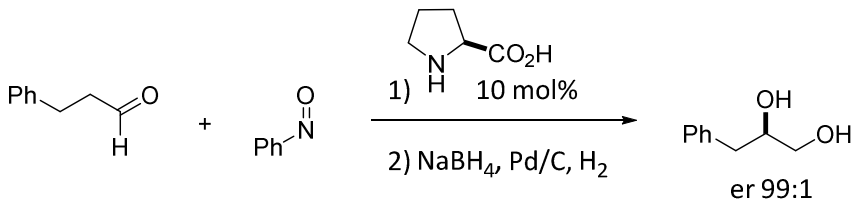
Scheme 2.46. Opening of epoxides.

Enantioenriched 1,2-diols can be obtained from α-hydroxyketones via asymmetric hydrogenation (Scheme 2.47).[129]



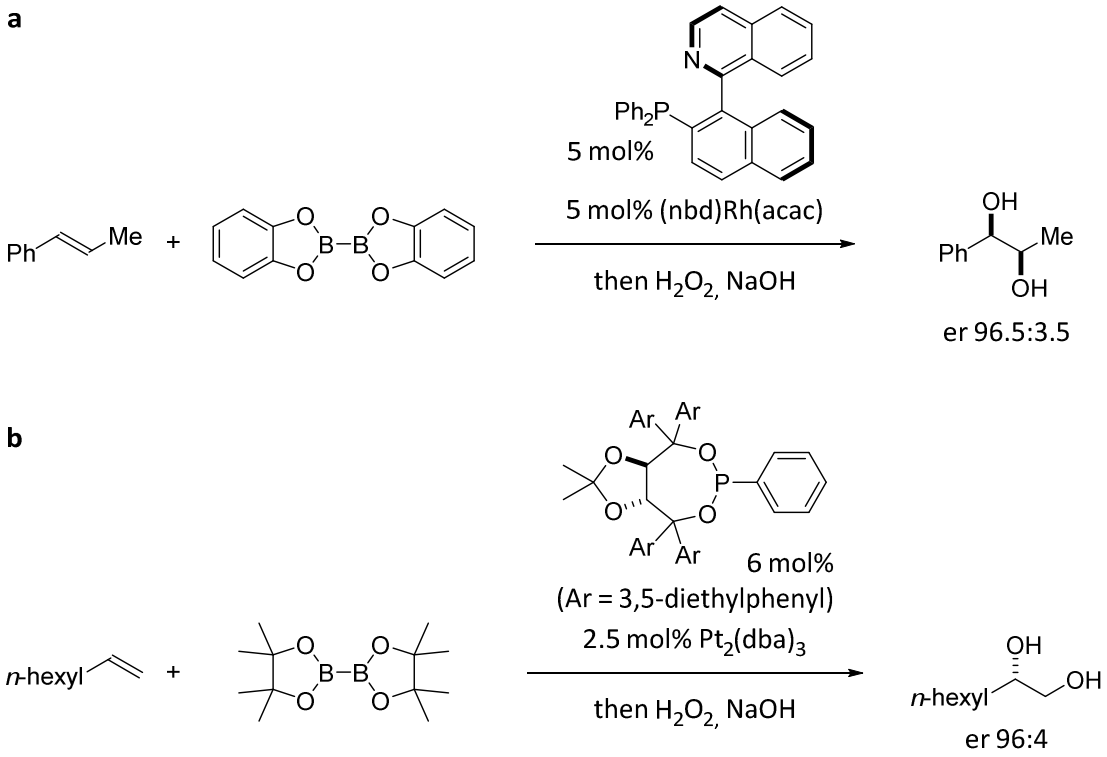
Scheme 2.47. Hydrogenation of α-hydroxyketones.

A proline catalyzed enantioselective α-oxyamination reaction of aldehydes with nitrosobenzene provides enantioenriched α-oxyamination products. Reduction of the product with $NaBH_4$, followed by hydrogenolysis of N-O bond gives the corresponding terminal 1,2-diol in high enantiomeric excess (Scheme 2.48).[130]



Scheme 2.48. α-Oxyamination of aldehydes/reduction.

The Morken group developed enantioselective diboration of alkenes in the presence of Rh or Pt catalysts obtaining the corresponding dihydroxylation products after oxidation (Scheme 2.49).[133, 135]



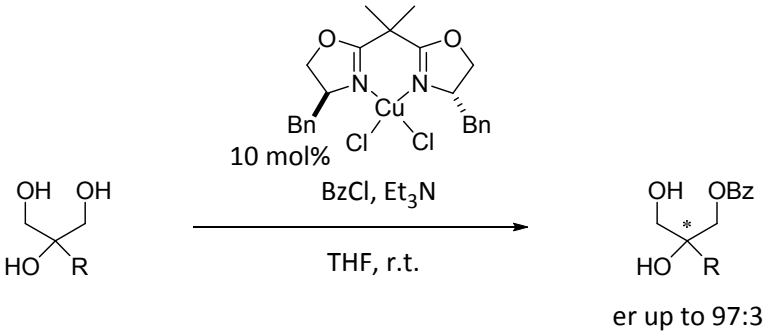
Scheme 2.49. Enantioselective diboration/oxidation of alkenes.

Although many more methods than the aforementioned approaches have been reported,[136-140] most of the methods are only amenable to 1,2-diols with secondary alcohol stereocenters although some can provide aryl,alkyl-substituted 1,2-diols with tertiary alcohol stereocenters with high enantioselectivity.

Diols with *teriary* alcohol stereocenter

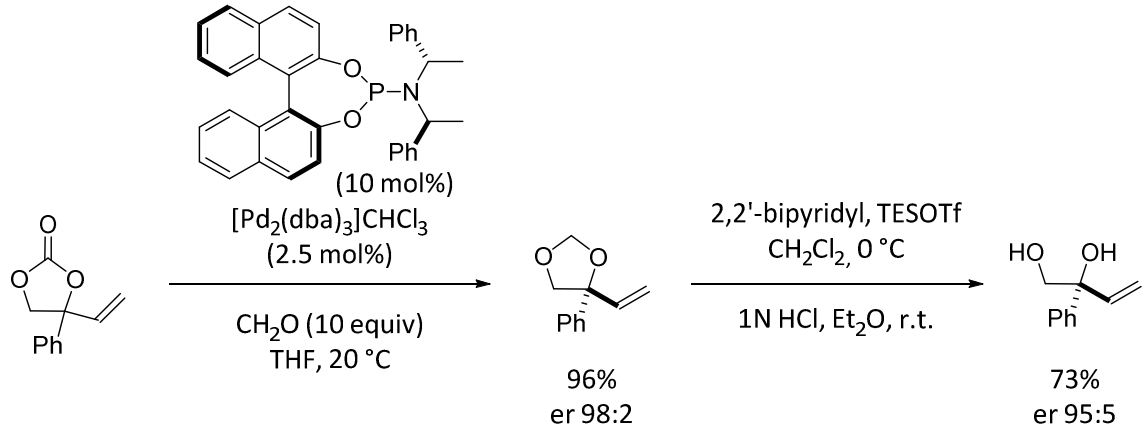
Highly enantioselective approaches capable of delivering diols with tertiary alcohol stereocenters are much less common.[120, 136, 138] Two selected approaches are given here.

The desymmetrization of prochiral 2-substituted glycerols via monobenzoylation was achieved with high enantioselectivity giving highly enantioenriched tertiary alcohols (Scheme 2.50).[136]



Scheme 2.50. Desymmetrization of triols.

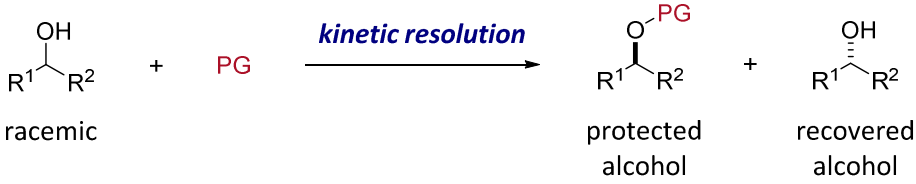
A recently reported Pd-catalyzed decarboxylative cycloaddition of vinylethylene carbonates with formaldehyde provides enantioenriched 1,3-dioxolanes which can be converted into the corresponding tertiary vinylglycols (Scheme 2.51).[138]



Scheme 2.51. Decarboxylative cycloaddition/deprotection.

2.5.2. Kinetic resolution of alcohols

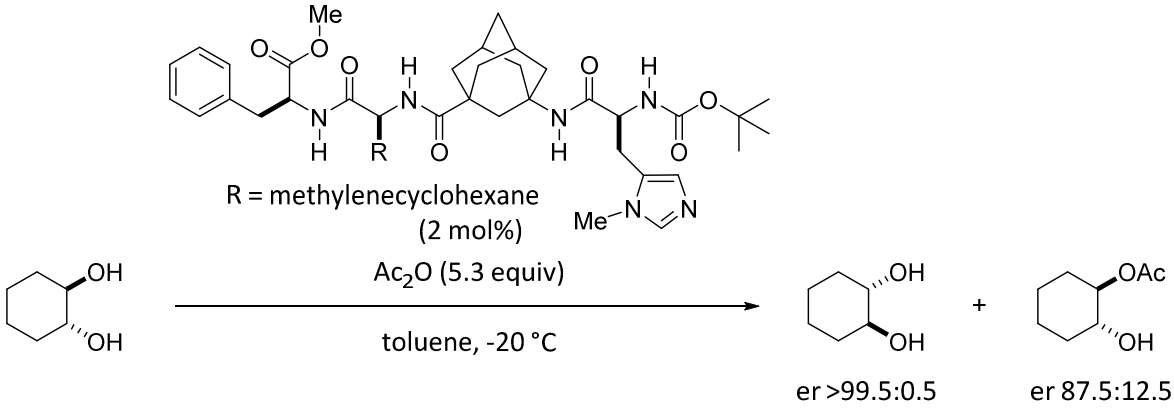
Due to the usually simple access to racemic alcohols, kinetic resolutions represent a popular strategy for the preparation of enantioenriched compounds.[141-142] Most practical methods involve reactions that enantioselectively introduce a common alcohol protecting group, which can be of use in further synthetic steps (Scheme 2.52).



Scheme 2.52. Kinetic resolution of alcohols by placing common alcohol protecting groups.

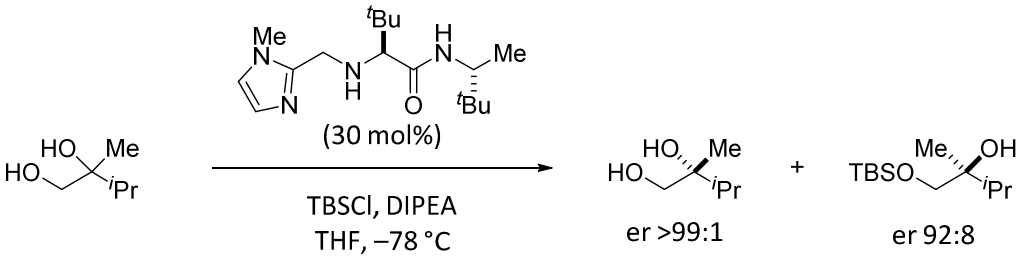
Numerous enzymatic and nonenzymatic methods for asymmetric acylation,[143-149] and more recently silylation[150-152] have been developed.

For example, a kinetic resolution of *trans*-cycloalkane-1,2-diols through an enantioselective acylation reaction catalyzed by a lipophilic chiral tetrapeptide was recently reported (Scheme 2.53).[149]



Scheme 2.53. Kinetic resolution of diols via acylation.

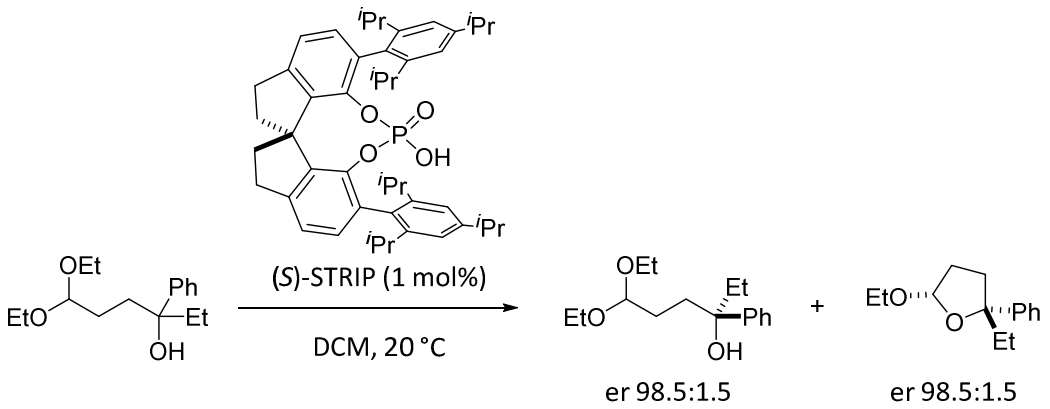
Most reported methods for the kinetic resolution of diols via asymmetric acylation and silylation enabled the enantioselective generation of enantioenriched diols with a *secondary* alcohol stereocenter, but they have rarely been applied to diols with *tertiary* alcohol stereocenters. Although several methods for the kinetic resolution via silylation have been developed and arisen as a popular strategy to access enantioenriched diols, there are only scarce examples that provide enantioenriched diols with a tertiary alcohol stereocenter. Hoveyda, Snapper *et al*. developed a kinetic resolution of *syn*-1,2-diols and vicinal diols that bear a tertiary alcohol through catalytic asymmetric silylation catalyzed by a simple chiral organocatalyst (Scheme 2.54). [152]



Scheme 2.54. Kinetic resolution of diols via asymmetric silylation.

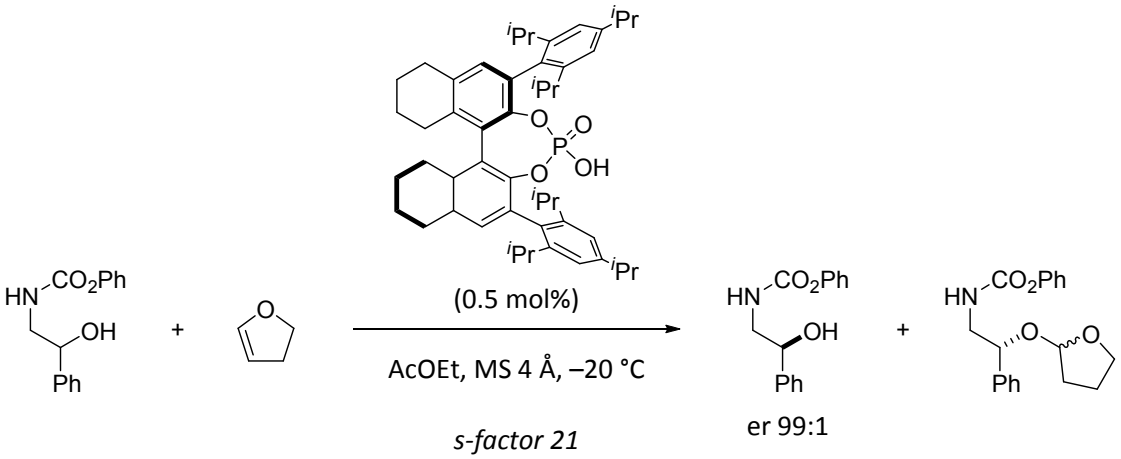
Next to ester and silyl groups, acetals are one of the most common protecting groups for alcohols. They possess complimentary stability properties to ester and silyl groups during further synthetic steps, and also alternative deprotection conditions. However, asymmetric acetalization reactions have been developed only very recently,[1, 15, 56, 67, 80, 104, 107-108, 110, 153-154] thus, processes for the kinetic resolution of alcohols via acetal formation are still underdeveloped.

The fist example of a kinetic resolution of alcohols via acetal formation was reported by the List group (Scheme 2.55).[56] The highly enantioselective kinetic resolution of acetal protected homoaldols via asymmetric transacetalization was achieved. The use of the spirocyclic phosphoric acid STRIP as the catalyst was the key to the resolution of a wide range of secondary and tertiary homoaldols.



Scheme 2.55. Kinetic resolution of homoaldols via transacetalization.

Simultaneously with the work described in this thesis,[68] the Terada group reported[155] the kinetic resolution of racemic amino alcohols through intermolecular acetalizations using H_8-TRIP as catalyst (Scheme 2.56).



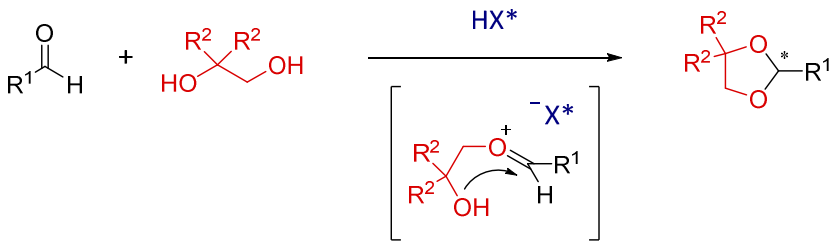
Scheme 2.56. Kinetic resolution of amino alcohols via acetalization.

3. OBJECTIVES OF THIS PH.D. WORK

3.1. Catalytic asymmetric acetalization of aldehydes with diols

The objective of this Ph.D. work was the development of direct asymmetric acetalization reactions of aldehydes, which would probably involve enantioselective control of the addition of nucleophiles to oxocarbenium ions. The goal was to identify suitable reaction partners and selective Brønsted acid catalysts.

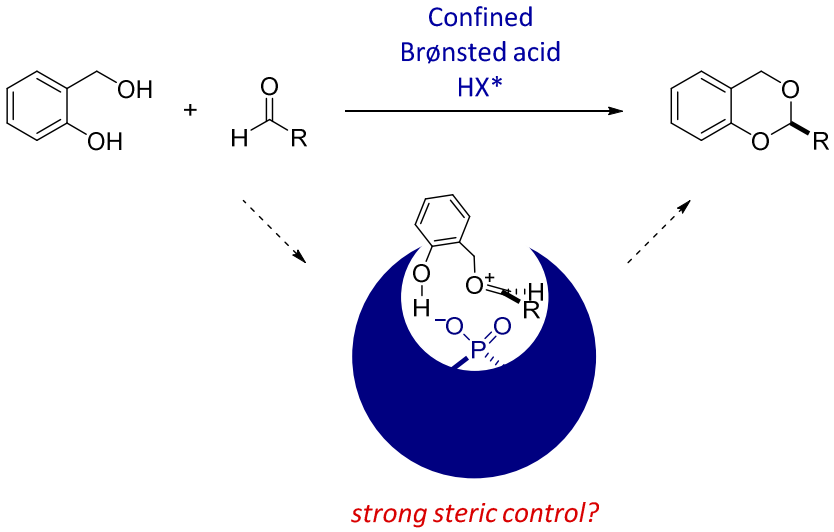
Although the Brønsted acid catalyzed acetalization of aldehydes with alcohols is one of the most common transformations in organic synthesis, an asymmetric variant remained elusive as controlling the enantioselective addition of nucleophiles to oxocarbenium ions is very challenging. An issue for Brønsted acid catalyzed enantioselective formation of *O,O*-acetals is the probable racemization of the acetal product in the presence of acids by reversible formation of the oxocarbenium ion. We hypothesized that this issue could potentially be avoided by employing diols which could form more stable cyclic acetal products that would be less prone to racemization (Scheme 3.1).



Scheme 3.1. Acetalization with diols.

Another issue, compared to asymmetric *N,X*-acetalizations (*X* = *O, N, S*) which involve iminium intermediates, is that the oxocarbenium ion possesses weaker hydrogen bonds with a chiral anion of the catalyst. Also, the presence of multiple weak hydrogen bonds results in more possibilities for substrate orientation and transition state geometries. Consequently the nucleophilic attack proceeds with low asymmetric induction.[1, 11]

Recently, our group developed confined Brønsted acids and employed them as catalysts for asymmetric spiroacetalizations.[15] Confined imidodiphosphoric acids could enable the control of oxocarbenium ion by providing an extremely sterically demanding chiral microenvironment. We envisioned that confined imidodiphosphoric acids would provide a suitable catalytic platform for the direct *O,O*-acetalization of aldehydes (Scheme 3.2).



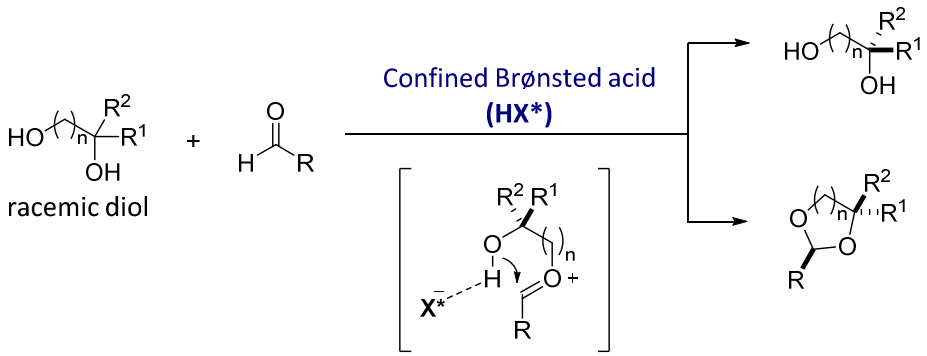
Scheme 3.2. Towards catalytic asymmetric *O,O*-acetalization.

3.2. Kinetic resolution of diols via acetal formation

After the realization an asymmetric acetalization reaction the next objective would be to explore potential applications.

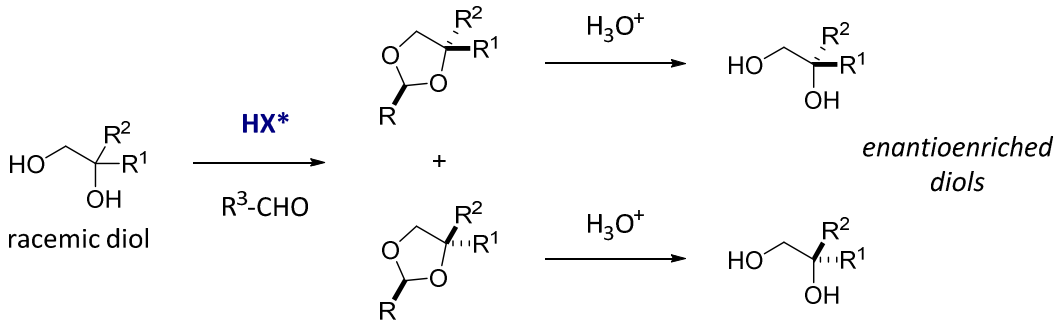
Next to the Sharpless dihydroxylation of olefins, numerous other methods have been developed for synthesizing enantioenriched diols. However, most of the reported methods are incapable of delivering diols possessing a tertiary alcohol stereocenter with high enantioselectivity. Kinetic resolution can be an attractive alternative strategy for synthesis of enantioenriched diols because of the accessibility of racemic diols. Although numerous studies of kinetic resolution of diols have been reported, these methods are rarely applied to diols bearing tertiary alcohol stereocenters. Meanwhile, acetals are particularly useful protecting groups possessing complementary stability properties to ester and silyl groups during further synthetic steps and also alternative deprotection conditions. Nevertheless, kinetic resolutions of alcohols proceeding by acetal formation are underdeveloped as asymmetric acetalization reactions were developed only recently.

We envisioned that confined imidodiphosphoric acid could discriminate the alcohol stereocenter of chiral racemic diols during an acetalization reaction thus enabling the kinetic resolution of diols (Scheme 3.3).



Scheme 3.3. Kinetic resolution of diols via asymmetric acetalization.

Additionally, as the acetalization reaction creates an additional stereocenter, a complementary stereodivergent resolution of diols into two separable diastereoisomers might be feasible (Scheme 3.4).



Scheme 3.4. Stereodivergent resolution of diols via asymmetric acetalization.

The objectives of this Ph.D work were the development of a direct asymmetric *O,O*-acetalization and a related highly enantioselective kinetic resolution of diols via asymmetric acetalization by using a chiral confined imidodiphosphoric acid catalyst.

4. RESULTS AND DISCUSSION

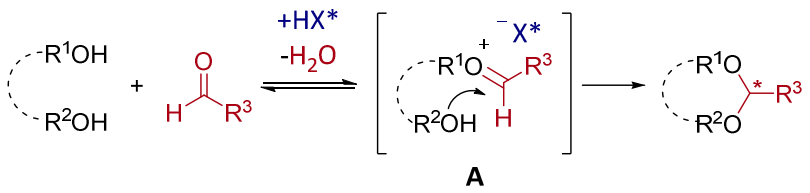
4.1. Catalytic asymmetric acetalization

4.1.1. Reaction design and optimization

(with I. Čorić)[67]

Acetals are among the most common stereocenters in nature, and classic protecting groups for aldehydes and ketones. Therefore, the Brønsted acid catalyzed acetalization of aldehydes with alcohols is one of the essential transformations in organic synthesis (Scheme 4.1). Although the non-enantioselective version of this reaction has probably been performed by every synthetic chemist, a catalytic asymmetric variant has been entirely unknown. Presumably, asymmetric reaction is challenging due to problems associated with asymmetric additions to oxocarbenium ions utilizing chiral Brønsted acid catalysts (Scheme 4.1). Despite the fact that our laboratory has developed numerous chiral Brønsted acid catalysts, and has studied the direct asymmetric acetalization of aldehydes with alcohols for many years, only very little success towards this goal was achieved.

We hoped that the new class of confined imidodiphosphoric acids might be able to control oxocarbenium ion intermediates and provide a suitable chiral sterically demanding environment. We focused on the acetalization with diols which presumably could give more stable cyclic products. Therefore the acetal product would not reversibly form oxocarbenium ion, a process, which leads to the racemization of initially enantioenriched acetal product.

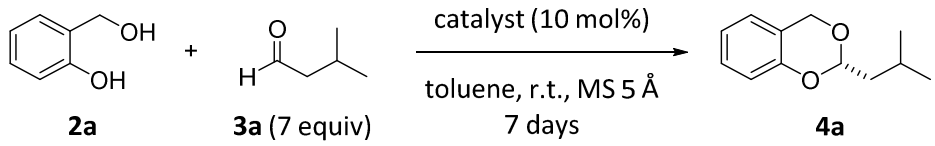


Scheme 4.1. Brønsted acid catalyzed acetalization of aldehydes with alcohols.

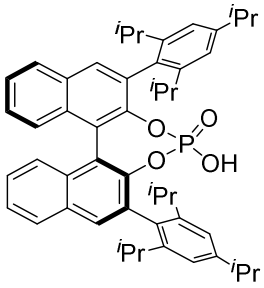
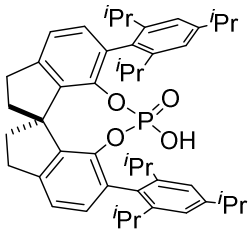
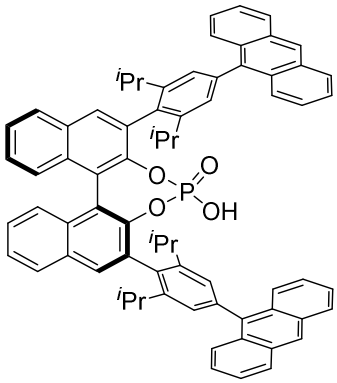
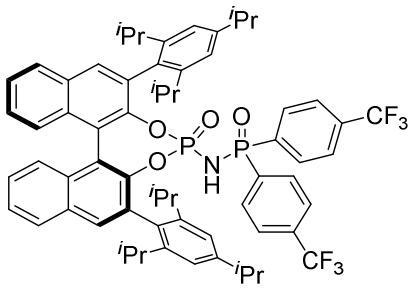
We initiated our investigation toward an asymmetric acetalization with diol **2a** and aldehyde **3a** to give acetal **4a** using one of the most successful phosphoric acid catalysts, **1a** ((*S*)-TRIP) with 2,4,6-$^{i}Pr_3C_6H_2$ substituents in the 3,3'-positions (Table 4.1). However, with 10 mol% of (*S*)-TRIP in toluene at room temperature only poor enantioselectivity (er 66.5:33.5) was achieved

for cyclic acetal **4a** with a conversion of 66% after 7 days. The recently developed spirocyclic analogue STRIP **1b**, which surpassed TRIP in several transformations, gave a slightly improved e.r. of 79:21, but significantly lower reactivity with a conversion of 19% after 7 days. Neither enantioselectivity nor reactivity improved by using catalysts **1c** and **1d**, which gave excellent results for the related *N*,*N* and *N*,*O*-acetalizations of aldehydes. This striking failure highlights the difficulties arising when dealing with oxocarbenium ion intermediates, such as **A** in Scheme 4.1, in Brønsted acid catalysis, even when using some of the most successful phosphoric acid catalysts.

Table 4.1. Initial catalyst screening for asymmetric acetalization.[a]



2a **3a** (7 equiv) **4a**

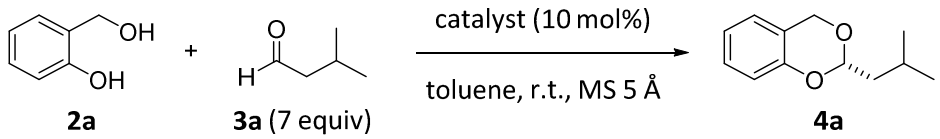
Catalyst[44-45, 156]		
	(*S*)-**1a** (TRIP)	(*R*)-**1b** (STRIP)
er[b]	66.5:33.5	79:21
conv.[c]	66%	19%
Catalyst[64, 157]		
	(*S*)-**1c**	(*S*)-**1d**
er[b]	52.5: 47.5	51.5:48.5
conv.[c]	50%	31%

a) Reactions were performed on 0.05 mmol scale with molecular sieves (30 mg/0.05 mmol) in toluene (0.1 ml) and terminated with a few drops of triethylamine after the indicated times. b) Samples for HPLC analysis were isolated by thin layer chromatography using EtOAc/hexanes as the eluent. Enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase. c) Incomplete conversions were determined by ^{1}H NMR.

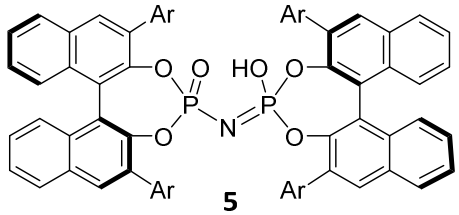
Recently, a new generation of chiral confined Brønsted acids based on a C_2-symmetric imidodiphosphate anion has been developed in our group.[15] The architecture of these catalysts has provided superb results for the first catalytic asymmetric spiroacetalization, and for the asymmetric sulfoxidation with hydrogen peroxide, reactions that involve sterically little demanding and/or loosely organized transitions states.[15, 66] We expected that confined catalysts could enable a putative oxocarbenium ion intermediate to be geometrically restrained. Consequently, this would reduce the diversity of transition states, resulting in increased enantioselectivity.[11] However, the use of our previously reported confined acids **5a** and **b** did not lead to the improvement of either the enantioselectivity or the reactivity for the acetalization reaction (Table 4.2, entries 1 and 2).

We reasoned that imidodiphosphoric acids **5a** and **b** might be either too sterically demanding or of inappropriate geometrical shape to create the chiral environment for supporting the transition state of the acetalization reaction efficiently. However, the imidodiphosphoric acids enable the construction of a wide variety of chiral environments. The steric demand of the active site remains very high even with less sterically demanding substituents due to the presence of four aryl-substituents (Ar). In comparison, with phosphoric acids that possess only two substituents, which are often required to be very bulky, limiting the choice of the substituent and consequently the geometrical variability of the chiral environment.

Table 4.2. Acetalization with confined Brønsted acids.[a]



2a **3a** (7 equiv) **4a**



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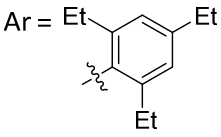
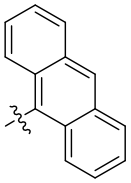
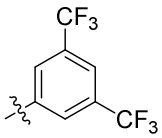


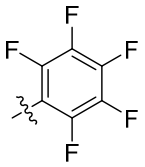
5a



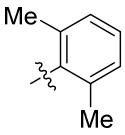
5b



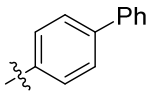
5c



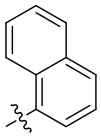
5d



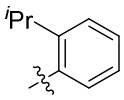
5e



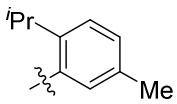
5f



5g



5h



5i

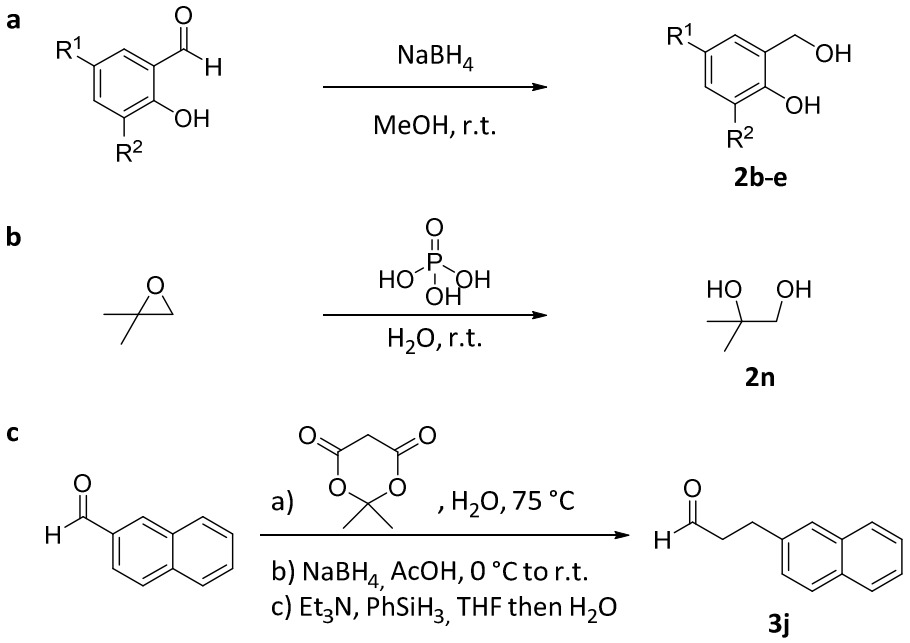
entry	catalyst	time	conv. (%)[b]	er[c]
1	**5a**	7 days	66	79:21
2	**5b**	7 days	< 5	–
3	**5c**	2 h	> 99	71:29
4	**5d**	2 h	> 99	41.5:58.5
5	**5e**	7 days	91	81:19
6	**5f**	3 h	> 99	84.5:15.5
7	**5g**	20 h	> 99	90:10
8	**5g** (5 mol%)	22 h	> 99	90.5:9.5
9	**5h** (5 mol%)	4 days	> 99	93.5:6.5
10	**5i** (5 mol%)	48 h	> 99	95:5
11[d]	**5i** (5 mol%)	48 h	> 99	95.5:4.5

*a) Reactions were performed on 0.05 mmol scale with molecular sieves (30 mg/0.05 mmol) in toluene (0.1 ml) and terminated with a few drops of triethylamine after the indicated times. b) Incomplete conversions were determined by ^1H NMR. c) Samples for HPLC analysis were isolated by thin layer chromatography using EtOAc/hexanes as the eluent. Enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase. d) With 2 equiv of **3a**, 10 mg of molecular sieves, 0.1 M concentration.*

We examined several imidodiphosphoric acid catalysts **5c**-**i** with a variety of substituents Ar. Catalysts **5c** and **5d** with electron-withdrawing 3,5-$(CF_3)_2C_6H_3$ and C_6F_5 substituents were especially active, giving full conversion in two hours, although with low enantioselectivity (Table 4.2, entries 3 and 4). Catalysts **5e**-**g** with various substitution patterns all gave improved enantioselectivity and reactivity compared to catalysts **1a**-**d**, and **5a**, **b** (Table 4.2, entries 5-7). The striking differences in the reactivity and selectivity between catalysts **5a**, **b** and **5e**, compared to catalysts **5f**, **g** indicate the structural versatility of the active sites available with confined acids. For example, while catalyst **5f** with *p*-biphenyl substituents gave full conversion in 3 h, catalyst **5b** was almost inactive. Presumably, access of the substrates to the active site of catalyst **5b** is completely blocked by the four 9-anthracenyl substituents. Gratifyingly, confined imidodiphosphoric acid **5g** with the unsymmetrical 1-naphthyl substituent provided a promising enantiomeric ratio of 90:10 and allowed for lower catalyst loading (Table 4.2, entries 7 and 8). Focusing on nonsymmetric Ar substituents, we next examined the *o*-isopropylphenyl-substituted catalyst **5h**, and further improvement of the enantioselectivity was observed (Table 4.2, entry 9). It was hypothesized that having an extra substituent in the 4- or 5-position on the 2-isopropylphenyl group to increase the steric interaction between different substituents might provide a more rigid catalyst structure. To our delight, a highly enantioselective reaction was achieved with catalyst **5i**, which was derived from the natural product thymol, delivering acetal **4a** with an enantiomeric ratio of 95.5:4.5 and enabling the use of a lower amount of aldehyde **3a** (Table 4.2, entries 10 and 11). Additional screening of solvents (CH_2Cl_2, diethyl ether, hexane), and molecular sieves (3 Å, 4 Å, without MS) with catalyst **5i** resulted in inferior results in terms of reactivity and selectivity.

4.1.2. Substrate scope

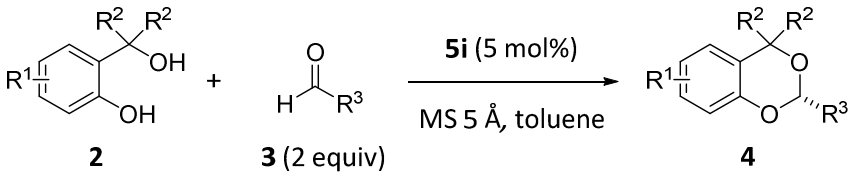
With optimized conditions in hand, we set out to explore the generality of the reaction. The starting materials, diols **2** and aldehydes **3** were available in one or three steps from commercially available chemicals (Scheme 4.2).



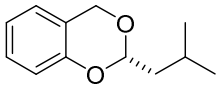
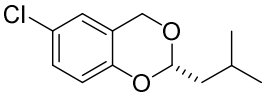
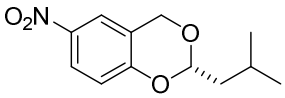
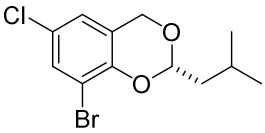
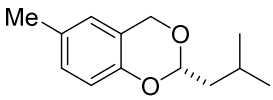
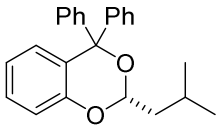
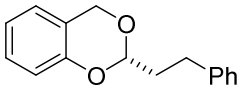
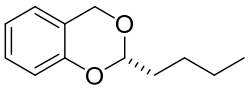
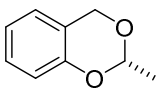
Scheme 4.2. Preparation of substrates.

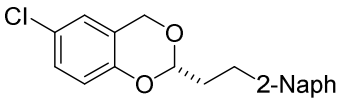
Placing chloro- or nitro-substituents on the aromatic ring of the diol does not significantly affect the enantioselectivity, albeit with the nitro-substituted diol the reactivity was significantly lower (Table 4.3, entries 2 and 3). The synthesis of disubstituted (chloro and bromo) acetal **4d** showed the lower reactivity, and only moderate enantioselectivity was achieved (Table 4.3, entry 4). Placing methyl substituents on the arene ring of the diol led to lower yield with good enantioselectivity (Table 4.3, entry 5). Interestingly, a significant decrease in the enantioselectivity was observed using a tertiary alcohol with phenyl substituents on the benzylic position of the diol (Table 4.3, entry 6). Different aldehydes still afforded good but slightly lower enantioselectivities (Table 4.3, entries 7-10).

Table 4.3. The acetalization reaction with aromatic diols.[a]



2 **3** (2 equiv) **4**

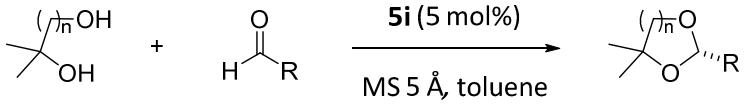
entry	temp./time	product		yield (%)	er
1	r.t./2 days		**4a**	86	96:4
2	r.t./4 days		**4b**	82	95:5
3	50 °C/10 days		**4c**	93	94.5:5.5
4	50 °C/5 days		**4d**	60	92:8
5	50 °C/8 days		**4e**	61	94:6
6	50 °C/2 days		**4f**	44	79:21
7	r.t./4 days		**4g**	83	94.5:5.5
8	r.t./4 days		**4h**	75	93.5:6.5
9[b]	0 °C/15 h		**4i**	88	87:13

10	r.t./4 days		**4j**	86	91.5:8.5

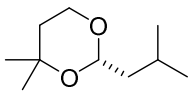
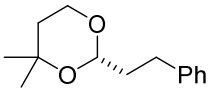
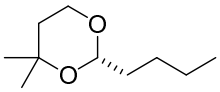
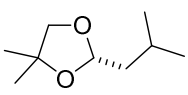
*a) Reactions were performed on 0.2 mmol scale (0.1 M solution), 5 Å MS (40 mg). Enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase. b) With 5 equiv. of **3i**.*

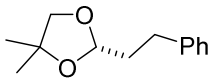
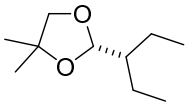
We next investigated the applicability of this catalytic system to other classes of diols. It was found that with a simple aliphatic 1,3-diol (3-methylbutane-1,3-diol, **2k**), the enantioselectivity was even higher and enantiomeric ratios between 95.5:4.5 and 97.5:2.5 could be obtained with various aldehydes (Table 4.4, entries 1-3). These results encouraged us to tackle the acetalization with a 1,2-diol to access five-membered acetals. 2-methylpropane-1,2-diol (**2n**) was readily prepared by opening of the epoxide in acidic conditions and used without further purification (Scheme 4.2, b). The reaction of isovaleraldehyde (**3a**) with 1,2-diol **2n** gave a superb acetalization reaction with an enantiomeric ratio of 99.8:0.2 at 0 °C (Table 4.4, entry 4). Linear and α-branched aldehydes could be employed with equal success in the reaction (Table 4.4, entries 5 and 6) although lower reactivity was observed with the *α*-branched aldehyde.

Table 4.4. The acetalization reaction with aliphatic diols.[a]



2 **3** (2 equiv) **4**

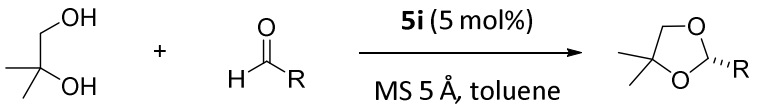
entry	temp./time	product		yield (%)	er
1	50 °C/6 days		**4k**	83	96.5:3.5
2	r.t./2 days		**4l**	93	95.5:4.5
3	r.t./2 days		**4m**	86	97.5:2.5
4	0 °C/22 h		**4n**	72	99.8:0.2

5	r.t./3 days		**4o**	72	99:1
6	r.t./10 days		**4p**	82	99.5:0.5

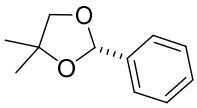
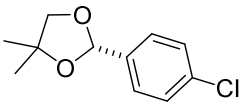
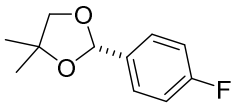
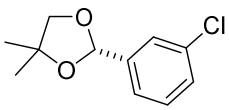
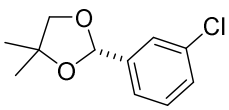
a) Reactions were performed on 0.2 mmol scale (0.1 M solution), 5 Å MS (40 mg). Enantiomeric ratios were determined by HPLC or GC analysis on a chiral stationary phase.

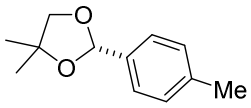
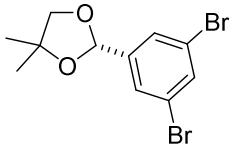
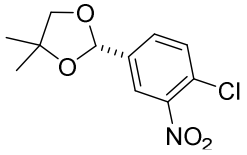
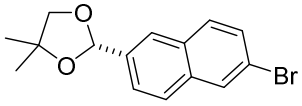
Although our asymmetric acetalization reaction could be performed with aliphatic aldehydes very efficiently, aromatic aldehydes present an additional challenge as the corresponding acetals are more sensitive towards acid catalyzed racemization under the reaction conditions. Gratifyingly, exploration of the substrate scope revealed that a variety of aromatic aldehydes also undergo a very efficient acetalization in the presence of 5 mol% of catalyst **5i** (Table 4.5).

Table 4.5. The acetalization reaction of aromatic aldehydes.[a]



2n **3** (2 equiv) **4**

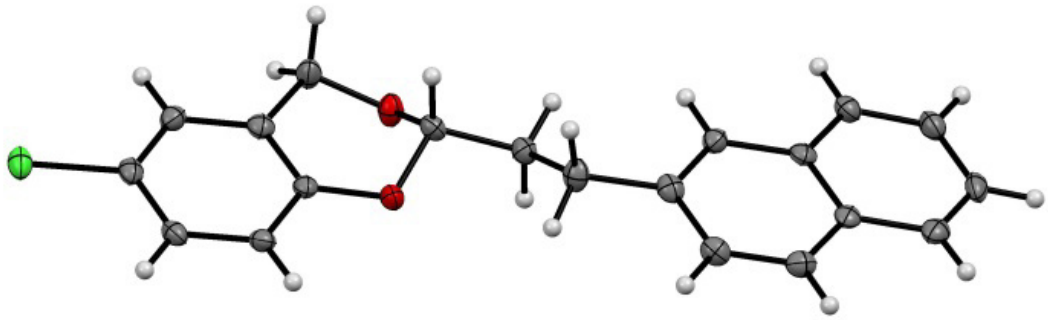
entry	temp./time	product		yield (%)	er
1	r.t./2 days		**4q**	89	95.5:4.5
2	r.t./62 h		**4r**	79	98:2
3	r.t./42 h		**4s**	74	96:4
4a	r.t./5 days		**4t**	65	98.5:1.5
4b	50 °C/4 days		**4t**	85	95:5

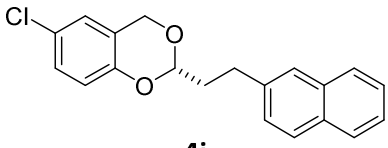
5	r.t./27 h		**4u**	86	88:12
6	50 °C/6 days		**4v**	83	99.5:0.5
7	50 °C/7 days		**4w**	79	97.5:2.5
8	r.t./52 h		**4x**	77	96.5:3.5

a) Reactions were performed on 0.2 mmol scale (0.1 M solution), 5 Å MS (40 mg). Enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase.

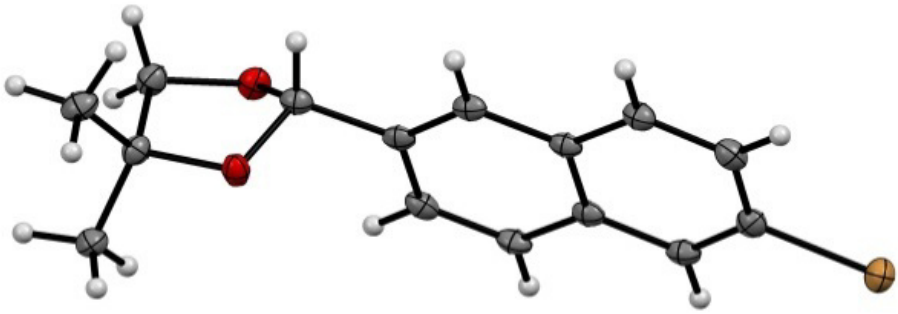
The asymmetric acetalization of benzaldehyde with 1,2-diol **2n** gave 5-membered acetal **4q** in 89% yield with e.r. of 95.5:4.5 (Table 4.5, entry 1). Acetals **4q**-**s** with electron-withdrawing substituents in either *p*- or *m*- positions on the phenyl ring could be obtained with excellent enantioselectivities (Table 4.5, entries 2-4), while acetal **4u** with a methyl substituent in *meta* position on the phenyl ring was obtained with lower selectivity (Table 4.5, entry 5). Excellent enantiomeric ratios of 99.5:0.5 and 97.5:2.5 were observed with disubstituted benzaldehydes **3v**-**w**, even at the slightly elevated reaction temperatures (Table 4.5, entries 6 and 7). Similarly, the asymmetric acetalization of 6-bromo-2-naphthaldehyde proceeded with high enantiomeric ratio of 96.5:3.5 (Table 4.5, entry 8).

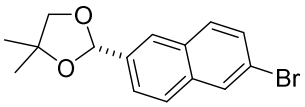
The absolute configurations of acetals **4j** and **4x** were determined to be (*S*) by single-crystal X-ray analysis (Figure 4.1), and configurations of other products were assigned by analogy.





4j



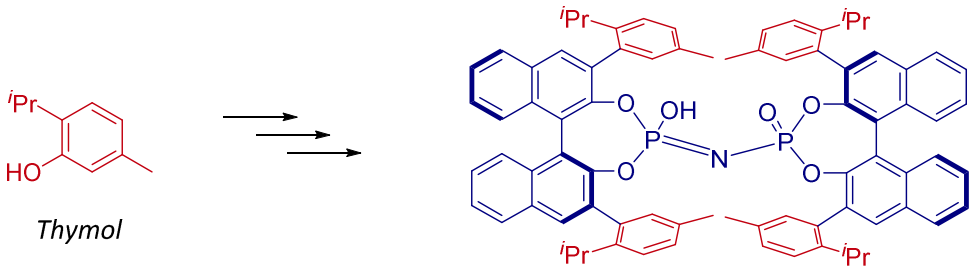


4x

Figure 4.1. X-ray structures of acetals **4j** and **4x**.

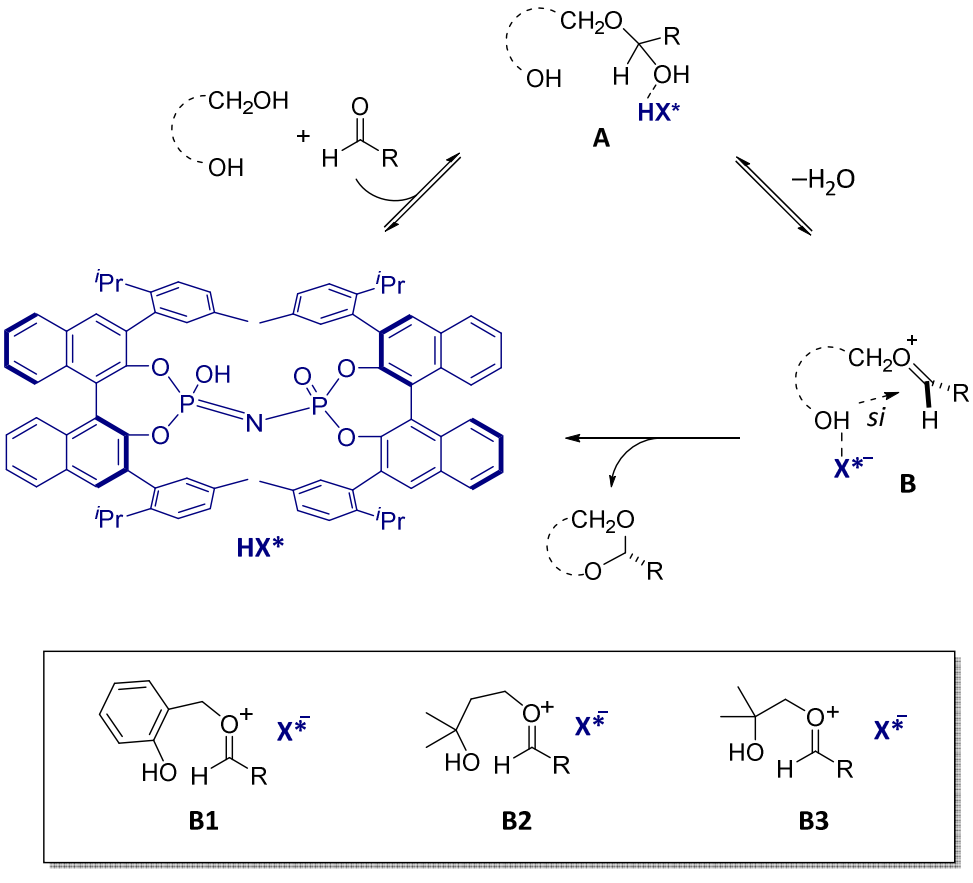
4.1.3. Discussion

The first catalytic asymmetric acetalization reaction of aldehydes was successfully established. Imidodiphosphoric acids proved to be an excellent platform for the construction of Brønsted acids with structurally versatile confined chiral microenvironments. A novel Brønsted acid, **5i**, readily available from natural product thymol (Scheme 4.3), drastically outperforms known catalysts and delivers acetals with excellent enantioselectivity.



Scheme 4.3. Thymol derived imidodiphosphoric acid.

Regarding the mechanism of the reaction, we believe that the reaction proceeds through primary alcohol derived oxocarbenium ions **B1**, **B2**, and **B3**, and that tertiary alcohol and phenol derived oxocarbenium ions are less probable (Scheme 4.4). Initially, the hemiacetal intermediate **A** is formed from the reversible addition of the primary alcohol moiety of the diol to the aldehyde. Protonation of its hydroxyl moiety by the catalyst leads to the expulsion of a water molecule and formation of the crucial oxocarbenium ion intermediate **B**. The chiral imidodiphosphate counteranion provides a chiral environment for the oxocarbenium cation, and functions as a base that directs the nucleophilic attack of the second alcohol moiety to the *si*-face of the oxocarbenium ion furnishing the (*S*)-configured cyclic acetal.

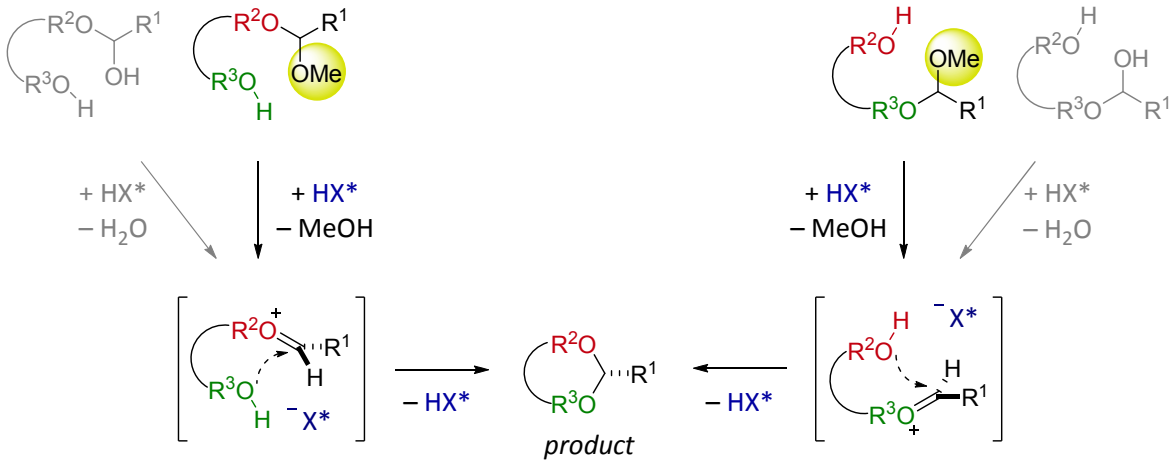


Scheme 4.4. Plausible mechanism.

Mechanistic studies

(with I. Čorić)[67]

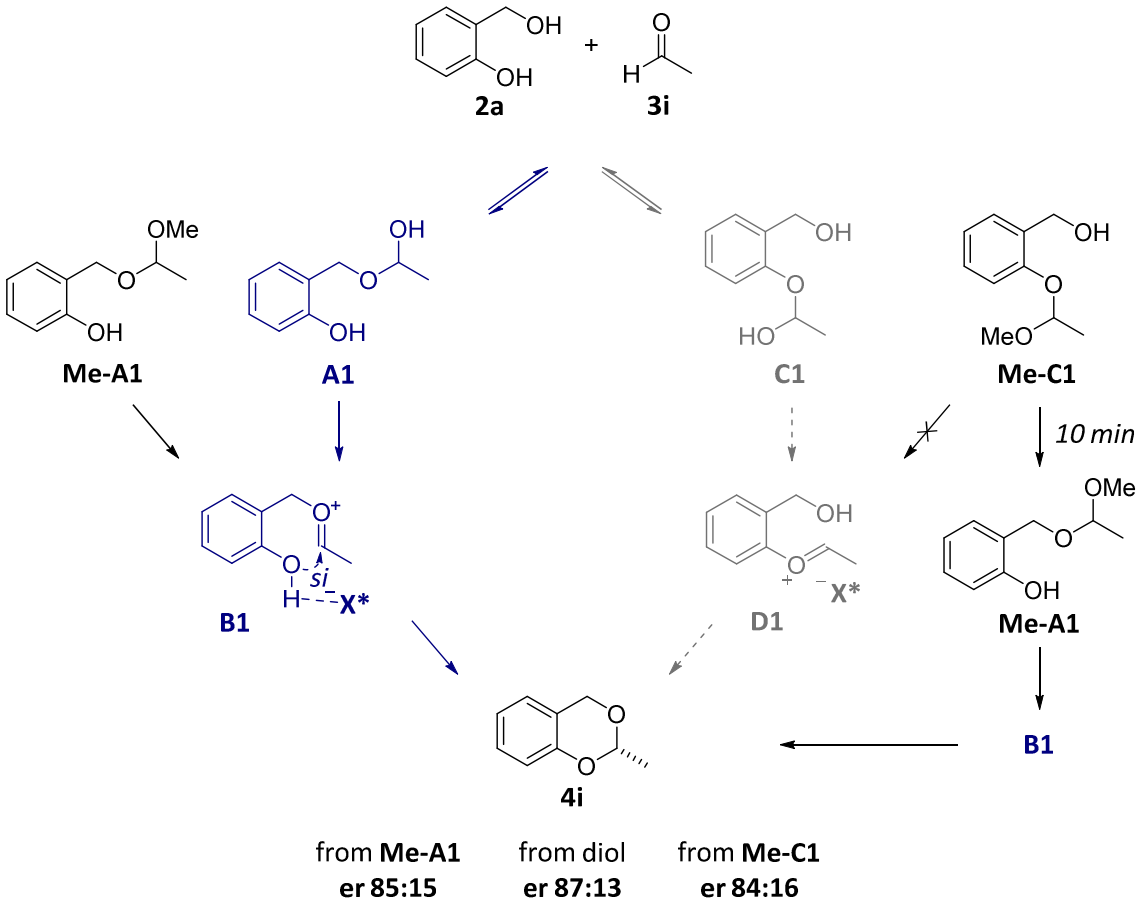
To get insight on the nature of the oxocarbenium ion intermediates we decided to make alternative precursors to the two potential oxocarbenium ions that could be formed from the two OH moieties of a diol. Methyl acetals can be prepared that could lead to either of the two potential oxocarbenium ions, similarly as from the two potential hemiacetal intermediates in the direct acetalization reaction (Scheme 4.5). Subsequent cyclization under the reaction conditions should proceed with similar enantioselectivity from the hemiacetal and from the corresponding methyl acetal because both proceed through the same oxocarbenium ion intermediate. Thus, the methyl acetal that would proceed through the "correct" oxocarbenium ion would give the same enantioselectivity as observed in the direct acetalization reaction. In contrast, the methyl acetal that would proceed through the "wrong" oxocarbenium ion would likely give a significantly different enantioselectivity and could then be excluded as intermediate in our direct acetalization reaction.



Scheme 4.5. Two alternative precursors of potential oxocarbenium ions.

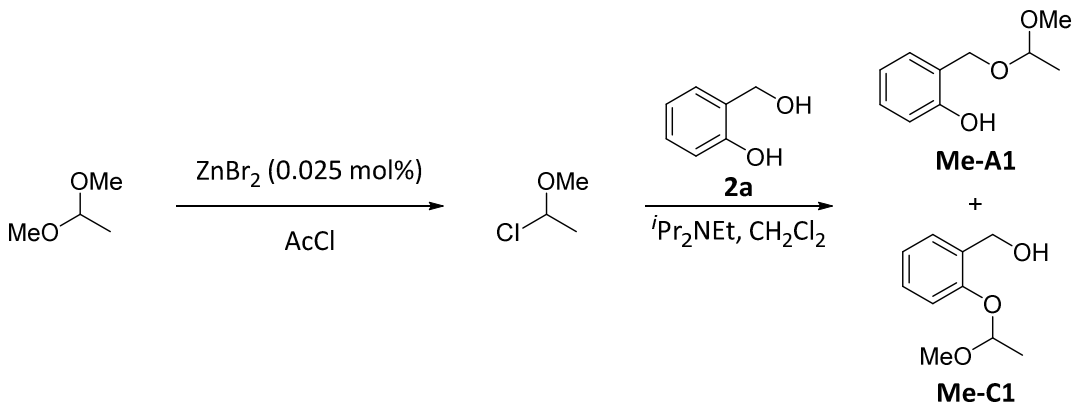
We thus prepared racemic methyl acetal derivatives of the proposed hemiacetal intermediates **A** (OMe instead of OH) in Scheme 4.4, as alternative precursors for oxocarbenium ions **B1** and **B3** in Scheme 4.4. Due to structural differences between diols **2a** and **2n** we performed mechanistic studies separately for diols **2a** and **2n**. The mechanism of the reaction with 1,3-diol **2k** as the substrate is proposed to proceed in analogy to that of the reactions of diols **2a** and **2n**.

The reaction of diol **2a** with acetaldehyde can be envisioned proceeding through two distinct oxocarbenium species **B1** and **D1** formed from hemiacetal intermediates **A1** and **C1**, respectively (Scheme 4.6).



Scheme 4.6. Mechanistic possibilities and experimental support for intermediates **A1** and **B1**.

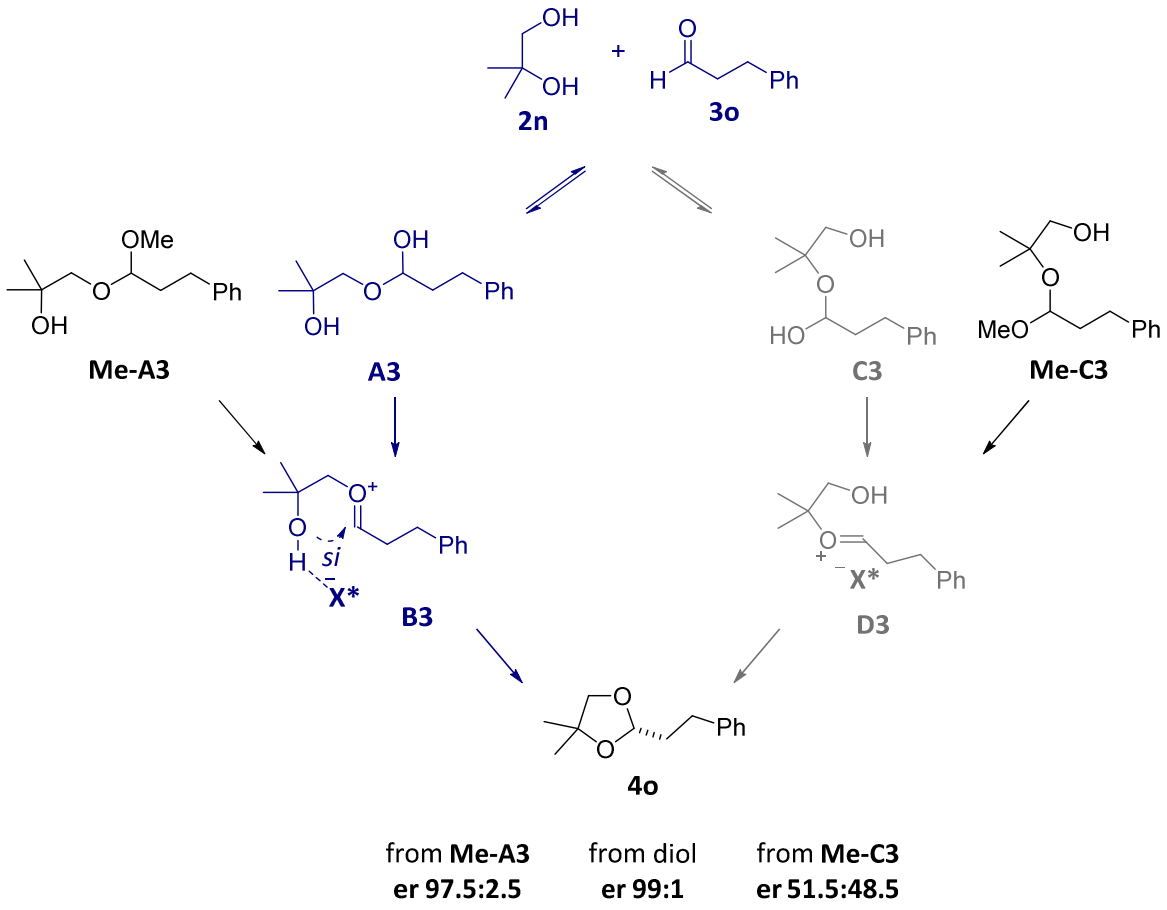
To examine these two pathways we synthesized acetals **Me-A1** and **Me-C1** which were expected to give two different oxocarbenium ions, imitating two hemiacetal intermediates **A1** and **C1**, respectively (Scheme 4.7).[158]



Scheme 4.7. Preparation of racemic methyl acetal derivatives **Me-A1** and **Me-C1**.

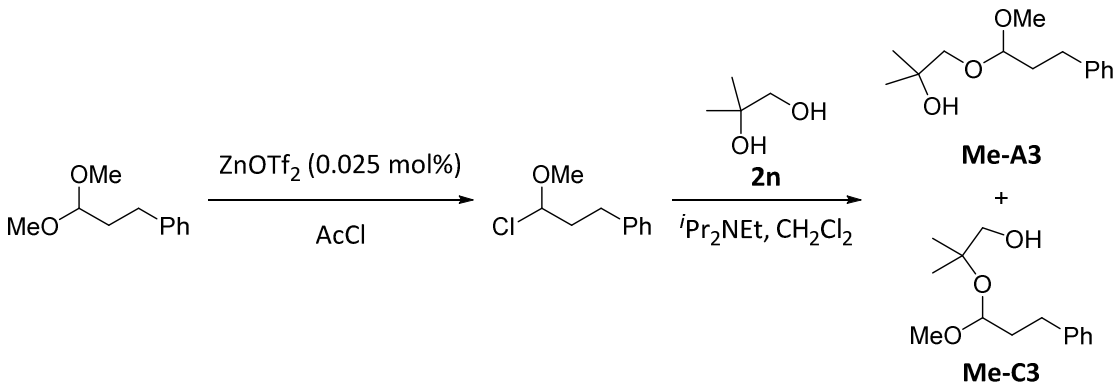
The reaction of acetal **Me-A1** proceeded with similar enantioselectivity as the direct acetalization of acetaldehyde, a result consistent with a common intermediate **B1** (Scheme 4.6). However, under the same reaction conditions, acetal **Me-C1** was first rapidly (<10 min) converted to acetal **Me-A1**, followed by the reaction that proceeded to give the acetal **4i**. These results indicate that oxocarbenium ion **D1** which could be formed from hemiacetal **C1** is improbable intermediate in the direct acetalization reaction, and corroborate to a pathway proceeding through **A1** and **B1**.

A similar set of experiments was designed for the acetalization with 1,2-diol **2n** (Scheme 4.8). The reaction with hydroxyacetal **Me-A3** provided **4o** with e.r. of 97.5:2.5, similarly to the direct acetalization, a result consistent with a common intermediate **B3**. Hydroxyacetal **Me-C3** which is a precursor for oxocarbenium ion **D3** gave only low enantioselectivity, excluding tertiary alcohol derived oxocarbenium ion **D3** as the intermediate in our direct acetalization reaction.



Scheme 4.8. Mechanistic possibilities and experimental support for intermediates **A3** and **B3**.

The racemic acetals **Me-A3** and **Me-C3** which imitate two hemiacetal intermediates **A3** and **C3** were prepared according to similar procedure as in Scheme 4.7 (Scheme 4.9).[158]

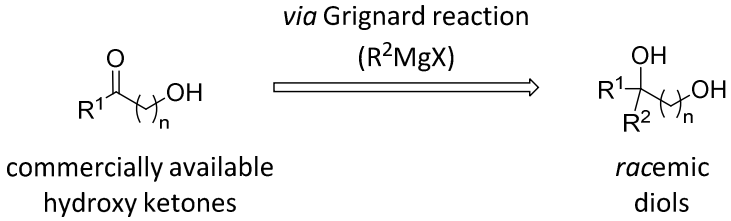


Scheme 4.9. Preparation of racemic methyl acetal derivatives **Me-A3** and **Me-C3**.

4.2. Resolutions of diols via catalytic asymmetric acetalization

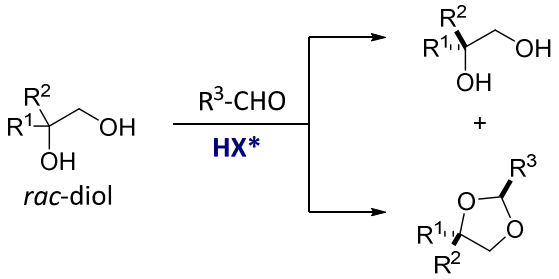
4.2.1. Reaction design and optimization

Due to simple access to racemic 1,2-diols, kinetic resolutions present a popular strategy for the preparation of enantioenriched compounds. For example, the addition of Grignard reagents to hydroxy ketones gives racemic 1,2- and 1,3-diols with tertiary alcohol centers (Scheme 4.10). Most practical methods for the kinetic resolution of diols involve asymmetric acylation and silylation reactions, and most reported methods provide enantioenriched diols with secondary alcohol stereocenters, but they have rarely been applied to diols with tertiary alcohol stereocenter.



Scheme 4.10. Readily accessible racemic diols.

Based on our direct acetalization of aldehydes with diols, we hypothesized that chiral catalysts might additionally discriminate the alcohol stereocenter of chiral alcohols during the acetalization reaction, thus promoting a kinetic resolution (Scheme 4.11).

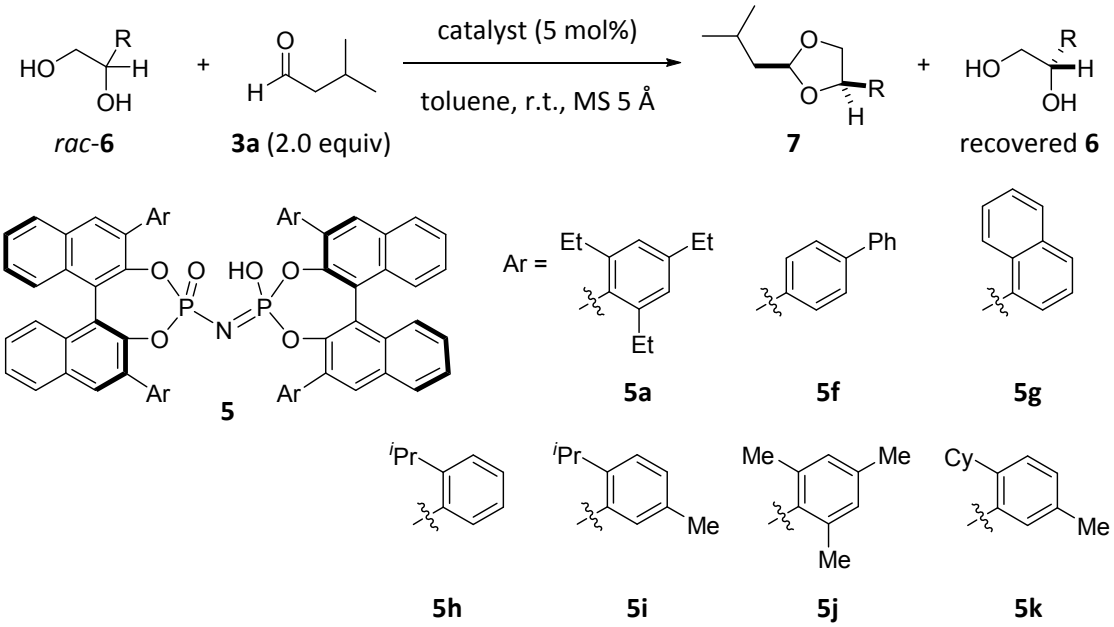


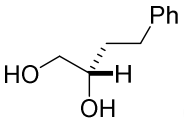
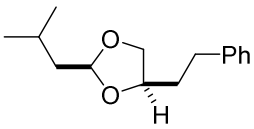
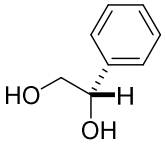
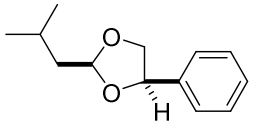
Scheme 4.11. Proposed kinetic resolution of diols via acetalization.

We initiated our studies on the kinetic resolution of diols by using 1,2-diol *rac*-**6a** with secondary alcohol stereocenter, which are usually preferred substrates for other kinetic resolutions and thymol-derived substituted imidodiphosphoric acid catalyst **5i**, which was identified as the best catalyst for our previous asymmetric acetalization studies. However, almost no selectivity was obtained for the resolution of diol **6a** under identical reaction

conditions (Table 4.6, entry 1). The product **7a** was obtained with very high enantioselectivity for both diastereomers. Although the catalyst controls the stereochemistry of the acetal stereocenter very well, little differentiation based on the stereochemistry of the alcohol stereocenter was observed giving recovered diol **6a** with an er of 61:39. Using various differently substituted catalysts, and using substrate **6b** with a phenyl substituent did not result in promising selectivity factors.

Table 4.6. Initial reaction development with secondary diols.[a]



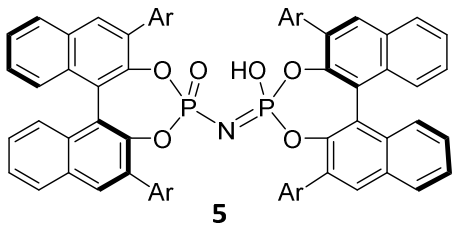
entry	cat.	conv.[b]	6	er 6[c,d]	7	er 7[c,e] er 7-*epi*-7[c,e]	dr 7[c]	*S*[f]
1	**5i**	70%	 **6a**	61:39	 **7a**	>99.5:0.5 94.5:5.5	1.1:1	1.4
2	**5a**	22%	**6a**	53.5:46.5	**7a**	>99.5:0.5 93:7	1.5:1	1.8
3[g]	**5k**	81%	**6a**	69:31	**7a**	99.5:0.5 95:5	1.1:1	1.6
4	**5a**	12%	 **6b**	55.5:44.5	 **7b**	96.5:3.5 >99.5:0.5	13:1	10

5	**5f**	82%	**6b**	71.5:28.5	**7b**	63:37 95:5	6:1	2
6	**5g**	91%	**6b**	72.5:27.5	**7b**	71:29 98.5:1.5	3:1	2
7	**5h**	47%	**6b**	62:38	**7b**	78.5:21.5 96.5:3.5	4:1	2
8[h]	**5i**	39%	**6b**	67:33	**7b**	85.5:14.5 >99.5:0.5	9:1	5
9	**5j**	22%	**6b**	54:46	**7b**	82:18 99:1	4:1	2

*a) Unless otherwise specified reactions were performed on 0.05 mmol scale with molecular sieves (10 mg/0.05 mmol) in toluene (0.5 ml) and terminated with a few drops of triethylamine. b) Theoretical conversion calculated from ee values of the product and the recovered starting material (see chapter 7.3.3). c) Samples for HPLC or GC analysis were isolated by thin layer chromatography using EtOAc/hexanes as the eluent. d) Determined by HPLC analysis on a chiral stationary phase. e) Determined by GC analysis on a chiral stationary phase. f) Calculated from theoretical conversion and enantiomeric excess of enantioenriched diol (see chapter 7.3.3). g) Reaction was performed on 0.50 mmol scale with 2 mol% of catalyst and 4.0 equiv of **3a** at 20 °C. Isolated yield: 10% (**6a**), 80% (**7a**). Samples for HPLC or GC analysis were isolated by silica chromatography. h) 4 equiv of **3a**, 20 °C.*

We next approached the kinetic resolution of diols with tertiary alcohol stereocenters. Although tertiary alcohols are usually worse substrates than secondary alcohols for kinetic resolutions, previous results with kinetic resolution of homoaldols via transacetalization proved that those could be very good substrates for acetalization reactions.[11, 56, 156] Indeed, increasing the bulkiness of the substrate under the standard reaction conditions using 2,4,6-$Et_3C_6H_2$ substituted catalyst **5a** led to significant improvement of the selectivity factor (Table 4.7, entry 1). Further screening of various imidodiphosphoric acids proved that thymol-derived catalyst **5i** is a superior catalyst for the kinetic resolution of tertiary diols (Table 4.7, entry 3). To our delight, using only 1 mol% of catalyst **5i** at 20 °C further improved the selectivity factor to 118 (Table 4.7, entry 6). It is noteworthy that with most of the well established methods for the kinetic resolution of diols, it is rare to achieve efficient resolution of diols with tertiary alcohol stereocenters.[152]

Table 4.7. Optimization of the reaction with tertiary diol.[a]



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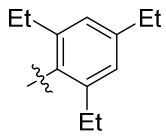
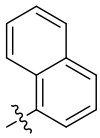
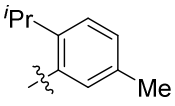


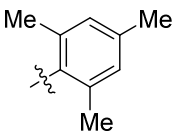
5a



5g



5i



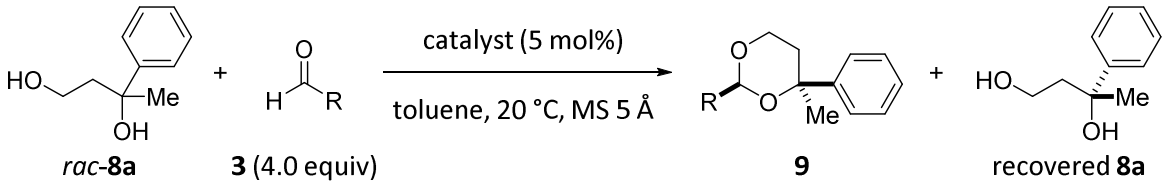
5j

entry	catalyst	conv.[b]	er **6c**[c,d]	er **7c**[c,e]	dr **7c**[c,f]	*S*[g]
1	**5a**	34%	74.5:25.5	98.5:1.5	49:1	47
2	**5g**	73%	98:2	81:19	5:1	7
3	**5i**	54%	>99.5:0.5	97:3	19:1	63
4	**5j**	54%	95:5	95.5:4.5	12:1	24
5[h]	**5i**	51%	98:2	98:2	23:1	93
6[h,i]	**5i**	50%	97.5:2.5	98.5:1.5	58:1	118

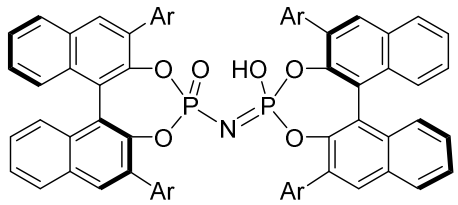
*a) Reactions were performed on 0.05 mmol scale with molecular sieves (10 mg/0.05 mmol) in toluene (0.5 ml) and terminated with a few drops of triethylamine. b) Theoretical conversion calculated from ee values of the product and the recovered starting material (see chapter 7.3.3). c) Samples for HPLC or GC analysis were isolated by thin layer chromatography using EtOAc/hexanes as the eluent. d) Determined by HPLC analysis on a chiral stationary phase. e) Determined by GC analysis on a chiral stationary phase. f) For most minor diastereomers er >99.5:0.5. g) Calculated from theoretical conversion and enantiomeric excess of enantioenriched diol (see chapter 7.3.3). h) 20 °C. i) 4 equiv of **3a**, 1 mol% of catalyst.*

We next investigated the applicability of our catalytic system to 1,3-diols. An additional screening of conditions was required because of their slightly lower reactivity and selectivity (Table 4.8). We prepared and used a new catalyst **5k** which is bulkier than **5i**, hoping to improve selectivity factors (Table 4.8, entry 2). Indeed catalyst **5k** provided improved results for the kinetic resolution of 1,3-diol **8a** giving selectivity factor of 19. Although the use of different aldehydes at 20 °C did not provide a significant improvement (Table 4.8, entries 3-6), using more reactive acetaldehyde enabled the reaction to be run at a lower temperature with 2 mol% catalyst loading resulting in a good selectivity factor of 28 (Table 4.8, entry 7).

Table 4.8. Optimization of the reaction with 1,3-diol (with I. Čorić).[a]



rac-**8a** **3** (4.0 equiv) **9** recovered **8a**



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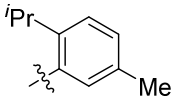
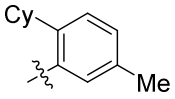
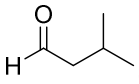
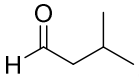
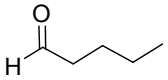
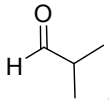
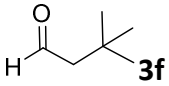
Ar =  

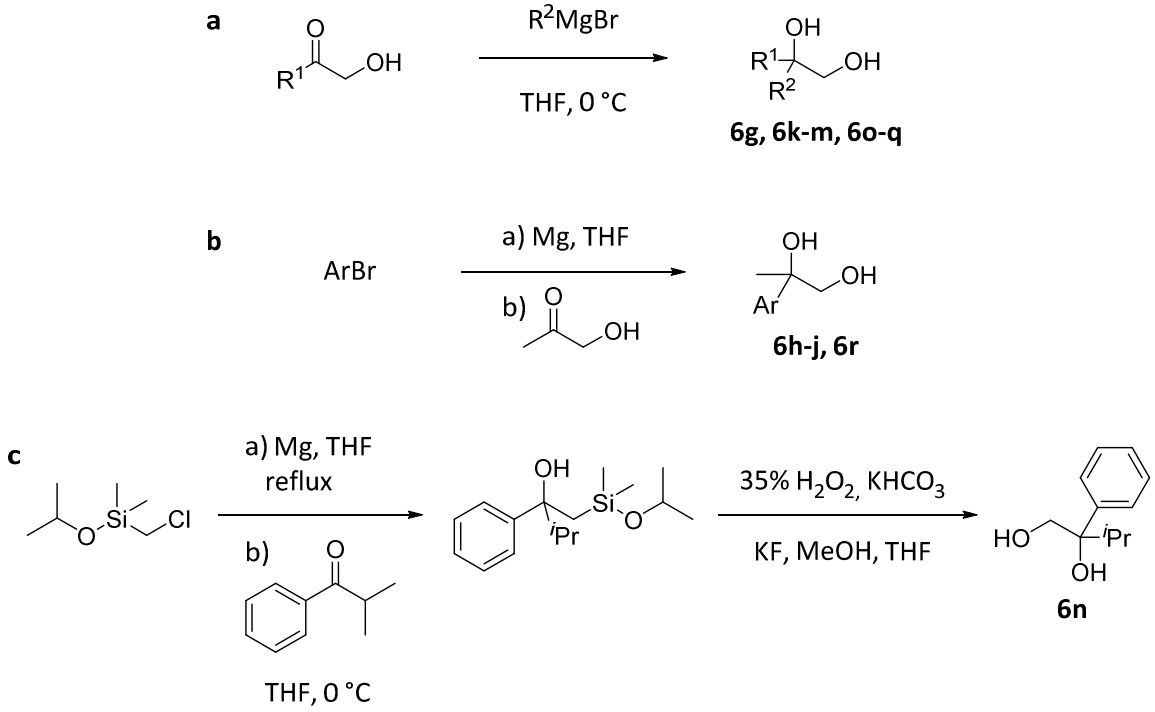
5i **5k**

entry	catalyst	aldehyde	time	conv.[b]	er **8a**[c,d]	er **9**[c,e]	dr **9**[e,f]	*S*[g]
1	**5i**	 **3a**	17 h	30%	67:33	97.5:2.5	11:1	12
2	**5k**	 **3a**	16 h	55%	95:5	93:7	12:1	19
3	**5k**	 **3b**	1 h	39%	77:23	95.5:4.5	27:1	20
4	**5k**	 **3c**	2.7 h	37%	75:25	97.5:2.5	22:1	23

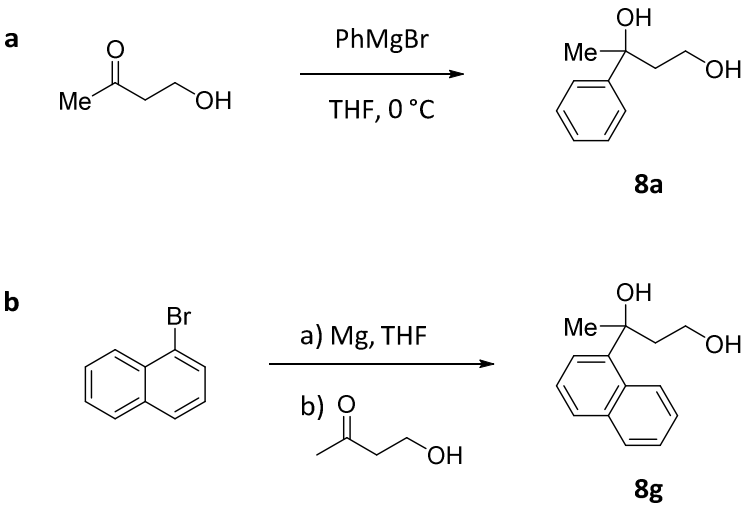
5	**5k**	 **3d**	16 h	33%	68:32	97.5:2.5	8:1	10
6	**5k**	 **3f**	16 h	23%	61:39	92:8	19:1	9
7[h]	**5k**	 **3b**	40 h	56%	98:2	92:8	22:1	28

a) Reactions were performed on 0.05 mmol scale with molecular sieves (10 mg/0.05 mmol) in toluene (0.5 ml) and terminated with a few drops of triethylamine. b) Theoretical conversion calculated from ee values of the product and the recovered starting material (see chapter 7.3.3). c) Samples for HPLC or GC analysis were isolated by thin layer chromatography using EtOAc/hexanes as the eluent. d) Determined by HPLC analysis on a chiral stationary phase. e) Determined by GC analysis on a chiral stationary phase. f) For most minor diastereomers er >99.5:0.5. g) Calculated from theoretical conversion and enantiomeric excess of enantioenriched diol (see chapter 7.3.3). h) 2 mol% of catalyst at 0 °C.

The starting racemic 1,2- and 1,3-diols required as starting materials are readily prepared via the addition of Grignard reagents to hydroxyl ketones or simple ketones (Scheme 4.12 and Scheme 4.13).



Scheme 4.12. Preparation of racemic 1,2-diols.

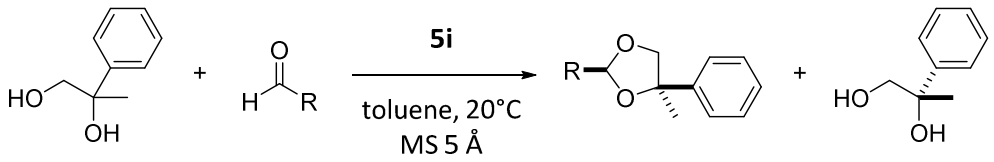


Scheme 4.13. Preparation of racemic 1,3-diols.

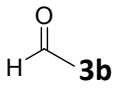
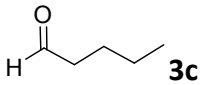
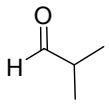
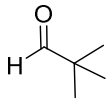
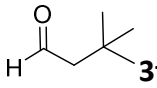
4.2.2. Substrate scope

Having optimized reaction conditions for 1,2- and 1,3-diols in hand, we started to evaluate the generality of the reaction. Examination of different aldehydes indicated that efficient kinetic resolution of diol *rac*-**6c** can be obtained in the presence of 1-2 mol% of **5i** to give a variety of 1,3-dioxolanes **7** with excellent enantioselectivities and diastereoselectivities (Table 4.9). Employing simple acetaldehyde or *n*-pentanal resulted in high selectivity factors of 39 and 64, respectively (Table 4.9, entry 1 and 2). Increased steric bulk at the α-position using isobutyraldehyde resulted in a higher selectivity factor of 79, although a higher catalyst loading was required (Table 4.9, entry 3). The reaction did not proceed at all when more sterically demanding pivaldehyde was employed (Table 4.9, entry 4). We wondered if increasing the bulkiness at the β-position of isovaleraldehyde could be beneficial since the highest selectivity factor was obtained when isovaleraldehyde was used which is bulkier than linear aldehydes and at the same time less bulky than α-trisubstituted aldehydes. Indeed, an excellent selectivity factor of 122 was observed with 3,3-dimethylbutyraldehyde (Table 4.9, entry 5). However, considering its lower reactivity compared to isovaleraldehyde (Table 4.7, entry 6), we used isovaleraldehyde for evaluating the diol scope of the acetalization.

Table 4.9. Kinetic resolution of tertiary 1,2-diols with different aldehydes.[a]



rac-**6c** **3** (4.0 equiv) **7** recovered **6c**

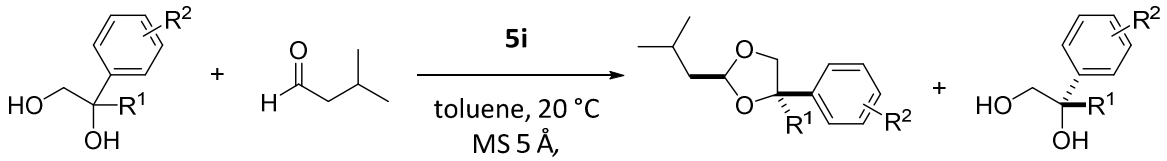
entry	catalyst loading	aldehyde	time	conv.[b]	yield **6c**[c]	er **6c**[d]	yield **7**[c]	er **7**[e,f]	dr **7**[e]	S[g]
1	1 mol%	 **3b**	23 h	55%	40%	99:1	48%	94:6	20:1	39
2	1 mol%	 **3c**	12 h	49%	47%	94.5:5.5	47%	97:3	57:1	64
3	2 mol%	 **3d**	36 h	52%	42%	99:1	49%	98:2	26:1	79
4	2 mol%	 **3e**	10 d	-	-	-	<2%[h]	-	-	-
5	2 mol%	 **3f**	96 h	52%	39%	99.5:0.5	47%	98:2	52:1	122

a) Reactions were performed on 0.50 mmol scale with molecular sieves (100 mg) in toluene (5 ml) and terminated with a few drops of triethylamine. b) Theoretical conversion calculated from ee values of the product and the recovered starting material (see chapter 7.3.3). c) Isolated yield on a 0.5 mmol scale. d) Determined by HPLC analysis on a chiral stationary phase. e) Determined by GC analysis on a chiral stationary phase. f) For most minor diastereomers er >99.5:0.5. g) Calculated from theoretical conversion and enantiomeric excess of enantioenriched diol (see chapter 7.3.3). h) Determined by ^{1}H NMR analysis.

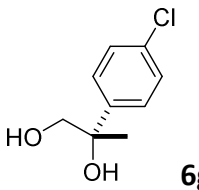
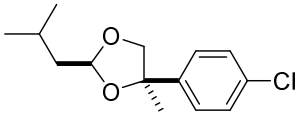
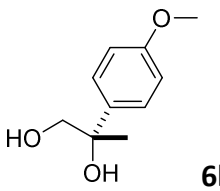
A variety of substituents on the aromatic ring of diols was examined for the kinetic resolution (Table 4.10, entries 1-6). By placing chloro-, methoxy-, or methyl-substituents at the *para*-position of the aromatic ring of the diol, we could achieve very high selectivity factors from 64 to 99 with 2-3 mol% of the catalyst (Table 4.10, entries 1-3). Employing diols with *meta*- or *ortho*-substituents resulted in increased enantioselectivity compared to those bearing *para*-substitution; with excellent selectivity factors of 110 and 135 obtained in these cases (Table

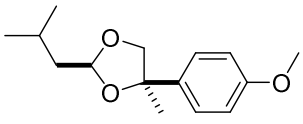
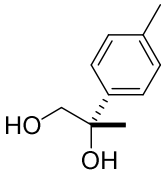
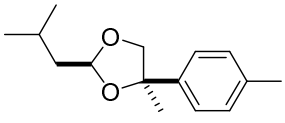
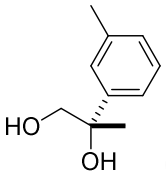
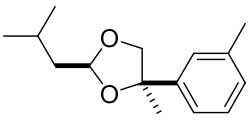
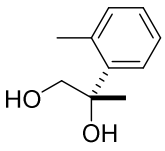
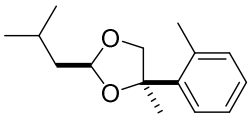
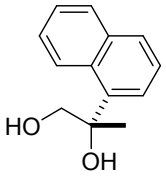
4.10, entries 4 and 5). A superb kinetic resolution was achieved with a selectivity factor of 389 when methyl,naphthyl-substituted diol *rac*-**6l** was employed providing enantioenriched diol **6l** with an er of 98.5:1.5, while 1,3-dioxolane **7l** was obtained with er over 99.5:0.5, and a dr of 93:1. Encouraged by these results, we next investigated the reaction with different diols, replacing the methyl group to other substituents. The reaction of ethyl-substituted diol *rac*-**6m** using 2 mol% of **5i** proceeded with a selectivity factor of 115 (Table 4.10, entry 7). Interestingly, even a diol with two similarly bulky substituents, phenyl and isopropyl, exhibited an impressive selectivity factor of 372, with only 1 mol% catalyst (Table 4.10, entry 8). The reaction proceeded to 50% conversion, whereby (*R*)-**6n** underwent acetalization with a dr of 191:1 and an er of 99.5:0.5 for acetal product **7n**, while (*S*)-**6n** was recovered with an er of 99:1.

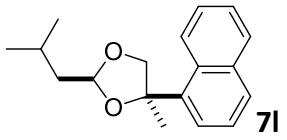
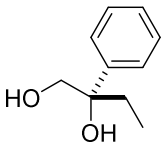
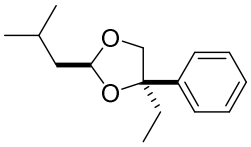
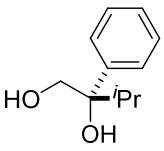
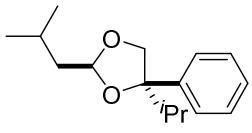
Table 4.10. Kinetic resolution of aryl,alkyl-substituted 1,2-diols.[a]



rac-**6** **3a** (4.0 equiv) **7** recovered **6**

entry	catalyst loading	time	conv.[b]	compound	yield[c]	er[d,e]	dr **7**[d]	*S*[f]
1	3 mol%	10 h	49%	 **6g**	47%	94.5:5.5		87
				 **7g**	45%	98.5:1.5	52:1	
2	2 mol%	17.5 h	50%	 **6h**	49%	96.5:3.5		99

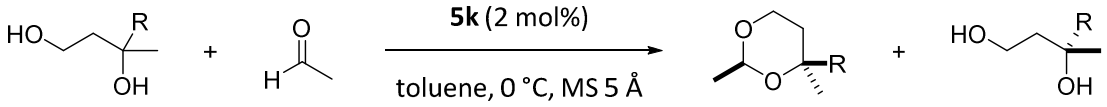
				 **7h**	48%	98.5:1.5	53:1	
3	2 mol%	13 h	52%	 **6i**	44%	97.5:2.5		64
				 **7i**	46%	96:4	52:1	
4	1 mol%	19 h	46%	 **6j**	54%	90.5:9.5		110
				 **7j**	45%	98.5:1.5	124:1	
5	1 mol%	17 h	49%	 **6k**	51%	96.5:3.5		135
				 **7k**	47%	98.5:1.5	92:1	
6	1 mol%	22 h	50%	 **6l**	45%	98.5:1.5		389

				 **7l**	44%	>99.5:0.5	93:1	
7	2 mol%	20 h	52%	 **6m**	46%	99.5:0.5		115
				 **7m**	44%	98:2	36:1	
8	1 mol%	11 h	50%	 **6n**	44%	99:1		372
				 **7n**	49%	99.5:0.5	191:1	

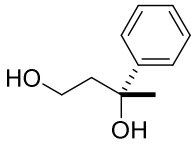
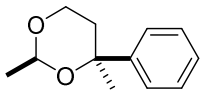
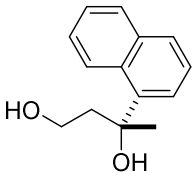
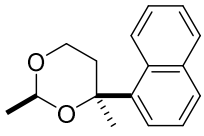
a) Reactions were performed on 0.50 mmol scale with molecular sieves (100 mg) in toluene (5 ml) and terminated with a few drops of triethylamine. b) Theoretical conversion calculated from ee values of the product and the recovered starting material (see chapter 7.3.3). c) Isolated yield on a 0.50 mmol scale. d) Determined by HPLC or GC analysis on a chiral stationary phase. e) For most minor diastereomers er >99.5:0.5. f) Calculated from theoretical conversion and enantiomeric excess of enantioenriched diol (see chapter 7.3.3).

We next investigated the applicability of our catalytic system to 1,3-diols. Due to their slightly declined reactivity and selectivity, an additional screening of conditions was required (see, Table 4.8). Using a bulkier catalyst **5n** and acetaldehyde at 0 °C resulted in good selectivity factor of 29 for resolution of 1,3-diol *rac*-**8a** (Table 4.11, entry 1). A methyl,naphthyl-substituted 1,3-diol gave still good but slightly lower selectivity factor of 16 (Table 4.11, entry 2). In both cases enantioenriched diols could be isolated in good yields and high enantiomeric ratios of 99:1 and 94.5:5.5, respectively.

Table 4.11. Kinetic resolution of 1,3-diols.[a]



rac-**8** **3b** (4.0 equiv) **9** recovered **8**

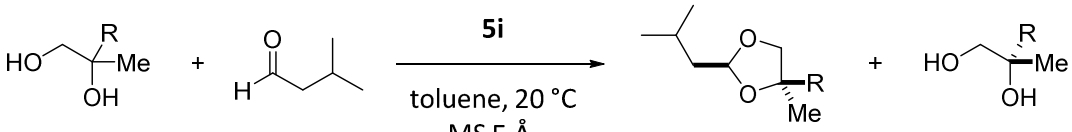
entry	time	conv.[b]	compound	yield[c]	er[d,e]	dr **7**[d]	*S*[f]
1	38 h	58%	 **8a**	40%	99:1		29
			 **9b**	54%	91:9	17:1	
2	40 h	56%	 **8g**	38%	94.5:5.5		16
			 **9g**	55%	89:11	20:1	

a) Reactions were performed on 0.50 mmol scale with molecular sieves (100 mg) in toluene (5 ml) and terminated with a few drops of triethylamine. b) Theoretical conversion calculated from ee values of the product and the recovered starting material (see chapter 7.3.3). c) Isolated yield on a 0.50 mmol scale. d) Determined by HPLC or GC analysis on a chiral stationary phase. e) For most minor diastereomers er >99.5:0.5. f) Calculated from theoretical conversion and enantiomeric excess of enantioenriched diol (see chapter 7.3.3).

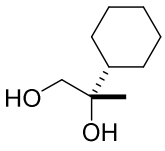
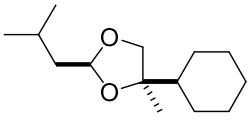
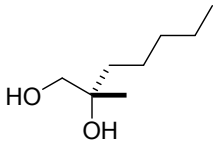
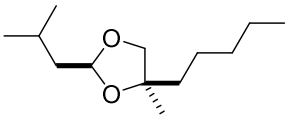
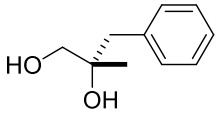
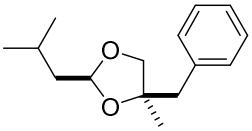
Dialkyl-substituted 1,2-diols

The exceptional results with aryl,alkyl-substituted 1,2-diols encouraged us to explore the kinetic resolution of dialkyl-substituted 1,2-diols. Although aryl,alkyl-substituted diols proved as excellent substrates for our kinetic resolution, dialkyl substituted diols were expected to result in diminished selectivities due to more similar substituents on the stereogenic center.

Table 4.12. Kinetic resolution of alkyl,alkyl-substituted 1,2-diols.[a]



rac-**6** **3a** (4.0 equiv) **7** recovered **6**

entry	catalyst loading	time	conv.[b]	compound	yield[c]	er[d,e]	dr **7**[d]	S^f
1	2 mol%	15 h	55%	 **6o**	45%	95.5:4.5		23
				 **7o**	49%	95.5:4.5	11:1	
2	2 mol%	15 h	61%	 **6p**	33%	93:7		9
				 **7p**	54%	98.5:1.5	4:1	
3	2 mol%	17 h	62%	 **6a**	32%	91:9		7
				 **7a**	62%	99.5:0.5	3:1	

a) Reactions were performed on 0.50 mmol scale with molecular sieves (100 mg) in toluene (5 ml) and terminated with a few drops of triethylamine. b) Theoretical conversion calculated from ee values of the product and the recovered starting material (see chapter 7.3.3). c) Isolated yield on a 0.50 mmol scale. d) Determined by HPLC or

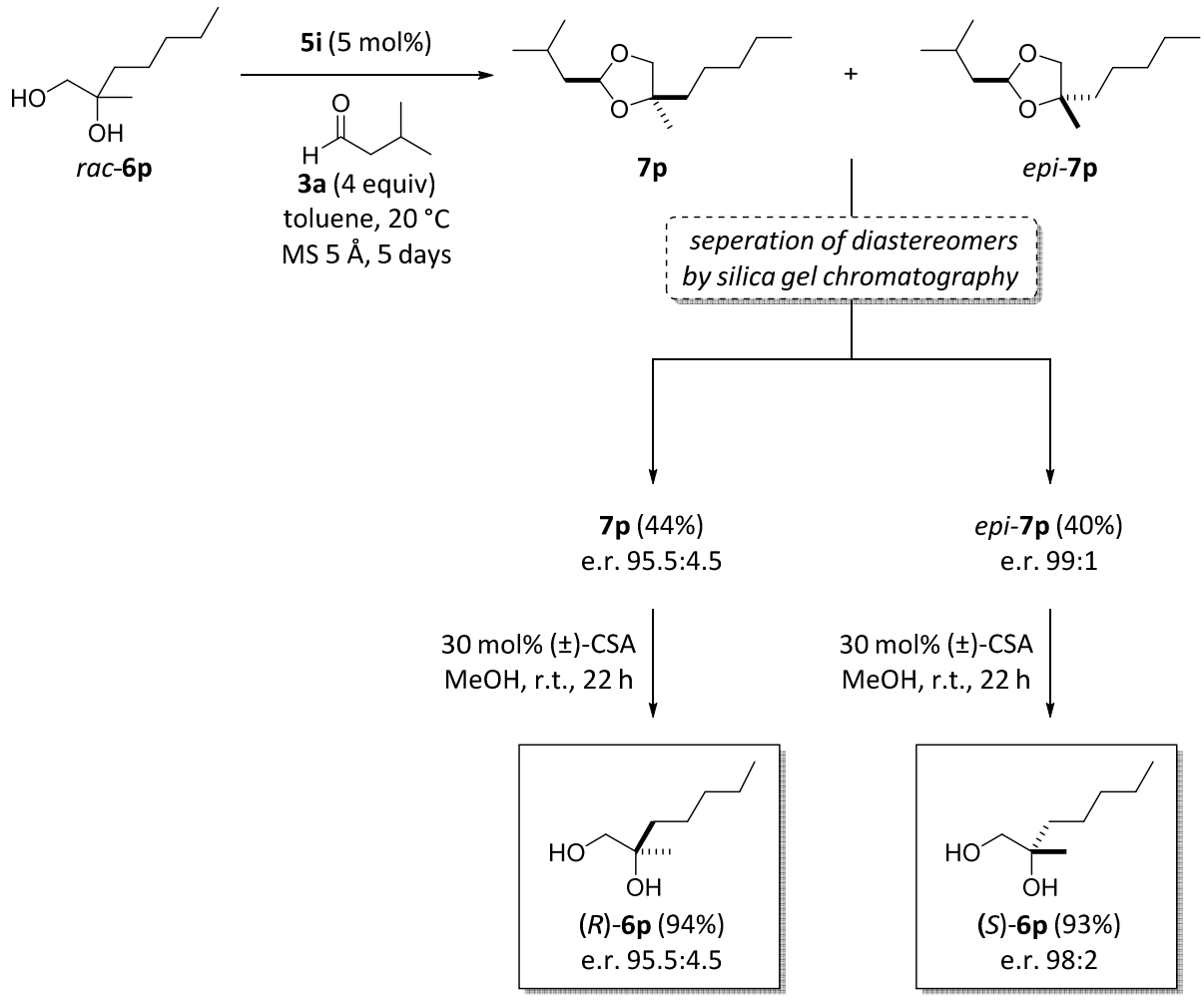
GC analysis on a chiral stationary phase. e) For most minor diastereomers er >99.5:0.5. f) Calculated from theoretical conversion and enantiomeric excess of enantioenriched diol (see chapter 7.3.3).

Gratifyingly, the reaction of methyl,cyclohexyl-substituted diol proceeded with a high selectivity factor of 23 with 2 mol% of the catalyst (Table 4.12, entry 1). With methyl,hexyl-substituted diol, the reaction proceeded with a lower selectivity factor 9 (Table 4.12, entry 2), but recovered diol (*S*)-**6p** could still be obtained in 33% yield with a good er of 93:7, and the acetal product **7p** was isolated with excellent er of 98.5:1.5, although the diastereoselectivity was low. A slightly lower selectivity factor of 7 was observed with the reaction of methyl,benzyl-substituted diol (Table 4.12, entry 3). These examples demonstrate how excellent stereocontrol of the acetal stereocenter formation can be accomplished by the catalyst regardless of the diol substrate. Even if the reactions of dialkyl-substituted diols do not give particularly high selectivity factors, still good enantioselectivities and acceptable yields of dialkyl-substituted diols could be obtained at higher conversion of the reaction. It is noteworthy that highly enantioenriched 1,2-diols with very similar aliphatic substituents at the tertiary alcohol stereocenter could be obtained by our kinetic resolution process, which are hard to obtain by other methods.

4.2.3. Stereodivergent access to enantioenriched diols

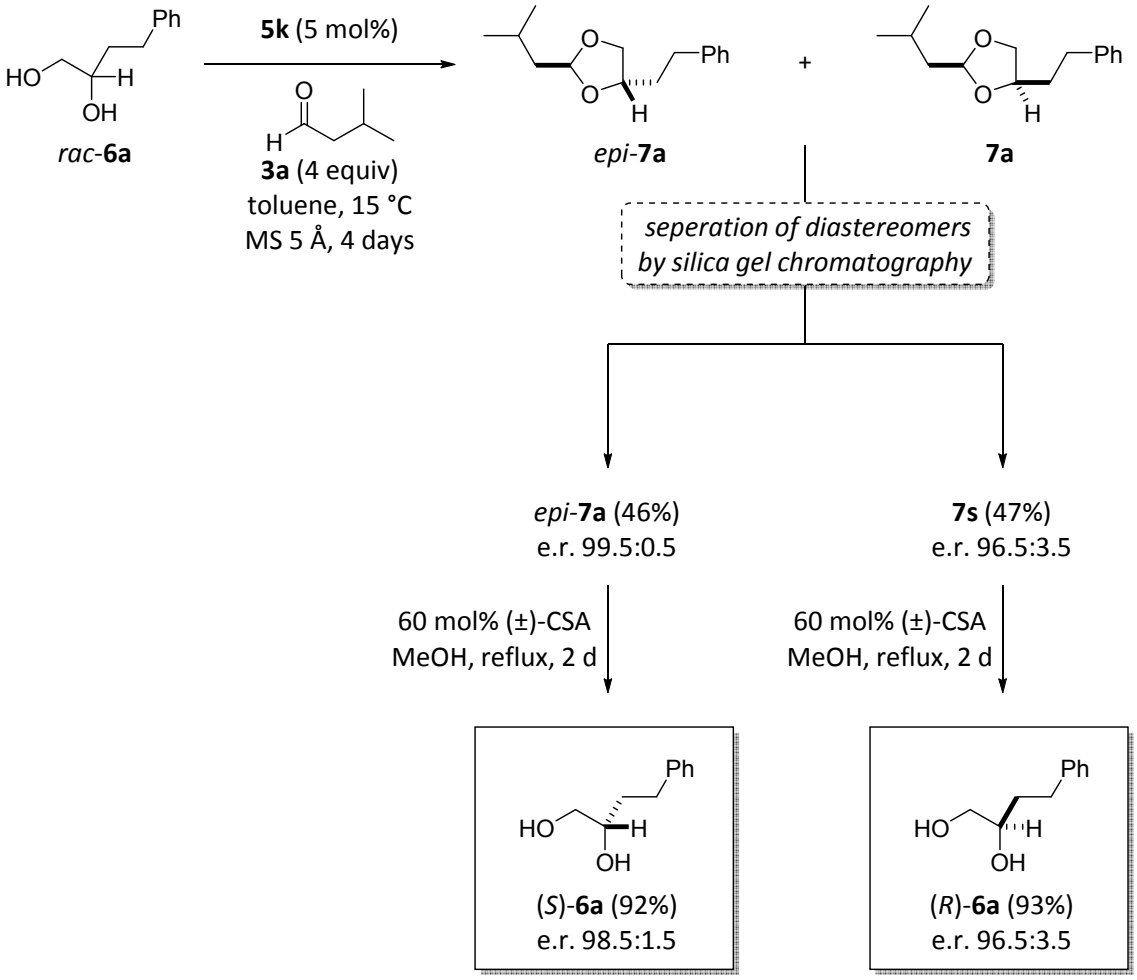
Our initial attempts towards the kinetic resolution of diols with a secondary alcohol stereocenter delivered disappointing results showing almost no selectivities (Table 4.6). However, both diastereomers of the acetal product were obtained in an excellent er of 99.5:0.5 and er of 95:5 respectively and in a combined yield of 80% (Table 4.6, entry 3). This example illustrates an important aspect of our acetalization reaction. As an additional acetal stereocenter is created in the acetalization reaction, a complementary divergent reaction on a racemic mixture is possible if the catalyst can control its formation very well. Thus, even in the cases where the actual enantiomer differentiation of the starting diol substrate is poor, the less reactive enantiomer is converted into the minor diastereomer. Indeed our catalyst enabled an exceptionally high degree of control in creating the acetal stereogenic center as shown in entry 3, Table 4.6, and also in entries 2-3, Table 4.12.

We first examined the stereodivergent resolution with racemic diol **6p** which gave the selectivity factor 9 (Table 4.12, entry 2). A higher catalyst loading was needed to increase the reactivity at lower temperature. The diol enantiomers are converted into two different acetal diastereomers after complete conversion of the starting material (Scheme 4.14). Subsequently, the acetal products can be separated by chromatography on silica gel providing acetal protected diols **7p** and *epi*-**7p** with an excellent er of 95.5:4.5 in 44% isolated yield and an er of 99:1 in 40% isolated yield, respectively. After subsequent deprotection using 30 mol% of (±)-CSA in methanol, the enantioenriched diols (*R*)-**6p** and (*S*)-**6p** could be obtained from the corresponding acetals.



Scheme 4.14. Stereodivergent access to enantioenriched diols **6p**.

Encouraged by this successful stereodivergent reaction, we also examined whether diols with secondary alcohol stereocenters can be applied to this process. Gratifyingly, the substrate *rac*-**6a**, which gave almost no selectivity (s factor 1.6, Table 4.6, entry 3) in our kinetic resolution, afforded two acetal diastereomers *epi*-**7a** and **7a** with an excellent er of 99.5:0.5 in 46% and an er of 96.5:3.5 and 47% isolated yield respectively, when catalyst **5k** was employed at 15 °C (Scheme 4.15). Highly enantioenriched diols (*S*)-**6a** and (*R*)-**6a** can be obtained after removal of the acetal protecting group.



Scheme 4.15. Stereodivergent access to enantioenriched diols **6a**.

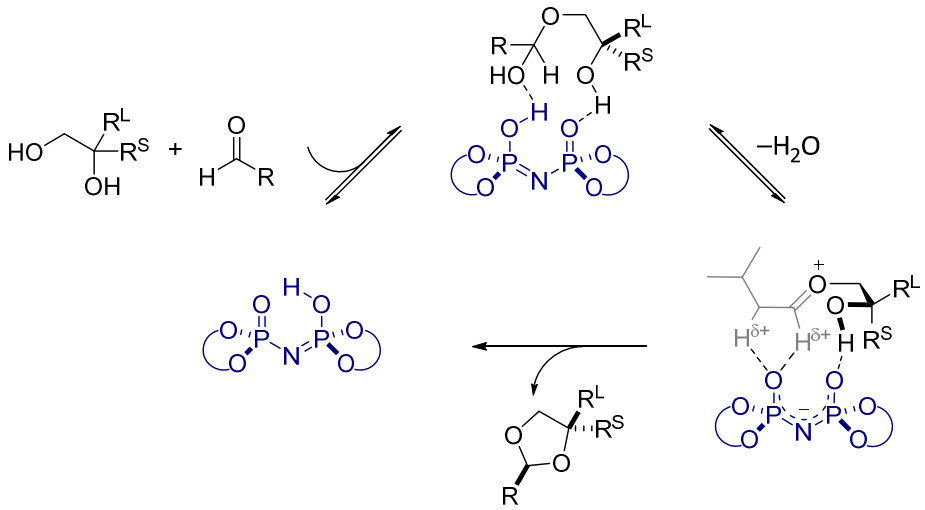
It is noteworthy that, from a single asymmetric reaction using one configuration of catalyst, both (*R*)- and (*S*)-enantiomers of diols *rac*-**6p** and *rac*-**6s** could be obtained with very high enantiomeric ratios.

4.2.4. Discussion

We have developed a highly enantioselective kinetic resolution of diols possessing quaternary stereocenters via an asymmetric acetalization reaction. Exceptional selectivity factors of up to 389 can be obtained. In most cases both acetal product and recovered diol can be obtained with er over 95:5. Furthermore, due to exceptional enantiocontrol of our catalyst in creating the acetal stereogenic center, a complementary stereodivergent resolution of diols into two separable diastereoisomers was possible. This process can be applied in cases where the kinetic enantiomer differentiation is not satisfactory. It is noteworthy that our kinetic

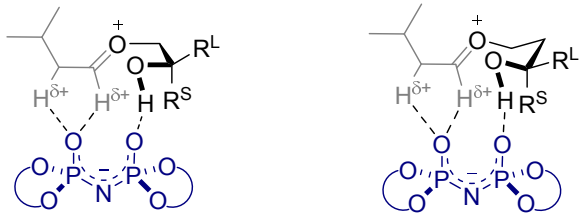
resolution represents a method that can provide enantioenriched diols possessing tertiary alcohol stereocenters. Also, our process is a very atom economic method forming water as the only byproduct.

Based on our previous asymmetric acetalization results, we believe that the reaction proceeds through the oxocarbenium ion which is derived from the primary hydroxyl functionality and subsequent attack of the tertiary alcohol. This cyclization step is probably the enantio-discriminating step, as hemiacetal formation is presumably reversible (Scheme 4.16). The alcohol group of the tertiary stereocenter of the diol presumably possesses hydrogen bonding with the chiral imidodiphosphate anion, placing the alcohol stereocenter in its close vicinity, to achieve an efficient kinetic resolution in the cyclization step. Potentially, the transition state can be stabilized further by additional oxocarbenium C–H···anion hydrogen bonding.[159]



Scheme 4.16. Suggested mechanism.

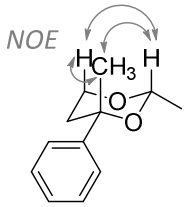
All of our kinetic acetal products are *cis*-isomers which are also thermodynamically favored over the corresponding *trans*-isomers.[160] The aldehyde alkyl chain and the larger alcohol substituent both take pseudoequatorial positions in the five-membered transition state, resulting in their *cis* relationship in the products (Figure 4.2). The six-membered transition state for 1,3-diols follows in the same manner by bulky substituents taking equatorial positions.



5-membered pre-transition state *6-membered pre-transition state*

Figure 4.2. Pre-transition state assembly explaining the preferred *cis*-diastereomer selectivity.

Absolute configurations of quaternary carbon stereocenters in acetal products were assigned opposite configurations to those observed in the recovered diols. The configuration of acetal stereocenters were assigned by analogy to the results from our asymmetric acetalization studies.[67] The *cis*-configuration of the product **9b** was verified by NOESY correlation (Figure 4.3).



9b

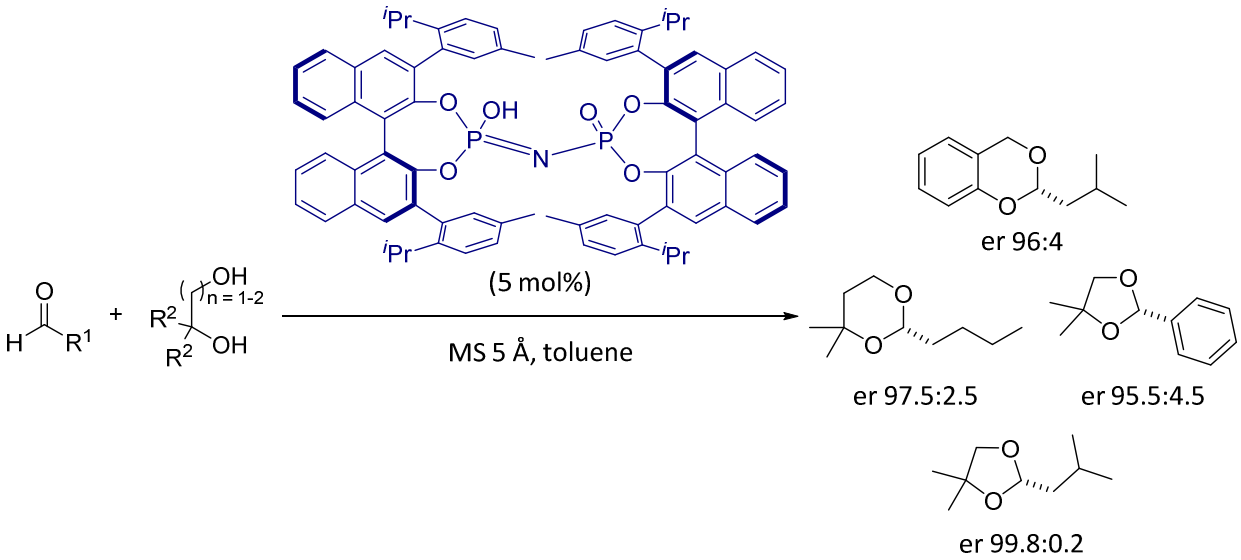
Figure 4.3. Determination of the relative stereochemistry of **9b** by NOESY correlation.

5. SUMMARY

5.1. Catalytic asymmetric acetalization

Stereogenic acetals are frequently found motifs in a variety of natural products and bioactive compounds. Acetal formation from aldehydes and alcohols catalyzed by Brønsted acids is one of the most common transformations in organic synthesis. However, the asymmetric version of this reaction was unknown prior to our work. The success of Brønsted acid catalyzed asymmetric *N,X*-acetalizations (*X* = *O, N, S*) is based on the well-established ability of chiral phosphoric acids to control the enantioselective addition of nucleophiles to imine substrates and intermediates. However, *O,O*-acetalizations which require enantioselective additions to oxocarbenium ion intermediates remained underdeveloped. One of the challenges is that *O,O*-acetals could reversibly form oxocarbenium ions resulting in racemization of the acetal products in the presence of acid.

We have developed the first catalytic asymmetric acetalization of aldehydes with diols.[67] Imidodiphosphoric acid with isopropyl, methyl substituents in the 2- and 5-position on the aryl group, readily available from natural product thymol, drastically outperformed known catalysts and delivered *O,O*-acetals with excellent enantioselectivity (Scheme 5.1). The reaction provides highly enantioenriched acetal products, and even the reaction of a small substrate can proceed with exceptional enantioselectivity giving product with an er of 99.8:0.2.

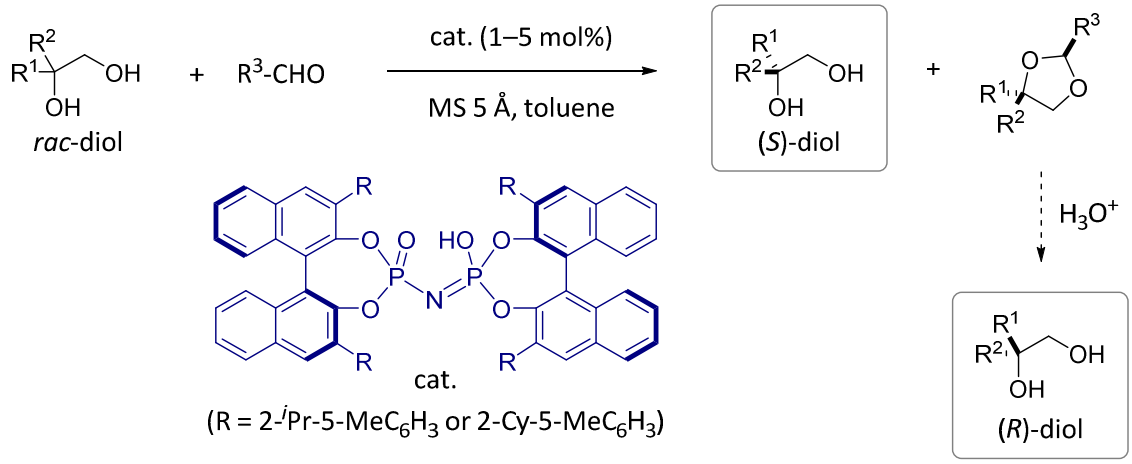


Scheme 5.1. Catalytic asymmetric acetalization.

5.2. Kinetic resolution of diols via catalytic asymmetric acetalization

Enantiomerically pure diols are common scaffolds in natural products and are valuable synthetic building blocks. Although many synthetic approaches to enantioenriched diols have been developed, synthetic methods that deliver diols with tertiary alcohol stereocenters with high enantioselectivity are very limited. Since racemic diols are readily accessible, kinetic resolution is a popular strategy for preparation of enantioenriched diols. Methods for kinetic resolution of diols through asymmetric acylation and silylation are well known. Next to ester and silyl groups, acetals are among the most common protecting groups for alcohols, with complementary stability and deprotection conditions. However, processes for the kinetic resolution of diols via acetalization reaction are unknown prior to our work.

We have developed a kinetic resolution of diols based on our asymmetric acetalization reaction (Scheme 5.2).[68] The reaction gives free enantioenriched 1,2- and 1,3-diols with tertiary alcohol stereocenters and acetal-protected diols with excellent enantioselectivities. Selectivity factors up to 389 can be achieved. Furthermore, a complementary stereodivergent resolution of diols into two separable diastereoisomers is possible, giving both enantiomers of a diol with high enantioselectivities after removal of acetal protecting group.



Scheme 5.2. Kinetic resolution of diols via acetalization.

This work has been disclosed in part in the following publications:

"Resolution of Diols via Catalytic Asymmetric Acetalization", J. H. Kim, I. Čorić, C. Palumbo, B. List, *J. Am. Chem. Soc.* **2015**, *137*, 1778.

"The Catalytic Asymmetric Acetalization", J. H. Kim, I. Čorić, S. Vallalath, B. List, *Angew. Chem. Int. Ed.* **2013**, *52*, 4474.

6. OUTLOOK

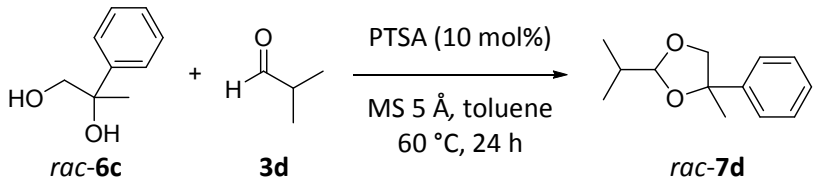
6.1. Acetals for fragrance chemistry

Acetal compounds can sometimes provide pleasant scent, and subsequently the synthesis of acetals attracts attention of perfumery companies. Enantiomers of chiral acetal compounds can have very distinct and characteristic odors. For example, an important blackcurrant odorant contains the (2*S*),(4*R*)-1,3-oxathiane moiety and the odor is mainly caused by this stereoisomer of the acetal compound (**A**, Figure 6.1).[161] Okoumal is found to have a woody odor, and its stereoisomers possess different strengths of the odor depending on the configuration at the acetal stereocenter (**B**, Figure 6.1).[162]

A: (+)-(2*S*,4*R*)-1,3-oxathiane **B**: (2*S*,4*R*)-Okoumal

Figure 6.1. Acetal compounds with interesting scents.

During our studies on kinetic resolutions of diols via asymmetric acetalization reactions we have found that one of our acetal products smells interesting. In order to evaluate the properties of the compound as an odorant we prepared the racemic mixture *rac*-**7d**.



rac-**6c** **3d** *rac*-**7d**

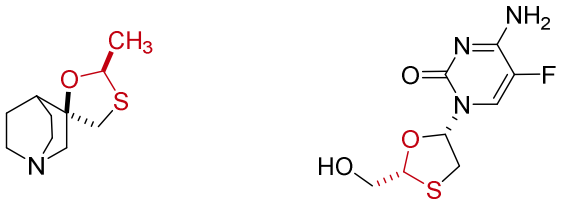
Scheme 6.1. Preparation of acetal product *rac*-**7d**.

The compound was analysed by Dr. P. Kraft from the Fragrance Research department of Givaudan Schweiz AG and found that it possesses “a herbal-fruity odor in the direction of clary sage, with reminiscence to Claritone and Labienone”. The odor threshold is 66 ng/L air, which is rather weak, while good odorants are around 1.0 ng/L air or at least below 10.0 ng/L air.

These results demonstrate that even our simple acetal products could provide interesting properties, and that asymmetric acetalizations in the future might be employed for fragrance production.

6.2. Brønsted acid catalyzed asymmetric *S,O*-acetalization

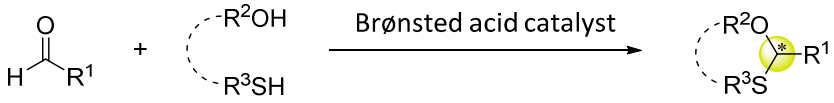
Next to stereogenic *O,O*-acetals, the stereogenic *S,O*-acetal motif can also be found in drugs (Figure 6.2). Cevimeline is used in the treatment of dry mouth in patients with Sjögren's syndrome,[163] and Emtricitabine for the treatment of HIV. However, catalytic asymmetric transformations that involve the formation of *S,O*-acetal stereocenters to give enantioenriched *S,O*-acetal products are very rare. The direct catalytic asymmetric *S,O*-acetalization of aldehydes is unknown.



Cevimeline Emtricitabine

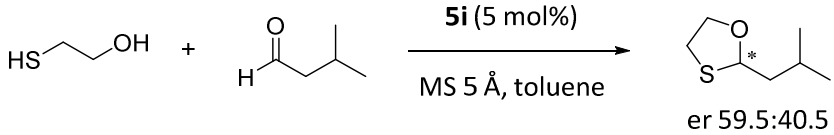
Figure 6.2. Stereogenic *S,O*-acetals in drug.

As our investigations on the direct asymmetric *O,O*-acetalization reaction were successful, we have started to investigate the direct asymmetric *S,O*-acetalization reaction catalyzed by confined imidodiphosphoric acids to obtain enantioenriched *S,O*-acetal products (Scheme 6.2).



Scheme 6.2. Towards the asymmetric *S,O*-acetalization.

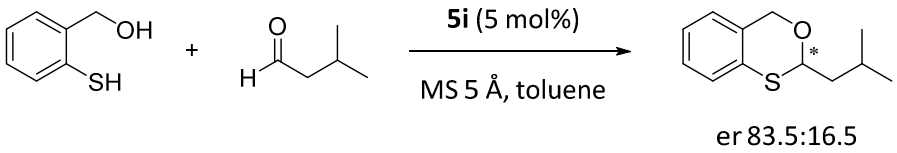
We initiated our investigations using commercially available simple mercaptoethanol and confined imidodiphosphoric acid catalyst **5i**, which has previously been identified as an excellent catalyst for asymmetric *O,O*-acetalizations (Scheme 6.3). However, the reaction with isovaleraldehyde using 5 mol% of the catalyst gave cyclic acetal product with a poor enantioselectivity (er of 59.5:40.5).



er 59.5:40.5

Scheme 6.3. Initial attempt at asymmetric *S,O*-acetalization.

We next tested the reaction with 2-mercaptobenzyl alcohol, which is bulkier than mercaptoethanol, and a significantly improved er of 83.5:16.5 was observed (Scheme 6.4).



Scheme 6.4. Use of 2-mercaptobenzyl alcohol for *S,O*-acetalization.

We speculated that there might be a competition to form the oxocarbenium and thiocarbenium ions resulting potentially in low enantioselectivity (Figure 6.3).

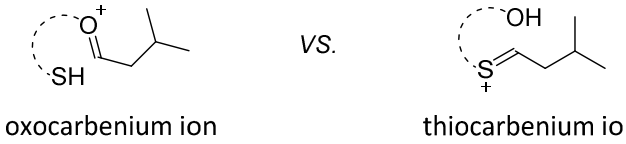
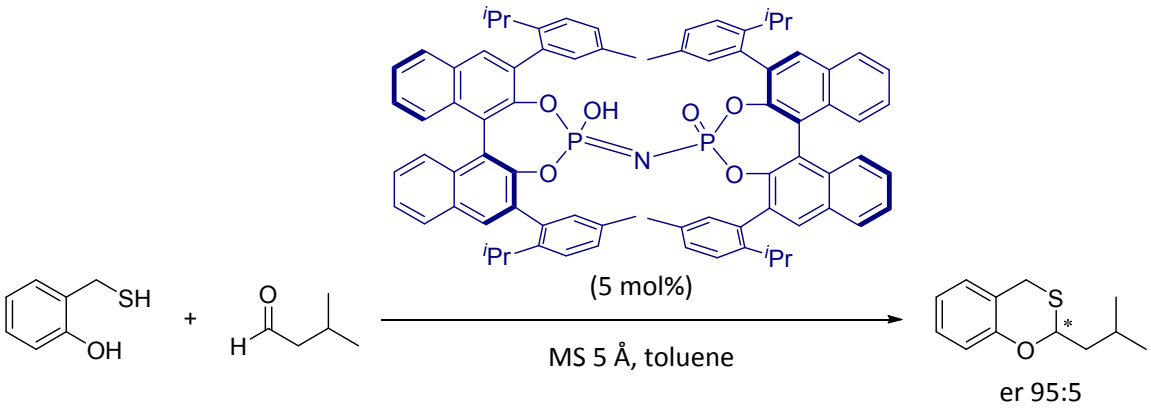


Figure 6.3. The formation of potential carbenium ion intermediates.

We next synthesized 2-(mercaptomethyl)phenol which possesses the benzylic thiol instead of alcohol, and employed it to the asymmetric acetalization reaction (Scheme 6.5). Gratifyingly, this substrate enabled us to obtain the *S,O*-acetal product with high enantioselectivity, er 95:5.



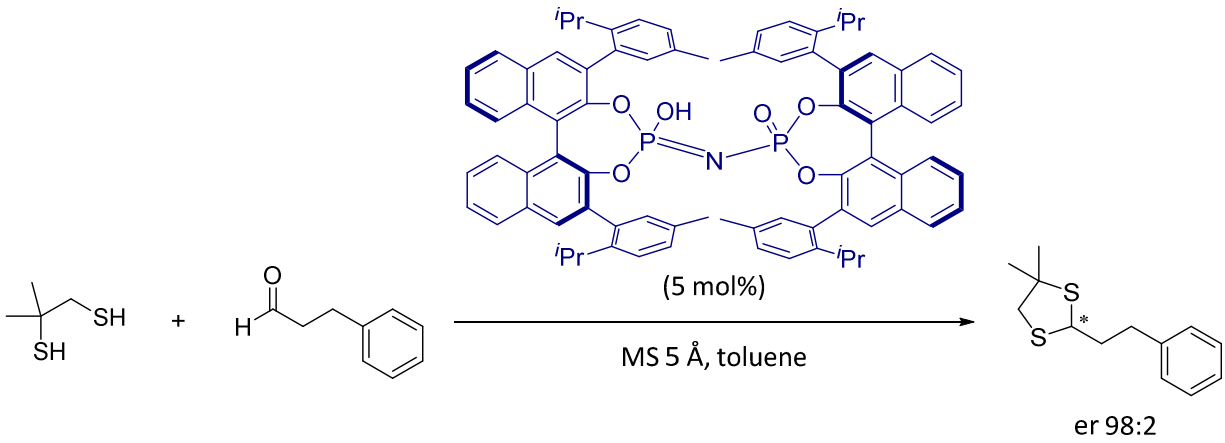
Scheme 6.5. Catalytic asymmetric *S,O*-acetalization.

Further exploration of the reaction conditions and substrate scope will hopefully lead to a general methodology for the asymmetric S,O-acetalization, and analogous reactions may be envisioned for the kinetic resolution of chiral racemic thioalcohols via *S,O*-acetal formation.

6.3. Brønsted acid catalyzed asymmetric *S,S*-acetalization

Dithioacetals are common protecting group for carbonyl compounds. They can be formed from thiols and aldehydes or ketones with Lewis or Brønsted acid catalysts. Dithioacetals are frequently used to provide umpolung of carbonyl group. However, a catalytic asymmetric thioacetalization is unkown.

We wondered if our catalytic system can be applied to provide enantioenriched *S,S*-acetals potentially through the formation of thiocarbenium ion intermediate.



Scheme 6.6. Catalytic asymmetric *S,S*-acetalization.

Gratifyingly, the asymmetric *S,S*-acetalization can be achieved using thymol-derived imidodiphosphoric acid, giving cyclic thioacetal product with high er of 98:2 (Scheme 6.6).

Exploration of the substrate scope is expected to result in the first catalytic asymmetric thioacetalization and this reaction could be applied to kinetic resolution of dithiols via dithioacetal formation. It would be interesting to determine if *S,S*-acetalization reactions proceed through the asymmetric addition of nucleophiles to thiocarbenium ions.

7. EXPERIMENTAL SECTION

7.1. General experimental conditions

Solvents and reagents

All solvents used in the standard procedures were purified by distillation. Absolute diethyl ether, tetrahydrofuran, n-hexane and toluene were obtained by distillation over sodium with benzophenone as indicator; absolute chloroform and dichloromethane were obtained by distillation over calcium hydride, and ethanol, isopropanol and methanol were dried by distillation over magnesium. Anhydrous acetone, acetonitrile, benzene, cyclohexane, DMF, DMSO, pyridine, and 1,4-dioxane were purchased from Sigma-Aldrich and used as received. NEt_3 were purified by distillation over $LiAlH_4$. All dried solvents and purified reagents were distilled prior to use or stored under an inert argon atmosphere. Commercial reagents were obtained from various sources and used without further purification unless indicated. All aldehydes were distilled prior to use or stored under an inert argon atmosphere.

Known Brønsted acid catalysts

Chiral Brønsted acid catalysts in Table 4.1 were kindly supplied by the coworkers from the List group and were prepared according to the literature procedures referenced in Table 4.1.

Imidodiphosphoric acid catalysts

Chiral imidodiphosphoric acid catalysts in Table 4.2, Table 4.6, Table 4.7, and Table 4.8 were developed and initially prepared by I. Čorić.[11]

Inert gas atmosphere

All air and moisture sensitive reactions were conducted in flame-dired glass ware under and inert argon atmosphere using standard Schlenk techniques. Dry argon was purchased from Air Liquide with higher than 99.5% purity. Unless otherwise stated, all organocatalytic reactions were performed under an ambient atmosphere without the exclusion of moisture or air.

Thin layer chromatography (TLC)

Reactions were monitored by thin layer chromatography on silica gel or aluminum oxide pre-coated plastic sheets (0.2 mm, Macherey-Nagel). Visualization was accomplished by irradiation with UV light at 254 nm and different staining reagents; phosphomolybdic acid (PMA) stain: PMA (10 g) in EtOH (100 ml); anisaldehyde stain: *p*-anisaldehyde (3.5 ml), glacial acetic acid (15 ml), EtOH (350 ml), conc. H_2SO_4 (50 ml).

Column chromatography

Column chromatography was performed under elevated pressure on silica gel (60, particle size 0.040-0.063 mm, Merck) or aluminum oxide (neutral, activated, Brockmann I, Sigma-Aldrich; Activity II with 3% H_2O; Activity III with 6% H_2O).

High pressure liquid chromatography (HPLC)

HPLC analyses on a chiral stationary phase were performed on a Shimadzu LC-2010C system equipped with a UV detector. Commercial HPLC-grade solvents were used, and measurements were conducted at 25 °C. The chiral stationary phase of the columns is specified in each experiment. The enantiomeric ratios were determined by comparing the samples with the appropriate racemic mixtures.

Gas chromatography (GC)

GC analyses on a chiral stationary phase were performed on HP 6890 and 5890 series instruments equipped with a split-mode capillary injection system and a flame ionization detector (FID) using hydrogen as a carrier gas. Detailed conditions are given in the individual experiment. The enantiomeric ratios were determined by comparing the samples with the appropriate racemic mixtures.

Nuclear magnetic resonance spectroscopy (NMR)

Proton, carbon, and phosphorus NMR spectra were recorded on Bruker AV-500 or Bruker AV-400 spectrometers in deuterated solvents at room temperature (298 K). Proton chemical shifts are reported in ppm (δ) relative to tetramethylsilane with the solvent resonance employed as the internal standard (C_6D_6, δ 7.16 ppm; DMSO-d_6, δ 2.49 ppm; CD_2Cl_2, δ 5.32 ppm; $CDCl_3$, δ 7.24 ppm; acetone-d_6, δ 2.04 ppm). ^{31}P chemical shifts are reported in ppm

relative to H_3PO_4 as the external standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. Slight shape deformation of the peaks in some cases due to weak coupling is not explicitly mentioned. ^{13}C chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (C_6D_6, δ 128.06 ppm; DMSO-d_6, δ 39.5 ppm; CD_2Cl_2, 53.8 ppm; $CDCl_3$, δ 77.0 ppm; acetone-d_6, δ 206.0, 29.8 ppm).

Mass spectrometry (MS)

Mass spectra were measured on a Finnigan MAT 8200 (70 eV) or MAT 8400 (70 eV) by electron ionization, chemical ionization or fast atom/ion bombardment techniques. Electrospray ionization (ESI) mass spectra were recorded on a Bruker ESQ 3000 spectrometer. High resolution mass spectra were obtained on a Finnigan MAT 95 or Bruker APEX III FT-MS (7 T magnet). All masses are given in atomic units/elementary charge (*m*/*z*).

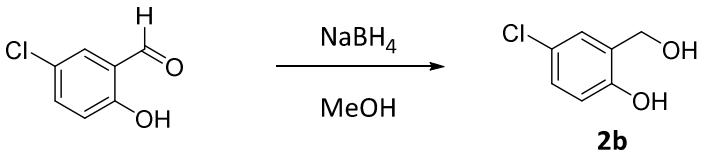
Specific rotation

Optical rotations were determined with Autopol IV automatic polarimeter (Rudolph Research Analytical) using a 50 mm cell with temperature control. The measurements were performed at 25 °C at a wavelength λ = 589 nm (sodium D-line) unless indicated. Concentrations (c) are given in g/100 ml.

7.2. Catalytic asymmetric acetalization

7.2.1. Starting materials

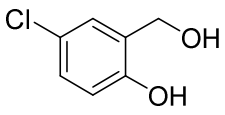
Representative procedure for compounds 2b-e



2b

To a solution of 5-chloro-2-hydroxybenzaldehyde (0.5 g, 3.19 mmol) in methanol (5 ml) at 0 °C was added $NaBH_4$ (0.24 g, 6.39 mmol) and the mixture was allowed to stir at 0 °C for 30 min. The reaction mixture was quenched with H_2O and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated.

4-chloro-2-(hydroxymethyl)phenol (2b)



Purification: 30% EtOAc/hexane.

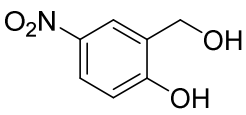
Yield: White solid, 0.41 g, 81%.

^{1}H NMR (500 MHz, C_6D_6) δ 7.34 (s, 1H), 6.95 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.63 (m, 2H), 3.95 (d, *J* = 5.0 Hz, 2H).

^{13}C NMR (125 MHz, C_6D_6) δ 155.5, 129.1, 127.5, 126.3, 124.5, 118.2, 64.0.

HRMS (EI (DE)) m/z calculated for $C_7H_7O_2Cl$ (M) 158.0135, found 158.0135.

2-(hydroxymethyl)-4-nitrophenolphenol (2c)



Purification: 30% EtOAc/hexane.

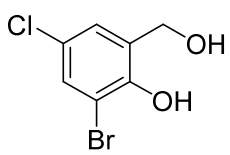
Yield: Yellow solid, 0.42 g, 83%.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.08 (brs, 1H), 8.21 (s, 1H), 8.02 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.93 (d, *J* = 8.9 Hz, 1H), 5.39 (brs, 1H), 4.50 (s, 2H).

^{13}C NMR (125 MHz, DMSO-d_6) δ 160.5, 139.6, 130.3, 124.1, 122.7, 114.7, 57.4.

HRMS (EI (DE)) m/z calculated for $C_7H_7N_1O_4$ (M) 169.0375, found 169.0374.

2-bromo-4-chloro-6-(hydroxymethyl)phenol (2d)



Purification: 30% EtOAc/hexane.

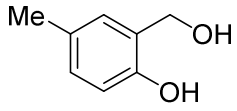
Yield: White solid, 0.39 g, 77%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 2.5 Hz 1H), 7.15 (d, *J* = 2.4 Hz, 1H), 6.77 (s, 1H), 4.77 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 131.0, 128.2, 127.4, 125.5, 110.7, 62.5.

HRMS (ESI+) *m/z* calculated for $C_7H_6Br_1Cl_1Na$ ($M+Na^+$) 258.9132, found 258.9132.

2-(hydroxymethyl)-4-methylphenol (2e)



Purification: 30% EtOAc/hexane.

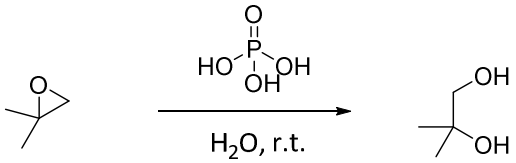
Yield: White solid, 0.37 g, 72%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05-6.95 (m, 1H), 6.84 (s, 1H), 6.78 (d, *J* = 8.1 Hz, 1H), 5.08 (s, 1H), 4.81 (s, 1H), 2.26 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 130.1, 130.0, 129.4, 128.6, 116.5, 64.8, 20.5.

HRMS (EI (DE)) m/z calculated for $C_8H_{10}O_2$ (M) 138.0681, found 138.0682.

Procedure for compounds 2n[164]



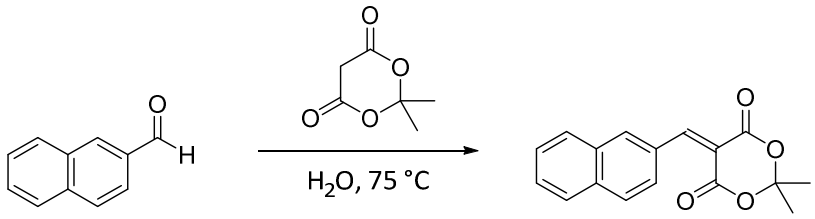
To a solution of the epoxide (3.7 ml, 41.6 mmol) in water (75 ml) was added 7 drops of phosphoric acid and the mixture was stirred overnight at room temperature. Solid $NaHCO_3$ was added until pH 7 and then the mixture was evaporated. EtOAc was added to the residue mixture, which was then dried (Na_2SO_4), filtered, and concentrated. No further purification was required.

Yield: Colorless oil, 3.1 g, 83%.

^{1}H NMR (500 MHz, C_6D_6) δ 3.20 (s, 2H), 2.49 (brs, 2H), 1.05 (s, 6H).

^{13}C NMR (125 MHz, C_6D_6) δ 71.1, 70.8, 25.8.

Procedure for compounds 3j[165]

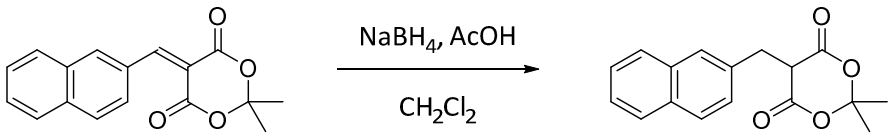


To a solution of Meldrum's acid (3.6 g, 25 mmol) in water (50 ml) was added 2-naphthaldehyde (4.3 g, 27.5 mmol). The reaction mixture was stirred at 75 °C for 2 h. After cooling, the reaction mixture was filtered and washed with water and hexane. The resulting solid was recrystallized from warm ethanol.

Yield: White solid, 2.39 g, 34%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.56 (s, 1H), 8.13 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.95 (d, *J* = 7.9 Hz 1H), 7.91-7.84 (m, 2H), 7.68-7.51 (m, 2H), 1.84 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.6, 160.1, 158.3, 137.2, 135.8, 132.8, 129.9, 129.6, 129.5, 128.5, 128.2, 127.9, 127.2, 114.5, 104.7, 27.8.

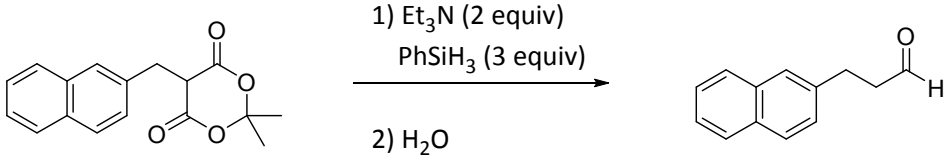


$NaBH_4$ (0.48 g, 12.7 mmol) was added in small portions to a solution of Meldrum's acid derivative (1.2 g, 4.3 mmol) and glacial acetic acid (6 ml) in CH_2Cl_2 (60 ml) at 0 °C. The reaction mixture was stirred for 1 hour at room temperature. The reaction mixture was diluted with CH_2Cl_2 and washed with brine and water. The organic phase was extracted, dried ($MgSO_4$) and concentrated.

Yield: White solid, 1.15 g, 95%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85-7.73 (m, 4H), 7.50-7.41 (m, 3H), 3.84 (t, *J* = 5.0 Hz, 1H), 3.66 (d, *J* = 5.0 Hz, 2H), 1.73 (s, 3H), 1.50 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 134.9, 133.5, 132.6, 128.7, 128.4, 128.0, 128.0, 127.7, 126.3, 126.0, 105.4, 48.4, 32.3, 28.6, 27.3.



To a solution of Meldrum's acid derivative (1.1 g, 4.1 mmol) in THF (24 ml) was added Et_3N (1.1 ml, 8.1 mmol) followed by $PhSiH_3$ (1.5 ml, 12.0 mmol). The reaction mixture was stirred for 2 hours at room temperature. Water (4 ml) was added to the reaction mixture and stirred for 15 min, then diluted with Et_2O, and washed with water and brine. The organic phase was extracted, dried ($MgSO_4$), filtered and concentrated.

Purification: 10% EtOAc/hexane.

Yield: White solid, 0.48 g, 65%.

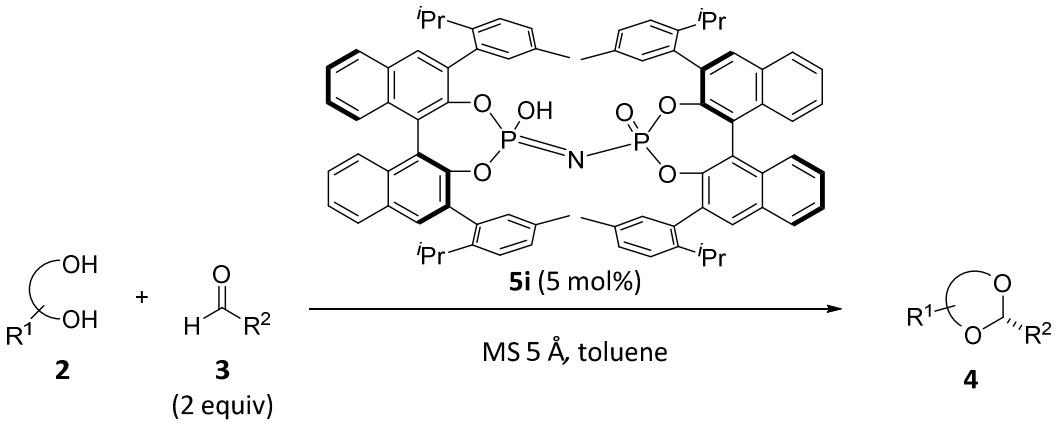
^{1}H NMR (500 MHz, C_6D_6) δ 9.27 (t, *J* = 1.2 Hz, 1H), 7.65-7.60 (m, 2H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.33 (s, 1H), 7.31-7.22 (m, 2H), 7.00 (dd, *J* = 8.4, 1.7 Hz, 1H), 2.71 (t, *J* = 7.6 Hz, 2H), 2.14-2.07 (m, 2H).

^{13}C NMR (125 MHz, C_6D_6) δ 199.7, 138.4, 134.2, 132.7, 128.4, 128.3, 128.0, 127.3, 126.9, 126.3, 125.7, 45.1, 28.3.

HRMS (EI (DE)) m/z calculated for $C_{13}H_{12}O$ (M) 184.0888, found 184.0889.

7.2.2. Products

General procedure for the catalytic asymmetric acetalization



The aldehyde (0.4 mmol) was added to a mixture of diol (0.2 mmol), catalyst **5i** (0.01 mmol, 5 mol%), and 5 Å molecular sieves (40 mg) in toluene (2 ml). The mixture was stirred vigorously at room temperature unless otherwise specified, for the indicated time and then treated with triethylamine (50 µl). Purification was performed by column chromatography on silica gel using EtOAc/hexanes or Et_2O/pentane (for volatile products) as the eluents. The absolute configuration of acetals **4j** and **4x** was determined by single crystal X-ray analysis. The absolute configurations of the other products were assigned by analogy.

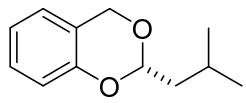
Preparation of the racemates

The samples of racemic products for HPLC/GC analysis were prepared from diol (0.05 mmol), aldehyde (0.1 mmol), and $(PhO)_2PO_2H$ (10 mol%) as the catalyst in toluene (0.5 ml) and isolated by thin layer chromatography using EtOAc/hexanes as the eluent.

Optimization

The small-scale reactions in Table 4.1 and Table 4.2 of the manuscript were performed with 0.05 mmol of the diol and after designated times quenched by adding a few drops of triethylamine. The samples for HPLC analysis were isolated by thin layer chromatography using EtOAc/hexanes as the eluent.

(*S*)-2-isobutyl-4*H*-benzo[*d*][1,3]dioxine (4a)



Reaction time: 2 days. Purification: 5% EtOAc/hexane.

Yield: Colorless oil, 33.1 mg, 86%. $[\alpha]^{25}_{D}$ = -112.8 (*c* 1.07, CH_2Cl_2).

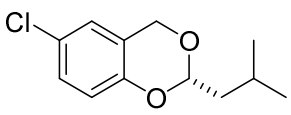
^{1}H NMR (500 MHz, C_6D_6) δ 6.98-6.93 (m, 2H), 6.75-6.72 (m, 1H), 6.57-6.55 (m, 1H), 4.89 (t, *J* = 5.5 Hz, 1H), 4.57-4.51 (m, 2H), 2.00-1.96 (m, 1H), 1.81-1.79 (m, 2H), 0.88 (d, *J* = 3.3 Hz, 3H), 0.87 (d, *J* = 3.3 Hz, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 153.9, 128.2, 125.2, 121.6, 121.0, 117.1, 99.4, 66.5, 43.6, 24.1, 23.0, 22.9.

HRMS (EI (FE)) *m/z* calculated for $C_{12}H_{16}O_2$ (M) 192.1150, found 192.1148.

HPLC (OJ-H), n-heptane/i-PrOH 99:1, 0.5 ml/min, λ = 254 nm, t_{major} = 10.58 min, t_{minor} = 13.75 min, er = 96:4.

(*S*)-6-chloro-2-isobutyl-4*H*-benzo[*d*][1,3]dioxine (4b)



Reaction time: 4 days. Purification: 5% EtOAc/hexane.

Yield: Colorless oil, 37.3 mg, 82%. $[\alpha]^{25}_{D}$ = -142.8 (*c* 1.39, CH_2Cl_2).

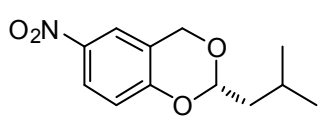
^{1}H NMR (500 MHz, C_6D_6) δ 6.88 (dd, *J* = 2.5, 8.7 Hz, 1H), 6.62 (d, *J* = 7.8 Hz, 1H), 6.47-6.46 (m, 1H), 4.72 (t, *J* = 5.4 Hz, 1H), 4.27 (s, 2H), 1.98-1.89 (m, 1H), 1.74-1.72 (m, 2H), 0.86 (d, *J* = 3.8 Hz, 3H), 0.85 (d, *J* = 3.8 Hz, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 152.2, 125.9, 125.2, 122.9, 118.3, 99.5, 65.9, 43.4, 24.0, 23.0, 22.9.

HRMS (EI (FE)) *m/z* calculated for $C_{12}H_{15}O_2Cl$ (M) 226.0761, found 226.0760.

HPLC (OJ-H), n-heptane/i-PrOH 99:1, 0.5 ml/min, λ = 220 nm, t_{major} = 11.09 min, t_{minor} = 14.20 min, er = 95:5.

(*S*)-2-isobutyl-6-nitro-4*H*-benzo[*d*][1,3]dioxine (4c)



Reaction time: 10 days at 50 °C. Purification: 5% EtOAc/hexane.

Yield: Yellow oil, 48.19 mg, 93%. $[\alpha]^{25}_{D}$ = -141.999 (*c* 1.72, CH_2Cl_2).

^{1}H NMR (500 MHz, C_6D_6) δ 7.74-7.71 (m, 1H), 7.38-7.37 (m, 1H),

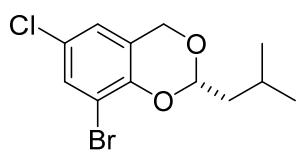
6.44 (d, *J* = 9.0 Hz, 1H), 4.61 (t, *J* = 5.3 Hz, 1H), 4.13-4.06 (m, 2H), 1.91-1.83 (m, 1H), 1.67-1.64 (m, 2H), 0.83 (d, *J* = 4.1 Hz, 3H), 0.82 (d, *J* = 4.1 Hz, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 158.2, 141.8, 124.1, 121.7, 121.2, 117.0, 100.1, 65.8, 43.1, 23.9, 22.9, 22.7.

HRMS (ESI+) *m/z* calculated for $C_{12}H_{15}NO_4Na$ ($M+Na^+$) 260.0893, found 260.0892.

HPLC (AD-3), n-heptane/i-PrOH 99.5:0.5, 1.0 ml/min, λ = 220 nm, t_{major} = 9.80 min, t_{minor} = 8.71 min, er = 94.5:5.5.

(*S*)-8-bromo-6-chloro-2-isobutyl-4*H*-benzo[*d*][1,3]dioxine (4d)



Reaction time: 5 days at 50 °C. Purification: 5% EtOAc/hexane.

Yield: Yellow oil, 36.47 mg, 60%.

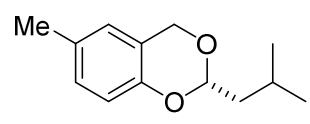
^{1}H NMR (500 MHz, C_6D_6) δ 7.25 (d, *J* = 2.4 Hz, 1H), 6.27-6.20 (m, 1H), 4.59 (t, *J* = 5.5 Hz, 1H), 4.10 (d, *J* = 3.5 Hz, 2H), 2.04-1.85 (m, 1H), 1.81-1.60 (m, 2H), 0.86 (dd, *J* = 6.7, 3.4 Hz, 6H).

^{13}C NMR (125 MHz, C_6D_6) δ 149.2, 131.2, 126.1, 124.2, 123.8, 111.5, 100.4, 65.6, 43.1, 24.1, 23.0, 22.8.

HRMS (EI (DE)) *m/z* calculated for C12H14O2BrCl (M) 303.9866, found 303.9864.

HPLC (OJ-H), n-heptane/i-PrOH 99:1, 1.0 ml/min, λ = 220 nm, t_{major} = 9.59 min, t_{minor} = 11.53 min, er = 92:8.

(*S*)-2-isobutyl-6-methyl-4*H*-benzo[*d*][1,3]dioxine (4e)



Reaction time: 8 days at 50 °C. Purification: 5% EtOAc/hexane.

Yield: Yellow oil, 25.30 mg, 61%.

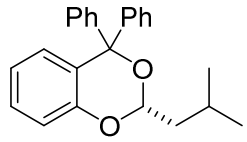
^{1}H NMR (500 MHz, C_6D_6) δ 6.93-6.87 (m, 1H), 6.78 (d, *J* = 8.3 Hz, 1H), 6.34 (s, 1H), 4.93 (t, *J* = 5.4 Hz, 1H), 4.58 (q, *J* = 14.5 Hz, 2H), 2.06 (d, *J* = 4.1 Hz, 3H), 2.05-1.98 (m, 1H), 1.86-1.79 (m, 2H), 0.89 (dd, *J* = 6.7, 3.3 Hz, 6H).

^{13}C NMR (125 MHz, C_6D_6) δ 151.7, 130.0, 128.8, 125.5, 121.2, 116.8, 99.4, 66.5, 43.7, 24.1, 23.0, 23.0, 20.6.

HRMS (EI (FE)) *m/z* calculated for $C_{13}H_{18}O_2$ (M) 206.1307, found 206.1306.

HPLC (OJ-H), n-heptane/i-PrOH 98:2, 0.5 ml/min, λ = 205 nm, t_{major} = 9.83 min, t_{minor} = 14.09 min, er = 94:6.

(*R*)-2-isobutyl-4,4-diphenyl-4*H*-benzo[*d*][1,3]dioxine (4f)



Reaction time: 2 days at 50 °C.

Purification: 5% EtOAc/hexane.

Yield: White solid, 30.0 mg, 44%.

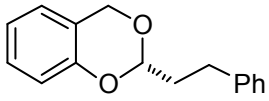
^{1}H NMR (500 MHz, C_6D_6) δ 7.47-7.40 (m, 4H), 7.12-6.98 (m, 7H), 6.98-6.93 (m, 1H), 6.89 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.66-6.59 (m, 1H), 5.23 (dd, *J* = 6.7, 4.1 Hz, 1H), 2.02-1.84 (m, 2H), 1.80-1.66 (m, 1H), 0.80 (d, *J* = 6.6 Hz, 3H), 0.63 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 153.3, 146.8, 145.1, 130.3, 129.9, 128.8, 128.7, 127.7, 126.0, 120.5, 117.6, 94.8, 84.8, 65.9, 43.8, 23.8, 23.4, 22.3, 15.6.

HRMS (ESI+) *m/z* calculated for $C_{24}H_{24}O_2Na$ ($M+Na^+$) 367.1669, found 367.1665.

HPLC (OD-H), n-heptane/i-PrOH 99.5:0.5, 0.5 ml/min, λ = 220 nm, t_{major} = 7.08 min, t_{minor} = 7.75 min, er = 79:21.

(*S*)-2-phenethyl-4*H*-benzo[*d*][1,3]dioxine (4g)



Reaction time: 4 days. The excess of aldehyde was reduced by adding MeOH (0.5 ml) and $NaBH_4$ (4 mg) to facilitate the purification.

Purification: 5% EtOAc/hexane.

Yield: Colorless oil, 39.8 mg, 83%. $[\alpha]^{25}_D$ = -94.7 (*c* 1.21, CH_2Cl_2).

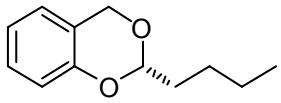
^{1}H NMR (500 MHz, C_6D_6) δ 7.15-7.12 (m, 2H), 7.08-7.04 (m, 3H), 7.00-6.93 (m, 2H), 6.75-6.71 (m, 1H), 6.54 (d, *J* = 7.7 Hz, 1H), 4.76 (t, *J* = 5.0 Hz, 1H), 4.53-4.47 (m, 2H), 2.81 (t, *J* = 8.0 Hz, 2H), 2.17-2.13 (m, 2H).

^{13}C NMR (125 MHz, C_6D_6) δ 153.7, 141.7, 128.8, 126.3, 125.2, 121.5, 121.1, 117.0, 99.2, 66.4, 36.4, 30.1.

HRMS (EI (DE)) *m/z* calculated for $C_{16}H_{16}O_2$ (M) 240.1150, found 240.1149.

HPLC (AD-3), n-heptane/i-PrOH 99:1, 1.0 ml/min, λ = 220 nm, t_{major} = 6.55min, t_{minor} = 5.30 min, er = 94.5:5.5.

(*S*)-2-butyl-4*H*-benzo[*d*][1,3]dioxine (4h)



Reaction time: 4 days. Purification: 5% EtOAc/hexane.

Yield: Colorless oil, 31.06 mg, 75%. $[\alpha]^{25}_{D}$ = -132.776 (*c* 1.56, CH_2Cl_2).

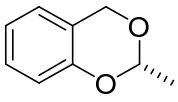
^{1}H NMR (500 MHz, C_6D_6) δ 6.98-6.94 (m, 2H), 6.75-6.72 (m, 1H), 6.56 (d, *J* = 7.8 Hz, 1H), 4.78 (t, *J* = 5.1 Hz, 1H), 4.59-4.52 (m, 2H), 1.88-1.84 (m, 2H), 1.52-1.46 (m, 2H), 1.27-1.20 (m, 2H), 0.84 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 153.9, 125.2, 121.5, 121.0, 117.1, 100.2, 66.5, 34.6, 26.1, 22.9, 14.2.

HRMS (EI (FE)) *m/z* calculated for $C_{12}H_{16}O_2$ (M) 226.0761, found 226.0760.

HPLC (OJ-H), n-heptane/i-PrOH 99:1, 0.5 ml/min, λ = 220 nm, t_{major} = 11.81 min, t_{minor} = 13.21 min, er = 93.5:6.5.

(*S*)-2-methyl-4*H*-benzo[*d*][1,3]dioxine (4i)



Reaction time: 15 hours. Purification: 5% EtOAc/hexane.

Yield: Colorless oil, 26.5 mg, 88%. $[\alpha]^{25}_{D}$ = -103.6 (*c* 0.94, CH_2Cl_2).

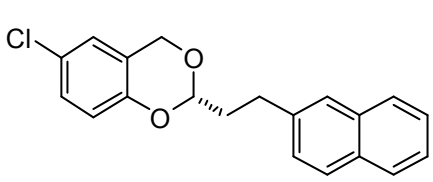
^{1}H NMR (500 MHz, C_6D_6) δ 6.97-6.91 (m, 2H), 6.74-6.71 (m, 1H), 6.54 (dd, *J* = 7.7, 0.5 Hz, 1H), 4.81 (q, *J* = 5.1 Hz, 1H), 4.54-4.47 (m, 2H), 1.40 (d, *J* = 5.1 Hz, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 153.8, 125.1, 121.3, 121.0, 117.0, 97.3, 66.4, 20.8.

HRMS (EI (FE)) *m/z* calculated for $C_9H_{10}O_2$ (M) 150.0681, found 150.0682.

HPLC (OD-3), n-heptane/i-PrOH 99.5:0.5, 1.0 ml/min, λ = 220 nm, t_{major} = 4.84 min, t_{minor} = 3.64 min, er = 87:13.

(*S*)-6-chloro-2-(2-(naphthalen-2-yl)ethyl)-4*H*-benzo[*d*][1,3]dioxine (4j)



Reaction time: 4 days. Purification: 5% EtOAc/hexane.

Yield: Colorless solid, 56.12 mg, 86%. $[\alpha]^{25}_{D}$ = -97.686 (*c* 1.25, CH_2Cl_2).

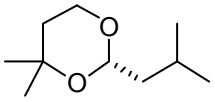
^{1}H NMR (500 MHz, C_6D_6) δ 7.70-7.54 (m, 3H), 7.49 (s, 1H), 7.33-7.17 (m, 3H), 6.88 (dd, *J* = 2.5, 8.7 Hz, 1H), 6.64 (d, *J* = 8.7 Hz, 1H), 6.49-6.40 (m, 1H), 4.62 (t, *J* = 5.1 Hz, 1H), 4.28 (d, *J* = 14.7 Hz, 1H), 4.23 (d, *J* = 14.7 Hz, 1H), 2.98-2.79 (m, 2H), 2.26-3.05 (m, 2H).

^{13}C NMR (125 MHz, C_6D_6) δ 152.1, 138.9, 134.3, 132.8, 128.5, 127.5, 127.0, 126.3, 126.0, 125.6, 125.3, 122.8, 118.3, 99.3, 65.9, 36.1, 30.1.

HRMS (EI(DE)) *m/z* calculated for $C_{20}H_{17}O_2Cl$ (M) 324.0917, found 324.0915.

HPLC (OD-3), n-heptane/i-PrOH 98:2, 1.0 ml/min, λ = 220 nm, t_{minor} = 7.00 min, t_{major} = 8.25 min, er = 91.5:8.5.

(*S*)-2-isobutyl-4,4-dimethyl-1,3-dioxane (4k)



Reaction time: 6 days at 50 °C. Purification: 5% Et_2O/pentane.

Yield: Colorless oil, 28.58 mg, 83%. $[\alpha]^{25}_D$ = -33.597 (*c* 0.51, CH_2Cl_2).

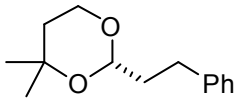
^{1}H NMR (500 MHz, C_6D_6) δ 4.83 (t, *J* = 5.4 Hz, 1H), 3.75-3.71 (m, 1H), 3.58-3.53 (m, 1H), 2.05-1.97 (m, 1H), 1.77-1.68 (m, 3H), 1.17 (s, 3H), 1.05 (s, 3H), 0.94 (s, 3H), 0.92 (s, 3H), 0.82-0.78 (m, 1H).

^{13}C NMR (125 MHz, C_6D_6) δ 94.9, 70.8, 63.0, 44.8, 36.1, 32.0, 24.3, 23.3, 23.0, 21.5.

HRMS (CI(FE) i-Butan) *m/z* calculated for $C_{10}H_{21}O_2$ (M+H) 173.1542, found 173.1540.

GC (Column: 30 m BGB-176/BGB-15 (2,3-dimethyl-6-tertbutyldimethylsilyl-β-cyclodextrin), i.D. 0.25 mm, df. 0.25 µl; Detector: FID; Temperature: injector 220 °C, detector 320 °C, oven 80 °C; gas: 0.4 bar H_2), t_{major} = 27.10 min, t_{minor} = 26.71 min, er = 96.5:3.5.

(*S*)-4,4-dimethyl-2-phenethyl-1,3-dioxane (4l)



Reaction time: 2 days. The excess of aldehyde was reduced by adding MeOH (0.5 ml) and $NaBH_4$ (4 mg) to facilitate the purification.

Purification: 5% EtOAc/hexane.

Yield: Colorless oil, 41.17 mg, 93%. $[\alpha]^{25}_D$ = -39.941 (*c* 1.35, CH_2Cl_2).

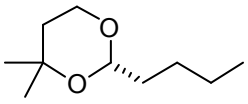
^{1}H NMR (500 MHz, C_6D_6) δ 7.15-7.11 (m, 4H), 7.07-7.03 (m, 1H), 4.68 (t, *J* = 5.0 Hz, 1H), 3.73-3.69 (m, 1H), 3.51-3.46 (m, 1H), 2.83-2.80 (m, 2H), 2.11-2.06 (m, 2H), 1.73-1.65 (m, 1H), 1.17 (s, 3H), 0.99 (s, 3H), 0.80-0.76 (m, 1H).

^{13}C NMR (125 MHz, C_6D_6) δ 142.5, 128.9, 128.7, 126.0, 94.9, 71.0, 62.9, 37.6, 36.1, 32.0, 30.7, 21.5.

HRMS (ESI+) *m/z* calculated for $C_{14}H_{20}O_2Na$ ($M+Na^+$) 243.1355, found 243.1353.

HPLC (AD-3), n-heptane/i-PrOH 99:1, 1.0 ml/min, λ = 220 nm, t_{major} = 4.51 min, t_{minor} = 3.92 min, er = 95.5:4.5.

(*S*)-2-butyl-4,4-dimethyl-1,3-dioxane (4m)



Reaction time: 2 days. Purification: 5% Et_2O/pentane.

Yield: Colorless oil, 32.2 mg, 86%. $[\alpha]^{25}_D$ = -36.557 (*c* 1.13, CH_2Cl_2).

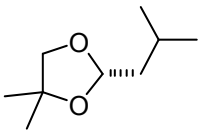
^{1}H NMR (500 MHz, C_6D_6) δ 4.73 (t, *J* = 5.1 Hz, 1H), 3.76-3.72 (m, 1H), 3.58-3.53 (m, 1H), 1.85-1.76 (m, 2H), 1.74-1.68 (m, 1H), 1.54-1.48 (m, 2H), 1.32-1.25 (m, 2H), 1.18 (s, 3H), 1.05 (s, 3H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.82-0.79 (m, 1H).

^{13}C NMR (125 MHz, C_6D_6) δ 95.9, 70.8, 63.0, 36.1, 35.8, 32.0, 26.8, 23.1, 21.6, 14.3.

HRMS (CI(FE) i-Butan) *m/z* calculated for $C_{10}H_{21}O_2$ (M+H) 173.1542. found 173.1541.

GC (Column: 30 m BGB-176/BGB-15 (2,3-dimethyl-6-tertbutyldimethylsilyl-β-cyclodextrin), i.D. 0.25 mm, df. 0.25 µl; Detector: FID; Temperature: injector 220 °C, detector 350 °C, oven 90 °C; gas: 0.5 bar H_2), t_{major} = 8.36 min, t_{minor} = 8.05 min, er = 97.5:2.5.

(*S*)-2-isobutyl-4,4-dimethyl-1,3-dioxolane (4n)



Reaction time: 22 hours at 0 °C. Purification: 5% Et_2O/pentane.

Yield: Colorless oil, 22.92 mg, 72%. $[\alpha]^{25}_D$ = -13.391 (*c* 0.58, CH_2Cl_2).

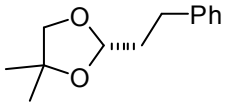
^{1}H NMR (500 MHz, C_6D_6) δ 5.10 (t, *J* = 5.1 Hz, 1H), 3.47 (d, *J* = 7.7 Hz, 1H), 3.31 (d, *J* = 7.7 Hz, 1H), 1.98-1.90 (m, 1H), 1.71-1.69 (m, 2H), 1.14 (s, 3H), 1.06 (s, 3H), 0.94 (d, *J* = 4.1 Hz, 3H), 0.93 (d, *J* = 4.1 Hz, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 103.4, 77.9, 76.2, 44.2, 27.2, 25.2, 24.9, 23.3, 23.2.

HRMS (CI(FE) i-Butan) *m/z* calculated for $C_9H_{19}O_2$ (M+H) 159.1385, found 159.1384.

GC (Column: 30 m BGB-176/BGB-15 (2,3-dimethyl-6-tertbutyldimethylsilyl-β-cyclodextrin), i.D. 0.25 mm, df. 0.25 µm; Detector: FID; Temperature: injector 220 °C, detector 320 °C, oven 60 °C; gas: 0.5 bar H_2), t_{major} = 15.45 min, t_{minor} = 15.13 min, er = 99.8:0.2.

(*S*)-4,4-dimethyl-2-phenethyl-1,3-dioxolane (4o)



Reaction time: 3 days. The excess of aldehyde was reduced by adding MeOH (0.5 ml) and $NaBH_4$ (4 mg) to facilitate the purification.

Purification: 5% EtOAc/hexane.

Yield: Colorless oil, 29.76 mg, 72%. $[\alpha]^{25}_D$ = +11.186 (*c* 0.59, CH_2Cl_2).

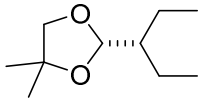
^{1}H NMR (500 MHz, C_6D_6) δ 7.15-7.08 (m, 4H), 7.07-7.01 (m, 1H), 5.01 (t, *J* = 4.6 Hz, 1H), 3.45 (d, *J* = 7.8 Hz, 1H), 3.20 (d, *J* = 7.70 Hz, 1H), 2.88-2.710 (m, 2H), 2.11-1.96 (m, 2H), 1.13 (s, 3H), 1.04 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 142.2, 128.8, 128.7, 126.1, 103.4, 78.2, 76.3, 36.9, 30.6, 27.0, 25.1.

HRMS (CI(DE) i-Butan) *m/z* calculated for $C_{13}H_{19}O_2$ (M+H) 207.1385, found 207.1385.

HPLC (OD-3), n-heptane/i-PrOH 99:1, 1.0 ml/min, λ = 220 nm, t_{major} = 6.44 min, t_{minor} = 7.36 min, er = 99:1.

(*S*)-4,4-dimethyl-2-(pentan-3-yl)-1,3-dioxolane (4p)



Reaction time: 10 days. Purification: 5% Et_2O/pentane.

Yield: Colorless oil, 30.66 mg, 82%. $[\alpha]^{25}_D$ = -11.421 (*c* 0.77, CH_2Cl_2).

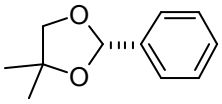
^{1}H NMR (500 MHz, C_6D_6) δ 4.99 (d, *J* = 4.6 Hz, 1H), 3.43 (d, *J* = 7.7 Hz, 1H), 3.31 (d, *J* = 7.7 Hz, 1H), 1.78-1.64 (m, 2H), 1.63-1.55 (m, 1H), 1.56-1.44 (m, 2H), 1.12 (s, 3H), 1.06 (s, 3H), 0.97 (dt, *J* = 2.3, 7.6 Hz, 6H).

^{13}C NMR (125 MHz, C_6D_6) δ 106.1, 77.8, 76.3, 45.3, 26.9, 25.1, 21.7, 21.6, 11.9, 11.8.

HRMS (CI(FE) i-Butan) *m/z* calculated for $C_{10}H_{21}O_2$ (M+H) 173.1542, found 173.1540.

GC (Column: 30 m BGB-176/BGB-15 (2,3-dimethyl-6-tertbutyldimethylsilyl-β-cyclodextrin), i.D. 0.25 mm, df. 0.25 µl; Detector: FID; Temperature: injector 220 °C, detector 320 °C, oven 80 °C; gas: 0.5 bar H_2) , t_{major} = 14.90 min, t_{minor} = 14.44 min, er = 99.5:0.5.

(*S*)-4,4-dimethyl-2-phenyl-1,3-dioxolane (4q)



Reaction time: 2 days. The excess of aldehyde was reduced by adding MeOH (0.5 ml) and $NaBH_4$ (4 mg) to facilitate the purification.

Purification: 10% Et_2O/pentane.

Yield: Colorless oil, 31.76 mg, 89%. $[\alpha]^{25}_D$ = +3.379 (*c* 0.95, CH_2Cl_2).

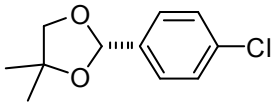
^{1}H NMR (500 MHz, C_6D_6) δ 7.60 (d, *J* = 7.5 Hz, 2H), 7.19-7.18 (m, 2H), 7.13-7.10 (m, 1H), 5.93 (s, 1H), 3.53 (d, *J* = 7.7 Hz, 1H), 3.42 (d, *J* = 7.7 Hz, 1H), 1.16 (s, 3H), 1.12 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 139.7, 129.0, 128.4, 127.0, 103.6, 79.0, 76.5, 26.7, 25.2.

HRMS (EI(FE)) *m/z* calculated for $C_{11}H_{14}O_2$ (M) 178.0994, found 178.0992.

HPLC (OD-H), n-heptane/i-PrOH 99:1, 0.5 ml/min, λ = 210 nm, t_{major} = 11.51 min, t_{minor} = 10.62 min, er = 95.5:4.5.

(*S*)-2-(4-chlorophenyl)-4,4-dimethyl-1,3-dioxolane (4r)



Reaction time: 62 hours. The excess of aldehyde was reduced by adding MeOH (0.5 ml) and $NaBH_4$ (4 mg) to facilitate the purification.

Purification: 10% EtOAc/hexane.

Yield: Colorless oil, 33.74 mg, 79%. $[\alpha]^{25}_D$ = +9.031 (*c* 1.06, CH_2Cl_2).

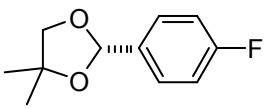
^{1}H NMR (500 MHz, C_6D_6) δ 7.30-7.28 (m, 2H), 7.13-7.11 (m, 2H), 5.75 (s, 1H), 3.45 (d, *J* = 7.8 Hz, 1H), 3.36 (d, *J* = 7.7 Hz, 1H), 1.10 (s, 3H), 1.09 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 138.2, 134.9, 128.7, 128.4, 102.8, 79.1, 76.4, 26.6, 25.1.

HRMS (EI(FE)) *m/z* calculated for $C_{11}H_{13}O_2Cl$ (M) 212.0604, found 212.0604.

HPLC (OD-H), n-heptane/i-PrOH 99.5:0.5, 0.5 ml/min, λ = 220 nm, t_{major} = 9.22 min, t_{minor} = 11.17 min, er = 98:2.

(*S*)-2-(4-fluorophenyl)-4,4-dimethyl-1,3-dioxolane (4s)



Reaction time: 42 hours. The excess of aldehyde was reduced by adding MeOH (0.5 ml) and $NaBH_4$ (4 mg) to facilitate the purification.

Purification: 10% EtOAc/hexane.

Yield: Colorless oil, 29.03 mg, 74%. $[\alpha]^{25}_{D}$ = +3.333 (*c* 0.24, CH_2Cl_2).

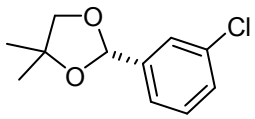
^{1}H NMR (500 MHz, C_6D_6) δ 7.38-7.34 (m, 2H), 6.83-6.78 (m, 2H), 5.78 (s, 1H), 3.48 (d, *J* = 7.6 Hz, 1H), 3.38 (d, *J* = 7.6 Hz, 1H), 1.12 (s, 3H), 1.10 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 163.6 (d, *J* = 247 Hz), 135.5 (d, *J* = 2.9 Hz), 128.9 (d, *J* = 8.2 Hz), 115.3 (d, *J* = 21.5 Hz), 102.9, 79.0, 76.4, 26.7, 25.1.

HRMS (EI(FE)) *m/z* calculated for $C_{11}H_{13}O_2F$ (M) 196.0900, found 196.0898.

HPLC (OJ-H), n-heptane/i-PrOH 95:5, 0.5 ml/min, λ = 220 nm, t_{major} = 21.99 min, t_{minor} = 24.58 min, er = 96:4.

(*S*)-2-(3-chlorophenyl)-4,4-dimethyl-1,3-dioxolane (4t)



For entry **4b** in Table 4.5; Reaction time: 4 days at 50 °C. The excess of aldehyde was reduced by adding MeOH (0.5 ml) and $NaBH_4$ (4 mg) to facilitate the purification.

Purification: 10% EtOAc/hexane.

Yield: Colorless oil, 36.06 mg, 85%. $[\alpha]^{25}_{D}$ = +6.315 (*c* 1.15, CH_2Cl_2).

^{1}H NMR (500 MHz, C_6D_6) δ 7.68-7.67 (m, 1H), 7.28 (d, *J* = 7.7 Hz, 1H), 7.08-7.06 (m, 1H), 6.83 (t, *J* = 7.9 Hz, 1H), 5.74 (s, 1H), 3.41 (d, *J* = 7.7 Hz, 1H), 3.34 (d, *J* = 7.8 Hz, 1H), 1.064 (s, 3H), 1.059 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 141.9, 134.6, 129.8, 129.1, 127.1, 125.0, 102.5, 79.3, 76.3, 26.5, 25.0.

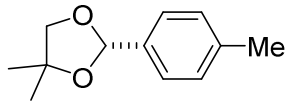
HRMS (EI(DE)) *m/z* calculated for $C_{11}H_{13}O_2Cl$ (M) 212.0604, found 212.0606.

HPLC (OD-H), n-heptane/i-PrOH 99.5:0.5, 0.5 ml/min, λ = 220 nm, t_{major} = 9.79 min, t_{minor} = 8.89, er = 95:5.

For entry **4a** in Table 4.5; Reaction time: 5 days at r.t.

Yield: 27.65 mg, 65%, $[\alpha]^{25}_{D}$ = +8.129 (*c* 0.99, CH_2Cl_2). er = 98.5:1.5.

(*S*)-4,4-dimethyl-2-(*p*-tolyl)-1,3-dioxolane (4u)



Reaction time: 27 hours. The excess of aldehyde was reduced by adding MeOH (0.5 ml) and $NaBH_4$ (4 mg) to facilitate the purification.

Purification: 10% EtOAc/hexane.

Yield: Colorless oil, 33.22 mg, 86%.

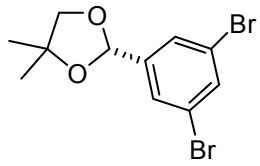
^{1}H NMR (500 MHz, C_6D_6) δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 7.8 Hz, 2H), 5.96 (s, 1H), 3.57 (d, *J* = 7.8 Hz, 1H), 3.44 (d, *J* = 7.8 Hz, 1H), 2.08 (s, 3H), 1.18 (s, 3H), 1.13 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 138.6, 136.8, 129.1, 127.1, 103.7, 78.8, 76.5, 26.9, 25.2, 21.2.

HRMS (ESI+) *m/z* calculated for $C_{12}H_{16}O_2Na$ (M+Na) 215.1042, found 215.1043.

HPLC (AS-H), n-heptane/i-PrOH 99.5:0.5, 0.5 ml/min, λ = 220 nm, t_{major} = 9.18 min, t_{minor} = 8.69 min, er = 88:12.

(*S*)-2-(3,5-dibromophenyl)-4,4-dimethyl-1,3-dioxolane (4v)



Reaction time: 6 days at 50 °C. The excess of aldehyde was reduced by adding MeOH (0.5 ml) and $NaBH_4$ (4 mg) to facilitate the purification.

Purification: 10% EtOAc/hexane.

Yield: Colorless oil, 55.47 mg, 83%. $[\alpha]^{25}_{D}$ = +7.62 (*c* 1.81, CH_2Cl_2).

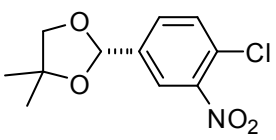
^{1}H NMR (500 MHz, C_6D_6) δ 7.57 (d, *J* = 1.9 Hz, 2H), 7.40 (t, *J* = 1.9 Hz, 1H), 5.52 (s, 1H), 3.29-3.24 (m, 2H), 1.01 (s, 3H), 0.97 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 143.7, 134.5, 128.7, 123.2, 101.4, 79.5, 76.0, 26.2, 24.9.

HRMS (EI(FE)) *m/z* calculated for $C_{11}H_{12}O_2Br_2$ (M) 333.9204, found 333.9201.

HPLC (OD-H), n-heptane/i-PrOH 99:1, 0.5 ml/min, λ = 220 nm, t_{major} = 8.25 min, t_{minor} = 7.81 min, er = 99.5:0.5.

(*S*)-2-(4-chloro-3-nitrophenyl)-4,4-dimethyl-1,3-dioxolane (4w)



Reaction time: 7 days at 60 °C. The excess of aldehyde was reduced by adding MeOH (0.5 ml) and $NaBH_4$ (4 mg) to facilitate the purification.

Purification: 10% EtOAc/hexane.

Yield: Colorless oil, 40.72 mg, 79%. $[\alpha]^{25}_{D}$ = +12.376 (*c* 1.66, CH_2Cl_2).

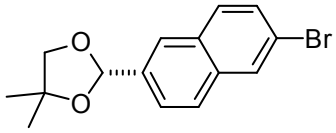
^{1}H NMR (500 MHz, C_6D_6) δ 7.75 (d, *J* = 1.9 Hz, 1H), 7.05 (dd, *J* = 1.9, 8.2 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 5.48 (s, 1H), 3.30-3.26 (m, 2H), 1.03 (s, 3H), 0.99 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 139.9, 131.6, 130.7, 127.1, 123.7, 101.2, 79.7, 76.2, 26.3, 24.9.

HRMS (ESI+) *m/z* calculated for $C_{11}H_{12}NO_4ClNa$ (M+Na) 280.0347, found 280.0350.

HPLC (OJ-H), n-heptane/i-PrOH 95:5, 0.5 ml/min, λ = 220 nm, t_{major} = 27.26 min, t_{minor} = 31.97 min, er = 97.5:2.5.

(*S*)-2-(6-bromonaphthalen-2-yl)-4,4-dimethyl-1,3-dioxolane (4x)



Reaction time: 52 hours. The excess of aldehyde was reduced by adding MeOH (0.5 ml) and $NaBH_4$ (4 mg) to facilitate the purification.

Purification: 10% EtOAc/hexane.

Yield: Colorless solid, 47.57 mg, 77%. $[\alpha]^{25}_D$ = +8.452 (*c* 1.82, CH_2Cl_2).

^{1}H NMR (500 MHz, C_6D_6) δ 7.82 (s, 1H), 7.73 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 1H), 7.22 (d, *J* = 8.7 Hz, 1H), 6.00 (s, 1H), 3.56 (d, *J* = 7.7 Hz, 1H), 3.46 (d, *J* = 7.7 Hz, 1H), 1.18 (s, 3H), 1.16 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 137.5, 135.2, 131.8, 130.3, 130.2, 129.7, 127.5, 126.3, 125.7, 120.6, 103.5, 79.3, 76.5, 26.7, 25.2.

HRMS (ESI+) *m/z* calculated for $C_{15}H_{15}O_2BrNa$ (M+Na) 329.0148, found 329.0150.

HPLC (AD), n-heptane/i-PrOH 99.5:0.5, 1.0 ml/min, λ = 220 nm, t_{major} = 9.63 min, t_{minor} = 8.42 min, er = 96.5:3.5.

7.2.3. X-Ray data for compounds 4j and 4x

Absolute configuration determination of **4j** by X-ray single-crystal structure analysis

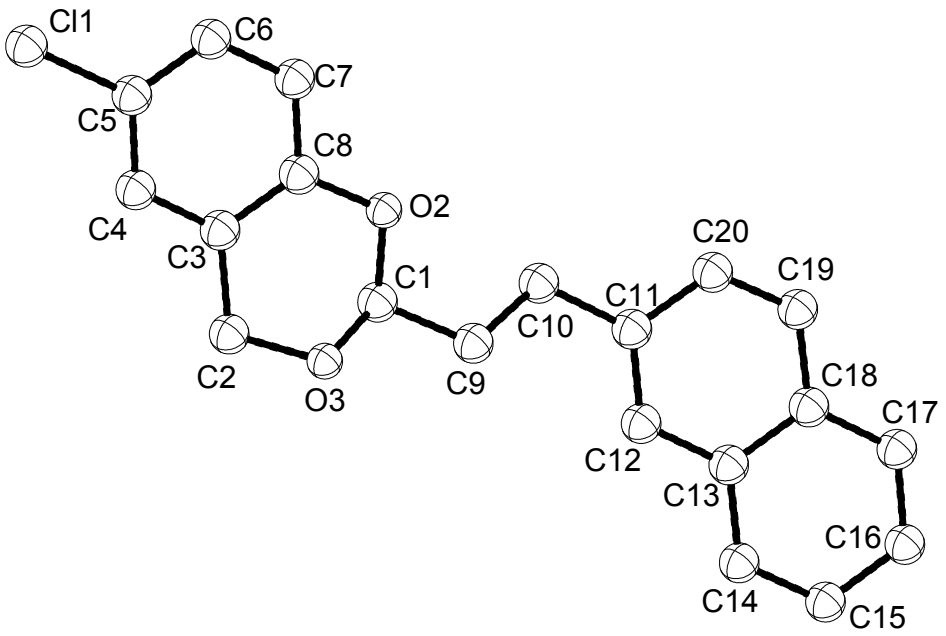


Figure 7.1. Single crystal structure of **4j.**

The crystals were grown in an open flask from an acetonitrile solution at 4 °C. X-ray crystallographic data have been deposited in the Cambridge Crystallographic Data Centre database (http://www.ccdc.cam.ac.uk/) under accession code CCDC 915231.

Crystal data and structure refinement for 4j.

Empirical formula	$C_{20}\ H_{17}\ Cl\ O_2$
Color	colourless
Formula weight	324.79 $g \cdot mol^{-1}$
Temperature	100 K
Wavelength	1.54178 Å
Crystal system	MONOCLINIC
Space group	c 2, (no. 5)

Unit cell dimensions	a = 21.464 (2) Å	α= 90°.
	b = 6.2342(6) Å	α= 126.357(4)°.
	c = 14.4025(14) Å	α= 90°.
Volume	1552.1(3) Å3	
Z	4	
Density (calculated)	1.390 $Mg \cdot m^{-3}$	
Absorption coefficient	2.231 mm^{-1}	
F(000)	680 e	
Crystal size	0.40 x 0.05 x 0.04 mm^3	
θ range for data collection	3.81 to 66.39°.	
Index ranges	-25 ≤ h ≤ 21, -7≤ k ≤ 7, -16 ≤ 1 ≤ 17	
Reflections collected	31210	
Independent reflections	2658 [R_{int} = 0.0464]	
Reflections with I>2σ(I)	2590	
Completeness to θ = 66.39°	99.4 %	
Absorption correction	Gaussian	
Max. and min. Transmission	0.92879 and 0.59764	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2658 / 1 / 208	
Goodness-of-fit on F^2	1.027	
Final R indices [I>2σ(I)]	R_1 = 0.0274	w R^2 = 0.0714
R indices (all data)	R_1 = 0.0282	w R^2 = 0.0721
Absolute structure parameter	-0.005(12)	
Largest diff. peak and hole	0.147 and -0.167 e · $Å^{-3}$	

Selected bond lengths [Å] and angles [°] for 4j.

C(1)-O(3)	1.404(2)	C(1)-O(2)	1.441(2)
C(1)-C(9)	1.505(2)	C(2)-O(3)	1.430(2)

C(2)-C(3)	1.509(2)	C(3)-C(4)	1.392(2)
C(3)-C(8)	1.395(2)	C(4)-C(5)	1.381(3)
C(5)-C(6)	1.394(3)	C(5)-Cl(1)	1.7491(17)
C(6)-C(7)	1.387(2)	C(7)-C(8)	1.395(2)
C(8)-O(2)	1.373(2)	C(9)-C(10)	1.524(3)
C(10)-C(11)	1.516(2)	C(11)-C(12)	1.373(2)
C(11)-C(20)	1.421(2)	C(12)-C(13)	1.417(2)
C(13)-C(14)	1.415(3)	C(13)-C(18)	1.424(3)
C(14)-C(15)	1.376(3)	C(15)-C(16)	1.411(3)
C(16)-C(17)	1.369(3)	C(17)-C(18)	1.421(2)
C(18)-C(19)	1.420(3)	C(19)-C(20)	1.366(3)

O(3)-C(1)-O(2)	110.09(13)	O(3)-C(1)-C(9)	108.37(14)
O(2)-C(1)-C(9)	109.49(13)	O(3)-C(2)-C(3)	110.29(14)
C(4)-C(3)-C(8)	119.33(16)	C(4)-C(3)-C(2)	121.76(16)
C(8)-C(3)-C(2)	118.86(15)	C(5)-C(4)-C(3)	119.71(16)
C(4)-C(5)-C(6)	121.46(16)	C(4)-C(5)-Cl(1)	119.29(14)
C(6)-C(5)-Cl(1)	119.20(14)	C(7)-C(6)-C(5)	118.92(16)
C(6)-C(7)-C(8)	120.01(16)	O(2)-C(8)-C(3)	121.85(15)
O(2)-C(8)-C(7)	117.59(15)	C(3)-C(8)-C(7)	120.54(15)
C(1)-C(9)-C(10)	113.47(14)	C(11)-C(10)-C(9)	113.77(15)
C(12)-C(11)-C(20)	118.33(16)	C(12)-C(11)-C(10)	122.78(17)
C(20)-C(11)-C(10)	118.87(15)	C(11)-C(12)-C(13)	121.80(17)
C(14)-C(13)-C(12)	121.82(18)	C(14)-C(13)-C(18)	118.85(15)
C(12)-C(13)-C(18)	119.31(16)	C(15)-C(14)-C(13)	120.93(17)
C(14)-C(15)-C(16)	120.05(18)	C(17)-C(16)-C(15)	120.49(17)
C(16)-C(17)-C(18)	120.71(18)	C(19)-C(18)-C(17)	122.96(17)
C(19)-C(18)-C(13)	118.03(16)	C(17)-C(18)-C(13)	118.95(16)
C(20)-C(19)-C(18)	121.05(16)	C(19)-C(20)-C(11)	121.42(16)
C(8)-O(2)-C(1)	112.99(12)	C(1)-O(3)-C(2)	110.17(13)

Absolute configuration determination of **4x** by X-ray single-crystal structure analysis

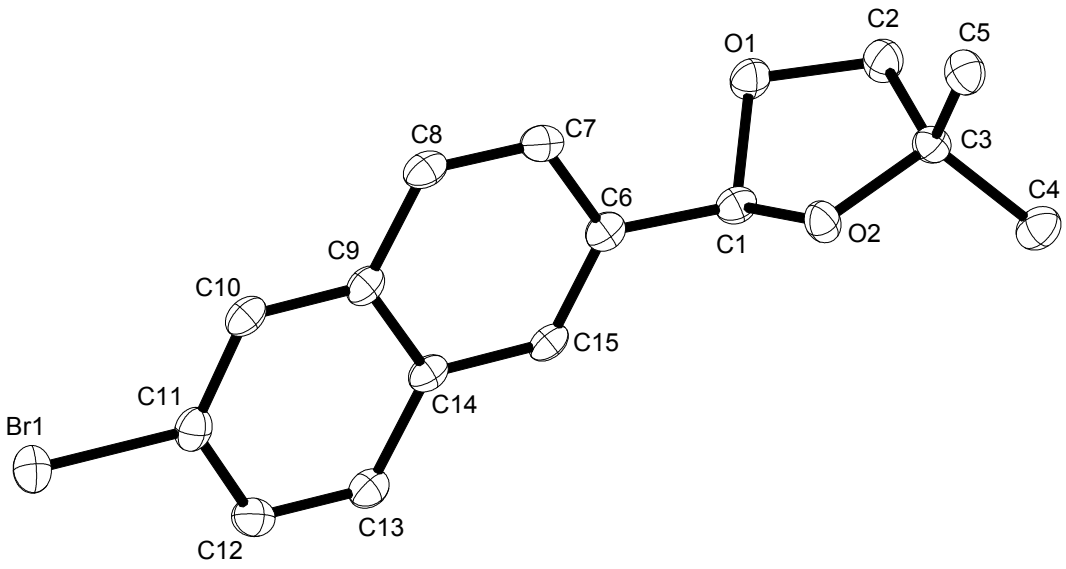


Figure 7.2. Single crystal structure of **4x**.

The crystals were grown in an open flask from a diethyl ether/hexane solution at 4 °C. X-ray crystallographic data have been deposited in the Cambridge Crystallographic Data Centre database (http://www.ccdc.cam.ac.uk/) under accession code CCDC 915232.

Crystal data and structure refinement for 4x.

Empirical formula	$C_{15}\ H_{15}\ Br\ O_2$
Color	colourless
Formula weight	307.18 $g \cdot mol^{-1}$
Temperature	100 K
Wavelength	1.54178 Å
Crystal system	ORTHORHOMBIC

Space group	p 21 21 21, (no. 19)	
Unit cell dimensions	a = 5.8173 (4) Å	α= 90°.
	b = 9.3911 (6) Å	α= 90°.
	c = 23.7120(16) Å	α= 90°.
Volume	1295.41(15) Å3	
Z	4	
Density (calculated)	1.575 $Mg \cdot m^{-3}$	
Absorption coefficient	4.251 mm^{-1}	
F(000)	624 e	
Crystal size	0.48 x 0.14 x 0.03 mm^3	
θ range for data collection	3.73 to 66.82°.	
Index ranges	$-6 \leq h \leq 6, -11 \leq k \leq 11, -28 \leq 1 \leq 28$	
Reflections collected	53866	
Independent reflections	2273 [R_{int} = 0.0398]	
Reflections with I>2σ(I)	2268	
Completeness to θ = 66.82°	99.6 %	
Absorption correction	Gaussian	
Max. and min. transmission	0.88120 and 0.31270	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2273 / 0 / 165	
Goodness-of-fit on F^2	1.136	
Final R indices [I>2σ(I)]	R_1 = 0.0184	w R^2 = 0.0480
R indices (all data)	R_1 = 0.0185	w R^2 = 0.0480
Absolute structure parameter	-0.014(14)	
Largest diff. peak and hole	0.217 and -0.239 e · $Å^{-3}$	

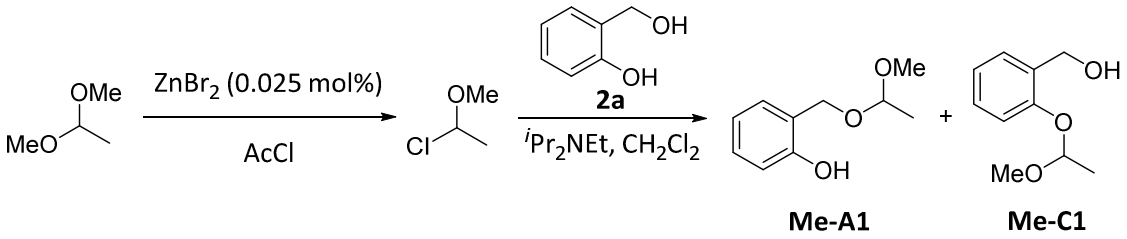
Bond lengths [Å] and angles [°] for 4x.

Br(1)-C(11)	1.9063(19)	C(1)-O(1)	1.413(2)
C(1)-O(2)	1.422(2)	C(1)-C(6)	1.503(3)
C(2)-O(1)	1.432(2)	C(2)-C(3)	1.547(3)
C(3)-O(2)	1.461(2)	C(3)-C(5)	1.513(3)
C(3)-C(4)	1.517(3)	C(6)-C(15)	1.370(3)
C(6)-C(7)	1.417(3)	C(7)-C(8)	1.363(3)
C(8)-C(9)	1.424(3)	C(9)-C(10)	1.417(3)
C(9)-C(14)	1.419(3)	C(10)-C(11)	1.365(3)
C(11)-C(12)	1.406(3)	C(12)-C(13)	1.370(3)
C(13)-C(14)	1.417(3)	C(14)-C(15)	1.417(3)
O(1)-C(1)-O(2)	105.29(13)	O(1)-C(1)-C(6)	111.53(15)
O(2)-C(1)-C(6)	109.82(14)	O(1)-C(2)-C(3)	104.86(14)
O(2)-C(3)-C(5)	107.06(14)	O(2)-C(3)-C(4)	109.50(15)
C(5)-C(3)-C(4)	111.97(16)	O(2)-C(3)-C(2)	102.63(13)
C(5)-C(3)-C(2)	113.44(16)	C(4)-C(3)-C(2)	111.67(15)
C(15)-C(6)-C(7)	119.89(17)	C(15)-C(6)-C(1)	119.77(15)
C(7)-C(6)-C(1)	120.33(16)	C(8)-C(7)-C(6)	120.21(17)
C(7)-C(8)-C(9)	121.13(17)	C(10)-C(9)-C(14)	119.35(17)
C(10)-C(9)-C(8)	121.95(17)	C(14)-C(9)-C(8)	118.70(17)
C(11)-C(10)-C(9)	119.24(17)	C(10)-C(11)-C(12)	122.55(18)
C(10)-C(11)-Br(1)	118.94(15)	C(12)-C(11)-Br(1)	118.51(14)
C(13)-C(12)-C(11)	118.69(18)	C(12)-C(13)-C(14)	121.24(18)
C(13)-C(14)-C(15)	122.25(17)	C(13)-C(14)-C(9)	118.92(17)
C(15)-C(14)-C(9)	118.83(17)	C(6)-C(15)-C(14)	121.20(17)
C(1)-O(1)-C(2)	103.50(14)	C(1)-O(2)-C(3)	106.55(12)

7.2.4. Mechanistic studies

(with I. Čorić)[67, 158]

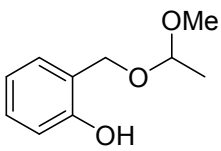
Procedure for compounds Me-A1 and Me-C1



2-((1-methoxyethoxy)methyl)phenol (Me-A1) and (2-(1-methoxyethoxy)phenyl)methanol (Me-C1)

Acetyl chloride (604 µl, 10 mmol) was added dropwise to a solution of zinc bromide (approximately 0.56 mg, 0.025 mol%) in 1,1-dimethoxyethane (1.06 ml, 10 mmol) under argon at room temperature. The temperature was maintained at room temperature with a water bath. After 2.5 h the mixture was added dropwise via syringe to the solution of diol **2a** (621 mg, 5 mmol) and *N*,*N*- diisopropylethylamine (5.2 ml, 30 mmol) in dichloromethane (25 ml) at 0 °C. After 13 h at room temperature, a concentrated aqueous solution of NH_4Cl (20 ml) was added and the resulting mixture stirred for 15 min. Water (20 ml) and MTBE (150 ml) were added and the organic layer was separated, washed with brine, dried ($MgSO_4$), filtered and concentrated. Chromatography on silica gel using EtOAc/hexane 10-30% as eluents yielded **Me-A1** (149 mg) and **Me-C1** (137 mg) as colorless oils.

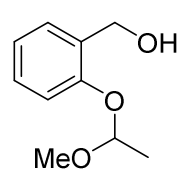
2-((1-methoxyethoxy)methyl)phenol (Me-A1)



^{1}H NMR (500 MHz, C_6D_6) δ 7.53 (s, 1H), 7.07 (td, *J* = 7.7, 1.5 Hz, 1H), 7.03 (dd, *J* = 8.0, 0.9 Hz, 1H), 6.92 (dd, *J* = 7.6 , 0.9 Hz, 1H), 6.75 (td, *J* = 7.3, 1.1 Hz, 1H), 4.56 (d, *J* = 12.2 Hz, 1H), 4.39 (d, *J* = 12.2 Hz, 1H), 4.33 (q, *J* = 5.3 Hz, 1H), 2.94 (s, 3H), 1.02 (d, *J* = 5.3 Hz, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 156.9, 129.8, 128.9, 123.4, 120.1, 117.0, 100.6, 66.3, 52.4, 19.0.

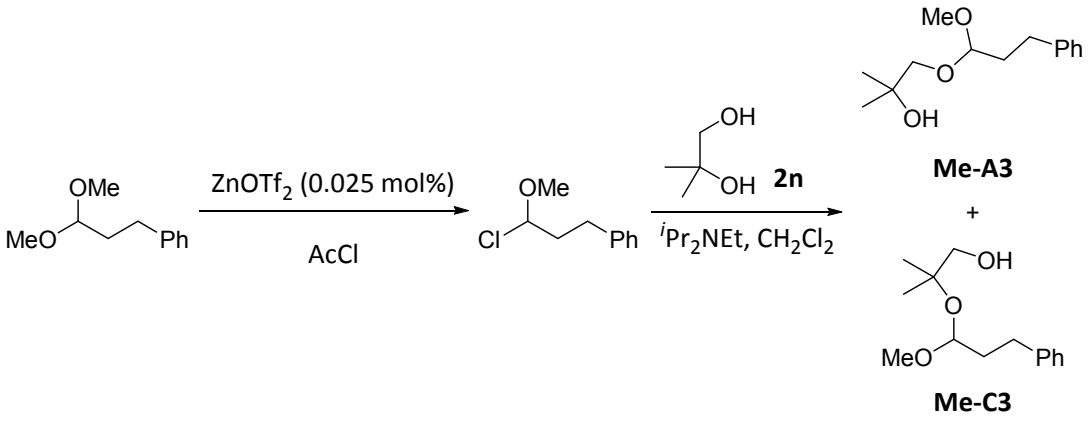
(2-(1-methoxyethoxy)phenyl)methanol (Me-C1)



^{1}H NMR (500 MHz, C_6D_6) δ 7.32 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.06 (td, *J* = 7.8 Hz, 1.5 Hz, 1H), 6.90-6.87 (m, 2H), 5.01 (q, *J* = 5.2 Hz, 1H), 4.75 (dd, *J* = 13.1, 2.0 Hz, 1H), 4.67 (dd, *J* = 13.2, 3.4 Hz, 1H), 3.01 (s, 3H), 2.36 (s, 1H), 1.21 (d, *J* = 5.2 Hz, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 155.2, 131.8, 128.9, 128.6, 122.2, 115.5, 100.8, 61.4, 52.8, 19.8.

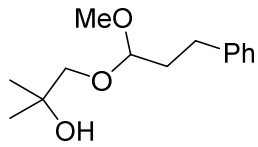
Procedure for compounds Me-A3 and Me-C3



1-(1-methoxy-3-phenylpropoxy)-2-methylpropan-2-ol (Me-A3) and 2-(1-methoxy-3-phenylpropoxy)-2-methylpropan-1-ol (Me-C3)

Acetyl chloride (302 µl, 5 mmol) was added dropwise to a solution of zinc triflate (approximately 0.43 mg, 0.025 mol%) in (3,3-dimethoxypropyl)benzene (901 mg, 5 mmol) under argon at room temperature. The temperature was maintained at room temperature with a water bath. After 30 min the mixture was added dropwise via syringe to the solution of diol **2n** (451 mg, 5 mmol) and *N*,*N*- diisopropylethylamine (2.6 ml, 15 mmol) in dichloromethane (12 ml) at 0 °C. After 14 h at room temperature, a concentrated aqueous solution of NH_4Cl (20 ml) was added and the resulting mixture stirred for 15 min. Water (10 ml) and MTBE (150 ml) were added and the organic layer was separated, washed with brine, dried ($MgSO_4$), filtered and concentrated. Chromatography on silica gel using EtOAc/hexane 10-20% as eluents yielded colorless oil (600 mg) containing **Me-A3** and **Me-C3** in a ratio 5:1. Repeating the chromatography with 200 g of silicagel and EtOAc/hexane 10-20% as eluents allowed the isolation of small amounts of pure isomers.

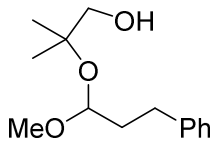
1-(1-methoxy-3-phenylpropoxy)-2-methylpropan-2-ol (Me-A3)



^{1}H NMR (500 MHz, C_6D_6) δ 7.16 (overlapped with solvent, 2H), 7.09-7.06 (m, 3H), 4.30 (t, *J* = 5.7 Hz, 1H), 3.26 (d, *J* = 9.1 Hz, 1H), 3.11 (d, *J* = 9.1 Hz, 1H), 3.08 (s, 3H), 2.60 (t, *J* = 7.8 Hz, 2H), 2.14 (s, 1H), 1.89-1.84 (m, 2H), 1.17 (s, 6H).

^{13}C NMR (125 MHz, C_6D_6) δ 142.0, 128.8, 126.3, 103.4, 74.2, 69.8, 52.7, 34.8, 31.3, 26.6, 26.5.

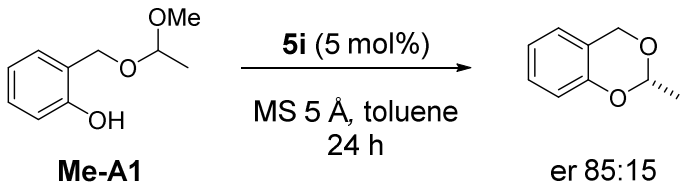
2-(1-methoxy-3-phenylpropoxy)-2-methylpropan-1-ol (Me-C3)



^{1}H NMR (500 MHz, C_6D_6) δ 7.15 (overlapped with solvent, 2H), 7.08- 7.05 (m, 3H), 4.53 (t, *J* = 5.3 Hz, 1H), 3.34 (d, *J* = 6.9 Hz, 2H), 3.12 (t, *J* = 6.9 Hz, 1H), 2.92 (s, 3H), 2.64-2.58 (m, 1H), 2.51-2.45 (m, 1H), 1.82-1.78 (m, 2H), 1.12 (s, 3H), 1.01 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 142.0, 128.7, 128.7, 126.2, 97.3, 77.1, 69.8, 49.8, 35.3, 31.3, 24.9, 21.9.

Representative procedure for reactions in Scheme 4.6



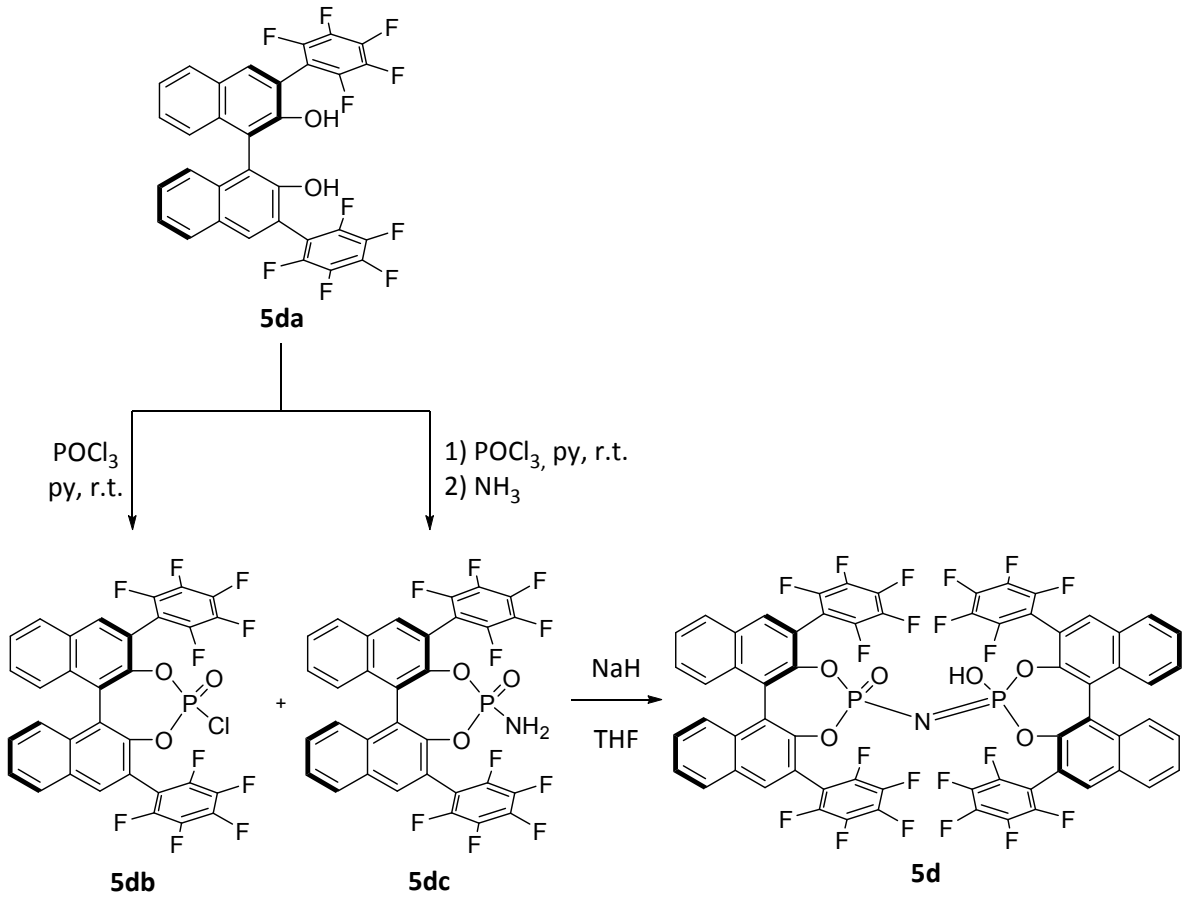
A solution of hydroxyacetal **Me-A1** (0.2 mmol) in toluene (2 ml) was added to a vial charged with catalyst **5i** (5 mol%) and 5 Å molecular sieves (40 mg) and the mixture was stirred at room temperature. After specific time, representative samples (ca. 300 µl) were removed from the mixture and quenched with a drop of Et_3N. Samples of the products were isolated by TLC and analyzed by HPLC to determine enantiomeric ratios.

The reactions with **Me-A3** and **Me-C3** were performed on a 0.05 mmol scale.

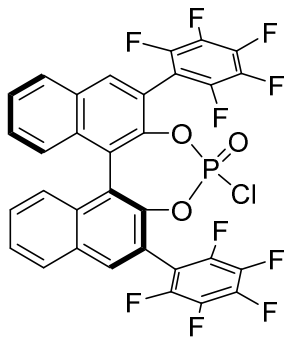
7.2.5. Synthesis of confined Brønsted acid

(with I. Čorić)[67]

5d (Derived from (*R*)-BINOL)



(*R*)-4-chloro-2,6-bis(perfluorophenyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide (5db)



To a solution of **5da** (480 mg, 0.78 mmol) in pyridine (2 ml) under argon, was added $POCl_3$ (217 µl, 357 mg, 2.33 mmol) at room temperature. The mixture was stirred for 18.5 h and then concentrated to dryness under vacuum. The residue was passed through a short silica gel column (5 g) using CH_2Cl_2 as the eluent yielding the title compound as a colorless solid (498 mg, 91%).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.19 (s, 1H), 8.18 (s, 1H), 8.10 (dd, *J* =

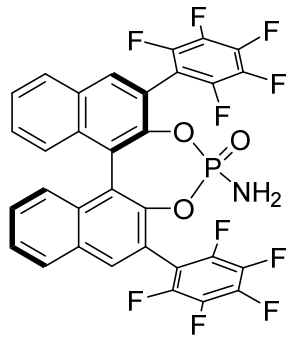
8.3, 2.9 Hz, 2H, two overlapped doublets), 7.68-7.65 (m, 2H), 7.53-7.47 (m, 4H).

^{13}C NMR (125 MHz, CD_2Cl_2) δ 144.2, 144.1, 144.0, 143.9, 134.9, 134.7, 133.11, 133.09, 132.1, 131.9, 129.4, 129.3, 128.9, 127.8, 127.5, 127.3, 122.92, 122.89, 122.88, 122.8, 118.8, 118.2 (heteronuclear coupling was not assigned).

^{31}P NMR (202 MHz, CD_2Cl_2): δ 8.68 (s).

HRMS (ESI+) m/z calculated for $C_{32}H_{10}O_3ClF_{10}PNa$ (M+Na) 720.9789, found 720.9792.

(*R*)-4-amino-2,6-bis(perfluorophenyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide (5dc)



To a solution of **5da** (345 mg, 0.56 mmol) in pyridine (1.7 ml) under argon was added $POCl_3$ (156 µl, 256 mg, 1.67 mmol) at room temperature. After 21.5 h, the mixture was cooled to –78 °C and anhydrous ammonia gas was condensed into the reaction flask (ca. 5 ml). The cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction mixture was then concentrated to dryness under vacuum. The residue was purified by chromatography on silica gel using CH_2Cl_2 as the eluent yielding the title compound as a colorless solid (153 mg, 40%).

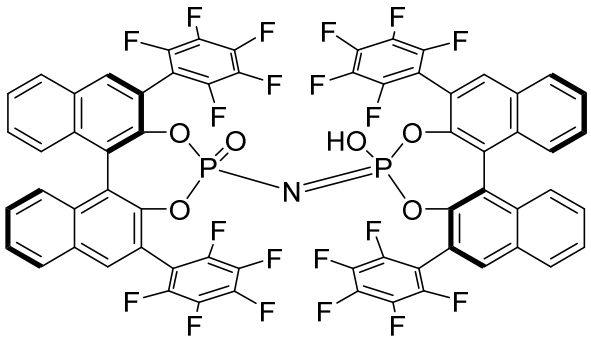
^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.13 (s, 1H), 8.09 (s, 1H), 8.07 (d, *J* = 8.3 Hz, 1H), 8.05 (d, *J* = 8.3 Hz, 1H), 7.64-7.60 (m, 2H), 7.51 (dd, *J* = 8.2, 3.4 Hz, 2H, two overlapped doublets) 7.48-7.45 (m, 2H), 3.16 (d, *J* = 7.44 Hz, 2H).

^{13}C NMR (125 MHz, CD_2Cl_2) δ 145.0, 144.9, 144.1, 144.0, 140.7 (m), 139.1 (m), 137.2 (m), 134.1, 133.9, 133.3, 133.2, 131.6, 131.5, 129.2, 129.1, 128.45, 128.39, 127.25, 127.20, 127.1, 127.0, 123.2, 123.1, 122.8, 122.7, 119.2, 119.0, 111.7 (m) (heteronuclear coupling was not assigned).

^{31}P NMR (202 MHz, CD_2Cl_2): δ 13.28 (s).

HRMS (ESI+) *m/z* calculated for $C_{32}H_{12}NO_3F_{10}PNa$ (M+Na) 702.0287, found 702.0283.

Imidodiphosphoric acid 5d



Sodium hydride (60% dispersion of in mineral oil, 24 mg, 0.60 mmol) was added to a solution of **5db** (169 mg, 0.24 mmol) and **5dc** (137 mg, 0.20 mmol) in THF (1.2 ml) under argon at room temperature. After 16 h at room temperature, water (10 ml) and 10% aqueous HCl solution (20 ml) were added and the mixture was extracted with CH_2Cl_2, washed with brine, filtered and concentrated. The residue was purified by column chromatography on silica gel using 0-14% EtOAc/DCM as the eluents giving a colorless solid. The solid was dissolved in CH_2Cl_2 (6 ml) and washed with 10% aqueous HCl (2·6 ml). The organic layer was concentrated under reduced pressure to give the title compound as a colorless solid (139 mg, 52%).

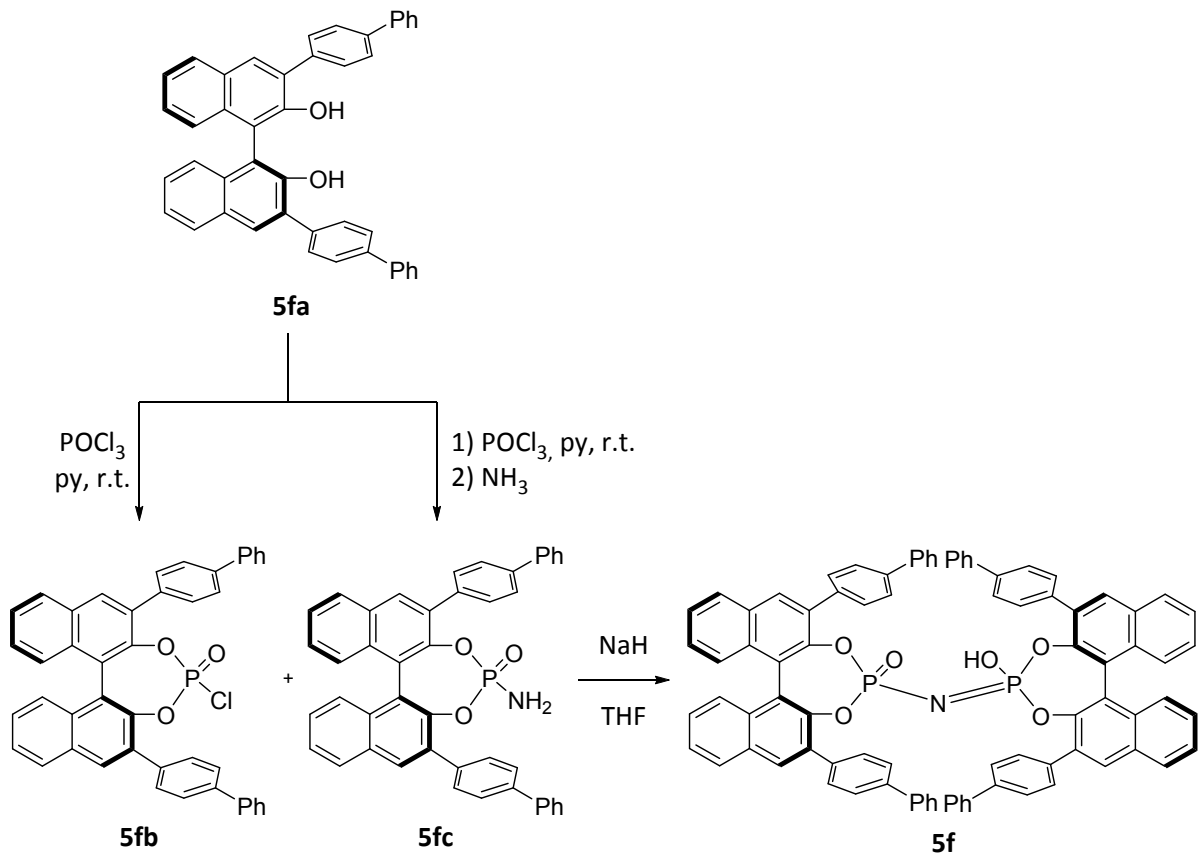
^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.07 (s, 2H), 8.03 (d, *J* = 7.7 Hz, 2H), 8.98 (d, *J* = 7.3 Hz, 2H), 7.78 (s, 2H), 7.64-7.57 (m, 6H), 7.50-7.40 (m, 9H, 6 C*H* + acidic *H* + H_2O).

^{13}C NMR (125 MHz, CD_2Cl_2) δ 145.9 (m), 145.5 (m), 145.0 (m), 144.0 (m), 143.6 (m), 142.4 (m), 140.4 (m), 139.2 (m), 138.7 (m), 136.7 (m), 133.6, 133.5, 133.4, 133.2, 131.6, 131.5, 129.1, 128.8, 128.2, 127.87, 127.86, 127.6, 127.4, 127.0, 126.6, 123.5, 122.5, 119.1, 111.9 (m), 111.4 (m) (heteronuclear coupling was not assigned).

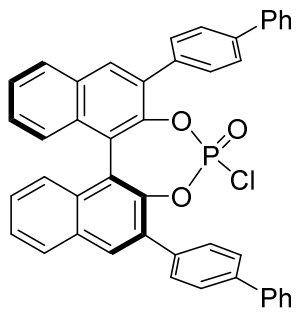
^{31}P NMR (202 MHz, CD_2Cl_2) δ 3.03 (s).

HRMS (ESI–) *m*/*z* calculated for $C_{64}H_{20}NO_6F_{20}P_2$ (M–H) 1340.0452, found 1340.0461.

5f



(*S*)-2,6-di([1,1'-biphenyl]-4-yl)-4-chlorodinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide (5fb)



To a solution of **5fa** (270 mg, 0.457 mmol) in pyridine (2 ml) under argon was added $POCl_3$ (128 µl, 210 mg, 1.37 mmol) at room temperature. The mixture was stirred for 18 h at room temperature and then concentrated to dryness under vacuum. The residue was passed through a short silica gel column (5 g) using DCM as the eluent yielding the title compound as a colorless solid (262 mg, 85%).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.23 (s, 1H), 8.20 (s, 1H), 8.08 (dd, *J* = 8.2, 3.4 Hz, 2H, two overlapped doublets), 7.87-7.84 (m, 2H), 7.81-7.76 (m, 6H), 7.73-7.70 (m, 4H), 7.62-7.58 (m, 2H), 7.50-7.45 (m, 5H), 7.42-7.36 (m, 5H).

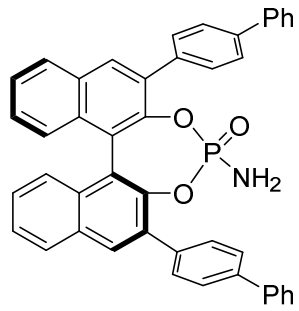
^{13}C NMR (125 MHz, CD_2Cl_2) δ 141.12, 141.06, 140.8, 140.7, 135.8, 135.7, 133.59, 133.57, 133.38, 133.35, 132.5, 132.4, 132.32, 132.27, 130.7, 130.6, 129.22, 129.21, 129.1, 129.0,

127.93, 127.88, 127.5, 127.41, 127.36, 127.3, 127.12, 127.07, 123.32, 123.29, 123.20, 123.18 (including signals due to unassigned C-P-coupling).

^{31}P NMR (202 MHz, CD_2Cl_2) δ 8.34 (s).

HRMS (ESI+) *m/z* calculated for $C_{44}H_{28}O_3ClPNa$ (M+Na) 693.1357, found 693.1356.

(*S*)-2,6-di([1,1'-biphenyl]-4-yl)-4-aminodinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide (5fc)



To a solution of **5fb** (120 mg, 0.18 mmol) in CH_2Cl_2 (2 ml) under argon at –78 °C, anhydrous ammonia gas was condensed (ca. 6 ml). The cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction mixture was passed through a short silica gel column (5 g) using DCM as the eluent yielding the title compound as a colorless solid (85 mg, 73%).

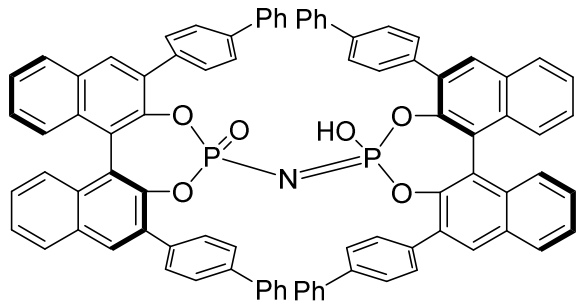
^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.19 (s, 1H), 8.14 (s, 1H), 8.05 (dd, *J* = 8.1, 3.9 Hz, 2H, two overlapped doublets), 7.92-7.89 (m, 2H), 7.84-7.81 (s, 2H), 7.78-7.74 (m, 4H), 7.72-7.69 (m, 4H), 7.58-7.54 (m, 2H), 7.50-7.44 (m, 5H), 7.40-7.34 (m, 5H), 2.76 (d, *J* = 7.0 Hz, 2H).

^{13}C NMR (125 MHz, CD_2Cl_2) δ 145.1, 145.0, 144.4, 144.3, 141.0, 140.9, 140.8, 140.7, 136.6, 136.4, 134.0, 133.9, 133.7, 133.6, 132.5, 132.3, 132.1, 132.0, 131.9, 131.7, 130.8, 130.6, 129.23, 129.18, 128.94, 128.88, 127.9, 127.8, 127.6, 127.40, 127.38, 127.3, 127.2, 127.12, 127.08, 126.53, 126.49, 123.65, 123.64, 123.11, 123.10 (including signals due to unassigned C-P-coupling).

^{31}P NMR (202 MHz, CD_2Cl_2) δ 12.1 (s).

HRMS (ESI+) *m/z* calculated for $C_{44}H_{30}NO_3PNa$ (M+Na) 674.1856, found 674.1860.

Imidodiphosphoric acid 5f



Sodium hydride (60% dispersion of in mineral oil, 15 mg, 0.37 mmol) was added to a solution of **5fb** (99 mg, 0.15 mmol) and **5fc** (80 mg, 0.123 mmol) in THF (2 ml) under argon at room temperature. After 3 days at room temperature, 10% aqueous HCl solution (5 ml) and DCM (5 ml) were added, and the mixture was stirred for 30 min. The organic layer was separated and the solvent was removed under reduced pressure. The residue was purified by column chromatography on aluminum oxide (activity IV) using 0-32% EtOAc/DCM as the eluents giving a colorless solid. The solid was dissolved in CH_2Cl_2 (5ml) and stirred with 3 N aqueous HCl (5 ml) for 2 h. The organic layer was separated and concentrated under reduced pressure to give the title compound as a colorless solid (77 mg, 49%).

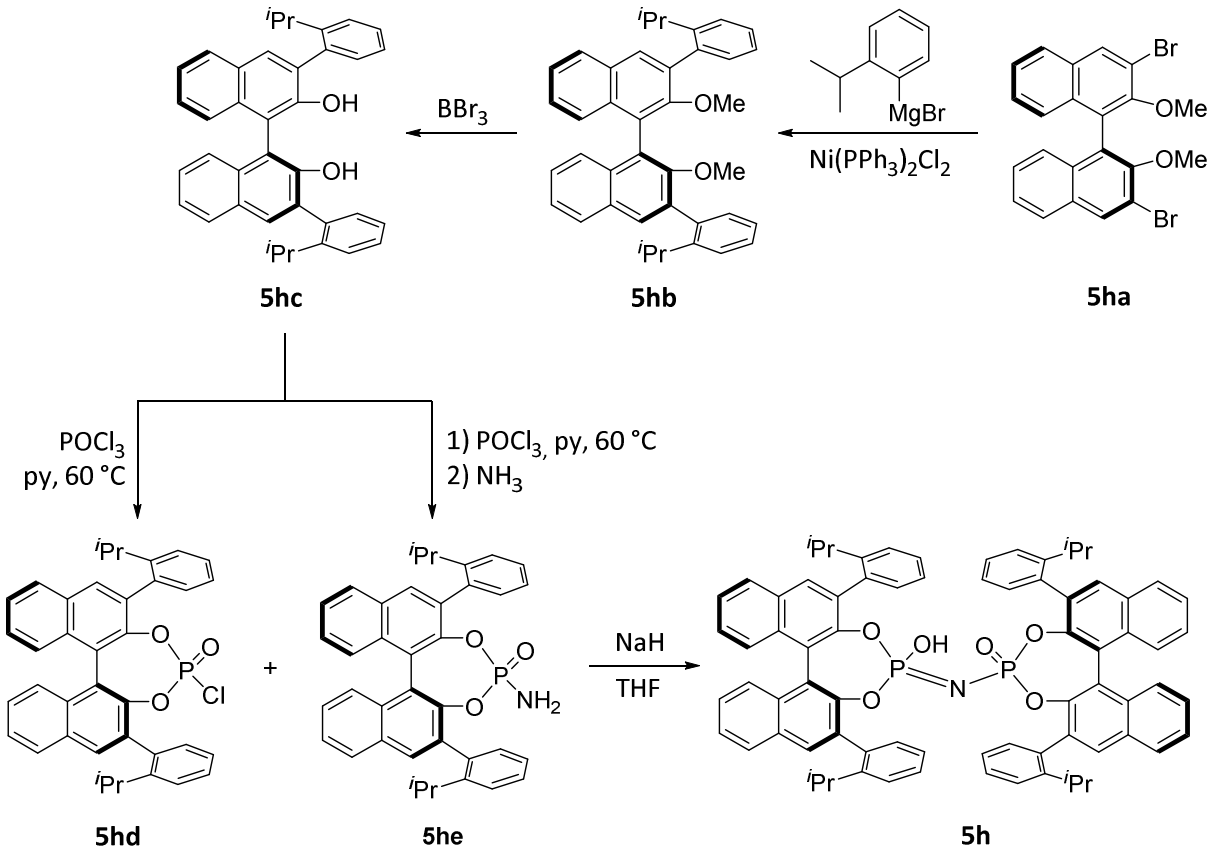
^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.21 (d, *J* = 7.4 Hz, 2H), 8.05-8.00 (m, 6H), 7.72 (t, *J* = 6.7 Hz, 2H), 7.61-7.49 (m, 16H), 7.41-7.38 (m, 10H), 7.31 (t, *J* = 7.3 Hz, 2H), 7.23-7.18 (m, 6H), 7.08 (bs, 4H), 6.88 (bs, 4H), 6.68 (bs, 4H), 3.78 (bs, 2.8H, acidic H + H_2O, overlapped).

^{13}C NMR (125 MHz, CD_2Cl_2) δ 140.8, 140.4, 133.6, 132.5, 132.3, 132.2, 132.0, 131.0, 130.5, 129.9, 129.2, 129.0, 129.0, 128.8, 127.6, 127.4, 127.2, 127.2, 127.1, 126.8, 126.6, 123.7, 122.6, (C-P-coupling was not assigned).

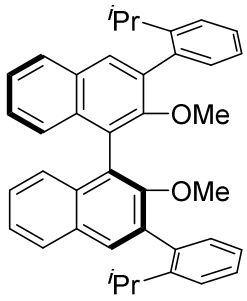
^{31}P NMR (202 MHz, CD_2Cl_2) δ -0.46 (s).

HRMS (ESI–) *m*/*z* calculated for $C_{88}H_{56}NO_6P_2$ (M–H) 1284.3588, found 1284.3582.

5h



(*S*)-3,3'-bis(2-isopropylphenyl)-2,2'-dimethoxy-1,1'-binaphthalene (5hb)



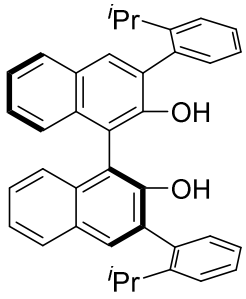
To magnesium turnings (292 mg, 12 mmol) activated with 1,2-dibromoethane in diethyl ether (2 ml), 1-bromo-2-isopropylbenzene (1.59 g, 8 mmol) and diethylether (10 ml) were added alternately during 30 min. After complete addition, the mixture was refluxed (oil bath heating) for 19 h. After cooling to ambient temperature, the solution was added to a mixture of (*S*)-3,3'-dibromo-2,2'-dimethoxy-1,1'-binaphthalene (**5ha**, 944 mg, 2.0 mmol) and $Ni(PPh_3)_2Cl_2$ (196 mg, 0.30 mmol) in anhydrous diethyl ether (20 mL). The reaction mixture was refluxed for 26 h, cooled to ambient temperature, carefully treated with saturated aqueous NH_4Cl solution (20 ml) and water (20 ml), and extracted with CH_2Cl_2 (100 ml, 20 ml). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel using 20% CH_2Cl_2/hexane as the eluent yielding the title compound as a colorless solid (920 mg, 84%).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.93-7.91 (m, 2H), 7.85 (s, 1.1H), 7.84 (s, 0.4H), 7.83 (s, 0.5H), 7.47-7.37 (m, 8H), 7.32-7.25 (m, 5.4H), 7.20 (d, *J* = 8.45 Hz, 0.6H), 3.25 (s, 1.7H), 3.15 (s, 1.1H), 3.14-3.05 (m, 0.8H), 3.03 (s, 3.2H), 3.02-2.94 (m, 1.2H), 1.24-1.15 (m, 7.1H), 1.08 (d, *J* = 6.9 Hz, 3.2H), 1.01 (d, *J* = 6.8 Hz, 1.7H) (spectra complicated due to presence of rotamers).

^{13}C NMR (125 MHz, CD_2Cl_2) δ 155.2, 154.8, 154.7, 154.5, 148.15, 148.09, 147.8, 138.05, 137.99, 137.93, 137.89, 136.2, 136.1, 136.0, 135.6, 134.1, 134.0, 133.9, 131.32, 131.29, 131.2, 131.11, 131.08, 131.01, 130.97, 130.9, 130.8, 130.7, 130.6, 130.5, 128.42, 128.39, 128.32, 128.25, 126.6, 126.42, 126.39, 126.3, 126.04, 126.03, 125.8, 125.74, 125.72, 125.67, 125.64, 125.61, 125.57, 125.50, 125.48, 125.4, 125.32, 125.28, 125.2, 125.1, 60.80, 60.76, 60.7, 60.4, 30.9, 30.8, 30.7, 30.6, 25.20, 25.16, 25.0, 24.9, 23.3, 23.0 (including signals due to presence of rotamers).

HRMS (ESI+) *m/z* calculated for $C_{40}H_{38}O_2Na$ (M+Na) 573.2764, found 573.2767.

(*S*)-3,3'-bis(2-isopropylphenyl)-[1,1'-binaphthalene]-2,2'-diol (5hc)



A 1 M solution of BBr_3 in CH_2Cl_2 (6.64 ml, 6.64 mmol) was added dropwise to a solution of (*S*)-**5hb** (914 mg, 1.66 mmol) in CH_2Cl_2 (20 ml) at 0 °C under argon. After 40 h at room temperature, the solution was cooled to 0 °C, water (50 ml) was carefully added, and the mixture was extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous Na_2CO_3 solution (50 ml), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel using 50% CH_2Cl_2/hexane as the eluent yielding the title compound as a colorless solid (824 mg, 95%).

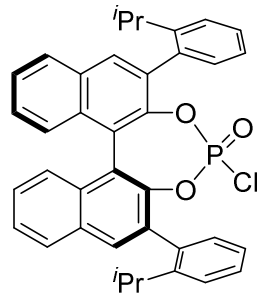
^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.93-7.91 (m, 2H), 7.87 (s, 0.5H), 7.87 (s, 1.5H), 7.48-7.22 (m, 14H), 5.19 (s, 0.5H), 5.18 (s, 0.5H), 5.16 (s, 1H), 3.06-2.98 (m, 1.1H), 2.95-2.88 (m, 0.9H), 1.23-1.21 (m, 3.4H), 1.19-1.15 (m, 6H), 1.11-1.08 (m, 2.6H) (spectra complicated due to the presence of rotamers).

^{13}C NMR (125 MHz, CD_2Cl_2) δ 150.9, 150.84, 150.78, 148.5, 148.4, 136.1, 136.02, 136.00, 135.9, 133.7, 133.6, 133.5, 133.4, 131.6, 131.5, 131.44, 131.39, 131.19, 131.17, 131.13, 131.12, 130.8, 130.7, 130.62, 130.59, 129.60, 129.56, 129.04, 129.01, 128.7, 128.6, 127.3, 127.2, 126.2, 126.1, 125.97, 125.95, 125.93, 125.88, 124.8, 124.6, 124.44, 124.42, 124.38,

124.29, 124.25, 112.9, 112.8, 112.7, 30.9, 30.8, 24.8, 24.73, 24.66, 23.44, 23.41, 23.37, 23.3 (including signals due to presence of rotamers).

HRMS (ESI+) *m/z* calculated for $C_{38}H_{34}O_2Na$ (M+Na) 545.2451, found 545.2451.

(*S*)-4-chloro-2,6-bis(2-isopropylphenyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide (5hd)



To a solution of (*S*)-**5hc** (408 mg, 0.78 mmol) in pyridine (3 ml) under argon was added $POCl_3$ (218 µl, 359 mg, 2.43 mmol) at room temperature. The mixture was stirred at 60 °C for 1.5 h and then concentrated to dryness under vacuum. The residue was passed through a short silica gel column (5 g) using CH_2Cl_2 as the eluent yielding the title compound as a colorless solid (467 mg, 99%).

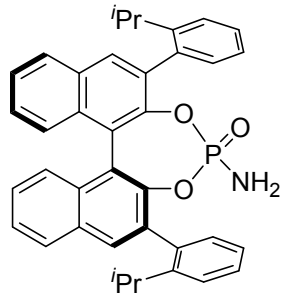
^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.04-7.98 (m, 4H), 7.61-7.57 (m, 2H), 7.54-7.52 (m, 0.4H), 7.47-7.20 (m, 11.6H), 3.23-3.15 (m, 0.2H), 3.12-3.02 (m, 0.2H), 2.90-2.79 (m, 1.6H), 1.50-1.48 (m, 0.5H), 1.38-1.36 (m, 0.6H), 1.25-1.22 (m, 2.5H), 1.20-1.15 (m, 3.5H), 1.08-1.07 (m, 2.4H), 1.00 (d, *J* = 6.8 Hz, 2.5H) (spectra complicated due to the presence of rotamers).

^{13}C NMR (125 MHz, CD_2Cl_2) δ 148.2, 147.7, 144.8, 144.7, 135.2, 135.1, 134.2, 133.93, 133.91, 133.3, 133.2, 133.1, 133.01, 132.97, 132.5, 132.42, 132.39, 131.92, 131.87, 131.6, 131.1, 129.3, 129.24, 129.17, 129.1, 128.92, 128.89, 128.85, 128.8, 127.55, 127.51, 127.4, 127.32, 127.29, 127.3, 127.25, 127.1, 127.0, 126.92, 126.90, 126.8, 125.8, 125.7, 125.6, 125.52, 125.46, 125.4, 125.2, 122.24, 122.22, 122.20, 122.09, 122.08, 31.2, 31.0, 30.5, 30.1, 26.8, 25.8, 25.2, 24.9, 23.8, 23.5, 23.3, 22.8 (including signals due to the presence of rotamers and unassigned C-P-coupling).

^{31}P NMR (202 MHz, CD_2Cl_2) δ 7.71 (major), 7.56, 7.44, 7.37 (including signals due to presence of rotamers).

HRMS (ESI+) *m/z* calculated for $C_{38}H_{32}O_3ClPNa$ (M+Na) 625.1670, found 625.1669.

(*S*)-4-amino-2,6-bis(2-isopropylphenyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide (5he)



To a solution of (*S*)-**5hc** (408 mg, 0.78 mmol) in pyridine (3 ml) under argon was added $POCl_3$ (218 µl, 359 mg, 2.34 mmol) at room temperature. After 1.5 h at 60 °C, the mixture was cooled to –78 °C and anhydrous ammonia gas was condensed into the reaction flask (ca. 10 ml). The cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction mixture was then concentrated to dryness under vacuum. The residue was passed through a short silica gel column (10 g) using 10% EtOAc/CH_2Cl_2 as the eluent yielding the title compound as a colorless solid (440 mg, 97%).

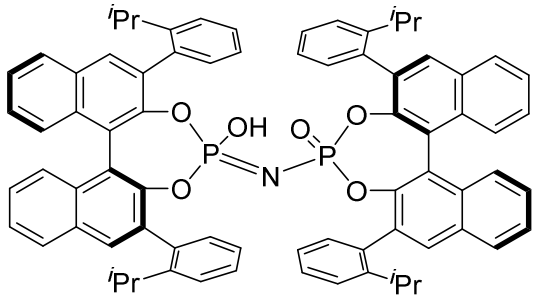
^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.02-7.90 (m, 4H), 7.57-7.53 (m, 2.1H), 7.51-7.34 (m, 8.6H), 7.32-7.22 (m, 3.1H), 7.15-7.05 (m, 0.2H), 3.19-3.05 (m, 0.3H), 2.95-2.79 (m, 1.7H), 2.70-2.57 (m, 2H), 1.49-1.46 (m, 0.4H), 1.35-1.33 (m, 0.7H), 1.25-1.22 (m, 2.8H), 1.20-1.18 (m, 0.7H), 1.14-1.07 (m, 5H), 1.01 (d, *J* = 6.9 Hz, 2.6H) (spectra complicated due to the presence of rotamers).

^{13}C NMR (125 MHz, CD_2Cl_2) δ 148.5, 147.6, 145.44, 145.36, 144.8, 144.7, 136.2, 136.0, 134.53, 134.51, 134.48, 134.46, 132.6, 132.5, 132.44, 132.41, 132.38, 132.3, 132.0, 131.83, 131.76, 131.20, 131.19, 131.0, 130.9, 129.15, 129.10, 128.8, 128.7, 127.4, 127.3, 126.94, 126.89, 126.8, 126.6, 126.4, 126.34, 126.31, 125.9, 125.82, 125.77, 125.75, 125.6, 125.18, 125.15, 124.9, 122.52, 122.51, 122.27, 122.25, 31.13, 31.11, 30.9, 30.5, 30.2, 25.7, 25.18, 25.6, 24.8, 23.5, 23.4, 22.9 (including signals due to presence of rotamers and unassigned C-P-coupling).

^{31}P NMR (202 MHz, CD_2Cl_2) δ 12.4, 12.1, 12.0 (major), 11.8 (including signals due to presence of rotamers).

HRMS (ESI+) *m*/*z* calculated for $C_{38}H_{34}NO_3PNa$ (M+Na) 606.2168, found 606.2170.

Imidodiphosphoric acid 5h



Sodium hydride (60% dispersion of in mineral oil, 70.4 mg, 1.76 mmol) was added to a solution of (*S*)-**5he** (257 mg, 0.44 mmol) and (*S*)-**5hd** (319 mg, 0.53 mmol) in THF (3 ml) under argon at room temperature. After 17 h at room temperature, 10% aqueous HCl solution (5 ml) and DCM (5 ml) were added, and the mixture was stirred for 5 min. The organic layer was separated and the solvent was removed under reduced pressure. The residue was purified by column chromatography on aluminum oxide (activity III, 20 g) using 0-100% EtOAc/DCM as the eluents giving a colorless solid. The solid was dissolved in CH_2Cl_2 (5 ml) and stirred with 3 N aqueous HCl (5 ml) for 20 min. The organic layer was separated and concentrated under reduced pressure to give the title compound as a colorless solid (233 mg, 46%).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.02-6.53 (m, 32H), 6.84 (s, 2H, acidic H + H_2O, overlapped), 5.70-5.36 (m, 4H), 4.00 (bs, 0.2H), 3.80 (bs, 0.1H), 3.04 (bs, 0.3H), 2.68-2.58 (m, 1.7H), 2.53-2.44 (m, 2H), 1.29-0.56 (m, 24H) (spectra complicated due to the presence of rotamers).

^{13}C NMR (125 MHz, CD_2Cl_2) δ 148.9, 147.8, 147.1, 145.8, 145.5, 136.5, 135.5, 135.1, 134.7, 132.7, 132.6, 132.4, 132.0, 131.8, 130.4, 128.8, 128.7, 128.4, 128.1, 127.9, 127.73, 127.77, 127.3, 127.2, 126.9, 126.7, 126.3, 126.0, 125.7, 125.6, 125.52, 125.45, 125.1, 124.6, 122.9, 122.2, 30.9, 30.7, 30.5, 29.8, 25.8, 25.2, 25.0, 24.5, 23.8, 23.2, 23.1, 22.5 (spectra complicated due to the presence of rotamers and unassigned C-P-coupling).

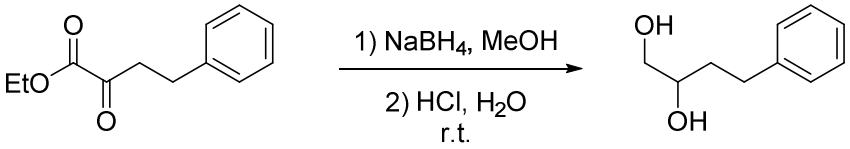
^{31}P NMR (202 MHz, CD_2Cl_2) δ 3.50 (major), 2.31, -0.59, -2.02 (including signals due to presence of rotamers).

HRMS (ESI–) *m*/*z* calculated for $C_{76}H_{64}NO_6P_2$ (M–H) 1148.4214, found 1148.4225.

7.3. Resolutions of diols via asymmetric acetalization

7.3.1. Synthesis of starting materials

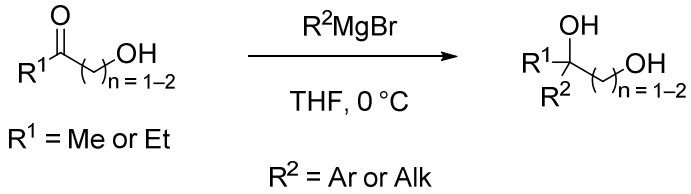
4-phenylbutane-1,2-diol (*rac*-6a)



The compound *rac*-**6a** was synthesized following a literature procedure.[166]

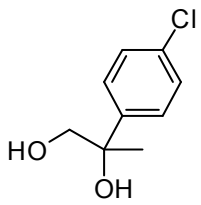
Yield: Colorless oil, 72%.

General procedure for *rac*-6g, 6k-m, 6o-p, 8a



A solution of aryl or alkyl magnesium bromide (3.0 equiv) was added dropwise to a solution of the hydroxy ketone (1.0 equiv) in THF (0.8 M) at 0 °C under an argon atmosphere. The cooling bath was removed and the mixture was allowed to warm to room temperature for 1 hour. The mixture was quenched with saturated aq. NH_4Cl and extracted with EtOAc. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The product was purified by column chromatography on silica gel using EtOAc/hexane as the eluent.

2-(4-chlorophenyl)propane-1,2-diol (*rac*-6g)



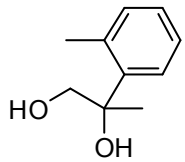
Yield: White solid, 65%.

^{1}H NMR (500 MHz, C_6D_6) δ 7.14-7.11 (m, 2H), 7.06-7.03 (m, 2H), 3.29 (d, *J* = 10.9 Hz, 1H), 3.22 (d, *J* = 10.9 Hz, 1H), 2.38 (s, 1H), 1.58 (bs, 1H), 1.18 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 144.4, 133.1, 128.6, 127.1, 74.3, 70.9, 26.0.

HRMS (EI (DE)) *m/z* calculated for $C_9H_{11}O_2Cl$ (M) 186.0448, found 186.0446.

2-*o*-tolylpropane-1,2-diol (*rac*-6k)



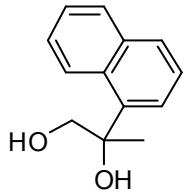
Yield: White solid, 88%.

^{1}H NMR (300 MHz, C_6D_6) δ 7.36-7.30 (m, 1H), 7.07-6.99 (m, 3H), 3.64 (d, *J* = 10.9 Hz, 1H), 3.39 (d, *J* = 10.9 Hz, 1H), 2.40 (s, 3H), 1.35 (s, 3H).

^{13}C NMR (75 MHz, C_6D_6) δ 142.9, 136.3, 133.0, 127.5, 126.7, 126.0, 75.7, 69.6, 25.6, 22.4.

HRMS (ESI+) *m/z* calculated for $C_{10}H_{14}O_2Na$ (M+Na) 189.0886, found 189.0887.

2-(naphthalen-1-yl)propane-1,2-diol (*rac*-6l)



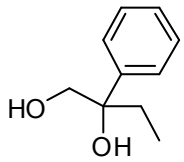
Yield: White solid, 53%.

^{1}H NMR (500 MHz, C_6D_6) δ 8.71 (d, *J* = 8.6 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.45 (d, *J* = 7.3 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 7.3 Hz, 1H), 7.20 (t, *J* = 7.7 Hz, 1H), 3.90 (d, *J* = 10.9 Hz, 1H), 3.56 (d, *J* = 11.0 Hz, 1H), 2.62 (bs, 1H), 1.63 (bs, 1H), 1.56 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 140.8, 135.5, 131.8, 129.5, 129.0, 127.3, 125.6, 125.4, 125.2, 124.4, 76.0, 70.0, 26.3.

HRMS (EI (DE)) *m/z* calculated for $C_{13}H_{14}O_2$ (M) 202.0994, found 202.0995.

2-phenylbutane-1,2-diol (*rac*-6m)



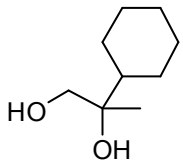
Yield:Colorless oil, 40%.

^{1}H NMR (500 MHz, C_6D_6) δ 7.32-1.29 (m, 2H), 7.19-7.17 (overlapped with solvent, 2H), 7.08 (t, *J* = 7.3 Hz, 1H), 3.45-3.36 (m, 2H), 2.24 (s, 1H), 1.72-1.65 (m, 1H), 1.59-1.52 (m, 1H), 0.97 (bs, 1H), 0.73 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 144.2, 128.4, 127.0, 126.0, 77.1, 70.6, 31.4, 7.7.

HRMS (EI (DE)) m/z calculated for $C_{10}H_{14}O_2$ (M) 166.0994, found 166.0992.

2-cyclohexylpropane-1,2-diol (*rac*-6o)



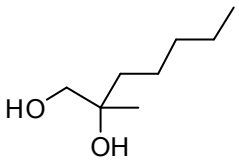
Yield:White solid, 10%.

^{1}H NMR (300 MHz, C_6D_6) δ 3.32 (d, *J* = 10.7 Hz, 1H), 3.18 (d, J = 10.7 Hz, 1H), 1.87 (m, 7H), 1.42-1.32 (m, 1H), 1.25-0.96 (m, 4H), 0.93 (s, 3H), 0.90-0.72 (m, 2H).

^{13}C NMR (75 MHz, C_6D_6) δ 74.3, 68.6, 45.3, 28.0, 27.1, 26.9, 20.4.

HRMS (ESI+) *m/z* calculated for $C_9H_{18}O_2Na$ (M+Na) 181.1199, found 181.1200.

2-methylheptane-1,2-diol (*rac*-6p)



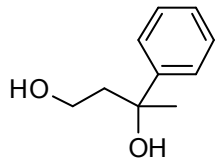
Yield:Colorless oil, 38%.

^{1}H NMR (300 MHz, C_6D_6) δ 3.21 (d, *J* = 10.6 Hz, 1H), 3.14 (d, *J* = 10.6 Hz, 1H), 1.51 (bs, 2H), 1.30-1.20 (m, 8H), 0.98 (s, 3H), 0.89 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, C_6D_6) δ 72.5, 70.0, 39.1, 32.9, 23.7, 23.5, 23.0, 14.3.

HRMS (ESI+) *m/z* calculated for $C_8H_{18}O_2Na$ (M+Na) 169.1199, found 169.1200.

3-phenylbutane-1,3-diol (*rac*-8a)



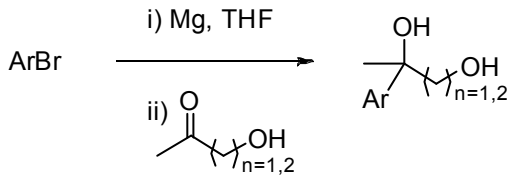
Yield: Colorless oil, 67%.

^{1}H NMR (500 MHz, C_6D_6) δ 7.38 (d, *J* = 7.9 Hz, 2H), 7.21 (t, *J* = 7.7 Hz, 2H), 7.09 (t, *J* = 7.3 Hz, 1H), 3.89 (bs, 1H), 3.43-3.39 (m, 1H), 3.35-3.31 (m, 1H), 2.29 (bs, 1H), 1.88-1.82 (m, 1H), 1.73-1.69 (m, 1H), 1.41 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 148.5, 128.4, 126.6, 125.3, 75.7, 60.3, 44.1, 31.2.

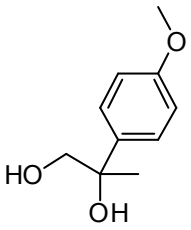
HRMS (CI(FE) i-Butane) *m/z* calculated for $C_{10}H_{15}O_2$ (M+H) 167.1072, found 167.1071.

General procedure for *rac*-6h-j, 8g



A solution of aryl bromide (3.0 equiv) in THF (1.2 M) was added dropwise to activated magnesium turnings (3.3 equiv, activated with 1,2-dibromoethane) and the resulting mixture was stirred for 0.5-3 h at 40 °C under argon until most of the magnesium was consumed. The mixture was cooled to 0 °C, the hydroxy ketone (1.0 equiv) in THF (0.8 M) was added and the mixture was stirred for 1 h at 0 °C to room temperature. The mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The product was purified by column chromatography on silica gel using EtOAc/hexane as the eluent.

2-(4-methoxyphenyl)propane-1,2-diol (*rac*-6h)



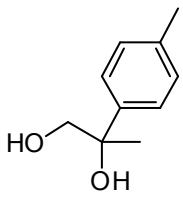
Yield: White solid, 60%.

^{1}H NMR (500 MHz, C_6D_6) δ 7.26 (d, *J* = 8.7 Hz, 1H), 6.80 (*J* = 8.6 Hz, 1H), 3.45 (d, *J* = 10.8 Hz, 1H), 3.35 (d, *J* = 10.9 Hz, 1H), 3.32 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 144.4, 133.1, 128.6, 127.1, 74.3, 70.9, 26.0.

HRMS (EI (DE)) *m/z* calculated for $C_{10}H_{14}O_2$ (M) 182.0943, found 182.0941.

2-*p*-tolylpropane-1,2-diol (*rac*-6i)



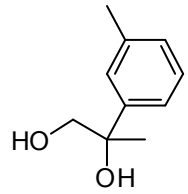
Yield: White solid, 50%.

^{1}H NMR (500 MHz, C_6D_6) δ 7.28 (d, *J* = 10.9 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 3.50 (d, *J* = 10.9 Hz, 1H), 3.39 (d, *J* = 10.9 Hz, 1H), 2.51 (bs, 1H), 2.13 (s, 3H), 1.79 (bs, 1H), 1.35 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 143.1, 136.4, 129.2, 125.5, 74.6, 71.3, 26.2, 21.0.

HRMS (EI (DE)) *m/z* calculated for $C_{10}H_{14}O_2$ (M) 166.0994, found 166.0992.

2-*m*-tolylpropane-1,2-diol (*rac*-6j)



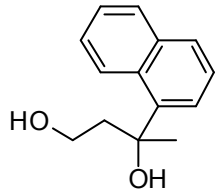
Yield: White solid, 70%.

^{1}H NMR (300 MHz, C_6D_6) δ 7.26-7.26 (m, 1H), 7.18-7.09 (overlapped with solvent, 2H), 6.94-6.91 (m, 1H), 3.49 (d, *J* = 10.9 Hz, 1H), 3.38 (d, *J* = 10.9 Hz, 1H), 2.16 (s, 3H), 1.34 (s, 3H).

^{13}C NMR (75 MHz, C_6D_6) δ 146.1, 137.9, 126.3, 122.7, 74.7, 71.3, 26.3, 21.6.

HRMS (ESI+) *m/z* calculated for $C_{10}H_{14}O_2Na$ (M+Na) 189.0886, found 189.0887.

3-(naphthalen-1-yl)butane-1,3-diol (*rac*-8g)



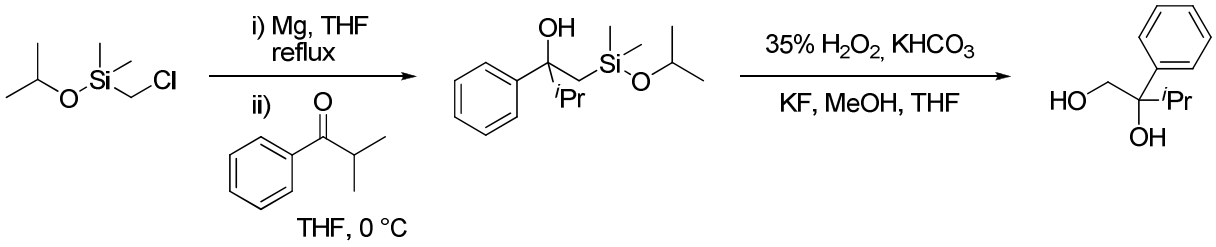
Yield: Colorless oil, 20%.

^{1}H NMR (300 MHz, C_6D_6) δ 8.47 (d, *J* = 8.3 Hz, 1H), 7.79-7.76 (m, 1H), 7.71-7.68 (m, 1H), 7.60 (d, *J* = 8.1 Hz, 1H), 7.33-7.23 (m, 3H), 3.46-3.36 (m, 2H), 3.27-3.18 (m, 1H), 2.36 (ddd, *J* = 14.8, 6.2, 3.8 Hz, 1H), 2.00 (ddd, *J* = 14.8, 8.3, 4.2 Hz, 1H), 1.67 (s, 3H).

^{13}C NMR (75 MHz, C_6D_6) δ 143.7, 135.5, 131.2, 129.7, 128.7, 126.8, 125.5, 125.4, 125.2, 124.3, 76.7, 60.5, 43.4, 30.2.

HRMS (ESI+) *m/z* calculated for $C_{14}H_{16}O_2Na$ (M+Na) 239.1042, found 239.1043.

3-methyl-2-phenylbutane-1,2-diol (*rac*-6n)[167]



A solution of (isopropoxydimethylsilyl)methyl chloride (4.55 ml, 4.21 g, 25.26 mmol) in THF (30 ml) was added dropwise to the activated magnesium turnings (0.85 g, 27.20 mmol, activated with 1,2-dibromoethane) and the resulting mixture was refluxed for 0.5 h under an argon atmosphere until most of the magnesium was consumed. The mixture was cooled to 0 °C, isobutyrophenone (2.91 ml, 2.88 g, 19.43 mmol) in THF (8 ml) was added dropwise with

stirring over 30 min. The resulting mixture was stirred for 30 min at 0 °C and aq. 10% solution of NH_4Cl was added dropwise at 0 °C. The organic layer was extracted, dried ($MgSO_4$), filtered, and concentrated with a rotary evaporator at room temperature.

To the crude 1-(isopropoxydimethylsilyl)-3-methyl-2-phenylbutan-2-ol were added THF/MeOH 1:1 (38 ml), $KHCO_3$ (1.95 g, 19.43 mmol), and KF (2.26 g, 38.86 mmol). To the resulting mixture 30% aq. H_2O_2 (7.25 ml, 64.12 mmol) was added. After 15 min an exothermic reaction starts, which was kept at 40-50 °C by cooling using a water bath. After the end of the exothermic reaction, the resulting mixture was stirred for 2 h at room temperature. The remaining H_2O_2 was decomposed by a slow addition of 50% aq. solution of $Na_2S_2O_3 \cdot 5\ H_2O$ with stirring over 30 min, keeping the temperature around 30 °C with an ice bath. A white precipitate was formed, the mixture was filtered and the residue washed with diethyl ether. The filtrate was concentrated, and dissolved in diethyl ether, washed with sat. aq. NaCl, dried ($MgSO_4$), filtered, and concentrated. The product was purified by column chromatography on silica gel using EtOAc/hexane as the eluent.

Yield: White solid, 1.43 g, 41%.

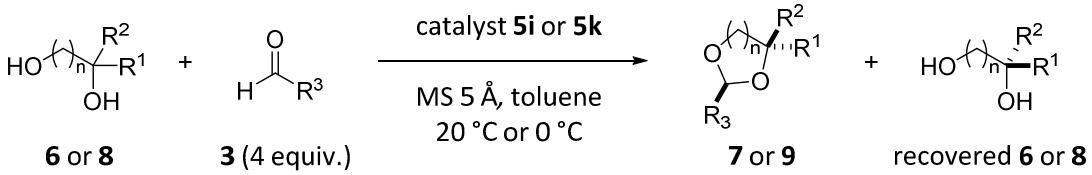
^{1}H NMR (500 MHz, C_6D_6) δ 7.31-7.28 (m, 2H), 7.18-7.15 (overlapped with solvent, 2H), 7.09-7.06 (m, 1H), 3.59 (s, 2H), 2.55 (bs, 1H), 1.90-1.81 (m, 1H), 1.13 (bs, 1H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.72 (d, *J* = 6.9 Hz, 3H).

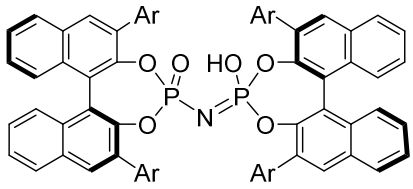
^{13}C NMR (125 MHz, C_6D_6) δ 144.0, 126.9, 126.6, 79.0, 68.4, 35.5, 17.6, 17.0.

HRMS (ESI+) *m/z* calculated for $C_{11}H_{16}O_2Na$ (M+Na) 203.1042, found 203.1043.

7.3.2. Kinetic resolution of diols

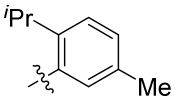
General procedure



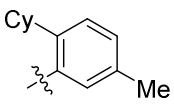


5

Ar =



5i



5k

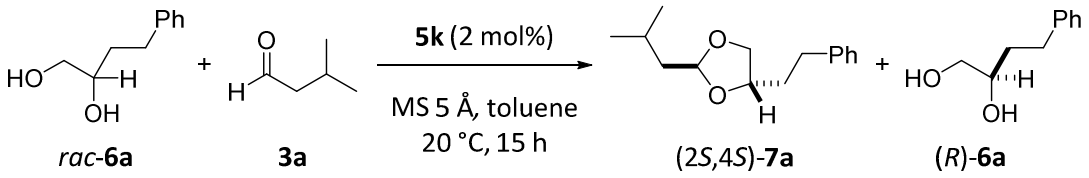
The aldehyde (2.0 mmol) was added to a mixture of diol (0.50 mmol), catalyst **5** (1-3 mol%) and 5 Å molecular sieves (100 mg) in toluene (5 ml). The mixture was stirred vigorously at designated temperature for indicated time and then quenched by adding a few drops of triethylamine. Purification was performed by column chromatography on silica gel using EtOAc/hexanes solvent gradient between 0-100%.

Absolute configurations of diols **6a**, **6c**, **6p** and **8a** were determined by comparison of specific optical rotation with literature values. Configurations of other diols were assigned by analogy. Major diastereomers of the corresponding acetal products were assigned opposite configurations at the alcohol sterocenter. Acetal sterocenter configurations were assigned in analogy to the results from our previous asymmetric acetalization studies[67] and NOESY experiment for **9b**.

Racemates

The samples of racemic products for GC or HPLC analysis were prepared from diol (0.05 mmol), aldehyde (0.2 mmol), 5 Å molecular sieves (10 mg), and $(PhO)_2PO_2H$ (5 mol%) as the catalyst in toluene (0.5 ml) and isolated by thin layer chromatography using EtOAc/hexanes as the eluent.

Products



rac-**6a** **3a** (2*S*,4*S*)-**7a** (*R*)-**6a**

conversion 81 %
***s*-factor 1.6**

(2*S*,4*S*)-2-isobutyl-4-phenethyl-1,3-dioxolane (7a)

Yield: Colorless oil, 93.7 mg, 80%.

^{1}H NMR (500 MHz, C_6D_6) δ 7.17-7.03 (m, 5H), 5.08 (t, *J* = 5.2 Hz, 1H), 3.87-3.82 (m, 1H), 3.77 (dd, *J* = 8.0, 6.2 Hz, 1H), 3.13 (dd, *J* = 7.9, 7.2 Hz, 1H), 2.67-2.62 (m, 1H), 2.50-2.44 (m, 1H), 1.98-1.90 (m, 1H), 1.77-1.71 (m, 1H), 1.68 (dd, *J* = 6.9, 5.2 Hz, 2H), 1.43-1.36 (m, 1H), 0.95-0.94 (m, 6H).

^{13}C NMR (125 MHz, C_6D_6) δ 142.0, 128.8, 128.7, 126.2, 103.4, 75.1, 70.4, 43.6, 35.5, 32.5, 25.0, 23.2, 23.2.

HRMS (ESI+) *m/z* calculated for $C_{15}H_{22}O_2$ (M) 257.1512, found 257.1513.

GC (Column: 25 m Hydrodex-β-TBDAC (tert-butyl-diacetyl-cyclodextrin), i.D. 0.25 mm; Detector: FID; Temperature: injector 220 °C, detector 350 °C, oven 80 °C to 133 °C with 0.3 °C/min, then to 245 °C with 10 °C/min; gas: 0.5 bar H_2), major diastereomer: t_{major} = 166.8 min, t_{minor} = 167.5 min; er = 99.5:0.5, minor diastereomer: t_{major} = 159.8 min, t_{minor} = 158.8 min; er = 95:5, dr = 1.1:1.

(*R*)-4-phenylbutane-1,2-diol (6a)

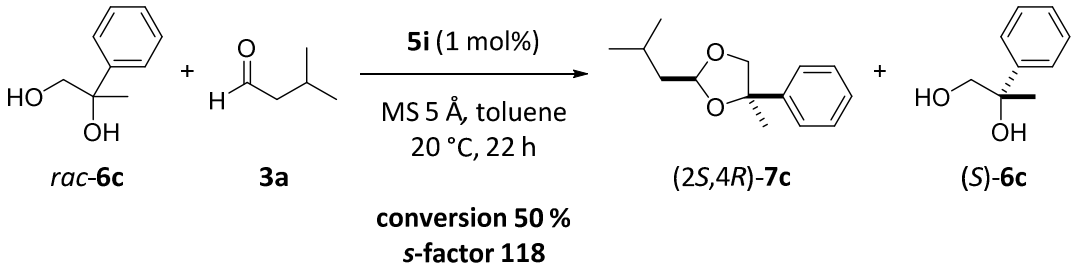
Yield: Colorless oil, 7.5 mg, 10%. Absolute configuration was determined by comparison of HPLC trace with those of (*R*)-**6a** and (*S*)-**6a**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.27 (m, 2H), 7.21-7.18 (m, 3H), 3.76-3.71 (m, 1H), 3.66 (dd, *J* = 11.0, 3.1 Hz, 1H), 3.47 (dd, *J* = 11.0, 7.6 Hz, 1H), 2.84-2.79 (m, 1H), 2.73-2.67 (m, 1H), 1.97 (bs, 2H), 1.82-1.71 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 141.8, 128.6, 128.5, 126.1, 71.6, 66.9, 34.8, 31.9.

HRMS (ESI+) *m/z* calculated for $C_{10}H_{14}O_2Na$ (M+Na) 189.0886, found 189.0886.

HPLC (OD-3), n-heptane/i-PrOH 95:5, 1.0 ml/min, λ = 210 nm, t_{major} = 19.00 min, t_{minor} = 28.87 min, er = 69:31.



(2*S*,4*R*)-2-isobutyl-4-methyl-4-phenyl-1,3-dioxolane (7c)

Yield: Colorless oil, 51.0 mg, 50%. $[\alpha]^{25}_{D}$ = -47 ° (*c* 1.59, CH_2Cl_2).

^{1}H NMR (500 MHz, C_6D_6) δ 7.38-7.37 (m, 2H), 7.20-7.18 (overlapped with solvent, 2H), 7.08 (t, *J* = 7.4 Hz, 1H), 5.26 (t, *J* = 5.2 Hz, 1H), 3.90 (d, *J* = 7.9 Hz, 1H), 3.60 (d, *J* = 7.9 Hz, 1H), 1.96 (dt, *J* = 13.4, 6.7 Hz, 1H), 1.80-1.71 (m, 2H), 1.39 (s, 3H), 0.94 (dd, *J* = 6.5, 4.3 Hz, 6H) (signals of the minor diastereomer are not included).

^{13}C NMR (125 MHz, C_6D_6) δ 146.7, 128.4, 127.1, 125.2, 104.0, 81.7, 77.5, 43.6, 26.3, 25.1, 23.2, 23.2 (signals of the minor diastereomer are not included).

HRMS (CI (DE) i-Butan) *m/z* calculated for $C_{14}H_{21}O_2$ (M+H) 221.1542, found 221.1539.

GC (Column: 25 m Lipodex G (Octakis-(2,3-di-O-pentyl-6-O-methyl)-γ-cyclodextrin), i.D. 0.25 mm; Detector: FID; Temperature: injector 220 °C, detector 320 °C, oven 100 °C to 125 °C with 1 °C/min; gas: 0.5 bar H_2), major diastereomer: t_{major} = 21.2 min, t_{minor} = 21.4 min; er = 98.5:1.5, minor diastereomer: t_{major} = 20.0 min, t_{minor} = 19.6 min; er = 98.5:1.5, dr = 58:1.

(*S*)-2-phenylpropane-1,2-diol (6c)

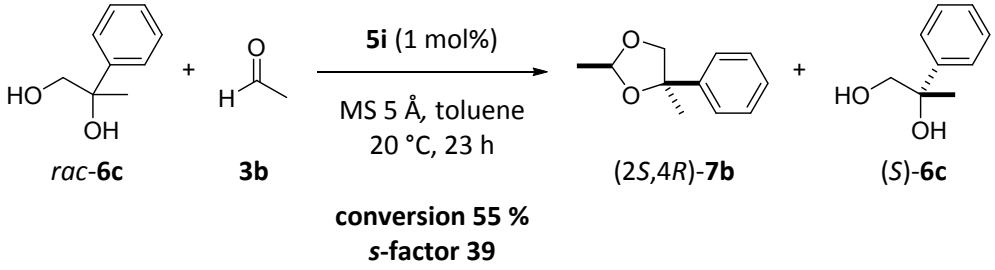
Yield: White solid, 38.0 mg, 46%. $[\alpha]^{25}_{D}$ = +6 ° (*c* 1.39, CH_2Cl_2).

^{1}H NMR (500 MHz, C_6D_6) δ 7.32 (d, *J* = 8.0 Hz, 2H), 7.20-7.16 (overlapped with solvent, 2H), 7.08 (t, *J* = 7.3 Hz, 1H), 3.40 (d, *J* = 10.9 Hz, 1H), 3.31 (d, *J* = 10.9 Hz, 1H), 2.12 (bs, 1H), 1.29 (s, 3H), 1.09 (bs, 1H).

^{13}C NMR (125 MHz, C_6D_6) δ 146.0, 128.5, 127.1, 125.5, 74.6, 71.2, 26.1.

HRMS (EI (FE)) m/z calculated for $C_9H_{12}O_2$ (M) 152.0837, found 152.0836.

HPLC (OD-3), n-heptane/i-PrOH 95:5, 1.0 ml/min, λ = 210 nm, t_{major} = 9.38 min, t_{minor} = 8.78 min; er = 97.5:2.5.



rac-**6c** **3b** (2*S*,4*R*)-**7b** (*S*)-**6c**

conversion 55 %
***s*-factor 39**

(2*S*,4*R*)-2,4-dimethyl-4-phenyl-1,3-dioxolane (7b)

Yield: Colorless oil, 43.1 mg, 48%. $[\alpha]^{25}_{D}$ = -41 ° (*c* 1.45, CH_2Cl_2).

^{1}H NMR (300 MHz, C_6D_6) δ 7.37-7.33 (m, 2H), 7.19-7.13 (overlapped with solvent, 2H), 7.10-7.04 (m, 1H), 5.23 (q, *J* = 4.8 Hz, 1H), 3.89 (d, *J* = 7.9 Hz, 1H), 3.59 (d, *J* = 7.9 Hz, 1H), 1.39 (d, *J* = 4.8 Hz, 3H), 1.37 (s, 3H) (signals of the minor diastereomer are not included).

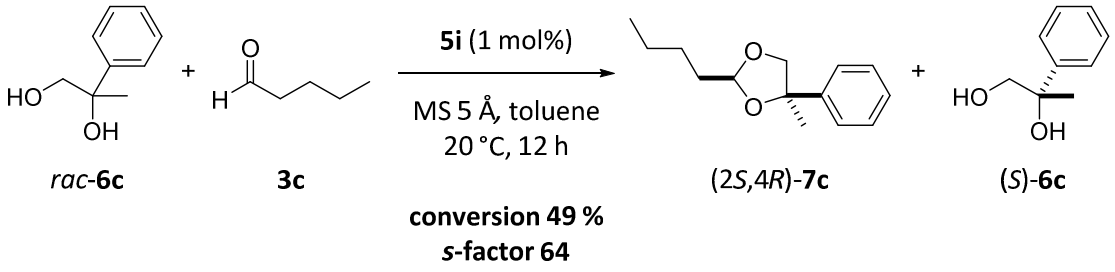
^{13}C NMR (725 MHz, C_6D_6) δ 146.7, 127.1, 125.2, 101.7, 82.0, 77.8, 26.2, 20.5 (signals of the minor diastereomer are not included).

HRMS (ESI+) *m/z* calculated for $C_{11}H_{14}O_2Na$ (M+Na) 201.0886, found 201.0886.

GC (Column: 30 m G-TA (Trifluoroacetyl-γ-cyclodextrin), i.D. 0.25 mm; Detector: FID; Temperature: injector 220 °C, detector 350 °C, oven 80 °C to 120 °C with 1 °C/min; gas: 0.5 bar H_2), major diastereomer: t_{major} = 20.9 min, t_{minor} = 21.7 min; er = 94:6, minor diastereomer: t_{major} = 19.3 min; er >99.5:0.5, dr = 20:1.

(*S*)-2-phenylpropane-1,2-diol (6c)

Yield: White solid, 30.8 mg, 40%. $[\alpha]^{25}_{D}$ = +4.7 ° (*c* 0.8, EtOH), lit.[168] $[\alpha]^{25}_{D}$ = +4.29 ° (*c* 0.96, EtOH) for (*S*)-enantiomer of 80% ee. er = 99:1.



rac-**6c** **3c** (2*S*,4*R*)-**7c** (*S*)-**6c**

(2*S*,4*R*)-2-butyl-4-methyl-4-phenyl-1,3-dioxolane (7c)

Yield: Colorless oil, 51.6 mg, 47%. $[\alpha]^{25}_{D}$ = -45 ° (*c* 1.50, CH_2Cl_2).

^{1}H NMR (300 MHz, C_6D_6) δ 7.39-7.35 (m, 2H), 7.20-7.17 (overlapped with solvent, 2H), 7.10-7.05 (m, 1H), 5.19 (t, *J* = 5.0 Hz, 1H), 3.90 (d, *J* = 7.8 Hz, 1H), 3.64 (d, *J* = 7.8 Hz, 1H), 1.85-1.77 (m, 2H), 1.55-1.45 (m, 2H), 1.41 (s, 3H), 1.35-1.23 (m, 2H), 0.84 (t, *J* = 7.3 Hz, 3H) (signals of the minor diastereomer are not included).

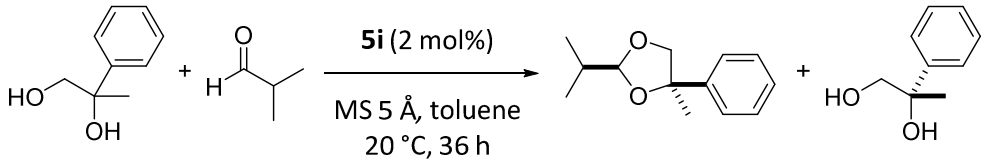
^{13}C NMR (75 MHz, C_6D_6) δ 146.6, 127.1, 125.2, 104.9, 81.8, 77.5, 34.6, 26.9, 26.3, 23.0, 14.2 (signals of the minor diastereomer are not included).

HRMS (ESI+) *m/z* calculated for $C_{14}H_{20}O_2Na$ (M+Na) 243.1356, found 243.1357.

GC (Column: 25 m Lipodex-G (Octakis-(2,3-di-O-pentyl-6-O-methyl)-γ-cyclodextrin), i.D. 0.25 mm; Detector: FID; Temperature: injector 220 °C, detector 350 °C, oven 100 °C to 130 °C with 1 °C/min; gas: 0.5 bar H_2), major diastereomer: t_{major} = 22.7 min, t_{minor} = 23.0 min; er = 97:3, minor diastereomer: t_{major} = 22.0 min, t_{minor} = 21.6 min; er = 97.5:2.5, dr = 57:1.

(*S*)-2-phenylpropane-1,2-diol (6c)

Yield: White solid, 35.4 mg, 47%. er = 94.5:5.5.



rac-**6c** **3d** (2*S*,4*R*)-**7d** (*S*)-**6c**

conversion 52 %
s-factor 79

(2*S*,4*R*)-2-isopropyl-4-methyl-4-phenyl-1,3-dioxolane (7d)

Yield: Colorless oil, 50.4 mg, 49%. $[\alpha]^{25}_{D}$ = -38 ° (*c* 0.29, CH_2Cl_2).

^{1}H NMR (300 MHz, C_6D_6) δ 7.36-7.32 (m, 2H), 7.20-7.14 (overlapped with solvent, 2H), 7.10-7.04 (m, 1H), 4.91 (d, *J* = 5.2 Hz, 1H), 3.84 (d, *J* = 7.7 Hz, 1H), 3.65 (d, *J* = 7.7 Hz, 1H), 1.99-1.89 (m, 1H), 1.39 (s, 3H), 1.05 (dd, *J* = 6.8, 3.1 Hz, 6H) (signals of the minor diastereomer are not included).

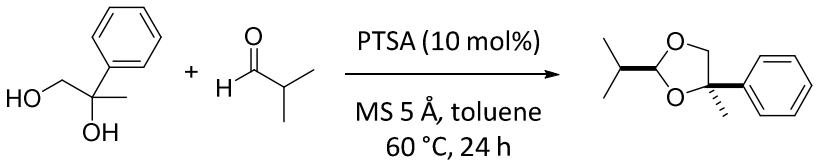
^{13}C NMR (75 MHz, C_6D_6) δ 146.2, 127.1, 125.1, 108.4, 81.9, 77.4, 33.0, 26.2, 17.5, 17.3 (signals of the minor diastereomer are not included).

HRMS (CI (DE)) *m/z* calculated for $C_{13}H_{19}O_2$ (M+H) 207.1385, found 207.1387.

GC (Column: 25m Cyclodextrin-H/OV-1701 (2,3-dimethyl-3-pentyl-γ-cyclodextrin), i.D. 0.25 mm; Detector: FID; Temperature: injector 220 °C, detector 350 °C, oven 100 °C to 135 °C with 0.5 °C/min; gas: 0.4 bar H_2), major diastereomer: t_{major} = 26.3 min, t_{minor} = 25.6 min; er = 98:2, minor diastereomer: t_{major} = 23.8 min; er >99.5:0.5, dr = 26:1.

(*S*)-2-phenylpropane-1,2-diol (6c)

Yield: White solid, 31.9 mg, 42%. er = 99:1.



rac-**6c** **3d** *rac*-**7d**
94% isolated yield

GC odor threshold measurement of racemic mixture of 7d (performed by Dr. P. Kraft in Givaudan Schweiz AG, Fragrance Research)

GC threshold value 65.98 ng/L air

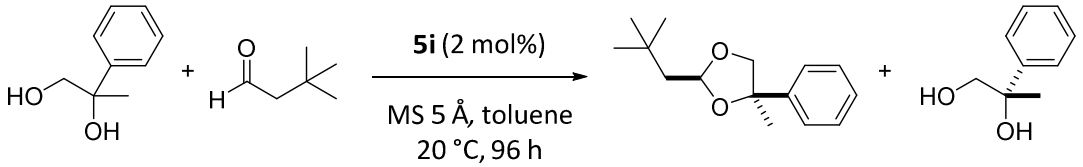
Olfactive note MAP: herbal fruity, clary sage claritone, labienone

Panelists: floral, ionone, woody, camphor.

GC DB-1 15 m x 0.53 mm (1.5 um)

Instrument: HP 6890

p = 38 kPa He, flow = 8 ml/min, T (iso) = 205°C



rac-**6c** **3f** (2*S*,4*R*)-**7f** (*S*)-**6c**

conversion 52 %
***s*-factor 122**

(2*S*,4*R*)-4-methyl-2-neopentyl-4-phenyl-1,3-dioxolane (7f)

Yield: Colorless oil, 55.5 mg, 47%. $[\alpha]^{25}_{D}$ = -47 ° (*c* 1.72, CH_2Cl_2).

^{1}H NMR (300 MHz, C_6D_6) δ 7.40-7.36 (m, 2H), 7.21-7.18 (overlapped with solvent, 2H), 7.11-7.05 (m, 1H), 5.33 (t, *J* = 5.0 Hz, 1H), 3.90 (d, *J* = 7.9 Hz, 1H), 3.59 (d, *J* = 7.9 Hz, 1H), 1.83 (dd, *J* = 5.0, 3.3 Hz, 1H), 1.39 (s, 1H), 1.02 (s, 9H) (signals of the minor diastereomer are not included).

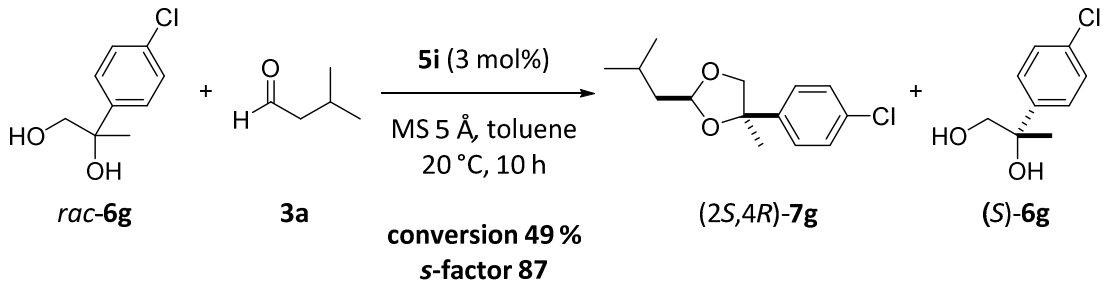
^{13}C NMR (75 MHz, C_6D_6) δ 146.8, 127.1, 125.2, 103.3, 81.6, 77.5, 48.0, 30.3, 29.4, 26.3 (signals of the minor diastereomer are not included).

HRMS (ESI+) *m/z* calculated for $C_{15}H_{22}O_2Na$ (M+Na) 257.1512, found 257.1512.

GC (Column: 24 m Lipodex G (Octakis-(2,3-di-O-pentyl-6-O-methyl)-γ-cyclodextrin), i.D. 0.25 mm; Detector: FID; Temperature: injector 220 °C, detector 350 °C, oven 100 °C to 150 °C with 1 °C/min; gas: 0.5 bar H_2), major diastereomer: t_{major} = 24.1 min, t_{minor} = 24.5 min; er = 98:2, minor diastereomer: t_{major} = 22.6 min; er >99.5:0.5, dr = 52:1.

(*S*)-2-phenylpropane-1,2-diol (6c)

Yield: White solid, 29.7 mg, 39%. er = 99.5:0.5.



rac-**6g** **3a** **conversion 49 %** *s*-**factor 87** (2*S*,4*R*)-**7g** (*S*)-**6g**

(2*S*,4*R*)-4-(4-chlorophenyl)-2-isobutyl-4-methyl-1,3-dioxolane (7g)

Yield: Colorless oil, 57.7 mg, 45%. $[\alpha]^{25}_{D}$ = -47 ° (*c* 1.50, CH_2Cl_2).

^{1}H NMR (500 MHz, C_6D_6) δ 7.13-7.12 (m, 2H), 7.08-7.06 (m, 2H), 5.18 (t, *J* = 5.2 Hz, 1H), 3.75 (d, *J* = 8.0 Hz, 1H), 3.50 (d, *J* = 8.0 Hz, 1H), 1.92 (dt, *J* = 13.5, 6.7 Hz, 1H), 1.71-1.68 (m, 2H), 1.27 (s, 3H), 0.94 (dd, *J* = 6.7, 1.6 Hz, 6H) (signals of the minor diastereomer are not included).

^{13}C NMR (125 MHz, C_6D_6) δ 145.2, 133.0, 128.5, 126.7, 104.1, 81.2, 77.4, 43.5, 26.1, 25.0, 23.1, 23.1 (signals of the minor diastereomer are not included).

HRMS (CI (DE) i-Butan) *m/z* calculated for $C_{14}H_{20}O_2Cl$ (M+H) 255.1152, found 255.1150.

GC (Column: 30 m BGB-176/SE-52 (2,3-dimethyl-6-tert-butyldimethyl-silyl-β-cyclodextrin), i.D. 0.25 mm; Detector: FID; Temperature: injector 220 °C, detector 320 °C, oven 140 °C; gas: 0.4 bar H_2), major diastereomer: t_{major} = 55.8 min, t_{minor} = 54.6 min; er = 98.5:1.5, minor diastereomer: t_{major} = 52.0 min; er >99.5:0.5, dr = 52:1.

(*S*)-2-(4-chlorophenyl)propane-1,2-diol (6g)

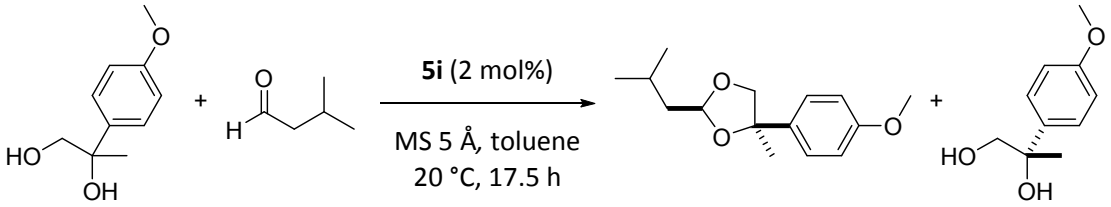
Yield: White solid, 44.3 mg, 47%. $[\alpha]^{25}_{D}$ = +10 ° (*c* 1.56, CH_2Cl_2).

^{1}H NMR (500 MHz, C_6D_6) δ 7.14-7.11 (m, 2H), 7.06-7.03 (m, 2H), 3.29 (d, *J* = 10.9 Hz, 1H), 3.22 (d, *J* = 10.9 Hz, 1H), 2.38 (s, 1H), 1.58 (bs, 1H), 1.18 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 144.4, 133.1, 128.6, 127.1, 74.3, 70.9, 26.0.

HRMS (EI (DE)) *m/z* calculated for $C_9H_{11}O_2Cl$ (M) 186.0448, found 186.0446.

HPLC (OD-3), n-heptane/i-PrOH 95:5, 1.0 ml/min, λ = 220 nm, t_{major} = 8.84 min, t_{minor} = 8.26 min, er = 94.5:5.5.



rac-**6h** **3a** (2*S*,4*R*)-**7h** (*S*)-**6h**

(2*S*,4*R*)-2-isobutyl-4-(4-methoxyphenyl)-4-methyl-1,3-dioxolane (7h)

Yield: Colorless oil, 60.1 mg, 48%. $[\alpha]^{25}_{D}$ = -42 ° (*c* 2.15, CH_2Cl_2).

^{1}H NMR (500 MHz, C_6D_6) δ 7.31 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 5.29 (t, *J* = 5.2 Hz, 1H), 3.92 (d, *J* = 7.8 Hz, 1H), 3.62 (d, *J* = 7.8 Hz, 1H), 3.32 (s, 3H), 1.98 (dt, *J* = 13.4, 6.7 Hz, 1H), 1.82-1.75 (m, 2H), 1.43 (s, 3H), 0.96 (dd, *J* = 6.5 Hz, 6H) (signals of the minor diastereomer are not included).

^{13}C NMR (125 MHz, C_6D_6) δ 159.2, 138.7, 126.4, 113.9, 104.0, 81.5, 77.7, 54.8, 43.7, 26.2, 25.1, 23.2, 23.2 (signals of the minor diastereomer are not included).

HRMS (ESI+) *m/z* calculated for $C_{15}H_{22}O_3Na$ (M+Na) 273.1461, found 273.1458.

GC (Column: 25 m Hydrodex-β-TBDAC (Heptakis-(2,3-di-O-acetyl-6-O-tert-butyldimethyl-silyl)-β-cyclodextrin), i.D. 0.25 mm; Detector: FID; Temperature: injector 220 °C, detector 320 °C, oven 145 °C; gas: 0.4 bar H_2), major diastereomer: t_{major} = 45.8 min, t_{minor} = 44.2 min; er = 98.5:1.5, minor diastereomer: t_{major} = 41.1 min, t_{minor} = 42.2 min; er = 98:2, dr = 53:1.

(*S*)-2-(4-methoxyphenyl)propane-1,2-diol (6h)

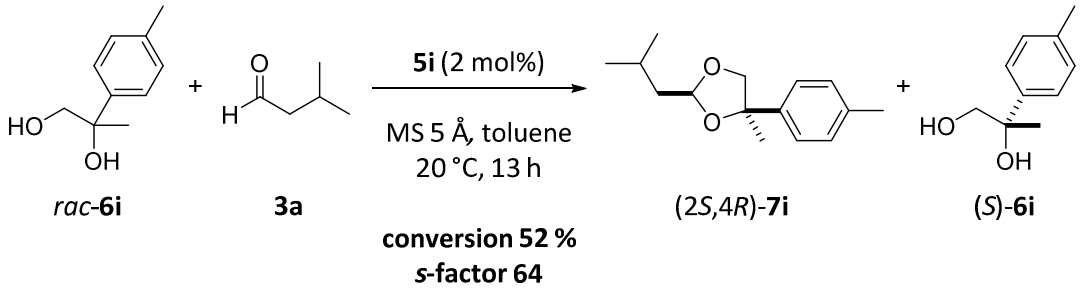
Yield: White solid, 45.0 mg, 49%. $[\alpha]^{25}_{D}$ = +9 ° (*c* 1.70, CH_2Cl_2).

^{1}H NMR (500 MHz, C_6D_6) δ 7.26 (d, *J* = 8.7 Hz, 1H), 6.80 (*J* = 8.6 Hz, 1H), 3.45 (d, *J* = 10.8 Hz, 1H), 3.35 (d, *J* = 10.9 Hz, 1H), 3.32 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 144.4, 133.1, 128.6, 127.1, 74.3, 70.9, 26.0.

HRMS (EI (DE)) *m/z* calculated for $C_{10}H_{14}O_2$ (M) 182.0943, found 182.0941.

HPLC (OD-3), n-heptane/i-PrOH 95:5, 1.0 ml/min, λ = 220 nm, t_{major} = 17.32 min, t_{minor} = 13.28 min, er = 96.5:3.5.



rac-**6i** **3a** (2*S*,4*R*)-**7i** (*S*)-**6i**

conversion 52 %
***s*-factor 64**

(2*S*,4*R*)-2-isobutyl-4-methyl-4-p-tolyl-1,3-dioxolane (7i)

Yield: Colorless oil, 54.1 mg, 46%. $[\alpha]^{25}_{D}$ = -42 ° (*c* 1.98, CH_2Cl_2).

^{1}H NMR (500 MHz, C_6D_6) δ 7.32 (d, *J* = 8.2 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 5.28 (t, *J* = 5.2 Hz, 1H), 3.94 (d, *J* = 7.8 Hz, 1H), 3.63 (d, *J* = 7.8 Hz, 1H), 2.13 (s, 3H), 1.97 (dt, *J* = 13.5, 6.7 Hz, 1H), 1.81-1.73 (m, 2H), 1.43 (s, 3H), 0.95 (dd, *J* = 6.7, 3.8 Hz, 6H) (signals of the minor diastereomer are not included).

^{13}C NMR (125 MHz, C_6D_6) δ 143.8, 136.4, 129.1, 125.2, 104.0, 81.7, 77.6, 43.7, 26.3, 25.1, 23.2, 23.2, 21.0 (signals of the minor diastereomer are not included).

HRMS (ESI+) *m/z* calculated for $C_{15}H_{22}O_2Na$ (M+Na) 257.1512, found 257.1511.

GC (Column: 25 m Hydrodex-β-TBDAC (Heptakis-(2,3-di-O-acetyl-6-O-tert-butyldimethyl-silyl)-β-cyclodextrin), i.D. 0.25 mm; Detector: FID; Temperature: injector 220 °C, detector 320 °C, oven 105 °C; gas: 0.4 bar H_2), major diastereomer: t_{major} = 112.9 min, t_{minor} = 110.4 min; er = 96:4, minor diastereomer: t_{major} = 99.3 min, t_{minor} = 101.7 min; er = 92.5:7.5, dr = 52:1.

(*S*)-2-p-tolylpropane-1,2-diol (6i)

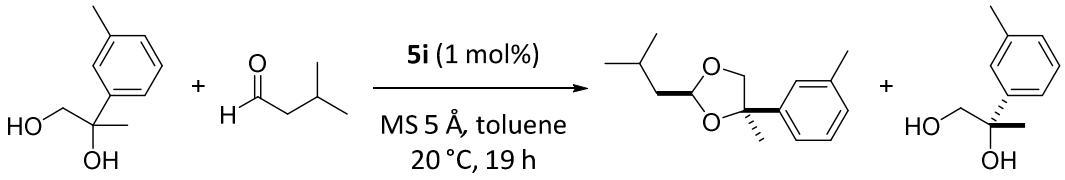
Yield: White solid, 36.4 mg, 44%. $[\alpha]^{25}_{D}$ = +11 ° (*c* 0.92, CH_2Cl_2).

^{1}H NMR (500 MHz, C_6D_6) δ 7.28 (d, *J* = 10.9 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 3.50 (d, *J* = 10.9 Hz, 1H), 3.39 (d, *J* = 10.9 Hz, 1H), 2.51 (bs, 1H), 2.13 (s, 3H), 1.79 (bs, 1H), 1.35 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 143.1, 136.4, 129.2, 125.5, 74.6, 71.3, 26.2, 21.0.

HRMS (EI (DE)) *m/z* calculated for $C_{10}H_{14}O_2$ (M) 166.0994, found 166.0992.

HPLC (OD-3), n-heptane/i-PrOH 98:2, 1.0 ml/min, λ = 220 nm, t_{major} = 19.75 min, t_{minor} = 17.38 min, er = 97.5:2.5.



rac-**6j** **3a** **conversion 46 %** *s*-**factor 110** (2*S*,4*R*)-**7j** (*S*)-**6j**

(2*S*,4*R*)-2-isobutyl-4-methyl-4-m-tolyl-1,3-dioxolane (7j)

Yield: Colorless oil, 53.0 mg, 45%. $[\alpha]^{25}_{D}$ = -38 ° (*c* 1.70, CH_2Cl_2).

^{1}H NMR (300 MHz, C_6D_6) δ 7.27-7.22 (m, 2H), 7.14-7.11 (overlapped with solvent, 1H), 6.93 (d, *J* = 7.4 Hz, 1H), 5.29 (t, *J* = 5.2 Hz, 1H), 3.95 (d, *J* = 7.8 Hz, 1H), 3.65 (d, *J* = 7.8 Hz, 1H), 2.16 (s, 3H), 1.97 (dt, *J* = 13.5, 6.7 Hz, 1H), 1.79-1.74 (m, 2H), 1.43 (s, 3H), 0.95 (dd, *J* = 6.6, 2.5 Hz, 6H) (signals of the minor diastereomer are not included).

^{13}C NMR (75 MHz, C_6D_6) δ 146.7, 137.8, 125.9, 122.4, 104.0, 81.8, 77.5, 43.7, 26.4, 25.1, 23.2, 23.2, 21.6 (signals of the minor diastereomer are not included).

HRMS (Cl (DE)) *m/z* calculated for $C_{15}H_{23}O_2$ (M+H) 235.1698, found 235.1696.

GC (Column: 25 m Lipodex G (Octakis-(2,3-di-O-pentyl-6-O-methyl)-γ-cyclodextrin), i.D. 0.25 mm; Detector: FID; Temperature: injector 220 °C, detector 320 °C, oven 100 °C to 145 °C with 1 °C/min; gas: 0.4 bar H_2), major diastereomer: t_{major} = 30.11 min, t_{minor} = 30.8 min; er = 98.5:1.5, minor diastereomer: t_{major} = 29.6 min; er >99.5:0.5, dr = 124:1.

(*S*)-2-p-tolylpropane-1,2-diol (6j)

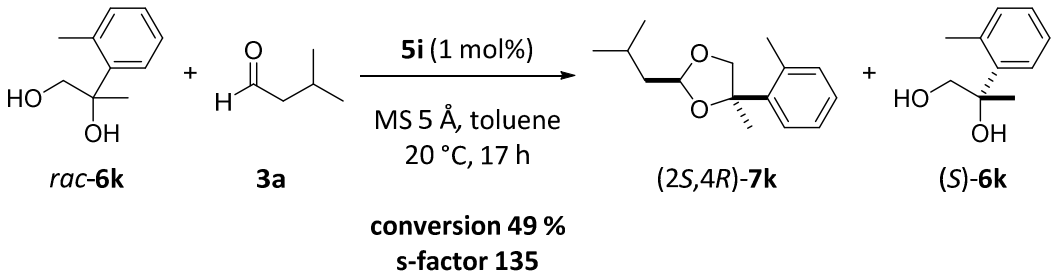
Yield: White solid, 44.7 mg, 54%. $[\alpha]^{25}_{D}$ = +7.8 ° (*c* 1.56, CH_2Cl_2).

^{1}H NMR (300 MHz, C_6D_6) δ 7.26-7.26 (m, 1H), 7.18-7.09 (overlapped with solvent, 2H), 6.94-6.91 (m, 1H), 3.49 (d, *J* = 10.9 Hz, 1H), 3.38 (d, *J* = 10.9 Hz, 1H), 2.16 (s, 3H), 1.34 (s, 3H).

^{13}C NMR (75 MHz, C_6D_6) δ 146.1, 137.9, 126.3, 122.7, 74.7, 71.3, 26.3, 21.6.

HRMS (ESI+) *m/z* calculated for $C_{10}H_{14}O_2Na$ (M+Na) 189.0886, found 189.0887.

HPLC (OD-3), n-heptane/i-PrOH 98:2, 1.0 ml/min, λ = 220 nm, t_{major} = 18.30 min, t_{minor} = 16.41 min, er = 90.5:9.5.



rac-**6k** **3a** (2*S*,4*R*)-**7k** (*S*)-**6k**

conversion 49 %
s-factor 135

(2*S*,4*R*)-2-isobutyl-4-methyl-4-o-tolyl-1,3-dioxolane (7k)

Yield: Colorless oil, 55.0 mg, 47%. $[\alpha]^{25}_{D}$ = -45 ° (*c* 1.47, CH_2Cl_2).

^{1}H NMR (300 MHz, C_6D_6) δ 7.74 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.12-6.96 (m, 3H), 5.30 (t, *J* = 5.2 Hz, 1H), 3.99-3.97 (m, 1H), 3.86 (d, *J* = 7.5 Hz, 1H), 2.07 (s, 3H), 1.94 (dt, *J* = 13.5, 6.6 Hz, 1H), 1.71-1.66 (m, 2H), 1.42 (s, 3H), 0.95 (dd, *J* = 6.7, 1.0 Hz, 6H) (signals of the minor diastereomer are not included).

^{13}C NMR (75 MHz, C_6D_6) δ 144.2, 133.5, 131.9, 127.3, 126.2, 126.0, 102.8, 82.8, 75.5, 43.7, 25.8, 25.0, 23.2, 23.2, 21.1 (signals of the minor diastereomer are not included).

HRMS (Cl (DE)) *m/z* calculated for $C_{15}H_{23}O_2$ (M+H) 235.1698, found 235.1700.

GC (Column: 30 m BGB-176/SE-52 (2,3-dimethyl-6-tert-butyldimethyl-silyl-β-cyclodextrin), i.D. 0.25 mm; Detector: FID; Temperature: injector 220 °C, detector 350 °C, oven 120 °C to 150 °C with 0.4 °C/min; gas: 0.4 bar H_2), major diastereomer: t_{major} = 51.7 min, t_{minor} = 52.4 min; er = 98.5:1.5, minor diastereomer: t_{major} = 50.0 min, t_{minor} = 49.1 min; er = 72:28, dr = 92:1.

(*S*)-2-o-tolylpropane-1,2-diol (6k)

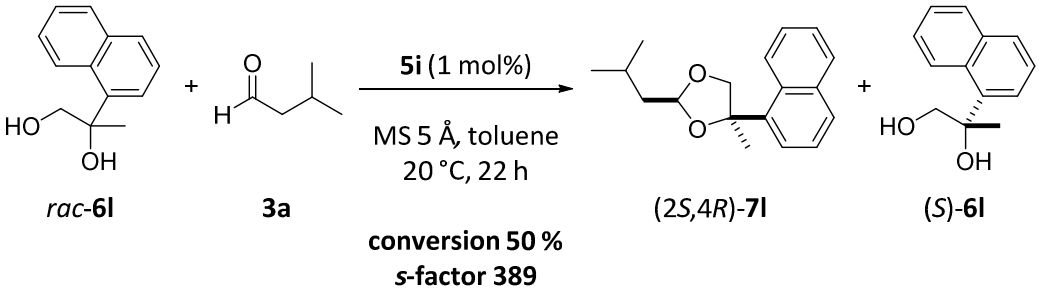
Yield: White solid, 44.0 mg, 51% (corrected for residual EtOAc in the sample). $[\alpha]^{25}_{D}$ = -0.11 ° (*c* 1.75, CH_2Cl_2).

^{1}H NMR (300 MHz, C_6D_6) δ 7.36-7.30 (m, 1H), 7.07-6.99 (m, 3H), 3.64 (d, *J* = 10.9 Hz, 1H), 3.39 (d, *J* = 10.9 Hz, 1H), 2.40 (s, 3H), 1.35 (s, 3H).

^{13}C NMR (75 MHz, C_6D_6) δ 142.9, 136.3, 133.0, 127.5, 126.7, 126.0, 75.7, 69.6, 25.6, 22.4.

HRMS (ESI+) *m/z* calculated for $C_{10}H_{14}O_2Na$ (M+Na) 189.0886, found 189.0887.

HPLC (OD-3), n-heptane/i-PrOH 95:5, 1.0 ml/min, λ = 220 nm, t_{major} = 8.32 min, t_{minor} = 7.51 min, er = 96.5:3.5.



rac-**6l** **3a** (2*S*,4*R*)-**7l** (*S*)-**6l**

conversion 50 %
***s*-factor 389**

(2*S*,4*R*)-2-isobutyl-4-methyl-4-(naphthalen-1-yl)-1,3-dioxolane (7l)

Yield: Colorless oil, 59.1 mg, 44%. $[\alpha]^{25}_{D}$ = -80 ° (*c* 1.90, CH_2Cl_2).

^{1}H NMR (500 MHz, C_6D_6) δ 8.01 (d, *J* = 7.2 Hz, 1H), 7.75-7.73 (m, 1H), 7.67-7.65 (m, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 7.27-7.22 (m, 2H), 5.36 (t, *J* = 5.2 Hz, 1H), 4.31 (d, *J* = 7.7 Hz, 1H), 4.05 (d, *J* = 7.7 Hz, 1H), 2.02-1.94 (m, 1H), 1.79-1.70 (m, 2H), 1.66 (s, 3H), 0.96 (dd, *J* = 6.6, 4.0 Hz, 6H) (signals of the minor diastereomer are not included).

^{13}C NMR (125 MHz, C_6D_6) δ 142.5, 135.0, 130.2, 129.7, 128.5, 125.9, 125.6, 125.3, 125.3, 123.5, 102.9, 82.6, 76.3, 43.6, 27.5, 25.0, 23.2, 23.2 (signals of the minor diastereomer are not included).

HRMS (ESI+) *m/z* calculated for $C_{18}H_{22}O_2Na$ (M+Na) 293.1512, found 293.1509.

GC (Column: 25 m Hydrodex-β-TBDAC (Heptakis-(2,3-di-O-acetyl-6-O-tert-butyldimethyl-silyl)-β-cyclodextrin), i.D. 0.25 mm; Detector: FID; Temperature: injector 220 °C, detector 320 °C, oven 145 °C; gas: 0.4 bar H_2), major diastereomer: t_{major} = 132.3 min; er >99.5:0.5, minor diastereomer: t_{minor} = 120.1 min; er >99.5:0.5, dr = 93:1.

(*S*)-2-(naphthalen-1-yl)propane-1,2-diol (6l)

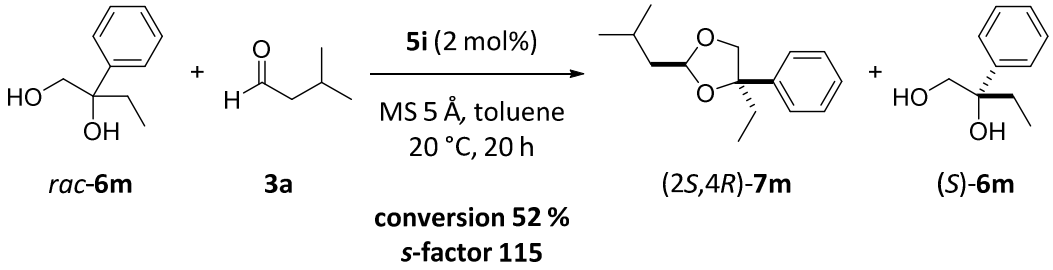
Yield: White solid, 45.5 mg, 45%. $[\alpha]^{25}_{D}$ = -2.7 ° (*c* 1.56, CH_2Cl_2).

^{1}H NMR (500 MHz, C_6D_6) δ 8.71 (d, *J* = 8.6 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.45 (d, *J* = 7.3 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 7.3 Hz, 1H), 7.20 (t, *J* = 7.7 Hz, 1H), 3.90 (d, *J* = 10.9 Hz, 1H), 3.56 (d, *J* = 11.0 Hz, 1H), 2.62 (bs, 1H), 1.63 (bs, 1H), 1.56 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 140.8, 135.5, 131.8, 129.5, 129.0, 127.3, 125.6, 125.4, 125.2, 124.4, 76.0, 70.0, 26.3.

HRMS (EI (DE)) *m/z* calculated for $C_{13}H_{14}O_2$ (M) 202.0994, found 202.0995.

HPLC (OD-3), n-heptane/i-PrOH 95:5, 1.0 ml/min, λ = 220 nm, t_{major} = 14.72 min, t_{minor} = 13.50 min, er = 98.5:1.5.



rac-**6m** **3a** (2*S*,4*R*)-**7m** (*S*)-**6m**

conversion 52 %
***s*-factor 115**

(2*S*,4*R*)-4-ethyl-2-isobutyl-4-phenyl-1,3-dioxolane (7m)

Yield: Colorless oil, 52.0 mg, 44%. $[\alpha]^{25}_{D}$ = -51 ° (*c* 1.10, CH_2Cl_2).

^{1}H NMR (500 MHz, C_6D_6) δ 7.33-7.31 (m, 2H), 7.20-7.19 (overlapped with solvent, 2H), 7.08 (t, *J* = 7.1 Hz, 1H), 5.25 (t, *J* = 5.2 Hz, 1H), 3.95 (d, *J* = 7.9 Hz, 1H), 3.70 (d, *J* = 7.9 Hz, 1H), 1.95 (dt, *J* = 13.4, 6.7 Hz, 1H), 1.82-1.69 (m, 3H), 1.66-1.59 (m, 1H), 0.96-0.93 (m, 6H), 0.79 (t, *J* = 7.3 Hz, 3H) (signals of the minor diastereomer are not included).

^{13}C NMR (125 MHz, C_6D_6) δ 145.0, 127.0, 125.7, 104.3, 84.9, 76.7, 43.7, 32.3, 25.1, 23.2, 23.1, 8.6 (signals of the minor diastereomer are not included).

HRMS (CI (DE) i-Butan) *m/z* calculated for $C_{15}H_{23}O_2$ (M+H) 235.1698, found 235.1698.

GC (Column: 25 m Lipodex G (Octakis-(2,3-di-O-pentyl-6-O-methyl)-γ-cyclodextrin), i.D. 0.25 mm; Detector: FID; Temperature: injector 220 °C, detector 320 °C, oven 110 °C; gas: 0.5 bar H_2), major diastereomer: t_{major} = 30.8 min, t_{minor} = 31.5 min; er = 98:2, minor diastereomer: t_{major} = 29.2 min, t_{minor} = 28.4 min; er = 99.5:0.5, dr = 36:1.

(*S*)-2-phenylbutane-1,2-diol (6m)

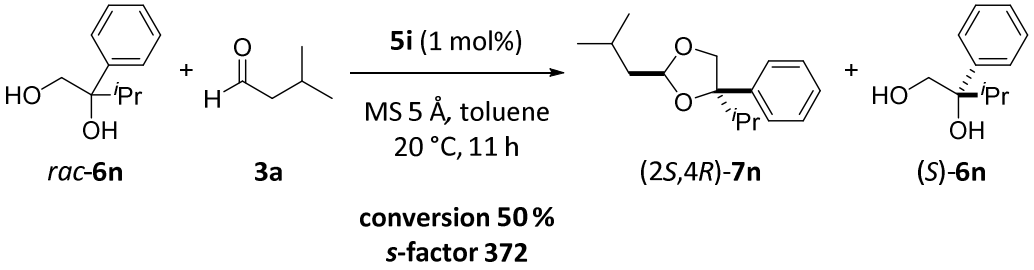
Yield: Colorless oil, 38.0 mg, 46%. $[\alpha]^{25}_{D}$ = -2 ° (*c* 2.20, CH_2Cl_2).

^{1}H NMR (500 MHz, C_6D_6) δ 7.32-1.29 (m, 2H), 7.19-7.17 (overlapped with solvent, 2H), 7.08 (t, *J* = 7.3 Hz, 1H), 3.45-3.36 (m, 2H), 2.24 (s, 1H), 1.72-1.65 (m, 1H), 1.59-1.52 (m, 1H), 0.97 (bs, 1H), 0.73 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 144.2, 128.4, 127.0, 126.0, 77.1, 70.6, 31.4, 7.7.

HRMS (EI (DE)) m/z calculated for $C_{10}H_{14}O_2$ (M) 166.0994, found 166.0992.

HPLC (OD-3), n-heptane/i-PrOH 95:5, 1.0 ml/min, λ = 210 nm, t_{major} = 8.33 min, t_{minor} = 7.66 min, er = 99.5:0.5.



(2*S*,4*R*)-2-isobutyl-4-isopropyl-4-phenyl-1,3-dioxolane (7n)

Yield: Colorless oil, 60.3 mg, 49%. $[\alpha]^{25}_{D}$ = -31 ° (*c* 2.04, CH_2Cl_2).

^{1}H NMR (300 MHz, C_6D_6) δ 7.32-7.28 (m, 2H), 7.20-7.17 (overlapped with solvent, 2H), 7.11-7.05 (m, 1H), 5.29 (t, *J* = 5.3 Hz, 1H), 4.10 (d, *J* = 8.3 Hz, 1H), 3.88 (d, *J* = 8.3 Hz, 1H), 1.99-1.83 (m, 2H), 1.70-1.55 (m, 2H), 0.93-0.88 (m, 9H), 0.72 (d, *J* = 6.9 Hz, 3H) (signals of the minor diastereomer are not included).

^{13}C NMR (75 MHz, C_6D_6) δ 144.2, 126.9, 126.6, 105.3, 87.2, 74.6, 44.1, 36.5, 25.1, 23.1, 23.1, 18.3, 17.6 (signals of the minor diastereomer are not included).

HRMS (EI (DE)) *m/z* calculated for $C_{16}H_{24}O_2$ (M) 248.1776, found 248.1778.

GC (Column: 30 m BGB-176/SE-52 (2,3-dimethyl-6-tert-butyldimethyl-silyl-β-cyclodextrin), i.D. 0.25 mm; Detector: FID; Temperature: injector 220 °C, detector 350 °C, oven 120 °C to 220 °C with 0.2 °C/min; gas: 0.4 bar H_2), major diastereomer: t_{major} = 41.9 min, t_{minor} = 41.0 min; er = 99.5:0.5, minor diastereomer: t_{major} = 39.4 min; er >99.5:0.5, dr = 191:1.

(*S*)-3-methyl-2-phenylbutane-1,2-diol (6n)

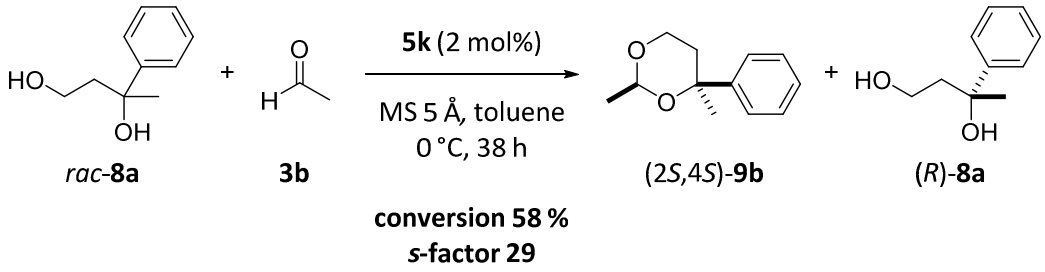
Yield: White solid, 39.5 mg, 44%. $[\alpha]^{25}_{D}$ = -19 ° (*c* 1.90, CH_2Cl_2).

^{1}H NMR (500 MHz, C_6D_6) δ 7.31-7.28 (m, 2H), 7.18-7.15 (overlapped with solvent, 2H), 7.09-7.06 (m, 1H), 3.59 (s, 2H), 2.55 (bs, 1H), 1.90-1.81 (m, 1H), 1.13 (bs, 1H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.72 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 144.0, 126.9, 126.6, 79.0, 68.4, 35.5, 17.6, 17.0.

HRMS (ESI+) *m/z* calculated for $C_{11}H_{16}O_2Na$ (M+Na) 203.1042, found 203.1043.

HPLC (OD-3), n-heptane/i-PrOH 95:5, 1.0 ml/min, λ = 220 nm, t_{major} = 7.84 min, t_{minor} = 7.12 min, er = 99:1.



(2*S*,4*S*)-2,4-dimethyl-4-phenyl-1,3-dioxane (9b)

Yield: Colorless oil, 52.3 mg, 54%. $[\alpha]^{25}_{D}$ = -49 ° (*c* 1.17, CH_2Cl_2). The absolute configuration of the quaternary carbon stereocenter was assigned opposite to the configuration in the recovered diol, and the relative configuration of the acetal stereocenter was determined from NOESY spectra.

^{1}H NMR (500 MHz, C_6D_6) δ 7.46 (dd, *J* = 8.4, 1.1 Hz, 2H), 7.23 (t, *J* = 7.8 Hz, 2H), 7.11 (t, *J* = 7.4 Hz, 1H), 4.98 (q, *J* = 5.0 Hz, 1H), 3.70 (ddd, *J* = 11.6, 5.5, 1.5 Hz, 1H), 3.59 (dt, *J* = 12.4, 2.4 Hz, 1H), 1.93 (dt, *J* = 13.0, 5.4 Hz, 1H), 1.45 (d, *J* = 5.0 Hz, 3H), 1.32 (s, 3H), 1.20 (td, *J* = 13.3, 1.9 Hz, 1H) (signals of the minor diastereomer are not included).

^{13}C NMR (125 MHz, C_6D_6) δ 149.8, 128.4, 126.8, 124.3, 92.7, 74.3, 62.9, 36.1, 22.9, 22.0 (signals of the minor diastereomer are not included).

HRMS (ESI+) *m/z* calculated for $C_{12}H_{16}O_2Na$ (M+Na) 215.1042, found 215.1043.

GC (Column: Supelco/Astec 30 m G-TA (γ-cyclodextrin-trifluoroacetyl), i.D. 0.25 mm; Detector: FID; Temperature: injector 220 °C, detector 320 °C, oven 80 °C to 180 °C with 1 °C/min; gas: 0.6 bar H_2), major diastereomer: t_{major} = 31.3 min, t_{minor} = 31.7 min; er = 91:9, minor diastereomer: t_{major} = 25.1 min, t_{minor} = 24.4 min; er = 97:3, dr = 17:1.

(*R*)-3-phenylbutane-1,3-diol (8a)

Yield: Colorless oil, 33.2 mg, 40%. $[\alpha]^{25}_{D}$ = +55 ° (*c* 0.9, C_6H_6), the absolute configuration was assigned by comparison with literature value.[169]

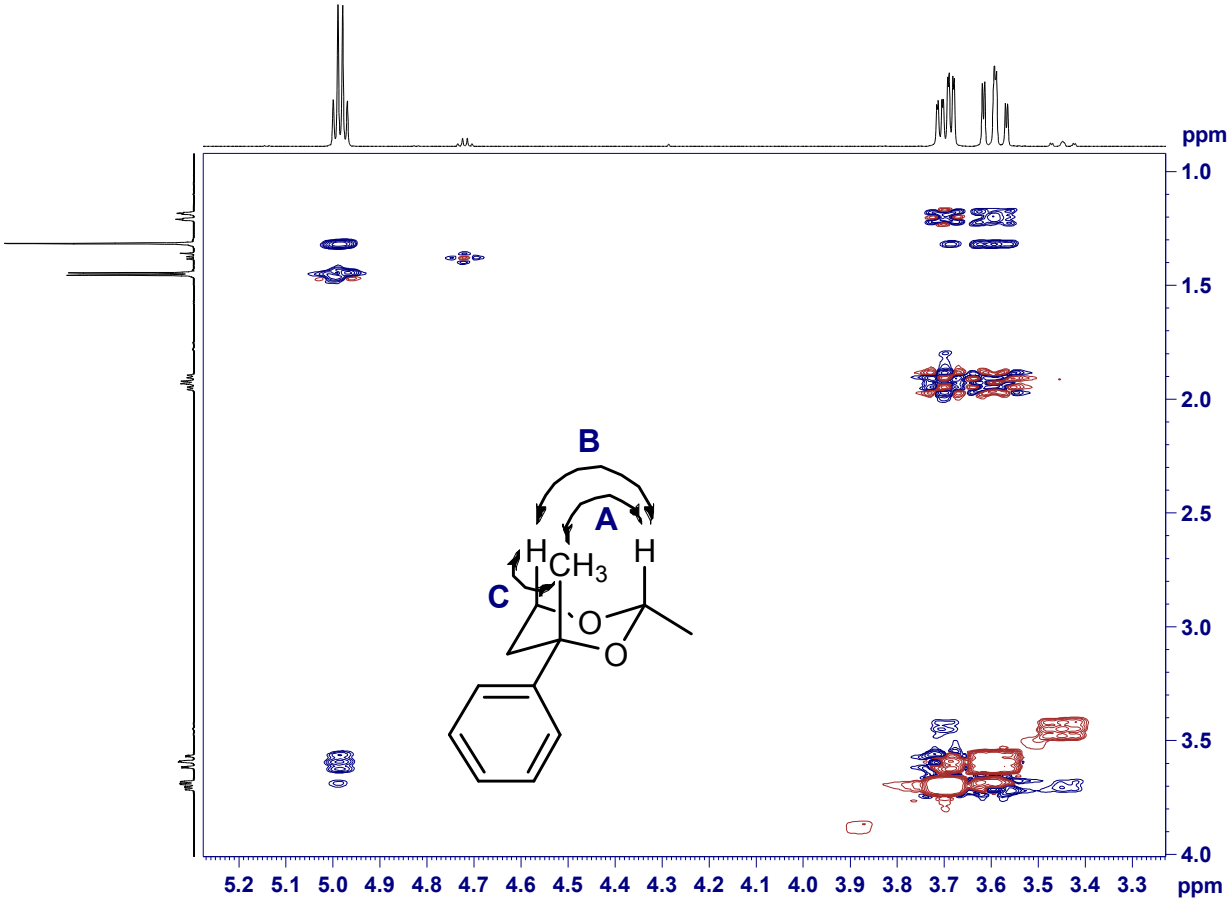
^{1}H NMR (500 MHz, C_6D_6) δ 7.38 (d, *J* = 7.9 Hz, 2H), 7.21 (t, *J* = 7.7 Hz, 2H), 7.09 (t, *J* = 7.3 Hz, 1H), 3.89 (bs, 1H), 3.43-3.39 (m, 1H), 3.35-3.31 (m, 1H), 2.29 (bs, 1H), 1.88-1.82 (m, 1H), 1.73-1.69 (m, 1H), 1.41 (s, 3H).

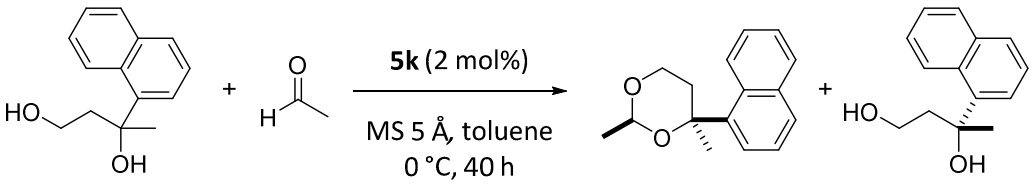
^{13}C NMR (125 MHz, C_6D_6) δ 148.5, 128.4, 126.6, 125.3, 75.7, 60.3, 44.1, 31.2.

HRMS (CI(FE) i-Butane) *m/z* calculated for $C_{10}H_{15}O_2$ (M+H) 167.1072, found 167.1071.

HPLC (OD-3), n-heptane/i-PrOH 98:2, 1.0 ml/min, λ = 210 nm, t_{major} = 25.03 min, t_{minor} = 22.61 min, er = 99:1.

NOESY experiments of compound 9b





rac-**8g** **3b** **conversion 56 %** *s*-**factor 16** (2*S*,4*S*)-**9g** (*R*)-**8g**

(2*S*,4*S*)-2,4-dimethyl-4-(naphthalen-1-yl)-1,3-dioxane (9g)

Yield: Colorless oil, 66.4 mg, 55%. $[\alpha]^{25}_{D}$ = -13 ° (*c* 2.55, CH_2Cl_2).

^{1}H NMR (300 MHz, C_6D_6) δ 8.77 (d, *J* = 8.8 Hz, 1H), 7.71-7.69 (m, 1H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.56 (d, *J* = 7.3 Hz, 1H), 7.40-7.37 (m, 1H), 7.30-7.25 (m, 2H), 5.10 (q, *J* = 5.0 Hz, 1H), 3.81-3.69 (m, 2H), 2.40 (td, *J* = 12.9, 5.6 Hz, 1H), 1.59 (s, 3H), 1.45 (d, *J* = 5.0 Hz, 3H), 1.43-1.39 (m, 1H) (signals of the minor diastereomer are not included).

^{13}C NMR (75 MHz, C_6D_6) δ 144.0, 135.6, 131.2, 129.6, 128.9, 127.5, 125.3, 125.2, 125.1, 122.7, 92.8, 76.1, 63.1, 35.7, 22.0, 21.9 (signals of the minor diastereomer are not included).

HRMS (ESI+) *m/z* calculated for $C_{16}H_{18}O_2Na$ (M+Na) 265.1199, found 265.1199.

GC (Column: 30 m Cyclodextrin-H/OV-1701 (2,3-dimethyl-3-pentyl-γ-cyclodextrin), i.D. 0.25 mm; Detector: FID; Temperature: injector 220 °C, detector 350 °C, oven 120 °C; gas: 0.6 bar H_2), major diastereomer: t_{major} = 50.2 min, t_{minor} = 50.6 min; er = 94.5:5.5, minor diastereomer: t_{major} = 40.0 min, t_{minor} = 38.3 min; er = 89:11, dr = 20:1.

(*R*)-3-(naphthalen-1-yl)butane-1,3-diol (8g)

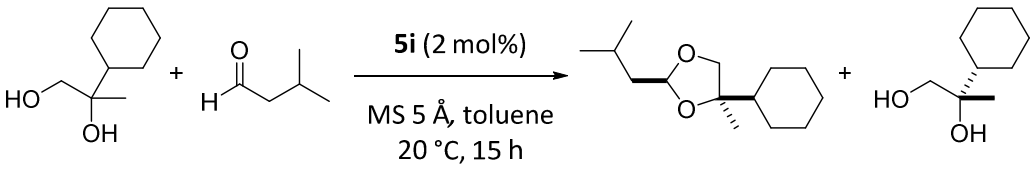
Yield: Colorless oil, 40.9 mg, 38%. $[\alpha]^{25}_{D}$ = +12 ° (*c* 1.50, CH_2Cl_2).

^{1}H NMR (300 MHz, C_6D_6) δ 8.47 (d, *J* = 8.3 Hz, 1H), 7.79-7.76 (m, 1H), 7.71-7.68 (m, 1H), 7.60 (d, *J* = 8.1 Hz, 1H), 7.33-7.23 (m, 3H), 3.46-3.36 (m, 2H), 3.27-3.18 (m, 1H), 2.36 (ddd, *J* = 14.8, 6.2, 3.8 Hz, 1H), 2.00 (ddd, *J* = 14.8, 8.3, 4.2 Hz, 1H), 1.67 (s, 3H).

^{13}C NMR (75 MHz, C_6D_6) δ 143.7, 135.5, 131.2, 129.7, 128.7, 126.8, 125.5, 125.4, 125.2, 124.3, 76.7, 60.5, 43.4, 30.2.

HRMS (ESI+) *m/z* calculated for $C_{14}H_{16}O_2Na$ (M+Na) 239.1042, found 239.1043.

HPLC (OD-3), n-heptane/i-PrOH 95:5, 1.0 ml/min, λ = 220 nm, t_{major} = 18.00 min, t_{minor} = 16.70 min, er = 94.5:5.5.



rac-**6o** **3a** (2*S*,4*R*)-**7o** (*S*)-**6o**

conversion 55 %
***s*-factor 23**

(2*S*,4*R*)-4-cyclohexyl-2-isobutyl-4-methyl-1,3-dioxolane (7o)

Yield: Colorless oil, 55.2 mg, 49%. $[\alpha]^{25}_{D}$ = -19 ° (*c* 2.00, CH_2Cl_2).

^{1}H NMR (300 MHz, C_6D_6) δ 5.11 (t, *J* = 5.1 Hz, 1H), 3.71 (d, *J* = 8.0 Hz, 1H), 3.29 (d, *J* = 7.9 Hz, 1H), 2.00-1.86 (m, 2H), 1.73-1.55 (m, 7H), 1.46 (m, 1H), 1.23-1.08 (m, 3H), 1.05 (s, 3H), 0.96 (d, *J* = 8.0 Hz, 3H), 0.93 (d, *J* = 1.0 Hz, 3H), 0.92-0.83 (m, 1H) (signals of the minor diastereomer are not included).

^{13}C NMR (75 MHz, C_6D_6) δ 102.9, 82.6, 74.0, 47.1, 43.7, 28.5, 27.9, 26.9, 26.9, 26.8, 25.0, 23.3, 23.2, 20.6 (signals of the minor diastereomer are not included).

HRMS (CI (FE) i-Butan) *m/z* calculated for $C_{14}H_{27}O_2$ (M) 227.2011, found 227.2009.

GC (Column: 25 m Lipodex G (Octakis-(2,3-di-O-pentyl-6-O-methyl)-γ-cyclodextrin), i.D. 0.25 mm; Detector: FID; Temperature: injector 220 °C, detector 350 °C, oven 80 °C; gas: 0.4 bar H_2), major diastereomer: t_{major} = 44.3 min, t_{minor} = 45.3 min; er = 95.5:4.5, minor diastereomer: t_{major} = 46.0 min, t_{minor} = 44.8 min; er = 96.5:3.5, dr = 11:1.

(*S*)-2-cyclohexylpropane-1,2-diol (6o)

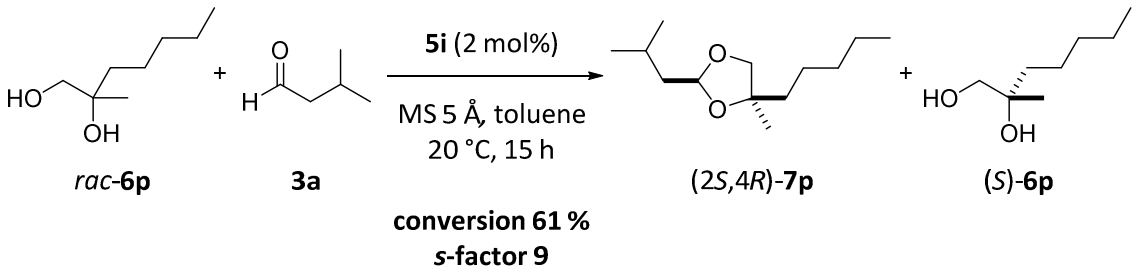
Yield: White solid, 35.3 mg, 45%. $[\alpha]^{25}_{D}$ = -11 ° (*c* 1.07, CH_2Cl_2).

^{1}H NMR (300 MHz, C_6D_6) δ 3.32 (d, *J* = 10.7 Hz, 1H), 3.18 (d, J = 10.7 Hz, 1H), 1.87 (m, 7H), 1.42-1.32 (m, 1H), 1.25-0.96 (m, 4H), 0.93 (s, 3H), 0.90-0.72 (m, 2H).

^{13}C NMR (75 MHz, C_6D_6) δ 74.3, 68.6, 45.3, 28.0, 27.1, 26.9, 20.4.

HRMS (ESI+) *m/z* calculated for $C_9H_{18}O_2Na$ (M+Na) 181.1199, found 181.1200.

GC (Column: 30 m BGB-178/BGB-15 (2,3-diethyl-6-tert-butyldimethyl-silyl-β-cyclodextrin), i.D. 0.25 mm; Detector: FID; Temperature: injector 220 °C, detector 350 °C, oven 80 °C to 140 °C with 0.5 °C/min; gas: 0.4 bar H_2), t_{major} = 56.95 min, t_{minor} = 57.58 min; er = 95.5:4.5.



rac-**6p** **3a** (2*S*,4*R*)-**7p** (*S*)-**6p**

conversion 61 %
***s*-factor 9**

(2*S*,4*R*)-2-isobutyl-4-methyl-4-pentyl-1,3-dioxolane (7p)

Yield: Colorless oil, 58.4 mg, 54%. $[\alpha]^{25}_{D}$ = -10 ° (*c* 2.18, CH_2Cl_2).

^{1}H NMR (300 MHz, C_6D_6) δ 5.13 (t, *J* = 5.09 Hz, 1H), 3.61 (d, *J* = 7.9 Hz, 1H), 3.33 (d, *J* = 7.9 Hz, 1H), 2.02-1.88 (m, 1H), 1.73-1.69 (m, 2H), 1.52-1.19 (m, 8H), 1.09 (s, 3H), 0.95 (dd, *J* = 6.7, 0.8 Hz, 6H), 0.87 (t, *J* = 7.0 Hz, 3H) (signals of the minor diastereomer are not included or overlapped with major diastereomer. For NMR characterization of the minor diastereomer see ***epi*-7p** from the stereodivergent resolution).

^{13}C NMR (75 MHz, C_6D_6) δ 103.2, 80.3, 75.1, 43.9, 40.6, 32.7, 25.0, 24.3, 23.5, 23.3, 23.0, 14.2 (signals of the minor diastereomer are not included. For NMR characterization of minor diastereomer see ***epi*-7p** from stereodivergent resolution).

HRMS (CI (DE)) *m/z* calculated for $C_{13}H_{27}O_2$ (M) 215.2011, found 215.2012.

GC (Column: 30 m BGB-178/BGB-15 (2,3-diethyl-6-tert-butyldimethyl-silyl-β-cyclodextrin), i.D. 0.25 mm; Detector: FID; Temperature: injector 220 °C, detector 350 °C, oven 80 °C to 105 °C with 0.2 °C/min; gas: 0.3 bar H_2), major diastereomer: t_{major} = 92.3 min, t_{minor} = 90.5 min; er = 98.5:1.5, minor diastereomer: t_{major} = 93.5 min; er >99.5:0.5, dr = 4:1.

(*S*)-2-methylheptane-1,2-diol (6p)

Yield: Colorless oil, 24.4 mg, 33%. $[\alpha]^{25}_{D}$ = -2 ° (*c* 0.90, CH_2Cl_2).

^{1}H NMR (300 MHz, C_6D_6) δ 3.21 (d, *J* = 10.6 Hz, 1H), 3.14 (d, *J* = 10.6 Hz, 1H), 1.51 (bs, 2H), 1.30-1.20 (m, 8H), 0.98 (s, 3H), 0.89 (t, *J* = 6.9 Hz, 3H).

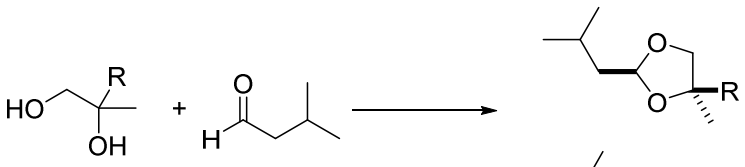
^{13}C NMR (75 MHz, C_6D_6) δ 72.5, 70.0, 39.1, 32.9, 23.7, 23.5, 23.0, 14.3.

HRMS (ESI+) *m/z* calculated for $C_8H_{18}O_2Na$ (M+Na) 169.1199, found 169.1200.

GC (Column: 25 m Hydrodex-β-TBDAC (Heptakis-(2,3-di-O-acetyl-6-O-tert-butyldimethyl-silyl)-β-cyclodextrin), i.D. 0.25 mm; Detector: FID; Temperature: injector 220 °C, detector 350

°C, oven 80 °C to 135 °C with 1 °C/min; gas: 0.4 bar H_2), t_{major} = 46.3 min, t_{minor} = 47.3 min; er = 93:7.

7.3.3. Determination of conversion and selectivity factors



A = starting alcohol
A_{maj} = major enantiomer of A
A_{min} = minor enantiomer of A

B = product, major diastereomer
B_{maj} = major enantiomer of B
B_{min} = minor enantiomer of B

C = product, minor diastereomer
C_{maj} = major enantiomer of C
C_{min} = minor enantiomer of C

The ee and dr values used for the calculations of conversions and s-factors were obtained from the relative area values given in HPLC and GC traces and were not significantly rounded before the calculations. Conversions were calculated from ee values of recovered starting materials and ee and dr (dr = n(B)/n(C)) values of products using formula (1).

$$\text{conversion} = \frac{1}{\frac{dr \cdot ee(B) - ee(C)}{ee(A) \cdot (1+dr)} + 1} \qquad (1)$$

The formula was derived from two reasonable assumptions[56]:

a) Since the reactions are very clean and no observable byproducts are formed, the conversion can be represented by (2).

$$\text{conversion} = \frac{n(B) + n(C)}{n(A) + n(B) + n(C)} = \frac{n(B) \cdot (1+1/dr)}{n(A) + n(B) \cdot (1+1/dr)} \qquad (2)$$

b) The alcohol stereocenter is not racemizing under the reaction conditions. The absolute configuration of this stereocenter in the major enantiomer of the major diastereomer is opposite to the configuration in the major enantiomer of the minor diastereomer and the starting material. As the starting material is racemic, the total number of molecules which have a tertiary alcohol derived stereocenter in *S* configuration has to be equal to the total number of molecules which have this stereocenter in *R* configuration:

$$n(A_{maj}) + n(B_{min}) + n(C_{maj}) = n(A_{min}) + n(B_{maj}) + n(C_{min}) \qquad (3)$$

Reorganizing (3) gives :

$$n(A_{maj}) - n(A_{min}) = n(B_{maj}) - n(B_{min}) - (n(C_{maj}) - n(C_{min})) \qquad (4)$$

and from the definition of ee value (X being A, or B, or C):

$$n(X_{maj}) - n(X_{min}) = ee(X) \cdot (n(X_{maj}) + n(X_{min})) = ee(X) \cdot n(X)$$

we get:

$$ee(A) \cdot n(A) = ee(B) \cdot n(B) - ee(C) \cdot n(C) \qquad (5)$$

Using n(C) = n(B)/dr, gives, after rearrangement:

$$n(A) = \frac{n(B) \cdot (ee(B) - 1/dr \cdot ee(C))}{ee(A)} \qquad (6)$$

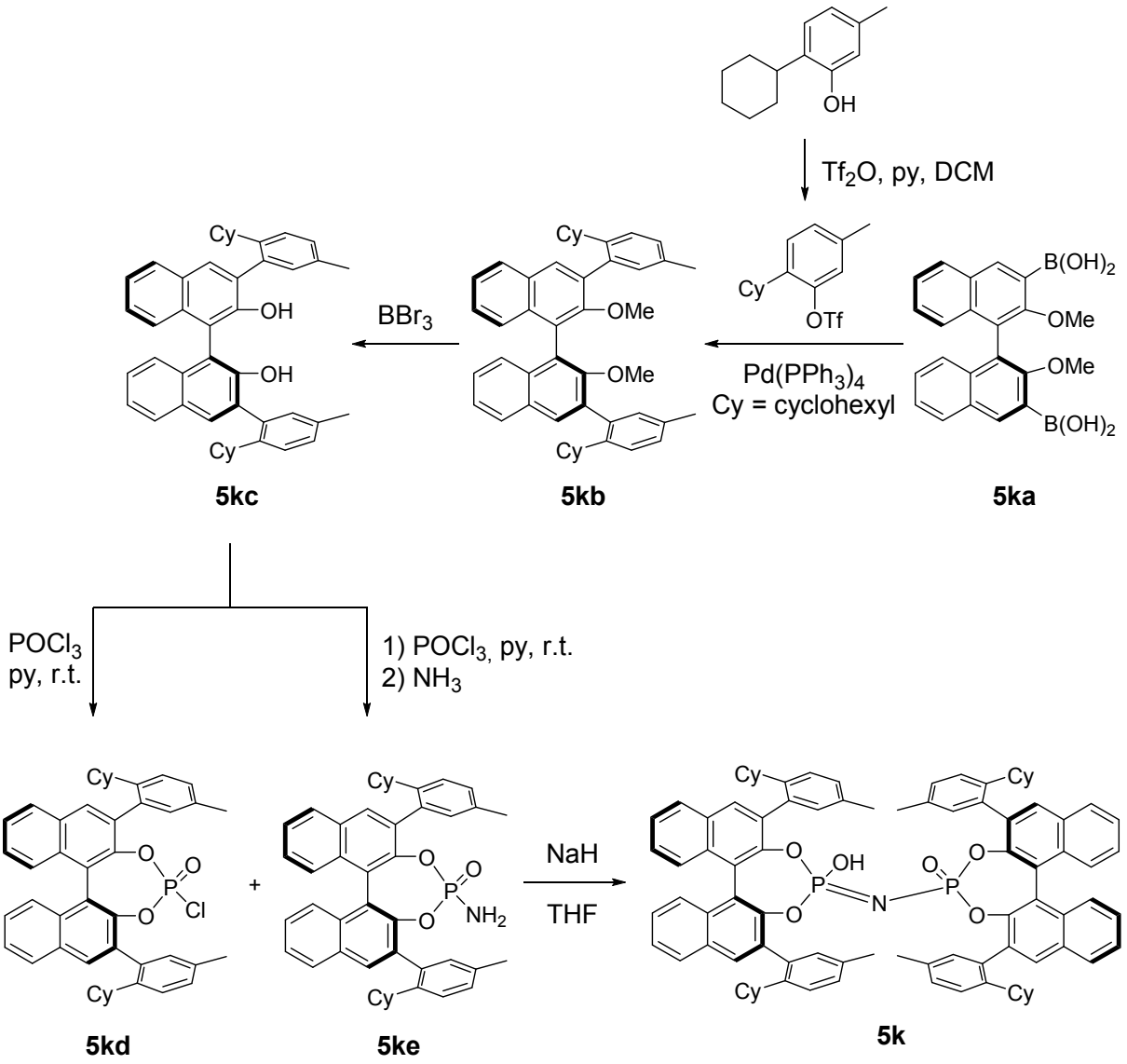
Placing this expression for n(A) into (2), gives after cancelling n(B), an expression which can be simplified to (1).

$$\text{conversion} = \frac{1+1/dr}{\frac{ee(B) - 1/dr \cdot ee(C)}{ee(A)} + 1+1/dr} \quad \begin{matrix} / (1+1/dr) \\ / (1+1/dr) \end{matrix}$$

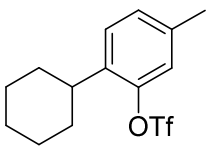
S-factors were determined using conversion from (1) and ee of the recovered starting material according to literature.[141]

7.3.4. Synthesis of catalyst 5k

(performed by I. Čorić)[68]



2-cyclohexyl-5-methylphenyl trifluoromethanesulfonate



Trifluoromethanesulfonic anhydride (6.1 ml, 10.2 g, 36 mmol) was added dropwise to the solution of 2-cyclohexyl-5-methylphenol (5.71 g, 30 mmol) and pyridine (7.3 ml) in dry CH_2Cl_2 (30 ml) at 0 °C under argon. The mixture was stirred at room temperature for 19.5 h. Then water (60 ml) was added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with aq. 1 N

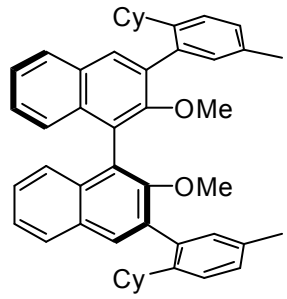
HCl, water, and brine, dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure yielding the title compound as a colorless liquid. Yield: 9.28 g, 96%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 7.9 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.03 (s, 1H), 2.85-2.79 (m, 1H), 2.34 (s, 3H), 1.85-1.75 (m, 5H), 1.46-1.34 (m, 4H), 1.30-1.22 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 147.1, 137.8, 137.2, 129.4, 128.2, 121.7, 118.8 (q, *J*(C-F) = 320 Hz), 37.2, 33.7, 26.8, 26.1, 21.0.

HRMS (ESI+) *m/z* calculated for $C_{14}H_{17}O_3F_3SNa$ (M+Na) 345.0743, found 345.0745.

(*S*)-3,3'-bis(2-cyclohexyl-5-methylphenyl)-2,2'-dimethoxy-1,1'-binaphthalene (5kb)



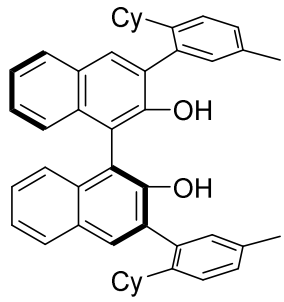
A suspension of **5ka** (2.41 g, 6.0 mmol), 2-cyclohexyl-5-methylphenyl trifluoromethanesulfonate (7.73 g, 24 mmol) and $Ba(OH)_2{\cdot}8H_2O$ (7.5 g, 24 mmol) in dioxane/water 3:1 (60 ml) was degassed by bubbling argon gas for 15 min. $Pd(PPh_3)_4$ (348 mg, 0.3 mmol) was added and the mixture was stirred for 1.5 h at room temperature, and further 1 h at 100 °C. After being cooled at room temperature, water (500 ml) was added and the mixture extracted with CH_2Cl_2 (2 · 250 ml). Combined organic extracts were washed with water (500 ml), dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel using 10-40% CH_2Cl_2/hexane as the eluents yielding the title compound as a colorless solid (2.35 g, 59%).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.94-7.90 (m, 2H), 7.85-7.79 (4 singlets, 2H), 7.46-7.40 (m, 2H), 7.35-7.20 (m, 10H), 3.20 (s, 1.6H), 3.19 (s, 1.6H), 3.06 (s, 1.25H), 3.05 (s, 1.55H), 2.72-2.54 (m, 2H), 2.40 (s, 3.2H), 2.39 (s, 1.25H), 2.37 (s, 1.55H), 1.95-1.48 (m, 11.8H), 1.35-1.11 (m, 7H), 1.01-0.89 (m, 1.4H) (spectra complicated due to presence of rotamers).

^{13}C NMR (125 MHz, CD_2Cl_2) δ 155.4, 154.7, 154.6, 154.6, 144.4, 144.2, 144.1, 143.9, 138.4, 138.2, 138.1, 138.0, 136.7, 136.4, 136.2, 135.8, 135.2, 135.1, 134.9, 134.2, 134.1, 133.9, 133.9, 131.9, 131.7, 131.6, 131.3, 131.2, 131.2, 131.1, 131.1, 131.0, 130.9, 130.8, 129.0, 129.0, 128.9, 128.8, 128.4, 128.3, 126.5, 126.5, 126.3, 126.3, 126.1, 126.1, 126.0, 126.0, 125.6, 125.3, 125.3, 125.2, 125.0, 125.0, 124.9, 61.2, 61.0, 60.8, 60.6, 41.4, 41.3, 41.0, 40.7, 36.1, 36.0, 35.8, 33.5, 33.4, 33.4, 33.3, 27.7, 27.6, 27.5, 27.4, 27.3, 27.2, 27.0, 26.7, 26.6, 26.6, 26.4, 21.1 (spectra complicated due to presence of rotamers).

HRMS (ESI+) *m/z* calculated for $C_{48}H_{50}O_2Na$ (M+Na) 681.3703, found 681.3704.

(S)-3,3'-bis(2-cyclohexyl-5-methylphenyl)-[1,1'-binaphthalene]-2,2'-diol (5kc)



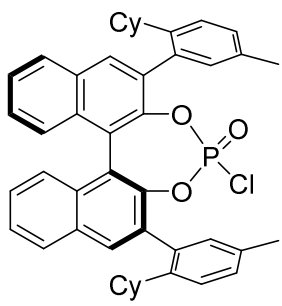
A 1 M solution of BBr_3 in CH_2Cl_2 (14.3 ml, 14.3 mmol) was added dropwise to the solution of (*S*)-**5kb** (2.35 g, 3.57 mmol) in CH_2Cl_2 (37 ml) at 0 °C under argon. After 23 h at room temperature, the solution was cooled to 0 °C, water (110 ml) was carefully added, and the mixture was extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous Na_2CO_3 solution (100 ml), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel using 30% CH_2Cl_2/hexane as the eluent yielding the title compound as a colorless solid. Yield: 1.95 g, 87%.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.94-7.83 (m, 4H), 7.44-7.17 (m, 12H), 5.20 (s, 0.4H), 5.15 (s, 1H), 5.13 (s, 0.6H), 3.62-2.56 (m, 1.4H), 2.52-2.43 (m, 0.7H), 2.40 (s, 1.1H), 2.39 (s, 1.9H), 2.37 (s, 3.0H), 1.86-1.60 (m, 9.7H), 1.58-1.44 (m, 2H), 1.44-1.13 (m, 7.3H), 1.09-0.94 (m, 1.3H) (spectra complicated due to presence of rotamers).

^{13}C NMR (125 MHz, CD_2Cl_2) δ 151.1, 150.9, 150.9, 150.8, 144.5, 144.5, 144.4, 136.2, 136.0, 135.9, 135.9, 135.8, 135.8, 133.9, 133.7, 133.6, 133.5, 131.6, 131.6, 131.5, 131.5, 131.4, 131.4, 131.3, 129.7, 129.7, 129.7, 129.6, 128.8, 128.8, 128.7, 128.7, 127.3, 127.1, 126.8, 126.6, 126.6, 126.5, 124.9, 124.5, 124.4, 124.4, 124.3, 113.0, 112.9, 112.8, 112.7, 41.4, 41.4, 41.3, 35.5, 35.4, 35.3, 35.3, 34.2, 34.1, 34.0, 33.8, 27.6, 27.5, 27.3, 27.3, 26.6, 26.5, 21.0, 21.0 (spectra complicated due to presence of rotamers).

HRMS (ESI+) *m/z* calculated for $C_{46}H_{46}O_2Na$ (M+Na) 653.3390, found 653.3394.

(*S*)-4-chloro-2,6-bis(2-cyclohexyl-5-methylphenyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide (5kd)



To a solution of (*S*)-**5kc** (500 mg, 0.793 mmol) in pyridine (2.6 ml) under argon was added $POCl_3$ (222 µl, 365 mg, 2.38 mmol) at room temperature. The mixture was stirred at room temperature for 17 h and then concentrated to dryness under vacuum. The residue was passed through a short silica gel column (13 g) using 50-100% CH_2Cl_2/hexane as eluents yielding the title compound as a colorless solid. Yield: 512 mg, 91%.

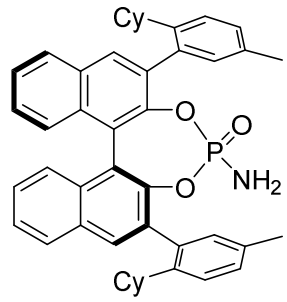
^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.05-7.93 (m, 4H), 7.61-7.56 (m, 2H), 7.44-7.35 (m, 4.5H), 7.30-7.19 (m, 5.3H), 7.12-7.11 (m, 0.2H), 2.80-2.63 (m, 0.4H), 2.43-2.31 (m including large singlets at 2.39, 2.37 and 2.31 ppm, 7.6H), 2.26-2.23 (m, 0.3H), 2.10-2.06 (m, 0.2H), 1.89-1.40 (m, 11.6H), 1.36-1.08 (m, 4.7H), 1.01-0.84 (m, 3.2H) (spectra complicated due to presence of rotamers).

^{13}C NMR (125 MHz, CD_2Cl_2) δ 144.9, 144.9, 144.8, 144.8, 144.2, 144.0, 143.9, 143.6, 143.3, 135.2, 135.2, 135.1, 135.0, 134.7, 134.6, 134.4, 134.1, 134.1, 134.0, 133.9, 133.1, 132.9, 132.9, 132.8, 132.5, 132.5, 132.4, 132.3, 132.2, 132.1, 132.0, 131.7, 131.6, 129.8, 129.7, 129.6, 129.5, 128.9, 128.8, 127.6, 127.4, 127.4, 127.3, 127.2, 127.1, 127.1, 127.0, 126.9, 126.9, 126.8, 126.1, 126.0, 126.0, 122.1, 122.1, 122.1, 122.1, 41.6, 41.6, 41.5, 41.5, 40.8, 40.8, 40.7, 37.9, 36.8, 35.8, 35.7, 35.3, 34.2, 33.8, 33.6, 33.0, 32.9, 27.5, 27.4, 27.3, 27.3, 27.2, 27.1, 26.9, 26.6, 26.4, 21.0, 21.0, 20.9 (including signals due to the presence of rotamers and unassigned C-P-coupling).

^{31}P NMR (202 MHz, CD_2Cl_2) δ 7.57 (major), 7.34, 7.21 (spectra complicated due to the presence of rotamers).

HRMS (ESI+) *m*/*z* calculated for $C_{46}H_{44}O_3ClPNa$ (M+Na) 733.2609, found 733.2611.

(*S*)-4-amino-2,6-bis(2-cyclohexyl-5-methylphenyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide (5ke)



To a solution of (*S*)-**5kc** (416 mg, 0.66 mmol) in pyridine (2.1 ml) under argon was added $POCl_3$ (185 µl, 304 mg, 1.98 mmol) at room temperature. After 18.5 h at room temperature, the mixture was cooled to –78 °C and anhydrous ammonia gas was condensed into the reaction flask (ca. 10 ml). The cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction mixture was then concentrated to dryness under vacuum. Residue was passed through short silica gel column (20 g) using 0-64% EtOAc/CH_2Cl_2 as eluents yielding the title compound as a colorless solid. Yield: 402 mg, 88%.

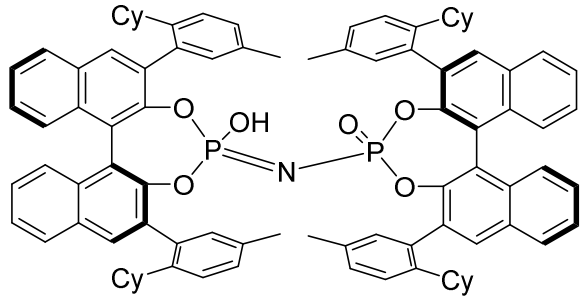
^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.09 (d, *J* = 8.2 Hz, 0.24H), 8.02-7.88 (m, 3.5H), 7.80 (s, 0.24H), 7.61-7.51 (m, 2H), 7.46-7.30 (m, 5.7H), 7.27-7.09 (m, 3.8H), 7.01 (d, *J* = 1.1 Hz, 0.23H), 2.76-2.63 (m, 2.4H), 2.44-2.21 (m including large singlet at 2.38 ppm, 7H), 2.09-1.77 (m, 2.6), 1.71-1.08 (m, 14.7H), 1.03-0.82 (m, 3.2H) (spectra complicated due to the presence of rotamers).

^{13}C NMR (125 MHz, CD_2Cl_2) δ 145.5, 145.4, 144.9, 144.8, 144.4, 144.3, 144.0, 143.6, 142.8, 136.3, 136.2, 136.1, 136.1, 135.3, 135.1, 135.0, 134.6, 134.6, 134.6, 134.4, 134.4, 133.7, 132.7, 132.6, 132.5, 132.4, 132.2, 132.2, 132.1, 132.0, 131.9, 131.9, 131.8, 131.3, 131.2, 129.7, 129.6, 129.5, 129.3, 128.8, 128.7, 128.7, 128.4, 127.5, 127.3, 127.1, 127.1, 127.0, 126.9, 126.8, 126.8, 126.4, 126.3, 126.3, 126.2, 126.1, 125.7, 123.1, 122.6, 122.5, 122.5, 122.2, 122.2, 41.5, 41.3, 41.3, 40.9, 40.3, 37.5, 36.6, 35.7, 35.6, 35.2, 34.5, 33.9, 33.8, 33.7, 33.0, 27.6, 27.5, 27.4, 27.3, 27.2, 27.1, 27.0, 26.7, 26.6, 26.5, 26.4, 21.1, 21.0, 21.0, 21.0, 20.7 (including signals due to the presence of rotamers and unassigned C-P-coupling).

^{31}P NMR (202 MHz, CD_2Cl_2) δ 13.8, 12.0 (major), 11.7 (spectra complicated due to the presence of rotamers).

HRMS (ESI+) *m*/*z* calculated for $C_{46}H_{46}NO_3PNa$ (M+Na) 714.3107, found 714.3105.

Imidodiphosphoric acid 5k



Sodium hydride (60% dispersion of in mineral oil, 83 mg, 2.08 mmol) was added to a solution of (*S*)-**5ke** (359 mg, 0.519 mmol) and (*S*)-**5kd** (442 mg, 0.622 mmol) in THF (3.9 ml) under argon at room temperature. After 18 h at room temperature, 10% aqueous HCl solution (5 ml) and DCM (5 ml) were added, and the mixture was stirred for 10 min. The organic layer was separated, and aqueous layer was extracted with DCM (2 · 10 ml). Organic layers were combined, and the solvent removed under reduced pressure. The residue was purified by column chromatography on aluminum oxide (activity III, 20 g) using 50% DCM/hexane and 0-32% EtOAc/DCM as the eluents giving a colorless solid. The solid was dissolved in CH_2Cl_2 (10 ml) and stirred with 10% aqueous HCl (10 ml) for 10 min. The organic layer was separated, washed with 10% aqueous HCl (10 ml), and concentrated under reduced pressure to give the title compound as a colorless solid. Yield: 386 mg, 54%.

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.33 (s, 0.7H), 8.19 (d, *J* = 8.0 Hz, 0.7H), 8.05-7.97 (m, 3.4H), 7.88-7.81 (m, 2.0H), 7.56-7.54 (m, 2.0H), 7.43-7.38 (m, 3.7H), 7.33-7.19 (m, 7.9H), 7.13-6.94 (m, 6.8H), 6.84-6.72 (m, 2.7H), 6.61-6.60 (m, 0.9H), 6.49 (s, 0.1H), 6.21 (s, 0.1H), 6.14-6.11 (m, 0.8H), 5.93 (s, 0.1H), 5.51 (bs, 3H, acidic H+ water), 2.62-2.60 (m, 1.0H), 2.31 (s, 2.3H), 2.27 (s, 2.3H), 2.20-2.14 (m, 3.9H), 2.08 (s, 0.5H), 1.98-0.96 (m, 40.0H), 0.67-0.63 (m, 3.2H), 0.53-0.45 (m, 4.1H), 0.26-0.24 (m, 0.9H), -0.42 to -0.45 (m, 0.6H).

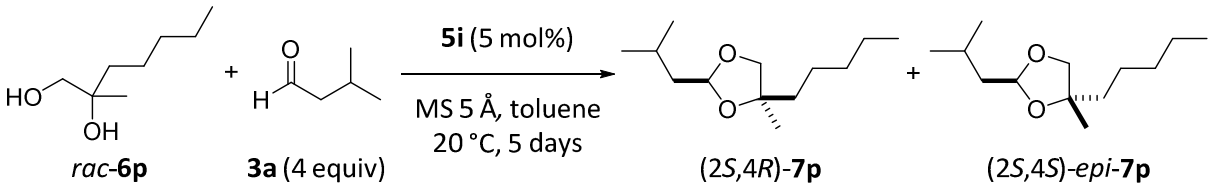
^{13}C NMR (125 MHz, DMSO-d_6) δ 147.2, 146.0, 145.9, 142.2, 142.0, 141.9, 141.8, 135.8, 135.7, 135.6,,134.8, 134.2, 133.7, 133.5, 133.2, 133.0, 132.6, 131.9, 131.5, 131.3, 131.2, 131.0, 130.6, 130.5, 130.1, 129.9, 129.6, 129.5, 128.6, 128.3, 128.2, 128.2, 128.1, 127.5, 126.4, 125.8, 125.5, 125.1, 125.0, 124.8, 124.0, 123.7, 122.7, 121.9, 121.1, 120.5, 35.5, 35.1, 34.8, 34.3, 33.9, 33.4, 32.9, 32.6, 30.1, 26.7, 26.6, 26.6, 26.4, 25.8, 25.5, 25.4, 25.4, 25.3, 20.8, 20.3, 20.1, 20.0 (spectra complicated due to the presence of rotamers, C-P-coupling was not assigned).

^{31}P NMR (202 MHz, DMSO-d_6) δ 3.6, -15.7 (major), 14.9, 0.4, 0.1, -1.3 (minor) (spectra complicated due to the presence of rotamers).

HRMS (ESI–) *m*/*z* calculated for $C_{92}H_{88}NO_6P_2$ (M–H) 1364.6092, found 1364.6091.

7.3.5. Stereodivergent resolution of diols

Resolution of *rac*-6p



rac-**6p** **3a** (4 equiv) (2*S*,4*R*)-**7p** (2*S*,4*S*)-*epi*-**7p**

Aldehyde **3a** (2.0 mmol) was added to the mixture of diol *rac*-**6p** (0.50 mmol), catalyst **5i** (5 mol%) and 5 Å molecular sieves (100 mg) in toluene (5 ml). The mixture was stirred vigorously at 20 °C for 5 days and then quenched by adding a few drops of triethylamine. The purification was performed by column chromatography on silica gel, using CH_2Cl_2/pentane solvent gradient between 0-100%.

(2*S*,4*R*)-2-isobutyl-4-methyl-4-pentyl-1,3-dioxolane (7p)

Yield: Colorless oil, 47.4 mg, 44%.

^{1}H NMR (300 MHz, C_6D_6) δ 5.13 (t, *J* = 5.09 Hz, 1H), 3.61 (d, *J* = 7.9 Hz, 1H), 3.33 (d, *J* = 7.9 Hz, 1H), 2.02-1.88 (m, 1H), 1.73-1.69 (m, 2H), 1.52-1.19 (m, 8H), 1.09 (s, 3H), 0.95 (dd, *J* = 6.7, 0.8 Hz, 6H), 0.87 (t, *J* = 7.0 Hz, 3H)

^{13}C NMR (75 MHz, C_6D_6) δ 103.2, 80.3, 75.1, 43.9, 40.6, 32.7, 25.0, 24.3, 23.5, 23.3, 23.0, 14.2.

HRMS (CI (DE)) *m/z* calculated for $C_{13}H_{27}O_2$ (M) 215.2011, found 215.2012.

GC (Column: 25 m Cyclodextrin-H (2,3-dimethyl-3-pentyl-γ-cyclodextrin), i.D. 0.25 mm; Detector: FID; Temperature: injector 220 °C, detector 350 °C, oven 100 °C to 115 °C with 0.5 °C/min; gas: 0.3 bar H_2), t_{major} = 20.2 min, t_{minor} = 17.3 min; er = 95.5:4.5, dr >100:1.

(2*S*,4*S*)-2-isobutyl-4-methyl-4-pentyl-1,3-dioxolane (*epi*-7p)

Yield: Colorless oil, 42.8 mg, 40%.

^{1}H NMR (500 MHz, C_6D_6) δ 5.12 (t, *J* = 5.1 Hz, 1H), 3.52 (d, *J* = 7.9 Hz, 1H), 3.43 (d, *J* = 7.9 Hz, 1H), 2.02-1.90 (m, 1H), 1.75-1.70 (m, 2H), 1.57-1.44 (m, 1H), 1.41-1.18 (m, 7H), 1.17 (s, 3H), 0.95 (dd, *J* = 6.7, 4.0 Hz, 6H), 0.88 (t, *J* = 7.1 Hz, 3H).

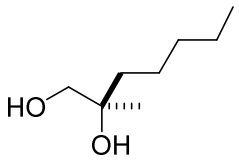
^{13}C NMR (125 MHz, C_6D_6) δ 103.8, 80.4, 75.6, 44.3, 38.9, 32.7, 25.1, 25.0, 24.3, 23.3, 23.2, 23.0, 14.3.

GC (Column: 25 m Cyclodextrin-H (2,3-dimethyl-3-pentyl-γ-cyclodextrin), i.D. 0.25 mm; Detector: FID; Temperature: injector 220 °C, detector 350 °C, oven 100 °C to 115 °C with 0.5 °C/min; gas: 0.3 bar H_2), t_{major} = 17.9 min, t_{minor} = 19.8 min; er = 99:1, dr = 88:1.

Methanolysis[170] for (*R*)-6p, (*S*)-6p

(±)-Camphorsulfonic acid (30 mol%) was added to the acetal in MeOH (0.1 M). The mixture was stirred at r.t. for 22 h and then quenched by adding a few drops of triethylamine. The purification was performed by column chromatography on silica gel, using EtOAc/hexanes solvent gradient between 0-100%.

(*R*)-2-methylheptane-1,2-diol ((*R*)-6p)

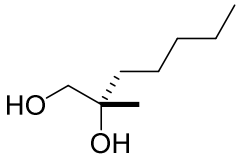


Yield: Colorless oil, 94%.

$[\alpha]^{23}_D$ = +1.2 ° (*c* 0.8, $CHCl_3$), lit.[171] $[\alpha]^{23}_D$ = +1.9 ° (*c* 1.0, $CHCl_3$) for (*R*)-enantiomer of 78% ee.

GC (Column: 30 m Hydrodex-β-TBDAC (Heptakis-(2,3-di-O-acetyl-6-O-tert-butyldimethyl-silyl)-β-cyclodextrin), i.D. 0.25 mm; Detector: FID; Temperature: injector 220 °C, detector 350 °C, oven 80 °C to 130 °C with 1 °C/min; gas: 0.4 bar H_2), t_{major} = 47.5 min, t_{minor} = 48.1 min; er = 95.5:4.5.

(*S*)-2-methylheptane-1,2-diol ((*S*)-6p)

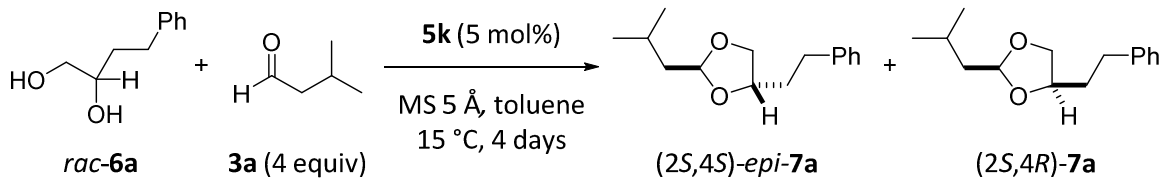


Yield: Colorless oil, 93%.

$[\alpha]^{23}_D$ = -3.4 ° (*c* 1.1, $CHCl_3$).

GC (Column: 30 m Hydrodex-β-TBDAC (Heptakis-(2,3-di-O-acetyl-6-O-tert-butyldimethyl-silyl)-β-cyclodextrin), i.D. 0.25 mm; Detector: FID; Temperature: injector 220 °C, detector 350 °C, oven 80 °C to 130 °C with 1 °C/min; gas: 0.4 bar H_2), t_{major} = 47.4 min, t_{minor} = 48.2 min; er = 98:2.

Resolution of *rac*-6a



rac-**6a** **3a** (4 equiv) (2*S*,4*S*)-*epi*-**7a** (2*S*,4*R*)-**7a**

Aldehyde **3a** (2.0 mmol) was added to the mixture of diol *rac*-**6a** (0.50 mmol), catalyst **5k** (5 mol%) and 5 Å molecular sieves (100 mg) in toluene (5 ml). The mixture was stirred vigorously at 15 °C for 4 days and then quenched by adding a few drops of triethylamine. The purification was performed by column chromatography on silica gel, using CH_2Cl_2/hexanes solvent gradient between 0-100%.

(2*S*,4*S*)-2-isobutyl-4-phenethyl-1,3-dioxolane (*epi*-7a)

Yield: Colorless oil, 53.8 mg, 46%. $[\alpha]^{25}_D$ = -6.8 ° (*c* 0.5, CH_2Cl_2).

^{1}H NMR (500 MHz, C_6D_6) δ 7.17-7.03 (m, 5H), 5.08 (t, *J* = 5.2 Hz, 1H), 3.87-3.82 (m, 1H), 3.77 (dd, *J* = 8.0, 6.2 Hz, 1H), 3.13 (dd, *J* = 7.9, 7.2 Hz, 1H), 2.67-2.62 (m, 1H), 2.50-2.44 (m, 1H), 1.98-1.90 (m, 1H), 1.77-1.71 (m, 1H), 1.68 (dd, *J* = 6.9, 5.2 Hz, 2H), 1.43-1.36 (m, 1H), 0.95-0.94 (m, 6H).

^{13}C NMR (125 MHz, C_6D_6) δ 142.0, 128.8, 128.7, 126.2, 103.4, 75.1, 70.4, 43.6, 35.5, 32.5, 25.0, 23.2, 23.2.

GC (Column: 25 m Hydrodex-β-TBDAC (Heptakis-(2,3-di-O-acetyl-6-O-tert-butyldimethyl-silyl)-β-cyclodextrin), i.D. 0.25 mm; Detector: FID; Temperature: injector 220 °C, detector 350 °C, oven 80 °C to 133 °C with 0.3 °C/min, then to 245 °C with 10 °C/min; gas: 0.5 bar H_2), t_{major} = 166.3 min, t_{minor} = 166.9 min; er = 99.5:0.5, dr = 85:1.

(2*S*,4*R*)-2-isobutyl-4-phenethyl-1,3-dioxolane (7a)

Yield: Colorless oil, 55.2 mg, 47%. $[\alpha]^{25}_D$ = -1.2 ° (*c* 0.5, CH_2Cl_2).

^{1}H NMR (500 MHz, C_6D_6) δ 7.15-7.03 (m, 5H), 4.93 (t, *J* = 5.1 Hz, 1H), 3.74-3.69 (m, 1H), 3.54 (dd, *J* = 7.5, 7.0 Hz, 1H), 3.29 (dd, *J* = 7.65, 6.5 Hz, 1H), 2.68-2.62 (m, 1H), 2.56-2.50 (m, 1H),

1.99-1.91 (m, 1H), 1.83-1.76 (m, 1H), 1.73 (dd, *J* = 6.9, 5.1 Hz, 2H), 1.58-1.51 (m, 1H), 0. 94 (d, *J* = 6.7 Hz, 6H).

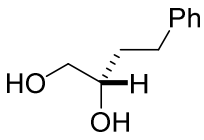
^{13}C NMR (125 MHz, C_6D_6) δ 142.0, 128.8, 128.7, 126.2, 104.2, 75.8, 69.6, 43.6, 35.9, 32.4, 25.0, 23.3, 23.2.

GC (Column: 25 m Hydrodex-β-TBDAC (tert-butyl-diacetyl-cyclodextrin), i.D. 0.25 mm; Detector: FID; Temperature: injector 220 °C, detector 350 °C, oven 80 °C to 133 °C with 0.3 °C/min, then to 245 °C with 10 °C/min; gas: 0.5 bar H_2), t_{major} = 158.2 min, t_{minor} = 159.3 min; er = 96.5:3.5, dr >100:1.

Methanolysis for (*S*)-6a, (*R*)-6a

(±)-Camphorsulfonic acid (60 mol%) was added to the acetal in MeOH (0.025 M). The mixture was stirred at reflux for 2 days and then quenched by adding a few drops of triethylamine. The purification was performed by column chromatography on silica gel after evaporation of MeOH, using 80% EtOAc/hexanes.

(*S*)-4-phenylbutane-1,2-diol ((*S*)-6a)

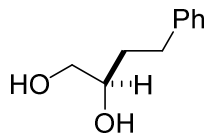


Yield: Colorless oil, 92%

$[\alpha]^{20}_D$ = -12.5 ° (*c* 1.2, $CHCl_3$), lit.[135] $[\alpha]^{20}_D$ = -16.2 ° (*c* 1.1, $CHCl_3$) for (*S*)-enantiomer of 94% ee.

HPLC (OD-3), n-heptane/i-PrOH 95:5, 1.0 ml/min, λ = 210 nm, t_{major} = 28.34 min, t_{minor} = 18.89 min, er = 98.5:1.5.

(*R*)-4-phenylbutane-1,2-diol ((*R*)-6a)



Yield: Colorless oil, 93%.

$[\alpha]^{20}_D$ = +12.4 ° (*c* 0.9, $CHCl_3$).

HPLC (OD-3), n-heptane/i-PrOH 95:5, 1.0 ml/min, λ = 210 nm, t_{major} = 18.5 min, t_{minor} = 28.7 min, er = 96.5:3.5.

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9. APPENDIX

9.1. Erklärung

“Ich versichere, dass ich die von mir vorgelegte Dissertation selbständig angefertigt, die benutzten Quellen und Hilfsmittel vollständig angegeben und die Stellen der Arbeit – einschließlich Tabellen, Karten und Abbildungen – , die anderen Werken im Wortlaut oder dem Sinn nach entnommen sind, in jedem Einzelfall als Entlehnung kenntlich gemacht habe; dass diese Dissertation noch keiner anderen Fakultät oder Universität zur Prüfung vorgelegen hat; dass sie – abgesehen von unten angegebenen Teilpublikationen – noch nicht veröffentlicht worden ist sowie, dass ich eine solche Veröffentlichung vor Abschluss des Promotionsverfahrens nicht vornehmen werde. Die Bestimmungen der Promotionsordnung sind mir bekannt. Die von mir vorgelegte Dissertation ist von Herrn Professor Dr. Benjamin List betreut worden.“

Mülheim an der Ruhr, Oktober 2015

Bisher sind folgende Teilpublikationen veröffentlicht worden:

“Resolution of Diols via Catalytic Asymmetric Acetalization”, J. H. Kim, I. Čorić, C. Palumbo, B. List, *J. Am. Chem. Soc.* **2015**, *137*, 1778.

“The Catalytic Asymmetric Acetalization”, J. H. Kim, I. Čorić, S. Vallalath, B. List, *Angew. Chem. Int. Ed.* **2013**, *52*, 4474.

9.2. Lebenslauf

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