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DISSERTATION

Titel der Dissertation

"**Chiral auxiliaries and ligands derived from tartaric acid: synthetic access and application in asymmetric catalysis**"

Verfasserin

Tuvshinjargal Budragchaa

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Zusammenfassung

Die Dissertation beschreibt die Entwicklung geeigneter Synthesekonzepte zum Erhalt maßgeschneiderter chiraler C_4 Einheiten mit zwei bis vier Asymmetriezentren in wenigen Schritten, ausgehend von natürlicher Weinsäure und Anwendungen in asymmetrischen Transformationen. Eine Bibliothek von TADDOL Analoga mit umfangreicher Variation des Kohlenstoffskeletts wurde ausgearbeitet und umfaßt sowohl die Einführung einer Vielzahl, elektronisch wie sterisch unterschiedlicher aromatischer Substituenten in den Positionen 1 und 4, als auch den Austausch des Dimethyldioxolan Fragments gegen andere OH-Schutzgruppen, beides mit dem Ziel, wirkungsvollere Auxiliare für die asymmetrische Organokatalyse zu entwickeln. Weiters wurde eine rationale Strategie ausgearbeitet, um schrittweise bis zu vier unterschiedliche aliphatische und aromatische Substituenten an C1 und C4 mit vorhersagbare relativer Stereoselektivität einzuführen. Diastereomere Produktmischungen wurden chromatographisch aufgetrennt. Ihre bevorzugte Bildung war bedingt durch Starrheit des Substrats, Größe des Reagenz und Stabilität von Chelat-Zwischenstufen und konnte teilweise gesteuert werden. Insgesamt wurden 44 di-*sec.* und di-*tert.* Carbinole hergestellt. Darüber hinaus wurden die meisten in einer Eintopfreaktion in zyklische Phosphoramidite oder Phosphate umgewandelt. Letztere Verbindungsklasse war in einer zwei- oder vierstufigen Sequenz zu synthetisieren.

Relativkonfigurationen verschiedener Schlüsselverbindungen konnten durch Kristallstrukturanalyse ermittelt werden.

Die so erhaltenen Phosphorsäuren wurden in der Folge in Mannich- und Aza-Diels-Alder Reaktionen eingesetzt, wobei in ersterem Fall bis zu 96% e.e. erreicht werden konnten. Diol Auxiliare mit unterschiedlichen Schutzgruppen und wirksam durch Aktivierung über H-Bindungen fanden Verwendung in Oxo-Diels-Alder Reaktionen. Auch hier wurden asymmetrische Induktionen bis 96% e.e. beobachtet. Phosphoramidite mit α-chiralen Zentren und 2,2-Dimethyl-1,3-dioxolan-Schutzgruppe katalysierten die allylische Alkylierung von 1,3-Diphenyl-2-propenylacetat mit Dimethylmalonat mit bis zu 91% e.e. Schließlich wurden Diol-Auxiliare auch in der Ti-vermittelten Cyanosilylierung von Benzaldehyd getestet, wobei aber nur mäßige Enantioselektivitäten erzielt wurden.

Basierend auf Röntgenstrukturanalysen einiger Phosphorsäuren, die vermutlich energetisch günstige Konformationen repräsentieren, wurden näherungsweise Geometrien für Substrat-Komplexe mit Aldimin-Auxiliar Interaktionen angegeben, die mit den beobachteten Produktgeometrien im Einklang stehen.

Somit konnten, ausgehend von Weinsäure, Gruppen chiraler Hilfsstoffe in wenigen Schritten und mäßiger bis sehr guter Ausbeute zugänglich gemacht werden, wobei ein modulares Synthesekonzept verfolgt wurde. Die Effizienz der Auxiliare wurde in verschiedenen organo- und Übergangsmetall-katalysierten Reaktionen untersucht und zeigte in einer Reihe von Fällen deutlich verbesserte asymmetrische Induktion als mit bisher verwendeten vergleichbaren Auxiliaren beschrieben.

Abstract

The thesis describes a detailed investigation of synthetic routes to tailored C_4 entities with two to four chiral carbon centers, accessible from natural tartaric acid in few steps and their application in asymmetric transformations. A library of TADDOL analogs with extended structural modification of the skeleton was worked out comprising the introduction of various sterically and electronically divergent aromatic substituents in position 1 and 4 as well as replacement of the dimethyldioxolane moiety with other OH-protecting groups in order to discover more efficient auxiliaries for asymmetric organocatalytic transformations. Moreover, a general strategy was developed for stepwise introduction of up to four different aromatic or aliphatic substituents at C1 and C4 with predictable stereoselectivity. In case of products containing additional stereogenic centers at terminal carbon atoms, diastereomeric products had to be separated. Their relative predominance was controlled through rigidity of the substrate, size of reagents, and stabilities of chelate intermediates. A total of 44 di-*sec*. and di-*tert*. carbinols were prepared. In addition, most of these diols were cyclized to various phosphoramidites in a one-pot procedure or to cyclic phosphoric acids using alternatively a 2-step or 4-step protocol.

Relative configurations of several key intermediates were confirmed by X-ray structure determination.

The obtained phosphoric acids were applied in Mannich type reactions and aza-Diels-Alder reactions reaching up to 96% e.e. in the former case. Diols with various protecting groups were used as H bonding catalysts in oxo-Diels-Alder reaction affording high enantioselectivity of 96% e.e. Phosphoramidite derivatives based on 1,3-dioxolane protected α-chiral diols catalysed asymmetric alkylations of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate and offered as high as 91% e.e. Finally, diol auxiliaries were evaluated in Ti catalysed cyanosilylation of benzaldehyde and moderate enantioselectivities could be obtained.

Based on crystal structure analysis of some phosphoric acids with presumably most stable conformers, their tentative transition states with the aldimine substrate were suggested to rationalize the observed selectivities for Mannich type and aza-Diels-Alder reactions.

Summarizing, families of chiral auxiliaries are now directly available in acceptable yield starting from tartaric acid using modular approaches. The efficiencies of the auxiliaries were demonstrated in various organo and transition metal catalysed reactions showing in some cases enhanced selectivities than did the existing similar types of catalysts.

Acknowledgement

This thesis is completed with help of many people to whom I am deeply indebted and grateful. I would like to take this opportunity to acknowledge my gratitude to those people.

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This thesis is dedicated to my parents and my family

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1. Introduction

1.1. Chirality and enantioselective synthesis

Any object that is not superimposable into its mirror image is termed chiral. Chirality is a symmetry property particularly important on the molecular level since it controls basically all types of stereoselective interactions between (bio)molecules and is essential for understanding biologically and physiologically important processes. The two mirror images of chiral molecules are called enantiomers (*Figure 1*) and display different biological and physiological activities.

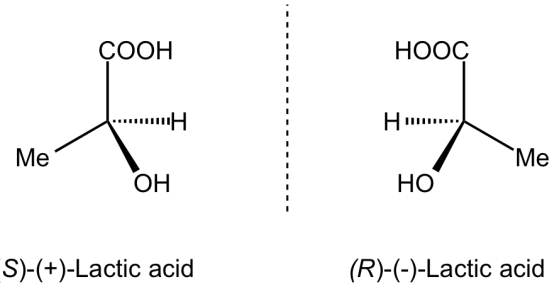
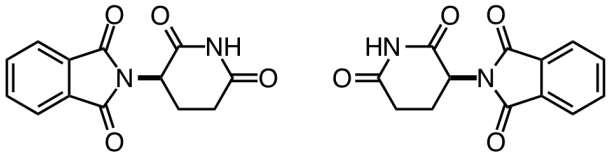


Figure 1. Enantiomers are non-superimposable mirror images of each other

Therefore, it is not surprising that many vital molecules such as proteins, amino acids, nucleic acids DNA and RNA are present in only one enantiomeric form. Likewise, enzymes bind only to the proper enantiomers at their active site as a key fits into a lock. The well-known case of thalidomide represents a tragic but remarkable example of the importance of chirality. Marketed in 1957, the drug was sold as a racemic mixture (both enantiomers in 1 : 1 ratio) to alleviate morning sickness of pregnant women. While the (+)(*R*)-enantiomer is an effective sedative, the (-)(*S*)-form hinders the development of fetus and causes functional disability (*Figure 2*). Soon after the drug was marketed, there were over 10 000 cases reported of infant phocomelia (malformation of the limbs) due to (racemic) thalidomide. Therefore, it is crucial to identify the active enantiomer, determine its mode of actions and apply it in a single enantiomeric form.



R-(+)-Thalidomide sedative

S-(-)-Thalidomide mutagenic

Figure 2. Physiological effects of Thalidomide enantiomer

Thus, enantioselective synthesis of chiral compounds has become a top priority theme in academic research in the last 30 years. The 2001 Nobel Prize in Chemistry awarded to William S. Knowles, K. Barry Sharpless and Ryoji Noyori for their contribution to the development of asymmetric catalysis underlines the importance of the field in modern organic chemistry. Pharmaceutical industry is a prime area where chirality and chiral separation play a major role and the development of new and efficient synthetic methods to obtain complex and multifunctional drugs in enantiomerically pure form makes up a large part of research. The advantages are obvious; the absence of the undesired enantiomer reduces the chance of negative side effects and stress for kidney and other excretory organs. More significantly, as a consequence of the thalidomide incident, US Food and Drug Administration (USFDA) and other international regulatory agencies established regulations and provisions, which specifically promoted the marketing of non-racemic drugs. Also, from the view point of economy, it is profitable to work with pure enantiomers rather than with a racemate as in the latter case clinical tests have to be conducted threefold; one for each enantiomer and one for the racemate. Therefore, whenever possible, chiral drugs are administered as pure enantiomers. Better than separation of enantiomers is the selective production of the desired enantiomer by asymmetric synthesis which reduces costs for production and waste disposal. Despite of this, the pharmaceutical companies invest still more in the enantiomer separation of existing drugs rather than setting up total new processes. “In 2005, single enantiomer drugs comprised 225 billion US$ (37%) of the total market of 600 billion US$. The compound annual growth rate for single enantiomer products for the last five years by then was 11%, which was equivalent to the growth of the pharmaceutical market as a whole”.[1]

Several approaches are used to access non-racemic target molecules. Depending on availability of starting materials, either chiral pool synthesis, optical

resolution procedures or asymmetric synthesis (stoichiometric or catalytic) may be applied. Chiral pool synthesis makes use of readily available, naturally occurring, enantiomerically pure starting materials and manipulates them through series of diastereoselective reactions to obtain a target molecule as a single diastereomer. Chiral pool synthesis is very useful when a starting material and the target molecule have substructures with same configuration of stereogenic centers. On the other hand, the term "optical resolution" denotes any separation method of enantiomers (present as a racemic mixture). In optical resolution procedures, enantiomers are resolved based on their different ability to crystallize under specific conditions (spontanous crystallization of one enantiomer when added a proper seeding crystal), dissimilar behaviors in chiral environment (chiral chromatography, formation of inclusion complexes) and chemical and physical differences of the corresponding diastereomeric derivatives (diastereometric salt formation and separation through fractional crystallisation). Kinetic resolution represents a special case of optical resolution and is based on different reactivities of the enantiomers towards chiral molecules. In ideal cases, after 50% conversion, one enantiomer has reacted completely while the other one remains unaffected. Finally, in asymmetric synthesis, enantiomerically pure entities (“chiral auxiliaries”) are temporarily bound to prochiral substrates to control the configuration of new stereogenic centers. After a diastereoselective transformation has been performed, leading eventually to the target structure with the desired absolute configuration, the auxiliary has to be cleaved in a separate step. Since auxiliaries are applied in stoichiometric amounts, their recovery (and purification) for reuse is desired. More convenient is asymmetric catalysis, which requires only small amount of chiral, catalytically active species to promote the selective formation of a single enantiomer in large amount.

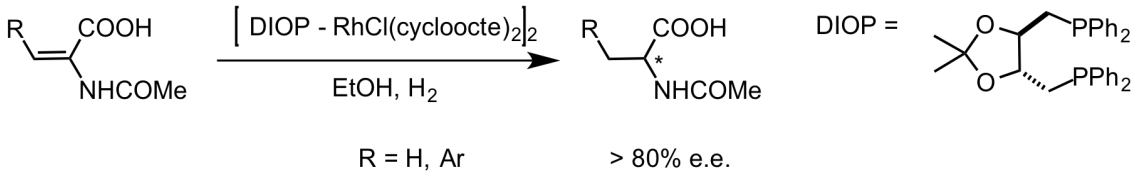
Asymmetric catalysis is the most efficient approach to synthesize target molecules with desired absolute configuration owing to its atom economy and versatility. Due to the fact that the catalysts are often effective at impressive low concentration, enantioselective catalysis found broad range of applications both in academic research and industrial area. Therefore, development of efficient chiral ligands and catalysts, which can perfectly control stereochemistry of the target molecule, is essential in modern day organic synthesis. Until recently, organometallic catalysts and enzymes dominated the field of asymmetric catalysis. Enzymes are particularly used in enantioselective synthesis of precursors for natural product synthesis and provide high degrees of enantioselectivity, typically close to 100 %. However, scope of these types of reactions is limited as enzymes exhibit high substrate specificity thus hindering the reactions to be

applied in more general scope. Furthermore, the opposite enantiomer cannot be obtained by enzyme catalysed reactions.

1.2. Transition metal catalysed asymmetric synthesis

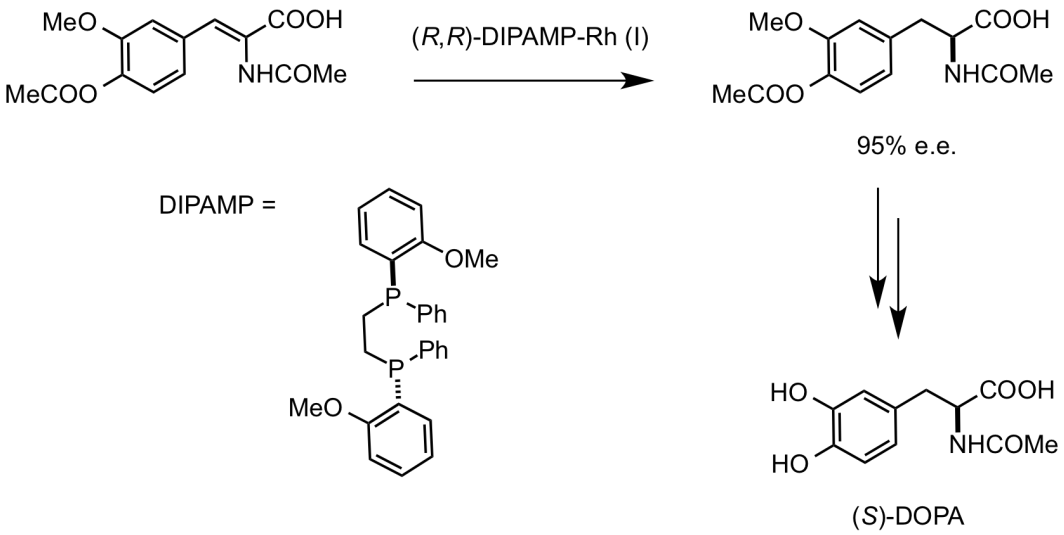
Compared to the enzyme catalysed reactions, organometallic catalysis is characterized by its broad scope due to the variability of auxiliary structure, acting as mono- or bidendate ligands in complexes with transition metals. Such species can react with reagents before or after coordinating the substrate to form diastereomeric substrate complexes. These traverse separate catalytic cycles, but with significantly different rate to produce either product enantiomer. When diastereomeric transition states in the configuration determining step differ by around 3 kcal, chiral products are usually obtained with more than 99% e.e. Transition metal catalysed asymmetric reaction use small amounts, often less than 1 mol% of chiral ligands to produce a large amount of non-racemic products from prochiral starting materials and such catalysts are applied to wide range of asymmetric reactions. Many milestone achievements have been done in this field.[2]

First enantioselective synthesis using transition metal complexes dates back to mid 1960s when Nozaki et al. reacted styrene and ethyl diazoacetate in the presence of 1 mol% of a chiral Schiff base–Cu (II) complex and obtained the cyclopropane derivative with 10% e.e.[3] A huge number of asymmetric organometallic catalyses with excellent stereoselectivities was developed since then. Kagan et al. opened a new era when they used a chiral diphosphine ligand DIOP, derived from tartaric acid, in a Rh (I) catalyzed asymmetric hydrogenation of α-(acylamino)acrylic acids. The reaction proceeded under mild conditions with high yield and enantioselectivities up to 80% e.e. (*Scheme 1*).[4]



Scheme 1. Asymmetric hydrogenation of α-(acylamino)acrylic acids

Following this achievement, B. Knowles et al. designed the P-chiral DIPAMP-Rh complex which proved to be an excellent catalyst for asymmetric hydrogenation of olefins reaching up to 95% e.e. This work was the basis for an industrial synthesis of *L*-DOPA [(*S*)-3-(3,4-dihydroxyphenyl)alanine], an anti-Parkinson drug and later earned Knowles the Nobel prize (Scheme 2).[5]

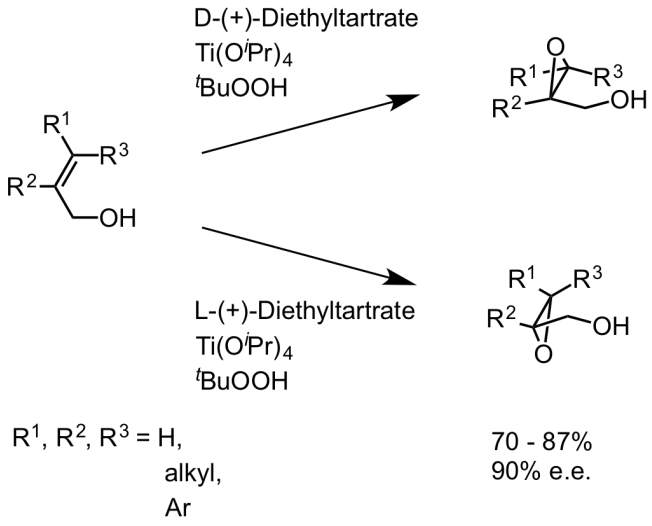


Scheme 2. Asymmetric hydrogenation with (*R,R*)-DIPAMP

Sharpless epoxidation of allylic alcohols with chiral Ti(IV)–tartrate catalysts marks another milestone in asymmetric catalysis (*Scheme 3*)[6] since chiral epoxides are valuable key intermediates in natural product synthesis and easily converted into various functional groups such as diols, amino alcohols, ethers etc. Sharpless epoxidation was applied to a wide range of primary and secondary allylic alcohols and products are usually obtained in excellent yield and with more than 90% e.e.[2]

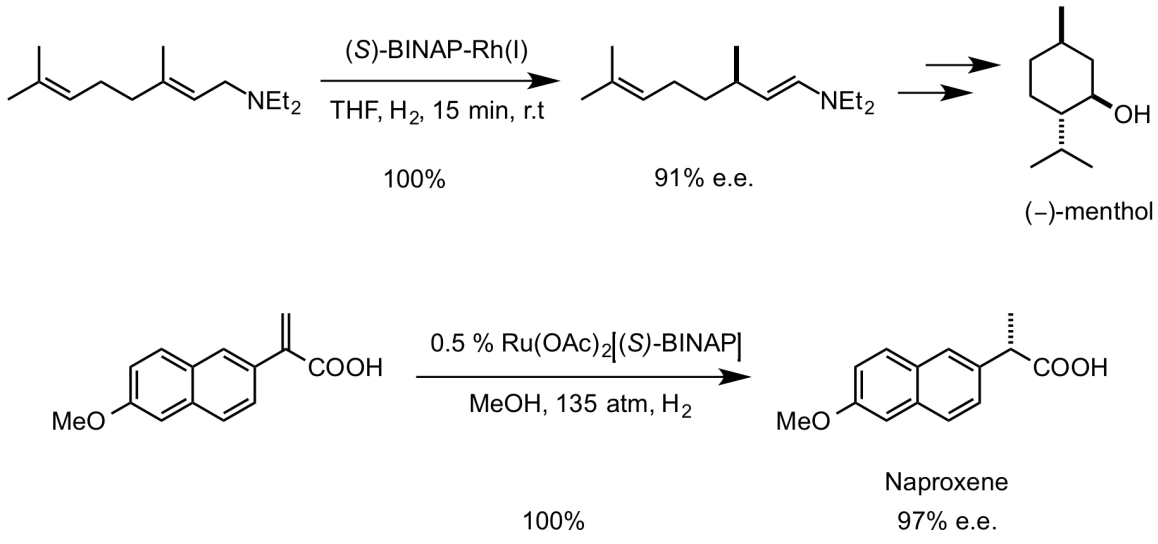
Noyori and co-workers developed the privileged family of BINAP ligands forming complexes with various transition metals, particularly with Rh (I), Ru (II) or Pd (II). These were found to catalyze a multitude of synthetically useful asymmetric transformations[7] with excellent enantioselectivity like hydrogenation of functionalised alkenes, including α,β-unsaturated carboxylic acids,[8] enamides,[9] functionalised ketoesters,[10] and cyclic sulfonimides[11] or the isomerization of allylic amines (90–99% e.e.).[12] Many enantiopure products are important key structures in multistep drug synthesis and some have become the basis of large scale industrial processes. For example, hydrogenation of enamines with BINAP affords important intermediates for the synthesis of

tetrahydroapaverine, laudanosine, norrecticuline and (S)-tretoquinol (a bronchodilating agent).



Scheme 3. Sharpless epoxidation

In addition, the synthesis of the side chain of α-tocopherol (vitamin E),[12] citronellol,[13] a scent in perfume or insect repellent manufacturing, and α or β-aminoacids[14] involve hydrogenation steps using BINAP complexes. In the majority of cases the corresponding products were isolated in quantitative yield and 96–99% e.e.[15]



Scheme 4. Industrial applications of BINAP

(*S*)-BINAP)Ru$(OAc)_2$ is used for the commercial production of enantiomerically pure naproxen, an anti-inflammatory drug and BINAP-Rh(COD)Cl in the production of menthol, via isomerization of an allylic diethylamine precursor derived from myrcene (*Scheme 4*).

As mentioned above, chiral transition metal catalysts are versatile and make use of tiny amounts of enantiomerically pure ligands to produce non-racemic products on large scale from achiral starting materials. However, the most (transition) metal complexes are sensitive to water and air, therefore require strict reaction conditions such as inert gas, absolute solvents, purified substrates, etc. Moreover, costs increase when expensive transition metals are used and there is always a potential pollution of the product by the metal residues, an issue which is always of concern when target material is used in pharmaceutical industry.

1.3. Organocatalysis

These shortcommings made synthetic chemists look for alternatives and organocatalysis, which applies small enantiomerically pure organic molecules as catalysts, gained much attention in recent years. Initially emerged as an attempt to use low molecular weight organic molecules to mimic the selectivity and catalytic activity of enzymes, organocatalysis developed into a powerful concept to synthesize a multitude of organic molecules for it holds many advantages over conventional biocatalysts or transition metal catalysts. Many organocatalysts are available from naturally occurring chiral precursors, easily accessible also in large amount and therefore cheap. In addition, typically organocatalysts are stable in water and air and do not require rigorous exclusion of humidity and oxygen. Thus, organocatalytic transformations are operationally simple and proceed under mild reaction conditions. Furthermore, as no metals are involved in the active part of the catalyst, there are less toxicity issues.

The first successful asymmetric transformation using small organic molecules was an intramolecular aldol reaction mediated through *L*-proline, independently reported by Hajos, Parish[16] and Eder, Wiechert, Sauer[17] in 1970s. The origin of enantioselection was not clear until recently. Calculation studies revealed that proline acts as a dual catalyst and the key to success of this reaction was hydrogen bonding (*Figure 3*).

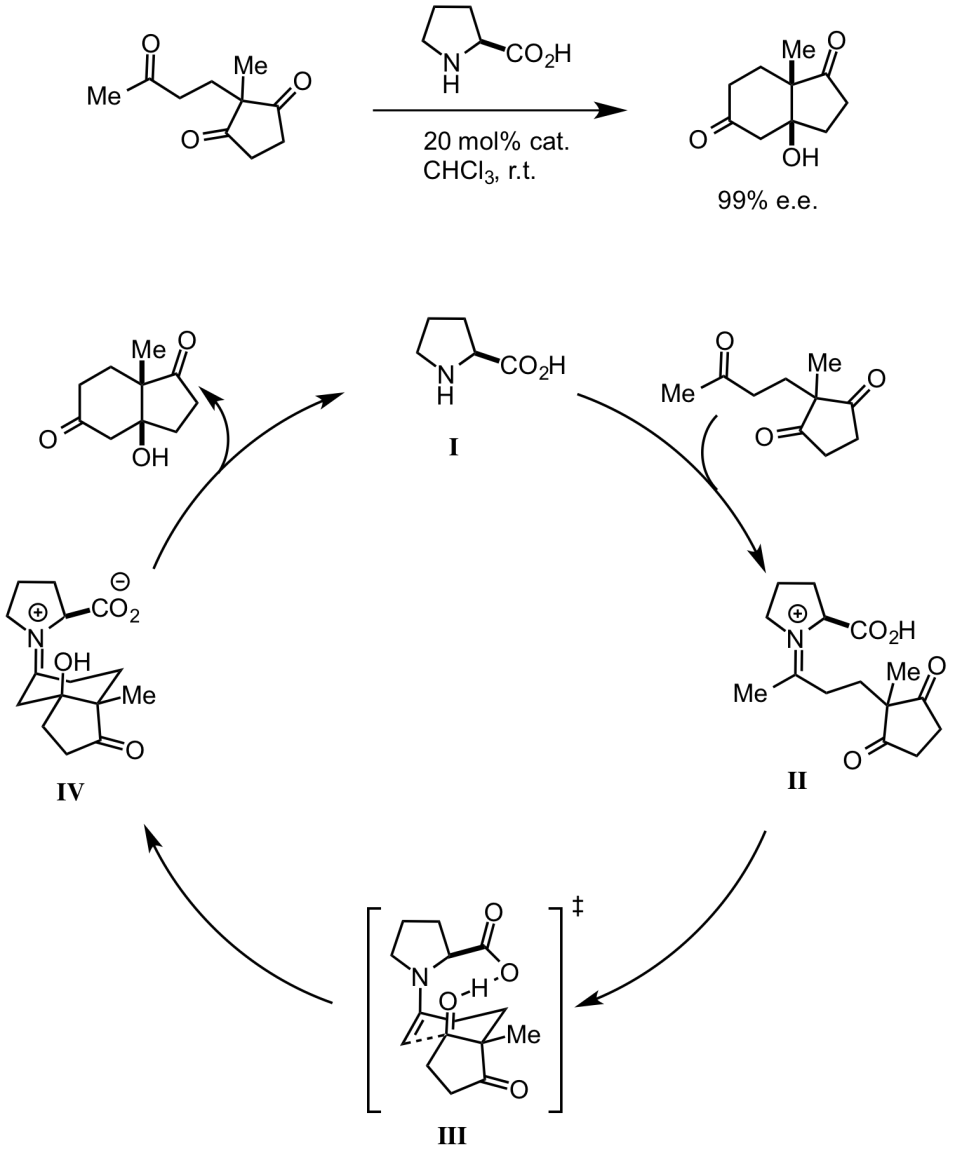


Figure 3. Proline catalysed intramolecular aldol reaction[19]

The secondary amine of *L*-proline (**I**) transforms a carbonyl group of the substrate into an iminium ion (**II**), meanwhile, the carboxylic acid moiety activates the electrophiles through hydrogen bonding interaction and dictates the stereochemical outcome of the reaction. The iminium ion is deprotonated and reveals a nucleophilic enamine intermediate. Consequently, the carboxylate moiety coordinates the electrophile in a sterically least demanding conformation forming a Zimmermann-Traxler transition state (**III**) with a pronounced facial discrimination of carbonyls. Finally, proton transfer from the carboxylic acid to the carbonyl oxygen forms a zwitterionic intermediate **IV** from which the product is liberated.

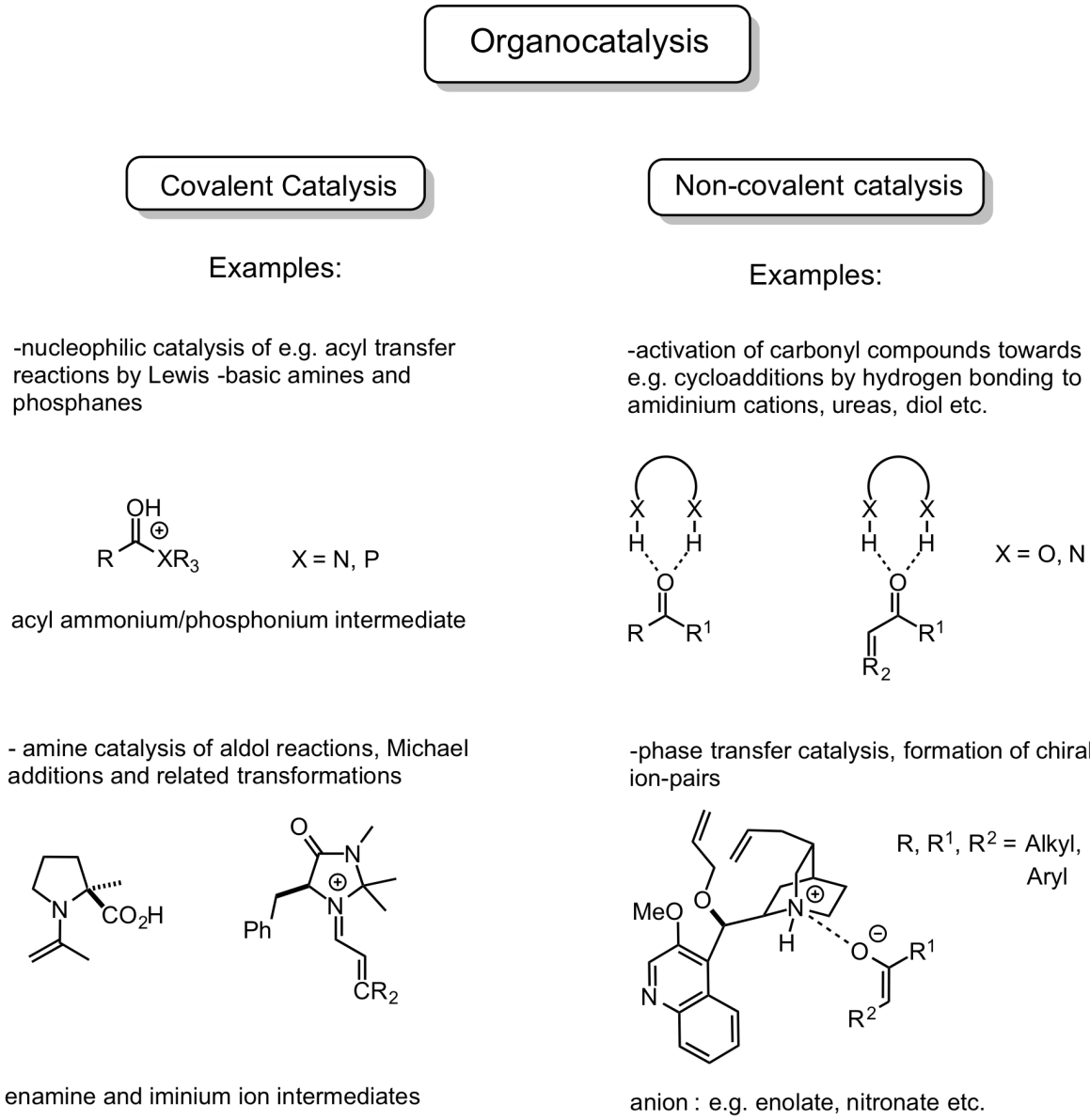


Figure 4. Organocatalytic interactions with the substrate[18]

More than 30 years after Hajos-Parrish's seminal publication, the pioneering work of List and co-workers[19] revealed that the underlying mechanism of Hajos-Parrish reaction could represent a general activation concept with broad applicability when using *L*-proline in enantioselective intermolecular aldol reactions. Most importantly, the study demonstrated that low-molecular weight organic molecules could promote chemical reactions typically catalysed by enzymes following similar mechanisms. Since then, the scope of the organocatalytic reactions is expanding rapidly and a broad range of reactions such as aldol condensation, conjugate 1,4-addition, Diels-Alder reaction,

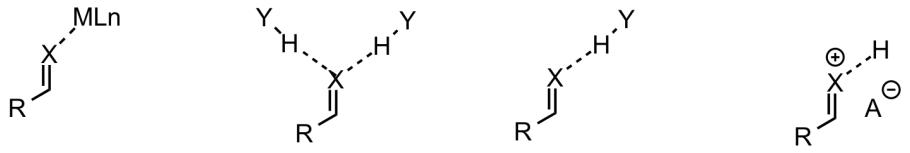
Friedel-Crafts alkylation, epoxidation, hydrocyanation, cyanosilylation, etc.[20] have been performed with high enantioselectivity. In addition, many previously typical transition metal catalysed C-C couplings such as Sonogashira,[21] Ullman,[22] Suzuki coupling[23] and Tsuji-Trost reaction[24] etc. can be now performed in the presence of organocatalysts.

The modes of activating substrates in organocatalysis are various. Reactive intermediates may be formed either by covalent bonding (enamine and iminium catalysts), by non-covalent bonding such as hydrogen bonding (Brønsted acids) or via ion-pair complexes (phase transfer catalysts) (*Figure 4*). Various amino acid derivatives, peptides, or cinchona alkaloids can serve as auxiliaries and the majority catalyse the reaction through formation of enamine and iminium ion intermediates. List and co-workers[19] as well as MacMillan and co-workers[25] have performed excellent work in this field. Meantime, the most organocatalysts are bifunctional, commonly bearing a Brønsted acid and Lewis base center. These types of catalysts activate both the electrophile and nucleophile thus leading to accelerated reactions as well as higher enantioselectivities.

1.3.1. Hydrogen bonding catalysts / Brønsted acid catalysts

Besides *L*-proline, many other organic molecules were used as H bonding catalysts in early studies and impressive results were obtained. For example Inoue et al. investigated diketopiperazine in the hydrocyanation of benzaldehydes[26] and Merck chemists applied *N*-alkyl cinchona alkaloid derivatives as phase–transfer catalysts in enolate alkylation reaction.[27] Both reactions proceeded with excellent yield and enantioselectivity.

Finally, Brønsted acid catalysts are attracting much attention since Jacobsen's and Corey's groups independently reported enantioselective Strecker reactions using hydrogen bond donor catalysts in 1998[28] and 1999,[29] respectively. In Brønsted acid catalysis, a chiral organic molecule with hydrogen bond donor ability activates C=X bond (X = O, NR, CR_2). The chiral catalyst moiety, which stays in close proximity to the activated electrophile, controls enantioselectivity of the reaction. This strategy, using hydrogen bonding instead of conventional metal centered Lewis acid activation to create a chiral environment around the electrophile has opened a new path in enantioselective catalysis (*Figure 5*).



Lewis acid catalysis | a) Hydrogen bonding catalysts | b) Stronger Brønsted acid catalysts

X = O, N; $A^{\ominus}$ = chiral conjugate base of Brønsted Acid; Y or L = chirality inducing parts

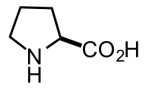
Figure 5. Activation modes of Lewis-acid catalysis and Brønsted acid catalysis

Indeed, based on a similar concept, Jacobsen's group later developed a range of chiral thiourea catalysts useful in various asymmetric reactions such as hydrophosphorylation,[30] Mannich[31] and nitro-Mannich[32] reactions. Under optimized conditions, corresponding products were obtained with high enantioselectivities (up to 97% e.e.) Hydrogen donor catalysts greatly vary in their structural and functional framework as well as their H-bond donor motifs (*Figure 6*). Although mechanisms for the electrophile activation differ significantly depending on reaction type, hydrogen bond donor catalysts share a general feature, which comprises a single or dual H-bond donor site and additional functionalities such as aromatic, weakly or strongly acidic and basic site etc. for secondary interaction with the substrate.

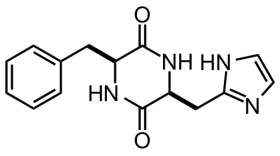
Among the hydrogen bond donor catalysts those with amide, urea, and thiourea functionality, often attached to the cinchona skeleton or BINOL and TADDOL moieties, are most frequently used.

Thioureas belong to the most thoroughly investigated hydrogen donor catalysts, successfully applied in enantioselective Friedel-Crafts alkylations of indols with nitroalkenes,[33] Michael and Aza-Henry reactions,[34] enantioselective Pictet-Spengler reactions[35] and Baylis-Hillman[36] reactions.

A remarkably large number of auxiliaries is based on BINOL that is easily modified by substitution particularly with bulky aryl groups in position 3 and 3'. Successful applications as hydrogen bond donors were reported for Morita-Baylis-Hillman,[37] aza-Baylis-Hillman reaction,[38] nitroso-Diels-Alder reaction,[39] phase transfer catalysed nucleophilic epoxidation,[40] and Michael addition.[41]

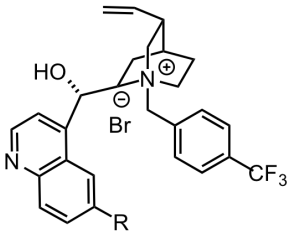


Hajos, Parrish,
Eder, Sauer,
Weichert, 1970s
aldol cyclization

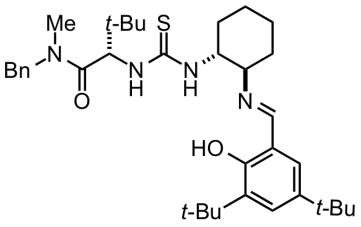


Barbas, List, 2000
Direct Aldol reaction

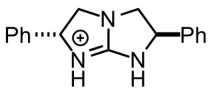
Inoue, 1981
hydrocyanation of aldehydes



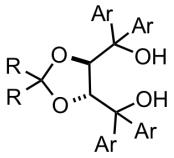
Grabowski, 1984
Enolate alkylation



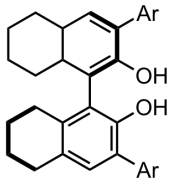
Jacobsen, 1998
Strecker reaction



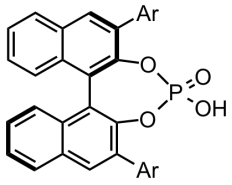
Corey, 1999
Strecker reaction



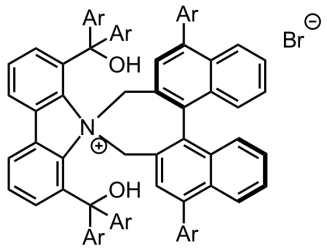
Rawal, 2003,
hetero-Diels-Alder
cycloaddition



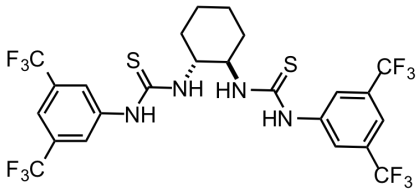
Schaus, 2003
Baylis-Hillman reaction



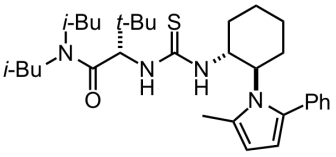
Akiyama, Terada, 2004
Mannich reaction



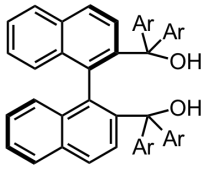
Maruoka, 2004
epoxidation



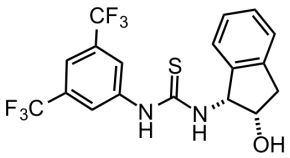
Nagasawa, 2004
Baylis-Hillman reaction



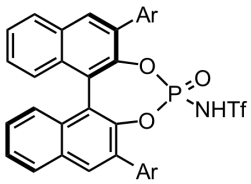
Jacobsen, 2004
Pictet-Spengler reaction



Rawal, Yamamoto, 2005
hetero-Diels-Alder
cycloaddition



Ricci, 2005
Friedel-Crafts addition
to nitroolefins



Yamamoto, 2006
Diels-Alder cycloaddition

Figure 6. Representative hydrogen bond donor catalysts[42]

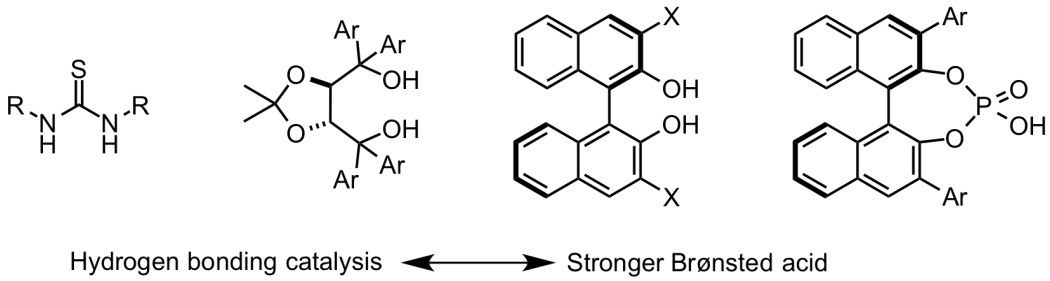
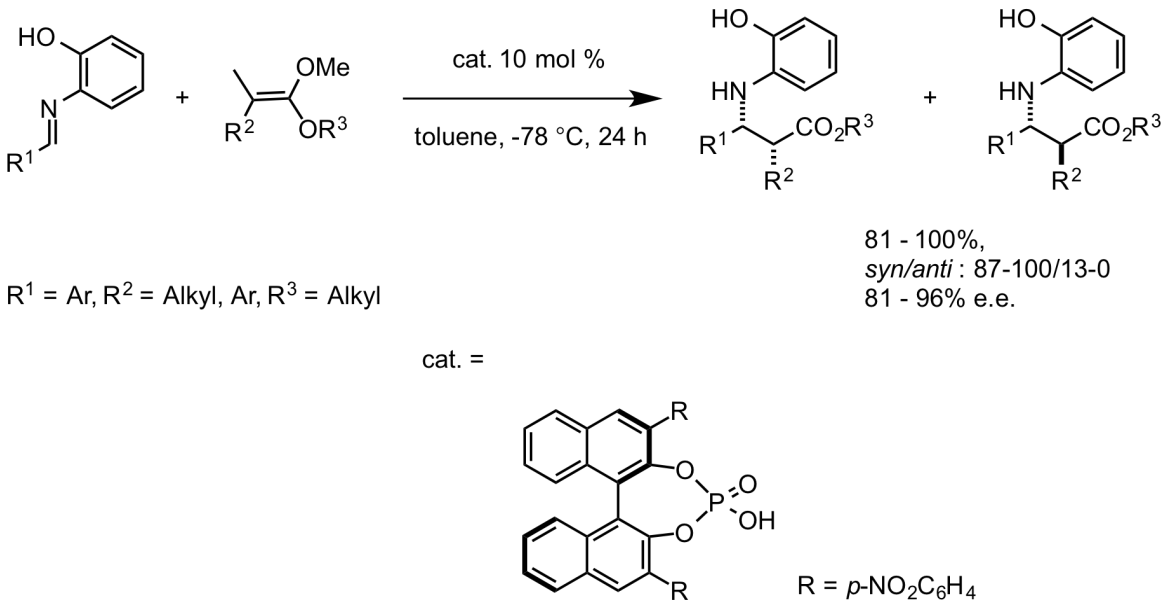
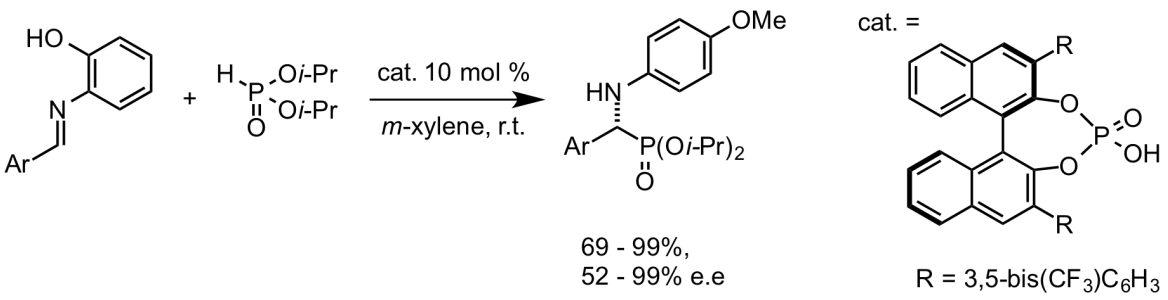


Figure 7. Auxiliaries with various H bond donor abilities

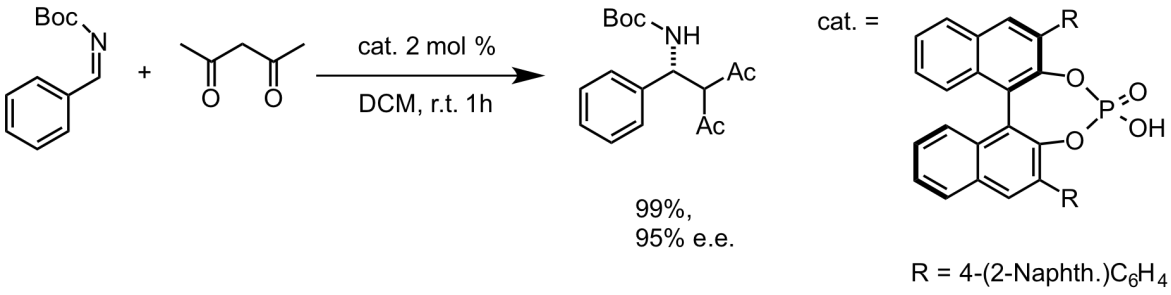
However, acidity of the thiourea and aliphatic alcohols is moderate with pKa of 20–28 (in DMSO)[43] and they are rather considered hydrogen bonding catalysts than typical Brønsted acids (*Figure 7*). In an effort to search for functionalities with increased acidity, Akiyama and co-workers and Terada and co-workers independently discovered BINOL based cyclic phosphoric acids (pKa 4)[44] and successfully applied these in enantioselective Mannich type reactions (*Scheme 5*),[45] hydrophosphonylations of imines (*Scheme 6*)[46] and direct Mannich reactions (*Scheme 7*), [47] respectively.



Scheme 5. Diastereoselective Mannich type reactions catalysed by BINOL phosphate



Scheme 6. Chiral Brønsted acid catalysed hydrophosphorylation



Scheme 7. BINOL phosphate catalysed Mannich reaction

It is anticipated that these phosphoric acids display bifunctional catalytic interaction, activating the electrophile through hydrogen bonding with P-O-H while phosphoryl oxygen would function as a Brønsted basic site activating the nucleophile. Moreover, cyclic phosphoric acids are likely to restrain conformational flexibility of the backbone and various substitutents at 3,3' position have been introduced for electronic and steric fine-tuning (*Figure 8*).[43]

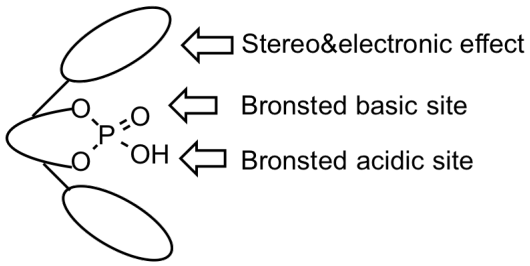


Figure 8. Dual catalytic function of BINOL phoshate catalysts[48]

With pKa around 4 (in DMSO), these cyclic phosphoric acid derivatives are considered significantly stronger Brønsted acids activating a wider range of substrates. Reactions such as Pictet-Spengler reactions,[49] aza-Friedel-Crafts alkylation,[50] direct alkylation of α-diazo esters,[51] reverse electron demand aza Diels-Alder reactions,[52] Biginelli reactions,[53] and transfer hydrogenations etc.[54] are now catalysed by BINOL based phosphoric acids and the corresponding products were obtained with high to excellent enantioselectivities despite low catalyst loadings (0.1–2 mol%).[55]

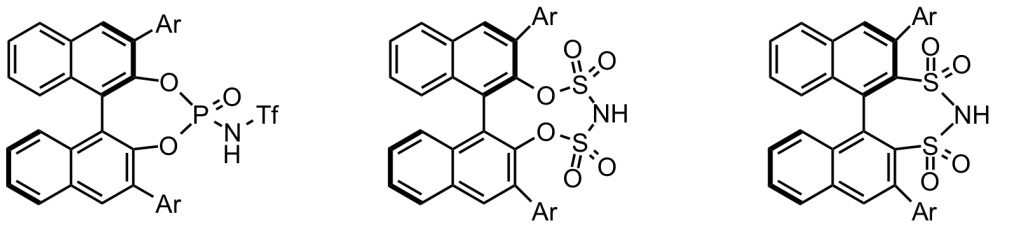
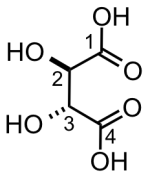


Figure 9. Various structural motifs of BINOL based Brønsted acid

However, due to still moderate acidity of BINOL-phosphoric acids, the scope of electrophiles is limited to quite strongly basic aldimines, ketimines and aziridines. To extend it further to rather weakly basic electrophiles such as carbonyls, BINOL derived N-triflylphosphoramides (NTPAs, pKa 3), bis(sulfuryl) imides (JINGLES, pKa 2) and bis(sulfonyl) imides (BINBAM, pKa 0.15 in DMSO[56]) were designed (*Figure 9).* NTPAs activate carbonyl electrophiles and catalyse Diels-Alder reactions,[57] Nazarov cyclizations,[58] Friedel-Crafts alkylations,[59] Mukaiyama aldol reactions of silyl enol ethers,[60] and asymmetric ene reactions[61] with excellent chemical yield and enantioselectivities. In addition, NTPAs were used in reactions where BINOL phosphoric acids were previously applied. They gave improved yield and stereoselection with significantly lower loading (1–5 mol%) than their phosphoric acids counterparts.[62]

1.4. Tartaric acid

Tartaric acid **1** (*Figure 10*) has long been used as a convenient starting material in asymmetric synthesis and a countless number of chiral ligands and auxiliaries derived from it have been employed in chiral drugs and natural products syntheses, both in academic and industrial area.

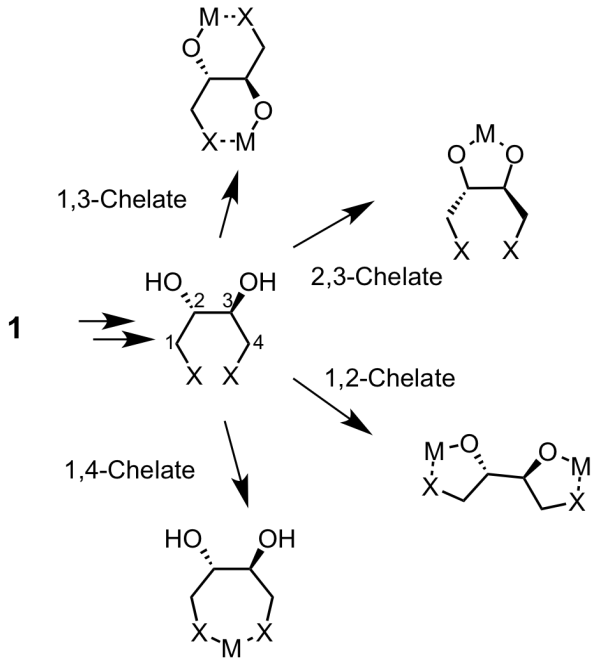


1

Figure 10. *L*-(+)-tartaric acid

This valuable precursor with C_2 symmetry is a naturally occurring chiral compound available in enantiomerically pure form in kilogram quantities. It has dihydroxy and carboxylic groups, which can be independently converted into various other functional groups. Bearing electron withdrawing or donating groups they can act as Lewis or Brønsted base or acid in various catalytic reactions and affect the stereochemical outcome. In addition, tartaric acid's relative non-toxicity, cost efficiency and simplicity when handled make it one of the most widely used chiral starting materials from the chiral pool.

These densely functionalized C_4 moieties are able to participate in plethora of enantioselective syntheses and induce chirality by forming five to seven membered chelate rings between functionalities in positions 1/4, 1/2, 2/3, and 1/3, respectively (*Scheme 8*).[63] Most successful examples are Sharpless epoxidation,[6] asymmetric allylation,[64] asymmetric Diels-Alder, and aldol reactions[65] that used simple tartaric acid derivatives and obtained wide range of products with high enantioselectivity. Especially derivatives with vicinal hydroxy groups protected as cyclic ketal and carboxylic groups transformed into different functionalities have become popular. Well known examples are $\alpha,\alpha,\alpha',\alpha'$-tetraaryl-1,3-dioxane-4,5-dimethanol (TADDOL **2**) (*Figure 11*) and 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane (DIOP) (See *Scheme 1*).[4,66,67]



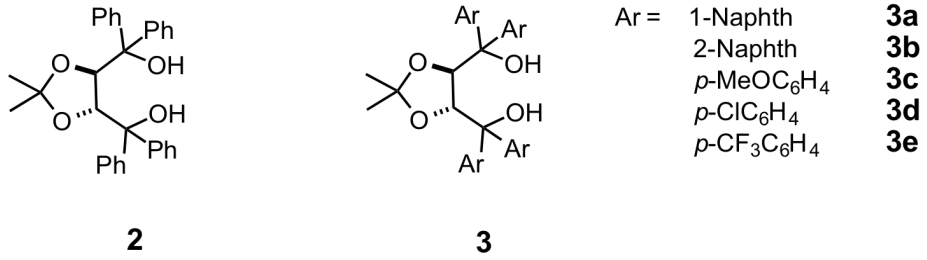
Scheme 8. Various chelation possbilities for tartaric acid

1.5. TADDOLs

1.5.1. Synthesis of TADDOLs and related α–chiral diols

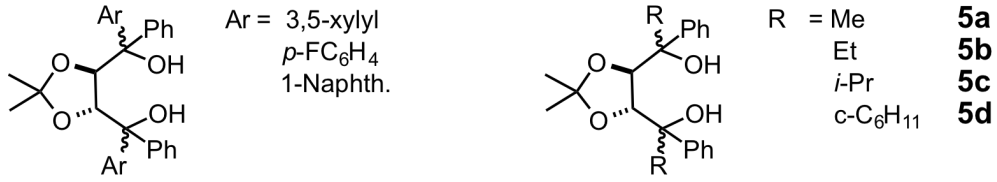
Particularly, TADDOLs **2** and **3** with various aromatic substituents (*Figure 11*), first introduced by Seebach et al. in 1987, are easily obtained starting from commercially available dimethyl or diethyl tartrate. Upon treatment with an appropriate aldehyde or ketone under acid catalysis and azeotropic removal of water the 1,3-dioxolane-4,5-dicarboxylates are formed and were further reacted with aryl Grignard or aryllithium reagents to obtain di-tertiary alcohols **3**. The majority of TADDOLs contain four identical aryl groups at C-1 and C-4 providing a considerable number of auxiliaries with different spatial and electronic features.

On the other hand, TADDOL analogues like **4** and **5** with two different geminal substituents at terminal carbons are rare. Seebach and co-workers synthesized few variations of C_2- and C_1-symmetrical diastereomers α,α'-bis(R/Ph) TADDOLs **4** and **5a** (*Figure 12*).[68]



2 **3**

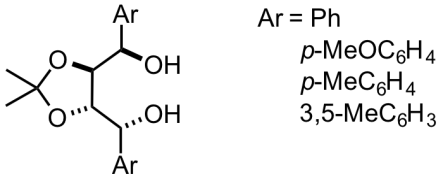
Figure 11. Parent TADDOL **2** and related *di-tert.* diols **3** with varying aryl groups



4 **5**

Figure 12. TADDOLs with different geminal substituents at C1 and C4

Further extensions were reported by Prasad's group replacing one of the geminal aryl substituents with alkyl or H to obtain C_2-symmetrical TADDOLs **5** and secondary diols **6**, respectively (*Figure 13*).[69]



6

Figure 13. TADDOL analogues with *sec*. diols

1.5.2. Diols as chiral ligands in transition metal catalysed reactions

TADDOLs and their analogues are widely used in transition metal catalysed reactions due to their unique structural features. The O-atoms of diarylmethanol groups of TADDOLs stay in close proximity to each other as a result of intramolecular hydrogen bonding.

The increased conformative rigidity also helps to stabilize a (roughly) overall C_2 symmetry where the aryl substituents adopt pseudo-axial and -equatorial positions and a propeller shaped arrangement. The bridging H-atom would be situated on the C_2 axis, the same position where a metal ion would reside to form a 7 membered chelate ring (as in Ti-TADDOLates) (*Figure 14*).[67a]

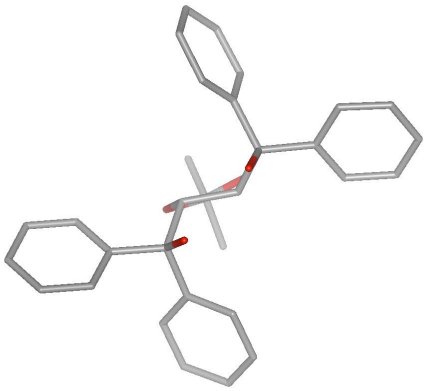


Figure 14. X-ray structure of TADDOL **2**

The second hydroxy group, now with increased acidity, is available for activation through intermolecular hydrogen bonding.[70] Various metal-TADDOLates mostly with Ti, Zr, Mg and Al catalyzed numerous enantioselective reactions such as nucleophilic addition including organozinc addition to aldehydes,[71] allylation,[72] aldol reaction,[73] methylation with $MeTi(OiPr)_3$,[74] hydrocyanation,[75] trimethylsilylcyanation,[76] Diels-Alder,[77] and hetero-Diels-Alder reactions,[78] cyclopropanation of allylic alcohols,[79] chlorination of β-ketoesters, etc.[80] (*Figure 15*).

On the contrary, TADDOLs with pairwise different substituents were less explored in asymmetric reactions. To the best of our knowledge, diols **4** with 1,4-bis(3,5-xylyl/Ph) and 1,4-bis(*p*-F-C_6H_4/Ph) substituents were only used in mechanistic calculations of titanium mediated asymmetric Diels-Alder reaction.[81] Meanwhile, TADDOLs **4** with 1,4-bis(1-naphthyl/Ph) and **5a** were applied in methyltitanium and diethylzinc additions to benzaldehyde.[68] Interestingly, in case of diol **5a** which has small Me substituents (C_2-, C_1-, C_2'-symmetrical, each) the products were formed with low to moderate e.e. (12–76%), but diol **4** (C_1-symmetrical) with bulky 1-naphth/Ph substituents performed well with good yield and selectivities up to 98% e.e. Also, 1,4-bis(alkyl/Ph) substituted diols **5a**–**5d** were tested in vinylogous Mukaiyama aldol reactions.[69] Lower e.e.s (5–23%) were obtained obviously as a consequence of the fact that alkyl groups cannot build up

enough steric interaction. No other results were reported to date on their use in asymmetric catalysis.

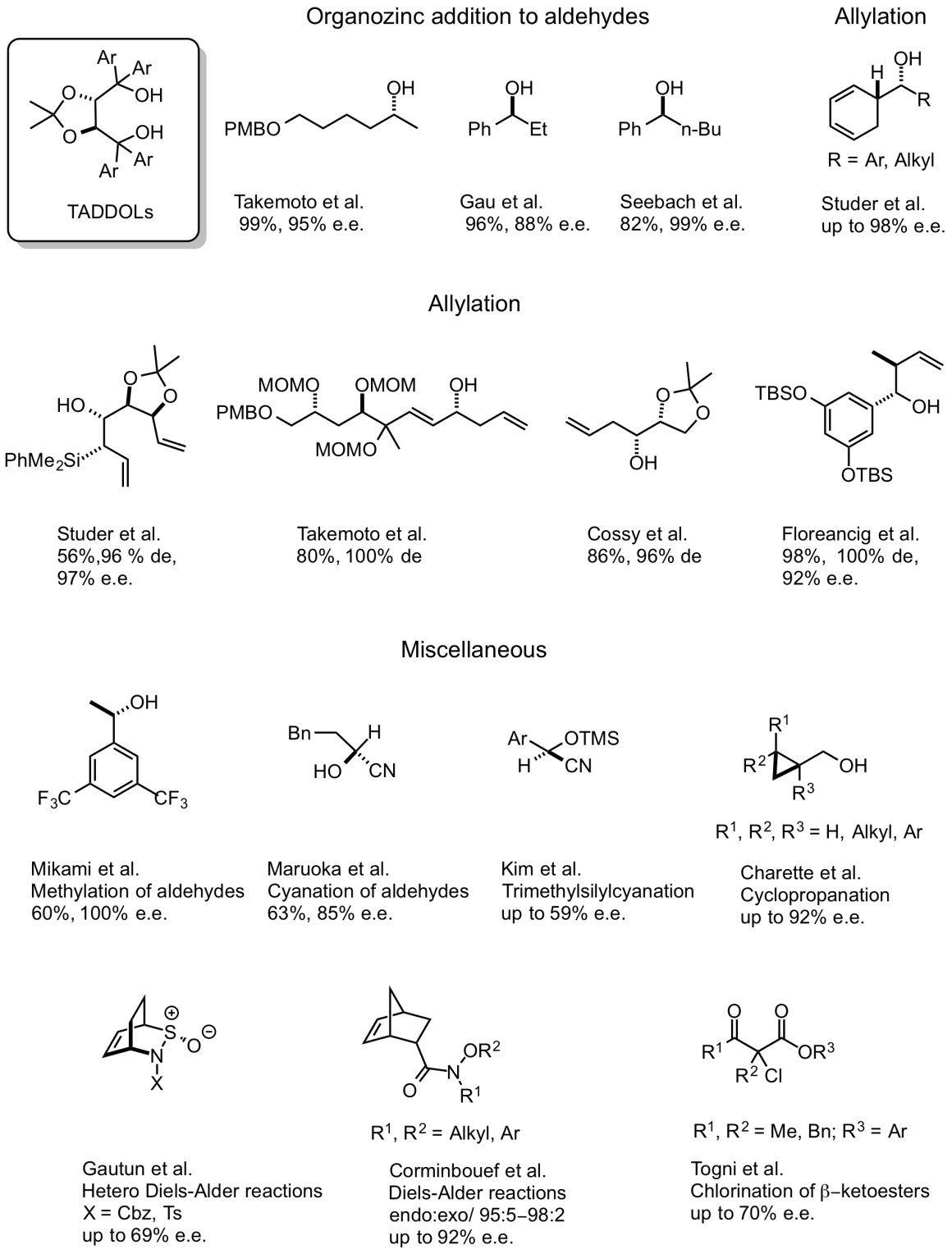


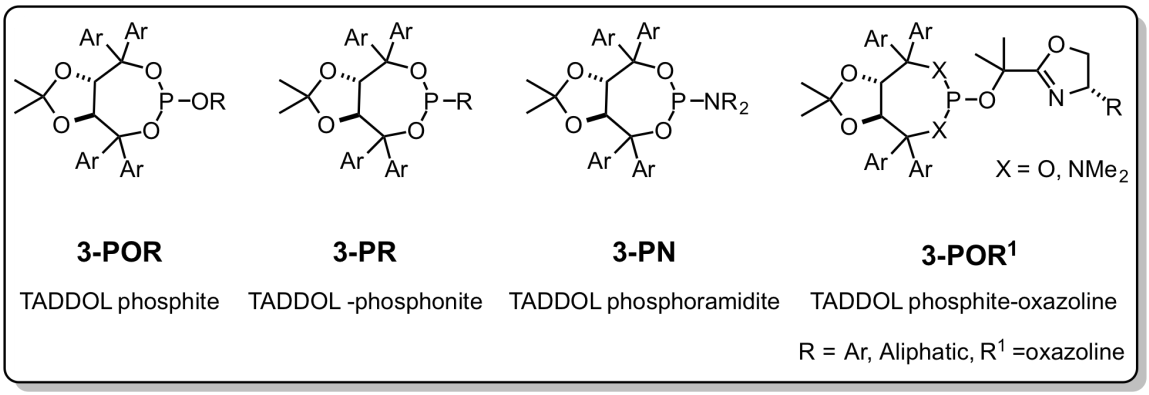
Figure 15. Chiral TADDOLates in catalysis

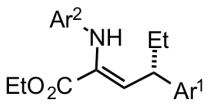
1.5.3. Cyclic phosphorus ligands

Besides the diols, which usually chelate with metals as bidendate ligands**,** cyclic, trivalent phoshorus containing, monodendate TADDOL derivatives such as phosphites (**3-POR**), phosphonites (**3-PR**), phosphoramidites (**3-PN**) or phosphor-oxazolines (**3-POR**[1]) have proven to be effective ligands (*Figure 17*). Combination of TADDOLs and substituents at P atom enables electronic and structural fine tuning of ligands. This results in optimised binding to the metal center and improved stereodiscrimination. Auxiliaries are readily obtained from TADDOLs in a modular way. Corresponding complexes with transition metals catalyse numerous important enantioselective reactions with high stereoselectivities.[82,83] The majority of the phosphorus cycles serve as monodendate ligands[84] and were particularly effective in hydroborations[85] and diborations of various functionlized alkenes,[83] allylic aminations,[86] nucleophilic allylations of dialkylidene ketones[87] (usually over 90% e.e.). Lower enantioselectivities (31–86% e.e.) were reported for hydrosilylations of ketones,[88] conjugate addition reactions of various electrophiles,[89] hydrogenations of olefins,[90] etc. Few reactions together with products from phosphite, phosphonite, and phosphoramidite catalyzed transformations are depicted in *Figure 16*. Bidendate ligands consisting of two subunits of the TADDOL backbone were also applied albeit with limited success.[83]

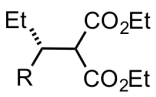
1.5.3.1. Phosphoramidite ligands

Among P containing ligands, phosphoramidites **3-PN** containing two P–O bonds and one P–N bond were most thoroughly studied. Electron pairs on both the phosphorus and the nitrogen atom are potential metal binding sites. Modification of the substituents at the nitrogen atom allows further adjustment of electronic properties of the metal complex leading to higher steric interaction. In this respect, bulky substituents at N atom played a dominant role being mainly responsible for high stereodiscrimination. This was demonstrated for the Cu catalysed conjugate additions of diethyl zinc to cyclohexenone



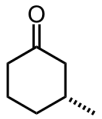


Palacios et al.
Conjugate addition to
α,β–unsaturated imines
up to 88 % e.e.

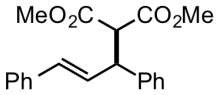


R = Me, n-Bu, Ph

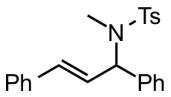
Alexakis et al.
Conjugate addition
to alkylidene malonates
up to 73% e.e.



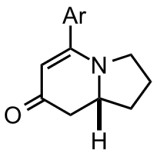
Alexakis et al.
Conjugate addition
y. = 95, ee = 96 %



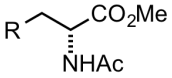
Leeuwen et al.
Allylic alkylation
89% e.e.



Takacs et al.
Allylic amination
82%, 97% e.e.

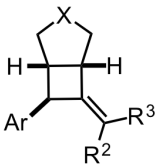


Rovis et al.
[2+2+2] Cycloadditions
up to 99% e.e.



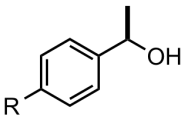
R = Ph, H

Waasenar et al.
Hydrogenation of
dehydroaminoesters
up to 91% e.e.



X = C(COOMe)2
C(COOBn)2
C(COOt-Bu)2
NTs

Fuerstner et al.
[2+2] Cycloaddition
up to 99% e.e.

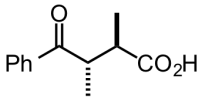


R = H, Me, OMe,
CF3, Cl, F

Takacs et al.
Hydroboration of 4-
substituted styrenes
up to 96% e.e.

R1, R2 = Ar, Alkyl

Finn et al.
Enantioselective
hydrosilylation
up to 94% e.e.

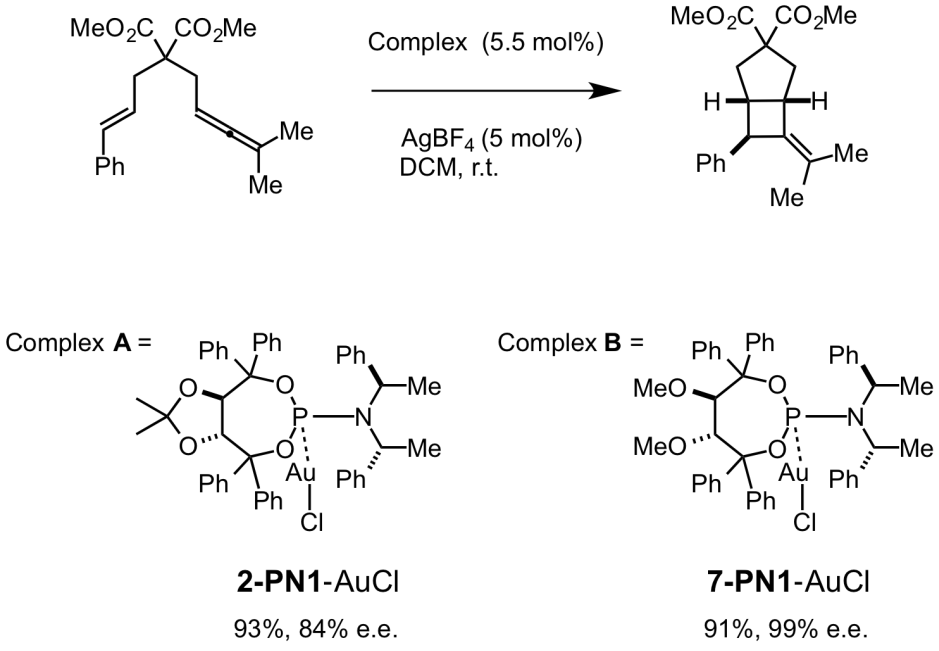


Rovis et al.
Enantioselective
desymmetrization
up to 88% e.e.

Figure 16. TADDOL-phosphoramidite, -phosphonite, and -phosphite ligands and some of the products from catalytic transformation

(up to 96% e.e.)[91] and α,β-unsaturated imines (76–88% e.e.)[92] in the presence of phosphoramidites **3PN**. With Pd, they catalyse diboration of terminal allenes (84–98% e.e.)[93], hydrogenation of dehydroamino acid ester (74–91% e.e.),[94] and allylic alkylations (64–89% e.e.).[89,95,] and Heck cyclizations (78–98% e.e.) etc.[96] In addition, **3-PN**s complex with Rh and catalyse hydroborations of vinylarenes (90–96% e.e.),[97] [2+2+2] cycloaddition reactions of various alkynes (aryl alkynes: 87–94% e.e., alkyl alkynes: 49–85% e.e., conjugated alkynes: 83–91% e.e., terminal alkynes: 88–99% e.e.)[83] and desymmetrizations of cyclic *meso*-anhydrides with arylzinc reagent (up to 88% e.e.) etc.[98]

Fürstner et al. reported an interesting study when changing the *O*-protecting group of TADDOL phosphoramidite in a gold catalysed intramolecular [2+2] cycloaddition between allene and alkene (*Scheme 9*).[99] With dioxolane protected TADDOL phosphoramidite **2-PN1**, the bicyclic product was obtained in 84% e.e. From replacement of the acetal moiety with dimethyl ether it was expected that a resulting seven membered *P*-containing ring would be free from dioxolane ring strain and thus adopt an optimal conformation around metal center eventually resulting in high asymmetric induction. Indeed, this was the case and phosphoramidite **7-PN1** showed greatly improved enantioselectivity to 99% e.e.



Scheme 9. Gold catalysed [2+2] cycloaddition catalysed by **2-PN1** and **7-PN1**

1.5.4. TADDOLs as organocatalysts

Whereas TADDOLs were extensively studied in transition metal catalysed reactions, their applications in organocatalysis were explored to a lesser extent. TADDOLs were mainly employed as hydrogen bond donor catalysts and it will be discussed in the next chapter.

Other applications of TADDOLs as organocatalysts are sparse. Phosphite **2-POH** (*Figure 17*) catalysed a cross-silyl benzoin condensation (41–91% e.e.),[100] *C*-acylation of nitrones (92–97% e.e.),[101] and conjugate additions of acylsilane to unsaturated amides (up to 74% e.e.).[102] Quaternary ammonium salts **8** with similar geometry and TADDOLate **9** served as efficient phase transfer catalysts promoting the α-alkylation of Schiff bases (82% e.e.)[103] and Michael addition of aminophosphonate (72% e.e.).[104]

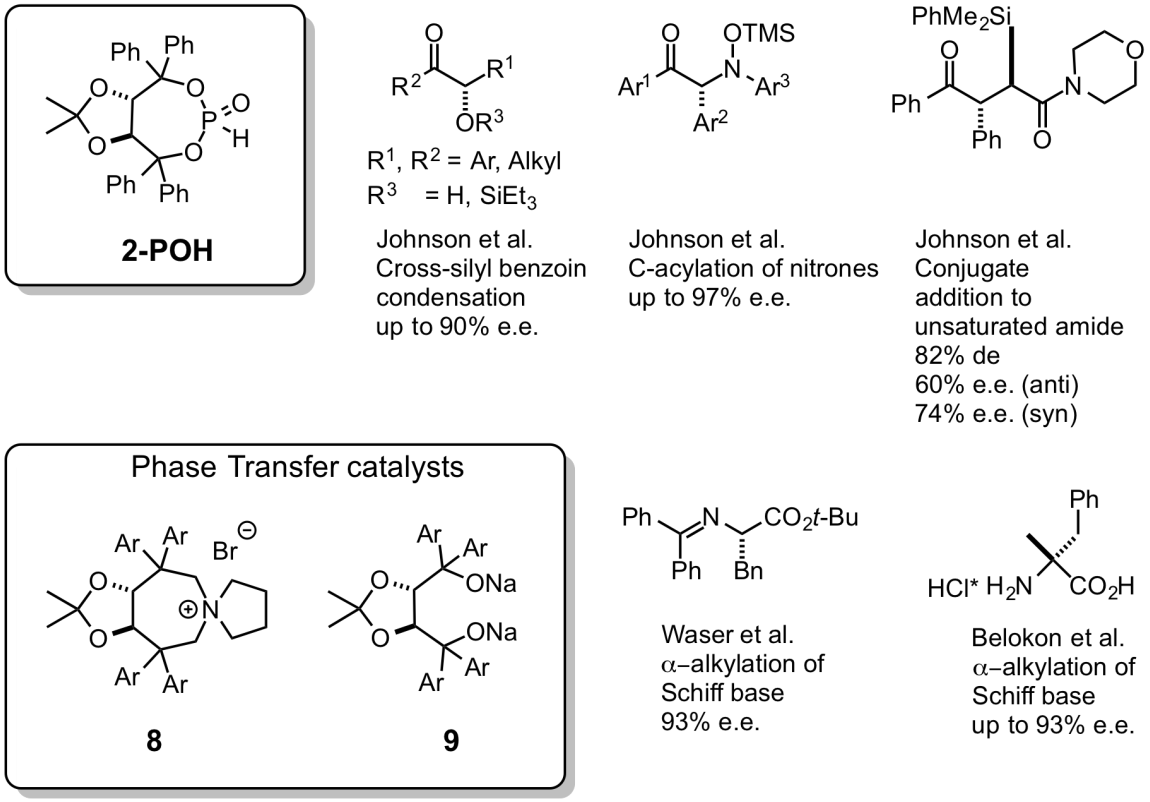
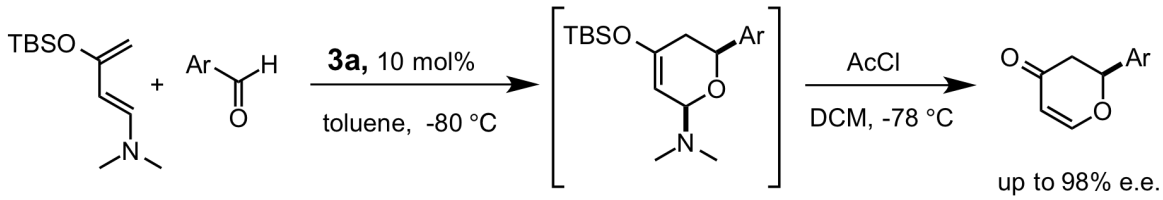


Figure 17. TADDOLs in organocatalysis

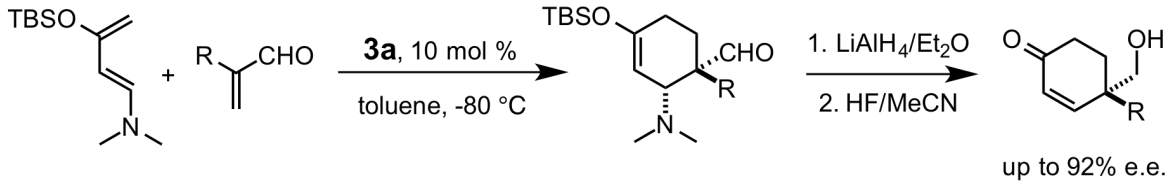
1.5.4.1 TADDOLs as chiral Brønsted acids

As mentioned earlier, the intramolecular hydrogen bonding within TADDOL enhances Brønsted acidity of the second H atom, which is available for intermolecular interaction. This Brønsted acid assisted Brønsted acidicity (BBA) was found to effectively catalyse various enantioselective reactions. Rawal and co-workers first successfully applied 1-naphthyl substituted TADDOL ($\alpha,\alpha,\alpha',\alpha'$-tetra(1-naphthyl)-1,3-dioxane-4,5-dimethanol) **3a** as hydrogen bonding catalyst in hetero Diels-Alder reactions of 1-dimethylamino-3-siloxy-1,3-butadiene with various aromatic aldehydes and obtained excellent yield and enantioselectivities (86–98% e.e.) (*Scheme 10*).[105]



Scheme 10. Asymmetric hetero Diels-Alder reactions

Later, they extended this study to acrolein dienophiles to afford products with 73–92% e.e. (*Scheme 11*)[106]



Scheme 11. Diels-Alder reaction with acrolein dienophiles

Based on these results, they proposed that TADDOL and aldehydes complex through two-point interactions where the carbonyl group is activated by hydrogen bonding while the electron deficient carbonyl group is stabilized by π–π interaction of a proximal equatorial 1-naphthyl group. This π–π stacking effectively shields one face of the dienophile and leads to *Si* face attack.[107] Computational investigations by various groups

to elucidate the origin of enantioselectivity[108] and hydrogen bonding interactions[109] also supported the two-point interaction transition state. Particularly, 1-naphthyl TADDOL showed high stereoselection as the aryl groups are arranged in a unique way where pseudoequatorial groups point away from the dioxolane backbone while pseudoaxial groups point to it. This arrangement makes rotation around (quaternary) carbon-naphthyl bonds more restricted and will lead to highly organized internally hydrogen-bonded arrangement (*Figure 18*).

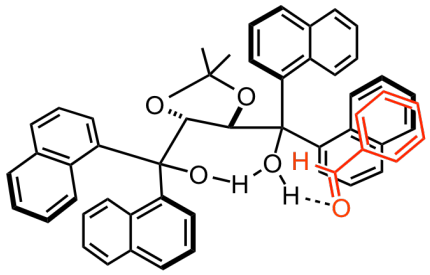
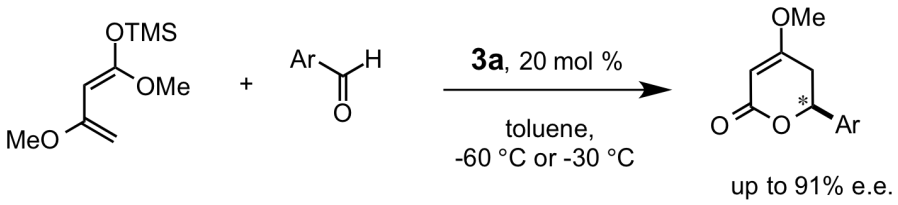


Figure 18. TADDOL **3a**-aldehyde complex

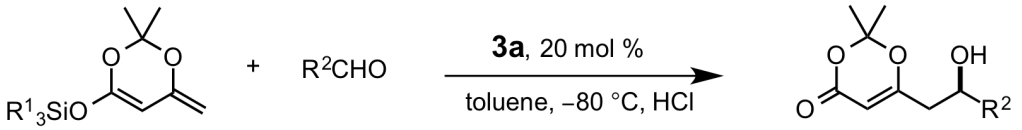
Dihydropyranones obtained by HDA reactions were later converted to β-lactones, which have found extended application in natural products synthesis. A direct synthesis of β-lactone derivatives was first published by Ding and co-workers when they developed highly selective HDA reactions of electron rich Brassard's diene with aromatic aldehydes catalysed by **3a** with up to 91% e.e. (*Scheme 12*).[110]



Ar = Ph, *p*-MeOC$_6$H$_4$, *p*-Cl-C$_6$H$_4$, *m*-MeOC$_6$H$_4$ etc.

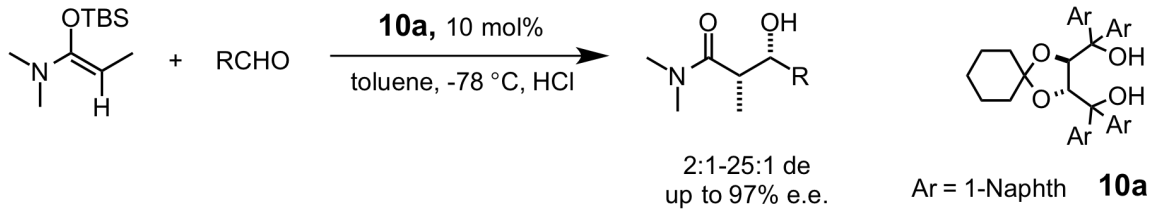
Scheme 12. Diels-Alder reactions of Brassard's diene

Rawal's group extended the application of H bonding catalysts to vinylogous Mukaiyama aldol reactions. Again **3a** was most effective yielding products with up to 87% e.e. (*Scheme 13*).[111]



Scheme 13. Vinylogous Mukaiyama aldol reaction

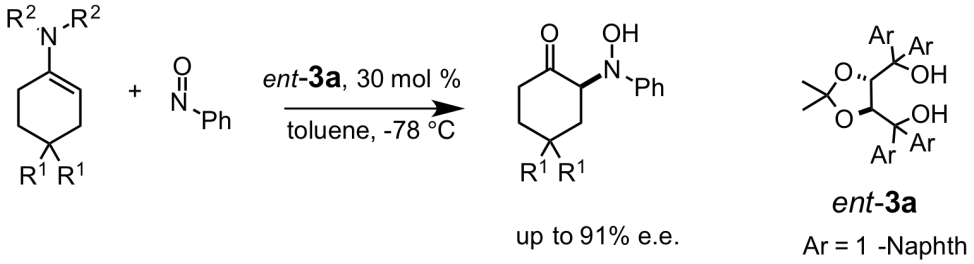
A TADDOL analogue with spirocyclic backbone **10a** was synthesized by the same group and tested in Mukaiyama aldol reactions with different nucleophiles, namely, *O*-silyl-*N,O*-ketene acetals (*Scheme 14*). The reaction proceeded smoothly and the β-hydroxyamides were obtained with excellent stereoselectivities.[112]



R = Ph, *p*-$NO_2C_6H_4$, *p*-$CF_3C_6H_4$, *p*-ClC_6H_4, *m*-$MeOC_6H_4$ etc.

Scheme 14. Mukaiyama aldol reaction of *O*-silyl-*N,O*-ketene acetals

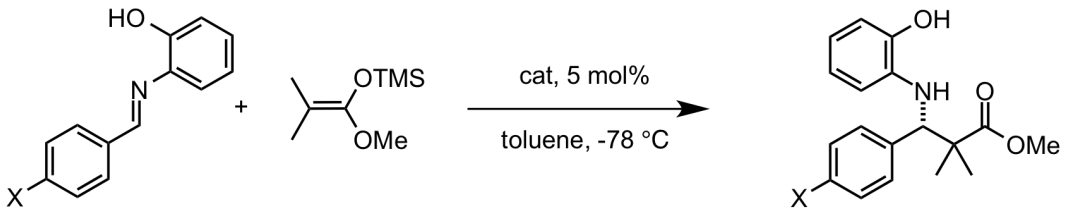
Yamamoto and co-workers employed *ent*-**3a** in highly enantioselective *N*-nitroso-aldol reaction (*Scheme 15*).[113]



R^1 = H, Me
R^2 = $(CH_2)_5$, $(CH_2)_4$, $(CH_2)_2O(CH_2)_2$ etc.

Scheme 15. Enantioselective N-nitrosoaldol reactions

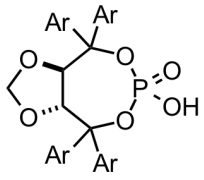
Besides TADDOLs, the more acidic cyclic phosphoric acids **3** were obtained by Akiyama's group and explored in Mannich type reactions. Various 4-substituted arylaldimines were tested and enantioselectivities reached up to 92%. The effect of acetal moieties of the TADDOL backbone was explored and **11-POOH** afforded the best product in 73% e.e. However, when they changed to catalyst **3e-POOH** with 2,2-dimethyl dioxolane backbone**,** e.e. dropped to 56% (*Scheme 16*).[114]

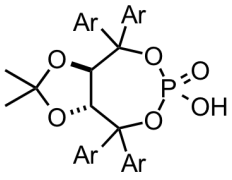


X = H, Cl, F, MeO, Me

up to 92% e.e. with **11-POOH**

cat. =





11-POOH **3e-POOH**

When R = H 97%, 73% e.e. 62%, 56% e.e. Ar = *p*-$CF_3C_6H_4$

Scheme 16. Enantioselective Mannich reaction catalysed by TADDOL phosphate

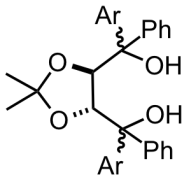
2. Aims of the thesis

Aims of the thesis comprise two parts; synthesis of ligands and auxiliaries and their application in asymmetric catalysis.

2.1. Synthesis of chiral ligands and auxiliaries

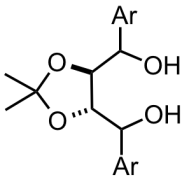
2.1.1. The C_2-symmetrical TADDOL analogues with α-chirality

Introducing two different geminal substituents at C1 and C4 positions of TADDOLs will create additional stereogenic centers in proximity to the chelating metal. This might induce more pronounced discrimination during diastereomeric transition states leading to products with higher enantiopurity. Furthermore, by introducing substituents with different electronic and steric properties it might be possible to investigate trends in reactivity and stereoselectivity. Based on published results on the use of diols with α-chirality; **4** with four aromatic substituents and **5a**–**5d** with alkyl and aryl substituents (*Figure 12*), it was concluded that alkyl groups do not build up enough steric interaction for efficient asymmetric induction.[68,69] Therefore, it was hypothesized that improved stereoinduction may be achieved with diols **4a**–**4g** with pairwise different geminal aryl groups (*Figure 19*).



4

Ar = *p*-ClC_6H_4 **4a**
p-$MeOC_6H_4$ **4b**
o-ClC_6H_4 **4c**
o-$MeOC_6H_4$ **4d**
Bn **4e**
4-$C_6H_5C_6H_4$ **4f**
p-$MeC_6H_4C_6H_5$ **4g**
2-naphth. **4h**
4-dibenzofuryl **4i**



6

Ar = Ph **6a**
p-ClC_6H_4 **6b**
p-$MeOC_6H_4$ **6c**
2-naphth. **6d**

Figure 19. 2,3-Dioxolane protected diols with pairwise different substituents

On the other hand, if steric interaction at C1 and C4 positions becomes outsized, alternative structures like **6** with Ar/H substituents might be worth to investigate. The two aryl groups in secondary diols **6** would eventually adopt different conformations compared to their tertiary diol counterparts **4** and therefore resulting in transition states with different geometry. Accordingly, synthesis of **6** will be attempted (*Figure 19*) all the more so as, to the best of our knowledge, no records were published where these secondary diols were applied as chiral catalysts or auxiliaries.

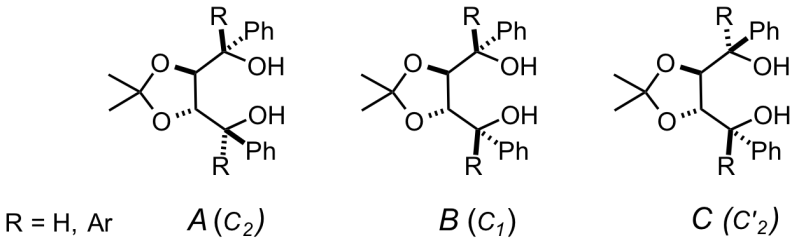
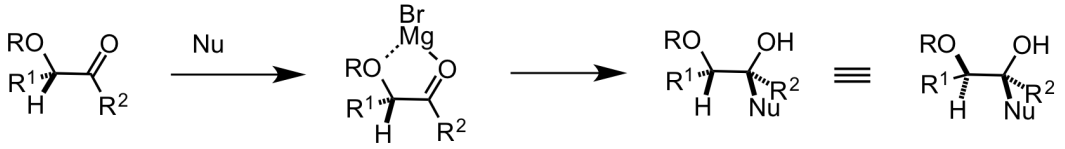


Figure 20. Three diastereomers of diols with α-chirality

From the synthesis of diols with pairwise different substituents up to three diastereomers are expected; two with C_2 symmetry and one with C_1 symmetry (*Figure 20*). Upon treatment with Grignard reagents α-alkoxy carbonyls form 1,2-chelates to which nucleophile is added from a less hindered side, forming *syn* alcohols predominantly (*Scheme 17*).[115]



Scheme 17. Cramm's rule to predict *d.r.* of Grignard addition reaction to α-alkoxy carbonyls

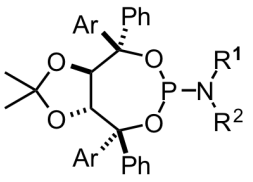
Consequently, C_2-symmetrical species *A* in which the incoming nucleophile and the adjacent alkoxy of the dioxolane ring *syn* to each other will be formed as a major isomer. In their study of TADDOLs and TADDOL analogues as titanium ligands in enantioselective addition of methyltitanium to benzaldehyde, Seebach et al. showed that among three diastereomers of diol **5a,** the main isomer *A* showed superior

stereoselectivity (76% e.e.) compared to other two isomers *B* and *C* (18% and 52% e.e., respectively).[68] To that end, the main isomers *A* will be the central focus of the synthesis of diols **4**. In conclusion, a series of TADDOL ligands with α chirality will be synthesized and synthetic attempts will be focused on

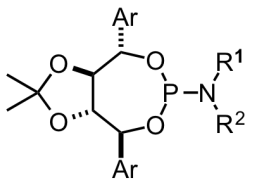
a) diols **4a**-**4g** with Ar/Ph substituents
b) diols **6a**-**6d** with Ar/H groups.

2.1.2. TADDOL phosphoramidites derived from C_2-symmetrical diols

Once the C_2-symmetrical diols **4** and **6** are obtained, synthesis of their phosphoramidite derivatives **4**-**PN** and **6**-**PN** will be performed next as various phosphoramidites (*Figure 21*) are readily accessible from diols in modular way and efficiently catalyse wide array of reactions.



4-PN



6-PN

Ar = *p*-ClC_6H_4	**4a-PN**
p-$MeOC_6H_4$	**4b-PN**
o-ClC_6H_4	**4c-PN**
o-$MeOC_6H_4$	**4d-PN**
Bn	**4e-PN**
4-$C_6H_5C_6H_4$	**4f-PN**
p-$MeC_6H_4OC_6H_4$	**4g-PN**
2-naphth.	**4h-PN**
4-dibenzofuryl	**4i-PN**

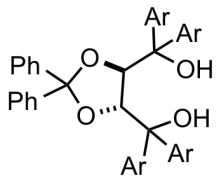
Ar = Ph	**6a-PN**
p-$MeOC_6H_4$	**6b-PN**
p-ClC_6H_4	**6c-PN**
2-naphth.	**6d-PN**

R^1, R^2 = *i*-Pr;
R^1-N-R^2 = piperdine

Figure 21. Phosphoramidites derived from diols **4** and **6** with pairwise different substituents

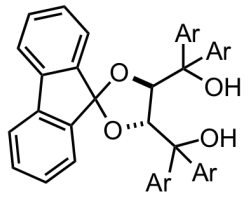
2.1.3. TADDOL analogues with various protecting groups

Not only will the introduction of aryl substituents at C1 and C4 significantly affect the overall conformation but also variation of protecting groups at C2 and C3 will influence geometries of transition states.[99] Therefore, synthesis of diols with varied cyclic and non-cyclic 2,3-*O,O*- protecting groups will be carried out. Compared to the most frequently used 2,2-dimethyl dioxolane, bulky diphenyl substituents will exert more pronounced effect on the conformation of diols **12** (*Figure 22*).



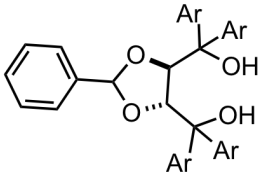
12

Ar = Ph	**12a**
p-ClC_6H_4	**12b**
p-FC_6H_4	**12c**
p-$CF_3C_6H_4$	**12d**
2-naphth.	**12e**
1-naphth.	**12f**



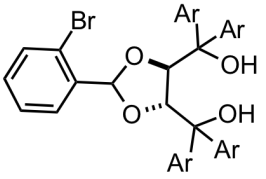
13

Ar = Ph	**13a**
p-ClC_6H_4	**13b**
p-FC_6H_4	**13c**
p-$CF_3C_6H_4$	**13d**
2-naphth.	**13e**
1-naphth.	**13f**



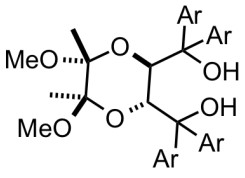
14

Ar = Ph	**14a**
p-ClC_6H_4	**14b**
p-FC_6H_4	**14c**
p-$CF_3C_6H_4$	**14d**
2-naphth.	**14e**
1-naphth.	**14f**



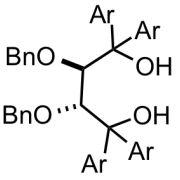
15

Ar = Ph	**15a**
p-ClC_6H_4	**15b**
p-FC_6H_4	**15c**
p-$CF_3C_6H_4$	**15d**
2-naphth.	**15e**
1-naphth.	**15f**



16

Ar = Ph	**16a**
p-ClC_6H_4	**16b**
p-FC_6H_4	**16c**
p-$CF_3C_6H_4$	**16d**
2-naphth.	**16e**
1-naphth.	**16f**



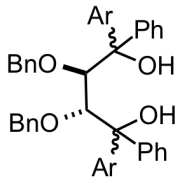
17

Ar = Ph	**17a**
p-ClC_6H_4	**17b**
p-FC_6H_4	**17c**
p-$CF_3C_6H_4$	**17d**
2-naphth.	**17e**
1-naphth.	**17f**

Figure 22. TADDOLs with various protecting groups and four identical aryl substituents

Likewise, diols **13** with a fluorenyl acetal will adopt similar geometry but with less conformative freedom. Furthermore, mono-aryl substitution and an enlarged acetals ring will be introduced to tune the conformational rigidity and eventually discover the optimal TS-geometry. In this respect, diols **14**, **15** and **16** will be synthesized. Finally, diols **17** with 2,3-*O,O*-dibenzyl protecting groups will be prepared as conformationally nearly unrestricted candidates. From simply steric reasons an *anti*-conformation of OBn groups is expected.

The variation of 2,3-protecting groups will also be extended to the diols with α-chirality and synthesis of diols analogue to **4** is planned. From the viewpoint of synthetic economy, 2,3-*O,O*-dibenzyl ether protected diols **18** will be prepared first which supposedly display the most distinct characteristics in comparison to **4** (*Figure 23*).



18

Ar =	*p*-ClC_6H_4	**18a**
	p-$MeOC_6H_4$	**18b**
	o-ClC_6H_4	**18c**
	o-$MeOC_6H_4$	**18d**
	Bn	**18e**
	4-$C_6H_5C_6H_4$	**18f**
	p-$MeC_6H_4OC_6H_4$	**18g**
	2-naphth.	**18h**
	4-dibenzofuryl	**18i**

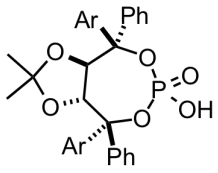
Figure 23. 2,3-*O,O*-dibenzyl ether TADDOLs with pairwise different substituents

Thus, syntheses will further comprise

a) various acetal protected diols **12**–**17** with four identical aryl groups
b) dibenzylether protected diols **18** with pairwise different subsituents.

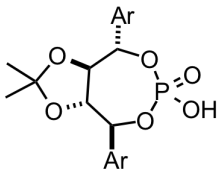
2.1.4. Brønsted acid catalysis, cyclic phosphoric acids

Based on diols **4**, **6** and **12**–**18**, their phosphoric acid derivatives will be synthesized (*Figure 24*, *25*) and used in organocatalytic reactions where stronger Brønsted acids are required for electrophile activation. In total, 58 different phosphoric acids will be synthesized and applied in asymmetric reactions.



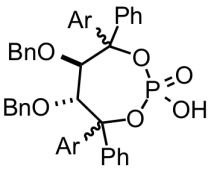
4-POOH

Ar = *p*-ClC_6H_4	**4a-POOH**
p-$MeOC_6H_4$	**4b-POOH**
o-ClC_6H_4	**4c-POOH**
o-$MeOC_6H_4$	**4d-POOH**
Bn	**4e-POOH**
4-$C_6H_5C_6H_4$	**4f-POOH**
p-$MeC_6H_4OC_6H_4$	**4g-POOH**
2-naphth.	**4h-POOH**
4-dibenzofuryl	**4i-POOH**



6-POOH

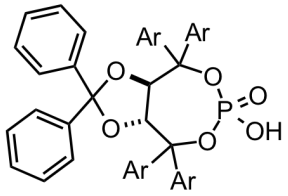
Ar = Ph	**6a-POOH**
p-$MeOC_6H_4$	**6b-POOH**
p-ClC_6H_4	**6c-POOH**
2-Naphth.	**6d-POOH**



18-POOH

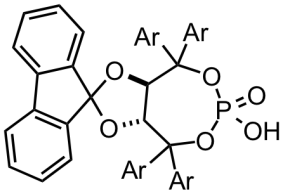
Ar = *p*-ClC_6H_4	**18a-POOH**
p-$MeOC_6H_4$	**18b-POOH**
o-ClC_6H_4	**18c-POOH**
o-$MeOC_6H_4$	**18d-POOH**
Bn	**18e-POOH**
4-$C_6H_5C_6H_4$	**18f-POOH**
p-$MeC_6H_4OC_6H_4$	**18g-POOH**
2-naphth.	**18h-POOH**
4-dibenzofuryl	**18i-POOH**

Figure 24. Phosphoric acid derivatives of **4, 6** and **18** with pairwise different substituents



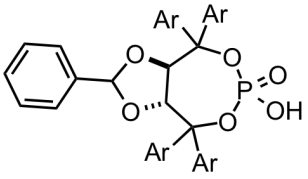
12-POOH

Ar = Ph	**12a-POOH**
p-ClC_6H_4	**12b-POOH**
p-FC_6H_4	**12c-POOH**
p-$CF_3C_6H_4$	**12d-POOH**
2-naphth.	**12e-POOH**
1-naphth.	**12f-POOH**



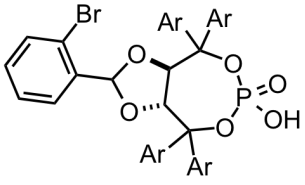
13-POOH

Ar = Ph	**13a-POOH**
p-ClC_6H_4	**13b-POOH**
p-FC_6H_4	**13c-POOH**
p-$CF_3C_6H_4$	**13d-POOH**
2-naphth.	**13e-POOH**
1-naphth.	**13f-POOH**



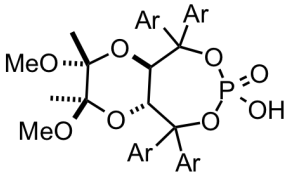
14-POOH

Ar = Ph	**14a-POOH**
p-ClC_6H_4	**14b-POOH**
p-FC_6H_4	**14c-POOH**
p-$CF_3C_6H_4$	**14d-POOH**
2-naphth.	**14e-POOH**
1-naphth.	



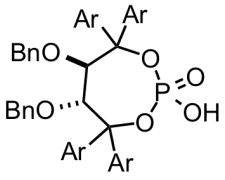
15-POOH

Ar = Ph	**15a-POOH**
p-ClC_6H_4	**15b-POOH**
p-FC_6H_4	**15c-POOH**
p-$CF_3C_6H_4$	**15d-POOH**
2-naphth.	**15e-POOH**
1-naphth.	**15f-POOH**



16-POOH

Ar = Ph	**16a-POOH**
p-ClC_6H_4	**16b-POOH**
p-FC_6H_4	**16c-POOH**
p-$CF_3C_6H_4$	**16d-POOH**
2-naphth.	**16e-POOH**
1-naphth.	**16f-POOH**



17-POOH

Ar = Ph	**17a-POOH**
p-ClC_6H_4	**17b-POOH**
p-FC_6H_4	**17c-POOH**
p-$CF_3C_6H_4$	**17d-POOH**
2-naphth.	**17e-POOH**
1-naphth.	**17f-POOH**

Figure 25. Phosphoric acid derivatives of 1,4- di.*tert.* diols **12**–**17** with various protecting groups

2.2. Catalytic reactions

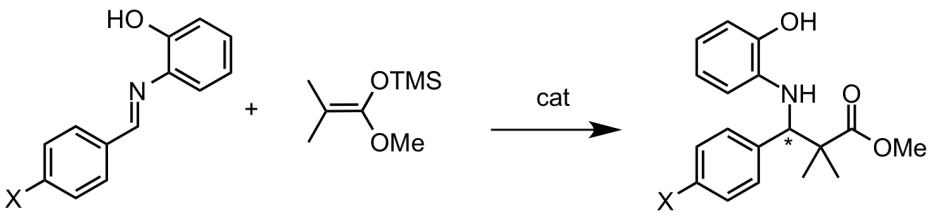
The choice for following test reactions was based on several considerations:

a) Only low activity or selectivity has been reported so far and therefore a good chance for improvement exists.
b) Type of conversion might have some practical significance being eventually useful in drug synthesis.
c) The reaction has not been catalyzed by any TADDOL derivatives before.

2.2.1. Organocatalysis

2.2.1.1. Mannich type reactions

The enantioselective Mannich reactions of enolates or enolate equivalents with aldimines afford chiral β-aminocarbonyl compounds, which are the precursors of biologically important β-lactams and β-aminoacids. The first example of this type of reaction catalysed by TADDOL phosphoric acid reached 73% e.e. after varying substituents at α,α'-positions as well as at the dioxolane backbone.[114] An improved enantioselectivity can be achieved by further varying the size and substituents at acetal moiety as well as aryl subsituents at C1 and C4. Thus, I intend to improve enantioselectivities in Mannich reactions by using phosphoric acids **4-POOH, 6-POOH** and **12-POOH**–**18-POOH** (*Scheme 18*).



X = H, Cl, F, MeO, Me

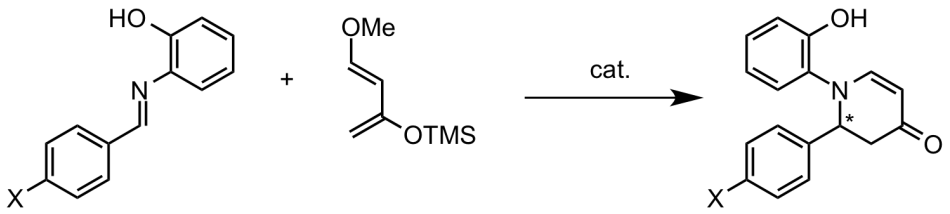
cat. = **4-POOH, 6-POOH, 12-POOH–18-POOH**

Scheme 18. Stronger Brønsted acid catalysed enantioselective Mannich type reactions

2.2.1.2. Aza-Diels-Alder reaction

Application of aza-Diels-Alder reactions is a powerful method to construct optically active nitrogen containing six membered rings, which are found in wide range of natural and biologically active compounds. To the extent of our knowledge, no TADDOL phosphoric acids were applied in aza-Diels-Alder reactions albeit similar BINOL derived phosphoric acids catalyse the reaction with high e.e.[116]

TADDOL phosphoric acids could be interesting alternatives as they are more easily accessible and cheaper then BINOL phosphates. Therefore, I intend to employ TADDOL phosphates **4-POOH, 6-POOH** and **12-POOH–18-POOH** in this strategically important reaction to access enantioselectively α-aryl substituted tetrahydropyridines in a more economic way (*Scheme 19*).



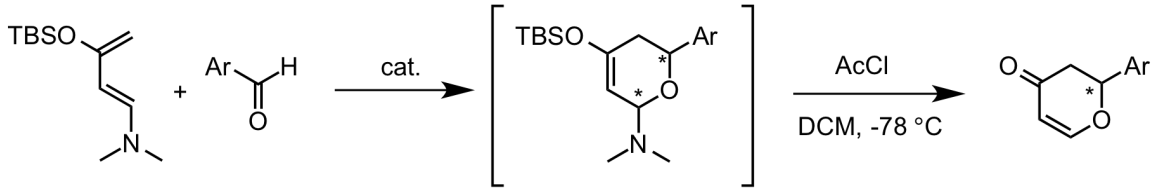
X = H, Cl, F, MeO, Me

cat. = **4-POOH, 6-POOH, 12-POOH–18-POOH**

Scheme 19. Enantioselective aza-Diels-Alder reactions catalysed by phosphoric acids **4-POOH**, **6-POOH**, **12POOH–18POOH**

2.2.1.3. Oxo-Diels-Alder reactions

Oxo-Diels-Alder reaction is a powerful method to synthesize optically enriched dihydropyrans, which are versatile building blocks in the synthesis of natural products. So far, H bonding catalysts employed in oxo-Diels-Alder reactions of Rawal's or Brassard's diene and aldehydes afforded only *S* products.[117] Obtaining dihydropyrans in both enantiomers would be valuable as it would open straightforward access to synthetically useful building blocks.



cat. = **4, 6, 12–18**

Ar = Ph, *p*-ClC_6H_4, *p*-MeC_6H_4, *p*-$MeOC_6H_4$ etc.

Scheme 20. Enantioselective oxo-Diels-Alder reactions catalysed by H- bond donor catalysts **4**, **6**, and **12–18**

Diols **4, 6, 12–18** with cyclic acetals of different sizes/substituents or *O*-Bn as protecting groups should display varied conformations eventually affecting the absolute configuration and enantioselectivity of the product (*Scheme 20*). Thus, the thesis aims to investigate effects of the varied protecting groups of the diols on the stereoselectivity of the reactions and eventually obtain the enantiomerically enriched *R* product.

2.2.2. Transition metal catalysed reactions

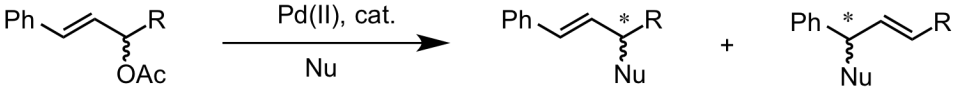
Besides being applied as Brønsted acids, the diols and the corresponding phosphoramidites can serve as ligands in transition metal catalysed reactions.

2.2.2.1. Pd catalysed allylic alkylation

Asymmetric allylic alkylation (AAA) is an attractive method for forming C–C and C-heteroatom bonds. Among many metal complexes designed to catalyse AAA reactions, chiral Pd species are the most versatile. Boele et al. investigated TADDOL based phosphoramidite-Pd complexes in AAA and reported high e.e. (up to 93% e.e.) with symmetrically substituted substrate 1,3-diphenyl-2-propenyl acetate.[95] When the amine is chiral, stereoselectivity is further increased up to 93% e.e. (Cooperative effect was observed when the amine moiety and TADDOLate backbone have the opposite configuration) On the other hand, low e.e. was reported for unsymmetrically substituted

allylic substrates (7–32% e.e.), even though bulky phosphoramidites was shown to drive the regioselectivity of monosubstituted allylic compounds towars the chiral, branched products.

Likewise phosphoramidites with chiral amines, **4-PN** and **6-PN** with α-chirality close to the P-N bond are expected to induce more pronounced stereoselectivity further increasing e.e. of AAA of unsymmetrically substituted substrates. Thus, the project aims to employ ligands **4-PN** and **6-PN** to improve Pd catalysed allylic alkylations of unsymmetrically substituted allylic acetates (*Scheme 21*).

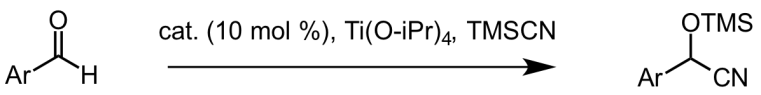


cat. = **4-PN**, **6-PN**
R = H, Me, Et etc.
Nu= $CH(COOMe)_2$ etc.

Scheme 21. Pd catalysed allylic alkylations of unsymmetricallly substituted allylic acetates

2.2.2.2. Trimethylsilylcyanations

Cyanohydrines are important chiral building blocks, which can be easily transformed into a wide range of synthetically important 1,2-difunctional compounds. Trimethylsilylcyanide (TMSCN) is the most commonly used cyanide source due to its safe handling, relative stability and fair reactivity.[118] For the Ti-TADDOLate complex of **2** moderate e.e. were reported. No further studies on TADDOLs' acetal moieties or substituents' effects have been carried out.[76]



cat. = **4**, **6, 12**–**18**

Ar = Ph, *p*-ClC_6H_4, *p*-MeC_6H_4, *p*-$MeOC_6H_4$ etc.

Scheme 22. Enantioselective Ti catalysed TMSCN reactions

For this reason, with diols **4, 6, 13**–**20,** I plan to investigate the effects of changed acetal moieties and substituents of TADDOL backbones on Ti catalysed TMSCN additions to aromatic aldehydes (*Scheme 22*).

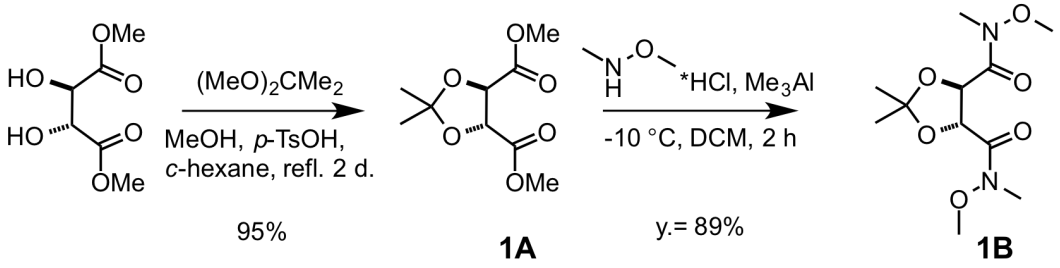
3. Results and Discussion

3. 1. Synthesis of ligands and catalysts

3.1.1. Synthesis of 1,4-diols with α-chirality

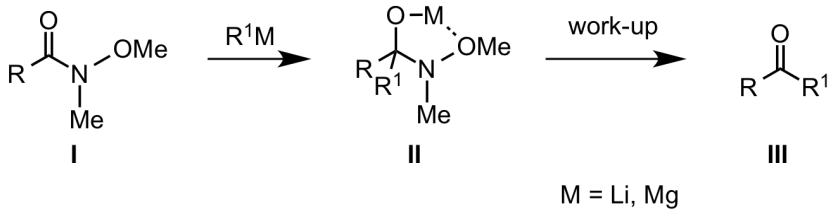
3.1.1.1. Synthesis and desymmetrisation of sec.diols with α-chirality

Synthesis of diols **4** and **6** with α chirality was done in a stepwise manner through Weinreb amide intermediate **1B**. Starting from (+)-dimethyl *L*-tartrate, two hydroxy groups of which were protected as 2,2-dimethyldioxolane **1A** in the next step, **1B** was obtained in 85% overall yield in 2 steps (*Scheme 23*).



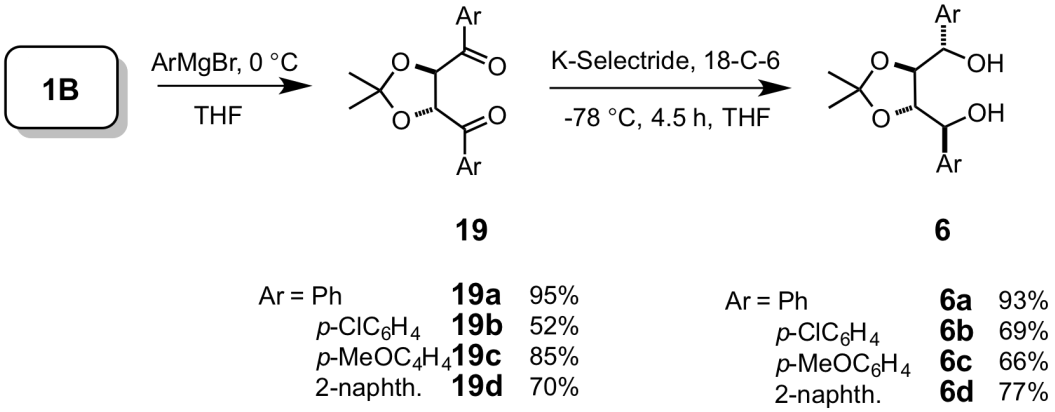
Scheme 23. Synthesis of Weinreb amide intermediate **1B**

Weinreb amide **I** formation is a reliable way to ketones **III** from corresponding esters as it forms a stable intermediate **II** upon first equvalent of nucleophilic addition and thus prevents further addition of the nucleophile (*Scheme 24*).



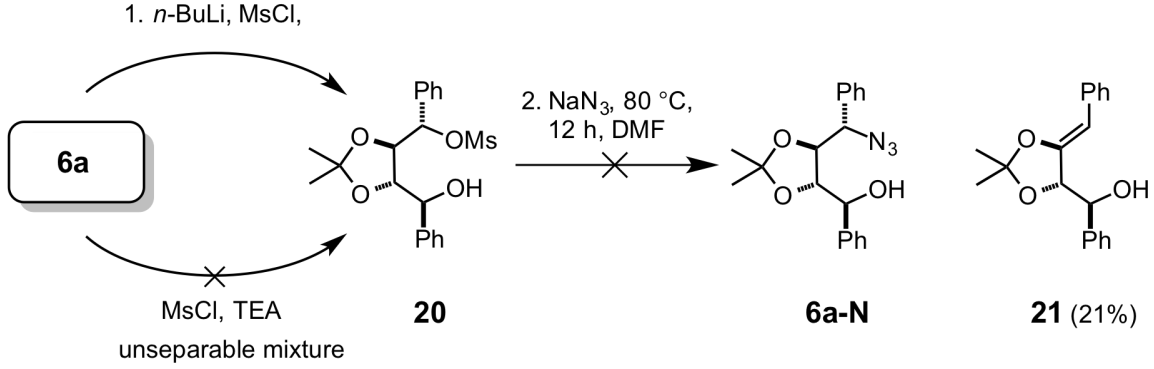
Scheme 24. Weinreb amides form ketones

Thus, various 1,4- diketones **19a**–**19d** were obtained in high yield (52–95%) from the Weinreb amide intermediate **1B** upon treatment with appropriate Grignard reagents (*Scheme 25*). Stereoselective reduction of ketones **19** with K-selectride in presence of crown ether 18-C-6 afforded the desired *sec*. diols **6a-b** in 66–78% (Yields refer to isolated yield of C_2-symmetrical product).



Scheme 25. Synthesis of 1,4-*sec*. diols **6a**-**6d** from Weinreb amide **1B**

Next, attemtps to desymmetrise these 1,4- diols were performed on **6a** as an example (*Scheme 26*). Synthesis of amino alcohol of **6a** through mono azide derivative **6a-N** was not succesfull due to a propensity of H at *sec.* C to eliminate. Thus, at lower temperature, azide nucleophile did not attack at *sec*. C, therefore, starting material **6a** was recovered. When the temperature is elevated to 80 °C, instead of the azide **6a-N**, elimination product **21** was formed in 21% yield. The attempts to isolate monomesylate **20** was also troublesome. Mono and dimesylated compounds were formed in 1:1 ratio along with other unidentified side products which were not separable by chromatography.

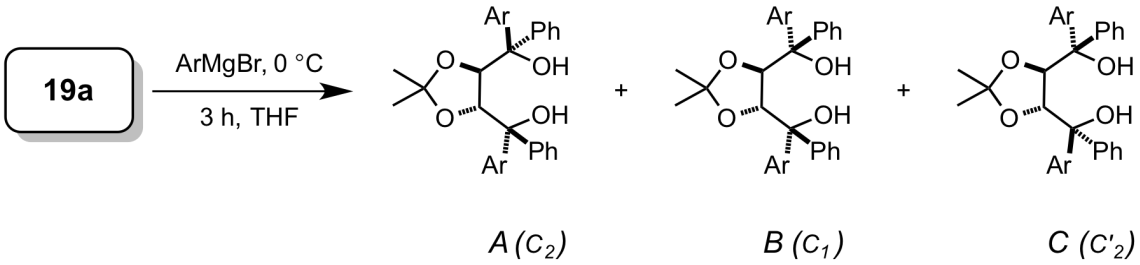


Scheme 26. Attempts to desymmetrise *sec*.diol **6a**

Therefore, 4 different C_2-symmetrical *sec.* diols **6** were obtained. The attempts to synthesize the desired unsymmetrical products based on diols **6** were not successful.

3.1.1.2. Synthesis of tert. diols with α-chirality

Next, the focus was shifted to the synthesis of tertiary diols **4a-i** with pairwise different aryl groups. Upon treatment with appropriate Grignard reagents diketone **19a** forms three diastereomers: two C_2- and one C_1-symmetrical diol (*Scheme 27*).



Scheme 27. Three diastereomers formed upon Grignard addition to 1,4-diketone **19a**

Table 1. Diastereoselectivity of synthesis of *tert*. diols **4a-i**

Entry	*Product*	*Ar*	*Yield, %*	*A(C_2)*	*B(C_1)*	*C(C'_2)*	*Ratio* A : B*
1	**4a**	*p*-ClC_6H_4	90	90	10	-	10:1
2	**4b**	*p*-$MeOC_6H_4$	75	79	21	-	5:1
3	**4c**	*o*-ClC_6H_4	43	82	18	-	6:1
4	**4d**	*o*-$MeOC_6H_4$	59	44	56	-	pure
5	**4e**	Bn	50	91	9	-	pure
6	**4f**	4-C_6H_5-C_6H_4	78	69	22	9	8.5:1
7	**4g**	*p*-MeC_6H_4-O-C_6H_4	69	63	21	16	6:1
8	**4h**	2-naphth.	75	71	20	9	3.5:1
9	**4i**	4-dibenzofuryl	50	69	31	-	2:1

* After chromatography

As expected, generally high *d.r.* in favor of C_2-symmetrical diol *A*, controlled by the 1,2-chelation,[115] was obtained in all cases with small amount of C_1-symmetrical diol along with minimum amount of C'_2-symmetrical species in few cases. The reactions proceeded with generally good yield of up to 90% (*Table 1*).

Nucleophiles with *ortho* substituents such as *o*-ClC_6H_4, *o*-$MeOC_6H_4$ and 2-dibenzofuryl, presumably due to steric interactions, gave moderate yield of 43–59% (Entry 3, 4 and 9). In case of Bn diol **4e**, a lower yield of 50% is attributed to difficulty to prepare BnMgBr, a characteristic problem encountered during synthesis of allyl and benzyl Grignards reagents (Entry 5).[119]

The relative configurations of the major diastereomers were determined based on the absolute configuration of **4e** (*Figure 26*).

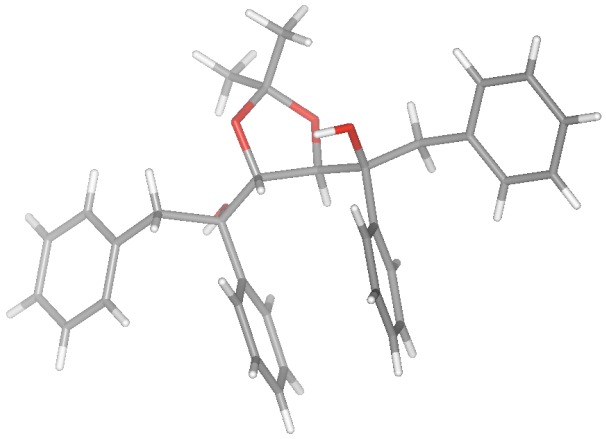
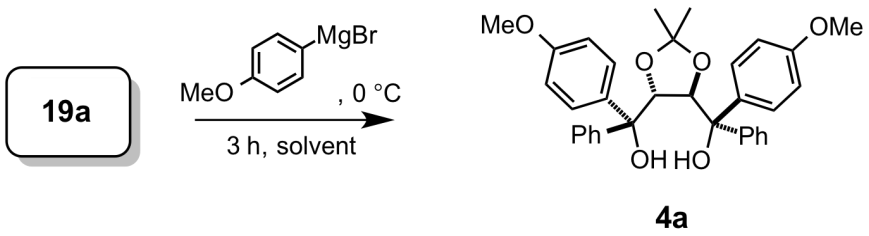


Figure 26. X-ray structure of **4e**

Despite the diastereomeric ratio was relatively high for C_2-symmetrical diols (up to 10:1/C_2:C_1), separation of *A* (C_2) and *B* (C_1) diastereomers for most of the diols proved difficult. For diols **4d** and **4e**, simple chromatographic separation provided pure diastereomers *A*. For the rest of the diols even after crystallization, smaller amounts of *B* (C_1) were present in the crystals. Therefore, experiments to increase *d.r.* of the reaction, if possible exclusively form the desired C_2 diol, were performed with investigations of solvent, temperature and additive chelating agents.

3.1.1.2.1. Solvents effect on the stereoselectivity

Generally, Grignard reagents in THF are known to give high stereoselectivity in reactions with α-hydroxy protected ketones.[120] However, not many variations of ether solvents were explored for the effect on stereoselectivity. Thus, various ether solvents were tested and *p*-$MeOC_6H_4MgBr$ was chosen as a nucleophile (*Scheme 28*).



4a

Scheme 28. Investigations of solvents effect on *d.r.* of the Grignard addition to 1,4-diketone **19a**

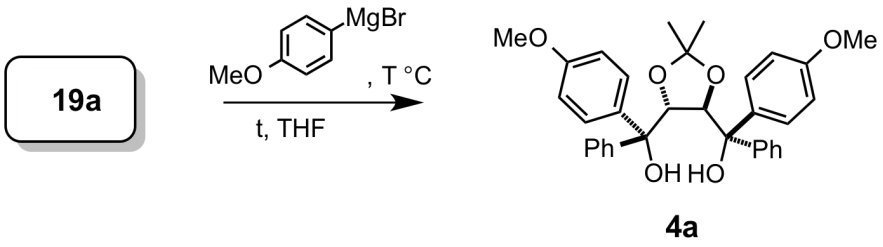
According to experimental results, dimethoxyethane (DME) and 1,4-dioxane were not selective (A:B / 50:50) while THF and Et_2O proved to give highest *d.r.* (79:21 and 75:25, respectively, *Table 2*). Also, in view of better solubility for other Grignard reagents, THF was chosen as a standard solvent for further optimization studies.

Table 2. Solvents effect on the *d.r.*

Solvent	*A (C_2)*	*B (C_1)*
DME	50	50
1,4-dioxane	50	50
Et_2O	75	25
THF	**79**	**21**

3.1.1.2.2. Temperature effect

Investigations of temperature effect on the *d.r.* were carried out at five different temperatures (*Scheme 29*). Surprisingly, formation of C_1-symmetrical diol was favored at low temperatures (*Table 3*).



Scheme 29. Temperature effect on the *d.r.* of Grignard addition reaction to diketone **19a**

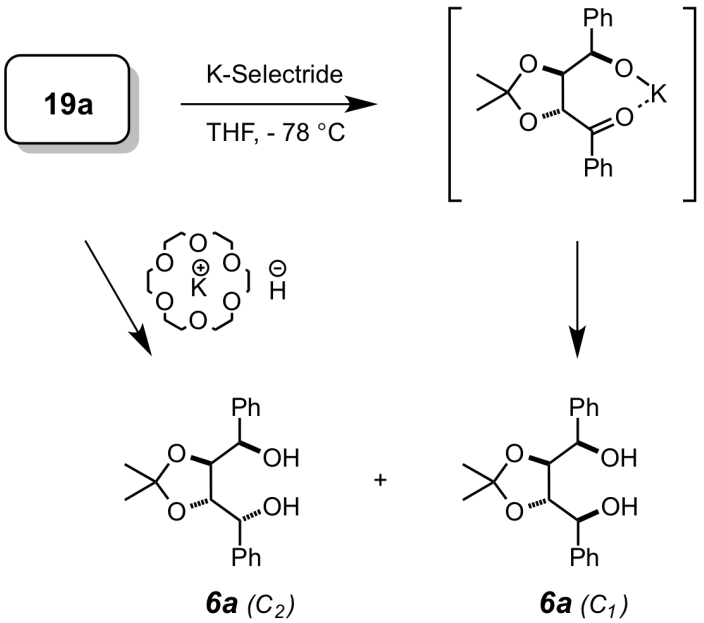
Table 3. Temperature dependence of *d.r.*

Entry	*T, °C*	*t*	*A* (C_2)	*B* (C_1)
1	r.t.	5 h	75	25
2	0	6 h	**79**	**21**
3	-20	6 h	54	46
4	-40	12 h	60	40
5	-70	12 h	14	86

At –70 °C, diol *B* (C_1) formed predominantly (A:B / 86:14, Entry 5) and when the temperature was raised, the *d.r.* shifted in favor of C_2 diastereomer *A* (A:B / 60–54 : 40-46, Entries 3, 4). Finally, the best selectivity for *A* (79:21, Entry 2) was obtained at 0 °C although *d.r.* slightly decreased again when the reaction was conducted at room temperature (75:25, Entry 1).

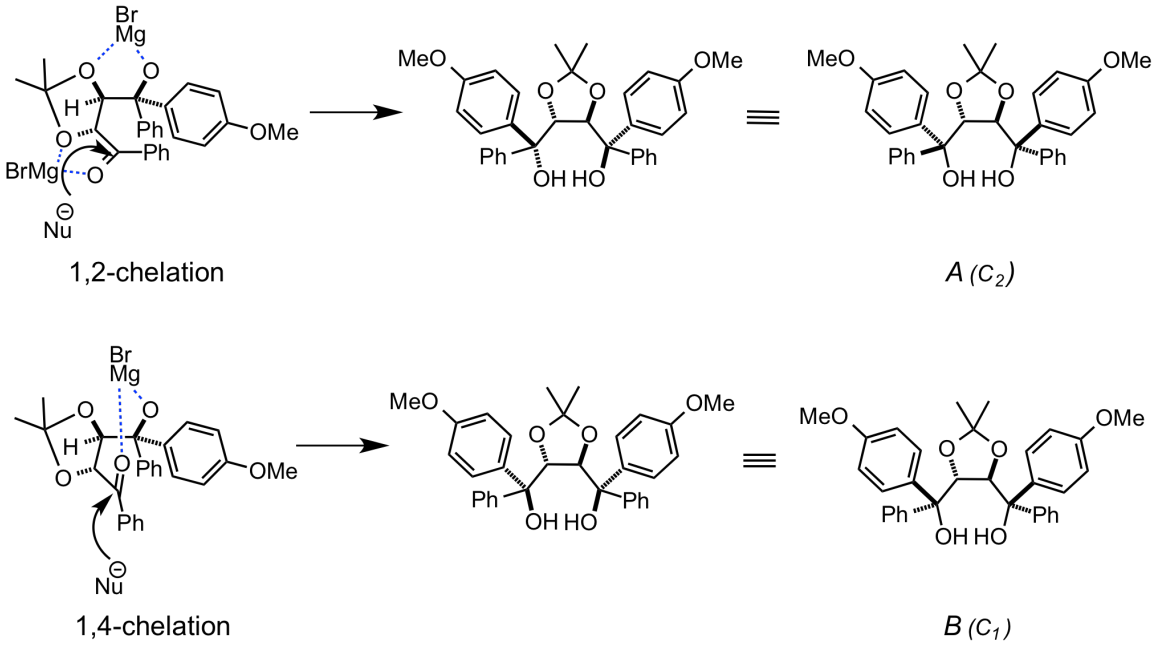
Chandrakumar et al., in their study on stereoselective reduction of 1,4-diketones by K-Selectride in presence of a crown ether 18-C-6, explained the origin of C_1-symmetrical diol **6a** as a result of a 1,4-stereocontrol. They postulated that a potassium alkoxide, formed when one of the keto groups is reduced, chelates to the second keto group. This directs the second nucleophile attack from the same side as the first nucleophile did ending up with the C_1 symmetry (*Scheme 30*).

Likewise, in *p*-$MeOC_6H_4MgBr$ addition to **19a**, magnesium alkoxide, formed after the first equivalent of the nucleophile attack is not only 1,2-chelated to the α alkoxy of the dioxolane ring, but also to the second carbonyl group by 1,4 chelation (*Scheme 31*). Therefore, 1,2-chelation leads to C_2-symmetrical diol *A* while 1,4-chelation favors diol *B* with C_1 symmetry.



without 18-C-6	70	:	30
when 18-C-6 present	91	:	9

Scheme 30. Origin of C_1 symmetry and stereoselective reduction of 1,4-diketones



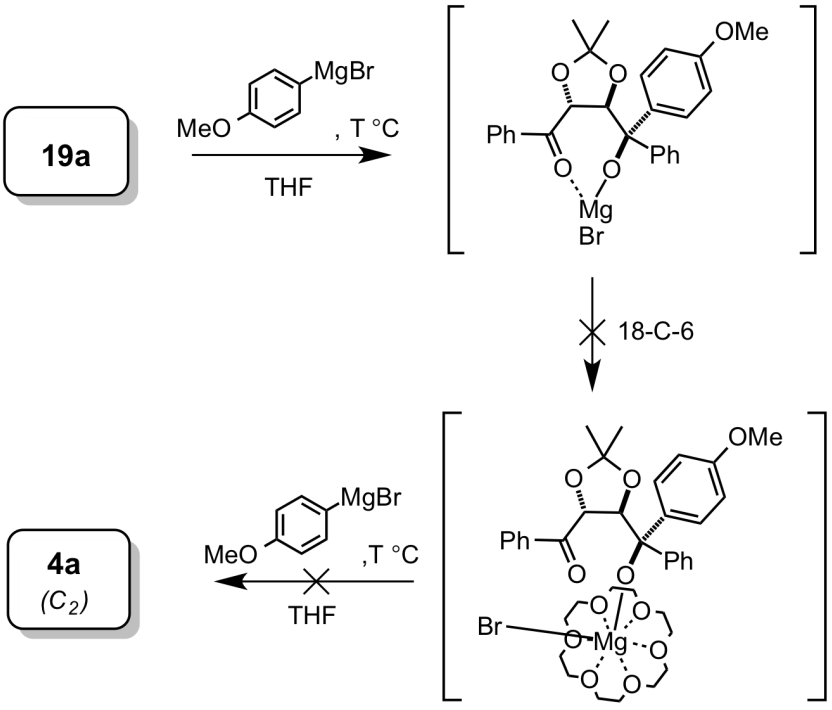
Scheme 31. Origin of preference for C_2- and C_1- symmetrical products in Grignard addition to **19a**

Therefore, it is concluded that 1,4-chelation dominates at lower temperature. The nucleophilic attack is faster in this state as the second keto group is activated through

the 1,4-chelation resulting in more C_1 product (see Section 3.1.1.2.3. for explanation of the activation). On the other hand, at higher tempearure, the nucleophilic attack occurs mostly free from the 1,4-stereocontrol. The reason behind different stability of the two chelations at different temperature is unknown at the time.

3.1.1.2.3 Diastereoselectivity through chelation control

Chandrakumar et al. managed to increase selectivity in reduction of 1,4-diketones by adding 18-C-6, thus hindering the potassium alkoxide from forming the 1,4-chelate (*Scheme 30*). 18-C-6, by capturing potassium ion, enabled the second keto group to be reduced independently of the 1,4-stereo control, thus forming C_2 symmetrical diol preferably. In a similar expectation, effects of added chelating agents were studied to increase the *d.r.* In order to monitor the effects in each step, two different protocols were developed.

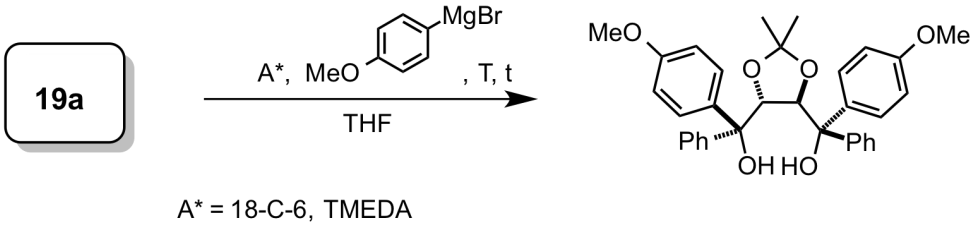


Scheme 32. 2-step protocol involving 18-C-6 to prevent forming 1,4-chelate

First, a 2-step protocol would start with an addition of one equivalent of Grignard reagent to **19a** forming magnesiumalkoxide (*Scheme 32*). At this stage, an addition of

the chelating agent would compete successfully with the keto group for Mg^+ and hinder forming 1,4-chelate. The second equivalent of Grignard reagent would then have been added. However, when the first equivalent of the nucleophile was added, the intermediate monoketone reacted with the second nucleophile before the starting material **19a** was completely consumed. The 1,4-chelation activated the second carbonyl towards the nucleophilic attack and the intermediate monoketone and the starting material compete for the nucleophile attack.

Therefore, an alternative protocol was followed. In this one-step protocol, the chelating agent and the starting material were put together before adding the nucleophile (*Scheme 33*). TMEDA and 18-C-6 were chosen as additives and the reaction was conducted at –78 °C and at room temperature (*Table 4*).



Scheme 33. One-step protocol to increase *d.r.* with the help of added chelating agents

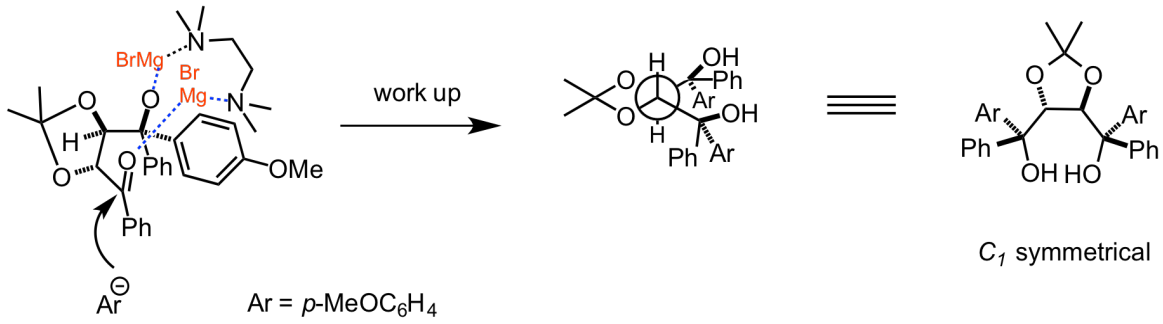
Table 4. Effects of chelating agents on *d.r.* at different temperatures

Entry	*Additive*	*T, °C*	*t*	C_2/C_1
1	-	r.t.	5 h	75/25
2	18-C-6	r.t.	3 h	60/40
3	TMEDA	r.t.	3 h	60/40
4	-	-78	12 h	14/86
5	18-C-6	-78	12 h	14/86
6	TMEDA	-78	4 h	**4/96**

Contrary to the expectation, the chelating agents generally increased the *d.r.* in favor of the C_1 diol. At room temperature, *d.r.* of the reaction with the additives were 60:40 (C_2/C_1, Entry 2, 3) in both cases while *d.r.* without any added chelating agents was 76:24 (Entry 1). Furthermore, at –78 °C, C_1-symmetrical diol formed almost exclusively

when TMEDA was added (C_2/C_1 = 4/96, Entry 6). In case of 18-C-6, the *d.r.* was the same as the *d.r* without any additives (*d.r* = 14/86, Entry 4, 5).

Clearly, both additives exert an effect favoring the 1,4-chelation. In case of 18-C-6, it might not be a suitable size to capture Mg, therefore it does not show pronounced effect. On the other hand, one of the nitrogens of TMEDA is chelated to the alkoxide-Mg and through the second nitrogen TMEDA keeps the second keto group on the same side leaving the nucleophile attack from *Si* face forming C_1 diol (*Scheme 34*).



Scheme 34. C_1 symmetry originated from TMEDA chelation

In other words, TMEDA further stabilizes the 1,4-chelation. At –78 °C, the chelation is the most stable and coupled with the fast nucleophile attack, TMEDA forms almost exclusive C_1 diol.

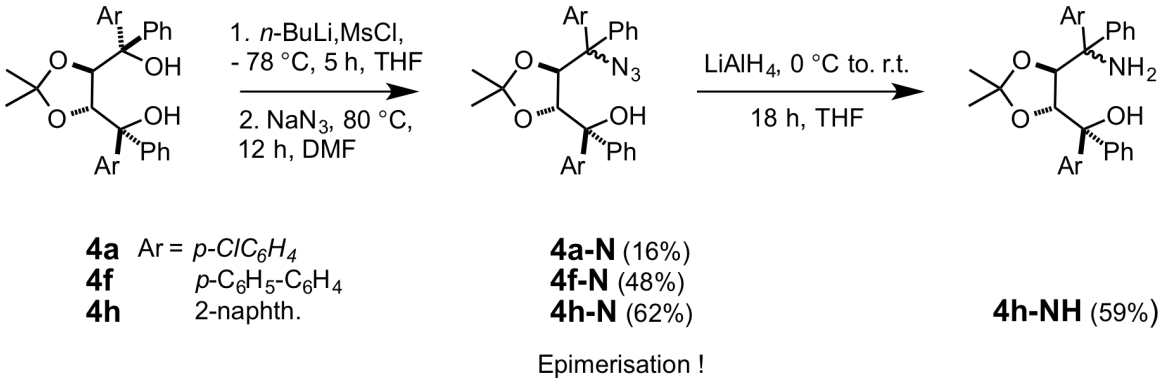
As a result, the optimal condition for the best *d.r.* for the diols **4** with α chiral, pairwise different aryl substituents was found to be in THF at 0 °C in the absence of chelating additives. In this way, 9 diols were synthesized. Diols **4d** and **4e** were isolated as single diastereomers. The other diols were contaminated with small traces of C_1 diastereomers after chromatographic separations and taken for further conversions with an expectation to separate them in the next step.

3.1.1.3. Desymmetrisation of tert. diols with α-chirality

Attempts were made to synthesise aminoalcohols from the diols **4a**-**i** (*Scheme 35*). Monomesylation of **4a, 4f** and **4h** followed by introduction of azide proceeded with low to fair yield (16–62%). However, the carbon center to which azide is introduced were partly epimerized as this is a quarternary center and S_N1 reaction took place.*

* No useful level of stereocontrol from adjacent chiral centers was observed.

Regardless, the product **4h-N** was taken further for reduction to see if separation of epimeric amines was possible (Yield = 59%). Unfortunately, aminoalcohols are extremely polar and gave a broad peak when eluted from chromatographic column making the separation of the diastereomers impossible. Therefore, desymmetrisation was not further carried out.



Scheme 35. Attempts to desymmetrize diols **4**

3.1.2. Synthesis of phosphoramidites based on C_2-symmetrical diols with α-chirality

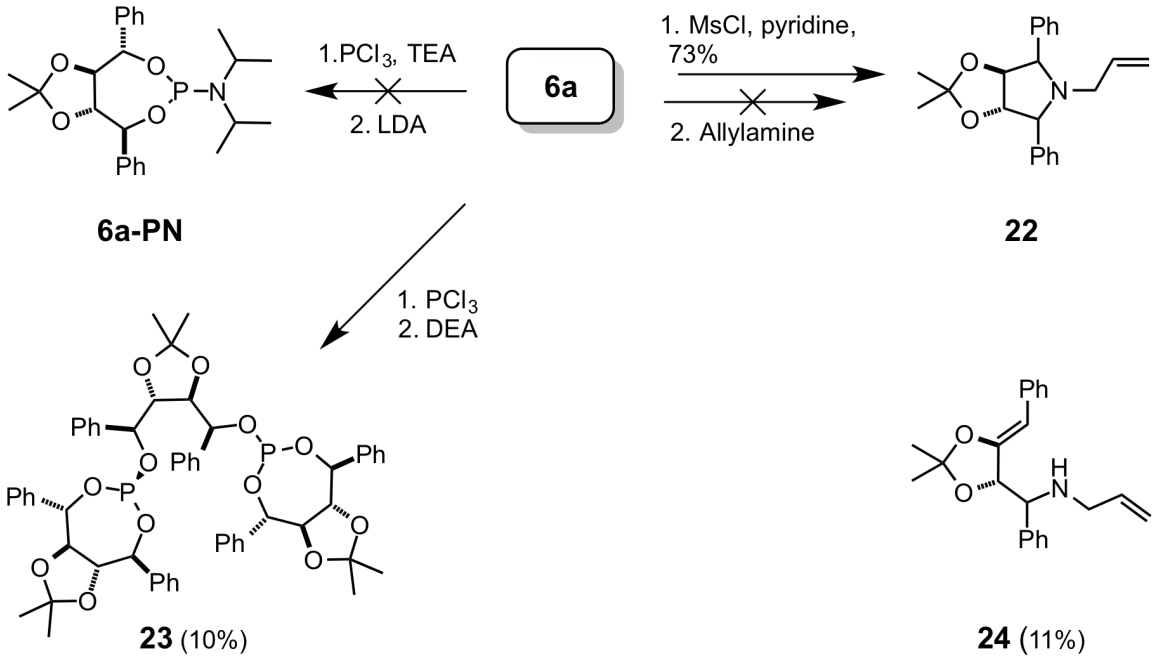
3.1.2.1. Synthesis of phosphoramidites based on sec. diols

With the C_2 symmetrical diols **4** and **6** in hand, the synthesis of their cyclic phosphoramidite derivatives was the next target. Attempts to cyclize *sec*. diols **6** were not successful. Treatment of **6a** with PCl_3 followed by lithiumdiisopropylamine (LDA) resulted in unseparable mixture (*Scheme* 36). In order to monitor the reaction in each step, diethylamine (DEA) was added instead of LDA and disubstituted product **23** was formed in small amount (10%). (The product decomposed after 2 days.) In this case, hydroxy group of the diol was competing with the DEA for substitution reaction with dialkylphosphorchloride intermediate *i.e.* the amine is not reactive enough. When a strong base LDA was used, it probably removed Hs from *sec*. carbons (at either C1/C4

or C2/C3) of the intermediate or the phosphite **23** facilitating elimination and other background reactions.

Not unexpectedly, attempts to cyclize **6a** into pyrrolidine derivative **22** failed due to *trans* geometry of the ketal bridge. Disubstitution worked smoothly giving dimesylated product in 73% yield. However, cyclic product **22** from the dimesylate was not observed. In this case, eliminated product **24** was obtained in 11% yield.

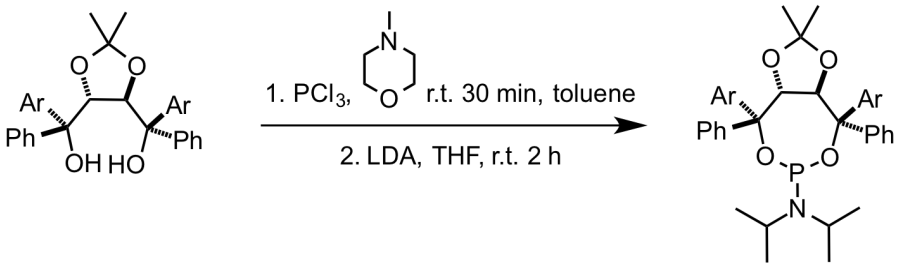
Therefore, it was concluded that *sec*. diols **6a-d** were not suitable to prepare cyclic phosphoramidites and H at *sec*. diol was prone to elimination. As a result, the desired cyclic **6-PNs** were not obtained.



Scheme 36. Attempts to cyclize *sec*. diol **4** into 5 and 7 membered rings

3.1.2.2. Synthesis of phosphoramidites based on tert. diols

In contrast to *sec.* diols **6**, synthesis of cyclic phosphoramidite derivatives of C_2-symmetrical diols **4a**-**i** with pairwise different four aryl groups were successfully carried out. Diols **4a**-**i** were treated with PCl_3 in the presence of *N*-methylmorpholine followed by addition of LDA to yield phosphoramidites **4a-PN**–**4i-PN** (*Scheme 37*) in low to fair yield of 15–58% (*Table 5*).



4 **4-PN**

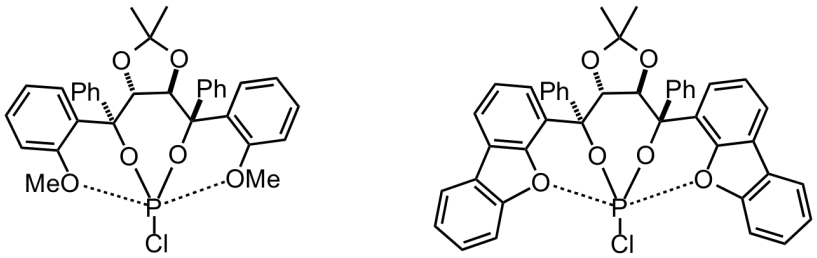
Scheme 37. Synthesis of phosphoramidites derived from C_2-symmetrical diols **4a**-**4i**

Table 5. Phosphamidite products derived from diols **4a-4i** and purity

Entry	*Product #*	*Ar*	*Yield, %*	*Purity, %*
1	**4a-PN**	*p*-ClC_6H_4	49	>99
2	**4b-PN**	*p*-$MeOC_6H_4$	58	90
3	**4c-PN**	*o*-ClC_6H_4	15	>99*
4	**4d-PN**	*o*-$MeOC_6H_4$	-	-
5	**4e-PN'**	Bn	66	>99
6	**4f-PN**	4-C_6H_5-C_6H_4	58	91
7	**4g-PN**	*p*-MeC_6H_4-O-C_6H_4	44	84
8	**4h-PN**	2-naphth.	39	86
9	**4i-PN**	4-dibenzofuryl	-	-

*the product started decomposing after several hours during ^{13}C measurement

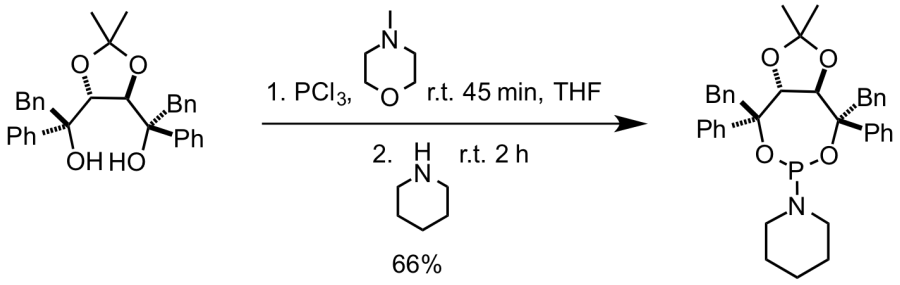
Not surprisingly, diols with *ortho* substituted Ar groups failed to give the expected products (*Table 5*, Entry 4, 9). Especially, *ortho* alkoxy groups due to their close spatial arrangement to the hydroxy groups of the starting material and strong affinity to P atom, supposedly hamper the formation of the cyclic phosphite (*Figure 27*). In these cases, inseparable mixtures were formed.



4d + PCl_3 **4i** + PCl_3

Figure 27. Possible connections between PCl_3 and the diols with *ortho* alkoxy groups

For the same reason, *ortho*-Cl of **4c** might be responsible for poor yield (15%) and poor stability (*Table 5*, Entry 3). The product **4c-PN** started decomposing several hours after chromatography. Benzyl substituted diol **4e** was not soluble in toluene therefore a modified procedure with THF as solvent and piperidine instead of diisopropylamine was followed (*Scheme 38*).



4e **4e-PN'**

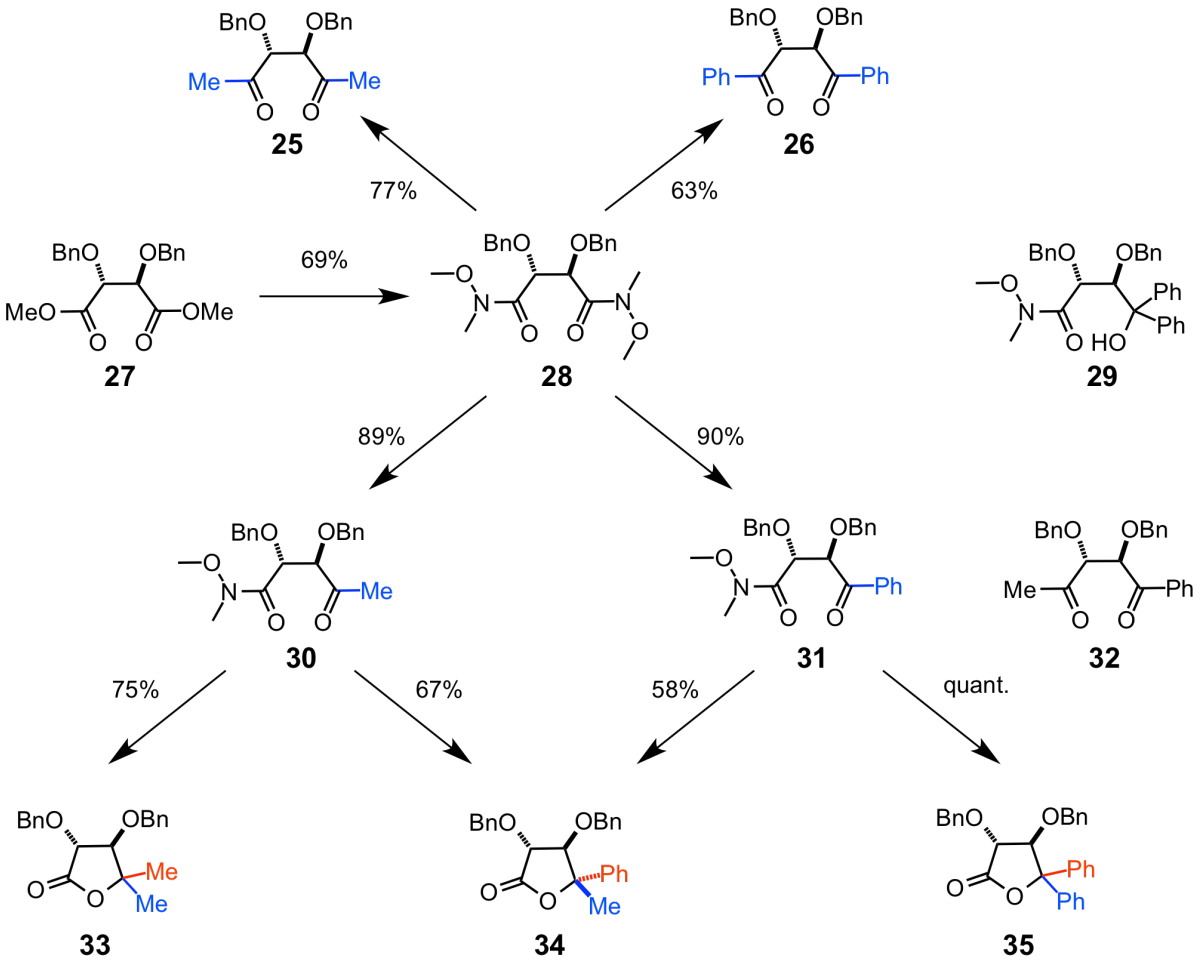
Scheme 38. Piperidine phosphoramidite derivative of **4e**

Although, the diastereomeric mixtures, which were present in the starting materials, were significantly enriched with C_2-symmetrical phosphoramidite products **4PN,** they were not completely separable by means of conventional chromatography (See *Table 1 and Table 5* for comparison).

Finally, 7 cyclic phosphoramidites derived from α-chiral diols **4** were synthesized in moderate yields. **4a-PN**, **4c-PN**, **4e-PN'** were isolated as single diastereomers. The rest of the phosphoramidites were obtained in *d.r.* of 5:1 to 10:1.

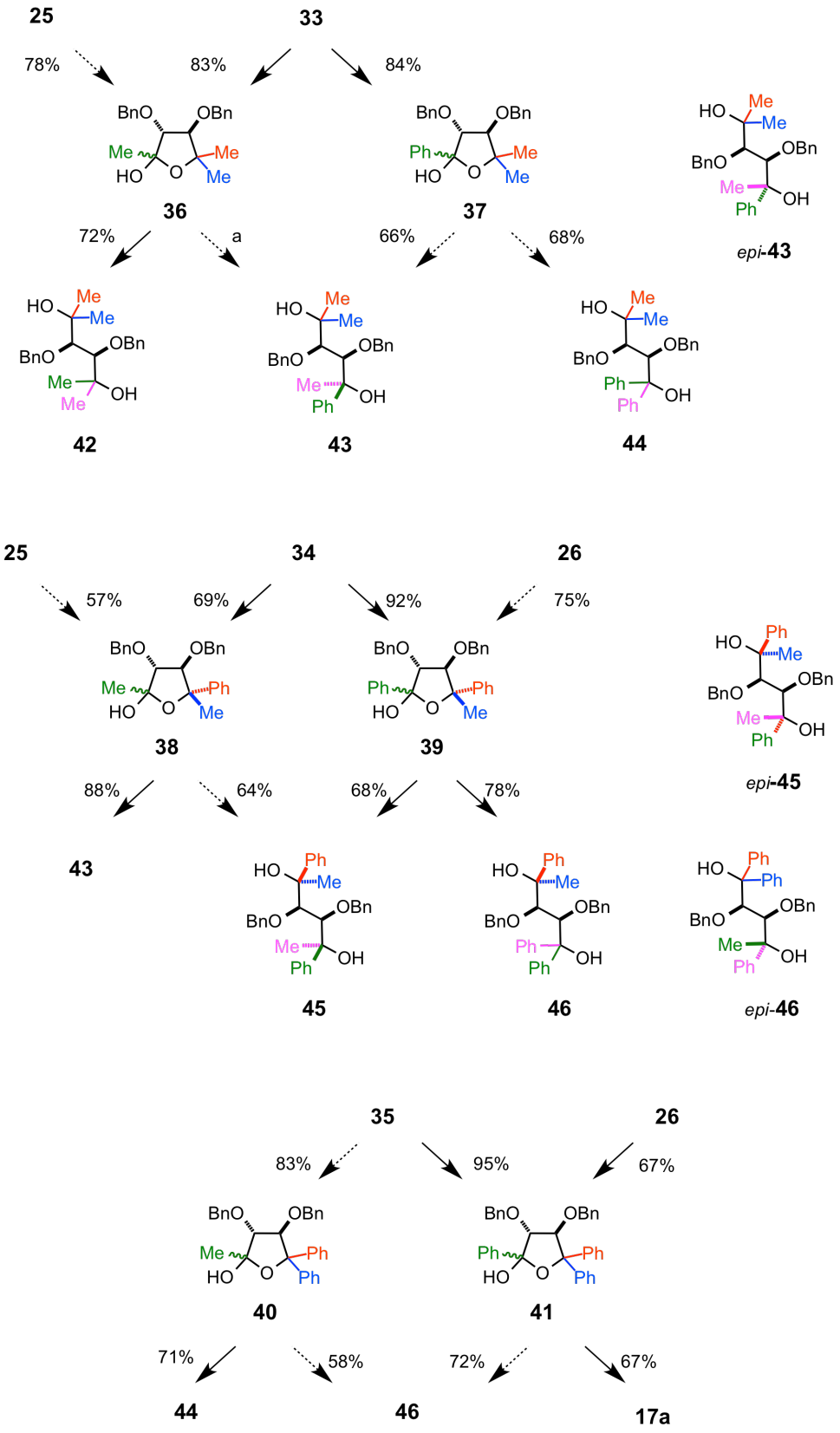
3.1.3. Synthesis of 2,3-bis(benzyloxy) protected diols with α-chirality

The difficulties arised during the separation of the diastereomers of **4** led to a search for alternative starting materials like 2,3-*O,O*-bis(benzyl) protected tartrate **27** (*Scheme 39*).[121]



Scheme 39. Synthesis of diketones **25** and **26** and lactones **33**–**35** from **27** and optimized yields (For conditions see *Table 6*. Plain arrows denote best yields for each compound; dashed arrows denote alternative approaches proceeding with lower yield. The substituents are colorized according to the sequence of introduction; blue (1), red (2).

This substrate is less rigid and is expected to prefer rather an *anti*-conformation of OBn groups thus eventually suppressing the 1,4-chelation of intermediates. It was observed that the *O*-benzyl protected bis-Weinreb amide **28** selectively reacted either at one or both functionalities depending on the use of Mg- or Li-organic reagents and when the temperature and amount of added reagents were carefully adjusted (*Table 6*).[122] Under optimized conditions methyl ketone **30** and phenyl ketone **31** were isolated in 89%



Scheme 40. Synthesis of diols **17a**, **42-46** and optimized yields for the main products. (For conditions see *Table 6*. The substituents are colorized according to the sequence of introduction; blue (1.), red (2.), green (3.), violett (4). In conflicting cases the colorization follows the conversion with highest yield. See also note in *Scheme 39*). [a] No useful conditions could be found.

and 90% yield or symmetrical diketones **25** and **26** in 77% and 63% yield, respectively (Entry 6–9).

The introduction of the second substituent proceeded expectedly through preferred or exclusive attack at the ketone yielding symmetrical products **33** and **35** (Entry 11 and 15) as well as the phenylmethyl substituted product **34**, the latter always as a single diastereomer (3*R*,4*R*,5*S*), irrespectively of the used precursor **30** or **31** (67% and 58% yield) when using PhLi or MeMgBr, respectively (Entry 12 and 14). On the other hand, treatment of ketone **30** with PhMgBr afforded a mixture of **34** and its epimers with 3*R*,4*R*,5*R* configuration in a ratio of 1:2 in low yield. (15%, Entry 13) In all cases the isolated products were lactones generated through intramolecular attack of the intermediate Mg alkoxide.

The relative configuration at the new chiral center was confirmed by X-ray structure analysis of **34** (*Figure 28*). Typically MeLi and PhLi were less selective affording up to 10% of **25** and **32** from **30** (Entry 10 and 12).

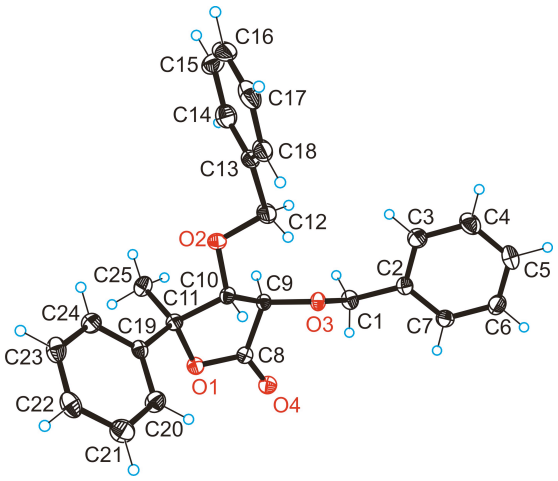


Figure 28. ORTEP view of lactone **34**.

Table 6.
Synthesis of 1,4-diols **42-47** and precursors through reaction with Grignard reagents and lithium organyls.

Entry	*Substr.*	*R-M(X)*	*Equiv.*	*T/°C*	*t/h*	*Prod.*	*Yield/%*	*Prod.*	*Yield/%*
1	**25**	MeMgBr	4	-78	4	**36**	78		
2	**25**	PhLi	4	-78	2	**38**	57		
3	**26**	MeMgBr	4	-78	6	**39**	75		
4	**26**	PhLi	4	-78	6	**41**	23		

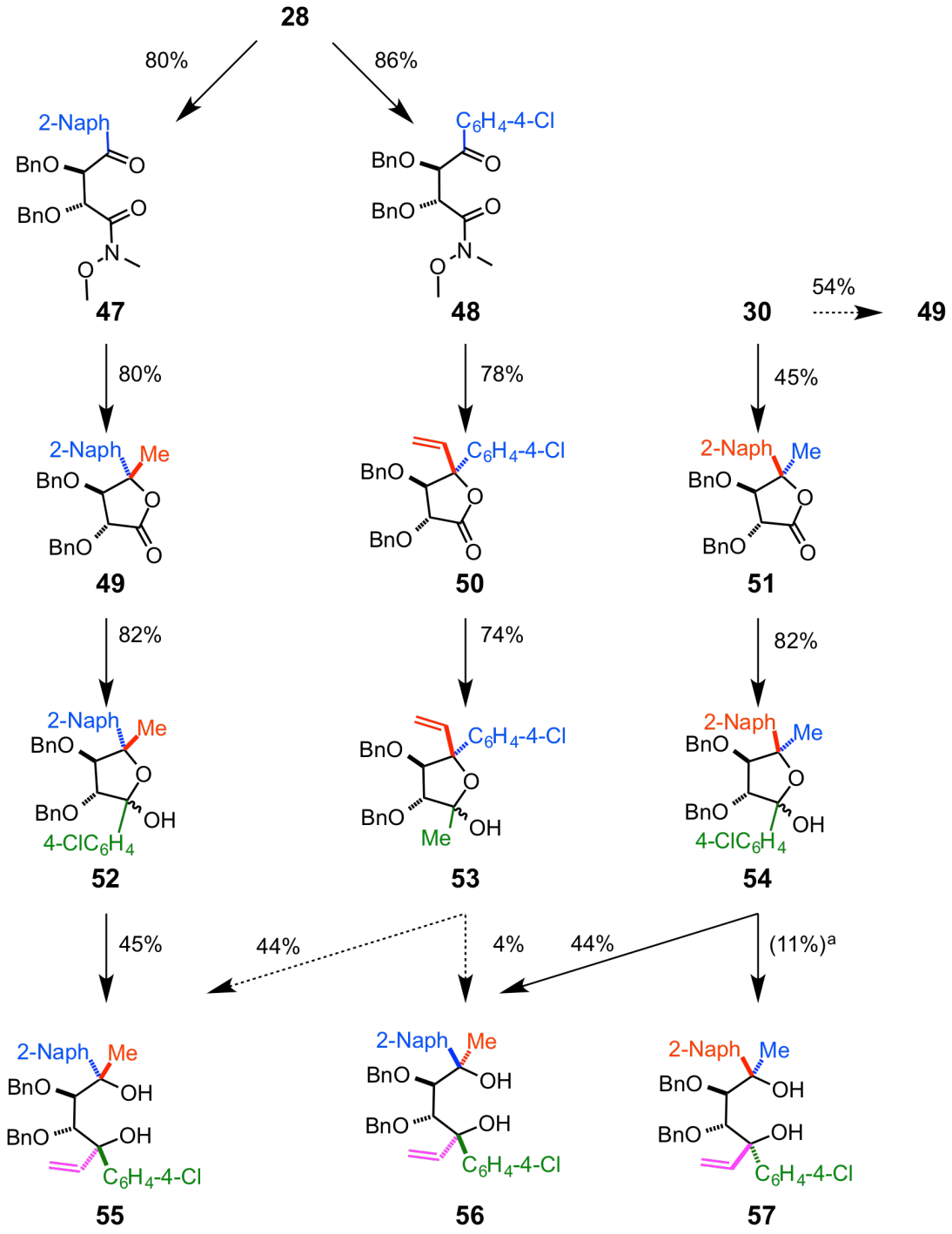
Entry	*Substr.*	*R-M(X)*	*Equiv.*	*T/°C*	*t/h*	*Prod.*	*Yield/%*	*Prod.*	*Yield/%*
5	**26**	PhMgBr	4	-40	1	**41**	67		
6	**28**	MeMgBr	3	0	3	**25**	77		
7	**28**	PhLi	6	-78	3	**26**	63		
8	**28**	MeMgBr	1.6	-40	4	**30**	89		
9	**28**	PhMgBr	3	0	3	**31**	90		
10	**30**	MeLi	2	-78	1	**33**	40	**25**	10
11	**30**	MeMgBr	2	-78	8	**33**	75		
12	**30**	PhLi	3	-78	14	**34**	67	**32**	10
13	**30**	PhMgBr	2	-40	6	**34**	(5)	*epi* **34**[a]	
14	**31**	MeMgBr	1.5	-78	6	**34**	58		
15	**31**	PhLi	2	-78	2	**35**	24	**29**	50
16	**31**	PhMgBr	2	-78	14	**35**	quant.		
17	**33**	MeMgBr	2	-40	3	**36**	83		
18	**33**	PhLi	1	-78	5	**37**	50		
19	**33**	PhMgBr	2	-40	2.5	**37**	84		
20	**34**	MeLi	1.5	-78	1.5	**38**	45		
21	**34**	MeMgBr	3.5	-40	6.5	**38**	69		
22	**34**	PhLi	1.5	-78	1.5	**39**	42		
23	**34**	PhMgBr	3	-40	6.5	**39**	92		
24	**35**	MeMgBr	3	-40	24	**40**	83		
25	**35**	PhMgBr	2	-40	6	**41**	95		
26	**36**	MeMgBr	5	0-r.t.	2	**42**	72		
27	**36**	PhLi	6	0	5	**43**	[b]	*epi* **43**	[b]
28	**36**	PhMgBr	6	r.t.	24	**43**	(50)[c]		
29	**37**	MeMgBr	4	0-r.t.	24	**43**	66	*epi* **43**	0
30	**37**	PhLi	6	0	5	**44**	68		
31	**38**	MeMgBr	4	0-r.t.	5	**43**	88		
32	**38**	PhLi	4	0	4.5	**45**	64	*epi* **28**	6
33	**38**	PhMgBr	6	r.t.	24	**45**	(50)[b]		
34	**39**	MeMgBr	4	20	24	**45**	68	*epi* **28**	11
35	**39**	PhLi	3	0	3	**46**	78		
36	**39**	PhMgBr	2	r.t.	6	**--**	[d]		

Entry	*Substr.*	*R-M(X)*	*Equiv.*	*T/°C*	*t/h*	*Prod.*	*Yield/%*	*Prod.*	*Yield/%*
37	**40**	MeMgBr	6	20	4.5	**44**	71		
38	**40**	PhLi	6	0	5	**46**	58	*epi* **46**	12
39	**41**	MeMgBr	6	20	4.5	**46**	72	*epi* **29**	13
40	**41**	PhLi	6	0	5	**17a**	67		

[a] *epi*- **34** has (2*R*,3*R*,4*R*)configuration. [b] Reaction not complete, complex mixture. [c] Conversion % (NMR). [d] Inseparable mixture.

The introduction of the third substituent was best performed with Grignard reagents and afforded six hemiketals (**36–41,** 69–95 %) as mixtures of epimers. (Entry 17–25, *Scheme 40*). While their original ratio after work-up varied from entry to entry, the subsequent chromatography (partly) shifted the ratio towards the thermodynamic equilibrium ranging from 50:50 to >95:<5. It is worth to note that the reaction stopped at this substitution stage when performed with excess of Grignard reagents at –40 °C and even with diketones **25** and **26** (Entry 1–5). Stereoselective introduction of the fourth substituent seemed most critical due to the kinetic lability of the hemiketal (Entry 26–40). The outcome is determined by the relative accessibility of *Re*- and *Si*-face of the carbonyl, a preferred conformation of which is influenced by 1,2- (with adjacent *O*-Bn group) or 1,4-chelation (to the alkoxy group) as well as substituents of the carbonyl.

This approach to 1,1,4,4-tetrasubstituted tartaric acid derivates with complete regiocontrol and predictable stereochemistry was next applied in the synthesis of diols **56** and **57** bearing four different substituents (*Scheme 41*). Two sequences were investigated; **28**→**48**→**50**→**53**→**55** and **28**→**47**→**49**→**52**→**55** affording total yields of the final product **55** in 22% and 24%, respectively (*Table 7*). While the first three steps in both sequences performed satisfactorily (74–86% for each step, Entry 1, 5, 7 and 2, 6, 8), the introduction of the last substituent proved to be tricky. The reaction of **53** with 2-naphthyllithium gave a 11:1 mixture of **55** and **56** (Entry 11). In contrast, the vinylation of **52** proceeded slowly (2 d, r.t.) but produced a single diastereomer **55** albeit in moderate yield (45%, Entry 10). During optimization experiments **49** was also obtained upon treatment of **30** with 2-naphthyllithium (-78 °C, 54%, Entry 3). If **30** was arylated with 2-naphthylmagnesium bromide epimer **51** was formed exclusively (45%, Entry 4) which in turn gave hemiketal **54** (82%, Entry 9). Unfortunately, the subsequent vinylation afforded an inseparable mixture of **56** and **57** (Entry 12).



Scheme 41. Synthesis of diastereomeric diols **55–57** with four different substituents

Finally, the OBn protecting groups of **17a**, **42–46** and **55** were easily removed by hydrogenation (Pd/H_2, 1 bar) affording almost quantitative yields of tetrahydroxy compounds **17a-OH**, **42-OH**–**46-OH** (structures not shown). Not unexpectedly, in the case of **55-OH** also the vinyl substituent was hydrogenated. No epimerisation was observed.

Table 7. Synthesis of 1,4-diols **47**–**57** and precursors through reaction with Grignard reagents and lithium organyls.

Entry	*Subst.*	*R-M(X)*	*Equiv.*	*T/°C*	*t/h*	*Prod*	*Yield /%*	*Prod*	*Yield ,%*
1	**28**	2-Naphth.MgBr	3	0	2	**47**	80		
2	**28**	*p*-Cl-C_6H_4-MgBr	3	0	1.5	**48**	86		
3	**30**	2-Naphth.Li	2	-78	1.5	**49**	54		
4	**30**	2-Naphth.MgBr	3	-40	14	**51**	45		
5	**47**	MeMgBr	1.5	-78	14	**49**	80		
6	**48**	VinylMgBr	1.4	-78	2	**50**	78		
7	**49**	*p*-Cl-C_6H_4-MgBr	3	-40	4	**52**	82		
8	**50**	MeMgBr	2	-40	6	**53**	74		
9	**51**	*p*-Cl-C_6H_4-MgBr	2	-40	5	**54**	82		
10	**52**	VinylMgBr	8	r.t.	24	**55**	45		
11	**53**	2-NaphthylLi	4	-40	48	**55**	44	**56**	5
12	**54**	VinylMgBr	4	r.t.	14	**56**	(44)[a]	**57**	(11)[a]

[a] *NMR yield, inseparable mixture.*

Based on these results a promising route for the independent introduction of up to four substituents into **27** was established. From **27** Weinreb-amide **28**, a valuable key intermediate can be prepared on multigram scale and stored for several months without decomposition. The first substitution yielding a keto-amide proceeds smoothly at low temperature (–40 to 0 °C) using Grignard reagents. The second substituent adds predominantly or even exclusively to the keto functionality. This step is best performed at –78 °C to give a single diastereomer with *anti* stereochemistry of the larger (aryl) substituent and the adjacent OBn group at C4 and regardless of whether Ar-Li or alkyl-MgBr is used. Alkyl-Li and Ar-Li show some side reactions affording also diketones. At this stage the outcome using aromatic Grignard reagents is less predictable yielding to some extent, or with bulky Ar even exclusively, the stereoisomer with opposite chirality. Typically the isolated intermediates are lactones originating from intramolecular attack of X-Mg-O-R at the C=O of the Weinreb amide at C1.

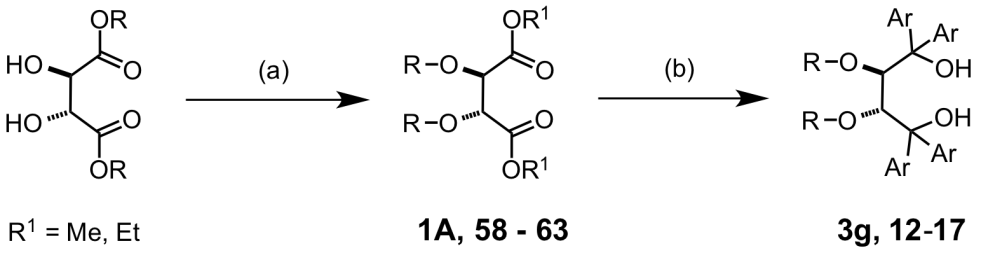
In cases of steric hindrance (two aryl groups at C4) this conversion can be promoted through stirring the amido carbinol in slightly acidic or alkaline medium (dioxane/HCl or $NaHCO_3$). The third step always produces hemiketals usually isolated as anomeric mixtures. To stop the reaction at this stage Grignard reagents are preferred and the

temperature had to be kept below –40 °C. Reaction times of 2–24 h and isolated yields of 70–95% are typical. Lithio compounds gave generally lower yields and unidentified side products have been observed. The introduction of the last substituent at C4 proceeds either with excess of Grignard reagents at room temperature or with Ar-Li at 0 °C. Also in these cases the stereoselectivity was found to be high (86–100%) in favor of *anti* stereochemistry at C4, provided the larger substituent was introduced in the final step. The moderate reactivity of hemiketals require higher temperature which causes partial decomposition of Ar-Li. Aromatic Grignard reagents proved to be largely inactive. For the synthesis of C_2-symmetrical diols such as **17a** symmetrical diketones like **25** and **26** are preferred starting materials.

Summarizing, a modular approach to various potential chiral auxiliaries with up to four contiguous steric centers is presented. The approach allows stepwise introductions of four substituents that proceed with a high degree of stereocontrol from OBn-protected tartaric acid.[123] This concept will also offer a convenient access to higher carbon sugars through manipulation of vinyl substituents, as was introduced in **50**, and final removal of OBn groups under mild conditions.

3.1.4. Synthesis of diols with various protecting groups

After successfully introducing α-chirality closer to the active site, the focus was shifted to adjustment of protecting groups of the diols. For this purpose, diols with varied ketal sizes or non-cyclic protecting groups with identical four aryl substituents were synthesized.



Scheme 42. Synthesis of diols **3g**, **12**-**17** with various protecting groups

(a) $Me_2C(OMe)_2$ (for **1A**, 95%),[67a] $Ph_2C(OMe)_2$[124] (for **58,** 82%), 9,9-dimethoxy-9-H-fluorene (for **59,** 82%),[147] C_6H_5CHO (for **60,** 70%),[125] *o*-BrC_6H_4CHO (for **61**, R = Me, 64%), $MeCOCOMe/CH(OMe)_3$ (for **62,** 82%),[126] NaH, BnBr, DMF (for **63,** 93%).[127] (b) Ar-MgBr, THF reflux, 1 h (8 h for **13f**).

Synthesis of 1,4-dihydroxy auxiliaries followed reported procedures (*Scheme 42*); dimethyl/ethyl tartrate was ketalyzed with corresponding dimethylketal (**1A**,[67] **58**,[124] **59**[147]), aldehyde (**60**,[125] **61**), diketone (**62**),[126] or *O*-benzylated with benzyl bromide (**63**),[127] followed by reaction of the diester **1B**, **58**–**63** with excess ArMgBr refluxing in THF for 1 h giving the diol **3g**, **12**–**17**. *Figure 29* and *Figure 30* illustrate the synthesized diesters and the corresponding diols. Synthesis of diols **3g, 12, 13, 14a** and **16** proceeded with good overall yield of 61–94% (*Table* 8, Entry 2, 3–12, 15, 17, 18). Diols **13f** and **13g** with bulky subtituents (Ar = 1-naphthyl, dibenzofuryl) afforded the products in fair yield (50% and 49% respectively, Entry 13, 14). The moderate yield of **15a** is probably due to *ortho* bromide interference with Grignard attack and its contribution to undesired side products (50%, Entry 16). 2,3-*O,O*-Bis(benzyloxy) diols **17** were obtained in moderate to good yields (33–73%, Entry 19–23). This is due the fact that with *O*-benzyl protecting groups, molecule is less rigid compared to other ketal protected tartrates leading keto groups situated as far from each other as possible eventually leading to less pronounced chelate control. Compared to chelated carbonyl group, which is more activated towards nucleophile, the non-chelated carbonyl group is sluggish to nucleophilic attack. If more rigorous reaction conditions with high temperature and longer reaction times were applied, alkoxy group was occasionally eliminated leaving the alkene product.

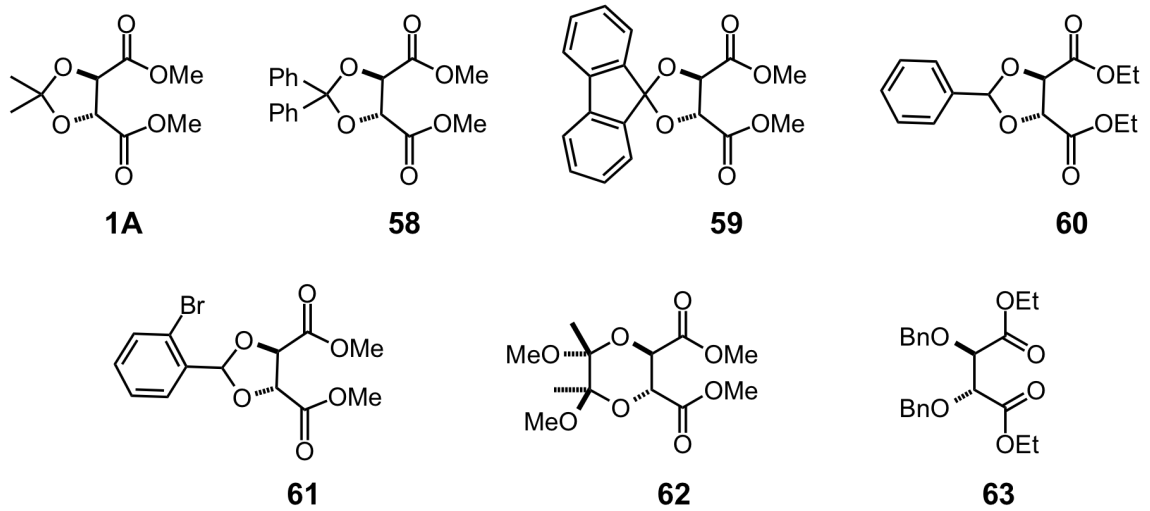
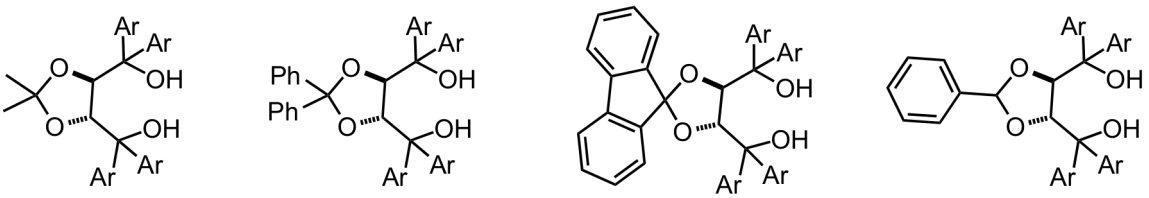


Figure 29. Ester intermediates from *L*-(+)-dimethyl/ethyl tartrate



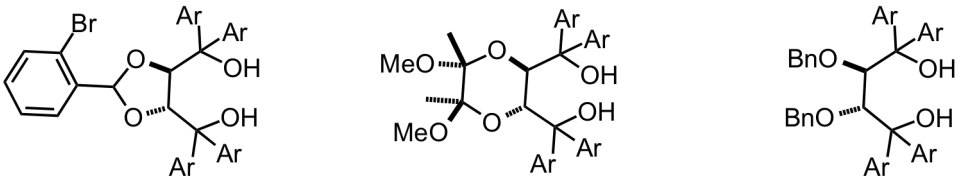
3g **12** **13** **14a**

Ar = dibenzoduran-4-yl

Ar = C_6H_5 **12a**
p-ClC_6H_4 **12b**
p-FC_6H_4 **12c**
p-$CF_3C_6H_4$ **12d**
2-naphth. **12e**

Ar = C_6H_5 **13a**
p-ClC_6H_4 **13b**
p-FC_6H_4 **13c**
p-$CF_3C_6H_4$ **13d**
2-naphth. **13e**
1-naphth. **13f**
dibenzofuran-4-yl **13g**

Ar = C_6H_5 **14a**



15a **16** **17**

Ar = C_6H_5 **15a**

Ar = C_6H_5 **16a**
2-naphth. **16e**

Ar = C_6H_5 **17a**
p-ClC_6H_4 **17b**
p-FC_6H_4 **17c**
p-$CF_3C_6H_4$ **17d**
2-naphth. **17e**

Figure 30. Di-t*ert*. tetraaryl diols **3g**, **12**–**17**

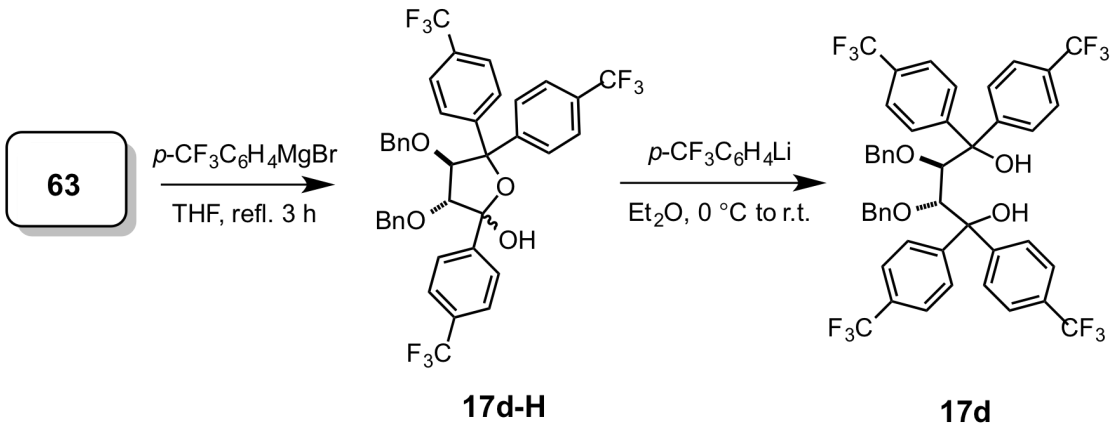
Table 8. Isolated yields of diols **3g**, **12-17**

Entry	*Product #*	*Ar*	*Yield, %*
1	**2**	Ph	76
2	**3g**	dibenzofuryl	71
3	**12a**	Ph	75
4	**12b**	*p*-ClC_6H_4	65
5	**12c**	*p*-FC_6H_4	65
6	**12d**	*p*-$CF_3C_6H_4$	61
7	**12e**	2-naphth.	74
8	**13a**	Ph	81
9	**13b**	*p*-ClC_6H_4	84

Entry	*Product #*	*Ar*	*Yield, %*
10	**13c**	*p*-FC_6H_4	69
11	**13d**	*p*-$CF_3C_6H_4$	83
12	**13e**	2-naphth.	96
13	**13f**	1-naphth.	50
14	**13g**	dibenzofuryl	49
15	**14a**	Ph	82
16	**15a**	Ph	50
17	**16a**	Ph	73
18	**16e**	2-naphth.	60
19	**17a**	Ph	67
20	**17b**	*p*-ClC_6H_4	52
21	**17c**	*p*-FC_6H_4	73
22	**17d**	*p*-$CF_3C_6H_4$	40*
23	**17e**	2-naphth.	59

* after 2 steps

Treatment of **63** with *p*-$CF_3C_6H_4MgBr$ resulted in a mixture of **17d** and a hemiketal **17d-H** (5:1, 79%), the ratio of which remained the same after 8 h of refluxing (*Scheme 43*). The mixture was separated and again treated with *p*-$CF_3C_6H_4Li$ in ether affording **17d** with 50% yield. One-pot treatment of **63** with the organolithium resulted in unseparable mixture.



17d-H **17d**

Scheme 43. Synthesis of **17d** through hemiketal intermediate **17d-H**

Tetraphenyl substituted diols with various protecting groups were first tested in cyanosilylation reactions (Results will be discussed in Section 3.2. Catalytic reactions). Since results were disappointing, further synthesis of the diols **14**, **15** and **16** with various substituents were not performed. However, results of the Mannich type reactions showed that diols with bulky substituents might give better results (See Section 3.2.1.1). To this end, diols **3g** and **13g** were additionally synthesized. Furthermore, based on results of oxo-Diels-Alder and aza-Diels-Alder reactions, **16e** was made.

Introduction of more desired 1-naphthyl substituents proved difficult and only **13f** was obtained of which X-ray crystallographic structure was determined (*Figure 31*). The synthesis of diols **12f**, **16f** and **17f** (Ar = 1-naphthyl) were not successful. Compound **17f,** synthesized via a hemiketal path (analogue to *Scheme 44*), was obtained as an inseparable mixture with the cleaved compound. Careful investigation of optimal reaction conditions might reveal a successful isolation of **17f**. However, time limit for this thesis did not allow further study of the optimal conditions.

All in all, 23 1,4-diols with various protecting groups and four aryl substituents were synthesized in moderate to high yields.

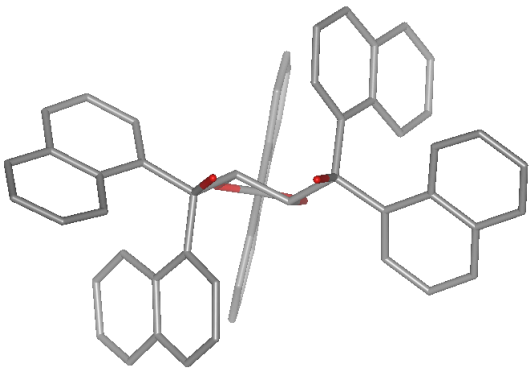


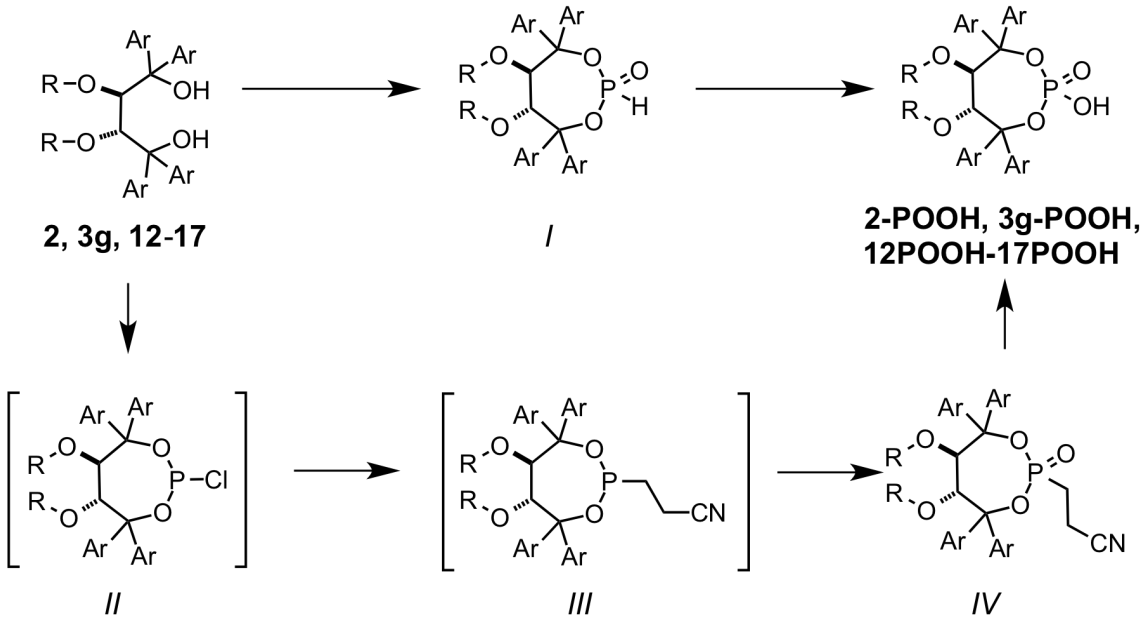
Figure 31. X-ray structure of diol **13f**

3.1.5. Synthesis of cyclic dialkyl phosphoric acids

3.1.5.1. Phosphoric acids synthesis of tetraaryl 1,4- diols

Next, syntheses of cyclic phosphoric acids from the above diols were performed. Several protocols can be found in the literature. While for binaphthol derivatives,

cyclization with $POCl_3$ in the presence of base and subsequent hydrolysis worked well, the analog reaction with TADDOL (**2**) was less satisfying, moreover, the intermediate acid chloride was hydrolyzed only under harsh conditions.[128] More general protocols in either four or two steps involve cyclisation with PCl_3 (*II*), reaction with 3-hydroxypropionitrile (*III*), hydrogen peroxide oxidation (*IV*) and finally cleavage with DBU[129], or a short cut, oxidizing the phosphite (*I*) with I_2/H_2O in pyridine (*Scheme 44*).[130]

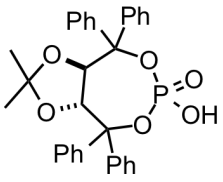


Scheme 44. Synthesis of cyclic phosphoric acids

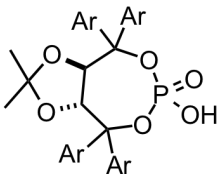
The last step of the synthesis, cleavage of propionitile protection or oxidation of phosphite generally proceeded with high yield of 78–100% yield. *Figure 32* illustrates the synthesized phosphoric acids and *Table 9* shows the preferred paths along with alternative paths.

In the majority of cases, the synthesis followed the procedure involving the propioxynitrile protected phosphate intermediate as the product was isolated through a simple chromatography and further cleavage with DBU afforded the desired phosphoric acid in pure form in all cases. In few cases, especially the diols with stronger electron withdrawing substituents such as **12d** as well as dioxane protected diols **16** were prone to cleavage and formed phosphite even though the 4-step procedure was followed under strict inert atmosphere (Entry 7, 16, 17). In these cases, the shorter synthesis involving phosphite oxidation with I_2 was followed. However, during the oxidation step, a side product, phosphoric acid anhydride was formed in minute amount that was difficult to

remove. *O*-Benzyl protected diols **17b** and **17c** with electron withdrawing substituents afforded low yield to both the phosphite and propionitrile intermediates.

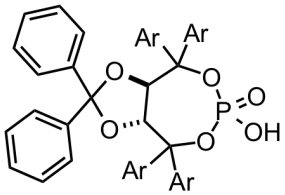


2-POOH



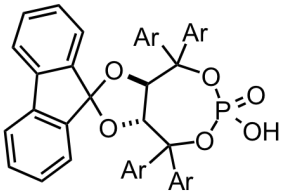
3g-POOH

Ar = dibenzofuryl



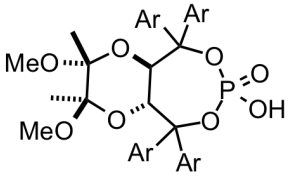
12-POOH

Ar = Ph **12a-POOH**
p-ClC_6H_4 **12b-POOH**
p-FC_6H_4 **12c-POOH**
p-$CF_3C_6H_4$ **12d-POOH**
2-naphth. **12e-POOH**



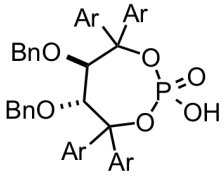
13-POOH

Ar = Ph **13a-POOH**
p-ClC_6H_4 **13b-POOH**
p-FC_6H_4 **13c-POOH**
p-$CF_3C_6H_4$ **13d-POOH**
2-naphth. **13e-POOH**
1-naphth. **13f-POOH**
dibenzofuryl **13g-POOH**



16-POOH

Ar = Ph **16a-POOH**
2-naphth. **16e-POOH**



17-POOH

Ar = Ph **17a-POOH**
2-naphth. **17e-POOH**

Figure 32. Synthesized phosphoric acids based on tetraaryl diols with various protecting groups

Table 9. Synthesized cyclic phosphates and intermediates

Entry	*Diol*	*Ar*	*II (P-Cl) %*	*I (POH) %*	*IV (POR[1]) %*	*POOH, %*
1	**2**	Ph			59	89
2	**3g**	dibenzoduryl		30		88
3	**4a**	*p*-ClC_6H_4			59	[a]
4	**12a**	Ph		36	60	100
5	**12b**	*p*-ClC_6H_4			66	100
6	**12c**	*p*-FC_6H_4			54	90

Entry	*Diol*	*Ar*	*II (P-Cl) %*	*I (POH) %*	*IV (POR^1) %*	*POOH, %*
7	**12d**	*p*-$CF_3C_6H_4$		28		96
8	**12e**	2-naphth			58	82
9	**13a**	Ph	28	33	60	100
10	**13b**	*p*-ClC_6H_4			39	78
11	**13c**	*p*-FC_6H_4			46	100
12	**13d**	*p*-$CF_3C_6H_4$			36	98
13	**13e**	2-naphth			68	90
14	**13f**	1-naphth			50	91
15	**13g**	dibenzofuryl		49		99
16	**16a**	Ph		63	21	95
17	**16e**	2-naphth		52		90
18	**17a**	Ph		48	30	80
19	**17b**	*p*-ClC_6H_4		13	17	[a]
20	**17c**	*p*-FC_6H_4		13	7	[a]
21	**17e**	*2-naphth*		9	60	100
22	**45**	Me			71	99

Yields written in **red** are of the main intermediates through which the cyclic phosphoric acids were synthesized. **Blue** - side products from the preffered path. **Green** - alternative way to synthesize the intermediate but was not followed due to low yield compared to the preffered method. **Purple** - side product during the alternative synthesis. **Black** refers to the synthesis of the last step (from **red** to **black**). R^1 = propionitrile, [a]: not performed

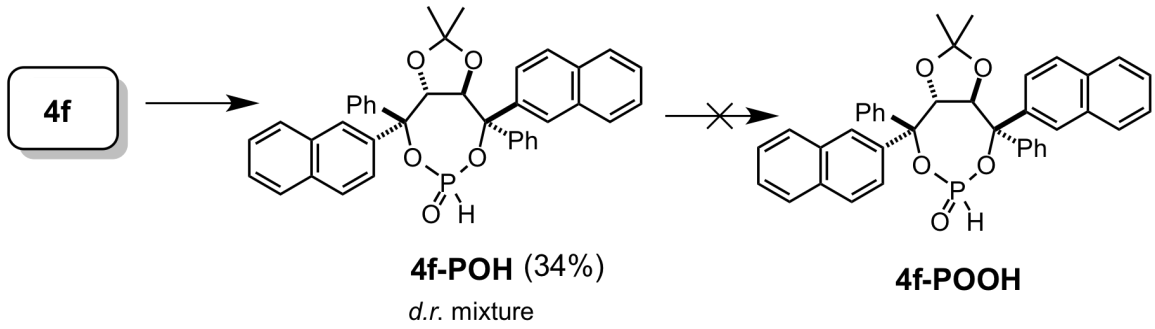
Therefore, the final steps to **17d-POOH** and **17c-POOH** were not performed (Entry 19, 20). In contrast, diols with electron donating substituents gave acceptable yield of 47–70% after 2 steps. The *C_1*-symmetrical diols **14a** and **15a** were not converted to cyclic phosphoric acids since diastereomeric mixture would result.

Alltogether, 22 phosphoric acids based on tetraaryldiols with various protecting groups were synthesized.

3.1.5.2. Phosphoric acids syntheses of C_2-symmetrical diols with α-chirality

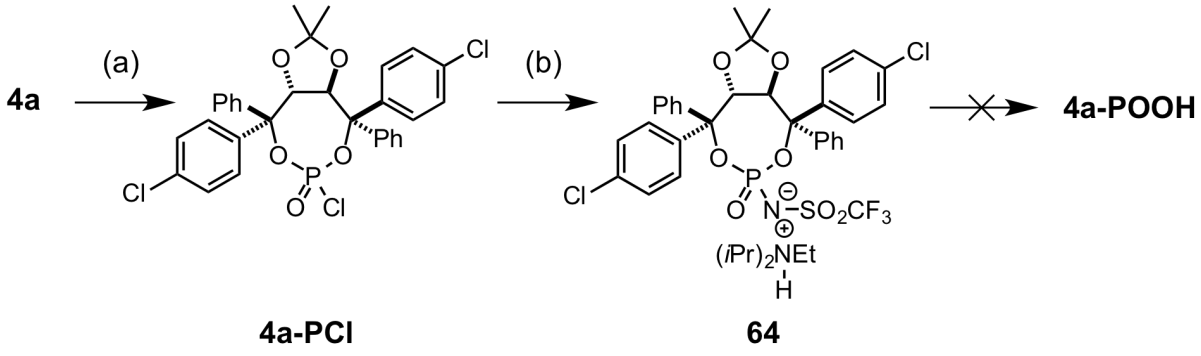
In addition to phosphoric acids based on diols with four identical aryl groups and varied protecting groups, syntheses of the acids derived from diols **4** and **45** with pairwise different four aryl groups (α chiral) were performed.

First, the shorter path, which involves forming phosphite and subsequent oxidation with I_2, was attempted and phosphite **4f-POH** was obtained in 34% yield. However, diastereomeric mixture of substrate **4f** was also not separable on the stage of phosphite **4f-POH** (*Scheme 45*). Therefore, the final step to **4f-POOH** was not carried out since isolation of the product would involve only acidic work up hence require the substrate, free of any impurities.



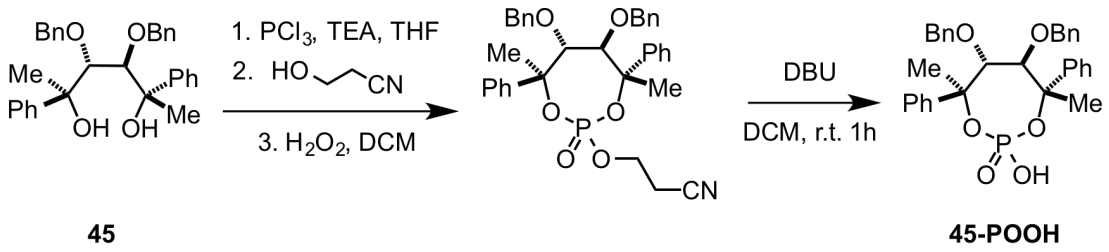
Scheme 45. Experiment to synthesize **4f-POOH**

On the other hand, preliminary results showed that when **4a** was treated with *n*-BuLi followed by $POCl_3$ corresponding dialkoxyphosphoroxychloride **4a-PCl** was formed in 31% as a single isomer (*Scheme 46*). According to Seebach et al. the similar acid chloride was extremely hard to hydrolize (24 h reflux with THF/H_2O).[67d] Therefore, it was treated with trifluoromethylsulfonamide in presence of Hünig's base to afford its ammonium salt **64** in 55% yield. Nevertheless, the salt was also very inert and failed to give the corresponding free acid after washed with 6N HCl. Consequently, further synthesis of **4-POOH** was not done.



Scheme 46. (a) *n*-BuLi, $POCl_3$[67d], 31%. (b) $CF_3SO_2NH_2$, $(iPr)_2NEt$[67e], 55%.

Meanwhile, *O*-benzylated diol **45** successfully afforded cyclic phosphoric acid **45-POOH** in 70 % overall yield through the 4-step protocol (*Scheme 47*, Table 9, Entry 22).



45 **45-POOH**

Scheme 47. Synthesis of **45-POOH** through 4-step protocol

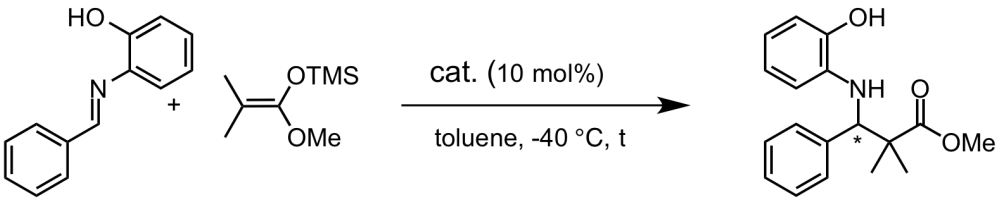
In conclusion, 22 different phosphoric acids derived from 1,1,4,4-tetraaryl diols with varied protecting groups were obtained in 25–66% yield. In addition, α-chiral cyclic phosphoric acid **45-POOH** was synthesized in 70% yield starting from diol **45**.

3.2. Catalytic reactions

3.2.1. Organocatalysis

3.2.1.1. Mannich type reactions

Compounds **12-POOH**, **13-POOH**, **16a-POOH**, **17a-POOH, 45-POOH** were investigated as Brønsted acid catalysts in Mannich type reaction of 2-(benzylideneamino)phenol and ((1-methoxy-2-methylprop-1-en-1-yl)oxy)trimethylsilane (*Scheme 48*). The reactions were performed in presence of 10 mol% catalysts at –40 °C in toluene. (Preliminary results showed conducting the reactions at –78 °C resulted in significantly longer reaction time while increasing the enantioselectivity only 1–2 % or in some cases no reaction took place).



cat. = **12a-POOH**, **13a-POOH, 16a-POOH**, **17a-POOH, 45-POOH**

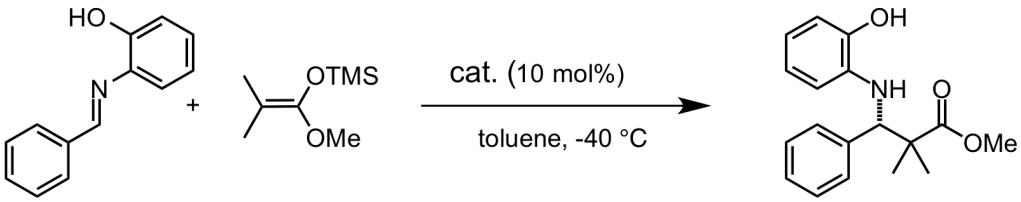
Scheme 48. Brønsted acid catalysed Mannich type reactions

Table 10. Mannich reaction catalysed by phosphoric acid derivatives

Entry	*Catalyst*	*t*	*T, °C*	*Yield, %*	*e.e., %*	*notes*
1	**12a-POOH**	2 d	-40	16	31	*S*
2	**13a-POOH**	2 d	-40	58	67	*S*
3	**16a-POOH**	2 d	-40	45	49	*R*
4	**17a-POOH**	1 d	-40	**44**	**85**	*S*
5	**45-POOH**	2 d	-40	13	30	*R*

Initial screening of auxiliaries with various protecting groups and phenyl substituents showed that benzyl protected **17a-POOH** was the most efficient catalyst providing the fastest conversion and the highest selectivity (44% in 24 h, 85% e.e., *Table 10*, Entry 4). **13a-POOH** afforded moderate yield and good e.e. (60%, 67% *e.e*., Entry 2) In contrast, with supposedly similar acid **12a-POOH**, the reaction proceeded with low yield and enantioselectivity (16%, 31% e.e. Entry 1). In addition, the 6 membered ketal protected **16a-POOH** catalysed the reaction with the opposite enantioselectivity (49% e.e. *R*) and 45% yield (Entry 3). Interestingly, when one of *gem.* phenyl groups of **17a-POOH** at C1 and C4 changed into Me, the otherwise same phosphate **45-POOH** gave the opposite enantiomer (*R*) albeit in poor selectivity (30% e.e. Entry 5).

Subsequently, substituents effect on the selectivity of the reaction was studied on acids **13-POOH** since benzyl protected moiety **17-POOH** were not available in many α-substituent variations (*Scheme 49*, *Table 11*). As expected, catalysts with electron withdrawing substituents activated the imine most efficiently. Especially, **13b-POOH** (Ar = *p*-ClC_6H_4) and **13d-POOH** (Ar = *p*-$CF_3C_6H_4$) increased the yield in 24 h reaching up to 83% and 91%, respectively (Entry 2, 4). The more acidic H makes the imine more electrophilic thus accelerates the reaction.



cat. = **13a-POOH**, **13b-POOH, 13c-POOH**, **13d-POOH, 13e-POOH, 13f-POOH**

Scheme 49. Investigation of substituent effect on the selectivity of Mannich type reaction

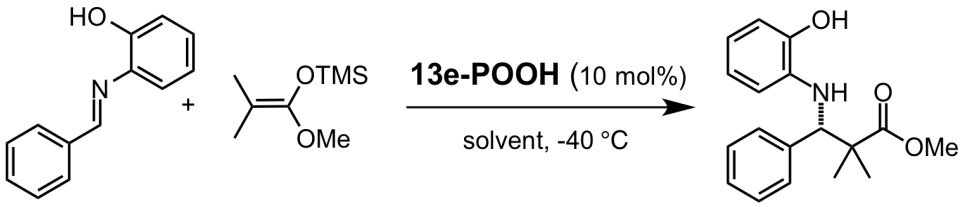
Table 11. Fine tuning of catalyst **13-POOH**

Entry	*Catalyst*	*Ar*	*t,*	*Yield, %*	*ee, %*
1	**13a-POOH**	Ph	48 h	58	67
2	**13b-POOH**	*p*-ClC_6H_4	24 h	**83**	**75**
3	**13c-POOH**	*p*-FC_6H_4	24 h	54	65
4	**13d-POOH**	p-$CF_3C_6H_4$	24 h	**91**	65
5	**13e-POOH**	2-naphth	48 h	67	**91**
6	**13f-POOH**	1-naphth	48 h	49	64
7	**13g-POOH**	dibenzofuryl	24 h	76	28
8	**3g-POOH**	dibenzofuryl	24 h	60	2 (*S*)

Even though, compared to the above two catalysts, **13c-POOH** (Ar = *p*-FC_6H_4) afforded lower yield (54%, Entry 3), the reaction was still almost twice faster than it was with catalysts **13a-POOH**, **13e-POOH** and **13f-POOH** which offered 49–67% yield after 48 h (Entry 1, 5, 6). The highest enantioselectivity was obtained with bulky 2-napthyl substituted **13e-POOH** reaching 91% e.e. Surprisingly, when equally spatially demanding 1-naphthyl substituted **13f-POOH** was used, the stereoselectivity dropped to 64% e.e. (Entry 6). X-ray crystal structure of the parent diol **13f** (See *Figure 31* for X-ray of **13f**) reveals that *gem*. 1-naphthyl groups are clustered around each other forming two distinct propellers at each C1 and C4 and leaving the rest of the space not occupied. Thus it was not able to provide sufficient enantiodiscrimination during the transition state. On the contrary to their impressive results on chemical yield, catalysts with electron withdrawing substituents provided only moderate e.e. (65% e.e. for both **13c-POOH** and **13d-POOH**), the highest among which (75% e.e) was provided by **13b-POOH**. Based on

the above results, it was concluded that bulky electron rich substituents might improve stereoselectivity. Thus, catalysts **13g-POOH** and **3g-POOH** (Ar = dibenzofuryl) were tested. However, both catalysts afforded low e.e. (28% and 2% (*S*) for **13g-POOH** and **3g-POOH**, respectively, Entry 7, 8). Presumably, 4-dibenzofuryls are in the same spatial arrangement as 1-naphthyls are in **13f** *i.e*. *gem*. substituents are positioned around each other leaving empty space for the rest of the molecule. Thus, it does not have sufficient barrier to make enantiotopic discrimination during the attack of the ketyl silyl acetal.

After exploring the substituents effects, solvents effects were studied employing the best catalyst **13e-POOH** (*Scheme 50*).



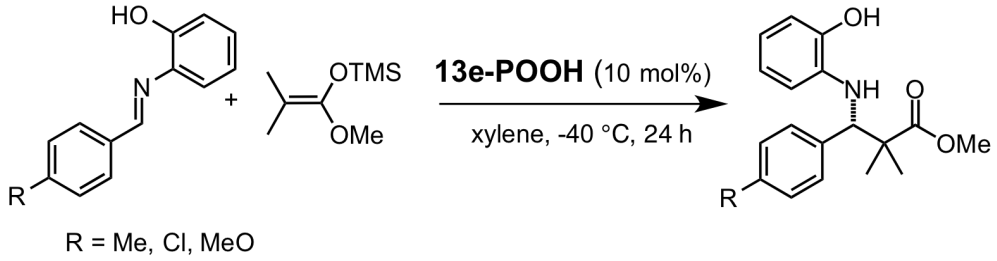
Scheme 50. Study on solvent effects on the selectivity of Mannich type reactions

Table 12. Solvents effects on the selectivity

Solvent	*t,*	*Yield, %*	*e.e., %*
EtOH	24 h	92	7
DCM	24 h	67	52
$CHCl_3$	20 h	**93**	68
mesytilene	24 h	56	**91**
xylene	24 h	**80**	**93**
toluene	24 h	67	**92**

According to the results, EtOH was the least selective solvent affording only 7% e.e (*Table 12*). In contrast, $CHCl_3$ raised the enantioselectivity to 68% e.e. with high chemical yield (93%). As expected, all the tried nonpolar solvents, mesitylene, xylene and toluene provided the best enantioselectivity reaching 91–93% e.e. The solubililty of the catalyst might contribute to the different yield since xylene, being the most soluble, provided the highest yield of 80%.

Finally, substrate scope was explored by varying substituents at *para* position of the parent aldehyde (*Scheme 51*). The reactions were conducted with 10 mol% **13e-POOH** in xylene at –40 °C and high yield and stereoselectivies were obtained (68–89%, 81–93% e.e. *Table 13*).



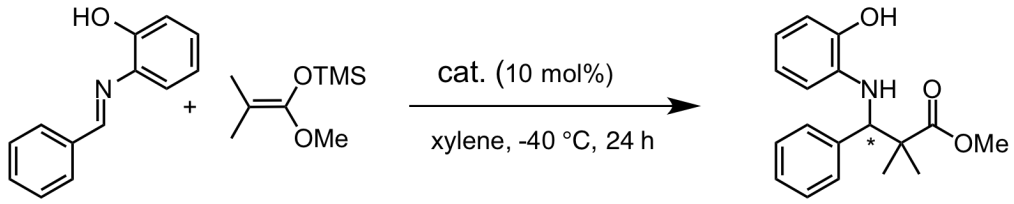
Scheme 51. Mannich type reactions with various imines catalysed by **13e-POOH**

Electron donating substituents showed beneficial effects on both the yield and stereoselectivity. Specifically, with aldimine **D** (R = *p*-MeO), the chemical yield and selectivity could reach as high as 89% and 91% e.e. The highest enantioselectivity *of* 93% e.e. was obtained with aldimine **B** (R = *p*-Me). When the substituent was changed to *p*-Cl (aldimine **C**), both the enantioselectivity and yield decreased to 81% e.e., 68%, respectively.

Table 13. Effect of substituents on aldehyde of the aldimine

R	*Product*	*Yield, %*	*e.e., %*
H	**A**	67	91
Me	**B**	73	**93**
Cl	**C**	68	81
MeO	**D**	89	91

Since, 2-naphthyl substituent provided the highest stereoselectivity, syntheses of 2-naphthyl substituted phosphates with various protecting groups were attempted. With this intention, **16e-POOH** and **17e-POOH** were synthesized and evaluated (*Scheme 52*). With *O*-benzyl protected phosphate **17e-POOH** the reaction reached excellent 96% e.e. and 96% yield. Dioxane protected phosphate **16e-POOH** also increased the opposite enantiomer reaching 70% e.e. (*R*) and 93% yield.



cat. = **16e-POOH** 93%, 70% e.e. (*R*)
17e-POOH 96%, 96% e.e. (*S*)

Scheme 52. (2-Naphthyl) substituted phosphoric acids in Mannich reaction

Based on the X-ray structures of **13e-POOH** (*Figure 33*) and **16e-POOH** (*Figure 34*), tentative 9 membered cyclic complexes between each catalyst and the aldimine were offered which correlate to the experimental findings (*Figure 35* and *36*).

Furthermore, based on preliminary calculations, the best fit of catalyst substrate interaction in the case of **17e-POOH** was determined as depicted in *Figure 37* which reasonably explains experimental findings. It is assumed that bulky *O*-Bn groups which have no ring constrains hover around the main backbone and form a crowded active site causing a high enantiodiscrimination of 96% e.e.

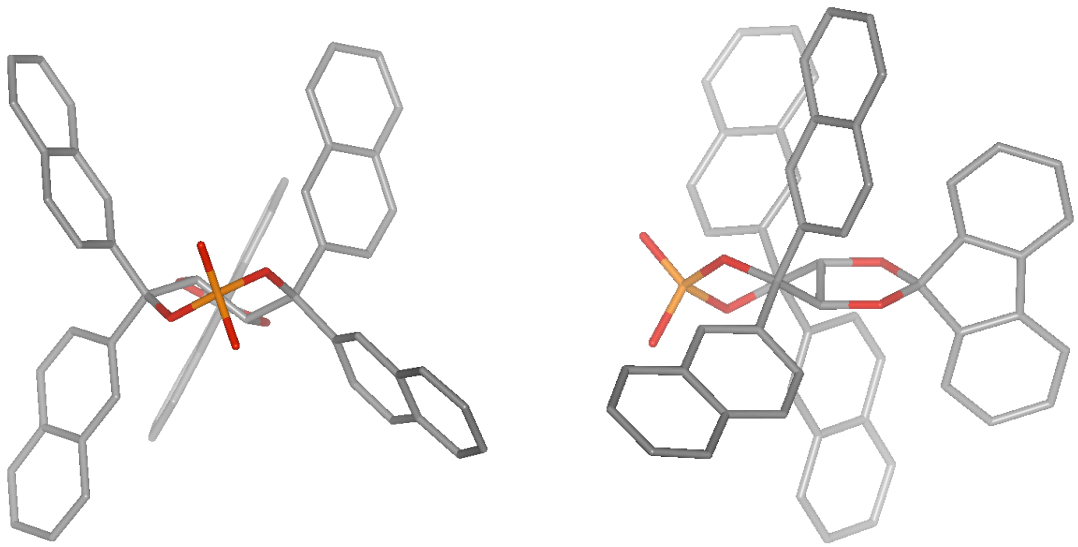


Figure 33. X-ray crystal structure of **13e-POOH**: a) bottom-up view and b) side-view

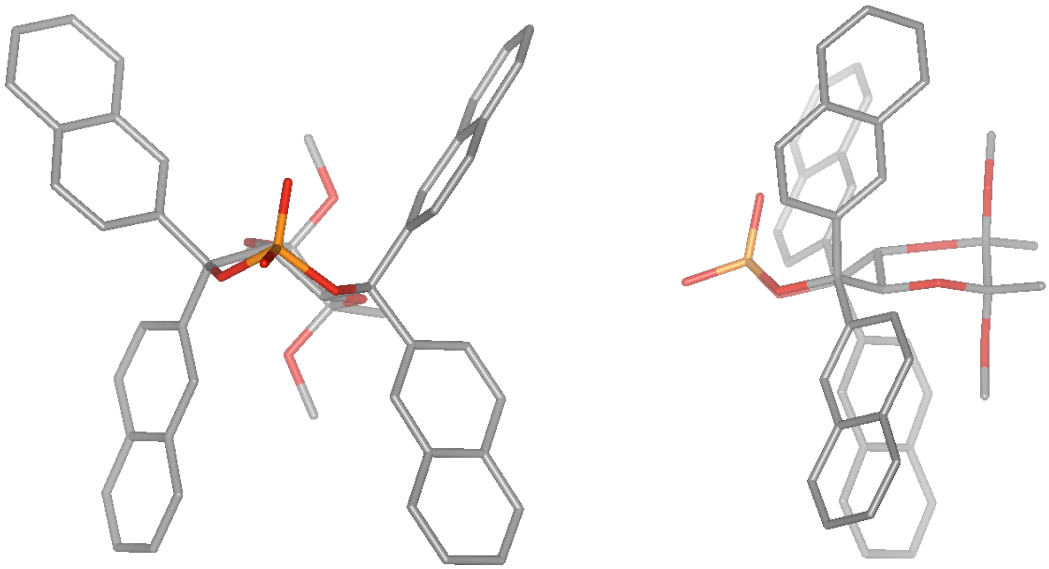


Figure 34. X-ray crystal structure of **16e-POOH:** a) bottom-up view b) side-view

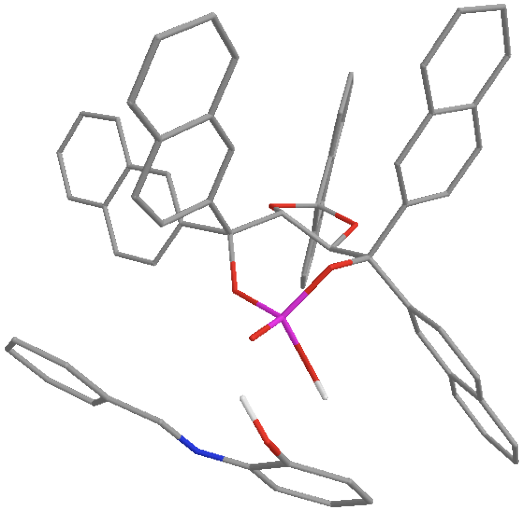


Figure 35. 9 Membered complex between **13e-POOH** and the aldimine that favors *Re* face attack

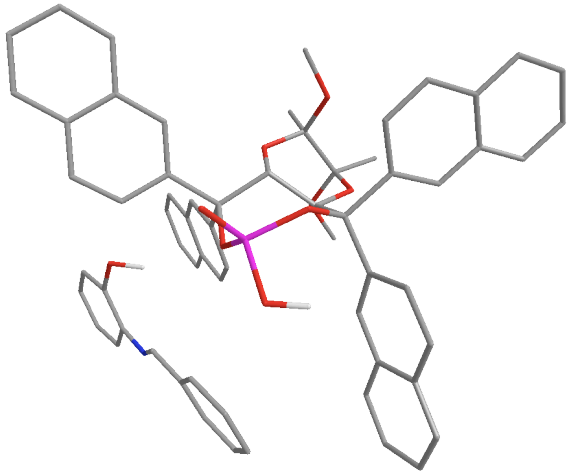


Figure 36. **16e-POOH** and the aldimine forming a substrate complex of which *Si* face is open to the nucleophilic attack

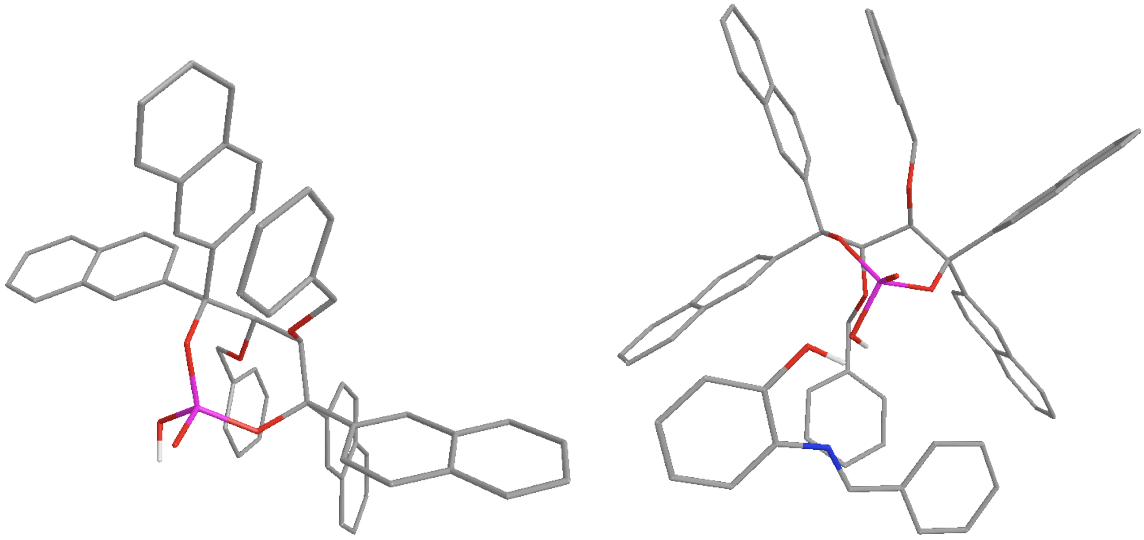
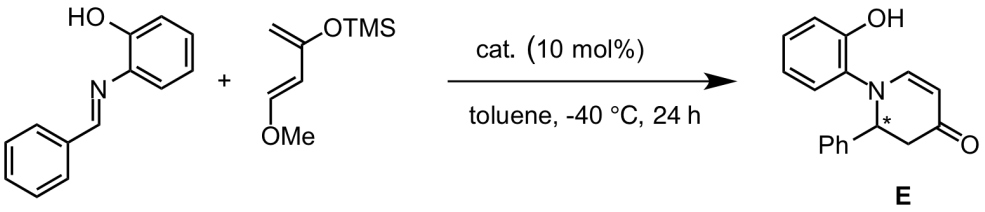


Figure 37. Substrate complex of **17e-POOH** and the aldimine favors *Re* face attack

3.2.1.2. Aza-Diels-Alder reactions

Aza-Diels-Alder reaction of *N*-(phenolyl)-benzaldimine and Danishefsky's diene ((*E*)-((4-methoxybuta-1,3-dien-2-yl)oxy)trimethylsilane) with 10 mol% catalyst using **3g-POOH**, **12-POOH**, **13-POOH**, **16a-POOH**, **16e-POOH**, **17e-POOH**, **45-POOH** were

performed at –40 °C in toluene (*Scheme 53*, Table 14) and piperidinone **E** was obtained in up to 80% yield and low enantioselectivites (4–39% e.e.).



E

cat.= **3g-POOH**, **12-POOH, 13-POOH, 16-POOH, 17e-POOH, 45-POOH**

Scheme 53. Catalyst screening for ADA reaction

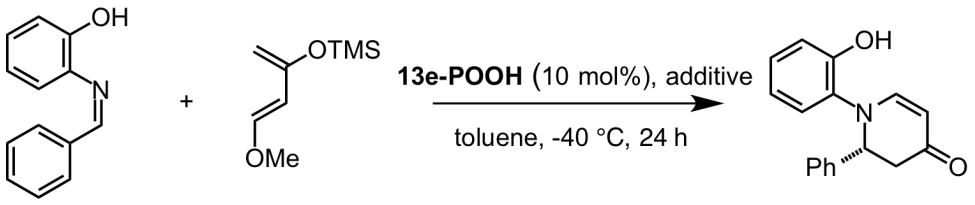
Table 14. Cyclic phosphoric acids in aza-DA reaction

Entry	*Catalyst*	*Yield, %*	*e.e.%*
1	**3g-POOH**	25	15 (*S*)
2	**12a-POOH**	28	7 (*R*)
3	**12b-POOH**	60	8 (*R*)
4	**12c-POOH**	30	4 (*R*)
5	**12d-POOH**	78	10(*R*)
6	**12e-POOH**	45	18 (*R*)
7	**13a-POOH**	63	11 (*R*)
8	**13b-POOH**	**80**	13 (*R*)
9	**13c-POOH**	50	7 (*R*)
10	**13d-POOH**	68	8 (*R*)
11	**13e-POOH**	50	20 (*R*)
12	**13f-POOH**	23	**24** (*R*)
13	**13g-POOH**	33	17 (*R*)
14	**16a-POOH**	35	5 (*S*)
15	**16e-POOH**	41	22 (S)
16	**17e-POOH**	65	**39** (*R*)
17	**45-POOH**	23	7 (*S*)

Generally, catalysts **13-POOH** performed better than catalysts **12-POOH**. Furthermore, phosphoric acids with electron withdrawing substituents such as *p*-ClC_6H_4 (**12b-POOH**, **13b-POOH**) and *p*-$CF_3C_6H_4$ (**12d-POOH**, **13d-POOH**) gave the high chemical yield between 60–80% (Entry 3, 5, 8, 10). On the contrary, *p*-FC_6H_4 substituted **12c-POOH** and **13c-POOH** did not display as good performance and only resulted 30% and 50% yield, respectively (Entry 4, 9). The low yield (23%) of **13f-POOH** is attributed to low solubility of the catalyst in toluene (Entry 12).

Overall, catalysts with bulky substituents (Ar = 2-naphthyl, 1-naphthyl, dibenzofuryl etc.) afforded better selectivity between 18–39% e.e. (Entry 6, 11–13, 15, 16) in contracts to the catalysts with electron withdrawing groups (4–10% e.e.). *O*-Bn protected **17e-POOH** proved to be the best one furnishing 65% yield and 39% e.e. This finding is close to the results (31%, 42% e.e.) obtained by Akiyama et al.[116] when they used chiral phosphoric acids derived from (*R*)-BINOL in ADA reaction of the same substrates.

Among the phosphoric acids with the same protecting groups, 1-naphthyl substituents gave the best selectivity (Entry 12). However, synthesis of 1-naphthyl substitueted diols with different backbone failed. As expected, six-membered ketal protected **16a-POOH** and **16e-POOH** favored the opposite enantiomer (*S,* Entry 14, 15). Furthermore, when instead of **17e-POOH**, structurally similar **45-POOH** was used enantiomeriomeric preference was switched to the opposite enantiomer (7% e.e., (*S*), Entry 17).



Scheme 54. Effect of acidic additives on enantioselective ADA reaction of phenylaldimine and Danishefsky's diene

Finally, effects of three acidic additives were studied with 10 mol% **13e-POOH**. Benzoic acid, 4-nitrobenzoic acid and 3,5-dinitrobenzoic acids were investigated (*Scheme 54*). According to *Table 15*, all the tested additives have detrimental effects on yield (28–45% instead of 50%) and increased the e.e. only by 6%. Therefore, further exploration of the reaction with different substrates was not carried out.

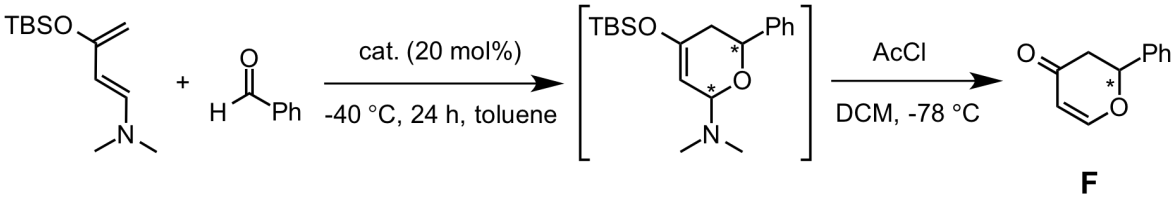
Table 15. Effects of the acidic additives on stereoselectivity

Additive	*Yield,*	*e.e., %*
None	50	20
3,5-$(NO_2)_2C_6H_3COOH$	28	16
4-$NO_2C_6H_4COOH$	40	22
PhCOOH	45	26

In conclusion, cyclic phosphoric acids derived from tartaric acid were investigated in ADA for the first time and the corresponding piperidinone was obtained in moderate yield and poor enantioselectitvies.

3.2.1.3. Oxo-Diels-Alder reactions

Diols **12**, **13**, **16e**, **17e** were tested in oxo-DA reaction between Rawal's diene (*trans*-3-(*tert*-butyldimethylsilyloxy)-*N*,*N*-dimethyl-1,3-butadien-1-amine and benzaldehyde (*Scheme 55*, *Table 16*).



F

cat. = **12a**-**12e**, **13a**-**13f, 16e, 17e**

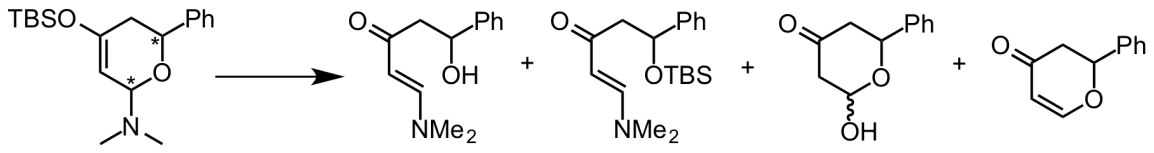
Scheme 55. Oxo-Diels-Alder reaction of benzaldehyde and Rawal's diene

The diols with strong electron withdrawing substituents such as *p*-ClC_6H_4, *p*-FC_6H_4, *p*-$CF_3C_6H_4$ generally gave product **F** in low yield and considerable amounts of side products (Entry 2, 4 and 9). (The obtained side-products were not among expected hydrolysis products. *Scheme 56*) In all cases, diols **13** with spiro(fluorenyldioxolane)

backbone afforded better selectivity (61–96% *e.e.*) than diols **12** with diphenyldioxolane backbone (16–43% *e.e.*).

Table 16. Catalyst screening for oxo-DA reaction

Entry	*Catalyst*	*Yield, %*	*e.e., %*
1	**12a**	55	43 (*S*)
2	**12b**	32	32 (*S*)
3	**12c**	46	32 (*S*)
4	**12d**	21	36 (*S*)
5	**12e**	67	16 (*S*)
6	**13a**	44	63 (*S*)
7	**13b**	48	65 (*S*)
8	**13c**	41	64 (*S*)
9	**13d**	28	62 (*S*)
10	**13e**	24	61 (*S*)
11	**13f**	7	**96** (*S*)
12	**16e**	55	10 (*R*)
13	**17e**	53	46 (*R*)



Scheme 56. Possible hydrolysis products of the cycloadduct from oxo-DA reaction[131]

As expected, with **13f** (Ar = 1-naphth) the enantioselectivity jumped to 96% *e.e*. (Entry 11). Low yield (7%) of the reaction with **13f** is due to poor solubilty of the catalyst in toluene. Analog to Rawal and other's explanation,[107,108,109] the high stereoselectivity of **13f** can be explained as the result of the H bonding of the hydroxyl group of the diol and carbonyl oxygen plus $\pi-\pi$ interaction of the phenyl group of benzaldehyde and 1-napthyl

group, thus effectively shielding the nucleohilie. Attack from one side resulting exclusive *Si* face attack (Refer to *Figure 18*).

Since 1-naphthyl substituents lead the best enantioselectivity, it was logical to attempt to modify the protecting groups while keeping 1-naphthyl substituents to see how protecting groups affect conformation of the molecules hence the selectivity of the reaction. However, the synthesis of the diols with supposed (6 membered) dioxane ring or non-cyclic bisBnO were not successful. Instead, synthesis of **16e** and **17e** with similarly bulky 2-naphthyl substituents was successfully carried out and these diols were investigated in oxo-DA reaction. In both cases, the stereoselectivity was reversed favoring *R* enantiomer (10% and 46% e.e., respectively, Entry 12, 13).

It is speculated that if the optimization of reaction conditions for its synthesis turns out successful, **17f** (Ar = 1-naphthyl) would significantly increase enantioselectivity in oxo-DA reaction in reverse direction and afford *R* enantiomer directly from Rawal or Brassard's diene.

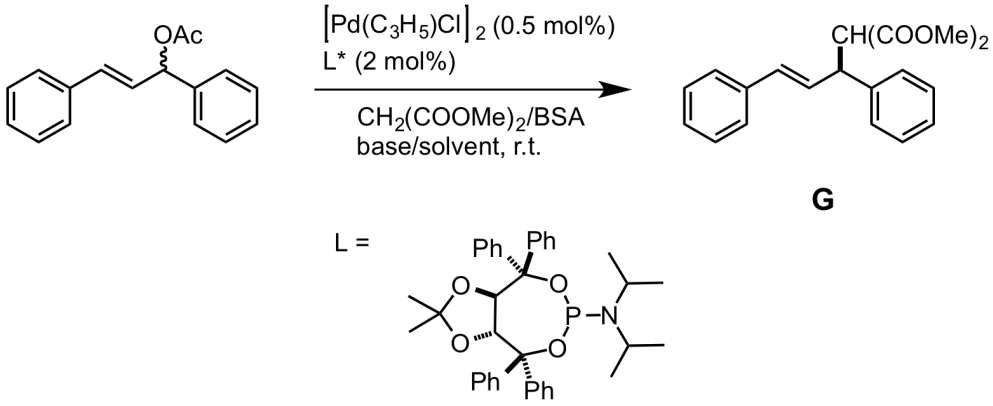
In conclusion, *tert*. diols derived from tartaric acid with varied protecting groups and substituents were successfully applied in ODA reactions reaching up 96% e.e. It was demonstrated that by adjusting size of the cyclic ketals or replacing ketals with non-cyclic protecting groups, geometry of the active species could be changed eventually altering the absolute configuration of the product.

3.2.2. Transition metal catalysed reactions

3.2.2.1. Pd catalysed allylic alkylation of 1,3-diphenyl-2-propenyl acetate with phosphoramidite ligands 4-PN

Phosphoramidites **4-PN** were tested in well-known benchmark reaction namely, Pd catalysed asymmetric alkylations of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate, to evaluate the effect of the newly formed (α-) chirality compared to their TADDOL derived phosphoramidite analogs with identical four aryl subsituents. Optimizations of reaction conditions were performed with **2-PN** varying solvents and bases. (*Scheme 57, Table 17*). The results show that DCM and LiOAc is the best combination to afford **G** in good yield and selectivity (90%, 85% e.e.).

After the optimal reaction conditions were established, ligands **4-PN** were tested (*Scheme 58*) and afforded generally high yield (70–95%) and e.e. (73–91%, *Table 18*). Ligand **4c-PN** (Ar = *o*-ClC_6H_4) was not applied in the reaction as it decomposed within few hours. The reaction catalysed by ligand **4f-PN** was sluggish and after 3 days at room temperature 65% of the starting material was recovered (Entry 4).



Scheme 57. Optimization of reaction conditions of allylic alkylation of diphenyl-2-propenyl acetate with **2-PN**

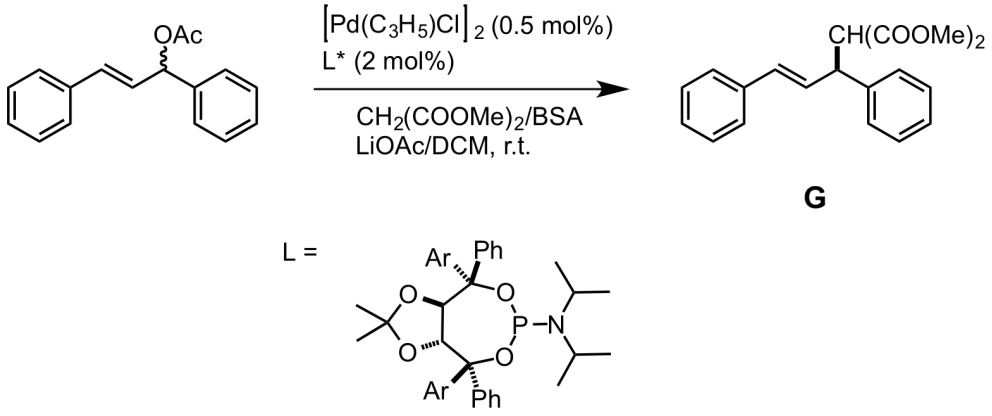
Table 17. Results of the optimization of reaction conditions of AAA with **2-PN**

Solvent	*Base*	*t*	*Yield*	*e.e., %*
DCM	KOAc	2 d	**90**	83
CH_3CN	KOAc	2 d	**95**	71
$C_2H_4Cl_2$	KOAc	2 d	90	56
toluene	KOAc	5 d	80	33
DCM	LiOAc	20 h	90	**85**

Ligand **4a-PN** with electron withdrawing substituents (*p*-ClC_6H_4) afforded the lowest stereoselectivity of 73% e.e. (Entry 2), while electron donating substituents such as *p*-$MeOC_6H_4$ (**4b-PN**), 4-C_6H_5-C_6H_4 (**4f-PN**), *p*-MeC_6H_4-O-C_6H_4 (**4g-PN**) improved e.e. (86–90% e.e., Entry 3–5).

Ligand **4h-PN** (Ar = 2-naphthyl) was the most efficient ligand giving the highest yield (95%) after 18 h and stereoselectivity (91% e.e., Entry 6) whereas with other ligands the reaction required 2–3 days to be complete.

It is interesting that phosphoramidite ligands derived from diols with 1,1,4,4-tetraphenyl and 1,1,4,4-tetrakis(2-naphthyl)-subsitution each gave lower e.e. (85% and 61% e.e., respectively) while the ligands with α-chirality and Ph/2-naphthyl pairs gave higher e.e. (91%). Assumingly, the chiral center, created by Ph/2-naphthyl pair close to the active site of the transition state, creates more discriminated geometry that eventually leads to better asymmetric induction.



Scheme 58. AAA reaction catalysed by ligands **4-PN**

Table 18. Results of the AAA reaction catalysed by ligands 4-PN

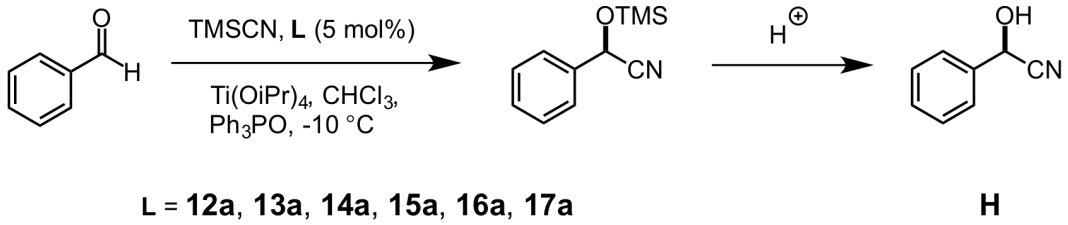
Entry	*Product*	*Ar*	*t*	*Yield, %*	*e.e., %*
1	**2-PN**	Ph	20 h	90	85
2	**4a-PN**	*p*-ClC_6H_4	3 d	87	73
3	**4b-PN**	*p*-MeOPh	2 d	**90**	**90**
4	**4f-PN**	4-C_6H_5-C_6H_4	3 d	30	86
5	**4g-PN**	*p*-MeC_6H_4-O-C_6H_4	2.5 d	70	89
6	**4h-PN**	2-naphth.	18 h	**95**	**91**

However, since most of the phosphoramidite ligands, except **4a-PN**, were isolated as diastereomeric mixtures in varied ratios, their stereochemical behaviour could

not be clearly accounted to only the main isomers. For this reason, not much attention has been paid to the further applications of these ligands in other reactions.

3.2.2.2. Ti catalysed cyanosilylation of benzaldehyde with diols 12–17

Finally, α,α,α',α'-tetraphenyl diols **12a**-**17a** with varied protecting groups were tested in TMSCN addition to benzaldehyde (*Scheme 59*) for initial screening of optimal protecting groups.



Scheme 59. Cyanosilylation of benzaldehyde catalysed by diols with various protecting groups

Table 19. Backbone adjustment of ligands for TMSCN addition to benzaldehyde

Entry	*Diol*	*t*	*Yield, %*	*e.e., %*
1	**12a**	2.5 d	59	19
2	**13a**	2.5 d	57	23
3	**14a**	2.5 d	60	1
4	**15a**	2.5 d	29	**30**
5	**16a**	18 h	70	6
6	**17a**	2.5 d	**67**	**25**

After the intial screeining of the ligands, substituents effect was studied with 2,3-*O,O*-bisBn protected diols **17** (*Table 20*). The study did not show a clear trend of EWG or spatial groups' effects on the selectivity. Eventhough electron withdrawing (Ar = *p*-ClC_6H_4, *p*-FC_6H_4) groups yielded acceptable yield (62%, 70%, Entry 2, 3), which is similar to that of **17a**, they had detrimental effect on stereoselectivity affording only 16%

and 20% e.e. respectively. With *p*-$CF_3C_6H_4$ substituted **17d**, the reaction afforded only decomposed product. Additionally, the reaction catalysed by 2-naphthyl substituted **17e** resulted in low yield and e.e. (35%, 5% e.e. Entry 5)

According to the results, *O*-Bn protected diol **17a** afforded cyanohydrin **H** with the highest yield and moderate e.e. (67%, 25% e.e. *Table 19*, Entry 6). The reaction with diol **13a** resulted in similar outcome (57%, 23% e.e., Entry 2). Eventhough 2-(2-bromophenyl)-dioxolane protected diol **15a** offered the highest selectivity (30% e.e., Entry 5), the reaction was not efficient giving only 29% yield.

Table 20. Fine tuning of ligands **17a**-**17d**

Entry	*Diol*	*t*	*Yield, %*	*e.e., %*
1	**17a**	2.5 d	67	25
2	**17b**	2.5 d	62	16
3	**17c**	2.5 d	70	20
4	**17d**	2.5 d	decomposed	-
5	**17e**	7 h	35	5

In conclusion, diols with various backbones were tested in TMSCN addition to benzaldehyde affording acceptable yield but poor e.e. Electron withdrawing and bulky substituents have detrimental effect on selectivity. *O*-Benzyl protected **17a** (Ar = Ph) afforded the best result of 67% yield and 25% e.e.

4. Conclusion

The thesis describes a detailed investigation of synthetic routes to tailored C_4-entities with two to four chiral carbon centers accessible from natural tartaric acid in few steps and their application in asymmetric transformations. A library of TADDOL analogs with extended structural modification of the skeleton was worked out comprising the introduction of various sterically and electronically divergent aromatic substituents in position 1 and 4 as well as replacement of the dimethyldioxolane moiety with other OH-protecting groups in order to discover more efficient auxiliaries for asymmetric organocatalytic transformations.

Starting from *L*-(+)-tartrate, 13 dimethyldioxolane protected *sec*. and *tert.* diols with pairwise different substituents were synthesized in 35–75% overall yield using a 4-step modular approach.

During the synthesis of the *tert*. diols, separation of the C_2-symmetrical product from its C_1-symmetrical epimer, which was formed as a result of 1,4-stereoinduction, caused a major problem. In order to overcome this difficulty, the rigid cyclic ketal of the tartrate moiety was replaced with 2,3-*O,O*-bis(benzyl) protecting groups that have more freedom to rotate suppressing 1,4-chelation of the intermediate. Based on this strategy, a modular synthetic approach to construct diols with up to four different stereogenic centers with predictable stereochemistry was developed. Using this tactics 8 *O*-benzyl protected 1,4-di-*tert*. diols with various combination of aliphatic and aromatic substituents were synthesized.

Meanwhile, modifications of OH- protecting groups resulted in 23 tetraaryl diols with five or six-membered, asymmetrically or symmetrically substituted cyclic ketals or *O*-benzyl protecting groups in 32–79% overall yield in 2–3 steps starting from *L*-(+)-tartrate.

In addition, 7 cyclic phosphoramidites were obtained from 1,4-di-*tert*. diols α-chirality in one-pot procedure and 22 cyclic phosphoric acids with various protecting groups and electronically and sterically divergent substituents were synthesized using alternatively a 2-step or 4-step protocol.

Relative configurations of several key intermediates were confirmed by X-ray structure determination.

Phosphoric acids were applied as Brønsted acid catalysts in Mannich type reaction and aza-Diels-Alder reaction. Catalysts performed especially well in Mannich type reaction with various aldimines and ketene silyl acetal (((1-methoxy-2-methylprop-1-

en-1-yl)oxy)trimethylsilane) affording high yield (67–96%) and selectivity of 81–96% e.e. *O*-Bn protected phosphoric acid **17e-POOH** catalysed the reaction with excellent 96% yield and 96% e.e. and displayed the significantly better performance than similar catalyst reported in the literature (73% e.e.). It is assumed that bulky *O*-Bn groups which have no ring constrains hover around the main backbone and form a crowded active site facilitating a high enantiodiscrimination. Cyclic phosphoric acids derived from tartaric acid were also employed in aza-Diels-Alder reaction for the first time but the corresponding piperidinone was obtained in only moderate yield and poor enantioselectivity. Eventually, change of the aldimine structure might lead to higher selectivity as it was reported with BINAP catalyst.

Diols with various protecting groups were used as H bonding catalysts in oxo-Diels-Alder reaction affording high enantioselectivity up to 96% e.e. Cyclic phosphoramidite derivatives were employed as ligands in Pd catalysed asymmetric alkylations of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate and offered as high as 91% e.e. Finally, diol auxiliaries were evaluated in Ti catalysed cyanosilylation of benzaldehyde and moderate enantioselectivities could be obtained.

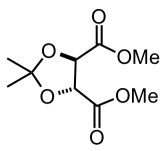
In conclusion, the thesis opened a modular approach to chiral auxiliaries derived from tartaric acid and describe their application in asymmetric synthesis. In total, 44 TADDOL analogs with extended structural modification of the skeleton were synthesized comprising sterically and electronically divergent aromatic substituents in position 1 and 4 as well as various OH- protecting groups, 22 cyclic phosphoric acids and 7 cyclic phosphoramidites were synthesized. The efficiencies of the catalysts and ligands were demonstrated in various organo and transition metal catalysed reactions and showed in part excellent selectivities. The study opens access to the catalysts derived from cheap source and affords catalysts with superior performance.

5. Experimental Part

General: Melting points: Kofler melting point apparatus, uncorrected. NMR: recorded at 400.27 MHz (^{1}H), 100.66 MHz (^{13}C) and 162.04 MHz (^{31}P) in $CDCl_3$. Chemical shifts δ are reported in ppm; for ^{1}H rel. to (residuals non-deuterated) solvent signals (chloroform-*d*: 7.24 ppm), for ^{13}C to $CDCl_3$ at 77.00 ppm, respectively. Coupling patterns are designated as s(inglett), d(oublett), t(riplett), q(uartet), m(ultiplet), ps(eudo), and br(oad). $^{13}C\{^{1}H\}$ NMR spectra are recorded in a *J*-modulated mode; signals are assigned as C, CH, CH_2, and CH_3. MS: ESI TOF mass spectrometer, Bruker Maxis. Preparative liquid chromatography was performed with an Isolera One automated flash purification system (Biotage) (MPLC) using self packed cartridges as well as conventional column chromatography on SiO_2, 40–63 µm. HPLC analysis was carried out on an Agilent 1100 series instrument with auto sampler and diode array detector. Optical rotations were measured using a micro cell with a 1 dm path length on Perkin-Elmer polarimeter 242 at 589 nm, 578 nm and 546 nm at 20 °C.

Absolute THF were distilled from sodium benzophenone ketyl, dichloromethane (DCM), mesitylene, toluene and xylene from CaH_2 and diethyl ether (Et_2O) from $LiAlH_4$. Benzaldehyde, $CHCl_3$, dimethylformamide (DMF), 1,4-dioxane, methanesulfonyl chloride (MsCl), *N*-methylmorpholine, PCl_3, triethylamine (TEA), trimethylorthoformate were distilled prior to use. Technical grade hexane, heptane fraction, DCM and ethyl acetate (EtOAc) were distilled and used for work-up. Solutions of *n*-BuLi, MeMgBr, MeLi, vinylmagnesium bromide, and PhLi were purchased from Aldrich and Alfa-Aesar. Other Grignard reagents were prepared according to known procedures.[132] Diluted solutions were applied where appropriate. The actual content was determined by titration prior use.[133] All the other chemicals were analytical grade and used without further purification.

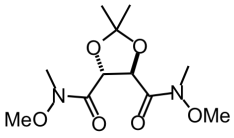
Dimethyl (4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate **1A***:*[134]



L-Tartaric acid (101 g, 0.67 mol) and 2,2-dimethoxypropane (190 mL, 161 mg, 1.54 mol), MeOH (40 mL) and *p*-TSA monohydrate (0.4 g, 2.1 mmol) were placed into a 1 L, round bottom flask and was warmed on a steam bath with occasional swirling until a dark-red homogenous solution was obtained. Additional 2,2-dimethoxypropane (95 mL, 80.5 g, 0.77 mol) and cyclohexane (450 mL) were added and fitted with Vigreux column and a

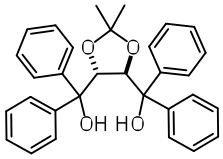
variable reflux distilling head. The mixture was refluxed for 40 h and the acetone-cyclohexane and MeOH-cyclohexane azeotropes were removed. After the mixture had cooled to room temperature, anhydrous K_2CO_3 (1 g, 7.2 mmol) was added and the mixture was stirred until the red color abated. The mixture was concentrated under reduced pressure and the residue was fractionally distilled under vacuum to afford 138.8 g (95%) of the dimethyl diester **1A** as pale yellow oil. Bp 97–101 °C (0.5 mm). ^{1}H NMR δ: 1.47 (s, 6H); 3.80 (s, 6H); 4.79 (s, 2H) ppm.*

2,3-O-Isopropylidene-L-tartaric Acid N-Methyl-N-methoxyamide **1B**:[135]



To a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (2.49 g, 25.7 mmol) in DCM (25 mL) was added trimethylaluminum (12.85 mL of a 2M solution in hexane, 25.7 mmol) over 30 min at 0 °C . The solution was allowed to warm to room temperature. After stirring for 15 min, the solution was cooled to –10 °C, and dimethyldiester **1A** (1 g, 5.7 mmol) in DCM (20 mL) was added over 30 min. After the mixture had stirred for 2 h, the reaction was carefully quenched with 1N HCl (10 mL) solution. The inorganic phase was extracted with DCM (3× 20 mL). The combined organic phases were washed brine, dried over $MgSO_4$, filtered and evaporated. The residue was chromatographed using MeOH/DCM (5/95) to give **1B** as a white solid in 7.66 g yield 83%). ^{1}H NMR δ: 1.52 (s, 6 H); 3.23 (s, 6 H), 3.69 (s, 6 H), 5.17 (s, 2 H) ppm.*

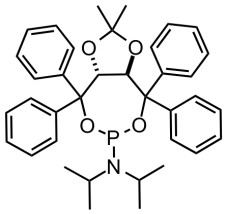
((4R,5R)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(diphenylmethanol) **2**:[136]



General Procedure A:[137] Dimethyl diester **1A** (310 mg, 1.4 mmol) was dissolved in THF (3 mL) and phenylmagnesium bromide (6 mmol) in THF (12 mL) was added dropwise for 10 min at 0 °C. The ice bath was removed and the reaction was refluxed for 1 h. The mixture was cooled to room temperature and sat. aq. ammonium chloride solution (10 mL) was carefully added. The mixture was extracted with EtOAc (2× 30 mL), the combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and the solvent was removed on a rotary evaporator. The crude product was purified by column chromatography with EtOAc/hexane (15/85) affording 444 mg of **2** (76%). ^{1}H NMR δ: 1.02 (s, 6H); 3.90 (br.s, 2H); 4.55 (s, 2H); 7.15–7.60 (m, 20H) ppm.*

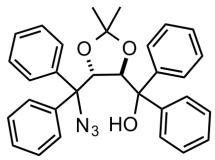
* Spectroscopic data are in accordance with literature.

(1R,7R)-4-(Diisopropylamino)-9,9-dimethyl-2,2,6,6-tetraphenyl-3,5,8,10-tetraoxa-4-phosphabicyclo[5.3.0] decane **2-PN**:



General Procedure B:[138] A solution of **2** (200 mg, 0.42 mmol) and *N*-methylmorpholine (92.3 μL, 85 mg, 0.84 mmol) in toluene (1.5 mL) was added to an ice-cold solution of PCl_3 (36 μL, 57.7 mg, 0.42 mmol) in toluene (1 mL). The resulting suspension was stirred for 30 min at room temperature, cooled to –78 °C, filtered under argon and solvents were removed under reduced pressure. The pale-yellow residue was dissolved in THF (1.3 mL) and then added dropwise to a solution of LDA* in THF at –78 °C. The solution was kept at room temperature for 2 h and finally concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel in cyclohexane/Et_3N (95/5), affording **2-PN** as a white solid in 183 mg (73%) yield. ^{1}H NMR δ: 0.32 (s, 3H); 1.15 (d, *J* = 6.8 Hz, 6H); 1.20 (d, *J* = 6.8 Hz, 6H); 1.40 (s, 3H); 3.96 (m, 2H); 5.11 (d, *J* = 8.6 Hz, 1H); 5.73 (dd, *J* = 8.6, 3.9 Hz, 1H); 6.93–7.25 (m, 12H); 7.72–7.78 (m, 2H); 7.82–7.92 (m, 4H); 8.11–8.17 (m, 2H) ppm.*

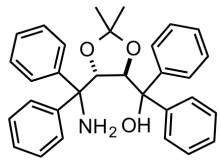
((4R,5S)-5-(Azidodiphenylmethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)diphenylmethanol **2-N**:[139]



General Procedure C: Diol **2** (100mg, 0.21 mmol) was dissolved in THF (1 mL) and cooled to –78 °C. A solution of *n*-BuLi (0.25 mL of 1.6M solution in hexane, 0.42 mmol) was slowly introduced. The resulting yellow solution was warmed to –30 °C, then cooled again to –78 °C. At this temperature methanesulfonylchloride (32.5 μL, 48 mg, 0.42 mmol) was added and the mixture turned into a white suspension. After 5 h the volatiles were evaporated under vacuum. The residue was dissolved in DMF (1mL) and NaN_3 (119 mg, 0.84 mmol) was added. The mixture was stirred at 80 °C for 12 h and cooled to room temperature. Et_2O (15 mL) was added and washed with H_2O (4× 5 mL), dried over Na_2SO_4 and concentrated under vacuum. Column chromatography applying EtOAc/hexane (10/90) afforded 60 mg of **2-N** (58%). ^{1}H NMR δ: 1.07 (s, 6H); 3.63 (s, 1H); 4.59 (d, *J* = 7.3 Hz, 1H); 4.83 (d, *J* = 7.3 Hz, 1H); 7.19–7.51 (m, 20H) ppm.*

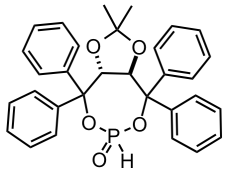
* LDA was prepared by addition of *n*-butyl lithium (262 μL of 1.6 M solution in hexane, 0.42 mmol) to a solution of diisopropylamine (65 μL, 0.47 mmol) in THF (1.3 mL) at 0 °C and stirred at the same temperature for 30 min.

((4R,5S)-5-(Aminodiphenylmethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)diphenylmethanol **2-NH**:[139]



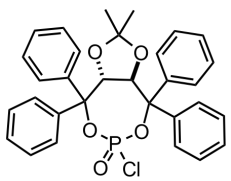
To a suspension of $LiAlH_4$ (8 mg, 0.21 mmol) in THF (0.5 mL) at 0 °C was added a solution of the monoazide **2-N** (37 mg, 0.075 mmol) in THF (0.5 mL). After stirring at room temperature for 18 h, 1N NaOH (0.5 mL) was added carefully and the mixture was diluted with Et_2O (2 mL). Na_2SO_4 was added and the reaction mixture was stirred further for 2 h at room temperature, filtered through a pad of celite with the aid of Et_2O. The filtrate was dried over K_2CO_3 and concentrated. The residue was purified by a column chromatography using Et_2O /hexane (30/70) to give **2-NH** as a white crystalline solid in 25 mg (71%) yield. ^{1}H NMR δ: 0.89 (s, 3H); 1.26 (s, 3H); 2.20 (brs, 2H); 4.18 (d, *J* = 8.4 Hz, 1H); 4.28 (d, *J* = 8.4 Hz, 1H); 7.16–7.46 (m, 18H); 7.71–7.73 (m, 2H) ppm.*

(3aR,8aR)-2,2-Dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide **2-POH**:[101]



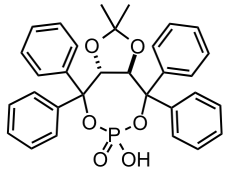
General Procedure D: In a Schlenk tube PCl_3 (0.17 mL, 275 mg, 2.0 mmol) was dissolved in THF (5 mL), cooled to 0 °C and TEA (0.47 mL, 344 mg, 3.4 mmol) was added followed by **2** (467 mg, 1.0 mmol) dissolved in THF (5 mL). The reaction was stirred for 1.5 h at 0 °C, TEA (101 mg, 0.14 mL, 1 mmol) and H_2O (18 µL, 1.0 mmol) were added. The mixture was allowed to warm to room temperature and continued to stir for 1 h. Solid triethylammonium chloride was separated by filtration through a pad of celite and the solvent was removed in vacuum. The crude product was purified by MPLC applying a solvent gradient EtOAc (5→40%)–heptane to afford **2a-POH** in 220 mg (43%) yield. ^{1}H NMR δ: 0.61 (s, 3H); 0.80 (s, 3H); 5.25 (d, *J* = 8.1 Hz, 1H); 5.40 (d, *J* = 8.1 Hz, 1H); 7.11 (d, J_{HP} = 325.1 Hz, 1H); 7.29–7.77 (m, 16H); 7.64 (t, *J* = 7.6 Hz, 4H) ppm.*

(3aR,8aR)-6-Chloro-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide **2-PCl**:[67d] Formed as a side product during the synthesis of **2-POH**; yield: 16%. ^{1}H NMR δ: 0.57 (s, 3H); 0.62 (s, 3H); 5.32 (d, *J* = 7.9 Hz, 1H); 5.37 (d, *J* = 7.9 Hz, 1H); 7.25–7.42 (m, 16H); 7.58 (t, *J* = 7.8 Hz, 4H) ppm.*



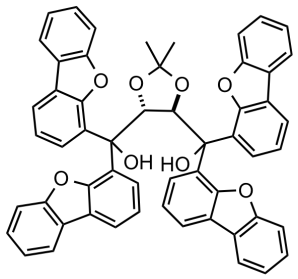
* Spectroscopic data are in accordance with literature.

(3aR,8aR)-6-Hydroxy-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide **2-POOH**:[67e]



General Procedure E:[140] Iodine (77 mg, 0.3 mmol) was dissolved in pyridine/H_2O (2 mL, v/v : 98/2), added to **2-POH** (78 mg, 0.15 mmol) and stirred at room temperature for 3 days. Subsequently, $CHCl_3$ (30 mL) was added, the organic phase was washed with 5% aqueous sodium bisulfite (20 mL), and the aqueous phase was washed back with $CHCl_3$ (10 mL). The combined organic phase was concentrated under vacuum, dissolved in EtOH and washed through a column of Dowex-50 resins. The solvent was once more removed under vacuum to afford 70 mg (88%) of **2-POOH**. ^{1}H NMR δ: 0.63 (s, 6H); 5.19 (s, 2H); 7.21–7.36 (m, 16H); 7.52–7.54 (m, 4H); 8.24 (br.s, 1H) ppm.*

((4R,5R)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(bis(dibenzo[b,d]furan-4-yl)methanol) **3g**:[141]

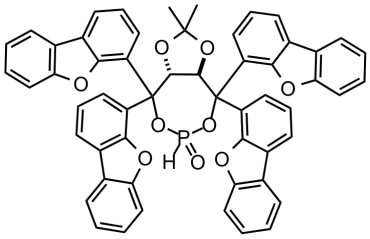


In an oven-dried Schlenk tube Mg (122 mg, 5 mmol) turnings were added to dry, degassed THF (1 mL) followed by a drop of dichloroethane. 4-Iododibenzo[b,d]furan (1.359 g, 4.60 mmol) was dissolved in THF (3 mL), degassed and added dropwise to the Mg in THF (0.3 mL) via Teflon cannola. After the first few drops, the mixture was slightly heated with a hotgun to initiate the reaction. After refluxing for 1 h the reaction mixture was cooled to 0 °C. Dimethyl dister **1A** (0.2 mL, 168 mg, 0.77 mmol) dissolved in THF (2 mL) was added to the Grignard reagent and stirred further for 1 h. The reaction was quenched by addition of MeOH (5 mL). Water (5 mL) and 2M HCl (3 mL) was added. The water phase was extracted with toluene (3× 10 mL), the combined organic phases were dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by MPLC applying a solvent gradient EtOAc (5→40%)–heptane affording **3g** as a white solid. The product was recrystallized from $CHCl_3$/hexane mixture and **3g** was obtained as a white crystalline in 503 mg (71%) yield. $[\alpha]_{578}^{20}$ -172 (*c* 0.96, $CHCl_3$). ^{1}H NMR δ: 1.54 (s, 6H); 4.84 (br.s, 2H); 6.16 (pt, *J* = 7.6 Hz, 2H); 6.29 (br.s, 2H); 7.01 (dd, *J* = 7.6, 1.1 Hz, 2H); 7.21 (m, 4H); 7.25-7.34 (m, 8H); 7.37 (pt, *J* = 7.7Hz, 2H); 7.61 (dm, *J* ~7.7Hz, 4H); 7.73 (dd, *J* = 7.7, 1.2 Hz, 2H); 7.77 (dm, *J* = 7.7 Hz, 2H); 8.27 (dd, *J* = 7.8, 1.2 Hz, 2H) ppm. ^{13}C NMR δ: 28.2 (CH_3); 79.2 (C); 80.2 (CH); 111.2 (CH); 111.4 (CH);

* Spectroscopic datas are in accordance with literature.

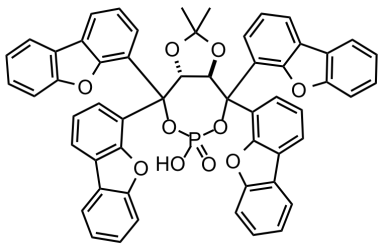
113.3 (C); 119.5 (CH); 119.9 (2CH); 120.3 (CH); 121.3 (CH); 121.8 (CH); 122.2 (CH); 122.7 (CH); 123.6 (CH); 123.9 (2C); 124.2 (C); 124.3 (C); 126.5 (CH); 126.6 (C); 126.7 (CH); 127.9 (C); 128.2 (CH); 151.4 (C); 153.6 (C); 155.3 (2C) ppm. HRMS (ESI): *m/z* calcd for $C_{55}H_{38}NaO_8$ $[M+Na]^+$: 849.2464; found: 849.2482.

(3aR,8aR)-4,4,8,8-Tetrakis(dibenzo[b,d]furan-4-yl)-6-hydroxy-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide **3g-POH:**



General Procedure D. MPLC applying a solvent gradient of DCM(100→75)–MeOH afforded the product as a white powder in 30% yield. ^{1}H NMR δ: 0.35 (s, 3H); 0.43 (s, 3H); 6.50 (br.s, 2H); 7.13 (m, 2H); 7.20–7.38 (m, 11H); 7.23 (d, J_{PH} = 738 Hz, 1H); 7.44 (ptd, *J* = 7.8, 1.0 Hz, 2H); 7.50 (br.m, 1H); 7.51 (pt, *J* = 7.6 Hz, 1H); 7.80 (dm, *J* = 7.8 Hz, 1H); 7.86 (dm, *J* = 7.5 Hz, 1H); 7.89–7.97 (m, 5H); 7.99 (dd, *J* = 7.6, 1.0 Hz, 1H); 8.03 (dd, *J* = 7.6, 1.0 Hz, 1H); 8.06 (ddd, *J* = 8.7, 7.7, 1.2 Hz, 2H) ppm. ^{13}C NMR δ: 26.0 (CH_3); 26.2 (CH_3); 79.7 (CH); 80.4 (CH); 86.1 (C); 86.2 (C); 111.6 (2CH); 111.9 (CH); 112.0 (CH); 114.0 (C); 120.3 (3CH); 120.4 (CH); 121.0 (CH); 121.1 (CH); 121.7(CH); 121.7 (CH); 121.9 (CH); 122.1 (CH); 122.4 (2CH); 122.5 (2CH); 122.7 (2CH); 123.4 (C); 123.5 (2C); 123.8 (C); 123.9 (2C); 124.9 (C); 125.3 (C); 125.4 (C); 125.7 (C); 125.9 (CH); 126.1 (C); 126.6 (C); 126.6 (CH); 126.8 (2CH); 126.9 (CH); 127.1 (CH); 127.3 (CH); 128.0 (CH); 153.6 (C); 153.8 (C); 153.9 (C); 154.0 (C); 155.7 (2C); 156.1 (C); 156.2 (C) ppm. ^{31}P NMR δ: –3.73 ppm. HRMS (ESI): *m/z* calcd for $C_{55}H_{37}NaO_9P$ $[M+Na]^+$: 895.2073; found: 895.2093.

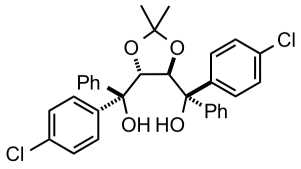
3aR,8aR)-4,4,8,8-Tetrakis(dibenzo[b,d]furan-4-yl)-6-hydroxy-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide **3g-POOH**:



General Procedure E. The ammonium salt of the phosphate **3g-POOH** was dissolved in MeOH and washed with Dowex-50 to afford **3g-POOH** as a white powder in 88% yield. M.p. 245–247 °C; ^{1}H NMR δ: 0.27 (s, 6H); 6.28 (br.s, 2H); 6.97–7.03 (m, 2H); 7.04–7.10 (m, 4H); 7.11–7.18 (m, 4H); 7.24–7.32 (m, 6H); 7.65 (br.m, 4H); 7.74 (m, 2H); 7.80-7.86 (m, 4H); 7.88 (dd, *J* = 7.6, 1.1 Hz, 2H) ppm. ^{13}C NMR δ: 26.0 (CH_3); 79.5 (CH); 85.7 (d, J_{CP} = 6 Hz, C); 111.8 (CH); 111.9 (CH); 113.1 (C); 120.0 (2CH); 120.6 (CH); 121.2 (CH); 121.8 (CH); 122.1 (CH); 122.2 (2CH); 123.4 (C); 123.7 (C); 124.5 (d, J_{PC} = 11 Hz, C); 124.8 (C); 125.1 (C); 125.7 (d, J_{CP} = 2 Hz, C); 126.7

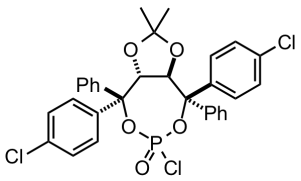
(CH); 126.8 (CH); 127.1 (CH); 127.2 (CH); 153.8 (C); 154.0 (C); 155.6 (C); 156.1 (C) ppm. ^{31}P NMR δ: –8.69 ppm. HRMS (ESI): *m/z* calcd for $C_{55}H_{36}O_{10}P$, $[M\text{-}H]^-$: 887.2052; found: 887.2078.

(1R,1'R)-((4R,5R)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis((4-chlorophenyl)(phenyl)-methanol) **4a**: *General Procedure F*:[69]



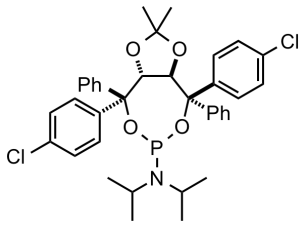
In a Schlenk tube ketone **19a** (250 mg, 0.8 mmol) was dissolved in THF (3 mL) and cooled to 0 °C. A solution of *p*-chlorophenyl magnesiumbromide (712 mg, 3.3 mmol) in THF (7 mL) was added dropwise over 20 min. The greenish brown solution was stirred overnight gradually reaching room temperature and the color changed to clear yellow. The reaction mixture was cautiously quenched with sat. aq. NH_4Cl solution (4 mL), poured into H_2O (3 mL), and extracted with Et_2O (3× 10 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under vacuum. The crude product was subjected to column chromatography using EtOAc/hexane (20/80) to give 385 mg (90%) of **4a** as a white solid (*d.r.* = 10:1). ^{1}H NMR (Main isomer) δ: 1.09 (s, 6H); 4.02 (s, 2H); 4.54 (s, 2H); 7.28–7.35 (m, 14H); 7.48–7.50 (m, 4H) ppm. ^{13}C NMR δ: 27.2 (CH_3); 77.9 (C); 80.7 (CH); 109.7 (C); 127.5 (2CH); 127.9 (CH); 128.3 (CH); 130.0 (CH); 133.4 (C); 141.2 (C); 145.3 (C) ppm. HRMS: m/z calcd for $C_{31}H_{27}Cl_2O_4$ $[M–H]^-$: 533.1286, found 533.1304.

(3aR,4R,8R,8aR)-6-chloro-4,8-bis(4-chlorophenyl)-2,2-dimethyl-4,8-diphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide **4a-PCl**:[67]



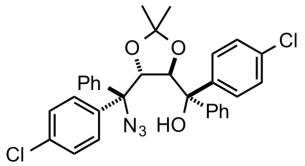
To a solution of 4a (268 mg, 0.5 mmol) in THF (2.5 mL) was added *n*-BuLi (0.73 mL of 1.1 M solution in hexane, 0.8 mmol) at –78 °C. The mixture was warmed to room temperature, stirred for 1 h, then cooled to –78 °C and $POCl_3$ was added (60 µL, 99.7 mg, 0.65 mmol). The mixture was stirred for 3 h at –78 °C, the reaction was quenched with sat. aq. $NaHCO_3$ solution and the mixture was diluted with Et_2O (5 mL). The organic layer was washed with sat. aq. $NaHCO_3$ solution (2× 5 mL), brine, dried over $MgSO_4$ and the solvent was removed uner reduced pressure. MPLC with a solvent gradient EtOAc (2→20%)–heptane afforded **4a-PCl** in 31% yield. ^{1}H NMR δ: 0.72 (s, 3H); 0.74 (s, 3H); 5.27 (d, *J* = 8.0 Hz, 1H); 5.30 (d, *J* = 8.0 Hz, 1H); 7.22–7.34 (m, 6H); 7.41–7.60 (m, 12H) ppm. ^{31}P NMR δ: –9.63 ppm.

(1R,7R)-4-(Diisopropylamino)-9,9-dimethyl-2,6-bis(p-chlorophenyl)-2,6-diphenyl-3,5,8,10-tetraoxa-4 phosphabicyclo[5.3.0]decane **4a-PN**:



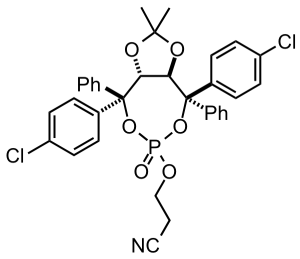
General Procedure B. Deactivation of chromatography column was done with *c*-hexane/TEA (97/3, 2× column volume (CV)) followed by DCM/*c*-hexane (10/90, 1× CV) prior to use. A chromatography applying DCM/*c*-hexane (10/90) afforded **4a-PN** as white foam; yield 49 %. ^{1}H NMR δ: 0.32 (s, 3H), 1.15 (d, *J* = 6.8 Hz, 6H), 1.20 (d, *J* = 6.8 Hz, 6H), 1.39 (s, 3H), 3.91 (m, 2H), 4.52 (d, *J* = 8.6 Hz, 1H), 5.06 (dd, *J* = 8.6, 3.8 Hz, 1H), 7.18–7.42 (m, 14H), 7.54–7.56 (m, 2H), 7.71–7.74 (m, 2H) ppm. ^{13}C NMR δ: 24.1 (d, J_{CP} = 7.0 Hz, CH_3), 24.4 (d, J_{CP} = 7.0 Hz, CH_3), 25.3 (CH_3), 27.7 (CH_3), 44.3 (d, J_{CP} = 14.9 Hz, CH), 80.6 (d, J_{CP} = 2.9 Hz, C), 80.8 (d, J_{CP} = 10.6 Hz, C), 82.2 (d, J_{CP} = 21.9 Hz, CH), 82.8 (d, J_{CP} = 3.7 Hz, CH), 111.5 (C), 126.9 (CH); 127.1 (CH); 127.2 (CH); 127.3 (CH); 127.5 (CH); 127.7 (CH); 127.7 (CH); 127.9 (CH); 130.2 (d, J_{CP} = 5.3 Hz, CH); 130.4 (CH); 133.0 (C); 133.2 (C); 140.7 (C); 141.3 (C); 146.3 (d, J_{CP} = 3.0 Hz, C); 146.9 (C) ppm. ^{31}P NMR δ: 140.62 ppm. HRMS: *m*/*z* calcd for $C_{37}H_{40}Cl_2NNaO_4P$ $[M+Na]^+$: 686.1970; found: 686.1946

(S)-((4R,5S)-5-((S)-Azido(4-chlorophenyl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)(4-chlorophenyl)(phenyl)methanol **4a-N**:



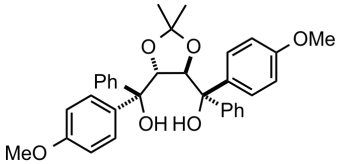
General Procedure C. Column chromatography with EtOAc/hexane (10/90) afforded **4a-N** in 16% yield (epimers C_2 : C_1/3 : 1). ^{1}H NMR δ: 1.07 (s, 3H); 1.13 (s, 3H); 3.67 (s, 1H); 4.56 (d, *J* = 7.3 Hz, 1H); 4.75 (d, *J* = 7.3 Hz, 1H); 7.13 (d, *J* = 8.4 Hz, 2H); 7.19–7.36 (m, 14H); 7.42 (d, *J* = 8.8 Hz, 2H) ppm. ^{13}C NMR δ: 27.1 (CH_3); 27.7 (CH_3); 73.0 (C); 77.6 (C); 79.6 (CH); 81.8 (CH); 110.2 (C); 127.2 (CH); 127.4 (CH); 127.7 (CH); 127.9 (CH); 128.0 (CH); 128.3 (CH); 128.4 (CH); 129.5 (CH); 129.8 (CH); 131.1 (CH); 133.2 (C); 134.2 (C); 138.6 (C); 139.5 (C); 142.6 (C); 144.9 (C) ppm. HRMS: *m*/*z* calcd for $C_{31}H_{27}Cl_2N_3NaO_3$ $[M+Na]^+$: 582.1327; found: 582.1327.

*3-(((3aR,4S,8S,8aR)-4,8-Bis(4-chlorophenyl)-2,2-dimethyl-6-oxido-4,8-diphenyltetrahydro- [1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)oxy)propanenitrile***:**



General Procedure G:[142] To a solution of **4a** (200 mg, 0.37 mmol) and TEA (0.17 mL, 128 mg, 1.3 mmol) in dry THF (1.5 mL) was added PCl_3 (34 µL, 54 mg, 0.39 mmol) at 0 °C and the mixture was stirred for 1 h. 3-Propioxynitrile (29 mg, 28 µL, 0.4 mmol) dissolved in dry THF (1.5 mL) was added dropwise via cannula and the mixture was stirred for 2 h at room temperature. THF was added, triethylammonium chloride was filtered through a pad of celite and the solvent was removed under vacuum. The remaining oil was dissolved in DCM (3 mL) and H_2O_2 (0.22 mL of a 30% aq. solution, 2.2 mmol) was added and stirred for 1 h at room temperature. A sat. aq. $NaHCO_3$ solution was added and the mixture was extracted with DCM. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. MPLC with a solvent gradient EtOAc(20→60%)–heptane afforded the product as a white solid in 142 mg (59%) yield. ^{1}H NMR δ: 0.64 (s, 3H); 0.81 (s, 3H); 2.01–2.09 (m, 1H); 2.28–2.36 (m, 1H); 3.39–3.46 (m, 1H); 3.94–4.02 (m, 1H); 5.10 (d, *J* = 8.1 Hz, 1H); 5.27 (d, *J* = 8.1 Hz, 1H); 7.22–7.25 (m, 2H); 7.28–7.31 (m, 6H); 7.33–7.43 (m, 6H); 7.49–7.54 (m, 4H) ppm. ^{13}C NMR δ: 19.1 (d, J_{CP} = 8.4 Hz, CH_2); 26.6 (CH_3); 26.8 (CH_3); 62.2 (d, J_{CP} = 5.1 Hz, CH_2); 78.0 (CH); 79.5 (CH); 88.0 (d, J_{CP} = 8.3 Hz, C); 88.7 (d, J_{CP} = 7.3 Hz, C); 114.1 (C); 116.0 (C); 126.7 (CH); 127.2 (CH); 127.5 (CH); 127.8 (CH); 128.5 (CH); 128.6 (CH); 128.7 (CH); 128.8 (CH); 129.8 (CH); 130.4 (CH); 134.2 (2C); 137.6 (d, J_{CP} = 9.7 Hz, C); 137.9 (d, J_{CP} = 8.7 Hz, C); 142.5 (d, J_{CP} = 2.9 Hz, C); 143.1 (d, J_{CP} = 1.6 Hz, C) ppm. ^{31}P NMR δ: –13.16 ppm. HRMS: m/z calcd for $C_{34}H_{30}Cl_2NNaO_6P$ $[M+Na]^+$: 672.1085; found 672.1085.

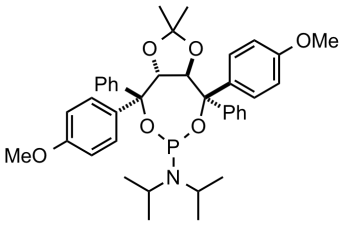
(1R,1'R)-((4R,5R)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis((4-methoxyphenyl)(phenyl) methanol) **4b**:



General Procedure F. Column chromatography with a solvent gradient EtOAc(8→40%)–hexane afforded **4b** in 75% yield as a white solid (*d.r.* = 5:1). ^{1}H NMR (Main isomer) δ: 1.04 (s, 6H); 3.80 (s, 6H); 4.06 (s, 2H); 4.54 (s, 2H); 6.83 (d, *J* = 8.9 Hz, 4H); 7.23 (m, 6H); 7.32 (m, 4H); 7.41 (d, *J* = 8.9 Hz, 4H) ppm. ^{13}C NMR δ: 27.2 (CH_3); 55.2 (CH_3); 77.9 (C); 81.0 (CH); 109.4 (C); 112.6 (CH); 127.5

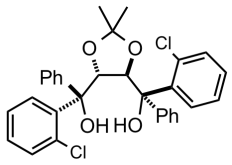
(CH); 127.6 (CH); 128.1 (CH); 129.7 (CH); 134.9 (C); 146.2 (C); 158.7 (C) ppm. HRMS: *m*/*z* calcd for $C_{33}H_{34}NaO_6$ $[M+Na]^+$: 549.2253; found: 549.2258.

(1R,7R)-4-(Diisopropylamino)-9,9-dimethyl-2,6-bis(p-methoxyphenyl)-2,6-biphenyl-3,5,8,10-tetraoxa-4 phosphabicyclo[5.3.0]decane **4b-PN**:



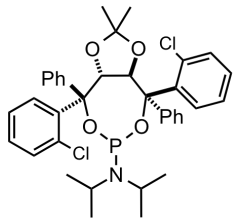
General Procedure B. Column chromatography using deactivated SiO_2 (DCM/c-hexane/TEA:10/90/0.03); DCM/hexane (10/90) eluted **4b-PN;** 58% yield (*d.r.* = 9:1) ^{1}H NMR (Main isomer) : 0.28 (s, 3H), 1.17 (d, *J* = 6.6 Hz, 6H); 1.21 (d, *J* = 6.6 Hz, 6H); 1.42 (s, 3H), 3.72 (s, 3H); 3.76 (s, 3H); 3.92–4.00 (m, 2H); 4.54(d, *J* = 8.8 Hz, 1H); 5.06 (dd, *J* = 8.8, 3.8 Hz, 1H); 6.74–6.81 (m, 5H); 7.14–7.26 (m, 5H); 7.32 (d, *J* = 9.1 Hz, 2H); 7.43 (d, *J* = 7.9 Hz, 2H); 7.59 (d, *J* = 7.8 Hz, 2H); 7.72 (d, *J* = 9.0 Hz, 2H) ppm. ^{13}C NMR δ: 24.1 (d, J_{CP} = 7.1 Hz, CH_3); 24.3 (d, J_{CP} = 7.0 Hz, CH_3); 25.2 (CH_3); 27.8 (CH_3); 44.2 (d, J_{CP} = 14.2 Hz, CH); 55.0 (CH_3); 55.1 (CH_3); 80.4 (d, J_{CP} = 3.4 Hz, C); 80.9 (d, J_{CP} = 10.2 Hz, C); 82.5 (d, J_{CP} = 21.2 Hz, CH); 83.2 (d, J_{CP} = 3.8 Hz, CH); 110.9 (C); 112.5 (CH); 112.8 (CH); 126.7 (CH); 127.0 (CH); 127.1 (CH); 127.3 (CH); 127.4 (CH); 127.7 (CH); 129.8 (d, *J* = 4.3 Hz, CH); 130.1 (CH); 134.5 (d, J_{CP} = 2.0 Hz, C); 134.9 (d, J_{CP} = 1.5 Hz, C); 147.2 (d, J_{CP} = 2.6 Hz, C); 147.7 (C); 158.4 (C); 158.5 (C) ppm. ^{31}P NMR δ: 139.93 ppm. HRMS: *m*/*z* calcd for $C_{39}H_{46}KNO_6P$ $[M+K]^+$: 694.2700; found: 694.2712.

(1R,1'R)-((4R,5R)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis((2-chlorophenyl)(phenyl) methanol) **4c**:



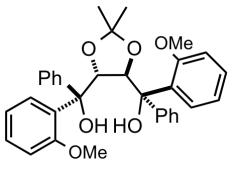
General Procedure F. Column chromatography applying EtOAc/hexane (10/90) afforded **4c** as white foam in 43% yield (*d.r.* = 6:1). ^{1}H NMR (Main isomer) δ: 1.44 (s, 6H); 3.57 (brs, 2H); 5.35 (s, 2H); 6.91–6.96 (m, 8 H); 7.16–7.35 (m, 8H); 7.93 (d, *J* = 7.4 Hz, 2H) ppm. ^{13}C NMR δ: 28.3 (CH_3); 80.4 (C); 81.6 (CH); 113.5 (C); 126.0 (CH); 126.6 (CH); 126.7 (CH); 127.9 (CH); 128.6 (CH); 130.6 (CH); 131.7 (CH); 133.9 (C); 141.7 (C); 142.6 (C) ppm. HRMS: *m*/*z* calcd for $C_{31}H_{28}Cl_2NaO_4$ $[M+Na]^+$: 557.1263; found: 557.1274.

(3aR,4S,8S,8aR)-4,8-Bis(2-chlorophenyl)-N,N-diisopropyl-2,2-dimethyl-4,8-diphenyl-tetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-amine **4c-PN**:



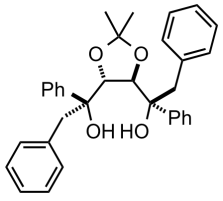
General Procedure **B**. MPLC; a gradient EtOAc(0→10%)–hexane afforded **4c-PN** as a white foam in 15% yield. ^{1}H NMR δ: 0.24 (s, 3H); 0.99 (d, J_{CP} = 7.2 Hz, 6H); 1.15 (d, J_{CP} = 7.2 Hz, 6H); 1.58 (s, 3H); 3.89–3.98 (m, 2H); 4.39–4.44 (m, 1H); 5.99 (dd, *J* = 8.7, 4.7 Hz, 1H); 7.14–8.38 (m, 18H) ppm. ^{13}C NMR δ: 24.0 (pt, J_{CP} = 6.5 Hz, 2CH_3); 24.3 (CH_3), 27.9 (CH_3); 44.3 (d, J_{CP} = 14.0 Hz, CH); 79.0 (d, J_{CP} = 9.7 Hz, C); 81.7 (d, J_{CP} = 14.2 Hz, CH); 84.7 (d, *J* = 3.7 Hz, CH); 110.7 (C); 124.9 (CH); 125.7 (CH); 126.7 (CH); 126.9 (CH); 127.1 (CH); 127.3 (3CH); 128.8 (CH); 128.9 (CH); 131.9 (CH); 132.7 (CH); 135.6 (C); 139.5 (C); 139.6 (C); 139.7 (C); 144.8 (C); 144.9 (C) ppm.* (Product started decomposing after 1 day) ^{31}P NMR δ: 138.13 ppm. HRMS: *m*/*z* calcd for $C_{37}H_{40}Cl_2NNaO_4P$ $[M+Na]^+$: 686.1970; found: 686.1979.

(1R,1'R)-((4R,5R)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis((2-methoxyphenyl)(phenyl) methanol) **4d:**



General procedure F. Column chromatography; EtOAc/hexane (20/80) afforded **4d** in 59% yield. ^{1}H NMR δ: 1.53 (s, 6H); 3.39 (s, 6H); 5.12 (s, 2H); 5.26 (s, 2H); 6.71–6.77 (m, 8H); 6.91 (d, *J* = 8.9 Hz, 4H); 6.9 (dd, *J* = 7.6, 1.8 Hz, 2H); 7.15 (m, 2H); 7.78 (dd, *J* = 7.8, 1.6 Hz, 2H) ppm. ^{13}C NMR δ: 28.2 (CH_3); 55.9 (CH_3); 80.9 (C); 81.5(CH); 112.8 (CH); 113.8 (C); 120.7 (CH); 125.9 (CH); 126.0 (CH); 127.5 (CH); 128.0 (CH); 129.3 (CH); 134.2 (C); 144.2 (C); 157.4 (C) ppm. HRMS: *m*/*z* calcd for $C_{33}H_{34}NaO_6$ $[M+Na]^+$: 549.2253; found: 549.2255.

(1S,1'S)-1,1'-((4R,5R)-(2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(1,2-diphenylethanol) **4e**:

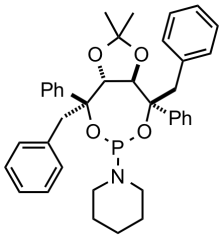


General procedure F. (BnMgBr was prepared according to a published procedure.[119]) A column chromatography with EtOAc/hexane (15/85) afforded **4e** as clear colorless crystals in 32% yield. ^{1}H NMR δ: 1.71 (s, 6H); 2.15 (s, 2H); 3.06 (d, *J* = 13.6 Hz, 2H); 3.31 (d, *J* = 13.5, 2H); 4.63 (s, 2H); 6.63 (dd, *J* = 8.0, 1.6 Hz, 4H);

* 2CHs were not observed

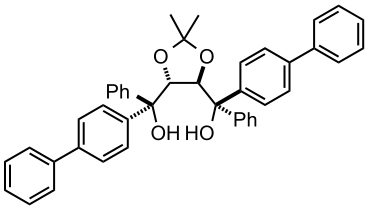
7.02 (m, 16H) ppm. ^{13}C NMR δ: 28.3 (CH_3); 44.2 (CH_2); 77.8 (C); 83.9 (CH); 112.8 (C); 126.0 (CH); 126.5 (CH); 126.6 (CH); 127.8 (CH); 127.9 (CH); 130.6 (CH); 135.7 (C); 142.2 (C) ppm. HRMS: *m*/*z* calcd for $C_{33}H_{34}NaO_4$ $[M+Na]^+$: 517.2353; found: 517.2355.

1-((3aR,4R,8R,8aR)-4,8-Dibenzyl-2,2-dimethyl-4,8-diphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)piperidine **4e-PN[1]**:[143]



Diol **4e** (208 mg, 0.42 mmol) was dissolved in THF (6 mL) and cooled to 0 °C. TEA (0.2 mL, 151 mg, 1.49 mmol) and PCl_3 (50 μL, 51 mg, 0.52 mmol) were added dropwise. The solution was warmed to room temperature for 45 min, cooled again to 0 °C and piperidine (86 μL, 74 mg, 0.87 mmol) was added. The reaction was stirred for 2 h and Et_2O (10 mL) was added. Triethylamine hydrochloride was filtered off over celite, washed with diethyl ether (3x 10 mL) and the filtrate was concentrated in vacuum. The crude product was subjected to chromatography applying EtOAc/hexane (2/98) to afford **4e-PN** in 168 mg (66%) yield. ^{1}H NMR δ: 1.37–1.48 (m, 4H); 1.54 (s, 3H); 1.54–1.58 (m, 2H); 1.65 (s, 3H); 3.08–3.23 (m, 6H); 3.53 (dd, *J* = 14.1, 2.2 Hz, 2H); 4.52 (d, *J* = 9.3 Hz, 1H); 5.13 (dd, *J* = 9.3, 2.7 Hz, 1H); 6.72 (d, *J* = 6.7 Hz, 2H); 6.85 (d, *J* = 8.0 Hz, 2H); 6.93–7.07 (m, 6H); 7.19–7.28 (m, 6H); 7.36–7.38 (m, 2H); 7.60 (d, *J* = 7.3 Hz, 2H) ppm. ^{13}C NMR δ: 25.2 (CH_2); 27.0 ($2CH_2$); 27.4 (CH_3), 27.7 (CH_3), 38.2 (d, J_{CP} = 4.2 Hz, CH_2), 43.2 (CH_2); 44.7 (CH_2); 44.9 (CH_2); 79.3 (d, J_{CP} = 8.9 Hz, C); 79.4 (C); 82.3 (d, J_{CP} = 21.6 Hz, CH); 83.5 (d, J_{CP} = 4.5 Hz, CH); 109.5 (C); 125.6 (CH); 125.8 (CH); 126.6 (d, J_{CP} = 3.0 Hz, CH); 126.7 (CH); 126.9 (CH); 127.0 (2CH); 127.1 (CH); 127.2 (CH); 127.4 (CH); 131.2 (d, J_{CP} = 4.2 Hz, CH); 131.5 (CH); 136.1 (C); 136.6 (C); 144.6 (C); 145.2 (C) ppm. ^{31}P NMR δ: 134.39 ppm. HRMS: *m*/*z* calcd for $C_{38}H_{42}NNaO_4P$ $[M+Na]^+$: 607.2851; found 607.2834.

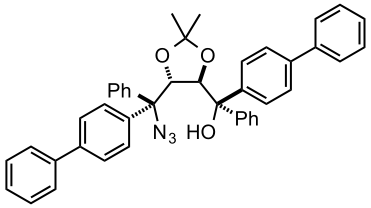
(1R,1'R)-((4R,5R)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(biphenyl-4-yl(phenyl)methanol) **4f**:



General Procedure F. Column chromatography applying EtOAc/Hexane (15/85) gave **4f** as a white solid in 78% yield (*d.r.* = 8.5:1). ^{1}H NMR (Main isomer) δ: 1.80 (s, 6H); 3.88 (s, 2H); 4.66 (s, 2H); 7.26–7.47 (m, 16H); 7.55–7.58 (m, 8H); 7.61–7.64 (m, 4H) ppm. ^{13}C NMR δ: 27.3 (CH_3); 78.2 (C); 81.2 (CH); 109.7 (C); 125.9 (CH); 127.0 (CH); 127.3 (CH); 127.6 (CH); 127.7 (CH); 128.2 (CH); 128.8 (CH); 128.9 (CH); 139.9 (C);

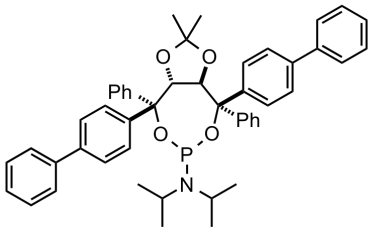
140.7 (C); 141.9 (C); 145.8 (C) ppm. HRMS: *m*/*z* calcd for $C_{43}H_{38}NaO_4$ $[M+Na]^+$: 641.2668; found: 641.2675.

(R)-[1,1'-biphenyl]-4-yl((4S,5S)-5((R)-[1,1'-biphenyl]-4-yl(azido)(phenyl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)(phenyl)methanol **4f-N**:



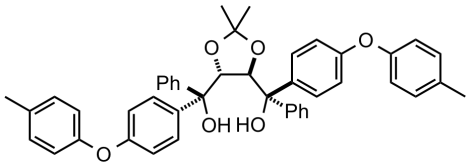
General Procedure C. Column chromatography with EtOAc/hexane (15/85) afforded **4f-N** in 48% yield (epimers (derived from) C_2 : C_1/2 : 1). ^{1}H NMR δ: 1.16 (s, 3H); 1.25 (s, 3H); 3.97 (s, 1H); 4.72 (d, *J* = 7.6 Hz, 1H); 5.00 (d, *J* = 7.6 Hz, 1H); 7.27–7.73 (m, 28H) ppm. ^{13}C NMR δ: 27.2 (CH_3); 27.6 (CH_3); 73.3 (C); 77.8 (C); 79.6 (CH); 82.2 (CH); 110.0 (C); 126.2 (CH); 126.3 (CH); 126.8 (CH); 127.0 (2CH); 127.3 (CH); 127.6 (CH); 127.9 (2CH); 128.3 (CH); 128.5 (2CH); 128.8 (2CH); 128.9 (CH); 129.7 (CH); 138.1 (C); 138.9 (C); 139.8 (C); 140.2 (C); 140.7 (C); 140.8 (C); 143.1 (C); 145.4 (C) ppm. HRMS: *m*/*z* calcd for $C_{43}H_{37}N_3NaO_3$ $[M+Na]^+$: 666.2733; found: 666.2741.

(3aR,4S,8S,8aR)-4,8-Di(biphenyl-4-yl)-N,N-diisopropyl-2,2-dimethyl-4,8-diphenyl-tetrahydro-[1,3]dioxolo[4,5-e][1,3,2]-dioxaphosphepin-6-amine **4f-PN**:



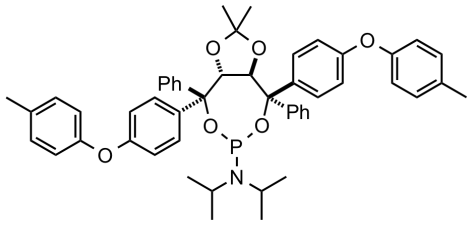
General Procedure B. The crude product was purified by column chromatography using deactivated SiO_2 (*c*-hexane/TEA:97/3). Eluent DCM/c-hexane (10/90), yield 58% (*d.r.* = 10:1). ^{1}H NMR (Main isomer) δ: 0.32 (s, 3H), 1.23 (d, *J* = 6.9 Hz, 6H), 1.28 (d, *J* = 6.9 Hz, 6H), 1.47 (s, 3H), 3.97–4.07 (m, 2H), 4.67 (d, *J* = 8.9 Hz, 1H), 5.25 (dd, *J* = 8.6, 3.6 Hz, 1H), 7.20–7.32 (m, 8H); 7.40 (dd, *J* = 14.6, 7.3 Hz, 4H); 7.48–7.57 (m, 10H); 7.61 (d, *J* = 7.6 Hz, 2H); 7.68 (d, *J* = 7.7 Hz, 2H); 7.91 (d, *J* = 8.6 Hz, 2H) ppm. ^{13}C NMR δ: 24.2 (d, J_{CP} = 7.6 Hz, CH_3); 24.4 (d, J_{CP} = 7.0 Hz, CH_3); 25.2 (CH_3); 27.8 (CH_3); 44.3 (d, J_{CP} = 14.6 Hz, CH); 80.7 (d, J_{CP} = 3.7 Hz, C); 81.1 (d, J_{CP} = 10.4 Hz, C); 82.6 (d, J_{CP} = 21.2 Hz, CH); 83.2 (d, J_{CP} = 3.8 Hz, CH); 111.0 (C); 125.8 (CH); 126.2 (CH); 126.8 (CH); 126.9 (CH); 127.0 (CH); 127.1 (CH); 127.2 (CH); 127.3 (CH); 127.4 (CH); 127.5 (CH); 127.9 (CH); 128.6 (CH); 128.7 (CH); 129.1 (CH); 129.2 (CH); 129.5 (CH); 139.6 (C); 139.7 (C); 140.7 (C); 140.8 (C); 141.3 (d, J_{CP} = 1.6 Hz, C); 141.9 (d, J_{CP} = 1.4 Hz, C); 146.9 (d, J_{CP} = 2.9 Hz, C); 147.4 (C) ppm. ^{31}P NMR δ: 140.45 ppm. HRMS: *m*/*z* calcd for $C_{49}H_{50}NNaO_4P$ $[M+Na]^+$: 770.3375; found: 770.3390.

(1R,1'R)-((4R,5R)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(phenyl(4-(p-tolyloxy)phenyl)-methanol) **4g:**.



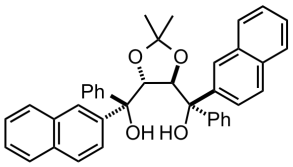
General Procedure F. Column chromatography, EtOAc/hexane (15/85), 69% yield (*d.r.* = 6:1). ^{1}H NMR (Main isomer) δ: 1.04 (s, 6H); 2.32 (s, 6H); 3.75 (s, 2H); 4.60 (s, 2H); 6.90–6.93 (m, 10H); 7.11–7.13 (m, 4H); 7.24–7.37 (m, 8H); 7.43 (d, *J* = 6.6 Hz, 4H) ppm. ^{13}C NMR δ: 20.7 (CH_3); 27.2 (CH_3); 78.0 (C); 81.1 (CH); 109.7 (C); 116.9 (CH); 119.2 (CH); 127.5 (CH); 127.6 (CH); 128.2 (CH); 129.9 (CH); 130.2 (CH); 133.0 (C); 137.2 (C); 145.9 (C); 154.5 (C); 157.0 (C) ppm. HRMS: *m*/*z* calcd for $C_{45}H_{42}NaO_6$ $[M+Na]^+$: 701.2879; found: 701.2865.

(3aR,4S,8S,8aR)-N,N-Diisopropyl-2,2-dimethyl-4,8-diphenyl-4,8-bis(4-(p-tolyloxy)phenyl)tetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-amine **4g-PN**:



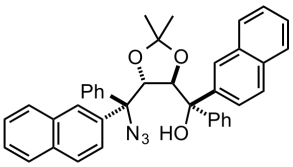
General procedure B. Column chromatography using deactivated SiO_2 (DCM/*c*-hexane/TEA:2/97/3) and a solvent gradient DCM(2→20%)–*c*-hexane afforded **4g-PN** in 44% yield (*d.r.* = 5:1). ^{1}H NMR (Main isomer) δ: 0.34 (s, 3H); 1.17 (d, *J* = 6.8 Hz, 6H); 1.20 (d, *J* = 6.8 Hz, 6H); 1.42 (s, 3H); 2.29 (s, 3H); 2.32 (s, 3H); 3.91–3.97 (m, 2H); 4.54 (d, *J* = 8.6 Hz, 1H); 5.14 (dd, *J* = 8.6, 3.6 Hz, 1H); 6.80–6.86 (m, 6H); 6.94 (d, *J* = 8.2 Hz, 2H); 7.07 (d, *J* = 8.2 Hz, 2H); 7.12 (d, *J* = 8.3 Hz, 2H); 7.19–7.26 (m, 6H); 7.34 (d, *J* = 9.0 Hz, 2H); 7.43 (d, *J* = 7.4 Hz, 2H); 7.62 (d, *J* = 7.2 Hz, 2H); 7.73 (d, *J* = 9.0 Hz, 2H) ppm. ^{13}C NMR δ: 20,6 (CH_3); 20.7 (CH_3); 24.1 (d, J_{CP} = 6.9 Hz, CH_3), 24.3 (d, J_{CP} = 6.9 Hz, CH_3), 25.2 (CH_3), 27.8 (CH_3), 44.3 (d, J_{CP} = 14.6 Hz, CH); 80.3 (d, J_{CP} = 3.2 Hz, C); 81.1 (d, J_{CP} = 10.4 Hz, C); 82.6 (d, J_{CP} = 21.2 Hz, CH); 83.2 (d, J_{CP} = 3.8 Hz, CH); 111.0 (C); 116.5 (CH); 116.9 (CH); 119.0 (CH); 119.7 (CH); 126.8 (CH); 127.1 (CH); 127.2 (CH); 127.3 (CH); 127.5 (CH); 127.8 (CH); 130.0 (CH); 130.1 (CH); 130.2 (CH); 130.3 (CH); 132.8 (C); 133.1 (C); 136.6 (C); 136.8 (C); 146.9 (d, J_{CP} = 1.4 Hz, C); 147.5 (C); 154.1 (C); 154.7 (C); 156.7 (C); 157.0 (C) ppm. ^{31}P NMR δ: 140.22 ppm. HRMS: *m*/*z* calcd for $C_{51}H_{54}NNaO_6P$ $[M+Na]^+$: 830.3586; found: 830.3577.

(1R,1'R)-((4R,5R)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(naphthalen-2-yl(phenyl)-methanol) **4h**:



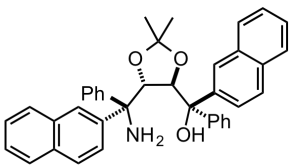
General procedure F. Column chromatography applying EtOAc/hexane (15/85) afforded **4h** as yellow foam in 75% yield (*d.r.* = 3.5:1). ^{1}H NMR (Main isomer) δ: 1.06 (s, 6H); 4.21 (s, 2H); 4.70 (s, 2H); 7.21–7.23 (m, 5H); 7.31–7.34 (m, 5H); 7.47–7.50 (m, 4H); 7.61 (dd, *J* = 8.6, 1.8 Hz, 2H); 7.76 (m, 2H), 7.84 (m, 4H); 8.13 (s, 2H) ppm. ^{13}C NMR δ: 27.3 (CH_3); 78.3 (C); 81.2 (CH); 109.6 (C); 125.9 (CH); 126.0 (CH); 126.6 (CH); 127.0 (CH); 127.3 (CH); 127.4 (CH); 127.7 (2CH); 128.2 (CH); 128.5 (CH); 132.6 (2C); 140.4 (C); 145.7 (C) ppm. HRMS: *m*/*z* calcd for $C_{39}H_{34}NaO_4$ $[M+Na]^+$: 589.2355; found: 589.2355.

(S)-((4R,5S)-5-((S)-Azido(naphthalen-2-yl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)(naphthalen-2-yl)(phenyl)methanol **4h-N**:



General Procedure C. Column chromatography applying EtOAc/hexane (15/85) afforded **4h-N** in 62% yield (epimers 2:1). ^{1}H NMR (Main isomer) δ: 1.12 (s, 3H); 1.21 (s, 3H); 3.90 (s, 1H); 4.78 (d, *J* = 7.3 Hz, 1H); 4.97 (d, J = 7.3 Hz, 1H); 7.12–7.86 (m, 23H); 8.05 (s, 1H) ppm. ^{13}C NMR δ: 27.1 (CH_3); 27.7 (CH_3); 73.7 (C); 78.0 (C); 79.9 (CH); 82.3 (CH); 109.9 (C); 125.9 (CH); 126.0 (CH); 126.2 (CH); 126.3 (CH); 126.5 (CH); 126.7 (CH); 126.9 (CH); 127.0 (CH); 127.2 (CH); 127.4 (CH); 127.4 (CH); 127.5 (2CH); 127.8 (CH); 127.9 (CH); 128.3 (CH); 128.5 (CH); 128.6 (CH); 128.7 (CH); 129.7 (CH); 132.5 (C); 132.6 (C); 132.7 (C); 132.8 (C); 138.1 (C); 141.6 (C); 145.2 (C); 145.4 (C) ppm. HRMS: *m*/*z* calcd for $C_{39}H_{33}N_3NaO_3$ $[M+Na]^+$: 614.2420; found: 614.2405.

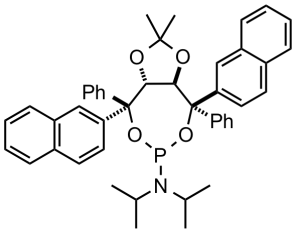
(S)-((4R,5S)-5-((S)-Amino(naphthalen-2-yl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)(naphthalen-2-yl)(phenyl)methanol **4h-NH**:



To a suspension of $LiAlH_4$ (21 mg, 0.56 mmol) in THF (1.5 mL) at 0 °C was added a solution of the monoazide **4h-N** (123 mg, 0.2 mmol) in THF (1.5 mL). After stirring at room temperature for 18 h, 1N NaOH (1.5 mL) was added carefully and the mixture was diluted with Et_2O (6 mL). Na_2SO_4 was added and the reaction mixture was stirred further for 2 h at room temperature, filtered through a pad of celite with the aid of Et_2O. The filtrate was dried over K_2CO_3 and concentrated.

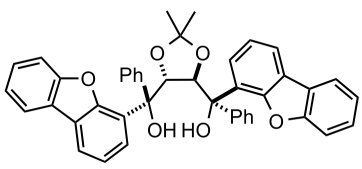
The residue was purified by a column chromatography using Et_2O /hexane (30/70) to give **4h-NH** in 59% yield (epimers = 1.5:1). (Main isomer) ^{1}H NMR δ: 0.91 (s, 3H); 1.35 (s, 3H); 2.32 (s, 2H); 4.32 (d, *J* = 8.3 Hz, 1H); 4.44 (d, *J* = 8.3 Hz, 1H); 7.03–8.06 (m, 23H); 8.26 (s, 1H) 9.1 (br.s, 1H) ppm. ^{13}C NMR δ: 26.5 (CH_3), 27.4 (CH_3), 62.7 (C); 76.3 (C); 80.1 (CH); 82.3 (CH); 108.3 (C); 125.4 (CH); 125.6 (CH); 125.7 (CH); 125.8 (CH); 126.2 (CH); 126.6 (CH); 126.7 (CH); 127.1 (CH); 127.2 (CH); 127.3 (CH); 127.4 (CH); 127.5 (CH); 127.6 (CH); 127.7 (2CH); 127.8 (2CH); 128.4 (CH); 128.5 (CH); 129.5 (CH); 132.4 (C); 132.6 (C); 132.8 (C); 132.9 (C); 138.6 (C); 140.7 (C); 142.1 (C); 146.4 (C) ppm. HRMS: *m*/*z* calcd for $C_{39}H_{36}NO_3$ $[M+H]^+$: 566.2695; found: 566.2695.

(3aR,4S,6S,8S,8aS)-N,N-Diisopropyl-2,2-dimethyl-4,8-di(naphthalen-2-yl)-4,8-diphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-amine **4h-PN**:



General procedure B. Column chromatography using deactivated SiO_2 (DCM/*c*-hexane/TEA:2/95/3) and a gradient DCM(2→20%)–*c*-hexane afforded **4h-PN** in 39% yield (*d.r.* = 6:1). (Main isomer) ^{1}H NMR δ: 0.15 (s, 3H); 1.23 (d, J_{HP} = 7.1 Hz, 6H); 1.32 (d, J_{HP} = 6.8 Hz, 6H); 1.56 (s, 3H), 4.02–4.14 (m, 2H); 4.75 (d, *J* = 8.7 Hz, 1H); 5.41 (dd, *J* = 8.7, 3.8 Hz, 1H); 7.15–7.30 (m, 5H); 7.40–7.54 (m, 9H); 7.65 (t, *J* = 7.9 Hz, 4H); 7.75 (d, *J* = 8.6 Hz, 2H); 7.85 (d, *J* = 7.4 Hz, 2H); 8.08 (s, 1H); 8.6 (s, 1H) ppm. ^{13}C NMR δ: 24.2 (d, J_{CP} = 7.6 Hz, CH_3), 24.4 (d, J_{CP} = 6.9 Hz, CH_3), 25.3 (CH_3), 27.9 (CH_3), 44.3 (d, J_{CP} = 14.0 Hz, CH); 80.6 (d, J_{CP} = 4.6 Hz, C); 81.2 (d, J_{CP} = 10.2 Hz, C); 82.7 (d, J_{CP} = 21.9 Hz, CH); 83.5 (d, J_{CP} = 3.6 Hz, CH); 111.0 (C); 125.6 (CH); 125.8 (CH); 125.9 (CH); 126.0 (CH); 126.2 (CH); 126.8 (CH); 126.9 (CH); 127.0 (CH); 127.1 (CH); 127.2 (CH); 127.2 (CH); 127.3 (CH); 127.4 (CH); 127.4 (CH); 127.5 (CH); 127.6 (CH); 127.8 (CH); 127.9 (CH); 128.5 (CH); 128.6 (CH); 132.4 (C); 132.5 (C); 132.6 (C); 132.7 (C); 139.9 (d, J_{CP} = 1.5 Hz, C); 140.6 (d, J_{CP} = 1.7 Hz, C); 146.5 (d, J_{CP} = 3.7 Hz, C); 147.3 (C) ppm. ^{31}P NMR δ: 140.14 ppm.

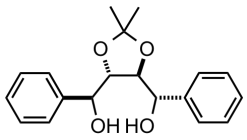
(1R,1'R)-((4R,5R)(2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(dibenzo[b,d]furan-4-yl(phenyl)methanol **4i:**



General procedure F. After filtering through short plug of silica gel, the crude mixture was subjected to MPLC using EtOAc/hexane (15/85) to afford **4i** as yellow foam in 50% yield (*d.r.* = 2:1). (Main isomer) ^{1}H NMR δ: 0.98 (s, 6H);

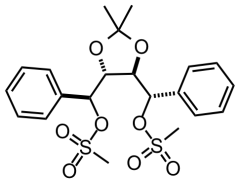
3.73 (s, 2H); 5.61 (s, 2H); 6.96–7.62 (m, 24H) ppm. ^{13}C NMR δ: 27.6 (CH_3); 79.2 (C); 82.1 (CH); 111.0 (C); 111.7 (CH); 120.0 (CH); 120.5 (CH); 122.4 (CH); 122.8 (CH); 123.9 (C); 124.9 (C); 126.9 (CH); 127.2 (CH); 127.4 (CH); 127.9 (CH); 128.1 (CH); 129.7 (C); 144.4 (C); 153.6 (C); 155.7 (C) ppm. HRMS: *m*/*z* calcd for $C_{43}H_{34}NaO_6$ $[M+Na]^+$: 669.2253; found: 669.2242.

((4S,5S)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(phenylmethanol) **6a:** [144]



General Procedure H: To a solution of 18-C-6 (380 mg, 1.44 mmol) in THF (3 mL) was added K-Selectride (0.96 mL of 1 M solution in THF, 0.96 mmol) at room temperature and the mixture was stirred for 5 min. Then, a solution of diketone **19a** (75 mg, 0.24 mmol) in THF (3 mL) was added at –78 °C dropwise under argon. The resulting deep orange brown solution was stirred for 4.5 h at the same temperature and the reaction was quenched with aqueous 2 N NaOH (1 mL) followed by H_2O_2 (0.5 mL of 30% (w/v) solution in H_2O). At this point the mixture became colorless and 2 phases were formed. It was then allowed to warm up to room temperature and stirred for 3 h. The suspension was filtered through a pad of celite and the celite pad was washed with Et_2O (10 mL). The filtrate was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography applying a solvent gradient EtOAc(15→50%)–hexane. Diol **6a** was obtained as white crystalline solid in 70 mg (93%). ^{1}H NMR δ: 1.43 (s, 6H); 2.75 (d, *J* = 5.4 Hz, 2H); 4.04–4.17 (m, 4H); 7.13–7.29 (m, 10H) ppm*.

(1S,1'S)-((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(phenyl-methylene)dimethane-sulfonate **6a-M**:[145]

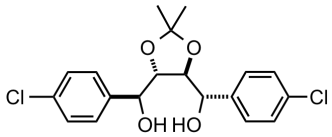


To a solution of methanesulfonyl chloride (62 µL, 91.6 mg, 0.8 mmol) in DCM (3 mL) at –20 °C was added a solution of **6a** (100 mg, 0.31 mmol) in DCM (3 mL) followed by TEA (0.13 mL, 95.3 mg, 0.94 mmol). The mixture was stirred at the same temperature for 1.5 h and sat. aq. $NaHCO_3$ solution (2 mL) was added. The mixture was concentrated to 2.5 mL and diluted with EtOAc (12 mL). The organic phase was washed with mixture of water/brine/sat. $NaHCO_3$ (1/2/1, 4× 3 mL) and sat. aq. $NaHCO_3$ solution (2× 3 mL), filtered through Celite, dried over $MgSO_4$ and concentrated in vacuum to afford 102 mg of **6a-M** (70%). The resulting clear colorless oil was used directly in the next step. ^{1}H

* Spectroscopic datas are in accordance with literature.

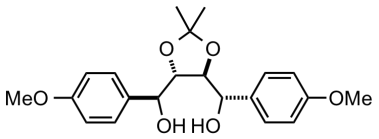
NMR δ: 1.49 (s, 6H); 2.75 (s, 6H); 4.25 (d, *J* = 3.3 Hz, 2H); 5.03 (d, *J* = 3.3 Hz, 2H); 7.18–7.21 (m, 4H); 7.31–7.40 (m, 6H) ppm. ^{13}C NMR δ: 27.4 (CH_3); 39.2 (CH_3); 79.4 (CH); 82.7 (CH); 111.9 (C); 127.7 (CH); 129.1(CH); 129.7 (CH); 134.6 (C) ppm. HRMS: *m*/*z* calcd for $C_{21}H_{26}NaO_8S_2$ $[M+Na]^+$: 493.0967; found: 493.0987.

((4S,5S)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis((4-chlorophenyl)methanol) **6b**:



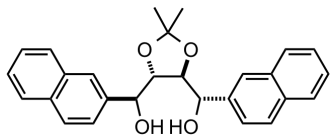
General Procedure H. Column chromatography using a solvent gradient EtOAc(15 → 30%)–hexane gave **6b** as white needls. Yield; 84%; mp 151–153 °C; $[\alpha]_D^{20}$ +21.2 (*c* 0.98, $CHCl_3$). ^{1}H NMR δ: 1.46 (s, 6H); 2.71 (d, *J* = 5.6 Hz, 2H); 4.01–4.05 (m, 2H); 4.21–4.28 (m, 2H); 7.07–7.10 (m, 4H); 7.21−7.25 (m, 4H) ppm. ^{13}C NMR δ: 27.8 (CH_3); 73.7 (CH); 81.4 (CH); 110.9 (C); 128.1 (CH); 128.7 (CH); 134.2 (C); 138.0 (C) ppm. HRMS: *m*/*z* calcd for $C_{19}H_{19}Cl_2O_4$ $[M–H]^–$: 381.0660; found: 381.0657.

((4S,5S)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis((4-methoxyphenyl)methanol) **6c**:[69]



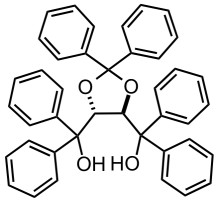
General Procedure H. Column chromatography using EtOAc/hexane (35/65) afforded **6c** as clear colorless oil in 66% yield. ^{1}H NMR δ: 1.48 (s, 6H); 2.62 (d, *J* = 5.2 Hz, 2H); 3.77 (s, 6H); 4.02–4.09 (m, 2H); 4.11–4.18 (m, 2H); 6.77 (d, *J* = 8.6 Hz, 4H); 7.07 (d, *J* = 8.6 Hz, 4H) ppm.*

((4S,5S)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(naphthalen-2-ylmethanol) **6d:**



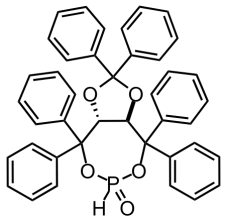
General Procedure H. Column chromatography using EtOAc/hexane (30/70) afforded **6d** in 84% yield. Mp 186–188 °C; $[\alpha]_D^{20}$ +45.5 (*c* 0.99, $CHCl_3$). ^{1}H NMR δ: 1.52 (s, 6H); 2.87 (d, *J* = 5.6 Hz, 2H); 4.23–4.27 (m, 2H), 4.33–4.38 (m, 2H); 7.18 (dd, *J* = 8.7, 1.9 Hz, 2H); 7.41–7.45 (m, 6H); 7.52 (d, *J* = 8.7 Hz, 2H); 7.61–7.71 (m, 4H) ppm. ^{13}C NMR δ: 27.9 (CH_3); 74.7 (CH); 81.9 (CH); 111.0 (C); 124.1 (CH); 125.9 (CH); 126.1 (CH); 126.3 (CH); 127.7 (CH); 127.8 (CH); 128.4 (CH); 133.0 (C); 133.2 (C); 137.0 (C) ppm. HRMS: *m*/*z* calcd for $C_{27}H_{25}O_4$ $[M–H]^–$: 413.1753; found: 413.1763.

((4R,5R)-2,2-Diphenyl-1,3-dioxolane-4,5-diyl)bis(diphenylmethanol) **12a**:[146]



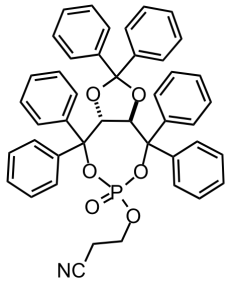
General procedure A. MPLC with a solvent gradient EtOAc(3→30%)–heptane afforded **12a** in 75% yield. ^{1}H NMR δ: 2.12 (s, 2H); 5.60 (s, 2H); 6.95–7.56 (m, 30H) ppm*.

(3aS,6R)-2,2,4,4,8,8-Hexaphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide **12a-POH**:



General procedure D. MPLC applying a solvent gradient EtOAc (5→30%)–heptane afforded **12-POH** in 36% yield. Mp 155–157 °C; ^{1}H NMR δ: 5.52 (d, *J* = 8.6 Hz, 1H); 5.60 (d, *J* = 8.6 Hz, 1H); 6.74 (d, *J* = 8.2 Hz, 2H); 6.87 (d, *J* = 8.2Hz, 2H); 6.91–7.01 (m, 7H); 7.05 (d, J_{HP} = 762.8 Hz, 1H); 7.07 (pst, *J* = 7.2 Hz, 4H); 7.13–7.23(m, 5H); 7.34–7.47 (m, 6H); 7.65 (d, *J* = 7.3 Hz, 4H) ppm. ^{13}C NMR δ: 81.8 (d, J_{CP} = 1.4 Hz, CH); 81.9 (d, J_{CP} = 2.9 Hz, CH); 88.1 (d, J_{CP} = 9.3 Hz, C); 88.5 (d, J_{CP} = 8.9 Hz, C); 114.2 (C); 125.5 (CH); 125.6 (CH); 126.8 (CH); 126.9 (CH); 127.2 (CH); 127.5 (2CH); 127.7 (2CH); 127.8 (2CH); 127.9 (2CH); 128.3 (2CH); 128.5 (CH); 128.7 (2CH); 138.5 (d, J_{CP} = 6.5 Hz, C); 138.7 (d, J_{CP} = 8.4 Hz, C); 141.7 (C); 142.1 (C); 143.1 (d, J_{CP} = 2.8 Hz, C); 143.5 (d, J_{CP} = 3.8 Hz, C) ppm. ^{31}P NMR δ: –4.16 ppm.

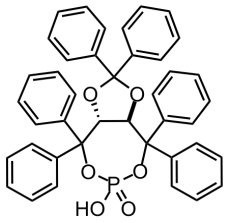
3-(((3aR,8aR)-6-Oxido-2,2,4,4,8,8-hexaphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)oxy)propanenitrile:



General Procedure G. MPLC applying a gradient mixture of EtOAc(10→65%)–heptane afforded the product in 48% yield. Mp 162–165 °C. ^{1}H NMR δ: 1.93–2.03 (m, 1H); 2.09–2.17 (m, 1H); 3.41–3.48 (m, 1H); 3.76–3.82 (m, 1H); 5.42 (d, *J* = 8.3 Hz, 1H); 5.74 (d, *J* = 8.3 Hz, 1H); 6.67 (d, *J* = 7.3 Hz, 2H); 6.84–7.06 (m, 11H); 7.10−7.17 (m, 5H); 7.22–7.24 (m, 2H); 7.34–7.46 (m, 6H) 7.59 (d, *J* = 7.0 Hz, 2H); 7.66 (d, *J* = 7.2 Hz, 2H) ppm. ^{31}P NMR δ: –12.43 ppm. HRMS: *m*/*z* calcd for $C_{44}H_{36}NNaO_6P$ $[M+Na]^+$: 728.2178; found: 728.2187.

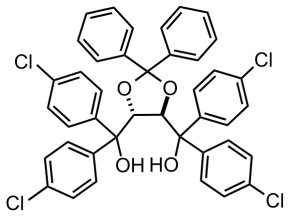
* Spectroscopic datas are in accordance with literature.

(3aR,8aR)-6-Hydroxy-2,2,4,4,8,8-hexaphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide **12a-POOH:**



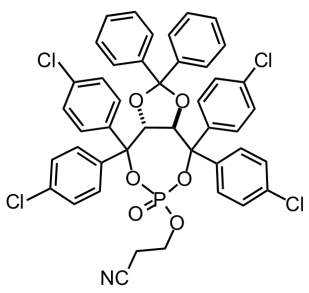
General procedure J:[142] Phosphepinyloxypropannitrile **12a-POR**[1] (R^1 = propionitrile) (100 mg, 0.14 mmol) was dissolved in dry DCM (1.5 mL) and 1,8-diazabicyclo[5,4,0]-undec-7-ene (DBU) (22 µL, 23 mg, 0.15 mmol) was added at room temperature. The reaction was monitored by TLC. After 1 h, the solvent was removed and the residue was dissolved in MeOH and washed through a short column of Dowex-50. The solvent was again removed and **12a-POOH** was obtained as a white solid in 91 mg (quantitative) yield. Mp 162–163 °C; $[\alpha]_{578}^{20}$ -66.9 (c 0.98, $CHCl_3$). ^{1}H NMR δ: 5.49 (s, 2H); 6.80–6.87 (m, 8H); 6.95 (pst, *J* = 7.3 Hz, 2H); 7.01 (pst, *J* = 7.0 Hz, 4H); 7.08 (pst, *J* = 7.3 Hz, 2H); 7.15 (d, *J* = 7.3 Hz, 4H); 7.24–7.33 (m, 6H); 7.59 (d, *J* = 6.9 Hz, 4H); 7.69 (br.s, 1H) ppm. ^{13}C NMR δ: 81.5 (CH); 87.4 (d, J_{CP} = 6.8 Hz, C); 113.7 (C); 125.5 (CH); 126.9 (CH); 127.0 (CH); 127.4 (2CH); 127.6 (CH); 128.1 (CH); 128.2 (CH); 128.3 (CH); 139.0 (d, J_{CP}= 8.1 Hz, C); 142.1 (C); 143.4 (d, J_{CP} = 2.8 Hz, C) ppm. ^{31}P NMR δ: –8.19 ppm. HRMS: *m*/*z* calcd for $C_{41}H_{32}O_6P$ $[M–H]^-$: 651.1942; found: 651.1942.

((4R,5R)-2,2-Diphenyl-1,3-dioxolane-4,5-diyl)bis(bis(4-chlorophenyl)methanol) **12b**:



*General Procedure A***.** MPLC applying a solvent gradient EtOAc(1→10%)–heptane afforded **12b** in 65% yield**.** Mp 122–125 °C; $[\alpha]_D^{20}$ -124 (*c* 0.99, $CHCl_3$) ^{1}H NMR δ: 1.97 (s, 2H); 5.42 (s, 2H); 6.82 (d, *J* = 8.8, 4H); 6.87 (d, *J* = 8.8 Hz, 4H); 7.19–7.34 (m, 10H); 7.30–7.32 (m, 4H); 7.39 (d, *J* = 8.9 Hz, 4H) ppm. ^{13}C NMR δ: 79.1 (C); 83.2 (CH); 112.9 (C); 124.7 (CH); 126.8 (CH); 128.1 (CH); 128.2 (CH); 128.3 (CH); 128.4 (CH); 128.8 (CH); 132.9 (C); 133.1 (C); 139.9 (C); 144.1 (C), 144.2 (C) ppm. HRMS: *m*/*z* calcd for $C_{41}H_{30}Cl_4NaO_4$ $[M+Na]^+$: 751.0766; found: 751.0754.

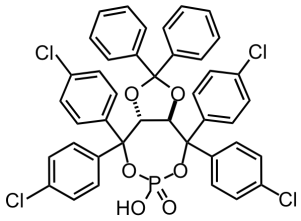
3-(((3aR,8aR)-4,4,8,8-Tetrakis(4-chlorophenyl)-6-oxido-2,2-diphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)oxy)propanenitrile:



General Procedure G. MPLC applying a solvent gradient of EtOAc (10→66%)–heptane afforded the product in 66% yield. ^{1}H NMR δ: 2.26–2.33 (m, 1H); 2.42–2.50 (m, 1H); 3.65–3.74 (m, 1H); 3.99–4.06 (m, 1H); 5.42 (d, *J* = 8.0 Hz, 1H); 5.50 (d,

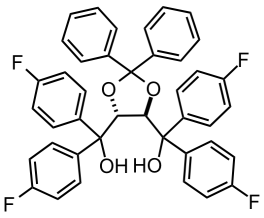
J = 8.0 Hz, 1H); 6.74 (d, *J* = 8.2 Hz, 2H); 6.78 (d, *J* = 8.8 Hz, 2H); 6.85 (pst, *J* = 8.8 Hz, 4H); 7.00–7.06 (m, 6H); 7.11 (ps.t, *J* = 8.0 Hz, 2H); 7.17–7.23 (m, 2H); 7.39 (d, *J* = 8.8 Hz, 2H); 7.43 (d, *J* = 8.9 Hz, 2H); 7.52 (ps.t, *J* = 8.8 Hz, 4H) ppm. ^{31}P NMR δ: –12.45 ppm.

(3aR,8aR)-4,4,8,8-Tetrakis(4-chlorophenyl)-6-hydroxy-2,2-diphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide **12b-POOH**:



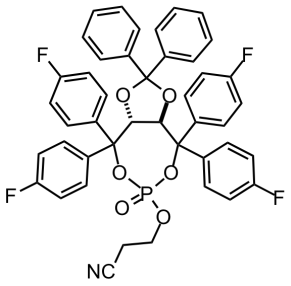
General Procedure J. The ammonium salt of the phosphate was dissolved in MeOH and washed through a short plug of Dowex-50. The solvent was removed under vacuo affording **12b-POOH** in quantitative yield. Mp 183–185 °C; $[\alpha]_D^{20}$ -70.8 (*c* 0.89 $CHCl_3$). ^{1}H NMR δ: 5.38 (s, 2H); 6.81 (d, *J* = 8.8 Hz, 4H); 6.83 (d, *J* = 8.2 Hz, 4H); 7.01 (d, *J* = 8.8 Hz, 4H); 7.12 (ps.t, *J* = 7.6 Hz, 4H); 7.23–7.28 (m, 2H); 7.34 (d, *J* = 8.7 Hz, 4H); 7.48 (d, *J* = 8.7 Hz, 4H) ppm. ^{13}C NMR δ: 81.5 (CH); 86.9 (d, J_{CP} = 6.9 Hz, C); 115.0 (C); 125.4 (CH); 127.5 (CH); 127.9 (2CH); 128.1 (CH); 128.7 (CH); 129.4 (CH); 134.2 (C); 134.5 (C); 136.2 (d, J_{CP} = 8.2 Hz, C); 141.0 (d, J_{CP} = 3.6 Hz, C); 141.5 (C) ppm. ^{31}P NMR δ: –8.42 ppm. HRMS: *m*/*z* calcd for $C_{41}H_{28}Cl_4O_6P$ $[M–H]^-$: 789.0348; found: 789.0373.

((4R,5R)-2,2-Diphenyl-1,3-dioxolane-4,5-diyl)bis(bis(4-fluorophenyl)methanol) **12c**:



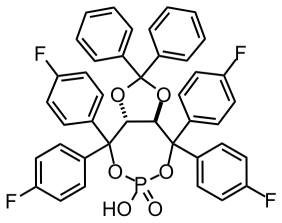
General Procedure A. MPLC applying a solvent gradient EtOAc(2→16%)–heptane afforded **12c** in 65% yield**.** Mp 197 °C; $[\alpha]_D^{20}$ +177 (*c* 1.05, $CHCl_3$). ^{1}H NMR δ: 2.01 (s, 2H); 5.41 (s, 2H); 6.59 (d, *J* = 8.8, 4H); 6.87–6.97 (m, 8H); 7.18–7.20 (m, 6H); 7.27–7.30 (m, 4H); 7.41 (d, *J* = 5.3 Hz, 2H); 7.43 (d, *J* = 5.3 Hz, 2H) ppm. ^{13}C NMR δ: 78.9 (C); 83.5 (CH); 112.6 (C); 114.7 (d, J_{CF} = 21.2 Hz, CH); 114.8 (d, J_{CF} = 21.2 Hz, CH); 124.8 (CH); 127.4 (d, J_{CF} = 8.8 Hz, CH); 128.2 (CH); 128.7 (CH); 128.8 (d, J_{CF} = 8.1 Hz, CH); 137.8 (d, J_{CF} = 2.8 Hz, C); 141.4 (d, J_{CF} = 3.0 Hz, C); 144.2 (C); 161.4 (d, J_{CF} = 247.2 Hz, C); 161.8 (d, J_{CF} = 247.2 Hz, C) ppm. HRMS: *m*/*z* calcd for $C_{41}H_{30}F_4NaO_4$ $[M+Na]^+$: 685.1978; found: 685.1981.

3-(((3aR,8aR)-4,4,8,8-Tetrakis(4-fluorophenyl)-6-oxido-2,2-diphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)oxy)propanenitrile:



General Procedure G. MPLC applying a solvent gradient EtOAc (30→90%)–heptane affording the product in 54% yield. ^{1}H NMR δ: 2.22–2.29 (m, 1H); 2.39–2.45 (m, 1H); 3.60–3.68 (m, 1H); 3.95–4.02 (m, 1H); 5.43 (d, *J* = 8.1 Hz, 1H); 5.56 (d, *J* = 8.1 Hz, 1H); 6.51 (t, *J* = 8.7 Hz, 2H); 6.57 (t, *J* = 8.7 Hz, 2H); 6.75 (d, *J* = 8.0 Hz, 2H); 6.90 (d, *J* = 8.0 Hz, 2H); 7.01–7.22 (m, 14H); 7.54−7.61 (m, 4H) ppm. ^{13}C NMR δ: 19.4 (d, J_{CP} = 7.4 Hz, CH_2); 62.4 (d, J_{CP} = 4.8 Hz, CH_2); 80.6 (CH); 81.8 (CH); 87.8 (d, J_{CP} = 6.4 Hz, C); 88.1 (d, J_{CP} = 6.4 Hz, C); 114.1 (d, J_{CF} = 21.6 Hz, CH); 114.4 (d, J_{CF} = 21.4 Hz, CH); 115.5 (d, J_{CF} = 21.4 Hz, CH); 115.7 (d, J_{CF} = 21.4 Hz, CH) 115.0 (C); 115.9 (C); 125.3 (2CH); 127.8 (2CH); 128.0 (2CH); 128.7 (d, J_{CF} = 8.4 Hz, CH); 129.1 (d, J_{CF} = 8.1 Hz, CH); 129.8 (d, J_{CF} = 8.1 Hz, CH); 130.2 (d, J_{CF} = 8.2 Hz, CH); 133.4 (C); 133.9 (C); 138.6 (C); 139.0 (C); 141.6 (C); 141.7 (C); 162.3 (d, J_{CF} = 248 Hz, 2C); 162.6 (d, J_{CF} = 249 Hz, C); 162.7 (d, J_{CF} = 249 Hz, C) ppm. ^{31}P NMR δ: –12.49 ppm.

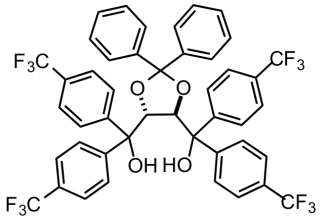
(3aR,8aR)-4,4,8,8-Tetrakis(4-fluorophenyl)-6-hydroxy-2,2-diphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide **12c-POOH**:



General Procedure J. The ammonium salt of the phosphate was dissolved in MeOH and washed through a short plug of Dowex-50. The solvent was removed under vacuum affording **12c-POOH** in 90% yield. Mp 135–136 °C; $[\alpha]_D^{20}$ -50.84 (*c* 1.07 $CHCl_3$). ^{1}H NMR δ: 5.37(s, 2H); 6.48 (t, *J* = 8.8 Hz, 4H); 6.82 (d, *J* = 6.8 Hz, 4H); 6.97–7.09 (m, 12H); 7.17 (t, *J* = 7.4Hz, 2H); 7.48–7.52 (m, 4H) ppm. ^{13}C NMR δ: 81.7 (CH); 88.7 (d, J_{CP} = 6.7 Hz, C); 114.1 (d, J_{CF} = 21.2 Hz, CH); 114.6 (C); 115.3 (d, J_{CF} = 21.2 Hz, CH); 125.4 (CH); 127.9 (2CH); 128.6 (d, J_{CF} = 8.6 Hz, CH); 129.9 (d, J_{CF} = 8.8 Hz, CH); 134.1 (dd, $J_{CP,CF}$ = 8.8, 3.2 Hz, C); 138.9 (t, *J* = 2.8 Hz, C*); 141.8 (C); 162.2 (d, J_{CF} = 246.6 Hz, C); 162.5 (d, J_{CF} = 248.2, C) ppm. ^{31}P NMR δ: –8.87 ppm. HRMS: *m*/*z* calcd for $C_{41}H_{28}F_4O_6P$ $[M–H]^-$: 723.1560; found: 723.1588.

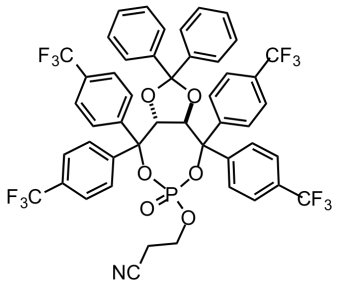
* It was not clear whether the coupling was between C-F or C-P

((4R,5R)-2,2-Diphenyl-1,3-dioxolane-4,5-diyl)bis(bis(4-(trifluoromethyl)phenyl)methanol) **12d**:



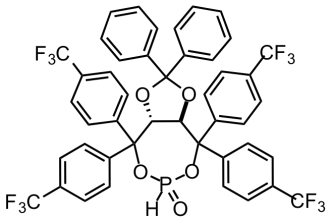
General Procedure A. MPLC applying a gradient mixture of EtOAc (2→14%)–heptane afforded **12d** in 61% yield**.** Mp 236–240 °C; $[\alpha]_D^{20}$ +135 (*c* 0.97, $CHCl_3$)**.** ^{1}H NMR δ: 2.16 (s, 2H); 5.59 (s, 2H); 7.07 (d, *J* = 8.4 Hz, 4H); 7.15 (d, *J* = 8.4 Hz, 4H); 7.21–7.24 (m, 6H); 7.31–7.33 (m, 4H); 7.55 (d, *J* = 8.6 Hz, 4H); 7.59 (d, *J* = 8.6 Hz, 4H) ppm. ^{13}C NMR δ: 79.4 (C); 83.1 (CH); 113.3 (C); 123.6 (q, J_{CF} = 272.7 Hz, C); 123.7 (q, J_{CF} = 272.8 Hz; C); 124.6 (CH); 125.0–125.3 (2CH); 125.8 (CH); 127.2 (CH); 128.6 (CH); 128.9 (CH); 129.2 (q, J_{CF} = 33.2 Hz, C); 129.6 (q, J_{CF} = 32.6 Hz, C) 143.7 (C); 144.8 (C); 148.8 (C) ppm. HRMS: *m*/*z* calcd for $C_{45}H_{29}F_{12}O_4$ $[M–H]^–$: 861.1874; found: 861.1872

3-(((3aR,8aR)-6-oxido-2,2-diphenyl-4,4,8,8-tetrakis(4-(trifluoromethyl)phenyl)tetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)oxy-)-propanenitrile:



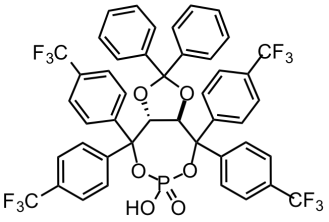
General Procedure G. MPLC applying a solvent gradient EtOAc (3→40%)–heptane afforded the product in 46% yield. ^{1}H NMR δ: 2.33–2.40 (m, 1H); 2.49–2.57 (m, 1H); 3.81–3.88 (m, 1H); 4.10–4.18 (m, 1H); 5.56 (d, *J* = 8.0 Hz, 1H); 5.61 (d, *J* = 8.0 Hz, 1H); 6.78–6.84 (m, 4H); 7.02–7.30 (m, 14H); 7.71–7.77 (m, 8H) ppm. ^{31}P NMR δ: –12.18 ppm

As a side product *(3aR,8aR)-2,2-Diphenyl-4,4,8,8-tetrakis(4-(trifluoro-methyl-)phenyl) tetrahydro-[1,3]dioxolo[4,5-e][1,3,2]-dioxaphosphepine 6-oxide* **12d-POH** was formed in 28% yield. Mp 145–146 °C ^{1}H NMR δ: 5.34 (d, *J* = 8.0 Hz, 1H); 5.71(d, *J* = 8.0 Hz, 1H); 6.65 (d, *J* = 8.4 Hz, 2H); 6.75 (d, *J* = 8.0 Hz, 2H); 6.90 – 7.07 (m, 12H); 7.13 (d, J_{HP} = 760 Hz, 1H); 7.27 (d, *J* = 8.3 Hz, 2H); 7.59–7.69 (m, 8H) ppm. ^{13}C NMR δ: 81.5 (d, J_{CP} = 2.6 Hz, CH); 82.6 (d, J_{CP} = 2.4 Hz, CH); 86.9 (d, J_{CP} = 8.6 Hz, C); 89.3 (d, J_{CP} = 11.4 Hz, C); 116.5 (C); 123.6 (q, J_{CF} = 271.1 Hz, C); 123.7 (q, J_{CF} = 272.4 Hz, 2C); 123.8 (q, J_{CF} = 273.3 Hz, C); 124.3 (CH); 124.4 (CH); 124.9 (CH); 125.1 (CH); 125.9 (q, J_{CF} = 3.7 Hz, CH); 126.0 (d, J_{CF} = 3.7 Hz, CH); 127.0 (CH); 127.2 (CH); 128.0 (CH); 128.1 (CH); 128.2 (CH); 128.5 (CH); 128.6 (CH); 129.0 (CH); 130.3 (q, J_{CF} = 32.2 Hz, C); 130.4 (q, J_{CF} = 33.1 Hz, CH); 131.2 (q, J_{CF} = 32.8 Hz, C); 131.3 (q, J_{CF} = 32.2 Hz, C); 140.5 (C); 140.7



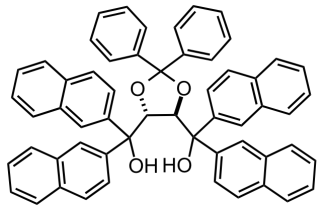
(C); 141.2 (C); 141.3 (C); 145.8 (C); 146.6 (q, J_{CF} = 5.2 Hz, C) ppm. ^{31}P NMR δ: –2.00 ppm.

(3aR,8aR)-6-Hydroxy-2,2-diphenyl-4,4,8,8-tetrakis(4-(trifluoromethyl)phenyl)tetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide **12d-POOH**:



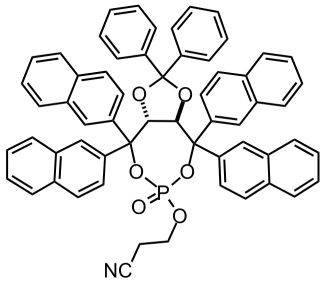
General procedure E. Yield: 96%; mp 187 °C; $[\alpha]_D^{20}$ -42.5 (*c* 0.99 $CHCl_3$). ^{1}H NMR δ: 5.42 (s, 2H); 6.80 (d, *J* = 7.2 Hz, 4H); 7.03–7.07 (m, 8H); 7.13–7.21 (m, 6H); 7.56 (d, *J* = 8.3 Hz, 4H); 7.64 (d, *J* = 8.3 Hz, 4H) ppm. ^{13}C NMR δ: 81.6 (CH); 86.9 (d, J_{CP} = 5.2 Hz, C); 115.5 (C); 123.6 (q, J_{CF} = 272.6 Hz, C); 123.8 (q, J_{CF} = 272.6 Hz, C); 124.3 (q, J_{CF} = 3.5 Hz, CH); 124.9 (CH); 125.6 (q, J_{CF} = 3.5 Hz, CH); 126.9 (CH); 128.1 (CH); 128.4 (CH); 128.5 (CH); 130.3 (q, J_{CF}= 32.8 Hz, C); 130.9 (q, J_{CF} = 32.8 Hz, C); 141.0 (d, J_{CP} = 7.8 Hz, C); 141.2 (C); 145.8 (C) ppm. ^{31}P NMR δ: –8.54 ppm. HRMS: *m*/*z* calcd for $C_{45}H_{28}F_{12}O_6P$ $[M–H]^-$: 923.1432; found 923.1413.

((4R,5R)-2,2-Diphenyl-1,3-dioxolane-4,5-diyl)bis(di(naphthalen-2-yl)methanol) **12e**:



General Procedure A. MPLC applying a solvent gradient EtOAc (2→10%)–heptane afforded **12e** in 74% yield**.** Mp 145–150 °C ;$[\alpha]_D^{20}$ +292 (*c* 1.05 $CHCl_3$). ^{1}H NMR δ: 2.32 (s, 2H); 6.06 (s, 2H); 6.10 (d, *J* = 8.7 Hz, 2H); 6.32 (dd, *J* = 8.7, 1.5 Hz, 2H); 7.18–7.21 (m, 6 H); 7.29–7.36 (m, 6H); 7.43–7.55 (m, 10H); 7.63–7.65 (m, 2H); 7.69 (d, *J* = 8.8 Hz, 2H); 7.78 (d, *J* = 7.8 Hz, 2H); 7.97 (d, *J* = 8.2 Hz, 2H); 8.12 (brs, 2H); 8.27 (br.s, 2H) ppm. ^{13}C NMR δ: 80.3 (C); 83.7 (CH); 112.9 (C); 123.4 (CH); 123.8 (CH); 124.8 (2CH); 125.4 (CH); 125.7 (CH); 125.9 (CH); 126.0 (CH); 127.1 (CH); 127.2 (CH); 127.4 (CH); 127.7 (CH); 127.9 (CH); 128.1 (CH); 128.5 (CH); 128.7(2CH); 131.8 (C); 132.3 (C); 132.8 (C); 132.9 (C); 138.7 (C); 143.3 (C); 144.8 (C) ppm. HRMS: *m*/*z* calcd for $C_{57}H_{41}O_4$ $[M–H]^-$: 789.3005; found: 789.2977.

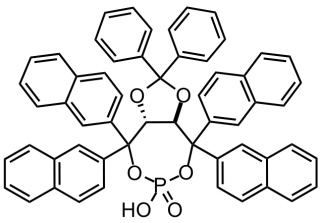
3-(((3aR,8aR)-4,4,8,8-Tetra(naphthalen-2-yl)-6-oxido-2,2-diphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)oxy)-propanenitrile:



General Procedure G. MPLC applying a solvent gradient EtOAc(10→66%)–heptane afforded the product in 58% yield.

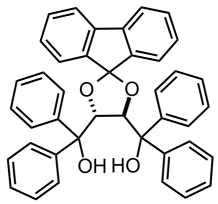
^{1}H NMR δ: 1.46–1.53 (m, 1H); 1.64–1.71 (m, 1H); 3.16–3.23 (m, 1H); 3.55–3.62 (m, 1H); 5.63 (d, *J* = 8.4 Hz, 1H); 6.03 (d, *J* =8.4 Hz, 1H); 6.32–6.36 (m, 2H); 6.43–6.48 (m, 3H); 6.80–7.44 (m, 23H); 7.65–7.70 (m, 5H); 7.79–7.87 (m, 3H); 8.15 (s, 1H); 8.24 (s, 1H) ppm. ^{31}P NMR δ: –11.48 ppm.

(3aR,8aR)-6-Hydroxy-4,4,8,8-tetra(naphthalen-2-yl)-2,2-diphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 6-oxide **12e-POOH**:



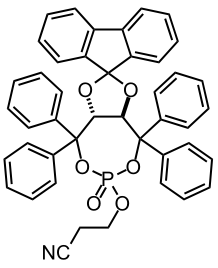
General Procedure J. The ammonium salt of the phosphate was dissolved in MeOH and washed through a short plug of Dowex-50. The solvent was removed under vacuum affording **12e-POOH** in 82% yield. Mp 181 °C; $[\alpha]_D^{20}$ -95.7 (*c* 0.99 $CHCl_3$). ^{1}H NMR δ: 5.84 (s, 2H); 6.71–6.74 (m, 4H); 6.81–6.85 (m, 6H); 7.13 (d, *J* = 8.9 Hz, 2H); 7.16 (dd, *J* = 8.9, 1.0 Hz, 2H); 7.30–7.38 (m, 6H); 7.42−7.49 (m, 6H); 7.58 (dd, *J* = 8.9, 1.1 Hz, 2H); 7.66–7.69 (m, 4H); 7.85–7.92 (m, 4H); 8.19 (s, 2H) ppm. ^{13}C NMR δ: 82.1 (CH); 87.5 (d, J_{CP} = 6.7 Hz, C); 113.6 (C); 125.3 (CH); 125.4 (2CH); 125.5 (CH); 126.0 (CH); 126.1 (CH); 126.4 (CH); 126.5 (CH); 126.9 (CH); 127.0 (CH); 127.2 (CH); 127.3 (CH); 127.4 (CH); 127.6 (CH); 128.1 (CH); 128.7 (CH); 128.8 (CH); 132.2 (C); 132.6 (C); 132.7 (C); 133.0 (C); 136.2 (d, J_{CP} = 8.3 Hz, C); 140.4 (d, J_{CP} = 3.6 Hz, C); 141.7 (C) ppm. ^{31}P NMR δ: –6.94 ppm. HRMS: *m*/*z* calcd for $C_{57}H_{40}O_6P$ $[M–H]^-$: 851.2563; found: 851.2597.

((4'R,5'R)-spiro[Fluorene-9,2'-[1,3]dioxolane]-4',5'-diyl)bis(diphenylmethanol) **13a**:[147]



General Procedure A. MPLC with a solvent gradient EtOAc(5→30%)–hexane afforded the product as a white crystalline solid in 81% yield. ^{1}H NMR δ: 4.62 (s, 2H); 4.96 (s, 2H); 6.44 (d, *J* = 7.6 Hz, 2H); 7.05 (t, *J* = 7.6 Hz, 2H); 7.18–7.53 (m, 24H) ppm*.

3-(((3a'R,8a'R)-6'-Oxido-4',4',8',8'-tetraphenyl-3a',4',8',8a'-tetrahydrospiro[fluorene-9,2'-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin]-6'-yl)oxy)propanenitrile:

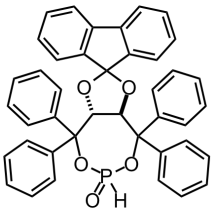


General Procedure G. MPLC applying a solvent gradient EtOAc(20→60%)–heptane afforded the product as a white solid with 60% yield. Mp 162–165 °C; $[\alpha]_D^{20}$ -218 (*c* 1.09 $CHCl_3$). ^{1}H NMR δ: 2.19–2.26 (m, 1H); 2.43–2.54 (m, 1H); 3.59–3.67 (m, 1H); 4.10–4.21

* Spectroscopic datas are in accordance with literature.

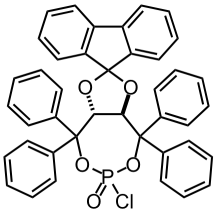
(m, 1H); 5.27 (d, *J* = 7.5 Hz, 1H); 5.45 (d, *J* = 7.5 Hz, 1H); 5.73 (d, *J* = 8.6 Hz, 1H); 5.74 (d, J = 8.6 Hz, 1H); 6.71–6.80 (m, 2H); 7.14−7.40 (m, 20H); 7.56–7.62 (m, 4H) ppm. ^{13}C NMR δ: 19.2 (d, J_{CP} = 8.2 Hz, CH_2); 62.2 (d, J_{CP} = 5.5 Hz, CH_2); 78.4 (CH); 79.7 (CH); 88.7 (d, J_{CP} = 8.7 Hz, C); 89.6 (d, J_{CP} = 8.6 Hz, C); 116.1 (C); 116.3 (C); 119.2 (2CH); 123.7 (CH); 123.8 (CH); 126.6 (CH); 127.1 (CH); 127.8 (CH); 127.9 (3CH); 128.0 (CH); 128.1 (CH); 128.4 (CH); 128.5 (CH); 128.6 (CH); 128.7 (CH); 128.8 (CH); 129.5 (CH); 130.0 (CH); 130.1 (CH); 139.0 (C); 139.1 (C); 139.2 (d, J_{CP} = 9.2 Hz, C); 139.3 (d, J_{CP} = 8.7 Hz, C); 142.4 (2C); 142.9 (d, J_{CP} = 1.4 Hz, C); 143.6 (d, J_{CP} = 1.5 Hz, C) ppm. ^{31}P NMR δ: –13.62 ppm. HRMS: *m*/*z* calcd for $C_{44}H_{34}NNaO_6P$ $[M+Na]^+$: 726.2021; found: 726.2024

(3a'R,8a'R)-4',4',8',8'-Tetraphenyl-3a',4',8',8a'-tetrahydrospiro[fluorene-9,2'-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine] 6'-oxide **13a-POH**:[148]



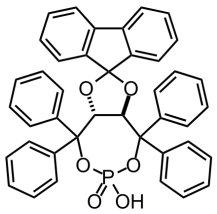
General Procedure D. MPLC applying a solvent gradient EtOAc(5→30%)–heptane to afford the product in 33% yield. Mp 226–228 °C; $[\alpha]_D^{20}$ -283.6 (*c* 1.05, $CHCl_3$). ^{1}H NMR δ: 5.39 (d, *J* = 7.6 Hz, 1H); 5.43 (d, *J* = 7.6 Hz, 1H); 5.65 (d, *J* = 8.8 Hz, 1H); 5.84 (d, *J* = 8.8 Hz, 1H); 6.75 (dt, *J* = 7.4, 1.0 Hz, 2H); 7.12–7.45 (m, 20H); 7.26 (d, J_{HP} = 730 Hz, 1H); 7.59–7.63 (m, 4H) ppm. ^{13}C NMR δ: 80.1 (d, J_{CP} = 1.4 Hz, CH); 80.5 (d, J_{CP} = 1.6 Hz, CH); 89.1 (d, J_{CP} = 9.5 Hz, C); 89.3 (d, J_{CP} = 9.5 Hz, C); 116.7 (C); 119.2 (CH); 119.3 (CH); 123.7 (CH); 123.8 (CH); 126.5 (CH); 126.6 (CH); 127.8 (CH); 127.9 (3CH); 128.0 (CH); 128.1 (CH); 128.4 (CH); 128.6 (CH); 128.7 (CH); 128.8 (CH); 128.9 (CH); 129.3 (CH); 130.0 (CH); 130.1 (CH); 138.9 (d, J_{CP} = 5.8 Hz, C); 139.0 (C); 139.2 (d, J_{CP} = 9.5 Hz, C); 139.3 (C); 142.5 (2C); 143.2 (C); 143.0 (d, J_{CP} = 2.9 Hz, C) ppm. ^{31}P NMR δ: –4.32 ppm. HRMS: *m*/*z* calcd for $C_{41}H_{31}NaO_5P$ $[M+Na]^+$: 657.1807; found: 657.1801.

As a side product *(3a'R,8a'R)-6'-Chloro-4',4',8',8'-tetraphenyl-3a',4',8',8a'-tetrahydrospiro[fluorene-9,2'- [1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine] 6'-oxide* **13a-PCl** was formed in 28% yield; mp 208–210 °C; $[\alpha]_D^{20}$ -230 (*c* 1.05, $CHCl_3$). ^{1}H NMR δ: 5.23 (d, *J* = 7.4 Hz, 1H); 5.32 (d, *J* = 7.4 Hz, 1H); 5.68 (d, *J* = 8.5 Hz, 1H); 5.72 (d, *J* = 8.5 Hz, 1H); 6.66–6.71 (m, 2H); 7.11 (pst, *J* = 7.5 Hz, 2H); 7.20–7.22 (m, 6H); 7.26–7.32 (m, 12H); 7.51–7.53 (m, 2H); 7.56 (d, *J* = 8.7 Hz, 2H) ppm. ^{13}C NMR δ: 79.2 (CH); 79.8 (CH); 91.9 (d, J_{CP} = 11.6 Hz, C); 92.6 (d, J_{CP} = 9.6 Hz, C); 116.9 (C); 119.2 (CH); 119.3 (CH); 123.5 (CH); 123.7 (CH); 126.6 (CH); 127.2 (CH); 127.9 (CH); 128.0 (2CH); 128.1 (2CH);



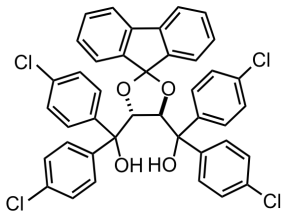
128.2 (CH); 128.4 (CH); 128.6 (CH); 128.7 (2CH); 128.9 (CH); 129.0 (CH); 129.2 (CH); 130.2 (CH); 138.6 (d, J_{CP} = 11.8 Hz, C); 138.9 (d, J_{CP} = 11.6 Hz, C); 139.1 (C); 139.2 (C); 141.4 (C); 141.9 (C); 142.3 (C); 142.4 (C) ppm. ^{31}P NMR δ: –9.71 ppm. HRMS: *m*/*z* calcd for $C_{41}H_{30}ClNaO_5P$ $[M+Na]^+$: 691.1417; found: 691.1416.

(3a'R,8a'R)-6'-Hydroxy-4',4',8',8'-tetraphenyl-3a',4',8',8a'-tetrahydrospiro[fluorene-9,2'-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine] 6'-oxide **13a-POOH:**



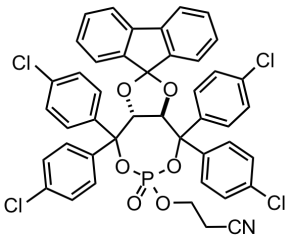
General procedure J. The ammonium salt of the phosphate was dissolved in MeOH and washed through Dowex-50 and concentrated under vacuum. Phosphate **13a-POOH** was obtained as a white solid in quantitative yield. Mp 262–263 °C; $[\alpha]_D^{20}$ -239 (*c* 0.8, $CHCl_3$). ^{1}H NMR δ: 5.36 (d, *J* = 7.4 Hz, 2H); 5.67 (s, 2H); 6.49 (dt, *J* = 7.4, 0.7 Hz, 2H); 7.16 (dt, *J* = 7.4, 0.6 Hz, 2H), 7.17−7.24 (m, 4H); 7.28–7.38 (m, 14H); 7.59–7.61 (m, 4H) ppm. ^{13}C NMR δ: 79.7 (CH); 88.4 (d, J_{CP} = 7.0 Hz, C); 116.0 (C); 119.2 (CH); 123.9 (CH); 126.7 (CH); 127.7 (CH); 127.8 (CH); 128.0 (CH); 128.3 (CH); 128.4 (CH); 129.3 (CH); 129.9 (CH); 139.1 (C); 139.6 (d, J_{CP} = 8.8 Hz, C); 142.7 (C); 143.4 (C) ppm. ^{31}P NMR δ: –9.07 ppm. HRMS: *m*/*z* calcd for $C_{41}H_{30}O_6P$ $[M–H]^–$: 649.1780; found: 649.1792.

((4'R,5'R)-spiro[Fluorene-9,2'-[1,3]dioxolane]-4',5'-diyl)bis(bis(4-chlorophenyl)methanol) **13b**:



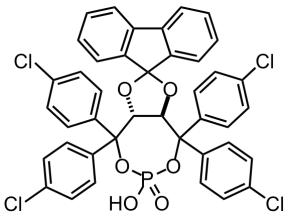
General Procedure A. MPLC applying a solvent gradient EtOAc(3→19%)–hexane afforded **13b** as a white crystalline solid in 84% yield. Mp 336 °C; $[\alpha]_D^{20}$ -46.4 (*c* 1.05, $CHCl_3$). ^{1}H NMR δ: 4.56 (s, 2H); 4.81 (s, 2H); 6.41 (d, *J* = 7.7 Hz, 2H); 7.11 (dt, *J* = 7.7, 0.9 Hz, 2H); 7.16 (d, *J* = 8.9 Hz, 4H); 7.23 (d, *J* = 8.9 Hz, 4H); 7.28–7.33 (m, 6H); 7.41 (d, *J* = 8.7 Hz, 4H); 7.45 (d, *J* = 7.7 Hz, 2H) ppm. ^{13}C NMR δ: 77.7 (C); 81.2 (CH); 112.1 (C); 119.8 (CH); 124.0 (CH); 127.9 (CH); 128.1 (CH); 128.6 (CH); 128.8 (CH); 130.3 (CH); 130.5 (CH); 133.9 (C); 134.0 (C); 139.6 (C); 140.3 (C), 143.2 (C); 143.4 (C) ppm. HRMS: *m*/*z* calcd for $C_{41}H_{27}Cl_4O_4$ $[M–H]^–$: 723.0663; found: 723.0661.

3-(((3a'R,8a'R)-4',4',8',8'-Tetrakis(4-chlorophenyl)-6'-oxido-3a',4',8',8a'-tetrahydrospiro-[fluorene-9,2'-[1,3]dioxolo[4,5-e][1,3,2]-dioxaphosphepin]-6'-yl)-oxy)propanenitrile:



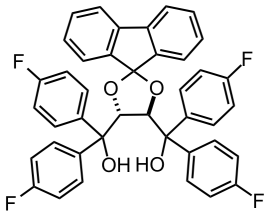
General Procedure G. MPLC applying a solvent gradient EtOAc(10→61%)–heptane afforded the product as a white solid in 39% yield. Mp 176–179 °C; $[\alpha]_D^{20}$ -178 (*c* 0.98, $CHCl_3$). ^{1}H NMR δ: 2.41–2.49 (m, 1H); 2.62–2.69 (m, 1H); 3.84–3.91 (m, 1H); 4.21–4.29 (m, 1H); 5.39 (d, *J* = 7.7 Hz, 1H); 5.46 (d, *J* = 7.7 Hz, 1H); 5.51 (d, *J* = 8.4 Hz, 1H); 5.57 (d, *J* = 8.4 Hz, 1H); 6.89 (d, *J* = 7.7 Hz, 1H); 6.93 (d, *J* = 7.7 Hz, 1H); 7.21–7.38 (m, 16H); 7.46−7.51 (m, 4H) ppm. ^{13}C NMR δ: 19.5 (d, J_{CP} = 8.5 Hz, CH_2); 62.8 (d, J_{CP} = 4.9 Hz, CH_2); 78.8 (CH); 79.3 (CH); 88.0 (d, J_{CP} = 6.3 Hz, C); 88.5 (d, J_{CP} = 8.2 Hz, C); 116.1 (C); 116.6 (C); 119.5 (CH); 119.6 (CH); 123.3 (CH); 123.4 (CH); 127.8 (CH); 127.9 (CH); 128.0 (CH); 128.1 (CH); 128.2 (CH); 128.3 (CH); 128.9 (2CH); 130.2 (CH); 130.6 (CH); 130.7 (CH); 130.8 (CH); 134.8 (C); 135.0 (C); 135.1 (C); 136.8 (C); 136.9 (C); 137.0 (d, J_{CP} = 1.4 Hz, C); 139.1 (C); 139.2 (C); 140.7 (C); 141.4 (d, J_{CP} = 2.1 Hz, C); 141.8 (C); 141.9 (C) ppm. ^{31}P NMR δ: –12.99 ppm. HRMS: *m*/*z* calcd for $C_{44}H_{30}Cl_4NNaO_6P$ $[M+Na]^+$: 864.0433; found 864.0455.

(3a'R,8a'R)-4',4',8',8'-Tetrakis(4-chlorophenyl)-6'-hydroxy-3a',4',8',8a'-tetrahydro-spiro[fluorene-9,2'-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine] 6'-oxide **13b-POOH**:



General Procedure J. The ammonium salt of the phosphate was dissolved in MeOH and washed through Dowex-50 and concentrated under vacuum to afford **13b-POOH** as a white solid. Yield: 78%; mp 245–247 °C; $[\alpha]_D^{20}$ -161 (*c* 1.05, $CHCl_3$). ^{1}H NMR δ: 5.43 (d, *J* = 7.6 Hz, 2H); 5.47 (s, 2H); 6.91 (dt, *J* = 7.6, 1.0 Hz, 2H); 7.21–7.29 (m, 14H); 7.38 (d, *J* = 7.5 Hz, 2H); 7.48 (d, *J* = 8.6 Hz, 4H) ppm. ^{13}C NMR δ: 79.5 (CH); 87.6 (d, J_{CP} = 6.3 Hz, C); 116.5 (C); 119.6 (CH); 123.4 (CH); 127.9 (2CH); 128.2 (CH); 128.8 (CH); 130.4 (CH); 130.6 (CH); 134.7 (C); 137.2 (C); 137.3 (C); 139.2 (C); 141.2 (C); 142.7 (C); 142.0 (C) ppm. ^{31}P NMR δ: –9.65 ppm. HRMS: *m*/*z* calcd for $C_{41}H_{26}Cl_4O_6P$ $[M–H]^–$: 787.0192; found: 787.0207.

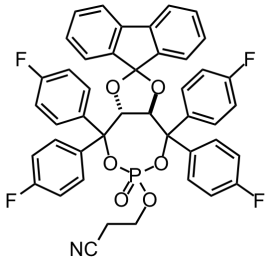
((4'R,5'R)-spiro[Fluorene-9,2'-[1,3]dioxolane]-4',5'-diyl)bis(bis(4-fluorophenyl)methanol)



13c:

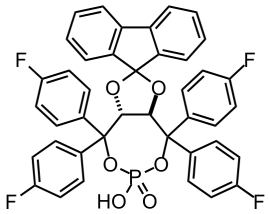
General procedure A was followed. MPLC with a solvent gradient EtOAc(5→22%)–hexane afforded **13c** as a white crystalline solid in 69% yield. Mp 137–140 °C; $[\alpha]_D^{20}$ -77.7 (*c* 0.95, $CHCl_3$). ^{1}H NMR δ: 4.75 (s, 2H); 4.82 (s, 2H); 6,46 (d, *J* = 7.6 Hz, 2H); 6.89 (t, *J* = 8.6, 4H); 7.06 (t, *J* = 8.6 Hz, 4H); 7.11 (t, *J* = 7.5 Hz, 2H); 7.24 – 7.32 (m, 6H); 7.45–7.48 (m, 6H) ppm. ^{13}C NMR δ: 77.7 (C); 81.3 (CH); 111.8 (C); 114.5 (d, J_{CF} = 20.9; CH); 115.2 (d, J_{CF} = 21.6 Hz, CH); 119.8 (CH); 124.1 (CH); 128.1 (CH); 129.3 (d, J_{CF} = 7.9 Hz, CH); 130.4 (CH); 130.7 (d, J_{CF} = 8.3 Hz, CH); 137.6 (d, J_{CF} = 2.8 Hz, C); 139.6 (C); 141.1 (d, J_{CF} = 3.5 Hz, C), 143.4 (C); 162.1 (d, J_{CF} = 248.1 Hz, C); 162.4 (d, J_{CF} = 247.5 Hz, C) ppm. HRMS: *m*/*z* calcd for $C_{41}H_{27}F_4O_4$ $[M–H\ ]^-$: 659.1850; found: 659.1845.

3-(((3a'R,8a'R)-4',4',8',8'-Tetrakis(4-fluorophenyl)-6'-oxido-3a',4',8',8a'-tetrahydrospiro-[fluorene-9,2'-[1,3]dioxolo[4,5-e][1,3,2]-dioxaphosphepin]-6'-yl)-oxy)propanenitrile:



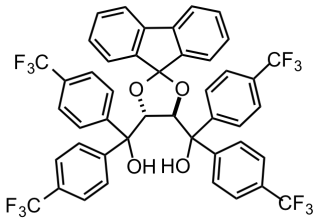
General Procedure G. MPLC applying a solvent gradient EtOAc(10→60%)–heptane afforded the product as a white solid in 46% yield. Mp 165–167 °C; $[\alpha]_D^{20}$ -197 (*c* 1.10, $CHCl_3$). ^{1}H NMR δ: 2.39–2.47 (m, 1H); 2.62–2.70 (m, 1H); 3.80–3.88 (m, 1H); 4.19–4.28 (m, 1H); 5.43 (d, *J* = 7.5 Hz, 1H); 5.53 (d, *J* = 7.5 Hz, 1H); 5.56 (d, *J* = 8.5 Hz, 1H); 5.61 (d, *J* = 8.5 Hz, 1H); 6.84–6.93 (m, 2H); 6.93–7.09 (m, 8H); 7.19–7.25 (m, 2H); 7.26−7.39 (m, 6H); 7.51–7.56 (m, 4H) ppm. ^{13}C NMR δ: 19.6 (d, J_{CP} = 8.0 Hz, CH_2); 62.6 (d, J_{CP} = 5.7 Hz, CH_2); 78.8 (CH); 79.5 (CH); 88.3 (d, J_{CP} = 6.5 Hz, C); 88.6 (d, J_{CP} = 8.1 Hz, C); 114.9 (d, J_{CF} = 21.9 Hz, CH); 115.0 (d, J_{CF} = 21.9 Hz, CH); 115.6 (d, J_{CF} = 21.9 Hz, CH); 115.7 (d, J_{CF} = 21.8 Hz, CH) 116.1 (C); 116.4 (C); 119.5 (CH); 119.6 (CH); 123.3 (CH); 123.4 (CH); 127.9 (CH); 128.0 (CH); 128.5 (d, J_{CF} = 8.7 Hz, CH); 128.9 (d, J_{CF} = 8.2 Hz, CH); 130.5 (CH); 130.6 (CH); 130.7 (d, J_{CF} = 8.8 Hz, CH); 131.4 (d, J_{CF} = 8.0 Hz, CH); 134.6 (d, J_{CF} = 3.6 Hz, C); 134.7 (t, J_{CF}= 2.9 Hz, 2C); 138.5 (d, J_{CF} = 3.6 Hz, C); 139.1 (C); 139.2 (C); 142.0 (C); 142.1 (C); 162.6 (d, J_{CF} = 249.2 Hz, C); 162.7 (d, J_{CF} = 249.4 Hz, C); 162.8 (d, J_{CF} = 248.3 Hz, 2C) ppm. ^{31}P NMR δ: –13.16 ppm. HRMS: *m*/*z* calcd for $C_{44}H_{30}F_4NNaO_6P$ $[M+Na]^+$: 798.1645; found 798.1653.

(3a'R,8a'R)-4',4',8',8'-Tetrakis(4-fluorophenyl)-6'-hydroxy-3a',4',8',8a'-tetrahydrospiro[fluorene-9,2'-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine] 6'-oxide **13c-POOH**:



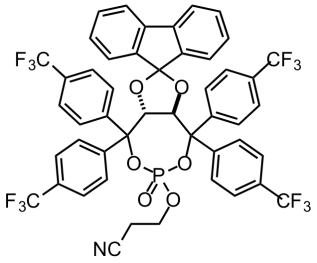
General Procedure J. The ammonium salt of the phosphate was dissolved in MeOH, washed through Dowex-50 and concentrated under vacuum. **13c-POOH** was obtained as a white solid in quantitative yield. Mp 225–227 °C; $[\alpha]_D^{20}$ -196 (*c* 1.03 $CHCl_3$). ^{1}H NMR δ: 5.47 (d, *J* = 7.7 Hz, 2H); 5.52 (s, 2H); 6.87 (dt, *J* = 7.7, 0.9 Hz, 2H); 6.95 (t, *J* = 8.4 Hz, 4H); 6.99 (t, *J* = 8.6 Hz, 4H); 7.20–7.25 (m, 2H); 7.28 (d, *J* = 5.2 Hz, 2H); 5.31 (d, *J* = 5.2 Hz, 2H); 7.37 (d, *J* = 7.6 Hz, 2H); 7.51 (d, *J* = 5.2 Hz, 2H); 7.54 (d, *J* = 5.2 Hz, 2H) ppm. ^{13}C NMR δ: 79.5 (CH); 87.9 (d, J_{CP} = 6.5 Hz, C); 114.8 (d, J_{CF} = 24.6 Hz, CH); 115.5 (d, J_{CF} = 21.2 Hz, CH); 116.3 (C); 119.6 (CH); 123.3 (CH); 128.0 (CH); 128.5 (d, J_{CF} = 8.8 Hz, CH); 130.6 (CH); 130.9 (d, J_{CF} = 8.1 Hz, CH); 134.9 (dd, $J_{CF,\ CP}$ = 9.6, 2.9 Hz, C); 138.9 (d, J_{CF} = 2.0 Hz, C); 139.2 (C); 142.2 (C); 162.6 (d, J_{CF} = 248.4 Hz, C); 162.8 (d, J_{CF} = 248.9, C) ppm. ^{31}P NMR δ: –9.22 ppm. HRMS: *m*/*z* calcd for $C_{41}H_{26}F_4O_6P$ $[M\text{-}H]^-$: 721.1403; found: 721.1414.

((4'R,5'R)-spiro[Fluorene-9,2'-[1,3]dioxolane]-4',5'-diyl)bis(bis(4-(trifluoromethyl)phenyl)-methanol) **13d**:



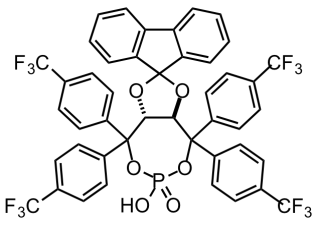
General Procedure A. MPLC with a solvent gradient EtOAc (3→20%)–hexane afforded **13d** as a white crystalline solid in 83% yield. Mp 290–293 °C; $[\alpha]_D^{20}$ -63.2 (*c* 0.95, $CHCl_3$). ^{1}H NMR δ: 4.65 (s, 2H); 4.91 (s, 2H); 6.22 (d, *J* = 7.5 Hz, 2H); 7.00 (dt, *J* = 7.5, 0.9 Hz, 2H); 7.31 (dt, *J* = 7.6, 0.9 Hz, 2H); 7.44–7.51 (m, 10 H); 7.59 (d, *J* = 9.2 Hz, 4H); 7.62 (d, *J* = 9.2 Hz, 4 H) ppm. ^{13}C NMR δ: 78.1 (C); 80.9 (CH); 112.5 (C); 120.0 (CH); 123.6 (CH); 123.7 (q, J_{CF} = 271.8 Hz; C); 124.1 (q, J_{CF} = 270.9 Hz, C); 124.9 (q, J_{CF} = 3.9 Hz, CH); 125.6 (q, J_{CF} = 3.6 Hz, CH); 127.7 (CH); 128.2 (CH); 129.3 (CH); 130.4 (q, J_{CF} = 32.9 Hz, C); 130.5 (q, J_{CF} = 32.2 Hz, C); 130.8 (CH); 139.6 (C); 142.9 (C): 145.3 (C); 148.3 (C) ppm. HRMS: *m*/*z* calcd for $C_{45}H_{27}F_{12}O_4$ $[M\text{-}H]^-$: 859.1718; found: 859.1733.

3-(((3a'R,8a'R)-6'-Oxido-4',4',8',8'-tetrakis(4-(trifluoromethyl)phenyl)-3a',4',8',8a'-tetrahydrospiro[fluorene-9,2'-[1,3]dioxolo[4,5-e][1,3,2]-dioxaphosphepin]-6'-yl)oxy)-propanenitrile:



General procedure G. MPLC applying a solvent gradient EtOAc(5→40%)–heptane afforded the product as a white solid in 36% yield. Mp 170–175 °C; $[\alpha]_D^{20}$ -181 (*c* 1.20, $CHCl_3$). ^{1}H NMR δ: 2.46–2.53 (m, 1H); 2.66–2.73 (m, 1H); 3.98–4.05 (m, 1H); 4.29–4.37 (m, 1H); 5.28 (pst, *J* = 8.0 Hz, 2H); 5.57 (d, *J* = 8.6 Hz, 1H); 5.67 (d, *J* = 8.6 Hz, 1H); 6.76 (d, *J* = 8.4 Hz, 1H); 6.80 (d, *J* = 8.4 Hz, 1H); 7.21–7.25 (m, 2H); 7.38 (d, *J* = 7.6 Hz, 2H); 7.44 (d, *J* = 8.4 Hz, 2H); 7.52–7.59 (m, 6H); 7.64−7.72 (m, 8H) ppm. ^{13}C NMR δ: 19.6 (d, J_{CP} = 7.3 Hz, CH_2); 63.2 (d, J_{CP} = 4.3 Hz, CH_2); 79.1 (CH); 79.2 (CH); 87.6 (d, J_{CP} = 5.7 Hz, C); 88.7 (d, J_{CP} = 8.1 Hz, C); 115.9 (C); 116.8 (C); 119.7 (CH); 119.8 (CH); 122.7 (CH); 122.9 (CH); 123.7 (q, J_{CF} = 260.8 Hz, 2C); 123.8 (q, J_{CF} = 272.3 Hz, 2C); 125.1 (q, J_{CF} = 3.6 Hz, CH); 125.2 (d, J_{CF} = 3.6 Hz, CH); 125.9 (q, J_{CF} = 3.9 Hz, 2CH); 126.9 (CH); 127.2 (CH); 128.0 (CH); 128.1 (CH); 129.2 (CH); 129.9 (CH); 130.9 (CH); 131.0 (CH); 131.0 (q, J_{CF} = 33.2 Hz, C); 131.1 (q, J_{CF} = 33.3 Hz, C); 131.3 (q, J_{CF} = 33.0 Hz, C); 131.4 (q, J_{CF} = 32.8 Hz, C); 139.2 (C); 139.3 (C); 141.5 (C); 141.6 (C); 141.7 (C); 141.8 (C); 145.4 (C); 146.3 (C) ppm. ^{31}P NMR δ: –12.59 ppm. HRMS: *m*/*z* calcd for $C_{48}H_{30}F_{12}NNaO_6P$ $[M+Na]^+$: 998.1517; found 998.1506.

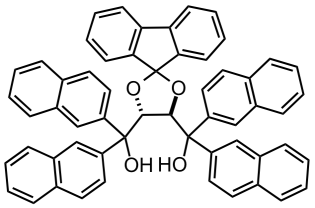
(3a'R,8a'R)-6'-Hydroxy-4',4',8',8'-tetrakis(4-(trifluoromethyl)phenyl)-3a',4',8',8a'-tetrahydrospiro[fluorene-9,2'-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine] 6'-oxide **13d-POOH**:



General Procedure J. The ammonium salt of the phosphate was dissolved in MeOH, washed through Dowex-50 and concentrated under vacuum to afford **13d-POOH** as a white solid. Yield: 98%; mp 225–230 °C; $[\alpha]_D^{20}$ -142 (*c* 1.08, $CHCl_3$). ^{1}H NMR δ: 5.30 (d, *J* = 7.6 Hz, 2H); 5.57 (s, 2H); 6.78 (t, *J* = 7.7 Hz, 2H); 7.23 (t, *J* = 8.1 Hz, 2H); 7.39 (d, *J* = 7.5 Hz, 4H); 7.48 (d, *J* = 8.4 Hz, 4H); 7.55 (d, *J* = 8.4 Hz, 4H); 7.63 (d, *J* = 8.4 Hz, 4H); 7.71 (d, *J* = 8.4 Hz, 4H); 8.17 (brs, 1H) ppm. ^{13}C NMR δ: 79.4 (CH); 87.8 (d, J_{CP} = 6.3 Hz, C); 116.8 (C); 119.8 (CH); 122.8 (CH); 123.8 (q, J_{CF} = 272.4 Hz, C); 123.9 (q, J_{CF} = 272.4 Hz, C); 125.1 (d, J_{CF} = 3.6 Hz, CH); 125.8 (d, J_{CF} = 3.6 Hz, CH); 126.9 (CH); 128.1 (CH); 129.5 (CH); 130.9 (CH); 131.0 (d, J_{CF} = 32.9 Hz, C); 131.2 (d, J_{CF} = 32.9 Hz, C); 139.3

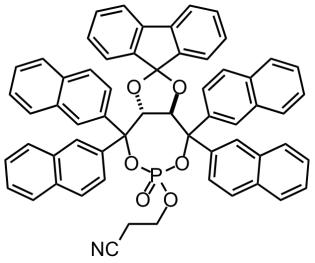
(C); 141.6 (C); 141.9 (d, $J_{CF,\ CP}$ = 9.2 Hz, C); 145.8 (C) ppm. ^{31}P NMR δ: –8.99 ppm. HRMS: *m*/*z* calcd for $C_{45}H_{26}F_{12}O_6P$ $[M-H]^-$: 921.1275; found 921.1278.

((4'R,5'R)-spiro[Fluorene-9,2'-[1,3]dioxolane]-4',5'-diyl)bis(di(naphthalen-2-yl)methanol) **13e**:



General Procedure A. MPLC applying a solvent gradient EtOAc (3→30%)–hexane afforded **13e** as a white crystalline solid in 96% yield. Mp 173–175 °C; $[\alpha]_D^{20}$ -66.4 (*c* 0.98, $CHCl_3$). ^{1}H NMR δ: 4.80 (s, 2H); 5.24 (s, 2H); 6.45 (d, *J* = 7.5 Hz, 2H); 6.77 (dt, *J* = 7.5, 0.9 Hz, 2H); 7.21 (dt, *J* = 7.5, 1.1 Hz, 2H); 7.29–7.38 (m, 6 H); 7.41 (d, *J* = 7.5 Hz, 2H); 7.46–7.56 (m, 6H); 7.58 (d, *J* = 8.6 Hz, 2H); 7.66 (d, *J* = 8.0 Hz, 2H); 7.73 (dd, *J* = 8.7, 1.7 Hz, 2H); 7.76 (d, *J* = 8.0 Hz, 2H); 7.81 (d, *J* = 8.7 Hz, 2H); 7.88–7.92 (m, 4H); 8.12 (brs, 2H) ppm. ^{13}C NMR δ: 78.6 (C); 81.9 (CH); 112.0 (C); 119.6 (CH); 124.4 (CH); 125.6 (CH); 125.9 (CH); 126.0 (CH); 126.2 (CH); 126.3 (CH); 126.4 (CH); 127.1 (CH); 127.2 (CH); 127.3 (CH); 127.5 (CH); 127.8 (CH); 127.9 (CH); 128.1 (CH); 128.6 (CH); 128.7 (CH); 130.1 (CH); 132.6 (C); 132.6 (C); 132.7 (C); 132.8 (C); 139.6 (C); 139.7 (C); 142.5 (C); 143.7 (C) ppm. HRMS: *m*/*z* calcd for $C_{57}H_{40}NaO_4$ $[M+Na]^+$: 811.2824; found: 811.2804.

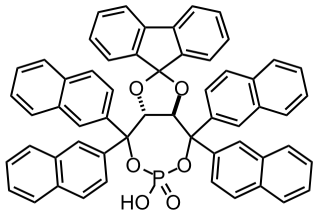
3-(((3a'R,8a'R)-4',4',8',8'-Tetra(naphthalen-2-yl)-6'-oxido-3a',4',8',8a'-tetrahydrospiro-[fluorene-9,2'-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin]-6'-yl)oxy)propanenitrile:



General Procedure G. MPLC applying a solvent gradient EtOAc (5→40%)–heptane afforded the product as a white solid in 56% yield. Mp 200–203 °C; $[\alpha]_D^{20}$ -162 (*c* 1.07, $CHCl_3$). ^{1}H NMR δ: 1.99–2.07 (m, 1H); 2.33–2.39 (m, 1H); 3.61–3.69 (m, 1H); 4.18–4.24 (m, 1H); 4.98 (d, *J* = 7.4 Hz, 1H); 5.18 (d, *J* = 7.4 Hz, 1H); 5.99 (dd, *J* = 7.5, 0.9 Hz, 1H); 6.05 (dd, *J* = 7.5, 0.9 Hz, 1H); 6.08 (d, *J* = 8.4 Hz, 1H); 6.11 (d, *J* = 8.4 Hz, 1H); 6.97 (dd, *J* = 7.6, 0.9 Hz, 1H); 7.01 (d, *J* = 7.6, 0.9 Hz, 1H); 7.18–7.29 (m, 4H); 7.45–7.59 (m, 11H); 7.65 (dd, *J* = 8.6, 2.0 Hz, 1H); 7.79 – 7.90 (m, 10H); 8.15 (d, *J* = 1.5 Hz, 1H); 8.21 (d, *J* = 1.2 Hz, 2H); 8.23 (d, *J* = 1.5 Hz, 1H) ppm. ^{13}C NMR δ: 19.2 (d, J_{CP} = 8.0 Hz, CH_2); 62.3 (d, J_{CP} = 4.3 Hz, CH_2); 79.1 (CH); 80.4 (CH); 89.8 (d, J_{CP} = 7.8 Hz, C); 89.8 (d, J_{CP} = 6.8 Hz, C); 116.1 (C); 116.8 (C); 119.1 (CH); 119.2 (CH); 123.7 (CH); 123.8 (CH); 124.9 (CH); 125.2 (CH); 125.3 (CH); 125.6 (CH); 126.3 (2CH); 126.4 (CH); 126.7 (2CH); 126.8 (2CH); 127.1 (CH); 127.2 (CH); 127.3 (4CH); 127.4

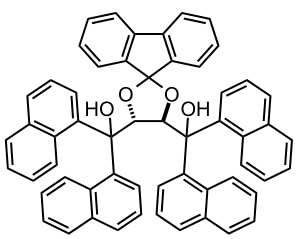
(3CH); 127.5 (CH); 127.6 (2CH); 127.7 (CH); 127.8 (CH); 128.6 (CH), 128.7 (CH); 128.8 (CH); 128.9 (3CH); 129.9 (CH); 130.0 (CH); 132.5 (C); 132.6 (C); 132.7 (C); 132.8 (C); 132.9 (2C); 133.0 (C); 133.3 (C); 136.2 (C); 136.3 (C); 136.4 (C); 136.5 (C); 139.0 (d, J_{CP} = 3.0 Hz, C); 139.9 (C); 140.1 (C); 142.1 (d, J_{CP} = 4.4 Hz, C) ppm. ^{31}P NMR δ: –12.97 ppm. HRMS: *m*/*z* calcd for $C_{60}H_{42}NNaO_6P$ $[M+Na]^+$: 926.2647; found 926.2643.

(3a'R,8a'R)-6'-Hydroxy-4',4',8',8'-tetra(naphthalen-2-yl)-3a',4',8',8a'-tetrahydrospiro-[fluorene-9,2'- [1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine] 6'-oxide **13e-POOH**:



Cyanoethyl phosphate of **13e** (288 mg, 0.32 mmol) was dissolved in DCM (3.5 mL) and DBU (51 mg, 0.34 mmol, 50 μL) was added at room temperature. The solution was stirred for 1 h and AcOH (18 μL) was added followed by H_2O (18 mL). 6N HCl (5 mL) was added and stirred at room temperature for 30 min. The organic phase washed with brine, dried over $MgSO_4$, filtered and concentrated affording **13e-POOH** as a white powder in 245 mg. The product was recrystallized from EtOAc/heptane to give white crystals. Yield: 90%; mp 145–146 °C; $[\alpha]_D^{20}$ -109 (*c* 1.05, $CHCl_3$). ^{1}H NMR δ: 5.05 (d, *J* = 7.5 Hz, 2H); 5.99 (dd, J = 7.5, 1.0 Hz, 2H); 6.02 (s, 2H); 6.98 (dt, *J* = 7.5, 0.8 Hz, 2H); 7.21−7.27 (m, 4H); 7.37 (dd, *J* = 6.9, 0.9 Hz, 2H); 7.41–7.45 (m, 2H); 7.46 (s, 2H); 7.49 (s, 2H); 7.53 (pst, *J* = 8.4 Hz, 2H); 7.69–7.73 (m, 6H); 7.77–7.80 (m, 6H); 8.19 (s, 2H); 8.20 (s, 2H) ppm. ^{13}C NMR δ: 80.3 (CH); 88.9 (d, J_{CP} = 7.7 Hz, C); 116.6 (C); 119.1 (CH); 123.7 (CH); 125.1 (CH); 125.2 (CH); 126.1 (CH); 126.2 (CH); 126.5 (CH); 126.6 (CH); 127.1 (CH); 127.3 (CH); 127.4 (2CH); 127.7 (2CH); 128.5 (CH); 128.5 (CH); 128.8 (CH); 129.9 (CH); 132.7 (d, J_{CP} = 4.2 Hz, C); 132.9 (C); 133.2 (C); 136.6 (C); 136.7 (C); 139.0 (C); 140.1 (C); 142.3 (C) ppm. ^{31}P NMR δ: –8.22 ppm. HRMS: *m*/*z* calcd for $C_{57}H_{37}O_6P$ $[M-H]^-$: 849.2406; found: 849.2440.

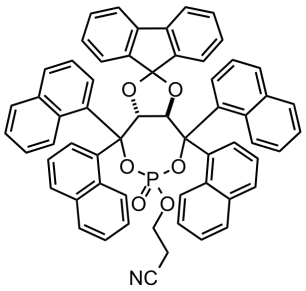
((4'R,5'R)-spiro[Fluorene-9,2'-[1,3]dioxolane]-4',5'-diyl)bis(di(naphthalen-1-yl)methanol) **13f:**



In a Schlenk tube Mg (118 mg, 4.9 mmol) turinings were placed followed by THF (1 mL) and a speck of iodine. 1-Naphthylbromide (0.66 mL, 974 mg, 4.7 mmol) in THF (9 mL) was added to this. Diester **59** (200 mg, 0.59 mmol) in THF (2 mL) was added and the mixture was heated to reflux for 8 h. The reaction mixture was cooled and sat. aq. NH_4Cl was

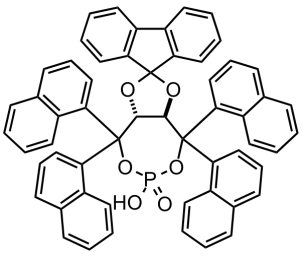
added. The inorganic layer was extracted with EtOAc (3× 10 mL), combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed. The crude mixture was separated to MPLC using a solvent gradient of EtOAc (3→30%)–hexane to afford the product as a white crystalline solid. The product was recrystallized from EtOAc/heptane to give **13f** as a clear colorless crystal in 50% yield. Mp 222–227 °C; $[\alpha]_D^{20}$ -155 (*c* 1.05, $CHCl_3$). Due to extensive line broadening ^{1}H NMR was not informative (See *Figure* 26 for X-ray structure). ^{13}C NMR δ: 60.4 (C); 79.7 (C); 82.0 (CH); 118.8 (CH); 123.1 (CH); 124.3 (CH); 124.5 (2CH); 125.0 (CH); 125.3 (CH); 125.5 (CH); 125.7 (CH); 126.7 (CH); 127.5 (2CH); 128.1 (CH); 128.9 (CH); 129.2 (CH); 129.4 (CH); 129.5 (2CH); 131.1 (C); 132.9 (C); 134.5 (C); 134.7 (C); 138.9 (C); 139.9 (C); 141.4 (C); 142.87 (C) ppm. HRMS: *m*/*z* calcd for $C_{57}H_{40}NaO_4$ $[M+Na]^+$: 811.2824; found: 811.2798.

3-(((3a'R,8a'R)-4',4',8',8'-Tetra(naphthalen-1-yl)-6'-oxido-3a',4',8',8a'-tetrahydrospiro-[fluorene-9,2'-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin]-6'-yl)oxy)propanenitrile:**13f-POP**



General Procedure G. MPLC applying a solvent gradient EtOAc (7→70%)–heptane afforded the product as a white solid in 50% yield. ^{1}H NMR δ: 1.58–1.71 (m, 1H); 1.96–1.98 (m, 1H); 2.91–2.93 (m, 1H); 3.57–3.73 (m, 1H); 4.78 (d, *J* = 7.1 Hz, 1H); 4.82 (d, *J* = 7.1 Hz, 1H); 6.34–8.99 (m, 36H) ppm. ^{31}P NMR δ: –14.92 ppm. HRMS: *m*/*z* calcd for $C_{60}H_{42}NNaO_6P$ $[M+Na]^+$: 926.2647; found 926.2666.

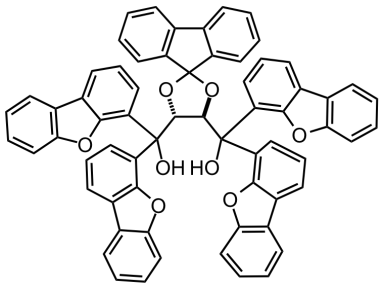
(3a'R,8a'R)-6'-Hydroxy-4',4',8',8'-tetra(naphthalen-1-yl)-3a',4',8',8a'-tetrahydrospiro-[fluorene-9,2'- [1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine] 6'-oxide **13f-POOH:**



General Procedure J. The ammonium salt of the phosphate was washed with 6N HCl (5 mL), organic phase was concentrated on the rotavapor. The product was crystallized from MeOH/$CHCl_3$ to give **13f-POOH** as white crystals. Yield: 91%; mp 170–175 °C; $[\alpha]_D^{20}$ -131 (*c* 0.96, $CHCl_3$). ^{1}H NMR δ: 4.74 (d, *J* = 3.8 Hz, 2H); 6.33–7.65 (m, 36H) ppm. ^{13}C NMR δ: 80.1 (CH); 89.3 (C); 113.4 (C); 118.5 (CH); 122.9 (CH); 124.2 (CH); 124.6 (CH); 125.3 (3CH); 126.2 (CH); 127.2 (2CH); 127.3 (2CH); 127.6 (CH); 128.5 (2CH); 129.3 (CH); 130.3 (CH); 130.5 (CH); 131.6 (C); 133.1 (C); 134.5 (C); 134.8

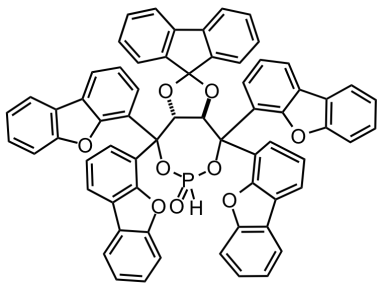
(C); 137.1 (C); 138.2 (C); 138.5 (C); 144.2 (C) ppm. ^{31}P NMR δ: –11.78 ppm. HRMS: *m*/*z* calcd for $C_{57}H_{37}O_6P$ $[M-H]^-$: 849.2406; found: 849.2415.

((4'R,5'R)-Spiro[fluorene-9,2'-[1,3]dioxolane]-4',5'-diyl)bis(bis(dibenzo[b,d]furan-4-yl)methanol) **13g**:



Dibenzo[b,d]furan (378 mg, 2.3 mmol) was dissolved in THF (5 mL), degassed and cooled to –78 °C. *n*-BuLi (1.55 mL of 1.52M solution in hexane, 2.3 mmol) was added dropwise. The mixture was stirred at room temperature for 30 min and diester **59** (170 mg, 0.5 mmol) dissolved in THF (2.5 mL) was added dropwise at –78 °C. The resulting mixture was stirred at –40 °C for 11 h. The reaction was quenched by addition of water (20 mL), the mixture was extracted with EtOAc (3× 5 mL), washed with brine, dried over $MgSO_4$ and concentrated. The crude mixture was purified MPLC applying a solvent gradient EtOAc (5→25%)–heptane and afforded **13g** as a white solid in 63 % (331 mg) yield. ^{1}H NMR δ: 5.2 (s, 2H); 6.51 (s, 2H); 6.73 (t, *J* = 7.7 Hz, 2H); 6.890–7.26 (m, 22H); 7.44 (d, *J* = 7.8 Hz, 2H); 7.62 (d, *J* = 7.9 Hz, 2H); 7.67 (d, *J* = 7.7 Hz, 2H); 7.61–7.85 (m, 6H) ^{13}C NMR δ: 78.2 (C); 81.7 (CH); 111.4 (CH); 111.6 (CH); 112.6 (C); 119.3 (CH); 119.9 (CH); 120.0 (CH); 120.1 (CH); 120.2 (CH); 122.0 (CH), 122.2 (CH); 122.3 (2CH); 123.7 (C); 124.0 (C); 124.1 (CH); 124.4 (C); 125.0 (C); 125.1 (CH); 126.5 (CH); 126.8 (CH); 127.8 (C); 127.9 (CH); 128.0 (C); 128.1 (CH); 129.6 (CH); 139.5 (C); 144.5 (C); 152.8 (C); 153.6 (C); 155.4 (C); 155.8 (C) ppm.

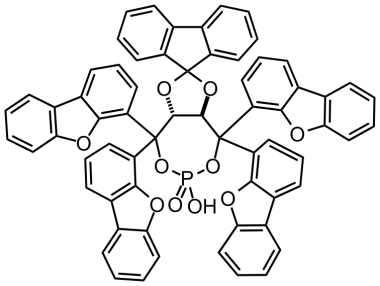
(3a'R,8a'R)-4',4',8',8'-Tetrakis(dibenzo[b,d]furan-4-yl)-3a',4',8',8a'-tetrahydrospiro-[fluorene-9,2'-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine] 6'-oxide **13g-POH**:



General Procedure D. MPLC applying a solvent gradient EtOAc(10 →100)–heptane provided **13g-POH** as a white powder in 49% yield. ^{1}H NMR δ: 5.46 (d, *J* = 7.4 Hz, 1H); 5.66 (d, *J* = 7.4 Hz, 1H); 6.55 (ptd, *J* = 7.5, 1.0 Hz, 1H); 6.56 (ptd, *J* = 7.5, 1.0 Hz, 1H); 6.82 (br.m, 2H); 6.96 (ptd, *J* = 7.5, 1.0 Hz, 2H); 6.90-7.40 (m, ~17H); 7.43 (d, J_{PH} = 740 Hz, 1H); 7.47 (pt, *J* = 7.7 Hz, 1H); 7.50 (pt, *J* = 7.7 Hz, 1H); 7.70 (br.m, 1H); 7.78 (br.d, *J* = 7.2 Hz, 1H); 7.90-7.97 (m, 6H); 8.05 (br.d, *J* ~7.5 Hz, 1H); 8.07 (dd, *J* = 7.7, 1.0 Hz, 1H); 8.10 (dd, *J* = 7.7, 1.0 Hz, 1H) ppm. ^{13}C NMR

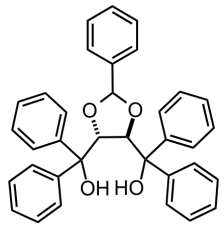
δ: 80.4 (CH); 81.3 (CH); 111.4 (CH); 111.7 (CH); 111.9 (CH); 112.0 (CH); 116.0 (C); 119.1 (CH); 119.2 (CH); 120.0 (CH); 120.2 (2CH); 120.4 (CH); 120.8 (CH); 121.0 (CH); 121.9 (CH); 122.0 (CH); 122.3 (2CH); 122.5 (CH); 122.6 (2CH); 122.7 (2CH); 122.9 (CH); 123.1 (CH); 123.2 (CH); 123.3 (C); 123.4 (2C); 123.8 (C); 124.5 (br. C); 125.5 (2C); 125.7 (C); 125.8 (C); 126.3 (C); 126.4 (CH); 126.7 (CH); 127.0 (CH); 127.1 (CH); 127.3 (br. CH); 127.4 (CH); 127.5 (CH); 127.6 (CH); 129.7 (CH); 129.8 (CH); 138.9 (2C); 139.2 (C); 143.0 (C); 143.1 (C); 153.4 (C); 153.5 (C); 153.6 (C); 153.7 (C); 155.5 (2C); 156.1 (C); 156.2 (C) ppm.* ^{31}P NMR δ: –4.81 (br) ppm. HRMS (ESI): *m/z* calcd for $C_{65}H_{39}NaO_9P$ $[M+Na]^+$: 1017.2229; found: 1017.2220.

(3a'R,8a'R)-4',4',8',8'-Tetrakis(dibenzo[b,d]furan-4-yl)-6'-hydroxy-3a',4',8',8a'-tetrahydrospiro[fluorene-9,2'-[1,3]dioxolo[4,5-e][1,3,2]-dioxaphosphepine] 6'-oxide **13g-POOH**.



General Procedure E. The ammonium salt of the phosphate was acidified with 2 N HCl (5 mL) and extracted with EtOAc, washed with brine and concentrated. The water residue was removed by addition of toluene and concentration on rotary evaporator three times. Yield: 99%; white powder. ^{1}H NMR δ: 5.50 (br.s, 2H); 6.51 (pt, *J* = 7.2 Hz, 2H); 6.60-7.25 (m, 20H); 7.34 (pt, *J* = 7.2 Hz, 2H); 7.60 (br.s 2H); 7.68-8.00 (m, 8H); 8.09 (m, 2H) ppm. ^{13}C NMR δ: 80.6 (CH), 111.7 (CH); 118.9 (CH); 119.8 (CH); 120.0 (CH); 120.5 (CH); 121.2 (CH); 122.1 (3CH); 122.4(CH); 123.2 (CH); 123.3 (C); 123.5 (C); 124.9 (C); 125.4 (2C); ~125.6 (C); 125.6 (CH); 126.5 (C); 126.7 (2CH); 127.4 (2CH); 129.5 (CH); 139.0 (C); 141.1 (CH); 143.3 (C); 143.4 (CH); 153.6 (C); 153.8 (C); 155.5 (C); 155.9 (C) ppm.* ^{31}P NMR δ: –8.91 ppm. HRMS (ESI): *m/z* calcd for $C_{65}H_{38}O_{10}P$ $[M-H]^-$: 1009.2208; found: 1009.2228.

((4R,5R)-2-Phenyl-1,3-dioxolane-4,5-diyl)bis(diphenylmethanol) **14a:**[136]



General Procedure A. MPLC applying EtOAc/hexane (10/90) afforded **14a** in 82% yield. ^{1}H NMR δ: 2.09 (s, 1H); 3.27 (s, 1H); 5.13 (d, J = 5.0 Hz, 1H); 5.17 (s, 1H); 5.32 (d, J = 5.0 Hz, 1H); 7.00–7.70 (m, 25H) ppm.**

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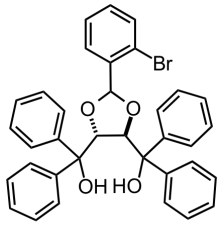
* 2 quaternary C were not observed

* 2 quaternary C were not observed

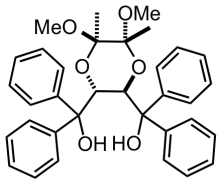
** Spectroscopic datas are in accordance with literature.

((4R,5R)-2-(2-Bromophenyl)-1,3-dioxolane-4,5-diyl)bis(diphenylmethanol) **15a**:



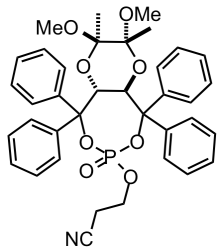
General Procedure A. MPLC applying a solvent gradient EtOAc(2→20%)–hexane afforded **15a** in 50% yield. Mp 83 °C; $[\alpha]_D^{20}$ -3.40 (*c* 0.9, $CHCl_3$). ^{1}H NMR δ: 2.24 (s, 1H); 3.21 (s, 1H); 5.14 (d, *J* = 5.1 Hz, 1H); 5.31 (d, *J* = 5.1 Hz, 1H); 5.62 (s, 1H); 7.11–7.50 (m, 24H) ppm. ^{13}C NMR δ: 78.6 (C); 78.8 (C); 80.9 (CH); 81.5 (CH); 103.7 (CH); 123.1 (C); 126.9 (CH); 127.1 (CH); 127.2 (CH); 127.3 (2CH); 127.4 (CH); 127.6 (CH); 127.7 (CH); 128.0 (CH); 128.1 (2CH); 128.2 (CH); 128.3 (CH); 128.4 (CH); 130.6 (CH); 132.8 (CH); 135.9 (C); 142.8 (C); 144.2 (C); 144.4 (C); 145.9 (C) ppm. HRMS: *m*/*z* calcd for $C_{35}H_{28}BrO_4$ $[M-H]^-$: 591.1176; found: 591.1174.

((2R,3R,5R,6R)-5,6-Dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(diphenylmethanol) **16a**:[149]



General Procedure A. MPLC applying EtOAc/hexane(10/90) afforded **16a** in 73% yield. ^{1}H NMR δ: 1.01 (s, 6H); 2.58 (s, 6H); 4.34 (s, 2H); 4.40 (s, 2H); 7.04–7.13 (m, 10H); 7.33–7.44 (m, 6H); 7.97–7.99 (m, 4H) ppm.*

3-(((2R,3R,4aR,9aR)-,3-Dimethoxy-2,3-dimethyl-7-oxido-5,5,9,9-tetraphenylhexahydro-[1,4]dioxino[2,3-e][1,3,2]dioxaphosphepin-7-yl)oxy)propanenitrile:



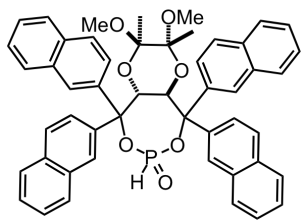
General Procedure G. MPLC applying a solvent gradient EtOAc(4→40%)–heptane afforded the product in 21% yield. $[\alpha]_D^{20}$ -210 (*c* 1.00 $CHCl_3$). ^{1}H NMR δ: 1.04 (s, 3H); 1.05 (s, 3H); 2.23–2.39 (m, 2H); 2.36 (s, 3H); 2.74 (s, 3H); 3.61–3.69 (m, 1H); 3.89–3.94 (m, 1H); 4.70 (d, *J* = 10.4 Hz, 1H); 5.01 (d, *J* = 10.4 Hz, 1H); 7.08−7.23(m, 10H); 7.35–7.41 (m, 6H); 7.89–7.93 (m, 4H) ppm. ^{13}C NMR δ: 16.9 (CH_3); 17.0 (CH_3); 19.3 (d, J_{CP} = 8.2 Hz, CH_2); 47.3 (CH_3); 47.9 (CH_3); 61.6 (d, J_{CP} = 5.2 Hz, CH_2); 73.0 (CH); 73.6 (CH); 88.6 (d, J_{CP} = 6.6 Hz, C); 88.7 (d, J_{CP} = 8.7 Hz, C); 98.7 (2C); 116.4 (C); 127.0 (CH); 127.3 (CH); 127.4 (CH); 127.5 (2CH); 127.6 (2CH); 127.8 (CH); 128.1 (CH); 128.3 (CH); 129.8 (CH); 130.2 (CH); 137.4 (d, J_{CP} = 2.9 Hz, C); 139.2 (C); 144.4 (d, J_{CP} = 10.5 Hz, C); 145.2 (d, J_{CP} = 11.9 Hz, C) ppm. ^{31}P NMR δ: –11.96 ppm. HRMS: *m*/*z* calcd for $C_{37}H_{38}NNaO_8P$ $[M+Na]^+$: 678.2233; found 678.2246.

As a side product *(2R,3R,4aR,9aR)-2,3-Dimethoxy-2,3-dimethyl-5,5,9,9-tetraphenyl-hexahydro-[1,4]dioxino[2,3-e][1,3,2]dioxaphosphepine 7-oxide* **16a-POH** was forned in 63% yield. ^{1}H NMR δ: 1.06 (s, 3H); 1.07 (s, 3H); 2.39 (s, 3H); 2.54 (s, 3H); 4.82 (d, *J* = 10.6 Hz, 1H); 4.86 (d, *J* = 10.6 Hz, 1H); 6.78 (d, J_{HP} = 731.3 Hz, 1H); 7.04−7.23 (m, 10H); 7.38–7.43 (m, 6H); 7.92–7.94 (m, 2H); 8.08 (dd, *J* = 8.0 Hz, 1.4 Hz, 2H) ppm. ^{13}C NMR δ: 16.8 ($2CH_3$); 47.3 (CH_3); 47.6 (CH_3); 74.5 (2CH); 87.2 (d, J_{CP} = 7.3 Hz, C); 88.5 (d, J_{CP} = 9.5 Hz, C); 99.1 (C); 99.3 (C); 126.9 (CH); 127.0 (CH); 127.4 (2CH); 127.5 (CH); 127.7 (2CH); 128.2 (CH); 128.6 (2CH); 129.6 (CH); 129.9 (CH); 137.7 (d, J_{CP} = 4.4 Hz, C); 138.3 (d, J_{CP} = 2.2 Hz, C); 144.4 (d, J_{CP} = 10.9 Hz, C); 145.0 (d, J_{CP} = 9.8 Hz, C) ppm. ^{31}P NMR δ: –3.06 ppm. HRMS: *m*/*z* calcd for $C_{34}H_{35}NNaO_7P$ $[M+Na]^+$: 609.2018; found 609.2020.

(2R,3R,4aR,9aR)-7-Hydroxy-2,3-dimethoxy-2,3-dimethyl-5,5,9,9-tetraphenylhexahydro-[1,4]dioxino[2,3-e][1,3,2]dioxaphosphepine 7-oxide **16a-POOH**: *General Procedure E*. Yield: 95%; mp 145–150 °C; $[\alpha]_D^{20}$ +34.5 (*c* 0.98 $CHCl_3$). ^{1}H NMR δ: 1.05 (s, 6H); 2.52 (s, 6H); 4.79 (s, 2H); 7.08−7.12 (m, 10H); 7.27–7.33 (m, 6H); 7.87 (dd, *J* = 8.0 Hz, 2.0 Hz, 4H) ppm. ^{13}C NMR δ: 16.9 (CH_3); 47.5 (CH_3); 73.8 (CH); 87.8 (d, J_{CP} = 6.7 Hz, C); 98.6 (C); 126.9 (CH); 127.2 (2CH); 127.7 (CH); 127.9 (CH); 130.0 (CH); 138.1 (d, J_{CP} = 2.2 Hz, C); 145.1 (d, J_{CP} = 12.5 Hz, C) ppm. ^{31}P NMR δ: –7.98 ppm. HRMS: *m*/*z* calcd for $C_{34}H_{35}NaO_8P$ $[M+Na]^+$: 625.1967; found 625.1945.

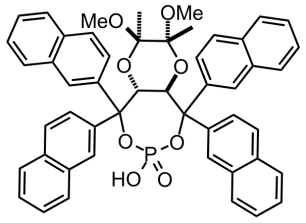
((2R,3R)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-diyl)bis(di(naphthalen-2-yl)methanol) **16e**: *General Procedure A*. MPLC applying a solvent gradient EtOAc(2→23%)–heptane afforded the product in 60% yield. Mp 154–155 °C, $[\alpha]_{578}^{20}$ +68.8 (*c* 0.98 $CHCl_3$). ^{1}H NMR δ: 1.05 (s, 6H); 2.63 (s, 6H); 4.66 (s, 2H); 4.81 (s, 2H); 7.20–7.35 (m, 6H); 7.43–7.57 (m, 10H); 7.65 (d, *J* = 8.6 Hz, 2H); 7.91−7.95 (m, 6H); 8.11 (d, *J* = 8.6 Hz, 2H); 8.69 (s, 2H) ppm. ^{13}C NMR δ: 17.3 (CH_3); 48.0 (CH_3); 75.8 (CH); 80.0 (C); 98.7 (C); 125.5 (CH); 125.7 (2CH); 125.8 (CH); 125.9 (CH); 126.2 (CH); 126.5 (CH); 126.6 (CH); 127.2 (CH); 127.3 (2CH); 127.5 (CH); 128.4 (CH); 128.9 (CH); 132.4 (C); 132.5 (C); 132.8 (C); 133.2 (C); 140.6 (C); 143.4 (C) ppm. HRMS: *m*/*z* calcd for $C_{50}H_{44}NNaO_6$ $[M+Na]^+$: 763.3036; found 763.3036.

(4aR,9aR)-2,3-dimethoxy-2,3-dimethyl-5,5,9,9-tetra(naphthalen-2-yl)hexahydro-[1,4]dioxino[2,3-e][1,3,2]dioxaphosphepine 7-oxide **16e-POH**:



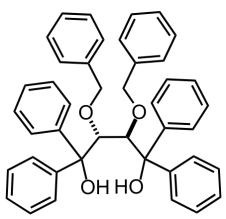
General Procedure E. MPLC applying a solvent gradient EtOAc (6→50%)–heptane afforded the product in 52% yield. Mp 197–201 °C, $[\alpha]_{546}^{20}$ +295 (*c* 1.13 $CHCl_3$). ^{1}H NMR δ: 1.15 (s, 3H); 1.17 (s, 3H); 2.44 (s, 3H); 2.59 (s, 3H); 5.26 (d, *J* = 10.9 Hz, 1H); 5.29 (d, *J* = 10.9 Hz, 1H); 7.00 (d, J_{HP} = 733.9 Hz, 1H); 7.15−7.93 (m, 26H); 9.05 (d, *J* = 10.0 Hz, 2H) ppm. ^{13}C NMR δ: 16.9 (CH_3); 17.0 (CH_3); 47.7 (CH_3); 47.9 (CH_3); 74.6 (CH); 74.7 (CH); 87.6 (d, J_{CP} = 7.7 Hz, C); 88.9 (d, J_{CP} = 10.1 Hz, C); 99.4 (C); 99.5 (C); 125.7 (CH); 125.8 (2CH); 126.1 (2CH); 126.2 (2CH); 126.3 (2CH); 126.5 (2CH); 126.7 (2CH); 127.2 (CH); 127.3 (2CH); 127.5 (2CH); 127.7 (CH); 127.8 (CH); 128.2 (CH); 128.4 (CH); 128.6 (3CH), 129.0 (2CH); 129.3 (CH); 132.3 (2C); 132.5 (2C); 132.6 (2C); 133.0 (C); 133.4 (C); 134.4 (d, J_{CP} = 3.1 Hz, C); 135.5 (d, J_{CP} = 2.2 Hz, C); 141.4 (d, J_{CP} = 10.4 Hz, C); 141.7 (d, J_{CP} = 9.7 Hz, C) ppm. ^{31}P NMR δ: –2.92 ppm. HRMS: *m*/*z* calcd for $C_{50}H_{42}O_7P$ $[M\text{-}H\ ]^-$: 785.2668; found 785.2694

(4aR,9aR)-7-hydroxy-2,3-dimethoxy-2,3-dimethyl-5,5,9,9-tetra(naphthalen-2-yl)hexahydro- [1,4]dioxino[2,3-e][1,3,2]dioxaphosphepine 7-oxide **16e-POOH**:



*General Procedure E***.** The reaction was complete in 3 h. Yield: 90%; mp 175–177 °C. ^{1}H NMR δ: 1.09 (s, 6H); 2.49 (s, 6H); 5.20 (s, 2H); 7.36−76 (m, 24H); 8.13 (brs, 2H); 8.87 (brs, 2H) ppm. ^{13}C NMR δ: 17.0 (CH_3); 47.7 (CH_3); 73.9(CH); 88.2 (d, J_{CP} = 6.1 Hz, C); 98.9 (C); 125.5 (CH); 125.7 (CH); 125.9 (CH); 126.2 (CH); 126.3 (2CH); 126.4 (CH); 126.9 (CH); 127.2 (CH); 127.7 (CH); 128.6 (CH); 128.7 (CH); 128.9 (CH); 129.1 (CH); 132.3 (C); 132.4 (C); 132.5 (C); 133.1 (C); 135.1 (C); 141.9 (d, J_{CP} = 11.9 Hz, C) ppm. ^{31}P NMR δ: –7.79 ppm. HRMS: *m*/*z* calcd for $C_{50}H_{42}O_8P$ $[M\text{-}H]^-$: 801.2617; found 801.2630

(2R,3R)-2,3-Bis(benzyloxy)-1,1,4,4-tetraphenylbutane-1,4-diol **17a**:

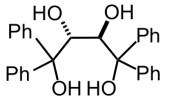


a) From ester **63**: General Procedure **A.** Yield = 50%.

b) (*Table 6*, entry 40, *General Procedure K,* 0.5 mM). Flash chromatography with a solvent gradient EtOAc (2→20%) / hexane afforded 202 mg (67%) of diol **17a** as a white foam; $[\alpha]_D^{20}$ -60.1 (c 4.82, $CHCl_3$). ^{1}H NMR δ: 3.44 (d, *J* = 9.7 Hz, 2H), 3.85 (d, *J* = 9.7

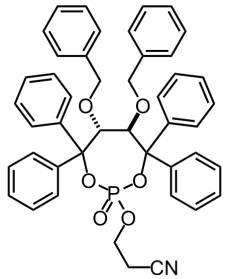
Hz, 2H), 4.80 (s, 2H), 4.85 (s, 2H), 6.98–7.01 (m, 4H), 7.19 (ps.t, *J* = 7.4 Hz, 2H), 7.23–7.31 (m, 10H), 7.38 (t, *J* = 7.3 Hz, 2H), 7.50 (t, *J* = 7.8 Hz, 4H), 7.67–7.73 (m, 8H) ppm. ^{13}C NMR δ: 74.5 (CH_2), 80.3 (C), 82.9 (CH), 126.2 (CH), 126.5 (CH), 126.9 (CH), 127.3 (CH), 127.7 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.5 (CH), 137.4 (C), 145.2 (C), 145.6 (C) ppm. HRMS: *m/z* calcd for $C_{42}H_{38}NaO_4$ $[M+Na]^+$: 629.2668; found: 629.2670.

(2R,3R)-1,1,4,4-Tetraphenylbutane-1,2,3,4-tetraol **17a-OH.**[150]



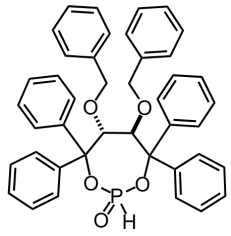
Diol **17** (48 mg, 0.08 mmol) was dissolved in EtOH (1 mL). To this solution 10% Pd/C (6 mg) was added at room temperature and the mixture was stirred under an atmosphere of hydrogen (balloon) for 3 h. Filtration over a pad of celite and removal of the solvent gave tetraol **17-OH** as a clear colorless oil. Yield: 35 mg (quantitative). ^{1}H NMR δ: 3.74 (d, *J* = 4.5 Hz, 2H); 4.42 (d, *J* = 4.5 Hz, 2H); 4.62 (s, 2H); 7.15 (ps.t, *J* = 7.2 Hz, 2H); 7.20–7.35 (m, 18H) ppm.*

3-(((5R,6R)-5,6-Bis(benzyloxy)-2-oxido-4,4,7,7-tetraphenyl-1,3,2-dioxaphosphepan-2-yl)oxy)propanenitrile:



General Procedure G. MPLC applying a solvent gradient EtOAc(10→80%)–hexane afforded the product in 26% yield. ^{1}H NMR δ: 2.08–2.15 (m, 1H); 2.26–2.37 (m, 1H); 3.27–3.35 (m, 1H); 3.76 (d, *J* = 11.2 Hz, 1H); 3.81 (d, *J* = 11.2, 1H); 3.90–3.99 (m, 1H); 3.91 (d, *J* = 11.4 Hz, 1H); 4.01 (d, *J* = 11.4 Hz, 1H); 5.06 (d, *J* = 6.8 Hz, 1H); 5.09 (d, *J* = 6.8 Hz, 1H); 6.75–6.83 (m, 4H); 7.08–7.15 (m, 6H); 7.31–7.45 (m, 16H); 7.59–7.62 (m, 4H) ppm. ^{31}P NMR δ: –12.54 ppm.

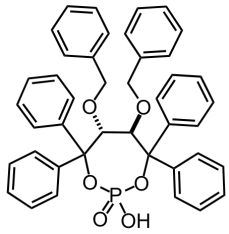
(5R,6R)-5,6-Bis(benzyloxy)-4,4,7,7-tetraphenyl-1,3,2-dioxaphosphepane 2-oxide **17a-POH**: *General Procedure D*. Yield: 48%; $[\alpha]_D^{20}$ -38.0 (*c* 1.0 $CHCl_3$). ^{1}H NMR δ: 3.83 (d, *J* = 11.2 Hz, 1H); 3.91 (d, *J* = 11.3 Hz, 1H); 4.08 (d, *J* = 11.2 Hz, 1H); 4.09 (d, *J* = 11.3 Hz, 1H); 4.98 (d, *J* = 7.2 Hz, 1H); 5.21 (d, *J* = 7.2 Hz, 1H); 6.81 (dd, *J* = 8.0, 2.0 Hz, 2H); 6.85 (dd, *J* = 8.0, 1.9 Hz, 2H); 7.12−7.18 (m, 6H); 7.24 (d, *J* = 730.8 Hz, 1H); 7.31–7.47 (m, 16H); 7.64 (dd, *J* = 7.9, 1.3 Hz, 2H); 7.74 (d, J = 7.9, 1.3 Hz, 2H) ppm. ^{13}C NMR δ: 73.9 (CH_2); 74.1 (CH_2); 78.9 (CH); 79.2 (d, *J* = 1.4 Hz,



* Spectroscopic data are in accordance with literature.

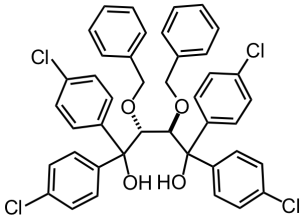
CH); 88.5 (d, J_{CP} = 8.5 Hz, C); 88.9 (d, J_{CP} = 8.5 Hz, C); 127.2 (CH); 127.3 (4CH); 127.4 (CH); 127.5 (CH); 128.0 (2CH); 128.2 (3CH); 128.4 (2CH); 128.5 (CH); 128.6 (CH); 128.9 (CH); 137.5 (2C); 138.9 (d, J_{CP} = 6.9 Hz, C); 139.1 (d, J_{CP} = 8.6 Hz, C); 142.9 (d, J_{CP} = 2.2 Hz, C); 143.0 (d, J_{CP} = 3.9 Hz, C) ppm.* ^{31}P NMR δ: –4.11 ppm. HRMS: *m*/*z* calcd for $C_{42}H_{37}NaO_5P$ $[M+Na]^+$: 675.2276; found: 675.2264.

(5R,6R)-5,6-Bis(benzyloxy)-2-hydroxy-4,4,7,7-tetraphenyl-1,3,2-dioxaphosphepane-2-oxide **17a-POOH**:



General Procedure J. The organic layer was washed with 0.3M HCl solution, brine, dried over $MgSO_4$, filtered and concentrated under vacuum affording **17a-POOH** in 80% yield. Mp 196–199 °C, $[\alpha]_D^{20}$ -44.2 (*c* 0.98 $CHCl_3$). ^{1}H NMR δ: 3.77 (d, *J* = 11.3 Hz, 2H); 3.95 (d, *J* = 11.3 Hz, 2H); 4.93 (s, 2H); 6.75−6.78 (m, 4H); 7.07–7.36 (m, 22H); 7.59–7.61 (m, 4H) ppm. ^{13}C NMR δ: 73.8 (CH_2); 78.5 (CH); 87.8 (d, J_{CP} = 4.0 Hz, C); 127.2 (2CH); 127.4 (CH); 127.5 (CH); 127.8 (CH); 127.9 (2CH); 128.0 (CH); 128.9 (CH); 137.8 (C); 139.6 (d, J_{CP} = 8.8 Hz, C); 142.8 (d, J_{CP} = 2.0 Hz, C) ppm. ^{31}P NMR δ: –8.09 ppm. HRMS: *m*/*z* calcd for $C_{42}H_{36}O_6P$ $[M-H]^-$: 667.2250; found: 667.2268.

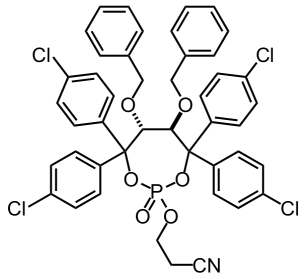
(2R,3R)-2,3-Bis(benzyloxy)-1,1,4,4-tetrakis(4-chloropheny)lbutane-1,4-diol **17b**:



General Procedure A. MPLC with a solvent gradient EtOAc (5→11%)–heptane afforded **17b** in 52% yield. Mp 75–79 °C; $[\alpha]_D^{20}$ -40.3 (*c* 1.04 $CHCl_3$). ^{1}H NMR δ: 3.73 (d, *J* = 10.2 Hz, 2H); 4.11 (d, *J* = 10.2 Hz, 2H); 4.67 (s, 2H); 4.75 (s, 2H); 7.07−7.09 (m, 4H); 7.38–7.42 (m, 10H); 7.55 (d, *J* = 8.8 Hz, 4H); 7.62 (d, *J* = 8.6 Hz, 4H); 7.68 (d, *J* = 8.8 Hz, 4H) ppm. ^{13}C NMR δ: 74.6 (CH_2); 79.8 (C); 82.1 (CH); 127.6 (CH); 127.8 (CH); 127.9 (CH); 128.0 (CH); 128.2 (CH); 128.3 (CH); 128.8 (CH); 133.3 (C); 133.6 (C); 136.9 (C); 143.0 (C); 143.4 (C) ppm. HRMS: *m*/*z* calcd for $C_{42}H_{34}Cl_4NaO_4$ $[M+Na]^+$: 765.1109; found: 765.1107.

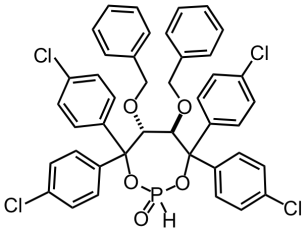
* 1 CH was not obeserved.

3-(((5R,6R)-5,6-Bis(benzyloxy)-4,4,7,7-tetrakis(4-chlorophenyl)-2-oxido-1,3,2-dioxaphosphepan-2- yl)oxy)propanenitrile:



General Procedure G. MPLC with a solvent gradient EtOAc (5→50%)–heptane afforded the product in 17% yield. ^{1}H NMR δ: 2.19–2.27 (m, 1H); 2.41–2.48 (m, 1H); 3.48–3.56 (m, 1H); 3.80 (t, *J* = 10.7 Hz, 2H); 3.96–4.02 (m, 2H); 4.05 (d, *J* = 11.2 Hz, 1H); 4.84 (d, *J* = 6.9 Hz, 1H); 4.88 (d, *J* = 6.9 Hz, 1H); 6.72–6.75 (m, 4H); 7.10–7.34 (m, 18H); 7.43–7.47 (m, 4H) ppm. ^{13}C NMR δ: 19.5 (d, J_{CP} = 7.4 Hz, CH_2); 62.1 (d, J_{CP} = 4.4 Hz, CH_2); 74.2 (CH_2); 74.3 (CH_2); 77.1 (CH); 77.8 (CH); 87.9 (d, J_{CP} = 2.9 Hz, C); 88.0 (C); 116.1 (C); 127.5 (2CH); 127.8 (2CH); 127.9 (2CH); 128.3 (2CH); 128.7 (2CH); 129.1 (CH); 129.9 (2CH); 130.3 (CH); 134.8 (C); 134.9 (2C); 135.0 (C); 136.7 (2C); 137.2 (d, J_{CP} = 7.3 Hz, C); 137.3 (d, J_{CP} = 7.3 Hz, C); 140.1 (d, J_{CP} = 1.4 Hz, C); 140.5 (d, J_{CP} = 1.9 Hz, C) ppm. ^{31}P NMR δ: –12.36 ppm. HRMS: *m*/*z* calcd for $C_{45}H_{36}Cl_4NNaO_6P$ $[M+Na]^+$: 880.0903; found: 880.0912.

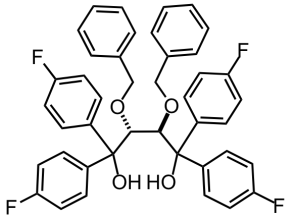
As a side product *(5R,6R)-5,6-Bis(benzyloxy)-4,4,7,7-tetrakis(4-chlorophenyl)-1,3,2-dioxaphosphepane 2-oxide* **17b-POH** was formed in 13% yield.



Mp 183–184 °C; $[\alpha]_{546}^{20}$ -70.3 (*c* 1.06 $CHCl_3$). ^{1}H NMR δ: 3.73 (d, *J* = 11.1 Hz, 1H); 3.94 (d, *J* = 11.2 Hz, 1H); 4.13 (d, *J* = 11.2 Hz, 1H); 4.25 (d, *J* = 11.1 Hz, 1H); 4.73 (d, *J* = 7.4 Hz, 1H); 5.08 (d, *J* = 7.4 Hz, 1H); 6.75 (d, *J* = 7.9 Hz, 2H); 6.85 (d, *J* = 7.6 Hz, 2H); 6.95 (d, J_{HP} = 739.5 Hz, 1H); 7.14−7.38 (m, 18H); 7.48 (d, *J* = 8.8 Hz, 2H); 7.61 (d, *J* = 8.8 Hz, 2H) ppm. ^{13}C NMR δ: 44.5 (CH_2); 74.7 (CH_2); 78.9 (CH); 79.7 (CH); 87.7 (d, J_{CP} = 9.0 Hz, C); 88.0 (d, J_{CP} = 8.9 Hz, C); 127.5 (2CH); 127.9 (2CH); 128.0 (CH); 128.3 (2CH); 128.5 (CH); 128.6 (CH); 128.8 (2CH); 129.8 (CH); 130.2 (CH); 134.8 (3C); 134.9 (C); 136.6 (C); 136.7 (C); 136.9 (d, J_{CP} = 6.1 Hz, C); 137.2 (d, J_{CP} = 8.8 Hz, C); 140.7 (d, J_{CP} = 1.7 Hz, C); 141.0 (d, J_{CP} = 4.0 Hz, C) ppm. ^{31}P NMR δ: –3.65 ppm. HRMS : *m*/*z* calcd for $C_{42}H_{32}Cl_4NO_5P$ $[M - H]^-$: 789.0741; found: 789.0745.*

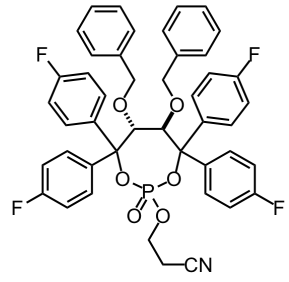
* 1 CH was not observed.

(2R,3R)-2,3-Bis(benzyloxy)-1,1,4,4-tetrakis(4-chloropheny)lbutane-1,4-diol **17c**:



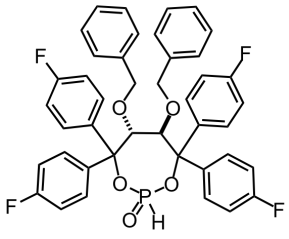
General Procedure A. MPLC with a solvent gradient EtOAc (2→15%)–heptane afforded **17c** in 73% yield. Mp 134–135 °C; $[\alpha]_D^{20}$ -15.8 (*c* 0.98 $CHCl_3$). ^{1}H NMR δ: 3.51 (d, *J* = 10.1 Hz, 2H); 3.91 (d, *J* = 10.1 Hz, 2H); 4.48 (s, 2H); 4.56 (s, 2H); 6.89−6.92 (m, 4H); 6.95 (t, *J* = 8.6 Hz, 4H); 7.09 (d, *J* = 8.7 Hz, 4H); 7.19–7.21 (m, 6H); 7.46–7.57 (m, 8H) ppm. ^{13}C NMR δ: 74.5 (CH_2); 79.7 (C); 82.3 (CH); 114.8 (d, J_{CF} = 21.3 Hz, CH); 115.4 (d, J_{CF} = 21.3 Hz, CH); 127.8 (2CH); 128.0 (d, J_{CF} = 8.4 Hz, CH); 128.3 (CH); 128.5 (d, J_{CF} = 8.1 Hz, CH); 137.2 (C); 140.3 (d, J_{CF} = 3.0 Hz, C); 141.0 (d, J_{CF} = 3.6 Hz, C); 161.9 (d, J_{CF} = 247.9 Hz, 2C) ppm. HRMS: *m*/*z* calcd for $C_{42}H_{34}F_4NaO_4$ $[M+Na]^+$: 701.2293; found: 701.2276.

3-(((5R,6R)-5,6-Bis(benzyloxy)-4,4,7,7-tetrakis(4-fluorophenyl)-2-oxido-1,3,2-dioxaphosphepan-2- yl)oxy)propanenitrile:



General Procedure G. MPLC with a solvent gradient EtOAc (5→60%)–heptane afforded the product in 7% yield. ^{1}H NMR δ: 2.24–2.31 (m, 1H); 2.46–2.54 (m, 1H); 3.48–3.56 (m, 1H); 3.81 (d, *J* = 11.3 Hz, 1H); 3.86 (d, *J* = 11.3 Hz, 1H); 4.00 (d, *J* = 11.3 Hz, 1H); 4.00–4.06 (m, 1H); 4.07 (d, *J* = 11.3 Hz, 1H); 4.94 (d, *J* = 6.8 Hz, 1H); 4.96 (d, *J* = 6.8 Hz, 1H); 6.78–6.81 (m, 4H); 6.96–7.19 (m, 14H); 7.28–7.36 (m, 4H); 7.53–7.58 (m, 4H) ppm. ^{13}C NMR δ: 19.5 (d, J_{CP} = 8.0 Hz, CH_2); 61.9 (d, J_{CP} = 4.3 Hz, CH_2); 74.0 (CH_2); 74.2 (CH_2); 76.9 (CH); 77.8 (CH); 88.1 (d, J_{CP} = 7.7 Hz, C); 88.3 (d, J_{CP} = 5.7 Hz, C); 114.5 (d, J_{CF} = 21.3 Hz, CH); 114.6 (d, J_{CF} = 21.3 Hz, CH); 115.3 (d, J_{CF} = 21.3 Hz, CH); 115.4 (d, J_{CF} = 21.3 Hz, CH); 116.2 (C); 127.4 (2CH); 127.8 (2CH); 128.3 (2CH); 129.4 (d, $J_{CF,\ CP}$ = 8.0 Hz, CH); 129.7 (d, $J_{CF,\ CP}$ = 8.0 Hz, CH); 130.4 (d, J_{CF} = 8.1 Hz, CH); 130.8 (d, J_{CF} = 8.0 Hz, CH); 134.8 (d, J_{CF} = 1.9 Hz, C); 134.9 (d, J_{CF} = 2.5 Hz, C); 136.9 (2C); 137.7 (C); 138.1 (C); 162.5 (d, J_{CF} = 249.9 Hz, C); 162.7 (d, J_{CF} = 249.9 Hz, C); 162.8 (d, J_{CF} = 249.1 Hz, 2C) ppm. ^{31}P NMR δ: –12.46 ppm. HRMS: *m*/*z* calcd for $C_{45}H_{36}F_4NNaO_6P$ $[M+Na]^+$: 816.2114; found: 816.2104.

As a side product *(5R,6R)-5,6-Bis(benzyloxy)-4,4,7,7-tetrakis(4-fluorophenyl)-1,3,2-dioxaphosphepan-2*-oxide **17c-POH** was formed in 13% yield.

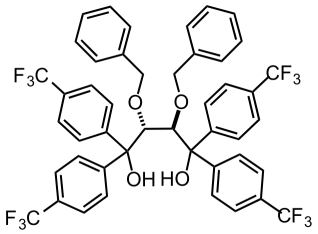


^{1}H NMR δ: 3.74 (d, *J* = 11.2 Hz, 1H); 3.92 (d, *J* = 11.2 Hz, 1H); 4.10 (d, *J* = 11.2 Hz, 1H); 4.19 (d, *J* = 11.2 Hz, 1H); 4.78 (d, *J* = 7.2 Hz, 1H); 5.09 (d, *J* = 7.2 Hz, 1H); 6.77 (d, *J* = 7.6 Hz, 2H);

6.85 (d, J = 7.8 Hz, 2H); 6.93 (d, J_{HP} = 737.2 Hz, 1H); 6.94−7.36 (m, 18H); 7.52–7.68 (m, 4H) ppm. ^{13}C NMR δ: 74.4 (CH_2); 74.5 (CH_2); 78.9 (CH); 79.7 (CH); 87.9 (d, J_{CP} = 8.4 Hz, C); 88.1 (d, J_{CP} = 8.8 Hz, C); 114.6 (d, J_{CF} = 21.6 Hz, CH); 114.7 (d, J_{CF} = 21.6 Hz, CH); 115.3 (d, J_{CF} = 22.0 Hz, CH); 115.5 (d, J_{CF} = 22.0 Hz, CH); 127.4 (2CH); 127.8 (2CH); 128.3 (2CH); 129.1 (d, J_{CF} = 8.3 Hz, CH); 129.4 (d, J_{CF} = 8.8 Hz, CH); 130.4 (d, J_{CF} = 8.8 Hz, CH); 130.8 (d, J_{CF} = 8.0 Hz, CH); 134.5 (dd, $J_{CP, CF}$ = 5.8, 3.0 Hz, C); 134.7 (dd, $J_{CP, CF}$ = 9.0, 3.6 Hz, C); 136.9 (2C); 138.4 (d, J = 2.8 Hz, C); 138.7 (ps.t, J = 3.6 Hz, C); 162.6 (d, J_{CF} = 249.0 Hz, 2C); 162.7 (d, J_{CF} = 249.0 Hz, C); 162.8 (d, J_{CF} = 249.0 Hz, C) ppm. ^{31}P NMR δ: –3.89 ppm. HRMS: *m*/*z* calcd for $C_{42}H_{33}F_4NaO_5P$ $[M+Na]^+$: 747.1899; found: 747.1903.

(2R,3R)-2,3-Bis(benzyloxy)-1,1,4,4-tetrakis(4-(trifluoromethyl)phenyl)butane-1,4-diol

17d:

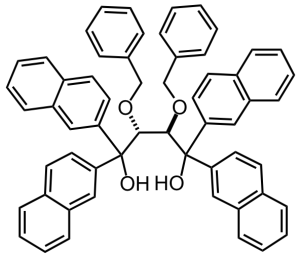


Diethyl diester **63** (290 mg, 0.72 mmol) was dissolved in THF (2 mL) and *p*-CF_3PhMgBr (4.4 mmol, prepared by following standard synthesis for Grignard reagent[137]) in THF (10 mL) was added dropwise at 0 °C. The mixture was heated to reflux for 3.5 h and cooled to 0 °C. Saturated solution of NH_4Cl was added and the mixture was extracted with EtOAc (3× 10 mL), washed with brine, dried over $MgSO_4$ and concentrated. Crude product was purified by MPLC applying a solvent gradient EtOAc(1→13%)–hexane to yield 500 mg of **17d**/hemiketal **17a-H** (5:1) mixture. This mixture (500 mg, 0.68 mmol) was dissolved in Et_2O (1.5 mL) and cooled to –78 °C and 4-(trifluromethyl)phenyllithium* (1.5 mmol) in Et_2O (3 mL) was added dropwise and gradually warmed up to room temperature. After 4 h, sat. aq. solution of NH_4Cl was added. The organic layer was extracted with EtOAc, washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by MPLC applying a solvent gradient EtOAc(1→13%)–hexane affording **17c** as a clear colorless oil in 300 mg (40% in two steps) yield. $[\alpha]_{578}^{20}$ -5.30 (*c* 0.6 $CHCl_3$). ^{1}H NMR δ: 3.60 (d, J = 10.3 Hz, 2H); 4.03 (d, J = 10.3 Hz, 2H); 4.47 (s, 2H); 4.69 (s, 2H); 6.82 (d, J = 7.3 Hz, 4H); 7.16–7.22 (m, 6H); 7.54 (d, J = 8.3 Hz, 4H); 7.59–7.67 (m, 8H); 7.71 (d, J = 8.3 Hz, 4H) ppm. ^{13}C NMR δ: 74.8 (CH_2); 80.1 (C); 81.9 (CH); 123.7 (q, J_{CF} = 246.6 Hz, C); 123.9 (q, J_{CF} = 245.9 Hz, C); 125.2 (q, J_{CF} = 3.7 Hz, CH); 125.8 (q, J_{CF} = 3.7 Hz, CH); 126.6 (CH); 126.9 (CH), 127.7 (CH); 128.0 (CH); 128.4 (CH); 129.9 (q, J_{CF} = 33.0 Hz, C);

* Prepared by addition of *n*-BuLi (0.95 mL of 1.6M in hexane solution, 1.5 mmol) into solution of 4-(trifluromethyl)phenyl bromide (0.23 mL, 1.6 mmol) in Et_2O (2 mL) at –78 °C and warming up to 0 °C. The mixture was stirred for 30 min and cooled back to –78 °C.

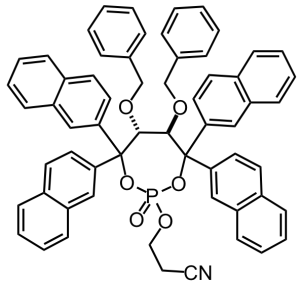
130.2 (J_{CF} = 33.2 Hz, C); 136.7 (C); 148.1 (2C) ppm. HRMS: *m*/*z* calcd for $C_{46}H_{34}F_{12}NaO_4$ $[M + Na]^+$: 901.7304; found: 901.2141.

(2R,3S)-2,3-bis(benzyloxy)-1,1,4,4-tetra(naphthalen-2-yl)butane-1,4-diol **17e**:



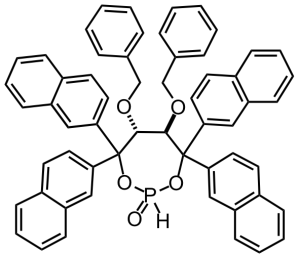
General Procedure A. MPLC with a solvent gradient EtOAc (2→20%)–heptane afforded **17e** in 59% yield. Mp 91–955 °C; $[\alpha]_D^{20}$ -146 (*c* 1.06 $CHCl_3$). ^{1}H NMR δ: 3.43 (d, *J* = 9.9 Hz, 2H); 3.84 (d, *J* = 9.9 Hz, 2H); 5.13 (s, 2H); 5.22 (s, 2H); 6.86 (d, *J* = 7.6 Hz, 4H); 7.13−7.16 (m, 6H); 7.35–7.93 (m, 22H); 8.00 (d, *J* = 8.7 Hz, 2H); 8.21 (brs, 2H); 8.26 (brs, 2H) ppm. ^{13}C NMR δ: 74.8 (CH_2); 80.8 (C); 82.9 (CH); 124.5 (CH); 124.7 (CH); 125.2 (CH); 125.5 (CH); 125.9 (CH); 126.0 (CH); 126.4 (CH); 126.5 (CH); 127.3 (CH); 127.5 (CH); 127.7 (2CH); 128.2 (2CH); 128.3 (CH); 128.4 (2CH); 132.3 (C); 132.6 (C); 133.1 (C); 133.3 (C); 137.0 (C); 142.3 (C); 142.9 (C) ppm. HRMS: *m*/*z* calcd for $C_{58}H_{45}O_4$ $[M-H]^-$: 805.3318; found: 805.3333.

3-(((5R,6R)-5,6-bis(benzyloxy)-4,4,7,7-tetra(naphthalen-2-yl)-2-oxido-1,3,2-dioxaphosphepan-2-yl)oxy)propanenitrile

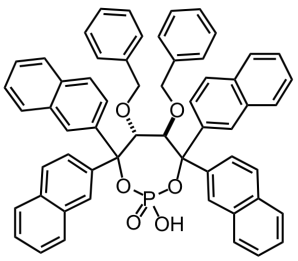


General Procedure G. MPLC applying a solvent gradient EtOAc (6→60%)–heptane afforded the product as a white crystal in 53% yield. $[\alpha]_{578}^{20}$ -164 (*c* 0.93 $CHCl_3$). ^{1}H NMR δ: 1.78–1.86 (m, 1H); 2.11–2.19 (m, 1H); 3.24–3.32 (m, 1H); 3.77 (d, *J* = 11.6 Hz, 1H); 3.93–4.02 (m, 3H); 4.19 (d, *J* = 11.6 Hz, 1H); 5.46 (d, *J* = 6.9 Hz, 1H); 5.53 (d, *J* = 6.9 Hz, 1H); 6.63 (d, *J* = 7.6 Hz, 2H); 6.76 (d, *J* = 7.2 Hz, 2H); 6.99 (pst, *J* = 7.6 Hz, 2H); 7.05–7.14 (m, 4H); 7.39–8.05 (m, 26H); 8.39 (brs, 1H); 8.45 (brs, 1H) ppm. ^{13}C NMR δ: 19.0 (d, J_{CP} = 9.3 Hz, CH_2); 61.6 (d, J_{CP} = 4.4 Hz, CH_2); 73.9 (d, CH_2); 74.1 (CH_2); 76.9 (CH); 78.2 (CH); 88.8 (d, J_{CP} = 8.0 Hz, C); 89.6 (d, J_{CP} = 6.0 Hz, C); 116.1 (C); 125.8 (CH); 126.0 (CH); 126.1 (CH); 126.4 (4CH); 126.6 (CH); 126.7 (4CH); 126.9 (CH); 127.1 (2CH); 127.2 (CH); 127.3 (CH); 127.4 (2CH); 127.5 (3CH); 127.6 (4CH); 127.7 (CH); 128.1 (2CH); 128.2 (CH); 128.3 (CH); 128.7 (CH); 128.8(CH); 128.9 (CH); 132.4 (2C); 132.6 (2C); 132.9 (3C); 133.2 (C); 136.8 (C); 136.9 (C); 137.2 (C); 137.4 (C); 139.2 (2C) ppm. ^{31}P NMR δ: –12.06 ppm. HRMS: *m*/*z* calcd for $C_{61}H_{48}NNaO_6P$ $[M+Na]^+$: 944.3117; found: 944.3114.

As a side product *(5R,6R)-5,6-bis(benzyloxy)-4,4,7,7-tetra(naphthalen-2-yl)-1,3,2-dioxaphosphepane 2-oxide* **17e-POH** was formed. Yield = 9%, white solid. $[\alpha]_{578}^{20}$ -152 (c 0.8 $CHCl_3$). ^{1}H NMR δ: 3.85 (d, *J* = 11.9 Hz, 1H); 3.99 (d, *J* = 11.2 Hz, 1H); 4.19 (d, *J* = 11.2 Hz, 1H); 4.21 (d, *J* = 11.9 Hz, 1H); 5.40 (d, *J* = 7.2 Hz, 1H); 5.62 (d, *J* = 7.2 Hz, 1H); 6.69 (d, *J* = 8.6 Hz, 2H); 6.78 (d, *J* = 8.6 Hz, 2H); 6.97 (d, J_{HP} = 656.3 Hz, 1H); 7.03−7.17 (m, 6H); 7.44–8.00 (m, 26H); 8.31 (s, 1H); 8.50 (s, 1H) ppm. ^{13}C NMR δ: 74.0 (CH_2); 74.3 (CH_2); 78.9 (CH); 79.1 (CH); 88.5 (d, J_{CP} = 8.0 Hz, C); 89.4 (d, J_{CP} = 9.1 Hz, C); 125.6 (2CH); 125.8 (CH); 125.9 (CH); 126.1 (CH); 126.3 (CH); 126.5 (2CH); 126.7 (3CH); 126.8 (CH); 126.9 (CH); 127.0 (CH); 127.1 (CH); 127.3 (2CH); 127.4 (CH); 127.5 (4CH); 127.6 (3CH); 128.2 (3CH); 128.3 (CH); 128.5 (CH); 128.7 (3CH); 128.9 (CH); 132.5 (3C); 132.6 (C); 132.9 (2C); 133.1 (C); 133.2 (C); 136.6 (d, J_{CP} = 7.6 Hz, C); 136.7 (d, J_{CP} = 9.1 Hz, C); 137.3 (2C); 139.7 (d, J_{CP} = 5.9 Hz, C); 139.8 (d, J_{CP} = 5.2 Hz, C) ppm. ^{31}P NMR δ: –3.54 ppm. HRMS: *m*/*z* calcd for $C_{58}H_{45}F_4NaO_5P$ $[M+Na]^+$: 875.2902; found: 875.2923.

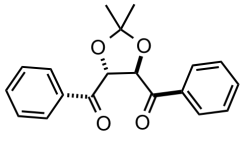


(5R,6R)-5,6-bis(benzyloxy)-2-hydroxy-4,4,7,7-tetra(naphthalen-2-yl)-1,3,2-dioxaphosphepane 2-oxide **17e-POOH**:



General Procedure J. The ammonium salt of the phosphate was dissolved in MeOH, washed through a short column of Dowex-50 and concentrated under vacuum affording **17e-POOH** in 98% yield. Mp 155–157 °C, $[\alpha]_D^{20}$ -127 (*c* 1.015 $CHCl_3$). ^{1}H NMR δ: 3.82 (d, *J* = 11.4 Hz, 2H); 4.14 (d, *J* = 11.4 Hz, 2H); 5.32 (s, 2H); 6.68 (d, *J* = 8.4 Hz, 4H); 6.99−7.10 (m, 6H); 7.32–7.89 (m, 26H); 8.38 (s, 2H) ppm. ^{13}C NMR δ: 74.3 (CH_2); 79.4 (CH); 88.1 (d, J_{CP} = 6.1 Hz, C); 125.9 (2CH); 126.1 (2CH); 126.3 (CH); 126.4 (CH); 126.7 (CH); 127.2 (CH); 127.3 (CH); 127.4 (3CH); 127.5 (CH); 127.9 (CH); 128.0 (CH); 128.7 (2CH); 132.5 (2C); 132.8 (C); 132.9 (C); 137.1 (d, J_{CP} = 8.9 Hz, C); 137.5 (C); 139.8 (d, J_{CP} = 2.5 Hz, C) ppm. ^{31}P NMR δ: –7.41 ppm. HRMS: *m*/*z* calcd for $C_{58}H_{44}O_6P$ $[M-H]^-$: 867.2876; found: 867.2914.

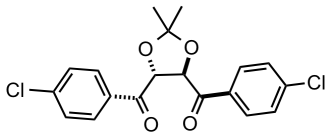
((4R,5R)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(phenylmethanone) **19a**:



General procedure I:[135] Phenyllmagnesium bromide (133 mL of 0.75 M solution in ether, 100 mmol) was added dropwise to a solution of Weinreb amide **1B** (4.5 g, 16.3 mmol) in THF (150 mL)

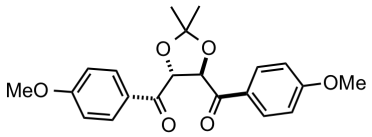
at 0 °C. After 3 h, the reaction was quenched with sat. aq. NH_4Cl (30 mL) solution, acidified with 1 N HCl (30 mL) and extracted with EtOAc (3× 100 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product wsa purified by column chromatography using EtOAc/hexane (10/90) to give bisketone **19a** as a white crystalline solid in 4.15 g (82%) yield. ^{1}H NMR δ: 1.41 (s, 6H); 5.82 (s, 2H); 7.46 (t, *J* = 7.7 Hz, 4H); 7.57 (t, *J* = 7.5 Hz, 2H); 8.08–8.11 (m, 4H) ppm*.

((4R,5R)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis((4-chlorophenyl)methanone) **19b**:



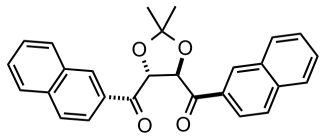
General Procedure I. Column chromatography applying EtOAc/hexane (10/90) afforded diketone **19b** in 52% yield. ^{1}H NMR δ: 1.39 (s, 6H); 5.76 (s, 2H), 7.46 (d, *J* = 8.6 Hz, 4H); 8.07 (d, *J* = 8.6 Hz, 4H) ppm. ^{13}C NMR δ: 26.6 (CH_3); 79.0 (CH); 113.4 (C); 129.0 (CH); 131.1 (CH); 133.1 (C); 140.5 (C); 195.2 (C) ppm. HRMS: *m*/*z* calcd for $C_{19}H_{16}Cl_2O_4$ $[M]^+$: 378.0426; found: 378.0419.

((4R,5R)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis((4-methoxyphenyl)methanone) **19c**:[69]



General procedure I. Column chromatography applying EtOAc/hexane (10/90) afforded the product **19c** in 84% yield. ^{1}H NMR δ: 1.41 (s, 6H); 3.85 (s, 6H); 5.76 (s, 2H), 6.92 (d, *J* = 9.0 Hz, 4H); 8.08 (d, *J* = 9.0 Hz, 4H) ppm.*

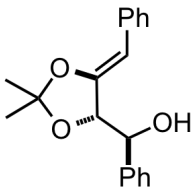
((4R,5R)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(naphthalen-2-ylmethanone) **19d**:



General procedure I. Column chromatography applying EtOAc/hexane (10/90) afforded **19d** as white crystals. Yield: 70%; mp 141–142 °C; $[\alpha]_D^{20}$ -10.9 (*c* 1.1, $CHCl_3$). ^{1}H NMR δ: 1.46 (s, 6H); 6.05 (s, 2H); 7.49–7.61 (m, 4H); 7.85 (d, *J* = 8.3 Hz, 2H); 7.89 (d, *J* = 8.7 Hz, 2H); 7.98 (d, *J* = 7.9 Hz, 2H); 8.12 (dd, *J* = 8.5, 1.7 Hz, 2H); 8.68 (s, 2H) ppm. ^{13}C NMR δ: 26.8 (CH_3); 79.3 (CH); 113.5 (C); 124.6 (CH); 126.8 (CH); 127.8 (CH); 128.5 (CH); 128.9 (CH); 130.0 (CH); 132.0 (CH); 132.2 (C); 132.5 (C); 135.9 (C); 196.4 (C) ppm. HRMS: *m*/*z* calcd for $C_{27}H_{23}O_4$ $[M+H]^+$: 411.1598; found: 411.1608.

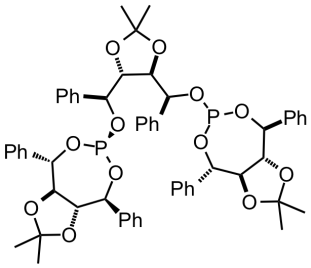
* Spectroscopic datas are in accordance with literature.

(S)-((S)-5-((Z)-benzylidene)-2,2-dimethyl-1,3-dioxolan-4-yl)(phenyl)methanol **21:**



Diol **6a** (100mg, 0.318 mmol) in THF (3 ml) was cooled to –78 °C and *n*-BuLi (0.52mL of 1.22M solution in hexane, 0.63 mmol) was slowly introduced. The resulting yellow solution was warmed to –30 °C, then cooled again to –78 °C. Methanesulfonylchloride (48.5 µl, 72.2 mg, 0.63 mmol) was added and a white suspension formed. After 5 hours the volatiles were evaporated under vacuum. The residue was dissolved in DMF (3ml) and NaN_3 (82.6 mg, 1.3 mmol) was added. The mixture was stirred at 80^0C for 12h and cooled to room temperature, Et_2O (15 mL) was added and the mixture was washed water (4× 2 mL). The organic layer was dried over Na_2SO_4 and the solvent was evaporated. Column chromatography with a solvent gradient EtOAc (15→30%)/hexane afforded 20 mg (21%) of alkene **21**. ^{1}H NMR δ: 1.48 (s, 3H); 1.67 (s, 3H); 2.70 (d, *J* = 3.8 Hz, 1H); 4.75 (pst, *J* = 5.2 Hz, 1H); 4.79 (d, *J* = 1.9 Hz, 1H); 4.91 (dd, *J* = 5.2, 1.5 Hz, 1H); 7.11–7.45 (m, 10H) ppm. ^{13}C NMR δ: 26.3 (CH_3); 26.9 (CH_3); 75.9 (CH); 82.5 (CH); 98.4 (CH); 112.9 (C); 125.6 (CH); 127.6 (CH); 127.7 (CH); 128.2 (CH); 128.4 (2CH); 135.5 (C); 139.3 (C); 149.4 (C) ppm. HRMS: *m*/*z* calcd for $C_{19}H_{20}O_3$ $[M]^+$: 296.1412; found: 296.1416

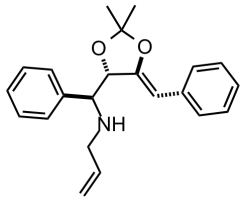
(3aR,3a'R, 4S,4'S,8S,8aR,8'S,8a'R)-6,6'((((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(phenylmethylene))bis(oxy))bis(2,2-dimethyl-4,8-diphenyltetrahydro-[1,3]-dioxolo[4,5-e][1,3,2]-dioxaphosphepine) **23**:



To a flame-dried round bottom flask charged with a magnetic stir bar was added 4 Å molecular sieves, diol **6a** (120 mg, 0.38 mmol) in THF (1 mL). To the reaction mixture was added TEA (0.18 mL, 130.9 mg, 1.3 mmol) and PCl_3 (39.8 µL, 62.7 mg, 0.45 mmol) dropwise at 0 °C. The mixture was allowed to warm to ambient temperature and stirred for 40 minutes. A solution of diethylamine (0.39 mL, 3.8 mmol) in THF (2 mL) was added slowly at 0 °C. The reaction was allowed to stir overnight at ambient temperature before it was diluted with Et_2O and filtered. The filtrate was concentrated under vacuum and the resulting crude material was chromatographed using 10% EtOAc/hexane solution to afford phosphite **23** as a clear colorless oil in 12 mg (10%) yield. ^{1}H NMR δ: 0.67 (s, 6H); 0.73 (s, 6H); 1.48 (s, 6H); 4.29–4.30 (m, 2H); 4.62–4.70 (m, 4H); 4.76–4.79 (m, 2H); 5.32 (t, *J* = 6.3 Hz, 2 H); 5.52 (t, *J* = 6.3 Hz, 2H); 7.17–7.34 (m, 30H) ppm. ^{13}C NMR δ: 26.1 (CH_3); 26.3 (CH_3); 27.6 (CH_3); 75.2 (CH); 75.8 (2CH); 76.0 (d, J_{CP} = 13.5 Hz, CH); 76.9 (CH);

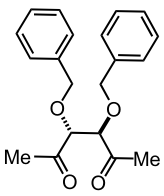
80.7 (d, J_{CP} = 6.1 Hz, CH); 110.9 (C); 112.3 (C); 127.4 (2CH); 127.5 (CH); 127.6 (2CH); 127.9 (2CH); 128.3 (CH); 128.4 (CH); 136.6 (d, J_{CP} = 4.6 Hz, C); 136.9 (d, J_{CP} = 2.8 Hz, C); 138.5 (C) ppm. ^{31}P NMR δ: 134.34 ppm.

N-((S)-((S)-5-((Z)-benzylidene)-2,2-dimethyl-1,3-dioxolan-4-yl)(phenyl)methylprop-2-en-1-amine **24**:



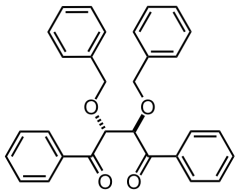
Allylamine (4.6 mL, 3.51 g, 61.6 mmol) was added to a dimesylate **6a-M** (100 mg, 0.2 mmol) at 0 °C and stirred for 14 h. The mixture was warmed to room temperature and excess allylamine was removed under vacuum. The residue was dissoleve in ether (13 mL), washed with sat.d aq. solution of $NaHCO_3$ (2× 5 mL), dried over $MgSO_4$ and concentrated under vacuum to afford 7 mg (11%) of **24**. ^{1}H NMR δ: 1.36 (s, 3H); 1.39 (s, 3H); 3.08 (ddt, *J* = 14.1, 6.4, 1.2 Hz, 1H); 3.21 (ddt, *J* = 14.1, 6.4, 1.2 Hz, 1H); 3.95 (d, *J* = 3.8 Hz, 1H); 5.04–5.15 (m, 3H); 5.21 (d, J = 1.4 Hz, 1H); 5.84–5.94 (m, 1H); 7.06–7.47 (m, 10H) ppm. ^{13}C NMR δ: 26.1 ($2CH_3$); 50.0 (CH_2); 65.0 (CH); 82.1 (CH); 98.1 (CH); 112.8 (C); 116.1 (C); 125.3 (CH); 127.4 (CH); 127.5 (CH); 127.8 (CH); 128.2 (CH); 129.0 (CH); 135.9 (C); 136.6 (CH); 138.1 (C); 150.7 (C) ppm. HRMS: *m/z* calcd for $C_{22}H_{26}NO_2$ $[M+H]^+$: 336.1964; found: 336.1972.

(3R,4R)-3,4-Bis(benzyloxy)hexane-2,5-dione **25:**



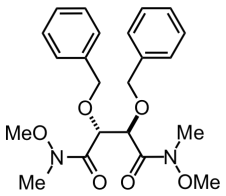
Diamide **28** (1.06 g, 2.6 mmol) was dissolved in THF and cooled to 0 °C. MeMgBr (7.7 mmol, 4.5 mL of a 3 M solution in Et_2O) was added dropwise and the mixture was stirred for 3 h. The reaction was quenched with sat. cold NH_4Cl solution and acidified with 1 N HCl. The mixture was extracted with EtOAc and the combined organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated. Flash chromatography applying a solvent gradient EtOAc (2→20%) / hexane afforded diketone **25** as a white crystalline solid. Yield: 653 mg (77%); mp 58–59 °C; $[\alpha]_D^{20}$ +133 (c 1.10, $CHCl_3$). ^{1}H NMR δ: 2.13 (s, 6H); 4.15 (s, 2H); 4.37 (d, *J* = 11.5 Hz, 2H); 4.63 (d, *J* = 11.5 Hz, 2H); 7.24–7.34 (m, 10H) ppm. ^{13}C NMR δ: 27.4 (CH_3); 74.0 (CH_2); 85.1 (CH); 128.3 (CH); 128.4 (CH); 128.6 (CH); 136.5 (C); 208.8 (C) ppm. HRMS: *m/z* calcd for $C_{20}H_{22}NaO_4$ $[M+Na]^+$: 349.1416; found: 349.1414.

(2R,3R)-2,3-Bis(benzyloxy)-1,4-diphenylbutane-1,4-dione **26**:



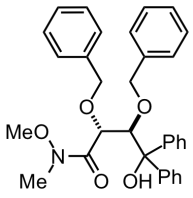
Diamide **28** (250 mg, 0.6 mmol) was dissolved in THF and cooled to -78 °C. PhLi (3.6 mmol, 1.9 mL of a 1.9 M solution in dibutylether) was added dropwise and the mixture was strirred for 3 h at the same temperature. The reaction was quenched with water and the inorganic layer was extracted with EtOAc. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated. Flash chromatography applying a solvent gradient of EtOAc (7→40%)/hexane afforded the product **9** as a white crystalline solid. Yield: 170 mg (63%); mp 56−58 °C; $[\alpha]_D^{20}$ +103 (c 1.50, $CHCl_3$). ^{1}H NMR δ: 4.27 (d, *J* = 11.5 Hz, 2H); 4.60 (d, *J* = 11.5 Hz, 2H); 5.06 (s, 2H); 6.96 (d, *J* = 8.0 Hz, 4H); 7.08–7.15 (m, 6H); 7.40 (ps.t, *J* = 7.8 Hz, 4H); 7.54 (ps.t, *J* = 6.4 Hz, 2H); 8.01 (dd, *J* = 8.2, 1.1 Hz, 4H) ppm. ^{13}C NMR δ: 73.0 (CH_2); 82.9 (CH); 127.8 (CH); 128.1 (CH); 128.2 (CH); 128.4 (CH); 129.1 (CH); 133.3 (CH); 135.7 (C); 136.4 (C); 198.4 (C) ppm. HRMS*: m/z* calcd for $C_{30}H_{26}NaO_4$ $[M+Na]^+$: 473.1729; found: 473.1737.

(2R,3R)-2,3-Bis(benzyloxy)-N^1,N^4-dimethoxy-N^1,N^4-dimethylsuccinamide **28:**



To a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (18.09 g, 186 mmol) in CH_2Cl_2 (160 mL) was added at 0 °C trimethylaluminum (199 mmol, 99.5 mL of a 2 M solution in hexane) over 40 min. The reaction was allowed to warm to r.t. and stirring was continued for 15 min. The solution was again cooled to -10 °C (set into the cooling bath for about 30 min) and (2*R*,3*R*)-dimethyl 2,3-bis(benzyloxy)succinate **27**[10] (14.76 g, 41.1 mmol) dissolved in CH_2Cl_2 (140 mL) was added over 1 h. After the mixture had stirred for 4 h, the reaction was carefully quenched with hydrochloric acid (50 mL, 1 N) and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated. Flash chromatography applying a solvent gradient EtOAc (40→90%)/hexane afforded bis-Weinreb amide **28** as a white crystalline solid. Yield: 11.80 g (69%); mp 69–71 °C; $[\alpha]_D^{20}$ +56.4 (c 1.01, $CHCl_3$). ^{1}H NMR δ: 3.14 (br.s, 6H); 3.65 (s, 6H); 4.67–4.82 (m, 6H); 7.12–7.32 (m, 10H) ppm. ^{13}C NMR δ: 32.0 (CH_3); 61.4 (CH_3); 73.2 (CH_2); 76.2 (CH); 127.7 (CH); 128.0 (CH); 128.2 (CH); 138.4 (C); 169.9 (C) ppm. HRMS*: m/z* calcd for $C_{22}H_{28}N_2NaO_6$ $[M+Na]^+$: 439.1845; found: 439.1830.

(2R,3R)-2,3-Bis(benzyloxy)-4-hydroxy-N-methoxy-N-methyl-4,4-diphenylbutanamide **29:**

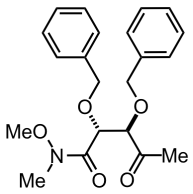


Ketoneamide **31** (140 mg, 0.29 mmol) was dissolved in THF (2 mL) and cooled to –78 °C. To this was added PhLi (0.72 mmol, 3.8 mL of a 0.19 M solution in dibutylether) and the reaction was stirred for 2 h. The reaction was quenched with water and the inorganic layer was extracted with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and evaporated. Flash chromatography applying a solvent gradient of EtOAc (7→40%)/hexane afforded 31 mg (24%) of lactone **35** and 74 mg (50%) of **29** respectively. Compound **29** gradually turned into lactone **35** during work-up. This process could be accelerated by stirring **29** in dioxane with $NaHCO_3$ at room temperature.

29: Clear colorless oil. (incomplete characterization) ^{1}H NMR δ: 3.06 (s, 3H); 3.25 (br.s, 3H); 4.04 (d, *J* = 10.4 Hz, 1H); 4.27–4.30 (m, 2H); 4.48 (d, *J* = 3.2 Hz, 1H); 4.62–4.66 (m, 1H); 4.80 (br.s, 1H); 4.85 (d, *J* = 3.2 Hz, 1H); 6.92–6.95 (m, 2H); 7.08–7.11 (m, 2H); 7.15–7.21 (m, 8H); 7.26–7.29 (m, 4H); 7.59 (d, *J* = 7.5 Hz, 2H); 7.65 (d, *J* = 7.7 Hz, 2H) ppm.

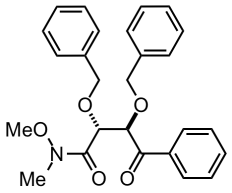
35: For characterization see below.

(2R,3R)-2,3-Bis(benzyloxy)-N-methoxy-N-methyl-4-oxopentanamide **30:**



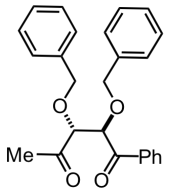
General Procedure K: Bis-Weinreb amide **28** (2.06 g, 4.9 mmol) was dissolved in THF (40 mL) and cooled to –40 °C. MeMgBr (7.9 mmol, 2.6 mL of a 3 M solution in Et_2O) was added dropwise and the mixture was stirred for 6 h. The reaction was quenched with cold sat. NH_4Cl solution and acidified with 1N HCl. The mixture was extracted with EtOAc and the combined organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated. Flash chromatography with a solvent gradient EtOAc (7→60%)/hexane gave amide **30** as a white crystalline solid. Yield: 1.619 g (89%); mp 55–57 °C; $[\alpha]_D^{20}$ +126 (c 2.01, $CHCl_3$). ^{1}H NMR δ: 2.24 (s, 3H); 3.07 (s, 3H); 3.42 (s, 3H); 4.19 (d, *J* = 4.2 Hz, 1H); 4.40 (d, *J* = 11.3 Hz, 1H); 4.48 (d, *J* = 12.0 Hz, 1H); 4.53 (d, *J* = 4.2 Hz, 1H); 4.71 (d, *J* = 12.0 Hz, 1H); 4.74 (d, *J* = 11.3 Hz, 1H); 7.23–7.32 (m, 10H) ppm. ^{13}C NMR δ: 27.8 (CH_3); 32.3 (CH_3); 61.0 (CH_3); 72.4 (CH_2); 73.7 (CH_2); 76.8 (CH); 83.4 (CH); 127.9 (CH); 128.0 (CH); 128.2 (CH); 128.3 (CH); 128.4 (CH); 128.4 (CH); 136.9 (C); 136.9 (C); 169.3 (C); 209.6 (C) ppm. HRMS: *m/z* calcd for $C_{21}H_{25}NNaO_5$ $[M+Na]^+$: 394.1630; found: 394.1626.

(2R,3R)-2,3-Bis(benzyloxy)-N-methoxy-N-methyl-4-oxo-4-phenylbutanamide **31:**



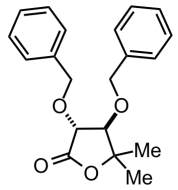
(*Table 6*, Entry 9, *General Procedure K*, 5 mM). Flash chromatography applying a solvent gradient EtOAc (7→60%)/hexane afforded ketoneamide **31** as a clear yellow oil. Yield: 1.67 g (90%); $[\alpha]_D^{20}$ +114 (c 1.26, $CHCl_3$). ^{1}H NMR δ: 3.04 (s, 3H); 3.48 (s, 3H); 4.46 (d, *J* = 12.1 Hz, 1H); 4.50 (d, *J* = 11.8 Hz, 1H); 4.70 (d, *J* = 12.1 Hz, 1H); 4.73–4.77 (m, 2H); 5.08 (d, *J* = 5.4 Hz, 1H); 7.13–7.25 (m, 10H); 7.39 (ps.t, *J* = 7.8 Hz, 2H); 7.52 (ps.t, *J* = 7.6 Hz, 1H); 7.97 (d, *J* = 8.6 Hz, 2H) ppm. ^{13}C NMR δ: 32.1 (CH_3); 61.0 (CH_3); 72.4 (CH_2); 72.9 (CH_2); 76.4 (CH); 80.9 (CH); 127.6 (CH); 127.8 (CH); 128.0 (CH); 128.1 (CH); 128.1 (CH); 128.2 (CH); 128.3 (CH); 128.9 (CH); 133.1 (CH); 135.9 (C); 137.0 (C); 137.2 (C); 169.12 (C); 198.3 (C) ppm. HRMS: m/z calcd for $C_{26}H_{27}NNaO_5$ $[M+Na]^+$: 456.1787, found*:* 456.1791.

(2R,3R)-2,3-Bis(benzyloxy)-1-phenylpentane-1,4-dione **32**:



(side product from Entry 12, *Table 6*) (incomplete charactersization, 2 mM) Yield: 78 mg (10%), clear colorless oil. ^{1}H NMR δ: 2.23 (s, 3H); 4.23 (d, *J* = 3.2 Hz, 1H); 4.30 (d, *J* = 11.6 Hz, 1H); 4.31 (d, *J* = 11.7 Hz, 1H); 4.51 (d, *J* = 11.7 Hz, 1H); 4.65 (d, *J* = 11.6 Hz, 1H); 4.97 (d, *J* = 3.2 Hz, 1H); 7.02–7.04 (m, 2H); 7.13–7.18 (m, 5H); 7.25–7.29 (m, 3H); 7.39 (ps.t, *J* = 7.9 Hz, 3H); 7.96 (d, *J* = 8.4 Hz, 2H) ppm. ^{13}C NMR δ: 27.7 (CH_3); 73.1 (CH_2); 73.9 (CH_2); 83.2 (CH); 84.8 (CH); 128.1 (CH); 128.1 (CH); 128.3 (CH); 128.3 (CH); 128.3 (CH); 128.4 (CH); 128.5 (CH); 128.9 (CH); 133.4 (CH); 135.5 (C); 136.2 (C); 136.6 (C); 197.7 (C); 209.3 (C) ppm.

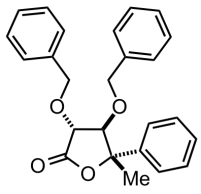
(3R,4R)-3,4-Bis(benzyloxy)-5,5-dimethyldihydrofuran-2(3H)-one **33.**



(*Table 6*, Entry 11, *General Procedure K*, 2 mM). Flash chromatography applying a solvent gradient EtOAc (2→20%)/hexane afforded lactone **33** as a clear colorless oil. Yield: 489 mg (75%); $[\alpha]_D^{20}$ +33.2 (c 1.04, $CHCl_3$). ^{1}H NMR δ: 1.36 (s, 3H); 1.41 (s, 3H); 3.95 (d, *J* = 7.8 Hz, 1H); 4.31 (d, *J* = 7.8 Hz, 1H); 4.59 (d, *J* = 11.8 Hz, 1H); 4.69 (d, *J* = 11.8 Hz, 1H); 4.73 (d, *J* = 11.5 Hz, 1H); 5.09 (d, *J* = 11.5 Hz, 1H); 7.24–7.40 (m, 10H) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.6 (CH_3); 27.5 (CH_3); 72.7 (CH_2); 72.9 (CH_2); 78.7 (CH); 82.8 (C); 85.1 (CH); 127.7 (CH); 128.0 (CH); 128.1 (CH); 128.3 (CH); 128.5 (CH); 128.5 (CH);

137.0 (C); 137.4 (C); 172.3 (C) ppm. HRMS: *m/z* calcd for $C_{20}H_{22}NaO_4$ $[M+Na]^+$: 349.1416; found: 349.1419.

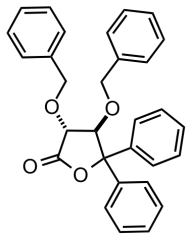
(3R,4R,5S)-3,4-Bis(benzyloxy)-5-methyl-5-phenyldihydrofuran-2(3H)-one **34.**



From **31**: (*Table 6*, Entry 14, *Standard Procedure K*, 1 mM). Flash chromatography applying a solvent gradient EtOAc (2→20%) / hexane afforded lactone **34** as a white crystalline solid. Yield: 225 mg (58%); mp 87–89 °C; $[\alpha]_D^{20}$ +25.2 (c 1.59, $CHCl_3$). ^{1}H NMR δ: 1.70 (s, 3H); 4.25 (d, *J* = 8.2 Hz, 1H); 4.45 (d, *J* = 8.2 Hz, 1H); 4.58 (d, *J* = 11.8 Hz, 1H); 4.68 (d, *J* = 11.8 Hz, 1H); 4.76 (d, *J* = 11.4 Hz, 1H); 5.14 (d, *J* = 11.4 Hz, 1H); 7.20–7.41 (m, 15H) ppm. ^{13}C NMR δ: 23.4 (CH_3); 72.7 (CH_2); 72.97 (CH_2); 78.75 (CH); 84.27 (C); 85.80 (CH); 124.0 (CH); 127.7 (CH); 127.9 (CH); 128.0 (CH); 128.2 (CH); 128.3 (CH); 128.4 (CH); 128.5 (CH); 128.6 (CH); 136.9 (C); 137.2 (C); 143.4 (C); 172.0 (C) ppm. HRMS: *m/z* calcd for $C_{25}H_{24}NaO_4$ $[M+Na]^+$: 411.1572; found*:* 411.1571.

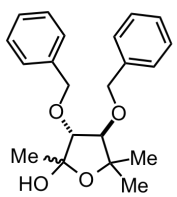
From **30**: (*Table 6*, Entry 12, *Standard Procedure K*, 2 mM). Yield: 522 mg (67%).

(3R,4R)-3,4-Bis(benzyloxy)-5,5-diphenyldihydrofuran-2(3H)-one **35:**



(*Table 6*, Entry 16, *General Procedure K*, 2 mM). Yield: 898 mg (quantitative), clear colorless oil; $[\alpha]_D^{20}$ +7.4 (c 2.09, $CHCl_3$). ^{1}H NMR δ: 4.40 (d, *J* = 8.5 Hz, 1H); 4.68 (d, *J* = 11.0 Hz, 1H); 4.78 (d, *J* = 12.0 Hz, 1H); 4.83 (d, *J* = 12.0 Hz, 1H); 4.84 (d, *J* = 8.5 Hz, 1H); 5.21 (d, *J* = 11.0 Hz, 1H); 7.23–7.25 (m, 2H); 7.31–7.46 (m, 18H) ppm. ^{13}C NMR δ: 72.9 (CH_2); 73.0 (CH_2); 78.8 (CH); 84.1 (CH); 86.3 (C); 126.0 (CH); 127.2 (CH); 127.7 (CH); 127.9 (CH); 128.0 (CH); 128.1 (CH); 128.1 (CH); 128.3 (CH); 128.4 (CH); 128.5 (CH); 137.0 (C); 137.1 (C); 138.9 (C); 142.1 (C); 172.3 (C) ppm. HRMS: *m/z* calcd for $C_{30}H_{26}NaO_4$ $[M+Na]^+$: 473.1729; found: 473.1721.

(3R,4R)-3,4-Bis(benzyloxy)-2,5,5-trimethyltetrahydrofuran-2-ol **36:**

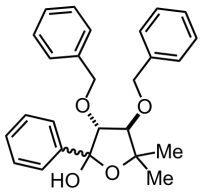


From **33**: (*Table 6*, Entry 17, *General Procedure K*, 1 mM). Flash chromatography applying a solvent gradient EtOAc (3→30%)/hexane afforded hemiketal **36** (anomers A:B = 50:50). Yield: 283 mg (83%). ^{1}H NMR (anomeric mixture) δ: 1.23 (s, 3H); 1.28 (s, 3H); 1.36 (s, 3H); 1.37 (s, 3H); 1.44 (s, 3H); 1.48 (s, 3H); 3.27 (s, 1H); 3.29 (s, 1H); 3.67 (d, *J* = 3.3 Hz, 1H); 3.83 (d, *J* = 6.3 Hz, 1H); 3.91 (d, *J* = 6.3 Hz, 1H); 3.93 (d, *J* = 3.3 Hz, 1H);

4.50 (d, *J* = 11.7 Hz, 1H); 4.55–4.62 (m, 4H); 4.61 (d, *J* = 11.7 Hz, 1H); 4.69 (dd, *J* = 15.3, 11.6 Hz, 2H); 7.26–7.37 (m, 20H) ppm. ^{13}C NMR δ: 23.0 (CH_3); 24.4 (CH_3); 24.8 (CH_3); 27.4 (CH_3); 28.7 (CH_3); 30.0 (CH_3); 72.3 (CH_2); 72.6 (CH_2); 72.8 (CH_2); 73.0 (CH_2); 80.0 (C); 82.6 (C); 87.1 (CH); 87.2 (CH); 88.0 (CH); 88.7 (CH); 99.9 (C); 105.4 (C); 127.5 (CH); 127.6 (CH); 127.7 (CH); 127.8 (CH); 127.9 (CH); 127.9 (CH); 128.0 (CH); 128.4 (CH); 128.5 (CH); 128.5 (CH); 137.5 (C); 137.6 (C); 137.8 (C); 138.1 (C) ppm. HRMS: *m/z* calcd for $C_{21}H_{26}NaO_4$ $[M+Na]^+$: 365.1729; found: 365.1728.

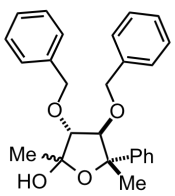
From **25**: (*Table 6*, Entry 1, *General Procedure K*, 1 mM). Yield: 265 mg (78%).

(3R,4R)-3,4-Bis(benzyloxy)-5,5-dimethyl-2-phenyltetrahydrofuran-2-ol **37:**



(*Table 6*, Entry 19, *General Procedure K,* 1 mM). Flash chromatography applying a solvent gradient EtOAc (3→30%) / hexane afforded hemiketal **37** as a clear colorless oil. Yield: 341 mg (84%). (anomers A:B = 70:30). ^{1}H NMR δ: 1.40 (s, $3H_A$); 1.46 (s, $3H_B$); 1.48 (s, $3H_A$); 1.50 (s, $3H_B$); 3.61 (s, $1H_A$); 3.76 (s, $1H_B$); 3.79 (d, *J* = 2.5 Hz, $1H_B$); 4.02–4.12 (m, $5H_{A+B}$); 4.38 (d, *J* = 11.6 Hz, $1H_A$); 4.45 (d, *J* = 11.6 Hz, $1H_A$); 4.48 (d, *J* = 12.3 Hz, $1H_B$); 4.62 (s, $2H_A$); 4.62 (d, *J* = 12.3 Hz, $1H_B$); 6.89–6.91 (m, $2H_B$); 7.10–7.13 (m, $2H_A$); 7.19–7.37 (m, $22H_{A+B}$); 7.57–7.60 (m, $2H_A$),;7.61–7.64 (m, $2H_B$) ppm. ^{13}C NMR (*note:* Slow decomposition was observed during recording of the spectrum overnight.) δ: 24.5 (CH_3); 25.0 (CH_3); 28.4 (CH_3); 30.5 (CH_3); 72.2 (CH_2); 72.6 (CH_2); 72.9 (CH_2); 73.1 (CH_2); 80.6 (C); 88.6 (CH); 88.7 (CH); 88.8 (CH); 89.4 (CH); 100.3 (C); 125.9 (CH); 127.4 (CH); 127.6 (CH); 127.6 (CH); 127.7 (CH); 127.7 (CH); 127.8 (CH); 127.9 (CH); 127.9 (CH); 128.2 (CH); 128.4 (CH); 128.4 (CH); 128.5 (CH); 137.3 (C); 138.2 (C); 142.8 (C) ppm. HRMS: *m/z* calcd for $C_{26}H_{28}NaO_4$ $[M+Na]^+$: 427.1885; found: 427.1881.

(3R,4R,5S)-3,4-Bis(benzyloxy)-2,5-dimethyl-5-phenyltetrahydrofuran-2-ol **38:**

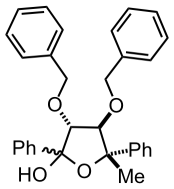


From **34:** (*Table 6*, Entry 21, *General Procedure K*, 1 mM). Flash chromatography applying a solvent gradient EtOAc (2→20%) / hexane afforded hemiketal **38** as a white crystalline solid (anomers A:B = 60:40). Yield: 279 mg (69%); mp 85–91 °C. ^{1}H NMR δ: 1.54 (s, $3H_B$); 1.58 (s, $3H_A$); 1.61 (s, $3H_B$); 1.65 (s, $3H_A$); 3.53 (s, $1H_B$); 3.54 (br.s, $1H_A$); 3.94 (d, *J* = 5.5 Hz, $1H_B$); 4.00 (d, *J* = 3.4 Hz, $1H_A$); 4.09 (d, *J* = 3.4 Hz, $1H_A$); 4.20 (d, *J* = 5.5 Hz, $1H_B$); 4.29 (d, *J* = 11.5 Hz, $1H_A$); 4.40 (d, *J* = 11.5 Hz, $1H_A$); 4.53–4.65 (m, $5H_{A+B}$); 4.69 (d, *J* = 11.9 Hz, $1H_A$); 6.91–6.93 (m, $2H_A$); 7.09–7.11 (m, $2H_B$); 7.19–7.38 (m,

24H_{A+B}); 7.46–7.49 (m, 2H_{A+B}) ppm. ^{13}C NMR (*note:* Signals could not be assigned to anomers A and B.) δ: 22.6 (CH_3); 25.4 (CH_3); 26.3 (CH_3); 27.8 (CH_3); 71.8 (CH_2); 72.8 (CH_2); 72.8 (CH_2); 72.9 (CH_2); 83.7 (C); 85.8 (C); 86.9 (CH); 87.6 (CH); 87.8 (CH); 88.8 (CH); 100.9 (C); 105.8 (C); 124.7 (CH); 125.0 (CH); 126.4 (CH); 126.7 (CH); 127.4 (CH); 127.6 (CH); 127.7 (CH); 127.8 (2CH); 128.0 (2CH); 128.1 (2CH); 128.2 (CH); 128.4 (CH); 128.6 (CH); 137.2 (C); 137.4 (C); 137.6 (C); 138.0 (C); 147.0 (C); 147.5 (C) ppm. HRMS: *m/z* calcd for $C_{26}H_{28}NaO_4$ $[M+Na]^+$: 427.1885; found: 427.1882.

From **25**: (*Table 6*, Entry 2, *General Procedure K*, 1 mM). Yield: 229 mg (57%).

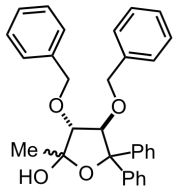
(3R,4R,5S)-3,4-Bis(benzyloxy)-5-methyl-2,5-diphenyltetrahydrofuran-2-ol **39.**



From **34**: (*Table 6*, Entry 23, *General Procedure K*, 1 mM). Flash chromatography applying a solvent gradient EtOAc (2→20%) / hexane afforded hemiketal **39** as a white crystalline solid. Yield: 426 mg (92%); *note*: Only one anomer was observed, mp 82–88 °C. ^{1}H NMR δ: 1.72 (s, 3H); 3.77 (s, 1H); 4.22 (d, *J* = 7.3 Hz, 1H); 4.31 (d, *J* = 11.4 Hz, 1H); 4.41 (d, *J* = 7.3 Hz, 1H); 4.42 (d, *J* = 11.4 Hz, 1H); 4.55 (d, *J* = 11.7 Hz, 1H); 4.61 (d, *J* = 11.7 Hz, 1H); 7.03–7.05 (m, 2H); 7.20–7.42 (m, 14H); 7.57 (d, *J* = 7.0 Hz, 2H); 7.70 (d, *J* = 7.0 Hz, 2H) ppm. ^{13}C NMR δ: 25.7 (CH_3); 72.9 (CH_2); 72.9 (CH_2); 83.6 (C); 88.9 (CH); 89.3 (CH); 100.7 (C); 124.9 (CH); 126.2 (CH); 126.8 (CH); 127.5 (CH); 127.7 (CH); 127.8 (CH); 128.0 (CH); 128.1 (CH); 128.3 (CH); 128.4 (CH); 137.0 (C); 138.1 (C); 142.9 (C); 147.8 (C) ppm. HRMS: *m/z* calcd for $C_{31}H_{30}NaO_4$ $[M+Na]^+$: 489.2042; found: 489.2039.

From **26**: (*Table 6*, Entry 3, *General Procedure K*, 1 mM). Yield: 351 mg (75%).

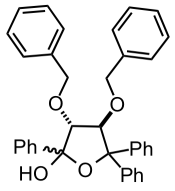
(3R,4R)-3,4-Bis(benzyloxy)-2-methyl-5,5-diphenyl-tetrahydrofuran-2-ol **40:**



(*Table 6*, Entry 24, *General Procedure K*, 1 mM). Flash chromatography applying a solvent gradient EtOAc (3→30%) / hexane afforded hemiketal **23** as a clear colorless oil (anomers A:B = 50:50). Yield: 391 mg (84%). ^{1}H NMR δ: 1.58 (s, 3H); 1.66 (s, 3H); 3.47 (s, 1H); 3.72 (d, *J* = 0.9 Hz, 1H); 3.96 (d, *J* = 4.4 Hz, 1H); 3.99 (d, *J* = 3.3 Hz, 1H); 4.35–4.46 (m, 6H); 4.48 (d, *J* = 11.5 Hz, 1H); 4.52 (d, *J* = 11.5 Hz, 1H); 4.60 (d, *J* = 3.6 Hz, 1H); 4.69 (d, *J* = 4.3 Hz, 1H); 6.91–6.93 (m, 2H); 7.01–7.05 (m, 4H); 7.10–7.12 (m, 2H); 7.16–7.31 (m, 24H); 7.39–7.43 (m, 4H); 7.48–7.50 (m, 2H); 7.55–7.58 (m, 2H) ppm. ^{13}C NMR δ: 22.4 (CH_3); 27.1 (CH_3); 71.8 (CH_2); 72.6 (CH_2); 72.9 (CH_2); 73.0 (CH_2); 85.8 (CH); 87.0 (CH); 87.4 (CH); 87.5 (CH); 87.7 (C); 89.1 (C); 102.0 (C); 106.3 (C); 126.6 (CH); 126.7 (CH); 126.8 (CH); 126.9 (CH); 127.0 (CH); 127.1 (CH); 127.4 (CH); 127.5

(CH); 127.5 (CH); 127.5 (CH); 127.60 (CH); 127.7 (CH); 127.7 (CH); 128.0 (CH); 128.0 (CH); 128.0 (CH); 128.2 (CH); 128.3 (CH); 128.4 (CH); 128.4 (CH); 137.0 (C); 137.2 (C); 137.6 (C); 137.7 (C); 142.4 (C); 142.9 (C); 145.3 (C); 145.4 (C) ppm. HRMS: *m/z* calcd for $C_{31}H_{30}NaO_4$ $[M+Na]^+$: 489.2042; found: 489.2045.

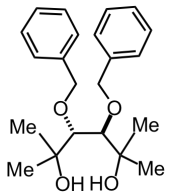
(3R,4R)-3,4-Bis(benzyloxy)-2,5,5-triphenyltetrahydrofuran-2-ol **41:**



From **35**: (Table 6, Entry 25, *General Procedure K*, 1 mM). Flash chromatography applying a solvent gradient EtOAc (2→20%) / hexane afforded hemiketal **41** as a clear colorless oil (anomers A:B = 60:40). Yield: 503 mg (95%). ^{1}H NMR δ: 3.63 (s, $1H_A$); 3.94 (d, *J* = 5.8 Hz, $1H_A$); 4.05 (d, *J* = 2.7 Hz, $1H_B$); 4.24–4.44 (m, $9H_{A+B}$); 4.74 (d, *J* = 2.7 Hz, $1H_B$); 4.83 (d, *J* = 4.4 Hz, $1H_A$); 6.63 (d, *J* = 7.3 Hz, $1H_A$); 6.89–7.68 (m, $29H_{A+B}$) ppm. ^{13}C NMR δ: 71.7 (CH_2); 72.3 (CH_2); 73.1 (CH_2); 73.2 (CH_2); 85.9 (CH); 87.7 (CH); 87.7 (CH); 88.8 (C); 89.3 (CH); 91.0 (C); 102.2 (C); 107.2 (C); 126.1 (CH); 126.3 (CH); 126.8 (CH); 126.9 (CH); 126.9 (CH); 127.1 (CH); 127.1 (CH); 127.3 (CH); 127.5 (CH); 127.6 (CH); 127.6 (CH); 127.7 (CH); 127.7 (CH); 127.8 (CH); 127.9 (CH); 128.0 (CH); 128.0 (CH); 128.0 (CH); 128.2 (CH); 128.2 (CH); 128.3 (CH); 128.3 (CH); 128.3 (CH); 128.4 (CH); 128.4 (CH); 136.8 (C); 137.1 (C); 137.6 (C); 137.6 (C); 139.0 (C); 142.6 (C); 142.8 (C); 143.4 (C); 144.2 (C); 144.8 (C) ppm. HRMS: *m/z* calcd for $C_{36}H_{32}NaO_4$ $[M+Na]^+$: 551.2198; found: 551.2196.

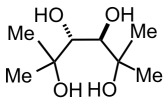
From **26**: (*Table 6*, Entry 5, *General Procedure K*, 1 mM). Yield: 355 mg (67%).

(3R,4R)-3,4-Bis(benzyloxy)-2,5-dimethylhexane-2,5-diol **42.**



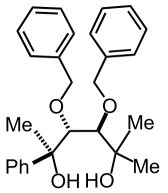
(Table 6, Entry 26, *General Procedure K*, 0.5 mM). Flash chromatography with a solvent gradient EtOAc (7→60%) / hexane afforded diol **25** as a white crystalline solid. Yield: 129 mg (72%); mp 92–93 °C; $[\alpha]_D^{20}$ -39.8 (c 0.59, $CHCl_3$). ^{1}H NMR δ: 1.32 (s, 6H); 1.34 (s, 6H); 2.98 (s, 2H); 3.52 (s, 2H); 4.47 (d, *J* = 11.1 Hz, 2H); 4.89 (d, *J* = 11.1 Hz, 2H); 7.22–7.31 (m, 10H) ppm. ^{13}C NMR δ: 25.3 (CH_3); 28.6 (CH_3); 72.8 (C); 74.7 (CH_2); 83.6 (CH); 127.4 (CH); 127.7 (CH); 128.2 (CH); 138.8 (C) ppm. HRMS: *m/z* calcd for $C_{22}H_{30}NaO_4$ $[M+Na]^+$: 381.2042; found: 381.2041.

(3R,4R)-2,5-Dimethylhexane-2,3,4,5-tetraol **42-OH.**[151]



General Procedure L: Diol **25** (30 mg, 0.08 mmol) was dissolved in EtOH (1 mL). To this solution 10% Pd/C (6 mg) was added at r.t. and the mixture was stirred under an atmosphere of hydrogen (balloon) for 3 h. Filtration over a pad of celite and removal of the solvent gave tetraol **25-OH** as a clear colorless oil. Yield: 15 mg (quantitative). ^{1}H NMR δ: 1.27 (s, 6H); 1.29 (s, 6H); 3.05 (br.s, 2H); 3.56 (s, 2H); 3.89 (br.s, 2H) ppm.*

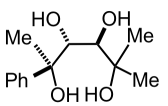
(3R,4R,5S)-3,4-Bis(benzyloxy)-2-methyl-5-phenylhexane-2,5-diol **43:**



From **38**: (Table 6, Entry 31, *General Procedure K*, 0.5 mM). Flash chromatography using a solvent gradient EtOAc (2→25%) / hexane afforded 174 mg (83%) of diol **43** as a clear colorless oil; $[\alpha]_D^{20}$ -56.3 (c 2.64, $CHCl_3$). ^{1}H NMR δ: 1.16 (s, 6H); 1.67 (s, 3H); 2.71 (s, 1H); 3.46 (d, *J* = 4.8 Hz, 1H); 3.69 (s, 1H); 3.77 (d, *J* = 4.8 Hz, 1H); 4.12 (d, *J* = 10.8 Hz, 1H); 4.44 (d, *J* = 11.1 Hz, 1H); 4.71 (d, *J* = 10.8 Hz, 1H); 4.83 (d, *J* = 11.1 Hz, 1H); 7.07 (d, *J* = 6.8 Hz, 2H); 7.14–7.25 (m, 9H); 7.29 (t, *J* = 7.3 Hz, 2H); 7.48 (ps.t, *J* = 1.3 Hz, 1H); 7.50 (ps.t, *J* = 2.0 Hz, 1H) ppm. ^{13}C NMR δ: 25.3 (CH_3); 25.3 (CH_3); 28.1 (CH_3); 73.0 (C); 74.6 (CH_2); 74.7 (CH_2); 76.3 (C); 83.4 (CH); 83.5 (CH); 126.0 (CH); 127.0 (CH); 127.4 (CH); 127.6 (CH); 127.9 (CH); 128.0 (CH); 128.1 (CH); 128.2 (CH); 138.4 (C); 138.8 (C); 146.7 (C) ppm. HRMS: *m/z* calcd for $C_{27}H_{32}NaO_4$ $[M+Na]^+$: 443.2198; found: 443.2195.

From **37**: (*Table 6*, Entry 29, *General Procedure K*, 0.5 mM). Yield: 138 mg (66%).

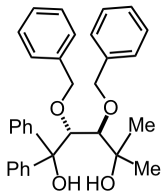
(3R,4R,5S)-2-Methyl-5-phenylhexane-2,3,4,5-tetraol **43-OH:**



(*General Procedure L*, 0.09 mM). Clear colorless oil. Yield: 23 mg (quantitative); $[\alpha]_D^{20}$ +30.9 (c 1.69, $CHCl_3$). ^{1}H NMR δ: 1.06 (s, 3H); 1.17 (s, 3H); 1.59 (s, 3H); 3.03 (s, 1H); 3.40 (br.s, 1H); 4.05 (s, 1H); 4.09 (br.s, 1H); 4.29 (br.s, 1H); 4.32 (br.s, 1H); 7.23–7.27 (m, 1H); 7.33–7.41 (m, 4H) ppm. ^{13}C NMR δ: 25.6 (CH_3); 26.7(CH_3); 27.9 (CH_3); 73.7 (C); 74.6 (CH); 75.0 (CH); 78.4 (C); 124.3 (CH); 127.0 (CH); 128.6 (CH) 144.6 (C) ppm. HRMS: *m/z* calcd for $C_{13}H_{20}NaO_4$ $[M+Na]^+$: 263.1259; found: 263.1244.

* Spectroscopic data are in accordance with literature.

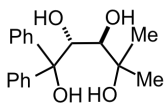
(2R,3R)-2,3-Bis(benzyloxy)-4-methyl-1,1-diphenylpentane-1,4-diol **44:**



From **40**: (*Table 6*, Entry 37, *General Procedure K*, 0.5 mM). Flash chromatography with a solvent gradient EtOAc (3→30%)/hexane afforded 171 mg (71%) of diol **44** as a clear colorless oil; $[\alpha]_D^{20}$ +21.3 (c 0.99, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.20 (s, 3H); 1.29 (s, 3H); 2.22 (s, 1H); 3.63 (d, *J* = 4.7 Hz, 1H); 4.09 (d, *J* = 10.5 Hz, 1H); 4.22 (d, *J* = 11.1 Hz, 1H); 4.50 (d, *J* = 11.1 Hz, 1H); 4.57 (s, 1H); 4.62 (d, *J* = 4.7 Hz, 1H); 4.69 (d, *J* = 10.5 Hz, 1H); 6.98 (d, *J* = 6.5 Hz, 2H); 7.18–7.36 (m, 14H); 7.56 (d, *J* = 8.6 Hz, 2H); 7.78 (d, *J* = 8.6 Hz, 2H) ppm. ^{13}C NMR δ: 25.5 (CH_3); 28.3 (CH_3); 73.5 (C); 74.5 (CH_2); 74.6 (CH_2); 79.8 (C); 82.3 (CH); 83.6 (CH); 127.0 (CH); 127.0 (CH); 127.3 (CH); 127.4 (CH); 127.4 (CH); 127.7 (CH); 127.8 (CH); 127.9 (CH); 128.0 (CH); 128.0 (CH); 128.2 (CH); 138.2 (C); 138.6 (C); 145.2 (C); 145.4 (C) ppm. HRMS: *m/z* calcd for $C_{32}H_{34}NaO_4$ $[M+Na]^+$: 505.2355; found: 505.2357.

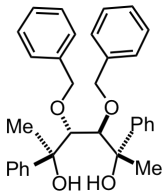
From **37**: (Table 6, Entry 30, *General Procedure K*, 0.5 mM). Yield: 164 mg (68%).

(2R,3R)-4-Methyl-1,1-diphenylpentane-1,2,3,4-tetraol **44-OH.**



(*General Procedure L*, 0.1 mM). Clear colorless oil. Yield: 30 mg (quantitative); $[\alpha]_D^{20}$ +115±10 (c 0.68, $CHCl_3$). ^{1}H NMR δ: 1.10 (s, 3H); 1.31 (s, 3H); 2.99 (s, 1H); 3.17 (d, *J* = 3.5 Hz, 1H); 3.85 (d, *J* = 3.9 Hz, 1H); 3.88 (br.s, 1H); 4.83 (s, 1H); 4.84 (s, 1H); 7.18–7.23 (m, 2H); 7.28–7.34 (m, 4H); 7.41 (br.d, *J* = 7.8 Hz, 2H); 7.56 (br.d, *J* = 7.6 Hz, 2H) ppm. ^{13}C NMR δ: 25.7 (CH_3); 26.8 (CH_3); 72.6 (CH); 73.8 (C); 74.5 (CH); 81.5 (C); 125.0 (CH); 126.3 (CH); 127.0 (CH); 127.3 (CH); 128.4 (CH); 128.6 (CH); 143.9 (C); 144.5 (C) ppm. HRMS: *m/z* calcd for $C_{18}H_{22}NaO_4$ $[M+Na]^+$: 325.1416; found: 325.1408.

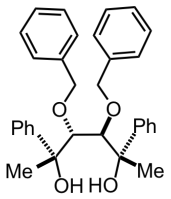
(2S,3R,4R,5S)-3,4-Bis(benzyloxy)-2,5-diphenylhexane-2,5-diol **45** *and (2R,3R,4R,5S)-3,4-bis(benzyloxy)-2,5-diphenylhexane-2,5-diol* **epi-45:**



From **39:** (Table 6, Entry 34) To a solution of hemiketal **39** (175 mg, 0.37 mmol) in THF (2 mL) was added MeMgBr (1.63 mmol, 0.49 mL of a 0.3 M solution in Et_2O/THF) at 0 °C. The solution was allowed to warm to room temperature and was stirred for 24 h. Water was added and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated. Flash chromatography with a solvent gradient EtOAc (2→20%)/hexane afforded 121 mg (68%)

of diol **45** as a clear colorless oil. $[\alpha]_D^{20}$ -27.4 (c 2.20, $CHCl_3$). ^1H NMR δ: 1.44(s, 6H); 3.54 (s, 2H); 3.60 (s, 2H); 4.31 (d, *J* = 10.4 Hz, 2H); 4.75 (d, *J* = 10.4 Hz, 2H); 7.16–7.27 (m, 20H) ppm. ^{13}C NMR δ: 27.49 (CH_3); 74.84 (CH_2); 77.58 (C); 82.96 (CH); 125.46 (CH); 126.82 (CH); 127.54 (CH); 127.69 (CH); 128.24 (CH); 128.29 (CH); 138.29 (C); 145.90 (C) ppm. HRMS*:* m/z calcd for $C_{32}H_{34}NaO_4$ $[M+Na^+]$: 505.2355, found: 505.2354.

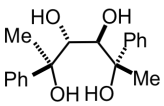
***epi*-45**:



Yield: 27 mg (11%); clear colorless oil (10% impurity). ^1H NMR δ: 1.46 (s, 3H); 1.68 (s, 3H) 3.41 (s, 2H); 3.80 (d, *J* = 3.6 Hz, 1H); 3.82 (d, *J* = 3.6 Hz, 1H); 3.97 (d, *J* = 10.9 Hz, 1H); 3.99 (d, *J* = 10.8 Hz, 1H); 4.35 (d, *J* = 10.9 Hz, 1H); 4.56 (d, *J* = 10.8 Hz, 1H); 7.08–7.11 (m, 4H); 7.17–7.30 (m, 10H); 7.34–7.38 (m, 4H); 7.48–7.50 (m, 2H) ppm. ^{13}C NMR δ: 26.4 (CH_3); 27.8 (CH_3); 74.3 (CH_2); 74.6 (CH_2); 76.3 (C); 76.9 (C); 82.7 (CH); 83.3 (CH); 125.7 (CH); 125.9 (CH); 126.8 (CH); 127.1 (CH); 127.4 (CH); 127.4 (CH); 127.9 (CH); 127.9 (CH); 128.1 (CH); 128.2 (CH); 128.2 (CH); 138.4 (C); 138.4 (C); 146.2 (C); 146.3 (C) ppm. HRMS*:* m/z calcd for $C_{32}H_{34}NaO_4$ $[M+Na^+]$: 505.2355; found: 505.2358.

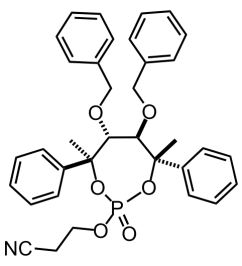
From **38**: (*Table 6*, Entry 32, *General Procedure K*, 0.5 mM). Yield: **45** (153 mg, 64%) and ***epi*-45** (15 mg, 6%).

(2S,3R,4R,5S)-2,5-Diphenylhexane-2,3,4,5-tetraol **45-OH:**



(*General Procedure L*, 0.1 mM). White crystalline solid. Yield: 31 mg (quantitative); mp130–132 °C; $[\alpha]_D^{20}$ -20.1±1 (c 2.08, $CHCl_3$). ^1H NMR δ: 1.37 (s, 6H); 3.51 (s, 2H); 3.81 (br.s, 2H); 3.86 (br.s, 2H); 7.13–7.15 (m, 4H); 7.27−7.29 (m, 2H); 7.31–7.34 (m, 4H) ppm. ^{13}C NMR δ: 27.6 (CH_3); 74.4 (CH); 78.4 (C); 124.3 (CH); 127.1 (CH); 128.5 (CH); 144.5 (C) ppm. HRMS: *m/z* calcd for $C_{18}H_{22}NaO_4$ $[M+Na]^+$: 325.1416; found: 325.1411.

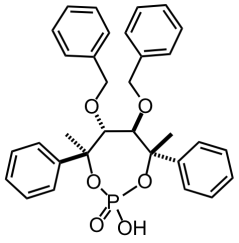
3-(((4S,5R,6R,7S)-5,6-Bis(benzyloxy)-4,7-dimethyl-2-oxido-4,7-diphenyl-1,3,2-dioxaphosphepan-2-yl)oxy)propanenitrile:



General Procedure G. MPLC applying a solvent gradient EtOAc(20→90%)–heptane afforded the product as a white crystal in 71% yield. mp 165–168 °C; ^1H NMR δ: 2.17 (s, 3H); 2.27 (s, 3H); 2.65–2.76 (m, 2H); 3.29 (d, *J* = 10.2 Hz, 1H); 3.32 (d, *J* = 10.2 Hz, 1H); 3.89 (d, *J* = 9.6 Hz, 1H); 3.92 (d, *J* = 9.6 Hz, 1H);

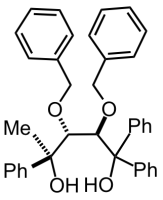
4.21–4.35 (m, 2H); 4.36 (d, *J* = 10.2 Hz, 1H); 4.38 (d, *J* = 10.2 Hz, 1H); 6.75–6.80 (m, 4H); 7.13–7.15 (m, 6H); 7.32−7.40 (m, 6H); 7.62 (d, *J* = 8.6 Hz, 2H); 7.66 (d, *J* = 8.0 Hz, 2H) ppm. ^{13}C NMR δ: 19.1 (CH_3); 19.7 (CH_3); 19.9 ($2CH_2$); 62.1 (d, J_{CP} = 4.2 Hz, CH_2); 75.5 (d, J_{CP} = 2.3 Hz, CH_2); 83.9 (d, J_{CP} = 4.6 Hz, C); 85.3 (d, J_{CP} = 8.4 Hz, C); 85.5 (CH); 85.7 (CH); 116.7 (C); 126.3 (CH); 126.7 (CH); 127.4 (3CH); 128.0 (2CH); 128.1 (CH); 128.2 (3CH); 137.6 (2C); 143.2 (d, *J* = 5.9 Hz, C); 143.3 (d, *J* = 4.4 Hz, C) ppm. (1CH is missing) ^{31}P NMR δ: –9.10 ppm.

(4S,5R,6R,7S)-5,6-Bis(benzyloxy)-2-hydroxy-4,7-dimethyl-4,7-diphenyl-1,3,2-dioxaphosphepane 2-oxide **45-POOH**:



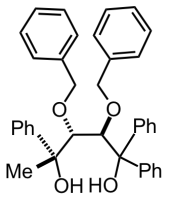
General Procedure J. The crude product was dissolved in EtOH and washed with Dowex-50. Yield: 99%; mp 168–170 °C; $[\alpha]_D^{20}$ -48.8 (*c* 0.92 $CHCl_3$). ^{1}H NMR δ: 2.16 (s, 6H); 3.28 (d, *J* = 10.4 Hz, 2H); 3.84 (s, 2H); 4.33 (d, *J* = 10.4 Hz, 2H); 6.77–6.80 (m, 4H); 7.10–7.16 (m, 6H); 7.25−7.34(m, 6H); 7.60 (d, *J* = 8.4 Hz, 4H); 10.5 (s, 1H) ppm. ^{13}C NMR δ: 19.0 (CH_3); 75.5 (CH_2); 83.7 (d, J_{CP} = 5.9 Hz, C); 85.8 (CH); 126.5 (CH); 127.3 (CH); 127.4 (CH); 127.9 (2CH); 128.0 (CH); 137.7 (C); 143.5 (d, J_{CP} = 11.7 Hz, C) ppm. ^{31}P NMR δ: –5.97 ppm. HRMS: *m*/*z* calcd for $C_{32}H_{32}O_6P$ $[M-H]^+$: 543.1937; found 543.1936.

(2R,3R,4S)-2,3-Bis(benzyloxy)-1,1,4-triphenylpentane-1,4-diol **46** and *(2R,3R,4R)-2,3-Bis(benzyloxy)-1,1,4-triphenylpentane-1,4-diol* ***epi*-46:**



From **39**: (Table 6, Entry 35, *Standard Procedure K,* 0.5 mM). Flash chromatography using a solvent gradient EtOAc (3→30%) / hexane afforded diol **46** as a white crystalline solid. Yield: 213 mg (78%); mp 146–148 °C; $[\alpha]_D^{20}$ -44.4 (c 1.05, $CHCl_3$). ^{1}H NMR δ: 1.55 (s, 3H); 3.59 (d, *J* = 9.9 Hz, 1H); 3.83 (s, 1H); 3.98 (d, *J* = 1.9 Hz, 1H); 4.31 (d, *J* = 10.5 Hz, 1H); 4.32 (d, *J* = 9.9 Hz, 1H); 4.41 (d, *J* = 1.9 Hz, 1H); 4.47 (d, *J* = 10.5 Hz, 1H); 4.49 (s, 1H); 7.03–7.05 (m, 2H); 7.13 (ps.t, *J* = 7.3 Hz, 1H); 7.19–7.40 (m, 16H); 7.48 (d, *J* = 4.3 Hz, 4H); 7.53 (d, *J* = 7.3 Hz, 2H) ppm. ^{13}C NMR δ: 27.9 (CH_3); 74.4 (CH_2); 74.9 (CH_2); 78.4 (C); 80.0 (C); 82.1 (CH); 83.2 (CH); 125.6 (CH); 126.0 (CH); 126.2 (CH); 126.8 (CH); 127.0 (CH); 127.2 (CH); 127.6 (CH); 127.7 (CH); 128.0 (CH); 128.0 (CH); 128.2 (CH); 128.3 (CH); 128.4 (CH); 137.7 (C); 137.9 (C); 145.3 (C); 145.8 (C); 146.0 (C) ppm. HRMS: *m/z* calcd for $C_{37}H_{36}NaO_4$ $[M+Na]^+$: 567.2511; found: 567.2516.

***epi*-46**:

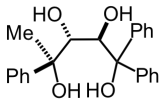


(partly characterised) ^{1}H NMR ($CDCl_3$): δ = 1.54 (s, 3H); 3.30 (s, 1H); 3.56 (d, *J* = 10.6 Hz, 1H); 3.74 (d, *J* = 10.2 Hz, 1H); 3.96 (d, *J* = 3.2 Hz, 1H); 4.03 (d, *J* = 10.6 Hz, 1H); 4.18 (s, 1H); 4.23 (d, *J* = 10.2 Hz, 1H); 4.69 (d, *J* = 3.2 Hz, 1H); 6.89–6.91 (m, 2H); 6.95–6.97 (m, 2H); 7.14–7.35 (m, 15H); 7.43–4.46 (m, 2H); 7.50–7.53 (m, 2H); 7.69–7.70 (d, *J* = 7.4 Hz, 2H) ppm.

From **41**: (Table 6, Entry 39, *Standard Procedure K*, 0.5 mM). Yield: **46** (196 mg, 72%) and ***epi*-46** (42 mg, ca. 13%, incomplete separation).

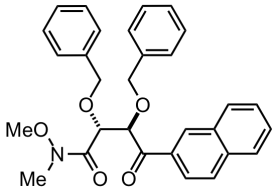
From **40**: (Table 1, entry 38, *Standard Procedure*, 0.5 mM). Yield: **46** (158 mg, 58%) and ***epi*-46** (38 mg, ca. 12%, incomplete separation).

(2R,3R,4S)-1,1,4-Triphenylpentane-1,2,3,4-tetraol **46-OH:**



(*General Procedure L*, 0.09 mM). Clear colorless oil. Yield: 32 mg (quantitative); $[\alpha]_D^{20}$ +59±3 (c 0.75, $CHCl_3$). ^{1}H NMR δ: 1.42 (s, 3H); 3.51 (s, 1H); 3.68 (s, 1H); 3.77 (br.s, 2H); 4.27 (s, 1H); 4.66 (s, 1H); 7.12 (ps.t, *J* = 7.2 Hz, 1H); 7.17–7.29 (m, 11H); 7.33 (ps.t, *J* = 7.2 Hz, 1H); 7.38–7.42 (m, 2H) ppm. ^{13}C NMR δ: 27.6 (CH_3); 72.1 (CH); 74.5 (CH); 78.6 (C); 81.4 (C); 124.4 (CH); 124.9 (CH); 125.9 (CH); 127.1 (CH); 127.1 (CH); 127.3 (CH); 128.4 (CH); 128.5 (CH); 128.6 (CH); 143.9 (C); 144.1 (C); 144.5 (C) ppm. HRMS: *m/z* calcd for $C_{23}H_{24}NaO_4$ $[M+Na]^+$: 387.1572; found: 387.1571.

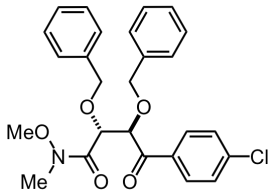
(2R,3R)-2,3-Bis(benzyloxy)-N-methoxy-N-methyl-4-(naphthalen-2-yl)-4-oxobutanamide **47:**



(*Table 7*, Entry 1, *General Procedure K*, 4 mM). Flash chromatography applying a solvent gradient of EtOAc (7→60%)/hexane afforded amide **47** as a clear colorless oil. Yield: 1.55 g (80%); $[\alpha]_D^{20}$ +84.0 (c 2.30, $CHCl_3$). ^{1}H NMR δ: 3.03 (s, 3H); 3.51 (s, 3H); 4.49 (d, *J* = 12.1 Hz, 1H); 4.52 (d, *J* = 11.6 Hz, 1H); 4.75–4.81 (m, 2H); 4.78 (d, *J* = 12.1 Hz, 1H); 5.20 (d, *J* = 5.2 Hz, 1H); 7.08–7.14 (m, 5H); 7.20–7.24 (m, 5H); 7.51 (dd, *J* = 8.3, 6.7 Hz, 1H); 7.59 (dd, *J* = 8.3, 6.7 Hz, 1H); 7.82–7.88 (m, 3H); 8.00 (dd, *J* = 8.6, 1.8 Hz, 1H); 8.55 (s, 1H) ppm. ^{13}C NMR δ:

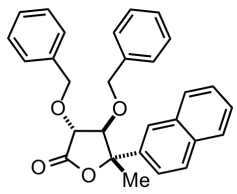
61.1 (CH_3); 72.5 (CH_2); 73.0 (CH_2); 81.1 (CH); 124.6 (CH); 126.6 (CH); 127.7 (CH); 127.9 (CH); 128.1 (CH); 128.1 (CH); 128.3 (CH); 128.6 (CH); 129.8 (CH); 131.1 (CH); 132.4 (C); 133.3 (C); 135.7 (C); 137.3 (C) ppm. (*Note*: signals of 1× CH_3 and 3× C are not obsd.) HRMS: *m/z* calcd for $C_{30}H_{29}NNaO_5$ $[M+Na]^+$: 506.1943; found: 506.1941.

(2R,3R)-2,3-Bis(benzyloxy)-4-(4-chlorophenyl)-N-methoxy-N-methyl-4-oxobutanamide **48:**



(*Table 7*, Entry 2, *General Procedure K*, 4 mM). Flash chromatography applying a solvent gradient EtOAc (7→60%) / hexane afforded amide **48** as a clear colorless oil. Yield: 1.62 g (86%); $[\alpha]_D^{20}$ +113 (c 1.08, $CHCl_3$). ^{1}H NMR δ: 3.06 (s, 3H); 3.48 (s, 3H); 4.41 (d, *J* = 12.1 Hz, 1H); 4.47 (d, *J* = 11.9 Hz, 1H); 4.68 (d, *J* = 12.1 Hz, 1H); 4.71 (d, *J* = 5.1 Hz, 1H); 4.75 (d, *J* = 11.9 Hz, 1H); 4.95 (d, *J* = 5.1 Hz, 1H); 7.11–7.36 (m, 10H); 7.34 (dt, *J* = 8.7, 2.3 Hz, 2H); 7.94 (d, *J* = 8.5 Hz, 2H) ppm. ^{13}C NMR δ: 32.2 (CH_3); 61.1 (CH_3); 72.6 (CH_2); 73.1 (CH_2); 76.6 (CH); 81.6 (CH); 127.9 (CH); 128.0 (CH); 128.1 (CH); 128.2 (CH); 128.3 (CH); 128.4 (CH); 128.6 (CH); 130.8 (CH); 134.3 (C); 137.0 (C); 139.7 (C); 136.9 (C); 169.0 (C); 197.9 (C) ppm. HRMS: *m/z* calcd for $C_{26}H_{26}ClNNaO_5$ $[M+Na]^+$: 490.1397; found: 490.1373.

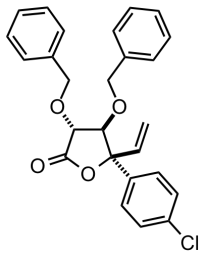
(3R,4R,5S)-3,4-Bis(benzyloxy)-5-methyl-5-(naphthalen-2-yl)dihydrofuran-2(3H)-one **49:**



From **48**: (*Table 7*, Entry 5, *General Procedure K*, 2 mM). Flash chromatography applying a solvent gradient of EtOAc (6→60%)/hexane afforded lactone **49** as a white crystalline solid. Yield: 699 mg (80%); mp 100–101 °C; $[\alpha]_D^{20}$ -21.0 (c 1.12, $CHCl_3$). ^{1}H NMR δ: 1.79 (s, 3H); 4.35 (d, *J* = 8.3 Hz, 1H); 4.51 (d, *J* = 8.3 Hz, 1H); 4.59 (d, *J* = 11.9 Hz, 1H); 4.69 (d, *J* = 11.9 Hz, 1H); 4.78 (d, *J* = 11.5 Hz, 1H); 5.14 (d, *J* = 11.5 Hz, 1H); 7.23–7.38 (m, 10H); 7.47–7.50 (m, 3H); 7.78–7.86 (m, 4H) ppm. ^{13}C NMR δ: 23.4 (CH_3); 72.7 (CH_2); 73.1 (CH_2); 78.8 (CH); 84.5 (C); 85.7 (CH); 122.1 (CH); 123.0 (CH); 126.4 (CH); 126.5 (CH); 127.6 (CH); 127.8 (CH); 128.0 (CH); 128.2 (CH); 128.3 (CH); 128.4 (CH); 128.5 (CH); 128.6 (CH); 132.8 (C); 133.0 (C); 136.9 (C); 137.2 (C); 149.6 (C); 172.1 (C) ppm. HRMS: *m/z* calcd for $C_{29}H_{26}NaO_4$ $[M+Na]^+$: 461.1729; found*:* 461.1725.

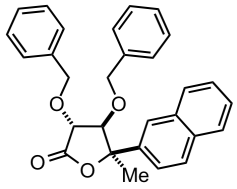
From **30**: (*Table 7*, Entry 3, *General Procedure K*, 1 mM). Yield: 238 mg (54%).

(3R,4R,5S)-3,4-Bis(benzyloxy)-5-(4-chlorophenyl)-5-vinyldihydrofuran-2(3H)-one **50:**



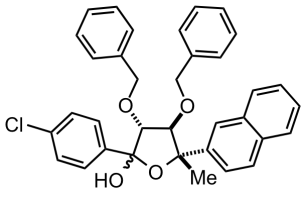
(*Table 7*, Entry 6, *General Procedure K*, 2 mM). Flash chromatography applying a solvent gradient EtOAc (2→20%) / hexane afforded lactone **50** as a white crystalline solid. Yield: 675 mg (78%); mp 66−68 °C; $[\alpha]_D^{20}$ -12.6 (c 1.45, $CHCl_3$). ^{1}H NMR δ: 4.26 (d, *J* = 8.6 Hz, 1H); 4.32 (d, *J* = 8.6 Hz, 1H); 4.54 (d, *J* = 11.8 Hz, 1H); 4.65 (d, *J* = 11.3 Hz, 1H); 4.66 (d, *J* = 11.8 Hz, 1H); 5.08 (d, *J* = 11.3 Hz, 1H); 5.24 (d, *J* = 10.8 Hz, 1H); 5.37 (dd, *J* = 17.3, 0.6 Hz, 1H); 6.32 (dd, *J* = 17.3, 10.8 Hz, 1H); 7.14–7.30 (m, 14H) ppm. ^{13}C NMR δ: 72.9 (CH_2); 73.2 (CH_2); 78.5 (CH); 83.7 (C); 85.5 (CH); 115.9 (CH_2); 126.3 (CH); 127.9 (CH); 128.1 (CH); 128.2 (CH); 128.3 (CH); 128.5 (CH); 128.6 (CH); 128.8 (CH); 134.2 (C); 135.5 (CH); 136.8 (C); 139.1 (C); 171.2 (C) ppm. HRMS: *m/z* calcd for $C_{26}H_{23}ClNaO_4$ $[M+Na]^+$: 457.1183; found: 457.1179.

(3R,4R,5R)-3,4-Bis(benzyloxy)-5-methyl-5-(naphthalen-2-yl)dihydrofuran-2(3H)-one **51:**



(*Table 7*, Entry 4, *General Procedure K*, 2 mM). Flash chromatography applying a solvent gradient of EtOAc (2→20%) / hexane afforded lactone **51** as a clear colorless oil. Yield: 392 mg (45%); $[\alpha]_D^{20}$ +174 (c 1.82, $CHCl_3$). ^{1}H NMR δ: 1.81 (s, 3H); 4.18 (d, *J* = 7.7 Hz, 1H); 4.23 (d, *J* = 7.7 Hz, 1H); 4.59 (d, *J* = 11.9 Hz, 1H); 4.62 (d, *J* = 11.1 Hz, 1H); 4.69 (d, *J* = 11.9 Hz, 1H); 5.10 (d, *J* = 11.1 Hz, 1H); 7.15–7.17 (m, 2H); 7.24–7.35 (m, 8H); 7.42 (dd, *J* = 8.8, 1.8 Hz, 1H); 7.47–7.50 (m, 2H); 7.80–7.84 (m, 4H) ppm. ^{13}C NMR δ: 27.8 (CH_3); 73.1 (CH_2); 73.1 (CH_2); 78.8 (CH); 85.0 (C); 85.1 (CH); 124.1 (CH); 124.5 (CH); 126.4 (CH); 126.4 (CH); 127.5 (CH); 127.6 (CH); 127.8 (CH); 128.0 (CH); 128.1 (CH); 128.1 (CH); 128.4 (CH); 128.5 (CH); 128.5 (CH); 132.8 (C); 132.8 (C); 136.9 (C); 137.0 (C); 137.1 (C); 172.8 (C) ppm. HRMS: *m/z* calcd for $C_{29}H_{26}NaO_4$ $[M+Na]^+$: 461.1729 ; found: 461.1626.

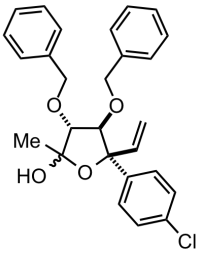
(3R,4R,5S)-3,4-Bis(benzyloxy)-2-(4-chlorophenyl)-5-methyl-5-(naphthalen-2-yl)tetra-hydrofuran-2-ol **52:**



(*Table 7*, Entry 7, *General Procedure K*, 1 mM). Flash chromatography applying a solvent gradient of EtOAc (1→15%) / hexane afforded hemiketal **52** as a clear colorless oil. (anomers A:B = 75:25). Yield: 452 mg, (82%). ^{1}H NMR δ:

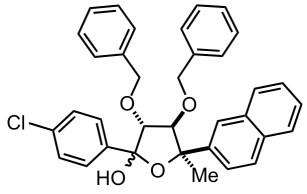
1.78 (s, 3H_A); 1.83 (s, 3H_B); 3.91 (s, 1H_A); 3.93 (s, 1H_B); 3.99 (d, *J* = 11.9 Hz, 1H_B); 4.04 (d, *J* = 11.9 Hz, 1H_B); 4.18 (d, *J* = 3.3 Hz, 1H_B); 4.19 (d, *J* = 6.6 Hz, 1H_A); 4.34 (d, *J* = 11.5 Hz, 1H_A); 4.35 (d, *J* = 3.3 Hz, 1H_B); 4.42 (d, *J* = 11.5 Hz, 1H_A); 4.48 (d, *J* = 6.6 Hz, 1H_A); 4.57 (d, *J* = 12.1 Hz, 1H_B); 4.61 (d, *J* = 11.8 Hz, 1H_A); 4.65 (d, *J* = 11.8 Hz, 1H_A); 4.75 (d, *J* = 12.1 Hz, 1H_B); 6.64 (d, *J* = 7.5 Hz, 2H_B); 6.73 (d, *J* = 8.7 Hz, 1H_B); 6.99–7.84 (m, 38 H_{A+B}); 7.98 (d, *J* = 2.1 Hz, 1H_A) ppm. ^{13}C NMR (*note:* 4× C were not obsd, no assignment of anomers.) δ: 25.7 (CH_3); 27.3 (CH_3); 71.8 (CH_2); 72.9 (CH_2); 72.9 (CH_2); 73.1 (CH_2); 84.4 (C); 86.6 (C); 88.6 (CH); 88.6 (CH); 89.1 (CH); 100.9 (C); 106.4 (C); 123.1 (CH); 123.3 (CH); 123.4 (CH); 123.6 (CH); 125.7 (CH); 125.8 (CH); 126.1 (CH); 127.5 (CH); 127.5 (CH); 127.5 (CH); 127.6 (CH); 127.6 (CH); 127.8 (CH); 127.8 (CH); 127.9 (CH); 127.9 (CH); 128.0 (CH); 128.0 (CH); 128.10 (CH); 128.2 (CH); 128.2 (CH); 128.3 (CH); 128.5 (CH); 128.6 (CH); 129.0 (CH); 129.5 (CH); 132.5 (C); 132.8 (C); 133.1 (C); 134.3 (C); 136.7 (C); 137.4 (C); 137.9 (C); 138.5 (C); 141.6 (C); 144.7 (C) ppm. HRMS: *m/z* calcd for $C_{35}H_{31}ClNaO_4$ $[M+Na]^+$: 573.1809; found: 573.1808.

(3R,4R,5S)-3,4-Bis(benzyloxy)-5-(4-chlorophenyl)-5-vinyltetrahydrofuran-2-ol **53:**



(*Table 7*, Entry 8, *General Procedure K*, 1 mM). Flash chromatography applying a solvent gradient of EtOAc (3→30%) / hexane afforded **53** as a clear colorless oil. (anomers A:B = 55:45). Yield: 331 mg (74%). ^{1}H NMR δ: 1.58 (s, 3H_B); 1.62 (s, 3H_A); 3.49 (s, 1H_A); 3.58 (s, 1H_B); 3.89 (d, *J* = 6.3 Hz, 1H_A); 3.93 (d, *J* = 3.6 Hz, 1H_B); 4.11 (d, *J* = 3.6 Hz, 1H_B); 4.28 (d, *J* = 6.3 Hz, 1H_A); 4.29 (d, *J* = 11.8 Hz, 1H_B); 4.42 (d, *J* = 11.8 Hz, 1H_B); 4.55–4.65 (m, 5H_{A+B}); 4.69 (d, *J* = 12.6 Hz, 1H_B); 5.19–5.23 (m, 2H_{A+B}); 5.29 (dd, *J* = 17.3, 1.8 Hz, 1H_A); 5.39 (dd, *J* = 17.1, 1.5 Hz, 1H_B); 6.30 (dd, *J* = 17.1, 10.9 Hz, 1H_B); 6.33 (dd, *J* = 17.3, 10.8 Hz, 1H_A); 6.90–6.95 (m, 2H_B); 7.13–7.15 (m, 2H_A); 7.21–7.41 (m, 24H_{A+B}). ^{13}C NMR (no assignment of anomers) δ: 22.3 (CH_3); 27.1 (CH_3); 71.9 (CH_2); 72.9 (CH_2); 73.1 (CH_2); 73.1 (CH_2); 84.1 (C); 86.2 (CH); 87.2 (CH); 87.3 (CH); 88.8 (CH); 100.9 (C); 106.1 (2C); 114.9 (CH_2); 115.2 (CH_2); 126.8 (CH); 127.2 (CH); 127.3 (CH); 127.6 (CH); 127.7 (CH); 127.7 (CH); 127.8 (CH); 127.9 (CH); 128.1 (CH); 128.10 (CH); 128.2 (CH); 128.2 (CH); 128.3 (CH); 128.4 (CH); 128.5 (CH); 128.6 (CH); 132.5 (C); 132.8 (C); 137.1 (C); 137.1 (C); 137.4 (C); 137.6 (C); 138.7 (CH); 139.5 (CH); 142.6 (C); 143.2 (C) ppm. HRMS: *m/z* calcd for $C_{27}H_{27}ClNaO_4$ $[M+Na]^+$: 473.1496; found: 473.1496.

(3R,4R,5R)-3,4-Bis(benzyloxy)-2-(4-chlorophenyl)-5-methyl-5-(naphthalen-2-yl)-tetra-hydrofuran-2-ol **54:**

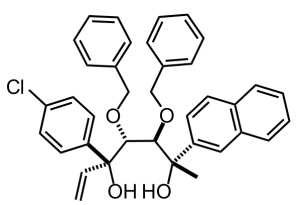


(*Table 7*, Entry 9, *General Procedure K*, 0.5 mM). Compound **54** was obtained as a colorless oil and used without any purification. (anomers A:B = 55:45). Yield: 223 mg (82%). ^{1}H NMR δ: 1.89 (s, 3H$_B$); 1.92 (s, 3H$_A$); 3.97 (s, 1H$_B$); 4.11–4.39 (m, 9H$_{A+B}$); 4.42 (s, 1H$_A$); 4.55 (s, 1H$_B$); 4.60 (s, 2H$_A$); 6.59 (d, *J* = 7.6 Hz, 2H$_B$); 6.91 (d, *J* = 7.8 Hz, 2H$_A$); 7.03 (d, *J* = 7.5 Hz, 2H$_A$); 7.16–7.49 (m, 22H$_{A+B}$); 7.68 (d, *J* = 8.7 Hz, 2H$_A$); 7.73 (d, *J* = 8.7 Hz, 2H$_B$); 7.79–7.91 (m, 8H$_{A+B}$); 7.99 (d, *J* = 1.5 Hz, 1H$_A$); 8.11 (d, *J* = 1.6 Hz, 1H$_B$) ppm. ^{13}C NMR ($CDCl_3$, *note*: No assignment of anomers.) δ: 28.8 (CH_3); 29.7 (CH_3); 72.1 (CH_2); 72.5 (CH_2); 72.5 (CH_2); 73.7 (CH_2); 86.5 (C); 87.2 (CH); 87.2 (CH); 88.7 (CH); 88.8 (CH); 89.9 (C); 102.1 (C); 107.4 (C); 124.5 (CH); 124.6 (CH); 125.0 (CH); 125.1 (CH); 125.6 (CH); 125.8 (CH); 125.9 (CH); 125.9 (CH); 127.1 (CH); 127.1 (CH); 127.4 (CH); 127.4 (CH); 127.6 (CH); 127.7 (CH); 127.8 (CH); 127.9 (CH); 127.9 (CH); 128.1 (CH); 128.1 (CH); 128.2 (CH); 128.3 (CH); 128.3 (CH); 128.3 (CH); 128.4 (CH); 128.6 (CH); 129.2 (CH); 132.4 (C); 132.4 (C); 133.0 (C); 133.1 (C); 134.0 (C); 134.3 (C); 136.1 (C); 136.7 (C); 137.2 (C); 137.2 (C); 137.3 (C); 140.5 (C); 141.5 (C); 141.9 (C) ppm. HRMS: *m/z* calcd for $C_{35}H_{31}ClNaO_4$ $[M+Na]^+$: 573.1809; found: 573.1799.

(2S,3R,4R,5S)-3,4-Bis(benzyloxy)-5-(4-chlorophenyl)-2-(naphthalen-2-yl)hept-6-ene-2,5-diol **55** and *(2R,3R,4R,5S)-3,4-Bis(benzyloxy)-5-(4-chlorophenyl)-2-(naphthalen-2-yl)hept-6-ene-2,5-diol* **56:**

From **53**: (*Table 7*, Entry 11, *General Procedure K*, 0.25 mM). The mixture of diastereoisomers was separated by flash chromatography applying a solvent gradient of EtOAc (1→30%) / hexane; dr of **55**:**56** = 11:1.

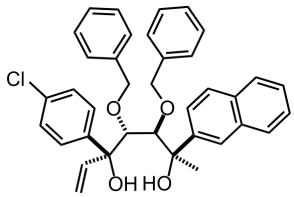
55:



Yield: 65 mg (44%, clear colorless oil); $[\alpha]_D^{20}$ -102 (c 1.82, $CHCl_3$). ^{1}H NMR δ: 1.58 (s, 3H); 3.71 (d, *J* = 2.2 Hz, 1H); 3.72 (s, 1H); 3.79 (d, *J* = 2.2 Hz, 1H); 3.89 (s, 1H); 4.36 (d, *J* = 10.4 Hz, 1H); 4.47 (d, *J* = 10.2 Hz, 1H); 4.64 (d, *J* = 10.2 Hz, 1H); 4.75 (d, *J* = 10.4 Hz, 1H); 5.06 (dd, *J* = 10.6, 1.3 Hz, 1H); 5.38 (dd, *J* = 17.0, 1.3 Hz, 1H); 6.08 (dd, *J* = 17.0, 10.6 Hz, 1H); 7.08 (d, *J* = 8.3 Hz, 1H); 7.16–7.30 (m, 12H); 7.38 (dd, *J* = 8.6, 2.0 Hz, 1H); 7.46–7.52 (m, 2H); 7.78–7.86 (m, 4H)

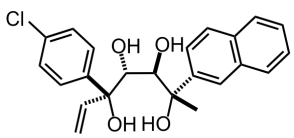
ppm. ^{13}C NMR δ: 27.5 (CH_3); 74.8 (CH_2); 75.1 (CH_2); 78.0 (C); 79.1 (C); 81.9 (CH); 82.6 (CH); 114.3 (CH_2); 123.7 (CH); 124.3 (CH); 126.0 (CH); 126.3 (CH); 127.0 (CH); 127.6 (CH); 127.7 (CH); 127.8 (CH); 127.8 (CH); 127.9 (CH); 128.0 (CH); 128.2 (CH); 128.3 (CH); 128.3 (CH); 128.5 (CH); 132.4 (C); 132.8 (C); 133.2 (C); 137.9 (C); 138.0 (C); 141.7 (CH); 142.4 (C); 143.3 (C) ppm. HRMS: *m/z* calcd for $C_{37}H_{35}ClNaO_4$ $[M+Na]^+$: 601.2122; found: 601.2116.

56: Yield: 7 mg (4%,white foam); $[\alpha]_D^{20}$ -14.6±1.5 (c 0.85, $CHCl_3$). ^{1}H NMR δ: 1.71 (s, 3H); 3.59 (s, 1H); 3.75 (d, *J* = 10.8 Hz, 1H); 3.83 (d, *J* = 3.8 Hz, 1H); 3.88 (d, *J* = 3.8 Hz, 1H); 3.97 (s, 1H); 4.06 (d, *J* = 10.8 Hz, 1H); 4.15 (d, *J* = 11.0 Hz, 1H); 4.62 (d, *J* = 11.0 Hz, 1H); 5.34 (dd, *J* = 10.7, 1.3 Hz, 1H); 5.56 (dd, *J* = 17.2, 1.3 Hz, 1H); 6.51 (dd, *J* = 17.2, 10.7 Hz, 1H); 6.78 (d, *J* = 6.9 Hz, 1H); 7.07–7.17 (m, 5H); 7.22–7.27 (m, 6H); 7.36 (d, *J* = 8.8 Hz, 2H); 7.43–7.49 (m, 2H); 7.55 (dd, *J* = 8.8, 1.7 Hz, 1H); 7.76–7.82 (m, 3H); 7.99 (s, 1H) ppm. ^{13}C NMR δ: 28.4 (CH_3); 74.1 (CH_2); 75.0 (CH_2); 76.6 (C); 78.1 (C); 82.0 (CH); 83.6 (CH); 115.1 (CH_2); 124.8 (CH); 125.0 (CH); 125.9 (CH); 126.1 (CH); 127.3 (CH); 127.4 (CH); 127.5 (CH); 127.5 (CH); 127.5 (CH); 127.8 (CH); 127.9 (CH); 127.9 (CH); 128.2 (CH); 128.2 (CH); 128.3 (CH); 132.5 (C); 133.0 (2× C); 137.4 (C); 138.4 (C); 140.5 (CH); 142.8 (C); 143.7 (C) ppm. HRMS: *m/z* calcd for $C_{37}H_{35}ClNaO_4$ $[M+Na]^+$: 601.2122; found: 601.2116.



From **52**: (Table 7, Entry 10, *Standard Procedure*, 0.2 mM). Yield: 52 mg (45%) of **55**.

(2S,3R,4R,5S)-5-(4-Chlorophenyl)-2-(naphthalen-2-yl)heptane-2,3,4,5-tetraol **55-OH**:

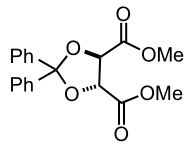


After applying *General Procedure L*, 0.09 mM, the crude mixture was subjected to flash chromatography using a solvent gradient MeOH (1→5%)/CH_2Cl_2 to give tetraol **55-OH** as clear colorless oil. Yield: 25 mg (73%); $[\alpha]_D^{20}$ -147 (c 1.25; $CHCl_3$). ^{1}H NMR δ: 0.47 (t, *J* = 7.4 Hz, 3H); 1.28–1.37 (m, 1H); 1.46 (s, 3H); 1.92–2.01 (m, 1H); 3.48 (s, 1H); 3.59 (s, 1H); 3.71–3.85 (br.s, 4H); 6.98–7.03 (m, 2H); 7.11 (dd, *J* = 8.5, 1.9 Hz, 1H); 7.28 (d, *J* = 8.5 Hz, 2H); 7.48–7.54 (m, 2H); 7.79–7.83 (m, 4H) ppm. ^{13}C NMR δ: 6.8 (CH_3); 27.7 (CH_3); 31.8 (CH_2); 74.4 (CH); 74.5 (CH); 78.6 (C); 80.7 (C); 122.5 (CH); 123.2 (CH); 126.1 (CH); 126.4 (CH); 126.6 (CH); 127.6 (CH); 128.2 (CH); 128.5 (CH); 132.4 (C); 132.9 (C); 133.3 (C); 140.8 (C); 141.7 (C) ppm. HRMS: *m/z* calcd for $C_{23}H_{25}ClNaO_4$ $[M+Na]^+$: 423.1339; found: 423.1331.

Reaction of hemiketal **54** *with vinylmagnesium bromide*.

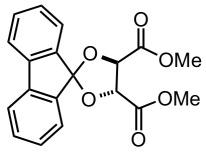
Vinylmagnesium bromide (0.64 mmol, 0.64 mL of a 1M solution in THF) was added to hemiketal **54** (90 mg, 0.16 mmol) in THF at 0 °C and stirred for 5 h. Similar work up as above gave an unseparable mixture of **56** and **57** (4:1). Yield: 55% (overall).

Dimethyl (4R,5R)-2,2-diphenyl-1,3-dioxolane-4,5-dicarboxylate **58:**[124]



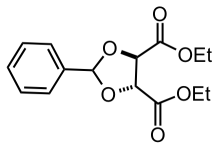
L-(+)-dimethyltartrate (3.67 g, 20.6 mmol) and dimethoxydiphenylmethane (4.7 g, 20.6 mmol) were dissolved in benzene (40 mL) and catalytic amount of *p*-TSA was added. The mixture was heated to reflux and benzene/MeOH azeotrope was distilled off with occasional addition of benzene. The mixture was washed with sat. aq. $NaHCO_3$ (2× 30 mL), brine, dried over $MgSO_4$ and concentrated. The crude product was crystallized from hexane affording the product as white solid in 4.9 g (65%) yield. ^{1}H NMR δ: 3.67 (s, 6H); 4.96 (s, 2H); 7.29–7.31 (m, 6H); 7.49–7.52 (m, 4H) ppm.*

Dimethyl (4'R,5'R)-spiro[fluorene-9,2'-[1,3]dioxolane]-4',5'-dicarboxylate **59**:[147]



9,9-dimethoxy-9H-fluorene (4.74 g, 20.9 mmol) and *L*-(+)-dimethyltartrate (3.7 g, 20.9 mmol) was dissolved in cyclohexane (40 mL) and *p*-TSA (catalytic amount) was added. The mixture was heated to reflux with occasional addition of cyclohexane and cyclohexane/MeOH azeotrope was distilled off. After the reaction was complete, TEA was added and the mixture was extracted with EtOAc (3× 30 mL), washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by MPLC applying a solvent gradient EtOAc(10→30%)–heptane afforded the product as a white solid in 5.9 g (82%). ^{1}H NMR δ: 3.91 (s, 6H); 5.25 (s, 2H); 7.28–7.51 (m, 8H) ppm.*

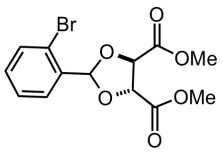
Diethyl (4R,5R)-2-phenyl-1,3-dioxolane-4,5-dicarboxylate **60**: [125, 152,]



A 100 mL, round bottomed flask equipped with a Dean Stark trap was charged with (*L*)-(+)-diethyl tartrate (6.24 g, 30 mmol), benzaldehyde (3.18 g, 30 mmol), cyclohexane (40 mL) and *p*-TSA monohydrate (190 mg, 1 mmol). The mixture is heated to reflux for 16 h with azeotropic removal of water. The solution is allowed to cool to room temperature and was concentrated by rotary evaporator. The residue was

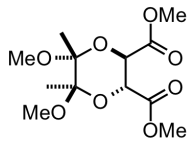
dissolved in Et_2O (30 mL), washed with saturated solution of $KHCO_3$ and with H_2O (2× 15 mL). The ethereal layer was dried over MgSO4, concentrated and triturated with hexane (9 mL) afforded **60** as clear colorless crystal in 6.18 g (70%) yield. ^{1}H NMR δ: 1.28 (t, *J* = 7.1 Hz, 3H); 1.34 (t, *J* = 7.1 Hz, 3H); 4.26 (q, *J* = 7.1 Hz, 2H); 4.31 (q, *J* = 7.1 Hz, 2H); 4.81 (d, *J* = 4.0 Hz, 1H); 4.92 (d, *J* = 4.0 Hz, 1H); 6.14 (s, 1H); 7.37–7.38 (m, 3H); 7.55–7.57 (m, 2H) ppm.*

Dimethyl (4R,5R)-2-(2-bromophenyl)-1,3-dioxolane-4,5-dicarboxylate **61***:*



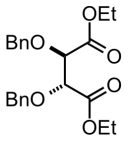
A solution of *L*-(+)-dimethyl tartrate (3.56 g, 20 mmol), 2-bromobenzaldehyde (2.32 mL, 3.7 g, 20 mmol) and TsOH (40 mg, 0.2 mmol, 1 mol%) in toluene (50 mL) was refluxed with a Dean Stark condenser. After 20 h, the solvent was removed under vacuum and the crude product was distilled using Kugelrohr apparatus to afford **61** in 4.4 g (64%) yield. ^{1}H NMR δ: 3.80 (s, 3H); 3.87 (s, 3H); 4.87 (d, *J* = 3.9 Hz, 1H); 4.99 (d, *J* = 3.9 Hz, 1H); 6.45 (s, 1H); 7.22–7.26 (m, 1H); 7.35 (t, *J* = 7.8 Hz, 1H); 7.55 (d, *J* = 8.4 Hz, 1H); 7.79 (d, *J* = 7.8 Hz, 1H) ppm.

Dimethyl (2R,3R,5R,6R)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-dicarboxylate ***62****:*[126]



Trimethyl orthoformate (2.2 mL, 2.1 g, 0.02 mol) and 2,3-butanedione (0.53 mL, 0.53 g, 6.1 mmol) were added to (*L*)-(+)-dimethyl tartrate (891 mg, 5.0 mmol) in MeOH (10 mL). The solution was heated to reflux for 24 h, cooled to room temperature and solid $NaHCO_3$ was added. The solvents were removed and the residue was washed with heptane. The removal of heptane afforded XX as a clear colorless solid in 1.2 g (82%). ^{1}H NMR δ: 1.32 (s, 6H); 3.29 (s, 6H); 3.73 (s, 6H); 4.50 (s, 2H) ppm.*

Diethyl (2R,3R)-2,3-bis(benzyloxy)succinate ***63****:*[127]

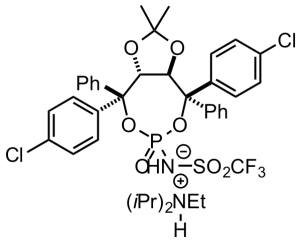


To a solution of NaH (60% in mineral oil, 2.72 g, 68.2 mmol) in dry DMF (80 mL) was added dropwise a solution of (*L*)-(+)-diethyl tartrate (7.02 g, 34 mmol) in DMF (20 mL) at -20 °C. The reaction was stirred for 30 min and BnBr (12.2 mL, 17.5 g, 0.1 mol) and the stirring was continued for 40 min. The mixture was stirred at 0 °C for 1 h. The reaction was quenched by cautionary addition of water (500 mL) and extracted with Et_2O (3×80 mL). The combined

* Spectroscopic data are in accordance with literature.

organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by MPLC applying a solvent gradient EtOAc(5→20%)-hexane to afford XX as yellow oil in 12.2 g (93%) yield. ^{1}H NMR δ: 1.17 (t, *J* = 7.1 Hz, 6H); 4.02–4.09 (m, 2H); 4.14–4.22 (m, 2H); 4.37 (s, 2H); 4.44 (d, *J* = 12.0 Hz, 2H); 4.84 (d, *J* = 12.0 Hz, 2H); 7.24–7.32 (m, 10H) ppm.*

N-ethyl-N-isopropylpropan-2-aminium((3aR,4R,8R,8aR)-4,8-bis(4-chlorophenyl)-2,2-dimethyl-6-oxido-4,8-diphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)((trifluoromethyl)sulfonyl)amide **64:**

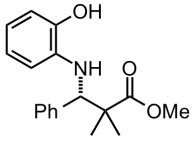


Phosphoroxichloride **4a-PCl** (79 mg, 0.13 mmol) was dissolved in $CDCl_3$ (1 mL) and *N,N*-diisopropylethylamine (131 μL, 0.77 mmol) was added followed by trifluoromethanesulfonamide (30 mg, 0.26 mmol). The mixture was heated for 12 h at 55 °C, cooled to room temperature and subjected to MPLC using a solvent gradient of MeOH (0→20%)–DCM to afford **64** in 60 mg (55%) yield. ^{1}H NMR δ: 0.23 (s, 3H), 0.83 (t, *J* = 7.3 Hz, 3H); 0.88–0.93 (m, 12H); 1.49 (s, 3H); 2.41–2.50 (m, 2H); 2.88–2.92 (m, 2H); 4.58 (d, *J* = 8.6 Hz, 1H); 5.71 (d, *J* = 8.6 Hz, 1H); 7.18–7.29 (m, 10H); 7.38 (d, *J* = 8.5 Hz, 2H); 7.44 (d, *J* = 7.2 Hz, 2H); 7.61 (d, *J* = 8.5 Hz, 2H); 7.74 (d, *J* = 8.6 Hz, 2H) ppm. ^{13}C NMR δ: 11.0 (CH_3); 17.0 (CH_3); 17.2 (CH_3); 18.2 ($2CH_3$); 25.2 (CH_3); 27.8 (CH_3); 40.9 (CH_2), 52.6 (CH); 52.8 (CH); 79.2 (CH); 82.6 (CH); 83.3 (d, J_{CP} = 8.8 Hz, C); 85.0 (d, J_{CP} = 5.9 Hz, C); 111.2 (C); 120.6 (q, J_{CF} = 328.4 Hz, C); 127.2 (CH); 127.3 (2CH); 127.4 (CH); 127.5 (2CH); 127.7 (CH); 127.9 (CH); 130.2 (CH); 130.9 (CH); 132.8 (C); 133.6 (C); 139.0 (d, J_{CP} = 11.4 Hz, C); 140.9 (C); 144.5 (d, J_{CP} = 12.0 Hz, C); 145.9 (C) ppm. ^{31}P NMR δ: –10.24 ppm. HRMS: *m*/*z* calcd for $C_{32}H_{26}Cl_2F_3NO_7PS$ $[M\text{-}C_8H_{20}N]^+$: 726.0502; found: 726.0521.

Catalytic reactions

Mannich type reaction:[114]

Methyl (S)-3-((2-hydroxyphenyl)amino)-2,2-dimethyl-3-phenylpropanoate **A**:

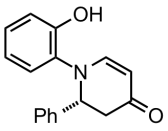


To a solution of 2-(benzylideneamino)phenol (29.6 mg, 0.15 mmol) and phosphate **17e-POOH** (13 mg, 0.015 mmol) in xylene (1 mL) was added 1-methoxy-2methyl-1-(trimethylsiloxy)propene (62 μL, 52 mg, 0.3 mmol) at -40 °C. The mixture was stirred for 24 h, cooled down to -78 °C and quenched with successive addition of saturated solution of $NaHCO_3$ (5 mL), saturated KF (3 mL) and MeOH/THF (3 mL). The mixture was left

stirring at room temperature for 30 min. and extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by MPLC applying a solvent gradient EtOAc (4→30%)–heptane to afford 43 mg of the product **A** (96 % yield, 96% *e.e*. *S*). HPLC: Daicel Chiralpak AD-H, heptane:*i*PrOH = 5:1, flow rate = 0.5 mL/min, UV = 254 nm, t_R = 11.2 min (*R*), t_R= 16.5 min (*S*). ^{1}H NMR δ: 1.19 (s, 3H); 1.22 (s, 3H); 3.67 (s, 3H) 4.52 (d, *J* = 7.8 Hz, 1H); 4.81 (brs, 1H); 5.17 (brs, 1H); 6.36–6.77 (m, 5H); 7.19–7.27 (m, 3H) ppm.*[*]

Aza-Diels-Alder reaction :[116]

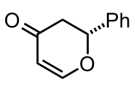
(R)-1-(2-hydroxyphenyl)-2-phenyl-2,3-dihydropyridin-4(1H)-one **E***:*



2-(Benzylideneamino)phenol (29.6 mg, 0.15 mmol) was dissolved in toluene (1 mL) and the phosphate **17e-POOH** (13 mg, 0.015 mmol) was added at -40 °C followed by Danishefsky's diene (62 µL, 52 mg, 0.3 mmol). After stirring for 24 h and saturated solution of $NaHCO_3$ was added. The mixture was extracted with EtOAc and the concentrated organic layers were concentrated under vacuum. The crude mixture was treated with THF (5 mL) and 1N HCl (0.5 mL) at 0 °C for 20 min. The mixture was extracted with EtOAc, the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by MPLC applying a solvent gradient EtOAc (60 →100%)-heptane to afford 32 mg of **E** (65% yield, 39% *e.e.*). HPLC: Daicel Chiralpak AD-H, hexane:EtOH = 9:1, flow rate = 0.5 mL/min, UV = 254 nm, t_R = 24.1 min (*R*), t_R = 28.5 min (*S*). ^{1}H NMR δ: 2.89 (dd, *J* = 16.7 Hz, 6.6 Hz, 1H); 3.29 (dd, J = 16.7, 7.3 Hz, 1H); 5.23 (d, *J* = 7.4 Hz, 1H); 5.33 (dd, *J* = 7.3, 6.6 Hz, 1H); 6.67 (dd, *J* = 7.3 Hz, 1H); 6.87–7.01 (m, 3H); 7.17–7.27 (m, 5H); 7.44 (d, J = 7.4 Hz, 1H); 9.92 (s, 1H) ppm.*

Oxo-Diels-Alder reaction:[105]

(R)-2-phenyl-2,3-dihydro-4H-pyran-4-one **F***:*



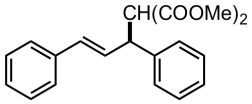
Rawal's diene (66 µL, mm 0.25 mmol) was added to a solution of diol **17e** (40 mg, 0.05 mmol) and benzaldehyde (51 µL, 57 mg, 0.5 mmol) in toluene (0.25 mL) at -40 °C. The mixture was stirred for 24 h and diluted with DCM (1 mL). Acetylchloride (51 µL, 0.5 mmol) was added at -78 °C and the mixture was further stirred for 15 min. The crude product was purified by MPLC applying

[*] Spectroscopic data are in accordance with literature.

a solvent gradient EtOAc (5 →30%)-heptane to afford **F** as yellow oil in 32 mg (53% yield, 46% *e.e.*). HPLC: Daicel Chiralcel OD-H, heptane:*i*PrOH = 9:1, flow rate = 0.9 mL/min, UV = 254 nm, t_R = 12.7 min (*S*), t_R = 14.7 min (*R*). ^{1}H NMR δ: 2.64 (ddd, *J* = 16.8 Hz, 3.5, 1.3 Hz, 1H); 2.88 (dd, *J* = 16.8, 14.5 Hz, 1H); 5.40 (d, *J* = 14.5, 3.5 Hz, 1H); 5.50 (dd, *J* = 6.3, 1.3 Hz, 1H); 7.36–7.46 (m, 6H) ppm.*

Pd catalysed allylic alkylation reaction:[95]

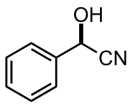
Dimethyl (S,E)-2-(1,3-diphenylallyl)malonate **G**:



A flame-dried Schlenk vessel was charged with [{Pd(allyl)Cl}$_2$] (1.8 mg, 0.005 mmol) and ligand (13.1 mg, 0.02 mmol) in DCM (1 mL). 1,3-diphenyl-2-propenyl acetate (251 mg, 1.0 mmol) and dimethyl malonate (341 µL, 3 mmol) were added and the mixture was stirred at room temperature for 15 min. The reaction was started by addition N,O-bis(trimethylsilyl) acetamide (0.74 mL, 3 mmol) and LiOAc (1 mg). The reaction was monitored by TLC. After 70 h, the mixture was diluted with Et_2O (10 mL), washed with saturated NH_4Cl solution (5 mL) and dried over $MgSO_4$. The crude product was concentrated under vacuum and subjected to flash chromatography using DCM:hexane (50:50) to yield 291 mg of **G** (90% yield, 90% *e.e.*) HPLC: Daicel Chiralcel OD, hexane:*i*PrOH = 98:2, 0.5 mL/min, UV = 254 nm, t_R = 18.8 min (*R*), t_R = 20.2 min (*S*). ^{1}H NMR δ: 3.50 (s, 3H); 3.69 (s, 3H); 3.93 (d, *J* = 10.8 Hz, 1H); 4.24 (dd, *J* = 10.8, 8.6 Hz, 1H); 6.31 (dd, *J* = 15.8, 8.6 Hz, 1H); 6.46 (d, J = 15.8 Hz, 1H); 7.18–7.31 (m, 10H) ppm.*

Trimethylsilylcyanide addition to benzaldehyde:[153 +76]

(*R)-2-hydroxy-2-phenylacetonitrile* **H***:*



To a stirred solution of **17a** (31 mg, 0.05 mmol) in $CHCl_3$ (1 mL) was added titanium tetraisopropoxide (15 µL, 14 mg, 0.05 mmol) under argon at room temperature and the mixture was stirred for 1 h. Trimethylsilyl cyanide (125 µL, 99 mg, 1 mmol) was added and stirred for an additional 30 min. The reaction mixture was cooled to -10 °C, PPh_3O (14 mg, 0.05 mmol) was added and stirred further 30 min. Benzaldehyde was added to the reaction mixture and the reaction was monitored by TLC. After completion of the reaction, $CHCl_3$ was evaporated. The crude product was treated with THF (2 mL) and 1N HCl (1 mL) and stirred for 1 h at room temperature. The mixture was extracted with $CHCl_3$, dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by MPLC applying a solvent gradient EtOAc (5→25%)-

* Spectroscopic datas are in accordance with literature.

heptane to afford 45 mg of **H** (67% yield, 25% *e.e.* (*R*)). HPLC: Daicel Chiralpak IA, hexane:*i*PrOH:EtOH:AcOH = 97:3:0.1, flow rate = 1.0 mL/min, UV = 220 nm, t_R = 18.1 min (*S*), t_R = 16.2 min (*R*). ^{1}H NMR δ: 3.42 (s, 1H); 5.49 (s, 1H); 7.40–7.50 (m, 5H) ppm.

***Crystal Structure Determination*:**

X-ray diffraction data were collected at 120(2) K on a Bruker X8 APEX-II CCD instrument with MoKα radiation (λ = 0.71073 Å).

Crystal data for **4e**: empirical formula $C_{33}H_{34}O_4$; formula weight 494.60; triclinic; space group P1 (no. 1); *a* = 8.3081(4) Å; *b* = 9.6166(4) Å; *c* = 9.6643(4) Å; *α* = 60.469(2)°; *β* = 72.302(2)°; *γ* = 77.538(2)°; *V* = 638.00(5) Å^3; *Z* = 1; *Dcalc* = 1.287 g/cm^3; *T* = 150.00 K; μ(MoKα) = 0.083 mm^{-1}; 27487 reflections measured (4.884° ≤ 2Θ ≤ 60.258°); 6826 unique (R_{int} = 0.0416, R_{sigma} = 0.0318) which were used in all calculations. The final R_1 was 0.0363 (I > 2σ(I)) and wR_2 was 0.0987 (all data).

Crystal data for **34**: empirical formula $C_{25}H_{24}O_4$; formula weight 388.44; monoclinic; space group $P2_1$; *a* = 10.7047(4) Å; *b* = 6.0583(2) Å; *c* = 15.7886(5) Å; *β* = 103.439(2)°; *V* = 995.89(6) Å^3; *Z* = 2; D_{calc} = 1.295 g/cm^3; *T* = 120(2) K; μ(MoKα) = 0.087 mm^{-1} *F*(000) = 604; crystal size = 0.25 × 0.10 × 0.08 mm.

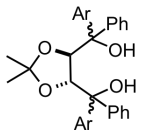
Crystal data for **13e-POOH**: empirical formula $C_{57}H_{38}O_6P$; formula weight 850.24; orthorhombic, space group $P2_12_12_1$ (no. 19), *a* = 13.1704(9) Å, *b* = 22.8973(15) Å, *c* = 34.644(2) Å, *V* = 10447.5(12) Å^3, *Z* = 4, D_{calc} = 1.308 g/cm^3, μ(MoKα) = 0.333 mm^{-1}, *T* = 100.0 K, 426426 reflections measured (2.132° ≤ 2Θ ≤ 50.7°), 19111 unique (R_{int} = 0.0546, R_{sigma} = 0.0286) which were used in all calculations. The final R_1 was 0.0490 (I > 2σ(I)) and wR_2 was 0.1360 (all data).

Crystal Data for **13f**: empirical formula $C_{65}H_{56}O_8$; formula weight 965.09; monoclinic; space group P 1 21 1; *a* = 11.7269(4) Å; *b* = 18.3771(6) Å; *c* = 12.4795(4) Å; β = 107.1638(14)°; *V* = 2569.64(15) Å^3; *Z* = 2; D_{calc} = 1.247 Mg m^3; *T* = 100.0 K; μ(MoKα) = 0.081 mm^{-1}; 53870 reflections measured (2.04 ° ≤ 2Θ ≤ 25.35°); 9406 unique (R_{int} = 0.0370) which were used in all calculations. The final R_1 was 0.0524(I > 2σ(I)) and wR_2 was 0.1404 (all data).

Crystal data for **16e-POOH** (triethylammonium salt): empirical formula $C_{58}H_{60}Cl_6NO_8P$; formula weight 1142.74; orthorhombic; space group P 2_1 2_1 2_1; *a* = 12.2509(5) Å; *b* = 22.5057(10) Å; *c* = 40.6256(18) Å; *V* = 11201.1(8) Å^3; *Z* = 8; D_{calc} = 1.355 g/cm^3; *T* = 100.0 K, μ(MoKα) = 0.390 mm^{-1}; 85260 reflections measured (1.03 ° ≤ 2Θ ≤ 25.35°);

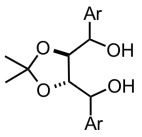
20497 unique (R_{int} = 0.0386) which were used in all calculations. The final R_1 was 0.0653(I > 2σ(I)) and wR_2 was 0.1725 (all data).

Attachment 1. Summary of synthesized auxiliaries



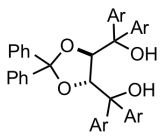
4

Ar = *p*-ClC$_6$H$_4$	**4a**
p-MeOC$_6$H$_4$	**4b**
o-ClC$_6$H$_4$	**4c**
o-MeOC$_6$H$_4$	**4d**
Bn	**4e**
4-C$_6$H$_5$C$_6$H$_4$	**4f**
p-MeC$_6$H$_4$OC$_6$H$_4$	**4g**
2-naphth.	**4h**
4-dibenzofuryl	**4i**



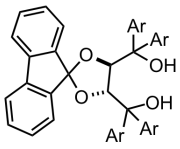
6

Ar = Ph	**6a**
p-ClC$_6$H$_4$	**6b**
p-MeOC$_6$H$_4$	**6c**
2-naphth.	**6d**



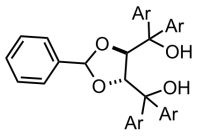
12

Ar = C$_6$H$_5$	**12a**
p-ClC$_6$H$_4$	**12b**
p-FC$_6$H$_4$	**12c**
p-CF$_3$C$_6$H$_4$	**12d**
2-naphth.	**12e**



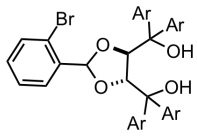
13

Ar = C$_6$H$_5$	**13a**
p-ClC$_6$H$_4$	**13b**
p-FC$_6$H$_4$	**13c**
p-CF$_3$C$_6$H$_4$	**13d**
2-naphth.	**13e**
1-naphth.	**13f**
dibenzofuran-4-yl	**13g**



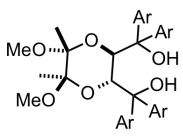
14a

Ar = C$_6$H$_5$



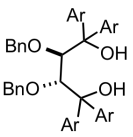
15a

Ar = C$_6$H$_5$



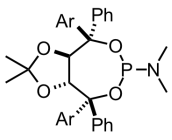
16

Ar = C$_6$H$_5$	**16a**
2-naphth.	**16e**



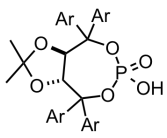
17

Ar = C$_6$H$_5$	**17a**
p-ClC$_6$H$_4$	**17b**
p-FC$_6$H$_4$	**17c**
p-CF$_3$C$_6$H$_4$	**17d**
2-naphth.	**17e**



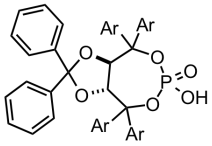
4-PN

Ar = *p*-ClC$_6$H$_4$	**4a-PN**
p-MeOC$_6$H$_4$	**4b-PN**
o-ClC$_6$H$_4$	**4c-PN**
Bn	**4e-PN**
4-C$_6$H$_5$C$_6$H$_4$	**4f-PN**
p-MeC$_6$H$_4$OC$_6$H$_4$	**4g-PN**
2-naphth.	**4h-PN**



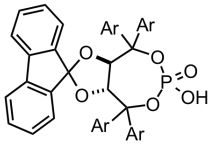
3g-POOH

Ar = dibenzofuryl



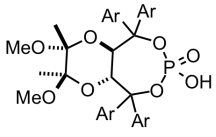
12-POOH

Ar = Ph	**12a-POOH**
p-ClC$_6$H$_4$	**12b-POOH**
p-FC$_6$H$_4$	**12c-POOH**
p-CF$_3$C$_6$H$_4$	**12d-POOH**
2-naphth.	**12e-POOH**



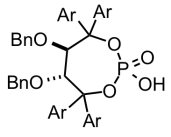
13-POOH

Ar = Ph	**13a-POOH**
p-ClC$_6$H$_4$	**13b-POOH**
p-FC$_6$H$_4$	**13c-POOH**
p-CF$_3$C$_6$H$_4$	**13d-POOH**
2-naphth.	**13e-POOH**
1-naphth.	**13f-POOH**
dibenzofuryl	**13g-POOH**



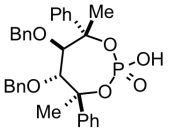
16-POOH

Ar = Ph	**16a-POOH**
2-naphth.	**16e-POOH**



17-POOH

Ar = Ph	**17a-POOH**
2-naphth.	**17e-POOH**



45-POOH

Attachment 2. Research stay at Professor Seidel's lab

During September 2012–March 2013, I stayed at Professor Seidel's lab as an exchange student and was involved in a project which aimed to develop internally conjugate-base stabilized Brønsted acid catalysts. These catalysts contain acidic functionality as well as strong hydrogen bonding sites such as thiourea/urea. The acidic functional groups form intramolecular hydrogen bond between urea/thiourea and free H of the acid thus increase the acidity.

The synthesised catalysts would be used to increase electrophilicity of the substrate of normally sluggish reactions such as Pictet-Spengler reaction of unmodified tryptamine. The reaction with reported catalysts took place with excess amount of acidic additives at elevated temperature and was complete within 10 days.[154] In a scope of this project, various carboxylic acids incorporated into thiourea/urea moiety derived from *trans*-1,2-diaminocyclohexane or (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol were synthesized.

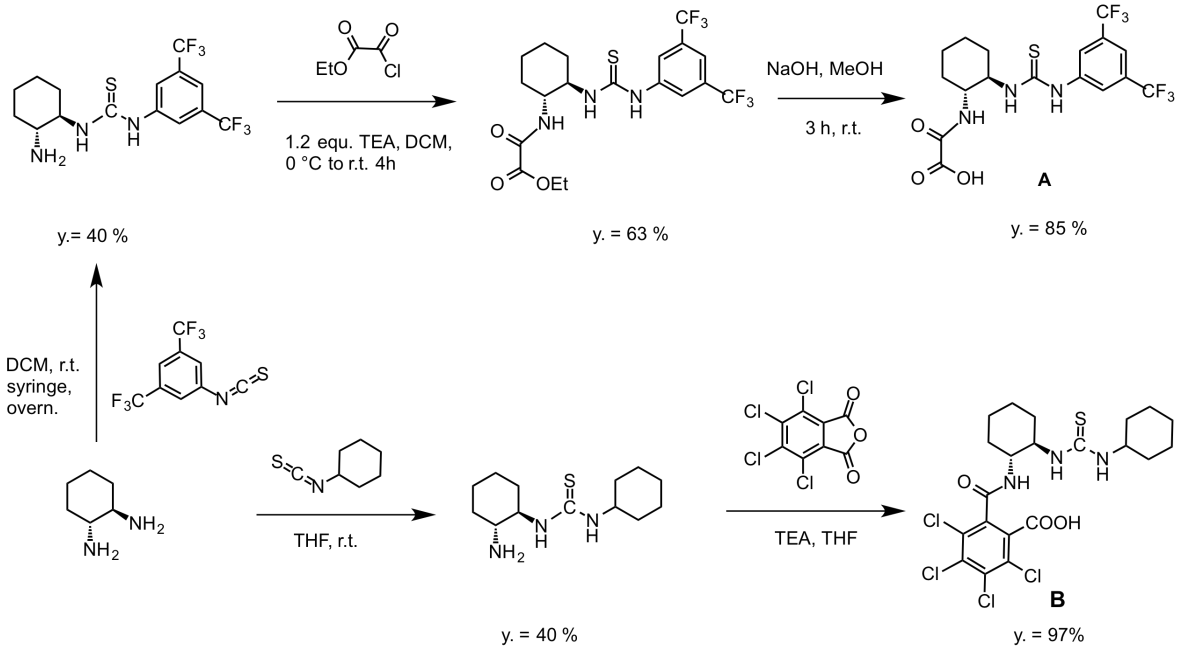
In addition, as a part of this project, H bonding catalysts derived from 1-amino-2-indanol were synthesized. The catalysts would be applied to increase reaction rate of indole addition to nitrostyrene. The previously reported H bonding catalysts afforded high enantioselectivity but long reaction time of 3.5 days was required.[155]

Synthesis

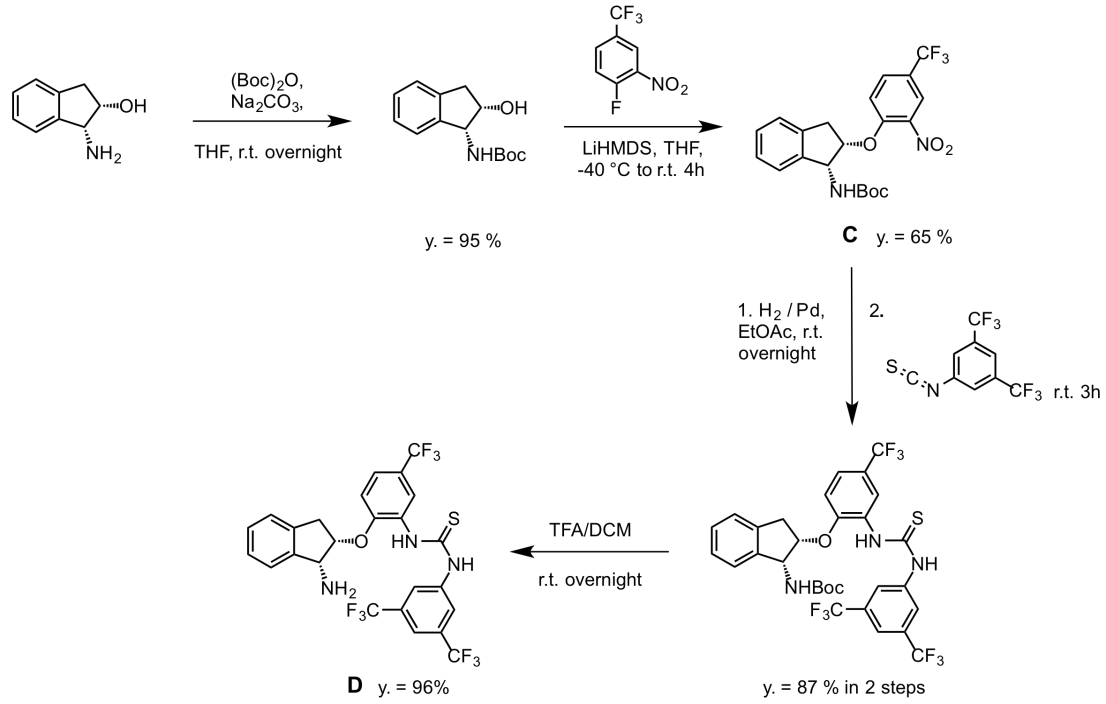
Thiourea-containing carboxylic acids **A** and **B** were synthesized from diaminocyclohexane in 21% (3 steps) and 39% (2 steps) overall yield (*Scheme 1*).

Thiourea intermediate **D** (for further conversion into its carboxylic acid) derived from 1-amino-2-indanol was obtained in 52% overall yield (5 steps, *Scheme 2*) and urea containing carboxylic acid **E** and **F** were available through intermediate **C** (*Scheme 3 and 4*) in 13–24% overall yield.

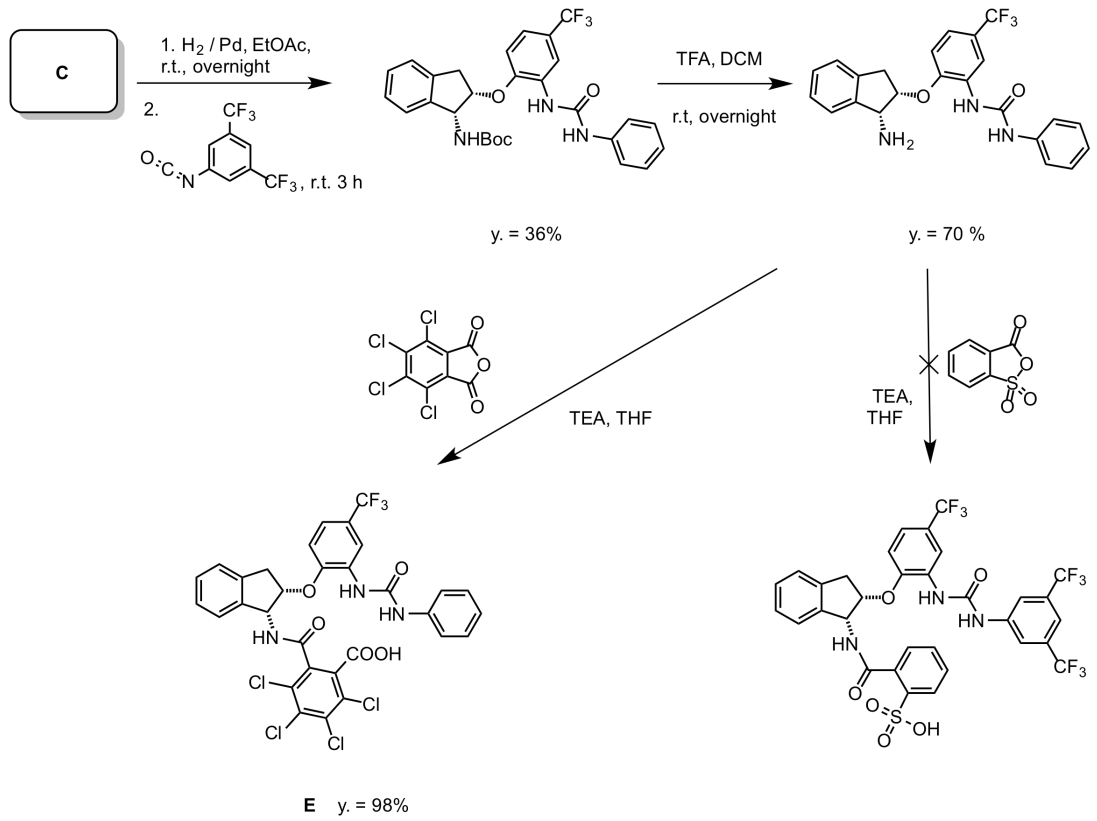
Furthermore, H bonding catalysts, **G** and **H** were synthesized from indanol in 54% and 15% yield, respectively.



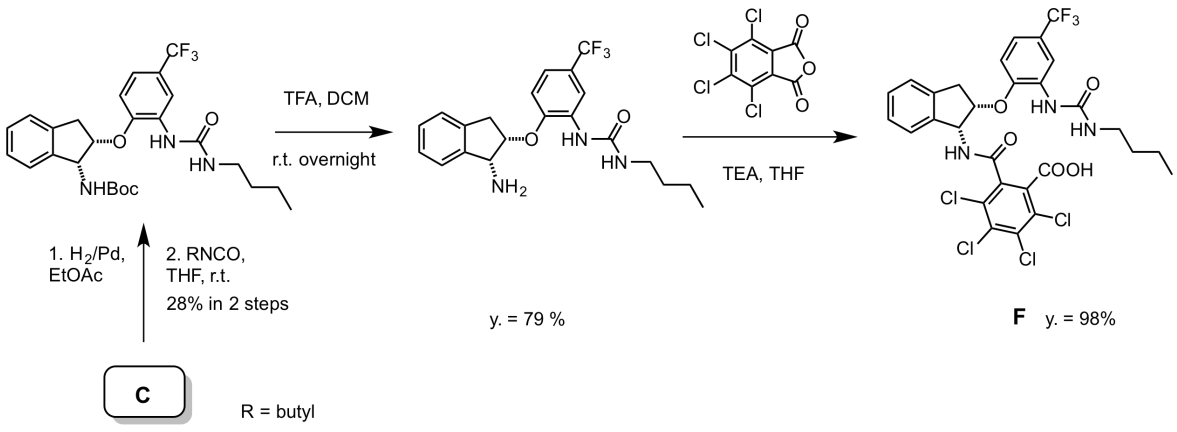
Scheme 1. Synthesis of Brønsted acids **A** and **B**



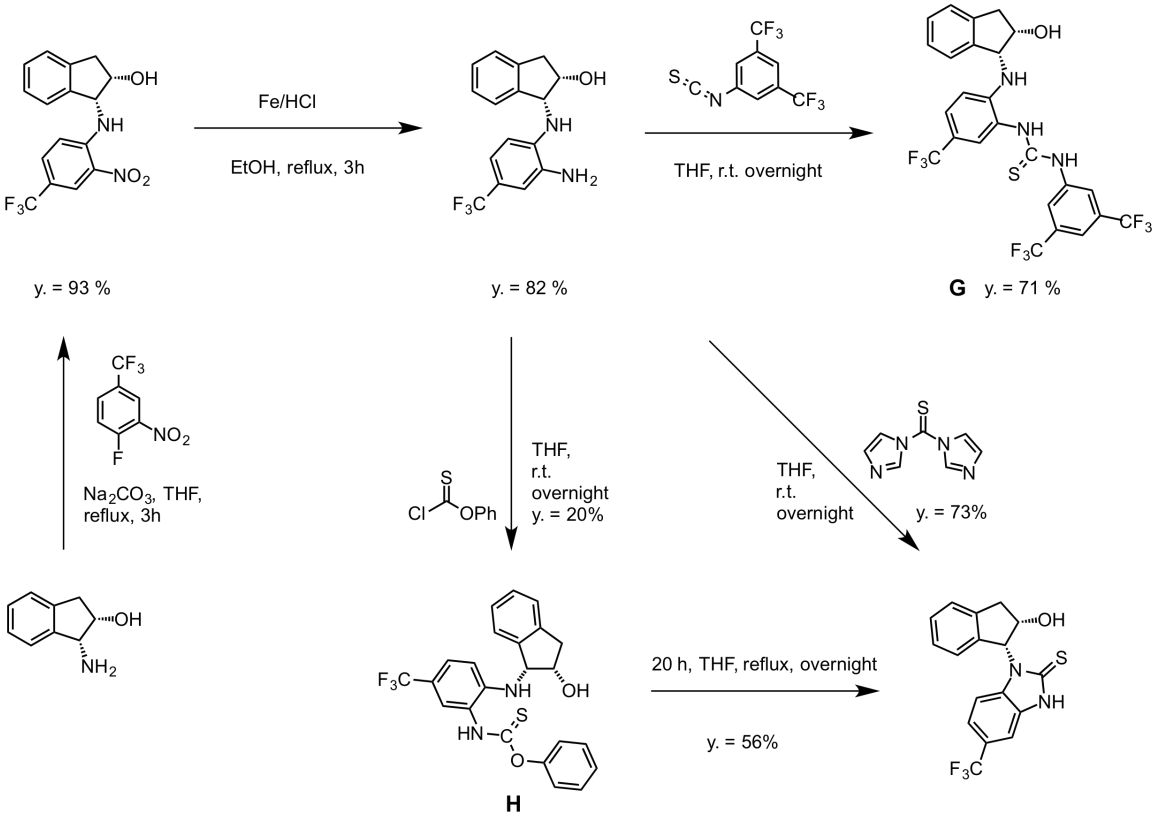
Scheme 2. Synthesis of thiourea intermediate **C** for further conversion into its carboxylic acid



Scheme 3. Synthesis of urea containing Brønsted acid **E** derived from 1-amino-2-indanol



Scheme 4. Synthesis of urea containing Brønsted acid **F**

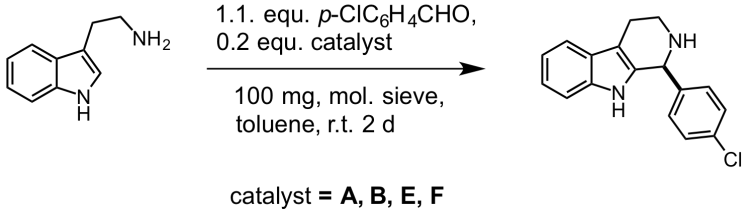


Scheme 5. Synthesis of H bonding catalysts **G** and **H**

Catalytic reactions

Pictet-Spengler reaction of unfunctionalised tryptamine

Catalysts **A**, **B**, **E** and **F** were tested in Pictet Spengler reaction of unfunctionalised tryptamine (*Scheme 6*). Overall, the reactions with catalysts **A**, **E** and **F** were sluggish and only a trace amount of the product β-carboline was formed after 2 days at room temperature (*Table 1*). Acid **B** afforded the product in low yield and enantioselectivity (33% of 21% e.e.)



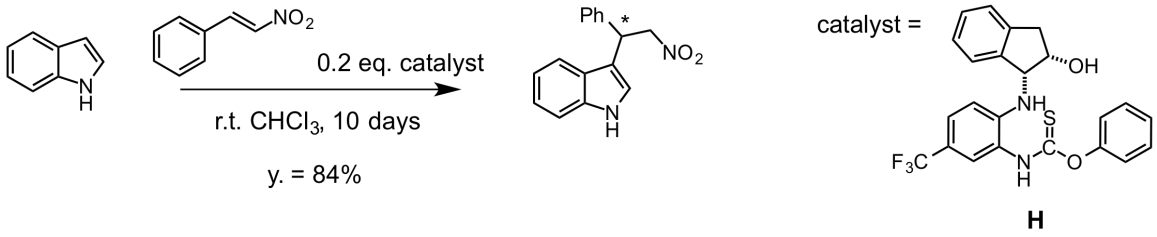
Scheme 6. Pictet-Spengler reaction of unfunctionalised tryptamine with Brønsted acid catalysts

Table 1. Results of Pictet-Spengler reaction of unfunctionalised tryptamine catalysed **A**, **B**, **E** and **F**

Catalyst	*Yield, %*	*e.e, %*
A	trace	-
B	33	21
E	trace	-
F	trace	-

Indole addition to nitrostyrene

Catalyst **H** was applied in indole addition to nitrostyrene. The reaction was very sluggich and was complete after 10 days. (Enantioselectivity was not deteremined since the reaction was not fast enough.)



H

Scheme 7. Indole addition to nitrostyrene catalysed by H bonding catalyst **H**

As a result, various carboxylic acid catalysts with urea/thiourea moiety were synthesized in 13–39% overall yield starting from *trans*-1,2-diaminocyclohexane or (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol. The catalysts were applied in Pictet-Spengler reaction of unmodified tryptamine and only low yield and enantioselectivity was observed in one case. In addition, H-bonding catalyst derived from 1-amino-2-indanol was synthesised and employed in indole addition to nitrostyrene. The catalyst could not efficiently accelerate the reaction.

6. Curriculum Vitae

Tuvshinjargal Budragchaa

Date of Birth: 18.03.1976

Address: Meissnergasse 18/22, 1220, Vienna, Austria

Phone: 0699-18933190 (mobile)

E-mail: tuvshin9@yahoo.com
tuvshinjargal.budragchaa@univie.ac.at

Education

Since 06/2010	PhD study, Institute of Organic Chemistry, University of Vienna, Austria
09/1999 – 01/2001	Master of Science in Chemistry, National University of Mongolia
09/1993 – 07/1997	Bachelor of Science in Chemistry, National University of Mongolia

Professional Experience

Since 06/2010	Research Associate, University of Vienna,
09/2012 – 03/2013	Research stay at Prof. D. Seidel's lab, Rutgers University, the State University of New Jersey
07/1997 – 12 /1998	Researcher, Institute of Chemistry, Academy of Sciences Mongolia,

Teaching Experience

Four Semester	Teaching Assistant in Student Lab "Organic Chemistry-Advanced OC-2", University of Vienna

Publications

Regio- and Stereoselective Approach to 1,4-Di-tert. Carbinols from Dimethyl Tartrate, Tuvshinjargal Budragchaa, Alexander Roller, and Michael Widhalm, *Synthesis*, **2012**, *44*, 3238–3250

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"Zarim neriin ulamjlalt makhan khoolny khimiin nairlagyn sudalgaa" ("Study on Chemical Composition of Some Traditional Meat Products"), a master thesis submitted to the Faculty of Chemistry, national university of Mongolia, **2000**, 39 pages.

Conferences

Poster presentation titled "Regio- and stereoselective approach to 1,4-ditertiary carbinols from dimethyl tartrate" in 14th Tetrahedron Symposium, 25–28th June, 2013, Vienna, Austria

Languages:

English (fluent), Japanese (fluent), Russian (reading) German (A2/1) and Mongolian (native)

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