Asymmetric Counteranion-Directed Transition Metal Catalysis: Enantioselective Epoxidation and Sulfoxidation with Ion-Pair Catalysts

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Abstract

Based on the concept of "asymmetric counteraion-directed catalysts (ACDC)", a series of ion-pair catalysts containing an achiral metallosalen cation and a chiral anion was designed and prepared for the asymmetric epoxidation of unfunctional alkenes and the oxidation of sulfides. With the optimal ion-pair catalyst that consits of an achiral Mn-salen cation and a chiral BINOL-derived phosphate anion, high yields and enantioselectivities were obtained in the epoxidation of various alkenes like chromenes and cinnamates. With this type of ion-pair catalysts, a level of enantioselectivity similar to Jacobsen's Mn-salen catalyst was observed in the asymmetric oxidation of sulfides. The corresponding iron complex was found much more efficient for sulfoxidation, and the high enantioselectivities observed in the cases of electron-poor sulfides are unprecedented in Mn- or Fe-based metallosalen systems.

The combination of chiral salen ligands and chiral counteranions has also been investigated. In the epoxidation of alkenes with the configuration-matched ion pairs the enantioselectivity of the Mn-salen complexes consisting of only chiral salen ligands can be further improved.

The application of the ACDC concept to porphyrin chemistry was also attempted. Substantial albeit low enantioselectivity was observed in epoxidation reactions. These results further demonstrate that ACDC can be employed as a general strategy in the arena of asymmetric transition metal catalysis.

Kurzzusammenfassung

Basierend auf dem Konzept der “asymmetrischen Gegenion-vermittelten Katalyse” (engl. asymmetric counteranion-directed catalysis - ACDC), wurden eine Reihe von Ionenpaaren als Katalysatoren, bestehend aus achiralen Metallosalen-Kationen und chiralen Gegenionen, modelliert und synthetisiert. Diese konnten für die asymmetrische Epoxidierung von unfunktionalisierten Alkenen sowie die Oxidation von Sulfiden eingesetzt werden. Mit dem optimalen Katalysator, der Kombination eines achiralen Mn-Salen Kations und einem chiralen BINOL-abgeleiteten Phosphat-Anion, konnten hohe Ausbeuten und Enantioselektivitäten in der Epoxidierung von Alkenen, wie zum Beispiel Chromenen und Cinnamaten, erzielt werden. Ebenso konnten mit diesem Ionenpaar Sulfide asymmetrisch oxidiert werden, die Enantioselektivitäten waren ebenbürtig zu den Ergebnissen, welche mit Jacobsen`s Mn-Salen Katalysatoren erzielt wurden. Der entsprechende Eisenkomplex zeigte sich effizienter bezüglich der Sulfoxidierung elektronenarmer Sulfide, und konnte verglichen mit bisherigen Mn- oder Fe-basierten Metallosalen-Systemen überlegene Ergebnisse liefern.

Die Kombinationen aus chiralen Salen-Liganden und chiralen Gegenionen wurden ebenfalls untersucht. Hierbei stellte sich heraus, dass die Enantioinduktion in der Epoxidierung von Alkenen mit den konfigurativ passenden Ionenpaaren (engl. matched pair) weiter verbessert werden konnte.

Die Anwendung des ACDC-Konzeptes in der Porphyrin-Chemie wurde ebenfalls untersucht. Vielversprechende Enantioselektivitäten konnten auch hier für verschiedene Epoxidierungsreaktionen erzielt werden. Diese Tatsache unterstreicht das große Potential von ACDC als genereller Strategie in der asymmetrischen Übergangsmetallkatalyse.

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1 Introduction

The biological activity of many pharmaceuticals, agrochemicals, flavors and fragrances is associated with their absolute molecular configuration, because in biological systems, most of naturally occurring compounds like amino acids and sugars are of the same chirality: amino acids are L and sugars are D, and under this *macro-chiral* environment in biology, the two enantiomers of a molecule may interact in a different way, even though two enantiomers normally behave identically to each other when in an *achiral* environment. An example is the different odor of the two enantiomers of celery ketone (Figure 1.1), which have been made recently in our laboratory via enantioselective intramolecular aldolization.[1] The two enantiomers differ as strikingly in their olfactory properties as in the rare case of carvone.[2] Only the stronger R enantiomer is responsible for the characteristic celery note of the racemate, whereas the S enantiomer has an aniseed-like liquorice smell with minty facets. These smell different to most people because our olfactory receptors are chiral molecules (like enzymes) which can discriminate the two enantiomers, leading to different biological responses.

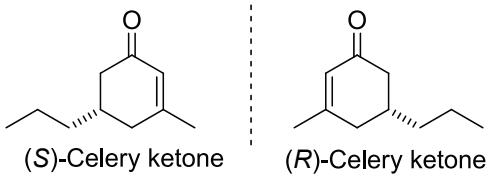


Figure 1.1: The two enantiomeric forms of the natural compound celery ketone.

These differences become especially important, when considering the biological activity of chiral potential pharmaceutical compounds. Usually, only one enantiomer of a chiral drug is active, the other enantiomer is less active or without activity, and can even be detrimental to our body. It is thus highly important and desirable to prepare molecules in an enantiomerically pure form for meaningful investigation of their biological effects and other properties, and the demand is growing.

Enantiomerically pure molecules can be prepared by resolution of racemic compounds or by asymmetric synthesis from chiral or achiral starting materials. Chiral resolution is a classic way to obtain optically pure compounds and well established in industry, while this approach is not atom economic, because the highest yield of the desired enantiomers is only 50%. For

asymmetric synthesis, there are four major types of approaches: substrate-, auxiliary-, reagent- and catalyst-controlled asymmetric synthesis. In the former three asymmetric synthetic methods, stoichiometric amounts of chiral compounds are required and consumed to obtain the desired chiral products, while in the catalyst-controlled asymmetric synthesis chiral catalysts are used as the source of chirality. Thus, the asymmetric catalytic approach stands as the most economic way to produce chiral compounds, because the chiral catalysts are kept intact after the transformation and the multiplicity of chirality can be infinite.

Asymmetric biocatalysis, metal catalysis, and organocatalysis are the three principal areas in the field of asymmetric catalysis. Over the last forty years, asymmetric catalysis has been the focus of intensive studies in the chemical community, and significant progress have been achieved in this area, like the 2001 Nobel Prize in Chemistry awarded to K. Barry Sharpless, William S. Knowles and Ryoji Noyori for their contribution to the asymmetric transition-metal catalysis[3] and the renaissance of organocatalysis in the last decades.[4]

Similar to the classification of chemical bonds, based on the association and interaction between chiral sources and substrates, the modes of asymmetric induction in catalysis can be mainly divided into three classes: covalent, ionic, and weak interaction (Figure 1.2). The covalent induction is most common in asymmetric catalysis like the activation of double or triple bonds by noble metals and the enamine formation in aminocatalysis (**A**, Figure 1.2). Weak interacions (π-π, H-bonding etc.) in catalysis are also widely employed, especially in organocatalysis, like thiourea- and Brønsted acid-mediated reactions (**B**, Figure 1.2). Comparing with the covalent activation and weak interaction in asymmetric catalysis, the type of ionic interaction, where the chirality is delivered to the substrate via contact cation/anion ion-pair communication from the chiral counterions, is far less studied and employed. The most known examples meight be the chiral ammonium-medated phase-transfer catalysis (**C**, Figure 1.2).

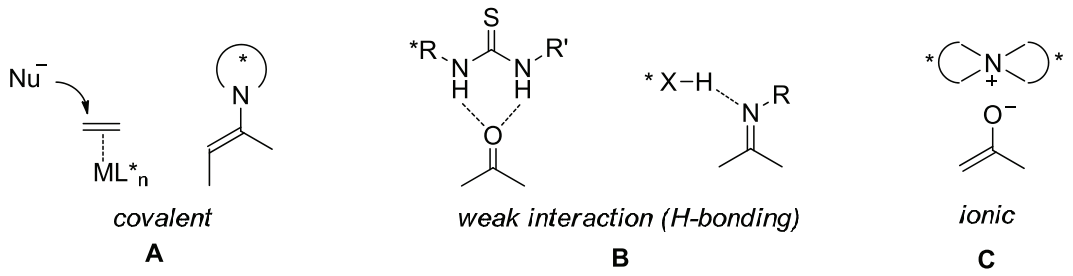


Figure 1.2: The modes of chiral induction in asymmetric catalysis.

Interestingly, if we define the type **C** catalysis in Figure 1.2 as "asymmetric *counteraction*-directed catalysis", its counterpart, namely, "asymmetric *counteranion*-directed catalysis" (Figure 1.3) only sporadically appeared in the literature before 2006, and in those earlier attempts none of them provided practical enantioselectivity.[5] Breakthroughs have been made in 2006-2007 in this special area, and unprecedented high levels of enantioselectivity have been achieved in both organocatalysis and transition-metal catalysis: chiral salt-mediated transfer hydrogenation (**A**, Figure 1.3),[6] Au-catalyzed alloxylation of allenes,[7] and Pd-catalyzed Tsuji-Trost-type allylation of aldehydes[8] (**B**, Figure 1.3).

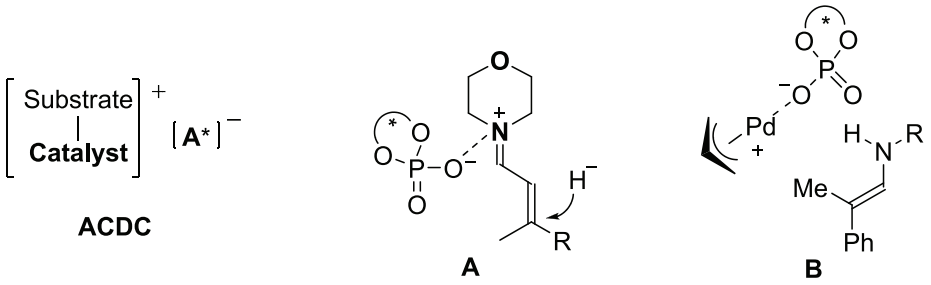


Figure 1.3: Asmmetric counteranion directed catalysis (ACDC).

In the field of asymmetric catalysis the major tasks, also the challenges, lie in the design of a novel and effective chiral catalyst for a given reaction.[9] The concept of "Asymmetric Counteranion-Directed Catalysis (ACDC)", which has been neglected for a long time, will undoubtedly attract more and more research interest, and the potential of this novel concept as a general strategy in the design of catalysts and asymmetric reactions will be well demonstrated under the pursuits of our chemists in the future.

2 Background

In an enantioselective catalytic reaction, the transfer of chirality from the catalyst to the product normally occurs in the transition state (TS) of the enantio-determining step (Figure 2.1). Because the catalyst is chiral, when the prochiral substrate interacts with the catalyst, two diastereotopic transition state namely TS_R and TS_S are generated, leading to the (*R*)-configured and (*S*)-configured product, respectively. The activation energy difference (E_R vs. E_S) between the two diastereotopic TS determines the enantioselectivity of the reaction, and the pathway with the lower activation energy TS (like E_R in Figure 2.1) will result in the major enantiomer of the product.

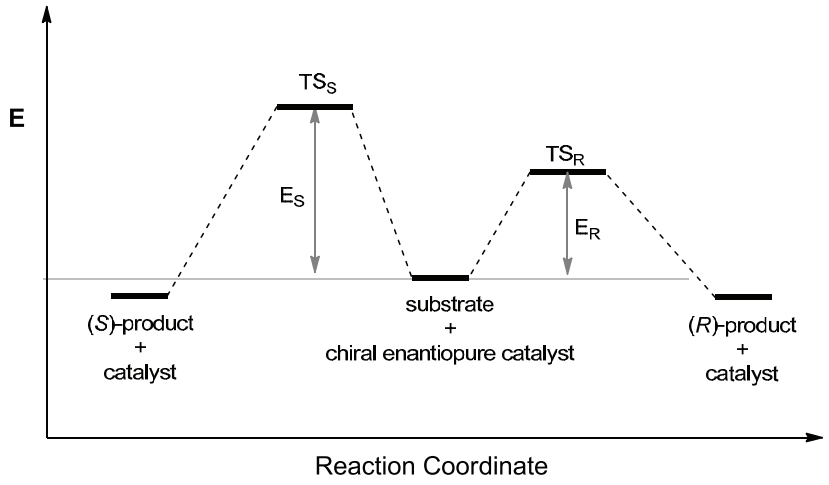


Figure 2.1: The reaction coordinate of an enantioselective catalytic reaction.

The rate constant for the formation of each enantiomer in Figure 2.1 can be given by the Arrhenius equation:

$$k_R = Ae^{-E_R/RT} \text{ and } k_S = Ae^{-E_S/RT}$$

where E_R and E_S are the activation energy for the corresponding enantiomers. Since the ratio of the enantiomers (e.r.) formed is equal to the ratio of their rate constants, the selectivity of an enantioselective catalytic reaction can be expressed as:

$$\text{e.r. (R/S)} = k_R/k_S = e^{-(E_R-E_S)/RT}$$

If the energy difference between two diastereotopic TS is 3.0 kcal/mol at 25 °C, the two enantiomers would be formed in a ratio of 99.4:0.6 equal to 98.8% ee. Accordingly, improving the enantioselectivity from 40% ee to 95% ee, only an energy barrier of 1.7 kcal/mol has to be created.[10] As a result, asymmetric catalytic reactions are sensitive to a variety of factors. To optimize a given asymmetric reaction, apart from the catalysts and substrates, reaction conditions like temperature, solvent, additive also have to be taken into consideration. While most chemical reactions proceed via charged intermediates or transition states, another special factor, the cationic or anionic counterions, may also play an important role in the control of stereoselectivity.

As aforementioned, asymmetric induction is an extremely sensitive phenomenon, a small difference in transition state energies can enable a significant change in enantioselectivity. This implies that it may be possible to use some subtle features like the counterion effect to conduct a highly selective asymmetric transformation in those reactions proceeding via charged intermediates or transition states. These counterion-directed asymmetric reactions can be divided into two classes according to the charge of the chiral counterion source: countercation-directed asymmetric reactions and counteranion-directed asymmetric reactions (Figure 2.2).

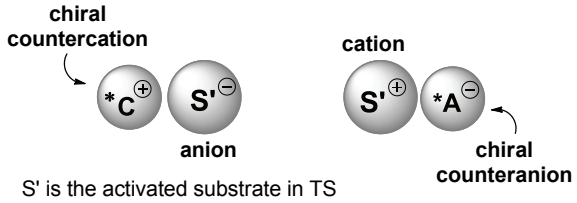
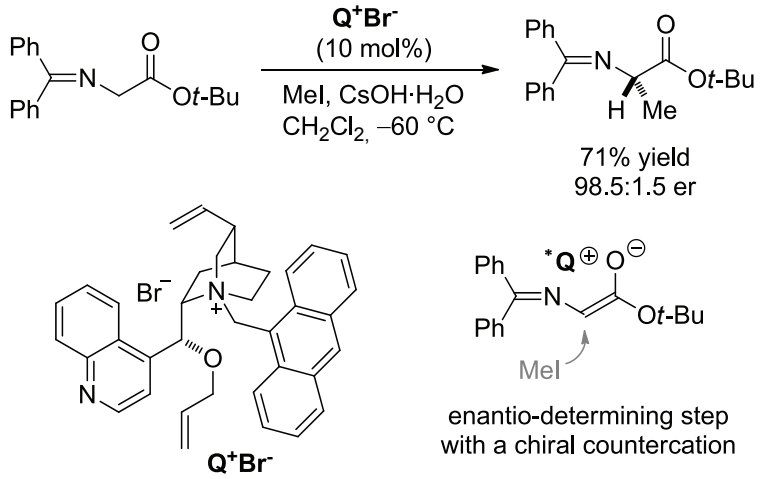


Figure 2.2: Two classes of counterion-directed asymmetric transformation.

For the countercation-directed asymmetric reactions, phase transfer catalysis using chiral ammonium salts represents a typical example.[11] The high level of enantioselectiviy results from the high degree of organization between the anionic enolate and cationic ammonium. As shown in Scheme 2.1, one face of the enolate can be efficiently shielded by the chiral ammonium cation, exposing the other face of the enolate to MeI attack (Scheme 2.1).[12]



Scheme 2.1: The enantioselective alkylation via phase transfer catalysis.

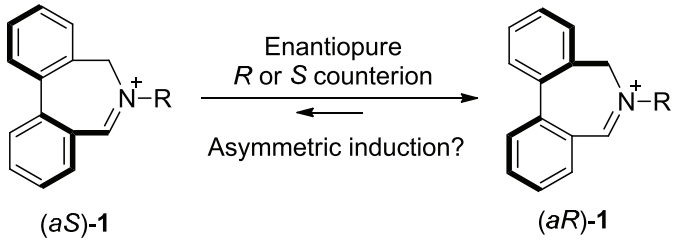
In comparison, the counteranion-directed asymmetric reactions are far less explored. The chiral counteranion strategy was first employed by Arndtsen and co-workers in the Cu-catalyzed aziridination and cyclopropanation of olefins using chiral borate anions, however, only up to 10% ee was observed.[13] Later on, there were some trials using this principle, but none of them provided practical enantioselectivity.[5] Interestingly, highly enantioselective counteranion-directed reactions were first achieved in organocatalysis,[6] a novel and rapidly developing area,[14] six years after the first attempts of the principle in transition metal catalysis. The enantioselectivity observed was excellent and unprecedented in counteranion-directed transformations, and it was also the time when the term of ACDC (asymmetric conteranion-directed catalysis) was coined. The next section will give a review over the development of asymmetric counteranion-directed catalysis.

2.1 Asymmetric Conteranion-Directed Catalysis (ACDC)

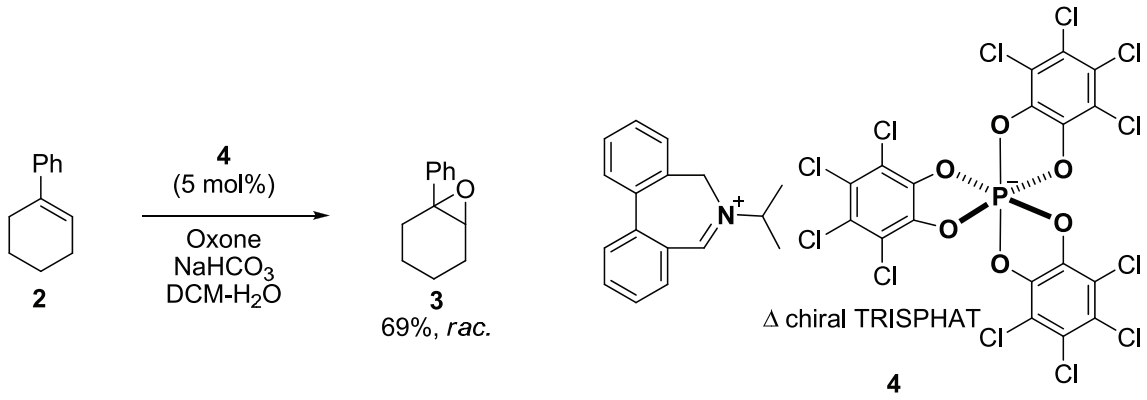
2.1.1 Asymmetric Counteranion-Directed Organocatalysis

Organic salts that contain a chiral anion as the sole chiral source have rarely been employed as organocatalysts. Only two reports appeared in the literature before 2006: one was from the Lacour group[15] and the other was from the Nelson group[16] using chiral hexacoordinated phosphate anions (TRISPHAT) and D_2-symmetric chiral borate anions, respectively. During that time, the enantioselectivity observed were generally low (< 15% ee).

As shown in Scheme 2.2, diphenylazepinium cations **1** would exhibit atropisomeric (a*R*) and (a*S*) conformations, which would interconvert freely in solution by rotation around the biphenyl axis. Lacour and co-workers[15] envisioned that introduction of an enantiopure anion would shift the conformational equilibrium to one preferred conformer (a*R*) or (a*S*) by a diastereomeric ion-pair interaction. However, with the iminium salt catalyst **4,** no enantioselectivity was observed in the epoxidation reaction of alkene **2** (Scheme 2.3). One possible explanation was the poor asymmetric induction of chiral TRISPHAT anion onto the (a*S*) and (a*R*) conformational equilibrium of **1**, because no induction was observed in the VT-NMR experiments at 253 K.

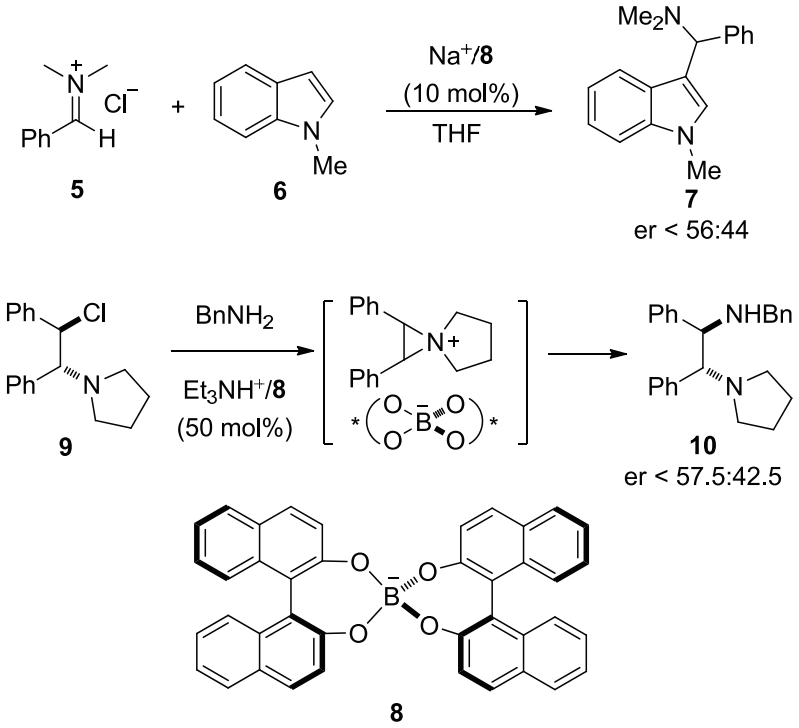


Scheme 2.2: Possible asymmetric induction of chiral counteranions on the conformation equilibrium.



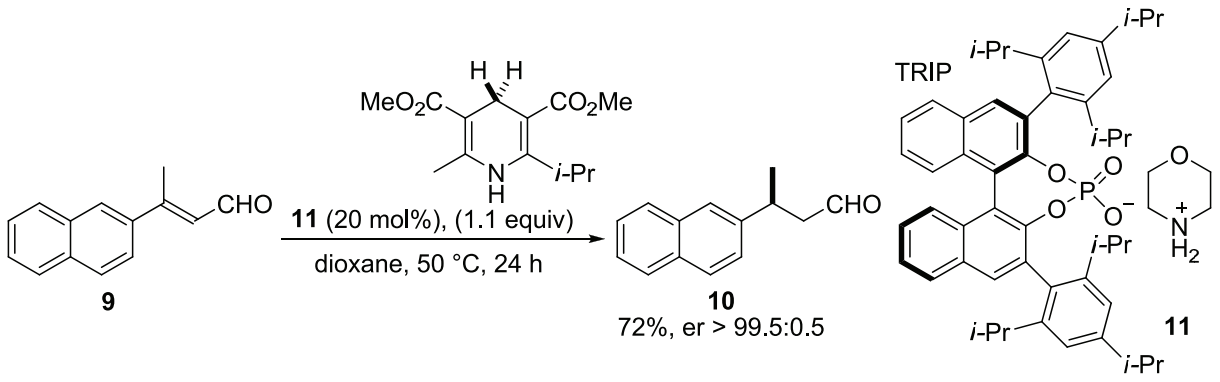
Schem 2.3: Epoxidation catalyzed by iminium/chiral TRISPHAT **4**.

Nelson et al. investigated the possibility of inducing asymmetry using a D_2-symmetric chiral borate anion in both Mannich reaction and aziridinium-opening reactions via a phase transfer mechanism.[16] Because the imine salt **5** was insoluble in the reaction mixture, the transition of the iminium to the organic phase was supposed to be achieved by replacement of the chloride anion with the chiral borate anion **8**. The reaction of iminium **5** and indole **6** gave the Mannich product **7** in a moderate yield, but the enantiomeric excess was low (< 10%). Better selectivity (er < 57.5:42.5) was observed in the reaction of chloroamine **9** with benzylamine that involved the asymmetric ring-opening of the *meso*-aziridinium cation in the presence of the chiral borate counteranion (Scheme 2.4).



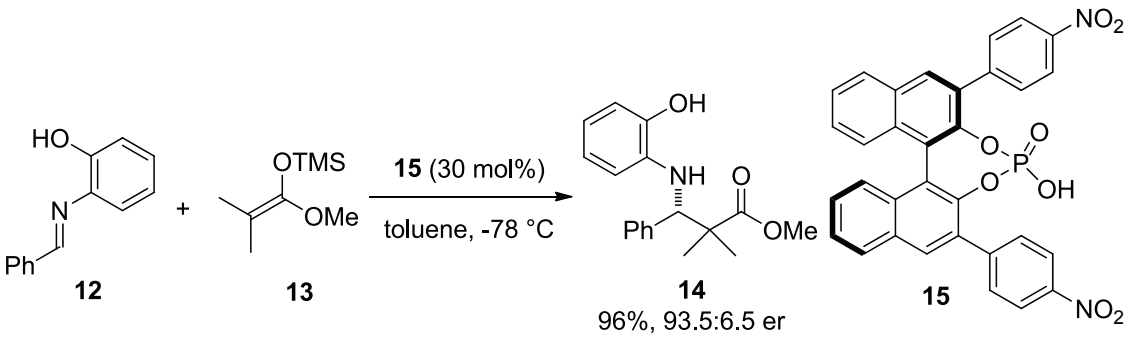
Scheme 2.4: Chiral borate anion-directed Mannich reactions and aziridinium-openings.

In 2006, the List group reported a highly enantioselective transfer hydrogenation of α,β-unsaturated aldehydes **9** catalyzed by a morpholine phosphoric acid salt **11** (Scheme 2.5), in which unprecedentedly high enantioselectivities were achieved.[6]



Scheme 2.5: Morpholine TRIP salt-catalyzed asymmetric reduction of enals.

Usually in iminium catalysis, acid additives are added to accelerate the dehydration-iminium formation step. During this process, if the counteranion generated from the acid additive was thoroughly separated from the iminium cation by the solvent molecules, there should be no counteranion influence on the enantioselectivity. However, a significant counteranion effect was observed in the chiral imidazolinone-catalyzed transfer hydrogenation of α,β-unsaturated aldehydes,[17] which aroused the authors' interest to perform the same reaction via a chiral counteranion control. Another inspiration for this work was from imine-activation chemistry with chiral phosphoric acids, which are introduced by Akiyama and Terada in 2004.[18] A 9-membered cyclic transition state including double H-bondings between the aldimine and the acid has been proposed (Figure 2.3, left) by Akiyama for the chiral phosphoric acid catalyzed Mannich reaction (Scheme 2.6).[19] The interaction between the chiral acid catalyst and the imine can be viewed as an H-bonding activation, but considering the strong acidity of phosphoric acids (like **15**) and basicity of imines (like **12**) the asymmetric communication via a protonated imine/phosphate ion-pair model, which is more interesting to us, is also possible.



Scheme 2.6: Chiral Brøsted acid-catalyzed Mannich reactions.

Even though there is no clear cut between the H-bonding interaction and the ion-pair interaction in this phosphoric acid-catalyzed reaction, this kind of obvious H-bonding interaction as shown in Figure 2.3 (left) would be not possible in a secondary ammonium phosphate salt-catalyzed reaction (right, Figure 2.3). Comparing with the phosphoric acid behavior in the imine activation, when the secondary amine acid salt catalyst **11** was used, a C=N···H-O or C=N^+-H···O hydrogen bonding interaction is not possible, and the cation/anion electrostatic interaction of the aldiminium/chiral phosphate would play a principal role in the stereochemical control (Figure 2.3, right).

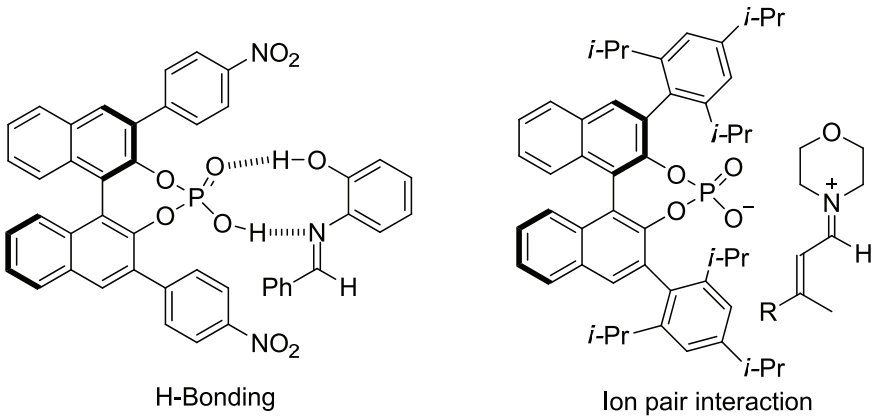
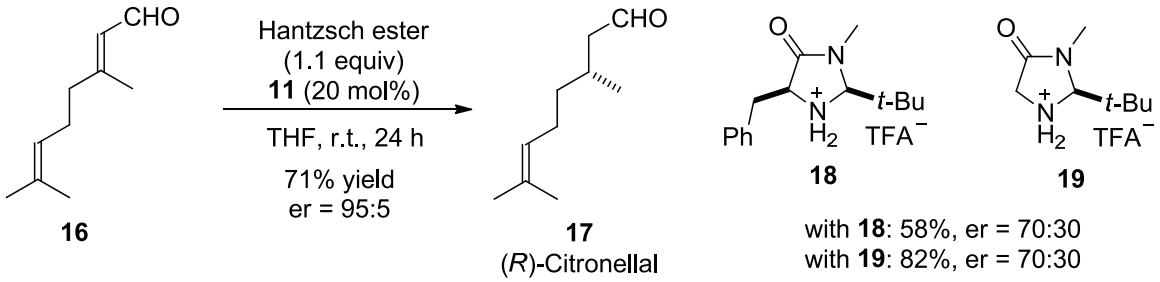


Figure 2.3: The proposed imine-activation model by Akiyama and a proposed ion-pair interaction.

The power of this concept was demonstrated in the transfer hydrogenation of citral **16**. The salt **11** mediated the reduction with high enantioselectivity (95:5 er), while the MacMillan imidazolinones **18** and **19**, which have been employed in the asymmetric transfer hydrogenation of α,β-unsaturated aldehydes,[17;20] only gave an enantiomeric ratio of 70:30 (Scheme 2.7).

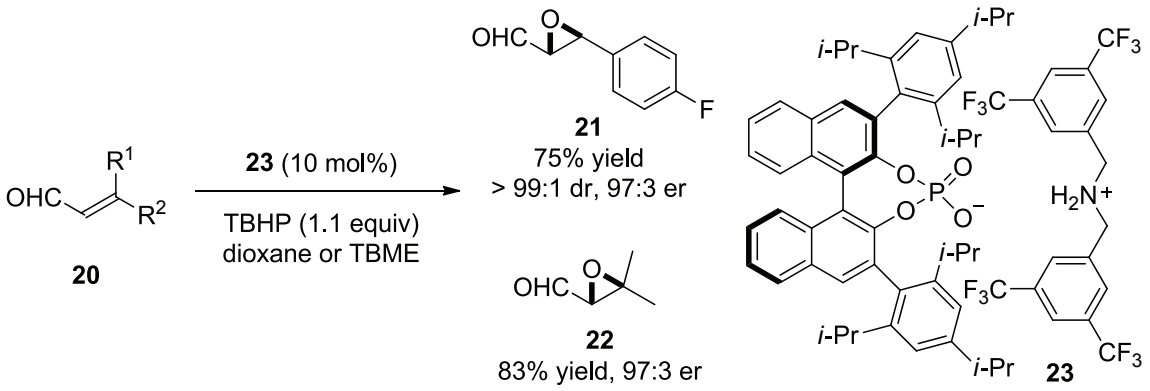


Scheme 2.7: Asymmetric transfer hydrogenation of citral.

Comparing with the chiral anions employed in the earlier trials, the BINOL-derived phosphoric acids introduced may have unique structural properties favoring the counterion

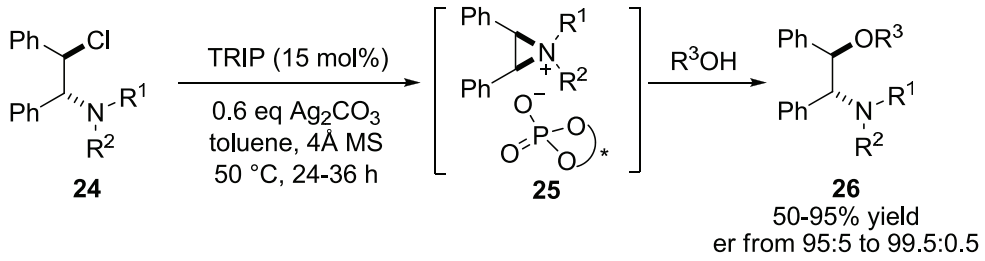
control. The 3,3'-substituents of the phosphoric acids extend and amplify the axial chirality, leading to a chiral microenvironment, like a cavity or a bowl, to accommodate the cation species. The privilege of these phosphate anions as versatile chiral counteranions has been well demonstrated in the reports coming up since their first debut in the asymmetric transfer hydrogenation.

Later on, List and co-workers further applied this counteranion strategy to the enantioselective epoxidation of α,β-unsaturated aldehydes (Scheme 2.8).[21] Salt **23** promoted the epoxidation of β,β-disubstitured α,β-unsaturated aldehydes **20** with high enantioselectivities, thus, successfully bringing trisubstituted α,β-unsaturated aldehydes into the substrate scope of asymmetric iminium-catalytic epoxidation using chiral amine catalysts.[22]



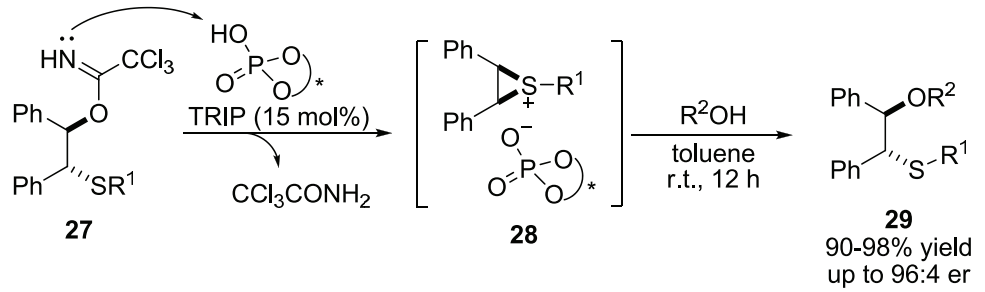
Scheme 2.8: Chiral organic salt-mediated epoxidation of enals.

Recently, Toste's group has applied the counteranion control strategy to enantioselective ring-openings of *meso*-aziridiniums (Scheme 2.9) and *epi*-sulfoniums (Scheme 2.10).[23] In order to turn over the chiral anion in the opening of *meso*-ariridiniums (**25**), the addition of stoichiometric amount of achiral Ag(I) source was necessary, but the accompanying achiral counteranion of the Ag salt can lead to a competing nonselective reaction. Finally, insoluble Ag_2CO_3 solid was chosen as the silver source, and the reaction works in a way of chiral anion-mediated phase transfer catalysis. Due to the different solubility of Ag_2CO_3 and Ag chiral phosphate in toluene, the nonselective reaction promoted by achiral CO_3 anion was efficiently suppressed. In contrast, and as expected, addition of more soluble silver compounds such as AgOTs led to significantly decreased ee due to the competition from the achiral counteranion ($^-$OTs).



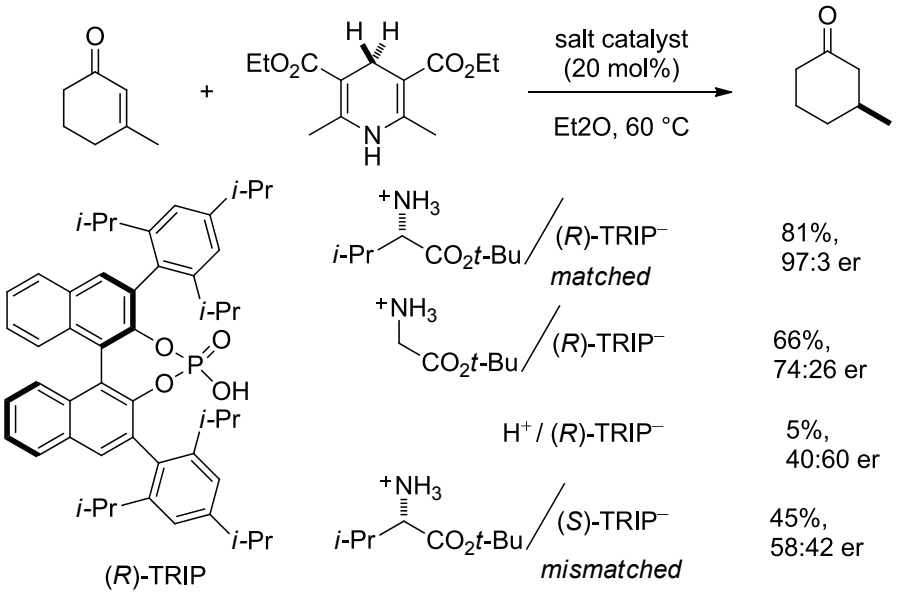
Scheme 2.9: Enantioselective ring-openings of *meso*-aziridiniums.

In the cases of ring openings of *epi*-sulfoniums, since the sulfides **27** would likely bind to Ag^+, the cation generation by means of silver-halide abstraction was not employed; thus, trichloroacetimidate was chosen as the leaving group. The desired sulfonium cations (**28**) can be generated upon the protonation of the imidates **27** followed by a ring-closure step (Scheme 2.12), and under these conditions, chiral phosphoric acids can be directly used. Interception of the episulfonium/chiral phosphate ion-pair intermediates **28** with an alcohol nucleophile provided the chiral sulfide products **29** in high yields and up to 96:4 er.



Scheme 2.10: Enantioselective ring-openings of *epi*-sulfoniums.

In the above mentioned examples, the chiral counteranion is the only chiral source for these asymmetric catalytic transformations. Inspired by the concept of asymmetric counteranion-directed catalysis (ACDC), to improve the performance of chiral amine catalysts, the influence of chiral counteranions are more often taken into consideration.[24] Higher levels of enantioselectivity than that obtained with only chiral amines or chiral acids can be achieved with the matched combination of a chiral amine and a chiral counteranion (Scheme 2.11). Because chiral amines are required, these counteranion-directed transformations will not be discussed in this section.

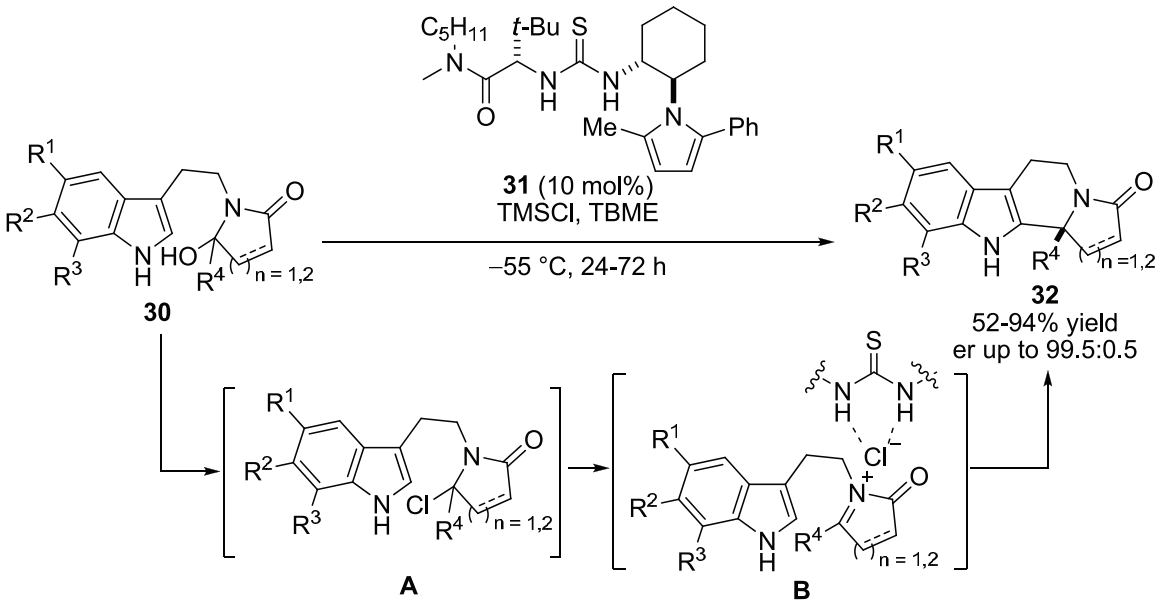


Scheme 2.11: ACDC with chiral amines and chiral phosphate counteranions.

2.1.1.1 Counteranion Control via Anion-Bindings

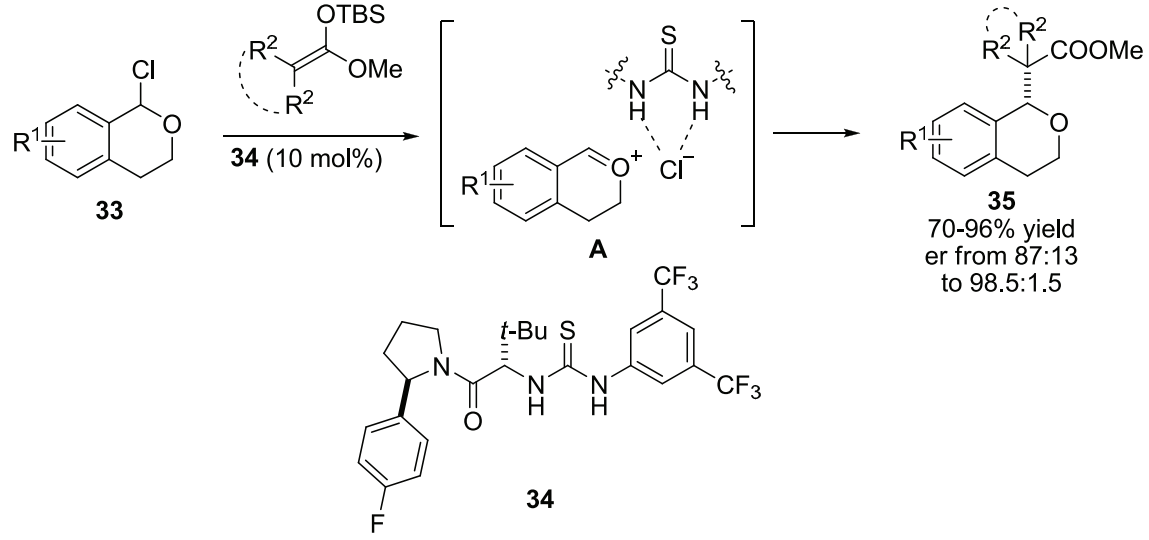
An alternative asymmetric counteranion-directed catalysis strategy has been developed by Jacobsen and co-workers. Rather than using ion-pair catalysts like iminium salts or secondary amine acid salts aforementioned, chiral thiourea hydrogen-bonding catalysts are employed as counteranion controller via an anion-binding mechanism. The principle was first demonstrated by Jacobsen and co-workers in the enantioselective Pictet-Spengler-type cyclization of hydroxylactams **30** in the presence of TMSCl or AcCl as a dehydrating agent (Scheme 2.12).[25] Since the enantio-determining step could be either the addition of the indole to the *N*-acyliminium ion or subsequent alkyl migration of the spiroindoline, catalyst interaction with at least one of these species is required. However, there is no viable Lewis basic site for productive catalyst binding to *N*-acyliminium ions, and DFT calculations of fully ionized *N*-acyliminium ions interacting with thiourea derivatives failed to converge on any ground state bound structure. Thus, the authors proposed that the asymmetric induction could arise from the interaction between *N*-acyliminium cation and the chiral thiourea-bound chloride counteranion (Scheme 2.12, **B**). As would be expected within this activation model, pronounced halide counterion effects (replacement of Cl^- with Br^- or I^- resulted in a dramatic drop in enantioselectivity) and solvent influence on the enantioselectivity were observed. Catalysis and enantioinduction may thus result from initial abstraction of a chloride anion from **A** by thiourea **31** in an SN_1-type rate-determining step and subsequent cyclization mediated by the resulting anion-bound thiourea. The enhanced reactivity when R^4 = alkyl

versus R^4 = H, also pointed to the SN_1-type mechanism. Later on, an intermolecular version of the addition of indoles to cyclic *N*-acyl iminium ions has also been developed[26]



Scheme 2.12: Thiourea-catalyzed Pictet-Spengler-type reactions and the anion-binding model.

This hydrogen-bond catalysis via anion binding was later extended to the reactions involving oxocarbenium intermediates (Scheme 2.13).[27] Chiral thiourea catalyst **34** was shown to catalyze the enantioselective substitution of silyl ketene acetals onto racemic 1-chloroisochromans **33** with high enantioselectivity. The discovery of thiourea anion-binding mechanisms (like **A** in Scheme 2.13 and **B** in Scheme 2.12) has expanded the arena of hydrogen bonding catalysis to reactions involving cationic intermediates lacking Lewis or Brønsted basic sites for productive catalyst binding.



Scheme 2.13: Anion binding catalysis involving oxocarbenium intermediates.

2.1.2 Asymmetric Counteranion-Directed Transition Metal Catalysis

Traditionally, chiral transition metal catalysts, no matter if charged or neutral, employed in asymmetric transformation are generated via the coordination of chiral ligands to transition metals. The chiral ligands are the chiral source in the asymmetric induction (Figure 2.4, **A** and **B**). However, the asymmetric induction is a sensitive communication of chirality, which suggests the possibility of controling the stereochemical communication process via some subtle interactions rather than the rather strong coordination of chiral ligands to the metal. In the cases of charged metal catalysts (**B**) or positively charged intermediates in the enantio-determining step, principally, a chiral counteranion should be able to exert some influence on the asymmetric induction. Thus a new type of chiral transiton metal catalysts can be envisioned when employing a chiral counteranion as the only chiral source (Figure 2.5, **C**), whereas the combination of chiral ligands and chiral counteranions would also lead to another new type of catalysts (Figure 2.5, **D**). Although the effect of counteranion on reaction rate and selectivity has been well appreciated, enantioselective reactions mediated by a chiral counteranion as the only chiral source only sporadically appeared and with low enantioselectivity in the history of asymmetric transition metal catalysis until 2007, the time when unprecedentedly high enantioselectivity was achieved.[7][8]

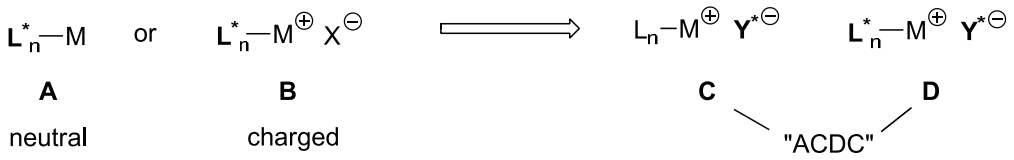
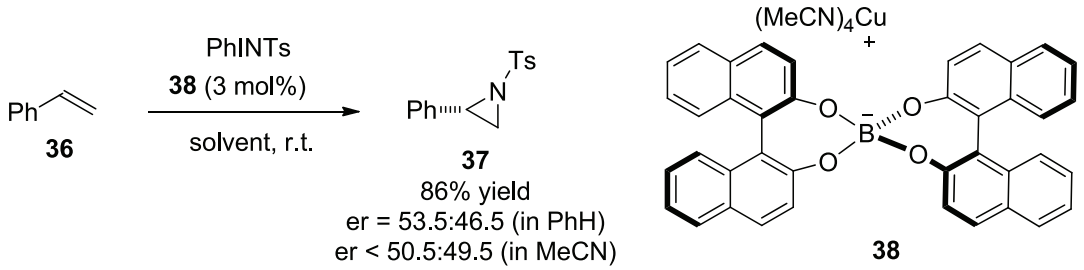


Figure 2.4: The chiral source (*) in transition metal catalysts.

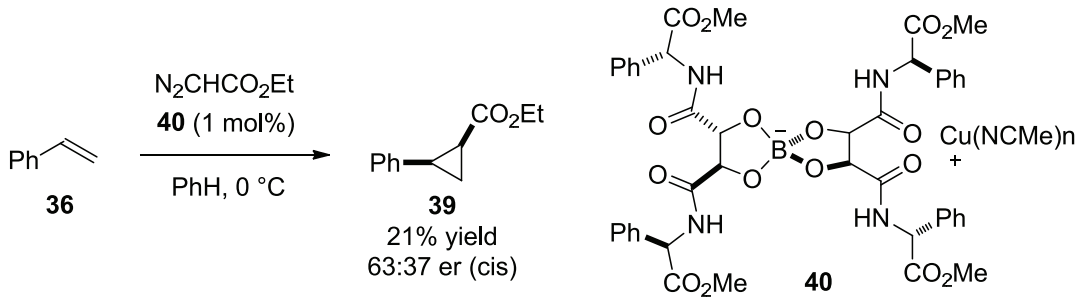
In 2000, Arndtsen and coworks reported a copper-catalyzed olefin aziridination reaction using Cu/chiral borate ion-pair catalysts (Scheme 2.14).[13] This work represents the earlier trials using a non-coordinating chiral counteranion to induce asymmetry in the transition metal catalysis. Though only up to 7% of enantiomeric excess was achieved, the potential of chiral counteranions as stereochemical controllers was well demonstrated. The change of the solvent from nonpolar benzene to polar acetonitrile resulted in a drop in enantiomeric excess from 7% to 1%. This solvent influence on the stereoselectivity well reflected the ion-pair properties of the catalyst. Addition of achiral bipyridine ligand further increased the selectivity to 10% ee in benzene. They also showed the examples of aziridination and cyclopropanation reactions

using combination of chiral bisoxazoline ligands and chiral counterions. Significant counteranion influences together with the "matched" and "mis-matched" phenomenon were observed.



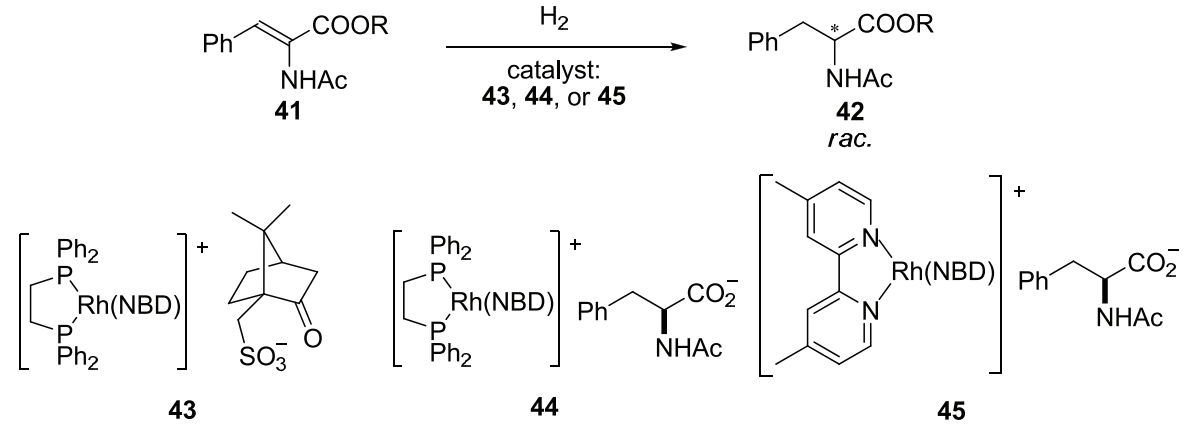
Scheme 2.14: Copper/chiral borate-catalyzed aziridination reactions.

The enantioselectivity of cyclopropanation was later increased to 63:37 er by using the borate anion **40** prepared from tartric acid and amino acids (Scheme 2.15),[28] and optimization of the peptide arms[29] further improved the selectivity to 67:33 er.



Scheme 2.15: Copper borate-catalyzed cyclopropanation reactions.

A counteranion strategy was also attempted in the Rh-catalyzed hydrogenation of methyl-(*Z*)-α-acetoamidocinnamates **41** (Scheme 2.16). Dorta, Milstein and co-works[30] prepared three different achiral P,P or N,N bidentate ligand-coordinated Rh catalysts (**43**, **44**, and **45**) associated with a chiral anion derived from camphor sulfonic acid or phenylalanine. However, all the three catalysts delivered the hydrogenation products **42** in a racemic form even with a coordinating anionic ligands (**44** and **45**), and these catalysts were less reactive than the corresponding rhodium BF_4 salts.



Scheme 2.16: Rh-catalyzed hydrogenation reactions.

With regard to Rh catalyzed reactions, anionic ligands are widely employed in the Rh-catalyzed carbenoid reactions such as cyclopropanation[31], C-H insertion[32], aziridination[33], which appeared in a number of publications since early 1990s.[31a] The anionic ligands listed in Figure 2.5 are the most popular types of anionic ligands in rhodium-catalyzed carbenoid reactions. $Rh_2(BNP)_4$ was first used by Pirrung and Zhang[31a] in the asymmetric dipolar cycloaddition of diazocompounds, and 74.5:25.5 er was observed in the reaction between diazocyclohexane-1,3-dione **46** and furan (Scheme 2.17).

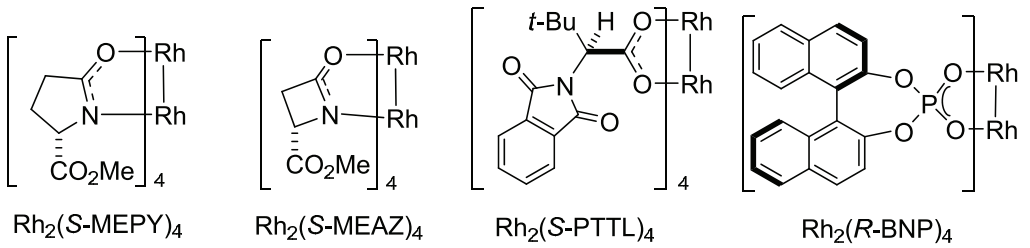
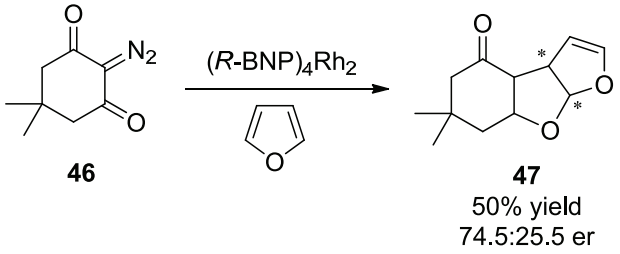


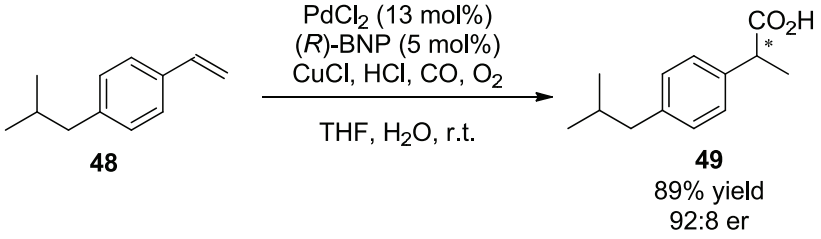
Figure 2.5: Popular chiral rhodium(II) catalysts used in carbenoid chemistry.



Scheme 2.17: $Rh_2(BNP)_4$ mediated dipolar cycloaddition of diazocompounds.

The employment of chiral BINOL-derived phosphate especially BNP as an anionic ligand can be dated back to 1990. Alper and Hamel[34] discovered that the combination of BNP with $PdCl_2$ could provide excellent enantioselectivities in the hydrocarboxylation of olefins **48**

(Scheme 2.18). Before this work no highly enantioselective transformation using chiral neutral ligands or chiral additives had been realized, and only regioselective hydrocarboxylation reactions of vinyl arenes have been reported. With regard to the reaction mechanism, the chiral phosphoric acid was proposed to act as an anionic ligand coordinating to palladium. Considering the aqueous and strongly acidic reaction conditions and the presence of other anions like Cl^-, the high enantioselectivity was very unlikely caused by the BNP anion being a counteranion. Further investigation of the role of the chiral acid in this reaction should be of interest.



Scheme 2.18: BNP/$PdCl_2$ catalyzed hydrocarboxylation of olefins.

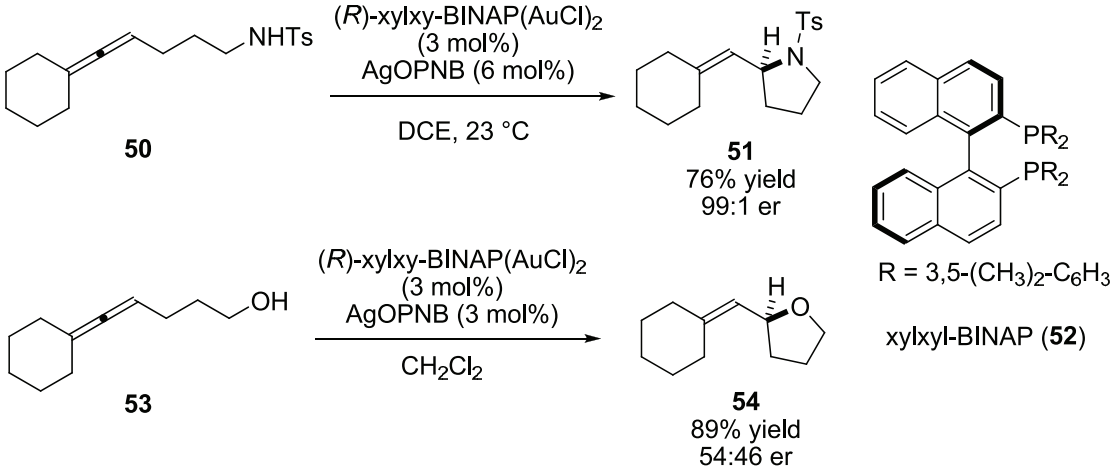
Another important contribution to the chiral BNP-type anionic ligand chemistry was from Inanaga and co-workers.[35] BINOL-derived phosphates were integrated to the lanthanide- and rare-earth-metal complexes, and these metal (La, Yb, Sc)/phosphate complexes could act as Lewis acid catalysts to mediate hetero-Diels–Alder reactions[36], asymmetric fluorinations of β-ketoesters[37] and Michael addition reactions[38] with high enantioselectivity.

Phosphate anions in these catalysts and the aforementioned rhodium related catalysts behaved more like coordinating ligands due to their affinity toward the transition metals, and in these publications they have never been mentioned as a counterion.

In 2007, two independent breakthrough works in the field of couteranion-directed transition metal catalysis were unveiled: one is the gold(I)-catalyzed hydroamination, hydroalkoxylation and hydrocarboxylation of allenes from the Toste group[7]and the other is from the List group[8], the Pd-catalyzed Troji-Trost-type allylation of aldehydes.

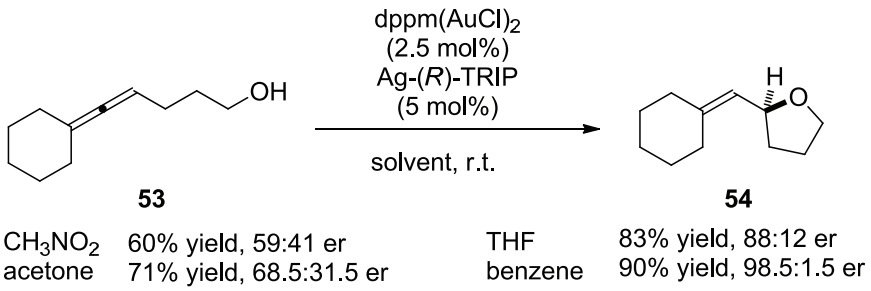
Chiral phosphine ligands have been proved efficient for certain Au(I)-catalyzed reactions, but these transformations are usually particularly difficult to achieve with broad substrate scope and high enantioselectivity, due to the linear coordination geometry of gold, which places the chiral ligand and substrate far away from each other. (*R*)-Xylxyl-BINAP$(AuCl)_2$ in combination with AgOPNB (silver *p*-nitrobenzoate) was an efficient catalyst for the intramolecular hydroamination of allene **50**,[39] but when the authors applied this catalyst to the hydroalkoxylation of allene **53**, only 54:46 er was observed (Scheme 2.19). In the former

Au(I)-catalyzed hydroamination, a dramatic counteranion effect on the stereoselectivity was observed, where the corresponding BF_4^- salts (compared with $^-$OPNB) gave a fast reaction but nearly lost the stereoselectivity. In light of this observation, the authors envisioned that a chiral counteranion could provide a particularly advantageous alternative to the traditional chiral ligand approach in the hydroalkoxylation or even in the whole arena of gold chemistry.



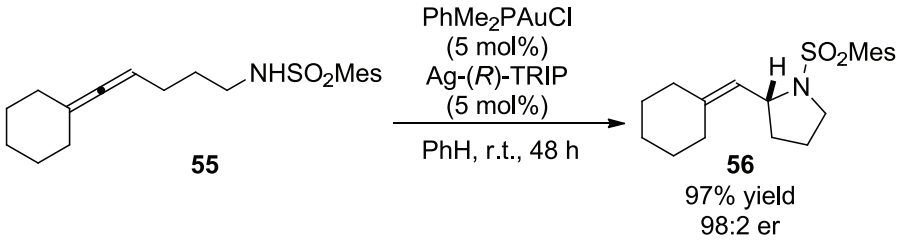
Scheme 2.19: Au-catalyzed intramolecular hydroamination and hydroalkoxylation with chiral phosphine ligands.

The ion-pair catalyst generated in situ from Ph_3PAuCl and chiral silver phosphate (Ag-(*R*)-TRIP) in dichloromethane promoted the hydroalkoxylation with moderate enantioselectivity (82.5:17.5 er), and the selectivity was further improved to 98.5:1.5 er by using a bidentate ligand (dppm) and nonpolar benzene as the solvent (Scheme 2.20).



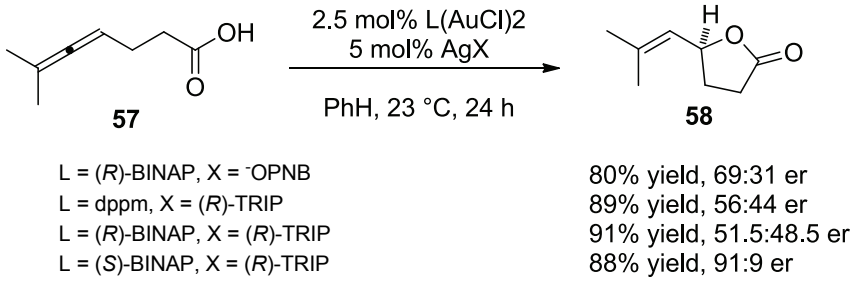
Scheme 2.20: Solvent effect in the counteranion-directed intramolecular hydroalkoxylation of allenes.

This counteranion system also worked well in the hydroamination when changing the achiral phosphine ligand to phenydimethylphosphine (Scheme 2.21).



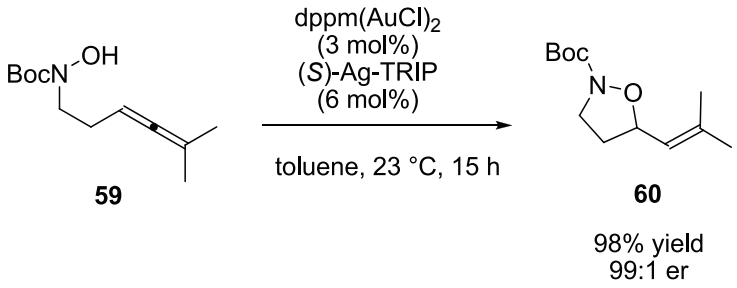
Scheme 2.21: Counteranion-directed intramolecular hydroamination of allenes.

In the asymmetric hydrocarboxylations (Scheme 2.22), chiral ligand/achiral phosphate as well as achiral ligand/ chiral phosphate both gave poor enantioselectivity, while the matched combination of a chiral ligand ((*R*)-BINAP) and a chiral phosphate anion ((*R*)-TRIP$^-$) promoted the reaction in a highly enantioselective manner (91:9 er).



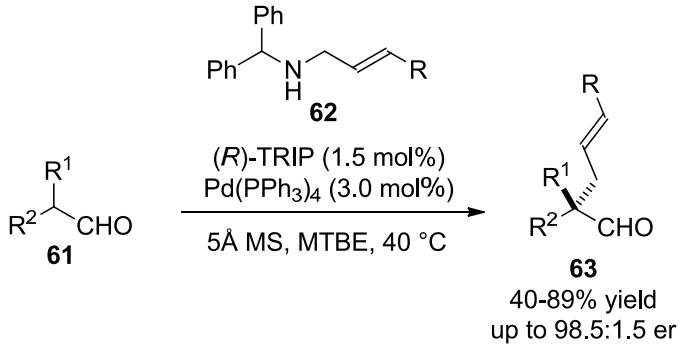
Scheme 2.22: Match/mismatch effects in the intramolecular hydrocarboxylation of allenes.

More recently, this system was further extended to the hydroalkoxylation with hydroxylamines as internal nucleophiles (Scheme 2.23).[40]



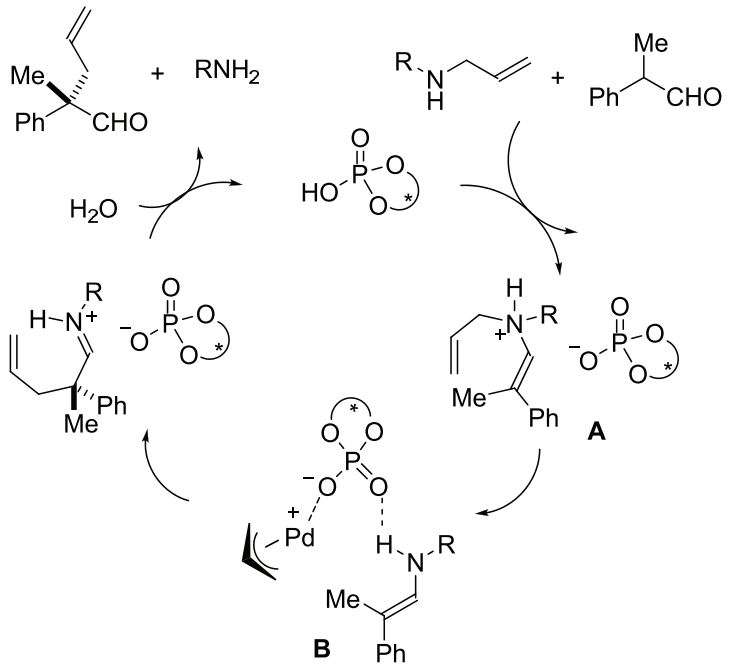
Scheme 2.23: Counteranion-directed hydroalkoxylation with hydroxylamines.

The work from the List group is an extension of their ACDC concept into the transition metal catalysis. In this anion-directed asymmetric allylation of aldehydes **61** (Scheme 2.24), the chiral phosphate anion (TRIP$^-$) was introduced into a key cationic Pd intermediate other than preforming the metal phosphate salts. It is the first time that a chiral anionic ligand is applied for achieving asymmetric induction in a palladium-catalyzed direct allylic alkylation reaction.



Scheme 2.24: Pd/Brønsted acid-catalyzed direct α-allylation of aldehydes.

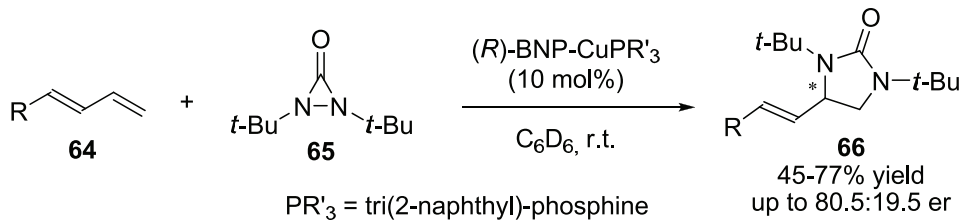
The chiral Brønsted acid in this reaction played at least two roles in the catalytic cycle (Scheme 2.25). The first was to promote the enamine formation and subsequently to activate the allylamine for the Pd cleavage of the N-C bond (**A**). The second was to control the allyl transfer from the palladium to the enamine in an enantioselective way via the ion-pair association with the cationic *p*-allyl palladium complex (**B**). It is crucial to use allylamine **62** as the alkylation reagent which can be activated by acid and release no achiral counteranion after the Pd oxidative addition (RNH_2 is generated). If allyl acetate was used as the alkylating reagent, the achiral anion AcO^- would be generated and compete with the enantioselective process, thus leading to the racemic product. On the other hand, the *N*-benzhydryl allylamine **62** can also activate the aldehyde via enamine formation. It would be interesting to know the results of a reaction which directly uses allyl alcohol as the alkylating agent; in this case no other achiral counteranions would be generated and the only byproduct is water.



Scheme 2.25: The catalytic cycle of Pd/Brønsted acid-catalyzed α-allylation of aldehydes.

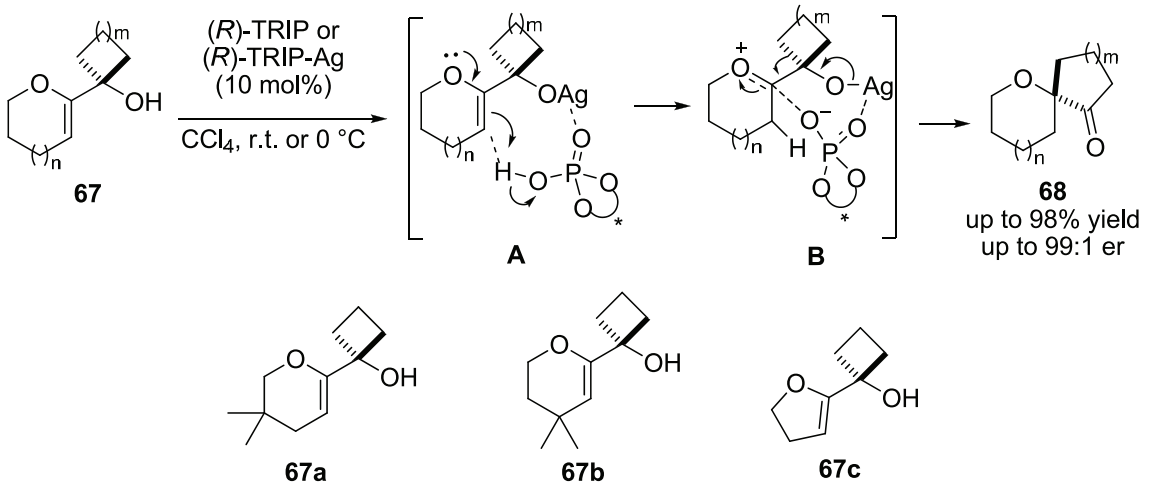
Since these two cornerstone works, where high enantioselectivity was achieved for the first time in the transition metal catalysis employing a chiral counteranion strategy, counteranions have been more and more often taken into consideration for asymmetric transformations. This thesis work was also inspired by these achievements. The following part will give an overview on the development in this field during this thesis work and thereafter.

Although highly enantioselective diamination of dienes and trienes has been achieved with Pd catalysts using tetramethylpiperidine-based phosphorus amidite ligands,[41] the Cu(I)-catalyzed diamination is more challenging to achieve with high enantioselectivity. Attempts in the Shi group using a chiral neutral ligand only afforded moderate enantioselectity (up to 87:13 er using (*R*)-DT-BM-SEGPHOS as the chiral ligand) in the diamination of conjugate dienes,[41b] which intrigued the authors to explore the possibility of conducting an asymmetric reaction using Cu(I) catalysts bearing chiral anions.[42] In general, Cu(I) salts with more electronegative counteranions show better activities (like CuCl), but copper(I) diphenylphosphate also showed comparable activity as CuCl. Various chiral copper complexes were prepared by treating mesitylcopper with chiral acids or alcohols (eg. BNP, quinine, BINOL, proline) and examined in the diamination of conjugate dienes **64** with di-*tert*-butyl-diaziridinone **65** as the nitrogen source, but only the BNP-derived copper catalyst gave promising enantioselectivities (up to 80.5:19.5 er, Scheme 2.26).



Scheme 2.26: Catalytic asymmetric diamination of conjugated dienes.

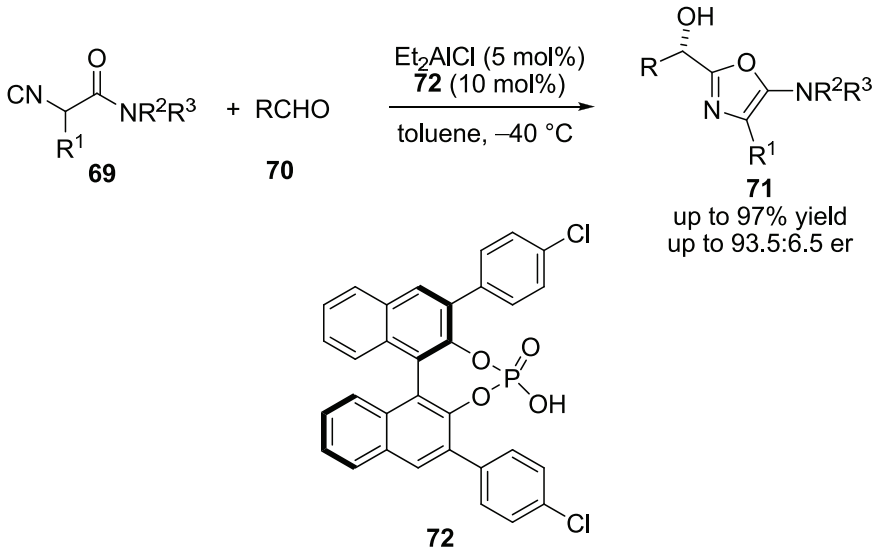
In 2009, a highly enantioselective ring expansion-type semipinacol rearrangement reaction of 2-oxo allylic alcohols **67** to chiral spiroethers **68** was reported by Tu and co-workers,[43] using chiral silver phosphates. The corresponding phosphoric acids were suggested as the real catalysts, which can be generated from the silver salt precatalyst by a silver-proton exchange process with the starting alcohols **67** (Scheme 2.27). The asymmetric semipinacol rearrangement was initiated by the enantioselective protonation of the enol ether moiety (**A**), and the following 1,2-immigration of the carbon atom might proceed via an ion-pair transition state (**B**) to establish the stereocenter.



Scheme 2.27: TRIP or TRIP-Ag-promoted asymmetric semipinacol rearrangements.

The silver phosphate precatalysts and the corresponding phosphoric acid catalysts showed comparable enantioselectivities in most cases, but the different catalytic behaviors between them were also observed. For the sterically demanding substrates like **67a** and **67b**, the acid catalysts were found more efficient, whilst the silver phosphates were more compatible for acid-sensitive substrate like dihydrofurans **67c** (94.5:5.5 er), in which case only 75:25 er was obtained using the acid catalyst.

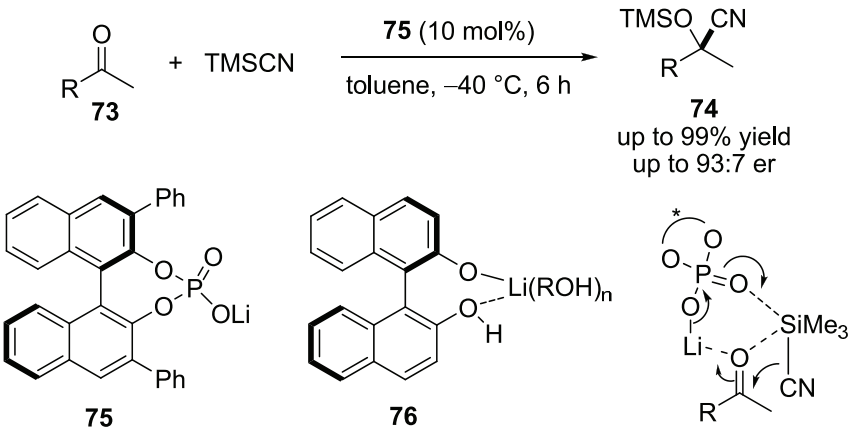
In 2009, Wang, Zhu and co-workers reported a catalytic asymmetric Passerini-type addition reaction of isocyanides **69** to aldehydes **70**, using chiral aluminum phosphate complexes (Scheme 2.28).[44]



Scheme 2.28: Catalytic asymmetric Passerini-type reaction of isocyanides to aldehydes.

The chiral aluminium phosphate catalyst was generated in situ by mixing 2.0 equivalents of chiral phosphoric acid **72** with 1.0 equivalent of Et_2AlCl. In the presence of a catalytic amount of the Al complex (0.05 equiv.), reaction between isocyanoacetamides **69** and aldehydes **70** afforded the corresponding 5-aminooxazoles **71** in good yields and up to 93.5:6.5 er. Complex [**72**-H]$_2Al^{III}Cl$ could also be isolated as a white solid and displayed similar reactivity as that generated in situ. The chiral acid/Et_2AlCl (2:1) ratio is crucial for the high enantioselectivity, whereas a 1:1 ratio resulted in a reversed sense of enantioselectivity.

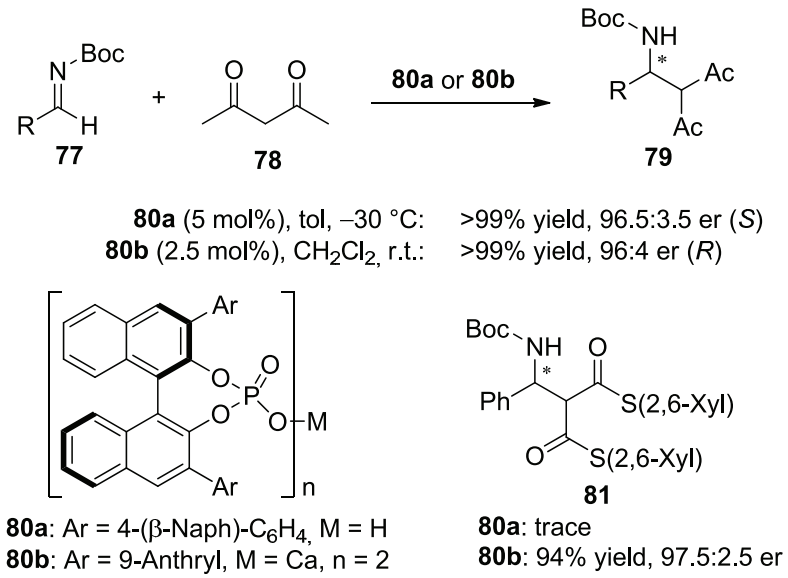
Ishihara and coworkers developed a catalytic enantioselective cyanosilylation of aromatic ketones **73** using lithium salts of chiral phosphoric acids (Scheme 2.29).[45] In the presence of 10 mol% of chiral lithium phosphate catalyst **75**, the corresponding tertiary cyanohydrins **74** could be obtained in high yields (up to 99%) with moderate to high enantioselectivities (up to 93:7 er). Chiral lithium binaphtholate **76**, which works well for the cyanosilylation of aromatic aldehydes,[46] were inefficient for ketones under the same reaction conditions, only giving poorly enantioenriched even racemic products. A six-membered transition state was proposed as shown in Scheme 2.28, in which the chiral lithium salts of phosphoric acids acted as Lewis acid–base conjugate catalysts. Both Li cation-activation of the ketone and basic P=O activation of TMSCN were involved.



Scheme 2.29: Catalytic enantioselective cyanosilylation of ketones using lithium salts.

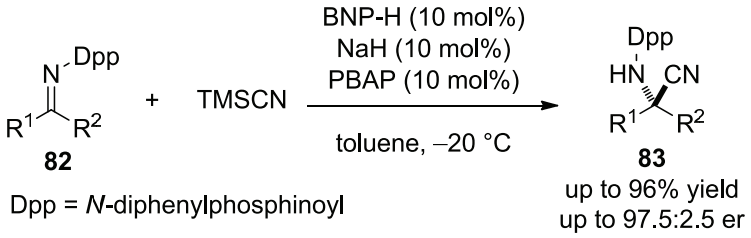
Recently, Ishihara and coworkers[47] revisited the Mannich reaction between aldimines and 1,3-dicarbonyl compounds (Scheme 2.30) which was reported before by Terada[18b] using chiral phosphoric acid catalysts. Because the phosphoric acids could be neutralized to adventitious metal salts such as alkali or alkaline-earth metal salts during the purification with silica gel chromatography, they prepared and tested several metal phosphate salts. It was found that the free Brønsted acid **80a** and the calcium salt **80b** exhibited comparable activity

and selectivity in the reaction between *N*-Boc-benzaldimine **77** (R = Ph) and acetylacetone **78**, but the addition product **79** (R = Ph) was obtained with comparable but opposite enantioselectivity. The calcium phosphate **80b** was particularly efficient for the reaction of aldimines with thiomalonate. For example, in the reaction of *S*-2,6-xylyl thiomalonate, the Mannich product **81** was obtained in 94% yield and 97.5:2.5 er, while the free acid **80a** only gave trace amount of the desired product.



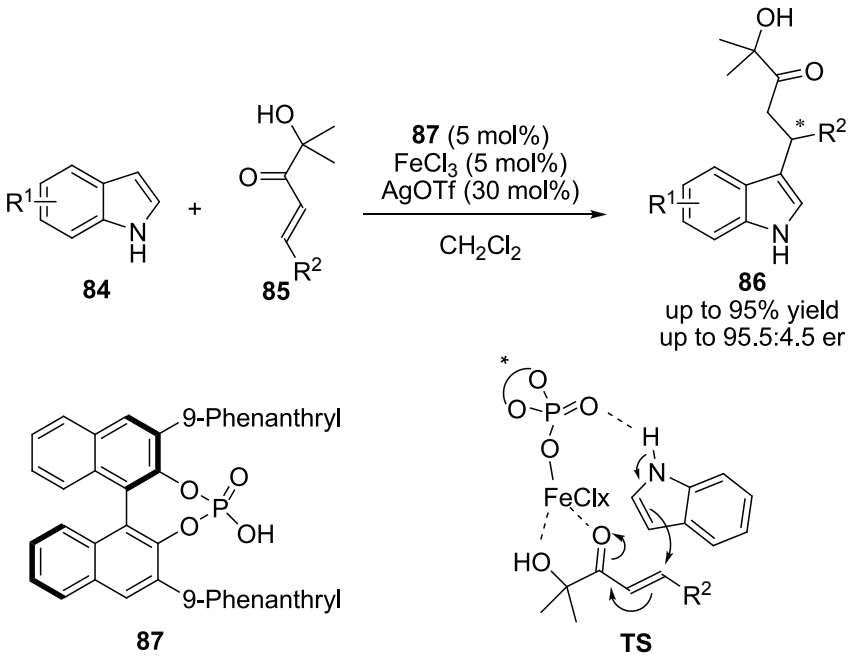
Scheme 2.30: Calcium phosphate-catalyzed Mannich reactions.

Feng and co-workers reported a facile and efficient enantioselective Strecker reaction of ketimines catalyzed by a chiral sodium phosphate salt (Scheme 2.31).[48] The hydrocyanation of aldimines **82** had previously been performed by Rueping using chiral phosphoric acids as the catalyst.[49] In Feng's report, with the sodium salt derived from the simple BINOL-derived phosphoric acid (BNP) and 10 mol% *p*-Bu-o-adamantyl phenol (PBAP) as an additive, up to 96% yield and up to 97.5:2.5 er were achieved. Both aliphatic and aromatic ketimines, especially sterically hindered cyclic ketimines derived from β-acetonaphthone, α-indanone, and α-tetralone were found suitable for this reaction. Other alkaline metal sources such as KO*t*-Bu and $CsOH \cdot H_2O$ were less selective, and lithium salt gave racemic products. Using HCN instead of TMSCN (TMS=trimethylsilyl) as the cyanide source afforded the product in a racemic form, so the key role of PBAP was not to generate HCN as it does in most Strecker reactions involving TMSCN. The formation of reactive hexacoordinate silicon intermediate should be crucial for the asymmetric induction.



Scheme 2.31: Asymmetric Strecker reaction of ketimines catalyzed by BNP-Na.

Huang and co-workers recently developed a cooperative catalytic system, a combination of an iron salt and a chiral Brønsted acid, for the asymmetric Friedel-Crafts alkylation of indoles **84** with β-aryl α'-hydroxy enones **85**.[50] High yields and enatioselectivities (up to 95.5:4.5 ee) were observed for a variety of α'-hydroxy enones and indoles (Scheme 2.32). Chiral silver phosphate salt of **87** without an acidic proton was less active and selective, suggesting that the Brønsted acid here not only acts as chiral counteranion but also provides a free proton source (generating HCl or HOTf) for facilitating catalytic turnover through accelerating the proton-transfer step of the Friedel–Crafts reaction, thus suppressing the $FeCl_3$-catalyzed nonenantioselective background reaction. Moreover, addition of silver triflate could further improve the selectivity of the reaction. A possible transition state was proposed for the stereoselectivity, where the chiral phosphate has a dual function. On one hand, it coordinated to the iron atom to activate the hydroxyl enones, and on the other hand the basic site of the phosphate P=O oxygen could direct the indole via a hydrogen bonding. The key catalytic species in the catalytic system, the Fe^{III} salt of the phosphoric acid, which was thought to be responsible for the high activity and enantioselectivity, was confirmed by ESI-MS studies.



Scheme 2.32: Iron phosphate catalyzed asymmetric Friedel-Crafts reactions.

As discussed in this section, after the Toste's and List's cornerstone works, a number of asymmetric transition metal-involved reactions have been developed based on the counteranion strategy, like Au-catalyzed hydroamination and hydroalkoxylation, Pd-catalyzed allylation, Cu-catalyzed diamination, Al-catalyzed Passerini-type addition and Fe-catalyzed Friedel-Crafts reaction. Interesting is that in most cases BINOL-derived phosphates were employed as the chiral anions of choice.[51] Although the roles of the phosphate anion as a counterion or anionic ligand or even to generate the corresponding acid are not clear in some reactions, they were also discussed here as long as a "metal cation/phosphate anion" interaction was proposed.

2.2 Jacobsen-Katsuki Epoxidation

Inspired by the achiral Mn-salen complex-catalyzed epoxidation reactions discovered by Kochi[52], in 1990 Jacobsen[53] and Katsuki[54] independently reported an enantioselective version of the epoxidation reaction of unfunctionalized alkenes using chiral salen manganese complexes. This achievement represents another great breakthrough in the area of asymmetric epoxidation after the discovery of titanium tartrate-catalyzed epoxdation of allylic alcohols by Sharpless and Katsuki in 1980.[55] The main restriction in Sharpless epoxidation that the alkene to be epoxidized must bear a pendant functional group was well overcome in the manganese salen catalytic system, and a broad range of unfunctionalized alkenes could be epoxidized with greater than 90% ee.

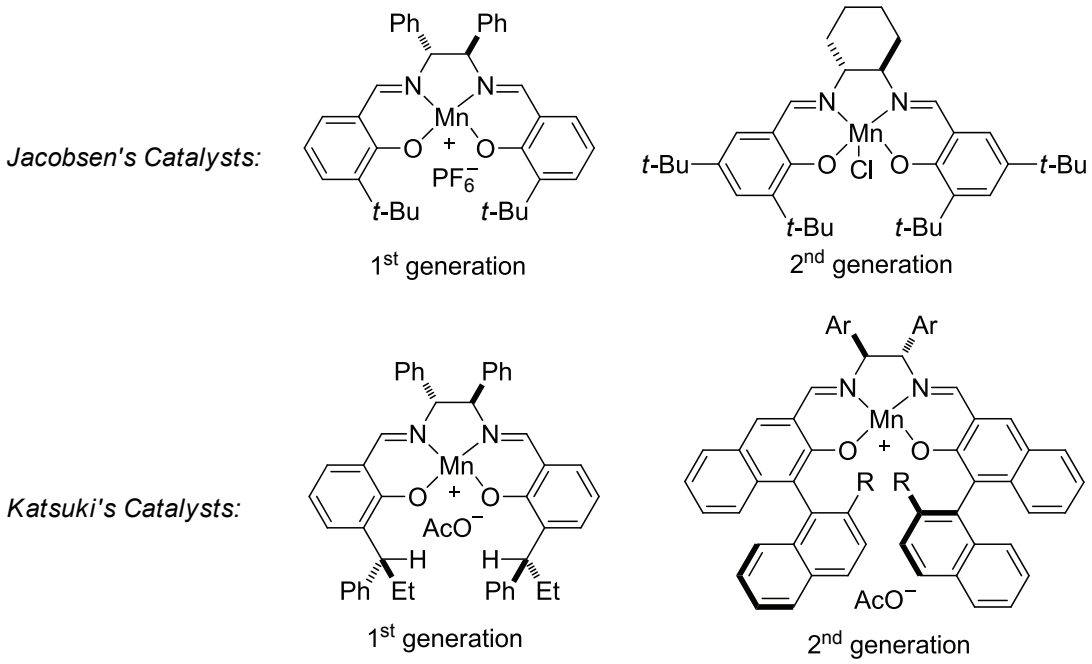


Figure 2.6: Jacobsen's and Katsuki's Mn-salen catalysts

Since the first reports of Mn-salen catalyzed asymmetric epoxdation of unfunctionalized alkenes in 1990, this system has attracted many efforts and expanded greatly. From the first generation[53-54] of Jacobsen's and Katsuki's Mn-salen catalysts to the second generation[56](Figure 2.6), more alkenes like tri-substituted and tetra-substituted olefins have successfully been included into the substrate scope of this highly enantioselective epoxidation reaction.[57] On the other hand, the chiral metal-salen complexs represent one of the most versatile chiral catalysts developed in the recent century,[9] and various asymmetric reactions such as epoxide ring-openings, Diels-Alder reaction, imine cyanation, conjugate addition etc.

apart from atom transfer reactions (epoxidation, aziridination, and cyclopropanation) have been developed based on this type of privileged structures. The development in these areas has been reviewed from time to time in journals [57-58] or books [59].

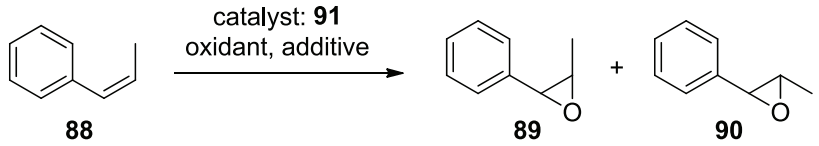
2.2.1 Effects of Added Donor Ligands

The ability of nitrogen- and oxygen-donor ligands to influence the outcome of manganese salen-mediated epoxidations has been known since the initial work by Kochi and co-workers in a nonenantioselective reaction.[52] It was found that the addition of pyridine or PyO (pyridine *N*-oxide) (5-10 equiv with respect to the catalyst) could lead to increased yields by 20-30% in the epoxidation of 1-octene but had little or no effect on the yields of electron-rich alkenes like *Z*-stilbene or *Z*-α-methylstyrene. However, large amounts (> 25 equiv.) of pyridine had a deleterious effect, resulting in lower yields. No effect on the stereochemistry of the epoxide was observed, but formation of carbonyl side products was suppressed significantly when pyridine was present in the reaction.

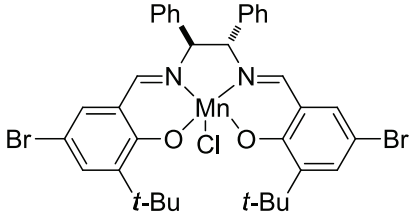
In the Jacobsen-Katsuki epoxidation, the effects of the donor ligands on the reaction outcomes are frequently observed, and extra donor ligands are typically added to increase the reaction rate, yield and enantioselectivity.[57] In the asymmetric epoxidation of *Z*-ethyl cinnamate, Jacobsen and co-workers found the addition of 4-phenylpyridine *N*-oxide (4-PPNO) was crucial to the success of the reaction, since in the absence of the additive epoxidation took place with 10-15% lower selectivity and proceeded with only partial conversion of the olefins, even with higher catalyst loadings (15-20 mol %).[60] However, in their later detailed study on the effect of the donor ligand,[61] little effect was observed on either enantioselectivity or cis/trans ratios of the cinnamate epoxides. The donor ligands usually led to increased rates of epoxidation and total catalyst TONs, and the effects were more pronounced for relatively unreactive substrates. Based on these observations, the effects on the rate, yield, and catalyst lifetime were ascribed to the effect of PyO derivatives on the equilibrium between of Mn^{V}=O comeplexes and Mn^{IV}-O-Mn^{IV} dimers and the protection of the Lewis acidic Mn complex against irreversible reactions involving either substrate or epoxide products.[57] In the asymmetric epoxidation of trisubstituted alkenes,[62] the addition of catalytic levels of pyridine *N*-oxide derivatives gave a slightly, yet consistently beneficial effect on enantioselectivity, reaction rate, and product yield.

Jacobsen and co-workers in their mechanistic studies systematically examined the effects of donor ligands in the epoxidation of *cis*-β-methylstrene **88** using different oxidants, and

significant variation on the *cis*/*trans* ratios and enantiomeric ratios, as well as rates and yields was observed (Scheme 2.32).[63]



Oxidant	Additive (eq)	t (h)	Conv.	Yield	*cis*/*trans*	er_{cis}
NaOCl (aq)	4-PPNO (0.2)	0.5	100%	98%	19:1	90.5:9.5
NaOCl (aq)	-	2	78%	62%	18:1	85.5:14.5
PhIO	4-PPNO (0.2)	8.5	81%	76%	3:1	86:14
PhIO	-	8.5	54%	2%	2:1	84.5:15.5
oxone/K_2CO_3	NMO(2.0)	17	100%	99%	27:1	91:9
oxone/K_2CO_3	-	41	24%	11%	4:1	70:30



91

Scheme 2.33: Epoxidation of *cis*-β-methylstyrene with **91** as the catalyst.

To rationalize these donor ligand effects, the authors suggested that the observed rate acceleration induced by the *N*-oxides can be attributed to the association of the additive with the metal center during the generation of reactive oxo intermediates, and the increase in the turnover numbers of the catalyst may result from the stabilization of the highly reactive $O=Mn^{V}$(salen) by *N*-oxides ligation. Mn-salen catalyst **92** with a built-in PyO moiety (Figure 2.7) was synthesized as evidence that *N*-oxide additives function as axial ligands during the transfer of the oxygen to the alkenes. Just as predicted, X-ray crystal structure showed that the tethered *N*-oxide unit was axially coordinated to the nearly planar salen-Mn unit and was opposite to the chloride counterion. Furthermore, catalyst **92** alone afforded results nearly identical to those obtained with the combination of **93** and 4-PPNO.

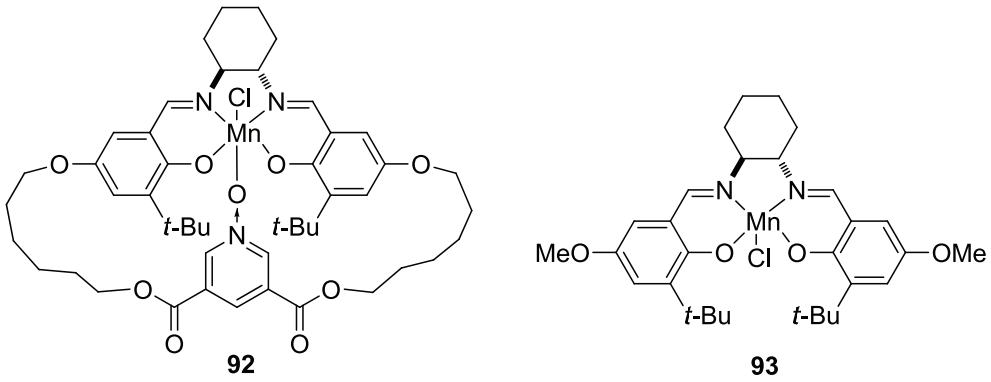
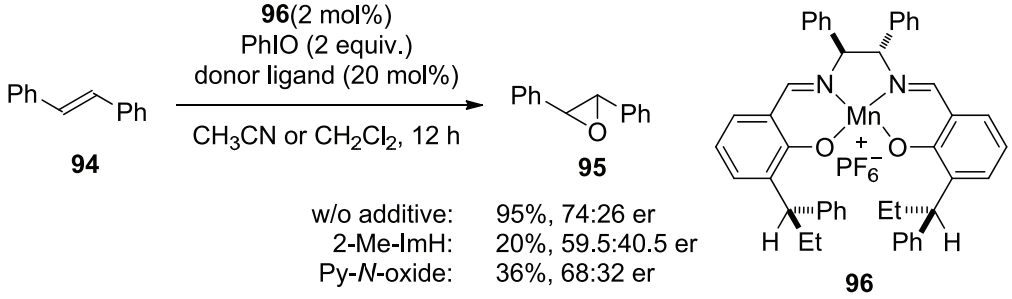


Figure 2.7: Mn-salen catalysts with a built-in PyO donor ligand (left).

The donor ligand influence is more often observed in Katsuki's system,[64] but the effects are not always beneficial. In the case of *E*-stilbene,[64a] the addition of 2-methyl imidazole (2-Me-ImH) or pyridine *N*-oxide gave retarded and less selective reactions (Scheme 2.33).



Scheme 2.33: The donor ligand effects on the epoxidation of *trans*-stilbene.

In 1997, Katsuki and co-workers reported an asymmetric epoxidation transformation using achiral Mn-salen complexes in the presence of a chiral amine.[65] Even though the ethylenedimine moiety does not have a chiral element, the achiral salen/manganese complex is considered to be inherently chiral and exist in equilibrium between two enantiomeric conformation isomers in solution (Figure 2.8). The added chiral donor ligand can preferentially coordinate to one conformer and thus shift the equilibrium to one side. Under these conditions, achiral Mn-salen complexes can also induce an asymmetric epoxidation reaction.

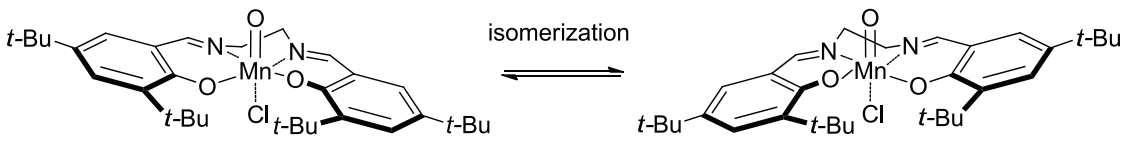
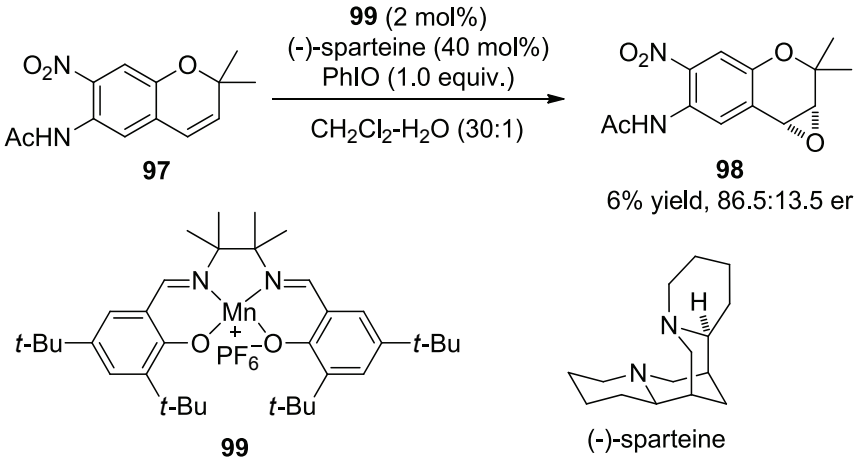


Figure 2.8: The equilibrium of conformation isomers of achiral Mn-salen oxides.

After screening of several chiral amines and pyrazoles, the commercially available (-)-sparteine provided the best selectivity and up to 86.5:13.5 er was achieved, in the combination with achiral Mn-salen **99** (Scheme 2.34). Application of this system to the asymmetric oxidation of methyl phenyl sulfide to its sulfoxide, up to 62.5:37.5 er was obtained.



Scheme 2.34: Achiral Mn-salen-catalyzed epoxidation in the presence of chiral amines.

The low yields and moderate enantioselectivities have later been improved using axially chiral 3,3'-dimethyl-2,2'-bypyridine *N*,*N*'-dioxides (Figure 2.9).[66] In the presence of 5 mol% (+)-**101**, 4 mol% of achiral Mn-salen complex **100** could epoxidize **97** smoothly with high enantioselectivity (65% yield, 91:9 er). In this improved catalyst combination **100**/**101**, the ethylenedimine bridge was used to replace the tetramethylethylenedimine (see **99** in Scheme 2.34), which is not ideal for the control of the pathway of incoming olefins, because of the steric repulsion between the tetramethylethylenediimine bridge and the bulky substituent of olefin which should be directed to the diimine bridge to avoid the steric interaction with C5-substituents at the salen ligand.

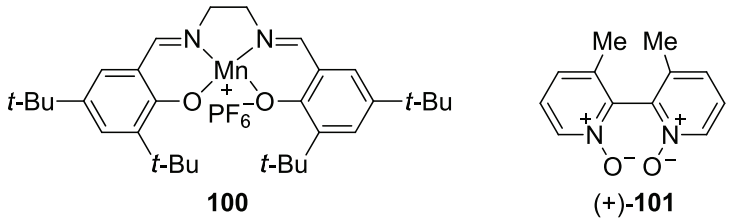
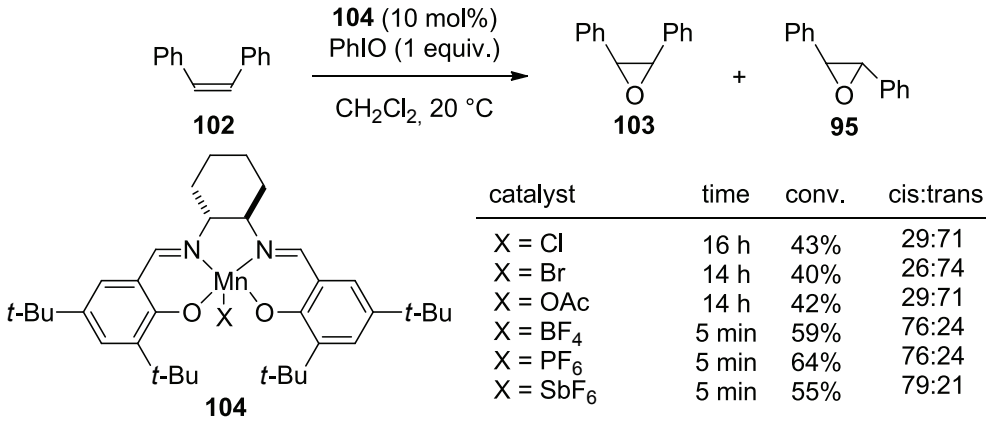


Figure 2.9: Achiral Mn-salen complex **100** and the chiral *N*-oxide **101**.

2.2.2 Effects of Anions and Counteranions

Apart from the added donor ligands, the effect of the anions and counteranions on the outcome of the asymmetric epoxidation has also been observed, but limited to the *achiral* anions or counteranions.

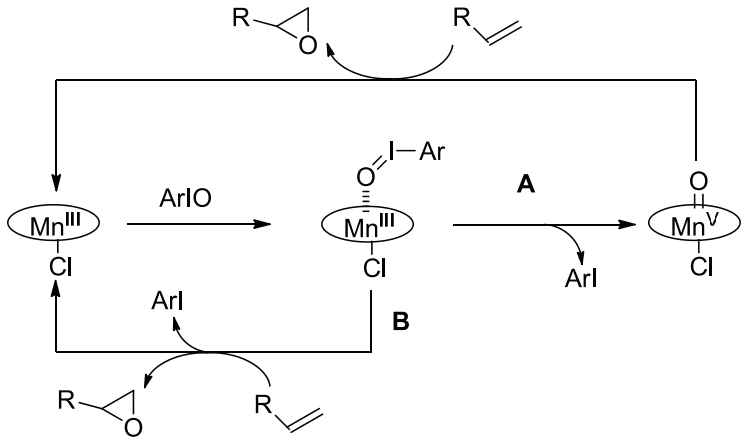
Roschmann and co-workers have shown that among the factors that influence the diastereoselectivity in the epoxidation of *cis*-stilbene **102**, the ligation of the counterion (X^-) in the Mn-salen complex plays an important role (Scheme 2.35).[67] The *cis/trans* stilbene epoxide ratio (**103**/**95**) was ca. 30:70 with extensive isomerization, when complexes **104** were employed with the ligating counterions Cl^-, Br^-, and AcO^-. In contrast, the cis/trans ratio was ca. 75:25 (moderate isomerization) with the nonligating counterions BF_4^-, PF_6^-, and SbF_6^-. This counterion effect was rationalized mechanistically in terms of the two-state reactivity model. They suggested that an axial chloride ligand in the radical intermediate alters the t-q gap compared to the ‘‘naked’’ (like with BF_4^-) one due to changes in the electronic properties of the manganese centre.



catalyst	time	conv.	cis:trans
X = Cl	16 h	43%	29:71
X = Br	14 h	40%	26:74
X = OAc	14 h	42%	29:71
X = BF_4	5 min	59%	76:24
X = PF_6	5 min	64%	76:24
X = SbF_6	5 min	55%	79:21

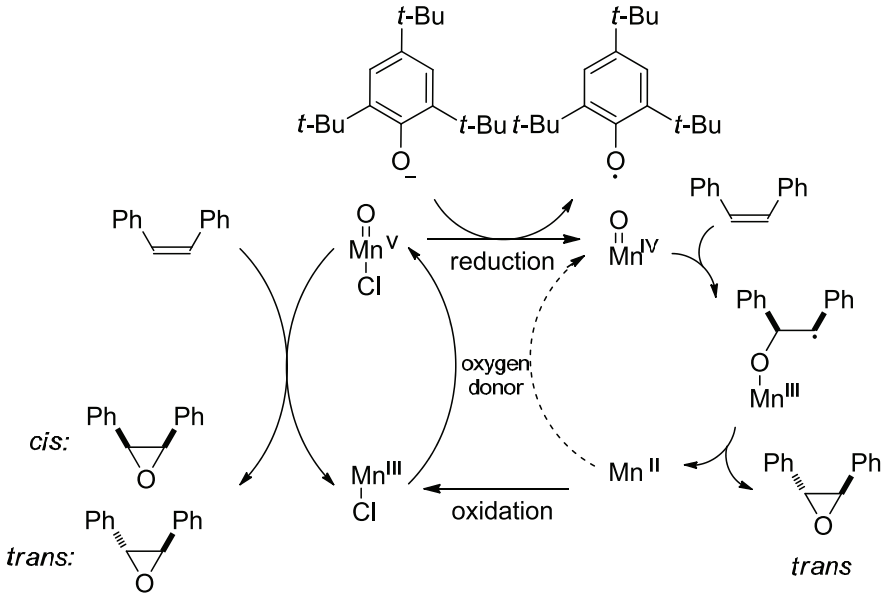
Scheme 2.35: Counterion effects on the *cis/trans* ratio in the epoxidation of *cis*-stilbene.

Collman and co-workers also observed the similar influence of counterions on the epoxidation of *Z*-stilbene.[68] The relative amounts of *cis*- and *trans*-epoxide varied by as much as 58% with Jacobsen’s catalyst, depending on the choice of anionic counterions (22:78 with Cl^- and, 80:20 with BF_4^-). For the reason they proposed that two epoxidizing pathways (Scheme 2.36, **A** and **B**) might operate in competition and the counterions have shown to influence the dominance of one pathway over the other.



Scheme 2.36: Proposed bifurcated mechanism in the Mn-salen-catalyzed epoxidation of olefins.

Åkermark and co-workers reported that in the presence of 2,4,6-tri-*tert*-butylphenolate generated from the corresponding phenol and BuLi, in the Mn-salen catalyzed epoxidation of *cis*-stilbene with iodosobenzene, increased *trans/cis* ratio of the epoxide (from 75:25 to 92:8) was observed (Scheme 2.37).[69] The increased yields of *trans*-products were attributed to the phenolate anion which favored one-electron reduction of an oxomanganese(V) intermediate to an oxomanganese(IV) complex, which will react via diradicals and thus be more *trans*-selective than the oxomanganese(V) species.



Scheme 2.37: Proposed catalytic cycle of epoxidation in the presence of phenolate.

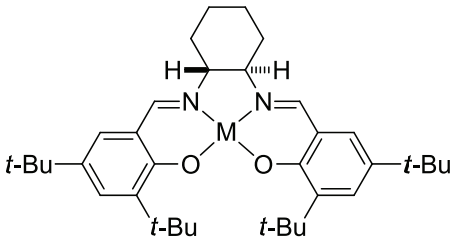
In conclusion, nitrogen- and oxygen-donor ligands such as pyridine *N*-oxides and imidazols can significantly affect the outcome of Mn-salen catalyzed asymmetric epoxidations. Reaction rate, yield, catalyst stability, enantio- and diastereo-selectivity can all be influenced by the

extra donor ligands. Though the roles of the donor ligands depend on the reaction conditions (like solvent, oxidant), axial coordination of the donor ligand to the active Mn center is generally accepted to explain their influence on the stereochemical outcome. Catalysts designed with a built-in donor ligand have been proved quite effective in the asymmetric epoxidation. Furthermore, the principle to achieve asymmetric epoxidation using achiral Mn-salen complexes in the presence of added chiral donor ligands has also been demonstrated. However, as a more direct approach than the addition of extra neutral donor ligands, the introduction of chiral counteranions into the achiral Mn-salen catalysts during their preparation have not yet been reported and the effect of chiral counteranions is unknown.

3 Concept

This thesis work started in October of 2007, just after the reports of Toste's gold-catalyzed allene cyclizations [7] and our group's work on the palladium-catalyzed Tsuji–Trost-type α-allylation of aldehydes[8], two breakthrough works in the area of asymmetric counteranion-directed transition metal catalysis. The successes of our initial proof of asymmetric counteranion-directed catalysis (ACDC) concept with organocatalytic transfer hydrogenations, epoxidations and further extension to transition-metal catalysis with the palladium-catalyzed allylation convinced us that the ACDC concept can be employed as a general strategy for asymmetric catalysis. Thus, the further exploration of the potential of the ACDC concept in transition-metal catalysis to different types of reactions should be of great interest and significance.

Metallosalen complexes first drew our attention, because they represent one type of the most versatile chiral catalysts in asymmetric catalysis.[9;58e;58g;70] For example, the *trans*-cyclohexanediamine-derived metallosalen complexes in Figure 3.1 developed in the Jacobsen group have been shown to be capable of promoting a munber of transformation with high enantioselectivity, like Mn-salen-catalyzed epoxidations, chromium and cobalt-catalyzed epoxide ring-openings, aluminum complex-promoted conjugate additions of azides to unsaturated imides.[9]



Metal-salen complexes

M = MnCl, CrCl, CoOAc, AlCl, AlMe etc.

epoxidation
epoxide ring-opening
Diels-Alder reaction
imine cyanation
conjugate addition

Figure 3.1: Metallosalens as one type of the most privileged chiral catalysts.

We are interested in the manganese-salen complexes, which is the most studied metallosalen system and can be employed in a series of asymmetric atom-transfer reactions like epxodation,

sulfoxidation, aziridination.[58c] Although these manganese complexes display a broad substrate scope in the epoxidation reaction, certain olefin classes like terminal alkenes and *trans* olefins still fail to be converted with high enantioselectivity.[57]

Cationic Mn–salen complexes are C2-symmetric and inherently chiral—even when the salen ligand itself is achiral. In case of the Jacobsen–Kastuki epoxidation, the chiral backbone of the salen ligand fixes the complex in one of the two enantiomorphic conformations.[66] It can be envisioned that the replacement of the achiral anionic counterion (X^-) with a chiral counterion should be also possible to induce one enantiomorphic conformation of the achiral cationic complex. When BINOL-derived phosphoric acid anions were employed, these anions may also amplify the chiral microenvironment around the metal center with suitable 3,3'-substituents (Figure 3.2).

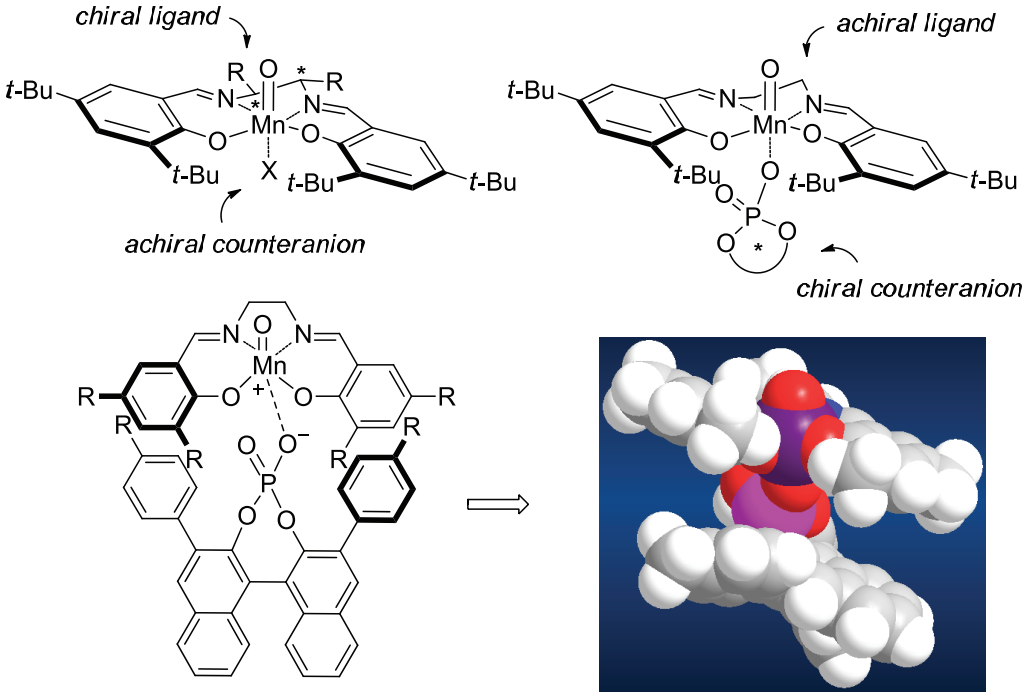


Figure 3.2: Design principle and modeling of a chiral ion-pair catalyst (R=CH_3 in 3D model).

The following can be expected from this novel Mn-salen system: 1) a different substrate scope; 2) no extra donor ligand is required; 3) more reactive due to the sterically overloaded ion pairs of Mn-salen phosphates; 4) a new model for mechanistic studies and investigation on the trajectory of alkenes.

Another aspect regards the ACDC concept itself. In the palladium-catalyzed Tsuji–Trost-type α-allylation of aldehydes and Toste's gold-catalyzed allene cyclizations, the interaction possibly via hydrogen-bond formation (Figure 3.3, **A** and **B**) between the counteranions and

the substrate cannot be excluded. Even though the percentage contribution of this interaction to the high level of enantioselectivity in these two reactions is not clear, we are interested in building a model where this direct interaction between the chiral counteranion and the substrate is not involved. The Mn-salen system seems ideal for this goal, because it is known that substrates approach the Mn=O spicies from the opposite side of the counterions (X^-) or axial ligands (Figure 3.3, **C**).

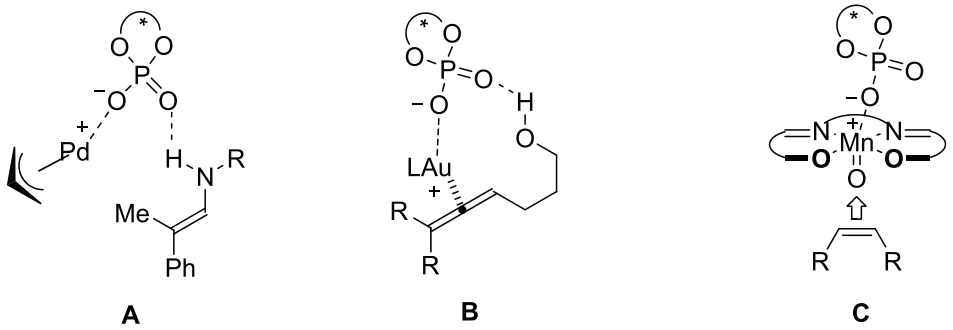


Figure 3.3: Possible interaction between the chiral counteranions and substrates.

Overall, the design based on ACDC concept may lead to a new type of chiral Mn–salen catalyst with unique properties, providing possible solutions to unmet problems in the Jacobsen-Katsuki epoxidation and a novel platform for further exploration of the metallosalen system. Furthermore, other aspects related to the mechanism, trajectory of olefins are still under debate,[57;71] and the Mn-salen catalysts designed based on the ACDC concept can act as a new model for these studies.

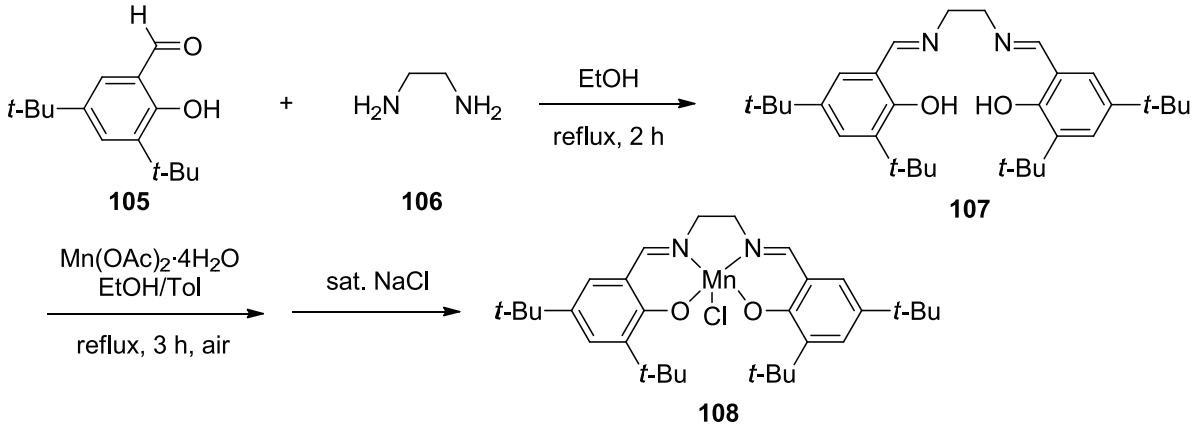
4 Results and Discussion

4.1 Enantioselective Epoxidation of Alkenes with Mn^{III}-Salen Phosphate Ion-Pair Catalysts

4.1.1 The Initial Studies

4.1.1.1 Synthesis of Achiral Manganese(III) Salen Complexes

The preparation of achiral and chiral manganese(III) salen complexes has been well described in the literature. The synthesis of achiral salen ligands and the corresponding manganese(III)-salen complexes in this thesis work was according to the method developed by Jacobsen, Gao and co-workers in 1994 for a large-scale preparation of the Jacobsen catalyst.[72]



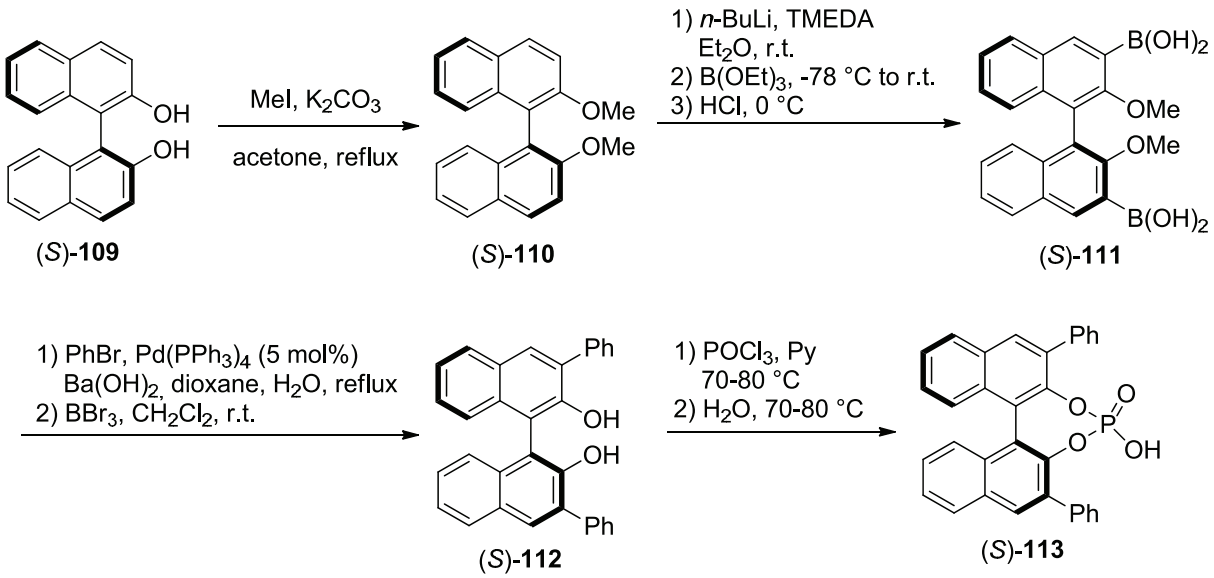
Scheme 4.1: Synthesis of achiral Mn^{III}-salen complex **108**.

The salen ligand was obtained via the condensation of 1,2-diaminoethane **106** and 3,5-di-*tert*-butylsalicylaldehyde **105** in a 1:2 ratio in EtOH. Full conversion can be achieved by overnight stirring of the reaction mixture at room temperature or 2 hours of reflux. The reaction mixture was then cooled to room temperature and stored in the freezer overnight. The yellow crystals formed were collected by filtration and washed with cold EtOH. The metallation was carried out with $Mn(OAc)_2 \bullet 4H_2O$ (3.0 equiv.) as the metal source. Refluxing the mixture of ligand **107** and the metal source in ethanol for 2 hours resulted in a brown solution, and then air was slowly bubbled through the reaction mixture for 1 h. The solution eventually turned dark brown. When TLC (EtOAc/hexanes, 1:4) showed complete disappearance of the ligand,

saturated aqueous NaCl was added and the mixture was cooled down to room temperature. Extraction with dichloromethane, drying and removal of the solvent furnished the crude product as a brown solid. The pure fine needle-like product **108** was obtained by recrystallization from dichloromethane/hexanes.

4.1.1.2 Synthesis of Chiral Phosphoric Acids

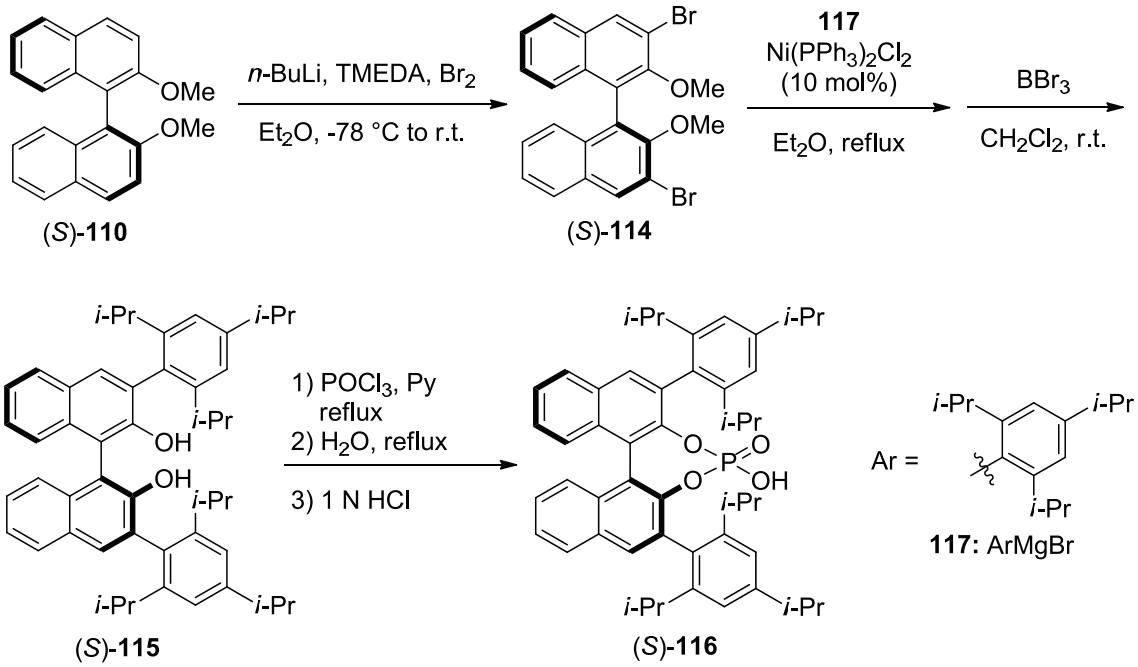
The phosphoric acid **113** bearing 3,3'-phenyl substituents was prepared via a Suzuki cross-coupling reaction as shown in Scheme 4.2, according to the procedure developed by Jørgensen et al.[73] and Wipf et al.[74]. The key step was a palladium-catalyzed cross coupling of boronic diacid **111** and PhBr to install the 3,3'-phenyl substituents. The boronic diacid needed for the Suzuki cross-coupling step was synthesized by *ortho*-lithiation of compound (*S*)-**110**, followed by treatment with triethylborate and hydrolysis with acid. Deprotection of the methyl group with BBr_3, phosphorylation with $POCl_3$, and subsequent hydrolysis afforded the desired phosphoric acid (*S*)-**113** as a white solid.



Scheme 4.2: Synthesis of phosphoric acid (*S*)-**113** via a Suzuki coupling.

3,3'-Bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (TRIP) was prepared via Kumada cross-coupling, because the 3,3' highly sterically hindered substituents resulted in poor yields when Suzuki cross-coupling was employed. The key step of this process was a nickel-catalyzed cross coupling of dibromide compound **114** with the aryl magnesium bromide **117** (Scheme 4.3).

The preparation of (*S*)-TRIP **116** was developed and optimized in our laboratory by *A. M. Seayad*[75] according to the procedures of Schrock et al.[76] and Akiyama et al.[77] (*S*)-3,3'-Dibromo-2,2'-dimethoxy-1,1'-binaphthyl **114** needed for the Kumada cross-coupling reaction was prepared via *ortho*-lithiation of (*S*)-**110** in the presence of *n*-butyl lithium and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) followed by quenching with bromine.



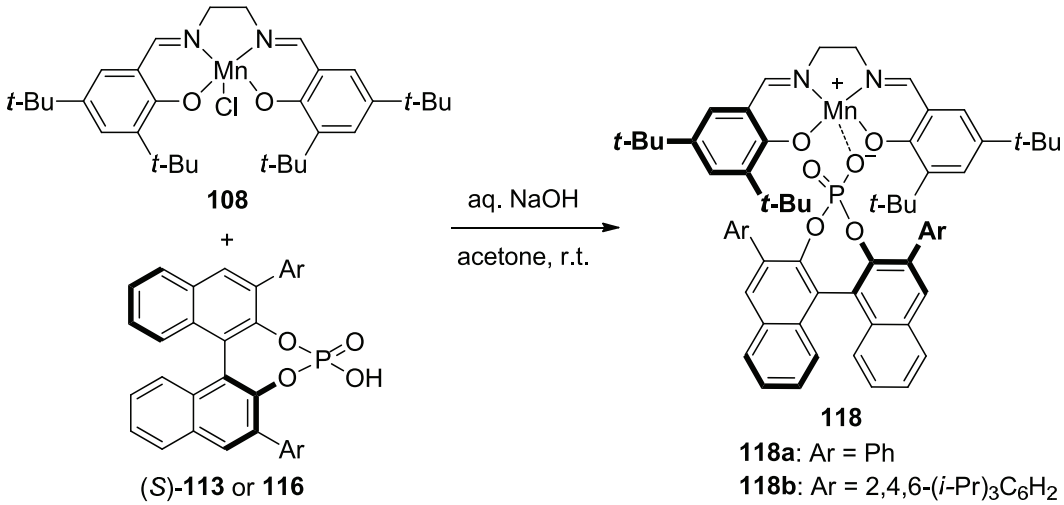
Scheme 4.3: Synthesis of (*S*)-TRIP via Kumada cross-coupling.

The nickel-catalyzed Kumada cross-coupling of (*S*)-3,3'-dibromo-2,2'-dimethoxy-1,1'-binaphthyl (*S*)-**114** with 2,4,6-triisopropylphenyl magnesium bromide **117** allowed the introduction of highly sterically hindered 2,4,6-triisopropylphenyl substituents at the 3,3'-positions of (*S*)-**114**. Deprotection of the methyl groups with boron tribromide delivered (*S*)-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diol (*S*)-**115** as a white solid in 75% yield. Phosphorylation of (*S*)-**115** was achieved using phosphoryl chloride in pyridine under reflux conditions. Finally, hydrolysis by addition of water followed by a treatment with hydrochloric acid (1 N) afforded the desired phosphoric acid (*S*)-**116**.

Both phosphoric acids were readily available in our group with the help of our technician team.

4.1.1.3 Synthesis of Mn-salen/Phosphate Ion-Pair Catalysts

The ion-pair catalysts were prepared by anion exchange. Phosphoric acid (*S*)-**113** or (*S*)-**116** and achiral Mn-salen chloride **108** were dissolved in acetone in a 1:1 molar ratio, and then 1.0 equivalent of aq. NaOH (0.5 mol/L) was followed. The resulting mixture was stirred at room temperature until the anion exchange finished. TLC (alumina) was very convenient to monitor the anion exchange process. The desired Mn-salen phosphate products (**118a-b**) were much less polar than the starting phosphoric acids and the Mn-salen chloride. The retention factor of the product **118b** was around 0.40 (2% EtOH in EtOAc), while the phosphoric acid **116** and salen-Mn chloride **108** were strongly retained by the stationary phase with an Rf < 0.1. Silica gel coated thin-layer plates are not suitable for this analysis; the phosphate anion in the product can be partially exchanged by anions that were contained in the coating materials. The anion exchange underwent fast and usually finished in one hour. After 3 h of stirring at room temperature, solvent was then removed under reduced pressure. DCM was added to dissolve the dark brown solid, and NaCl formed during the reaction was filtered off through a filter (0.45 μm). After drying in vacuo, the catalysts were obtained as a dark brown solid and directly used in the epoxidation without further purification.



Scheme 4.4: Synthesis of ion-pair catalysts **118a-b** via anion exchanges.

4.1.1.4 Testing of Ion-Pair Catalysts

Considering that good enantioselectivity had been realized by Katsuki et al. in the epoxidation of chromene derivatives using achiral Mn^{III}-salen complexes in the presence of axially chiral

bipyridine *N,N'*-dioxide,[66] their reaction conditions (dichloromethane as the solvent and PhIO as the oxidant) were employed in our initial study. 6-Cyano-2,2-dimethylchromene was chosen as the model substrate because it is commercially available and its structural features are quite suitable as the standard substrate for Jacobsen-Katsuki epoxidation.[61] After examining a broad range of alkenes for the epoxidation, Jacobsen found that substrates including the following properties (Figure 4.1) favor high yields and enantioselectivity: 1) an aryl, alkenyl, or alkynyl group conjugated to the alkene, 2) a *cis* double bond linkage, 3) a bulky R group, and 4) the presence of an allylic oxygen substituent. Combination of 3 or more of these properties results in alkenes that are excellent substrates for asymmetric epoxidation with Mn-salen complexes. Furthermore, chromene epoxidation products are important pharmaceutical intermediates in natural product synthesis and pharmaceutical research.[78]

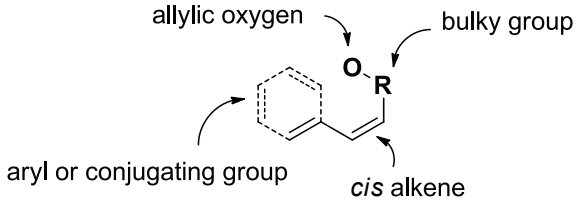
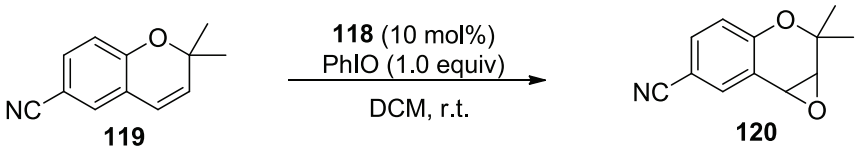


Figure 4.1: Substrate properties favoring asymmetric epoxidation with Jacobsen's catalysts.

The reactions using both ion-pair catalysts underwent smoothly (Scheme 4.5), and most of the starting material was consumed (checked by TLC) in 3 hours. After 20 h, the conversions were determined to be 66-79% by GCMS. Pure epoxides can be easily isolated in good yields (60-80%) with a short silica gel column. However, the enantioselectivities were not satisfactory, and only 54:46 er was observed with **118b**. For the phenyl substituted phosphate derived ion-pair catalyst **118a**, the selectivity was even lower (51:49 er).

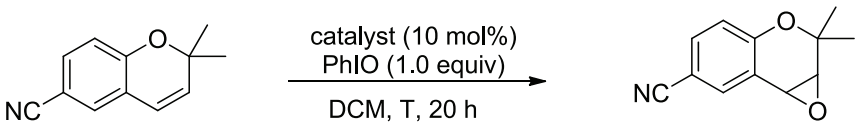


Scheme 4.5: Test of ion-pair catalysts in the asymmetric epoxidation reactions.

In Katsuki's epoxidation using combination of an achiral Mn(III)-salen complex with an axially chiral bipyridine *N,N'*-dioxide, the best results were obtained at -20°C.[66] We also performed the reaction at a lower temperature. As shown in table 4.1, lowering the temperature could readily improve the enantioselectivity to 66:34 er (entry 7) with **118b**, and

the conversions were also slightly increased from 66% to 78%. Lower temperature usually provided a cleaner reaction as judged by TLC, which can be attributed to the suppressed decomposition of the catalyst at lower temperatures. This phenomenon can also account for the increased yields even at lower temperatures. Prolonging the reaction time to 48 h further increased the conversion.

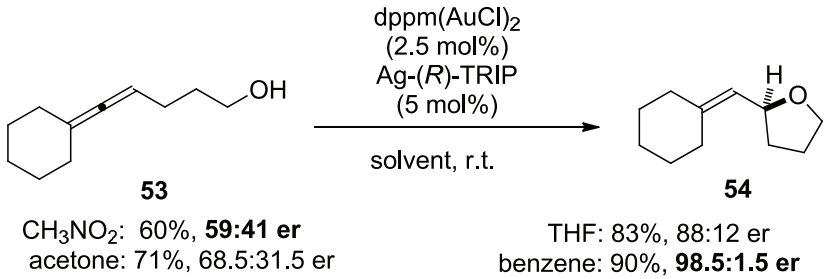
Table 4.1: Temperature influence on the epoxidation



119 **120**

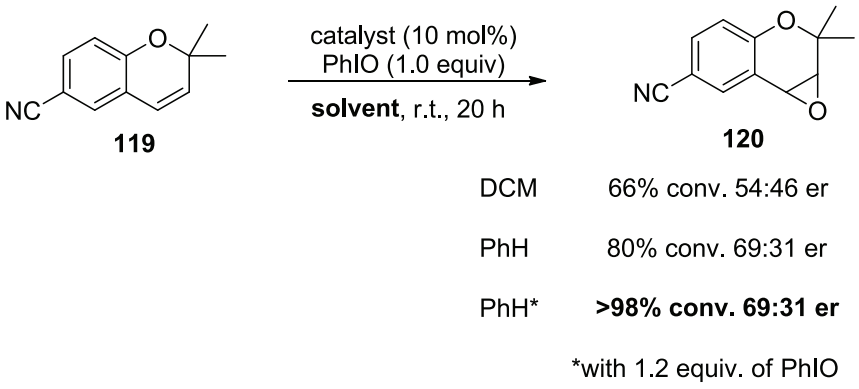
Entry	Catalyst	Temperature	Conversion	e.r.
1	**118a**	r.t.	79%	51:49
2	**118a**	0 °C	80%	51.5:48.5
3	**118a**	-30 °C	82%	54:46
4	**118a**	-78 °C	89%	53.5:46.5
5	**118b**	r.t.	66%	54:46
6	**118b**	0 °C	71%	59:41
7	**118b**	-30 °C	78%	66:34
8	**118b**	-78 °C	78%	65:35

The increased enantioselectivity at a lower temperature may be explained in two ways: 1) at low temperatures, the decomposition of the catalyst was suppressed and thus increased the concentration of the active catalytic species during the reaction; 2) a tighter ion-pair catalyst may form at a lower temperature. Considering the latter reason, the polarity of solvent may exert a significant influence on the stereochemical outcome. In nonpolar solvents, contact ion pairs are preferentially formed, while in polar solvents the ion pairs can be separated to some extent by the solvent molecules. In Toste's gold-catalyzed allene cyclizations, a dramatic solvent influence was observed.[7] Change of the solvent from polar nitromethane to nonpolar benzene significantly increased the enantioselectivity to 98.5:1.5 er from 59:41 er (Scheme 4.6). The similar observation has been made in our laboratory encouraged us to examine the solvent effect before we began more intensive screening of the ion-pair catalysts.



Scheme 4.6: Effect of solvent polarity on the Au-catalyzed hydroalkoxylation of allenes.

As expected, when we performed the reaction in nonpolar benzene at room temperature, the enantiomeric ratio was increased to 69:31 (Scheme 4.7). Furthermore, a slight excess of the oxidant (1.2 equiv) enabled full conversion of the substrate. These improvements and encouraging results provided us with the confidence to initiate further catalyst screenings and reaction condition optimizations.



Scheme 4.7: Effect of solvent polarity on the epoxidation.

4.1.2 Structural Optimization of the Ion-pair Catalysts

4.1.2.1 Screening of Chiral Counteranions

4.1.2.1.1 Synthesis of BINOL-derived Phosphoric Acids

BINOL-derived phosphoric acids **121a-j** in Figure 4.2 were synthesized from the commercially available enantiomerically pure BINOL via Suzuki cross-coupling to install the 3,3'-aryl substituents, according to the procedure described before for (*S*)-**113** (see Scheme 4.2 in Chapter 4.1.1). For convenience, the corresponding acid anions are designated as **121x**$^{-}$, for example **121a**$^{-}$.

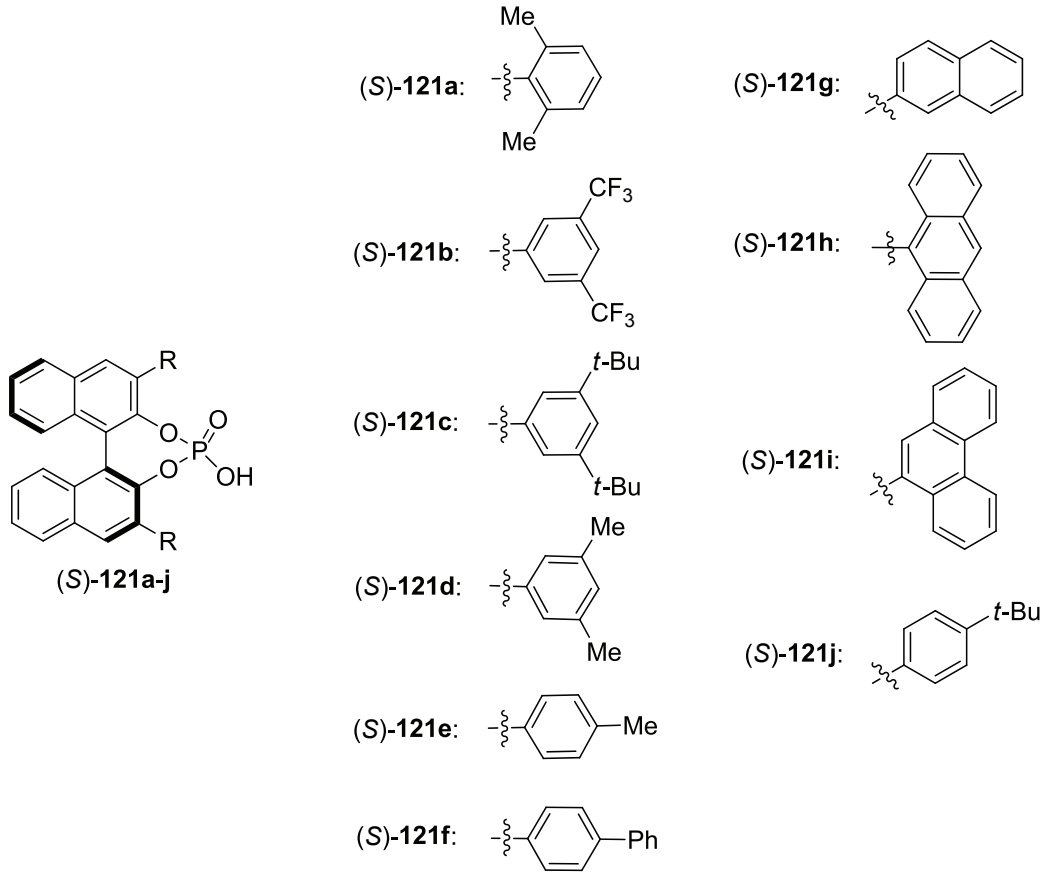


Figure 4.2: BINOL-derived phosphoric acids **121a-j** synthesized via Suzuki cross-coupling.[79]

Yamamoto-type *N*-sulfonyl phosphoramide **122** and *N*-phosphinyl phosphoramide **123**, were prepared by *S. Vellalath*.[80] Disulfonimidate **124** was prepared by *P. Garcia-Garcia*.[81] Disulfonic acid **125** was prepared by *G.-X. Jiang*, according to the procedure developed by *P. Garcia-Garcia* and *F. Lay* in our laboratory.[81] Octahydro-BINOL-derived phosphoric acid **126** was prepared via the Suzuki cross-coupling of methyl-protected 3,3'-dibromo octahydro-

BINOL and 4-*tert*-butylbenzene boronic acid, followed by the deprotection, phosphorylation and hydrolysis.

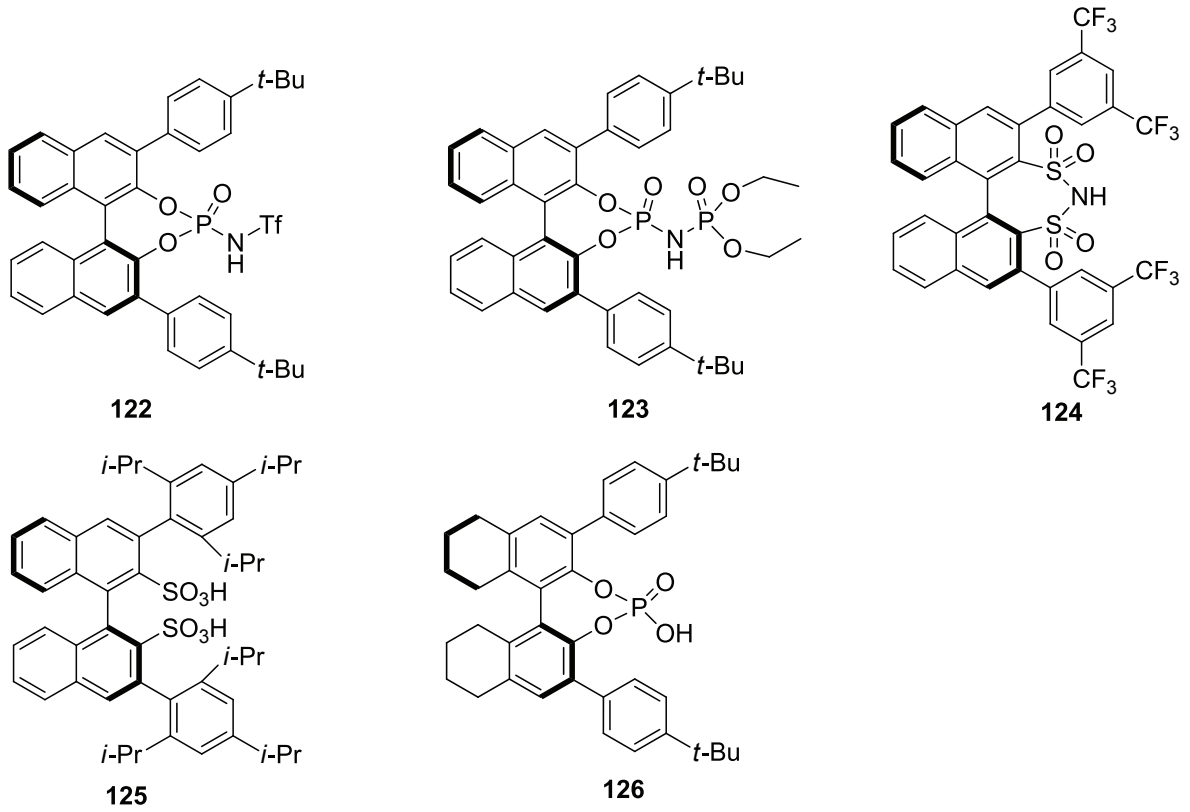
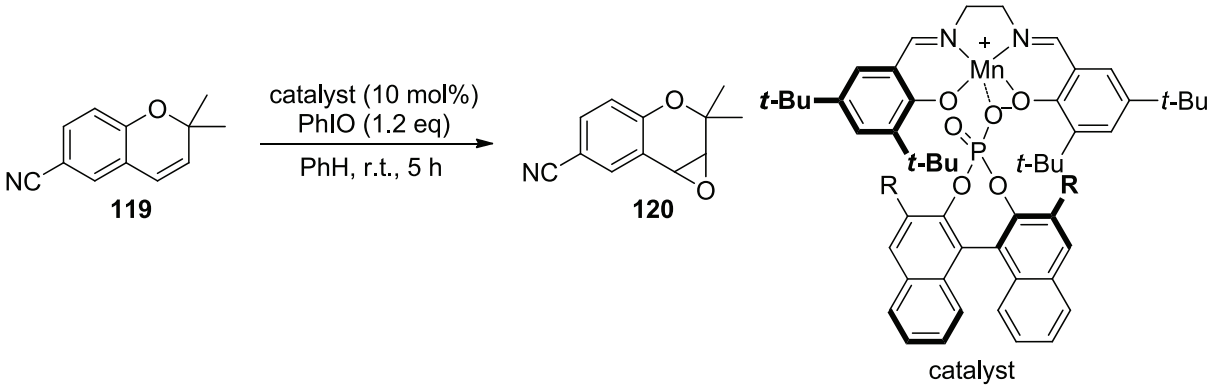


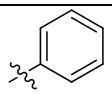
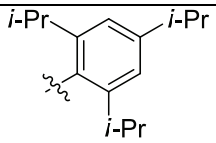
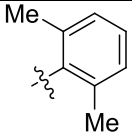
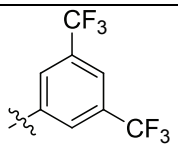
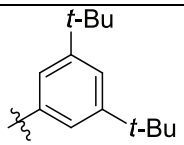
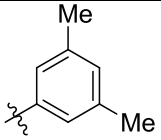
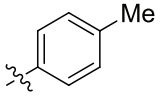
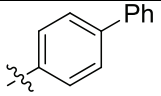
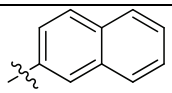
Figure 4.3: Other chiral acids for the counteranion screening.

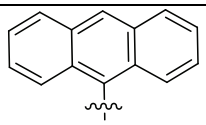
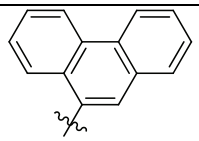
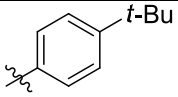
4.1.2.1.2 Screening of Chiral Counteranions

The screening of chiral phosphates or other acid anions was carried out under the following conditions established with **118a** in our initial studies: 0.1 mmol scale, 10 mol% ion-pair catalyst, iodosobenzene (PhIO) as the oxidant (1.2 equiv.), in benzene [0.1 mol/L] at room temperature. The conversions and er's are listed in Table 4.2.

Table 4.2: Screening of chiral phosphate anions



Entry	R	Catalyst	Conv.[a]	e.r.
1		**$108^+/113^-$** (**118a**)	89%	53.5:46.5
2		**$108^+/116^-$** (**118b**)	>99%	69:31
3		**$108^+/121a^-$**	>99%	75:25
4		**$108^+/121b^-$**	>99%	75:25
5		**$108^+/121c^-$**	>99%	65:35
6		**$108^+/121d^-$**	>99%	70:30
7		**$108^+/121e^-$**	>99%	71:29
8		**$108^+/121f^-$**	87%	79:21
9		**$108^+/121g^-$**	>99%	75:25

10		**108$^+$/121h$^-$**	83%	56:44
11		**108$^+$/121i$^-$**	>99%	74:26
12		**108$^+$/121j$^-$**	>99%	95:5

[a] Determined by GCMS.

Among the phosphate anions with substituents at different positions of the 3,3'-phenyl groups, the most sterically hindered anion **116$^-$** gave 69:31 er (entry 2), while the least sterically hindered anion **113$^-$** gave the nearly racemic product (entry 1). However, the anions **121e$^-$** and **121f$^-$** with a *para*-substituent gave a higher level of enantioselectivity (entries 7-8). When increasing the size of the *para*-substituent from methyl to phenyl, the selectivity was improved to 79:21 e.r. (entry 8). Chiral BINOLl-derived phosphates with other aromatic substituents (2-naphthyl, 9-anthryl, 9-phenathryl) were also examined but did not lead to improved enantioselectivity (entries 9-11). All the catalysts provided a fast and clean reaction except the one with the anthryl substituted anion (entry 10). The lower conversion may result from the decomposition of the anion which is light sensitive. Reasoning that *para*-substitution at the 3,3'-aryl groups may be critical in extending the remote axial chirality of the binaphthyl catalyst core into close vicinity to the presumed Mn^V–oxo active center, possibly preventing certain olefin trajectories, the phosphate (entry 12) with a 4-*tert*-butylphenyl-substitutent was synthesized and tested. To our delight, ion-pair catalyst **108$^+$/121j$^-$** promoted the epoxidation smoothly with excellent enantioselectivity (95:5 er, entry 12). In fact, with this catalyst the olefin was completely consumed after 30 min and the epoxide could be isolated in nearly quantitative yield (>98%).

Under the same reaction conditions, other acid anions (Figure 4.4) with different scaffolds were also examined in the hope of finding a new and better structural motif, like Yamamoto-type phosphoric acid derived anion **127k$^-$**, *N*-phosphinyl phosphoramidate **127l$^-$**, disulfonimidate **127m$^-$**, disulfonic acid derived anion (1:2) **127n$^-$**, and octahydro-BINOLl derived phosphate anion **127o$^-$**. All the ion-pair catalysts **108$^+$/127k-o$^-$** gave full conversion, and the er's obtained with these catalysts are given in parentheses, but none of them gave

better selectivity than **108**$^{+}$**/121j**$^{-}$. The octahydro anion **127o**$^{-}$, that has a smaller O-C-C-C-C-O dihedral angle than **121j**$^{-}$ around the axis, showed the similar result (94:6 er) to **108**$^{+}$**/121j**$^{-}$.

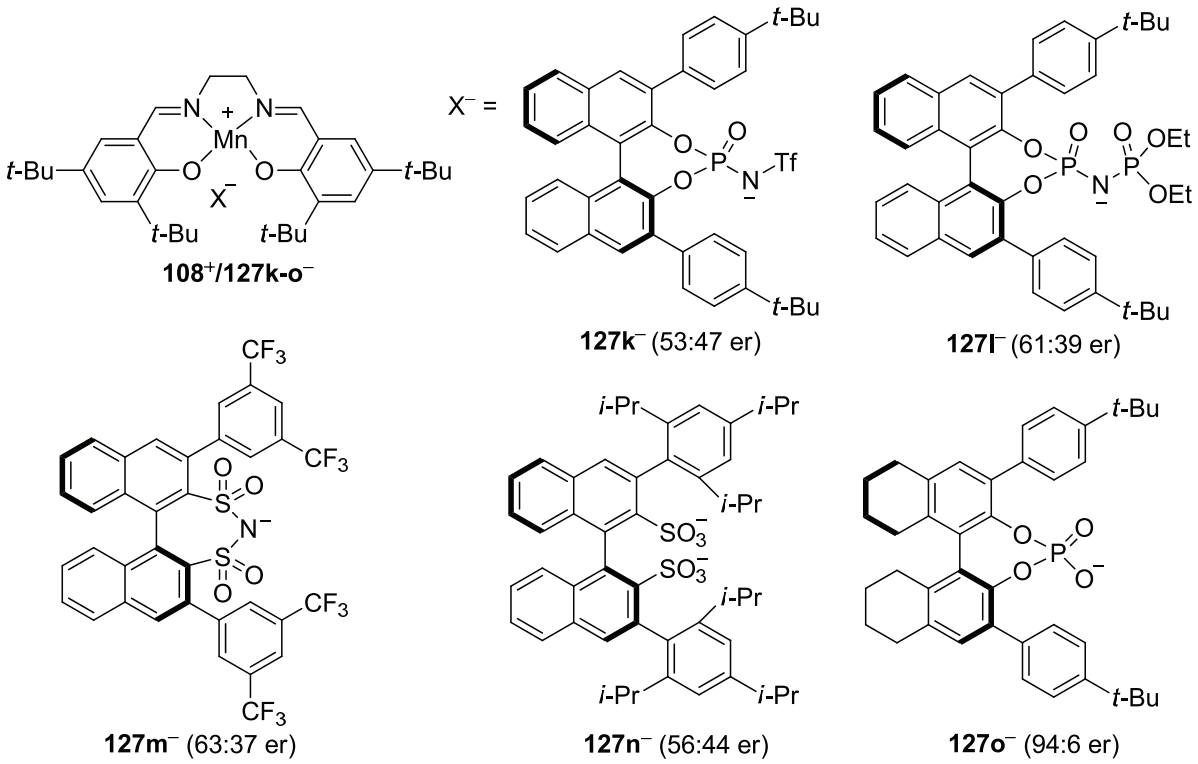
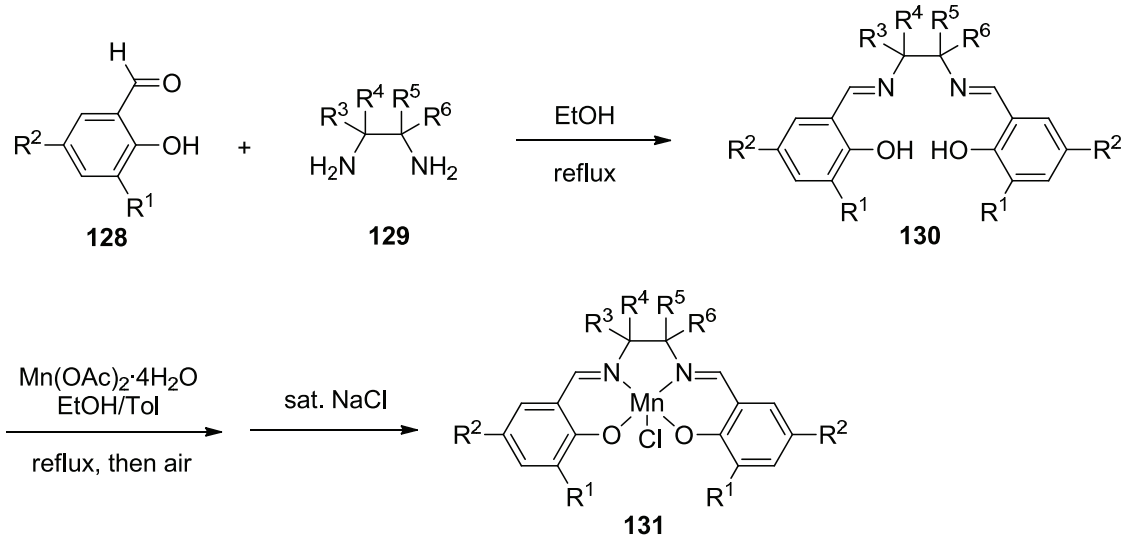


Figure 4.4: Screening of other chiral anions with different scaffolds.

4.1.2.2 Screening of Achiral Mn-salen Cations

4.1.2.2.1 Synthesis of Achiral Salen Ligands

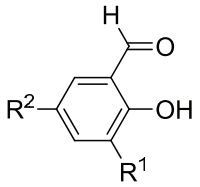
The preparation of all the achiral salen manganese(III) complexes was conducted according to the procedure developed by Jacobsen, Gao and co-workers[72] as described in Chapter 4.1.1.1. The salen ligands were obtained via the condensation of diamines **129** and salicylaldehydes **128** (2 equiv.) in EtOH. Reflux conditions were often employed to achieve full conversion in a short time. The salen ligands **130** would crystallize out when the reaction solution was cooled down to room temperature or stored in the freezer (-20 °C) overnight. The yellow crystals formed were collected by filtration and washed with cold EtOH. More crops of salen ligands could be obtained by concentrating the filtrate or by adding cold methanol. The metallation was carried out using excess $Mn(OAc)_2 \cdot 4H_2O$ (3.0 equiv.) as the metal source. The Mn-salen complexes **131** were purified by recrystallization from dichloromethane/hexanes (Scheme 4.8).



Scheme 4.8: General synthetic route for achiral Mn^{III}-salen complexes.

Synthesis of Substituted Salicylaldehydes:

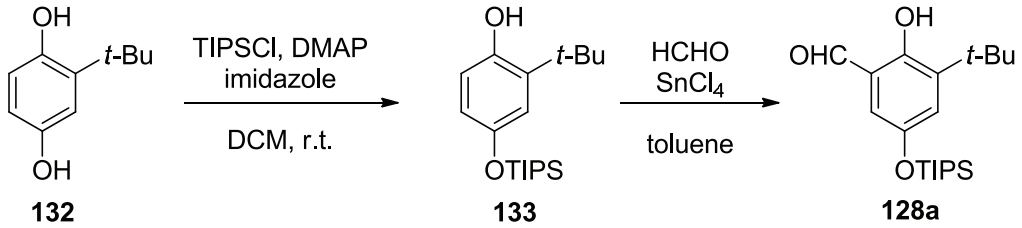
3-*tert*-Butylsalicylaldehyde **128c** and 5-*tert*-butylsalicylaldehyde **128g** were commercially available. Salicylaldehyde **128d** and **128e** were prepared by bromination[82] and nitration[83] of **128c**, respectively (Figure 4.5).



128a: R^1 = *t*-Bu, R^2 = OSi(*i*-Pr)$_3$
128b: R^1 = *t*-Bu, R^2 = OMe
128c: R^1 = *t*-Bu, R^2 = H
128d: R^1 = *t*-Bu, R^2 = Br
128e: R^1 = *t*-Bu, R^2 = NO_2
128f: R^1 = *t*-Bu, R^2 = CPh_3
128g: R^1 = H, R^2 = *t*-Bu

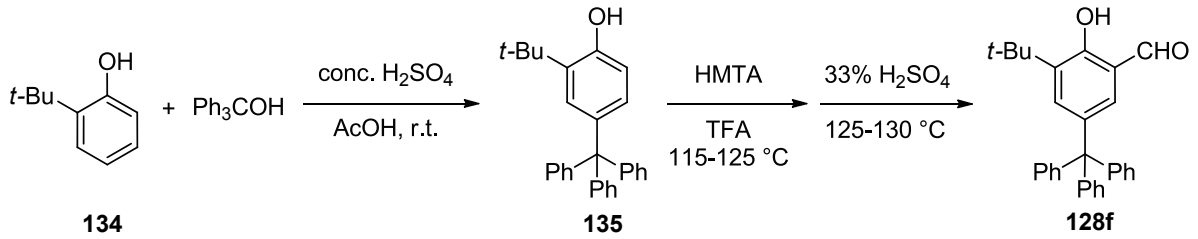
Figure 4.5: Salicylaldehydes used in the synthesis of salen ligands.

Synthesis of **128a** started with TIPS-protection of 2-*tert*-butylhydroquinone **132**, followed by formylation with paraformaldehyde and $SnCl_4$ (Scheme 4.9).[84]



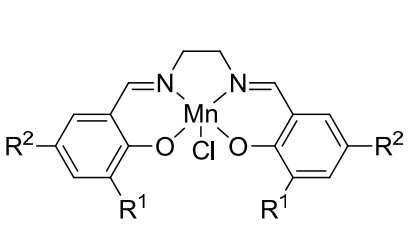
Scheme 4.9: Synthesis of 3-*tert*-butyl-5-triisopropylsilyloxysalicylaldehyde **128a**.

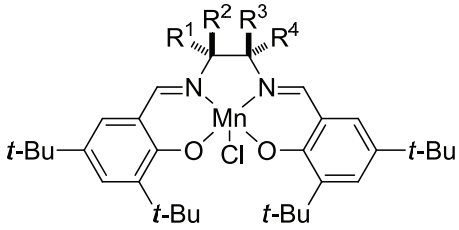
5-Methoxy-3-*tert*-butyl-salicylaldehyde **128b** was made by formylation of 2-*tert*-butyl-4-methoxyphenol with hexamethylenetetramine (HMTA) in acetic acid under reflux conditions.[72] 5-Triphenylmethyl-3-*tert*-butyl-salicylaldehyde **128f** was synthesized from 2-*tert*-butylphenol **134**. Triphenylmethylation was carried out with triphenylmethanol in acetic acid in the presence of conc. sulfuric acid.[85] The following formylation was performed in TFA with HMTA as the formylating agent (Scheme 4.10).



Scheme 4.10: Synthesis of 5-triphenylmethyl-3-*tert*-butyl-salicylaldehyde **128f**.

By combining salicylaldehydes **105** and **128a-g** with different diamines like 1,2-ethylenediamine, benzene-1,2-diamine and *cis*-cyclohexanediamine, various Mn-salen complexes **131a-k** with different electronic and steric properties were prepared. The corresponding cations resulted from the removal of Cl^- are designated as **131x**$^-$ like **131a**$^-$ (Figure 4.6).





108: R^1 = *t*-Bu, R^2 = *t*-Bu
131a: R^1 = *t*-Bu, R^2 = OSi(*i*-Pr)$_3$
131b: R^1 = *t*-Bu, R^2 = OMe
131c: R^1 = *t*-Bu, R^2 = H
131d: R^1 = *t*-Bu, R^2 = Br
131e: R^1 = *t*-Bu, R^2 = NO_2
131f: R^1 = *t*-Bu, R^2 = CPh_3
131g: R^1 = H, R^2 = *t*-Bu

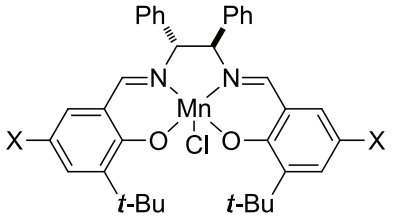
131h: R^1, R^2= Me, R^3, R^4= H
131i: R^1, R^2, R^3, R^4= Me
131j: R^1, R^4= H, R^2, R^3= $(CH_2)_4$
131k: R^1, R^2, R^3, R^4= 

Figure 4.6: Achiral Mn-salen complexes prepared for the cation screening.

4.1.2.2.2 Screening of Achiral Mn-salen Cations

Influence of 5-Substituents

In 1991, Jacobsen and co-workers reported their investigation on the electronic tuning of Mn-salen catalysts for the asymmetric epoxidation of alkenes.[86] Using catalysts **136a-e** for the asymmetric epoxidation of three *cis*-alkenes (2,2-dimethylchromene, *cis*-β-methylstyrene, and *cis*-2,2-dimethyl-3-hexene), they obtained a correlation between the ee's and the substituent constants (σ_p) of the 5,5'-substituents. In the case of 2,2-dimethylchromene, the enantioselectivity varied from 22% ee with **136e** (X = NO_2) to 96% ee with **136a** (X = OMe). This dramatic change in enantioselectivity by manipulation of the electronic structure of the catalyst is highly impressive. The results were rationalized by the 5,5'-substituents altering the reactivity of the O=Mn(salen)+ species, which were supposed to be responsible for the oxo transfer to the alkene. The milder oxidant formed from **136a** (X = OMe) will have a more product-like transition state (TS), while the more reactive oxidant formed from **136e** (X = NO_2) will have a more reactant-like transition state. A more product-like transition state should involve more specific nonbonded interactions between the substrate and the oxidant, thus giving a higher selectivity. With oxo transfer as the irreversible ee-determining step in a purely bimolecular process (i.e., no substrate precoordination), the more reactant-like ee-determining transition state with greater separation between substrate and catalyst would result in concomitantly poorer steric differentiation of diastereomeric transition structures.[86]



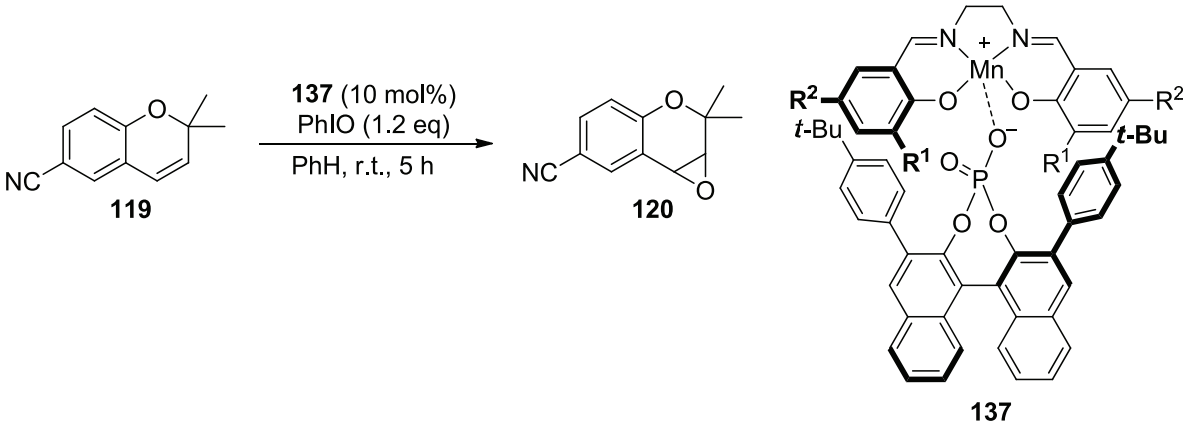
136

136a: X = OMe
136b: X = Me
136c: X = H
136d: X = Cl
136e: X =NO_2

Figure 4.7: Electronic tuning of Mn-salen catalysts for the asymmetric epoxidation of alkenes.

To examine the effect of the 5,5'-substituents of the salen ligands in our ion-pair catalyst system, a series of Mn-salen complexes **131a-e** with different electron-donating groups or electron-withdrawing groups were synthesized. Since chiral phosphate anion **121j**$^-$ stood out as the best chiral phosphate, these Mn-salen cations were investigated in combination with this anion under the same reaction conditions. The results of the electronic tuning of the Mn–salen complexes revealed that the observed enantioselectivity depends not only on the electronic nature of the substituent but also on its size (Table 4.3). It had been shown earlier that Jacobsen catalysts give higher enantioselectivities with electron-donating substitutents, but this trend was not observed in our system. For example, the methoxy-substituted catalyst **131b**$^+$**/121j**$^-$ gave lower enantioselectivity than the bromine-substituted complex **131d**$^+$**/121j**$^-$ (entries 2 and 5, Table 4.3). In our cases, because the catalysts are ion pairs, electron-donating groups may make the Mn-salen cationic center less positive, thus decreasing the cation/anion interaction and leading to a loose ion pair. Considering that the Mn-salen cations without a 3,3'-substituents may form a tighter ion pair, catalyst **131g**$^+$**/121j**$^-$ without *tert*-butyl groups at 3,3'-position were prepared and tested, but a sharp drop in selectivity was observed (from 95:5 er to 57:43 er). Ion pair **131a**$^+$**/121j**$^-$ and **131b**$^+$**/121j**$^-$ may indicate that the substitutent size should also play an important role. However, when replacing the *tert*-butyl group with a more bulky group (Ph_3C), no improvement on the eantioselectivity was observed (entry 7).

Table 4.3: Electronic and steric tuning of ion-pair catalysts



Entry	R^1	R^2	Catalyst	Conv.[a]	e.r.
1	*t*-Bu	OSi(*i*-Pr)$_3$	**131a$^+$/121j$^-$**	90%	82:18
2	*t*-Bu	OMe	**131b$^+$/121j$^-$**	>99%	68:32
3	*t*-Bu	*t*-Bu	**108$^+$/121j$^-$**	>99%	95:5
4	*t*-Bu	H	**131c$^+$/121j$^-$**	>99%	83:17
5	*t*-Bu	Br	**131d$^+$/121j$^-$**	>99%	82:18
6	*t*-Bu	NO_2	**131e$^+$/121j$^-$**	>99%	72:28
7	*t*-Bu	CPh_3	**131f$^+$/121j$^-$**	>99%	93:7
8	H	*t*-Bu	**131g$^+$/121j$^-$**	>99%	57:43

[a] Determined by GCMS.

Influence of the Diimine Bridge

According to the original design of the ion-pair catalyst, the diimine linker should exert an important influence on the conformation of the catalyst. At first, the diimine bridge will affect the degree of the stepped conformation of the Mn-salen structure, like the chiral 1,2-diphenylethylenediamine and *trans* 1,2-cyclohexanediamine-derived Mn-salen complexes. Another aspect which is more special in our case is that the steric properties of the bridge will change the interaction between the cation and anion moiety, leading to a different ion-pair conformation or a different distance between the cation and anion. To check the influence of the diimine bridge, several salen ligands with a variation at the diimine moiety were prepared and tested. The results are displayed in Figure 4.8, and the conversion and er's are given in parentheses. As shown in the figure, the cations with a sterically hindered bridge like tetramethyl (**131h$^+$**) or planar phenyl (**131i$^+$**), gave much lower selectivity, and in the case of phenyl diimine bridge the sense of selectivity was reversed. Further comparing with other

linkers like *cis* cyclohexane (**131j**$^+$) or geminal dimethyl (**131k**$^+$), ethylenediimine proved to be optimal. Although the ethylenediimine bridge lacks other steric elements, but successfully maintains the required space around the linker for the extension of the 3,3'-substitutents of the chiral phosphate anion. On the other hand, less sterically hindered linkers can avoid steric repulsion between the cation and anion and bring them together, leading to a tighter ion-pair catalyst.

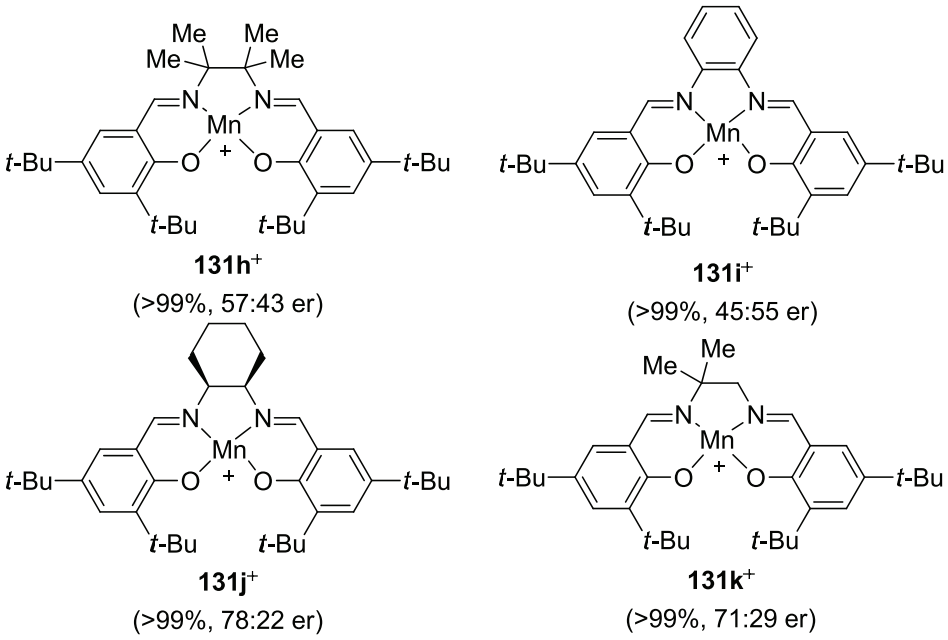


Figure 4.8: The influence of the diamine bridge.

4.1.2.3 Further Optimization of the Phosphate Anion

As the chiral phosphate anion **121j**$^-$ and ethylenediamine-derived Mn-salen cation **108**$^+$ proved optimal so far, we decided to elaborate the chiral phosphate structure, in the hope of further improving the enantioselectivity.

Considering the importance of the bulky *para* substituent and the properties of ion-pair catalysts, there are two approaches to conduct the modification. One is to introduce an acetylene linker between the bulky aryl group and the BINOL scaffold (**A**, Figure 4.9); this smaller linker may decrease the steric repulsion between the cation and the anion, leading to a tighter ion-pair complex. The other approach is to install a bulkier group than *tert*-butyl at the *para* position. Silyl groups were chosen for this variation, considering the ease of manipulation of the silyl substituent and their wide availability (**B**, Figure 4.9).

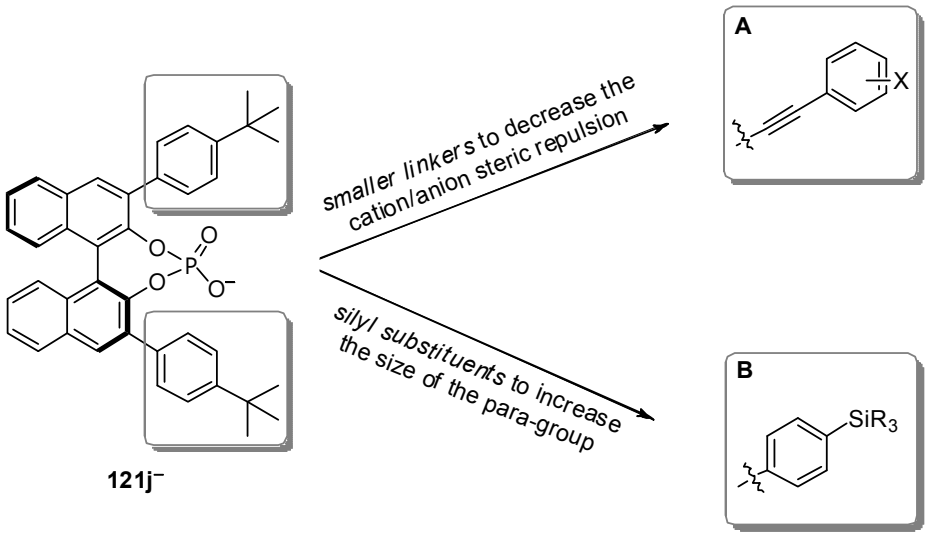
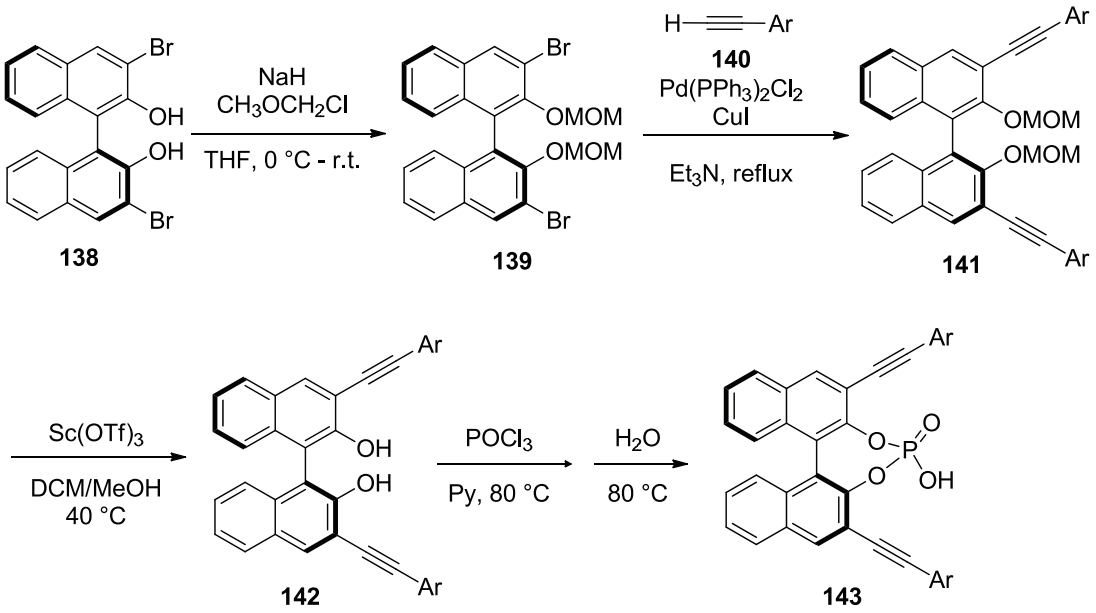


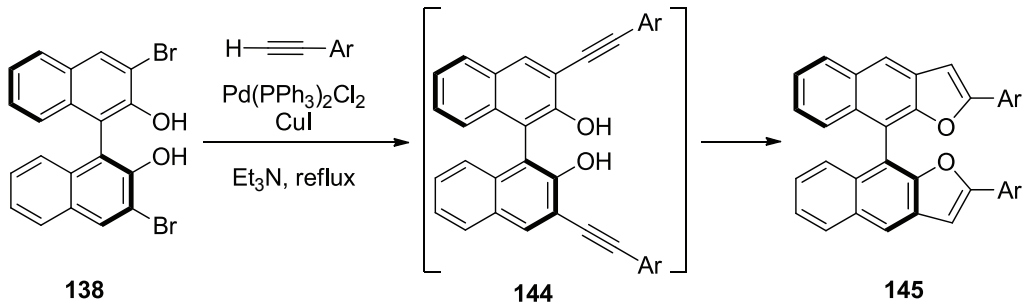
Figure 4.9: The logic of the design of new phosphate anions.

4.1.2.3.1 Preparation of 3,3'-Diarylacetylene-Substituted Phosphoric Acids



Scheme 4.11: Synthesis of of 3,3'-arylacetylene-substituted phosphoric acids.

The key step in the synthesis is the Sonogashira cross-coupling of 3,3'-dibromo MOM-protected BINOL **139** and the corresponding arylacetylenes **140** (Scheme 4.11). The direct cross coupling of 3,3'-dibromobinol **138** with arylacetylenes caused a further intramelcular aryloxylation product **145** after the coupling step and resulted in a low yield of the desired products **142** (Scheme 4.12).

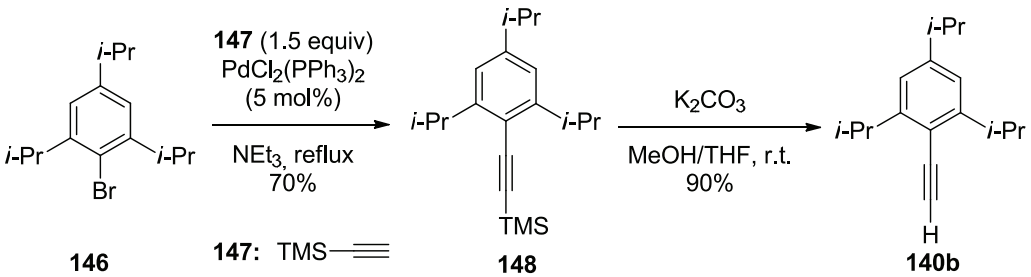


Scheme 4.12: The direct Sonogashira coupling of 3,3'-dibromobinol.

The MOM-protected 3,3'-dibromobinol (**139**, Scheme 4.11) was prepared according to the known procedure,[87] using a slight excess of chlorodimethylether. In the Sonogashira cross-coupling step, reaction conditions described by Zimmer et al. and Ishihara et al. were followed with minor modifications.[88] The reactions were carried out in degassed triethylamine, using $PdCl_2(PPh_3)_2$/CuI as the catalyst and four equivalents of arylacetylene **140**. The coupling products **141** were obtained in good yields (>80%) after purification by column chromatography.

The MOM-deprotection was performed in a solvent mixture THF/MeOH (1:1) with $Sc(OTf)_3$ as the catalyst (Scheme 4.11).[88b] Phosphorylation of the diols **142** was achieved using phosphoryl chloride in pyridine at an elevated temperature (70-80 °C). Finally, hydrolysis followed by treatment with hydrochloric acid (10 %) afforded the phosphoric acids **143** as a pale yellow solid in reasonable yields (64-87%).

The mesitylacetylene **140a** and *para-tert*-butylphenylacetylene **140b** were commercially available. 2,4,6-Triisopropylphenylacetylene **140b** required for the cross-coupling was prepared from the corresponding arylbromide **146** via Sonogashira cross-coupling[89] with trimethylsilylacetylene **147** followed by the base-mediated desilylation.[88b] Three or more equivalents of **147** were necessary to achieve a good yield, because of the homocoupling of **147**. Later, we found that 70% yield of 1-(2,4,6-triisopropylphenyl)-2-trimethylsilylacetylene **148** could be obtained in the absence of CuI and with only 1.5 equivalents of trimethylsilylacetylene (Scheme 4.13).



Scheme 4.13: Synthesis of 2,4,6-triisopropylphenylacetylene.

According to the procedures described above, three different phosphoric acids **143a-c** were prepared (Figure 4.10).

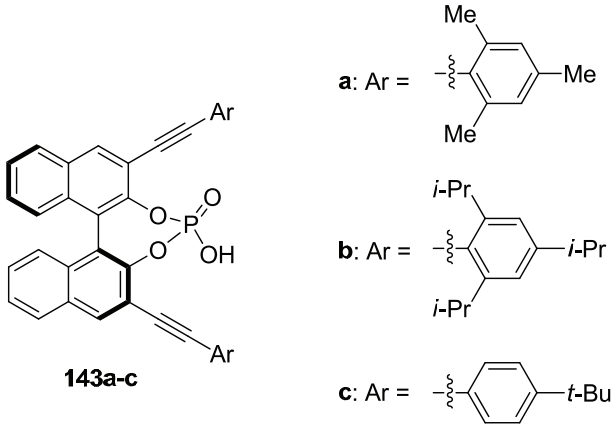
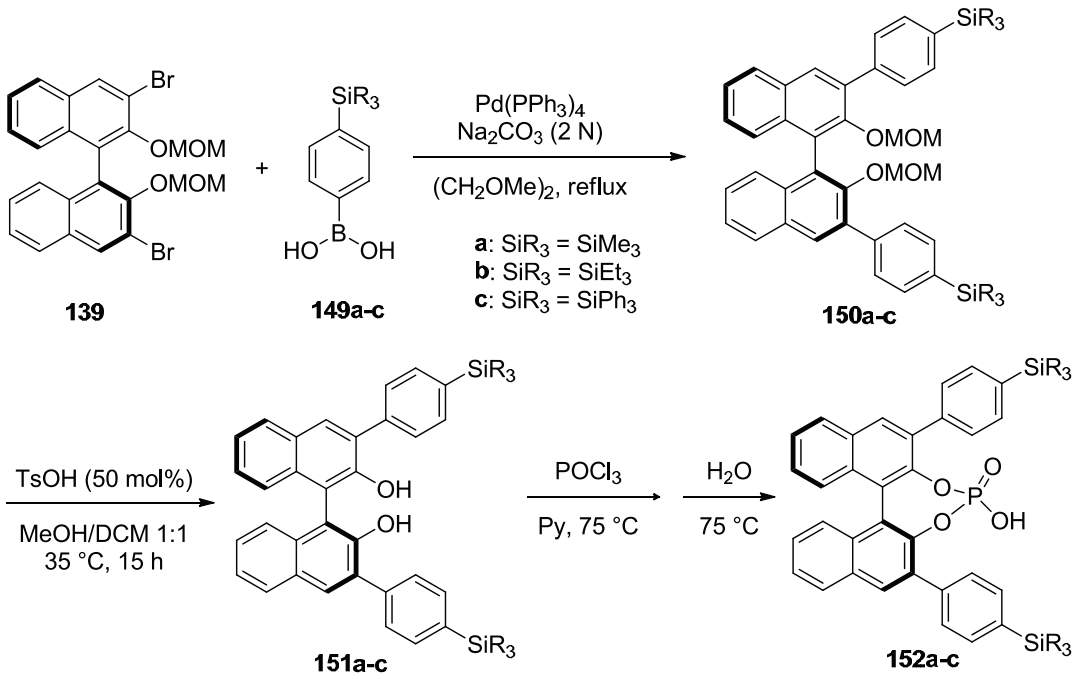


Figure 4.10: 3,3'-Arylacetylene-substituted phosphoric acids **143**.

4.1.2.3.2 Preparation of 3,3'-Bis(4-Silylphenyl)-Substituted Phosphoric Acids

MOM-protected 3,3'-dibromobinol **139** was chosen as the starting material for the synthesis of this type of phosphoric acid. Using methyl protected 3,3'-dibromobinol caused some problems in the deprotection step. The deprotection of methyl group with BBr_3 gave a dirty reaction and desilylated side products were observed. Deprotection[90] with NaSEt did furnish the deprotection product in good yields, but the reaction conditions of heating in DMF (~100 °C and basic) led to some extent of racemization.



Scheme 4.14: Synthesis of of silyl-substituted phosphoric acids **152**.

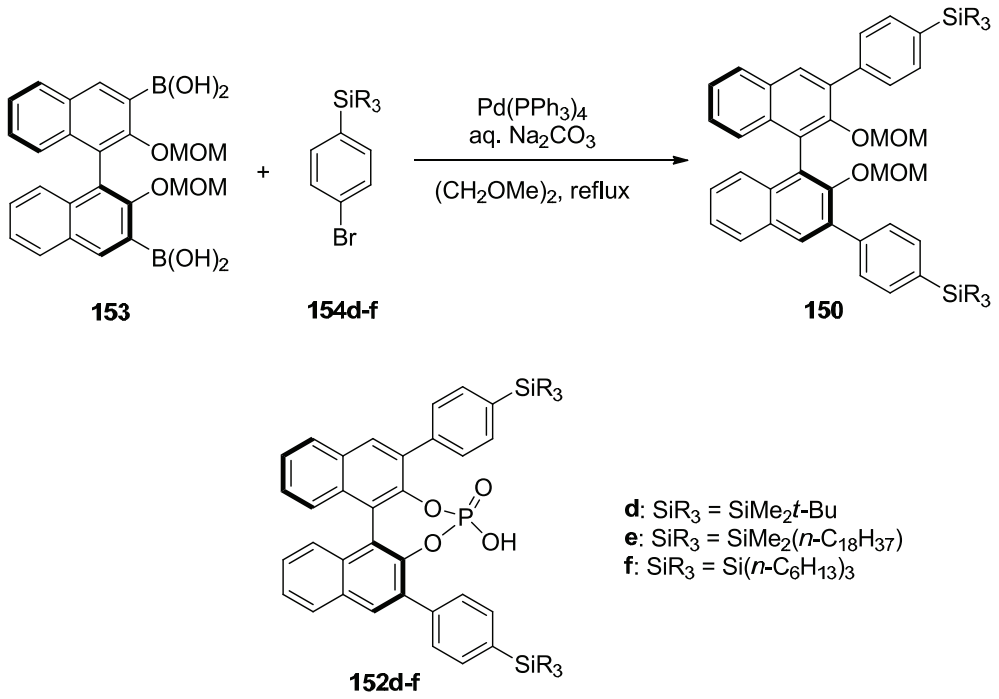
The Suzuki coupling was performed under standard reaction conditions:[91] a degassed solution of MOM-protected BINOL **139** (1.0 equiv.), $Pd(PPh_3)_4$ (0.1 equiv.), arylboronic acids **149a-c** (3.0 equiv.) and aq. Na_2CO_3 (5 equiv.) in DME was heated to reflux until no further conversion. Purification by flash column chromatography gave the products **150a-c** as a white fluffy solid generally in high yields (81-95%).

The deprotection was performed with TsOH monohydrate (0.5 equiv.) in DCM/MeOH (1:1) at 35-40 °C.[92] The reactions were clean, and the free diols **151a-c** were obtained generally in quantitative yields.

The following phosphorylation and hydrolysis were carried out under the same reaction conditions as described in Chapter 4.1.1.2. Free diols **151a-c** were dissolved in pyridine [0.2-0.5 M], and then 2 equivalents of $POCl_3$ were added in two portions. The resulting mixture was stirred at 75 °C until the TLC showed the disappearance of the starting material. Distilled water was then added with caution, and the solution was stirred for additional several hours at the same temperature. After the hydrolysis of the phosphoryl chloride had finished, the reaction mixture was diluted with dichloromethane, treated with 10 % HCl, washed with brine, and dried over anhydrous sodium sulfate. Purification by column chromatography and acidification with 6N HCl afforded the desired phosphoric acids **152a-c**.

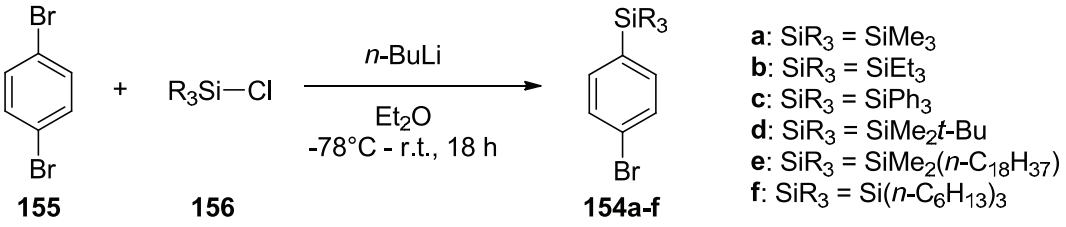
Later on, a more concise of synthetic route was developed involving a Suzuki cross-coupling of MOM-protected bisboronic acid **153** with the silyl substituted bromobenzenes **154d-f**. In these cases, bromobenzenes **154** were directly used and the conversion of each bromobenzene

to corresponding boronic acids was avoided. The following deprotection, phosphorylation and hydrolysis steps were performed according to the same protocols as described above. Phosphoric acids **152d-f** were prepared via this synthetic route (Scheme 4.15).



Scheme 4.15: Suzuki cross-coupling of bisboronic acid **153** with 4-silylbromobenzenes.

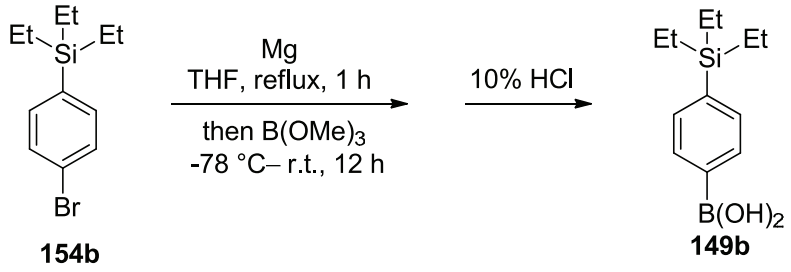
4-Silylbromobenzenes **154** were prepared according to the literature procedures,[93] starting with 1,4-dibromobenzene **155**. Halide-lithium exchange in a cold (-78°C) solution of abs. ether with *n*-BuLi and the subsequent treatment with the corresponding silylchloride **156** afforded the crude **154**. The pure compounds **154a-b, d-f** were obtained as an oil by bulb-to-bulb distillation under reduced pressure.



Scheme 4.16: Synthesis of 4-silylbromobenzenes.

A literature procedure for the synthesis of mesitylboronic acid described by Wipf and Jung[74] was followed to prepare 4-triethylsilylbenzeneboronic acid **149b**. The Grignard reagent was prepared from 4-triethylsilylbromobenzene **154b**, which was later treated with 1.5 equivalents of trimethylborate at -78 °C. The reaction was warmed up to room temperature and quenched

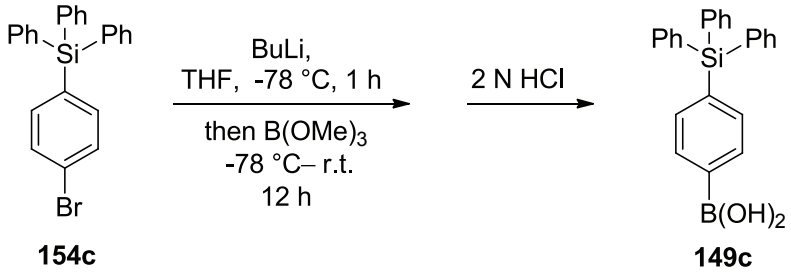
with 10% HCl after eight hours. Purification by column on silica gel gave the product **149b** in 74% yield



154b **149b**

Scheme 4.17: Synthesis of 4-triethylsilylbenzeneboronic acid.

4-Triphenylbenzeneboronic acid **149c** was prepared via the halide-lithium exchange and subsequent treatment with trimethylborate.[93b] Purification by flash column chromatography on silica gel afforded the product as a white powder in 17% yield. Some product was lost during the extraction, due to the poor solubility of the product in ethyl acetate.



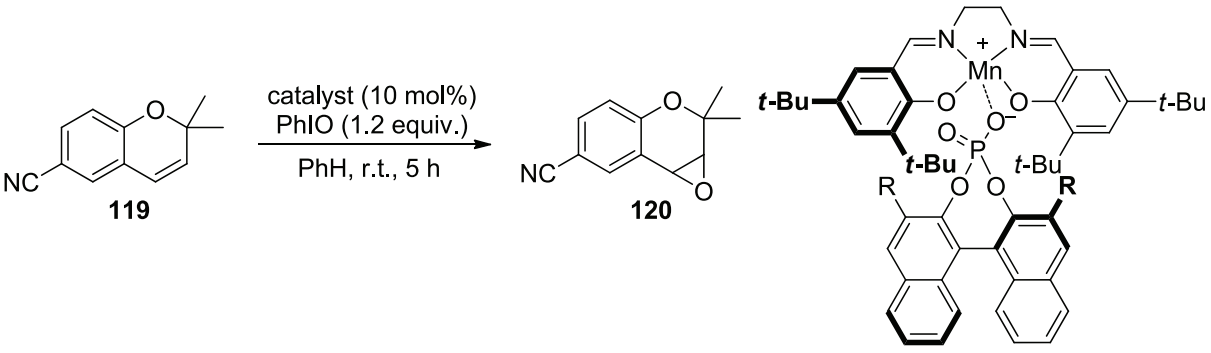
154c **149c**

Scheme 4.18: Synthesis of 4-triphenylbenzeneboronic acid.

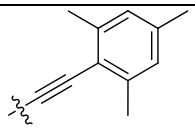
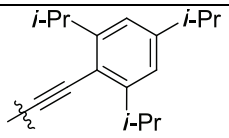
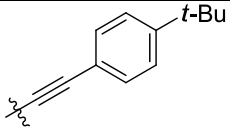
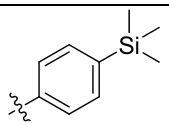
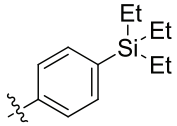
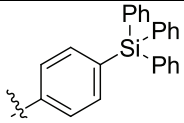
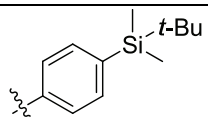
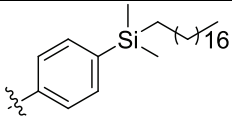
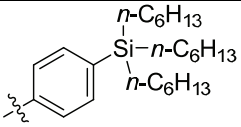
4.1.2.3.3 Screening of the New Phosphate Counteranions

The corresponding ion-pair catalysts **108$^+$/143a-c$^-$** and **108$^+$/152a-f$^-$** derived from these two new types of phosphoric acids (**143a-c** & **152a-f**) were prepared and investigated in the model epoxidation reaction. The results are tabulated in Table 4.4. The three 3,3'-arylacetylene substituted phosphate anions **143a-c$^-$** gave similar enantioselectivities (entries 1-3), which seem to be independent on the size and substituents of the aryl groups. This phenomenon may indicate that the aryl groups linked by acetylene are not placed in the right position or the aryl groups are far away from the metal center, thus exerting little effect on the stereochemical control.

Table 4.4: Screening of new chiral phosphate anions



catalyst: **108$^+$/143a-c$^-$** or **152a-f$^-$**

Entry	R	Catalyst	Conv.*	er
1		**108$^+$/143a$^-$**	>99%	61:39
2		**108$^+$/143b$^-$**	>99%	65:35
3		**108$^+$/143c$^-$**	>99%	65:35
4		**108$^+$/152a$^-$**	>99%	95:5
5		**108$^+$/152b$^-$**	>99%	91:9
6		**108$^+$/152c$^-$**	>99%	88:12
7		**108$^+$/152d$^-$**	>99%	93:7
8		**108$^+$/152e$^-$**	>99%	92.5:7.5
9		**108$^+$/152f$^-$**	>99%	88:12

* Determined by GC-MS.

A trend can be found among the enantioselectivities obtained with 3,3'-silylphenyl substituted phosphate anions (entries 4-9). The selectivity declined as the size of the silyl groups increased. Trimethylsilyl (TMS) group gave the same er as *tert*-butyl group (entry 4). When we introduced a bigger group like TES (entry 5), TBS (entry 7), unfortunately the selectivities were not improved. The TMS or *tert*-butyl group seems to be optimal. Change from TMS group to TPS group also resulted in a drop in enantioselectivity (entry 4 vs entry 6). The relatively high level of enantioselectivity obtained with these silyl-substituted phosphate anions **152a-f**$^-$ demonstrated that a shape of the 3,3'-substitutents of the phosphate anion resembling 4-*tert*-butylphenyl group is beneficial to the stereoselectivity. Although the phosphate anion **152a**$^-$ with a TMS group gave the same results as the anion **121j**$^-$ with a *tert*-butyl group, the acid **121j** is much easier to prepare and the corresponding ion-pair catalyst **108**$^+$/**121j**$^-$ was chosen as the catalyst for our further investigation.

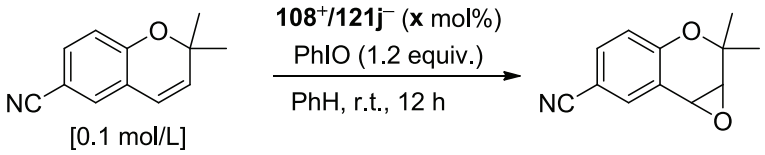
4.1.3 Further Optimization of Reaction Conditions

The influence of the solvent, temperature, catalyst loading, concentration, oxidants and additives was examined in the model epoxidation reaction of 6-cyano-2,2-dimethylchromene (**19**) with cation **108**$^{+}$/anion **121j**$^{-}$ combination as the catalyst.

4.1.3.1 Catalyst Loading

The catalyst loading was checked first to see the efficiency of the ion-pair catalysts. If the catalyst loading could be decreased, more catalyst can be saved during the course of further reaction condition optimizations.

Table 4.5: Influence of catalyst loading



Entry	Catalyst Loading	Conv.*	e.r.
1	20 mol%	>95%	95.2:4.8
2	10 mol%	>95%	95.4:4.6
3	5 mol%	>95%	95.2:4.8
4	2 mol%	~90%	94.9:5.1

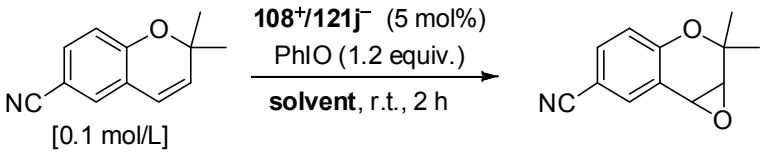
* Determined by TLC.

From Table 4.5, we can see that when lowering the catalyst loading from 20 mol% to 2 mol%, the enantiomeric ratios were only slightly decreased. Considering the reaction time, a 5 mol% catalyst loading was employed for the solvent screening in the next step. In fact, at this catalyst loading, with 1.2 equivalents of freshly prepared PhIO as the oxidant, full conversion can be achieved in less than 2 hours, whereas 12 hours or longer was required to get full conversion with a 2 mol% catalyst loading (entry 4).

4.1.3.2 Solvent Influence

Nonpolar aprotic solvent like pentane, benzene, toluene were first checked in the asymmetric epoxidation. As shown in Table 4.6, the reaction in pentane was less selective (entry 1); benzene, flurobenzene and chlorobenzene gave similar results (entries 2-4). When toluene or xylene was used as the solvent, low conversion and selectivity were observed (entries 5-6). The reason was supposed to be the competing benzyl oxidation of the solvent molecules. When toluene was used as solvent, the generation of benzyl alcohol and benzaldehyde was confirmed by GCMS analysis. Oxidant was partially consumed by the benzyl oxidation of the solvent. Furthermore, the benzyl alcohol generated can also intervene with the catalyst, thus exerting a deleterious effect on the enantioselectivity. This can be seen in entry 14, where much lower enantioselectivity was observed when EtOH was used as the solvent. The reactions in ether and THF were much slower (entries 7 and 10); presumably, the solvent molecules can compete with the oxidant PhIO for coordination with the catalyst, thus diminishing the efficiency of Mn=O formation. Less coordinating solvents like esters and acetone afforded full conversion and moderate selectivities (entries 8-9 and 12). Dichloromethane and acetonitrile exhibited a significant detrimental effect on the stereoselectivity (entries 11 and 13). Benzene is optimal for the reaction at room temperature with respect to both the yield and enantioselectivity. The reaction in benzene was very clean, and the epoxidation product can generally be isolated in nearly quantitative yields. Other benzene derivatives like fluorobenzene provided a chance to further increase the selectivity by lowering the temperature.

Table 4.6: The solvent influence on the asymmetric epoxidation



Entry	Solvent	Conv.*	er
01	pentane	~90%	85:15
02	PhF	>95%	94:6
03	PhCl	>95%	94:6
04	benzene	>95%	**95:5**
05	p-xylene	~35%	75:25
06	toluene	~70%	81:19
07	Et_2O	~30%	86.5:13.5
08	EtOAc	>95%	**90.5:9.5**

09	C_2H_5COOEt	>95%	86:14
10	THF	~20%	90:10
11	DCM	~75%	70.5:29.5
12	acetone	>95%	**92:8**
13	CH_3CN	>95%	77:23
14	EtOH	~80%	70.5:29.5

* Determined by TLC or GCMS

4.1.3.3 Temperature Effects

Although benzene provided the best results during the solvent screening, it is difficult to carry out the reaction in benzene at a lower temperature like 0 °C or even lower. Thus, to check the temperature effect, other solvents like fluorobenzene and acetone were also examined. The enantioselectivities (ee) were plotted against the temperature as shown in Figure 4.11. It is unusual that lowering the temperature or raising the temperature all led to an eroded enantioselectivity. When benzene was used as the solvent, 86% ee was obtained at 40 °C with ca. 4% loss of the selectivity, comparing to 90% ee obtained at 10 °C or room temperature (~25 °C). When the reaction in fluorobenzene was cooled down, the ee decreased gradually as the temperature was lowered down (81% ee at 0 °C and 73% ee at -20 °C).

The non-linear relationship between the temperature and enantioselectivity has also been observed by Katsuki and co-workers in the asymmetric epoxidation of dihydronaphthalene, 1,3-cyclooctadiene, *p*-nitrostyrene, and styrene.[94] In these cases a maximum enantioselectivity was observed at a specific temperature. Pericàs[95]and Pozzi[82;96] also found ee's were improved by increasing temperature. The non-linear effect can be attributed to the existence of multiple oxidation pathways or several different active oxidative species. In our case, there is another possible reason that due to non- or weak coordination of the phosphate anion to the salen-Mn cation, the rotation of anion around the Mn^+---O^- axial may lead to several different conformational isomers of the ion-pair catalyst. These conformers were supposed to be of different selectivity, and their contributions to the observed enantioselectivity may vary with the reaction temperature.

An exception was toluene; when lowering the temperature, an improvement of enantioselectivity was observed (80% ee at -78 °C vs 60% ee at r.t.). However, this is a special case, and could be largely attributed to the suppression of the benzyl oxidation process at a lower temperature.

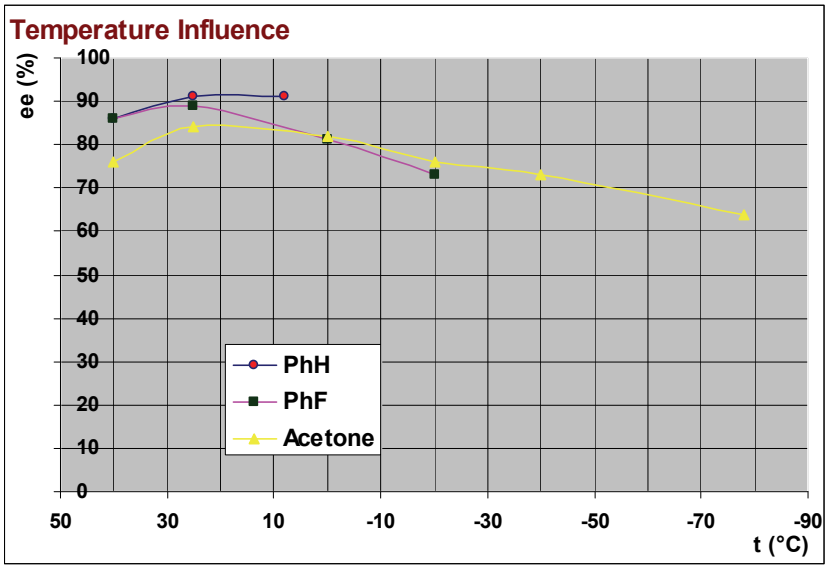
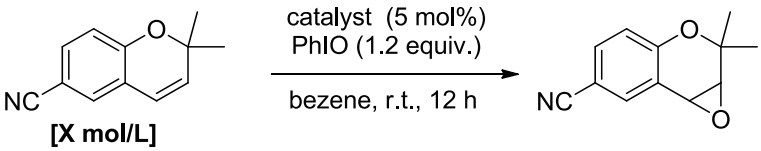


Figure 4.11: The influence of temperature.

4.1.3.4 Influence of Concentration

The concentration of the substrate was varid in the range of 0.025~1.0 mol/L. There is a trend that the enantioselectivity was slightly improved in dilute solution (entry 5). However, the reaction became slower upon diluting the solution. From a practical point of view, further decreasing of the concentration was not performed.

Table 4.7: The influence of concentration



Entry	Concentration	Conv.	er
1	1.0 M	>95%	93:7
2	0.5 M	>95%	94:6
3	0.2 M	>95%	95:5
4	0.1 M	>95%	95:5
5	0.05 M	>95%	96.5:3.5
6	0.025 M	90%	96.5:3.5

Because the solubility of the oxidant PhIO generally is not good in benzene, it is possible that in a dilute medium the chance of interaction or reaction between the catalyst and oxidative species generated from the catalyst like $O=Mn^{+}$ was reduced, which was reported to be the reason that causes the decomposition of the Mn-salen catalysts (via a μ-oxo-dimer: Mn-O-Mn)[57].

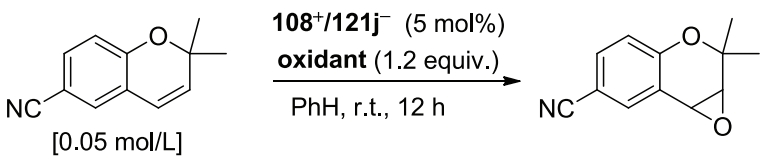
4.1.3.5 The Choice of the Oxidants

PhIO (iodosobenzene) and aq. NaOCl (bleach) were the two major oxidants employed in Jacobsen-Katsuki epoxidations. Because the reactions using PhIO as oxidant are generally carried out in organic solvents, conditions which are more compatible with our ion-pair catalysts, PhIO was first chosen as the oxidant for our investigation.

Although in most cases, the Jacobsen-Katsuki epoxidation is believed to proceed via an O=Mn intermediate in the enantio-determining step, yields and selectivity have previously been shown to be oxidant dependent. Collman and co-workers have found that when they changed the oxidant (PhIO, C_6F_6IO, MesIO), both the cis/trans ratios of *cis*-stilbene epoxidation product and enantioselectivitis of styrene varied,[68] though the coordination of the oxidant (ArIO) as an apical ligand cannot be excluded.

As shown in Table 4.8, in our ion-pair system, MesIO gave the same results as PhIO (entries 1-2). The diacetate of PhIO (entry 3) provided full conversion but the selectivity was lower (86:14 er). Although in this case the same oxidative species like $O=Mn^{V}$ may be formed as in the case of PhIO, the achiral acetate anion (AcO^{-}) may exert a detrimental effect by replacing the chiral phosphate counteranion. Hydrogen peroxide-type oxidants were not a good choice for our system, and only trace amount of the desired product was detected with Ph_3COOH or HOOH (entries 5 and 8). In the case of TBHP, 20% conversion was observed and the sense of selectivity was reversed, indicating a different transition state or oxidative intermediate (entry 6). m-CPBA has been used in the low temperature epoxidation in combination of 5.0 equivalents of NMO as the additive and base.[97] Here, a reversal of the enantioselectivity was also observed and the background reaction was difficult to suppress at room temperature.

Table 4.8: Asymmetric epoxidation with different oxidants



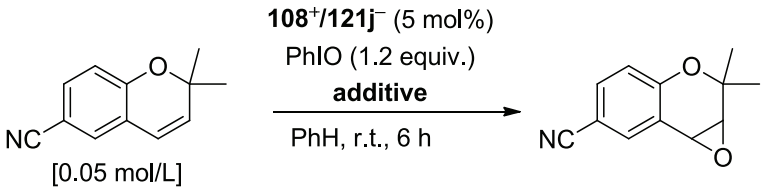
Entry	Oxidant	Conv.*	er
1	PhIO	>95%	96.5:3.5
2	MesIO	>95%	96:4
3	$PhI(OAc)_2$	>95%	86:14
4	$PhIO_2$	<5%	n.d.
5	Ph_3COOH	<5%	n.d.
6	*t*-BuOOH	~20%	27:73
7	*m*-CPBA	~70%	44:46
8	HOOH (30%)	<5%	n.d.

* Determined by TLC.

4.1.3.6 The Effect of Additives

As discussed in the background section, neutral donor ligands are commonly added to Jacobsen-Katsuki epoxidation reaction mixtures to increase the reactivity and enantioselectivity by displacing the apically coordinated anion of the Mn-salen complexes. In our system, the external donor ligand is not necessary, and the addition of other donor ligand may have a deleterious effect on the enantioselectivity by replacing the chiral phosphate anion. The additives of 4-MPNO (4-methoxypyridine *N*-oxide) and NMO were checked and the results are listed in Table 4.9. The influence of water was also investigated.

Table 4.9: The effect of additives



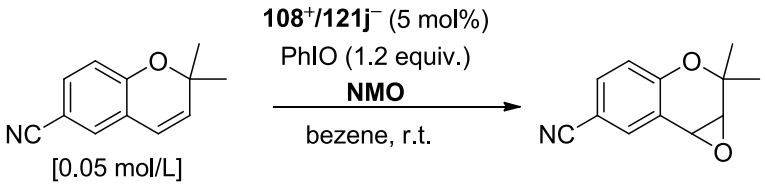
Entry	Additive	Amount	Conv.	er
1	4-MPNO	100 mol%	14%	56:44
2	NMO	100 mol%	11%	52:48
3	H_2O	100 mol%	90%	90:10
4	H_2O	100 eq.	88%	88.5:11.5

In the presence of extra donor liands like NMO, the catalyst was deactivated. In both cases of 4-MPNO and NMO, the conversion fell down to 11-14%, together with a significant

detrimental effect on the stereoselectivity (entry 1-2). The addition of water reduced the enantioselectivity (entry 3-4). The conversion was reasonable, but the decomposition of catalysts was observed by TLC in the presence of water.

The effect of NMO as the additive was investigated by varying its amounts. As shown in table 4.10, the addition of NMO did not accelerate the epoxidation but even retarded the reaction to some extent. The addition of 100 mol% of NMO brought the conversion down to 7% from 99%, and even when prolonging the reaction time to 80 h, only half of the substrate was epoxidized (entry 5). In a sharp contrast, without the additive the reaction completely finished in 3 hours (entry 6).

Table 4.10: The effect of addition of NMO on the conversion



Entry	Amount	Conversion			
		0.5 h	3 h	24 h	80 h
1	5 mol%	12%	72%	>99%	>99%
2	15 mol%	9%	47%	80%	98%
3	25 mol%	6%	29%	66%	94%
4	50 mol%	~3%	14%	66%	89%
5	100 mol%	~2%	7%	40%	51%
6	/	25%	>99%	>99%	>99%

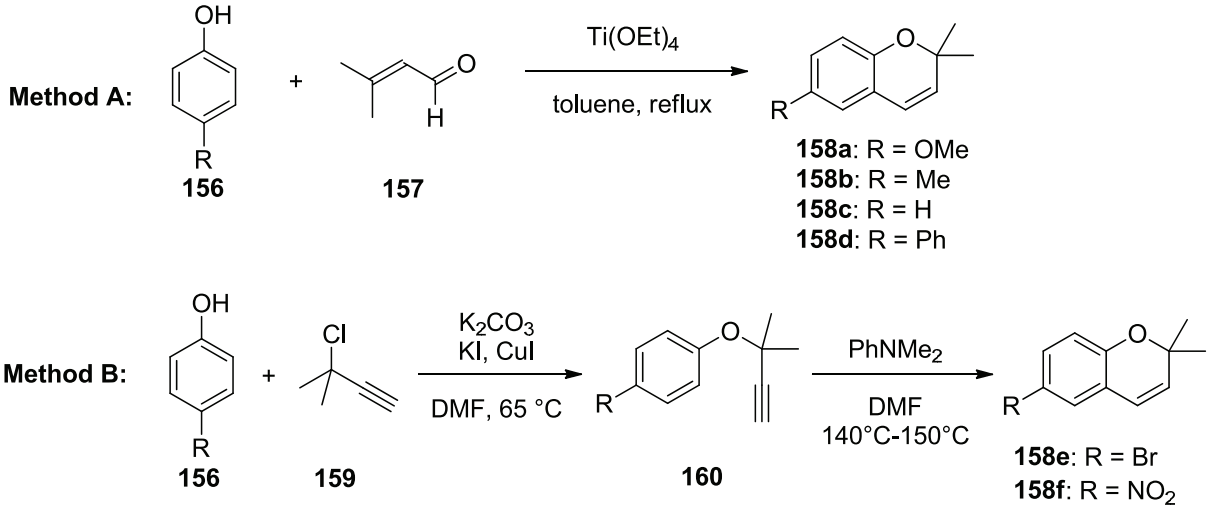
The significant effect of donor ligand on the reactivity reflected the stability and Lewis acidity of our ion-pair catalyst. The strong Lewis activity of our ion-pair catalyst may result from the weakened covalent character of the sterically overloaded (“frustrated”) manganese–phosphate ion pair. The extra donor ligand was supposed to coordinate to the Lewis acidic Mn center and prevent the approach of PhIO and thus impede the oxo-transfer from the oxidant to Mn to generate the active species.

4.1.4 Substrate Scope and Limitation

Based on the optimization of the catalysts, oxidants and other reaction parameters, the following protocol was used for the substrate scope evaluation: substrate (0.1 mmol), freshly prepared iodosobenzene (26 mg, 0.12 mmol), and catalyst **108**$^{+}$**/121j**$^{-}$ (0.005 mmol, 5 mol%), in benzene (2 mL). The epoxide products were purified by column chromatography. The optical purity was determined by HPLC or GC analysis.

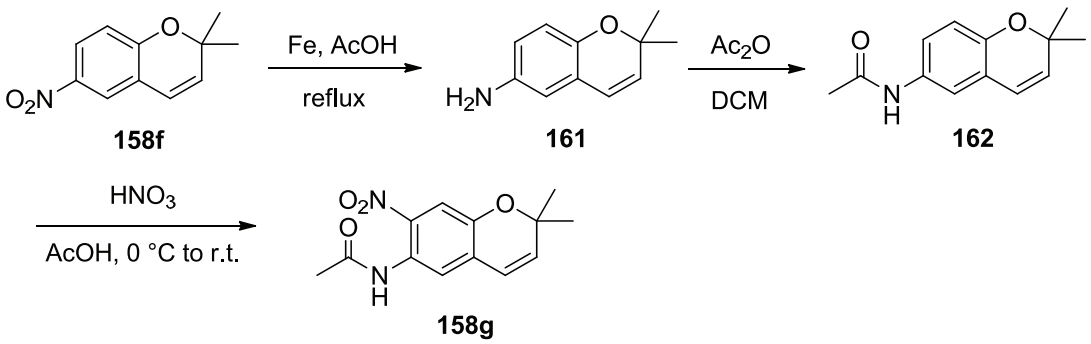
4.1.4.1 Synthesis of Alkene Substrates

While 6-cyano-2,2-dimethylchromene **19** was commercially available, the other chromene compounds **158a-e** were prepared via Method A or Method B (Scheme 4.19). For the electron rich phenols, Method A was preferred. Compounds (**158a-d**) were prepared via the condensation of the phenols **156** with 3-methylbut-2-enal **157** in the presence of titanium tetraethoxide as the catalyst. For the electron poor phenols, Method B generally provided better yields. The substitutition of the chloride of 3-chloro-3-methylbut-1-yne **159** with phenols gave the compounds **160**, which were then subject to the cyclization reaction. In the literature *N, N*-diethylaniline was used, but *N,N*-dimethylaniline was found to be more efficient, providing a clean reaction and quantitative yields in a shorter reaction time.



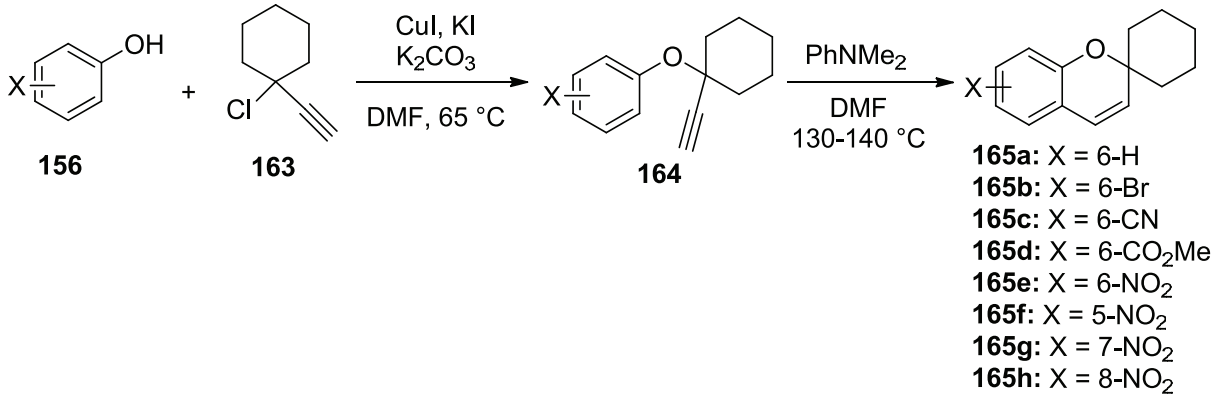
Scheme 4.19: Two methods for the synthesis of chromene substrates.

Chromene **158g** was prepared from **158f**, via reduction[98], acylation[98] and nitration[99] according to the known procedure (Scheme 4.20).



Scheme 4.20: Synthesis of chromene **158g**.

Spiro-chromenes **165a-h** was made according to Method B using 1-chloro-1-ethynylcyclohexane **163** instead of 3-chloro-3-methyl-1-butyne **159** (Scheme 4.21). The cyclization reactions were slower than **160**, due to the bulky cyclohexyl group. A prolonged reaction time or a slightly higher temperature can ensure good conversion. **165g** was isolated as a region-isomer in the preparation of **165f**, starting from 3-nitrophenol.



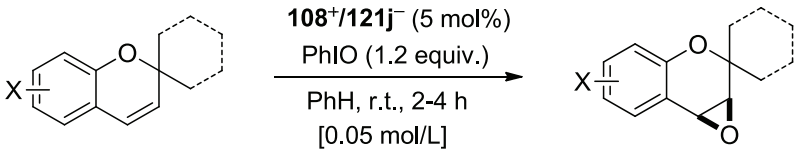
Scheme 4.21: Synthesis of spiro-chromenes **158g-i**.

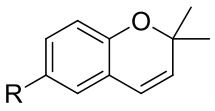
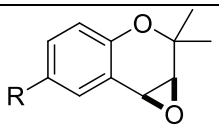
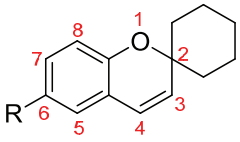
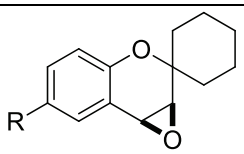
4.1.4.2 Reaction Scope

The chromene derivatives prepared were examined under the typical reaction conditions, and the results are given in Table 4.11. All of the chromene derivatives including relatively electron-rich (entries 1-3), electron-poor (entries 6-7), 5-substituted (entry 14), 7-substituted (entry 15) were epoxidized with a high level of enantioselectivity. The chromenes bearing electron-withdrawing groups like CN and NO_2 were slightly more favored in terms of enantioselectivity and yields (entries 6-7). The lower yields obtained with methoxy and

methyl-substituted chromenes were mainly caused by the epoxide to ketone Meinwald rearrangement. Usually around 10% of the ketone product was detected by GC-MS analysis

Table 4.11: Asymmetric epoxidation of chromenes



Entry	Chromene	Product	Yield[a]	er
				
1	**158a**: R = OMe	**166a**: R = OMe	83%	96:4
2	**158b**: R = Me	**166b**: R = Me	81%	95:5
3	**158c**: R = H	**166c**: R = H	82%	94:6
4	**158d**: R = Ph	**166d**: R = Ph	97%	95:5
5	**158e**: R = Br	**166e**: R = Br	88%	96:4
6	**19**: R = CN	**20**: R = CN	98%	97:3
7	**158f**: R = NO_2	**166f**: R = NO_2	98%	98:2
8	**158g**: R = 7-NO_2, 6-NHAc	**166g**: R = 7-NO_2, 6-NHAc	98%	95:5
				
9	**165a**: R = H	**167a**: R = H	93%	97:3
10	**165b**: R = Br	**167b**: R = Br	98%	97:3
11	**165c**: R = CN	**167c**: R = CN	99%	97:3
12	**165d**: R = COOMe	**167d**: R = COOMe	97%	97:3
13	**165e**: R = NO_2	**167e**: R = NO_2	99%	98:2
14	**165f**: R = 5-NO_2	**167f**: R = 5-NO_2	98%	95:5
15	**165g**: R = 7-NO_2	**167g**: R = 7-NO_2	98%	97:3
16	**165h**: R = 8-NO_2	**167h**: R = 8-NO_2	98%	n.d.[b]

[a] Isolated yields. [b] The two enantiomers can not be separated by HPLC.

in these cases. The epoxide to ketone rearrangement, as it is known, can be promoted by Lewis acids like $InCl_3$, $Cu(BF_4)_2$.[100] This side reaction indirectly indicated the Lewis acidity

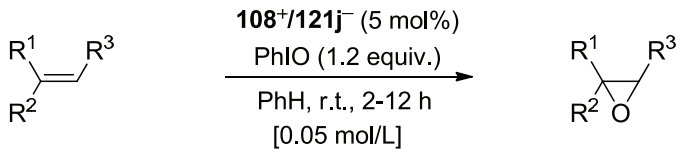
of the ion-pair catalysts. In the case of chromenes with an electron-withdrawing group, generally a clean reaction was observed together with high enantiomeric ratios and nearly quantitative yields.

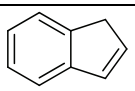
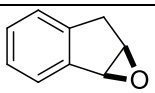
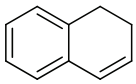
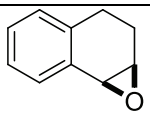
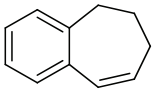
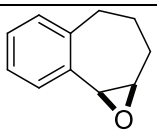
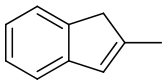
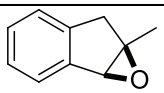
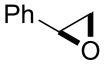
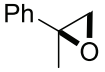
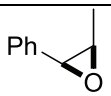
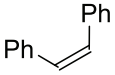
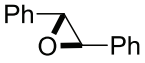
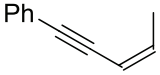
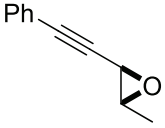
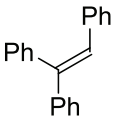
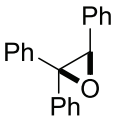
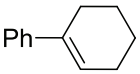
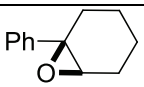
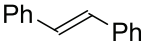
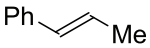
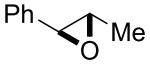
The absolute configuration of epoxide **20** was determined to be *S,S* when ion pair **108**$^{+}$/(*S*)-**121j**$^{-}$ was used, by comparison of the HPLC retention times and the optical rotation with literature values. The observed absolute configuration is consistent with our initial conformational analysis of the ion-pair catalyst. Accordingly, the *S*-configured phosphate **121j**$^{-}$ stabilizes one enantiomorphic conformation of the cationic Mn complex. This specific "absolute conformation" is apparently identical to that of the (*S,S*)-Jacobsen catalyst where it is induced from the chiral salen backbone. The configuration of other chromene epoxides was assigned by analogy.

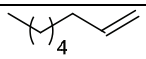
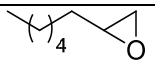
To investigate the substrate scope of the ion-pair catalyst, various cyclic, acyclic *cis*-alkenes like indene, styrene, enyls and *trans*-alkenes were also tested in our reaction system. The yields and er values are summarized in Table 4.12.

For the cyclic alkenes, as the ring size increases in the order of indene, 1,2-dihydronaphthanene and benzosuberene, the enantioselectivity declined from 90:10 er to 84:16 er (entries 1-3). 2-Methylindene gave a higher yield and enantioselectivity than indene (entry 4). For the terminal alkenes, styrene was oxidized with moderate selectivity while α-methylstyrene was oxidized with lower selectivity (entries 5-6). 1-Octene can also be epoxidized with our ion-pair catalyst, but both the yield and selectivity were low (entry 14). *Cis*-β-methylstyrene was transformed with much higher enantioselectivity than styrene (entry 7). Trisubstituted substrates (entries 4, 10 and 11) can also be oxidized with good enantioselectivity under this condition. The stereoselectivities for *trans* alkenes were much lower than *cis* alkenes. In the epoxidation of *trans*-β-methylstyrene, only 66:34 er was observed (entry 13).

Table 4.12: Asymmetric epoxidation of *cis*- and *trans*-alkenes



Entry	Alkene	Epoxide	Yield	er
1	**168a**: 	**169a**: 	53%	90:10
2	**168b**: 	**169b**: 	67%	85:15
3	**168c**: 	**169c**: 	71%	84:16
4	**168d**: 	**169d**: 	92%	92:8
5	**36**: 	**170**: 	80%	85:15
6	**171**: 	**172**: 	81%	68:32
7	**88**: 	**89**: 	81% (6:1)	94:6 (cis)
8	**102**: 	**95**: 	30%	80:20
9	**173**: 	**174**: 	97% (1:2)	96:4 (trans)
10	**175**: 	**176**: 	94%	84:16
11	**2**: 	**3**: 	90%	86:14
12	**94**: 	**95**: 	95%	55:45
13	**177**: 	**90**: 	90%	66:34

14	**178**: 	**179**: 	32%[a]	58:42

[a] Conversion determined by GCMS

From the above results, we found that the ion-pair catalyst prefers relatively electron-poor substrates (entries 7, 13-15, Table 4.11), comparing with the Jacobsen catalyst in terms of enantioselectivity and yield. At this point, we envisioned that cinnamate-type alkenes might be a favored type of substrates in our epoxidation system. It was known that the ester group of cinnamates plays an important role in the stereochemical control,[61] so the corresponding methyl, ethyl, and isopropyl cinnamates were prepared and tested. The asymmetric epoxidation results were summerized in Figure 4.12, and the ee's in the parentheses are that reported with the Jacobsen catalyst.[61] As expected, excellent enantioselectivities were obtained, and in all cases, the enantioselectivity was slightly better than the Jacobsen catalyst. The er's of *trans* products are also very high, which indicated a highly stereoselective control in the first C-O bond formation step.

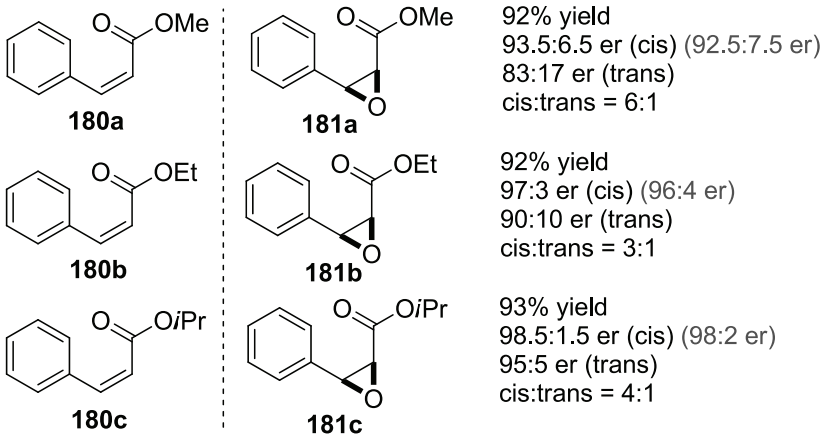


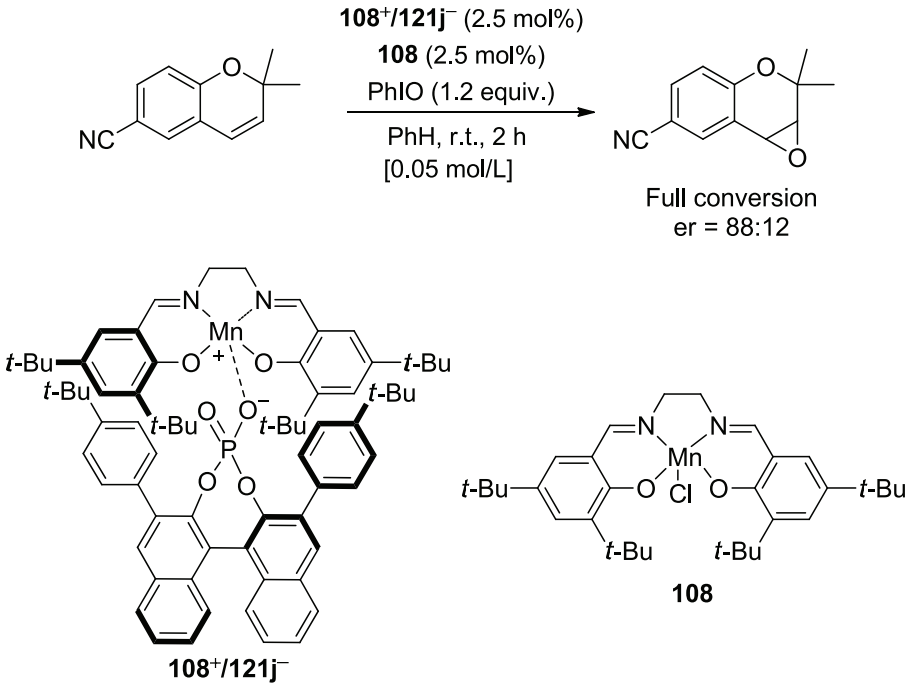
Figure 4.12. Asymmetric epoxidation of cinnamates.

In conclusion, different types of olefins can be epoxidized efficiently within a short reaction time, providing the corresponding chromene (Table 4.11), acyclic *cis*-alkene (Table 4.12), and cinnamate epoxides (Figure 4.12) in high yields and enantioselectivities (up to 98:2 e.r.). Various functional groups such as ether, nitro, ester, and nitrile were well tolerated. Overall, the extent of enantioselectivity we observed using our ion-pair catalyst **108^{+}/121j^{-}** closely resembles that obtained with the Jacobsen catalyst, although with our catalyst in the cases of electron-deficient alkenes (entries 7 in Table 4.11 and Figure 4.12), slightly higher enantioselectivities were achieved. The observed absolute configuration is in agreement with our conformational analysis of the ion-pair catalyst.

4.1.5 Other Aspects Considering the Ion-Pair Catalysts

4.1.5.1 The Reactivity of Ion-pair Catalysts

It is interesting to know the relative reactivity of the ion-pair catalysts, when compared with the typical Jacobsen catalysts. To follow the model reaction of 6-cyano-2,2-dimethylchromene is not convenient, because the reaction is very fast and completed in a short time (1-2 hours). We decided to compare the reactivity of ion-pair catalyst **108$^+$/121j$^-$** with achiral salen-Mn chloride **108** by adding these two catalysts to the reaction in a 1:1 molar ratio. Because the achiral salen-Mn chloride **108** will lead to the racemic product, if the two catalysts are equally active, the enantiomeric ratio should be 72:28. However, 88:12 er was observed when using the mixture of the chiral ion-pair catalyst and the achiral Mn-salen complex. These results suggested that the ion-pair catalyst **108$^+$/121j$^-$** is about 6 times as active as the Mn-salen chloride complex **108**.

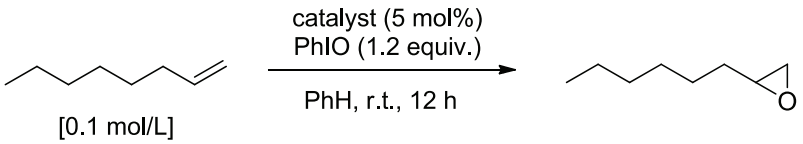


Scheme 4.22: The reactivity of ion-pair catalyst **108$^+$/121j$^-$** vs. Mn-salen complex **108**.

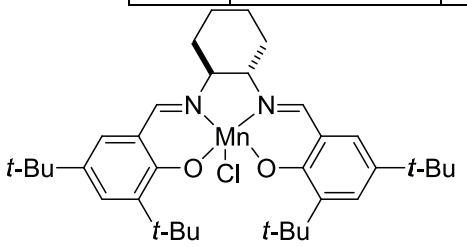
In the Jacobsen-Katsuki epoxidation, usually extra donor ligands are added to increase the reactivity of the catalysts. To compare the reactivity of our ion-pair catalyst with Jacobsen's catalysts under similar conditions, the reactions using 1-octene as the substrate was carried out with 40 mol% of NMO adding to the reaction mixtures in the cases of **104a** and **182**. After

12 hours at room temperature, the conversion of 1-octene was determined by GCMS. From the results in Table 4.13, we could see that even under these reaction conditions, the reactivity of the ion-pair catalyst toward the epoxidation of 1-octene still better than the combination of Mn-salen chloride complexes and the NMO activator.

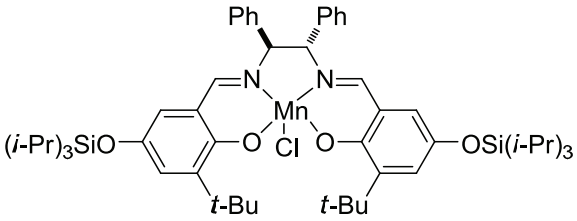
Table 4.13: The reactivity of ion-pair catalyst **108$^+$/121j$^-$** vs Mn-salen complexes/NMO



Entry	Catalyst	Additive	Conversion
1	**108$^+$/121j$^-$**	/	32%
2	**108**	NMO (40 mol%)	9%
3	**104a**	NMO (40 mol%)	10%
4	**182**	NMO (40 mol%)	7%



104a



182

4.1.5.2 The Structure of Ion-pair Catalysts and Trajectory of Alkene Approach

Because the oxo species of Mn-salen complexes are very unstable and have not been isolated so far, usually the trajectory of alkene approach was proposed based on the crystal structure of Mn-salen catalysts and the stereochemical outcomes. Although to get a crystal structure of ion-pair catalysts has been pursued with great intensity, we have not obtained a crystal of enough quality for X-ray structure analysis yet. At this point, we built a model of the ion-pair catalyst **108$^+$/121j$^-$** with ChemBio3D ultra 11.0 (Figure 4.12), based on the reported crystal structures of the Jacobsen catalyst[101] and the phosphoric acid.[102]

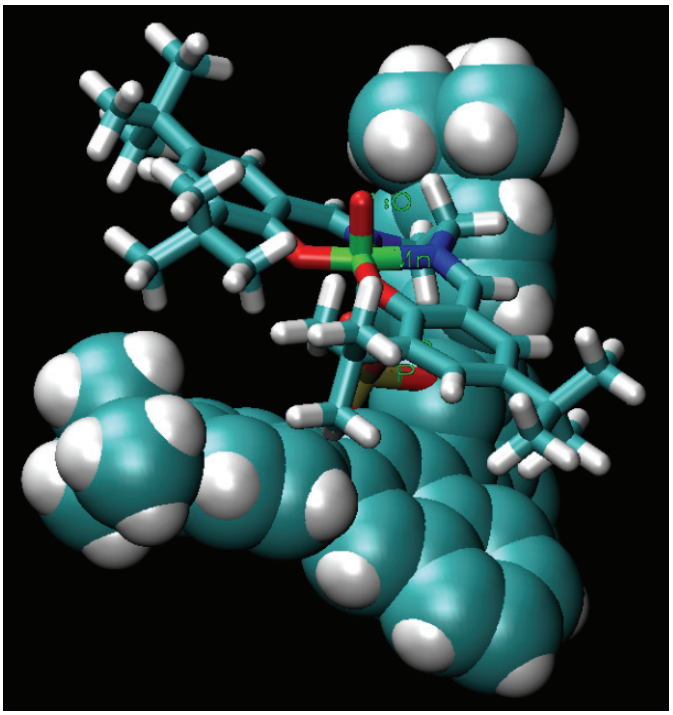


Figure 4.12: The structural model of oxygenated (O=Mn) ion-pair catalyst $\mathbf{108^{+}/121j^{-}}$.[103]

In the proposed model, the Mn-salen cation moiety displaying in a stepped conformation and the chiral anion with the 3,3'-substituents (*tert*-butylphenyl group) extended over the diimine bridge are assembled together via the cation/anion electrostatic interaction. In a sense, the role of the anion in our system can be compared to that of a hand holding a tool (Figure 4.12). By virtue of the chirality of the hand, the entire assembly becomes chiral.

According to the trajectory proposed by Jacosen and Katsuki,[57] the alkenes probably approach to the Mn=O active site from the right side with the bulky group (R_L) protruding away from the *tert*-butyl groups of the phosphate and the *tert*-butyl group at 5-position of the salen ligand (Figure 4.13).

The stereochemical results obtained from experiments are consistent with this trajectory. In the epoxidation of 6-cyano-2,2-dimethylchromene, the sense of enantioselectivity obtained with *S*-configured phosphate is identical to that with the (*S,S*)-Jacobsen catalyst.

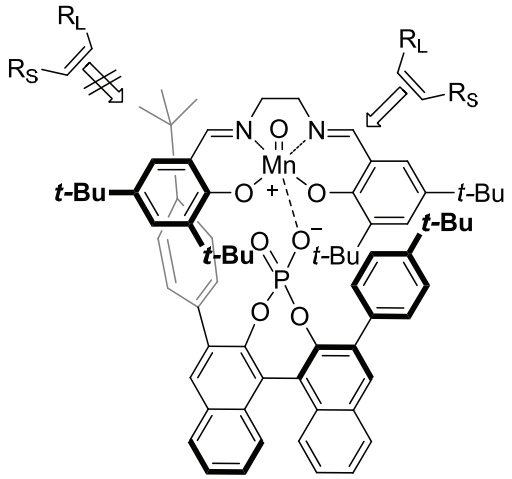
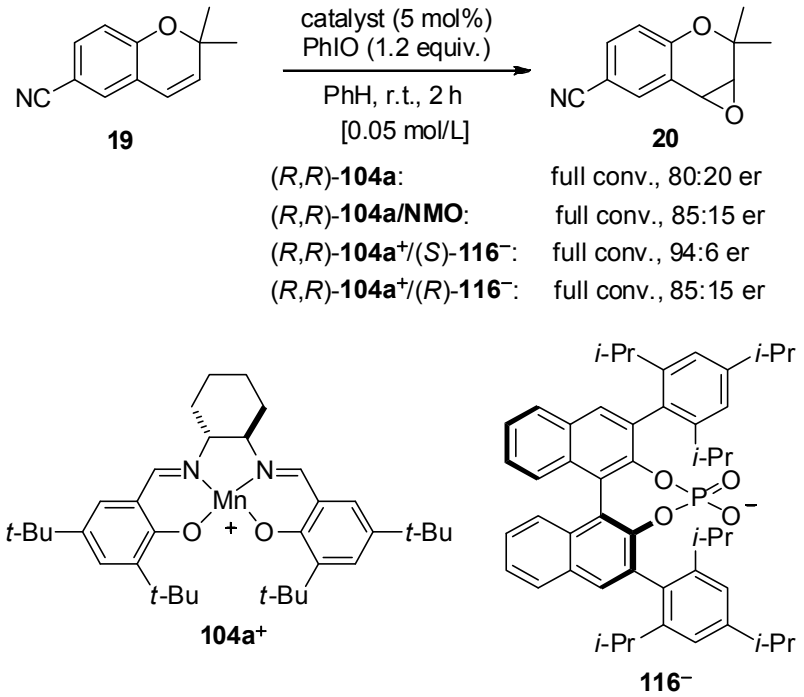


Figure 4.13: The trajectory of alkene approach.

4.1.5.3 Enantioselective Epoxidation of Alkenes with Chiral Mn-salen/Chiral Phosphate Ion Pairs

When the chloride anion in Jacobsen's Mn-salen catalysts (**104a** or **182**) was replaced by a chiral phosphate anion, a new type of ion-pair catalyst can be generated. Because both the salen ligand and the anion are chiral, the resulted match/mismatch ion pair may provide different enantioselectivity. We first tested the combination of the Jacobsen catalyst (*R*,*R*)-**104a** with (*R*) or (*S*)-TRIP (**116**) in the model reaction (Scheme 4.23). Although **104a** can catalyze the epoxidation of **19** with 98.5:1.5 er in a basic buffer solution with bleach as the oxidant (Jacobsen's typical reaction conditions), under our optimized reaction conditions only 80:20 er was observed. The addition of NMO (40 mol%) can improve the enantiomeric ratio to by 85:15. A match/mismatch effect was observed: the matched ion pair (*R*,*R*)-**104a**$^{+}$/(*S*)-**116**$^{-}$ gave the epoxide **20** in 94:6 er, while the mismatched ion pair (*R*,*R*)-**104a**$^{+}$/(*R*)-**116**$^{-}$ gave much lower enantioselectivity (85:15 er).



Scheme 4.23: Epoxidation with ion pairs of chiral Mn-salen cations/chiral TRIP anions.

Attempts to improve the enantioselectivity of some difficult substrates like styrene and 1-octene have also been tried with great intensity. Both the (*R*,*R*)- and (*S*,*S*)-**104a** and **182** have been prepared and combined with various anions as shown in Figure **4.14**. Unfortunately, in the epoxdiation of 1-octene, none of these ion pairs gave significant better selectivity (< 30% ee) than **104a**, even though the ion-pair catalysts were generally more reactive. In the case of styrene, the improvements (<10% ee) were also quite limited.

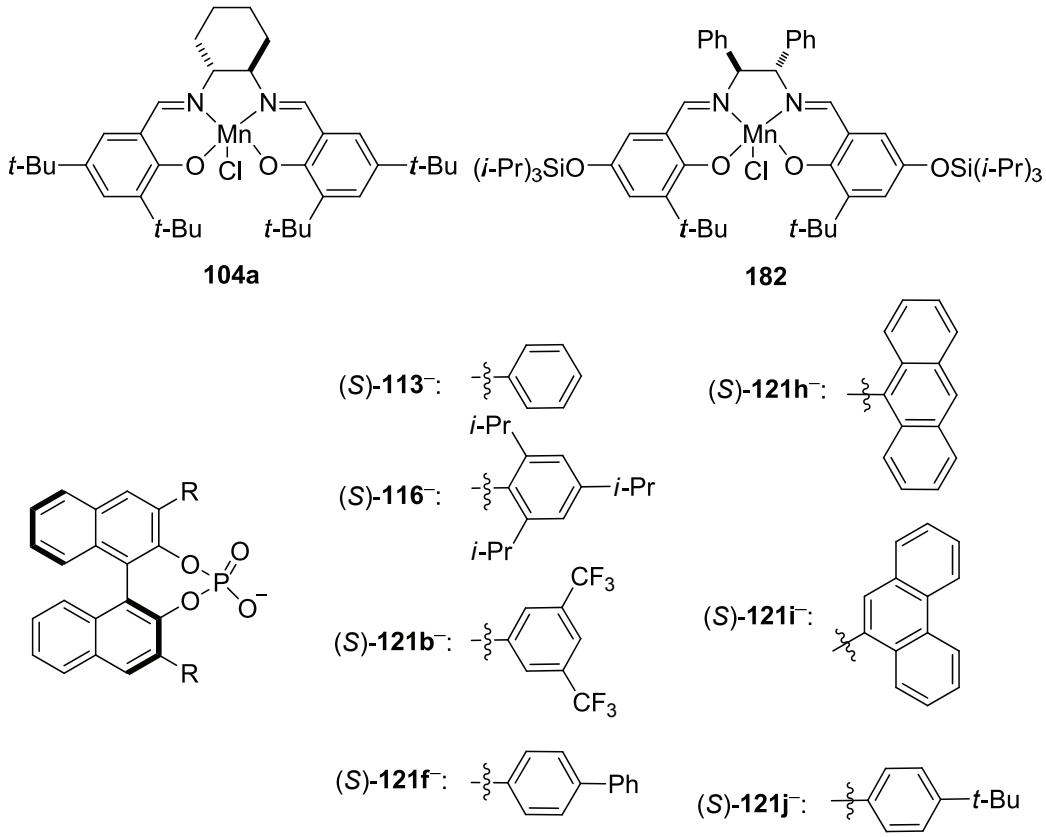
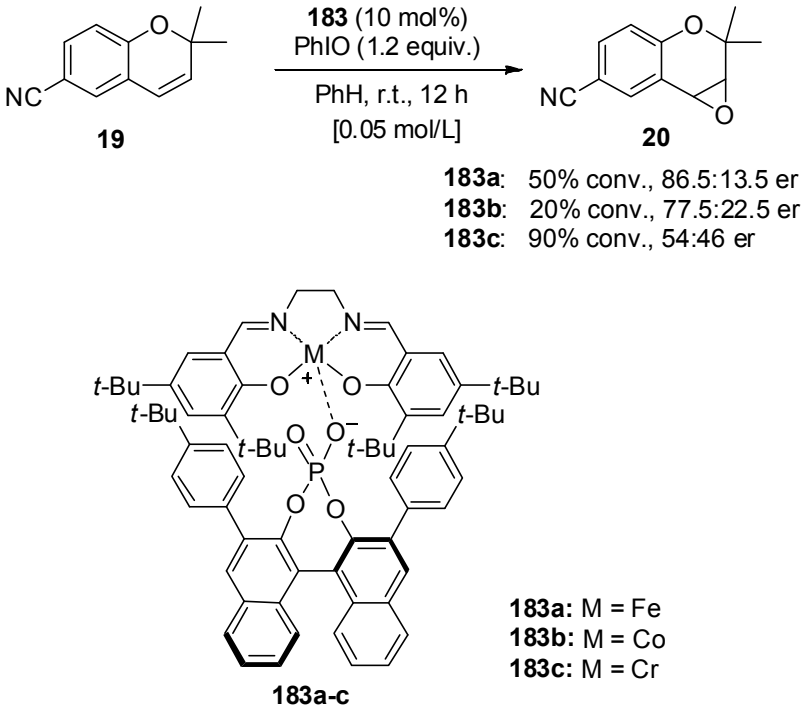


Figure 4.14: Chiral Mn-salens and phosphate anions employed in the combination studies.

4.1.5.4 Epoxidation with Other Metallosalen Chiral Phosphate Ion Pairs

As aforementioned, once ACDC was well realized in the Mn-salen system, the concept should find wide application in other metallosalen systems. Ion-pair catalysts **183a-c** with different metal centers (Fe, Co, Cr) were prepared and examined in the model reaction. To our delight, all of the three ion-pair catalysts could promote the epoxidation with some extent of enantioselectivity. The iron catalyst **183a** gave the best enantioselectivity (86.5:13.5 er), while the cobalt catalyst **183b** gave lower selectivity. Chromium **183c** exhibited the highest reactivity among the three catalysts, but it provided the lowest stereoselectivity. These results at least demonstrated that other achiral metallosalen rather than Mn-salen complexes can also deliver an asymmetric transformation by introducing a chiral counteranion into these complexes. Their potential might be found in other substrates or other types of reactions.



Scheme 4.24: Epoxidation with other metal-salen phosphate catalysts.

4.1.6 Conclusion

The ACDC (asymmetric counteranion-directed catalysis) concept has been successfully applied to the asymmetric Jacobsen-Katsuki epoxidation of alkenes. With the ion-pair epoxidation catalyst **108$^+$/121j$^-$**, which consists of an achiral Mn–salen cation and a chiral phosphate counteranion, high yields (up to 99%) and enantioselecitivities (up to 98:2 er) were achieved with various alkene substrates. This novel ion-pair catalyst system has shown some unique properties, when compared to typical Jacobsen's Mn-salen system.

1) Chiral counteranions are the only chiral source in the ion-pair catalysts, while the salen ligands are achiral.
2) With the ion-pair catalyst **108$^+$/121j$^-$**, various olefins can be epoxidized with high level of enantioselectivity with the preference to *cis*-1,2-disubstituted alkenes like chromemes, cinnamates, enyls and relatively electron-poor substrates.
3) The reaction conditions are mild and neutral, while Jacobsen epoxidation typically carried out in an aq. buffer solution (pH = 11.3).
4) The ion-pair catalysts are more reactive, efficient and more Lewis acidic.
5) No extra donor ligand is required.

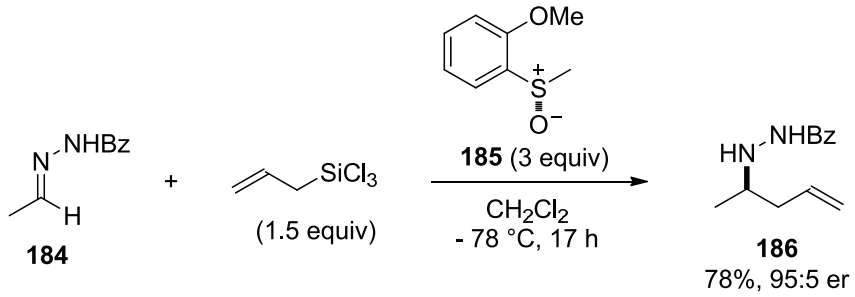
Furthermore, no direct interaction between the substrate and the chiral counteranion is involved in the transition state. This ion-pair system also represents a new platform for the investigation of conformation of O=Mn species and the trajectory of alkenes.

The combination of chiral salen ligands with chiral anions was also explored, and via this strategy the enantioselectivity with Jacobsen's catalysts can be further improved. Asymmetric epoxidation using other metallosalen (Fe, Cr, Co) complexes in combination of chiral counteranions has also been demonstrated, suggesting the great potential of the application of the ACDC concept to other metallosalen systems and other reaction types.

4.2 Enantioselective Oxidation of Sulfides with Mn- and Fe-Salen Phosphate Ion-Pair Catalysts

4.2.1 Introduction

Optically active sulfoxides are valuable and efficient reagents in the field of asymmetric synthesis. They are widely used as chiral intermediates, auxiliaries and ligands in morden organic chemistry.[104] Quite recently, nonracemic sulfoxides were also employed as Lewis base organocatalysts in enantioselective synthesis.[14] [105] For example, chiral sulfoxide **185** can promote the asymmetric allylation of *N*-benzoylhydrazone **184** with high enantioselectivity (95:5 er).



Scheme 4.25: Sulfoxide-promoted asymmetric allylation of *N*-benzoylhydrazones.

Another aspect of nonracemic sulfoxides is their wide presence in numerous biologically active compounds and sulfur-containing therapeutic agents (Figure 4.15).[106] For example, Esomeprazole **187**, the *S* form of omeprazole, which is used to cure and relieve symptoms of gastric or duodenal ulcers, is counted among the world's most sold pharmaceuticals.[107] The (*R*)-enantiomer of modafinil **188** is a stimulant drug approved for treatment of sleep disorders.[108]

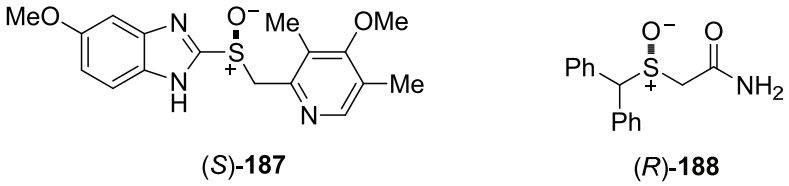
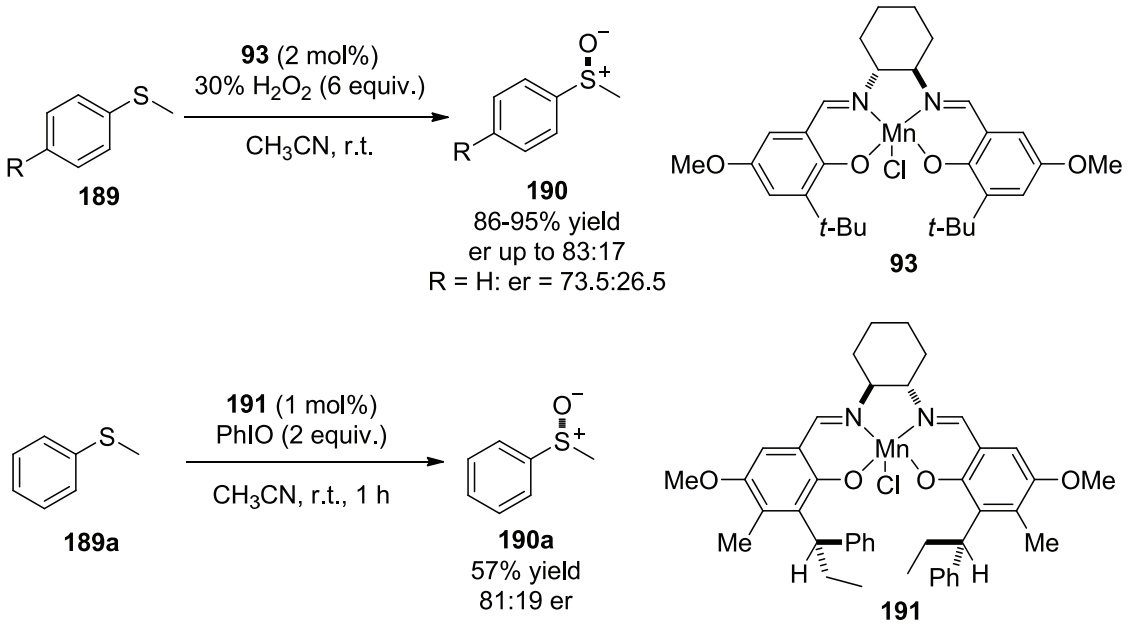


Figure 4.15: Esomeprazole and modafinil.

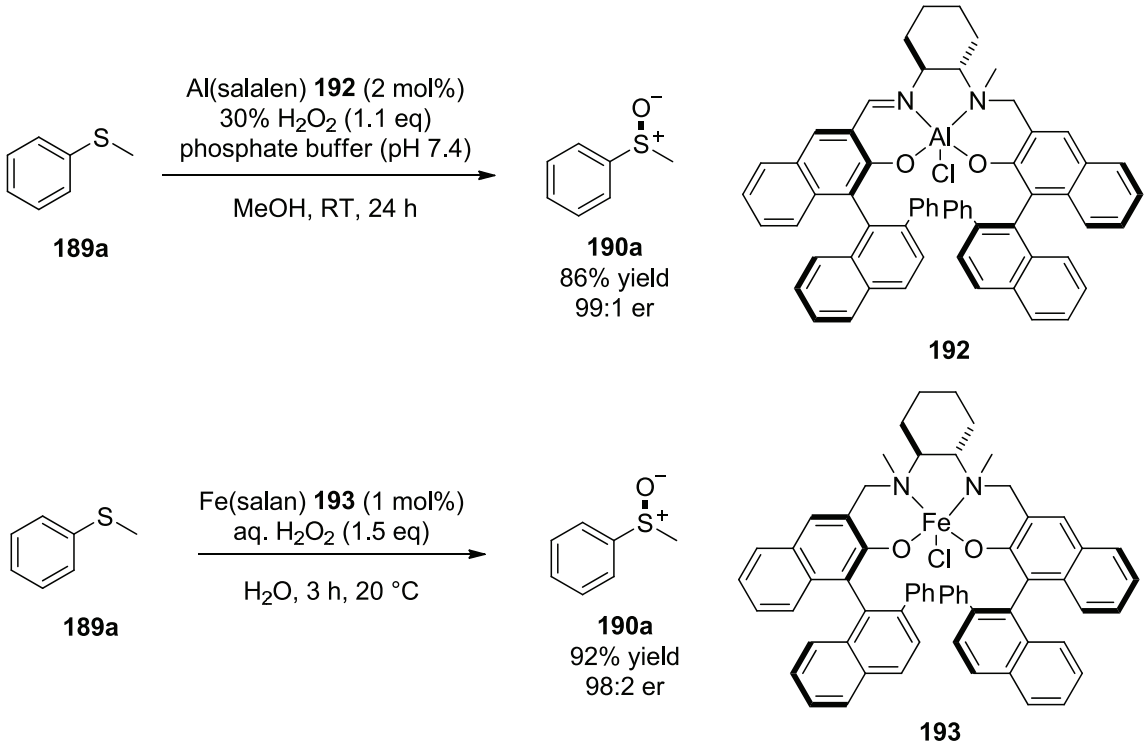
Although, principally, nonracemic sulfoxides can be prepared by three approaches involving separation of a racemic mixture, transformation from the chiral pool, or the use of chiral catalysts for enantioselective synthesis, the asymmetric catalytic oxidation of sulfides is considered as the most direct and efficient approach. Many methods for asymmetric sulfoxidation have been developed during the last three decades.[104d;109] The recent development of organocatalytic transformation of sulfides to sulfoxides have also been reviewed recently by Tosgeva.[109c] In the field of transition metal catalysis, Kagan et al.[110] and Modena et al.[111] reported the first catalytic systems for asymmetric oxidation of sulfides in 1984, based on the application of several modified Sharpless epoxidation reagents. In 1995, Bolm and Bienewald reported a highly efficient sulfoxidation employing [$VO(acac)_2$] in combination with Schiff bases derived from chiral aminoalcohols.[112] Chiral metallosalen complexes were also employed for this kind of transformation. Jacobsen et al. reported the first utilization of chiral Mn-salen complexes in the catalytic enantioselective sulfoxidation with aqueous H_2O_2 as the oxidant, but only moderate enantioselectivities were obtained.[113] The performance was improved by introducing additional chiral centers to the Mn-salen complexes as described by Katsuki et al (Scheme 4.26).[114]



Scheme 4.26: Asymmetric sulfoxidation with Mn-salen complexes

Recent important progress in this field is the Al-salalen **192**[115]and Fe-salan **193**[116] complexes-catalyzed asymmetric sulfoxidation developed by Katsuki and co-workers (Scheme 4.27). However, as shown in the Scheme 4.26, with Jacobsen-Katsuki-type Mn-salen complexes, the level of enantioselectivity is lower than that observed in the epoxidation

reaction. As our ion-pair catalysts have already showed a comparable enantioselectivity to the typical Jacobsen's Mn-salen catalyst in the epoxidation of alkenes, it became of interest to study their performance in the asymmetric oxidation of sulfides, where Jacobsen's Mn-salen catalysts failed to provide a high level of enantioselectivity.



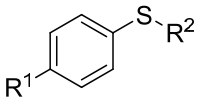
Scheme 4.27: Asymmetric oxidation of sulfides with Al-salalen or Fe-salan complexes

4.2.2 Investigation of the Reaction Scope

4.2.2.1 Preparation of Sulfide Substrates and Racemic Sulfoxides

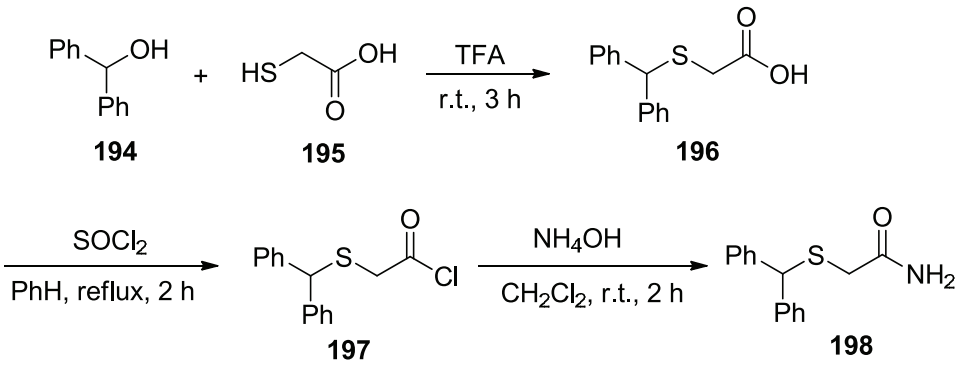
Synthesis of Sulfide Substrates

Sulfides **189a-g** were commercially available and directly used in our oxidation reactions.



189a: R^1 = H, R^2 = Me
189b: R^1 = OMe, R^2 = Me
189c: R^1 = Me, R^2 = Me
189d: R^1 = Br, R^2 = Me
189e: R^1 = CN, R^2 = Me
189f: R^1 = NO_2, R^2 = Me
189g: R^1 = H, R^2 = *i*-Pr

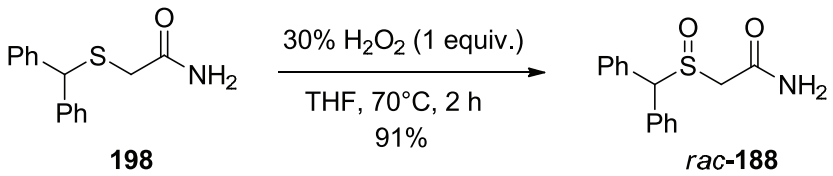
The synthesis of acetamide **198** followed a known procedure.[117] The condensation of benzhydrol **194** with thioglycolic acid **195** in trifluoroacetic acid afforded benzhydrylsulfanylacetic acid **196** in 98% yield. The acid was then treated with thionyl chloride to prepare the corresponding acid chloride **197**. Upon the reaction with concentrated ammonium hydroxide, the desired acetamide **198** was obtained as a white solid in 82% yield (Scheme 4.28).



Scheme 4.28: Synthesis of (2-benzhydrylsulfanyl)acetamide **198**.

Synthesis of Racemic Sulfoxides

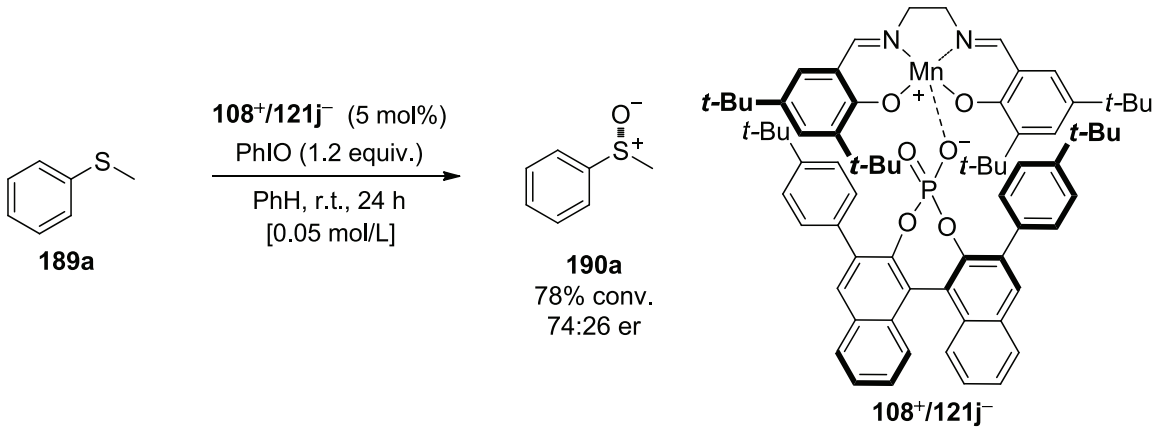
The racemic sulfoxides were prepared according to the literature procedure (Scheme 4.29).[118] The oxidation reactions of sulfides were performed neat or in THF or MeOH at 70 °C, with 1.0 equivalent of H_2O_2 (30 % in water) as the oxidant. After column chromatography on silica gel (EtOAc, Rf = 0.29), the desired racemic sulfoxides were obtained in generally high yields (>90%). The racemic modafinil was obtained in 91% yield.



Scheme 4.28: Synthesis of racemic modafinil.

4.2.2.2 Optimization of Reaction Conditions

The optimized reaction conditions established for the asymmetric epoxidation of alkenes were employed for the model sulfoxidation reaction of pheny methyl sulfide: catalyst **108$^+$/121j$^-$** (5 mol%), freshly prepared iodosobenzene (1.2 equiv.) as the oxidant, in benzene [0.05 mol/L].



Scheme 4.29: Enantioselective sulfoxidation with the ion pair **108$^+$/121j$^-$**.

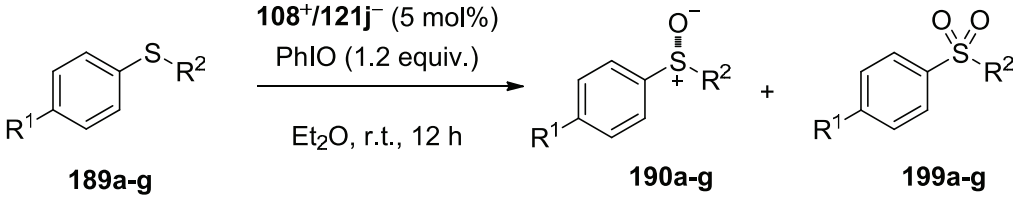
The reaction was followed by TLC, but full conversion was not achieved even after prolonging the reaction time to 24 hours. However, the reaction mixture turned to clear in one hour, which suggested that the PhIO might be completely consumed. Then a sample of reaction mixture was subjected to GCMS analysis, and the conversion was determined to be 78% with ca. 20% of over-oxidation product sulfone. The over-oxidation is probably due to the high reactivity of the sulfide and sulfoxide toward the oxidative species. Thus, a lower temperature might be helpful to further improve the enantioselectivity and chemoselectivity. A search for a proper solvent for low temperature reactions was carried out. A similar solvent influence to the oxidation of alkenes was observed: 69:31 er in pentane or flurobenzene, 62:38 er in DCM, 71:29 er in acetone and 73:27 er in ethyl acetate. One exception was diethylether, in which a better er value of 78:22 than benzene was observed. However, when we conducted the reaction in ether at lower temperatures, the enantioselectivity went down gradually (77:23 er at 0 °c, 72:28 er at -20 °C).

4.2.2.3 Reaction Scope with Mn-Salen Phosphate Ion-pair Catalysts

Various sulfides (**189a-g**) were subjected to the optimized reaction conditions (in ether). As shown in Table 4.14, the electron-rich sulfides were generally oxidized with lower selectivity

(entries 1-3), while the sulfides attached with an electron-withdrawing group were generally converted into the corresponding sulfoxides with a higher level of enantioselectivity (entries 5-6). Over-oxidation of the sulfoxides to sulfones was observed in all the cases, especially severe in the cases of sterically hindered and electron-rich sulfides (entries 1-3 and 7). The reaction in ether was slower than that in benzene, but the chemoselectivity was better (**190a/199a**, 3:1 vs. 2.5:1). The enantioselectivity was comparable to that obtained with the Jacobsen Mn-salen catalyst.[113]

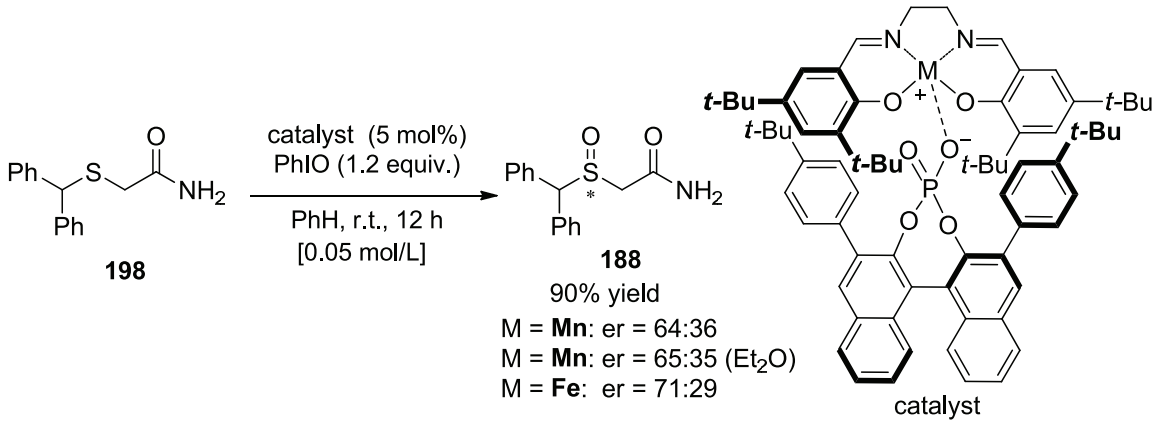
Table 4.14: Reaction scope of sulfoxidation with ion pair **108$^+$/121j$^-$**



Entry	R^1	R^2	Substrate	Conv.[a]	**188:197**[a]	er
1	H	Me	**187a**	73%	3:1	79:21
2	OMe	Me	**187b**	74%	3.5:1	63:37
3	Me	Me	**187c**	78%	3.5:1	71:29
4	Br	Me	**187d**	78%	3.5:1	80:20
5	CN	Me	**187e**	79%	4:1	92:8
6	NO_2	Me	**187f**	87%	5:1	88:12
7	H	*i*-Pr	**187g**	73%	3:1	77:23

[a] Determined by crude NMR.

The asymmetric oxidation of mandril **198** was also carried out under these reaction conditions with ion pair **108$^+$/121j$^-$** as the catalyst. The sulfoxide **188** was isolated in high yield after 24 hours, but the enantioselectivity was not satisfactory (64:36 er).



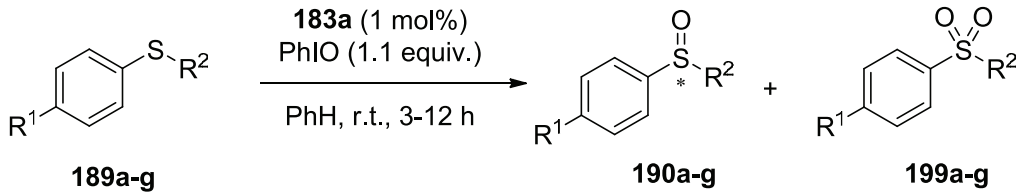
Scheme 4.30: Asymmetric oxidation of mandril.

Normally, the oxidation of sulfides was rapid. We monitored the oxidation of phenyl methyl sulfide in $CDCl_3$ by NMR, where the reaction can reach full conversion in 30 min with 2 equiv. of PhIO. Thus, if a less active catalyst could lead to a more selective and product-like transition state, the corresponding iron complex **183a**, which is less reactive than the manganese, may be a better choice. To our delight, in the iron ion pair promoted oxidation of mandril in benzene, the enantiomeric excess was improved by 14% (Scheme 4.30). This exciting result intrigued us to examine the substrate scope with the iron ion-pair catalyst.

4.2.2.4 Reaction Scope with the Fe-salen Phosphate Ion-pair Catalyst

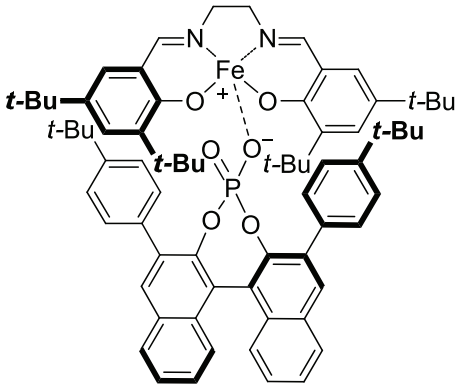
The oxidation reactions of sulfides with ferric ion pair **183a** were carried out in dry benzene (0.05 M) with 1.1 equivalents of fresh PhIO as the oxidant. The sulfoxide/sulfide ratios were determined by crude NMR analysis. As mentioned before, Mn ion pair exhibited a better selectivity in ether, but the oxidation of **189a** in ether with the Fe ion pair gave the nearly racemic product (entry 1). The reactions in benzene was more selective (entry 2), and the enantioselectivity can be further improved to 85:15 er when lowering the catalyst loading to 1 mol% (entry 3). Thus, the reaction scope was investigated under these reaction conditions (in benzene with 1 mol% catalyst).

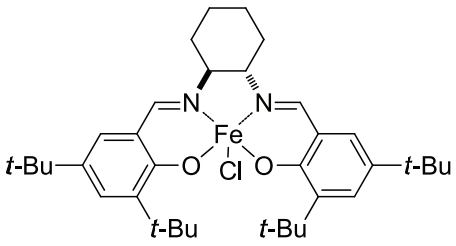
Table 4.14b: Reaction scope of sulfoxidation with ferric ion pair **183a**



Entry	R^1	R^2	Substrate	t (h)	Yield[a]	**188:197**[b]	er
1[c]	H	Me	**189a**	4 h	60%	15:1	54:46
2[d]	H	Me	**189a**	4 h	93%	12:1	80:20
3	H	Me	**189a**	8 h	93%	14:1	85:15
4	OMe	Me	**189b**	6 h	90%	12:1	73:27
5	Me	Me	**189c**	10 h	92%	12:1	83:17
6	Br	Me	**189d**	10 h	93%	14:1	92:8
7	CN	Me	**189e**	10 h	93%	13:1	97:3
8	NO_2	Me	**189f**	12 h	95%	16:1	99:1
9[e]	NO_2	Me	**189f**	24 h	90%	15:1	97:3
10	H	*i*-Pr	**189g**	10 h	92%	14:1	93:7

[a] Isolated yield. [b] Determined by crude NMR analysis. [C] The reaction was carried out in ether. [d] The reactions was carried out with 5 mol% catalyst. [e] The reactions was carried out with 0.5 mol% catalyst.





In the ferric ion pair catalyzed sulfide oxidations, the sulfoxides were obtained generally in high yields and high sulfoxide/sulfone ratios. The enantioselectivities were better than those with the corresponding manganese ion pair in all cases, and the selectivities were also much higher than those with Fe-analogue of the Jacobsen Mn-salen catalyst.[119] It was worth noting that the catalyst loading can be further reduced to 0.5 mol% (entry 9). The enantioselectivities observed with relatively electron-poor sulfides (entries 7-9) represent the best results so far in

both the Mn and Fe-salen systems. The enantioselectivities reported with the Fe-analogue catalyst for **189a** and **189f** were 61:39 er and 80:20 er.[119b]

4.2.3 Conclusion

In the asymmetric oxidation of sulfides, the manganese ion-pair catalyst provided moderate enantioselectivity similar to the Jacobsen's Mn-salen catalysts. The electron-poor sulfides were converted to the sulfoxides generally with higher enantioselectivity than the electron-rich sulfides. The corresponding iron ion-pair catalyst **183a** has exhibited much better chemo- and enantio-selectivity than the Fe-analogue of the Jacobsen Mn-salen catalyst and our manganese ion-pair catalyst **104a**$^{+}$/**121j**$^{-}$. Especially in the cases of electron-poor sulfides, up to 99:1 er was obtained together with high suloxide/sulfone ratios. These results obtained with our ion-pair catalyst represented the best so far among all the chiral salen ligand-derived Mn- and Fe-salen complexes, and the substrate preference is also a good complement to the Kagan, Bolm, and Katsuki systems.

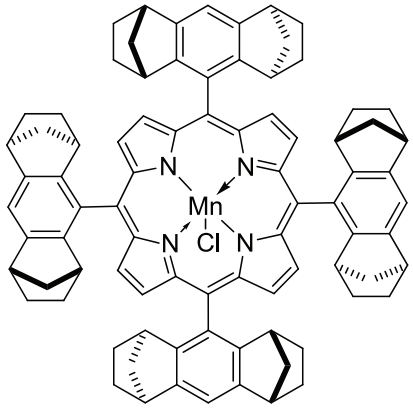
4.3 Enantioselective Epoxidation of Alkenes with Ferric Porphyrin Phosphate Ion-Pair Catalysts

4.3.1 Introduction

In the field of asymmetric oxidation, porphyrin ligand-based catalysts play an important role and have long been the focus of vigorous research activity. Although only limited success and no synthetically useful systems had been developed in the earlier stage, significant improvements in enantioselectivity and catalytic activity have been achieved during the last 15 years.[59b;120]

The metal coordination sphere of porphyrin ligands is sp2 hybridized and essentially flat, to mimic the natural enzymes, stereochemical elements in a chiral porphyrin complex relatively remote from the reaction center must be drawn close to the active site to achieve good stereochemical communication.[59b;120] In natural hemoproteins, the control of the access of substrate to the active site is made by the protein chain and amino acid residues present in the vicinity of the metal center. Thus, special care has to be taken in designing the superstructure of the model in order to accurately control the access of the substrate to the active site. That is why numerous chiral porphyrin structures have appeared during the last thirty years but only a few of them were very successful in enantioselective epoxidation catalysis.[121] According to their structural features, they can be devided into two groups: single-faced protected porphyrins and bis-faced protected porphyrins.[120]

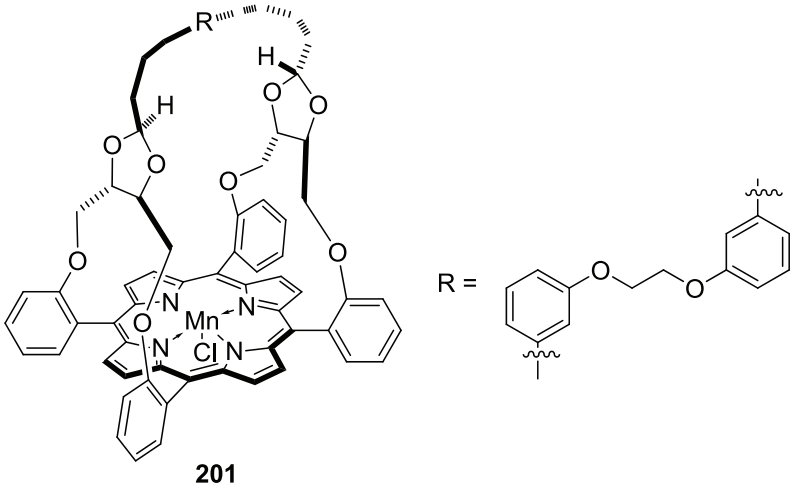
In 1991, Halterman and Jan disclosed a type of D_4-chiral bis-faced picket porphyrin for asymmetric epoxidation (Figure 4.16).[122] Using the porphyrin-Mn-Cl complex **200** and excess of sodium hypochlorite in the presence of 4-*tert*-butylpyridine, (*S*)-Styrene oxide was obtained in 90% yield and 76:24 er in 1 h. The corresponding iron(III) complex was less selective, and only 54:46 er was observed for styrene.



200

Figure 4.16: D_4-symmetric bis-faced picket porphyrin **200** (Halterman, 1991).

The Collman group contributed most significantly to the development of single faced protected porphyrin catalysts. In 1993, they reported a type of threitol-strapped porphyrins with a bridge spanning the center of the porphyrin planar (Figure 4.17).[123] Epoxidation of styrene with **201a** as the catalyst afforded the desired epoxide product in 86% yield and 84.5:15.5 er. Because the epoxidation of alkenes using this strapped catalyst can also occur on the achiral open face, a bulky donor ligand, 1,5-dicyclohexylimidazol, was required to block the non-enantioselective approach.



201

Figure 4.17: Single faced protected porphyrins (Collman, 1993).

In 1999, Collman and Rose groups prepared a type of bis-strapped porphyrin iron complexes (Figure 4.18).[124] The $\alpha^2\beta^2$-tetrakis-(2'-aminophenyl)porphyrin atropisomer **202a** was used for the asymmetric epoxidation, terminal alkenes like styrene and pentafluorostyrene were epoxidized with high enantioselectivities (91.5:8.5 and 94:6 er, respectively). At that time, those results jointly obtained in the two groups exceeded the highest values reported by any

catalytic systems. It was worth noting that the epoxidation of 3,3-dimethyl-1-butene, an alkyl terminal alkene, was also achieved with excellent selectivity (95:5 er). Recently, a so-called ‘‘homologated’’ catalyst (**202b**, n = 2) was prepared by the Rose group, hoping it would provide more access to the metal center than **201a**. This strategy appeared extremely successful as in the epoxidation of styrene, **202b** afforded (*R*)-styrene oxide in 96% yield and 98.5:1.5 er at -10 °C and 95:5 er at room temperature. Furthermore, the catalyst appeared highly stable as the enantiomeric excess remained close to 80% after 16000 TON at room temperature.[125]

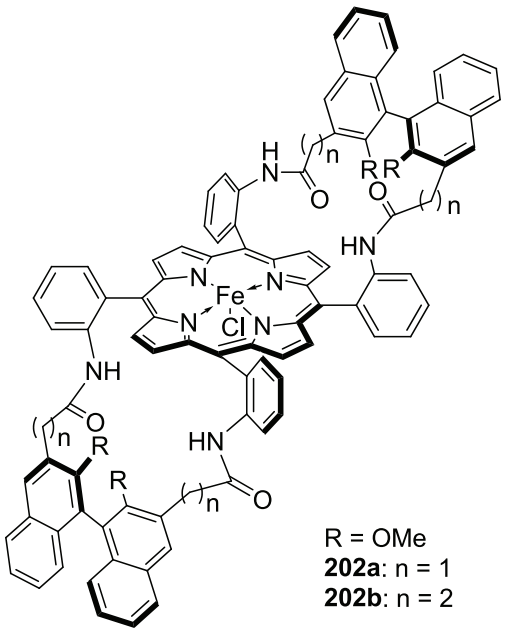


Figure 4.18: The bis-binaphthyl strapped porphyrins (Collman and Rose).

As already mentioned in the Chapter 2.2, Jacobsen and Katsuki epoxidation can transform *cis*-1,2-di-, tri- and some tetra-substituted olefins with high enantioselectivity, but for terminal alkenes like styrene, a low temperature is required to achieve a high level of enantioselectivity (styrene: 78.5:21.5 er at 5 °C; 93:7 er at -78 °C) and the selectivity was even worse for aliphatic terminal alkenes (eg. 1-octene: ca. 60:40 er at r.t.). In comparison with the Mn-salen system, porphyrin catalysts like **202** can provide better stereoselectivity and higher turnover numbers in the cases of aliphatic terminal olefins. Another drawback of the Mn-salen system is the reactivity and stability of the catalysts. When standard reaction conditions and catalysts are used, the decomposition of the Mn^{III}-salen catalysts usually occurs and results in a turnover number of the order of hundreds or less (TON ≈ 40 for styrene), though an order of magnitude can be improved by adding extra donor ligands. Ferric tetrakis-(2’,6’-dichlorophenyl)porphyrin **203**, as it does not undergo μ-oxo dimer formation and oxidative

destruction, was found to be unusually robust with TON reaching 10000 for the epoxidation of norbornene in 20 min in the presence of pentafluoroiodosobenzene.[126]

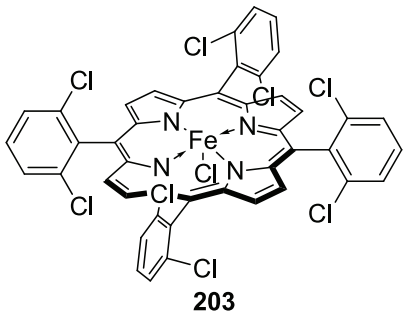


Figure 4.19: An example of robust porphyrin iron complexes.

These results have demonstrated the highly remarkable potential of porphyrin-based catalysts for practical asymmetric epoxidation of terminal alkenes. However, the preparation of these chiral porphyrin ligands is not a trivial task. Although the influence of anionic ligands on the reactivity and selectivity was well known in the metalloporphyrin-catalyzed oxidation reactions, the influence of chiral anions is still elusive and has not been investigated.[127] Encouraged by the success of the application of the ACDC concept to the Mn-salen system, we envision that a chiral conformation of achiral porphyrin iron complexes can also be induced by introducing a chiral anionic counterion (Figure 4.20). If a C_2-symmetric chiral counteranion like the BINOL-derived phosphate anion was attached to the Fe^+ center, the repulsion between the C3-substituents (R') of the phosphate anion and the four phenyl groups of the porphyrin would force the four phenyl groups to rotate. If the degree of the rotation of the phenyl groups (e.g. at C5 and C10) is different, a chiral open space (e.g. between the C5 and C10-phenyl groups) would be created for the approach of the alkene substrate. In this part, we will describe our preliminary results obtained in our pursuit of enantioselective epoxidation of olefins using achiral porphyrin ligands.

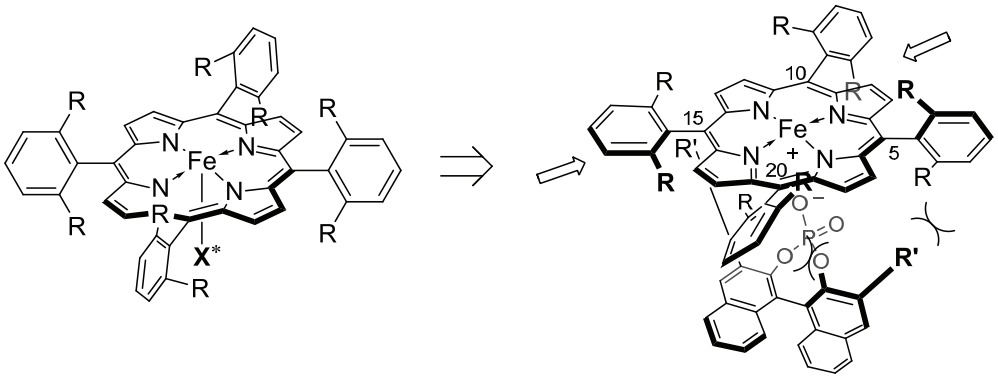


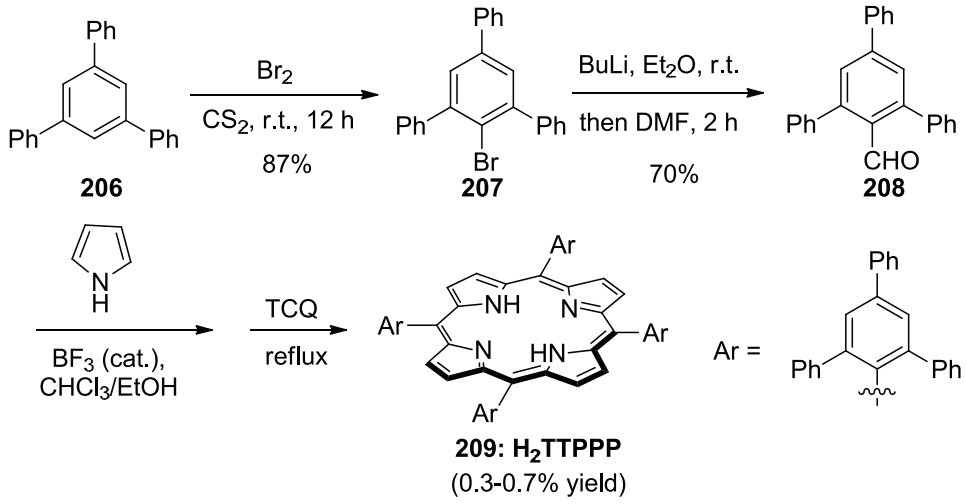
Figure 4.20: Possible chiral counteranion induction on the conformation of achiral porphyrins.

4.3.2 Preparation of Ferric Porphyrin Phosphate Ion Pairs

4.3.2.1 Synthesis of Achiral Porphyrin Ligands

Synthesis of 5,10,15,20-Tetrakis(2',4',6'-triphenylphenyl)porphyrin (H_2TTPPP)

The preparation of H_2TTPPP ligand started from 1,3,5-triphenylbenzene **206** (Scheme 4.33). Bromination of **206** in carbondisulfide afforded triphenylbromobenzene **207** in 96% yield.[128] Subsequent lithium-halide exchange and formylation delivered the 2,4,6-triphenylbenzaldehyde **208** in around 70% yield.[129] Pure aldehyde as white crystals was obtained by means of recrystallization from hot ether. The condensation of pyrrole with the aldehyde **208** was performed according to the method developed by Lindsey,[130] with freshly distilled $BF_3{\cdot}OEt_2$ (10 mol%) as the catalyst and chloroform/EtOH (0.1 M) as the solvent. To obtain the pure porphyrin, usually 4 or 5 column chromatography purification are necessary. The isolated yields were in the range of 0.3-0.7 %.

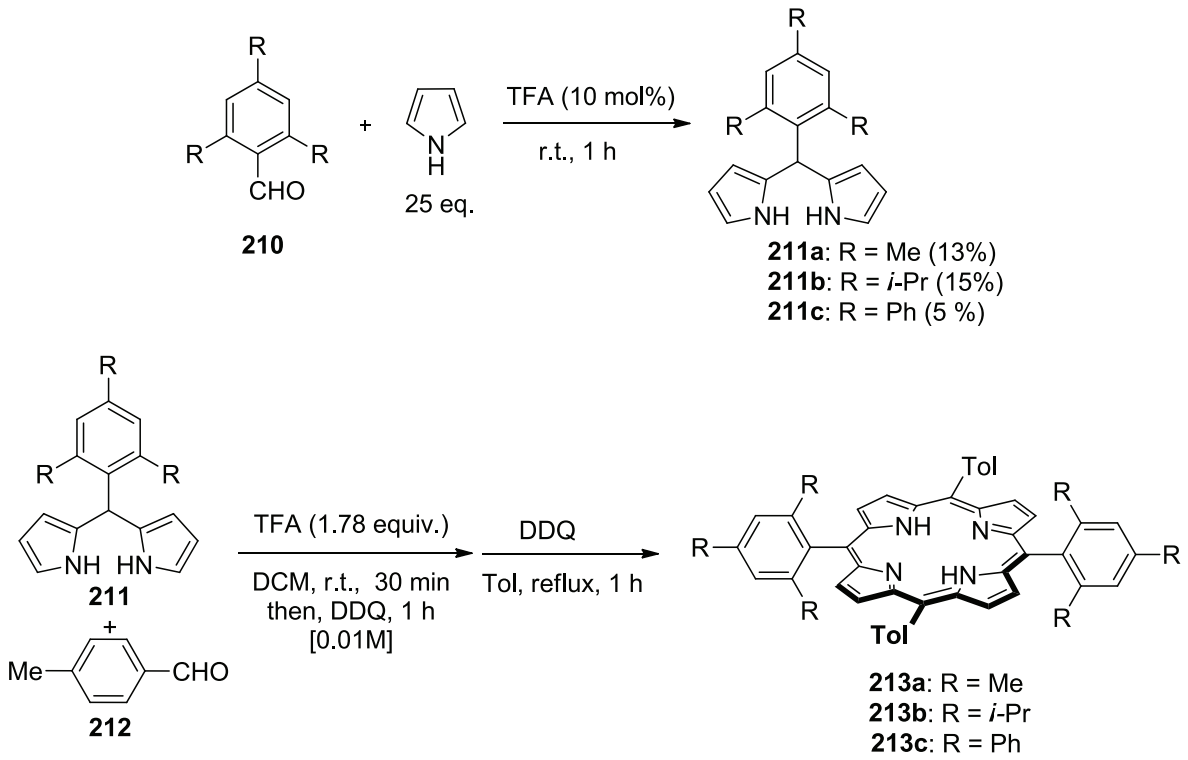


Scheme 4.33: Synthesis of porphyrin ligand H_2TTPPP.

Synthesis of trans-Porphyrins (ABAB)

To synthesize of *trans*-porphyrins of the ABAB type (Scheme 4.34), the methods developed by Lindsey [131] were followed. Dipyrrolemethanes **209a-b** were obtained via the condensation of the aldehydes **210** with a large excess of pyrrole (25-40 equiv.) in the presence of TFA (0.17 equiv.) as the acid catalyst. The aldehydes generally could be completely consumed in 1 h, and the reaction was then quenched with triethylamine or aq.

NaOH. Pure compounds **211a-b** were obtained in 13-15% yields by bulb-to-bulb distillation at reduced pressure (0.05 mbar). Compound **211c** was obtained in 5% yield after purification by chromatography.



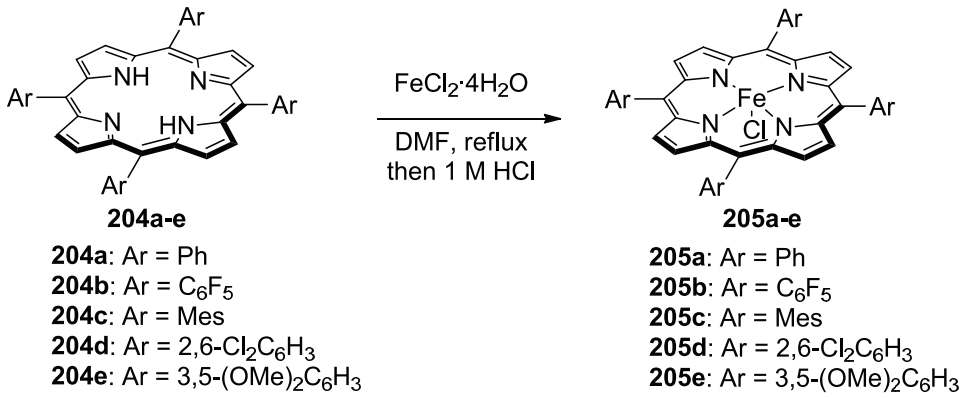
Scheme 4.34: Synthesis of *trans*-porphyirns **213a-b** (ABAB).

The condensation of dipyrromethane **211** and *p*-tolualdehyde **212** was carried out in CH_2Cl_2 with TFA (1.28 equiv.) as the catalyst. Purification by column chromatography on alumina furnished the desired porphyrins **213a-b** in 18% and 34% yield, respectively. The attempts to prepare **213c** proved to be difficult, because both the reactions of preparation of dipyrrolemethane **211c** and porphyrin **213c** were messy and low yielding (< 5% yield). Further attempts to make **213c** were discontinued. Alternative methods rather than the direct condensation may be the better choice to prepare **211c** in a big amount.

4.3.2.2 Synthesis of Achiral Ferric Porphyrin Complexes

Metal free porphyrin ligands **204a-e** were commercially available. The corresponding chloroiron(III)porphyrins **205a-e** were prepared according to the standard procedure developed by Kobayashi.[132]The metallation was carried out in DMF under reflux conditions

with $FeCl_2 \cdot 4H_2O$ (30 equiv.) as the iron source. The desired chloroiron(III)porphyrins **205a-e** can be obtained in nearly quantitative yields after purification by a short silica gel column.



204a-e

204a: Ar = Ph
204b: Ar = C_6F_5
204c: Ar = Mes
204d: Ar = 2,6-$Cl_2C_6H_3$
204e: Ar = 3,5-$(OMe)_2C_6H_3$

205a-e

205a: Ar = Ph
205b: Ar = C_6F_5
205c: Ar = Mes
205d: Ar = 2,6-$Cl_2C_6H_3$
205e: Ar = 3,5-$(OMe)_2C_6H_3$

Scheme 4.32: Synthesis of chloroiron(III)porphyrins **205a-d**.

The metallation of **213a-b** was also performed, following the standard reaction conditions. However, the standard conditions did not work for H_2TTPPP ligand (**209**). A brown solid can also be isolated after reflux in DMF for 3 days, but the UV absorption was not fully consistent with the reported data, while reflux in toluene with $Fe(CO)_5/I_2$ did provide the desired ferric porphyrin in 77% yield.[133]

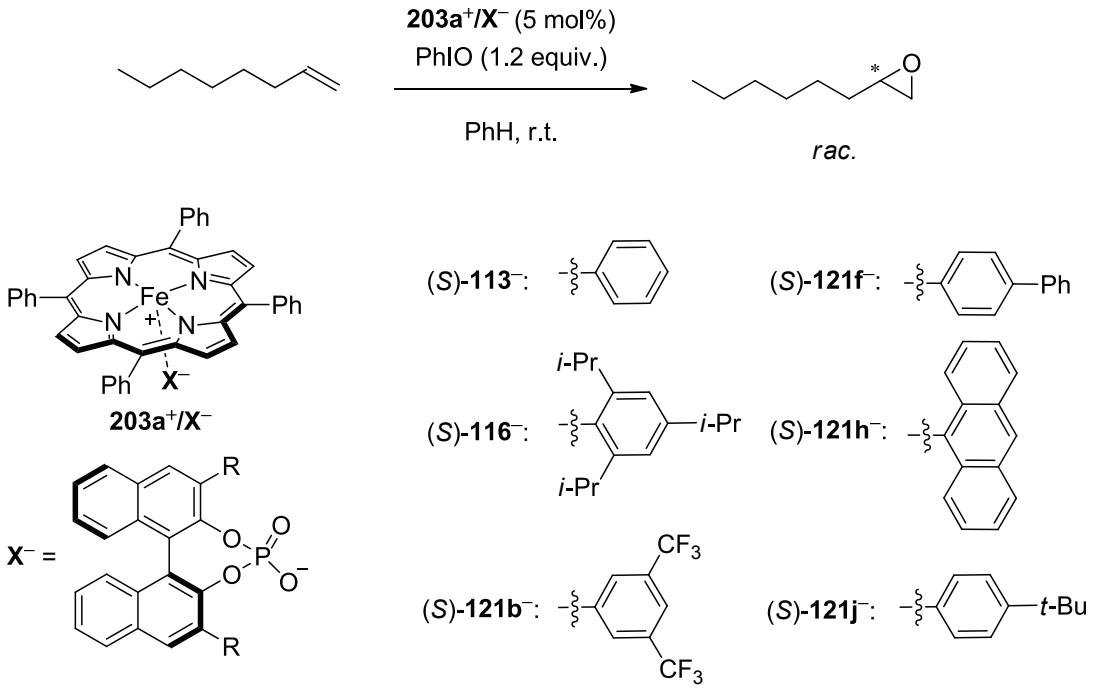
4.3.2.3 Preparation of Porphyrins Ion-pair Catalysts by Anion Exchange

The anion exchange of Cl^- in achiral porphyrin iron complexes was performed in $CDCl_3$, and monitored by ^{31}P-NMR analysis. Once the anion exchange was complete, due to the paramagnetic Fe^{III}, the formation of contact ion pair of porphyrin-Fe^{III}/phophate will cause the disappearance of the ^{31}P peaks in the 0-15 ppm range, which belong to the silver phosphates. Upon the completion of the anion exchange, the AgCl generated was filtered off. After removal of the solvent and drying *in vacuo*, the ion-pair catalysts were directly used in the epoxidation reaction without further purification.

4.3.3 Preliminary Results and Limitation

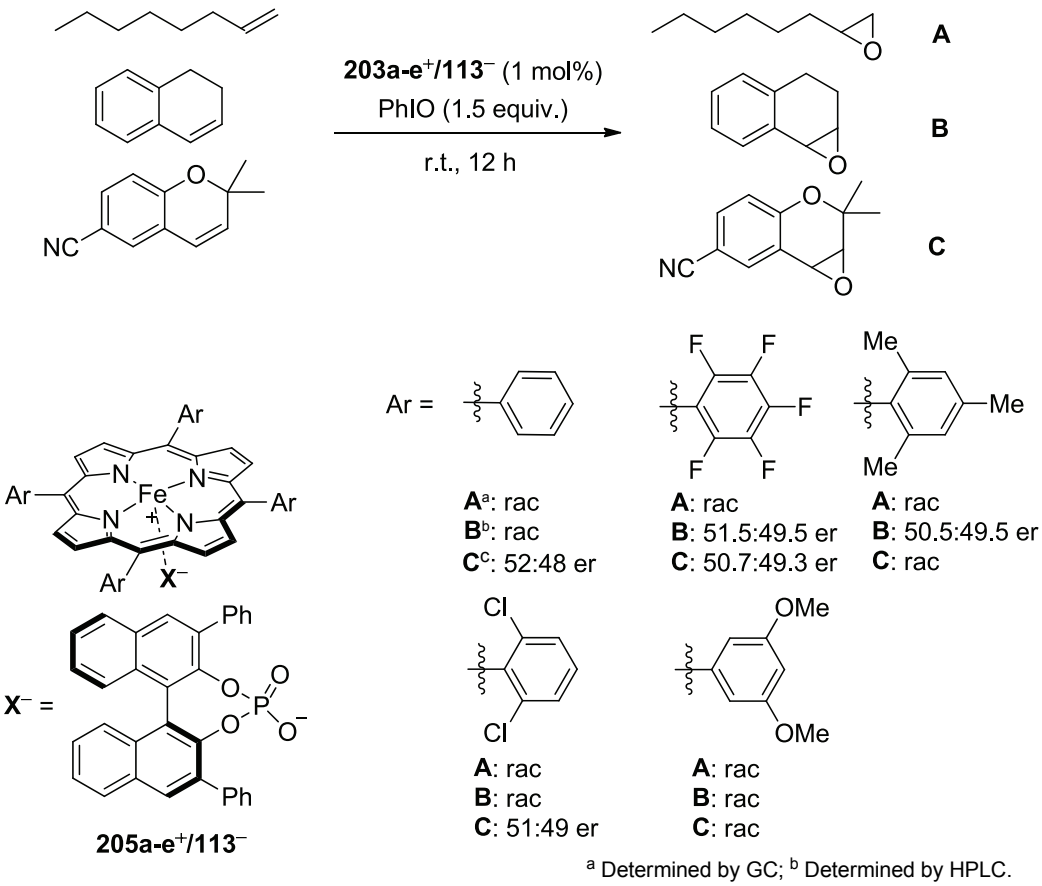
The commercially available ferric porphyrin **205a** was first tested in the epoxidation of 1-octene in the combination with various phosphate anions as shown in Scheme 4.35.

Unfortunately, only racemic 1-octene oxide was obtained with these ion-pair catalysts **205a**$^+$ **/X**$^-$.



Scheme 4.35: Epoxidatin of 1-octene with phorphyrin-Fe phosphate ion pairs.

Later, a series of porphyrins with different substituents was examined, and 1-octene, 1,2-dihydronaphthalene and chromene **19** were taken as the substrates in the porphyrin screening. The observed enantioselectivities in the epoxides (**A**, **B** and **C**) are presented in Scheme 4.36. However, none of these ion-pair catalysts gave substantial enantioselectivity, even though **205a**$^+$ **/113**$^-$ delivered epoxide **C** in 52:48 er rather than in a completely racemic form.



Scheme 4.36: Epoxidation with various porphyrin iron/phosphate catalysts.

At this point, sterically hindered porphyrin iron complex **214**, which has been shown of a good shape-selectivity in the epoxidation reactions,[134] was prepared (Figure 4.21). However, this ferric porphyrin complex exhibited quite low activity in the epoxidation of 1-octene, and only 5% conversion was observed by NMR analysis after 24 h with 1 mol% catalyst at room temperature. Moreover, a complete anion exchange with silver phosphate could not be accomplished even under reflux conditions in toluene.

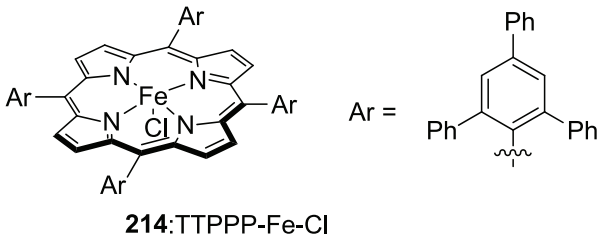
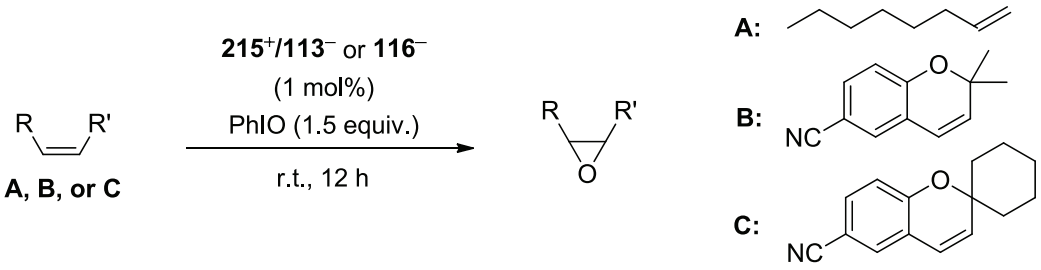


Figure 4.21: Bulky TTPPP-iron complex **214**.

We then turned to *trans*-porphyrins of an ABAB type. These achiral ABAB porphyrin ligands would provide a C_2-symmetric chiral environment around the iron center under the influence of a chiral anion. Phosphate anion **113**$^-$ and **116**$^-$ were chosen as the chiral anion considering

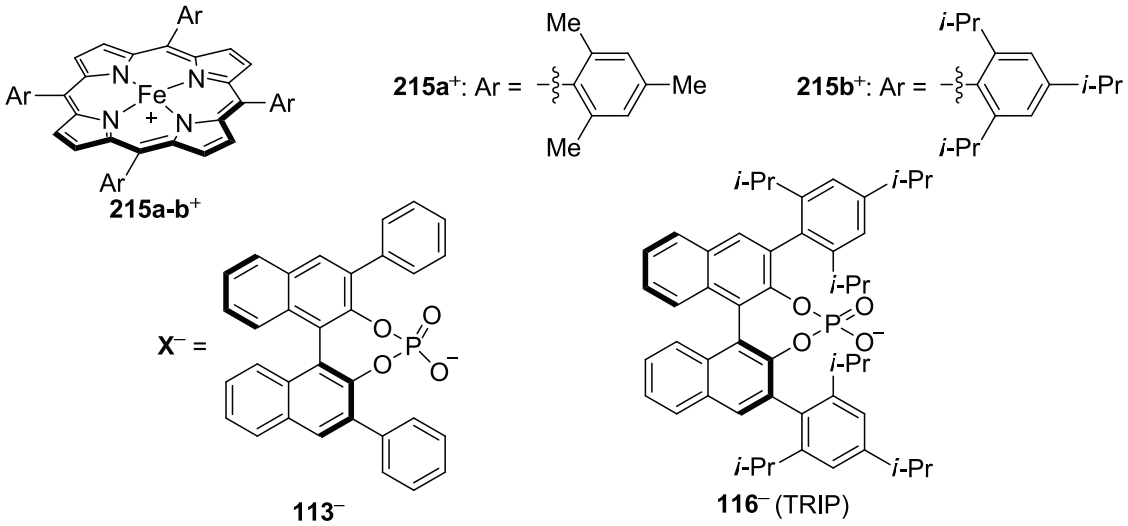
the effect of the size of 3,3'-substituents. The cross-combinations of the two phosphate anions with ABAB porphyrin iron cations **213a-b$^+$** were tested in the epoxidations of 1-octene and chromene **B**. Considering the quite low enantioselectivities in our previous study with these porphyrin-derived ion-pair catalysts, a more sterically-demanding substrate **C** was also examined. The enantiomeric excess obtained with these ion pairs are tabulated in Table 4.15. Although the enantioselectivies obtained were quite low in all cases, substantial stereoselectivity (up to 56:44 er) was observed in the epoxidation of sterically-demanding substrates **B** and **C** with relatively bulky porphyrin ligands/bulkyl phosphate combinations (entries 8, 10 and 12).

Table 4.15: Epoxidation with ABAB-type porphyrin iron/ phosphate ion-pair catalysts



Entry	Substrate	Catalyst	er[a]
1	**A**	**215a$^+$/113$^–$**	rac[b]
2	**A**	**215a$^+$/116$^–$**	rac[b]
3	**A**	**215b$^+$/113$^–$**	rac[b]
4	**A**	**215b$^+$/116$^–$**	rac[b]
5	**B**	**215a$^+$/113$^–$**	rac
6	**B**	**215a$^+$/116$^–$**	50.5:49.5
7	**B**	**215b$^+$/113$^–$**	rac
8	**B**	**215b$^+$/116$^–$**	**56:44**
9	**C**	**215a$^+$/113$^–$**	50.5:49.5
10	**C**	**215a$^+$/116$^–$**	54:46
11	**C**	**215b$^+$/113$^–$**	51:49
12	**C**	**215b$^+$/116$^–$**	**55:45**

[a] Determined by HPLC analysis; [b] Determined by chiral GC.



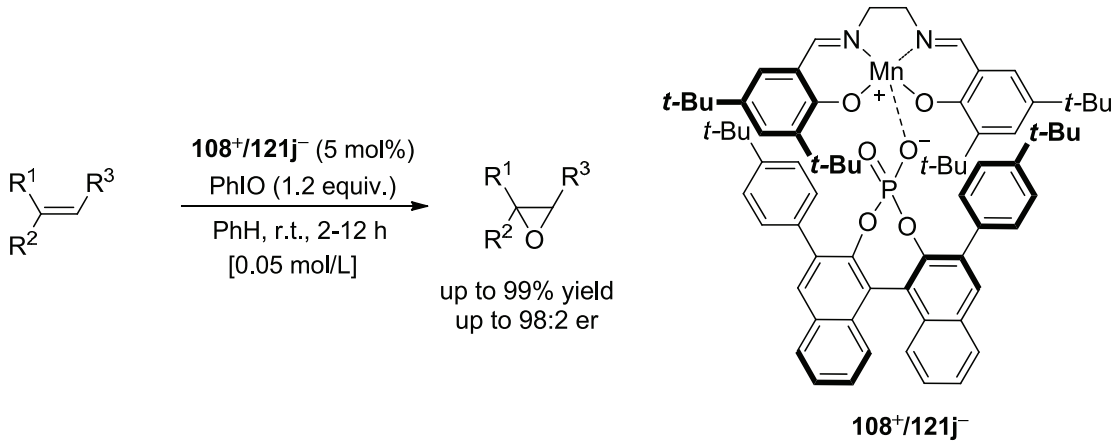
There is a possibility to increase the enantioselectivity with these ABAB porphyrin-derived ion-pair catalysts by installing an appropriate and bigger substituent onto the porphyrin moiety, but the problem is that the preparation of these sterically hindered achiral porphyrins usually is not an easy task. Due to the hindrance of bulky substitutents like the 2,4,6-triphenylphenyl group, the cyclization to form porphyrin becomes quite difficult, resulting in a low-yielding reaction. In any case, the substantial enantioselectivity (up to 56:44 er) observed with these ion-pair catalysts (achiral ferric porphyrin cation/chiral phosphate anion) has demonstrated the possibility to induce a chiral conformation from achiral porphyrin ligands.

4.3.4 Conclusion

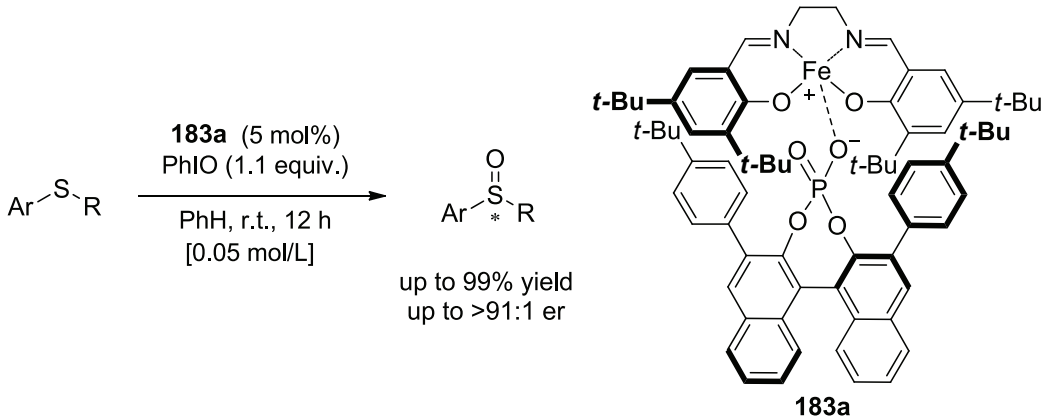
Two different types of porphyrin were prepared and examined in the combination of various chiral BINOL-derived phosphate anions in the epoxidation of teminal alkenes and chromenes. Although in the Fe^{III}-porphyrin/chiral phosphate ion-pair system, low levels of enantioselectivity were observed, the substantial selectivity (up to 56:44 er) rather than racemic product has proved the feasibility of inducing a chiral conformation from an achiral porphyrin by indroducing a chiral counteranion. This counteranion strategy can be employed in the development of new porphyrin catalysts that consist of achiral porphyrin ligands, and can also be employed to improve the performce of chiral metalloporphyrin complexes.

5 Summary and Outlook

In this thesis work, ion-pair catalysts were designed and prepared based on the concept of "Asymmetric Counteranion Directed Catalysis (ACDC)". In the asymmetric epoxidation of alkenes, ion pair **108$^+$/121j$^-$** stood out as the most efficient catalyst, providing a high level of enantioselectivity in the epoxidation of a series of alkenes. According to the model of the ion-pair catalyst, the chiral counterion (*S*)-**121j$^-$** can induced a conformation of the achiral Mn-salen resembling the (*S,S*)-Jacobsen catalyst.



A similar level of enantioselectivity to the Jacobsen catalyst has also been observed in the asymmetric oxidation of sulfides with ion pair **108$^+$/121j$^-$**. Interestingly, the corresponding ferric ion-pair catalyst **183a** has exhibited much better selectivity than the chiral Fe-salen catalyst and our manganese ion-pair catalyst **108$^+$/121j$^-$**. Especially in the cases of electron-poor sulfides, up to >99:1 er was obtained together with high chemoselectivity (suloxide/sulfone > 15:1). These results obtained with our ion-pair catalyst represent the best so far among all the chiral salen ligand-derived Mn- and Fe-salen complexes.



The application of the ACDC concept to the ferric porphyrin-catalyzed epoxidation was also attempted. Albeit low, substantial enantioselectivity (up to 56:44 er) has been observed. This chiral anion strategy provides a new approach to understand the role of axial ligands like the residue of cysteine in the P-450 related enzymes.

As already demonstrated in the asymmetric oxidation of sulfides, the success of ion pair-catalyzed epoxidation has paved the way for the further application of the ACDC concept to other metallosalen systems and other types of transformation. Due to the similar mechanism, atom-transfer reactions like cyclopropanation and aziridination are most feasible. The enhanced Lewis acidity of these frustrated Lewis ion pairs suggests another potential of these ion pairs as Lewis acid catalysts.

Even though the enantioselectivity obtained so far with the ion pairs of achiral metalloporphyrins/chiral anions is too low to envision their practical application, the substantial enantioselectivity observed may suggest the counteranion strategy could provide an alternative and simple approach to construct chiral metalloporphyrin catalysts. Further investigation to search for suitable achiral porphyrin ligands and compatible chiral anions will lead to a better understanding of the required conformation of the ion-pair catalyst for highly stereoselective control.

6 Experimental Part

6.1 General Experimental Conditions

Solvents and Reagents

All solvents were purified by distillation before use following standard procedures.[154] Absolute diethyl ether, tetrahydrofuran and toluene were obtained by distilling over sodium, using benzophenone as indicator. Absolute acetonitrile, chloroform and dichloromethane were obtained by distillation over calcium hydride. Absolute *tert*-butanol was obtained by distilling over calcium oxide. Ethanol, *iso*-propanol and methanol were dried by distilling over magnesium. Dimethylformamide was refluxed over calcium hydride and distilled under an inert atmosphere with reduced pressure (15 mbar, 75 °C). Commercial reagents were obtained from various commercial sources and used as received.

Inert Gas Atmosphere

Air and moisture-sensitive reactions were conducted under an argon atmosphere. Argon was obtained from the company *L'Air Liquide* with purity higher than 99.5%.

Thin Layer Chromatography (TLC)

Materials: *Macherey-Nagel* MN POLYGRAM Sil G/UV254 plates (0.20 mm thick)
Macherey-Nagel MN POLYGRAM ALOX N/UV254 plates (0.20 mm thick)

The spots were visualized in UV-light (λ = 254 nm) and/or by staining with iodine, ninhydrin, vanilline or phosphomolybdic acid.

Flash Column Chromatography

Materials: Silicagel 60 (*Merck* 60 Å, 230-400 mesh 0.040-0.063 mm).

Gas chromatography (GC)

Apparatus: *Agilent Technolgy* GC 6890 N (Carrier gas: Helium) with HP 6890 Series Injector

Materials: *FS LIPODEX-G* (25 m, 0.25 mm, 0.25 μm film thickness)

BGB 178 (30 m, 0.25 mm, 0.25 µm film thickness)

Gas Chromatography with Mass Spectrometric Detector (GC/MS)

Apparatus: *Agilent Technolgy* GC 6890 Series and MSD 5973 (Carrier gas: Helium) with HP6890 Series Injector

Materials: *MN Optima 5* (30 m, 0.25 mm, 0.25 µm film thickness)

Analytical High Performance Liquid Chromatography (HPLC)

Apparatus: *Shimadzu* LC-2010C HPLC-system equipped with a spectrophotometric detector.

Materials: *Daicel* Chiralcel OJ-H column (0.46 cm × 25 cm)
Daicel Chiralcel OB-H column (0.46 cm × 25 cm)
Daicel Chiralcel OD-H column (0.46 cm × 25 cm)
Daicel Chiralcel AD-H column (0.46 cm × 25 cm)
Daicel Chiralcel AS-H column (0.46 cm × 25 cm)

Nuclear magnetic resonance spectroscopy (NMR)

Apparatus: *Bruker* DPX 300 (^{1}H: 300 MHz, ^{13}C: 75 MHz)
Bruker AV 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz)
Bruker AV 500 (^{1}H: 500 MHz, ^{13}C: 125 MHz)

Spectra were recorded at room temperature (298 K) unless otherwise stated. Chemical shifts for protons and carbons were reported in parts per million (ppm) downfield from tetramethylsilane (TMS) and were referenced to residual proton in the NMR solvents (e.g. $CHCl_3$: δ 7.26 in ^{1}H) and carbon resonances of the solvents (e.g. $CDCl_3$: δ 77.0) respectively. The coupling constants (*J*) were reported in Hertz (Hz). For the fine structure interpretation the abbreviations of the signals are the following: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

Mass Spectrometry (MS)

Apparatus: *Finnigan* MAT 8200 (70 eV)
Finnigan MAT 8400 (70 eV)
Bruker ESQ 3000
Bruker APEX III FT-MS (7 T magnet)

Mass spectra were measured on a Finnigan MAT 8200 (70 eV) by electron ionization, chemical ionization, of fast atom/ion bombardment techniques. Accurate mass determinations were obtained on a Bruker APEX III FT-MS (7 T magnet).

Melting Point (MP)

Apparatus: *Büchi* 540 Melting Point

All the melting points were measured in open glass capillary and the values are uncorrected.

Specific Rotation ([α])

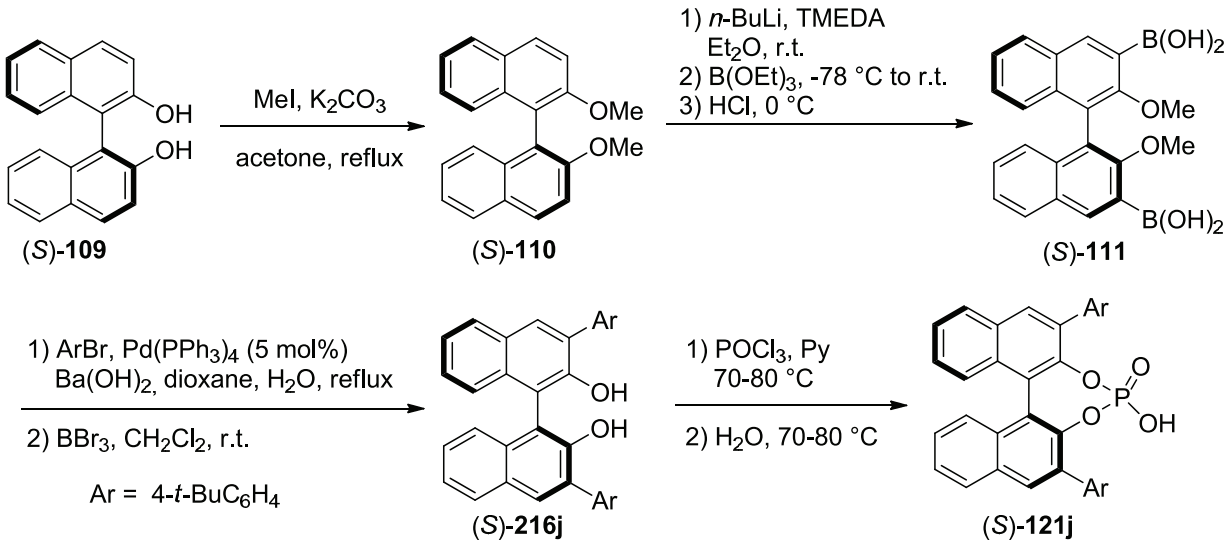
Apparatus: *Perkin Elmer* 343

Optical rotations were measured using a 1 mL cell with a 1 dm path length. Measurements were carried out in different wavelengths using sample solution in chloroform at 20 °C. The sample concentrations are given in g/100 mL unit.

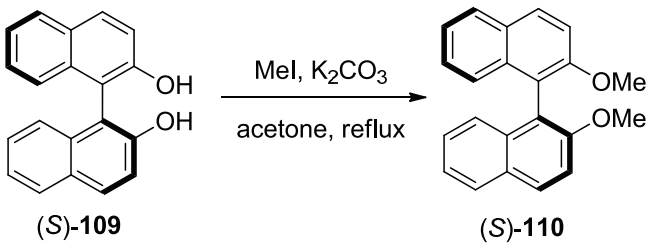
6.2 Preparation of Mn-Salen Phosphate Complexes

6.2.1 Preparation of BINOL-Derived Phosphoric Acids

6.2.1.1 Synthesis of (*S*)-3,3'-Bis(4-*tert*-butylphenyl)-1,1'-binaphthyl-2,2'-diyl Hydrogen Phosphate ((*S*)-121j)



Preparation of (S)-2,2'-dimethoxy-1,1'-binaphthyl ((S)-110):[74]

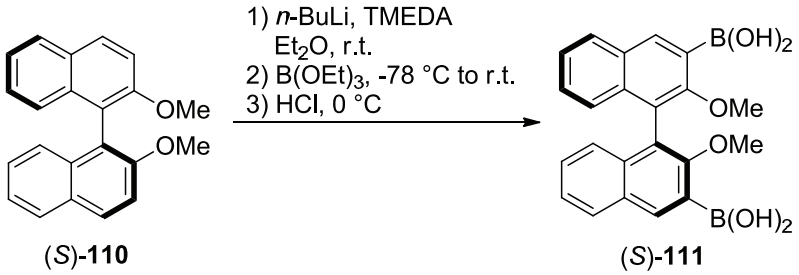


A suspension of (*S*)-BINOL (**109**, 5.10 g, 17.81 mmol) in acetone (40 mL) was heated at reflux to give a homogeneous solution. To this solution were added potassium carbonate (8.30 g, 60.00 mmol) and methyl iodide (9.94 g, 70.00 mmol), and the mixture was gently refluxed for 24 hours. If the starting BINOL was not completely consumed, additional methyl iodide was added. The solvent was then evaporated to leave a volume of 30 mL, which was cooled to room temperature and treated with water (150 mL). After the mixture was stirred for 8 hours, the resulting solid was collected by filtration, washed with water, and dried *in vacuo*. The

desired protected BINOL was obtained as a white solid in quantitative yield (5.47 g, 98% yield).

(*S*)-**110**: $C_{22}H_{18}O_2$ (314.38 g/mol);
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.68 (s, 6H, OC*H*$_3$), 7.02 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.12 (t, *J* = 7.4 Hz, 2H, Ar*H*), 7.23 (t, *J* = 7.3 Hz, 2H, Ar*H*), 7.37 (d, *J* = 9.0 Hz, 2H, Ar*H*), 7.78 (d, *J* = 8.1 Hz, 2H, Ar*H*), 7.89 (d, *J* = 9.0 Hz, 2H, Ar*H*);
^{13}C NMR (100 MHz, $CDCl_3$): δ 56.6, 113.9, 119.3, 123.1, 124.9, 125.9, 127.6, 128.9, 129.0, 133.7, 154.6.

Preparation of (S)-2,2'-dimethoxy-1,1'-binaphthyl-3,3'-diyldiboronic acid((S)-111):[74]



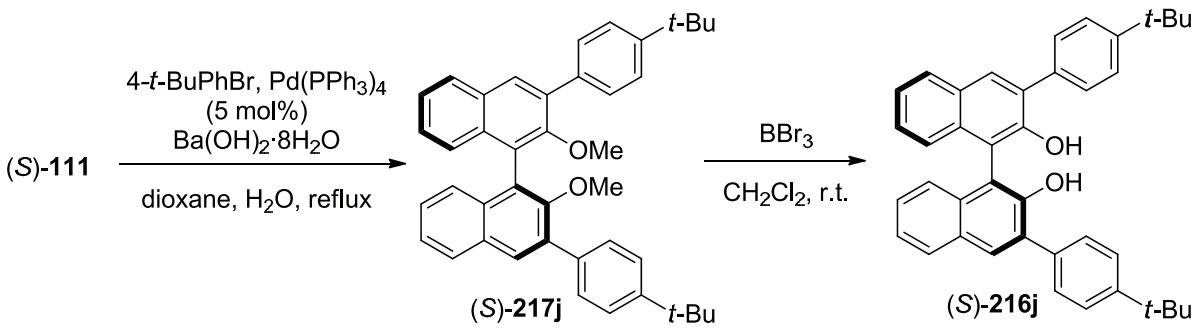
(*S*)-**110** (*S*)-**111**

To a solution of TMEDA (5.89 mL, 39 mmol) in ether (200 mL) was added *n*-BuLi (2.5 M in hexane, 15.6 mL, 39 mmol) at room temperature. After the reaction solution was stirred for 30 min, solid (*S*)-2,2'-dimethoxy-1,1'-binaphthyl (4.07 g, 13 mmol) was added in one portion, and the resulting mixture was stirred for another 3 hours. The light brown suspension was cooled to −78 °C, and ethyl borate (15.48 mL, 91 mmol) was added over 10 min. The reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was then cooled to 0 °C, and 1 N HCl solution (100 mL) was slowly added. The resulting solution was stirred for additional 2 hours at room temperature. The organic layer was then separated, washed with 1 N HCl and brine, dried over Na_2SO_4, and concentrated. The crude product (pale yellow solids) was recrystallized from toluene to give (*S*)-**111** (3.75 g, 73% yield) as colorless crystals.

(*S*)-**111**: $C_{22}H_{20}B_2O_6$ (402.01 g/mol);
^{1}H-NMR (400 MHz, acetone-d_6): δ 2.06 (s, 4H, O*H*), 3.43 (s, 6H, C*H*$_3$), 7.12 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.36-7.32 (m, 2H, Ar*H*), 7.46 (t, *J* = 7.4 Hz, 2H, Ar*H*), 8.05 (d, *J* = 8.1 Hz, 2H, Ar*H*), 8.57 (s, 2H, Ar*H*);

^{13}C-NMR (100 MHz, acetone-d_6): δ 62.1, 124.6, 126.0, 126.5, 128.5, 129.4, 130.0, 131.8, 137.0, 139.4, 161.6.

Synthesis of (S)-3,3'-bis(4-tert-butylphenyl)-1,1'-binaphthalenyl-2,2'-diol((S)-216j).[74]



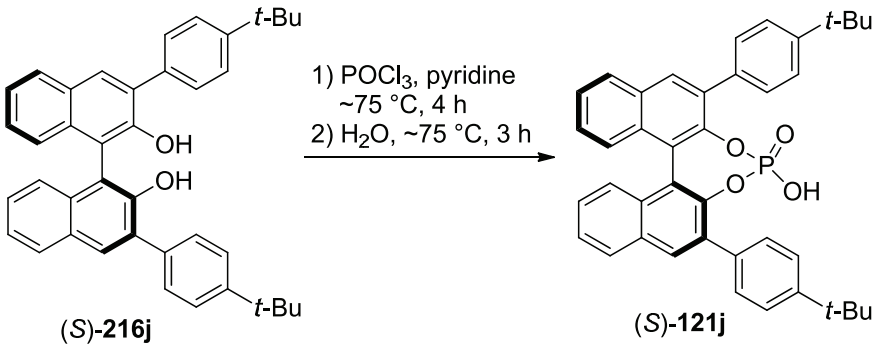
To a solution of (*S*)-**111** (3.00 g, 7.5 mmol) in degassed dioxane/water (60 mL, 3:1) were added 4-*tert*-butylphenyl (4.80 g, 22.5 mmol), $Ba(OH)_2 \cdot 8H_2O$ (6.50 g, 20.50 mmol), and $Pd(PPh_3)_4$ (450 mg, 0.39 mmol). The reaction mixture was heated at reflux temperature for 24 hours, and then cooled to room temperature. After removal of dioxane, the resulting residue was dissolved with CH_2Cl_2, washed with 1 N HCl solution and brine, dried (Na_2SO_4), and concentrated. A fast column chromatography on silica gel (EtOAc/hexanes, 1:20) gave 3.86 g of the coupling product. To a solution of the coupling product in CH_2Cl_2 (150 mL) at 0 °C was added a solution of BBr_3 in CH_2Cl_2 (1.0 M, 30.0 mL, 30 mmol). The reaction mixture was warmed to room temperature and stirred for 5 hours, and then quenched with water (10 mL) in an ice bath. The mixture was then slowly poured into a stirred mixture of CH_2Cl_2 and water. The resulting organic layer was separated, washed with brine, dried (Na_2SO_4), and concentrated. Chromatography on silica gel (EtOAc/hexanes, 1:20) gave the free diol (*S*)-**216j** (3.05 g, 75% yield over two steps) as a white solid.

(*S*)-**217j**: $C_{42}H_{42}O_2$ (578.78 g/mol);
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (s, 18H, C*H*$_3$), 3.25 (s, 6H, OC*H*$_3$), 7.29 (m, 4H, Ar*H*), 7.44 (m, 2H, Ar*H*), 7.52 (d, *J* = 8.4 Hz, 4H, Ar*H*), 7.75 (d, *J* = 8.4 Hz, 4H, Ar*H*), 7.94 (d, *J* = 8.3 Hz, 2H, Ar*H*), 8.02 (s, 2H, Ar*H*);
^{13}C NMR (125 MHz, $CDCl_3$): δ 31.5, 34.6, 60.6, 124.9, 125.3, 125.83, 125.85, 126.1, 128.0, 128.9, 130.4, 130.8, 133.5, 134.9, 135.9, 150.2, 154.3.

(*S*)-**216j**: $C_{40}H_{38}O_2$ (550.73 g/mol);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.39 (s, 18H, C*H*$_3$), 5.44 (s, 2H, O*H*), 7.25 (s, 4H, Ar*H*), 7.33 (m, 2H, Ar*H*), 7.50 (d, *J* = 7.4 Hz, 4H, Ar*H*), 7.68 (d, *J* = 7.4 Hz, 4H, Ar*H*), 7.88 (d, *J* = 8.3 Hz, 2H, Ar*H*), 8.04 (s, 2H, Ar*H*);
^{13}C NMR (125 MHz, $CDCl_3$): δ 31.6, 34.8, 112.8, 124.5, 124.6, 125.7, 127.4, 128.7, 129.6, 129.8, 130.9, 131.4, 133.2, 134.8, 150.6, 150.9.

Synthesis of (S)-3,3'-bis(4-tert-butylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate ((S)-121j).[18a;135]



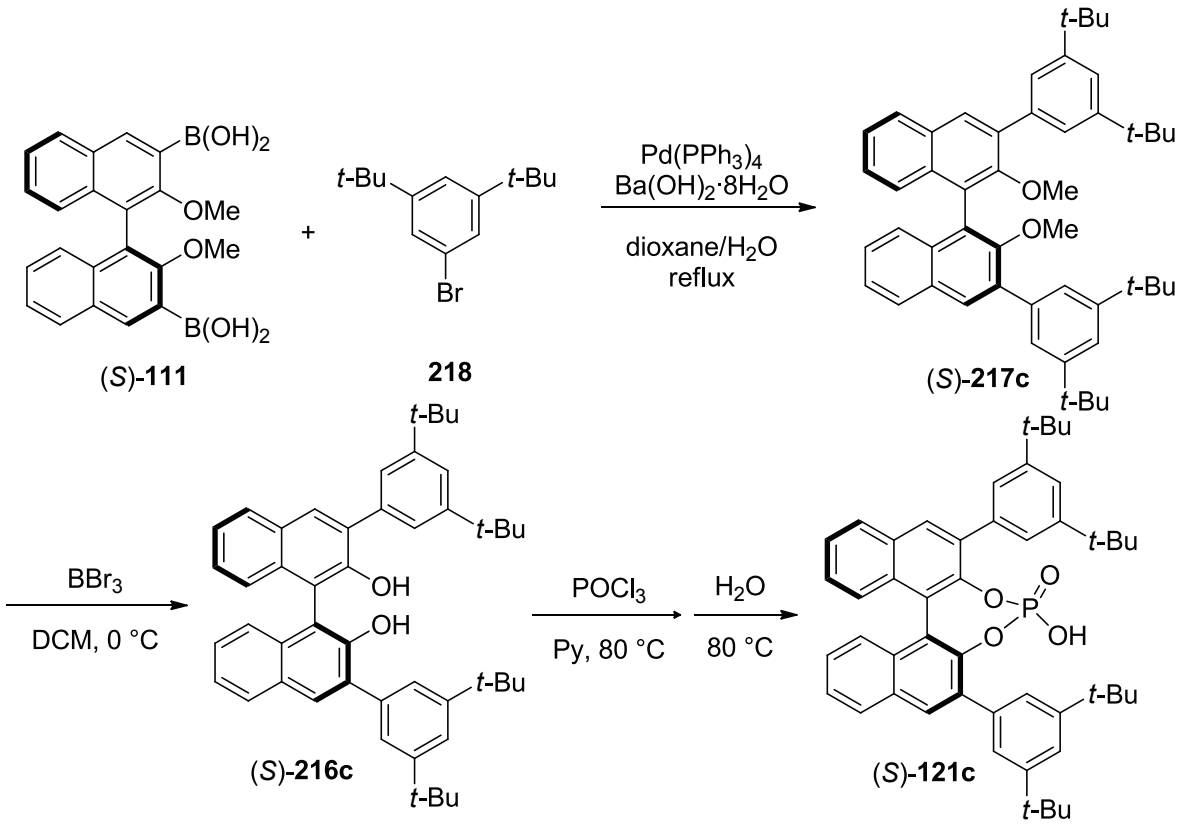
(*S*)-**216j** (*S*)-**121j**

To a suspension of the diol (3.00 g, 5.5 mmol) in pyridine (20.0 mL) in a two-necked flask, was added phosphorous oxychloride (1.65 g, 11. 0 mmol) dropwise at room temperature with rapid stirring, and the resulting mixture was heated to 75 °C. When the free diol was completely consumed (4 hours, followed by TLC), 10 mL of water was then added slowly to the reaction mixture. The resulting biphasic suspension was stirred for additional 3 hours at this temperature. The reaction mixture was then diluted with CH_2Cl_2 and pyridine was removed by washing with 1 N HCl. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product as a pale yellow solid. Purification by flash column chromatography on silica gel (gradient from 2% to 5% EtOH in CH_2Cl_2) yielded the phosphoric acid (*S*)-**121j** (after acidified with 6 N HCl) as a pale yellow solid (3.20 g, 96% yield).

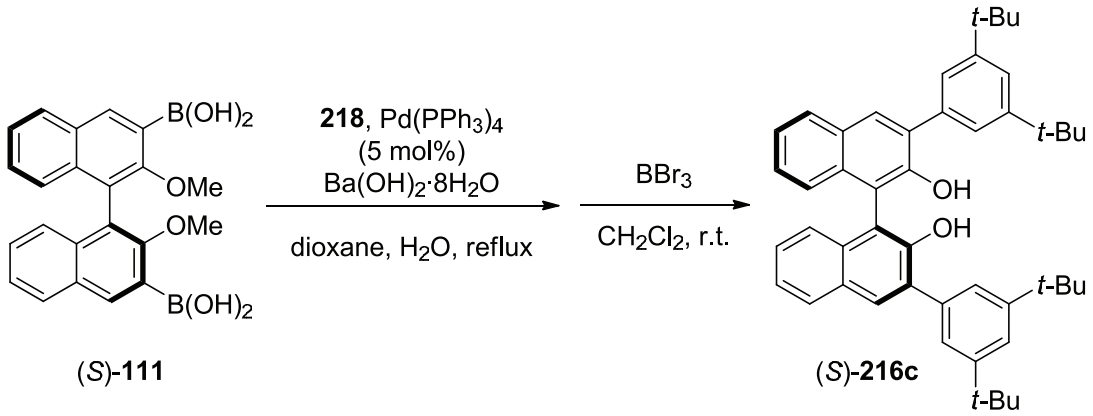
(*S*)-**121j**: $C_{40}H_{37}O_4P$ (612.69 g/mol);
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09 (s, 18H, C*H*$_3$), 7.29-7.37 (m, 8H, Ar*H*), 7.50 (t, *J* = 6.8 Hz, 2H, Ar*H*), 7.55 (d, *J* = 8.4 Hz, 4H, Ar*H*), 7.95 (d, *J* = 8.2 Hz, 2H, Ar*H*), 8.02 (s, 2H, Ar*H*);
^{13}C NMR (125 MHz, $CDCl_3$): δ 31.1, 34.4, 122.5, 125.3, 125.9, 126.4, 127.2, 128.4, 129.4, 131.4, 131.7, 131.9, 133.8, 133.9, 144.6 (d), 150.5;
^{31}P NMR (202 MHz, $CDCl_3$): δ 3.71;

HPLC (to determine the optical purity): (*S*)-**121j** (99.6% ee), (*R*)-**121j** (98.4% ee). Chiralpak QN-AX (150 mm, 4.6 mm) MeOH/AcOH/NH_4Ac = 98/2/0.5 (V/V/W), 1.0 mL/min, 254 nm; t_r(R) = 20.30 min, t_r(S) = 23.68 min.

6.2.1.2 Synthesis of (*S*)-3,3'-Bis(3,5-di-tert-butylphenyl)-1,1'-binaphthyl-2,2'-diyl Hydrogen Phosphate ((*S*)-121c)



***Synthesis of (S)-3,3'-bis(3,5-di-tert-butylphenyl)-1,1'-binaphthyl-2,2'-diol((S)-216c)**:*



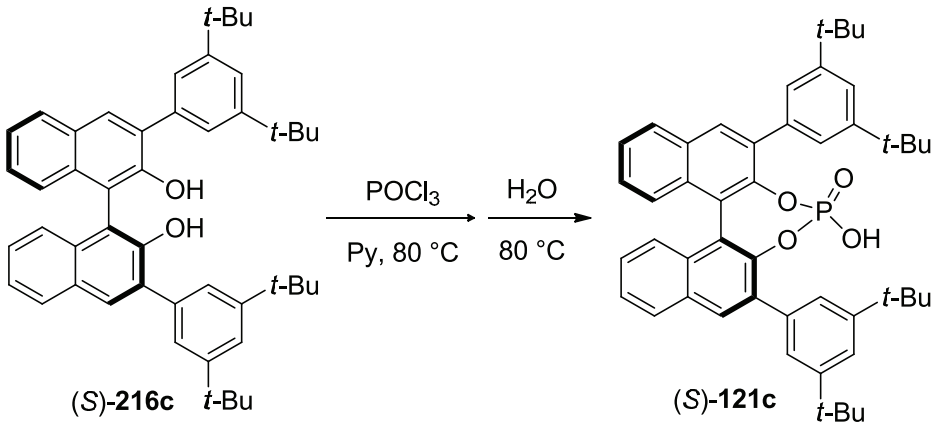
To a solution of boronic acid (*S*)-**111** (402 mg, 1.00 mmol) in degassed dioxane/water (8 mL, 3:1) were added aryl bromide **218** (672 mg, 2.50 mmol), $Ba(OH)_2 \cdot 8H_2O$ (870 mg, 2.8 mmol), and $Pd(PPh_3)_4$ (120 mg, 0.10 mmol). The reaction mixture was heated to reflux for 24 hours and then cooled down to room temperature. After the solvent was removed, the resulting residue was dissolved in CH_2Cl_2, washed with 1 N HCl and brine, dried ($MgSO_4$), and concentrated under reduced pressure to give the coupling product. The crude product was dissolved in dichloromethane (5 mL) and treated with BBr_3 (in DCM, 1.0 mol/L, 5 mL, 5.0 mmol) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 4 hours, and later quenched with water (1 mL) in an ice bath. Purification by column chromatography on silica gel (DCM/hexanes, 1:5) gave the desired diol as a white solid (550 mg, 83% yield over two steps).

(*S*)-**216c**: $C_{48}H_{54}O_2$ (662.94 g/mol);

^{1}H-NMR (500 Mz, $CDCl_3$): δ 1.38 (s, 36H, *t*-Bu-*H*), 5.48 (s, br, 2H, O*H*), 7.23-7.39 (m, 6H, Ar*H*), 7.49 (m, 2H, Ar*H*), 7.56 (d, *J* = 1.7 Hz, 4H, Ar*H*), 7.92 (d, *J* = 8.0 Hz, 2H, Ar*H*), 8.02 (s, 2H, Ar*H*);

^{13}C-NMR (125 Mz, $CDCl_3$): δ 31.6, 35.0, 113.0, 122.0, 123.9, 124.1, 124.6, 127.0, 128.4, 129.4, 131.0, 131.6, 133.0, 136.5, 150.0, 151.0.

Synthesis of (S)-3,3'-bis(3,5-di-tert-butylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate(*(*S*)-121c*)*:



Diol (*S*)-**216c** (550 mg, 0.83 mmol) was dissolved in pyridine (2.0 mL) in a Schlenk tube, and to this solution, phosphoryl chloride (0.2 mL, 2.0 mmol) was added dropwise at room temperature via a syringe. The resulting mixture was stirred for 3 hours at 80 °C until all the starting diol was consumed (monitored by TLC). Then, 1.5 mL of water was added with caution, and the resulting suspension was stirred for additional 3 hours at 80 °C. The reaction mixture was then cooled to room temperature, diluted with dichloromethane (30 mL), washed with 1 N HCl. The organic phase was separated, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product. Purification by flash column chromatography on silica gel (3% EtOH in DCM) yielded the phosphoric acid as a white solid (506 mg, 85% yield).

(*S*)-**121c**: $C_{48}H_{53}O_4P$ (724.91 g/mol);

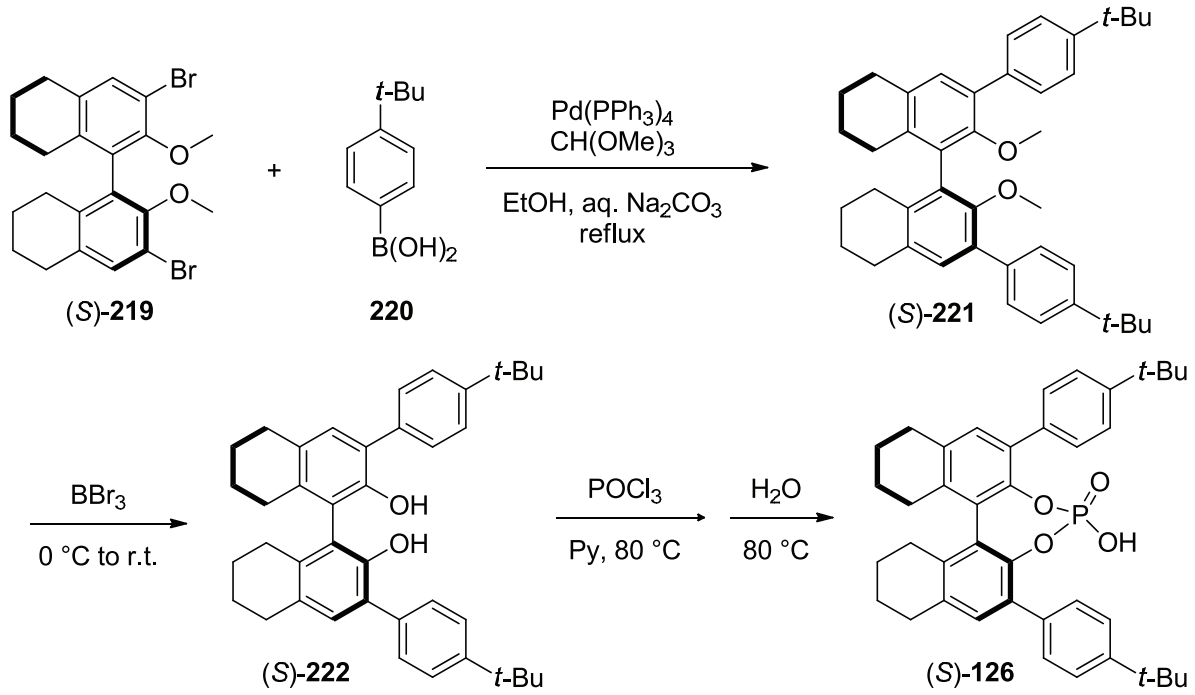
^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.14 (s, 36H, *t*-Bu-*H*), 5.14 (s br, 1H, O*H*), 7.28-7.32 (m, 4H, Ar*H*), 7.36 (d, *J* = 1.8 Hz, 4H, Ar*H*), 7.38 (d, *J* = 8.6 Hz, 2H, Ar*H*), 7.49 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.94-7.95 (m, 4H, Ar*H*);

^{13}C-NMR (125 MHz, $CDCl_3$): δ 31.3, 34.7, 121.4, 122.5, 124.2, 125.7, 126.2, 127.1, 128.2, 131.4, 131.5, 131.9, 135.3, 136.2, 144.8 (d), 150.4;

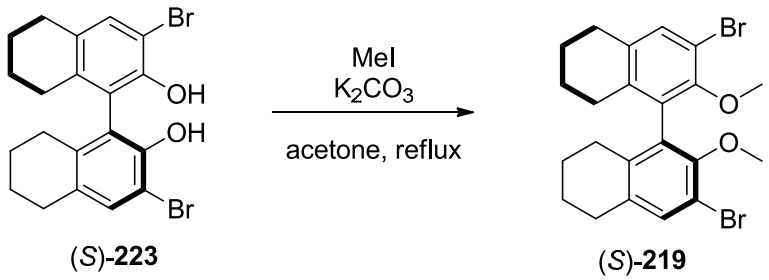
^{31}P-NMR (202 MHz, $CDCl_3$): δ 1.45;

HRMS (ESIneg): calculated for ($[C_{48}H_{52}O_4P_1]^-$) 723.360446, found 723.360873.

6.2.1.3 Synthesis of (*S*)-3,3'-Bis-(4-*tert*-butylphenyl)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthalenyl-2,2'-diyl Hydrogen Phosphate ((*S*)-126)



Synthesis of (S)-3,3'-dibromo-2,2'-dimethoxy-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl ((S)-219):[136]



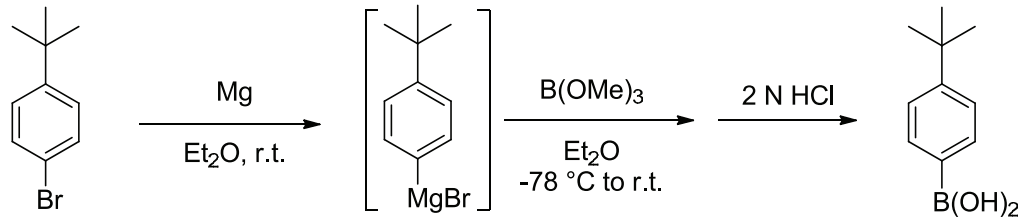
Following the reported procedure for the BINOL methyl protection, a suspension of (*S*)-**223** (1.00 g, 2.2 mmol) in acetone (20 mL) was heated to form a homogeneous solution. To this solution were added potassium carbonate (1.66 g, 12 mmol) and methyl iodide (2.00 g, 14 mmol), and the resulting mixture was heated to reflux for 22 h until completed consumption of the starting diol. The solvent was then evaporated under reduced pressure, and the resulting solid was washed with water and dried *in vacuo* to afford the desired product (*S*)-**219** as a white powder (1.05 g, 99%).

(*S*)-**219**: $C_{22}H_{24}Br_2O_2$ (480.23 g/mol);

^{1}H-NMR (500MHz, $CDC1_3$): δ 1.72 (m, 8H, C*H*$_2$), 2.08 (m, 2H, C*H*$_2$), 2.26 (m, 2H, C*H*$_2$), 2.76 (m, 4H, C*H*$_2$), 3.57 (s, 6H, OC*H*$_3$), 7.32 (s, 2H, Ar*H*);

^{13}C-NMR (125 MHz, $CDC1_3$): δ 22.7, 22.7, 27.4, 29.3, 60.4, 113.8, 131.9, 132.9, 134.7, 135.9, 151.5.

Synthesis of 4-tert-butylbenzeneboronic acid (220):[137]



220

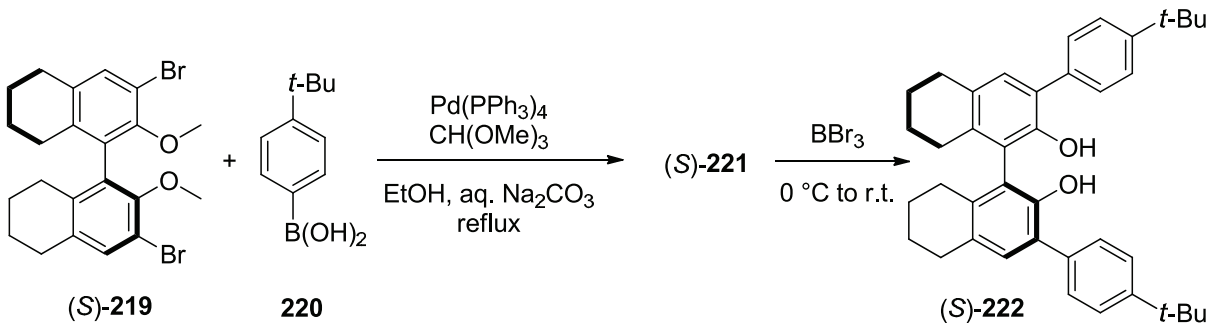
A 100 mL two-necked flask was charged with magnesium turnings (1.3 g, 55 mmol) and a crystal of iodine, and then a solution of 4-*tert*-butylbromobenzene (10.6 g, 50 mmol) in dry Et_2O (50 mL) was added via an addition funnel. The resulting exotherm maintained the reaction mixture at reflux temperature for several minutes. The resulting solution of 4-*tert*-butylphenylmagnesium bromide (50 mmol) was cooled to room temperature and cannulated onto a stirred solution of $B(OMe)_3$ (5.2 g, 50 mmol) in Et_2O (25 mL) during 20 minutes at -78 °C under a positive pressure of argon. The reaction mixture was warmed to room temperature and stirred overnight, and then the resulting thick-grey slurry was poured into 30 mL of aq. HCl (2 N). The aqueous layer was extracted with Et_2O (2×20 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford a yellow oil. Addition of Et_2O (25 mL) followed by hexanes (150 mL), and cooling in the freezer (-20 °C) overnight precipitated the desired product as white needle crystals (2.5 g, 28%). Further crops could be obtained by concentrating the mother liquor.

220: $C_{10}H_{15}BO_2$ (178.04 g/mol);

^{1}H-NMR (300 Mz, $CDCl_3$): δ 1.38 (s, 9H, *t*-Bu-*H*), 7.54 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.48 (d, *J* = 8.4 Hz, 2H, Ar*H*);

^{13}C-NMR (75 Mz, $CDCl_3$): δ 31.2, 35.1, 124.9, 133.4, 135.6, 156.0.

***Synthesis of (S)-3,3'-bis-(4-tert-butylphenyl)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthalenyl-2,2'-diol ((S)-222)**:*

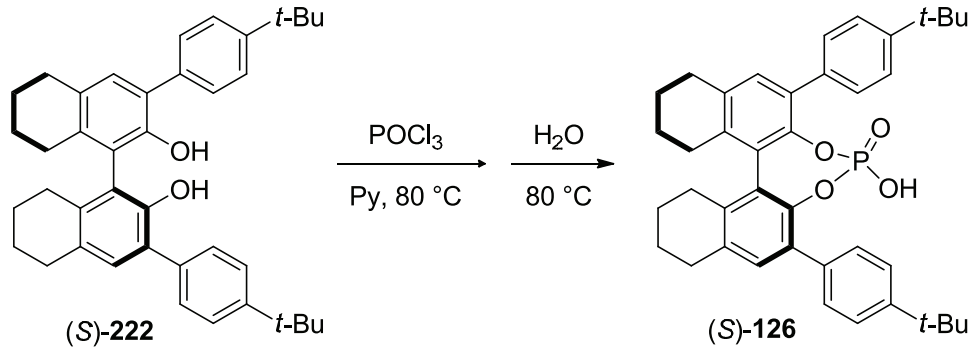


(*S*)-**219** **220** (*S*)-**222**

According to the literature procedure,[138] to a mixture of dibromo compound **219** (480 mg, 1 mmol) and Pd catalyst (35 mg, 0.03 mmol) in 5 mL of glyme was added bronic acid **220** (535 mg, 3 mmol) in 5 mL of ethanol, followed by aq. Na_2CO_3 (2.0 mol/L, 2.0 mL). After degassed under argon for 15 min, the reaction mixture was heated to reflux for 48 h before quenched with sat. NH_4Cl. The solution was extracted with ether, washed with brine, and dried over anhydrous sodium sulfate. After the solvent was evaporated under reduced pressure, the resulting solid was subjected to flash column chromatography (Rf = 0.27, DCM/hexanes, 1:10), giving the coupling product (*S*)-**221** as a white solid. Deprotection was carried out with BBr_3 and 5 hours of stirring at room temperature, furnishing the desired diol (*S*)-**222** as a white solid (475 mg, 85% yield over two steps).

(*S*)-**221**: $C_{42}H_{50}O_2$ (586.85 g/mol);
^{1}H-NMR (500 Mz, $CDCl_3$): δ 1.35 (s, 18H, *t*-Bu-*H*), 1.70 (m, 4H, CH_2), 1.78 (m, 4H, CH_2), 2.23 (m, 2H, CH_2), 2.42 (m, 2H, CH_2), 2.82 (m, 4H, CH_2), 3.25 (s, 6H, OCH_3), 7.10 (s, 2H, Ar*H*), 7.40 (d, *J* = 8.4 Hz, 4H, Ar*H*), 7.53 (d, *J* = 8.4 Hz, 4H, Ar*H*);
^{13}C-NMR (125 Mz, $CDCl_3$): δ 23.1, 23.2, 27.6, 29.5, 31.4, 34.5, 60.3, 125.0, 128.5, 130.8, 131.3, 131.5, 132.5, 135.6, 136.4, 149.5, 152.9.

***Synthesis of (S)-3,3'-bis-(4-tert-butylphenyl)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthalenyl-2,2'-diyl hydrogen phosphate ((S)-126)**:*



Diol (*S*)-**222** (475 mg, 0.85 mmol) was dissolved in pyridine (2.0 mL) in a Schlenk tube, and phosphoryl chloride (0.2 mL, 2.0 mmol) was added via a syringe. The resulting mixture was stirred for 4 hours at 80 °C until the starting diol was completely consumed (monitored by TLC). Then, water (1.5 mL) was added cautiously. The resulting suspension was stirred for additional 2 hours at 80 °C. The reaction mixture was cooled to room temperature and diluted with dichloromethane (30 mL). The pyridine was removed by washing with 1 N HCl. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product. Purification by flash column chromatography on silica gel (3-4% EtOH in DCM) gave the phosphoric acid as a white solid (458 mg, 87% yield).

(*S*)-**126**: $C_{40}H_{45}O_4P$ (620.76 g/mol);

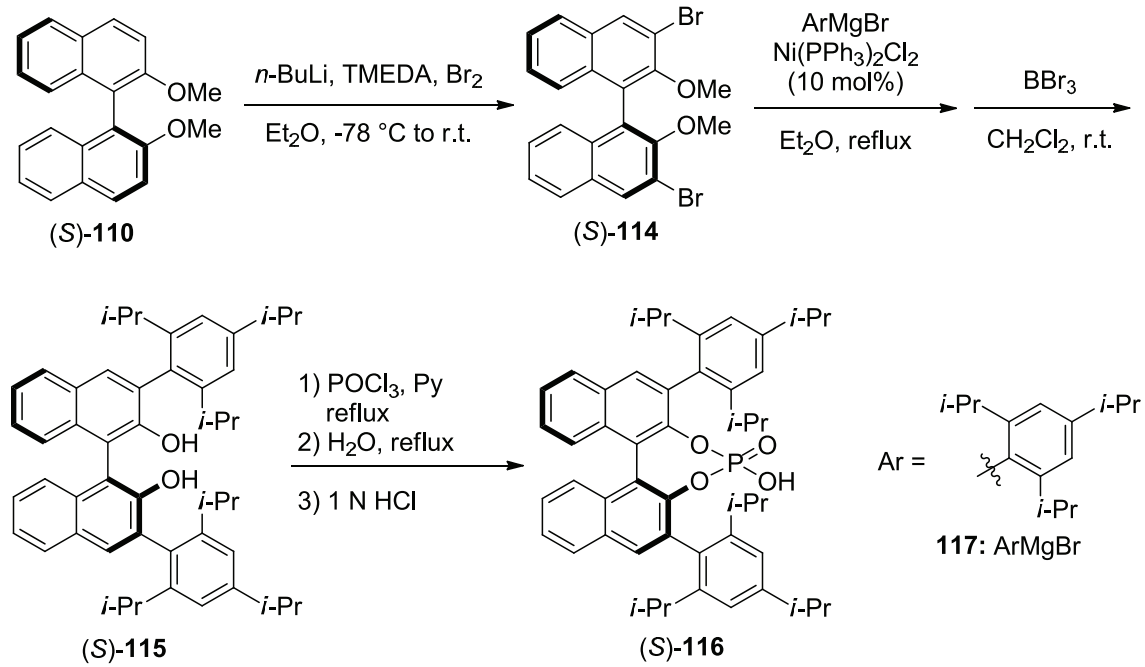
^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.18 (s, 18H, *t*-Bu-*H*), 1.63 (m, 2H, CH_2), 1.82 (m, 6H, CH_2), 2.33 (m, 2H, CH_2), 2.68 (m, 2H, CH_2), 2.84 (m, 4H, CH_2), 4.42 (s, 1H, O*H*), 7.14 (s, 2H, Ar*H*), 7.28 (d, *J* = 8.4 Hz, 4H, Ar*H*), 7.41 (d, *J* = 8.4 Hz, 4H, Ar*H*);

^{13}C-NMR (125 MHz, $CDCl_3$): δ 22.65, 22.73, 27.8, 29.2, 31.2, 34.4, 125.1, 127.0, 129.0, 131.3, 131.5, 133.9, 135.1, 136.9, 142.8 (d), 149.8;

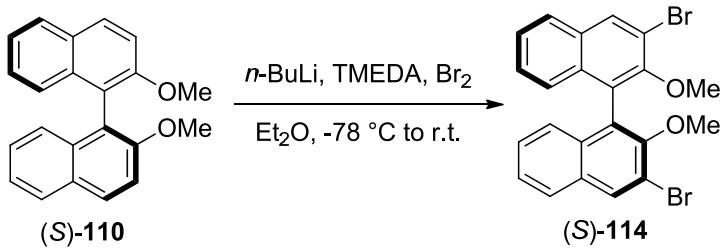
^{31}P-NMR (202 MHz, $CDCl_3$): δ 1.93;

HRMS (ESIneg): calculated for ($[C_{40}H_{44}O_4P_1]^-$): 619.298474, found 619.298276.

6.2.1.4 Synthesis of (*S*)-3,3'-Bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl Hydrogen Phosphate ((*S*)-TRIP, (*S*)-116)[75]

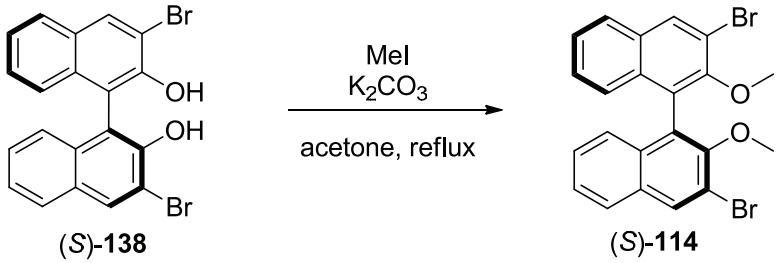


Preparation of (S)-3,3'-dibromo-2,2'-dimethoxy-1,1'-binaphthyl ((S)-114).[76]



To a solution of TMEDA (1.92 mL, 12.74 mmol) in diethyl ether (100 mL) was added *n*-butyllithium (2.5 M in hexane, 7.0 mL, 17.5 mmol) at room temperature. After the solution was stirred for 15 minutes, solid methyl protected BINOL (*S*)-**110** (1.82 g, 5.79 mmol) was added in one portion, and the reaction mixture was stirred for three hours at room temperature. The resulting light brown suspension was cooled to -78 °C, and bromine (3.6 mL, 70.00 mmol) was added over a period of ten minutes. The mixture was allowed to warm to room temperature, and after four hours, a saturated aqueous solution of sodium sulfite (60 mL) was added cautiously. The reaction mixture was stirred for additional four hours, and diluted with diethyl ether and water. The organic layer was separated, washed with brine, dried over magnesium sulfate, and concentrated. The crude product was purified by flash chromatography on silica gel (8% of ethyl acetate in hexaness), providing (*S*)-**114** (1.80 g, 67%) as a pale yellow powder.

Another method was also employed to prepare this compound, starting with dibromobinol (*S*)-**138**.



(*S*)-**138** (*S*)-**114**

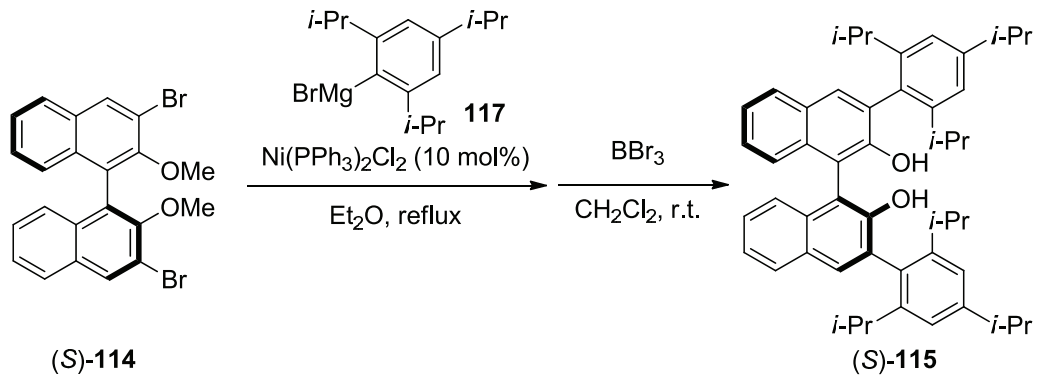
Following the procedure for the *O*-methyl protection of BINOL, a suspension of (*S*)-**138** (1.00 g, 2.25 mmol) in acetone (20 mL) was heated to form a homogeneous solution. To this solution were added potassium carbonate (1.66 g, 12 mmol) and methyl iodide (2.00 g, 14 mmol), and the mixture was heated to reflux for 22 h until completed consumption of the binol. The solvent was then evaporated, and the resulting solid was washed with water and dried to afford (*S*)-**114** as a white powder (1.02 g, 96%).

(*S*)-**114**: $C_{22}H_{16}Br_2O_2$ (472.17 g/mol);
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.43 (s, 6H, OC*H*$_3$), 7.00 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.19 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.34 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.74 (d, *J* = 8.5 Hz, 2H, Ar*H*), 8.20 (s, 2H, Ar*H*);
^{13}C NMR (125 MHz, $CDCl_3$): δ 61.1, 117.5, 125.8, 125.9, 126.5, 126.9, 127.1, 131.4, 133.0, 133.1, 152.5.

Preparation of (2,4,6-triisopropylphenyl)magnesium bromide(117):[76]

A three-necked round-bottomed flask containing activated magnesium turnings (3.00 g, 125.00 mmol) was equipped with a condenser and an addition funnel. A solution of 2,4,6-triisopropylphenyl bromide (20.00 g in 50 mL of diethyl ether, 70.60 mmol) was prepared, and 10 mL of this solution were added to the reaction mixture via the addition funnel. After five minutes, a catalytic amount of 1,2-dibromoethane (0.20 mL, 0.002 mmol) was added to the mixture. Once the solution began to reflux, the remaining 2,4,6-triisopropylphenyl bromide solution (40 mL) was slowly added over one hour. After the addition was complete, the reaction was allowed to reflux for 12 hours and then cooled to room temperature.

Preparation of (S)-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diol ((S)-115):[75]



(*S*)-3,3'-Dibromo-2,2'-dimethoxy-1,1'-binaphthyl ((*S*)-**114**, 4.00 g, 8.50 mmol) and bis(triphenylphosphine) nickel(II) dichloride (0.60 g, 0.90 mmol) were suspended in diethyl ether (100 mL). To this suspension was added the freshly prepared (2,4,6-triisopropylphenyl)magnesium bromide (0.8 M in diethyl ether, 31.7 mL, 25.40 mmol) slowly at room temperature. The mixture was stirred at room temperature for ten minutes and the resulting dark green solution was then refluxed for eight hours. The reaction was cooled to 0 °C and quenched by the slow addition of aq. HCl (1.0 M, 50 mL). The resulting aqueous layer was separated from the organic phase and extracted with diethyl ether. The combined organic layers were dried over magnesium sulfate and the solvent was removed under reduced pressure to afford the coupling product (4.65 g, 76% yield) as a colorless solid after re-crystallization from dichloromethane and hexanes. For the de-protection, to a solution of (*S*)-2,2'-dimethoxy-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl (4.00 g, 5.60 mmol) in dichloromethane (150 mL) was slowly added a dichloromethane solution of boron tribromide (1.0 M, 39.0 mL, 38.90 mmol) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred at this temperature for 24 hours. When the TLC indicated full conversion, the mixture was then cooled to 0 °C, and quenched by the slow addition of water (50 mL). After separation of the two resulting phases, the aqueous layer was extracted twice with dichloromethane. The combined organic layers were dried over sodium sulfate and the solvent was removed to yield a colorless solid, which was washed with hexanes and dried *in vacuo* to afford the desired diol (3.80 g, 98% yield) as a white solid.

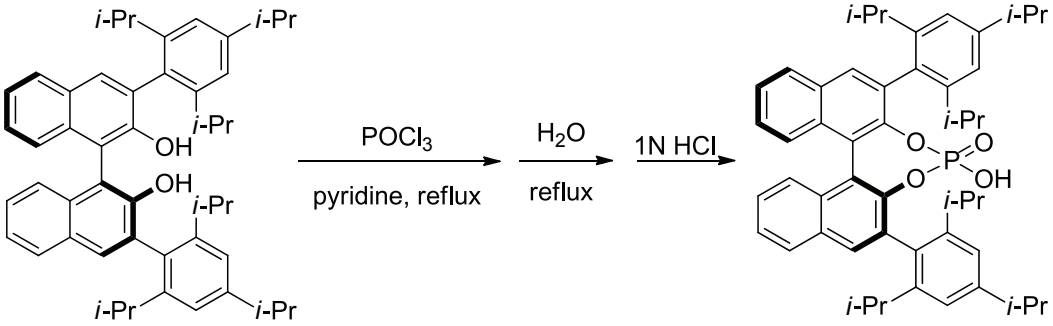
(*S*)-**115**: $C_{50}H_{58}O_2$ (690.99 g/mol);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (d, *J* = 6.9 Hz, 6H, C*H*$_3$), 1.04-1.00 (m, 12H, C*H*$_3$), 1.12 (d, *J* = 6.8 Hz, 6H, C*H*$_3$), 1.24 (d, J = 6.9 Hz, 12H, C*H*$_3$), 2.64-2.59 (m, 2H, C*H*Me$_2$), 2.80-

2.75 (m, 2H, C*H*Me$_2$), 2.91-2.86 (m, 2H, C*H*Me$_2$), 4.85 (s, 2H, O*H*), 7.05 (d, *J* = 8.3 Hz, 4H, Ar*H*), 7.26-7.20 (m, 4H, Ar*H*), 7.30 (t, *J* = 6.7 Hz, 2H, Ar*H*), 7.69 (s, 2H, Ar*H*), 7.79 (d, *J* = 8.1 Hz, 2H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 23.7, 23.9, 24.0, 24.1, 24.30, 24.34, 30.8, 30.9, 34.3, 121.2, 121.2, 123.8, 124.5, 126.6, 128.2, 129.0, 129.1, 130.4, 130.7, 133.4, 147.7, 147.8, 149.1, 150.6.

Preparation of (S)-3,3'-Bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate ((S)-TRIP, (S)-116): [75]



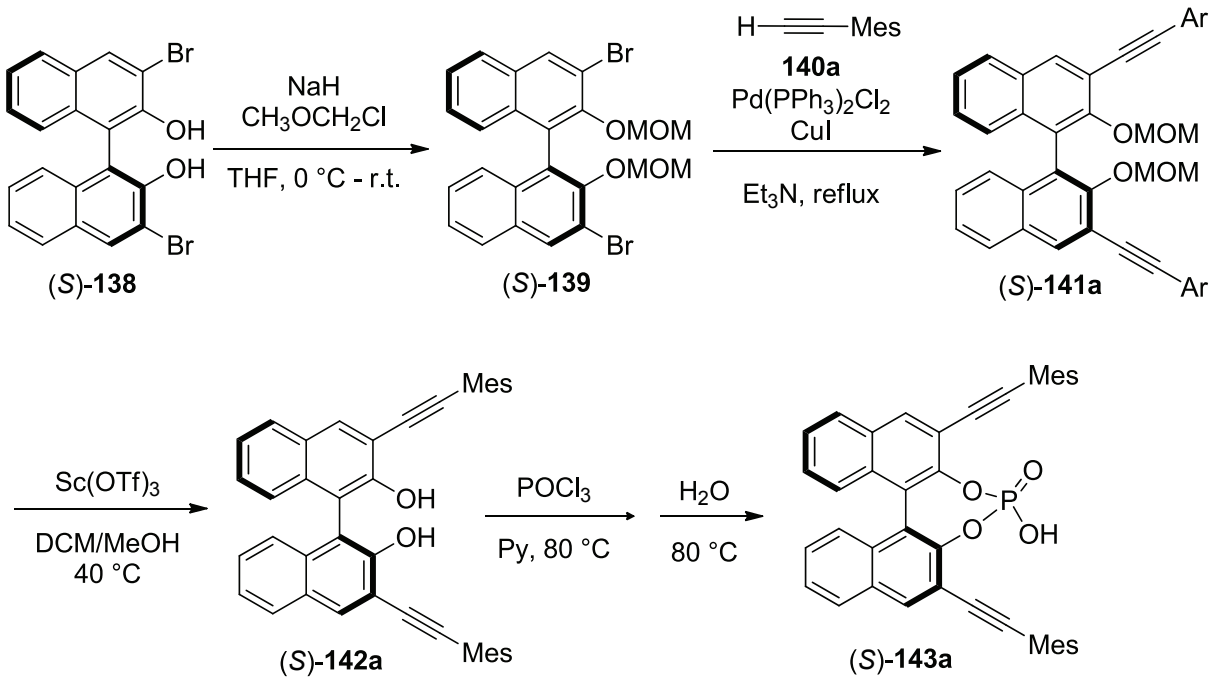
Free diol (*S*)-**115** (1.38 g, 2.0 mmol) was suspended in pyridine (8.0 mL) in a two-necked flask, followed by the dropwise addition of phosphorous oxychloride (0.62 g, 0.38 mL, 4.0 mmol) at room temperature. The resulting suspension was refluxed for 24 hours until all of the starting diol was consumed. The reaction mixture was then cooled to room temperature and 2 mL of water was added cautiously. The resulting mixture was heated to 100 °C and stirred for additional 24 hours. The reaction mixture was then diluted with dichloromethane and pyridine was removed by washing with hydrochloric acid (1 N). The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash column chromatography (2-10% of EtOH in dichloromethane) and acidified with 6 N aq. HCl, yielding (*S*)-TRIP (1.40 g, 93%) as a slightly yellowish solid.

(*S*)-**116**: $C_{50}H_{57}O_4P$ (752.96 g/mol);

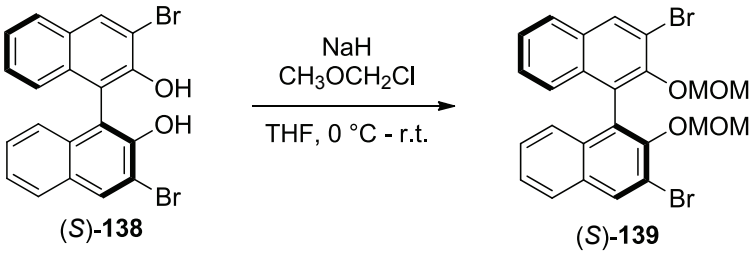
^{1}H NMR (500 MHz, DMSO-d6): δ 0.83 (d, *J* = 6.8 Hz, 6H, C*H*$_3$), 1.00 (d, *J* = 6.9 Hz, 6H, C*H*$_3$), 1.05 (d, *J* = 6.7 Hz, 6H, C*H*$_3$), 1.09 (d, *J* = 6.9 Hz, 6H, C*H*$_3$), 1.18 (dd, *J* = 1.6, 6.9 Hz, 12H, C*H*$_3$), 2.48-2.43 (m, 2H, C*H*Me$_2$), 2.65-2.60 (m, 2H, C*H*Me$_2$), 2.87-2.82 (m, 2H,

C*H*Me$_2$), 6.98 (s, 3H, Ar*H*), 7.00 (s, 1H, Ar*H*), 7.06 (d, *J* = 1.5 Hz, 2H, Ar*H*), 7.29 (t, *J* = 7.3 Hz, 2H, Ar*H*), 7.43 (t, *J* = 7.2 Hz, 2H, Ar*H*), 7.93 (s, 2H, Ar*H*), 8.00 (d, *J* = 8.1 Hz, 2H, Ar*H*); **^{13}C NMR** (125 MHz, DMSO-d6): δ 22.8, 23.2, 24.0, 24.1, 24.6, 26.2, 30.3, 30.7, 33.6, 119.9, 120.8, 121.2, 125.6, 125.7, 126.7, 128.5, 130.4, 131.6, 131.7, 132.3, 145.8, 145.9, 146.5, 147.3, 147.8.

6.2.1.5 Preparation of (*S*)-3,3'-Bis(mesitylethynyl)-1,1'-binaphthyl-2,2'-diyl Hydrogen Phosphate ((*S*)-143a)



***Synthesis of (S)-3,3'-dibromo-2,2'-di(methoxymethoxy)-1,1'-binaphthyl((S)-139)**:*

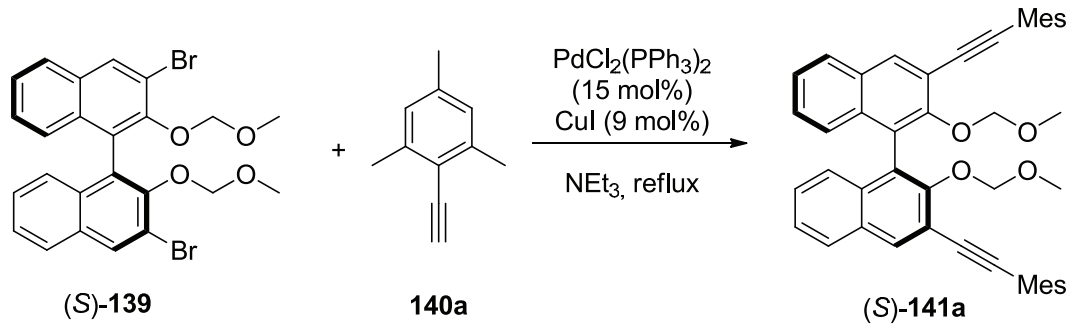


According to the known procedure,[87] to a THF (20 mL) solution of the brominated binol (*S*)-**138** (1.33 g, 3 mmol) was added NaH (0.173 g) at 0 °C. After stirred for 15 min,

chlorodimethylether (0.58 g, 7 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for additional 2 h. After quenched with water, extracted with dichloromethane, and dried over Na_2SO_4, the desired product was obtained as a white solid (1.44 g, 90% yield).

(*S*)-**139**: C24H20Br2O4 (532.22 g/mol);
^{1}H NMR (300 MHz, $CDCl_3$): δ 2.56 (s, 6H, OC*H*$_3$), 4.81, 4.82 (d, 4H, *J* = 6.0 Hz, OC*H*$_2$O), 7.19 (d, *J* = 8.3 Hz, 2H, Ar*H*), 7.26-7.34 (m, 2H, Ar*H*), 7.44 (dd, *J* = 1.2, 8.3 Hz, 2H, Ar*H*), 7.81 (d, *J* = 7.9 Hz, 2H, Ar*H*), 8.27 (s, 2H, Ar*H*);
^{13}C NMR (75 MHz, $CDCl_3$): δ 56.1, 98.9, 117.1, 125.8, 126.3, 127.1, 127.2, 127.6, 131.3, 132.8, 132.9, 149.9.

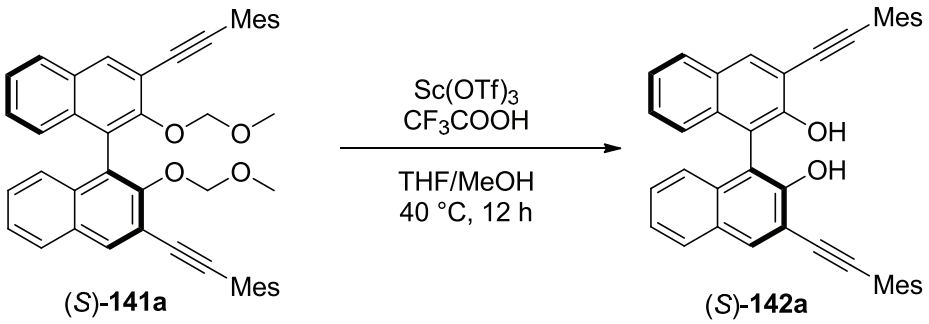
***Synthesis of (S)-3,3'-bis(mesitylethynyl)-2,2'-di(methoxymethoxy)-1,1'-binaphthyl ((S)-141a)**:*



(*S*)-**139** **140a** (*S*)-**141a**

The reaction was carried out according to the literature procedure with modification.[88] A mixture of (*S*)-**139** (0.350 g, 0.66 mmol), trimethylbenzeneethylene (0.380 g, 2.64 mmol), $PdCl_2(PPh_3)_2$ (72 mg, 0.1 mmol), and CuI (12 mg, 0.06 mmol) in 15 mL of degassed triethylamine was heated to reflux for 24 h. After cooled down to room temperature and the solvent removed under reduced pressure, the resulting slurry was dissolved in 15 mL of ethyl acetate and filtered through a short pad of Celite. The filtrate was combined, washed with aq. HCl (1 N) and brine, and dried over anhydrous sodium sulfate. Purification by flash column chromatography on silica gel (0-10%EtOAc in hexanes) gave the coupling product (*S*)-**141a** as a pale yellow solid (357 mg, 82%).

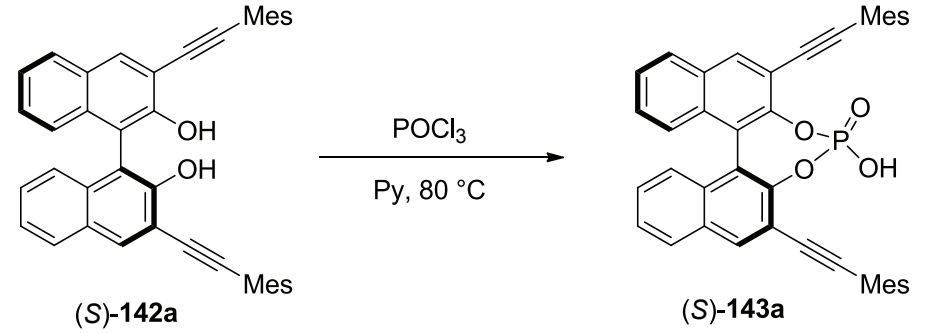
Synthesis of (S)-3,3'-bis(mesitylethynyl)-1,1'-binaphthyl-2,2'-diol:



According to the literature procedure,[88b] the MOM-protected binol (*S*)-**141a** (130 mg, 0.2 mmol) was dissolved in THF/MeOH (6 ml, 1:1), and $Sc(OTf)_3$ (10 mg, 0.02 mmol) and TFA (15 µL, 0.2 mmol) were added. The reaction mixture was stirred at 40 °C until the starting material disappeared (12 h). The solvent was then evaporated under reduced pressure, and the resulting solid was subjected to flash column chromatography (5% EtOAc in hexaness), giving the deprotection product as a white solid (70 mg, 60%).

(*S*)-**142a**: $C_{42}H_{34}O_2$ (570.72 g/mol);
^{1}H-NMR (300 Mz, $CDCl_3$): δ 2.34 (s, 6H, C*H*$_3$), 2.54 (s, 12H, C*H*$_3$), 5.93 (s, 2H, O*H*), 6.95 (s, 4H, Ar*H*), 7.23 (dd, *J* = 8.4, 0.9 Hz, 2H, Ar*H*), 7.31-7.43 (m, 4H, Ar*H*), 7.90 (d, *J* = 7.5 Hz, 2H, Ar*H*), 8.22 (s, 2H, Ar*H*);
^{13}C-NMR (75 Mz, $CDCl_3$): δ 21.6, 21.8, 91.9, 94.8, 113.5, 113.9, 119.7, 124.7, 125.2, 128.1, 128.2, 128.5, 129.2, 133.1, 134.1, 138.9, 140.6, 151.1.

Synthesis of (S)-3,3'-bis(mesitylethynyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate ((S)-143a):



Diol (*S*)-**142a** (100 mg, 0.18 mmol) was dissolved in pyridine (2.0 mL) in a Schlenk tube. Phosphoryl chloride (0.1 mL, 1.0 mmol) was added dropwise at room temperature via a syringe. The resulting mixture was stirred for 4 hours at 80 °C until the starting diol was

consumed (followed by TLC). Then, 1.5 mL of water was added cautiously. The resulting suspension was stirred for additional 2 hours at 80 °C. The reaction mixture was then cooled to room temperature and diluted with dichloromethane (30 mL). Pyridine was removed by washing with 1 N HCl. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product. Purification by flash column chromatography on silica gel (3-4% EtOH in DCM) afforded the phosphoric acid as a pale yellow solid (71 mg, 64% yield).

(*S*)-**143a**: $C_{42}H_{33}O_4P$ (632.68 g/mol);

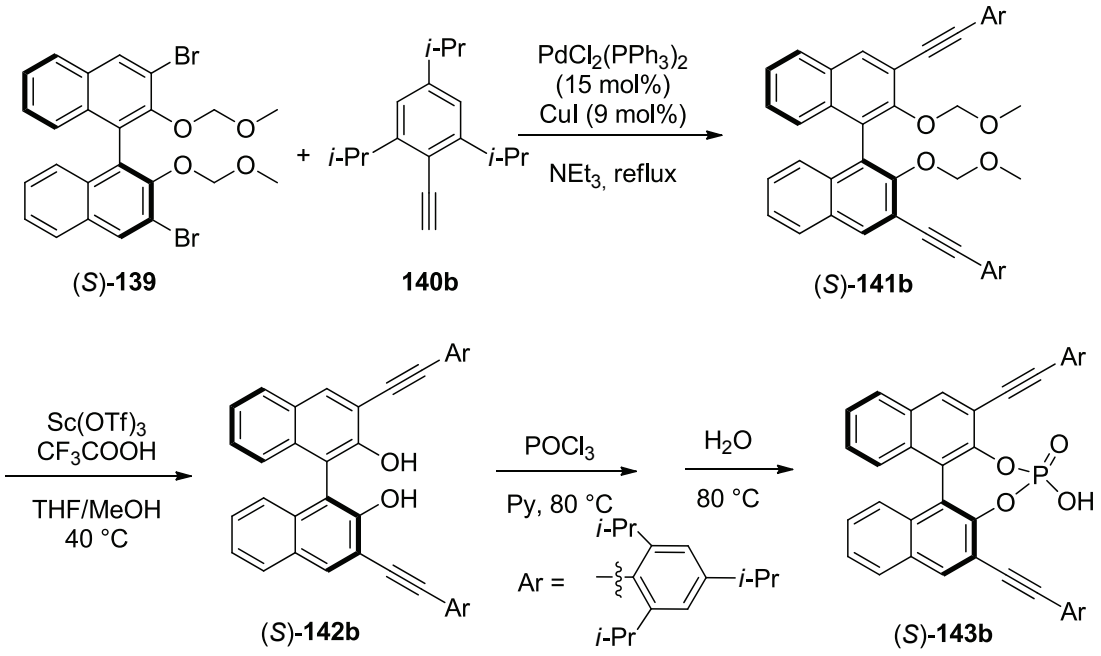
^{1}H-NMR (500 Mz, $CDCl_3$): δ 2.10 (s, 6H, C*H*$_3$), 2.47 (s, 12H, C*H*$_3$), 6.4 (s br, 1H, O*H*), 6.65 (s, 4H, Ar*H*), 7.29 (d, *J* = 3.6 Hz, 4H, Ar*H*), 7.49 (m, 2H, Ar*H*), 7.92 (d, *J* = 8.2 Hz, 2H, Ar*H*), 8.24 (s, 2H, Ar*H*);

^{13}C-NMR (125 Mz, $CDCl_3$): δ 21.1, 21.3, 91.4, 93.0, 117.08, 117.10, 119.4, 121.8, 126.2, 127.1, 127.3, 128.1, 131.3, 131.6, 134.6, 137.8, 140.6, 145.7 (d);

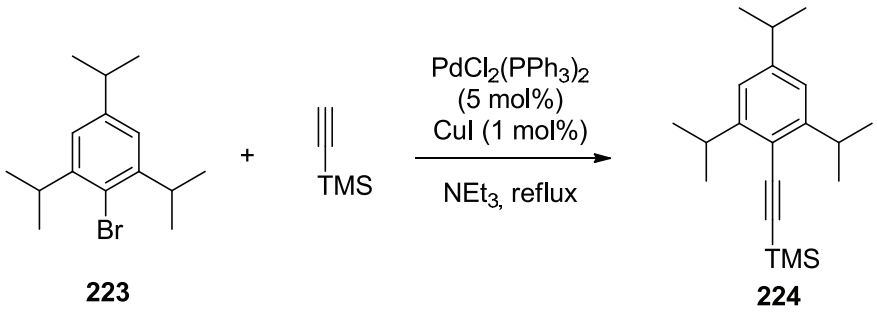
^{31}P-NMR (202 Mz, $CDCl_3$): δ 4.10;

HRMS (ESIneg) calculated for ($[C_{42}H_{32}O_4P_1]^-$) 631.204727, found 631.204376.

6.2.1.6 Preparation of (*S*)-3,3'-Bis(2,4,6-triisopropylphenylethynyl)-1,1'-binaphthyl-2,2'-diyl Hydrogen Phosphate ((*S*)-143b)



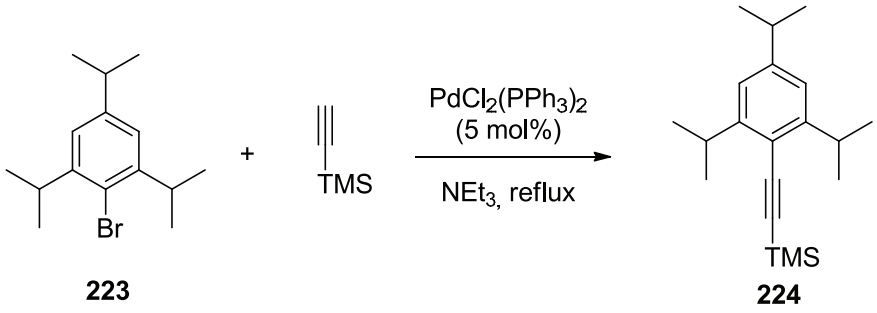
Synthesis of 1-(2,4,6-triisopropylphenyl)-2-trimethylsilylacetylene(224):



223 **224**

According to the literature method,[89] a mixture of bromobenzene **223** (1.416 g, 5.0 mmol), $Pd(PPh_3)_2Cl_2$ (175 mg, 0.25 mmol), PPh_3 (33 mg, 0.125 mmol), and trimethylsilylacetylene (736 mg, 7.5 mmol) in 20 mL of triethylamine was stirred for 20 min at room temperature, and 12 mg (0.06 mmol) of CuI was then added. After the reaction mixture was stirred for 24 h at 100 °C, additional trimethylsilylacetylene (0.70 g) was added, and the reaction mixture was stirred for another 24 h. After filtration through Celite and evaporation of the solvent, the resulting liquid was subjected to column chromatography (pentane). The product was isolated as a colorless oil (0.45 g, 30% yield).

The modified procedure without CuI:



223 **224**

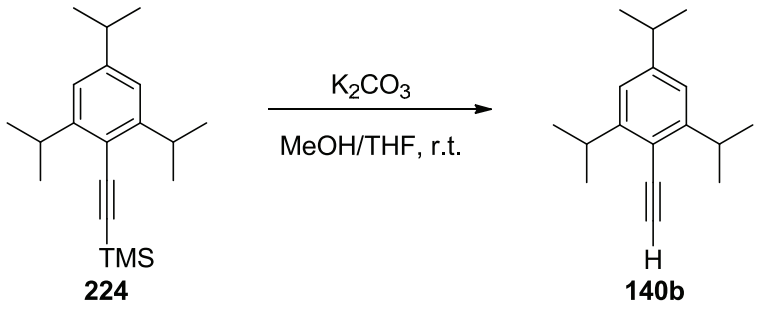
A mixture of bromobenzene **223** (2.83 g, 10.0 mmol), $Pd(PPh_3)_2Cl_2$ (350 mg, 0.5 mmol), PPh_3 (66 mg, 0.25 mmol), and trimethylsilylacetylene (1.47 g, 15 mmol) in 30 mL of triethylamine was degassed for 20 min. After stirred for 48 h at 95 °C, the reaction mixture was cooled to room temperature and filtered through a short pad of Celite. After the solvent was removed under reduced pressure, the resulting residue was subjected to silica gel column (pentane). The product was isolated as a slightly yellow oil (2.10 g, 70% yield).

224: $C_{20}H_{32}Si$ (300.55 g/mol);

^{1}H-NMR (300 Mz, $CDCl_3$): δ 0.32 (s, 9H, TMS-*H*), 1.32 (t, 12H + 6H, *o*,*p*-CH(CH_3)$_2$), 2.93 (m, 1H, *p*-C*H*Me$_2$), 3.57 (m, 2H, *o*-C*H*Me$_2$), 7.02 (s, 2H, Ar*H*);

^{13}C-NMR (75 Mz, $CDCl_3$): δ 23.1, 23.9, 31.7, 34.5, 101.7, 102.6, 118.5, 120.1, 149.2, 151.0.

Synthesis of 2,4,6-triisopropylphenylacetylene (140b):



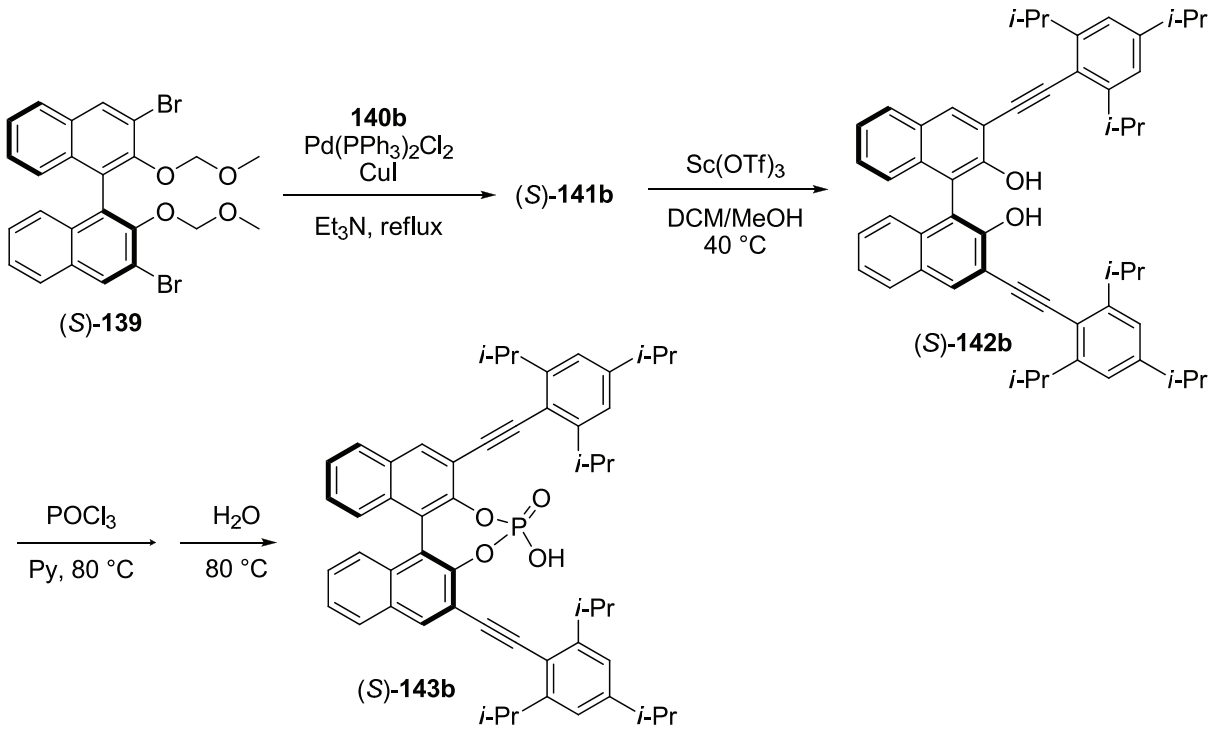
The desilylation was carried out according to the literature procedure,[88b] the TMS protected acetylene **224** (1.50 g, 5 mmol) was dissolved in THF/MeOH (20 mL, 1:1, and K_2CO_3 (0.7 g, 5 mmol) was added in one portion. After stirred for 12 h at room temperature, the reaction mixture was concentrated under reduced pressure, diluted with ether, washed with water, and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was purified by column chromatography on silica gel (pentane), giving the product as an orange oil (1.02 g, 90% yield).

140b: $C_{17}H_{24}$ (228.37 g/mol);

^{1}H-NMR (300 Mz, $CDCl_3$): δ 1.29 (m, 18H, *o*,*p*-CH(CH_3)$_2$), 2.92 (m, 1H, *p*-C*H*Me$_2$), 3.44 (s, 1H, ≡*H*), 3.58 (m, 2H, *o*-C*H*Me$_2$), 7.02 (s, 2H, Ar*H*);

^{13}C-NMR (75 Mz, $CDCl_3$): δ 23.3, 23.9, 31.7, 34.6, 80.8, 84.3, 117.4, 120.3, 149.5, 151.4.

Synthesis of (S)-3,3'-bis(2,4,6-triisopropylphenylethynyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate((S)-143b):



Following the procedure described for (*S*)-3,3'-bis(mesitylethynyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate ((*S*)-**143a**), a mixture of (*S*)-**139** (400 mg, 0.75 mmol), 2,4,6-triisopropybenzeneethylene (460 mg, 2.01 mmol), $PdCl_2(PPh_3)_2$ (84 mg, 0.12 mmol), and CuI (8 mg, 0.04 mmol) in 15 mL of triethylamine was heated to reflux for 24 h. Purification by flash column chromatography on silica gel (DCM/hexanes, 1:3) gave the coupling product (*S*)-**141b** as a pale yellow solid. Deprotection with $Sc(OTf)_3$ (50 mg, 0.1 mmol) and TFA (75 µL) in THF/MeOH (30 mL, 1:1) at 40 °C took 20 h to achieve full conversion (487 mg, 88% yield over two steps). Finally, the free binol (*S*)-**142b** was dissolved in 2.5 mL of pyridine, and 200 µL of phosphoryl chloride was added in two portions. After stirred at 80 °C for 4 h, the reaction mixture was treated with 2 mL of distilled water and stirred for additional 2 h. Purification by column chromatography on silica gel (4% EtOH in DCM) gave the desired phosphoric acid (*S*)-**143b** as a pale yellow solid (460 mg, 87% yield).

(*S*)-**143b**: C54H57O4P (801.00 g/mol);

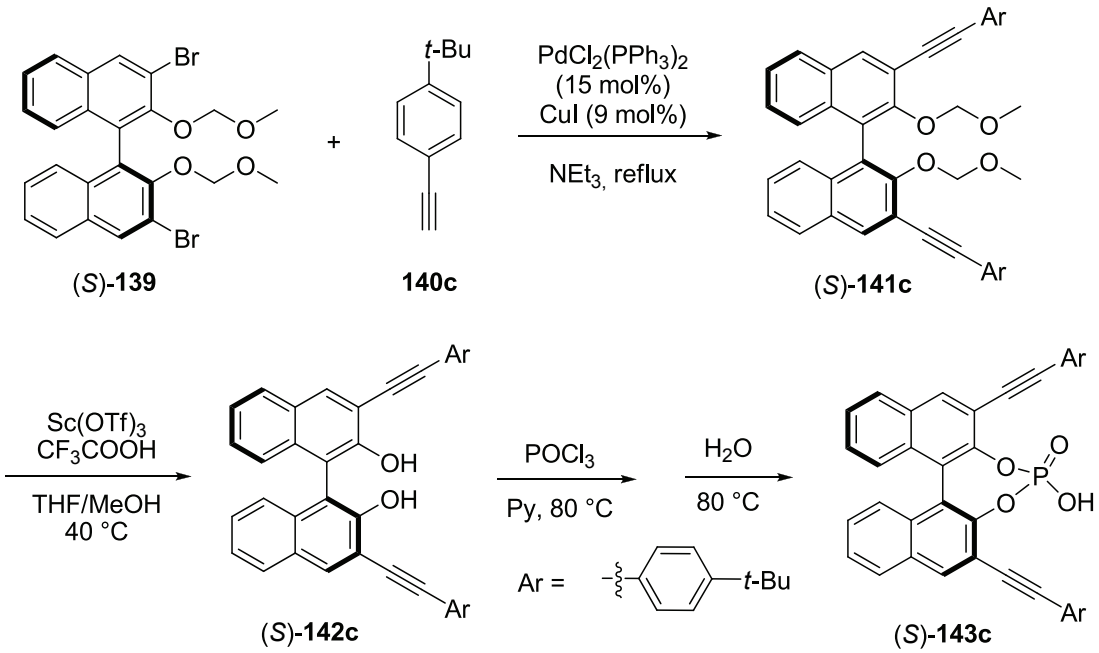
^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.10 (d, *J* = 6.8 Hz, 12H, C*H*$_3$), 1.15 (d, *J* = 6.8 Hz, 12H, C*H*$_3$), 1.25 (d, *J* = 6.8 Hz, 12H, C*H*$_3$), 2.78 (m, 2H, C*H*), 3.58 (m, 4H, C*H*), 6.51 (s br, 1H, O*H*), 6.87 (s, 4H, Ar*H*), 7.28 (d, *J* = 3.6 Hz, 4H, Ar*H*), 7.48 (m, 2H, Ar*H*), 7.90 (d, *J* = 8.2 Hz, 2H, Ar*H*), 8.19 (s, 2H, Ar*H*);

^{13}C-NMR (125 MHz, $CDCl_3$): δ 22.9, 23.5, 23.8, 23.9, 31.9, 34.5, 91.5, 92.3, 117.19, 117.21, 118.1, 120.2, 122.0, 126.2, 127.0, 128.0, 131.2, 131.5, 134.5, 145.67, 145.74, 149.4, 151.2;

^{31}P-NMR (202 MHz, $CDCl_3$): δ 3.89;

HRMS (ESIneg) calculated for ($[C_{54}H_{56}O_4P_1]^-$) 799.391776, found 799.392173.

6.2.1.7 Preparation of (*S*)-3,3'-Bis(4-tert-butylphenylethynyl)-1,1'-binaphthyl-2,2'-diyl Hydrogen Phosphate ((*S*)-143c)



Following the procedure described for (*S*)-3,3'-bis(mesitylethynyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate ((*S*)-**143a**), a mixture of dibromo compound (*S*)-**139** (400 mg, 0.75 mmol), 4-*tert*-butylbenzeneethylene (500 mg, 3.16 mmol), $PdCl_2(PPh_3)_2$ (84 mg, 0.11 mmol), and CuI (13 mg, 0.067 mmol) in 15 mL of triethylamine was heated to reflux for 72 h (additional 20 mg of palladium catalyst and 4 mL of TEA were added after 60 hours). Purification by flash column chromatography on silica gel (0-4%EtOAc in hexanes) gave the coupling product as a pale yellow solid. Deprotection with $Sc(OTf)_3$ (50 mg, 0.1 mmol) in THF/MeOH (10 mL, 1:1) at 40 °C took 12 h to achieve full conversion. Finally, the free binol (*S*)-**142c** was dissolved in 2.5 mL of pyridine, and 200 µL of phosphoryl chloride was added in two portions. After stirred at 80 °C for 4 h, the reaction mixture was treated with 2 mL of distilled water and stirred for additional 3 h. Purification by column chromatography on silica gel (4% EtOH in DCM) gave the desired phosphoric acid (*S*)-**143c** as a pale yellow solid (250 mg, 50% overall yield).

(*S*)-**143c**: C44H37O4P (660.74 g/mol);

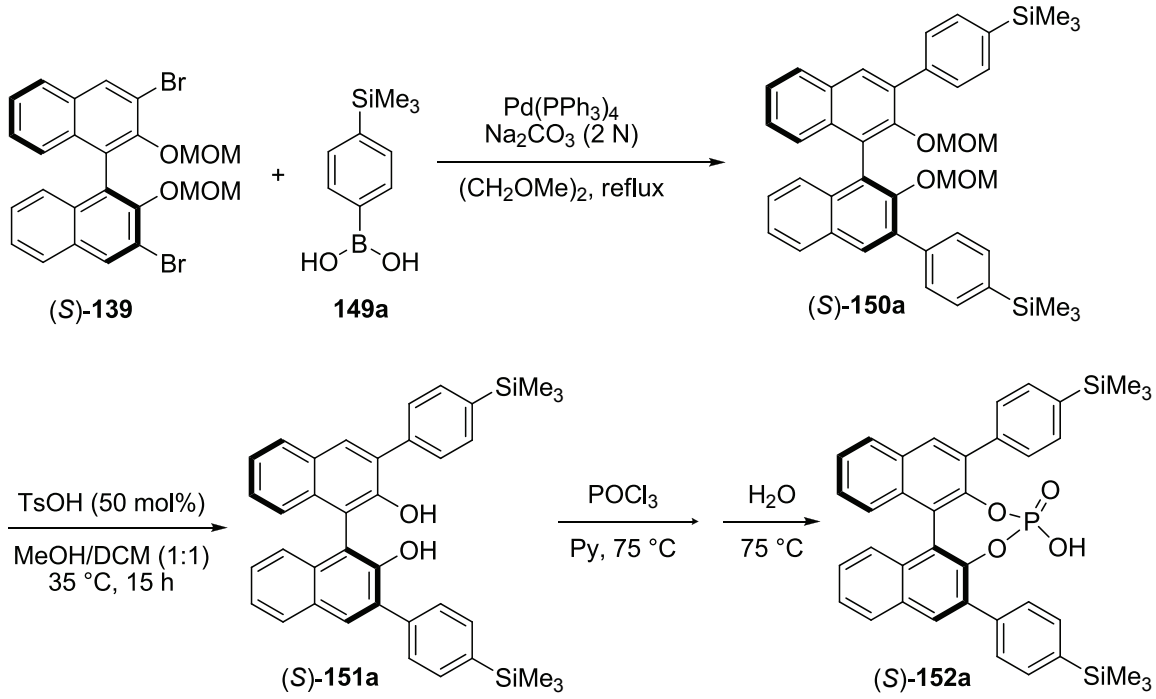
^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.04 (s, 18H, *t*-Bu-*H*), 7.13 (d, *J* = 8.4 Hz, 4H, Ar*H*), 7.27-7.34 (m, 4H, Ar*H*), 7.46-7.49 (m, 6H, Ar*H*), 7.90 (d, *J* = 8.2 Hz, 2H, Ar*H*), 8.24 (s, 2H, Ar*H*), 9.44 (s br, 1H, O*H*);

^{13}C-NMR (125 Mz, $CDCl_3$): δ 30.9, 34.5, 83.0, 95.9, 116.81, 116.83, 119.4, 121.7, 125.2, 126.3, 127.0, 127.2, 128.3, 131.3, 131.5, 131.7, 134.2, 146.0, 146.1, 151.4;

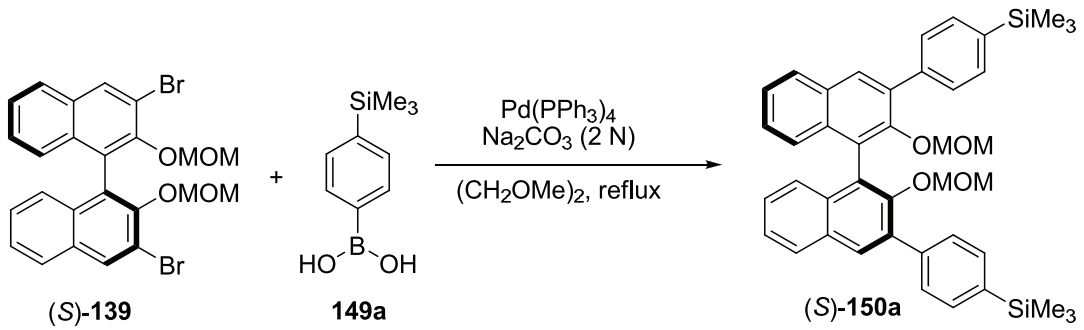
^{31}P-NMR (202 Mz, $CDCl_3$): δ 5.66;

HRMS (ESIneg): calculated for ($[C_{44}H_{36}O_4P_1]^-$) 659.236048, found 659.235674.

6.2.1.8 Preparation of (*S*)-3,3'-Bis(4-trimethylsilylphenyl)-1,1'-binaphthyl-2,2'-diyl Hydrogen Phosphate ((*S*)-152a)



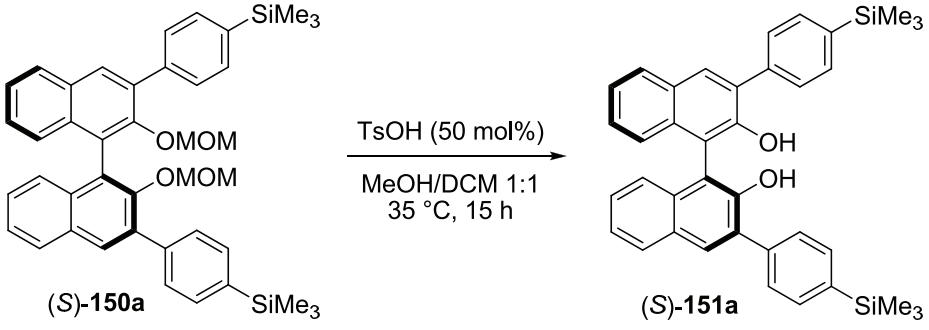
Synthesis of (S)-3,3'-bis(4-trimethylsilylphenyl)- 2,2'-di(methoxymethoxy)-1,1'-binaphthyl ((S)-150a):



Following the literature procedure,[91] a degassed solution of MOM-protected dibromobinol (*S*)-**139** (532 mg, 1 mmol), $Pd(PPh_3)_4$ (115 mg, 0.1 mmol), 4-trimethylsilylbenzeneboronic acid (582 mg, 3 mmol) and Na_2CO_3 (530 mg, 5 mmol, in 2.5 mL of water) in DME (7.5 mL) was heated to reflux for 7 h till the disappearance of the starting dibromo compound. After cooled to room temperature, the reaction mixture was filtered through a short pad of celite, diluted with DCM, and washed with aq. NH_4Cl and brine. Purification by flash column chromatography (5% EtOAc in hexanes) on silica gel gave the coupling product as a white fluffy solid (0.638 g, 95% yield).

(*S*)-**150a**: $C_{42}H_{46}O_4Si_2$ (670.98 g/mol);
^{1}H-NMR (500 Mz, $CDCl_3$): δ 0.30 (s, 18H, SiC*H*$_3$), 2.32 (s, 6H, OC*H*$_3$), 4.37 (d, *J* = 5.7 Hz, 2H, OC*H*$_2$), 4.42 (d, *J* = 5.7 Hz, 2H, OC*H*$_2$), 7.29 (m, 4H, Ar*H*), 7.41 (m, 2H, Ar*H*), 7.62 (d, *J* = 8.0 Hz, 4H, Ar*H*), 7.75 (d, *J* = 8.0 Hz, 4H, Ar*H*), 7.88 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.95 (s, 2H, Ar*H*);
^{13}C-NMR (125 Mz, $CDCl_3$): δ 1.05, 56.8, 99.6, 126.2, 127.4, 127.5, 127.6, 128.9, 129.9, 131.6, 131.9, 134.4, 134.7, 136.4, 140.41, 140.42, 152.4.

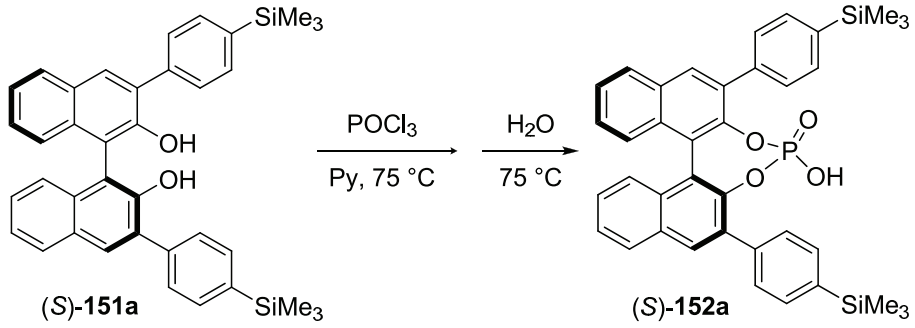
Synthesis of (S)-3,3'-bis(4-trimethylsilylphenyl)-1,1'-binaphthyl-2,2'-diol ((S)-151a):



According to the literature method,[92] to a solution of MOM-protected binol (*S*)-**150a** (525 mg, 0.78 mmol) in DCM/MeOH (10 mL/10 mL) was added TsOH monohydrate (74 mg, 0. 39 mmol) as the catalyst. The resulting mixture was stirred at 35 °C until the starting material completely converted to the free diol (15 h). Purification by column on silica gel (5% EtOAc in hexanes) gave the deprotection product as a white solid (492 mg, 99% yield).

(*S*)-**151a**: $C_{38}H_{38}O_2Si_2$ (582.88 g/mol);
^{1}H-NMR (500 Mz, $CDCl_3$): δ 0.31 (s, 18H, SiC*H*$_3$), 5.36 (s, 2H, O*H*), 7.23 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.30 (m, 2H, Ar*H*), 7.38 (m, 2H, Ar*H*), 7.65 (d, *J* = 8.0 Hz, 4H, Ar*H*), 7.73 (d, *J* = 8.0 Hz, 4H, Ar*H*), 7.92 (d, *J* = 8.0 Hz, 2H, Ar*H*), 8.02 (s, 2H, Ar*H*);
^{13}C-NMR (125 Mz, $CDCl_3$): δ 1.09, 113.4, 125.38, 125.41, 128.4, 129.6, 129.9, 130.6, 131.7, 132.5, 134.0, 134.6, 138.9, 141.1, 151.3.

Synthesis of (S)-3,3'-bis(4-trimethylsilylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate ((S)-152a):



Free diol (*S*)-**151a** (390 mg, 0.67 mmol) was dissolved in 2 mL of pyridine, and then 200 µL of $POCl_3$ was added. The resulting mixture was stirred at 75 °C for 4 h until the disappearance of starting material (monitored by TLC). 2 mL of distilled water was then added, and the solution was stirred for another 2 h. The reaction mixture was diluted with 30 mL of dichloromethane, washed with 10 % HCl, brine, and dried over anhydrous sodium sulfate. Purification by column chromatography on silica gel (3% EtOH in DCM) gave the desired phosphoric acid as a white solid (420 mg, 98% yield).

(*S*)-**152a**: $C_{38}H_{37}O_4PSi_2$ (644.84 g/mol);

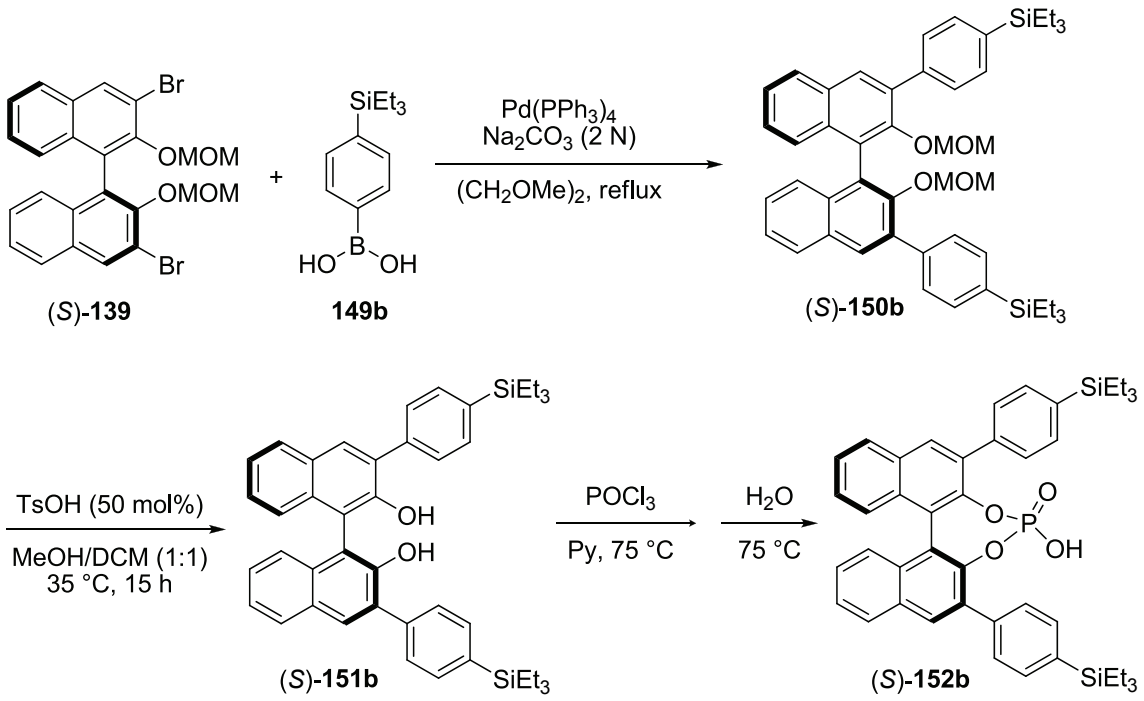
^{1}H-NMR (500 Mz, $CDCl_3$): δ 0.03 (s, 18H, SiC*H*$_3$), 7.30-7.38 (m, 4H, Ar*H*), 7.47-7.53 (m, 6H, Ar*H*), 7.60 (d, *J* = 8.0 Hz, 4H, Ar*H*), 7.96 (d, *J* = 8.4 Hz, 2H, Ar*H*), 8.03 (s, 2H, Ar*H*), 8.22 (s, 1H, O*H*);

^{13}C-NMR (125 Mz, $CDCl_3$): δ -1.39, 122.42, 122.43, 126.0, 126.5, 127.2, 128.4, 128.9, 131.5, 131.6, 131.9, 133.3, 133.94, 133.96, 137.0, 139.6, 144.33, 144.41;

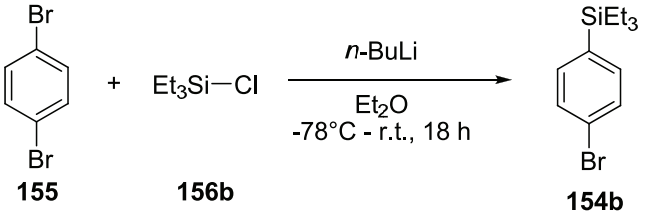
^{31}P-NMR (202 Mz, $CDCl_3$): δ 3.83;

HRMS (ESIneg) calculated for ($[C_{38}H_{37}O_4P_1Si_2]^-$) 643.189632, found 643.189533.

6.2.1.9 Preparation of (*S*)-3,3'-Bis(4-triethylsilylphenyl)-1,1'-binaphthyl-2,2'-diyl Hydrogen Phosphate ((*S*)-152b)



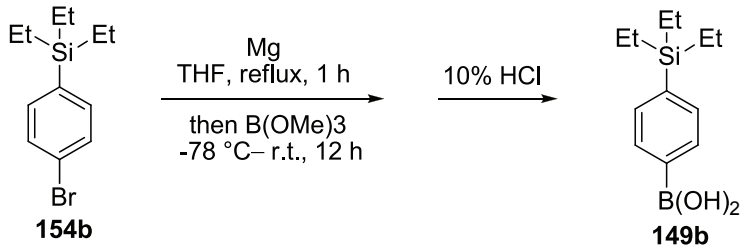
Synthesis of 4-triethylsilylbromobenzene (154b):



According to the literature procedure[93] with minor modification, under an atmosphere of argon, *n*-BuLi (2.5 M in hexane, 9 mL, 22.5 mmol) was slowly added to the cold (-78°C) solution of 1,4-dibromobenzene (4.71 g, 20 mmol) in 40 mL of abs. ether. After stirred for 1 h at -78°C, the reaction mixture was warmed up to room temperature and stirred for another hour. Triethylsilylchloride (3.01 g, 20 mmol) was then added slowly over 30 min. Three hours later, the reaction was quenched by adding 100 mL of water, extracted with ether, washed with brine, dried over $MgSO_4$. The pure product was obtained as a colorless oil by bulb-to-bulb distillation under reduced pressure (4.50 g, 83% yield).

154b: $C_{12}H_{19}BrSi$ (271.27 g/mol);
^{1}H-NMR (500 Mz, $CDCl_3$): δ 0.77 (q, *J* = 8.0 Hz, 6H, C*H*$_2$), 0.94 (t, *J* = 8.0 Hz, 9H, C*H*$_3$), 7.34 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 7.47 (d, *J* = 8.0 Hz, 2 H, Ar*H*);
^{13}C-NMR (125 Mz, $CDCl_3$): δ 3.2, 7.3, 123.5, 130.8, 135.8, 136.2.

Synthesis of 4-triethylsilylbenzeneboronic acid (149b):

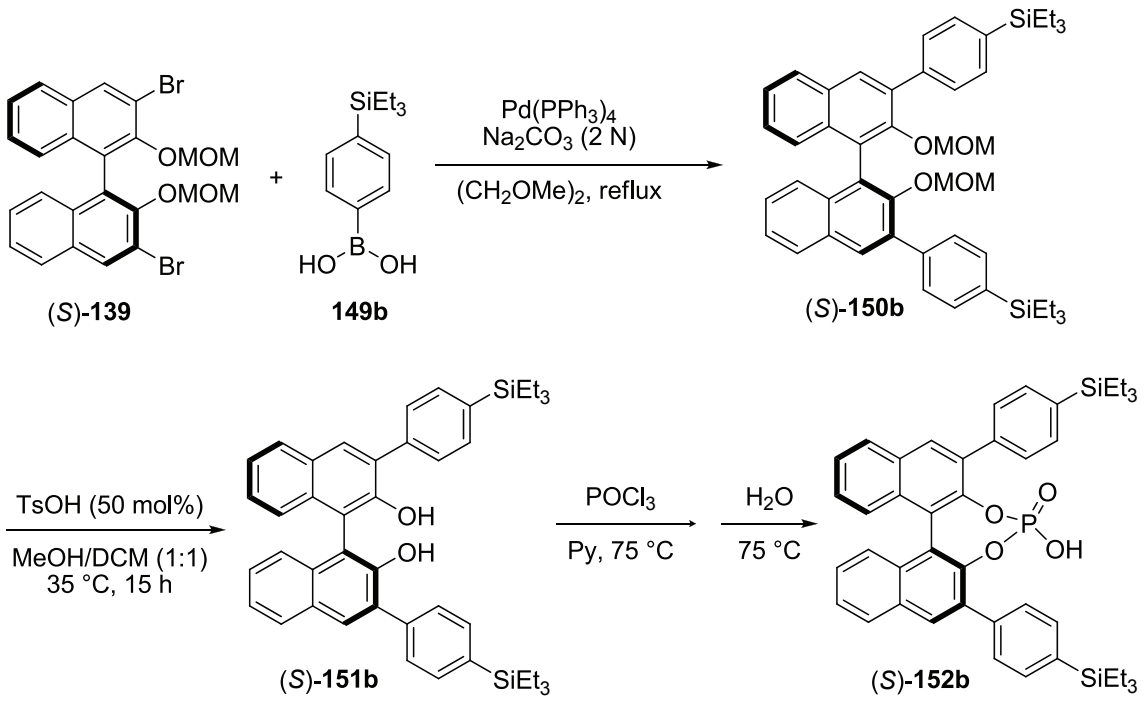


The boronic acid was prepared according to the literature procedure,[74] The Grignard reagent was made by slowly adding ArBr (2.70 g, 10 mmol, in 20 mL of THF) to magnesium turnings (0.26 g, 11 mmol). After refluxed for 2 h, the yellow solution was cooled to -78 °C. $B(OMe)_3$ (1.55 g, 1.5 mmol, 1.5 eq.) was then added dropwise via a syringe. The resulting mixture was warmed up to room temperature, and stirred for additional 8 hours before the reaction was quenched by addition of 10% HCl. Purification by column on silica gel gave the desired product in 74% yield (1.74 g).

149b: $C_{12}H_{21}BO_2Si$ (236.19 g/mol);
^{1}H-NMR (500 Mz, $CDCl_3$): δ 0.85 (q, *J* = 7.3 Hz, 6H, C*H*$_2$), 0.99 (t, *J* = 7.3 Hz, 9H, C*H*$_3$), 7.64 (d, *J* = 7.0 Hz, 2H, Ar*H*), 8.20 (d, *J* = 7.0 Hz, 2H, Ar*H*);

^{13}C-NMR (125 Mz, $CDCl_3$): δ 3.3, 7.4, 130.4, 133.8, 134.6, 143.2.

Synthesis of (S)-3,3'-bis(4-triethylsilylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate ((S)-152b):



Following the procedure described for (*S*)-3,3'-bis(4-trimethylsilylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate ((*S*)-**152b**), the degassed solution of MOM-protected binol (130 mg, 0.25 mmol), $Pd(PPh_3)_4$ (40 mg, 0.035 mmol), 4-triethylsilylbenzeneboronic acid (236 mg, 1.0 mmol) and Na_2CO_3 (150 mg, 1.4 mmol, in 1 mL of water) in DME (4 mL) was heated to reflux for 12 h. Purification by flash column chromatography on silica gel (DCM/hexanes, 1:3) gave the coupling product as a white solid (140 mg, 76% yield). The deprotection was carried out with 50 mol% TsOH (30 mg) in DCM/MeOH. Eight hours at 35 °C provided full conversion (120 mg, 98% yield).

The obtained free diol (110 mg, 0.165 mmol) was dissolved in 1.5 mL of pyridine, and followed by the addition of 70 µL of $POCl_3$ in two portions at an interval of 30 min. The resulting mixture was stirred at 75 °C for 2 h until the disappearance of starting material (monitored by TLC). Two mL of distilled water was then added cautiously, and the solution was stirred for another 2 h. The reaction mixture was diluted with 30 mL of dichloromethane, washed with 10 % HCl, brine, and dried over anhydrous sodium sulfate. Purification by

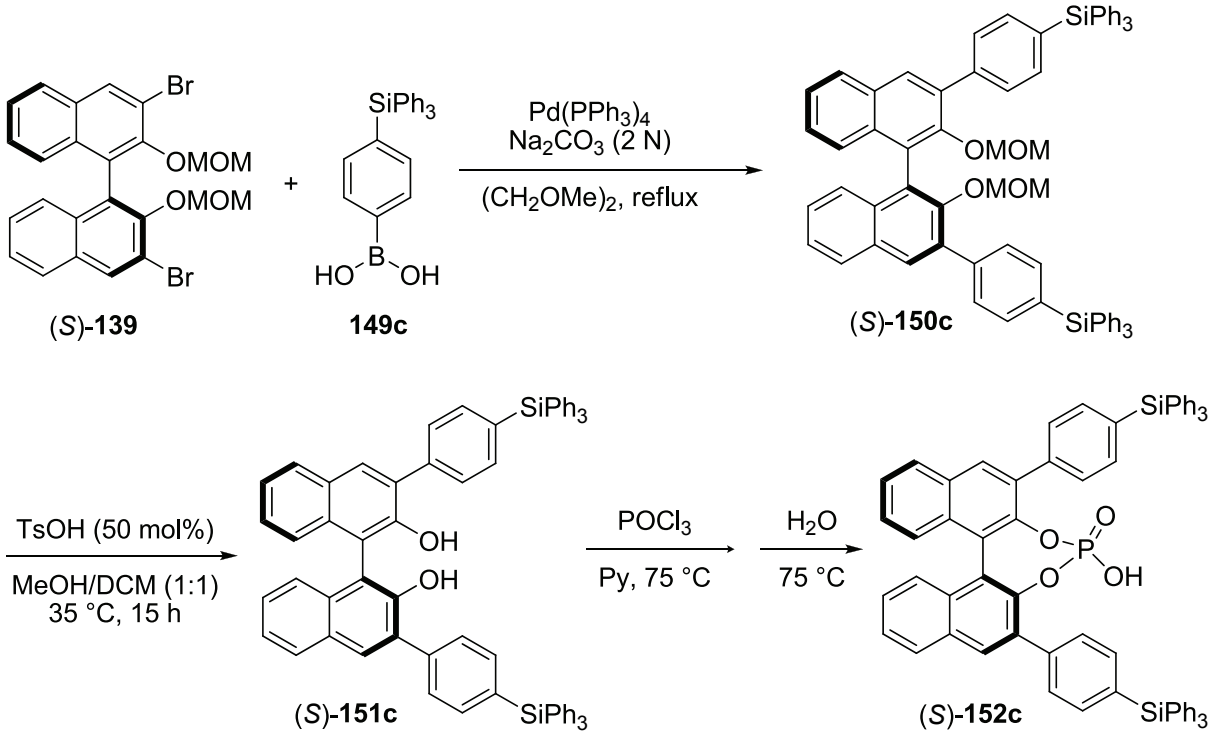
column chromatography on silica gel (4% EtOH in DCM) gave the desired phosphoric acid as a white solid (108 mg, 90% yield).

(*S*)-**150b**: $C_{48}H_{58}O_4Si_2$ (755.14 g/mol);
^{1}H-NMR (500 Mz, $CDCl_3$): δ 0.84 (q, *J* = 7.8 Hz, 12H, SiC*H*$_2$CH$_3$), δ 0.99 (t, *J* = 7.8 Hz, 18H, SiCH$_2$C*H*$_3$), 2.34 (s, 6H, OC*H*$_3$), 4.37 (d, *J* = 5.8 Hz, 2H, OC*H*$_2$), 4.41 (d, *J* = 5.8 Hz, 2H, OC*H*$_2$), 7.28 (m, 4H, Ar*H*), 7.40 (m, 2H, Ar*H*), 7.58 (d, *J* = 8.0 Hz, 4H, Ar*H*), 7.74 (d, *J* = 8.0 Hz, 4H, Ar*H*), 7.88 (d, *J* = 8.2 Hz, 2H, Ar*H*), 7.96 (s, 2H, Ar*H*);
^{13}C-NMR (125 Mz, $CDCl_3$): δ 3.4, 7.4, 55.8, 98.6, 125.1, 126.3, 126.40, 126.43, 127.9, 128.9, 130.5, 130.8, 133.6, 134.2, 135.6, 136.2, 139.3, 151.4.

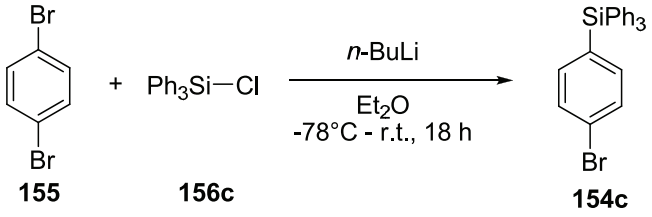
(*S*)-**151b**: $C_{44}H_{50}O_2Si_2$ (667.04 g/mol);
^{1}H-NMR (500 Mz, $CDCl_3$): δ 0.84 (q, *J* = 7.8 Hz, 12H, SiC*H*$_2$CH$_3$), δ 1.00 (t, *J* = 7.8 Hz, 18H, SiCH$_2$C*H*$_3$), 5.38 (s, 2H, O*H*), 7.22 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.30 (m, 2H, Ar*H*), 7.38 (m, 2H, Ar*H*), 7.62 (d, *J* = 8.0 Hz, 4H, Ar*H*), 7.72 (d, *J* = 8.0 Hz, 4H, Ar*H*), 7.92 (d, *J* = 8.0 Hz, 2H, Ar*H*), 8.04 (s, 2H, Ar*H*);
^{13}C-NMR (125 Mz, $CDCl_3$): δ 3.4, 7.4, 112.4, 124.3, 127.3, 128.5, 128.7, 129.5, 130.6, 131.4, 132.9, 134.4, 137.1, 137.7, 150.2.

(*S*)-**152b**: $C_{44}H_{49}O_4PSi_2$ (729.00 g/mol);
^{1}H-NMR (500 Mz, $CDCl_3$): δ 0.58 (q, *J* = 7.8 Hz, 12H, SiC*H*$_2$CH$_3$), δ 0.75 (t, *J* = 7.8 Hz, 18H, SiCH$_2$C*H*$_3$), 6.08 (s br, 1H, O*H*), 7.28-7.35 (m, 4H, Ar*H*), 7.42 (d, *J* = 8.0 Hz, 4H, Ar*H*), 7.48 (m, 2H, Ar*H*), 7.58 (d, *J* = 8.0 Hz, 4H, Ar*H*), 7.95 (d, *J* = 8.3 Hz, 2H, Ar*H*), 8.03 (s, 2H, Ar*H*);
^{13}C-NMR (125 Mz, $CDCl_3$): δ 3.2, 7.2, 122.5, 125.9, 126.4, 127.1, 128.4, 128.9, 131.4, 131.6, 132.0, 133.9 (d), 134.1, 136.7, 136.9, 144.38, 144.45;
^{31}P-NMR (202 Mz, $CDCl_3$): δ 3.66;
HRMS (ESIneg): calculated for ($[C_{44}H_{48}O_4P_1Si_2]^-$) 727.283814, found 727.283433.

6.2.1.10 Preparation of (*S*)-3,3'-Bis(4-triphenylsilylphenyl)-1,1'-binaphthyl-2,2'-diyl Hydrogen Phosphate ((*S*)-152c)



Synthesis of 4-triphenylbromobenzene (154c):



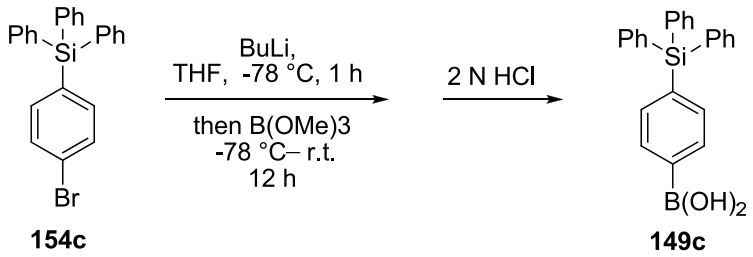
Following to the known procedure,[93b] to the stirred cold (-78 °C) solution of *p*-dibromobenzene (4.71 g, 20 mmol) in abs. ether (40 mL), 9 mL of *n*-BuLi (2.5 M in hexane, 22.5 mmol) was added slowly under argon. Two hours later, the reaction mixture was warmed to room temperature and stirred for additional 2 h. Triphenylsilylchloride (5.90 g, 20 mmol) was then added. After 14 h, the solution was poured into 100 mL of water and extracted with ether (2×500 mL). Reprecipitation from THF/MeOH gave the desired product as a white powder (7.1 g, 85% yield).

154c: $C_{24}H_{19}BrSi$ (415.40 g/mol);

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (m, 6H, Ar*H*), 7.43 (m, 3H, Ar*H*), 7.50 (d, J = 8.0 Hz, 2H, Ar*H*), 7.54 (d, J = 7.7 Hz, 6H, Ar*H*), 7.57 (d, J = 7.7 Hz, 2H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 128.1, 128.2, 129.5, 129.8, 131.3, 136.5, 136.6, 138.1.

Synthesis of 4-triphenylbenzeneboronic acid (149c):



154c **149c**

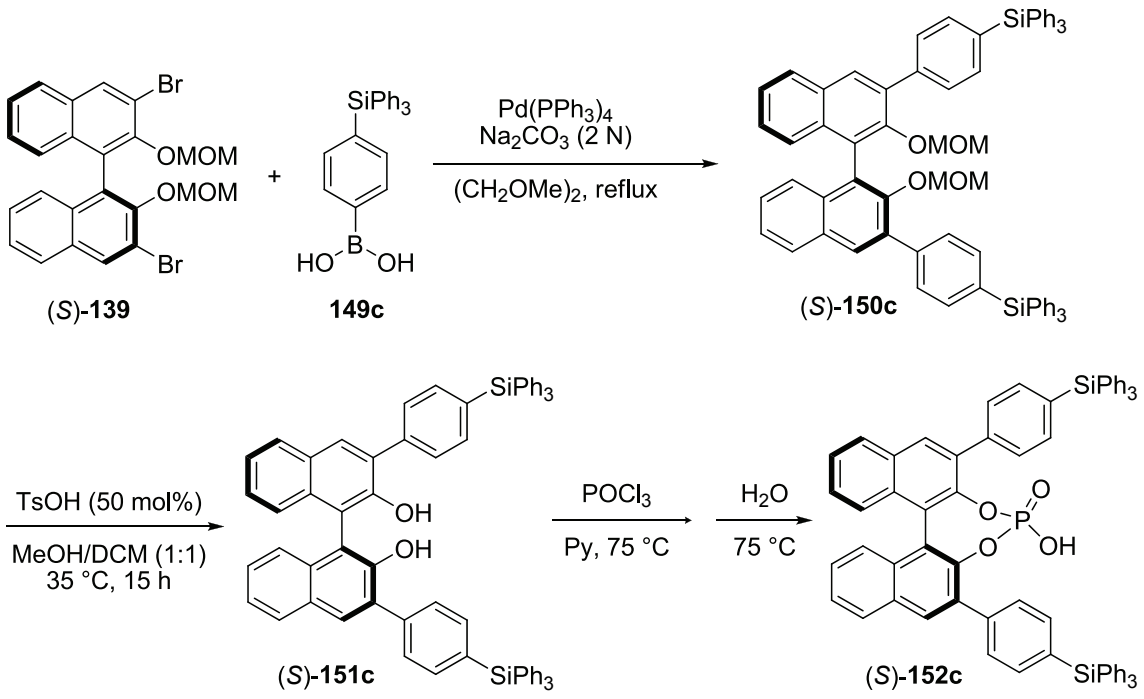
Following the known procedure,[93b] to a cold (-78 °C) solution of 4-triphenylsilylbromobenzene (1.66 g, 4 mmol) in 20 mL of abs. THF, 2 mL of *n*-BuLi (2.5 M in hexane, 5.0 mmol) was added via syringe under argon. After 1 h, trimethylborate (0.60 g, 6 mmol) was added over 10 min. The reaction mixture was warmed to room temperature, and stirred for 2 h. Finally, the reaction mixture was poured into 200 mL of water, acidified with aq. 2N HCl, and extracted with EtOAc. Purification by flash column chromatography on silica gel (hexanes/ether, 1:1) yielded the desired product as a white powder (0.26 g, 17% yield).

149c: $C_{24}H_{21}BO_2Si$ (380.32 g/mol);

^{1}H-NMR (500 Mz, $CDCl_3$): δ 5.01 (s, br, O*H*), 6.82 (m, 2 H, Ar*H*), 7.35 (m, 6H, Ar*H*), 7.41 (m, 5H, Ar*H*), 7.55 (m, 6H, Ar*H*);

^{13}C-NMR (125 Mz, $CDCl_3$): δ 115.1, 125.1, 127.8, 129.5, 134.5, 136.3, 138.1, 156.9.

Synthesis of (S)-3,3'-bis(4-triphnylsilylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate ((S)-152c):



The procedure described for (*S*)-**152a** was followed. A degassed solution of MOM-protected binol (*S*)-**139** (518 mg, 1 mmol), $Pd(PPh_3)_4$ (115 mg, 0.1 mmol), 4-triphenylsilylbenzeneboronic acid (1.25 g, 3.0 mmol) and Na_2CO_3 (530 mg, 5 mmol, in 2.5 mL of water) in DME (10 mL) was heated to reflux for 12 h. Purification by flash column chromatography (DCM/hexanes, 1:2) gave the coupling product as a white solid. Deprotection was carried out in DCM/MeOH (10 mL/10mL) at 40 °C using 50 mol% TsOH (110 mg) as the catalyst. Full conversion was achieved after 24 hours (monitored by TLC, hexanes/DCM, 1.8:1, Rf = 0.4). The free diol (*S*)-**151c** was then dissolved in 2.5 mL of pyridine, and 200 µL of $POCl_3$ was added. The resulting mixture was stirred at 75 °C for 5 h until the disappearance of the starting diol (monitored by TLC). Then, two mL of distilled water was added with caution, and the solution was stirred for another 2 h. Purification by column chromatography on silica gel (3% EtOH in DCM) gave the desired phosphoric acid as a white solid (610 mg, 60% overall yield).

(*S*)-**151c**: $C_{68}H_{50}O_2Si_2$ (955.29 g/mol);

^{1}H-NMR (500 Mz, $CDCl_3$): δ 5.37 (s, 2H, O*H*), 7.22 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.29-7.62 (m, 34H, Ar*H*), 7.69 (d, *J* = 8.0 Hz, 4H, Ar*H*), 7.75 (d, *J* = 8.0 Hz, 4H, Ar*H*), 7.92 (d, *J* = 8.0 Hz, 2H, Ar*H*), 8.06 (s, 2H, Ar*H*).

(*S*)-**152c**: $C_{68}H_{49}O_4PSi_2$ (1017.26 g/mol);

^{1}H-NMR (500 Mz, DMSO): δ 7.06 (d, *J* = 8.6 Hz, 2H, Ar*H*), 7.30 (t, *J* = 7.7 Hz, 2H, Ar*H*), 7.43-7.57 (m, 20H, Ar*H*), 7.61-7.64 (m, 16H, Ar*H*), 8.11 (d, *J* = 8.2 Hz, 2H, Ar*H*), 8.20 (s, 2H, Ar*H*), 8.22 (d, *J* = 8.0 Hz, 4H, Ar*H*);

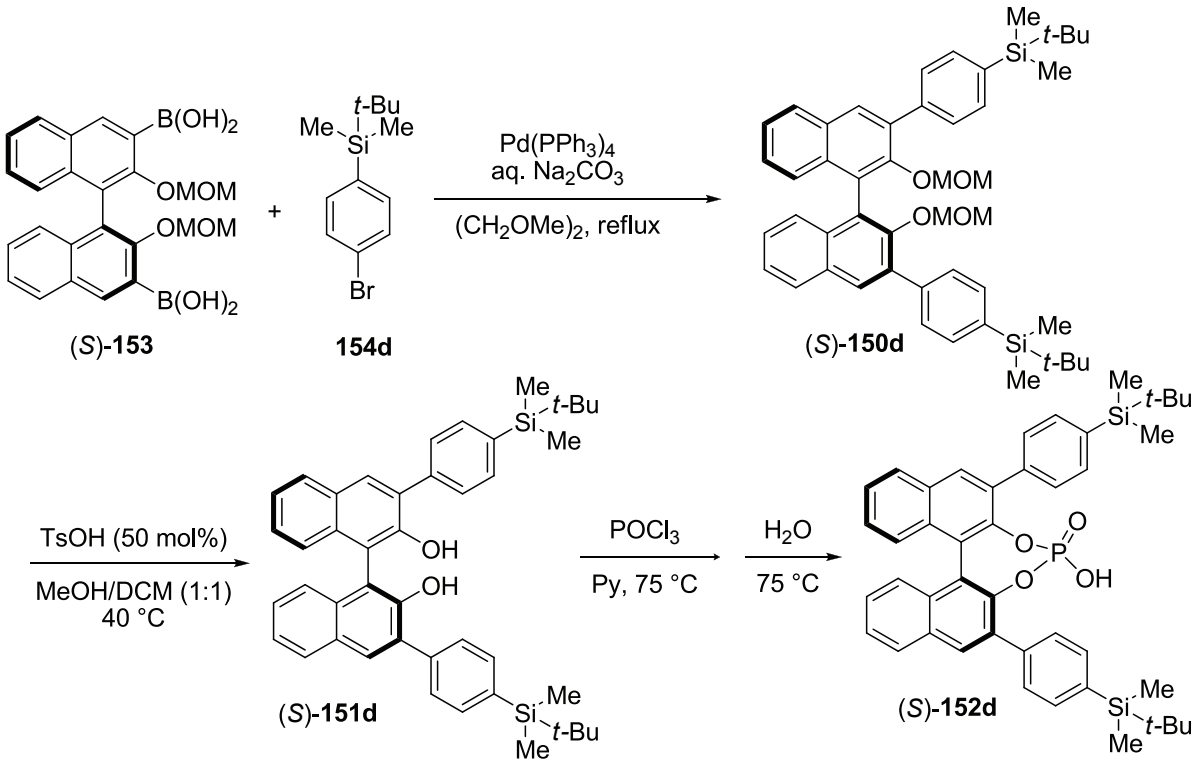
^{1}H-NMR (500 Mz, $CDCl_3$): δ 6.33 (s br, 1H, O*H*), 6.90 (t, *J* = 7.4 Hz, 6H, Ar*H*), 6.99 (t, *J* = 7.4 Hz, 12H, Ar*H*), 7.33-7.40 (m, 18H, Ar*H*), 7.42 (d, *J* = 8.0 Hz, 4H, Ar*H*), 7.47 (d, *J* = 8.6 Hz, 2H, Ar*H*), 7.54 (t, *J* = 7.5 Hz, 2H, Ar*H*), 8.00 (d, *J* = 8.3 Hz, 2H, Ar*H*), 8.07 (s, 2H, Ar*H*);

^{13}C-NMR (125 Mz, $CDCl_3$): δ 122.81, 122.82, 126.1, 126.7, 127.2, 127.6, 128.6, 129.1, 129.2, 131.5, 131.8, 132.1, 133.4, 133.96, 133.98, 134.1, 136.1, 136.2, 137.7, 144.38, 144.45;

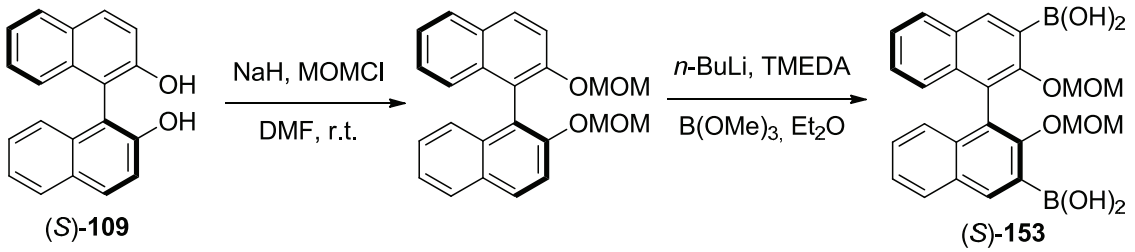
^{31}P-NMR (202 Mz, $CDCl_3$): δ 4.29;

HRMS (ESIneg): calculated for ($[C_{68}H_{48}O_4P_1Si_2]^-$) 1015.283750, found 1015.283430.

6.2.1.11 Preparation of (*S*)-3,3'-Bis(4-(*tert*-butyldimethylsilyl)phenyl)-1,1'-binaphthyl-2,2'-diyl Hydrogen Phosphate ((*S*)-152d)



Synthesis of 2,2'-dimethoxymethoxy-1,1'-binaphthyl-3,3'-bisboronic acid((S)-153):

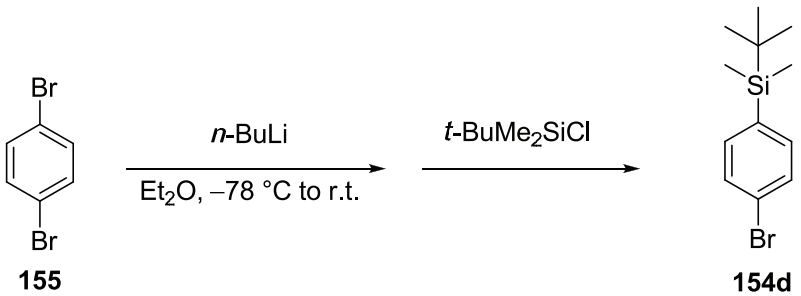


(*S*)-**109** (*S*)-**153**

The MOM-protected binol was prepared according to the literature procedure with minor modification.[139] To a solution of NaH (6.43 g, 160 mmol) in DMF (50 mL) was added a solution of (*S*)-BINOL (20 g, 70 mmol) in DMF (50 mL) at 0 °C. The reaction was stirred for 30 min, and chloromethyl methyl ether (11.7 ml, 160 mmol) was then added over 20 min. The reaction was followed by TLC and completed in 2 h after the addition of chloromethyl methyl ether. The reaction mixture was then poured into 500 ml of cold water and the product was collected by filtration. After drying *in vacuo*, the desired MOM-protected BINOL was obtained as a white solid in quantitative yield. The diboronic acid (*S*)-**153** was prepared according to the protocol for (*S*)-2,2'-dimethoxy-1,1'-binaphthyl-3,3'-diyldiboronic acid (*S*)-**111** and obtained in 66% yield.

(*S*)-**153**: $C_{24}H_{24}B_2O_8$ (462.06 g/mol);
^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.55 (s, 4H, O*H*), 3.04 (s, 6H, OCH_3), 4.38, 4.42 (d, *J* = 7.5 Hz, 4H, OCH_2), 7.19 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.34 (m, 2H, Ar*H*), 7.46 (m, 2H, Ar*H*), 8.00 (d, *J* = 8.1 Hz, 2H, Ar*H*), 8.60 (s, 2H, Ar*H*).

Synthesis of 4-(tert-butyldimethylsilyl)bromobenzene (154d):



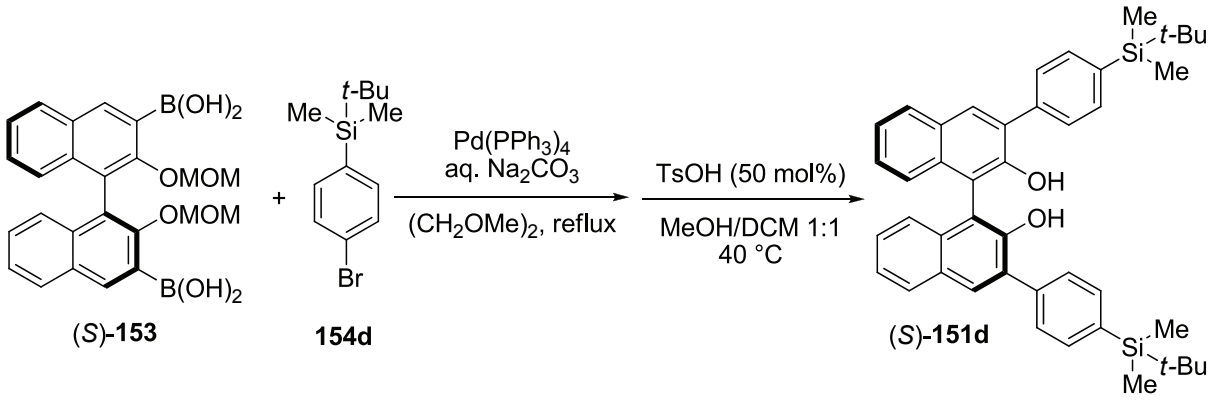
155 **154d**

According to the procedure described for the synthesis of 4-triethylsilylbromobenzene, under the atmosphere of argon, *n*-BuLi (2.5 M in hexane, 9 mL, 22.5 mmol) was slowly added to the cold (- 78°C) solution of 1,4-dibromobenzene (4.71 g, 20 mmol). After stirred for 1 h, the reaction mixture was warmed to room temperature and stirred for another hour. *Tert*-

Butyldimethylsilylchloride (2.75 g, 20 mmol) was then added dropwise via a syringe. Three hours later, the reaction was quenched with 100 mL of water, extracted with ether, washed with brine, and dried over $MgSO_4$. The pure product (3.47 g, 64% yield) was obtained by distillation under reduced pressure (120 °C/5 mbar).

154d: $C_{12}H_{19}BrSi$ (271.27 g/mol);
^{1}H-NMR (500 Mz, $CDCl_3$): δ 0.25 (s, SiC*H*$_3$, 6H), 0.86 (s, *t*-Bu-*H*, 9H), 7.36 (d, *J* = 8 Hz, ArH, 2H), 7.48 (d, *J* = 8 Hz, ArH, 2H);
^{13}C-NMR (125 Mz, $CDCl_3$): δ -6.3, 16.8, 26.4, 123.6, 130.6, 136.0, 136.6.

Synthesis of (S)-3,3'-bis(4-(tert-butyldimethylsilyl)phenyl)- 1,1'-binaphthyl-2,2'-diol((S)-151d):

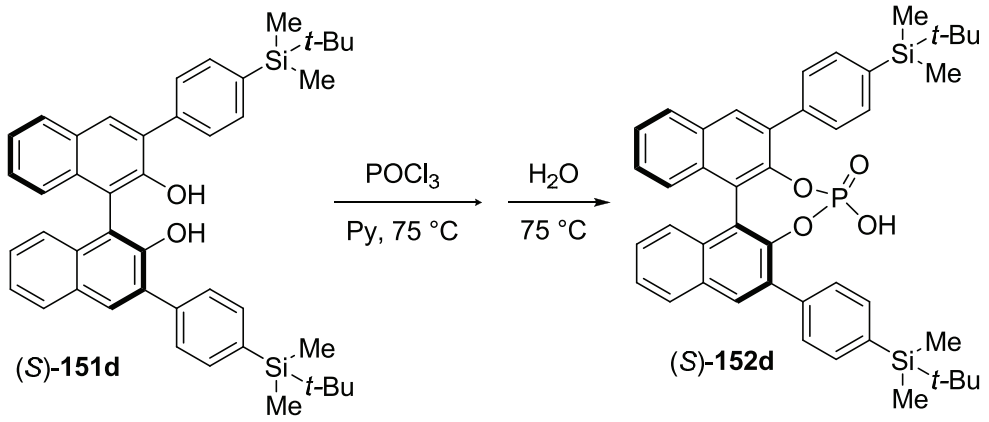


According to the procedure described for (*S*)-3,3'-bis(4-trimethylsilylphenyl)-1,1'-binaphthyl-2,2'-diol (**151a**) with minor changes, a degassed solution of MOM-protected bisboronic acid (700 mg, 1.35 mmol), $Pd(PPh_3)_4$ (156 mg, 0.135 mmol.), 4-(*tert*-butyldimethylsilyl)bromobenzene (1.09 g, 4.05 mmol) and Na_2CO_3 (715 mg, 6.75 mmol) in DME/water (10.8 mL, 3:1) was heated to reflux for 12 h. The reaction mixture was diluted with dichloromethane, washed with water and dried over $MgSO_4$. Purification by flash column chromatography on silica gel (5 % EtOAc in hexanes) gave the coupling product as a white solid (614 mg, 60% yield). The Deprotection was carried out using TsOH (65 mg, 50 mol%) in DCM/MeOH (14 mL, 1:1). Ten hours at 40 °C gave full conversion. Purification by column (1% EtOAc in hexanes) gave the desired diol in a quantitative yield.

(*S*)-**151d**: $C_{44}H_{50}O_2Si_2$ (667.04 g/mol);

^{1}H-NMR (400 Mz, $CDCl_3$): δ 0.31 (s, 12H, SiCH_3), 0.92 (s, 18H, CCH_3), 5.30 (s, 2H, O*H*), 7.22 (d, *J* = 8.2 Hz, 2H, Ar*H*), 7.31 (m, 2H, Ar*H*), 7.39 (m, 2H, Ar*H*), 7.63 (d, *J* = 8.1 Hz, 4H, Ar*H*), 7.71 (d, *J* = 8.1 Hz, 4H, Ar*H*), 7.92 (d, *J* = 8.0 Hz, 2H, Ar*H*), 8.04 (s, 2H, Ar*H*);
^{13}C-NMR (125 Mz, $CDCl_3$): δ -6.1, 17.0, 26.6, 112.4, 124.4, 127.4, 128.5, 128.6, 129.5, 130.6, 131.4, 133.0, 134.7, 137.4, 137.8, 150.2.

Synthesis of (S)-3,3'-bis(4-(tert-butyldimethylsilyl)phenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate ((S)-152d):

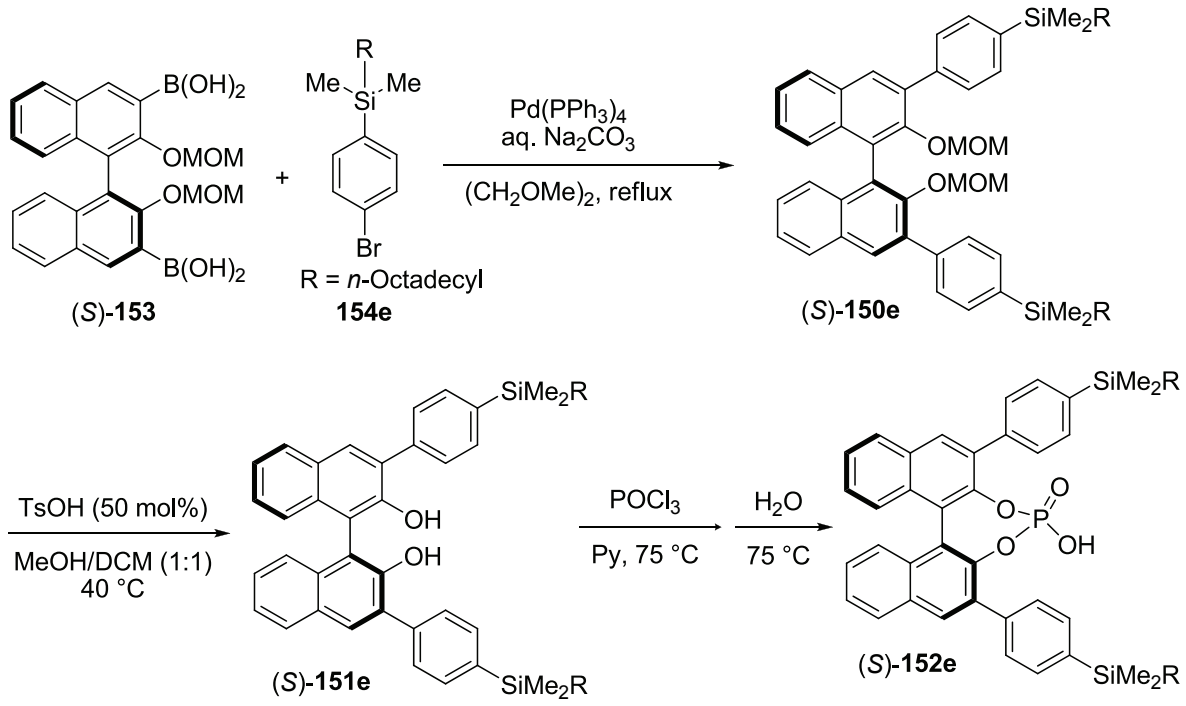


According to the procedure described for (*S*)-3,3'-bis(4-trimethylsilylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (**151a**), free diol (*S*)-**151d** (463 mg, 0.69 mmol.) was dissolved in 2 mL of pyridine, and then 129 μL of $POCl_3$ was added. The resulting mixture was stirred at 75 °C for 2 h until the disappearance of starting material (monitored by TLC). Two mL of distilled water was then added cautiously, and the solution was stirred for another 2 h at 75 °C. The reaction mixture was cooled to room temperature and diluted with 30 mL of dichloromethane, washed with 10 % HCl and brine, and dried over anhydrous sodium sulfate. Purification by column chromatography on silica gel (hexanes/EtOAc, 70:30) gave the desired product as a white solid (406 mg, 87% yield).

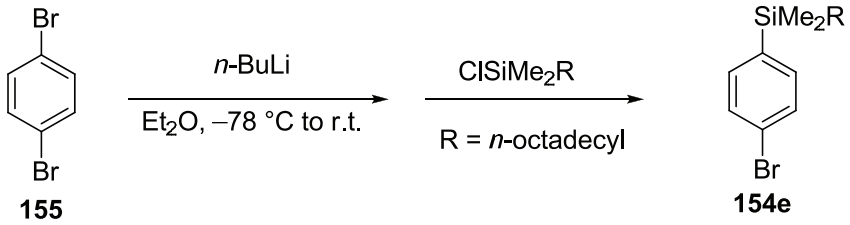
(*S*)-**152d**: $C_{44}H_{49}O_4PSi_2$ (729.00 g/mol);
^{1}H-NMR (400 Mz, $CDCl_3$): δ 0.02 (d, *J* = 24 Hz, 12H, SiCH_3), 0.70 (s, 18H, CCH_3), 7.20-7.32 (m, 8H, Ar*H*), 7.45-7.52 (m, 6H, Ar*H*), 7.92 (s, 2H, Ar*H*), 8.00 (d, *J* = 8.2 Hz, 2H, Ar*H*);
^{13}C-NMR (125 Mz, $CDCl_3$): δ -6.25 (d), 16.8, 26.3, 123.1, 125.5, 126.2, 127.1, 128.2, 129.0, 131.1, 131.2, 132.3, 134.1, 134.1, 136.7, 144.1;
^{31}P-NMR (202 Mz, $CDCl_3$): δ 2.51;

HRMS (ESIneg): calculated for ($[C_{44}H_{48}O_4P_1Si_2]^-$) 727.283484, found 727.283431.

6.2.1.12 Preparation of (*S*)-3,3'-Bis(4-octadecyldimethylsilylphenyl)-1,1'-binaphthyl-2,2'-diyl Hydrogen Phosphate ((*S*)-152e)



Synthesis of 4-octadecyldimethylsilylbromobenzene (154e):



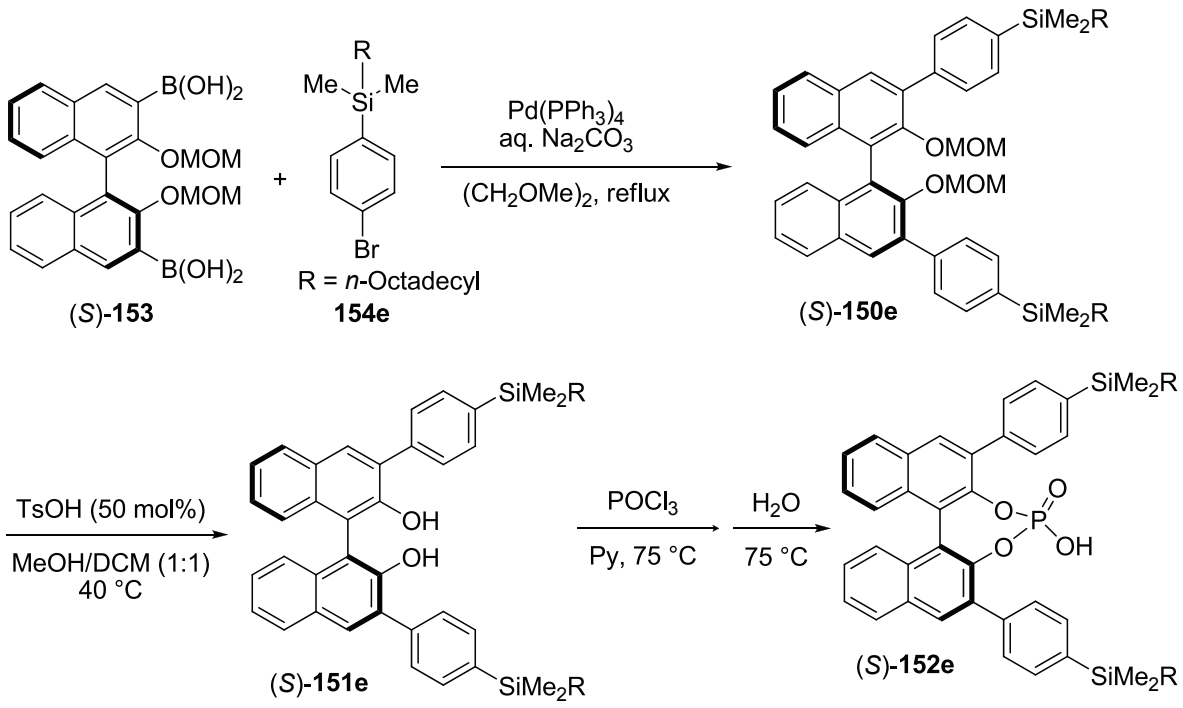
According to the procedure described for the synthesis of 4-triethylsilylbromobenzene, under the atmosphere of argon, *n*-BuLi (2.5 M in hexane, 4.4 mL, 11 mmol) was slowly added to a cold (-78°C) solution of 1,4-dibromobenzene (2.35 g, 10 mmol) in 18 mL of ether. After the reaction was stirred for 1 h at -78 °C and 3 hour at room termperature, *n*-octadecyldimethylsilylchloride (3.82 g, 11 mmol) was added. Distillation under reduced pressure (230 °C/0.4 mbar) gave the product as a pale yellow oil (3.80 g, 81% yield).

154e: $C_{26}H_{47}BrSi$ (467.64 g/mol);

^{1}H-NMR (500 Mz, $CDCl_3$): δ 0.23 (s, 6H, SiCH_3), 0.71 (t, J = 7.8 Hz, 2H, SiCH_2), 0.88 (t, J = 6.8 Hz, 3H, CH_3), 1.25 (m, 32H, CH_2), 7.35 (d, J = 8.1 Hz, 2 H, ArH), 7.48 (d, J = 8.1 Hz, 2 H, ArH);

^{13}C-NMR (125 Mz, $CDCl_3$): δ -3.1, 14.1, 15.6, 22.7, 23.8, 29.3, 29.4, 29.6, 29.67, 29.7, 31.9, 33.5, 123.5, 130.8, 135.2, 138.6.

Synthesis of (S)-3,3'-bis(4-octadecyldimethylsilylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate((S)-152e):



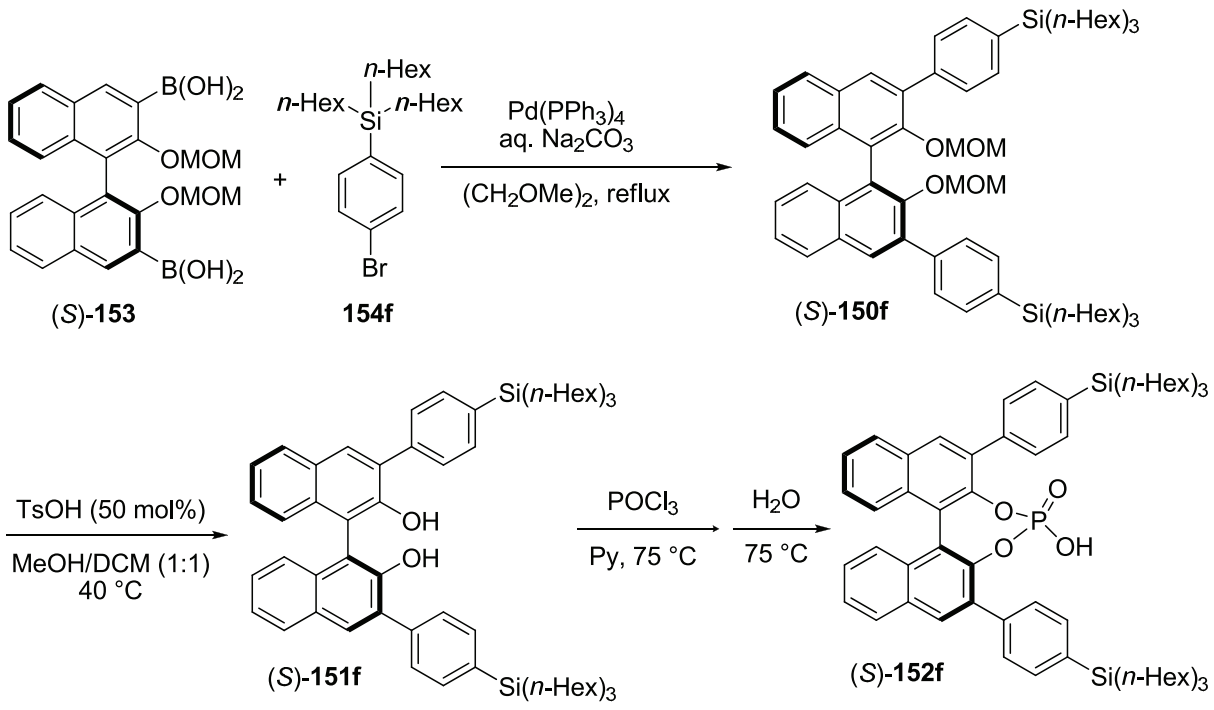
According the procedure described for (*S*)-3,3'-bis(4-(*tert*-butyldimethylsilyl)phenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (**152d**), a degassed solution of MOM-protected bisboronic acid (1.0 g, 1.93 mmol), $Pd(PPh_3)_4$ (223 mg, 0.193 mmol.), 4-octadecyldimethylsilylbromobenzene (2.70 g, 5.79 mmol) and Na_2CO_3 (1.02 g, 9.65 mmol) in DME/water (15.4 mL, 3:1) was heated to reflux for 19 h. The reaction mixture was then diluted with dichloromethane, washed with water and dried over $MgSO_4$. Purification by flash column chromatography on silica gel (1% EtOAc in hexanes) gave the crude product as a white solid (1.58 g, 71% yield). The deprotection of 1.32 g of the obtained product was carried out using 50 mol% of TsOH (126 mg) in DCM/MeOH (24 mL, 1:1) for 12 hours at 40

°C. Purification by column (20% CH_2Cl_2 in hexanes) provided the desired diol (1.06 g, 75% yield). Free diol (*S*)-**151e** (1.01 g, 0.95 mmol.) was dissolved in 2 mL of pyridine, and then 170 µL of $POCl_3$ (1.90 mmol) was added. The resulting mixture was stirred at 75 °C overnight. Two mL of distilled water was then added cautiously, and the solution was stirred for another 2 h at 70 °C. Purification by column chromatography on silica gel (4% EtOH in CH_2Cl_2) gave the desired product as a pale yellow oil (990 mg, 93% yield).

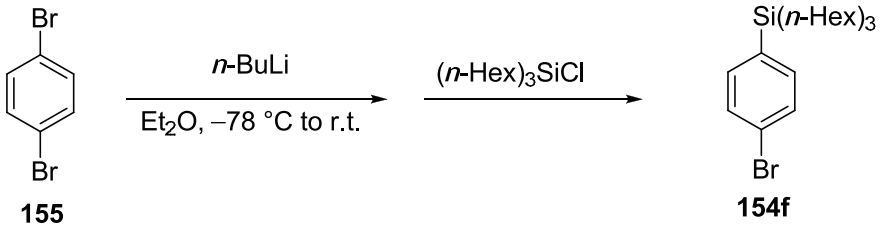
(*S*)-**151e**: $C_{72}H_{106}O_2Si_2$ (1059.78 g/mol);
^{1}H-NMR (500 Mz, $CDCl_3$): δ 0.29 (s, 12H, SiC*H*$_3$), 0.78 (t, *J* = 7.9 Hz, 4H, SiC*H*$_2$), 0.88 (t, *J* = 6.9 Hz, 6H, C*H*$_3$), 1.24-1.35 (m, 64H, C*H*$_2$), 7.22 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.31 (m, *2*H, Ar*H*), 7.39 (m, *2*H, Ar*H*), 7.62 (d, *J* = 8.0 Hz, 4H, Ar*H*), 7.71 (d, *J* = 8.0 Hz, 4H, Ar*H*), 7.92 (d, *J* = 8.0 Hz, 4H, Ar*H*), 8.03 (s, 2H, Ar*H*);
^{13}C-NMR (125 Mz, $CDCl_3$): δ -2.9, 14.1, 15.7, 22.7, 23.9, 29.4, 29.6 (m), 29.7, 31.9, 33.7, 112.4, 124.3, 127.3, 128.5, 128.8, 129.5, 130.6, 131.4, 133.0, 133.8, 137.7, 139.3, 150.2.

(*S*)-**152e**: $C_{72}H_{105}O_4PSi_2$ (1121.75 g/mol);
^{1}H-NMR (500 Mz, $CDCl_3$): δ 0.14 (d, *J* = ~9 Hz, 12H, SiC*H*$_3$), 0.72 (m, 4H, SiC*H*$_2$), 1.00 (t, *J* = 6.9 Hz, 6H, C*H*$_3$), 1.29-1.44 (m, 64H, C*H*$_2$), 7.31 (t, *J* = 7.8 Hz, *2*H, Ar*H*), 7.48 (d, *J* = 8.6 Hz, 2H, Ar*H*), 7.56-7.60 (m, 6H, Ar*H*), 7.72 (d, *J* = 7.8 Hz, 4H, Ar*H*), 8.04 (d, *J* = 8.3 Hz, 2H, Ar*H*), 8.14 (s, 2H, Ar*H*);
^{13}C-NMR (125 Mz, $CDCl_3$): δ -3.09, -3.05, 14.3, 15.7, 22.9, 24.0, 29.5, 29.6, 29.8 (m), 29.9, 32.1, 33.7, 122.6, 126.0, 126.5, 127.3, 128.5, 129.1, 131.6, 131.7, 132.1, 133.7, 134.2 (d), 137.1, 139.1, 144.6 (d);
^{31}P-NMR (202 Mz, $CDCl_3$): δ 3.65;
HRMS (ESIneg): calculated for ($[C_{72}H_{104}O_4P_1Si_2]^-$) 1119.720984, found 1119.721632.

6.2.1.13 Preparation of (*S*)-3,3'-Bis(4-trihexylsilylphenyl)-1,1'-binaphthyl-2,2'-diyl Hydrogen Phosphate ((*S*)-152f)



*Synthesis of 4-trihexylsilylbromobenzene (**154f**):*



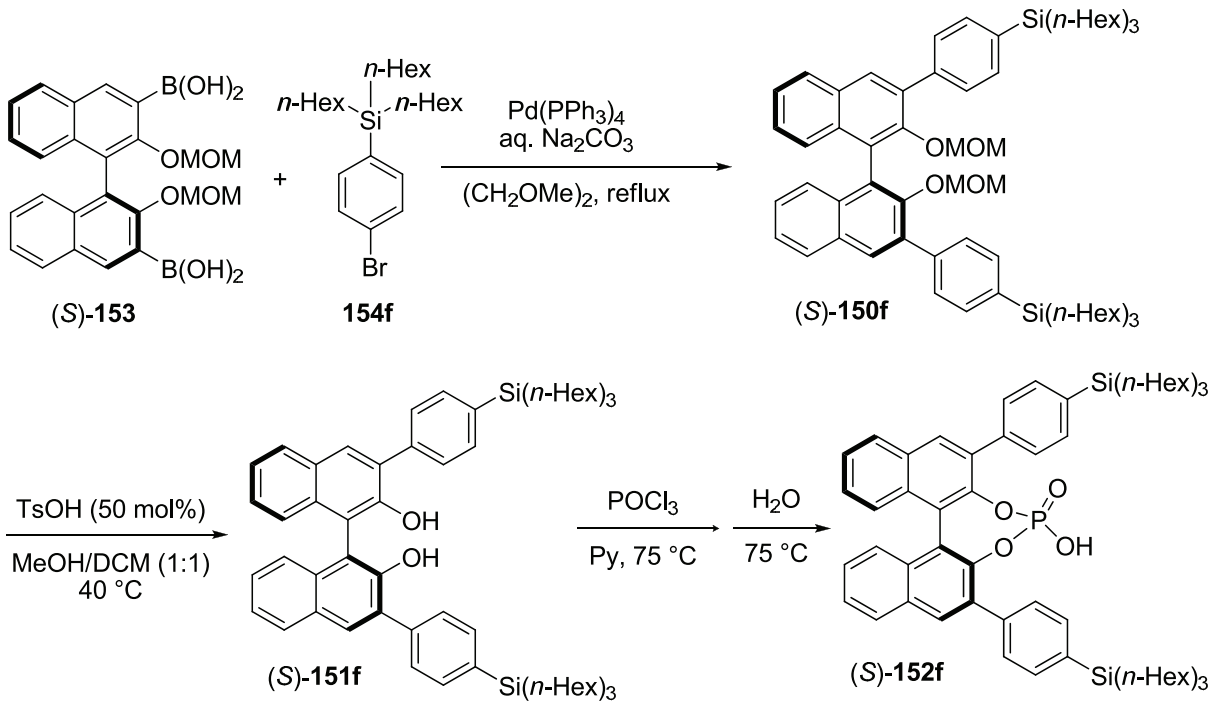
According to the procedure described for the synthesis of 4-triethylsilylbromobenzene, under the atmosphere of argon, *n*-BuLi (2.3 M in hexane, 4.4 mL, 11 mmol) was slowly added to the cold (-78°C) solution of 1,4-dibromobenzene (**155**, 2.35 g, 10 mmol). After the reaction was stirred for 1 h at -78 °C and another hour at room termperature, trihexylsilylchloride (4.03 mL, 11 mmol) was added. Distillation under reduced pressure (220 °C/0.4 mbar) gave the product as a pale yellow oil (4.12 g, 94% yield).

154f: $C_{24}H_{43}BrSi$ (439.59 g/mol);

^{1}H-NMR (500 Mz, $CDCl_3$): δ 0.78 (m, 6H, SiCH_2), 0.90 (t, *J* = 6.8 Hz, 9H, CH_3), 1.20 (m, 24H, CH_2), 7.35 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 7.47 (d, *J* = 8.5 Hz, 2 H, Ar*H*);

^{13}C-NMR (125 Mz, $CDCl_3$): δ 12.3, 14.1, 22.6, 23.7, 31.5, 33.4, 123.4, 130.8, 135.7, 137.1.

*Synthesis of (S)-3,3'-bis(4-trihexylsilylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate((S)-**152f**):*



According to the procedure described for (*S*)-3,3'-bis(4-(*tert*-butyldimethylsilyl)phenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (**152d**), a degassed solution of MOM-protected bisboronic acid (*S*)-**153** (1.0 g, 1.93 mmol), $Pd(PPh_3)_4$ (223 mg, 0.193 mmol.), 4-trihexylsilylbromobenzene (2.54 g, 5.79 mmol) and Na_2CO_3 (1.02 g, 9.65 mmol) in DME/water (15.4 mL, 3:1) was heated to reflux for 12 h. The reaction mixture was then diluted with dichloromethane, washed with water and dried over $MgSO_4$. Purification by flash column chromatography on silica gel (5-10 % CH_2Cl_2 in hexanes) gave the product as a white solid (1.41 g, 67% yield). The deprotection of 1.30 g of the coupling product was carried out using 50 mol% of TsOH (114 mg) in DCM/MeOH (24 mL, 1:1) for 24 hours at 40 °C. Purification by column (10% CH_2Cl_2 in hexanes) gave the desired free diol as a white solid (949 mg, 80% yield). The free diol (*S*)-**151f** (839 mg, 0.84 mmol.) was then dissolved in 2 mL of pyridine, and 156 µL of $POCl_3$ (1.68 mmol) was added via a syringe. The resulting mixture was stirred at 75 °C overnight. After the disappearance of starting material (monitored by TLC), 2 mL of distilled water was added cautiously, and the solution was stirred for another 2 h at 70 °C. Purification by column chromatography on silica gel (hexanes/ CH_2Cl_2, 50:50) gave the desired product as a pale yellow solid (870 mg, 91% yield).

(*S*)-**151f**: $C_{68}H_{98}O_2Si_2$ (1003.68 g/mol);

^{1}H-NMR (500 Mz, $CDCl_3$): δ 0.81 (m, 12H, SiC*H*$_2$), 0.87 (t, *J* = 8.5 Hz, 18H, C*H*$_3$), 1.26, 1.32 (m, 48H, C*H*$_2$), 5.39 (s, 2H, O*H*), 7.22 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.30 (m, *2*H, Ar*H*), 7.38 (m, *2*H, Ar*H*), 7.59 (d, *J* = 8.1 Hz, 4H, Ar*H*), 7.70 (d, *J* = 8.1 Hz, 4H, Ar*H*), 7.91 (d, *J* = 8.0 Hz, 4H, Ar*H*), 8.04 (s, 2H, Ar*H*);

^{13}C-NMR (125 Mz, $CDCl_3$): δ 12.5, 14.1, 22.6, 23.8, 31.5, 33.5, 112.5, 124.3, 127.3, 128.4, 128.7, 129.5, 130.6, 131.3, 132.9, 134.3, 137.5, 137.9, 150.1.

(*S*)-**152f**: $C_{68}H_{97}O_4PSi_2$ (1065.64 g/mol);

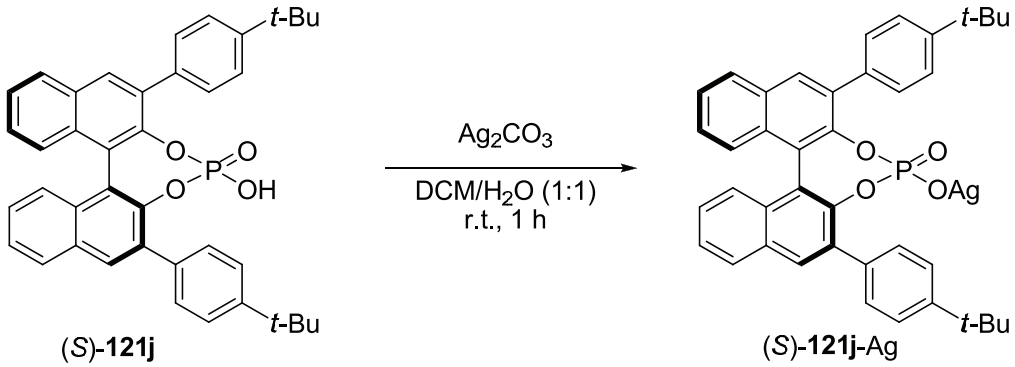
^{1}H-NMR (500 Mz, $CDCl_3$): δ 0.73 (m, 12H, SiC*H*$_2$), 0.86 (t, *J* = 6.8 Hz, 18H, C*H*$_3$), 1.26-1.30 (m, 48H, C*H*$_2$), 7.20 (t, *J* = 8.0 Hz, 2H, Ar*H*), 7.27 (d, *J* = ~9 Hz, *2*H, Ar*H*), 7.40 (m, 2H, Ar*H*), 7.49 (d, *J* = 8.0 Hz, 4H, Ar*H*), 7.87 (d, *J* = 8.0 Hz, 4H, Ar*H*), 7.93 (s, 2H, Ar*H*), 8.13 (d, *J* = 5.2 Hz, 2H, Ar*H*);

^{13}C-NMR (125 Mz, $CDCl_3$): δ 12.6, 14.1, 22.6, 23.8, 31.5, 33.6, 123.2, 125.1, 126.0, 128.2, 129.3, 131.0, 132.3, 133.9, 134.4 (d), 136.9, 138.2, 141.8, 143.4, 146.4 (d);

^{31}P-NMR (202 Mz, $CDCl_3$): δ 2.41;

HRMS (ESIneg): calculated for ([$C_{68}H_{96}O_4P_1Si_2$]$^-$) 1063.659000, found 1063.659031.

6.2.2 Synthesis of Silver Phosphates



Typical procedure: according to the known method,[7] to a solution of the phosphoric acid (61.3 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) was added Ag_2CO_3 (13.8 mg, 0.05 mmol) in one portion, followed by 1 mL of distilled water. After 1 h of vigorous stirring in the dark, the mixture was diluted with CH_2Cl_2 (4 mL) and H_2O (4 mL). The layers of the biphasic

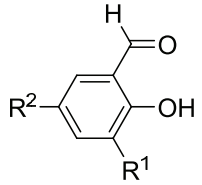
suspension were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic phases were filtered through Celite and concentrated, affording the product as a fluffy white solid (67 mg, 93% yield). Other silver phosphates were prepared according to the same procedure, and the purity was determined by ^{31}P-NMR.

(*S*)-**121j**-Ag: $C_{40}H_{36}AgO_4P$ (719.55 g/mol);
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.00 (s, 18H, C*H*$_3$), 7.30 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.42-7.46 (m, 8H, Ar*H*), 7.69 (d, *J* = 6.6 Hz, 4H, Ar*H*), 7.94 (d, *J* = 8.2 Hz, 2H, Ar*H*), 7.98 (s, 2H, Ar*H*);
^{13}C NMR (125 MHz, $CDCl_3$): δ 30.9, 34.5, 123.4, 124.9, 125.4, 126.2, 127.1, 128.3 (m), 130.7, 131.4, 132.4, 133.6, 134.9, 145.5, 146.2 (d);
^{31}P-NMR (202 Mz, $CDCl_3$): δ 10.7.

6.2.3 Preparation of Achiral Mn-Salen Complexes

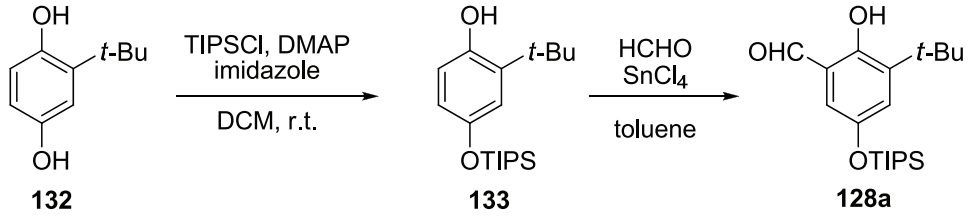
6.2.3.1 Preparation of Salicylaldehydes

3,5-Di-*tert*-butylsalicylaldehyde **105**, 3-*tert*-butylsalicylaldehyde **128c** and 5-*tert*-butylsalicylaldehyde **128g** were commercially available. The other salicylaldehydes were synthesized according to the following procedures.



128a: R^1 = *t*-Bu, R^2 = OSi(*i*-Pr)$_3$
128b: R^1 = *t*-Bu, R^2 = OMe
128c: R^1 = *t*-Bu, R^2 = H
128d: R^1 = *t*-Bu, R^2 = Br
128e: R^1 = *t*-Bu, R^2 = NO_2
128f: R^1 = *t*-Bu, R^2 = CPh_3
128g: R^1 = H, R^2 = *t*-Bu

Synthesis of 3-tert-butyl-5-triisopropylsilyloxysalicylaldehyde (128a):



According to the known procedure,[84] to a solution of *tert*-butylhydroquinone (2.50 g, 15.1 mmol) in dichloromethane (100 mL) was added imidazole (1.33 g, 19.6 mmol) and 4-dimethylaminopyridine (DMAP) (0.93 g, 7.6 mmol), followed by the addition of triisopropylsilyl chloride (3.48 g, 18.1 mmol, in 8 mL of dichloromethane) in a dropwise manner. The reaction mixture was stirred for 15 h at room temperature, and then concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (EtOAc/hexanes, 1:4) to yield the TIPS-protected phenol as a clear liquid (4.11 g, 85% yield). Then, a three-necked round-bottomed flask equipped with an addition funnel, reflux condenser and a magnetic stir-bar was connected to a nitrogen inlet and was charged with 2,6-lutidine (1.6 mL, 13.5 mmol), TIPS-protected phenol **133** (3.6 g, 11.2 mmol), $SnCl_4$ (0.4 mL, 3.35 mmol) and toluene (100 mL). The reaction mixture was stirred at room temperature under argon for 10 min followed by the addition of paraformaldehyde (1.35 g, 46.8 mmol). The mixture was heated to reflux for 6 h. After the reaction finished, the reaction mixture was cooled to room temperature, quenched with water (100 mL), and diluted with diethyl ether (100 mL). The resulting emulsion was filtered through a short pad of Celite, and the organic layer was separated, washed successively with water and brine, and dried over anhydrous Na_2SO_4. The crude product was purified by flash column chromatography on silica gel (EtOAc/hexanes, 1:9), affording the desired salicylaldehyde as a pale yellow oil (2.55 g, 66% yield).

133: $C_{19}H_{34}O_2Si$ (322.56 g/mol);

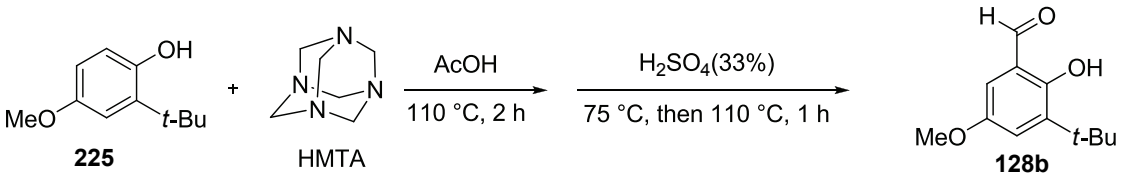
^{1}H-NMR (500 Mz, $CDCl_3$): δ 1.08 (d, *J* = 2.4 Hz, 18H, $CH(CH_3)_2$), 1.22 (m, 3H, $CH(CH_3)_2$)), 1.37 (s, $C(CH_3)_3$, 9H), 6.50 (d, *J* = 8.5 Hz, 1H, Ar*H*), 6.57 (dd, *J* = 8.5, 2.9 Hz, 1H, Ar*H*), 6.81 (d, *J* = 2.9 Hz, 1H, Ar*H*);

^{13}C-NMR (125 Mz, $CDCl_3$): δ 12.6, 17.9, 29.5, 34.5, 116.8, 117.2, 118.8, 137.0, 148.1, 149.5.

128a: $C_{20}H_{34}O_3Si$ (350.57 g/mol);

^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.10 (d, *J* = 7.3 Hz, 18H, CH(C*H*$_3$)$_2$), 1.25 (m, 3H, C*H*(CH$_3$)$_2$), 1.40 (s, 9H, *t*-Bu-H), 6.84 (d, *J* = 3.0 Hz, 1H, Ar*H*), 7.13 (d, *J* = 3.0 Hz, 1H, Ar*H*), 9.78 (s, 1H, C*H*O), 11.40 (s, 1H, O*H*);
^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.6, 17.9, 29.1, 34.9, 119.9, 120.2, 127.6, 139.5, 148.3, 156.0, 196.7.

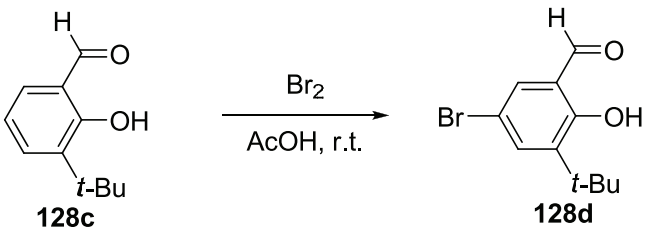
Synthesis of 5-methoxy-3-tert-butyl-salicylaldehyde (*128b*):



According to the known method,[72] a stirred mixture of 2-*tert*-butyl-4-methoxyphenol (7.36 g, 40 mmol.), HMTA (11.33 g, 80 mmol), and acetic acid (40 mL) was heated at 110 °C for 2 h. Then, 20 mL of 30% H_2SO_4 was added. After 1 h at 110 °C, the mixture was cooled to room temperature, extracted with diethyl ether, washed with water and brine. The organic layer was dried over anhydrous sodium sulfate. Purification by flash column chromatography on silica gel (EtOAc/hexanes, 1:10) yielded the product as a yellow oil (4.70 g, 56% yield).

128b: $C_{12}H_{16}O_3$ (208.25 g/mol);
^{1}H-NMR (500 Mz, $CDCl_3$): δ 1.41 (s, 9H, *t*-Bu-*H*), 3.81 (s, 3H, O*CH*$_3$), 6.81 (d, *J* = 3.0 Hz, 1H, Ar*H*), 7.17 (d, *J* = 3.0 Hz, 1H, Ar*H*), 9.84 (s, 1H, C*H*=O), 11.50 (s, 1H, O*H*);
^{13}C-NMR (125 Mz, $CDCl_3$): δ 29.1, 35.0, 55.8, 111.7, 119.8, 123.9, 140.2, 152.0, 156.2, 196.6.

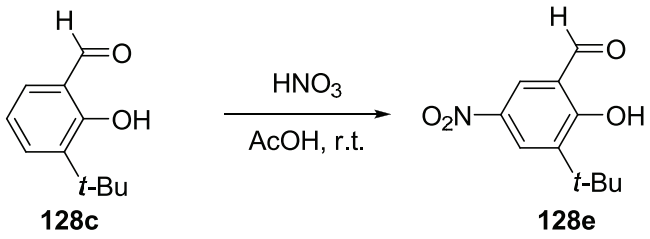
Synthesis of 5-bromo-3-tert-butyl-salicylaldehyde(128d):



A known procedure was followed.[82] To a solution of phenol **128c** (1.78 g, 10 mmol) in 5 mL of acetic acid was slowly added bromine (0.53 mL, 10.3 mmol, in 2 mL of AcOH) over 15 min (color changed from orange to dark red). After 2 h at room temperature, the reaction was diluted with 30 mL of dichloromethane, washed successively with aq. Na_2SO_3, sat. $NaHCO_3$, brine, and dried over anhydrous sodium sulfate. Crystallization from ethanol gave the pure product as needle-like crystals (1.52 g, 60% yield).

128d: $C_{11}H_{13}BrO_2$ (257.12 g/mol);
^{1}H-NMR (500 Mz, $CDCl_3$): δ 1.41 (s, 9H, *t*-Bu-*H*), 7.52 (d, *J* = 2.5 Hz, 1H, Ar*H*), 7.58 (d, *J* = 2.5 Hz, 1H, Ar*H*), 9.81 (s, 1H, C*H*=O), 11.73 (s, 1H, O*H*);
^{13}C-NMR (125 Mz, $CDCl_3$): δ 29.0, 35.2, 111.1, 121.7, 133.6, 137.0, 141.1, 160.2, 196.0.

Synthesis of 5-nitro-3-tert-butyl-salicylaldehyde (*128e*):

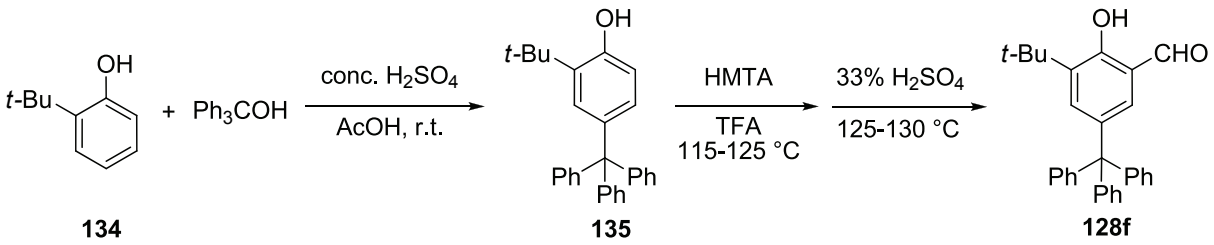


128c **128e**

According to the known method,[83] fuming nitric acid (1.15 mL, 24 mmol) was slowly added to a solution of 3-*tert*-butyl-salicyladehyde (1.78 g, 10 mmol) in 5 mL of acetic acid at 5 °C. After stirred for 3 h (1 h at 5 °C, 2 h at room temperature), the reaction mixture was poured into ice/water (100 mL), and the crude product was collected by filtration. Crystallization from ethanol gave the pure product as slightly yellow flakes (1.80 g, 80% yield).

128e: $C_{11}H_{13}NO_4$ (223.23 g/mol);
^{1}H-NMR (500 Mz, $CDCl_3$): δ 1.46 (s, 9H, *t*-Bu-*H*), 8.42 (s, 2H, Ar*H*), 9.98 (s, 1H, C*H*=O), 12.44 (s, 1H, O*H*);
^{13}C-NMR (125 Mz, $CDCl_3$): δ 28.9, 35.5, 119.3, 127.9, 128.7, 140.7, 165.9, 196.2.

Synthesis of 5-triphenylmethyl-3-tert-butyl-salicylaldehyde (*128f*):



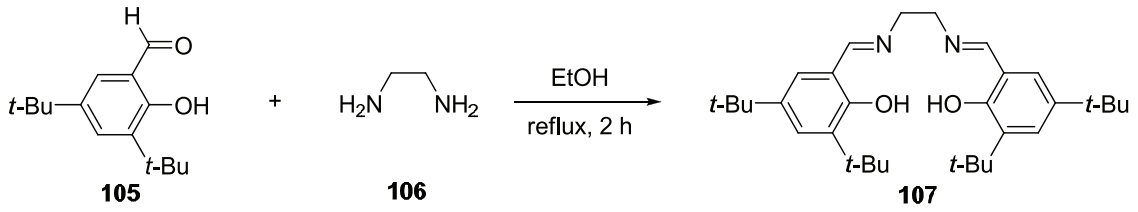
134 **135** **128f**

According to the literature procedure,[85] triphenylmethanol (3.00 g, 11.5 mmol) and 2-*tert*-butylphenol (5.00 g, 33 mmol) were dissolved in 30 mL of acetic acid under heating. The solution was cooled to room temperature, and stirred until the precipitate was formed (1.5 hours), and then conc. H_2SO_4 (5 mL) was added slowly. The resulting dark brown mixture was stirred overnight. The precipitate (3.70 g, 63% yield) was collected and washed with AcOH and MeOH. 2.00 g of the solid (5.1 mmol) and hexamethylenetetramine (HMTA, 1.43 g, 10.2 mmol) were dissolved in 5 mL of TFA. The mixture was heated for 4 h at 125-130 °C, and then cooled to 70 °C, and 5 mL of 33% aq. H_2SO_4 was added. The mixture was heated for another 2 hours at 125-130 °C. After the reaction mixture was cooled to room temperature, 10 mL of ethyl acetate and 15 mL of water were added. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined extracts were washed with water and brine, and dried over anhydrous sodium sulfate. Purification by column gave the desired product as a white solid (1.56 g, 73% yield).

128f: $C_{30}H_{28}O_2$ (420.54 g/mol);
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 (s, 9H, *t*-Bu-*H*), 7.19 (m, 9H, Ar*H*), 7.26 (m, 7H, Ar*H*), 7.36 (s, 1H, Ar*H*), 9.67 (s, 1H, C*H*=O), 11.81 (s, 1H, O*H*);
^{13}C NMR (125 MHz, $CDCl_3$): δ 29.2, 34.9, 64.4, 119.6, 126.2, 127.7, 131.0, 133.0, 137.1, 137.6, 138.2, 146.4, 159.4, 197.4.

6.2.3.2 Synthesis of Achiral Salen Ligands

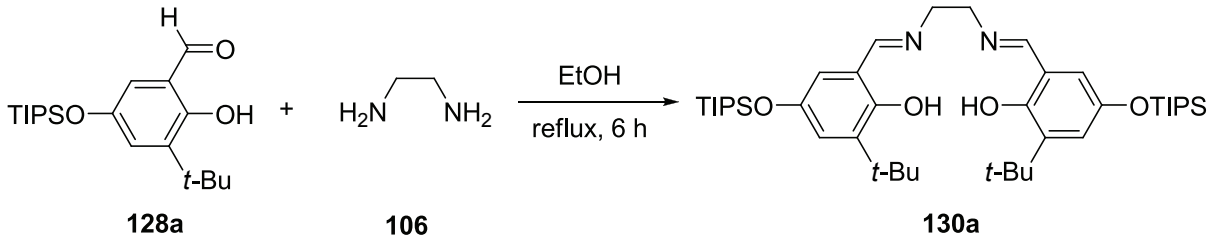
Synthesis of N,N'-bis(3,5-di-tert-butylsalicylidene)-1,2-ethylenediamine (107) (A typical procedure):[140]



According to the procedure described by Jacobsen et al for the practical synthesis of the Jacobsen Mn-salen catalyst,[72] to a solution of 3,5-di-*tert*-butylsalicylaldehyde (2.34 g, 10 mmol) in EtOH (50 mL) was added a solution of 1,2-diaminoethane (0.30 g, 5 mmol) in EtOH (10 mL) over 20 min. The mixture was then heated to reflux for 2 hours (monitored by TLC). After the reaction finished, the reaction mixture was cooled to room temperature and then stored in the freezer (-20 °C) overnight. The yellow crystals formed were collected by filtration and washed with cold EtOH. After drying *in vacuo*, the desired salen ligand was obtained as yellow crystals (2.37 g, 96%).

107: $C_{32}H_{48}N_2O_2$ (492.74 g/mol);
^{1}H-NMR (300 Mz, $CDCl_3$): δ 1.30 (s, 18H, C(C*H*$_3$)$_3$), 1.45 (s, 18H, C(C*H*$_3$)$_3$), 3.94 (s, 4H, C*H*$_2$), 7.08 (d, *J* = 2.4 Hz, 2H, Ar*H*), 7.38 (d, *J* = 2.4 Hz, 2H, Ar*H*), 8.40 (s, 2H, C*H*=N), 13.70 (s, br, 2H, O*H*);
^{13}C-NMR (75 Mz, $CDCl_3$): δ 29.8, 31.9, 34.5, 35.4, 60.0, 118.2, 126.4, 127.4, 137.0, 140.4, 158.4, 168.0.

***Synthesis of N,N'-bis(3-tert-butyl-5-triisopropylsilyloxysalicylidene)-1,2-ethylenediamine(*130a*)*:**[141]*



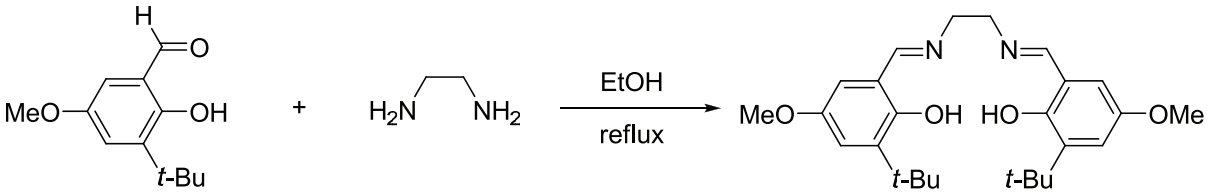
The reaction was carried out on a 2-mmol scale according to the typical procedure described above. The desired ligand was obtained as yellow crystals (1.23 g, 85% yield).

130a: $C_{42}H_{72}N_2O_4Si_2$ (725.20 g/mol);

^{1}H-NMR (500 Mz, $CDCl_3$): δ 1.08 (d, *J* = 7.2 Hz, 36H, CHC*H*$_3$), 1.20 (m, 6H, C*H*CH$_3$), 1.40 (s, 18H, C(C*H*$_3$)$_3$), 3.91 (s, 4 H, C*H*$_2$), 6.60 (d, *J* = 3.0 Hz, 2H, Ar*H*), 6.91 (d, *J* = 3.0 Hz, 2H, Ar*H*), 8.30 (s, 2H, C*H*=N), 13.33 (s, br, 2H, O*H*);

^{13}C-NMR (125 Mz, $CDCl_3$): δ 11.6, 16.9, 28.2, 33.8, 58.6, 117.2, 117.8, 121.4, 137.3, 146.1, 153.6, 165.9.

Synthesis of N,N'-bis(3-tert-butyl-5-methoxysalicylidene)-1,2-ethylenediamine(130b):[140]



128b **106** **130b**

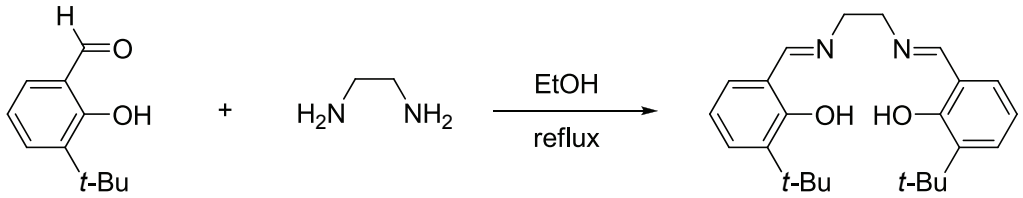
The reaction was carried out on a 2-mmol scale according to the typical procedure described above. The desired ligand was obtained as yellow crystals (0.74 g, 86% yield).

130b: $C_{26}H_{36}N_2O_4$ (440.58 g/mol);

^{1}H-NMR (500 Mz, $CDCl_3$): δ 1.41 (s, 18H, *t*-Bu-*H*), 3.75 (s, 6H, O*CH*$_3$), 3.94 (s, 4H, N*CH*$_2$), 6.58 (d, *J* = 3.0 Hz, 2H, Ar*H*), 6.96 (d, *J* = 3.0 Hz, 2H, Ar*H*), 8.35 (s, 1H, C*H*=N), 13.42 (s, br, 2H, O*H*);

^{13}C-NMR (125 Mz, $CDCl_3$): δ 29.2, 35.0, 55.8, 59.5, 111.4, 117.8, 118.5, 139.0, 151.2, 154.9, 167.1;

Synthesis of N,N'-bis(3-tert-butylsalicylidene)-1,2-ethylenediamine(130c): [142]

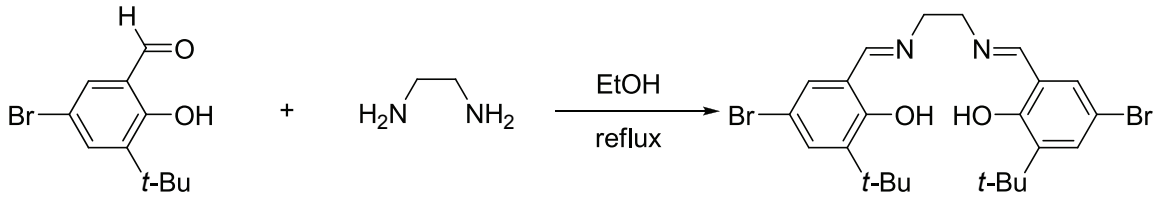


128c **106** **130c**

The reaction was carried out on a 2-mmol scale according to the typical procedure described above. The salen ligand was obtained as yellowish crystals (0.68 g, 89% yield).

130c: $C_{24}H_{32}N_2O_2$ (380.52 g/mol);
^{1}H-NMR (500 Mz, $CDCl_3$): δ 1.42 (s, 18H, *t*-Bu-*H*), 3.94 (s, 4H, CH_2), 6.79 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.10 (dd, *J* = 7.5, 1.5 Hz, 2H, Ar*H*), 7.30 (dd, *J* = 7.5, 1.5 Hz, 2H, Ar*H*), 8.39 (s, 2H, C*H*=N), 13.82 (s, br, 2H, O*H*);
^{13}C-NMR (125 Mz, $CDCl_3$): δ 29.3, 34.8, 59.5, 117.9, 120.1, 129.6, 129.8, 137.4, 167.2.

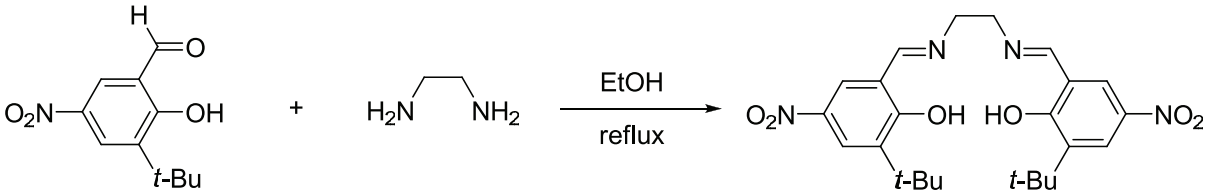
Synthesis of N,N'-bis(3-tert-butyl-5-bromosalicylidene)-1,2-ethylenediamine(130d): [143]



The reaction was carried out on a 2-mmol scale according to the typical procedure described above. The ligand was obtained as a yellowish solid (0.99g, 92% yield).

130d: $C_{24}H_{30}Br_2N_2O_2$ (538.32 g/mol);
^{1}H-NMR (500 Mz, $CDCl_3$): δ 1.40 (s, 18H, *t*-Bu-*H*), 3.94 (s, 4H, CH_2), 7.20 (d, *J* = 2.4 Hz, 2H, Ar*H*), 7.37 (d, *J* = 2.4 Hz, 2H, Ar*H*), 8.29 (s, 2H, C*H*=N), 13.85 (s, br, 2H, O*H*);
^{13}C-NMR (125 Mz, $CDCl_3$): δ 29.1, 35.1, 59.2, 109.8, 119.7, 131.6, 132.5, 140.1, 159.5, 166.1.

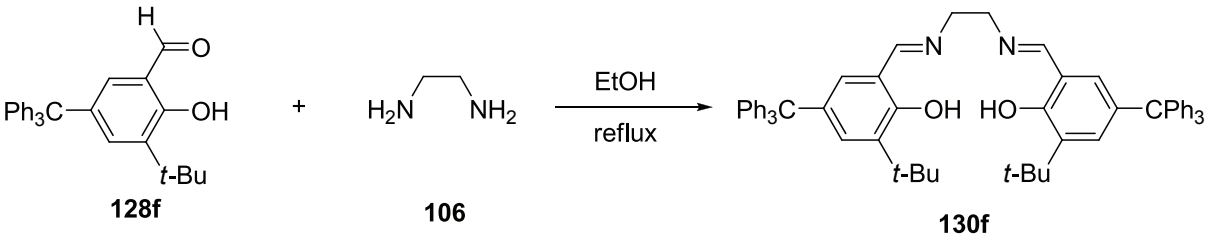
Synthesis of N,N'-bis(3-tert-butyl-5-nitrosalicylidene)-1,2-ethylenediamine(130e): [144]



The reaction was carried out on a 1-mmol scale according to the typical procedure described above. The ligand was obtained as a yellowish solid (0.42 g, 89% yield). The NMR was in agreement with the literature.

130e: $C_{24}H_{30}N_4O_6$ (470.52 g/mol);
^{1}H-NMR (500 Mz, $CDCl_3$): δ 1.44 (s, 18H, *t*-Bu-*H*), 4.05 (s, 4H, *CH*$_2$), 8.11 (d, *J* = 2.7 Hz, 2H, Ar*H*), 8.23 (d, *J* = 2.7 Hz, 2H, Ar*H*), 8.47 (s, 2H, C*H*=N), 14.99 (s, br, 2H, O*H*);
^{13}C-NMR (125 Mz, $CDCl_3$): δ 28.9, 35.3, 61.1, 117.03, 125.3, 126.3, 132.9, 139.8, 166.3.

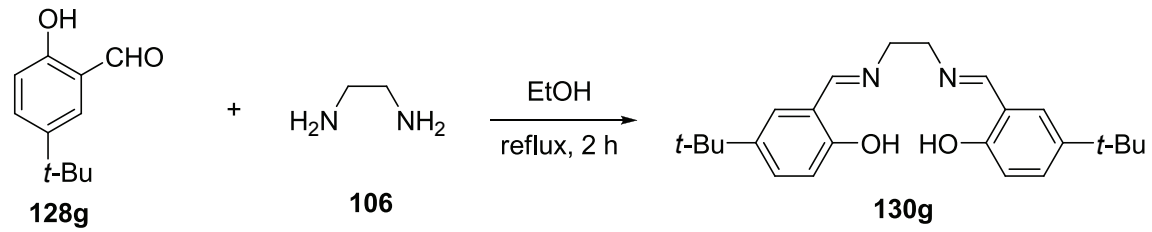
Synthesis of N,N'-bis(3-tert-butyl-5-triphenylmethylsalicylidene)-1,2-ethylenediamine(130f):



The reaction was carried out on a 1-mmol scale according to the typical procedure described above. The desired ligand was obtained as yellow crystals (0.75 g, 89% yield).

130f: $C_{62}H_{60}N_2O_2$ (865.15 g/mol);
^{1}H-NMR (500 Mz, $CDCl_3$): δ 1.25 (s, 18H, *t*-Bu-*H*), 3.83 (s, 4H, NC*H*$_2$), 6.93 (d, *J* = 2.4 Hz, 2H, Ar*H*), 7.13 (d, *J* = 2.4 Hz, 2H, Ar*H*), 7.16-7.26 (m, 30H, Ar*H*), 8.23 (s, 2H, C*H*=N), 13.80 (s, br, 2H, O*H*);
^{13}C-NMR (125 Mz, $CDCl_3$): δ 29.3, 34.9, 59.6, 64.4, 117.3, 125.9, 127.4, 131.1, 131.4, 133.7, 135.9, 136.2, 146.9, 158.6, 167.4.

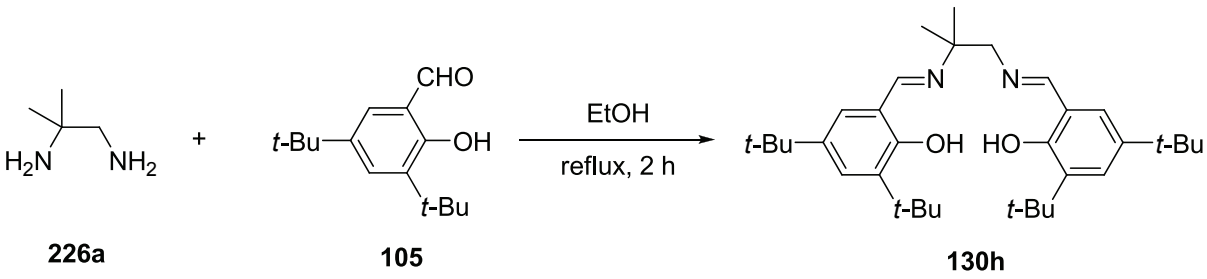
Synthesis of N,N'-bis(5-tert-butylsalicylidene)-1,2-ethylenediamine(130g): [145]



The reaction was carried out on a 2-mmol scale according to the typical procedure described above. The desired ligand was obtained as a yellowish solid (0.71 g, 93% yield).

130g: $C_{24}H_{32}N_2O_2$ (380.52 g/mol);
^{1}H-NMR (500 Mz, $CDCl_3$): δ 1.28 (s, 18H, *t*-Bu-*H*), 3.93 (s, 4H, CH_2), 6.88 (d, *J* = 8.6 Hz, 2H, Ar*H*), 7.19 (d, *J* = 2.5 Hz, 2H, Ar*H*), 7.32 (dd, *J* = 8.6, 2.5 Hz, 2H, Ar*H*), 8.35 (s, 2H, C*H*=N), 13.01 (s, br, 2H, O*H*);
^{13}C-NMR (125 Mz, $CDCl_3$): δ 31.4, 33.9, 59.9, 116.4, 117.9, 127.9, 129.7, 141.3, 158.6, 166.8.

Synthesis of N,N'-bis(3,5-di-tert-butyl-salicylidene)-2-methyl-1,2-propylenediamine (130h).[145]

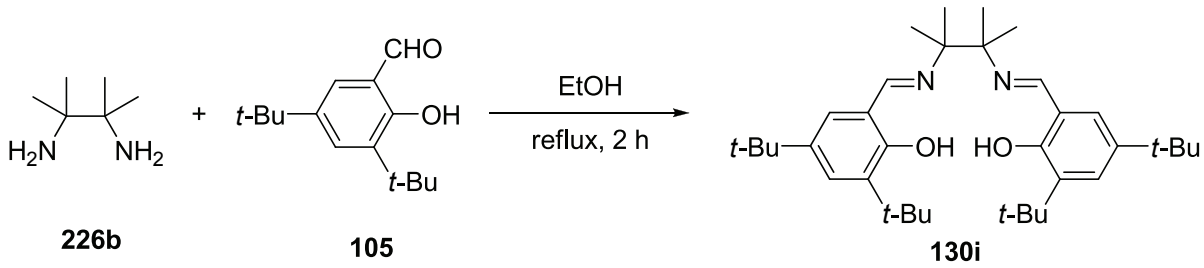


The reaction was carried out on a 5-mmol scale according to the typical procedure described above. The desired ligand was obtained as yellow crystals (2.30 g, 88% yield).

130h: $C_{34}H_{52}N_2O_2$ (520.79 g/mol);
^{1}H-NMR (500 Mz, $CDCl_3$): δ 1.282, 1.288 (s, 18H, *t*-Bu-*H*), 1.427, 1.433 (s, 24H, C(CH_3)$_2$ & *t*-Bu-*H*), 3.71 (s, 2H, NCH_2), 7.07, 7.09 (d, *J* = 2.4 Hz, 2H, Ar*H*), 7.35, 7.36 (d, *J* = 2.4 Hz, 2H, Ar*H*), 8.35, 8.39 (s, 2H, C*H*=N), 13.71, 14.18 (s, br, 2H, O*H*);

^{13}C-NMR (125 Mz, $CDCl_3$): δ 25.5, 29.40, 29.43, 31.45, 31.48, 34.1, 35.0, 60.0, 70.5, 117.8, 117.9, 126.1, 126.2, 126.9, 127.1, 136.6, 136.7, 139.9, 140.0, 158.1, 158.3, 162.7, 167.6.

Synthesis of N,N'-bis(3,5-di-tert-butyl-salicylidene)-2,3-dimethyl-2,3-butylenediamine(130i): [146]

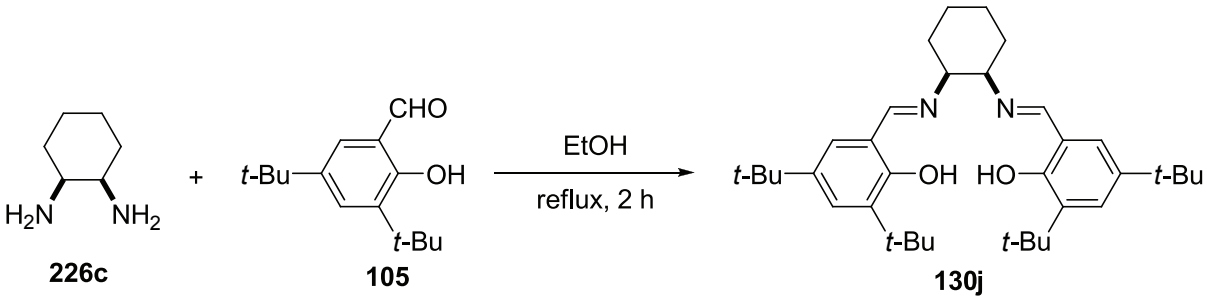


226b **105** **130i**

The reaction was carried out on a 1-mmol scale according to the typical procedure described above. The desired ligand was obtained as yellow crystals (0.45 g, 82% yield).

130i: $C_{36}H_{56}N_2O_2$ (548.84 g/mol);
^{1}H-NMR (300 Mz, $CDCl_3$): δ 1.29 (s, 18H, C(C*H*$_3$)$_3$), 1.40 (s, 12H, C(C*H*$_3$)$_2$), 1.44 (s, 18H, C(C*H*$_3$)$_3$), 7.10 (d, *J* = 2.4 Hz, 2H, Ar*H*), 7.36 (d, *J* = 2.4 Hz, 2H, Ar*H*), 8.40 (s, 2H, C*H*=N), 14.29 (s, br, 2H, O*H*);
^{13}C-NMR (75 Mz, $CDCl_3$): δ 23.2, 29.4, 31.5, 34.1, 35.0, 65.0, 118.0, 126.2, 126.8, 136.7, 139.8, 158.4, 162.7.

Synthesis of N,N'-bis(3,5-di-tert-butyl-salicylidene)-cis-1,2-cyclohexanediamine(130j): [147]

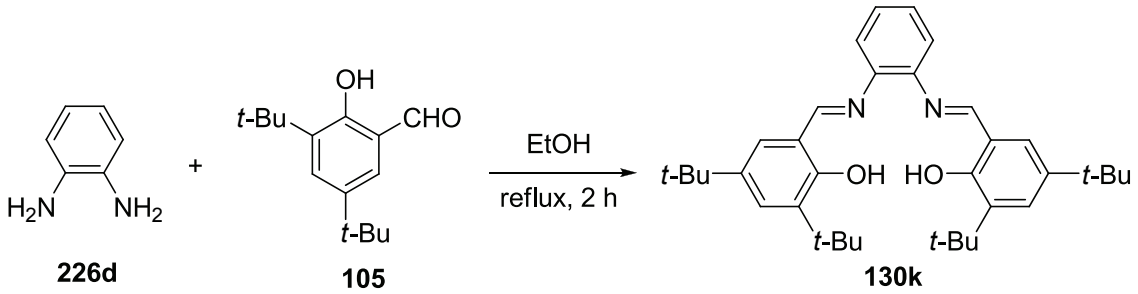


226c **105** **130j**

The reaction was carried out on a 2-mmol scale according to the typical procedure described above. The desired ligand was obtained as yellow crystals (0.98 g, 90% yield).

130j: $C_{36}H_{54}N_2O_2$ (546.83 g/mol);
^{1}H-NMR (500 Mz, $CDCl_3$): δ 1.28 (s, 18H, *t*-Bu-*H*), 1.40 (s, 18H, *t*-Bu-*H*), 1.59 (m, 2H, C*H*$_2$), 1.76 (m, 2H, C*H*$_2$), 1.98 (m, 4H, C*H*$_2$), 3.59 (s, 2H, N*CH*), 7.05 (d, *J* = 2.4 Hz, 2H, Ar*H*), 7.34 (d, *J* = 2.4 Hz, 2H, Ar*H*), 8.36 (s, 2H, C*H*=N), 13.75 (s, br, 2H, O*H*);
^{13}C-NMR (125 Mz, $CDCl_3$): δ 22.7, 29.4, 30.4, 31.5, 34.1, 35.0, 69.2, 117.9, 125.9, 126.8, 136.6, 139.8, 158.1, 165.2.

Synthesis of N,N'-bis(3,5-di-tert-butylsalicylidene)-1,2-benzenediamine(130k): [148]



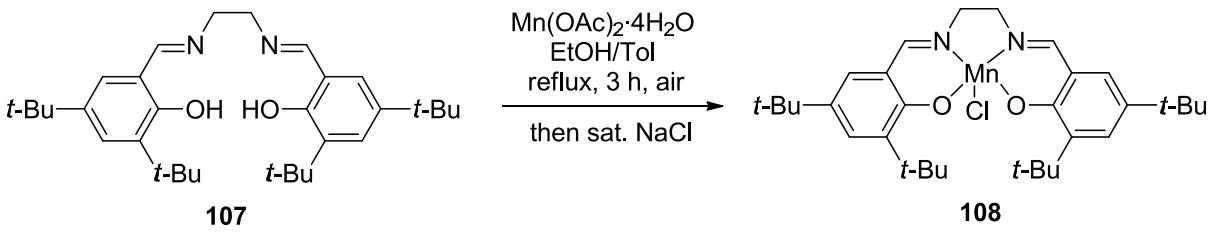
The reaction was carried out on a 3-mmol scale according to the typical procedure described above. The desired ligand was obtained as yellow crystals (1.20 g, 74% yield).

130k: $C_{36}H_{48}N_2O_2$ (540.78 g/mol);
^{1}H-NMR (500 Mz, $CDCl_3$): δ 1.32 (s, *t*-Bu-*H*, 18H), 1.43 (s, *t*-Bu-*H*, 18H), 7.21 (d, *J* = 2.4 Hz, Ar*H*, 2H), 7.23 (m, Ar*H*, 2H), 7.30 (m, Ar*H*, 2H), 7.44 (d, *J* = 2.4 Hz, Ar*H*, 2H), 8.66 (s, C*H*=N, 2H), 13.54 (s, 2H, O*H*);
^{13}C-NMR (125 Mz, $CDCl_3$): δ 29.4, 31.5, 34.2, 35.1, 118.4, 119.8, 126.8, 127.3, 128.2, 137.2, 140.3, 142.8, 158.6, 164.7.

6.2.3.3 Synthesis of Achiral Mn-Salen Complexes:

Synthesis of [N,N-bis(3,5-di-tert-butylsalicy1idene)-1,2-ethylenediaminato(

***2-)]manganese(III) chloride (108) (A Typical Procedure)*:**[149]



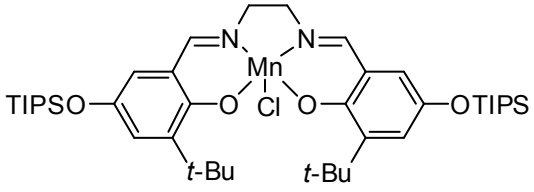
107 **108**

The literature procedure described by Jacobsen et al[72] was followed with minor modifications. $Mn(OAc)_2 \bullet 4H_2O$ (0.735 g, 3 mmol) was dissolved in ethanol (8 ml) and heated to reflux, and then a toluene solution of the salen ligand **107** (0.50 g, 1 mmol, in 4 mL of toluene) was added slowly over 30 min. The addition funnel was rinsed with toluene (1 mL), and the mixture was stirred at reflux for 2 h. The addition funnel was replaced with a gas dispersion tube and air was slowly bubbled through the reaction mixture for 1 h. The reaction was monitored by TLC (EtOAc/hexanes, 1:4) until the ligand disappeared. At this point, saturated aqueous NaCl (10 ml) was added and the mixture was cooled to room temperature and rinsed into a separatory funnel with toluene (20 mL). The brown organic layer was separated and washed successively with water (3×10 mL) and brine (10 mL), and then dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure yielded a brown solid. The pure compound was obtained by crystallization from dichloromethane/hexanes. After dried *in vacuo*, the Mn-salen chloride catalyst was obtained as a brown crystalline solid (0.52 g, 89% yield).

108: $C_{32}H_{46}ClMnN_2O_2$ (581.11 g/mol);
IR (neat): 2956, 2906, 2896, 1609, 1532, 1463, 1410, 1306, 1250, 1173, 834, 749 cm^{-1};
MS (EI): *m*/*z* (%) = 580 (15), 546 (35), 545 (100), 544 (16), 530 (22), 529 (10), 258 (19), 257 (13);
HRMS (EI): calculated for $[C_{32}H_{46}MnN_2O_2]^+$: 545.293156(M-Cl^+), found 545.293431.

Synthesis of [N,N-bis(3-tert-butyl-5-triisopropylsilylsalicy1idene)-1,2-ethylenediaminato(2-)]manganese(III) chloride (131a):

Complex **131a** was prepared on a 0.48-mmol scale according to the typical procedure described above. The desired product was obtained as a brown solid



(0.25 g, 64% yield).

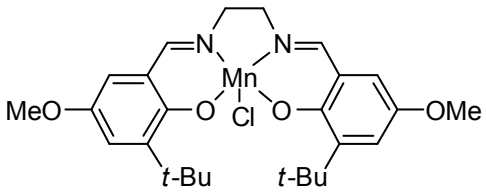
131a: $C_{42}H_{70}ClMnN_2O_2Si_2$ (813.58 g/mol);

IR (neat): 2943, 2866, 1626, 1540, 1410, 1343, 1291, 1231, 1207, 1160, 1040, 1010, 961, 880, 866, 852, 774, 751, 681 cm^{-1};

MS (EI): *m*/*z* (%) = 814 (19), 813 (20), 812 (34), 779 (22), 778 (56), 777 (100), 339 (11);

HRMS (ESIpos): calculated for $[C_{42}H_{70}MnN_2O_2Si_2]^+$: 777.425235 (M-Cl $^+$), found 777.424915.

Synthesis of [N,N-bis(3-tert-butyl-5-methoxysalicy1idene)-1,2-ethylenediaminato(2-)]manganese(III) chloride (131b):



Complex **131b** was prepared on a 1-mmol scale according to the typical procedure described above. The desired product was obtained as a brown solid (0.47 g, 89% yield).

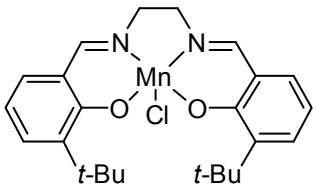
131b: $C_{26}H_{34}ClMnN_2O_4$ (528.95 g/mol);

IR (neat): 2950, 1608, 1543, 1410, 1348, 1291, 1197, 1154, 1055, 815, 795, 773 cm^{-1};

MS (EI): *m*/*z* (%) = 528 (34), 494 (29), 493 (100), 478 (28), 231 (15);

HRMS (ESIpos): calculated for $[C_{26}H_{34}MnN_2O_2]^+$: 493.189727 (M-Cl $^+$), found 493.189361.

Synthesis of [N,N-bis(3-tert-butylsalicy1idene)-1,2-ethylenediaminato(2-)]manganese(III) chloride (131c):



Complex **131c** was prepared on a 1.6-mmol scale according to the typical procedure described above. The desired product was obtained as a brown solid (0.71 g, 93% yield).

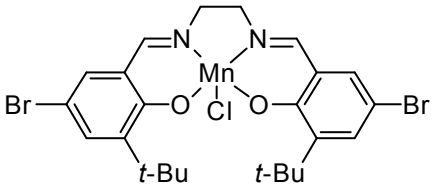
131c: $C_{24}H_{30}ClMnN_2O_2$ (468.90 g/mol);

IR (neat): 2952, 1614, 1591, 1541, 1389, 1293, 1195, 1146, 1089, 866, 753 cm^{-1};

MS (EI): *m*/*z* (%) = 468 (15), 434 (26), 433 (100), 432 (22), 418 (30), 417 (20), 201 (12), 187 (10), 173 (15);

HRMS (ESIpos): calculated for $[C_{24}H_{30}MnN_2O_2]^+$: 433.168339 (M-Cl $^+$), found 433.168232.

Synthesis of [N,N-bis(3-tert-butyl-5-bromosalicy1idene)-1,2-ethylenediaminato(2-)]manganese(III) chloride (131d):



Complex **131d** was prepared on a 1-mmol scale according to the typical procedure described above. The desired product was obtained as a brown solid (0.54 g, 87% yield).

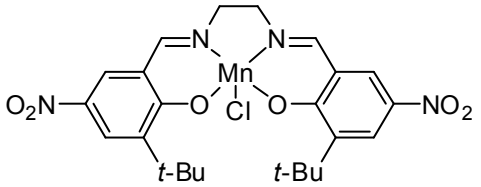
131d: $C_{24}H_{28}Br_2ClMnN_2O_2$ (626.69 g/mol);

IR (neat): 2958, 2867, 1616, 1581, 1530, 1402, 1294, 1286, 1171, 811, 779, 731, 684 cm^{-1};

MS (EI): *m*/*z* (%) = 626 (11), 594 (13), 593 (51), 592 (32), 591 (100), 590 (25), 589 (53), 578 (13), 577 (11), 576 (26), 575 (13), 574 (15);

HRMS (ESIpos): calculated for $[C_{24}H_{28}Br_2MnN_2O_2]^+$: 588.989856 (M-$Cl^+$), found 588.989284.

Synthesis of [N,N-bis(3-tert-butyl-5-nitrosalicy1idene)-1,2-ethylenediaminato(2-)]manganese(III) chloride (131e):



Complex **131e** was prepared on a 1-mmol scale according to the typical procedure described above. The desired product was obtained as a brown solid (0.44 g, 78% yield).

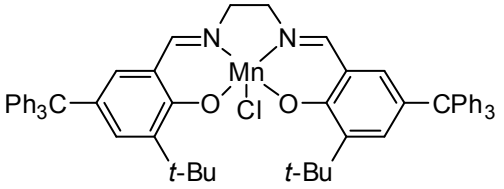
131e: $C_{24}H_{28}ClMnN_4O_6$ (558.89 g/mol);

IR (neat): 3507, 2963, 2920, 1637, 1590, 1302, 1199, 1111, 732 cm^{-1};

MS (ESIpos): *m*/*z* (%) = 523 (M-Cl^+);

HRMS (ESIpos): calculated for $[C_{24}H_{28}MnN_4O_6]^+$: 523.138802 (M-Cl^+), found 523.138390.

Synthesis of [N,N-bis(3-tert-butyl-5-triphenylmethylsalicy1idene)-1,2-ethylenediaminato(2-)]manganese(III) chloride (131f):



Complex **131f** was prepared on a 0.47-mmol scale according to the typical procedure described above. Due to the bad solubility of the product in toluene, DCM was better for extraction. The desired product was obtained as a brown solid (0.37 g, 82% yield).

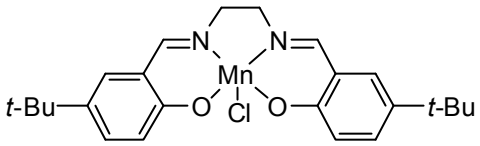
131f: $C_{62}H_{58}ClMnN_2O_2$ (953.53 g/mol);

IR (neat): 3056, 3028, 2951, 2867, 1607, 1531, 1490, 1440, 1407, 1302, 1189, 1165, 868, 718, 698, 656 cm^{-1};

MS (ESIpos): *m*/*z* (%) = 917 ($M\text{-}Cl^+$)

HRMS (ESIpos): calculated for $[C_{62}H_{58}MnN_2O_2]^+$: 917.387541 ($M\text{-}Cl^+$), found 917.387327.

Synthesis of [N,N-bis(5-tert-butylsalicy1idene)-1,2-ethylenediaminato(2-)]manganese(III) chloride (131g):



Complex **131g** was prepared on a 1.0-mmol scale according to the typical procedure described above. The desired product was obtained as a brown solid (0.70 g, 92% yield).

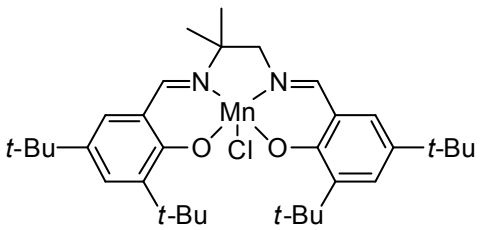
131g: $C_{24}H_{30}ClMnN_2O_2$ (468.90 g/mol);

IR (neat): 3025, 2954, 2865, 1637, 1626, 1537, 1473, 1359, 1301, 1259, 1182, 1189, 1145, 1083, 1045, 849, 829, 807, 750, 711, 668 cm^{-1};

MS (ESIpos): *m*/*z* (%) = 433 ($M\text{-}Cl^+$);

HRMS (ESIpos): calculated for $[C_{24}H_{30}MnN_2O_2]^+$: 433.168093 ($M\text{-}Cl^+$), found 433.168230.

Synthesis of [N,N-bis(3,5-di-tert-butylsalicy1idene)-1,1-dimethyl-1,2-ethylenediaminato(2-)]manganese(III) chloride (131h):



Complex **131h** was prepared on a 1-mmol scale according to the typical procedure described above. The desired product was obtained as a brown solid (0.57 g, 94% yield).

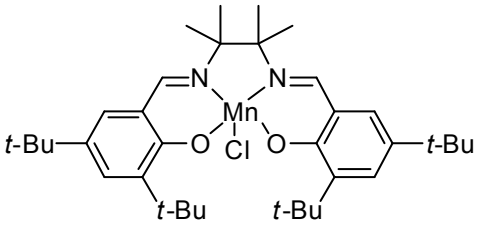
131h: $C_{34}H_{50}ClMnN_2O_2$ (609.16 g/mol);

IR (neat): 2957, 2906, 2868, 1612, 1602, 1592, 1532, 1382, 1310, 1251, 1172, 1156, 1072, 842, 777, 751 cm^{-1};

MS (EI): *m*/*z* (%) = 610 (13), 609 (12), 608 (32), 574 (36), 573 (100), 572 (22), 558 (14), 557 (15), 272 (29), 271 (12);

HRMS (ESIpos): calculated for $[C_{34}H_{50}MnN_2O_2]^+$: 573.324146 ($M\text{-}Cl^+$), found 573.324733.

Synthesis of [N,N-bis(3,5-di-tert-butylsalicy1idene)-1,1,2,2-tetramethyl-1,2-ethylenediaminato(2-)]manganese(III) chloride (131i):



Complex **131i** was prepared on a 0.5-mmol scale, according to the typical procedure described above. The desired product was obtained as a brown solid (0.28 g, 87% yield).

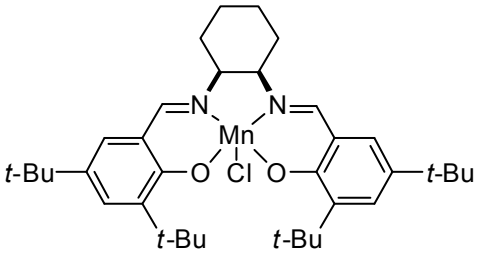
131i: $C_{36}H_{54}ClMnN_2O_2$ (637.22 g/mol);

IR (neat): 2953, 2904, 2866, 1597, 1535, 1391, 1356, 1253, 1147, 1135, 834, 780, 747 cm^{-1};

MS (EI): *m*/*z* (%) = 638 (13), 637 (13), 636 (32), 602 (39), 601 (100), 600 (14), 363 (11), 286 (25);

HRMS (ESIpos): calculated for $[C_{36}H_{54}MnN_2O_2]^+$: 601.355497(M-Cl^+), found 601.356031.

Synthesis of [N,N-bis(3,5-di-tert-butylsalicy1idene)-1,2-(cis)-cyclohexenediaminato(2-)]manganese(III) chloride (131j):



Complex **131j** was prepared on a 1-mmol scale according to the typical procedure described above. The desired product was obtained as a brown solid (0.60 g, 95% yield).

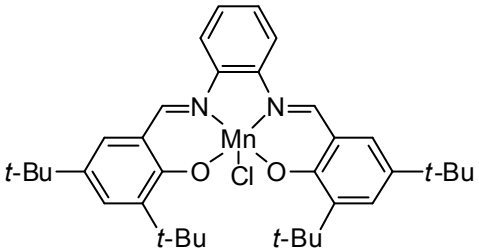
131j: $C_{36}H_{52}ClMnN_2O_2$ (635.20 g/mol);

IR (neat): 2950, 2906, 2868, 1605, 1537, 1463, 1249, 1175, 841, 780, 750 cm^{-1};

MS (EI): *m*/*z* (%) = 634 (18), 600 (38), 599 (100), 598 (24), 584 (12), 285 (33);

HRMS (ESIpos): calculated for $[C_{36}H_{52}MnN_2O_2]^+$: 599.340877 (M-Cl^+), found 599.340381.

Synthesis of [N,N-bis(3,5-di-tert-butylsalicy1idene)-1,2-benzenediaminato(2-)]manganese(III) chloride (131j):



Complex **131k** was prepared on a 1-mmol scale according to the typical procedure described above. The desired product was obtained as a brown solid (0.40 g, 64% yield).

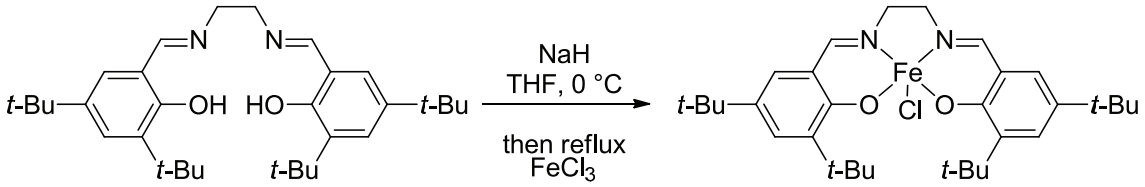
131k: $C_{36}H_{46}ClMnN_2O_2$ (629.15 g/mol);

IR (neat): 2954, 2905, 2868, 1596, 1575, 1527, 1461, 1421, 1289, 1258, 1248, 1179, 836, 747 cm^{-1};

MS (EI): *m*/*z* (%) = 628 (22), 594 (39), 593 (100), 578 (20), 562 (11), 281 (23);
HRMS (ESIpos): calculated for $[C_{36}H_{46}MnN_2O_2]^+$: 593.293526 (M-Cl $^+$), found 593.293427.

6.2.4 Preparation of Achiral Cr, Fe, and Co-Salen Complexes

Synthesis of [N,N-bis(3,5-di-tert-butylsalicy1idene)-1,2-ethylenediaminato(2-)]iron(III) chloride (183a):

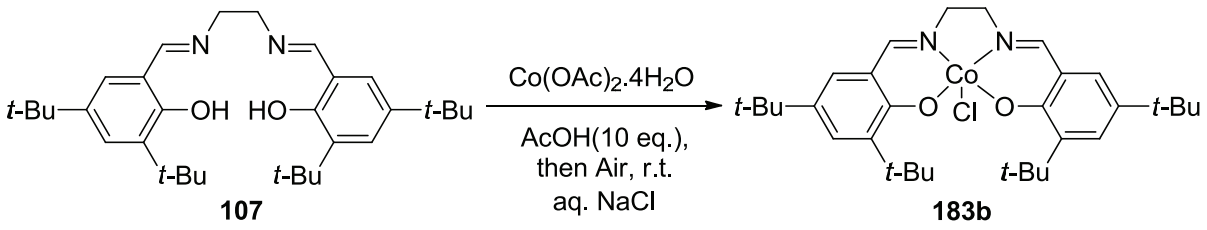


107 **183a**

Complex **183a** was prepared according to the literature procedure.[150] A solution of *N,N′*-bis-(3,5-di-*tert*-butylsalicylidene)-1,2-ethalenediamine (**107**, 0.492 g, 1.0 mmol) in THF (5 mL) was added to a suspension of NaH (48 mg, 2.0 mmol) in THF (5 mL) at 0 °C. After the evolution of gas has ceased, the mixture was refluxed for 2 h and cooled to room temperature before $FeCl_3$ (500 mg, 3.0 mmol) was introduced and reflux was continued for 4 h. Standard extractive work-up followed by evaporation of the solvent provides complex **183a** as a dark-red solid (0.585 g, 95% yield).

183a: $C_{32}H_{46}ClFeN_2O_2$ (582.02 g/mol);
IR (neat): 2953, 2905, 2868, 1630, 1608, 1535, 1437, 1385, 1302, 1271, 1253, 1172, 837, 778, 750 cm^{-1};
MS (EI): *m*/*z* (%) =584 (11), 583 (32), 582 (32), 581 (84), 568 (15), 567 (15), 566 (39), 547 (38), 546 (100), 532 (18), 531 (60), 530 (66), 516(12), 515 (32), 276 (15), 275 (21), 258 (51), 250 (39);
HRMS (ESIpos): calculated for $[C_{32}H_{46}FeN_2O_2]^+$: 546.290601 (M-Cl $^+$), found 546.290311.

Synthesis of [N,N-bis(3,5-di-tert-butylsalicy1idene)-1,2-ethylenediaminato(2-)]cobalt(III) chloride (183b):

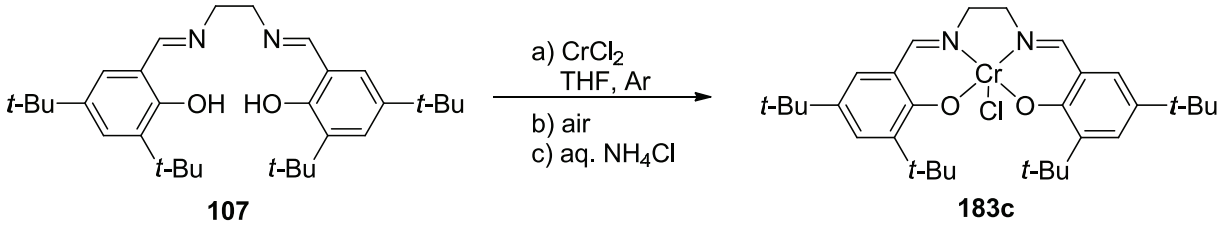


107 **183b**

Complex **183b** was prepared according to the literature procedure.[151] *N,N′*-Bis-(3,5-di-*tert*-butylsalicylidene)-1,2-ethalenediamine (**107**, 0.985 g, 2.0 mmol), anhydrous $Co(OAc)_2$ (1.00 g, 2.1 mmol), and 10 mL of glacial AcOH were added to a 50-mL round flask. The stirred mixture turned brown within a few minutes. After 20 min the flask was equipped with a vacuum adaptor and a dip tube so that air could be pulled through the reaction mixture (5 h). Excess acetic acid was removed under reduced pressure, and was further dried *in vacuo* over night. The solid was dissolved and vigorously stirred in 10 mL methanol and then precipitated by slow addition of water (10 mL over 60 min). The catalyst was filtered, rinsed (3 × 10 mL water) and dried *in vacuo* to afford the product as a brown solid (1.20 g, 90% yield).

183b: $C_{32}H_{46}ClCoN_2O_2$ (585.11 g/mol);
IR (neat): 2953, 2906, 2867, 1602, 1524, 1460, 1434, 1388, 1359, 1268, 1249, 1200, 1175, 833, 782, 745 cm^{-1};
MS (EI): *m*/*z* (%) = 550 (35), 549 (100), 535 (18), 534 (52), 260 (48);
HRMS (ESIpos): calculated for $[C_{32}H_{46}CoN_2O_2]^+$: 549.289051 (M-Cl^+), found 549.288570.

Synthesis of [N,N-bis(3,5-di-tert-butylsalicy1idene)-1,2-ethylenediaminato(2-)]chromium(III) chloride (183c):



107 **183c**

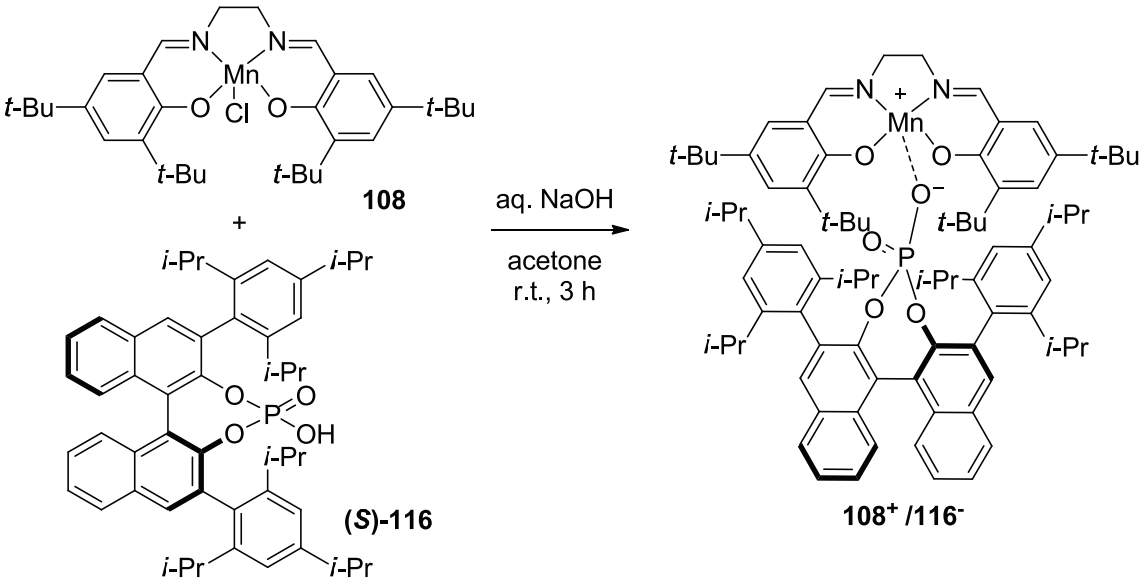
According to the literature procedure,[152] salen ligand (0.50 g, 1 mmol, 1.0 eq.), $CrCl_2$ (0.18 g, 1.5 mmol, 1.5 eq.) and THF (20 mL) were combined in a Schlenk tube under an argon atmosphere, and the resulting brown solution was stirred under argon for 3 h and then opened

to the air for additional 10 h. The solvent was removed, and the crude brown solid was dissolved in dichloromethane, washed with sat. NH_4Cl followed by brine. After drying over anhydrous sodium sulfate and removal of the solvent, crystallization of the crude product from DCM/ether gave the desired compound as a dark brown solid (0.41 g, 71% yield).

183c: $C_{32}H_{46}ClCrN_2O_2$ (578.17 g/mol);
IR (neat): 2952, 2905, 2868, 1618, 1530, 1434, 1386, 1315, 1255, 1167, 832, 784, 747 cm^{-1};
MS (EI): *m*/*z* (%) = 579 (23), 578 (24), 577 (50), 562 (15), 544 (14), 543 (48), 542 (100), 541 (11), 540 (19), 528 (15), 527 (38), 526 (30), 511 (13), 256 (43), 248 (28);
HRMS (ESIpos): calculated for $[C_{32}H_{46}CrN_2O_2]^+$: 542.296459 (M-Cl $^+$), found 542.295894.

6.2.5 Preparation of Ion-Pair Catalysts

***Preparation of Ion-Pair Catalyst 108$^+$/116$^-$ (A Typical Procedure)**:*



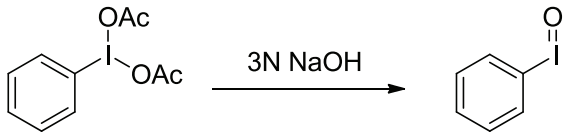
The phosphoric acid ((*S*)-**116**, containing MeCN 1:1, 80 mg, 0.1 mmol) and achiral Mn-salen chloride (**108**, 58 mg, 0.1 mmol) were dissolved in 5 mL of acetone, and then 200 µL of aq. NaOH (0.5 mol/L, 0.1 mmol) was added. The resulting mixture was stirred at room temperature for 3 h (The anion exchange proceeds very fast, usually half an hour is enough) until the acid and Mn-salen chloride disappeared (TLC, alumina, 2% EtOH in EtOAc). Acetone was then removed under reduced pressure and 5 mL of DCM was added to dissolve

the dark brown solid. After the NaCl formed during the reaction was filtered off through a filter (0.45 μm), the solvent was removed under reduced pressure. The ion-pair catalyst **108**$^{+}$**/116**$^{-}$ was obtained as a dark brown solid (126 mg, 97%) after drying *in vacuo* overnight.

The anion-exchanges of other Mn-salen chloride complexes and iron-salen complexes with phosphoric acid anions were performed according to the same procedure. The corresponding Cr, Co ion-pair catalysts were prepared by mixing the achiral metallosalen chloride with silver phosphates in the dark. The reactions were monitored by the disappearance of the ^{31}P peak of the silver phosphates. After the anion exchange completed, additional 5 hours of stirring was followed. The workup was carried out as described above.

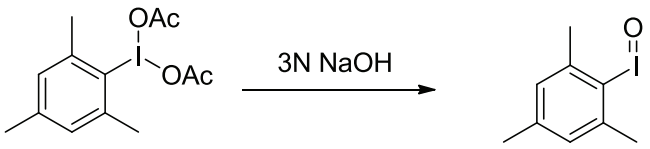
6.3 Preparation of Oxidants

Preparation of Iodosobenzene:



Following the procedure depicted in Organic Syntheses.[153] Iodosobenzene diacetate powder (3.22 g, 10 mmol) was placed in a 50-ml. beaker, and 15 mL of 3 N NaOH was added over 5 min with vigorous stirring. The lumps of solid formed were triturated with a spatula for 15 minutes, and the reaction mixture was stood for additional 45 min. Ten mL of water was then added, the mixture was stirred vigorously, and the crude, solid iodosobenzene was collected by filtration. The wet solid was triturated again in 20 mL of water. The solid was then collected on the Büchner funnel, washed with water. Final purification was performed by triturating the solid in 10 mL of chloroform. Iodosobenzene was obtained as a slightly yellow solid (m.p. 209 °C, 2.01 g, 91 %). The oxidant was kept in the freezer (-20 °C) and replaced every three months.

Preparation of Iodosomesitylene:

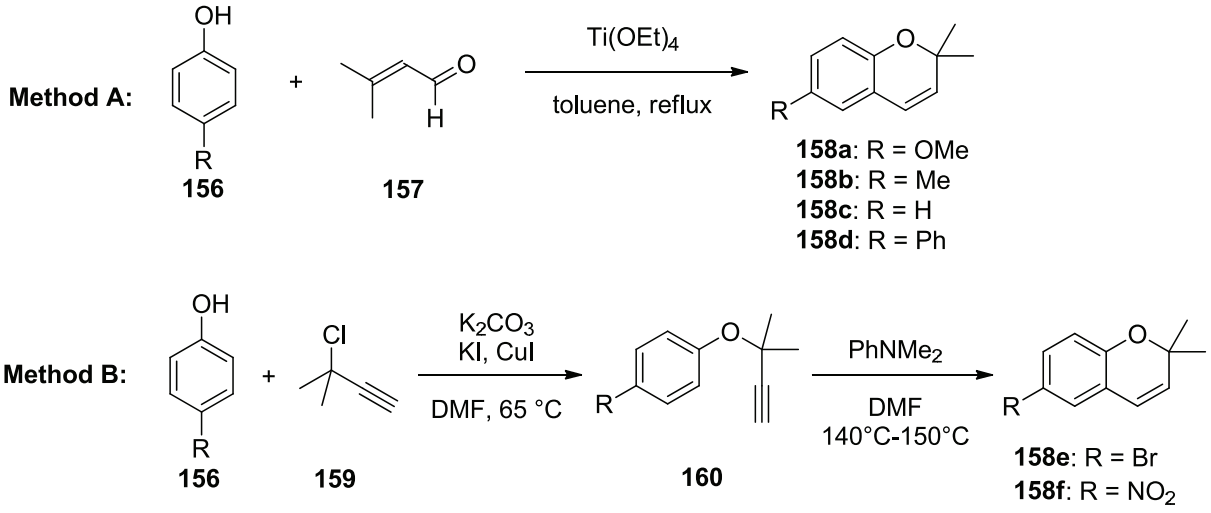


Following the procedure depicted in Organic Syntheses.[153] Iodosomesitylene diacetate powder (3.64 g, 10 mmol) was placed in a 50-ml. beaker, and 15 mL of 3 N NaOH was added over 5 min with vigorous stirring. The lumps of solid formed were triturated with a spatula, and the reaction mixture was standed for additional 45 min. Ten mL of water was added, the mixture was stirred vigorously, and the solid was collected by filtration. The wet solid was placed in the beaker and triturated again in 20 mL of water. The solid was then collected on the Büchner funnel, washed with water. Final purification was performed by triturating the solid in 10 mL of chloromethane. The product was obtained as a slightly yellow powder (2.31 g, 88 %). The oxidant was kept in the freezer (-20 °C) and replaced every three months.

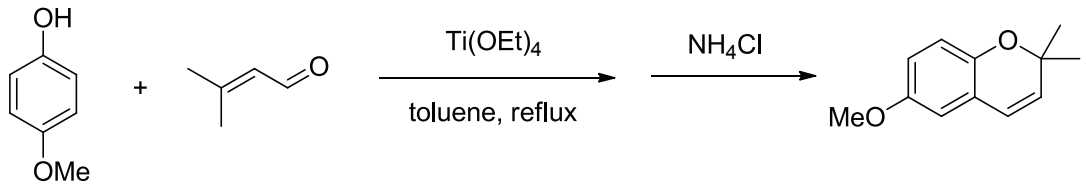
6.4 Synthesis of Alkene Substrates

6.4.1 Synthesis of Chromene Substrates

6-Cyano-2,2-dimethylchromene **19** is commercially available, the other chromene compounds **158a-f** were prepared via Method A or Method B (Scheme 4.19). For the electron rich phenols, Method A was preferred. Compounds (**158a-d**) were prepared via the condensation of the phenols **156** and 3-methylbut-2-enal **157** in the presence of titanium tetraethoxide as the catalyst. For the electron poor phenols, Method B generally provided better yields. Spiro-chromene **165a-g** was made according to Method B using 1-chloro-1-ethynylcyclohexane instead of 3-chloro-3-methyl-1-butyne **159**. For the cyclization step, a prolonged reaction time and a slightly higher temperature were employed to ensure good conversion.



Synthesis of 6-methoxyl-2,2-dimethylchromene (158a)[154] (Method A):

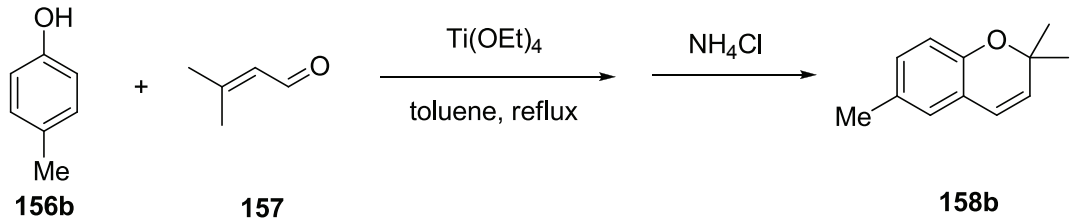


According to the literature method,[155] to a solution of titanium tetraethoxide (1.14 g, 5 mmol) in 10 mL of toluene was added 4-methoxyphenol (2.48 g, 20 mmol) in 10 mL of toluene at room temperature under argon. This orange-red solution was refluxed for 30 min and then slowly distilled under reduced pressure to remove the ethanol formed. After cooling to room

temperature, a solution of 3-methylbut-2-enal (2.52 g, 30 mmol) in 40 mL of toluene was added dropwise, and the resulting mixture was heated to reflux overnight. The reaction was quenched with saturated aqueous solution of ammonium chloride, extracted with diethyl ether, washed with brine, and dried over anhydrous sodium sulfate. The pure product (3.08 g, 81%) was obtained by distillation under reduced pressure (140-145 °C/10 mbar).

158a: $C_{12}H_{14}O_2$ (190.24 g/mol);
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (s, 6H, C*H*$_3$), 3.75 (s, 3H, Ph-C*H*$_3$), 5.64 (d, *J* = 9.8 Hz, 1H, =C*H*), 6.28 (d, *J* = 9.8 Hz, 1H, =C*H*), 6.55 (d, *J* = 2.7 Hz, 1H, Ar*H*), 6.67 (d, *J* = 2.7 Hz, 1H, Ar*H*), 6.69 (s, 1H, Ar*H*);
^{13}C NMR (75 MHz, $CDCl_3$): δ 27.6, 55.7, 75.8, 111.5, 114.2, 116.8, 121.9, 122.4, 131.8, 146.7, 153.7;
MS (EI): m/z = 190 (M^+).

Synthesis of 6-methyl-2,2-dimethylchromene (158b):

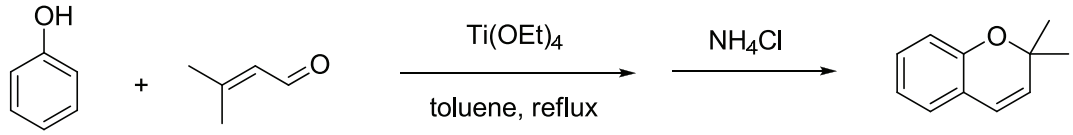


According to Method A described for **158a**, to a solution of titanium tetraethoxide (1.14 g, 5 mmol) in 10 mL of toluene was added 4-methylphenol (2.16 g, 20 mmol) in 10 mL of toluene at room temperature under argon. This orange-red solution was refluxed for 30 min and then slowly distilled under reduced pressure to remove the formed ethanol. After cooling to room temperature, a solution of 3-methylbut-2-enal (2.52 g, 30 mmol) in 40 mL of toluene was added dropwise, and the resulting mixture was heated to reflux overnight. The reaction was quenched with saturated aqueous solution of ammonium chloride, extracted with diethyl ether, washed with brine, and dried over anhydrous sodium sulfate. The pure product (2.54 g, 73%) was obtained by distillation under reduced pressure (105-108 °C/3 mbar).

158b: $C_{12}H_{14}O$ (174.24 g/mol)

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (s, 6H, C*H*$_3$), 2.24 (s, 3H, Ph-C*H*$_3$), 5.60 (d, *J* = 9.6 Hz, 1H, =C*H*), 6.26 (d, *J* = 9.6 Hz, 1H, =C*H*), 6.67 (d, *J* = 8.0 Hz, 1H, Ar*H*), 6.84 (t, *J* = 7.4 Hz, 1H, Ar*H*), 6.98 (d, *J* = 7.4 Hz, 1H, Ar*H*), 7.10 (t, *J* = 7.4 Hz, 1H, Ar*H*);
^{13}C NMR (75 MHz, $CDCl_3$): δ 18.6, 38.7, 65.1, 65.4, 124.9, 125.8, 126.1, 128.3, 141.8, 144.5;
MS (EI): m/z 174 (M^+).

Synthesis of 2,2-dimethylchromene (158c):

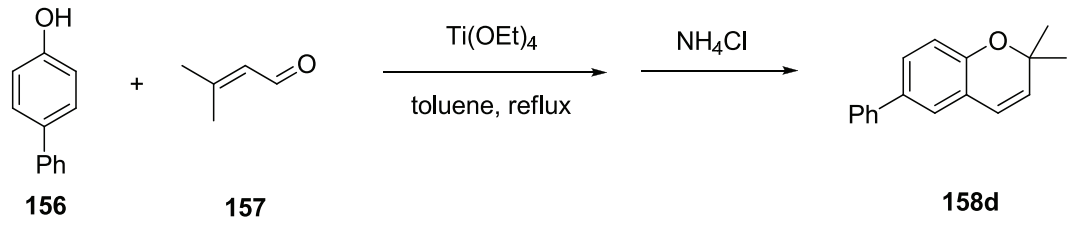


156c **157** **158c**

According to Method A described for **158a**, to a solution of titanium tetraethoxide (1.14 g, 5 mmol) in 10 mL of toluene was added phenol (1.88 g, 20 mmol) in 10 mL of toluene at room temperature under argon. This orange-red solution was refluxed for 30 min and then slowly distilled to completely remove the ethanol formed. After cooling to room temperature a solution of 3-methylbut-2-enal (**157**, 2.52 g, 30 mmol) in 40 mL of toluene was added dropwise, and the resulting mixture was heated to reflux for 8 h. The reaction was quenched with saturated aqueous solution of ammonium chloride, extracted with diethyl ether, washed with brine, and dried over anhydrous sodium sulfate. Purification by flash column chromatography on silica gel (hexanes) afforded the pure product as a pale yellow oil (1.50 g, 47%).

158c: $C_{11}H_{12}O$ (160.21 g/mol);
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 6H, C*H*$_3$), 5.60 (d, *J* = 9.6 Hz, 1H, =C*H*), 6.31 (d, *J* = 9.6 Hz, 1H, =C*H*), 6.76 (d, *J* = 8.4 Hz, 1H, Ar*H*), 6.83 (m, 1H, Ar*H*), 6.96 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar*H*), 7.08 (m, 1H, Ar*H*);
^{13}C NMR (75 MHz, $CDCl_3$): δ 28.0, 76.1, 116.3, 120.7, 121.3, 122.3, 126.3, 129.0, 130.7, 152.9;
MS (EI): m/z 160 (M^+);
HRMS (EI): calculated for ($C_{11}H_{12}O_1$) 160.088913, found 160.088814.

Synthesis of 6-phenyl-2,2-dimethylchromene(158d):



156 **157** **158d**

According to Method A described for **158a**, to a solution of titanium tetraethoxide (1.14 g, 5 mmol) in 10 mL of toluene was added 4-phenylphenol (3.40 g, 20 mmol) in 10 mL of toluene at room temperature under argon. This orange-red solution was refluxed for 30 min and then slowly distilled to remove the formed ethanol. After cooling to room temperature a solution of 3-methylbut-2-enal (2.52 g, 30 mmol) in 40 mL of toluene was added dropwise, and the resulting mixture was heated to reflux for 8 h. The reaction was quenched with saturated aqueous solution of ammonium chloride, extracted with diethyl ether, washed with brine, and dried over anhydrous sodium sulfate. Purification by flash column chromatography on silica gel (4% EtOAc in hexanes) afforded the pure product as a white solid (1.65 g, 35%, 64% based on the recovered phenol).

158d: $C_{17}H_{16}O$ (236.31 g/mol);

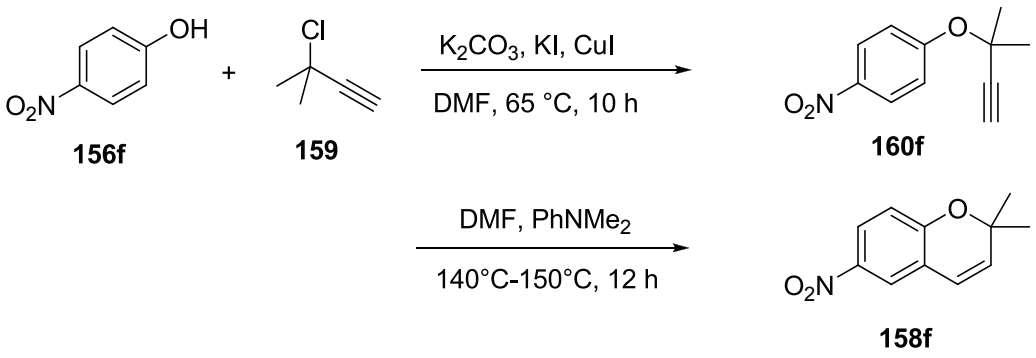
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.44 (s, 6H, C*H*$_3$), 5.62 (d, *J* = 9.8 Hz, 1H, C*H*=), 6.35 (d, *J* = 9.8 Hz, 1H, C*H*=), 6.83 (d, *J* = 8.3 Hz, 1H, Ar*H*), 7.18 (d, *J* = 2.1 Hz, 1H, Ar*H*), 7.27 (t, *J* = 7.4 Hz, 1H, Ar*H*), 7.32 (dd, *J* = 2.2, 8.3 Hz, 1H, Ar*H*), 7.38 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.51 (d, *J* = 7.2 Hz, 2H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 28.0, 76.4, 116.6, 121.4, 122.3, 124.9, 126.6, 127.7, 128.6, 131.0, 133.8, 140.8, 152.5;

MS (EI): m/z 236 (M^+);

HRMS (EI): calculated for ($C_{17}H_{16}O_1$) 236.120194, found 236.120118.

Synthesis of 6-nitro-2,2-dimethylchromene (158f, Method B):



According to the literature procedure,[156] 3-chloro-3-methylbut-1-yne (**159**, 1.02g, 10 mmol) was added to a mixture of 4-nitrophenol (0.70g, 5 mmol), K_2CO_3 (1.38g, 10 mmol), KI (1.41g, 8.5 mmol), and CuI (20 mg, 0.1 mmol) in dry DMF (5 mL) under Ar, and the reaction was stirred at 65°C until no further conversion took place (monitored by TLC). On cooling, water (40 mL) was added and the mixture was extracted with hexanes (3×50 mL). The combined hexane extracts were washed successively with 2 N NaOH (40 mL), 2 N HCl (40 mL) and water (40 mL). After drying over Na_2SO_4 and filtration, the crude product was subjected to a short silica gel column. The purified product was dissolved in 5 mL of DMF, treated with 0.5 mL of $PhNMe_2$ and heated to 140-150°C overnight. DMF was then removed under reduced pressure, and the residue was purified by column chromatography on silica gel (10% EtOAc in hexanes), affording pure 6-nitro-2,2-dimethylchromene (0.89 g , 87% yield over two steps) as a yellow solid.

158f: $C_{11}H_{11}NO_3$ (205.21 g/mol)

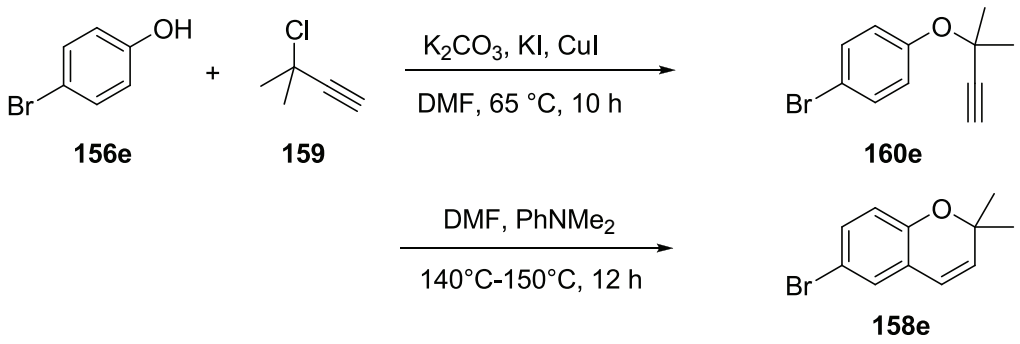
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 (s, 6H, C*H*$_3$), 5.75 (d, *J* = 10 Hz, 1H, C*H*=), 6.35 (d, *J* = 10 Hz, 1H, C*H*=), 6.80 (d, *J* = 9.0 Hz, 1H, Ar*H*), 7.88 (d, *J* = 2.5 Hz, 1H, Ar*H*), 8.01 (dd, *J* = 9.0, 2.5 Hz, 1H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 28.5, 78.5, 112.6, 120.8, 122.0, 125.2, 132.3, 141.4, 158.7;

MS (EI): m/z 205 (M^+);

HRMS (EI): calculated for ($C_{11}H_{11}N_1O_3$) 205.073756, found 205.073893.

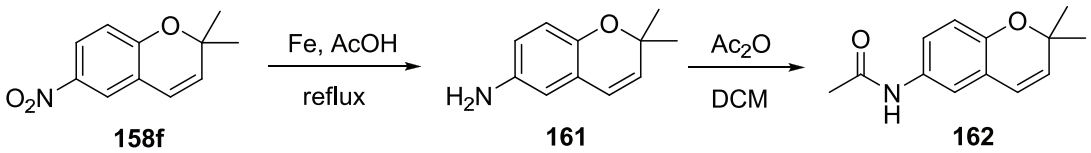
Synthesis of 6-bromo-2,2-dimethylchromene (158e):



The preparation was carried out on a 5-mmol scale according to the procedure described for 6-nitro-2,2-dimethylchromene (**158f**). After purification by column chromatography on silica gel (5% EtOAc in hexanes), the pure chromene was obtained as a white solid (0.97 g, 81% yield).

158e: $C_{11}H_{11}BrO$ (239.11 g/mol);
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (s, 6H, C*H*$_3$), 5.64 (d, *J* = 9.8 Hz, 1H, C*H*=), 6.24 (d, *J* = 9.8 Hz, 1H, C*H*=), 6.65 (d, *J* = 8.6 Hz, 1H, Ar*H*), 7.08 (d, *J* = 2.0 Hz, 1H, Ar*H*), 7.17 (dd, *J* = 8.6, 2.0 Hz, 1H, Ar*H*);
^{13}C NMR (125 MHz, $CDCl_3$): δ 27.9, 76.5, 112.6, 118.1, 121.3, 123.1, 128.7, 131.5, 131.9, 152.0;
MS (EI): m/z 238 (M^+);
HRMS (EI): calculated for ($C_{11}H_{12}O_1Br_1$) 237.999166, found 237.999342.

Synthesis of 6-acetamino-2,2-dimethylchromene:

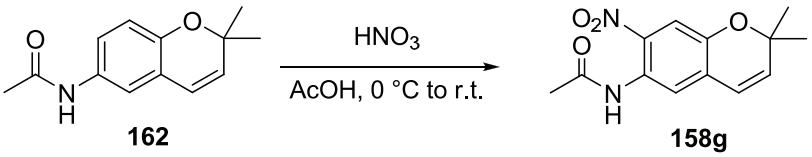


According to the reported procedure,[98] to a solution of nitrochromene **158f** (200 mg, 1 mmol) in ethanol (5 mL) was added 20% AcOH/H_2O (1 mL) and Fe powder (90 mg, 1.60 mmol) in 3 portions. The reaction mixture was refluxed for 24 h to achieve full conversion. The undissolved compound was filtered off, and the filtrate was concentrated under reduced pressure and then diluted with EtOAc. After washing with aq. $NaHCO_3$ and drying with anhydrous sodium sulfate, the organic phase was concentrated and the residue was subjected

to column chromatography on silica gel (EtOAc/hexanes, 1:3). The reduction product was obtained as an off-white solid. The acylation was performed in 5 mL of dichloromethane in the presence of 10 equivalents of acetic acid anhydride. After stirred overnight, the reaction mixture was concentrated and the residue was subjected to flash column chromatography (EtOAc/hexanes, 1:1.5), furnishing the desired product as a white solid (170 mg, 80% yield over two steps).

162: $C_{13}H_{15}NO_2$ (217.26 g/mol);
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.40 (s, 6H, C*H*$_3$), 2.11 (s, 3H, COC*H*$_3$), 5.60 (d, *J* = 9.8 Hz, 1H, =C*H*), 6.25 (d, *J* = 9.8 Hz, 1H, =C*H*), 6.70 (d, *J* = 8.5 Hz, 1H, Ar*H*), 7.06 (dd, *J* = 8.5, 2.5 Hz, 1H, Ar*H*), 7.24 (d, *J* = 2.5 Hz, 1H, Ar*H*), 7.58 (s, br, 1H, N*H*);
^{13}C NMR (125 MHz, $CDCl_3$): δ 24.3, 27.8, 76.2, 116.4, 118.9, 121.3, 121.5, 122.2, 131.0, 131.4, 149.7, 168.5;
MS (EI): m/z 217 (M^+);
HRMS (EI): calculated for ($C_{13}H_{15}N_1O_2$) 217.110469, found 217.110278.

Synthesis of 6-acetamino-7-nitro-2,2-dimethylchromene (158g):



162 **158g**

Following the reported procedure,[99] to a stirred solution of 6-(acetylamino)-2,2-dimethyl-2*H*-l-benzopyra (217 mg, 1 mmol, 1.0 eq.) in AcOH (2 mL) at 0 °C was added dropwise a solution of fuming HNO_3 (4.8 mL, 1.25 mmol, 1.25 eq) in AcOH (2 mL). After stirring for 45 min at room temperature, the solution was poured onto ice, and the solid was collected by filtration. Further purification by column chromatography on silica gel (EtOAc/hexanes, 1:4) gave the desired product as orange needle-like crystals (157 mg, 60% yield).

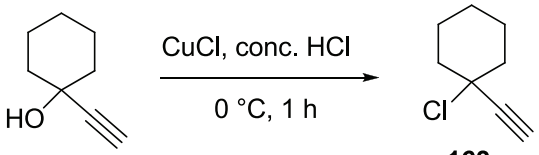
158g: $C_{13}H_{14}N_2O_4$ (262.26 g/mol);
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.40 (s, 6H, C*H*$_3$), 2.25 (s, 3H, COC*H*$_3$), 5.90 (d, *J* = 9.9 Hz, 1H, =C*H*), 6.40 (d, *J* = 9.9 Hz, 1H, =C*H*), 7.59 (s, 1H, Ar*H*), 8.37 (s, 1H, Ar*H*), 10.19 (s, 1H, N*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 25.5, 27.9, 77.1, 112.4, 119.5, 121.3, 128.8, 128.9, 135.9, 136.6, 148.1, 168.9;

MS (EI): m/z 262 (M^+);

HRMS (EI): calculated for ($C_{13}H_{14}N_2O_4$) 262.095477, found 262.095355.

Synthesis of 1-chloro-1-ethynylcyclohexane (163):



227 **163**

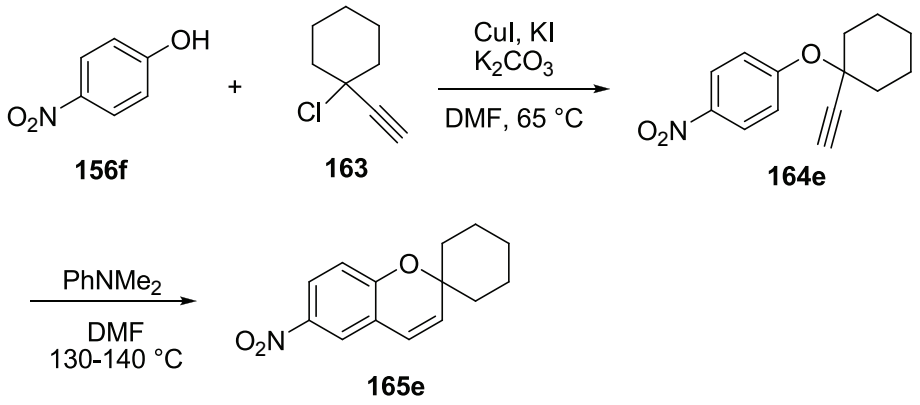
Following the literature method,[157] to a cold solution of CuCl (2.00 g, 0.02 mol) in 50 mL of conc. HCl (in an ice-water bath), 12.4 g of 1-ethynylcyclohexanol (0.10 mol) was added in several portions. The resulting mixture was stirred for 1 hour, and the lower layer was separated and discarded. The upper layer was washed with conc. HCl and aq. K_2CO_3. After drying overnight over K_2CO_3, the oil was distilled under reduced pressure (50 °C, 13 mbar), giving 1-ethynylcyclohexyl chloride as a colorless oil (13.5 g, 87% yield).

163: $C_8H_{11}Cl$ (142.63 g/mol);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.37 (m, 1H, CH_2), 1.50 (m, 1H, CH_2), 1.65 (m, 2H, CH_2), 1.70 (m, 2H, CH_2), 1.98 (m, 2H, CH_2), 2.15 (m, 2H, CH_2), 2.67 (s, 1H, ≡-*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 23.4, 24.7, 42.3, 62.3, 73.5, 85.3.

Synthesis of 6-nitrospiro[chromene-2,1'-cyclohexane] (165e):



According to the procedure described for 6-nitro-2,2-dimethylchromene (**158f**), 1-ethynylcyclohexyl chloride (**163**, 1.42g, 10 mmol) was added to a mixture of 4-nitrophenol (**156f**, 0.70g, 5 mmol), K_2CO_3 (1.38g, 10 mmol), KI (1.41g, 8.5 mmol), and CuI (20 mg, 0.1 mmol) in dry DMF (5 mL) under Ar, and the reaction was stirred at 65°C for 24 hours. On cooling, water (40 mL) was added and the mixture was extracted with hexanes (3×50 mL). The combined hexane extracts were washed successively with 2 N NaOH (40 mL), 2 N HCl (40 mL) and water (40 mL). After drying over Na_2SO_4 and filtration, the crude product was subjected to a short silica gel column, giving 0.50 g of the product in 41 % yield. The propagylation product (0.48 g) was dissolved in 5 mL of DMF, treated with 0.5 mL of $PhNMe_2$ and heated to 130-140°C for 48 hours. Purification by column chromatography on silica gel (5-10% EtOAc in hexanes) afforded the pure chromene product as a yellow solid (0.44 g, 92%).

164e: $C_{14}H_{15}NO_3$ (245.27 g/mol);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 (m, 1H, C*H*$_2$), 1.42-1.62 (m, 5H, C*H*$_2$), 1.80 (m, 2H, C*H*$_2$), 2.00 (m, 2H, C*H*$_2$), 2.68 (s, 1H, ≡-*H*), 7.22 (d, *J* = 9.1 Hz, 2H, Ar*H*), 8.05 (d, *J* = 9.1 Hz, 2H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 21.3, 23.9, 36.3, 75.3, 76.3, 82.6, 118.0, 124.1, 140.9, 160.1;

MS (EI): m/z 245 (M^+).

165e: $C_{14}H_{15}NO_3$ (245.27 g/mol);

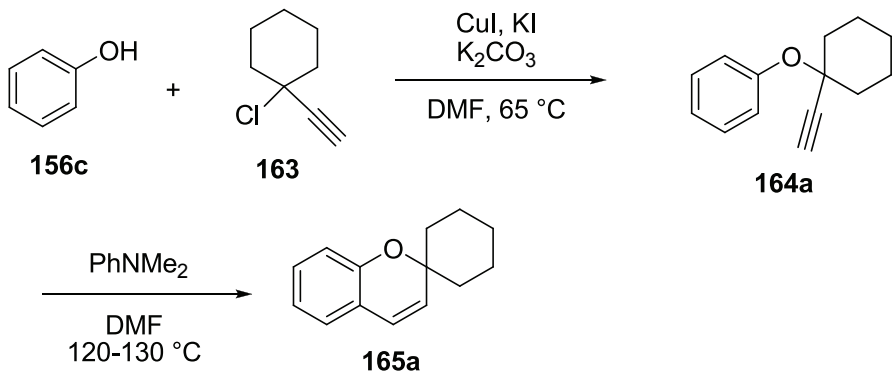
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32-1.39 (m, 1H), 1.49-1.64 (m, 5H), 1.69-1.78 (m, 2H), 1.93-1.96 (m, 2H), 5.76 (d, *J* = 10.0 Hz, 1H), 6.35 (d, *J* = 10.0 Hz, 1H), 6.84 (d, *J* = 8.9 Hz, 1H), 7.86 (d, *J* = 2.7 Hz, 1H), 8.00 (dd, *J* = 2.7, 8.9 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 21.1, 25.0, 36.4, 79.2, 116.6, 121.2, 121.7, 122.0, 125.1, 132.1, 141.4, 158.7;

MS (EI): m/z 245 (M^+);

HRMS (EI): calculated for ($C_{14}H_{15}N_1O_3$) 245.105004, found 245.105197.

Synthesis of chromene-2,1'-cyclohexane (165a):



According to the procedure described for 6-nitrospiro[chromene-2,1'-cyclohexane] (**165e**), 1-ethynylcyclohexyl chloride (1.42g, 10 mmol) was added to a mixture of phenol (0.47g, 5 mmol), K_2CO_3 (1.38g, 10 mmol), KI (1.41g, 8.5 mmol), and CuI (20 mg, 0.1 mmol) in dry DMF (5 mL) under Ar, and the reaction was stirred at 65°C for 24 hous. On cooling, water (40 mL) was added and the mixture was extracted with hexanes (3×50 mL). The combined hexane extracts were washed successively with 2 N NaOH (40 mL), 2 N HCl (40 mL) and water (40 mL). After drying over Na_2SO_4 and filtration, the crude product was subjected to a short silica gel column (5-10% DCM in hexanes), giving 0.17 g of the product in 17 % yield. The propagylation product (0.17 g) was dissolved in 5 mL of DMF, treated with 0.5 mL of $PhNMe_2$ and heated to 120-130°C for 48 hours. Purification by column chromatography on silica gel (hexanes) afforded the pure chromene product as a colorless liquid (0.13 g, 77% yield).

165a: $C_{14}H_{16}O$ (200.28 g/mol);

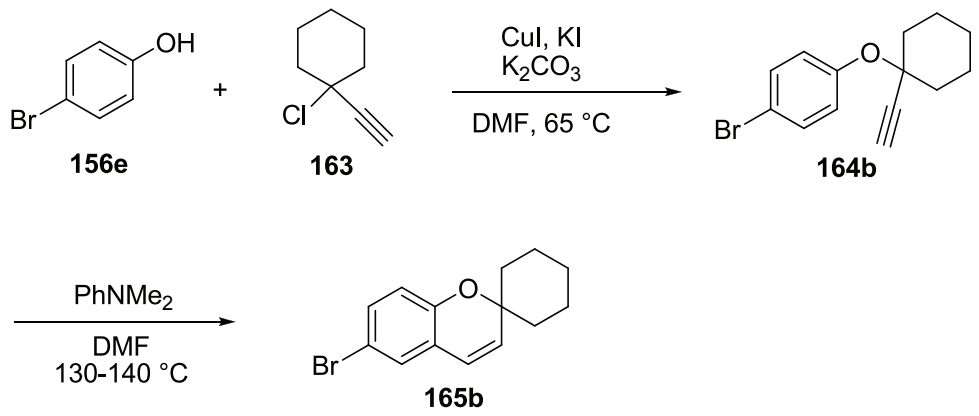
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.36-1.40 (m, 1H, C*H*$_2$), 1.51-1.66 (m, 5H, C*H*$_2$), 1.75-1.82 (m, 2H, C*H*$_2$), 1.95-2.00 (m, 2H, C*H*$_2$), 5.66 (d, *J* = 9.8 Hz, 1H, =C*H*), 6.36 (d, *J* = 9.8 Hz, 1H, =C*H*), 6.86 (m, 2H, Ar*H*), 7.00 (dd, *J* = 7.6, 1.4 Hz, 1H, Ar*H*), 7.14 (ddd, *J* = 7.6, 1.4 Hz, 1H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 21.4, 25.4, 36.0, 76.7, 116.5, 120.7, 122.2, 122.8, 126.3, 128.9, 130.5, 152.9;

MS (EI): m/z 200 (M^+);

HRMS (EI): calculated for ($C_{14}H_{16}O_1$) 200.119998, found 200.120112.

Synthesis of 6-bromospiro[chromene-2,1'-cyclohexane] (165b):



According to the procedure described for 6-nitrospiro[chromene-2,1'-cyclohexane] (**165e**), 1-ethynylcyclohexyl chloride (1.42g, 10 mmol) was added to a mixture of 4-nitrophenol (0.87g, 5 mmol), K_2CO_3 (1.38g, 10 mmol), KI (1.41g, 8.5 mmol), and CuI (20 mg, 0.1 mmol) in dry DMF (5 mL) under Ar, and the reaction was stirred at 65°C for 24 hours. After workup, the crude product was subjected to a short silica gel column, giving 0.44 g of the product in 32 % yield. The propagylation product was then dissolved in 5 mL of DMF, treated with 0.5 mL of $PhNMe_2$ and heated to 130-140°C for 48 hours. Purification by column chromatography on silica gel (hexanes) afforded the pure chromene product as a slightly yellow solid (0.33 g, 75%).

164b: $C_{14}H_{15}BrO$ (279.17 g/mol);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.34 (m, 1H, C*H*$_2$), 1.52-1.62 (m, 3H, C*H*$_2$), 1.71 (m, 2H, C*H*$_2$), 1.81 (m, 2H, C*H*$_2$), 2.01 (m, 2H, C*H*$_2$), 2.63 (s, 1H, ≡-*H*), 7.12 (d, *J* = 8.8 Hz, 2H, Ar*H*), 7.35 (d, *J* = 8.8 Hz, 2H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 22.6, 25.1, 37.6, 76.1, 76.2, 84.8, 115.3, 123.1, 131.8, 154.4;

MS (EI): m/z 278 (M^+).

165b: $C_{14}H_{15}BrO$ (279.17 g/mol);

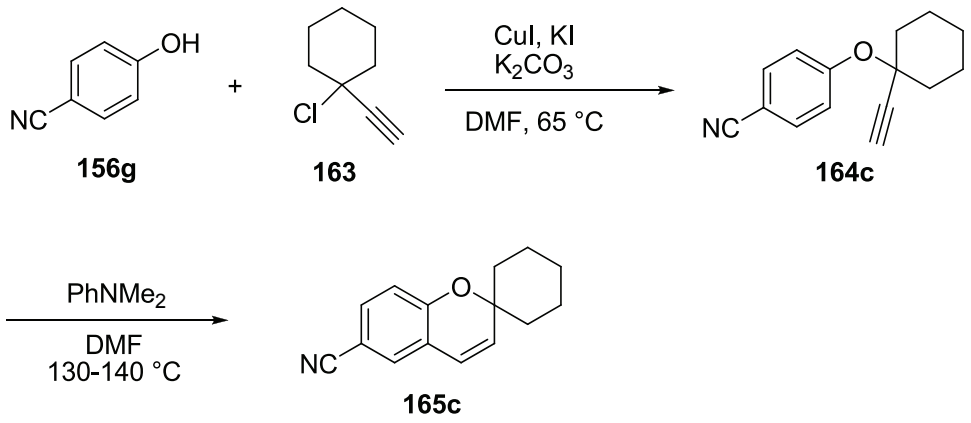
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35-1.93 (m, 10H), 5.67 (d, *J* = 9.9 Hz, 1H), 6.26 (d, *J* = 9.9 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 7.08 (d, *J* = 2.4 Hz, 1H), 7.18 (dd, *J* = 2.4, 8.4 Hz, 1H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 21.2, 25.2, 35.8, 76.6, 112.6, 118.2, 121.7, 124.0, 128.7, 131.4, 131.8, 151.9;

MS (EI): m/z 278 (M^+);

HRMS (EI): calculated for ($C_{14}H_{15}O_1Br_1$) 278.030825, found 278.030641.

Synthesis of 6-cyanospiro[chromene-2,1'-cyclohexane] (165c):



According to the procedure described above for 6-nitrospiro[chromene-2,1'-cyclohexane] (**165e**), 1-ethynylcyclohexyl chloride (1.42g, 10 mmol) was added to a mixture of 4-nitrilphenol (0.60g, 5 mmol), K_2CO_3 (1.38g, 10 mmol), KI (1.41g, 8.5 mmol), and CuI (20 mg, 0.1 mmol) in dry DMF (5 mL) under Ar, and the reaction was stirred at 65°C for 24 hours. After workup, the crude product was subjected to a short silica gel column. The propagylation product was then dissolved in 5 mL of DMF, treated with 0.5 mL of $PhNMe_2$ and heated to 130-140°C for 24 hours. Purification by column chromatography on silica gel (6% EtOAc in hexanes) afforded the pure chromene product as a white solid (0.73 g, 65% yield).

165c: $C_{15}H_{15}NO$ (225.29 g/mol);

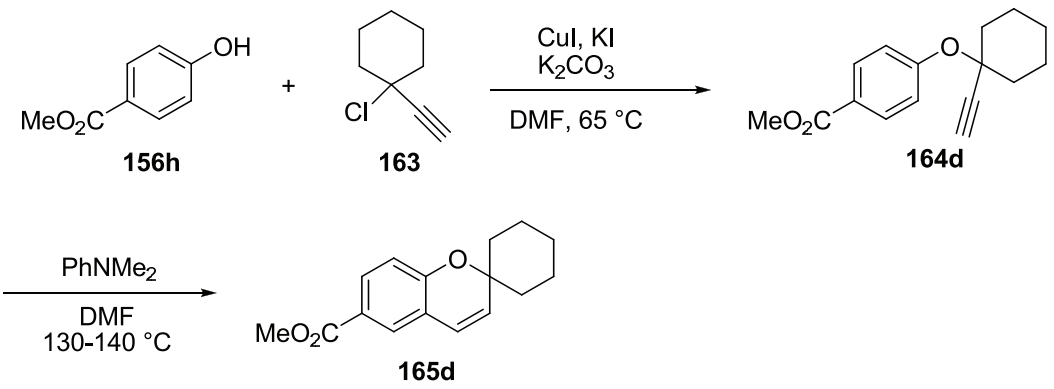
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.31-1.39 (m, 1H), 1.49-1.65 (m, 5H), 1.70-1.77 (m, 2H), 1.91-1.95 (m, 2H), 5.74 (d, *J* = 10.0 Hz, 1H), 6.30 (d, *J* = 10.0 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 7.24 (d, *J* = 2.0 Hz, 1H), 7.38 (dd, *J* = 2.0, 8.4 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 21.1, 25.0, 36.3, 78.5, 103.7, 117.3, 119.3, 121.1, 122.6, 130.1, 132.0, 133.3, 156.8;

MS (EI): m/z 225 (M^+);

HRMS (EI): calculated for ($C_{15}H_{15}N_1O_1$) 225.115251, found 225.115336.

Synthesis of 6-methoxycarbonylspiro[chromene-2,1'-cyclohexane] (165d):



According to the procedure described for 6-nitrospiro[chromene-2,1'-cyclohexane] (**165e**), 1-ethynylcyclohexyl chloride (1.42g, 10 mmol) was added to a mixture of 4-methoxycarbonylphenol (0.76 g, 5 mmol), K_2CO_3 (1.38g, 10 mmol), KI (1.41g, 8.5 mmol), and CuI (20 mg, 0.1 mmol) in dry DMF (5 mL) under Ar, and the reaction was stirred at 65°C for 24 hours. After workup, the crude product was subjected to a short silica gel column. The propagylation product was then dissolved in 5 mL of DMF, treated with 0.5 mL of $PhNMe_2$ and heated to 150-160°C for 48 hours (not finished). Purification by column chromatography on silica gel (hexanes) afforded the pure chromene product as a white solid (0.30 g, 24% yield).

165d: $C_{16}H_{18}O_3$ (258.31 g/mol);

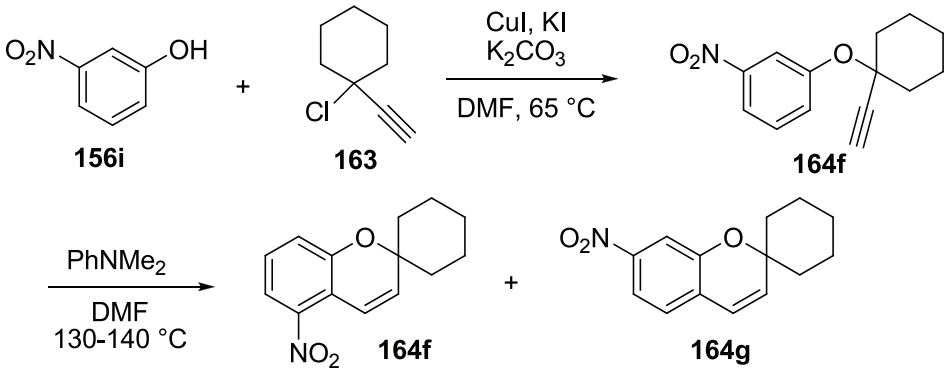
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.29-1.36 (m, 1H), 1.45-1.61 (m, 5H), 1.69-1.77 (m, 2H), 1.89-1.94 (m, 2H), 3.85 (s, 3H), 5.65 (d, J = 9.9 Hz, 1H), 6.33 (d, J = 9.9 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 2.1 Hz, 1H), 7.80 (dd, J = 2.1, 8.4 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 21.2, 25.2, 36.3, 51.8, 77.9, 116.2, 121.5, 122.1, 122.5, 128.0, 130.8, 131.0, 157.1, 166.8;

MS (EI): m/z 258 (M^+);

HRMS (EI): calculated for ($C_{16}H_{18}O_3$) 258.125327, found 258.125594.

Synthesis of 5-nitrospiro[chromene-2,1'-cyclohexane] and 7-nitrospiro[chromene-2,1'-cyclohexane] (*165f and 165g*):



According to the procedure described for 6-nitrospiro[chromene-2,1'-cyclohexane] (**165e**), 1-ethynylcyclohexyl chloride (1.42g, 10 mmol) was added to a mixture of 3-nitrophenol (0.70g, 5 mmol), K_2CO_3 (1.38g, 10 mmol), KI (1.41g, 8.5 mmol), and CuI (20 mg, 0.1 mmol) in dry DMF (5 mL) under Ar, and the reaction was stirred at 65°C for 24 hours. After workup and removal of solvent, the crude product was subjected to a short silica gel column. The isolated propagylation product was then dissolved in 5 mL of DMF, treated with 0.5 mL of $PhNMe_2$ and heated to 130-140°C for 48 hours. Purification by column chromatography on silica gel (5% EtOAc in hexanes) afforded the pure two regioisomers (7-nitrochromene: 85 mg, 7% yield and 5-nitro chromene: 250 mg, 20% yield).

165f: $C_{14}H_{15}NO_3$ (245.27 g/mol);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (m, 1H, C*H*$_2$), 1.51-1.61 (m, 5H, C*H*$_2$), 1.73 (m, 2H, C*H*$_2$), 1.95 (m, 2H, C*H*$_2$), 5.90 (d, *J* = 10.2 Hz, 1H, =C*H*), 6.95 (d, *J* = 10.2 Hz, 1H, =C*H*), 7.09 (d, *J* = 8.1 Hz, 1H, Ar*H*), 7.19 (t, *J* = 8.1 Hz, 1H, Ar*H*), 7.52 (d, *J* = 8.2 Hz, 1H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 21.3, 25.1, 35.6, 76.9, 117.0(d), 118.0, 121.9, 128.2, 134.3, 146.0, 154.1;

MS (EI): m/z 245 (M+);

HRMS (EI): calculated for ($C_{14}H_{15}N_1O_3$) 245.105395, found 245.105196.

165g: $C_{14}H_{15}NO_3$ (245.27 g/mol);

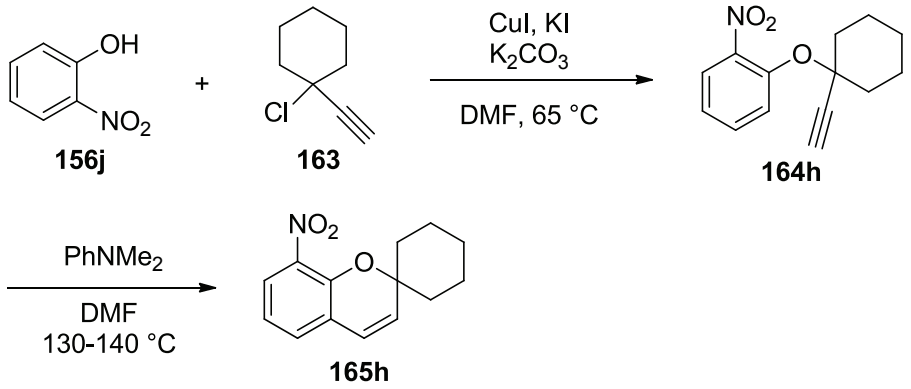
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.31-1.42 (m, 1H), 1.50-1.70 (m, 5H), 1.72-1.80 (m, 2H), 1.94-1.98 (m, 2H), 5.85 (d, *J* = 9.9 Hz, 1H), 6.39 (d, *J* = 9.9 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 1H), 7.65 (d, *J* = 2.0 Hz, 1H), 7.71 (dd, *J* = 2.1, 8.2 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 21.2, 25.1, 36.0, 78.0, 111.8, 116.2, 121.5, 126.3, 128.1, 134.7, 148.0, 153.2;

MS (EI) m/z 245 (M^+);

HRMS (EI): calculated for ($C_{14}H_{15}N_1O_3$) 245.105395, found 245.105197.

Synthesis of 8-nitrospiro[chromene-2,1'-cyclohexane] (165h):



According to the procedure described for 6-nitrospiro[chromene-2,1'-cyclohexane] (**165e**), 1-ethynylcyclohexyl chloride (1.42g, 10 mmol) was added to a mixture of 2-nitrophenol (0.70g, 5 mmol), K_2CO_3 (1.38g, 10 mmol), KI (1.41g, 8.5 mmol), and CuI (20 mg, 0.1 mmol) in dry DMF (5 mL) under Ar, and the reaction was stirred at 65°C for 24 hours. After workup and removal of solvent, the crude product was subjected to a short silica gel column. The isolated propagylation product was then dissolved in 5 mL of DMF, treated with 0.5 mL of $PhNMe_2$ and heated to 130-140°C for 48 hours. Purification by column chromatography on silica gel (5% EtOAc in hexanes) afforded the pure 8-nitro chromene as a yellow solid (750 mg, 62% yield).

165h: $C_{14}H_{15}NO_3$ (245.27 g/mol);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 (m, 1H, C*H*$_2$), 1.46-1.56 (m, 4H, C*H*$_2$), 1.68 (m, 1H, C*H*$_2$), 1.79-1.88 (m, 2H, C*H*$_2$), 2.04 (d, *J* = 13.6 Hz, 2H, C*H*$_2$), 5.74 (d, *J* = 10.0 Hz, 1H, =C*H*), 6.36 (d, *J* = 10.0 Hz, 1H, =C*H*), 6.87 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.15 (dd, *J* = 7.6, 1.0 Hz, 1H, Ar*H*), 7.71 (dd, *J* = 8.2, 1.0 Hz, 1H, Ar*H*);

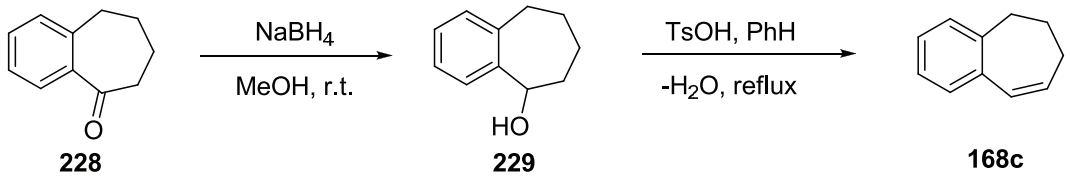
^{13}C NMR (125 MHz, $CDCl_3$): δ 20.9, 25.1, 36.1, 79.5, 119.8, 121.6, 124.6, 124.8, 130.7, 132.2, 138.7, 147.5;

MS (EI): m/z 245 (M^+);

HRMS (EI): calculated for ($C_{14}H_{15}N_1O_3$) 245.105395, found 245.105194.

6.4.2 Synthesis of Other Alkene Substrates

Synthesis of 1,2-benzo-l,3-cyclopeptadiene (168c):

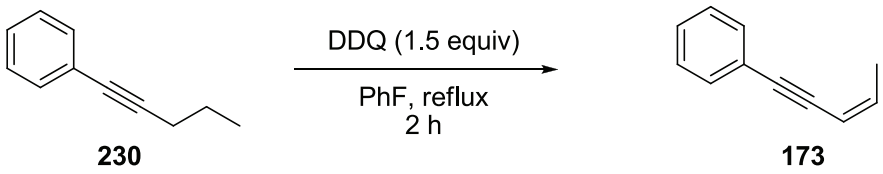


Following the literature procedure,[158] 1-benzosuberone (**228**, 1.60 g, 10 mmol, 4.8 eq) was reduced in ethanol (15 ml) by the slow addition of $NaBH_4$ (0.45 g, 12 mmol). The reaction was stirred at room temperature for 30 min (full conversion, monitored by TLC, Rf = 0.37, EtOAc/hexanes, 1:5), 30 mL of distilled water was added and the reaction mixture was extracted with ethyl acetate. After drying over anhydrous sodium sulfate, the solvent was evaporated to give the reduction product as a white solid. 2,3-Benzo-2-cyclohepten-l-ol obtained was then dehydrated in benzene (40 mL) in the presence of *p*-toluenesulfonic acid monohydrate (85 mg), and the water generated was removed using a Dean-Stark trap. After 24 h of reflux, the solution was cooled to room temperature, washed with 30 mL of water, dried with anhydrous sodium sulfate, filtered, and concentrated to give a pale yellow oil (1.40 g, 97% yield over two steps).

229: $C_{11}H_{14}O$ (162.23 g/mol);
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.49 (m, 1 H, C*H*$_2$), 1.80 (m, 4 H, C*H*$_2$), 1.96 (m, 1 H, C*H*$_2$), 2.06 (m, 1 H, C*H*$_2$), 2.72 (dd, *J* = 10.0, 14.0 Hz, 1H, C*H*$_2$), 2.92 (dd, *J* = 8.4, 14.0 Hz, 1H, C*H*$_2$), 4.94 (d, *J* = 7.8 Hz, 1H, C*H*-OH), 7.10 (d, *J* = 7.2 Hz, 1H, Ar*H*), 7.15 (ddd, *J* = 7.4, 7.4, 1.1 Hz, 1H, Ar*H*), 7.21 (ddd, *J* = 7.4, 7.4, 1.1 Hz, 1H, Ar*H*), 7.42 (d, *J* = 7.4 Hz, 1H, Ar*H*).

168c:$C_{11}H_{12}$ (144.21 g/mol);
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.98 (m, 2H, C*H*$_2$), 2.42 (m, 2H, C*H*$_2$), 2.86 (m, 2H, C*H*$_2$), 5.90 (m, 1 H, =C*H*), 6.41 (dd, *J* = 12.2, 1.6 Hz, 1 H, =C*H*), 7.10 (m, 2H, Ar*H*), 7.15 (m, 2H, Ar*H*);
^{13}C NMR (125 MHz, $CDCl_3$): δ 26.9, 32.5, 36.1, 125.9, 126.6, 129.0, 129.8, 130.8, 132.3, 136.3, 141.7.

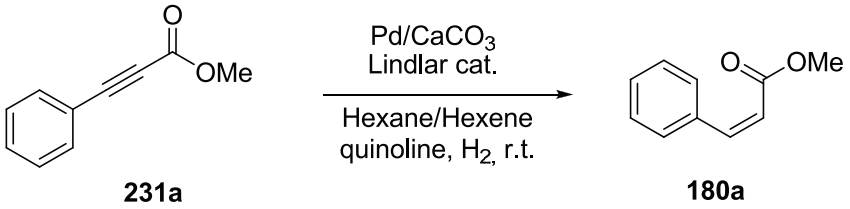
Synthesis of (Z)-pent-3-en-1-yn-1-ylbenzene (173):



Following the reported procedure,[159] a solution of pent-1-ynylbenzene (0.43 g, 3 mmol) and DDQ (1.0 g, 4.5 mmol) in PhF (30 mL) was heated to reflux for 2 h. The black solid formed was filtered off and the solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel (hexanes) furnished the enyl product as a colorless oil (0.42, 98% yield).

173: $C_{11}H_{10}$ (142.20 g/mol);
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.96 (dd, *J* = 6.9 Hz, 1.7 Hz, 3H, C*H*$_3$), 5.70 (m, 1H, =C*H*), 6.05 (m, 1H, =C*H*), 7.28-7.46 (m, 5H, Ar*H*);
^{13}C NMR (125 MHz, $CDCl_3$): δ 16.1, 86.2, 93.9, 110.0, 123.7, 127.9, 128.3, 131.4, 138.7.

Synthesis of (Z)-methyl 3-phenylacrylate (180a):

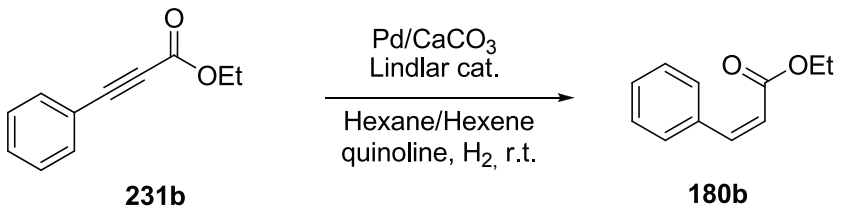


According to the known procedure,[160] under an atmosphere of dry argon, methyl phenylpropiolate (0.80 g, 5 mmol, 1.0 equiv) was dissolved in a mixture of hexane and 1-hexene (2:1, v/v, 50 mL), and then quinoline (2.08 g) and palladium on calcium carbonate (Lindlar catalyst, 0.168 g) were added. The Schlenk tube was then connected to a hydrogen filled balloon (1 atm) and stirred at room temperature. After the starting alkyne was completely consumed (monitored by GCMS), the reaction mixture was filtered through a short Celite pad. The filtrate was then washed with 10% acetic acid, water, saturated $NaHCO_3$, and dried over $MgSO_4$. The product was obtained as a colorless oil (0.78 g, 96% yield, containing ca. 3% over-reduced product) after purification by column chromatography on

silica gel (4% EtOAc in hexanes), and the *E/Z* ratio was determined by GCMS (*E/Z* = 2:98) and NMR (*E/Z* = 3.6:96.4).

180a: $C_{10}H_{10}O_2$ (162.19 g/mol);
^{1}H NMR (300 MHz, $CDCl_3$): δ 3.70 (s, 3H, O-C*H*$_3$), 5.96 (d, *J* = 12.6 Hz, 1H, =C*H*), 6.96 (d, *J* = 12.6 Hz, 1H, =C*H*), 7.31-7.39 (m, 3H, Ar*H*), 7.58 (m, 2H, Ar*H*);
^{13}C NMR (75 MHz, $CDCl_3$): δ 51.4, 119.3, 128.0, 129.1, 129.7, 134.8, 143.4, 166.6;
MS (EI): m/z = 162 (M^+).

Synthesis of (Z)-ethyl 3-phenylacrylate (180b):

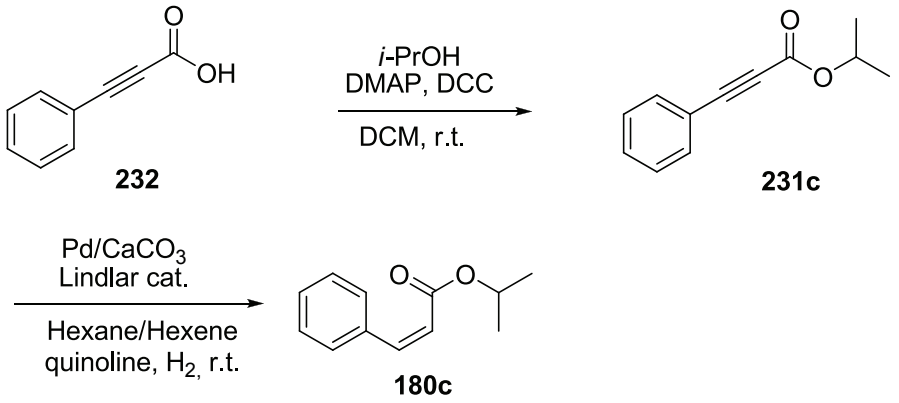


231b **180b**

The reaction was performed on a 5-mmol scale, following the procedure described above for (*Z*)-methyl 3-phenylacrylate. Purification by column chromatography on silica gel (4% EtOAc in hexanes) gave the desired cinnamate product as a colorless oil (0.88 g, 99% yield, *Z/E* = 94:6 by NMR, 98:2 by GCMS).

180b: $C_{11}H_{12}O_2$ (176.21 g/mol);
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 3.70 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$), 5.86 (d, *J* = 12.6 Hz, 1H, =C*H*), 6.85 (d, *J* = 12.6 Hz, 1H, =C*H*), 7.25 (m, 3H, Ar*H*), 7.50 (d, *J* = 7.2 Hz, 2H, Ar*H*);
^{13}C NMR (75 MHz, $CDCl_3$): δ 13.2, 59.4, 117.2, 126.9, 127.9, 128.7, 133.8, 142.0, 165.2;
MS (EI): m/z = 176 (M^+).

Synthesis of (Z)-isopropyl 3-phenylacrylate (180c):



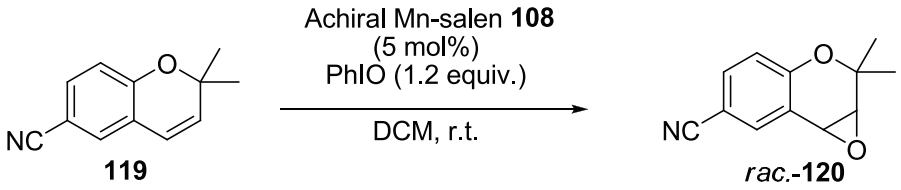
Following the procedure reported by Jacobsen,[61] to the cold solution (0 °C) of phenylpropionic acid (1.46g, 10 mmol), DMAP (0.10 g, 0.8 mmol), and isopropanol (2.3 mL, 30 mmol) in DCM (10 mL), DCC (2.27 g, 11 mmol) was added in four portions. The reaction was then warmed up to room temperature and stirred overnight. Filtration and removal of the solvent furnished the crude product as a brown oily residue. Chromatography (3-4% EtOAc in hexanes) on silica gel gave the pure compound as a colorless oil 1.40 g (96 %). After reduction with Lindlar catalyst (6 hours at room temperature) according to the method described above for (*Z*)-methyl 3-phenylacrylate and purification by flash column chromatography (4% EtOAc in hexanes), the product was obtained as a colorless oil (97 % yield, *Z*/*E* = 94:6 by NMR, *Z*/*E* = 98:2 by GCMS).

231c: $C_{12}H_{12}O_2$ (188.22 g/mol);
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.34 (d, *J* = 6.3 Hz, 6H, C*H*$_3$), 5.16 (m, *J* = 6.3 Hz, 1H, C*H*$_1$), 7.37 (t, *J* = 7.8 Hz, 2H, Ar*H*), 7.44 (m, *J* = 7.8 Hz, 1.4 Hz, 1H, Ar*H*); 7.58 (d, *J* = 7.8 Hz, 2H) , Ar*H*;
^{13}C NMR (125 MHz, $CDCl_3$): δ 21.7, 70.0, 81.1, 85.7, 119.7, 128.5, 130.5, 133.0, 153.7;
MS (EI): m/z = 188 (M^+).

180c: $C_{12}H_{14}O_2$ (190.24 g/mol);
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22 (d, *J* = 6.3 Hz, 6H, C*H*$_3$), 5.03 (m, *J* = 6.3 Hz, 1H, C*H*$_1$), 5.93 (d, *J* = 12.6 Hz, 1H, =C*H*), 6.93 (d, *J* = 12.6 Hz, 1H, =C*H*), 7.34 (m, 3H, Ar*H*), 7.57 (d, *J* = 7.5 Hz, 2H, Ar*H*);
^{13}C NMR (125 MHz, $CDCl_3$): δ 21.7, 67.8, 120.5, 128.0, 128.8, 129.6, 135.0, 142.5, 165.8;
MS (EI): m/z = 190 (M^+).

6.5 Synthesis of Racemic Epoxidation Products

***Synthesis of Racemic 2,2-Dimethyl-2,7b-dihydro-1aH-oxireno[2,3-c]chromene-6-carbonitrile (A Typical Procedure)**:*



The racemic epoxides were prepared using achiral Mn-Salen chloride **108** as the catalyst. To a solution of the chromene (92 mg, 0.5 mmol) and the achiral Mn-Salen catalyst (15 mg, 0.025 mmol) in dichloromethane (5 mL) was added iodosobenzene (130 mg, 0.6 mmol). The resulting mixture was stirred at room temperature for 12 h. After the removal of solvent, the resulting solid was subjected to silica gel column chromatography. The desired epoxide was isolated as a white solid (92 mg, 92%).

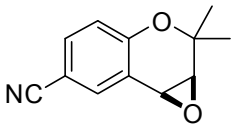
The racemic epoxides of other substrates were also prepared following this typical procedure on different reaction scales.

6.6 Asymmetric Epoxidation of Alkenes with Ion-Pair Catalysts

Typical Procedure: 6-Cyano-2,2-dimethylchromene (**119**, 18 mg, 0.1 mmol), iodosobenzene (26 mg, 0.12 mmol) and the ion-pair catalyst (0.005 mmol, 5 mol%) were dissolved in dry benzene (2 mL). The resulting mixture was stirred at room temperature. Upon the finish of the reaction (2 h, monitored by TLC), the solvent was removed under reduced presure and the residue was subjected to column chromatography on silica gel (15% EtOAc in hexanes), giving the corresponding epoxide as a white solid. The optical purity of the epoxide was determined by HPLC analysis. The absolute configuration of the epoxide was determined by comparison of the HPLC retention times and the optical rotation with the literature values.[161]

(1aS,7bS)-2,2-dimethyl-2,7b-dihydro-1aH-oxireno[2,3-c]chromene-6-carbonitrile:

(*S,S*)-**120**: $C_{12}H_{11}NO_2$ (201.22 g/mol), white solid, purified by column chromatography on silica gel (15% EtOAc in hexanes), 98% yield;



^{1}H NMR (500 MHz, $CDCl_3$): δ 1.29 (s, 3H, C*H*$_3$), 1.59 (s, 3H, C*H*$_3$), 3.54 (d, *J* = 4.3 Hz, 1H, OC*H*), 3.90 (d, *J* = 4.3 Hz, 1H, OC*H*), 6.86 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.52 (dd, *J* = 1.4, 8.4 Hz, 1H, Ar*H*), 7.65 (d, *J* = 1.4 Hz, 1H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 23.0, 25.5, 49.9, 62.3, 74.7, 104.3, 118.7, 119.0, 121.1, 133.8, 134.4, 156.5;

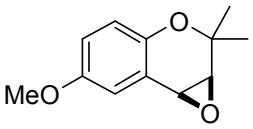
MS (EI): m/z 201 (M^+);

HRMS (EI): calculated for ($C_{12}H_{11}N_1O_2$) 201.079116, found 201.078978.

HPLC: The optical purity (er = 97:3) was determined by HPLC (DAICEL OJ-H, heptane/isopropanol 50:50, flow rate: 0.5 mL/min, 220 nm, t_r = 15.6 and 24.8 min).

(1aS,7bS)- 6-methoxy-2,2-dimethyl-2,7b-dihydro-1aH-oxireno[2,3-c]chromene:

(*S,S*)-**166a**: $C_{12}H_{14}O_3$ (206.24 g/mol), white solid, purified by column chromatography on silica gel (5% EtOAc in hexanes), 83% yield;



^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 (s, 3H, C*H*$_3$), 1.57 (s, 3H, C*H*$_3$), 3.46 (d, *J* = 4.2Hz, 1H, OC*H*), 3.77 (s, 3H, C*H*$_3$), 3.86 (d, *J* = 4.2 Hz, 1H, OC*H*), 6.74 (d, *J* =9.0Hz, 1H, Ar*H*), 6.80 (dd, *J* =9.0Hz, 2.8 Hz, 1H, Ar*H*), 6.89 (d, *J* =2.8 Hz, 1H, Ar*H*);

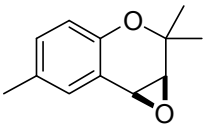
^{13}C NMR (125 MHz, $CDCl_3$): δ 22.2, 25.7, 51.1, 55.8, 62.8, 72.7, 114.7, 115.6, 118.7, 120.7, 146.5, 154.0;

MS (EI): m/z 206 (M^+);

HPLC: The optical purity (er = 96:4) was determined by HPLC (DAICEL OD-H, heptane/isopropanol 90:10, flow rate: 0.5 mL/min, 220 nm, t_r = 14.7 and 16.7 min).

(1aS,7bS)-2,2,6-trimethyl-2,7b-dihydro-1aH-oxireno[2,3-c]chromene:

(*S,S*)-**166b**: $C_{12}H_{14}O_2$ (190.24 g/mol), white solid, purified by column chromatography on silica gel (4% EtOAc in hexanes), 81% yield;



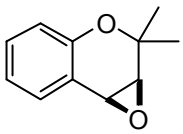
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (s, 3H, C*H*$_3$), 1.57 (s, 3H, C*H*$_3$), 2.28 (s, 3H, Ar-C*H*$_3$), 3.47 (d, *J* = 4.4Hz, 1H, OC*H*), 3.85 (d, *J* = 4.4 Hz, 1H, OC*H*), 6.70 (d, *J* = 8.0Hz, 1H, Ar*H*), 7.03 (d, *J* = 8.0Hz, 1H, Ar*H*), 7.13 (d, *J* = 2.0 Hz, 1H, Ar*H*);

MS (EI): m/z 190 (M^+);

HPLC: The optical purity (er = 95:5) was determined by HPLC (DAICEL OD-H, heptane/isopropanol 98:2, flow rate: 0.5 mL/min, 220 nm, t_r= 13.5 and 14.5 min).

2,2-dimethyl-2,7b-dihydro-1aH-oxireno[2,3-c]chromene:

(*S,S*)-**166c**: $C_{11}H_{12}O_2$ (176.21 g/mol), white solid, purified by column chromatography on silica gel (4% EtOAc in hexanes), 82% yield;



^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (s, 3H, C*H*$_3$), 1.58 (s, 3H, C*H*$_3$), 3.50 (d, *J* = 4.4 Hz, 1H, OC*H*), 3.90 (d, *J* = 4.4 Hz, 1H, OC*H*), 6.81 (d, *J* = 8.2 Hz, 1H, Ar*H*), 6.9 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.22 (t, *J* = 7.9 Hz, 1H, Ar*H*), 7.34 (d, *J* = 7.4 Hz, 1H, Ar*H*);

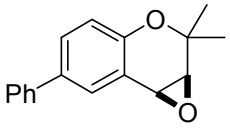
^{13}C NMR (125 MHz, $CDCl_3$) δ 22.6, 25.7, 51.0, 62.9, 73.0, 118.0, 121.0, 129.6, 129.9, 130.3, 152.6;

MS (EI): m/z 176 (M^+);

HPLC: The optical purity (er = 94:6) was determined by HPLC (DAICEL OJ-H, heptane/isopropanol 50:50, flow rate: 0.5 mL/min, 254 nm, t_r = 17.6 and 19.1 min).

(1aS,7bS)-2,2-dimethyl-6-phenyl-2,7b-dihydro-1aH-oxireno[2,3-c]chromene:

(*S,S*)-**166d**: $C_{17}H_{16}O_2$ (252.31 g/mol), white solid, purified by column chromatography on silica gel (2% EtOAc in hexanes), 97% yield;



^{1}H NMR (500 MHz, $CDCl_3$): δ 1.30 (s, 3H, C*H*$_3$), 1.60 (s, 3H, C*H*$_3$), 3.53 (d, *J* = 4.4 Hz, 1H, OC*H*), 3.97 (d, *J* = 4.4 Hz, 1H, OC*H*), 6.88 (d, *J* = 8.3 Hz, 1H, Ar*H*), 7.32 (m, 1H, Ar*H*), 7.42 (m, 2H, Ar*H*), 7.47 (dd, *J* = 2.2, 8.4 Hz, 1H, Ar*H*), 7.53-7.57 (m, 3H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 22.7, 25.7, 51.1, 62.8, 73.3, 118.4, 120.1, 126.7, 126.9, 128.3, 128.8, 129.0, 134.3, 140.4, 152.1;

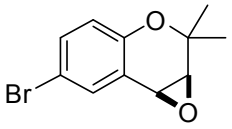
MS (EI): m/z 252 (M^+);

HRMS (EI): calculated for ($C_{17}H_{16}O_2$) 252.115206, found 252.115031;

HPLC: The optical purity (er = 95:5) was determined by HPLC (DAICEL OD-H, heptane/isopropanol 95:5, flow rate: 0.5 mL/min, 220 nm, t_r = 13.9 and 16.8 min).

(1aS,7bS)-6-bromo-2,2-dimethyl-2,7b-dihydro-1aH-oxireno[2,3-c]chromene:

(*S,S*)-**166e**: $C_{11}H_{11}BrO_2$ (255.11 g/mol), white solid, purified by column chromatography on silica gel (2% EtOAc in hexanes), 88% yield;



^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 (s, 3H, C*H*$_3$), 1.58 (s, 3H, C*H*$_3$), 3.49 (d, *J* = 4.4 Hz, 1H, OC*H*), 3.84 (d, *J* = 4.4 Hz, 1H, OC*H*), 6.70 (d, *J* = 8.8 Hz, 1H, Ar*H*), 7.33 (dd, *J* = 2.4, 8.8 Hz, 1H, Ar*H*), 7.45 (d, *J* = 2.4 Hz, 1H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 22.6, 25.6, 50.3, 62.6, 73.4, 112.8, 119.9, 122.1, 132.1, 133.1, 155.9;

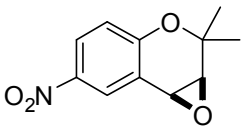
MS (EI): m/z 253 (M^+);

HRMS (EI): calculated for ($C_{11}H_{11}O_2Br_1$) 253.994128, found 253.994258.

HPLC: The optical purity (er = 96:4) was determined by HPLC (DAICEL OJ-H, heptane/isopropanol 50:50, flow rate: 0.5 mL/min, 254 nm, t_r = 12.7 and 17.5 min).

(1aS,7bS)-2,2-dimethyl-6-nitro-2,7b-dihydro-1aH-oxireno[2,3-c]chromene:

(*S,S*)-**166f**: $C_{11}H_{11}NO_4$ (221.21 g/mol), white solid, purified by column chromatography on silica gel (25% EtOAc in hexanes), 98% yield;



^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32 (s, 3H, C*H*$_3$), 1.62 (s, 3H, C*H*$_3$), 3.57 (d, *J* = 4.3 Hz, 1H, OC*H*), 3.98 (d, *J* = 4.3 Hz, 1H, OC*H*), 6.88 (d, *J* = 8.9 Hz, 1H, Ar*H*), 8.15 (dd, *J* = 2.7, 8.9 Hz, 1H, Ar*H*), 8.30 (d, *J* = 2.7 Hz, 1H, Ar*H*);

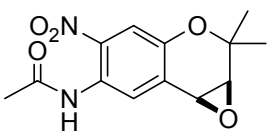
^{13}C NMR (125 MHz, $CDCl_3$): δ 23.1, 25.5, 50.0, 62.1, 75.2, 118.5, 120.3, 125.8, 126.3, 141.4, 158.3;

MS (EI): m/z 221 (M^+);

HRMS (EI) calculated for ($C_{11}H_{11}O_2Br_1$) 221.068774, found 221.068812;

HPLC: The optical purity (er = 98:2) was determined by HPLC (DAICEL OJ-H, heptane/isopropanol 50:50, flow rate: 0.5 mL/min, 254 nm, t_r = 18.6 and 30.4 min).

(1aS,7bS)-N-(2,2-dimethyl-5-nitro-2,7b-dihydro-1aH-oxireno[2,3-c]chromen-6-yl)acetamide: (*S,S*)-**166g**: $C_{13}H_{14}N_2O_5$ (278.26 g/mol), yellow solid, purified by column chromatography on silica gel (50% EtOAc in hexanes), 98% yield;



^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 (s, 3H, C*H*$_3$), 1.59 (s, 3H), 2.28 (s, 3H, C*H*$_3$), 3.54 (d, *J* = 4.2 Hz, 1H, OC*H*), 3.97 (d, *J* = 4.2 Hz, 1H, OC*H*), 7.63 (s, 1H, Ar*H*), 8.79 (s, 1H, Ar*H*), 10.09 (s, 1H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 22.6, 25.46, 25.50, 50.0, 62.7, 74.1, 114.3, 123.5, 128.3, 129.1, 137.3, 147.8, 168.9;

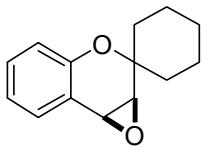
MS (EI): m/z 278 (M^+);

HRMS (EI): calculated for ($C_{13}H_{14}N_2O_5$) 278.090240, found 278.090271;

HPLC: The optical purity (er = 95:5) was determined by HPLC (DAICEL OJ-H, heptane/isopropanol 50:50, flow rate: 0.5 mL/min, 254 nm, t_r = 26.1 and 31.5 min).

(1a'S,7b'S)-1a',7b'-dihydrospiro[cyclohexane-1,2'-oxireno[2,3-c]chromene:

(*S,S*)-**167a**: $C_{14}H_{16}O_2$ (216.28 g/mol), colorless oil, purified by column chromatography on silica gel (5% EtOAc in hexanes), 93%yield;



^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32-2.10 (m, 10H, C*H*$_2$), 3.48 (d, *J* = 4.4 Hz, 1H, OC*H*), 3.86 (d, *J* = 4.4 Hz, 1H, OC*H*), 6.85 (d, *J* = 8.2 Hz ,1H, Ar*H*), 6.92 (t, *J* = 7.4 Hz ,1H, Ar*H*), 7.24 (t, *J* = 7.4 Hz ,1H, Ar*H*), 7.32 (d, *J* = 7.4 Hz ,1H, Ar*H*);

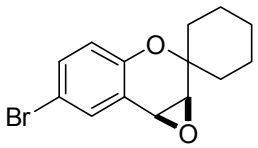
^{13}C NMR (125 MHz, $CDCl_3$): δ 20.9, 21.2, 25.4, 30.3, 34.1, 50.5, 62.5, 73.5, 118.1, 121.0, 129.6, 129.8, 130.2, 152.3;

MS (EI): m/z 216 (M^+);

HPLC: The optical purity (er = 97:3) was determined by HPLC (DAICEL OJ-H, heptane/isopropanol 50:50, flow rate: 0.5 mL/min, 220 nm, t_r = 18.2 and 21.1 min).

(1a'S,7b'S)-6'-bromo-1a',7b'-dihydrospiro[cyclohexane-1,2'-oxireno[2,3-c]chromene]:

(*S,S*)-**167b**: $C_{14}H_{15}BrO_2$ (295.17 g/mol), white solid, purified by column chromatography on silica gel (5% EtOAc in hexanes), 98% yield;



^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33-2.10 (m, 10H, C*H*$_2$), 3.47 (d, *J* = 4.4 Hz, 1H, OC*H*), 3.81 (d, *J* = 4.4 Hz, 1H, OC*H*), 6.75 (d, *J* = 8.6 Hz, 1H, Ar*H*), 6.92 (dd, *J* = 8.6, 2.4 Hz , 1H, Ar*H*), 7.44 (d, *J* = 2.4 Hz ,1H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 20.8, 21.1, 25.3, 30.2, 34.0, 49.8, 62.2, 74.0, 112.8, 119.9, 122.9, 132.1, 133.0, 151.4;

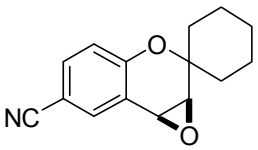
MS (EI): m/z 294 (M^+);

HRMS (EI): calculated for ($C_{14}H_{15}O_2Br_1$) 294.025368, found 294.025559;

HPLC: The optical purity (er = 96.5:3.5) was determined by HPLC (DAICEL OJ-H, heptane/isopropanol 50:50, flow rate: 0.5 mL/min, 254 nm, t_r = 11.3 and 15.8 min).

(1a'S,7b'S)-1a',7b'-dihydrospiro[cyclohexane-1,2'-oxireno[2,3-c]chromene]-6'-carbonitrile:

(*S,S*)-**167c**: $C_{15}H_{15}NO_2$ (241.29 g/mol), white solid, purified by column chromatography on silica gel (10% EtOAc in hexanes), 99% yield;



^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33-2.11 (m, 10H, C*H*$_2$), 3.54 (d, *J* = 4.4 Hz, 1H, OC*H*), 3.88 (d, *J* = 4.4 Hz, 1H, OC*H*), 6.92 (d, *J* = 8.6 Hz, 1H, Ar*H*), 7.53 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar*H*), 7.64 (d, *J* = 2.0 Hz, 1H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 20.7, 21.1, 25.2, 30.8, 33.9, 49.4, 61.9, 75.3, 104.3, 118.8, 119.1, 121.9, 133.8, 134.4, 156.3;

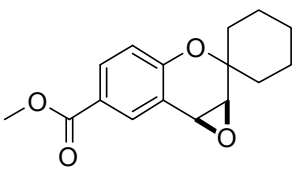
MS (EI): m/z 241 (M^+);

HRMS (EI): calculated for ($C_{15}H_{15}N_1O_2$) 241.110110, found 241.110278;

HPLC: The optical purity (er = 97:3) was determined by HPLC (DAICEL OJ-H, heptane/isopropanol 50:50, flow rate: 0.5 mL/min, 254 nm, t_r = 14.4 amd 20.7 min).

(1a'S,7b'S)-methyl 1a',7b'-dihydrospiro[cyclohexane-1,2'-oxireno[2,3-c]chromene]-6'-carboxylate:

(*S,S*)-**167d**: $C_{16}H_{18}O_4$ (274.31 g/mol), white solid, purified by column chromatography on silica gel (15% EtOAc in hexanes), 97% yield;



^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32-2.12 (m, 10H, CH_2), 3.52 (d, *J* = 4.4 Hz, 1H, OC*H*), 3.89 (s, 3H, OCH_3) 3.92 (d, *J* = 4.4 Hz, 1H, OC*H*), 6.88 (d, *J* = 8.6 Hz, 1H, Ar*H*), 7.94 (dd, *J* = 8.5, 2.2 Hz, 1H, Ar*H*), 8.06 (d, *J* = 2.1 Hz, 1H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 20.8, 21.2, 25.3, 30.7, 34.0, 50.1, 52.0, 62.1, 74.8, 118.1, 120.5, 123.0, 131.6, 132.1, 156.6, 166.5;

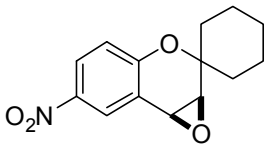
MS (EI): m/z 274 (M^+);

HRMS (EI): calculated for ($C_{16}H_{18}O_4$) 274.120258, found 274.120510;

HPLC: The optical purity (er = 98:2) was determined by HPLC (DAICEL OJ-H, heptane/isopropanol 50:50, flow rate: 0.5 mL/min, 254 nm, t_r = 19.7 and 20.9 min).

(1a'S,7b'S)-6'-nitro-1a',7b'-dihydrospiro[cyclohexane-1,2'-oxireno[2,3-c]chromene]:

(*S,S*)-**167e**: $C_{14}H_{15}NO_4$ (261.27 g/mol), white solid, purified by column chromatography on silica gel (20% EtOAc in hexanes), 99% yield;



^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33-2.13 (m, 10H, CH_2), 3.56 (d, *J* = 4.3 Hz, 1H, OC*H*), 3.95 (d, *J* = 4.3 Hz, 1H, OC*H*), 6.93 (d, *J* = 8.9 Hz, 1H, Ar*H*), 8.15 (dd, *J* = 8.9, 2.7 Hz, 1H, Ar*H*), 8.28 (d, *J* = 2.7 Hz, 1H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$) δ 20.7, 21.1, 25.1, 31.0, 33.9, 49.6, 61.7, 75.9, 118.6, 121.0, 125.8, 126.3, 141.4, 158.1;

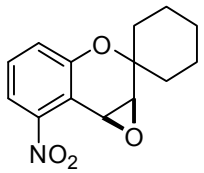
MS (EI): m/z 261 (M^+);

HRMS (EI): calculated for ($C_{14}H_{15}N_1O_4$) 261.100135, found 261.100106;

HPLC: The optical purity (er = 98:2) was determined by HPLC (DAICEL OJ-H, heptane/isopropanol 50:50, flow rate: 0.5 mL/min, 254 nm, t_r = 16.4 and 23.4 min).

(1a'S,7b'S)-7'-nitro-1a',7b'-dihydrospiro[cyclohexane-1,2'-oxireno[2,3-c]chromene]:

(*S,S*)-**167f**: $C_{14}H_{15}NO_4$ (261.27 g/mol), white solid, purified by column chromatography on silica gel (3% EtOAc in hexanes), 98% yield;



^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31-2.08 (m, 10H, CH_2), 3.55 (d, *J* = 4.5 Hz, 1H, C*H*-O), 4.63 (d, *J* = 4.5 Hz, 1H, C*H*-O), 7.12 (d, *J* = 8.2 Hz, 1H, Ar*H*), 7.33 (t, *J* = 8.2 Hz, 1H, Ar*H*), 7.57 (d, *J* = 8.2 Hz, 1H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$) δ 20.8, 21.2, 25.2, 30.7, 33.9, 45.5, 61.9, 74.4, 115.9, 117.6, 123.5, 129.5, 150.9, 153.8;

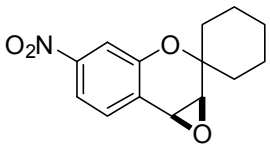
MS (EI): m/z 261 (M^+);

HRMS (EI): calculated for ($C_{14}H_{15}N_1O_4$) 261.100135, found 261.100105;

HPLC: The optical purity (er = 95:5) was determined by HPLC (DAICEL OJ-H, heptane/isopropanol 70:30, flow rate: 0.5 mL/min, 254 nm, t_r = 14.7 and 17.7 min).

(1a'S,7b'S)-5'-nitro-1a',7b'-dihydrospiro[cyclohexane-1,2'-oxireno[2,3-c]chromene]:

(*S,S*)-**167g**: $C_{14}H_{15}NO_4$ (261.27 g/mol), white solid, purified by column chromatography on silica gel (10% EtOAc in hexanes), 98% yield;



^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32-2.13 (m, 10H, C*H*$_2$), 3.56 (d, *J* = 4.3 Hz, 1H, OC*H*), 3.93 (d, *J* = 4.3 Hz, 1H, OC*H*), 7.49 (d, *J* = 8.2 Hz, 1H, Ar*H*), 7.71 (d, *J* = 1.9 Hz, 1H, Ar*H*), 7.79 (dd, *J* = 2.3, 8.2 Hz, 1H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 20.8, 21.1, 25.2, 30.4, 33.9, 49.5, 62.5, 74.9, 113.5, 115.9, 127.9, 130.1, 149.4, 153.0;

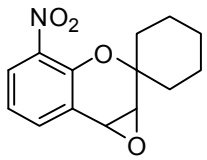
MS (EI): m/z 261 (M^+);

HRMS (EI): calculated for ($C_{14}H_{15}N_1O_4$) 261.100135, found 261.100112;

HPLC: The optical purity (er = 97:3) was determined by HPLC (DAICEL OJ-H, heptane/isopropanol 50:50, flow rate: 0.5 mL/min, 254 nm, t_r = 13.5 and 26.8 min).

4'-nitro-1a',7b'-dihydrospiro[cyclohexane-1,2'-oxireno[2,3-c]chromene]:

167h: $C_{14}H_{15}NO_4$ (261.27 g/mol), white solid, purified by column chromatography on silica gel (5% EtOAc in hexanes), 98% yield;



^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25-1.77 (m, 8H, C*H*$_2$), 1.94 (m, 1H, C*H*$_2$), 2.18 (m, 1H, C*H*$_2$), 3.54 (d, *J* = 4.4 Hz, 1H, C*H*-O), 3.94 (d, *J* = 4.4 Hz, 1H, C*H*-O), 7.00 (dd, *J* = 8.2, 7.4 Hz, 1H, Ar*H*), 7.56 (d, *J* = 7.4 Hz, 1H, Ar*H*), 7.85 (d, *J* = 8.2 Hz, 1H, Ar*H*);

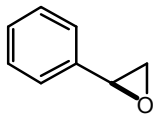
^{13}C NMR (125 MHz, $CDCl_3$) δ 20.5, 20.9, 25.3, 30.7, 34.0, 49.7, 61.9, 76.5, 120.1, 123.7, 126.2, 134.3, 139.7, 146.6;

MS (EI): m/z 261 (M^+);

HRMS (EI): calculated for ($C_{14}H_{15}N_1O_4$) 261.100135, found 261.100108;

HPLC: failed to separate the two enantiomers by HPCL.

(S)-2-phenyloxirane:



(*S*)-**170**: C_8H_9O (120.15 g/mol), colorless oil, purified by column chromatography on silica gel (1% EtOAc in hexanes), 80% yield.

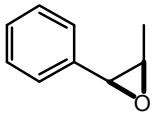
^{1}H NMR (300 MHz, $CDCl_3$): δ 2.72 (dd, *J* = 5.6, 2.6 Hz, 1H, OC*H*$_2$), 3.06 (dd, *J* = 5.6, 4.2 Hz, 1H, OC*H*$_2$), 3.78 (dd, *J* = 4.2, 2.6 Hz, 1H, OC*H*), 7.16-7.29 (m, 5H, Ar*H*);

^{13}C NMR (75 MHz, $CDCl_3$): δ 51.3, 52.5, 125.6, 128.3, 128.6, 137.7;

MS (EI): m/z 120 (M^+);

GC: The optical purity (er = 85:15) was determined by GC (Chiral BGB-178 column, 80 °C/30 min, t_r = 16.3 and 18.5 min).

(2R,3S)-2-methyl-3-phenyloxirane:



(*R,S*)-**89**: $C_9H_{10}O$ (134.18 g/mol), colorless oil, purified by column chromatography on silica gel (1% EtOAc in hexanes), 81% yield.

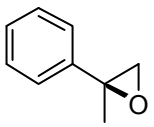
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09 (d, *J* = 5.5 Hz, 3H, C*H*$_3$), 3.34 (m, 1H, OC*H*), 4.06 (d, *J* = 4.2 Hz, 1H, OC*H*), 7.26-7.37 (m, 5H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 12.5, 55.1, 57.5, 126.6, 127.5, 128.0, 135.5;

MS (EI): m/z 134 (M^+);

GC: The optical purity (cis er = 94:6, trans er = 77:23) was determined by GC (Chiral BGB-178 column, $t_{r(trans)}$ = 22.0 and 22.6 min, $t_{r(cis)}$ = 23.3 and 24.5 min).

(S)-2-methyl-2-phenyloxirane:



(*S*)-**172**: $C_9H_{10}O$ (134.18 g/mol), colorless oil, purified by column chromatography on silica gel (2% EtOAc in hexanes), 81% yield;

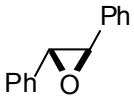
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.72 (s, 3H, C*H*$_3$), 2.80 (d, *J* = 5.4 Hz, 1H, C*H*-O), 2.98 (d, *J* = 5.4 Hz, 1H, C*H*-O), 7.26 (m, 1H, Ar*H*), 7.32-7.39 (m, 5H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 21.8, 56.8, 57.0, 125.3, 127.5, 128.3, 141.2;

GC: The optical purity (er = 68:32) was determined by GC (Chiral BGB-178 column, 80 °C/35 min, t_r = 28.3 and 29.2 min).

(2R,3R)-2,3-diphenyloxirane:

(*R,R*)-**95**: $C_{14}H_{12}O$ (196.24 g/mol), white solid, purified by column chromatography on silica gel (5% EtOAc in hexanes), 94% yield from *E*-stilbene;



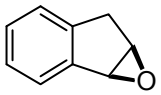
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.87 (s, 2H, C*H*-O), 7.24-7.31 (m, 10H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 62.8, 125.5, 128.3, 128.6, 137.1;

HPLC: The optical purity (er (*Z*) = 80:20, er (*E*) = 55:45) was determined by HPLC (DAICEL OD-H, heptane/isopropanol 80:20, flow rate: 1.0 mL/min, 254 nm, t_r = 12.08 and 15.71 min).

(1aR,6aS)-6,6a-dihydro-1aH-indeno[1,2-b]oxirene:

(*S,R*)-**169a**: C_9H_8O (132.16 g/mol), colorless oil, purified by column chromatography on silica gel (4% EtOAc in hexanes), 53% yield;



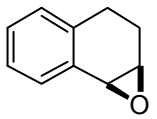
^{1}H NMR (300 MHz, $CDCl_3$): δ 2.97 (dd, *J* = 18.1, 2.7 Hz, 1H, CH_2), 3.21 (d, *J* = 17.6 Hz, 1H, CH_2), 4.13 (t, *J* = 3.0 Hz, 1H, C*H*-O), 4.26 (dd, *J* = 2.8, 1.1 Hz, 1H, C*H*-O), 7.14-7.29 (m, 3H, Ar*H*), 7.49 (dd, *J* = 6.6, 1.7 Hz, 1H, Ar*H*);

^{13}C NMR (75 MHz, $CDCl_3$): δ 34.6, 57.6, 59.1, 125.2, 126.1, 126.2, 128.5, 140.9, 143.5;

GC: The optical purity (er = 90:10) was determined by GC (Chiral BGB-178 column, 80 °C/30 min, t_r = 17.4 and 19.1 min).

(1aR,7bS)-1a,2,3,7b-tetrahydronaphtho[1,2-b]oxirene:

(*S,R*)-**169b**: $C_{10}H_{10}O$ (146.19 g/mol), colorless oil, purified by column chromatography on silica gel (4% EtOAc in hexanes), 67% yield;



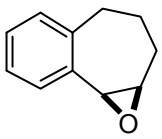
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.76 (ddd, *J* = 13.8, 5.6 Hz, 1H, CH_2), 2.41 (m, 1H, CH_2), 2.55 (dd, *J* = 15.5, 5.5 Hz, 1H, CH_2), 2.78 (ddd, *J* = 14.4, 6.3 Hz, 1H, CH_2), 3.73 (t, *J* = 3.3 Hz, 1H, C*H*-O), 3.85 (d, *J* = 4.1 Hz, 1H, C*H*-O), 7.09 (d, *J* = 7.2 Hz, 1H, Ar*H*), 7.20 (d, *J* = 7.2 Hz, 1H, Ar*H*), 7.24 (m, 1H, Ar*H*), 7.40 (d, *J* = 7.4 Hz, 1H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 21.8, 24.4, 52.8, 55.1, 126.1, 128.4, 128.43, 129.5, 132.5, 136.7;

GC: The optical purity (er = 85:15) was determined by GC (Chiral BGB-178 column, 100°C/15min, 5 °C/min, 140 °C/10 min, t_r = 26.70 and 27.80 min).

(1aR,8bS)-2,3,4,8b-tetrahydro-1aH-benzo[3,4]cyclohepta[1,2-b]oxirene:

(*S,R*)-**169c**: $C_{11}H_{12}O$ (160.21 g/mol), colorless oil, purified by column chromatography on silica gel (4% EtOAc in hexanes), 71% yield;



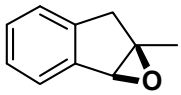
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.53-1.71 (m, 2H, CH_2), 1.85 (m, 1H, CH_2), 2.16 (m, 1H, CH_2), 2.76 (m, 1H, CH_2), 2.88 (m, 1H, CH_2), 3.40 (m, 1H, C*H*-O), 4.02 (d, *J* = 4.2 Hz, 1H, C*H*-O), 7.07 (m, 1H, Ar*H*), 7.24 (m, 2H, Ar*H*), 7.50 (m, 1H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 22.2, 28.0, 32.7, 55.7, 57.0, 126.5, 128.4, 129.3, 131.2, 134.5, 139.5;

GC: The optical purity (er = 84:16) was determined by GC (Chiral BGB-178 column, 80°C/20min, 5 °C/min until 100 °C, 100 °C/10 min, t_r = 28.22 and 28.60 min).

(1S,2R)-2-Methyl-indane-1,2-epoxide:

(*S,R*)-**169d**: $C_{10}H_{10}O$ (146.19 g/mol), colorless oil, purified by column chromatography on silica gel (1% EtOAc in hexanes), 81% yield;



^{1}H NMR (500 MHz, $CDCl_3$): δ 1.70 (s, 3H, CH_3), 2.90 (d, *J* = 18 Hz, 1H, CH_2), 3.16 (d, *J* = 18 Hz, 1H, CH_2), 4.05 (s, 1H, OC*H*), 7.15-7.25 (m, 3H, Ar*H*); 7.45 (d, *J* = 7.3 Hz, 1H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 18.6, 38.7, 65.1, 65.4, 124.9, 125.8, 126.1, 128.3, 141.8, 144.5;

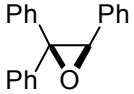
MS (EI): m/z 146 (M^+);

HRMS (EI): calculated for ($C_{10}H_{10}O$) 146.073031, found 146.073168;

GC: The optical purity (er = 92:8) was determined by GC (Chiral BGB-178 column, t_r = 14.1 and 15.4 min).

(R)-2,2,3-triphenyloxirane:

(*R*)-**176**: $C_{20}H_{16}O$ (272.34 g/mol), white solid, purified by column chromatography on silica gel (5% EtOAc in hexanes), 94% yield;



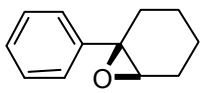
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.25 (s, 1H, C*H*-O), 6.95 (m, 2H, Ar*H*), 7.06 (m, 3H, Ar*H*), 7.1-7.32 (m, 10H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 68.0, 68.6, 126.3, 126.7, 127.5, 127.6, 127.7, 127.76, 127.8, 128.3, 129.2, 130.0, 130.4, 135.4, 135.7, 140.5, 140.9;

HPLC: The optical purity (cis er = 84:16) was determined by HPLC (DAICEL OD-H, heptane/isopropanol 80:20, flow rate: 1.0 mL/min, 254 nm, t_r = 8.04 and 13.24 min).

(1R,6R)-1-phenyl-7-oxabicyclo[4.1.0]heptane:

(*R,R*)-**3**: $C_{12}H_{14}O$ (174.24 g/mol), colorless oil, purified by column chromatography on silica gel (4% EtOAc in hexanes), 90% yield;



^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32 (m, 1H, C*H*$_2$), 1.48 (m, 1H, C*H*$_2$), 1.60 (m, 2H, C*H*$_2$), 2.00 (m, 1H, C*H*$_2$), 2.28 (m, 1H, C*H*$_2$), 3.07 (d, *J* = 2.8 Hz, 1H, C*H*O-), 7.24-7.43 (m, 5H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 19.8, 20.1, 24.7, 28.8, 60.2, 61.9, 125.3, 127.2, 128.3, 142.5;

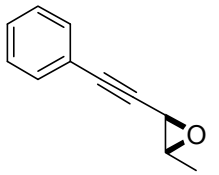
MS (EI): m/z = 174 (M^+);

HRMS (EI) calculated for ($C_{12}H_{14}O_1$) 174.104308 found 174.104468;

GC: The optical purity (er = 86:14) was determined by GC analysis (BGB-176, 120 min at 110 °C, t_r = 87.9 min and 95.2 min).

(2R,3R)-2-methyl-3-(phenylethynyl)oxirane:

(*R,R*)-**174**: $C_{11}H_{10}O$ (158.20 g/mol), colorless oil, purified by column chromatography on silica gel (2% EtOAc in hexanes), 97% yield.



^{1}H NMR (500 MHz, $CDCl_3$): δ 1.39 (d, *J* = 5.1 Hz, 3H, C*H*$_3$), 3.26 (dd, *J* =5.2Hz, 2.1 Hz, 1H, OC*H*), 3.30 (d, *J* = 2.1 Hz, 1H, OC*H*), 7.30-7.46 (m, 5H, Ar*H*);

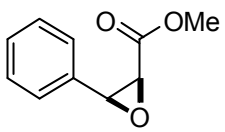
^{13}C NMR (125 MHz, $CDCl_3$): δ 14.8, 46.7, 57.0, 83.5, 85.8, 122.1, 128.3, 128.7, 131.8;

MS (EI): m/z 158 (M^+);

HPLC: The optical purity (cis er = 77.6:22.4, trans er = 96:4, cis:trans = 1:3) was determined by HPLC (DAICEL OD-H, heptane/isopropanol 90:10, flow rate: 0.5 mL/min, 240 nm, $t_{r(cis)}$ = 10.2 and 11.5 min, $t_{r(trans)}$ = 16.3 and 42.2 min).

(2S,3S)-Methyl 3-phenyloxirane-2-carboxylate:

(*S,S*)-**181a**: $C_{10}H_{10}O_3$ (178.18 g/mol), colorless oil, purified by column chromatography on silica gel (5% EtOAc in hexanes), 92% yield;



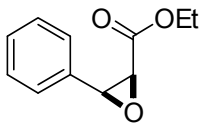
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.55 (s, 3H, C*H*$_3$), 3.85 (d, *J* = 4.6 Hz, 1H, C*H*-O), 4.27 (d, *J* = 4.6 Hz, 1H, C*H*COOMe), 7.30-7.42 (m, Ar*H*, 5H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 52.1, 55.8, 57.5, 125.8, 126.6, 128.1, 128.5, 167.1;

MS (EI): m/z = 178 (M+);

HPLC: The optical purity (cis er = 94:6, trans er = 84:16, cis:trans = 3:1) was determined by HPLC (DAICEL OD-H, heptane/isopropanol 70:30, flow rate: 0.5 mL/min, 220 nm, $t_{r(cis)}$ = 9.6 and 11.3 min, $t_{r(trans)}$ = 13.2 and 16.2 min).

(2S,3S)-ethyl 3-phenyloxirane-2-carboxylate:



(*S,S*)-**181b**: $C_{11}H_{12}O_3$ (192.21 g/mol), colorless oil, purified by column chromatography on silica gel (5% EtOAc in hexanes), 92% yield;

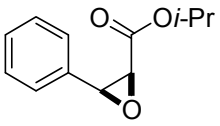
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.02 (t, *J* = 7.1 Hz, 3H, C*H*$_3$), 3.82 (d, *J* = 4.7 Hz, 1H, OC*H*), 4.00 (q, *J* = 7.1 Hz, 2H, C*H*$_2$), 4.27 (d, *J* = 4.7 Hz, 1H, OC*H*), 7.30-7.35 (m, 3H, Ar*H*), 7.42 (dd, *J* = 8.0 Hz, 1.4 Hz, 2H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 13.8, 55.8, 57.4, 61.2, 126.7, 128.0, 128.4, 132.9, 167.0;

MS (EI): m/z 192 (M^+);

HPLC: The optical purity (cis er = 97:3, trans er = 90:10, cis:trans = 3:1) was determined by HPLC (DAICEL OD-H, heptane/isopropanol 97:3, flow rate: 0.5 mL/min, 220 nm, $t_{r(cis)}$ = 13.8 and 19.3 min, $t_{r(trans)}$ = 20.4 and 21.4 min).

(2S,3S)-isopropyl 3-phenyloxirane-2-carboxylate:



(*S,S*)-**181c**: $C_{12}H_{14}O_3$ (206.24 g/mol), colorless oil, purified by column chromatography on silica gel (5% EtOAc in hexanes), 93% yield;

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.99 (d, *J* = 6.2 Hz, 6H, C*H*$_3$), 3.80 (d, *J* = 4.6 Hz, 1H, OC*H*), 4.26 (d, *J* = 4.6 Hz, 1H, OC*H*), 4.85 (h, *J* = 6.2 Hz, 1H, OC*H*), 7.29-7.34 (m, 3H, Ar*H*), 7.42 (dd, *J* = 8.1 Hz, 1.4 Hz, 2H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 21.3, 21.5, 55.8, 57.2, 69.1, 126.7, 128.0, 133.2, 166.4;

MS (EI): m/z 206 (M^+);

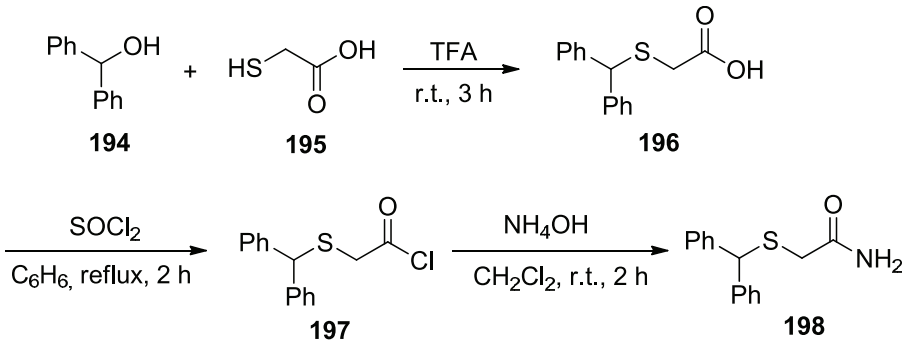
HPLC: The optical purity (cis er = 98:2, trans er = 95:5, cis:trans = 4:1) was determined by HPLC (DAICEL OD-H, heptane/isopropanol 97:3, flow rate: 0.5 mL/min, 210 nm, $t_{r(cis)}$ = 11.6 and 15.5 min, $t_{r(trans)}$ = 12.6 and 13.6 min).

6.7 Asymmetric Oxidation of Sulfides with Mn^{III} and Fe^{III} Ion-Pair Catalysts

6.7.1 Synthesis of Sulfide Substrates and Racemic Sulfoxides

All the sulfides were commercially available except **198**, which was prepared as the following method.

Synthesis of 2-(benzhydrylthio)acetamide (198):



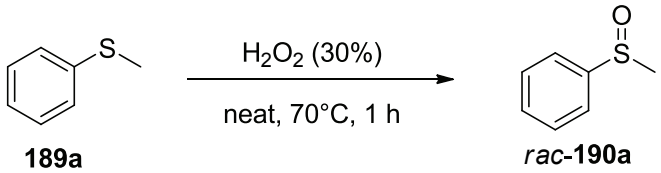
Following the literature procedure,[117]a mixture of benzhydrol (5.00 g, 27.14 mmol) and thioglycolic acid (2.50 g, 27.14 mmol) in trifluoroacetic acid (30 mL) was stirred at room temperature for 4 h. The solvent was then removed under reduced pressure, and 30 mL of water was added. The resulting precipitate was collected by filtration, washed with hexanes, and dried *in vacuo*, affording the acid product as a white solid (6.90 g, 98% yield). The dry solid (2.58 g, 10 mmol) was dissolved in benzene (15 mL), and a solution of thionyl chloride (2.7 mL, 35 mmol) in benzene (5 mL) was added dropwise. After the resulting mixture was refluxed for 2 hours, the solvent was removed under reduced pressure. The oil obtained was diluted with 10 mL of dichloromethane and this solution was added cautiously to a vigorously stirred solution of conc. NH_4OH (30 mL). The mixture was stirred vigorously for additional 2 hours and the layers were then separated. The aqueous mixture was extracted with dichloromethane (2×10 mL). The combined DCM layers were washed with 5% $NaHCO_3$ (3×10mL) and sat. NaCl and dried over Na_2SO_4. The pure compound was obtained as a white solid (2.10 g, 82% yield) by crystallization from isopropyl ether.

198: $C_{15}H_{15}NOS$ (257.35 g/mol);

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.08 (s, 2H, C*H*$_2$), 5.18 (s, 1H, C*H*), 5.78 (s, br, 1H, N*H*$_2$), 6.53 (s, br, 1H, N*H*$_2$), 7.23-7.27 (m, 2H, Ar*H*), 7.31-7.34 (m, 4H, Ar*H*), 7.40-7.42 (m, 4H, Ar*H*);

^{13}C NMR (125 Hz, $CDCl_3$): 35.6, 54.7, 127.7, 128.3, 128.8, 140.2, 171.2.

Synthsis of Racemic Methyl Phenyl Sulfoxide (A Typical Procedure):



189a *rac*-**190a**

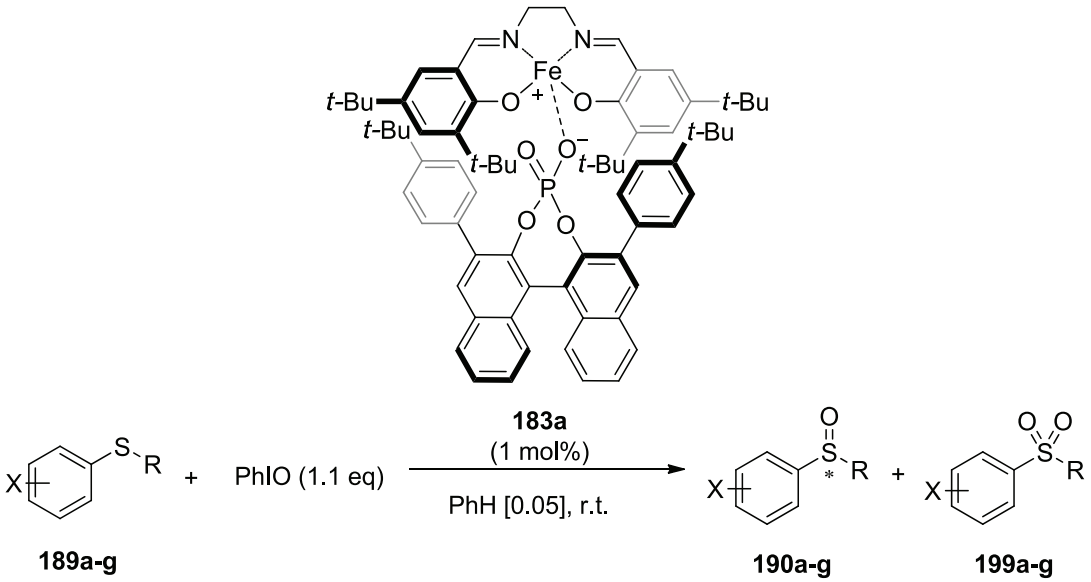
The reaction was carried out according to the literature method.[118] A Schlenk tube was charged with methyl phenyl sulide (1.24 g, 10 mmol) and H_2O_2 (34 % in water, 1 mL, 10 mmol). The reaction mixture was vigorously stirred at 70 °C for 1 h. After the reaction finished (monitored by TLC), the mixture was then cooled to room temperature and extracted with dichloromethane. After drying over anhydrous Na_2SO_4, the organic mixture was concentrated and the resulting liquid was subjected to column chromatography on silica gel (EtOAc, Rf = 0.29). The desired product was obtained as a white solid (1.30 g, 93% yield).

Other racemic sulfoxides were also prepared following this typical protocol. In the cases of solid sulfides, THF or MeOH was added to dissolve the starting materials.

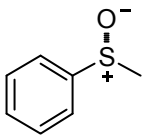
6.7.2 Enanstioselective Oxidation of Sulfides with Ion-Pair Catalysts

Typical Procedure: Phenyl methyl sulfide (12 μL, 0.1 mmol) and the ion-pair catalyst **183a** (1.2 mg, 1.0 μmol, 1.0 mol%) were weighted into a 4-mL vial and dissolved with dry benzene (2 mL), and then iodosobenzene (24 mg, 0.11 mmol) was added in one portion. The resulting mixture was stirred at room temperature. Upon the finish of the reaction (a clear and homogeneous solution will formed due to the completely consumption of PhIO), the reaction mixture was subjected to column chromatography on silica gel (EtOAc), giving the desired

sulfoxide as a white solid. The ratios of sulfoxide/sulfone were determined by the NMR analysis of the crude product. The optical purity of the epoxide was determined by HPLC analysis. The absolute configuration of the epoxide was determined by comparison of the HPLC retention times and the optical rotation with the literature values.[115-116]



(R)-Methyl phenyl sulfoxide:



(R)-**190a**: C_7H_8OS (140.20 g/mol), white solid, purified by column chromatography on silica gel (EtOAc), 93% yield;

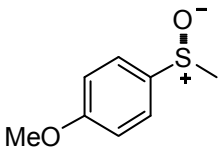
^{1}H NMR (300 MHz, $CDCl_3$): δ 2.73 (s, 3H, C*H*$_3$), 7.50-7.55 (m, 3H, Ar*H*), 7.66 (d, *J* = 7.8 Hz, 2H, Ar*H*);

^{13}C NMR (75 MHz, $CDCl_3$): δ 44.0, 123.5, 129.4, 131.0, 145.7 (d);

MS (EI): m/z 140 (M^+);

HPLC: The optical purity (er = 85:15) was determined by HPLC (DAICEL OB-H, heptane/isopropanol 50:50, flow rate: 0.5 mL/min, 254 nm, t_r= 10.4 and 15.6 min.

(R)-Methyl 4-methoxyphenyl sulfoxide:



(R)-**190b**: $C_8H_{10}O_2S$ (170.23 g/mol), white solid, purified by column chromatography on silica gel (EtOAc/hexanes, 1:1), 90% yield;

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.70 (s, 3H, C*H*$_3$), 3.86 (s, 3H, OC*H*$_3$), 7.03 (dt, *J* = 8.8, 2.0 Hz, 2H, Ar*H*), 7.60 (dt, *J* = 8.8, 2.0 Hz, 2H, Ar*H*);

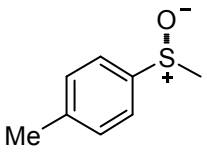
^{13}C NMR (125 MHz, $CDCl_3$): δ 44.0, 55.5, 114.8, 125.5, 136.6, 162.0;

MS (EI): m/z 170 (M^+);

HPLC: The optical purity (er = 73:27) was determined by HPLC (DAICEL OB-H, heptane/isopropanol 50:50, flow rate: 0.5 mL/min, 254 nm, t_r= 12.3 and 20.4 min.

(R)-Methyl 4-methylphenyl sulfoxide:

(R)-**190c**: $C_8H_{10}OS$ (154.23 g/mol), white solid, purified by column chromatography on silica gel (EtOAc/hexanes, 1:1), 92% yield;



^{1}H NMR (500 MHz, $CDCl_3$): δ 2.41 (s, 3H, Ar-CH_3), 2.71 (s, 3H, CH_3), 7.33 (d, *J* = 8.2 Hz, 2H, Ar*H*), 7.54 (d, *J* = 8.2 Hz, 2H, Ar*H*);

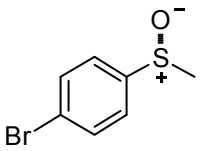
^{13}C NMR (125 MHz, $CDCl_3$): δ 21.4, 44.0, 123.6, 130.1, 141.5, 142.5;

MS (EI): m/z 154 (M^+);

HPLC: The optical purity (er = 83:17) was determined by HPLC (DAICEL OB-H, heptane/isopropanol 50:50, flow rate: 0.5 mL/min, 220 nm, t_r= 9.6 and 15.4 min.

(R)-4-Bromophenyl methyl sulfoxide:

(R)-**190d**: C_7H_7BrOS (219.10 g/mol), white solid, purified by column chromatography on silica gel (EtOAc/hexanes, 1:1), 93% yield.



^{1}H NMR (500 MHz, $CDCl_3$): δ 2.72 (s, 3H, CH_3), 7.52 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.68 (d, *J* = 8.5 Hz, 2H, Ar*H*);

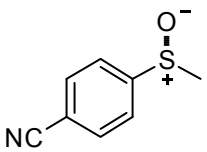
^{13}C NMR (125 MHz, $CDCl_3$): δ 44.0, 125.2, 125.5, 132.6, 144.9;

MS (EI): m/z 220 (M^+);

HPLC: The optical purity (er = 92:8) was determined by HPLC (DAICEL OB-H, heptane/isopropanol 50:50, flow rate: 0.5 mL/min, 254 nm, t_r= 10.7 and 13.1 min.

(R)-4-Cyanophenyl methyl sulfoxide:

(R)-**190e**: C_8H_7NOS (165.21 g/mol), white solid, purified by column chromatography on silica gel (EtOAc), 93% yield;



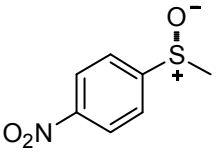
^{1}H NMR (500 MHz, $CDCl_3$): δ 2.77 (s, 3H, CH_3), 7.78 (dt, *J* = 8.6, 2.0 Hz, 2H, Ar*H*), 7.84 (dt, *J* = 8.6, 2.0 Hz, 2H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 43.8, 114.8, 117.7, 124.3, 133.0, 151.5;

MS (EI): m/z 165 (M^+);

The optical purity (er = 97:3) was determined by HPLC (DAICEL OB-H, heptane/isopropanol 50:50, flow rate: 0.5 mL/min, 254 nm, t_r= 23.1 and 29.2 min.

(R)-Methyl 4-nitrophenyl sulfoxide:



(R)-**190f**: $C_7H_7NO_3S$ (185.20 g/mol), white solid, purified by column chromatography on silica gel (EtOAc), 95% yield;

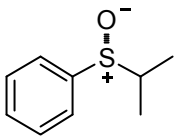
^{1}H NMR (500 MHz, $CDCl_3$): δ 2.80 (s, 3H, C*H*$_3$), 7.84 (dt, *J* = 8.7, 1.9 Hz, 2H, Ar*H*), 7.85 (dt, *J* = 8.7, 1.9 Hz, 2H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 43.9, 124.5, 124.7, 149.5, 153.3;

MS (EI): m/z 185 (M^+);

The optical purity (er = 99:1) was determined by HPLC (DAICEL OB-H, heptane/isopropanol 50:50, flow rate: 0.5 mL/min, 254 nm, t_r= 26.6 and 31.8 min.

(R)-Isopropyl phenyl sulfoxide:



(R)-**190g**: C9H12OS (168.26 g/mol), colorless oil, purified by column chromatography on silica gel (EtOAc/hexanes, 1:1), 93% yield.

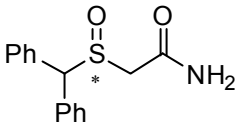
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.14 (d, *J* = 6.9 Hz, 3H, C*H*$_3$), 1.23 (d, *J* = 6.9 Hz, 3H, C*H*$_3$), 2.84 (m, 1H, C*H*), 7.50 (m, 3H, Ar*H*), 7.60 (m, 2H, Ar*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 15.9, 54.5, 125.0, 128.9, 131.0, 141.7;

MS (EI): m/z 168 (M^+);

The optical purity (er = 93:7) was determined by HPLC (DAICEL OB-H, heptane/isopropanol 50:50, flow rate: 0.5 mL/min, 254 nm, t_r= 8.7 and 11.7 min.

2-(Benzhydrylsulfinyl)acetamide:



188a: $C_{15}H_{15}NO_2S$ (273.35 g/mol), white solid, purified by column chromatography on silica gel (EtOAc), 80% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.10 (d, *J* = 14.4 Hz, 1H, C*H*$_2$), 3.40 (d, *J* = 14.4 Hz, 1H, C*H*$_2$), 4.20 (s, 1H, C*H*), 5.62 (s, br, 1H, N*H*$_2$), 7.06 (s, br, 1H, N*H*$_2$), 7.34-7.45 (m, 8H, Ar*H*), 7.49-7.51 (m, 2H, Ar*H*);

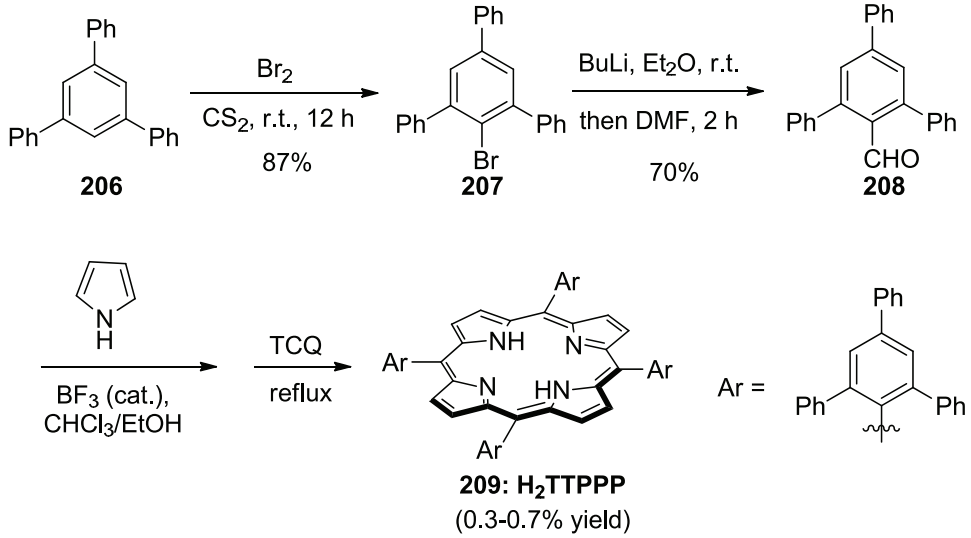
^{13}C NMR (125 MHz, $CDCl_3$): δ 51.2, 71.6, 128.7, 128.8, 128.9, 129.0, 129.3, 129.5, 134.1, 134.3, 166.1;

HPLC: The optical purity (er = 71:29) was determined by HPLC (DAICEL OB-H, heptane/isopropanol 70:30, flow rate: 0.5 mL/min, 220 nm, t_r = 10.9 and 13.3 min).

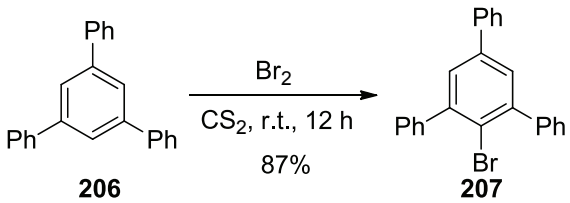
6.8 Epoxidation with Fe^{III}-Porphyrin Phosphate Ion-Pair Catalysts

6.8.1 Synthesis of Porphyrin Ligands

6.8.1.1 Synthesis of 5,10,15,20-Tetrakis(2',4',6'-triphenylphenyl)porphyrin (H_2TTPPP, 209)



Synthesis of 2,4,6-triphenylbromobenzene (207):

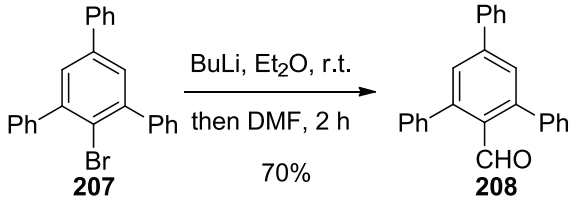


Following the reported method,[128b] to a 2-L three-necked flask fitted with a HBr absorption apparatus and charged with 1 L of CS_2 and 300 g of 1,3,5-triphenybenzene (1.0 mol) was added liquid bromine (108 mL, ca. 2.0 mol) in a slow stream. The color turned dark brown and later to dark red. After about 12 hours, when the GCMS showed the complete conversion of 1,3,5-triphenylbenzene, the reaction mixture was cooled in an ice/water bath. Then aq. $NaSO_3$ (ca. 100 g) was added to the cold reaction mixture with rigorous stirring in several portions till the solution became slightly yellowish. At this point, CS_2 was removed under

reduced pressure and the resulting solid was collected by filtration. The solid was placed in a 2-L beaker, and 1.5-2 L of CH_2Cl_2 was slowly added with stirring, and the insoluble solid was filtered off. The CH_2Cl_2 layer was washed with water and dried over anhydrous sodium sulfate. After removal of CH_2Cl_2, the crude product was obtained as a slightly yellow solid. Recrystallization from CH_2Cl_2/Et_2O afforded the pure product as white crystals (365 g, 96.5% yield). Some yellow impurities in the last portion of the crystals could be washed away with methanol.

207: $C_{24}H_{17}Br$ (385.30 g/mol);
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32-7.50 (m, 13H, Ar*H*), 7.54 (s, 2H, Ar*H*), 7.60-7.63 (m, *J* = 2H, Ar*H*);
MS (EI): m/z 384 and 386 (M^+).

Synthesis of 2,4,6-triphenylbenzaldehyde (208):



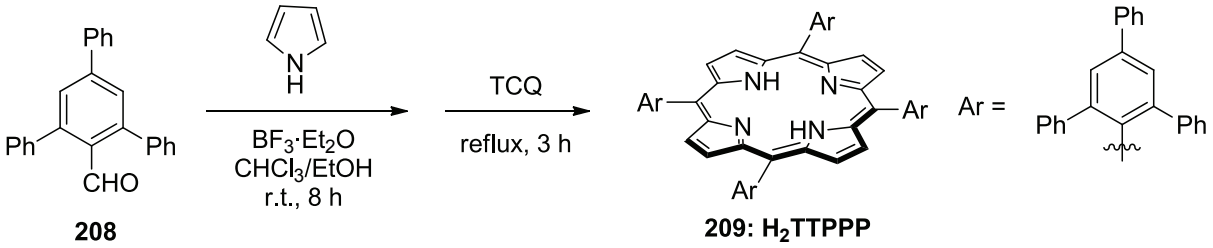
A literature procedure was followed.[129] 2,4,6-Triphenylbromobenzene (100 g, 0.260 mol) was suspended in 1000 mL abs. ether and *n*-butyllithium (135 mL, 2.5 mol/L in hexanes, 0.337 mol) was added slowly over 30 min. After the reaction was stirred at room temperature for 3 h, an excess of DMF (60 mL) was added via an addition funnel. After 2 h at room temperature, the reaction was quenched with H_2O and extracted with ether. The combined ether portions were washed with water, dried with $MgSO_4$, concentrated under reduced pressure, and stored at −20 °C overnight. Off-white crystals formed were collected by filtration (63 g, 72%).

208: $C_{25}H_{18}O$ (334.41 g/mol);
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40-7.50 (m, 13H, Ar*H*), 7.62 (s, 2H, Ar*H*), 7.65-7.70 (m, 2H, Ar*H*), 9.98 (s, 1H, C*H*O);

^{13}C NMR (125 MHz, $CDCl_3$): δ 127.4, 127.7, 128.2, 128.5, 129.0, 129.02, 129.6, 131.6, 139.3, 139.8, 144.2, 145.2, 193.0;

MS (EI): m/z 334 (M^+).

Synthesis of 5,10,15,20-tetrakis(2',4',6'-triphenylphenyl)porphyrin (H_2TTPPP, 209):



A procedure developed by Lindsey[130] was followed with minor changes. A 2-L three-necked round-bottomed flask fitted with a septum, reflux condenser, and argon inlet port was charged with 1.0 L of dry $CHCl_3$, 8 mL of EtOH, 2,4,6-triphenylbenzaldehyde (**208**, 33.4 g, 100 mmol), and freshly distilled pyrrole (8.0 g, 120 mmol). After the solution was purged with argon for 10 min, 1.3 mL of freshly distilled $BF_3{\cdot}OEt_2$ (12 mmol) was added via syringe. The reaction was stirred at room temperature for 7-10 hours. Then TCQ (18 g, 75 mmol) was added to the dark purple solution, and the reaction mixture was gently refluxed for 3 h. The reaction mixture was then cooled to room temperature and 2 mL of triethylamine was added to quench the reaction. The resulting reaction mixture was poured through a short pad of silica gel and washed with $CHCl_3$. After removal of $CHCl_3$, the purple solid was further purified by column chromatography on silica gel (CH_2Cl_2/hexanes, 1:3). To obtain the pure porphyrin, usually 4 or 5 times of column chromatography are required. The pure product was gained as purple crystals in 0.3-0.7 % isolated yields.

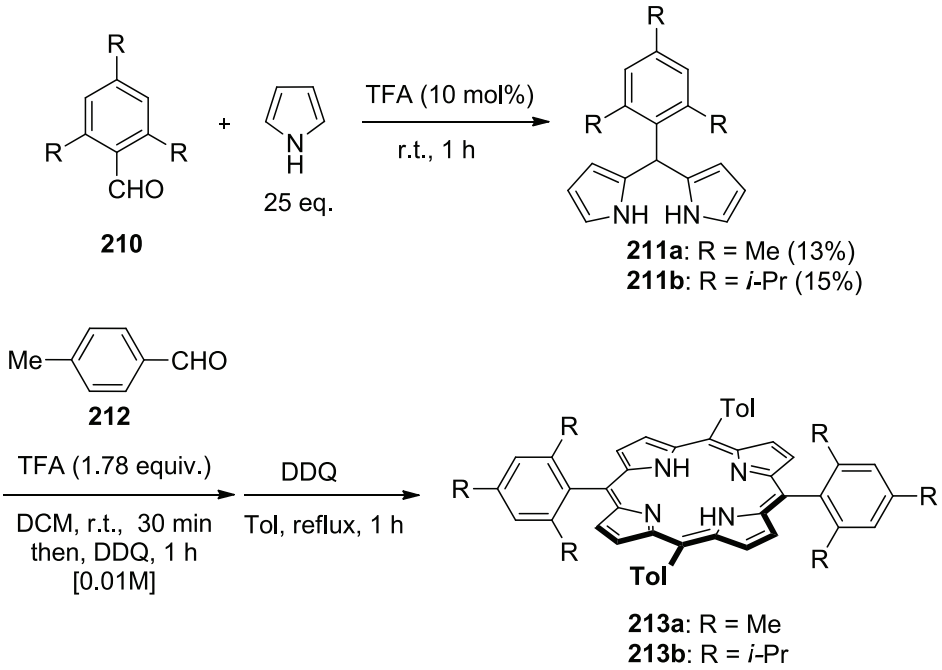
209: $C_{116}H_{78}N_4$ (1527.89 g/mol);

^{1}H NMR (500 MHz, $CDCl_3$): δ -3.34 (s, 2H, N*H*), 6.26 (t, *J* = 7.6 Hz, 16H, Ar*H*), 6.43 (t, *J* = 7.4 Hz, 8H, Ar*H*), 6.61 (d, *J* = 7.5 Hz, 16H, Ar*H*), 7.46 (t, *J* = 7.5 Hz, 4H, Ar*H*), 7.57 (t, *J* = 7.5 Hz, 8H, Ar*H*), 7.93 (m, 16H, Ar*H*), 8.28 (s, 8H, Pyrrole-*H*);

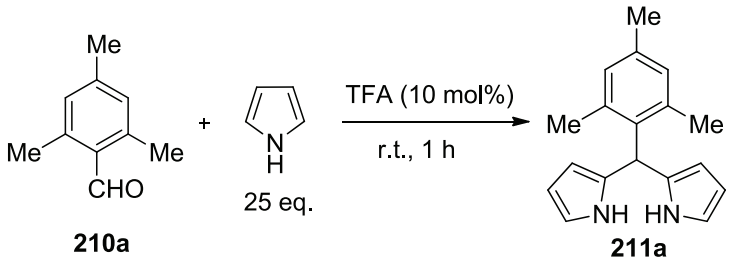
^{13}C NMR (125 MHz, $CDCl_3$): δ 115.7, 125.3, 126.6, 127.3, 127.35, 127.7, 129.0, 129.3, 137.8, 140.6, 141.0, 142.0, 146.0;

UV: λmax (Tol) = 442, 536, 572, 614, 673 nm.

6.8.1.2 Synthesis of 5,15-Dimesityl-10,20-bis(aryl)porphyrin (213a-b)



Synthesis of 5-mesityldipyrromethane (211a):



The method developed by Lindsey[131a] was followed. Pyrrole (50.0 mL, 720 mmol) and mesitaldehyde (**210**, 4.27 g, 28.8 mmol) were added to a 250-mL flask and degassed with a stream of argon for 15 min. TFA (222 µL, 5.00 mmol) was then added, and the solution was stirred under Ar at room temperature for 1 h and then quenched with triethylamine (1.00 mL). Toluene (200 mL) was then added, and the organic phase was washed with brine (2 ×150 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give a black oil. Bulb-to-bulb distillation at 170-180 °C (0.05 mbar) gave the product as yellow crystals (0.99 g, 13% yield, the fraction before 150 °C was discarded).

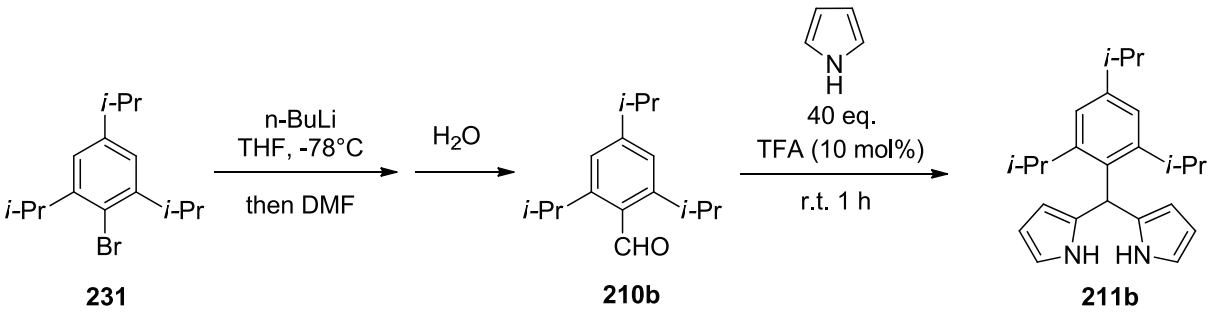
211a: $C_{18}H_{20}N_2$ (265.36 g/mol);

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.06 (s, 6H, C*H*$_3$), 2.28 (s, 3H, C*H*$_3$), 5.93 (s, 1H, C-*H*), 6.01 (s, 2H, Pyrro-*H*), 6.17-6.19 (q, 2H, Pyrro-*H*), 6.67 (s, 2H, Pyrro-*H*), 6.87 (s, 2H, Ar*H*), 7.94 (br s, 2H, N*H*);

^{13}C NMR (125 MHz, $CDCl_3$): δ 20.6, 20.8, 38.3, 106.5, 108.7, 116.2, 130.3, 131.2, 134.5, 136.6, 137.6;

MS (EI): m/z 264 (M^+).

Synthesis of 5-(2,4,6-triisopropylphenyl)dipyrromethane (211b):



231 **210b** **211b**

2,4,6-Triisopropylbenzaldehyde was prepared according to the literature procedure.[162]To a solution of the arylbromide (5.66 g, 20 mmol) in dry THF (40 mL) kept under argon at -78 °C, were added 10 mL of *n*-BuLi (25 mmol, 2.5 M in hexane) over 30 min. The solution was left stirring for additional 30 min, then 2.0 mL of dry DMF (22 mmol) were slowly added dropwise keeping the temperature below -75 °C. After stirring for 15 min the mixture was allowed to warm to -10 °C, then was quenched with water, extracted with ether and dried over anhydrous Na_2SO_4. After removing the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel (hexanes/EtAc, 20/1). The pure product was obtained as a colorless oil (4.64 g, 99%).

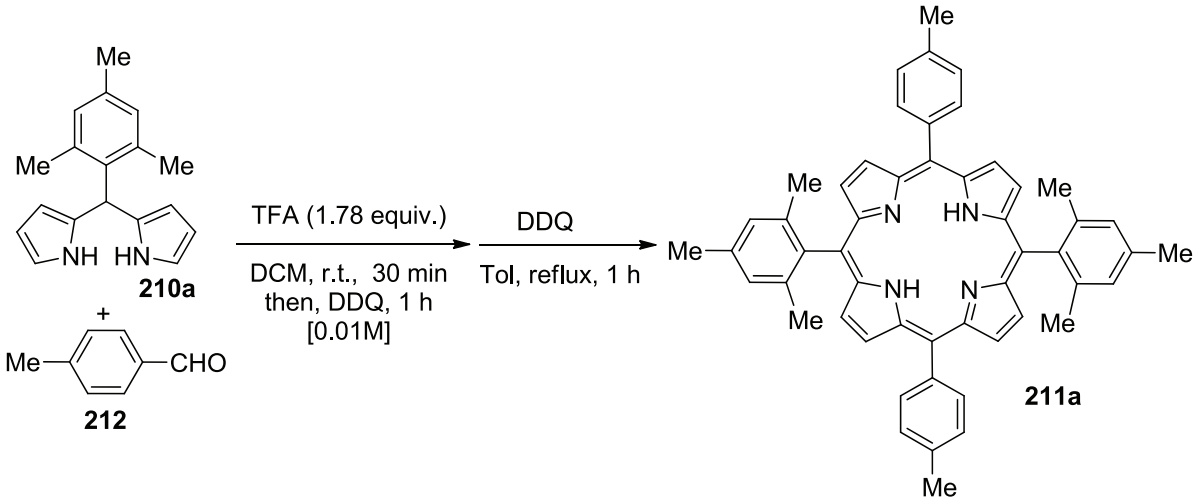
The dipyrromethane was prepared according to the procedure described for 5-mesityldipyrromethane. Distilled pyrrole (35 mL) and 2,4,6-triisopropylbenzaldehyde (4.64 g, 20 mmol) were added to a dry 100-mL flask and degassed with a stream of argon for 15 min. TFA (150 μL, 2.0 mmol) was then added, and the solution was stirred under Ar at room temperature for 1 h and then quenched with 20 mL of aq. NaOH (0.1 M). EtOAc (200 mL) was then added, and the organic phase was washed with brine (2 ×150 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give a black oil. Bulb-to-bulb distillation at 170-180 °C (0.03 mbar) gave a dark brown solid, which was

then submitted to column chromatography (5% EtOAc in hexanes). The pure product was obtained as a yellow solid (0.98 g, 14% yield).

210b: $C_{16}H_{24}O$ (232.36 g/mol);
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 (d, *J* = 6.9 Hz, 6H, C*H*$_3$), 1.27 (d, *J* = 6.9 Hz, 12H, C*H*$_3$), 2.92 (m, 1H, C*H*), 3.60 (m, 2H, C*H*), 7.11 (s, 2H, Ar*H*), 10.66 (s, 1H, C*H*O);
^{13}C NMR (125 MHz, $CDCl_3$): δ 23.7, 24.2, 28.7, 34.7, 121.6, 130.2, 150.4, 153.6, 195.0;
MS (EI): m/z 232 (M^+).

211b: $C_{24}H_{32}N_2$ (348.52 g/mol);
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.65 (br s, 6H, C*H*$_3$), 1.16 (br s, 6H, C*H*$_3$), 1.20 (d, *J* = 7.0 Hz, 6H, C*H*$_3$), 2.82 (m, 1H, C*H*), 2.93 (br s, 1H, C*H*), 3.18 (br s, 1H, C*H*), 5.99 (s, 1H, C*H*), 6.04 (s, 2H, Pyrro-*H*), 6.11 (m, 2H, Pyrro-*H*), 6.57 (d, *J* = 1.4 Hz, 2H, Pyrro-*H*), 6.97 (s, 2H, Ar*H*), 7.87 (br s, 2H, N*H*); the br s peaks are caused by the hindered rotation of 2,6-isopropyl groups;
^{13}C NMR (125 MHz, $CDCl_3$): δ 24.0, 30.1, 34.1, 36.6, 106.2, 108.6, 115.9, 131.9, 132.3, 147.9;
^{13}C NMR (125 MHz, DMSO) δ 24.0, 24.1, 29.4, 33.3, 36.8, 54.8, 105.8, 106.8, 116.4, 132.9, 133.8, 146.0;
MS (EI): m/z 348 (M^+).

Synthesis of 5,15-dimesityl-10,20-bis(4-methylphenyl)porphyrin(211a):

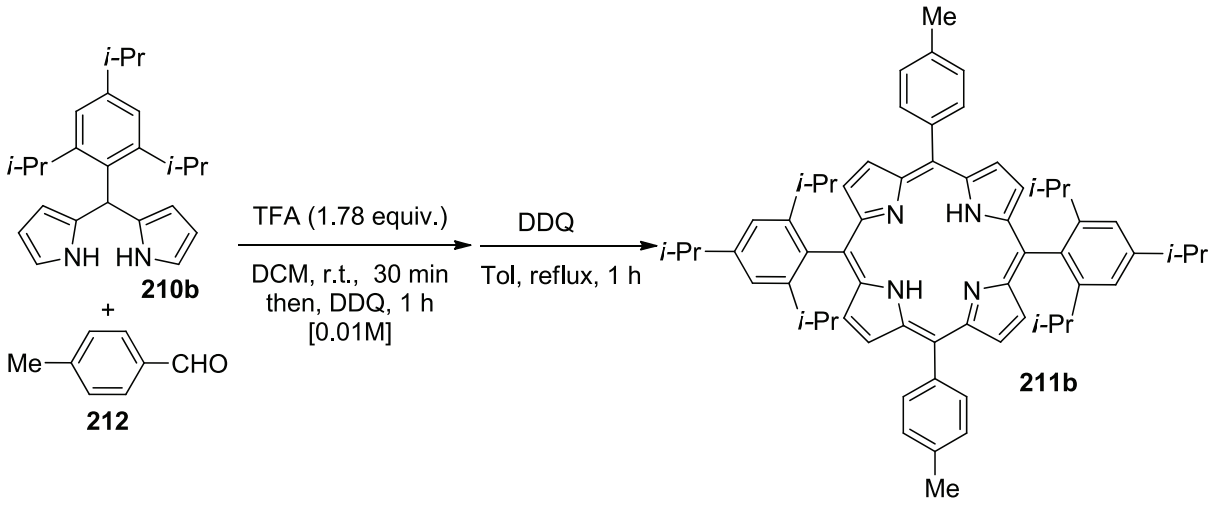


A literature procedure was followed.[131b] 5-Mesityldipyrromethane (528 mg, 2.0 mmol) and *p*-tolualdehyde (249 mg, 2.0 mmol) were dissolved in CH_2Cl_2 (200 mL) in a 500-mL round-

bottomed flask, and then TFA (228 μL, 2.56 mmol) was added slowly over 30 s via a syringe. The reaction was stirred at room temperature. After 30 min, DDQ (450 mg, 2.0 mmol) was added, and the reaction mixture was stirred at room temperature for another 1 h. The reaction mixture was poured onto a short pad of alumina (8 cm) and eluted with CH_2Cl_2 until the eluting solution was pale brown. The solvent was removed under reduced pressure to give a black solid which was dissolved in toluene (40 mL) and heated under reflux for 1 h in the presence of DDQ (450 mg, 2.0 mmol) to oxidize any remaining chlorin. After cooled to room temperature, the entire reaction mixture was passed through a pad of alumina (10 cm) and eluted with CH_2Cl_2 until the purple material had completely eluted. Removal of the solvent gave purple crystals (243 mg, 34%). If the obtained product contained some impurity, one more time of purification by column chromatography on alumina was performed.

211a: $C_{52}H_{46}N_4$ (726.95 g/mol);
^{1}H NMR (500 MHz, $CDCl_3$): δ -2.61 (s, 2H, N*H*), 1.85 (s, 12H, CH_3), 2.64 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 7.29 (s, 4H, Ar*H*), 7.55 (d, *J* = 7.7 Hz, 4H, Ar*H*), 8.11 (d, *J* = 7.7 Hz, 4H, Ar*H*), 8.68 (d, *J* = 4.6 Hz, 4H, Pyrro-*H*), 8.82 (d, *J* = 4.6 Hz, 4H, Pyrro-*H*);
^{13}C NMR (125 MHz, $CDCl_3$): δ 21.5, 21.6, 21.7, 118.1, 119.4, 127.5, 127.7, 128.2, 129.1, 134.5, 137.3, 137.7, 138.6, 139.1, 139.5;
UV: λmax (DCM) = 418, 516, 550, 592, 648 nm.

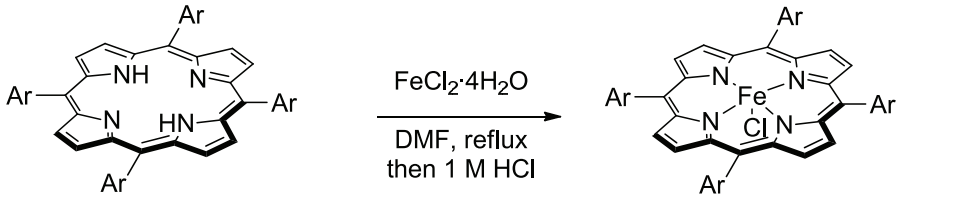
Synthesis of 5,15-bis(2,4,6-triisopropylpheny l)-10,20-bis(4-methylphenyl)porphyrin (211b):



According to the procedure described for **211a**, 5-(2,4,6-triisopropylphenyl)dipyrromethane (697 mg, 2.0 mmol) and *p*-tolualdehyde (249 mg, 2.0 mmol) were dissolved in CH_2Cl_2 (200 mL) in a 500-mL round-bottomed flask, and then TFA (228 µL, 2.56 mmol) was added slowly over 30 s via syringe. The reaction was stirred at room temperature. After 30 min, DDQ (450 mg, 2.0 mmol) was added, and the reaction mixture was stirred at room temperature for another 1 h. The reaction mixture was poured onto a short pad of alumina (8 cm) and eluted with CH_2Cl_2 until the eluting solution was pale brown. The solvent was removed under reduced pressure to give a black solid which was dissolved in toluene (40 mL) and heated under reflux for 1 h in the presence of DDQ (450 mg, 2.0 mmol) to oxidize any remaining chlorin. After cooling to room temperature, the entire reaction mixture was passed through a pad of alumina (10 cm) and eluted with CH_2Cl_2 until the purple material had completely eluted. Removal of the solvent under reduced pressure gave a purple solid. The obtained crude product was further purified by column chromatography on silica gel (CH_2Cl_2/Hexanes, 1:4), giving the pure porphyrin as purple crystals (165 mg, 18%).

211b: $C_{64}H_{70}N_4$ (726.95 g/mol);
^{1}H NMR (500 MHz, $CDCl_3$): δ -2.59 (s, 2H, N*H*), 0.85 (d, *J* = 6.8 Hz, 24H, CH_3), 1.55 (d, *J* = 6.8 Hz, 12H, CH_3), 2.22 (m, 4H, C*H*), 2.69 (s, 6H, CH_3), 3.24 (m, 2H, C*H*), 7.37 (s, 4H, Ar*H*), 7.54 (d, *J* = 7.7 Hz, 4H, Ar*H*), 8.12 (d, *J* = 7.7 Hz, 4H, Ar*H*), 8.68 (d, *J* = 4.6 Hz, 4H, Pyrro-*H*), 8.80 (d, *J* = 4.6 Hz, 4H, Pyrro-*H*);
^{13}C NMR (125 MHz, $CDCl_3$): δ 21.6, 24.2, 24.4, 31.3, 34.5, 117.9, 119.6, 120.1, 127.4, 134.6, 135.9, 137.2, 139.1, 149.2, 149.8;
UV: λmax (DCM) = 420, 518, 553, 594, 650 nm.

6.8.2 Synthesis of Achiral Fe^{III}-Porphyrin Complexes



204a-e

204a: Ar = Ph
204b: Ar = C_6F_5
204c: Ar = Mes
204d: Ar = 2,6-$Cl_2C_6H_3$
204e: Ar = 3,5-$(OMe)_2C_6H_3$

205a-e

205a: Ar = Ph
205b: Ar = C_6F_5
205c: Ar = Mes
205d: Ar = 2,6-$Cl_2C_6H_3$
205e: Ar = 3,5-$(OMe)_2C_6H_3$

Chloroiron(III)porphyrin complexes were prepared following the standard reaction conditions developed by Kobayashi.[132a]

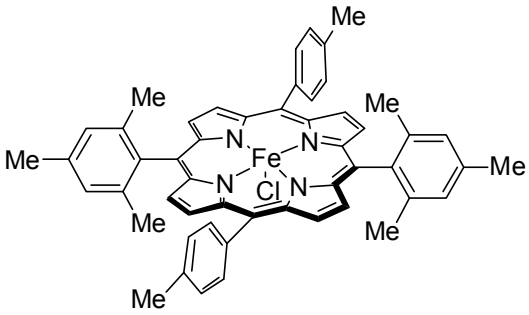
TPP-Fe-Cl (205a, A Standard Procedure): The solution of TPP-H_2 (**204a**, 100 mg, 0.16 mmol) in dimethylformamide (50 mL) was heated to reflux with stirring. $FeCl_2{\cdot}4H_2O$ (960 mg, 30 equiv., in 50 mL of DMF) was added over 30 min. When thin-layer chromatography (alumina) indicated no free porphyrin ligands, the reaction mixture was cooled to room temperature. 200 mL of CH_2Cl_2 was added, and the organic layer was washed three times with 100 mL of 1 M HCl and twice with water. The organic layer was dried over anhydrous sodium sulfate and concentrated to afford a dark violet solid. The solid was further purified by through a short silica gel column (5% EtOH in CH_2Cl_2). 107 mg of brown/purple solid were obtained (94% yield).

Synthesis of ferric porphyrin complex 215a:

The standard reaction conditions were employed. The metallation was carried out using **211a** (140 mg) and $FeCl_2{\cdot}4H_2O$ (1.20 g) in 50 mL of DMF. The reaction completed in 2 hours. Complex **215a** was obtained as a brown solid (146 mg, 93% yield).

215a: $C_{52}H_{44}ClFeN_4$ (816.23 g/mol);

IR (neat): 2916, 2852, 1676, 1612, 1496, 1437, 1381, 1331, 1203, 1181, 1082, 1066, 998, 831, 798, 722 cm^{-1};

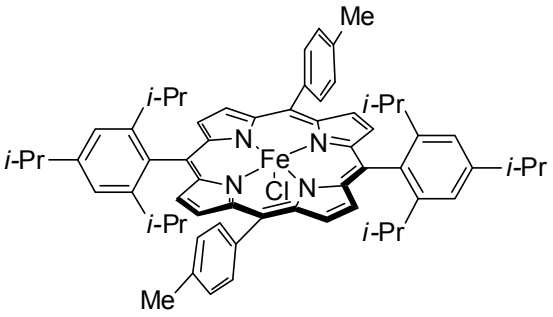


HRMS (ESIpos): calculated for $[C_{52}H_{44}FeN_4]^+$: 780.291160 (M-Cl $^+$), found 780.290985.
UV: λmax (DCM) = 378, 419, 512, 580 nm.

Synthesis of ferric porphyrin complex 215b:

The standard reaction conditions were followed. The metallation was carried out using **211b** (120 mg) and $FeCl_2 \cdot 4H_2O$ (1.20 g) in 50 mL of DMF. The reaction completed in 2 hours. Complex **215b** was obtained as a dark purple/brown solid (120 mg, 91% yield).

215b: $C_{64}H_{68}ClFeN_4$ (984.55 g/mol);

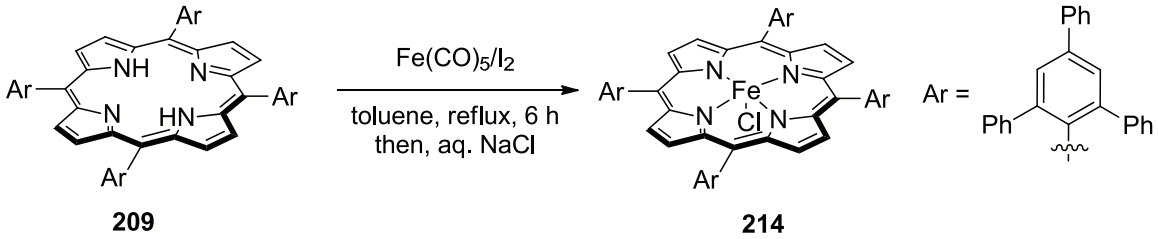


IR (neat): 3024, 2960, 2925, 2866, 1681, 1605, 1494, 1457, 1380, 1361, 1333, 1315, 1202, 1067, 998, 877, 801, 759, 724 cm^{-1};

HRMS (ESIpos): calculated for $[C_{64}H_{68}FeN_4]^+$: 948.479521 (M-Cl $^+$), found 948.478781.

UV: λmax (DCM) = 378, 421, 512, 580 nm.

Synthesis of TTPPP-Fe^{III}-Cl (214):

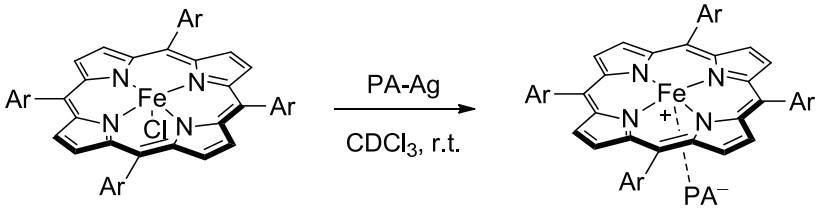


A literature procedure[163] was followed. To a mixture of porphyrin H_2TTPPP (46mg, 30 μmol) and iodine (76 mg, 300 μmol) in toluene (15mL) was added $Fe(CO)_5$ (1.26 mL, 10 mmol) via a syringe under an argon atmosphere. The mixture was refluxed for 6 h and then passed through an alumina short column (CH_2Cl_2). The porphyrin fraction was washed with 5% aqueous HCl solution and dried with NaCl. The crude product was purified by silica gel column (30-100% DCM in hexanes), and the desired ferric porphyrin was obtained as a brown solid (37 mg, 77% yield).

214: $C_{116}H_{76}ClFeN_4$ (1617.17 g/mol);

IR (neat): 3054, 3029, 2924, 2852, 1737, 1595, 1510, 1493, 1442, 1326, 1260, 1237, 1180, 1068, 1029, 996, 885, 798, 752, 694 cm^{-1};
HRMS (ESIpos): calculated for $[C_{116}H_{76}FeN_4]^+$: 1580.540178 (M-Cl^+), found 1580.541383.
UV: λmax (Tol) = 376 (0.3), 445 (1.0), 525 (0.1), 586 (0.003) nm.

6.8.3 Synthesis of Fe^{III}-Porphyrin Phosphate Ion-Pair Catalysts



The anion exchange was carried out in $CDCl_3$ at room temperature or in toluene under reflux conditions, using 1.0 equivalent of phosphoric acid silver salt (PA-Ag). The reaction was monitored by ^{31}P-NMR analysis. When the chloride anion was completely replaced by the phosphate anion, the ^{31}P peak of the silver phosphate would disappear. At this point, the reaction solution was passed through a filter (0.45 μm) to remove AgCl. After removal of the solvent, the desired ferric porphyrin phosphate complex was further dried *in vacuo*.

6.8.4 Asymmetric Epoxidation with Fe^{III}-Porphyrin Phosphate Ion-Pair Catalysts

Typical procedure for the epoxidation with porphyrin Fe^{III} phosphate complexes: 1-octene (12 μL, 0.1 mmol) and the porphyrin ion-pair catalyst (1.2 mg, 1.0 μmol, 1.0 mol%) were dissolved in dry benzene (1 mL), and iodosobenzene (33 mg, 0.15 mmol, 1.5 equiv.) was then added. The resulting mixture was stirred at room temperature. The reaction was followed by GCMS. Purification was performed by column chromatography on silica gel (2% EtOAc in hexanes). The epoxide was obtained as a colorless oil. The optical purity of the epoxide was determined by GC analysis (Lipodex-G, 80 °C/30 min, t_r = 12.0, 13.0 min). The optical purity of the other epoxides was measured according to the methods described in Chapter 6.6.

7 References

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9 Appendix

9.1 List of Abbreviations

abs.	absolute (distilled and dried)
Ac	acetyl
ACDC	asymmetric conteranion directed catalysis
Alk	alkyl group
aq.	aqueous
Ar	aryl group
Boc	*tert*-butyloxycarbonyl
Bn	benzyl
BINOL	1,1'-bi-2-naphthol
BINAP	(1,1’-binaphthalene-2,2’-diyl)bis(diphenylphosphine)
BNP	binapthylphosphoric acids
t-Bu	*tert*-butyl
cat.	catalyst
conc.	concentrate
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DFT	density functional theory
DKR	dynamic kinetic resolution
DMAP	*N*,*N*-dimethylamino pyridine
DMF	*N*,*N*-dimethyl formamide
DMSO	dimethylsulfoxide
dppm	bis(diphenylphosphino)methane
dr	diastereomeric ratio
DTBM-SEGPHOS	5,5’-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4’-bi-1,3-benzodioxole
ee	enantiomeric excess
er	enantiomeric ratio

ent	enantiomer
equiv.	equivalent
Et	ethyl
GC	gas chromatography
h	hour
HPLC	high performance liquid chromatography
HR-MS	high resolution mass spectrometry
Hz	Hertz
KR	kinetic resolution
Me	methyl
Mes	mesityl
min	minute
MS	molecular sieves
Naph	naphthyl
NBD	norbornadiene
NMR	nuclear magnetic resonance
PBAP	*p*-butyl-o-adamantyl phenol
PG	protecting group
Ph	phenyl
PhIO	iodosobenzene
Piv	pivaloyl
PMP	para-methoxy phenyl
PNB	*p*-nitrobenzoate
PO	pyridine-*N*-oxide
ppm	parts per million
4-PPNO	4-phenylpyridine *N*-oxide
Pr	propyl
i-Pr	*iso*-propyl
PTC	phase transfer catalyst
Py	pyridine
quant	quantitative
rac.	racemic
R_f	retention factor
r.t.	room temperature

salen	*N,N'*-bis(salicylidene)ethylenediamine
sat.	saturated
SEGPHOS	4,4'-bi-1,3-benzodioxole-5,5'-diylbis(diphenylphosphane)
TBS	*tert*-butyldimethylsilyl
TCQ	tetrachloro-1,2-benzoquinone
TES	triethylsilyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilyl
TMS	tetramethylsilane
Tol	*p*-tolyl
TPS	triphenylsiyl
TRIP	3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate
TRISPHAT	tris(tetrachlorobenzenediolato) phosphate(V)
TS	transition state
Ts	*p*-toluenesulfonyl
UV	ultraviolet
vs.	versus
Xyl	xylyl, xylenyl
…	

9.2 Erklärung

„Ich versichere, dass ich die von mir vorgelegte Dissertation selbständig angefertigt, die benutzten Quellen und Hilfsmittel vollständig angegeben und die Stellen der Arbeit – einschließlich Tabellen, Karten und Abbildungen –, die anderen Werken im Wortlaut oder dem Sinn nach entnommen sind, in jedem Einzelfall als Entlehnung kenntlich gemacht habe; dass diese Dissertation noch keiner anderen Fakultät oder Universität zur Prüfung vorgelegen hat; dass sie – abgesehen von unten angegebenen Teilpublikationen – noch nicht veröffentlicht worden ist sowie, dass ich eine solche Veröffentlichung vor Abschluss des Promotionsverfahrens nicht vornehmen werde. Die Bestimmungen der Promotionsordnung sind mir bekannt. Die von mir vorgelegte Dissertation ist von Herrn Professor Dr. Benjamin List betreut worden."

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Saihu Liao

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