博士論文

Enantioselective Synthesis of Planar-Chiral Metallocenes and Their Application in Asymmetric Catalysis

（面不斉メタロセン類のエナンチオ選択的合成法の開発と不斉触媒反応への応用）

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Abbriviations

Me	methyl
Et	ethyl
^{n}Bu	*normal*-butyl
^{t}Bu	*tertiary*-butyl
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
Ph	phenyl
Bn	benzyl
Ar	aryl
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl
r.t.	room temperature
cat.	catalyst
L	ligand
DMF	*N*,*N*'-dimethylformamide
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
TRAP	2,2''-bis-[1-(diphenylphosphino)ethyl]-1,1''-biferrocene
PPFA	*N*,*N*-dimethyl-1-[2-(diphenylphosphino)ferrocenyl]ethylamine
BPPFA	*N*,*N*-dimethyl-1-[1,2-bis-(diphenylphosphino)ferrocenyl] -ethylamine
(+)-MTPA-Cl	(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride
ee	enantiomeric excess
de	diastereomeric excess
eq.	equivalent
GPC	gel permeation chromatography
NMR	nuclear magnetic resonance
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
RCM	ring-closing metathesis
ARCM	asymmetric ring-closing metathesis

s	singlet
d	doublet
t	triplet
q	quartet
m	multiplet
br	broad

Chapter I

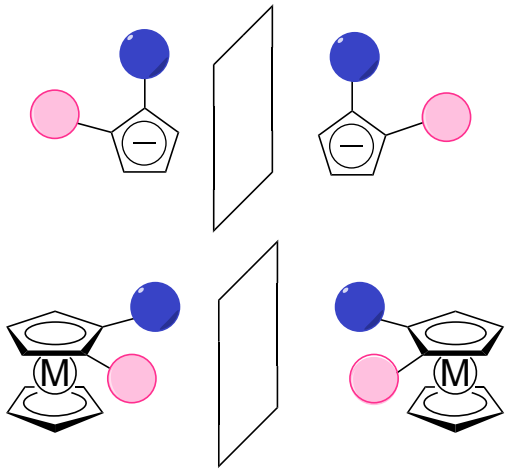
General Introduction

Section 1

Planar-Chiral Metallocenes

When a cyclopentadienyl anion has more than two different substituents in an unsymmetrical fashion, the anion has two enantiotopic faces. Upon the η^5-coordination of the cyclopentadienyl ligand to a metal cation, which discriminates the two enantiotopic faces, this complex becomes chiral. This type of chirality has the special name "**planar chirality**" (Figure 1-1).

Figure 1-1



Planar-Chiral Metallocene

Section 2

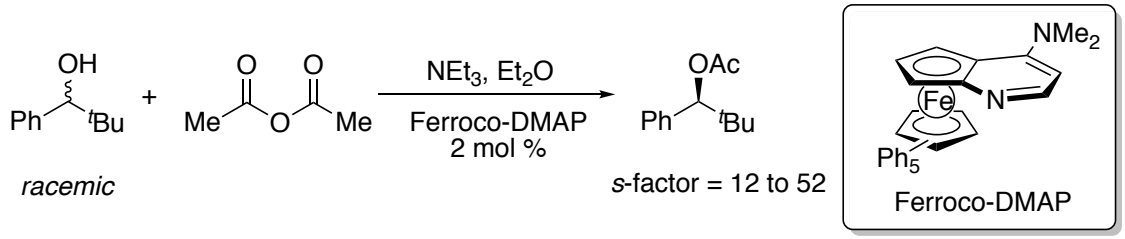
Application of Planar-Chiral Metallocenes

Planar-chiral metallocenes are useful compounds in asymmetric organic synthesis, and various such transition-metal complexes have been used as chiral ligands or chiral catalysts.

1-2-1 Chiral Catalysts

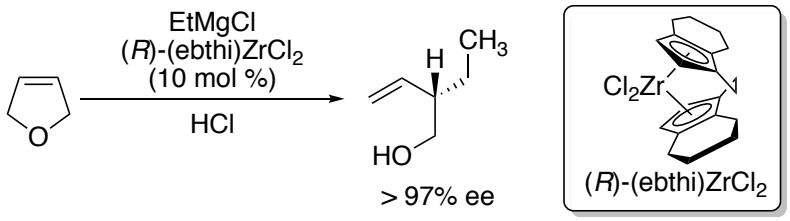
Planar-chiral ferrocene-fused 4-dimethylaminopyridine derivatives (Fc^*-DMAP) were developed by Fu in 1996.[1,2] Fc^*-DMAP has shown excellent enantioselectivity in a wide range of asymmetric reaction, including the acylation of alcohols,[3] cyanosilylation of aldehydes,[4] and addition of alcohols to ketenes. In addition, Fc^*-DMAP affects the kinetic resolution of secondary alcohols with excellent enantioselectivity (Scheme 1-1). The steric bulkiness of the η^5-C_5Ph_5 group in the catalyst is important to achieve high enantioselectivity in this reaction.[5]

Scheme 1-1



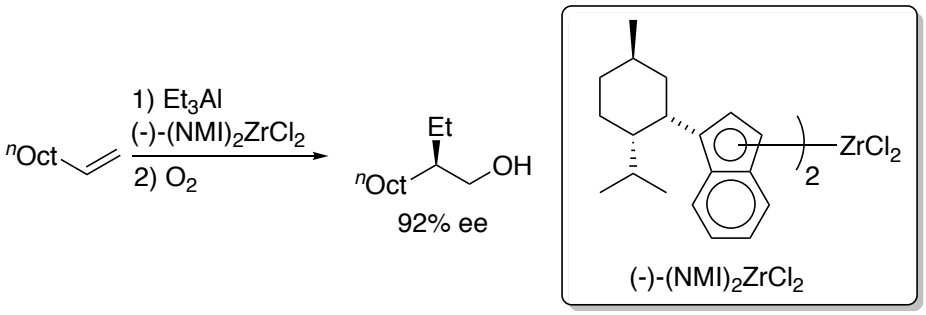
The first highly enantioselective carbomagnesation was reported by Hoveyda in 1993.[6,7] The catalytic asymmetric carbomagnesation reaction of 2,5-dihydrofuran and EtMgCl as an alkylating agent. After treatment with hydrochloric acid, the unsaturated alcohol was obtained with high enantioselectivity in the presence of planar-chiral (ebthi)$ZrCl_2$ complex (Scheme 1-2).

Scheme 1-2



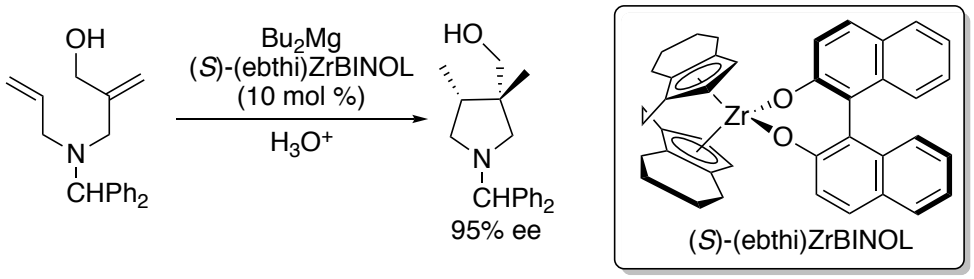
Zirconium-catalyzed asymmetric carboalumination of alkenes (ZACA reaction) was developed by Negishi in 1995.[8] The asymmetric carboalumination of monosubstituted alkenes with Et_3Al in the presence of planar-chiral $(NMI)_2ZrCl_2$ complex (8 mol %) afforded the corresponding primary alcohols with high enantioselectivity after oxidation (Scheme 1-3).[9]

Scheme 1-3



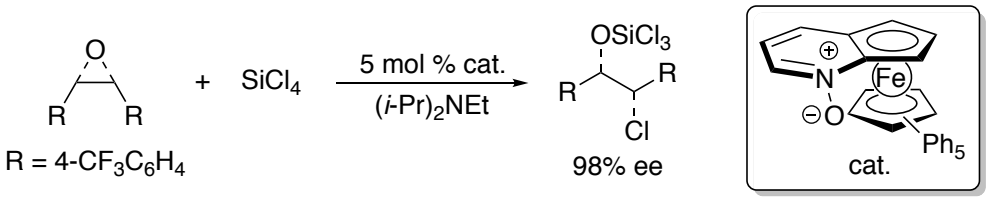
Zirconium-promoted cyclizations of enynes, dienes, and diynes are useful reactions in synthetic organic chemistry.[10] Various natural products have been synthesized using this procedure.[11] For example, the diene shown in the Scheme 1-4 was converted to the heterocyclic product in the presence of dibutylmagnesium and the zirconium complex. The heterocycle was obtained in high enantioselectivity of 95% ee.[12]

Scheme 1-4



A new family of chiral catalyst, planar-chiral pyridine *N*-oxide was designed and synthesized by Fu, et al. in 2001. This unique planar-chiral molecule catalyzed enantioselective desymmetrization of epoxides to afford the corresponding ring-opening products in good yields. The enantiomeric excess of the chlorohydrin shown below was in 98% ee (Scheme 1-5).[13]

Scheme 1-5

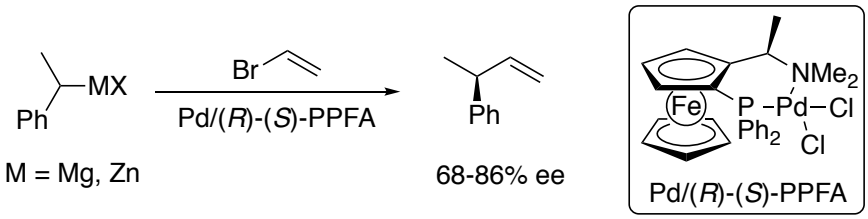


1-2-2 Chiral Ligands

In transition metal-catalyzed asymmetric organic synthesis, chiral phosphines are one of the most commonly used chiral ligands and played important roles.

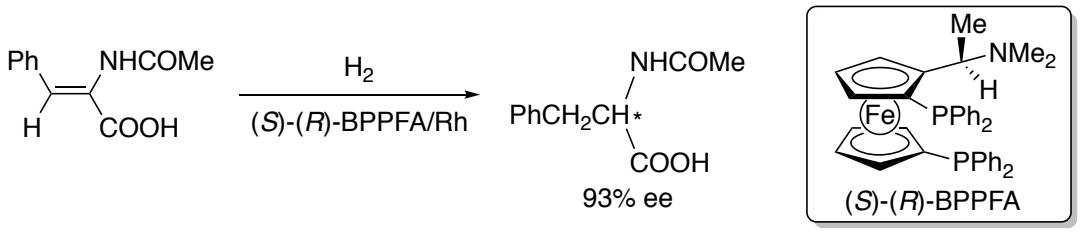
In 1974, Hayashi and Kumada reported the ferrocenylphosphine ligand called PPFA, which was with both planar and central chirality.[14] This chiral ligand was tested in a number of asymmetric reactions, such as hydrogenation, hydrosilylation, cross-coupling reactions, and addition of dialkylzinc to aldehydes, etc.[15-17] For example, the asymmetric cross-coupling reaction of a secondary alkylzinc reagent and a haloalkene in the presence of the palladium catalyst gives the optically active coupling product with moderate to excellent enantioselectivity (Scheme1-6).[18]

Scheme1-6



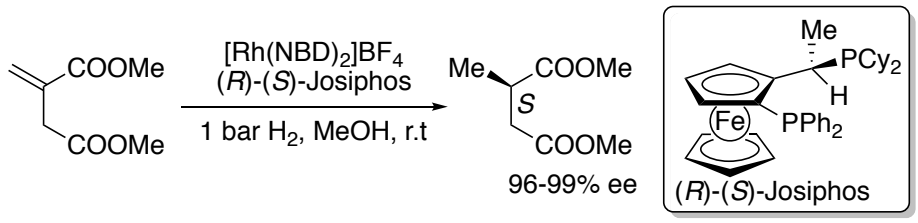
In addition, another well-known chiral ferrocenylphosphine (BPPFA) was reported by Hayashi and Kumada in 1980.[19] This chiral bisphosphine ligand was found to be highly effective for the rhodium-catalyzed asymmetric hydrogenation.[20] A high enantioselectivity was obtained in the hydrogenation of (*Z*)-(α)-acetaminocinnamic acid (Scheme 1-7).

Scheme 1-7



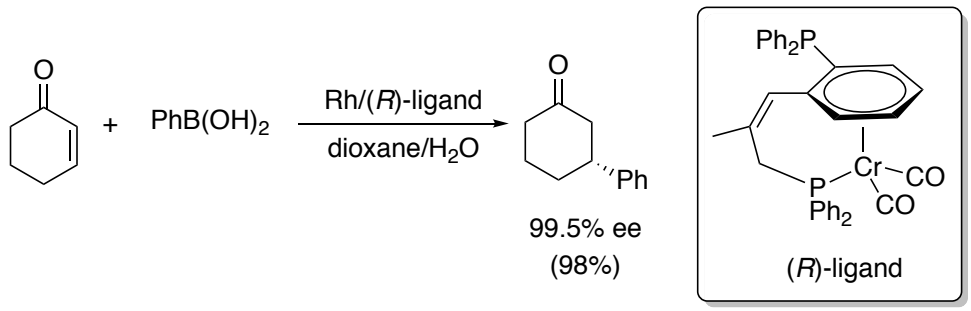
Josiphos ligand was developed by Togni in the 1990s based on the synthetic method for the ferrocenylphosphine ligands previously discovered by Hayashi. This chiral ligand could be used in the rhodium-catalyzed asymmetric hydrogenation and hydroboration as well as in the palladium-catalyzed allylic alkylation reactions. The asymmetric hydrogenation of dimethyl itaconate under 1 bar hydrogen pressure proceeded very efficiently in the presence of the catalyst (1 mol %), and the chiral product was obtained in more than 96% ee and 100% yield (Scheme 1-8).[21]

Scheme 1-8



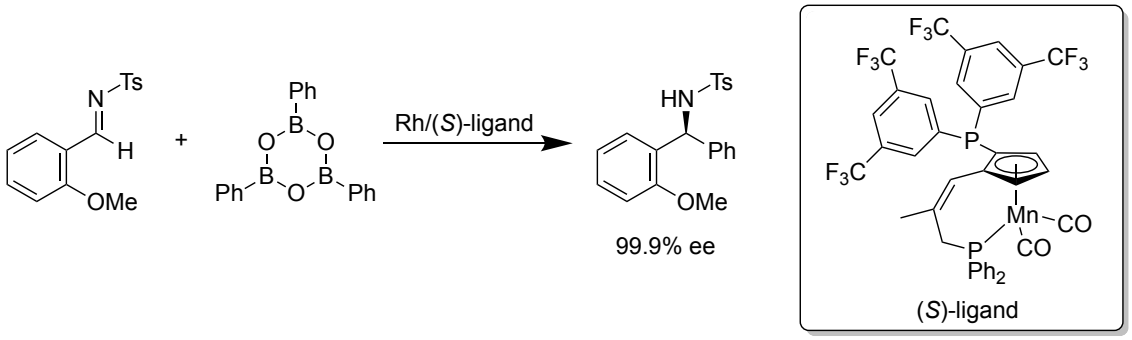
The planar-chiral (π-arene)$Cr(CO)_3$ species were utilized as chiral building blocks in the asymmetric total synthesis of various natural products.[22] Recently, Ogasawara reported the enantioselective synthesis of the planar-chiral phosphine-olefin (π-arene)-chromium ligands. These planar-chiral ligands were examined in the rhodium-catalyzed asymmetric reaction (Scheme 1-9). It was found that the planar-chiral ligands were extremely effective in the rhodium-catalyzed asymmetric 1,4-addition reaction of phenylboronic acid to cyclohexenone,[23] and (*R*)-3-phenylcyclohexanone was obtained in nearly quantitative yield (98%) and excellent enantioselectivity of up to 99.5% ee.[24]

Scheme 1-9



More recently, Ogasawara reported a series of chiral phosphine-olefin ligands, whose chirality was based on a planar-chiral (η^5-cyclopentadienyl)manganese(I) dicarbonyl scaffold. These newly prepared planar-chiral ligands were also suitable for the rhodium-catalyzed addition of an arylboroxine to an *N*-tosyl aldimine.[25] The asymmetric addition product was obtained in 99.9% optical yield (Scheme1-10).[26]

Scheme 1-10



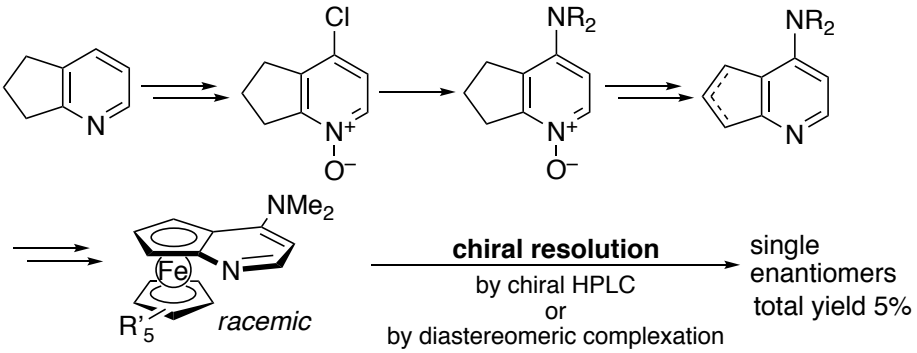
Section 3

Methods of Preparing Single-Enantiomeric Planar-Chiral Metallocenes

1-3-1 Preparation by Optical Resolution

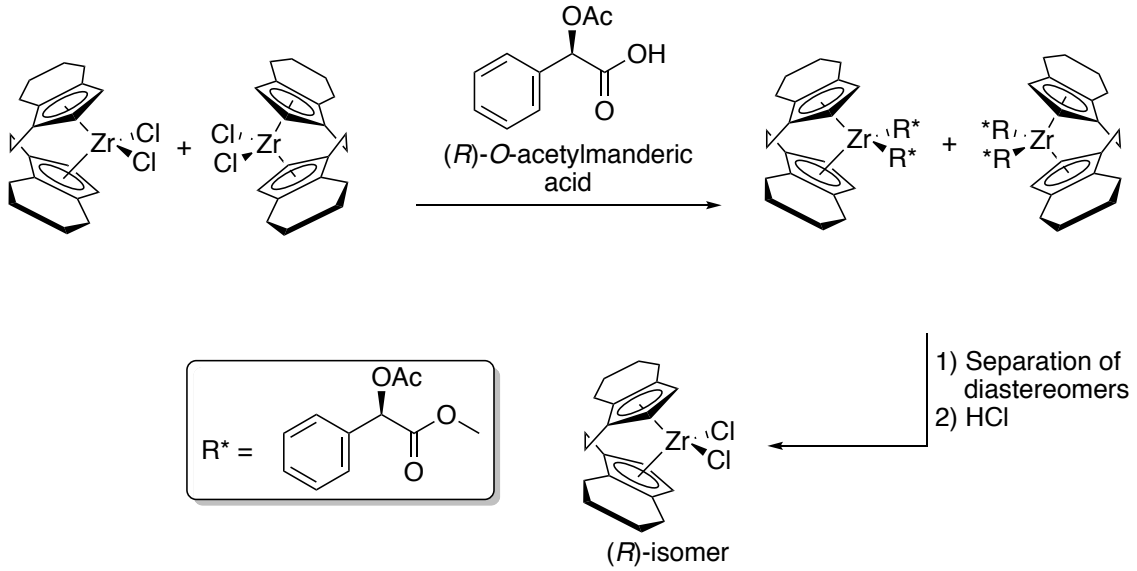
Fc*-DMAP derivatives were prepared from 2,3-cyclopentenopyridine in the racemic forms. The racemic Fc*-DMAP derivatives were separated into their respective enantiomers by the chiral HPLC resolution (Scheme 1-11).[1,2]

Scheme 1-11



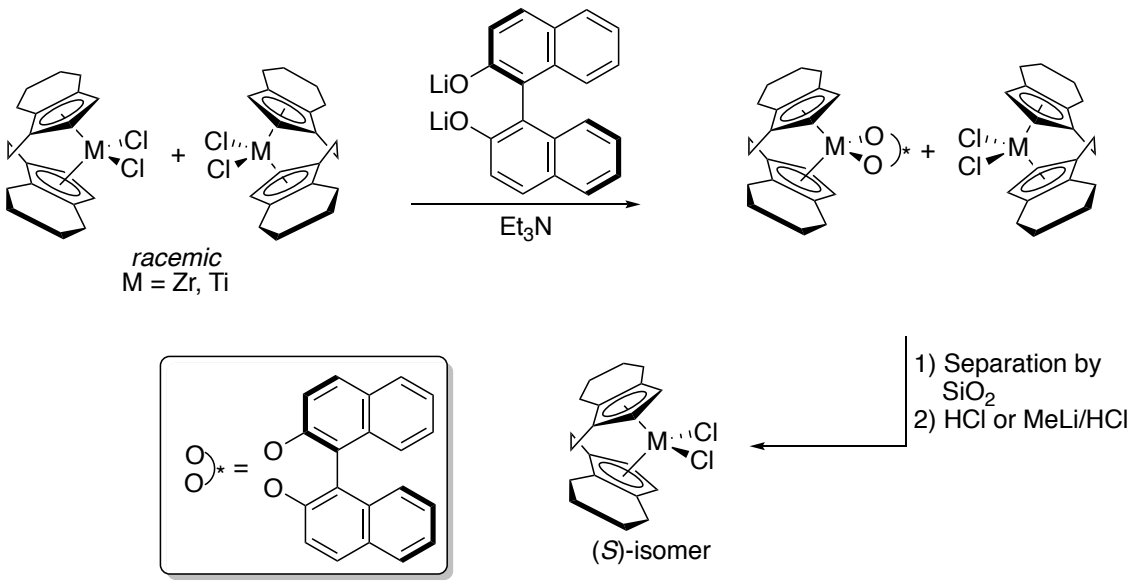
The planar-chiral zirconocene was also separated into the two enantiomers by the optical resolution of the preformed racemic complex. Derivatization of the racemic zirconium dichloride with (*R*)-*O*-acetylmanderic acid yielded diastereomers, which could be separated by recrystallization.[27] After treatment with hydrochloric acid, dichloro-complex was obtained in enantiomerically pure form (Scheme 1-12).

Scheme 1-12



Another well-established optical resolution procedure was using nonracemic binaphtholate salts.[28] In this complexation, only the (*S*)-enantiomer of the chiral metallocene was converted into the (*S*)-binaphthol derivative when a half-equivalent of (*S*)-binaphthol was treated with the racemic complex mixture. The mixture could be separated by silica gel column chromatography, and (*S*)-(ebthi)MCl_2 was obtained in an optically active form after treatment with hydrochloric acid or MeLi/HCl (Scheme 1-13).

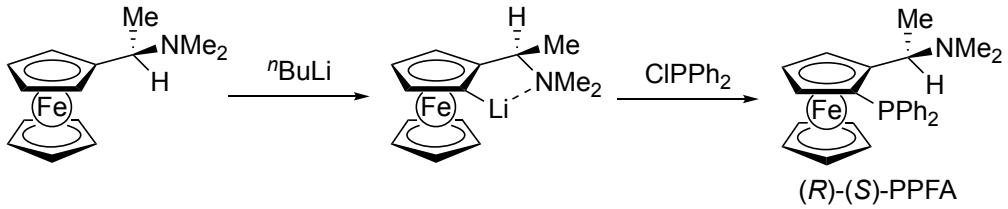
Scheme 1-13



1-3-2 Preparation using Chiral ortho-Directing Groups

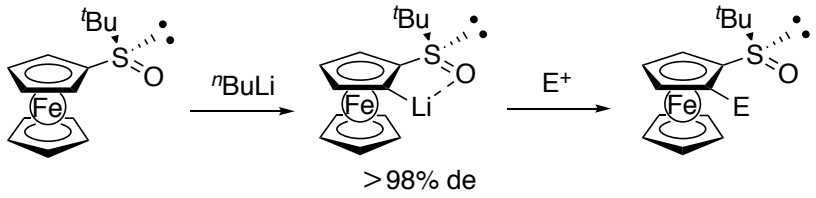
In 1970, Ugi reported that the *ortho*-lithiation of *N*,*N*-dimethylaminoethylferrocene possessing a centrally chiral directing group took place with high diastereoselectivity (92% de), and various planar-chiral ferrocenes were obtained after quenching with appropriate electrophiles. Notably, the planar-chiral ligand (*R*)-(*S*)-PPFA was successfully obtained through this method (Scheme1-14).[14]

Scheme 1-14



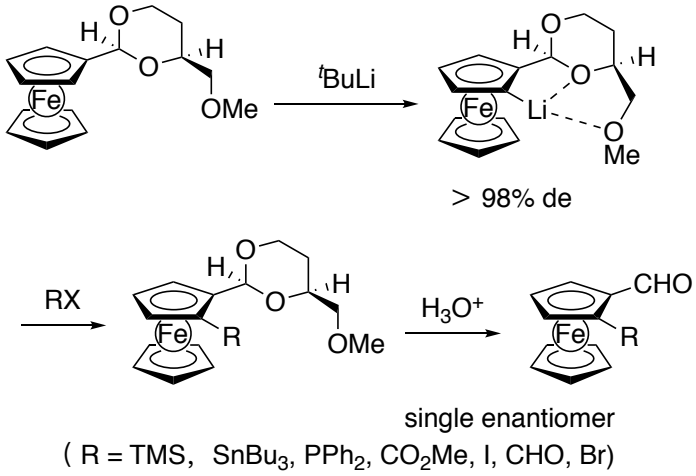
These diastereoselective *ortho*-lithiation reactions have been widely examined in the last two decades. The chiral directing groups, such as α-substituted methylamines, oxazolines, have been reported. In 1993, Kagan developed a general method for the highly diastereoselective *ortho*-lithiation of ferrocenyl sulfoxides (Scheme 1-15).[29] Furthermore, many types of optically active ferrocenes were prepared from this elegant ferrocene sulfoxide.

Scheme 1-15



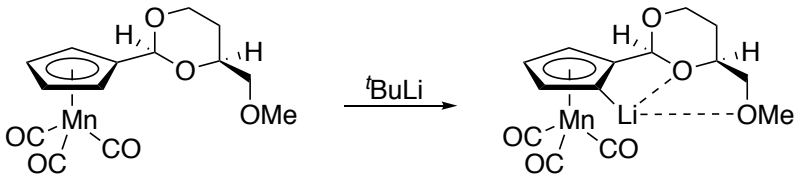
At the same time, the very general and efficient method for the diastereoselective synthesis of planar-chiral 1,2-disubstituted ferrocene derivatives via the *ortho*-lithiation of ferrocenyl acetals was developed by Kagan, et al. The *ortho*-lithiation proceeds with high diastereoselectivity (>98% de). Subsequently, after hydrolysis, various 1,2-disubstituted planar-chiral ferrocene products were obtained in the form of single enantiomers (Scheme 1-16).[30]

Scheme 1-16



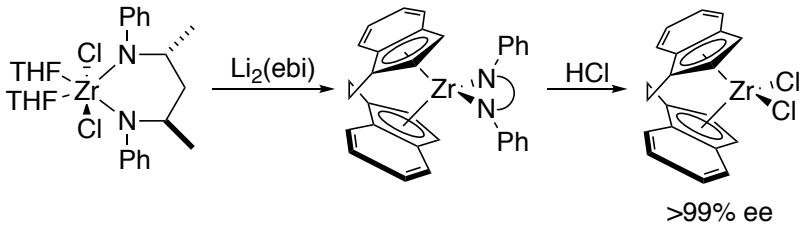
Afterward, similar diastereoselective lithiation of cymantrenyl acetal was reported by Jaouen, et al. in 2004.[31] The lithiation of the chiral acetal showed more than 98% de. Furthermore, this planar-chiral cymantrenyl acetal precursor was utilized as chiral building blocks in the asymmetric total synthesis of various compounds (Scheme 1-17).

Scheme 1-17



The first enantioselective synthesis of planar-chiral zirconocene was reported by Jordan, et al. in 2004. The treatment of chiral zirconium derivative with Li_2(ebi) salt in THF afforded the corresponding zirconocene in 95% yield. The zirconocene was converted to the corresponding enantiomerically pure dichloride (>99% ee) by the reaction with HCl in Et_2O. The chiral diamine could be recovered (Scheme1-18).[32]

Scheme 1-18



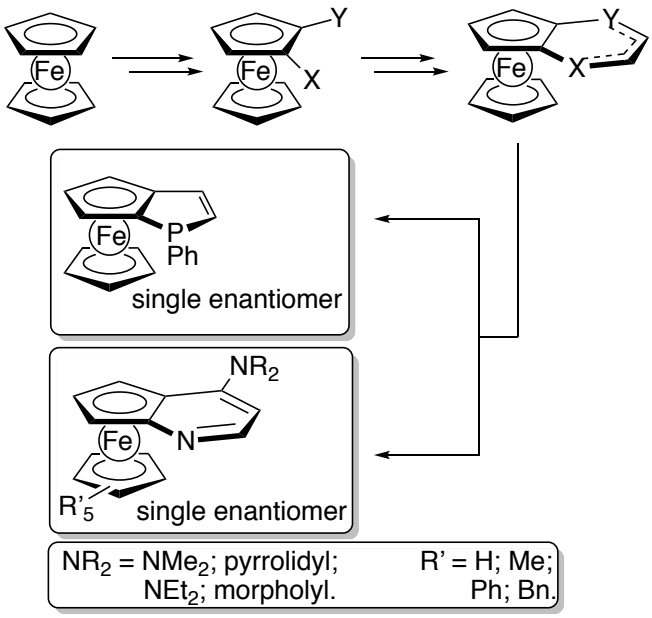
In the methods of diastereoselective/enantioselective *ortho*-lithiation utilizing the chiral auxiliary or optical resolution of racemic compounds, there are several drawbacks: (i) the reaction requires a stoichiometric or more than a stoichiometric amount of chiral reagents, and (ii) chiral HPLC separation columns are expensive. Therefore, it is highly desirable to develop catalytic asymmetric synthetic methods for preparing planar-chiral metallocene derivatives as single enantiomers.

Section 4

Our Strategy

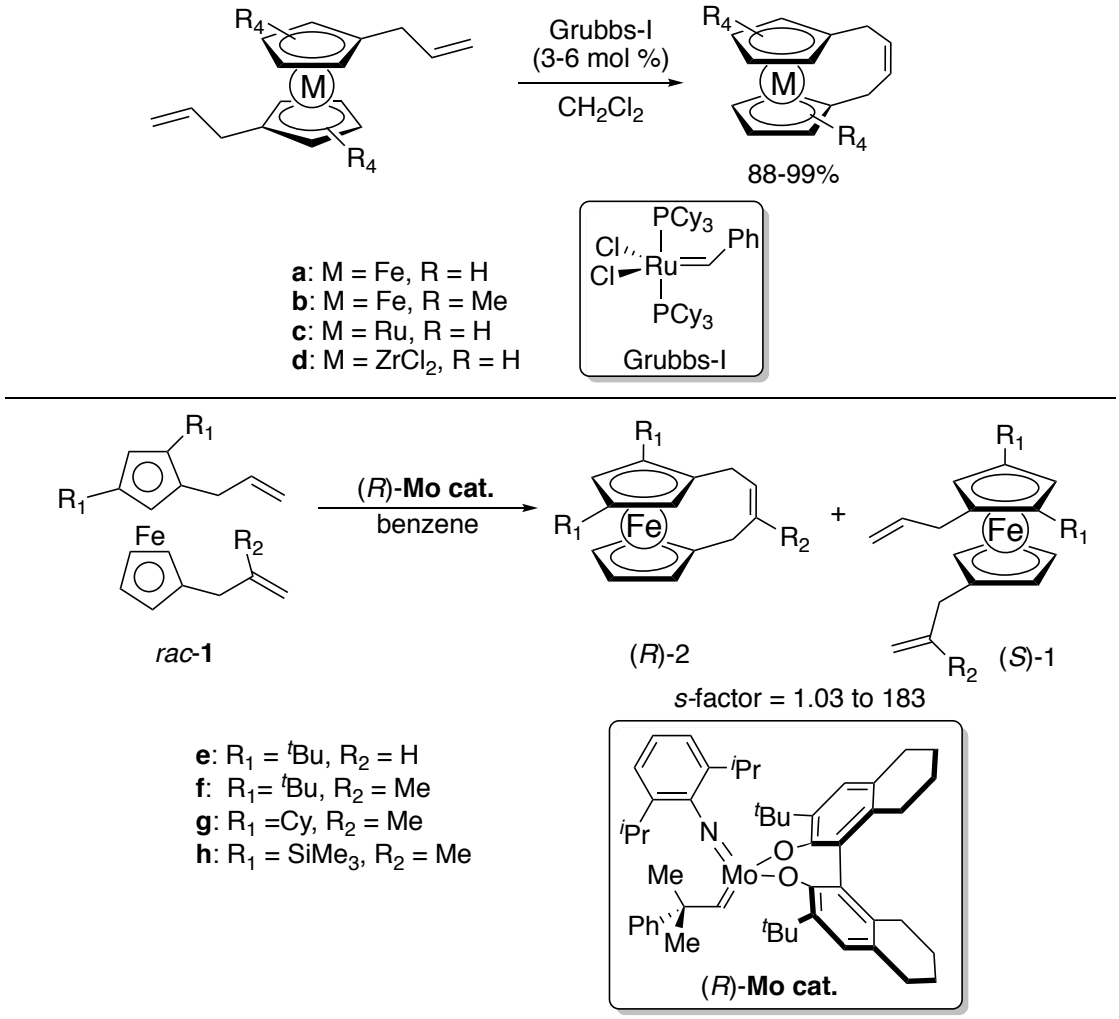
Planar-chiral ferrocene-fused 4-dialkylaminopyridines (Fc*-DAAPs) were developed by Fu in 1996.[1,2] Since then, various of Fc*-DAAPs were prepared and applied in asymmetric organocatalysis. However, the application of these molecules was rather limited probably due to the complicated synthetic protocol. Ogasawara's group focused on enantioselective synthesis of various planar-chiral Fc*-DAAPs in enantiomerically pure forms. Recently, Ogasawara developed a method for preparing various planar-chiral metallocenes in the form of single enantiomers. Their synthetic strategies are: (i) introduction of proper substituents at the 1- and 2-positions of a ferrocene platform with controlling its planar chirality, and (ii) construction of heterocyclic compounds by a ring-closure reaction between the two substituents at 1- and 2-ferrocenyl positions. This method could be applicable to the synthesis of various planar-chiral metallocenes, such as planar-chiral phospholes and planar-chiral Fc*-DAAPs (Scheme 1-21).[33]

Scheme 1-21



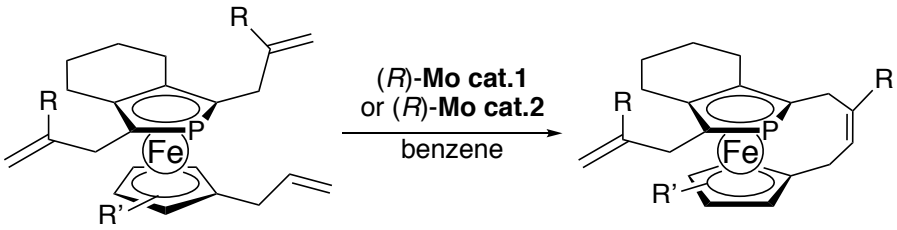
Since the discovery of the Grubbs' ruthenium catalyst,[34] olefin metathesis has become a powerful tool in organic synthetic chemistry. In the previous report, the 1,1'-diallylmetallocene served as a good substrate for the RCM reaction in the presence of Grubbs-I catalyst. The ring-closing metathesis reaction afforded the corresponding bridged metallocenes in high yields (Scheme 1-22, top).[35] In addition, the metathesis reactions were expended to the preparation of bridged planar-chiral ferrocenes. The asymmetric ring-closing metathesis of *rac*-**1** in the presence of a chiral molybdenum catalyst (5-10 mol %) proceeded to give (*R*)-bridged product and (*S*)-recovered substrate (*kinetic resolution*, Scheme 1-22, bottom).[36]

Scheme 1-22



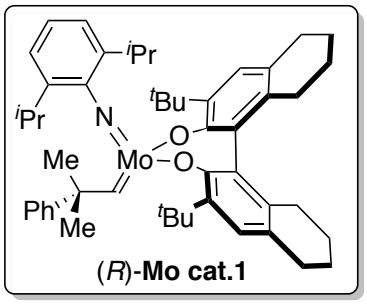
Various optically active planar-chiral ferrocenes are obtained on the basis of the resolution of racemates or diastereoselective metalation using chiral directing groups.[37] Recently, the catalytic enantioselective desymmetrization of planar-prochiral phosphaferrocenes by the Mo-catalyzed asymmetric ring-closing metathesis was reported by Ogasawara. The corresponding planar-chiral bridged phosphaferrocenes were obtained in high yields of up to 99% ee (Scheme 1-23).

Scheme 1-23

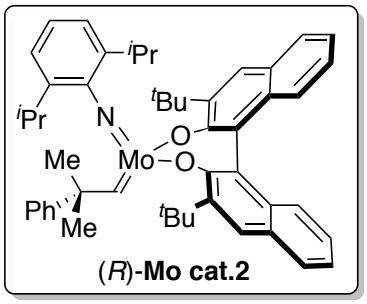


a: R = Me, R' = H
b: R = Me, R' = Me

substrate	temp.	(*R*)-Mo cat	product
a	23 ℃	cat.1	99% ee, 72%
b	60 ℃	cat.2	99% ee, 83%



(*R*)-**Mo cat.1**



(*R*)-**Mo cat.2**

Section 5

Outline of This Thesis

Recently, Ogasawara's group has developed various synthetic methods for preparing various planar-chiral metallocenes in the form of single enantiomers. In this thesis, these methods were applied to prepare two types of planar-chiral metallocenes. In addition, Ogasawara's group also developed methods for catalytically synthesizing planar-chiral "bridged" metallocenes by the Mo-catalyzed asymmetric ring-closing metathesis (ARCM). The usefulness of their methods was extended to the catalytic asymmetric synthesis of other planar-chiral transition-metal complexes.

In my doctoral study, I focused on two key areas. In Chapter II, I would like to discuss the enantioselective synthesis of various Fc^*-DAAPs as single enantiomers. The newly developed process is much shorter and less costly than the previous synthetic method, since it does not use expensive noble metal catalysts. More importantly, the new synthetic method can provide sterically demanding analogous Fc^*-DAAPs which have an $(\eta^5\text{-}C_5Ph_5)Fe$ or $(\eta^5\text{-}C_5Bn_5)Fe$ substructure as well as cymantrene-fused DAAPs, these compounds have been prepared for the first time through this study. The application of the prepared planar-chiral Fc^*-DAAPs was also described.

In Chapter III, I will discuss the design and synthesis of a ferrocene-based planar-chiral phosphorus Brønsted acid. Based on our previous synthetic strategy, the preparation of planar-chiral cyclic phosphonic acid was accomplished. The synthesis of phosphonic acid started with the Kagan's acetal, which could be *ortho*-lithiated in the highly diastereoselective fashion (>99% de), and the usual organic transformations afforded the corresponding products in each step at high yields. The cyclization could provide the desired planar-chiral cyclic phosphonic acid in high yield in the form of single enantiomer.

In Chapter IV, I would like to discuss the *catalytic asymmetric synthesis* of planar-chiral *anza*-zirconocenes by the molybdenum-catalyzed ARCM. The reaction afforded the corresponding planar-chiral bridged products with extremely high enantioselectivity of up to 98% ee. Furthermore, the prepared optically active planar-chiral *anza*-zirconocenes could be used as chiral catalysts in asymmetric carbometalations. Planar-chiral zirconium-catalyzed asymmetric carbomagnesiation showed good performance in high yield and moderate enantioselectivity.

[1] Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 7230.

[2] Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492.

[3] (a) Pyridine: Verley, A.; Bölsing, F. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 3354. (b) 4-(Dimethylamino)pyridine: Steglich, W.; Höfle, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981. (c) Litvinenko, L. M.; Kirichenko, A. I. *Dokl. Akad. Nauk SSSR, Ser. Khim.* **1967**, *176*, 97. (d) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

[4] (a) Evans, D. A.; Wong, R. Y. *J. Org. Chem.* **1977**, *42*, 350. (b) Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Lett.* **1991**, 537.

[5] Abbenhuis, H. C. L.; Burckhardt, U.; Gramlich, V.; Martelletti, A.; Spencer, J.; Steiner, I.; Togni, A. *Organometallics* **1996**, *15*, 1614.

[6] Morken, J. P.; Didiuk, M. T.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993***, 115*, 6997.

[7] Didiuk, M. T.; Johannes, C. W.; Morken, J. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995***, 117*, 7097.

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Chapter II

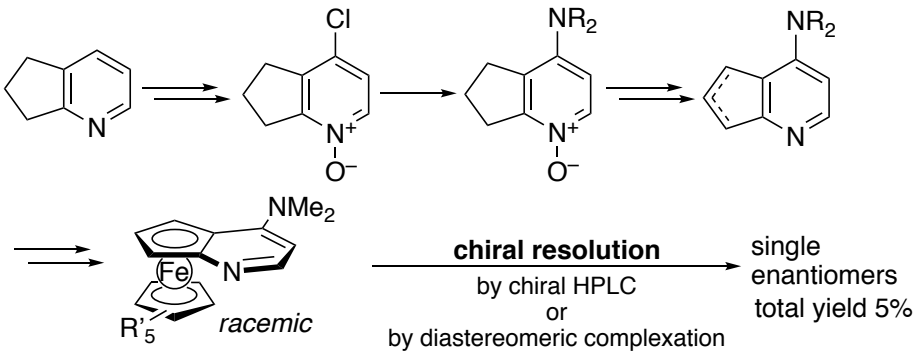
Enantioselective Synthesis of Ferrocene-Fused Planar-Chiral 4-(Dialkylamino)pyridine Derivatives and Their Application in Asymmetric Catalysis

Section 1

Introduction for Chapter II

Planar-chiral metallocenes are useful templates in organometallic chemistry and have been applied as asymmetric catalysts and chiral ligands in many ways. Notable examples of utilizing the architectures of planar-chiral metallocenes are a series of planar-chiral ferrocene-fused 4-dialkylaminopyridines derivatives (Fc*-DAAPs) which were developed by G. C. Fu since 1996. Fu have been exploring the utility of planar-chiral Fc*-DAAP derivatives as catalysts for a range of transformations, including an asymmetric synthesis of β-lactams, asymmetric addition of amines to ketenes. Fc*-DAAPs showed excellent enantioselectivity in a variety of asymmetric synthesis. However, the applications of these elegant molecules are rather limited probably due to the complicated synthesis as well as necessity of the enantiomeric resolution (Scheme 2-1).[1] Later, Fu reported an improved synthetic route of Fc*-DAAPs, but the modified method also included an optical resolution process of the racemates.[2] Furthermore, the long-sequential synthesis as well as the independent optical resolution were indispensable for the preparation of different Fc*-DAAP derivatives. It seems that this synthetic limitation might be a major reason to hamper the applications of the unique chiral organocatalysts.

Scheme 2-1

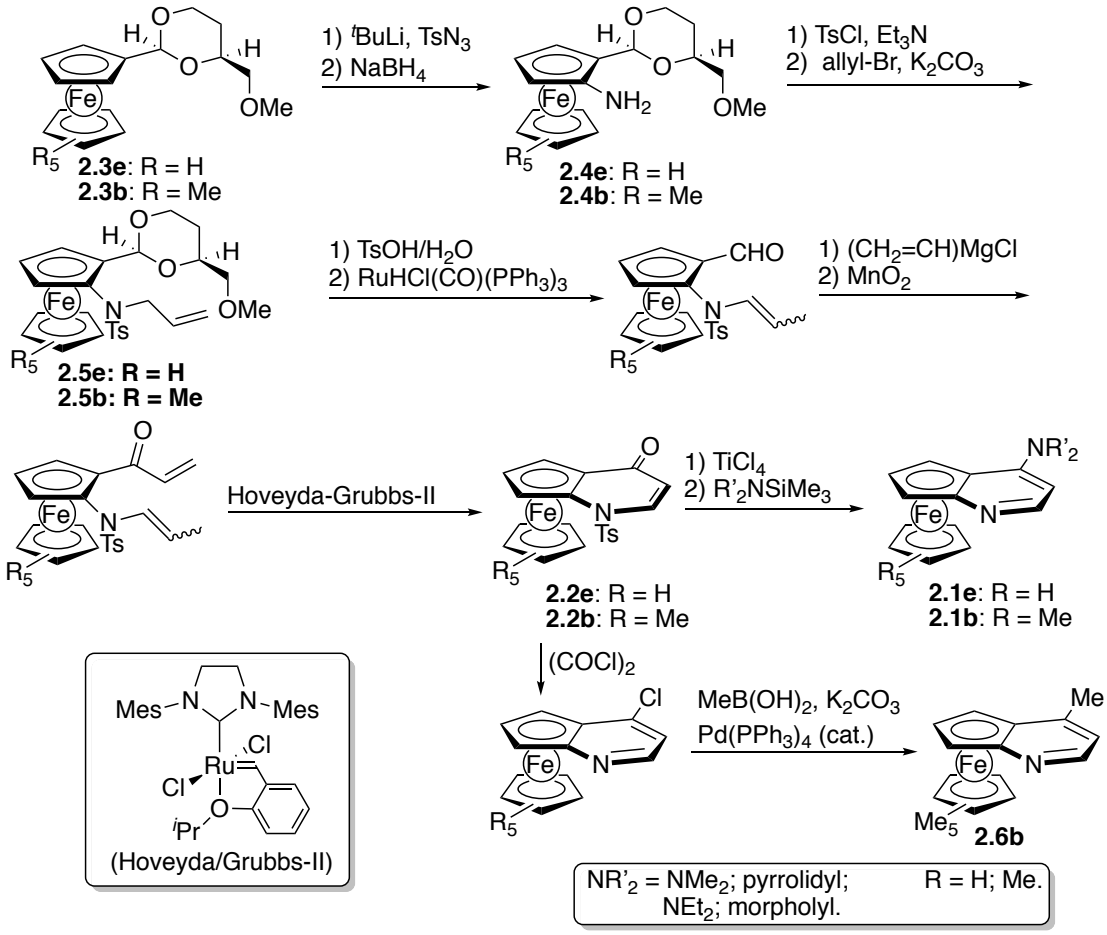


In the early studies, Ogasawara established the enantioselective synthesis of planar-chiral Fc*-DAAPs and related compounds, which *partly* overcame the drawbacks in the Fu's original synthesis of Fc*-DAAPs (Scheme 2-2).

The three features of their synthetic strategy are: (i) introduction of proper substituents at the 1- and 2-positions of a ferrocene platform with controlling its planar chirality utilizing a chiral *ortho*-directing group (**2.3** to **2.4** in Scheme 2-2), (ii)

construction of the ferrocene-fused 4-pyridones by the ring-closing metathesis reaction,[3-5] and (iii) the last stage introduction of various substituents at the 4-position of the ferrocene-fused pyridines (**2.2** to **2.1** and **2.6**). The chiral 1,3-dioxan-2-yl group in **2.3**, developed by Kagan and his coworkers, is a powerful chiral directing group for the highly diastereoselective lithiation of **2.3** (>99% de). Planar-chiral 4-pyridones **2.2**, obtained in essentially enantiomerically pure forms, are versatile synthetic intermediates, and they could be converted to the various pyridine derivatives with retention of the planar chirality in **2.2**. An analogous synthetic strategy was applied to the synthesis of metallocene-fused planar-chiral phospholes recently.

Scheme 2-2



Although the synthetic method in Scheme 2-2 provided a library of the planar-chiral pyridine-based nucleophilic organocatalysts, including previously unknown species, without enantiomeric resolution, it still have room for further improvement. For example, the reaction sequence in Scheme 2-2 is somewhat lengthy, and some steps need the uses of expensive noble metal catalysts, such as the

Hoveyda-Grubbs-II catalyst,[6] with relatively high catalyst loading. Furthermore, this "first-generation synthesis" shows severe steric hindrance. The method can be used for the preparation of the Cp- and Cp*-derivatives (R = H or Me), but the corresponding η^5-C_5Ph_5-analogues were not obtained in the same way. It should be mentioned that the C_5H_5-derivatives of **2.1** are synthetically far less important due to the low-enantioselectivity on their applications in asymmetric catalysis, and the sterically demanding η^5-C_5Ph_5-analogues show much better performance in many reactions.

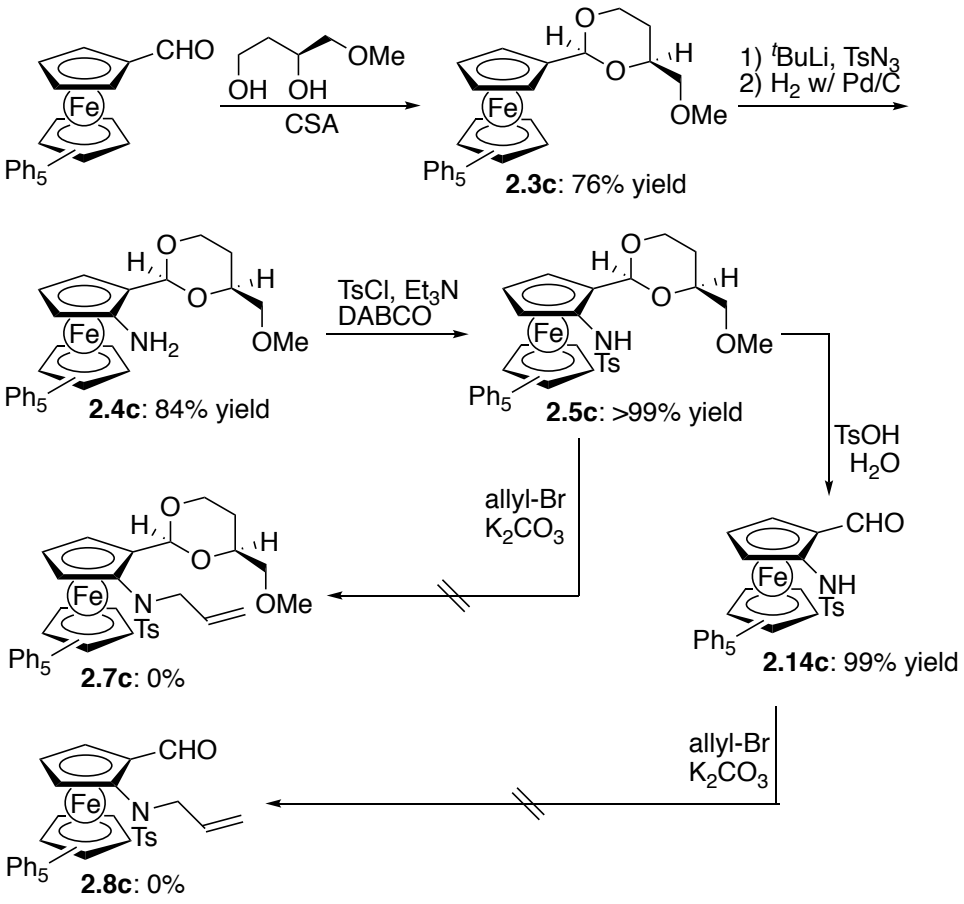
With the background mentioned above, I started the present studies with intention to overcome the limitations of the first generation enantioselective synthesis of Fc*-DAAPs (Scheme 2-2). The improved "second-generation synthesis" developed in this study is much shorter (i. e., more effective) and much less costly without using the expensive noble metal catalysts. And more importantly, the newly developed synthesis can provide sterically demanding analogues of Fc*-DAAPs which are with an (η^5-C_5Ph_5)Fe or (η^5-C_5Bn_5)Fe substructure. These bulky Fc*-DAAP derivatives are synthetically more useful showing better enantioselectivity in many cases. It should be mentioned that the (η^5-C_5Bn_5)Fe derivatives are previously unknown and prepared for the first time through this study.

As mentioned in the introduction section, the original method of enantioselective synthesis of Fc*-DAAPs, shown in Scheme 2-2, works only for the η^5-C_5H_5- and η^5-C_5Me_5-derivatives, and the corresponding η^5-C_5Ph_5-derivatives could not be prepared in the same way.

The results of the unsuccessful attempts at preparing the η^5-C_5Ph_5-derivatives by our "first-generation synthesis" are summarized in Scheme 2-3. Chiral acetal (–)-**2.3c** was prepared from 1-formyl-1',2',3',4',5'-pentaphenylferrocene and (*S*)-4-methoxybutane-1,3-diol in 76% yield. Chiral (2*S*,4*S*)-4-methoxymethyl-1,3-dioxan-2-yl substituent in **2.3c** is an excellent chiral directing group, and deprotonation of **2.3c** took place with high diastereoselectivity of >99.5% de. Lithiation of **2.3c** using ^{t}BuLi at –78 °C in THF followed by a reaction with tosyl azide gave the corresponding ferrocenyl azide, and subsequently the crude azide was reduced under a hydrogen atmosphere in the presence of Pd/C to give ferrocenylamine (–)-**2.4c** in 84% yield (for two steps). The ^{1}H- and ^{13}C-NMR analyses of (–)-**2.4c** clarified the compound to be essentially diastereomerically pure. After

N-tosylation of (–)-**2.4c** in >99%, *N*-allylation of (–)-**2.5c** was examined. To my disappointment, the *N*-allylation did not proceed under the conditions in Scheme 2-3 and desired **2.7c** could not be obtained. It was suspected that the robustness of (–)-**2.5c** toward the *N*-allylation might be ascribed to the steric hindrance by the bulky η^5-C_5Ph_5 ligand. To diminish the steric problems in (–)-**2.5c** as much as possible, the *N*-allylation was also examined after deprotection of the chiral 1,3-dioxanyl moiety, but the reaction of aldehyde (*S*)**-2.14c** did not afford *N*-allylated species **2.8c**. At this stage, I gave up to pursue the synthesis of the (η^5-C_5Ph_5)Fe-derivatives by the method in Scheme 2-3.

Scheme 2-3



Section 2

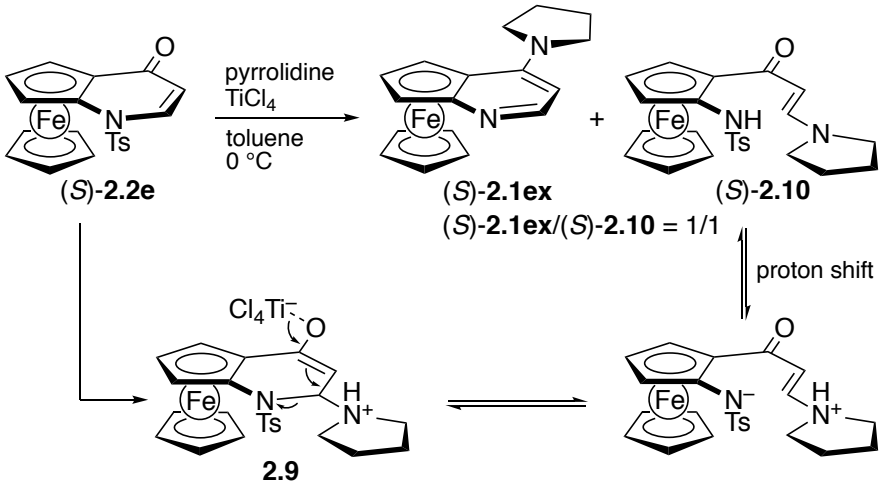
Enantioselective Synthesis of Ferrocene-Fused Planar-Chiral 4-(Dialkylamino) pyridine Derivatives

In this section, I would like to report the details of an innovative second-generation enantioselective synthesis of various planar-chiral Fc^*-DAAPs as single enantiomers. In addition, the corresponding cymantrene-fused DAAPs could also be prepared by the same method.

2-2-1 Development of Transition-Metal Free Iodide-Catalyzed Cyclization Producing 4-Pyridones 2.2

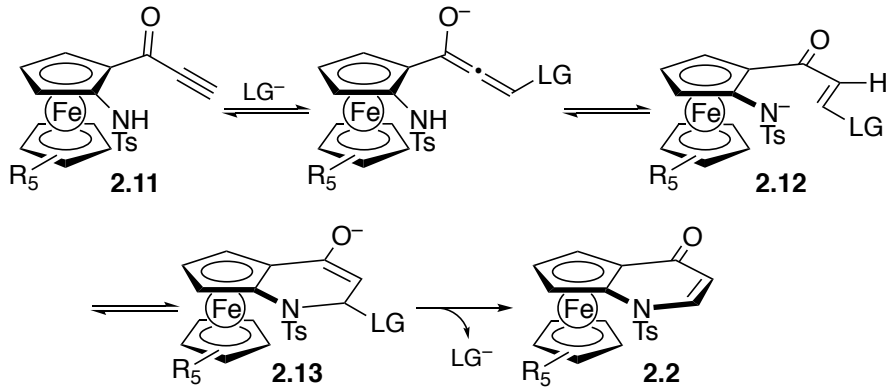
During our investigations on the transformation of pyridone (*S*)-**2.2e** to pyridine (*S*)-**2.1ex**,[7] we encountered the formation of unexpected "ring-opening" product (*S*)-**2.10** using an equimolar mixture of pyrrolidine and titanium(IV) chloride under the unoptimized conditions. The formation of (*S*)-**2.10** was rationalized as depicted in Scheme 2-4. In the presence of Lewis-acidic $TiCl_4$, pyrrolidine attacks at the β-olefinic carbon in (*S*)-**2.2e** to give intermediate **2.9**, which subsequently eliminates the tosylamide anion to give the ring-opening product via a proton shift (Scheme 2-4).

Scheme 2-4



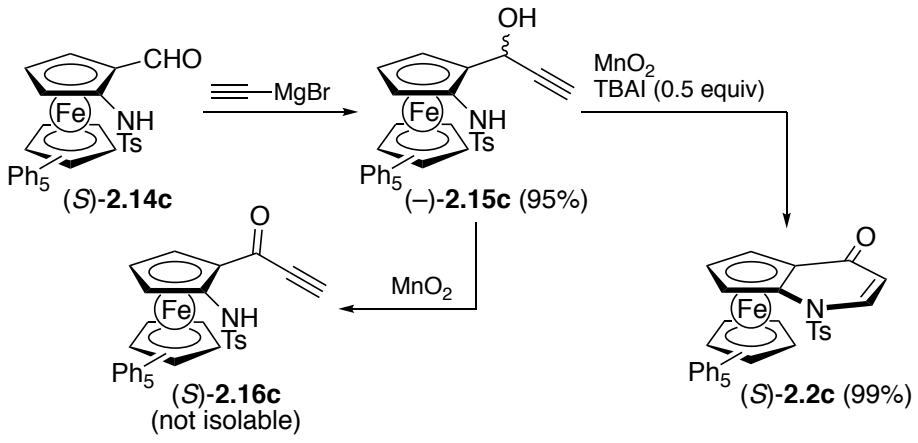
On the assumption that the reaction steps between intermediate **2.9** and (*S*)-**2.10** were reversible, a novel transition-metal-free cyclization process producing 4-pyridones **2.2** was pursued (Scheme 2-5).[8] I envisioned that enone **2.12**, which possesses a potential leaving group (i.e., a weak nucleophile) on the β-sp^2 carbon, might undergo a cyclization providing pyridone **2.2** as in Scheme 2-5. For the success of this pyridone formation instead of the ring-opening as in Scheme 2-4, the LG substituent in **2.13** must be a better leaving group than the tosylamide moiety. Cyclization precursor **2.12** could be generated *in situ* by the conjugate addition of a nucleophilic LG^- to ynone **2.11**. Whereas LG^- would be regenerated at the transformation of **2.13** to **2.2**, a substoichiometric (catalytic) amount of LG^- might be sufficient (Scheme 2-5).

Scheme 2-5



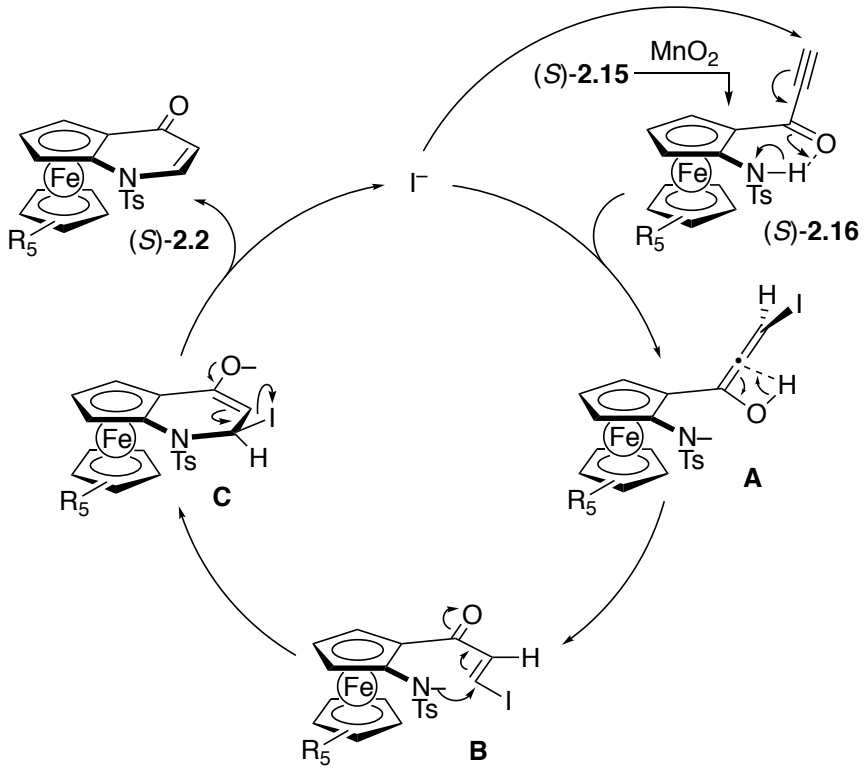
At the outset, this idea was examined in the synthesis of pentaphenylferroco-pyridone **2.2c**, which could not be prepared by the first generation synthesis as mentioned in the previous section. The results are summarized in Scheme 2-6. Treatment of aldehyde (*S*)-**2.14c**, which was prepared as in Scheme 2-3, with ethynylmagnesium bromide afforded propargylic alcohol (–)-**2.15c** in 95% yield as a diastereomeric mixture. Ynone (*S*)-**2.16c** could be prepared by the MnO_2-oxidation of (–)-**2.15c** in dichloromethane, but the compound was easily polymerized into uncharacterized gummy materials and was not isolable. Due to the susceptibility of (*S*)-**2.16c**, a direct conversion of (–)-**2.15c** into (*S*)-**2.2c** "in one pot" was tested. That is, propargylic alcohol (–)-**2.15c** was reacted with manganese(IV) oxide in the presence of a catalytic nucleophile. After an extensive survey of various nucleophiles, which include pyridine, DMAP, DABCO, triethylamine, copper(I) iodide, etc., it was found that a reaction using tetrabutylammonium iodide (TBAI; 0.5 equiv. to **2.15c**) proceeded cleanly to produce (*S*)-**2.2c** in 99% yield.

Scheme 2-6



Scheme 2-7 shows a plausible reaction mechanism for the iodide-catalyzed cyclization of 1-propynoyl-2-*N*-(*p*-toluenesulfonyl)aminoferrocenes producing the ferrocene-fused *N*-toslyl-4-pyridones. Iodide anion attacks the alkynyl terminal in ynone (*S*)-**2.16**, which is generated *in situ* by the oxidation of propargylic alcohol (*S*)-**2.15** with manganese(IV) oxide, to give intermediate **A**. After the isomerization of allenol **A** into enone **B**, an intramolecular conjugate addition of the anionic tosylamide to the enone moiety affords intermediate **C**. Subsequent elimination of iodide anion from **C** gives pyridone (*S*)-**2.2** to complete the catalytic cycle. For the effective synthesis of (*S*)-**2.2**, the undesirable self-polymerization of (*S*)-**2.16** should be avoided. I.e., ynone (*S*)-**2.16**, generated by the oxidation of (*S*)-**2.15**, needs to react with iodide anion faster than the self-polymerization. This may be a reason why relatively high catalyst-loading (i.e., 50% TBAI) is required to realize the high yield in this process.

Scheme 2-7

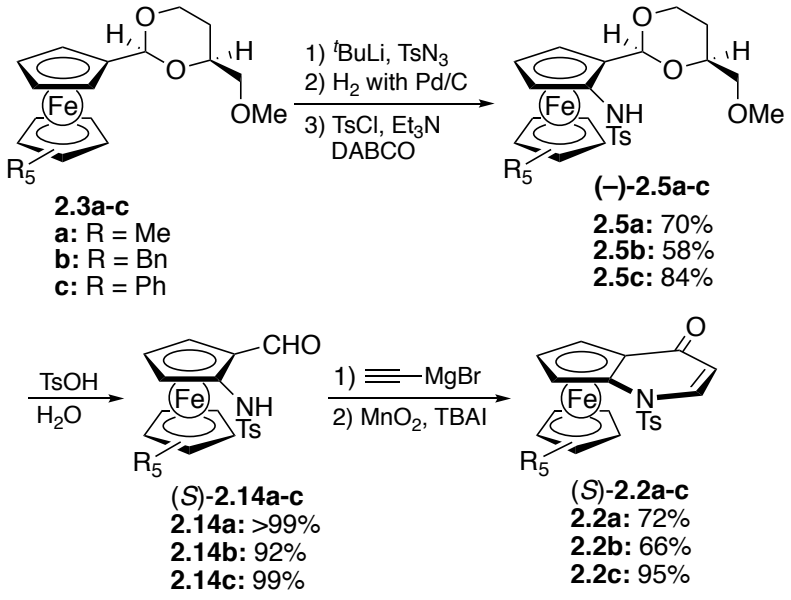


With the iodide-catalyzed cyclization reaction in my hands, the enantioselective synthesis of (*S*)-**2.2c** was finally accomplished. The synthetic sequence developed in this study is versatile and applicable to the synthesis of other ferrocene-fused pyridones, such as **2.2a** and **2.2b** which are with the (η^5-C_5Me_5)Fe and (η^5-C_5Bn_5)Fe moieties, respectively.

2-2-2 Preparation of Planar-Chiral Ferroco-Pyridones

To enhance the practicality of this "second-generation synthesis", the reaction conditions of each steps were thoroughly optimized to simplify the synthetic operations. The results are summarized in Scheme 2-8. The improved enantioselective synthesis of planar-chiral ferrocene-fused pyridones (*S*)-**2.2** starts from respective chiral acetals **2.3** and needs only three isolation/purification steps to (*S*)-**2.2**. The diastereoselective lithiation of (–)-**2.3** using ^{t}BuLi followed by a reaction with tosyl azide afforded the corresponding ferrocenyl azide, and the subsequent palladium-catalyzed reduction of the crude azide under a hydrogen atmosphere gave the ferrocenylamine, which was immediately tosylated without purification to provide *N*-tosylaminoferrocenyl acetal (–)-**2.5** in high yield ranging 58-84 %. Acetal (–)-**2.5**, purified by silica gel column chromatography, was confirmed to be diastereomerically pure by the ^{1}H- and ^{13}C-NMR analyses. The acid-catalyzed hydrolysis of (–)-**2.5** gave the corresponding aldehyde (*S*)-**2.14** in >92% yield in enantiomerically pure form. The purification/isolation of (*S*)-**2.14** may be skipped, but I checked the enantiomeric homogeneity of (*S*)-**2.14** at this stage. Aldehyde (*S*)-**2.14** was reacted with ethynylmagnesium bromide, and the crude propargylic alcohols, which was obtained by simple extraction, was applied to the iodide-catalyzed cyclization as in Schemes 2-6 and 2-7 to give planar-chiral 4-pyridone (*S*)-**2.2** in high yield ranging 66-95% (Scheme 2-8).

Scheme 2-8

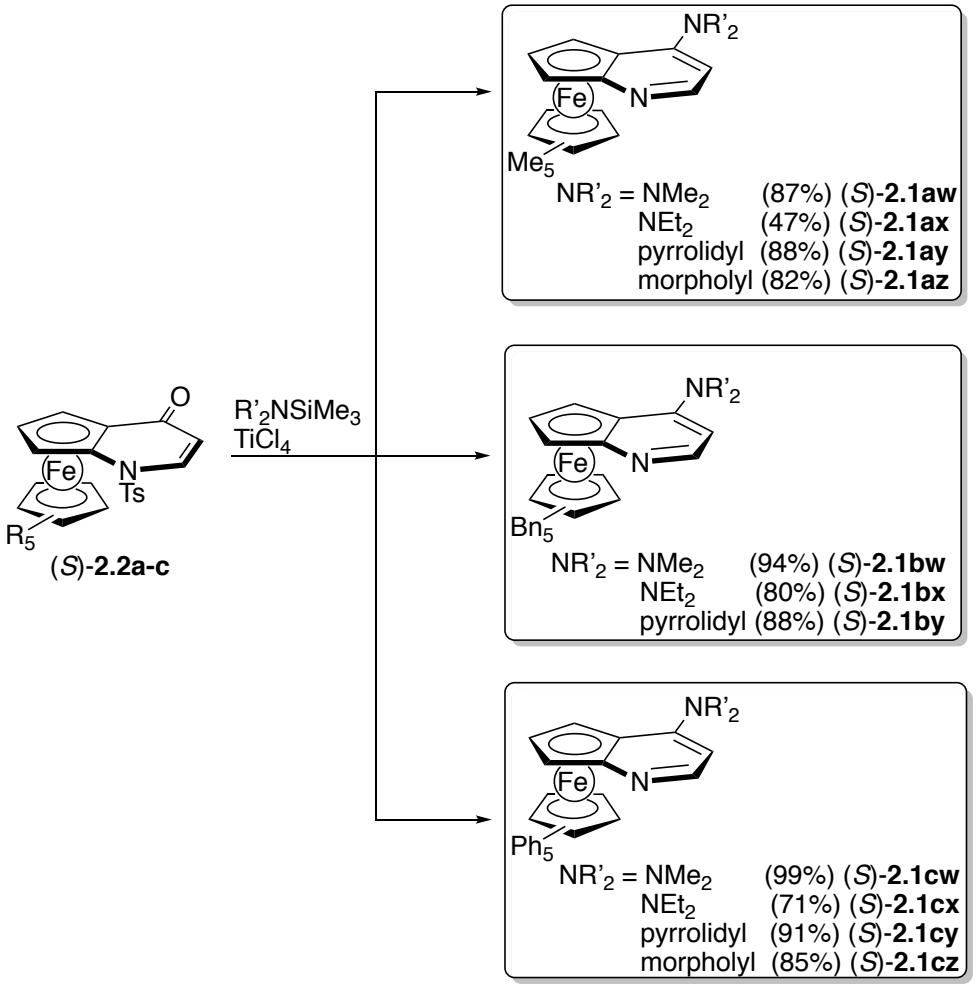


The second-generation synthesis of pyridones **2.2** developed here is much shorter with the simpler operations and the higher yields compared to the first-generation synthesis. Furthermore, the second-generation synthesis can afford the sterically demanding ferroco-pyridones such as **2.2b** and **2.2c**, which are not accessible by the first-generation synthesis. While the total yield from (–)-**2.3a** to (*S*)-**2.2a** was 35% in nine-steps by the first-generation synthesis, the second-generation synthesis according to Scheme 2-8 provided (*S*)-**2.2a** in 50% total yield starting with (–)-**2.3a** (Scheme 2-8). The synthesis of (*S*)-**2.2c** was more effective in 71% total yield from (–)-**2.3c**.

2-2-3 Preparation of Planar-Chiral Ferroco-Pyridines 2.1 from 4-Pyridones 2.2

In the previous report, Ogasawara demonstrated that planar-chiral *N*-tosyl-4-pyridones (*S*)-**2.2e** and (*S*)-**2.2a** were versatile precursors to various pyridine derivatives. The direct conversion of (*S*)-**2.2a** into a series of 4-dialkylaminopyridine derivatives (*S*)-**2.1a** was achieved by the reaction with an appropriate *N*-trimethylsilylamine in the presence of titanium(IV) chloride in good to excellent yields (see, Schemes 2-2 and 2-9). This detosylative amination reaction was found to be operative for the sterically demanding ferroco-pyridones such as (*S*)-**2.2c** and (*S*)-**2.2b** as well, and the results are summarized in Scheme 2-9. The reactions introducing dimethylamino, pyrroridyl, or morpholyl groups at the 4-position of the pyridine rings proceeded very cleanly and the corresponding Fc^*-DAAPs were obtained in excellent yields ranging 82-99%. On the other hand, the reaction with diethyl(trimethylsilyl)amine was somewhat slow and the yields of the 4-diethylaminopyridine derivatives are relatively low (47-80%). Steric influence of the η^5-C_5R_5 ligands on the detosylative amination reaction is minimal and three pyridones **2.2a-c** showed similar reactivity. The isolated yields of the η^5-C_5Me_5 derivatives are somewhat lower, which can be ascribed to their sensitivity toward air-oxidation, since the chromatographic purification was conducted under air.

Scheme 2-9



It should be emphasized that all the transformations shown in Schemes 2-8 and 2-9 are stereoretentive. Whereas (*S*)-**2.2a-c** obtained by new method are enantiomerically pure, planar-chiral ferroco-DAAP derivatives are also single-enantiomeric. Namely, I have established the divergent process preparing a library of various planar-chiral pyridine-based nucleophilic organocatalysts in enantiomerically pure forms without optical resolution. Our second-generation synthesis is fairly versatile and various substituents can be introduced both at the 4-pyridyl position as well as in the η^5-C_5R_5 moiety. The η^5-pentabenzylcyclopentadienyl derivatives (**2.1bw-by**) and 4-diethylamino-/4-morpholyl-ferroco-pyridines (**2.1ax**, **2.1cx**, **2.1bx**, **2.1az**, and **2.1cz**) are new compounds and prepared for the first time by our synthetic method.

Determination of Absolute Configuration of (+)-**2.1bw.** The single crystals of (+)-**2.1bw** were grown from pentane/dichloromethane as deep red prisms. The crystal structure of (+)-**2.1bw** is shown in the Figure 2-1 with the selected bond lengths and angles. The Flack parameter was determined to be 0.034(8) for the structure, and absolute configuration of (+)-**2.1bw** is unambiguously assigned to be *S*. The configuration of the other corresponding products was deduced by analogy. The iron atom in compound (+)-**2.1bw** coordinates to two η^5-ligand and located at the center of the two η^5-ligand: the distance from Fe1 to the least-squares planes $_{C4\text{-}C8}$ of the η^5-ligand and η^5-C_5Bn_5 are 2.042 Å and 1.902 Å, respectively. The two ligands are a little bent and the dihedral angle between the two ligand is 3.08°

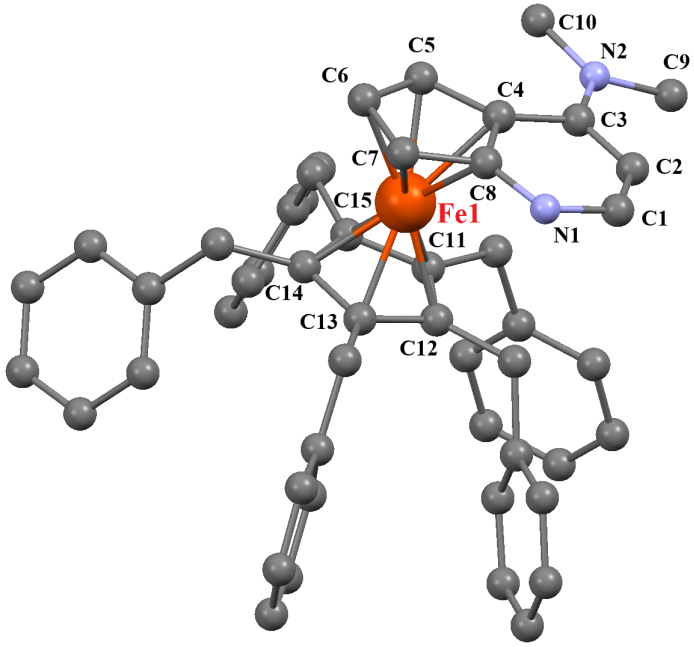
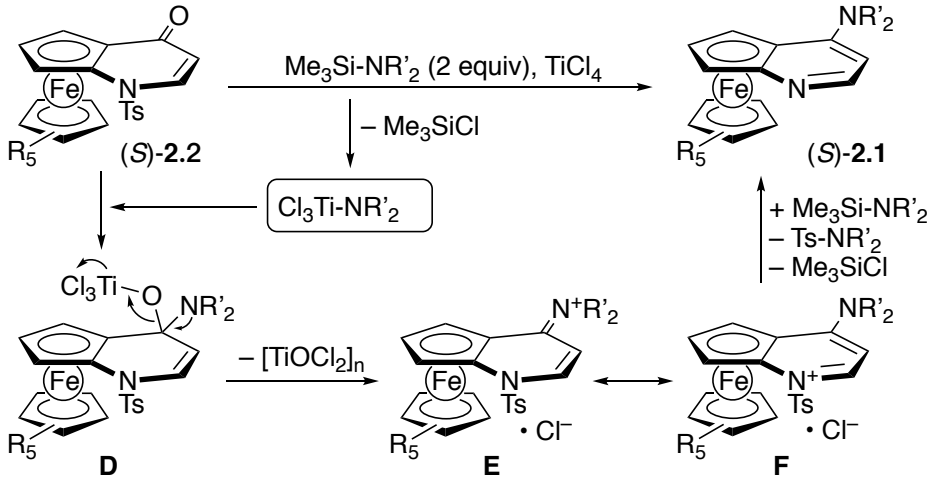


Figure 2-1. Ball-and-stick drawing of (***S***)-**(+)-2.1bw**. All hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg); N1-C1 = 1.38(1), N1-C8 = 1.378(6), N2-C9 = 1.448(8), N2-C10 = 1.42(1), C1-C2 = 1.38(1), C2-C3 = 1.339(8), C3-C4 = 1.452(7), C4-C5 = 1.442(7), C5-C6 = 1.399(7), C6-C7 = 1.402(7), C7-C8 = 1.404(8), Fe1-least-squares plane$_{C4\text{-}C8}$ = 2.042, Fe1-least-squares plane$_{C14\text{-}C15}$ = 1.902, C1-N1-C8 = 111.7(5), C3-N2-C9 = 116.8(5), C3-N2-C10 = 123.6(5), C9-N2-C10 = 119.4(5), dihedral angle between least-squares plane$_{C(4,5,6,7,8)}$ and least-squares plane$_{C(11,12,13,14,15)}$ = 3.08, Flack Parameter = 0.034(8).

A plausible reaction mechanism for the detosylative amination reaction is shown in Scheme 2-10. A reaction of a trimethylsilylamine with titanium(IV) chloride generates a titanium amide, $Cl_3Ti\text{-}NR'_2$, that attacks the carbonyl moiety in (*S*)-**2.2** to form intermediate **D**. Elimination of titanium(IV) oxodichloride gives iminium species **E**, that also exists in different resonance form **F**. The subsequent reaction of *N*-tosylpyridinium intermediate **F** with $Me_3Si\text{-}NR'_2$ affords the corresponding (*S*)-**2.1** together with tosylamide $TsNR'_2$, which was indeed isolated from the reaction mixture.

Scheme 2-10

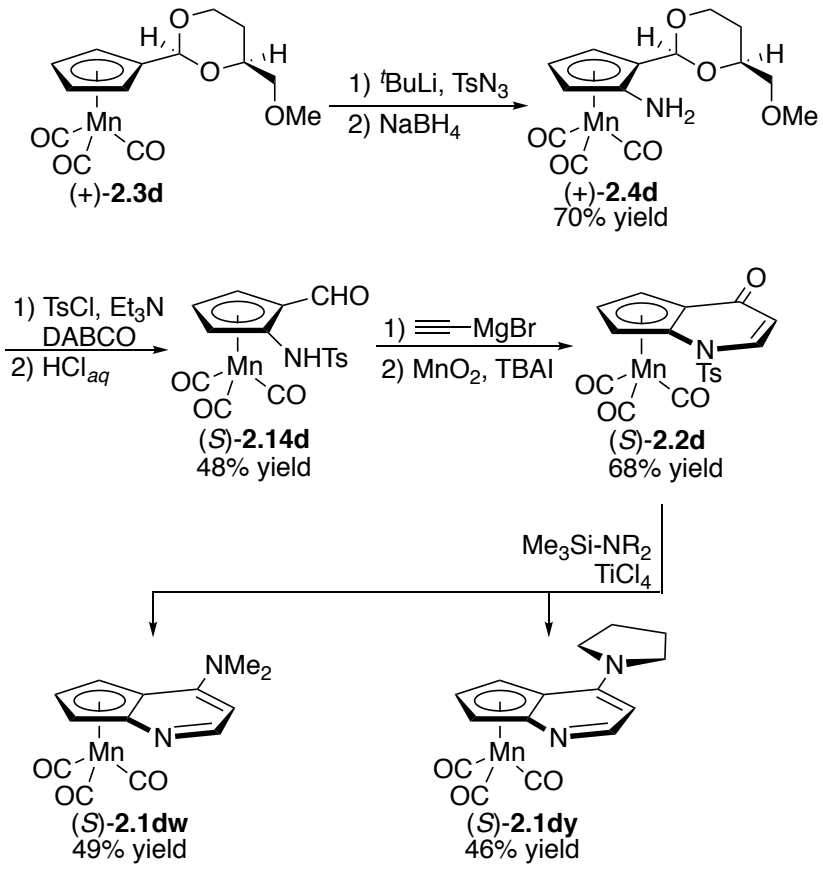


Section 3

Enantioselective Synthesis of Planar-Chiral Cymantrene-Fused DMAP (S)-2.1dw and PPY (S)-2.1dy

Generality of the synthetic method developed in this study was tested on preparation of DAAP derivatives fused with a metallocene other than ferrocenes. Cymantrene, (η^5-cyclopentadienyl)manganese(I) tricarbonyl, was chosen as a platform for this purpose, and the results are shown in Scheme 2-11. The synthesis began with known chiral cymantrenyl acetal (+)-**2.3d**, of which sequential diastereoselective lithiation, azidation, and $NaBH_4$ reduction gave aminocymantrene (+)-**2.4d** in 70% yield as a single-diastereomer.[9,10] After the *N*-tosylation of (+)-**2.4d**, the hydrolysis of the chiral acetal moiety using aqueous hydrochloric acid provided aldehyde (*S*)-**2.14d** in enantiomerically pure form in 48% yield. Treatment of (*S*)-**2.14d** in the same way as the ferrocene derivatives provided the corresponding cymantrene-fused 4-pyridone (*S*)-**2.2d** in 68% yield. Pyridone (*S*)-**2.2d** could be converted to cymantrene-fused DMAP (*S*)-**2.1dw** and PPY (*S*)-**2.1dy** in 49% and 46% yields, respectively.

Scheme 2-11



Although the yields of the cymantrene derivatives were lower than those of the ferrocene derivatives, probably due to the air sensitivity of the manganese complexes, the reaction sequence in Scheme 2-11 demonstrated the versatility and generality of the second-generation synthesis of the planar-chiral DAAP species.

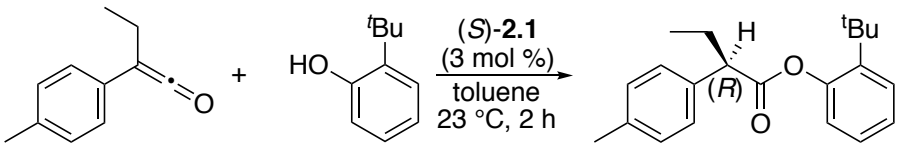
Section 4

Application in Asymmetric Organocatalysis

The library of the nucleophilic organocatalysts, (*S*)-**2.1**, obtained in this study was applied in the two prototypical asymmetric reactions and their catalytic performance was evaluated.

The first asymmetric reaction catalyzed by (*S*)-**2.1** is an addition reaction of 2-^{t}Bu-phenol (**2.18**) to ethyl(*p*-tolyl)ketene (**2.17**), which was suggested to take place by the Brønsted acid-catalyzed mechanism (Table 1).[11] The η^5-C_5Me_5 derivatives, (*S*)-**2.1aw-az**, could be prepared by the first-generation synthesis and their catalytic applications in this reaction were already examined in the previous report. The reported results are included in the table for comparison (entries 1-4).[12] Among them, ferroco-PPY (*S*)-**2.1ay**, which is Fu's original, showed good catalytic activity in the addition reaction to give ester **2.19** in 90% yield with 92% ee (entry 3). The η^5-C_5Ph_5-derivatives, (*S*)-**2.1cw-cz**, were poor catalyst for this transformation, and **2.19** was obtained in less than 8% yields with low enantioselectivities of 32% ee at most (entries 8-11). The poor performance of (*S*)-**2.1cw-cz**, which are with an electron-withdrawing η^5-C_5Ph_5 ligand, could be attributed to their lower basicity compared to (*S*)-**2.1aw-az**. And indeed, cymantro-pyridines (*S*)-**2.1dw** and (*S*)-**2.1dy**, which were low-basic due to the electron-withdrawing nature of the cymantrene framework, showed similar poor catalytic activities and enantioselectivities in the reaction (entries 12-13). On the other hand, η^5-C_5Bn_5-derivatives (*S*)-**2.1bw-by**, which are with a bulkier η^5-pentaalkylcyclopentadienide, can be regarded as refined variants of η^5-C_5Me_5-derivatives (*S*)-**2.1aw-az** and showed excellent catalytic activities (entries 5-7). Pyridine catalysts (*S*)-**2.1bw-by** provided (*R*)-**2.19** in excellent yields with better enantioselectivities compared to the products obtained by homologous (*S*)-**2.1aw-ay** (entries 1-3 *vs* entries 5-7). Notably, newly developed (*S*)-**2.1by** displayed the highest enantioselectivity of 94% ee in the present reaction and outperformed the other ferroco-/cymantro-pyridines.

Table 1. Enantioselective Addition of *o*-^{t}Bu-Phenol to Ethyl(*p*-tolyl)ketene Catalyzed by (*S*)-2.1[a]



2.17 **2.18** (*R*)-**2.19**

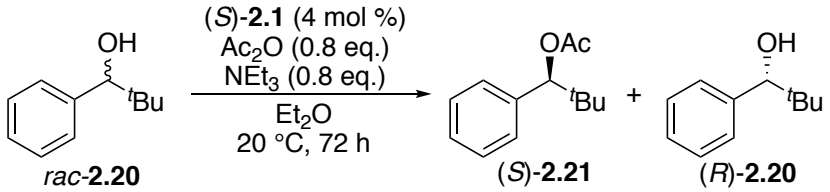
entry	catalyst	yield (%)[b]	% ee[c]
1[d]	(*S*)-**2.1aw**	92	79
2[d]	(*S*)-**2.1ax**	90	90
3[d]	(*S*)-**2.1ay**	90	92
4[d]	(*S*)-**2.1az**	84	79
5	(*S*)-**2.1bw**	92	90
6	(*S*)-**2.1bx**	93	90
7	(*S*)-**2.1by**	91	94
8	(*S*)-**2.1cw**	8	9
9	(*S*)-**2.1cx**	4	32
10	(*S*)-**2.1cy**	7	15
11	(*S*)-**2.1cz**	<1	---
12	(*S*)-**2.1dw**	5	40
13	(*S*)-**2.1dy**	16	15

[a] The reaction was carried out in toluene at 23 °C in the presence of catalyst (*S*)-**2.1** (3 mol %). The absolute configuration of the **2.19** was deduced by comparison with the reported results [ref 11]. [b] Isolated yield by silica gel chromatography. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Taken from ref. 12.

The second reaction examined is the kinetic resolution of racemic secondary alcohol *rac*-**2.20**. The acetylation of *rac*-**2.20** with acetic anhydride proceeds in an enantioselective fashion in the presence of (*S*)-**2.1** (4 mol %) to give ester (*S*)-**2.21** and recovered (*R*)-**2.20** (Table 2). The catalytic properties of the η^5-C_5Me_5 derivatives (*S*)-**2.1aw-az** were already examined in the previous report and the reported results are included in Table 2 for comparison (entries 1-4). Among the η^5-C_5Me_5 derivatives, (*S*)-**2.1ax** having a 4-diethylamino substituent showed the highest enantioselectivity with *s*-factor of 6.7 (entry 2). It was reported, however, that η^5-C_5Me_5 derivative **2.1aw** was not an appropriate catalyst for the analogous kinetic resolution of secondary alcohols and the corresponding η^5-C_5Ph_5-derivative **2.1cw** showed much better enantioselectivity.[13] With the second-generation synthesis of the planar-chiral DAAPs, a series of η^5-C_5Ph_5-derivatives (*S*)-**2.1cw-cz** were available for this study.

As expected, indeed, (*S*)-**2.1cw-cz** showed excellent enantioselectivities with *s*-factors ranging 13 to 69 (entries 8-11). The best selectivity (*s* = 69) was recorded using (*S*)-**2.1cz**, which was prepared for the first time in this study, but its catalytic activity was decreased due to the less electron-donating ability of the 4-morpholyl substituent (entry 11). The performance of η^5-C_5Bn_5 derivatives (*S*)-**2.1bw-by** was somewhat similar to that of (*S*)-**2.1aw-ay**, but the former showed slightly better selectivities than the latter (entries 5-7). Once again, (*S*)-**2.1bw-by** can be seen as improved variants of (*S*)-**2.1aw-ay**. Cymantrene-fused DMAP (*S*)-**2.1dw** and PPY (*S*)-**2.1dy** were also applied to the kinetic resolution of *rac*-**2.20**. The results were, however, unsatisfactory in terms of both catalytic activity and enantioselectivity, which can be ascribed to the less electron-donating and the less hindered nature of the cymantrene platform in (*S*)-**2.1dw** and **2.1dy** (entries 12 and 13).

Table 2. Acetylative Kinetic Resolution of *rac*-Alcohol Catalyzed by (*S*)-2.1



entry	(*S*)-**2.1**	conv.%[b]	%ee-**2.21**[c]	%ee-**2.20**[c]	*s*-factor[d]
1	**2.1aw**	65	41	75	5.0
2	**2.1ax**	70	39	92	6.7
3	**2.1ay**	62	43	70	5.0
4	**2.1az**	66	41	78	5.3
5	**2.1bw**	62	47	78	6.3
6	**2.1bx**	68	45	98	11
7	**2.1by**	66	43	83	6.0
8	**2.1cw**	41	89	62	33
9	**2.1cx**	45	75	60	13
10	**2.1cy**	46	91	76	48
11	**2.1cz**	7	97	8	69
12	**2.1dw**	31	50	23	3.7
13	**2.1dy**	27	54	19	4.0

[a] The reaction was carried out in ether at 20 °C in the presence of catalyst (*S*)-**2.1** (4 mol %). [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC analysis on a chiral stationary phase. The absolute configurations of **2.21** and recovered **2.20** were determined by comparison with the reported results [ref 14]. [d] Calculated based on a first-order equation [ref 15].

Conclusions for Chapter II

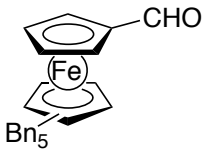
In this Chapter, I have developed an efficient and enantioselective method of preparing various metallocene-fused planar-chiral 4-pyridones and substantially renewed the first generation synthesis of Fc^*-DAAPs **2.1**. The improved second generation synthesis is efficient and practical. It takes over advantages of the first one, that are 1) the stereoselective synthesis of one enantiomer over another through a diastereoselective ortho-metalation strategy in combination with a chiral anchoring group, and 2) the divergent synthesis based on the last stage introduction of substituents at the 4-position of the ferrocene-fused pyridines enabling the construction of a flexible library. Besides these, the new method enabled the production of important η^5-C_5Ph_5-analogues **2.1c**, that could not be accomplished by the first generation synthesis. Taking the improvement, new series of **2.1**, that are η^5-C_5Bn_5-analogues **2.1b** and cymantrene-fused analogues **2.1d,** were prepared in short steps and launched into the society for the first time. Finally, these catalysts were applied to two different types of asymmetric reactions and proved their value and promising future.

Since the discovery by Fu in 1990s, Fc^*-DAAPs **2.1** have been recognized as one of the most attractive and versatile nucleophilic catalysts, applicable to a wide range of asymmetric reactions.

Experimental Section for Chapter II

All anaerobic and/or moisture sensitive manipulations were carried out with standard Schlenk techniques under predried nitrogen or with glovebox techniques under prepurified argon. ^{1}H NMR (400 MHz or 500 MHz) and ^{13}C NMR (100 MHz or 125 MHz) chemical shifts are reported in ppm downfield of internal tetramethylsilane. High-resolution mass spectra were recorded on Orbitrap mass spectrometers. Single crystal X-ray diffraction data were collected at 173 K on a CCD diffractometer with Mo *K*α (λ= 0.71073) radiation and graphite monochromator. Tetrahydrofuran, diethyl ether, toluene, and benzene were distilled from benzophenone-ketyl under nitrogen prior to use. Dichloromethane was distilled from CaH_2 under nitrogen prior to use. The following compounds were prepared according to the reported methods: *p*-toluenesulfonyl azide,[16] and ethyl(*p*-tolyl)ketene.[17] All the other chemicals were obtained from commercial sources and used as received unless otherwise noted.

Synthesis of 1-Formyl-1',2',3',4',5'-pentabenzylferrocene.[18,19]



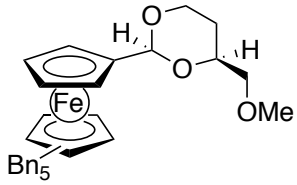
To a solution of sodium cyclopentadienide (2.38 g, 27.00 mmol) in THF (36 mL), was added methyl formate (2.43 g, 40.50 mmol), the solution was stirred at room temperature for 4 h. (Part A)

To a solution of pentabenzyl-1,3-cyclopentadiene (15.5 g, 30.0 mmol) in THF (70 mL), ^{n}BuLi (19.4 mL, 30.0 mmol) was slowly added, the solution was stirred at room temperature for 2 h. (Part B)

To a solution of $FeCl_2$ (3.42 g, 27.00 mmol) in THF (270 mL), the part (A) was transferred to this solution by means of the cannula, the mixture was stirred at room temperature for another 1 h. Then the part (B) was transferred to this solution, the mixture was stirred for the overnight. The reaction mixture was quenched with water and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator. The crude mixture was purified by silica gel chromatography (benzene/Et_2O = 20/1) to afford 12.4 g of title compounds as an orange solid (69% yield).

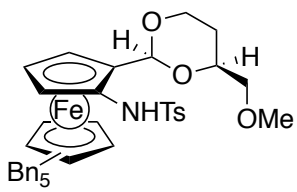
^{1}H NMR ($CDCl_3$): δ 3.84 (s, 10H), 4.25 (t, *J* = 1.9 Hz, 2H), 4.37 (t, *J* = 1.8 Hz, 2H), 6.59–6.61 (m, 10H), 6.89–6.97 (m, 15H), 9.87 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 32.8, 72.9, 77.9, 80.8, 87.5, 125.7, 127.9, 128.6, 139.8, 194.6. EI-HRMS Calcd for $C_{46}H_{40}FeO$: 664.2428. Found: 664.2450. Anal. Calcd for $C_{46}H_{40}FeO$: C, 83.12; H, 6.07.

Found: C, 83.09; H, 6.26.

1-[(2*S*,4*S*)-4-(Methoxymethyl)-1,3-dioxan-2-yl]-1',2',3',4',5'-pentabenzyl ferrocene (2.3b).  To a vessel containing the compound 1-formyl-1',2',3',4',5'-pentabenzylferrocene (12.0 g, 18.0 mmol), trimethyl orthoformate (30 mL), were added MeOH (11 mL), camphorsulfonic acid (83.63 mg, 0.36 mmol), the solution was stirred at 100 °C for overnight, the mixture was evaporated to dryness under reduced pressure. The residue was directly used for the next step without further purification.

To this residue was added another camphorsulfonic acid (167.26 mg, 0.72 mmol), (*S*)-4-meoxylbutane-1,3-diol (2.16 g, 18.00 mmol). The solution was stirred at 100 °C for overnight. The crude mixture was purified by silica gel chromatography (benzene/ether/Et_3N = 50/1/1) to afford 11 g of title compounds as yellow solid (80% yield).

^{1}H NMR (C_6D_6): δ 1.01–1.05 (m, 1H), 1.77 (qd, *J* = 12.1 and 5.3 Hz, 1H), 3.13 (s, 3H), 3.25 (dd, *J* = 10.1 and 4.3 Hz, 1H), 3.48 (dd, *J* = 10.1 and 6.2 Hz, 1H), 3.60 (td, *J* = 12.3 and 2.6 Hz, 1H), 3.72 (t, *J* = 4.5 Hz, 2H), 3.84–3.90 (m, 1H), 4.00 (dd, *J* = 11.4 and 4.0 Hz, 1H), 4.07 (s, 10H), 4.12–4.13 (m, 1H), 4.18–4.19 (m, 1H), 5.43 (s, 1H), 6.75–6.78 (m, 10H), 6.85–6.89 (m, 15H). ^{13}C NMR (C_6D_6): δ 28.2, 33.9, 59.1, 66.6, 70.5, 70.6, 73.36, 73.37, 76.1, 76.5, 86.5, 87.9, 100.3, 125.7, 128.1, 129.2, 141.4. EI-HRMS Calcd for $C_{51}H_{50}O_3Fe$: 766.3109. Found: 766.3096. Anal. Calcd for $C_{51}H_{50}FeO_3$: C, 79.89; H, 6.57. Found: C, 79.40; H, 6.58. $[\alpha]^{22}_D$ = –17 (*c* 1.0, $CHCl_3$).

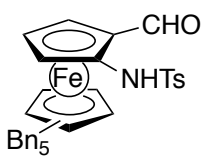
(S_p)-1-[(2*S*,4*S*)-4-(Methoxymethyl)-1,3-dioxan-2-yl]-2-(*p*-toluenesulfonamido)-1', 2',3',4',5'-pentabenzylferrocene (2.5b).  To a solution of **2.3b** (10 g, 13 mmol) in Et_2O (120 mL), ^{t}BuLi (12.0 mL, 19.5 mmol) was added dropwise at -78 °C, the solution was stirred in the room temperature for 1 h. The mixture was cooled to -78 °C again before TsN_3 (4.36 g, 22.11 mmol) was added. The mixture was stirred at room temperature overnight. The mixture was quenched with water, and extracted with CH_2Cl_2 twice. The organic layers were combined, washed with brine,

dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator. The residue was directly used for the next step without further purification.

The crude compound including azide was dissolved in Et_2O (60 mL), and to this $LiAlH_4$ (740.0 mg, 19.5 mmol) were added slowly. The reaction mixture was stirred in the room temperature for 1 h. The mixture was quenched with water and extracted with EtOAc twice. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator. The residue was directly used for the next step without further purification.

To a solution of residue in CH_2Cl_2 (60 mL) were added Et_3N (3.58 mL, 26 mmol), TsCl (2.97 g, 15.6 mmol) and trimethylamine hydrochloride (124.3 mg, 1.3 mmol) successively. The solution was stirred at 0 °C for 12 h. The reaction mixture was quenched with water and extracted with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The crude mixture was purified by silica gel column chromatography (hexane/EtOAc/Et_3N= 2/1/2%) to afford 7.05 g of title compounds as a yellow solid (58% yield).

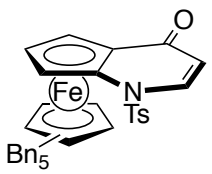
^{1}H NMR ($CDCl_3$): δ 1.39–1.43 (m, 1H), 1.86 (qd, *J* = 12.6 and 4.95 Hz, 1H), 2.37 (s, 1H), 3.45 (s, 3H), 3.51–3.67 (5H), 3.87–4.00 (12H), 4.56 (br, 1H), 4.79 (s, 1H), 6.55 (d, *J* = 2.8 Hz, 10H), 6.83–6.91 (m, 15H), 7.10 (s, 1H), 7.20 (d, *J* = 3.2 Hz, 2H), 7.59 (d, *J* = 3.28 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 21.6, 27.1, 32.7, 59.5, 66.1, 68.1, 69.9, 70.9, 74.6, 75.1, 75.5, 86.6, 92.4, 99.5, 125.3, 127.4, 127.7, 128.7, 129.2, 136.4, 140.5, 143.1. EI-HRMS Calcd for $C_{58}H_{57}O_5NSFe$: 935.3308. Found: 935.3312. Anal. Calcd for $C_{58}H_{57}O_5NSFe$: C, 74.43; H, 6.14; N, 1.50. Found: C, 74.13; H, 6.00; N, 1.48. $[\alpha]^{22}_D$ = –339 (*c* 0.1, $CHCl_3$).

(S_p)-1-Formyl-2-(*p*-toluenesulfonamido)-1',2',3',4',5'-pentabenzylferrocene (2.14b) 

To a solution of **2.5b** (6.6 g, 7.04 mmol) in CH_2Cl_2 (55 mL), were added the *p*-toluenesulfonic acid monohydrate (1.34 g, 7.04 mmol) and water (20 mL). The mixture was stirred at room temperature for 3 h, extracted with CH_2Cl_2 twice. The organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Column chromatography on silica gel (benzene/EtOAc= 20/1) provided 5.4 g of title compound as red solid (92% yield).

^{1}H NMR (C_6D_6): δ 1.74 (s, 3H), 3.56–3.57 (m, 1H), 3.75 (t, *J* = 1.08 Hz, 1H), 3.88 (s, 10H), 5.18 (br, 1H), 6.61–6.63 (m, 10H), 6.68 (d, *J* = 3.24 Hz, 2H), 7.84 (dt, *J* = 3.28 and 0.8 Hz, 2H), 8.46 (s, 1H), 9.54 (d, *J* = 0.28 Hz, 1H). ^{13}C NMR (C_6D_6): δ 21.0, 32.8, 67.0, 71.4, 72.3, 74.3, 88.2, 99.0, 125.9, 127.5, 128.5, 129.1, 129.7, 137.2, 140.0, 143.5, 197.3. EI-HRMS Calcd for $C_{53}H_{47}O_3NSFe$: 833.2627. Found: 833.2648. Anal. Calcd for $C_{53}H_{47}O_3NSFe$: C, 76.34; H, 5.68; N, 1.68. Found: C, 75.93; H, 5.60; N, 1.81. $[\alpha]^{22}_{D}$ = –853 (*c* 0.1, $CHCl_3$).

(S_p)-*N*-(*p*-Toluenesulfonyl)-1',2',3',4',5'-pentabenzylferroco[b]-4-pyridone (2.2b)

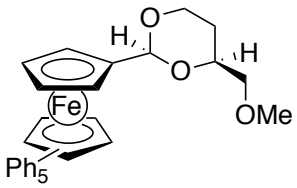


To a solution of **2.14b** (2.98 g, 3.57 mmol) in THF (55 mL), the ethynylmagnesium bromide solution (21 mL, 10.7 mmol) was added dropwise, the mixture was stirred in the room temperature for 30 min. The reaction mixture was quenched with $NH_4Cl_{(aq)}$ and extracted with EtOAc twice. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator. The residue without purification was directly used for next step.

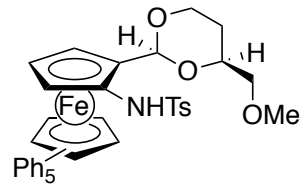
A solution of residue in CH_2Cl_2 (55 mL) was added over 30 min to a mixture containing the MnO_2 (3.2 g, 36.8 mmol) and TBAI (1.4 g, 36.8 mmol). The mixture was stirred in 0 °C for 2 days, the mixture was through the celite. The combined organic phase was dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. Silica gel column chromatography (hexane/EtOAc = 2/1) afforded 2.03 g of **2.2b** as red solid (66% yield).

^{1}H NMR (C_6D_6): δ 1.72 (s, 3H), 3.66 (t, *J* = 1.12 Hz, 1H), 4.02 (s, 10H), 4.54–4.55 (m, 1H), 5.16–5.17 (m, 1H), 5.98 (d, *J* = 3.36 Hz, 1H), 6.59 (d, *J* = 3.24 Hz, 2H), 6.64–6.66 (m, 10H), 6.67–6.85 (m, 15H), 7.58 (d, *J* = 3.32 Hz, 2H), 7.93 (d, *J* = 3.32 Hz, 2H). ^{13}C NMR (C_6D_6): δ 20.8, 32.3, 66.1, 66.7, 74.2, 74.3, 86.7, 100.0, 112.0, 125.6, 126.9, 127.9, 129.0, 129.9, 134.2, 136.3, 140.0, 145.1, 184.3. ESI-HRMS Calcd for $C_{55}H_{48}O_3NSFe$ (M+H): 858.2706. Found: 858.2706. $[\alpha]^{26}_{D}$ = –474 (*c* 0.1, $CHCl_3$).

1-[(2*S*,4*S*)-4-(Methoxymethyl)-1,3-dioxan-2-yl]-1',2',3',4',5'-pentaphenyl-ferrocene (2.3c). A mixture of 1-formyl-1',2',3',4',5'-pentaphenylferrocene (7.43 g, 12.5 mmol), $CH(OMe)_3$ (26 mL), MeOH (12 mL), and *p*-TsOH·H_2O (120 mg, 0.63 mmol) was stirred at 80 °C for 15 h, then concentrated under reduced pressure. The crude acetal was directly used for the next reaction without further purification. A mixture of the crude acetal, toluene (40 mL), camphorsulfonic acid (116 mg, 0.5 mmol), MS4A (6.5 g) and 4-methoxybutane-1,3-diol (1.32 g, 11.0 mmol) was stirred at 90 °C for 20 h. To the mixture was added K_2CO_3, and then the mixture was allowed to cool to room temperature, filtered through celite, concentrated under reduced pressure and the residue was purified by silica gel column chromatography (hexane/EtOAc/Et_3N = 28/4/1) to afford 6.66 g of **2.3c** as an orange solid (76% yield). ^{1}H NMR ($CDCl_3$): δ 1.32–1.37 (m, 1H), 1.69 (qd, *J* = 12.6 and 5.2 Hz, 1H), 3.34 (dd, *J* = 10.3 and 4.9 Hz, 1H), 3.38 (s, 1H), 3.42 (dd, *J* = 10.3 and 5.7 Hz, 1H), 3.49–3.56 (m, 1H), 3.58–3.65 (m, 1H), 4.05 (dd, *J* = 11.2 and 4.0 Hz, 1H), 4.14–4.18 (m, 2H), 4.42–4.45 (m, 1H), 4.49–4.52 (m, 1H), 7.03–09 (m, 20H), 7.10–7.15 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 27.9, 59.5, 66.0, 72.3, 75.3, 75.5, 75.7, 87.6, 88.1, 98.2, 98.2, 126.1, 127.1, 132.3, 135.6. ESI-HRMS Calcd for $C_{46}H_{41}O_3Fe$ (M+H): 697.2400. Found: 697.2390. $[\alpha]^{24}_D$ = –105 (*c* 1.0, $CHCl_3$).



[(2*S*,4*S*)-4-(Methoxymethyl)-1,3-dioxan-2-yl]-1',2',3',4',5'-pentaphenylferrocene (2.5c). To a solution of chiral acetal **2.3c** (603 mg, 0.87 mmol) in THF (2.6 mL), ^{t}BuLi (1.77 M in pentane, 0.54 mL, 0.95 mmol) was added at –78 °C. The reaction mixture was stirred for 30 minutes and then allowed to warm to room temperature. The mixture was cooled to –78 °C again before a solution of *p*-toluenesulfonyl azide (173 μL, 1.13 mmol) in THF (0.7 mL) was added to the mixture. The reaction mixture was allowed to warm to room temperature and stirred for 22 h. The mixture was quenched with H_2O, neutralized with saturated aqueous NH_4Cl, extracted with EtOAc, washed with brine. The organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4/1) to afford 644.8 mg of the azide as an orange solid (91% yield).



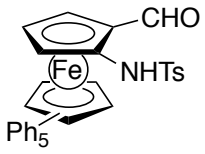
To a solution of the azide (114 mg, 0.15 mmol) in DMF (2.0 mL) was added palladium on carbon (ca. 10%w/w, 40 mg), and the resulting mixture was stirred at room temperature under hydrogen atmosphere (1 atm) for 27 h, filtered through celite and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2/1) to afford 100 mg of total compound as an orange solid (92% yield).

^{1}H NMR ($CDCl_3$): δ 1.32–1.38 (m, 1H), 1.72 (qd, *J* = 12.6 and 5.2 Hz, 1H), 3.10 (s, 1H), 3.25–3.36 (m, 5H), 3.53–3.65 (m, 2H), 3.72 (br, 1H), 3.82 (br, 1H), 4.10 (dd, *J* = 11.2 and 4.9 Hz, 1H), 4.15 (br, 1H), 5.27 (s, 1H), 7.00–7.09 (m, 20H), 7.09–7.15 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 27.7, 59.2, 66.0, 68.8, 70.3, 75.2, 75.4, 87.3, 99.5, 125.8, 126.7, 127.0, 132.3, 135.8. EI-HRMS Calcd for $C_{46}H_{41}FeO_3N$: 711.2430. Found: 711.2409. $[\alpha]^{24}_D = -15$ (*c* 1.0, $CHCl_3$).

The mixture of planar-chiral amine (211 mg, 0.297 mmol), DABCO (3.3 mg, 29.7 μmol, 10 mol %), $ClCH_2CH_2Cl$ (3.0 mL), and Et_3N (83 μL, 0.59 mmol) was slowly added a suspension of *p*-toluenesulfonyl chloride (96.2 mg, 0.51 mmol) in $ClCH_2CH_2Cl$ (3.0 mL). The reaction mixture was stirred at room temperature for 22 h under nitrogen. The mixture was quenched with saturated aqueous $NH_4Cl_{(aq)}$, extracted with CH_2Cl_2, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc/Et_3N = 16/4/1) to afford 254 mg of **2.5c** as an orange solid (90% yield).

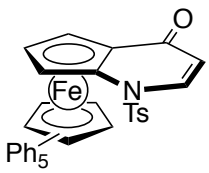
^{1}H NMR ($CDCl_3$): δ 1.20–1.27 (m, 1H), 1.49 (qd, *J* = 12.5 and 4.8 Hz, 1H), 2.31 (s, 3H), 3.22 (dd, *J* = 9.8 and 6.2 Hz, 1H), 3.33 (dd, *J* = 9.8 and 4.7 Hz, 1H), 3.43 (s, 3H), 3.41–3.53 (m, 2H), 3.82 (dd, *J* = 11.2 and 4.8 Hz, 1H), 3.94 (t, *J* = 2.6 Hz, 1H), 4.06 (dd, *J* = 2.8 and 1.6 Hz, 1H), 4.83–4.87 (m, 1H), 5.19 (s, 1H), 7.04–7.16 (m, 27H), 7.56 (d, *J* = 8.4 Hz, 5H). ^{13}C NMR ($CDCl_3$): δ 21.5, 27.2, 59.2, 65.7, 70.1, 70.5, 72.0, 73.4, 74.5, 75.4, 77.2, 87.9, 95.8, 98.9, 126.3, 127.2, 127.5, 129.0, 132.3, 134.9, 136.1, 143.0. ESI-HRMS Calcd for $C_{53}H_{48}FeO_5NS$ (M+H): 866.2597. Found: 866.2585. $[\alpha]^{26}_D = -235$ (*c* 0.1, $CHCl_3$).

(S_p)-1-Formyl-2-(*p*-toluenesulfonylamido)-1',2',3',4',5'-pentaphenylferrocene (2.14c). To a solution of the **2.5c** (217 mg, 0.25 mmol) in THF (5 mL), H_2O (5 mL) and *p*-toluenesulfonic acid monohydrate (72 mg, 0.377 mmol) were added. The resulting two-phase mixture was stirred vigorously, refluxed for 22 h under air and then allowed to cool to room temperature. A saturated aqueous $NaHCO_3$ was added to the mixture until generation of CO_2 gas ended. The organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/CH_2Cl_2 = 2/3) to afford 200 mg of **2.14c** as a red solid (99% yield).



^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H), 4.42 (t, *J* = 2.6 Hz, 1H), 4.52 (dd, *J* = 2.9 and 1.5 Hz, 1H), 5.13 (br, 1H), 6.96–7.00 (m, 10H), 7.06–7.12 (m, 12H), 7.15–7.20 (m, 5H), 7.28 (br, 1H), 7.45–7.48 (m, 2H), 9.69 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 21.5, 67.6, 73.5, 75.9, 76.5, 89.1, 97.4, 127.0, 127.2, 127.4, 129.3, 132.1, 133.7, 135.5. ESI-HRMS Calcd for $C_{48}H_{38}O_3NSFe$ (M+H): 764.1916. Found: 764.1895. $[\alpha]^{27}_D$ = –439 (*c* 0.01, $CHCl_3$). mp: 205 °C (decompose)

(S_p)-*N*-(*p*-Toluenesulfonyl)-1',2',3',4',5'-pentaphenylferroco[b]-4-pyridone (2.2c). A solution of ethynylmagnesium bromide (0.5 M in THF, 0.65 mL, 0.326 mmol) was added to a solution of **2.14c** (63.3 mg, 0.082 mmol) in THF (1.5 mL). The mixture was stirred for 20 min at 50 °C and quenched with H_2O. To the mixture was added saturated aqueous NH_4Cl until the formed precipitate dissolved, and the mixture was extracted with EtOAc twice. The combined extracts were dried over Na_2SO_4 and filtered. The organic phase was concentrated under reduced pressure. The residue was directly used for the next step without further purification.

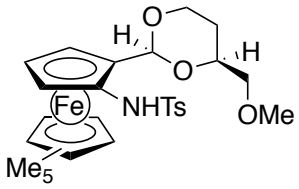


A solution of planar-chiral alcohol (172 mg, 0.222 mmol) in CH_2Cl_2 (3.5 mL) was added over 30 min to a mixture of MnO_2 (270 mg, 3.335 mmol), TBAI (41.1 mg, 0.111 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred at 35 °C for 2 h under nitrogen, filtered through celite, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2/EtOAc = 16/1) to afford 164 mg of **2.2c** as a red solid (99% yield).

^{1}H NMR ($CDCl_3$): δ 2.33 (s, 3H), 4.29 (t, *J* = 2.8 Hz, 1H), 4.81 (dd, *J* = 2.8 and 1.4

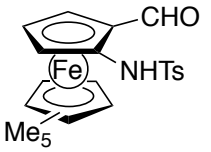
Hz, 1H), 5.55 (dd, J = 2.5 and 1.4 Hz, 1H), 5.81 (d, J = 8.5 Hz, 1H), 6.99–7.04 (m, 10H), 7.06–7.12 (m, 10H), 7.14–7.20 (m, 7H), 7.54 (m, 2H), 7.78 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 21.6, 67.7, 67.8, 74.2, 76.7, 87.7, 102.6, 114.7, 126.7, 127.0, 127.2, 130.1, 132.3, 133.4, 133.8, 137.7, 145.8, 185.6. ESI-HRMS Calcd for $C_{50}H_{38}NO_3SFe$ (M+H): 788.1916. Found: 788.1898. $[\alpha]^{24}_D$ = +165 (*c* 0.01, $CHCl_3$). mp: 194 °C (decompose).

(S_p)-1-[(2*S*,4*S*)-4-(Methoxymethyl)-1,3-dioxan-2-yl]-2-(*p*-toluenesulfonamido)-1',2',3',4',5'-pentamethylferrocene (2.5a). This compound was obtained according with the general procedure described above.



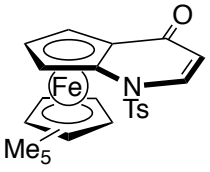
^{1}H NMR ($CDCl_3$): δ 1.30–1.35 (m, 1H), 1.63–1.74 (m, 1H), 1.85 (s, 15H) 2.33 (s, 3H), 3.44–3.50 (m, 1H), 3.48 (s, 5H), 3.49 (s, 1H), 3.52–3.58 (m, 1H), 3.75–3.85 (m, 2H), 4.28 (dt, J = 2.4 and 1.4 Hz, 1H), 4.75 (s, 1H), 6.83 (s, 1H), 7.13–7.15 (m, 2H), 7.50–7.53 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 10.6, 21.5, 27.1, 59.5, 65.9, 67.4, 69.5, 70.5, 73.5, 75.1, 75.3, 81.4, 91.1, 99.8, 127.4, 129.1, 136.4, 142.8. EI-HRMS Calcd for $C_{28}H_{37}O_5FeNS$: 555.1742. Found: 555.1725. $[\alpha]^{21}_D$ = –87 (*c* 1.0, $CHCl_3$).

(S_p)-1-Formyl-2-(*p*-toluenesulfonylamido)-1',2',3',4',5'-pentaphenylferrocene (2.14a). This compound was obtained according with the general procedure described above.



^{1}H NMR ($CDCl_3$): δ 1.79 (s, 15H), 2.32 (s, 3H), 3.88 (dd, J = 2.9 and 1.5 Hz, 1H), 3.97 (t, J = 2.9 Hz, 1H), 4.78 (t, J = 1.4 Hz, 1H), 7.14 (d, J = 8.0 Hz, 2H), 7.46 (s, 1H), 7.55–7.59 (m, 2H), 9.53 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 10.3, 21.4, 66.2, 70.6, 72.7, 74.1, 83.0, 96.3, 127.1, 129.3, 135.9, 143.4, 196.1. ESI-HRMS Calcd for $C_{23}H_{27}O_3FeNSNa$ (M+Na): 476.0953. Found: 476.0948. $[\alpha]^{24}_D$ = –1085 (*c* 0.01, $CHCl_3$).

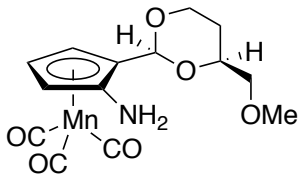
(S_p)-*N*-(*p*-Toluenesulfonyl)-1',2',3',4',5'-pentamethylferroco[b]-4-pyridone (2.2a). This compound was obtained according with the general procedure described above.



^{1}H NMR ($CDCl_3$): δ 1.74 (s, 15H), 2.35 (s, 3H), 3.86 (t, J = 2.7 Hz, 1H), 4.24 (dd, J = 1.3 and 2.7 Hz, 1H), 4.95 (dd, J = 2.8 and 1.3

Hz, 1H), 5.88 (d, J = 8.3 Hz, 1H), 7.23 (d, J = 8.0 Hz, 2H), 7.68 (m, 2H), 7.97 (d, J = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 9.8, 21.8, 64.9, 65.8, 73.0, 74.0, 81.5, 99.1, 111.0, 127.3, 130.2, 133.9, 136.1, 145.8, 186.3. EI-HRMS Calcd for $C_{25}H_{27}NO_3SFe$: 477.1061. Found: 477.1055. $[\alpha]^{20}_D$ = –1853 (*c* 0.01, $CHCl_3$).

(S_p)-1-[(2*S*,4*S*)-4-(Methoxymethyl)-1,3-dioxan-2-yl]-2-amidocymantrcene (2.4d).

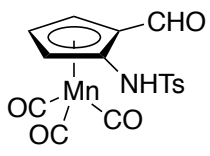


To a solution of **2.3d** (8.02 g, 24 mmol) in Et_2O (100 mL), at -78 °C dropwise the ^{t}BuLi (1.64M in pentane, 19 mL, 31.2 mmol) over 30 minutes, the mixture was stirred at -78 °C for 15 minutes, then warmed to the room temperature for another 45 minutes, was added TsN_3 (7.1 g, 36.0 mmol). The mixture was stirred at room temperature for the overnight. The reaction mixture was quenched with water and extracted with CH_2Cl_2 twice. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator. The residue was directly used for the next step without further purification.

The crude residue was dissolved in CH_2Cl_2 (60 mL), to this were added $NaBH_4$ (4.39 g, 116 mmol), water (20 mL) at 0 °C, the mixture was stirred at the room temperature for overnight. The reaction mixture was extracted with CH_2Cl_2 twice. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator. The crude mixture was purified by silica gel column chromatography (hexane/EtOAc/Et_3N = 1.5/1/2%) to afford 5.85 g of title compounds **2.4d** (70% yield).

^{1}H NMR ($CDCl_3$): δ 1.47–1.51 (m, 1H), 1.80–1.90 (m, 1H), 3.38 (s, 3H), 3.40–3.53 (m, 2H), 3.73 (s, 2H), 3.89 (t, J = 11.6 Hz, 1H), 4.14 (s, 1H), 4.19-4.23 (m, 1H), 4.39 (s, 1H), 4.68 (s, 1H), 5.33 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 27.7, 59.5, 64.9, 66.4, 75.2, 75.9, 76.0, 78.3, 82.8, 97.3, 126.6, 225.5. ESI-HRMS Calcd for $C_{14}H_{17}O_6NMn$ (M+H): 350.0436. Found: 350.0431. $[\alpha]^{24}_D$ = +86 (*c* 0.25, toluene).

(S_p)-1-Formyl-2-(*p*-toluenesulfonamido)-cymantrene (2.14d).



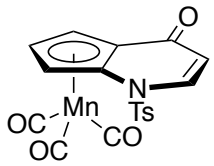
To a solution of **2.4d** (5.85 g, 16.7 mmol) in CH_2Cl_2 (100 mL), were added DABCO (187.3 mg, 1.67 mmol), Et_3N (1.69 g, 16.7 mmol), TsCl (3.19 g, 16.7 mmol), the mixture was stirred at 0 °C for the overnight. The reaction mixture was washed with water and extracted with

CH_2Cl_2 twice. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator. The residue was directly used for the next step without further purification.

The residue was dissolved in CH_2Cl_2 (150 mL), to this was added $HCl_{(aq)}$ (30%, 115 mL), the mixture was stirred at room temperature for 2 days. The reaction mixture was quenched by $KOH_{(aq)}$ (10%), extracted with CH_2Cl_2 twice. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator. The crude mixture was purified by nitrogen silica gel column chromatography (hexane/EtOAc= 2/1) to afford 3.19 g of title compounds as yellow solid (48% yield).

^{1}H NMR ($CDCl_3$): δ 2.44 (s, 3H), 4.58 (s, 1H), 5.15 (s, 1H), 5.33 (s, 1H), 7.36 (d, *J* = 3.24 Hz, 2H), 7.81 (d, *J* = 3.2 Hz, 2H), 8.35 (s, 1H), 9.59 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 21.7, 73.0, 75.8, 77.6, 83.3, 117.0, 127.8, 130.0, 134.6, 145.2, 190.4, 221.6. ESI-HRMS Calcd for $C_{16}H_{13}O_6NSMn$ (M+H): 401.9844. Found: 401.9850. $[\alpha]^{25}_D$ = –43 (*c* 0.1, toluene).

(S_p)-*N*-(*p*-Toluenesulfonyl)-cymantro-4-pyridone (2.2d).



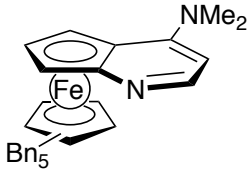
To a solution of **2.14d** (2.23 g, 5.56 mmol) in THF (35 mL), added the ethynylmagnesium bromide solution (33.36 mL, 16.68 mmol), the mixture was stirred in the room temperature for overnight. The mixture was quenched with $NH_4Cl_{(aq)}$ and extracted with EtOAc twice. The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The crude mixture was not purified.

A solution of planar-chiral alcohol (2.46 g, 5.75 mmol) in CH_2Cl_2 (60 mL) was added over 30 min to a mixture of MnO_2 (5.0 g, 57.5 mmol) and the TBAI (424.78 mg, 1.15 mmol). The mixture was stirred at room temperature for overnight, the reaction mixture was filtered through the celite. The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The crude mixture was purified by nitrogen silica gel column chromatography (benzene/EtOAc = 15/1) to afford 1.6 g of title compounds **2.2d** as yellow solid (68% yield).

^{1}H NMR ($CDCl_3$): δ 2.47 (s, 3H), 4.78 (t, *J* = 1.04 Hz, 1H), 5.4 (s, 1H), 5.55 (d, *J* = 1.0 Hz, 1H), 6.03 (d, *J* = 3.2 Hz, 1H), 7.43 (d, *J* = 3.28 Hz, 2H), 7.84 (d, *J* = 3.36 Hz, 2H), 7.96 (d, *J* = 3.2 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 21.8, 70.8, 76.7,, 81.0, 82.8, 111.9, 114.8, 128.0, 130.7, 132.3, 136.8，147.2, 180.0, 222.1. ESI-HRMS Calcd for $C_{18}H_{13}O_6NSMn$ (M+H): 425.9844. Found: 425.9852. $[\alpha]^{25}_D$ = +88 (*c* 0.06, Et_2O).

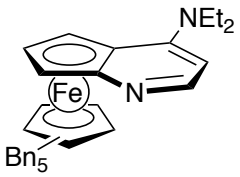
General Procedure for Synthesis of (*S*)-4-Dialkylamino-ferroco pyridines (2.1). To an oven dried Schlenk flask was added $TiCl_4$ (1.2 mL, 1.2 mmol). To the flask were added N-(Trimethylsilyl) dimethylamine (524.6 μl, 2.4 mmol). To the resulting green mixture was added a solution of **2.2** (343.2 mg, 0.4 mmol) in benzene (10 mL), and the solution was stirred at 55°C overnight, then allowed to cool to room temperature. To the reaction mixture, ice and 2.5 N $NaOH_{(aq)}$ were added successively. The mixture was extracted with CH_2Cl_2 and combined organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography EtOAc to EtOAc/Et_3N (9/1).

(S_p)-4-Dimethylamino-1',2',3',4',5'-pentabenzylferroco[*b*]pyridine (2.1bw).



This compound was obtained according with the general procedure described above. ^{1}H NMR ($CDCl_3$): δ 3.33 (s, 3H), 3.73 (s, 10H), 3.96 (t, *J* = 1.16 Hz, 1H), 4.55–4.56 (m, 1H), 4.84 (br, 1H), 5.94 (d, *J* =2.08 Hz, 1H), 6.45 (d, *J* = 2.84 Hz, 10H), 6.77–6.89 (m, 15H), 8.47 (d, *J* = 2.04 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 32.1, 41.9, 65.0, 67.9, 74.7, 75.4, 83.8, 95.9, 112.1, 125.4, 127.7, 128.7, 140.2, 152.7, 159.0. ESI-HRMS Calcd for $C_{50}H_{47}N_2Fe$ (M+H): 731.3090. Found: 731.3093. $[\alpha]^{26}_D$ = +2325 (*c* 0.1, EtOAc).

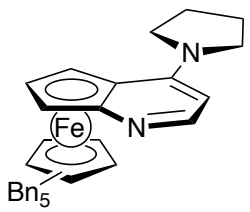
(S_p)-4-Diethylamino-1',2',3',4',5'-pentabenzylferroco[*b*]pyridine (2.1bx).



^{1}H NMR ($CDCl_3$): δ 1.40 (t, *J* = 6.86 Hz, 6H), 3.44–3.50 (m, 2H), 3.74 (s, 10H), 3.81–3.87 (m, 2H), 3.95 (t, *J* = 2.7 Hz, 1H), 4.36 (br, 1H), 4.83 (br, 1H), 5.95 (d, *J* = 5.0 Hz, 1H), 6.44–6.47 (m, 10H), 6.80–6.90 (m, 15H), 8.42 (d, *J* = 5.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 13.3, 32.2, 45.3, 64.7, 67.9, 73.8, 75.3, 83.7, 95.2, 112.7, 125.4, 127.7, 128.7, 140.3, 152.9, 157.2. ESI-HRMS Calcd for $C_{52}H_{51}N_2Fe$ (M+H): 759.3403.

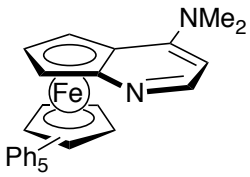
Found: 759.3398. $[\alpha]^{25}_{D}$ = +1196 (*c* 0.1, EtOAc).

(S_p)-4-Pyrrolidino-1',2',3',4',5'-pentabenzylferroco[*b*]pyridine (2.1by).



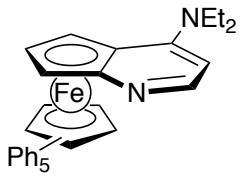
^{1}H NMR ($CDCl_3$): δ 2.12–2.15 (m, 4H), 3.68–3.77 (14H), 3.92–3.94 (t, *J* =1.08 Hz, 1H), 4.55 (br, 1H), 4.80 (br, 1H), 5.80-5.82 (m, 1H), 6.44–6.45 (d, *J* =3.08 Hz, 10H), 6.79–6.88 (m, 15H), 8.41–8.43 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 25.9, 32.1, 49.7, 64.7, 67.8, 74.3, 75.0, 83.7, 94.9, 112.2, 125.4, 127.7, 128.7, 140.3, 152.9, 160.0. ESI-HRMS Calcd for $C_{52}H_{49}N_2Fe$ (M+H): 757.3246. Found: 757.3250. $[\alpha]^{25}_{D}$ = +1196 (*c* 0.1, EtOAc).

(S_p)-4-Dimethylamino-1',2',3',4',5'-pentaphenylferroco[*b*]pyridine (2.1cw).



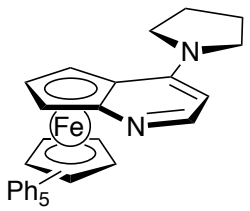
^{1}H NMR ($CDCl_3$): δ 2.96 (s, 6H), 4.62 (t, *J* = 2.8 Hz, 1H), 4.92 (dd, *J* = 3.0 and 1.0 Hz, 1H), 5.07 (dd, *J* = 2.8 and 1.2 Hz, 1H), 5.86 (d, *J* = 5.2 Hz, 1H), 6.91–6.99 (m, 10H), 7.01–7.09 (m, 10H), 7.10–7.17 (m, 5H), 8.17 (d, *J* = 5.6 Hz, 1H). ^{13}C NMR ($CHCl_3$): δ 41.5, 66.0, 77.2, 77.8, 85.7, 99.0, 112.9, 126.0, 126.9, 132.3, 135.0, 153.5, 158.6. ESI-HRMS Calcd for $C_{45}H_{37}N_2Fe$ (M+H): 661.2301. Found: 661.2283. $[\alpha]^{27}_{D}$ = +1018 (*c* 0.01, $CHCl_3$). mp: 151 °C (decompose).

(S_p)-4-Diethylamino-1',2',3',4',5'-pentabenzylferroco[*b*]pyridine (2.1cx).



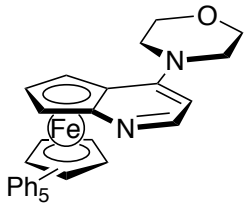
^{1}H NMR ($CDCl_3$): δ 1.06 (t, *J* = 7.2 Hz, 6H), 3.26 (2H), 3.56 (2H), 4.24 (t, *J* = 2.8 Hz, 1H), 4.86 (d, *J* = 2.0 Hz, 1H), 5.01 (d, *J* = 1.6 Hz, 1H), 5.90 (d, *J* = 5.6 Hz, 1H), 6.91–6.99 (m, 10H), 7.01–7.09 (m, 10H), 7.09–7.17 (m, 5H), 8.06 (d, *J* = 5.2 Hz, 1H) ESI-HRMS Calcd for $C_{47}H_{41}N_2Fe$ (M+H): 689.2614. Found: 689.2598.

(S_p)-4-Pyrrolidino-1',2',3',4',5'-pentaphenylferroco[*b*]pyridine (2.1cy).



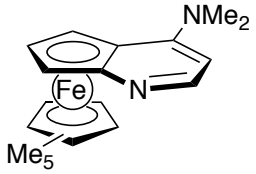
^{1}H NMR ($CDCl_3$): δ 1.82–2.01 (m, 2H), 2.01–2.16 (m, 2H), 3.10–3.90 (m, 4H), 4.22 (t, *J* = 2.4 Hz, 1H), 4.90 (d, *J* = 2.8 Hz, 1H), 5.00 (d, *J* = 2.4 Hz, 1H), 5.70 (d, *J* = 5.2 Hz, 1H), 6.91–6.99 (m, 10H), 7.01–7.09 (m, 10H), 7.10–7.17 (m, 5H), 8.10 (d, *J* = 5.2 Hz, 1H). ESI-HRMS Calcd for $C_{47}H_{39}N_2Fe$ (M+H): 687.2457. Found: 687.2441.

(S_p)-4-Morpholino-1',2',3',4',5'-pentaphenylferroco[*b*]pyridine (2.1cz).



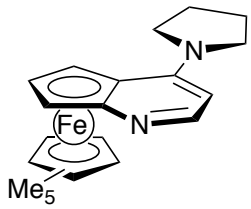
^{1}H NMR ($CDCl_3$): δ 2.57–2.73 (m, 2H), 3.30–3.47 (m, 2H), 3.66–3.81 (m, 2H), 3.87–4.01 (m, 2H), 4.28 (t, *J* = 2.0 Hz, 1H), 4.88 (t, *J* = 1.2 Hz, 1H), 5.12 (t, *J* = 1.6 Hz, 1H), 6.16 (d, *J* = 4.8 Hz, 1H), 6.89–6.99 (m, 10H), 7.01–7.09 (m, 10H), 7.10–7.17 (m, 5H), 8.35 (d, *J* = 4.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 50.0, 64.6, 64.7, 66.2, 70.1, 70.2, 78.2, 78.7, 85.7, 103.9, 111.9, 126.1, 126.9, 132.4, 134.8, 153.7, 159.0. ESI-HRMS Calcd for $C_{47}H_{39}ON_2Fe$ (M+H): 703.2406. Found: 703.2386.

(S_p)-4-Dimethylamino-1',2',3',4',5'-pentamethylferroco[*b*]pyridine (2.1aw).



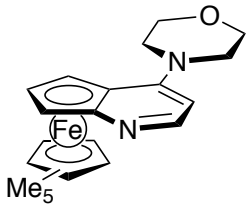
This compound was obtained in 87% yield according to the general procedure described above, and the ^{1}H- and ^{13}C NMR data as well as the $[\alpha]_D$ value were consistent with the reported data. $[\alpha]^{21}_D$ = +1640 (*c* 0.08, $CHCl_3$) [lit.[20] $[\alpha]^{20}_D$ = +1560 (*c* 0.10, $CHCl_3$)].

(S_p)-4-Pyrrolidino-1',2',3',4',5'-pentamethylferroco[*b*]pyridine (2.1ay).



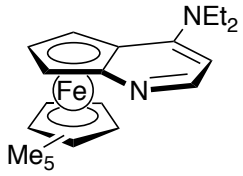
This compound was obtained in 88% yield according with the general procedure described above, and the ^{1}H- and ^{13}C-NMR data as well as the $[\alpha]_D$ value were consistent with the reported data. $[\alpha]^{19}_D$ = +2075 (*c* 0.01, $CHCl_3$) [lit.[21] $[\alpha]^{20}_D$ = +2030 (*c* 0.0075, $CHCl_3$)].

(S_p)-4-Morpholino-1',2',3',4',5'-pentamethylferroco[*b*]pyridine (2.1az).



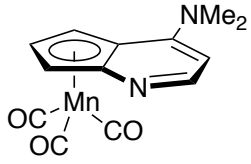
^{1}H NMR ($CDCl_3$): δ 1.64 (s, 15H), 3.26–3.30 (m, 2H), 3.54–3.59 (m, 2H), 3.86–3.87 (m, 1H), 3.86–3.99 (m, 4H), 4.18 (m, 1H), 4.72(m, 1H), 6.02 (d, *J* = 5.1 Hz, 1H), 8.36 (d, *J* = 5.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 9.9, 49.6, 62.9, 66.9, 67.4, 75.4, 76.8, 78.6, 98.5, 110.6, 151.6, 160.3. EI-HRMS Calcd for $C_{22}H_{28}FeN_2O$: 392.1551. Found: 392.1554. $[\alpha]^{20}_D$ = –509 (*c* 0.01, $CHCl_3$).

(S_p)-4-Diethylamino-1',2',3',4',5'-pentamethylferroco[*b*]pyridine (2.1ax).



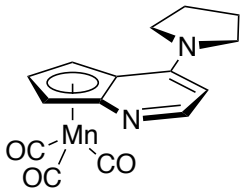
^{1}H NMR ($CDCl_3$): δ 1.33 (t, *J* = 7.3 Hz, 6H), 1.67 (s, 15H), 3.41 (dq, *J* = 14.4 and 7.1 Hz, 2H), 3.75 (t, *J* = 2.5 Hz, 1H), 3.77 (dq, *J* = 14.4 and 7.1 Hz, 2H), 4.21 (dd, *J* = 3.0 and 0.9 Hz, 1H), 4.56 (dd, *J* = 2.5 and 0.9 Hz, 1H), 5.75 (d, *J* = 5.4 Hz, 1H), 8.21 (d, *J* = 5.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 9.8, 13.0, 44.8, 63.6, 67.1, 72.8, 74.5, 78.4, 94.0, 111.7, 151.9, 157.5. ESI-HRMS Calcd for $C_{22}H_{31}FeN_2$ (M+H): 379.1831. Found: 379.1821. $[\alpha]^{22}_D$ = +1576 (*c* 0.01, $CHCl_3$).

(S_p)-4-Dimethylamino-cymantro-pyridine (2.1dw).



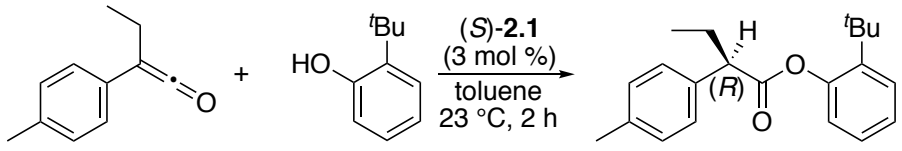
^{1}H NMR ($CDCl_3$): δ 3.32 (s, 6H), 4.98 (s, 1H), 5.29 (d, *J* = 1.7 Hz, 1H), 5.82(s,1H), 8.19 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 41.6, 71.4, 71.6, 76.7, 84.7, 86.0, 97.4, 129.1, 155.6, 224.4. ESI-HRMS Calcd for $C_{13}H_{12}O_3N_2Mn$ (M+H): 299.0228. Found: 299.0236. $[\alpha]^{25}_D$ = +2069 (*c* 0.1, EtOAc).

(S_p)-4-Pyrrolidino-cymanto-pyridine (2.1dy).



^{1}H NMR ($CDCl_3$): δ 2.08 (s, 4H), 3.66 (s, 4H), 4.95 (s, 1H), 5.30 (s, 2H), 5.69 (s, 1H), 8.15 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 25.0, 49.0, 70.9, 71.3, 84.7, 85.6, 97.3, 129.7, 152.7, 155.4, 224.3. ESI-HRMS Calcd for $C_{15}H_{14}N_2O_3Mn$ (M+H): 325.0385. Found: 325.0383. $[\alpha]^{25}_D$ = +2390 (*c* 0.14, EtOAc)

General Procedure for Ferroco-pyridine-Catalyzed Asymmetric Synthesis of Ester 2.19 from Ketene 2.17 and Phenol 2.18. Catalyst **2.1** (0.011 mmol, 3 mol %)



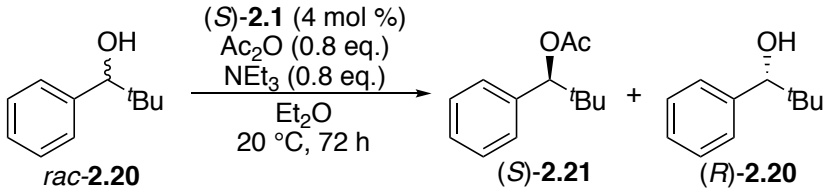
2.17 **2.18** (*R*)-**2.19**

was weighed into a flask, which was then purged with nitrogen. To this were added toluene (30 mL) and 2-*tert*-butylphenol (**2.18**; 58.6 mg, 0.390 mmol) successively. A solution of ethyl(*p*-tolyl)ketene (**2.17**; 60.1 mg, 0.375 mmol) in toluene (1.0 mL) was slowly added to the flask using a syringe-pump over 30 minutes. The reaction mixture was stirred at room temperature for 2 h, and

then *n*-propylamine (50 μL) was added. The resulting solution was passed through a plug of silica gel (eluent: hexane/Et_2O = 1/1). The ester was then purified by preparative TLC to give product **2.19** as a colorless oil. The enantiomeric purity of the ester was determined on a Daicel Chiralcel IC-3 column (eluent: hexane/^{i}PrOH = 500/1; flow = 1.0 mL/min; retention times: 11.7 min (*S*-enantiomer), 12.6 (*R*-enantiomer)). Characterization data for ester **2.19**.

^{1}H NMR ($CDCl_3$): δ 0.99 (t, *J* = 7.6 Hz, 3H), 1.21 (s, 9H), 1.92 (d of quint, *J* = 14.0 and 7.6 Hz, 1H), 2.25 (d of quint, *J* = 14.0 and 7.6 Hz, 1H), 2.35 (s, 3H), 3.67 (t, *J* = 7.8 Hz, 1H), 6.82 (dd, *J* = 7.8 and 1.6 Hz, 1H), 7.08–7.19 (m, 4H), 7.26–7.31 (m, 2H), 7.33 (dd, *J* = 7.8 and 2.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 12.2, 21.1, 26.3, 30.0, 34.3, 53.6, 123.6, 125.5, 126.7, 127.0, 128.1, 129.4, 135.0, 137.0, 141.0, 149.5, 172.6. APCI-HRMS Calcd for $C_{21}H_{27}O_2$ (M+H): 311.2006. Found: 311.1999. $[\alpha]^{20}_D$ = –61.6 (*c* 1.00, $CHCl_3$; for the sample of 92% ee).

General Procedure for Ferroco-pyridine-Catalyzed Kinetic Resolution/Acetylation of *rac*-alcohol. Catalyst **2.1** (0.02 mmol, 4 mol %) and *rac*-**2.20** (82.1 mg, 0.500 mmol) were weighed into a flask, which was then purged with nitrogen. To this were added Et_2O (1.0 mL), Et_3N (0.375 mmol, 52.3 μL), and acetic anhydride (0.375 mmol, 35.4 μL) successively. This reaction mixture was stirred at 20 °C for 72 h. The ester (*S*)-**2.21** and recovered (*R*)-**2.20** were separated by silica gel column chromatography (EtOAc/Hexane = 1/1). The enantiomeric purities of **2.21** and **2.20** were determined on a Daicel Chiralcel OD-H column (eluent: hexane/^{i}PrOH = 95/5; flow = 1.0 mL/min; retention times; 3.9 min (ester **2.21**: *R*-enantiomer), 4.2 min (ester **2.21**: *S*-enantiomer), 6.2 min (alcohol **2.20**: *S*-enantiomer), 8.0 min (alcohol **2.20**: *R*-enantiomer).



^{1}H NMR ($CDCl_3$): δ 0.99 (t, *J* = 7.6 Hz, 3H), 1.21 (s, 9H), 1.92 (d of quint, *J* = 14.0 and 7.6 Hz, 1H), 2.25 (d of quint, *J* = 14.0 and 7.6 Hz, 1H), 2.35 (s, 3H), 3.67 (t, *J* = 7.8 Hz, 1H), 6.82 (dd, *J* = 7.8 and 1.6 Hz, 1H), 7.08–7.19 (m, 4H), 7.26–7.31 (m, 2H),

7.33 (dd, J = 7.8 and 2.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 12.2, 21.1, 26.3, 30.0, 34.3, 53.6, 123.6, 125.5, 126.7, 127.0, 128.1, 129.4, 135.0, 137.0, 141.0, 149.5, 172.6.

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Chapter III

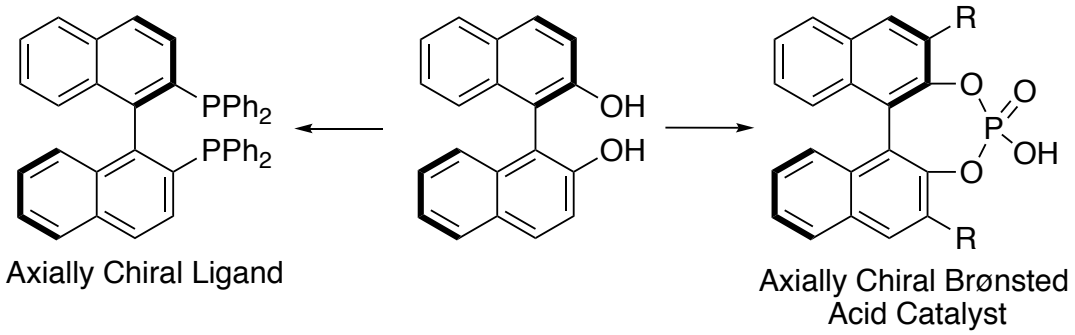
Enantioselective Synthesis of Ferrocene-Fused Planar-Chiral Cyclic Phosphonic Acid

Section 1

Introduction for Chapter III

Optically active 1,1'-bi-2-naphthol (BINOL) is a versatile axially chiral reagent[1] and was first prepared by von Richter in 1873.[2] Since then, the application of this molecule has been intensively studied. A wide variety of binaphthyl-based chiral organophosphorus ligands and catalysts can be prepared from BINOL (Scheme 3-1).[3]

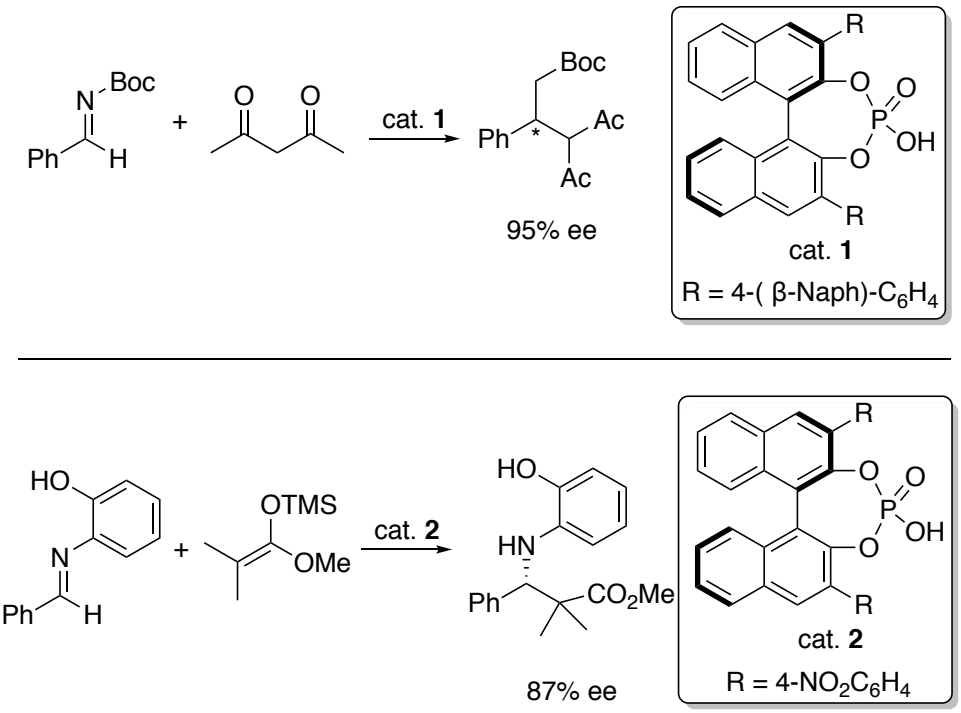
Scheme 3-1



In 1980, Noyori reported the atropisomeric C_2-symmetric bisphosphine ligand BINAP. This chiral ligand has been applied extensively in various asymmetric catalysis.[4-7] In 1986, a major breakthrough was achieved in BINAP-Ru chemistry when Noyori, et al. prepared a BINAP-Ru dicarboxylate complex for the asymmetric hydrogenation of various functionalized olefins.[8]

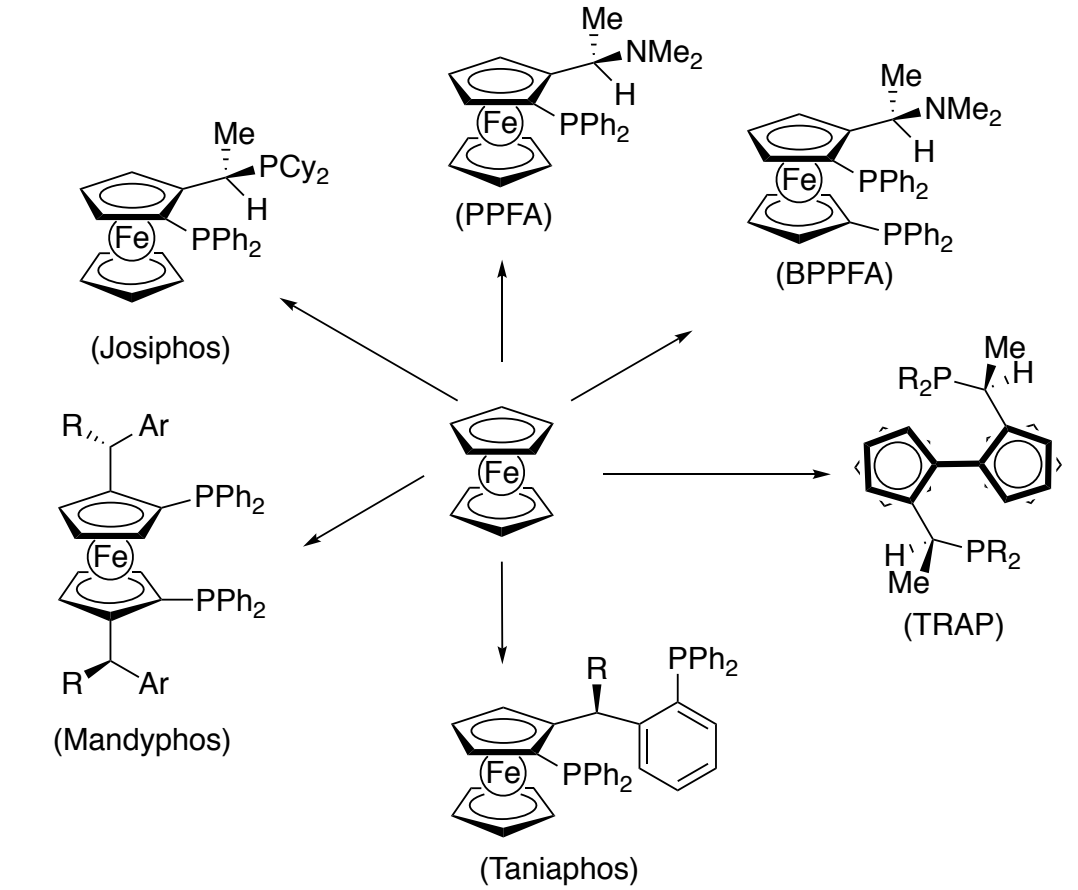
Binaphthyl-derived chiral phosphoric acids were developed in parallel by Akiyama, et al. and Terada, et al.[9,10] These molecules are versatile and efficient catalysts that can promote a variety of enantioselective transformations. The chiral phosphoric acid catalysts were successful for facilitating a large number of asymmetric carbon-carbon and carbon-heteroatom bond-forming processes (Scheme 3-2).[11,12]

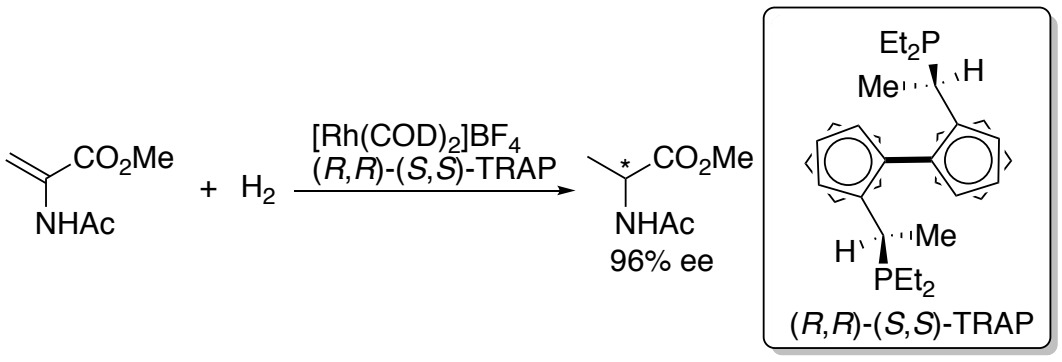
Scheme 3-2



Ferrocene possesses unique structural and electronic characteristics, and its derivatives could be regarded as universal modifiers for organic compounds. Due to its stable sandwich structure, many excellent chiral ferrocene-based phosphine ligands with interesting structural variations have been developed in the past two decades (Scheme 3-3, top). These chiral ferrocenylphosphines (such as PPFA, TRAP,[13] Taniaphos[14] and Josiphos) are some of the most successful chiral ligands, along with axially chiral biaryl-based phosphines (such as BINAP, and MeO-MOP[15]). For example, ferrocenylphosphines were employed as chiral ligands in transition-metal-catalyzed asymmetric organic synthesis, such as the Pd- or Rh-catalyzed asymmetric hydrogenation reactions (Scheme 3-3, bottom).[16]

Scheme 3-3





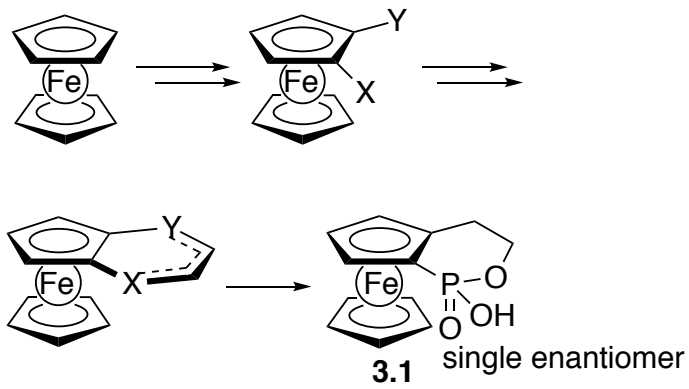
However, in the field of organophosphorus derivatives, most studies focused on ferrocenylphosphines as ligands,[17] and reports on Brønsted acid derivatives of ferrocene were extremely rare. To the best of our knowledge, no previous reports on ferrocene-derived planar-chiral phosphonic acid have been appeared.

Recently, we developed a novel and efficient method for the enantioselective synthesis of various planar-chiral metallocene-fused pyridones/pyridines in optically

active forms without chiral resolution (Chapter II). A similar strategy could be applicable for the asymmetric synthesis of other planar-chiral heterocycles.[18]

In this Chapter, the focus will be on the design and synthesis of ferrocene-fused planar-chiral cyclic phosphorus Brønsted acids. My design concept is that the phosphorus substituent is directly attached to a planar-chiral ferrocene core, which provides a good chiral environment at the acidic P(O)OH moiety in compound **3.1** (Scheme 3-4).

Scheme 3-4



3.1

Section 2

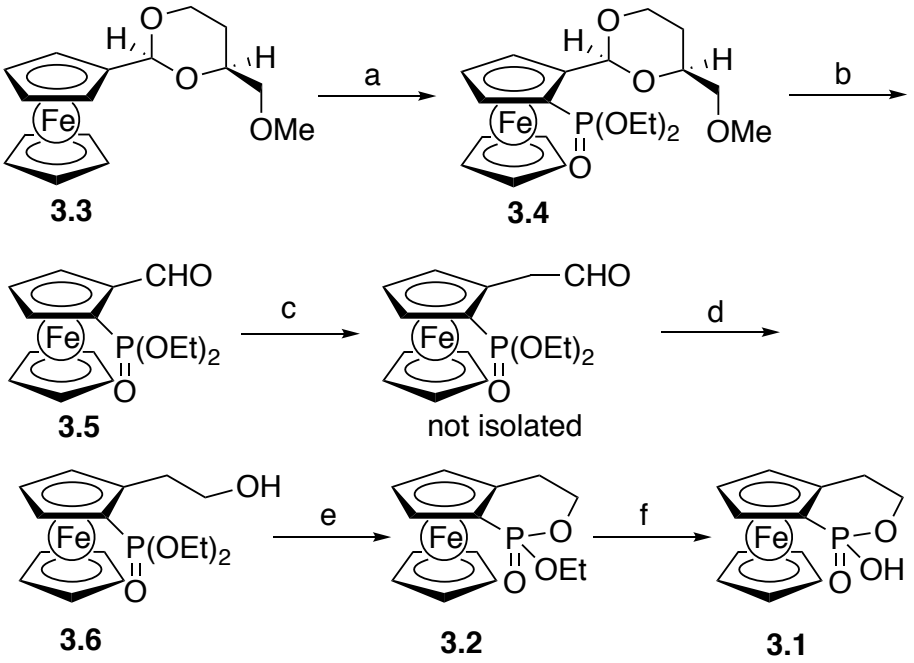
Enantioselective Synthesis of Ferrocene-Fused Planar-Chiral Cyclic Phosphonic Acid

In this section, the enantioselective synthesis of a novel ferrocene-based planar-chiral cyclic phosphonic acid as a single enantiomer is described. My strategy consists of two features: (i) chiral substituent-directed *ortho*-lithiation on the ferrocene platforms takes place in high diastereoselectivity (>99% de) to induce the planar chirality in the ferrocenes, (ii) after appropriate conversion of the two substituents at the 1- and 2-positions of the ferrocene cores, a cyclization process affords the planar-chiral cyclic phosphonic acids as single-enantiomers in high to excellent yields.

3-2-1 Enantioselective Synthesis of Ferrocene-Fused Planar-Chiral Cyclic Phosphonic Acid

The synthesis of planar-chiral cyclic phosphonic acid (*S*)-**3.1** was achieved as in Scheme 3-5. Starting with Kagan's acetal **3.3**, diastereoselective lithiation (>99% de), then a reaction with diethyl chlorophosphate[19] followed by hydrolysis of the chiral acetal moiety afforded aldehyde (*S*)-**3.5** as a single enantiomer. Compound (*S*)-**3.5** was converted to alcohol (*S*)-**3.6** by sequential Wittig reaction[20] with Ph_3P=CHOMe/hydrolysis/reduction with $NaBH_4$. Treatment of (*S*)-**3.6** with NaH facilitated the cyclization by an intramolecular alcohol exchange to give (*S*)-**3.2** in 99% yield. The chemoselective hydrolysis in (*S*)-**3.2** was achieved by using bromotrimethylsilane to give designed planar-chiral cyclic phosphonic acid (*S*)-**3.1** in 40% yield as a single enantiomer.[21,22] The enantiomeric homogeneity in (*S*)-**3.5** was retained during the reaction sequence shown in Scheme 3-5, and the final product (*S*)-**3.1** was also single enantiomeric.

Scheme 3-5



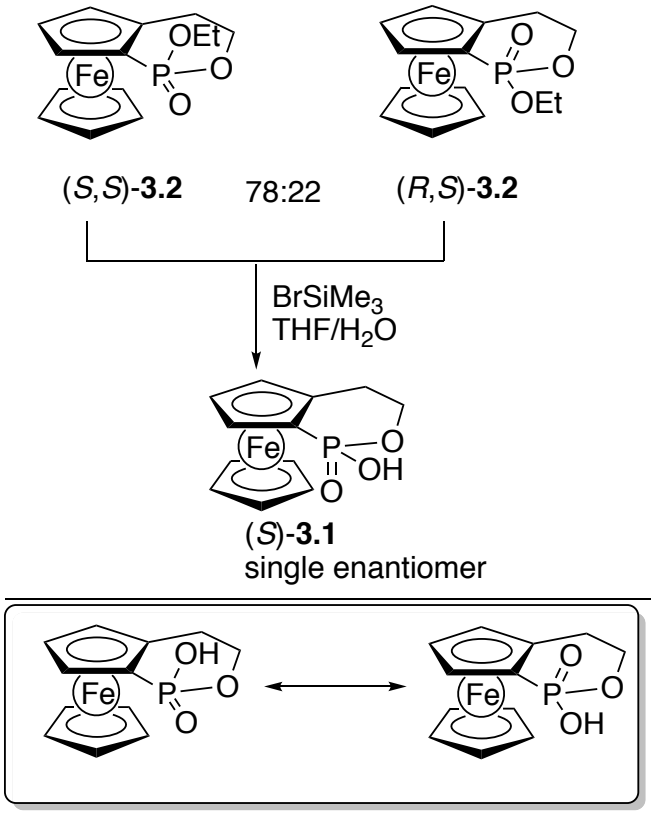
a) ^{t}BuLi, $ClPO(OEt)_2$; b) TsOH, H_2O; c) Ph_3P=CHOMe, then H_3O^+;
d) $NaBH_4$; e) NaH; f) $BrSiMe_3$, THF/H_2O

The cyclization step in Scheme 3-5 is worth mentioning. The NMR measurements revealed that there were two isomeric forms in (*S*)-**3.2** with the 78:22 molar ratio (determined by the ^{1}H NMR spectroscopy). Since the phosphorus atom in

3.2 is stereogenic, the compound possesses both planar- and central-chirality. Therefore, compound (*S*)-**3.2** exists in two diastereomeric forms. The minor isomer in (*S*)-**3.2** could be removed by column chromatography on silica gel, and the major isomer was obtained as a single diastereomer.

The hydrolysis of two diastereomers lead to the same product (*S*)-**3.1** as a single enantiomer. In contrast to (*S,S*)/(*R,S*)-**3.2**, the P(O)OH moiety in (*S*)-**3.1** exists in resonance forms (Scheme 3-6, bottom), which makes the phosphorus atom in (*S*)-**3.1** non-stereogenic. Therefore, compound (*S*)-**3.1** possesses *only* planar chirality.

Scheme 3-6



X-ray crystal structure of (–)-3.2. The single crystals of the major isomer in **3.2** were grown in pentane/dichloromethane at low temperature. The crystal structure is shown in Figure 3-1 with selected bond lengths and angles, and the absolute configuration was determined to be (*S*,*S*). The *S*-configuration at P1 could be ascribed to the steric repulsion between Fe(η^5-C_5H_5) and the P*OEt* group, and the ethoxy group takes the position opposite to the Fe(η^5-C_5H_5) moiety in (–)-**3.2**. The distance from Fe1 to the least-squares plane $_{C3\text{-}C7}$ of the η^5-ligand and η^5-C_5H_5 are 1.916 and 1.921 Å, respectively. The two ligands are nearly parallel, and the dihedral angle is 2.18°.

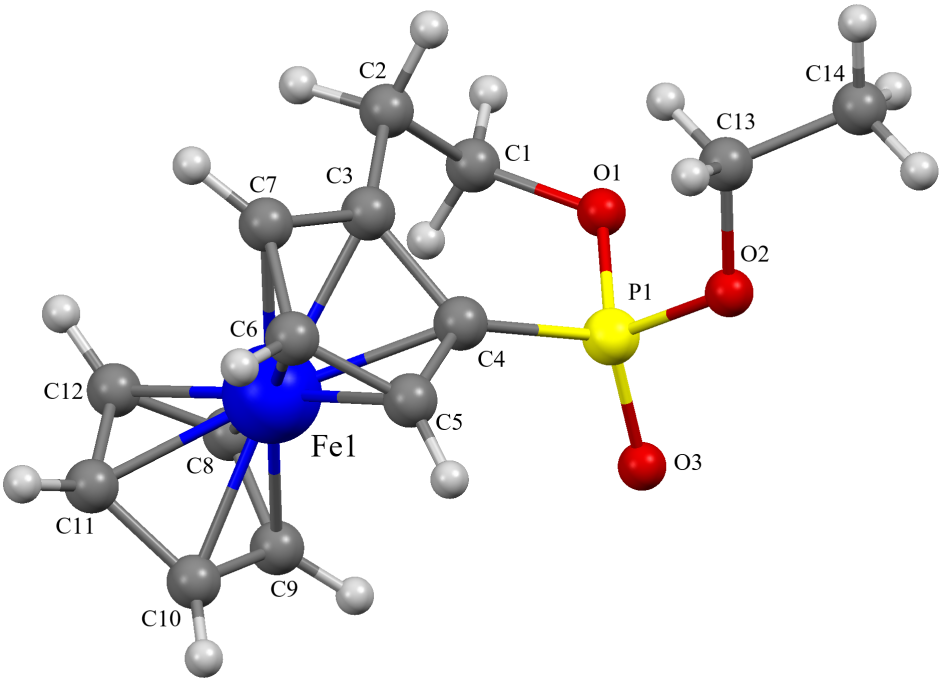


Figure 3-1. Ball-and-stick drawing of **(*S*)-(–)-3.2.** Selected bond lengths (Å) and angles (deg); P1-O1 = 1.588(5), P1-O2 = 1.579(4), P1-O3 = 1.467(5), P1-C4 = 1.772(8), O1-C1 = 1.461(6), O2-C13 = 1.461(7), C1-C2 = 1.52(1), C2-C3 = 1.51(1), C13-C14 = 1.45(1), Fe1 to the least-squares plane $_{C3\text{-}C4}$ of the η^5-ligand and η^5-C_5H_5 are 1.916 Å and 1.921 Å, O1-P1-O2 = 101.7(2), O1-P1-O3 = 116.2(3), O2-P1-O3 = 109.8(3), O1-P1-C4 = 102.6(3), P1-O2-C13 = 120.9(4), C9-N2-C10 = 119.4(5), dihedral angle between least-squares plane$_{C(3,4,5,6,7)}$ and least-squares plane$_{C(8,9,10,11,12)}$ = 2.18

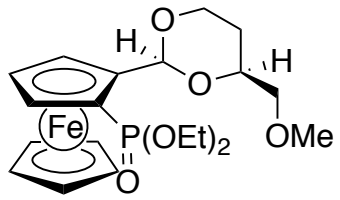
Conclusions for Chapter III

In this chapter, I developed a concise way to synthesize new ferrocene-fused planar-chiral cyclic phosphonic acid. The ferrocene-derived planar-chiral cyclic phosphonic acid (*S*)-**3.1** was obtained in an enantiomerically pure form without chiral resolution, and the present protocol for preparing ferrocene-based phosphorus Brønsted acid (*S*)-**3.1** on a multigram scale was accomplished without any difficulties. In addition, the analogous phosphonic acid with an (η^5-C_5Me_5)Fe substructure could be prepared by the same method in good yield, which is now under study in our research group. My strategy clearly indicated that various metallocene-fused planar-chiral heterocycles could be prepared by the similar strategy.

Experimental Section for Chapter III

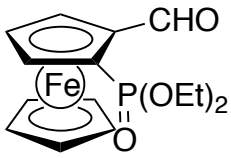
All anaerobic and/or moisture sensitive manipulations were carried out with standard Schlenk techniques under predried nitrogen or with glovebox techniques under prepurified argon. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) chemical shifts are reported in ppm downfield of internal tetramethylsilane. ^{31}P NMR (162 MHz) chemical shifts are externally referenced to 85% H_3PO_4. Tetrahydrofuran, diethyl ether, and benzene were distilled from benzophenone-ketyl under nitrogen prior to use. Dichloromethane was distilled from CaH_2 under nitrogen prior to use. All chemicals were obtained from commercial sources and used as received unless otherwise noted.

(S_p)-1-[(2*S*,4*S*)-4-(Methoxymethyl)-1,3-dioxan-2-yl]-2-(diethoxyphosphoryl)ferrocene (3.4). To a solution of Kagan's acetal **3.3** (1.1 g, 3.5 mmol) in THF (10 mL) was added ^{t}BuLi (1.64 M in pentane, 3.2 mL, 5.25 mmol) dropwise at –78 °C. The reaction mixture was stirred for 30 min at this temperature, to this mixture chlorodiethylphosphate (909.5 mg, 5.25 mmol) was added at –78 °C. The mixture was stirred in the room temperature for 12 h. The reaction mixture was quenched with water and extracted with $CHCl_3$ twice. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The crude mixture was purified by silica gel column chromatography (Et_2O/Acetone/Et_3N = 5/1/2%) to afford 1.43 g of title compound **3.4** as a red oil (90% yield).



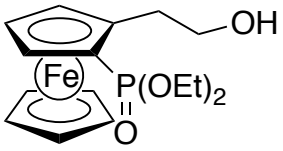
^{1}H NMR ($CDCl_3$): δ 1.26 (t, *J* = 6.9 Hz, 3H), 1.39 (t, *J* = 6.9 Hz, 3H), 1.47–1.51 (m, 1H), 1.79 (qd, *J* = 18.6 and 4.6 Hz, 1H), 3.30 (s, 3H) 3.32 (d, *J* = 4.6 Hz, 1H) 3.43 (dd, *J* = 10.1 and 6.0 Hz, 1H), 3.98–4.33 (m, 12H), 4.35–4.37 (m, 1H), 4.40–4.42 (m, 1H), 4.68–4.69 (m, 1H), 5.84 (s, 1H). ^{31}P NMR ($CDCl_3$): δ 25.2. ^{13}C NMR ($CDCl_3$): δ 16.4 (d, J_{CP}= 6.7 Hz), 16.6 (d, J_{CP}= 6.4 Hz), 28.1, 59.1, 61.4 (d, J_{CP}= 6.0 Hz), 61.8 (d, J_{CP}= 5.5 Hz), 65.3 (d, J_{CP}= 210.5 Hz), 66.9, 69.9 (d, J_{CP}= 13.5 Hz), 70.4 (d, J_{CP}= 13.3 Hz), 70.8, 72.8 (d, J_{CP}= 13.3 Hz), 75.6 (d, J_{CP}= 24.7 Hz), 88.6, 88.8, 99.0. ESI-HRMS Calcd for $C_{20}H_{29}O_6FePNa$ (M+Na): 475.0949. Found: 475.0940. $[\alpha]^{22}_{D}$ = –19 (*c* 0.24, $CHCl_3$).

(S_p)-1-Formyl-2-(diethoxyphosphoryl)ferrocene (3.5). To a solution of **3.4** (904.5 mg, 2.0 mmol) in THF (40 mL), added the *p*-toluenesulfonic acid monohydrate (380.4 mg, 2.0 mmol) and water (8.5 mL) successively, the mixture was stirred at 40 °C for overnight. The reaction mixture was extracted with EtOAc twice. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator. The crude mixture was purified by silica gel column chromatography (Et_2O/Acetone = 5/1) to afford 665.3 mg of title product **3.5** as black oil (95% yield).



^{1}H NMR ($CDCl_3$): δ 1.36 (t, *J* = 7.1 Hz, 6H), 4.16–4.22 (m, 4H), 4.41 (s, 5H), 4.80 (s, 1H), 4.91 (s, 1H), 5.13 (s, 1H), 10.33 (s, 1H). ^{31}P NMR ($CDCl_3$): δ 23.6. ^{13}C NMR ($CDCl_3$): δ 16.47 (d, J_{CP}= 11.0 Hz), 16.48, 62.2 (d, J_{CP}= 6.0 Hz), 70.2 (d, J_{CP}= 212.7 Hz), 70.6 (d, J_{CP}= 31.0 Hz), 71.4 (d, J_{CP}= 12.0 Hz), 71.6, 74.5 (d, J_{CP}= 13.5 Hz), 78.1 (d, J_{CP}= 13.5 Hz), 81.0 (d, J_{CP}= 16.0 Hz), 194.2. ESI-HRMS Calcd for $C_{15}H_{19}O_4FePNa$ (M+Na): 373.0268. Found: 373.0275. $[\alpha]^{27}_D$ = +120 (*c* 1.23, $CHCl_3$).

(S_p)-1-(2-Hydroxyethy)-2-(diethoxyphosphoryl)ferrocene (3.6). To a solution of Ph_3PCH_2OMeCl (377.1 mg, 1.1 mmol) in THF (1.5 mL) was added the ^{t}BuOK (134.7 mg, 1.2 mmol), the mixture was stirred at 0 ℃ for 30 min. To this mixture, the compound **3.5** (319.2 mg, 1.0 mmol) in THF (2.0 mL) was added, and the solution was stirred at room temperature for another 2 h. To the mixture was added saturated aqueous $NH_4Cl_{(aq)}$ until the precipitate dissolved, and the mixture was extracted with CH_2Cl_2 twice. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator. The crude mixture was directly used for the next step without further purification.



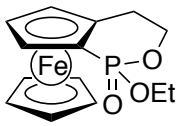
To this crude mixture was added $HCl_{(aq)}$ (12 N, 0.23 mL), and the solution was stirred in room temperature for 2 h. The reaction mixture was extracted with $CHCl_3$ twice. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator. The crude aldehyde was directly used for the next step without further purification.

To a vessel containing the crude planar-chiral aldehyde was added $NaBH_4$ (189.2 mg, 5.0 mmol), H_2O (22 mL) and MeOH (35 mL) successively. The reaction mixture was

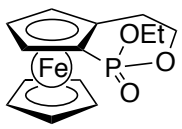
stirred at 40 °C for 4 h, the reaction mixture was extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator. The crude mixture was purified by silica gel column chromatography ($CHCl_3$/Acetone= 5/1 to 3/1) to afford 219.7 mg of the title compound **3.6** over three steps (60% yield).

^{1}H NMR ($CDCl_3$): δ 1.32 (t, *J* = 6.96 Hz, 3H), 1.39 (t, *J* = 6.95 Hz, 3H), 2.69–2.76 (m, 1H), 2.96–3.04 (m, 2H), 3.68–3.76 (m, 2H), 4.10 (s, 2H), 4.21–4.22 (m, 2H), 4.26 (s, 5H), 4.32 (s, 1H), 4.39 (s, 1H), 4.43 (s, 1H). ^{31}P NMR ($CDCl_3$): δ 27.8. ^{13}C NMR ($CDCl_3$): δ 16.4 (d, J_{CP}= 6.5 Hz), 16.5 (d, J_{CP}= 6.7 Hz), 32.0, 61.7 (d, J_{CP}= 6.0 Hz), 61.8 (d, J_{CP}= 6.2 Hz), 63.5, 66.1 (d, J_{CP}= 212.5 Hz), 69.9 (d, J_{CP}= 13.7 Hz), 70.4, 72.4 (d, J_{CP}= 15.3 Hz), 72.6 (d, J_{CP}= 14.8 Hz), 88.7 (d, J_{CP}= 16.8 Hz). ESI-HRMS Calcd for $C_{16}H_{23}O_4FePNa$ (M+Na): 389.0581. Found: 389.0598. $[\alpha]^{21}_D$ = −120 (*c* 0.17, Et_2O).

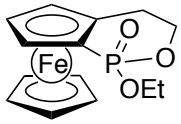
Ferrocene-fused planar-chiral cyclic phosphonate (3.2). To an over dried Schlenk



flask was added NaH (72 mg, 3.0 mmol). A solution of **3.6** (146.4 mg, 0.4 mmol) in anhydrous THF (12 mL) was transferred to "dried Schlenk flask" and the mixture was stirred at room temperature for 30 min. The reaction mixture was quenched with water and extracted with $CHCl_3$. The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The crude mixture was purified by silica gel column chromatography (Et_2O/Acetone= 4/1) to afford 52 mg of the title compound **3.2** (99% yield).

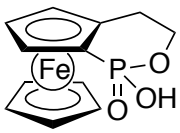


Major Isomer (*S*,*S*)-3.2: ^{1}H NMR ($CDCl_3$): δ 1.28 (t, *J* = 6.96 Hz, 3H), 2.59–2.66 (m, 1H), 2.77–2.84 (m, 1H), 3.97–4.09 (m, 2H), 4.34 (s, 5H), 4.36–4.45 (3H), 4.52–4.53 (m, 1H), 4.63–4.72 (m, 1H). ^{31}P NMR ($CDCl_3$): δ 22.9. ^{13}C NMR ($CDCl_3$): δ 16.6 (d, J_{CP}= 6.0 Hz), 26.8, 61.9 (d, J_{CP}= 5.7 Hz), 66.0 (d, J_{CP}= 199.6 Hz), 67.4 (d, J_{CP}= 6.6 Hz), 68.0 (d, J_{CP}= 13.8 Hz), 68.5 (d, J_{CP}= 11.3 Hz), 70.2 (d, J_{CP}= 16.0 Hz). 70.4， 90.5 (d, J_{CP}= 11.8 Hz). $[\alpha]^{24}_D$ = −88 (*c* 0.45, CH_2Cl_2).



Minor Isomer (*R*,*S*)-3.2: ^{1}H NMR ($CDCl_3$): δ 1.47 (t, *J* = 6.96 Hz, 3H), 2.55–2.63 (m, 1H), 2.73–2.81 (m, 1H), 4.20–4.50 (10H), 4.54–4.55 (m, 1H), 4.63–4.71 (m, 1H). ^{31}P NMR ($CDCl_3$): δ 23.9. ^{13}C NMR ($CDCl_3$): δ 16.3 (d, J_{CP}= 6.1 Hz), 26.6, 62.2 (d, J_{CP}= 5.9 Hz), 64.8 (d, J_{CP}= 195.5 Hz), 67.5 (d, J_{CP}= 6.1 Hz), 67.8 (d, J_{CP}= 14.1 Hz), 69.1 (d, J_{CP}= 11.6 Hz), 70.0 (d, J_{CP}= 15.0 Hz). 70.8， 90.0 (d, J_{CP}= 11.4 Hz). $[\alpha]^{33}_{D}$ = –397 (*c* 0.2, CH_2Cl_2).

(S_p)-Ferrocene-fused planar-chiral cyclic phosphonic acid (3.1).



To a vessel containing the **3.2** (128 mg, 0.4 mmol) in CH_2Cl_2 (3.0 mL) was cooled at 0 °C, to this solution Me_3SiBr (81.0 μL, 0.6 mmol) was added at 0 °C. The reaction mixture stirred at room temperature for 2 h. The reaction was quenched with MeOH，and the solvent was removed under reduced pressure. The crude mixture was purified by recrystallization (hexane/$CHCl_3$) to afford 46.8 mg of compound (*S*)-**3.1** (40% yield).

^{1}H NMR ($CDCl_3$): δ 2.94–3.03 (m, 1H), 3.38–3.46 (m, 2H), 3.60–3.65 (m, 1H), 4.34 (s, 5H), 4.38–4.39 (m, 1H), 4.46 (s, 1H), 4.64 (s, 1H). ^{31}P NMR ($CDCl_3$): δ 32.6. ^{13}C NMR ($CDCl_3$): δ 32.5 (d, J_{CP}= 4.4 Hz), 70.2, 70.4, 70.7, 73.2, 73.3, 73.5, 88.2 (d, J_{CP}= 16.6 Hz). ESI-HRMS Calcd for $C_{12}H_{14}O_3FeP$ (M+H): 293.0030. Found: 293.0040. $[\alpha]^{24}_{D}$ = +11 (*c* 0.25, CH_2Cl_2).

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Chapter IV

Catalytic Asymmetric Synthesis of Planar-Chiral Zirconocenes by ARCM and Their Application in Asymmetric Carbometalations

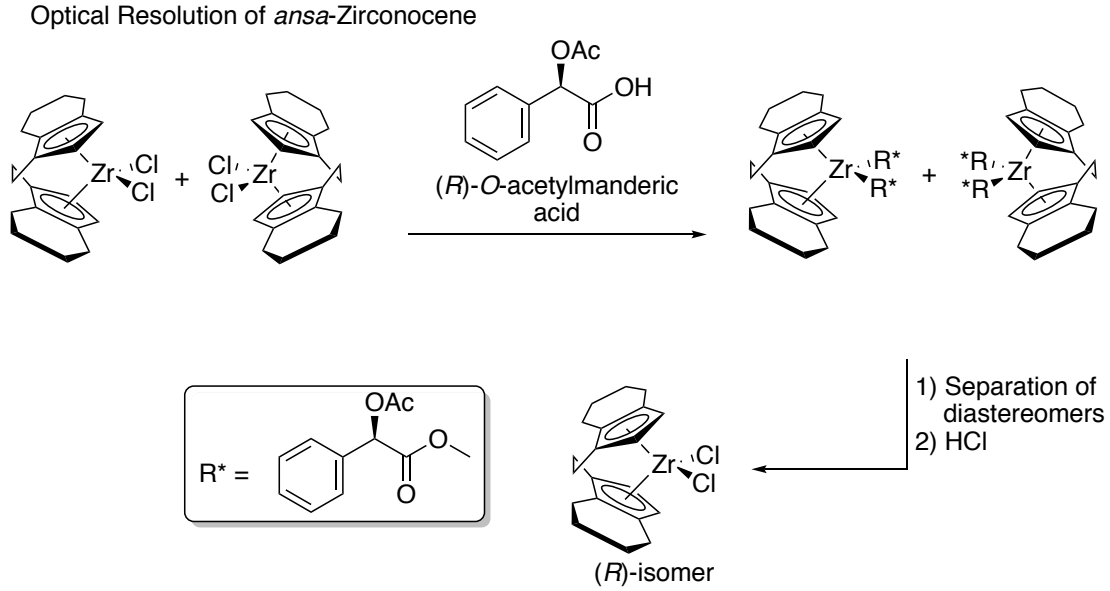
Section 1

Introduction for Chapter IV

Planar-chiral metallocenes are important chiral scaffolds in organic and organometallic chemistry that have been utilized in various asymmetric reactions as ligands[1] or catalysts[2] with fair success. Particularly, planar-chiral "Brintzinger type" group 4 *ansa*-metallocene complexes exhibit high stereodirecting ability in many reactions.[3-5] However, the group 4 *ansa*-metallocenes have been underutilized in enantioselective catalysis, due in large part to the limited availability of the enantiomerically pure catalysts.[6-8]

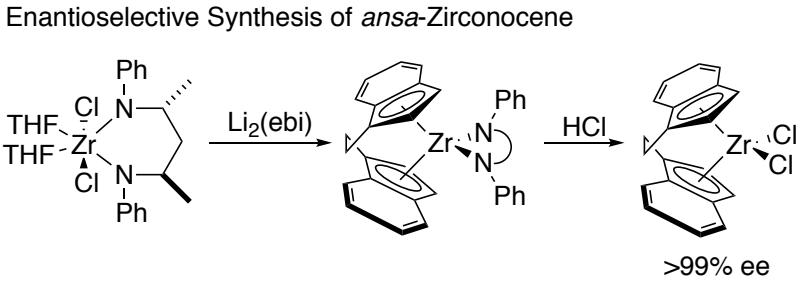
Their preparative methods in optically active forms are rather limited, and *catalytic asymmetric synthesis* of such zirconocene species has not been appeared yet. Majority of scalemic planar-chiral zirconocenes were obtained by optical resolution of preformed racemic compounds (Chapter I, Section 3). A typical procedure is shown in Scheme 4-1.

Scheme 4-1



The first enantioselective synthesis of planar-chiral zirconocene was reported by Jordan in 2004 using a stoichiometric chiral auxiliary. Treatment of racemic zirconocene dichloride with acetyl-*R*-mandelic acid yielded a pair of diastereomers, which could be separated by recrystallization. After treatment with hydrochloric acid, dichloro-complex was obtained in enantiomerically pure form. The Jordan's enantioselective synthesis of planar-chiral *ansa*-zirconocene is shown in Scheme 4-2.

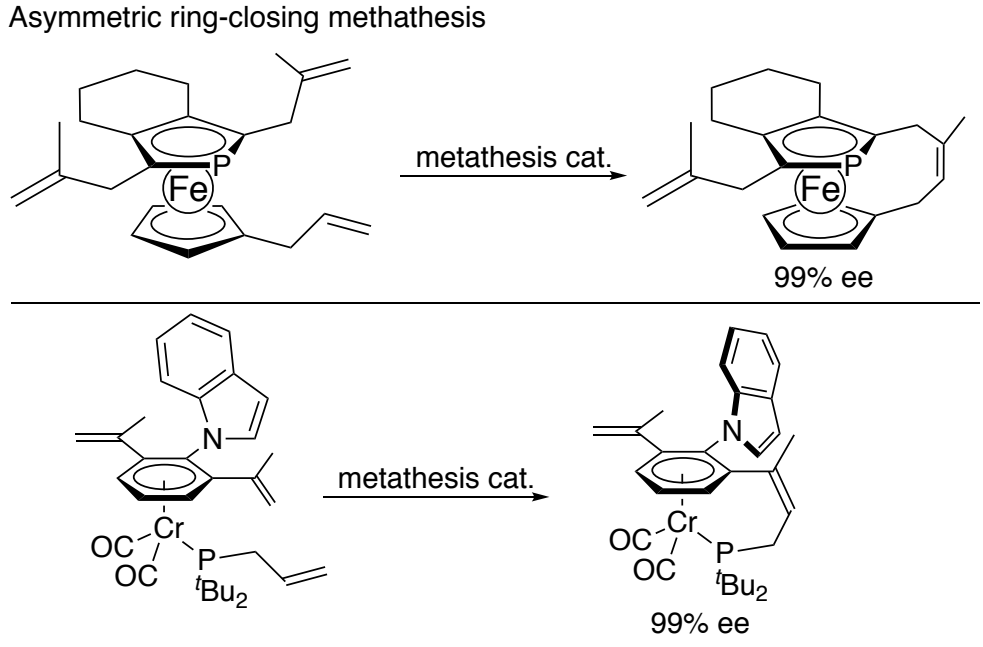
Scheme 4-2



However, the methods of enantioselective synthesis using a chiral auxiliary or the optical resolution of preformed racemic compounds were inefficient. These methods require stoichiometric or excess amounts of chiral reagents/auxiliaries and are hampered by low yields and tedious separation/purification steps.

Recently, Ogasawara has developed asymmetric ring-closing metathesis (ARCM) protocols for the preparation of various planar-chiral transition-metal complexes, which include planar-chiral ferrocenes,[9] phosphaferrocenes (Scheme 4-3, top)[10] and (π-arene)chromium complexes (Scheme 4-3, bottom).[11]

Scheme 4-3



The substrates so far they have employed in the asymmetric reactions are relatively robust "18-electron" organometallics which are easy to handle. Both ferrocenes and (π-arene)chromium complexes are useful chiral templates, however, in general the metal centers in these complexes are *not* catalytically active in metal-catalyzed organic transformations. To expand the synthetic usefulness of the

methodology, I have decided to challenge the asymmetric synthesis of planar-chiral zirconocene species, which are "16-electron" and potential catalysts in various asymmetric reactions and possess a Lewis acidic metal center.

With the previous results obtained on the Mo^{*}-catalyzed ARCM in hand, here, I would like to describe expansion of our method for the *catalytic asymmetric synthesis* of planar-chiral zirconocene species which was indeed realized excellent enantioselectivity.

Section 2

Desymmetrization of C_s-Symmetric Zirconium Complexes by Asymmetric Ring-Closing Metathesis

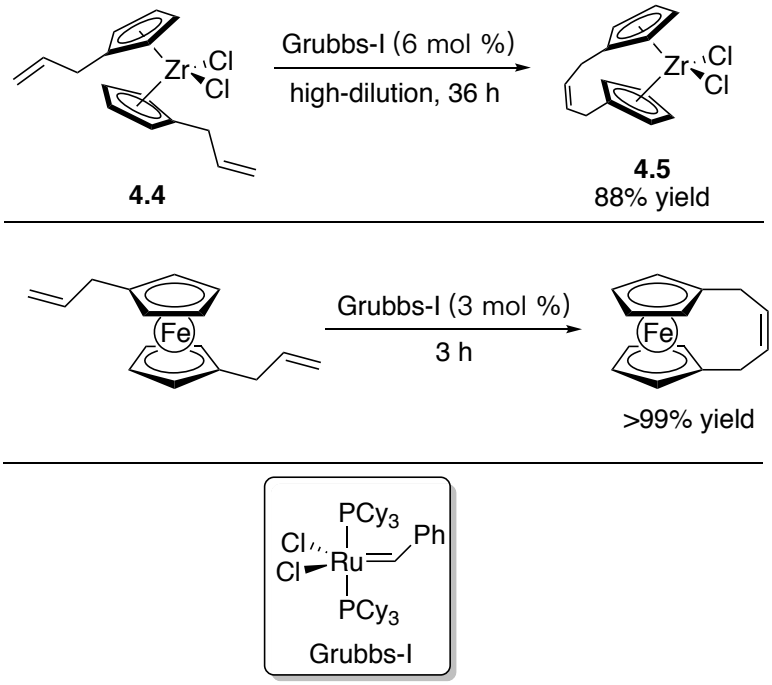
The ARCM method for connecting two coordinating ligands in ferrocenes and (π-arene)chromium complexes proceeds with extremely high enantioselectivities to give various "bridged" planar-chiral complexes (Chapter IV, Section 1), and an analogous reaction was used for the desymmetrization of zirconium complexes.

In this section, I would like to report the further extension of the molybdenum-catalyzed ARCM method to the enantioselective desymmetrization of the C_s-symmetric zirconium complexes, which provides the corresponding "bridged" products in high yields and with excellent enantioselectivity. Furthermore, the prepared optically active planar-chiral zirconium complexes could be used as chiral catalysts in asymmetric carbometalations.

4-2-1 Catalytic Asymmetric Synthesis of Planar-Chiral Zirconocenes

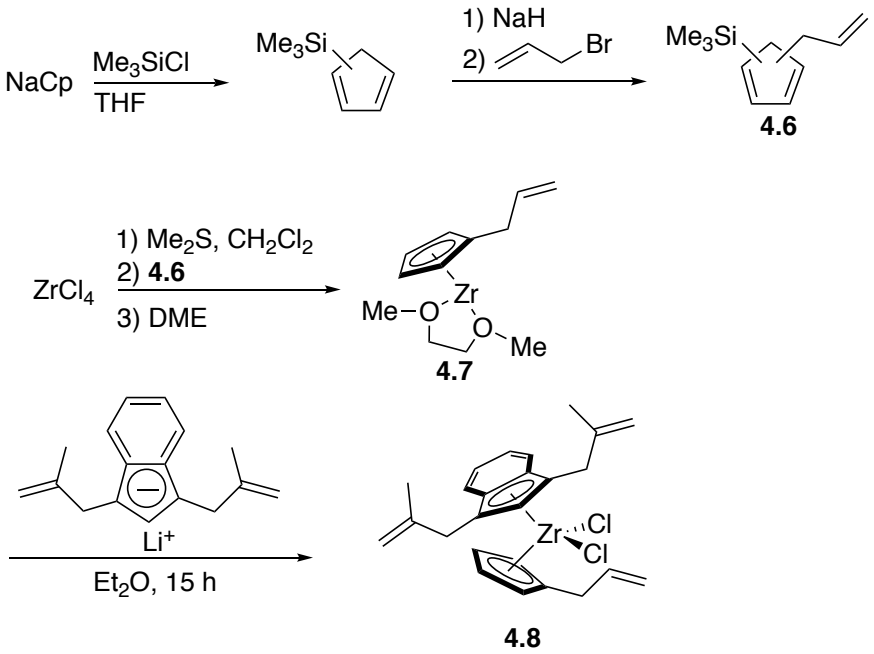
In the previous report,[12] it was demonstrated that the 1,1'-diallylzirconocene dichloride (**4.4**) served as a good substrate in the ruthenium-catalyzed ring-closing metathesis reaction. The 1,1'-diallylzirconocene dichloride **4.4** was treated with the Grubbs-I catalyst (6 mol %) for 36 h in the refluxing CH_2Cl_2 under the high-dilution conditions to give the *ansa*-zirconocene **4.5** in 88% yield (Scheme 4-2, top). Although the RCM reaction proceeded smoothly, the high yield was obtained on the basis of the high catalyst loading and the long reaction time under the high-dilution conditions (Scheme 4-4, top *vs* bottom).

Scheme 4-4



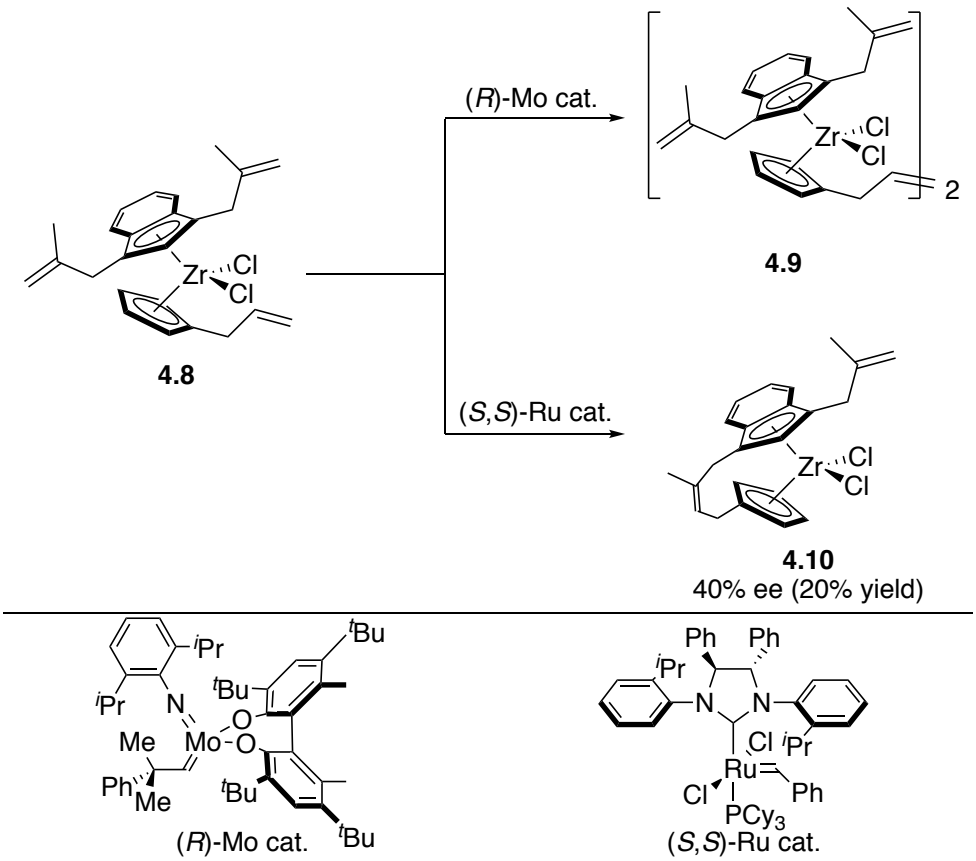
Based on this result, planar-prochiral C_s-symmetric zirconocene substrate **4.8** was designed. The substrate was prepared as shown in Scheme 4-5.[13]

Scheme 4-5



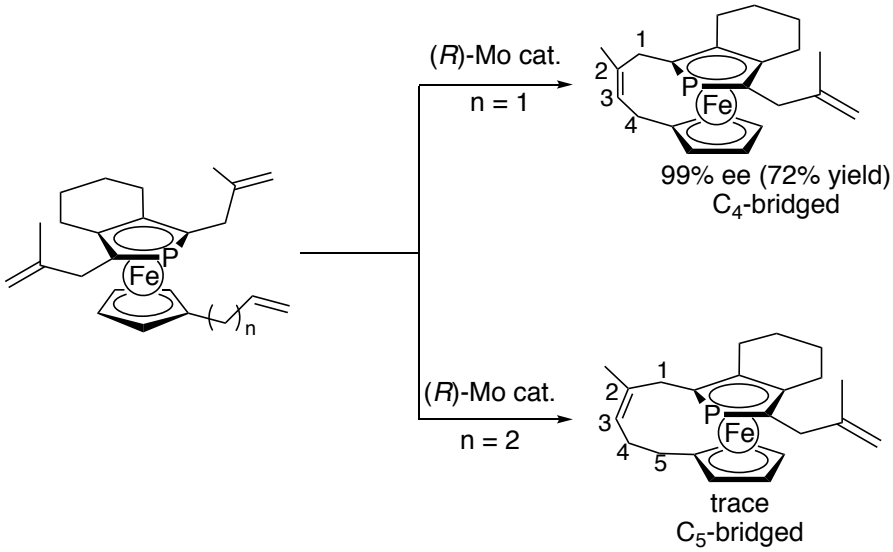
The prepared substrate was examined in the ARCM reaction. However, to my disappointment, the Mo*-catalyst[14] gave undesired homo-cross-metathesis dimer **4.9** and RCM product **4.10** was not detected. On the other hand, the ARCM of substrate **4.8** in the presence of Ru*-catalyst (5 mol %) afforded the desired *ansa*-zirconocene **4.10** in 20% yield with 40% ee (Scheme 4-6).

Scheme 4-6



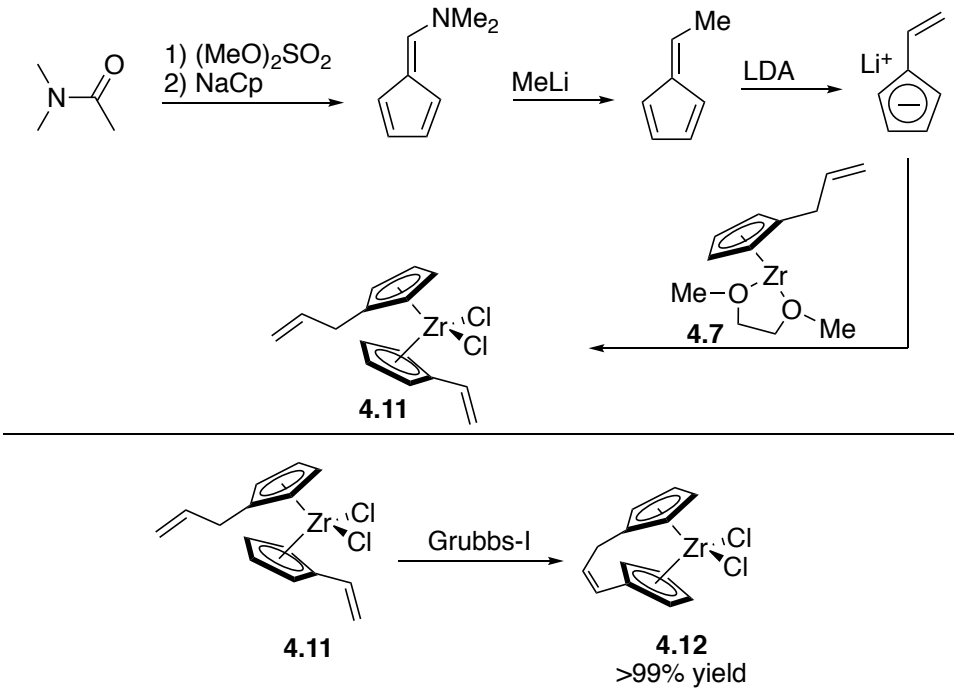
On the ARCM reactions of planar-chiral ferrocenes and (π-arene)chromium complexes reported previously, the length of olefinic tethers showed the dramatic influences in both chemical yields as well as the enantioselectivity of the ARCM products. In the case of the synthesis of ferrocenophanes, the best results were obtained in the C_4-bridged products, which were from the 1,1'-diallyl substrates. Treatment of phosphaferrocene substrate with Mo^*-catalyst (20 mol %) in benzene at 23 °C resulted corresponding C_4-bridged phospha[4]ferrocenophane with 99% ee in 72% yield. In contrast, the corresponding C_5-bridged product was obtained only in trace amount under the similar conditions (Scheme 4-7).

Scheme 4-7

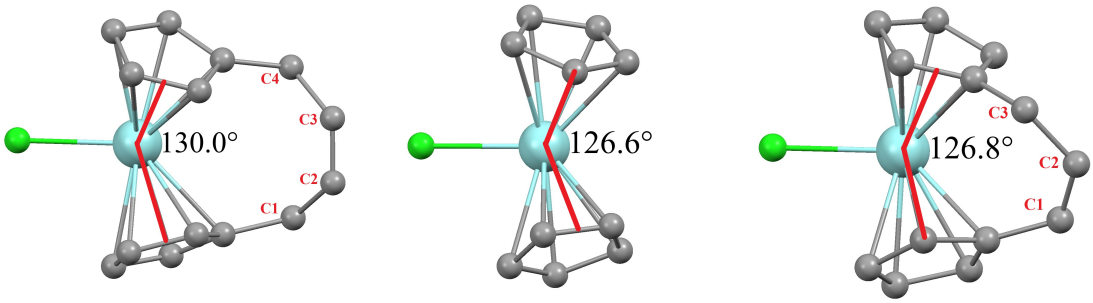


Whereas the bent metallocene structure of the zirconium species puts the two Cp ligands in closer proximity, the C_4-bridge in the ARCM product might be too long for the ARCM synthesis of *ansa*-zirconocenes. To confirm this hypothesis, the substrate for the C_3-bridged zirconocene, 1-allyl-1'-vinylzirconocene dichloride **4.11** was prepared (Scheme 4-8, top). The RCM of zirconocene **4.11** was examined. A mixture of **4.11** and Grubbs-I catalyst (5 mol %) was dissolved in benzene and the solution was heated at 60 °C, the substrate was consumed completely within 12 h. Indeed, as expected, the corresponding *ansa*-zirconocene dichloride **4.12** was obtained in more than 99% yield (Scheme 4-8, bottom).

Scheme 4-8



As revealed by the X-ray structure of zirconocene **4.5** (Figure 4-1), the Cp(centroid)-Zr-Cp(centroid) angle in **4.5** is 130.0°, which is considerably larger than that in the parent zirconocene dichloride (130.0° *vs* 126.6°). This indicates that the C_4-bridge in **4.5** causes the distortion in the RCM product which leads to the relatively low yield. This finding is consistent with what was observed in ARCM synthesis of ferrocenophane complexes (Chapter IV, Scheme 4-7). On the other hand, the structure of zirconocene **4.12**, the Cp(centroid)-Zr-Cp(centroid) angle is almost the same with Cp_2ZrCl_2 (126.8° *vs* 126.6°). Since the C_3-bridged zirconocene keeps the nearly ideal structure of zirconocene dichloride, it was produced quantitatively in the RCM reaction.

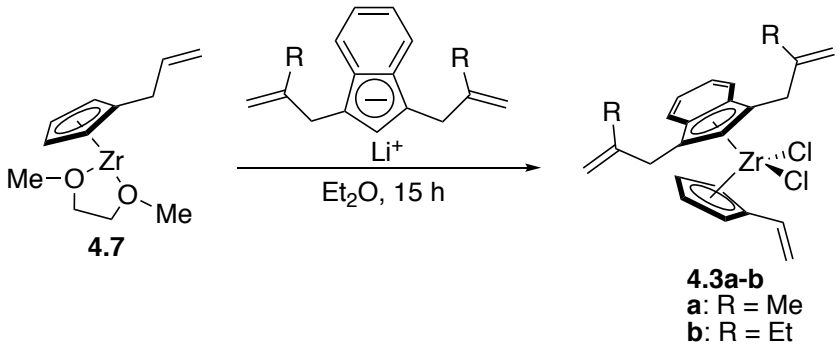


4.5 **Cp_2ZrCl_2** **4.12**

Figure 4-1. Comparison of Cp(centroid)-Zr-Cp(centroid) Angle (deg) between **4.5**, Cp_2ZrCl_2 and **4.12**.

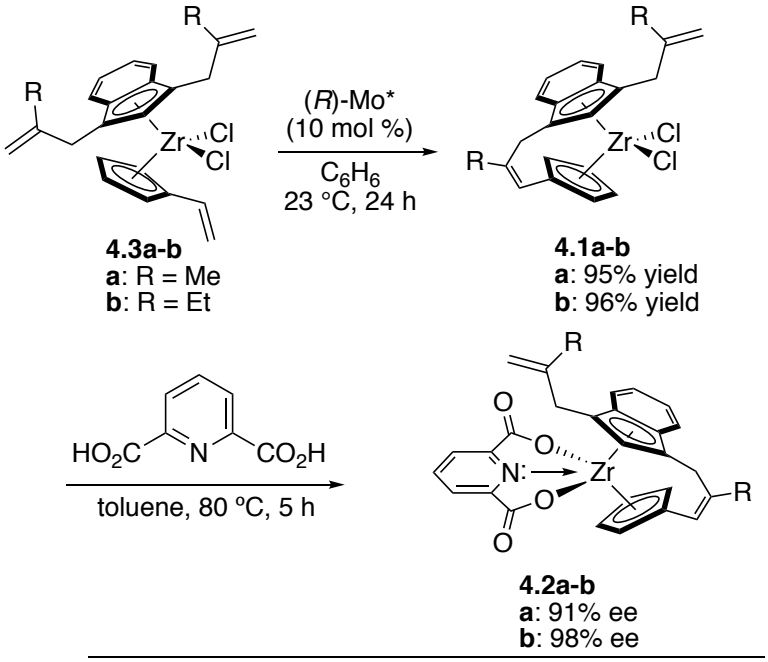
After these considerations, the C_s-symmetric planar-prochiral zirconocenes **4.3a** and **4.3b**, which should afford the corresponding C_3-bridged planar-chiral *ansa*-zirconocenes by the ring-closing metathesis, was prepared. General procedure for the synthesis of zirconocene **4.3** was summarized in Scheme 4-9.

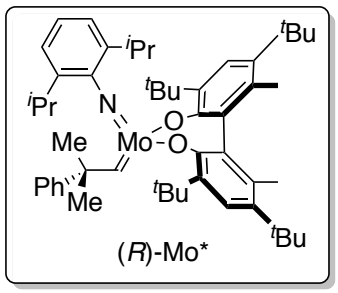
Scheme 4-9



These new zirconocenes are, indeed, the excellent substrates for the ARCM reaction. The reaction was carried out in the benzene at 23 ℃ in the presence of an appropriate chiral molybdenum catalyst (10 mol %), that was generated *in situ* from the catalyst precursor, (pyrrolyl)$_2$Mo(=CHCMe$_2$Ph)(=N-C$_6$H$_3$-2,6-^{i}Pr$_2$), and axially chiral (*R*)-3,3',5,5'-^{t}Bu$_4$-6,6'-Me$_2$-2,2'-biphenol ligand. The ARCM reaction gave **4.1a** in 95% yield with 91% ee. In addition, the enantioselectivity of the ARCM reaction could be further improved to 98% ee by replacing the methyl groups of the methallyl side-arms with ethyl substituents in **4.3a**/**4.3b** under the same reaction conditions (Scheme 4-10). The obtained complex **4.1** was sensitive to the air. Therefore, compound **4.1** was converted to the corresponding zirconocene dipicolinate by the treatment with dipicolinic acid in the presence of triethylamine. The enantiomeric excess of compound **4.2** was determined by chiral HPLC analysis.

Scheme 4-10


R
R
Zr
Cl
Cl
(R)-Mo*
(10 mol %)
C6H6
23 °C, 24 h
4.3a-b
a: R = Me
b: R = Et
4.1a-b
a: 95% yield
b: 96% yield
HO2C
N
CO2H
toluene, 80 °C, 5 h
O
O
N:
Zr
4.2a-b
a: 91% ee
b: 98% ee


iPr
iPr
N
Me
Mo
O
O
Ph
Me
tBu
tBu
tBu
(R)-Mo*

Determination of Absolute Configuration of (–)-4.2b. Single crystals of **(–)-4.2b** were grown in pentane/dichloromethane. The crystal structure of **(–)-4.2b** is shown in the Figure 4-2 with selected bond lengths and angles. The Flack parameter was determined to be -0.005(6) for the structure, and absolute configuration of **(–)-4.2b** is unambiguously assigned to be *S*. The distance from zirconium atom to the least-squares planes $_{C23\text{-}C24}$ of the η^5-ligand and planes $_{C1\text{-}C9}$ of the η^5-ligand are 2.419 and 2.405 Å, respectively. The dihedral angle between the two cyclopentadienyl ligands is 54.55°

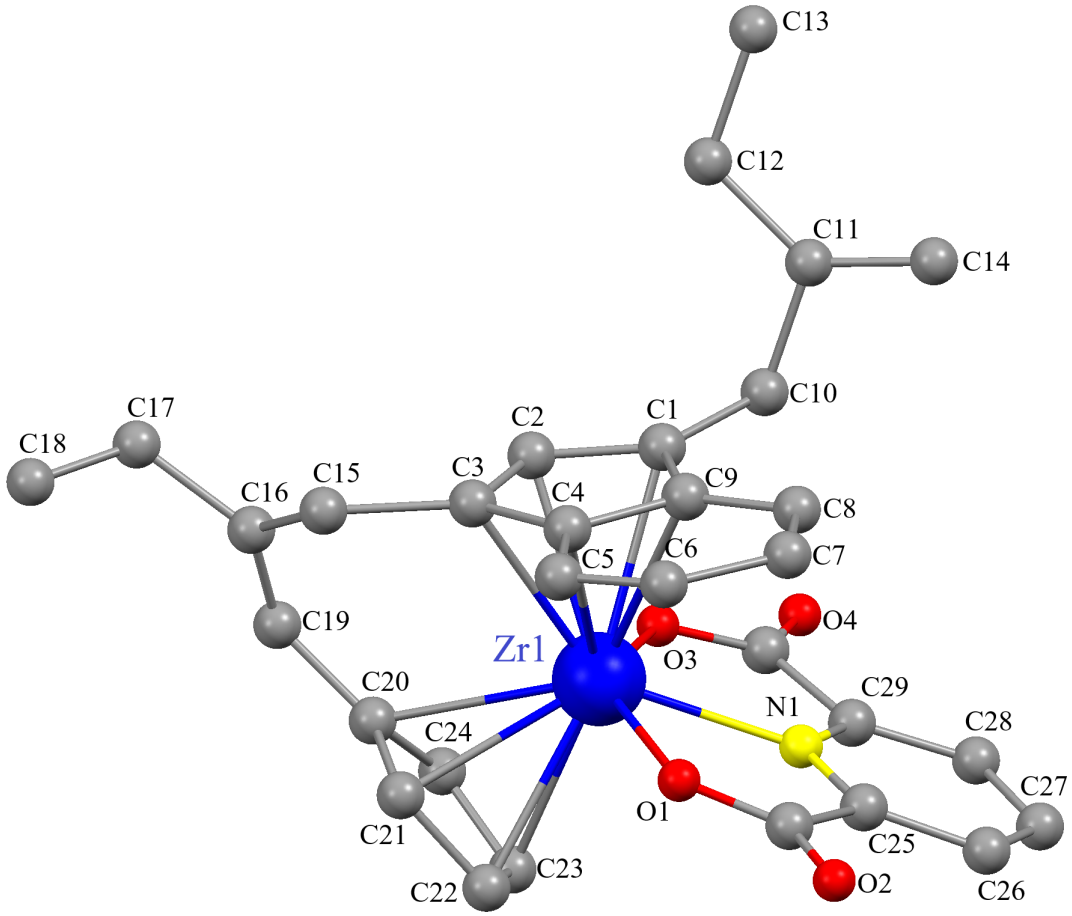


Figure 4-2. Ball-and-stick drawing of **(*S*)-(–)-4.2b**. All hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg); Zr1-N1 = 2.299 (4), Zr1-O3 = 2.162(4), Zr1-O1 = 2.149(4), O3-C31 = 1.297(7), O4-C31 = 1.214(6), O1-C30 = 1.269(7), O2-C30 = 1.215(6), N1-C29 = 1.359(7), N1-C25 = 1.310(7), C4-C5 = 1.43(1), C5-C6 = 1.28(2), C6-C7 = 1.44(2), C7-C8 = 1.35(2), C8-C9 = 1.39(2), C25-C26 = 1.403(9), C26-C27 = 1.361(9), C27-C28 = 1.351(9), C28-C29 = 1.397(9)

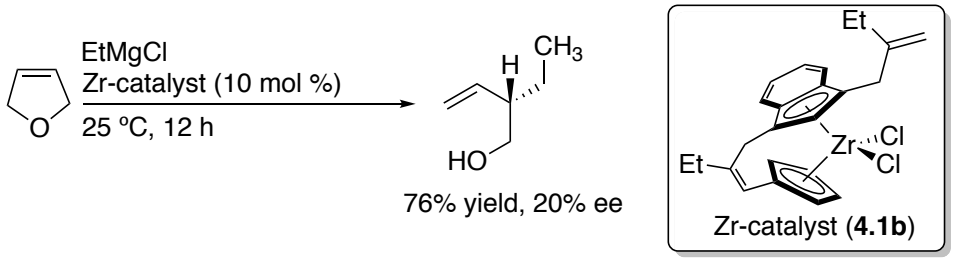
Zr1-least-squares $plane_{C23\text{-}C24}$ = 2.419, Zr1-least-squares $plane_{C1\text{-}C9}$ = 2.405, O3-Zr1-O1 = 136.7(2), O3-Zr1-N1 = 68.6(2), O1-Zr1-N1 = 68.1(2), Zr1-O3-C31 = 126.6(4), Zr1-O1-C30 = 127.8(4), Zr1-N1-C25 = 119.3(4), C25-N1-C29 = 121.6(5), O3-C31-O4 = 126.2(6), O3-C31-C29 = 113.0(5), O4-C31-C29 = 120.8(6), O2-C30-O1 = 127.0(6), O2-C30-C25 = 121.5(6), O1-C30-C25 = 111.5(5), dihedral angle between least-squares $plane_{C(1,2,3,4)}$ and least-squares $plane_{C(21,22,23,24)}$ = 54.55, Flack Parameter = -0.005(6).

Section 3

Application of Planar-Chiral Zirconocene in Asymmetric Carbometalations

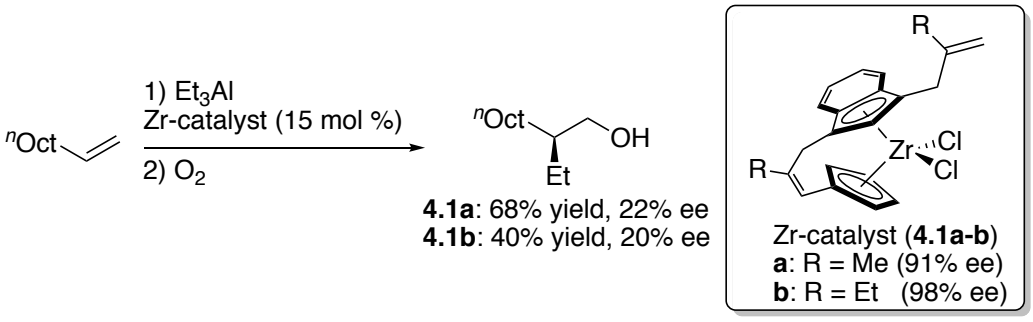
The synthetic utilities of the planar-chiral zirconium species as chiral catalysts were examined in two prototypical asymmetric carbometalation reactions.[15] The newly prepared zirconium species (*S*)-**4.1b** (10 mol %) was a fairly effective chiral catalyst in the asymmetric carbomagnesation. The reaction between 2,5-dihydrofuran and EtMgCl gave the unsaturated alcohol in 76% yield and 20% ee in the presence of 10 mol % planar-chiral zirconium complex (*S*)-**4.1b** of 98% ee (Scheme 4-11).

Scheme 4-11



The second asymmetric reaction examined was the zirconium-catalyzed asymmetric carboalumination of alkenes (ZACA reaction). The Mo*-catalyzed ARCM afforded the corresponding planar-chiral zirconium species **4.1a** and **4.1b** in 91% ee and 98% ee, respectively (Chapter IV, Scheme 4-10), and these planar-chiral zirconium species were examined in the ZACA reaction. The reaction between 1-decene and Et_3Al catalyzed by (*S*)-**4.1a** (15 mol %) gave the corresponding alcohol in 68% yield with 22% ee after oxidation. In addition, almost the same enantioselectivity (20% ee) was observed in the presence of planar-chiral zirconium complex (*S*)-**4.1b** (15 mol %) under the same reaction conditions. The primary alcohol was obtained in 40% yield (Scheme 4-12).

Scheme 4-12



To my disappointment, both zirconium-catalyzed asymmetric reactions examined displayed low enantioselectivity in 20% ee, which could be ascribed to the structure in **4.1a-b**. In other words, the structure of **4.1a-b** is not suitable for the catalytic application in the carbometalations.

Conclusions for Chapter IV

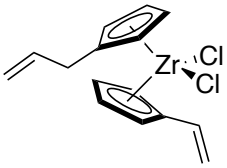
In this Chapter, the first efficient and general *catalytic asymmetric synthesis* of planar-chiral zirconocene was described. The Mo^{*}-catalyzed ARCM afforded planar-chiral zirconocene species in excellent enantioselectivity of up to 98% ee. The prepared planar-chiral zirconocenes could be used as the chiral catalysts in the asymmetric carbometalation. The Zr-catalyzed asymmetric carbometalation showed high catalytic activity and offered an important opportunity for C-C bond formation. This protocol can be regarded as a novel catalytic method for the preparation of a planar-chiral zirconocene as a single enantiomer.

Experimental Section for Chapter IV

All anaerobic and/or moisture sensitive manipulations were carried out with standard Schlenk techniques under predried nitrogen or with glovebox techniques under prepurified argon. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) chemical shifts are reported in ppm downfield of internal tetramethylsilane. Tetrahydrofuran and benzene were distilled from benzophenone-ketyl under nitrogen prior to use. 1,1-dichloroethane was distilled from CaH_2 under nitrogen prior to use. The following compounds were prepared according to the reported methods:

(*R*)-3,3',5,5'-^{t}Bu$_4$-6,6'-Me$_2$-2,2'-biphenol,[16] (*S*,*S*)-Ru*-catalyst,[14] NaCp,[17] and Mo(=NC$_6$H$_3$-2,6-^{i}Pr$_2$)(=CHCMe$_2$Ph)(NC$_4$H$_4$)$_2$[18] were prepared according to the reported methods. All the other chemicals were obtained from commercial sources and used as received unless otherwise noted.

(η^5-1-Allylcyclopentadienyl)(η^5-1'-vinylcyclopentadienyl)zirconocene dichloride (4.11).[19,20] A solution of 6-(Dimethylamino)fulvene (11.3 g, 93 mmol) in Et_2O (70 mL), to this MeLi (1.2 eq.) was added dropwise at 0 ˚C. The mixture was stirred at room temperature for 6 h. The reaction mixture was quenched with water and extracted with Et_2O, the organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated on a rotary evaporator. The crude mixture was purified by silica gel column chromatography to afford 4.3 g of total product (6-methylfulvene) as an yellow oil.



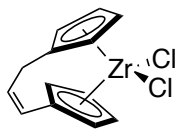
A solution of HN^{i}Pr$_2$ (1.9 mL, 14 mmol) in THF (10 mL), ^{n}BuLi (14 mmol) was added dropwise at -78 ˚C, the mixture was stirred at room temperature for 2 h. Then a 6-methylfulvene (1.01 g, 11.0 mmol) in THF (10 mL) was added to the solution slowly at -30 ˚C. The mixture was stirred at room temperature for overnight. The reaction mixture was concentrated on a rotary evaporator. The crude product was directly used for next step.

(η^5-1-Allylcyclopentadienyl) zirconium dimethoxyethane complex (4.26 g, 11 mmol) in THF (100 mL), the crude product in THF (20 mL) was added to the solution at -78 ˚C. The mixture was stirred at room temperature for 6 h. The solvent was removed under reduced pressure. The reaction mixture was extracted with CH_2Cl_2, the organic layers were combined, filtered, and concentrated on a rotary evaporator. The crude

mixture was recrystallized from hexane to afford 2.14 g of **4.11** as an yellow solid (55% yield).

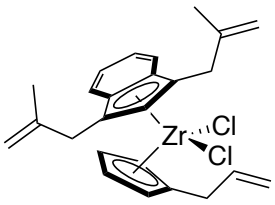
^{1}H NMR (C_6D_6): δ 3.38 (d, *J* = 5.4 Hz, 2H), 4.95–5.02 (m, 4H), 5.29–5.30 (m, 1H), 5.67–5.68 (m, 2H), 5.82–5.90 (m, 4H), 5.99–6.01 (m, 2H), 6.26–6.33 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 34.3, 112.9, 114.1, 114.2, 114.3, 115.4, 116.2, 116.9, 129.8, 136.2. EI-HRMS Calcd for $C_{15}H_{16}Cl_2Zr$: 355.9676. Found: 355.9676.

1,1'-(1-Propen-1,3-diyl)zirconocene dichloride (4.12). To a solution of **4.11** (58 mg, 28 mmol) in benzene (10 mL) was added Hoveyda/Grubbs-I catalyst (8 mg, 1.4 mmol, 5 mol %), and the solution was stirred at 60 °C for 12 h. The reaction mixture was quenched by ethyl vinyl ether, and the crude mixture was recrystallized from hexane to afford 32 mg of **4.12** as an yellow solid (60% yield).



^{1}H NMR (C_6D_6): δ 2.67 (dd, *J* = 6.2 Hz and 1.6 Hz, 2H), 5.31 (t, *J* = 2.7 Hz, 2H), 5.70 (dt, *J* = 10.5 Hz and 6.2 Hz, 1H), 5.80 (t, *J* = 2.8 Hz, 2H), 5.91 (dt, *J* = 10.5 Hz and 1.6 Hz, 1H), 6.36 (t, *J* = 2.8 Hz, 2H), 6.56 (t, *J* = 2.7 Hz, 2H). ^{13}C NMR (C_6D_6): δ 26.8, 110.2, 114.3, 120.3, 121.3, 123.0, 124.4, 131.8, 138.0. EI-HRMS Calcd for $C_{13}H_{12}Cl_2Zr$: 327.9363. Found: 327.9372.

(η^5-1,3-Dimetallylindenyl)(η^5-1'-allylcyclopentadienyl)zirconocene dichloride (4.8). A solution of $ZrCl_4$ (14.7 g, 63 mmol) in CH_2Cl_2 (100 mL). To this solution was added Me_2S (9.4 mL, 126 mmol) dropwise at 0 ˚C. The mixture was stirred at 0 ˚C for 1 h, and the mixture was filtered through the celite. The (trimethylsilyl)allylcyclopentadiene (11.3 g, 63 mmol) was added dropwise at 0 ˚C. The mixture was stirred at room temperature for another 5 h, and to this mixture, DME (40 mL) was added dropwise. The residue was extracted with toluene, washed by hexane to afford 17.5 g of Zr(dme) as gray solid.



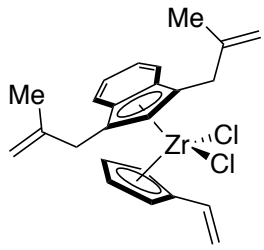
^{1}H NMR ($CDCl_3$): δ 3.63 (dt, *J* = 6.5 and 1.4 Hz, 2H), 3.92 (br, 4H), 4.15 (br, 6H), 5.02–5.09 (m, 2H), 5.97–6.04 (m, 1H), 6.43–6.44 (m, 2H), 6.51–6.52 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 35.4, 116.2, 118.5, 120.1, 133.9, 136.8.

Zr(dme) complex (2.3 g, 5.85 mmol) in Et_2O (150 mL), 1,3-dimethallylindenyl lithium (1.35 g, 5.85 mmol) in Et_2O (30 mL) was added to the solution slowly. The

mixture was stirred at room temperature for another 15 h. The solvent was removed under reduced pressure, and the residue was recrystallized from hexane to afford 2.28 g of **4.8** as an yellow solid.

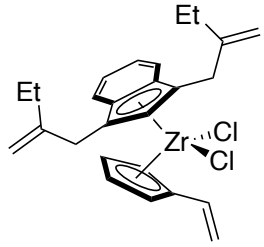
^{1}H NMR ($CDCl_3$): δ 1.68 (s, 6H), 3.29 (d, *J* = 6.6 Hz, 2H), 3.44 (d, *J* = 16.1 Hz, 2H), 3.76 (d, *J* = 16.1 Hz, 2H), 4.54 (br, 2H), 4.76 (br, 2H), 4.96–5.04 (m, 2H), 5.63–5.64 (m, 2H), 5.78–5.89 (m, 3H), 6.63 (s, 1H), 7.23–7.27 (m, 2H), 7.56–7.60 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 22.3, 34.2, 36.9, 111.6, 114.6, 116.4, 117.6, 124.4, 125.1, 125.2, 127.7, 133.6, 136.2, 144.1. EI-HRMS Calcd for $C_{25}H_{28}Cl_2Zr$: 488.0623. Found: 488.0642.

(η^5-1,3-Dimetallylindenyl)(η^5-1'-vinylcyclopentadienyl)zirconocene dichloride (4.3a).



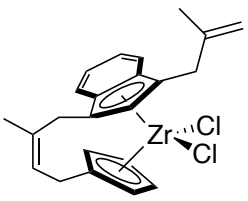
^{1}H NMR ($CDCl_3$): δ 1.68 (s, 6H), 3.42 (d, *J* = 15.8 Hz, 2H), 3.74 (d, *J* = 15.8 Hz, 2H), 4.54 (br, 2H), 4.76 (br, 2H), 5.27 (dd, *J* = 17.4 and 10.7 Hz, 1H), 5.51 (dd, *J* = 17.4 and 10.7 Hz, 1H), 5.63–5.65 (m, 2H), 6.16–6.17 (m, 2H), 6.45–6.52 (m, 1H), 6.60 (s, 1H), 7.25–7.28 (m, 2H), 7.56–7.62 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 22.3, 36.8, 111.6, 115.0, 115.1, 115.7, 116.7, 124.4, 125.3, 125.5, 127.3, 129.2, 129.6, 144.1. EI-HRMS Calcd for $C_{24}H_{26}Cl_2Zr$: 474.0443. Found: 474.0464.

[η^5-1,3-Di(2-methylenebutyl)indenyl)](η^5-1'-vinylcyclopentadienyl)zirconocene dichloride (4.3b).



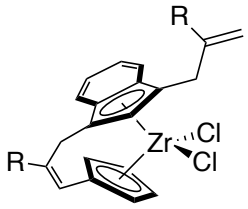
^{1}H NMR (C_6D_6): δ 0.89 (t, *J* = 7.4 Hz, 6H), 1.82 (q, *J* = 7.4 Hz, 4H), 3.44 (d, *J* = 15.8 Hz, 2H), 3.75 (d, *J* = 15.8 Hz, 2H), 4.59 (m, 2H), 4.72 (m, 2H), 5.11 (dd, *J* = 10.8 and 1.1 Hz, 1H), 5.32–5.33 (m, 2H), 5.38 (dd, *J* = 10.8 and 1.1 Hz, 1H), 5.70–5.71 (m, 2H), 5.92–5.94 (m, 2H), 6.43–6.50 (m, 1H), 6.55 (s, 1H), 6.83–6.86 (m, 2H), 7.38–7.41 (m, 2H). ^{13}C NMR (C_6D_6): δ 12.1, 28.5, 35.5, 109.3, 114.9, 115.0, 115.3, 116.0, 124.3, 124.9, 125.3, 128.9, 129.0, 129.8, 149.6. EI-HRMS Calcd for $C_{26}H_{30}Cl_2Zr$: 502.0771. Found: 502.0768.

1,1'-(2-Methyl-2-buten-1,4-diyl)(η^5-3-methallylindenyl)](cyclopentadienyl)-zirconocene dichloride (4.10).



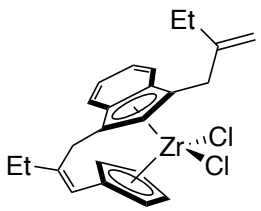
In a glovebox under prepurified argon, Ru*-catalyst (5 mg, 5 μmol) and **4.8** (49.1 mg, 0.1 mmol) were dissolved in dry CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for 14 h. The reaction mixture was quenched by ethyl vinyl ether. The resulting yellow color solution was filtrated and concentrated under reduced pressure. ^{1}H NMR ($CDCl_3$): δ 1.68 (s, 3H), 2.06 (s, 3H), 3.52–3.55 (m, 2H), 3.62 (d, *J* = 16.1 Hz, 1H), 3.69 (d, *J* = 17.0 Hz, 2H), 4.54 (br, 2H), 4.73 (br, 2H), 5.85–5.87 (m, 1H), 5.95–6.02 (m, 1H), 6.21–6.24 (m, 1H), 6.38 (s, 1H), 6.42–6.45 (m, 2H), 7.22–7.26 (m, 1H), 7.32–7.36 (m, 1H), 7.47–7.49 (m, 1H), 7.61–7.64 (m, 1H). EI-HRMS Calcd for $C_{23}H_{23}Cl_2Zr$ (M-H): 459.0224. Found: 459.0236.

General Procedure Enantioselective Synthesis of Planar-Chiral Zirconocene by Asymmetric Desymmetrization.



In a glovebox under prepurified argon, Mo(=NC_6H_3-2,6-^{i}Pr$_2$)(=$CHCMe_2Ph$)(NC_4H_4)$_2$ (16.1 mg, 0.03 mmol) and (*R*)-3,3',5,5'-^{t}Bu$_4$-6,6'-Me$_2$-2,2'-biphenol (13.2 mg, 0.03 mmol) were dissolved in benzene (15 mL). After stirring the mixture for 15 min at room temperature, to this mixture was added 15 mL of benzene and substrate **4.3** (0.3 mmol). The Schlenk was sealed tightly and taken out of the glovebox. The Schlenk was immersed in an oil bath maintained at 23 °C and the mixture was stirred for 24 h. The resulting yellow color solution was filtrated and concentrated under reduced pressure.

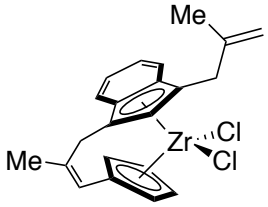
1,1'-(2-Methylenebutyl-1-propen-1,3-diyl)-[η^5-3-(2-methylenebutyl)indenyl)]-(cyclopentadienyl)zirconocene dichloride (4.1b).



^{1}H NMR ($CDCl_3$): δ 1.03 (t, *J* = 7.4 Hz, 3H), 1.26 (t, *J* = 7.4 Hz, 3H), 2.0 (q, *J* = 11.2 Hz, 2H), 2.48 (q, *J* = 11.2 Hz, 2H), 3.51–3.58 (m, 2H), 3.72–3.76 (m, 1H), 3.96–4.0 (m, 1H), 4.53 (br, 1H), 4.72 (br, 1H), 5.89 (s, 1H), 6.15–6.17 (m, 1H), 6.23–6.26 (m, 2H), 6.29 (br, 1H), 6.35–6.37 (m, 1H), 7.14–7.18 (m, 1H), 7.28–7.32 (m, 1H), 7.44 (dt, *J* = 8.7 and 1.0 Hz, 1H), 7.55 (dt, *J* = 8.7 and

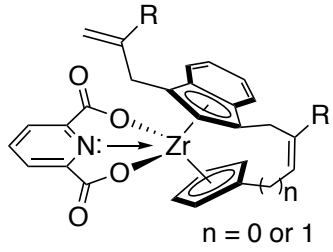
1.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 12.3, 12.7, 28.9, 30.3, 32.7, 35.4, 109.2, 111.2, 116.5, 116.8, 117.4, 117.7, 120.2, 120.7, 121.9, 122.7, 123.5, 124.4, 124.7, 126.1, 126.4, 129.7, 148.1, 150.1.

1,1'-(2-Methyl-1-propen-1,3-diyl)-[η^5-3-methallylindenyl](cyclopentadienyl)-zirconocene dichloride (4.1a).

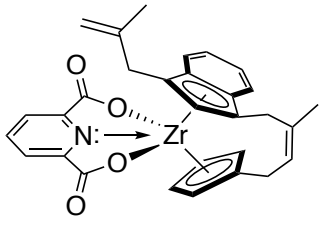


^{1}H NMR ($CDCl_3$): δ 1.70 (s, 3H), 2.20 (s, 3H), 3.49 (d, *J* = 16.1 Hz, 1H), 3.57 (d, *J* = 17.0 Hz, 1H), 3.73 (d, *J* = 16.1 Hz, 1H), 3.93 (d, *J* = 17.0 Hz, 1H), 4.57 (br, 1H), 4.72 (br, 1H), 5.97 (s, 1H), 6.11–6.13 (m, 1H), 6.23–6.25 (m, 2H), 6.32 (s, 1H), 6.34–6.37 (m, 1H), 7.14–7.18 (m, 1H), 7.27–7.30 (m, 1H), 7.41–7.43 (m, 1H), 7.54–7.57 (m, 1H). ^{13}C NMR (C_6D_6): δ 22.4, 25.6, 30.8, 36.9, 111.4, 111.7, 116.2, 117.0, 117.7, 118.2, 119.1, 119.9, 121.7, 121.7, 122.4, 124.3, 124.5, 125.9, 126.1, 129.7, 142.0, 144.5. EI-HRMS Calcd for $C_{22}H_{22}Cl_2Zr$: 446.0146. Found: 446.0139.

General Procedure for Synthesis of Zirconocene Dipicolinate.[21] To a vessel containing 1,1',3-Triallylzirconocene (0.03 mmol) and dipicolinic acid (5 mg, 0.03 mmol) in toluene (2 mL) was added the triethylamine (6.1 mg, 0.06 mmol) in the toluene (1 mL) at 80 °C, the solution was stirred at 80 °C for 5 h. The mixture was evaporated to dryness under reduced pressure. The crude mixture was purified by gel permeation chromatography.



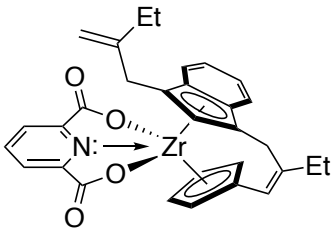
1,1'-(2-Methyl-2-buten-1,4-diyl)-[η^5-3-methallylindenyl)]-(cyclopentadienyl)-(dipicolinato)zirconocene.



^{1}H NMR ($CDCl_3$): δ 1.72 (s, 3H), 2.14 (s, 3H), 3.12 (d, *J* = 15.8 Hz, 1H), 3.20 (dd, *J* = 16.5 and 7.6 Hz, 1H), 3.30 (d, *J* = 16.3 Hz, 1H), 3.65–3.71 (m, 2H), 4.10 (d, *J* = 15.8 Hz, 1H), 4.57 (br, 1H), 4.73 (br, 1H), 5.74-5.79 (m, 3H), 6.04–6.08 (m, 1H), 6.26–6.30 (m, 1H), 6.52–6.56 (m, 1H), 6.77 (s, 1H), 6.79–6.80 (m, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 8.00–8.14 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 22.7, 25.7, 26.0, 28.3, 29.8, 35.9, 105.5, 110.3, 111.6, 112.8, 113.6, 114.3, 115.6, 120.1, 122.6, 123.3, 124.5, 124.8, 125.1,

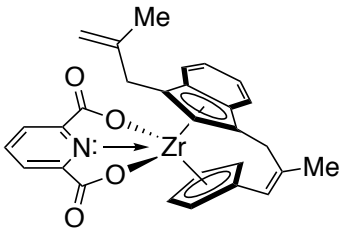
125.8, 126.0, 126.7, 129.0, 138.6, 143.6, 144.4, 150.4, 151.2, 165.8, 166.1. EI-HRMS Calcd for $C_{30}H_{27}NO_4Zr$: 555.0987. Found: 555.0986.

1,1'-(2-Methylenebutyl-1-propen-1,3-diyl)-[η^5-3-(2-methylenebutyl]indenyl)]-(cyclopentadienyl)(dipicolinato)zirconocene (4.2b).



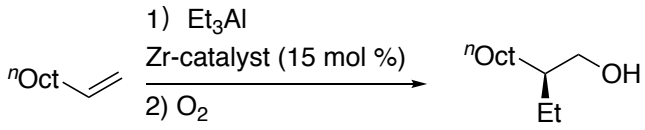
^{1}H NMR ($CDCl_3$): δ 0.91 (t, *J* = 7.3 Hz, 3H), 1.30 (t, *J* = 7.3 Hz, 3H), 1.84 (q, *J* = 11.0 Hz, 2H), 2.53 (q, *J* = 11.0 Hz, 2H), 2.72 (d, *J* = 15.8 Hz, 1H), 3.14 (d, *J* = 15.8 Hz, 1H), 3.58 (d, *J* = 17.2 Hz, 1H), 4.19 (br, 1H), 4.35 (br, 1H), 4.60 (br, 1H), 5.84–5.87 (m, 1H), 5.90–5.92 (m, 1H), 6.04–6.07 (m, 2H), 6.10 (s, 1H), 6.49 (br, 1H), 6.60–6.62 (m, 1H), 6.78–6.82 (m, 1H), 7.10–7.14 (m, 1H), 7.53–7.55 (m, 1H), 8.10–8.12 (m, 1H), 8.20–8.27 (m, 2H). EI-HRMS Calcd for $C_{31}H_{29}NO_4Zr$: 569.1144. Found: 569.1154. Chiral HPLC Analysis Conditions: Chiralcel OD-H; eluent, hexane/^{i}PrOH = 4/1; flow rate, 0.75 mL/min; t_1 = 40.6 min, t_2 = 47.5 min. $[\alpha]^{21}_D$ = –40 (*c* 0.65, $CHCl_3$ for the sample of 96% ee).

1,1'-(2-Methyl-1-propen-1,3-diyl)-[η^5-3-(methallylindenyl)](cyclopentadienyl)-(dipicolinato)zirconocene (4.2a).



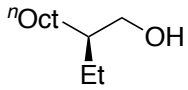
^{1}H NMR ($CDCl_3$): δ 1.54 (s, 3H), 2.24 (s, 3H), 2.73 (d, *J* = 15.4 Hz, 1H), 3.10 (d, *J* = 15.3 Hz, 1H), 3.57 (d, *J* = 17.2 Hz, 1H), 4.13 (d, *J* = 17.2 Hz, 1H), 4.38 (br, 1H), 4.60 (br, 1H), 5.80–5.82 (m, 1H), 5.91–5.93 (m, 1H), 6.00–6.08 (m, 2H), 6.18 (s, 1H), 6.34 (d, *J* = 8.6 Hz, 1H), 6.51 (s, 1H), 6.76–6.77 (m, 1H), 7.09–7.10 (m, 1H), 7.49–7.52 (m, 1H), 8.07–8.10 (m, 1H), 8.18–8.27 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 22.5, 25.4, 26.6, 29.8, 30.8, 35.6, 111.5, 111.8, 115.4, 116.2, 117.1, 118.7, 119.1, 119.7, 120.2, 123.4, 125.0, 125.9, 126.1, 126.3, 126.5, 126.9, 140.9, 143.6, 143.8, 150.1, 150.4, 165.5, 166.2. EI-HRMS Calcd for $C_{39}H_{25}NO_4Zr$: 541.0831. Found: 541.0830. Chiral HPLC Analysis Conditions: Chiralcel OD-H; eluent, hexane/^{i}PrOH = 2/1; flow rate, 0.75 mL/min; t_1 = 18.1 min, t_2 = 22.4 min. $[\alpha]^{21}_D$ = –41 (*c* 0.6, benzene for the sample of 91% ee).

Procedure for the Enantioselective Zirconium-Catalyzed Carboalumination. To a



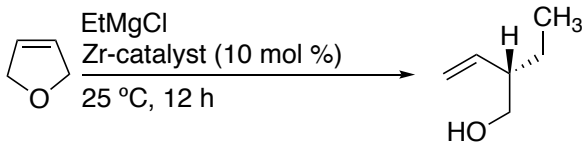
solution of Zr-catalyst (0.075 mmol) in anhydrous 1,1-dichloroethane (2.0 mL), added the Et_3Al (0.75 mL, 0.75 mmol). To this mixture was added 1-decene (70.2 mg, 0.5 mmol). After stirring the reaction mixture at 0 ℃ for 12 h, oxygen was bubbled through for 30 min. The resultant mixture was further stirred under oxygen atmosphere for 6 h, then treated with 15% aqueous $NaOH_{(aq)}$, extracted with Et_2O, washed with brine, dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator. The crude mixture was purified by silica gel column chromatography (pentane/Et_2O = 10/1 to 5/1) affording 64.9 mg of title compound (68% yield).

(2*R*)-2-Ethyl-1-decanol.



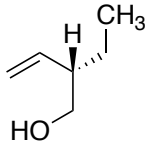
^1H NMR ($CDCl_3$): δ 0.86–0.92 (m, 6H), 1.27–1.42 (m, 17H), 3.55 (d, *J* = 4.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 11.2, 14.2, 22.7, 23.4, 26.9, 29.4, 29.7, 30.1, 30.5, 31.9, 42.0, 65.4.

Procedure for the Enantioselective Zirconium-Catalyzed Carbomagnesation.



To a solution of Zr-catalyst (9.5 mg, 0.02 mmol) in anhydrous THF (0.5 mL), added the ethylmagnesuim chloride solution (1.0 mL, 1.0 mmol) in THF, the mixture was stirred at room temperature for 45 min. In a separate flask, EtMgCl (0.2 mL, 0.02 mmol) was added to 2,5-dihydrofuran (14.02 mg, 0.2 mmol) in anhydrous THF (0.3 mL). The latter solution was then transferred to the "catalyst solution" and the mixture was stirred for 12 h. The solution was then cooled to 0 ℃ and excess Grignard reagent was quenched by dropwise addition of 0.1 M solution of $HCl_{(aq)}$. The mixture was diluted with 10 mL of distilled of H_2O and washed with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator. The crude mixture was purified by silica gel column chromatography (pentane/Et_2O = 10/1 to 5/1) to afford 15.6 mg of title compound as a color oil (76% yield).

(*S*)-2-Ethyl-3-butene-1-ol.



^{1}H NMR ($CDCl_3$): δ 0.91 (t, *J* = 7.3 Hz, 3H), 1.24–1.32 (m, 1H), 1.43–1.46 (m, 2H), 2.10–2.18 (m, 1H), 3.43 (dd, *J* = 10.6 and 8.3 Hz, 1H), 3.56 (1H), 5.12–5.19 (m, 2H), 5.59 (ddd, *J* =17.4, 10.5 and 8.7 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 11.6, 23.6, 48.8, 65.4, 117.5, 139.8.

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List of Publications

Chapter II. Enantioselective Synthesis of Ferrocene-Fused Planar-Chiral 4-(Dialkylamino)pyridine Derivatives and Their Application in Asymmetric Catalysis

(1) "Versatile and Enantiospecific Preparation of Planar-Chiral Metallocene-Fused 4-Dialkylaminopyridines and Their Application in Asymmetric Organocatalysis" Kazuhiro Yoshida, Qiang, Liu, Risa Yasue, Shiro Wada, Ryosuke Kimura, and Masamichi Ogasawara, submitted

In addition to above, the author also contributed following paper

(2) "Kinetic Resolution of Planar-Chiral (η^5-Bromocyclopentadienyl)manganese (I) Complexes by Molybdenum-Catalyzed Asymmetric Ring-Closing Metathesis" Masamichi Ogasawara, Ya-Yi Tseng, Qiang, Liu, Ninghui Chang, Xicheng Yang, Tamotsu Takahashi, and Ken Kamikawa. *Organometallics* **2017**, *36*, 1430.

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