A Concise Update on the Applications of Chiral Ferrocenyl Phosphines in Homogeneous Catalysis Leading to Organic Synthesis

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Received February 11, 2003

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Thomas J. Colacot received his Ph.D. from the Indian Institute of Technology, Madras, India (end of 1989), in the area of organophosphines and their applications in the synthesis of P, S, N heterocycles while working with Prof. M. N. S. Rao. Soon after he joined the University of Alabama, Birmingham, to teach general chemistry and conduct research under the supervision of Professors Krannich (former Chair) and Watkins (Assoc. Dean) in the area of organophosphines, arsines, and stibines for electronic and catalytic applications. In 1992, he became an Assistant Professor at Florida A & M University while collaborating in research with Prof. Will Rees of Florida State University. In 1993, he moved to Texas to work on an AMOCO/ATP project in the area of metallocenes and metallacarboranes for Ziegler–Natta Catalysis, under the guidance of Prof. Hosmane (formerly at SMU). Dr. Colacot joined Johnson Matthey in 1995 and is involved in the new product and process development of various homogeneous/polymer-supported catalysts for C–C/C–N coupling, hydroformylation, hydrogenation, hydrosilation, cyclopropantion, etc. In addition to his strong involvement in translating laboratory synthesis to pilot and plant, he uses high-throughput screening techniques to screen these catalysts for various organic transformations. Part of his job is to provide technical assistance to the fine chemical and pharmaceutical customers. Dr. Colacot teaches graduate courses in organometallic chemistry/homogeneous catalysis at Rutgers University as a part-time professor. This enables him to keep abreast of current developments. He is nearing completion of his MBA program, specializing in strategic management/acquisitions/new ventures. Dr. Colacot has published about 40 peer-reviewed articles in organic/organometallic chemistry. Currently he serves as the immediate past chair of the ACS South Jersey section. His hobbies are cooking and landscaping; in addition, he enjoys music, walking, hiking, working out in the gym, and family life.

1. Introduction

The discovery of the unique "sandwich"-structured ferrocene molecule[1] constituted a quantum leap in the history of modern inorganic chemistry, with the launch of a new era of "organometallic chemistry".[2] Incorporating ferrocene as part of a phosphorus(III) system led to the generation of a new class of chiral and nonchiral organophosphines, which are very powerful ligands in metal-catalyzed organic reactions. The industrial successes in the production of (+)-Biotin (Lonza), (*S*)-Metolachlor (Ciba-Geigy/Novartis/Syngenta/Solvias), and (+)-*cis*-methyl dihydrojasmonate (Firmenich) using "privileged" [3] Josiphos-type ligands have sparked tremendous interest in this area.[4]

Hayashi's[5] book chapter describes the synthesis and applications of chiral ferrocenyl phosphines up to 1995, and it is one of the most cited publications in this area. Reviews or monographs by Kagan,[6] Hayashi,[7] Richards,[8] Knochel,[9] Togni,[10] Ito,[11] and Blaser[12] describe the synthesis and homogeneous catalysis applications of the chiral ferrocenyl phosphine ligands, mainly pertaining to their areas of

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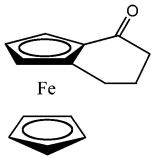
10.1021/cr000427o CCC: $44.00
Published on Web 07/29/2003

research. Santelli[13] very briefly provided the synthesis schemes of the various ligands up to 1999, while Lemaire's[14] review article mentions the applications of selected ferrocenyl ligands containing nitrogen atom(s).

In the light of our recent short review[15] on the applications of nonchiral ferrocenyl phosphines in coupling reactions, the focus of this article will be on the applications of chiral systems in homogeneous catalysis. Since the earlier reviewers concentrated their efforts mainly on the synthesis aspects of chiral ferrocenyl phosphine ligands, emphasis will be given to the applications of these ligands in catalysis, relevant to organic synthesis. To my knowledge, as of now, not a single concise report describing the applications of all the different types of chiral ferrocenyl phosphines is available. The purpose of this article is not to duplicate any of the earlier efforts, but to highlight the recent advances in the chemistry of all the well-known chiral ferrocenyl phosphines in homogeneous catalysis, with a special thrust to consolidate all the important work in this area. I have also made a conscious attempt to provide the necessary background, basic principles, and some history, with a view to help readers who are not well exposed to this area. However, importance has been given to the applications, such as asymmetric coupling, allylations, C═C, C═O, and C═N hydrogenations, hydrogen transfer, and other synthetically relevant reactions.

2. Chirality in Ferrocenyl Phosphines

One of the ways to induce chirality into a ferrocene molecule is by breaking its *plane of symmetry*. This is normally accomplished by electrophilic substitution reactions on the cyclopentadiene ring. Thus, a ferrocene molecule containing at least two different substituents on the same ring could exist as a racemic mixture. One of the advantages of *planar chirality* is that it does not undergo racemization. The first example of a chiral ferrocene (see **1**) was isolated by resolution in 1959.[16] Subsequently, trisubstituted

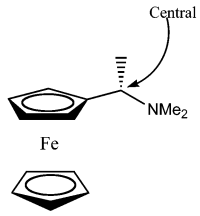


1

First example of a chiral ferrocene with planar chirality

ferrocenes were also isolated in optically pure form.[17] Since then, numerous examples of ferrocenes with *planar chirality* have been reported in the literature. The term *planar chirality* was proposed by Cahn, Ingold, and Prelog (CIP)[18] to characterize chirality associated with the substitution of compounds containing a plane of symmetry of the molecules, such as ferrocene, paracyclophanes, benzenechromiumtricarbonyl, etc. The CIP rule gives *R* configuration to **1**, as the observer sees the molecule from the upper ring and the substituents are analyzed clockwise with decreasing priority on the ring. Schlögl proposed an alternate nomenclature, where the molecule is viewed from above: a clockwise or anticlockwise sequence of groups of decreasing priority determines the *R* and *S* configuration (see **3**).[19] A revised CIP rule has also been proposed for trisubstituted chiral ferrocenes.[20]

Another way to induce chirality in ferrocene is to introduce a *lateral chirality* (also known as *central chirality*) unit into the ferrocene, as in the case of the Ugi-amine (**2**),[21] an excellent starting material for several chiral ferrocenyl phosphines.

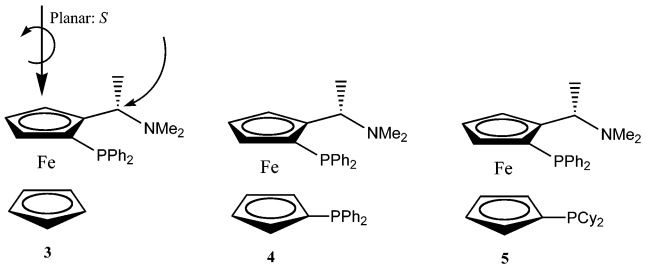


2

Central chirality in Ugi-amine

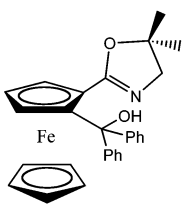
Normally for the nomenclature of *planar-central* chiral ligands, the first *R* or *S* designates the chirality for the side chain (central), followed by the *R* or *S* for the plane.

The utilization of both *planar* and *central chirality* (**3**−**5**) has been cleverly exploited to make several examples of chiral ferrocenyl phosphines. Although



3 **4** **5**

many ferrocenyl phosphines possess both *planar* and *central* chirality, several reports show that *planar* chirality has a significant effect on *enantioselectivity*,[22] while other systems show very little effect.[23] Kumada and Hayashi showed that *planar chirality* in PPFA (**3**)-type ligands exerted a very strong influence in deciding the *enantiomeric excess* (ee) and absolute configuration of the products resulting from a coupling reaction,[24] while Bolm and co-workers observed a significant reduction in ee in the Et_2Zn addition reaction when the *central chirality* in the hydroxyoxazolinyl ligand (**6**) was removed.[25] Studies conducted by Fu et al. revealed that a single *planar chiral* ferrocene ligand (**7**) was highly efficient for asymmetric catalysis.[26] Recent work by Hou and co-



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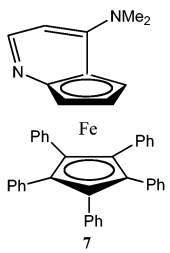

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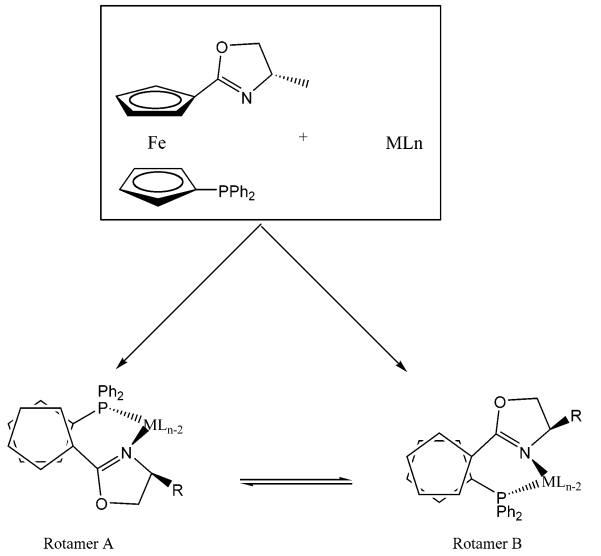
workers clearly demonstrated the dominance of *planar chirality* in producing higher enantiomeric

excess and absolute configuration in the Pd-catalyzed Heck reaction and allylic alkylation reaction using oxazoline-based ferrocenyl phosphines.[22a,27] They were able to provide experimental evidence as to why planar chirality is important and how it works. Hou's allylic substitution studies[22a] also revealed that "the matching of planar and central chiralities is essential for excellent asymmetric induction and the absolute configuration of the product are mainly governed by the central chirality." Although planar chirality has not been reported for 1,1′-disubsituted ferrocenes, a new type of chirality, called *axial chirality*, is formed when such ligands coordinate with a metal to form two rotamers, A and B, as in Scheme 1.[27b]

Scheme 1. Hou's Demonstration of Axial Chirality in a Metal Complex of Ferrocene-Based Bidentate Ligand



3. Types of Ligands: A Survey

3.1. Ligands Derived from Ugi-Amine

The pioneering work of Hayashi and Kumada during the mid-1970s led to the synthesis of the first example[28] of a chiral ferrocenyl phosphine, PPFA (**3**), by the diasteroselective ortho-lithiation of Ugi-amine followed by reaction with an electrophile (e.g., Ph_2PCl). Subsequently, the same group[5] as well as various other groups utilized Ugi-amine further to prepare numerous examples of chiral ferrocenyl ligands (Scheme 2). Another important class of ligands in this area (Josiphos-type ligands[29]) emerged when Togni introduced a second step, wherein the dimethylamino group in the Ugi-amine is replaced by nucleophilic substitution (S_N-1 type) using a secondary phosphine (R_2PH) or pyrazoles in polar solvents (see **11**−**13** in Scheme 2). Ito also exploited the principle of the stereospecific replacement of the NMe_2 group in Ugi-amine to make C_2-symmetric biferrocene with trans coordination geometry.[11] These types of ligands are abbreviated as TRAP. Very recently, Boaz elegantly developed a new class of phosphine−aminophosphine-based ligands (BoPhoz)[30] by reacting Ugi-amine with Ac_2O, followed by a reaction with a primary amine and R'_2PCl.

3.2. Oxazoline-Containing Ligands

Pfaltz, Williams, and Helmchen discovered that phosphines based on asymmetric oxazolines (Figure 1a) are useful ligands in chiral catalysis.[31] By virtue of the ortho-directing ability of oxazoline, Richards,[32] Sammakia,[33] and Uemura[34] simultaneously developed methods to make chiral ferrocenyl-based ligands by lithiation of the ferrocenyl oxazoline. The ratio of the diastereoisomers resulting from the lithiation could be controlled by the reaction solvent and by the temperature, as well as by the type of lithiating agent used (e.g., *n*-BuLi, *s*-BuLi). Quenching of these lithiations by phosphination provided an array of (*S*)−(*S*) phosphine ferrocene (phosferrox) ligands. The corresponding (*S*)−(*R*) ligands were synthesized by the introduction of a removable Me_3Si group.[35] During the same time, Ahn and Park[36] and Ikeda[37] reported the lithiation and phosphination of the 1,1′-bis(oxazolinyl)ferrocenes. As in the case of monolithiation, the solvent as well as the type of BuLi employed in the study dictates the distribution of the products. Examples of mono- and bis-oxazoline-based ferrocenyl phosphines with general structures are given in Figure 1b.

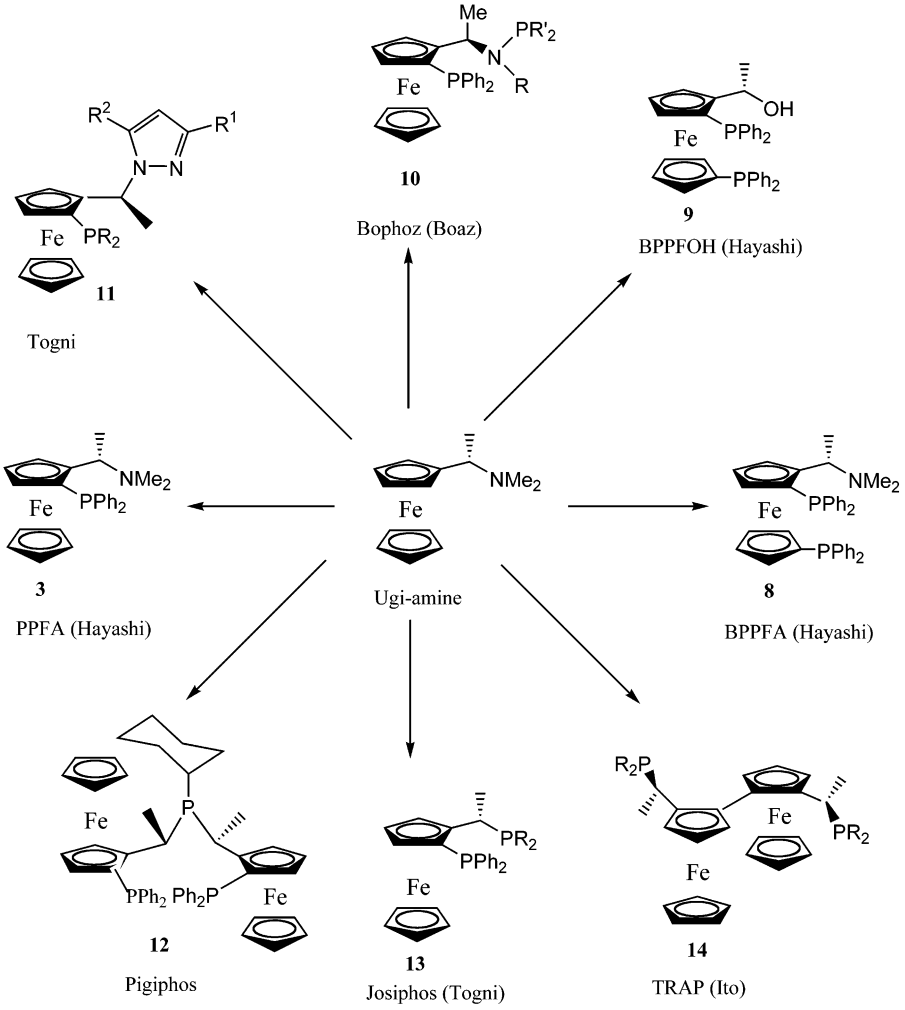
Ikeda also reported a multistep synthesis of a ligand (**17**) containing oxazoline and Ph_2P moieties on two different Cp rings, using ferrocene as the starting material.[37,38] This compound does not possess any planar chirality on the ferrocene backbone. By introducing a group such as Me, Me_3Si, or Me_3Sn to the Cp ring containing oxazoline (**18**), Hou et al. introduced the element of planar chirality (Scheme 3) and compared the effects of various chiralities.[27a,39] Very recently, the same group reported the synthesis and preliminary studies of a novel class of ligands (**19** and **20** in Scheme 4) with additional chirality on the P due to the incorporation of BINOL.[27,39]

3.3. 1,1′-Bis-Substituted Ligands

Although limited examples of C_2-symmetrical ferrocenes with *planar* or *planar-central* chirality have been reported by Hayashi, Ito, Ahn, and Ikeda, there has been a renewed interest in this area during the past few years.[8,13,40] One of the notable contributions in this area is the introduction of a new class of ligands called "Ferriphos" by Knochel.[9,41] These ligands were developed by the Corey−Bakshi−Shibata (CBS) reduction of 1,1′-diacylferrocenes to the corresponding diols, followed by nucleophilic substitution reaction. During the product formation, full retention of configuration is observed. Examples of C_2-symmetric ligands (**21**, **22**) developed by Knochel are given in Figure 2. Ferriphos ligands of the type **22** were renamed as Mandyphos by Degussa/OMG.

Reetz has been able to synthesize and fully characterize a chiral BINOL-based phosphite ligand (**23**) by using 1,1′-bis(dichloro)ferrocene as starting material (Figure 3).[42] Subsequently, Zhang prepared an analogous BINAP-based ligand, f-binaphane (**24**), and recently a novel sugar-substituted ligand, **25** (Figure 4).[43] A couple of years ago, Burk reported the synthesis of a 1,1′-disubstituted ferrocenyl phosphine (FerroTANE, **26**), accomplished by attaching two

Scheme 2. Examples of Various Types of Chiral Ferrocenyl Phosphines Derived from Ugi-Amine



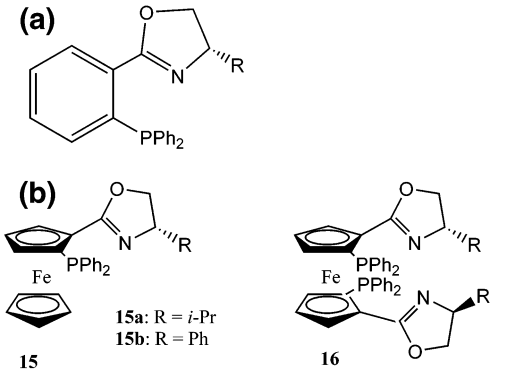


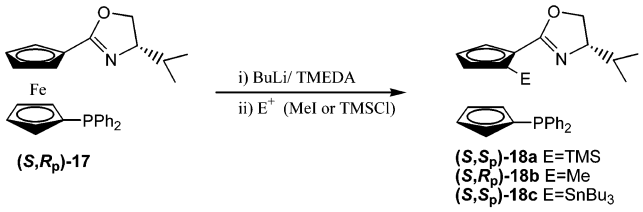
Figure 1. (a) Pfaltz–Helmchen–Williams ligand. (b) Mono- and bis-oxazoline-based ferrocenyl phosphines.

phosphetanyl fragments to the ferrocene ring.[44] The synthetically challenging *P*-stereogenic 1,1′-bis(phosphino)ferrocenes (**27**), prepared simultaneously by two independent groups (Widhalm et al., Mezzetti et al.)[45] using Jugé's method, have been explored efficiently in chiral hydrogenation reactions. The structures of these ligands are shown in Figure 5.

3.4. Other Types of Ligands

In addition to the ligands mentioned in the above sections, there are many other examples of ferrocenyl ligands known today. Since the scope of this review

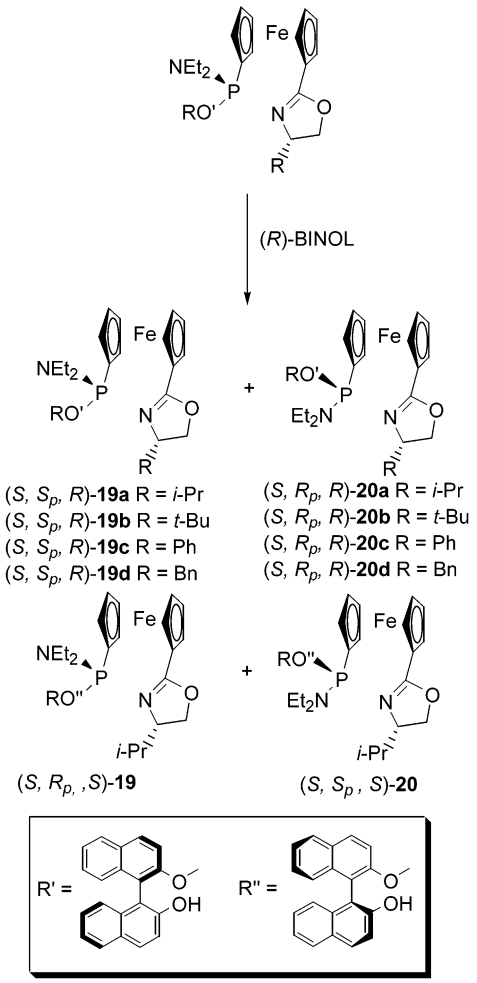
Scheme 3. Introducing Planar Chirality into the 1,1′-P,N-Ferrocene Ligands



is on the applications, it is not possible to mention each ligand developed in this area. To a certain extent, the earlier reviewers[5–14] mentioned several of those ligands. However, a few ligands, reported recently, are summarized below, mainly due to their applications in catalysis.

Zhang[46] and Hou[47] independently reported the synthesis of a new class of ferrocene-based "Trost-type ligand"[48] (**28**, **29** in Figure 6) and demonstrated their applications in different reactions. Enders synthesized a novel planar-central chiral ligand (**30** in Figure 7) having a stereogenic center at the *β*-position of the ferrocene backbone using the SAMP/RAMP ((*S*)- or (*R*)-1-amino-2-(methoxymethyl)pyrrolidine) hydrazone method.[49] Snieckus' (−)-sparteine-mediated lithiation methodology[50] was very cleverly explored to make a symmetrical diphosphine ligand in 99% ee.[51] However, the nonavailability of (+)-

Scheme 4. Hou's BINOL-Based Ferrocenyl Phosphine Ligands[a]

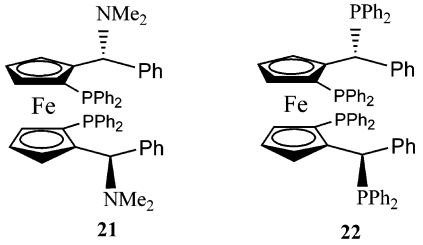


(*S*, S_p, *R*)-**19a** R = *i*-Pr
(*S*, S_p, *R*)-**19b** R = *t*-Bu
(*S*, S_p, *R*)-**19c** R = Ph
(*S*, S_p, *R*)-**19d** R = Bn

(*S*, R_p, *R*)-**20a** R = *i*-Pr
(*S*, R_p, *R*)-**20b** R = *t*-Bu
(*S*, R_p, *R*)-**20c** R = Ph
(*S*, R_p, *R*)-**20d** R = Bn

(*S*, R_p, *S*)-**19** (*S*, S_p, *S*)-**20**

[a] S_p and R_p represent chirality on the phosphorus.



21 **22**

Figure 2. Knochel's C_2-symmetric Ferriphos-type ligands.

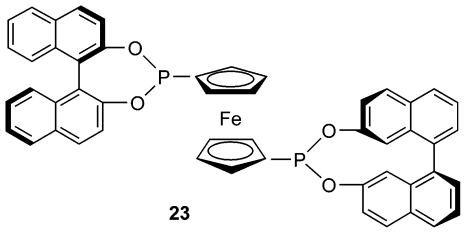


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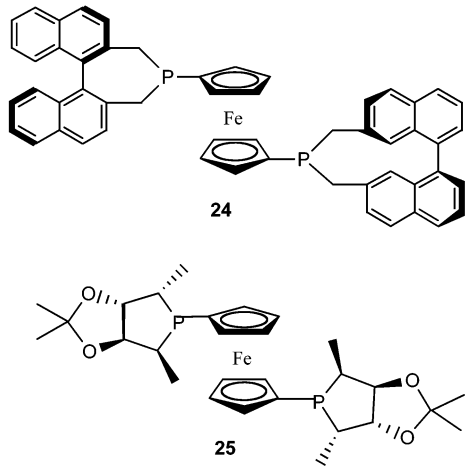
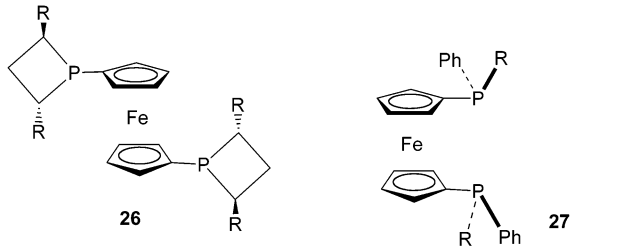
Figure 3. Ferrocene-based diphosphonite developed by Reetz.

sparteine was a problem in making the other enantiomers. Very recently, Snieckus has been able to circumvent this problem by using chiral ortho-substituted trimethylsilyl-based ferrocenyl amides.[52] Weissensteiner also developed a unique class of homo- and heteroannularly bridged ligands (**31** and **32**),[53] as shown in Figure 8. Diasteroselective ortho-metalation of stereogenic ferrocenyl phosphine oxides has been used for the asymmetric synthesis of the first enantiopure phosphorus-chiral 2,2′-bis(diarylphosphino)-1,1′-biferrocenyls.[54]



24 **25**

Figure 4. Zhang's f-binaphane- (**24**) and sugar-based (**25**) 1,1′-bis-substituted ligands.

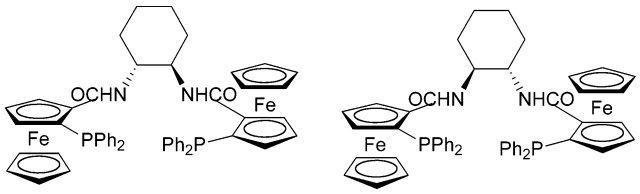


26 **27**

R = Et, n-Pr, i-Pr and t-Bu **(a-d)**
Ferro-TANE (Burk)

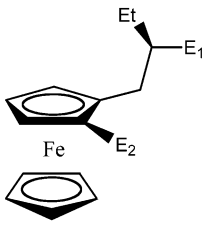
R =Naphthyl, o-methoxyphenyl **(a-b)**
Jugé's type stereogenicphosphines.

Figure 5. Other examples of 1,1′-substituted ligands.



(*R, R, Sp, Sp*)-**28** (*S, S, Sp, Sp*)-**29**

Figure 6. Trost-type pocket ligands developed independently by Hou and Zhang.



30

E_1 = PPh_2, SMe, S^iPr

E_2 = PPh_2, P^iPr_2, SeMe, STol, SePh

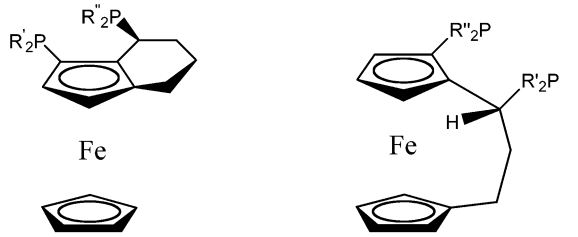
Figure 7. Enders' planar chiral ferrocenyl ligands bearing a sterogenic center in the β-position.

4. Applications in Organic Chemistry

As far as the chiral applications are considered, there is no universal chiral phosphine ligand for

Table 1. Pd-Catalyzed Asymmetric Cross Coupling of (1-Phenylethyl)magnesium Chloride with Vinyl Bromide or *β*-Bromostyrene

entry	substrate	Pd complex of **21**	R of **21**	yield (%)	ee (%)	additive
1	vinyl bromide	**21′b**	Pent	82	64	
2	vinyl bromide	**21′c**	Ph	81	63	
3	vinyl bromide	**21′d**	2-naphthyl	84	63	
4	vinyl bromide	**21′c**	Ph	88	76	$ZnCl_2$
5	vinyl bromide	**21′c**	Ph	86	82	ZnI_2
6	vinyl bromide	**21′a**	Me	73	68	
7	*β*-bromostyrene	**21′b**	Pent	78	80	
8	*β*-bromostyrene	**21′c**	Ph	89	93	
9	*β*-bromostyrene	**21′c**	Ph	82	29	$ZnCl_2$



31 R' = Ph; R" = Ph, Cy

32 R' = Ph, alkyl; R" = Ph, Cy, alkyl

Figure 8. Weissensteiner's homo- and heteroannular ligands.

catalysis. This statement is applicable even in the family of chiral ferrocenyl phosphines. The pioneering work of Hayashi and Kumada in identifying both chiral and nonchiral ferrocenyl phosphines in cross-coupling reactions was a significant starting point in the development of various ferrocenyl phosphine ligands for a wide variety of organic transformations related to this area. Subsequent industrial applications of Josiphos-type ligands constituted a quantum leap in the area of asymmetric catalysis. The major applications of the ligands from this area are summarized below, with an emphasis on the systems with maximum enantioselectivity.

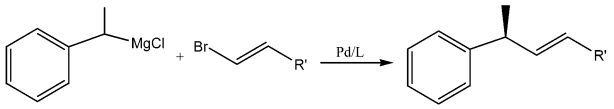
4.1. Asymmetric Coupling Reactions

Carbon−carbon bond-forming reactions represent one of the fastest growing areas of research in homogeneous catalysis for the synthesis of fine chemicals and pharmaceutical materials. Although numerous reports are available today on various coupling reactions, asymmetric induction is not applicable in all the named reactions, due to the lack of unsaturation in the substrates. The most widely studied enantioselective coupling reaction is allylation. Heck coupling is another area which has great potential in natural products synthesis. Recent studies indicate that even saturated molecules could be utilized in Suzuki coupling to make chiral molecules; however, the current application of this method is limited to the synthesis of substituted diaryls. Ferrocenyl phosphine-based catalysts played a significant role in the asymmetric coupling reactions. Following are descriptions of some of the most important work in this area.

4.1.1. Asymmetric Kumada–Hayashi Coupling

The nickel-catalyzed asymmetric cross-coupling reactions of 1-phenylmagnesium chloride with vinyl bromide using PPFA and BPPFA ligands were reported initially by Kumada and Hayashi in the late 1970s and early 1980s.[5,55] The coupling product, 3-phenyl-1-butene (Scheme 5), was obtained in over

Scheme 5. Cross-Coupling Reaction of 1-Phenylmagnesium Chloride with Vinyl Bromide



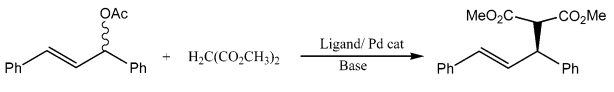
65% ee. In 1998, Knochel studied[9a] the same chemistry using Pd complexes with the ligands prepared by his group (**21**). For the reactions (Table 1) involving the substrate, vinyl bromide (R′ = H), the ee of the product, 3-phenyl-1-butene, was around 65%, irrespective of the substituent R in the ligand. Interestingly, the ee's were improved to 76 and 82%, respectively, by the addition of 2 equiv of $ZnBr_2$ and ZnI_2 to the Grignard reagent. In the case of *β*-bromostyrene substrate, the ee's increased significantly from 68 to 80 and 93% respectively by changing the substituent R in the ligand (**21**) from methyl to pentyl and phenyl. In 1989, Baker et al. reported 73% ee for this specific reaction.[56]

The coupling of vinyl bromides with *s*-BuMgCl seems to be more challenging. However, reactions of α-$(R_3Si)C_6H_5CHMgBr$ with vinyl bromide in the presence of Pd complexes of (*R*)-(*S*)-PPFA give high yields of (*R*)-allylsilanes, with ee's up to 95%.[57]

4.1.2. Enantioselective Allylic Alkylations

Numerous reports are available on the chemistry of allylic alkylations using ferrocenyl ligands. Hayashi's article[5] summarizes the work in this area up to 1995. For some reason, the major focus in academia has been on the allylic alkylation of 1,3-diphenyl-2-propenyl acetate (Scheme 6), although

Scheme 6. Allylic Alkylation of Diphenyl-2-propenyl Acetate

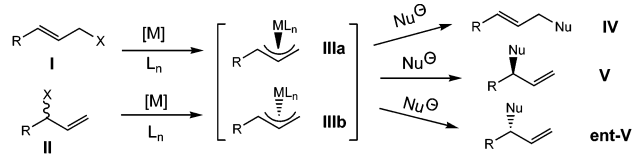


this system does not seem to have any industrial importance. Interestingly, oxazoline-based ligands developed by Pfaltz, Williams, and Helmchen,[31,58] Burgess,[59] Gilbertson,[60] and Zhang[61] were successfully utilized for allylic alkylations of similar systems. This trend has been true even in the family of chiral ferrocenes. For example, Zhang and Ikeda obtained

95−99% ee's when the ligands shown in Figure 1b were used.[38] By introducing planar chirality to the ligands of the type **17** with groups such as Me_3Si and Me, Hou[27b] recently prepared ligands of the type **18**, which achieved ee's very close to 99%. Enders' thio-substituted ligand, **30a** (E_1 = SMe; E_2 = PPh_2), also gave a 99% yield with 97% ee at −20 °C.[62] However, the ee decreased to 90% when the reaction temperature was 20 °C. Knochel obtained 99% ee for the same system, while the *enantiomeric excess* decreased to 85% when 1,3,3-triphenylprop-2-enyl acetate reacted with diethyl malonate.[63] Recently, Carretero also reported similar results using a readily available sulfur-containing ligand, 1-phosphino-2-sulfenylferrocene.[22h,64]

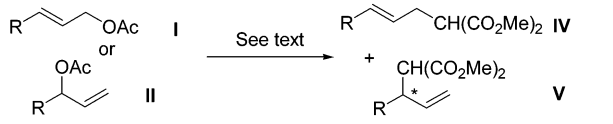
The regio- and enantioselectivity of monosubstituted substrates (Scheme 7) in Pd-catalyzed allylic

Scheme 7. Allylic Alkylation of Unsymmetrical Monosubstituted Substrates Showing the π-Allyl Intermediates



substitution reactions remain one of the more challenging areas of research. Recently, Hou very successfully demonstrated the usage of ligand **19d**, described in Scheme 4, for a wide variety of systems with very high regio- and enantioselectivity (Table 2).[27,39] Prior to this, Hayashi found that the 2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl ligand (MeO-MOP) gave good regio- and enatioselectivity in the Pd-catalyzed alkylation of **II** but a very low regioselectivity for substrate **I**.[7,65] Pfaltz's phosphite oxazoline ligands were also used to control the regio- and enantioselectivity in the Pd-catalyzed allylic alkylation of **I** or **II**. Of the various alkyl and aryl systems that Pfaltz studied, 3-(1-naphthyl)-3-allyl acetate gave very good regio- and enantioseletivity, while other systems gave modest to moderate selectivity.[66]

Table 2. Pd-Catalyzed Allylic Alkylation with Ligand 19d[a]

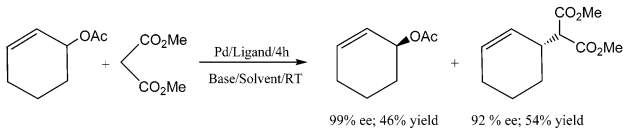


entry	substrate, R	*T* (°C)	time (h)	yield (%)[b]	V/IV[c]	ee (%)[d]
1	**Ia**, phenyl	0	2	98	95/5	95
2	**Ib**, 1-naphthyl	0	1	95	>99/1	93
3	**Ib**, 1-naphthyl	−43	7	97	>99/1	97
4	**Ic**, 4-MeO-Ph	−20	2	97	93/7	97
5	**Id**, 4-Me-Ph	0	9	91	98/2	92
6	**Ie**, 4-Cl-Ph	0	1	97	94/6	94
7	**If**, 4-CN-Ph	0	1	96	90/10	95
8	**Ig**, 2-thienyl	0	1	95	80/20	87
9	**Ih**, methyl	0	2	83	>97/3	94

[a] Molar ratio [Pd(π-C_3H_5)Cl]$_2$/**19d**/KOAc/substrate/$CH_2(CO_2Me)_2$/BSA = 2/4/3/100/300/300. CH_2Cl_2 and toluene were the solvents. [b] Isolated yield. [c] Determined by 300-MHz ^{1}H NMR of the crude product after column chromatography. [d] Determined by chiral HPLC.

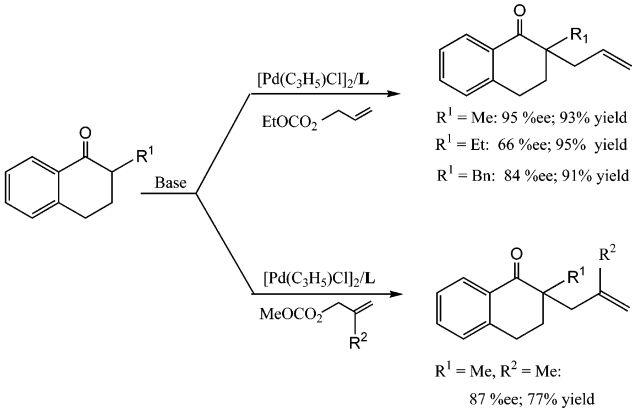
Zhang[46] has reported the usage of the chiral pocket ligands (see Figure 6) for the Pd-catalyzed allylation of 2-cyclohexenyl esters using dimethyl malonate as the nucleophile (Scheme 8). A very efficient resolution

Scheme 8. Kinetic Resolution of the Substrate, 2-Cyclohexenyl Acetate, during the Asymmetric Allylation



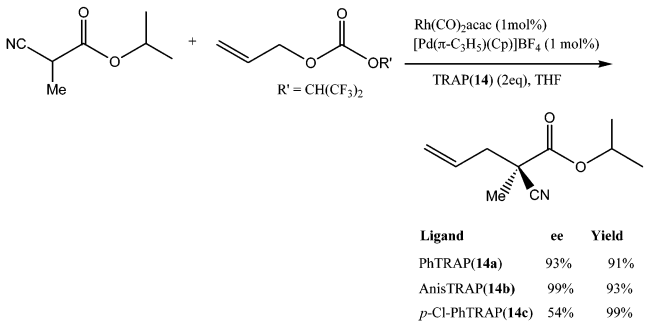
of 2-cyclohexenyl acetate was observed during the alkylation. The longer reaction time seems to have a positive effect on the conversion and a negative effect on ee's of the coupled product, while the ee's of the kinetically resolved substrate remain constant (>99%). However, the reaction has never reached 100% conversion, even after 24 h. Although it is fairly difficult to explain the whole phenomenon, Zhang proposed that the stereochemistry of the allylic substrate has an influence over the intermediate π-allyl/Pd complex prior to the attack. At the moment, it is not clear whether the so-called *memory effect* has any significance in this transformation.[67] Meanwhile, Hou examined another challenging substrate, ketone enolates, using the same type of chiral pocket ligand[47b] with ee's up to 95% (Scheme 9).

Scheme 9. Chiral Allylation of Ketone Enolates in the Presence of L·2H_2O, Where L Is a Chiral Pocket Ligand, Shown in Figure 6



Ito's two-component Rh−Pd-catalyzed allylic alkylation of activated nitriles using the TRAP ligands (**14**) is one of the novel reactions described in this area.[68] As described in Scheme 10, allylation of the cyano ester with allyl hexafluoroisopropyl carbonate using a combination of $Rh(acac)(CO)_2$ and [Pd(π-C_3H_5)(Cp)]BF_4 in the presence of (*S*,*S*)-(*R*,*R*)-PhTRAP (**14a**; R = Ph in **14**) proceeds smoothly in 4 h at −25 °C to give the coupled product in 93% ee (*R*) and 91% yield, respectively. The electronic effect of the substituent R on the ligand, TRAP (**14**), seems to have a profound influence on the ee's of the product. For example, AnisTRAP (**14b**, R = *p*-MeO-Ph) gave 97% ee (*R*) and 99% ee (*R*) at −25 and −40 °C respectively, while *p*-Cl-PhTRAP (**14c**, R = *p*-Cl-Ph) gave only 54% ee at −25 °C. The byproducts of the reactions were

Scheme 10. Ito's TRAP-Based Two-Component Catalyst System for the Allylations of Nitrile



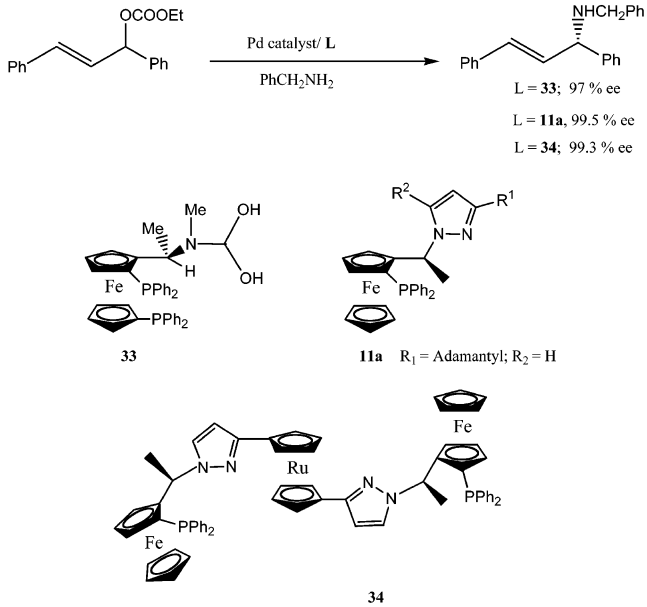
R′OH and CO_2. The Pd−Rh/PhTRAP-based two-component systems were also applicable for the enantioselective allylation of *N*-methoxy-*N*-cyanopropionamide as well as diethyl (1-cyanoethyl)phosphonate. The respective ee's were 87 and 92%.

In a recent review, Lautens and Fagnou highlighted the applications of halide effects in improving the reactivity of allylic alkylations, using various ligands including some ferrocenyl phosphines.[69]

4.1.3. Enantioselective Allylic Aminations

Allylic amination reactions are extensions of allylic alkylations. Reactions of 1,3-diphenyl-2-propenylethyl carbonate with benzylamine (Scheme 11) pro-

Scheme 11. Allylic Amination Reaction of Ethyl (1,3-Diphenylallyl)carbonate with Benzylamine

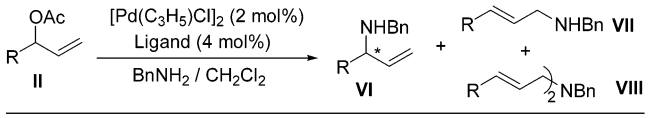


ceeded very smoothly to give a quantitative yield of the coupled amine product with over 97% ee by using Hayashi's ligands.[70] High ee's were obtained only with the ligands containing hydroxyl groups (**33**).[70] Interestingly, Togni obtained >99.5% ee for the same reaction using a pyrazole-based ligand [(*R*)-(S)-**11a**].[71] Subsequent work from the same group also identified a ruthenocene−ferrocene-based bimetallic ligand (**34**) for obtaining comparable ee's.[72]

As in the case of allylic alkylations, 1,3-diphenyl-2-propenyl acetate and its derivatives have been successfully aminated by several groups, including Hou,[27b] Knochel,[63] and Enders,[62] to yield the aminated products in high ee's.

A recent report by Hou (Table 3) indicated that BINOL-based ferrocenyl ligands are suitable for the amination of some of the challenging substrates.[39]

Table 3. Pd-Catalyzed Allylic Amination[a] with Ligand 20c[a]



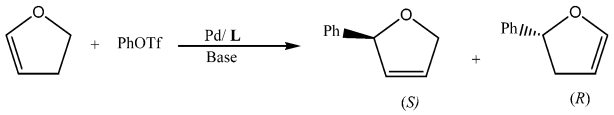
entry	substrate, R	time (h)	yield (%)[b]	**VI/VII/ VIII**[c]	**B/L**[d]	ee (%)[e]
1	**IIa**, phenyl	7	94	95/3/2	94/6	98
2	**IIb**, 1-naphthyl	8	87	94/6/−	96/4	97
3	**IIc**, 4-MeO-Ph	8	86	87/13/−	85/15	94
4	**IId**, 4-Me-Ph	6	89	94/6/−	90/10	95
5	**IIe**, 4-Cl-Ph	3	76	86/9/5	87/13	97
6	**IIf**, 2-thienyl	8	85	90/9/1	90/10	98
7	**IIg**, methyl	4	78	>97/3/−	>97/3	84

[a] Proceeded at 0 °C in CH_2Cl_2 with molar ratio [Pd(π-C_3H_5)Cl]$_2$/**20c**/substrate/$BnNH_2$ = 2/4/100/300. [b] Isolated yield. [c] Determined by GC of the crude product after column chromatography. [d] Determined by 300-MHz ^{1}H NMR of the crude product after column chromatography; **B/L** represents ratio of **VI**/(**VII** + **VIII** × 2). [e] Determined by chiral HPLC.

4.1.4. Asymmetric Heck Coupling

The Heck reaction is one of the most important C−C coupling reactions in modern organic chemistry.[73] However, the first intramolecular asymmetric Heck reactions were only described in 1989, independently by Shibasakai[74] and Overman.[75] A couple of years later, Hayashi reported intermolecular Heck reactions using BINAP as the ligand.[76] Pfaltz extended this work, using the diphenylphosphineoxazoline (PHOX) ligands, and achieved the highest (97%) enantioselectivity on the arylation of dihydrofuran.[77] Hou studied the same system (Scheme 12)

Scheme 12. Asymmetric Heck Reaction of a Model Substrate, Dihydrofuran, Yielding Regioisomers

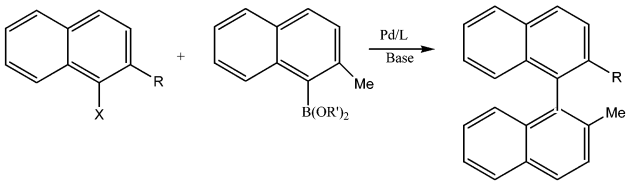


using a ferrocenyl phosphine-based oxazoline ligand and achieved 92.1% ee and 75% yield.[78] Since this is an important reaction in synthetic organic chemistry, more work in this area is highly relevant.

4.1.5. Asymmetric Suzuki Coupling

Although Suzuki coupling is a widely practiced aryl−aryl coupling reaction in industry,[79] there are not many reports available in the literature on the asymmetric aspects of Suzuki cross-coupling reactions. Part of the reason for this is the inherent difficulty in transferring chirality to a system which does not directly utilize any multiple bonds. In 2000, Cammidge reported the first asymmetric Suzuki coupling reaction (Scheme 13), leading to the formation of a binaphthalene derivative in up to 85% ee by coupling bromo- or iodonaphthalene with naph-

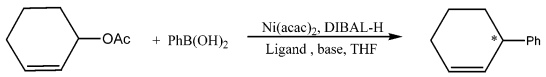
Scheme 13. Asymmetric Suzuki Coupling Leading to Chiral Binaphthalenes



thalene boronate ester.[80] Interestingly, in this Pd-catalyzed reaction, a monodentate ferrocenyl phosphine (**3**) was used as a ligand. However, the usage of bidentate ligands, including ferrocenyl phosphines, gave inferior ee's, as in the case of the Kumada–Hayashi coupling reactions described by Hayashi to produce the chiral biaryls.[5,81] So far, this is the highest *enantiomeric excess* that has been reported for the formation of binaphthalenes using the Suzuki coupling reaction. During the same time, Buchwald[82] also published an article on chiral Suzuki coupling for the synthesis of axially chiral biaryl compounds, using Cy_2P- or *t*-Bu_2P-substituted binaphthyls as ligands. According to Buchwald, "this is the first example of a catalytic enantioselective cross coupling procedure that allows for the preparation of functionalized biaryls". The highest ee's that resulted from this reaction for the binaphthalene systems was 73%. However, ee's increased dramatically to 92% when one of the aryl groups was a substituted phenyl.

In the year 2000, Uemura reported a Suzuki-type Ni(0)-catalyzed cross-coupling reaction[83] of allylic compounds (Scheme 14), using chiral oxazolinylferrocenyl phosphine ligand (**15**). The aryl boronic acid is known to act as a "hard" nucleophile in these types of reactions. The coupled products were obtained in very good yield, but with moderate enantioselectivities (up to 53% ee). This is the first example of an allylic substitution using organoboron compounds.

Scheme 14. A Chiral Suzuki-Type Allylation Reaction

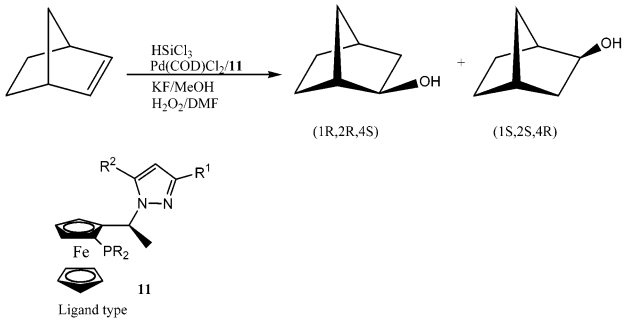


4.2. Enantioselective Hydrosilation and Hydroamination

Hayashi's PPFA-based Pd complexes were utilized for the hydrosilation of olefins and ketones with moderate ee's.[5] However, Hayashi's more recent work showed that Pd complexes of MOP ligands are very efficient catalysts in the hydrosilation of olefins with trichlorosilane. High enantioselectivities and chemoselectivities have been obtained for many olefins.[7] Togni's pyrazole-based ferrocenyl ligands, in the presence of $Pd(COD)Cl_2$, gave up to 99.5% ee during the enantioselective hydrosilation (Scheme 15) of norbornene with trichlorosilane.[84] However, moderate ee's were obtained for para-substituted styrenes.

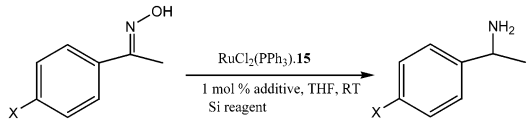
Ito used Rh-catalyzed hydrosilation as a useful methodology to obtain chiral alcohols of up to 96% ee from carbonyl compounds. Richards' review provides a brief overview of the work.[8]

Scheme 15. Pd-Catalyzed Hydrosilation of Norbornene



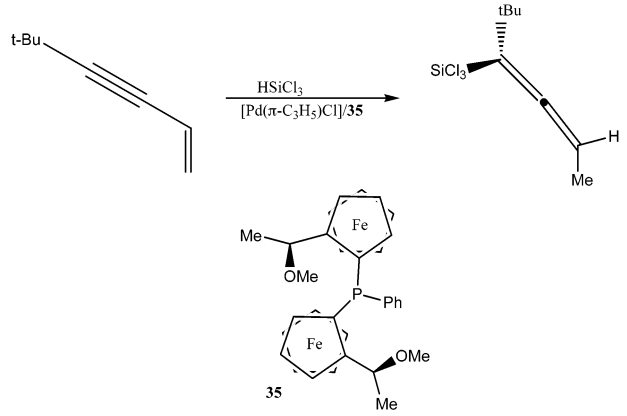
Uemura and Hidai have found that Ru(II)-based oxazolinylferrocenyl phosphines (**15**) are effective for catalyzing the asymmetric hydrosilation of ketoximes to give primary amines with ee's up to 89% after hydrolysis (Scheme 16).[85]

Scheme 16. Asymmetric Hydrosilation of Ketoximes



Hayashi developed a breakthrough catalytic allene synthesis using a Pd-catalyzed hydrosilation of but-1-en-3-ynes with trichlorosilane in the presence of a ferrocenyl phosphine (Scheme 17).[86]

Scheme 17. Enantioselective Synthesis of Allenes Using the Hydrosilation Approach



Togni reported the intermolecular versions of the asymmetric olefin hydroamination using the Ir complexes of Josiphos-type ligands.[87] The maximum ee's obtained for the products of hydroamination of norbornene with aniline using these ligands was 60%, while BINAP gave up to 95% ee at 75 °C in the presence of 4 equiv of fluoride.

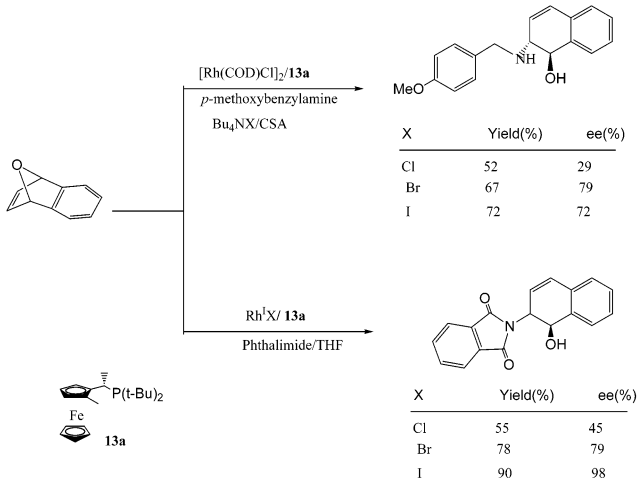
Uemura and Hidai also reported the hydrosilation of ketones and an imine using the $RuCl_2$(**15a** or **15b**)-PPh_3.[88]

4.3. Asymmetric Ring-Opening Reactions

Lautens et al. studied the $[Rh(COD)Cl_2]_2$-catalyzed ring-opening reactions[89] of oxabenzonorbornadiene with nucleophiles such as amines and phenols in the

presence of PPF−P(*t*-Bu)$_2$ and related ligands. The products were isolated in very good yields and enantiomeric excesses. However, these researchers observed catalyst poisoning when substrates such as *p*-methoxybenzylamine and phthalimide were used (Scheme 18). With the same catalyst system, ali-

Scheme 18. Rh-Catalyzed Enantioselective Ring-Opening in the Presence of a Josiphos-Type Ligand and the Effect of Halides on Conversion and Selectivity



phatic amines did not react at all. This trend in reactivity was observed for the Rh-catalyzed ring opening of vinyl epoxides.[90] To overcome the catalyst poisoning, the use of additives was examined. It was found that the combined use of protic and halide additives effectively alleviates catalyst poisoning. The choice of the halides also seems to be important. Both the ee's and the yields were increased in the order Cl < Br < I, while F was not at all useful. In the methoxybenzylamine system, the ee's increased from 52 to 72%, while in the case of the phthalimide system, the ee's increased from 45 to 98% upon changing chloride to iodide. This trend was observed for several examples of activated amines.[91]

4.4. Asymmetric Hydrogenation Reactions

Several examples of chiral ferrocenyl phosphines have been used for the hydrogenation of various multiply bonded systems, such as olefins, carbonyls, imines, etc. A few selected examples are provided below.

4.4.1. Ru-Catalyzed Hydrogen-Transfer Reactions

In 1997, Sammakia reported the hydrogen-transfer reactions of alkyl and aryl ketones using the catalyst prepared in situ from $RuCl_2(PPh_3)$ and oxazolinylferrocenyl phosphine at 80 °C.[92] NMR spectral studies of the reaction mixture of $RuCl_2(PPh_3)$ and [2-(4′-phenyloxazolin-2′-yl)ferrocenyl]diphenylphosphine indicated that the produced catalysts consisted of two diastereomers in ca. 5:1 ratio. Acetophenone was reduced by the use of this catalyst with up to 94% ee. Uemura and Hidai isolated the diastereomerically pure form of the Ru catalyst (Figure 9), solved the crystal structure, and studied the transfer hydrogenation of ketones with *i*-PrOH (Scheme 19) and chiral

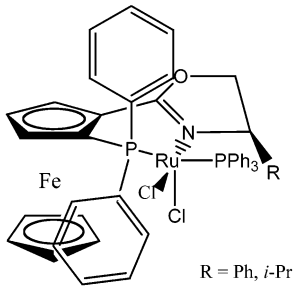
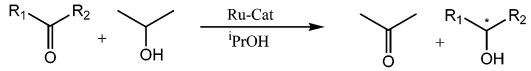


Figure 9. $RuCl_2(PPh_3)$**15** isolated in diastereomerically pure form.

Scheme 19. Asymmetric Transfer Hydrogenation of Ketones to Alcohols



oxidation of racemic secondary alcohols with acetone by kinetic resolution (Scheme 20).[93] Tables 4 and 5

Scheme 20. Kinetic Resolution of Alcohols in the Presence of a Chiral Ru Catalyst

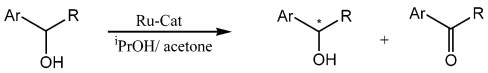


Table 4. $RuCl_2(PPh_3P)$15a-Catalyzed Asymmetric Hydrogen-Transfer Reactions of Ketones

entry	substrate	time (h)	conv (%)	ee (%)
1	C_6H_5COMe	2	94	99.6
2	C_6H_5COEt	8	99	99.7
3	$C_6H_5CO(n\text{-}Bu)$	4	99	98.7
4	$p\text{-}MeC_6H_4COMe$	4	98	99.3
5	$p\text{-}FC_6H_4COMe$	2	99	97.3
6	$p\text{-}ClC_6H_4COMe$	2	99	98.7
7	$m\text{-}MeC_6H_4COMe$	1	98	99.9
8	$m\text{-}FC_6H_4COMe$	3	98	99.6
9	$m\text{-}ClC_6H_4COMe$	2	99	98.7
10	$o\text{-}MeC_6H_4COMe$	1	99	99.9
11	$o\text{-}FC_6H_4COMe$	1	92	96.6
12	*t*-BuCOMe	16	81	99

Table 5. $RuCl_2(PPh_3P)$15a-Catalyzed Kinetic Resolution of Secondary Alcohols

entry	substrate	time (h)	unreated alcohol (%)	ee (%)	k_f/k_s
1	$C_6H_5CH(OH)Me$	4	48	98.8	>110
2	$p\text{-}MeC_6H_4CH(OH)Me$	1	49	99.9	>368
3	$p\text{-}FC_6H_4CH(OH)Me$	2	39	99.7	>10
4	$p\text{-}BrC_6H_4CH(OH)Me$	2	49	99.8	>368
5	$o\text{-}MeC_6H_4CH(OH)Me$	18	43	99.8	>46

show the results of the study. Several examples of ketones (Table 4) were reduced to alcohols with ee's up to 99.9%. The reverse reactions (Table 5) also gave very high ee's (up to 99.9%). Figure 10 shows a pictorial representation of the transition-state model of a Ru catalyst involving in a hydrogen-transfer process. The active species in the catalytic cycle is the Ru(II) hydride. Acetophenone (R′ = Me) approaches the complex in such a way as to minimize steric interactions among the phenyl group of ketone, the phenyl groups of two phosphines, and the substituent of the oxazoline group. The reaction proceeding through this

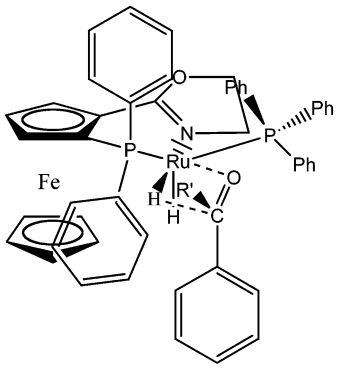


Figure 10. Pictorial representation of the hydrogen transfer during the asymmetric induction of ketone.

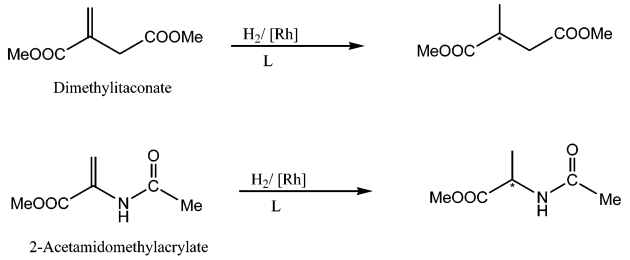
intermediate state results in the formation of the *R* alcohol.

4.4.2. Asymmetric Hydrogenation of Olefins

This is one of the most important reactions in the area of asymmetric catalysis. Almost all of the asymmetric ferrocenyl ligands have been tried in attempts to hydrogenate various olefins. As mentioned in the Introduction, several groups had reviewed the hydrogenation work, mainly pertaining to their own ligands.[6−11,14] Therefore, mainly the recent work will be highlighted here.

Many ligands have been used to test the model systems, such as dimethyl itaconate and acetamidomethyl acrylate (Scheme 21). An interesting recent

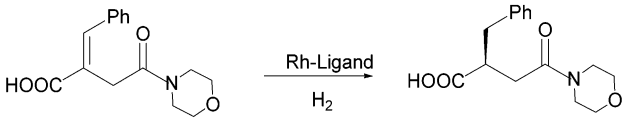
Scheme 21. Chiral Hydrogenation of the Model Substrates



result obtained in this area is from Reetz, who used [Rh(COD)**23**]BF_4 catalyst (**23** is a diphosphonite ligand resulting from reaction of ferrocene and BINOL) very effectively to hydrogenate the above systems.[42] For both systems, the ee's were over 99.5%. Burk's (*S,S*)-Et FerroTANE (**26a**)[44] also gave 98% (*R*) derivative when dimethyl itaconate was used as the substrate. The *n*-Pr analogue (**26b**) also gave a very good ee (97%); however, low ee's were observed for ligands with bulkier substituents. For example, **26d** (R = *t*-Bu) gave only 1% ee, while **26c** (R = *i*-Pr) gave 78% ee. The well-known Et-DuPhos-Rh catalyst, under identical conditions, gave 97% ee for the same transformation.[94] Togni had earlier demonstrated the very efficient use of Josiphos in the presence of $Rh(NBD)_2BF_4$ to hydrogenate methyl acetamidocinnamate under 1 bar of H_2 pressure.[29] The hydrogenated product was obtained in quantitative yield with 96% ee. On the other hand, when acetamidocinnamic acid was used as the substrate, significantly lower ee's (84%) were obtained. The related 1,1′-disubstituted olefin, methyl acetamidoacrylate, gave similar results (88% ee).

The asymmetric hydrogenation of amidoitaconate (Table 6) seems to be fairly challenging. Well-known

Table 6. Rh-Catalyzed Chiral Hydrogenation of Amido Itaconate Using (*S,S*)-Et-FerroTANE

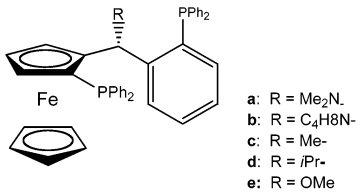


entry	ligand	conv(%)[b]	ee (%)
1	(*S,S*)-Et-FerroTANE	100	98 (*R*)
2	(*S,S*)-Et-DuPHOS	5	85 (*R*)
3	(*R,R*)-DIPAMP	10	87 (*R*)
4	(*S,S*)-BPPM	75	79 (*S*)
5	(*S*)-Tol-BINAP	11	43 (*S*)
6	(S)-PHANEPHOS	60	62 (*S*)

ligands such as DUPHOS, DIPAMP, BPPM, Tol-BINAP, PHANEPHOS, etc. have given moderate ee's, while Et-FerroTANE gave 98% ee.[44]

An unprecedented high enantiosletivity was obtained when dimethyl itaconate was hydrogenated to obtain dimethyl (*S*)-2-methylsuccinate in 100% yield and 98−99% optical purity using the Rh-based Josiphos.[29] The maximum ee that has been obtained using the BoPhoz ligands was reported[30] to be 94% for dimethyl itaconate; however, the ee's were up to 99% when itaconic acid was used.

Knochel[41b,c] used his C_2-symmetric type of Ferriphos ligands (Figure 2) to carry out hydrogenation of several α-acetoamidoacrylic acid derivatives. The ee's were 97−99%. Subsequently, Knochel and Ireland developed another interesting type of ligand (**35a**−**d**), also known as Taniaphos, and studied the effective chiral hydrogenations of methyl α-acetamidocinnamates and dimethyl itaconate with ee's over 95%.[95] Recently, Knochel's group tuned the ligand by

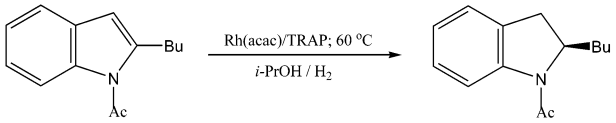


35 (Knochel's Taniaphos type ligands)

replacing the NMe_2 group of the Taniaphos by OMe (**35e**) in order to further improve the enantiomeric excess to 98−99% in several model systems, such as (*S*)-*N*-acetylphenylalanine methyl ester, dimethyl itaconate, and α-acetoxyacrylic acid methyl ester.[96] One of the interesting results in this area has come very recently from Zhang' group.[43b] Using a sugar-substituted ferrocenyl phosphine (**25**), Zhang was able to hydrogenate α-acetamidocinnamte, α-dehydroamino acid derivatives, as well as itaconic acid over 99.5% ee, with a turnover number (TON) of 10 000. The mono- and bis-methyl esters of the itaconic acid derivatives gave slightly lower ee's (89.9−95.5%).

Ito's TRAP ligands, in the presence of $Rh(COD)_2ClO_4$, were also used for the highly enantioselective hydrogenation of β-oxy-α-acetamidoacrylates.[97] This method is very useful for the enantioselective synthesis of β-hydroxy-α-amino acids. Ito also reported the enantioselective Rh-catalyzed hydrogenation of heteroaromatic compounds (indoles) (Scheme 22) using (*S*,*S*)-(*R*,*R*)-PhTRAP (**14a**).[98] For example,

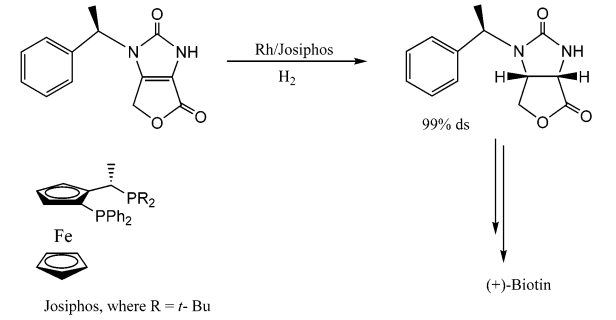
Scheme 22. Catalytic Chiral Hydrogenation of Heteroaromatic Compounds, Indoles



(*R*)-acetyl-2-butylindoline was hydrogenated with 85% ee when Rh(acac)(COD) was used as the catalyst precursor. On further investigation, $Rh(NBD)_2SbF_4$ was found to be a better catalyst in comparison to Rh(acac)(COD). It was noted that addition of base is necessary for the achievement of high enatioselectivity and high conversion. The $Rh(NBD)_2SbF_4$-(*S*,*S*)-(*R*,*R*)-PhTRAP scarcely promoted the hydrogenation in the absence of a base, giving the product in only 7% ee (*S*). Addition of bases such as Et_3N or Cs_2CO_3 brought remarkable improvement of the enantioselectivity (94% ee) and catalytic activity (100% conversion). However, pyridine did not activate the catalyst at all, while K_2CO_3 gave 44% conversion with 76% ee.

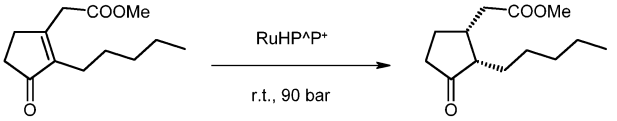
One of the notable industrial applications of ferrocenyl phosphine-type ligands is Lonza's Rh-catalyzed asymmetric synthesis of (+)-Biotin using the *t*-Bu_2P-based Josiphos (Scheme 23).[99] The hydrogenated intermediate was obtained in very high diastereomeric excess (de) and ee.

Scheme 23. Rh-Catalyzed Enantio- and Diastereoselective Synthesis of (+)-Biotin Intermediate Using Josiphos-Type Ligands



Firmenich developed a multi-tons-per-year process for the stereoselective production of (+)-*cis*-methyl dihydrojasmonate (Scheme 24). The results are remarkable in that classical Ru complexes and conditions for the hydrogenation of C=C bonds did not work. Not only the enantioselectivity but also the chemo- and cis-selectivity were problematic, in addition to the inherent difficulty associated with hydrogenation of tetrasubstituted C=C bonds. A broad screening of Ru catalysts showed that [Ru(H)(COD)ligand)]BF_4 (RuHP^P$^+$) complexes with selected Josiphos ligands and Me-duphos gave by far the best performance. At a substrate-to-catalyst (s/c) ratio of 2000, both Me-duphos and PPF−PCy_2 gave full conversions and cis/trans ratios of 99/1. For the Me-duphos complex, an ee of 76% and a TOF of 120 h^{-1} were reached, whereas PPF−PCy_2 showed an ee of 88% and a TOF of 200 h^{-1}. The process (Scheme 24) is now used for the technical production of (+)-*cis* methyl dihydrojasmonate.[100]

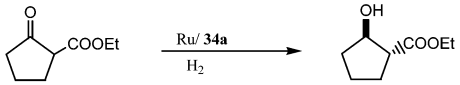
Scheme 24. Asymmetric Hydrogenation of Methyl Jasmonate, Leading to the Formation of (+)-*cis*-Methyl Dihydrojasmonate



4.4.3. Asymmetric Hydrogenation of Carbonyls

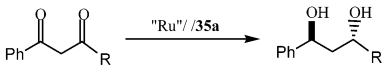
Knochel's Taniaphos ligands (**35a**−**d**) have been successfully used in the Ru-catalyzed hydrogenation of β-ketoesters to obtain β-hydroxyesters with very good ee's (92−96%) (Table 7).[95] The modified version of Taniaphos (**35e**) reported recently gave ee's up to 99%.[96] Similar systems were investigated earlier by Togni using the Ru-Josiphos catalyst. The hydroxy ethyl ester was obtained in 97% ee, while for the methyl ester, the reduction product was obtained in only 84% ee.[29] The hydrogenation can be applied to cyclic keto esters such as ethyl 2-oxocyclopentanecarboxylate to give (1*R*,2*R*)-ethyl 2-hydroxy-1-cyclopentanecarboxylate with 98.2% de and 90.9% ee (Scheme 25).[95] Interestingly, symmetrical diketones such as dibenzoylmethane undergo a double reduction using these ligands to obtain C_2-symmetrical 1,3-diol with 98.2% ee (Scheme 26).[95] Unsymmetrical diketones such as 1-phenyl-1,3-butanedione also undergo diastereoselective reduction to obtain (1*S*,3*R*)-1-phenyl-1,3-butanediol with 98.4% ee and 97.2% de (Scheme 26).[95,96] However, the opposite isomer was obtained in only 91.8% ee.

Scheme 25. Enantio- and Diastereoselective Hydrogenation of β-Dicarbonyl Compounds



de = 98.2%; ee = 90.9 (1*R*, 2*R*)

Scheme 26. Enantio- and Diastereoselective Hydrogenation of β-Dicarbonyl Compounds

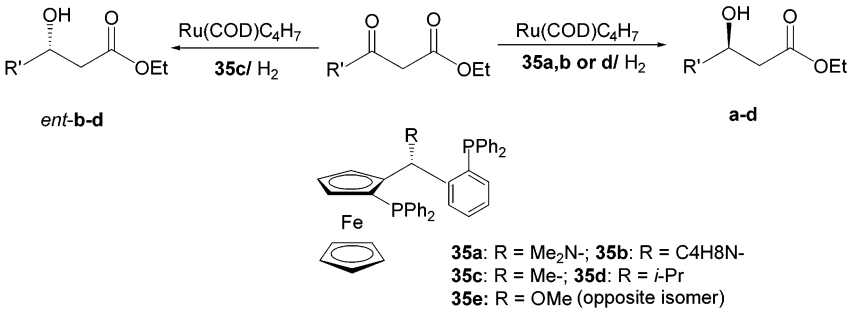


R = Ph: de = 90.5; ee = 91.6 (1*S*, 3*S*)
R = Me: de = 97.2; ee = 98.4 (1*S*, 3*S*)

4.4.4. Asymmetric Hydrogenation of Imines

Although preparation of optically active pure amines by catalytic asymmetric hydrogenation of imines is still a challenging task, promising methodologies have been developed.[101] However, the largest industrial process known today using chiral catalysis

Table 7. Ru-Catalyzed Chiral Hydrogenation of β-Ketoesters Using Knochel's Ligand



entry	ligand	substrate (R′)	product	ee (%)	entry	ligand	substrate (R′)	product	ee (%)
1	**35a**	Me		95.5	6	**35c**	*i*-Pr	*ent*-	96.5
2	**35d**	Me		91.6	7	**35a**	Ph		95.0
3	**35a**	*n*-Pr		96.5	8	**35d**	Ph		96.0
4	**35**	*n*-Pr	*ent*-	92.7	9	**35c**	Ph	*ent*-	93.7
5	**35a**	*i*-Pr		95.9	10	**35e**	Ph	*R*	98

involves asymmetric hydrogenation of an imine for the synthesis of (*S*)-Metolachlor.[102]

Metolachlor, the active ingredient of Dual, is one of the most important grass herbicides for use in maize and a number of other crops. This *N*-chloroacetylated, *N*-alkoxyalkylated ortho-disubstituted aniline was introduced as a commercial product on the market in 1976 as a mixture of four stereoisomers (Figure 11) and was produced via a Pt/C-catalyzed

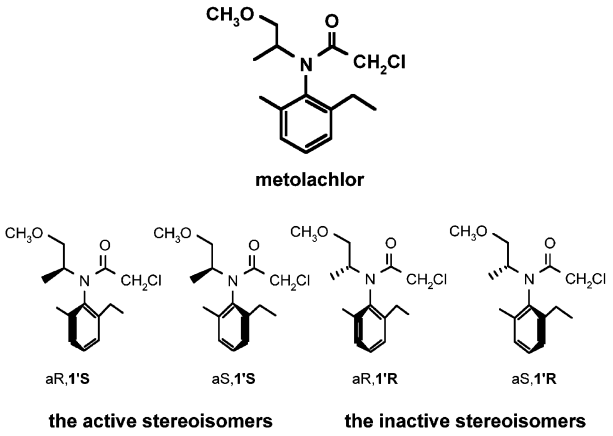


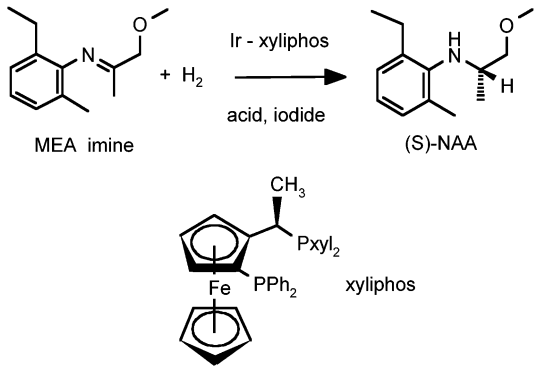
Figure 11. Basic structure of Metolachlor with different stereoisomers

reductive alkylation of 2-methyl-5-ethylaniline (MEA) with aqueous methoxyacetone, followed by chloroacetylation.[103]

During the early 1980s, it was found that about 95% of the herbicidal activity of metolachlor was due to the two (1′*S*)-diastereomers. After years of intensive research, in 1997, Dual Magnum, with a content of approximately 90% (1′*S*)-diastereomers and with the same biological effect at about 65% of the use rate of the racemate, was introduced in the USA. This "chiral switch" was made possible by the new technical process that is briefly described below.

The key step of this new synthesis is the chiral hydrogenation of the isolated MEA imine, as shown in Scheme 27.[12] The process operates at 80 bar of hydrogen and 50 °C with a catalyst generated in situ from $[Ir(cod)Cl]_2$ and PPF−$PXyl_2$, a Josiphos-type ligand at a s/c ratio of >1 000 000. The reaction is

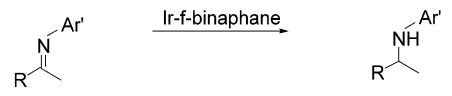
Scheme 27. Enantioselective Hydrogenation of MEA Imine



completed within 4 h, the initial TOF exceeds 1 800 000 h^{-1}, and the enantioselectivity is approximately 80%. The use of iodide and acid as additives and the high purity of MEA imine are the other factors for the success of this process.[12]

Zhang's Ir complex of f-binaphane (**24**) has been used recently to hydrogenate *N*-arylimines.[43] For many substrates, the *E* isomers of the imines can be formed exclusively. By removing the *N*-aryl groups, it provides an attractive method for making chiral amines. As shown in Table 8, use of *N*-(1-phenylethylidene)aniline (entry 1) and the Ir-f-binaphane catlyst gave 84% ee. Interestingly, the neutral Ir

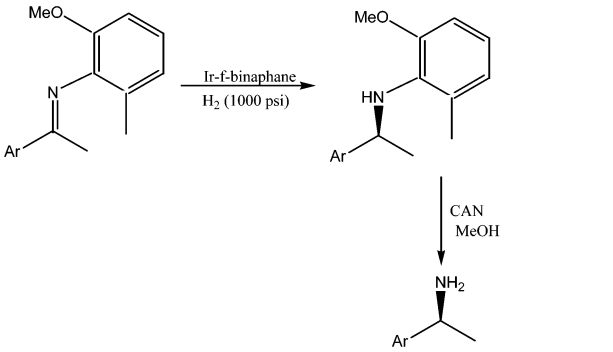
Table 8. Imine Hydrogenation Using Ir-f-binaphane



entry	substrate	R	Ar′	conv (%)	ee (%)
1	**a**	Ph	Ph	100	84
2	**b**	Ph	2,6-dimethyl-C_6H_3	77	>99
3	**c**	4-MeO-C_6H_4	2,6-dimethyl-C_6H_3	77	98
4	**d**	4-CF_3-C_6H_4	2,6-dimethyl-C_6H_3	80	99
5	**e**	*t*-Bu	2,6-dimethyl-C_6H_3	15	8
6	**f**	*i*-Pr	2,6-dimethyl-C_6H_3	29	23
7	**g**	Cy	2,6-dimethyl-C_6H_3	24	31
8	**h**	Ph	4-MeO-C_6H_4	100	77
9	**i**	Ph	4-MeO-C_6H_4	100	81

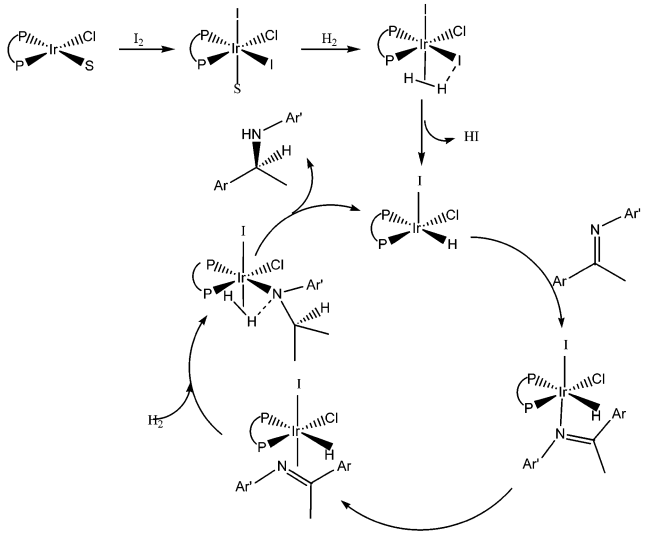
complex, $[Ir(COD)Cl]_2$, gave much higher ee's compared to a cationic complex, $Ir(COD)_2PF_6$. In the case of a 2,6-dimethyl-*N*-phenyl group (entry 2), 99% ee was accomplished. However, when the R group on the carbon terminal of the C═N bond is an alkyl group, low ee's were observed (entries 5−7). Using cerium ammonium nitrate (CAN), the hydrogenation products of *N*-arylimines with 2-methyl-6-methoxyphenyl groups were hydrolyzed to primary amines of very high enantiomeric excess (Scheme 28).

Scheme 28. Synthesis of Chiral Amines Using the Imine Hydrogenation Route



As observed in the case of imine hydrogenation reactions using Josiphos ligands,[104] Zhang also identified the effect of additives, especially iodide, in the chiral hydrogenation of acyclic imines. The ee's and conversions were significantly improved in many cases. Scheme 29 represents the proposed mecha-

Scheme 29. Zhang's Proposed Mechanism for the Ir-f-binaphane-Catalyzed Imine Hydrogenation



nism, showing that the presence of I_2 helps to initiate the oxidation of Ir(I) to Ir(III) during the oxidative addition of iodine.

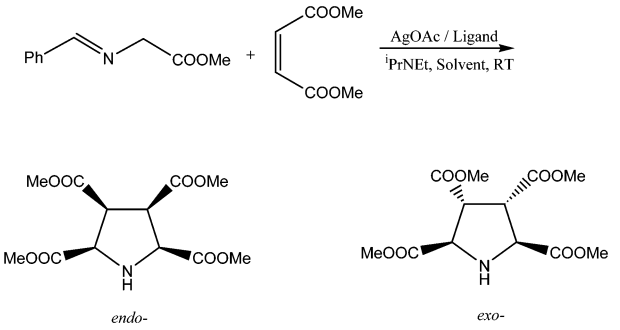
Apart from the ferrocene-based ligands, Pfaltz's oxazoline-based ligands have also been utilized recently for imine hydrogenations with some promising results.[105]

4.5. Asymmetric Cycloaddition Reactions

4.5.1. Enantioselective [3 + 2] Cycloadditions

Zhang carried out a highly enantioselective Ag(I)-catalyzed [3 + 2] cycloaddition of azomethine ylides (Table 9) using the chiral pocket ligands.[106] Screening studies (Scheme 30) using various ligands gave the

Scheme 30. Ag-Catalyzed [3 + 2] Cycloaddition of Azomethine Ylides

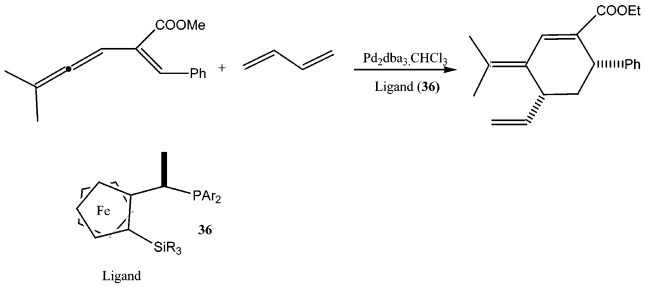


endo diasteromer under identical conditions, except for BINAP. BINAP[107] and Me-DuPHOS[108] ligands gave only 13% and 23% ee's, respectively, and poor de was observed in the case of BINAP. PennPhos and BICP, developed by the same group,[109] gave poor ee's. The Trost ligand[110] gave fairly good ee (59%) under identical conditions. The Zhang−Hou ligands (**28**, **29**) are also very similar to the Trost ligand, except for the fact that the Zhang−Hou ligand has additional chirality due to the ferrocene backbone. The endo derivative was isolated in 94% yield and 76% ee. By changing the PPh_2 substituent on the original Zhang−Hou ligand (**28**) to $P(Xylyl)_2$ (**28a**), Zhang was able to further improve the ee's to 86%. Table 9 shows the general applicability of this route to a wide variety of α-iminoester substrates. However, α-(alkylimino)-esters are less reactive.

4.5.2. Enantioselective [4 + 2] Cycloadditions

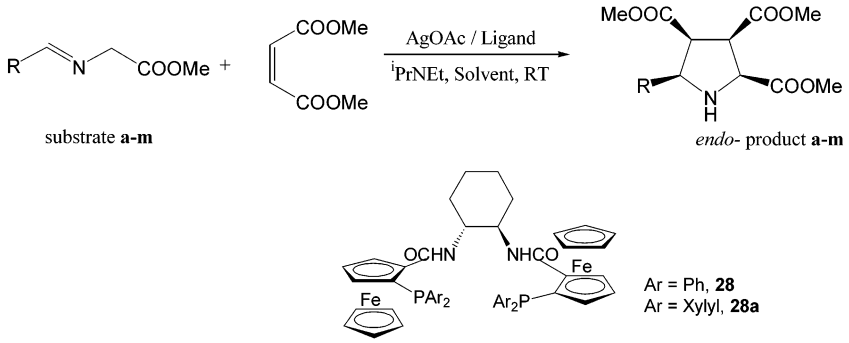
Ito and Murakami developed a Pd-catalyzed [4 + 2] cycloaddition reaction (Scheme 31) of a vinylallene

Scheme 31. Pd-Catalyzed [4 + 2] Cycloaddition of Vinylallene



with buta-1,3-diene using an R_3Si-substituted ferrocene-based monophosphine ligand (**36**).[111] It appears that the presence of electron-withdrawing groups such as F and CF_3 on the *P*-phenyl ring of the ligand has a very positive effect on the ee's. For example, when Ar of the ligand is an electron-donating group such as cyclohexyl, the enantiomeric

Table 9. Zhang's [3 + 2] Cycloaddition Using the Zhang−Hou Ligand, 28a



substrate **a-m**

endo- product **a-m**

Zhang-Hou pocket ligand

entry	substrate	R	time (h)	yield (%)	ee (%)	entry	substrate	R	time (h)	yield (%)	ee (%)
1	**a**	Ph	7	87	87	8	**h**	*o*-tolyl	7	97	90
2	**b**	*p*-tolyl	7	93	88	9	**i**	1-naphthyl	7	73	85
3	**c**	*p*-anisole	7	98	92	10	**j**	2-naphthyl	14	98	97
4	**d**	4-chlorophenyl	7	96	92	11	**k**	3-pyridyl	7	98	84
5	**e**	4-fluorophenyl	7	96	90	12	**l**	*i*-Pr	48	82	70
6	**f**	4-cyanophenyl	7	90	96	13	**m**	cyclohexyl	48	82	81
7	**g**	2-chlorophenyl	7	96	86						

excess was only 18%, while the presence an electron-withdrawing group, 3,5-$(CF_3)_2C_6H_3$, on the ligand gave 83% ee of the product. As in the case of [3 + 2] addition, highly reputed ligands such as CHIRAPHOS, DuPHOS, etc. gave very poor ee's, while BINAP did not give any conversion at all.

5. Supported Ferrocenyl Phosphine Ligands

One of the main thrusts in homogeneous catalysis today is to immobilize the catalysts on a support. The major forces behind this developing technology are to minimize the metal leaching into products, recycle the expensive ligands, and make the process more environmentally friendly. Recently, an entire issue of *Chemical Reviews* has been devoted to this topic, indicating the importance of this area.[112] Chiral ferrocenyl ligands have also been immobilized on various supports to study their reactivity as well as selectivity.

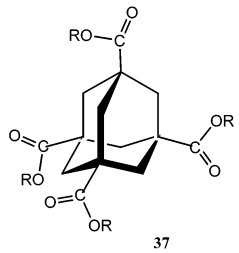
Chiral ferrocenyl phosphines, especially the Josiphos-type ligands, have been immobilized on various supports, such as dendrimers, silica, MCM-41, etc.

5.1. Dendrimeric Supported Ligands

Examples of Josiphos-based dendrimers containing adamantane and cyclophosphazene cores (**37** and **38**) have been synthesized, well characterized, and utilized in the Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate.[113] Part of the work was reviewed recently.[114] The best ligands with both adamantyl and cyclophosphazene cores gave ee's very close to that of the homogeneous system (99%). The separation of catalysts was achieved by nanofiltration through a Millipore Centricon-3 membrane. The filtered Rh-complexed catalysts retained their activity.

5.2. Silica-Supported Ligands

Pugin found that Ir complexes of xyliphos tend to lose their activity during the hydrogenation of imine



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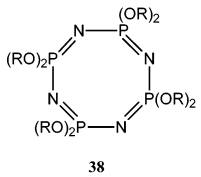
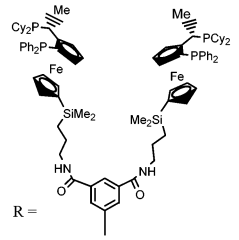


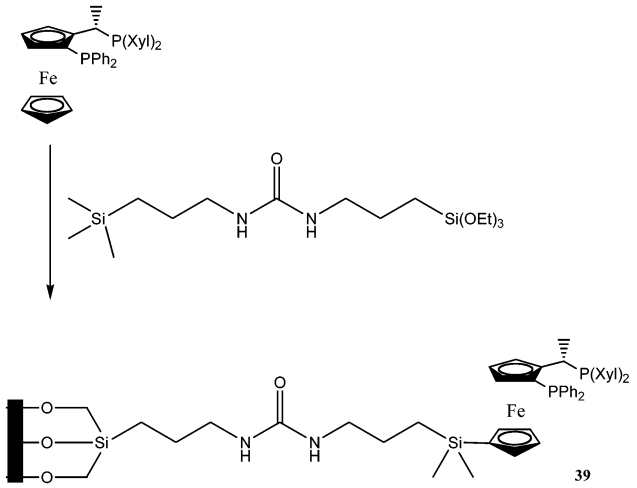
38



to form (*S*)-Metolachlor (Scheme 27), as the catalyst can form a chloride-bridged dimer.[115] To circumvent this problem, Ciba-Geigy researchers utilized the concept of site isolation and immobilization of the ligand on a silica support (Scheme 32). The supported catalyst, **39** (Scheme 33), gave selectivity (79% ee) close to that of the homogeneous system. However, the TON was only 120 000[116] for the supported catalyst, compared to 1 000 000 for the homogeneous system, and therefore **39** was not commercialized for the production of (*S*)-Metolachlor.

It has been observed by Corma et al. that the geometrical constraints have a positive effect on the performance compared to the homogeneous system.[117] Thomas et al.[118] utilized the mesoporous channel of MCM-41 to confine the substrate molecule, which has a strong influence in transferring the chirality from the catalyst to the substrate, a situation different from that in the solution phase (Scheme 33). The constrained Pd catalyst (**41**) gave 17% ee with a TON of 291 for the hydrogenation of 1,4,5,6-tetrahydronicotinate to afford nipecotic acid ethyl ester, while the homogeneous catalyst (**40**) gave only racemic prod-

Scheme 32. Silica-Supported Josiphos



ucts. Although these results are not remarkable, the concept is very novel.

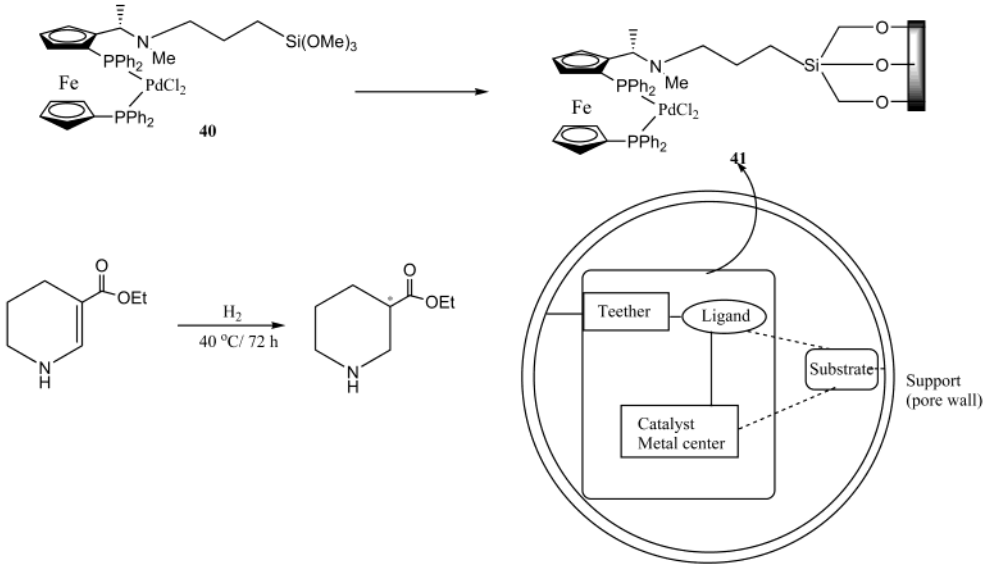
In a very similar system, Johnson et al.[119] studied the allylic amination of cinnamyl acetate. Interestingly, the catalyst immobilized in the inner walls of mesoporous MCM-41 exhibited superior selectivity, compared to the catalyst anchored on a Carbosil or even a homogeneous system. The MCM-41-supported catalyst gave over 99% conversion, with 49% straight-chain and 51% branched products. The ee of the branched product was 99%, while the Carbosil-supported catalyst gave 98% conversion, 98% straight-chain product. The ee of the 2% branched product was 43%. The homogeneous system gave 76% conversion. In this case, only the linear product was isolated.

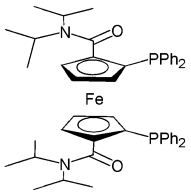
Chan's recent review article compares the activity of polymer-supported Josiphos-type ligands with that of the silica-supported ones.[114b] Both *P*-cyclohexyl- and *P*-*tert*-butyl-based Josiphos ligands were studied for the Rh-catalyzed isomerization reactions. The activities of the polymer-supported ligands were lower than those of the silica-supported ones. The silica gel-supported catalysts gave similar or better stereoselectivity compared to the corresponding homogeneous analogues.

6. Conclusion

Ferrocenyl phosphines are very practical ligands for asymmetric catalysis. The industrial success of Josiphos ligands could be one of the reasons for this area to develop very rapidly. Industries such as Solvias, Chirotech, Chiral Quest, Johnson Matthey, Degussa/OMG, Eastman, Novartis, Ciba-Geigy, Strem,[120] etc. have been putting a lot of effort into commercializing various ferrocenyl phosphine ligands for the asymmetric metal-catalyzed organic reactions. Only after undertaking the task of writing this review did I realize how rapidly this area is developing! For example, immediately after the submission of this manuscript, Togni published a paper on the synthesis of the first tridendate phosphine ligand containing planar phosphorus−carbon chirality.[121] Another paper of interest is Fu's discussion of a new family of planar chiral P,N ligands and their applications for the highly enantioselective hydrosilation of aryl and alkyl ketones.[122] Recently, with the acquisition of Synetix and its Chiral Technologies Group, Johnson Matthey has created Johnson Matthey Catalysts and within this the new business unit Catalysis & Chiral Technologies. According to JM's F. Hancock (Cambridge), "Chiral Technologies has been very active in the development of asymmetric catalytic processes and now has a portfolio of technologies for the synthesis of chiral molecules." As part of this it has an exclusive license to (*R*)- or (*S*)-1,1′-bis(diphenylphosphino) 2,2′-bis(*N*,*N*-diisopropylamido)ferrocene, abbreviated as JAFAPhos (**42**) from Aventis Pharma Germany. This ligand can be used very effectively for asymmetric hydrogenation, allylic alkylation, Grignard cross coupling, and aldol reactions with excellent ee's.[123] Because of the space and time constraints, it was not possible for me to include each paper published in this area. For the same reason, I did not make any mention of some of the earlier, previously reviewed work, such as hydroboration reactions, Ito's gold-catalyzed reactions, etc., although

Scheme 33. The Constrained Pd Catalyst on MCM-41





JAFA Phos (**42**)

these are synthetically useful reactions in organic chemistry. However, this review provides a concise update of all the synthetically important work up to 2002.

Since this area is growing rapidly, it would be very useful if someone could write a book dedicated to this topic within the next 2−3 years. One of the reviewers of this article mentioned that the description of planar chirality using different concepts is confusing, especially between Schlögl's nomenclature and the CIP rule. Therefore, it would be of great value if a stereochemistry expert could write a review or book chapter covering those aspects as well.

7. Acknowledgments

I am extremely thankful to Professors Togni, Zhang, Knochel (and his group), Ito, Hou, and Snieckus, Dr. Boaz, and Dr. Blaser for sending me the reprints of their work. Members of my family—Reena (wife), Manu (son), and Rebekah (daughter)—are also acknowledged for their support, as this article was written completely at home using family time.

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