

Accounts

Development of Benzylic-Substituted Ligands for Asymmetric Catalysis

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This account demonstrates our recent work in the design and synthesis of benzylic-substituted chiral ligands and their applications in metal-catalyzed asymmetric catalysis. High catalytic activity and asymmetric induction have been shown in many enantioselective transformations. The relationship of flexibility and rigidity as well as the impact of substituents at the benzylic position of ligands on the reactions has been revealed. The switch of enantioselectivity in the palladium-catalyzed Heck reaction was observed using ligands with different substituents at the benzylic position of the ligands. Based upon the benzylic-substituted framework, palladacycles were synthesized, which served as a real catalyst in the ring opening reaction of oxabicyclic alkenes with organozinc halides. Highly efficient kinetic resolution of 2-aryl-1-hydroxy-1,2-dihydronaphthalenes has also been developed via dehydration using benzylic-substituted chiral palladacycles.

1. Introduction

Remarkable advancements have been achieved in asymmetric catalytic synthesis since the late 20th century. Transition metal-catalyzed asymmetric catalysis as one of the most important fields attracts significant attention from the scientific community, as it provides chemists with novel and powerful tools for the efficient synthesis of enantiopure organic compounds.[1] One of the key factors that influence the efficiency and asymmetric induction in transition metal-catalyzed asymmetric catalysis is the structure of the chiral ligand. Thus, the design and synthesis of new chiral ligands has continuously been a challenge.

This account summarizes briefly our recent results on the design, synthesis, as well as the applications of benzylic-substituted ligands. Their unique catalytic activity and stereocontrol ability in reactions have also been demonstrated.

2. *N*,*S*- and *N*,*Se*-Planar Chiral [2.2]Paracyclophane

The study of benzylic-substituted ligands started with an occasional finding. We have been interested in the synthesis of novel chiral ligands with planar chirality and their applications in asymmetric catalysis.[2] A series of chiral ligands were prepared based on the framework of ferrocene and [2.2]paracyclophane. The later is rigid, linearly chiral, chemically stable, and undergoes racemization only at relatively high temperature.[3] For understanding the role of planar chirality of [2.2]paracyclophane in asymmetric induction, in 2000, we designed various *N*,*S*- and *N*,*Se*-ligands with both planar and central chiralities based on the [2.2]paracyclophane backbone.[4]

The *N*,*S*- and *N*,*Se*-ligands were readily accessible from the racemic 4-[2.2]paracyclophane carboxylic acid (**1**), which was converted to oxazoline **2** as a mixture of two diastereoisomers in high yield in three steps. Direct *ortho*-lithiation of oxazoline **2** followed by quenching with PhSSPh or PhSeSePh gave rise to the expected products **3a**, **3b**, **5a**, and **5b** (Scheme 1). Surprisingly, additional products, the benzylic-substituted **4** and **6**, were also afforded. The structure of **4**, determined by ^{1}H NMR spectroscopy and confirmed by X-ray crystallography, is unique in the planar chiral cyclophane family. The planar chirality of these ligands was readily determined by comparison with that of products derived from optically pure **1a** and **1b** as starting materials.[5] The absolute configuration of C-2 in ligand **4** was assigned as (*R*) based on the (*S*)-configuration of C-19 in the oxazoline moiety. We proposed that the benzylic-substituted cyclophanes **4** and **6** were produced owing to the nonplanarity of benzene rings in cyclophane and the steric effect of the *iso*-propyl group of the oxazoline.

Palladium-catalyzed asymmetric allylic alkylation[6] showed that all ligands **3**–**6** catalyzed the reaction to provide the substitution product **8** in almost quantitative yields. However, the benzylic-substituted ligand **4** provided far better enantioselectivity, and the reactivity of ligand **4** was also much higher than that of **3a** and **3b**. In case of *N*,*Se*-ligands **5a**, **5b**, and **6**, the same phenomena were observed (Scheme 2).

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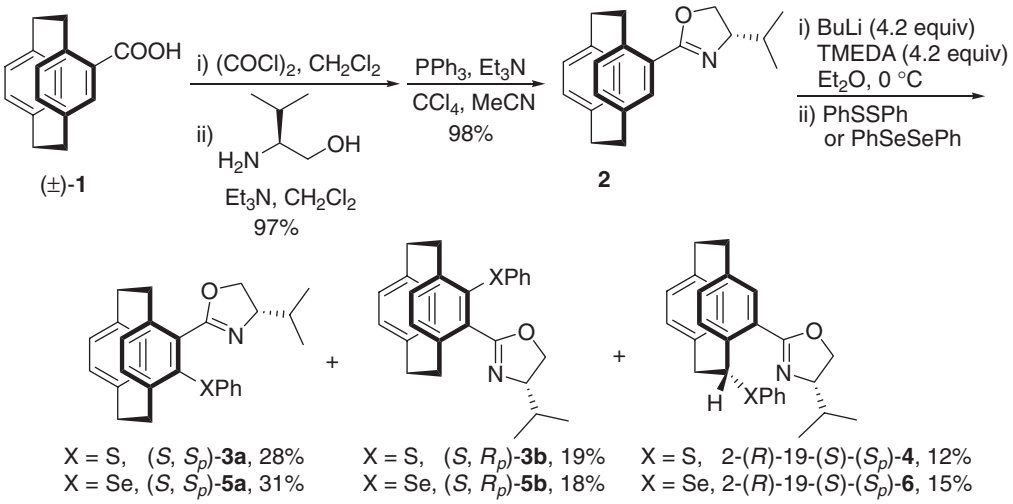
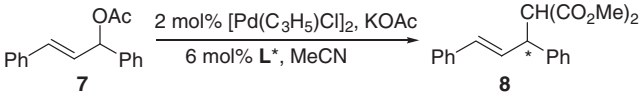


Scheme 1. Synthesis of *N*,*S*- and *N*,*Se*-planar chiral [2.2]paracyclophane.



L*	time	yield	ee	L*	time	yield	ee
3a:	32 h,	98%,	54% (*R*)	**5a**:	20 h,	98%,	57% (*R*)
3b:	21.5 h,	98%,	63% (*S*)	**5b**:	30 h,	98%,	73% (*S*)
4:	1.5 h,	98%,	94% (*S*)	**6**:	2 h,	98%,	93% (*S*)

Scheme 2. The effect of different planar chiral *N*,*S*- and *N*,*Se*-ligands on the enantioselective palladium-catalyzed allylic substitution reaction.

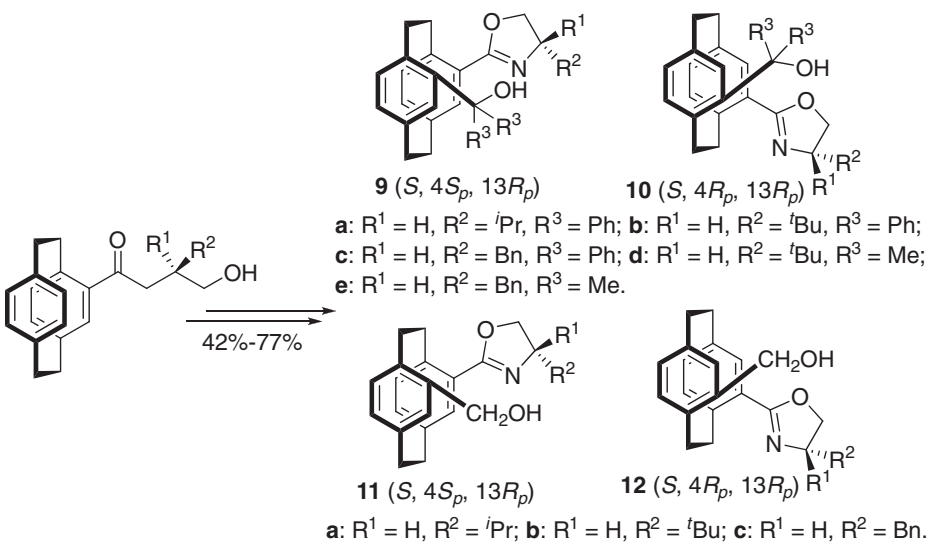
These results clearly showed that the ligand with the two coordinating atoms at benzylic and benzene ring-positions is more effective than that with both the coordinating atoms at benzene ring-positions. This is presumably due to the increased tether length between the donor atoms which coordinate palladium in ligands **4** and **6**, bringing the asymmetric environment closer to the allyl species during the reaction.

3. *N*,*O*-Planar Chiral [2.2]Paracyclophane

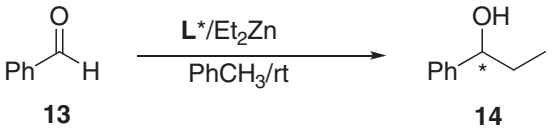
The salient features of the benzylic-substituted ligands **4** and **6** prompted us to study other [2.2]paracyclophanes with coordinating atoms at benzylic positions. Thus we designed and synthesized several chiral *N*,*O*-[2.2]paracyclophane ligands **9**–**12** through simple transformations (Scheme 3).[7]

With these new ligands in hand, the addition reaction of diethylzinc to benzaldehyde was used to examine their efficacy (Scheme 4).[8] Using ligands **11a**–**11c** the reaction gave enantioselectivity equal to or greater than that employing ligands **9a**–**9c** having a hydroxydiphenylmethyl moiety. Notably, ligands **9d** and **9e** with a 1-hydroxy-1-methylethyl group not only showed higher reactivity but also provided better enantioselectivity (97.9% and 98.4% ee, respectively) than ligands **9a**–**9c** and **11a**–**11c**.

These results reflect the influence of the rigidity and flexibility of ligands on the enantioselectivity of the reaction. Many examples have shown the effects of the rigidity and flexibility of ligands on enantioselectivity,[9] however most of



Scheme 3. Synthesis of *N*,*O*-planar chiral [2.2]paracyclophane.

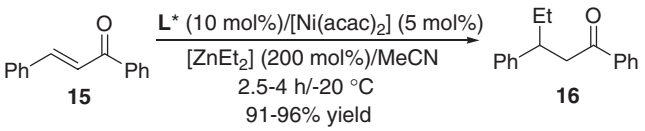


13 **14**

L*	time	yield	ee
9a	9 h	96%	93%
11a	5 h	94%	91%
10a	24 h	35%	5%
12a	24 h	49%	25%
9c	7 h	93%	93%
11c	5 h	94%	91%
10c	24 h	12%	7%
12c	24 h	51%	45%

L*	time	yield	ee
9b	24 h	37%	32%
11b	7 h	93%	94%
10b	24 h	13%	7%
12b	24 h	46%	36%
9d	3.5 h	93%	97.9%
9e	1.5 h	95%	98.4%
10e	48 h	6%	--

Scheme 4. Enantioselective addition of diethylzinc to benzaldehyde with planar chiral *N*,*O*-ligands.



15 **16**

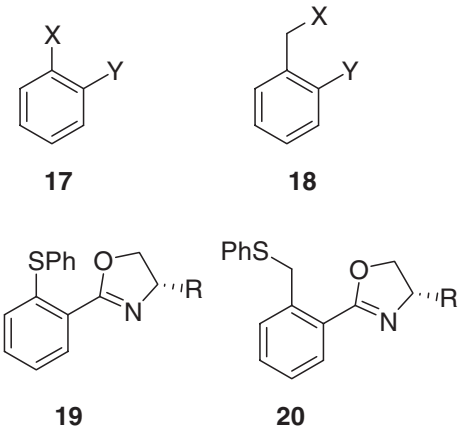
L*	ee	L*	ee
9a-c	0% ee	**11b**	63% ee
9e	8% ee	**12b**	0% ee
11a	52% ee	**11c**	53% ee
12a	0% ee	**12c**	4% ee

Scheme 5. Enantioselective 1,4-addition of diethylzinc to chalcone with planar chiral *N*,*O*-ligands.

them revealed that the enantioselectivity increases with an increase in the rigidity of the ligands.[9b–9d] In particular, the introduction of a hydroxydiphenylmethyl group, known as a magic group, into a chiral ligand usually leads to an increase of enantioselectivity in various reactions.[10] Only a few reports have noted that the introduction of flexibility provided excellent enantioselectivity in the reaction.[11] Interestingly, in our case the less sterically demanding 1-hydroxy-1-methylethyl group gave better results than the more bulky hydroxydiphenylmethyl group. It may reflect that the backbone of cyclophane is rigid, the introduction of a more sterically demanding hydroxydiphenylmethyl group into the rigid [2.2]paracyclophane backbone should make the ligand even more rigid, while the 1-hydroxy-1-methylethyl group makes the ligand flexible, which enables it to assume a more favorable conformation in the reaction.

Ni-catalyzed asymmetric 1,4-addition of diethylzinc reagent to chalcone provided a further example (Scheme 5).[12] With ligands **9a**–**9c**, the reaction provided the corresponding addition product in good yield but zero enantioselectivity, while ligand **9e**, which showed excellent enantioselectivity in the addition of diethylzinc to benzaldehyde, gave an enantiomeric excess of only 8%. However, ligands **11** with an even less sterically demanding hydroxymethyl group provide far better results.

If we consider the above results along with those obtained previously in the *N*,*S*/*Se*-ligand system (Scheme 2), we can see that an increase in the flexibility of the rigid [2.2]paracyclophane framework leads to a remarkable increase in enantioselectivity. This regulation of the flexibility of [2.2]paracyclophane ligands is very crucial for obtaining excellent results. This valuable information led us to design some other new chiral ligands based on another structural scaffold.



17 **18**

19 **20**

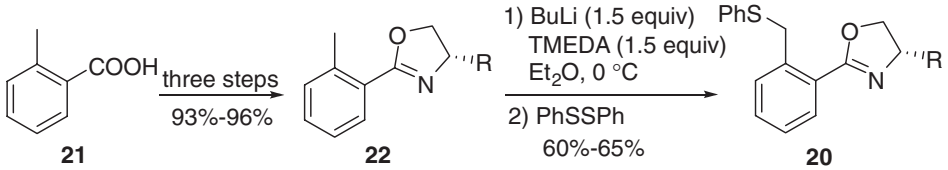
Scheme 6.

4. Benzylic Oxazoline *N*,*S*-Ligands

Based upon the above information, the structure **18** emerged by simplifying the structure of cyclophane ligands **4** and **6**. The ligands with substituted pattern **17**[13] are well known but little attention has been paid to ligands substituted as **18**,[14] though they seem simple (Scheme 6). Thus, ligand **20** was designed and synthesized (Scheme 7).[15] Williams reported Pd-catalyzed asymmetric allylic substitution using benzene-substituted ligands **19**.[16] Under this condition, our ligands were tested (Scheme 8). The enantioselectivity using ligands **20** was similar to that Williams obtained,[16] but the reactions proceeded much faster. When the amount of ligand decreased from 10 to 1 mol %, the ee value changed a little. These results showed better catalytic activity for benzylic-substituted ligands again.

5. Benzylic Oxazoline *N*,*P*-Ligands

5.1 Benzylic Substituents of Ligands in Asymmetric Heck Reaction: Switch of Enantioselectivity. The intriguing phenomena from the reaction using benzylic-substituted ligand

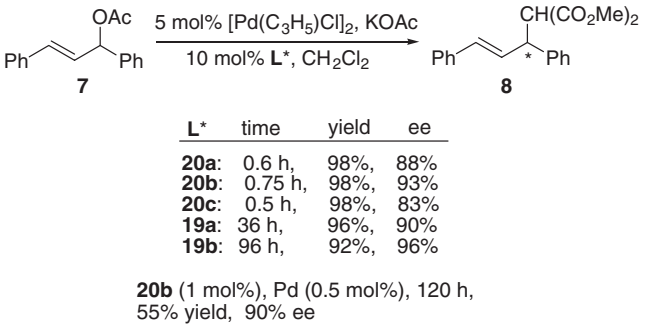


21 **22** **20**

a. R = ^{i}Pr; **b**. R = ^{t}Bu; **c**. R = Bn

Scheme 7. Synthesis of benzylic oxazoline *N*,*S*-ligands **20**.

20 stimulated us to investigate this kind of ligand further. Ligand **27** was chosen as our target since the corresponding ligand, chiral phosphinooxazoline (PHOX),[13a,17] is a good reference to test the behaviors of our ligand in asymmetric catalysis.

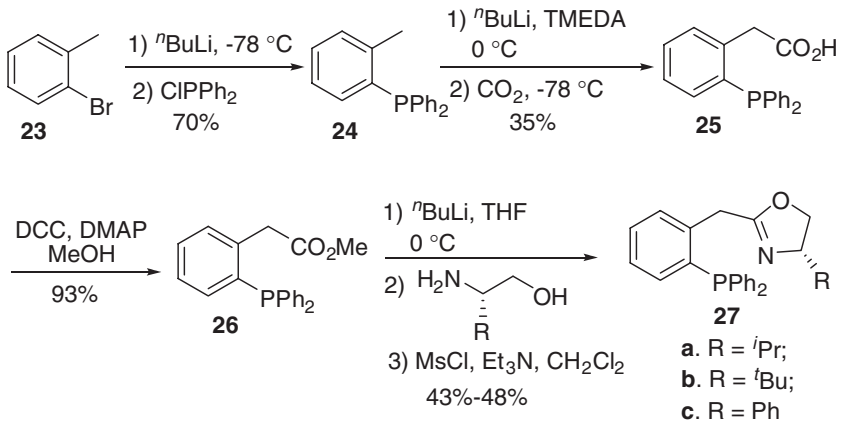


Scheme 8. Asymmetric Pd-catalyzed allylic substitution reaction.

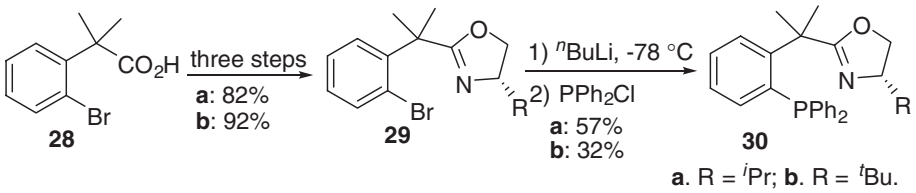
The synthetic route to ligands **27** with an oxazoline ring as the substituent at the benzylic position is depicted in Scheme 9.[18] Lithiation of *o*-bromotoluene (**23**) followed by quenching with Ph_2PCl afforded phosphine **24**. Acid **25** was prepared by direct benzylic-lithiation of phosphine **24** and then quenching with CO_2. Esterification of acid **25** followed by treatment with amino alcohol salts and ring-closure gave rise to ligands **27a**–**27c**.

In order to understand the influence of substituents at the benzylic position of ligand, ligand **30** with two methyl groups at the benzylic position were also prepared. The synthesis of ligand **30** is outlined in Scheme 10. Acid **28** was transformed to oxazolines **29** in three steps. Lithiation of **29** followed by quenching with PPh_2Cl resulted in ligands **30**.

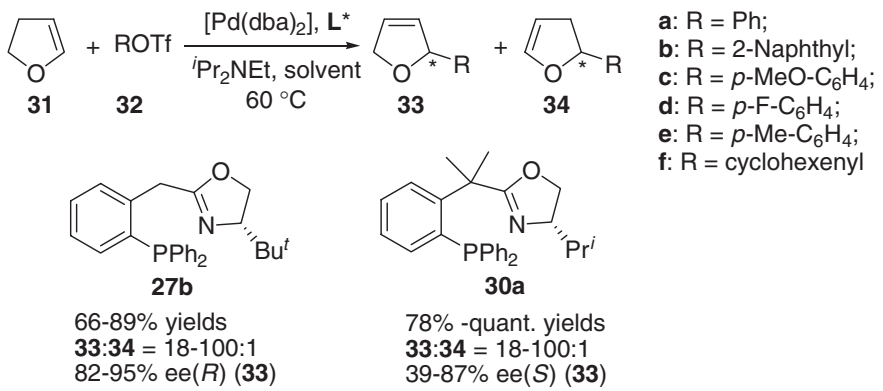
The ligands **27** and **30** were applied to the Pd-catalyzed asymmetric intermolecular Heck reaction of 2,3-dihydrofuran (**31**) with aryl triflates **32a**–**32e** and cyclohexenyl triflate (**32f**) (Scheme 11).[19] All the reactions completed in 20 h, providing 2-substituted-2,5-dihydrofuran **33** predominantly, while 4–5



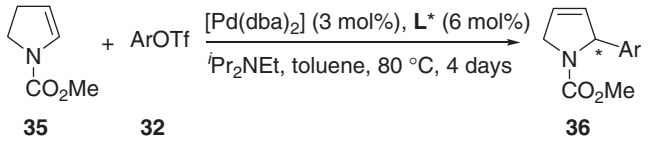
Scheme 9. Synthesis of benzylic oxazoline *N*,*P*-ligands **27**.



Scheme 10. Synthesis of benzylic oxazoline *N*,*P*-ligands **30**.



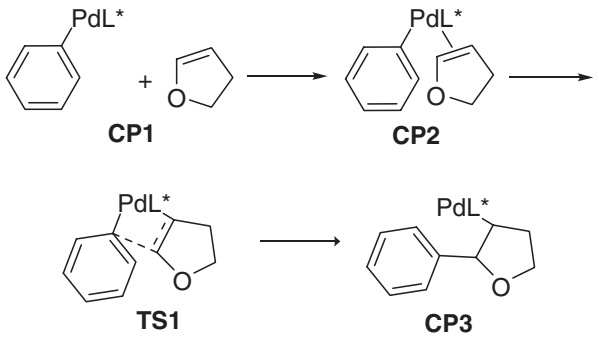
Scheme 11. Pd-catalyzed asymmetric Heck reaction using ligands **27b** and **30a**.



L* = 27b: { **36c**: Ar = *p*-MeO-C_6H_4, Yield = 46%, ee = 70% (*R*)
36d: Ar = *p*-F-C_6H_4; Yield = 48%, ee = 60% (*R*)

L* = 30a: { **36c**: Ar = *p*-MeO-C_6H_4, Yield = 63%, ee = 89% (*S*)
36d: Ar = *p*-F-C_6H_4; Yield = 83%, ee = 87% (*S*)

Scheme 12. Pd-catalyzed asymmetric Heck reaction of methyl 2,3-dihydropyrrole-1-carboxylate (**35**) using ligands **27b** and **30a**.



Scheme 13. Asymmetric insertion step of the Heck reaction.

days were needed for completion employing PHOX as the ligands.[17] When the catalyst loading was 0.5 mol %, the ee was maintained at 93%, which was the same as that using 3 mol % of catalyst although the yield was slightly lower (54%). These results demonstrated the high catalytic activity of the ligands **27** and **30** in the intermolecular Heck reaction.

To our surprise a dramatic switch of the configuration of the product **33** was observed by using these ligands with different substituents at the benzylic position. The reaction provided products in (*R*)-configuration when ligands **27a**–**27c** with H at the benzylic position were used, while (*S*)-**33** was afforded utilizing ligands **30a** and **30b** with methyl substituents at the benzylic position, though the chiral center in ligands **27** and **30** has the same configuration. These results reveal that the substituent at the benzylic position of the ligand has a significant impact on the stereochemistry of the reactions.[20]

In order to verify further the reversal of the enantioselectivity using these ligands, Heck reactions of methyl 2,3-dihydropyrrole-1-carboxylate (**35**) with some aryl triflates were carried out (Scheme 12).[19a,21] Still, ligand **27b** yielded products **36** as (*R*)-enantiomers while ligand **30a** led to (*S*)-enantiomers.

To reveal the effect of the methyl groups at the benzylic position of the ligand and rationalize the reversal of the enantioselectivity, density functional theory (DFT)[22] study was carried out to model the Heck reaction (Scheme 13 and Figure 1) and concluded that:

(1) The coordination of complexes **27a**–Pd and **30a**–Pd with 2,3-dihydrofuran **11** can be either *cis* or *trans* with respect to ligand oxazoline *N*. The calculations indicate that for intermediate complex **CP2**, the *cis*-mode is more stable than the *trans*-mode, but the *trans*-mode of the transition states (**TS1**)

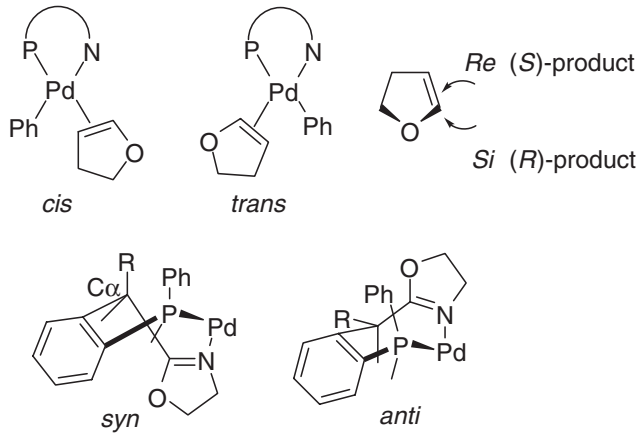


Figure 1. The modes in the asymmetric phenyl insertion reaction.

is much more stable than the *cis*-mode with both ligands **27a** and **30a**.

(2) The seven-membered ring formed by the ligands **27a** and **30a** coordinating with Pd can be in either the *syn*- or *anti*-conformation according to the orientation of the benzylic substituent and the phenyl group on phosphorus. Calculations indicate that the *syn*-conformation is more stable than the *anti* (by 1–2 kcal mol^{-1}) both in the **CP2** and in the **TS1** with ligand **27a**. On the other hand, ligand **30a** with two methyl groups at the benzylic position favors forming the *anti*-conformation of **CP2** and **TS1** (by 1–2 kcal mol^{-1}).

(3) The addition of a phenyl group can be on either the *Re* or *Si* face of dihydrofuran. Overall, eight transition states are possible. Calculations indicate no matter whether the ligand is **27a** or **30a**, the *trans–syn–Si* transition state is more stable than the *trans–syn–Re* transition state by 0.7–0.9 kcal mol^{-1}. On the other hand, the *trans–anti–Si* transition state is less stable than the *trans–anti–Re* transition state by 0.7–1.0 kcal mol^{-1}. Since *trans–syn* is more stable than *trans–anti* for ligand **27a**, the (*R*)-product is predicted to be the major product when the ligand is **27a**. In contrast, *trans–anti* is more stable than *trans–syn* for ligand **30a**, and the (*S*)-product is predicted to be the major product when the ligand is **30a**. These predictions are in qualitative agreement with experimental observations.

The X-ray analysis of $PdCl_2$–**27a** and $PdCl_2$–**30a** complexes indicates that $PdCl_2$–**27a** is in a *syn*-conformation and $PdCl_2$–**30a** is in an *anti*-conformation, which provides further experimental support for the rational of our observations (Figure 2).

5.2 Chiral Benzylic-Substituted *P,N*-Ligands in Enantioselective Ir-Catalyzed Hydrogenation. To explore the utility of benzylic-substituted *P,N*-ligands **27** and **30** in asymmetric synthesis further, asymmetric hydrogenation was investigated using these ligands.[23]

The asymmetric hydrogenation of unfunctionalized olefins had been the challenge for a long time and a breakthrough appeared when Pfaltz used Ir-catalyst incorporating the well-known PHOX ligands.[24] Since then, many *P,N*-ligands have been used in the Ir-catalyzed asymmetric hydrogenation of this type of olefin, some of which provided products in high enantioselectivity. Thus, the asymmetric hydrogenation of olefin **37a** was chosen to test the effectiveness of the ligands.

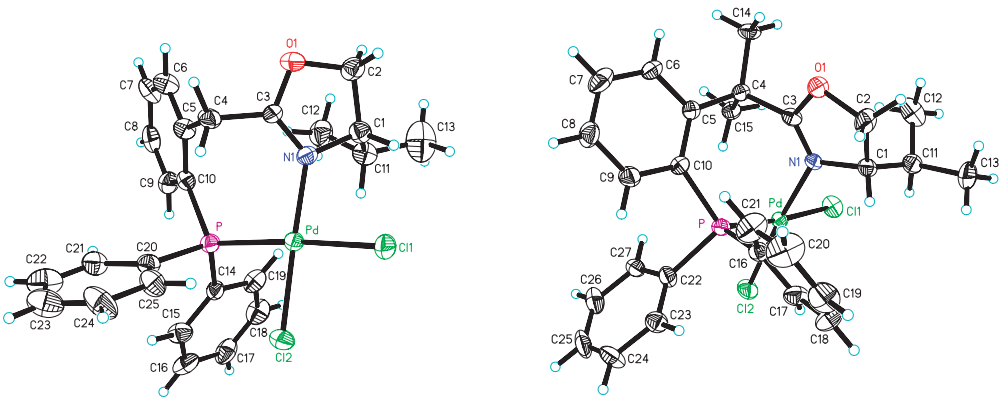
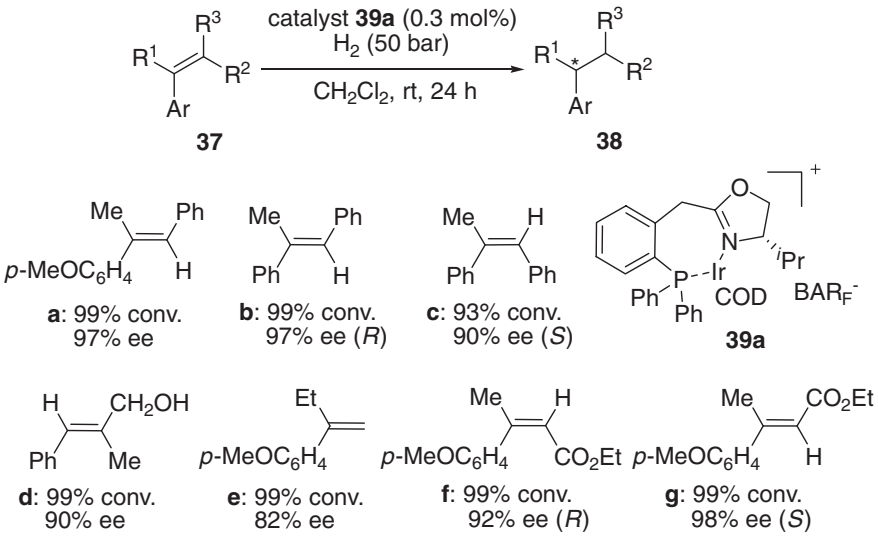


Figure 2. ORTEP drawings of X-ray crystal structures of $PdCl_2$–**27a** and $PdCl_2$–**30a** complexes.



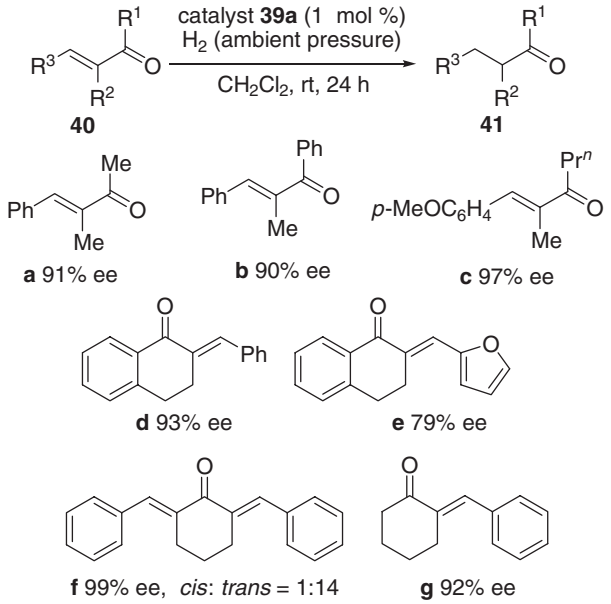
Scheme 14. Ir-catalyzed asymmetric hydrogenation of olefins.

It showed that product **38a** in 97% ee with 100% conversion was obtained using catalyst **39a** while 70% ee was observed when ^{i}Pr–PHOX was the ligand (Scheme 14).

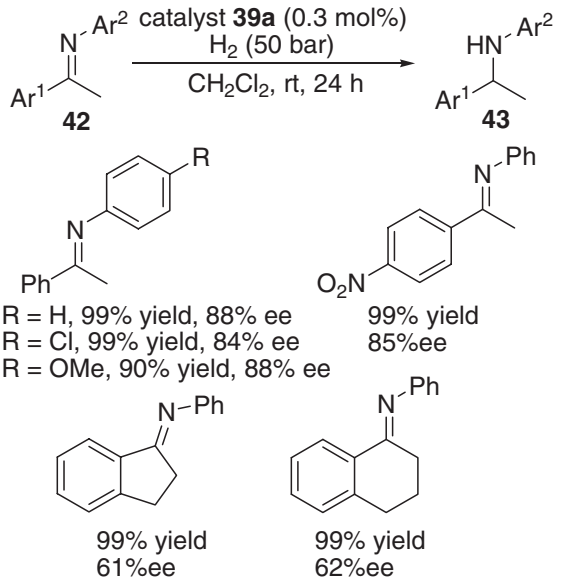
A variety of substrates, including trisubstituted olefins and terminal disubstituted olefins, regardless of whether the substitute on the aromatic ring was electron-withdrawing or -donating, were suitable substrates in this asymmetric hydrogenation using **39a** as catalyst, providing the corresponding products in excellent enantioselectivities with full conversion (Scheme 14).[23] High enantioselectivities were also realized when β-disubstituted α,β-unsaturated esters were the substrate. It is worth noting that both (*E*)- and (*Z*)-olefins, such as **37b** and **37c**, **37f**, and **37g**, were smoothly hydrogenated using catalyst with benzylic-substituted ligand to produce products in similar enantioselectivities with opposite configuration, while many reports showed that olefins in (*Z*)-configuration did not provide good ee values using catalysts with other *P*,*N*-ligands.[25]

Preparation of ketones with an α-chiral center is important as they are very useful compounds in organic synthesis.[26] However, few procedures have achieved high enantioselectivity in the synthesis of α-substituted ketones, since the products suffer from racemization of the chiral carbon via enolization. Great challenges remain for the synthesis of ketones with an α-chiral center. It seems that they could be obtained by asymmetric hydrogenation of corresponding α-substituted α,β-unsaturated ketones. To our surprise, few examples were found in the literature to establish a chiral center at the α-position of a carbonyl group via α,β-unsaturated ketones using hydrogenation,[27] though the asymmetric hydrogenation of α,β-unsaturated ketones has well been investigated, allyl alcohols being the products in general.

It is interesting that when α,β-unsaturated ketones were the substrates in hydrogenation in the presence of Ir-complexes derived from benzylic ligands, high enantioselectivities were realized (Scheme 15). Reaction of both acyclic ketones and cyclic ketones provided chiral ketones in excellent ee, being 79–99% using catalyst **39a**. The α,α'-dibenzylidene ketone **40f** was also smoothly hydrogenated to provide corresponding ketone in high diastereo- and enantioselectivities, being >99% ee with a ratio of 1:14 using catalyst **39a** and the configuration of the major product was *trans*. It is worth noting that even higher enantioselectivity was achieved when we used ^{t}Bu–PHOX as the ligand.[28] At almost the same time, Bolm reported the similar results.[29]



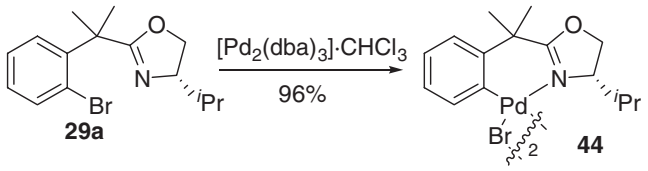
Scheme 15. Ir-catalyzed asymmetric hydrogenation of α,β-unsaturated ketones.



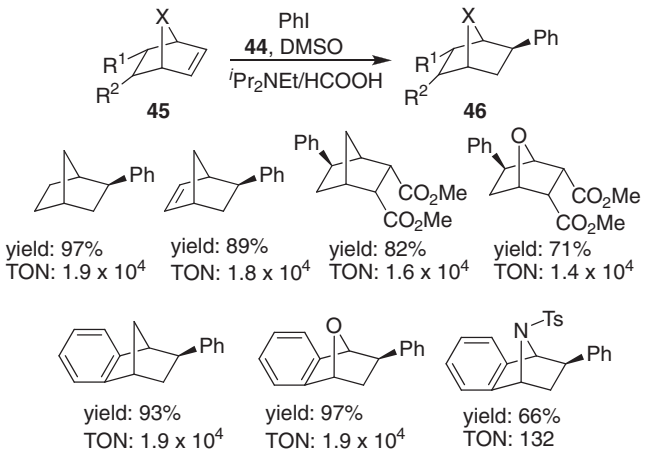
Scheme 16. Ir-catalyzed asymmetric hydrogenation of imines.

The effectiveness of benzylic-substituted ligand derived Ir-catalyst **39a** was also revealed in the hydrogenation of imines (Scheme 16). As low as 0.3 mol % of catalyst is enough in the hydrogenation of *N*-(1-arylethylidene)arylamines **42**, affording the chiral amines in $\geq$75% ee. Imines derived from 1-indanone and 1-tetralone were hydrogenated with full conversion to provide the products in 61% ee and 62% ee, respectively.[23]

As a seven-membered ring is produced when benzylic-substituted ligand formed a complex with Ir metal, it should be more flexible than the six-membered ring formed from many other *P*,*N*-ligands so that it has more chance to fit the demands of different substrates. The X-ray analysis of catalyst **39f** also showed that it has a little bit larger P–Ir–N bite angle. These results provide the support for the above hypothesis to some extent.[23]



Scheme 17. Synthesis of palladacycle **44**.



Scheme 18. Catalytic hydrophenylation of different bicyclic alkenes with palladacycle **44**.

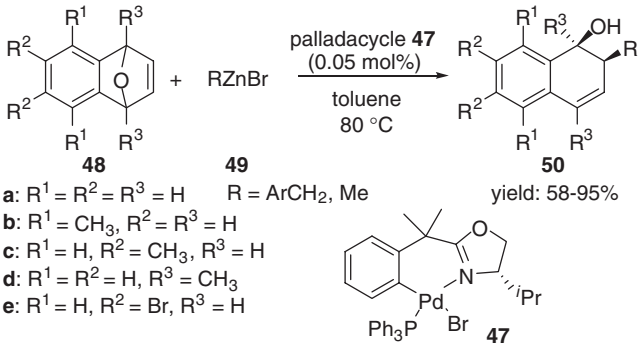
6. Benzylic-Substituted Palladacycles

Palladacycles are a class of metal complexes with versatile backbones and air and moisture stability.[30] They are easily prepared and have showed high catalytic activity in many carbon–carbon bond forming reactions. High catalytic activity has also been demonstrated by palladacycles derived from benzylic-substituted frameworks.

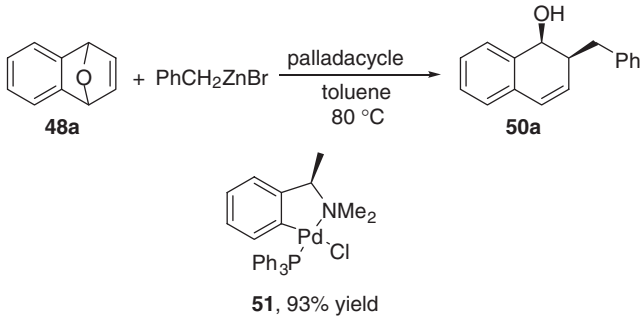
The synthesis is simple. Palladacycle **44** was afforded in high yield as a yellow powder after the reaction of benzylic-substituted oxazoline **29a** with $[Pd_2(dba)_3]\cdot CHCl_3$ (Scheme 17), which is air-stable and has a dimeric structure with a distorted square-planar geometry as showed from the X-ray diffraction analysis.[31]

Hydroarylation, similar to the Heck reaction, is a useful methodology employed successfully in the synthesis of natural product analog epibatidine alkaloids.[32] Benzylic-substituted palladacycle **44** showed excellent catalytic activity in this hydrophenylation reaction when 2.5×10^{-3} mol % of palladacycle **44** was used as catalyst under aerobic condition without exclusion of water. Different kinds of bicyclic alkenes, including norbornene, norbornadiene, and oxabicyclic alkenes, reacted with PhI to provide corresponding products in high yields, TON being $1.6–1.9 \times 10^4$. Aza-bicyclic alkene was also suitable substrate, in this case, 0.25 mol % of catalyst should be used because of its low reactivity (Scheme 18).

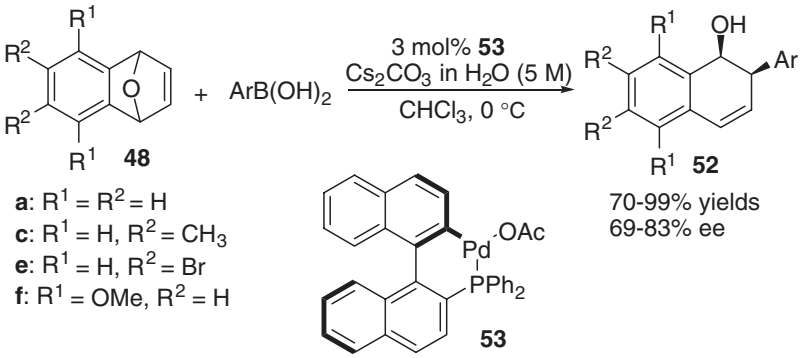
Although palladacycles have shown many advantages in catalysis, they usually serve as catalyst precursor[33] and are mainly used in Heck-type reactions and coupling reactions.[30]



Scheme 19. Palladacycle **47** catalyzed ring-opening reaction of oxabicyclic alkenes **48** with alkylzinc reagents **49**.



Scheme 20. Palladacycle **51** catalyzed ring-opening reaction of oxabicyclic alkene **48a** with benzyl zinc bromide.



Scheme 21. Palladacycle-catalyzed asymmetric ring-opening reaction of oxabicyclic alkenes with arylboronic acids.

Racemic products are very often obtained in spite of chiral palladacycles being used.[31,34,35] Asymmetric induction has been realized in some examples, however chiral palladacycles serve as Lewis acid in most cases.[36] To explore the applications of palladacycles as real transition metal catalysts in asymmetric catalysis, some other reactions using benzylic-substituted palladacycles as catalyst were investigated.

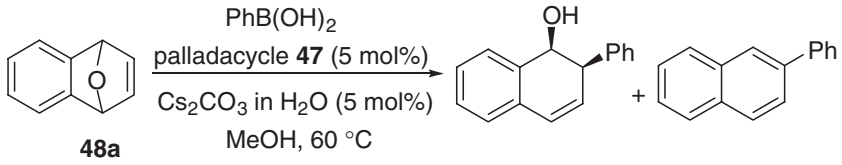
The ring-opening reaction of oxabicyclic compounds is a useful methodology in the synthesis of cyclic compounds with multiple stereocenters.[37] Many metal complexes have been used as catalyst in the regio- and enantioselective nucleophilic ring-opening reaction of oxabicyclic alkenes. However, no report using palladacycle as catalyst appeared for this reaction. When we employed palladacycle monomer **47** as catalyst in the reaction of 7-oxabenzonorbornadiene (**48a**) with benzyl zinc bromide **49a**, ring-opening product **50a** in 95% yield was delivered, while only 10% of **50a** was afforded accompanied by the formation of palladium black using palladacycle dimer **44**.[35]

Still, high catalytic activity of benzylic-substituted palladacycle was shown in this reaction. A variety of ring-opening products **50** have been produced by using as low as 0.05 mol % of palladacycle **47** as catalyst in the reaction of oxabicyclic alkenes **48** with different alkylzinc bromide derivatives (Scheme 19).

In most cases when the palladacycle served as a precatalyst, the reaction proceeds at temperature higher than 120 °C, at which active Pd species is released,[30] however in our case the reaction proceeded at 80 °C or lower. In addition, no visible palladium black was observed in the reaction. ^{31}P NMR study showed that the palladacycle **47** remained intact in the reaction. We also found that the reaction of **48a** with benzylzinc bromide was catalyzed by 0.5 mol % of palladacycle **51** to give 93% yield of product **50a** (Scheme 20). ^{31}P NMR investigation revealed that the structure of palladacycle **51** remained unchanged during the reaction. These experimental results implied that palladacycles **47** and **51** were a real catalyst in the reaction though the products are racemic. However, optically active ring-opening product was afforded when bicyclic alkene **48a** was treated with phenylboronic acid using palladacycle **47** as catalyst, albeit the ee was only moderate. This promising result means that the palladacycle served as real catalyst and encourages us to study further.[38]

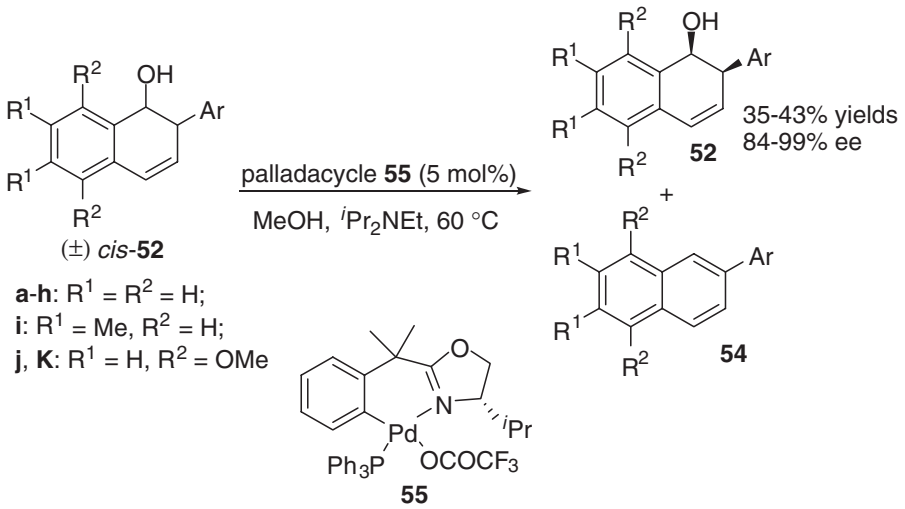
It was found that all *N*-containing palladacycles afforded ring-opening product in low yields and low ee was given using pincer complex and Overman's palladacycle, while *P*-containing palladacycle showed its highly catalytic activity, providing product **54** in high yield. Based upon the results, chiral *P*-containing palladacycle **53** was designed and synthesized from MOP.[39] High yields with high ee were obtained for products **52** when *P*-containing palladacycle **53** was the catalyst in the reaction of oxabicyclic alkenes **48** with a variety of arylboronic acids (Scheme 21).[38]

During the study of the reaction of oxabicyclic alkene **48a** with $PhB(OH)_2$ using palladacycle **47** as catalyst, we found that as reaction time was prolonged, the yield of ring-opening product **52a** decreased while the ee of the adduct **52a** increased, meanwhile the yield of the side product **54a** increased. Based upon these results, we deduced that there should be a kinetic resolution process for the compound **52a** (Scheme 22).



Time	52a	54a
40 min	23% yield, 33% ee	
1.5 h	98% yield, 33% ee	
2 h	86% yield, 41% ee	12% yield
3 h	52% yield, 84% ee	40% yield
4 h	45% yield, 97% ee	45% yield
12 h		90% yield

Scheme 22. Palladacycle **47** catalyzed asymmetric ring-opening reaction of oxabicyclic alkene **48a** with phenylboronic acid.



Scheme 23. Kinetic resolution of 1,2-*cis*-**52** catalyzed by palladacycle **55**.

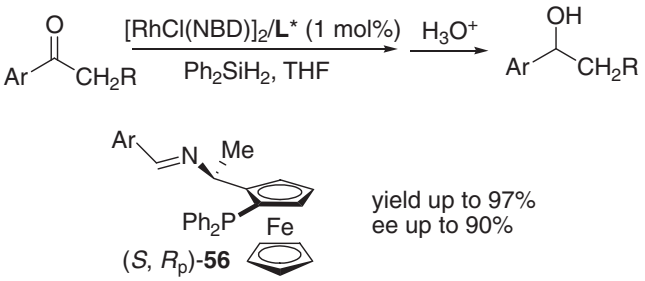
The kinetic resolution of **52a** was confirmed by treatment of racemic **52a** with Cs_2CO_3 and palladacycle **47** in MeOH, providing optically active **52a** in 19% yield and 11% ee accompanied by 67% of **54a**. Investigations on the influence of the structure of palladacycles and other parameters on the reaction led the use of palladacycle **55**, providing optically active **52** with the yields ranging from 35 to 43% and with high ee value ranging from 84 to 99% (*S* factor: 9–26) (Scheme 23).[40]

7. Other Benzylic Ligands

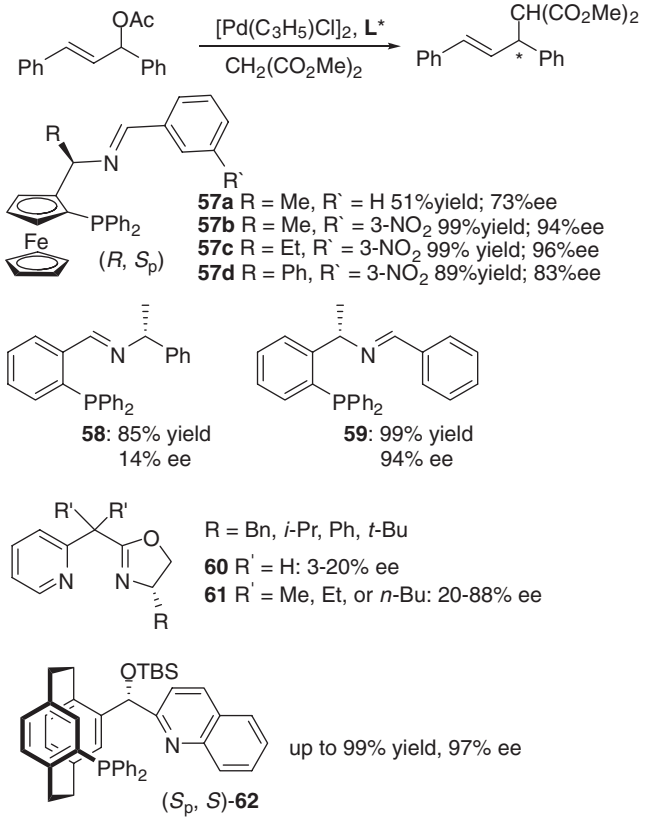
As mentioned above, the structure of chiral ligands has played a key role in asymmetric catalysis and a variety of ligands with different structures have been synthesized. Benzylic ligands were also reported by other groups such as phosphine ligand (*R*)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]-ethyldicyclohexylphosphine (Josiphos).[41a] Some of them will be discussed briefly.

Ito synthesized a series of (*S*,*S*)-2,2″-bis[(*R*)-l-(dialkylphosphino)ethyl]-1,1″-biferrocene (TRAP) benzylic-substituted ligands. *n*-BuTRAP is the first effective chiral phosphane ligand for the rhodium-catalyzed asymmetric hydrosilylation of hindered saturated ketones and simple ketones lacking secondary coordinating functional groups.[41b,41c] The authors suggested that the chiral environment created by the *trans*-spanning biferrocenyl backbone of the ligands is the critical element for stereocontrol. Chiral ferrocenylphosphines **56** containing an imino group at the side chain, were reported by the Hayashi group in 1995.[41d] The imino–phosphine ligands **56** were found to be very effective for rhodium-catalyzed asymmetric hydrosilylation of prochiral ketones with diphenylsilane to give optically active alcohols of up to 90% ee (Scheme 24).

Following this work, Zheng synthesized a series of (R, S_p)-ferrocenylphosphine–imine ligands **57** and applied them in the Pd-catalyzed AAA reaction.[42] The substituent at the benzylic position has great effect on enantioselectivity, and 96% ee was achieved when the ligand **57c** was used (Scheme 25). Later, the Zheng group developed chiral phosphine–imine ligands **59**,[43] which were found to be effective for the Pd-catalyzed AAA reaction, up to 94% ee being obtained, in contrast to 14% ee using phosphine–imine ligands **58** reported by the Hashimoto



Scheme 24. Rhodium-catalyzed asymmetric hydrosilylation of ketones.

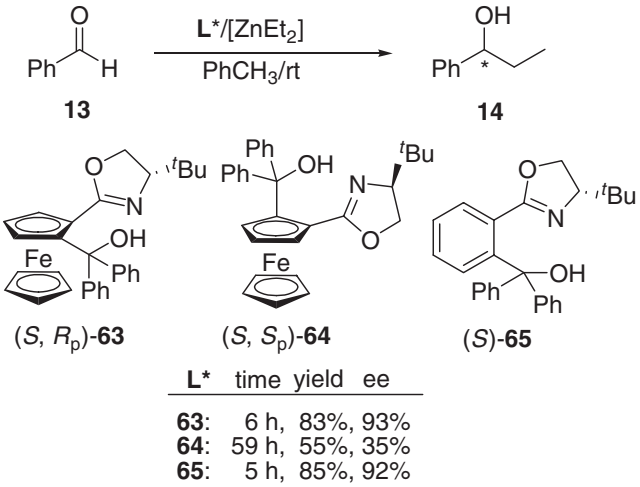


Scheme 25. Palladium-catalyzed asymmetric allylic substitution reaction.

group.[44] The authors suggested that the chirality of ligand **59** residing on the chelate ring of P–Pd–N complex is more effective for the transfer of stereochemical information, while the chirality of Hashimoto's phosphine–imine ligand **58** lay the outside of P–Pd–N chelate ring.

Chelucci reported that pyridinylmethyl-oxazolines **60**,[45] initially developed by Fryzuk,[46] could be used as ligands in the palladium-catalyzed AAA reaction, however, the enantioselectivities were rather poor. Zhou synthesized dialkylmethylene-bridged pyridinyl–oxazoline ligands **61**,[47] which provided ee values of 20–88% in the palladium-catalyzed AAA reaction, higher than that provided by unsubstituted analogs **60** (Scheme 25).

[2.2]Paracyclophane-derived *P,N*-ligand **62** was designed and synthesized by Jiang's group.[48] Their abilities of asymmetry induction in Pd-catalyzed AAA reaction were examined, and high yields and enantioselectivities (i.e., 99% yield, 97% ee) were observed (Scheme 25). The author suggested the structural flexibility brought by the long side chain and the rigidity originating from the rigid paracyclophane skeleton cooperated to provide a fixed chiral environment.



Scheme 26. Enantioselective addition of diethylzinc to benzaldehyde with ligands **63**–**65**.

The Bolm group synthesized chiral ferrocene-based hydroxyoxazolines (*S*, R_p)-**63** and (*S*, S_p)-**64** as well as benzene analog (*S*)-**65** (Scheme 26).[49] The results from the reaction of diethylzinc to benzaldehyde demonstrated the importance of planar chirality in the reaction and the catalytic activity of ligand **65**.

8. Summary

We have shown the efficiency of benzylic-substituted ligands in asymmetric catalysis. They are simple and easily accessible. Because of the increased tether length between the donor atoms, the flexibility and rigidity are adjustable, which gives them good catalytic activity and stereocontrol in many enantioselective transformations. The substituents at benzylic positions provide the ligands extra power for tuning the stereochemistry of the reaction. For the present, only a few types of ligands have been synthesized and applied in asymmetric catalysis. We believe that in the future, more new ligands with different coordination atoms will be synthesized and new applications will be found with the understandings of them.

We wish to thank all our collaborators, whose names are mentioned in relevant references, for their extraordinary contributions, without which this account would not have materialized. Financial support from the Major Basic Research Development Program (No. 2010CB833300), National natural Science Foundation of China (Nos. 20872161, 20821002, and 20932008), the External Cooperation Program of Chinese Academy of Sciences (No. GJHZ200816), Chinese Academy of Sciences, the Technology Commission of Shanghai Municipality (No. 10ZR1436800), and the Croucher Foundation of Hong Kong are acknowledged.

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