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Homogeneous palladium-catalyzed asymmetric hydrogenation

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The transition metal catalyzed asymmetric hydrogenation of unsaturated compounds arguably presents one of the most attractive methods for the synthesis of chiral compounds. Over the last few decades, Pd has gradually grown up as a new and popular metal catalyst in homogeneous asymmetric hydrogenation the same as traditional Ru, Rh and Ir catalysts. Much progress has been successfully achieved in the asymmetric reduction of imines, enamines, olefins, ketones and heteroarenes. It was also found that palladium catalyzed asymmetric hydrogenation could be used as a key step in tandem reactions to quickly synthesize chiral compounds. This tutorial review intends to offer an overview of recent progress in homogeneous palladium catalyzed asymmetric hydrogenation and should serve as an inspiration for further advances in this area.

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Key learning points

(1) The general mechanism for homogeneous palladium catalyzed asymmetric hydrogenation.
(2) The palladium catalysts' tolerance against acid, water and air in the hydrogenation process.
(3) The substrate scopes and limitations in these transformations.
(4) The common hydrogen sources used in these catalytic systems.
(5) The general solvent-dependent phenomena in these transformations.

1. Introduction

The catalytic asymmetric hydrogenation has been recognized as one of the most important methods for the synthesis of various chiral compounds which are of great synthetic importance in the preparation of pharmaceuticals, natural products, agrochemicals, and so on.[1–6] Therefore, Knowles and Noyori were awarded the Nobel Prize in Chemistry in 2001 for their pioneering work in catalytic asymmetric hydrogenation.[7,8] The success of asymmetric hydrogenation depends largely on the proper combination of a metal and a ligand. Compared with myriad chiral ligands,[2,9] the choice of the metal is limited within the periodic table especially the transition metal. Furthermore, the platinum group metals Ru, Rh and Ir were the most predominant metal catalysts in asymmetric hydrogenations for a long period (Fig. 1). Thus, the search for a new and popular metal within the periodic table hopefully stimulates further advances in this field.

Palladium, another platinum group metal, has been used as powerful catalysts in the formation of C–C, C–O, C–N bonds, *etc.* in modern synthetic chemistry (Fig. 1).[10–15] In addition, the heterogeneous palladium catalyst (such as Pd/C, Lindlar catalyst) is also well known to be one of the most effective catalysts in the hydrogenation of unsaturated double bonds. However, the homogeneous palladium-catalyzed asymmetric hydrogenation has been in silence as a ''sleeping beauty'' for a long time until 2001.[1,16] Over the last few decades, Pd has gradually grown up as a new and popular metal catalyst in homogeneous asymmetric hydrogenation the same as traditional Ru, Rh and Ir catalysts. In addition, palladium is cheaper than rhodium and iridium, so from an industrial perspective this is also highly useful.

	VIII	IX	X	
	44 Ru	45 Rh	46 **Pd**	
	76 Os	77 Ir	78 Pt	

Fig. 1 The platinum group metals.

In this tutorial review, we focus on the recent advances in homogeneous palladium catalyzed asymmetric hydrogenations over the past few years (up to July 2012). These reactions are classified by the substrate types including imines, enamines,

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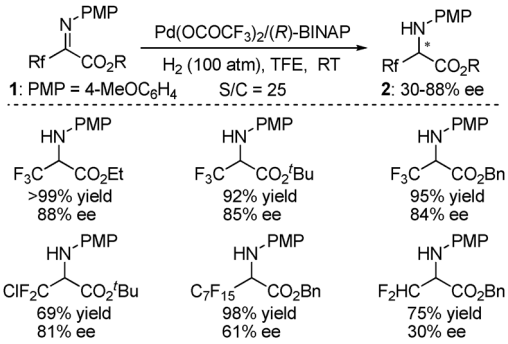
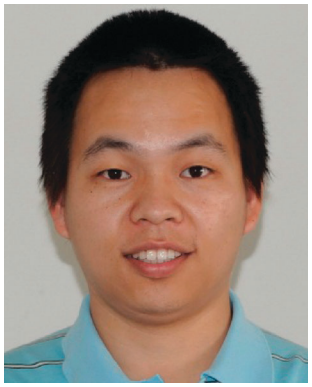
ketones, olefins and heteroarenes. The asymmetric tandem reactions using palladium catalyzed asymmetric hydrogenation as the key step will also be covered. In our opinion, these efforts have substantially broadened the scope of asymmetric hydrogenations. In addition, we would like to briefly describe a few examples on homogeneous palladium catalyzed asymmetric transfer hydrogenation employing EtOH or HCO_2H as a hydrogen source. The enantioselective hydrogenation promoted by heterogeneous palladium catalysts was not included in this review.



Scheme 1 Asymmetric hydrogenation of fluorinated iminoesters.

2. Palladium catalyzed asymmetric hydrogenation of imines

In 2001, Amii and Uneyama *et al.* reported an efficient approach for the synthesis of fluoro amino acid derivatives through Pd(II) catalyzed asymmetric hydrogenation (Scheme 1).[16] A dramatic solvent effect was observed in the asymmetric hydrogenation of α-fluorinated iminoesters. Ordinary solvents (toluene, AcOH,



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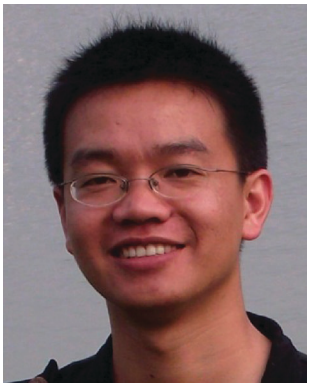
Qing-An Chen was born in Fujian Province, China, in 1984. *After receiving his BS degree from University of Science and Technology of China in* 2007, *he joined the research group of Zhou at Dalian Institute of Chemical Physics, Chinese Academy of Sciences. He is currently working on his PhD thesis and his research interests are centered on biomimetic asymmetric hydrogenation reaction as well as ligand synthesis for asymmetric reactions.*



Zhi-Shi Ye

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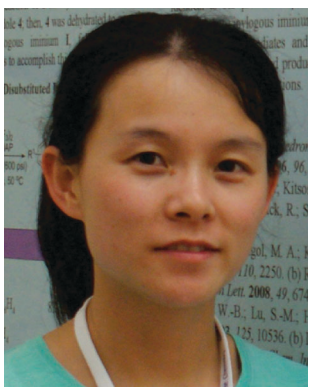


Ying Duan

Ying Duan was born in Henan province, China, in 1986. *She obtained her BS degree in* 2008 *from Shaanxi Normal University. Then she joined Dalian Institute of Chemical Physics for PhD degree under the supervision of Prof. Yong-Gui Zhou. Her working interest was mainly focused on the asymmetric hydrogenation of indoles and the mechanism of the Pd-catalyzed asymmetric hydrogenation.*

Yong-Gui Zhou

Yong-Gui Zhou was born in Hubei Province, China, in 1970. *He received BS degree from Huaibei Coal Industrial Teachers' College in* 1993 *and PhD degree from Shanghai Institute of Organic Chemistry in* 1999, *under the supervision of Prof. Li-Xin Dai and Xue-Long Hou. Then he joined Xumu Zhang's group at the Pennsylvania State University as a postdoctoral fellow. In* 2002, *he began his independent research career at the Dalian Institute of Chemical Physics, Chinese Academy of Sciences, where he is currently a professor of chemistry. His research interests include the development of catalytic asymmetric reactions, mechanistic elucidation, and asymmetric synthesis.*

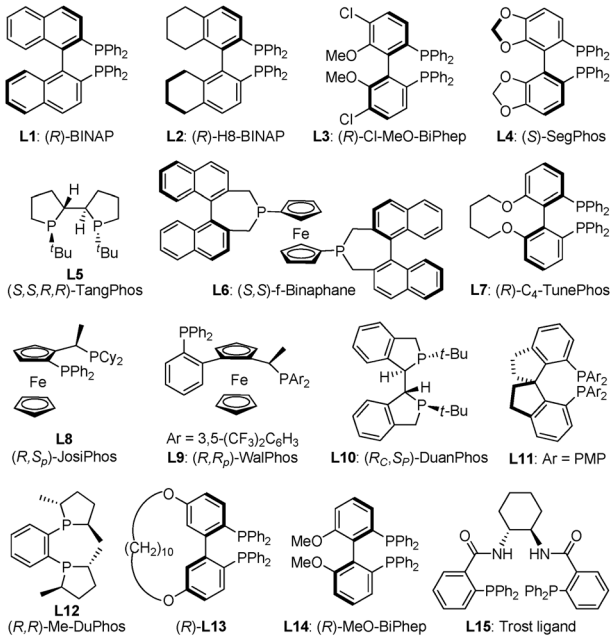


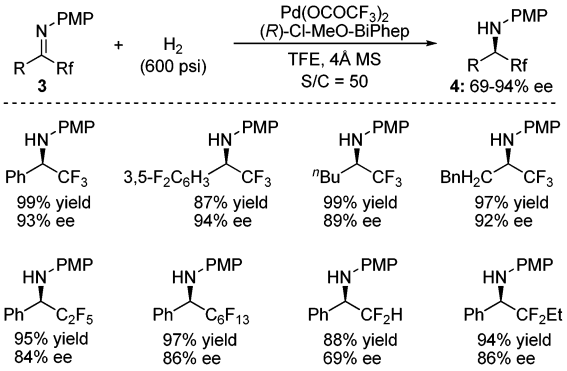
Fig. 2 Chiral phosphine ligands used in this text.

*i*PrOH, MeOH, EtOH) gave α-aminoesters with low to moderate enantioselectivities and yields. However, both the reactivities and enantioselectivities were dramatically improved by employing fluorinated alcohols such as CF_3CH_2OH (TFE), giving maximum ee of up to 88%. The main role of TFE was suggested as a stabilizer of the active palladium catalyst through weak coordination.[17] Moreover, TFE might activate α-fluorinated iminoesters by protonation or hydrogen bonding of the imino group.

Besides the solvent, the palladium complexes played a great part in the control of enantioselectivity. The combination of weakly coordinative palladium(II) trifluoroacetate and BINAP (Fig. 2) gave the best results (>99% yield, 88% ee). In contrast, poor results were observed when palladium complexes bearing coordinative groups ($PdCl_2$, $Pd_2(dba)_3$) or other chiral bisphosphine ligands (DIOP and ChiraPhos) were used.

The homogeneous protocol was applicable to the asymmetric hydrogenation of other trifluoro and chlorodifluoromethylated iminoesters **1** (Scheme 1). A drop in enantioselectivity was observed in the reduction of iminoester with a long perfluoroalkyl chain or an α-difluoro moiety. The obtained aminoesters served as general precursors of enantioenriched β-fluorinated amino acids. It was notable that the catalytic asymmetric hydrogenation of bromodifluoromethylated iminoester delivered a product in 88% ee with no hydrogenolysis of C–Br bonds.[18]

In 2010, Zhou and co-workers reported another easy access to chiral fluorinated amines through Pd-catalyzed asymmetric hydrogenation of fluorinated imines **3** (Scheme 2).[19] Different from Uneyama's work,[16] it was found that an α-ester group was not necessary to obtain high yield or enantioselectivity. Substrates with an electron donating or an electron withdrawing group on aryl substituents can be successfully hydrogenated to give the corresponding fluorinated amines with high ees. The yields could be enhanced in the presence of 4 Å molecular

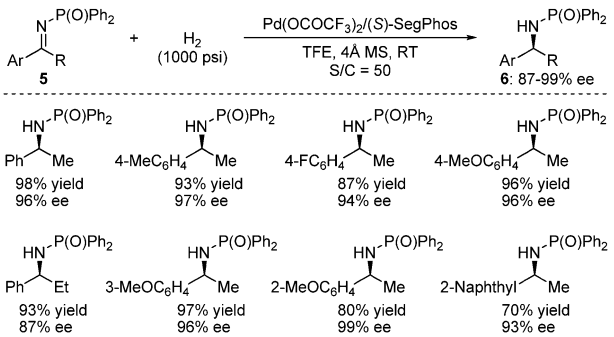


Scheme 2 Asymmetric hydrogenation of fluorinated imines.

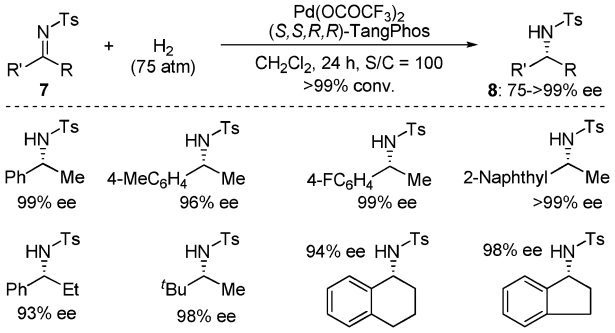
sieves which might remove traces of water to make the substrates more stable. It is noteworthy that excellent enantioselectivities were also obtained in the hydrogenation of alkyl substituted fluorinated imines. Only a slight decrease in enantioselectivity (84–86% ee) was observed in the hydrogenation of imines bearing longer perfluoroalkyl chains. This method was also applicable to the hydrogenation of more challenging difluoro substituted substrates (69–86% ee). The protecting group (PMP) on the products could be readily removed through oxidative cleavage with $Ce(NH_4)_2(NO_3)_6$ (CAN) giving chiral β-fluorinated primary amines.

By introducing the strong electron-withdrawing group on the nitrogen atom, palladium catalyzed asymmetric hydrogenation could be extended to nonfluorinated imines. In 2006, Zhou and co-workers disclosed a highly enantioselective hydrogenation of *N*-diphenylphosphinyl imines **5** using a chiral Pd complex (Scheme 3).[20] As a strong electron-withdrawing group, diphenylphosphinyl could reduce the inhibitory effect of the substrates on the palladium catalyst. On the other hand, *N*-diphenylphosphinyl imines are relatively stable and can be easily obtained from the corresponding oximes exclusively as a single *E* isomer which might lead to higher enantioselectivity. Under optimized conditions, a variety of *N*-diphenylphosphinyl imines were converted into their corresponding amines **6** with good yields and high enantioselectivities (87–99% ee).

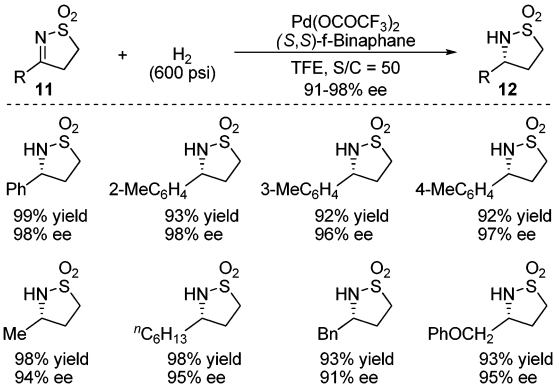
Owing to the strongly electron-withdrawing character, the tosyl group could also be used as an activated group in palladium catalyzed asymmetric hydrogenation of imines.



Scheme 3 Asymmetric hydrogenation of *N*-diphenylphosphinyl imines.



Scheme 4 Asymmetric hydrogenation of *N*-tosylimines.



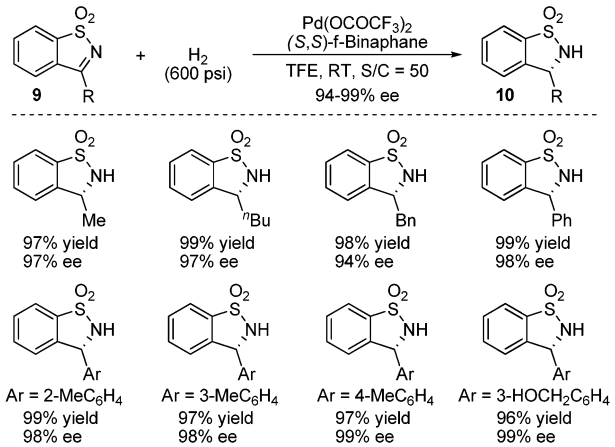
Scheme 6 Asymmetric hydrogenation of cyclic *N*-sulfonylimines.

In 2006, Zhang's group reported an efficient Pd-catalyzed asymmetric hydrogenation of *N*-tosylimines **7** (Scheme 4).[21] Using electron-donating rigid TangPhos as the ligand, the screening of metal precursors showed that Pd(II) is better than Rh(I) for the hydrogenation of *N*-tosylimines in terms of enantioselectivity. It was also found that the counterion accompanying Pd(II) played an important role in this transformation. A palladium precursor with a weakly coordinating $CF_3CO_2^-$ ion gave the best yield and ee. Notably, the reaction proceeded smoothly in CH_2Cl_2 rather than in TFE which was commonly the best choice for Pd/bisphosphine catalysts in asymmetric hydrogenation. Interestingly, when SynPhos was used as the ligand instead of TangPhos, only TFE gave high conversion and enantioselectivity while other solvents, such as CH_2Cl_2 and THF, delivered products in low conversions.[22]

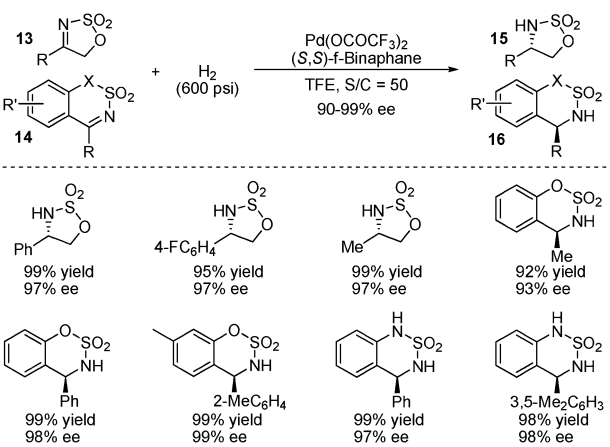
Besides the flexible acyclic imines, the hydrogenation of geometry-fixed cyclic imines **9** had also been well developed. In 2006, Zhang *et al.* documented that the Pd-TangPhos catalyst could facilitate the asymmetric hydrogenation of cyclic *N*-sulfonylimines with 94% ee.[21] Subsequently, Zhou and co-workers found that this reaction also proceeded smoothly using SegPhos as the ligand in TFE giving chiral sultam in 92% ee.[22] After further screening of the effects of ligands, (*S*,*S*)-*f*-binaphane emerged as the best ligand for this transformation with respect to enantioselectivities (94–99%, Scheme 5).[23] Employing the palladium catalyzed asymmetric hydrogenation as the key step, a chiral sultam with anti-HIV activity can be conveniently synthesized from the methylation of the hydrogenated product **10**.[23]

Using $Pd(OCOCF_3)_2$–(*S*,*S*)-*f*-binaphane catalytic systems, a series of non-benzofused cyclic *N*-sulfonylimines **11** were hydrogenated to afford their corresponding sulfonamides in excellent isolated yields and enantioselectivities (Scheme 6).[22,23] Gram-scale chiral sulfonamides could be obtained from this transformation at S/C 100 without the loss of enantioselectivity. Noteworthily, enantiopure homoallylic amine derivatives could be obtained from a simple derivation of sulfonamides with no loss of optical purity.[23]

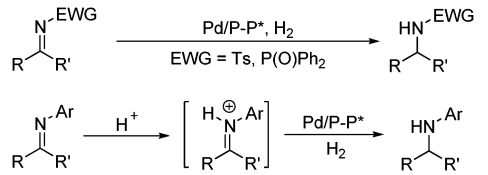
In addition to acyclic and cyclic sulfonamides, Zhou *et al.* found that palladium catalyzed asymmetric hydrogenation also delivered chiral cyclic sulfamidates **14** in excellent yields and enantioselectivities (Scheme 7).[24] It was notable that the asymmetric hydrogenation could be operated in air with the same reactivity and enantioselectivity. (**Caution**: mixtures of air and hydrogen are highly explosive. Do not admit hydrogen gas to an autoclave containing air, but rather first flush with nitrogen before admitting hydrogen gas.) This method worked well in the asymmetric hydrogenation of assorted six-membered benzo-fused imines **14**. The nucleophilic ring opening of these cyclic sulfamidates gave chiral α- and β-amino alcohols which served



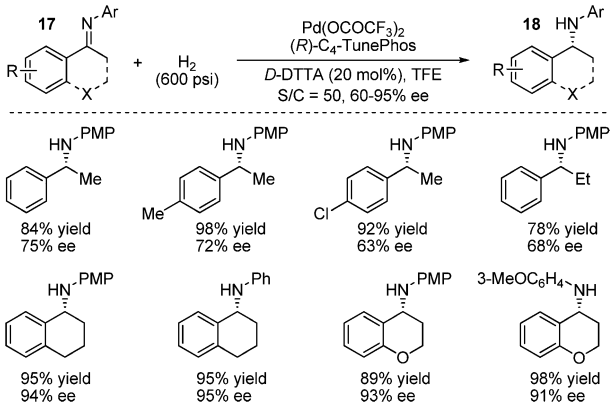
Scheme 5 Asymmetric hydrogenation of cyclic *N*-sulfonylimines.



Scheme 7 Asymmetric hydrogenation of cyclic *N*-sulfonylimines.



Scheme 8 The strategy for the activation of imines.



Scheme 9 Asymmetric hydrogenation of simple ketimines.

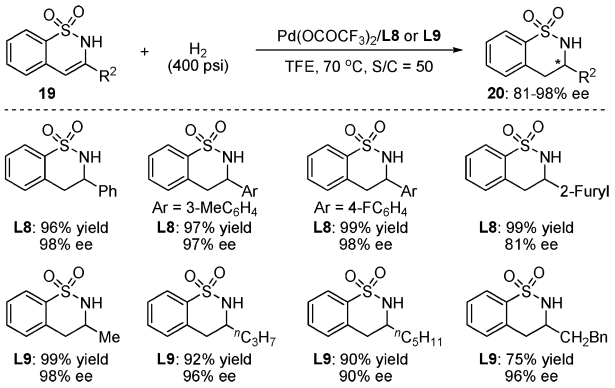
as important building blocks in organic synthesis as well as structural units of agricultural and pharmaceuticals agents.[24]

Despite the fact that much progress has been achieved in the asymmetric hydrogenation of activated imines, little attention has been paid to the Pd-catalyzed asymmetric hydrogenation of simple ketimines (Scheme 8). Two key features may be responsible for this phenomenon: the activated imines generally have strong electron-withdrawing groups, such as tosyl, diphenylphosphinyl, which will reduce the inhibitory effect of the starting material on the catalyst. On the other hand, activated imines exist exclusively as the *E* isomer. Therefore, activated imines rather than simple imines are more suitable substrates for Pd-catalyzed asymmetric hydrogenation in view of reactivity and enantioselectivity.

To meet this challenge, Zhou and co-workers developed an efficient Pd-catalyzed asymmetric hydrogenation of simple ketimines **17** using catalytic amount of Brønsted acid as an additive (Schemes 8 and 9).[25] The addition of Brønsted acid could not only play a great part in the activation of the substrate, but also reduce the inhibitory effect of the substrate on the palladium catalyst the same as the electron-withdrawing group played. Interestingly, this protocol was more effective for the asymmetric hydrogenation of ketimines derived from tetralone than that from simple acetophenones (Scheme 9).

3. Palladium catalyzed asymmetric hydrogenation of sulfonated enamines

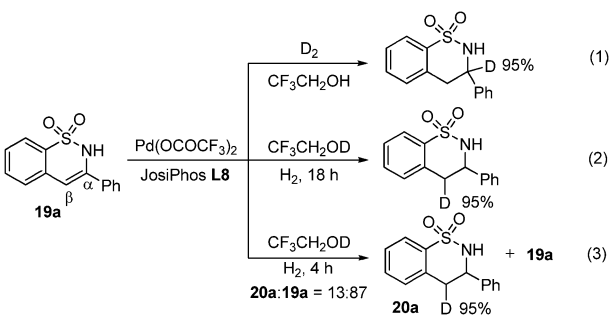
The asymmetric hydrogenation of enamines offers an alternative way for the synthesis of chiral amines.[4] Recently, Zhou *et al.* reported an efficient synthesis of chiral cyclic sultams through



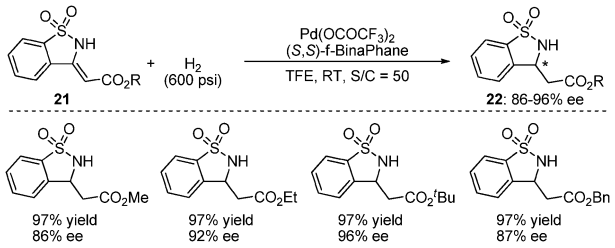
Scheme 10 Asymmetric hydrogenation of endocyclic enamines.

Pd-catalyzed asymmetric hydrogenation of trisubstituted enamines (Scheme 10).[26] Using palladium–bisphosphine catalytic systems, the asymmetric hydrogenation of cyclic enesulfonamides proceeded smoothly in TFE. Excellent enantioselectivities and high isolated yields were obtained regardless of the electronic properties and steric hindrance of the phenyl ring of enesulfonamides **19**. Only a slight decrease in ee (from 98% to 93%) was observed when the reaction was carried out under mild conditions (1 atm). Especially, (R,R_P)-WalPhos **L9** was a better ligand for the hydrogenation of alkyl substituted enesulfonamides **19** giving chiral products with up to 98% ee.

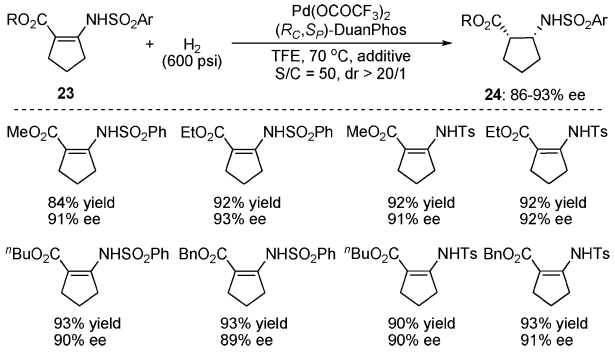
A series of isotopic labeling experiments were conducted to probe the process of hydrogenation. When the reaction was operated under D_2 gas, one deuterium atom was incorporated to the α-position with no deuterium atom at the β-position (eqn (1)). The hydrogenation of **19a** in CF_3CH_2OD afforded the product in full conversion with one deuterium atom at the β-position (eqn (2)). No deuterium atom was observed in the recovered starting material **19a** from kinetic study of the quenching reaction in shorter time (eqn (3)). The observed isotope experiments indicated that the hydrogenation of enesulfonamides proceeded *via* imine intermediates, and the tautomerization process of enesulfonamides to *N*-sulfonylimine intermediates was the rate determining step for the hydrogenation.



Not only endocyclic enamines but also exocyclic enamines could undergo asymmetric hydrogenation in the presence of the palladium catalyst (Scheme 11).[26] Complete conversion and excellent enantioselectivities were obtained in the asymmetric hydrogenation exocyclic **21** enesulfonamides using Pd/(S,S)-*f*-binaphane as a catalyst in TFE.

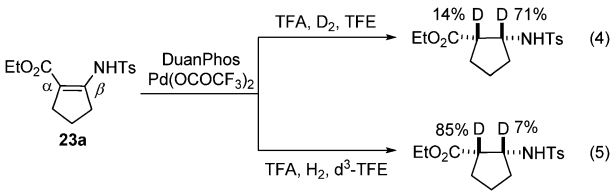


Scheme 11 Asymmetric hydrogenation of exocyclic enamines.



Scheme 12 Asymmetric hydrogenation of tetrasubstituted enamines.

In 2012, Zhou's group demonstrated an efficient and highly enantioselective Pd-catalyzed hydrogenation of cyclic arylsulfonamidoacrylates **23** with up to 93% ee (Scheme 12).[27] Different from the previously reported trisubstituted enamines, a dynamic kinetic resolution process was involved in the asymmetric hydrogenation tetrasubstituted enamines. Owing to the ability to accelerate the enamine–imine tautomerization, the addition of TFA could significantly improve the reactivity and enantioselectivity. It was notable that high diastereoselectivities were also obtained in the hydrogenation of a series of five-membered endocyclic enamines. The obtained chiral amines could be easily transferred to the key intermediate of the potential drugs for Alzheimer's disease.[27] Unfortunately, poor diastereoselectivities were observed in the hydrogenation of the acyclic enamines or six-membered cyclic enamines.



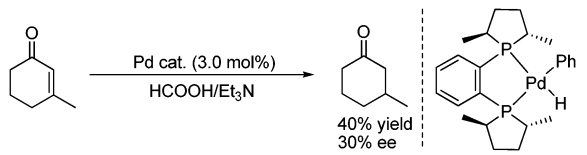
Two isotopic labeling experiments were carried out to investigate the process of the transformation. The observed result under D_2 gas suggested that the hydrogenation of tetrasubstituted enamines mainly proceeded *via* imine intermediates in the presence of acids (eqn (4)). On the other hand, the use of d^3-TFE gave products with a significant α-deuterium substitution which can be attributed to the tautomerization between enamine and imine under acidic conditions (eqn (5)). These results indicated that the tautomerization was faster than the hydrogenation process. Therefore, high diastereoselectivities could be obtained through a dynamic kinetic resolution process.

4. Palladium catalyzed asymmetric hydrogenation of olefins

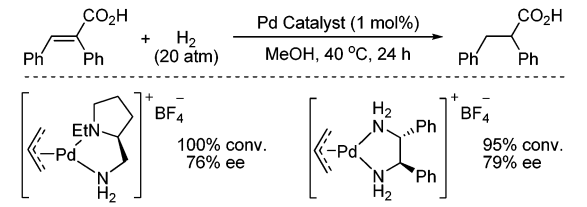
Asymmetric hydrogenation of olefins is one of the most useful reactions for the synthesis of optically active compounds. In 2002, Drago and Pregosin reported a primary result on palladium-catalyzed asymmetric transfer hydrogenation of 3-methyl-2-cyclohexenone (Scheme 13).[28] Although only low yield and ee were obtained, it indicated that the palladium complex could also be employed in the asymmetric hydrogenation of olefins.

Besides bisphosphine ligands, chiral diamine could be also used as efficient ligands for palladium catalyzed asymmetric hydrogenation. Complete conversions and 76% ee were obtained in the asymmetric hydrogenation of (*E*)-α-phenylcinnamic acid using (*S*)-(−)-2-aminomethyl-1-ethylpyrrolidine as ligands (Scheme 14).[29] The use of (*R*,*R*)-1,2-diphenylethylenediamine led to a slight increase in ee.

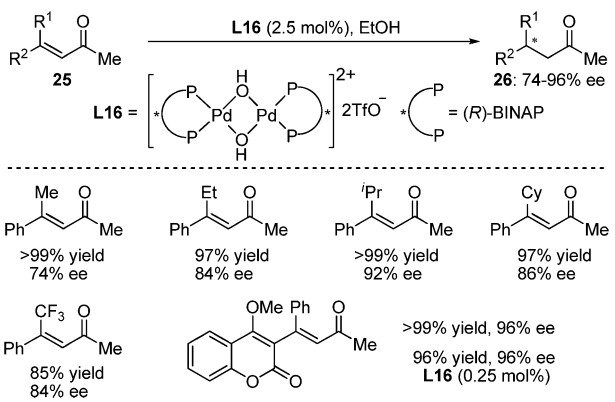
Employing alcohol as the hydride source and solvent, Sodeoka *et al.* described an efficient asymmetric conjugate reduction of enones **25** under mild conditions (Scheme 15).[30]



Scheme 13 Asymmetric transfer hydrogenation of cyclohexenone.



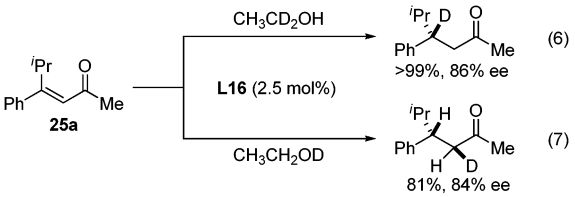
Scheme 14 Asymmetric hydrogenation of cinnamic acid.



Scheme 15 Asymmetric reduction of enones.

It was found that chiral palladium triflate exhibited better catalytic activity over chiral palladium chloride. This method displayed high functional group selectivity (1,4 reduction *vs.* 1,2 reduction) with no reduction of the carbonyl group. Interestingly, the reaction rate and ee were significantly enhanced as the bulkiness of the β-substituent increases. Within one hour, the reduction of the substrate bearing *i*-Pr or *c*-Hex was completed and afforded the reduced products in excellent yields and good ees. This reaction was shown to be applicable to the asymmetric synthesis of (*S*)-warfarin (a well-known anticoagulant) with excellent yield and selectivity (96% ee).[30] Furthermore, the amount of catalyst could be reduced to as little as 0.25 mol% with no loss of enantioselectivity.

Isotopic labeling experiments were operated to examine the mechanism of the reaction. The use of CH_3CD_2OH (ethyl-1,1-d2 alcohol) as a hydrogen source afforded products having a deuterium at the β-position (eqn (6)). Selective deuterium incorporation at the α-position was observed when the reduction of **25a** was conducted in CH_3CH_2OD (eqn (7)).



A possible catalytic cycle is proposed in Fig. 3 according to the isotopic labeling experiments. The Pd hydride species is generated *via* β-hydride elimination of Pd–ethoxide **A**. Subsequently, the coordination of enones to Pd complex **B** would undergo hydride transfer to give Pd enolate **C** which is protonated by ethanol to regenerate the Pd–ethoxide complex **A**. In this catalytic cycle, two different hydrogen atoms in ethanol (H^1 and H^2) are selectively incorporated into the reduced product **26**. The authors suggested that the formation of the Pd hydride species may be the rate determining step. Later, they found that the use of a more electron-rich phosphine ligand (^{i}Pr-DuPhos) could enhance the nucleophilicity of the Pd–H intermediate and gave a more reactive catalytic system than that of BINAP.[31] However, lower enantioselectivities were observed in most cases.

The Pd hydride species could also be generated under hydrogen gas and employed in the asymmetric hydrogenation

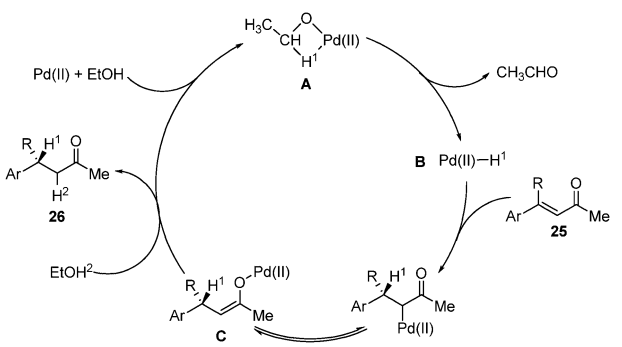
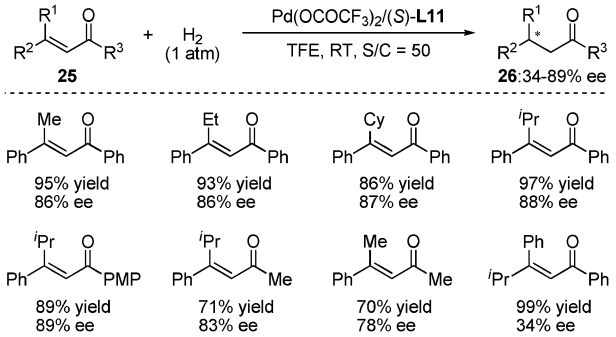
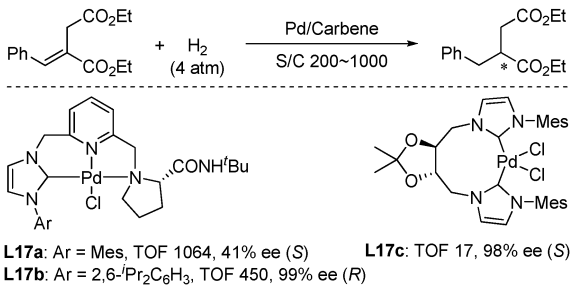


Fig. 3 Proposed mechanism for asymmetric transfer hydrogenation of ketones.



Scheme 16 Asymmetric hydrogenation of enones.



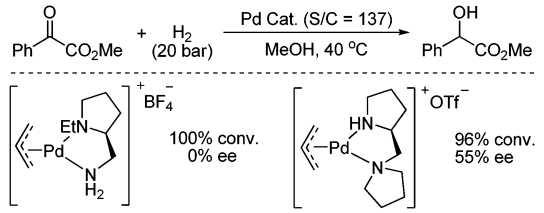
Scheme 17 Asymmetric hydrogenation of olefins.

of a C=C double bond of α,β-unsaturated ketones. Zhou and co-workers found that this reaction proceeded smoothly in TFE under mild conditions (1 atm of H_2, room temperature) with no 1,2 reduction (Scheme 16).[32] A control experiment was carried out to distinguish this catalytic system from Sodeoka's.[30] No product was obtained when the reaction was performed in TFE without hydrogen suggesting that it was hydrogen not TFE acted as the hydride source. Generally, the reactions completed within 12 hours with good to excellent enantioselectivities.

Lower toxicity makes carbene ligands safer to be used instead of phosphine ligands in palladium catalyzed asymmetric hydrogenation. Recently, Iglesias *et al.* successfully synthesized several electron-rich palladium-pincer complexes with *N*-heterocyclic carbene and (*S*)-proline moieties (Scheme 17).[33] Their performances in hydrogenation showed that the enantioselectivity is very sensitive to the *N*-substituent on the NHC ligand (**L17a** *vs.* **L17b**). To the best of our knowledge, the complexes gave the best TOF in the homogeneous palladium catalyzed asymmetric hydrogenation. Palladium bis-NHC complex **L17c** with a chiral dioxolane backbone displayed lower activity but similar enantioselectivity to that of pincer complexes.[34]

5. Palladium catalyzed asymmetric hydrogenation of ketones

Asymmetric hydrogenation of α-keto esters has also been studied with some homogeneous palladium catalysts. The use of diamine ligands to control enantioselectivity in palladium catalyzed asymmetric hydrogenation of benzoylformate was



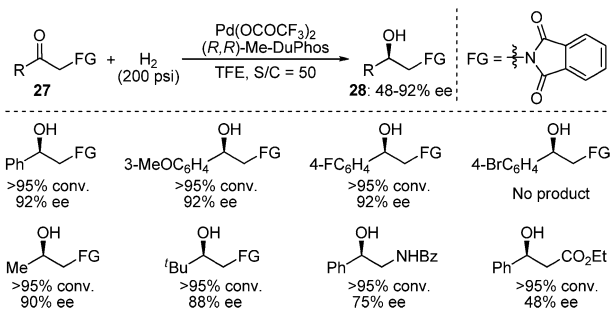
Scheme 18 Asymmetric hydrogenation of α-keto esters.

first attempted by Raja and co-workers (Scheme 18).[29,35] These homogeneous palladium catalysts showed good reactivities but only moderate enantioselectivities ($\leq$55%).

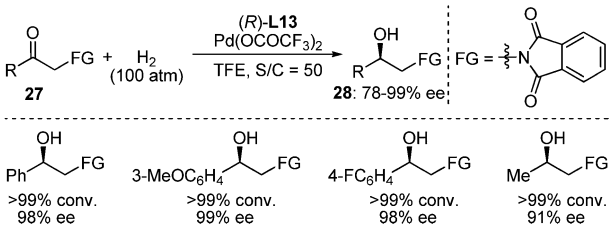
The first successful example of homogeneous palladium catalyzed highly enantioselective hydrogenation (>90% ee) of ketones was reported by Zhou and co-workers in 2005 (Scheme 19).[36] It was found that catalyst precursors played great roles in the reactivity. Neutral $PdCl_2$ gave low catalytic activity, while Pd precursors with weakly coordinating anions such as OTf^- and $CF_3CO_2^-$ provided complete conversions. Pd(0) species $[Pd_2(dba)_3]$ showed no ability to catalyze this reaction. In the presence of $Pd(OCOCF_3)$/(*R*,*R*)-Me-DuPhos, a variety of aryl and alkyl substituted α-phthalimide ketones **27** were hydrogenated smoothly to yield their corresponding secondary alcohols in TFE with up to 92% ee. No desired product was obtained for the substrate with a bromo group owing to catalyst poisoning for oxidative addition of palladium and aromatic bromine. Furthermore, this method could be used as the key step in the synthesis of chiral crotonimide B which has potential for cancer chemoprevention.[37] Several other ketones have been examined to further expand the utility of this Pd-catalyzed asymmetric hydrogenation of ketones, but lower enantioselectivities were observed.

In 2010, Zhang *et al.* synthesized a new class of atropisomeric diphosphine ligands with a wide range of dihedral angles (Scheme 20).[38] They found that there was a correlation between the dihedral angles of ligands and the enantioselectivity in Pd-catalyzed asymmetric hydrogenation of α-phthalimide ketones **27**. The use of ligand (*R*)-**L13** with the biggest dihedral angle gave the excellent enantioselectivities with up to 99% ee which is the highest ee achieved so far in the homogeneous Pd-catalyzed asymmetric hydrogenation of ketones.

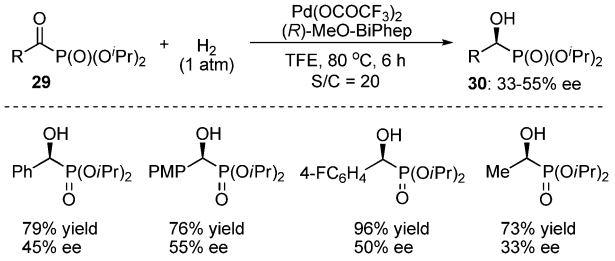
Homogeneous palladium-catalyzed asymmetric hydrogenation was also applicable to the synthesis of chiral α-hydroxyl phosphonates which are an important class of biologically



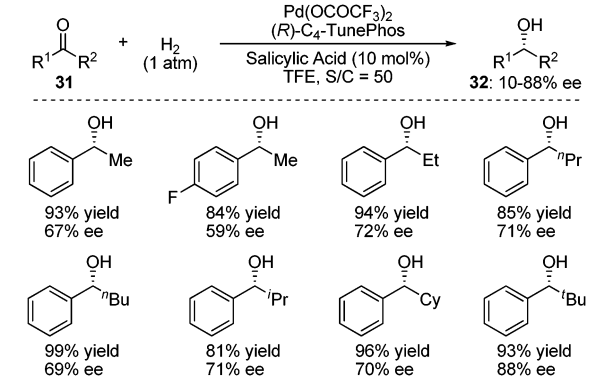
Scheme 19 Asymmetric hydrogenation of functionalized ketones.



Scheme 20 Asymmetric hydrogenation of functionalized ketones.



Scheme 21 Asymmetric hydrogenation of α-keto phosphonates.



Scheme 22 Asymmetric hydrogenation of simple ketones.

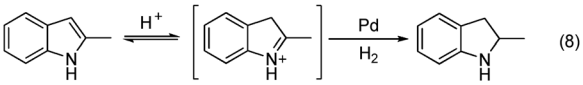
active compounds. Under atmospheric hydrogen pressure, the combination of $Pd(OCOCF_3)_2$–(*R*)-MeO-BiPhep as the catalytic system resulted in asymmetric hydrogenation of the α-keto phosphonates **29** in good yields and moderate enantioselectivities (Scheme 21).[39]

Using catalytic amount of Brønsted acid as an activator, Zhou and co-workers recently disclosed a homogeneous Pd-catalyzed asymmetric hydrogenation of simple ketones **31** with up to 88% ee (Scheme 22).[40] Salicylic acid was found to be the best activator in terms of activity and enantioselectivity. Low conversions were observed when much stronger acids (TFA or TsOH) were used as additives.

6. Palladium catalyzed asymmetric hydrogenation of aromatic compounds

Compared to the various examples on homogeneous palladium catalyzed asymmetric hydrogenation of imines, enamines,

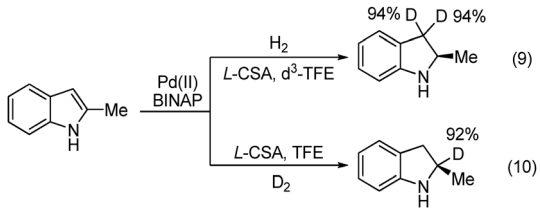
olefins and ketones, little attention has been paid to the Pd-catalyzed asymmetric hydrogenation of aromatic compounds until 2010.[41] High stability of aromaticity and the lack of secondary coordinating group in simple aromatic compounds may be responsible for the difficulty in achieving high activity or enantioselectivity.[6]



(8)

Recently, Zhou and co-workers described a new strategy for Pd-catalyzed highly enantioselective hydrogenation of unprotected indoles using a Brønsted acid as the activator with up to 96% ee (eqn (8) and Scheme 23).[41] It was found that L-camphorsulfonic acid (L-CSA) could react with the simple unprotected indoles to form the iminium salt by protonation of the carbon–carbon double bond. This protonation partially destroyed the aromaticity of indole, thus the *in situ* formed iminium salts would be prone to be hydrogenated. Using the $Pd(OCOCF_3)_2$–(*R*)-H_8-BINAP catalyst system, a variety of 2-alkylsubstituted indoles **33** were hydrogenated smoothly with high yields and enantioselectivities regardless of steric hindrance and length of the side chain (Scheme 23). The present study provides an efficient route to chiral indolines which are ubiquitous structural motifs in naturally occurring alkaloids and many biologically active molecules.[42]

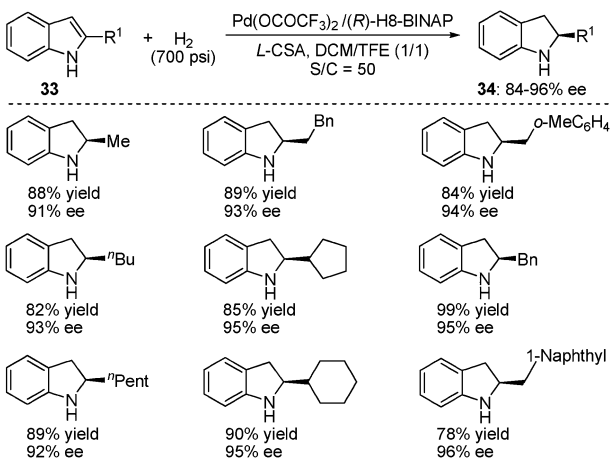
Two isotopic labeling experiments were carried out to confirm that the simple unprotected indole can be activated by a Brønsted acid to form iminium *in situ*, which was then hydrogenated by the Pd-catalyst. The use of deuterated TFE afforded the product with two deuterium atoms incorporated to the 3-position which indicated that a reversible process of protonation and deprotonation existed (eqn (9)). Owing to the fact that equilibrium was faster than hydrogenation, thus two deuterium atoms were imported to the 3-position of the 2-methylindoline before hydrogenation occurred. As expected, the use of D_2 gave 2-methylindoline with deuterium at the 2-position other than the 3-position (eqn (10)).



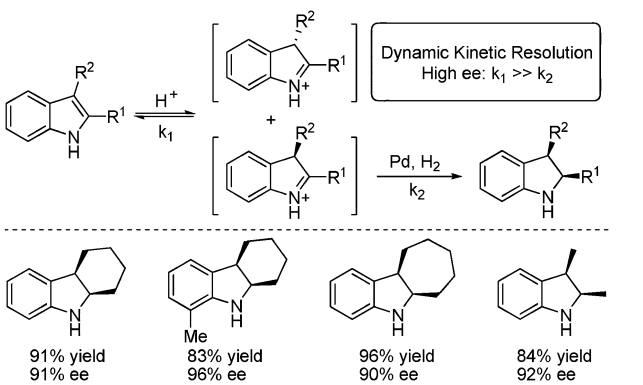
The strategy developed by Zhou *et al.* could also be extended to 2,3-disubstituted indoles.[41] Using the same catalytic system, the hydrogenation of 2,3-disubstituted indoles proceeded smoothly to give the *cis*-indolines with good yields and excellent enantioselectivities (Scheme 24). The hydrogenation mechanism of 2,3-disubstituted indoles was slightly different from that of 2-substituted indoles. In fact a dynamic kinetic resolution process was involved in the hydrogenation of 2,3-disubstituted indoles, and the enantioselectivity-controlled step of 2,3-disubstituted indole is the protonation of the carbon–carbon double bond. The high ee obtained is ascribed to the rate of protonation k_1 is faster than the rate of hydrogenation k_2.

In 2011, Zhou and co-workers developed another efficient and rapid access to chiral 2,3-disubstituted indolines by dehydration triggered asymmetric hydrogenation of 3-(α-hydroxyalkyl)indoles **35** (Scheme 25).[43] It was found that strong Brønsted acid was indispensable to obtain the desired product. No product was observed when weak acid (for example, benzoic acid) was applied in this transformation. Commercially available *para*-toluenesulfonic acid monohydrate ($TsOH{\cdot}H_2O$) emerged as the best acid with regard to yield and enantioselectivity. Under the optimized conditions, a variety of 2,3-disubstituted indolines **36** were obtained with excellent yields and enantioselectivities (88–97%).

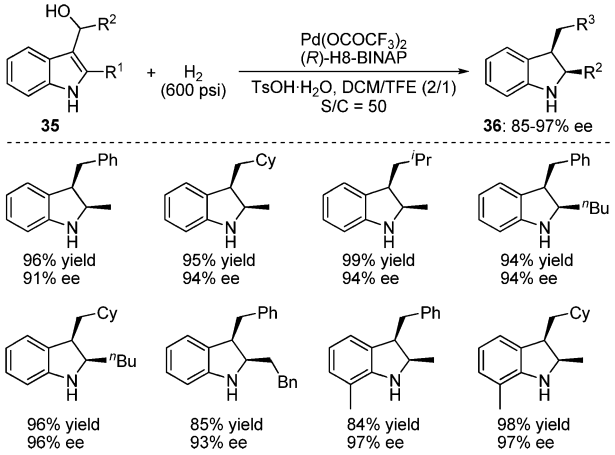
A proposed process was suggested by Zhou *et al.* according to a series of investigation mechanisms (Scheme 26). It is assumed that the first step in the asymmetric hydrogenation is the dehydration of 3-(α-hydroxyalkyl)indole **35a** promoted by the Brønsted acid TsOH to generate the vinylogous iminium **A**. Subsequently, the vinylogous iminium **A** undergoes 1,4-hydride



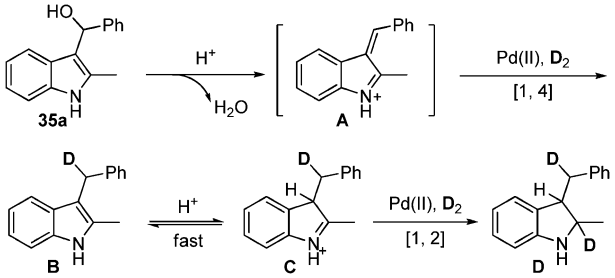
Scheme 23 Asymmetric hydrogenation of indoles.



Scheme 24 Asymmetric hydrogenation of 2,3-disubstituted indoles.



Scheme 25 Asymmetric hydrogenation of 3-(α-hydroxyalkyl)indoles.

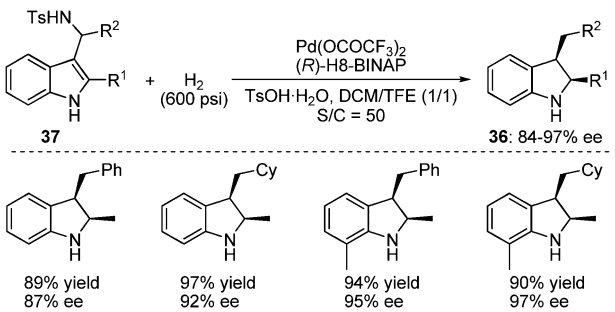


Scheme 26 Proposed process for the asymmetric hydrogenation of 3-(α-hydroxyalkyl)indoles.

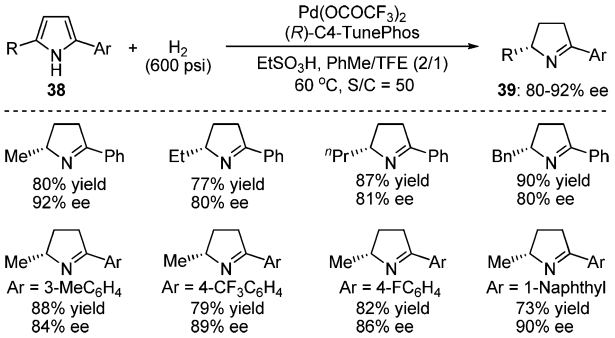
addition and gives simple 2,3-disubstituted indole **B**. The further hydrogenation of the indole is activated by strong acid to form the other iminium intermediate **C** which was hydrogenated *via* 1,2-hydride addition as disclosed in their previous work.[41]

Besides the hydroxyl group, NHTS could be employed as the leaving group in palladium catalyzed homogeneous hydrogenation of indoles (Scheme 27). Owing to the formation of the same vinylogous iminium intermediate as that of 3-(α-hydroxyalkyl)-indoles, similar results with regard to yield and enantioselectivity were obtained using the chiral Pd catalyst.[44]

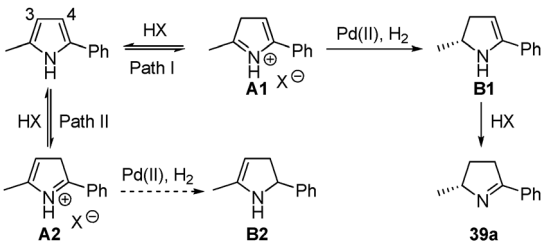
Different from the hydrogenation of indoles, the asymmetric hydrogenation of pyrroles is more difficult owing to its complete loss of aromaticity after the hydrogenation process.



Scheme 27 Asymmetric hydrogenation of 3-(toluenesulfon-amidoalkyl)-indoles.



Scheme 28 Asymmetric hydrogenation of pyrroles.



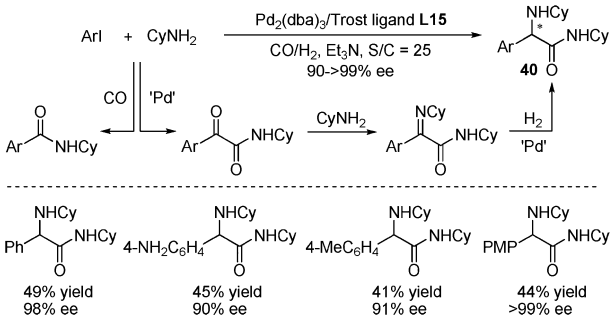
Scheme 29 Reaction pathway for asymmetric hydrogenation of pyrroles.

However, pyrroles are electron enriched arenes and can be protonated by Brønsted acid the same as indoles. Considering this similarity, Zhou and co-workers developed an efficient Pd-catalyzed asymmetric hydrogenation of simple 2,5-disubstituted pyrroles with strong Brønsted acid as the activator (Scheme 28).[45] The hydrogenation proceeded smoothly whereas with unexpected partially hydrogenated pyrroline as the sole product and no complete hydrogenated product was observed in the reaction mixture. A series of enantioenriched 5-alkyl-2-aryl-1-pyrrolines **39** were obtained with 80–92% ee under the current catalytic system. The further derivatization of the hydrogenated products can be conveniently realized by utilizing the chemistry of imine.

A possible mechanism is proposed as follows (Scheme 29): in the first step, the simple unprotected pyrrole was activated by strong Brønsted acid to form the iminium salt **A1** by protonation of the carbon–carbon double bond at the 3-position (Path I). The *in situ* formed iminium salt was hydrogenated to give the intermediate enamine **B1** which is subsequently transformed into more stable product **39a** through an acid-catalyzed isomerization. Owing to the incapability of the homogeneous palladium(II) catalyst in the hydrogenation of *N*-alkylimines, partially hydrogenated pyrroline survives under this catalytic system.[45] The pyrrole can also be protonated at the 4-position in the presence of strong Brønsted acid (Path II). However, the pathway II was excluded for kinetic effects through DFT calculations based on a B3LYP/cc-pVTZ(f)//B3LYP/6-31G** level.

7. Palladium catalyzed asymmetric hydrogenation in asymmetric tandem reaction

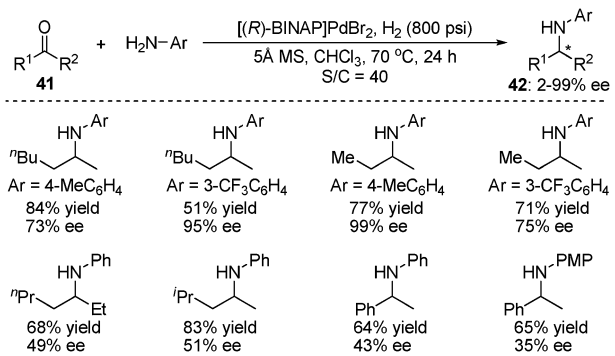
Besides direct hydrogenation, palladium catalyzed asymmetric hydrogenation could be used as the key step in tandem



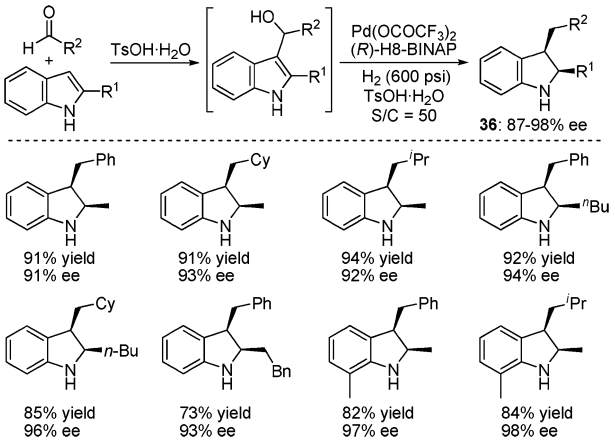
Scheme 30 Asymmetric double carbohydroamination.

reactions to quickly synthesize chiral compounds. In 2003, Alper and Nanayakkara demonstrated a novel one-pot synthesis of α-amino amides **40** from iodoarenes and cyclohexylamine *via* a palladium-catalyzed double carbohydroamination (Scheme 30).[46] The double carbohydroamination consisted of double carbonylation, amine condensation and Pd-catalyzed asymmetric hydrogenation which was the enantioselectivity-controlled step. It was notable that the Pd(0) precursor $[Pd_2(dba)_3]\cdot CHCl_3$ gave the best result with respect to yields and enantioselectivities. As far as we know, this is the only example of homogeneous asymmetric hydrogenation catalyzed by Pd(0) rather than Pd(II) species. In most cases, only moderate yields were obtained owing to the formation of cyclohexylamide and α-*N*-cyclohexylimino amide as by-products. The observed by-products also offered some indication about the mechanism. Only trace amounts of the double carbohydroamination product were observed when bromobenzene, benzylbromide and vinyl iodide were used instead of iodoarenes.

In 2009, Rubio-Pérez *et al.* reported one-pot asymmetric reductive amination of various carbonyl compounds **41** using preformed air stable chiral palladium catalyst $[(R)\text{-BINAP}]PdBr_2$.[47] Generally, the asymmetric transformations of aryl–alkyl ketones give better enantioselectivities than that of dialkyl ketones owing to easier enantiofacial discrimination of the two substituents on carbonyl groups. However, Rubio-Pérez and co-workers found that higher enantioselectivities were obtained in the palladium catalyzed asymmetric reductive amination of dialkyl ketones (up to 99% ee) whose two substituents on the carbonyl groups are more sterically and electronically similar than that of aryl–alkyl ketones (<43% ee, Scheme 31). It was also notable that no side



Scheme 31 Asymmetric reductive amination.

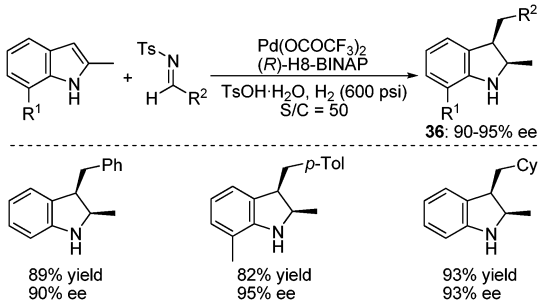


Scheme 32 The synthesis of chiral 2,3-disubstituted indolines by tandem reaction.

hydrogenation of ketones **41** to the corresponding secondary alcohols promoted by the palladium catalytic system was observed by GC-MS (EI) analysis in all entries.

By combining reductive alkylation of 2-substituted indoles and palladium catalyzed asymmetric hydrogenation of 2,3-disubstituted indoles, Zhou and co-workers described a rapid and divergent approach to chiral 2,3-disubstituted indolines **36** with up to 98% ee from 2-substituted indoles and aldehydes (Scheme 32).[48] It was believed that the first step in this tandem reaction was Friedel–Crafts reaction of 2-alkylindoles and aldehydes promoted by Brønsted acid. Subsequently, the afforded 3-(α-hydroxyalkyl)-indole dehydrated to give a vinylogous iminium intermediate which was subjected to asymmetric hydrogenation in the presence of palladium complexes. The vinylogous iminium intermediate could be observed *via* electrospray ionization mass spectroscopic analysis of the solution of control experiments.[48] It was also notable that no 2-substituted indoline was observed under the optimized conditions. This result suggested that the Friedel–Crafts reaction between 2-substituted indoles and aldehydes was faster than the hydrogenation.

The 2,3-disubstituted indoles could also be easily achieved from the Friedel–Crafts reaction of 2-substituted indoles with imines. Therefore, Zhou and co-workers attempted the tandem reaction (Friedel–Crafts/asymmetric hydrogenation) of 2-substituted indoles and *N*-tosyl imines giving products with up to 95% ee (Scheme 33).[44]



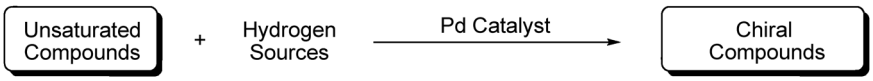
Scheme 33 The synthesis of chiral 2,3-disubstituted indolines by tandem reaction.

8. Conclusion

In this tutorial review, we have demonstrated that the homogeneous palladium-catalyzed asymmetric hydrogenation has emerged as an extremely powerful and versatile tool for the rapid construction of chiral building blocks over the past few years (Table 1). A great deal of new methods have been developed for the asymmetric reduction of imines, enamines, olefins and ketones to the corresponding saturated compounds in an enantioenriched manner which acts as an important supplementary to the traditional asymmetric hydrogenation reactions based on other transition metal complexes. Taking advantage of the activation in which Brønsted acid played, the palladium catalyst achieved its potential in the hydrogenation of more challenging unprotected heteroarenes, such as indoles and pyrroles. It was also found that palladium catalyzed asymmetric hydrogenation could be used as the key step in tandem reactions to quickly synthesize chiral compounds.

A general mechanism for homogeneous Pd(II)-catalyzed asymmetric hydrogenation could be proposed according to

Table 1 Typical results obtained for homogeneous palladium catalyzed asymmetric hydrogenation



Hydrogen Sources: H_2, EtOH, HCO_2H

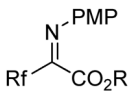
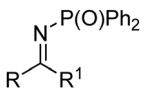
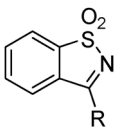
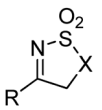
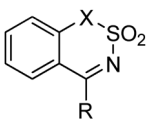
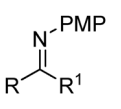
Substrates		Catalytic system	S/C	ee (%)	Scheme	Ref.
		P–P*/H_2	25	88	1	16 and 18
		P–P*/H_2	50	94	2	19
		P–P*/H_2	50	99	3	20
		P–P*/H_2	100	>99	4	21 and 22
Imines		P–P*/H_2	50	99	5	21–23
		P–P*/H_2 (X = CH_2) P–P*/H_2 (X = O)	50 50	98 97	6 7	22 and 23 24
		P–P*/H_2 (X = O) P–P*/H_2 (X = NH)	50 50	99 98	7 7	24 24
		P–P*/acid/H_2	50	95	9	25

Table 1 (*continued*)

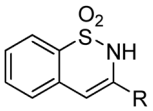
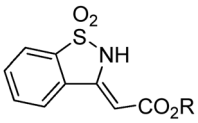
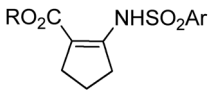
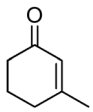
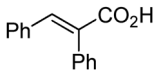
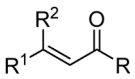
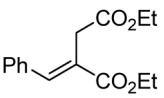
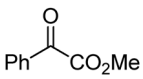
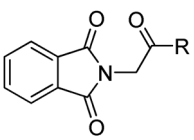
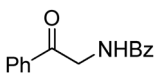
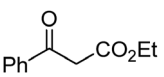
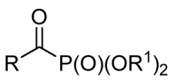
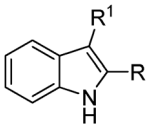
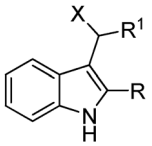
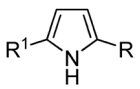
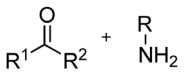
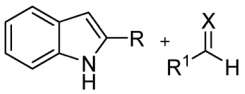
Substrates		Catalytic system	S/C	ee (%)	Scheme	Ref.
		P–P*/H_2	50	98	10	26
Enamines		P–P*/H_2	50	96	11	26
		P–P*/H_2	50	93	12	27
		P–P*/HCO_2H	33	30	13	28
		N–N*/H_2	100	79	14	29
Olefins		P–P*/EtOH P–P*/H_2	200 50	96 89	15 16	30 and 31 32
		NHC/H_2	1000	99	17	33 and 34
		N–N*/H_2	137	55	18	29 and 35
		P–P*/H_2	50	99	19 and 20	36 and 38
		P–P*/H_2	50	75	19	36
Ketones		P–P*/H_2	50	48	19	36
		P–P*/H_2	20	55	21	39
		P–P*/acid/H_2	50	88	22	40

Table 1 (*continued*)

Substrates		Catalytic system	S/C	ee (%)	Scheme	Ref.
Heteroarenes		P–P*/acid/H_2	50	96	23 and 24	41
		P–P*/acid/H_2 (X = OH)	50	97	25	43
		P–P*/acid/H_2 (X = NHTs)	50	97	27	44
		P–P*/acid/H_2	50	92	28	45
Tandem reactions	Arl + 2 CO + 2 $CyNH_2$ double carbohydroamination	P–P*/H_2	25	>99	30	46
		P–P*/H_2	40	99	31	47
		P–P*/acid/H_2 (X = O)	50	98	32	48
		P–P*/acid/H_2 (X = NHTs)	50	95	33	44

S/C and ee indicate the highest values; P–P*: chiral bisphosphine ligand; N–N*: chiral diamine ligand, NHC: *N*-heterocyclic carbene ligand.

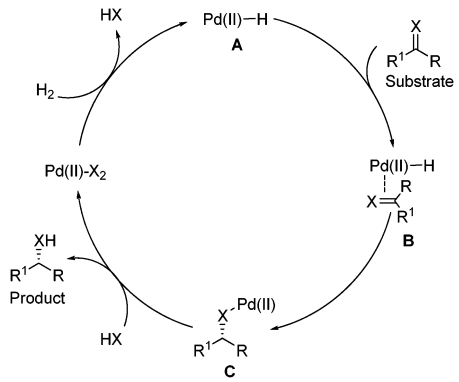


Fig. 4 Proposed mechanism for homogeneous Pd(II)-catalyzed asymmetric hydrogenation.

the aforementioned work (Fig. 4). The heterolytic cleavage of H_2 by the chiral Pd(II)–X_2 complex (X = weakly coordinating anions) generates monohydride species Pd(II)–H **A** and HX. Then the unsaturated substrate will coordinate with Pd(II)–H **A** in a η^2 fashion **B**. Migratory insertion of the substrate into the Pd(II)–H bond forms Pd(II) complex **C**. The protonolysis of Pd(II) complex **C** with HX yields the product and regenerates the Pd(II)–X_2 complex for the next catalytic cycle.

Despite that significant progress has been made in recent years, there are still many challenges which limit the applications of homogeneous palladium-catalyzed asymmetric hydrogenation. By far bisphosphine ligands gave the best results with regard to activities and enantioselectivities in most cases. Future research in this area is expected to be the development of new chiral ligands with high activity and enantioselectivity. Recent advances demonstrated that NHC–carbene maybe a promising candidate for this purpose. In order to meet the growing demands of a variety of enantiopure compounds, the substrate scope of the hydrogenations also needs to be extended. Finally, the future development in this field is closely associated with mechanistic investigations. The current mechanistic understanding of the generation of intermediate Pd–H and its transformations remains in infancy. The mechanistic studies about the interplay between the palladium catalyst and solvent (TFE) are expected to elucidate the common solvent-dependent phenomena in the field.[49] By overcoming the current problems, it is reasonable to believe that new advances in palladium-catalyzed asymmetric hydrogenation can be foreseen to come.

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