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TUTORIAL REVIEW

Recent advances in transition metal-catalyzed enantioselective hydrogenation of unprotected enamines

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Received 10th January 2012
DOI: 10.1039/c2cs35007f

Transition metal-catalyzed enantioselective hydrogenation of enamines is undoubtedly a useful and environment-friendly method for the preparation of optically pure chiral amines and amine derivatives. Over the last few decades, the use of transition metal catalysts containing chiral phosphorus or phosphine–oxazoline ligands attracted much attention for the hydrogenation of unprotected enamines. A number of efficient chiral catalysts have been developed, and some of them have shown high potential for the application in the synthesis of optical chiral amines in both laboratory and industry. This *tutorial review* focuses on the contributions concerning the transition metal-catalyzed enantioselective hydrogenation of unprotected enamines for the synthesis of chiral amines and amine derivatives.

1. Introduction

Optically pure chiral amines are very important building blocks for the construction of a wide range of useful compounds including pharmaceuticals, agrochemicals, and materials of technological interest. Numerous methods including catalytic asymmetric synthesis using transition metals or organocatalysts[1–4] and biotransformation using biocatalysts[5] have been developed for the preparation of chiral amines in high enantioselectivity over the past decades. Since the pioneering works of Dang and Kagan[6] on the enantioselective hydrogenation of *N*-acyl α-dehydroamino acids using a rhodium complex of (*R*,*R*)-DIOP (**1**) as catalyst in 1971 (Scheme 1), and of Knowles *et al.*[7] on the successful application of catalytic enantioselective hydrogenation in the industrial preparation of L-DOPA, an effective agent for treatment of Parkinson's disease, with a Rh-(*S*,*S*)-DIPAMP catalyst in 1970s (Scheme 2), transition metal-catalyzed enantioselective hydrogenation of *N*-acyl enamines has become a reliable and useful method for the synthesis of chiral amines protected with acyl (usually acetyl) groups.[8]

Although great progress has been made in the transition metal-catalyzed enantioselective hydrogenation of *N*-acyl enamines, this method has a major drawback that the high enantioselectivity can only be achieved when the substrate

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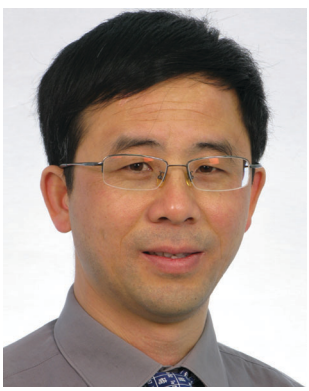
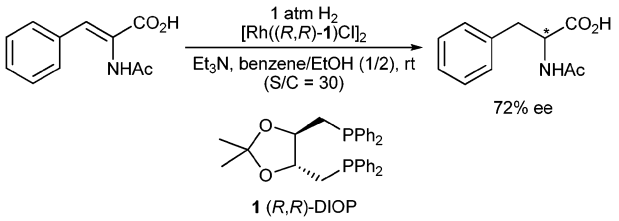


Jian-Hua Xie

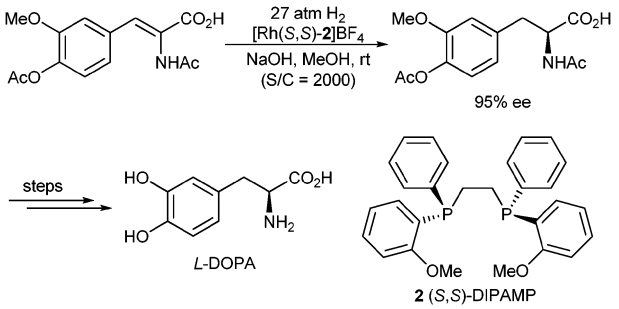
Jian-Hua Xie was born in 1968. He received his PhD in 2003 under the supervision of Professor Qi-Lin Zhou at the Institute of Elemento-Organic Chemistry, Nankai University. He then worked in the same institute and was promoted to associate professor in 2005 and to full professor in 2010. In 2007, he spent one year as a postdoctoral fellow in Prof. Michael Doyle's group at Maryland University. His research interests focus on asymmetric catalysis and asymmetric synthesis of natural products and chiral drugs.

Shou-Fei Zhu

Shou-Fei Zhu was born in Anhui Province, China, in 1977. He received his BS degree in chemistry from Nankai University in 2000. In 2005, he received his PhD degree in chemistry under the supervision of Prof. Qi-Lin Zhou at the Institute of Elemento-Organic Chemistry, Nankai University. He then joined the faculty of the same institute and was promoted to associate professor in 2008. He now is working with Prof. Eiichi Nakamura in the University of Tokyo as a postdoctoral research fellow. His research interests focus on the developments of chiral ligands and catalysts as well as new asymmetric reactions.



Scheme 1 Enantioselective hydrogenation of *N*-acyl α-dehydroamino acids with Rh-(*R*,*R*)-DIOP.



Scheme 2 Enantioselective synthesis of L-DOPA.

contains an *N*-acyl protecting group. The introduction and removal of the protecting group reduce the efficiency of enantioselective hydrogenation of enamines and limit its applications in the synthesis of optically active amines.[9] To overcome that drawback, significant efforts have been devoted to the development of new chiral catalysts for the enantioselective hydrogenation of unprotected enamines.

An acyl protecting group on the nitrogen of enamines was considered prerequisite for achieving good enantioselectivity in the transition metal-catalyzed hydrogenation by forming a chelate complex with the metal of catalyst in the transition state.[10,11] The unprotected enamines have long been regarded as challenging substrates in the enantioselective hydrogenations because they have no chelating group like *N*-acyl (Fig. 1). There were very few reports on the study of catalytic enantioselective hydrogenation of unprotected enamines until the beginning of this century. In 1994, Lee and Buchwald reported an example of enantioselective hydrogenation of *N*,*N*-dialkyl enamines.[12] By using 5 mol% chiral titanocene catalyst [(*S*,*S*,*S*)-(EBTHI)-TiO_2-binaphthol] (**3**) they achieved excellent enantioselectivities (up to 98% ee) (Scheme 3). However, the use of large amounts of an air and water-sensitive reagent like *n*-BuLi and an expensive reagent like phenylsilane is a disadvantage of that method. In 2000, Börner *et al.* used chiral rhodium complexes of diphosphine ligand (*R*,*R*)-BDPCH (**4**) for the hydrogenation of 1,3,3-trimethyl-2-methyleneindoline, however, the enantioselectivity of the reaction was only moderate (up to 72% ee) (Scheme 4).[13]

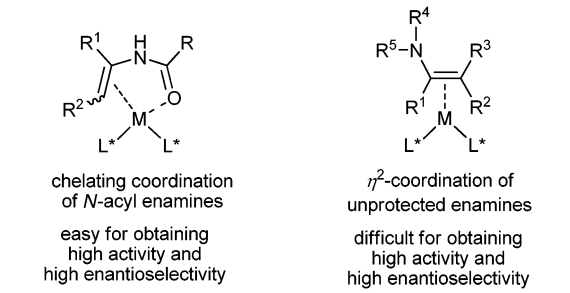
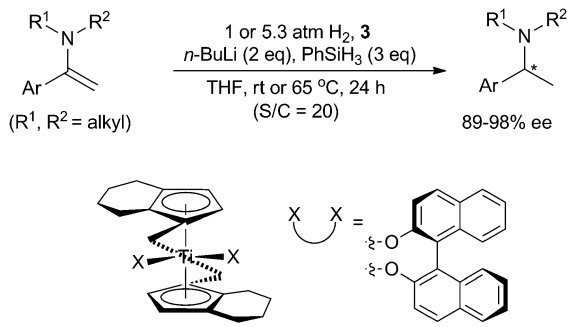
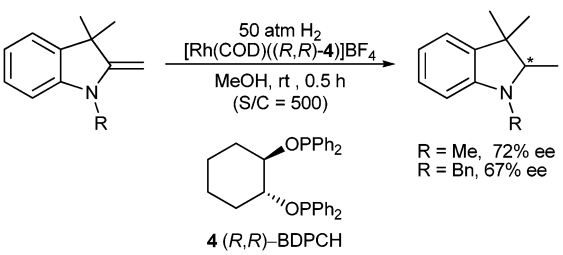


Fig. 1 The coordination models of enamines to the metal center of catalysts.



Scheme 3 Enantioselective hydrogenation of enamines with titanium catalyst **3**.

Since the beginning of this century, many researchers have been involved in enantioselective hydrogenation of unprotected enamines, and a number of efficient chiral catalysts have been developed. And the enantioselective hydrogenation of unprotected enamines now has become a highly efficient, economical, and environment-friendly method for the synthesis of a wide range of chiral amines (Fig. 2). Some of these catalysts have been successfully applied in the industrial synthesis of chiral drugs and intermediates. In this short review, we would like to briefly



Scheme 4 Enantioselective hydrogenation of enamines with Rh-**4**.

Qi-Lin Zhou

Qi-Lin Zhou received his BS degree from Lanzhou University in 1982 and PhD degree from Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences under the supervision of Prof. Yao-Zeng Huang in 1987. After doing postdoctoral research abroad for several years he joined the East China University of Science and Technology, Shanghai in 1996. In 1999 he moved to Nankai University as a Cheung Kong Scholar. His current research interests include transition metal catalyzed reactions, asymmetric catalysis, and synthesis of biologically active compounds.

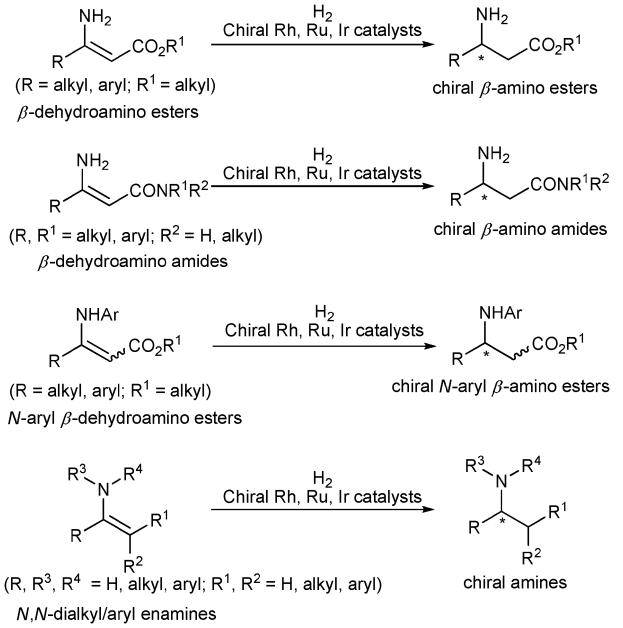


Fig. 2 Catalytic enantioselective hydrogenation of unprotected enamines.

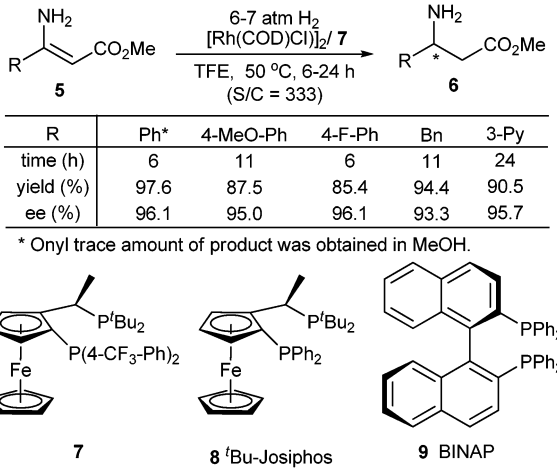
describe the recent accomplishments in the transition metal-catalyzed enantioselective hydrogenation of unprotected enamines for the direct synthesis of chiral amines. The well-reviewed enantioselective hydrogenation of *N*-acyl enamines was not included in this review.[14–16]

2. Enantioselective hydrogenation of unprotected β-enamine esters/amides

Chiral β-amino acids are very important components in synthetic peptides with interesting biological properties. The enantioselective synthesis of chiral β-amino acids and their derivatives has been extensively explored.[17–19] However, most of the reported reactions used *N*-acyl-β-dehydroamino esters as substrates.[20,21] Recently, a breakthrough was made in this reaction by two research groups at Merck and Takasago, respectively. By using rhodium or ruthenium complexes of chiral bidentate phosphine ligands, they accomplished highly enantioselective hydrogenations of unprotected β-dehydroamino esters and/or amides.[22,23] These creative works attracted many researchers involved in this challenging research field. Consequently, a number of efficient catalysts including rhodium, ruthenium and iridium complexes of chiral phosphorus ligands have been developed, and the scope of substrates was also expanded from *N*-unsubstituted β-dehydroamino esters to *N*-aryl β-dehydroamino esters. More gratifying is that the enantioselective hydrogenation of unprotected β-dehydroamino esters has been successfully applied to the synthesis of chiral drugs such as Sitagliptin.[24]

2.1 Enantioselective hydrogenation of *N*-unsubstituted β-dehydroamino esters/amides

2.1.1 With chiral rhodium catalysts. In 2004, Hsiao *et al.*[22] at Merck investigated the enantioselective hydrogenation of *N*-unsubstituted β-dehydroamino esters/amides for the synthesis



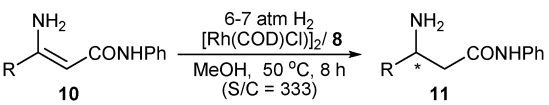
R	Ph*	4-MeO-Ph	4-F-Ph	Bn	3-Py
time (h)	6	11	6	11	24
yield (%)	97.6	87.5	85.4	94.4	90.5
ee (%)	96.1	95.0	96.1	93.3	95.7

* Onyl trace amount of product was obtained in MeOH.

Scheme 5 Rh-catalyzed enantioselective hydrogenation of β-dehydroamino esters **5**.

of unprotected β-amino acid derivatives. After screening a diverse array of commercially available chiral diphosphine ligands (or their complexes), they found that the chiral rhodium complex of Josiphos-type ligand **7** with a *para*-trifluoromethyl group on the *P*-phenyl rings of the ligand gave the best result in both yield (93.7%) and enantioselectivity (96.1% ee) for the hydrogenation of (*Z*)-methyl 3-amino-3-phenylacrylate (**5**, R = Ph) (Scheme 5). However, the ruthenium complex of BINAP (**9**) and the iridium complex of Josiphos-type ligand **7** were inefficient for this transformation, providing only a trace amount of the desired product. Although a good enantioselectivity of 84.7% ee was obtained by the iridium complex of the ligand ^{t}Bu-Josiphos (**8**), the conversion of the reaction was very low (11%). With catalyst Rh-**7**, a series of *N*-unsubstituted β-dehydroamino esters **5** were hydrogenated to the corresponding chiral β-amino acid esters **6** in high yields (85.4–97.6%) with excellent enantioselectivities (93.3–96.1% ee) at 0.3 mol% (S/C = 333) catalyst loading under 6–7 atm of H_2 (Scheme 5).

Under similar reaction conditions, but using MeOH instead of trifluoroethanol (TFE) as solvent the rhodium complex of ^{t}Bu-Josiphos (**8**) was found to be an efficient catalyst for the enantioselective hydrogenation of *N*-unsubstituted β-dehydroamino amides **10** (Scheme 6). Good to high yields (74.3–94.0%) and excellent enantioselectivities (95.6–97.1% ee) were obtained. Interestingly, solvent plays a critical role in the reactions, for example, the hydrogenation of β-dehydroamino esters **5** gave high reactivity and selectivity in TFE and almost no reaction



R	Ph*	4-MeO-Ph	4-F-Ph	Bn
time (h)	8	8	8	8
yield (%)	74.6	82.0	74.3	94.0
ee (%)	95.6	96.3	96.0	97.1

* with TFE as a solvent: 18 h, 94.1%, 82.2% ee.

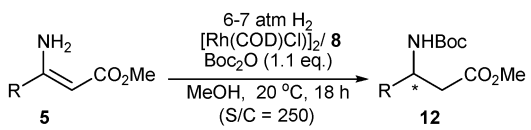
Scheme 6 Rh-catalyzed enantioselective hydrogenation of β-dehydroamino amides **10**.

took place in MeOH. On the other hand, the hydrogenation of β-dehydroamino amides **10** gave much higher selectivity in MeOH than in TFE.

Further studies by Hansen *et al.* also at Merck disclosed that the unprotected amino group (NH_2) in the hydrogenation products brought some drawbacks which limit the performance of the reaction.[25] The amine compounds are known to have deleterious effects on the performance of the catalytic hydrogenation by poisoning the chiral transition metal catalyst through coordinating to the metal center of the catalysts. The basicity/nucleophilicity of the amine compounds may also render them unstable under the reaction conditions, especially in the case of amino ester compounds in methanol. However, these drawbacks could be attenuated or eliminated by *in situ* protection of the amino group of amine products with di-*tert*-butyl dicarbonate (Boc_2O). In the presence of 1.1 equivalent of Boc_2O and with 0.4 mol% of Rh-**8** as catalyst, both *N*-unsubstituted β-dehydroamino esters **5** and amides **10** can be hydrogenated in MeOH in good to high yields (57–99%) and excellent enantioselectivities (91–99% ee) (Scheme 7).

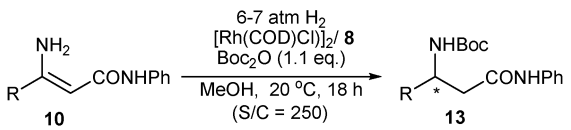
It deserved to be noted that in the presence of Boc_2O the hydrogenation of unprotected β-dehydroamino esters **5** could also be performed in methanol. This suggested that a potential role of TFE, which is considerably more acidic than methanol (pK_a in DMSO: TFE, 23.59; MeOH, 29),[26] may be to stabilize the amino ester product by attenuating the nucleophilicity of the primary amine in the absence of Boc_2O. *In situ* protection of the amine product with Boc_2O has a similar effect as TFE and allows for a more economical solvent, methanol, to be used.

In the search for an efficient catalytic enantioselective hydrogenation method for the synthesis of β-homophenylalanine **15**, a key intermediate to chiral drugs, Kubryk and Hansen[27] at Merck investigated the asymmetric hydrogenation of *N*-unsubstituted β-dehydroamino ester **14** (Scheme 8). They found that the direct hydrogenation of **14** provided β-amino ester **15a** in 89% yield and 93% ee with 0.1 mol% of catalyst Rh-**7** under 14 atm of H_2 at 40 °C in TFE. The performance of



R	Me	Bn	^{i}Pr	^{t}Bu	Ph[b]
yield (%)	85 (< 10)[a]	93	75	62	57
ee (%)	96	99	95	91	97

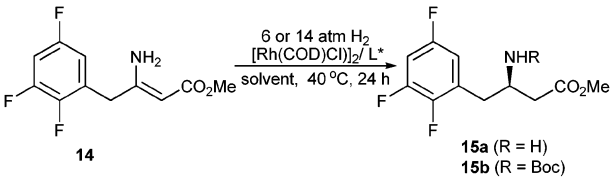
[a] Boc_2O added after hydrogenation was complete.
[b] with 3.0 mol% catalyst



R	Me	Bn[b]	Ph
yield (%)	84(63)[a]	97	98
ee (%)	97(97)[a]	97	98

[a] Boc_2O added after hydrogenation was complete.
[b] The same results were obtained at 3 atm H_2.

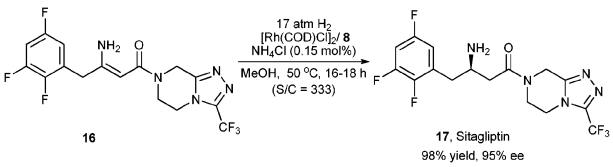
Scheme 7 Enantioselective hydrogenation of β-dehydroamino esters **5** and amides **10** in the presence of Boc_2O.



Ligand	mol% cat.	solvent	PH_2 (atm)	yield (%)	ee (%)
7	0.1	TFE	14	89	93
8	1.0	MeOH	6	80	93
8*	0.6	MeOH	6	88	97

* reaction performed with 1.1 equiv. of Boc_2O at 25 °C.

Scheme 8 Enantioselective hydrogenation of *N*-unsubstituted β-dehydroamino ester **14**.



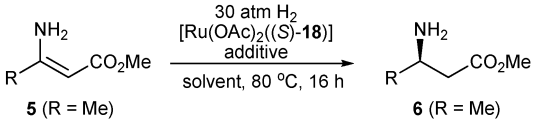
Scheme 9 Enantioselective hydrogenation of *N*-unsubstituted β-enamine amide **16**.

in situ protection of **15a** using Boc_2O gave the *N*-Boc β-amino ester **15b** in 88% yield and 97% ee with 0.6 mol% of catalyst Rh-**8** under 6 atm of H_2 at 25 °C in MeOH.

Clausen *et al.*[28] at Merck investigated the enantioselective hydrogenation of *N*-unsubstituted β-dehydroamino amide **16** toward the preparation of Sitagliptin (Scheme 9), a dipeptidyl peptidase IV (DPP IV) inhibitor for the treatment of diabetes. During the process study, they found that the individual starting material gave a variable result in a range of 82% conversion and 89% ee to 99% conversion and 95% ee in the Rh-**8**-catalyzed hydrogenations of **16**. This investigation led to a finding that the trace amount of ammonium chloride (0.38–1.14 mol% related to amide) in the amide substrate **16** is beneficial to the hydrogenation in terms of reaction rate and enantioselectivity.

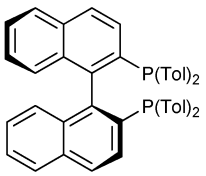
Further work to optimize the reaction conditions by Hansen *et al.* led to a more efficient and practical procedure for the preparation of Sitagliptin.[29] They found that the Ir- and Ru-catalysts gave poor results and Rh-catalysts, in particular with ferrocenyl-based Josiphos-type ligands, afforded both high conversions (up to >99%) and enantioselectivities (up to 98% ee). Finally, the *N*-unsubstituted β-enamine amide **16** was hydrogenated to Sitagliptin (**17**) in the presence of 0.15 mol% of NH_4Cl, 0.15 mol% of $[Rh(COD)Cl]_2$, and 0.155 mol% of ^{t}Bu-Josiphos (**8**) in MeOH under 17 atm of H_2 at 50 °C for 16–18 h (Scheme 9).

2.1.2 With chiral ruthenium catalysts. At almost the same time with the Merck group, Matsumura *et al.*[23] at Takasago patented a similar hydrogenation reaction, but with ruthenium complexes of diphosphine ligands as catalysts. For example, they reported that the ruthenium diacetate complex ligated with Tol-BINAP (**18**) was able to hydrogenate the methyl 3-aminocrotonate **5** (R = Me) to β-amino ester with moderate ee value (54% ee) in the presence of 1 equivalent of HOAc as an additive. When TFE was used as a solvent and in the



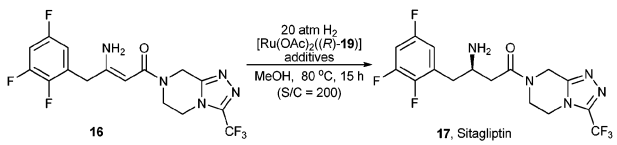
5 (R = Me) **6** (R = Me)

S/C	solvent	Additive	select. (%)	ee (%)
200	MeOH	AcOH (1 eq)	97	54
100	TFE	-	96	94
200	MeOH	AcOH (1 eq), TFE (1 eq)	98	83



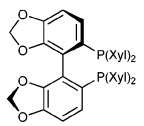
18 (*S*)-Tol-BINAP

Scheme 10 Ru-catalyzed enantioselective hydrogenation of β-enamine ester **5** (R = Me).



16 **17**, Sitagliptin

additive (eq)	yield (%)	ee (%)
none	2	86.9
acetic acid (1)	32	98.2
benzoic acid (1)	15	97.5
$ClCH_2CO_2H$ (1)	74	>99
salicylic acid (1)	75	99.5
HSA (1) and NH_4SA (3)	96	99.5



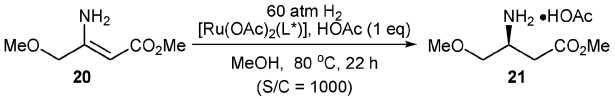
19 (*R*)-Xyl-Segphos

Scheme 11 Ru-catalyzed enantioselective hydrogenation of β-enamine amide **16**.

absence of HOAc the enantioselectivity of the reaction was dramatically enhanced to 94% ee (Scheme 10).[30]

The enantioselective hydrogenation of *N*-unsubstituted β-enamine amide **16** with chiral Ru-diacetate catalysts has also been investigated by researchers from Merck and Takasago.[31] The ruthenium diacetate complex ligated by (*R*)-Xyl-Segphos (**19**) was found to be an efficient catalyst toward hydrogenation of enamine amide **16** in the presence of acid additives (Scheme 11). By adding 1 equivalent of salicylic acid (HSA) and 1 equivalent of ammonium salicylate (NH_4SA) as additives the hydrogenation of **16** offered chiral amine product **17** in 96% ee with nearly perfect enantioselectivity (99.5% ee) under 20 atm of H_2 at 80 °C.

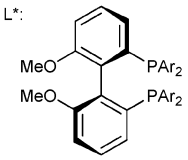
Recently, Schmid *et al.*[32] at Hoffmann-Roche reported the ruthenium-catalyzed enantioselective hydrogenation of unprotected γ-methoxy substituted β-enamine ester **20** to (*S*)-3-amino-4-methoxybutan-1-ol (**21**). In the presence of 1 equivalent of HOAc as an additive the enamine ester **20** was hydrogenated to amino ester acetate salt **21** with ruthenium diacetate complexes of MeO-BIPHEP-type ligands in low to high yields (33–90%) and good to excellent enantioselectivities (80–97.2% ee) (Scheme 12). The ruthenium catalysts containing (*R*)-MeO-BIPHEP (**22**) and sterically moderate demanding MeO-BIPHEP-type ligands such as (*R*)-Tol-MeO-BIPHEP (**23**) or (*R*)-Xyl-MeO-BIPHEP (**24**) performed well, providing ee values of 97%. The catalysts containing bulky bisphosphine ligands, particularly the ligand (*R*)-3,5-^{t}Bu-MeO-BIPHEP (**26**), led to



20 **21**

L*	conv. (%)	yield (%)*	ee (%)
22	>99	89	97.2
23	>99	89	97.2
24	>99	89	97.0
25	99	90	96.2
26	66	33	80

* GC yield.



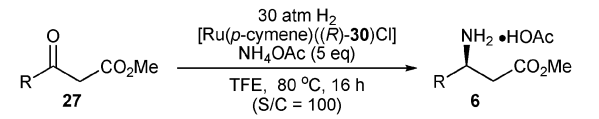
22 (*R*)-MeO-BIPHEP(Ar = Ph)
23 (*R*)-Tol-MeO-BIPHEP(Ar = 4-Me-Ph)
24 (*R*)-Xyl-MeO-BIPHEP(Ar = 3,5-$(Me)_2$-Ph)
25 (*R*)-3,5-^{i}Pr-MeO-BIPHEP(Ar = 3,5-$(^iPr)_2$-Ph)
26 (*R*)-3,5-^{t}Bu-MeO-BIPHEP(Ar = 3,5-$(^tBu)_2$-Ph)

Scheme 12 Ru-catalyzed asymmetric hydrogenation of enamine ester **20**.

a substantial drop in activity and enantioselectivity. The use of 1 equivalent of HOAc as an additive was also crucial for a high catalyst performance, and no conversion was observed in the absence of HOAc.

Another feature of chiral ruthenium catalysts is the capability to catalyze the enantioselective hydrogenation of β-enamines generated *in situ* from β-keto esters/amides and a simple ammonium salt, a process called direct reductive amination,[33] providing the corresponding chiral unprotected β-amino esters/amides in high yields and excellent enantioselectivities.

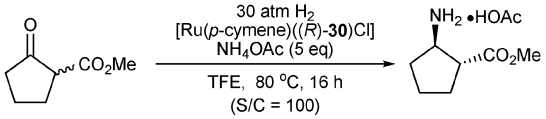
In 2005, Bunlaksananusorn and Rampf[34] at Lanxess reported an example of efficient enantioselective reductive amination of β-keto esters for the one-pot synthesis of unprotected β-amino esters (Scheme 13). Using 1 mol% of ruthenium complex of biphosphine ligand (*R*)-Cl-MeO-BIPHEP (**30**) as a catalyst, β-keto ester **27** (R = Ph) was successfully transferred to β-amino ester **6** (R = Ph) in 88% yield with 98% ee and high



27 **6**

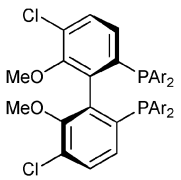
R	Ph[a]	4-MeO-Ph	4-Cl-Ph	4-F-Ph	3-MeO-Ph	3-Cl-Ph	Me
yield (%)	88	83	79	80	88	81	80
ee (%)	98	98	99	96	96	98	96
select.[b]	99:1	99:1	99:1	99:1	94:6	99:1	99:1

[a] with [Ru(OAc)2((*R*)-**30**)] as a catalyst yielded similar results.
[b] β-amino ester: β-hydroxy ester.



28 **29**

70% yield, 82% ee
58% de (*trans*:*cis*)
selectivity, 99:1



30 (*R*)-Cl-MeO-BIPHEP

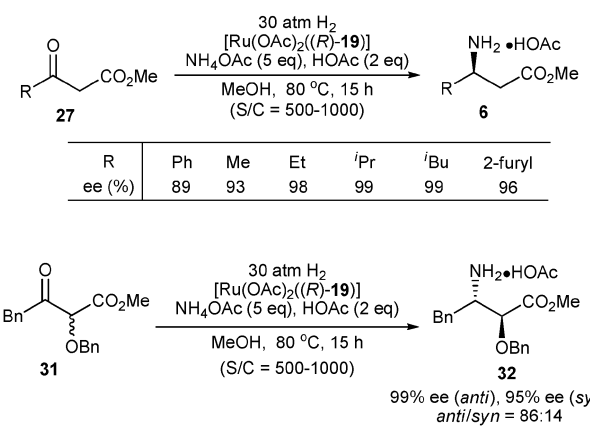
Scheme 13 Ru-catalyzed reductive amination of β-keto esters **27** and **28**.

selectivity (>99 : 1 of β-amino ester : β-hydroxy ester) under the reductive amination conditions in the presence of 5 equivalent of ammonium acetate (NH_4OAc) under 30 atm of H_2. A series of β-keto esters **27** were evaluated under reductive amination conditions with 1 mol% of catalyst [Ru(*p*-cymene)((*R*)-**30**)Cl], and good yields (79–88%) with high enantioselectivities (96–99% ee) and high selectivities (96 : 4–99 : 1) were obtained. The ruthenium catalyst [Ru(*p*-cymene)((*R*)-**30**)Cl] was also efficient for the reductive amination of cyclic β-keto ester **28**, yielding an amine product **29** in moderate enantioselectivity (82% ee) and diastereoselectivity (58% de) with high selectivity (99 : 1).

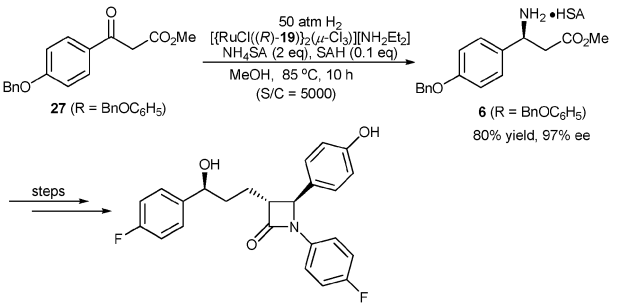
Matsumura and Saito[35] at Takasago reported independently a ruthenium-catalyzed reductive amination of β-keto esters toward the synthesis of unprotected β-amino esters (Scheme 14). Upon comparing different chiral diphosphine ligands they found that the ruthenium diacetate complex containing ligand (*R*)-Xyl-Segphos (**19**) was an efficient catalyst, giving 93% ee and 93% selectivity for the reductive amination of methyl 3-oxobutanoate (**27**, R = Me) in the presence of 2 equivalent of HOAc under 30 atm of H_2. Several β-alkyl and aryl substituted β-keto esters **27** were hydrogenated to the corresponding chiral β-amino esters in excellent enantioselectivities (93–99% ee). The ruthenium-catalyzed enantioselective reductive amination of methyl 2-(benzyloxy)-3-oxo-4-phenylbutanoate (**31**) *via* dynamic kinetic resolution (DKR) also gave good results (99% ee for *anti*-isomer, *anti*/*syn* 86 : 14).

Recently, Busscher *et al.*[36] at DSM successfully applied ruthenium-catalyzed enantioselective reductive amination for the synthesis of ezetimibe, a member of a class of lipid-altering agents known as cholesterol absorption inhibitors.[37,38] After screening a wide range of ammonium salts and chiral ruthenium catalysts, they found that using [{RuCl((*R*)-**19**)}$_2$-(μ-Cl_3)][NH_2Et_2] or [$Ru(OAc)_2$((*R*)-**19**)] as a catalyst, NH_4SA as an ammonium source, and HSA as an additive, the enantioselective reductive amination of β-keto ester **27** (R = $BnOC_6H_4$) was highly effective, even at an unprecedented low catalyst loading (0.02 mol%, S/C = 5000). The β-amino ester **6** (R = $BnOC_6H_4$) was isolated in 80% yield with 97% ee (Scheme 15).

To establish a convenient process for multigram synthesis of (*S*)-3-amino-4-methoxybutan-1-ol (**21**), Schmid *et al.*[32] at



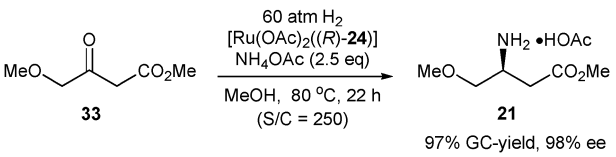
Scheme 14 Ru-catalyzed enantioselective reductive amination of β-keto esters **27** and **31**.



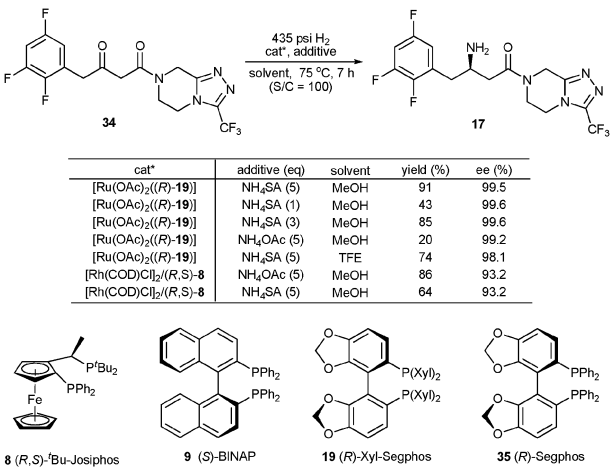
Scheme 15 Ru-catalyzed enantioselective reductive amination of β-keto ester **27** (R = $BnOC_6H_4$).

Hoffmann-Roche investigated the ruthenium-catalyzed reductive amination of β-keto ester **33** (Scheme 16). The ruthenium complex containing a biphosphine ligand (*R*)-Xyl-MeO-BIPHEP (**24**) was found to be the best catalyst, affording the desired chiral amine product **21** in 97% yield with 98% ee (Scheme 16).

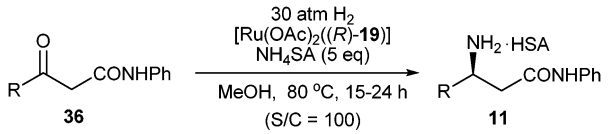
On the other hand, in an effort to develop a more effective process for Sitagliptin, researchers at Merck and Takasago investigated the ruthenium-catalyzed enantioselective reductive amination of β-keto amides.[31] The results listed in Scheme 17 showed that the NH_4SA was the best nitrogen source among the ammonium salts tested when ruthenium diacetate complex [$Ru(OAc)_2$((*R*)-**19**)] was used as catalyst. With 5 equivalent of NH_4SA, the reaction afforded β-amino amide **17** in 91% yield and 99.5% ee, and only a small amount (<3%) of β-hydroxyl amide resulting from direct hydrogenation of β-keto amide **34**. Excellent results were also obtained using the ruthenium complexes of other chiral biphosphine ligands, such as BINAP (**9**, 85% yield, 99.1% ee) and Segphos



Scheme 16 Ru-catalyzed enantioselective reductive amination of β-keto ester **33**.



Scheme 17 Asymmetric reductive amination of β-keto amide **34**.



R	time (h)	yield (%)*	ee (%)
Me	15	91	94.7
Et	15	92	98.1
^{i}Pr	15	89	98.9
Ph	15	96	99.2
4-MeO-Ph	15	95	99.6
4-F-Ph	15	96	99.4
2-thienyl	24	82	99.6

* HPLC yield.

Scheme 18 Ru-catalyzed enantioselective reductive amination of β-keto amides **36**.

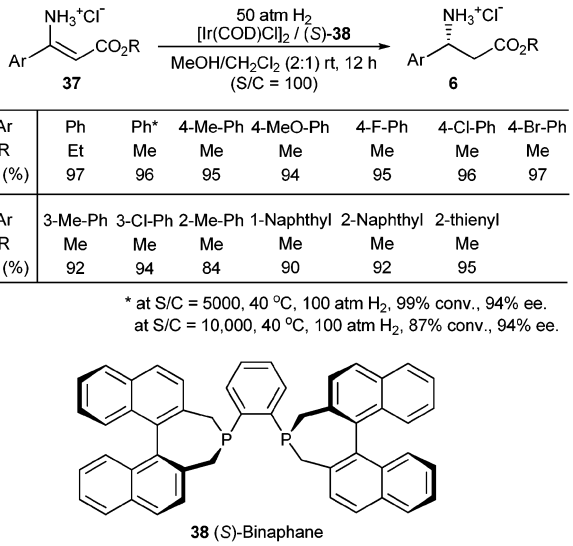
(**35**, 80% yield, 99.8% ee). Under the optimal reaction conditions a series of β-keto amides **36**, either β-alkyl or β-aryl-substituted β-keto amides, were hydrogenated by catalyst [Ru(OAc)$_2$((*R*)-**19**)], providing the corresponding chiral β-amino amides **11** in good to high yields (81–96%) with excellent enantioselectivities (94.7–99.6% ee) (Scheme 18).

2.1.3 With chiral iridium catalysts. In 2004, Hsiao *et al.*[22] reported the enantioselective hydrogenation of *N*-unsubstituted β-enamine esters using chiral iridium catalysts based on chiral diphosphine ligands and obtained good enantioselectivity (85% ee), but the conversion (11%) was very low (Scheme 5). They also tried the hydrogenation of unprotected β-enamine amide **16** for the synthesis of Sitagliptin with iridium catalysts. However, the reaction had low conversion (<70%) and low enantioselectivity (<10% ee).[30]

Zhang *et al.* recently reported a highly efficient iridium-catalyzed enantioselective hydrogenation of unprotected β-enamine esters.[39] By using an iridium complex of ligand (*S*,*S*)-Binaphane (**38**) as catalyst the hydrogenation of β-enamine hydrochloride esters **37** was performed in a mixed solvent of MeOH and CH_2Cl_2 (2 : 1 v/v) under 100 atm of H_2 and at room temperature, providing the corresponding chiral amine products **6** in high yields (>90%) and good to high enantioselectivities (84–97% ee) (Scheme 19). It was deserved to note that the catalyst loading of this reaction could be reduced to as low as 0.01 mol% (S/C = 10 000) with only slight erosion of the conversion of the reaction and ee value of the product (87%, 94% ee). This result presents the highest turnover for enantioselective hydrogenation of unprotected β-enamine ester to date.

2.2 Enantioselective hydrogenation of *N*-aryl β-enamine esters

2.2.1 With chiral rhodium catalysts. Optically pure *N*-aryl β-amino acid derivatives are also key intermediates for the synthesis of many natural products and chiral drugs.[40,41] The enantioselective hydrogenation of prochiral *N*-aryl enamines is a potentially cost-efficient and atom-economic method for the preparation of optically pure *N*-aryl β-amino acid derivatives. Zhang *et al.* investigated the rhodium-catalyzed enantioselective hydrogenation of *N*-aryl β-amino esters and found that the rhodium complex of ligand Tangphos (**43**) was an efficient catalyst for this transformation (Scheme 20).[42] Same as in the



Ar	Ph	Ph*	4-Me-Ph	4-MeO-Ph	4-F-Ph	4-Cl-Ph	4-Br-Ph
R	Et	Me	Me	Me	Me	Me	Me
ee (%)	97	96	95	94	95	96	97

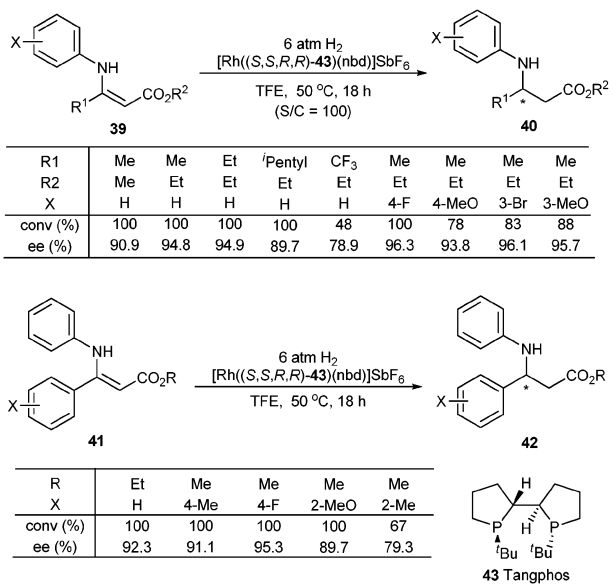
Ar	3-Me-Ph	3-Cl-Ph	2-Me-Ph	1-Naphthyl	2-Naphthyl	2-thienyl
R	Me	Me	Me	Me	Me	Me
ee (%)	92	94	84	90	92	95

* at S/C = 5000, 40 °C, 100 atm H_2, 99% conv., 94% ee.
at S/C = 10,000, 40 °C, 100 atm H_2, 87% conv., 94% ee.

Scheme 19 Ir-catalyzed enantioselective hydrogenation of β-enamine hydrochloride esters **37**.

aforementioned rhodium-catalyzed hydrogenation of *N*-unsubstituted enamine esters **6**,[22] TFE was the best solvent for achieving both high conversion and high enantioselectivity in the hydrogenation of *N*-aryl β-amino esters **39**. Under the optimal reaction conditions and with Rh-**43** as a catalyst, good to high enantioselectivities were obtained for both *N*-aryl β-alkyl β-enamine esters **39** (78.9–96.3% ee) and *N*-aryl β-aryl β-enamine esters **41** (79.3–95.3% ee).

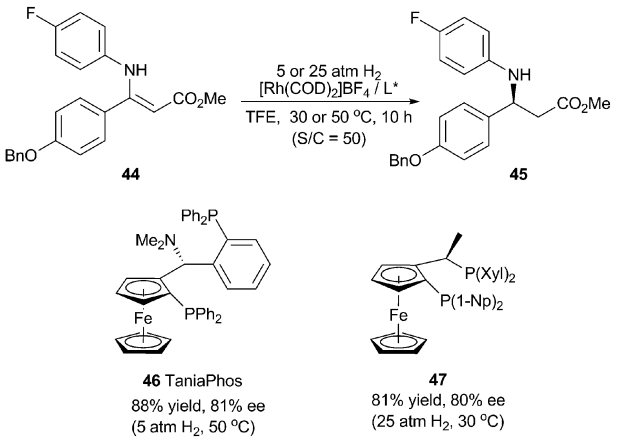
In search for an efficient methodology for the preparation of ezetimibe, Busscher *et al.* at DSM have studied the rhodium-catalyzed enantioselective hydrogenation of *N*-aryl β-enamine ester **44**.[36] They found that Zhang's catalyst Rh-(*S*,*S*,*R*,*R*)-**43** could give an acceptable enantioselectivity (*ca.* 87% ee), albeit the activity was low (<50% yield). Further studies showed that the ferrocene-based chiral ligands **46** and Josiphos type



R1	Me	Me	Et	^{i}Pentyl	CF_3	Me	Me	Me	Me
R2	Me	Et	Et	Et	Et	Et	Et	Et	Et
X	H	H	H	H	H	4-F	4-MeO	3-Br	3-MeO
conv (%)	100	100	100	100	48	100	78	83	88
ee (%)	90.9	94.8	94.9	89.7	78.9	96.3	93.8	96.1	95.7

R	Et	Me	Me	Me	Me
X	H	4-Me	4-F	2-MeO	2-Me
conv (%)	100	100	100	100	67
ee (%)	92.3	91.1	95.3	89.7	79.3

Scheme 20 Rh-catalyzed enantioselective hydrogenation of *N*-aryl β-enamine esters **39** and **41**.

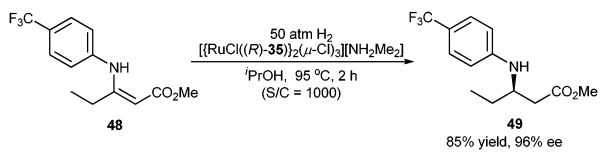


Scheme 21 Rh-catalyzed enantioselective hydrogenation of *N*-aryl β-enamine esters **44**.

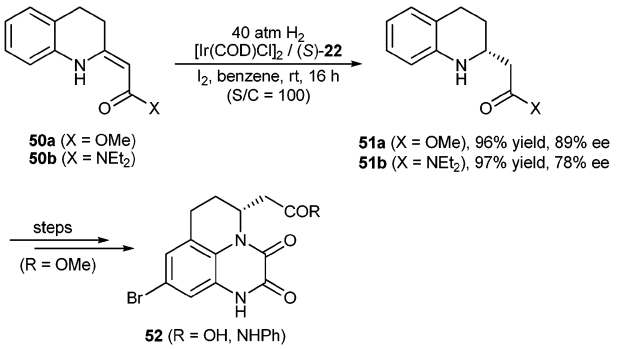
ligand **47** gave best results in terms of yield and enantioselectivity (Scheme 21).

2.2.2 With chiral ruthenium catalysts. The first and also the only example of ruthenium-catalyzed enantioselective hydrogenation of *N*-aryl β-enamine esters to chiral *N*-aryl β-enamine esters was reported by Moroi *et al.* at Takasago in 2004.[43] In order to develop an efficient method for preparing optically pure tetrahydroquinolines, they investigated the ruthenium-catalyzed enantioselective hydrogenation of *N*-aryl β-enamine esters, obtaining the chiral *N*-aryl β-amine esters in good yields with high enantioselectivity. For instance, the (*Z*)-methyl 3-(4-(trifluoromethyl)phenylamino)-pent-2-enoate (**48**) was hydrogenated by catalyst $[\{RuCl((R)\text{-}\mathbf{35})\}_2(\mu\text{-}Cl)_3][NH_2Me_2]$ in 2-propanol under 50 atm of H_2 at 95 °C to the chiral amine **49** in 85% yield with 96% ee (Scheme 22).

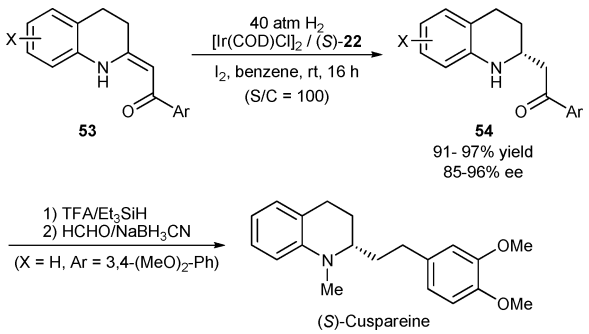
2.2.3 With chiral iridium catalysts. In 2009, Zhou *et al.* successfully introduced chiral iridium catalysts in the hydrogenation of unprotected *N*-aryl β-enamine derivatives.[44] In the presence of iodine as an additive and an iridium complex of (*S*)-MeO-BIPHEP (**22**) as a catalyst, the unprotected exocyclic *N*-aryl β-enamine ester **50a** was hydrogenated to the corresponding chiral amine **51a**, a key intermediate for the synthesis of NMDA–glycine antagonists,[45] in 96% yield with 89% ee. But only 78% ee was obtained for the hydrogenation of *N*-aryl β-enamine amide **50b** (Scheme 23). It is worthwhile to mention that when the unprotected *N*-aryl β-enamine ester/amide was changed to the corresponding *N*-aryl β-enamine ketones the enantioselectivity of the hydrogenation was dramatically increased to up to 96% ee; and this efficient iridium-catalyzed hydrogenation was successfully applied in the enantioselective synthesis of tetrahydroquinoline alkaloid (*S*)-Cuspareine (Scheme 24).



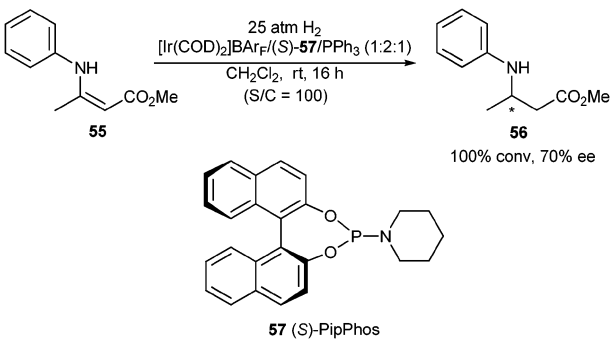
Scheme 22 Ru-catalyzed enantioselective hydrogenation of *N*-aryl β-enamine ester **48**.



Scheme 23 Ir-catalyzed enantioselective hydrogenation of *N*-aryl enamine ester/amide **50**.



Scheme 24 Ir-catalyzed enantioselective hydrogenation of *N*-aryl enamine ketones **53**.

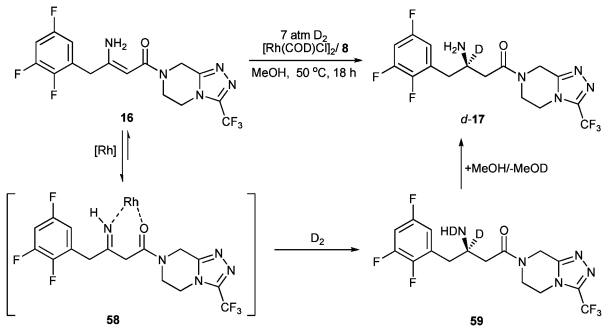


Scheme 25 Ir-catalyzed enantioselective hydrogenation of *N*-aryl enamine ester **55**.

Recently, Minnaard *et al.* have also investigated the iridium-catalyzed enantioselective hydrogenation of *N*-aryl β-enamine esters using mixed monodentate ligands (Scheme 25).[46] By examining various iridium catalysts *in situ* generated from $[Ir(COD_2)]BAr_F$ (BAr_F: tetrakis[(3,5-trifluoromethyl)phenyl-borate]) and chiral binaphthyl-based monodentated phosphoramidite ligands, they found that the iridium catalyst ligated with PipPhos (**57**) and achiral triphenylphosphine gave complete conversion and moderate enantioselectivity (100% conversion, 70% ee).

2.3 Mechanism of enantioselective hydrogenation of unprotected β-enamine esters/amides

Although the catalytic enantioselective hydrogenation of unprotected β-enamine esters/amides has become an efficient



Scheme 26 Plausible mechanism of the enantioselective hydrogenation of β-enamine amide **16**.

direct method for preparing optically pure unprotected β-amino acid derivatives, the mechanism of these hydrogenations is still poorly understood. Deuterium-labeling studies performed by Hsiao *et al.*[22,29] revealed that the product incorporated deuterium only at the β-position in the hydrogenation of unprotected β-enamine amides using a chiral rhodium catalyst bearing ligand ^{t}Bu-Josiphos (**8**) (Scheme 26). These results suggested that the hydrogenation proceeded plausibly through the imine tautomer rather than directly through the enamine, despite that it is the predominant form of the substrate. Based on these results Xiao *et al.* suggested a mechanism involving the formation of a chelating complex between the imine tautomer and the rhodium catalyst, which is analogous to the hydrogenations of β-ketoester and β-ketoamide (Scheme 26).

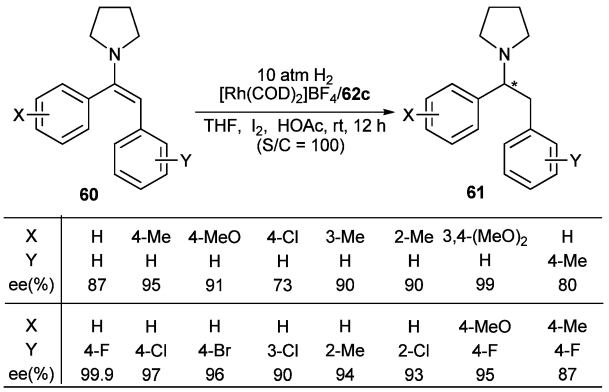
However, in the study of the iridium-catalyzed enantioselective hydrogenation of the β-enamine hydrochloride esters **37** (Scheme 19), Zhang *et al.* observed high reactivity of the reaction.[39] Because the aminium group in the substrate **37** has no coordination with iridium, its hydrogenation was supposed to proceed *via* a "nonchelate" mechanism.

3. Enantioselective hydrogenation of *N*-substituted enamines

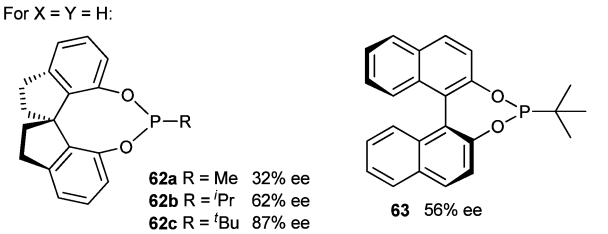
In contrast to the catalytic enantioselective hydrogenation of unprotected β-enamine esters/amides, the hydrogenation of *N*,*N*-dialkyl and *N*-alkyl or *N*-aryl substituted enamines, also called simple enamines, is more difficult for obtaining high activity and enantioselectivity. The major challenge is that only a double bond in the substrates can coordinate to the metal center of the catalysts (Fig. 1, right), and such an η^2-coordination model is considered to be inefficient for enantiocontrol. Nevertheless, several breakthroughs have recently been made in the enantioselective hydrogenation of such intractable prochiral substrates. In addition to Buchwald's chiral titanium catalyst,[12] the chiral rhodium and iridium catalysts containing a range of phosphorus ligands or/and phosphine–oxazoline ligands have been demonstrated to be highly efficient for the hydrogenation of *N*,*N*-dialkyl/aryl enamines.

3.1 With chiral rhodium catalysts

In 2006, Zhou *et al.*[47] reported a highly enantioselective rhodium-catalyzed hydrogenation of unprotected enamines, providing a highly efficient enantioselective approach to optically



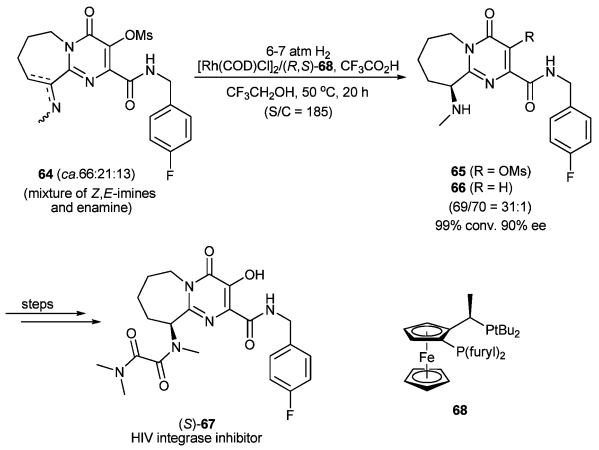
X	H	4-Me	4-MeO	4-Cl	3-Me	2-Me	3,4-(MeO)$_2$	H
Y	H	H	H	H	H	H	H	4-Me
ee(%)	87	95	91	73	90	90	99	80
X	H	H	H	H	H	H	4-MeO	4-Me
Y	4-F	4-Cl	4-Br	3-Cl	2-Me	2-Cl	4-F	4-F
ee(%)	99.9	97	96	90	94	93	95	87



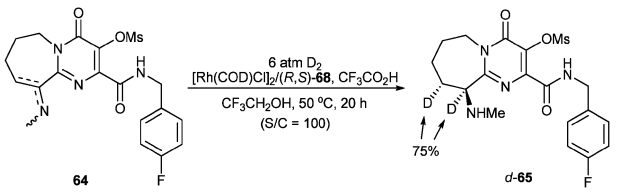
Scheme 27 Rh-catalyzed enantioselective hydrogenation of unprotected enamines **60**.

pure tertiary amines. They evaluated a number of chiral phosphorus ligands including chiral spiro phosphorus ligands in the hydrogenation of 1-(1,2-diarylvinyl)pyrrolidines **60**, a new type of unprotected enamines (Scheme 27). In the presence of 2 mol% of I_2 and 20 mol% of HOAc as additives, the rhodium complex generated *in situ* from $[Rh(COD)_2]BF_4$ and chiral spiro monophosphonite **62c** catalyzed the hydrogenation of 1-(1,2-diphenylvinyl)pyrrolidine (**60**, X = Y = H) to the chiral amine **61** in 100% conversion with 87% ee. Of all the chiral ligands tested, the spiro monophosphonite **62c**, with a bulky *tert*-butyl on the phosphorus atom was the best ligand. The corresponding binaphthyl-based monophosphonite **63** gave moderate ee value (56% ee). However, the bidentate phosphorus ligands such as BINAP (**9**) and ^{t}Bu-Josiphos (**8**) were inefficient in this reaction. The enantioselectivity of the reaction was also sensitive to the nature of the substitutents of the enamine substrates. Generally, the substrates with electron-donating substituents on the α-phenyl ring (X group) and/or electron-withdrawing substituents on the β-phenyl ring (Y group) gave higher enantioselectivity. The highest enantioselectivity (99.9% ee) was achieved in the hydrogenation of the enamine having a 4-F on the β-phenyl ring of the substrate (Scheme 27).

In 2009, Zhong *et al.*[48] at Merck developed an efficient rhodium-catalyzed enantioselective hydrogenation of a highly functionalized mixture of imines/enamine **64** for the synthesis of HIV integrase inhibitor (*S*)-**67** (Scheme 28). They screened a range of rhodium and iridium catalysts bearing chiral diphosphine ligands and found that the rhodium complex of Josiphos-type ligand **68** gave the desired product **65** in high conversion and enantioselectivity. For example, by using 0.5 equivalent of trifluoroacetic acid (TFA) and acidic solvent TFE to disrupt coordination of the product to the catalyst *via* protonation of the amine product, the substrate **64** was successfully transformed to chiral amine **65** (R = OMs) in



Scheme 28 Rh-catalyzed enantioselective hydrogenation of imines/enamine **64**.



Scheme 29 Hydrogenation of imines/enamine **64** with D_2.

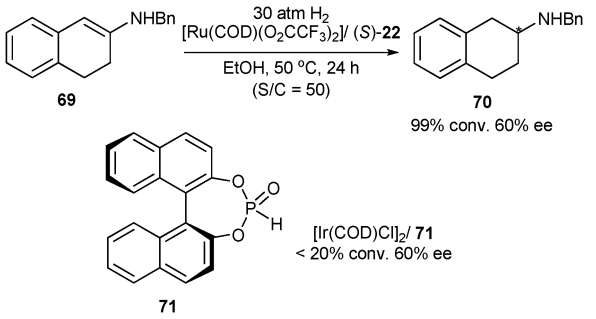
99% conversion and 90% ee by the rhodium catalyst generated *in situ* from $[Rh(COD)Cl]_2$ and (*R*,*S*)-**68**.

Interestingly, although the substrate **64** was dominated by imine form (*ca.* ratio of *Z*-imine/*E*-imine/enamine *ca.* 66 : 21 : 13),[49] the hydrogenation proceeded predominantly through the enamine tautomer. A deuteration experiment shows that the deuterium was incorporated at *ipso* and alpha positions of the amine product *d*-**65** in roughly equal proportion (Scheme 29). This result is in contrast to those observed by Hsiao *et al.* in the study of unprotected β-enamine amides which were hydrogenated predominantly through the imine tautomer.[21,28]

3.2 With chiral ruthenium catalysts

In 2010, Bondarev and Bruneau[50] reported the enantioselective hydrogenation of *N*-benzyl cyclic enamine **69** derived from 2-tetralone. After comparing a series of rhodium, iridium and ruthenium catalysts bearing chiral diphosphine, phosphine–oxazoline or monodentate phosphorus ligands, they found that the ruthenium complex of chiral diphosphine MeO-BIPHEP (**22**) gave the best result (Scheme 30). When the reaction was performed under 30 atm of H_2 at 50 °C for 24 h in EtOH, the catalyst Ru-**22** gave the amine product **70** in 99% conversion with 60% ee. The iridium complex of monophosphorus ligand **71** gave a comparable enantioselectivity, however the conversion of the substrate was very low (<20%).

The catalyst Ru-**22** was also applied for the direct reductive amination of 2-tetralone in the presence of benzylamine as a nitrogen source, but only lower enantioselectivity (47% ee) was obtained.



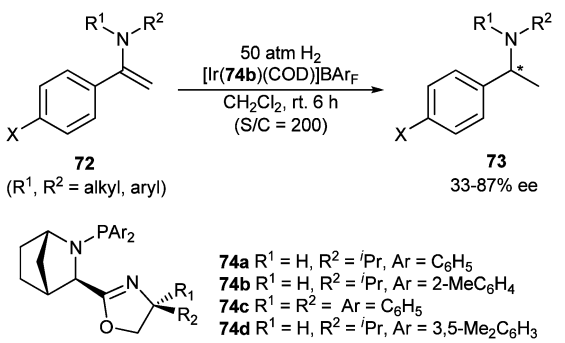
Scheme 30 Ru-catalyzed enantioselective hydrogenation of enamine **69**.

3.3 With chiral iridium catalysts

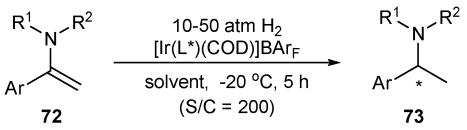
Recently, iridium catalysts bearing chiral phosphorus–nitrogen ligands, which have been demonstrated to be highly efficient for the enantioselective hydrogenation of unfunctional olefins, have received increasing attention in the enantioselective hydrogenation of *N*,*N*-dialkyl/aryl enamines. In 2008, Andersson *et al.*[51] reported that the iridium complexes containing chiral phosphine–oxazoline ligands **74** were efficient catalysts for the hydrogenation of simple enamines **72**, providing the corresponding chiral tertiary amines **73** in moderate enantioselectivities (33–87% ee). However, these catalysts were less efficient for the hydrogenation of the substrates with a cyclic dialkylamino group, *e.g.* the hydrogenation of 1-(1-phenylvinyl)pyrrolidine gave only 33% ee (Scheme 31).

Baeza and Pfaltz[52] introduced phosphine–oxazoline ligands **75** and **76** in this transformation. They found that the iridium complex of PHOX ligand **75** had high enantioselectivities (90–91% ee) for the hydrogenation of α-arylethenamines **72** with a methyl and an aryl group on the nitrogen atom. The iridium complex of Threphox ligand **76** derived from L-threonine was efficient for the hydrogenation of α-arylethenamines **72** with a methyl and a benzyl group on the nitrogen atom. However, both catalysts Ir-**75** and Ir-**76** showed low enantioselectivities (<54% ee) for the hydrogenation of the α-phenylethenamines **72** with pyrrolidyl and *N*,*N*-diethyl groups (Scheme 32).

The hydrogenation of cyclic 1,2-disubstituted enamines **77** derived from 6-methoxytetralone was also evaluated by a range of iridium catalysts of chiral phosphorus–nitrogen ligands. The iridium complex of Threphox ligand **76** provided the best result for the hydrogenation of enamine **77** with a pyrrolidyl group (87% ee). The iridium complex of pyridine–phosphinite



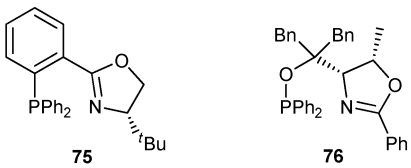
Scheme 31 Ir-catalyzed enantioselective hydrogenation of enamines **72** with Ir–**74**.



72 73

substrate	Ir-**75**[a]	Ir-**76**[b]
R^1 = Me, R^2 = aryl	90-91% ee	13-55% ee
R^1 = Me, R^2 = Bn	19-78% ee	50-92.5% ee
R^1, R^2 = $(CH_2)_4$	44% ee	8% ee
R^1 = R^2 = Et	18% ee	54% ee

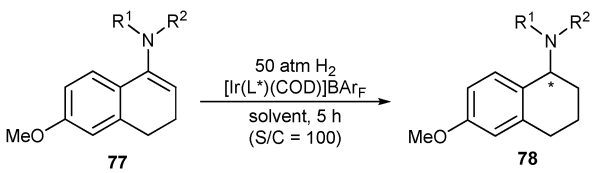
[a] 10-50 atm H_2, CH_2Cl_2. [b] 10 atm H_2, ^{t}BuOMe.



75 76

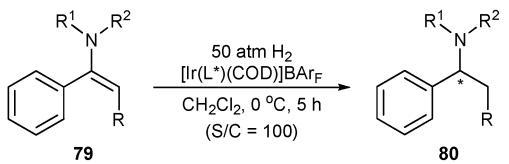
Scheme 32 Ir-catalyzed enantioselective hydrogenation of enamines **72** with Ir–**75** and Ir–**76**.

ligand **82** gave high reaction rate for the hydrogenation of *N*-methyl-*N*-benzyl enamine **77** although only moderate enantioselectivity (71% ee) was obtained. However, when the R^2 group of enamines **77** was changed to the phenyl group (R^2 = Ph), no reaction took place (Scheme 33). Furthermore, the catalyst Ir-**82** was also found to be efficient for the hydrogenation of acyclic *N*-benzyl 1,2-disubstituted enamine **79** (R = R^1 = Me, R^2 = Bn), but only moderate enantioselectivity (67% ee) was obtained (Scheme 33). It is noteworthy that in the hydrogenation of enamine **79** with a pyrrolidyl group (R = Ph, R^1, R^2 = $(CH_2)_4$) the catalyst Ir-**82** gave lower enantioselectivity (69% ee) than the catalyst Rh-**62c** (87% ee, Scheme 27).



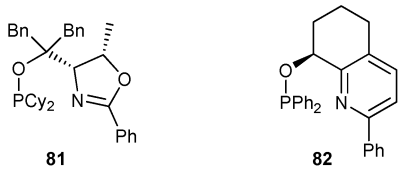
77 78

R^1,R^2 = $(CH_2)_4$, 87% ee (Ir-**76**, ^{t}BuOMe, -20 °C)
R^1 = Me, R^2 = Bn, 71% ee (Ir-**82**, CH_2Cl_2, 0 °C)
R^1 = Me, R^2 = Ph, no reaction (Ir-**82**, CH_2Cl_2, 0 °C)



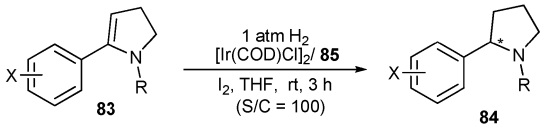
79 80

R, R^1 = Me, R^2 = ph no reaction (Ir-**82**)
R, R^1 = Me, R^2 = Bn, 67% ee (Ir-**82**)
R = Ph, R^1, R^2 = $(CH_2)_4$, 69% ee (Ir-**81**)



81 82

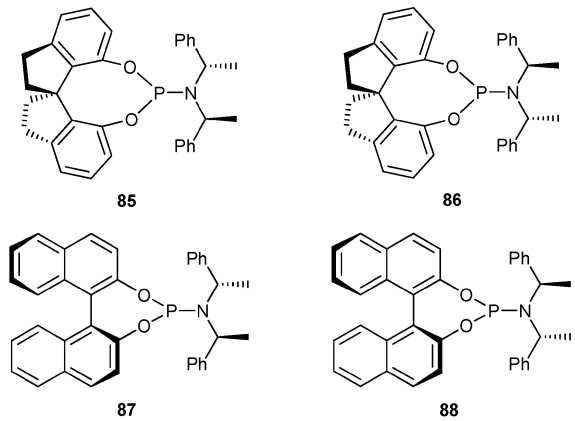
Scheme 33 Ir-catalyzed enantioselective hydrogenation of 1,2-disubstituted enamines **77** and **79**.



83 84

R	Me	Et	^{i}Pr	Me	Me	Me	Me	Me	Me
X	H	H	H	4-Me	4-MeO	4-F	4-Cl	4-Br	3-Me
ee (%)	94	95	96	91	94	92	95	97	89
R	Me	Me	Me	Me	Et	Et	Et	Et	Me
X	3-MeO	3-F	2-Me	2-Cl	4-MeO	4-F	4-Cl	4-Br	^{n}Bu[a]
ee (%)	93	92	87	82	90	97	94	94	94

[a] 5-butyl substituted enamine

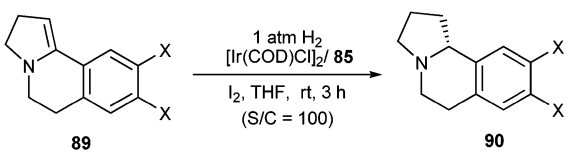


85 86 87 88

Scheme 34 Ir-catalyzed enantioselective hydrogenation of cyclic *N*,*N*-dialkyl enamine **83**.

Zhou *et al*. reported a highly enantioselective iridium catalyst bearing spiro monophosphoramidite ligand (Siphos-pe, **85**) for the hydrogenation of cyclic *N*,*N*-dialkyl enamine **83** (Scheme 34).[53] The addition of I_2 is significant for obtaining full conversion and high enantioselectivity in this reaction. Compared with other monodentate phosphorus ligands such as phosphoramidites **87** and **88** and bidentate phosphorus ligands such as BINAP (**9**) and ^{t}Bu-Josiphos (**8**) the spiro phosphoramidite ligand **85** was proved to be the most efficient ligand for the hydrogenation of 2-aryl-dihydropyrrole derivatives **83**. A variety of chiral cyclic tertiary amines **84** with a five-membered ring could be prepared with 82–97% ee by the catalyst Ir-**85** (Scheme 34). However, this catalyst is less efficient for the hydrogenation of the cyclic enamines with a six-membered ring.

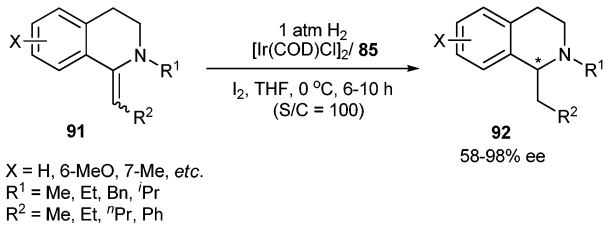
The catalyst Ir-**85** was also effective for the enantioselective hydrogenation of *N*,*N*-dialkyl enamines **89** with a fused ring (Scheme 35). Under the optimal reaction conditions the catalyst Ir-**85** successfully converted the tricyclic enamines **89** to tricyclic amines **90** with 82% ee (X = H) and 90% ee



89 90

X = H 82% ee
X = MeO (crispine A) 90% ee

Scheme 35 Ir-catalyzed enantioselective hydrogenation of *N*,*N*-dialkyl tricyclic enamines **89**.



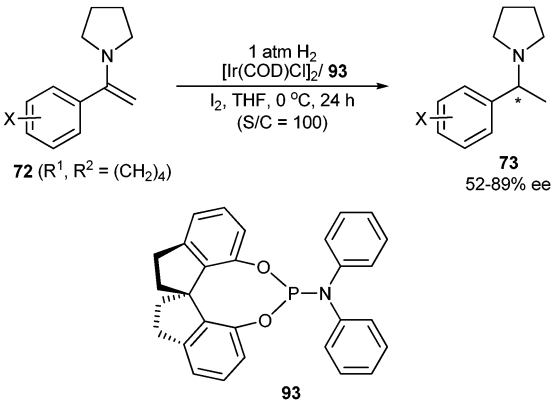
Scheme 36 Ir-catalyzed enantioselective hydrogenation of exocyclic enamines **91**.

(X = MeO), respectively. This reaction provided a convenient approach to isoquinoline alkaloid crispine A (**90**, X = MeO),[54,55] which was isolated from Carduus crispus, Linn. (welted thistle) and had significant cytotoxic activities.[56,57]

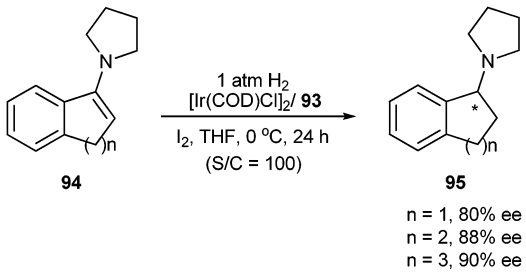
Tetrahydroisoquinoline, widely present in plants and several tissues in mammalian species, is a common structural motif of numerous alkaloids.[58] The enantioselective hydro genation of the easily obtained *N*-alkyl-1-alkylidenetetra hydroisoquinolines **91**, a class of enamines with an exocyclic double bond, is a direct method for synthesis of optically pure *N*-alkyltetrahydroisoquinolines, such as carnegine,[59] glaucine[60] and cularine.[61] Zhou *et al.*[62] studied iridium-catalyzed enantioselective hydrogenation of **91** with different ligands. The spiro phosphoramidite **85** with a bis[(*S*)-1-phenylethyl]amine moiety again was the most efficient ligand for the hydrogenation of **91**. In combination with iodine or potassium iodide the Ir-**85** catalyst hydrogenated **91** at ambient hydrogen pressure (1 atm H_2), providing chiral *N*-alkyl tetrahydroisoquinolines **92** in high yields with up to 98% ee (Scheme 36). The substituent on the phenyl ring of the substrate has little effect on the enantioselectivity of the reaction. However, the hydrogenation reaction is sensitive to the steric hindrance of the alkyl groups on the *N*-atom and on the double bond of the enamine, and a small R^1 or/and R^2 was necessary for achieving high ee values of the products. It is worthy of mention that if the R^2 group on the terminal carbon of the double bond was not hydrogen, the substrates were usually prepared as a *Z*/*E* mixture, and the Ir-**85** catalyst was efficient for the hydrogenations of both the (*Z*)- and (*E*)-isomers.

Despite Andersson *et al.*[51] and Pfaltz *et al.*[52] reported that the iridium catalysts based on chiral phosphorus–nitrogen ligands can catalyze the hydrogenation of enamines **72** (R^1, R^2 = $(CH_2)_4$), the enantioselectivity of the reaction was very low (<50% ee, Scheme 32). Recently, Zhou *et al.*[63] found that the iridium complex of chiral spiro *N*,*N*-diarylphosphoramidite **93** gave moderate to good enantioselectivities (52–89% ee) for the hydrogenation of enamines **72** (Scheme 37). The addition of iodine was also crucial for the reaction and no hydrogenation took place without iodine.

Further studies showed that the catalyst Ir-**93** was efficient for the hydrogenation of enamines **94** derived from benzo-cycloalkanones (Scheme 38). Under the optimal reaction conditions the Ir-**93** catalyst gave good enantioselectivity (80–90% ee) for the hydrogenation of cyclic enamines **94**, and the highest enantioselectivity (90% ee) was obtained in the hydrogenation of the relatively flexible seven-membered cyclic substrate (*n* = 3).



Scheme 37 Ir-catalyzed enantioselective hydrogenation of enamines **72**.



Scheme 38 Ir-catalyzed enantioselective hydrogenation of cyclic enamines **94**.

3.4 Mechanism of enantioselective hydrogenation of *N*-disubstituted enamines

Several efficient chiral catalysts, especially chiral iridium complexes bearing monodentate phosphoramidite ligands, have been developed for the hydrogenation of *N*-substituted simple enamines, providing chiral tertiary amines in high yields and high enantioselectivities, but little information is available for the mechanism of this hydrogenation.

In 1994, Lee and Buchwald suggested a mechanism involving a side-on approach of olefin to the Ti–H complex for obtaining maximum overlap between the LUMO of the olefin and the HOMO of the metal hydride for the Ti-catalyzed enantio-selective hydrogenation of *N*,*N*-dialkyl enamines (Fig. 3).[12] In that approach, the phenyl group of the enamine is twisted out of conjugation with the olefin, whereas the nitrogen's lone pair remains conjugated with olefin.[64] The interaction between the cyclohexyl portion of the tetrahydroindenyl ligand and the alkyl groups on the nitrogen of the enamine substrate is minimized in transition state **A**. This reaction model well explained the experimental result that the catalyst (*S*,*S*,*S*)-**3** produced (*R*)-amine (Scheme 3).

To understand the mechanism of the iridium-catalyzed enantioselective hydrogenation of *N*-alkyl tetrahydroisoquinoline enamines **93** (Scheme 36), Zhou *et al.* recently performed deuterium-labeling studies.[63] The deuteration of the 2-methyl-1-methylene-1,2,3,4-tetrahydroisoquinoline took place at both the α- (80%) and β-positions (average 82%) (Scheme 39). This result implied that a H/D exchange took place at the β-position. The ^{13}C NMR analysis also showed six deuterated components in the product. But, the most surprising observation was that

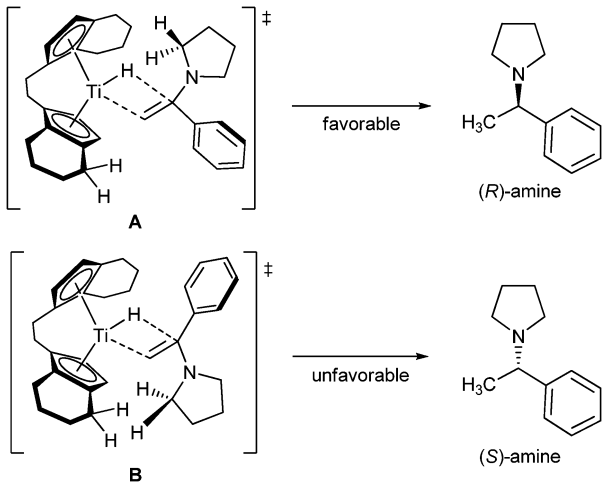
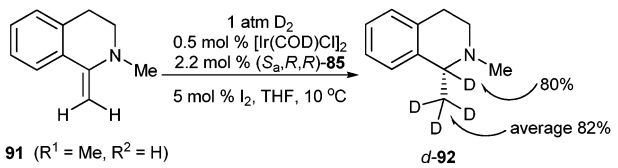


Fig. 3 Possible mechanism of the hydrogenation of *N*,*N*-dialkyl enamines with a Ti-catalyst.



Scheme 39 Ir-catalyzed hydrogenation of enamine **91** with D_2.

the hydrogenation of 2-methyl-1-methylene-1,2,3,4-tetrahydroisoquinoline (**91**, R^1 = Me, R^2 = H) with D_2 was faster than that with H_2, indicating that an inverse isotope effect existed in this reaction.[65] Based on these results and the observations of the detection of the active iridium species of Ir-**85**, an Ir(I)–Ir(III) catalytic cycle involving an Ir-hydride species was proposed (Fig. 4).

In the proposed mechanism the real catalyst Ir(I)-complex **B** (or its dimer **C**) is generated with the help of excess I_2 or KI. The oxidative addition of H_2 to the Ir(I)-complex **B** forms the Ir(III)-dihydride intermediate **D**. The enamine coordinates to the metal of intermediate **D** in an η^2 fashion to form complex **E**.

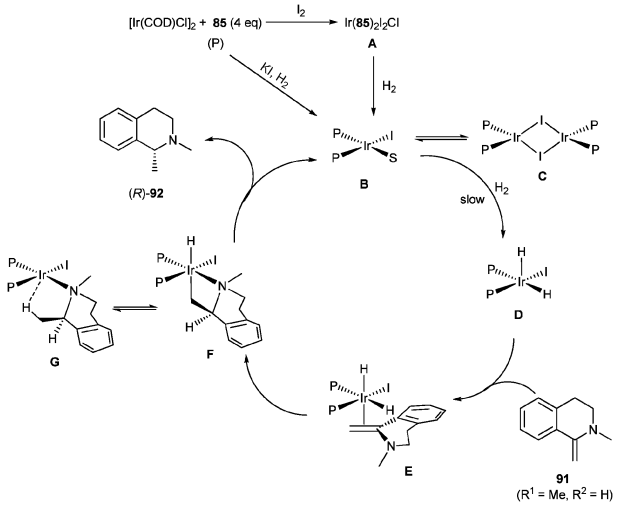


Fig. 4 Possible mechanism of the hydrogenation of *N*,*N*-dialkyl enamines with an Ir-catalyst.

A hydride was transferred from the metal to the unsaturated carbon adjacent to the nitrogen atom, generating alkyl hydride complex **F**. Subsequently, the reductive elimination of alkyl and hydride in complex **F** gives the amine product (**92**, R^1 = Me, R^2 = H) and regenerates Ir(I)-complex **B**.

The oxidative addition of H_2 to Ir(I)-complex **B** is generally recognized as the rate-determining step in the hydrogenation of olefins[66,67] and the inverse isotope effect has also been reported in this step in several examples.[68–70] Furthermore, the reductive elimination step likely involved a C–H/C–D bond-forming/bond-breaking process *via* the C–H···Ir intermediate **G**,[71] explaining the formation of multiple-deuterated products in the deuteration of 2-methyl-1-methylene-1,2,3,4-tetrahydroisoquinoline.

4. Summary and outlook

As can be seen from this short review, transition metal-catalyzed enantioselective hydrogenation of unprotected enamines, which are generally regarded as challenging substrates, has received increasing attention in recent years. Several efficient methods have been demonstrated in the synthesis of optically pure chiral amines not only in laboratory but also in industry. The progress made in this challenging hydrogenation is mainly due to the discovery of new catalysts and catalytic systems having high activity and enantioselectivity. The chiral Ir–Binaphane catalyst shows high enantioselectivities with a TON of as high as 10 000 for the enantioselective hydrogenation of unprotected β-enamine esters. The Rh-^{t}Bu-Josiphos catalyzed enantioselective hydrogenation of unprotected β-enamine amide has been successfully applied in the industrial synthesis of chiral drugs Sitagliptin. The chiral iridium catalysts bearing spiro monodentate phosphoramidite ligand Siphos-pe exhibits excellent enantioselectivity for the hydrogenation of *N*,*N*-dialkyl enamines. However, despite significant progress has been made, there are still many challenges which limit the applications of transition metal-catalyzed hydrogenation of unprotected enamines. Further research focus in this area is expected to be the development of new chiral catalysts or/and catalytic systems with high activity and high enantioselectivity. The substrate scope of the reactions also needs to be expanded to meet the growing demands of a variety of optically pure amines.

Acknowledgements

We thank the National Natural Science Foundation of China, the National Basic Research Program of China (2012CB821600), and the "111" project (B06005) of the Ministry of Education of China for financial support.

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