HETEROCYCLES, Vol. 88, No. 1, 2014, pp. 103 - 127. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 5th June, 2013, Accepted, 8th July, 2013, Published online, 16th July, 2013
DOI: 10.3987/REV-13-SR(S)2

ADDITIVE EFFECTS ON ASYMMETTRIC HYDROGENATION OF *N*-HETEROAROMATICS

Takuto Nagano, Atsuhiro Iimuro, Kenta Yamaji, Yusuke Kita, and Kazushi Mashima*

Department of Materials Engineering Schience, Osaka University, 1-3, Machikaneyama, Toyonaka, Osaka 560-8531, Japan
mashima@chem.es.osaka-u.ac.jp

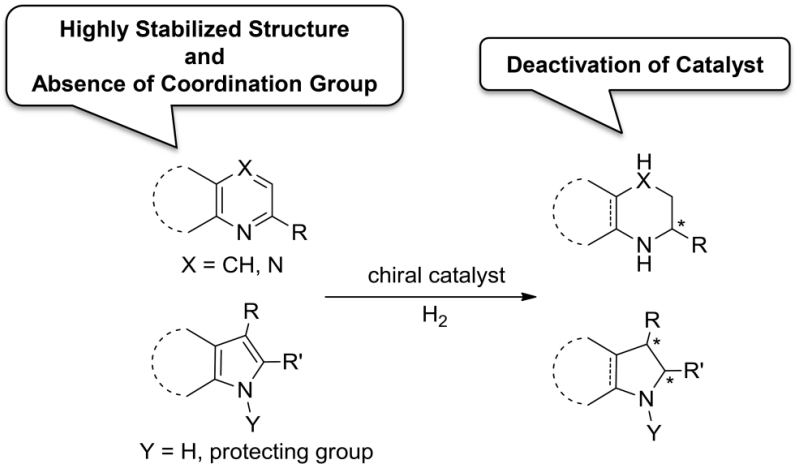
Dedicated to Professor Victor Snieckus on the occasion of his 77th birthday

Abstract – The multiplication of chiral information is one of the most important tasks in organic chemistry. Chiral catalysis is the most elegant way to achieve this and organic chemists developed a variety of catalytic asymmetric reaction systems, in which the addition of some chemicals effectively improves the performance of transition-metal-catalysis. In this review, we summarize development of additive effects in the asymmetric hydrogenation of *N*-heteroaromatic compounds based on interactions of additives with catalysts and substrates.

1. INTRODUCTION

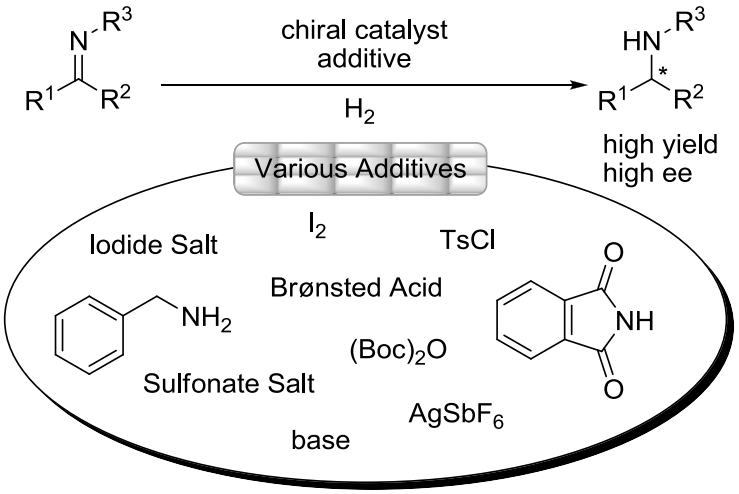
Optically active amines are ubiquitous functional motifs abundant in many biologically active compounds, and efficient synthetic methods are in high demand for pharmaceutical, agricultural, and fine chemical applications. The homogeneous transition-metal-catalyzed asymmetric hydrogenation of *N*-heteroaromatic compounds as well as imines, providing chiral cyclic and acyclic amines, are some of the most straightforward atom-economical synthetic protocols. Although there has been remarkable development of homogeneous asymmetric hydrogenation over the last few decades, e.g., chiral complexes of late-transition-metals, such as rhodium, ruthenium, and iridium are highly effective for the asymmetric hydrogenation of various unsaturated bonds such as C=C (favored by Rh species), C=O (favored by Ru species), and C=N bonds (favored by Ir species),[1] enantioselective reduction of heteroaromatic compounds has been considered a difficult task presumably because: 1) heteroaromatic compounds are highly stable due to their aromaticity, and thus relatively harsh conditions are needed; 2) heteroatoms involved in the aromatic ring, especially the nitrogen atom, have high coordination ability for catalytic active metals to

deactivate or retard the catalytic reaction; and 3) the absence of proximate functional groups that work as directing groups toward a metal center results in low catalytic activity and low enantioselectivity (Scheme 1).[2]



Scheme 1. Disadvantages of asymmetric hydrogenation of *N*-heteroaromatic compounds

The addition of some chemicals improves the catalytic performance. Suitable additives drastically increase not only the catalytic activity but also the enantiomeric excess of chiral products. In fact, catalytic activity and enantioselectivity for asymmetric hydrogenation of imines are effectively enhanced by various additives, such as iodine,[3,4] iodide salts,[5-8] imides,[9] benzylamines,[10,11] sulfonate salts,[12] silver salts,[13] TsCl,[14] $(Boc)_2O$,[15] Brønsted acids[16] or bases[17] (Scheme 2), and some of these additives have been applied to the asymmetric hydrogenation of *N*-heteroaromatic compounds to afford chiral cyclic amine products with high yield and high enantioselectivity. Although the precise functions of these additives are not clear in many cases, some mechanisms have been speculated; e.g., additives act to (1) prevent the aggregation of catalytic active species, (2) accelerate catalytic cycle by exchanging the product by substrate



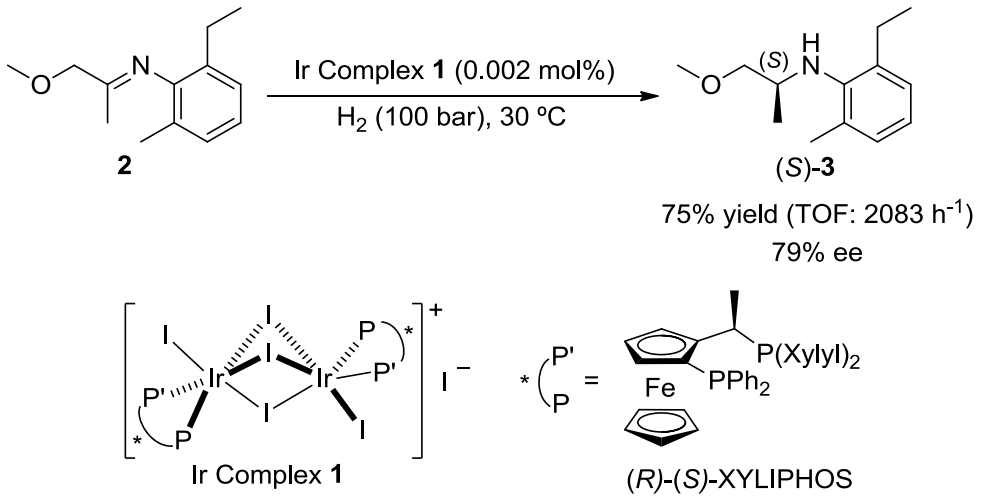
Scheme 2. Various additives used in asymmetric hydrogenation of imines

at the metal center, (3) coordinate to the metal center to make the catalyst more active and selective, (4) tune the electronic properties, and (5) generate catalytic active species by oxidizing catalytic metal precursors.[18] The asymmetric hydrogenation of imines and heteroaromatic compounds was recently reviewed by Kuwano,[19] Kalck,[20] Claver,[21] Zhou,[2] and Yu.[22] In this review, we focus on the recent progress of additive effects in the asymmetric hydrogenation of *N*-heteroaromatic compounds, along with some typical examples of imine hydrogenations based on interactions with catalysts and substrates.

2. ADDITIVE EFFECTS ON CATALYSTS

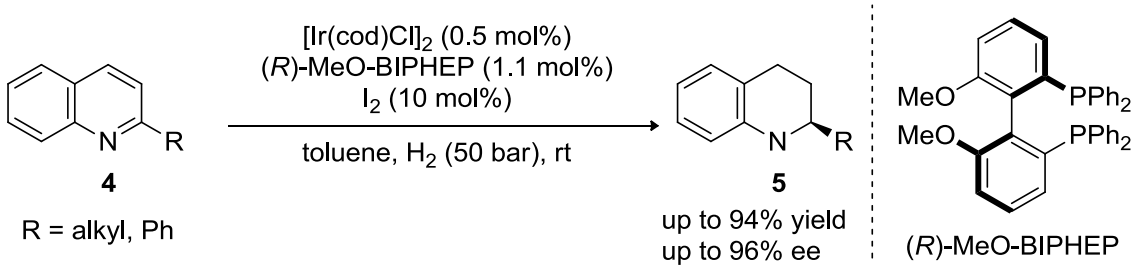
2.1 Halide and Halogen

Halides and halide salts are used as potent additives for promoting the asymmetric hydrogenation of imines. The first positive effects of KI were reported for Rh-catalyzed asymmetric hydrogenation of imines by Markó *et al*. in 1984,[5] and later by Kutney *et al*.[6] The efficiency of adding iodine for iridium-catalyzed asymmetric hydrogenation of imines was first noted by Blaser and Spindler, and the addition of I_2 to an Ir^I precursor in the presence of a chiral diphosphine ligand dramatically improves both the catalytic activity and enantioselectivity.[7] Based on the clear demonstration by Osborn and co-workers that some Ir^{III} complexes bearing iodo ligands and a chelating diphosphine ligand are active catalysts for the asymmetric hydrogenation of imines, it was assumed that iodine is oxidatively added to the Ir^I species to generate a catalytically active Ir^{III} species.[23] More direct evidence was later reported by Togni *et al.*, who prepared an iodine-bridged dinuclear iridium complex **1** with a chelating diphosphine ligand such as Josiphos-derivatives, and used the complex as a catalyst for asymmetric hydrogenation of imines to achieve a high turnover frequency (TOF) (Scheme 3).[3]



Scheme 3. Catalytic activity of an iodine-bridged dinuclear iridium complex **1** bearing (*R*)-(*S*)-Xyliphos

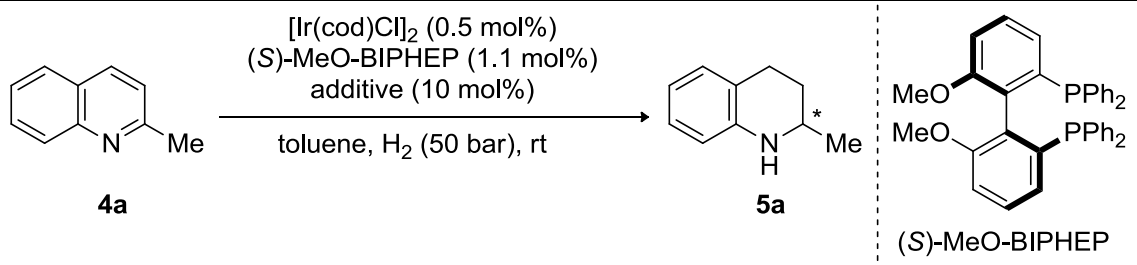
In association with the remarkable effects of iodine for iridium-assisted asymmetric hydrogenation of imines, Zhou *et al.* reported a similar advantageous application of iodine with an Ir^{I}/chiral diphosphine ligand system in the asymmetric hydrogenation of 2-substituted quinolines **4** (Scheme 4).[24] Additive effects of halides were also observed for asymmetric hydrogenation of quinolines,[25-27] quinoxalines,[25,28] and isoquinolines,[29] together with non-asymmetric hydrogenation of quinolines.[30]

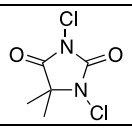
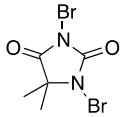


Scheme 4. Asymmetric hydrogenation of 2-substituted quinolines in the presence of iodine

As summarized in Table 1, DBDMH and DCDMH also served as halide sources equal to iodine to give Ir^{III} species that hydrogenated 2-methylquinoline (**4a**) in an enantioselective manner.[31] The same additive was also effective for asymmetric hydrogenation of 3,4-disubsituted isoquinolines.[29]

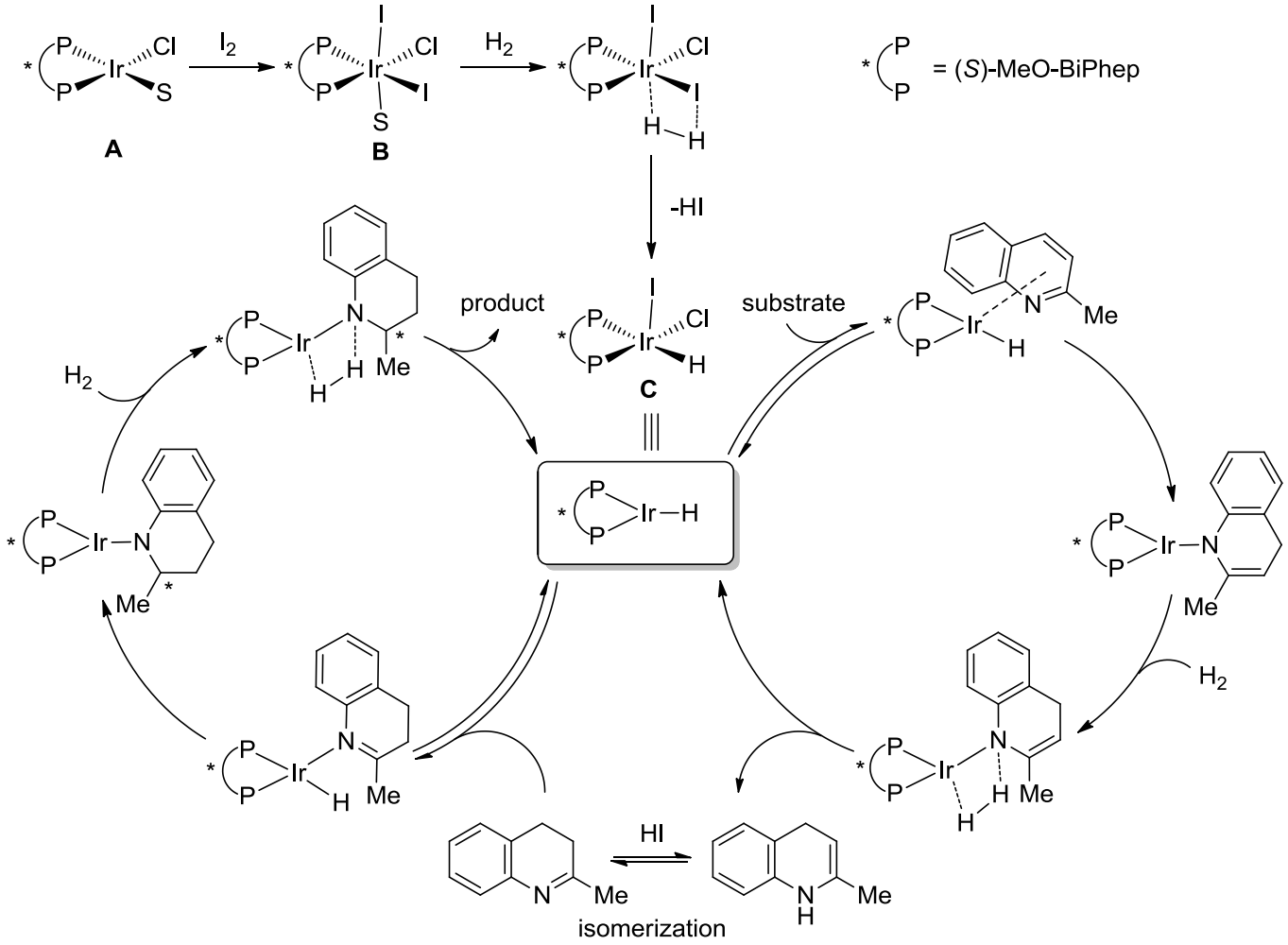
Table 1. Additive effects of various halide sources in Ir-catalyzed asymmetric hydrogenation of 2-methylquinoline



Entry	Additive	Yield (%)[a]	Ee (%)[b]
1	None	<5	–
2	I_2	>95	94
3	 DCDMH	>95	91
4	 DBDMH	>95	92
5	KI	15	2
6	MeI	40	71

[a] Determined by ^{1}H NMR analysis. [b] Determined by HPLC analysis.

Preliminary-prepared Ir^{III} complexes bearing halide ligands were reported to work well without any halide additives for the asymmetric hydrogenation of quinoxalines.[32] Thus, the functions of iodine and the other halide salts were ascribed to its oxidation ability to turn Ir^{I} species **A** to Ir^{III} species **B** as a key step to initiate the reduction of *N*-heteroaromatic compounds (Scheme 5). In the particular case, iodine was assumed to be a source of HI that accelerated the isomerization of 1,4-hydrogenated quinolines to 1,2-hydrogenated quinolines. Interestingly, mechanical studies and theoretical computations suggested that the coexistence of chloride and iodide ligands on a catalytically active complex was necessary for high reactivity and enantioselectivity.

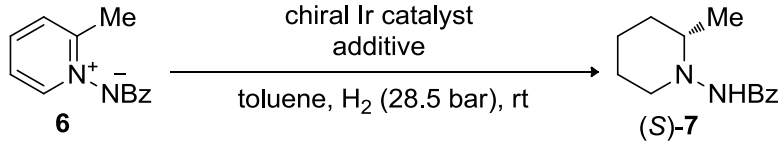


Scheme 5. A proposed mechanism for Ir-catalyzed asymmetric hydrogenation of 2-methylquinoline

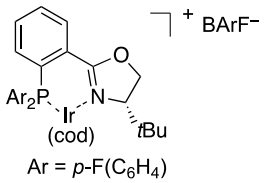
Additive effect of iodine enabled the asymmetric hydrogenation of pyridine derivatives which was identified as difficult substrate for hydrogenation catalyzed by transition metal complex. When an activated-pyridine derivative **6** was hydrogenated by an Ir^{I}/(*S*)-BINAP catalyst in the presence of I_2 or iodide anion (nBu$_4$NI), iodine was a better additive for increasing the catalytic activity (Table 2),[33]

presumably due to the smooth formation of an active Ir^{III} species by oxidizing an Ir^{I} precursor by I_2. High enantioselectivity was observed using iridium complex **8** bearing chiral P,N-ligand. Oxidation of cationic Ir^{I} complex **8** by I_2 afforded a more active and enantioselective catalyst.

Table 2. Additive effects of iodide and iodo anion in asymmetric hydrogenation of activated pyridine derivatives

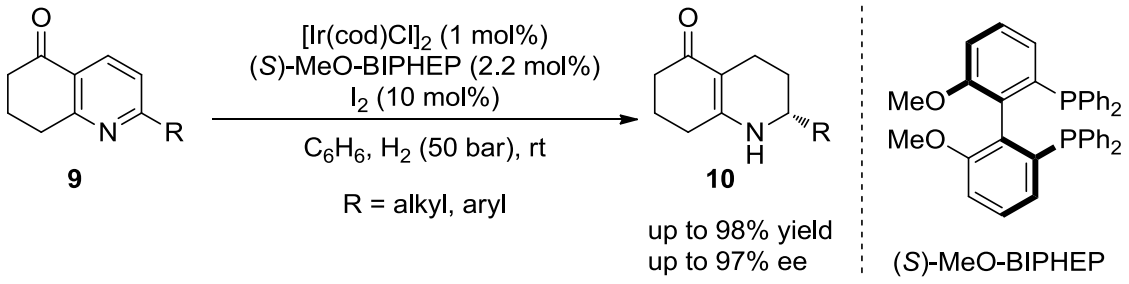


6 (*S*)-**7**

Entry	Chiral Ir Catalyst	Additive	Conversion (%)[a]	Ee (%)[b]
1	[Ir(cod)Cl]$_2$ (1 mol%) + (*S*)-BINAP (2.5 mol%)	None	24	8
2		*n*Bu$_4$NI (5 mol%)	45	8
3		I_2 (2 mol%)	>95	13
4	 Ar = *p*-F(C$_6$H$_4$) **8**	I_2 (2 mol%)	>95	90

[a] Determined by ^{1}H NMR analysis. [b] Determined by HPLC analysis using a chiralpak AD-H.

The addition of iodine to a system of [IrCl(cod)]$_2$ and (*S*)-MeO-BIPHEP was also essentially required to achieve high catalytic activity and enantioselectivity for asymmetric hydrogenation of pyridine derivative **9** to give the corresponding tetrahydrogenated products **10** (Scheme 6).[34] Interestingly, the carbonyl group and C=C double bond, which conjugated with the carbonyl moiety, were kept intact under the reducing conditions.

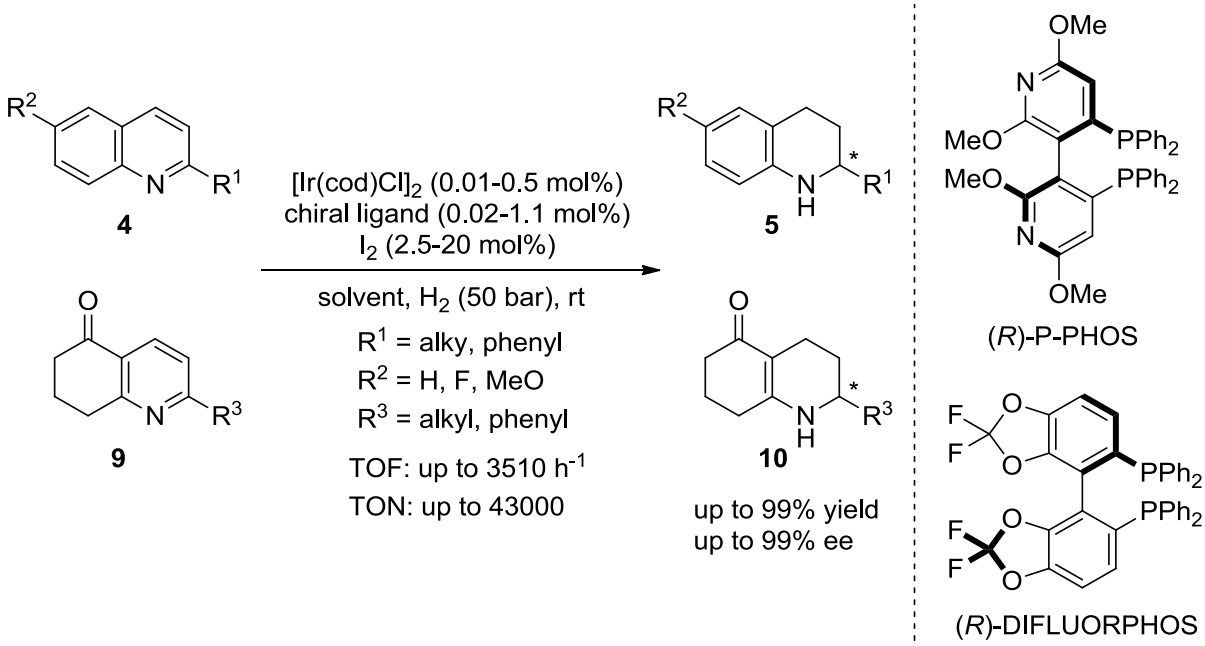


9 **10**

Scheme 6. Asymmetric hydrogenation of pyridine derivatives catalyzed by the Ir/I_2 system

Chan *et al.* reported that the addition of suitable amounts of iodine to Ir^{I}/P-PHOS (or Ir^{I}/DIFLUPRPHOS) increased enantioselectivity and catalytic activity in the hydrogenation of quinolines **4** with high TOF and turnover number (TON).[26,35] This catalytic system was applicable for the reduction of pyridine derivatives

9, 7,8-dihydroquinoline-5(6H)-ones, to afford the corresponding tetrahydrogenated products **10** (Scheme 7). Thus, it was concluded that iodine worked as an oxidant of the Ir(I) precursor to produce the Ir(III) species and partial salt formation of the substrates. The choice of halogen source is important to achieve high efficient and selective catalytic system.



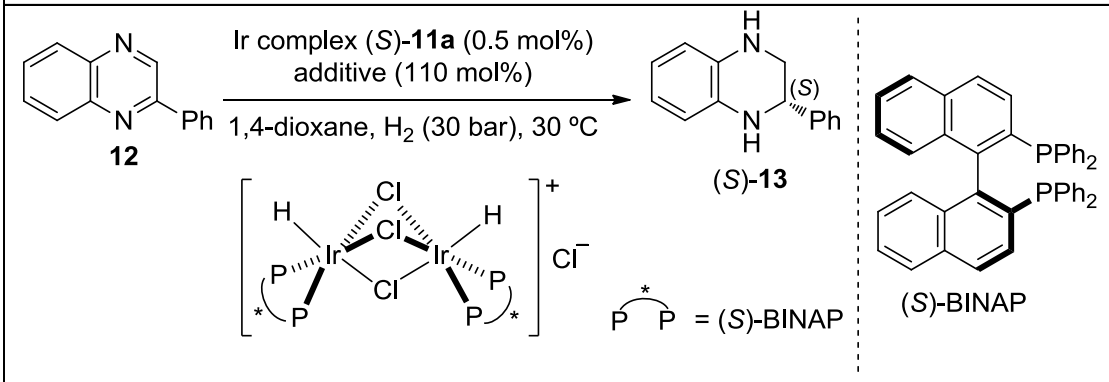
Scheme 7. Catalytic asymmetric hydrogenation of quinolines and pyridine derivatives

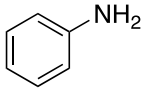
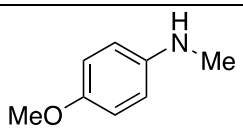
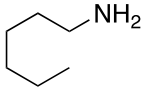
2.2 Amines

The first amine additive effects were reported by Tani and coworkers: the addition of catalytic amounts of primary amines, such as benzylamine, butylamine, and aniline, as well as a secondary amine such as *N*-methylbenzylamine effectively improved catalytic activity for asymmetric hydrogenation of imines catalyzed by a chiral Ir^{I} complex, whereas a tertiary amine *N*,*N*-dimethylbenzylamine was not effective.[10] Quite recently, Mashima, Ohshima, Togni, and co-workers reported the additive effects of aniline derivatives in asymmetric hydrogenation of 2-substituted quinoxalines catalyzed by a halide-bridged chiral iridium dinuclear complex (*S*)-**11a** (Table 3).[36] An electron-rich secondary aniline derivative, *N*-methyl-*p*-methoxyaniline (abbr. MPA) (pK_a = 5.93), was the best additive for enriching both reactivity and enantioselectivity. On the other hand, the addition of large amounts of alkyl amines (pK_a around 10) significantly delayed the reaction because such amines coordinated tightly to the iridium center to suppress catalytic activity. Notably, quinolones **9** could be smoothly reduced because a nitrogen atom of the corresponding product attached to C(sp^2) and kept the pK_a value below 10, while isoquinolines and simpler pyridine substrates could not be readily hydrogenated. Controlled mechanistic studies revealed that the Ir-catalyzed hydrogenation of **12** involved two independent catalytic cycles, where the additional aniline derivative played an important role in converting an initial low active catalytic cycle to the other cycle with

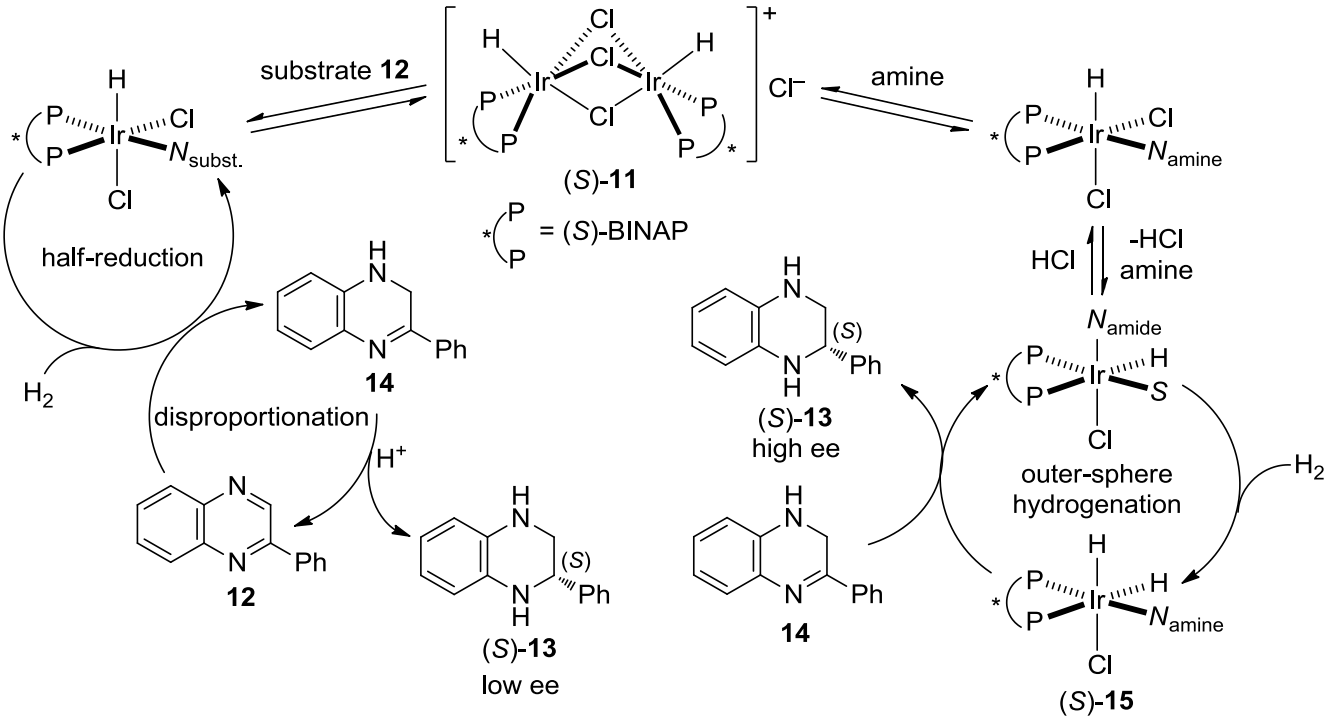
high activity and enantioselectivity (Scheme 8). In the initial cycle, the reduction proceeded to give half-reduced quinoxaline derivative **14** followed by acid-catalyzed disproportionation of dihydroquinoxaline **14** to afford the quinoxaline **12** and the product amine (*S*)-**13** with low enantioselectivity, and hence the aniline derivative served as a Brønsted base to suppress the low enantioselective disproportionation by trapping acidic protons. Zhou *et al*. recently reported a highly enantioselective disproportionation of dihydroquinoxaline to give quinoxaline and chiral tetrahydroquinoxaline that caused by an addition of chiral phosphoric acid.[37,38] In another highly active catalytic cycle, additive amines acted as amine/amide ligands to generate highly reactive and enantioselective Ir^{III} dihydride species (*S*)-**15**, which catalyzed asymmetric hydrogenation via an outer-sphere mechanism.[39] Surprisingly, the chiral product of 2-phenylquinoxaline, which was also a kind of aniline derivative, showed the same additive effects to improve not only the catalytic activity but also the enantioselectivity. Accordingly, the reaction rate and enantioselectivity increased exponentially as the reaction proceeded, demonstrating the first example of positive-feedback enhancement of asymmetric hydrogenation rationalized by the proposed dual mechanism.

Table 3. Additive screening in asymmetric hydrogenation of 2-phenylquinoxaline



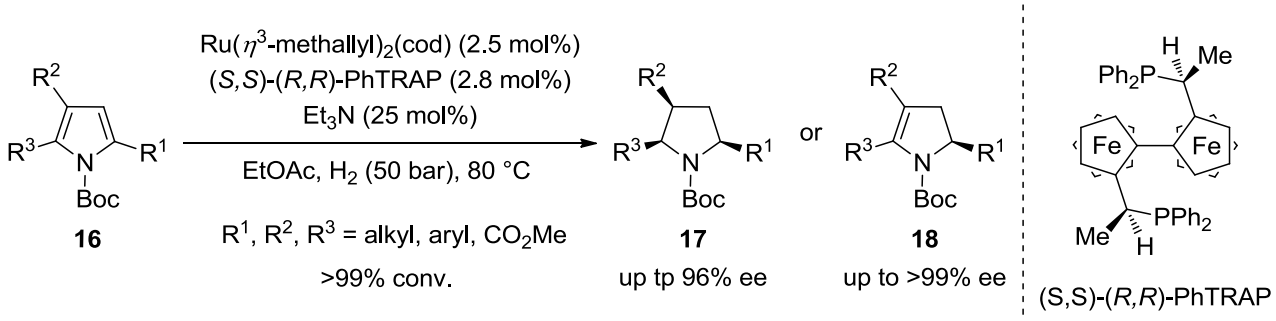
Entry	Additive	Conversion (%)[a]	Ee (%)[b]
1	None	>99	59
2		>99	63
3	 (MPA)	>99	85
4[c]		>99	92
5		No Reaction	–

[a] Determined by ^{1}H NMR analysis of the crude product. [b] Determined by HPLC analysis (Chiralcel OD-H column). [c] In toluene, 100 mol% of MPA was used, H_2 (10 bar).

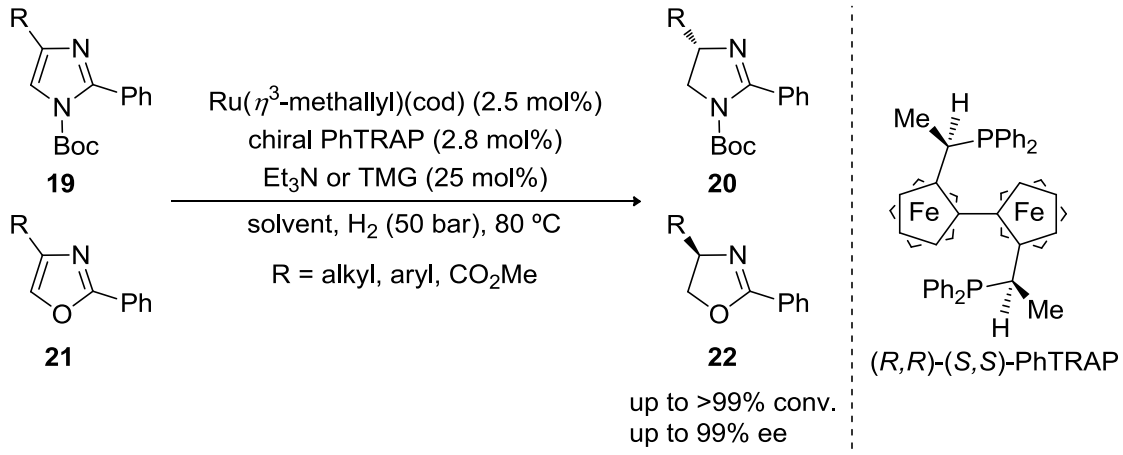


Scheme 8. Proposed dual mechanism for asymmetric hydrogenation of quinoxaline **12** in the presence of aniline derivatives

Tertiary amines act as simple bases to activate a ruthenium complex bearing a chiral trans-chelating diphosphine ligand PhTRAP, by which five-membered *N*-heteroaromatic compounds were successfully hydrogenated to give the corresponding cyclic amines in an enantioselective manner. *N*-Protected substrates, 2,3,5-trisubstituted *N*-Boc-pyrroles **16**, were hydrogenated by a Ru/PhTRAP system activated using Et_3N as a base (Scheme 9).[40] A similar catalytic system using Et_3N and *N*,*N*,*N*,*N*-tetramethyl-guanidine (TMG) efficiently induced the asymmetric hydrogenation of substituted imidazoles **19** and oxazoles **21** giving the corresponding imidazolines **20** and oxazolines **22** with high enantioselectivity (Scheme 10).[41] The function of amine can be classified to two categolies; one is simple base and the other is amine/amide ligand.



Scheme 9. Asymmetric hydrogenation of *N*-Boc pyrroles catalyzed by Ru/PhTRAP

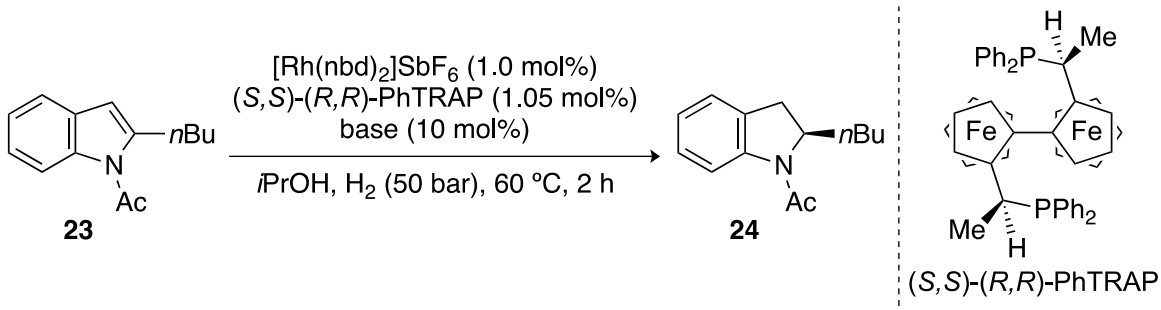


Scheme 10. Asymmetric hydrogenation of *N*-Boc imidazoles and oxazoles catalyzed by Ru/PhTRAP

2.3 Inorganic Base

Inorganic bases are used to generate active metal-hydride species from H_2-coordinated metal complex for asymmetric hydrogenation of simple unsaturated bonds.[42] Kuwano *et al.* used Cs_2CO_3 to activate rhodium and ruthenium complexes of PhTRAP that catalyzed hydrogenations of various five-membered *N*-heteroaromatic compounds. The addition of Cs_2CO_3 was essential for achieving high catalytic reactivity and high enantioselectivity for Rh-catalyzed asymmetric hydrogenation of *N*-acetyl-2-substituted indoles **23** (Table 4).[43] In this reaction, Et_3N also worked as a base as seen in previous section. Similarly, asymmetric hydrogenation of *N*-tosyl-3-substituted indole derivatives **25** was improved by Cs_2CO_3 to give the corresponding chiral indolines **26** (Scheme 11).[44] The use of Cs_2CO_3 to activate a Ru/PhTRAP system

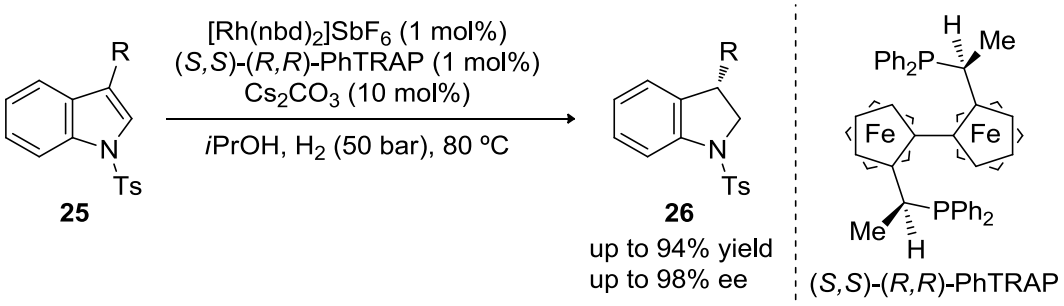
Table 4. Additive effects of inorganic bases together with some organic bases in asymmetric hydrogenation of *N*-acetyl-2-*n*-butylindole



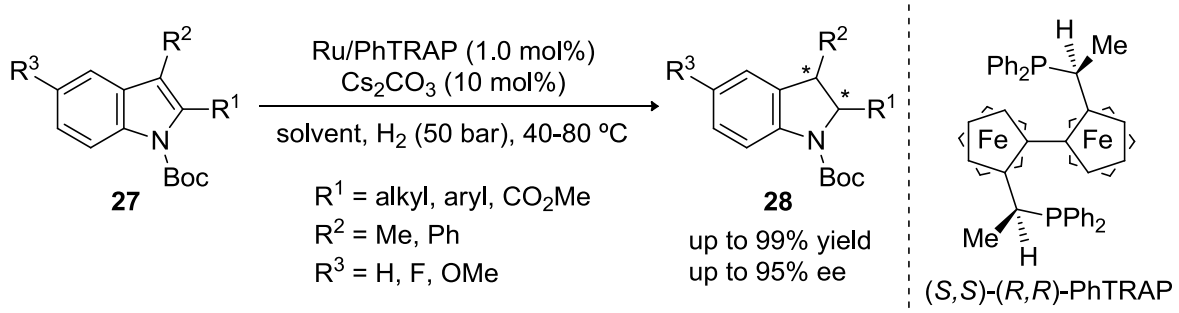
Entry	Base	Conversion (%)[a]	Ee (%)[b]
1	None	trace	7 (*S*)
2	Cs_2CO_3	100	94 (*R*)
3	K_2CO_3	44	76 (*R*)
4	Et_3N	100	94 (*R*)

[a] Determined by ^1H NMR analysis of the crude product. [b] Determined by HPLC analysis with Chiralpak AD.

led to the proficient hydrogenation of 2-substituted or 3-substituted *N*-Boc-protected indole derivatives **27** to give the corresponding indolines **28** (Scheme 12).[45]

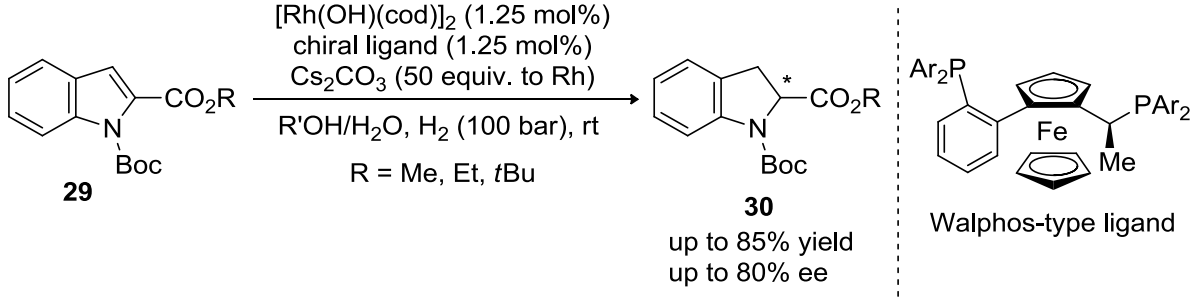


Scheme 11. Asymmetric hydrogenation of *N*-tosyl indole catalyzed by Rh/PhTRAP



Scheme 12. Asymmetric hydrogenation of *N*-Boc indole catalyzed by Ru/PhTRAP

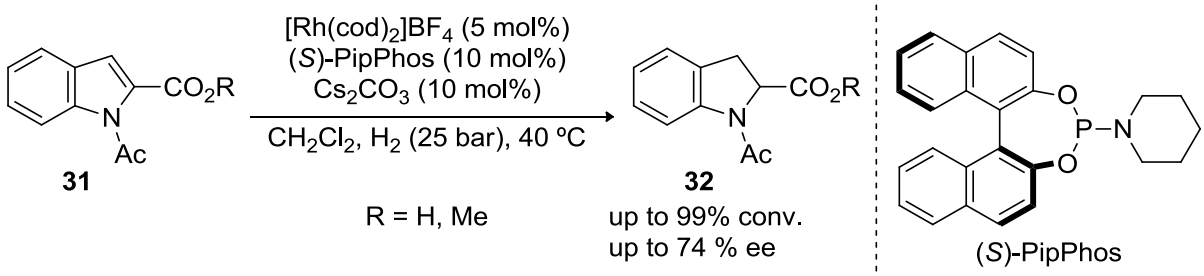
Agbossou-Niedercorn *et al.* hydrogenated *N*-Boc indole derivatives **29** using a Rh/Walphos system in the presence of Cs_2CO_3 (Scheme 13).[46] The addition of Cs_2CO_3, however, caused unwanted side reactions, such as alcoholysis of Boc-protection and transesterification of the substituent, though the side reactions were diminished by optimizing the reaction conditions.



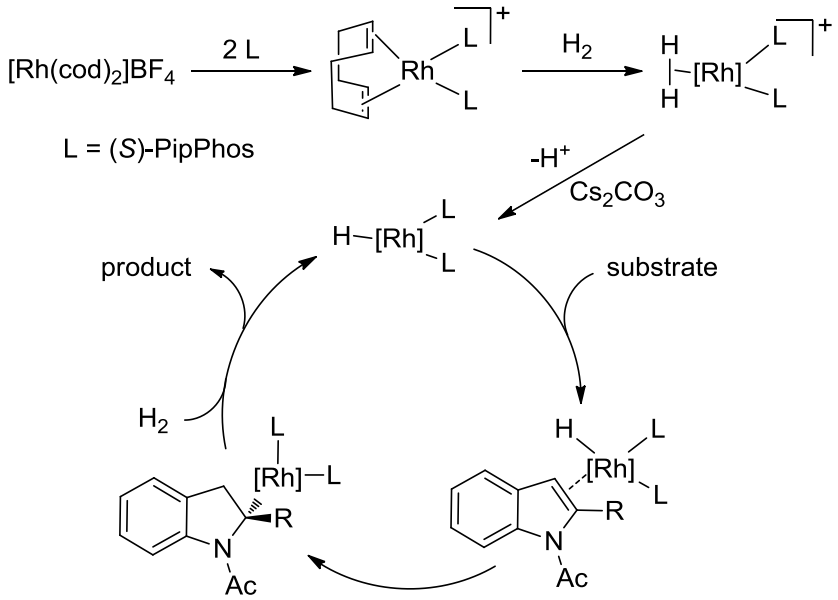
Scheme 13. Asymmetric hydrogenation of *N*-Boc indoles catalyzed by Rh/Walphos

Feringa and de Vries pointed out the competence of additive bases such as Cs_2CO_3, CsF, and KOAc, as well as Et_3N, for asymmetric hydrogenation of *N*-protected indoles **31** catalyzed by a rhodium complex bearing

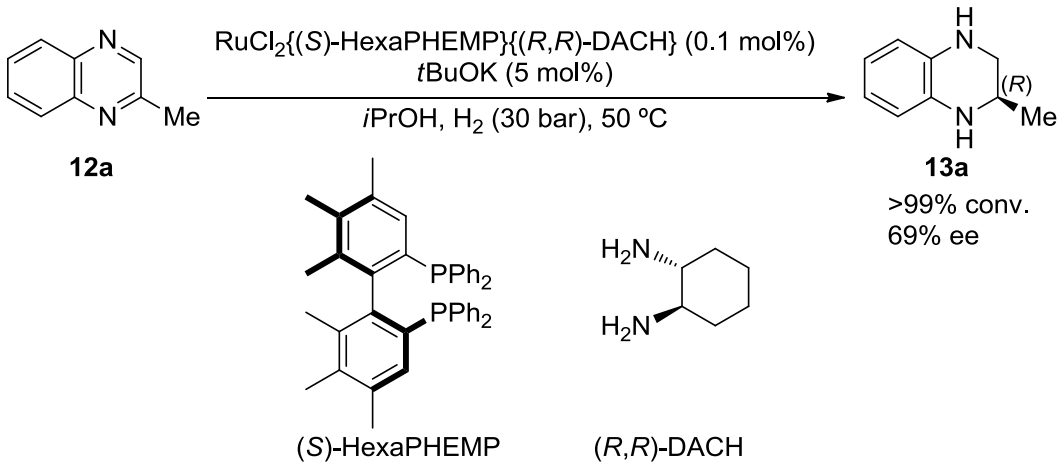
monodentate phosphoramidite ligand (*S*)-PipPhos (Scheme 14).[47] *N*-Boc-protection was not sufficient to gain high enantioselectivity in this system. The role of the base was proposed to trap a proton from a cationic



Scheme 14. Asymmetric hydrogenation of *N*-protected indoles



Scheme 15. Proposed mechanism of asymmetric hydrogenation of *N*-protected indoles



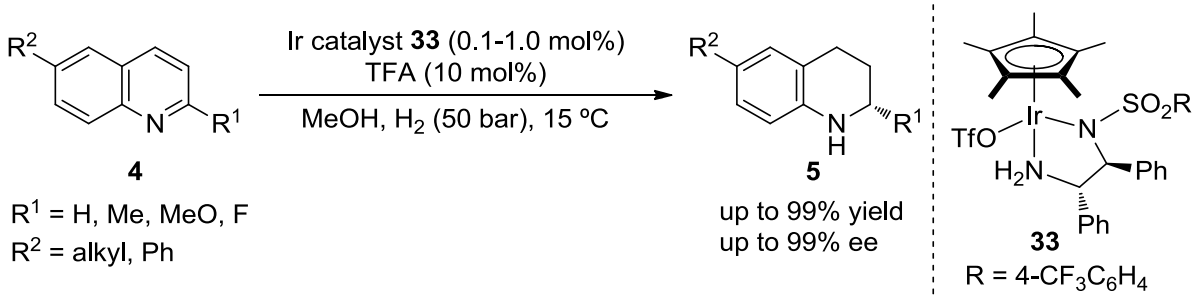
Scheme 16. Asymmetric hydrogenation of 2-methylquinoxaline **12a** catalyzed by a Ru/diphosphine/diamine system

Rh—(η^2-H_2) species and generate an active Rh-hydride species (Scheme 15). Overall, all five-membered *N*-heteroaromatic substrates required a suitable protecting group, which was assumed to act as a directing group, at the nitrogen atom to achieve high reactivity and high enantioselectivity. Henschke *et al*. reported that the asymmetric hydrogenation of quinoxalines was catalyzed in high yield and moderate enantioselectivity by $RuCl_2$(HexaPHEMP)(diamine) complexes upon activation by *t*BuOK (Scheme 16),[48] which was originally developed by Noyori *et al.*[49]

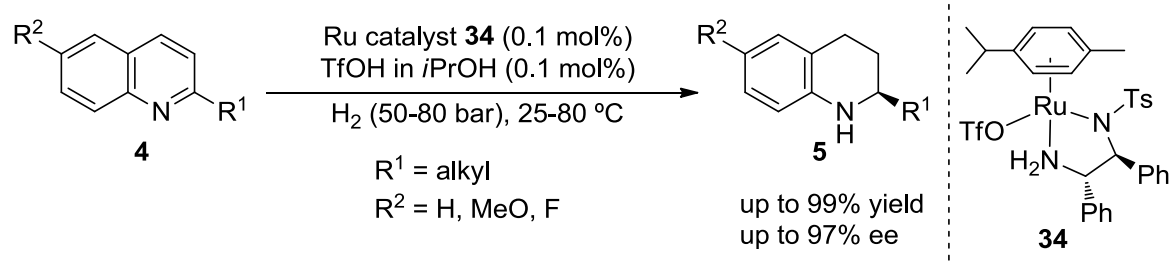
3. Additive Effects on Substrates

3.1 Brønsted acid

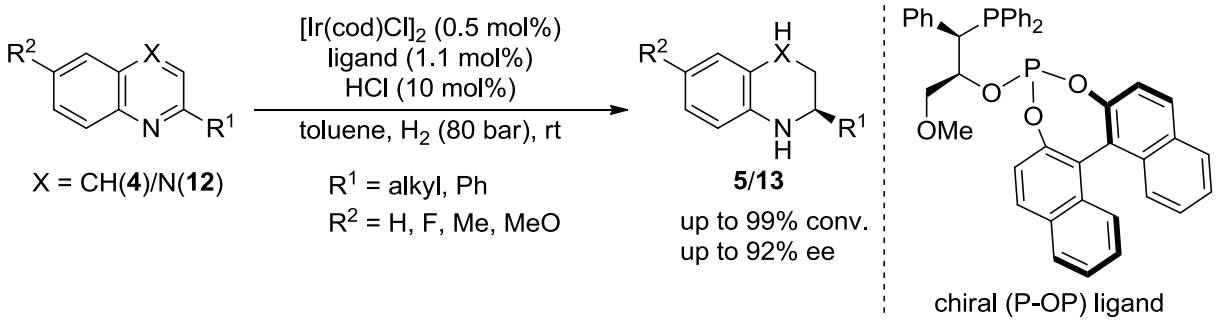
Some Brønsted acids interact directly with *N*-heteroaromatic compounds to reduce or break their aromaticity.[22] Enantioselective hydrogenation of 2-substituted quinolines was catalyzed by a modified Noyori-type half-metallocene complex **33** of iridium (Scheme 17), in which the addition of 10 mol% of trifluoroacetic acid (TFA) increased both the reaction rate and enantioselectivity.[50] Similar additive effects of Brønsted acid were reported by Fan and co-workers, who used a small amount of TfOH (0.1 mol%) to achieve high enantioselectivity in the asymmetric hydrogenation of quinolines catalyzed by a modified Noyori-type Ru complex **34** (Scheme 18).[51] The addition of HCl (10 mol%) to a mixture of $[IrCl(cod)]_2$ and a chiral P-OP ligand became an efficient catalyst for the asymmetric hydrogenation of quinolines and



Scheme 17. Asymmetric hydrogenation of quinolines by an iridium/diamine complex

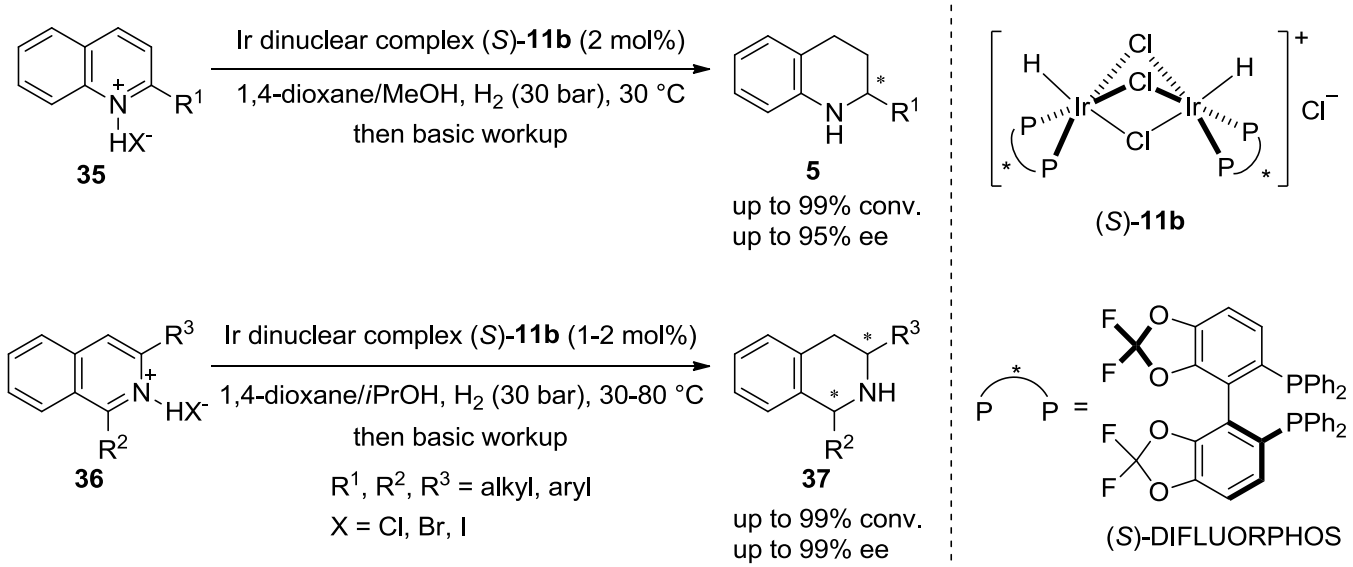


Scheme 18. Additive effects of TsOH in asymmetric hydrogenation of quinolines by a ruthenium/diamine complex



Scheme 19. Additive effects of HCl in Ir-catalyzed asymmetric hydrogenation of *N*-heteroaromatic compounds

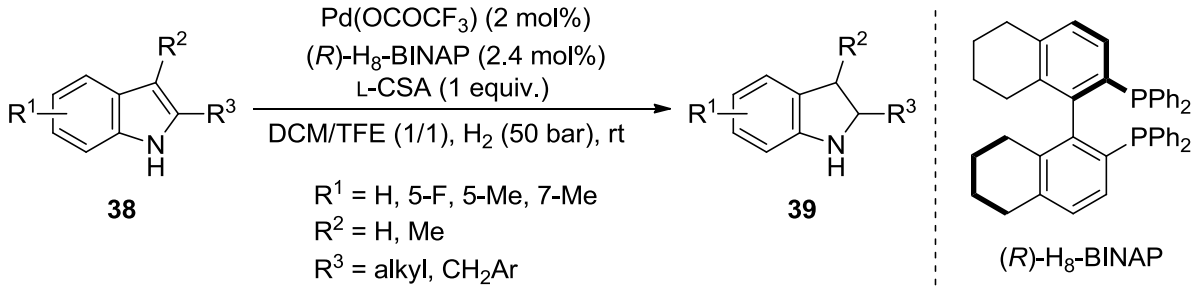
quinoxalines (Scheme 19).[52] Additives such as iodine sources and other Brønsted acids did not produce any notable improvement in this case. Mashima *et al.* reported asymmetric hydrogenation of 2-substituted quinolinium HX (X = Cl, Br, I) salts **35** and 1- or 3-substituted isoquinolinium HX salts **36** by chiral iridium dinuclear complex (*S*)-**11b** (Scheme 20).[53] The use of salts of the substrate afforded better enantioselectivity than the corresponding neutral substrates. It was noteworthy that the chloro- and bromo-iridium complexes had higher catalytic activity than an iodo-iridium complex, in contrast to the general tendency of the halide effects, iodide anion being better than others.



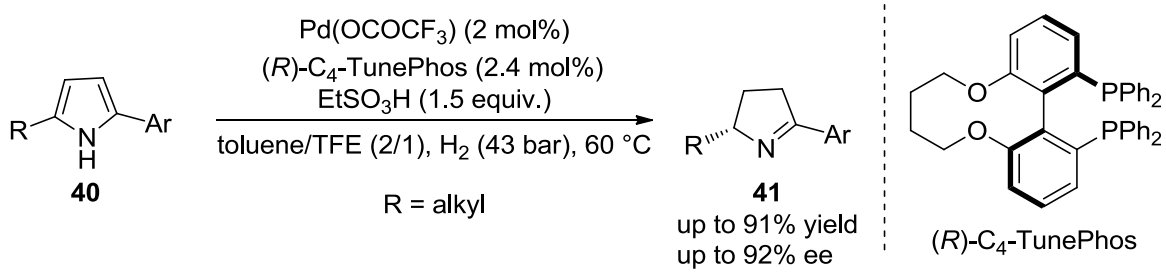
Scheme 20. Asymmetric hydrogenation of HX salts of quinolines and isoquinolines by iridium dinuclear complexes

The formation of iminium salts caused by the Brønsted acid was essential to activate *N*-unprotected 5-membered *N*-heteroaromatic substrates, for which $Pd(OCOCF_3)_2$/chiral phosphine became a catalyst. Asymmetric hydrogenation of *N*-unprotected indoles **38** by a palladium catalyst in the presence of one equivalent of chiral Brønsted acid (L-camphorsulfonic acid; L-CSA), which has matched chirality with

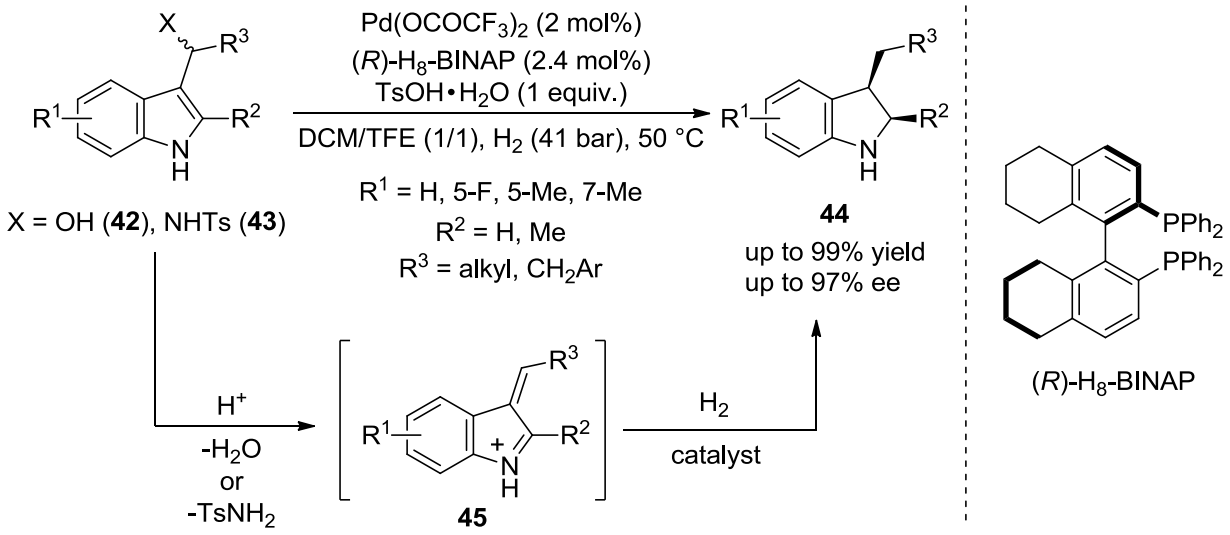
chiral diphosphine ligand, was reported by Zhou *et al.* (Scheme 21).[54] Protonation of the C=C bond destroyed the aromaticity of indoles, leading to hydrogenation. Achiral sulfonic acid, $EtSO_3H$, also worked



Scheme 21. Asymmetric hydrogenation of unprotected indoles



Scheme 22. Asymmetric hydrogenation of unprotected pyrroles

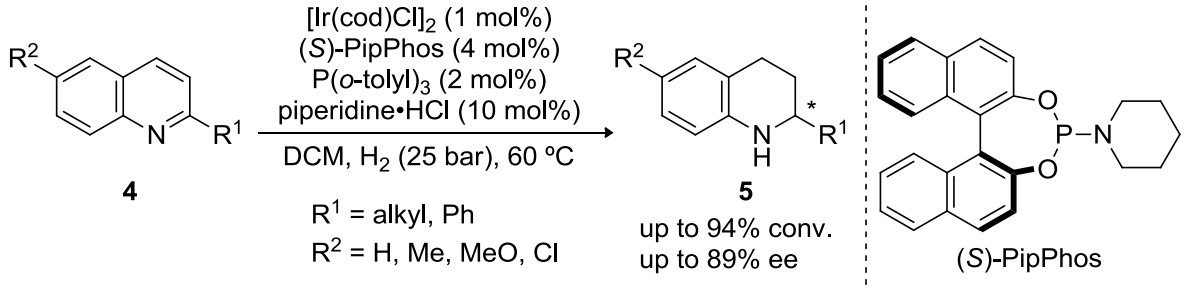


Scheme 23. Dehydration or deamidation triggered asymmetric hydrogenation of indole derivatives catalyzed by $Pd(OCOCF_3)_2$

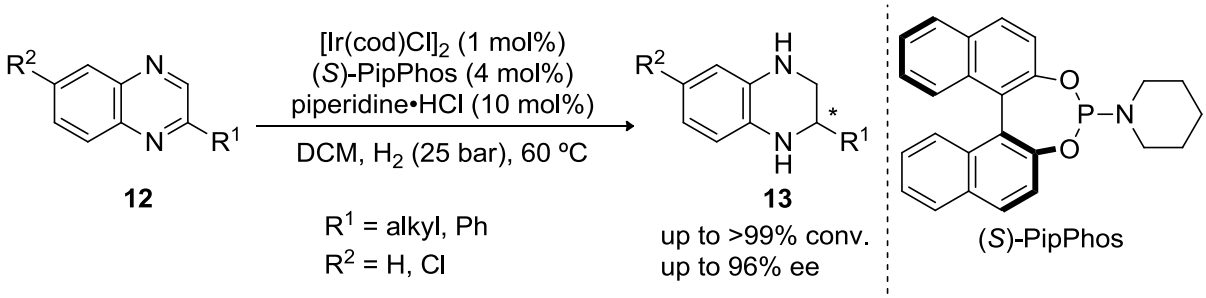
well for asymmetric hydrogenation of 2,5-disubstituted pyrroles **40** to give the corresponding chiral pyrrolines **41** (Scheme 22).[55] Pyrroles were first protonated by a Brønsted acid to form the corresponding iminium salts, which were hydrogenated to give enamines followed by isomerization to cyclic imines. For special substrates, 3-(α-hydroxyalkyl)indoles **42**, and 3-(α-aminoalkyl)indoles **43**, the first step was

acid-catalyzed dehydration or deamidation, which provided vinylogous iminium intermediate **45** prior to be hydrogenated by Pd complex (Scheme 23).[56]

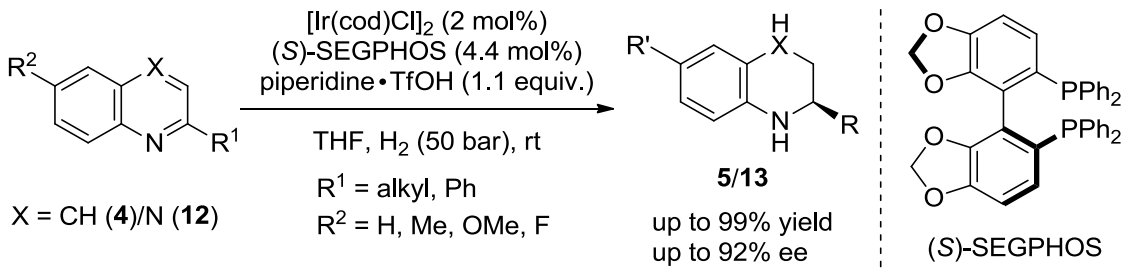
The addition of a Brønsted acid produced clear additive effects; the HCl salt of piperidine became an activator. Feringa *et al.* reported asymmetric hydrogenation of quinolines catalyzed by an Ir^{I} complex with chiral monodentate phosphine in the presence of the HCl salt of piperidine (Scheme 24),[57] and asymmetric hydrogenation of quinoxalines was also efficiently achieved by using the same HCl salt of piperidine (Scheme 25).[58] Zhou *et al*. reported similar positive effects of the TfOH salt of piperidine for the iridium-catalyzed asymmetric hydrogenation of quinolines (Scheme 26).[59]



Scheme 24. Asymmetric hydrogenation of quinolines catalyzed by Ir/PipPhos/tri-ortho-tolylphosphine/piperidine hydrochloride salt system



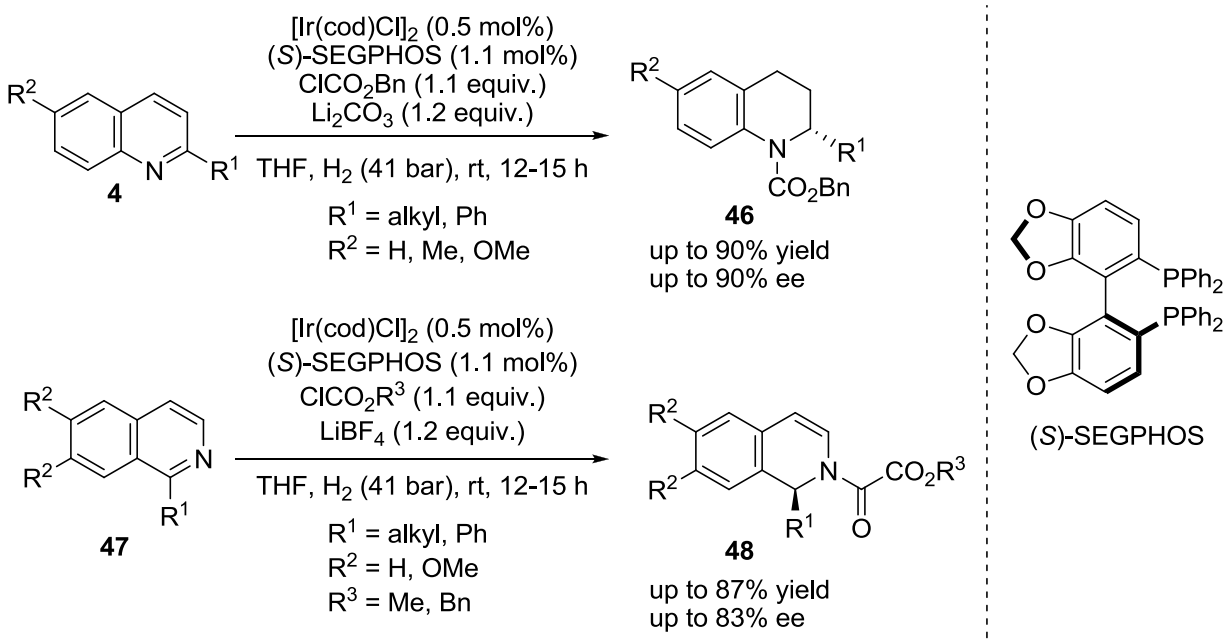
Scheme 25. Asymmetric hydrogenation of quinoxaline catalyzed by Ir/PipPhos/piperidine hydrochloride salt system



Scheme 26. Additive effect of TfOH salt of piperidine for asymmetric hydrogenation of quinolines and quinoxalines

3.2 Protecting reagents

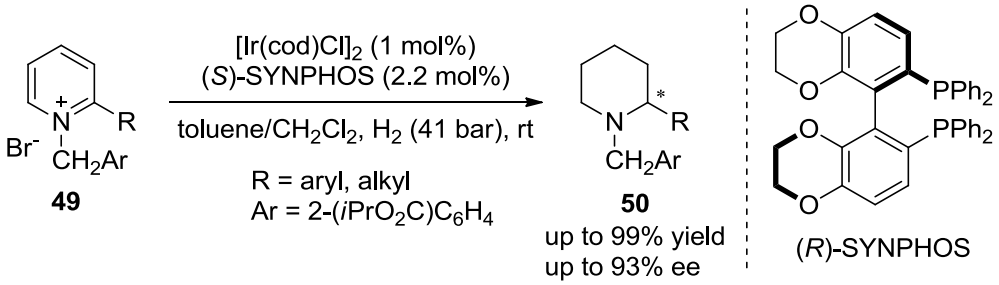
Introduction of a protecting group at the nitrogen atom is an effective method for the metal-catalyzed reduction of C=N bonds due to the activation of substrates by electronic tuning and the prevention of catalyst poisoning and retarding by coordination of products although deprotection under harsh conditions was required to obtain free cyclic amines. Asymmetric hydrogenation of *N*-heteroaromatic compounds such as quinolines and isoquinolines was successfully performed using chloroformates (Scheme 27).[60]



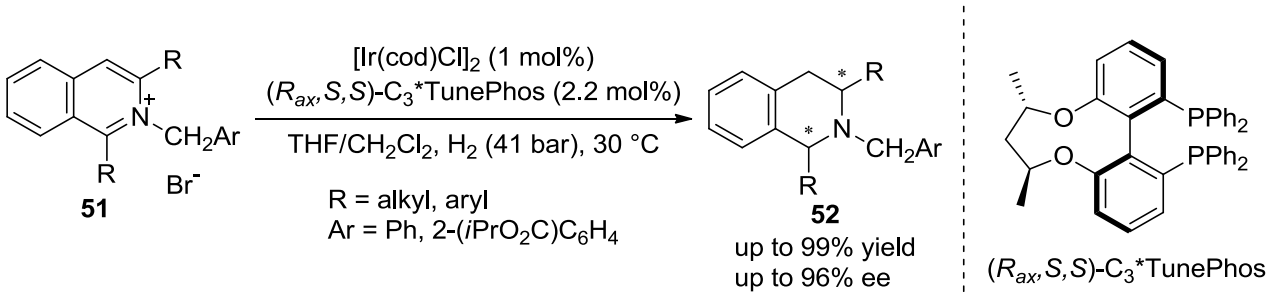
Scheme 27. Activation of *N*-heteroaromatic compounds using chloroformates

Asymmetric hydrogenation in the presence of equimolar amounts of chloroformates and one equivalent of base gave the corresponding formates, which were hydrogenated to give the corresponding *N*-protected tetrahydroquinolines **46** and *N*-protected 1,2-dihydroisoquinolines **48** with high enantioselectivity. The protecting reagents are assumed to avoid poisoning of the catalyst by reducing coordination ability and to facilitate the control of enantioselectivity by the coordination of the attached CO_2R group.

Recently, Zhou *et al.* demonstrated that asymmetric hydrogenation of *N*-benzyl-pyridinium salts **49** afforded the corresponding chiral *N*-benzylated piperidines **50** using the Ir/SYNPHOS system as the catalyst (Scheme 28).[61] Similar benzylation strategy could be applied to asymmetric hydrogenation of 1- or 3-substituted isoquinolinium salts **51** using Ir/TunePhos system (Scheme 29).[62] The counter anion of the substrate and the bulky substituent on the nitrogen atom played critical roles for achieving high reactivity and enantioselectivity; a bromide anion and a bulky and coordinating substituent were found to be optimal. Similarly, hydrogenation of activated *N*-iminopyridinium ylides smoothly proceeded to give the corresponding piperidine derivatives (Table 2) (*vide supra*).



Scheme 28. Asymmetric hydrogenation of *N*-benzylpyridinium salts



Scheme 29. Asymmetric hydrogenation of *N*-benzylisoquinolinium salts

4. Outlook

Hydrogenation of *N*-heteroaromatic compounds using transition metals has been considered difficult due to the aromatic conjugation of these substrates. In the last decade, however, some additives have been developed that dramatically improve the catalytic performance of iridium complexes, as well as rhodium, ruthenium, and palladium complexes, and the effects of these additives are classified as catalyst activators or substrate activators.

The most important function of catalyst activators such as halides, amines and inorganic bases, is to assist the generation of catalytically active species. Halide additives generate catalytically active Ir^{III} species bearing halide ligands, and the choice of halide ligands on the active species is a critical factor for high reactivity and high enantioselectivity. Some amines act as ligands of catalytically active species that hydrogenate unsaturated bonds via outer-sphere mechanism. Organic and inorganic bases assist the generation of highly active species to improve catalytic activity and selectivity.

The function of substrate activators is to reduce or break the aromaticity of substrate. Six-membered *N*-heteroaromatic compounds are efficiently activated by the formation of the Brønsted acid salts as well as the introduction of protecting groups on the nitrogen atom of substrates. In the case of five-membered *N*-heterocyclic compounds, substrates are protonated to be cyclic iminium cations, which are easier to be hydrogenated than aromatic form. Some of protecting groups have an extra function as directing groups or bulky substituents to increase reactivity and enantioselectivity.

In the hydrogenation of *N*-heteroaromatic compounds, substrates and product amines were regarded as catalytic poisons to decrease catalytic activity and enantioselectivity. A recent report for Ir-catalyzed asymmetric hydrogenations of quinoxalines in the presence of amines clearly demonstrated that the pK_a value of the coexisting amines was a sensitive factor for determining whether or not *N*-heteroaromatic compounds could be efficiently hydrogenated. In other words, generated chiral cyclic amines are not always harmful to the catalytic active species; some catalysts are tolerant for the coexistence of amino group, or chiral amines can even be activators in specific case. Thus, asymmetric hydrogenation of unprotected *N*-heteroaromatics may be achieved by using robust and well-designed catalysts. The previously reported combinations of substrates and catalytic system were limited to specific patterns (e.g. iridium and halide, or ruthenium/rhodium and base). Therefore, investigation of various combinations of metal and additive would be valuable for exploration of more reactive, selective and unique asymmetric hydrogenations. Furthermore, although such reported additive effects were remarkable in the hydrogenation of stable *N*-heteroaromatic compounds, more detailed mechanistic investigations are required to gain more insight and systematic understandings for designing practical catalyst systems. We hope this perspective review contributes to the outlook of the attractive research field of additives.

ACKNOWLEDGEMENTS

We appreciate for the financial support by The Core Research for Evolutional Science and Technology (CREST), program of the Japan Science and Technology Agency (JST), and a Grant-in-Aid for Scientific Research on Innovative Areas, "Molecular Activation Directed toward Straightforward Synthesis", from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan. T.N. and A.I. thank a JSPS Reseach Fellowship.

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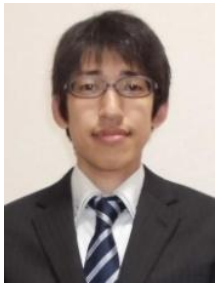
Takuto Nagano was born in Kyoto, Japan in 1985. He completed his B.Eng. in 2008 and M.Eng. in 2010 at Graduate School of Engineering Science, Osaka University and received his Ph.D. in 2013 from Osaka University under the supervision of Professor Kazushi Mashima.

Atsuhiro Iimuro was born in Osaka, Japan in 1987. He was received his B.Eng. (2011) and M.Eng. (2013) degrees from Osaka University. Currently, he is working on his Ph.D. thesis under the direction of Professor Kazushi Mashima. Since April 2013, he has also been a Research Fellow of the Japan Society for the Promotion of Science (JSPS). His research fields are organic synthesis and organometallic chemistry.

Kenta Yamaji was born in1989 and received his B.Eng. in 2012 from Osaka University under the direction of Professor Kazushi Mashima. His research focuses on asymmetric hydrogenation of *N*-heteroaromatic compounds. Currently, he is working on his M.S. thesis about its mechanistic study.



Yusuke Kita is an Assistant Professor at Graduate School of Engineering Science, Osaka University. He graduated from Osaka University in 2006. He received his Ph.D. degree in 2010 from Osaka University under the direction of Professor Naoto Chatani. He started his academic career as an Assistant Professor at Graduate School of Engineering Science, Osaka University, working with Professor Kazushi Mashima. He received DIC Award in Synthetic Organic Chemistry, Japan in 2012. His research program focuses on the development of new methods of organic synthesis.

Kazushi Mashima received his Doctor degree (1986) from Osaka University under the surpervision of Professor A. Nakamura. He became an Assistant Professor at Institute for Molecular Science, Okazaki National Institutes in 1983. He moved to Faculty of Engineering, Kyoto University as an Assistant Professor in1989, and then to Faculty of Science, Osaka University in 1991. He was promoted to an Associate Professor at Faculty of Engineering Science, Osaka University in 1994, and then to a full Professor at Graduate School of Engineering Science, Osaka University in 2003. He worked with Professor M. A. Bennett, Australia National University in 1992 and Professor W. A. Hermann, Technisch Universität München in 1993. He received Progress Award in Synthetic Organic Chemistry, Japan in 1994, BCSJ Award in 2000, The Chemical Society of Japan Award for Creative Work for 2008, The 9th Green and Sustainable Chemistry Award in 2010, and the Award of the Society of Polymer Science, Japan in 2010.