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CATALYTIC ASYMMETRIC HYDROGENATION OF 5-MEMBERED HETEROAROMATICS

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Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday

Abstract – Catalytic asymmetric hydrogenation of heteroaromatics had been a formidable issue in organic synthesis. However, the catalytic asymmetric hydrogenation has remarkably progressed during the past decade. This review surveys the recent progress of the asymmetric hydrogenation of 5-membered heteroaromatics, indoles, pyrroles, furans, and benzofurans.

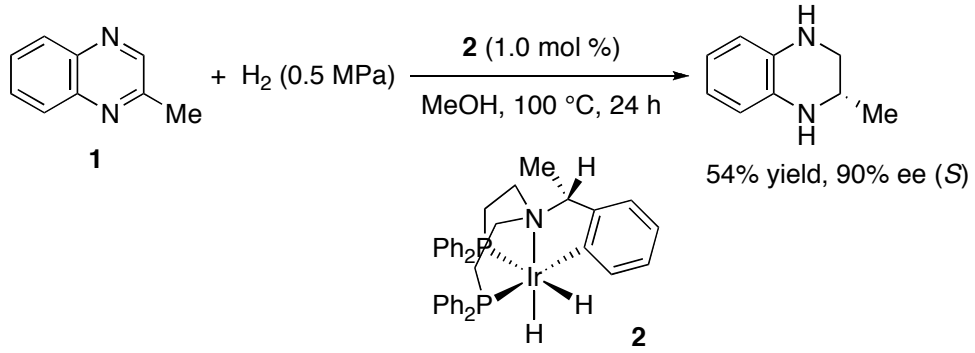
1. INTRODUCTION

Catalytic enantioselective hydrogenation of double bonds, such as olefins, ketones, and imines, is one of well-established asymmetric reactions.[1] Nowadays, the asymmetric hydrogenation is regarded as a powerful method for preparing optically active compounds. Many chiral compounds have been synthesized through the catalytic asymmetric hydrogenation in manufacturing production as well as in lab scale. Meanwhile, enantioselective hydrogenation of heteroaromatics will offer a straightforward approach to a wide range of optically active heterocycles; furthermore, multiple chiral centers can be created through the asymmetric reaction when unsymmetrical multi-substituted heteroaromatics are employed as starting materials.[2] Nevertheless, the asymmetric catalysis for the stereoselective reduction of heteroaromatics had been unexplored until recently.

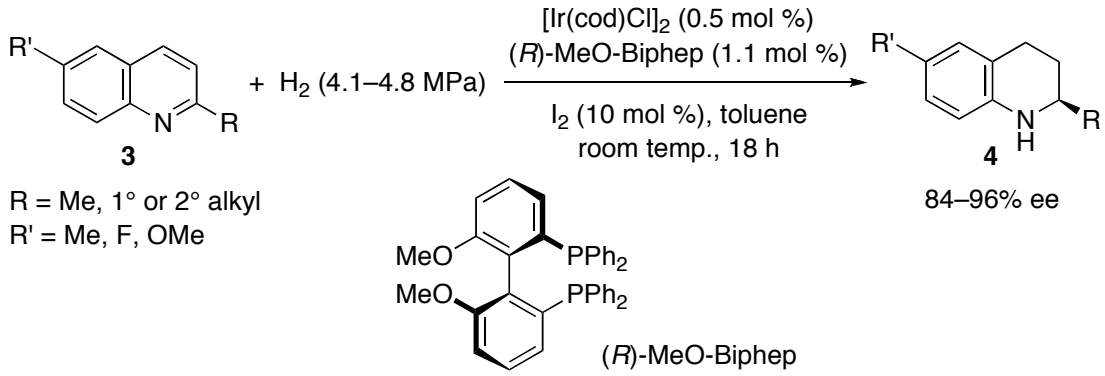
Hydrogenation of heteroaromatics has traditionally been conducted by using a heterogeneous catalyst.[3] The catalytic process has been employed for preparing achiral or racemic heterocycles, and carried out with no consideration to stereoselectivity in most cases. The heterogeneous catalyst is not easy to be precisely decorated with a chiral organic molecule in order to prepare an enantioselective catalyst.[4] Consequently, realization of the asymmetric hydrogenation of heteroaromatics had required the discover

of metal complex possible to be ornamented with a chiral ligand as well as exhibiting good or moderate catalytic activity. Some transition metal complexes were known to be useful as catalysts for the reduction of heteroaromatics,[5–7] but they are unsuitable for asymmetric catalysis because of their limited scope and difficulty in modification with a chiral ligand. Moreover, the hydrogenation of heteroaromatics is accompanied by loss of aromatic stabilization.[8] The resulting diminution of the resonance energy had remained the asymmetric hydrogenation a formidable issue in organic synthesis.

The first example of highly enantioselective hydrogenation of heteroaromatics was reported by Bianchini and co-workers in 1998.[9] They successfully achieved 90% ee for the catalytic hydrogenation of 2-methylquinoxaline (**1**) by using a chiral iridium complex **2**, while no other quinoxalines were examined for the iridium-catalyzed asymmetric reduction (Scheme 1). Five years later, high enantioselectivity was attained for the hydrogenation of 2-alkylquinolines **3** by Zhou *et al.* (Scheme 2).[10] Since then, many

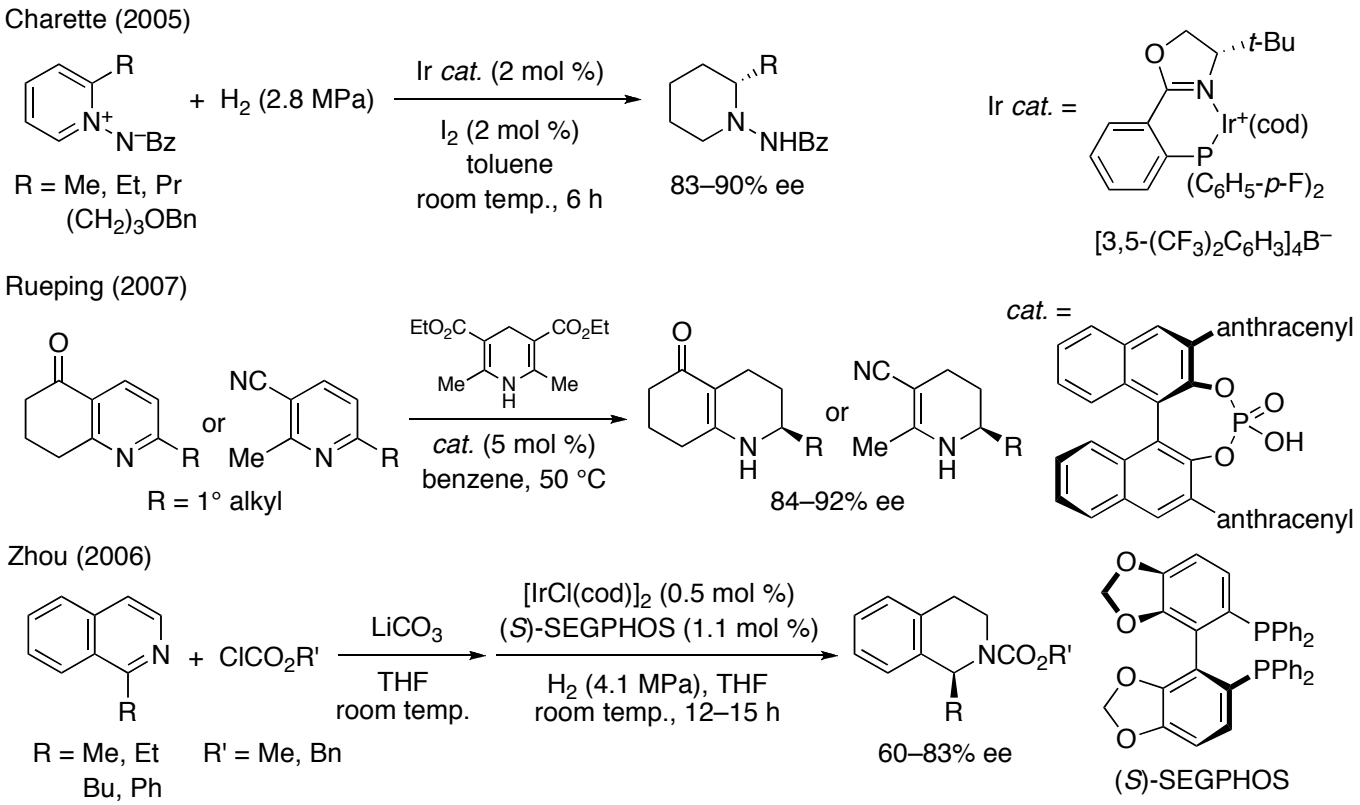


Scheme 1. Catalytic asymmetric hydrogenation of 2-methylquinoxaline (**1**) by Bianchini



Scheme 2. Catalytic asymmetric hydrogenation of 2-alkylated quinolines **3** by Zhou

researchers devoted their efforts toward developing the asymmetric hydrogenation of 6-membered nitrogen-containing heteroaromatics, especially 2-substituted quinolines. Many chiral catalysts,[11–14] including organocatalysis,[15] are known to transform **3** into the chiral 1,2,3,4-tetrahydroquinolines **4** with high enantioselectivity. Pyridines[16–18] and 1-substituted isoquinolines[12] have successfully been hydrogenated in over 80% ee with asymmetric catalysis (Scheme 3).



Scheme 3. Catalytic asymmetric hydrogenations of nitrogen containing heteroaromatics other than **3**

In contrast to 6-membered heterocycles, only a few research groups have disclosed successful examples of the asymmetric reduction of 5-membered heteroaromatics since we first reported the enantioselective hydrogenation of 2-substituted indoles in 2000. To date, limited indoles, furans, and pyrroles have been transformed into the corresponding chiral heterocycles with high enantiomeric excess. This review describes works from my laboratory along with recent progress of the catalytic asymmetric hydrogenation of 5-membered heteroaromatics.

2. ASYMMETRIC HYDROGENATION OF INDOLES

To the best of my knowledge, no success in the asymmetric hydrogenation of heteroaromatics had been reported before we directed our interest to the research project. One of the reasons for no success was because metal complex suitable for developing the asymmetric catalysis had been unknown for the hydrogenation of heteroaromatics. Consequently, we started to dredge up transition metal complexes exhibiting good catalytic activity as well as easy to be decorated with a chiral ligand.

We chose indoles as the initial target because of the following reasons (Figure 1). Reactivity of the indole substrate can be controlled by the protecting group at its nitrogen atom. The protecting group may work as a directing group to achieve high stereoselectivity. Another reason was that indoles possess only one carbon–carbon double bond out of their benzene rings and can react with only one

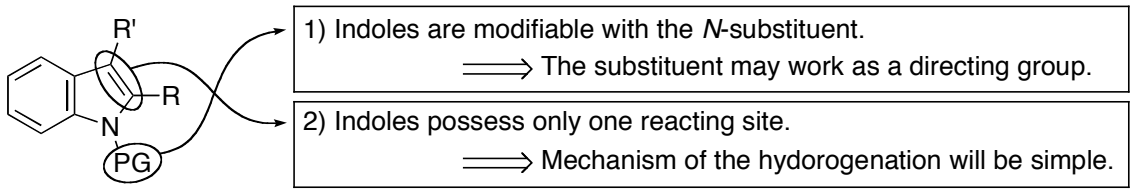
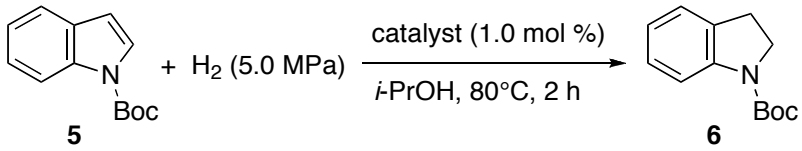


Figure 1. The reasons why we chose the asymmetric hydrogenation of indoles as an initial target

hydrogen molecule. Other heteroaromatics, such as pyrroles and quinolines, possess plural unsaturated bonds possible to react with hydrogen. The presence of the plural reactive sites will complicate the mechanistic consideration of the hydrogenation, because the consideration will require thinking over the fashion of the hydrogen addition (1,2- or 1,4-) as well as the site reacting with hydrogen first. The structural feature of indoles would reduce the number of possible reaction pathways of the catalytic hydrogenation. The simplification of the pathway might lead to facilitate the design of chiral catalyst.

We evaluated the catalytic activities of various phosphine-ligated metal complexes for the hydrogenation of *N*-Boc-indole (**5**) (Table 1).[19] As the results of the evaluation, the hydrogenation proceeded well in

Table 1. Rhodium-catalyzed hydrogenation of **5**



5 **6**

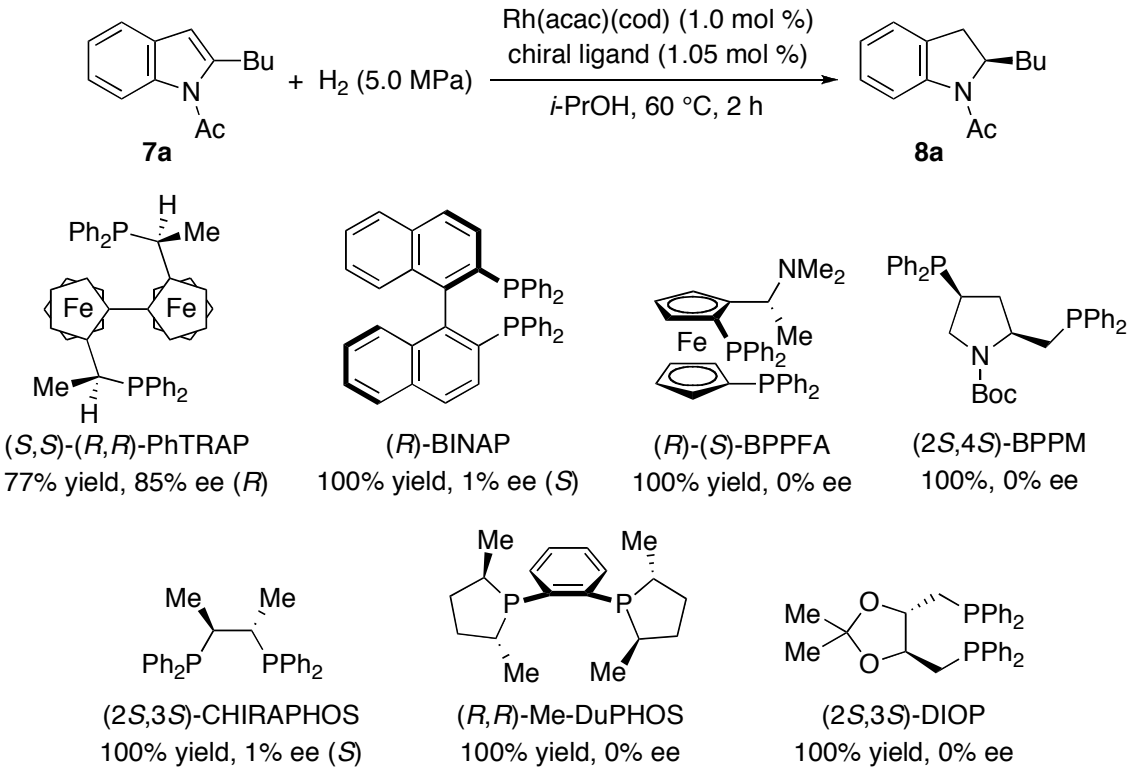
Entry	Catalyst[a]	Yield (%)
1	$Rh(acac)(cod) + 2PPh_3$	100
2	$RhCl(PPh_3)_3$	11
3	$[Rh(nbd)_2]SbF_6 + 2\ PPh_3$	18
4	Rh(acac)(cod) + DPPF	100

[a] acac = acetylacetonato, cod = 1,5-cyclooctadiene, nbd = 2,5-norbornadiene, DPPF = 1,1'-Bis(diphenylphosphino)ferrocene

the presence of the rhodium complex prepared from Rh(acac)(cod) and triphenylphosphine, yielding *N*-Boc-indoline (**6**) quantitatively (entry 1). Interestingly, conventional rhodium precursors for the catalytic hydrogenations of olefins, *e.g.* $RhCl(PPh_3)_3$ and $[Rh(diene)_2]^+$, failed to produce the hydrogenation product **6** in high yield (entries 2 and 3). The observations suggested that the hydrogenation of **5** proceeded through a reaction pathway different from the typical mechanism proposed for the hydrogenation of olefins using homogeneous rhodium catalysts.[20] It was noteworthy that the rhodium complex chelated by bidentate bisphosphine DPPF was comparable to Rh(acac)(cod)–triphenylphosphine catalyst (entry 4). The result indicated that the rhodium catalyst

could be modified with various chiral bidentate bisphosphines.

As the results of the screening of chiral bisphosphines, the hydrogenation of *N*-acetyl-2-butylindole (**7a**) proceeded with 85% ee only by using PhTRAP as a chiral ligand (Scheme 4).[21,22] The chiral ligand

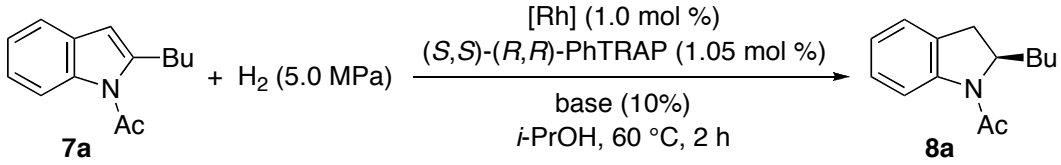


Scheme 4. Ligand screening on the catalytic asymmetric hydrogenation of **7a**

PhTRAP is possible to form a trans-chelate complex, in which the two phosphine atoms are located at the trans-position of each other.[23] Use of any chiral phosphines other than PhTRAP resulted in the formation of racemic **8a**. The ability to form trans-chelate complex may be crucial for the high stereoselectivity in the catalytic hydrogenation of indole. The stereoselectivity was enhanced to over 90% ee by addition of cesium carbonate to the rhodium catalyst (Table 2, entry 1). Cesium carbonate merely acts as a base, because no change of the yield and enantiomeric excess was occurred by use of triethylamine in place of cesium carbonate (entries 5 and 6). In the presence of base, choice of rhodium precursors has little effect on the stereoselectivity (entries 1, 3, and 5). Consequently, the additional base may be required for the generation of active catalyst species, monohydrido-rhodium(I), from the rhodium precursors.[24] Acetylacetonato ligand might work as a base when Rh(acac)(cod) was used for the catalytic hydrogenation.[25]

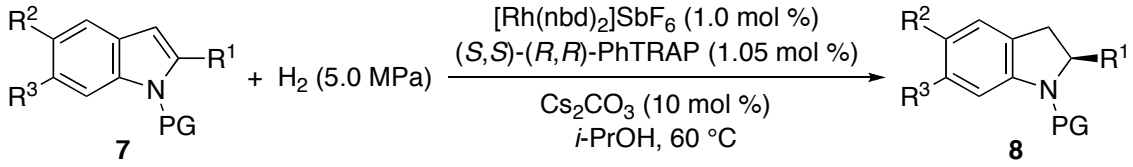
The PhTRAP–rhodium catalyst showed high enantioselectivity for the hydrogenation of various *N*-acetylindoles **7b**–**g** having a primary alkyl, an aryl, or an alkoxycarbonyl group at the 2-position (Table 3, entries 1–6). The substituent on the benzene ring scarcely affected the enantioselectivity. However,

Table 2. Effect of base on the catalytic asymmetric hydrogenation of **7a**



Entry	[Rh]	Base	Yield (%)	Ee (%)	Config.
1	Rh(acac)(cod)	Cs_2CO_3	100	93	*R*
2	$[RhCl(cod)]_2$	none	9	33	*R*
3	$[RhCl(cod)]_2$	Cs_2CO_3	68	94	*R*
4	$[Rh(nbd)_2]SbF_6$	none	<5	7	*S*
5	$[Rh(nbd)_2]SbF_6$	Cs_2CO_3	100	94	*R*
6	$[Rh(nbd)_2]SbF_6$	Et_3N	100	94	*R*

Table 3. Scope and limitation of the catalytic asymmetric hydrogenation of *N*-acetylindoles **7**



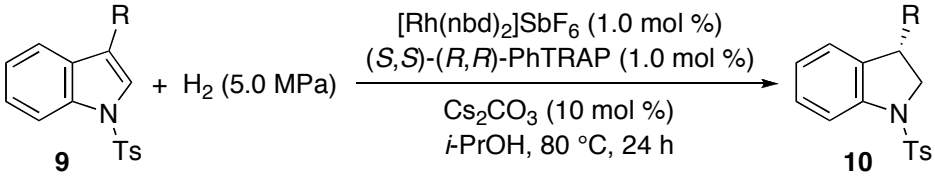
						Product (**8**)	
Entry	R^1	R^2	R^3	PG	**7**	Yield (%)	Ee (%)
1	CH_2(*i*-Pr)	H	H	Ac	**7b**	91	91
2	Ph	H	H	Ac	**7c**	91	87
3[a]	CO_2Me	H	H	Ac	**7d**	95	95 (*S*)
4	Bu	CF_3	H	Ac	**7e**	84	92
5	Bu	H	CF_3	Ac	**7f**	83	92
6	Bu	H	OMe	Ac	**7g**	98	94
7	*c*-C_6H_{11}	H	H	Ac	**7h**	27	19
8	Bu	H	H	Boc	**7i**	94	77
9	Me	H	H	Ts	**7j**	45	78

[a] The reaction was conducted at 100 °C and 10 MPa hydrogen pressure. Et_3N was used in place of Cs_2CO_3.

the reaction of 2-cyclohexylindole **7h** proceeded sluggishly, yielding the hydrogenation product **8h** with low ee value (entry 7). The enantioselectivity was affected by the protecting group on nitrogen of the indole substrate (entries 8 and 9). When 2-alkylindole protected by *tert*-butoxycarbonyl (**7i**) or *p*-toluenesulfonyl (**7j**) group was employed as a substrate, the asymmetric hydrogenation produced the desired chiral indoline with 77–78% ee.

As with the asymmetric hydrogenation of 2-substituted indoles, a variety of 3-substituted substrates was hydrogenated in high enantioselectivity by means of the PhTRAP–rhodium catalyst.[22,26] The chiral catalyst transformed *N*-tosyl-protected 3-methylindole **9a** into the desired chiral indoline **10a** with 98% ee (Table 4, entry 1). The chiral induction by PhTRAP was significantly affected by the *N*-protecting group of indole. The reaction of *N*-acetyl-3-methylindole gave 3-methylindoline with 84% ee, but in only 24% yield. The low yield was caused by the competitive solvolysis of the acetyl group. Surprisingly, the hydrogenation of *N*-Boc-3-methylindole proceeded with only 16% ee. As shown in Table 4, various *N*-tosylindolines **10** possessing a stereocenter at 3-position were obtained with high enantiomeric excess from the asymmetric hydrogenation catalyzed by the PhTRAP–rhodium complex.

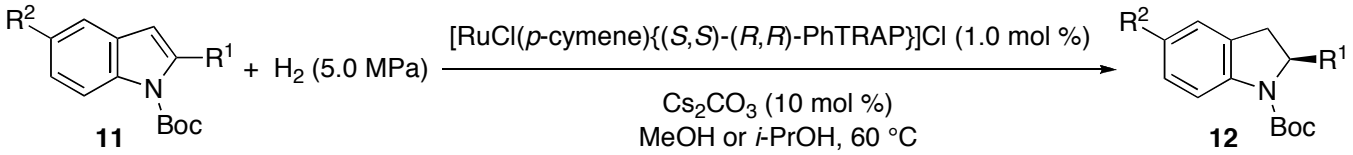
Table 4. Catalytic asymmetric hydrogenation of 3-substituted *N*-tosylindoles **9**



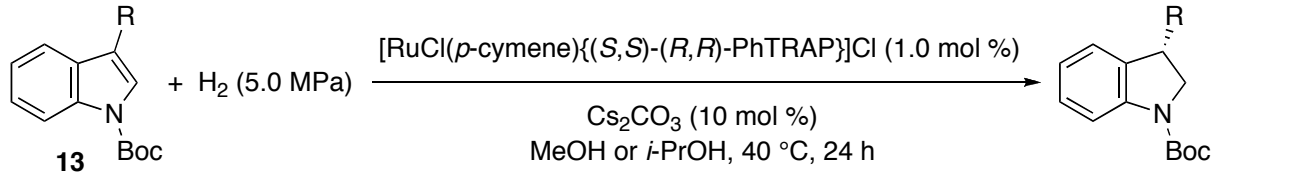
			Product (**10**)	
Entry	R	**9**	Yield (%)	Ee (%)
1	Me	**9a**	96	98 (*S*)
2	*i*-Pr	**9b**	94	97
3	Ph	**9c**	93	96
4	$(CH_2)_2OTBS$	**9d**	94	98
5	$(CH_2)_2NHBoc$	**9e**	71	95
6	$(CH_2)_2CO_2(t\text{-Bu})$	**9f**	93	97

From the viewpoint of organic synthesis, *tert*-butoxycarbonyl is an ideal *N*-protecting group for the catalytic asymmetric hydrogenation of indole. The protecting group readily attaches to the indole substrate by treatment with $(Boc)_2O$ and catalytic DMAP.[27] The removal of Boc is readily achieved under mild acidic conditions in general. However, the PhTRAP–rhodium catalyst was useless for the enantioselective hydrogenation of *N*-Boc-indoles as shown in Table 3. The reaction of the Boc-protected indoles proceeded with high enantioselectivity when ruthenium was employed as a catalyst in place of rhodium.[28] Ruthenium complex, [RuCl(*p*-cymene){(*S*,*S*)-(*R*,*R*)-PhTRAP}]Cl, catalyzed the hydrogenation of *N*-Boc-2-methylindole (**11a**), yielding the desired chiral *N*-Boc-indoline **12a** with 95% ee (*R*) (Table 5, entry 1). As with the rhodium catalyst, the ruthenium catalyst was effective for the asymmetric reduction of both *N*-Boc-indoles **11** and **13**, which have a substituent at their 2- and 3-positions respectively (Table 5, entries 2–8 and Scheme 5). 2-Cyclohexylindole **11e**, which was

Table 5. Catalytic asymmetric hydrogenation of 2-substituted *N*-Boc-indoles **11**

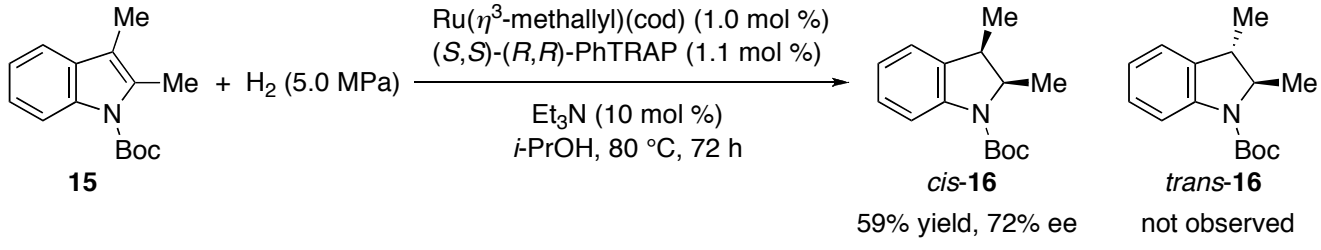


				Product (**12**)	
Entry	R^1	R^2	**11**	Yield (%)	Ee (%)
1	Me	H	**11a**	99	95 (*R*)
2	Me	OMe	**11b**	97	91
3	Me	F	**11c**	96	90
4	Bu	H	**11d**	94	92
5	*c*-C_6H_{11}	H	**11e**	92	87
6	Ph	H	**11f**	99	95
7	C_6H_4-*p*-F	H	**11g**	95	93
8	CO_2Me	H	**11h**	91	90 (*S*)



Scheme 5. Ruthenium-catalyzed asymmetric hydrogenation of 3-substituted *N*-Boc-indoles **13**

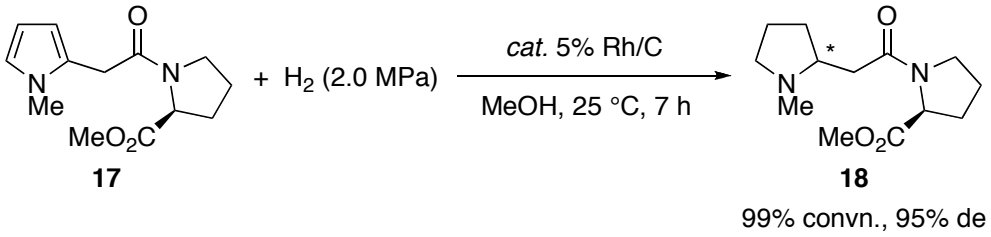
hydrogenated in low stereoselectivity by PhTRAP–rhodium catalyst, was converted into indoline **12e** with 87% ee by the ruthenium catalyst (entry 5). PhTRAP–ruthenium catalyst was applicable to asymmetric hydrogenation of 2,3-dimethylindole **15**, which was transformed into chiral indoline *cis*-**16** possessing two vicinal stereocenters (Scheme 6). No formation of *trans*-**16** was observed in the stereoselective reaction.



Scheme 6. Catalytic asymmetric hydrogenation of 2,3-dimethylindole **15**

3. ASYMMETRIC HYDROGENATION OF PYRROLES

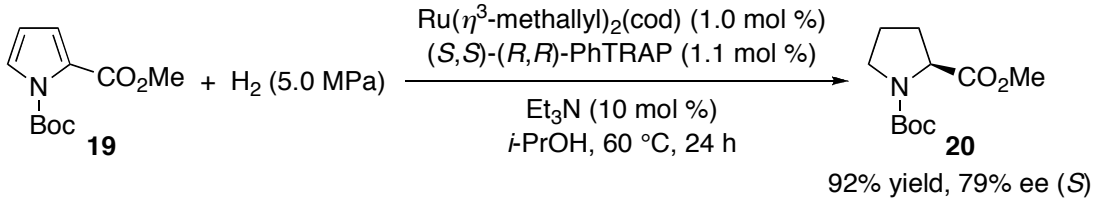
Stereoselective reduction of pyrroles is an attractive target in synthetic organic chemistry, because chiral pyrrolidine skeletons appear in many alkaloids. In 2001, Tungler *et al*. reported the stereoselective hydrogenation of a pyrrole modified with (*S*)-proline (Scheme 7).[29] The chiral (2-pyrrolyl)acetamide **17**



Scheme 7. Asymmetric hydrogenation of proline-modified pyrrole **17** by Tungler

was subjected to hydrogenation using 5% Rh/C catalyst in methanol, yielding pyrrolidine **18** with 95% de. However, the method using the chiral auxiliary was applied to only the reduction of (2-pyrrolyl)acetic acid.

In 2008, we disclosed a highly enantioselective hydrogenation of pyrroles. The hydrogenation of *N*-Boc-pyrrole-2-carboxylate **19** proceeded with good enantioselectivity by using the ruthenium catalyst generated *in situ* from Ru(η^3-methallyl)$_2$(cod) and (*S*,*S*)-(*R*,*R*)-PhTRAP ligand (Scheme 8).[30] Most

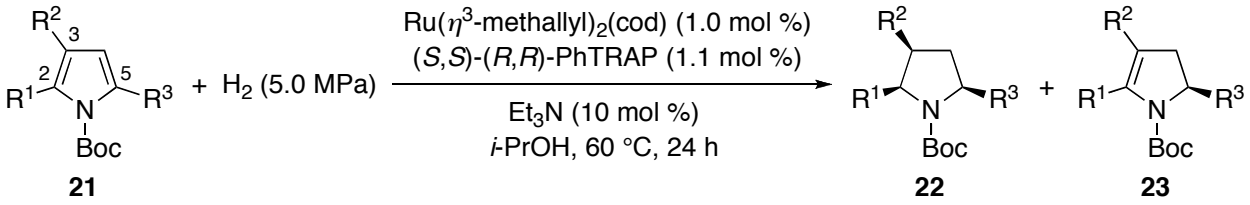


Scheme 8. Catalytic asymmetric hydrogenation of *N*-Boc-pyrrole-2-carboxylate **19**

chiral bisphosphines failed to achieve efficient chiral induction for the enantioselective reaction, yielding almost racemic pyrrolidine **20**. The observations suggest that the trans-chelation mode of PhTRAP may be required for the achievement of the high stereoselectivity.

The PhTRAP–ruthenium catalyst showed excellent performance for the asymmetric hydrogenation of 2,3,5-trisubstituted pyrroles **21** bearing a large substituent at the 5-position (Table 6). The substrates **21** were fully hydrogenated to give optically active pyrrolidines **22** with high enantiomeric excess when both substituents R^1 and R^2 were methyl or primary alkyl (entries 1 and 2). The three substituents, R^1, R^2, and R^3 of **22** were located cis to one another. No formation of any diastereomers of **22a** or **22b** was observed in the ruthenium-catalyzed hydrogenation. The hydrogenations of **21a** and **21b** created three chiral centers with high level of stereocontrol in a single process. Meanwhile, the hydrogenation of

Table 6. Catalytic asymmetric hydrogenation of 2,3,5-trisubstituted *N*-Boc-pyrroles **21**

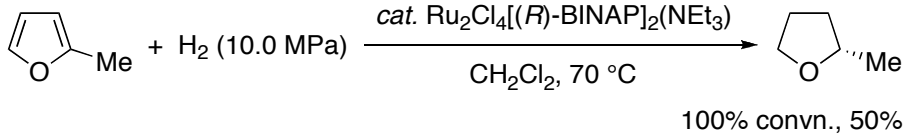


					Product (**22** or **23**)		
Entry	R^1	R^2	R^3	**21**	**22** : **23**	Yield (%)	Ee (%)
1	Me	Me	CO_2Me	**21a**	100 : 0	85 (**22a**)	96
2	Me	Pr	Ph	**21b**	100 : 0	96 (**22b**)	93
3	-$(CH_2)_4$-		CO_2Me	**21c**	16 : 84	70 (**23c**)	95
4	Ph	Ph	Ph	**21d**	0 : 100	>99 (**23d**)	99.7
5	Ph	Ph	C_6H_4-*p*-F	**21e**	0 : 100	99 (**23e**)	99.3
6	Ph	Ph	C_6H_4-*p*-OMe	**21f**	0 : 100	96 (**23f**)	98
7	C_6H_4-*p*-CF_3	Ph	Ph	**21g**	0 : 100	>99 (**23g**)	99.6
8	C_6H_4-*p*-OMe	Ph	Ph	**21h**	0 : 100	97 (**23h**)	99.2

4,5,6,7-tetrahydroindole **21c** mainly produced monohydrogenation product **23c** with 95% ee (entry 3). The reaction of 2,3,5-triarylpyrroles **21d–h** proceeded with 98–99.7% ee (entries 4–8). The substrates **21d–h** were selectively transformed into dihydropyrroles **23d–h** because the following hydrogenation of the cyclic enamines **23** would be obstructed by the steric repulsion between their aryl substituents.

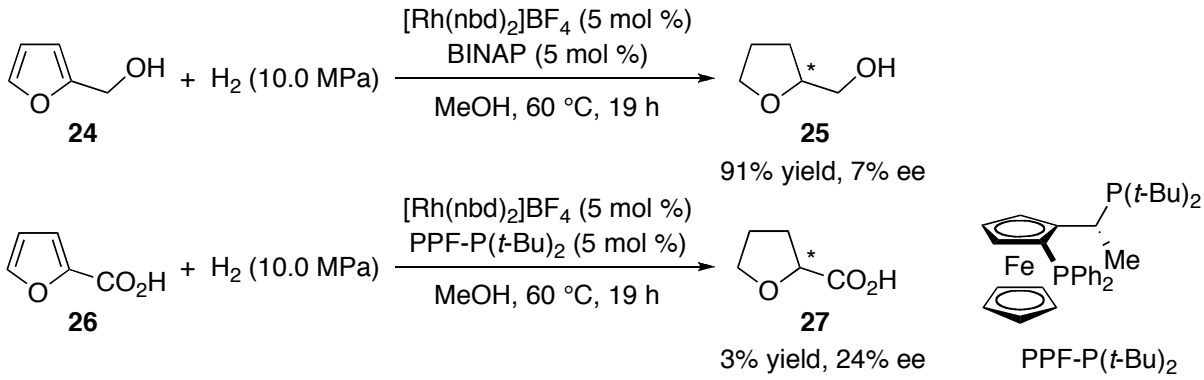
4. AYMMETRIC HYDROGENATION OF FURANS

The first attempt of catalytic asymmetric reduction of furans was reported by Takaya *et al*. to the best of my knowledge (Scheme 9). They used $Ru_2Cl_4[(R)\text{-BINAP}]_2(NEt_3)$ as a catalyst for the asymmetric



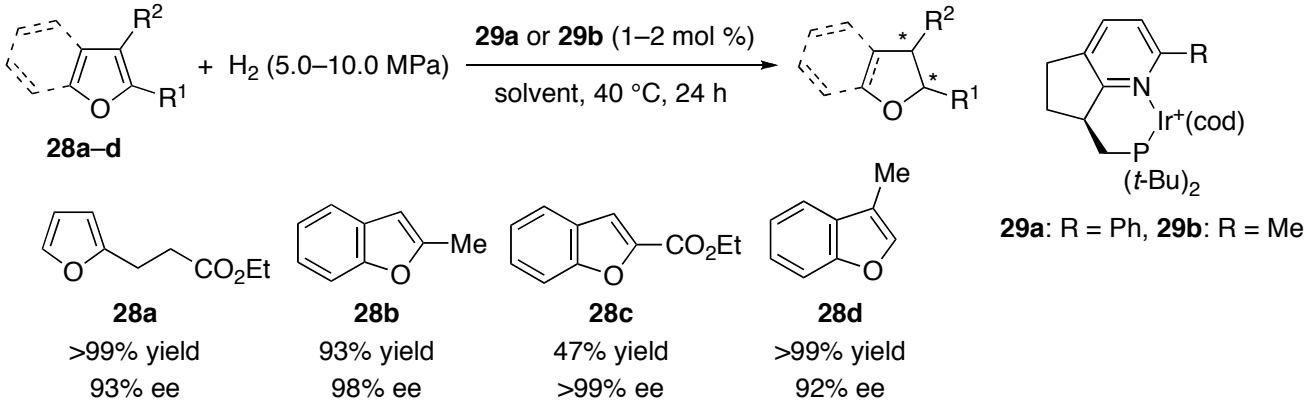
Scheme 9. Catalytic asymmetric hydrogenation of 2-methylfuran by Takaya

hydrogenation of 2-methylfuran, obtaining (*S*)-2-methyltetrahydrofuran with 50% ee.[31] Studer *et al*. reported an attempt to develop the asymmetric hydrogenation of 2-substituted furans **24** and **26** by using chiral rhodium catalyst (Scheme 10).[32] However, each reaction afforded the chiral tetrahydrofuran **25** or **27** with only 7% or 24% ee, respectively.



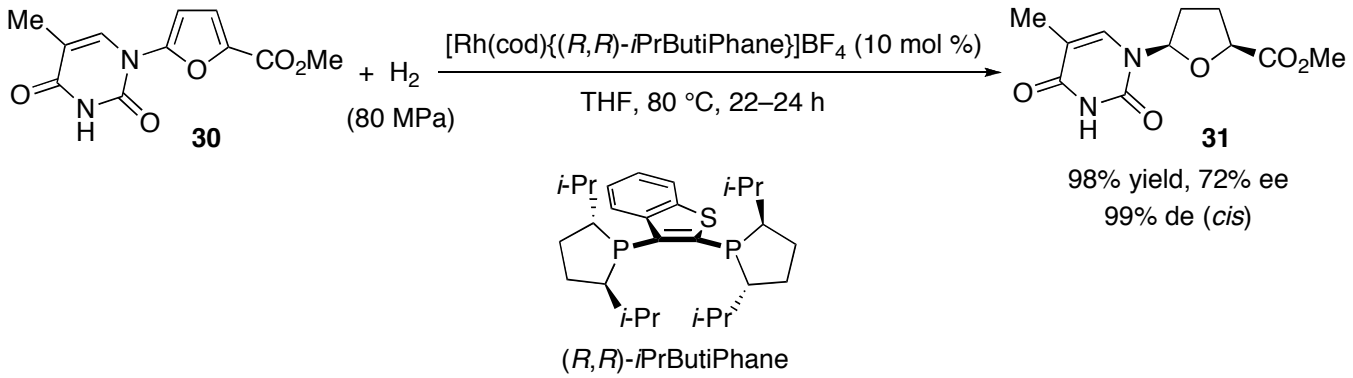
Scheme 10. Catalytic asymmetric hydrogenation of furans **24** and **26** by Studer

In 2006, Pfaltz *et al*. were achieved high enantioselectivity for the hydrogenation of furans (Scheme 11).[33] They designed a series of chiral pyridine-phosphinite ligands, and then evaluated them for the iridium-catalyzed asymmetric reduction of furans **28a–d**, including benzofurans. Pyridine-phosphinite-ligated iridium complex **29a** or **29b**, which possess bulky electron-rich $(t\text{-Bu})_2$P group, was found to be the best catalyst for the catalytic asymmetric reaction. The iridium catalyst transformed 2-substituted furan **28a** with 93% ee quantitatively. Optically active dihydrobenzofurans were obtained with 92–>99% ee through the asymmetric hydrogenation of **28b–d** using **29**. Choice of the substituents at the phosphorus atom of **29** strongly affected the catalytic activity as well as the enantioselectivity. Replacement of the *tert*-butyl by cyclohexyl group caused lower conversion and ee value. Use of diphenylphosphinite ligands resulted in no hydrogenation.



Scheme 11. Catalytic asymmetric hydrogenation of furans **28** by Pfaltz

Albert and co-workers reported the rhodium-catalyzed asymmetric hydrogenation of 5-thyminyl-2-furoate **30**, which was transformed into dideoxynucleoside **31** (Scheme 12).[34] For the asymmetric reduction, a DuPHOS-type bisphosphine, *i*PrButiPhane, was the most effective chiral ligand, yielding the desired *cis*-product **31** with 72% ee and 99% de. Surprisingly, no reduction of the thymine moiety was observed in the transformation. The reason for the high chemoselectivity is unclear.



Scheme 12. Catalytic asymmetric hydrogenation of furan **30** by Albert

5. CONCLUSION

This review surveyed the recent progress in the catalytic asymmetric hydrogenation of 5-membered heteroaromatics. Nitrogen-containing 5-membered heteroaromatics were successfully hydrogenated with high enantioselectivity by using the rhodium or ruthenium complex ligated by a trans-chelating ligand, PhTRAP. High enantioselectivity was achieved in the hydrogenation of some furans by using the pyridine-phosphinite–iridium complex as a catalyst.

Although high degree of stereocontrol has so far been attained in the catalytic asymmetric hydrogenation of indoles, pyrroles, furans, and benzofurans, only limited heteroaromatic substrates were successfully converted into the desired chiral heterocycles with high enantiomeric excess. The limited scope might cause few applications of the asymmetric hydrogenation of 5-membered heteroaromatics to organic synthesis as compared with 6-membered ones.[35, 36] Moreover, thiophenes are remained as an unexplored target in the catalytic asymmetric hydrogenation. Further improvement of the scope of the asymmetric catalysis will be required for enhancement of the synthetic utility.

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