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Iridium-Catalyzed Asymmetric Hydrogenation of Cyclic Enamines

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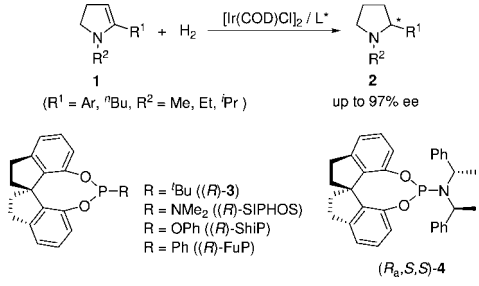
The asymmetric hydrogenation of enamides, that is, *N*-acyl enamines, catalyzed by Rh and Ru complexes bearing chiral phosphine ligands is an elegant and efficient method for the enantioselective synthesis of chiral *N*-acyl secondary amines.[1] In this hydrogenation reaction, the *N*-acyl group in the substrates is required to obtain high enantioselectivity by forming a chelate complex with the metal of the catalyst in the transition state.[2] Therefore, the chiral catalysts that proved to be successful in the asymmetric hydrogenation of enamides cannot be simply applied in the asymmetric hydrogenation of *N*,*N*-dialkyl enamines. Actually, the direct preparation of chiral tertiary amines by catalytic asymmetric hydrogenation of the *N*,*N*-dialkyl enamines remains a challenge and the reported efficient chiral catalysts are very limited.[3] Recently, we demonstrated that the Rh-complex of chiral spiro phosphonite (*R*)-**3** is a highly efficient catalyst for the asymmetric hydrogenation of enamines, (*E*)-1-(1-pyrrolidinyl)-1,2-diarylethenes, providing the corresponding tertiary amines with up to 99.9% ee.[4] When we tried to apply the catalyst Rh/(*R*)-**3** for the hydrogenation of cyclic *N*,*N*-dialkyl enamines **1a**, we obtained very poor enantioselectivity (20% ee). For developing efficient methods for the preparation of optically active cyclic tertiary amines, we investigated iridium catalysts and found that the complex Ir/(R_a,*S*,*S*)-**4** is a highly efficient catalyst for the hydrogenation of enamines **1** (Scheme 1). In this Communication, we report the first highly enantioselective hydrogenation of cyclic *N*,*N*-dialkyl enamines by using chiral iridium complexes of spiro phosphoramidites[5] and its application in the synthesis of optically active cyclic tertiary amines, including the natural product crispine A.

Scheme 1



Chiral cyclic tertiary amines are essential structural units in natural products and drugs.[6] The asymmetric hydrogenation of cyclic *N*,*N*-dialkyl enamines provides a direct approach to the synthesis of optically active cyclic tertiary amines. During the development of efficient methods for the enantioselective synthesis of chiral alkaloids, we became interested in the asymmetric hydrogenation of cyclic enamines **1**. The hydrogenation of **1a** was first catalyzed by Ir/(*R*)-**3** complex in THF and the cyclic tertiary amine **2a** was isolated in quantitative yield with 71% ee (Table 1, entry 1). Systematic examination on the phosphorus ligands in the reaction showed that the monodentate spiro phosphoramidite ligand (R_a,*S*,*S*)-**4** was most enantioselective (92% ee, entry 8). Ligands (S_a,*S*,*S*)- and (S_a,*R*,*R*)-Monophos-Pe[7] also gave modest to good enantioselectivity (70% ee and 88% ee, respectively) (Table 1, entries 5 and 6). Other types of monodentate phosphorus ligands including the ligands SIPHOS, ShiP, and FuP and bidentate diphosphine ligands such as BINAP,[8] SDP,[9] Me-Duphos,[10] Josiphos,[11] and Synphos,[12] showed very low enantioselectivities (entries 2−4, 10−14). The activity of the catalyst Ir/(R_a,*S*,*S*)-**4** was remarkable, it can hydrogenate the enamine **1a** under 1 atm of H_2 pressure, affording an even higher enantioselectivity (94% ee, entry 9). The catalyst loading can even be lowered to 0.1 mol % and the enantioselectivity is retained (entry 25). In addition to THF, dioxane and dimethoxyethane (DME) are also suitable solvents for the hydrogenation of enamine **1a** (entries 23 and 24). The investigation of the effect of additives in the reaction showed that the addition of I_2 is significant for obtaining full conversion and high enantioselectivity (entry 9 vs entries 15−18). The role of I_2 in this reaction is presumably the same as that in the Ir-catalyzed hydrogenation of imines.[13] The oxidative addition of I_2 to the Ir(I) precursor generates Ir(III) complex, which has a higher activity and enantioselectivity in the hydrogenation of enamines.

The secondary interaction between metal and ligands in the catalysts has been reported in the Ir-catalyzed substitution and Ru-catalyzed cyclopropanation using Monophos-Pe ligand.[14] We have

Table 1. Ir-Catalyzed Asymmetric Hydrogenation of Enamine **1a**, Optimizing Reaction Conditions[a]

entry	ligand	PH_2 (atm)	solvent	additive	conv (%)[b]	ee (%)[c]
1	(*R*)-**3**	50	THF	I_2	100	71 (*S*)
2	(*R*)-SIPHOS	50	THF	I_2	100	44 (*S*)
3	(*R*)-ShiP	50	THF	I_2	100	18 (*S*)
4	(*R*)-FuP	50	THF	I_2	100	36 (*S*)
5	(S_a,*S*,*S*)-Monophos-Pe	50	THF	I_2	100	70 (*S*)
6	(S_a,*R*,*R*)-Monophos-Pe	50	THF	I_2	100	88 (*R*)
7	(R_a,*R*,*R*)-**4**	50	THF	I_2	100	57 (*S*)
8	(R_a,*S*,*S*)-**4**	50	THF	I_2	100	92 (*S*)
9	(R_a,*S*,*S*)-**4**	1	THF	I_2	100	94 (*S*)
10	(*R*)-SDP	1	THF	I_2	100	31 (*R*)
11	(*S*)-BINAP	1	THF	I_2	100	4 (*S*)
12	(*R*,*S*)-Josiphos	1	THF	I_2	100	60 (*S*)
13	(*R*,*R*)-Me-Duphos	1	THF	I_2	58	47 (*S*)
14	(*R*)-Synphos	1	THF	I_2	35	35 (*S*)
15	(R_a,*S*,*S*)-**4**	1	THF	none	5	10 (*S*)
16	(R_a,*S*,*S*)-**4**	1	THF	AcOH	7	26 (*S*)
17	(R_a,*S*,*S*)-**4**	1	THF	Et_3N	4	14 (*S*)
18	(R_a,*S*,*S*)-**4**	1	THF	Bu_4NI	52	86 (*S*)
19	(R_a,*S*,*S*)-**4**	1	CH_2Cl_2	I_2	65	85 (*S*)
20	(R_a,*S*,*S*)-**4**	1	Toluene	I_2	30	80 (*S*)
21	(R_a,*S*,*S*)-**4**	1	Et_2O	I_2	22	86 (*S*)
22	(R_a,*S*,*S*)-**4**	1	MeOH	I_2	100	55 (*S*)
23	(R_a,*S*,*S*)-**4**	1	Dioxane	I_2	100	92 (*S*)
24	(R_a,*S*,*S*)-**4**	1	DME	I_2	100	94 (*S*)
25[d]	(R_a,*S*,*S*)-**4**	50	THF	I_2	100	94 (*S*)

[a] Reaction conditions: 0.5 mol % $[Ir(COD)Cl]_2$, 2.2 mol % ligand, 5 mol % additive, [substrate] = 0.1 M, room temperature (15−20 °C). [b] Determined by GC. [c] Determined by chiral GC using a Supelco alpha-Dex 120 column (30 m × 0.25 mm × 0.25 μm). [d] S/C = 1000.

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Table 2. The Asymmetric Hydrogenation of Enamines Catalyzed by Ir/(R_a,*S,S*)-**4**[a]

entry	R^1	R^2	product	ee (%)[b]
1	C_6H_5	Me	**2a**	94 (*S*)
2	C_6H_5	Et	**2b**	95
3	C_6H_5	^{i}Pr	**2c**	96
4	4-MeC_6H_4	Me	**2d**	91
5	4-MeOC_6H_4	Me	**2e**	94
6	4-FC_6H_4	Me	**2f**	92
7	4-ClC_6H_4	Me	**2g**	95
8	4-BrC_6H_4	Me	**2h**	97
9	3-MeC_6H_4	Me	**2i**	89
10	3-MeOC_6H_4	Me	**2j**	93
11	3-FC_6H_4	Me	**2k**	92
12	2-MeC_6H_4	Me	**2l**	87
13	2-ClC_6H_4	Me	**2m**	82
14	4-MeOC_6H_4	Et	**2n**	90
15	4-FC_6H_4	Et	**2o**	97
16	4-ClC_6H_4	Et	**2p**	94
17	4-BrC_6H_4	Et	**2q**	94
18[c]	^{n}C$_4$H$_9$	Me	**2r**	72

[a] Reaction conditions are the same as those of Table 1, entry 9, yields >90%. [b] Determined by chiral GC (see Supporting Information). [c] (S_a,*R,R*)-Monophos-Pe gave 66% ee. Very low ee values were obtained with other monodentate phosphorus ligands listed in Table 1.

tried to detect if there is a secondary interaction between iridium and ligands (R_a,*S,S*)-**4** and (R_a,*S,S*)-Monophos-Pe. However, ^{1}H and ^{31}P NMR analyses in the beginning or the end of the reaction showed no cyclometallated Ir-complex generated by cyclometalation at the methyl group of phosphoramidite ligand like in the Ir-catalyzed substitution reaction.[14a,b]

Encouraged by the promising result obtained in the hydrogenation of enamine **1a**, a variety of dihydropyrrole substrates **1** were examined using catalyst Ir/(R_a,*S,S*)-**4**. The alkyl group R^2 on the nitrogen atom in the substrates has no obvious influence on the reactivity and enantioselectivity of the reaction. The hydrogenations of enamines with *N*-Me (**1a**), *N*-Et (**1b**), and *N*-^{i}Pr (**1c**) produced the corresponding tertiary amines with comparable enantiomeric excesses (94−96% ee, Table 2, entries 1−3). The aryl group (R^1) on the α-position of substrates **1** is necessary for obtaining high enantioselectivity. When the R^1 group was phenyl or a substituted phenyl, the hydrogenated products were isolated with high yields (>90%) with 82−97% ee (entries 1−17). However, the hydrogenation of substrate **1r**, when R^1 was ^{n}Bu, afforded the amine **2r** with a lower ee value (72%, entry 18). The electronic property of substituents on the aryl ring of the substrate has very little effect to the enantiomeric excess of the product. The substituent at the *ortho*-position of the aryl ring of the substrate slightly diminished the enantioselectivity of the reaction. For example, the hydrogenations of 1-methyl-5-*o*-tolyl-2,3-dihydropyrrole (**1l**) and 1-methyl-5-(*o*-chlorophenyl)-2,3-dihydropyrrole (**1m**) yielded the cyclic amines **2l** and **2m** in 87% ee and 82% ee, respectively (entries 12 and 13).

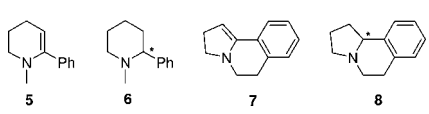
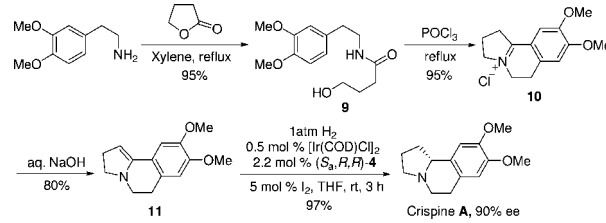


Figure 1

The catalyst Ir/(R_a,*S,S*)-**4** was also applied to the hydrogenation of enamines having a six-membered ring or a fused ring. In the hydrogenation of 1-methyl-6-phenyl-1,2,3,4-tetrahydropyridine (**5**), the cyclic tertiary amine **6** was provided in 21% ee. Other available monodentate phosphorus ligands listed in Table **1** were also tested and no more than 20% ee were obtained. In contrast, the hydrogenation of tricyclic enamine **7** yielded the corresponding amine **8** with 82% ee (Figure 1). This result prompted us to utilize this asymmetric hydrogenation reaction to synthesize the isoquinoline alkaloid crispine A,[15] which was isolated from *Carduus crispus,* Linn. (welted thistle) and has a significant cytotoxic activity.[16] The tricyclic enamine **11** was conveniently synthesized from 2-(3,4-dimethoxyphenyl)ethamine in 72% yield by a literature method.[15b] The asymmetric hydrogenation of enamine **11** was performed under the optimized conditions using the catalyst Ir/(S_a,*R,R*)-**4** to produce crispine A in 97% yield with 90% ee (Scheme 2).

Scheme 2



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Supporting Information Available: Experimental procedures, the characterizations of substrates and products, and the analysis of ee values of hydrogenation products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Monophos-Pe = *O,O*′-(1,1′-dinaphthyl-2,2′-diyl)-*N,N*′-di(1-phenylethyl)-phosphoramidite.
(8) BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.
(9) SDP = 7,7′-bis(diphenylphosphino)-1,1′-spirobiindane.
(10) Me-Duphos = 1,2-bis(2,5-dimethylphospholano)benzene.
(11) Josiphos = 1-[2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine.
(12) Synphos = (5,6),-(5′,6′)-bis(ethylenedioxy)-2,2′-bis(diphenylphosphino)-1,1′-biphenyl.
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