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Iridium-Catalyzed Enantioselective Hydrogenation of Cyclic Imines

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Abstract: A catalytic complex made from $[Ir(COD)Cl]_2$ [di-μ-chloro-bis(1,5-cyclooctadiene)diiridium(I)] precursor and (*S,S*)-f-Binaphane ((*R*,*R*)-1,1′-bis{(*R*)-4,5-dihydro-3*H*-dinaphtho[1,2-*c*:2′,1′-*e*]-phosphepino}ferrocene) ligand effectively catalyzed the enantioselective hydrogenation of cyclic imines with high reactivity and good enantioselectivity.

Keywords: asymmetric catalysis; cyclic imines; enantioselectivity; hydrogenation; iridium

Catalytic asymmetric hydrogenation of cyclic imines is a highly efficient approach for the synthesis of chiral cyclic amines, which are ubiquitous moieties in many natural products,[1] and in pharmaceutical drugs and drug candidates,[2] for example, nicotine,[3] BMS-394136[4] and LY-394681[5] (Figure 1). In contrast to the progress achieved in the asymmetric hydrogenation of acyclic imines,[6] there have been few reports on the enantioselective hydrogenation of cyclic imines.[7]

During the past two decades, Ti, Rh, Ru and Ir complexes have been investigated in the asymmetric hydrogenation of cyclic imines. The chiral titanocene developed by Buchwald et al. showed good reactivity and high enantioselectivity[8] for both cyclic imines and acyclic imines. Highly enantioselective cationic Rh(I) catalysts were applied by Xiao et al. in the asymmetric hydrogenation of imines to afford tetrahydroisoquinolines and tetrahydro-β-carbolines.[9] Catalyzed by $\{RuCl_2[(S)\text{-MeO-BIPHEP}][(S,S)\text{-ANDEN}]\}$ system, the hydrogenation of 2,3,3-trimethylindolenine was achieved with up to 88% *ee*.[10] Despite the successful complexes from various metals in asymmetric hydrogenation we decided to focus on Ir catalyst systems based on our studies of the asymmetric hydrogenation of N−H imines using the Ir-f-Binaphane catalyst[6b] and other reports on Ir(I)[11] and Ir(III)[12] complexes with chiral phosphines in the asymmetric hydrogenation of cyclic imines. We envisioned that the ferrocene-based electron-donating bisphosphine f-Binaphane could possibly minimize the inhibitory effect from the amine product[13] and the embedded axial chirality in the ligand could facilitate the enantiocontrol. Herein, we report the efficient enantioselective hydrogenation of a series of cyclic imines using Ir-f-Binaphane catalyst with high enantioselectivity (up to 89% *ee*).

With 2-phenyl-1-pyrroline as the standard substrate, initially several Ir(I) precursors with chiral f-Bina-

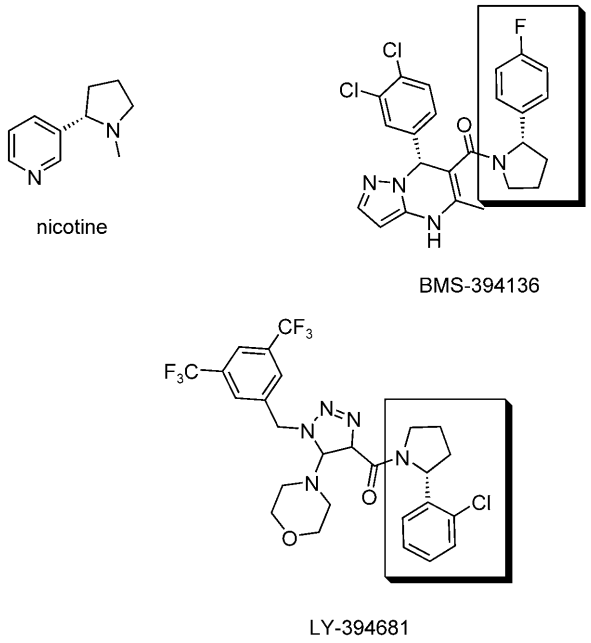


Figure 1. Structures of nicotine, BMS-394136 and LY-394681.

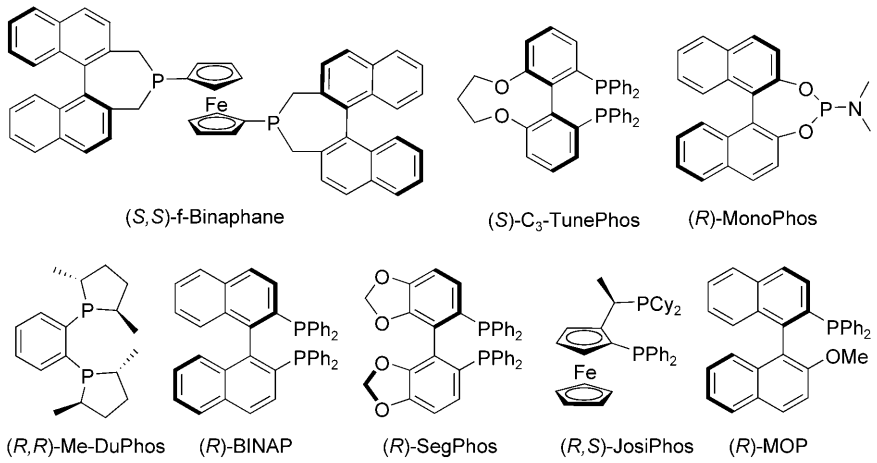
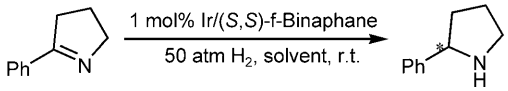


Figure 2. Structures of chiral phosphine ligands.

phane (Figure 2) were explored as hydrogenation catalysts. Results are summarized in Table 1 (entries 1–3). The Ir catalyst prepared *in situ* from $[Ir(COD)Cl]_2$ precursor and f-Binaphane ligand developed by our group,[14] gave 85% *ee* with good conversion (Table 1, entry 1). f-Binaphane is featured with high electron donation and a flexible backbone allowing it to accommodate sterically demanding cyclic imines to the Ir center. Subsequently the effect of solvents was investigated (Table 1, entries 4–8). The highest enantioselectivity was achieved from the combination of ethyl acetate/dichloromethane in a ratio of 2:1 (Table 1, entry 8). Interestingly no reaction occurred when dichloromethane itself was used as a solvent. The halide effect[15] was also explored. The reaction was completed with a full conversion in the presence of 2 mol% of I_2, but the enantiomeric excess dropped dramatically (Table 1, entry 9). Inspired by the wotk

Table 1. Asymmetric hydrogenation of 2-phenyl-1-pyrroline by Ir-f-Binaphane.[a]



Entry	Ir precursor	Solvent	Additive	Conversion [%][b]	*ee* [%] (Config.)[b]
1	$[Ir(COD)Cl]_2$	THF	–	65	85 (+)
2	$[Ir(COD)_2]BARF$	THF	10 mol% I_2	>99	61 (+)
3	$[Ir(COD)_2]BARF$	THF	–	5	30 (+)
4	$[Ir(COD)Cl]_2$	Toluene	–	53	85 (+)
5	$[Ir(COD)Cl]_2$	EtOAc	–	61	85 (+)
6	$[Ir(COD)Cl]_2$	MeOH	–	33	31 (+)
7[c]	$[Ir(COD)Cl]_2$	CH_2Cl_2	–	n.r.	n.d.
8	$[Ir(COD)Cl]_2$	EtOAc/CH_2Cl_2 2:1	–	89	88 (+)
9	$[Ir(COD)Cl]_2$	EtOAc/CH_2Cl_2 2:1	2 mol% I_2	>99	68 (+)
10[d]	$[Ir(COD)Cl]_2$	EtOAc/CH_2Cl_2 2:1	HI	>99	83 (+)
11[e]	$[Ir(COD)Cl]_2$	EtOAc/CH_2Cl_2 2:1	HI	>99	73 (+)
12[f]	$[Ir(COD)Cl]_2$	EtOAc/CH_2Cl_2 2:1	HI	75	72 (+)
13[g]	$[Ir(COD)Cl]_2$	EtOAc/CH_2Cl_2 2:1	–	>99	84 (+)

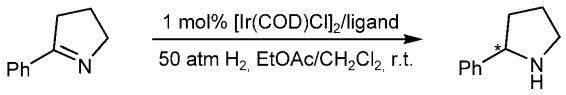
[a] The reactions were carried out with 0.2 mmol of substrate in 2.4 mL of solvent in the presence of 1 mol% of *in situ* prepared Ir catalyst under an initial hydrogen pressure of 50 atm for 25 h.
[b] Conversions and enantiomeric excesses were determined by chiral GC after the amine products were converted to the corresponding trifluoroacetamides.
[c] n.r. = no reaction, n.d. = not determined.
[d] HI was used for preparation of the iodine-bridged dimeric iridium complex $[\{Ir(H)[(S,S)\text{-f-Binaphane}]\}_2(\mu\text{-}I)_3]^+I^-$ to enhance the catalytic reactivity according to ref.[12c] The $[\{Ir(H)[(S,S)\text{-f-Binaphane}]\}_2(\mu\text{-}I)_3]^+I^-$ loading is 1 mol%; S/C = 100.
[e] The $[\{Ir(H)[(S,S)\text{-f-Binaphane}]\}_2(\mu\text{-}I)_3]^+I^-$ loading is 0.1 mol%; S/C = 1000; reaction temperature 50 °C.
[f] The $[\{Ir(H)[(S,S)\text{-f-Binaphane}]\}_2(\mu\text{-}I)_3]^+I^-$ loading is 0.01 mol%; S/C = 10000; reaction temperature 50 °C.
[g] Reaction temperature 50 °C.

of Genêt and co-workers,[12c] we prepared the iodine-bridged dimeric iridium complex [{Ir(H)[(*S,S*)-(f)-Binaphane]}$_2$(μ-I)$_3$]$^+$I$^-$. As expected, this complex was more reactive and yielded 83% *ee* (Table 1, entry 10); using 0.1 mol% of Ir catalyst, the reaction still proceeded smoothly but afforded lower *ee* (Table 1, entry 11); when the catalyst loading was further decreased to 0.01 mol%, 75% conversion and 72% *ee* were obtained (Table 1, entry 12). The enhanced catalytic reactivity of this iodine-bridged dimeric iridium complex was assumed to be due to the cleavage of Ir–N bond of the hydrogenation intermediate by HI.[12c]

Other additives, such as acetic acid[16] and phthalimide[11g] were also investigated and proved to have no effect on this hydrogenation. Without any additive, when the reaction temperature was increased to 50 °C, complete conversion was achieved with slightly lower *ee* (Table 1, entry 13). In a control study, [Ir(COD)Cl]$_2$ with other chiral phosphines was investigated (Table 2). None of the ligands offered higher enantioselectivity or conversion compared with f-Binaphane. Two monodentate ligands (*R*)-MOP and (*R*)-MonoPhos were tested and yielded poor conversions and enantioselectivities (Table 2, entries 1 and 2). Interestingly BINAP (Table 2, entry 6) and its analogues such as SegPhos (Table 2, entry 7) and C_3-TunePhos (Table 2, entry 8) showed good *ee*s.

To explore the applicability of this Ir-f-Binaphane catalytic system, a range of substituted arylpyrrolines, an alkylpyrroline, 2,3,4,5-tetrahydro-6- phenylpyridine and 2-phenyl-4,5,6,7- tetrahydro-3*H*-azepine were prepared and hydrogenated under the optimal conditions. The results are summarized in Table 3. It is evident that the electronic properties of the substituents at the *para* position of phenyl ring have no obvious effects on conversion and enantioselectivity (Table 3, entries 1–6). But when the substituents are located in *meta* and *ortho* positions, the enantioselectivity varies dramatically with different substituted groups (Table 3, entries 7–10). On increasing the ring size of

Table 2. Screening of chiral phosphine ligands.[a]

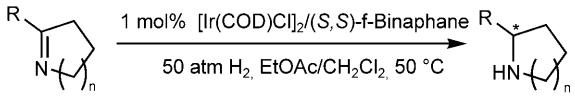


Entry	Ligand	Conv. [%][b]	*ee* [%] (Config.)[b]
1	(*R*)-MOP	10	4 (+)
2	(*R*)-MonoPhos	13	9 (−)
3	(*R,S*)-JosiPhos	20	13 (+)
4	(*R,R*)-Me-DuPhos	46	2 (+)
5	(*S*)-C_3-TunePhos	58	69 (+)
6	(*R*)-BINAP	64	74 (+)
7	(*R*)-SegPhos	63	78 (+)
8	(*S,S*)-f-Binaphane	89	88 (+)

[a] The reactions were carried out with 0.2 mmol of substrate in 2.4 mL of solvent in the presence of 1 mol% of *in situ* prepared Ir catalyst under an initial hydrogen pressure of 50 atm for 25 h.

[b] Conversions and enantiomeric excesses were determined by chiral GC after the amine products were converted to the corresponding trifluoroacetamides.

Table 3. Asymmetric hydrogenation of cyclic imines by Ir-f-Binaphane.[a]



Entry	R	n	Conversion [%][b]	*ee* [%] (Config.)[b]
1	C_6H_5	1	>99	85 (+)
2	4-Me-C_6H_4	1	>99	84 (+)
3	4-MeO-C_6H_4	1	>99	84 (+)
4	4-F-C_6H_4	1	>99	85 (+)
5	4-Cl-C_6H_4	1	>99	86 (+)
6	4-Br-C_6H_4	1	>99	84 (+)
7	3-Cl-C_6H_4	1	99	80 (+)
8	3-Me-C_6H_4	1	98	66 (+)
9	3-MeO-C_6H_4	1	96	74 (+)
10	2-MeO-C_6H_4	1	98	50 (+)
11	*n*-Bu	1	>99	58 (+)
12	C_6H_5	2	99	89 (+)
13	C_6H_5	3	99	75 (+)

[a] The reactions were carried out with 0.2 mmol of substrate in 2.4 mL of solvent in the presence of 1 mol% of *in situ* prepared Ir catalyst under an initial hydrogen pressure of 50 atm for 25 h at 50 °C.

[b] Conversions and enantiomeric excesses were determined by chiral GC after the products were converted to the corresponding trifluoroacetamides.

the cyclic imine from 5-membered to 6-membered, the enantiomeric excess was slightly improved (Table 3, entries 1 and 12); when it was 7-membered, the enantioselectivity dropped to 75% (Table 3, entry 13). This catalytic system does not work well for alkyl-substituted pyrroline and only 58% *ee* was achieved with one substrate (Table 3, entry 10).

In conclusion, an Ir-(*S,S*)-f-Binaphane catalyst has been applied in the asymmetric hydrogenation of a series of cyclic imines. With this system, readily prepared from $[Ir(COD)Cl]_2$ and air-stable (*S,S*)-f-Binaphane ligand, high reactivity and good enantioselectivity were achieved. Using HI as additive, high turnover number (>5000) was achieved. This highly reactive catalytic system provides us with an efficient approach for the synthesis of chiral cyclic amines.

Experimental Section

General remarks

All reactions were performed in the nitrogen-filled glovebox or under nitrogen using standard Schlenk techniques unless otherwise noted. Column chromatography was performed using Sorbent silica gel 60 (230–450 mesh). ^1H NMR spectral data were obtained from Bruker 400 MHz spectrometers. Chemical shifts are reported in ppm. Enantiomeric excess values were determined by chiral GC on Agilent 7890 GC equipment after converting the amine products into the corresponding trifluoroacetamindes. Cyclic imines were synthesized according to a modified literature method.[17]

General Procedure for Synthesis of Cyclic Imines

All of the cyclic imines were prepared from the corresponding 2-pyrrolidinone or 2-piperidinone and arylmagnesium bromide or alkyllithium reagent. To a solution of 1-(trimethylsilyl)-2-pyrrolidinone or 1-(trimethylsilyl)-2-piperidinone (0.018 mol) in anhydrous THF (15 mL) was added arylmagnesium bromide or alkyllithium reagent (0.022 mol in THF). Then the reaction was heated to reflux for 3 h before being quenched with aqueous NH_4Cl solution and extracted with EtOAc for 3 times. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified with column chromatography (EtOAc/hexane) or distillation to afford the desired products; yields: 25–92%.

General Procedure for Asymmetric Hydrogenation

In the nitrogen-filled glove-box, $[Ir(COD)Cl]_2$ (5.4 mg, 0.008 mmol) and (*S,S*)-f-Binaphane (12.8 mg, 0.016 mmol) were dissolved in anhydrous CH_2Cl_2 (6.4 mL) and equally divided into 8 vials charged with imine substrates (0.2 mmol) in anhydrous ethyl acetate solution (1.6 mL). The resulting solution was transferred to an autoclave, which was charged with 50 atm of H_2. The hydrogenation was performed at 50 °C for 25 h and the hydrogen was released carefully. The solvent was then evaporated and the residue was purified by column chromatography to give the corresponding hydrogenation product. The chiral amine products were reacted with trifluoroacetic anhydride to yield the corresponding trifluoroacetamides, which were then analyzed by chiral GC (Gamma Dex 225 or Beta Dex 390) to determine the enantiomeric excesses.

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