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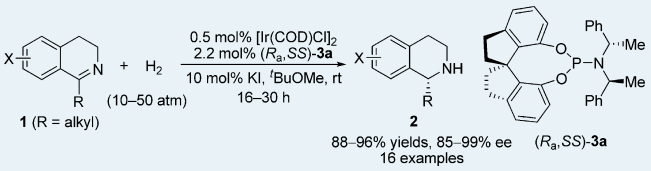
Asymmetric Hydrogenation of Cyclic Imines Catalyzed by Chiral Spiro Iridium Phosphoramidite Complexes for Enantioselective Synthesis of Tetrahydroisoquinolines

Jian-Hua Xie, Pu-Cha Yan, Qian-Qian Zhang, Ke-Xing Yuan, and Qi-Lin Zhou*

State Key Laboratory and Institute of Elemento-organic Chemistry, Nankai University, Tianjin 300071, China

Supporting Information

ABSTRACT: An efficient asymmetric hydrogenation of 1-alkyl 3,4-dihydroisoquinolines catalyzed by chiral spiro iridium phosphoramidite complexes has been developed, providing very useful chiral 1-alkyl tetrahydroisoquinolines with high yields (88−96%) and good to excellent enantioselectivities (85−99% ee). This reaction also affords a convenient synthetic route to tetracyclic alkaloid (*S*)-xylopinine.



KEYWORDS: *asymmetric hydrogenation, cyclic imine, iridium, phosphoramidite, spiro catalyst, tetrahydroisoquinoline*

Tetrahydroisoquinolines are important targets for the synthesis due to their significant biological and pharmacological activities.[1−4] Among them, 1-alkyl substituted tetrahydroisoquinolines, represented by examples such as (*S*)-salsolidine,[5] (*S*)-norlaudanosine,[6] and (*S*)-norreticuline (Figure 1), are of great interest to synthetic chemists because they have

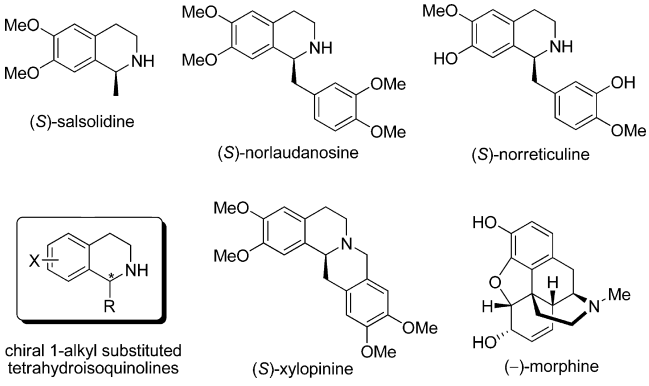


Figure 1. Chiral 1-alkyl tetrahydroisoquinoline and related alkaloids.

simple structures and are also key intermediates for the synthesis of more complex alkaloids such as (*S*)-xylopinine[7,8] and (−)-morphine.[9,10] Great efforts have been devoted to the development of methods for the enantioselective preparation of chiral 1-alkyl tetrahydroisoquinolines over recent decades.[11−13] The catalytic asymmetric hydrogenation of 1-alkyl 3,4-dihydroisoquinolines was proven to be one of the most efficient and straightforward approaches.[14−21] However, only a few reported chiral catalysts show high enantioselectivity for the hydrogenation of 1-alkyl 3,4-dihydroisoquinolines. The chiral *ansa*-titanocene catalyst [(EBTHI)Ti-binaphthol] exhibited high enantioselectivity (98% ee) for the hydrogenation of 1-methyl-3,4-dihydro-6,7-dimethoxyisoquinoline.[16,17] The rhodium complex of Ts-DPEN afforded up to 99% ee for the hydrogenation of 1-alkyl 3,4-dihydroisoquinolines.[18] Recently, the iridium complex of chiral diphosphine ligand (*S*,*S*)-*f*-binaphane was also demonstrated to be highly enantioselective for the hydrogenation of both 1-alkyl and 1-aryl 3,4-dihydroisoquinolines.[21]

As part of our efforts in exploring highly efficient methods for direct synthesis of unprotected chiral amines, we developed an efficient catalytic asymmetric hydrogenation of unfunctionalized cyclic enamines by using the iridium complex of chiral spiro phosphoramidite ligand (R_a,*S*,*S*)-SIPHOS-pe ((R_a,*S*,*S*)-**3a**).[22,23] Our recent work on this topic led us to find that this chiral iridium catalyst was also efficient for the hydrogenation of isoquinoline-type cyclic imines. In this paper, we report our primary results on the asymmetric hydrogenation of 1-alkyl 3,4-dihydroisoquinolines **1** catalyzed by iridium complex of (R_a,*S*,*S*)-**3a**, providing 1-alkyl tetrahydroisoquinolines **2** with up to excellent enantioselectivity (up to 99% ee) (Scheme 1).

The Ir-catalyzed enantioselective hydrogenation of 1-methyl-3,4-dihydroisoquinoline (**1a**) was performed for evaluating chiral ligands. The spiro phosphoramidites **3** were found to be efficient ligands for the hydrogenation of **1a**, with (R_a,*S*,*S*)-**3a** being the best ligand (Table 1, entries 1−4). The hydrogenation of **1a** catalyzed by 1 mol % Ir-(R_a,*S*,*S*)-**3a**, generated in situ from 0.5 mol % of $[Ir(COD)Cl]_2$ and 2.2 mol % of ligand (R_a,*S*,*S*)-**3a**, was completed within 18 h in THF under 50 atm H_2 at room temperature, yielding the product (*S*)-**2a** in 91% ee (entry 1). The spiro phosphite **4** and the spiro phosphonites **5** were less efficient ligands (entries 5−7). Solvent experiments showed that the hydrogenation reactions performed in Et_2O, ^{t}BuOMe, and toluene gave higher enantioselectivity (up to 99%

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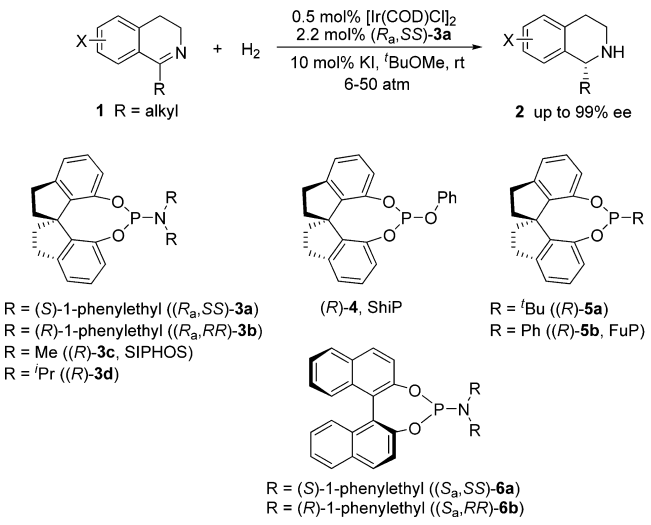
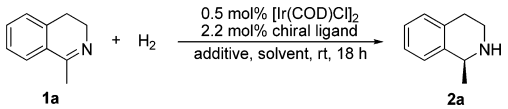
Scheme 1. Asymmetric Hydrogenation of 1-Alkyl-3,4-dihydroisoquinolines 1 with Ir-Catalysts



ee) (entries 8−10). Moreover, when the reaction was carried out in ^{t}BuOMe, the hydrogen pressure could be reduced to 20 atm without compensation of conversion and enantioselectivity (entry 12). The addition of iodine was crucial for the reaction.[24−26] Less than 10% hydrogenation product was formed if iodine was omitted in the reaction (entry 13). In addition to iodine, iodides such as Bu_4NI, LiI, and KI are also able to promote the hydrogenation reaction, and comparable results were obtained, with LiI or KI being an additive (entries 15 and 16). In addition, by using KI, the hydrogen pressure can be lowered to 6 atm in the hydrogenation of **1a** (entry 19). As a comparison, the binaphthol-based phosphoramidites (S_a,*S*,*S*)-monophos-pe ((S_a,*S*,*S*)-**6a**) and (S_a,*R*,*R*)-monophos-pe ((S_a,*R*,*R*)-**6b**) were also investigated, and the ligand (S_a,*S*,*S*)-**6a** yielded (*S*)-**2a** in 87% ee and 95% conversion (entry 17). These results indicated that ligands with a chiral spiro structure gave an advantage for the enantiocontrol in the hydrogenation of 1-alkyl 3,4-dihydroisoquinolines.

Under the optimal reaction conditions, a variety of 1-alkyl 3,4-dihydroisoquinolines **1** were hydrogenated to chiral 1-alkyl tetrahydroisoquinolines **2** with good to excellent enantioselectivities (85−99% ee, Table 2). The bulk of the 1-alkyl of the substrate has a remarkable effect on both reaction rate and enantioselectivity of the reaction. Increasing the bulk of the 1-alkyl group leads to a lower reaction rate and enantioselectivity (entries 1−6). For example, the hydrogenation of **1e** with a 1-isobutyl group needs to be performed under 20 atm H_2, giving the product **2e** with 85% ee (entry 5). The hydrogenation of **1f** with a 1-isopropyl group required 2 mol % catalyst and 50 atm H_2 for completion (entry 6). The substitution on the benzene ring of substrate with two electron-donating methoxy groups (**2h** and **2k**) or an electron-withdrawing fluoro group (**2i**) slightly lowered the enantioselectivity of the reaction (entries 8, 11 and 9). We were delighted to find that the 1-benzyl-3,4-dihydroisoquinolines (**1l−o**) also could be hydrogenated in high enantioselectivities (96−97% ee) (entries 12−15). The hydrogenation products, 1-benzyl tetrahydroisoquinolines **2l−o** are key intermediates for the synthesis of wide range of important alkaloids.[20,27−29] The asymmetric hydrogenation of 1-benzyloxylmethyl-3,4-dihydroisoquinoline (**1p**) gave product **2p** with 95% ee (entry 16). This result was better than that obtained with Ir-BINAP catalyst;[30] however, 1-phenyl-3,4-

Table 1. Asymmetric Hydrogenation 1-Methyl-3,4-dihydroisoquinoline (1a); Optimizing the Reaction Conditions[a]



entry	ligand	solvent	additive[b]	*P*, H_2 (atm)	conversion (%)[c]	ee (%)[d]
1	(R_a,*S*,*S*)-**3a**	THF	I_2	50	100	91 (*S*)
2	(R_a,*R*,*R*)-**3b**	THF	I_2	50	44	51 (*S*)
3	(*R*)-**3c**	THF	I_2	50	100	69 (*S*)
4	(*R*)-**3d**	THF	I_2	50	100	66 (*S*)
5	(*R*)-**4**	THF	I_2	50	100	16 (*S*)
6	(*R*)-**5a**	THF	I_2	50	90	77 (*S*)
7	(*R*)-**5b**	THF	I_2	50	100	24 (*S*)
8	(R_a,*S*,*S*)-**3a**	Et_2O	I_2	50	100	99 (*S*)
9	(R_a,*S*,*S*)-**3a**	^{t}BuOMe	I_2	50	100	99 (*S*)
10	(R_a,*S*,*S*)-**3a**	Toluene	I_2	50	100	95 (*S*)
11	(R_a,*S*,*S*)-**3a**	DCM	I_2	50	100	84 (*S*)
12	(R_a,*S*,*S*)-**3a**	^{t}BuOMe	I_2	20	100	99 (*S*)
13	(R_a,*S*,*S*)-**3a**	^{t}BuOMe	none	20	9	
14	(R_a,*S*,*S*)-**3a**	^{t}BuOMe	Bu_4NI	20	46	89 (*S*)
15	(R_a,*S*,*S*)-**3a**	^{t}BuOMe	LiI	20	100	99 (*S*)
16	(R_a,*S*,*S*)-**3a**	^{t}BuOMe	KI	20	100	99 (*S*)
17	(S_a,*S*,*S*)-**6a**	^{t}BuOMe	KI	20	95	87 (*S*)
18	(S_a,*R*,*R*)-**6b**	^{t}BuOMe	KI	20	22	82 (*R*)
19	(R_a,*S*,*S*)-**3a**	^{t}BuOMe	KI	6	100	99 (*S*)

[a]Reaction conditions: Ir/ligand/additive/substrate = 1:2.2:5:100, [substrate] = 0.1 M, room temperature, 18 h. [b]5 mol % of additive for entries 1−12 and 10 mol % of additive for entries 14−19. [c]Determined by ^{1}H NMR. [d]Determined by chiral HPLC (see Supporting Information).

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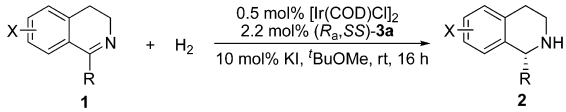
Table 2. Asymmetric Hydrogenation of 1-Alkyl 3,4-Dihydroisoquinolines 1 with Ir-(R_a,*SS*)-3a[a]



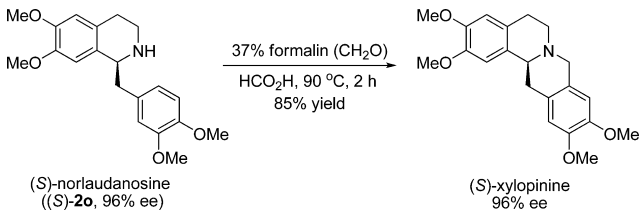
entry	R	X	2	*P*, H_2 (atm)	yield (%)[b]	ee (%)[c]
1	Me	H	**2a**	6	92	99 (*S*)
2	Et	H	**2b**	6	94	98 (*S*)
3	^{n}Bu	H	**2c**	6	94	96 (*S*)
4	$C_6H_5CH_2CH_2$	H	**2d**	6	96	95 (*S*)
5	^{i}Bu	H	**2e**	20	95	85
6[d]	^{i}Pr	H	**2f**	50	90	96 (*S*)
7	Me	6-MeO	**2g**	6	92	98
8	Me	6,7-$(MeO)_2$	**2h**	6	93	94 (*S*)
9	Me	5-F	**2i**	6	92	91
10	Et	6-MeO	**2j**	6	96	97
11	Et	6,7-$(MeO)_2$	**2k**	6	94	93 (*S*)
12	$C_6H_5CH_2$	H	**2l**	20	96	97 (*S*)
13	4-$BrC_6H_4CH_2$	H	**2m**	20	94	96
14	2-$BrC_6H_4CH_2$	H	**2n**	20	93	97 (*S*)
15[e]	3,4-$(MeO)_2C_6H_3CH_2$	6,7-$(MeO)_2$	**2o**	20	88	96 (*S*)
16	$BnOCH_2$	6,7-$(MeO)_2$	**2p**	20	94	95 (*R*)

[a]Reaction conditions are the same as those in Table 1, entry 19, 16 h, 100% conversion. [b]Isolated yield. [c]Determined by chiral HPLC (see the Supporting Information). [d]2 mol % catalyst loading, 30 h. [e]THF as a solvent.

dihydroisoqiunoline was a less reactive substrate, giving only 18% conversion at 50 atm H_2 pressure for 48 h.

To demonstrate the usefulness of this efficient catalytic asymmetric hydrogenation reaction, we performed a synthesis of tetracyclic alkaloid (*S*)-xylopinine starting from 1-benzyl-tetrahydroisoquinoline ((*S*)-**2o**, (*S*)-norlaudanosine)[7,8] (Scheme 2). The compound (*S*)-**2o** (96% ee) reacted with

Scheme 2. Enantioselective Synthesis of (*S*)-Xylopinine



(*S*)-norlaudanosine ((*S*)-**2o**, 96% ee)

(*S*)-xylopinine 96% ee

37% formalin solution (CH_2O) in formic acid at 90 °C for 2 h to produce (*S*)-xylopinine in 85% yield (96% ee, $[\alpha]_D^{20}$ −281.8 (*c* 0.5, $CHCl_3$) [lit.[7] $[\alpha]_D^{20}$ −281.7 (*c* 0.1, $CHCl_3$)].

In conclusion, we have developed an efficient iridium-catalyzed enantioselective hydrogenation of dihydroisoquinoline-type imines, which provided very useful chiral 1-alkyl tetrahydroisoquinolines with good to excellent enantioselectivities. Further applications of this iridium catalyst for the enantioselective hydrogenation of other imines toward the direct synthesis of chiral amines are in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data for all new compounds, and the HPLC charts for the determination of the ee values of compounds **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: qlzhou@nankai.edu.cn.

Notes

The authors declare no competing financial interest.

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