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Iridium-catalyzed asymmetric hydrogenation of cyclic iminium salts†

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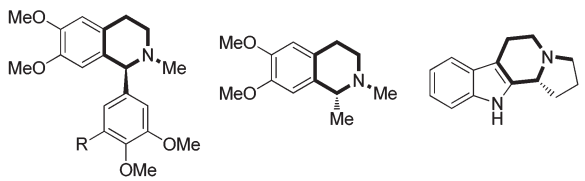
An enantioselective hydrogenation of cyclic iminium salts has been successfully realized by employing $[Ir(COD)Cl]_2$ and chiral diphosphine ligands as catalyst, furnishing chiral *N*-alkyl tetrahydroisoquinolines and *N*-alkyl tetrahydro-β-carbolines with up to 96% ee and 88% ee, respectively. The hydrogenation provides a direct, simple and efficient protocol toward chiral tertiary amines. Meanwhile, asymmetric hydrogenation at the gram scale was also conducted smoothly without loss of reactivity and enantioselectivity.

Enantiomerically pure tertiary amines with a tetrahydroisoquinoline[1] (THIQ) core or tetrahydro-β-carboline[2] (THC) core are important in natural alkaloids (Fig. 1). Their promising pharmacological activities such as anti-tumor, anti-amoebic, anti-inflammation, and anti-virus have attracted much attention of chemists and pharmaceutists.[1,2] For example, (*R*)-carnegine was significant in inhibition of human monoamine oxidase A and B.[3] Besides, (*R*)-harmicine also displayed potent antimicrobial and anti-HIV activities.[4] Several strategies were developed for the enantioselective synthesis of these types of tertiary amines, such as asymmetric nucleophilic addition of iminium salts, cross-dehydrogenative coupling reaction and annulation.[5] The complexity and speciality of structures and multiple reaction steps impeded the further development of enantioselective synthesis of THIQs and THCs. However, developing a direct, convenient and efficient methodology for the synthesis of enantiomerically pure tertiary amines is important and desirable.



(*S*)-Cryptostyline II (R = H)
(*S*)-Cryptostyline III (R = MeO)
(*R*)-Carnegine
(*R*)-Harmicine

Fig. 1 Selected biologically active molecules of tertiary amines.

Asymmetric hydrogenation of iminium salts bearing a dihydroisoquinoline (DHIQ) or dihydro-β-carboline (DHC) moiety should be the preferred approach for obtaining tertiary amines in terms of simplicity and atom economy. Although the enantioselective hydrogenation of imines has been widely developed,[6] iminium salts are still challenging substrates for the asymmetric hydrogenation to tertiary amines with only a few examples. Asymmetric hydrogenation of iminium salts is of significant disadvantage as regards the following aspects that need to be settled: (1) the decreased coordination ability of substrate to catalyst results in less control of the enantioselectivity; (2) the strong coordinative nitrogen atom of the product can easily poison the catalyst. In 2005, Czarnocki and co-workers initially reported the Ru/TsDPEN-catalyzed enantioselective hydrogenation of iminium salts using $HCOOH/Et_3N$ as hydrogen source, furnishing (*R*)-crispine A with up to 96% yield and 92% ee (Scheme 1, eqn (1)).[7] Subsequently, several other groups also achieved the Ru/diamine-catalyzed asymmetric transfer hydrogenation of cyclic iminiums bearing a DHIQ core or DHC core.[8] Notably, NAD(P)H-dependent reductase, which received wide attention of chemists, was successfully applied in the asymmetric reduction of cyclic iminium salts to furnish tertiary amines, such as 2-alkyl THIQs[9] and 1-alkyl indolines with up to 92% ee and 99% ee respectively, but only 40% conversion for 2-alkyl THIQs (Scheme 1, eqn (2) and (3)).[10]

Iridium-catalyzed asymmetric hydrogenation of imines and heteroaromatics has been rapidly and widely developed in the past few years.[11] Iridium/diphosphine catalyst also provided great promise for the asymmetric hydrogenation of iminium salts from the following aspects. First, in general, iminium salts exhibited higher reactivity than the corresponding

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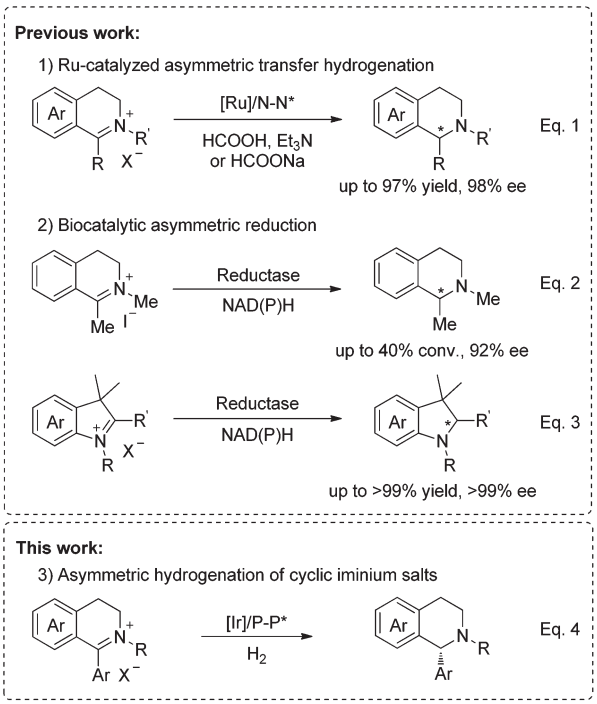
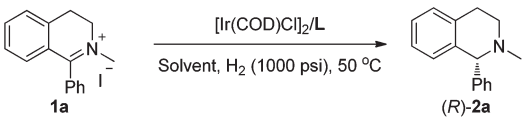
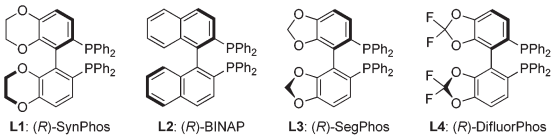


Scheme 1 Synthetic strategies for asymmetric hydrogenation of cyclic iminium salts to chiral tertiary amines.

Table 1 The evaluation of reaction parameters[a]



Entry	Solvent	L	Conv.[b] (%)	ee[c] (%)
1	THF	**L1**	63	25
2	Dioxane	**L1**	52	47
3	Toluene	**L1**	20	46
4	MeOH	**L1**	>95	39
5	DCM	**L1**	69	6
6	DCE	**L1**	93	86
7	DCE	**L2**	88	71
8	DCE	**L3**	85	93
9	DCE	**L4**	89	91
10[d]	DCE	**L3**	>95	91



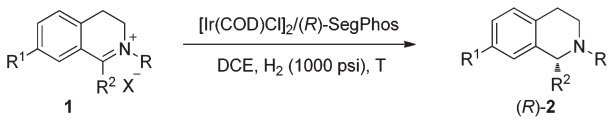
[a] Reaction conditions: **1a** (0.1 mmol), $[Ir(COD)Cl]_2$ (1 mol%), **L** (2.2 mol%), H_2 (1000 psi), solvent (3.0 mL), 24 h, 50 °C. [b] Determined by ^1H NMR analysis with 1,3,5-trimethoxybenzene as the internal standard. [c] Determined by HPLC analysis. [d] 70 °C.

imines. Second, the Brønsted acid generated *in situ* during the hydrogenation could form salts with the tertiary amine products, which efficiently decreased the coordination ability of reduction products with catalyst. In 2009, iridium-catalyzed asymmetric hydrogenation of iminium salts to primary amines was initially and successfully achieved by the Zhang and Gosselin group with excellent results.[12] Besides, by employing alkyl bromides, chloroformates and Brønsted acids as substrate activators, iridium-catalyzed asymmetric hydrogenation of heteroaromatics has been developed *via* the formation of pyridinium and isoquinolinium salts in the past decade.[13] Notably, we realized deracemization of tertiary amines *via* iminium salt intermediates using the redox combination of NBS oxidation and iridium-catalyzed asymmetric hydrogennation.[14] Inspired by these previous researches, we turned our attention to the asymmetric hydrogenation of cyclic iminium salts. Herein, we report an iridium-catalyzed asymmetric hydrogenation of cyclic iminium salts with high enantioselectivity (Scheme 1, eqn (4)).

At the outset of our study, 2-methyl-1-phenyl-3,4-dihydroisoquinolin-2-ium iodide **1a**, which can be synthesized through the reaction of iodomethane and 1-phenyl-3,4-dihydroisoquinoline,[13c] was chosen as the model substrate for investigation. To our delight, in the presence of $[Ir(COD)Cl]_2$/(*R*)-SynPhos, the hydrogenation of **1a** was conducted smoothly in THF with 25% ee and 63% conversion to furnish the desired tertiary amine **2a** (Table 1, entry 1). The reaction produced one equivalent of hydriodic acid, which could efficiently inhibit the coordination of metal and tertiary amine product *via* the formation of salt. Encouraged by this promising result, we then turned our attention to the solvent effect (entries 2–6). To our surprise, the ee value dramatically increased to 86% ee in dichloroethane (DCE), which was quite different from that in dichloromethane (DCM) (entry 6). Some commercially available chiral diphosphine ligands were screened (entries 7–9). (*R*)-SegPhos proved to be the best choice with 93% ee but moderate conversion. With temperature increased to 70 °C, a full conversion with slightly reduced ee of 91% was achieved (entry 10). Thus, the optimized reaction conditions were established: $[Ir(COD)Cl]_2$/(*R*)-SegPhos/DCE/70 °C/1000 psi H_2.

With the aforementioned optimal reaction conditions in hand, a variety of 1-substituted 2-alkyl 3,4-dihydroisoquinolin-2-ium salts were subsequently evaluated to demonstrate the generality and practicality of this method. As expected, a diverse array of substrates could be smoothly and effectively transformed, giving the corresponding products in excellent enantioselectivity and yield (Table 2). For X = I, the electronic properties of the substituent on the 1-aryl ring had a marginal effect on the reactivity and enantioselectivity (entries 1–7). However, the enantioselectivity is sensitive to the electronic properties of the substituent on the 7-position. The electron-withdrawing group chloro and the strongly electron-donating group methoxy both gave a slightly lower enantioselectivity (entries 8–10). The reaction was performed smoothly in the standard condition with 1-phenethyl-substituted substrate but with only 26% ee, which may be ascribed to the deficiency of π–π stacking interaction between the catalyst and substrate (entry 11). Notably, the current system was highly compatible with benzyl bromide substrates with high enantioselectivity

Table 2 Asymmetric hydrogenation of 2-alkyl 3,4-dihydroisoquinolin-2-ium salts[a]

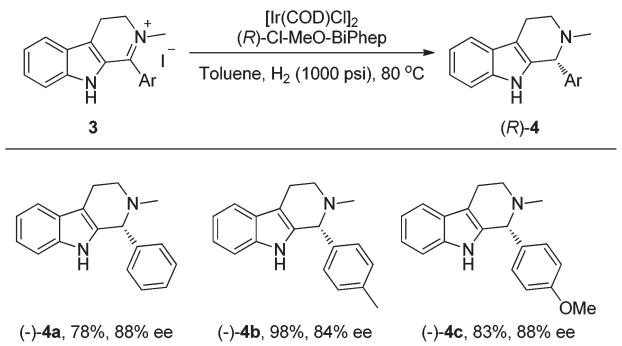


Entry	R/R^1/R^2	X	Yield[b] (%)	ee[c] (%)
1	Me/H/C_6H_5	I	99 (**2a**)	91 (*R*)
2	Me/H/3-MeC_6H_4	I	99 (**2b**)	90 (−)
3	Me/H/4-MeC_6H_4	I	97 (**2c**)	90 (−)
4[d]	Me/H/4-MeOC_6H_4	I	91 (**2d**)	89 (−)
5	Me/H/4-FC_6H_4	I	94 (**2e**)	90 (−)
6	Me/H/4-ClC_6H_4	I	97 (**2f**)	87 (−)
7	Me/H/4-BrC_6H_4	I	98 (**2g**)	87 (−)
8	Me/Me/C_6H_5	I	97 (**2h**)	93 (−)
9[e]	Me/MeO/C_6H_5	I	91 (**2i**)	86 (−)
10	Me/Cl/C_6H_5	I	93 (**2j**)	84 (−)
11	Me/H/$CH_2CH_2C_6H_5$	I	99 (**2k**)	26 (+)
12	Bn/H/C_6H_5	Br	95 (**2l**)	96 (−)
13	Bn/H/4-MeC_6H_4	Br	97 (**2m**)	95 (−)
14	Bn/H/4-MeOC_6H_4	Br	96 (**2n**)	96 (−)
15	Bn/H/4-ClC_6H_4	Br	93 (**2o**)	95 (−)
16[e]	Bn/MeO/C_6H_5	Br	91 (**2p**)	93 (−)
17	Bn/Cl/C_6H_5	Br	96 (**2q**)	95 (−)

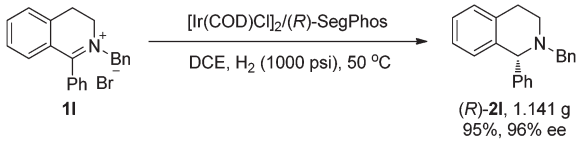
[a] Reaction conditions: **1** (0.2 mmol), $[Ir(COD)Cl]_2$ (1 mol%), (*R*)-SegPhos (2.2 mol%), H_2 (1000 psi), 24 h; X = I, DCE (5.0 mL), T = 70 °C; X = Br, DCE (3.0 mL), T = 50 °C. [b] Isolated yields. [c] Determined by HPLC analysis. [d] $[Ir(COD)Cl]_2$ (1.5 mol%), (*R*)-SegPhos (3.3 mol%). [e] 48 h.

regardless of the electronic properties of substituents in the 4-position of 1-aryl ring (entries 12–15). A slightly lower ee was obtained when 7-methoxyl was introduced (entry 16).

Additionally, we evaluated the generality of our synthetic methodology with regard to other types of iminium salts as potential substrates, providing *N*-alkyl THCs (Scheme 2). To our satisfaction, iminium salt **3b** was also subjected to the standard conditions with full conversion and 60% enantioselectivity. A modified condition was established by further optimization of solvents and ligands. Using (*R*)-Cl-MeO-BiPhep as chiral diphosphine ligand and toluene as solvent, a significant improvement in enantioselectivity was observed from 60% ee to 84% ee (see ESI†). The electronic effect of 1-aryl of



Scheme 2 Enantioselective synthesis of 2-methyltetrahydro-β-carbolines *via* hydrogenation.



Scheme 3 Gram-scale experiment.

substrates was investigated under the modified optimal condition, giving the desired products with moderate to excellent yields and good enantioselectivities, which are significant motifs of biological molecules.

To further highlight the practical utility of this attractive protocol, the asymmetric hydrogenation of **1l** was performed at the gram scale to give the desired product **2l** in 95% yield and 96% ee (Scheme 3). With several simple transformations, **2l** could also be conveniently converted into pharmaceutical molecules such as (+)-solifenacin[15] and (+)-FR115427.[16]

Notably, for the analogous simple acyclic iminium salts, pure iminium salt substrates could not obtained under the standard conditions described above, which might be ascribed to low reactivity and existence of multiple isomers.

Conclusion

In conclusion, we have successfully developed an efficient and convenient method for synthesis of *N*-alkyl tetrahydroisoquinolines or *N*-alkyl tetrahydro-β-carbolines through iridium-catalyzed asymmetric hydrogenation of cyclic iminium salts in good to excellent yields and with up to 96% ee and 88% ee, respectively. Furthermore, cyclic tertiary amines, such as *N*-alkyl tetrahydroisoquinolines as some of the most important drug molecules, can be easily obtained through this single-operation process without further alkylation. Further investigations of related strategies are currently ongoing in our laboratory.

Experimental

A typical procedure for asymmetric hydrogenation of 1a

A mixture of $[Ir(COD)Cl]_2$ (1.3 mg, 0.002 mmol) and (*R*)-SegPhos (2.7 mg, 0.0044 mmol) in dichloroethane (1.0 mL) was stirred at room temperature for 10 min in a nitrogen-filled glove box. Subsequently, the catalyst was transferred by a syringe to a solution of 2-methyl-1-phenyl-3,4-dihydroisoquinolin-2-ium iodide **1a** (69.8 mg, 0.2 mmol) in 4.0 mL dichloroethane. The hydrogenation was performed at 70 °C with a hydrogen pressure of 1000 psi for 24 h. After carefully releasing the hydrogen, the mixture was concentrated in vacuum and further purification was performed by a silica gel column eluted with hexanes/ethyl acetate to give the chiral product (*R*)-**2a** as a pale oil (44 mg, 99% yield, 91% ee). Enantiomeric excess was determined by HPLC (OD-H column, hexane/^{i}PrOH

98/2, 0.70 mL min^{-1}, 230 nm), 30 °C, t_1 = 6.0 min, t_2 = 6.3 min (maj).

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