Asymmetric Catalysis

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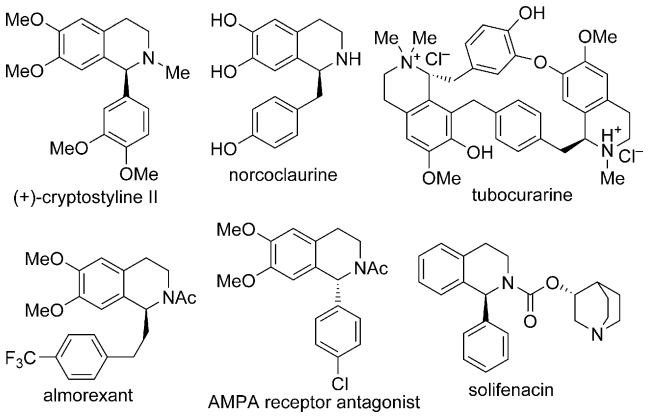
One-Pot N-Deprotection and Catalytic Intramolecular Asymmetric Reductive Amination for the Synthesis of Tetrahydroisoquinolines

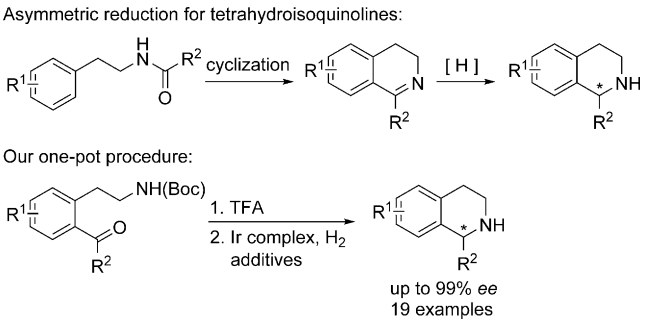
*Huan Zhou, Yuan Liu, Suhua Yang, Le Zhou, and Mingxin Chang**

Abstract: *A one-pot N-Boc deprotection and catalytic intramolecular reductive amination protocol for the preparation of enantiomerically pure tetrahydroisoquinoline alkaloids is described. The iodine-bridged dimeric iridium complexes displayed superb stereoselectivity to give tetrahydroisoquinolines, including several key pharmaceutical drug intermediates, in excellent yields under mild reaction conditions. Three additives played important roles in this reaction: Titanium(IV) isopropoxide and molecular iodine accelerated the transformation of the intermediate imine to the tetrahydroisoquinoline product; p-toluenesulfonic acid contributed to the stereocontrol.*

Stereogenic 1-substituted tetrahydroisoquinolines have attracted great attention in life science owing to their biological activity.[1] This structural motif is present ubiquitously in natural products and pharmaceuticals, for example, in naturally occurring (+)-cryptostyline II,[2a] norcoclaurine,[2b] and tubocurarine (the functional ingredient of arrow poison used by South American native people centuries ago to hunt animals),[2c] in an AMPA receptor antagonist,[2d] and in the pharmaceutical drugs almorexant[2e] and solifenacin[2f] (Scheme 1). To satisfy the demand for enantiomerically pure tetrahydroisoquinolines, many synthetic methods have been developed.[3] As compared with the highly efficient asymmetric hydrogenation and transfer hydrogenation of the corresponding imines (Scheme 2),[4] the approach of asymmetric reductive amination bypasses the preparation of the imine, and is thus more concise, more efficient, and more promising.



Scheme 1. Bioactive 1-substituted tetrahydroisoquinolines.



Scheme 2. One-pot reductive amination for the preparation of tetrahydroisoquinolines. Boc = *tert*-butoxycarbonyl, TFA = trifluoroacetic acid.

The reductive amination reaction is one of the most important C–N bond-construction tools both in biological systems and synthetic organic chemistry.[5] Since the first asymmetric reductive amination reaction reported by Blaser et al. in 1999 for the production of the herbicide metolachlor,[6] some progress has been made in the synthesis of chiral amines through intermolecular asymmetric reductive amination.[7] As for the intramolecular reaction, only two examples have been reported. In 2003, Wills and co-workers applied the Noyori transfer-hydrogenation catalytic system in the first intramolecular asymmetric reductive amination reaction to prepare 1-methyl-6,7-dimethoxytetrahydroisoquinoline in 85% yield with 88% *ee*.[8a] Merck chemists successfully utilized the same type of catalyst to construct the key stereogenic center of suvorexant, a drug approved by the FDA in 2014 for the treatment of insomnia, in 97% yield with 95% *ee*.[8b] Unlike the intermolecular counterpart, which could be deliberately designed by selecting from various nitrogen donors to accommodate the catalyst spatial and electronic requirements for better stereocontrol, the substrate for intramolecular reductive amination bears certain moieties, and difficulties may be encountered during the formation of the imine intermediate and the following reduction process.

Owing to the limited advances yet promising utility of the intramolecular asymmetric reductive amination reaction for the synthesis of chiral amines, the development of this reaction is challenging and highly desirable. Herein, we report the highly efficient combination of N-Boc deprotection and intramolecular hydrogenative asymmetric reductive amination in a one-pot process for the preparation of tetrahydroisoquinolines (Scheme 2). Catalyzed by iodine-

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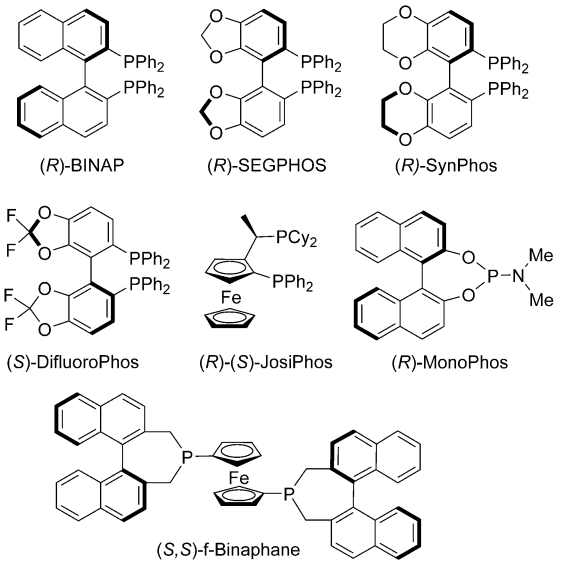
bridged dimeric iridium complexes and promoted by additives, this efficient reaction led to chiral tetrahydroisoquinolines in excellent yields with excellent enantioselectivity (up to 99% *ee*).

Initially, the N-Boc protecting group of the standard substrate *tert*-butyl 2-benzoylphenethylcarbamate (**1a**) was removed under acidic conditions. After all volatile components had been removed, the resulting substance underwent asymmetric reductive amination with the iridium–BINAP

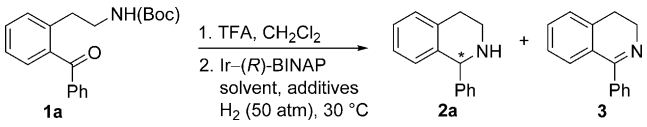


Scheme 3. Structures of chiral phosphine ligands.

(Scheme 3) catalytic system. Iridium–diphosphine complexes were chosen since iridium has displayed potential for imine reduction in the presence of various additives as compared with other transition metals.[4b,9] Several additives were examined (Table 1, entries 1–5).[10] Without any additive, the reaction yielded only imine intermediate **3**. It is commonly believed that $Ti(OiPr)_4$ can promote the formation of the imine intermediate during the reductive amination process.[7] Our study showed that it also accelerated the transformation of imine **3** into product **2a** (Table 1, entry 2). Although the addition of iodine alone did not help the reaction, its combination with $Ti(OiPr)_4$ did enhance the reduction of imine **3** as well as the enantioselectivity of the process. Brønsted acids have manifested positive effects on asymmetric reductive amination.[6,10b–d] In our study, upon the addition of *p*-toluenesulfonic acid, the *ee* value of the product was improved to 40%. From solvent screening, a 4:1 tetrahydrofuran/toluene mixture was found to provide the best yield and enantioselectivity (Table 1, entry 9).

We then screened several commercially available chiral phosphine ligands (Scheme 3). The doubly oxygenated atropisomeric C_2-symmetric bisphosphine ligands SEGPHOS, SynPhos, and DifluoroPhos, in conjunction with [{Ir(cod)Cl}$_2$], displayed good enantioselectivity in the asymmetric reductive amination of **1a** (Table 2, entries 2–4). The superior performance of those ligands might be related to their smaller dihedral angles, as compared with that of BINAP, and their electronic properties.[11] Iodine-bridged dimeric iridium complexes, initially reported by Genêt, Mashima, and co-workers,[12] showed outstanding performance in our previous studies on the asymmetric hydrogenation of 2-aryl 1-pyrrolines and 1-aryl 3,4-dihydroisoquinolines.[4c,13] Therefore, the complex [{Ir(H)[(*R*)-SEGPHOS]}$_2$(μ-I)$_3$]$^+$I$^-$ (**A**) was also prepared and examined in the reaction of **1a**. To our delight, the *ee* value of the product, which was formed in 99% yield, was dramatically improved to 97% (Table 2, entry 8). When trifluoroacetic acid (TFA; 10 mol%) was used instead of *p*-toluenesulfonic

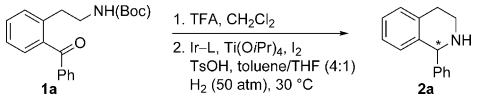
Table 1: Study of additives and solvents for the reductive amination of **1a**.[a]



Entry	Solvent	Additives[b]	**2a**/**3**[c]	*ee* [%][c]
1	CH_2Cl_2	–	1:99	–
2	CH_2Cl_2	$Ti(OiPr)_4$	40:60	15
3	CH_2Cl_2	I_2	1:99	–
4	CH_2Cl_2	$Ti(OiPr)_4$, I_2	68:32	22
5	CH_2Cl_2	$Ti(OiPr)_4$, I_2, TsOH	19:81	40
6	EtOAc	$Ti(OiPr)_4$, I_2, TsOH	98:2	16
7	THF	$Ti(OiPr)_4$, I_2, TsOH	95:5	15
8	toluene	$Ti(OiPr)_4$, I_2, TsOH	72:28	25
9[d]	toluene/THF	$Ti(OiPr)_4$, I_2, TsOH	98:2	24

[a] Reaction conditions: [Ir]/(*R*)-BINAP/**1a** (1:1:100), H_2 (50 atm), 13 h. [b] $Ti(OiPr)_4$ (1.1 equiv); TsOH = *p*-toluenesulfonic acid (10 mol%); I_2 (10 mol%). [c] Ratios and *ee* values were determined by HPLC on a chiral stationary phase after the products were converted into the corresponding acetamides. [d] Toluene/THF (4:1).

Table 2: Screening of chiral ligands.[a]



Entry	Ligand	Yield [%][b]	*ee* [%][c]
1	(*R*)-BINAP	98	24
2	(*R*)-SEGPHOS	98	74
3	(*R*)-Synphos	99	77
4	(*S*)-DifluoroPhos	99	75
5	(*S*)-(*R*)-Josiphos	62	15
6	(*R*)-Monophos	98	0
7	(*S*,*S*)-f-Binaphane	99	89
8[d]	(*R*)-SEGPHOS	99	97
9[d,e]	(*R*)-SEGPHOS	99	89
10[d,f]	(*R*)-SEGPHOS	98	98
11[d,g]	(*R*)-SEGPHOS	93	98

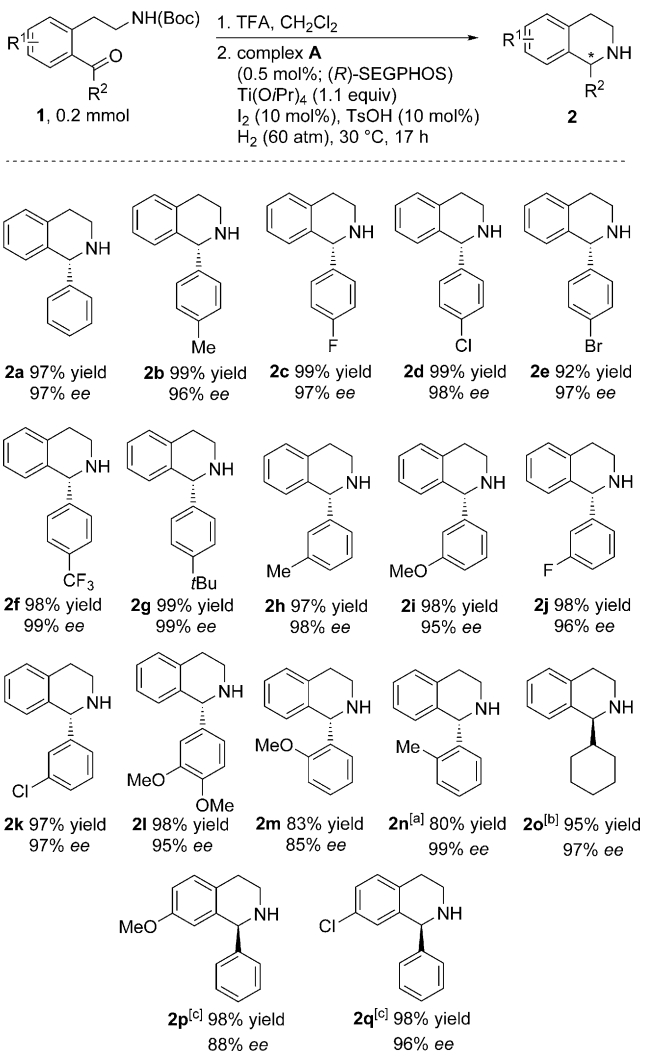
[a] Reaction conditions: [Ir]L$^-$/I_2/**1a** (1:1:10:100), $Ti(OiPr)_4$ (1.1 equiv), TsOH (10 mol%), H_2 (50 atm), 24 h. [b] Yields were calculated from ^{1}H NMR spectra. [c] The *ee* value was determined by HPLC on a chiral stationary phase after the product was converted into the corresponding acetamide. [d] Complex **A** was the catalyst. [e] TFA (10 mol%) was used instead of TsOH. [f] The H_2 pressure was 20 atm. [g] The H_2 pressure was 10 atm.

acid, the reaction remained quantitative, but the *ee* value dropped to 89% (entry 9). At a H_2 pressure of 20 atm, the reaction proceeded without a noticeable difference. When the H_2 pressure was further decreased to 10 atm, the yield dropped slightly to 93%, but the enantioselectivity was not affected (Table 2, entries 10 and 11).

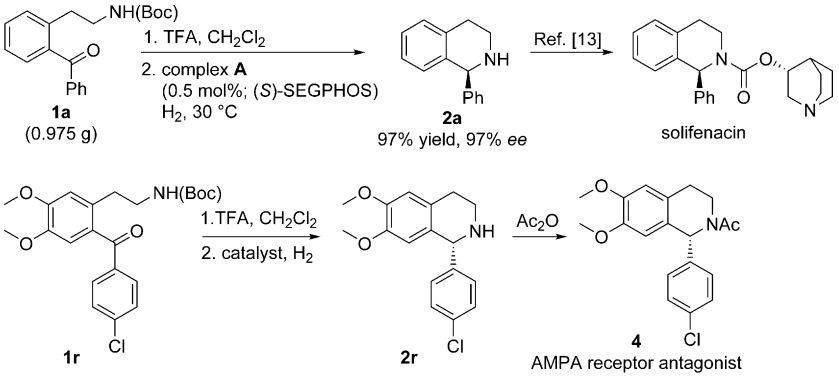
To explore the utility of the iodine-bridged dimeric iridium–SEGPHOS complex **A**, we prepared a range of 2-substituted *tert*-butyl benzoylphenethylcarbamate substrates **1** and studied them under the optimized conditions (Scheme 4). The electronic properties of the substrates exerted no evident effect on enantioselectivity or reactivity. However, the steric properties of certain substrates influenced their reactivity and the enantioselectivity of the reaction. When the substituents on the phenyl ring were at the *para* position (**1b**–**g**), the *meta* position (**1h**–**k**), or both *para* and *meta* (**1l**) positions, all substrates were converted into the corresponding tetrahydroisoquinoline alkaloids with high enantioselectivity (*ee* values all above 95%), regardless of the electronic nature of the substituents; for *ortho*-substituted substrates **1m** and **1n**, the results varied. The yield and *ee* value for **2m** was limited to 83 and 85%, respectively. Under the catalysis of complex **A** (1 mol%), **1n** was transformed into product **2n** with high enantioselectivity (99% *ee*). When the iodine-bridged dimeric Ir–(*S*,*S*)-f-Binaphane complex **B** was applied, the 2-alkylcarbonyl substrate **1o** was converted into the corresponding product **2o** in 95% yield with 97% *ee*. We also tested substrates with substituents on the aryl ring that forms part of the tetrahydroisoquinoline backbone of **2** and found that substrate **1q** with an electron-withdrawing substituent underwent a more enantioselective reaction than substrate **1p** with an electron-donating substituent.

To further demonstrate the practical utility of the newly developed method, we carried out the N-Boc deprotection and asymmetric reductive amination of **1a** on a gram scale. Catalyzed by complex **A** prepared from (*S*)-SEGPHOS, the reaction rendered the desired product (*S*)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**2a**) in 97% yield with 97% *ee*. Compound (*S*)-**2a** is the key intermediate for the pharmaceutical drugs (+)-solifenacin (Scheme 1)[14] and (+)-FR115427[15] (Scheme 5). We also examined substrate **1r**. With complex **A**, the corresponding acetamide **4**, an AMPA receptor antagonist (Scheme 1), was obtained in 95% yield with 75% *ee* (Scheme 5). The iodine-bridged dimeric iridium complex **B**, prepared from (*S*,*S*)-f-Binaphane (Scheme 3), afforded (*S*)-**4** in 95% yield with 97% *ee*.

In summary, we have developed a highly efficient and enantioselective protocol for the preparation of bioactive chiral 1-substituted tetrahydroisoquinolines. By this route, *tert*-butyl 2-benzoylphenethylcarbamates were effectively converted into the corresponding tetrahydroisoquinolines through N-Boc deprotection and direct asymmetric intramolecular reductive amination in a one-pot process. The iodine-bridged dimeric $[\{Ir(H)[(R)\text{-SEGPHOS}]\}_2(\mu\text{-}I)_3]^+I^-$ complexes **A** and **B** displayed excellent enantioselectivity and reactivity. Use of the Lewis acid titanium(IV) isopropoxide,



Scheme 4. Scope of the reaction. [a] The reaction was carried out with 1 mol% of complex **A**. [b] Complex **B** prepared from (*S*,*S*)-f-Binaphane was used. [c] $[\{Ir(H)[(S)\text{-SEGPHOS}]\}_2(\mu\text{-}I)_3]^+I^-$ was used.



Scheme 5. Larger-scale reductive amination of **1a** and synthesis of **4**.

molecular iodine, and the Brønsted acid *p*-toluenesulfonic acid as additives enhanced the performance of the catalyst. This catalytic system offers efficient access to various enantiomerically pure tetrahydroisoquinoline alkaloids, including the substructure of the pharmaceutical drugs solifenacin, (+)-FR115427, and AMPA receptor antagonist **4**. Further investigation of other intramolecular asymmetric reductive amination reactions for the preparation of chiral amines is in progress.

Experimental Section

General procedure: A mixture of substrate **1** (0.2 mmol) and TFA (6 equiv) in CH_2Cl_2 was stirred under nitrogen for 3 h. All volatile components were then removed, and the remaining material was transferred to a nitrogen-filled glovebox and dissolved in toluene (1 mL). $Ti(OiPr)_4$ (0.22 mmol), *p*-toluenesulfonic acid (0.02 mmol), complex **A** (0.001 mmol), and molecular iodine (0.02 mmol) were added to the above solution, and the volume of the solution was increased to 2.0 mL with toluene and THF so that the final toluene/THF ratio was 4:1. The vial with the resulting mixture was transferred to an autoclave, which was charged with H_2 (60 atm), and the mixture was stirred at 30 °C for 17 h. The solution was then neutralized with aqueous sodium bicarbonate solution, and the organic phase was concentrated and passed through a short column of silica gel to remove the metal complex and provide the chiral tetrahydroisopuinoline product. This product was then converted into the corresponding acetamide, the *ee* value of which was determined by HPLC on a chiral stationary phase.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · enantioselectivity · iridium · reductive amination · tetrahydroisoquinolines

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Communications

Asymmetric Catalysis

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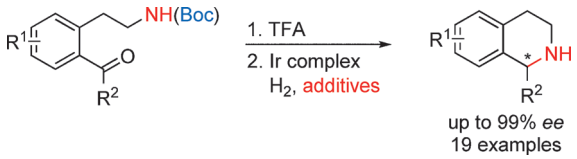
One-Pot N-Deprotection and Catalytic Intramolecular Asymmetric Reductive Amination for the Synthesis of Tetrahydroisoquinolines



Cool combo: N-Boc deprotection was combined with direct asymmetric intramolecular reductive amination in a one-pot process for the preparation of bioactive chiral 1-substituted tetrahydroisoquinolines (see scheme; Boc = *tert*-butoxycarbonyl). The iodine-bridged dimer $[\{Ir(H)[(R)\text{-SEGPHOS}]\}_2(\mu\text{-}I)_3]^+I^-$ was a very effective catalyst for the transformation, in which the additives $Ti(OiPr)_4$, *p*-toluenesulfonic acid, and I_2 played important roles.

