

Dual Stereocontrol for Enantioselective Hydrogenation of Dihydroisoquinolines Induced by Tuning the Amount of *N*-Bromosuccinimide

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ABSTRACT An efficient dual stereocontrol in iridium-catalyzed hydrogenation of 1-substituted 3,4-dihydroisoquinolines was realized by tuning the amount of *N*-bromosuccinimide using chiral ligand of single configuration, providing both enantiomers of 1-substituted 1,2,3,4-tetrahydroisoquinolines with up to 89% *ee* (*S*) and 98% *ee* (*R*), respectively. Dual activation role of *N*-bromosuccinimide is proposed to be responsible for the reversal of enantioselectivity under two hydrogenation conditions.

KEYWORDS reversal of enantioselectivity, hydrogenation, *N*-bromosuccinimide, 1,2,3,4-tetrahydroisoquinolines

Introduction

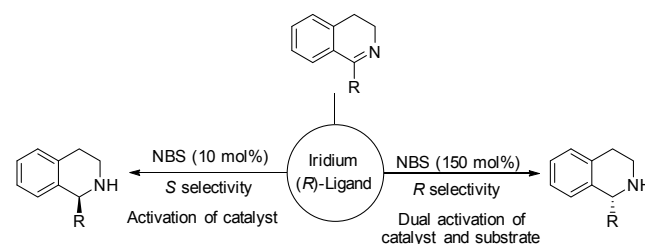
Since the tragedy of thalidomide event in 1950s, the completely different pharmacological activities of both enantiomers of chiral pharmaceuticals have drawn extensive attention from all around the world.^[1] According to regulations on Food and Drug Administration in United States in 1992, all the listed racemic medicines should be provided the details of two enantiomers in biological activity and toxicity.^[2] The complementary regulation in 1997 required that early listed racemic medicines should be replaced by the corresponding chiral enantiomer.^[3] Thus, the enantioselective synthesis of both enantiomers of a chiral pharmaceutical molecule is of great importance. Normally, both enantiomers of a chiral molecule were obtained by using two chiral reagents or ligands of opposite configuration. To prepare two enantiomers of a target compound from only one single-isomer of a chiral catalyst is an intriguing subject in synthetic community. The previous excellent researches suggested that modifying achiral parameters of reaction,^[4] such as metal,^[5] solvent,^[6] temperature,^[7] additives^[8] and others,^[9] would result in the reversal of enantioselectivity. However, the lack of exact knowledge and general regularity on switch in enantioselectivity make it challenging for further application.

A great progress has been made in iridium-catalyzed asymmetric hydrogenation in the past decades.^[10] Iridium-catalyzed enantioselective hydrogenation of isoquinoline,^[11] isoquinoline-type imine^[12] and enamine^[13] can provide effective access to chiral 1,2,3,4-tetrahydroisoquinolines that represents one kind of privileged scaffolds in pharmaceutical molecules and natural alkaloids.^[14] Till now, despite of the achievements mentioned above, both enantiomers of a chiral 1,2,3,4-tetrahydroisoquinoline were traditionally obtained by chemical resolution with two chiral reagents or by asymmetric transformations with two ligands of opposite configuration.^[15] In view of chiral atom economy, dual enantioselective hydrogenation of isoquinoline-type imine with single chiral catalyst is undoubtedly highly preferred and desirable.

For the past few years, our group has worked on iridium-catalyzed asymmetric hydrogenation of heteroaromatics.^[11a–11d] It was found that oxidizing agents containing halogen, such as *N*-iodosuccinimide (NIS) and *N*-bromosuccinimide (NBS), could significantly improve the performance of the catalyst by elevating the valence state of iridium (IrI to IrIII).^[16] Besides, halogen source could also react with imines or amines as oxidants.^[17] The dual activation of catalyst and substrate with halogen source inspired us to conduct further investigation of dual stereocontrol for

asymmetric hydrogenation of dihydroisoquinolines. Herein, we describe an effective dual stereocontrol in iridium-catalyzed asymmetric hydrogenation of 1-substituted 3,4-dihydroisoquinoline derivatives solely upon tuning the amount of NBS (Scheme 1).

Scheme 1 The reversal of enantioselectivity induced by the amount of NBS



Results and Discussion

Initially, 1-phenyl-3,4-dihydroisoquinoline **1a** was chosen as the model substrate using [Ir(COD)Cl]₂/(*R*)-BINAP as the chiral hydrogenation catalyst to evaluate the hydrogenation parameters (Table 1). To our delight, the desired product 1-phenyl-1,2,3,4-tetrahydroisoquinoline was obtained in the presence of 10 mol% NBS in 1,2-dichloroethane with full conversion and 82% *ee* (Table 1, Entry 1). Whereas further examinations focused on solvents and chiral bisphosphine ligands gave relatively lower enantioselectivities (Entries 2–7). When reaction temperature decreased to 0 °C, an enhancement of the enantioselectivity with 86% *ee* was observed (Entry 8).

In the next experiment investigation on the effect of NBS, it was found that increasing the amount of NBS resulted in a lower reactivity and the hydrogenation would be completely dead with 150 mol% NBS as additive. Fortunately, the hydrogenation was carried out smoothly in full conversion when with the addition of sodium carbonate. However, as the amount of NBS increased to 50 mol%, the *ee* value was decreased dramatically (Entry 10). Further research turned out that the *ee* value of product then sharply jumped up to 91% with 150 mol% NBS to afford a product with the reversed enantioselectivity after meeting with an almost racemate (Entries 9–15). These results showed that the enantioselectivity almost has a linear dependence relation with the amount of NBS (Figure 1) and the reversed enantioselectivity may be attributed to two completely different reaction modes. Thus, the amount of NBS was vital to establish the final systems (Entries 8 and 15) on the dual enantioselective hydrogenation of 1-sub-

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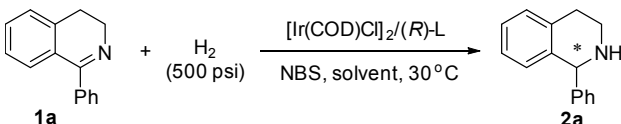
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stituted 3,4-dihydroisoquinolines **1**.

Table 1 Optimization of reaction conditions^a



Entry	Solvent	NBS, Na ₂ CO ₃ /mol%	(<i>R</i>)-L	<i>ee</i> ^b /%
1	DCE	10, 0	(<i>R</i>)-BINAP	82 (<i>S</i>)
2	toluene	10, 0	(<i>R</i>)-BINAP	79
3	THF	10, 0	(<i>R</i>)-BINAP	71
4 ^c	MeOH	10, 0	(<i>R</i>)-BINAP	68
5	DCE	10, 0	(<i>R</i>)-H8-BINAP	75
6	DCE	10, 0	(<i>R</i>)-SynPhos	63
7	DCE	10, 0	(<i>R</i>)-DifluoroPhos	65
8 ^d	DCE	10, 0	(<i>R</i>)-BINAP	86
9 ^d	DCE	10, 5	(<i>R</i>)-BINAP	86
10	DCE	50, 25	(<i>R</i>)-BINAP	55
11	DCE	75, 38	(<i>R</i>)-BINAP	13
12	DCE	90, 45	(<i>R</i>)-BINAP	-16
13	DCE	100, 50	(<i>R</i>)-BINAP	-53
14	DCE	120, 60	(<i>R</i>)-BINAP	-88
15	DCE	150, 75	(<i>R</i>)-BINAP	-91 (<i>R</i>)

^a Reaction conditions: **1a** (0.2 mmol), [Ir(COD)Cl]₂ (1.0 mol%), (*R*)-L (2.2 mol%), NBS, Na₂CO₃, solvents (3 mL), 24 h, 30 °C, H₂ (500 psi); conversions are over 95% determined by ¹H NMR, unless mentioned. ^b Determined by HPLC for the corresponding benzamide derivatives; ^c 91% conversion; ^d 0 °C, 36 h.

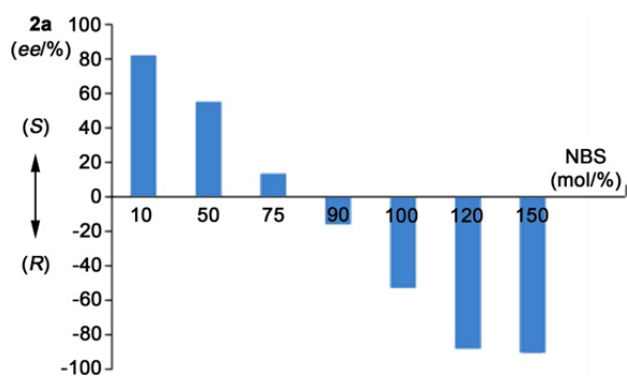
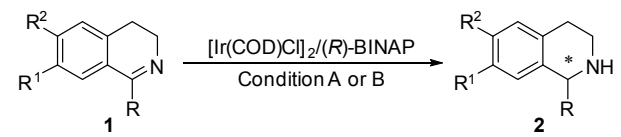


Figure 1 The effect of amount of NBS on enantioselectivity.

With the optimized conditions established, we then set out to demonstrate the generality of iridium-catalyzed dual enantioselective hydrogenation of 3,4-dihydroisoquinoline derivatives and the results are summarized in Table 2. Generally, the reactions were performed smoothly, giving the desired products with two isomers in good to excellent yields and enantioselectivities. For 1-aryl substituted substrate, high enantioselectivities were achieved regardless of the electronic properties of the substrates under condition A. On the contrary, the electronic properties of *R* group played an important role in the enantioselectivity of the reaction under condition B. It showed that an upward tendency of *ee* values was achieved as the enhanced electron-deficiency of the aryl group. And higher *ees* were obtained with electronically deficient substituent groups (Table 2, Entries 16, 18, 20). However, electron-donating groups on the C-1 aryl ring made negative effects on enantioselectivity (Entries 10, 12, 14). Significantly, with a methoxy group on 1-aryl of the substrate, a dramatic decrease in

enantioselectivity with 66% *ee* was observed (Entry 14). The isopropyl substituted substrate could also be hydrogenated smoothly but only in moderate enantioselectivity under both conditions (Entries 23, 24).

Table 2 Iridium-catalyzed dual enantioselective hydrogenation of 3,4-dihydroisoquinolines **1**^a



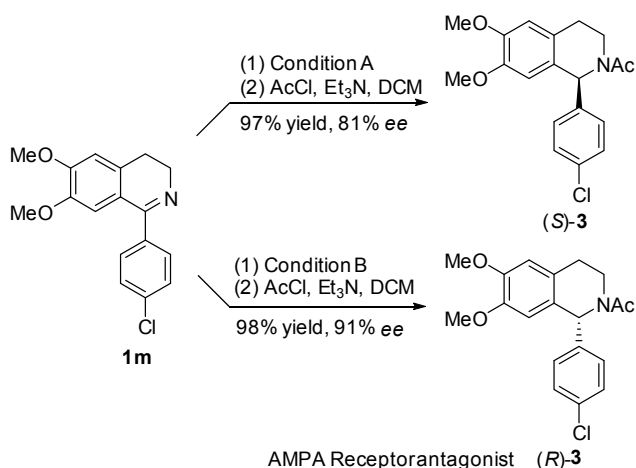
Entry	1	R ¹ /R ² /R	Condition	Yield ^b /%	<i>ee</i> ^c /%
1	1a	H/H/C ₆ H ₅	A	92	86 (<i>S</i>)
2			B	94	92(<i>R</i>)
3	1b	Me/H/C ₆ H ₅	A	92	89 (-)
4			B	88	98 (+)
5	1c	MeO/H/C ₆ H ₅	A	93	89 (-)
6			B	85	95 (+)
7	1d	MeO/MeO/C ₆ H ₅	A	89	88 (-)
8			B	85	90 (+)
9	1e	H/H/3-MeC ₆ H ₄	A	95	89 (+)
10			B	91	89 (-)
11	1f	H/H/4-MeC ₆ H ₄	A	95	84 (+)
12			B	88	83 (-)
13	1g	H/H/4-MeOC ₆ H ₄	A	93	84 (+)
14			B	85	66 (-)
15	1h	H/H/4-FC ₆ H ₄	A	96	86 (+)
16			B	94	95 (-)
17	1i	H/H/4-ClC ₆ H ₄	A	95	86 (+)
18			B	93	94 (-)
19	1j	H/H/4-BrC ₆ H ₄	A	98	85 (+)
20			B	92	93 (-)
21	1k	H/H/2-Naphthyl	A	93	85 (+)
22			B	90	91 (-)
23	1l	H/H/ ⁱ Pr	A	92	75 (-)
24			B	78	60 (+)

^a Condition A: **1** (0.3 mmol), [Ir(COD)Cl]₂ (2 mol%), (*R*)-BINAP (4.4 mol%), NBS (10 mol%), DCE (3 mL), 36 h, 0 °C, H₂ (500 psi); condition B: **1** (0.3 mmol), [Ir(COD)Cl]₂ (1 mol%), (*R*)-BINAP (2.2 mol%), NBS (150 mol%), Na₂CO₃ (75 mol%), DCE (4 mL), 24 h, 30 °C, H₂ (500 psi). ^b Isolated yields. ^c Determined by HPLC for the corresponding benzamide derivatives.

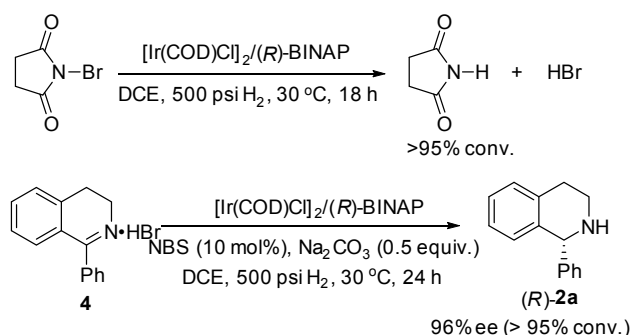
Furthermore, both enantiomers of a biologically active compound **3** were conveniently prepared through dual enantioselective hydrogenation under the above standard conditions and acylation in 81% *ee* (*S*) and 91% *ee* (*R*), respectively (Scheme 2). Notably, (*R*)-**3** is a potent noncompetitive AMPA receptor antagonist.^[18]

To gain more information on the role of NBS in reaction, some control experiments were conducted in the presence of iridium catalyst and hydrogen. The hydrogenolysis of NBS performed smoothly using the above chiral iridium complex as catalyst,^[11h] giving the succinimide and hydrogen bromide in full conversion (Scheme 3). Next, 1-phenyl-3,4-dihydroisoquinoline hydrobromide **4** was synthesized and subjected to the iridium-catalyzed enantioselective hydrogenation under the above standard condition B, providing the desired product **2a** in identical 96% *ee* with (*R*)-configuration, which is in accordant with the result of condition B. Therefore, the hydrogenation with 150 mol% NBS could be probably illustrated as the enantioselective hydrogenation of 1-phenyl-3,4-dihydroisoquinoline hydrobromide, which is consid-

Scheme 2 Dual enantioselective synthesis of AMPA receptor antagonist



Scheme 3 Control experiments



ered to be formed *in situ* with substrate and hydrogen bromide. As to the role of sodium carbonate, so far it is hard to explain exactly how it works. Neutralizing a part of excess acid to keep a subtle pH condition may be very crucial for reactivity and enantioselectivity of this process.

Combining these results and the related mechanistic research,^[16,19] a proposal on the stereocontrol mode for dual enantioselective hydrogenation of dihydroisoquinolines is illustrated as follows. In the presence of 10 mol% NBS, the hydrogenation proceeds mainly through a four-membered cyclic transition state TS₁. In the presence of 150 mol% NBS, the hydrogenation proceeds via a six-membered cyclic transition state TS₂ due to the formation of salts between substrate and the hydrogen bromide *in situ* generated from the hydrogenolysis of NBS (Figure 2). Consequently, NBS was not only used to improve the performance of catalyst by elevating the valence state of the center metal, but also to activate the imine substrate through hydrogen bromide.

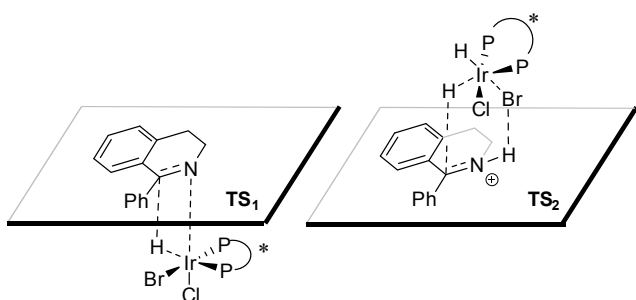


Figure 2 The two probable transition state of hydrogenation.

Conclusions

In summary, we have successfully developed an effective dual stereocontrol in iridium-catalyzed asymmetric hydrogenation of 1-substituted 3,4-dihydroisoquinolines. It provides a simple and convenient route to two enantiomers of 1-substituted tetrahydroisoquinolines with up to 89% ee (*S*) and 98% ee (*R*) only using (*R*)-BINAP, respectively. Dual activation role of *N*-bromosuccinimide is proposed to be responsible for the reversal of enantioselectivity under two different hydrogenation conditions. Further investigations on mechanism and application of this catalysis system with dual stereocontrol are ongoing in our group.

Experimental

General procedure for iridium-catalyzed dual enantioselective hydrogenation of 3,4-dihydroisoquinoline

Condition A. A mixture of [Ir(COD)Cl]₂ (4.0 mg, 0.006 mmol) and (*R*)-BINAP (8.2 mg, 0.0132 mmol) in 1,2-dichloroethane (DCE, 1.0 mL) was stirred at room temperature in the glove box. After 10 min, *N*-bromosuccinimide (NBS, 5.3 mg, 0.03 mmol) was added to the mixture with another 10 min's stirring. And then the catalyst was transferred by a syringe to the solution of 1-substituted 3,4-dihydroisoquinolines **1** (0.3 mmol) in 1,2-dichloroethane (2 mL). The hydrogenation was performed at 0 °C and at a hydrogen pressure of 500 psi for 36 h. After carefully releasing the hydrogen gas, the mixture was concentrated *in vacuo* and purification was performed by a silica gel column eluted with hexanes/ethyl acetate to give the enantiomerically enriched products (*S*)-**2**.

Condition B. A mixture of [Ir(COD)Cl]₂ (2.0 mg, 0.003 mmol) and (*R*)-BINAP (4.1 mg, 0.0066 mmol) in 1,2-dichloroethane (1.0 mL) was stirred at room temperature for 10 min in the glove box. Then the catalyst was transferred by a syringe to the mixture of 1-substituted 3,4-dihydroisoquinolines **1** (0.3 mmol), *N*-bromosuccinimide (80.1 mg, 0.45 mmol), sodium carbonate (23.9 mg, 0.225 mmol) and 1,2-dichloroethane (3 mL) with 10 min's stirring. Subsequently, the hydrogenation was performed at 30 °C and at a hydrogen pressure of 500 psi for 24 h. After carefully releasing the hydrogen gas, the mixture was extracted with diethyl ether twice and the combined organic extracts were dried over sodium sulfate and then concentrated in vacuum and purification was performed by a silica gel column eluted with hexanes/ethyl acetate to give the chiral products (*R*)-**2**.

(S)-1-Phenyl-1,2,3,4-tetrahydroisoquinoline (2a). Condition A: 57 mg, 92% yield, 86% ee, pale yellow solid, [α]_D²⁵ +15.17 (c 1.14, CHCl₃), *R*_T = 0.45 [V(hexanes) : V(ethyl acetate) = 2 : 1]; ¹H NMR (400 MHz, CDCl₃) δ : 7.34–7.25 (m, 5H), 7.14 (d, *J* = 4.1 Hz, 2H), 7.03 (dt, *J* = 8.1, 4.2 Hz, 1H), 6.75 (d, *J* = 7.7 Hz, 1H), 5.10 (s, 1H), 3.30–3.24 (m, 1H), 3.13–3.01 (m, 2H), 2.87–2.79 (m, 1H), 1.90 (brs, 1H); ¹³C NMR (100 MHz, CDCl₃) δ : 144.9, 138.3, 135.5, 129.1, 129.0, 128.5, 128.1, 127.4, 126.3, 125.7, 62.1, 42.3, 29.8; Enantiomeric excess was determined by HPLC for the corresponding benzamide [AD-H column, hexane/*i*-PrOH 70/30, 0.80 mL/min, 230 nm]: *t*₁ = 12.9 min (major), *t*₂ = 15.6 min.

(R)-1-Phenyl-1,2,3,4-tetrahydroisoquinoline (2a). Condition B: 59 mg, 94% yield, 92% ee, [α]_D²⁵ –15.33 (c 0.30, CHCl₃).

Supporting Information

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/cjoc.201700634> or from the author.

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