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

Yue Ji,[a]Jie Wang,[a]Mu-Wang Chen,[a]Lei Shi*[a,b]and Yong-Gui Zhou*[a]

[a]*State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023,P. R. China*

[b]*State Key Laboratory of Fine Chemicals, Dalian University of Technology, Dalian 116024, P. R. China*

An efficient dual stereocontrolin 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-tetrahydroisoquinolineswith 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.

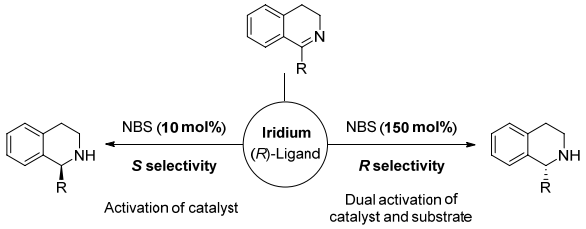
Keywords: Reversal of enantioselectivity, hydrogenation, *N*-bromosuccinimide, 1,2,3,4-tetrahydroisoquinolines

Introduction

Since the tragedy of thalidomide event in 1950s, the completely different pharmacological activities of both enantiomers of chiral pharmaceuticals has drew 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 hydrogenationin 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 alkoloids.[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.

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



For the past few years, our group has worked on iridium-catalyzed asymmetric hydrogenation of heteroaromatics.[11a-d] It was found that oxidizing agents containing halogen, such as *N*-iodosuccinimide (NIS), *N*-bromosuccinimide (NBS), could significantly improve the performance of the catalyst by elevating the valence state of iridium (Ir^{I} to Ir^{III}).[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-substituted3,4-dihydroisoquinoline derivatives solely upon tuning the amount of NBS(Scheme 1).

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/cjoc.201700634

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*-bromosuccinimde (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-dichlorethane (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 wasperformed 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*-bromosuccinimde (80.1 mg, 0.45 mmol), sodium carbonate (23.9 mg, 0.225 mmol) and 1,2-dichlorethane (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 ethertwice and the combined organic extracts 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**.

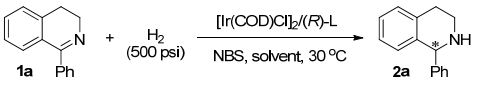
(*S*)-1-Phenyl-1,2,3,4-tetrahydroisoquinoline (2a): Condition A: 57 mg, 92% yield, 86% ee, pale yellow solid, $[\alpha]^{25}_D$ = +15.17 (*c*1.14, $CHCl_3$), R_f = 0.45 (hexanes/ethyl acetate 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.25 (m, 5H), 7.14 (d, *J* = 4.1 Hz, 2H), 7.03 (dt, *J* = 8.1, 4.2 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);^{13}C NMR (100 MHz, $CDCl_3$) 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, $[\alpha]^{25}_D$ = -15.33 (*c*0.30, $CHCl_3$).

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-dichloroethanewith full conversion and 82% ee (Table 1, entry 1). Whereas further examinations focused on solvents and chiral bisphosphine ligands gave relatively lower enenatioselectivities (entries 2-7). When reaction temperature decreased to 0 °C, an enhancement of the enantioselectivity with 86% ee was observed (entry 8).

Table 1 Optimization of reaction conditions[a]



entry	solvent	NBS, Na_2CO_3 (mol %)	(*R*)-L	ee (%)[b]
1	DCE	10, 0	(*R*)-BINAP	82 (S)
2	toluene	10, 0	(*R*)-BINAP	79
3	THF	10, 0	(*R*)-BINAP	71
4[c]	MeOH	10, 0	(*R*)-BINAP	68
5	DCE	10, 0	(*R*)-H8-BINAP	75
6	DCE	10, 0	(*R*)-SynPhos	63
7	DCE	10, 0	(*R*)-DifluroPhos	65
8[d]	DCE	10, 0	(*R*)-BINAP	86
9[d]	DCE	10, 5	(*R*)-BINAP	86
10	DCE	50, 25	(*R*)-BINAP	55
11	DCE	75, 38	(*R*)-BINAP	13
12	DCE	90, 45	(*R*)-BINAP	-16
13	DCE	100, 50	(*R*)-BINAP	-53
14	DCE	120, 60	(*R*)-BINAP	-88
15	DCE	150, 75	(*R*)-BINAP	-91 (*R*)

[a] Reaction conditions: **1a** (0.2 mmol), $[Ir(COD)Cl]_2$ (1.0 mol%), (*R*)-L (2.2 mol%), NBS, Na_2CO_3, solvents (3 mL), 24 h, 30 °C, H_2 (500 psi); Conversions are over 95% determined by ^{1}H NMR, unless mentioned; [b] Determined by HPLC for the corresponding benzamidederivatives;[c]91% conversion; [d] 0 °C, 36 h.

In the next experiment investigation on the effect of NBS, it were 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-substituted 3,4-dihydroisoquinolines **1**.

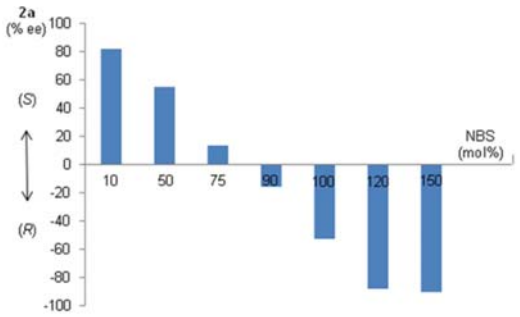
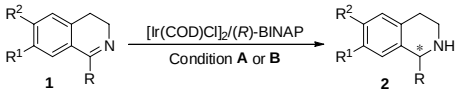


Figure 1 The effect of amount of NBS on enantioselectivity.

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 enatioselectivity 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).

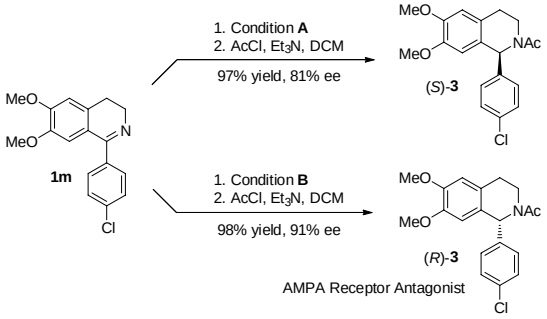
Table2 Iridium-catalyzed dual enantioselective hydrogenation of 3,4-dihydroisoquinolines 1[a]



entry	1	$R^1/R^2/R$	condition	yield (%)[b]	ee (%)[c]
1	**1a**	H/H/C_6H_5	**A**	92	86 (*S*)
2			**B**	94	92(*R*)
3	**1b**	Me/H/C_6H_5	**A**	92	89 (-)
4			**B**	88	98 (+)
5	**1c**	MeO/H/C_6H_5	**A**	93	89 (-)
6			**B**	85	95 (+)
7	**1d**	MeO/MeO/C_6H_5	**A**	89	88 (-)
8			**B**	85	90 (+)
9	**1e**	H/H/3-MeC_6H_4	**A**	95	89 (+)
10			**B**	91	89 (-)
11	**1f**	H/H/4-MeC_6H_4	**A**	95	84 (+)
12			**B**	88	83 (-)
13	**1g**	H/H/4-$MeOC_6H_4$	**A**	93	84 (+)
14			**B**	85	66 (-)
15	**1h**	H/H/4-FC_6H_4	**A**	96	86 (+)
16			**B**	94	95 (-)
17	**1i**	H/H/4-ClC_6H_4	**A**	95	86 (+)
18			**B**	93	94 (-)
19	**1j**	H/H/4-BrC_6H_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 (+)

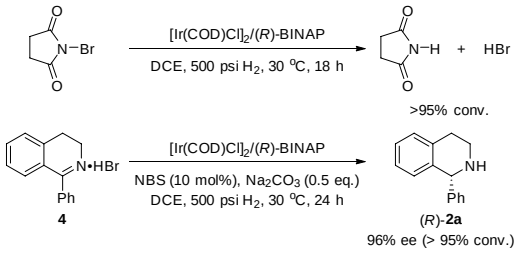
[a]Condition**A**: **1** (0.3 mmol), $[Ir(COD)Cl]_2$ (2 mol%), (*R*)-BINAP (4.4 mol%), NBS (10 mol%), DCE(3 mL), 36 h, 0 °C, H_2 (500 psi); Condition**B**:**1** (0.3 mmol), $[Ir(COD)Cl]_2$ (1 mol%), (*R*)-BINAP (2.2 mol%), NBS (150 mol%), Na_2CO_3 (75 mol%), DCE(4 mL), 24 h, 30 °C, H_2 (500 psi); [b] Isolated yields. [c] Determined by HPLC for the corresponding benzamide derivatives.

Scheme 2 Dual enantioselective synthesis of AMPA receptor antagonist



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]

Scheme 3 Control experiments



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-dihydroiso-quinoline 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 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 considered 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.

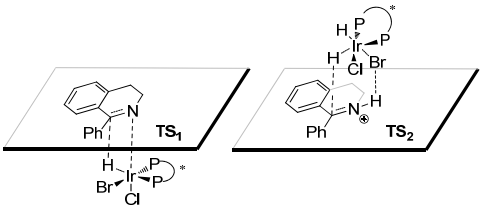


Figure 2 The two probable transition state of hydrogenation.

Combining with these results and the related mechanistic research,[16,19] a proposal on the stereo-control 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 TS_1. In the presence of 150 mol% NBS, the hydrogenation proceeds *via* a six-membered cyclic transition state TS_2 due tothe formation of salts betweensubstrate 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 substratethrough hydrogen bromide.

Conclusions

In summary, we have successfully developed an effective dual stereocontrol in iridium-catalyzed asymmetric hydrogenation of 1-substituted 3,4-dihydroiso-quinolines. 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*-bromosuccinimideis 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 stereo- control are ongoing in our group.

Acknowledgement

We are grateful for the financial support from National Natural Science Foundation of China (21472188, 21690074), State Key Laboratory of Fine Chemicals (KF1503) and Youth Innovation Promotion Association of Chinese Academy of Sciences (2014167).

References

[1] (a) Burley, D. M.; Lenz, W. *Lancet***1962**, *279*, 271. (b) Stephans, T. D. *Teratology***1988**, *38*, 229.

[2] Regulations on Food and Drug Administration of listed racemic pharmaceuticals in **1992**, see: http://www.fda.gov/drugs/guidance complianceregulatoryinformation/guidances/ucm122883.htm.

[3] Regulations on Food and Drug Administration of listed racemic pharmaceuticals in **1997**, see: http://www.fda.gov/drugs/guidance complianceregulatoryinformation/guidances/ucm134966.htm.

[4] For recent reviews on dual stereocontrol of asymmetric reactions: (a) Bartók, M. *Chem. Rev.* **2010**, *110*, 1663. (b) Escorihuela, J.; Burgueteb, M. I.; Luis, S. V. *Chem. Soc. Rev.* **2013**, *42*, 5595.

[5] Wang, Z.; Yang, Z.; Chen, D.; Liu, X.; Lin, L.; Feng, X. *Angew. Chem. Int. Ed.* **2011**, *50*, 4928.

[6] (a) Zhou, J.; Ye, M.-C.; Huang, Z.-Z.; Tang, Y. *J. Org. Chem.***2004**, *70*, 1309. (b) Sohtome, Y.; Tanaka, S.; Takada, K.; Yamaguchi, T.; Nagasawa, K.; *Angew. Chem. Int. Ed.***2010**, *49*, 9254. (c) Haddad, N.; Qu, B.; Rodriguez,S.;van der Veen, L.; Reeves, D. C.; Gonnella, N. C.; Lee, H.; Grinberg, N.; Ma, S.; Krishnamurthy, D.; Wunberg, T.; Senanayake, C. H. *Tetrahedron Lett.***2011**, *52*, 3718. (d) Yu, H.; Xie, F.; Ma, Z.; Liu, Y.; Zhang, W. *Org. Biomol. Chem.* **2012**, *10*, 5137. (e) Burés, J.; Dingwall, P.; Armstrong, A.; Blackmond, D. G. *Angew. Chem. Int. Ed*. **2014**, *53*, 8700. (f) Vijaya, P. K.; Murugesan, S.; Siva, A. *Tetrahedron Lett*. **2015**, *56*, 5209.

[7] (a) Chan, V. S.; Chiu, M.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.***2009**, *131*, 6021. (b) Chaubey, N. R.; Ghosh, S. K. *RSC Adv.***2011**, *1*, 393.

[8] (a) Arseniyadis, S.; Subhash, P. V.; Valleix, A.; Mathew, S. P.; Blackmond, D. G.; Wagner, A.; Mioskowski, C. *J. Am. Chem. Soc.* **2005**, *127*, 6138. (b) Abermil, N.; Masson, G.; Zhu, J. *Org. Lett.* **2009**, *11*, 4648. (c) Blackmond, D. G.; Moran, A.; Hughes, M.; Armstrong, A. *J. Am. Chem. Soc.* **2010**, *132*, 7598. (d) Moteki, S. A.; Han, J.; Arimitsu, S.; Akakura, M.; Nakayama, K.; Maruoka, K.*Angew. Chem. Int. Ed.***2012**, *51*, 1187.

[9] (a) Zeng, W.; Chen, G.-Y.; Zhou, Y.-G.; Li, Y.-X.*J. Am. Chem. Soc.***2007**, *129*, 750. (b) Lutz, F.; Igarashi, T.; Kinoshita, T.; Asahina, M.; Tsukiyama, K.; Kawasaki, T.; Soai, K. *J. Am. Chem. Soc.* **2008**, *130*, 2956. (c) Szőri, K.; Balázsik, K.; Cserényi, S.; Szőllősi, G.; Bartók, M. *Appl. Catal. A: Gen.***2009**, *362*, 178. (d) Shibata, N.; Okamoto, M.; Yamamoto, Y.; Sakaguchi, S. *J. Org. Chem.***2010**, *75*, 5707. (e) Szőllősi, G.; Busygin, I.; Hermán, B.; Leino, R.; Bucsi, I.; Murzin, D. Y.; Fülöp, F.; Bartók, M. *ACS Catal.***2011**, *1*, 1316. (f) Ding, Z.-Y.; Chen, F.; Qin, J.; He, Y.-M.; Fan, Q.-H. *Angew. Chem. Int. Ed.***2012**, *51*, 5706. (g) Wang, D.; Cao, P.; Wang, B.; Jia, T.; Lou,Y.; Wang, M.; Liao, J.*Org. Lett.***2015**, *17*, 2420. (h) Ordóñez, M.; Hernández-Fernández, E.; Rojas-Cabrera, H.; Labastida-Galván, V. *Tetrahedron: Asymmetry***2008**, *19*, 2767. (i) Ivšić, T.; Hameršak, Z. *Tetrahedron: Asymmetry***2009**, *20*, 1095. (j) Tin, S.; Fanjulb, T.; Clarke, M. L. *Catal. Sci. Technol.***2016**, *6*, 677.

[10] For selected reviews: (a) Lu, S.-M.; Han, X.-W.; Zhou, Y.-G. *Chin. J. Org. Chem.***2005**, *25*, 634. (b) Zhou, Y.-G. *Acc. Chem. Res.***2007**, *40*, 1357. (c) Church, T. L.; Andersson, P. G. *Coord. Chem. Rev.***2008**, *252*, 513. (d) Xie, J.-H.; Zhu, S.-F.; Zhou, Q.-L. *Chem. Rev.* **2011**, *111*, 1713. (e) Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.;

Zhou, Y.-G. *Chem. Rev.***2012**, *112*, 2557. (f) Bartoszewicz, A.; Ahlsten, N.; Martn-Matute, B. *Chem. Eur. J.***2013**, *19*, 7274. (g) He, Y.-M.; Song, F.-T.; Fan, Q.-H. *Top. Curr. Chem.***2014**, *343*, 145.(h) Verendel, J. J.; Pàmies, O.; Diéguez, M.; Andersson, P.G. *Chem. Rev.***2014**, *114*, 2130. (i)Margarita, C.; Andersson, P. G. *J. Am. Chem. Soc*. **2017**, *139*, 1346. (j) Wang, Y.; Zhang, Z.; Zhang, W. *Chin. J. Org. Chem.* **2015**, *35*, 528. (k) Yang, W.; Pan, X.; Yang, D. *Chin. J. Org. Chem.***2015**, *35*, 1216.

[11] For the selected examples: (a) Lu, S.-M.; Wang, Y.-Q.; Han, X.-W.; Zhou, Y.-G. *Angew. Chem. Int. Ed.***2006**, *45*, 2260. (b) Shi, L.; Ye, Z.-S.; Cao, L.-L.; Guo, R.-N.; Hu, Y.; Zhou, Y.-G. *Angew. Chem. Int. Ed.***2012**, *51*, 8286. (c) Guo, R.-N.; Cai, X.-F.; Shi, L.; Ye, Z.-S.; Chen, M.-W.; Zhou, Y.-G. *Chem. Commun.***2013**, *49*, 8537. (d) Ye, Z.-S.; Guo, R.- N.; Cai, X.-F.; Chen, M.-W.; Shi, L.; Zhou, Y.-G. *Angew. Chem. Int. Ed.***2013**, *52*, 3685. (e) Iimuro, A.; Yamaji, K.; Kandula, S.; Nagano, T.; Kita, Y.; Mashima, K. *Angew. Chem. Int. Ed.***2013**, *52*, 2046. (f) Ding, Z.-Y.; Wang, T.; He, Y.-M.; Chen, F.; Zhou, H.-F.; Fan, Q.-H.; Guo, Q.; Chan, A. S. C. *Adv. Synth. Catal.***2013**, *355*, 3727. (g) Wen, J.; Tan, R.; Liu, S.; Zhao, Q.; Zhang, X. *Chem. Sci*. **2016**, *7*, 3047. (h) Chen, M.-W.; Ji, Y.; Wang, J.; Chen, Q.-A.; Shi, L.; Zhou, Y.-G. *Org.Lett.***2017**, *19*, 4988.

[12] For the selected examples: (a) Chang, M.; Li, W.; Zhang, X. *Angew. Chem. Int. Ed.***2011**, *50*, 10679. (b) Xie, J.-H.; Yan, P.-C.; Zhang, Q.-Q.; Yuan, K.-X.; Zhou, Q.-L. *ACS Catal.***2012**, *2*, 561 (c) Berhal, F.; Wu, Z.; Zhang, Z.; Ayad, T.; Ratovelomanana-Vidal, V. *Org. Lett.***2012**, *14*, 3308. (d) Ružič, M.; Pečavar, A.; Prudič, D.; Kralj, D.; Scriban, C.; Zanotti-Gerosa, A. *Org. Process Res. Dev.***2012**, *16*, 1293. (e) Wu, J.; Barnard, J. H.; Zhang, Y.; Talwar, D.; Robertson, C. M.; Xiao, J. *Chem. Commun.* **2013**, *49*, 7052. (f) Schwenk, R.; Togni, A. *Dalton Trans.***2015**, *44*, 19566. (g)Ji, Y.; Shi, L.; Chen, M.-W.; Feng, G.-S.; Zhou, Y.-G. *J. Am. Chem. Soc*.**2015**, *137*, 10496. (h) Ji, Y.; Feng, G.-S.; Chen, M.-W.; Shi, L.; Du H.; Zhou, Y.-G. *Org. Chem. Front*. **2017**, *4*, 1125. (i) Zhou, H.; Liu, Y.; Yang, S.; Zhou, L.; Chang, M. *Angew. Chem. Int. Ed.***2017**, *56*, 2725. (j) Li, H.; Tian, P.; Xu, J.-H.; Zheng, G.-W. *Org. Lett.***2017**, *18*, 3151.

[13] For the selected examples: (a) Yan, P.-C.; Xie, J.-H.; Hou, G.-H.; Wang, L.-X.; Zhou, Q.-L. *Adv. Synth. Catal.***2009**, *351*, 3243. (b) Hou, G.-H.; Xie, J.-H.; Yan, P.-C.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2009**,*131,* 1366.

[14] (a) Liu, W.; Liu, S.; Jin, R.; Guo, H.; Zhao, J. *Org. Chem. Front.***2015**, *2*, 288. (b) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669.

[15] (a) Trinadhachari, G. N.; Kamat, A. G.; Balaji, B. V.; Prabahar, K. J.; Naidu, K. M.; Babu, K. R.; Sanasi, P. D. *Org. Process Res. Dev.***2014**, *18*, 934. (b) Zhu, R.; Xu, Z.; Ding, W.; Liu, S.; Shi, X.; Lu, X. *Chin. J. Chem.* **2014**, *32*, 1039.

[16] Wang, D.-W.; Wang, X.-B.; Wang, D.-S.; Lu, S.-M.; Zhou, Y.-G.; Li, Y.-X. *J. Org. Chem.***2009**, *74*, 2780.

[17] (a) Castellote, I.; Morón, M.; Burgos, C.; Alvarez-Builla, J.; Martin, A.; Gómez-Sal, P.; Vaquero, J. J. *Chem. Commun.***2007**, 1281. (b) Bolchi, C.; Pallavicini, M.; Fumagalli, L.; Straniero, V.; Valoti, E. *Org. Process Res. Dev*. **2013**, *17*, 432.

[18] (a) Gitto, R.; Barreca, M. L.; De Luca, L.; De Sarro, G.; Ferreri, G.; Quartarone, S.; Russo, E.; Constanti, A.; Chimirri, A. *J. Med. Chem.***2003**, *46*, 197. (b) Gitto, R.; Ficarra, R.; Stancanelli, R.; Guardo, M.; Luca, L. D.; Barreca, M. L.; Pagano, B.; Rotondo, A.; Bruno, G.; Russo, E.; Sarro, G. D.; Chimirri, A. *Bioorg. Med. Chem.***2007**, *15*, 5417.

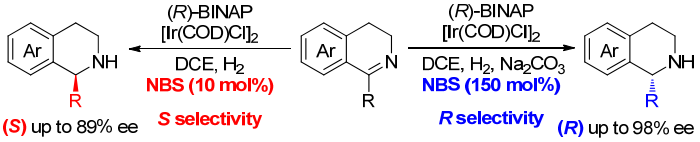
[19] Kita, Y.; Yamaji, K.; Higashida, K.; Sathaiah, K.; Iimuro, A.; Mashima, K. *Chem. Eur. J.* **2015**, *21*, 1915.

Entry for the Table of Contents

Page No.

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

Yue Ji, Jie Wang, Mu-Wang Chen,Lei Shi*andYong-Gui Zhou*



An efficient dual stereocontrolin iridium-catalyzed hydrogenation of 1-substituted 3,4-dihydroisoquinolines was realized by tuning the amount of *N*-bromosuccinimide using chiral ligand of single configuration.The dual activation role of *N*-bromosuccinimideis proposed to be responsible for the reversal of enantioselectivity under two hydrogenation conditions.