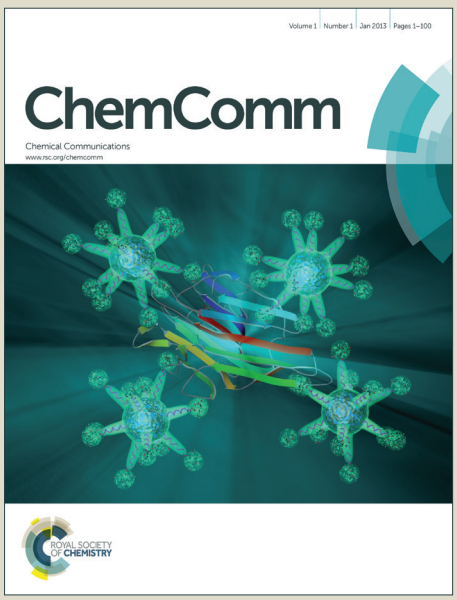
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Journal Name

RSCPublishing

COMMUNICATION

Highly Efficient Iridium-Catalyzed Asymmetric Hydrogenation of β-Acylamino Nitroolefins†

Cite this: DOI: 10.1039/xoxxoooooox

Qiaozhi Yan,‡ Man Liu,‡ Duanyang Kong, Guofu Zi, and Guohua Hou*

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

www.rsc.org/

The first highly efficient Ir-catalyzed enantioselective hydrogenation of β-acylamino nitroolefins is reported. This reaction provides straightforward access to chiral β-amino nitroalkanes in high yields and excellent enantioselectivities (up to >99.9% ee) catalyzed by an Ir-(*R*,*R*)-f-spiroPhos complex.

Enantiomerically pure β-amino nitroalkanes are valuable synthetic intermediates that can be easily converted to useful compounds such as α-amino acids[1] and diamines,[2] and to various moieties present in pharmaceuticals and biologically active molecules,[3] such as, Tamiflu, which is used to treat influenza,[4] and clopidogrel, a platelet aggregation inhibitor used to reduce the risk of strokes and heart attacks (Figure 1).[5]

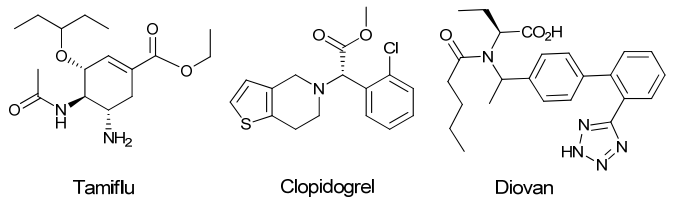
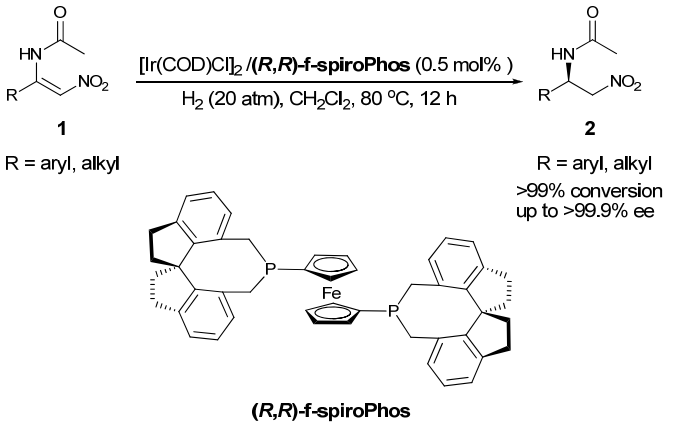


Figure 1. Key structural elements in chiral pharmaceuticals.

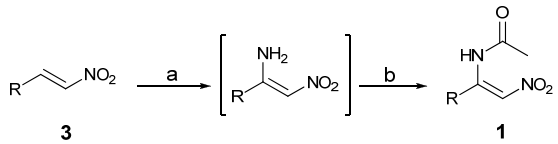
Because of the utility of chiral β-amino nitroalkanes in chemical synthesis, many methods have been developed for their enantioselective synthesis, the main method being the asymmetric aza-Henry reaction.[6] In addition, asymmetric aza-Michael addition of amines to nitroalkenes is a useful approach.[7] More recently, Sun and co-workers reported the asymmetric hydrosilylation of β-amino nitroalkanes as another route to chiral β-amino nitroalkanes.[8]

Asymmetric catalytic hydrogenation is one of the most powerful approaches to chiral compounds, and great progress on its use has been made.[9] Many types of olefins bearing functional groups such as amino,[10] carbonyl,[11] and cyano groups[12] have been hydrogenated in high enantioselectivities and efficiency. However, only one example of asymmetric hydrogenation of β-amino nitroalkenes has been reported using the Rh-Tangphos complex as the catalyst, by Zhang and co-workers;[13] the best enantioselectivity was 93% ee for aryl β-amino nitroalkenes, and rather poor enantioselectivities (only 8–22% ee) was observed for alkyl substrates. Thus, hydrogenation of β-amino nitroalkenes remains an active research area, and the development of new chiral catalyst systems is a desirable and challenging goal.[14] Herein, we report the first example of an Ir-catalyzed asymmetric hydrogenation of β-acylamino nitroolefins to generate chiral β-amino nitroalkanes in high yields and excellent enantioselectivities (up to >99.9% ee) using the novel chiral ligand (*R*,*R*)-f-spiroPhos (Scheme 1), which can be prepared from enantiomerically pure (*R*)-1,1′-spirobiindane-7,7′-diol (SPINOL) with Zhou's procedure (see Supplementary Information).[15]



Scheme 1. Ir-Catalyzed Asymmetric Hydrogenation of β-Acylamino Nitroolefins **1**.

The β-acylamino nitroolefin substrates were easily prepared in two steps from readily accessible nitroalkenes **3** in good yields (Scheme 2). To evaluate various ligands and optimize the reaction conditions for the hydrogenation, we used (*Z*)-*N*-(2-nitro-1-phenylvinyl)acetamide (**1a**) as a model substrate, and the hydrogenation was initially performed under 100 atm of H_2 in CH_2Cl_2 at room temperature with an iridium catalyst generated *in situ* from 0.5 mol% $[Ir(COD)Cl]_2$ and various chiral phosphorus ligands (Figure 2, Table 1). Of the ligands available in our laboratory, monodentate phosphorus ligands, such as MonoPhos and SIPHOS, were inefficient for this transformation, and very low conversions were obtained (≤2%, table 1, entries 1–2). Most of the bidentate diphosphine ligands we evaluated, including Binap, DuanPhos, SegPhos, and JosiPhos, also gave low conversions and poor enantioselectivities (≤43% ee, table 1, entries 3–7), except for f-spiroPhos, which afforded chiral β-acylamino nitroalkane **2a** in excellent enantioselectivity (99% ee), although the conversion was low (Table 1, entry 8).



Scheme 2. Synthesis of β-acylamino nitroolefins. Conditions: (a) CH_3ONH_2-HCl, ^{t}BuOK, in DMF, 0 °C. (b) Ac_2O, DMAP, pyridine, in CH_2Cl_2.

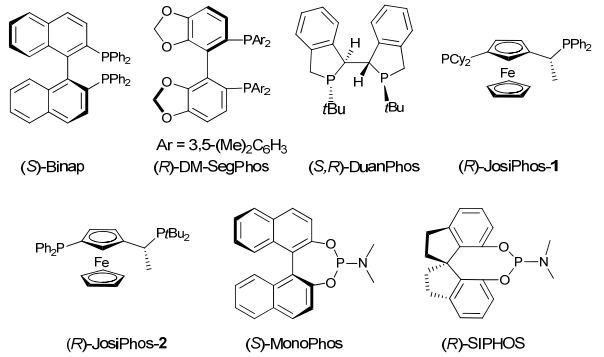
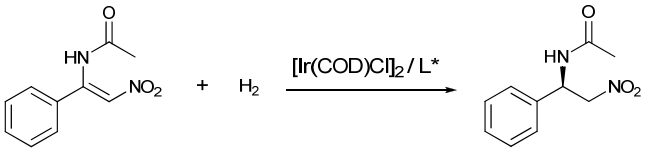


Figure 2. Structures of phosphine ligands evaluated in the hydrogenation of (*Z*)-*N*-(2-nitro-1-phenylvinyl) acetamide (**1a**).

In the evaluation of solvents in this catalytic transformation, poor conversions (≤22%) and moderate to high enantioselectivities were observed in THF, toluene, DME, dioxane, ether, and MeOH (Table 1, entries 9–14). The reaction temperature was crucial for this transformation. Increasing the reaction temperature from room temperature to 80 °C resulted in complete conversion in 12 h, albeit with a slight loss in enantioselectivity (98% ee, table 1, entry 15). Remarkably, the hydrogenation could also be achieved at a much lower pressure of H_2: under 20 atm of H_2 pressure, hydrogenation of **1a** was complete in 12 h and afforded **2a** in 99% ee (Table 1, entry 16). Lowering the H_2 pressure further, to 10 atm, excellent enantioselectivity remained, although conversion slightly decreased (92%; Table 1, entry 17).

Table 1. Optimization of Conditions for Ir-Catalyzed Asymmetric Hydrogenation of β-Acylamino Nitroolefin 1a[a].



1a **2a**

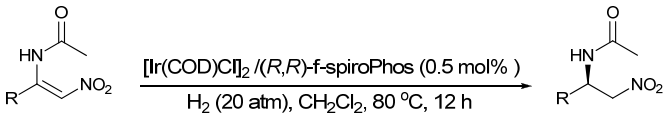
entry	ligand	solvent	*T* (°C)	PH_2 (atm)	con. (%)[b]	ee. (%)[c]
1	(*S*)-MonoPhos	CH_2Cl_2	rt	100	<1	ND
2	(*R*)-SIPHOS	CH_2Cl_2	rt	100	2	ND
3	(*S*)-Binap	CH_2Cl_2	rt	100	6	15
4	(*R*)-DM-SegPhos	CH_2Cl_2	rt	100	15	39
5	(*S*,*R*)-DuanPhos	CH_2Cl_2	rt	100	12	43
6	(*R*)-JosiPhos-**1**	CH_2Cl_2	rt	100	23	19
7	(*R*)-JosiPhos-**2**	CH_2Cl_2	rt	100	61	28
8	(*R*,*R*)-f-spiroPhos	CH_2Cl_2	rt	100	37	99
9	(*R*,*R*)-f-spiroPhos	THF	rt	100	17	91
10	(*R*,*R*)-f-spiroPhos	toluene	rt	100	22	66
11	(*R*,*R*)-f-spiroPhos	DME	rt	100	18	91
12	(*R*,*R*)-f-spiroPhos	dioxane	rt	100	14	90
13	(*R*,*R*)-f-spiroPhos	Et_2O	rt	100	8	82
14	(*R*,*R*)-f-spiroPhos	MeOH	rt	100	7	83
15[d]	(*R*,*R*)-f-spiroPhos	CH_2Cl_2	80	100	>99	98
16[d]	(*R*,*R*)-f-spiroPhos	CH_2Cl_2	80	20	>99	99
17[d]	(*R*,*R*)-f-spiroPhos	CH_2Cl_2	80	10	92	99

[a] Reaction conditions: $[Ir(COD)Cl]_2$/phosphine/substrate ratio = 0.5:2:100, 100 atm H_2, 24 h. [b] Conversion, determined by GC analysis. [c] Determined by chiral GC using a Supelco Gamma-Dex 225 column (30 m × 0.25 mm × 0.25 μm). [d] 12 h.

Encouraged by the promising result obtained in the hydrogenation of the substrate **1a**, we next subjected a variety of β-acylamino nitroolefins substrates (**1b**–**1q**) to the hydrogenation reaction under the optimized conditions: $[Ir(COD)Cl]_2$/(*R*,*R*)-f-spiroPhos in CH_2Cl_2 at 80 °C under 20 atm of H_2 pressure (Table 2). We found that hydrogenation of all the substrates provide the desired β-amino nitroalkanes with high conversions and excellent ee values. The electronic properties of the substituents on the phenyl group of the substrates had no obvious influence on the conversion or enantioselectivity of the reaction. Substrates bearing electron-donating substituents (methyl and methoxyl) or electron-withdrawing substituents (F, Cl, Br, and CF_3) at the *para* or *meta* position of the phenyl group were all smoothly hydrogenated with complete conversions and excellent enantioselectivities (99–99.9% ee, table 2, entries 2–11). Even substrates with a F, Cl, or Me substituent at the *ortho* position of the phenyl group were hydrogenated with complete conversions and excellent enantioselectivities (98–99.3% ee, table 2, entries 12–14). These results indicate that steric hindrance due to the *ortho* substituent had no effect on the reactivity or enantioselectivity of this transformation. Two fused-ring substrates, 1-napthyl and 2-napthyl β-acylamino nitroolefins, were also hydrogenated with similar excellent enantioselectivities (97% and 99% ee respectively) and full conversions (Table 2, entries 15 and 16). A slightly decreased enantioselectivity (97% ee) was observed for the hydrogenation of furyl β-acylamino nitroolefin **1o** (Table 2, entry 17). It is noteworthy that alkyl β-acylamino nitroolefins could also be smoothly and completely converted to the corresponding products in excellent enantioselectivities. For example, a substrate with an isopropyl or

cyclohexyl group gave the corresponding product with complete conversion and excellent ee values, 96% and 98% ee respectively (Table 2, entries 19 and 20). However, for n-butyl substrate, a slightly lower ee value was observed (Table 2, entry 18).

Table 2. Ir-Catalyzed Asymmetric Hydrogenation of β-Acylamino Nitroolefins 1[a]

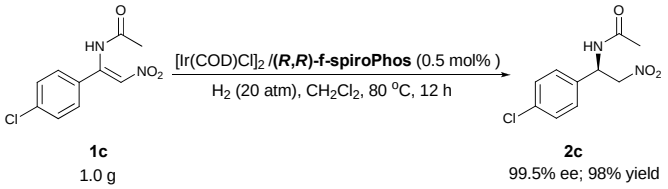


1 2

entry	R	product	con (%)[b]	ee (%)[c]
1	C_6H_5 (**1a**)	**2a**	>99 (98)	99
2	4-FC_6H_4 (**1b**)	**2b**	>99 (99)	99
3	4-ClC_6H_4 (**1c**)	**2c**	>99 (97)	>99.9
4	4-BrC_6H_4 (**1d**)	**2d**	>99 (98)	>99.9
5	4-$MeOC_6H_4$ (**1e**)	**2e**	>99 (96)	99.3
6	4-MeC_6H_4 (**1f**)	**2f**	>99 (97)	99
7	4-$CF_3C_6H_4$ (**1g**)	**2g**	>99 (99)	99.6
8	3-FC_6H_4 (**1h**)	**2h**	>99 (99)	99
9	3-ClC_6H_4 (**1i**)	**2i**	>99 (98)	99.2
10	3-MeC_6H_4 (**1j**)	**2j**	>99 (95)	99
11	3-$MeOC_6H_4$ (**1k**)	**2k**	>99 (98)	99
12	2-FC_6H_4 (**1l**)	**2l**	>99 (97)	98
13	2-ClC_6H_4 (**1m**)	**2m**	>99 (96)	99
14	2-MeC_6H_4 (**1n**)	**2n**	>99 (96)	99.3
15	1-napthyl (**1o**)	**2o**	>99 (98)	97
16	2-napthyl (**1p**)	**2p**	>99 (99)	99
17	1-furyl (**1q**)	**2q**	>99 (99)	97
18	n-butyl (**1r**)	**2r**	>99 (99)	91
19	isopropyl (**1s**)	**2s**	>99 (96)	96
20	cyclohexyl (**1t**)	**2t**	>99 (93)	98

[a] Unless otherwise mentioned, all reactions were carried out at a $[Ir(COD)Cl]_2$/(*R*,*R*)-f-spiroPhos/substrate ratio of 0.5:1:100 in CH_2Cl_2 at 20 atm H_2 and 80 °C for 12 h. [b] Conversion, determined by ^1H NMR spectroscopy or GC analysis; data in parentheses are isolated yields. [c] Determined by chiral GC or HPLC analysis.

The performance of the new Ir-f-spiroPhos catalyst system in the asymmetric hydrogenation of β-acylamino nitroolefins was also evaluated on a gram scale. Under optimized reaction conditions, substrate **1c** (1.0 g) was smoothly hydrogenated providing the conresponding product in excellent yield (98% isolated yield) almost without any loss of enantioselectivity, 99.5% ee (Scheme 3).



Scheme 3. Gram scale experiment.

Conclusions

In summary, we developed a highly enantioselective Ir-catalyzed hydrogenation of β-acylamino nitroolefins for direct synthesis of enantiomerically pure β-amino nitroalkanes, which are versatile synthetic intermediates. Further studies on the extension of this novel catalytic system to other types of substrates are underway and will be reported in due course.

We are grateful for the financial support from the National Natural Science Foundation of China (grant nos. 21272026, 21172022 and 21472013), the Fundamental Research Funds for the Central Universities, Specialized Research Fund for the Doctoral Program of Higher Education of China and Beijing Municipal Commission of Education for generous financial support. We also thank Professors Qi-Lin Zhou and Xumu Zhang for providing chiral SPINOL and for helpful discussions.

Notes and references

College of Chemistry, Beijing Normal University, 19 Xinjiekouwaidajie, Beijing 100875, China. E-mail: ghhou@bnu.edu.cn.

† Electronic Supplementary Information (ESI) available: details of experimental procedures and characterization of the compounds, supplementary experimental data and figures. See DOI:

‡ These authors contributed equally to this work.

1 (a) E. Forestim, G. Palmieri, M. Petrini, R. Profeta, *Org. Biomol. Chem.* 2003, **1**, 4275-4281. (b) R. Ballini, M. Petrini, *Tetrahedron*, 2004, **60**, 1017-1047.

2 (a) D. Lucet, T. Le Gall, C. Mioskowski, *Angew. Chem. Int. Ed.* 1998, **37**, 2580-2627. (b) J. Wu, D. Wang, F. Wu, B. Wan, *J. Org. Chem.* 2013, **78**, 5611-5617. (c) C. A. Sandoval, T. Ohkuma, K. Muniz, R. Noyori, *J. Am. Chem. Soc.* 2003, **125**, 13490-13503. (d) H. Ooka, N. Arai, K. Azuma, N. Kurono, T. Ohkuma, *J. Org. Chem.* 2008, **73**, 9084-9093.

3 (a) F. A. Davis, Y. Zhang, D. Li, *Tetrahedron Lett.* 2007, **48**, 7838-7840. (b) M. E. Flanagan, T. A. Blumenkopf, W. H. Brissette, M. F. Brown, J. M. Casavant, C. Shang-Poa, J. L. Doty, E. A. Elliott, M. B. Fisher, M. Hines, C. Kent, E. M. Kudlacz, B. M. Lillie, K. S. Magnuson, S. P. McCurdy, M. J. Munchhof, B. D. Perry, P. S. Sawyer, T. J. Strelevitz, C. Subramanyam, J. Sun, D. A. Whipple, P. S. Changelian, *J. Med. Chem.* 2010, **53**, 8468-8484.

4 V. Karthick, K. Ramanathan, *Cell Biochem Biophys.* 2014, **68**, 291-299.

5 G. Deray, C. Bagnis, R. Brouard, J. Necciari, A. F. Leenhardt, F. Raymond, A. Baumelou, *Clin. Drug Investig.* 1998, **16**, 319-328.

6 (a) E. Marqués-López, P. Merino, T. Tejero, R. P. Herrera. *Eur. J. Org. Chem.* 2009, 2401-2420. (b) A. Ting, S. E. Schaus, *Eur. J. Org. Chem.* 2007, 5797-5815. (c) A. Noble, J. C. Anderson, *Chem. Rev.* 2013, **113**, 2887-2939.

7 (a) L. Wang, S. Shirakawa, K. Maruoka, *Angew. Chem. Int. Ed.* 2011, **50**, 5327-5330. (b) D. Uraguchi, D. Nakashima, T. Ooi, *J. Am. Chem. Soc.* 2009, **131**, 7242-7243. (c) L. Lykke, D. Monge, M. Nielsen, K. A. Jorgensen, *Chem. Eur. J.* 2010, **16**, 13330-13334. (d) J. Wang, H. Li, L. Zu, W. Wang, *Org. Lett.* 2006, **8**, 1391-1394.

8 X.-W. Liu, Y. Yan, Y.-Q. Wang, C. Wang, J. Sun, *Chem. Eur. J.* 2012, **18**, 9204-9207.

9 (a) W. S. Knowles, M. J. Sabacky, *J. Chem Soc. Chem. Commun.* 1968, 1445-1446. (b) L. Horner, H. Siegel, H. Büthe, *Angew. Chem. Int. Ed.* 1968, **7**, 942-943. (c) T. Ohkuma, M. Kitamura, R. Noyori In *Catalytic Asymmetric Synthesis*, 2nd ed., (Ed.: Ojima, I.), Wiley, New York, 2000, p 1. (d) H.-U. Blaser, F. Spindler In *Comprehensive*

Asymmetric Catalysis, Vol. 1 (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, 1999, p 247. (e) W. Tang, X. Zhang, *Chem. Rev.* 2003, **103**, 3029-3069. (f) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.* 2011, **111**, 1713-1760. (g) D.-S. Wang, Q.-A. Chen, Y.-G. Zhou, *Chem. Rev.* 2012, **112**, 2557-2590.

10 (a) N. E. Lee, S. L. Buchwald, *J. Am. Chem. Soc.* 1994, **116**, 5985-5986. (b) V. I. Tararov, R. Kadyrov, T. H. Riermeier, J. Holz, A. Börner, *Tetrahedron Lett.* 2000, **41**, 2351-2355. (c) G.-H. Hou, J.-H. Xie, L.-X. Wang, Q.-L. Zhou, *J. Am. Chem. Soc.* 2006, **128**, 11774-11775. (d) G.-H. Hou, J.-H. Xie, P.-C. Yan, Q.-L. Zhou, *J. Am. Chem. Soc.* 2009, **131**, 1366-1367. (e) Y. Hsiao, N. R. Rivera, T. Rosner, S. W. Krska, E. Njolito, F. Wang, Y.-K. Sun, J. D. Armstrong, E. J. J. Grabowski, R. D. Tillyer, F. Spindler, C. Malan, *J. Am. Chem. Soc.* 2004, **126**, 9918-9919. (f) K. B. Hansen, Y. Hsiao, F. Xu, N. Rivera, A. Clausen, M. Kubryk, S. Krska, T. Rosner, T. Simmons, J. Balsells, N. Ikemoto, Y. Sun, F. Spindler, C. Malan, E. J. J. Grabowski, J. D. III. Armstrong, *J. Am. Chem. Soc.* 2009, **131**, 8798-8804. (g) A. A. Bisset, A. Shiibashi, J. L. Desmond, A. Dishington, T. Jones, G. J. Clarkson, T. Ikariya and M. Wills, *Chem. Commun.* 2012, **48**, 11978-11980. (h) G. Hou, W. Li, M. Ma, X. Zhang, X. Zhang, *J. Am. Chem. Soc.* 2010, **132**, 12844-12846.

11 (a) J. Shang, Z. Han, Y. Li, Z. Wang, K. Ding, *Chem. Commun.* 2012, **48**, 5172-5174. (b) L. Qiu, Y. M. Li, F. Y. Kwong, W. Y. Yu, Q. H. Fan, A. S. C. Chan, *Adv. Synth. Catal.* 2007, **349**, 517-520. (c) H. Geng, W. Zhang, J. Chen, G. Hou, L. Zhou, Y. Zou, W. Wu, X. Zhang, *Angew. Chem. Int. Ed.* 2009, **48**, 6052-6054.

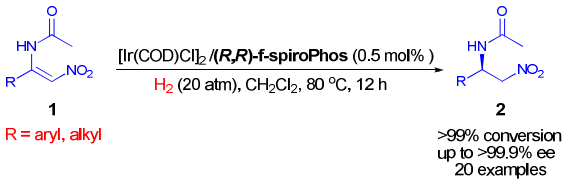
12 M. Ma, G. Hou, T. Sun, X. Zhang, W. Li, J. Wang, X. Zhang, *Chem. Eur. J.* 2010, **16**, 5301-5304.

13 M. Zhou, D. Dong, B. Zhu, H. Geng, Y. Wang, X. Zhang, *Org. Lett.* 2013, **15**, 5524-5527.

14 For the hydrogenation of nitroalkenes see: (a) S. Li, K. Huang, B. Cao, J. Zhang, W. Wu, X. Zhang, *Angew. Chem. Int. Ed.* 2012, **51**, 8573-8576. (b) Q. Zhao, S. Li, K. Huang, R. Wang, X. Zhang, *Org. Lett.* 2013, **15**, 4014-4017. (c) S. Li, K. Huang, J. Zhang, W. Wu, X. Zhang, *Chem. Eur. J.* 2013, **19**, 10840-10844.

15 (a) S.-F. Zhu, Y. Yang, L.-X. Wang, B. Liu, Q.-L. Zhou, *Org. Lett.* 2005, **7**, 2333-2335. (b) W. Zhang, S.-F. Zhu, X.-C. Qiao, Q.-L. Zhou, *Chem. Asian. J.* 2008, **12**, 2105-2111. (c) D. Xiao, X. Zhang, *Angew. Chem. Int. Ed.* 2001, **40**, 3425-3428.

TOC:



A highly Ir-catalyzed enantioselective hydrogenation of β-acylamino nitroolefins is first reported, which provides straightforward access to chiral β-amino nitroalkanes in excellent enantioselectivities (up to >99.9% ee).