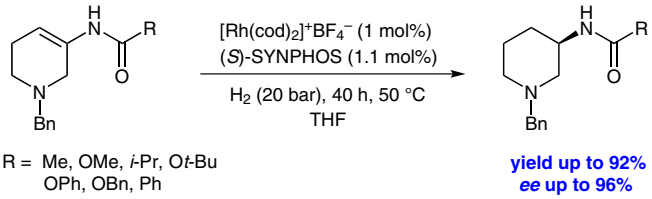
Synlett T. Royal et al. Letter

Rhodium-Catalyzed Asymmetric Hydrogenation of *N*-(1-benzylpiperidin-3-yl)-enamides: An Efficient Access to Valuable Enantioenriched 3-Aminopiperidine Derivatives

Titouan Royal[a]
Yohan Dudognon[a]
Farouk Berhal[a]
Yvon Bastard[b]
Bernard Boudet*[b]
Tahar Ayad[a]
Virginie Ratovelomanana-Vidal*[a]

[a] PSL Research University, Chimie ParisTech – CNRS, Institut de Recherche de Chimie Paris, 75005 Paris, France
virginie.vidal@chimie-paristech.fr
[b] Orgapharm, 25 Rue du Moulin de la Canne 45300 Pithiviers, France



Received: 08.03.2016
Accepted after revision: 23.04.2016
Published online: 19.05.2016
DOI: 10.1055/s-0035-1562235; Art ID: st-2016-d0167-l

Abstract An efficient synthetic entry to enantioenriched 3-aminopiperidine derivatives using rhodium-catalyzed asymmetric hydrogenation of *N*-(1-benzylpiperidin-3-yl)enamides is described. This method provides an atom-economical and attractive route to both enantiomers of the valuable 3-aminopiperidine moiety, which is an important structural unit that can be found in many natural products and pharmaceutical drugs encompassing a broad range of biological activities. Under optimized reaction conditions, the targeted 3-aminopiperidine derivatives were obtained in high yields up to 92% and with enantiomeric excesses up to 96% after a single crystallization.

Key words rhodium, asymmetric hydrogenation, enamide, synphos, 3-aminopiperidine

The 3-aminopiperidine moiety is an important structural unit that can be found in many natural products and pharmaceutical drugs encompassing a broad range of biological activities.[1] Representative examples of this important class of compounds include alogliptin[2] and linagliptin,[3] which are selective marketed dipeptidyl peptidase IV (DPPIV) inhibitors developed by Takeda Pharmaceuticals and Boehringer Ingelheim, respectively, for the treatment of type II diabetes mellitus. Tofacitinib[4] is a potent and selective Janus kinase 3 (JAK3) inhibitor discovered by Pfizer for the treatment of autoimmune diseases and organ-transplant rejection whereas compound **I** has been used in the treatment of several chronic diseases, including osteoporosis, rheumatoid arthritis, and restenosis[5] (Figure 1). In view of their high potential as pharmaceutical drug candidates, the synthesis of such structural motif has attracted much attention from both academia and industries. To date, several synthetic approaches have been developed.[6] However, most of these methods involve the use of chiral starting building blocks combined with long reaction sequences and multiple tedious purification steps or rely on diastereoselective reactions using a stoichiometric amount of chiral sources. Consequently, the development of catalytic enantioselective methods that would allow a more practical, convenient, and atom-economically efficient access to valuable 3-aminopiperidine frameworks, with high enantioselectivity, is highly desirable. In connection with our ongoing research program toward the use of metal-catalyzed asymmetric reductions for the synthesis of biologically relevant active compounds,[7] we report herein a rhodium-catalyzed asymmetric hydrogenation of *N*-(1-benzylpiperidin-3-yl)-enamides as an efficient synthetic access to both enantiomers of enantioenriched 3-aminopiperidine scaffolds in high yields and with enantioselectivities up to 96%. Surprisingly, and to the best of our knowledge, such an enantioselective approach has never been reported.

Compounds **1a**–**g** chosen for this investigation were readily prepared on a gram scale from cheap and commercially available 3-aminopyridine in three steps according to known procedures.[6d] With the aforementioned enamides and ene carbamates **1a**–**g** in hand, asymmetric hydrogenation of the *N*-(1-benzyl-1,2,3,4-tetrahydropyridin-3-yl)-benzamide (**1a**) was attempted using rhodium catalysts containing atropisomeric diphosphine ligands, as these rhodium complexes proved to be highly selective and efficient for the asymmetric hydrogenation of trisubstituted enamide compounds.[8] Initially, the reaction was carried out in various solvents using 1 mol% of in situ generated rhodium catalyst prepared from $[Rh(cod)_2]^+BF_4^-$ with (*S*)-SYNPHOS[9] ligand at 50 °C under an hydrogen pressure of 20 bar. The results of these experiments are given in Table 1. To our delight, the desired hydrogenated product **2a** was formed with good conversions in all tested solvents with enantio-

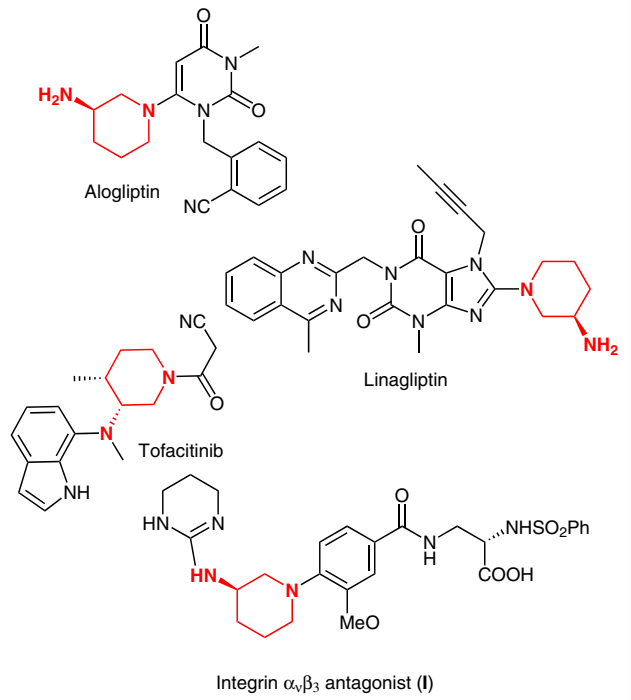


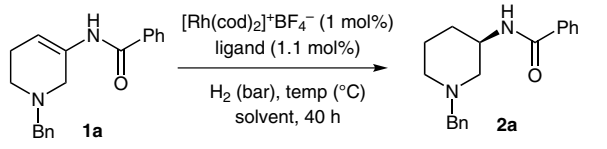
Figure 1 Pharmaceutical drugs incorporating 2-aminopiperidine moiety

selectivities depending on the solvent employed (Table 1, entries 1–6). Solvent screening revealed that THF was the ideal solvent for the transformation affording the desired 3-aminopiperidine **2a** of *R* configuration[10] in complete conversion and excellent enantiomeric excess of 92.5% (Table 1, entry 6), whereas use of more polar solvents such as MeOH and EtOAc resulted in low enantioselectivities and somewhat slightly lower conversions (Table 1, entries 1 and 2, 11% and 50% ee, 100% and 95% conversion, respectively). With this excellent result, we further studied the effect of other parameters that might influence the catalytic activity and stereochemical course of the reaction, such as, the hydrogen pressure, temperature and chiral diphosphines.

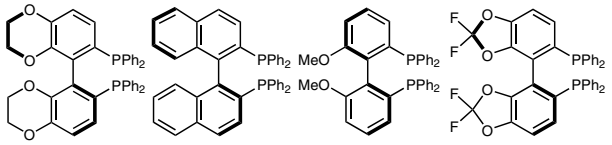
As shown in Table 1, variation of the hydrogen pressure from 50 to 10 bar did not affect conversion, but a slight decrease of the enantioselectivity was observed when the reaction was conducted at pressures higher than 20 bar (Table 1, entries 7–10). The data of Table 1 also illustrated that a change in the reaction temperature from 50 °C to 30 °C or 10 °C had a negative impact on the reactivity of the reaction without affecting the enantioinductions, providing compound **2a** in 95% and 80% conversions and high enantiomeric excesses of 90.5% and 91%, respectively (Table 1, entries 11 and 12). Finally, atropisomeric diphosphine ligands, including (*S*)-BINAP[11] (**L2**), (*S*)-MeO-BIPHEP[12] (**L3**) and the in-house developed (*S*)-DIFLUORPHOS[13] (**L4**), were evaluated in this process. It turned out that the efficiency of the reaction was highly sensitive to the electronic nature of the diphosphine used. Indeed, electron-rich ligands **L2** and **L3** exhibited similar catalytic activity than those obtained with the (*S*)-SYNPHOS[9] (**L1**), whereas rhodium catalyst containing the electron-poor (*S*)-DIFLUORPHOS (**L4**) performed poorly in terms of both conversion and asymmetric induction (Table 1, entry 6 vs. entries 13–15).

Having achieved an optimized set of conditions for the hydrogenation of **1a**, our attention then focused on the hydrogenation of various 3-aminopiperidine derivatives. We studied the influence of the enamide substitution on the stereochemical outcome of the reaction (Table 2, entries 1–7).

Table 1 Optimization of the Reaction Conditions[a]

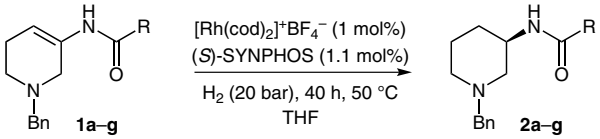


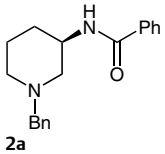
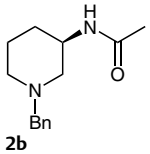
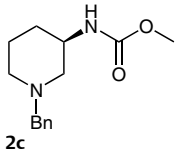
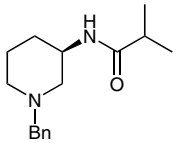
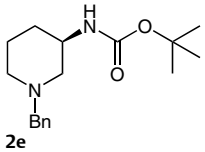
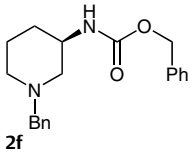
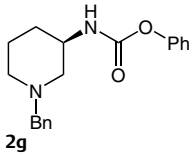
Entry	Solvent	Ligand	Temp (°C)	H_2 (bar)	Conv. (%)[b]	ee (%)[c]
1	MeOH	**L1**	50	20	100	11
2	EtOAc	**L1**	50	20	95	50
3	CH_2Cl_2	**L1**	50	20	100	71
4	toluene	**L1**	50	20	100	70
5	Et_2O	**L1**	50	20	90	80
6	THF	**L1**	50	20	100	92.5
7	THF	**L1**	50	10	100	92
8	THF	**L1**	50	30	100	88.5
9	THF	**L1**	50	40	100	88.5
10	THF	**L1**	50	50	100	88
11	THF	**L1**	30	20	95	90.5
12	THF	**L1**	10	20	80	91
13	THF	**L2**	50	20	95	90
14	THF	**L3**	50	20	97	91
15	THF	**L4**	50	20	60	34



[a] Unless otherwise specified, all reactions were performed with 1 mmol of substrate **1a** for 40 h using 1 mol% of catalyst; cod = cyclooctadienyl.
[b] Determined by ^{1}H NMR spectrum of crude reaction mixture.
[c] Determined by HPLC chromatography using a Chiralcel AD-H column. Absolute configuration was determined to be *R* by comparison of the specific rotation of reported data.

Table 2 Scope of the Hydrogenation[a]



Entry	Product **2**	Conv. (%)[b]	Yield (%)[c]	ee (%)[d]
1	 **2a**	100	92	92.5 (96)[e]
2	 **2b**	100	94	58
3	 **2c**	100	93	54
4	 **2d**	80	74	7
5	 **2e**	50	48	–
6	 **2f**	100	91	80
7	 **2g**	100	92	88

[a] Unless otherwise specified, all reactions were performed using 1 mmol of substrate **1** for 40 h using 1 mol% of catalyst; cod = cyclooctadienyl.
[b] Determined by ^{1}H NMR spectrum of crude reaction mixture.
[c] Isolated yield after purification by flash column chromatography.
[d] Determined by chiral stationary phase supercritical-fluid chromatography (CSP-SCF). Absolute configuration was determined to be *R* by comparison of the specific rotation of reported data.
[e] Ee Obtained after a single crystallization in EtOH.

Reduction of enamides **1b** and ene carbamate **1c** containing a methyl or a methoxy group led to the corresponding 3-aminopiperidine derivatives **2b** and **2c** with full conversions, excellent isolated yields albeit with significantly lower ee values of 58% and 54%, respectively, than those obtained for **2a** (Table 2, entry 1 vs. entries 2 and 3). Reaction conducted with enamide **1d** and ene carbamate **1e** bearing a more sterically demanding isopropyl or *tert*-butyl substituents provided the desired products **2d** and **2e** with poor catalytic activity, whereas hydrogenation of benzyl and phenyl ene carbamates **1f** and **1g** restored the catalytic activity, producing **2f** and **2g**, in complete conversions, high yields, and good ee values (Table 2, entries 4–7). Finally, from this screening, the enebenzamide **1a** appeared to be the most appropriate substrate to reach the best results in terms of both reactivity and selectivity (Table 2, entry 1, 92% yield, 92.5% ee). It is worth noting that this process that can be carried out on a gram scale allows the preparation of both enantiomers of **2a** with similar results by simply switching the ligand configuration (e.g., *S* to *R*, 93% yield, 92% ee). Moreover, enantiomeric excess of the hydrogenated product **2a** could be easily upgraded to 96% after a single crystallization in EtOH.[14]

In conclusion, a novel strategy for the enantioselective synthesis of enantioenriched aminopiperidine scaffolds has been developed through Rh-SYNPHOS-catalyzed asymmetric hydrogenation of *N*-(1-benzylpiperidin-3-yl)enamides. This practical method provides, in high yields up to 92%, and with excellent level of enantiomeric excesses up to 96%, an atom-economical and attractive route to both enantiomers of the valuable 3-aminopiperidine moiety, which is an important structural unit that can be found in many natural products and bioactive drugs of medicinal interest. Further studies on expanding the substrate scope and exploring the synthetic utility of this valuable synthon for the synthesis of compounds of pharmaceutical interest are currently underway in our laboratory.

Acknowledgment

This work was supported by Orgapharm. We also thank the Centre National de la Recherche Scientifique (CNRS) and the Ministère de l'Education Nationale, de l'Enseignement Supérieur et de la Recherche.

References and Notes

(1) For representative examples, see: (a) Dax, S. L.; Wei, C. C. *J. Org. Chem.* **1992**, *57*, 744. (b) Bouzard, D.; Di Cesare, P. D.; Essiz, M.; Jacquet, J.-P.; Ledoussal, B.; Remuzon, P.; Kessler, R. E.; Fung-Tomc, J. *J. Med. Chem.* **1992**, *35*, 518. (c) Tattersall, F. D.; Rycroft, W.; Hill, R. G.; Hargreaves, R. J. *Neuropharmacology* **1994**, *33*, 259. (d) Lin, H.-S.; Richett, M. E. WO 9952265, **1999**; *Chem. Abstr.* **1999**, *131*, 295575 (e) Alcaraz, L.; Furber, M.; Mortimore, M. WO 0061569, **2000**; *Chem. Abstr.* **2000**, *133*, 309908a (f) Ishikawa, M.; Kubota, D.; Yamamoto, M.; Kuroda, C.; Iguchi,

M.; Koyanagi, A.; Murakami, S.; Ajito, K. *Bioorg. Med. Chem.* **2006**, *14*, 2109. (g) Eckhardt, M.; Langkopf, E.; Mark, M.; Tadayyon, M.; Thomas, L.; Nar, H.; Pfrengle, W.; Guth, B.; Lotz, R.; Sieger, P.; Fuchs, H.; Himmelsbach, F. *J. Med. Chem.* **2007**, *50*, 6450. (h) Graul, A. I.; Cruces, E. *Drugs Today* **2011**, *47*, 27. (i) Berggren, K.; Vindebro, R.; Bergström, C.; Spoerry, C.; Persson, H.; Fex, T.; Kihlberg, J.; Pawel-Rammingen, U.-V.; Luthman, K. *J. Med. Chem.* **2012**, *55*, 2549. (j) Oza, V.; Ashwell, S.; Almeida, L.; Brassil, P.; Breed, J.; Deng, C.; Gero, T.; Grondine, M.; Horn, C.; Ioannidis, S.; Liu, D.; Lyne, P.; Newcombe, N.; Pass, M.; Read, J.; Ready, S.; Rowsell, S.; Su, M.; Toader, D.; Vasbinder, M.; Yu, D.; Yu, Y.; Xue, Y.; Zabludoff, S.; Janetka, J. *J. Med. Chem.* **2012**, *55*, 5130.

(2) Feng, J.; Zhang, Z.; Wallace, M. B.; Stafford, J. A.; Kaldor, S. W.; Kassel, D. B.; Navre, M.; Shi, L.; Skene, R. J.; Asakawa, T.; Takeuchi, K.; Xu, R.; Webb, D. R.; Gwaltney, S. L. *J. Med. Chem.* **2007**, *50*, 2298.

(3) Lajara, R. *Expert Opin. Pharmacother.* **2012**, *13*, 2663.

(4) Flanagan, M. E.; Blumenkopf, T. A.; Brissette, W. H.; Brown, M. F.; Casavant, J. M.; Shang-Poa, C.; Doty, J. L.; Elliott, E. A.; Fisher, M. B.; Hines, M.; Kent, C.; Kudlacz, E. M.; Lillie, B. M.; Magnuson, K. S.; McCurdy, S. P.; Munchhof, M. J.; Perry, B. D.; Sawyer, P. S.; Strelevitz, T. J.; Subramanyam, C.; Sun, J.; Whipple, D. A.; Changelianr, P. S. *J. Med. Chem.* **2010**, *53*, 8468.

(5) Ishikawa, M.; Hiraiwa, Y.; Kubota, D.; Tsushima, M.; Watanabe, T.; Murakami, S.; Ouchi, S.; Ajito, K. *Bioorg. Med. Chem.* **2006**, *14*, 2131.

(6) For selected examples, see: (a) Diez, A.; Voldoire, A.; López, I.; Rubiralta, M.; Segarra, V.; Pagès, L.; Palacios, J. M. *Tetrahedron* **1995**, *51*, 5143. (b) Jean, L.; Baglin, I.; Rouden, J.; Maddaluno, J.; Lasne, M.-C. *Tetrahedron Lett.* **2001**, *42*, 5645. (c) Hu, X. E.; Kim, N. K.; Ledoussal, B. *Org. Lett.* **2002**, *4*, 4499. (d) Reilly, M.; Anthony, D. R.; Gallagher, C. *Tetrahedron Lett.* **2003**, *44*, 2927. (e) Brown Ripin, D. H. WO 2004046112, **2004**. (f) Brown Ripin, D. H.; Abele, S.; Cai, W.; Blumenkopf, T.; Casavant, J. M.; Doty, J. L.; Flanagan, M.; Koecher, C.; Laue, K. W.; McCarthy, K.; Meltz, C.; Munchhoff, M.; Pouwer, K.; Shah, B.; Sun, J.; Teixeira, J.; Vries, T.; Whipple, D. A.; Wilcox, G. *Org. Process Res. Dev.* **2003**, *7*, 115. (g) Cai, W.; Colony, J. L.; Frost, H.; Hudspeth, J. P.; Kendall, P. M.; Krishnan, A. M.; Makowski, T.; Mazur, D. J.; Phillips, J.; Brown Ripin, D. H.; Ruggeri, S. G.; Stearns, J. F.; White, T. D. *Org. Process Res. Dev.* **2005**, *9*, 51. (h) Cox, J. M.; Harper, B.; Mastracchio, A.; Leiting, B.; Sinha Roy, R.; Patel, R. A.; Wu, J. K.; Lyons, K. A.; He, H.; Xu, S.; Zhu, B.; Thornberry, N. A.; Weber, A. E.; Edmondson, S. D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4579. (i) Martini, E.; Ghelardini, C.; Dei, S.; Guandalini, L.; Manetti, D.; Melchiorre, M.; Norcini, M.; Scapecchi, S.; Teodori, E.; Romanelli, M. N. *Bioorg. Med. Chem.* **2008**, *16*, 1431. (j) Rao, T. S.; Zhang, C. WO 2010123919, **2010**. (k) Cochi, A.; Gomez Pardo, D.; Cossy, J. *Org. Lett.* **2011**, *13*, 4442. (l) Cochi, A.; Gomez Pardo, D.; Cossy, J. *Eur. J. Org. Chem.* **2012**, 2023. (m) Patil, Y. S.; Bonde, N. L.; Kekan, A. S.; Sathe, D. G.; Das, A. *Org. Process Res. Dev.* **2014**, *18*, 1714.

(7) For selected examples, see: (a) Tone, H.; Buchotte, M.; Mordant, C.; Guittet, E.; Ayad, T.; Ratovelomanana-Vidal, V. *Org. Lett.* **2009**, *11*, 1995. (b) Tadaoka, H.; Cartigny, D.; Nagano, T.; Gosavi, T.; Ayad, T.; Genêt, J.-P.; Ohshima, T.; Ratovelomanana-Vidal, V.; Mashima, K. *Chem. Eur. J.* **2009**, *15*, 9990. (c) Pautigny, C.; Debouit, C.; Vayron, P.; Ayad, T.; Ratovelomanana-Vidal, V. *Tetrahedron: Asymmetry* **2010**, *21*, 1382. (d) Cartigny, D.; Nagano, T.; Ayad, T.; Genêt, J.-P.; Ohshima, T.; Mashima, K.; Ratovelomanana-Vidal, V. *Adv. Synth. Catal.* **2010**, *352*, 1886. (e) Wu, Z.; Ayad, T.; Ratovelomanana-Vidal, V. *Org. Lett.* **2011**, *13*, 3782. (f) Prevost, S.; Ayad, T.; Phansavath, P.; Ratovelomanana-Vidal, V. *Adv. Synth. Catal.* **2011**, *353*, 3213. (g) Cartigny, D.; Berhal, F.; Nagano, T.; Phansavath, P.; Ayad, T.; Genêt, J.-P.; Ohshima, T.; Mashima, K.; Ratovelomanana-Vidal, V. *J. Org. Chem.* **2012**, *77*, 4544. (h) Berhal, F.; Wu, Z.; Zhang, Z.-G.; Ayad, T.; Ratovelomanana-Vidal, V. *Org. Lett.* **2012**, *14*, 3308. (i) Wu, Z.; Perez, M.; Ayad, T.; Scalone, M.; Ratovelomanana-Vidal, V. *Angew. Chem. Int. Ed.* **2013**, *52*, 4925. (j) Gauthier, S.; Larquetoux, L.; Nicolas, M.; Ayad, T.; Maillos, P.; Ratovelomanana-Vidal, V. *Synlett* **2014**, *25*, 1606. (k) Perez, M.; Echeverria, P.-G.; Martinez-Arripe, E.; Ez-Zoubir, M.; Touati, R.; Zhang, Z.; Genêt, J.-P.; Phansavath, P.; Ayad, T.; Ratovelomanana-Vidal, V. *Eur. J. Org. Chem.* **2015**, *27*, 5949. (l) Echeverria, P.-G.; Prévost, S.; Cornil, J.; Férard, C.; Reymond, S.; Guérinot, A.; Cossy, J.; Ratovelomanana-Vidal, V.; Phansavath, P. *Org. Lett.* **2014**, *16*, 2390. (m) Monnereau, L.; Cartigny, D.; Scalone, M.; Ayad, T.; Ratovelomanana-Vidal, V. *Chem. Eur. J.* **2015**, *27*, 11799.

(8) (a) Li, W.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 5871. (b) Gridnev, I. D.; Yasutake, M.; Higashi, N.; Imamoto, T. *J. Am. Chem. Soc.* **2001**, *123*, 5268. (c) Lee, S.-G.; Zhang, Y. J.; Song, C. E.; Lee, J. K.; Choi, J. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 847. (d) Van den Berg, M.; Haak, R. M.; Minnaard, A. J.; de Vries, A. H.M.; de Vries, J. G.; Feringa, B. L. *Adv. Synth. Catal.* **2002**, *344*, 1003. (e) Hu, A.-G.; Fu, Y.; Xie, J.-H.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* **2002**, *41*, 2348. (f) Xie, J. H.; Zhu, S. F.; Zhou, Q. L. *Chem. Rev.* **2011**, *111*, 1713. (g) Gopalaiah, K.; Kagan, H. B. *Chem. Rev.* **2011**, *111*, 4599. (h) Li, W.; Rodriguez, R.; Duran, A.; Sun, X.; Tang, W.; Premasiri, A.; Wang, W.; Sidhu, K.; Patel, N. D.; Savoie, J.; Qu, B.; Lee, H.; Haddad, N.; Lorenz, J. C.; Nummy, L.; Hossain, A.; Yee, N.; Lu, B.; Senanayake, C. H. *Org. Process Res. Dev.* **2013**, *17*, 1061. (i) Etayoa, P.; Vidal-Ferran, A. *Chem. Soc. Rev.* **2013**, *42*, 728. (j) Kleman, P. A.; Pizzano, A. *Tetrahedron Lett.* **2015**, *56*, 6944. (k) Jiang, J.; Lu, W.; Lv, H.; Zhang, X. *Org. Lett.* **2015**, *17*, 1154.

(9) (a) Duprat de Paule, S.; Champion, N.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Dellis, P. FR 2830254, **2001**. (b) Duprat de Paule, S.; Champion, N.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Dellis, P. WO 03029259, **2003**. (c) Duprat de Paule, S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Champion, N.; Dellis, P. *Eur. J. Org. Chem.* **2003**, 1931. (d) Duprat de Paule, S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Champion, N.; Deschaux, G.; Dellis, P. *Org. Process Res. Dev.* **2003**, *7*, 399.

(10) The absolute configuration was determined to be *R* by comparison of the specific rotation of the 3-aminopiperidine dihydrochloride ($[\alpha]_D^{20}$ –3.7 (*c* 1, H_2O) for 96% ee) obtained from **2a** after full deprotection with commercially available (*R*)-(–)-3-aminopiperidine dihydrochloride from Sigma-Aldrich ($[\alpha]_D^{20}$ –2.0 ± 0.5 (*c* 1, H_2O) for 90% ee).

(11) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932.

(12) Schmid, R.; Broger, E. A.; Cereghetti, M.; Crameri, Y.; Foricher, J.; Lalonde, M.; Müller, R. K.; Scalone, M.; Schoettel, G.; Zutter, U. *Pure Appl. Chem.* **1996**, *68*, 131.

(13) (a) Jeulin, S.; Duprat de Paule, S. V.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Champion, N. *Angew. Chem. Int. Ed.* **2004**, *43*, 320. (b) Jeulin, S.; Duprat de Paule, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Champion, N.; Dellis, P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5799. (c) Genêt, J.-P.; Ayad, T.; Ratovelomanana-Vidal, V. *Chem. Rev.* **2014**, *114*, 2824.

(14) **Typical Procedure for the Asymmetric Hydrogenation of 1a**
The rhodium complex $[Rh(cod)_2]^+BF_4^-$ (3.0 mg, 0.0074 mmol, 1% mol) and the (*S*)-SYNPHOS ligand (0.0081 mmol, 1.1% mol)

were placed in a tubular reactor under argon. THF was added (3 mL), and the solution was stirred at room temperature for 30 min after three vacuum/argon cycles. The enamide **1a** (1 equiv) was then added in one portion, and the reactor was put in a stainless steel autoclave after three vacuum/argon cycles. The hydrogenation was performed at 50 °C under 20 bar of hydrogen pressure for 40 h. After careful releasing of the hydrogen gas, the reaction mixture was concentrated under vacuum, and the residue was purified by flash column chromatography on silica gel to give the 3-aminopiperidine derivative (*R*)-**2a**.

***N*-(1-Benzylpiperidin-3-yl)benzamide [(*R*)-2a]**

White solid; yield 270.5 mg (92%); mp 133 °C; R_f = 0.4 (EtOAc); $[\alpha]_D^{20}$ +2.6 (*c* 1, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7. 79 (t, *J* = 7.8 Hz, 2 H), 7.55–7.39 (m, 3 H), 7.39–7.18 (m, 5 H), 6.87 (s, 1 H), 4.28 (s, 1 H), 3.58 (d, *J* = 13.0 Hz, 1 H), 3.47 (d, *J* = 13.1 Hz, 1 H), 2.60–2.70 (m, 2 H), 2.52–2.13 (m, 2 H), 1.63–1.80 (m, 2 H), 1.61–1.42 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.6, 136.7, 129.1, 128.5, 128.3, 128.2, 128.1, 127.3, 66.5, 63.0, 58.2, 53.4, 46.7, 29.3, 21.8. MS (CI, NH_3): *m/z* = 295 $[M + H]^+$. HRMS (ESI^+): *m/z* $[M + Na]^+$ calcd for $C_{19}H_{22}N_2ONa^+$: 317.1630; found: 317.1624. The enantiomeric excess of (*R*)-**2a** was determined by SFC (Chiralcel AD-H, $scCO_2$/MeOH = 90:10 + 0.1% Et_3N, 4 mL/min, P = 150 bar, λ = 215 nm): t_R (*S*) = 5.76 min (minor), t_R (*R*) = 7.17 min (major, ee 92.5%), upgraded to 96% ee after a single crystallization in EtOH.