JOC Article
pubs.acs.org/joc

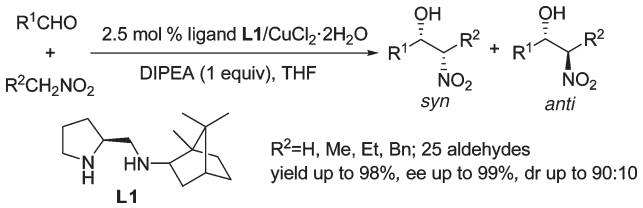
Synthesis of C_1-Symmetric Chiral Secondary Diamines and Their Applications in the Asymmetric Copper(II)-Catalyzed Henry (Nitroaldol) Reactions

Yirong Zhou, Junfang Dong, Fanglin Zhang,* and Yuefa Gong*

School of Chemistry and Chemical Engineering, Huazhong University of Science and Technology, 1037 Luoyu Road, Wuhan 430074, People's Republic of China

hyvzfl@gmail.com; gongyf@mail.hust.edu.cn

Received October 28, 2010



A small library of C_1-symmetric chiral diamines (**L1**−**L9**) was constructed via condensing *exo*-(−)-bornylamine or (+)-(1*S*,2*S*,5*R*)-menthylamine with various Cbz-protected amino acids. Among them, ligand **L1**/$CuCl_2 \cdot 2H_2O$ complex (2.5 mol %) shows outstanding catalytic efficiency for Henry reaction between a variety of aldehydes and nitroalkanes to afford the expected products in high yields (up to 98%) with excellent enantioselectivities (up to 99%) and moderate to good diastereoselectivities (up to 90:10). This process is air- and moisture tolerant and has been applied to the synthesis of (*S*)-2-amino-1-(3,4-dimethoxyphenyl)ethanol (**9**), a key intermediate for (*S*)-epinephrine and (*S*)-norepinephrine. On the basis of HRMS and X-ray diffraction analysis of the **L1**/$CuCl_2$ complex, a transition-state model was proposed to explain the origin of asymmetric induction. The low catalyst loading, excellent yields and enantioselectivities, inexpensive copper salt, and mild reaction conditions make our catalytic system to be practically useful.

Introduction

The Henry (nitroaldol) reaction is one of the most important atom-economical carbon−carbon bond-constructing methodologies, providing β-nitroalcohols which can be transformed into valuable building blocks, such as 1,2-amino alcohols and α-hydroxyl carboxylic acids, especially in an enantiopure form.[1] Since the pioneering work of Shibasaki in 1992,[2] great effort has been devoted toward the development of catalytic asymmetric Henry reaction by metal catalysis and organocatalysis.[3] Dinuclear zinc−amino alcohol and copper(II)−bis(oxazoline) (BOX) are two classical catalytic systems for the direct asymmetric Henry reaction of unmodified nitroalkanes with aldehydes developed early by Trost[4] and Evans,[5] respectively. Subsequently, many other successful examples have appeared by the combination of various chiral ligands and metal ions.[6] Although steady progress has been hitherto achieved, there still remain some limitations. Few systems are suitable for a broad scope of both aromatic and aliphatic aldehydes.[7] Meanwhile, nitroalkanes other than nitromethane are less explored, too.[8]

The discovery and development of novel chiral ligands could always open a new era of asymmetric catalysis variants. BOX-type and salen-type are two privileged classes

(1) (a) Henry, L.; Hebd, C. R. *Séances Acad. Sci.* **1895**, *120*, 1265–1267. (b) Rosini, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 2, pp 321−340. (c) Shibasaki, M.; Gröer, H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Berlin, 1999; Vol. III, pp 1075−1090. (d) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915–945. (e) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001.

(2) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418–4420.

(3) For recent reviews on the catalytic asymmetric Henry reaction, see: (a) Palomo, C.; Oiarbide, M.; Mielgo, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5442–5444. (b) Boruwa, J.; Gogoi, N.; Saikia, P. P.; Barua, N. C. *Tetrahedron: Asymmetry* **2006**, *17*, 3315–3326. (c) Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, 2561–2574.

(4) (a) Trost, B. M.; Yeh, V. S. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 861–863. (b) Trost, B. M.; Yeh, V. S. C.; Ito, H.; Bremeyer, N. *Org. Lett.* **2002**, *4*, 2621–2623.

(5) Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692–12693.

Published on Web 12/29/2010 DOI: 10.1021/jo102124d

of C_2-symmetric ligands which have been widely used in a great number of asymmetric metal-catalyzed reactions including Henry reaction.[9] Compared with the former C_2-symmetric ligands, the structures and electronic properties of C_1-symmetric ligands are more feasible to adjust. Nevertheless, the latter are less developed until very recently. Besides natural sparteine,[10a] (+)-NME ((+)-*N*-methylephedrine)[10b] and brucine-derived amino alcohol,[10c] there are a few artificial C_1-symmetric ligands suitable for catalytic asymmetric Henry reaction such as aminopyridine,[10d,e] 9-oxabispidine[10f] and bipiperidine.[10g] Generally, the reported C_1-symmetric diamine ligands with two N (sp^3) coordinating atoms can be divided into three types: two tertiary amines,[10f,11a] one tertiary amine plus one sulfonylamine,[11b,c] and one tertiary amine plus one secondary amine.[10g] Considering the successful applications of C_2-symmetric secondary diamine ligands derived from chiral 1,2-cyclohexanediamine and 1,2-diphenylethylenediamine in copper-catalyzed asymmetric Henry reactions,[12] we are interested in developing C_1-symmetric diamine ligands with two secondary amines for the ease of structure modification in order to improve the shortcomings of the previous asymmetric catalyst systems for Henry reaction such as high catalyst loading, sensitivity to air or moisture, and narrow substrate variation.

Toward this end, we designed and prepared a series of C_1-symmetric diamine ligands from the commercially available chiral materials such as D-camphor, L-menthone, and natural amino acids. Herein, we present a highly enantioselective and practically useful Henry reaction between a variety of aldehydes and nitroalkanes catalyzed by a newly developed chiral diamine ligand **L1**/$CuCl_2 \cdot 2H_2O$ complex.

Results and Discussions

The D-camphor and L-menthone as two classical kinds of chiral scaffolds have been widely utilized in preparing chiral reagents and ligands.[13] The natural amino acids are another type of chiral starting material employed usually in developing various chiral ligands and organocatalysts for asymmetric catalysis.[14] For our purpose, *exo*-(−)-bornylamine and (+)-(1*S*,2*S*,5*R*)-menthylamine were first prepared from natural D-camphor and L-menthone, respectively (for the general procedure see Scheme 1). Then, a series of chiral diamine ligands (**L1**−**L9**) were obtained via condensing the two chiral amines with various Cbz-protected amino acids in three steps (for the general procedure see Scheme 2). We found these chiral diamine ligands are stable enough to be stored at ambient temperature without special precautions

(6) Selected examples for Zn-catalyzed asymmetric Henry reaction: (a) Zhong, Y.; Tian, P.; Lin, G. *Tetrahedron: Asymmetry* **2004**, *15*, 771–776. (b) Gao, J.; Zigaro, R. A.; Reibenspires, J. H.; Martell, A. *Org. Lett.* **2004**, *6*, 2453–2455. (c) Liu, S.; Wolf, C. *Org. Lett.* **2008**, *10*, 1831–1834. (d) Bulut, A.; Aslan, A.; Dogan, Ö. *J. Org. Chem.* **2008**, *73*, 7373–7375. Selected examples for Co-catalyzed asymmetric Henry reaction: (e) Kogami, Y.; Nakajima, T.; Ashizawa, T.; Kezuka, S.; Ikeno, T.; Yamada, T. *Chem. Lett.* **2004**, *33*, 614–615. (f) Park, J.; Lang, K.; Abboud, K. A.; Hong, S. *J. Am. Chem. Soc.* **2008**, *130*, 16484–16485. Selected examples for Cr-catalyzed asymmetric Henry reaction: (g) Kowalczyk, R.; Sidorowicz, Ł.; Skarżewski, J. *Tetrahedron: Asymmetry* **2007**, *18*, 2581–2586. (h) Kowalczyk, R.; Kwiatkowski, P.; Skarżewski, J.; Jurczak, J. *J. Org. Chem.* **2009**, *74*, 753–756. (i) Zulauf, A.; Mellah, M.; Schulz, E. *J. Org. Chem.* **2009**, *74*, 2242–2245. Selected examples for Mg-catalyzed asymmetric Henry reaction: (j) Choudary, B. M.; Ranganath, K. V. S.; Kantam, U.; Pal, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, *127*, 13167–13171. Selected examples for Cu-catalyzed asymmetric Henry reaction: (k) Gan, C.; Lai, G.; Zhang, Z.; Wang, Z.; Zhou, M. *Tetrahedron: Asymmetry* **2006**, *17*, 725–728. (l) Lai, G.; Wang, S.; Wang, Z. *Tetrahedron: Asymmetry* **2008**, *19*, 1813–1819. (m) Blay, G.; Climent, E.; Fernández, I.; Hernández-Olmos, V.; Pedro, J. R. *Tetrahedron: Asymmetry* **2006**, *17*, 2046–2049. (n) Blay, G.; Climent, E.; Fernández, I.; Hernández-Olmos, V.; Pedro, J. R. *Tetrahedron: Asymmetry* **2007**, *18*, 1603–1612. (o) Jiang, J.; Shi, M. *Tetrahedron: Asymmetry* **2007**, *18*, 1376–1382. (p) Ma, K.; You, J. *Chem.—Eur. J.* **2007**, *13*, 1863–1871. (q) Bandini, M.; Benaglia, M.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *Org. Lett.* **2007**, *9*, 2151–2153. (r) Qin, B.; Xiao, X.; Liu, X.; Huang, J.; Wen, Y.; Feng, X. *J. Org. Chem.* **2007**, *72*, 9323–9328. (s) Arai, T.; Yokoyama, N.; Yanagisawa, A. *Chem.—Eur. J.* **2008**, *15*, 2052–2059. (t) Rachwalski, M.; Leśniak, S.; Sznajder, E.; Kiełbasiński, P. *Tetrahedron: Asymmetry* **2009**, *20*, 1547–1549. (u) Selvakumar, S.; Sivasankaran, D.; Singh, V. K. *Org. Biomol. Chem.* **2009**, *7*, 3156–3162. (v) Mayani, V. J.; Abdi, S. H. R.; Kureshy, R. I.; Khan, N. H.; Das, A.; Bajaj, H. C. *J. Org. Chem.* **2010**, *75*, 6191–6195.

(7) Selected examples for both aromatic and aliphatic aldehydes are studied systematically: (a) Tanaka, K.; Hachiken, S. *Tetrahedron Lett.* **2008**, *49*, 2533–2536. (b) Spangler, K. Y.; Wolf, C. *Org. Lett.* **2009**, *11*, 4724–4727; also see refs 6c, 12b, and 12g.

(8) Selected examples for diastereo- and enantioselective Henry reaction: (a) Sasai, H.; Tokunaga, T.; Watanabe, S.; Suzuki, T.; Itoh, N.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 7388–7389. (b) Arai, T.; Yamada, Y. M. A.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *Chem.—Eur. J.* **1996**, *2*, 1368–1372. (c) Handa, S.; Nagawa, K.; Sohtome, Y.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3230–3233. (d) Nitabaru, T.; Kumagai, N.; Shibasaki, M. *Tetrahedron Lett.* **2008**, *49*, 272–276. (e) Nitabaru, T.; Nojiri, A.; Kobayashi, M.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 13860–13869. (f) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Eur. J. Org. Chem.* **2006**, 2894–2897. (g) Sohtome, Y.; Takemura, N.; Takada, K.; Takagi, R.; Iguchi, T.; Nagasawa, K. *Chem. Asian J.* **2007**, *2*, 1150–1160. (h) Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392–12393. (i) Cheng, L.; Dong, J.; You, J.; Gao, G.; Lan, J. *Chem.—Eur. J.* **2010**, *16*, 6761–6765. (j) Kanagaraj, K.; Suresh, P.; Pitchumani, K. *Org. Lett.* **2010**, *12*, 4070–4073; also see refs 9h, 10d, 10g, 11b, and 12d.

(9) For recent reviews, see: (a) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691–1693. (b) Desimoni, G.; Faita, G.; Jøgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561–3651. (c) Achard, T. R. J.; L. Clutterbuck, A.; North, M. *Synlett* **2005**, *12*, 1828–18470. Selected examples for BOX-type ligand catalyzed asymmetric Henry reaction: (d) Christensen, C.; Juhl, K.; Jøgensen, K. A. *Chem. Commun.* **2001**, 2222–2223. (e) Christensen, C.; Juhl, K.; Hazell, R. G.; Jøgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4875–4881. (f) Risgaard, T.; Gothelf, K. V.; Jøgensen, K. A. *Org. Biomol. Chem.* **2003**, *1*, 153–156. (g) Ginotra, S. K.; Singh, V. K. *Org. Biomol. Chem.* **2007**, *5*, 3932–3937. (h) Toussaint, A.; pfaltz, A. *Eur. J. Org. Chem.* **2008**, 4591–4597. (i) Gaab, M.; Bellemin-Laponnaz, S.; Gade, L. H. *Chem.—Eur. J.* **2009**, *15*, 5450–5462. (j) Lang, K.; Park, J.; Hong, S. *J. Org. Chem.* **2010**, *75*, 6424–6435; also see reference 5. Selected examples for salen-type ligand catalyzed asymmetric Henry reaction: see refs 6f 6g, 6h, and 6i.

(10) (a) Maheswaran, H.; Prasanth, K. L.; Krishna, G. G.; Ravikumar, K.; Sridhar, B.; Kantam, M. L. *Chem. Commun.* **2006**, 4066–4068. (b) Palomo, C.; Oiarbide, M.; Laso, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3881–3884. (c) Kim, H. Y.; Oh, K. *Org. Lett.* **2009**, *11*, 5682–5685. (d) Blay, G.; Domingo, L. R.; Hernández-Olmos, V.; Pedro, J. R. *Chem.—Eur. J.* **2008**, *14*, 4725–4730. (e) Blay, G.; Hernández-Olmos, V.; Pedro, J. R. *Org. Lett.* **2010**, *12*, 3058–3061. (f) Breuning, M.; Hein, D.; Steiner, M.; Gessner, V. H.; Strohmann, C. *Chem.—Eur. J.* **2009**, *15*, 12764–12769. (g) Noole, A.; Lippur, K.; Metsala, A.; Lopp, M.; Kanger, T. *J. Org. Chem.* **2010**, *75*, 1313–1316.

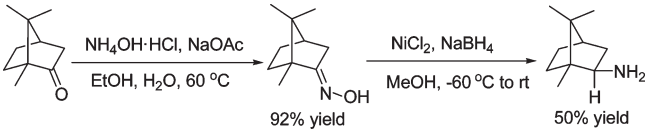
(11) (a) Arai, T.; Watanabe, M.; Yanagisawa, A. *Org. Lett.* **2007**, *9*, 3595–3597. (b) Arai, T.; Takashita, R.; Endo, Y.; Watanabe, M.; Yanagisawa, A. *J. Org. Chem.* **2008**, *73*, 4903–4906. (c) Steurer, M.; Bolm, C. *J. Org. Chem.* **2010**, *75*, 3301–3310.

(12) (a) Arai, T.; Watanabe, M.; Fujiwara, A.; YokoyamaN.; Yanagisawa, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5978–5981. (b) Bandini, M.; Piccinelli, F.; Tommasi, S.; Umani-Ronchi, A.; Ventrici, C. *Chem. Commun.* **2007**, 616–618. (c) Kowalczyk, R.; Sidorowicz, Ł.; Skarżewski, J. *Tetrahedron: Asymmetry* **2008**, *19*, 2310–2315. (d) Kowalczyk, R.; Skarżewski, J. *Tetrahedron: Asymmetry* **2009**, *20*, 2467–2473. (e) Zhang, G.; Yashima, E.; Woggon, W. D. *Adv. Synth. Catal.* **2009**, *351*, 1255–1262. (f) Xiong, Y.; Wang, F.; Huang, X.; Wen, Y.; Feng, X. *Chem.—Eur. J.* **2007**, *13*, 829–833. (g) Jin, W.; Li, X.; Huang, Y.; Wu, F.; Wan, B. *Chem.—Eur. J.* **2010**, *16*, 8259–8261.

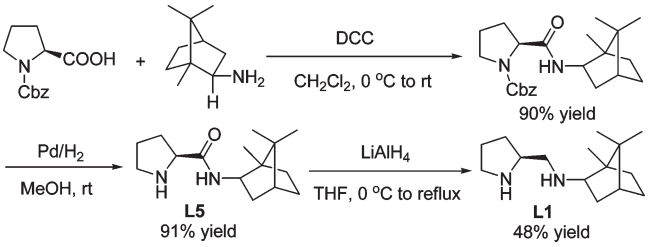
(13) For recent reviews, see: (a) Wolfgang, O. *Tetrahedron* **1987**, *43*, 1969–2004. (b) Gennari, C. *Pure Appl. Chem.* **1997**, *69*, 507–512. (c) Giorigio, C. *Chem. Soc. Rev.* **2006**, *35*, 1230–1243. (d) Luo, Y.; Zhang, H.; Wang, Y.; Xu, P. *Acc. Chem. Res.* **2010**, *43*, 1317–1330.

(14) For recent reviews, see: (a) Mori, A.; Abet, H.; Inoue, S. *Appl. Organomet. Chem.* **1995**, *9*, 189–197. (b) Severin, K.; Bergs, R.; Beck, W. *Angew. Chem., Int. Ed.* **1998**, *37*, 1634–1654. (c) Hoveyda, A. H.; Hird, A. W.; Kacprzynski, M. A. *Chem. Commun.* **2004**, 1779–1785. (d) Javro, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481–2495. (e) List, B. *Tetrahedron* **2002**, *58*, 5573–5590. (f) Note, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580–591. (g) Paradowska, J.; Stodulski, M.; Mlynarski, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 4288–4297. (h) Xu, L.; Luo, J.; Lu, Y. *Chem. Commun.* **2009**, 1807–1821.

SCHEME 1. Preparation of the *exo*-(−)-Bornylamine



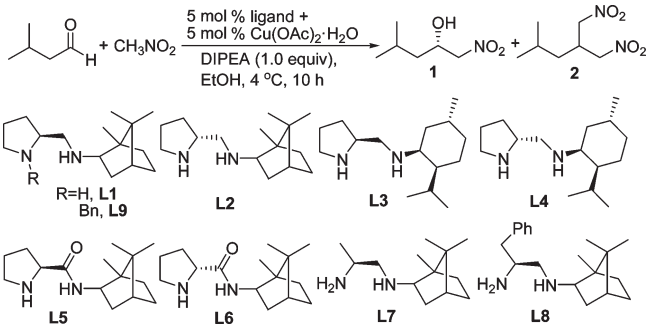
SCHEME 2. Synthetic Route for the Chiral Diamine Ligands L5 and L1



against water or oxygen for several months, without any loss of catalytic performance. With the set of ligands in hand, the parent Henry reaction was chosen to evaluate the asymmetric induction ability of our novel C_1-symmetric diamine ligands.

We chose the reaction between isovaleraldehyde and nitromethane as the model reaction (Table 1) since the aliphatic aldehydes are less systematically studied. On the basis of Evans's explanation[5] and Pedro's work,[10a] copper acetate was used to screen the above new chiral ligands with diisopropylethylamine (DIPEA) as the additive base in ethanol at 4 °C. Among the ligands **L1**−**L9**, **L1** was found as a potential ligand for the reaction. Although a minor byproduct **2** was generated through Michael addition of the excess nitromethane to the accompanying dehydration product (nitroolefin),[15] the main nitroaldol product **1** was obtained in 65% yield with 91% enantiomeric excess after 10 h (entry 1). When the ligand **L2** derived from D-proline was used instead, the opposite *R*-configuration product was yielded with much lower enantioselectivity (entry 2). A similar change in stereoselectivity was also observed in the cases of **L3** and **L4** derived from (+)-(1*S*,2*S*,5*R*)-menthylamine, but the enantioselectivity for **L3** was apparently lower than that of **L1** (entries 3 and 4). The ligands **L5** and **L6** gave very low enantiomeric excesses (entries 5 and 6), probably due to the poor coordinating ability of amide nitrogen atom. These results clearly indicate that there do exist configurationally "match" and "mismatch" relationships between the two chiral parts of the ligands, and the stereochemistry for the process is mainly controlled by the configuration of proline moiety. In addition, the ligands **L7** and **L8** bearing a primary amine, which were respectively derived from L-alanine and L-phenylalanine, also showed inferior results (entries 7 and 8). Interestingly, when the N−H group of the pyrrolidine ring of **L1** was blocked by benzyl moiety, the ee value sharply decreased to 61% (entry 9), indicating that the N−H group of the pyrrolidine ring is a pivotal element for the asymmetric induction probably through the formation of a hydrogen bond between the nitronate and the N−H group of the pyrrolidine ring.[10d]

TABLE 1. Ligand Screening[a]



entry	ligand	yield of **1** (%)	yield of **2** (%)	ee (%)[b]
1	**L1**	65	16	91
2	**L2**	56	15	−37
3	**L3**	61	20	76
4	**L4**	66	6	−60
5	**L5**	49	22	11
6	**L6**	53	18	−16
7	**L7**	68	10	24
8	**L8**	70	5	16
9	**L9**	63	8	61

[a]Reactions were carried out on a 0.5 mmol scale of isovaleraldehyde with 10 equiv of nitromethane in a mixture of 2.0 mL of ethanol, 5 mol % ligand and 5 mol % $Cu(OAc)_2 \cdot H_2O$ in the presence of 1.0 equiv of DIPEA at 4 °C for 10 h. [b]Enantiomeric excess was determined by HPLC analysis using Chiracel AD-H as a column; the absolute configuration was established as *S* by comparison with literature data.

Encouraged by the preliminary results, we systematically carried out optimization of the reaction conditions, and the results are illustrated in Table 2. First, various copper salts were evaluated in combination with the chiral ligand **L1** and DIPEA in ethanol at 4 °C for 10 h (entries 1−4).[16] As a consequence, several divalent copper salts were effective for the asymmetric Henry reaction, and $CuCl_2 \cdot 2H_2O$ gave the best ee value of 95% (entry 2). Next, a group of solvents were examined (entries 5−14). Aprotic solvents such as nitromethane, acetonitrile, DMF, diethyl ether, and THF (entries 7−9 and 13−14) afforded better enantioselectivity than protic solvents such as methanol and 2-propanol (entries 5−6) and halogenated solvents such as dichloromethane and chloroform (entries 10−11). Gratifyingly, when THF, diethyl ether, or toluene was employed in this system, the former byproduct **2** was no longer detected (entries 12−14). THF proved to be the most suitable solvent for this reaction in view of the enantioselectivity and yield (entry 14). Finally, a series of organic bases was investigated as the additive.[17] DIPEA turned out to be the best choice with 97% ee and 84% yield (entry 14), while TEA induced almost the same result (entry 15).

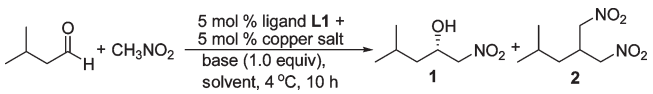
For its importance in potential industrial application, the catalyst loading was further assessed. We found that 2.5 mol % of the catalyst was sufficient to provide the

(15) The analogous byproduct, see: (a) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A. *Synthesis* **2004**, *12*, 1938–1940. (b) Komura, K.; Kawamura, T.; Sugi, Y. *Catal. Commun.* **2007**, *8*, 644–648. (c) Motokura, K.; Tada, M.; Iwasawa, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 9230–9235.

(16) Other metal salts, such as CuCl, CuCN, $CoCl_2 \cdot 6H_2O$, $Co(OAc)_2 \cdot 4H_2O$, $NiCl_2 \cdot 6H_2O$, $CrCl_3 \cdot 6H_2O$, $ZnCl_2$, $MnSO_4 \cdot H_2O$, $AgSO_4$, and AgOAc were also screened in combination with ligand **L1** under the identical conditions, but all of them gave results inferior to those of $CuCl_2 \cdot 2H_2O$.

(17) Other organic bases, such as DBU, TMEDA, DMAP, imidazole, pyridine, pyrrolidine, and quinine, were also screened under the identical conditions but were found to be inferior to DIPEA.

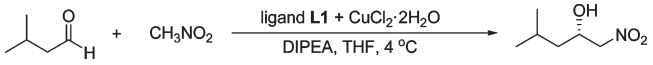
TABLE 2. Optimization of Reaction Conditions[a]



entry	copper salt	solvent	base	yield of **1** (%)	yield of **2** (%)	ee (%)[b]
1	$Cu(OAc)_2 \cdot H_2O$	EtOH	DIPEA	65	16	91
2	$CuCl_2 \cdot 2H_2O$	EtOH	DIPEA	63	15	95
3	$CuSO_4 \cdot 5H_2O$	EtOH	DIPEA	60	12	80
4	$CuBr_2$	EtOH	DIPEA	46	25	93
5	$CuCl_2 \cdot 2H_2O$	MeOH	DIPEA	60	18	88
6	$CuCl_2 \cdot 2H_2O$	*i*-PrOH	DIPEA	73	20	89
7	$CuCl_2 \cdot 2H_2O$	$MeNO_2$	DIPEA	65	9	93
8	$CuCl_2 \cdot 2H_2O$	MeCN	DIPEA	69	8	95
9	$CuCl_2 \cdot 2H_2O$	DMF	DIPEA	74	15	95
10	$CuCl_2 \cdot 2H_2O$	CH_2Cl_2	DIPEA	46	16	88
11	$CuCl_2 \cdot 2H_2O$	$CHCl_3$	DIPEA	48	15	82
12	$CuCl_2 \cdot 2H_2O$	PhMe	DIPEA	72	–	91
13	$CuCl_2 \cdot 2H_2O$	Et_2O	DIPEA	82	–	96
14	$CuCl_2 \cdot 2H_2O$	THF	DIPEA	84	–	97
15	$CuCl_2 \cdot 2H_2O$	THF	TEA	81	–	97

[a]Reactions were carried out on a 0.5 mmol scale of isovaleraldehyde with 10 equiv of nitromethane in a mixture of 2.0 mL of solvent, 5 mol % ligand **L1** and 5 mol % copper salt in the presence of 1.0 equiv of base at 4 °C for 10 h. [b]Determined by chiral HPLC analysis.

TABLE 3. Catalyst and Reagents Loading Screening[a]



entry	**L1**/$CuCl_2 \cdot 2H_2O$ (mol %)	DIPEA (equiv)	$MeNO_2$ (equiv)	time (h)	yield (%)	ee (%)[b]
1	5.0	1.0	10	10	84	97
2	2.5	0.5	10	10	76	97
3	1.0	0.25	10	20	35	88
4	2.5	1.0	10	20	95	97
5	2.5	0.5	10	20	90	97
6	2.5	0.25	10	20	91	97
7	2.5	0.125	10	20	65	97
8	2.5	0	10	20	37	97
9	5.0	0	10	20	88	97
10	2.5	1.0	6	20	85	97
11	2.5	1.0	3	20	80	97
12	2.5	1.0	3	40	94	97

[a]Reactions were carried out on a 0.5 mmol scale of isovaleraldehyde with nitromethane in a mixture of 2.0 mL of THF, ligand **L1**, and $CuCl_2 \cdot 2H_2O$ in the presence of DIPEA at 4 °C for specified time. [b]Determined by chiral HPLC analysis.

excellent yield and enantioselectivity (Table 3, entry 4). The amount of base additive had little influence on the enantioselectivity but was responsible for the reaction rate (entries 4−8). While the catalyst loading increased to 5.0 mol %, the reaction could go to completion within 20 h even in the absence of DIPEA in 88% yield with 97% ee (entry 9). This indicates our catalytic system can tolerate a broad range of quantities of base additive, and the uncoordinated base-promoted background reaction is negligible. Meanwhile, it was found that 3 equiv of nitromethane was enough for the reaction to complete smoothly over 40 h with 94% yield and 97% ee (entry 12).

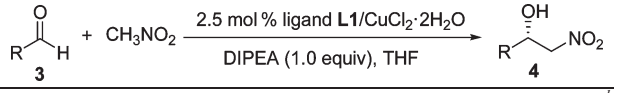
On the basis of the optimized reaction parameters, the scope of aliphatic aldehydes was explored by treating with 10 equiv of nitromethane in the presence of 2.5 mol % of the catalyst and 1.0 equiv of DIPEA in THF at 4 °C (Table 4, entries 1−14). To our delight, both unbranched (entries 1, 2, 4, 7, 8, and 9) and branched aliphatic aldehydes (entries 3, 5, 6, and 10) were compatible at 4 °C, to provide high yields (up to 98%) and excellent enantioselectivitives (up to 97% ee). It is noteworthy that neither the carbon chain length of aliphatic aldehydes nor the steric bulk has an obvious influence on the enantioselectivity and yield. Cinnamaldehyde (**3k**) and 3-benzyloxypropionaldehyde (**3l**) were also tolerated with excellent enantioselectivitives and good yields (entries 11 and 12). When the reaction temperature was lowered to −20 °C, up to 99% ee was achieved for isovaleraldehyde (**3e**), and 98% ee for 3-phenylpropionaldehyde (**3i**), respectively (entries 13 and 14). Then, the estimation of our catalyst system was extended to aromatic aldehydes (entries 15−28). In general, regardless of whether the aromatic aldehydes were electron-poor (entries 16−20 and 23), electron-rich (entries 21−22 and 24−27), or sterically hindered (entries 16 and 23), all of them smoothly underwent the Henry reactions with excellent enantioselectivitives (up to 97%) and high yields (up to 97%). The highest ee value of 98% accompanied with 94% yield was furnished for 2-furancarboxaldehyde (**3x**) (entry 26). Comparable to isovaleraldehyde (**3e**), 3 equiv of nitromethane was sufficient for benzaldehyde (**3m**) without any decline in enantioselectivity and yield (entry 28).

Subsequently, in view of the less explored nitroalkanes substrate scope, nitroethane, 1-nitropropane, and 2-nitroethylbenzene were tested in this asymmetric catalysis process (Table 5). High yields (up to 95%), excellent enantioselectivitives (up to 98%), and moderate to good diastereoselectivitives (up to 90:10, favoring the *syn* product) were obtained. Neither the electronic property of the aromatic aldehydes, nor the steric hindrance of aliphatic aldehydes has a limited effect on the diastereoselectivitives and enantioselectivitives. Compared with the cases of nitroethane, diastereoselectivities of 1-nitropropane are always higher (entries 2, 4, and 6 versus 1, 3, and 5). When 2-nitroethylbenzene was utilized to react with benzaldehyde (**3m**), high yield and excellent enantioselectivity were observed, albeit with poorer diastereoselectivity than with 1-nitropropane (entry 7 versus 6). For the reaction of benzaldehyde (**3m**) with nitroethane, opposite diastereoselectivities were generated for the systems of $Cu(OAc)_2 \cdot H_2O/Et_2O$ and $CuCl_2 \cdot 2H_2O$/THF, respectively, albeit with no significant changes in both enantioselectivitives and yields (entry 5). In the case of 1-nitropropane, the same diastereoselectivities were achieved for the above two systems (entries 4 and 8). Interestingly, optical purities of minor *anti*-adducts are usually lower than those of *syn*-adducts for most aldehydes except 3-phenylpropionaldehyde (**3i**). These results demonstrate that minor *anti*-adducts were not generated by epimerization of the nitro group.[8a] Moreover, 3 equiv of nitroethane was also sufficient for the reaction of benzaldehyde (**3m**) to finish smoothly over 90 h without any significant changes in the results (entry 12).

For more details of this asymmetric catalysis process, the influence of water and benzoic acid on the reaction between benzaldehyde (**3m**) and nitromethane was studied under the identical reaction conditions to test our system's flexibility. Addition of 20 μL of water or 2.5 mol % benzoic acid has negligible influence on the catalytic efficiency (Table 6). However, when the amount of benzoic acid increased to 5.0 mol % (entry 4), the reaction rate decreased, but the enantioselectivity remained unchanged.

In addition, during solvent screening, we noticed that the complex **L1**/$CuCl_2 \cdot 2H_2O$ could not be dissolved well in diethyl ether. After the reaction completed, the mixture

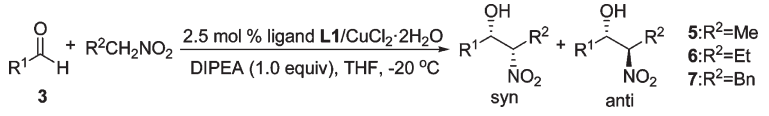
TABLE 4. Enantioselective Henry Reaction of Aldehydes with Nitromethane[a]



entry	aldehyde (R)	temp (°C)	time (h)	yield (%)	ee (%)[b]
1	CH_3CH_2 (**3a**)	4	20	92	96
2	$CH_3CH_2CH_2$ (**3b**)	4	20	93	94
3	$(CH_3)_2CH$ (**3c**)	4	20	94	97
4	$CH_3(CH_2)_2CH_2$ (**3d**)	4	20	95	96
5	$(CH_3)_2CHCH_2$ (**3e**)	4	20	95	97
6	$(CH_3)_3C$ (**3f**)	4	20	93	97
7	$CH_3(CH_2)_3CH_2$ (**3g**)	4	20	98	94
8	$CH_3(CH_2)_4CH_2$ (**3h**)	4	24	92	96
9	$Ph(CH_2)_2$ (**3i**)	4	15	91	96
10	cyclohexyl (**3j**)	4	20	94	96
11	PhCH=CH (**3k**)	4	12	80	90
12	$BnOCH_2CH_2$ (**3l**)	4	16	83	94
13	$(CH_3)_2CHCH_2$ (**3e**)	−20	40	94	99
14	$Ph(CH_2)_2$ (**3i**)	−20	15	87	98
15	Ph (**3m**)	−20	18	94	97
16	2-ClC_6H_4 (**3n**)	−20	12	97	97
17	3-$NO_2C_6H_4$ (**3o**)	−20	6	96	93
18	4-$NO_2C_6H_4$ (**3p**)	−20	8	95	95
19	4-ClC_6H_4 (**3q**)	−20	12	95	97
20	4-FC_6H_4 (**3r**)	−20	12	97	96
21	4-MeC_6H_4 (**3s**)	−20	24	92	96
22	4-$MeOC_6H_4$ (**3t**)	−20	24	93	96
23	2,4-diClC_6H_3 (**3u**)	−20	14	97	94
24	3,4-di$MeOC_6H_3$ (**3v**)	−20	20	90	97
25	3,4-$(OCH_2O)C_6H_3$ (**3w**)	−20	20	91	98
26	2-furyl (**3x**)	−20	14	94	98
27	2-thiophenyl (**3y**)	−20	18	97	92
28[c]	Ph (**3m**)	−20	22	95	97

[a]Reactions were carried out on a 0.5 mmol scale of aldehydes with 10 equiv of nitromethane in a mixture of 2.0 mL of THF, 2.5 mol % ligand **L1**, and 2.5 mol % $CuCl_2 \cdot 2H_2O$ in the presence of 1.0 equiv of DIPEA at indicated temperature for specified time. [b]Determined by chiral HPLC analysis. [c]Reaction was carried out using 3 equiv of nitromethane.

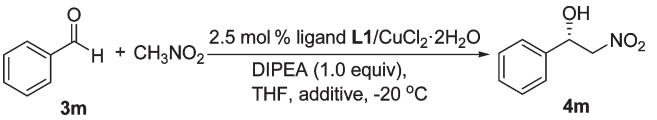
TABLE 5. Asymmetric Henry Reaction of Other Nitroalkanes[a]



entry	aldehyde (R^1)	R^2	time (h)	yield (%)	*syn*/*anti* (%)[b]	ee (%)[c]
1	$Ph(CH_2)_2$ (**3i**)	Me	40	91	71:29	95/95
2	$Ph(CH_2)_2$ (**3i**)	Et	80	85	75:25	93/96
3	cyclohexyl (**3j**)	Me	50	86 (83)[d]	88:12 (87:13)	96/88 (96/85)
4	cyclohexyl (**3j**)	Et	90	80 (75)	90:10 (89:11)	nd[e]
5	Ph (**3m**)	Me	30	93 (95)	55:45 (37:63)	96/90 (96/92)
6	Ph (**3m**)	Et	60	94	74:26	98/83
7[f]	Ph (**3m**)	Bn	15	92	64:36	97/90
8	4-ClC_6H_4 (**3q**)	Et	60	93 (94)	70:30 (70:30)	97/80 (95/86)
9	4-FC_6H_4 (**3r**)	Et	60	92	78:22	96/60
10	4-MeC_6H_4 (**3s**)	Et	80	95	77:23	96/67
11	2-furyl (**3x**)	Et	60	93	74:26	98/80
12[g]	Ph (**3m**)	Me	90	92	59:41	97/85

[a]Reactions were carried out on a 0.5 mmol scale of aldehydes with 10 equiv of nitroalkanes in a mixture of 2.0 mL of THF, 2.5 mol % ligand **L1** and 2.5 mol % $CuCl_2 \cdot 2H_2O$ in the presence of 1.0 equiv of DIPEA at −20 °C for certain time. [b]Determined by ^1H NMR spectroscopy analysis after rough purification using silica gel column chromatography. [c]Determined by chiral HPLC analysis. [d]Values in parentheses were generated by $Cu(OAc)_2 \cdot H_2O$ in Et_2O under identical conditions. [e]Enantiomeric excesses were not determined for the chiral HPLC separations for the product were not fully resolved. [f]Reaction was carried out on a 0.25 mmol scale in 1.0 mL of THF under identical conditions. [g]Reactions was carried out using 3 equiv of nitroethane.

TABLE 6. Other Additive Effects on the Henry Reaction of Benzaldehyde[a]



entry	additive	time (h)	yield (%)	ee (%)[b]
1	20 μL H_2O	18	92	97
2	0.5 mol % PhCOOH	22	94	97
3	2.5 mol % PhCOOH	22	90	97
4	5.0 mol % PhCOOH	100	86	97

[a]Reactions were carried out on a 0.5 mmol scale of benzaldehyde (**3m**) with 10 equiv of nitromethane in a mixture of 2 mL of THF, 2.5 mol % ligand **L1** and 2.5 mol % $CuCl_2 \cdot 2H_2O$ in the presence of 1.0 equiv of DIPEA at −20 °C for specified time. [b]Determined by chiral HPLC analysis.

was centrifuged, and the precipitate could be reused directly as the catalytic active species for three cycles without any decrease in enantioselectivity (Table 7).

As a synthetic application of this asymmetric catalysis procedure, 3,4-dimethoxybenzaldehyde (**3v**) was directly used as the starting material to react with nitromethane to give the nitroaldol adduct (*S*)-1-(3,4-dimethoxyphenyl)-2-nitroethanol (**4v**) in 94% yield and 97% ee on 10 mmol scale (Scheme 3, $[\alpha]_D^{25} = +15.6$ (c = 1.1 in EtOH; lit: $[\alpha]_D^{25} = +26.7$[4a] in CH_2Cl_2, 78% ee)). After completion of the reaction, the ligand **L1** could be recovered in 70% yield by simple aqueous acid/base workup and reused directly for the second cycle to afford 80% yield and 97% ee. Followed by catalytic hydrogenation in the presence of 1.5 equiv of acetic acid,[18] the nitro alcohol compound **4v** was converted into the corresponding ammonium acetate **8** in 92% yield and then was neutralized by aqueous sodium hydroxide. Subsequent extraction using ethyl acetate afforded (*S*)-2-amino-1-(3,4-dimethoxyphenyl)ethanol (**9**) (Scheme 3, $[\alpha]_D^{25} = +30.2$ (c = 1.0 in EtOH)), which is the key intermediate for (*S*)-epinephrine and (*S*)-norepinephrine.[19]

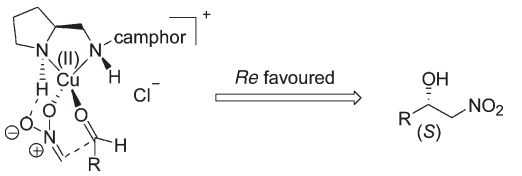


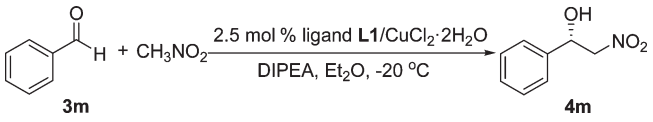
FIGURE 1. Proposed transition state model.

To account for the stereochemical outcome of the reaction, the formation of **L1**/$CuCl_2$ complex was studied by ESI-HRMS [calcd for $C_{15}H_{28}N_2CuCl^+$: 334.1232; found: 334.1231]. Then, the X-ray crystal structure of **L1**/$CuCl_2$ complex revealed the expected tetrahedral geometry at the central copper atom (see SI). On the basis of the preliminary experimental investigations and previously reported steric and electronic considerations,[10f] a possible transition state model was proposed as illustrated in Figure 1. In the transition state, the nucleophilic nitronate would orient toward the inside position perpendicular to the ligand plane and be fixed with the hydrogen bonding with the N−H group of the pyrrolidine ring, whereas the electrophilic aldehyde should occupy the outside site, avoiding the steric hindrance of the camphor scaffold. Thus, the nitronate would attack the aldehyde from the *Re* face, and the corresponding nitroaldol adduct was obtained with *S* configuration.

Conclusion

We have developed a unique chiral secondary diamine **L1** that is an efficient ligand for the copper-catalyzed asymmetric nitroaldol reaction. This catalyst system enables us to prepare

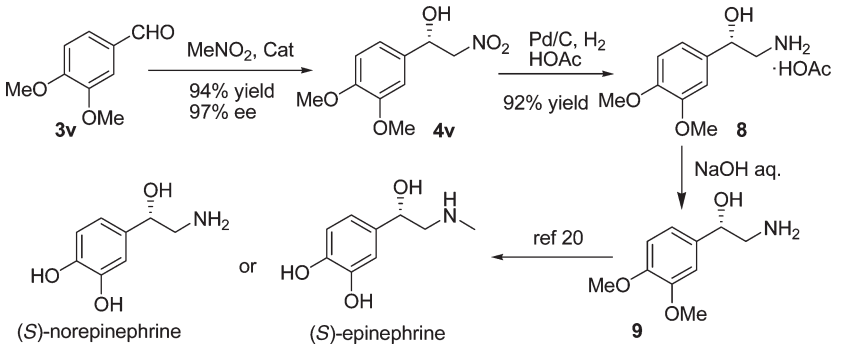
TABLE 7. Cyclic Reuse of the Catalyst[a]



cycle	scale (mmol)	$MeNO_2$ (equiv)	DIPEA (equiv)	time (h)	yield (%)	ee (%)[b]
first	2.0	6	0.6	30	94	97
second	2.0	6	0.6	60	93	97
third	2.0	6	0.6	100	88	97

[a]Reactions were carried out on a 2.0 mmol scale in 6 mL of Et_2O. [b]Determined by chiral HPLC analysis.

SCHEME 3. Synthesis of (*S*)-2-Amino-1-(3,4-dimethoxyphenyl)ethanol (9)



β-nitroalchohols with excellent enantioselectivities and high yields for a broad scope of aldehydes including aliphatic and aromatic aldehydes, as well as heteroaromatic and unsaturated aldehydes. Starting from commercially available 3,4-dimethoxybenzaldehyde (**3v**), the corresponding amino alcohol **9**, a key intermediate for (*S*)-epinephrine and (*S*)-norepinephrine, has been successfully obtained in three steps. Nitroalkanes such as nitromethane, nitroethane, 1-nitropropane, and 2-nitroethylbenzene are suitable substrates for our catalyst system with excellent enantioselectivities and moderate to good diastereoselectivites. With its stable secondary amine moiety, the ligand **L1** could be recovered after the completion of reaction in good yield without loss of catalytic activity by simple aqueous acid/base workup. Apparently, the simple and inexpensive preparation of the stable ligand **L1**, easy operation without special precautions to exclude moisture or air, low to 2.5 mol % catalyst loading and excellent enantioselectivities and high yields make this an attractive option for practical industrial utilization. More work is needed to shed light on the nature of catalytic species and the catalytic process. Further studies of asymmetric applications of this new chiral secondary diamine ligand and immobilization of the catalyst for heterogeneous catalysis are currently underway in our laboratory.

Experimental Section

General Information. THF was dried over Na and distilled prior to use. Nitroalkanes were dried over anhydrous $CaCl_2$ and distilled prior to use. Aliphatic aldehydes were obtained from commercial sources and were distilled before use. Aromatic aldehydes were treated by dissolved in CH_2Cl_2 and washed by 5 M aqueous NaOH solution, dried over anhydrous K_2CO_3 and concentrated in vacuum. Reactions were monitored by TLC analysis using Silica Gel 60 Å F-254 thin layer plates. Flash column chromatography was performed on silica gel 60 Å, 10−40 μm. Optical rotations were measured by polarimeter in the solvent indicated. ^{1}H NMR spectra were recorded on instruments (400 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, d = 7.26). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants (Hz) and integration. ^{13}C NMR spectra were recorded on instruments (100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from the tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$, d = 77.0). HRMS was measured on an Apex III (7.0 T) Fourier transform ion cyclotron resonance (FTICR) mass spectrometer equipped with an ESI source in the positive-ion mode. X-ray intensity data were measured on a SMART APEX CCD based diffractometer. Enantiomer ratios were determined by chiral HPLC analysis on Daicel Chiralcel AD-H, OD-H, and AS-H in comparison with the authentic racemates. Retention times are given in minutes. The absolute configuration of nitroaldol adducts was assigned by comparison to literature compounds. Diastereomeric ratios were determined by ^{1}H NMR, and absolute stereochemistry of both diastereomers was assigned by comparison of the retention times in HPLC with literature data or by analogy to other compounds. For the stereochemical notation of these compounds, i.e. (1*S*,2*R*), 1 always refers to the C−OH carbon and 2 always refers to the C−NO_2 carbon.

General Procedure for the Preparation of Chiral Ligands. D-(+)-Camphor Oxime. A solution of hydroxylamine hydrochloride (4.17 g, 60 mmol) and sodium acetate (4.12 g, 50 mmol) in water (30 mL) was treated with a solution of D-(+)-camphor (6.08 g, 40 mmol) in ethanol (20 mL) and the mixture was heated at 60 °C for 20 h. The resulting clear solution was concentrated under reduced pressure until crystals of camphor oxime began to form. The suspension was set aside at 4 °C to complete the crystallization, and the product was collected by filtration and washed with distilled water. The crystalline material was collected and dried under vacuum to afford D-(+)-camphor oxime (6.14 g, 92% yield). Mp: 117−120 °C (lit[20] mp 118−119 °C); $[\alpha]_D^{25}$ = −37.5 (c = 1.0 in EtOH; lit:[20a] $[\alpha]_D^{25}$ = −36.8 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 9.18 (br s, 1H), 2.56 (dt, J = 17.6, 4.0 Hz, 1H), 2.05 (d, J = 18.0 Hz, 1H), 1.92 (t, J = 4.4 Hz, 1H), 1.88−1.80 (m, 1H), 1.70 (td, J = 12.4, 4.0 Hz, 2H), 1.50−1.43 (m, 1H), 1.27−1.21 (m, 1H), 1.01 (s, 3H), 0.92 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 169.9, 51.8, 48.3, 43.7, 33.1, 32.7, 27.3, 19.5, 18.6, 11.1.

***exo*-(−)-Bornylamine.** Sodium borohydride (2.28 g, 60 mmol) was added portionwise to a solution of D-(+)-camphor oxime (3.34 g, 20 mmol) and $NiCl_2$ (5.18 g, 40 mmol) in anhydrous MeOH (60 mL) at −60 °C over a period of 2 h (**Caution: gas evolution!**). After complete addition, the resulting black slurry was allowed to warm up to −30 °C and stirred at this temperature until no more starting material was detected (4−5 h). Then, the reaction mixture was warmed to room temperature, and 10 mL of concentrated ammonium hydroxide in 30 mL of water was added with vigorous stirring. The resulting slurry was extracted with diethyl ether (3 × 100 mL), and the combined organic layers were washed with brine (2 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuum. The crude product was purified by flash chromatography eluting with dichloromethane and methanol to afford *exo*-(−)-bornylamine as a foamy white solid (1.53 g, 50% yield).[21a] $[\alpha]_D^{25}$ = −48.5 (c = 1.8 in EtOH; lit: $[\alpha]_D^{25}$ = −49.9,[21b] −48.7[21c] in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.70 (dd, J = 8.8, 5.2 Hz, 1H), 1.77−1.63 (m, 3H), 1.57−1.48 (m, 2H), 1.29 (br s, 2H), 1.10−0.98 (m, 2H), 0.97 (s, 3H), 0.87 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 60.4, 48.1, 46.6, 45.0, 40.6, 36.4, 27.2, 20.9, 20.3, 11.9.

(−)-(*E*)-(1*R*,4*S*)-Menthyl Oxime. The same procedure that was used for the synthesis of D-(+)-camphor oxime was used, starting from L-menthone (4.62 g, 30 mmol). After the completion of the reaction, EtOH was removed under reduced pressure, and the mixture was diluted with H_2O (30 mL) and extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was purified by column chromatography eluting with petroleum ether and ethyl acetate to afford (−)-(*E*)-(1*R*,4*S*)-menthyl oxime as a white solid (3.74 g, 74% yield). $[\alpha]_D^{25}$ = −39.6 (c = 1.8 in EtOH; lit: $[\alpha]_D^{25}$ = −39.4[22] in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 9.18 (br s, 1H), 3.07−3.03 (m, 1H), 2.17−2.09 (m, 1H), 1.92−1.79 (m, 3H), 1.75−1.64 (m, 2H), 1.42−1.32 (m, 1H), 1.20−1.11 (m, 1H), 0.98 (d, J = 6.0 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 161.4, 48.8, 32.8, 32.4, 31.9, 26.8, 26.4, 21.7, 21.4, 19.1.

(18) The retro-Henry reaction happened in the absence of acetic acid.

(19) (a) Singer, R. A.; Carreira, E. M. *Tetrahedron Lett.* **1997**, *38*, 927–930. (b) Dong, L.; Crowe, M.; West, J.; Ammann, J. R. *Tetrahedron Lett.* **2004**, *45*, 2731–2733.

(20) (a) Gamble, D. L.; Hems, W. P.; Ridge, B. *J. Chem. Soc. Pak.* **2001**, 248–260. (b) Page, P. C. B.; Murrell, V. L.; Limousin, C.; Laffan, D. D. P.; Bethell, D.; Slawin, A. M. Z.; Smith, T. A. D. *J. Org. Chem.* **2000**, *65*, 4204–4207.

(21) (a) Neisius, N. M.; Plietker, B. *J. Org. Chem.* **2008**, *73*, 3218–3227. (b) Trojanek, J.; Pospisek, J.; Cekan, Z. *Chem. Commun.* **1961**, 2602–2611. (c) Carman, R. M.; Greenfield, K. L. *Aust. J. Chem.* **1984**, *37*, 1785–1790.

(22) Schopohl, M. C.; Bergander, K.; Kataeva, O.; Fröhlich, R.; Waldvogel, S. R. *Synthesis* **2003**, *17*, 2689–2694.

(+)-(1*S*,2*S*,5*R*)-Menthylamine. Following the same procedure as for the synthesis of *exo*-(−)-bornylamine starting from (−)-(*E*)-(1*R*, 4*S*)-menthyl oxime (1.69 g, 10 mmol) afforded (−)-(1*S*, 2*S*, 5*R*)-menthylamine (0.83 g, 53% yield), which was purified by column chromatography eluting with petroleum ether and ethyl acetate. $[\alpha]_D^{25} = +5.4$ (c = 0.6 in $CHCl_3$; lit: $[\alpha]_D^{25} = +6.5$[23] in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.23 (d, J = 2.8 Hz, 1H), 1.72−1.60 (m, 4H), 1.46−1.37 (m, 1H), 1.22−1.06 (m, 4H), 0.92 (t, J = 6.4 Hz, 7H), 0.86 (d, J = 6.4 Hz, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 48.0, 47.3, 43.3, 35.4, 29.3, 25.6, 23.9, 22.6, 21.3, 20.7.

Ligand L5. To a stirred mixture of (*S*)-*N*-benzyloxycarbonylproline (1.74 g, 7 mmol) in anhydrous dichloromethane (20 mL) was added dropwise a dichloromethane (15 mL) solution of dicyclohexylcarbodiimide (1.46 g, 7 mmol) at 0 °C followed by a dichloromethane (15 mL) solution of *exo*-(−)-bornylamine (1.03 g, 6.7 mmol). The mixture was stirred at 0 °C for 30 min and then warmed to room temperature for another 2 h. After the reaction completed, 0.5 mL of acetic acid was added, and the mixture was stirred for an additional 30 min. Insoluble dicyclohexylurea was removed by filtration. After removing the solvent, the residue was dissolved in diethyl ether and then filtered again. The excessive (*S*)-*N*-benzyloxycarbonylproline was removed though washing with saturated $NaHCO_3$ aqueous (2 × 30 mL) and brine (2 × 30 mL), and the organic phase was dried over anhydrous Na_2SO_4. Evaporation of the organic solvent afforded the product as a colorless oil (2.32 g, 90% yield), which was used directly for the next steps without further purification. To a stirred solution of the residue in MeOH (30 mL) was added Pd/C (170 mg, 10% w/w), and the resulting suspension was stirred under H_2 atmosphere (1 atm) at room temperature. After stirring overnight, the reaction mixture was filtered through a pad of Celite and washed with MeOH. Then the filtrate was concentrated under vacuum. The crude product was purified by column chromatography eluting with dichloromethane and methanol to afford **L5** as a white solid (1.37 g, 91% yield). $[\alpha]_D^{25} = -76.9$ (c = 1.3 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.83−7.81 (br s, 1H), 3.84 (dt, J = 9.6, 4.8 Hz, 1H), 3.70 (dd, J = 8.8, 4.4 Hz, 1H), 3.02 (dt, J = 10.4, 6.8 Hz, 1H), 2.80 (dt, J = 10.4, 6.2 Hz, 1H), 2.17−2.07 (m, 1H), 2.03 (br s, 1H), 1.98−1.90 (m, 1H), 1.82 (dd, J = 13.2, 9.2 Hz, 1H), 1.75−1.67 (m, 4H), 1.60−1.52 (m, 2H), 1.33−1.27 (m, 1H), 1.18−1.12 (m, 1H), 0.93 (s, 3H), 0.83 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 174.1, 60.6, 55.6, 48.6, 47.3, 47.0, 44.9, 38.9, 35.8, 31.0, 27.1, 26.2, 20.3, 20.0, 11.7; HRMS (ESI, pos.): m/z calcd for $C_{15}H_{27}N_2O$ $[M + H]^+$: 251.2118; found: 251.2110.

Ligand L1. To a stirred mixture of $LiAlH_4$ (0.31 g, 8 mmol) in anhydrous THF (15 mL) was added dropwise a THF (15 mL) solution of **L5** (1.00 g, 4 mmol) at 0 °C. The mixture was warmed to room temperature and then heated to reflux for 5 h. After the reaction completed, saturated Na_2SO_4 aqueous was added dropwise to quench the reaction at 0 °C. The resulting white precipitation was removed by filtration. The filtrate was dried over anhydrous K_2CO_3 and then concentrated under vacuum. The crude product was purified by column chromatography eluting with dichloromethane and methanol to afford **L1** as a light-yellow oil (0.45 g, 48% yield). $[\alpha]_D^{25} = -61.1$ (c = 1.0 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.18−3.11 (m, 1H), 2.98−2.84 (m, 2H), 2.59 (dd, J = 11.4, 5.0 Hz, 1H), 2.50 (t, J = 6.6 Hz, 1H), 2.39 (dd, J = 11.4, 7.8 Hz, 1H), 2.11 (br s, 2H), 1.89−1.81 (m, 1H), 1.74−1.65 (m, 4H), 1.56−1.45 (m, 3H), 1.37−1.28 (m, 1H), 1.08−1.04 (m, 2H), 1.02 (s, 3H), 0.87 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 67.1, 58.9, 53.8, 48.4, 46.7, 46.5, 45.3, 39.1, 36.9, 29.7, 27.4, 25.6, 20.6, 20.5, 12.2; HRMS (ESI, pos.): m/z calcd for $C_{15}H_{29}N_2$ $[M + H]^+$: 237.2325; found: 237.2315.

L6. Following the same procedure as for the synthesis of **L5**, starting from (*R*)-*N*-benzyloxycarbonylproline (1.74 g, 7 mmol) and *exo*-(−)-bornylamine (1.03 g, 6.7 mmol) afforded **L6** as a colorless oil (1.35 g, 81% yield). $[\alpha]_D^{25} = -67.1$ (c = 1.0 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.82−7.81 (br s, 1H), 3.79 (dt, J = 9.2, 4.8 Hz, 1H), 3.72 (dd, J = 9.2, 5.2 Hz, 1H), 3.01 (dt, J = 10.0, 6.8 Hz, 1H), 2.85 (dt, J = 10.0, 6.4 Hz, 1H), 2.15 (br s, 1H), 2.17−2.06 (m, 1H), 1.94−1.91 (m, 2H), 1.74−1.65 (m, 4H), 1.60−1.50 (m, 2H), 1.33−1.27 (m, 1H), 1.19−1.12 (m, 1H), 0.93 (s, 3H), 0.84 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 174.0, 60.6, 56.0, 48.4, 47.3, 47.0, 45.0, 39.3, 35.9, 30.7, 27.1, 26.2, 20.3, 20.1, 11.8; HRMS (ESI, pos.): m/z calcd for $C_{15}H_{27}N_2O$ $[M + H]^+$: 251.2118; found: 251.2112.

L2. Following the same procedure as for the synthesis of **L1**, starting from **L6** (0.50 g, 2 mmol) afforded **L2** as a light-yellow oil (0.21 g, 45% yield). $[\alpha]_D^{25} = -59.6$ (c = 1.0 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.18−3.11 (m, 1H), 2.95 (dt, J = 10.0, 6.4 Hz, 1H), 2.86 (dt, J = 10.0, 7.0 Hz, 1H), 2.53−2.43 (m, 3H), 1.88−1.78 (m, 3H), 1.75−1.69 (m, 2H), 1.68−1.65 (m, 2H), 1.56−1.45 (m, 2H), 1.38−1.29 (m, 1H), 1.09−1.04 (m, 2H), 1.02 (s, 3H), 0.87 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 66.8, 58.5, 53.6, 48.3, 46.6, 46.3, 45.3, 39.0, 36.9, 29.4, 27.4, 25.4, 20.6, 20.5, 12.2; HRMS (ESI, pos.): m/z calcd for $C_{15}H_{29}N_2$ $[M + H]^+$: 237.2325; found: 237.2318.

L3-1. Following the same procedure as for the synthesis of **L5**, starting from (*S*)-*N*-benzyloxycarbonylproline (1.74 g, 7 mmol) and (−)-(1*S*,2*S*,5*R*)-menthylamine (1.02 g, 6.6 mmol) afforded **L3-1** as a white solid (1.32 g, 80% yield). $[\alpha]_D^{25} = -16.8$ (c = 1.3 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.88−7.67 (br s, 1H), 4.27−4.25 (m, 1H), 3.73−3.70 (m, 1H), 3.05−2.99 (m, 1H), 2.92−2.87 (m, 1H), 2.17−2.11 (m, 1H), 2.08 (br s, 1H), 1.96−1.88 (m, 1H), 1.83−1.77 (m, 2H), 1.74−1.67 (m, 3H), 1.44−1.29 (m, 2H), 1.08−1.03 (m, 3H), 0.90−0.86 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 173.9, 60.8, 47.3, 46.4, 45.4, 40.4, 34.9, 30.8, 29.7, 27.0, 26.2, 25.4, 22.3, 20.9, 20.8; HRMS (ESI, pos.): m/z calcd for $C_{15}H_{29}N_2O$ $[M + H]^+$: 253.2275; found: 253.2270.

L3. Following the same procedure as for the synthesis of **L1**, starting from **L3-1** (0.90 g, 3.6 mmol) afforded **L3** as a light-yellow oil (0.34 g, 40% yield). $[\alpha]_D^{25} = +11.1$ (c = 1.0 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.24−3.17 (m, 1H), 3.02−2.87 (m, 3H), 2.67 (dd, J = 11.6, 7.6 Hz, 1H), 2.48 (dd, J = 11.6, 6.0 Hz, 1H), 2.43 (br s, 2H), 1.92−1.84 (m, 2H), 1.80−1.50 (m, 6H), 1.42−1.33 (m, 1H), 1.24−1.13 (m, 1H), 0.90−0.84 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 58.9, 53.9, 52.0, 48.5, 46.2, 38.3, 35.5, 29.4, 29.0, 25.6, 25.4, 25.0, 22.6, 21.4, 20.8; HRMS (ESI, pos.): m/z calcd for $C_{15}H_{31}N_2$ $[M + H]^+$: 239.2482; found: 239.2475.

L4-1. Following the same procedure as for the synthesis of **L5**, starting from (*R*)-*N*-benzyloxycarbonylproline (1.74 g, 7 mmol) and (−)-(1*S*,2*S*,5*R*)-menthylamine (1.02 g, 6.5 mmol) afforded **L4-1** as a white solid (1.42 g, 86% yield). $[\alpha]_D^{25} = +85.4$ (c = 1.1 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.94−7.92 (br s, 1H), 4.27−4.24 (m, 1H), 3.74 (dd, J = 9.2, 4.8 Hz, 1H), 3.01 (dt, J = 10.0, 7.0 Hz, 1H), 2.89 (dt, J = 10.0, 6.4 Hz, 1H), 2.17−2.07 (m, 1H), 2.05 (br s, 1H), 1.94−1.80 (m, 3H), 1.76−1.65 (m, 3H), 1.49−1.40 (m, 1H), 1.28−1.19 (m, 1H), 1.08−1.01 (m, 3H), 0.90−0.86 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 174.0, 60.9, 47.4, 46.4, 45.3, 40.3, 34.8, 31.0, 29.9, 27.0, 26.2, 25.7, 22.3, 21.2, 20.7; HRMS (ESI, pos.): m/z calcd for $C_{15}H_{29}N_2O$ $[M + H]^+$: 253.2275; found: 253.2269.

L4. Following the same procedure as for the synthesis of **L1**, starting from **L4-1** (0.90 g, 3.6 mmol) afforded **L4** as a

(23) Jumaryatno, P.; Rands-Trevor, K.; Blanchfield, J. T.; Garson, M. J. *ARKIVOC* **2007**, 157–166.

light-yellow oil (0.43 g, 51% yield). $[\alpha]_D^{25} = +12.6$ ($c = 1.8$ in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.19−3.16 (m, 1H), 2.95−2.84 (m, 3H), 2.77−2.74 (m, 1H), 2.32−2.27 (m, 1H), 2.07 (br s, 2H), 1.90−1.82 (m, 2H), 1.76−1.61 (m, 5H), 1.56−1.51 (m, 1H), 1.41−1.33 (m, 1H), 1.25−1.16 (m, 1H), 0.90−0.83 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 59.1, 54.5, 52.6, 48.5, 46.2, 38.6, 35.5, 29.5, 29.0, 25.5, 25.4, 25.0, 22.5, 21.4, 20.7; HRMS (ESI, pos.): m/z calcd for $C_{15}H_{31}N_2$ $[M + H]^+$: 239.2482; found: 239.2473.

L7-1. Following the same procedure as for the synthesis of **L5**, starting from (*S*)-*N*-benzyloxycarbonylalanine (1.23 g, 5.5 mmol) and *exo*-(−)-bornylamine (0.76 g, 5.0 mmol) afforded **L7-1** as a white solid (1.01 g, 93% yield). $[\alpha]_D^{25} = -31.0$ ($c = 1.2$ in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.46 (br s, 1H), 3.86 (dt, J = 9.2, 4.8 Hz, 1H), 3.46 (q, J = 6.8 Hz, 1H), 1.84 (dd, J = 13.2, 9.2 Hz, 1H), 1.76−1.67 (m, 2H), 1.61−1.53 (m, 2H), 1.44 (br s, 2H), 1.32 (d, J = 6.8 Hz, 3H), 1.31−1.28 (m, 1H), 1.19−1.13 (m, 1H), 0.95 (s, 3H), 0.84 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 174.7, 55.7, 50.8, 48.5, 47.0, 45.0, 39.0, 35.9, 27.1, 22.1, 20.3, 20.1, 11.6; HRMS (ESI, pos.): m/z calcd for $C_{13}H_{25}N_2O$ $[M + H]^+$: 225.1962; found: 225.1958.

L7. Following the same procedure as for the synthesis of **L1**, starting from **L7-1** (0.90 g, 4.0 mmol) afforded **L7** as a light-yellow oil (0.43 g, 51% yield). $[\alpha]_D^{25} = -51.9$ ($c = 1.1$ in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.93−2.86 (m, 1H), 2.55 (dd, J = 11.8, 4.6 Hz, 1H), 2.48 (dd, J = 8.0, 5.2 Hz, 1H), 2.27 (dd, J = 11.6, 8.0 Hz, 1H), 1.69−1.48 (m, 9H), 1.09−1.03 (m, 5H), 1.01 (s, 3H), 0.88 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 67.2, 57.7, 48.5, 47.2, 46.7, 45.3, 39.5, 36.9, 27.4, 21.9, 20.7, 20.5, 12.3; HRMS (ESI, pos.): m/z calcd for $C_{13}H_{27}N_2$ $[M + H]^+$: 211.2169; found: 211.2161.

L8-1. Following the same procedure as for the synthesis of **L5**, starting from (*S*)-*N*-benzyloxycarbonylphenylalanine (1.30 g, 4.3 mmol) and *exo*-(−)-bornylamine (0.61 g, 4.0 mmol) afforded **L8-1** as a white solid (1.11 g, 92% yield). $[\alpha]_D^{25} = -65.7$ ($c = 0.9$ in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.40−7.38 (br s, 1H), 7.33−7.27 (m, 2H), 7.25−7.22 (m, 3H), 3.87 (dt, J = 9.2, 4.8 Hz, 1H), 3.56 (dd, J = 9.2, 4.2 Hz, 1H), 3.27 (dd, J = 14.0, 4.2 Hz, 1H), 2.67 (dd, J = 14.0, 9.2 Hz, 1H), 1.83 (dd, J = 13.2, 8.8 Hz, 1H), 1.73−1.66 (m, 2H), 1.60−1.50 (m, 2H), 1.36 (br s, 2H), 1.34−1.27 (m, 1H), 1.20−1.13 (m, 1H), 0.87 (s, 3H), 0.83 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 173.2, 138.1, 129.3, 128.7, 126.7, 56.5, 55.0, 48.5, 47.0, 45.0, 41.2, 39.1, 36.0, 27.1, 20.3, 20.1, 11.8; HRMS (ESI, pos.): m/z calcd for $C_{19}H_{29}N_2O$ $[M + H]^+$: 301.2275; found: 301.2272.

L8. Following the same procedure as for the synthesis of **L1**, starting from **L8-1** (0.90 g, 3.0 mmol) afforded **L8** as a light-yellow oil (0.36 g, 42% yield). $[\alpha]_D^{25} = -44.5$ ($c = 0.9$ in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.29 (t, J = 7.2 Hz, 2H), 7.20 (t, J = 7.2 Hz, 3H), 3.06−2.99 (m, 1H), 2.80 (dd, J = 13.2, 4.8 Hz, 1H), 2.65 (dd, J = 11.6, 4.4 Hz, 1H), 2.48 (dd, J = 13.2, 8.0 Hz, 1H), 2.37 (dd, J = 11.6, 8.0 Hz, 1H), 1.70−1.62 (m, 2H), 1.59−1.48 (m, 3H), 1.38 (br s, 3H), 1.08−1.04 (m, 2H), 1.02 (s, 3H), 0.88 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 139.5, 129.2, 128.4, 126.1, 67.3, 55.5, 53.1, 48.5, 46.7, 45.3, 42.8, 39.5, 36.9, 27.4, 20.6, 20.5, 12.3; HRMS (ESI, pos.): m/z calcd for $C_{19}H_{31}N_2$ $[M + H]^+$: 287.2482; found: 287.2472.

L9-1. To a solution of **L5** (0.75 g, 3.0 mmol) and triethylamine (0.86 mL, 6.0 mmol) in ice-cold THF (25 mL) was added dropwise benzyl bromide (0.36 mL, 3.0 mmol) with vigorous stirring. When the addition was completed, the reaction mixture was stirred for 3 h at 0 °C and warmed to room temperature. After the reaction completed, the solvent was evaporated, and the residue was extracted with $CHCl_3$ and washed successively with water, $NaHCO_3$ aqueous, and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuum. The crude product was purified by flash chromatography eluting with dichloromethane and methanol to afford **L9-1** as a white solid (0.88 g, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.53−7.51 (br s, 1H), 7.33−7.25 (m, 5H), 3.88−3.82 (m, 2H), 3.50 (d, J = 13.2 Hz, 1H), 3.20 (dd, J = 10.0, 4.4 Hz, 1H), 3.07−3.02 (m, 1H), 2.39−2.34 (m, 1H), 2.28−2.18 (m, 1H), 1.94−1.88 (m, 1H), 1.79−1.66 (m, 5H), 1.58−1.51 (m, 1H), 1.48−1.41 (m, 1H), 1.33−1.27 (m, 1H), 1.18−1.11 (m, 1H), 0.92 (s, 3H), 0.83 (s, 3H), 0.81(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 173.7, 138.7, 128.6, 128.5, 127.2, 67.5, 60.1, 55.5, 54.2, 48.8, 47.0, 44.9, 38.9, 35.8, 31.1, 27.0, 24.4, 20.3, 20.2, 11.7; HRMS (ESI, pos.): m/z calcd for $C_{22}H_{33}N_2O$ $[M + H]^+$: 341.2588; found:341.2580.

L9. Following the same procedure as for the synthesis of **L1**, starting from **L9-1** (0.68 g, 2.0 mmol) afforded **L9** as yellow oil (0.30 g, 46% yield). $[\alpha]_D^{25} = -84.7$ ($c = 0.6$ in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.30−7.22 (m, 5H), 4.04 (d, J = 13.2 Hz, 1H), 3.29 (d, J = 12.8 Hz, 1H), 2.91 (br s, 1H), 2.62−2.56 (m, 3H), 2.49−2.46 (m, 1H), 2.21−2.15 (m, 1H), 1.92−1.88 (m, 1H), 1.71−1.46 (m, 9H), 1.08−1.03 (m, 2H), 1.02 (s, 3H), 0.87 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 128.8, 128.2, 126.7, 67.1, 64.1, 60.0, 54.6, 52.6, 48.5, 46.7, 45.3, 39.2, 36.8, 29.4, 27.4, 23.0, 20.7, 20.4, 12.3; HRMS (ESI, pos.): m/z calcd for $C_{22}H_{35}N_2$ $[M + H]^+$: 327.2795; found: 327.2790.

HRMS Analysis of the L1/$CuCl_2$ Complex. Ligand **L1** (3.0 mg, 0.0125 mmol) and $CuCl_2 \cdot 2H_2O$ (2.1 mg, 0.0125 mmol) were added to a test tube containing EtOH (2 mL) and stirred for 30 min at ambient temperature to generate the catalyst. The mixture was diluted and analyzed directly by ESI-HRMS.

X-ray Crystallographic Analysis of the L1/$CuCl_2$ Complex. Ligand **L1** (6.0 mg, 0.025 mmol) and $CuCl_2 \cdot 2H_2O$ (4.2 mg, 0.025 mmol) were dissolved in MeCN (2 mL), after stirring for 1 h at ambient temperature, the resulting green solution was filtered, and the filtrate was left standing over a few days. The bright-blue block-like crystals suitable for X-ray crystallography were obtained.

General Procedure for the Catalytic Enantioselective Henry Reaction. Ligand **L1** (3.0 mg, 0.0125 mmol, 2.5 mol %) and $CuCl_2 \cdot 2H_2O$ (2.1 mg, 0.0125 mmol, 2.5 mol %) were added to a test tube containing absolute THF (2 mL). The solution was stirred for 1 h to give a green solution at room temperature. To the resulting solution were successively added the aldehyde (0.5 mmol), the nitroalkane (5 mmol, 10 equiv), and DIPEA (87.1 μL, 0.5 mmol, 1 equiv), and the tube was introduced in a bath at the reaction temperature without special precautions to exclude moisture or air. After the indicated time, 180 μL of 3 M HCl aqueous was added, and the mixture was concentrated and directly purified by column chromatography on silica gel, eluting with petroleum ether and ethyl acetate to afford the corresponding product.

(*S*)-1-Nitrobutan-2-ol (4a). The title compound was prepared according to the general procedure and purified by column chromatography (petroleum ether/ethyl acetate, 9:1) to give a colorless oil in 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 4.45 (dd, J = 13.2, 3.2 Hz, 1H), 4.39 (dd, J = 13.2, 8.4 Hz, 1H), 4.29−4.23 (m, 1H), 2.48 (br s, 1H), 1.64−1.55 (m, 2H), 1.03 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 80.4, 70.0, 26.9, 9.6. Enantiomeric excess (96%, Table 4, entry 1) was determined by HPLC (Chiralcel AD-H, hexane/isopropanol, 90:10 v/v, 0.5 mL/min, 26 °C, UV 210 nm): major enantiomer (*S*) t_R = 45.67 min, minor enantiomer (*R*) t_R = 25.45 min.

(*S*)-1-Nitropentan-2-ol (4b). The title compound was prepared according to the general procedure and purified by column chromatography (petroleum ether/ethyl acetate, 9:1) to give a

colorless oil in 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 4.46−4.38 (m, 2H), 4.35−4.30 (m, 1H), 2.48 (br s, 1H), 1.58−1.39 (m, 4H), 0.97 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 80.7, 68.4, 35.8, 18.5, 13.8. Enantiomeric excess (94%, Table 4, entry 2) was determined by HPLC (Chiralcel AS-H, hexane/isopropanol, 95:5 v/v, 0.5 mL/min, 26 °C, UV 210 nm): major enantiomer (*S*) t_R = 35.42 min, minor enantiomer (*R*) t_R = 38.97 min.

(*S*)-3-Methyl-1-nitrobutan-2-ol (4c). The title compound was prepared according to the general procedure and purified by column chromatography (petroleum ether/ethyl acetate, 9:1) to give a colorless oil in 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 4.48 (dd, J = 13.2, 2.8 Hz, 1H), 4.41 (dd, J = 13.2, 9.2 Hz, 1H), 4.13−4.09 (m, 1H), 2.42 (br s, 1H), 1.85−1.77 (m, 1H), 1.02 (d, J = 6.8 Hz, 3H), 1.00 (d, J = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 79.3, 73.4, 31.8, 18.4, 17.5. Enantiomeric excess (97%, Table 4, entry 3) was determined by HPLC (Chiralcel OD-H, hexane/isopropanol, 98:2 v/v, 0.5 mL/min, 26 °C, UV 210 nm): major enantiomer (*S*) t_R = 46.25 min, minor enantiomer (*R*) t_R = 39.91 min.

(*S*)-1-Nitrohexan-2-ol (4d). The title compound was prepared according to the general procedure and purified by column chromatography (petroleum ether/ethyl acetate, 9:1) to give a colorless oil in 95% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 4.46−4.35 (m, 2H), 4.34−4.28 (m, 1H), 2.58 (br s, 1H), 1.57−1.45 (m, 3H), 1.41−1.34 (m, 3H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 80.7, 68.7, 33.4, 27.3, 22.4, 13.9. Enantiomeric excess (96%, Table 4, entry 4) was determined by HPLC (Chiralcel AD-H, hexane/isopropanol, 95:5 v/v, 0.5 mL/min, 26 °C, UV 210 nm): major enantiomer (*S*) t_R = 37.99 min, minor enantiomer (*R*) t_R = 25.89 min.

(*S*)-4-Methyl-1-nitropentan-2-ol (4e). The title compound was prepared according to the general procedure and purified by column chromatography (petroleum ether/ethyl acetate, 9:1) to give a colorless oil in 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 4.43−4.35 (m, 3H), 2.89 (br s, 1H), 1.88−1.78 (m, 1H), 1.54−1.47 (m, 1H), 1.27−1.20 (m, 1H), 0.97 (d, J = 6.0 Hz, 3H), 0.95 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 81.1, 67.0, 42.5, 24.3, 23.2, 21.7. Enantiomeric excess (99%, Table 4, entry 13) was determined by HPLC (Chiralcel AD-H, hexane/isopropanol, 95:5 v/v, 0.5 mL/min, 26 °C, UV 210 nm): major enantiomer (*S*) t_R = 32.73 min, minor enantiomer (*R*) t_R = 21.44 min.

(*S*)-3,3-Dimethyl-1-nitrobutan-2-ol (4f). The title compound was prepared according to the general procedure and purified by column chromatography (petroleum ether/ethyl acetate, 10:1) to give a colorless oil in 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 4.52 (dd, J = 13.2, 2.0 Hz, 1H), 4.37 (dd, J = 13.2, 10.4 Hz, 1H), 4.03 (dd, J = 10.4, 2.0 Hz, 1H), 2.46 (br s, 1H), 1.57−1.48 (m, 3H), 0.98 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 78.3, 76.2, 34.3, 25.6. Enantiomeric excess (97%, Table 4, entry 6) was determined by HPLC (Chiralcel OD-H, hexane/isopropanol, 98:2 v/v, 0.5 mL/min, 26 °C, UV 210 nm): major enantiomer (*S*) t_R = 41.37 min, minor enantiomer (*R*) t_R = 34.92 min.

(*S*)-1-Nitroheptan-2-ol (4g). The title compound was prepared according to the general procedure and purified by column chromatography (petroleum ether/ethyl acetate, 9:1) to give a colorless oil in 98% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 4.46−4.35 (m, 2H), 4.33−4.31 (m, 1H), 2.50 (br s, 1H), 1.57−1.48 (m, 3H), 1.40−1.32(m, 5H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 80.7, 68.7, 33.7, 31.5, 24.8, 22.5, 13.9. Enantiomeric excess (94%, Table 4, entry 7) was determined by HPLC (Chiralcel AD-H, hexane/isopropanol, 95:5 v/v, 0.5 mL/min, 26 °C, UV 210 nm): major enantiomer (*S*) t_R = 40.88 min, minor enantiomer (*R*) t_R = 25.34 min.

(*S*)-1-Nitrooctan-2-ol (4h). The title compound was prepared according to the general procedure and purified by column chromatography (petroleum ether/ethyl acetate, 9:1) to give a colorless oil in 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 4.46−4.35 (m, 2H), 4.34−4.29 (m, 1H), 2.54 (br s, 1H), 1.57−1.48 (m, 3H), 1.36−1.30 (m, 7H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 80.7, 68.7, 33.7, 31.6, 29.0, 25.1, 22.5, 14.0. Enantiomeric excess (96%, Table 4, entry 8) was determined by HPLC (Chiralcel AD-H, hexane/isopropanol, 95:5 v/v, 0.5 mL/min, 26 °C, UV 210 nm): major enantiomer (*S*) t_R = 45.43 min, minor enantiomer (*R*) t_R = 26.49 min.

(*S*)-1-Nitro-4-phenylbutan-2-ol (4i). The title compound was prepared according to the general procedure and purified by column chromatography (petroleum ether/ethyl acetate, 8:1) to give a white solid in 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.32−7.29 (m, 2H), 7.24−7.19 (m, 3H), 4.41−4.39 (m, 2H), 4.35−4.27 (m, 2H), 2.90−2.83 (m, 1H), 2.79−2.71 (m, 1H), 2.47 (br s, 1H), 1.92−1.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 140.6, 128.7, 128.4, 126.4, 80.6, 67.8, 35.1, 31.4. Enantiomeric excess (98%, Table 4, entry 14) was determined by HPLC (Chiralcel AD-H, hexane/isopropanol, 90:10 v/v, 0.5 mL/min, 26 °C, UV 210 nm): major enantiomer (*S*) t_R = 27.67 min, minor enantiomer (*R*) t_R = 26.61 min.

(*S*)-1-Cyclohexyl-2-nitroethanol (4j). The title compound was prepared according to the general procedure and purified by column chromatography (petroleum ether/ethyl acetate, 9:1) to give a colorless oil in 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 4.49 (dd, J = 13.2, 2.8 Hz, 1H), 4.42 (dd, J = 13.2, 8.8 Hz, 1H), 4.12−4.08 (m, 1H), 2.42 (br s, 1H), 1.85−1.78 (m, 3H), 1.71−1.65 (m, 2H), 1.50−1.44 (m, 1H), 1.29−1.17 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 79.3, 72.9, 41.5, 28.8, 28.0, 26.1, 25.9, 25.8. Enantiomeric excess (96%, Table 4, entry 10) was determined by HPLC (Chiralcel AD-H, hexane/isopropanol, 95:5 v/v, 0.5 mL/min, 26 °C, UV 210 nm): major enantiomer (*S*) t_R = 32.30 min, minor enantiomer (*R*) t_R = 28.62 min.

(*S*,*E*)-1-Nitro-4-phenylbut-3-en-2-ol (4k). The title compound was prepared according to the general procedure and purified by column chromatography (petroleum ether/ethyl acetate, 6:1) to give a colorless oil in 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.39−7.25 (m, 5H), 6.76 (d, J = 15.6 Hz, 1H), 6.13 (dd, J = 16.0, 6.4 Hz, 1H), 5.03 (qd, J = 6.0, 1.2 Hz, 1H), 4.50 (d, J = 6.0 Hz, 2H), 2.93 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 135.6, 133.6, 128.8, 128.6, 126.8, 125.0, 80.0, 69.6. Enantiomeric excess (90%, Table 4, entry 11) was determined by HPLC (Chiralcel AD-H, hexane/isopropanol, 95:5 v/v, 0.5 mL/min, 26 °C, UV 210 nm): major enantiomer (*S*) t_R = 73.46 min, minor enantiomer (*R*) t_R = 69.33 min.

(*S*)-4-(Benzyloxy)-1-nitrobutan-2-ol (4l). The title compound was prepared according to the general procedure and purified by column chromatography (petroleum ether/ethyl acetate, 8:1) to give a colorless oil in 83% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.38−7.30 (m, 5H), 4.52 (s, 2H), 4.57−4.50 (m, 1H), 4.43 (d, J = 6.0 Hz, 2H), 3.74−3.65 (m, 2H), 3.35 (br s, 1H), 1.84 (q, J=11.2, 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ=137.5, 128.6, 128.0, 127.8, 80.4, 73.5, 67.9, 67.3, 33.3. Enantiomeric excess (94%, Table 4, entry 12) was determined by HPLC (Chiralcel AD-H, hexane/isopropanol, 90:10 v/v, 0.5 mL/min, 26 °C, UV 210 nm): major enantiomer (*S*) t_R = 29.16 min, minor enantiomer (*R*) t_R = 24.20 min.

(*S*)-2-Nitro-1-phenylethanol (4m). The title compound was prepared according to the general procedure and purified by column chromatography (petroleum ether/ethyl acetate, 9:1) to give a colorless oil in 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.41−7.36 (m, 5H), 5.40 (dd, J = 9.6, 3.2 Hz, 1H), 4.56 (dd, J = 13.2, 9.6 Hz, 1H), 4.46 (dd, J = 13.2, 3.2 Hz, 1H), 3.01 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C,

TMS): δ = 138.2, 129.1, 129.0, 126.0, 81.2, 71.0. Enantiomeric excess (97%, Table 4, entry 15) was determined by HPLC (Chiralcel OD-H, hexane/isopropanol, 85:15 v/v, 0.5 mL/min, 26 °C, UV 210 nm): major enantiomer (*S*) t_R = 25.73 min, minor enantiomer (*R*) t_R = 21.22 min.

(***S*)-1-(2-Chlorophenyl)-2-nitroethanol (4n).** The title compound was prepared according to the general procedure and purified by column chromatography (petroleum ether/ethyl acetate, 9:1) to give a colorless oil in 97% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.63 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.38−7.26 (m, 3H), 5.81 (d, *J* = 9.6, 1H), 4.64 (dd, *J* = 13.6, 2.4 Hz, 1H), 4.43 (dd, *J* = 13.6, 9.6 Hz, 1H), 3.35 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 135.6, 131.5, 130.0, 129.7, 127.6, 127.5, 79.4, 67.9. Enantiomeric excess (97%, Table 4, entry 16) was determined by HPLC (Chiralcel OD-H, hexane/isopropanol, 97:3 v/v, 0.5 mL/min, 26 °C, UV 210 nm): major enantiomer (*S*) t_R = 51.61 min, minor enantiomer (*R*) t_R = 48.40 min.

(***S*)-2-Nitro-1-(3-nitrophenyl)ethanol (4o).** The title compound was prepared according to the general procedure and purified by column chromatography (petroleum ether/ethyl acetate, 5:1) to give a white solid in 96% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.30 (s, 1H), 8.18 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 5.63 (dd, *J* = 7.2, 5.2 Hz, 1H), 4.70−4.61 (m, 2H), 3.69 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 148.4, 140.5, 132.2, 130.1, 123.8, 121.2, 80.8, 69.9. Enantiomeric excess (93%, Table 4, entry 17) was determined by HPLC (Chiralcel OD-H, hexane/isopropanol, 85:15 v/v, 0.5 mL/min, 26 °C, UV 210 nm): major enantiomer (*S*) t_R = 38.73 min, minor enantiomer (*R*) t_R = 34.33 min.

(***S*)-2-Nitro-1-(4-nitrophenyl)ethanol (4p).** The title compound was prepared according to the general procedure and purified by column chromatography (petroleum ether/ethyl acetate, 5:1) to give white solid in 95% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.27 (d, *J* = 8.8 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 5.62 (dd, *J* = 7.6, 3.6 Hz, 1H), 4.64−4.56 (m, 2H), 3.19 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 148.2, 144.9, 127.0, 124.2, 80.6, 70.0. Enantiomeric excess (95%, Table 4, entry 18) was determined by HPLC (Chiralcel OD-H, hexane/isopropanol, 85:15 v/v, 0.5 mL/min, 26 °C, UV 210 nm): major enantiomer (*S*) t_R = 45.03 min, minor enantiomer (*R*) t_R = 36.49 min.

(***S*)-1-(4-Chlorophenyl)-2-nitroethanol (4q).** The title compound was prepared according to the general procedure and purified by column chromatography (petroleum ether/ethyl acetate, 9:1) to give a colorless oil in 95% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.39−7.32 (m, 4H), 5.43 (dd, *J* = 9.6, 3.2 Hz, 1H), 4.57 (dd, *J* = 13.6, 9.6 Hz, 1H), 4.48 (dd, *J* = 13.6, 3.2 Hz, 1H), 3.00 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 136.6, 134.8, 129.2, 127.4, 81.0, 70.0. Enantiomeric excess (97%, Table 4, entry 19) was determined by HPLC (Chiralcel AD-H, hexane/isopropanol, 85:15 v/v, 0.5 mL/min, 26 °C, UV 210 nm): major enantiomer (*S*) t_R = 20.65 min, minor enantiomer (*R*) t_R = 16.54 min.

(***S*)-1-(4-Fluorophenyl)-2-nitroethanol (4r).** The title compound was prepared according to the general procedure and purified by column chromatography (petroleum ether/ethyl acetate, 9:1) to give a colorless oil in 97% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.39−7.36 (m, 2H), 7.10−7.06 (m, 2H), 5.43 (dd, *J* = 9.6, 3.2 Hz, 1H), 4.57 (dd, *J* = 13.2, 9.6 Hz, 1H), 4.47 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.99 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 2 5 °C, TMS): δ = 162.82, 134.0, 127.8, 115.9, 81.2, 70.4; ^{19}F NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = −112.60. Enantiomeric excess (96%, Table 4, entry 20) was determined by HPLC (Chiralcel OD-H, hexane/isopropanol, 85:15 v/v, 0.5 mL/min, 26 °C, UV 210 nm): major enantiomer (*S*) t_R = 20.17 min, minor enantiomer (*R*) t_R = 17.42 min.

(***S*)-2-Nitro-1-*p*-tolylethanol (4s).** The title compound was prepared according to the general procedure and purified by column chromatography (petroleum ether/ethyl acetate, 9:1) to give a colorless oil in 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.28 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 5.40 (dd, *J* = 9.6, 2.8 Hz, 1H), 4.59 (dd, *J* = 13.2, 9.6 Hz, 1H), 4.47 (dd, *J* = 13.2, 2.8 Hz, 1H), 2.84 (br s, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 139.0, 135.2, 129.7, 125.9, 81.3, 70.9, 21.2. Enantiomeric excess (96%, Table 4, entry 21) was determined by HPLC (Chiralcel OD-H, hexane/isopropanol, 85:15 v/v, 0.5 mL/min, 26 °C, UV 210 nm): major enantiomer (*S*) t_R = 25.60 min, minor enantiomer (*R*) t_R = 20.64 min.

(***S*)-1-(4-Methoxyphenyl)-2-nitroethanol (4t).** The title compound was prepared according to the general procedure and purified by column chromatography (petrol ether/ethyl acetate, 7:1) to give a colorless oil in 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.26−7.30 (m, 2H), 6.91−6.88 (m, 2H), 5.35 (dd, *J* = 9.6, 3.2 Hz, 1H), 4.56 (dd, *J* = 13.2, 9.6 Hz, 1H), 4.44 (dd, *J* = 13.2, 3.2 Hz, 1H), 3.79 (s, 3H), 3.05 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 159.9, 130.4, 127.4, 114.4, 81.3, 70.7, 55.4. Enantiomeric excess (96%, Table 4, entry 22) was determined by HPLC (Chiralcel OD-H, hexane/isopropanol, 85:15 v/v, 0.5 mL/min, 26 °C, UV 210 nm): major enantiomer (*S*) t_R = 35.69 min, minor enantiomer (*R*) t_R = 28.81 min.

(***S*)-1-(2,4-Dichlorophenyl)-2-nitroethanol (4u).** The title compound was prepared according to the general procedure and purified by column chromatography (petrol ether/ethyl acetate, 7:1) to give a white solid in 97% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.60 (d, *J* = 8.4 Hz, 1H), 7.39 (d, *J* = 2.0 Hz, H), 7.33 (dd, *J* = 8.4, 2.0 Hz, 1H), 5.77 (dd, *J* = 9.6, 2.0 Hz, 1H), 4.64 (dd, *J* = 13.6, 2.0 Hz, 1H), 4.41 (dd, *J* = 13.6, 9.6 Hz, 1H), 3.37 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 135.2, 134.2, 132.0, 129.5, 128.6, 128.0, 79.1, 67.5. Enantiomeric excess (94%, Table 4, entry 23) was determined by HPLC (Chiralcel AD-H, hexane/isopropanol, 90:10 v/v, 0.5 mL/min, 26 °C, UV 210 nm): major enantiomer (*S*) t_R = 19.66 min, minor enantiomer (*R*) t_R = 16.19 min.

(***S*)-1-(3,4-Dimethoxyphenyl)-2-nitroethanol (4v).** The title compound was prepared according to the general procedure and purified by column chromatography (petrol ether/ethyl acetate, 6:1) to give a light-yellow solid in 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 6.92−6.85 (m, 3H), 5.39 (dd, *J* = 9.6, 2.8 Hz, 1H), 4.60 (dd, *J* = 13.2, 9.6 Hz, 1H), 4.48 (dd, *J* = 13.2, 2.8 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.03 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 149.4, 130.8, 118.4, 111.3, 108.9, 81.4, 70.9, 56.0, 55.9. Enantiomeric excess (97%, Table 4, entry 24) was determined by HPLC (Chiralcel AD-H, hexane/isopropanol, 85:15 v/v, 0.5 mL/min, 26 °C, UV 210 nm): major enantiomer (*S*) t_R = 65.28 min, minor enantiomer (*R*) t_R = 49.73 min.

(***S*)-1-(3,4-Methylenedioxyphenyl)-2-nitroethanol (4w).** The title compound was prepared according to the general procedure and purified by column chromatography (petrol ether/ethyl acetate, 7:1) to give a yellow solid in 91% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 6.89−6.80 (m, 3H), 5.98(s, 2H), 5.37 (dd, *J* = 9.6, 2.8 Hz, 1H), 4.57 (dd, *J* = 13.6, 9.6 Hz, 1H), 4.46 (dd, *J* = 13.6, 3.2 Hz, 1H), 2.82 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 148.3, 148.1, 132.0, 119.6, 108.6, 106.4, 101.4, 81.2, 70.9. Enantiomeric excess (97%, Table 4, entry 25) was determined by HPLC (Chiralcel OD-H, hexane/isopropanol, 85:15 v/v, 0.5 mL/min, 26 °C, UV 210 nm): major enantiomer (*S*) t_R = 43.76 min, minor enantiomer (*R*) t_R = 36.13 min.

(***R*)-1-(Furan-2-yl)-2-nitroethanol (4x).** The title compound was prepared according to the general procedure and purified by column chromatography (petrol ether/ethyl acetate, 7:1) to give a colorless oil in 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$,

25 °C, TMS): δ = 7.41 (s, 1H), 6.39−6.37 (m, 2H), 5.44 (dd, J = 9.2, 3.6 Hz, 1H), 4.76 (dd, J = 13.2, 9.2 Hz, 1H), 4.65 (dd, J = 13.2, 3.6 Hz, 1H), 3.24 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 150.8, 143.2, 110.7, 108.2, 78.4, 64.8. Enantiomeric excess (98%, Table 4, entry 26) was determined by HPLC (Chiralcel AD-H, hexane/isopropanol, 95:5 v/v, 0.5 mL/min, 26 °C, UV 210 nm): major enantiomer (*R*) t_R = 43.14 min, minor enantiomer (*S*) t_R = 39.28 min.

(*R*)-2-Nitro-1-(thiophen-2-yl)ethanol (4y). The title compound was prepared according to the general procedure and purified by column chromatography (petrol ether/ethyl acetate, 7:1) to give a light-yellow oil in 97% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.32 (dd, J = 5.2, 1.2 Hz, 1H), 7.05−6.99 (m, 2H), 5.67 (dd, J = 5.2, 3.2 Hz, 1H), 4.68 (dd, J = 13.2, 9.2 Hz, 1H), 4.58 (dd, J = 13.2, 3.2 Hz, 1H), 3.24 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 141.3, 127.3, 126.2, 125.1, 80.8, 67.1. Enantiomeric excess (92%, Table 4, entry 27) was determined by HPLC (Chiralcel OD-H, hexane/isopropanol, 90:10 v/v, 0.5 mL/min, 26 °C, UV 210 nm): major enantiomer (*R*) t_R = 36.03 min, minor enantiomer (*S*) t_R = 32.46 min.

4-Nitro-1-phenylpentan-3-ol (5i). The title compound was prepared according to the general procedure and purified by column chromatography (petrol ether/ethyl acetate, 8:1) to give a colorless oil in 91% yield. Diastereomeric ratios (*syn*/*anti*, 71:29, Table 5, entry 1) were determined by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.30−7.27 (m, 2H, *anti* + *syn*), 7.21−7.18 (m, 3H, *anti* + *syn*), 4.56−4.44 (m, 1H, *anti* + *syn*), 4.18−4.14 (m, 0.29H, *anti*), 3.91−3.86 (m, 0.71H, *syn*), 2.91−2.83 (m, 1H, *anti* + *syn*), 2.75−2.63 (m, 1H, *anti* + *syn*), 2.61 (br s, 1H, *anti* + *syn*), 1.87−1.68 (m, 2H, *anti* + *syn*), 1.52−1.49 (t, J = 7.0 Hz, 3H, *anti* + *syn*). Enantiomeric excesses (95% for *syn*, 95% for *anti*) were determined by HPLC (Chiralcel AD-H, hexane/isopropanol, 95:5 v/v, 0.5 mL/min, 26 °C, UV 210 nm): $anti_{major}$(1*S*,2*R*) t_R = 29.42 min, $anti_{minor}$-(1*R*,2*S*) t_R = 31.22 min, syn_{major}(1*S*,2*S*) t_R = 42.56 min, syn_{minor}-(1*R*,2*R*) t_R = 39.16 min.

4-Nitro-1-phenylhexan-3-ol (6i). The title compound was prepared according to the general procedure and purified by column chromatography (petrol ether/ethyl acetate, 9:1) to give a colorless oil in 85% yield. Diastereomeric ratios (*syn*/*anti*, 75:25, Table 5, entry 2) were determined by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.31−7.27 (m, 2H, *anti* + *syn*), 7.22−7.18 (m, 3H, *anti* + *syn*), 4.41−4.34 (m, 1H, *anti* + *syn*), 4.03−3.98 (m, 0.25H, *anti*), 3.91−3.87 (m, 0.75H, *syn*), 2.90−2.83 (m, 1H, *anti* + *syn*), 2.76−2.64 (m, 1H, *anti* + *syn*), 2.54 (br s, 1H, *anti* + *syn*), 2.14−1.95 (m, 1H, *anti* + *syn*), 1.88−1.77 (m, 3H, *anti* + *syn*), 0.98−0.92 (m, 3H, *anti* + *syn*). Enantiomeric excesses (93% for *syn*, 96% for *anti*) were determined by HPLC (Chiralcel AD-H, hexane/isopropanol, 95:5 v/v, 0.5 mL/min, 26 °C, UV 210 nm): $anti_{major}$(1*S*,2*R*) t_R = 24.24 min, $anti_{minor}$(1*R*,2*S*) t_R = 25.79 min, syn_{major}(1*S*,2*S*) t_R = 37.24 min, syn_{minor}(1*R*,2*R*) t_R = 34.34 min.

1-Cyclohexyl-2-nitropropan 1-ol (5j). The title compound was prepared according to the general procedure and purified by column chromatography (petrol ether/ethyl acetate, 10:1) to give a colorless oil in 86% yield. Diastereomeric ratios (*syn*/*anti*, 88:12, Table 5, entry 3) were determined by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 4.72 (dq, J = 6.8, 6.8 Hz, 0.88H, *syn*), 4.65 (qd, J = 6.8, 3.2 Hz, 0.12H, *anti*), 3.95 (dd, J = 8.4, 3.2 Hz, 0.13H, *anti*), 3.66 (dd, J = 6.8, 4.8 Hz, 0.87H, *syn*), 1.79−1.78 (m, 2H, *anti* + *syn*), 1.69−1.66 (m, 3H, *anti* + *syn*), 1.55 (m, 3H, *anti* + *syn*), 1.44−1.40 (m, 1H, *anti* + *syn*), 1.30−1.12 (m, 5H, *anti* + *syn*). Enantiomeric excesses (96% for *syn*, 88% for *anti*) were determined by HPLC (Chiralcel AD-H, hexane/isopropanol, 97:3 v/v, 0.7 mL/min, 26 °C, UV 210 nm): $anti_{minor}$(1*R*,2*S*) t_R = 19.89 min, syn_{major}(1*S*,2*S*) t_R = 23.67 min, $anti_{major}$(1*S*,2*R*) t_R = 25.63 min, syn_{minor}(1*R*,2*R*) t_R = 36.42 min.

1-Cyclohexyl-2-nitrobutan-1-ol (6j). The title compound was prepared according to the general procedure and purified by column chromatography (petrol ether/ethyl acetate, 10:1) to give a colorless oil in 80% yield. Diastereomeric ratios (*syn*/*anti*, 90:10, Table 5, entry 4) were determined by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 4.57 (ddd, J = 10.4, 6.0, 4.4 Hz, 0.90H, *syn*), 4.51 (ddd, J = 9.4, 4.4, 3.2 Hz, 0.10H, *anti*), 3.79 (dd, J = 6.4, 4.8 Hz, 0.12H, *anti*), 3.63 (t, J = 6.0 Hz, 0.90H, *syn*), 2.10−2.01 (m, 1H, *anti* + *syn*), 1.89−1.83 (m, 1H, *anti* + *syn*), 1.79−1.74 (m, 3H, *anti* + *syn*), 1.69−1.66 (m, 2H, *anti* + *syn*), 1.40−1.36 (m, 1H, *anti* + *syn*), 1.29−1.12 (m, 6H, *anti* + *syn*), 0.99 (t, J = 7.2 Hz, 3H, *anti* + *syn*). Enantiomeric excesses were not determined because the chiral HPLC separations for the product were not fully resolved.

2-Nitro-1-phenylpropan-1-ol (5m). The title compound was prepared according to the general procedure and purified by column chromatography (petrol ether/ethyl acetate, 9:1) to give a colorless oil in 93% yield. Diastereomeric ratios (*syn*/*anti*, 55:45, Table 5, entry 5) were determined by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.40−7.32 (m, 5H, *anti* + *syn*), 5.36 (d, J = 3.6 Hz, 0.45H, *anti*), 4.99 (d, J = 9.2 Hz, 0.55H, *syn*), 4.79−4.65 (m, 1H, *anti* + *syn*), 2.76 (br s, 1H, *anti* + *syn*), 1.47 (d, J = 6.8 Hz, 1.40H, *anti*), 1.29 (d, J = 6.8 Hz, 1.60H, *syn*). Enantiomeric excesses (96% for *syn*, 90% for *anti*) were determined by HPLC (Chiralcel AD-H, hexane/isopropanol, 95:5 v/v, 0.5 mL/min, 26 °C, UV 210 nm): $anti_{major}$(1*S*,2*R*) t_R = 26.87 min, $anti_{minor}$(1*R*,2*S*) t_R = 29.75 min, syn_{major}-(1*S*,2*S*) t_R = 36.45 min, syn_{minor}(1*R*,2*R*) t_R = 40.30 min.

2-Nitro-1-phenylbutan-1-ol (6m). The title compound was prepared according to the general procedure and purified by column chromatography (petrol ether/ethyl acetate, 9:1) to give a colorless oil in 93% yield. Diastereomeric ratios (*syn*/*anti*, 74:26, Table 5, entry 6) were determined by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.41−7.32 (m, 5H, *anti* + *syn*), 5.11 (d, J = 5.2 Hz, 0.26H, *anti*), 4.98 (d, J = 8.8 Hz, 0.74H, *syn*), 4.62−4.53 (m, 1H, *anti* + *syn*), 2.80 (br s, 1H, *anti* + *syn*), 2.16−2.06 (m, 0.25H, *anti*), 1.92−1.76 (m, 1H, *anti* + *syn*), 1.43−1.32 (m, 0.75H, *syn*), 0.91 (t, J = 7.2 Hz, 0.78H, *anti*), 0.84 (t, J = 7.2 Hz, 2.26H, *syn*). Enantiomeric excesses (98% for *syn*, 83% for *anti*) were determined by HPLC (Chiralcel AS-H, hexane/isopropanol, 90:10 v/v, 0.5 mL/min, 26 °C, UV 210 nm): $anti_{major}$(1*S*,2*R*) t_R = 16.86 min, $anti_{minor}$(1*R*,2*S*) t_R = 18.69 min, syn_{major}(1*S*,2*S*) t_R = 20.66 min, syn_{minor}(1*R*,2*R*) t_R = 25.18 min.

2-Nitro-1,3-diphenylpropan-1-ol (7m). The title compound was prepared according to the general procedure and purified by column chromatography (petrol ether/ethyl acetate, 9:1) to give a colorless oil in 92% yield. Diastereomeric ratios (*syn*/*anti*, 64:36, Table 5, entry 7) were determined by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.40−7.36 (m, 5H, *anti* + *syn*), 7.24−7.19 (m, 3H, *anti* + *syn*), 7.05−6.98 (m, 2H, *anti* + *syn*), 5.20 (d, J = 5.2 Hz, 0.36H, *anti*), 5.03 (d, J = 8.4 Hz, 0.64H, *syn*), 4.94−4.86 (m, 1H, *anti* + *syn*), 3.36 (dd, J = 14.8, 10.8 Hz, 0.36H, *anti*), 3.15 (dd, J = 14.8, 2.8 Hz, 0.36H, *anti*), 3.08 (dd, J = 14.4, 10.8 Hz, 0.68H, *syn*), 2.86 (br s, 1H, *anti* + *syn*), 2.71 (dd, J = 14.4, 3.6 Hz, 0.73H, *syn*). Enantiomeric excesses (97% for *syn*, 90% for *anti*) were determined by HPLC (Chiralcel OD-H, hexane/isopropanol, 90:10 v/v, 0.5 mL/min, 26 °C, UV 210 nm): $anti_{major}$(1*S*,2*R*) t_R = 37.49 min, $anti_{minor}$-(1*R*,2*S*) t_R = 21.67 min, syn_{major}(1*S*,2*S*) t_R = 28.79 min, syn_{minor}(1*R*,2*R*) t_R = 25.33 min.

1-(4-Chlorophenyl)-2-nitrobutan-1-ol (6q). The title compound was prepared according to the general procedure and purified by column chromatography (petrol ether/ethyl acetate, 9:1) to give a colorless oil in 93% yield. Diastereomeric ratios (*syn*/*anti*, 70:30, Table 5, entry 8) were determined by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.40−7.30 (m, 4H, *anti* + *syn*), 5.16 (d, J = 4.8 Hz, 0.30H, *anti*), 5.02 (d, J = 8.8 Hz, 0.70H, *syn*), 4.59−4.51 (m, 1H, *anti* + *syn*), 2.60 (br s, 1H, *anti* + *syn*), 2.18−2.08

(m, 0.36H, *anti*), 1.91−1.81 (m, 1H, *anti* + *syn*), 1.47−1.37 (m, 0.74H, *syn*), 0.93 (t, J = 7.4 Hz, 0.91H, *anti*), 0.88 (t, J = 7.4 Hz, 2.17H, *syn*). Enantiomeric excesses (97% for *syn*, 80% for *anti*) were determined by HPLC (Chiralcel AD-H, hexane/isopropanol, 90:10 v/v, 0.5 mL/min, 26 °C, UV 210 nm): $anti_{major}$(1*S*,2*R*) t_R = 13.67 min, $anti_{minor}$(1*R*,2*S*) t_R = 15.03 min, syn_{major}(1*S*,2*S*) t_R = 21.61 min, syn_{minor}(1*R*,2*R*) t_R = 18.08 min.

1-(4-Fluorophenyl)-2-nitrobutan-1-ol (6r). The title compound was prepared according to the general procedure and purified by column chromatography (petrol ether/ethyl acetate, 9:1) to give a colorless oil in 92% yield. Diastereomeric ratios (*syn*/*anti*, 78:22, Table 5, entry 9) were determined by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.36−7.32 (m, 2H, *anti* + *syn*), 7.11−7.03 (m, 2H, *anti* + *syn*), 5.12 (d, J = 5.2 Hz, 0.22H, *anti*), 5.01 (d, J = 8.8 Hz, 0.78H, *syn*), 4.59−4.51 (m, 1H, *anti* + *syn*), 2.75 (br s, 1H, *anti* + *syn*), 2.16−2.05 (m, 0.24H, *anti*), 1.94−1.77 (m, 1H, *anti* + *syn*), 1.44−1.34 (m, 0.79H, *syn*), 0.93 (t, J = 7.4 Hz, 0.68H, *anti*), 0.86 (t, J = 7.4 Hz, 2.41H, *syn*). Enantiomeric excesses (96% for *syn*, 60% for *anti*) were determined by HPLC (Chiralcel AS-H, hexane/isopropanol, 95:5 v/v, 0.5 mL/min, 26 °C, UV 210 nm): $anti_{major}$(1*S*,2*R*) t_R = 32.68 min, $anti_{minor}$(1*R*,2*S*) t_R = 36.04 min, syn_{major}(1*S*,2*S*) t_R = 45.81 min, syn_{minor}(1*R*,2*R*) t_R = 57.74 min.

2-Nitro-1-*p*-tolylbutan-1-ol (6s). The title compound was prepared according to the general procedure and purified by column chromatography (petrol ether/ethyl acetate, 9:1) to give a colorless oil in 95% yield. Diastereomeric ratios (*syn*/*anti*, 77:23, Table 5, entry 10) were determined by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.26−7.16 (m, 4H, *anti* + *syn*), 5.08 (d, 0.23H, J = 9.2 Hz, *anti*), 4.96 (d, J = 9.2 Hz, 0.77H, *syn*), 4.61−4.52 (m, 1H, *anti* + *syn*), 2.53 (br s, 1H, *anti* + *syn*), 2.36 (s, 2.32H, *syn*), 2.34 (s, 0.72H, *anti*), 2.17−2.08 (m, 0.23H, *anti*), 1.95−1.88 (m, 0.24H, *anti*), 1.86−1.76 (m, 0.78H, *syn*), 1.44−1.34 (m, 0.82H, *syn*), 0.92 (t, J = 7.4 Hz, 0.72H, *anti*), 0.85 (t, J = 7.4 Hz, 2.48H, *syn*). Enantiomeric excesses (96% for *syn*, 67% for *anti*) were determined by HPLC (Chiralcel AD-H, hexane/isopropanol, 95:5 v/v, 0.5 mL/min, 26 °C, UV 210 nm): $anti_{major}$(1*S*,2*R*) t_R = 24.18 min, $anti_{minor}$(1*R*,2*S*) t_R = 26.23 min, syn_{major}(1*S*,2*S*) t_R = 40.71 min, syn_{minor}(1*R*,2*R*) t_R = 38.07 min.

1-(Furan-2-yl)-2-nitrobutan-1-ol (6x). The title compound was prepared according to the general procedure and purified by column chromatography (petrol ether/ethyl acetate, 8:1) to give a colorless oil in 93% yield. Diastereomeric ratios (*syn*/*anti*, 74:26, Table 5, entry 11) were determined by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.43−7.40 (m, 1H, *anti* + *syn*), 6.41−6.35 (m, 2H, *anti* + *syn*), 5.14 (d, J = 6.0 Hz, 0.26H, *anti*), 5.07 (d, J = 9.2 Hz, 0.74H, *syn*), 4.84−4.73 (m, 1H, *anti* + *syn*), 2.89 (br s, 1H, *anti* + *syn*), 2.19−2.09 (m, 0.26H, *anti*), 2.08−1.98 (m, 0.26H, *anti*), 1.90−1.80 (m, 0.76H, *syn*), 1.58−1.48 (m, 0.76H, *syn*), 0.98 (t, J = 7.4 Hz, 0.82H, *anti*), 0.91 (t, J = 7.4 Hz, 2.29H, *syn*). Enantiomeric excesses (98% for *syn*, 90% for *anti*) were determined by HPLC (Chiralcel AD-H, hexane/isopropanol, 97:3 v/v, 0.5 mL/min, 26 °C, UV 210 nm for *anti*, Chiralcel AS-H, hexane/isopropanol, 95:5 v/v, 0.5 mL/min, 26 °C, UV 210 nm for *syn*): $anti_{major}$(1*S*,2*R*) t_R = 43.12 min, $anti_{minor}$(1*R*,2*S*) t_R = 45.93 min, syn_{major}(1*S*,2*S*) t_R = 48.65 min, syn_{minor}(1*R*,2*R*) t_R = 56.25 min.

Large-Scale Reaction in Scheme 3. Ligand **L1** (60 mg, 0.25 mmol, 2.5 mol %) and $CuCl_2 \cdot 2H_2O$ (42 mg, 0.25 mmol, 2.5 mol %) were added to a test tube containing absolute THF (30 mL). The solution was stirred for 1 h to give a green solution at room temperature. To the resulting solution were successively added 3,4-dimethoxybenzaldehyde (**3v**) (1.66 g, 10 mmol), the nitromethane (5.4 mL, 100 mmol, 10 equiv), and DIPEA (1.74 mL, 10 mmol, 1.0 equiv), and the tube was introduced into a bath at −20 °C for 18 h. After the reaction completed, 30 mL of EtOAc and 20 mL of 2 M HCl aqueous were added, and stirring was continued until the green color disappeared. The mixture was then extracted with EtOAc (2 × 15 mL), and the organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography (petrol ether/ethyl acetate, 9:1) to afford the nitroaldol adduct **4v** as a yellow solid (2.13 g, 94% yield, 97% ee). $[\alpha]_D^{25}$ = +15.6 (c = 1.1 in EtOH; lit: $[\alpha]_D^{25}$ = +26.7[4a] in CH_2Cl_2, 78% ee). To recover the ligand **L1** from the aqueous phase, saturated Na_2CO_3 aqueous was added dropwise to the aqueous phase until pH = 10. Then, the mixture was extracted with EtOAc (3 × 15 mL), and the organic layers were dried over anhydrous Na_2SO_4, and evaporated in vacuo to afford ligand **L1** (42 mg, 70% recovered yield). Then, the recovered ligand **L1** was reused directly for the second cycle (7 mmol scale) to afford the product **4v** in 80% yield and 97% ee.

(*S*)-2-Amino-1-(3,4-dimethoxyphenyl)ethanol (9). (*S*)-1-(3,4-dimethoxyphenyl)-2-nitroethanol **4v** (1.13 g, 5 mmol), Pd/C (57 mg, 10% w/w), acetic acid (428 uL, 7.5 mmol, 1.5 equiv) was added in MeOH (30 mL), and the resulting suspension was stirred under H_2 atmosphere (1 atm) at room temperature overnight. After the reaction completed, the reaction mixture was filtered through a pad of Celite and washed with MeOH, and the filtrate was concentrated under reduced pressure to afford the corresponding ammonium acetate **8** in 92% yield, which was used directly for next steps without further purification. Then, the ammonium acetate **8** was neutralized by 5 M NaOH aqueous until pH = 10 and subsequently extracted by ethyl acetate, and the organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography eluting with dichloromethane and methanol to afford (*S*)-2-amino-1-(3,4-dimethoxyphenyl)ethanol **9** as a yellow solid. $[\alpha]_D^{25}$ = +30.2 (c = 1.0 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 6.91−6.90 (m, 1H), 6.89−6.81 (m, 2H), 4.60 (q, J = 4.0 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.95 (dd, J = 12.8, 3.6 Hz, 1H), 2.81 (dd, J = 12.8, 8.0 Hz, 1H), 2.69 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 149.0, 148.4, 135.1, 118.1, 111.0, 109.0, 73.9, 55.9, 55.8, 49.1; HRMS (ESI, pos.): m/z calcd for $C_{10}H_{15}NO_3Na$ $[M + Na]^+$: 220.0944; found: 220.0940.

Acknowledgment. This work was financially supported by grants from National Natural Science Foundation of China (no. 20872041, 20572028). The Center of Analysis and Testing of Huazhong University of Science and Technology is gratefully acknowledged for characterization of the new compounds.

Supporting Information Available: Characterization data of all new compounds as well as X-ray structural data (CIF), NMR spectras and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.