Tetrahedron: *Asymmetry* 22 (2011) 1097–1102

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Isoquinoline-based diimine ligands for Cu(II)-catalyzed enantioselective nitroaldol (Henry) reactions

Michael J. Rodig, Hwimin Seo, Dimitri Hirsch-Weil, Khalil A. Abboud, Sukwon Hong *

Department of Chemistry, University of Florida, PO Box 117200, Gainesville, FL 32611-7200, USA

ARTICLE INFO

Article history:
Received 27 April 2011
Accepted 26 May 2011
Available online 15 July 2011

ABSTRACT

A series of isoquinoline-based chiral diimine ligands are conveniently prepared via Bischler–Napieralski cyclization. The C_2-symmetric diimine ligand **1a** is effective in Cu(II)-catalyzed enantioselective Henry reactions between nitromethane and various aldehydes (11 examples), showing 50–89% yield and 75–93% ee.

1. Introduction

The nitroaldol (Henry) reaction constitutes an important C–C bond formation that yields β-nitroalcohols from carbonyl compounds and nitroalkanes. The β-nitroalcohols produced contain at least one newly formed stereogenic center and are valuable intermediates in the construction of synthetically important building blocks.[1] The value of these reaction products has prompted the development of a number of successful asymmetric variants including organocatalysts[2] and numerous Lewis acid based catalysts employing metals, such as lanthanides,[3] Cr(III),[4] Co(II),[5] Zn(II),[6] Cu(I),[7] and Cu(II).[8–10] Of the Lewis acids described, copper in particular has gained considerable attention, due in part to its availability, low toxicity and ease of handling. The Cu metal center is often supported by nitrogen-based chiral ligands bearing amine,[7a–f,8] imine (or pyridine),[7h,i,9] oxazoline,[7j,10a–h] oxazolidine,[7k,10i] or imidazoline[10j–l] moieties.

Recently, we developed synthetic routes to isoquinoline-based chiral diaminocarbenes via Bischler–Napieralski cyclization and several chiral diimines such as **1**[11a] and **3**[11b] were prepared as precursors to those carbenes (Fig. 1). The aforementioned literature precedence of imine-containing ligands for the asymmetric Henry reaction as well as our experience in this reaction,[5a,7j] led us to question whether the isoquinoline-based imine ligands **1** and **3** could be effective in the enantioselective Henry reaction. Herein we report the applications of isoquinoline-based chiral diimines in Cu(II)-catalyzed asymmetric Henry reactions.

2. Results and discussion

Scheme 1 summarizes a concise synthesis of various isoquinoline-based diimines **1** and **3** from phenethylamine precursors **5a–d**. The C_2-symmetric diimines **1a–d**[11a] as well as a C_1-symmetric diimine **3a**[11b] were prepared by the procedures previously reported by our group. The isoquinoline-based diimine ligands were evaluated in the copper catalyzed Henry reaction of nitromethane and 4-nitrobenzaldehyde (Table 1). A C_2-symmetric diimine with an *i*Bu group **1a** gave higher enantioselectivity than a structurally related C_1-symmetric diimine **3a** (entry 2 vs entry 1). When the R group in the C_2-symmetric diimines was varied, more sterically demanding substituents resulted in lower enantioselectivities and longer reaction time (*i*Bu ~ CH_2Cy > *i*Pr ≫ *t*Bu, entries 2–5). Thus, the best result was obtained when using the C_2-symmetric diimine with an *i*Bu substituent **1a**, affording nitroaldol product **10a** in 89% yield and 77% ee after 24 h.

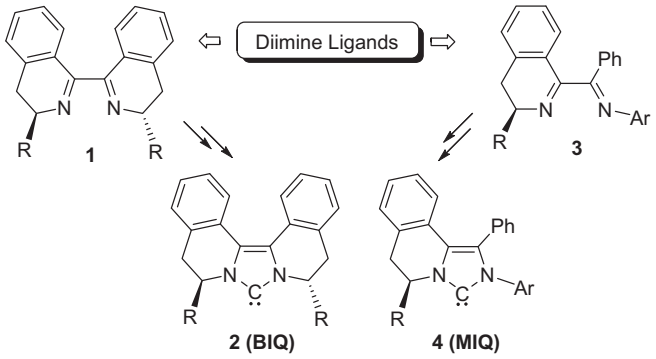
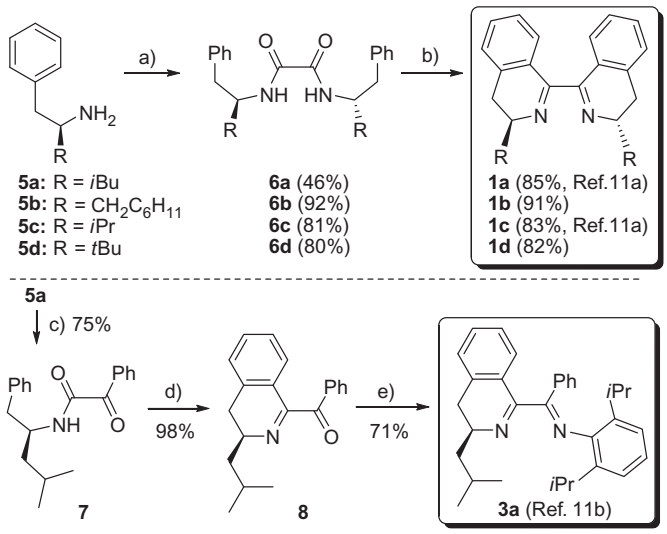


Figure 1. Isoquinoline-based chiral carbene ligands.

Attempts were made to further optimize the reaction conditions by changing the Lewis acid metal and the solvent (Table 2). Replacing $Cu(OAc)_2$ with another divalent metal acetate such as $Ni(OAc)_2$ or $Zn(OAc)_2$ resulted in lower enantioselectivities (entry 1 vs entries 2–3). Protic solvents (EtOH or *i*PrOH) proved to be better than aprotic solvents (THF or CH_2Cl_2), giving higher yields and ees (entries 1 and 4 vs entries 5–6).

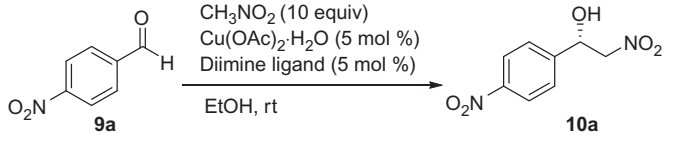
* Corresponding author. Fax: +1 352 846 0296.
E-mail address: sukwon@ufl.edu (S. Hong).

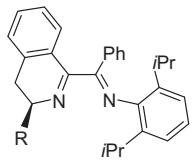
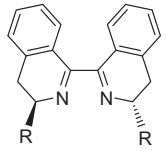
0957-4166/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2011.05.018



Scheme 1. Synthesis of isoquinoline-containing chiral imine ligands. Reagents and conditions: (a) oxalyl chloride, Et_3N, THF, 0 °C to rt, 12 h; (b) PCl_5, $Zn(OTf)_2$, toluene, 85 °C, 12 h; (c) 2-oxo-2-phenylacetic acid, EDC, HOBt, rt, 12 h; (d) Tf_2O, DMAP, toluene, 90 °C, 8 h; (e) 2,6-diisopropylaniline, $TiCl_4$, Et_3N, toluene, rt, 12 h.

Table 1
Ligand survey[a]

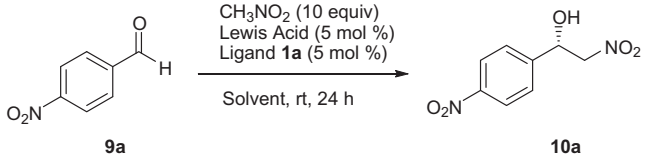


Entry	Ligand	Time (h)	Yield[b] (%)	ee[c] (%)
1	 **3a** (R = *i*Bu)	48	84	11
2	 **1a** (R = *i*Bu)	24	89	77
3	**1b** (R = CH_2Cy)	24	90	75
4	**1c** (R = *i*Pr)	48	90	65
5	**1d** (R = *t*Bu)	48	48	5

[a] All reactions were performed on a 0.5 mmol scale at a 0.4 M concentration. Reactions were run at room temperature in a screw-capped vial for the indicated time.
[b] Values are isolated yields after chromatographic purification.
[c] Enantiomeric excess was determined by HPLC using Chiralpak IB column.

With the optimal ligand structure and reaction conditions selected, we decided to explore the scope of the reaction. (Table 3) In general, high enantiomeric excesses (75–93% ee) were observed at room temperature with various substrates. While yields were decreased in some cases, additional reaction time was not found to improve those yields. It was observed however that increasing the catalyst loading to 10 mol % for a sluggish substrate such as benzaldehyde **9b**, could improve the yield without a loss of selectivity (entry 2). *Ortho*-, *meta*- and *para*-substituted benzaldehydes

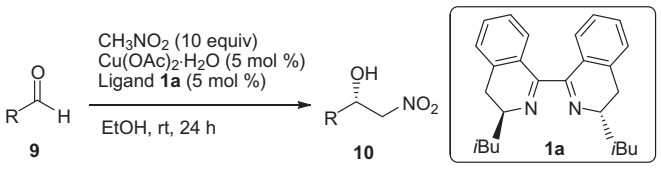
Table 2
Optimization of reaction conditions[a]



Entry	Lewis acid	Solvent	Yield[b] (%)	ee[c] (%)
1	$Cu(OAc)_2·H_2O$	EtOH	89	77
2	$Ni(OAc)_2·4H_2O$	EtOH	91	30
3	$Zn(OAc)_2·2H_2O$	EtOH	64	0
4	$Cu(OAc)_2·H_2O$	*i*PrOH	84	72
5	$Cu(OAc)_2·H_2O$	THF	59	40
6	$Cu(OAc)_2·H_2O$	CH_2Cl_2	38	54

[a] All reactions were performed on a 0.5 mmol scale at a 0.4 M concentration. Reactions were run at room temperature in a screw-capped vial.
[b] Values are isolated yields after chromatographic purification.
[c] Enantiomeric excess was determined by HPLC using Chiralpak IB column.

Table 3
Substrate scope[a]



Entry	R	Product	Yield[b] (%)	ee[c] (%)
1	Ph	**10b**	55	91
2[d]	Ph	**10b**	80	90
3	2-MeO–C_6H_4	**10c**	57	77
4	2-Cl–C_6H_4	**10d**	87	90
5	2-F–C_6H_4	**10e**	52	93
6	3-F–C_6H_4	**10f**	51	91
7	4-F–C_6H_4	**10g**	59	90
8	4-Cl–C_6H_4	**10h**	78	88
9	4-NO_2–C_6H_4	**10a**	89	77
10	4-Ph–C_6H_4	**10i**	78	81
11	1-Naphthyl	**10j**	68	87
12	PhCH=CH	**10k**	50	75

[a] All reactions were performed on a 0.5 mmol scale at a 0.4 M concentration. Reactions were run at room temperature in a screw-capped vial.
[b] Values are isolated yields after chromatographic purification.
[c] Enantiomeric excess was determined by HPLC using Chiralpak IB or Whelk-O1 columns.
[d] 10 mol % of $Cu(OAc)_2·H_2O$ and 10.0 mol % of ligand **1a** were used.

gave uniformly good enantiomeric excesses (77–93% ee, entries 3–11). It is interesting to note that the substrate scope is not limited to benzaldehydes, as cinnamaldehyde was an effective substrate, affording nitro-aldol product **10k** in 75% ee (entry 12).

The X-ray structure of **1a–$PdCl_2$** shed some light on the unique structural features of the isoquinoline-based C_2-symmetric diimines. The *i*Bu substituent takes the axial position on the six-membered azacycle, that is, folded into a boat-like conformation. In addition, helical (or axial) chirality seems to exist due to the severe steric repulsion between two phenyl rings. Compound **1a–$PdCl_2$** shows *P* helicity (or axial chirality) as well as (*S*)-stereogenic centers.

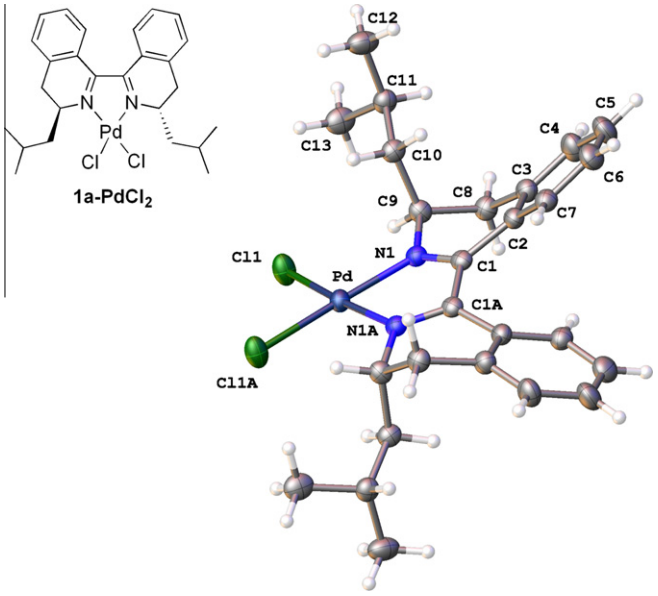


Figure 2. X-ray structure of **1a**–$PdCl_2$. Thermal ellipsoids are drawn at the 50% probability level. Selected bond lengths (Å), angles (°), and torsion angles (°): Pd–N1: 2.0095(18), N1–C1: 1.302 (3), N1–Pd–N1A: 79.32(7), N1–C1–C1A: 113.9(2), Pd–N1–C1–C1A: 11.1(2), C2–C1–C1A–C2A:-25.1(3).

3. Conclusion

In conclusion, a series of chiral isoquinoline-based imine ligands have been conveniently prepared via Bischler–Napieralski cyclization. The *i*Bu-substituted, C_2-symmetric diimine ligand **1a** is effective in Cu(II)-catalyzed enantioselective Henry reactions between nitromethane and various aldehydes (11 examples), showing 50–89% yield and 75–93% ee. The application of these diimine ligands in other asymmetric catalysis is currently ongoing.

4. Experimental

4.1. General

All reactions were conducted in flame-dried glassware under an inert atmosphere of dry argon unless otherwise specified. THF, CH_2Cl_2, CH_3CN and Et_2O were passed through two packed columns of neutral alumina under positive pressure of argon prior to use. All other chemicals used were commercially available and were used as received without further purification. NMR spectra were recorded using an FT-NMR machine, operating at 300 MHz for ^1H NMR and at 75.4 MHz for ^{13}C NMR. All chemical shifts for ^1H and ^{13}C NMR spectroscopy were referenced to Me_4Si (δ 0.0 ppm) for ^1H and ^{13}C or residual signals from ($CDCl_3$) (δ 7.24 ppm) for ^1H and (δ 77.23) for ^{13}C. High resolution mass spectra were recorded on a DIP-CI-MS spectrometer, an APCI-TOF spectrometer, an ESI-TOF spectrometer, or a TOF-LC/MS spectrometer. Specific optical rotations were obtained on a JASCO P-2000 Series Polarimeter (wavelength = 589 nm). Enantiomeric ratios were determined by chiral HPLC analysis (Shimadzu) using Chiralpak IB and (*S*,*S*) Whelk-O1 column. Known compounds have been identified by comparison of spectral data (^1H NMR, and ^{13}C NMR) with those previously reported.

4.2. Preparation of ligands

4.2.1. (*S*)-2-(Cyclohexylmethyl)-1-toluenesulfonylaziridine

To a solution of (*S*)-2-amino-3-cyclohexylpropan-1-ol[12] (1.620 g, 10.3 mmol) and triethylamine (7.2 mL, 52 mmol) in CH_2Cl_2 (20 mL), *p*-toluenesulfonyl chloride (2.260 g, 11.9 mmol) was added portionwise at −30 °C. The cooled mixture was stirred for 2 h at −30 °C and then for 1 h at room temperature. The stirred mixture was cooled to −30 °C, and methanesulfonyl chloride (0.84 mL, 11 mmol) was added. After stirring for 2 h at −30 °C, the reaction mixture was stirred for 10 h at room temperature. The reaction solution was diluted with CH_2Cl_2 (100 mL) and washed with 1 M aqueous HCl solution (100 mL) and then with a saturated $NaHCO_3$ solution (50 mL). The organic solution was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silicagel, 5:1 hexane/EtOAc) to afford the aziridine (2.298 g, 7.84 mmol, 76% yield). $[\alpha]_D^{24} = -6.4$ (*c* 0.22, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 2.82–2.69 (m, 1H), 2.65 (d, *J* = 2.8 Hz, 1H), 2.44 (s, 3H), 2.02 (d, *J* = 4.8, 1H), 1.73–1.47 (m, 5H), 1.43–0.94 (m, 6H), 0.93–0.69 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 135.5, 129.9, 128.2, 39.4, 39.2, 36.3, 34.1, 33.6, 32.8, 26.5, 26.3, 26.2, 21.9. HRMS (ESI) calcd for $C_{16}H_{23}NO_2S$ $(M+Na)^+$: 316.1342; found: 316.1356.

4.2.2. (*S*)-1-Cyclohexyl-3-phenylpropan-2-amine 5b

4.2.2.1. Synthesis of (*S*)-*N*-(1-cyclohexyl-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide. To a suspension of CuI (0.276 g, 1.45 mmol) in THF (5.0 mL), PhMgCl solution (2.0 M in THF, 4.8 mL, 9.6 mmol) was slowly added at −30 °C. After 30 min stirring at −30 °C, (*S*)-2-(cyclohexylmethyl)-1-toluenesulfonylaziridine (1.42 g, 4.84 mmol) was added. The reaction temperature was slowly increased to room temperature for 3 h. The reaction was cautiously quenched by a saturated aqueous NH_4Cl solution (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic mixture was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was filtered through a column of silica gel with EtOAc as an eluent to afford the sulfonamide.

4.2.2.2. Synthesis of (*S*)-1-cyclohexyl-3-phenylpropan-2-amine. To a suspension of Li (0.50 g, 72 mmol) in THF (30 mL) under argon, naphthalene (50 mg, 0.39 mmol) was added at room temperature. After 30 min, the solution turned dark blue. (*S*)-*N*-(1-Cyclohexyl-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide was added at −78 °C, and the reaction temperature was slowly warmed to room temperature. After 12 h, the solution was transferred through a canula to another flask to remove the remaining Li. The solution was quenched by a saturated aqueous NH_4Cl solution (50 mL) and rinsed with water (100 mL). To the organic solution was added 1 M HCl aqueous solution (15 mL), and the organic layer was discarded. To the acidic aqueous solution was added 20% NaOH aqueous solution (20 mL). The aqueous layer was extracted by Et_2O (3 × 20 mL) and was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford the phenethylamine (0.600 g, 2.76 mmol, 57% yield). $[\alpha]_D^{23} = +9.7$ (*c* 0.27, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.02 (m, 5H), 3.10 (br. s, 1H), 2.78 (dd, *J* = 4.3, 13.3 Hz, 1H), 2.41 (dd, *J* = 8.8, 13.5 Hz, 1H), 1.89–0.71 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.0, 129.5, 128.6, 126.3, 49.9, 45.9, 45.5, 34.7, 34.4, 33.2, 26.9, 26.6, 26.5. HRMS (ESI) calcd for $C_{15}H_{23}N$ $(M+H)^+$: 218.1903; found: 218.1906.

4.2.3. *N*,*N*′-Bis((*S*)-1-cyclohexyl-3-phenylpropan-2-yl)oxalamide 6b

To a cooled, magnetically stirred solution of (*S*)-1-cyclohexyl-3-phenylpropan-2-amine **5b** (90.2 mg, 0.415 mmol) and triethylamine (65 μL, 0.46 mmol) in THF (5.0 mL) under argon, oxalyl chloride (17.6 μL, 0.202 mmol) was added dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature and was then stirred for 12 h. The reaction mixture was cooled to

0 °C before quenching with water (10 mL). The mixture was extracted with $CHCl_3$ (3 × 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 3:1 chloroform/hexane) to afford the oxalamide (90.1 mg, 0.184 mmol, 92% yield) $[\alpha]_D^{23} = -21.9$ (*c* 0.29, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.10 (m, 12H), 4.32–4.11 (m, 2H), 2.78 (d, *J* = 6.4 Hz, 4H), 1.89–1.49 (m, 12H), 1.43–1.05 (m, 11H), 1.01–0.63 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 137.7, 129.6, 128.6, 126.7, 48.7, 41.9, 41.6, 34.5, 34.0, 32.8, 26.7, 26.4, 26.3. HRMS (ESI) calcd for $C_{32}H_{44}N_2O_2$ $(M+Na)^+$: 511.3295; found: 511.3308.

4.2.4. (3S,3′S)-3,3′-Bis(cyclohexylmethyl)-3,3′,4,4′-tetrahydro-1,1′-biisoquinoline 1b

To a solution of *N*,*N*-Bis((*S*)-1-cyclohexyl-3-phenylpropan-2-yl) oxalamide **6b** (0.450 g, 0.921 mmol) in toluene (45 mL) under nitrogen was added $Zn(OTf)_2$ (1.00 g, 2.76 mmol) and PCl_5 (1.15 g, 5.52 mmol). The reaction mixture was heated at 85 °C for 12 h and then was cooled to room temperature before quenching with a 30% aqueous NH_4OH solution (20 mL). The mixture was extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude product by flash column chromatography (silica gel, 5:1 hexanes/EtOAc) afforded the biisoquinoline (0.380 g, 0.839 mmol, 91% yield) $[\alpha]_D^{23} = -12.9$ (*c* 0.37, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.04 (m, 8H), 3.98–3.75 (m, 2H), 2.93 (dd, *J* = 5.6, 15.8 Hz, 2H), 2.64 (dd, *J* = 11.1, 15.8 Hz, 2H), 1.98–1.48 (m, 16H), 1.38–1.06 (m, 6H), 1.06–0.75 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 137.5, 131.1, 128.6, 128.0, 127.1, 126.9, 54.5, 43.5, 34.6, 34.1, 33.3, 31.6, 26.9, 26.6. HRMS (ESI) calcd for $C_{32}H_{40}N_2$ $(M+H)^+$: 453.3264; found: 453.3286.

4.2.5. (*S*)-2-(*tert*-Butyl)-1-touenesulfonylaziridine[13]

88%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 2.46–2.60 (m, 2H), 2.43 (s, 3H), 2.16 (d, *J* = 4.25 Hz, 1H), 0.78 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 135.4, 129.8, 128.4, 49.1, 30.5, 26.4, 21.9.

4.2.6. (*R*)-3,3-Dimethyl-1-phenylbutan-2-amine 5d

93%. $[\alpha]_D^{22} = +48.6$ (*c* 0.88, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.27 (m, 2H), 7.25–7.18 (m, 3H), 2.98 (dd, *J* = 2.3, 13.3 Hz, 1H), 2.69 (dd, *J* = 2.4, 10.9 Hz, 1H), 2.21 (dd, *J* = 11.0, 13.3 Hz, 1H), 1.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 129.4, 128.7, 126.3, 62.3, 39.0, 34.5, 26.6. HRMS (ESI) calcd for $C_{12}H_{19}N$ $(M+H)^+$: 178.1590; found: 178.1582.

4.2.7. *N*,*N*′-Bis((R)-3,3-dimethyl-1-phenylbutan-2-yl)oxalamide 6d

80%. $[\alpha]_D^{22} = +36.3$ (*c* 0.54, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21–7.00 (m, 12H), 3.86 (td, *J* = 2.8, 11.0 Hz, 2H), 3.01 (dd, *J* = 2.8, 14.2 Hz, 2H), 2.36 (dd, *J* = 11.3, 14.2 Hz, 2H), 0.97 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 138.8, 129.0, 128.5, 126.4, 60.1, 36.6, 35.1, 26.7. HRMS (ESI) calcd for $C_{26}H_{36}N_2O_2$ $(M+Na)^+$: 431.2669; found: 431.2671.

4.2.8. (3R,3′R)-3,3′-Di-*tert*-butyl-3,3′,4,4′-tetrahydro-1,1′-biisoquinoline 1d

82%. $[\alpha]_D^{22} = +204.8$ (*c* 0.62, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.9 Hz, 2H), 7.35–7.27 (m, 2H), 7.24–7.11 (m, 4H), 3.23 (dd, *J* = 5.0, 15.1 Hz, 2H), 2.86–2.56 (m, 4H), 1.09 (s, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 139.1, 130.5, 128.9, 127.7, 127.5, 126.5, 66.4, 34.3, 27.1, 26.9. HRMS (ESI) calcd for $C_{26}H_{32}N_2$ $(M+H)^+$: 373.2638; found: 373.2639.

4.2.9. Dichloro[(3S,3′S)-3,3′-diisobutyl-3,3′,4,4′-tetrahydro-1,1′-biisoquinoline]-palladium(II) 1a–$PdCl_2$

To a solution of **1a** (0.205 g, 0.550 mmol) in toluene (3 mL), $PdCl_2(CH_3CN)_2$ (0.130 g, 0.500 mmol) was added, and the solution was stirred at room temperature for 12 h. The precipitated product was filtered and washed with hexanes (20 mL). (0.271 g, 98.6%) $[\alpha]_D^{23} = -702.5$ (*c* 0.43, $CHCl_3$); ^{1}H NMR (300 MHz,$CDCl_3$) δ 7.55 (m, 2H), 7.34 (d, *J* = 7.4 Hz, 2H), 7.13 (m, 2H), 6.86 (d, *J* = 7.6 Hz, 2H), 5.04–4.86 (m, 2H), 3.26–3.06 (m, 2H), 3.04–2.84 (m, 2H), 2.11–1.87 (m, 2H), 1.67–1.40 (m, 2H), 1.00 (d, *J* = 6.8 Hz, 6H), 0.91–0.80 (m, 2H), 0.78 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 135.7, 134.4, 129.4, 129.2, 126.8, 126.7, 56.4, 35.1, 29.3, 25.9, 24.2. Anal. Calcd for $C_{26}H_{32}Cl_2N_2Pd$: C, 56.79; H, 5.87; N, 5.09. Found: C, 57.00; H, 6.00; N, 5.01.

4.3. General procedure for the enantioselective Henry reaction

To a 3.0 mL screw cap vial, a magnetic stirrer bar and ligand (0.025 mmol) were added followed by absolute EtOH (1.25 mL). After the ligand was fully dissolved, $Cu(OAc)_2{\cdot}H_2O$ (4.99 mg, 0.025 mmol) was then added and allowed to stir at room temperature for 1 hour. Next, CH_3NO_2 was added (0.27 mL, 5.0 mmol) followed by aldehyde (0.50 mmol) and allowed to stir for the indicated time. The reaction mixture was purified by flash column chromatography on silica gel and the enantiomeric ratios were determined by chiral HPLC analysis (Shimadzu) using Chiralpak IB and (*S*,*S*) Whelk-O1 columns

4.3.1. (*S*)-2-Nitro-1-(4-nitrophenyl)ethanol 10a

Enantiomeric excess was determined by HPLC with a Chiralpak IB column (85:15 hexanes/isopropanol, 1.0 mL/min, 254 nm); minor t_r = 12.87 min; major t_r = 14.47 min; 77% ee. Configuration assignment: absolute configuration of the major isomer was determined to be (*S*) by comparison of the retention time with literature data.[7j]

4.3.2. (*S*)-2-Nitro-1-phenylethanol 10b

Enantiomeric excess was determined by HPLC with a Chiralpak IB column (85:15 hexanes/isopropanol, 0.8 mL/min, 215 nm); minor t_r = 8.94 min; major t_r = 9.82 min; 91% ee. Configuration assignment: absolute configuration of the major isomer was determined to be (*S*) by comparison of the retention time with literature data.[7j]

4.3.3. (*S*)-1-(4-Methoxyphenyl)-2-nitroethanol 10c

Enantiomeric excess was determined by HPLC with a Chiralpak IB column (85:15 hexanes/isopropanol, 0.8 mL/min, 215 nm); minor t_r = 8.64 min; major t_r = 9.32 min; 77% ee. Configuration assignment: absolute configuration of the major isomer was determined to be (*S*) by comparison of the retention time with literature data.[5a,7j]

4.3.4. (*S*)-1-(2-Chlorophenyl)-2-nitroethanol 10d

Enantiomeric excess was determined by HPLC with a (*S*,*S*) Whelk-O1 column (95:5 hexanes/isopropanol, 1.0 mL/min, 215 nm); minor t_r = 8.53 min; major t_r = 9.39 min; 90% ee. Configuration assignment: absolute configuration of the major isomer was determined to be (*S*) by comparison of the retention time with literature data.[5a,7j]

4.3.5. (*S*)-1-(2-Fluorophenyl)-2-nitroethanol 10e

Enantiomeric excess was determined by HPLC with a (*S*,*S*) Whelk-O1 column (95:5 hexanes/isopropanol, 0.8 mL/min, 215 nm); major t_r = 10.6 min; minor t_r = 11.5 min; 93% ee. Configuration assignment: absolute configuration of the major isomer was

determined to be (*S*) by comparison of the retention time with literature data.[5a,7j]

4.3.6. (*S*)-1-(3-Fluorophenyl)-2-nitroethanol 10f

$[\alpha]_D^{22} = +26.8$ (*c* 0.26, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.45 (m, 1H), 7.10–7.21 (m, 2H), 7.04 (td, *J* = 8.4, 2.5 Hz, 1H), 5.46 (dd, *J* = 8.8, 3.4 Hz, 1H), 4.43–4.64 (m, 2H), 3.11 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3 (d, J_{CF} = 246.0 Hz), 140.8 (d, J_{CF} = 6.8 Hz), 130.9 (d, J_{CF} = 8.3 Hz), 121.7 (d, J_{CF} = 3.0 Hz), 116.1 (d, J_{CF} = 21.0 Hz), 113.3 (d, J_{CF} = 22.5 Hz), 81.2, 70.5 (d, J_{CF} = 1.5 Hz); HRMS (DART) calcd for $C_8H_{26}FN_2O_3$ $[M+NH_4]^+$: 203.0826, found: 203.0809; Enantiomeric excess was determined by HPLC with a Chiralpak IB column (85:15 hexanes/isopropanol, 1.0 mL/min, 215 nm); minor t_r = 6.84 min; major t_r = 7.42 min; 91% ee; Configuration assignment: absolute configuration of major isomer was determined to be (*S*) by analogy of the retention time with other products.

4.3.7. (*S*)-1-(4-Fluorophenyl)-2-nitroethanol 10g

Enantiomeric excess was determined by HPLC with a Chiralpak IB column (90:10 hexanes/isopropanol, 1.0 mL/min, 215 nm); minor t_r = 9.11 min; major t_r = 9.97 min; 90% ee. Configuration assignment: absolute configuration of the major isomer was determined to be (*S*) by comparison of the retention time with literature data.[5a,7j]

4.3.8. (*S*)-1-(4-Chlorophenyl)-2-nitroethanol 10h

Enantiomeric excess was determined by HPLC with a Chiralpak IB column (85:15 hexanes/isopropanol, 1.0 mL/min, 254 nm); minor t_r = 7.38 min; major t_r = 8.15 min; 88% ee. Configuration assignment: absolute configuration of the major isomer was determined to be (*S*) by with literature data.[8g,10g,14]

4.3.9. (*S*)-1-(Biphenyl-4-yl)-2-nitroethanol 10i

Enantiomeric excess was determined by HPLC with a (*S*,*S*) Whelk-O1 column (85:15 hexanes/isopropanol, 1.0 mL/min, 215 nm); minor t_r = 8.53 min; major t_r = 10.51 min; 81% ee. Configuration assignment: absolute configuration of the major isomer was determined to be (*S*) by comparison with literature data.[14]

4.3.10. (*S*)-1-(Naphthalen-1-yl)-2-nitroethanol 10j

Enantiomeric excess was determined by HPLC with a Chiralpak IB column (85:15 hexanes/isopropanol, 1.0 mL/min, 215 nm); minor t_r = 8.15 min; major t_r = 10.7 min; 87% ee. Configuration assignment: absolute configuration of the major isomer was determined to be (*S*) by comparison of the retention time with literature data.[5a,7j]

4.3.11. (*S*,*E*)-1-Nitro-4-phenylbut-3-en-2-ol 10k

Enantiomeric excess was determined by HPLC with a Chiralpak IB column (85:15 hexanes/isopropanol, 0.8 mL/min, 215 nm); minor t_r = 18.56 min; major t_r = 17.16 min; 75% ee. Configuration assignment: absolute configuration of the major isomer was determined to be (*S*) by comparison with literature data.[6a]

4.4. Crystal structure analysis

Data were collected at 173 K on a Siemens SMART PLATFORM equipped with a CCD area detector and a graphite monochromator utilizing MoKα radiation (λ = 0.71073 Å) (Table 4). Cell parameters were refined using up to 8192 reflections. A full sphere of data (1850 frames) was collected using the ω-scan method (0.3° frame width). The first 50 frames were re-measured at the end of data collection to monitor instrument and crystal stability (maximum correction on *I* was <1%). Absorption corrections by integration were applied based on measured indexed crystal faces. The structure was solved by the Direct Methods in SHELXTL6,[15] and refined using full-matrix least squares. The non-H atoms were treated anisotropically, whereas the hydrogen atoms were calculated in ideal positions and were riding on their respective carbon atoms. The asymmetric unit consists of a half complex (located on a two-fold rotation symmetry element) and a dichloromethane molecule. A total of 168 parameters were refined in the final cycle of refinement using 3615 reflections with $I > 2\sigma(I)$ to yield R_1 and wR_2 of 2.48% and 6.40%, respectively. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif (CCDC 812994). The thermal ellipsoid drawing (Fig. 2) was produced using OLEX2.[16]

Table 4
Crystal data and structure refinement for **1a–$PdCl_2$**

Identification code	**1a–$PdCl_2$**
Empirical formula	$C_{28}H_{36}Cl_6N_2Pd$
Formula weight	719.69
Temperature (K)	173(2)
Wavelength (Å)	0.71073
Crystal system	Tetragonal
Space group	$P4_12_12$
Unit cell dimensions	
a (Å)	12.8898(3)
b (Å)	12.8898(3)
c (Å)	19.4625(9)
α (°)	90
β (°)	90
γ (°)	90
Volume (Å^3)	3233.63(18)
Z	4
Density (calculated) (Mg/m^3)	1.478
Absorption coefficient (mm^{-1})	1.090
F(0 0 0)	1464
Crystal size (mm^3)	0.32 × 0.32 × 0.26
θ range for data collection (°)	1.89–27.49
Index ranges	$-16 \le h \le 14$, $-8 \le k \le 16$, $-25 \le l \le 20$
Reflections collected	18011
Independent reflections	3722 [*R*(int) = 0.0591]
Completeness to θ = 27.49° (%)	100.0
Absorption correction	Integration
Max. and min. transmission	0.7995 and 0.7030
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3722/0/168
Goodness-of-fit on F^2	1.078
Final *R* indices [$I > 2\sigma(I)$]	R_1 = 0.0248, wR_2 = 0.0640 [3615]
R indices (all data)	R_1 = 0.0259, wR_2 = 0.0646
Absolute structure parameter	−0.03(3)
Largest diff. peak and hole (e Å^{-3})	0.447 and −0.533

Acknowledgments

We thank the James & Esther King Biomedical Research Program, Florida Department of Health (08KN-04) and the Petroleum Research Fund administered by the American Chemical Society (PRF 46157-G1). K.A.A. wishes to acknowledge the National Science Foundation and the University of Florida for funding for the new X-ray equipment. We also thank Mr. Jongwoo Park and Mr. Kai Lang for discussion.

References

1. Recent reviews: (a) Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, 2561–2574; (b) Boruwa, J.; Gogoi, N.; Saikia, P. P.; Barua, N. C. *Tetrahedron: Asymmetry* **2006**, *17*, 3315–3326; (c) Palomo, C.; Oiarbide, M.; Mielgo, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5442–5444; (d) Luzio, F. A. *Tetrahedron* **2001**, *57*, 915–945.
2. (a) Uraguchi, D.; Nakamura, S.; Ooi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 7562–7565; (b) Uraguchi, D.; Sasaki, D.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392–12393; (c) Chen, X.; Wang, J.; Zhu, Y.; Shang, D.; Gao, B.; Liu, X.; Feng, X.; Su, Z.; Hu, C. *Chem. Eur. J.* **2008**, *14*, 10896–10899; (d) Takada, K.; Takemura, N.; Cho, K.; Sohtome, Y.; Nagasawa, K. *Tetrahedron Lett.* **2008**, *49*, 1623–1626; (e) Sohtome, Y.; Takemura, N.; Takada, K.; Takagi, R.; Iguchi, T.; Nagasawa, K.

Chem. Asian J. **2007**, *2*, 1150–1160; (f) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Eur. J. Org. Chem.* **2006**, 2894–2897; (g) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Adv. Synth. Catal.* **2005**, *347*, 1643–1648; (h) Ube, H.; Terada, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3895–3898; (i) Alcaide, B.; Almendros, P.; Luna, A. *Tetrahedron* **2007**, *63*, 3102–3107; (j) Mandal, T.; Samanta, S.; Zhao, C. *Org. Lett.* **2007**, *9*, 943–945; (k) Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 732–733; (l) Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J. H.; Hiemstra, H. *Synlett* **2005**, 2817–2819.

3. (a) Nitabaru, T.; Nojiri, A.; Kobayashi, M.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 13860–13869; (b) Handa, S.; Nagawa, K.; Sohtome, Y.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3230–3233; (c) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418–4420; (d) Shibasaki, M.; Kanai, M.; Matsunaga, S.; Kumagai, N. *Acc. Chem. Res.* **2009**, *42*, 1117–1127. and references therein; (e) Tur, F.; Saá, J. M. *Org. Lett.* **2007**, *9*, 5079–5082.
4. (a) Zulauf, A.; Mellah, M.; Schulz, E. *J. Org. Chem.* **2009**, *74*, 2242–2245; (b) Kowalczyk, R.; Kwiatkowski, P.; Skarżewski, J.; Jurczak, J. *J. Org. Chem.* **2009**, *74*, 753–756; (c) Kowalczyk, R.; Sidorowicz, Ł.; Skarżewski, J. *Tetrahedron: Asymmetry* **2007**, *18*, 2581–2586.
5. (a) Park, J.; Lang, K.; Abboud, K. A.; Hong, S. *J. Am. Chem. Soc.* **2008**, *130*, 16484–16485; (b) Tsuchiya, S.; Sunazuka, T.; Hirose, T.; Mori, R.; Tanaka, T.; Iwatsuki, M.; Omura, S. *Org. Lett.* **2006**, *8*, 5577–5580; (c) Kogami, Y.; Nakajima, T.; Ashizawa, T.; Kezuka, S.; Ikeno, T.; Yamada, T. *Chem. Lett.* **2004**, *33*, 614–615; (d) Kogami, Y.; Nakajima, T.; Ikeno, T.; Yamada, T. *Synthesis* **2004**, 1947–1950.
6. (a) Liu, S.; Wolf, C. *Org. Lett.* **2008**, *10*, 1831–1834; (b) Bulut, A.; Aslan, A.; Dogan, O. *J. Org. Chem.* **2008**, *73*, 7373–7375; (c) Palomo, C.; Oiarbide, M.; Laso, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3881–3884; (d) Gao, J.; Zingaro, R. A.; Reibenspies, J. H.; Martell, A. E. *Org. Lett.* **2004**, *6*, 2453–2455; (e) Trost, B. M.; Yeh, V. S. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 861–863; (f) Trost, B. M.; Yeh, V. S. C.; Ito, H.; Bremeyer, N. *Org. Lett.* **2002**, *4*, 2621–2623.
7. (a) Jin, W.; Li, X.; Wan, B. *J. Org. Chem.* **2011**, *76*, 484–491; (b) Steurer, M.; Bolm, C. *J. Org. Chem.* **2010**, *75*, 3301–3310; (c) Kim, H. Y.; Oh, K. *Org. Lett.* **2009**, *11*, 5682–5685; (d) Arai, T.; Taneda, Y.; Endo, Y. *Chem. Commun.* **2010**, *46*, 7936–7938; (e) Arai, T.; Takashita, R.; Endo, Y.; Watanabe, M.; Yanagisawa, A. *J. Org. Chem.* **2008**, *73*, 4903–4906; (f) Xiong, Y.; Wang, F.; Huang, X.; Wen, Y.; Feng, X. *Chem. Eur. J.* **2007**, *13*, 829–833; (g) Qin, B.; Xiao, X.; Liu, X.; Huang, J.; Wen, Y.; Feng, X. *J. Org. Chem.* **2007**, *72*, 9323–9328; (h) Qi, G.; Ji, Y. Q.; Judeh, J. M. A. *Tetrahedron* **2010**, *66*, 4195–4205; (i) Jiang, J.-J.; Shi, M. *Tetrahedron: Asymmetry* **2007**, *18*, 1376–1382; (j) Lang, K.; Park, J.; Hong, S. *J. Org. Chem.* **2010**, *75*, 6424–6435; (k) Spangler, K. Y.; Wolf, C. *Org. Lett.* **2009**, *11*, 4724–4727.
8. (a) Zhou, Y.; Dong, J.; Zhang, F.; Gong, Y. *J. Org. Chem.* **2011**, *76*, 588–600; (b) Jin, W.; Li, X.; Huang, Y.; Wu, F.; Wan, B. *Chem. Eur. J.* **2010**, *16*, 8259–8261; (c) Noole, A.; Lippur, K.; Metsala, A.; Lopp, M.; Kanger, T. *J. Org. Chem.* **2010**, *75*, 1313–1316; (d) Breuning, M.; Hein, D.; Steiner, M.; Gessner, V. H.; Strohmann, C. *Chem. Eur. J.* **2009**, *15*, 12764–12769; (e) Sanjeevakumar, N.; Periasamy, M. *Tetrahedron: Asymmetry* **2009**, *20*, 1842–1847; (f) Selvakumar, S.; Sivasankaran, D.; Singh, V. K. *Org. Biomol. Chem.* **2009**, *7*, 3156–3162; (g) Zhang, G.; Yashima, E.; Woggon, W.-D. *Adv. Synth. Catal.* **2009**, *351*, 1255–1262; (h) Kowalczyk, R.; Skarżewski, J. *Tetrahedron: Asymmetry* **2009**, *20*, 2467–2473; (i) Rachwalski, M.; Lesniak, S.; Sznajder, E.; Kiezbasinski, P. *Tetrahedron: Asymmetry* **2009**, *20*, 1547–1549; (j) Arai, T.; Watanabe, M.; Yanagisawa, A. *Org. Lett.* **2007**, *9*, 3595–3597; (k) Bandini, M.; Benaglia, M.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *Org. Lett.* **2007**, *9*, 2151–2153; (l) Bandini, M.; Piccinelli, F.; Tommasi, S.; Umani-Ronchi, A.; Ventrici, C. *Chem. Commun.* **2007**, 616–618; (m) Mansawat, W.; Saengswang, I.; U-prasitwong, P.; Bhanthumnavin, W.; Vilaivan, T. *Tetrahedron Lett.* **2007**, *48*, 4235–4238; (n) Maheswaran, H.; Prasanth, K. L.; Krishna, G. G.; Sridhar, B.; Kantam, M. L. *Chem. Commun.* **2006**, 4066–4068.
9. (a) Blay, G.; Hernández-Olmos, V.; Pedro, J. R. *Org. Lett.* **2010**, *12*, 3058–3061; (b) Blay, G.; Domingo, L. R.; Hernández-Olmos, V.; Pedro, J. R. *Chem. Eur. J.* **2008**, *14*, 4725–4730; (c) Blay, G.; Hernández-Olmos, V.; Pedro, J. R. *Org. Biomol. Chem.* **2008**, *6*, 468–476; (d) Blay, G.; Climent, E.; Fernández, I.; Hernández-Olmos, V.; Pedro, J. R. *Tetrahedron: Asymmetry* **2007**, *18*, 1603–1612; (e) Blay, G.; Climent, E.; Fernández, I.; Hernández-Olmos, V.; Pedro, J. R. *Tetrahedron: Asymmetry* **2006**, *17*, 2046–2049; (f) Xin, D.; Ma, Y.; He, F. *Tetrahedron: Asymmetry* **2010**, *21*, 333–338; (g) Çolak, M.; Aral, T.; Hoşgören, H.; Demirel, N. *Tetrahedron: Asymmetry* **2007**, *18*, 1129–1133; (h) Lai, G.; Wang, S.; Wang, Z. *Tetrahedron: Asymmetry* **2008**, *19*, 1813–1819; (i) Gan, C.; Lai, G.; Zhang, Z.; Wang, Z.; Zhou, M.-M. *Tetrahedron: Asymmetry* **2006**, *17*, 725–728.
10. (a) Kawthekar, R. B.; Chakka, S. K.; Francis, V.; Andersson, P. G.; Kruger, H. G.; Maguire, G. E. M.; Govender, T. *Tetrahedron: Asymmetry* **2010**, *21*, 846–852; (b) Yang, W.; Liu, H.; Du, D.-M. *Org. Biomol. Chem.* **2010**, *8*, 2956–2960; (c) Rasappan, R.; Olbrich, T.; Reiser, O. *Adv. Synth. Catal.* **2009**, *351*, 1961–1967; (d) Toussaint, A.; Pfaltz, A. *Eur. J. Org. Chem.* **2008**, 4591–4597; (e) Ginotra, S. K.; Singh, V. K. *Org. Biomol. Chem.* **2007**, *5*, 3932–3937; (f) Du, D.-M.; Lu, S.-F.; Fang, T.; Xu, J. *J. Org. Chem.* **2005**, *70*, 3712–3715; (g) Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692–12693; (h) Christensen, C.; Juhl, K.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4875–4881; (i) Xu, H.; Wolf, C. *Chem. Commun.* **2010**, 8026–8028; (j) Cheng, L.; Dong, J.; You, J.; Gao, G.; Lan, J. *Chem. Eur. J.* **2010**, *16*, 6761–6765; (k) Ma, K.; You, J. *Chem. Eur. J.* **2007**, *13*, 1863–1871; (l) Arai, T.; Suzuki, K. *Synlett* **2009**, 3167–3170.
11. (a) Seo, H.; Hirsch-Weil, D.; Abboud, K. A.; Hong, S. *J. Org. Chem.* **2008**, *73*, 1983–1986; (b) Hirsch-Weil, D.; Abboud, K. A.; Hong, S. *Chem. Commun.* **2010**, 7525–7527.
12. (a) Specific rotation value for the commercially available (*S*)-2-amino-3-cyclohexyl-1-propanol hydrochloride: $[\alpha]_D^{20} = +2.6$ (*c* 1.0, CH_3OH). (b) The enantiomeric purity of this amino alcohol compound was confirmed by derivatization to the known cyclic carbamate, (*S*)-4-(cyclohexylmethyl)oxazolidin-2-one: $[\alpha]_D^{22} = -15.3$ (*c* 1.0, $CHCl_3$) versus literature value $[\alpha]_D = -14.9$ ($CHCl_3$). See Ishizuka, T.; Kimura, K.; Ishibuchi, S.; Kuneida, T. *Chem. Lett.* **1992**, 991–994.
13. Kawamura, K.; Fukuzawa, H.; Hayashi, M. *Org. Lett.* **2008**, *10*, 3509–3512.
14. Kowalczyk, R.; Sidorowicz, Ł.; Skarzewski, J. *Tetrahedron: Asymmetry* **2008**, *19*, 2310–2315.
15. SHELXTL6; Bruker-AXS: Madison, Wisconsin, USA, 2000.
16. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. *J. Appl. Crystallogr.* **2009**, *42*, 339–341.