JOC The Journal of Organic Chemistry

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Highly Enantioselective Nitroaldol Reactions Catalyzed by Copper(II) Complexes Derived from Substituted 2-(Pyridin-2-yl)imidazolidin-4-one Ligands

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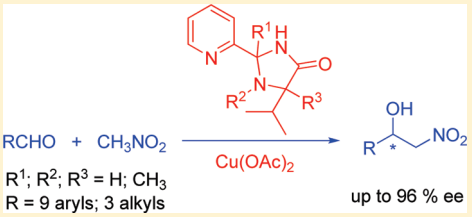
Supporting Information

ABSTRACT: Ten optically pure substituted 2-(pyridin-2-yl)imidazolidin-4-ones, **1a**−**d**, **2a**−**4a**, and **2b**−**4b**, were prepared and characterized. The absolute configurations of individual ligands were determined by X-ray analysis or NOESY experiments. The Cu(II) complexes of the respective ligands were studied as enantioselective catalysts of the nitroaldol (Henry) reaction of aldehydes with nitromethane, giving the corresponding substituted 2-nitroalkanols. In the case of an anti arrangement of the imidazolidin-4-one ring, the obtained result was 91−96% ee, whereas in the case of syn arrangement, a significant drop to 25−27% ee was observed.

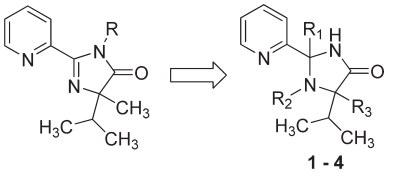


The nitroaldol (Henry) reaction represents one of the basic processes in organic synthesis for producing a carbon−carbon bond and is a key step in the synthesis of many significant compounds. The asymmetric variant of the Henry reaction plays a significant role in the synthesis of pharmaceutical precursors, in particular.[1,2] The general procedure of this asymmetric synthesis requires the application of a suitable optically pure chiral ligand, often in combination with metal ions. In the case of the nitroaldol reaction, complexes with Cu(II) have proven particularly useful.[2]

The Cu(II) complexes derived from 2-(pyridin-2-yl)-4-isopropyl-4-methyl-4,5-dihydro-1*H*-imidazol-5-ones (Scheme 1), which we prepared earlier, were also efficient catalysts of the Henry reaction. However, in the case of these complexes, the resulting enantioselectivity was only low (maximum 19% ee).[2b,c] Since one of the described methods for the preparation of substituted 4,5-dihydro-1*H*-imidazol-5-ones consists of oxidation of substituted imidazolidin-4-ones,[3] we also decided to test the enantioselectivity of these types of ligands, which are very similar in structure to the well-known MacMillan organocatalysts.[4] Thanks to the sp^3 configuration at the 2-carbon atom, the imidazolidin-4-ones are less rigid than the substituted 4,5-dihydro-1*H*-imidazol-5-ones. In addition to that, the sp^3-hybridized carbon atom at the 2-position of imidazolidin-4-one represents another stereogenic center, which can lead to an increase in enantioselectivity from the standpoint of enantiocatalytic properties (Scheme 1). A similar example was encountered in the catalysis of the Henry reaction in the case of Cu(II) complexes derived from substituted pyridylimidazolidines as compared with the Cu(II) complexes derived from pyridylimidazolines.[2f]

The aim of this work was to prepare and characterize optically pure substituted 2-(pyridin-2-yl)imidazolidin-4-ones **1**−**4** and their Cu(II) complexes. Another aim of the work was to test the potential application of these complexes as enantioselective

Scheme 1. Substituted 4,5-Dihydro-1*H*-imidazol-5-ones and Substituted Imidazolidin-4-ones 1−4



1: R^1 = H; R^2 = H; R^3 = CH_3;
2: R^1 = CH_3; R^2 = H; R^3 = CH_3;
3: R^1 = CH_3; R^2 = H; R^3 = H
4: R^1 = H; R^2 = CH_3; R^3 = CH_3;

catalysts for the Henry reaction. The suggested ligands **1**−**4** differed in the position and in some cases also in the number of the methyl group(s) attached to the imidazolidin-4-one ring, which determined the different geometries of the corresponding Cu(II) complexes with possible impacts on the catalytic activity of the individual complexes.

Since our suggested ligands **1**−**4** contained two stereogenic centers in the molecule (C-2, C-5), it was suitable to prepare the optically pure isomers from precursors containing one defined stereogenic center. Such easily accessible precursors were (*S*)-2-amino-2,3-dimethylbutanamide,[5] (*R*)-2-amino-2,3-dimethylbutanamide,[5] (*S*)-2-amino-3-methylbutanamide (valinamide), and (*S*)-2-*N*-methylamino-2,3-dimethylbutanamide.[6] The ring closure reaction of these amino amides with pyridine-2-carbaldehyde or

Received: April 4, 2011
Published: May 02, 2011

2-acetylpyridine produced the second stereogenic center at the 2-position of the imidazolidin-4-one ring. The reaction of pyridine-2-carbaldehyde with (*S*)-2-amino-2,3-dimethylbutanamide gave the diastereoisomeric products (5*S*)-5-isopropyl-2-methyl-2-(pyridin-2-yl)imidazolidin-4-ones (**1a,b**), and the reaction with (*R*)-2-amino-2,3-dimethylbutanamide gave (5*R*)-5-isopropyl-2-methyl-2-(pyridin-2-yl)imidazolidin-4-ones (**1c,d**). The prepared pairs of diastereomers were separated chromatographically into the individual optically pure isomers: i.e., **1a,b** and **1c,d**.

Similarly, the diastereoisomeric mixture obtained from the reaction of 2-acetylpyridine with (*S*)-2-amino-2,3-dimethylbutanamide was chromatographically separated to give the optically pure derivatives **2a,b**. The analogous reaction of valinamide with 2-acetylpyridine and subsequent chromatographic separation gave the optically pure derivatives **3a,b**, and the condensation of pyridine-2-carbaldehyde with (*S*)-2-*N*-methylamino-2,3-dimethylbutanamide and subsequent separation of diastereoisomeric mixture gave the optically pure products **4a,b** (Scheme 2, Chart 1).

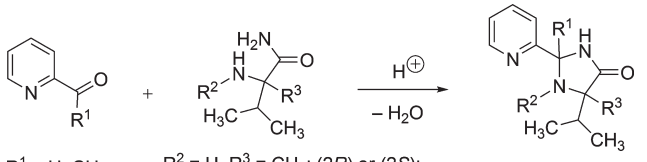
The cyclization reaction in the syntheses of compounds **1** and **4** was carried out by refluxing (8 h) the reactants in methanol with acetic acid as the catalyst. The preparation of products **2** and **4** required the application of 1,2-dichlorobenzene due to the lower reactivity of 2-acetylpyridine. However, partial racemization at the C5 position was observed in the case of derivative **3**. Therefore, we tested several solvents and found that the reaction in isopropyl alcohol proceeded at a satisfactory rate and without racemization. The structures of the prepared diastereoisomeric mixtures and optically pure products were verified by means of ^{1}H and ^{13}C NMR spectroscopy. In all the cases of prepared diastereomeric mixtures, spectroscopy showed double signals corresponding to a mixture of two diastereoisomers in a 1:1 ratio. The separation into optically pure isomers was performed by means of column chromatography on silica gel with the appropriate mobile phase. This method enabled the isolation of the individual optically pure isomers whose survey, together with the indicated absolute configurations, is presented in Chart 1.

The relative configuration at the imidazolidin-4-one ring of compound **1a** was determined on the basis of X-ray single-crystal analysis. Figure 1 shows the *R* configuration at the 2-position with respect to the known *S* configuration at the 5-position. Hence, diastereomer **1b** must have the *S* configuration at the 2-position.

Compound **1c** had negative optical rotation, but its absolute value was identical with that of compound **1a**. Also, the NMR spectra of the two compounds were identical, which confirmed the fact that they were mutual enantiomers; the configuration of compound **1c** is therefore 2*S*,5*R*. Compound **1d** is a diastereoisomer of compounds **1a,c** and an enantiomer of compound **1b**; hence, the configuration of compound **1d** is 2*R*,5*R*. In the case of compounds **2a** and **3a,** the relative configuration was determined on the basis of X-ray single-crystal analysis of the corresponding Cu(II) complexes **5a**−**7a**. These complexes were prepared by the reaction of ligands **1a**−**3a** with Cu(II) acetate in methanol at room temperature (Scheme 3).

With regard to the known *S* configuration at the 5-position of both complexes **6a** and **7a**, Figure 2 shows the *R* configurations at the 2-position of the imidazolidin-4-one ring. This means that the

Scheme 2. Synthesis of Imidazolidin-4-ones 1−4



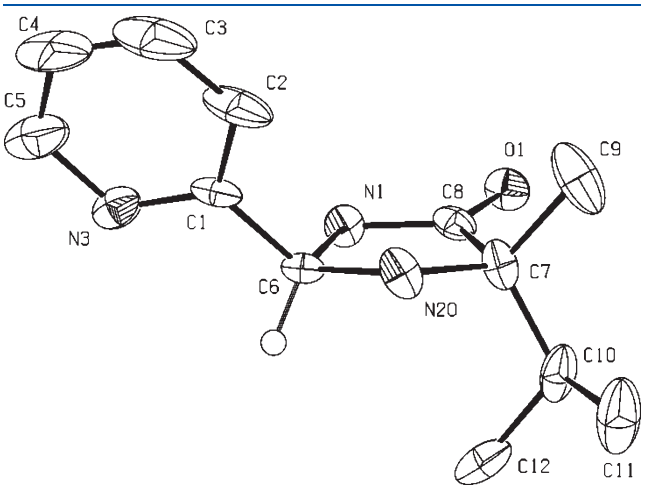
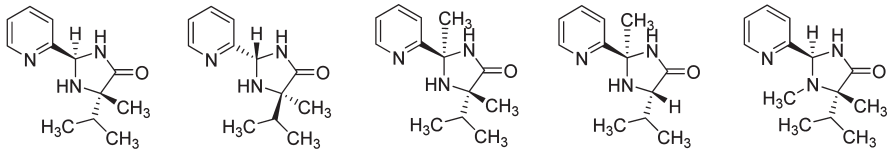
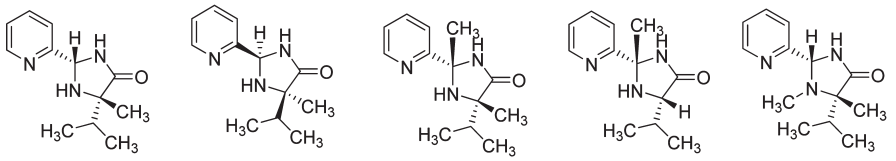


Figure 1. ORTEP drawing of the molecular structure of ligand **1a** at the 50% probability level. Hydrogen atoms are omitted, except for one hydrogen atom at the C-2 position of the imidazolidin-4-one ring for clarity.

Chart 1. Survey of Prepared Optically Pure Substituted Imidazolidin-4-ones 1a−d, 2a,b, 3a,b, and 4a,b with Their Respective Absolute Configurations





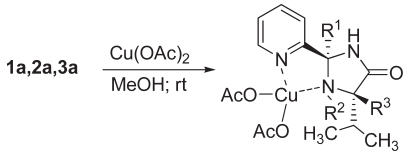
dx.doi.org/10.1021/jo200703j |*J. Org. Chem.* 2011, 76, 4787–4793

corresponding diastereomeric compounds **2b** and **3b** must have the *S* configuration at the 2-position.

In the case of compounds **1b** and **4a,b**, the absolute configuration at the stereogenic centers, i.e. the 2- and 5-carbon atoms, was determined by means of a 1D NOESY pulse sequence.[7] In all cases, separate selective excitation concerned the proton at the 2-carbon atom and the protons of the 5-methyl group. Observed NOE interactions are presented in Figure 3.

The next part of this work consisted of testing the nitroaldol (Henry) reaction of benzaldehyde, substituted benzaldehydes, cyclohexanecarbaldehyde, pentanal, and 2,2-dimethylpropanal with nitromethane, giving the corresponding substituted 2-nitroalkanols (Tables 1 and 2). The reaction was catalyzed by the complexes of Cu(II) acetate with the above-mentioned optically pure ligands **1a**−**d**; **2a,b**; **3a,b** and **4a,b** prepared *in situ*. Table 1 reports the values of enantioselectivity and chemical yields attained with the individual ligands; the yields were determined by means of ^{1}H NMR of the crude product, and the yields of the isolated product are given in brackets.[8] In the case of ligands **1a** and **1c** (entries 1 and 3), the attained chemical yields and enantioselective excess values were virtually the same for the corresponding 1-phenyl-2-nitroethanols with opposite configurations (>97% and 92% ee, and >97% and −91% ee, respectively). This finding agrees with the fact that ligands **1a** and **1c** are enantiomers. In the case of enantiomers **1b** and **1d** (entries 2 and 4), the results were mutually comparable but the enantioselective excess values were markedly lower (−25% ee and 27% ee, respectively) than those obtained with ligands **1a** and **1c**. The same conclusions also follow from the comparisons of ligands **2a** with **2b** (entries 5 and 6) and **3a** with **3b** (entries 7 and 8).

Scheme 3. Preparation of Complexes 5a−7a



5a: R^1= H; R^2= H; R^3= CH_3;
6a: R^1= CH_3; R^2= H; R^3= CH_3;
7a: R^1= CH_3; R^2= H; R^3= H

The measurement results presented in Table 1 show that the Cu(II) complexes derived from the ligands having the anti

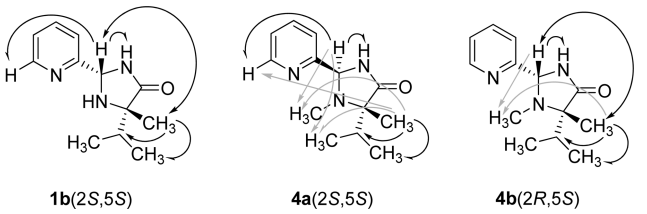
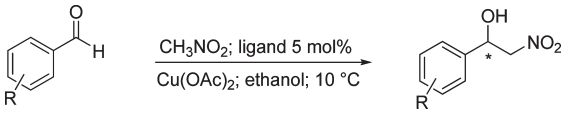


Figure 3. 1D NOESY experiments with compounds **1b** and **4a,b**.

Table 1. Screening of Ligands for the Asymmetric Henry Reaction



entry	catalyst	R	time (h)	conversion[a] (%)	ee[b](%)
1	**1a**	H	36	>97 (68)	92
2	**1b**	H	48	85 (55)	−25
3	**1c**	H	36	>97 (70)	−91
4	**1d**	H	48	84 (52)	27
5	**2a**	H	36	>97 (63)	89
6	**2b**	H	48	80 (49)	−23
7	**3a**	H	36	>97 (61)	62
8	**3b**	H	48	90 (55)	−63
9	**4a**	H	48	78 (42)	15
10	**4b**	H	48	0 (0)	
11	**1a**	2-OCH_3	30	>97 (68)	92
12	**2a**	2-OCH_3	30	>97 (65)	89
13	**3a**	2-OCH_3	30	>97 (70)	63
14	**1a**	4-NO_2	24	>97 (89)	90
15	**2a**	4-NO_2	24	>97 (90)	88
16	**3a**	4-NO_2	24	>97 (88)	61
17	**3b**	4-NO_2	24	>97 (75)	−44

[a] Values are isolated yields after chromatographic purification. [b] Enantiomeric excess determined by HPLC using Chiralcel OD-H.

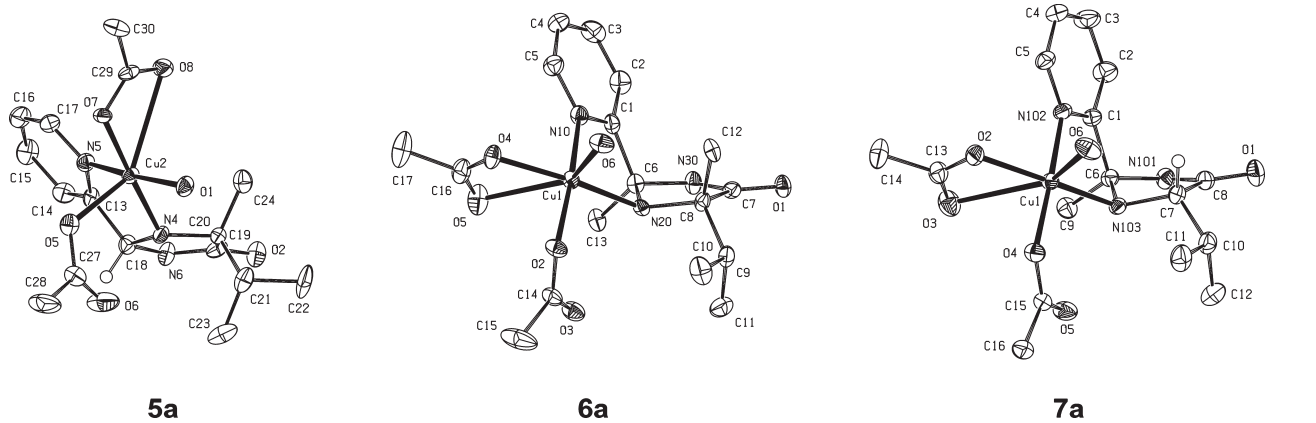
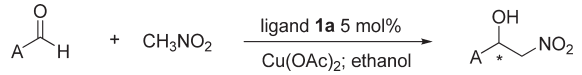


Figure 2. ORTEP drawings of the molecular structures of complexes **5a**−**7a** at the 50% probability level. Hydrogen atoms (except hydrogen atoms at the stereogenic centers) and molecules of solvent are omitted for clarity. Only one molecule of the dimeric form of complex **5a** is shown.

dx.doi.org/10.1021/jo200703j |*J. Org. Chem.* 2011, 76, 4787–4793

Table 2. Henry Reaction of Nitromethane with Various Aldehydes Catalyzed by a Cu(II) Complex of 1a



entry	A	time (h)	temp (°C)	conversion[a] (%)	ee[b] (%)
1	Ph	36	10	>97 (66)	92
2	2-MeOC$_6$H$_4$	30	10	>97 (68)	92
3	4-ClC$_6$H$_4$	36	10	>97 (64)	90
4	4-FC$_6$H$_4$	36	10	>97 (54)	89
5	4-PhC$_6$H$_4$	36	10	>97 (77)	92
6	2-NO$_2$C$_6$H$_4$	24	10	>97 (81)	90
7	4-BrC$_6$H$_4$	36	10	>97 (80)	92
8	4-NCC$_6$H$_4$	30	10	>97 (87)	90
9	4-NO$_2$C$_6$H$_4$	30	10	>97 (89)	90
10	cyclohexyl	72	18	86	92
11	*n*-Bu	72	18	82	87
12	*t*-Bu	72	18	87	96

[a] Values are isolated yields after chromatographic purification. [b] Enantiomeric excess determined by HPLC using Chiralcel OD-H and Chiralpak AD-H columns.

arrangement (**1a,c** and **2a**−**4a**) were distinctly more efficient catalysts than the complexes derived from ligands with the syn arrangement. This finding is in accordance with results published earlier.[2a,e,f,i,9]

Furthermore, the results presented in Table 1 were compared from the standpoint of the effectiveness of the Cu(II) complexes derived from ligands with the anti arrangement differing in the position of the methyl group on the imidazolidin-4-one skeleton. Introduction of the second methyl group into the 2-position of the ligand resulted in negligible lowering of enantioselectivity: see **1a** and **2a** (entries 1 and 5; 92 and 89% ee). On the other hand, ligand **2a** was much more stable than ligand **1a**, since it could not undergo racemization through proton exchange[10] or easy oxidation to substituted 4,5-dihydro-1*H*-imidazol-5-one.[3] Surprisingly, a marked lowering of enantioselectivity was observed in the case of the complex derived from ligand **3a** (entries 7, 13, and 16; 62, 63, and 61% ee), where the 5-methyl group was replaced by a hydrogen substituent, which indicates that this derivative of a coded amino acid (valine) is less selective than the compounds derived from a chiral amino acid with a quaternary α-carbon atom; their general advantage lies in the fact that they do not undergo racemization, in contrast to the amino acids with a hydrogen substituent at the α-carbon atom. However, the most dramatic lowering of enantioselectivity (15% ee) was observed after the introduction of a methyl group on the nitrogen atom at the 1-position: i.e., in the case of the complex derived from ligand **4a** (entry 9). This marked decrease in enantioselectivity was most likely due to worsened coordination properties of the ligand. The same character of influence of the methyl substitution in ligands **1a**−**3a** can also be seen in the second part of Table 1 concerning the nitroaldol reactions of 2-methoxybenzaldehyde (entries 11−13) and 4-nitrobenzaldehyde (entries 14−16) with nitromethane.

Table 2 compares the individual yields of nitroaldol reactions of nitromethane with various substituted benzaldehydes and other aldehydes such as cyclohexanecarbaldehyde, pentanal, and 2,2-dimethylpropanal, catalyzed with a complex of Cu(II) acetate and ligand **1a**.

The results presented in Table 2 show that the enantioselectivity was only minimally affected by substituents on the benzene ring of the substituted benzaldehydes (entries 1−9). The nitroaldol reaction of aliphatic aldehydes was slower (entries 10−12). The highest enantioselective excess was attained in the case of the bulky 2,2-dimethylpropanal (entry 12, 96% ee).

CONCLUSION

Imidazolidin-4-ones are less rigid, due to the sp^3 configuration at the 2-carbon atom, as compared to 4,5-dihydro-1*H*-imidazol-5-ones,[3] which as expected dramatically increased the enantioselectivity of the Henry reaction catalyzed with the corresponding Cu(II) complexes (from 19% ee up to 96% ee). The geometry of the Cu(II) complex formed determined the enantioselectivity of the Henry reaction, which in the case of anti arrangement gave 91−96% ee. In the case of the syn arrangement of the imidazolidin-4-one skeleton, the enantiomeric excess markedly decreased to as low as 25−27% ee. Also, the position of the methyl group on the imidazolidin-4-one skeleton substantially affected the enantioselectivity of the respective complexes. Decreased enantioselectivity was observed in the case of the complex derived from ligand **3a** (61−63% ee), where the 5-methyl group was replaced by a hydrogen substituent. However, the most significant decrease in enantioselectivity (15% ee) resulted after the introduction of a methyl group on the 1-nitrogen atom. The aforementioned findings show that the studied ligands can be relatively easily prepared, are stable, and possess high catalytic potential for the Henry reaction; in the future these ligands may find applications in the organocatalysis of other reactions.[11]

EXPERIMENTAL SECTION

General Procedure for Preparation of Substituted Imidazolidin-4-one Derivatives 1−4. A mixture of 2-acetylpyridine or pyridine-2-carbaldehyde (11 mmol) and 2-aminoamide (10 mmol) with 3 drops of acetic acid was refluxed in 20 mL of the corresponding solvent (methanol for **1** and **4** (8 h), isopropyl alcohol for **3** (48 h), and 1,2-dichlorobenzene for **2** (1 h)). The solvent was evaporated in vacuo until dry, and the residue was treated with 10 mL of a 10% aqueous solution of Na_2CO_3. The suspension was extracted with CH_2Cl_2 (2 × 10 mL). The combined extracts were dried over Na_2SO_4, and after distilling off of solvent under reduced pressure the residue was chromatographed (silica gel; ethyl acetate/CH_2Cl_2/acetone (50/5/45; v/v/v)) to provide the optical pure syn and anti diastereomers.

*(2R,5S)-5-Isopropyl-5-methyl-2-(pyridin-2-yl)imidazolidin-4-one (**1a**).* Yield: 0.45 g (21%). Mp: 106−107 °C (cyclohexane). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.57−8.55 (m, 2H), 7.85 (td, 1H, *J* = 7.6, 1.7 Hz), 7.50 (dt, 1H, *J* = 8.0, 1.0 Hz), 7.37 (ddd, 1H, *J* = 7.6, 4.7, 1.0 Hz), 5.37 (d, 1H, *J* = 6.2 Hz), 3.18 (d, 1H, *J* = 6.2 Hz), 1.82−1.75 (m, 1H), 1.16 (s, 3H), 0.92 (d, 6H, *J* = 6.9 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 178.7, 160.5, 148.9, 137.2, 123.6, 121.6, 71.0, 63.6, 34.6, 23.7, 17.7, 16.4. $[\alpha]_D^{25}$ = +37.0° (*c* 1.00, CH_2Cl_2). Anal. Calcd for $C_{12}H_{17}N_3O$: C, 65.73; H, 7.81; N, 19.16. Found: C, 65.82; H, 7.75; N, 19.05.

*(2S,5S)-5-Isopropyl-5-methyl-2-(pyridin-2-yl)imidazolidin-4-one (**1b**).* Yield: 0.37 g (17%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (ddd, 1H, *J* = 4.8, 1.7, 0.9 Hz), 8.36 (s, 1H), 7.70 (td, 1H, *J* = 7.6, 1.7 Hz), 7.52−7.50 (m, 1H), 7.24 (ddd, 1H, *J* = 7.6, 4.8, 1.0 Hz), 5.62 (s, 1H), 2.72 (br s, 1H), 1.98−1.88 (m, 1H), 1.34 (s, 3H), 0.94 (d, 3H, *J* = 6.9 Hz), 0.88 (d, 3H, *J* = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.4, 158.7, 148.9, 136.8, 123.3, 120.9, 69.6, 64.7, 33.1, 21.6, 17.6, 16.1. $[\alpha]_D^{25}$ = −54.6° (*c* 1.49, CH_2Cl_2). Anal. Calcd for $C_{12}H_{17}N_3O$: C, 65.73; H, 7.81; N, 19.16. Found: C, 65.94, H, 8.00, N, 19.03.

dx.doi.org/10.1021/jo200703j |*J. Org. Chem.* 2011, 76, 4787–4793

*(2S,5R)-5-Isopropyl-5-methyl-2-(pyridine-2-yl)imidazolidine-4-one (**1c**).* Yield: 0.52 g (24%). Mp: 106−107 °C (cyclohexane). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57−8.55 (m, 2H), 7.85 (td, 1H, J = 7.7, 1.8 Hz), 7.50 (dt, 1H, J = 7.9, 1.0 Hz), 7.37 (ddd, 1H, J = 7.6, 4.8, 1.0 Hz), 5.37 (d, 1H, J = 6.7 Hz), 3.18 (d, 1H, J = 6.7 Hz), 1.84−1.73 (m, 1H), 1.16 (s, 3H), 0.92 (d, 6H, J = 6.9 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 178.7, 160.5, 148.9, 137.3, 123.6, 121.7, 71.0, 63.6, 34.7, 23.7, 17.7, 16.4. $[\alpha]_D^{25}$ = −36.7° (c 1.00, CH_2Cl_2). Anal. Calcd for $C_{12}H_{17}N_3O$: C, 65.73; H, 7.81; N, 19.16. Found: C, 65.79; H, 7.88; N, 19.25.

*(2R,5R)-5-Isopropyl-5-methyl-2-(pyridin-2-yl)imidazolidin-4-one (**1d**).* Yield: 0.43 g (20%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52−8.50 (m, 1H), 8.45 (s, 1H), 7.70 (td, 1H, J = 7.6, 1.7 Hz), 7.52−7.50 (m, 1H), 7.24−7.21 (m, 1H), 5.62 (s, 1H), 2.80 (br s, 1H), 1.98−1.88 (m, 1H), 1.34 (s, 3H), 0.94 (d, 3H, J = 6.9 Hz), 0.88 (d, 3H, J = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.4, 158.7, 148.8, 136.7, 123.2, 120.9, 69.5, 64.7, 33.0, 21.6, 17.6, 16.0. $[\alpha]_D^{25}$ = +54.1° (c 1.00, CH_2Cl_2). Anal. Calcd for $C_{12}H_{17}N_3O$: C, 65.73; H, 7.81; N, 19.16. Found: C, 65.91, H, 7.66, N, 18.97.

*(2R,5S)-5-Isopropyl-2,5-dimethyl-2-(pyridin-2-yl)imidazolidin-4-one (**2a**).* Yield: 0.81 g (36%). Mp: 142−144 °C (cyclohexane). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.98 (s, 1H), 8.55 (d, 1H, J = 4.3), 7.85 (td, 1H, J = 7.8, 1.6 Hz), 7.54 (d, 1H, J = 7.8 Hz), 7.32 (ddd, 1H, J = 7.6, 4.7, 1.0 Hz), 3.29 (s, 1H), 1.76−1.69 (m, 1H), 1.50 (s, 3H), 0.91−0.85 (m, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 177.1, 165.3, 148.3, 137.2, 122.5, 118.9, 73.7, 63.9, 33.8, 31.6, 23.5, 17.9, 16.2. $[\alpha]_D^{25}$ = −36.0° (c 1.00, CH_2Cl_2); Anal. Calcd. for $C_{13}H_{19}N_3O$: C, 66.92; H, 8.21; N, 18.01. Found: C, 66.70; H, 8.35; N, 18.23.

*(2S,5S)-5-Isopropyl-2,5-dimethyl-2-(pyridin-2-yl)imidazolidin-4-one (**2b**).* Yield: 0.55 g (24%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (dt, 1H, J = 4.8, 1.3 Hz), 8.14 (br s, 1H), 7.70−7.64 (m, 2H), 7.18−7.16 (m, 1H), 2.51 (s, 1H), 1.83−1.74 (m, 1H), 1.70 (s, 3H), 1.43 (s, 3H), 0.92 (d, 3H, J = 6.9 Hz), 0.62 (d, 3H, J = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.0, 164.1, 148.5, 136.6, 122.2, 118.9, 74.5, 65.4, 34.1, 33.1, 26.8, 24.6, 17.8, 16.3. $[\alpha]_D^{25}$ = −14.8° (c 1.00, CH_2Cl_2). Anal. Calcd for $C_{13}H_{19}N_3O$: C, 66.92; H, 8.21; N, 18.01. Found: C, 67.09; H, 8.40; N, 17.92.

*(2R,5S)-5-Isopropyl-2-methyl-2-(pyridin-2-yl)imidazolidin-4-one (**3a**).* Yield: 0.37 g (17%). Mp: 69−71 °C (cyclohexane). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.91 (s, 1H), 8.55 (ddd, 1H, J = 4.8, 1.7, 0.9 Hz), 7.84 (td, 1H, J = 7.8, 1.7 Hz), 7.57 (dt, 1H, J = 7.8, 0.9 Hz), 7.32 (ddd, 1H, J = 7.6, 4.8, 1.0 Hz), 3.52 (d, 1H, J = 8.0 Hz), 3.23 (dd, 1H, J = 7.9, 3.6 Hz), 1.93−1.86 (m, 1H), 1.52 (s, 3H), 0.94 (d, 3H, J = 6.9 Hz), 0.88 (d, 3H, J = 6.8 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.7, 164.2, 148.5, 137.2, 122.7, 119.1, 74.7, 62.6, 30.2, 29.3, 19.3, 16.8. $[\alpha]_D^{25}$ = −3.4° (c 1.00, CH_2Cl_2). Anal. Calcd for $C_{12}H_{17}N_3O$: C, 65.73; H, 7.81; N, 19.16. Found: C, 65.75; H, 7.90; N, 19.15.

*(2S,5S)-5-Isopropyl-2-methyl-2-(pyridin-2-yl)imidazolidin-4-one (**3b**).* Yield: 0.50 g (23%). Mp: 68−70 °C (cyclohexane). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.71 (s, 1H), 8.52 (br d, 1H, J = 4.2 Hz), 7.82 (br t, 1H, J = 7.2 Hz), 7.67 (br d, 1H, J = 7.8 Hz), 7.29 (br t, 1H, J = 5.5 Hz), 3.53 (br s, 1H), 3.45 (br s, 1H), 1.82−1.77 (m, 1H), 1.59 (s, 3H), 0.89 (d, 3H, J = 6.9 Hz), 0.68 (d, 3H, J = 6.9 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.7, 164.4, 148.1, 136.8, 122.4, 119.6, 75.0, 62.9, 29.7, 29.4, 19.4, 17.3. $[\alpha]_D^{25}$ = −21.6° (c 1.00, CH_2Cl_2). Anal. Calcd for $C_{12}H_{17}N_3O$: C, 65.73; H, 7.81; N, 19.16. Found: C, 65.64; H, 7.96; N, 19.32.

*(2S,5S)-5-Isopropyl-1,5-dimethyl-2-(pyridin-2-yl)imidazolidin-4-one (**4a**).* Yield: 0.72 g (31%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (ddd, 1H, J = 4.9, 1.7, 0.9 Hz), 7.92 (s, 1H), 4.64 (td, 1H, J = 7.7, 1.6 Hz), 7.46 (dt, 1H, J = 7.8, 0.9 Hz), 7.12 (ddd, 1H, J = 7.6, 4.9, 1.0 Hz), 5.16 (s, 1H), 2.32 (s, 3H), 1.98−1.90 (m, 1H), 1.25(s, 3H), 0.98 (d, 3H, J = 6.9 Hz), 0.93 (d, 3H, J = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 159.7, 148.0, 137.1, 123.3, 120.7, 77.6, 65.7, 34.2, 29.7, 22.6, 18.2, 18.0. $[\alpha]_D^{25}$ = +29.4° (c 3.88, CH_2Cl_2). Anal. Calcd for $C_{13}H_{19}N_3O$: C, 66.92; H, 8.21; N, 18.01. Found: C, 66.86; H, 8.11; N, 17.96.

*(2R,5S)-5-Isopropyl-1,5-dimethyl-2-(pyridin-2-yl)imidazolidin-4-one (**4b**).* Yield: 0.61 g (26%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (ddd, 1H, J = 4.9, 1.7, 0.9 Hz), 7.77 (td, 1H, J = 7.6, 1.7 Hz), 7.69 (dt, 1H, J = 7.7, 1.0 Hz), 7.27 (ddd, 1H, J = 7.5, 4.9, 1.1 Hz), 7.00 (s, 1H), 4.88 (s, 1H), 2.28 (s, 3H), 1.95−1.88 (m, 1H), 1.28 (s, 3H), 1.07−1.05 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.1, 159.5, 148.6, 137.4, 123.7, 121.2, 66.5, 34.3, 33.0, 17.8, 17.3, 14.9. $[\alpha]_D^{25}$ = −54.3° (c 1.00, CH_2Cl_2). Anal. Calcd for $C_{13}H_{19}N_3O$: C, 66.92; H, 8.21; N, 18.01. Found: C, 67.25; H, 8.37; N, 18.03.

General Procedure for Preparation of Complexes 5a−7a. A mixture of one of the ligands **1a**−**3a** (0.55 mmol) and $Cu(OAc)_2$ (91 mg; 0.50 mmol) in 10 mL of methanol was stirred at room temperature for 1 h. The resulting solution was evaporated until dry, and the residue was mixed with ether (10 mL). The suspension was filtered off, washed with another portion of ether (20 mL), and dried in a desiccator.

*Complex **5a**.* Yield: 182 mg (91%). Mp: 157−161 °C. $[\alpha]_D^{25}$ = −301.3°, $[\alpha]_{546}^{25}$ = −278.2° (c 0.078, CH_3OH). Anal. Calcd for $C_{30}H_{42}N_6O_8Cu_2$: C, 48.58; H, 5.71; N, 11.33. Found: C, 48.69; H, 6.02; N, 11.14.

*Complex **6a**.* Yield: 192 mg (93%). Mp: 151−155 °C. $[\alpha]_D^{25}$ = −551.2°, $[\alpha]_{546}^{25}$ = −539.5° (c 0.086, CH_3OH). Anal. Calcd for $C_{17}H_{25}N_3O_5Cu$: C, 49.21; H, 6.07; N, 10.13. Found: C, 48.99; H, 6.25; N, 9.88.

*Complex **7a**.* Yield: 179 mg (90%). Mp: 144−148 °C. $[\alpha]_{578}^{25}$ = −76.25°, $[\alpha]_{546}^{25}$ −31.25° (c 0.080, CH_3OH). Anal. Calcd for $C_{16}H_{23}N_3O_5Cu$: C, 47.93; H, 5.78; N, 10.48. Found: C, 47.56; H, 6.01; N, 10.12.

General Procedure for Asymmetric Henry Reaction. One of the ligands **1**−**4** (0.055 mmol) and $Cu(OAc)_2$ (9.1 mg, 0.05 mmol) were stirred for 1 h in a mixture of EtOH (1.5 mL) and CH_3NO_2 (0.54 mL, 10 mmol) at room temperature to generate the catalyst. The solution was cooled to the appropriate temperature, and then the aldehyde (1 mmol) was added. The mixture was stirred for the time indicated in Table 1 or 2. The solvents were removed under reduced pressure, and the crude product was purified by column or flash chromatography (AcOEt/hexane; 1/4 (v/v)).

*(R)-1-Phenyl-2-nitroethanol (**A1**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42−7.37 (m, 5H), 5.47 (dt, 1H, J = 9.5, 3.3 Hz), 4.61 (dd, 1H, J = 13.3, 9.5 Hz), 4.52 (dd, 1H, J = 13.3, 3.1 Hz), 2.80 (d, 1H, J = 3.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0, 129.0, 128.9, 125.9, 81.2, 71.0. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90/10 hexanes/*i*-PrOH, 0.8 mL/min, 220 nm): major enantiomer t_r = 17.95 min, minor enantiomer t_r = 22.52; 92% ee. $[\alpha]_D^{25}$ = −39.1° (c 0.93, CH_2Cl_2).

*(R)-1-(2-Methoxyphenyl)-2-nitroethanol (**A2**).* Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (dd, 1H, J = 7.5, 1.6 Hz), 7.32 (td, 1H, J = 7.5, 1.7 Hz), 7.00 (td, 1H, J = 7.5, 1.0 Hz), 6.91 (dd, 1H, J = 8.2, 0.9 Hz), 5.61 (ddd, 1H, J = 9.2, 6.2, 3.2 Hz), 4.63 (dd, J = 13.0, 3.2 Hz), 4.55 (dd, J = 13.0, 9.2 Hz), 3.88 (s, 3H), 3.24 (d, 1H, J = 6.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9, 129.7, 127.2, 125.9, 121.1, 110.5, 79.8, 67.8, 55.4. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90/10 hexanes/*i*-PrOH, 0.8 mL/min, 220 nm): major enantiomer t_r = 14.92 min, minor enantiomer t_r = 17.13; 92% ee. $[\alpha]_D^{25}$ = −46.7° (c 1.22, CH_2Cl_2).

*(R)-1-(4-Fluorophenyl)-2-nitroethanol (**A3**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41−7.36 (m, 2H), 7.12−7.07 (m, 2H), 5.45 (dt, 1H, J = 9.4, 3.0 Hz), 4.58 (dd, 1H, J = 13.3, 9.5 Hz), 4.49 (dd, J = 13.3, 3.1 Hz), 2.97 (d, 1H, J = 3.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9 (d, J = 248.0 Hz), 133.8 (d, J = 3.0 Hz), 127.8 (d, J = 8.1 Hz), 116.0 (d, J = 22.0 Hz), 81.1, 70.3. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90/10 hexanes/*i*-PrOH, 0.8 mL/min, 220 nm): major enantiomer t_r = 15.52 min, minor enantiomer t_r = 18.45; 89% ee. $[\alpha]_D^{25}$ = −41.2° (c 1.11, CH_2Cl_2).

*(R)-1-(4-Chlorophenyl)-2-nitroethanol (**A4**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.30 (m, 4H), 5.40 (dt, 1H, J = 9.1, 3.5 Hz), 4.58−4.52 (m, 1H), 4.47 (dd, J = 13.3, 3.2 Hz), 3.29 (d, 1H, J = 3.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.5, 134.6, 129.1, 127.3, 80.9, 70.2. The enantiomeric excess was determined by HPLC with a Chiralcel

OD-H column (90/10 hexanes/*i*-PrOH, 0.8 mL/min, 220 nm): major enantiomer t_r = 18.45 min, minor enantiomer t_r = 23.15; 90% ee. $[\alpha]_D^{25} = -47.0°$ (*c* 1.30, CH_2Cl_2).

*(R)-1-(4-Bromophenyl)-2-nitroethanol (**A5**).* Colorless crystalline solid. Mp: 55−58 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56−7.54 (m, 2H), 7.31−7.28 (m, 2H), 5.45 (dt, 1H, *J* = 9.5, 3.5 Hz), 5.57 (dd, *J* = 13.4, 9.4 Hz), 4.49 (dd, *J* = 13.5, 3.2 Hz), 2.85 (d, 1H, *J* = 3.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.0, 131.9, 127.5, 122.7, 80.7, 70.2. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90/10 hexanes/*i*-PrOH, 0.8 mL/min, 220 nm): major enantiomer t_r = 17.20 min, minor enantiomer t_r = 23.99; 92% ee. $[\alpha]_D^{25} = -34.6°$ (*c* 1.00, CH_2Cl_2).

*(R)-1-(4-Cyanophenyl)-2-nitroethanol (**A6**).* Colorless crystalline solid. Mp: 101−104 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27−7.70 (m, 2H), 7.58−7.55 (m, 2H), 5.57−5.53 (m, 1H), 4.62−4.52 (m, 2H), 3.18 (d, 1H, *J* = 4.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.1, 132.8, 126.7, 118.2, 112.7, 80.6, 70.1. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90/10 hexanes/*i*-PrOH, 0.8 mL/min, 220 nm): major enantiomer t_r = 38.02 min, minor enantiomer t_r = 44.13; 90% ee. $[\alpha]_D^{25} = -43.9°$ (*c* 1.00, CH_2Cl_2).

*(R)-1-(4-Nitrophenyl)-2-nitroethanol (**A7**).* Yellow crystalline solid. Mp: 80−82 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29−8.26 (m, 2H), 7.65−7.62 (m, 2H), 5.64−5.60 (m, 1H), 4.64−4.55 (m, 2H), 3.17 (d, 1H, *J* = 3.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.1, 144.9, 126.9, 124.2, 80.6, 69.9. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90/10 hexanes/*i*-PrOH, 0.8 mL/min, 220 nm): major enantiomer t_r = 36.53 min, minor enantiomer t_r = 46.55; 90% ee. $[\alpha]_D^{25} = -38.3°$ (*c* 1.04, CH_2Cl_2).

*(R)-1-(2-Nitrophenyl)-2-nitroethanol (**A8**).* Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (dd, 1H, *J* = 8.2, 1.2 Hz), 7.94 (dd, 1H, *J* = 8.0, 1.1 Hz), 7.75 (td, 1H, *J* = 7.6, 1.2 Hz), 7.57−7.53 (m, 1H), 6.01 (dd, 1H, *J* = 9.1, 2.2 Hz), 4.84 (dd, *J* = 13.5, 2.3 Hz), 4.55 (dd, *J* = 13.5, 9.2 Hz), 3.58 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.9, 134.4, 134.1, 129.6, 128.6, 124.8, 80.0, 66.7. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90/10 hexanes/*i*-PrOH, 0.8 mL/min, 220 nm): major enantiomer t_r = 18.80 min, minor enantiomer t_r = 21.31; 90% ee. $[\alpha]_D^{25} = -215.4$ (*c* 1.09, CH_2Cl_2).

*(R)-1-(4-Phenylphenyl)-2-nitroethanol (**A9**).* Colorless crystalline solid. Mp: 126−128 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63−7.61 (m, 2H), 7.58−7.56 (m, 2H), 7.47−7.43 (m, 4H), 7.39−7.35 (m, 1H), 5.49 (dt, 1H, *J* = 9.5, 3.2 Hz), 4.63 (dd, 1H, *J* = 13.3, 9.5 Hz), 4.54 (dd, 1H, *J* = 13.3, 3.2 Hz), 2.89 (d, 1H, *J* = 3.7, Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.9, 140.2, 136.9, 128.6, 127.7, 127.6, 127.1, 126.4, 81.1, 70.7. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90/10 hexanes/*i*-PrOH, 0.8 mL/min, 220 nm): major enantiomer t_r = 30.69 min, minor enantiomer t_r = 37.43; 92% ee. $[\alpha]_D^{25} = -39.7°$ (*c* 1.00, CH_2Cl_2).

*(R)-1-Nitrohexan-2-ol (**A10**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.44 (dd, 1H, *J* = 12.8, 2.7 Hz), 4.38 (dd, 1H, *J* = 12.8, 8.2 Hz), 4.35−4.27 (m, 1H), 2.56 (d, 1H, *J* = 4.6 Hz), 1.60−1.45 (m, 3H), 1.42−1.34 (m, 3H), 0.94−0.91 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 80.6, 68.6, 33.4, 27.3, 22.4, 13.7. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (97/3 hexanes/*i*-PrOH, 0.8 mL/min, 215 nm): major enantiomer t_r = 24.13 min, minor enantiomer t_r = 32.03; 87% ee. $[\alpha]_D^{25} = -8.4°$ (*c* 1.31, CH_2Cl_2).

*(R)-3,3-Dimethyl-1-nitrobutan-2-ol (**A11**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.53 (dd, 1H, *J* = 13.0, 2.1 Hz), 4.37 (dd, 1H, *J* = 13.0, 10.2 Hz), 4.04 (ddd, 1H, *J* = 10.2, 4.7, 2.1 Hz), 2.48−2.43 (m, 1H), 0.98 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 78.2, 76.2, 34.3, 25.6. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (97/3 hexanes/*i*-PrOH, 0.8 mL/min, 215 nm): major enantiomer t_r = 14.65 min, minor enantiomer t_r = 17.09; 96% ee. $[\alpha]_D^{25} = -37.2°$ (*c* 0.95, CH_2Cl_2).

*(R)-1-Cyclohexyl-2-nitroethanol (**A12**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.48 (dd, 1H, *J* = 13.2, 3.0 Hz), 4.42 (dd, 1H, *J* = 13.0, 9.0 Hz), 4.12−4.06 (m, 1H), 2.40 (d, 1H, *J* = 4.4 Hz), 1.86−1.76 (m, 3H), 1.71−1.64 (m, 2H), 1.52−1.43 (m, 1H), 1.32−1.05 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 79.3, 72.8, 41.4, 28.8, 27.9, 26.1, 25.9, 25.7. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (97/3 hexanes/*i*-PrOH, 0.8 mL/min, 215 nm): major enantiomer t_r = 26.57 min, minor enantiomer t_r = 28.83; 92% ee. $[\alpha]_D^{25} = -16.4°$ (*c* 1.07, CH_2Cl_2).

■ ASSOCIATED CONTENT

Supporting Information. Figures giving ^{1}H and ^{13}C NMR spectra of all new compounds and ^{1}H NMR 1D NOESY experiments (for **1b** and **4a**,**b**), a table giving X-ray experimental information, and CIF files giving crystallographic data for compounds **1a** and **5a**−**7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

We acknowledge financial support from Project No. MSM 002 162 7501.

■ DEDICATION

Dedicated to Professor Pavel Kočovský on the occasion of his 60th birthday.

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