DOI: 10.1002/ejoc.201100579

Efficient Asymmetric Copper(I)-Catalyzed Henry Reaction Using Chiral *N*-Alkyl-C_1-tetrahydro-1,1′-bisisoquinolines

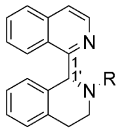
Yao Qiong ji,[a] Gao Qi,[a] and Zaher M. A. Judeh*[a]

Keywords: Asymmetric synthesis / C–C coupling / Copper / Diastereoselectivity / Nitroaldol reactions / Ligand design

A series of closely related chiral *N*-alkyl-C_1-tetrahydro-1,1′-bisisoquinoline ligands only differing in the steric bulk of the alkyl groups has been examined in the asymmetric Henry reaction. A complex derived from the (*R*)-*N*-methyl-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline and copper(I) chloride proved to be a very efficient catalyst system that can promote the reaction of a wide range of aromatic and aliphatic aldehydes to give the expected nitroalcohol products in high yields (up to 99 %), excellent enantioselectivities (up to 94 % *ee*), and moderate diastereoselectivities (up to 1.6:1). This catalyst system is very general, requires no additives for activation, and is also simple in operation because no special precautions are taken to exclude moisture or air from the reaction flask.

Introduction

We have been interested in the synthesis, chemistry, and catalytic application of 1,1′-bisisoquinolines for several years.[1] Recently, we disclosed a straightforward synthesis of chiral C_1-tetrahydro-1,1′-bisisoquinoline (*R*)-**1a** (Figure 1) and its derivatives with the intention of using them as chiral ligands for various asymmetric reactions.[2,3] Based on our DFT calculations[4] and X-ray crystallographic analyses[2,3] we found that the two isoquinoline units are structurally different: the ring containing the sp^2-*N* atom was found to be flat due to its aromatic nature, whereas the ring containing the sp^3-*N* atom was found to predominantly assume a distorted boat conformation. We also found that the size of the dihedral angle N_1–C_1–C_1'–N_1' (Figure 1) is a function of the type (alkyl, acyl, sulfonyl) and the size (bulkiness) of the substituent on the sp^3-*N*.[2–4] This discovery allows us to tune the bite-angle to a great extent. This angle is understood to significantly affect the level of selectivity and reactivity. Because our major aim is to explore the application of 1,1′-bisisoquinolines in various asymmetric reactions, it was logical to methodically examine the effect of substituents at the sp^3-*N* of (*R*)-**1a**.[2] We hypothesized that elucidating the effect of carefully selected alkyl substituents should facilitate the design of very effective ligands of type (*R*)-**1a**.



(*R*)-**1a:** R = H
(*R*)-**1b:** R = CH_3
(*R*)-**1c:** R = CH_2CH_3
(*R*)-**1d:** R = $CH(CH_3)_2$
(*R*)-**1e:** R = $CH_2C_6H_5$
(*R*)-**1f:** R = $CH_2C_6H_3$-2-OH-5-NO_2

Figure 1. C_1-Tetrahydro-1,1′-bisisoquinoline (*R*)-**1a** and its chiral *N*-alkyl derivatives (*R*)-**1b**–**f**.

The Henry reaction is a powerful C–C bond-forming protocol in organic synthesis. Its enantioselective version, which provides enantioenriched nitroalcohol adducts, was discovered by Shibasaki in 1992 using chiral heterobimetallic catalysts.[5] The adducts can be transformed into many valuable chiral building blocks such as nitro alkenes, amino alcohols, amino acids, etc.[6] Various types of metal-catalytic and organocatalytic systems have been developed for this reaction. Most catalysts that have been developed use copper[7] because of its excellent chelating properties to bi- and poly-dentate ligands. Nevertheless, other metals such as Zn,[8] Co,[9] Cr,[10] Pd,[11] and rare metals[5,11,12] have also been examined with variable success. The majority of ligands developed, for example, bisoxazolines,[13] bisoxazolidines,[14] diamines,[15] (–)-sparteine,[16] sulfonyldiamines,[7c] sulfonimidamides,[7a] aminopyridines,[17] tetrahydrosalens,[18] and *N*,*N*′-dioxides,[7b] are nitrogen-based with a variety of structural features that modulate their reactivity and enantioselectivity. Limitations such as ligand complexity, low substrate scope, high catalyst loading, and requirement for strict reaction conditions mandate the development of more robust and efficient ligands.[15e]

Herein, we systematically explore the modular effects of various alkyl substituents attached to the sp^3-*N* of (*R*)-**1a** on the reactivity and selectivity in the enantioselective Henry reaction, with the ultimate aim of obtaining very effective ligands that can be applied to a range of asymmetric reactions.

[a] School of Chemical and Biomedical Engineering,
Nanyang Technological University,
62 Nanyang Drive, N1.2 B1-14,
Singapore 637459, Singapore
Fax: +65-67947553
E-mail: zaher@ntu.edu.sg

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201100579.

WILEY ONLINE LIBRARY
© 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

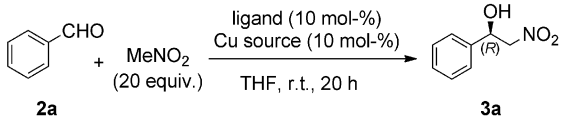
Results and Discussion

We envisioned that by introducing different alkyl substituents at the sp^3-*N* of (*R*)-**1a** (Figure 1), the steric hindrance at the chelating centers can easily be modulated and the effect of steric crowding can be delineated. Such insights are extremely important in the design of an optimum catalyst. Therefore, selected *N*-alkyl derivatives (*R*)-**1b**–**f** were synthesized by reacting (*R*)-**1a** with the corresponding haloalkanes (see the Supporting Information).[2,3]

Initial studies were carried out to screen the selectivity and reactivity of ligands (*R*)-**1a**–**f** (Figure 1) using a range of copper sources under standard enantioselective Henry reaction conditions. In a typical experiment, the ligand (10 mol-%) and copper source (10 mol-%) were stirred in tetrahydrofuran (THF) (1.5 mL) for 1 h followed by dropwise sequential addition of nitromethane (20 equiv.) and benzaldehyde (0.2 mmol), and the reaction was allowed to proceed for 20 h at room temperature. No special precautions were taken to exclude air or moisture. The results are summarized in Table 1. Initially, CuBr was chosen as the copper source for screening. The parent ligand (*R*)-**1a**, bearing no substituent, gave product **3a** in 94% yield and 68%*ee* (Table 1, Entry 1). Ligand (*R*)-**1b**, bearing the smallest *N*-alkyl (*N*-CH_3) substituent, proved to be the most efficient, giving product **3a** in 98% yield and 83%*ee* (Table 1, Entry 2). Ligands (*R*)-**1c**–**e**, bearing larger *N*-alkyl substituents, afforded the product in comparable yields to (*R*)-**1b** but with lower *ee* (Table 1, Entries 3–5). Surprisingly, ligand (*R*)-**1f** was found to be completely inactive (Table 1, Entry 6). Presumably, complexation between the copper and the nitrogen atoms of (*R*)-**1f** was not sufficient for effective catalysis. From the results summarized in Table 1, it is evident that the steric bulk of the *N*-alkyl group contributes significantly to the selectivity and reactivity in the Henry reaction. Subsequently, screening of other copper sources was accomplished using the most efficient ligand (*R*)-**1b** (Table 1, Entries 7–11). The results obtained revealed that Cu^I sources are superior to Cu^{II} sources in terms of both yield and enantioselectivity (Table 1, Entries 2, 7, 8 vs. 9–11). Both, CuCl and CuI gave similar results to those with CuBr (Table 1, Entries 7 and 8 vs. Entry 2), indicating that the counter anion had no prominent effect. Among the Cu^{II} salts tested, $Cu(OAc)_2$ gave the highest enantioselectivity (65%*ee*). Considering that CuCl is cheaper and less toxic, this metal salt was chosen as the copper source for further studies.

Further optimization of the reaction conditions were conducted by examining the effect of solvents using the (*R*)-**1b**/CuCl catalyst system (Table 2). The solvents examined showed similarly good enantioselectivities, affording **3a** in 83–86%*ee*. However, *i*PrOH, THF, and $(iPr)_2O$ gave **3a** in much higher yields (89, 99, and 90%, respectively) compared with $CHCl_3$ and CH_3CN (65 and 12%, respectively; Table 2, Entries 1, 4, 5 vs. 2 and 3). Considering the yield and *ee*, we selected $(iPr)_2O$ for further optimization. We believed that conducting the reaction at a lower temperature would result in the reaction proceeding at an acceptable rate with increased enantioselectivity. Indeed, when the reaction was conducted at 0 °C, the enantioselectivity of **3a** increased from 86 to 91%*ee* while the yield decreased from 90 to 65% (Table 2, Entry 5 vs. 6). In an attempt to maximize both the yield and *ee* of **3a**, a range of (*R*)-**1b**/CuCl ratios and loadings were examined at 0 °C. Changing the (*R*)-**1b**/CuCl ratio from 1:1 to 1:2 or 2:1 resulted in a slight decrease in the enantioselectivity and a remarkable decrease in the yield of **3a** (Table 2, Entries 7 and 8). Using a 1:1 ratio of (*R*)-**1b**/CuCl, attempts to increase the catalyst loading from 10 to 20 mol-% provided **3a** in higher yield (90%) but lower enantioselectivity (86%) (Table 2, Entry 6 vs. 9)

Table 1. Screening of ligands (*R*)-**1a**–**f** and copper sources for the asymmetric Henry reaction.

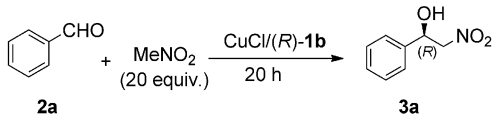


2a **3a**

Entry	Ligand	Cu salt	Yield [%][a]	*ee* [%][b]
1	(*R*)-**1a**	CuBr	94	68
2	(*R*)-**1b**	CuBr	98	83
3	(*R*)-**1c**	CuBr	98	65
4	(*R*)-**1d**	CuBr	95	67
5	(*R*)-**1e**	CuBr	85	69
6	(*R*)-**1f**	CuBr	0	–
7	(*R*)-**1b**	CuCl	99	83
8	(*R*)-**1b**	CuI	99	70
9	(*R*)-**1b**	$CuCl_2$	40	31
10	(*R*)-**1b**	$Cu(OAc)_2$	70	65
11	(*R*)-**1b**	$Cu(OTf)_2$	75	3

[a] Yield of isolated product. [b] Enantiomeric excess values were determined by HPLC using a Chiralcel OD-H column. The absolute configuration (*R*) was determined by comparison with the literature data.[13a]

Table 2. Optimization of the reaction conditions using (*R*)-**1b**/CuCl for the asymmetric Henry reaction.



2a **3a**

Entry	Solvent	*T* [°C]	(*R*)-**1b** [mol-%]	CuCl [mol-%]	Yield [%][a]	*ee* [%][b]
1[c]	*i*PrOH	r.t.	10	10	89	85
2	$CHCl_3$	r.t.	10	10	65	83
3	CH_3CN	r.t.	10	10	12	86
4	THF	r.t.	10	10	99	83
5	$(iPr)_2O$	r.t.	10	10	90	86
6	$(iPr)_2O$	0	10	10	65	91
7[c]	$(iPr)_2O$	0	10	5	35	82
8[c]	$(iPr)_2O$	0	10	20	18	63
9	$(iPr)_2O$	0	20	20	90	86
10[c]	$(iPr)_2O$	0	5	5	20	80

[a] Yield of isolated product. [b] Enantiomeric excess values were determined by HPLC using a Chiralcel OD-H column. The absolute configuration (*R*) was determined by comparison with the literature data.[13a] [c] Reacted for 48 h.

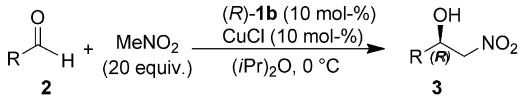
 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

whereas attempts to decrease the catalyst loading from 10 to 5 mol-% afforded **3a** in lower *ee* (80%) and unreasonably low yield (20%), even after extending the reaction time for 48 h (Table 2, Entry 10). Overall, the most effective conditions were found to be 10 mol-% (*R*)-**1b**/CuCl in a ratio of 1:1 at 0 °C in $(i\text{Pr})_2\text{O}$, which gave **3a** with the highest *ee* (91%) and acceptable yield (65%) (Table 2, Entry 6). It is worth noting that the reaction using ligand (*R*)-**1b** (20 mol-%) and Cu(OAc)_2 (10 mol-%) gave **3a** in 80% yield and 70%*ee*. When (*R*)-**1b** was used to catalyze the reaction without CuCl, racemic **3a** was obtained in only 10% yield.

The substrate scope of the reaction was then studied under the optimized conditions described in Table 2, Entry 6. Pleasingly, the reaction was found to be very general and applicable to a variety of aromatic, heteroaromatic, and aliphatic aldehydes (Table 3). Aromatic aldehydes gave the expected products **3a**–**i** in moderate to excellent yields and excellent enantioselectivities, with *ee* values above 86%. The position and electronic nature of the substituent on the aromatic ring seems to have no great bearing on the yields and enantioselectivities of the products (Table 3, Entries 1–9). Most outstanding, the reaction proceeded smoothly with straight chain (Table 3, Entries 10–14), branched (Table 3, Entries 15 and 16), and cyclic aldehydes (Table 3, Entry 17) to give products **3j**–**q** in excellent enantioselectivities with *ee* values ranging from 90–94% and with very good to excellent yields (70–99%). The yields for aliphatic aldehydes are generally better than those for the aromatic aldehydes due to their inherently higher reactivities, and reactions with the former substrates could therefore be accomplished in a shorter time (Table 3, Entries 10–17 vs. 1–9). Moreover, heteroaromatic 2-furaldehyde and conjugated *trans*-cinnamaldehyde gave products **3r** and **3s**, respectively, in excellent yields and respectable enantioselectivities (Table 3, Entries 18 and 19).

Encouraged by the excellent results obtained from addition of nitromethane to various aldehydes (Table 3), we decided to examine the catalytic activity of (*R*)-**1b**/CuCl in the more challenging and less explored diastereoselective Henry reaction. Thus, nitroethane was treated with several aromatic and aliphatic aldehydes under our optimized conditions (Table 2, Entry 6) to give nitroaldol adducts **4a**–**g** (Table 4) in moderate diastereoselectivities (up to 1.6:1, *anti*/*syn*), and the *anti* product was obtained predominantly with *ee* values up to 90%.

Table 3. Enantioselective Henry reaction of various aldehydes with nitromethane catalyzed by (*R*)-**1b**/CuCl.

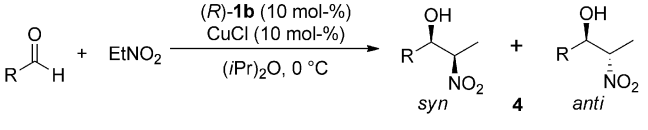


2 **3**

Entry	R	Product	Time [h]	Yield [%][a]	*ee* [%][b]
1	Ph	**3a**	20	65	91
2	4-FC_6H_4	**3b**	40	55	90
3	4-ClC_6H_4	**3c**	20	80	86
4	3-ClC_6H_4	**3d**	20	70	87
5	4-MeC_6H_4	**3e**	40	80	92
6	3-MeC_6H_4	**3f**	40	45	90
7	2-MeC_6H_4	**3g**	40	83	91
8	4-PhC_6H_4	**3h**	20	95	94
9	2-$MeOC_6H_4$	**3i**	40	86	90
10	Et	**3j**	20	95	93
11	*n*Pr	**3k**	20	85	91
12	*n*Bu	**3l**	20	90	94
13	*n*-C_5H_{11}	**3m**	20	94	90
14	*n*-C_8H_{17}	**3n**	20	75	90
15	*i*Pr	**3o**	20	99	92
16	*i*Bu	**3p**	20	99	91
17	cyclohexyl	**3q**	20	70	93
18	2-fural	**3r**	20	90	86
19	PhCH=CH	**3s**	20	95	84

[a] Yield of isolated products. [b] Enantiomeric excess values were determined by HPLC using Chiralcel OD-H, AD-H, or OJ-H columns. The absolute configuration (*R*) was determined by comparison with the literature data.[7b,14b,19]

Table 4. Diastereoselective Henry reaction of aldehydes with nitroethane catalyzed by CuCl/(*R*)-**1b**.



Entry	R	Product	Time [h]	Yield [%][a]	*anti*/*syn*[b]	*ee* [%][c]
1	4-ClC_6H_4	**4a**	48	70	1.4:1	61:82
2	2-FC_6H_4	**4b**	48	75	1.6:1	68:86
3	4-MeC_6H_4	**4c**	48	65	1.6:1	80:88
4	2-MeC_6H_4	**4d**	48	60	1.4:1	72:88
5	2-$MeOC_6H_4$	**4e**	72	71	1.4:1	76:91
6	*i*Bu	**4f**	48	50	1.1:1	90:84
7	*n*Pr	**4g**	48	70	1:1	82:80

[a] Yield of isolated products. [b] Determined by ^{1}H NMR analysis and HPLC using Chiralcel OJ-H or Chiralpak AD-H columns. [c] Enantiomeric excess values were determined by HPLC using Chiralcel OJ-H or Chiralpak AD-H columns.[15g,20]

When (*R*)-**1b** and CuCl were mixed in a 1:1 ratio in CH_2Cl_2 and the product analyzed by mass spectrometry, molecular ion peaks at *m*/*z* 611 [molecular formula $C_{38}H_{36}CuN_4$ = 2× (*R*)-**1b** + Cu] and at *m*/*z* 613 [molecular formula $C_{38}H_{38}CuN_4$ = 2× (*R*)-**1b** + Cu + $2H^+$] were observed, confirming the presence of a complex in a 2:1 ratio of (*R*)-**1b** and CuCl. Accordingly, chelation of copper(I) to (*R*)-**1b** is shown in Figure 2. The ligand acts as a base to deprotonate the nitromethane to generate the active nitronate nucleophile in the Cu^I transition state. The nitronate group assumes an axial position, as shown in Figure 2. After taking into account the stereoelectronic considerations and the observed absolute configuration of the product, the *Si*-face of the carbonyl of benzaldehyde must be favored for nucleophilic attack to give the corresponding (*R*)-product.

 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

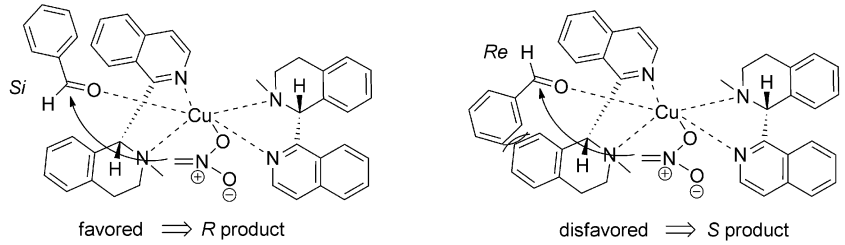


Figure 2. Proposed transition-state model for the asymmetric Henry reaction catalyzed by the (*R*)-**1b**/CuCl complex.

Conclusions

We have demonstrated the pivotal role of the *N*-alkyl substituents of C_1-tetrahydro-1,1′-bisisoquinoline on the reactivity and selectivity in the enantioselective Henry reaction. (*R*)-*N*-Methyl-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline [(*R*)-**1b**] proved to be very efficient and general ligand in the Cu^I-catalyzed asymmetric Henry reaction between nitroalkanes and various aldehydes. The desired nitroalcohol products were obtained in high yields (up to 99%) and good to excellent enantioselectivities (up to 94%*ee*) using a broad range of aliphatic, aromatic, heteroaromatic, and unsaturated aldehydes. We regard the moderate diastereoselectivities obtained (up to 1.6:1) as a promising starting point for further optimization. The operational procedure using the present catalyst system is very simple and does not require exclusion of air or moisture.

Experimental Section

General: All commercial chemicals were reagent grade unless otherwise specified. Analytical thin layer chromatography (TLC) was performed using F_{254} pre-coated silica gel plates (0.2 mm thickness). Separation of products was achieved using column chromatography on Silica Gel 60 (230–400 mesh). FTIR were recorded as thin films (KBr). NMR spectra were recorded at 300 MHz for ^{1}H and at 75.6 MHz for ^{13}C. Chemical shifts are given in ppm relative to TMS (δ = 0 ppm) or solvent residual peaks ($CDCl_3$: ^{1}H, δ = 7.26 ppm; ^{13}C, δ = 75 ppm) as internal standards. ^{1}H NMR multiplicities were designated as singlet (s), doublet (d), doublet of doublet (dd), doublet of doublet of doublet (ddd), triplet (t), triplet of doublet (td), quartet (q), pentet (p), multiplet (m), and broad (br). HPLC separations were performed using Diacel Chiralcel OD-H, OJ-H, and AD-H chiral columns.

Preparation and Characterization of Ligands (*R*)-1a–f: (*R*)-1′,2′,3′,4′-Tetrahydro-1,1′-bisisoquinoline (*R*)-**1a** and its derivatives [(*R*)-**1b**, (*R*)-**1c**, (*R*)-**1e**, and (*R*)-**1f**] were prepared according to our reported methods[1b,20] (see the Supporting Information). For a typical procedure, the preparation of (*R*)-**1d** is described here.

Preparation of (*R*)-*N*-Isopropyl-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline [(*R*)-1d]: 2-Bromopropane (67.6 mg, 51.6 μL, 0.55 mmol) was added to a solution of (*R*)-1′,2′,3′,4′-tetrahydro-1,1′-bisisoquinoline (*R*)-**1a** (130 mg, 0.5 mmol) in CH_3CN (4 mL) in the presence of K_2CO_3 (138 mg, 1.0 mmol), and the mixture was heated at reflux for 2 d (reaction monitored by TLC). The reaction mixture was filtered and K_2CO_3 was washed with CH_2Cl_2 (2 × 3 mL). The combined filtrates were evaporated under reduced pressure and the obtained gum was subjected to column chromatography purification to give (*R*)-**1d** as a white solid (84.6 mg, 56%). Enantiomeric purity (98%*ee*) was determined by HPLC (Daicel Chiralcel OD-H column; hexane/*i*PrOH, 98:2; 1.0 mL/min; 254 nm): t_R = 4.98 [(*S*)-**1d**], 5.42 [(*R*)-**1d**] min. $[a]_D^{25}$ = +157.5 (*c* = 0.86, CH_2Cl_2). FTIR (KBr): $\tilde{\nu}_{max}$ = 3402, 3052, 2965, 1623, 1585, 1560, 1496, 1452, 1342, 1171, 1057, 826, 734, 648 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 (d, *J* = 7.2 Hz, 3 H), 0.89 (d, *J* = 7.2 Hz, 3 H), 2.52–2.61 (m, 2 H), 3.21–3.40 (d, *J* = 15.9 Hz, 1 H), 3.16–3.20 (m, 1 H), 3.22–3.27 (m, 1 H), 5.47 (s, 1 H), 6.48 (d, *J* = 7.8 Hz, 1 H), 6.71 (t, *J* = 7.5 Hz, 1 H), 6.92 (t, *J* = 7.2 Hz, 1 H), 7.05 (d, *J* = 7.5 Hz, 1 H), 7.18 (t, *J* = 7.5 Hz, 1 H), 7.39 (t, *J* = 7.5 Hz, 1 H), 7.46 (d, *J* = 5.7 Hz, 1 H), 7.61 (d, *J* = 8.7 Hz, 1 H), 8.40 (d, *J* = 5.7 Hz, 1 H), 8.64 (d, *J* = 8.7 Hz, 1 H) ppm. ^{13}C NMR (75.6 MHz, $CDCl_3$): δ = 12.5, 21.3, 30.5, 41.5, 49.5, 70.7, 120.8, 125.7, 125.9, 126.0, 126.7, 126.8, 127.2, 127.8, 128.6, 129.7, 134.5, 137.3, 138.5, 141.0, 162.8 ppm. HRMS (EI$^+$): calcd. for $C_{21}H_{22}N_2$ 302.1861; found 303.1857 [M + 1].

General Procedure for Asymmetric Henry Reaction: Ligand (0.02 mmol, 10 mol-%) and CuCl (0.02 mmol, 10 mol-%) were mixed in $(iPr)_2O$ (1.5 mL) and the mixture was stirred at room temp. for 1 h, whereby a yellow solution was obtained. To the above stirred solution, nitromethane/nitroethane (4 mmol, 20 equiv.) and aldehyde (0.2 mmol) were added. The reaction mixture was then stirred at the given temperature for the specified time (reaction monitored by TLC). The β-nitroalcohol product was purified on silica gel by flash column chromatography.

(*R*)-1-Phenyl-2-nitroethanol [(*R*)-3a]: Prepared according to the general procedure and purified by column chromatography (hexane/EtOAc, 5:1) to give a colorless oil (65% yield). HPLC (Chiralcel OD-H column; *n*-hex/IPA, 90:10; flow rate 0.8 mL/min; 215 nm): t_R = 18.21 (major enantiomer), 21.91 (minor enantiomer) min; 91%*ee*. ^{1}H NMR ($CDCl_3$): δ = 2.76 (br. s, 1 H), 4.39–4.56 (m, 2 H), 5.37 (dd, *J* = 9.3, 9.6 Hz, 1 H), 7.34–7.40 (m, 5 H) ppm. ^{13}C NMR: δ = 71.0, 81.3, 126.0, 129.0, 129.1, 138.2 ppm.

(*R*)-1-(4-Fluorophenyl)-2-nitroethanol [(*R*)-3b]: Prepared according to the general procedure and purified by column chromatography (hexane/EtOAc, 7:3) to give a colorless oil (55% yield). HPLC (Chiralcel OD-H column; *n*-hex/IPA, 90:10; flow rate 0.8 mL/min; 215 nm): t_R = 14.66 (major enantiomer), 17.23 (minor enantiomer) min; 90%*ee*. ^{1}H NMR ($CDCl_3$): δ = 2.89 (s, 1 H), 4.46–4.63 (m, 2 H), 5.47 (d, *J* = 7.5 Hz, 1 H), 7.07–7.13 (m, 2 H), 7.37–7.42 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 70.3, 81.2, 115.9, 116.1, 116.3, 127.8, 134.0, 162.1, 164.1 ppm.

(*R*)-1-(4-Chlorophenyl)-2-nitroethanol [(*R*)-3c]: Prepared according to the general procedure and purified by column chromatography (hexane/EtOAc, 5:1) to give a colorless oil (85% yield). HPLC (Chiralcel OD-H column; *n*-hex/IPA, 90:10; flow rate 1.0 mL/min; 215 nm): t_R = 13.90 (major enantiomer), 17.70 (minor enantiomer) min; 86%*ee*. ^{1}H NMR ($CDCl_3$): δ = 2.89 (br. s, 1 H), 4.47–4.62 (m, 2 H), 5.44–5.47 (m, 1 H), 7.34–7.40 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 70.3, 80.1, 127.3, 129.3, 134.9, 136.5 ppm.

 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

(*R*)-1-(3-Chlorophenyl)-2-nitroethanol [(*R*)-3d]: Prepared according to the general procedure and purified by column chromatography (hexane/EtOAc, 5:1) to give a colorless oil (70% yield). HPLC (Chiralcel OD-H column; *n*-hex/IPA, 90:10; flow rate 1.0 mL/min; 215 nm): t_R = 13.6 (major enantiomer), 16.8 (minor enantiomer) min; 87%*ee*. ^{1}H NMR ($CDCl_3$): δ = 2.96 (br. s, 1 H), 4.49–4.63 (m, 2 H), 5.40 (m, 1 H), 7.26–7.73 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 70.3, 81.0, 124.0, 126.2, 129.1, 130.3, 135.0, 140.0 ppm.

(*R*)-1-(4-Methylphenyl)-2-nitroethanol [(*R*)-3e]: Prepared according to the general procedure and purified by column chromatography (hexane/EtOAc, 8:1) to give a colorless oil (80% yield). HPLC (Chiralcel OD-H column; *n*-hex/IPA, 90:10; flow rate 0.5 mL/min; 215 nm): t_R = 26.50 (major enantiomer), 34.02 (minor enantiomer) min; 92%*ee*. ^{1}H NMR ($CDCl_3$): δ = 2.36 (s, 3 H), 2.48 (s, 1 H), 4.46–4.64 (m, 2 H), 5.40–5.46 (m, 1 H), 7.26–7.30 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.2, 70.9, 81.3, 125.9, 129.7, 135.2, 139.0 ppm.

(*R*)-1-(3-Methylphenyl)-2-nitroethanol [(*R*)-3f]: Prepared according to the general procedure and purified by column chromatography (hexane/EtOAc, 5:1) to give a yellow oil (45% yield). HPLC (Chiralcel OD-H column; *n*-hex/IPA, 90:10; flow rate 0.5 mL/min; 215 nm): t_R = 22.91 (major enantiomer), 26.17 (minor enantiomer) min; 90%*ee*. ^{1}H NMR ($CDCl_3$): δ = 2.38 (s, 3 H), 2.81 (s, 1 H), 4.50–4.65 (m, 2 H), 5.37–5.45 (m, 1 H), 7.23–7.32 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.4, 71.1, 81.8, 123.0, 126.6, 128.9, 129.7, 138.0, 138.9 ppm.

(*R*)-1-(2-Methylphenyl)-2-nitroethanol [(*R*)-3g]: Prepared according to the general procedure and purified by column chromatography (hexane/EtOAc, 5:1) to give a colorless oil (83% yield). HPLC (Chiralcel OD-H column; *n*-hex/IPA, 90:10; flow rate 0.5 mL/min; 215 nm): t_R = 21.09 (major enantiomer), 31.46 (minor enantiomer) min; 91%*ee*. ^{1}H NMR ($CDCl_3$): δ = 2.40 (s, 3 H), 2.72 (d, J = 3.6 Hz, 1 H), 4.42–4.60 (m, 2 H), 5.67–5.72 (m, 1 H), 7.25–7.31 (m, 3 H), 7.51–7.56 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 18.9, 68.0, 80.2, 125.6, 126.8, 128.8, 130.9, 134.4, 136.2 ppm.

(*R*)-1-(4-Phenylphenyl)-2-nitroethanol [(*R*)-3h]: Prepared according to the general procedure and purified by column chromatography (hexane/EtOAc, 5:1) to give a pale-yellow crystalline solid (95% yield). HPLC (Chiralcel OD-H column; *n*-hex/IPA, 85:15; flow rate 0.8 mL/min; 215 nm): t_R = 19.44 (major enantiomer), 23.27 (minor enantiomer) min; 94%*ee*. ^{1}H NMR ($CDCl_3$): δ = 2.88 (d, J = 3.3 Hz, 1 H), 4.36–4.69 (m, 2 H), 5.52 (d, J = 9.3 Hz, 1 H), 7.34–7.64 (m, 9 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 70.8, 81.2, 126.4, 127.1, 127.7, 127.8, 128.9, 137.0, 140.3, 142.0 ppm.

(*R*)-1-(2-Methoxyphenyl)-2-nitroethanol [(*R*)-3i]: Prepared according to the general procedure and purified by column chromatography (hexane/EtOAc, 9:1) to give a yellow oil (86% yield). HPLC (Chiralcel OD-H column; *n*-hex/IPA, 90:10; flow rate 1.0 mL/min; 215 nm): t_R = 10.78 (major enantiomer), 12.55 (minor enantiomer) min; 90%*ee*. ^{1}H NMR ($CDCl_3$): δ = 3.24 (d, J = 6 Hz, 1 H), 3.90 (s, 3 H), 4.55–4.69 (m, 2 H), 5.62–5.68 (m, 1 H), 6.93 (d, J = 8.1 Hz, 1 H), 7.03 (t, J = 7.5 Hz, 1 H), 7.35 (t, J = 8.1 Hz, 1 H), 7.46 (d, J = 7.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 55.4, 67.8, 79.9, 110.6, 121.2, 126.0, 127.2, 129.8, 156.0 ppm.

(*R*)-1-Nitrobutan-2-ol [(*R*)-3j]: Prepared according to the general procedure and purified by column chromatography (hexane/EtOAc, 5:1) to give a yellow oil (95% yield). HPLC (Chiralcel AD-H column; *n*-hex/IPA, 98:2; flow rate 1.0 mL/min; 215 nm): t_R = 49.70(major enantiomer), 84.59 (minor enantiomer) min; 93%*ee*. ^{1}H NMR ($CDCl_3$): δ = 0.94–0.98 (m, 3 H), 1.46–1.61 (m, 2 H), 2.57 (br. s, 1 H), 4.18–4.59 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 9.6, 26.9, 69.9, 80.4 ppm.

(*R*)-1-Nitropentan-2-ol [(*R*)-3k]: Prepared according to the general procedure and purified by column chromatography (hexane/EtOAc, 5:1) to give a yellow oil (85% yield). HPLC (Chiralcel AD-H column; *n*-hex/IPA, 98:2; flow rate 1.0 mL/min; 215 nm): t_R = 32.52 (major enantiomer), 54.01 (minor enantiomer) min; 91%*ee*. ^{1}H NMR ($CDCl_3$): δ = 0.98 (t, J = 6.9 Hz, 3 H), 1.50–1.59 (m, 4 H), 2.53 (br. s, 1 H), 4.35–4.46 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.7, 18.4, 35.8, 68.4, 80.7 ppm.

(*R*)-1-Nitrohexan-2-ol [(*R*)-3l]: Prepared according to the general procedure and purified by column chromatography (hexane/EtOAc, 5:1) to give a yellow oil (90% yield). HPLC (Chiralcel AD-H column; *n*-hex/IPA, 98:2; flow 1.0 mL/min; 215 nm): t_R = 24.29 (major enantiomer), 32.13 (minor enantiomer) min; 94%*ee*. ^{1}H NMR ($CDCl_3$): δ = 0.94 (t, J = 6.9 Hz, 3 H), 1.34–1.61 (m, 6 H), 2.50 (br. s, 1 H), 4.31–4.49 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.9, 22.4, 27.3, 33.4, 68.7, 80.6 ppm.

(*R*)-1-Nitroheptan-2-ol [(*R*)-3m]: Prepared according to the general procedure and purified by column chromatography (hexane/EtOAc, 5:1) to give a yellow oil (94% yield). HPLC (Chiralcel AD-H column; *n*-hex/IPA, 98:2; flow 1.0 mL/min; 215 nm): t_R = 23.81 (major enantiomer), 35.60 (minor enantiomer) min; 90%*ee*. ^{1}H NMR ($CDCl_3$): δ = 0.84 (t, J = 6.9 Hz, 3 H), 1.15–1.53 (m, 8 H), 2.75 (br. s, 1 H), 4.24–4.40 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.9, 22.5, 24.8, 31.5, 33.7, 68.7, 80.7 ppm.

(*R*)-1-Nitrodecan-2-ol [(*R*)-3n]: Prepared according to the general procedure and purified by column chromatography (hexane/EtOAc, 5:1) to give a yellow oil (75% yield). HPLC (Chiralcel AD-H column; *n*-hex/IPA, 98:2; flow rate 1.0 mL/min; 215 nm): t_R = 20.15 (major enantiomer), 30.15 (minor enantiomer) min; 90%*ee*. ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, J = 6.3 Hz, 3 H), 1.47–1.50 (m, 14 H), 2.49 (d, J = 4.5 Hz, 1 H), 4.34–4.47 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1, 22.6, 25.2, 29.2, 29.3, 29.4, 31.8, 33.7, 68.7, 80.6 ppm.

(*R*)-3-Methyl-1-nitrobutan-2-ol [(*R*)-3o]: Prepared according to the general procedure and purified by column chromatography (hexane/EtOAc, 5:1) to give a yellow oil (99% yield). HPLC (Chiralcel OD-H column; *n*-hex/IPA, 98:2; flow 0.5 mL/min; 215 nm): t_R = 40.22 (major enantiomer), 44.57 (minor enantiomer) min; 92%*ee*. ^{1}H NMR ($CDCl_3$): δ = 0.70–0.78 (m, 6 H), 1.66–1.81 (m, 1 H), 2.58 (br. s, 1 H), 4.05 (m, 1 H), 4.30–4.44 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 17.4, 18.4, 31.8, 73.4, 79.3 ppm.

(*R*)-4-Methyl-1-nitropentan-2-ol [(*R*)-3p]: Prepared according to the general procedure and purified by column chromatography (hexane/EtOAc, 5:1) to give a yellow oil (99% yield). HPLC (Chiralcel AD-H column; *n*-hex/IPA, 95:5; flow 0.5 mL/min; 215 nm): t_R = 20.56 (major enantiomer), 29.13 (minor enantiomer) min; 91%*ee*. ^{1}H NMR ($CDCl_3$): δ = 0.85–0.91 (m, 6 H), 1.12–1.20 (m, 1 H), 1.39–1.49 (m, 1 H), 1.72–1.81 (m, 1 H), 2.53 (br. s, 1 H), 4.27–4.37 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.8, 23.2, 24.3, 42.4, 67.0, 81.0 ppm.

(*R*)-1-Cyclohexyl-2-nitroethanol [(*R*)-3q]: Prepared according to the general procedure and purified by column chromatography (hexane/EtOAc, 5:1) to give a yellow oil (70% yield). HPLC (Chiralcel AD-H column; *n*-hex/IPA, 98:2; flow 0.6 mL/min; 215 nm): t_R = 48.60 (major enantiomer), 51.90 (minor enantiomer) min; 93%*ee*. ^{1}H NMR ($CDCl_3$): δ = 1.00–1.23 (m, 5 H), 1.42–1.54 (m, 1 H), 1.60–1.70 (m, 2 H), 1.72–1.78 (m, 3 H), 2.38 (d, J = 5.1 Hz, 1 H), 4.02–4.04 (m, 1 H), 4.36–4.44 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.9, 28.0, 28.8, 41.4, 72.8, 79.3 ppm.

 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

(*R*)-1-(2-Furyl)-2-nitroethanol [(*R*)-3r]: Prepared according to the general procedure and purified by column chromatography (hexane/EtOAc, 5:1) to give a yellow oil (90% yield). HPLC (Chiralcel OJ-H column; *n*-hex/IPA, 90:10; flow rate 1.0 mL/min; 215 nm): t_R = 22.16 (major enantiomer), 26.73 (minor enantiomer) min; 86%*ee*. ^{1}H NMR ($CDCl_3$): δ = 2.90 (br. s, 1 H), 4.63–4.84 (m, 2 H), 5.40–5.50 (m, 1 H), 6.38–6.40 (m, 2 H), 7.40–4.41 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 64.9, 78.4, 108.2, 100.7, 143.2, 150.7 ppm.

(*R*,*E*)-1-Nitro-4-phenyl-3-buten-2-ol [(*R*,*E*)-3s]: Prepared according to the general procedure and purified by column chromatography (hexane/EtOAc, 5:1) to give a yellow oil (95% yield). HPLC (Chiralcel OD-H column; *n*-hex/IPA, 90:10; flow rate 0.8 mL/min; 215 nm): t_R = 55.63 (minor enantiomer), 62.71 (major enantiomer) min; 84%*ee*. ^{1}H NMR ($CDCl_3$): δ = 2.68 (d, J = 3.9 Hz, 1 H), 4.51–4.61 (m, 2 H), 5.06–5.12 (m, 1 H), 6.15 (dd, J = 6.3, 15.9 Hz, 1 H), 6.79 (d, J = 15 Hz, 1 H), 7.30–7.46 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 69.6, 79.9, 124.9, 126.7, 128.6, 128.8, 133.7, 135.5 ppm.

1-(4-Chlorophenyl)-2-nitropropan-1-ol (4a): Prepared according to the general procedure and purified by column chromatography (hexane/EtOAc, 5:1) to give a yellow oil (70% yield). Diastereomeric ratios (*anti*/*syn*, 1.4:1) were determined by ^{1}H NMR and HPLC. HPLC (Chiralpak AD-H column; *n*-hex/IPA, 95:5; 1.0 mL/min; 210 nm); t_R = 13.90 [$anti_{minor}$ (1*S*,2*R*)], 14.94 [$anti_{major}$ (1*R*,2*S*)], 19.90 [syn_{minor} (1*S*,2*S*)], 22.14 [syn_{major} (1*R*,2*R*)] min. *anti*/*syn* = 61%/82%*ee*. ^{1}H NMR (300 MHz, $CDCl_3$): δ (*anti* isomer) = 1.42 (d, J = 6.0 Hz, 3 H), 2.72 (s, 1 H), 4.60–4.68 (m, 1 H), 5.32 (br. s, 1 H), 7.20–7.30 (m, 4 H); δ (*syn* isomer) = 1.26 (d, J = 6.0 Hz, 3 H), 2.62 (s, 1 H), 4.60–4.68 (m, 1 H), 4.98 (d, J = 8.1 Hz, 1 H), 7.20–7.30 (m, 4 H) ppm. ^{13}C NMR (75.6 MHz, $CDCl_3$): δ (*anti* isomer) = 12.0, 73.2, 87.2, 127.4, 129.0, 134.4, 136.9; δ (*syn* isomer) = 16.4, 75.5, 88.2, 128.3, 129.2, 135.1, 136.8 ppm.

1-(2-Fluorophenyl)-2-nitropropan-1-ol (4b): Prepared according to the general procedure and purified by column chromatography (hexane/EtOAc, 5:1) to give a yellow oil (75% yield). Diastereomeric ratios (*anti*/*syn*, 1.6:1) were determined by ^{1}H NMR and HPLC. HPLC (Chiralpak AD-H column; *n*-hex/IPA, 95:5; 1.0 mL/min; 210 nm): t_R = 15.01 [$anti_{minor}$ (1*S*,2*R*)], 17.82 [$anti_{major}$ (1*R*,2*S*)], 22.26 [syn_{minor} (1*S*,2*S*)], 26.33 [syn_{major} (1*R*,2*R*)] min. *anti*/*syn* = 68%/86%*ee*. ^{1}H NMR (300 MHz, $CDCl_3$): δ (*anti* isomer) = 1.41 (d, J = 6.9 Hz, 3 H), 2.82 (d, J = 6.9 Hz, 1 H), 4.72–4.78 (m, 1 H), 5.66 (s, 1 H), 7.03–7.19 (m, 1 H), 7.28–7.57 (m, 3 H); δ (*syn* isomer) = 1.37 (d, J = 6.9 Hz, 3 H), 2.60 (s, 1 H), 4.72–4.78 (m, 1 H), 5.43–5.45 (m, 1 H), 7.03–7.19 (m, 1 H), 7.28–7.57 (m, 3 H) ppm. ^{13}C NMR (75.6 MHz, $CDCl_3$): δ (*anti* isomer) = 11.9, 68.3, 85.2, 115.4, 124.6, 125.4, 127.8, 130.1, 157.5; δ (*syn* isomer) = 16.2, 70.0, 87.9, 115.8, 125.0, 125.6, 128.3, 130.6, 160.8 ppm.

2-Nitro-1-*p*-tolylpropan-1-ol (4c): Prepared according to the general procedure and purified by column chromatography (hexane/EtOAc, 5:1) to give a yellow oil (65% yield). Diastereomeric ratios (*anti*/*syn*, 1.6:1) were determined by ^{1}H NMR and HPLC. HPLC (Chiralpak AD-H column; *n*-hex/IPA, 95:5; 1.0 mL/min; 210 nm): t_R = 12.72 [$anti_{minor}$ (1*S*,2*R*)], 14.03 [$anti_{major}$ (1*R*,2*S*)], 19.13 [syn_{minor} (1*S*,2*S*)], 22.78 [syn_{major} (1*R*,2*R*)] min. *anti*/*syn* = 80%/88%*ee*. ^{1}H NMR (300 MHz, $CDCl_3$): δ (*anti* isomer) = 1.51 (d, J = 6.9 Hz, 3 H), 2.36 (s, 3 H), 2.62 (br. s, 1 H), 4.67–4.81 (m, 1 H), 5.34 (d, J = 3 Hz, 1 H), 7.21–7.28 (m, 4 H); δ (*syn* isomer) = 1.37 (d, J = 6.9 Hz, 3 H), 2.36 (s, 3 H), 2.47 (br. s, 1 H), 4.67–4.81 (m, 1 H), 5.06 (d, J = 8.1 Hz, 1 H), 7.21–7.28 (m, 4 H) ppm. ^{13}C NMR (75.6 MHz, $CDCl_3$): δ (*anti* isomer) = 12.3, 21.1, 73.9, 87.5, 125.9, 129.4, 135.4, 138.4; δ (*syn* isomer) = 16.5, 29.7, 76.2, 88.5, 126.8, 129.7, 133.4, 139.2 ppm.

2-Nitro-1-*o*-tolylpropan-1-ol (4d): Prepared according to the general procedure and purified by column chromatography (hexane/EtOAc, 5:1) to give a yellow oil (60% yield). Diastereomeric ratios (*anti*/*syn*, 1.4:1) were determined by ^{1}H NMR and HPLC. HPLC (Chiralpak AD-H column; *n*-hex/IPA, 95:5; 1.0 mL/min; 210 nm): t_R = 10.17 [$anti_{minor}$ (1*S*,2*R*)], 11.38 [$anti_{major}$ (1*R*,2*S*)], 13.82 [syn_{minor} (1*S*,2*S*)], 16.94 [syn_{major} (1*R*,2*R*)] min. *anti*/*syn* = 72%/88%*ee*. ^{1}H NMR (300 MHz, $CDCl_3$): δ (*anti* isomer) = 1.43 (d, J = 6.9 Hz, 3 H), 2.29 (s, 3 H), 2.58 (s, 1 H), 4.54–4.57 (m, 1 H), 5.54 (s, 1 H), 7.08–7.19 (m, 3 H), 7.46 (d, J = 7.2 Hz, 1 H); δ (*syn* isomer) = 1.22 (d, J = 6.9 Hz, 3 H), 2.36 (s, 3 H), 2.48 (s, 1 H), 4.77–4.80 (m, 1 H), 5.27–5.30 (m, 1 H), 7.08–7.19 (m, 3 H), 7.29–7.32 (m, 1 H) ppm. ^{13}C NMR (75.6 MHz, $CDCl_3$): δ (*anti* isomer) = 11.5, 18.9, 70.9, 85.4, 126.0, 126.4, 128.4, 130.8, 134.3, 136.7; δ (*syn* isomer) = 16.1, 19.6, 72.2, 88.8, 126.5, 126.8, 128.8, 131.0, 135.9, 136.6 ppm.

1-(2-Methoxyphenyl)-2-nitropropan-1-ol (4e): Prepared according to the general procedure and purified by column chromatography (hexane/EtOAc, 8:1) to give a yellow oil (71% yield). Diastereomeric ratios (*anti*/*syn*, 1.4:1) were determined by ^{1}H NMR and HPLC. HPLC (Chiralpak OJ-H column; *n*-hex/IPA, 95:5; 0.6 mL/min; 210 nm): t_R = 43.95 [$anti_{minor}$ (1*S*,2*R*)], 48.44 [$anti_{major}$ (1*R*,2*S*)], 56.62 [syn_{minor} (1*S*,2*S*)], 60.12 [syn_{major} (1*R*,2*R*)] min. *anti*/*syn* = 76%/91%*ee*. ^{1}H NMR (300 MHz, $CDCl_3$): δ (*anti* isomer) = 1.39 (d, J = 6.9 Hz, 3 H), 3.07 (br. s, 1 H), 3.79 (s, 3 H), 4.79–4.86 (m, 1 H), 5.46 (s, 1 H), 6.80–6.94 (m, 2 H), 7.18–7.35 (m, 2 H); δ (*syn* isomer) = 1.25 (d, J = 6.9 Hz, 3 H), 3.27 (d, J = 3 Hz, 1 H), 3.83 (s, 3 H), 4.89–4.94 (m, 1 H), 5.04–5.06 (m, 1 H), 6.80–6.94 (m, 2 H), 7.18–7.35 (m, 2 H) ppm. ^{13}C NMR (75.6 MHz, $CDCl_3$): δ (*anti* isomer) = 12.6, 55.4, 70.8, 85.1, 110.4, 121.0, 126.3, 127.6, 129.5, 155.8; δ (*syn* isomer) = 16.6, 55.5, 74.1, 87.7, 111.0, 121.2, 125.9, 129.0, 130.1, 156.8 ppm.

5-Methyl-2-nitrohexan-3-ol (4f): Prepared according to the general procedure and purified by column chromatography (hexane/EtOAc, 5:1) to give a clear oil (50% yield). Diastereomeric ratios (*anti*/*syn*, 1.1:1) were determined by ^{1}H NMR and HPLC. HPLC (Chiralpak AD-H column; *n*-hex/IPA, 98:2; 0.8 mL/min; 220 nm): t_R = 19.50 [$anti_{minor}$ (1*S*,2*R*)], 20.89 [$anti_{major}$ (1*R*,2*S*)], 25.21 [syn_{major} (1*R*,2*R*)], 27.26 [syn_{minor} (1*S*,2*S*)] min. *anti*/*syn* = 90%/84%*ee*. ^{1}H NMR (300 MHz, $CDCl_3$): δ (*anti* isomer) = 0.86–0.91 (m, 6 H), 1.15–1.23 (m, 1 H), 1.48 (d, J = 6.6 Hz, 3 H), 1.76–1.80 (m, 2 H), 2.28 (br. s, 1 H), 4.20 (d, J = 6.6 Hz, 1 H), 4.40–4.46 (m, 1 H); δ (*syn* isomer) = 0.86–0.91 (m, 6 H), 1.06–1.14 (m, 1 H), 1.30–1.39 (m, 2 H), 1.49 (d, J = 6.9 Hz, 3 H), 2.28 (br. s, 1 H), 3.86–3.90 (m, 1 H), 4.40–4.46 (m, 1 H) ppm. ^{13}C NMR (75.6 MHz, $CDCl_3$): δ (*anti* isomer) = 16.3, 21.7, 23.6, 24.3, 42.0, 71.2, 86.7; δ (*syn* isomer) = 12.4, 21.4, 23.3, 24.5, 41.8, 70.2, 88.2 ppm.

2-Nitrohexan-3-ol (4g): Prepared according to the general procedure and purified by column chromatography (hexane/EtOAc, 5:1) to give a clear oil (70% yield). Diastereomeric ratios (*anti*/*syn*, 1:1) were determined by ^{1}H NMR and HPLC. HPLC (Chiralpak AD-H column; *n*-hex/IPA, 98:2; 0.8 mL/min; 220 nm): t_R = 23.65 [$anti_{minor}$ (1*S*,2*R*)], 25.23 [$anti_{major}$ (1*R*,2*S*)], 29.27 [syn_{major} (1*R*,2*R*)], 32.55 [syn_{minor} (1*S*,2*S*)] min. *anti*/*syn* = 82%/80%*ee*. ^{1}H NMR (300 MHz, $CDCl_3$): δ (*anti* isomer) = 0.87–0.92 (m, 5 H), 1.34–1.40 (m, 2 H), 1.46 (d, J = 6.9 Hz, 3 H), 2.13 (br. s, 1 H), 4.12–4.15 (m, 1 H), 4.42–4.50 (m, 1 H); δ (*syn* isomer) = 0.87–0.92 (m, 5 H), 1.34–1.40 (m, 2 H), 1.49 (d, J = 6.9 Hz, 3 H), 2.22 (br. s, 1 H), 3.75–3.85 (m, 1 H), 4.42–4.50 (m, 1 H) ppm. ^{13}C NMR

 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

(75.6 MHz, $CDCl_3$): δ (*anti* isomer) = 13.8, 16.3, 18.4, 35.1, 72.7, 86.4; δ (*syn* isomer) = 12.4, 13.9, 19.0, 29.7, 71.8, 87.7 ppm.

Supporting Information (see footnote on the first page of this article): NMR spectra, HRMS, and HPLC traces.

Acknowledgments

We are grateful to the Nanyang Technological University for financial support (RG27/07), and also appreciate scholarship support for Y. Q. J. from the China Scholarship Council.

[1] a) S. Busato, D. C. Craig, Z. M. A. Judeh, R. W. Read, *Tetrahedron* **2003**, *59*, 461–472; b) D. C. Craig, Z. M. A. Judeh, R. W. Read, *Aust. J. Chem.* **2002**, *55*, 733–736; c) Z. M. A. Judeh, C. B. Ching, J. Bu, A. McCluskey, *Tetrahedron Lett.* **2002**, *43*, 5089–5091; d) H. Y. Shen, L. Y. Ying, H. L. Jiang, Z. Judeh, *Int. J. Mol. Sci.* **2007**, *8*, 505–512; e) Q. J. Yao, Z. M. A. Judeh, *Tetrahedron* **2011**, *67*, 4086–4092; f) Q. J. Yao, Q. Gao, Z. M. A. Judeh, *Tetrahedron Asymmetry* **2011**, *22*, 11J2745 (accepted).

[2] G. Qi, Y. Q. Ji, Z. M. A. Judeh, *Tetrahedron* **2010**, *66*, 4195–4205.

[3] G. Qi, Z. M. A. Judeh, *Tetrahedron: Asymmetry* **2010**, *21*, 429–436.

[4] H. W. Xi, Z. M. A. Judeh, K. H. Lim, *THEOCHEM* **2009**, *897*, 22–31.

[5] H. Sasai, T. Suzuki, S. Arai, T. Arai, M. Shibasaki, *J. Am. Chem. Soc.* **1992**, *114*, 4418–4420.

[6] a) C. Palomo, M. Oiarbide, A. Mielgo, *Angew. Chem.* **2004**, *116*, 5558; *Angew. Chem. Int. Ed.* **2004**, *43*, 5442–5444; b) C. Palomo, M. Oiarbide, A. Laso, *Eur. J. Org. Chem.* **2007**, 2561–2574; c) N. Ono, *The Nitro Group in Organic Synthesis*, Wiley-VCH, New York, **2001**; d) J. Boruwa, N. Gogoi, P. P. Saikia, N. C. Barua, *Tetrahedron: Asymmetry* **2006**, *17*, 3315–3326; e) F. A. Luzzio, *Tetrahedron* **2001**, *57*, 915–945.

[7] a) M. Steurer, C. Bolm, *J. Org. Chem.* **2010**, *75*, 3301–3310; b) B. Qin, X. Xiao, X. Liu, J. Huang, Y. Wen, X. Feng, *J. Org. Chem.* **2007**, *72*, 9323–9328; c) T. Arai, R. Takashita, Y. Endo, M. Watanabe, A. Yanagisawa, *J. Org. Chem.* **2008**, *73*, 4903–4906.

[8] For Zn, see: a) B. M. Trost, V. S. C. Yeh, *Angew. Chem.* **2002**, *114*, 889; *Angew. Chem. Int. Ed.* **2002**, *41*, 861–863; b) B. M. Trost, V. S. C. Yeh, H. Ito, N. Bremeyer, *Org. Lett.* **2002**, *4*, 2621–2623; c) A. Bulut, A. Aslan, O. Z. Dogan, *J. Org. Chem.* **2008**, *73*, 7373–7375; d) H. Y. Kim, K. Oh, *Org. Lett.* **2009**, *11*, 5682–5685; e) C. Palomo, M. Oiarbide, A. Laso, *Angew. Chem.* **2005**, *117*, 3949; *Angew. Chem. Int. Ed.* **2005**, *44*, 3881–3884.

[9] For Co, see: a) Y. Kogami, T. Nakajima, T. Ikeno, T. Yamada, *Synthesis* **2004**, 1947–1950; b) J. Park, K. Lang, K. A. Abboud, S. Hong, *J. Am. Chem. Soc.* **2008**, *130*, 16484–16485.

[10] For Cr, see: a) A. S. Zulauf, M. Mellah, E. Schulz, *J. Org. Chem.* **2009**, *74*, 2242–2245; b) R. Kowalczyk, P. Kwiatkowski, J. Skarzewski, J. Jurczak, *J. Org. Chem.* **2009**, *74*, 753–756.

[11] For Pd, see: S. Handa, K. Nagawa, Y. Sohtome, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2008**, *120*, 3274; *Angew. Chem. Int. Ed.* **2008**, *47*, 3230–3233.

[12] a) T. Arai, Y. M. A. Yamada, N. Yamamoto, H. Sasai, M. Shibasaki, *Chem. Eur. J.* **1996**, *2*, 1368–1372; b) H. Sasai, T. Tokunaga, S. Watanabe, T. Suzuki, N. Itoh, M. Shibasaki, *J. Org. Chem.* **1995**, *60*, 7388–7389.

[13] a) D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw, C. W. Downey, *J. Am. Chem. Soc.* **2003**, *125*, 12692–12693; b) C. Christensen, K. Juhl, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2002**, *67*, 4875–4881; c) T. Risgaard, K. V. Gothelf, K. A. Jørgensen, *Org. Biomol. Chem.* **2003**, *1*, 153–156; d) S. K. Ginotra, V. K. Singh, *Org. Biomol. Chem.* **2007**, *5*, 3932–3937; e) K. Lang, J. Park, S. Hong, *J. Org. Chem.* **2010**, *75*, 6424–6435; f) S. F. Lu, D. M. Du, S. W. Zhang, J. Xu, *Tetrahedron: Asymmetry* **2004**, *15*, 3433–3441; g) D. M. Du, S. F. Lu, T. Fang, J. Xu, *J. Org. Chem.* **2005**, *70*, 3712–3715.

[14] a) S. Liu, C. Wolf, *Org. Lett.* **2008**, *10*, 1831–1834; b) K. Y. Spangler, C. Wolf, *Org. Lett.* **2009**, *11*, 4724–4727.

[15] a) S. Arai, S. Takita, A. Nishida, *Eur. J. Org. Chem.* **2005**, 5262–5267; b) T. Arai, M. Watanabe, A. Fujiwara, N. Yokoyama, A. Yanagisawa, *Angew. Chem.* **2006**, *118*, 6124; *Angew. Chem. Int. Ed.* **2006**, *45*, 5978–5981; c) T. Arai, M. Watanabe, A. Yanagisawa, *Org. Lett.* **2007**, *9*, 3595–3597; d) M. Bandini, M. Benaglia, R. Sinisi, S. Tommasi, A. Umani-Ronchi, *Org. Lett.* **2007**, *9*, 2151–2153; e) S. Selvakumar, D. Sivasankaran, V. K. Singh, *Org. Biomol. Chem.* **2009**, *7*, 3156–3162; f) R. Kowalczyk, L. Sidorowicz, J. Skarzewski, *Tetrahedron: Asymmetry* **2008**, *19*, 2310–2315; g) A. Noole, K. Lippur, A. Metsala, M. Lopp, T. N. Kanger, *J. Org. Chem.* **2010**, *75*, 1313–1316; h) W. Jin, X. Li, Y. Huang, F. Wu, B. Wan, *Chem. Eur. J.* **2010**, *16*, 8259–8261.

[16] H. Maheswaran, K. L. Prasanth, G. G. Krishna, K. Ravikumar, B. Sridhar, M. L. Kantam, *Chem. Commun.* **2006**, 4066–4068.

[17] a) G. Blay, E. Climent, I. Fernández, V. Hernández-Olmos, J. R. Pedro, *Tetrahedron: Asymmetry* **2006**, *17*, 2046–2049; b) G. Blay, V. Hernandez-Olmos, J. R. Pedro, *Org. Biomol. Chem.* **2008**, *6*, 468–476; c) G. Blay, E. Climent, I. Fernández, V. Hernández-Olmos, J. R. Pedro, *Tetrahedron: Asymmetry* **2007**, *18*, 1603–1612; d) T. Arai, K. Suzuki, *Synlett* **2009**, 3167–3175.

[18] Y. Xiong, F. Wang, X. Huang, Y. Wen, X. Feng, *Chem. Eur. J.* **2007**, *13*, 829–833.

[19] M. Bandini, F. Piccinelli, S. Tommasi, A. Umani-Ronchi, C. Venrici, *Chem. Commun.* **2007**, 616–618.

[20] a) R. Ballini, G. Bosica, E. Marcantoni, P. Vita, G. Bartoli, *J. Org. Chem.* **2000**, *65*, 5854–5857; b) D. Uraguchi, S. Sakaki, T. Ooi, *J. Am. Chem. Soc.* **2007**, *129*, 12392–12393; c) G. Blay, R. Domingo, V. Hernández-Olmos, R. Pedro, *Chem. Eur. J.* **2008**, *14*, 4725–4730; d) K. Kanagaraj, P. Suresh, K. Pitchumani, *Org. Lett.* **2010**, *12*, 4070–4073.

Received: April 25, 2011
Published Online: July 14, 2011

 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim