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Chiral 1,1′-binaphthylazepine derived amino alcohol catalyzed asymmetric Henry reaction

Zong-Liang Guo, Shi Zhong *, Yong-Bo Li, Gui Lu *

Institute of Drug Synthesis and Pharmaceutical Process, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, PR China

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This paper is dedicated to celebrate the 60th birthday of Professor Albert S.C. Chan

ABSTRACT

The catalytic asymmetric Henry reaction of nitromethane to various aldehydes has been developed using a chiral binaphthylazepine derived amino alcohol and $Cu(OAc)_2{\cdot}H_2O$ as the catalyst. High yields and good enantioselectivities (up to 97% ee) were obtained for both aromatic and aliphatic aldehydes. Moreover, this catalytic system also works well for the diastereoselective Henry reaction to afford the corresponding adducts in up to 95:5 *syn*/*anti* selectivity and 95% enantioselectivity.

1. Introduction

The Henry (nitroaldol) reaction is an important carbon–carbon bond forming reaction, which can produce a new stereogenic center at the β-position of the nitro functionality. Since the resulting β-nitro alcohol adducts are valuable synthetic intermediate and useful building blocks for many biological active compounds, much effort has been focused on the development of the asymmetric Henry reactions.

Since the first asymmetric version of the Henry reaction was reported by Shibasaki in 1992,[1] various effective catalytic systems based on metal[2–6] and non-metals[7–13] have been developed. Amongst them, the copper-containing system is particularly promising due to its ambifunctional character,[14] resulting in high catalytic activity and excellent enantioselectivity especially when in combination with chiral ligands such as bisoxazolines,[15–21] (−)-sparteine,[22] bisimidazolines,[23,24] diamines,[25–33] sulfonyldiamines,[34–36] aminopyridines,[37,38] salen[39–45] and *N*,*N*′-dioxides,[46] etc.

Although chiral amino alcohols have frequently been used in catalytic asymmetric synthesis, little research has been carried out on the copper-amino alcohol catalyzed stereoselective Henry reaction[47–49] and in most cases, only moderate enantioselectivities have been obtained, which is quite different from the analogous zinc-amino alcohol systems.[50–53]

We also noticed that in Arai's work, chiral binaphthylazepine derived diamines **1**[28] and sulfonyldiamine **2** (Fig. 1)[34,35] exhibited high efficiencies in the copper catalyzed Henry reaction. The steric repulsion between the binaphthyl backbone and the two phenyl groups were hypothesized to provide a better enantio-locking of the substrate with catalysts, which could be useful for the design and generation of other effective ligands for asymmetric Henry reactions, especially for diastereoselective reactions with a bulky nitroalkane.

Our recent studies involved utilization of the binaphthyl derived amino alcohol ($1R_a$,2*S*,3*R*)-**3** as an efficient catalyst for many asymmetric transformations such as alkynylation and arylation reaction,[54–56] which led us to reexamine this catalyst in the scope of the classic Henry reaction. Herein we report the development of a copper(II)-binaphthylazepine derived amino alcohol complex for the addition of nitroalkanes to a range of aldehydes. This asymmetric Henry reaction proceeds at room temperature and is operationally simple, scalable and has broad functional group compatibility.

2. Results and discussion

2.1. Optimization of the reaction conditions

An initial exploration was performed in the reaction of nitromethane with 4-nitrobenzaldehyde using 15 mol % copper salt and ($1R_a$,2*S*,3*R*)-**3**. Several commercial available copper salts were investigated at room temperature. Copper salt $Cu(OAc)_2$ turned out to be suitable Lewis acid for the model reaction, giving 90% yield and 87% ee (Table 1, entry 4). Also CuCl and $Cu(OTf)_2$ facilitated the reaction and afforded the nitroaldol adduct in good yields but with poor enantioselectivities (entries 1 and 3). The replacement of $Cu(OAc)_2$ with air stable $Cu(OAc)_2{\cdot}H_2O$ showed comparable ees and yields (entries 5 vs 6). Further optimization of catalyst loading revealed that lowering the ratio of $Cu(OAc)_2{\cdot}H_2O$ from 10 mol % to 5 mol % did not change the conversion or enantioselectivity significantly (entries 6 vs 7).

Next the effect of solvents was tested in the asymmetric Henry reaction (Table 2). Solvent Et_2O seemed to be the best for the reaction, affording the corresponding product in high enantioselectivity (entry 2), although a longer reaction time (60 h for 4-nitrobenzaldehyde) was needed. A further study revealed that for the more inert

* Corresponding authors. Tel./fax: +86 20 39943048.
E-mail address: lugui@mail.sysu.edu.cn (G. Lu).

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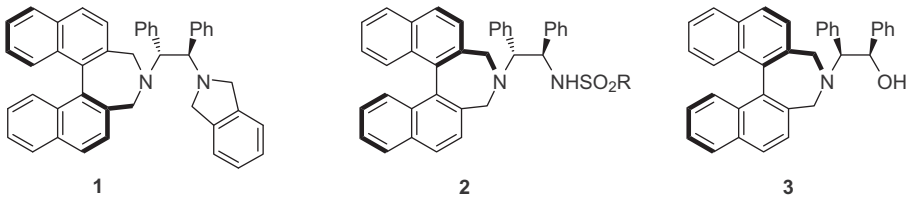
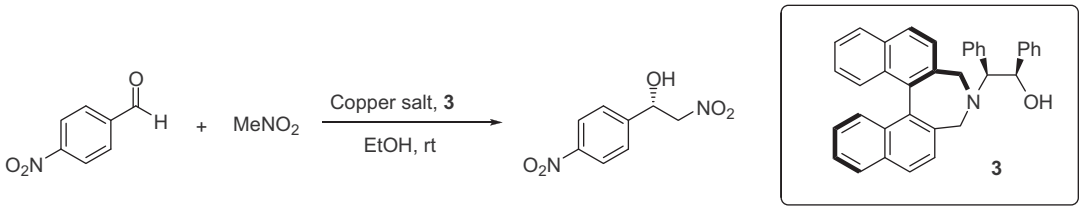


Figure 1. Some 1,1′-binaphthylazepine derived amino alcohol.

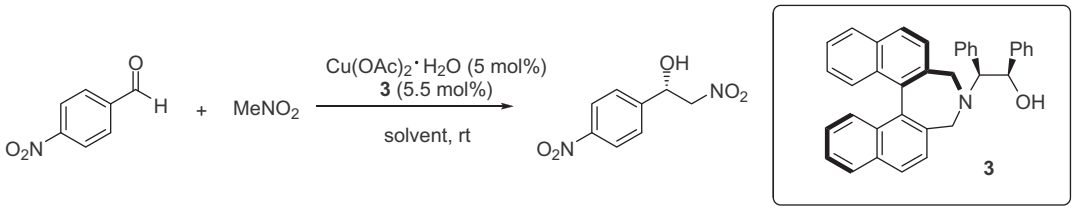
Table 1
Screening of copper salts in the asymmetric Henry reaction[a]



Entry	Copper salt	Catalyst loading (mol %)	Time (h)	Yield[b] (%)	ee[c] (%)
1	CuCl	15	24	92	rac
2	$CuBr_2$	15	96	Trace	—
3	$Cu(OTf)_2$	15	12	95	rac
4	$Cu(OAc)_2$	15	24	90	87
5	$Cu(OAc)_2$	10	24	90	88
6	$Cu(OAc)_2{\cdot}H_2O$	10	24	89	88
7	$Cu(OAc)_2{\cdot}H_2O$	5	24	86	87

[a] All reactions were performed on a 0.375 mmol scale of 4-nitrobenzaldehyde in 1.0 mL ethanol, and 10 equiv of nitromethane was used.
[b] Isolated yield.
[c] Enantiomeric excess was determined by HPLC analysis. The absolute configurations of the products were determined by comparison with the literature values.

Table 2
Effects of solvents in the asymmetric Henry reaction[a]

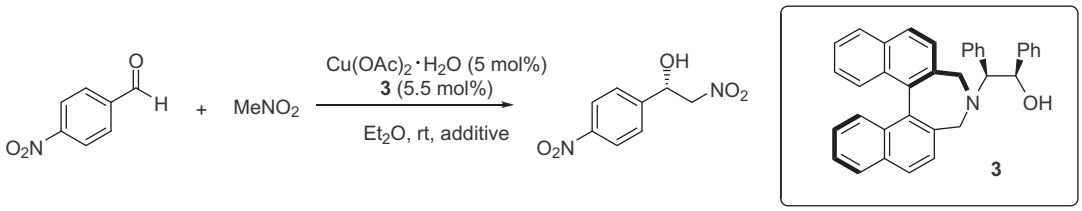


Entry	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	THF	48	60	80
2	Et_2O	60	73	93
3[d]	Et_2O	120	Trace	—
4	CH_2Cl_2	48	55	88
5	Toluene	48	25	45
6	MeOH	48	80	73
7	EtOH	24	88	87
8[d]	EtOH	120	80	89
9	*n*-PrOH	24	62	83

[a] All reactions were performed on a 0.375 mmol scale of 4-nitrobenzaldehyde in 1.0 mL solvent, and 10 equiv of nitromethane was used.
[b] Isolated yield.
[c] Enantiomeric excess was determined by HPLC analysis. The absolute configurations of the products were determined by comparison with the literature values.
[d] The reaction was performed with benzaldehyde.

benzaldehyde substrate, trace product can be obtained even after 120 h in Et_2O (entry 3). In general, protic solvents, such as methanol, ethanol, or *n*-propanol, helped to accelerate the reaction rate without compromising the stereoselectivity (entries 6–9). For example, when EtOH was used, the reaction could be completed in 24 h and obtained with 88% yield and 87% ee (entry 7).

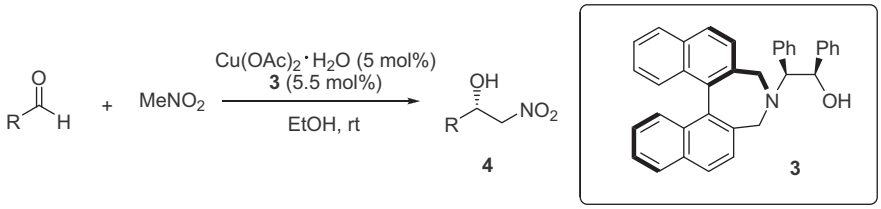
Table 3
Effects of organic bases in the asymmetric Henry reaction[a]



Entry	Additive	Time (h)	Yield[b] (%)	ee[c] (%)
1	—	60	73	93
2	Et_3N	24	84	74
3	Pyridine	48	52	34
4	DMAP	48	64	29
5	DBU	48	80	14
6	DIPEA	24	83	75

[a] All reactions were performed on a 0.375 mmol scale of 4-nitrobenzaldehyde in 1.0 mL Et_2O, and 10 equiv of nitromethane was used.
[b] Isolated yield.
[c] Enantiomeric excess was determined by HPLC analysis. The absolute configurations of the products were determined by comparison with literature values.

Table 4
Enantioselective Henry reaction of various aldehydes with nitromethane under optimal conditions[a]



Entry	R	Product	Time (h)	Yield[b] (%)	ee[c] (%)
1	C_6H_5	**4a**	120	80	89
2	*p*-$NO_2C_6H_4$	**4b**	24	88	87
3	*o*-$NO_2C_6H_4$	**4c**	36	83	92
4	*p*-$OMeC_6H_4$	**4d**	72	8	82
5	*o*-$OMeC_6H_4$	**4e**	96	52	91
6	*p*-ClC_6H_4	**4f**	60	74	90
7	*o*-ClC_6H_4	**4g**	72	65	88
8	*p*-BrC_6H_4	**4h**	72	76	89
9	*m*-BrC_6H_4	**4i**	72	66	83
10	*p*-FC_6H_4	**4j**	72	71	88
11	*p*-PhC_6H_4	**4k**	48	44	91
12	1-Naphthyl	**4l**	72	70	92
13	*i*-Pr	**4m**	72	65	95
14	*i*-Bu	**4n**	72	62	91
15	*n*-Bu	**4o**	72	80	94
16	Cyclohexyl	**4p**	72	79	97
17	$PhCH_2CH_2$	**4q**	72	70	96

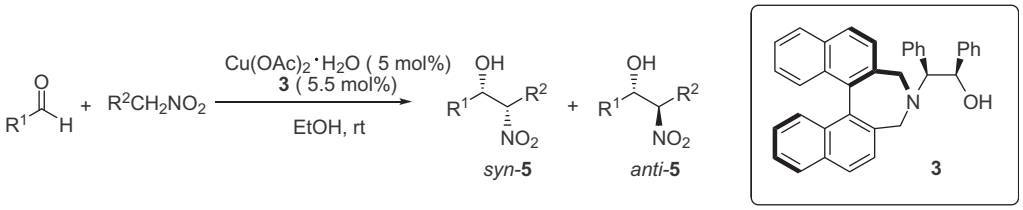
[a] All reactions were performed on a 0.375 mmol scale of 4-nitrobenzaldehyde in 0.5 mL ethanol, and 10 equiv of nitromethane was used.
[b] Isolated yield.
[c] Enantiomeric excess was determined by HPLC analysis. The absolute configurations of the products were determined by comparison with literature values.

We also attempted to improve the efficacy of these transformations in Et_2O, using 20 mol % of an organic base such as Et_3N, pyridine, DMAP, DBU or DIPEA as the additive in order to accelerate the reaction (Table 3), but this led to a significant decrease in ee values. Hence we chose EtOH as the optimal solvent and used it for further screening.

2.2. Scope and limitation of the catalytic system

Next, the scope of the reaction was examined. Various aromatic and aliphatic aldehydes were smoothly converted to β-nitro alcohols at room temperature, and in all cases, the (*S*)-enriched products were obtained by using the (*R*)-binaphthyl derived amino alcohol **3** (Table 4). Stereoselectivities were not considerably influenced by the electronic and steric character of substituents in the aromatic ring, and the enantiomeric purities were moderate to high. For example, the simplest aromatic aldehydes such as benzaldehyde was converted to the Henry adduct in 80% yield with 89% ee (entry 1). Aldehydes with electron-withdrawing substituents such as 2-NO_2 and 2-Cl (entries 3 and 7) led to products with similar enantioselectivities to aldehydes with electron-donating substituents such as 2-OMe (entry 5). The *para*-substituted aldehydes offered comparable enantiomeric excess with *ortho*-substituted aldehydes (2-Cl vs 4-Cl, entries 6 vs 7). An exception was the deactivated

Table 5
Diastereoselective Henry reactions of various aldehydes with other nitroalkanes[a]



Entry	Aldehyde	$R^2CH_2NO_2$	Product	Time (h)	Yield[b] (%)	dr (*syn*/*anti*)[c]	ee of *syn*[d] (%)
1	Isobutyraldehyde	$EtNO_2$	**5a**	72	77	95:5	95
2	2-Methylbutyraldehyde	$EtNO_2$	**5b**	72	75	91:9	93
3	Cyclohexanecarboxaldehyde	$EtNO_2$	**5c**	72	78	94:6	93
4	3-Phenylpropionaldehyde	$EtNO_2$	**5d**	72	73	80:20	91
5	Isobutyraldehyde	$PrNO_2$	**5e**	72	67	61:39	94
6	3-Phenylpropionaldehyde	$PrNO_2$	**5f**	72	58	80:20	92

[a] All reactions were performed on a 0.375 mmol scale of aldehyde in 0.5 mL ethanol, and 10 equiv of nitroalkane was used.
[b] Isolated yield.
[c] Diastereoselectivity was determined by ^{1}H NMR spectroscopy.
[d] Enantiomeric excess was determined by HPLC analysis. The absolute configurations of the products were determined by comparison with literature values.

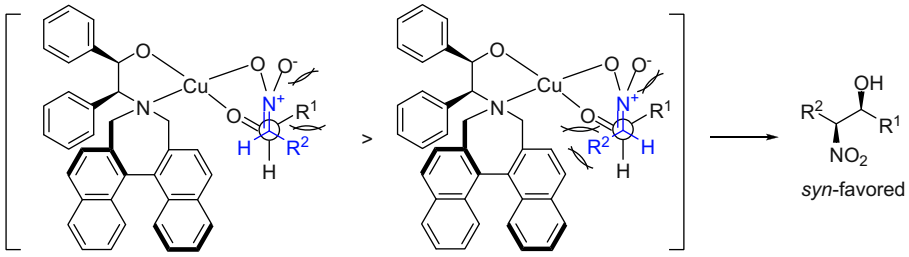


Figure 2. Possible transition structure for the *syn*-selective Henry reaction.

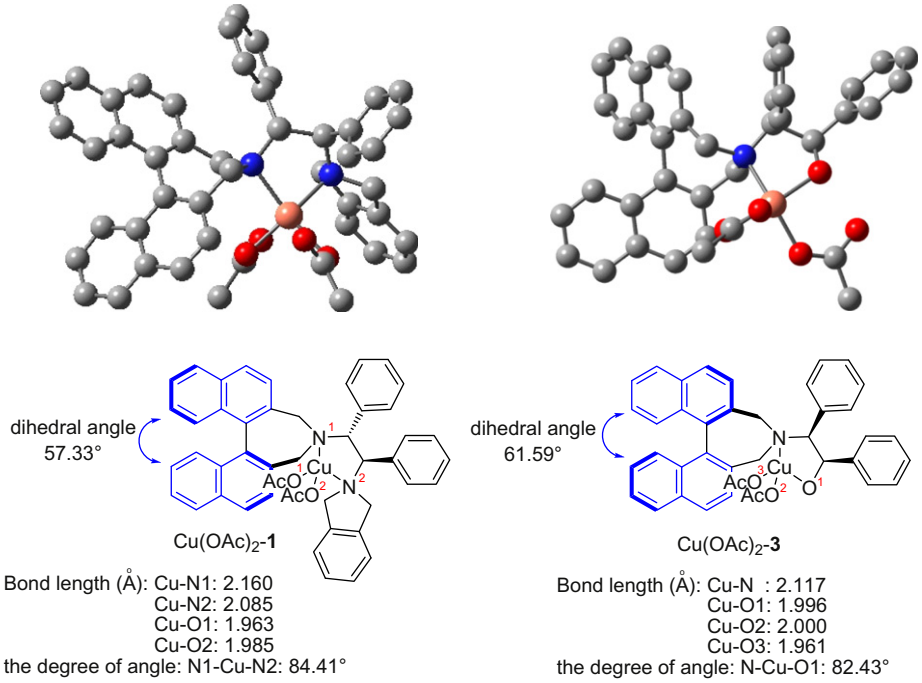


Figure 3. Computational geometry of $Cu(OAc)_2$-**1** and $Cu(OAc)_2$-**3** complexes (Cu: pink; N: blue; O: red; C: grey; H was omitted for clarity).

para-anisaldehyde, affording the dehydrated product in large quantity, which could be the result of the increased nucleophilicity of the substrate (entry 4).

Typically aliphatic aldehydes provided the corresponding adducts with higher enantioselectivities than aromatic aldehydes (entries 13–17), in particular α-branched aliphatic aldehydes such as cyclohexanecarboxaldehyde gave the product with excellent enantioselectivities of up to 97% (entry 16).

The optimized catalyst system was also applied to the diastereoselective Henry reaction, the latter can form two contiguous stereogenic centers simultaneously. Since aliphatic aldehydes showed better enantioselectivities than aromatic aldehydes, we studied the addition of nitroethane to various aliphatic aldehydes; the corresponding results are summarized in Table 5. Although the reaction of nitroethane was slow compared with nitromethane, it provided the adduct with good *syn*-selectivity (entries 1–4). Diastereoselectivities were significantly improved when the α-branched aliphatic aldehydes were used (entries 1 and 3). For example, the reaction of isobutyraldehyde with nitroethane gave the product in 77% yield with 95:5 *syn*/*anti* selectivity, and the enantiomeric excess of the *syn*-adduct was as high as 95% (entry 1). However, in the case of nitropropane, the diastereoselectivity decreased greatly to 61:39 while the enantiomeric excess of the major *syn* isomer remained at 94% for the bulky aliphatic aldehyde (entries 1 and 5).

These results showed that for the copper catalyzed asymmetric Henry reaction, binaphthylazepine derived amino alcohol (1R_a,2*S*,3*R*)-**3** was superior to sulfonyldiamine **2**[34] in both enantioselectivity and diastereoselectivity, while diamines **1**[28] exhibited comparable ee but lower dr than **3**.

2.3. Mechanism analysis

This *syn*-selectivity of the reaction can be explained by a possible transition state (see Fig. 2).[57] The orientation of the substituent (R^1) of the aldehyde could be regulated by the substituent (R^2) of the nitronate and the steric hindrance of the chiral ligand to induce the direct attack of the aldehyde onto *Si*-face, establishing the (*S*)-configuration at C1 position, whereas in the case of nitroethane, *syn*-product was favored. It was expected that the inclusion of bulky ligands such as binaphthylazepine in the coordination sphere of copper could result in higher stereocontrol, which was also proved by our experimental data and the results from Arai et al.[28,34]

To rationalize further the stereochemical outcome of the reaction, computational calculations of the geometry of the complexes $Cu(OAc)_2$-**1** and **3** and energetic parameters were also performed with the BHandHLYP/Gen method using the Gaussian 03 program. The optimal geometries are presented in Figure 3. It can be seen that two phenyl rings of the ethylenediamine moiety and the isoindoline ring of **1**, are all perpendicular to the nearly planar structure of the tetra-coordinated copper complex. According to the model proposed by Evans,[14] the most reactive transition structure was the nitromethane perpendicular to the ligand plane and the aldehyde in the ligand plane. Both $Cu(OAc)_2$-**1** and **3** afforded adducts with an (*S*)-configuration, indicating that the nitronate attacks the *Si*-face of the aldehyde. Better enantioselectivity was achieved by $Cu(OAc)_2$-**1**[28] since the perpendicular bulky isoindoline ring of **1** limits the orientation of aldehydes more efficiently. The higher diastereoselectivity of $Cu(OAc)_2$-**3** for a nitroalkane with a large steric hindrance can be explained by $Cu(OAc)_2$-**3** possessing a large dihedral angle between the two naphthyl groups (61.59°), which together with the more crowded (2*S*,3*R*)-diphenylethylenediamine moiety, helped to influence both the axial nitronate and the equatorial aldehyde.

3. Conclusion

In conclusion, we have demonstrated the application of copper-binaphthylazepine derived amino alcohol complexes to asymmetric nitroaldol reactions. High yields and good enantioselectivities were obtained for both aromatic and aliphatic aldehydes. Moreover, this catalytic system also works well for the diastereoselective Henry reaction to afford the corresponding adducts in up to 95:5 *syn*/*anti* selectivity and 95% enantioselectivity. Further detailed mechanistic studies are currently in progress.

4. Experimental

All reactions were carried out in flame-dried glassware under a nitrogen atmosphere. All solvents were freshly distilled from standard drying agents. Unless otherwise stated, commercial reagents purchased from Alfa Aesar, Acros and Aldrich chemical companies were used without further purification. Purification of reaction products was carried out by flash chromatography using Qing Dao Sea Chemical Reagent silica gel (200–300 mesh). ^{1}H NMR spectra were recorded on a Bruker Avance III spectrometer (400 MHz). HPLC analyses were conducted on an Agilent 1200 instrument using Chiralcel OD–H, OJ–H or AD–H columns (0.46 cm diameter × 25 cm length). Analytical TLC was performed using EM separations percolated silica gel 0.2 mm layer UV 254 fluorescent sheets.

4.1. General procedure for the catalytic Henry reaction of nitroalkanes with aldehydes

At first, (*R*)-*N*-[(1*S*,2*R*)-1,2-diphenyl-2-hydroxyethyl]-3,5-dihydro-4*H*-dinaphtho[2,1-*c*:1′,2′-*e*]-azepine **1** (10.1 mg, 0.021 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (3.75 mg, 0.019 mmol) were mixed in 1.0 mL CH_2Cl_2 and stirred overnight. Then the solvent was removed under reduced pressure, after which 0.5 mL EtOH, aldehyde (0.375 mmol) and nitromethane (0.2 mL, 3.75 mmol) were added to the residue. After the mixture was stirred at room temperature for 24–72 h, TLC indicated the completion of the reaction. The volatile components were removed under reduced pressure and the residue was purified by a silica gel column chromatography to afford the nitroaldol adduct. Diastereoselectivity was determined from the ^{1}H NMR spectrum and the enantiomeric excess was determined by HPLC analysis.

4.1.1. (*S*)-2-Nitro-1-phenylethanol 4a[14]

Compound **4a** was purified by silica gel column chromatography (CH_2Cl_2/petroleum ether = 3:1) to afford a colorless oil, 80% yield, 89% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.30 (m, 5H), 5.38–5.36 (m, 1H), 4.56–4.51 (m, 1H), 4.44 (dd, 1H, J = 3.2, 13.1 Hz), 3.43 (s, 1H). Enantiomeric excess was determined by HPLC with a Chiralcel OD–H column (hexane/isopropanol = 90:10, 0.8 mL/min, 215 nm), t_{major} = 17.4 min, t_{minor} = 14.5 min.

4.1.2. (*S*)-2-Nitro-1-(4-nitrophenyl)ethanol 4b[14]

Compound **4b** was purified by silica gel column chromatography (CH_2Cl_2/petroleum ether = 4:1) to afford an off-white solid, 88% yield, 87% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, 1H, J = 8.2 Hz), 7.64 (d, 1H, J = 8.3 Hz), 5.63–5.61 (m, 1H), 4.65–4.56 (m, 2H), 3.26 (s, 1H). Enantiomeric excess was determined by HPLC with a Chiralcel OD–H column (hexane/isopropanol = 85:15, 0.8 mL/min, 254 nm), t_{major} = 22.6 min, t_{minor} = 18.8 min.

4.1.3. (*S*)-2-Nitro-1-(2-nitrophenyl) ethanol 4c[14]

Compound **4c** was purified by silica gel column chromatography (CH_2Cl_2/petroleum ether = 4:1) to afford a brown solid, 83%

yield, 92% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06–8.03 (m, 1H), 7.95–7.93 (m, 1H), 7.77–7.73 (m, 1H), 7.57–7.52 (m, 1H), 6.02 (d, 1H, J = 7.1 Hz), 4.86–4.82 (m, 1H), 4.58–4.53 (m, 1H), 3.60 (s, 1H). Enantiomeric excess was determined by HPLC with a Chiralcel OD–H column (hexane/isopropanol = 90:10, 0.8 mL/min, 215 nm), t_{major} = 17.5 min, t_{minor} = 16.3 min.

4.1.4. (*S*)-1-(4-Methoxyphenyl)-2-nitroethanol 4d[14]

Compound **4d** was purified by silica gel column chromatography (EtOAc/hexane = 1:9) to afford a colorless oil, 8% yield, 82% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.30 (m, 2H), 6.94–6.90 (m, 2H), 5.40 (dd, 1H, J = 3.0, 9.6 Hz), 4.60 (dd, 1H, J = 9.6, 13.6 Hz), 4.47 (dd, 1H, J = 3.0, 13.6 Hz), 3.81 (s, 3H), 2.79 (br s, 1H). Enantiomeric excess was determined by HPLC with a Chiralcel OD–H column (hexane/isopropanol = 85:15, 0.8 mL/min, 215 nm), t_{major} = 27.8 min, t_{minor} = 22.1 min.

4.1.5. (*S*)-1-(2-Methoxyphenyl)-2-nitroethanol 4e[14]

Compound **4e** was purified by silica gel column chromatography (CH_2Cl_2/petroleum ether = 1:1) to afford a colorless oil, 52% yield, 91% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.42 (m, 1H), 7.36–7.30 (m, 1H), 7.02–6.98 (m, 1H), 6.92–6.90 (d, 1H, J = 8.4 Hz), 5.61 (m, 1H), 4.63 (dd, 1H, J = 3.2, 13.0 Hz), 4.56 (dd, 1H, J = 9.2, 13.0 Hz), 3.87 (s, 3H), 3.26 (d, 1H, J = 6.2 Hz). Enantiomeric excess was determined by HPLC with a Chiralcel OD–H column (hexane/isopropanol = 90:10, 0.8 mL/min, 215 nm), t_{major} = 14.5 min, t_{minor} = 12.4 min.

4.1.6. (*S*)-1-(4-Chlorophenyl)-2-nitroethanol 4f[14]

Compound **4f** was purified by silica gel column chromatography (CH_2Cl_2/petroleum ether = 1:1) to afford a colorless oil, 74% yield, 90% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.33 (m, 4H), 5.46–5.42 (m, 1H), 4.57 (dd, 1H, J = 9.4, 13.4 Hz), 4.48 (dd, 1H, J = 3.2, 13.4 Hz), 3.10 (s, 1H). Enantiomeric excess was determined by HPLC with a Chiralcel OD–H column (hexane/isopropanol = 90:10, 0.8 mL/min, 215 nm), t_{major} = 17.3 min, t_{minor} = 14.4 min.

4.1.7. (*S*)-1-(2-Chlorophenyl)-2-nitroethanol 4g[14]

Compound **4g** was purified by silica gel column chromatography (CH_2Cl_2/petroleum ether = 1:1) to afford a colorless oil, 65% yield, 88% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.64 (m, 1H), 7.39–7.30 (m, 3H), 5.76 (dd, 1H, J = 2.2, 9.6 Hz), 4.59 (dd, 1H, J = 2.4, 13.5 Hz), 4.37 (dd, 1H, J = 9.6, 13.5 Hz), 3.01 (s, 1H). Enantiomeric excess was determined by HPLC with a Chiralcel OJ–H column (hexane/isopropanol = 97:3, 0.8 mL/min, 215 nm), t_{major} = 44.6 min, t_{minor} = 40.2 min.

4.1.8. (*S*)-1-(4-Bromophenyl)-2-nitroethanol 4h[14]

Compound **4h** was purified by silica gel column chromatography (CH_2Cl_2/petroleum ether = 1:1) to afford a colorless oil, 76% yield, 89% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.50 (m, 2H), 7.27–7.25 (m, 2H), 4.56–4.52 (m, 1H), 4.39 (dd, 1H, J = 3.3, 13.2 Hz), 3.49 (s, 1H), 2.13 (s, 1H). Enantiomeric excess was determined by HPLC with a Chiralcel OD–H column (hexane/isopropanol = 90:10, 1.0 mL/min, 215 nm), t_{major} = 17.8 min, t_{minor} = 14.1 min.

4.1.9. (*S*)-1-(3-Bromophenyl)-2-nitroethanol 4i[14]

Compound **4i** was purified by silica gel column chromatography (CH_2Cl_2/petroleum ether = 1:1) to afford a colorless oil, 66% yield, 83% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (s, 1H), 7.49–7.47 (d, 1H, J = 8.0 Hz), 7.33–7.25 (m, 2H), 5.43–5.41 (d, 1H, J = 8.4 Hz), 4.59–4.47 (m, 2H), 3.34 (s, 1H). Enantiomeric excess was determined by HPLC with a Chiralcel OD–H column (hexane/*i*-PrOH = 90:10, 0.8 mL/min, 215 nm), t_{major} = 17.6 min, t_{minor} = 13.4 min.

4.1.10. (*S*)-1-(4-Fluorophenyl)-2-nitroethanol 4j[14]

Compound **4j** was purified by silica gel column chromatography (CH_2Cl_2/petroleum ether = 1:1) to afford a colorless oil, 71% yield, 88% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.36 (m, 2H), 7.11–7.07 (m, 2H), 5.60–5.43 (m, 1H), 4.61–4.56 (m, 1H), 4.49 (dd, 1H, J = 3.2, 13.3 Hz), 3.06 (s, 1H). Enantiomeric excess was determined by HPLC with a Chiralcel OD–H column (hexane/isopropanol = 90:10, 0.8 mL/min, 215 nm), t_{major} = 14.7 min, t_{minor} = 12.7 min.

4.1.11. (*S*)-1-(Biphenyl-4-yl)-2-nitroethanol 4k[14]

Compound **4k** was purified by silica gel column chromatography (CH_2Cl_2/petroleum ether = 1:1) to afford a yellow solid, 44% yield, 91% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65–7.62 (m, 2H), 7.60–7.56 (m, 2H), 7.43–7.49 (m, 4H), 7.39–7.35 (m, 1H), 5.54–5.51 (m, 1H), 4.69–4.63 (m, 1H), 4.49 (dd, 1H, J = 3.1, 13.4 Hz). Enantiomeric excess was determined by HPLC with a Chiralcel OD–H column (hexane/isopropanol = 90:10, 0.8 mL/min, 215 nm), t_{major} = 27.7 min, t_{minor} = 23.6 min.

4.1.12. (*S*)-1-(Naphthalen-1-yl)-2-nitroethanol 4l[14]

Compound **4l** was purified by silica gel column chromatography (CH_2Cl_2/petroleum ether = 3:1) to afford a yellow solid, 70% yield, 92% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, 1H, J = 8.4 Hz), 7.88 (d, 1H, J = 8.1 Hz), 7.83 (d, 1H, J = 8.2 Hz), 7.72 (d, 1H, J = 7.2 Hz), 7.59–7.46 (m, 3H), 6.22–6.20 (m, 1H), 4.66–4.58 (m, 2H), 3.18–3.15 (m, 1H). Enantiomeric excess was determined by HPLC with a Chiralcel OD–H column (hexane/isopropanol = 85:15, 0.8 mL/min, 215 nm), t_{major} = 17.9 min, t_{minor} = 12.6 min.

4.1.13. (*S*)-3-Methyl-1-nitrobutan-2-ol 4m[14]

Compound **4m** was purified by silica gel column chromatography (CH_2Cl_2/petroleum ether = 1:3) to afford a colorless oil, 65% yield, 95% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.51–4.38 (m, 2H), 4.12–4.05 (m, 1H), 3.18 (m, 1H), 1.83–1.74 (m, 1H), 1.00–0.96 (m, 6H). Enantiomeric excess was determined by HPLC with a Chiralcel OD–H column (hexane/isopropanol = 98:2, 0.8 mL/min, 215 nm), t_{major} = 29.9 min, t_{minor} = 27.7 min.

4.1.14. (*S*)-4-Methyl-1-nitropentan-2-ol 4n[14]

Compound **4n** was purified by silica gel column chromatography (CH_2Cl_2/petroleum ether = 1:3) to afford a colorless oil, 62% yield, 91% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.43–4.33 (m, 3H), 3.09 (s, 1H), 1.89–1.77 (m, 1H), 1.54–1.43 (m, 1H), 1.27–1.20 (m, 1H), 0.96 (s, 6H). Enantiomeric excess was determined by HPLC with a Chiralcel OJ–H column (hexane/isopropanol = 98:2, 0.6 mL/min, 215 nm), t_{major} = 40.2 min, t_{minor} = 35.9 min.

4.1.15. (*S*)-1-Nitrohexan-2-ol 4o[14]

Compound **4o** was purified by silica gel column chromatography (CH_2Cl_2/petroleum ether = 1:3) to afford a colorless oil, 80% yield, 94% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.44 (dd, 1H, J = 3.1, 12.7 Hz), 4.40–4.35 (m, 1H), 4.34–4.28 (m, 1H), 3.02 (br s, 1H), 1.57–1.47 (m, 3H), 1.34–1.25 (m, 3H), 0.92 (t, 3H, J = 7.2 Hz). Enantiomeric excess was determined by HPLC with a Chiralcel AD–H column (hexane/isopropanol = 98:2, 0.8 mL/min, 215 nm), t_{major} = 37.5 min, t_{minor} = 29.4 min.

4.1.16. (*S*)-1-Cyclohexyl-2-nitroethanol 4p[14]

Compound **4p** was purified by silica gel column chromatography (CH_2Cl_2/petroleum ether = 1:3) to afford a colorless oil, 79% yield, 97% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.51–4.35 (m, 2H), 4.10–4.01 (m, 1H), 3.27 (br s, 1H), 1.84–1.72 (m, 3H), 1.71–1.60 (m, 2H), 1.50–1.37 (m, 1H), 1.28–1.02 (m, 5H). Enantiomeric excess was determined by HPLC with a Chiralcel AD–H column (hexane/

isopropanol = 97:3, 0.8 mL/min, 215 nm), t_{major} = 23.9 min, t_{minor} = 22.9 min.

4.1.17. (*S*)-1-Nitro-4-phenylbutan-2-ol 4q[14]

Compound **4q** was purified by silica gel column chromatography (CH_2Cl_2/petroleum ether = 1:3) to afford a white solid, 70% yield, 96% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.28 (m, 2H), 7.24–7.18 (m, 3H), 4.38–4.33 (m, 2H), 4.29 (s, 1H), 2.88–2.80 (m, 2H), 2.76–2.69 (m, 1H), 1.89–1.73 (m, 2H). Enantiomeric excess was determined by HPLC with a Chiralcel OD–H column (hexane/isopropanol = 90:10, 0.8 mL/min, 215 nm), t_{major} = 24.0 min, t_{minor} = 25.6 min.

4.1.18. (3*S*,4*S*)-2-Methyl-4-nitropentan-3-ol 5a[34]

Compound **5a** was purified by silica gel column chromatography (CH_2Cl_2/petroleum ether = 1:1) to afford a colorless oil, 77% yield, 95:5 *syn*/*anti*, 95% ee (*syn*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.62–4.54 (m, 1H), 3.83–3.60 (m, 1H), 2.20 (br s, 1H), 1.82–1.63 (m, 1H), 1.55–1.52 (m, 3H), 1.00–0.95 (m, 3H), 0.87–0.83 (m, 3H). Enantiomeric excess was determined by HPLC with a Chiralcel OD–H column (hexane/isopropanol = 99:1, 0.8 mL/min, 220 nm), for syn-product, t_{major} = 19.2 min, t_{minor} = 16.6 min.

4.1.19. (2*S*,3*S*)-5-Methyl-2-nitrohexan-3-ol 5b[34]

Compound **5b** was purified by silica gel column chromatography (CH_2Cl_2/petroleum ether = 1:1) to afford a colorless oil, 75% yield, 91:9 *syn*/*anti*, 93% ee (*syn*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.47–4.33 (m, 1H), 3.94–3.85 (m, 1H), 2.06 (br s, 1H), 1.94–1.83 (m, 1H), 1.56–1.53 (m, 3H), 1.44–1.37 (m, 1H), 1.26–1.22 (m, 1H), 0.97–0.93 (m, 6H). Enantiomeric excess was determined by HPLC with a Chiralcel AD–H column (hexane/isopropanol = 97:3, 0.8 mL/min, 220 nm), for *syn*-product, t_{major} = 16.4 min, t_{minor} = 15.5 min.

4.1.20. (1*S*,2*S*)-1-Cyclohexyl-2-nitropropan-1-ol 5c[34]

Compound **5c** was purified by silica gel column chromatography (CH_2Cl_2/petroleum ether = 1:1) to afford a colorless oil, 78% yield, 94:6 *syn*/*anti*, 93% ee (*syn*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.68–4.56 (m, 1H), 3.87–3.56 (m, 1H), 1.82–1.75 (m, 2H), 1.70–1.63 (m, 2H), 1.56–1.52 (m, 3H), 1.39–0.90 (m, 7H). Enantiomeric excess was determined by HPLC with a Chiralcel AD–H column (hexane/isopropanol = 97:3, 1.0 mL/min, 220 nm), for syn-product, t_{major} = 14.0 min, t_{minor} = 21.2 min.

4.1.21. (3*S*,4*S*)-4-Nitro-1-phenylpentan-3-ol 5d[34]

Compound **5d** was purified by silica gel column chromatography (CH_2Cl_2/petroleum ether = 1:1) to afford a colorless oil, 73% yield, 80:20 *syn*/*anti*, 91% ee (*syn*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.16 (m, 2H), 7.12–7.05 (m, 3H), 4.56–4.44 (m, 1H), 4.00–3.85 (m, 1H), 2.89–2.82 (m, 1H), 2.74–2.64 (m, 1H), 2.21 (br s, 1H), 1.86–1.67 (m, 2H), 1.51–1.47 (m, 3H). Enantiomeric excess was determined by HPLC with a Chiralcel AD–H column (hexane/isopropanol = 96:4, 1.0 mL/min, 220 nm), for *syn*-product, t_{major} = 18.7 min, t_{minor} = 17.3 min.

4.1.22. (3*S*,4*S*)-2-Methyl-4-nitrohexan-3-ol 5e[21]

Compound **5e** was purified by silica gel column chromatography (EtOAc/hexanes = 15:85) to afford a colorless oil, 67% yield, 61:39 *syn*/*anti*, 94% ee (*syn*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.56–4.42 (m, 1H), 3.83–3.60 (m, 1H), 2.40–2.20 (m, 1H), 2.10–2.00 (m, 1H), 1.92–1.63 (m, 2H), 1.05–0.90 (m, 9H). Enantiomeric excess was determined by HPLC with a Chiralcel AD–H column (hexane/isopropanol = 95:5, 1.0 mL/min, 208 nm), for *syn*-product, t_{major} = 8.4 min, t_{minor} = 10.6 min.

4.1.23. (3*S*,4*S*)-4-Nitro-1-phenylhexan-3-ol 5f[21]

Compound **5f** was purified by silica gel column chromatography (EtOAc/hexanes = 15:85) to afford a colorless oil, 58% yield, 80:20 *syn*/*anti*, 92% ee (*syn*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.24 (m, 2H), 7.22–7.15 (m, 3H), 4.40–4.32 (m, 1H), 4.00–3.85 (m, 1H), 2.90–2.82 (m, 1H), 2.74–2.64 (m, 1H), 2.54–2.48 (m, 1H), 2.06–1.70 (m, 4H), 0.96–0.90 (m, 3H). Enantiomeric excess was determined by HPLC with a Chiralcel OD–H column (hexane/isopropanol = 95:5, 1.0 mL/min, 208 nm), for *syn*-product, t_{major} = 18.1 min, t_{minor} = 25.2 min.

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References

1. Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418.
2. Shibasaki, M.; Gröger, H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. III, p 1075.
3. Shibasaki, M.; Gröger, H.; Kanai, M. In *Comprehensive Asymmetric Catalysis, Supplement 1*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 2004; p 131.
4. Boruwa, J.; Gogoi, N.; Saikia, P. P.; Barua, N. C. *Tetrahedron: Asymmetry* **2006**, *17*, 3315.
5. Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, 2561.
6. Palomo, C.; Oiarbide, M.; Mielgo, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5442.
7. Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2054.
8. Allingham, M. T.; Howard-Jones, A.; Murphy, P. J.; Thomas, D. A.; Caulkett, P. W. R. *Tetrahedron Lett.* **2003**, *44*, 8677.
9. Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 929.
10. Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Eur. J. Org. Chem.* **2006**, *13*, 2894.
11. Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392.
12. Ube, H.; Terada, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3895.
13. Jammi, S.; Saha, P.; Sanyashi, S.; Sakthivel, S.; Punniyamurthy, T. *Tetrahedron* **2008**, *64*, 11724.
14. Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692.
15. Christensen, C.; Juhl, K.; Jorgensen, K. A. *Chem. Commun.* **2001**, 2222.
16. Christensen, C.; Juhl, K.; Hazell, R. G.; Jorgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4875.
17. Risgaard, T.; Gothelf, K. V.; Jorgensen, K. A. *Org. Biomol. Chem.* **2003**, *1*, 153.
18. Lu, S. F.; Du, D. M.; Zhang, S. W.; Xu, J. *Tetrahedron: Asymmetry* **2004**, *15*, 3433.
19. Du, D. M.; Lu, S. F.; Fang, T.; Xu, J. *J. Org. Chem.* **2005**, *70*, 3712.
20. Ginotra, S. K.; Singh, V. K. *Org. Biomol. Chem.* **2007**, *5*, 3932.
21. Toussaint, A.; Pfaltz, A. *Eur. J. Org. Chem.* **2008**, 4591.
22. Maheswaran, H.; Prasanth, K. L.; Krishna, G. G.; Ravikumar, K.; Sridhar, B.; Kantam, M. L. *Chem. Commun.* **2006**, 4066.
23. Ma, K. Y.; You, J. S. *Chem. Eur. J.* **2007**, *13*, 1863.
24. Bures, F.; Kulhanek, J.; Ruzicka, A. *Tetrahedron Lett.* **2009**, *50*, 3042.
25. Arai, T.; Watanabe, M.; Fujiwara, A.; Yokoyama, N.; Yanagisawa, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5978.
26. Bandini, M.; Piccinelli, F.; Tommasi, S.; Umani-Ronchi, A.; Ventrici, C. *Chem. Commun.* **2007**, 616.
27. Bandini, M.; Benaglia, M.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *Org. Lett.* **2007**, *9*, 2151.
28. Arai, T.; Watanabe, M.; Yanagisawa, A. *Org. Lett.* **2007**, *9*, 3595.
29. Kowalczyk, R.; Sidorowicz, L.; Skarzewski, J. *Tetrahedron: Asymmetry* **2008**, *19*, 2310.
30. Selvakumar, S.; Sivasankaran, D.; Singh, V. K. *Org. Biomol. Chem.* **2009**, *7*, 3156.
31. Sanjeevakumar, N.; Periasamy, M. *Tetrahedron: Asymmetry* **2009**, *20*, 1842.
32. Breuning, M.; Hein, D.; Steiner, M.; Gessner, V. H.; Strohmann, C. *Chem. Eur. J.* **2009**, *15*, 12764.
33. Noole, A.; Lippur, K.; Metsala, A.; Lopp, M.; Kanger, T. *J. Org. Chem.* **2010**, *75*, 1313.
34. Arai, T.; Takashita, R.; Endo, Y.; Watanabe, M.; Yanagisawa, A. *J. Org. Chem.* **2008**, *73*, 4903.
35. Arai, T.; Taneda, Y.; Endo, Y. *Chem. Commun.* **2010**, *46*, 7936.
36. Steurer, M.; Bolm, C. *J. Org. Chem.* **2010**, *75*, 3301.
37. Blay, G.; Climent, E.; Fernandez, I.; Hernández-Olmos, V.; Pedro, J. R. *Tetrahedron: Asymmetry* **2007**, *18*, 1603.
38. Blay, G.; Domingo, L. R.; Hernández-Olmos, V.; Pedro, J. R. *Chem. Eur. J.* **2008**, *14*, 4725.

39. Gan, C.; Lai, G.; Zhang, Z.; Wang, Z.; Zhou, M. M. *Tetrahedron: Asymmetry* **2006**, *17*, 725.
40. Xiong, Y.; Wang, F.; Huang, X.; Wen, Y.; Feng, X. *Chem. Eur. J.* **2007**, *13*, 829.
41. Jiang, J. J.; Shi, M. *Tetrahedron: Asymmetry* **2007**, *18*, 1376.
42. Colak, M.; Demirel, N. *Tetrahedron: Asymmetry* **2008**, *19*, 635.
43. Lai, G.; Wang, S.; Wang, Z. *Tetrahedron: Asymmetry* **2008**, *19*, 1813.
44. Guo, J.; Mao, J. *Chirality* **2009**, *21*, 619.
45. Xin, D.; Ma, Y.; He, F. *Tetrahedron: Asymmetry* **2010**, *21*, 333.
46. Qin, B.; Xiao, X.; Liu, X.; Huang, J.; Wen, Y.; Feng, X. *J. Org. Chem.* **2007**, *72*, 9323.
47. Mansawat, W.; Saengswang, I.; U-prasitwong, P.; Bhanthumnavin, W.; Vilaivan, T. *Tetrahedron Lett.* **2007**, *48*, 4235.
48. Ha, W.; Shan, Z. *Lett. Org. Chem.* **2008**, *5*, 79.
49. Constable, E. C.; Zhang, G.; Housecroft, C. E.; Neuburger, M.; Schaffner, S.; Woggon, W. D.; Zampese, J. A. *New J. Chem.* **2009**, *33*, 2166.
50. Trost, B. M.; Yeh, V. S. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 861.
51. Trost, B. M.; Yeh, V. S. C.; Ito, H.; Bremeyer, N. *Org. Lett.* **2002**, *4*, 2621.
52. Palomo, C.; Oiarbide, M.; Laso, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3881.
53. Bulut, A.; Aslan, A.; Dogan, Ö. *J. Org. Chem.* **2008**, *73*, 7373.
54. Lu, G.; Li, X. S.; Zhou, Z. Y.; Chan, W. L.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 2147.
55. Lu, G.; Kwong, F. Y.; Ruan, J. W.; Li, Y. M.; Chan, A. S. C. *Chem. Eur. J.* **2006**, *12*, 4115.
56. Liu, C.; Guo, Z. L.; Weng, J.; Lu, G.; Chan, A. S. C. *Chirality* **2010**, *22*, 159.
57. Sasai, H.; Tokunaga, T.; Watanabe, S.; Suzuki, T.; Itoh, N.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 7388.