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Asymmetric addition of diethylzinc to aldehydes catalyzed by a camphor-derived β-amino alcohol

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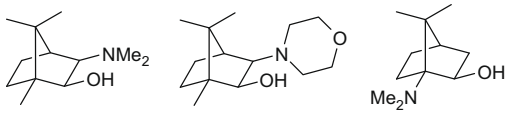
ABSTRACT

The asymmetric addition of diethylzinc to aromatic and aliphatic aldehydes, including linear aliphatic ones, catalyzed by 2 mol % of β-amino alcohol (1*S*, 2*R*)-7,7-dimethyl-1-morpholin-4-yl-bicyclo[2.2.1]heptan-2-ol **10** gave the corresponding secondary alcohols in high yields and with up to 94% ee at ambient temperature after 15 min.

1. Introduction

The enantioselective addition of organozincs[1,2] to carbonyl compounds in the presence of chiral catalysts has attracted the attention of synthetic organic chemists owing to its mild reaction conditions, wide functional group tolerance, and the low toxicity of the zinc metal. The concomitant construction of an asymmetric C–C bond and a new stereogenic center in the reaction has led to its application in the synthesis of optically active alcohols for the further synthesis of natural products and biologically active components.[3] Among the naturally occurring chiral substances, camphor and its derivatives are not only good chiral auxiliaries[4,5] in asymmetric synthesis, but also useful chiral scaffolds for asymmetric catalysts.[6,7] Chiral β-amino alcohol **1** (DAIB)[8] showed impressive results during catalytic organozinc addition reactions, while its modified analogue MIB **2**,[9] which bears a larger amino coordinator, gave better catalytic activities in the addition of diethylzinc, alkenylzincs, and arylzincs to aldehydes (Fig. 1).[10,11] In contrast, β-amino alcohol **3** was inferior in catalyzing the ethylation reaction (23% ee).[6b] However, an independent study of the chiral ligand **3** by our group in the asymmetric diethylzinc addition reaction with benzaldehyde gave as high as 82% ee of the corresponding adduct. The improved ee presumably arose from the use of less diethylzinc and lower reaction temperatures (Table 1, entry 1). Encouraged by these results and our early efforts on camphor-derived rigid ligands in asymmetric reactions,[7] we decided to develop a more effective and easily prepared ligand bearing a norbornane structure by enlarging the amino moiety of known β-amino alcohol **3** in an asymmetric organozinc addition reaction. Here, we report our findings on 1-*N*,*N*-dialkylamino-2-hydroxynorbornane as catalysts in the asymmetric addition of diethylzinc to aldehydes.



DAIB **1** MIB **2** **3**

Figure 1. Some isoborneol-based β-amino alcohols.

2. Results and discussion

The β-amino alcohol ligands **8–10** were synthesized from the corresponding amino ketone **4**[12] in two steps (Scheme 1). Treatment of amine **4** with 1,4-butane dibromide, 1,5-pentane dibromide, and bis-(2-bromoethyl)ether gave amino ketones **5–7,** respectively, in good yields. Finally, the diastereoselective reduction of ketones **5–7** with $NaBH_4/CeCl_3$ in methanol at −78 °C then slowly to 25 °C yielded the corresponding *exo*-alcohols **8–10**, respectively.[13]

The application of 10 mol % of β-amino alcohols **3** and **8–10** in the asymmetric addition of diethylzinc with benzaldehydes was initially tested at 0 °C, and good yields along with excellent ee were obtained (Table 1).

The addition reaction conditions were then optimized with ligand **10**, which gave the best yield and ee in the ethylation of benzaldehyde. Various reaction parameters, such as ligand loadings (Table 2, entries 1–3), addition methods (entries 4 and 5), and the amount of diethylzinc (entry 6) were examined. In general, excellent enantioselectivities (94% ee) were observed using 1.5 equiv of diethylzinc in the presence of 5 mol % of β-amino alcohol **10** at 0 °C. The use of less than 1.5 equiv of diethylzinc diminished the enantioinduction (entry 6).

The optimization was later focused on the solvent effect (Table 3). Reactions in pentane and heptane were studied at 0 °C, and

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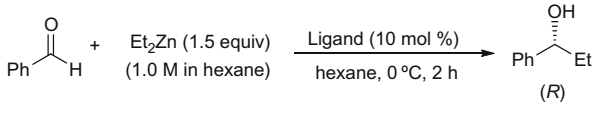
Table 1
Asymmetric diethylzinc addition with benzaldehyde catalyzed by β-amino alcohols **3** and **8–10**



Entry	Ligand	Yield[a] (%)	ee[b] (%)
1	**3**	91	82
2	**8**	89	94
3	**9**	91	95
4	**10**	95	95

[a] Isolated yield after column chromatography.
[b] Determination by HPLC on the OD-H chiral column.

showed excellent ee (entries 1 and 2). When the reaction was conducted in the presence of 5 mol % of β-amino alcohol **10** without solvent it showed no loss of enantioselectivity (entry 3). However, when 2 mol % of ligand was used, the ee value dropped to 78% (entry 4). Interestingly, when the reaction was carried out at ambient temperature, the presence of 2 mol % of ligand led to the corresponding adduct with 93% ee and 90% yield in 15 min (entry 5). There was no improvement in enantioselectivity when diethylzinc in toluene was used, or the reaction was carried out at either 40 °C or −10 °C (entries 6–8). Good enantioselectivity (91% ee) was obtained with 1 mol % of β-amino alcohol **10** at the expense of a longer reaction time (entry 9). Therefore the reaction conditions in entry 5 were utilized to study the scope of the reaction.

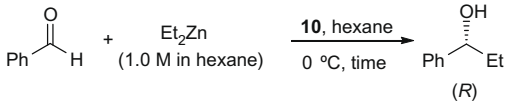
In order to understand the application and limitation of the catalytic system, aldehydes **11a–k** were carefully examined (Table 4). Optically active secondary alcohols with >91% ee were obtained in the cases of aromatic aldehydes (entries 1–6). Alkenyl (entry 7) and aliphatic aldehydes (entries 8–11) were also applicable in the system. It is noteworthy that this methodology could be applied to linear aliphatic aldehydes (entries 10 and 11).

The effect of the enantiomeric excess of the chiral ligand on the enantiomeric excess of the adducts has been demonstrated to show a positive non-linearity with either 5 mol % or 2 mol % of β-amino alcohol **10** (Fig. 2).[14] A higher level of (+)-non-linearity with 5 mol % of β-amino alcohol **10** was rationalized by the concentration of both the effective catalyst and the inactive dimer, which are proportional to ligand loading.[14d]

3. Conclusion

In conclusion, an effective chiral β-amino alcohol **10** for the catalytic asymmetric addition of diethylzinc to aldehydes has been demonstrated. The catalytic system could be applied to both aromatic and aliphatic aldehydes, including linear aliphatic ones, in 89–94% ee with 2 mol % of chiral ligand. The reaction required only equimolar amounts of diethylzinc, and was completed in 15 min at ambient temperature. The development of β-amino alcohol **10** offers a simple and effective chiral induction in the diethylzinc addition reaction for the preparation of chiral secondary alcohols.

Table 2
Optimization of the reaction conditions with β-amino alcohol **10**[a]



Entry	**10** (mol %)	Et_2Zn (equiv)	Time (h)	Yield[b] (%)	ee[c] (%)
1	5	1.5	6	92	94
2	2	1.5	18	86	84
3	1	1.5	36	75	47
4[d]	5	1.5	6	90	94
5[e]	5	1.5	6	92	94
6	5	1.05	6	85	85

[a] The reaction was carried out on a 1.0 mmol scale of benzaldehyde and 1.0 mL of hexane.
[b] Isolated yield after column chromatography.
[c] Determination by HPLC on the OD-H chiral column.
[d] Reverse addition sequence of diethylzinc and benzaldehyde.
[e] Benzaldehyde was slowly added over 10 min.

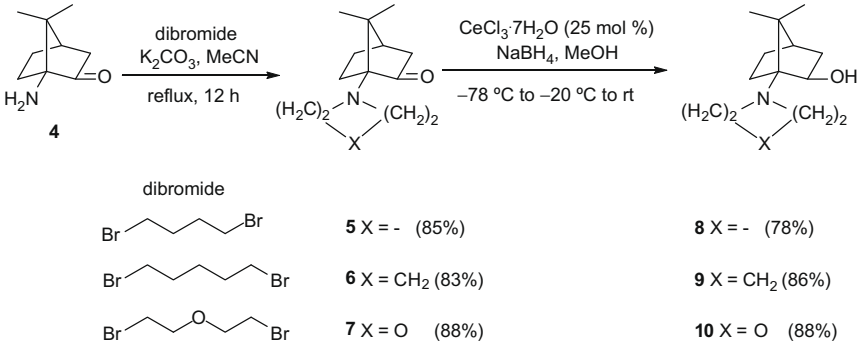
4. Experimental

4.1. General experimental procedure for the synthesis of α-amino ketones 5–7

A 10 mL round-bottomed flask containing α-amino ketone **4** (0.10 g, 0.65 mmol) and potassium carbonate (0.20 g, 1.45 mmol) was filled with argon and acetonitrile (2.5 mL) was added. After the mixture was added to the corresponding dibromide (0.70 mmol) and stirred at room temperature for 10 min, the mixture was heated under reflux for 12 h, and the reaction was stopped by the addition of water (5 mL). The mixture was then extracted with CH_2Cl_2 (5 mL × 3), and the combined organic solution was dried over Na_2SO_4 and concentrated to give the crude product, which was purified via column chromatography to yield the desired α-amino ketone.

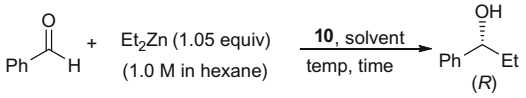
4.1.1. (1*S*)-7,7-Dimethyl-1-pyrrolidin-1-yl-bicyclo[2.2.1] heptan-2-one 5

$[\alpha]_D^{24} = +45.2$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.08–3.03 (m, 2H), 2.85–2.81 (m, 2H), 2.41–2.34 (m, 1H), 2.13 (dt, *J* = 12.8, 3.2 Hz, 1H), 2.05–1.98 (m, 1H), 1.91 (t, *J* = 4.6 Hz, 1H),



Scheme 1. Synthesis of β-amino alcohols bearing the isoborneol skeleton.

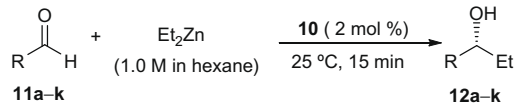
Table 3
Optimization of reaction conditions with β-amino alcohol **10** in different solvents[a]



Entry	**10**(mol %)	Solvent	Temp (°c)	Time (h)	Yield[b] (%)	ee[c] (%)
1	5	1.0 mL of pentane	0	2	92	94
2	5	1.0 mL of heptane	0	2	91	94
3	5	—	0	2	86	94
4	2	—	0	6	82	78
5	2	—	25	15 min	90	93
6[d]	2	—	25	15 min	87	91
7	2	—	40	5 min	85	81
8	2	—	−10	1	85	69
9	1	—	25	1	88	91
10	0.5	—	25	12	84	18

[a] The reaction was carried out on a 1.0 mmol scale of benzaldehyde.
[b] Isolated yield after column chromatography.
[c] Determination by HPLC on the OD-H chiral column.
[d] Et_2Zn (1.0 M in toluene) was used.

Table 4
Asymmetric addition of diethylzinc to aldehydes catalyzed by β-amino alcohol **10**



Entry	R	Yield[a] (%)	ee[b] (%)
1	3-F-Ph **11a**	95	93
2	3-Cl-Ph **11b**	93	92
3	2-Me-Ph **11c**	95	92
4	3-Me-Ph **11d**	94	91
5	3-MeO-Ph **11e**	97	94
6	1-Naphthyl **11f**	94	91
7	(2-Me-cinnamaldehyde) **11g**	96	92
8	(Hydrocinnamaldehyde) **11h**	89	92
9	Cyclohexyl **11i**	90	93[c]
10	10-Decenyl **11j**	90	94[d]
11	Pentyl **11k**	96	89[d]

[a] Isolated yield after column chromatography.
[b] Determination by chiral HPLC.
[c] The ee was determined via its benzoyl ester.
[d] The ee was determined via its *p*-nitrobenzoyl ester.

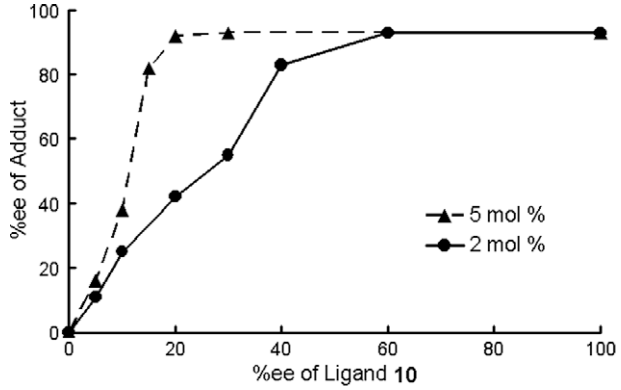


Figure 2. Nonlinear effect study of β-amino alcohol **10**.

1.86–1.67 (m, 6H), 1.40–1.33 (m, 1H), 1.08 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.4 (C), 77.0 (C), 48.0 (CH_2), 46.9 (C), 42.8 (CH), 42.6 (CH_2), 27.7 (CH_2), 25.9 (CH_2), 24.1 (CH_2), 22.0 (CH_3), 19.7 (CH_3); IR (neat) 2963 (s), 2876 (m), 1742 (s) cm^{-1}; HRMS calcd for $C_{13}H_{21}NO$ 207.1623, found 207.1620.

4.1.2. (1*S*)-7,7-Dimethyl-1-piperidin-1-yl-bicyclo[2.2.1]heptan-2-one 6

$[\alpha]_D^{24} = +91.4$ (*c* 1.0, $CHCl_3$); mp 78.0–79.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.90–2.82 (m, 2H), 2.78–2.70 (m, 2H), 2.42–2.32 (m, 1H), 2.15 (dt, *J* = 12.6, 3.6 Hz, 1H), 2.00–1.90 (m, 1H), 1.88–1.78 (m, 2H), 1.58–1.46 (m, 5H), 1.45–1.39 (m, 2H), 1.36–1.28 (m, 1H), 1.11 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.5 (C), 79.2 (C), 49.0 (CH_2), 47.4 (C), 43.6 (CH), 43.0 (CH_2), 26.8 (CH_2), 26.3 (CH_2), 25.7 (CH_2), 24.5 (CH_2), 23.3 (CH_3), 21.1 (CH_3); IR (neat) 2971 (w), 2926 (m), 1739 (s) cm^{-1}; HRMS calcd for $C_{14}H_{23}NO$ 221.1780, found 221.1792.

4.1.3. (1*S*)-7,7-Dimethyl-1-morpholin-4-yl-bicyclo[2.2.1]-heptan-2-one 7

$[\alpha]_D^{24} = +82.5$ (*c* 1.0, $CHCl_3$); mp 89.5–90.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (t, *J* = 4.8 Hz, 4H), 3.00–2.90 (m, 2H), 2.81–2.76 (m, 2H), 2.39–2.33 (m, 1H), 2.08 (dt, *J* = 12.4, 3.6 Hz, 1H), 2.00–1.92 (m, 1H), 1.85–1.80 (m, 2H), 1.57–1.50 (m, 1H), 1.34–1.31 (m, 1H), 1.09 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.1 (C), 78.6 (C), 67.7 (CH_2), 48.5 (CH_2), 47.5 (C), 43.8 (CH), 43.1 (CH_2), 26.0 (CH_2), 25.8 (CH_2), 23.3 (CH_3), 21.0 (CH_3); IR (neat) 2958 (s), 2889 (m), 2850 (s), 1743 (s) cm^{-1}; HRMS calcd for $C_{13}H_{21}NO_2$ 223.1572, found 223.1567.

4.2. General experimental procedure for the synthesis of α-amino alcohols 8–10

A 25 mL round-bottomed flask containing the α-amino ketone (0.45 mmol), $CeCl_3{\cdot}7H_2O$ (0.11 mmol), and methanol (3 mL) was cooled to −78 °C. Following the addition of $NaBH_4$ (2.11 mmol), the flask was slowly warmed to −20 °C. After 2 h at −20 °C, the flask was slowly warmed to room temperature, and was kept at ambient temperature for 6 h. The solvents were then removed in vacuo, and to the residue was added water (15 mL) and extracted with CH_2Cl_2 (15 mL × 3). The organic solution was combined, dried over Na_2SO_4, and concentrated to give the crude product, which was purified by column chromatography to yield the pure β-amino alcohol.

4.2.1. (1*S*, 2*R*)-7,7-Dimethyl-1-pyrrolidin-1-yl-bicyclo[2.2.1]-heptan-2-ol 8

$[\alpha]_D^{24} = +1.2$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (br, 1H), 3.66 (dd, *J* = 7.8, 3.0 Hz, 1H), 2.67–2.62 (m, 2H), 2.55–2.50 (m, 2H), 1.90–1.85 (m, 1H), 1.81–1.60 (m, 7H), 1.51 (t, *J* = 4.4 Hz, 1H), 1.16–1.06 (m, 1H), 1.10 (s, 3H), 1.03–0.96 (m, 1H), 0.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.1 (CH), 70.1 (C), 47.0 (CH_2), 46.3 (C), 45.7 (CH), 38.4 (CH_2), 26.1 (CH_2), 22.9 (CH_2), 22.8 (CH_3), 20.7 (CH_2), 20.1 (CH_3); IR (neat) 3422 (br), 2958 (s), 2877 (s), 2821 (m) cm^{-1}; HRMS calcd for $C_{13}H_{23}NO$ 209.1780, found 209.1774.

4.2.2. (1*S*, 2*R*)-7,7-Dimethyl-1-piperidin-1-yl-bicyclo[2.2.1]-heptan-2-ol 9

$[\alpha]_D^{24} = +14.2$ (*c* 1.0, $CHCl_3$); mp 88.5–89.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (d, *J* = 5.2 Hz, 1H), 2.58 (br, 4H), 1.90–1.70 (m, 3H), 1.68–1.36 (m, 8H), 1.18–0.98 (m, 2H), 1.14 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.6 (CH), 72.8 (C), 48.4 (CH_2), 46.7 (CH), 45.9 (C), 37.9 (CH_2), 26.7 (CH_2), 26.3 (CH_2), 24.4 (CH_2), 24.0 (CH_3), 22.3 (CH_2) 20.3 (CH_3); IR (neat) 3329 (br), 2958 (s), 2932 (s), 2805 (w) cm^{-1}; HRMS calcd for $C_{14}H_{25}NO$ 223.1936, found 223.1945.

4.2.3. (1*S*, 2*R*)-7,7-Dimethyl-1-morpholin-4-yl-bicyclo[2.2.1]heptan-2-ol 10

$[\alpha]_D^{24} = +11.0$ (*c* 1.0, $CHCl_3$); mp 35.0–36.0 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.74–3.66 (m, 5H), 2.67–2.61 (m, 2H), 2.57–2.50 (m, 2H), 1.92–1.76 (m, 3H), 1.69–1.62 (m, 1H), 1.52 (t, *J* = 4.6 Hz, 1H), 1.18–1.00 (m, 2H), 1.14 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.8 (CH), 71.8 (C), 66.7 (CH_2), 47.2 (CH_2), 46.0 (CH), 45.3 (C), 37.5 (CH_2), 25.7 (CH_2), 23.3 (CH_3), 21.7 (CH_2), 19.8 (CH_3); IR (neat) 3415 (br), 2956 (s), 2884 (s), 2850 (m) cm^{-1}; HRMS calcd for $C_{13}H_{23}NO_2$ 225.1729, found 225.1713.

4.3. General procedure for the asymmetric addition of diethylzinc with aldehydes catalyzed by β-amino alcohol 10

To a 10 mL round-bottomed flask containing ligand **10** (4.5 mg, 0.02 mmol) was added diethylzinc solution (1.05 mmol, 1.0 M in hexane) at room temperature. After being stirred at room temperature for 5 min, the aldehyde (1.0 mmol) was added to the mixture. The reaction was stopped after 15 min by the addition of aqueous NH_4Cl (3 mL, 1 M solution). The mixture was extracted with ether (10 mL × 3), and the combined organic solution was dried over Na_2SO_4, and concentrated to give the crude product, which was purified by column chromatography to yield the corresponding secondary alcohol. The ee value was determined by HPLC on a chiral stationary phase.

4.3.1. 1-(3-Fluoro-phenyl)-propan-1-ol 12a

Chiracel AD-H, UV 254 nm, isopropanol/hexanes (1:99), 0.5 mL/min. t_R = 10.2 min (3.5% for *S*), 12.7 min (96.5% for *R*); 93% ee.

4.3.2. 1-(3-Chloro-phenyl)-propan-1-ol 12b

Chiracel OD-H, UV 254 nm, isopropanol/hexanes (1:99), 0.5 mL/min. t_R = 38.7 min (4.2% for *S*), 40.5 min (95.8% for *R*); 92% ee.

4.3.3. 1-*o*-Tolyl-propan-1-ol 12c

Chiracel OB, UV 254 nm, isopropanol/hexanes (1:99), 0.5 mL/min. t_R = 12.0 min (3.8% for *S*), 13.5 min (96.2% for *R*); 92% ee.

4.3.4. 1-*m*-Tolyl-propan-1-ol 12d

Chiracel OD-H, UV 254 nm, isopropanol/hexanes (1:99), 0.5 mL/min. t_R = 9.4 min (95.6% for *R*), 11.9 min (4.4% for *S*); 91% ee.

4.3.5. 1-(3-Methoxy-phenyl)-propan-1-ol 12e

Chiracel OD-H, UV 254 nm, isopropanol/hexanes (2:98), 0.5 mL/min. t_R = 21.5 min (97.0% for *R*), 24.0 min (3.0% for *S*); 94% ee.

4.3.6. 1-Naphthalen-1-yl-propan-1-ol 12f

Chiracel OD-H, UV 254 nm, isopropanol/hexanes (2:98), 1.0 mL/min. t_R = 21.7 min (4.3% for *S*), 42.7 min (95.7% for *R*); 91% ee.

4.3.7. 2-Methyl-1-phenyl-pent-1-en-3-ol 12g

Chiracel OD-H, UV 254 nm, isopropanol/hexanes (2:98), 1.0 mL/min. t_R = 12.6 min (95.9% for *R*), 14.1 min (4.1% for *S*); 92% ee.

4.3.8. 1-Phenyl-pentan-3-ol 12h

Chiracel OD-H, UV 254 nm, isopropanol/hexanes (2:98), 1.0 mL/min. t_R = 16.5 min (96.2% for *R*), 27.8 min (3.8% for *S*); 92% ee.

4.3.9. Benzoic acid 1-cyclohexyl-propyl ester (benzoyl ester of alcohol 12i)

Chiracel AD-H, UV 254 nm, isopropanol/hexanes (1:99), 0.3 mL/min. t_R = 14.1 min (96.5% for *R*), 17.0 min (3.5% for *S*); 93% ee.

4.3.10. 4-Nitro-benzoic acid 1-ethyl-undec-10-enyl ester (4-nitro-benzoyl ester of alcohol 12j)

Chiracel OB, UV 254 nm, isopropanol/hexanes (1:400), 0.5 mL/min. t_R = 25.7 min (2.9% for *S*), 30.6 min (97.1% for *R*); 94% ee.

4.3.11. 4-Nitro-benzoic acid 1-ethyl-hexyl ester (4-nitro-benzoyl ester of alcohol 12k)

Chiracel OJ, UV 254 nm, isopropanol/hexanes (1:400), 0.5 mL/min. t_R = 14.3 min (5.6% for *S*), 16.0 min (94.4% for *R*); 89% ee.

Acknowledgment

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