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Preparation of highly enantiomerically pure linear secondary alcohols via asymmetric reduction of prochiral ketones with borane

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Abstract—An efficient and practical preparation of homochiral linear secondary alcohols, 1-(4-alkylphenyl) and 1-(4-alkoxylphenyl) alcohols, via the asymmetric oxazaborolidine-catalyzed borane reduction of prochiral ketones is described. The phenomenon of the enantioselectivity of 1-(4-alkoxylphenyl) alcohols lower than that of 1-(4-alkylphenyl) alcohols was found and rationalized to the coordination of the oxygen atom in the alkoxy groups to the catalyst and borane. Based on the rationale, the enantioselectivity of 1-(4-alkoxylphenyl) alcohols in the asymmetric reduction was improved with increasing the amount of the catalyst.

1. Introduction

Homochiral secondary alcohols are very important intermediates in organic synthesis. They are generally prepared via chemical or enzymatic resolution of racemic secondary alcohols,[1,2] chemical or enzymatic asymmetric reduction of prochiral ketones,[3,4] or asymmetric addition of dialkylzinc to aldehydes.[5] Optically active linear secondary alcohols are widely used in the preparation of chiral liquid crystal materials and other chiral optical materials.[6]

Recently we prepared highly enantiomerically pure linear secondary alcohols, 1-(4-alkylphenyl) alcohols, in satisfactory yields through chemical resolution.[1c] However, the method was unsuccessful for the resolution of 1-(4-alkoxyphenyl) alcohols. As part of a program directed towards the preparation of highly enantiomerically pure linear secondary alcohols, we sought to prepare homochiral 1-(4-alkoxyphenyl) alcohols.

During the last decade, there has been a large number of papers on the enantioselective reduction of ketones by a wide variety of reagents made by mixing aluminum or boron hydrides and various homochiral diols or amino alcohols.[3,7] Among these systems asymmetric borane reduction with chiral oxazaborolidines as catalysts is one of the most useful methods to synthesize optically active secondary alcohols.[3] This method, pioneered by Itsuno, was developed by Corey et al., and called as the CBS (named after Corey, Bakshi, and Shibata) reduction.[3] Herein, we report the preparation of highly enantiomerically pure linear secondary alcohols via the asymmetric reduction of prochiral ketones by borane.

2. Results and discussion

(*S*)-(Diphenylhydroxymethyl)pyrrolidine is one of the best amino alcohols used in the CBS process, and is commercially available or conveniently prepared from *L*-proline. The oxazaborolidine catalysts **1** derivated from (*S*)-(diphenylhydroxymethyl)pyrrolidine is an effective kind of catalyst, which behave like an enzyme since they bind both a ketone and a hydride and release them after the reaction.[3] Corey's group introduced, isolated, and identified the chiral oxazaborolidines **1a**–**c**.[8] Though the catalysts **1a**–**c** have been proved to be effective catalysts in the asymmetric borane reduction of ketones with excellent yields and enantioselectivities for a wide variety of ketones, they have not been entirely satisfactory, particularly for large-scale productions, owing to the necessity of relatively expensive reagents, such as trimethyl boroxine, methylboronic acid or *n*-butylboronic acid, to prepare the oxazaboro-

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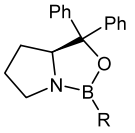
lidine catalysts **1a**–**c**.[3] On the other hand, they need to be prepared first before catalytic reactions in order to get excellent and stable enantioselectivity, and the catalyst **1a** is air and moisture sensitive.[3] Masui et al. modified the catalysts, developed and applied the catalyst **1d** successfully in enantioselective reduction of ketones.[9] They supposed that the *B*-methoxy oxazaborolidine **1d** should be a more efficient catalyst than the *B*-methyl oxazaborolidine **1b** due to its stronger Lewis acidity of the boron in the oxazaborolidine, produced by a stronger electron-withdrawing methoxy group. The advantage of the catalyst **1d** is that it can be prepared from (*S*)-(diphenylhydroxymethyl)pyrrolidine and inexpensive trimethyl borate, and used directly in asymmetric reduction without any further separation and purification. To develop a practical and efficient method to the preparation of homochiral linear secondary alcohols, we selected Masui's procedure to prepare our chiral alcohols in good yields and satisfactory enantioselectivities (Scheme 1 and Table 1).

From Table 1, relatively higher e.e. values were obtained for alkylphenyl ketones **2a**–**f** (entries 1–6 in Table 1), while lower e.e. values were obtained for



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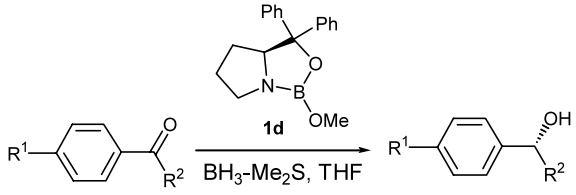
a: R = H, **b**: R = Me, **c**: R = n-Bu, **d**: R = MeO



2 **3**

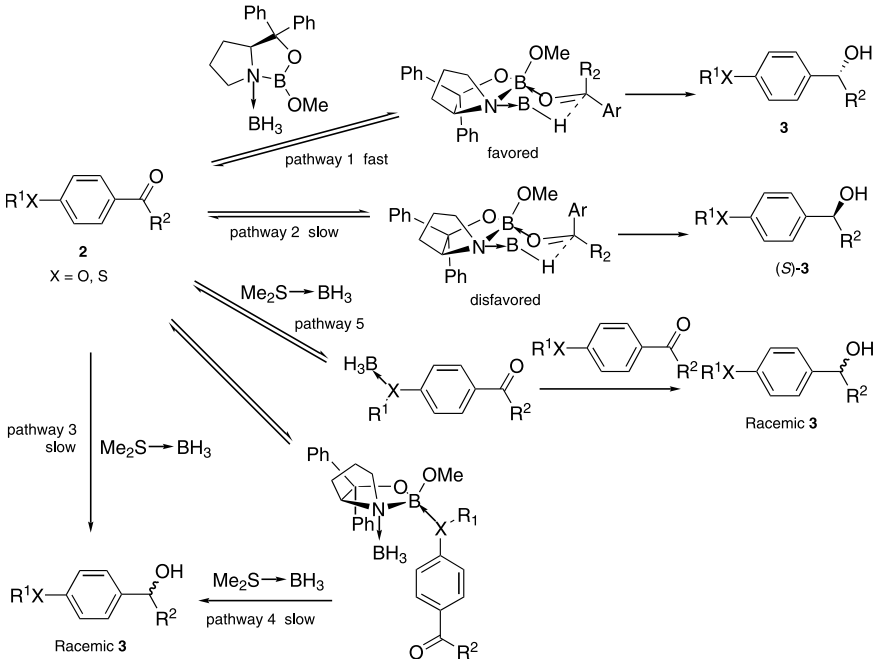
a: R^1= Et, R^2= Me; **b**: R^1= *n*-Pr, R^2= Me; **c**: R^1= *n*-Bu, R^2= Me; **d**: R^1= *n*-Am, R^2= Me; **e**: R^1= *n*-Am, R^2= Et; **f**: R^1= *n*-Am, R^2= *n*-Pr; **g**: R^1= *n*-BuO, R^2= Et; **h**: R^1= *n*-BuO, R^2= *n*-Bu; **i**: R^1= *n*-AmO, R^2= Et; **j**: R^1= *n*-AmO, R^2= *n*-Bu; **k**: R^1= *n*-HexO, R^2= Et; **l**: R^1= *n*-HexO, R^2= *n*-Bu; **m**: R^1= *n*-BuS, R^2= Et.

Scheme 1. Asymmetric borane reduction of ketones catalyzed by chiral oxazaborolidine **1d**.

Table 1. Asymmetric reduction of ketones catalyzed by 0.1 equivalent of the catalyst **1d**

Entry	Ketone	Time (h)	Yield (%)[a]	e.e. (%)[b]	Config.
1	**2a**	2	95	95[c]	*R*[h]
2	**2b**	2	99	93[d]	*R*[h]
3	**2c**	3	92	89[e]	*R*[h]
4	**2d**	3	95	91[e]	*R*[h]
5	**2e**	3	98	91[e]	*R*[i]
6	**2f**	5	97	85[f]	*R*[i]
7	**2g**	12	97	81[g]	*R*[i]
8	**2h**	14	95	80[f]	*R*[i]
9	**2i**	14	95	76[g]	*R*[i]
10	**2j**	14	96	75[f]	*R*[i]
11	**2k**	14	94	73[f]	*R*[i]
12	**2l**	14	91	71[g]	*R*[i]
13	**2m**	14	96	69[c]	*R*[i]

[a] Isolated yields after the column chromatography.
[b] E.e. values were determined by HPLC analysis using OD or OJ chiral columns (Chiralcel) and a mixture of *n*-hexane and 2-propanol as an eluent.
[c] OD column, *n*-hexane: 2-propanol (99: 1, v/v).
[d] OD column, *n*-hexane: 2-propanol (97: 3, v/v).
[e] OJ column, *n*-hexane: 2-propanol (98: 2, v/v).
[f] OJ column, *n*-hexane: 2-propanol (98: 2, v/v).
[g] OJ column, *n*-hexane: 2-propanol (97: 3, v/v).
[h] Configuration was assigned according to the rotation value. In each case a positive rotation was obtained, indicating that the selectivity was for the (*R*)-enantiomer in agreement with reported work (Refs. 1a,c, 2b, 8 and 9).
[i] Configuration was tentatively assumed according to the mechanism and their optical rotation signs.



Scheme 2. Rationale for enantioselective decrease of 1-(4-alkoxyphenyl) ketones.

alkoxyphenyl ketones **2g–l** (entries 7–12 in Table 1). In each case decreased enantioselectivity was reached with increasing length(s) of either R^1 and/or R^2 chain(s) of the ketones. The only difference between alkyl 1-(4-alkoxylphenyl) ketones **2g–l** and alkyl 1-(4-alkylphenyl) ketones **2a–f** is that the former have an ether-linked oxygen atom in the molecules. It was also found that the reduction rate of ketones **2g–l** is slower than that of ketones **2a–f** because the reduction of ketones **2g–l** needs longer. The enantioselective decrease of the reduction ketones **2g–l** could be rationalized as following (Scheme 2). In the reaction mixture there are several pathways to reduce ketones to alcohols. Generally pathway 1 catalyzed by the oxazaborolidine **1d** is a fast process to afford (*R*)-alcohols. Although pathway 2 is also catalyzed by the oxazoborolidine **1d**, it is disfavored because a larger group Ar (R^1XPh) occupies an axial position in a six-membered ring chair conformation in the transition state. Ketones could also be reduced directly by borane-dimethyl sulfide at very low rates through pathway 3.[3c] In most cases, the reduction occurs through pathway 1 to afford chiral alcohols with excellent enantioselectivity at a high reduction rate. However, for alkyl 1-(4-alkoxylphenyl) ketones **2g–l**, the reaction rate of pathway 1 is decreased because the ether-linked oxygen atom could coordinate with the boron atom in the oxazaborolidine **1d** and the amount of the oxazaborolidine **1d** participated in pathway 1 is decreased. Thus, the reduction needs longer and the reductive rates through pathways 3–5 are increased relatively as decrease of the rate in pathway 1. As the results, the enantioselectivity is decreased in these cases (Scheme 2).

To verify the rationale, a thioether-link containing ketone, 1-(4-butylthiophenyl)propanone **2m**, was designed and synthesized from thiophenol via alkylation with butyl bromide and acylation with propionyl chloride. The ketone **2m** should show a stronger coordi-

Table 2. Asymmetric reduction of alkyl alkoxylphenyl ketones **2g–l** and 1-(4-alkythiophenyl)propanone **2m** catalyzed by 0.5 equiv. of the catalyst **1d**

Entry	Ketone	Time (h)	Yield (%)[a]	E.e. (%)[b]	Config.[c]
1	**2g**	12	97	89	*R*
2	**2h**	12	96	86	*R*
3	**2i**	12	95	86	*R*
4	**2j**	12	95	85	*R*
5	**2k**	12	96	83	*R*
6	**2l**	12	93	81	*R*
7	**2m**	12	96	83	*R*

[a] Isolated yields after the column chromatography.
[b] E.e. values were determined as shown in Table 1.
[c] Configuration was assigned as shown in Table 1.

nation with the Lewis acid boron atom in the catalyst **1d** than the corresponding ether-link containing ketones **2g–l** because a sulfur atom is a much softer Lewis base than an oxygen atom. Coordination between a sulfur atom in a thioether and borane, and its effect on enantioselectivity was observed and reported in the literature.[10] The experimental results indicate that the asymmetric reduction enantioselectivity of ketone **2m** is lower than those of ketones **2e** and **2f**, which were selected as samples in the verification experiments since the length of their chains is same (entries 5, 6 and 13 in Table 1). The results support our rationale.

Based on the rationale, the reduction enantioselectivity of the alkyl 1-(4-alkoxylphenyl) ketones **2g–l** could be improved by increasing the amount of the catalyst **1d** because the increasing amount of the catalyst will decrease the partition of the ether oxygen coordinated catalyst relatively, the reduction rate of pathway 1 will be increased and the reaction rates in the pathways 3–5 will be decreased relatively. The experimental results indicated that the e.e. values were increased 8% and 14%, respectively, for ketones **2g** and **2m** when the catalyst was increased to 0.5 equivalent from 0.1 equivalent (entries 1 and 7 in Table 2). The e.e. value of ketone **2m** is still lower than that of ketone **2g** under this reaction conditions due to the stronger coordination of the sulfur atom. The results also support our rationale. Alkyl 1-(4-alkoxylphenyl) ketones **2f–l** were reduced under 0.5 equivalent of the catalyst **1d** and their e.e. values were improved significantly to 4–10% (as shown in Table 2).

3. Conclusion

Highly enantiomerically pure linear secondary alcohols, 1-(4-alkylphenyl)- and 1-(4-alkoxylphenyl)alcohols, were prepared in excellent yields via a practical and efficient one-pot borane asymmetric reduction of alkyl 4-alkylphenyl and 4-alkoxyphenyl ketones, catalyzed by an oxazaborolidine derivative, (*S*)-2-methoxy-4,4-diphenyl-3,1,2-oxazaboro[3.3.0]octane, prepared in situ from (*S*)-(diphenylhydroxymethyl)pyrrolidine and trimethyl borate without further separation and purification. The phenomenon of the enantioselectivity of 1-(4-alkoxylphenyl) alcohols lower than that of 1-(4-alkylphenyl) alcohols was found and rationalized to the coordination of the oxygen atom in the alkoxy groups to the catalyst and borane. The rationale was confirmed by the asymmetric reduction of a designed substrate 1-(4-butylthiophenyl)propanone. Based on the rationale, the enantioselectivity of 1-(4-alkoxylphenyl) alcohols in the asymmetric reduction was improved with increasing amount of the catalyst.

4. Experimental

4.1. General

IR spectra were recorded on a Bruker Vector 22 FT-IR spectrophotometer. ^{1}H spectra were recorded on a Varian Mercury 200 (200 MHz) spectrometer in $CDCl_3$ solution with TMS as an internal standard and chemical shifts are reported in ppm. Mass spectra were obtained on a VG-ZAB-HS spectrometer. CH analyses were performed on an Elementar Vario EL analyzer. Optical rotations were measured on a Perkin–Elmer model 341LC polarimeter with a thermally jacketed 10 cm cell (concentration *c* given as g/100 mL). HPLC analyses were performed on an HP1100 HPLC equipment. The e.e. values were determined by HPLC analysis with chiralcel OD or OJ columns (4.6×250 mm) with a mixture of hexane–isopropanol as an eluent at an eluent rate of 0.6 mL/min at monitoring wave 228 nm. All the starting materials were prepared according to the literature procedure.[1c] Trimethyl borate and borane–dimethyl sulfide complex were purchased from Acros Chemicals Co. Tetrahydrofuran was heated under reflux over sodium and distilled prior to use.

4.2. General procedure for asymmetric reduction of ketones

To a solution of (*S*)-2-diphenylhydroxymethylpyrrolidine (25 mg, 0.1 mmol) in dry THF (5 mL) was added trimethyl borate (12 mg, 0.12 mmol), and the mixture was stirred under nitrogen atmosphere at room temperature for 1 h. After 2 M borane–dimethyl sulfide complex in THF (0.75 mL, 1.5 mmol) was added, a solution of ketone (1 mmol) in dry THF (5 mL) was added dropwise over 30 min. The mixture was stirred at 0–5°C in an ice bath until the ketone disappeared on a thin layer chromatographic monitoring. The resulting mixture was quenched with 2 M HCl and extracted with diethyl ether (3×25 mL). The combined organic layers were successively washed with 2 M HCl and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified on a silica gel column with a mixture of petroleum ether (30–60°C) and acetone (10: 1, v/v) as an eluent to give a colorless oil chiral secondary alcohol.

4.2.1. (*R*)-1-(4-Ethylphenyl)ethanol 3a. Colorless liquid; $[\alpha]_D^{20}=+36.9$ (*c* 2.2, MeOH), e.e. 95%; Lit.:[1c] $[\alpha]_D^{20}=+47.0$ (*c* 1.2, $CHCl_3$), e.e. 98%.

4.2.2. (*R*)-1-(4-Propylphenyl)ethanol 3b. Colorless liquid; $[\alpha]_D^{20}=+33.2$ (*c* 2.2, MeOH), e.e. 93%; Lit.:[1c] $[\alpha]_D^{20}=+40.9$ (*c* 1.7, $CHCl_3$), e.e. 96%.

4.2.3. (*R*)-1-(4-Butylphenyl)ethanol 3c. Colorless liquid; $[\alpha]_D^{20}=+31.5$ (*c* 1.4, MeOH), e.e. 89%; Lit.:[1c] $[\alpha]_D^{20}=+42.1$ (*c* 1.4, $CHCl_3$), e.e. 98%.

4.2.4. (*R*)-1-(4-Pentylphenyl)ethanol 3d. Colorless liquid; $[\alpha]_D^{20}=+29.3$ (*c* 1.2, MeOH), e.e. 91%; Lit.:[1c] $[\alpha]_D^{20}=+33.2$ (*c* 1.5, $CHCl_3$), e.e. 92%.

4.2.5. (*R*)-1-(4-Pentylphenyl)propanol 3e. Colorless liquid; $[\alpha]_D^{20}=+28.4$ (*c* 2.3, MeOH), e.e. 91%; ^{1}H NMR (200 MHz, $CDCl_3$: δ 0.89 (t, $J=6.4$ Hz, 3H, CH_3), 0.92 (t, $J=7.4$ Hz, 3H, CH_3), 1.26–1.36 (m, 4H, $2CH_2$), 1.57–1.90 (m, 5H, OH, $2CH_2$), 2.59 (t, $J=7.6$ Hz, 2H, Ar$\mathbf{CH_2}$), 4.57 (t, $J=6.6$ Hz, 1H, CH), 7.14–7.27 (m, 4H,

ArH). MS (EI) m/z: 206 (M^+), 177, 91, 71, 43, 29; IR ν (cm^{-1}): 3362 (OH), 1099. Anal. calcd for $C_{14}H_{22}O$ (206.32): C, 81.50; H, 10.75. Found: C, 81.21; H, 10.71%.

4.2.6. (*R*)-1-(4-Pentylphenyl)-*n*-butanol 3f. Colorless liquid; $[\alpha]_D^{20}=+27.6$ (c 2.1, MeOH), e.e. 85%; ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, $J=6.4$ Hz, 3H, CH_3), 0.92 (t, $J=7.2$ Hz, 3H, CH_3), 1.24–1.46 (m, 5H, OH, $2CH_2$), 1.57–1.84 (m, 4H, $2CH_2$), 2.59 (t, $J=7.6$ Hz, 2H, Ar**CH**$_2$), 4.64 (t, $J=6.6$ Hz, 1H, CH), 7.13–7.27 (m, 4H, ArH). MS (EI) m/z: 220 (M^+), 177, 149, 91, 71, 56, 43; IR ν (cm^{-1}): 3363 (OH), 1106. Anal. calcd for $C_{15}H_{24}O$ (220.35): C, 81.76; H, 10.98. Found: C, 81.76; H, 11.02%.

4.2.7. (*R*)-1-(4-Butoxyphenyl)-*n*-propanol 3g. Colorless liquid; $[\alpha]_D^{20}=+29.9$ (c 2.2, MeOH), e.e. 89%; ^1H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, $J=7.4$ Hz, 3H, CH_3), 0.97 (t, $J=7.2$ Hz, 3H, CH_3), 1.40–1.60 (m, 2H, CH_2), 1.63–1.90 (m, 5H, OH, $3CH_2$), 3.95 (t, $J=6.6$ Hz, 2H, OCH_2), 4.52 (t, $J=6.6$ Hz, 1H, CH), 6.83–7.26 (m, 4H, ArH). MS (EI) m/z: 208 (M^+), 179, 123, 95, 77, 57, 43; IR ν (cm^{-1}): 3380 (OH), 1264, 1119. Anal. calcd for $C_{13}H_{20}O_2$ (208.30): C, 74.96; H, 9.68. Found: C, 74.80; H, 9.79%.

4.2.8. (*R*)-1-(4-Butoxyphenyl)-*n*-pentanol 3h. Colorless liquid; $[\alpha]_D^{20}=+26.6$ (c 2.0, MeOH), e.e. 86%; ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, $J=6.8$ Hz, 3H, CH_3), 0.97 (t, $J=7.6$ Hz, 3H, CH_3), 1.20–1.58 (m, 6H, $3CH_2$), 1.63–1.83 (m, 5H, OH, $2CH_2$), 3.95 (t, $J=6.4$ Hz, 2H, OCH_2), 4.60 (t, $J=6.6$ Hz, 1H, CH), 6.83–7.27 (m, 4H, ArH). MS (EI) m/z: 236 (M^+), 218, 189, 179, 133, 123, 95, 77, 57; IR ν (cm^{-1}): 3372 (OH), 1245, 1111. Anal. calcd for $C_{15}H_{24}O_2$ (236.35): C, 76.23; H, 10.24. Found: C, 76.10; H, 10.31%.

4.2.9. (*R*)-1-(4-Pentoxyphenyl)-*n*-propanol 3i. Colorless liquid; $[\alpha]_D^{20}=+26.8$ (c 1.7, MeOH), e.e. 86%; ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, $J=7.2$ Hz, 3H, CH_3), 0.92 (t, $J=6.8$ Hz, 3H, CH_3), 1.33–1.50 (m, 4H, $2CH_2$), 1.60–1.85 (m, 5H, OH, $2CH_2$), 3.94 (t, $J=6.6$ Hz, 2H, OCH_2), 4.52 (t, $J=6.6$ Hz, 1H, CH), 6.85–7.26 (m, 4H, ArH). MS (EI) m/z: 222 (M^+), 204, 193, 123, 95, 77, 43, 29; IR ν (cm^{-1}): 3372 (OH), 1246, 1098. Anal. calcd for $C_{14}H_{22}O_2$ (222.32): C, 75.63; H, 9.97. Found: C, 75.36; H, 10.01%.

4.2.10. (*R*)-1-(4-Pentoxyphenyl)-*n*-pentanol 3j. Colorless liquid; $[\alpha]_D^{20}=+23.6$ (c 2.2, MeOH), e.e. 85%; ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, $J=6.6$ Hz, 3H, CH_3), 0.92 (t, $J=6.8$ Hz, 3H, CH_3), 1.25–1.47 (m, 8H, $4CH_2$), 1.58–1.82 (m, 5H, OH, $2CH_2$), 3.95 (t, $J=6.4$ Hz, 2H, OCH_2), 4.60 (t, $J=6.6$ Hz, 1H, CH), 6.85–7.27 (m, 4H, ArH). MS (EI) m/z: 250 (M^+), 232, 193, 162, 133, 123, 95, 77, 43; IR ν (cm^{-1}): 3371 (OH), 1245, 1111. Anal. calcd for $C_{16}H_{26}O_2$ (250.38): C, 76.75; H, 10.47. Found: C, 76.69; H, 10.53%.

4.2.11. (*R*)-1-(4-Hexoxyphenyl)-*n*-propanol 3k. Colorless liquid; $[\alpha]_D^{20}=+24.5$ (c 1.9, MeOH), e.e. 83%; ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, $J=6.4$ Hz, 3H, CH_3), 0.91 (t, $J=6.4$ Hz, 3H, CH_3), 1.33–1.48 (m, 6H, $3CH_2$), 1.60–1.89 (m, 5H, OH, $2CH_2$), 3.94 (t, $J=6.6$ Hz, 2H, OCH_2), 4.52 (t, $J=6.6$ Hz, 1H, CH), 6.83–7.26 (m, 4H, ArH). MS (EI) m/z: 236 (M^+), 207, 123, 95, 77, 43; IR ν (cm^{-1}): 3381 (OH), 1245, 1098. Anal. calcd for $C_{15}H_{24}O_2$ (236.35): C, 76.23; H, 10.24. Found: C, 75.89; H, 10.57%.

4.2.12. (*R*)-1-(4-Hexoxyphenyl)-*n*-pentanol 3l. Colorless liquid; $[\alpha]_D^{20}=+19.6$ (c 1.9, MeOH), e.e. 81%; ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, $J=6.4$ Hz, 3H, CH_3), 0.91 (t, $J=6.4$ Hz, 3H, CH_3), 1.22–1.53 (m, 10H, $5CH_2$), 1.60–1.83 (m, 5H, OH and $2CH_2$), 3.94 (t, $J=6.6$ Hz, 2H, OCH_2), 4.60 (t, $J=6.2$ Hz, 1H, CH), 6.84–7.27 (m, 4H, ArH). MS (EI) m/z: 264 (M^+), 246, 207, 162, 133, 123, 95, 77, 57; IR ν (cm^{-1}): 3374 (OH), 1245, 1111. Anal. calcd for $C_{17}H_{28}O_2$ (264.40): C, 77.22; H, 10.67. Found: C, 77.04; H, 10.66%.

4.3. Synthesis of 1-(4-butylthiophenyl)propanone 2m

4.4 g (40 mmol) of thiophenol was dissolved in 20 mL of 50% NaOH. To the resulting solution was added dropwise 5.48 g (40 mmol) of butyl bromide and was kept stirring for 4 h. The reaction mixture was extracted with diethyl ether (2×20 mL), washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was distilled at boiling point 140–142°C/50 mmHg to afford a colorless oil butyl phenyl thioether 5.71 g in the yield of 86%.

To a mixture of butyl phenyl thioether (3.32 g, 20 mmol) and anhydrous aluminum trichloride (2.94 g, 22 mmol) was added propionyl chloride (1.85 g, 20 mmol) dropwise in an ice–water bath and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with 20 mL of ice–water and extracted with diethyl ether (2×20 mL). The combined organic layers were successively washed with water to neutration, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was crystallized from petroleum ether (30–60°C) to give colorless crystallines 2.87 g, yield 65%, mp 37–38°C; ^1H NMR (200 MHz, $CDCl_3$): δ 0.95 (t, $J=7.2$ Hz, 3H, CH_3), 1.22 (t, $J=7.4$ Hz, 3H, CH_3), 1.48 (tq, 2H, CH_2), 1.67 (tt, 2H, CH_2), 2.96 (q, $J=7.4$ Hz, 2H, CH_2), 2.99 (t, $J=7.6$, 2H, CH_2), 7.29 (d, $J=8.2$ Hz, 2H, ArH), 7.86 (d, $J=8.2$ Hz, 2H, ArH); IR (KBr) ν 2960, 1681 (C=O), 1592, 1555 cm^{-1}; EI-MS (70 eV) m/z (%): 222 (M^+, 30), 193 (100), 137 (48), 109 (17), 57 (13), 43 (17), 29 (24). Anal. calcd for $C_{13}H_{18}OS$ (222.35): C, 70.22; H, 8.16; Found: C, 70.19; H, 8.63%.

4.4. Asymmetric reduction of 1-(4-butylthiophenyl)-propanone

The procedure is the same as described in Section 4.2.

4.4.1. (*R*)-1-(4-Butylthiophenyl)-*n*-propanol 3m. Colorless liquid; $[\alpha]_D^{20}=+18.5$ (c 1.0, MeOH), e.e. 83%; ^1H NMR (200 MHz, $CDCl_3$): δ 0.91 (t, $J=7.4$ Hz, 3H, CH_3), 0.92 (t, $J=7.2$ Hz, 3H, CH_3), 1.39–1.84 (m, 7H, OH, $3CH_2$), 2.91 (t, $J=7.2$ Hz, 2H, SCH_2), 4.56 (dt,

$J = 3.0$, 6.4 Hz, 1H, CH), 7.22–7.32 (m, 4H, ArH). MS (EI) m/z: 224 (M^+, 18), 206 (4), 195 (100), 150 (5), 139 (19), 123 (5), 111 (24), 77 (10), 57 (15), 29 (15); IR ν (cm^{-1}): 3371 (OH), 1094, 819. Anal. calcd for $C_{13}H_{20}OS$ (224.36): C, 69.59; H, 8.98. Found: C, 69.38; H, 9.50%.

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References

1. (a) Stein, A. R.; Dawe, R. D.; Sweet, J. R. *Can. J. Chem.* **1985**, *63*, 3442; (b) Pallavicini, M.; Valoti, E.; Villa, L.; Piccolo, O. *Tetrahedron: Asymmetry* **1994**, *5*, 5; (c) Su, X. B.; Zhang, Q. H.; Wu, Y. Q.; Xu, J. X. *Chin. J. Org. Chem.* **2002**, *22*, 496 and references cited therein.
2. (a) Holland, H. L.; Bergen, E. J.; Chenchaiah, P. C.; Khan, S. H.; Munoz, B.; Ninniss, R. W.; Richards, D. *Can. J. Chem.* **1987**, *65*, 502; (b) Janssen, A. J. M.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1991**, *47*, 7645.
3. (a) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475; (b) Singh, V. K. *Synthesis* **1992**, 605; (c) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763; (d) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1986.
4. (a) Csuk, R.; Glanzer, B. I. *Chem. Rev.* **1991**, *91*, 49; (b) Yadav, J. S.; Reddy, P. T.; Nanda, S.; Rao, A. B. *Tetrahedron: Asymmetry* **2001**, *12*, 63; (c) Yadav, J. S.; Reddy, P. T.; Nanda, S.; Rao, A. B. *Tetrahedron: Asymmetry* **2001**, *12*, 3381.
5. (a) Berger, S.; Langer, F.; Lutz, C.; Knochel, P.; Mobley, T. A.; Reddy, C. K. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1496; (b) Zhang, F. Y.; Yip, C. W.; Cao, R.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 585; (c) Shan, Z. X.; Xiong, Y.; Li, W. Z.; Zhao, D. J. *Tetrahedron: Asymmetry* **1998**, *9*, 3985.
6. (a) Ohno, K.; Saito, S.; Miyazawa, K.; Ushioda, M. Inoue, H.; Yoshida, N. *EP270244*, **1988** (*Chem. Abstr.* **1988**, *110*, 31528x); (b) Koizumi, Y.; Matsui, S.; Takeuchi, H.; Kubo, Y.; Nakagawa, E. *JP2001114722*, **2001** (*Chem. Abstr.* **2001**, *134*, 318781f).
7. (a) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709; (b) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717.
8. Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.
9. Masui, M.; Shioiri, T. *Synlett* **1997**, 273.
10. Li, X. S.; Xie, R. G. *Tetrahedron: Asymmetry* **1996**, *7*, 2779.