Synthesis of enatiomerically enriched β-amino alcohol derivatives via chiral base mediated-asymmetric deprotonation of (benzyl methyl ether) tricarbonylchromium(0) complex and electrophilic trapping with imines

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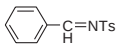
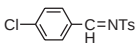
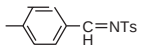
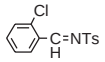
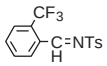
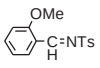
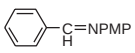
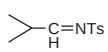
Deprotonation of (benzyl methyl ether)tricarbonylchromium(0) complex **1** by chiral base **2** followed by quenching reaction with imines **3** and subsequent decomplexation give β-amino alcohol derivatives **5** in good yields and high enantioselectivities (up to 96% e.e.).

Keywords: (benzyl methyl ether)tricarbonylchromium(0) complex, chiral base, imine, β-amino alcohol

Because of their widespread utility in different fields of chemistry, for example as key synthetic intermediates for biologically active natural products[1] and as chiral catalyst and auxiliaries in stereoselective synthesis,[2] optically active β-amino alcohol and their derivatives are of great importance. Although β-amino alcohols are often prepared by direct reduction of amino acids, a multitude of indirect methods for asymmetric synthesis of chiral β-amino alcohols has been developed.[3] Many known methods need multi-step reactions and one-step 'classical resolution' or another enantiomer separation technique to obtain the pure enantiomer.[4] On the other hand, usually, nucleophilic addition reactions to the chiral α-amino carbonyls, hydroxy imines, or hydroxyoximes are used for stereoselective synthesis of optically active β-amino alcohols.[5] However, as the stereogenic α-carbon of α-amino carbonyl compounds is labile, the optical purity was sometimes decreased. Therefore, the development of new synthetic methods for such compounds is still in high demand.

It is well documented that tricarbonylchromium (η^6-arene) complexes are important reagents and intermediates in organic synthesis.[6] Tricarbonylchromium (η^6-arene) complexes exhibit unique properties as compared to their parent free aromatic ligands. Changes of the reactivity arising upon the complexation of arene to the tricarbonylchromium fragment allow a variety of transformations to be carried out that are otherwise inaccessible. In particular, the complexation of a substituted aromatic ring to the tricarbonyl chromium moiety is known to facilitate α-carbanion formation. Gibson[7] discovered that the benzylic functionalisation of (arene)tricarbonylchromium(0) complex could be stereoselectively achieved by using chiral base for deprotonation and diphenyl disulfide as an electrophile to quench the reaction. After decomplexation, α-phenylsulfenylbenzyl ether was obtained in high enantioselectivity. Subsequently, several research works on stereoselective reactions of the chiral base-deprotonated (benzyl)tricarbonylchromium(0) complex with electrophiles such as alkyl halides, benzophenone, aldehydes, and chlorotrimethylsilane were reported.[8] The success of this approach is partially attributed to the configurational stability of the intermediate anion. To the best of our knowledge, imines have not been used as electrophiles in this reaction to date. More recently, we reported the synthesis of diarylmethylamine derivatives via

Table 1 Deprotonation of **1** by using chiral base **2** and elecrophilic quench reaction with imines **3**

Entry	Imine	Chiral base (%)[a] (*anti*/*syn*)[b]	Yield of **5** (%)	Ee (*syn*-**5**)[c] (%)	Ee (*anti*-**5**)[c]
1		(+)-**2**	**5a**, 83 (51/49)	96 (1*S*,2*S*)	95 (1*S*,2*R*)
2		(+)-**2**	**5b**, 57 (44/56)	94 (1*S*,2*S*)	96 (1*S*,2*R*)
3		(+)-**2**	**5c**, 69 (57/43)	93 (1*S*,2*S*)	92 (1*S*,2*R*)
4		(+)-**2**	**5d**, 62 (47/53)	93 (1*S*,2*S*)	90 (1*S*,2*R*)
5		(+)-**2**	**5e**, 75 (51/49)	94 (1*S*,2*S*)	93 (1*S*,2*R*)
6		(+)-**2**	**5f**, 81 (55/45)	94 (1*S*,2*S*)	91 (1*S*,2*R*)
7		(+)-**2**	nr		
8		(+)-**2**	nr		
9	**3a**	(-)-**2**	**5a**, 80 (51/49)	90 (1*R*,2*R*)	91 (1*R*,2*S*)
10	**3c**	(-)-**2**	**5c**, 70 (55/45)	94 (1*R*,2*R*)	93 (1*R*,2*S*)
11	**3d**	(-)-**2**	**5d**, 60 (46/54)	91 (1*R*,2*R*)	96 (1*R*,2*S*)

[a]isolated yield; [b]determined by ^{1}H NMR; [c]determined by chiral HPLC.

* Correspondence.

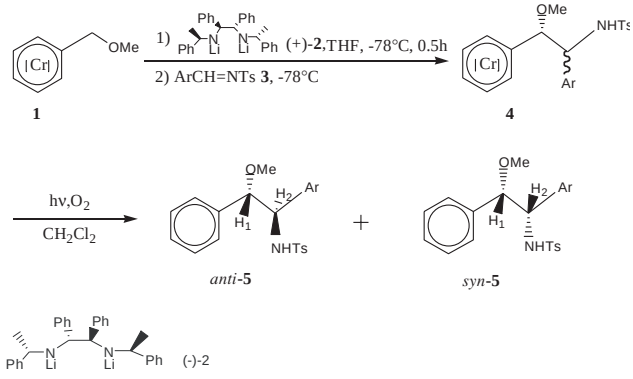
aromatic deprotonation of tricarbonyl (η^6-arene) chromium complexes followed by electrophilic trapping with imines.[9] Based on the results mentioned above, we envisioned that instead of *carbonyl compounds* and the *aromatic deprotonation* of tricarbonyl chromium complexes, the combination of *imines* as electrophile with chiral base-mediated *benzylic deprotonation* may provide a novel approach to chiral β-amino alcohol derivatives. Herein we wish to report results on the synthesis of chiral β-amino alcohol derivatives via bezylic deprotonation of tricarbonyl(η^6-arene) chromium complexes by chiral base followed by electrophilic trapping with imines.

Results and discussion

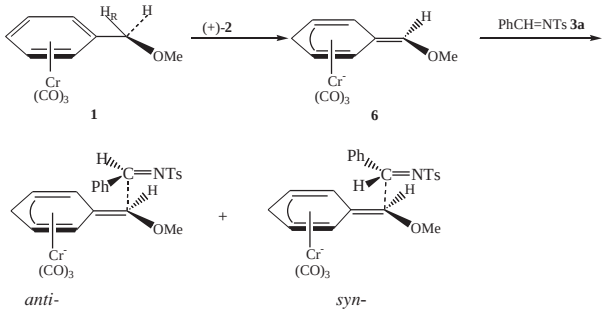
Accordingly, (benzyl methyl ether)tricarbonylchromium(0) complex **1**[10] and chiral base (+)-**2**[11] that was derived from chiral diamine and *n*-butyllithium were conveniently prepared according to standard procedure. The lithiation of **1** with (+)-**2** followed by the reaction with imines **3** and subsequent decomplexation were performed as illustrated in Scheme 1.

At first *N*-(*p*-methoxyphenyl)-benzylideneimine (**3g**) was employed as a substrate, but no reaction occurred (Table 1, entry 7), probably due to lower electrophilicity of the C=N bond of **3g**. Fortunately, the reaction of *N*-tosylbenzylideneimine **3a**, which is activated by the electron-withdrawing sulfonyl group on the nitrogen atom, with complex **1** in the presence of (+)-**2** proceeded at –70 °C smoothly to give the corresponding alkylated complex **4a**. Then, **4a** was subjected to the decomplexation condition (sunlight and air) and *N*-tosyl-2-amino-1,2-diphenyl-ethanol methyl ether **5a** was obtained in good overall yield (83%) (entry 1). **5a** is a mixture of *anti*- and *syn*-isomers. Their ratio was determined by ^{1}H NMR spectroscopy,[12] by which for *anti*-**5a**, the absorptions of H1 and H2 are located at 4.33 and 5.70 ppm ($J_{H1\text{-}H2}$ = 3.5 Hz), respectively, and for *syn*-**5a**, H1 and H2 are at 4.50 and 5.49 ppm ($J_{H1\text{-}H2}$ = 8.9 Hz). Although the diastereoselectivity is low, two diaostereomers, *anti*- and *syn*-**5a** can be easily separated by preparative TLC. Interestingly, the enantioselectivities of *anti*- and *syn*-**5a** are very high, 96% and 95% ee, respectively (entry 2), determined by chiral HPLC. The selection of THF as solvent is crucial to the reaction in that a change of solvent from THF to toluene or ethyl ether resulted in great decrease in yield and only traces of the desired product detected by TLC. It is noted that *N*-tosyl-alkyl imine (**3h**) does not work under the same reaction conditions (entry 8). Based on the experimental results, various aromatic imines bearing electron-withdrawing groups (**3b**, **3d**–**e**) or electron-donating groups (**3c** and **3f**) on the phenyl ring were examined. All the imines used reacted with **1** in the presence of (+)-**2** smoothly affording the desired β-amino alcohol derivatives (**5b–f**) in good overall yields after decomplexation. The enantioselectivities of the reactions are very high (90–96% e.e. entries 2–6) for both produced diastereomers no matter whether the substrates have *para*- or *ortho*-substitutions on the phenyl ring.

The absolute configuration of the newly created chiral center was determined on the basis of the X-ray diffraction analysis of the single crystals of *anti*-**5b** and *syn*-**5b** (Fig. 1, 2), thus assigned as (1*S*,2*R*) and (1*S*,2*S*) respectively. The stereochemical assignments of products (**5a**, **5c–f**) are based on the asummption that they are formed in an analogous manner to **5b**. According to the suggestion by Gibson,[7] the stereochemical outcome of this reaction, S-configuration of C1 of the product, may be rationalised by assuming the removal of the pro-*R* hydrogen from the conformation which places it antiperiplanar to chrominum and consequently the resultant stable anion (**6**) (Scheme 2) is alkylated on its *exo* face with high stereoselectivity due to the steric hindrance of



Scheme 1



Scheme 2

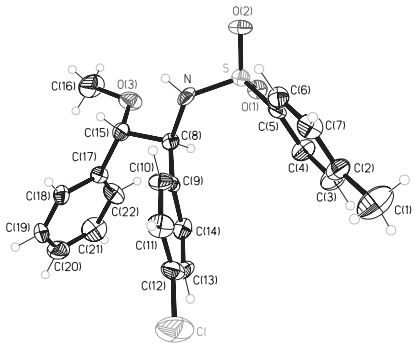


Fig. 1 ORTEP drawing of (1*S*,2*S*)-**5b**.

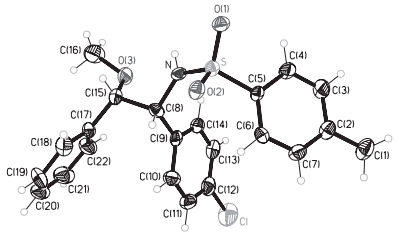


Fig. 2 ORTEP drawing of (1*S*,2*R*)-**5b**.

tricabonylchromium moiety. However, the stereocontrol to the attack to the *Si* or *Re* face of the C=N group is poor.

On the other hand, the deprotonation of complex **1** with chiral base (–)-**2** followed by quenching with the imines **3a**, **3c** or **3d** was also examined. The reactions also proceeded smoothly with good yields and high enatioselectivities (up to 96% ee). Compared with chiral HPLC data of (*1S*,2*S*)- and (1*S*,2*R*)-**5**, the absolute configuration of the products from the deprotonation by (–)-**2** should be deduced as 1*R*,2*R* and 1*R*,2*S*. Thus, since two diastereomers can be easily separated and the reactions have high enantioselectivities, four stereoisomers of 1,2-diaryl-2-amino-ethanol can be conveniently synthesised through a simple reaction pathway.

Experimental

IR spectra were recorded on a Perkin-Elmer 1710 infrared spectrometer. ^{1}H and ^{13}C NMR spectra were measured by Bruker a DMX-300 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Mass spectra were recorded on a Bruker APEX-2 spectrometer using the FBA technique. HPLC spectra were performed on a SHIMADZU CTO-10ASVP equipped with a given chiral cocolumn. Equipment for X-ray crystal analysis was a Rigaku R-axis Rapid IP and the software used was SHELX 97. All reactions were carried out under an argon atmosphere.

Typical experimental procedure was as follow. A solution of the chiral dilithium amide **2** was prepared by treatment of the corresponding diamine(0.1 mmol) in THF (2 ml) at –78 °C with *n*-butyllithium (1.6 mol l^{-1} in hexane; 0.125 ml, 0.2 mmol). The solution was allowed to warm to room temperature with stirring and then cooled to –78°C. To this resulting pink solution was added a solution of LiCl (4.2 mg, 0.1 mmol) in THF (2 ml) via a cannula. To this was added complex **1** (26 mg, 0.1 mmol) in THF (2ml) via a cannula over approximately 2 min. The yellow-orange solution was stirred at –78°C for 0.5 h and then imine **3a** (0.1 2 mmol) in THF (2 ml) was added. The solution was further stirred at –78 °C for 2 h, MeOH (1 ml) was added, the solution warmed to room temperature and the solvents removed in vacuum. The residue was purified by flash chromatography of residue on silicon gel (eluent: ethyl acetate-petroleum ether = 1:6) to give complex **4a**. Then, the solution of **4a** in CH_2Cl_2 (5 ml) was exposed to air and sunlight at room temperature until colourless. The solution was filtered through celite and evaporation of solvent under reduced pressure gave a mixture of *syn*-**5a** and *anti*-**5a** in 83% yield. Both diastereoisomers were obtained by preparative TLC separately.

(1S, 2S)-N-Tosyl-2-amino-1,2-diphenyl-ethyl methyl ether (***syn*-5a**): M.p. 159–160 °C. IR ν_{max}: 3277, 3030, 2922, 1494, 1455, 1326, 1159, 1093 cm^{-1}. δ_H 2.34 (s, 3H), 3.20 (s, 3H), 4.50 (m, 2H), 5.49 (d, 2H, *J* = 8.9 Hz), 6.69 (d, 2H, *J* = 7.5 Hz), 6.78 (d, 2H, *J* = 7.0 Hz), 6.93 (t, 2H, *J* = 7.4 Hz), 7.01–7.07 (m, 2H), 7.11–7.20 (m, 4H), 7.43 (d, 2H, *J* = 7.0 Hz); δ_C 21.3, 57.3, 62.4, 86.1, 126.9, 127.1, 127.3, 127.9, 128.0, 128.4, 129.1, 135.7, 136.7, 137.6, 142.8; HRMS (FAB) calcd for $C_{22}H_{24}NO_3S$ (M+H) 382.1471; Found 382.1471. HPLC (Daicel Chiralcel OD-H, hexane/isopropanol = 9/1, flow rate 0.8 ml/min): t_R (minor) = 11.52 min, t_R (major) = 13.44 min. In the case of chiral base (–)-**2**, (1*R*,2*R*)-**5a**: t_R (minor) = 14.01 min, t_R (major) = 11.74 min.

(1S, 2R)-N-Tosyl-2-amino-1,2-diphenyl-ethyl methyl ether (***anti*-5a**): M.p. 124–125 °C. IR ν_{max} 3287, 3062, 2930, 1599, 1494, 1452, 1325, 1159, 1092 cm^{-1}. δ_H 2.37 (s, 3H), 3.21 (s, 3H), 4.19 (d, 1H, *J* = 7.2 Hz), 4.33 (dd, 1H, *J* = 3.5, 7.2 Hz), 5.70 (d, 1H, *J* = 3.5 Hz), 6.94–6.97 (m, 4H), 7.01–7.12 (m, 5H), 7.15–7.25 (m, 3H), 7.40 (d, 2H, *J* =8.1 Hz); δ_C 21.4, 57.0, 63.7, 86.4, 127.2, 127.3, 127.4, 127.5, 128.0, 128.1, 128.2, 129.0, 137.0, 137.1, 137.2,142.7 HRMS (FAB) calcd for $C_{22}H_{24}NO_3S$ (M+H) 382.1471; Found 382.1460. HPLC (Daicel Chiralcel OD-H, hexane/isopropanol = 9/1, flow rate 1.0 ml/min): t_R (major) = 11.74 min, t_R (minor) = 14.13 min. In the case of chiral base (-)-**2**, (1*R*,2*S*)-**5a**: t_R (major) = 13.54 min, t_R (minor) = 11.20 min.

(1S, 2S)-N-Tosyl-2-amino-2-(4'-chlorophenyl)-1-phenyl-ethyl methyl ether (***syn*-5b**): M.p. 186–189 °C. IR ν_{max} 3275, 3030, 2924, 1597, 1492, 1451, 1326, 1160, 1093 cm^{-1}. δ_H 2.34 (s, 3H), 3.21 (s, 3H), 4.44–4.52 (m, 2H), 5.51 (d, 1H, *J* = 8.4 Hz), 6.60 (d, 2H, *J* = 8.3 Hz), 6.79 (m, 2H), 6.88 (d, 2H, *J* = 8.3 Hz), 7.03 (d, 2H, *J* = 8.0 Hz), 7.11–7.19 (m, 3H), 7.40 (d, 2H, *J* = 8.0 Hz); δ_C 21.4, 57.3, 61.9, 85.8, 126.9, 127.0, 127.4, 128.1, 128.2, 129.2, 129.8, 133.1, 134.2, 136.4, 137.4, 143.1. HRMS (FAB) calcd for $C_{22}H_{23}ClNO_3S$ (M+H) 416.1081; found 416.1077; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 40/1, flow rate 1.0 ml/min): t_R (major) = 35.70 min, t_R (minor) = 43.80min. The crystal used for the X-ray study had the dimensions 0.78 × 0.18 × 0.09 mm. Crystal data (CCDC No. 232288): $C_{22}H_{22}ClNO_3S$, M 415.92, orthorhombic, space group $P2_12_12_1$, *a* = 9.5309(3) Å, *b* = 14.7548(5) Å, *c* = 15.0496(4) Å, *V* = 2116.37(11) $Å^3$, *Z* = 4, D_{calcd} = 1.305 g/cm^3, F_0 = 872, Reflections collected: 4839, λ = 0.71073 Å, for [$I>2\sigma(I)$] *R* = 0.0282; *wR* = 0.0288.

(1S, 2R)-N-Tosyl-2-amino-2-(4'-chlorophenyl)-1-phenyl-ethyl methyl ether (***anti*-5b**): M.p. 151–152 °C. IR ν_{max} 3284, 3031, 2921, 1598, 1492, 1450, 1328, 1159, 1092 cm^{-1}. δ_H 2.40 (s, 3H), 3.21 (s, 3H), 4.13 (d, 1H, *J* = 7.4 Hz), 4.29 (dd, 1H, *J* = 3.2, 7.4 Hz), 5.69 (d, 1H, *J* = 3.2 Hz), 6.82 (d, 2H, *J* = 5.6 Hz), 6.94–6.97 (m, 2H), 7.00 (d, 2H, *J* = 8.4 Hz), 7.09 (d, 2H, *J* = 8.4 Hz), 7.19–7.23 (m,3H), 7.42 (d, 2H, *J* = 5.6 Hz); δ_C 21.4, 57.0, 63.2, 86.2, 127.2, 127.4, 127.9, 128.32, 128.36, 129.1, 129.5, 133.4, 135.7, 136.6, 136.9, 143.1. HRMS (FAB) calcd for $C_{22}H_{23}ClNO_3S$ (M+H) 416.1081; found 416.1078. HPLC (Daicel Chiralcel OD-H, hexane/isopropanol = 9/1, flow rate 0.5 ml/min): t_R (major) = 23.49 min, t_R (minor) = 27.22 min. The crystal used for the X-ray study had the dimensions 0.62 × 0.20 × 0.18 mm. Crystal data (CCDC No. 232289): $C_{22}H_{22}ClNO_3S$, M 415.92, orthorhombic, space group $P2_12_12_1$, α = 9.7248(3) Å, β = 14.0714(4) Å, χ = 15.8290(4) Å, *V* = 2166.06(11) $Å^3$, *Z* = 4, D_{calcd} = 1.275 g/cm^3, F_0 = 872, Reflections collected : 4961, λ = 0.71073 Å, for [$I>2\sigma(I)$] *R* = 0.0258; *wR* = 0.0462.

(1S, 2S)-N-Tosyl-2-amino-2-(4'-methylphenyl)-1-phenyl-ethyl methyl ether (***syn*-5c**): M.p. 179–180 °C; IR ν_{max} 3270, 2922, 1598, 1451, 1323, 1159, 1102 cm^{-1}. δ_H 2.24 (s, 3H), 2.35 (s, 3H), 3.23 (s, 3H), 4.47–4.51 (m, 2H), 5.45 (d, 1H, *J* = 7.7 Hz), 6.62 (d, 2H, *J* = 7.9 Hz), 6.78 (d, 2H, *J* = 7.9 Hz), 6.84–6.87 (m, 2H), 7.05 (d, 2H, *J* = 8.0 Hz), 7.15–7.24 (m, 3H), 7.46 (d, 2H, *J* = 8.0 Hz); δ_C 21.0, 21.3, 57.3, 62.2, 86.2, 127.0, 127.2, 127.9, 128.0, 128.1, 128.2, 129.1, 132.7, 136.7, 136.9, 137.7, 142.7. HRMS (FAB) calcd for $C_{23}H_{26}NO_3S$ (M+H) 396.1627; found 396.1633. HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 40/1, flow rate 0.8ml/min): t_R (major) = 30.31 min, t_R (minor) = 33.63 min. In the case of chiral base (–)-**2**, (1*R*,2*R*)-**5c**: t_R (major) = 33.03 min, t_R (minor) = 29.41min

(1S, 2R)-N-Tosyl-2-amino-2-(4'-methyl-phenyl)-1-phenyl-ethyl methyl ether (***anti*-5c**): M.p. 138–139 °C. IR ν_{max} 3288, 3029, 2924, 1514, 1493, 1324, 1159, 1098 cm^{-1}. δ_H 2.22 (s, 3H), 2.35 (s, 3H), 3.17 (s, 3H), 4.15 (d, 1H, *J* = 7.0 Hz), 4.24 (dd, 1H, *J* = 3.1, 7.0 Hz), 5.63 (d, 1H, *J* = 3.1 Hz), 6.78–6.85 (m, 4H), 6.93 (d, 2H, *J* = 6.5 Hz), 7.03 (d, 2H, *J* = 8.1 Hz), 7.15–7.18 (m, 3H), 7.36 (d, 2H, *J* = 8.1 Hz); δ_C 21.1, 21.4, 57.0, 63.5, 86.4, 127.2, 127.4, 127.9, 128.0, 128.1, 128.3, 128.5,129.0, 129.1, 134.1, 137.1, 142.7. HRMS (FAB) calcd for $C_{23}H_{26}NO_3S$ (M+H) 396.1627; found 396.1618; HPLC: (Daicel Chiralcel OD-H, hexane/isopropanol = 9/1, flow rate 0.5 ml/min): t_R (major) = 17.64 min, t_R (minor) = 20.74 min. In the case of chiral base (–)-**2**, (1*R*,2*S*)-**5c**: t_R (major) = 20.66 min, t_R (minor) = 17.82 min.

(1S,2S)-N-Tosyl-2-(2'-chlorophenyl)-1-phenyl-ethyl methyl ether (***syn*-5d**): M.p. 155–156 °C. IR ν_{max} 3289, 3036, 2928, 1598, 1446, 1403, 1331, 1160, 1088 cm^{-1}. δ_H 2.34 (s, 3H), 3.15 (s, 3H), 4.32 (d, 1H, *J* = 4.2 Hz), 4.86 (dd, 1H, *J* = 4.2, 5.8 Hz), 5.64 (d, 1H, *J* = 5.8 Hz), 7.00 (d, 2H, *J* = 8.1 Hz), 7.10–7.25 (m, 9H), 7.61 (d, 2H, *J* = 8.1 Hz); δ_C 21.4, 57.6, 59.4, 84.3, 126.5, 126.9, 127.3, 127.8, 127.9, 128.2, 128.5, 129.1, 129.6, 132.5, 136.4, 136.5, 137.3, 142.7; HRMS(FAB) calcd for $C_{22}H_{23}ClNO_3S$ (M+H) 416.1081; found 416.1078; HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 9/1, flow rate 1.0 ml/min): t_R (major) = 11.39 min, t_R (minor) = 17.03 min. In the case of (–)-**2a**, (1*R*,2*R*)-**5d**: t_R (major) = 17.61 min, t_R (minor) = 11.24 min.

(1S, 2R)-N-Tosyl-2-(2'-chlorophenyl)-1-phenyl-ethyl methyl ether (***anti*-5d**): M.p. 133–134 °C. IR ν_{max} 3279, 3029, 2928, 1598, 1473, 1447, 1328, 1160 cm^{-1}. δ_H 2.95 (s, 3H), 3.21 (s, 3H), 4.55 (d, 1H, *J* = 4.1 Hz), 5.17 (dd, 1H, *J* = 4.1, 8.6 Hz), 5.47 (d, 1H, *J* = 8.6 Hz), 6.79 (d, 2H, *J* = 7.4 Hz), 6.91–7.06 (m, 6H), 7.11–7.23 (m, 3H), 7.50 (d, 2H, *J* = 7.4 Hz); δ_C 21.3, 56.9, 84.7, 125.9, 126.9, 127.2, 127.9, 128.1, 128.3, 128.5, 129.1, 130.0, 133.5, 133.9, 135.8, 136.9, 142.9. HRMS (FAB) calcd for $C_{22}H_{23}ClNO_3S$ (M+H) 416.1081; found 416.1079; HPLC (Daicel Chiralpak AD-H, hexane/isopropano = 40/1, flow rate 0.8 ml/min) t_R (major) = 45.58 min, t_R (minor) = 52.10 min. In the case of chiral base (–)-**2**, (1*R*,2*S*)-**5d**: t_R (major) = 51.30 min, t_R (minor) = 45.82 min

(1S,2R)-N-Tosyl-2-amino-2-(2'-trifluromethylphenyl)-1-phenyl-ethyl methyl ether (***anti*-5e**): M.p. 142–143 °C. IR ν_{max} 3274, 3030, 1695, 1493, 1452, 1315, 1149 cm^{-1}. δ_H 2.23 (s, 3H), 3.08 (s, 3H), 4.35 (d, 1H, *J* = 4.3 Hz), 4.98 (dd, 1H, *J* = 4.3, 6.6 Hz), 5.36 (d, 1H, *J* = 6.6 Hz), 6.66 (d, 2H, *J* = 7.3 Hz),7.04–7.18 (m, 6H), 7.237–7.39 (m, 3H), 7.52 (d, 2H, *J* = 7.3 Hz); δ_C 21.4, 53.3, 57.0, 85.1, 122.1, 125.3 (q, $J_{C\text{-}F}$,= 261.15 Hz), 126.1, 126.9, 127.3 (q, $J_{C\text{-}F}$,= 32.92 Hz), 127.8, 128.3, 129.1, 130.2, 131.0, 135.5, 136.2, 135.7, 142.6; ; HRMS (FAB) calcd for $C_{23}H_{23}F_3NO_3S$ (M+H) 450.1345; found 450.1338. HPLC (Daicel Chiralcel OD-H, hexane/isopropanol = 40/1, flow rate 1.0 ml/min) t_R (minor) = 12.84 min, t_R (minor) = 16.65 min.

(1S,2R)-N-Tosyl-2-amino-2-(2'-trifluromethylphenyl)-1-phenyl-ethyl methyl ether (***anti*-5e**): M.p. 125–126 °C. IR ν_{max} 3284, 3032, 1602, 1494, 1452, 1310, 1159 cm^{-1}. δ_H 2.27 (s, 3H), 3.05 (s, 3H), 4.19 (s, 1H), 4.65 (d, 1H, *J* = 6.5 Hz), 5.60 (d, 1H, *J*=6.5 Hz), 6.83 (d, 2H, *J* = 8.0 Hz), 7.04–7.18 (m, 6H), 7.26–7.37 (m, 1H), 7.46 (d, 2H, *J* = 8.0 Hz), 7.62 (d, 2H, *J* = 7.9 Hz); δ_C 21.9, 56.2, 57.9, 84.7, 122.7, 126.5 (q, $J_{C\text{-}F}$,= 250.15 Hz), 127.0, 127.4, 127.8 (q, $J_{C\text{-}F}$,= 31.08 Hz), 128.1, 128.5, 129.2, 130.7, 131.6, 137.7, 136.8, 139.0, 143.1;HRMS (FAB) calcd for $C_{23}H_{23}F_3NO_3S$ (M+H) 450.1345; found 450.1346. HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 40/1, flow rate 1.0 ml/min): t_R (major) = 25.12 min, t_R (minor) = 29.33 min.

(1S, 2S)-N-Tosyl-2-amino-2-(2'-methoxyphenyl)-1-phenyl-ethyl methyl ether (***syn*-5f**): M.p. 120–121 °C; IR ν_{max} 3283, 3031, 2928, 1600, 1493, 1459, 1327 cm^{-1}. δ_H 2.07 (s, 3H), 3.14 (s, 3H), 3.39 (s, 3H), 4.44 (d, 1H, *J* = 5.1 Hz), 4.95 (dd, 1H, *J* = 5.1, 9.8 Hz), 5.54

(d, J = 9.8 Hz), 6.48 (d, 1H, J = 8.1 Hz), 6.63 (t, 1H, J = 7.4 Hz), 6.84–7.27 (m, 6H), 7.15–7.25 (m, 3H), 7.43 (d, 2H, J = 7.9 Hz); δ_C 21.4, 55.0, 56.9, 57.1, 85.2, 110.0, 120.0, 125.0, 126.9, 127.4, 127.7, 128.3, 128.9, 129.6, 137.5, 137.6, 142.6, 156.3, 1246, 1160; HRMS (FAB) calcd for $C_{23}H_{26}NO_4S$ (M+H) 412.1577; found 412.1578. HPLC (Daicel Chiralpak AD-H, hexane/isopropanol = 40/1, flow rate 1.0 ml/min): t_R (major) = 30.5 min, t_R (minor) = 33.9 min.

(1S, 2R)-N-Tosyl-2-amino-2-(2'-methoxyphenyl)-1-phenyl-ethyl methyl ether (***anti*-5f**): M.p. 135–136 ºC. IR ν_{max} 3294, 3030, 2932, 1599, 1493, 1459, 1326, 1244, 1159 cm^{-1}. δ_H 2.31(s, 3H),3.14 (s, 3H), 3.62 (s, 3H), 4.34 (d, 1H, J = 5.5 Hz), 4.74 (m, 1H), 5.68 (d, 1H, J = 6.5 Hz), 6.61(d, 1H, J = 8.2 Hz), 6.69 (t, 1H, J = 7.4 Hz), 7.16–7.69 (m, 9H), 7.37 (d, 2H, J = 8.1 Hz); δ_C 21.8, 55.5, 57.8, 59.6, 85.4, 110.6, 120.7, 126.7, 127.3, 128.0, 128.3, 128.8, 129.3, 129.7, 137.9, 138.8, 142.8, 156.7. HRMS (FAB) calcd for $C_{23}H_{26}NO_4S$ (M+H) 412.1577; found 412.1571. HPLC: (Daicel Chiralpak AD-H, hexane/isopropanol=40/1, flow rate 1.0 ml/min): t_R (major) = 12.5 min, t_R (minor) = 15.9 min.

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