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Synthesis of enantiopure 1,2-azido and 1,2-amino alcohols via regio- and stereoselective ring-opening of enantiopure epoxides by sodium azide in hot water

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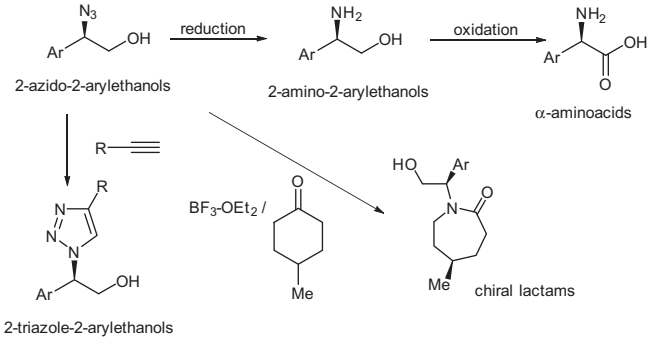
ABSTRACT

A practical and convenient method for the efficient and regio- and stereoselective ring-opening of enantiopure monosubstituted epoxides by sodium azide under hydrolytic conditions is reported. The ring-opening of enantiopure styryl and pyridyl (*S*)-epoxides by N_3^- in hot water takes place preferentially at the internal position with complete inversion of configuration to produce (*R*)-2-azido ethanols with up to 99% enantio- and regioselectivity, while the (*S*)-adamantyl oxirane provides mainly the (*S*)-1-adamantyl-2-azido ethanol in excellent yield. In general, 1,2-amino ethanols were obtained in high yield and excellent enantiopurity by the reduction of the chiral 1,2-azido ethanols with PPh_3 in water/THF, and then converted into the Boc or acetamide derivatives.

1. Introduction

Non-racemic 1,2-azido ethanols are well-known precursors for the synthesis of a broad variety of enantiopure 1,2-amino alcohols, unnatural amino acids, and triazole derivatives, which are essential building blocks for the preparation of important pharmaceutical products, particularly, neuroactive compounds.[1–3] In addition, chiral amino alcohols have been extensively used in asymmetric synthesis as organic catalysts,[4,5] chiral ligands,[1,6] and chirality transfer agents.[7] 2-Azido-2-arylethanols are particularly important intermediates for the synthesis of enantiopure 1,2-aminoethanols, which are widely used as chiral auxiliaries and chiral templates for the synthesis of chiral lactams[3c] and unnatural amino acids,[3d] as well as, chiral 2-triazole-2-arylethanols, as illustrated in Scheme 1.

Due to the recent availability of well-established synthetic routes for the asymmetric syntheses of monosubstituted epoxides,[8–12] the development of practical and environmentally friendly methods for the synthesis of highly enantiopure 1,2-amino ethanols is an area of great relevance. Aminolysis and azidolysis reactions of oxiranes have been extensively studied for the synthesis of racemic vicinal amino alcohols with a diversity of results.[13–16]



Scheme 1. (*R*)-2-Azido-2-arylethanols as key intermediates.

The regio- and stereoselective ring-opening reaction of epoxides depends greatly on the type of substrate, the nucleophilicity of the nitrogen, and the experimental reaction conditions, such as solvent, concentration, temperature, additive, catalyst, and process conditions.[14–16] Over the past two decades, water has played an important role not only as an ideal solvent, but also as a remarkable medium for a variety of catalyzed and uncatalyzed organic reactions.[15,16] Fringuelli et al.[16a] first studied the ring-opening of racemic epoxides in water at 30 °C with sodium azide under

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acidic (pH 4.2) and basic (pH 9.2) conditions, observing different regioselectivities for the catalyzed and uncatalyzed ring-opening of aromatic and aliphatic substituted epoxides. Recently, Qu et al.[16b] reported the ring-opening of racemic styrene oxide with sodium azide at 60 °C in water under neutral conditions and observed the preferential attack of the azide anion at the benzylic position. However, the application of this reaction to enantiopure aryl oxiranes has been completely neglected probably due to the concern that racemization could occur by a possible S_N1 mechanism, with water acting as a Lewis acid.[3c,16] To the best of our knowledge, there are very limited studies on the synthesis of nonracemic 2-azido-2-aryl-1-ethanols via uncatalyzed ring-opening of enantiopure aryl oxiranes in hot water.

A series of highly effective aminoborate esters derived from non-racemic amino alcohols, as shown in Figure 1, were previously prepared in our laboratory for the enantioselective borane reduction of ketones and benzyloximes.[17] Spiroaminoborate ester **1a**, derived from diphenyl prolinol and ethylene glycol, has been demonstrated to be a highly stable and a convenient catalyst for the borane reduction of a variety of aryl, heteroaryl, α-alkoxy and aliphatic ketones providing the desired chiral secondary alcohols with a CBS oxazaborolidine-like enantioselectivity.[18] As illustrated in Scheme 2, we recently reported a useful protocol for the borane-mediated reduction of 2-haloketones **2** catalyzed by the spiroaminoborate **1a** to obtain enantiopure aryl and aliphatic (*S*)-halohydrines **3**, which upon subsequent cyclization with NaOH, gave the corresponding chiral oxiranes **4**.[12] Preliminary studies of the ring–opening of (*S*)-styryl and (*S*)-4-chlorostyryl epoxides with sodium azide in water at 60 °C indicated the preferential formation of (*R*)-2-azido-2-arylethanols **5**, with almost complete inversion of configuration at the benzylic position. Thus, it was of great interest to examine the regio- and stereoselective ring-opening of representative aryl, pyridyl, and adamantyl (*S*)-oxiranes (Scheme 2) by sodium azide under neutral hydrolytic conditions. In addition, we also report a facile, efficient, and environmentally benign method for the reduction of the azides without racemization, which offers a suitable alternative for the enantioselective synthesis of important unnatural 1,2-amino alcohols and their corresponding Boc or acetamide derivatives.

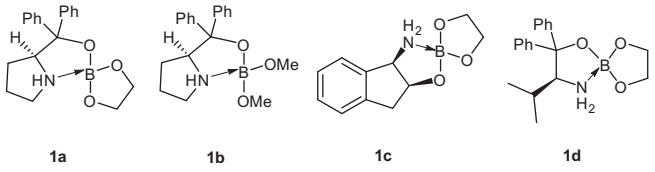
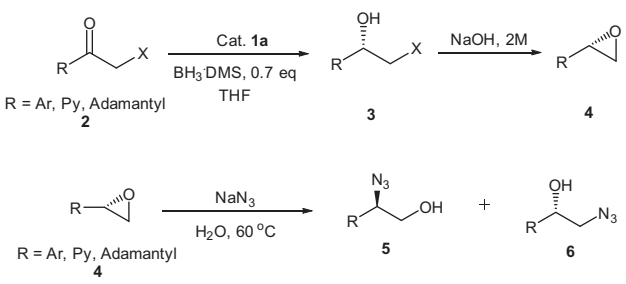


Figure 1. Aminoborate ester catalysts derived from non-racemic 1,2-amino alcohols.



Scheme 2. Synthesis and azidolysis of enantiopure (*S*)-epoxides.

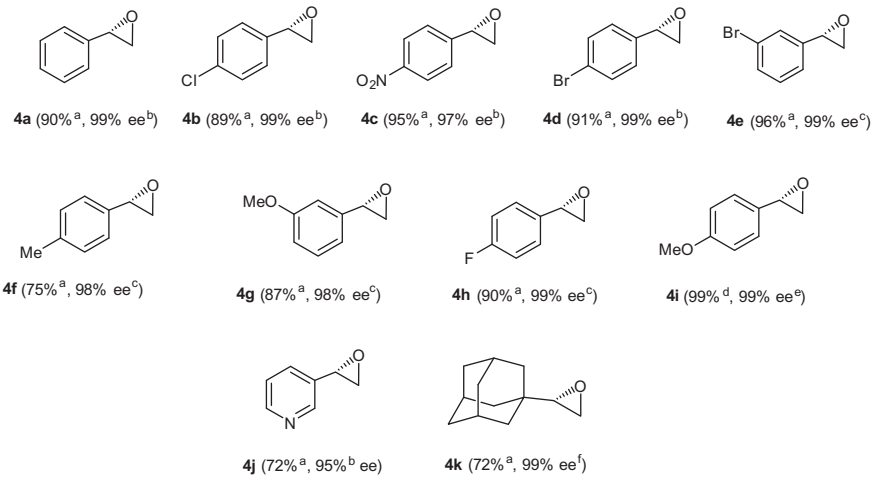
2. Results and discussion

Initially, representative (*S*)-styryl and adamantyl epoxides were prepared by the reduction of the 2-bromo-1-substituted ethanones **2** with 10% of spiroaminoborate **1a** and 0.7 equiv BH_3·DMS in THF at room temperature for 0.5 h, followed by the treatment of the crude halohydrines **3** with 2 M NaOH, or K_2CO_3 in acetone as in the case of 1-(4-methoxyphenyl)-2-bromoethanol. The corresponding pure non-racemic (*S*)-oxiranes **4a–i**, **4k** were afforded in good to excellent yields and with up to 99% ee, as shown in Table 1.

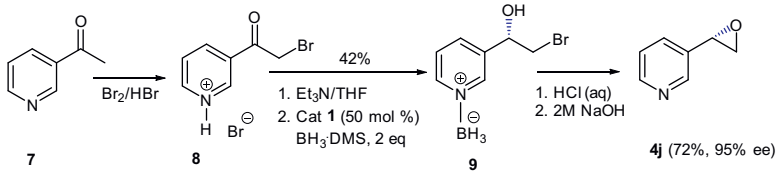
Due to the biological importance of enantiopure 3-pyridyl 1,2-azido alcohols,[19] we were also interested in the synthesis of (*S*)-3-pyridyl epoxide **4j**. As illustrated in Scheme 3, bromination of acetylpyridine **7** with bromine in HBr provided the stable 2-bromo-1-(pyridyl-3-yl)-ethanone hydrobromide salt **8**.[19a,19b] The removal of HBr from the pyridinium salt by different methods, without decomposition of the 2-bromo acetylpyridine, was a challenge. After treatment of the 2-bromo-acetyl pyridine-hydrobromide **8** with triethylamine in situ, and removal of the triethylamine hydrochloride salt from the solution, the unstable 2-bromo-(3-pyridyl) ethanone was immediately reduced with 0.5 equiv of the spiroaminoborate **1** and BH_3·DMS. The (*S*)-2-bromohydrin-1-3-pyridyl-borane complex **9** was isolated as a stable compound, which after acidic hydrolysis and subsequent NaOH treatment, gave pure (*S*)-pyridyl epoxide **4j** in 72% yield and with excellent enantiopurity (95% ee).

We then proceeded to study the regio- and enantioselectivity of the ring opening reaction of the prepared enantiopure (*S*)-oxiranes **4a**-**k**, shown in Table 2, with sodium azide in hot water. Optimal conditions were obtained by stirring a suspension of the epoxide (2 mmol) and sodium azide (4 mmol) in distilled water (10 mL) and heating the mixture at 60 °C. The reaction was usually complete in less than 4 h, as indicated by TLC. Except for (*S*)-epoxides **4c**, the main isolated products were the (*R*)-2-azido-2-aryl ethanols **5**, formed by the attack of the azide anion to the benzylic position, with almost complete inversion of configuration and with only a minor amount of the regioisomer **6**, as determined by GC–MS or ^{1}H NMR analysis of the crude product. The regio- and stereochemistry of the azido ethanols was confirmed by HPLC analysis on a Chiralpak AD-H column and by the specific rotation of the pure isolated products or derivatives. The regioselectivity for the ring-opening of 4-nitrostyrene oxide **4c** (entry 3) decreased substantially, giving the azido alcohols **5c** and **6c** in 67% and 33% ratio, respectively, with modest enantioselectivity (73% ee) of **5c**. It seems that the strong electron-withdrawing effect of the *p*-NO_2 group plays a detrimental role in the enantio- and regioselectivity of the reaction, while for the other halogen substituted aromatic compounds **5b**, **5d**, and **5h**, it had a mild effect. The regioselectivity for the azide ring-opening reaction of 3-pyridyl epoxide **4j** was modest, observing a 70:30 ratio for the 1,2-azido-1-ethanols **5j**/**6j** (entry 10a), while (*R*)-2-azido-2-pyridyl-1-ethanol **5j** was obtained with excellent enantiopurity (95% ee). However, the opposite regioselectivity was observed for the pyridyl epoxide–BH_3 complex **4j*** (entry 10b), producing the 1,2-azido ethanols **5j**/**6j** in a 30:70 ratio (entry 10b), due to the positive charge on the pyridyl nitrogen. Finally, as expected, the N_3^- addition to the (*S*)-adamantyl oxirane **4k** afforded the enantiopure (*S*)-1,2-azido ethanol **6k**, as indicated by ^{1}H and ^{13}C NMR. Nevertheless, since the NMR signals for the two regioisomers are very similar, the structure of the azido alcohol **6k** was evidenced by X-ray analysis of the corresponding acetamide derivative **11k**′, shown in Figure 2. In general, after purification by column chromatography and/or preparative TLC (Table 2), the (*R*)-2-azido-2-aryl-ethanols **5** and the (*S*)-1-adamantyl-2-azido ethanol **6k** were obtained in good to excellent yields and with excellent enantiomeric purity, as determined by HPLC

Table 1
Non-racemic epoxides (*S*)-**4a–k**[a]



[a] Isolated yield of purified product by flash chromatography.
[b] Enantiopurity determined by GC on chiral column (CP-Chirasil-Dex-CB).
[c] Determined by HPLC (Chiralcel AD-H) on the basis of β-azido alcohol.
[d] Crude product.
[e] Determined by HPLC (Chiralcel AD-H) of the chiral acetyl derivative of the β-bromo ethanol.
[f] Determined by HPLC (Chiralcel AD-H) of the chiral azido derivative **6k**.



Scheme 3. Synthesis of (*S*)-3-pyridyl epoxide **4j**.

analysis (>95% ee). Remarkably, no 1,2-diols were detected in this epoxide ring opening reaction in hot water.[15f]

Over the past several years, important advances have been made toward the synthesis of primary amine via the reduction of azides.[14,21–24] Generally, azides are reduced by hydrogen catalyzed by Pd/C,[21] sodium borohydride catalyzed by metal catalysts,[22] PPh_3/H_2O (Staudinger reaction),[14b,23] and $LiAlH_4$.[24] The Staudinger reaction was selected to reduce the N_3 group of the enantiopure azido alcohols due to the facile and mild reaction conditions required to prevent racemization. Initially, enantiopure 1,2-azido alcohols **5** and **6** were reacted with PPh_3/H_2O in THF at room temperature overnight. In some cases, the reaction mixture was heated at 70 °C for 2 h.[23] As shown in Table 3, the β-amino alcohols **10** were obtained in excellent yields and with high enantiomeric purity, up to 99% ee, as determined by HPLC analysis on a chiral column based on the Boc derivatives **11**, which were prepared in excellent yield (>90%) according to the method reported in the literature.[25]

3. Conclusion

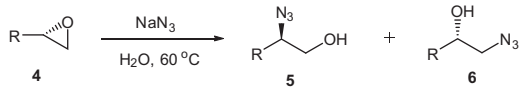
In conclusion, we have demonstrated that the ring–opening of enantiopure (*S*)-styryl and pyridyl oxiranes by NaN_3 in hot water takes place via nucleophilic attack, preferentially at the internal carbon of the aromatic monosubstituted epoxides providing the (*R*)-2-azido-2-aryl-ethanols as the main product with complete inversion of configuration (up to 99% ee) and with good to excellent chemical yield. Remarkably, this regio- and stereoselective ring-opening reaction takes place via an S_N2 type mechanism, hot water acting as a very weak Lewis acid.[15] As expected, the ring opening of adamantyl oxirane takes places at the less hindered position producing (*S*)-1-adamantyl-2-azido ethanol in excellent yield and with high enantiopurity. This novel regio- and enantioselective conversion of non-racemic oxiranes to 1,2-azido alcohols under mild and environmental favorable conditions provides an easy and rapid access to the synthesis of enantiopure 1,2-aminoethanols, suitable for the preparation of important biological active drugs.[20] Furthermore, considering the convenience and efficiency of this route, this methodology allow us a new facile way for the synthesis of enantiopure aromatic α-amino aldehydes and α-amino acids in the future.

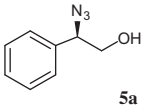
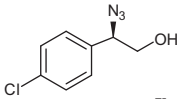
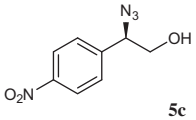
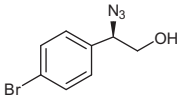
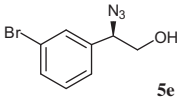
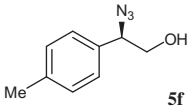
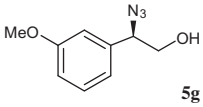
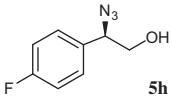
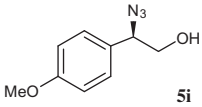
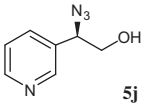
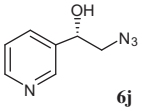
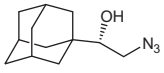
4. Experimental

4.1. General

Common solvents were dried and distilled by standard procedures. All reagents were obtained commercially unless otherwise noted. Air- and moisture sensitive reactions were carried out in dried glassware under an N_2 atmosphere. Chromatographic purification of products was accomplished using flash chromatography on a Merck silica gel® Si 60 Å (200–400 mesh). ^1H and ^{13}C spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. GC–MS analysis was processed on a Finnigan Trace GC/Polaris Q Mass detector using a Restek RTX-5MS column. Chiral gas

Table 2
Ring–opening of (*S*)-epoxides **4** with NaN_3 in hot water



Entry	Epoxide **4**	Major 1,2-azido alcohol	**5**/**6**[a] (%)	Yield[b] (%)	ee[c] (%)
1	**4a**	 **5a**	>99	91	99[d]
2	**4b**	 **5b**	>95	88	99[d]
3	**4c**	 **5c**	67/33	50	73 **5c** 90 **6c**
4	**4d**	 **5d**	>94	91	97
5	**4e**	 **5e**	>90	87	99
6	**4f**	 **5f**	>99	88	95
7	**4g**	 **5g**	95/5	81	99
8	**4h**	 **5h**	>99	92	99
9	**4i**	 **5i**	>99	83	99
10a	**4j**	 **5j**	70/30	69[e]	95
10b	**4j**[*]	 **6j**	30/70	71[e]	—
11	**4k**	 **6k**	1/99	85	99

[a] The ratio of **5** and **6** was determined by ^{1}H NMR.
[b] Isolated yield of azido alcohols purified by flash chromatography or preparative TLC.
[c] Enantiomeric excess determined by chiral HPLC analysis (Chiralpak AD-H).
[d] Determined by chiral HPLC on Chiralcel AD-H of the Boc amino derivative.
[e] Crude product.

chromatography analysis was processed on a Hewlett Packard GC 5890 equipped with a Chrompack Chiralsil-Dex-CB column (30 m × 0.25 mm × 0.25 μm). Chiral HPLC analysis was processed on an Agilent 1100 system Series 200 equipped with CHIRALPAK AD-H column and UV detector working at 254 nm and 220 nm. IR spectra were taken with a Perkin Elmer spectrophotometer fitted with ATR (Diamond/ZnSe) accessory. Optical rotation measurements were conducted using a Pekin Elmer digital polarimeter Model 341.

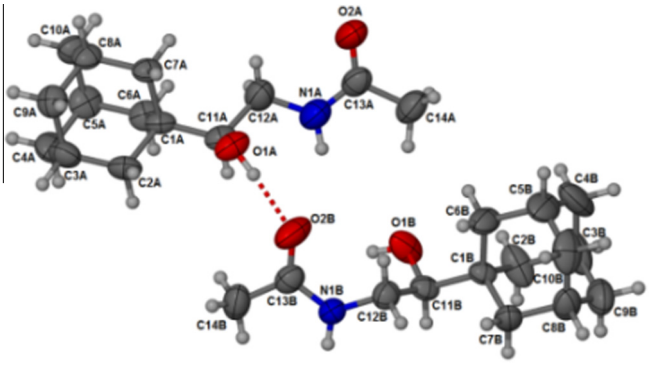


Figure 2. X-ray structure of the (*S*)-1-(1-adamantyl)-2-acetamido-1-ethanol **11k′**.

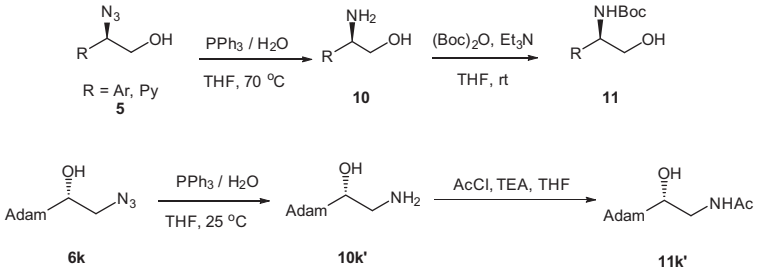
4.2. Synthesis of oxiranes

4.2.1. Typical method for the enantioselective synthesis of enantiopure epoxides: Synthesis of (*S*)-2-bromo-(4′-methoxyphenyl) ethanol 3i and subsequent epoxidation to obtain the epoxide-4i[12a,26]

In a dry 50 mL round bottomed flask at room temperature and under an N_2 atmosphere was placed the spiroaminoborate ester of diphenylprolinol **1a** (EG-DPP) (0.323 g, 1 mmol) and dissolved in freshly distilled THF (10 mL). Next, BH_3·DMS in THF (0.70 mL, 10 M, 7 mmol) was added to the solution via syringe, and the mixture was stirred for 1 h. Next, 2-bromo-(4′-methoxy)-acetophenone (2.29 g, 10 mmol) in dry THF (5 mL) was slowly added to the flask using an injection pump for 1 h, and then the mixture was stirred for 1 h at room temperature. The reaction mixture was cooled at 0 °C and quenched by the slow addition of MeOH (5 mL). The solvents were removed in a rotor-evaporator under vacuum at 35 °C and the colorless liquid was treated with a saturated aqueous NH_4Cl solution (10 mL) for 15 min. Next, the mixture was extracted with diethyl ether (3 × 10 mL) and the combined organic phases were washed with a brine solution (15 mL), dried over Na_2SO_4, and concentrated under high vacuum at 40 °C. Attempted purification of **3i** by column chromatography on silica gel failed due to the instability of the compound. The crude alcohol was a colorless oil (2.23 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.58 (m, 2H), 3.84 (s, 3H), 4.88 (m, 1H), 6.94 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.1, 55.4, 73.5, 114.1, 127.3, 132.7, 159.7.[26b]

O-Acetyl derivative of 2-bromo-(4′-methoxyphenyl)ethanol: In a 10 mL vial was placed the alcohol **3i** (20 mg), dry CH_2Cl_2 (2 mL), Et_3N (0.1 mL), acetic anhydride (0.1 mL), and a small DMAP crystal. TLC analysis revealed that the acetate formation was complete after 5 minutes of stirring at room temperature. Next, water (2 mL) was added followed by saturated aqueous solution of Na_2CO_3, while shaking until no more bubbling was observed. The aqueous solution was extracted with diethyl ether (2 mL), the organic phase concentrated under vacuum, and the crude acetate was dissolved in isopropanol HPLC grade (1 mL). The enantiopurity of the acetyl derivative of the (*S*)-isomer was 99% ee determined by HPLC: AD-H chiral column, hexane/isopropanol (95/5) with a 1.0 mL/min flow, t_R (12.96 min), 99.6, t_R (15.55 min), 0.42. $[\alpha]_D^{23}$ = +34 (*c* 1.5, $CHCl_3$); Lit.[26a] $[\alpha]_D^{23}$ = +36.7 (*c* 1.03, $CHCl_3$), 98.5% ee.

Table 3
Synthesis of enantiopure 1,2-amino ethanols by reduction of the 1,2-azido ethanols using PPh_3/H_2O



1,2-Azido ethanol	R	**10**[a] (%)	**11**[b] (%)	ee[c] (%)
5a	Ph	92	93	>99
5b	4-Cl-C_6H_4	87	91	>99
5d	4-Br-C_6H_4	90	96	>99
5e	3-Br-C_6H_4	95	95	99
5f	4-Me-C_6H_4	83	90	>99
5g	3-MeO-C_6H_4	89	92	99
5h	4-F-C_6H_4	93	95	>99
5i	4-MeO-C_6H_4	42	99	97
5j	3-Pyridyl	51	84[d]	95
6k	1-Adamantyl	96 **10k′**	89 **11k′**	96[e]

[a] Isolated yield.
[b] Purified by preparative TLC.
[c] Determined by chiral HPLC analysis (Chiralcel AD-H) of **11**.
[d] Crude product.
[e] Determined by chiral GC analysis of acetamide **11k′** on a CP-Chirasil-Dex CB column.

4.2.2. (*S*)-2-(4-Methoxyphenyl)oxirane 4i[12b]

In a 50 mL round bottomed flask was placed alcohol **3i** (2.24 g, 9.7 mmol), dissolved in dry acetone (20 mL) and treated with dry K_2CO_3 (2.68 g, 19.4 mmol). The mixture was stirred vigorously at room temperature until the reaction was complete as indicated by TLC analysis. The solution was filtered, washed with acetone, and the solvent removed under high vacuum. Oxirane **4i** was obtained as a clear unstable liquid (1.44 g, 99%); $[\alpha]_D^{22} = -13.0$ (*c* 3.3, $CHCl_3$), Lit.[12b] $[\alpha]_D^{20} = -26$ (*c* 1, $CHCl_3$) for 72% ee. ^1H NMR (400 MHz, $CDCl_3$): δ 2.85 (dd, $J_1 = 2.6$ Hz, $J_2 = 5.6$ Hz, 2H), 3.17 (dd, $J_1 = 4.0$ Hz, $J_2 = 5.6$ Hz, 2H), 3.85 (s, 3H), 3.87 (m, 1H), 6.93 (d, $J = 8.8$ Hz, 2H), 7.25 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.0, 52.2, 55.3, 114.0, 126.9, 129.5, 159.7; MS *m*/*z* (relative intensity): 150 $M^{\cdot+}$ (20%), 121 (100%), 91 (18%), 77 (14%).

4.2.3. Synthesis of 2-bromo-1-pyridin-3-yl-ethanone hydrobromide 8[27a]

In a two neck 100 mL round bottomed flask were placed 3-acetyl pyridine (5.0 mL, 47 mmol) and hydrogen bromide (15 mL, 48 wt %). The reaction mixture was heated at 80 °C and bromine (2.5 mL, 50 mmol, 1.0 equiv) was added dropwise. After the mixture was stirred for 1.5 h at 80 °C, it was allowed to cool to room temperature, and then to 0 °C. Acetone (5 mL) was added dropwise and a white solid precipitated, which was filtered using a Büchner funnel. The crude sample was transferred to a flask and dried under high vacuum to give as a bone white solid (9.42 g, 70%): mp 192–193 °C; Lit.[27b] mp 195–198 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 4.83 (s, 2H), 7.51 (t, $J = 6.6$ Hz, 1H), 8.71 (d, $J = 8.0$ Hz), 9.01 (d, $J = 5.2$ Hz, 1H), 9.34 (s, 1H); FT-IR (ATR): ν (cm^{-1}) 3281, 2585 (NH salt), 1709.

4.2.4. Synthesis of (*S*)-2-bromo-1-(pyridin-3-yl)ethanol *N*-borane complex 9[28a]

In a dried round bottomed flask under a nitrogen atmosphere was placed 2-bromo-3-acetyl pyridine-HBr salt **8** (2.81 g, 5.0 mmol, 1.0 equiv) and dissolved in freshly distilled THF (35 mL). The solution was cooled at 0 °C and triethylamine (767 μL, 5.5 mmol, 1.1 equiv) was added dropwise using a syringe-infusion pump (30 min). This mixture was stirred for 30 min and then decanted to remove the triethylamine hydrobromide salt. The clear solution was transferred via a syringe to another flask under nitrogen. Spiroborate **1a** (EG-DPP) (807 mg, 2.5 mmol, 0.1 equiv) was placed in a dried flask under nitrogen and dissolved in freshly distilled THF (30 mL). Next, BH_3·DMS (1.0 mL, 10 mmol, 2.0 equiv) was added dropwise to the catalyst solution and the mixture was stirred at room temperature for 1 h. The pyridyl ketone solution was added dropwise to a cold borane/catalyst solution at 0 °C using an infusion pump (1 h addition). The reaction mixture was left stirring at room temperature overnight and then, methanol (7 mL) was added dropwise to quench the reaction. After the solvents were removed under reduced pressure, the reaction mixture was diluted with 50 mL of ethyl acetate, transferred to a separatory funnel, and the organic solution was washed with a saturated aqueous solutions of NH_4Cl (30 mL) and then brine (30 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under vacuum at room temperature. The crude mixture was first purified by silica gel (40 g) column chromatography (14.5 cm long × 1.5 cm diameter) using hexane/ethyl acetate (1:1 v/v) and 1.0% of Et_3N as the mobile phase. Further purification by preparative TLC silica gel (20 cm × 20 cm, 1500 micron) using hexane/ethyl acetate (1:1 v/v) and Et_3N (1.0%), gave compound **9** as a bone white solid (1.12 g, 42%): mp 63–65 °C; 97% ee by GC of acetyl derivate: CP-Chirasil-Dex column, t_R (minor) = 28.64 min, (1.07%), t_R (major) = 28.83 min, (98.9%). $[\alpha]_D^{20} = +42$ (*c* 1.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 3.13 (s, 1H), 3.60 (dd, $J_1 = 7.6$, $J_2 = 10.7$ Hz, 1H), 3.71 (dd, $J_1 = 4.0$ Hz, $J_2 = 10.7$ Hz, 1H), 5.10 (dd, $J_1 = 4.0$ Hz, $J_2 = 7.6$ Hz, 1H) 7.59 (dd, $J_1 = 5.8$ Hz, $J_2 = 7.8$ Hz, 1H), 8.04 (d, $J_1 = 7.9$ Hz, 1H), 8.62 (d, $J = 5.6$ Hz, 1H), 8.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.5, 60.5, 125.2, 136.9, 138.9, 145.7, 147.0; ^{11}B NMR ($CDCl_3$, 128 MHz) δ −12 ppm (quart, $J = 96$ Hz, N-BH_3); FT-IR (ATR): ν (cm^{-1}): 3462 (OH), 3009–2920, 2385 (BH_3), 1629, 1157.

4.2.5. (*S*)-3-(2-Oxiranyl)pyridine 4j[12b,28b]

To a solution of (*R*)-2-bromo-1-(pyridin-3-yl)ethanol *N*-borane complex **9** (709 mg, 3.28 mmol) in water (2 mL) and THF (2 mL) at 0 °C, was added dropwise 1 M HCl aqueous solution (12 mL). The mixture was stirred at room temperature for 2 h, diluted with THF (10 mL), and stirred for 10 min. To the cooled mixture at 0 °C was added a 2 M NaOH aqueous solution (20 mL) and the mixture was stirred at room temperature for 3 h. The aqueous phase was extracted with ethyl acetate (50 mL), washed with brine solution (20 mL), dried over Na_2SO_4, filtered, and concentrated to obtain an unstable brown oil (165 mg, 72%), 95% ee by HPLC analysis: CHIRAL PAK-AD column, Hexane/IPA (88/12 v/v); flow 1.0 ml/min: t_R (minor) = 8.82 min, (2.3%), t_R (major) = 10.57 min (97.7%). $[\alpha]_D^{20}$ = +17 (*c* 4.17, $CHCl_3$); Lit.[28b] $[\alpha]_D^{25}$ = +18.3 (*c* 0.91, $CHCl_3$), 96% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.87 (dd, J = 2.8, J_2 = 5.2 Hz, 1H), 3.23 (dd, J_1 = 4.0, J_2 = 5.2 Hz, 1H), 3.92 (d, J_1 = 4.0, J_2 = 5.2 Hz, 1H), 7.30 (m, 1H), 7.59, (m, 1H), 8.58 (dd, J_1 = 1.6 Hz, J_2 = 4.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 50.3, 51.0, 123.4, 132.7, 133.2, 147.8, 148.6.

4.2.6. (*S*)-1-(Adamantan-1-yl)-2-bromo ethanol 3k[12a]

Colorless oil: (2.50 g, 97%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00–1.78 (m, 12H), 2.03 (s, 3H), 2.32 (br s, 1H), 3.36–3.54 (m, 2H), 3.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.0, 37.1, 37.4, 38.2, 38.3, 79.5.

4.2.7. (*S*)-2-(Adamantan-1-yl)oxirane 4k[12a]

Clear oil (1.28 g, 72%): >99% ee determined by chiral HPLC analysis of the 2-phenoxy ethanol derivative (90:10 hexane/*i*-PrOH, 0.5 mL min, 254 nm): $[\alpha]_D^{20}$ = +16 (*c* 1.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56 (s, 6H), 1.70 (m, 6H), 2.02 (br s, 3H), 2.62 (m, 2H), 2.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.0, 32.2, 37.0, 38.4, 43.0, 60.5. MS (*m*/*z*, relative intensity): 178 $M^{\cdot+}$ (14%), 163 (6%), 148 (52%), 135 (70%), 119 (32%), 106 (68%), 91 (100%), 79 (60%).

4.3. General procedure for the synthesis of enantiopure azido alcohols 5a–i

To a stirred suspension of the enantiopure epoxides **4** (2 mmol) in distilled water (10 mL) was added sodium azide (4 mmol, 260 mg). The mixture was stirred for 3.5 h at 60 °C, then cooled at room temperature, and 20 mL of water was added. The aqueous phase was extracted with ethyl acetate (2 × 15 mL) and the combined organic phase was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The pure products were obtained by preparative TLC.

4.3.1. (*R*)-2-Azido-2-phenylethanol 5a[29]

Colorless oil (297 mg, 91%); 99% ee by HPLC analysis based on the Boc derivative **8a** on Chiralpak® AD-H, hexane/*i*-PrOH (90:10), 0.8 mL/min, 254 nm, t_R (*R*) = 12.14 min, t_R (*S*) = 11.32 min. $[\alpha]_D^{22}$ = −268 (*c* 0.7, $CHCl_3$); Lit.[29] $[\alpha]_D^{20}$ = −221.1 (*c* 1.35, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.98 (t, J = 6.8 Hz, 1H), 3.74 (m, 2H), 4.67 (t, J = 6.8 Hz, 1H), 7.32–7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 66.5, 67.9, 127.2, 128.8, 129.0, 136.3.

4.3.2. (*R*)-2-Azido-2-(4-chlorophenyl)ethanol 5b[30]

White solid (348 mg; 88%); mp 74–76 °C; 98% ee by HPLC analysis based on compound **8b** on Chiralpak® AD–H, hexane/*i*-PrOH (90:10), 0.5 mL/min, 254 nm, t_R (major) = 18.87 min, t_R (minor) = 13.67 min. $[\alpha]_D^{22}$ = −151 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.93 (br s, 1H), 3.72 (d, J = 5.2 Hz, 2H), 4.65 (dd, J_1 = 5.2, J_2 = 7.6 Hz, 1H), 7.27 (m, 2H), 7.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 66.4, 67.1, 128.5, 129.2, 134.7, 134.9.

4.3.3. (*R*)-2-Azido-2-(4-nitrophenyl)ethanol 5c[31a,b]

Yellow oil (208 mg, 50%); 73% ee by HPLC analysis on Chiralpak® AD–H column, hexane/*i*-PrOH (90/10), 1.0 mL/min, 254 nm, t_R (major) = 15.46 min, t_R (minor) = 21.95 min. $[\alpha]_D^{22}$ = −111 (*c* 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.05 (t, J = 6.0 Hz, 1H), 3.80 (m, 2H), 4.80 (dd, J_1 = 4.4, J_2 = 7.6 Hz, 1H), 7.55 (m, 2H), 8.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 66.4, 66.8, 124.1, 128.1, 143.7, 148.1.

4.3.4. (*S*)-2-Azido-1-(4-nitrophenyl)ethanol 6c[31c]

Yellow solid (104 mg, 25%): mp 37–39 °C, Lit.[31d] mp 51–53; 90% ee by HPLC analysis on Chiralpak® AD-H column, hexane/*i*-PrOH (90:10), 1.0 mL/min, 254 nm, t_R (major) = 15.69 min, t_R (minor) = 14.42 min. $[\alpha]_D^{22}$ = +76 (*c* 0.22, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.54 (d, J = 3.6 Hz, 1H), 3.52 (m, 2H), 5.00 (m, 1H), 7.58 (m, 2H), 8.24 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 57.9, 72.5, 123.9, 126.8, 147.5.

4.3.5. (*R*)-2-Azido-2-(4-bromophenyl)ethanol 5d[14b]

White solid (441 mg, 91%); mp 99–100 °C; Lit.[14b] mp 110–111 °C; 97% ee by HPLC analysis on Chiralpak® AD–H column, hexane/*i*-PrOH (95:5), 0.5 mL/min, 254 nm, t_R (major) = 23.62 min, t_R (minor) = 29.92 min. $[\alpha]_D^{22}$ = −373 (*c* 0.15, $CHCl_3$); Lit.[14b] $[\alpha]_D^{22}$ = +188 (*c* 3.6, $CHCl_3$), 99% ee by HPLC for the (*S*)-configuration. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.93 (dd, J_1 = 5.6 Hz, J_2 = 7.2 Hz, 1H), 3.73 (m, 2H), 4.64 (dd, J_1 = 5.2 Hz, J_2 = 7.2 Hz, 1H), 7.23 (m, 2H), 7.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 66.4, 67.2, 122.8, 128.8, 132.2, 135.4.

4.3.6. (*S*)-2-Azido-1-(4-bromophenyl)ethanol 6d[15f]

Yellow oil (28 mg, 6%); $[\alpha]_D^{22}$ = +58 (*c* 0.28, $CHCl_3$); Lit.[15g] $[\alpha]_D^{20}$ = +61.3 (*c* 0.67, CH_3OH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.51 (s, 1H), 3.43 (m, 2H), 4.83 (dd, J_1 = 5.2 Hz, J_2 = 6.8 Hz, 1H), 7.25 (m, 2H), 7.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 57.9, 72.7, 122.2, 127.6, 131.8, 139.5.

4.3.7. (*R*)-2-Azido-2-(3-bromophenyl)ethanol 5e[32]

Colorless solid (421 mg, 87%);>99% ee by HPLC analysis on Chiralpak® AD–H column, hexane/*i*-PrOH (95:5), 0.3 mL/min, 254 nm, t_R (major) = 37.87 min, t_R (minor) = 39.42 min.; $[\alpha]^{22}{}_D$ = −174 (*c* 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95 (t, J = 5.6 Hz), 3.73 (m, 2H), 4.64 (dd, J_1 = 4.8 Hz, J_2 = 8.0 Hz, 1H), 7.25 (m, 2H), 7.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 66.5, 67.1, 123.1, 125.8, 130.2, 130.5, 131.9, 138.7.

4.3.8. (*S*)-2-Azido-1-(3-bromophenyl)ethanol 6e[33]

Yellow oil (42 mg, 8%); $[\alpha]_D^{22}$ = +125 (*c* 0.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.63 (s, 1H), 3.43 (m, 2H), 4.81 (dd, J_1 = 5.2, J_2 = 6.8 Hz, 1H), 7.25 (m, 2H), 7.43 (m, 1H), 7.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 57.9, 72.7, 122.8, 124.5, 129.1, 130.3, 131.4, 142.8.

4.3.9. (*R*)-2-Azido-2-(*p*-tolyl)ethanol 5f[34]

White solid (312 mg, 88%); mp 42–43 °C; 95% ee by HPLC analysis on Chiralpak® AD–H column, hexane/*i*-PrOH (95:5), 0.8 mL/min, 254 nm, t_R (major) = 12.98 min, t_R (minor) = 16.68 min; $[\alpha]_D^{22}$ = −190 (*c* 0.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.91 (t, J = 6.4 Hz, 1H), 2.36 (s, 3H), 3.73 (t, J = 6.4 Hz, 2H), 4.64 (t, J = 6.4 Hz, 1H), 7.19–7.25 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 66.5, 67.7, 127.2, 129.7, 133.2, 138.7.

4.3.10. (*R*)-2-Azido-2-(3-methoxyphenyl)ethanol 5g[35]

Colorless oil (313 mg, 81%) yield; >99% ee by HPLC analysis on Chiralpak® AD-H column, hexane/*i*-PrOH (98.5:1.5), 0.8 mL/min, 254 nm, t_R (major) = 58.87 min, t_R (minor) = 62.13 min.; $[\alpha]_D^{22}$ = −200 (*c* 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95

(t, J = 6.4 Hz, 1H), 3.75 (m, 2H), 3.83 (s, 3H), 4.64 (m, 1H), 6.90 (m, 3H), 7.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 66.5, 67.8, 112.9, 114.1, 119.4, 130.1, 137.8, 160.0.

4.3.11. (*S*)-2-Azido-1-(3-methoxyphenyl)ethanol 6g[15f,31c]

Yellow oil (15 mg, 4%); $[\alpha]_D^{22}$ = +78 (c 0.15, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.52 (s, 1H), 3.43 (m, 2H), 3.81 (s, 3H), 4.83 (dd, J_1 = 4.0, J_2 = 8.0 Hz, 1H), 6.84 (m, 1H), 6.92–6.93 (m, 2H), 7.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 58.1, 73.4, 111.5, 113.8, 118.2, 129.8, 142.3, 159.9.

4.3.12. (*R*)-2-Azido-2-(4-fluorophenyl)ethanol 5h[34]

Colorless oil (333 mg, 92%); >99% ee by HPLC analysis: Chiralpak® AD–H column, hexane/*i*-PrOH (90:10), 0.5 mL/min, 254 nm, t_R (major) = 12.76 min, t_R (minor) = 14.08 min; $[\alpha]_D^{22}$ = −182 (c 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95 (t, J = 6.4 Hz, 1H), 3.73 (m, 2H), 4.66 (dd, J_1 = 5.6, J_2 = 6.8 Hz, 1H), 7.06–7.12 (m, 2H), 7.29–7.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 66.5, 67.1, 115.9, 116.1, 128.9, 129.0, 132.1, 132.2, 162.8 (d, $J_{C\text{-}F}$ = 250 Hz).

4.3.13. (*R*)-2-Azido-2-(4-methoxyphenyl)ethanol 5i[35]

White solid (892 mg, 48%); mp 105–107 °C, Lit.[35] mp 110–112 °C; 98% ee by HPLC analysis on a Chiralpak® AD-H column, hexane/*i*-PrOH/Et_2NH (95:5:0.05), 0.8 mL/min, 280 nm, t_R (minor) = 21.8 min, (0.98%), t_R (major) = 18.5 min (99.02%). $[\alpha]_D^{22}$ = −148.0 (c 2, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.08 (t, J = 6.4 Hz, 1H), 3.78 (m, 2H,), 3.87 (s, 3H), 4.66 (t, J = 6.4 Hz, 1H), 6.94 (d, 2H), 7.25 (d, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 66.4, 67.4, 114.4, 128.5, 132.04, 159.9.

4.3.14. (*R*)-2-Azido-2-(3-pyridyl)ethanol 5j

Light yellow oil (74 mg, 41%): 95% ee by HPLC analysis on a Chiralpak® AD–H, column; hexane/*i*-PrOH (88:12), 1.0 mL/min, t_R (minor) = 11.06 min, t_R (major) = 12.69 min. $[\alpha]_D^{20}$ = −194 (c 3.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (s, 1H) 3.86 (m, 2H), 4.76 (dd, J_1 = 5.2 Hz, J_2 = 7.2 Hz, 1H), 7.39 (ddd, J_1 = 0.6, J_2 = 4.8, J_3 = 7.8 Hz, 1H), 7.75 (dt, J_1 = 2.0, J_2 = 8.0 Hz, 1H), 8.65 (d, J = 1.6, J_2 = 5.2 Hz, 1H), 8.66 (d, J_1 = 1.6, J_2 = 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 65.1, 66.1, 123.9, 135.3, 148.2, 149.3; FT-IR (ATR): ν (cm^{-1}) 3192.8, 2091.2, 1596–1598, 1426.9, 1257.1, 1073.8. H RMS [M+H] calc. $C_7H_8N_4O$ 165.0771, [M+H], found 165.0766.

4.3.15. (*S*)-2-Azido-1-(pyridin-3-yl)ethanol 6j

Light yellow oil (30 mg, 17%), $[\alpha]_D^{20}$ = +132 (c 1.4, $CHCl_3$), 62% ee by HPLC on a Chiralcel OD-H column, hexanes/*i*-PrOH (90:10): 0.8 mL/min, t_R (minor) = 19.1 min (19.1%), t_R (major) = 23.2 min (80.9%). ^{1}H NMR (400 MHz, $CDCl_3$); δ 3.46–3.56 (m, 2H), 4.96 (dd, J_1 = 4.6, J_2 = 7.0 Hz, 1H), 7.36 (dd, J_1 = 5.4, J_2 = 7.8 Hz, 1H), 7.81 (dd, J_1 = 1.8, J_2 = 7.8 Hz, 1H), 8.54 (s, 1H), 8.58 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 57.8, 71.0, 123.7, 132.4, 136.8, 147.5, 149.1.

4.3.16. *rac*-2-Azido-2-(pyridin-3-yl)ethan-1-ol 6j

The racemic epoxide–N-BH_3-complex **9** (70 mg, 0.58 mmol. 1.0 equiv) was dissolved in water (20 ml). The mixture was heated at 65 °C for 1 h. Sodium azide (43 mg, 0.66 mmol, 4.0 equiv) was added portionwise. The mixture was heated at 60 °C under stirring and the reaction progress was monitored by TLC. After 4 h the reaction was completed and the mixture was transferred into a separatory funnel and the aqueous phase was extracted with ethyl acetate (3 × 15 mL). The organic phase was washed with brine (15 mL) dried over Na_2SO_4, filtered, and concentrated to obtain a brown oil (70 mg, 71% yield). The crude product was purified by preparative TLC (20 × 20 cm plates, 1500 microns silica gel) using hexane/ethyl acetate (1:4) and 0.4% of Et_3N as a light yellow oil (21 mg, 22%). HPLC analysis on Chiralcel OD-H column, hexanes/*i*-PrOH (90:10); 0.8 mL/min: t_R (minor) = 20.3 min (49.62%), t_R (major) = 23.9 min (50.4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.46–3.56 (m, 2H), 4.96 (dd, J_1 = 4.6, J_2 = 7.0 Hz, 1H), 7.36 (dd, J_1 = 5.4, J_2 = 7.8 Hz, 1H), 7.81 (dd, J_1 = 1.8, J_2 = 7.8 Hz, 1H), 8.54 (s, 1H), 8.58 (s, 1H).

4.3.17. (*S*)-2-(Adamantan-1-yl)-2-azidoethan-1-ol 6k

Colorless oil (1.15 g, 85%, based in 2.0 mmol of epoxide); 99.5% ee by HPLC analysis on Chiralpak® AD-H column, hexane/*i*-PrOH gradients (98:2 to 90:10), 0.5 mL/min, 220 nm, t_R (major) = 13.94 min, t_R (minor) = 12.54 min. $[\alpha]_D^{20}$ = −18 (c 1.1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.58–1.71 (m, 12H), 2.05 (s, 3H), 3.35 (m, 2H). 3.48 (d, J = 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.20, 36.06, 37.07, 38.05, 52.94, 78.68; MS (m/z): 192, 165 (100), 147, 135, 119, 105, 91, 79; FT-IR ATR: ν (cm^{-1}) 3388, 2899, 2093, 1070.

4.4. General procedure for the synthesis of the non-racemic 1,2-aminoalcohols

To a solution of 1,2-azido alcohol **5** (1 mmol) in THF (5 mL) was added triphenylphosphine (393 mg, 1.5 mmol) and water (360 mg, 20 mmol). The mixture was heated at 70 °C for 1–2 h until TLC analysis showed that the reaction was complete. Next, the mixture was concentrated under vacuum and purified by preparative TLC to afford the desired product.

4.4.1. (*R*)-2-Amino-2-phenylethanol 10a[37]

Pale yellow solid (126 mg, 92%), mp 75–77 °C; Lit.[37a] mp 76–79 °C; >99% ee by HPLC of carbamate **11a** on a Chiralpak® AD-H column, hexane/*i*-PrOH (90:10), 0.8 mL/min, 254 nm, t_R(major) = 12.14 min, t_R(minor) = 11.32 min. $[\alpha]_D^{22}$ = −62 (c 0.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 3H), 3.55 (dd, J = 8.4, 10.4 Hz, 1H), 3.73 (dd, J = 4.0, 10.8 Hz, 1H), 4.05 (dd, J = 4.4, 8.0 Hz, 1H), 7.27–7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 57.4, 67.9, 126.5, 127.6, 128.7, 142.6.

4.4.2. (*R*)-2-Amino-2-(4-chlorophenyl)ethanol 10b[38]

White solid (149 mg, 87%); mp 72–73 °C; 99% ee by HPLC of carbamate **11b** on a Chiralpak® AD-H column, hexane/*i*-PrOH (90:10), 0.5 mL/min, 254 nm, t_R (major) = 18.87 min, t_R (minor) = 13.62 min. $[\alpha]_D^{22}$ = −68 (c 0.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.27 (s, 3H), 3.52 (dd, J = 8.0, 10.8 Hz, 1H), 3.70 (dd, J = 4.4, 10.8 Hz, 1H), 4.04 (dd, J = 4.4, 8.0 Hz, 1H), 7.26–7.32 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.8, 67.9, 127.9, 128.8, 133.2, 141.0.

4.4.3. (*R*)-2-Amino-2-(4-bromophenyl)ethanol 10d[14b]

Pale yellow solid (194 mg, 90%); mp 70–73 °C; >99% ee by HPLC of carbamate **11d** on a Chiralpak® AD-H column, hexane/*i*-PrOH (90:10), 0.5 mL/min, 254 nm, t_R (major) = 23.18 min, t_R (minor) = 15.34 min. $[\alpha]_D^{22}$ = −62 (c 0.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.47 (s, 3H), 3.54 (dd, J = 8.0, 10.8 Hz, 1H), 3.73 (dd, J = 4.0, 10.8 Hz, 1H), 4.05 (dd, J = 4.4, 8.0 Hz, 1H), 7.21–7.24 (m, 2H), 7.46–7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.7, 67.6, 121.5, 128.3, 131.8, 141.1.

4.4.4. (*R*)-2-Amino-2-(3-bromophenyl)ethanol 10e[39]

Pale yellow oil (205 mg, 95%); 99% ee by HPLC of carbamate analysis **11e** on a Chiralpak® AD-H column, hexane/*i*-PrOH (90:10), 0.5 mL/min, 254 nm, t_R (major) = 23.72 min, t_R (minor) = 17.08 min.; $[\alpha]_D^{22}$ = −51 (c 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.09 (s, 3H), 3.54 (dd, J = 8.0, 10.8 Hz, 1H), 3.73 (dd, J = 4.0, 10.4 Hz, 1H), 4.04 (dd, J = 4.0, 7.6 Hz, 1H), 7.19–7.27 (m, 2H), 7.39–7.42 (m, 1H), 7.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.9, 67.8, 122.8, 125.3, 129.7, 130.2, 130.7.

4.4.5. (*R*)-2-Amino-2-(*p*-tolyl)ethanol 10f[40]

Pale yellow solid (126 mg, 83; mp. 68–71 °C;>99% ee by HPLC of carbamate **11f** on a Chiralpak® AD-H column, hexane/*i*-PrOH (90:10), 0.5 mL/min, 254 nm, t_R (major) = 19.75 min, t_R (minor) = 16.03 min. $[\alpha]_D^{22} = -50$ (*c* 0.09, $CHCl_3$); Lit.[40] $[\alpha]_D^{20} = +26$ (*c* 1.0, EtOH) for the (*S*)-configuration. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.99 (s, 3H), 2.34 (s, 3H), 3.54 (dd, *J* = 8.4, 10.8 Hz, 1H), 3.73 (dd, *J* = 4.0, 10.8 Hz, 1H), 4.01 (dd, *J* = 4.4, 8.0 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 57.0, 68.0, 126.3, 129.3, 137.2, 139.8.

4.4.6. (*R*)-2-Amino-2-(3-methoxyphenyl)ethanol 10g[41]

Colorless oil (149 mg, 89%); 99% ee by HPLC of carbamate **11g** on a Chiralpak® AD-H column, hexane/*i*-PrOH (90:10), 0.5 mL/min, 254 nm, t_R (major) = 31.13 min, t_R (minor) = 23.18 min; $[\alpha]_D^{22} = -39$ (*c* 0.09, $CHCl_3$); Lit.[41b] for the (*S*)-isomer $[\alpha]_D^{20} = +36$ (*c* 0.6, $CHCl_3$) for 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.65 (s, 3H), 3.54 (dd, *J* = 8.4, 10.8 Hz, 1H), 3.72 (m, 1H), 3.79 (s, 3H), 4.00 (m, 1H), 6.78–6.81 (m, 1H), 6.88–6.90 (m, 2H), 7.22–7.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.2, 57.4, 67.8, 112.4, 112.7, 118.8, 129.6, 159.8.

4.4.7. (*R*)-2-Amino-2-(4-methoxyphenyl)ethanol 10i[36]

White solid (0.172 g, 21%); mp 95–98 °C (dichoromethane), Lit.[36] 92–93 °C; 97% ee by HPLC analysis of the cyclic carbamate derivative **11i** on a Chiralpak® AD-H column, hexane/*i*-PrOH (90:10), 0.8 mL/min, 254 nm, t_R (major) = 17.8 min (98.3%), t_R (minor) = 15.3 min (1.7%). $[\alpha]_D^{20} = -16$ (*c* 2, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (br s, 3H), 3.56 (m, 1H), 3.72 (m, 1H), 3.83 (s, 3H), 4.03 (m, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 56.8, 68.0, 114.0, 127.6, 134.8, 150.0; MS (*m*/*z*): 136 (100%), 121 (12%), 109 (78%), 94 (48%), 77 (14%).

4.4.8. (*R*)-2-Amino-2-(4-fluorophenyl)ethanol 10h[42]

Pale yellow solid (144 mg, 93%); mp 87–89 °C; >99% ee by HPLC analysis of carbamate **11h** on a Chiralpak® AD-H column, hexane/*i*-PrOH (90:10), 0.5 mL/ min, 254 nm, t_R (major) = 19.32 min, t_R (minor) = 14.70 min.; $[\alpha]_D^{22} = -58$ (*c* 0.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.93 (s, 3H), 3.52 (dd, *J* = 8.4, 10.8 Hz, 1H), 3.72 (dd, *J* = 4.0, 10.4 Hz, 1H), 4.05 (dd, *J* = 4.4, 8.0 Hz, 1H), 7.01–7.06 (m, 2H), 7.28–7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.6, 68.1, 115.4, 115.6, 128.0, 128.1, 162.5 (d, J_{C-F} = 250 Hz).

4.4.9. (*R*)-2-Amino-2-(pyridin-3-yl)ethanol 10j

Yellow oil (21 mg, 51%); 95% ee by HPLC analysis of carbamate **11j** on a Chiralpak® AD-H column, hexane/IPA (88:12), flow 0.8 ml/min, t_R (minor) = 14.43 min 2.5%, t_R (major) = 16.45 min (97.4%). $[\alpha]_D^{20} = -40$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.07 (s, 3H), 3.80 (m, 1H), 3.65 (m, 1H), 4.17 (m, 1H), 7.32 (q, *J* = 4.0 Hz, 1H), 7.76 (dt, *J* = 2.0 Hz, *J* = 4.0 Hz, 1H), 8.60 (d, *J* = 2.0 Hz, 2H).

4.4.10. (*S*) 1-(Adamantan-1-yl)-2-aminoethanol 10k′

White solid (0.95 mg, 96%); mp 135–138 °C; 96% ee by HPLC analysis of acetamide **11k′**. $[\alpha]_D^{20} = +19$ (*c* 1.1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67 (m, 12H), 1.84 (br s, 3H), 2.02 (s, 3H), 2.59 (t, *J* = 12 Hz,), 2.94 (d, *J* = 10.8 Hz, 1H), 3.02 (dd, J_1 = 2.4 Hz, J_2 = 10 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.36, 35.83, 37.32, 38.25, 41.31, 79.91. MS (*m*/*z*): 165, 136, 135 (100), 119, 105, 91; FT-IR ATR: ν (cm^{-1}) 3380, 2900, 2847, 1070.

4.5. General procedure for the synthesis of carbamates using $(Boc)_2O$

To a solution of the 1,2-amino alcohols (0.5 mmol) in THF (3 mL) was added $(Boc)_2O$ (163.7 mg, 0.75 mmol) and Et_3N (126.5 mg, 1.25 mmol). The reaction was stirred at room temperature for about 1–2 h until the TLC analysis showed that the reaction was complete. The mixture was concentrated under vacuum and purified by preparative TLC to afford the desired products.

4.5.1. (*R*)-*tert*-Butyl (2-hydroxy-1-phenylethyl)carbamate 11a[25]

White solid, (110 mg, 93%); mp 133–135 °C; Lit.[25] mp. 138–140 °C; >99% ee by chiral HPLC analysis on Chiralpak® AD-H column, hexane/*i*-PrOH (90:10), 0.8 mL/min, 254 nm, t_R (major) = 12.14 min, t_R (minor) = 11.32 min.; $[\alpha]_D^{22} = -35$ (*c* 0.33, $CHCl_3$); Lit.[25] $[\alpha]_D^{24} = -39.2$ (*c* 3.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 9H,), 2.30 (s, 1H), 3.85 (m, 2H), 4.78 (m, 1H), 5.21 (d, *J* = 4.8 Hz, 1H), 7.27–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.3, 57.1, 66.9, 80.0, 126.6, 127.8, 128.9, 154.6.

4.5.2. (*R*)-*tert*-Butyl (1-(4-chlorophenyl)-2-hydroxyethyl)carbamate 11b

White solid (124 mg, 91%); mp 136–138 °C; >99% ee by HPLC analysis on a Chiralpak® AD-H column, hexane/*i*-PrOH (90:10), 0.5 mL/min, 254 nm, t_R (major) = 18.87 min, t_R (minor) = 13.62 min). $[\alpha]_D^{22} = -48$ (*c* 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.04 (s, 1H), 3.83 (m, 2H), 4.74 (m, 1H), 5.21 (m, 1H), 7.23–7.26 (m, 2H), 7.31–7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.3, 56.4, 66.5, 80.2, 127.9, 128.9, 133.6, 138.5, 156.1.

4.5.3. (*R*)-*tert*-Butyl (1-(4-bromophenyl)-2-hydroxyethyl)carbamate 11d[43]

White solid (152 mg, 96%); mp 153–155 °C; >99% ee by HPLC on a Chiralpak® AD-H column, hexane/*i*-PrOH (90:10), 0.5 mL/min, 254 nm, t_R (major) = 23.18 min, t_R (minor) = 15.34 min. $[\alpha]_D^{22} = -56$ (*c* 0.31, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.03 (s, 1H), 3.85 (m, 2H), 4.73 (m, 1H), 5.23 (m, 1H), 7.18–7.20 (m, 2H), 7.46–7.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.3, 53.9, 66.7, 80.1, 126.1, 128.3, 131.9, 137.8, 156.2.

4.5.4. (*R*)-*tert*-Butyl [1-(3-bromophenyl)-2-hydroxyethyl]carbamate 11e[44]

Pale yellow solid (150 mg, 95%); mp 91–93 °C; 99% ee by HPLC analysis on a Chiralpak® AD–H column, hexane/*i*-PrOH (90:10), 0.5 mL/min, 254 nm, t_R (major) = 23.72 min, t_R (minor) = 17.08 min).; $[\alpha]_D^{22} = -38$ (*c* 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 1.43 (s, 9H), 3.85 (m, 2H), 4.73 (m, 1H), 5.36 (m, 1H), 7.20–7.25 (m, 2H), 7.39–7.42 (m, 1H), 7.450 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.3, 56.2, 66.3, 80.2, 122.8, 125.3, 129.7, 130.3, 130.8, 155.9.

4.5.5. (*R*)-*tert*-Butyl [2-hydroxy-1-(p-tolyl)ethyl]carbamate 11f[43]

White solid (113 mg, 90%); mp 107 = –109 °C;>99% ee by chiral HPLC analysis on a Chiralpak® AD-H column, hexane/*i*-PrOH (90:10), 0.5 mL/min, 254 nm, t_R (major) = 19.75 min, t_R (minor) = 16.03 min). $[\alpha]_D^{22} = -77$ (*c* 0.12, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 1.43 (s, 9H), 2.34 (s, 3H), 3.83 (m, 2H), 4.75 (m, 1H), 5.15 (m, 1H), 7.18 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 28.4, 57.0, 69.7, 80.0, 126.5, 129.5, 136.4, 137.8, 156.5.

4.5.6. (*R*)-*tert*-Butyl [2-hydroxy-1-(3-methoxyphenyl)ethyl]carbamate 11g

White solid (123 mg, 92%); white solid, mp 76–78 °C; 99% ee by HPLC analysis on a Chiralpak® AD-H column, hexane/*i*-PrOH (90:10), 0.5 mL/min, 254 nm: t_R (major) = 31.13 min, t_R (minor) = 23.18 min. $[\alpha]_D^{22} = -43$ (*c* 0.23, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (s, 9H), 2.25 (s, 1H), 3.81–3.84 (m, 5H), 4.75 (m, 1H), 5.21 (m, 1H), 6.84–6.89 (m, 3H), 7.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.4, 55.3, 57.0, 67.0, 80.0, 112.5, 113.0, 118.8, 129.9, 160.0, 164.9.

4.5.7. (*R*)-*tert*-Butyl [1-(4-fluorophenyl)-2-hydroxyethyl]carbamate 11h[42]

Pale yellow solid (121 mg, 95%); mp 85–87 °C; >99% ee by HPLC analysis on a Chiralpak® AD-H column, hexane/*i*-PrOH (90:10), 0.5 mL/min, 254 nm: t_R (major) = 19.32 min, t_R (minor) = 14.70 min.; $[\alpha]_D^{22} = -54$ (*c* 0.13, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.09 (s, 1H), 3.85 (m, 2H), 4.75 (m, 1H), 5.24 (m, 1H), 7.01–7.03 (m, 2H), 7.25–7.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.4, 56.2, 66.7, 80.1, 115.6, 115.8, 128.2, 128.3, 155.9, 162.3 ($J_{C\text{-}F}$ = 240 Hz).

4.5.8. (*R*)-*tert*-Butyl-(2-hydroxy-1-(4-methoxyphenyl)ethyl)carbamate 11i

White solid (78 mg, 97%); mp 137–138 °C; >97% ee by HPLC analysis on Chiralpak® AD-H column, (0.46 cm I.D. × 25 cm): hexane/*i*-PrOH (90:10), Flow 0.80 mL/min: t_R (minor) = 15.33 min (1.68%); t_R (major) = 17.71 min (98.31%); $[\alpha]_D^{20} = -58$ (*c* 1.1, MeOH). ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (s, 9H), 3.00 (s, 1H), 3.82 (br s, 5H), 4.73 (br s, 1H), 5.38 (br s, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.4, 55.2, 56.3, 66.7, 79.9, 114.1, 127.7, 131.7, 156.2, 159.0. GC/MS: Retention time 17.43 min, (*m*/*z*): 236 (9%, M−OCH_3), 180 (100%), 163 (4%), 151 (6%), 136 (31%), 121 (10%), 109 (35%).

4.5.9. (*R*)-*tert*-Butyl-(2-hydroxy-1-(pyridin-3-yl)ethyl)carbamate 11j[45]

Yellow oil (40 mg, 84%); 95% ee by HPLC analysis on a Chiralpak® AD-H column, hexane/*i*-PrOH (88:12), flow 0.8 ml/min: t_R (minor) = 14.43 min (2.5%); t_R (major) = 16.45 min (97.4%). ^1H NMR ($CDCl_3$, 400 MHz): δ 1.28 (s, 9H), 3.75 (s, 1H), 3.90 (s, 1H), 4.78 (s, 1H), 5.79 (s, 1H), 7.26 (m, 1H), 7.67 (d, *J* = 6.0 Hz, 1H), 8.38 (d, *J* = 8.0 Hz, 1H), 8.49 (d, *J* = 3.2 Hz, 1H).

4.5.10. Synthesis of *N*-((*S*)-2-(adamantyl-1-yl)-2-hydroxyethyl) acetamide 11k′

In a 5 mL round-bottomed flask, the amino alcohol (0.067 g, 0.345 mmol) was dissolved in dry freshly distilled THF (6.0 mL), after which triethylamine (0.06 mL, 0.410 mmol) was added. Next, acetyl chloride (0.03 mL) was added. The mixture was stirred for one hour at room temperature and then heated at reflux for 3 h. A white solid precipitated during cooling of the system. The crude mixture was acidified with 1 M HCl and extracted with $CHCl_3$ (10 mL). The organic phase was first washed with a saturated solution of Na_2CO_3 (3 × 5 mL), then with H_2O (3 × 5 mL) and dried over $MgSO_4$, filtered, and rotoevaporated to obtain a crude product (80 mg, 98%). A sample (54 mg) was purified by column chromatography (9 cm long/1 cm diameter) on silica gel (4 g) using a gradient flow of ethyl acetate/hexane (initial 20/80 to pure ethyl acetate) obtaining a white solid (49 mg, 60%); mp 150–152 °C, 96% ee by GC analysis on a CP-Chirasil-Dex CB column, temp.$_1$: 70 °C (10 min); ramp.$_1$: 4 °C/min; temp.$_2$: 120° (5 min); ramp.$_2$: 11 °C/min, temp. 3: 180 °C (20 min): t_R (minor) = 33.40 min (2.24%); t_R(major) = 37.17 (97.76%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.65 (m, 13H), 2.05 (s, 6H), 2.27 (s, 1H), 3.11 (m, 2H, *J* = 9.9 Hz), 3.67 (m, 1H), 5.96 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.3, 28.2, 36.2, 37.1, 37.9, 40.7, 79.5, 171.0; FT-IR (cm^{-1}): 3402, 3204, 2903, 1727, 1636. GC/MS (*m*/*z*): 238 $M^{\cdot+}$ (2), 220 (6), 178 (26), 135 (100), 107 (48), 91 (56), 79 (58).

Crystal data

Full crystallographic data for compound **11k′** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1413103. These data can obtained free of charge on application to CCDC, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223)336033; or e-mail: deposit@ccdc.cam.ac.uk.

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Supplementary data

Supplementary data (^1H and ^{13}C NMR spectra; HPLC and GC analysis of chiral compounds; X-ray data for compound **11K′**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2015.12.002.

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