Exploring asymmetric catalytic transformations

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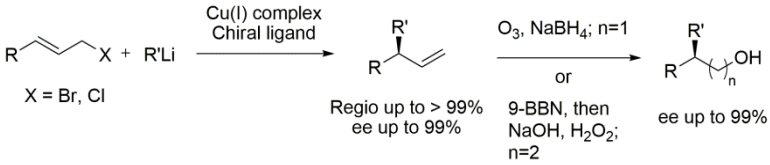
Chapter 2
Synthesis of Optically Active *β*- or *γ*-Alkyl Substituted Alcohols through Copper-Catalyzed Asymmetric Allylic Alkylation with Organolithium Reagents



An efficient one-pot synthesis of optically active *β*-alkyl-substituted alcohols through a tandem copper-catalyzed asymmetric allylic alkylation (AAA) with organolithium reagents and reductive ozonolysis is presented. Furthermore, hydroboration-oxidation following the Cu-catalyzed AAA leads to the corresponding homochiral *γ*-alkyl substituted alcohols.

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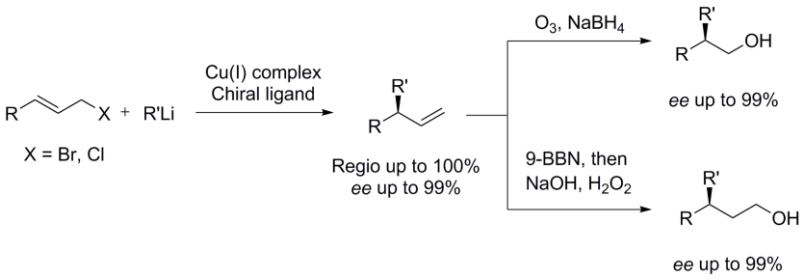
2.1 Introduction

Chiral nonracemic alcohols (and derivatives) are very important building blocks in the synthesis of numerous biologically active compounds. In particular, optically active primary alcohols bearing alkyl substitution at *β*- or *γ*-positions are key intermediates in the total synthesis of several natural products including arundic acid,[1] Lyrica,[2] bongkrekic acids,[3] gynnastatin A[4] and vitamins E and K.[5] There are a number of methods available for the synthesis of this type of alcohols based on chiral auxiliaries[6] and enzyme-catalyzed kinetic resolution of racemic compounds.[7] In 1995, Negishi reported a Zr-catalyzed asymmetric carboalumination of alkenes followed by a lipase catalyzed resolution method to access these building blocks in good yields with excellent enantiomeric excess.[8] The development of alternative catalytic enantioselective protocols remains an important challenge in view of the potential of these highly versatile building blocks.

Cu-catalyzed AAA is among the most powerful enantioselective C-C bond-forming reactions.[9] In sharp contrast with the well-known Pd-catalyzed asymmetric allylic alkylation reaction,[10] which is characterized by the use of soft and stabilized nucleophiles, Cu-catalyzed asymmetric allylic alkylation is characterized by the formation of C–C bonds with organometallic reagents, resulting in a complementary method. The reaction usually proceeds with high S_N2' selectivity and provides access to a carbon stereocenter next to a terminal olefin which can readily be further functionalized. Pioneered by Bäckvall and van Koten,[11] Cu-catalyzed AAA has been widely studied and its synthetic utility has been shown in the total synthesis of several natural products and biologically active compounds.[12] Recently, our group reported for the first time the use of highly reactive organolithium reagents in copper–catalyzed asymmetric allylic alkylation of allyl bromides with excellent regio- and enantioselectivity using Taniaphos as a chiral ligand.[13] We also implemented this methodology for both allyl bromides and chlorides in the enantioselective synthesis of tertiary and quaternary stereocenters using phosphoramidite ligands.[14]

Herein we present a highly enantioselective one pot synthesis of β-alkyl-substituted alcohols through Cu-catalyzed AAA of allyl bromides with various organolithium reagents followed by a reductive ozonolysis reaction. The direct use of organolithium reagents is also extended to the synthesis of γ-alkyl-substituted alcohols through Cu-catalyzed AAA of allyl bromides with RLi reagents followed by hydroboration-oxidation reactions (Scheme 1).[15]

Scheme1: Synthesis of optically active alcohols through copper-catalyzed asymmetric allylic alkylation with organolithium reagents

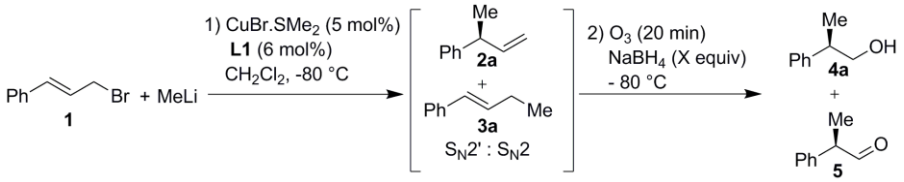


2.2 Results and Discussion

Our strategy is based on a tandem Cu-catalyzed AAA/reductive ozonolysis to achieve highly enantioenriched β-alkyl-substituted alkyl alcohols in a chemo-, regio- and enantioselective one-pot operation with no racemization. Using the well-established conditions for the Cu-catalyzed AAA with organolithium reagents,[13,14] we optimized the conditions for the synthesis of highly enantioenriched β-alkyl-substituted alcohols in a one-pot protocol (Table 1). We started our study with commercially available cinnamyl bromide **1a**. After Cu-catalyzed AAA of **1a**,[13] the reaction mixture was quenched with EtOH and purged with ozone for 20 min followed by purging with nitrogen. When 2.5 equiv of $NaBH_4$ were added to reduce the ozonide, a mixture of desired alcohol **4a** and aldehyde **5** was obtained in a 70:30 ratio (Table 1, entry 1). Doubling the amount of $NaBH_4$ did not lead to full conversion towards the desired alcohol either (Table 1, entry 2), probably due to the formation of the

corresponding acetal in the reaction mixture which was hydrolyzed during the workup giving rise to aldehyde **5**. In order to achieve full conversion to alcohol **4a**, 10 equiv of $NaBH_4$ and 10 equiv of water were used to hydrolyze the acetal in situ (Table 1, entry 3). Under these conditions, no aldehyde **5** was observed, and the desired alcohol **4a** was obtained in good overall yield with very high enantioselectivity (see Table 2, entry 1).[16]

Table 1: Optimization conditions for the one-pot Cu-catalyzed asymmetric allylic alkylation followed by reductive ozonolysis



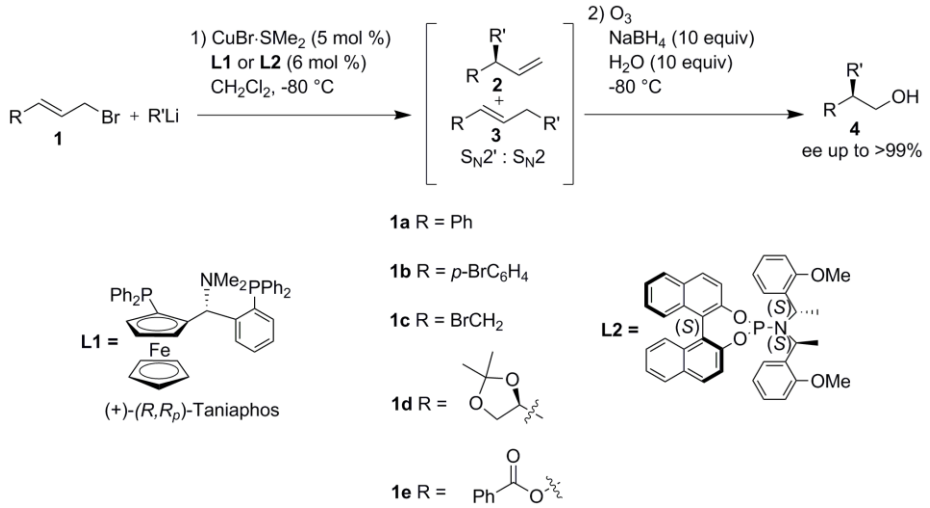
entry	$NaBH_4$ (x equiv)	4a : 5 (%)[a]
1	2.5	70:30
2	5	90:10
3[b]	10	>99:1

(a) The ratio was determined by ^{1}H-NMR and GC–MS. (b) 10 equiv of water added to the reaction mixture. **L1** = (+)-(R,R_p)-Taniaphos (see Table 2).

Having optimized conditions for the one-pot protocol for the synthesis of *β*-alkyl-substituted alcohols, the scope of the reaction was examined. We employed this tandem consecutive Cu-catalyzed **AAA**/reductive ozonolysis protocol with organolithium reagents such as MeLi, *n*-BuLi and *n*-HexLi on cinnamyl bromide **1a**, achieving excellent enantioselectivities (98−99%) and good overall yields (60–85%) (Table 2, entries 1−3). More hindered reagents, such as *i*-BuLi, could also be used in this tandem application leading to the desired alcohol **4d** in 70% overall yield with high ee of 84% (Table 2, entry 4). It is important to note that phosphoramidite ligand **L2**[17] had to be used in this case. To show the functional group tolerance of this protocol, we performed the reaction with *p*-bromo-substituted substrate **1b** using different

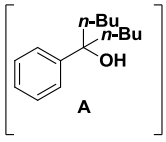
organolithium reagents. The tandem reaction provides the desired *β*-alkyl-substituted alcohols with excellent enantioselectivities 97–99% and high overall yields 75–90% without any traces of side products (i.e., halogen-lithium exchange) (Table 2, entries 5−7). The allyl bromide **1c** bearing an aliphatic bromide ($BrCH_2$ substituent) was converted with *n*-HexLi affording alcohol **4h** in 60% yield and again with excellent enantioselectivity (97% ee) (Table 2, entry 8). A decrease in the enantioselectivity was observed when **1c** was treated with MeLi as an alkylating source (Table 2, entry 9). The allyl bromide **1d** bearing an acetal protected chiral 1,2-diol functionality upon the tandem application with MeLi and *n*-HexLi provided excellent diastereoselectivity (*anti/syn* ratios of >99:1) (Table 2, entries 10 and 11). An ester functionality is also tolerated, and the one-pot Cu-catalyzed AAA/reductive ozonolysis of **1e** led to an exclusive S_N2' substitution that provided the desired alcohol **4l** in 73% yield with 97% ee (Table 2, entry 12).

Table 2: One-pot synthesis of *β*–alkyl-substituted alcohols through Cu-catalyzed asymmetric allylic alkylation of allyl bromides with organolithium reagents followed by reductive ozonolysis



entry[a]	1	R'	L	2:3 (%)[b]	4, yield (%)[c]	4, ee (%)[d]
1	**1a**	Me	**L1**	90:10	85	**4a**, 98
2	**1a**	*n*-Bu	**L1**	90:10	60	**4b**, 99
3	**1a**	*n*-Hex	**L1**	88:12	70	**4c**, 99
4	**1a**	*i*-Bu	**L2**	88:12	70	**4d**, 84
5	**1b**	Me	**L1**	90:10	84	**4e**, 99
6	**1b**	*n*-Bu	**L1**	85:15	75	**4f**, 97
7	**1b**	*n*-Hex	**L1**	87:13	90	**4g**, 99
8	**1c**	*n*-Hex	**L1**	100:0	60	**4h**, 97
9	**1c**	Me	**L1**	100:0	30[e]	**4i**, 72
10	**1d**	*n*-Hex	**L1**	90:10	65	**4j**, >99:1 (dr)[f]
11	**1d**	Me	**L1**	80:20	50	**4k**, >99:1 (dr)[f]
12[g]	**1e**	*n*-Bu	**L1**	100:0	73	**4l**, 97

(a) Reactions were run on a 0.2−0.5 mmol scale using 1.2 equiv of R'Li diluted with *n*-hexane (1.5 equiv diluted with toluene in the case of MeLi) which was added over 2 h using a syringe pump to a 0.1 M solution of substrate in CH_2Cl_2. (b) Ratio of S_N2':S_N2 products was determined by GC−MS and ^{1}H-NMR analysis of a sample taken before ozonolysis. (c) The corresponding alcohol obtained from the S_N2 product could be separated by column chromatography unless otherwise noted (see experimental section). (d) Determined by chiral HPLC. (e) The low yield is due to volatility issues. (f) Dr determined by ^{1}H-NMR. (g) 10% of double 1,2–addition product **A** was isolated in this case.



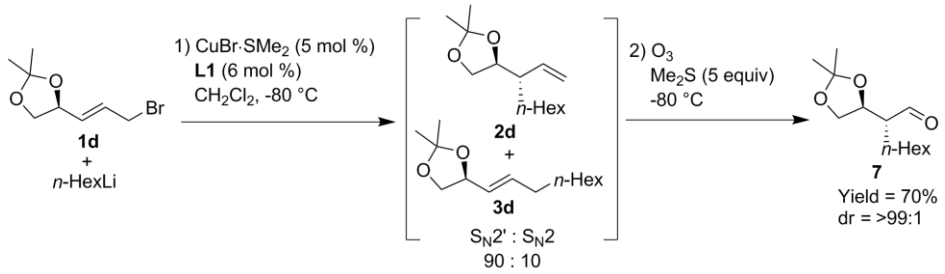
A

As the results summarized in Table 2 show, a highly versatile one-pot catalytic protocol to access a range of homochiral *β*-substituted alcohols is now available using common organolithium reagents and allyl bromides. This one-pot protocol, based on readily available compounds, avoids the isolation of the branched alkenes, which can be volatile (especially methyl-substituted compounds), thus affording better overall yields than the corresponding two steps version.

It is important to note that when the Cu-catalyzed AAA followed by ozonolysis was performed of **1d** with subsequent Me_2S treatment we

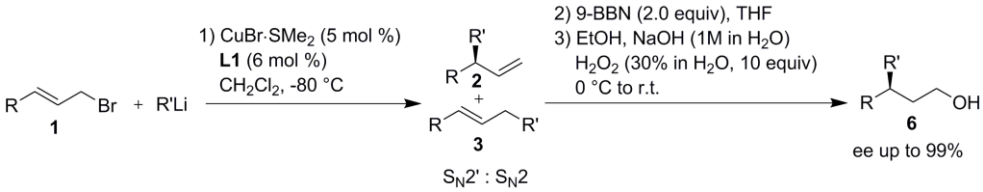
were able to isolate the corresponding α-alkyl-substituted aldehyde in good yield 70% with very high diastereomeric ratio (*anti*/*syn* = >99:1) without affecting the integrity of the stereogenic center (Scheme 2).

Scheme 2: One-pot synthesis of α–alkyl-substituted aldehyde through Cu−catalyzed asymmetric allylic alkylation of allyl bromides with organolithium reagents followed by ozonolysis



We also explored a similar strategy for the synthesis of highly enantioenriched γ−alkylated alcohols via Cu-catalyzed AAA followed by a hydroboration/oxidation reaction. First, we performed the Cu-catalyzed AAA on cinnamyl bromide **1a** using *n*-BuLi and *n*-HexLi. The corresponding olefins were formed in good yields of 88% and 86%, respectively, with excellent enantioselectivity. The hydroboration/oxidation reaction of these olefins using commercially available 9-BBN led to the corresponding γ-alkylated alcohols **6a** and **6b** in good yields (67% and 74%) without erosion of the enantiomeric excess (Table 3, entries 1 and 2). Olefins bearing a *p*-bromo substituent, obtained via Cu-catalyzed AAA from **1b**, were converted in a hydroboration/oxidation sequence to the corresponding alcohols **6c** and **6d** in 70% and 90% yield, respectively, being enantiomerically pure (99% ee) (Table 3, entries 3 and 4). Allyl bromide **1f**, bearing a benzyl ether functionality, was also be subjected to the Cu-catalyzed AAA/ hydroboration/oxidation sequence providing the corresponding alcohols **6e** and **6f** in good yields (75% and 93%) albeit with slightly lower enantioselectivities (81% and 88% ee, respectively) (Table 3, entries 5 and 6).

Table 3: Synthesis of *γ*-alkyl substituted alcohols through Cu-catalyzed asymmetric allylic alkylation of allyl bromides with organolithium reagents followed by a hydroboration/oxidation



1a R = Ph **1b** R = *p*-BrC$_6$H$_4$ **1f** R = BnOCH$_2$

entry[a]	**1**	**R′**	**L**	**2:3 (%)**[b]	**(2+3), yield (%)**	**6, yield (%)**[c]	**6, ee (%)**[d]
1	**1a**	*n*-Bu	**L1**	90:10	88	67	**6a**, 99
2	**1a**	*n*-Hex	**L1**	90:10	86	74	**6b**, 99
3	**1b**	Me	**L1**	90:10	90	70	**6c**, 99
4	**1b**	*n*-Hex	**L1**	87:13	93	90	**6d**, 99
5	**1f**	Me	**L1**	85:15	81	75	**6e**, 81
6	**1f**	*n*-Bu	**L1**	85:15	85	93	**6f**, 88

(a) Reactions were run on a 0.2 mmol scale using 1.2 equiv of R'Li diluted with *n*-hexane (1.5 equiv diluted with toluene in the case of MeLi) which was added over 2 h using a syringe pump to a 0.1 M solution of substrate in CH_2Cl_2. (b) Ratio of S_N2':S_N2 products was determined by GC–MS and crude ^{1}H-NMR. (c) Calculated based on **2**. (d) Determined by chiral HPLC.

As illustrated in Scheme 3, a *β*-alkyl-substituted aldehyde can also be readily synthesized. For instance, the oxidation of the corresponding primary alcohol **6e** with Dess-Martin periodinane (DMP) provided aldehyde **8**, an important intermediate in the total synthesis of danshenspiroketallactone.[18]

Scheme 3: Oxidation of primary alcohols to aldehydes with Dess–Martin periodinane

2.3 Conclusions

In summary, we have developed a highly enantioselective synthesis of *β*-alkyl-substituted alcohols through a one-pot Cu- catalyzed asymmetric allylic alkylation with organolithium reagents followed by reductive ozonolysis. The synthesis of *γ*-alkyl-substituted alcohols was also achieve through Cu-catalyzed asymmetric allylic alkylation with organolithium reagents followed by a hydroboration oxidation. These protocols do not compromise the stereochemical integrity and provide readily access to highly valuable chiral building blocks.

2.4 Experimental section

2.4.1 General Procedures

Flash column chromatography was performed on silica gel (230-400 mesh). Thin-layer chromatography was performed on silica plates. Compounds were visualized by UV and cerium/molybdenum or potassium permanganate staining. Progress and conversion of the reaction were determined by GC-MS and ^{1}H-NMR. Mass spectra were recorded on a mass spectrometer using orbitrap analyzer. ^{1}H- and ^{13}C-NMR were recorded on 400 MHz and 100.59 MHz using $CDCl_3$ as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 for ^{1}H, δ 77.0 for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling

constants (Hz), and integration. Optical rotations were measured on a polarimeter with a 10 cm cell (*c* given in g/100 mL). Enantiomeric excesses were determined by chiral HPLC analysis using a diode array detector.

All reactions were carried out under a nitrogen atmosphere using oven-dried glassware and using standard Schlenk techniques. All the reagents, starting materials, and ligand **L1** were purchased from commercial sources and used without further purification. Dichloromethane and toluene were used from the solvent purification system. *n*-Hexane was dried and distilled over sodium. Allylbromides **1b**,[19] **1d**,[20] **1e**[21] and **1f**[22] were prepared following literature procedures**.** Phosphoramidite ligand **L2** was prepared as reported in the literature.[23]

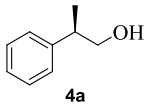
Racemic products were synthesized by reaction of the allyl bromides **1** and the corresponding organolithium reagent at -78 °C in CH_2Cl_2 in the presence of CuI (10 mol %) and PPh_3 (20 mol %).

2.4.2 General procedure for the one-pot synthesis of *β*–alkyl-substituted alcohols through Cu-catalyzed asymmetric allylic alkylation of allyl bromides with organolithium reagents followed by reductive ozonolysis

A Schlenk tube equipped with septum and stirring bar was charged with CuBr•SMe_2 (0.01 mmol, 2.06 mg, 5 mol %) and the appropriate ligand (0.012 mmol, 6 mol %). Dry dichloromethane (2 mL) was added, and the solution was stirred under nitrogen at room temperature for 15 min. Then, allyl bromide **1** (0.2 mmol) was added, and the resulting solution was cooled to −80 °C. In a separate Schlenk tube, the corresponding organolithium reagent (0.24 mmol, 1.2 equiv) was diluted with *n*-hexane (toluene in the case of MeLi, combined volume of 1 mL) under nitrogen and added dropwise to the reaction mixture over 2 h using a syringe pump. Once the addition was complete, the mixture was stirred for another 2 h at −80 °C. The reaction was quenched with EtOH (2 mL), and then ozone was bubbled through the solution for 20 min. After being

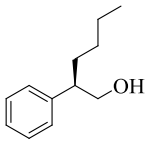
stirred for 20 min (solution stays blue), the reaction mixture was purged with nitrogen to remove excess ozone (disappearance of blue colour). Sodium borohydride (75.7 mg, 2 mmol, 10 equiv) was added, followed after 10 min by the addition of H_2O (10 equiv). Subsequently, the reaction mixture was warmed to room temperature and stirred overnight. The mixture was quenched by addition of extra water (5 mL). The layers were separated, and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic layers were dried with sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using different mixtures of *n*-pentane/Et_2O as eluent.

Note: The S_N2':S_N2 ratio was determined by GC-MS and ^{1}H-NMR analysis on a sample obtained after quenching with EtOH, which was passed through a short plug of silica gel to remove transition metal residues.



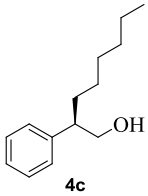
4a

(*R*)-2-Phenylpropan-1-ol (4a): Purification by flash column chromatography (SiO_2, 10 − 30% Et_2O/pentane, gradient) afforded an inseparable mixture of **4a** and benzyl alcohol in the ratio of 90:10 (51 mg, yield = 85%) as a colourless oil. 98% *ee*, $[\alpha]_D^{20}$ = +5.0 (c = 1 in $CHCl_3$); [lit.[24] (97% *ee*): $[\alpha]_D^{23}$ = +16.2 (c = 1 in $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.18 (m, 5H), 4.68 (s, 2H), 3.69 (d, J = 6.8 Hz, 2H), 2.9 – 3.0 (m, 1H), 1.63 (s, 1H), 1.28 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 140.9, 128.6, 128.5, 127.6, 127.5, 127.0, 126.7, 68.7, 65.3, 42.4, 17.6; HRMS (APCI+, *m/z*): calculated for C_9H_{11} $[M\text{-}H_2O]^+$: 119.08553, found: 119.08549. Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OB-H column, *n*-heptane/*i*-PrOH 90:10, 40 °C, 217 nm, retention times (min): 10.40 (major) and 11.11 (minor).



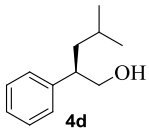
4b

(*R*)-2-Phenylhexan-1-ol (4b): Purification by flash column chromatography (SiO_2, 5 − 20% Et_2O/pentane, gradient) afforded **4b** (25 mg, yield = 60%) as a colourless oil. 99% *ee*, $[\alpha]_D^{20}$ = −11.0 (c = 1 in $CHCl_3$); [lit.[25] $[\alpha]_D^{20}$ = −18.0 (c = 3.73 in CH_2Cl_2)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.18 (m, 5H), 3.79 − 3.68 (m, 2H), 2.82 − 2.72 (m, 1H), 1.75 – 1.65 (m, 1H), 1.62 – 1.51 (m, 1H), 1.49 – 1.11 (m, 4H), 0.84 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 128.6, 128.1, 126.7, 67.6, 48.7, 31.8, 29.5, 22.7, 14.0; HRMS (APCI+, *m/z*): calculated for $C_{12}H_{17}$ $[M\text{-}H_2O]^+$: 161.13248, found: 161.13245. Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OJ-H column, *n*-heptane/*i*-PrOH 95:5, 40 °C, 220 nm, retention times (min): 13.51 (major) and 14.17 (minor).



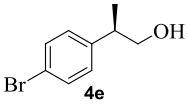
4c

(*R*)-2-Phenyloctan-1-ol (4c) Purification by flash column chromatography (SiO_2, 5 − 20% Et_2O/pentane, gradient) afforded **4c** (33 mg, yield = 70%) as a colourless oil. 99% *ee*, $[\alpha]_D^{20}$ = −14.2 (c = 1 in $CHCl_3$); [lit.[26] (***S***)-enantiomer (92% *ee*): $[\alpha]_D^{21}$ = +15.1 (c = 0.99 in $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.18 (m, 5H), 3.81 − 3.66 (m, 2H), 2.82 − 2.72 (m, 1H), 1.77 – 1.63 (m, 1H), 1.62 – 1.50 (m, 1H), 1.34 – 1.11 (m, 8H), 0.85 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 128.6, 128.0, 126.6, 67.6, 48.7, 32.0, 31.7, 29.3, 27.3, 22.6, 14.0; HRMS (APCI+, *m/z*): calculated for $C_{14}H_{21}$ $[M\text{-}H_2O]^+$: 189.16378, found: 189.16372. Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OJ-H column, *n*-heptane/*i*-PrOH 95:5, 40 °C, 220 nm, retention times (min): 10.63 (major) and 11.33 (minor).



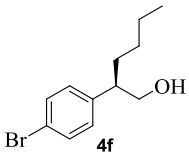
4d

(*R*)-4-Methyl-2-phenylpentan-1-ol (4d) Purification by flash column chromatography (SiO_2, 5 − 20% Et_2O/pentane, gradient) afforded **4d** (30 mg, yield = 70%) as a colourless oil. 84% *ee*, $[\alpha]_D^{20}$ = −10.2 (c = 1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.19 (m, 5H), 3.76 − 3.64 (m, 2H), 2.95 − 2.84 (m, 1H), 1.64 – 1.51 (m, 1H), 1.49 – 1.36 (m, 3H), 0.86 (t, *J* = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 128.6, 128.1, 126.7, 68.0, 46.4, 41.1, 25.2, 23.5, 21.8; HRMS (APCI+, *m/z*): calculated for $C_{12}H_{17}$ $[M\text{-}H_2O]^+$: 161.13248, found: 161.13238. Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel AD-H column, *n*-heptane/*i*-PrOH 95:5, 40 °C, 212 nm, retention times (min): 12.26 (major) and 13.04 (minor).



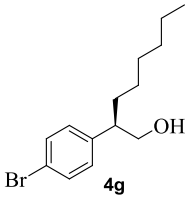
4e

(*R*)-2-(4-Bromophenyl)propan-1-ol (4e) Purification by flash column chromatography (SiO_2, 10 − 20% Et_2O/pentane, gradient) afforded an inseparable mixture of **4e** and *p*-bromo benzyl alcohol in the ratio of 90:10 (27 mg, yield = 84%) as a colourless oil. 99% *ee*, $[\alpha]_D^{20}$ = +8.6 (c = 1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 4.64 (s, 2H), 3.72 – 3.62 (m, 2H), 2.96 – 2.86 (m, 1H), 1.25 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 139.8, 131.6, 131.6, 129.2, 128.6, 121.4, 120.4, 68.4, 64.5, 41.9, 17.5; HRMS (APCI+, *m/z*): calculated for $C_9H_{10}Br$ $[M\text{-}H_2O]^+$: 196.99604, found: 196.99617. Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OB-H column, *n*-heptane/*i*-PrOH 95:5, 40 °C, 224 nm, retention times (min): 14.37 (minor) and 14.9 (major).



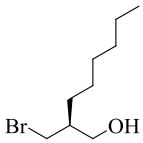
4f

(*R*)-2-(4-Bromophenyl)hexan-1-ol (4f) Purification by flash column chromatography (SiO_2, 10 − 20% Et_2O/pentane, gradient) afforded **4f** (34 mg, yield = 75%) as a colourless oil. 97% *ee*, $[\alpha]_D^{20}$ = −13.8 (c = 1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 3.77 – 3.64 (m, 2H), 2.78 – 2.68 (m, 1H), 1.80 – 1.60 (m, 1H), 1.58 – 1.45 (m, 1H), 1.38 – 1.04 (m, 2H), 0.84 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 131.7, 129.8, 120.4, 67.4, 48.2, 31.6, 29.4, 22.7, 13.9; HRMS (APCI+, *m/z*): calculated for $C_{12}H_{16}Br$ $[M\text{-}H_2O]^+$: 239.04299, found: 239.04261. Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel AD-H column, *n*-heptane/*i*-PrOH 95:5, 40 °C, 230 nm, retention times (min): 15.04 (major) and 16.01 (minor).



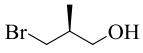
4g

(*R*)-2-(4-Bromophenyl)octan-1-ol (4g) Purification by flash column chromatography (SiO_2, 10 − 20% Et_2O/pentane, gradient) afforded **4g** (38 mg, yield = 90%) as a colourless oil. 99% *ee*, $[\alpha]_D^{20}$ = −13.2 (c = 1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 3.77 – 3.60 (m, 2H), 2.78 – 2.68 (m, 1H), 1.74 – 1.61 (m, 1H), 1.60 – 1.47 (m, 1H), 1.38 – 1.07 (m, 8H), 0.85 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 131.7, 129.8, 120.4, 67.4, 48.2, 31.9, 31.7, 29.3, 27.2, 22.6, 14.0; HRMS (APCI+, *m/z*): calculated for $C_{14}H_{20}Br$ $[M\text{-}H_2O]^+$: 267.07429 found: 267.07391. Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel AD-H column, *n*-heptane/*i*-PrOH 95:5, 40 °C, 226 nm, retention times (min): 14.20 (major) and 14.90 (minor).



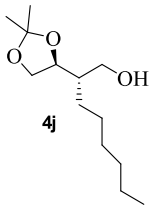
4h

(*S*)-2-(Bromomethyl)octan-1-ol (4h) Purification by flash column chromatography (SiO_2, 10 − 30% Et_2O/pentane, gradient) afforded **4h** (15 mg, yield = 60%) as a colourless oil. 97% *ee*, $[\alpha]_D^{20}$ = −9.4 (c = 1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.50 (dd, J = 10.5, 5.8 Hz, 2H), 3.41 (dd, J = 10.5, 6.5 Hz, 2H), 1.68 – 1.53 (m, 1H), 1.39 – 1.34 (m, 1H), 1.33 – 1.19 (m, 8H), 1.16 – 1.02 (m, 1H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.4, 35.7, 33.1, 31.8, 29.6, 26.9, 22.7, 16.7, 14.1; HRMS (ESI+, *m/z*): calculated for $C_9H_{20}BrO$ $[M+H]^+$: 223.09752 found: 223.09707. The enantiomeric excess was determined for the benzoate ester of the alcohol. Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OD-H column, *n*-heptane/*i*-PrOH 98:2, 40 °C, 232 nm, retention times (min): 8.43 (minor) and 9.06 (major).



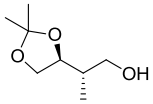
4i

(*S*)-3-Bromo-2-methylpropan-1-ol (4i) Purification by flash column chromatography (SiO_2, 10 − 30% Et_2O/pentane, gradient) afforded **4i** (22.5 mg, yield = 30%) as a colourless oil. 72% *ee*, $[\alpha]_D^{20}$ = +1.6 (c = 1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.67 – 3.56 (m, 2H), 3.54 – 3.45 (m, 2H), 2.08 – 1.97 (m, 1H), 1.43 (s, 1H), 1.03 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.4, 37.6, 37.3, 15.5. The enantiomeric excess was determined for the benzoate ester of the alcohol. Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OB-H column, *n*-heptane/*i*-PrOH 100:0, 40 °C, 226 nm, retention times (min): 27.92 (major) and 31.4 (minor).



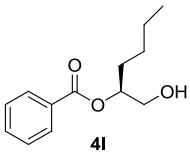
4j

(*S*)-2-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)octan-1-ol (4j) Purification by flash column chromatography (SiO_2, 10 − 40% Et_2O/pentane, gradient) afforded **4j** (25 mg, yield = 65%) as a colourless oil. *Anti*/*syn* = >99:1, $[\alpha]_D^{20}$ = +22.0 (c = 1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (dd, *J* = 7.9, 6.1 Hz, 1H), 4.02 (dd, *J* = 14.0, 7.7 Hz, 1H), 3.75 (dd, *J* = 11.2, 3.1 Hz, 1H), 3.69 – 3.60 (m, 3H), 1.71 – 1.61 (m, 1H), 1.41 (s, 3H), 1.35 (s, 3H), 1.33 – 1.18 (m, 10H), 0.87 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.1, 80.0, 68.8, 64.6, 44.0, 31.7, 29.5, 28.1, 27.0, 26.6, 25.5, 22.6, 14.0; HRMS (ESI+, *m/z*): calculated for $C_{13}H_{26}O_3Na$ $[M+Na]^+$: 253.17742 found: 253.17761. The diastereomeric ratio was determined by ^{1}H NMR.



4k

(*S*)-2-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)propan-1-ol (4k) Purification by flash column chromatography (SiO_2, 10 − 40% Et_2O/pentane, gradient) afforded **4k** (23 mg, yield = 50%) as a colourless oil. *Anti*/*syn* = >99:1, $[\alpha]_D^{20}$ = +15.2 (c = 1 in $CHCl_3$); [lit.[27] (*anti*:*syn* = >20:1): $[\alpha]_D^{25}$ = + 15.8 (c = 0.88 in $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (dd, *J* = 7.9, 6.1 Hz, 1H), 3.98 – 3.90 (m, 1H), 3.71 – 3.56 (m, 3H), 2.77 (br s, 1H), 1.91 – 1.78 (m, 1H), 1.41 (s, 3H), 1.35 (s, 3H), 0.82 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.4, 80.9, 68.8, 67.5, 39.2, 26.6, 25.7, 13.1; HRMS (ESI+, *m/z*): calculated for $C_8H_{16}O_3Na$ $[M+Na]^+$: 183.09917 found: 183.09885. The diastereomeric ratio was determined by ^{1}H NMR.

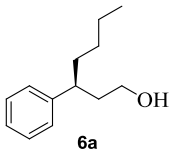


4l

(*S*)-1-Hydroxyhexan-2-yl benzoate (4l) Purification by flash column chromatography (SiO_2, 10 − 30% Et_2O/pentane, gradient) afforded **4l** (51 mg, yield = 53%) as a colourless oil. 97% *ee*, $[\alpha]_D^{20}$ = −23.0 (c = 1 in $CHCl_3$); [lit.[28] (94% *ee*): $[\alpha]_D^{23}$ = −24 (c = 0.4 in $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.3 Hz, 2H) 7.56 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 7.9 Hz, 2H), 5.20 – 5.12 (m, 1H), 3.85 – 3.71 (m, 2H), 2.29 (br s, 1H), 1.82 – 1.62 (m, 2H), 1.47 – 1.29 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 133.1, 130.2, 129.7, 128.4, 76.4, 64.9, 30.4, 27.5, 22.6, 13.9; HRMS (ESI+, *m/z*): calculated for $C_{13}H_{18}O_3Na$ $[M+Na]^+$: 245.11482 found: 245.11461. Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OB-H column, *n*-heptane/*i*-PrOH 95:5, 40 °C, 225 nm, retention times (min): 15.08 (major) and 15.91 (minor).

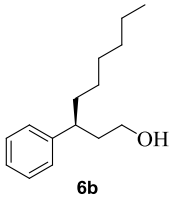
2.4.3 General procedure for the synthesis of γ–alkyl-substituted alcohols through Cu-catalyzed asymmetric allylic alkylation of allyl bromides with organolithium reagents followed by a hydroboration/oxidation

To a solution of the alkene (0.2 mmol) in dry THF (1 mL) was added a solution of 9-BBN in THF (0.5 M, 0.6 mmol, 3 equiv), and the mixture was stirred at room temperature for 2 h. Then the mixture was cooled to 0 ºC, ethanol (2.0 mL), an aq. solution of NaOH (6.0 M, 1.2 mL), and H_2O_2 (30 % in water, 4 mL) were added, and the mixture was warmed to room temperature while being stirred overnight. The reaction was quenched with an aq. solution of $Na_2S_2O_3$ (5 mL) and the mixture extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried with $MgSO_4$ and filtered and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography on silica gel using various mixtures of *n*-pentane/Et_2O as eluent.



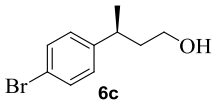
6a

(*S*)-3-Phenylheptan-1-ol (6a) Purification by flash column chromatography (SiO_2, 5 − 20% Et_2O/pentane, gradient) afforded **6a** (29 mg, yield = 67%) as a colourless oil. 99% *ee*, $[\alpha]_D^{20}$ = −1.6 (c = 1 in $CHCl_3$); [lit.[29] (94% *ee*): $[\alpha]_D^{20}$ = −1.28 (c = 1.02 in $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.05 (m, 5H), 3.52 − 3.37 (m, 2H), 2.68 - 2.58 (m, 1H), 1.97 – 1.85 (m, 1H), 1.83 – 1.70 (m, 1H), 1.69 – 1.41 (m, 4H), 1.29 – 0.98 (m, 4H), 0.79 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 128.4, 127.6, 126.1, 61.2, 42.4, 39.6, 36.7, 34.7, 29.7, 27.4, 22.7, 22.6, 14.0; HRMS (APCI+, *m/z*): calculated for $C_{13}H_{19}$ [M-H_2O]$^+$: 175.14813, found: 175.14825. Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel AS-H column, *n*-heptane/*i*-PrOH 95:5, 40 °C, 210 nm, retention times (min): 8.43 (major) and 8.87 (minor).



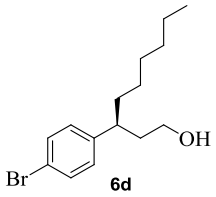
6b

(*S*)-3-Phenylnonan-1-ol (6b) Purification by flash column chromatography (SiO_2, 5 − 20% Et_2O/pentane, gradient) afforded **6b** (38 mg, yield = 74%) as a colourless oil. 99% *ee*, $[\alpha]_D^{20}$ = −4.8 (c = 1 in $CHCl_3$); [lit.[30] (***R***)-enantiomer (68% *ee*): $[\alpha]_D^{20}$ = +3.7 (c = 0.84 in $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.08 (m, 5H), 3.55 − 3.40 (m, 2H), 2.72 - 2.62 (m, 1H), 1.99 – 1.87 (m, 1H), 1.87 – 1.73 (m, 1H), 1.73 – 1.49 (m, 4H), 1.33 – 1.02 (m, 10H), 0.79 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 128.4, 127.6, 126.1, 61.2, 42.5, 39.6, 37.0, 34.7, 31.7, 29.3, 27.4, 25.2, 22.6, 14.0; HRMS (APCI+, *m/z*): calculated for $C_{15}H_{23}$ [M-H_2O]$^+$: 203.17943, found: 203.17960. Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel AS-H column, *n*-heptane/*i*-PrOH 95:5, 40 °C, 210 nm, retention times (min): 8.20 (major) and 8.75 (minor).



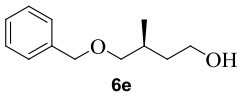
6c

(*S*)-3-(4-Bromophenyl)butan-1-ol (6c) Purification by flash column chromatography (SiO_2, 10 − 20% Et_2O/pentane, gradient) afforded **6c** (28 mg, yield = 70%) as a colourless oil. 99% *ee*, $[\alpha]_D^{20}$ = +21.2 (c = 1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.5 Hz, 2H), 3.65 – 3.41 (m, 2H), 2.97 – 2.76 (m, 1H), 1.95 – 1.68 (m, 2H), 1.24 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 131.5, 128.7, 119.7, 60.9, 40.7, 35.8, 22.2; HRMS (APCI+, *m/z*): calculated for $C_{10}H_{12}Br$ $[M\text{-}H_2O]^+$: 211.01169, found: 211.01177. Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OJ-H column, *n*-heptane/*i*-PrOH 95:5, 40 °C, 224 nm, retention times (min): 15.19 (major) and 15.96 (minor).



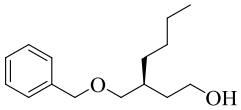
6d

(*S*)-3-(4-Bromophenyl)nonan-1-ol (6d) Purification by flash column chromatography (SiO_2, 10 − 20% Et_2O/pentane, gradient) afforded **6d** (48 mg, yield = 90%) as a colourless oil. 99% *ee*, $[\alpha]_D^{20}$ = −4.6 (c = 1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 3.54 – 3.46 (m, 1H), 3.45 – 3.37 (m, 1H), 2.70 – 2.60 (m, 1H), 1.96 – 1.86 (m, 1H), 1.78 – 1.66 (m, 1H), 1.66 – 1.48 (m, 2H), 1.43 (br s, 1H), 1.34 – 0.98 (m, 10H), 0.84 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 131.4, 129.4, 119.7, 60.9, 41.8, 39.5, 36.8, 34.7, 31.7, 29.3, 27.4, 22.6, 15.3, 14.1; HRMS (APCI+, *m/z*): calculated for $C_{15}H_{24}BrO$ $[M+H]^+$: 299.1005, found: 299.0996. Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OD-H column, *n*-heptane/*i*-PrOH 95:5, 40 °C, 226 nm, retention times (min): 12.56 (major) and 13.08 (minor).



6e

(*S*)-4-(Benzyloxy)-3-methylbutan-1-ol (6e) Purification by flash column chromatography (SiO_2, 5 − 20% Et_2O/pentane, gradient) afforded **6e** (26 mg, yield = 74%) as a colourless oil. 81% *ee*, $[\alpha]_D^{20}$ = −3.2 (c = 1 in $CHCl_3$); [lit.[15] (92% *ee*): $[\alpha]_D^{20}$ = −5.5 (c = 2.7 in $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.25 (m, 5H), 4.52 (s, 2H), 3.75 − 3.59 (m, 2H), 3.34 (ddd, *J* = 16.4, 9.1, 6.2 Hz, 2H), 2.38 (br s, 1H), 2.01 – 1.88 (m, 1H), 1.69 – 1.48 (m, 2H), 0.94 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 128.4, 127.7, 127.7, 76.1, 73.2, 61.1, 38.0, 31.4, 17.7; HRMS (ESI+, *m/z*): calculated for $C_{12}H_{18}O_2Na$ $[M+Na]^+$: 217.11990 found: 217.12006. Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OD-H column, *n*-heptane/*i*-PrOH 99:1, 40 °C, 213 nm, retention times (min): 55.99 (major) and 62.79 (minor).



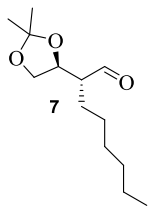
6f

(*S*)-3-((Benzyloxy)methyl)heptan-1-ol (6f) Purification by flash column chromatography (SiO_2, 5 − 30% Et_2O/pentane, gradient) afforded **6f** (26 mg, yield = 93%) as a colourless oil. 88% *ee*, $[\alpha]_D^{20}$ = −7.6 (c = 1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.22 (m, 5H), 4.52 (s, 2H), 3.76 − 3.55 (m, 2H), 3.47 (dd, *J* = 9.1, 3.9 Hz, 1H), 3.34 (dd, *J* = 9.0, 7.5 Hz, 1H), 2.47 (br s, 1H), 1.83 – 1.64 (m, 2H), 1.63 – 1.49 (m, 1H), 1.40 – 1.12 (m, 6H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 128.4, 127.7, 74.3, 73.3, 61.2, 36.6, 36.4, 31.8, 29.2, 22.9, 14.1; HRMS (ESI+, *m/z*): calculated for $C_{15}H_{24}O_2Na$ $[M+Na]^+$: 259.16685 found: 259.16709. Enantiomeric excess was determined by chiral HPLC analysis, Chiralcel OD-H column, *n*-heptane/*i*-PrOH 99:1, 40 °C, 212 nm, retention times (min): 41.12 (major) and 44.90 (minor).

2.4.4 General procedure for the one-pot synthesis of *α*–alkyl substituted aldehydes through Cu-catalyzed asymmetric allylic alkylation of allyl bromides with organolithium reagents followed by ozonolysis

A Schlenk tube equipped with septum and stirring bar was charged with CuBr•SMe_2 (0.01 mmol, 2.06 mg, 5 mol %) and the appropriate ligand (0.012 mmol, 6 mol %). Dry dichloromethane (2 mL) was added, and the solution was stirred under nitrogen at room temperature for 15 min. Then, allyl bromide **1** (0.2 mmol) was added, and the resulting solution was cooled to −80 °C. In a separate Schlenk, the corresponding organolithium reagent (0.24 mmol, 1.2 equiv) was diluted with *n*-hexane (toluene in the case of MeLi, combined volume of 1 mL) under nitrogen and the solution was added dropwise to the reaction mixture over 2 h using a syringe pump. Once the addition was complete, the mixture was stirred for another 2 h at -80 °C. The reaction was quenched with EtOH (2 mL) and ozone was bubbled for 20 min through the reaction mixture. After stirring for 20 min (solution stays blue) the reaction mixture was purged with nitrogen (disappearance of blue colour). Dimethyl sulfide (0.08 mL, 1 mmol, 5 equiv) was added and the mixture was allowed to warm to room temperature while stirred overnight. The reaction mixture was concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using different mixtures of *n*-pentane/Et_2O as eluent.

Note: The $S_N2':S_N2$ ratio was determined by GC-MS and ^{1}H-NMR analysis on a sample obtained after quenching with EtOH, which was passed through a short plug of silica gel to remove transition metal residues.

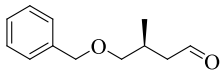


(*R*)-2-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)octanal (7) Purification by flash column chromatography (SiO_2, 5 − 20% Et_2O/pentane, gradient)

afforded **7** (28 mg, yield = 70%) as a colourless oil. *Anti*:*syn* = >99:1, $[\alpha]_D^{20}$ = −3.4 (c = 1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, *J* = 3.5 Hz, 1H), 4.28 (dd, *J* = 13.5, 6.6 Hz, 1H), 4.10 (dd, *J* = 8.4, 6.2 Hz, 1H), 3.69 (dd, *J* = 8.3, 6.8 Hz, 1H), 2.46 – 2.36 (m, 1H), 1.80 – 1.64 (m, 2H), 1.40 (s, 3H), 1.34 (s, 3H), 1.32 – 1.20 (m, 8H), 0.87 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.4, 109.5, 75.5, 67.7, 55.3, 31.5, 29.3, 27.1, 26.5, 26.3, 25.3, 22.5, 14.0; HRMS (ESI+, *m/z*): calculated for $C_{13}H_{24}O_3Na$ $[M+Na]^+$: 251.16177 found: 251.16153. The diastereomeric ratio was determined by ^{1}H-NMR.

2.4.5 General procedure for the synthesis of *β*-alkyl-substituted aldehydes through the oxidation of *γ*-alkyl substituted primary alcohols with Dess–Martin periodinane

To a stirred suspension of Dess–Martin periodinane (99 mg, 0.24 mmol, 1.8 equiv) and $NaHCO_3$ (33 mg, 0.39 mmol, 3 equiv) in dichloromethane (2 mL) at 0 °C was added dropwise a solution of the alcohol (25 mg, 0.13 mmol, 1 equiv) in 1 mL of dichloromethane. The reaction mixture was stirred at 0 °C for 2 h, silica gel was added, and the solvents were removed in vacuo. The crude mixture was purified by flash chromatography on silica gel using different mixtures of *n*-pentane/Et_2O as eluent.

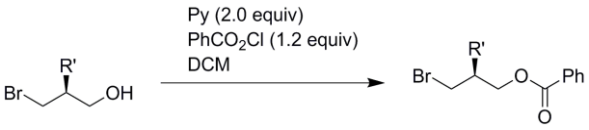


8

(*S*)-4-(Benzyloxy)-3-methylbutanal (8) Purification by flash column chromatography (SiO_2, 10 − 40 % Et_2O/pentane, gradient) afforded **8** (18 mg, yield = 75%) as a colourless oil. 81% *ee*, $[\alpha]_D^{20}$ = −10.6 (c = 1 in $CHCl_3$); [lit.[31] (100% *ee*): $[\alpha]_D^{20}$ = −11.2 (c = 1.7 in $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, *J* = 2.2 Hz, 1H), 7.50 – 7.12 (m, 5H), 4.50 (s, 2H), 3.42 (dd, *J* = 9.1, 5.2 Hz, 1H), 3.25 (dd, *J* = 9.1, 7.7 Hz, 1H), 2.56 (ddd, *J* = 16.1, 6.3, 2.3 Hz, 1H), 2.50 – 2.35 (m, 1H), 2.28 (ddd, *J* = 16.1, 6.9, 2.1 Hz, 1H), 0.99 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 128.4, 127.7, 127.7, 76.1, 73.2, 61.1, 38.0, 31.4, 17.7;

HRMS (ESI+, *m/z*): calculated for $C_{12}H_{16}O_2Na$ $[M+Na]^+$: 215.10425 found: 215.10405.

2.4.6 General Procedure for the synthesis of benzoate ester of the alcohols 4h and 4i



To a suspension of alcohol in (0.36 mmol, 1 equiv) dry DCM (3 mL) pyridine (0.72 mmol, 2 equiv) was added and the mixture was stirred at room temperature for 10 min. Then, benzoyl chloride (0.43 mmol, 1.2 equiv) was added dropwise and the mixture was stirred for 1 h. The reaction was quenched with 5 mL of 1N aq. HCl and the layers were separated. The aqueous layer was extracted with DCM (3 x 5 mL). The combined organic layers were washed with aqueous solution of saturated $NaHCO_3$ and dried with $MgSO_4$, filtered and the solvent was evaporated in vacuo resulting in the corresponding benzoate ester which was directly used for the determination of enantiomeric excess.

2.5 References

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