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Enantioselective Synthesis of 1,2-, 1,3- and 1,4- Aminoalcohols by the Addition of Dialkylzincs to 1,2-, 1,3- and 1,4- Aminoaldehydes

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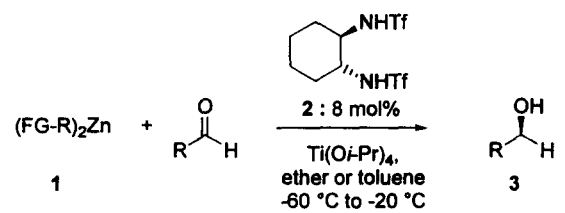
Abstract: Chiral 1,3- and 1,4- aminoalcohols were prepared by the addition of functionalized dialkylzincs to 1,3-aliphatic and 1,4–unsaturated aminoaldehydes with good to excellent enantioselectivity. *Syn-* or *anti*-1,2-aminoalcohols are stereoselectively obtained by asymmetric addition of dialkylzincs to α-aminoaldehydes depending on the choice of the chiral catalyst. A chelate controlled addition is observed if less than stoichiometric amounts of $Ti(O\textit{i}\text{-}Pr)_4$ are used.

Introduction

Recently, we have shown that functionalized diorganozincs ($(FG\text{-}R)_2Zn$ **1**)[1] can be added to various aliphatic and aromatic aldehydes in the presence of $Ti(OR)_4$ and the chiral catalyst (1*R*,2*R*)-*bis*(trifluoromethanesulfonamido)cyclohexane[2] **2** leading to polyfunctional secondary alcohols **3** with high enantioselectivity (Scheme 1).[3] Although many oxygen-containing functionalities like esters and ethers are well tolerated in this reaction, the presence of nitrogen-functionalities either in the zinc reagent or in the aldehyde leads to considerable loss of reactivity and enantioselectivity. This is a result of the strong coordinating ability of the amino function to the titanium metal center which desactivates the chiral catalyst and favours achiral addition pathways.



Scheme 1

Herein, we wish to report the preparation of various nitrogen protected 1,n-aminoaldehydes (n = 2, 3, 4) and the enantioselective addition of dialkylzincs leading to secondary aminoalcohols with good to excellent

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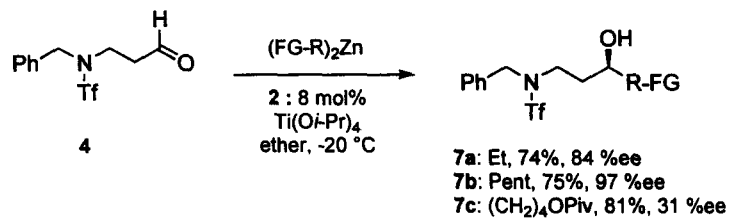
enantioselectivity. In previous work, we focused[4] our attention on the use of amino functionalized diorganozincs or introduced the nitrogen-functionality at a later state of the synthesis.[3b, 5] More recently, we have succeeded in the addition of dialkylzincs to some borane protected nitrogen-heterocyclic aldehydes.[6] We have now investigated the addition of dialkylzincs to various aliphatic aminoaldehydes. Only a few examples have been known so far.[7] Soai[7b] could show that in the case of α-aminoaldehydes the role of the added catalyst was to activate the dialkylzinc reagent and to allow a reaction by a non chelating Felkin-Anh-transition state.[8] Herein we report the successful addition of various dialkylzincs to protected 1,n-aminoaldehydes (n = 2, 3, 4) with good enantioselectivity.

Results and Discussion

We found, that various protective groups[9] like benzyl-, *tert*-butoxycarbonyl- and triflate groups are well tolerated in the asymmetric addition of diorganozincs to aldehydes. These protective groups are all well suited for the preparation of protected aminoaldehydes.[10] Racemization[11] and polymerization[12] which are often observed side-reactions with these substrates could be kept to a minimum.

The preparation of the starting aldehyde **4** was achieved in two steps using a substitution reaction of 3-chloropropanol (**5**) with N-benzyltrifluoromethanesulfonamide (**6**) followed by Swern oxidation[13] in 16 % overall yield. The catalytic enantioselective addition of dialkylzincs to **4** resulted in the formation of the desired alcohols **7a-c** in 74 - 81 % yield. With diethyl- and dipentylzinc, good to excellent enantioselectivities were obtained (84 % ee and 97 % ee; Scheme 2). Disappointingly, the enantiomeric excess dropped to 31 % ee by using the functionalized dialkylzinc reagent $(PivO(CH_2)_4)_2Zn$ (**7c**).

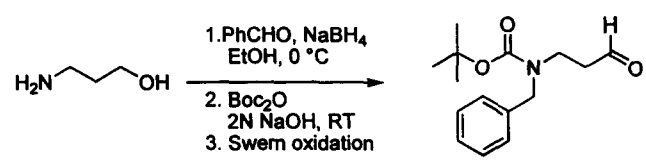


4

7a: Et, 74%, 84 %ee
7b: Pent, 75%, 97 %ee
7c: $(CH_2)_4OPiv$, 81%, 31 %ee

Scheme 2

Despite extensive experimentation, no further improvement could be obtained. We decided to use a Boc-protecting group instead of a triflamide. Access to aldehyde **8** was easily achieved by performing a reductive amination[14] with 3-aminopropanol (**9**) and benzaldehyde followed by conversion into an intermediate carbamate by the reaction with Boc_2O[9] and subsequent Swern oxidation[13] in 57 % overall yield (Scheme 3).

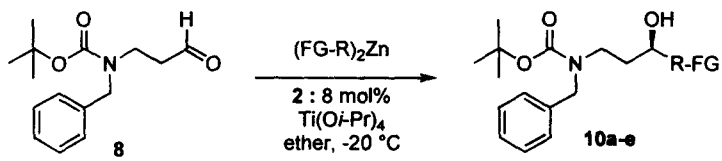


9

8: 57 %

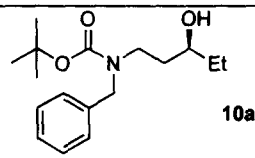
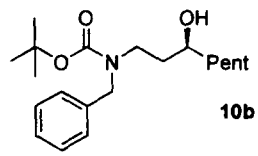
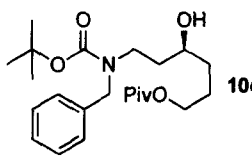
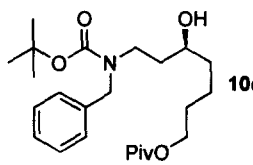
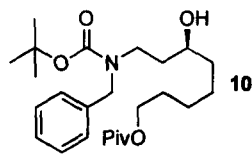
Scheme 3

The reaction of **8** with dialkylzincs under our standard reaction conditions affords the desired aminoalcohols **10a-e** in good to excellent yields and enantioselectivities (79 - 90 %, 95 - >98 % ee; Scheme 4). Moreover, *high enantioselectivities* were also observed with functionalized dialkylzincs (entries 3 - 5, Table 1).



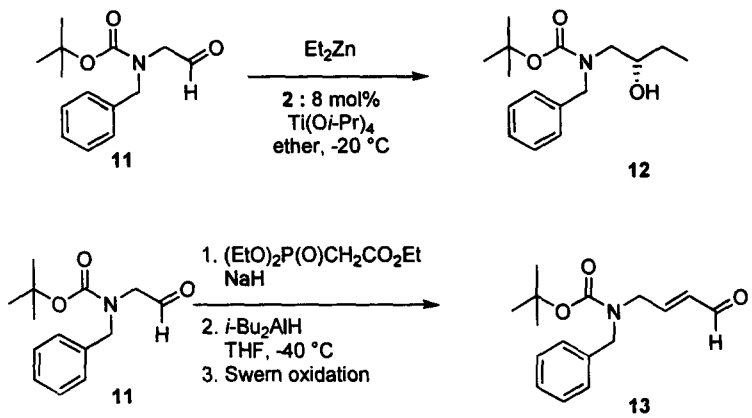
Scheme 4

Table 1. Preparation of γ-aminoalcohols **10a-e** by enantioselective addition of dialkylzincs to the aldehyde **8** in the presence of the catalyst **2**.

entry	$(FG\text{-}R)_2Zn$ (FG-R)	product of type **10**	yield (%)[a]	ee (%)[b]
1	Et	 **10a**	89	>98
2	Pent	 **10b**	90	>98
3	$(CH_2)_3OPiv$	 **10c**	79	95
4	$(CH_2)_4OPiv$	 **10d**	87	96
5	$(CH_2)_5OPiv$	 **10e**	90	97

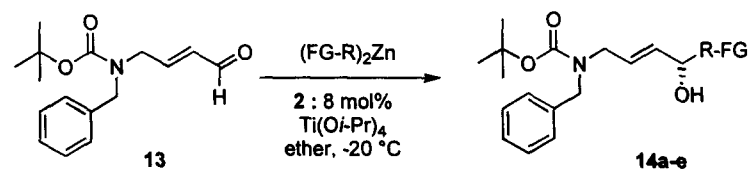
[a] Isolated yields of analytically pure products. [b] The enantiomeric excess was determined by HPLC analysis (Chiracel OD).

Next, we have examined the possibility of preparing chiral β-aminoalcohols. Synthesis of aldehyde **11** was achieved in analogy to **8** in 50 % overall yield, starting with commercially available 2-N-benzylaminoethanol. The addition of Et_2Zn gave the β-aminoalcohol **12** in only 42 % yield and 24 % ee showing a strong influence of the polar amino group in α position to the aldehyde function (Scheme 5).



Scheme 5

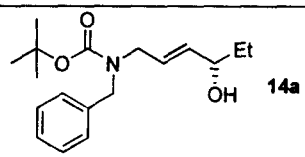
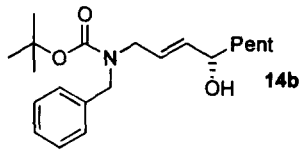
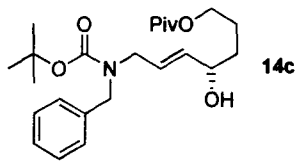
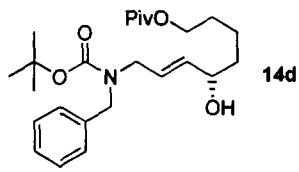
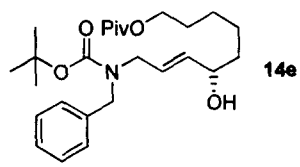
On the other hand, Wittig-Horner homologation[15] of aldehyde **11** with diethyl phosphonoacetate, followed by *i*-Bu_2AlH reduction,[16] Swern oxidation[13] resulted in the formation of a new α,β-unsaturated aminoaldehyde **13** in 59 % yield starting from **11** (Scheme 5). Catalytic enantioselective addition of dialkylzincs gave γ-aminoallylic alcohols **15a-e** in good yields and enantioselectivities: 66 - 85 %; 79 - 95 %ee (see Scheme 6 and Table 2).



Scheme 6

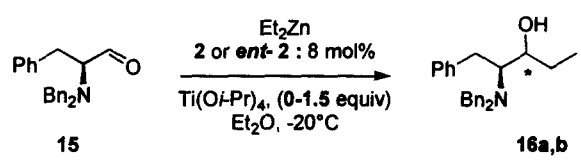
So far we have shown, that an amino functionality is well tolerated in the enantioselective synthesis of some 1,4- and 1,3-aminoalcohols using dialkylzincs. The remote position of the amino group prevents from interactions with the reactive carbonyl center and does not strongly interfer with the asymmetric addition. A more difficult situation arises when the amino group is in α-position to the carbonyl group.

Table 2. Preparation of γ-aminoallylic alcohols **14a-e** by enantioselective addition of dialkylzincs to the aldehyde **13** in the presence of catalyst **2**.

entry	$(FG\text{-}R)_2Zn$ (FG-R)	product of type **14**	yield (%)[a]	ee (%)[b]
1	Et	 **14a**	86	95
2	Pent	 **14b**	69	90
3	$(CH_2)_3OPiv$	 **14c**	66	79
4	$(CH_2)_4OPiv$	 **14d**	85	87
5	$(CH_2)_5OPiv$	 **14e**	75	90

[a] Isolated yields of analytically pure products. [b] The enantiomeric excess was determined by HPLC analysis (Chiracel OD).

Lewis acidic catalysts like **2** have the ability to induce chirality despite the presence of carbon and oxygen containing chiral center at the α-position. [3b,17] It is a challenging problem to examine the addition of diorganozincs to chiral α-aminoaldehydes of type **15**.[18] It was known that the addition of diethylzinc to **15** selectively affords *syn*-aminoalcohols in the absence of a chiral catalyst.[19]



Scheme 7

We have observed a strong dependence between the diastereomeric excess of products of type **16** and the number of equivalents of Ti(O*i*-Pr)$_4$ used (Scheme 7, Figure 1).

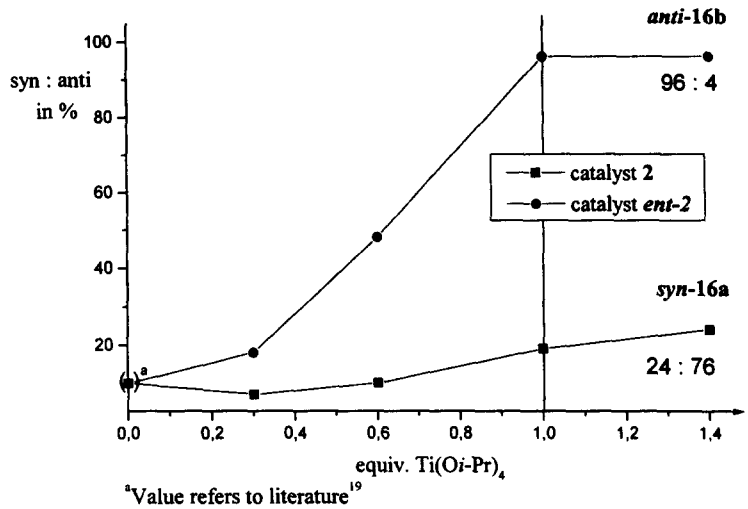
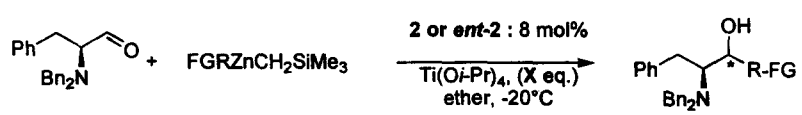


Figure 1. Diastereomeric excess of **16a,b** as a function of the amount of Ti(O*i*-Pr)$_4$ using either catalyst **2** or ***ent*-2**.

If more than one equivalent of Ti(O*i*-Pr)$_4$ is used, the diastereoselectivity is controlled by the topicity of the catalyst **2**. With **2** the *syn-product* (***syn*-16a**) is formed preferentially (*syn* : *anti* = 76 : 24) and with ***ent*-2**, the diastereomeric aminoalcohol (***anti*-16b**) is obtained with good *anti*-selectivity (*syn* : *anti* = 4 : 96). By using less than one equivalent of Ti(O*i*-Pr)$_4$, the *syn*-product (***syn*-16a**) is however obtained regardless of the topicity of the chiral catalyst. ***Syn*-16a** is also the product which would result from a chelate controlled reaction.[19] Thus, our results are best explained by assuming that the presence of at least one equivalent of Ti(O*i*-Pr)$_4$, the amine function is complexed with Ti(O*i*-Pr)$_4$ and therefore this "protected"-amino group does not interfer with the asymmetric addition which is entirely directed by the chiral catalyst (**2** or ***ent*-2**). However, if less than 0.4 equiv of Ti(O*i*-Pr)$_4$ are used, a Zn-induced chelate controlled reaction takes place leading to ***syn*-16a**. Similar results were obtained with the functionalized zinc reagent (PivO(CH$_2$)$_4$)$_2$Zn.

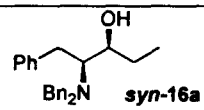
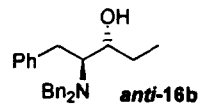
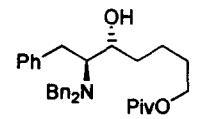
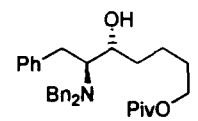
Further investigations under optimized reaction conditions (1.2 equiv Ti(O*i*-Pr)$_4$) using mixed dialkylzincs **17**[3d, 20] resulted in moderate yields (36 - 74 %, Scheme 8, Table 3), but good to excellent ***syn* : *anti*** ratios were observed.



15 **17** **16a-d** :36 - 74 %

Scheme 8

Table 3. Preparation of β-aminoalcohols **16a-d** by addition of dialkylzincs to the aldehyde **15**.

entry	$(FG\text{-}R)_2Zn$ (FG-R)	reaction conditions	syn : anti ratio[a]	product of type **16**	yield (%)[b]
1	Et	**2**; -20°C	84 : 16[a]	 ***syn*-16a**	74
2	Et	***ent*-2**; -20°C	4 : >96[a]	 ***anti*-16b**	66
3	$(CH_2)_4OPiv$	**2**; 0°C	84 : 16[a]	 ***syn*-16c**	47
4	$(CH_2)_4OPiv$	***ent*-2**; 0°C	15 : 85[a]	 ***anti*-16d**	36

[a] Determined by ^1H, ^{13}C NMRspectroscopy of the crude product. [b] Isolated yields of analytically pure products.

Conclusion

In summary, we have shown that protective groups like a triflamide, or Boc-carbamate are suitable for the catalytic enantioselective additions of dialkylzincs to some 1,3- or 1,4-aminoaldehydes giving rise to chiral aminoalcohols in up to >98 %ee. In the case of α-aminoaldehyde **15** both diastereomeric *syn-* or *anti-* 1,2-aminoalcohols can be obtained selectively by choosing the appropiate catalyst **2** or ***ent*-2**. Furthermore, a chelate controlled addition is observed if less than stoichiometric amounts of $Ti(O\textit{i}\text{-}Pr)_4$ are used.

Experimental Section

General Considerations

All reactions with organometallic reagents were carried out under argon. Solvents (toluene, ether) were dried and freshly distilled from sodium/benzophenone. Reactions were monitored by gas liquid phase chromatography (GC) and thin-layer chromatography (TLC) analysis of hydrolyzed aliquots. Optical purities were determined either by derivatisation using *Parker's* method[21] or chiral HPLC analysis (for details see below). ^1H and ^{13}C NMR spectra were recorded on a *Bruker ARX 200* and *AC 300* spectrometer. IR spectra were recorded on a *Perkin-Elmer 281* and *Nicolet 511* spectrometer. Optical rotations were measured with a *Perkin-Elmer 241* polarimeter. Mass spectra were recorded on *Varian MAT CH 7 A*. Elemental analyses were performed by the *Microanalytical Service Laboratory of the Fachbereich Chemie* (Marburg).

Starting materials

Ti(O*i*-Pr)$_4$ was distilled before use. The following starting materials were prepared according to literature procedures: dipentylzinc,[22] (*R,R*)-, (*S,S*)-1,2-*bis*(trifluoromethanesulfonamido)cyclohexane **2**.[2b] The alkyl iodides required for the preparation of the corresponding dialkylzincs **1** were prepared by standard methods: 3-iodopropyl pivalate, 4-iodobutyl pivalate, 5-iodopentyl pivalate,[23] and (2*S*)-2-dibenzylamino-3-phenylpropanal **15**.[18]

3-(N-Benzyl-N-trifluoromethanesulfonamido)propanal (**4**).

In a three necked flask, equipped with a reflux condenser, a magnetic stirring bar and a rubber septum, was charged with K_2CO_3 (3.32 g, 24 mmol), N-benzyl-trifluoromethanesulfonamide (3.54 g, 15 mmol) and NaI (2.44 g, 3 mmol) in DMF (10 mL). 3-Chloropropan-1-ol (1.4 mL, 17 mmol) was added and the reaction mixture was heated to 50 °C for 18 h. After hydrolysis with H_2O (50 mL) the product was extracted with ether (4 × 50 mL) and the combined organic phases were washed with brine. After drying ($MgSO_4$) and evaporation of the solvents, the crude product was purified by chromatography (hexanes/ether). The product was obtained in 71 % yield (3.18 g, 10.7 mmol). R_f = 0.13 (hexanes/ether 1:1); IR (neat): 3600 (br), 3500 (br), 3040 (w), 2958 (w), 2890 (w), 1456 (m), 1386 (s), 1227 (s), 1191 (s); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.45 - 7.29 (m, 5 H), 4.57 (s, 2 H), 3.59 - 3.32 (m, 5 H), 1.66 (quint, *J* = 5.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 134.5, 128.9, 128.7, 128.5, 120.2, (q, *J* = 321.5 Hz), 58.9, 52.7, 45.6, 30.8; MS (EI): *m/z* 164 (28), 91 (100); $C_{11}H_{14}F_3NO_3S$ (297.29): calcd C 44.44, H 5.65, N 4.71; found C 44.70, H 5.87, N 4.86. The aminoaldehyde **4** was prepared from 3-(N-benzyl-N-trifluoromethanesulfonamido)propan-1-ol (3.57 g, 12 mmol) by Swern oxidation[13] using oxalyl chloride (2.1 mL, 21 mmol), dimethylsulfoxide (2.8 mL, 39 mmol) and triethylamine (6.7 mL, 49 mmol) in 23 % yield (0.83 g, 2.8 mmol). R_f = 0.11 (hexanes/ether 4:1); IR (neat): 3036 (w), 2960 (w), 2842 (w), 2740 (w), 1730 (m), 1455 (w), 1387 (s), 1190 (s), 1145 (s), 1105 (m); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.56 (s, 1 H), 7.41 - 7.34 (m, 5 H), 4.51 (br s, 2 H), 3.63 (t, *J* = 7.0 Hz, 2 H), 2.59 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 198.6, 134.3, 129.3, 128.9, 128.6, 120.2 (q, *J* = 321.5 Hz), 53.6, 43.3, 42.3; MS (EI): *m/z* 91 (100), 84 (31), 57 (63); $C_{11}H_{12}F_3NO_3S$ (295.28): calcd C 44.74, H 4.09, N 4.74; found C 44.69, H 3.96, N 4.81.

3-(N-Benzyl-N-tert-butoxycarbonylamino)propanal (**8**).

A 100 mL flask equipped with a magnetic stirring bar was charged with 3-aminopropan-1-ol (3.8 mL, 50 mmol) and benzaldehyde (5.1 mL, 50 mmol) in ethanol (25 mL) at 0 °C. After 30 min, $NaBH_4$ (0.95 g, 25 mmol) was added and the reaction mixture was stirred for 18 h. The reaction mixture was quenched with H_2O (10 mL). After evaporation of the solvent in vacuo, stirring was continued for further 30 min. Extraction of the remaining aqueous phase with ether (5 × 80 mL), drying ($MgSO_4$) and evaporation of the solvent gave the crude product which was dissolved in 2 N NaOH solution (25 mL) and *tert*-butyl pyruvate (9.04 g, 48 mmol) was added. The reaction was stirred for 6 h at RT. After extraction of the aqueous phase with ether (4 × 80 mL), the combined organic phases were dried ($MgSO_4$). Evaporation of the solvent gave 3-(N-benzyl-N-*tert*-butoxycarbonylamino)propan-1-ol after chromatographical purification in 59 % yield (7.86 g, 19.6 mmol). R_f = 0.19 (hexanes/ether 1:1); IR (neat): 3500 (s), 3033 (w), 2930 (m), 2860 (m), 1670 (s), 1470 (s), 1415 (s), 1250 (s),

1166 (s); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.40 - 7.22 (m, 5 H), 4.40 (s, 2 H), 3.57 (t, *J* = 5.4 Hz, 2 H), 3.40 (s, 2+1 H), 1.65 (s, 2 H), 1.48 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 156.0, 138.2, 128.5, 127.3, 80.5, 58.6, 50.5, 42.4, 30.3, 28.4; MS (EI): *m/z* 229 (28), 165 (4), 164 (31), 151 (1), 150 (12), 121 (5), 120 (63), 106 (29), 91 (100); $C_{15}H_{23}NO_3$ (265.34). The analytical data are identical to those of the literature.[24] Aminoaldehyde **8** was prepared form 3-(N-benzyl-N-*tert*-butoxycarbonylamino)propan-1-ol (3.18 g, 12.0 mmol) by a Swern oxidation[13] using oxalyl chloride (2.2 mL, 21.6 mmol), dimethylsulfoxide (2.8 mL, 39.6 mmol) and triethylamine (6.8 mL, 50 mmol) in 97 % yield (3.05 g, 11.58 mmol). R_f = 0.20 (hexanes/ether 2:1); IR (neat): 3030 (w), 2978 (m), 1724 (s), 1696 (s), 1467 (m), 1415 (m), 1246 (s), 1167 (s); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.69 (s, 1 H), 7.32 - 7.20 (m, 5 H), 4.41 (s, 2 H), 3.46 (s, 2 H), 2.61 (s, 2 H), 1.42 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 202.0, 155.4, 138.0, 128.4, 127.2, 127.1, 80.2, 52.0, 43.0, 40.6, 28.3; MS (EI): *m/z* 235 (5), 178 (9), 109 (14), 91 (79), 57 (100); $C_{15}H_{21}NO_3$ (263.33); calcd C 68.41, H 8.04, N 5.32; found C 68.14, H 7.81, N 4.99.

2-(N-Benzyl-N-tert-butoxycarbonylamino)ethanal (**11**).

A 100 mL flask with a magnetic stirring bar was charged with 2-(benzylamino)ethanol (7.56 g, 50 mmol) dissolved in 2 N NaOH solution (25 mL). After cooling to 0 °C *tert*-butyl pyruvate (9.04 g, 48.0 mmol) was slowly added. The reaction mixture was stirred for 6 h at RT and diluted with ether (50 mL). Extraction with ether and drying ($MgSO_4$) gave 2-(N-benzyl-N-*tert*-butoxycarbonylamino)ethanol in 63 % yield (7.96 g, 31.6 mmol) after chromatographical purification (hexanes/ether). R_f = 0.15 (hexanes/ether 1:1); IR (neat): 3500 (s), 3030 (w), 2975 (s), 2930 (s), 2870 (m), 1690 (s), 1455 (s), 1415 (s), 1250 (s), 1170 (s); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.34 - 7.23 (m, 5 H), 4.50 (s, 2 H), 3.70 (s, 2H), 3.23 (s, 2 H), 3.19 (s, 1 H), 1.49 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.3, 128.6, 127.3 126.9, 80.5, 62.0, 52.0, 49.8, 28.4; MS (EI): *m/z* 220 (4), 195 (21), 164 (17), 120 (48), 91 (100), 57 (94), 41 (20); $C_{14}H_{21}NO_3$ (251.32); calcd C 5.57, H 66.90, N 8.42; found C 5.59, H 66.84, N 8.29. The analytical data are identical to those of the literature.[25] This aminoaldehyde **11** was prepared form 2-(N-benzyl-N-*tert*-butoxycarbonylamino)ethanol (1.26 g, 5.0 mmol) by a Swern oxidation[13] procedure using oxalyl chloride (0.9 mL, 9.0 mmol), dimethylsulfoxide (1.2 mL, 16.5 mmol) and triethylamine (2.8 mL, 21 mmol) in 80 % yield (1.00 g, 4.0 mmol). R_f = 0.24 (hexanes/ether 2:1); IR (neat): 3037 (w), 2980 (m), 2835 (m), 2735 (m), 1728 (m), 1455 (m), 1388 (s), 1226 (s), 1145 (s), 1100 (m); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.44 (s, 1 H), 7.32 - 7.16 (m, 5 H), 4.45 (s, 1 H), 4.34 (s, 1 H), 3.88 (s, 1 H), 3.74 (s, 1 H), 1.45 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 198.7, 156.0, 137.3, 128.7, 128.6, 128.2, 127.7, 127.6, 81.0, 56.4, 52.0, 51.6, 28.3; MS (EI): *m/z* 220 (10), 164 (12), 91 (81), 57 (100), 48 (19); $C_{14}H_{19}NO_3$ (249.30); calcd C 67.44, H 7.68, N 5.61; found C 67.02, H 7.53, N 5.27.

4-(N-Benzyl-N-tert-butoxycarbonylamino)but-2-enal (**13**).

A 100 mL two-necked flask with an argon inlet, a dropping funnel and a magnetic stirring bar was charged with sodium hydride (1.71 g, 54.6 mmol) and ether (70 mL). The resulting suspension was cooled to 0 °C and ethyl diethylphosphonoacetate (10.9 mL, 54.6 mmol) was slowly added over 5 min. Aminoaldehyde **11** (12.01 g, 47.8 mmol) dissolved in ether (20 mL), was added within 25 min. After warming to RT and stirring for 1 h, the reaction mixture was quenched with aq. sat. NH_4Cl solution (20 mL). After extraction with ether (3 × 80 mL), the combined organic phases were dried over $MgSO_4$ and the solvent was evaporated. After

chromatographical purification (hexanes/ether), (*E*)-ethyl 4-(N-benzyl-N-*tert*-butoxy-carbonylamino)but-2-enoate was isolated in 91 % yield (13.89 g, 43.5 mmol). R_f = 0.41 (hexanes/ether 2:1); IR (neat): 3030 (w), 2890 (s), 1720 (s), 1400 (s), 1270 (s), 1180 (s); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.33 - 7.19 (m, 5 H), 6.77 (br, 1 H), 5.80 (br d, *J* = 15.9 Hz, 1 H), 4.39 (br s, 2 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 3.93 - 3.83 (br s, 2 H), 1.44 (s, 9 H), 1.17 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 165.9, 155.4, 143.5, 137.6, 128.8, 128.5, 127.9, 127.3, 122.0, 80.3, 60.3, 50.0, 46.8, 28.3, 14.1; MS (EI): *m/z* 319 (M^+, 0.6), 263 (8), 146 (25), 128 (25), 106 (28), 91 (100), 57 (98); $C_{18}H_{25}NO_4$ (319.39); calcd C 67.69, H 4.39, N 7.89; found C 76.41, H 4.57, N 7.74.
Reduction of (*E*)-ethyl 4-(N-benzyl-N-*tert*-butoxy-carbonylamino)but-2-enoate (12.38 g, 38.8 mmol) at -30 °C with diisobutylaluminium hydride[16] (21 mL, 116 mmol) gave 4-(N-benzyl-N-*tert*-butoxycarbonylamino)but-2-en-1-ol in 72 % (7.74 g, 27.9 mmol). R_f = 0.22 (hexanes/ether 1:1); IR (neat): 3500 (br), 3030 (w), 2960 (m), 2870 (m), 1690 (s), 1460 (s), 1415 (s), 1250 (s), 1170 (s); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.32 - 7.18 (m, 5 H), 5.63 (br s, 2 H), 4.41 (br s, 2 H), 4.06 (br s, 2 H), 3.74 (br s, 2 H). 1.77 (br s, 1 H), 1.44 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 156.2, 138.3, 131.6, 128.5, 128.3, 127.2, 126.9, 79.8, 62.8, 49.5, 47.5, 28.3; MS (EI): *m/z* 277 (M^+, 0.6), 221 (11), 203 (23), 150 (7), 120 (12), 91 (100), 41 (17); $C_{16}H_{23}NO_3$ (277.35); calcd C 69.28, H 8.36, N 5.05; found C 68.91, H 8.20, N 5.38. Amino aldehyde **13** was obtained from 4-(N-benzyl-N-*tert*-butoxycarbonylamino)but-2-en-1-ol (1.39 g, 5.0 mmol) by Swern oxidation[13] procedure using oxalyl chloride (0.54 mL, 5.3 mmol) , dimethylsulfoxide (0.7 mL, 9.8 mmol) and triethylamine (1.7 mL, 12.0 mmol)in 83 % yield (1.15 g, 4.2 mmol). R_f = 0.18 (hexanes/ether 2:1); IR (neat): 3030 (w), 2960 (m), 2870 (m), 2720 (w), 1696 (s), 1454 (m), 1407 (m), 1165 (s); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.34 - 7.21 (m, 5 H), 6.65 (br s, 1 H), 6.06 (dd, *J* = 15.8 Hz, *J* = 5.9 Hz, 1 H), 4.42 (s, 2 H), 4.06 (br s, 2 H), 1.47 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 192.9, 155.3, 152.5, 137.4, 132.4, 128.6, 127.5, 80.6, 50.5, 47.4, 28.3; MS (EI): *m/z* 277 (M^+, 0.6), 221 (11), 203 (23), 150 (7), 120 (12), 91 (100), 41 (17); $C_{16}H_{21}NO_3$ (275.34); calcd C 69.79, H 7.69, N 5.09; found C 69.47, H 7.51, N 5.18.

General Procedure 1 for the Preparation of Functionalized Dialkyzinc Compounds via Iodine-Zinc-Exchange Reaction.

A 100 mL two necked-flask equipped with an argon inlet, a magnetic stirring bar, a dropping funnel and a septum cap was charged with an iodoalkane (50 mmol) and CuI (29 mg, 0.3 mol %). Diethylzinc (7.7 mL, 75 mmol, 1.5 equiv) was added dropwise to the iodoalkane at 25 °C. The reaction mixture was heated to 55 °C for 16 h. The conversion of the iodoalkane was checked by GC-analysis of hydrolyzed and iodolyzed aliquots. Finally, the reaction flask was connected to the vacuum line and the formed ethyl iodide and excess diethylzinc were distilled off (0.1 Torr, 55 °C) in two cooling traps filled with liquid nitrogen. After 2 h, decane (1.5 mL) was added and the evaporation was continued. This coevaporation procedure was repeated three times. The resulting dialkylzinc reagent was dissolved in ether (10 mL) and ready to use. The distilled diethylzinc collected in cooling traps was quenched by addition of mixtures of hexanes/acetone and warming to rt.

General Procedure 2 for the Asymmetric Addition of Functionalized Dialkylzincs **1** *to Aldehydes* **4**, **8**, **11**, **13**.

A 100 mL two-necked flask equipped with an argon inlet, a septum cap and a magnetic stirring bar was charged with ether (3 mL), Ti(O*i*-Pr)$_4$ (1.8 mL, 6.0 mmol, 1.2 equiv) and (*R*,*R*)-1,2-*bis*(trifluoromethanesulfonamido)cyclohexane **2** (165 mg, 8 mol %). After cooling to -20 °C, a solution of the functionalized dialkylzinc **1**

was slowly added (2.0-2.7 equiv). The mixture was stirred for 0.5-1 h and aldehyde **6** (5.0 mmol) was added as ca. 1 M solution in ether. The reaction was stirred for 16 h. It was diluted with ether and quenched with aq. sat. NH_4Cl and 10 % aq. HCl until a clear solution resulted. The aqueous layer was extracted with ether (3 x 50 mL). The combined organic layer was washed with aq. 2 N NaOH solution (20 mL) to remove the catalyst and dried ($MgSO_4$). After filtration and evaporation of the solvents, the residual oil was purified by flash chromatography (hexanes/ether) affording pure alcohol. The enantiomeric excess was determined in ^1H NMR analysis of the corresponding *O*-acetyl-mandelic ester prepared using (*S*)-(+)-*O*-acetyl-mandelic acid and DCC according to Parker's method,[21] or by HPLC analysis (for detailed description see below).

General Procedure 3 for the Asymmetric Addition of Mixed Zinc Reagents **17** *to Aldehyde* **15**.

A 100 mL two-necked flask equipped with an argon inlet and septum cap was charged with ether (3 mL), $Ti(Oi\text{-}Pr)_4$ (1.8 mL, 6.0 mmol, 1.2 equiv) and (*R,R*)-1,2-*bis*(trifluoromethanesulfonamido)cyclohexane **2** (165 mg, 8 mol %). Meanwhile the dialkylzinc (0.8 equiv) and $(Me_3SiCH_2)_2Zn$ were mixed at 25 °C in another Schlenk-flask. In the case of functionalized dialkylzinc $(FG\text{-}R)_2Zn$ **1** (1.2 equiv) and $(Me_3SiCH_2)_2Zn$ (1.3 equiv) was used. After cooling to -20 °C, the mixed zinc reagent **17** was slowly added. The mixture was stirred for 0.5-1 h and aldehyde **15** (5.0 mmol) was added as ca. 1 M solution in ether. The reaction was stirred for 16 h. It was diluted with ether (15 mL) and quenched with 10 % aq. citric acid (10 mL) and stirred until a almost clear solution was obtained. The aqueous layer was extracted with ether (3 x 50 mL). The combined organic layer was washed with aq. 2 N NaOH solution (10 mL) to remove the catalyst and dried ($MgSO_4$). After filtration and evaporation of the solvents, the residual oil was purified by flash chromatography (hexanes/ether) affording pure alcohol. The diastereomeric excess of the crude product was determined in ^1H NMR and ^{13}C NMR spectroscopy.

(S)-1-(N-Benzyl-N-trifluoromethanesulfonamido)pentan-3-ol (**7a**).

Aldehyde **4** (1.48 g, 5.0 mmol) was treated with diethylzinc (2 equiv) following *procedure 2* yielding aminoalcohol **7a** (1.21 g, 3.6 mmol, 74 %, 84 % ee). The enantiomeric excess was determined according to Parker's method.[21] R_f = 0.20 (hexanes/ether 2:1); α_D^{25} = +23.32 (c 5.06, $CHCl_3$); IR (neat): 3600 (br), 3500 (br), 3035 (w), 2970 (w), 2880 (w), 1458 (m), 1385 (s), 1226 (s) , 1188 (s), 1146 (m); ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.42 - 7.26 (m, 5 H), 4.48 (br s, 2 H), 3.51 - 3.40 (m, 3 H), 1.74 - 1.55 (m, 4 H), 0.82 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 134.6, 128.9, 128.7, 120.4, (q, *J* = 321.5 Hz), 70.0, 52.8, 45.9, 35.1, 30.2, 9.7; MS (EI): *m/z* 277 (M^+, 0.6), 221 (11), 203 (23), 150 (7), 120 (12), 91 (100), 41 (17); $C_{13}H_{18}F_3NO_3S$ (325.34); calcd C 47.99, H 5.58, N 4.31; found C 47.94, H 5.30, N 4.49.

(S)-1-(N-Benzyl-N-trifluoromethanesulfonamido)octan-3-ol (**7b**).

Aldehyde **4** (0.49 g, 1.7 mmol) was treated with dipentylzinc (2.5 equiv) following *procedure 2* yielding aminoalcohol **7b** (0.47 g, 1.3 mmol, 75 %, 98 % ee). The enantiomeric excess was determined according to Parker's method.[21] R_f = 0.42 (hexanes/ether 1:1); α_D^{25} = +14.30 (c 9.02, $CHCl_3$); IR (neat): 3500 (br), 3030 (w), 2930 (m), 2860 (w), 1456 (m), 1387 (s), 1226 (s), 1189 (s), 1145 (m); ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.41 - 7.24 (m, 5 H), 4.44 (br s, 2 H), 3.46 (br s, 3 H), 1.62 - 1.18 (m, 10 H), 0.87 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 134.7, 128.9, 128.7, 128.6, 68.7, 52.9, 45.9, 37.4, 35.5, 31.7, 25.1, 22.6, 13.9; MS

(EI): *m/z* 192 (14), 91 (100), 57 (5); $C_{16}H_{24}F_3NO_3S$ (367.42); calcd C 52.29, H 6.58, N 3.81; found C 52.03, H 6.37, N 3.94.

(S)-7-(N-Benzyl-N-trifluoromethanesulfonamido)-5-hydroxyheptyl pivalate (**7c**).

Aldehyde **4** (0.99 g, 3.3 mmol) was treated with di(4-pivaloxybutyl)zinc (2.5 equiv) following *procedure 2* yielding aminoalcohol **7c** (1.21 g, 2.6 mmol, 81 %, 35 % ee). The enantiomeric excess was determined according to Parker's method.[21] R_f = 0.09 (hexanes/ether 4:1); α_D^{25} = +8.54 (c 13.11, $CHCl_3$); IR (neat): 3500 (br), 3037 (w), 2960 (s), 2875 (m), 1728 (s), 1458 (m), 1385 (s), 1285 (s), 1188 (s); ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.33 - 7.26 (m, 5 H), 4.12 (br s, 2 H), 3.95 (t, *J* = 6.5 Hz, 2 H), 3.40 (m, 3 H), 1.54 - 1.31 (m, 8 H), 1.13 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 178.5, 134.6, 128.9, 128.6, 125.5, 120.1 (q, *J* = 321.5 Hz), 68.3, 63.9, 52.8, 45.9, 36.6, 36.8, 35.5, 28.4, 27.1, 21.8; MS (EI): *m/z* 320 (19), 91 (100), 57 (56); $C_{20}H_{30}F_3NO_5S$ (453.51); calcd C 52.96, H 6.67, N 3.09; found C 52.91, H 6.74, N 3.18.

(S)-1-(N-Benzyl-N-tert-butoxycarbonyl)pentan-3-ol (**10a**).

Aldehyde **8** (1.32 g, 5.0 mmol) was treated with diethylzinc (2.0 equiv) following *procedure 2* yielding aminoalcohol **10a** (1.31 g, 4.5 mmol, 89 %, >98 % ee). The enantiomeric excess was determined by HPLC analysis; Chiracel OD, heptane/isopropanol = 93 : 7; flow 0.6 mL/min. (6.92 min : minor isomer, 7.35 min : major isomer).[26] R_f = 0.14 (hexanes/ether 2:1); α_D^{25} = -11.2 (c 4.09, $CHCl_3$); IR (neat): 3500 (s), 3030 (w), 2970 (s), 2880 (s), 1675 (s), 1480 (s), 1250 (s), 1170 (s), 1070 (m); ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.29 - 7.15 (m, 5 H), 4.50 - 4.16 (m, 4 H), 3.72 (br, 1 H), 3.36 (br, 1 H), 2.96 (br, 1 H), 1.61 (br, 2 H), 1.40 (s, 9 H), 0.79 (t, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.2, 128.4, 127.2, 127.1, 80.2, 69.1, 50.4, 42.9, 34.9, 29.7, 28.3, 10.1; MS (EI): *m/z* 293 (M^+, 0.8), 237 (9), 120 (40), 106 (27), 91 (100), 57 (82); $C_{17}H_{27}NO_3$ (293.40); calcd C 69.59, H 9.28, N 4.78; found C 69.21, H 9.21, N 4.50.

(S)-1-(N-Benzyl-N-tert-butoxycarbonyl)octan-3-ol (**10b**).

Aldehyde **8** (1.24 g, 4.7 mmol) was treated with dipentylzinc (2.5 equiv) following *procedure 2* yielding aminoalcohol **10b** (1.42 g, 4.2 mmol, 90 %, >98 % ee). The enantiomeric excess was determined by HPLC analysis; Chiracel OD, heptane/isopropanol = 93 : 7; flow 0.6 mL/min. (6.39 min : minor isomer, 6.98 min : major isomer).[26] R_f = 0.09 (hexanes/ether 2:1); α_D^{25} = -7.3 (c 1.51, $CHCl_3$); IR (neat): 3500 (br), 3030 (w), 2930 (s), 2860 (m), 1690 (s), 1470 (w), 1420 (s), 1240 (m), 1170 (s), 1130 (m); ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.31 - 7.17 (m, 5 H), 4.35 - 4.18 (m, 2 H), 3.98 - 3.76 (m, 2 H), 3.45 (br, 1 H), 2.98 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.2, 128.4, 127.2, 127.1, 80.2, 69.1, 50.4, 42.9, 34.9, 29.7, 28.3, 10.1; MS (EI): *m/z* 335 (M^+, 1.29), 279 (8), 234 (8), 208 (4), 120 (5), 106 (39), 91 (100), 57 (76); $C_{20}H_{33}NO_3$ (335.47); calcd C 61.70, H 9.91, N 4.18; found C 61.39, H 9.55, N 3.97.

(S)-6-(N-Benzyl-N-tert-butoxycarbonyl)-3-hydroxyhexyl pivalate (**10c**).

Aldehyde **8** (1.14 g, 4.3 mmol) was treated with di(3-pivaloxypropyl)zinc (2.1 equiv) following *procedure 2* yielding aminoalcohol **10c** (1.39 g, 3.4 mmol, 79 %, 95 % ee). The enantiomeric excess was determined by HPLC analysis; Chiracel OD, heptane/isopropanol = 93 : 7; flow 0.6 mL/min. (12.70 min : minor isomer, 13.99 min : major isomer).[26] R_f = 0.10 (hexanes/ether 2:1); α_D^{25} = -89.6 (c 3.81, $CHCl_3$); IR (neat): 3500 (br), 3090

(w), 3030 (s), 2980 (m), 1725 (s), 1700 (s), 1690 (s), 1490 (s), 1410 (s), 1300 (s), 1180 (s); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.29 - 7.15 (m, 5 H), 4.51 (s, 1 H), 4.46 (s, 1 H), 4.21 - 4.07 (m, 3 H), 3.99 (t, *J* = 6.6 Hz, 2 H), 3.76 (br, 1 H), 3.42 (m, 2 H), 2.94 (br, 2 H), 1.72 - 1.50 (m, 4 H), 1.36 (s, 9 H), 1.16 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 178.6, 138.3, 128.6, 127.4, 80.6, 67.4, 64.5, 50.7, 43.1, 38.8, 35.7, 33.3, 28.5, 27.3, 25.3; MS (EI): *m/z* 120 (2), 85 (67), 83 (100), 47 (23); $C_{23}H_{37}NO_5$ (407.54); calcd C 67.78, H 9.15, N 3.44; found C 67.34, H 8.77, N 3.06.

(S)-7-(N-Benzyl-N-tert-butoxycarbonyl)-5-hydroxyheptyl pivalate (**10d**).

Aldehyde **8** (1.52 g, 5.8 mmol) was treated with di(3-pivaloxybutyl)zinc (2.3 equiv) following *procedure 2* yielding aminoalcohol **10d** (2.13 g, 5.1 mmol, 87 %, 96 % ee). The enantiomeric excess was determined by HPLC analysis; Chiracel OD, heptane/isopropanol = 93 : 7; flow 0.6 mL/min. (12.23 min : minor isomer, 18.75 min : major isomer).[26] R_f = 0.12 (hexanes/ether 2:1); α_D^{25} = -80,0 (c 1.50, $CHCl_3$); IR (neat): 3500 (br), 3030 (w), 2980 (s), 2870 (m), 1730 (s), 1700 (s), 1680 (s), 1480 (m), 1420 (m), 1290 (m), 1160 (s); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.27 - 7.14 (m, 5 H), 4.49 (s, 1 H), 4.44 (s, 1 H), 4.19 - 4.14 (m, 2 H), 3.97 (t, *J* = 6.6 Hz, 2 H), 3.72 (br, 1 H), 3.41 (br, 2 H), 2.94 (br, 2 H), 1.57 (m, 4 H), 1.39 (s, 9 H), 1.26 (m, 2 H), 1.12 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 178.7, 138.3, 128.6, 127.4, 80.5, 67.7, 64.5, 50.7, 43.1, 38.8, 36.9, 35.7, 28.7, 28.5, 27.3, 26.1, 25.7; MS (EI): *m/z* 421 (M^+, 0.03), 348 (2), 220 (5), 120 (61), 106 (71), 91 (75), 57 (100); $C_{24}H_{39}NO_5$ (421.56); HRMS: calcd.: 421.2818; found : 421.2819.

(S)-8-(N-Benzyl-N-tert-butoxycarbonyl)-6-hydroxyoctyl pivalate (**10e**).

Aldehyde **8** (1.52 g, 5.8 mmol) was treated with di(5-pivaloxypentyl)zinc (2.3 equiv) following *procedure 2* yielding aminoalcohol **10e** (2.27 g, 5.2, 90 %, 97 % ee). The enantiomeric excess was determined by HPLC analysis; Chiracel OD, heptane/isopropanol = 95 : 5; flow 0.6 mL/min. (13.35 min : minor isomer, 15.37 min : major isomer).[26] R_f = 0.14 (hexanes/ether 2:1); α_D^{25} = -70.7 (c 3.25, $CHCl_3$); IR (neat): 3500 (br), 3030 (w), 2940 (s), 2870 (m), 1730 (s), 1690 (s), 1480 (m), 1420 (m), 1370 (m), 1290 (m), 1180 (s); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.27 - 7.13 (m, 5 H), 4.48 (s, 1 H), 4.43 (s, 1 H), 4.20 (br, 2 H), 3.97 (t, *J* = 6.5 Hz, 2 H), 3.72 - 3.58 (br, 2 H), 3.41 (br, 2 H), 2.95 (br, 2 H), 2.59 - 1.50 (m, 2 H), 1.39 (s, 9 H), 1.34 - 1.31 (m, 2 H), 1.12 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 178.6, 154.0, 138.3, 128.5, 127.3, 80.4, 67.5, 64.3, 50.6, 43.1, 38.7, 36.5, 35.7, 28.6, 28.4, 27.2, 22.3; MS (EI): *m/z* 435 (M^+, 0.04), 362 (2), 334 (14), 164 (12), 120 (75), 106 (72), 91 (87), 57 (100), 41 (19); $C_{25}H_{41}NO_5$ (435.59); HRMS: calcd 435.29770; found C 435.29778.

(S)-1-(N-Benzyl-N-tert-butoxycarbonyl)butan-2-ol (**12**).

Aldehyde **11** (1.0 g, 4.0 mmol) was treated with diethylzinc (2.5 equiv) following *procedure 2* yielding aminoalcohol **12** (0.47 g, 1.6 mmol, 42 %, 24 % ee). The enantiomeric excess was determined by HPLC analysis; Chiracel OD, heptane/isopropanol = 95 : 5; flow 0.6 mL/min. (7.68 min : minor isomer, 9.20 min : major isomer).[26] R_f = 0.04 (hexanes/ether 4:1); α_D^{25} = -1.34 (c 11.21, $CHCl_3$); IR (neat): 3500 (br), 3030 (w), 2975 (s), 2930 (m), 2880 (m), 1694 (s), 1455 (s), 2366 (s), 1166 (s); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.31 - 7.17 (m, 5 H), 4.46 (br s, 2 H), 3.64 (s, 1 H), 3.42 (br s, 1+1 H), 3.14 (s, 2 H), 1.42 (s, 9 H), 0.87 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.1, 128.6, 128.4, 127.1, 80.4, 72.6, 53.2, 52.2, 28.3, 27.9, 9.6; MS

(EI): *m/z* 279 (M^+,0.5), 205 (14), 165 (22), 164 (12), 120 (49), 91 (100), 59 (22), 57 (73); $C_{16}H_{25}NO_3$ (279.37); calcd C 68.78, H 9.02, N 5.01; found C 68.73, H 8.89, N 5.24.

(S)-1-(N-Benzyl-N-tert-butoxycarbonyl)hex-2-en-4-ol (**14a**).

Aldehyde **13** (0.63 g, 2.3mmol) was treated with diethylzinc (2.0 equiv) following *procedure 2* yielding aminoalcohol **14a** (0.60 g, 1.9 mmol, 86 %, 89 % ee). The enantiomeric excess was determined by HPLC analysis; Chiracel OD, heptane/isopropanol = 95 : 5; flow 0.6 mL/min. (10.29 min : minor isomer, 13.23 min : major isomer).[27] R_f = 0.07 (hexanes/ether 2:1); α_D^{25} = +2.6 (c 3.83, $CHCl_3$); IR (neat): 3500 (br), 3033 (w), 2965 (m), 2870 (m), 1696 (s), 1455 (m), 1416 (m), 1246 (m), 1167 (s); ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.28 - 7.16 (m, 5 H), 5.45 (br s, 2 H), 4.33 (br s, 2 H), 3.91 (br s, 1 H), 3.76 - 3.66 (br s, 2 H), 1.70 (br s, 1 H), 1.41 (s, 9 H), 0.81 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 156.4, 138.2, 135.6, 128.3, 127.7, 127.3, 127.0, 126.2, 79.8, 73.4, 49.5, 47.5, 20.8, 18.3, 9.1; MS (EI): *m/z* 305 (M^+, 0.7, 231 (29), 150 (21), 98 (12), 91 (100), 83 (24), 57 (71), 41 (19); $C_{18}H_{26}NO_3$ (304.40); calcd C 70.78, H 8.91, N 4.59; found C 70.61, H 8.79, N 4.43.

(E)-(S)-1-(N-Benzyl-N-tert-butoxycarbonyl)non-2-en-4-ol (**14b**).

Aldehyde **13** (0.63 g, 2.3 mmol) was treated with dipentylzinc (2.0 equiv) following *procedure 2* yielding aminoalcohol **14b** (0.55 g, 1.6 mmol, 69 %, 90 % ee). The enantiomeric excess was determined by HPLC analysis; Chiracel OD, heptane/isopropanol = 95 : 5; flow 0.6 mL/min. (10.10 min : minor isomer, 12.80 min : major isomer).[27] R_f = 0.09 (hexanes/ether 2:1); α_D^{25} = +1.8 (c 5.2, $CHCl_3$); IR (neat) 3500 (br), 3030 (w), 2930 (s), 2860 (m), 1697 (s), 1454 (s), 1415 (s), 1246 (m), 1170 (s); ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.35 - 7.23 (m, 5 H), 5.54 (br s, 2 H), 4.40 (br s, 2 H), 4.05 (dd, *J* = 14.8 Hz, 6.0 Hz, 1 H), 3.75 (br s, 2 H), 1.65 (1 H), 1.48 (s, 9 H), 1.42 - 1.35 (m, 6 H), 0.89 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 156.3, 138.5, 136.0, 128.5, 127.5, 127.2, 126.2, 79.9, 72.3, 49.7, 47.7, 37.2, 31.8, 28.5, 25.1, 22.6, 14.1; MS (EI): *m/z* 291 (2), 273 (6), 150 (9), 108 (11), 91 (100), 60 (12), 57 (35), 41 (22); $C_{21}H_{33}NO_3$ (347.48); calcd C 72.58, H 9.57, N 4.03; found C 72.32, H 9.55, N 3.97.

(E)-(S)-7-(N-Benzyl-N-tert-butoxycarbonyl)-4-hydroxy-5-heptenyl pivalate (**14c**).

Aldehyde **13** (1.08 g, 3.9 mmol) was treated with di(3-pivaloxypropyl)zinc (2.4 equiv) following *procedure 2* yielding aminoalcohol **14c** (1.08 g, 2.6 mmol, 66 %, 79 % ee). The enantiomeric excess was determined by HPLC analysis; Chiracel OD, heptane/isopropanol = 95 : 5; flow 0.6 mL/min. (15.41 min : minor isomer, 23.12 min : major isomer).[27] R_f = 0.08 (hexanes/ether 2:1); α_D^{25} = -0.52 (c 13.4, $CHCl_3$); IR (neat): 3500 (br), 3030 (w), 2975 (s), 1728 (s), 1694 (s), 1481 (s), 1418 (s), 1370 (s), 1165 (s); ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.34 - 7.20 (m, 5 H), 5.52 (br s, 2 H), 4.39 (br s, 2 H), 4.06 (t, *J* = 6.5 Hz, 2 H), 3.75 (br s, 2 H), 1.77 - 1.51 (m, 4 H), 1.47 (s, 9 H), 1.19 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 178.5, 156.4, 135.4, 128.4, 127.1, 126.6, 79.9, 71.7, 64.1, 49.6, 47.6, 38.7, 33.3, 28.3, 27.1, 24.6; MS (EI): *m/z* 150 (1), 103 (12),, 91 (10), 85 (12), 57 (100), 41 (26); $C_{24}H_{37}NO_5$ (419.55); calcd C 68.70, H 8.89, N 3.33; found C 68.55, H 8.91, N 3.52.

(E)-(S)-8-(N-Benzyl-N-tert-butoxycarbonyl)-5-hydroxy-6 octenyl pivalate (**14d**).

Aldehyde **13** (1.48 g, 3.4 mmol) was treated with di(3-pivaloxybutyl)zinc (2.4 equiv) following *procedure 2* yielding aminoalcohol **14d** (1.98 g, 4.6 mmol, 85 %, 87 % ee). The enantiomeric excess was determined by HPLC analysis; Chiracel OD, heptane/isopropanol = 95 : 5; flow 0.6 mL/min. (21.60 min : minor isomer, 24.54 min : major isomer).[28] R_f = 0.17 (hexanes/ether 2:1); α_D^{25} = -1.34 (c 8.19, $CHCl_3$); IR (neat): 3030 (w), 2974 (s), 2875 (w), 1727 (s), 1695 (s), 1457 (w), 1414 (m), 1285 (m), 1162 (s); ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.26 - 7.15 (m, 5 H), 5.45 (br s, 2 H), 4.32 (br s, 2 H), 3.97 (t, *J* = 6.6 Hz, 2 H), 3.66 (br s, 2 H), 1.77 (s, 1 H), 1.61 - 1.43 (m, 6 H), 1.39 (s, 9 H), 1.11 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 178.6, 156.4, 138.3, 135.5, 128.3, 127.3, 127.1, 126.3, 79.9, 71.8, 64.1, 62.2, 49.7, 47.6, 38.6, 36.6, 29.0, 28.4, 27.1, 25.1, 21.7; MS (EI): *m/z* 315 (1), 103 (18), 91 (20), 85 (11), 57 (100), 55 (20), 41 (22); $C_{25}H_{39}NO_5$ (433.57); calcd C 69.25, H 9.07, N 3.23; found C 68.91, H 8.78, N 3.15.

(E)-(S)-9-(N-Benzyl-N-tert-butoxycarbonyl)-6-hydroxy-7-nonenyl pivalate (**14e**).

Aldehyde **13** (0.94 g, 3.4 mmol) was treated with di(5-pivaloxypentyl)zinc (3.3 equiv) following *procedure 2* yielding aminoalcohol **14e** (1.98 g, 4.6 mmol, 75 %, 90 % ee). The enantiomeric excess was determined by HPLC analysis; Chiracel OD, heptane/isopropanol = 95 : 5; flow 0.6 mL/min. (14.41 min : minor isomer, 21.43 min : major isomer)[27] R_f = 0.07 (hexanes/ether 2:1); α_D^{25} = -1.14 (c 4.93, $CHCl_3$); IR (neat): 3500 (br), 3060 (w), 2986 (s), 2870 (s), 1731 (s), 1683 (s), 1460 (s), 1415 (s), 1287 (s), 1190 (s), 1165 (s); ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.27 - 7.15 (m, 5 H), 5.45 (br s, 2 H), 4.32 (s, 2 H), 3.99 (dd, *J* = 16.0 Hz, *J* = 6.4 Hz, 1 H), 3.74 - 3.66 (m, 2 H), 3.56 (t, *J* = 6.5 Hz, 2 H), 1.84 (br s, 2 H), 1.64 - 1.48 (m, 8 H), 1.40 (s, 9 H), 1.12 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 178.7, 156.6, 138.4, 135.6, 128.5, 127.5, 127.2, 126.3, 79.9, 72.2, 64.3, 52.6, 49.8, 47.8, 38.8, 37.1, 32.3, 28.7, 28.5, 27.3, 25.9, 28.1, 22.3; MS (EI): *m/z* 103 (20), 85 (20), 69 (36), 68 (44), 57 (100), 41 (33); $C_{26}H_{41}NO_5$ (447.60); calcd C 69.76, H 9.23, N 3.23; found C 69.50, H 8.91, N 3.02.

(2S, 3S)-2-Dibenzylamino-1-phenylpentan-3-ol (***syn*-16a**).

Aldehyde **15** (0.66 g, 2.0 mmol) was treated with diethylzinc (0.35 mL, 2.8 mmol) and $(Me_3SiCH_2)_2Zn$ (0.76 g, 3.2 mmol) following *procedure 3* using catalyst **2**, yielding aminoalcohol ***syn*-16a** (532 mg, 1.48 mmol, 74 %) after chromatographical separation of the crude product (hexanes/Et_2O 9:1 → 4:1). The diastereomeric ratio 16 : 84 (***anti* : *syn***) of the crude product was determined by ^1H NMR and ^{13}C NMR spectroscopy. R_f = 0.11 (hexanes/ether 2:1); α_D^{25} = +16.44 (c 5.17, $CHCl_3$); IR (neat): 3500 (br), 3026 (s), 2930 (s), 2860 (s), 2800 (m), 1602 (w), 1493 (s), 1450 (s), 1360 (m); ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.40 - 7.26 (m, 15 H), 3.72 (m, 4 H), 3.11 (m, 2 H), 2.85 (q, *J* = 7.3, 1H), 2.17 (s, 1 H), 1.78 (m, 1 H), 1.43 (m, 1 H), 0.99 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 140.9, 140.0, 129.5, 128.9, 128.4, 128.3, 127.0, 125.9, 73.4, 63.2, 55.1, 32.0, 29.2, 28.0, 10.9; $C_{25}H_{29}NO$ (359.49). The obtained analytical data is identical to the literature.[19]

(2S, 3R)-2-Dibenzylamino-1-phenylpentan-3-ol (***anti*-16b**).

Aldehyde **15** (0.66 g, 2.0 mmol) was treated with diethylzinc (0.35 mL, 2.8 mmol) and $(Me_3SiCH_2)_2Zn$ (0.76 g, 3.2 mmol) following *procedure 3* using catalyst ***ent*-2**, yielding aminoalcohol ***anti*-16b** (474 mg, 1.32 mmol, 66 %) after chromatographical separation of the crude product (hexanes/Et_2O 9:1 → 4:1). The diastereomeric ratio 96 : >4 (***anti* : *syn***) of the crude product was determined by ^1H NMR and ^{13}C NMR spectroscopy. R_f =

0.24 (hexanes/ether 2:1); α_D^{25} = +26.44 (c 2.08, $CHCl_3$); IR (neat): 3500 (br), 3026 (s), 2930 (s), 2860 (s), 2800 (m), 1602 (w), 1493 (s), 1450 (s), 1360 (m); ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.38 - 7.23 (m, 15 H), 4.45 (s, 1 H), 3.95 (s, 1 H), 3.91 (s, 1 H), 3.56 (dt, *J* = 8.2 Hz, *J* = 3.7 Hz) 3.42 (s, 1 H), 3.38 (s, 1 H), 3.11 (m, 1 H), 2.93 (m, 1 H), 2.70 (m, 1 H), 1.52 (m, 1 H), 1.14 (m, 1 H), 0.83 (t, *J* = 7.38 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 140.6, 138.9, 129.4, 129.2, 128.5, 128.4, 127.2, 126.2, 71.6, 63.5, 53.9, 32.4, 27.0, 9.8; $C_{25}H_{29}NO$ (359.49). The obtained analytical data are identical to those of the literature.[19]

(5R, 6S)-6-Dibenzylamino-5-hydroxy-7-phenylheptyl pivalate (***syn*-16c**).

Aldehyde **15** (686 mg, 2.1 mmol) was treated with di(4-pivaloxybutyl)zinc (2.3 mmol, 1.1 equiv) and $(Me_3SiCH_2)_2Zn$ (0.76 g, 3.2 mmol, 1.5 equiv) following *procedure 3* using catalyst **2**, yielding aminoalcohol ***syn*-16c** (480 mg, 0.99 mmol, 47 %) after chromatographical separation of the crude product (hexanes/Et_2O 4:1 → 2:1). The diastereomeric ratio 16 : 84 (***anti* : *syn***) of the crude product was determined by ^1H NMR and ^{13}C NMR spectroscopy R_f = 0.36 (hexanes/ether 2:1); α_D^{25} = +19.75 (c 1.62, $CHCl_3$); IR (neat) 3500 (br), 3026 (s), 2930 (s), 2860 (s), 2800 (m), 1602 (w), 1493 (s), 1450 (s), 1360 (m); ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.25 - 7.15 (m, 15 H), 4.02 (t, *J* = 5.8 Hz, 2 H), 3.79 - 3.62 (m, 4 H), 3.04 (m, 2 H), 2.81 (m, 2 H), 2.19 (s, 1 H), 1.59 - 1.37 (m, 6 H), 1.21 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 178.5, 140.5, 139.7, 129.3, 128.7, 128.3, 128.2, 126.9, 125.9, 71.4, 64.2, 63.2, 55.1, 38.7, 34.3, 31.9, 28.5, 27.2, 22.7; MS (EI): *m/z* 486 (M^+, 0.2), 472 (1), 397 (11), 330 (5), 300 (79), 91 (100); $C_{32}H_{40}NO_3$ (486.65); HRMS: calcd 486.3007; found 486.3039.

(5S, 6S)-6-Dibenzylamino-5-hydroxy-7-phenylheptyl pivalate (***anti*-16d**).

Aldehyde **15** (686 mg, 2.1 mmol) was treated with di(4-pivaloxybutyl)zinc (2.3 mmol, 1.1 equiv) and $(Me_3SiCH_2)_2Zn$ (0.76 g, 3.2 mmol, 1.5 equiv) following *procedure 3* using catalyst *ent*-**2**, yielding aminoalcohol ***anti*-16d** (480 mg, 0.99 mmol, 36 %) after chromatographical separation of the crude product (hexanes/Et_2O 4:1 → 2:1). The diastereomeric ratio 85 : 16 (***anti* : *syn***) of the crude product was determined by ^1H NMR and ^{13}C NMR spectroscopy R_f = 0.17 (hexanes/ether 2:1); α_D^{25} = +10.17 (c 1.77, $CHCl_3$); IR (neat) 3500 (br), 3030 (s), 2870 (s), 1640 (s), 1560 (m),1490 (s), 1200 (s), 1110 (s); ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.36 - 7.14 (m, 15 H), 3.99 (t, *J* = 6.5 Hz, 2 H), 3.79 - 3.60 (m, 4 H), 3.12 - 2.99 (m, 2 H), 2.81 - 2.75 (m, 2 H), 2.15 (s, 1 H), 1.65 - 1.25 (m, 6 H), 1.18 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 178.6, 140.5, 139.7, 129.3, 128.8, 128.4, 128.3, 127.1, 126.0, 71.7, 64.2, 63.3, 55.2, 38.7, 34.3, 31.9, 28.6, 27.2, 22.7; MS (EI): *m/z* 397 (1), 396 (12), 301 (19), 300 (100), 92 (5), 91 (83), 57 (6); $C_{32}H_{40}NO_3$ (486.65); HRMS: calcd C 78.97, H 8.29, N 2.89; found C 78.76, H 7.99, N 2.65.

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