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New chiral amino alcohol ligands for catalytic enantioselective addition of diethylzinc to aldehydes

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Abstract. A study aimed at the synthesis and structure optimization of new, efficient, optically active β-amino alcohol ligands with a structure suitable for immobilization on magnetite nanoparticles has been carried out. The optimized homogeneous amino alcohol catalysts **13a** and **13b**, the chirality of which arises from the Sharpless epoxidation of suitable allyl alcohols, were tested by employing the well-established enantioselective amino alcohol-promoted addition of diethylzinc to benzaldehyde giving the corresponding benzyl alcohol with nearly quantitative yield and ee=95%. Then their broad applicability as chiral catalysts was evaluated by carrying out the same reaction on a family of aldehydes, including variously substituted aromatic ones as well as an aliphatic analogue. The results have confirmed the validity of the fine-tuning process performed on ligands **13a** and **13b**. In fact, both exhibited excellent catalytic activity as demonstrated by the chemical yields and *ee* obtained from all the tested aldehydes, almost independent of the position and type of substitution in the aromatic ring.

Introduction

In recent decades, research on asymmetric catalysis has grown considerably, culminating in award of the 2001 Nobel Prize in Chemistry to Knowles,[1] Noyori[2] and Sharpless[3] "for their work on chirally catalyzed hydrogenation and oxidation reactions". Most of the chiral catalysts developed so far are small, optically active organic molecules able to form complexes with transition metals trough heteroatoms incorporated in their structure (commonly P, O, N, S). Research on new efficient catalysts relies mostly on trial-and-error, thereby having a consistent number of structurally correlated molecules, available for testing in the selected enantioselective reaction becomes a decisive factor. For this reason, it is important to design a structure which includes an easily tunable site, in order to access to many potential catalysts with relatively modest effort.

β-amino alcohols represent one of the most studied classes of chiral ligands/auxiliaries. They have been used, both in acyclic- and cyclic-derivative form, since the beginning of asymmetric synthesis.[4] Enantioselective addition of organometallic reagents to aldehydes affords optically active secondary alcohols, and, at the same time, leads to the formation of a new C-C bond. After the work of Noyori,[5] 1,2-amino alcohols have become the preferred choice in the enantioselective addition of dialkylzincs to aldehydes. This reaction has become a classical test in the design of new amino alcohol chiral ligands, and many new catalysts have been developed. To mention some examples, N,N-dialkylnorephedrines[6] and substituted aminophenylalcohols[7,8] led to outstanding results. Due to our research on stereocontrolled synthesis of amino alcohols,[9,10] we were involved in the development of a novel class of amino alcohol ligands. Moreover, we focused on the design and synthesis of ligands that display a functionality suitable for their covalent anchoring to magnetite nanoparticles (Figure 1).[11, 12] The use of magnetic nanoparticles has recently led to the development of new catalysts that combine the advantages of both homogeneous and heterogeneous catalysis, leading to easily recyclable highly efficient systems, and thereby reducing the process's economic and environmental effects.[13]

Herein we report the design and synthesis of a novel, versatile and easily tunable class of amino alcohol ligands, developed through the well-established enantioselective addition of diethylzinc to aldehydes. Moreover, it is a specific feature of these new ligands that their stucture is enriched with a functionality for a future immobilization on magnetically recoverable nanoparticles.

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Results and Discussion

Unfunctionalized amino alcohol ligands

First, to understand the influence of regio- and stereochemistry of the amino alcohol moiety on the catalytic activity, amino alcohol ligands **1**, **2**, **3** were prepared (Figure 1).

All the ligands were obtained starting from the optical active epoxy alcohol **5a** carrying out the Sharpless AE on the allylic alcohol **4a**. The epoxy alcohol **5a** was transformed into the corresponding carboxylic acid, and then coupled with allylamine to afford the amide **6a** (Scheme 1).[§] The aminolysis of amide **6a** (Scheme 1) afforded the anti stereochemistry of the amino alcohol moiety in the mixture of regioisomers **1** and **2** (ratio 50:50). In contrast, obtaining the *syn* stereochemistry in the amino alcohol system required a two-step process: an initial oxirane ring opening by means of $MgBr_2$ in diethyl ether at room temperature followed by a nucleophilic substitution by azide (Scheme 2). Finally, the azido alcohol **8** was subjected to reduction employing PPh_3, thereby resulting in the corresponding amino alcohol ligand **3** (Scheme 2).

At this point, these optically active amino alcohols were tested in the addition of diethylzinc to benzaldehyde, employing a 6% molar amount of ligand and performing the reactions at room temperature in toluene. Unfortunately, these ligands had no significant catalytic activity: in all cases, reaction yields were comparable to those obtained in the absence of a ligand (24-44%) and no asymmetric induction was observed.

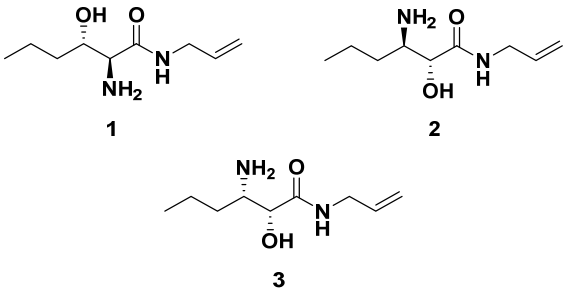
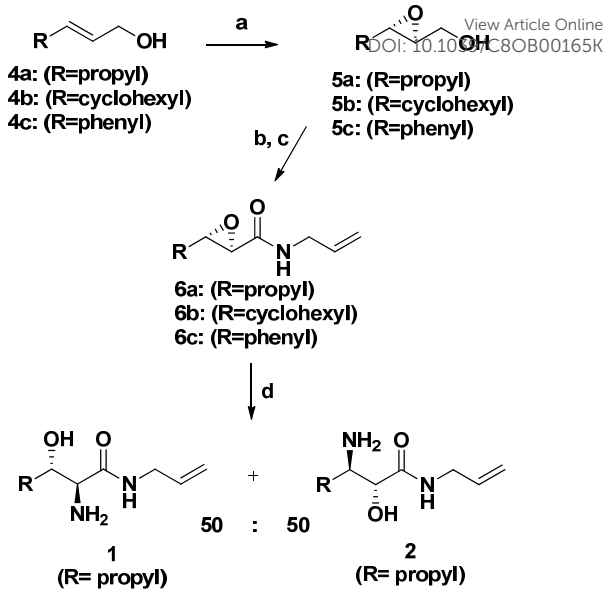
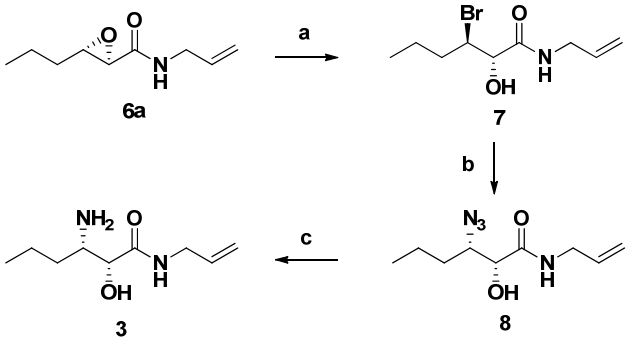


Figure 1: Structure of amino alcohol ligands **1**, **2** and **3**



Scheme 1: a) TBHP, $Ti(O\text{-}iPr)_4$, L-(+)-DET, CH_2Cl_2 dry, -20 °C, 12h, 88% b) $NaIO_4$, $RuCl_3$, CH_3CN/CCl_4/buffer pH 7, r.t., 12h c) allylamine, EDC/HOAt, CH_2Cl_2, r.t., 2h, 53-75% d) NH_3/H_2O, 65 °C, 12 h, 72%

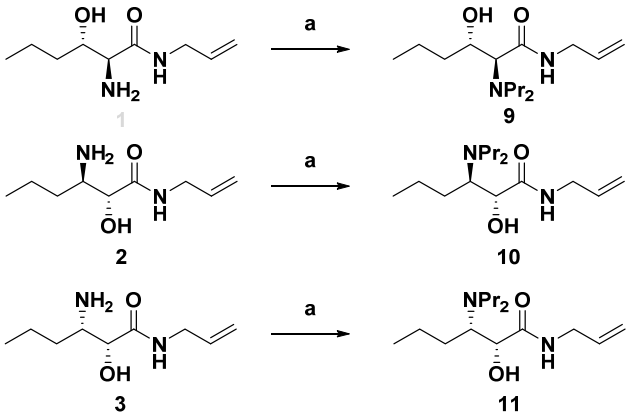


Scheme 2: a) $MgBr_2$, Et_2O, r.t., 8h, 73% b) NaN_3, 18-crown-6, DMSO, 60 °C, 12h, 88% c) PPh_3, $MeOH/H_2O$, r.t., 8h, 68%

N,N-dialkylated amino alcohol ligand

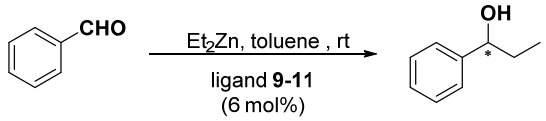
In light of the disappointing results obtained and considering the numerous examples of N,N-dialkylated amino alcohol ligands present in the literature, we decided to functionalize the nitrogen of **1**, **2** and **3**, which afforded the corresponding dipropyl derivatives in moderate yields (Scheme 3).

Amino alcohols **9-11** were then evaluated as ligands in the reaction test. As shown in Table 1, yields increased significantly and enantiomeric excesses, albeit modest, were observed. In particular, these preliminary results seem to indicate that the amino alcohol regiochemistry has no influence on catalytic efficiency (entries 1,2), whereas the *syn* stereochemistry (entry 3) is less efficient than that of the *anti* one (entries 1,2), in agreement with some results already reported.[14]



Scheme 3: a) *n*-PrI, K_2CO_3, CH_3CN, reflux, 12h, 55-70%

Table 1: Addition of Et_2Zn to benzaldehyde catalyzed by ligands **9**, **10** and **11**



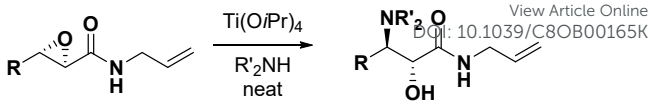
Entry	ligand	yield (%)[b]	*ee* (%)
1	**9**	89	28
2	**10**	86	27
3	**11**	76	0

[a] All the experiments were performed under identical conditions (6h).
[b] Chemical yields are referred to isolated compounds

Screening on the effect of the R and R' groups

The catalytic effect showed by ligands **9** and **10** prompted us to synthetize a set of N,N-dialkylated amino alcohols with different R and R' groups following a previously reported methodology (Scheme 4).[15]

The amino alcohols **12a**-**g** were evaluated as chiral ligands in the reaction test. As shown in Table 2, no significant effects of the R and R' groups were observed: yields were generally very good, even if the level of asymmetric induction remained very moderate. Lower catalytic activity was registered when R=phenyl, although the structure of **12f** and **12g** is very similar to that of efficient enantioselective ligands reported in literature.[7] The collected data have led us to hypothesize that a carbonyl group adjacent to the amino alcohol site has an unfavourable effect on the formation of the chiral complex responsible for the enantiofacial differentiation.[16-17]

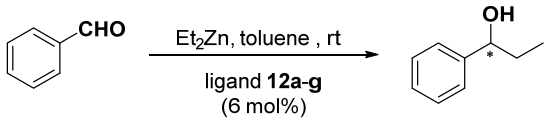


6a R = propyl
6b R = c-hexyl
6c R = phenyl

12a R = propyl NR'$_2$ = dibutylaminyl
12b R = *c*-hexyl NR'$_2$ = dipropylaminyl
12c R = *c*-hexyl NR'$_2$ = dibutylaminyl
12d R = *c*-hexyl NR'$_2$ = piperidinyl
12e R = *c*-hexyl NR'$_2$ = morpholinyl
12f R = phenyl NR'$_2$ = dibutylaminyl
12g R = phenyl NR'2 = piperidinyl

Scheme 4: 12h, r.t., 85-95%

Table 2: Addition of Et_2Zn to benzaldehyde catalyzed by ligands **12a-g**



entry	ligand	yield (%)[b]	*ee* (%)
1	**12a**	87	25
2	**12b**	88	29
3	**12c**	93	31
4	**12d**	78	16
5	**12e**	80	15
6	**12f**	61	7
7	**12g**	50	4

a) All the experiments were performed under identical conditions (6h). [b] Chemical yields are referred to isolated compounds

Optimization of ligand structure

To verify our hypothesis, we introduced a spacer between the carbonyl group and the amino alcohol moiety; in particular, we considered use of a double bond, expected to regioselectively direct the nucleophilic ring opening of the epoxide, to be appropriate. The α,β-unsaturated amides **13a**-**f** and **14** were synthesized in satisfactory yields from the corresponding optically active epoxy alcohol by means of the sequence described in Scheme 5. It is noteworthy that the final aminolysis of the epoxy ring, expected to be effortless due to the high reactivity of the allylic position, required testing of different reaction conditions to enable achievement of the desired amino alcohol in good yields.[§§] In particular, by employing $LiClO_4$ in refluxing acetonitrile, the α,β-unsaturated epoxy amide was completely converted into the corresponding amino alcohol derivatives **13a**-**e**. Whereas R=propyl and cyclohexyl substrates led to a single regioisomer, the reaction on substrate with R=phenyl produced both amino alcohols **13f** and **14**.[§§§]

Finally, the new set of amino alcohols **13a**-**f** and **14** was tested in the usual addition of diethylzinc to benzaldehyde. As reported in Table 3, the results with R=cyclohexyl were

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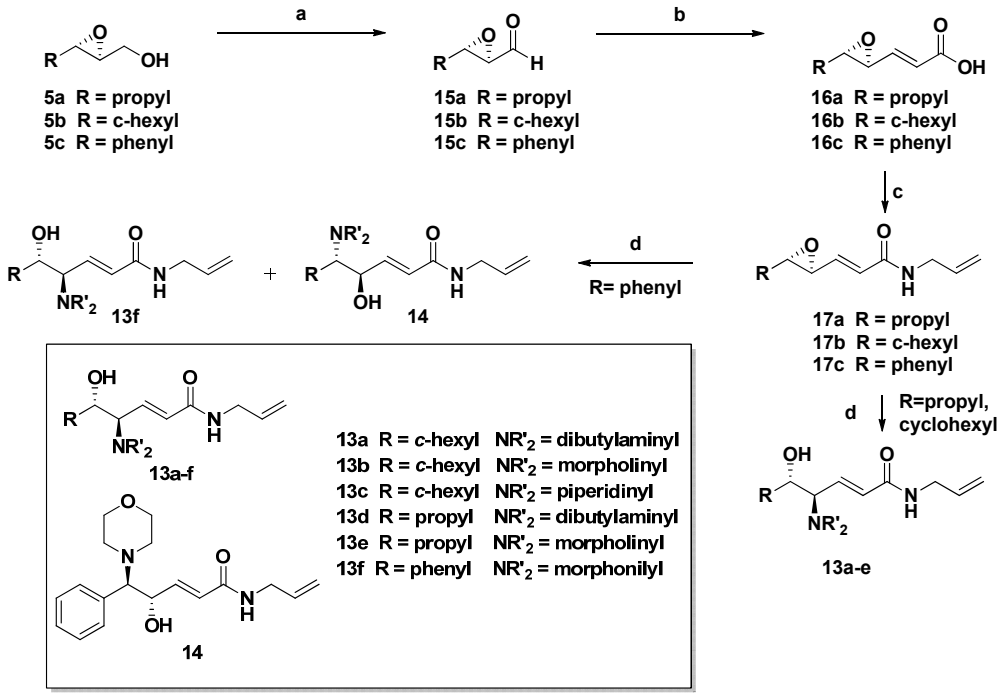
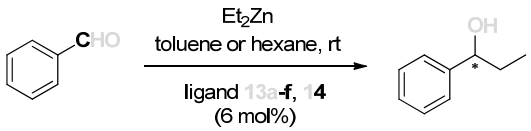
excellent, especially for R'=morpholine and dibutylamine (entries 1 and 2).



Scheme 5: a) TEMPO/IBDA, CH_2Cl_2, r.t., 4h, 72-81% b) diethylphosphonoacetic acid, BuLi, THF, -70°C., 8h c) allylamine, EDC, HOAt, CH_2Cl_2, r.t., 8h, 65-72% from **15** d) $LiClO_4$, R'_2NH, CH_3CN, reflux, 12h, 72-84%

Table 3: Addition of Et_2Zn to benzaldehyde catalyzed by ligands **13a-f** and **14**

Entry	ligand	yield (%)[b]	*ee* (%)
1	**13a**	>95	90
2	**13b**	>95	95
3	**13c**	84	83
4	**13d**	53	10
5	**13e**	39	54
6	**13f**	70	52
7	**14**	71	38



[a] All the experiments were performed under identical conditions (6h).

[b] Chemical yields are referred to isolated compounds

Scope

At this point, with the optimized ligands **13a** and **13b** in hand, we decided to employ them in the addition of diethylzinc to a family of aldehydes, including variously substituted aromatic ones as well as an aliphatic analogue. Results shown in Table 4 have confirmed the consistency of the fine-tuning process performed on ligands. Both **13a** and **13b** exhibited excellent catalytic activity as demonstrated by the chemical yields and *ee* obtained from all the tested aldehydes, almost independent of the position and type of substitution in the aromatic ring. Generally, **13b** seems to be a slightly more efficient ligand than **13a**, the difference being particularly noticeable with 4-MeO-benzaldehyde (entry 7). It is noteworthy that the catalytic efficiency and asymmetric induction remain remarkable also when the tested aldehyde was aliphatic (entry 4).

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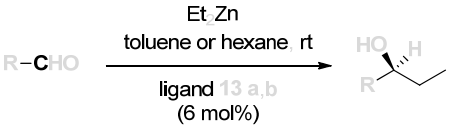
Table 4: Addition of Et_2Zn to different aldehydes catalyzed by ligands **13a** and **13b**



entry	Aldehyde	Yield (%)[b] 13a	Yield (%)[b] 13b	*ee* (%) 13a	*ee* (%) 13b	Product
1	**Benzaldehyde**	>95	>95	90	95	**18a**
2	**1-Naphthaldehyde**	>95	>95	83	97	**18b**
3	**Cinnamaldehyde**	88	88	88	87	**18c**
4	**3-Thiophenecarboxaldehyde**	>95	>95	92	95	**18d**
5	**Cyclohexanecarboxaldehyde**	90	88	88	80	**18e**
6	**2-Methoxybenzaldehyde**	>95	>95	96	96	**18f**
7	**3-Methoxybenzaldehyde**	60	60	92	97	**18g**
8	**4-Methoxybenzaldehyde**	65	99	58	97	**18h**
9	**2-Methylbenzaldehyde**	95	94	95	98	**18i**
10	**3-Methylbenzaldehyde**	>95	>95	93	98	**18j**
11	**4-Methylbenzaldehyde**	>95	>95	92	97	**18k**
12	**2-Fluorobenzaldehyde**	88	88	90	90	**18l**
13	**2-Chlorobenzaldehyde**	>95	>95	91	91	**18m**
14	**3-Bromobenzaldehyde**	>95	>95	88	88	**18n**
15	**4-Bromobenzaldehyde**	89	89	90	97	**18o**
16	**3-Cyanobenzaldehyde**	90	92	89	96	**18p**
17	**4-Cyanobenzaldehyde**	94	93	93	92	**18q**

[a] All the experiments were performed under identical conditions (6h). [b] Chemical yields are referred to isolated compounds

Conclusions

In conclusion, we have designed and fine-tuned new, efficient, optically active β-amino alcohol ligands, the chirality of which arises from the Sharpless epoxidation of suitable allyl alcohols. After optimizing the structures of **13a** and **13b** by employing the well-established enantioselective amino alcohol-promoted addition of diethylzinc to benzaldehyde, their broad applicability as chiral catalysts was evaluated by carrying out the same reaction on a family of aldehydes, including variously substituted aromatic ones as well as an aliphatic analogue. The results confirmed the validity of the fine-tuning process performed on ligands **13a** and **13b**. In fact, both exhibited excellent catalytic activity as demonstrated by the chemical yields and *ee* obtained from all the tested aldehydes, almost independent of the position and type of substitution in the aromatic ring.

In light of the reported results, we are currently investigating the catalytic efficiency of **13a** and **13b** in other reactions catalysed by amino alcohols, as well as the immobilization of the ligands on magnetite nanoparticles.

Experimental Section

General methods and materials

All anhydrous reactions were carried out in flame-dried glassware under argon atmosphere. Unless otherwise stated, commercial reagents were used without further purification. All chromatographic purifications were performed on silica gel (230-400 mesh). Thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F254 plates and visualization was achieved by inspection under UV light (Mineralight UVG 11 254 nm) followed by staining with phosphomolybdic acid dip [polyphosphomolybdic acid (12 g), ethanol (250 mL)] or Ninhydrin dip [ninhydrin (5 g), sulfuric acid (5 mL), *n*-butanol (100mL)]. Organic solvents used for the chemical synthesis and for chromatography were of analytical grade. Benzaldehyde was freshly distilled before use. For all known compounds the spectral characteristics were in agreement with those reported in the literature. NMR spectra

were recorded using a Varian Mercury 300 (^{1}H-NMR 300 MHz and ^{13}C-NMR 75 MHz) and chemical shifts are reported in ppm using the residual solvent peak as a reference. Analytical high performance liquid chromatography (HPLC) was performed using the indicated chiral column. Optical rotations were measured on a digital polarimeter Jasco DIP-370 with a cell path length of 1 cm at 589 nm; solution concentrations are reported in grams per 100 ml. Elemental analyses for C, H, and N were performed on an EA 1110 CHNS-O Instrument.

Synthesis of amino alcohol ligands

The following compounds were prepared following already known procedures[§§§§] and all experimental data were consistent with the ones reported in the literature **5a**,[18] **5b**,[19] **5c**,[18] **12a**,[15] **15a**,[20] **15b**[20]

General procedure for the preparation of compounds 6a, 6b, 6c: The epoxy alcohol (**5a** or **5b** or **5c**) (1 mmol) was dissolved in CCl_4 (2 mL), CH_3CN (2 mL) and phosphate buffer (pH = 7, 0.2 M, 3 mL) with vigorous stirring. Then $NaIO_4$ (2.8 mmol, 600 mg) and $RuCl_3$ (0.05 mmol, 10 mg) were added. After 12 h, CH_2Cl_2 and water were added. The organic layer was separated and the aqueous layer was extracted several times with CH_2Cl_2. The combined organic extracts were dried, concentrated and then filtered on a celite pad. The solvent was removed *in vacuo* affording the crude carboxylic acid. The crude product was dissolved in CH_2Cl_2 (5 mL) and allyl amine (1.1 mmol, 0,08 ml) was added. The solution was added to a solution of 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (170 mg, 1.1 mmol) and 1-Hydroxy-7-azabenzotriazole (136 mg, 1 mmol) in CH_2Cl_2 (5 mL) and the reaction was stirred at room temperature for 2 hours. CH_2Cl_2 and water were added. The organic layer was separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were washed with brine, dried and concentrated *in vacuo.* The crude material was purified by flash chromatography using hexane/EtOAc 70:30 as eluent.

(2*R*,3*S*)-*N*-allyl-3-propyloxirane-2-carboxamide (6a): obtained from **5a,** 130 mg, 75%, pale yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.25 (bs, 1H), 5.83-5.66 (m, 1H), 5.16-5.02 (m, 2H), 3.85-3.74 (m, 2H), 3.19 (d, 1H, *J* = 1.9 Hz), 2.94-2.86 (m, 1H), 1.68-1.36 (m, 4H), 0.93 (t, 3H, *J*=7.0 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 168.2, 133.4, 116.1, 59.1, 55.0, 40.8, 33.4, 18.7, 13.4; Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 64.03; H, 8.95; N, 8.29.

(2*R*,3*S*)-*N*-allyl-3-cyclohexyloxirane-2-carboxamide (6b): obtained from **5b**, 154.8 mg, 74%, pale yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.20 (bs, 1H), 5.89-5.71 (m, 1H), 5.23-5.09 (m, 2H), 3.93-3.81 (m, 2H), 3.30 (d, 1H, *J* = 2.2 Hz), 2.76 (dd, 1H, *J* = 6.4, 2.2 Hz), 1.88-1.62 (m, 5H), 1.40-1.05 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 168.5, 133.6, 116.6, 63.7, 54.3, 41.0, 39.5, 29.0, 28.6, 26.1, 25.5, 25.4. Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.91; H, 9.23; N, 6.82.

(2*R*,3*S*)-*N*-allyl-3-phenyloxirane-2-carboxamide (6c): obtained from **5c**, 107.7 mg, 53%, pale yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.81-7.68 (d, 1H, *J* = 7.2 Hz), 7.53-7.09 (m, 4H), 6.35 (bs, 1H), 6.00-5.72 (m, 1H), 5.30-4.99 (m, 2H), 4.16-3.95 (m, 2H), 3.95-3.77 (m, 1H), 3.55-3.40 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.2, 133.3, 131.2, 128.8, 128.4, 128.2, 126.8, 125.6, 116.5, 58.7, 42.2, 41.1. Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 71.15; H, 6.48; N, 6.92.

General procedure for the preparation of compounds 1 and 2: In a sealed tube epoxy amide **6a** (169 mg, 1 mmol) was placed and treated with aq 33% NH_4OH (10 mL). After two days with stirring at 60 °C the reaction mixture was concentrated *in vacuo* to give a pale yellow oil. The crude material was purified by flash chromatography (chloroform/methanol 92:8) giving **1**, 65 mg, 35% and **2**, 69 mg, 37%.

(2*S*,3*S*)-*N*-allyl-2-amino-3-hydroxyhexanamide 1: $[\alpha]^{25}_D$= -7.8 (c=1.6 in CH_3OH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.62 (bt, 1H, *J*= 5.6 Hz), 5.83-5.67 (m, 1H), 5.17-5.01 (m, 2H), 3.83-3.70 (m, 3H), 3.31 (d, 1H, *J*= 5.4 Hz), 2.89-2.71 (bs, 3H), 1.53-1.21 (m, 4H), 0.83 (t, *J*=7.1 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 173.9, 133.9, 116.2, 72.7, 59.2, 41.4, 34.2, 18.8, 14.0; Anal. Calcd for $C_9H_{18}N_2O_2$: C, 58.04; H, 9.74; N, 15.04. Found: C, 58.25; H, 9.75; N, 15.08.

(2*R*,3*R*)-*N*-allyl-3-amino-2-hydroxyhexanamide 2: $[\alpha]^{25}_D$= 31.1 (c=3.3 in CH_3OH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.48 (bt, 1H, *J*=6.0 Hz), 5.86-.71 (m, 1H), 5.20-5.05 (m, 2H), 4.01 (d, 1H, *J*=4.1 Hz), 3.89-3.80 (m, 2H), 3.50-3.20 (bs, 3H), 3.15-3.06 (m, 1H), 1.46-1.14 (m, 4H), 0.86 (t, 3H, *J*=6.5 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 172.7, 134.0, 116.3, 74.2, 53.6, 41.3, 33.6, 19.3, 14.1; Anal. Calcd for $C_9H_{18}N_2O_2$: C, 58.04; H, 9.74; N, 15.04. Found: C, 58.28; H, 9.85; N, 15.18.

(2*S*,3*R*)-*N*-allyl-3-bromo-2-hydroxyhexanamide 7: To a solution of compound **6a** (169 mg, 1 mmol) in Et_2O (15 mL) at -20°C under argon, $MgBr_2{\cdot}OEt_2$ (390 mg, 1.5 mmol) was added and the mixture was stirred for 12 h. The mixture was diluted with Et_2O and washed with water and brine. The organic layer was dried and concentrated *in vacuo*. The crude material was purified by flash chromatography (hexane/EtOAc 70:30) affording **7**. 182 mg, 73%, yellowish; $[\alpha]^{25}_D$= 51.3 (c=3.6 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.06 (bs, 1H), 5.88-5.68 (m, 1H), 5.23-5.03 (m, 2H), 4.53-4.30 (m, 2H), 4.05 (d, 1H, J=4.4 Hz), 3.90-3.81 (m, 2H), 1.88-1.70 (m, 1H), 1.62-1.45 (m, 2H), 1.44-1.25 (m, 1H), 0.88 (t, J=6.9 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 169.8, 133.4, 116.7, 76.0, 59.1, 41.4, 33.9, 21.1, 13.2; Anal. Calcd for $C_9H_{16}BrNO_2$: C, 43.22; H, 6.45; N, 5.60. Found: C, 43.35; H, 6.45; N, 5.65.

(2*R*,3*S*)-*N*-allyl-3-azido-2-hydroxyhexanamide 8: A solution of compound **7** (250 mg, 1 mmol), NaN_3 (260, 4 mmol) and 18-crown-6 (135 mg, 0.51 mmol) in DMSO (1.0 mL) was stirred at 65 °C under argon for 12 h. The mixture was diluted with Et_2O and washed several times with water and brine. The organic layer was then dried and concentrated *in vacuo*. Chromatographic purification (hexane/EtOAc 70:30) afforded **8**. 187 mg, 88%, pale yellow oil, $[\alpha]^{25}_D$= 24.5 (c=3.6 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.17 (bs, 1H), 5.89-5.70 (m, 1H), 5.25-5.08 (m, 2H), 4.70 (d, 1H, *J*=6.2 Hz), 4.10 (d, 1H, *J*=3.9 Hz), 3.92-3.80 (m, 2H), 3.72-3.64 (m, 1H), 1.77-1,33 (m, 4H), 0.93 (t, 3H, *J*= 6.5 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 172.1, 133.3, 116.3, 73.5, 62.9, 41.5, 32.3, 19.3, 13.6; Anal. Calcd for $C_9H_{16}N_4O_2$: C, 50.93; H, 7.60; N, 26.40. Found: C, 51.09; H, 7.65; N, 26.48.

***(2R,3S)-N*-allyl-3-amino-2-hydroxyhexanamide 3:** To a solution of **8** (186 mg, 1 mmol) in MeOH (15 ml) H_2O (1.5 ml) and PPh_3 (393 mg, 1.5 mmol) were added and allowed to stirred at room temperature for 12 h. Methanol was then evaporated and the aqueous layer extracted with $CHCl_3$. The organic layer was dried

and concentrated *in vacuo*. The crude product was purified by flash chromatography ($CHCl_3$/MeOH 98:2) giving **3**, 126.6 mg, 68%, pale yellow oil; $[\alpha]^{25}_D$= 12.5 (c=2.6 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.01 (bs, 1H), 5.90-5.67 (m, 1H), 5.24-5.01 (m, 2H), 3.96 (m, 3H), 3.28-3.15 (m, 1H), 1.64-1.15 (m, 4H), 0,88 (t, 3H, J= 7.3 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 173.4, 136.9, 115.8, 73.4, 52.7, 41.1, 35.5, 19.3, 13.8; Anal. Calcd for $C_9H_{18}N_2O_2$: C, 58.04; H, 9.74; N, 15.04. Found: C, 58.18; H, 9.81; N, 15.15.

General procedure for the preparation of compounds 9, 10, 11: A mixture of the substrate (**1** or **2** or **3**) (1.0 mmol), *n*-propyl iodide (0,194 ml, 2.0 mmol), K_2CO_3 (276 mg, 2.0 mmol) and CH_3CN (5 mL) was refluxed for 48 h. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography ($CHCl_3$/MeOH 98:2).

(2*S*,3*S*)-*N*-allyl-2-(dipropylamino)-3-hydroxyhexanamide 9: obtained from **1**, 175.7 mg, 65%, pale yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.53 (bt, 1H, *J* = 5.6 Hz), 5.18-4.99 (m, 2H), 3.91-3.71 (m, 4H), 3.06 (d, 1H, *J* = 4.6 Hz), 2.90-2.79 (m, 1H) 2.52-2.34 (m, 4H), 1.59-1.13 (m, 8H), 0.93-0.73 (m, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 173.0, 134.0, 116.1, 71.7, 67.5, 51.1, 41.3, 34.5, 23.3, 19.1, 13.9, 11.6; Anal. Calcd for $C_{15}H_{30}N_2O_2$: C, 66.62; H, 11.18; N, 10.36. Found: C, 66.85; H, 11.20; N, 10.42.

(2*R*,3*R*)-*N*-allyl-3-(dipropylamino)-2-hydroxyhexanamide 10: obtained from **2**, 189.3 mg, 70%, pale yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.75 (bs, 1H), 5.85-5.66 (m, 1H), 5.20-5.02 (m, 2H), 4.53 (bs, 1H), 3.90 (d, 1H, *J* = 7.4 Hz), 3.84-3.75 (m, 2H), 2.82-2.73 (m, 1H) 2.36-2.28 (m, 4H), 1.60-1.19 (m, 8H), 0.87 (t, 3H, J =7.4 Hz), 0.77 (t, 6H, J = 7.3 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 173.5, 133.9, 116.6, 68.8, 63.8, 53.3, 41.6, 27.5, 22.3, 21.2, 14.4, 11.7; Anal. Calcd for $C_{15}H_{30}N_2O_2$: C, 66.62; H, 11.18; N, 10.36. Found: C, 66.83; H, 11.22; N, 10.44.

(2*R*,3*S*)-*N*-allyl-3-(dipropylamino)-2-hydroxyhexanamide 11: obtained from **3**, 148.7, 55%, pale yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.49 (bs, 1H), 5.90-5.70 (m, 1H), 5.23-5.01 (m, 2H), 3.96 (d, 1H, J = 2.6 Hz), 3.91-3.80 (m, 2H), 3.15-3.04 (m, 2H) 2.73-2.49 (m, 4H), 1.78-1.32 (m, 8H), 0.96-0.81 (m, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 173.5, 133.7, 116.2, 69.6, 59.3, 49.6, 41.2, 33.5, 22.8, 19.4, 13.8, 11.3; Anal. Calcd for $C_{15}H_{30}N_2O_2$: C, 66.62; H, 11.18; N, 10.36. Found: C, 66.85; H, 11.21; N, 10.40.

General procedure for the preparation of compounds 12a-g: A mixture of the epoxy amide (**6a** or **6b** or **6c**) (1.0 mmol), amine (excess, 1 mL) and Ti(O-*i*Pr)$_4$ (1.5 mmol, 0,448 ml) was stirred at room temperature for 12 h. After this time, EtOAc was added and the organic layer was washed with an aqueous tartaric acid solution (0.5 M), dried and concentrated *in vacuo*. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 95:5, 0.2% NH_4OH).

(2*R*,3*R*)-*N*-allyl-3-cyclohexyl-3-(dipropylamino)-2-hydroxypropanamide 12b: obtained from **6b** and Pr_2NH, 279.2, 90%, colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.31 (bs, 1H), 5.89-5.68 (m, 1H), 5.26-5.03 (m, 2H), 4.12 (d, 1H, *J* = 4.9 Hz), 3.94-3.73 (m, 2H), 2.72-2.39 (m, 5H),), 2.31-2.12 (m, 1H), 1.93-0.87 (m, 15H), 0.82 (t, 6H, *J* = 7.4 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 173.3, 134.0, 116.7, 71.2, 67.5, 55.2, 41.5, 37.4, 32.7, 30.8, 26.5, 26.2, 25.9, 23.7, 11.5; Anal. Calcd for $C_{18}H_{34}N_2O_2$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.81; H, 11.09; N, 9.06.

(2*R*,3*R*)-*N*-allyl-3-cyclohexyl-3-(dibutylamino)-2-hydroxypropanamide 12c: obtained from **6b** and Bu_2NH, 322 mg, >95%, colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.33 (bs, 1H), 5.87-5.71 (m, 1H), 5.23-5.06 (m, 2H), 4.83 (bs, 1H), 4.16-4.06 (m, 1H), 3.93-3.71 (m, 2H), 2.70-2.42 (m, 4H), 2.23-2.14 (m, 1H), 1.84-1.13 (m, 19H), 0.87 (t, 6H, *J* = 7.5 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ:173.3, 133.9, 116.7, 70.9, 67.5, 53.0, 41.5, 37.4, 32.7, 30.8, 26.5, 26.2, 25.9, 20.4, 14.0; Anal. Calcd for $C_{20}H_{38}N_2O_2$: C, 70.96; H, 11.31; N, 8.28. Found: C, 71.21; H, 11.37; N, 8.30.

(2*R*,3*R*)-*N*-allyl-3-cyclohexyl-2-hydroxy-3-(piperidin-1-yl)propanamide 12d: obtained from **6b** and piperidine, 280 mg, >95%, colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.67 (bs, 1H), 5.84-5.68 (m, 1H), 5.20-5.00 (m, 2H), 4.58 (bs, 1H), 4.04 (d, 1H, *J* = 5.7 Hz), 3.89-3.67 (m, 2H), 2.75-2.46 (m, 4H), 2.41 (dd, 1H, J = 8.5, 6.4 Hz), 2.08-1.97 (m, 1H), 1.83-0.94 (m, 16H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 173.4, 133.9, 116.2, 73.5, 67.1, 51.4, 51.3, 41.2, 36.6, 32.7, 30.2, 26.9, 26.3, 26.1, 25.8, 24.3; Anal. Calcd for $C_{17}H_{30}N_2O_2$: C, 69.35; H, 10.27; N, 9.51. Found: C, 69.60; H, 10.30; N, 9.55.

(2*R*,3*R*)-*N*-allyl-3-cyclohexyl-2-hydroxy-3-morpholinopropanamide 12e: obtained from **6b** and morpholine, 257.8 mg, 87%, colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.48 (bt, 1H, *J* = 5.3 Hz), 5.84-5.67 (m, 1H), 5.20-5.05 (m, 2H), 4.15 (d, 1H, *J* = 4.4 Hz), 3.90-3.75 (m, 2H), 3.65-3.52 (m, 4H), 2.78-2.57 (m, 4H), 2.53 (dd, 1H, *J* = 9.0, 4.4 Hz), 2.08-1.82 (m, 3H), 1.72-1.55 (m, 3H), 1.30-0.92 (m, 5H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 173.4, 133.8, 116.5, 72.7, 67.6, 50.5, 41.3, 36.1, 32.2, 30.2, 26.3, 26.0, 25.9; Anal. Calcd for $C_{16}H_{28}N_2O_3$: C, 64.83; H, 9.52; N, 9.45. Found: C, 65.05; H, 9.56; N, 9.48.

(2*R*,3*R*)-*N*-allyl-3-(dibutylamino)-2-hydroxy-3-phenylpropanamide 12f: obtained from **6c** and Bu_2NH, 315 mg, >95%, colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.57 (bs, 1H), 7.30-7.15 (m, 5H), 5.55-5.39 (m, 1H), 5.00-4.83 (m, 2H), 4.44 (d, 1H, J = 7.1 Hz), 3.91 (d, 1H, J = 7.1 Hz), 3.70 (ddt, 2H, *J* = 15.7, 6.0, 1.3, Hz), 3.55 (ddt, 2H, *J* = 15.7, 5.5, 0.3 Hz), 2.61-2.47 (m, 2H), 2.36-2.22 (m, 2H), 1.44-1.31 (m, 4H), 1.28-1.08 (m, 4H), 0.81 (t, 6H, *J* = 7.3 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 172.1, 135.4, 133.9, 129.6, 127.8, 127.6, 116.3, 69.3, 67.4, 49.8, 41.4, 28.9, 20.6, 13.9; Anal. Calcd for $C_{20}H_{32}N_2O_2$: C, 72.25; H, 9.70; N, 8.43. Found: C, 72.54; H, 9.74; N, 8.46.

(2*R*,3*R*)-*N*-allyl-2-hydroxy-3-phenyl-3-(piperidin-1-yl)propanamide 12g: obtained from **6c** and piperidine, 275 mg, >95%, colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.89 (bs, 1H), 7.38-6.96 (m, 5H), 5.66-5.40 (m, 1H), 5.05-4.80 (m, 2H), 4.58 (d, 1H, J = 7.3 Hz), 4.10 (bs, 1H), 3.76-3.56 (m, 2H), 3.66 (d, 1H, *J* = 7.3 Hz), 2.60-2.20 (m, 4H), 1.63-1.21 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 172.3, 133.9, 129.3, 127.8, 127.6, 116.2, 71.6, 68.3, 51.4, 41.3, 26.3, 26.2, 24.2; Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 71.07; H, 8.42; N, 9.75.

(2*R*,3*S*)-3-phenyloxirane-2-carbaldehyde 15c: To a stirred solution of epoxy alcohol **5c** (150 mg, 1 mmol) in CH_2Cl_2 (8 ml) at 0°C, Et_3N (0.56 ml, 3.8 mmol) and $PySO_3$ (478 mg, 3 mmol) in DMSO (3 ml) were added. The mixture was stirred at room temperature for 12 h. Then the mixture was diluted with 20 ml of Et_2O and 40 ml of hexane, washed with $NaHCO_3$ s.s.; the aqueous layer was extracted with a mixture 1:2.8 Et_2O/hexane

and the organic layer washed with $NaHPO_4$ 1 M, and brine then dried and concentrated *in vacuo*. The crude material was purified by flash chromatography (hexane/EtOAc 85:25) giving **15c** , 120 mg, 81%, colorless oil; ^{1}H-NMR (300MHz, $CDCl_3$) δ: 9.20 (d, 1H, *J* = 6.0 Hz), 7.48-7.18 (m, 5H), 4.16 (d, 1H, *J* = 1.5 Hz), 3.44 (dd, 1H, *J* = 6.0, 1.5 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 196.7, 134.1, 129.1, 128.7, 125.6, 62.8, 56.6. Anal. Calcd for $C_9H_8O_2$: C, 72.96; H, 5.44. Found: C, 72.99; H, 5.47.

General procedure for the preparation of compounds 17a-c: A solution of aldehyde (**15a** or **15b** or **15c)** (1 mmol) in THF dry (8.0 ml) was added dropwise to a stirred solution of *n*-BuLi (1.5 mL of a 1.6 M hexane solution, 2.4 mmol) and diethylphosphonoacetic acid (0.2 mL, 1.1 mmol) in THF dry (1.5 mL) under an argon atmosphere at -70°C. After 2 hours the reaction mixture was allowed to reach the room temperature and then stirred for 12 hours. 0.1 M HCl aqueous solution was added until pH 2 and the aqueous layer was extracted several times with Et_2O. The combined organic extracts were dried and concentrated *in vacuo* affording the crude carboxylic acid **16a-c**. The crude product was dissolved in CH_2Cl_2 (5 mL) and allyl amine (1.1 mmol, 0,08 ml) was added. The solution was added to a solution of 1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide (170 mg, 1.1 mmol) and 1-Hydroxy-7-azabenzotriazole (136 mg, 1 mmol) in CH_2Cl_2 (5 mL) and the reaction was stirred at room temperature for 2 hours. CH_2Cl_2 and water were added. The organic layer was separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were washed with brine, dried and concentrated *in vacuo.* The crude material was purified by flash chromatography (hexane/EtOAc 70:30).

(*E*,2*S*,3*S*)-*N*-allyl-3-(3-propyloxiran-2-yl)acrylamide 17a: obtained from **16a**, 130.8 mg, 67% from **15a**, colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.58 (dd, 1H, *J* = 15.3, 6.7 Hz), 6.44 (bs, 1H), 6.14 (d, 1H, *J* = 15.3 Hz), 5.86-5.72 (m, 1H), 5.14-4.98 (m, 2H), 3.88 (bt, 2H, *J*=5.7 Hz), 3.16 (dd, 1H, *J* = 6.7, 1.8 Hz), 2.81 (ddd, 1H, J_1=J_2=5.2, 1.9 Hz), 1.59-1.37 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 164.8, 140.4, 133.8, 125.5, 116.3, 61.4, 56.4, 41.9, 33.8, 19.0, 13.7; Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.91; H, 8.80; N, 7.18.

(*E*,2*S*,3*S*)-*N*-allyl-3-(3-cyclohexyloxiran-2-yl)acrylamide 17b: obtained from **16b,** 97.4 mg, 72% from **15b**, colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.71 (bs, 1H), 6.54 (dd, 1H, *J* = 15.2, 6.6 Hz), 6.14 (d, 1H, *J* = 15.2 Hz), 5.83-5.68 (m, 1H), 5.10 (bd, 1H, *J* = 17.2 Hz), 5.04 (bd, 1H, *J* = 10.3 Hz), 3.84 (bt, 2H, *J* = 4.9 Hz), 3.23 (bd, 1H, J = 6.6 Hz), 2.60 (bd, 1H, *J* = 6.5 Hz), 1.81-1.53 (m, 5H),1.30-0.91 (m, 6H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 164.8, 140.5, 133.8, 125.4, 116.1, 65.7, 55.1, 41.8, 39.8, 29.3, 28.6, 26.0, 25.4, 25.3; Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.73; H, 9.00; N, 5.97.

(*E*,2*S*,3*S*)-*N*-allyl-3-(3-phenyloxiran-2-yl)acrylamide 17c: obtained from **16c**,149 mg, 65% from **15c**, colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.41-7.23 (m, 5H), 6.78 (dd, 1H, *J* = 15.3, 6.3 Hz), 6.19 (d, 1H, *J* = 15.3 Hz), 5.97 (bs, 1H), 5.93-5.79 (m, 1H), 5.19 (dd, 1H, *J* = 17.3, 1.3 Hz), 5.14 (dd, 1H, *J* = 10.3, 1.3 Hz), 3.95 (bt, 2H, *J* = 5.7 Hz), 3.78 (d, 1H, *J* = 1.5 Hz), 3.46 (dd, 1H, *J* = 6.3, 1.5 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 164.5, 139.7, 136.2, 133.8, 128.6, 128.5, 125.7, 125.4, 116.6, 61.2, 60.7, 42.0; Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.60; H, 6.62; N, 6.15.

General procedure for the preparation of compounds 13a-f, 14: The epoxy amide (**17a** or **17b** or **17c)** (1 mmol), $LiClO_4$ (1.59 g, 15 mmol), and the selected amine (10 mmol, excess) in acetonitrile (3 mL) were stirred at 55 °C for 24 h. Then H_2O was added, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried, concentrated *in vacuo* and purified by flash chromatography (CH_2Cl_2/MeOH 95:5).

(*E*,4*R*,5*S*)-*N*-allyl-5-cyclohexyl-4-(dibutylamino)-5-hydroxypent-2-enamide 13a: obtained from **17b** and Bu_2NH, 262.5 mg, 72%, colorless oil; $[\alpha]^{25}_D$= -16.5 (c=3.6 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.70 (dd, 1H, *J* = 15.4, 9.5 Hz), 6.38 (bs, 1H), 5.91 (d, 1H, *J* = 15.4 Hz), 5.87-5.70 (m, 1H), 5.13 (bd, 1H, *J* = 17.2 Hz), 5.06 (bd, 1H, *J* = 10.9 Hz), 3.87 (bt, 2H, *J* = 4.8 Hz), 3.39 (bt, 1H, *J* = 6.2 Hz), 3.09 (dd, 1H, *J* = 9.5, 6.2 Hz), 3.00 (bs, 1H), 2.52-2.26 (m, 4H), 1.82-1.40 (m, 6H), 1.40-0.90 (m, 13H), 0.83 (t, 6H, *J* = 7.1 Hz); ^{13}C-NMR (300 MHz, $CDCl_3$) δ: 165.2, 140.3, 134.0, 127.3, 116.2, 74.4, 64.5, 50.3, 41.8, 38.8, 29.8, 29.3, 27.3, 26.4, 26.1, 25.8, 20.3, 13.9; Anal. Calcd for $C_{22}H_{40}N_2O_2$: C, 72.48; H, 11.06; N, 7.68. Found: C, 72.73; H, 11.09; N, 7.70.

(*E*,4*R*,5*S*)-*N*-allyl-5-cyclohexyl-5-hydroxy-4-morpholinopent-2-enamide 13b: obtained from **17b** and morpholine, 251.5 mg, 78%, colorless oil; $[\alpha]^{25}_D$ = - 27.2 (*c* 3.2, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.74 (dd, *J* = 15.7, 9.9 Hz, 1H), 5.96 (d, *J* = 15.7 Hz, 1H), 5.92-5.78 (m, 1H), 5.72 (bs, 1H), 5.26-5.11 (m, 2H), 3.96 (bt, 2H, *J* = 5.7 Hz), 3.69 (bt, 4H, *J* = 4.4 Hz), 3.53 (dd, 1H, *J* = 8.5, 3.0 Hz), 3.20 (bs, 1H), 2.89 (dd, 1H, *J* = 9.8, 3.0 Hz), 2.65-2.41 (m, 4H), 2.03 (bd, 1H, *J* = 11.9 Hz), 1.78-1.48 (m, 4H), 1.41-0.76 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 164.6, 139.2, 133.9, 127.9, 116.8, 72.3, 68.9, 67.0, 51.6, 42.0, 39.4, 29.5, 27.9, 26.4, 25.6, 25.5; Anal. Calcd for $C_{18}H_{30}N_2O_3$: C, 67.05; H, 9.38; N, 8.69. Found: C, 67.30; H, 9.40; N, 8.70.

(*E*,4*R*,5*S*)-*N*-allyl-5-cyclohexyl-5-hydroxy-4-(piperidin-1-yl)pent-2-enamide 13c: obtained from **17b** and piperidine, 247 mg, 77%,colorless oil; $[\alpha]^{25}_D$ = - 27.3 (*c* 3.1, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.71 (dd, *J* = 15.3, 9.5 Hz, 1H), 6.09 (s, 1H), 5.92 (d, 1H, *J* = 15.3 Hz), 5.92-5.75 (m, 1H), 5.23-5.05 (m, 2H), 3.92 (bt, 2H, *J* = 5.0 Hz), 3.48 (bd, 1H, *J* = 7.9 Hz), 3.20 (bs, 1H), 2.82 (bd, 1H, *J* = 9.5 Hz), 2.54-2.24 (m, 4H), 1.96 (bd, 1H, *J* = 12.4 Hz), 1.80-0.75 (m, 16H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 165.0, 140.1, 134.0, 127.1, 116.5, 72.9, 68.9, 52.1, 42.0, 39.3, 29.2, 28.0, 26.4, 26.2, 25.7, 25.6, 24.4; Anal. Calcd for $C_{19}H_{32}N_2O_2$: C, 71.21; H, 10.06; N, 8.74. Found: C, 71.50; H, 10.12; N, 8.77.

(*E*,4*R*,5*S*)-*N*-allyl-4-(dibutylamino)-5-hydroxyoct-2-enamide 13d: obtained from **17a** and Bu_2NH, 237 mg, 73%, colorless oil; $[\alpha]^{25}_D$ = - 13.5 (*c* 2.7, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.79 (dd, 1H, *J* = 15.5, 9.7 Hz), 5.91 (d, 1H, *J* = 15.5 Hz), 5.92-5.76 (m, 2H), 5.24-5.11 (m, 2H), 3.95 (bt, 2H, *J* = 5.7 Hz), 3.75-3.64 (m, 1H), 3.03 (dd, 1H, *J* = 9.6, 5.6 Hz), 2.81 (bs, 1H), 2.61-2.32 (m, 4H), 1.59-1.05 (m, 12 H), 0.89 (t, 9H, *J* = 7.1 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 164.9, 140.2, 134.0, 127.6, 116.7, 70.4, 67.6, 50.9, 42.0, 35.9, 29.9, 20.4, 19.2, 14.1, 14.0; Anal. Calcd for $C_{19}H_{36}N_2O_2$: C, 70.32; H, 11.18; N, 8.63. Found: C, 70.58; H, 11.20; N, 8.65.

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(*E*,4*R*,5*S*)-*N*-allyl-5-hydroxy-4-morpholinooct-2-enamide 13e: obtained from **17a** and morpholine, 237 mg, 84%, colorless oil; $[\alpha]^{25}_D$ = - 38.0 (*c* 2.9, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.72 (dd, 1H, *J* = 15.5, 9.9 Hz), 6.01 (bs, 1H), 5.94 (d, 1H, *J* = 15.5 Hz), 5.90-5.76 (m, 1H), 5.24-5.09 (m, 2H), 3.99-3.82 (m, 3H), 3.69 (t, 4H, *J* = 4.5 Hz), 3.11 (bs, 1H), 2.70 (dd, 1H, *J* = 9.8, 3.3 Hz), 2.64-2.42 (m, 4H), 1.57-1.19 (m, 4H), 0.89 (t, 3H, *J* = 6.8 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 164.6, 139.2, 133.9, 128.3, 116.7, 71.6, 68.4, 67.0, 51.5, 42.0, 35.8, 19.1, 14.0; Anal. Calcd for $C_{15}H_{26}N_2O_3$: C, 63.80; H, 9.28; N, 9.92. Found: C, 64.02; H, 9.30; N, 9.95.

(4*R*,5*S*,*E*)-*N*-allyl-5-hydroxy-4-morpholino-5-phenylpent-2-enamide 13f: obtained from **17c** and morpholine, 66,4 mg, 21%, pale yellow oil; $[\alpha]^{25}_D$ = 35.0 (*c* 1.8, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.33-7.20 (m, 5H), 6.68 (dd, 1H, *J* = 15.5, 9.8 Hz), 5.85-5.71 (m, 1H), 5.46 (d, 1H, *J* = 15.5 Hz), 5.39 (bt, 1H, *J* = 5.2 Hz), 5.20-5.06 (m, 3H), 3.85 (bt, 2H, *J* = 5.7 Hz), 3.75 (t, 4H, *J* = 4.6 Hz), 3.03 (dd, 1H, *J* = 9.8, 3.3 Hz), 2.77-2.60 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 164.3, 133.8, 130.1, 128.7, 128.1, 127.4, 126.1, 116.5, 73.4, 71.4, 66.8, 51.6, 41.8; Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.65; H, 7.67; N, 8.86.

(4S,5R,E)-N-allyl-4-hydroxy-5-morpholino-5-phenylpent-2-enamide 14: obtained from **17c** and morpholine, 196 mg, 62%, pale yellow oil; $[\alpha]^{25}_D$ = -18.8 (*c* 2.8, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.33- 7.25 (m, 5H), 6.65 (dd, 1H, *J* = 15.2, 3.7 Hz), 5.89 (d, 1H, *J* = 15.2 Hz), 5.85-5.71 (m, 1H), 5.53 (bs, 1H), 5.15-5.04 (m, 2H), 4.93 (bs, 1H), 3.86 (bt, 2H, *J* = 5.5 Hz), 3.82-3.72 (m, 4H), 3.46 (bs, 1H), 2.74-2.49 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 165.1, 142.7, 135.2, 134.0, 129.3, 128.2, 128.1, 123.2, 116.2, 74.1, 68.6, 66.9, 51.6, 41.8; Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.67; H, 7.69; N, 8.85.

General procedure for the addition of diethylzinc to aldehydes: To a solution of the chiral amino alcohol (0.06 mmol, 6 mol%) toluene (2 mL) the aldehyde (1 mmol) was added at room temperature. The mixture was stirred for 20 min and then cooled to 0 °C. Diethylzinc (2.5 mL of a 1.0 M hexanes solution, 2.5 mmol) was added dropwise. Then the reaction mixture was allowed to reach the room temperature and stirred for the corresponding reaction time under argon. The reaction was quenched by the addition of a saturated NH_4Cl solution (10 mL). The mixture was then extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexane/EtOAc 90:10). Enantiomeric excesses were determined by HPLC analysis. Absolute configurations of the final alcohols were assigned by comparing the sign of the optical rotation or the retention time on HPLC with the literature value. The following data are related to the use of ligand **13b.**

(*S*)-1-phenylpropan-1-ol 18a:[21] 42 mg, > 95%; colorless oil; $[\alpha]^{25}_D$ = -47.2 (*c* 3.3, $CHCl_3$); *ee*=95% (HPLC: Chiralpack IB, hexane/i-PrOH 98:2, 0.9 mL/min, 258 nm, minor 12.1 min and major 12.4 min). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.65 - 7.21 (m, 5H), 4.54 (t, 1H, *J* = 6.6 Hz), 2.73 (bs, 1H), 1.86-1.67 (m, 2H), 0.91 (t, 3H, *J* = 7.4 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 144.6, 128.4, 127.4, 126.0, 75.9, 31.9, 10.1.

(*S*)-1-(naphthalen-1-yl)propan-1-ol 18b:[22] 178mg, > 95%; colorless oil; $[\alpha]^{25}_D$ = -62.0 (*c* 2.7, $CHCl_3$); *ee* = 97% (HPLC: Chiralpack IA, hexane/i-PrOH 95:5, 1 mL/min, 220 nm, major 8.8 min and minor 9.7 min); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.11-8.00 (m, 1H), 7.88-7.78 (m, 1H), 7.78-7.68 (m, 1H), 7.61-7.52 (m, 1H), 7.52-7.35 (m, 3H), 5.32 (dd, 1H, *J* = 7.2, 5.2 Hz), 2.19 (bs, 1H), 2.05-1.78 (m, 2H), 0.98 (t, 3H, *J* = 7.4 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 140.1, 133.7, 130.4, 128.8, 127.7, 125.8, 125.3, 125.3, 123.1, 122.8, 72.4, 31.0, 10.4.

(*E,S*)-1-phenylpent-1-en-3-ol 18c:[21] 142.7 mg, 88%; colorless oil; $[\alpha]^{25}_D$ = -10.1 (*c* 2.5, $CHCl_3$); *ee* = 87.5% (HPLC: Chiralpack IC, hexane/i-PrOH 98:2, 1 mL/min, 254 nm, minor 13.0 min and major 14.9 min); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.43-7.17 (m, 5H), 6.57 (d, 1H, *J* = 15.9 Hz), 6.22 (dd, 1H, *J* = 15.9, 6.7 Hz), 4.21 (dd, 1H, *J* = 12.3, 6.2 Hz), 1.88 (bs, 1H), 1.74-1.55 (m, 2H), 0.97 (t, 3H, *J* = 7.4 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 136.7, 132.2, 130.3, 128.5, 127.5, 126.4, 74.3, 30.2, 9.7.

(*S*)-1-(thiophen-3-yl)propan-1-ol 18d:[23] 135.7 mg, >95%; colorless oil; $[\alpha]^{25}_D$ = -33.0 (*c* 2.5, $CHCl_3$); *ee* = 94.7% (HPLC: Chiralpack IB, hexane/EtOH 99.6:0.4, 1.8 mL/min, 220 nm, minor 15.03 min and major 15.9 min); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.24 (dd, 1H, *J* = 4.9, 3.0 Hz), 7.12-7.05 (m, 1H), 7.02 (dd, 1H, *J* = 4.9, 1.2 Hz), 4.57 (t, 1H, *J* = 6.5 Hz), 3.18 (s, 1H), 1.80-1.63 (m, 2H), 0.88 (t, 3H, *J* = 7.4 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 145.9, 125.6, 125.5, 120.5, 71.5, 30.9, 9.8.

(*S*)-1-cyclohexylpropan-1-ol 18e:[24] 125.2 mg, 88%; colorless oil; $[\alpha]^{25}_D$ = -8.6 (*c* 1.9, $CHCl_3$); *ee* = 80.3% (HPLC on the *o*-bromo benzoyl ester derivative: Chiralpack IA, hexane/EtOH 99:1, 0.8 mL/min, 220 nm, minor 5.5 min and major 5.9 min); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.26 (ddd, 1H, *J* = 8.7, 5.4, 3.9 Hz), 1.87-0.98 (m, 16H), 0.94 (t, 3H, *J* = 7.4 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 77.6, 43.1, 29.3, 27.7, 26.8, 26.5, 26.4, 26.2, 10.2.

(*S*)-1-(2-methoxyphenyl)propan-1-ol 18f:[22] 160 mg, >95%; colorless oil; $[\alpha]^{25}_D$ = -22.1 (*c* 4.0, $CHCl_3$); *ee* = 95.7% (HPLC:Chiralpack IB, hexane/i-PrOH 97:3, 0.8 mL/min, 280 nm, major 10.9 min and minor 11.7 min); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.45 (d, 1H, *J* = 7.4 Hz), 7.23 (dd, 1H, J_1=J_2 = 7.7 Hz), 6.95 (dd, 1H, J_1=J_2 7.4 Hz), 6.86 (d, 1H, *J* = 8.1 Hz), 4.82 (t, 1H, *J* = 6.5 Hz), 3.80 (s, 1H), 3.01 (bs, 1H), 1.80 (dq, 2H, J_1=J_2 7.2 Hz), 0.96 (t, 3H, *J* = 7.3 Hz, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 156.3, 132.3, 127.9, 126.8, 120.5, 110.2, 71.8, 55.0, 30.0, 10.3.

(*S*)-1-(3-methoxyphenyl)propan-1-ol 18g:[25] 100 mg, 60%; colorless oil; $[\alpha]^{25}_D$ = -30.9 (*c* 2.5, $CHCl_3$); *ee* = 97.4% (HPLC: Chiralpack IA, hexane/i-PrOH 95:5, 1 mL/min, 220 nm, minor 9.9 min and major 10.5 min; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.25 (t, 1H, *J* = 7.9 Hz), 6.89 (s, 1H), 6.81 (d, 2H, *J* = 7.5 Hz), 6.86 (d, 1H, *J* = 8.1 Hz), 4.55 (t, 1H, *J* = 6.5 Hz), 3.80 (s, 1H), 2.08 (bs, 1H), 1.86-1.65 (m, 2H), 0.91 (t, 3H, *J* = 7.4 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 159.6, 146.3, 129.3, 118.3, 112.8, 111.3, 75.8, 55.1, 31.8, 10.1.

(*S*)-1-(4-methoxyphenyl)propan-1-ol 18h:[22] 159 mg, >95%; colorless oil; $[\alpha]^{25}_D$ = -45.1 (*c* 3.3, $CHCl_3$); *ee* = 97% (HPLC: Chiralpack IA, hexane/i-PrOH 99.5:0.5, 1 mL/min, 274 nm, minor 54.6 min and major 61.0 min). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.22 (d, 2H, *J* = 8.5 Hz), 6.85 (d, 2H, *J* = 8.5 Hz), 4.47 (t, 1H, *J* = 6.7 Hz), 3.77 (s, 3H), 2.46 (bs, 1H), 1.85-1.60 (m, 2H), 0.86 (t, 3H, *J* = 7.3 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 158.7, 136.7, 127.1, 113.6, 75.4, 55.1, 31.6, 10.1.

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(*S*)-1-(*o*-tolyl)propan-1-ol 18i:[22] 142 mg, 95%; colorless oil; $[\alpha]^{25}_D$ = -54.5 (*c* 4.4, $CHCl_3$); *ee* = 97.8% (HPLC: Chiralpack IA, hexane/i-PrOH 95:5, 0.8 mL/min, 220 nm, minor 7.6 min and major 8.3 min); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.46 (d, 1H, *J* = 7.4 Hz), 7.27-7.08 (m, 3H), 4.86 (t, 1H, *J* = 6.3 Hz), 2.34 (s, 3H), 1.82-1.68 (m, 3H), 0.98 (t, 3H, *J* = 7.3 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 142.7, 134.6, 130.3, 127.1, 126.2, 125.2, 72.0, 30.9, 19.1, 10.4.

(*S*)-1-(*m*-tolyl)propan-1-ol 18j:[26] 144 mg, >95%; colorless oil; $[\alpha]^{25}_D$ = -43.7 (*c* 3.3, $CHCl_3$); *ee* = 98.6% (HPLC: Chiralpack IA, hexane/i-PrOH 99.5/0.5, 1.5 mL/min, 220 nm, minor 29.7 min and major 31.21 min); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.29-7.20 (m, 1H), 7.20-7.04 (m, 3H), 4.49 (t, 1H, *J* = 6.6 Hz), 2.92 (s, 1H), 2.40 (s, 3H), 1.88-1.66 (m, 2H), 0.94 (t, 3H, *J* = 7.4 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 144.5, 137.6, 128.0, 127.9, 126.5, 122.9, 75.6, 31.6, 21.2, 10.0.

(*S*)-1-(*p*-tolyl)propan-1-ol 18k: [26] 144 mg, >95%; colorless oil; $[\alpha]^{25}_D$ = -41.0 (*c* 3.4, $CHCl_3$); *ee* = 97% (HPLC: Chiralpack IA, hexane/i-PrOH 98/2, 1 mL/min, 262 nm, minor 13.9 min and major 15.6 min); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.23 (d, 2H, *J* = 8.2 Hz), 7.17 (d, 2H, *J* = 8.2 Hz), 4.50 (t, 1H, *J* = 6.6 Hz), 2.73 (bs, 1H), 2.39 (s, 3H), 1.88-1.66 (m, 2H), 0.92 (t, 3H, *J* = 7.4 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 141.5, 136.7, 128.8, 125.8, 75.5, 31.6, 20.9, 10.0.

(*S*)-1-(2-fluorophenyl)propan-1-ol 18l:[27] 135 mg, 88%; colorless oil; $[\alpha]^{25}_D$ = -32.3 (*c* 2.8, $CHCl_3$); *ee* = 90% (HPLC: Chiralpack IA, hexane/i-PrOH 98/2, 0.9 mL/min, 267 nm, minor 13.6 min and major 14.2 min); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.42 (t, 1H, *J* = 7.4 Hz), 7.26-7.16 (m, 1H), 7.12 (t, 1H, *J* = 7.4 Hz), 6.99 (t, 1H, *J* = 9.1 Hz), 4 .89 (t, 1H, *J* = 6.5 Hz), 2.70 (bs, 1H), 1.83-1.66 (m, 2H), 0.91 (t, 3H, *J* = 7.3 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 159.7 (*J* = 245.1 Hz), 131.4 (*J* = 13.3 Hz), 128.5 (*J* = 8.3 Hz), 127.3 (*J* = 4.6 Hz), 124.1 (*J* = 3.5 Hz), 115.0 (*J* = 22.0 Hz), 69.3, 30.8, 9.8.

(*S*)-1-(2-chlorophenyl)propan-1-ol 18m:[26] 163 mg, >95%; colorless oil; $[\alpha]^{25}_D$ = -48.6; *ee* = 91% (HPLC: Chiralpack IA, hexane/i-PrOH 99.5/0.5, 1 mL/min, 225 nm, minor 29.6 min and major 32.4 min). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.49 (dd, 2H, *J* = 7.6, 1.7 Hz), 7.32-7.20 (m, 2H), 7.16 (dd, 2H, *J* = 7.7, 1.7 Hz), 5.02 (dd, 1H, *J* = 7.5, 4.9 Hz), 2.86 (bs, 1H), 1.85-1.60 (m, 2H), 0.95 (t, 3H, *J* = 7.3 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 141.9, 131.8, 129.1, 128.1, 127.1, 126.8, 71.6, 30.4, 9.9.

(*S*)-1-(3-bromophenyl)propan-1-ol 18n:[28] 205 mg, **>**95%; colorless oil; $[\alpha]^{25}_D$ = -26.2 (*c* 2.8, $CHCl_3$); *ee* = 88% (HPLC: Chiralpack IA, hexane/i-PrOH 98/2, 0.9 mL/min, 267 nm, minor 15.6 min and major 16.4 min); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.47-7.29 (m, 2H), 7.21-7.11 (m, 2H), 4.46 (t, 1H, *J* = 6.5 Hz), 2.90 (bs, 1H), 1.75-1.57 (m, 2H), 0.86 (t, 3H, *J* = 7.3 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 146.7, 130.2, 129.7, 128.9, 124.5, 122.3, 74.9, 31.7, 9.8.

(*S*)-1-(4-bromophenyl)propan-1-ol 18o:[28] 191.4 mg, 89%; colorless oil; $[\alpha]^{25}_D$ = -35.5 (*c* 3.8, $CHCl_3$); *ee* = 96.6% (HPLC: Chiralpack IC, hexane/i-PrOH 99/1, 1.5 mL/min, 220 nm, minor 7.4 min and major 8.6 min); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.44 (d, 2H, *J* = 8.4 Hz), 7.17 (d, 2H, *J* = 8.4 Hz), 4.51 (t, 1H, *J* = 6.5 Hz), 2.33 (bs, 1H), 1.81-1.57 (m, 2H), 0.87 (t, 3H, *J* = 7.4 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 143.4, 131.2, 127.6, 120.9, 75.0, 31.7, 9.9.

3-(1-hydroxypropyl)benzonitrile 18p: absolute configuration not available, 155 mg, >95%; colorless oil; $[\alpha]^{25}_D$ = -38.4 (*c* 4.4, $CHCl_3$); *ee* = 96% (HPLC: Chiralpack IA, hexane/i-PrOH 95/5, 1 mL/min, 220 nm, minor 13.06 min and major 14.22 min); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.54-7.30 (m, 4H), 4.52 (t, 1H, *J* = 6.6 Hz), 2.41 (bs, 1H), 1.73-1.54 (m, 2H), 0.82 (t, 3H, *J* = 7.3 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 146.0, 130.6, 130.4, 129.3, 128.8, 118.7, 111.6, 74.2, 31.7, 9.6.

(*S*)-4-(1-hydroxypropyl)benzonitrile 18q:[29] 150 mg, 93%; colorless oil; $[\alpha]^{25}_D$ = -37.7 (*c* 2.8, $CHCl_3$); *ee* = 92% (HPLC: Chiralpack IA, hexane/i-PrOH 95/5, 0.8 mL/min, 220 nm, minor 17.3 min and major 18.8 min); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.58 (d, 2H, *J* = 8.2 Hz), 7.42 (d, 2H, *J* = 8.2 Hz), 4.63 (t, 1H, *J* = 6.4 Hz), 2.57 (bs, 1H), 1.79-1.66 (m, 2H), 0.89 (t, 3H, *J* = 7.4 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 150.1, 131.8, 126.4, 118.6, 110.2, 74.4, 31.6, 9.5.

Conflicts of interest

There are no conflicts to declare.

Notes and references

§ The allyl group was chosen as it could eventually be converted through a Pt-catalyzed hydrosilylation into a trialcoxysilane, anchorable on magnetite nanoparticles.

§§ Using as Lewis acid Al_2O_3 (M. Noguchi, M. Yoshioka, S. Kakimoto, S. Kajigaeshi Bull. Chem. Soc. Jpn. 1987, 60, 3261-3267) $Ti(O\textit{i}\text{-}Pr)_4$ or $ZnCl_2$ the starting substrate was completely recovered even at high temperature and long reaction time.

§§§ Unfortunately, **13f** and **14** were chromatographically inseparable and the compounds' separation and identification was achieved by an acetylation of the hydroxyl group; a following hydrolysis allowed to obtain **13f** and **14**.

§§§§ All the substrates were prepared starting from the corresponding allylic alcohols. For the substrate with R=cyclohexyl the appropriate alcohol is not commercially available and it was synthesized from the cyclohexanecarboxaldehyde, by a Horner-Emmons reaction followed by a reduction of the ester using DIBAL (A. G. M. Barrett, W. W. Doubleday, G. J. Tustin, *Tetrahedron* **1996**, 52, *48*, 15325-15338).

1 W.S. Knowles, *Angew. Chem. Int. Ed.* 2002, **41**, 1998-2007
2 R. Noyori, *Angew Chem Int Ed.* 2002, **41**, 2008-2022.
3 K.B. Sharpless, *Angew. Chem. Int. Ed*. 2002, **41**, 2024-2032
4 a) D. Ager, I. Prakash, D. R. Schaad, *Chem Rev.* 1996, **96**, 835-876. b) J. Vicario, D. Badia, L. Carrillo, E. Reyes, J. Etxebarria, *Current Organic Chemistry* 2005, **9**, 219-235
5 M. Kitamura, S. Suga, K. Kawai, R. Noyori, *J. Am. Chem. Soc.* 1986, **108**, 6071-6072.
6 K. Soai, S. Yokoyama, T. Hayasaka, *J. Org. Chem.* 1991**, 56,** 4264-4268
7 A. Vidal-Ferran, A. Moyano, M. A. Pericàs, A. Riera *J. Org. Chem*. 1997, **62**, 4970-4982
8 W. A. Nugent *Org. Lett.* 2002*,* **4**, 2133-2136
9 G. Righi and S. Ciambrone, *Tetrahedron Lett*. 2004, **45**, 2103-2106.
10 G. Righi, P. Bovicelli and I. Tirotta, *Tetrahedron Lett.* 2013, **54**, 6439-6442.

Journal Name ARTICLE

View Article Online
DOI: 10.1039/C8OB00165K

11 Review: L. M. Rossi, N. J. S. Costa, F. P. Silva, R. Wojcieszak, *Green Chem.* 2014, **16**, 2906-2933.
12 R. De Palma, S. Peeters, M. J. Van Bael, H. Van den Rul, K. Bonroy, W. Laureyn, J. Mullens, G. Borghs, G. Maes, *Chem. Mater*. 2007, **19**, 1821-1831.
13 Review: S. Shylesh, V. Schuneman and W. R Thiel, *Angew. Chem., Int. Ed.* 2010, **49**, 3428-3459.
14 R. Noyori, M. Kitamura, *Angew. Chem., Int. Ed. Engl.* 1991, **30**, 49-69.
15 G. Righi, A. Mantineo, L. Suber, A. Mari, *Synlett* 2012, **23**, 1947-1949.
16 M.Yamakawa, R. Noyori, *J. Am. Chem. Soc.* 1995, **117**, 6327-6335.
17 M. Yamakawa, R. Noyori, *Organometallics* 1999, **18**, 128-133.
18 Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, K. B. Sharpless, *J. Am. Chem. Soc.* 1987, **109**, 5765-5780.
19 R. Nishizawa, T. Nishiyama, K. Hisaichi, C. Minamoto, M. Murota, Y. Takaoka, H. Nakai, H. Tada, K. Sagawa, S. Shibayama, D. Fukushima, K. Maeda, H. Mitsuya, *Bioorg. Med. Chem*. 2011**, 19**, 4028–4042.
20 G Righi, A Chionne, C. Bonini, *Eur. J. Org. Chem*. 2000, 3127-3131.
21 M. Asami, S. Inoue, *Bull. Chem. Soc. Jpn*. 1997, **70**, 1687–1690.
22 C. Andres, R. Infante, J. Nieto, *Tetrahedron: Asymmetry* 2010, **21**, 2230–2237.
23 M. A. Aga, B. Kumar, A. Rouf, B. A. Shah, S. C. Taneja, *Tetrahedron Lett*. 2014, **55**, 2639-2641
24 Z.-L. Wu, H.-L. Wu, P.-Y. Wu, B.-J. Uang, *Tetrahedron: Asymmetry* 2009, **20**, 1556–1560.
25 W.-X. Zhao, N. Liu, G.-W. Li, D.-L. Chen, A.-A. Zhang, M.-C. Wang, L. Liu, *Green Chemistry* 2015, **17**, 2924-2930.
26 X.-F. Yang, T. Hirose, G.-Y. Zhang, *Tetrahedron: Asymmetry* 2008, **19**, 1670–1675.
27 A. Kokura, S. Tanaka, T. Ikeno, T. Yamada, *Organic Letters* 2006, **8**, 3025-3027.
28 K. R. Prasad, O. Revu, *Tetrahedron* 2013, **69**, 8422-8428.
29 Y.-S. Shih, R. Boobalan, C. Chen, G.-H. Lee, *Tetrahedron Asymmetry* 2014, **25**, 327-333