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New β-Amino Alcohols Derived from L-Valine as Chiral Inductors for Enantioselective Reductions of, and Nucleophilic Additions to Carbonyl Compounds.

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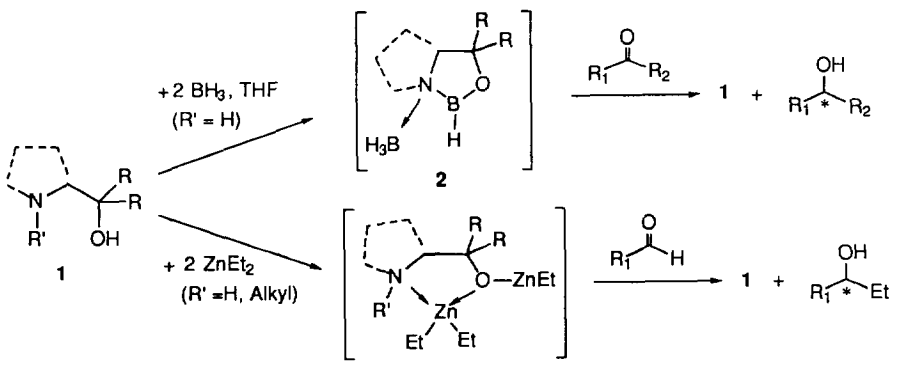
Abstract: β-Amino alcohols derived from L-valine were used as chiral ligands in oxazaborolidine reductions of ketones. Structural modifications, such as the introduction of alkyl groups on the carbinol carbon and the nitrogen atoms, were shown to influence unfavourably the enantioselectivity. In contrast, the addition of diethyl zinc to aldehydes occurs with enhanced e.e.'s using these modified inductors, which permit to reach useful enantioselectivities with various aldehydes.

Introduction

Enantioselective reactions on the carbonyl group -reductions using modified boron and aluminum hydrides, nucleophilic additions with chelated organometallics- have received considerable attention for a long time.[1,2] Reducing agents prepared from hydrides and a variety of ligands exhibit diverse degrees of enantioselectivity.[3] New families of inductors with the β-amino alcohol structural unit **1** were recently introduced in which the two functionnalities react with the hydride.[4] The resulting rigid geometry restricts the possibilities for the reagent-substrate complex to reach the transition state. A similar orientation was followed for the additions to the carbonyl group of aldehydes, an important part of the work being effected with zinc organometallics (Scheme 1).[2,5]



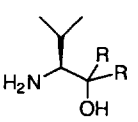
Scheme 1

A common feature for both types of reactions is the success (enantioselectivities up to 99 %) met with aromatic and some α,β-unsaturated (α-olefinic-, acetylenic-) compounds. The less frequently studied aliphatic ketones (for reductions) or aldehydes (for additions) generally give significantly lower selectivities. Examination

of literature data leads to some observations. Diverse types of inductors are used, derived from amino acids,[4,5] bornane,[6] or ephedrine,[7] or the less common ferrocene or arene-metal structures.[5b,8] Such a diversity indicates that finding highly selective inductors of broad applicability is still the objective of efforts. A second point is that aromatic groups are frequently present, especially on the carbinol carbon atom for compounds derived from amino acids, and the possibilities offered by totally aliphatic inductors are still largely to be explored. We undertook a study of the reactions mentionned above with new purely aliphatic β-amino-alcohols.[9] The expectation was that interactions of the saturated chains could be favorable in reactions involving aliphatic substrates, via the Van der Waals attractive (the so-called "lipophilic") forces,[10] with the hope to find out a structure able to provide good yields and enantioselectivities with a variety of aliphatic *and* aromatic substrates.

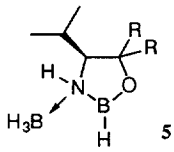
Results and discussion

Enantioselective reductions were first examined, with acetophenone **6a** (for the sake of comparison with literature data), 2-octanone **6b** as a model for aliphatic linear ketones, and cyclohexylmethylketone **6c**, for branched ones. The reductions with the oxazaborolidine-borane reagents **5** generated *in situ* from amino alcohols **4** with 2 equiv. of borane (Scheme 2) were performed as usual by stirring the ketone with **5** for 2 h at room temperature. After work-up, the alcohol is isolated and the inductor can be recovered in yields of at least 80%. Results are given in Table 1.



4a R= Ph
b R= 4-MeO-Ph
c R= 4-F-Ph

4 d R= *n*-C_4H_9
e R= *n*-$C_{10}H_{21}$
f R= *i*-C_4H_9



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Scheme 2

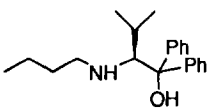
Table 1: Reduction of Ketones **6a-c** in the Presence of Inductors **4a-f**.

	Inductor					
Initial ketone	**4a**	**4b**	**4c**	**4d**	**4e**	**4f**
6a: Alcohol yield %	80	76	100	92	80	65
Alcohol[a] e.e.%	88	93	93	63	63	51
6b: Alcohol yield %	85	85	82	68	93	100
Alcohol[b] e.e. %	63	59	60	30	20	23
6c: Alcohol yield %	90	-	85	76	-	91
Alcohol[c] e.e. %	70	-	72	32	-	12

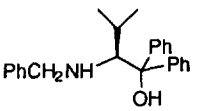
[a] Ref. 11. [b] Ref. 12. [c] Ref. 13.

Because of the important dispersion in the values of optical rotations found in the literature, estimation of the e.e.'s of the alcohols was made on their Mosher's esters,[14] which were examined by ^1H and ^{19}F NMR spectroscopy. In all the cases investigated, the reduction alcohol has the (R) absolute configuration. With respect to **4a**, the reduction yield of acetophenone **6a** is improved by using the 4-fluorophenyl substituted inductor **4c** and decreased with the 4-methoxylated one **4b**, suggesting a possible electronic effect. However, the

enantioselectivities obtained from both inductors is almost the same as with **4a**, making the effectiveness of the electronic factor questionable. The same conclusion was reached by Jones *et al.* for reductions in the presence of prolinol derivatives (see below).[15] For dialkyl ketones reductions, no improvement is observed. The reductions using aminoalcohol **4a** monosubstituted at the nitrogen by a butyl or a benzyl group (**7a** and **b,** scheme 3) give disappointingly low e.e.'s, less than 10% in all the cases tested. When aliphatic substituents are present on the carbinol carbon atom (compounds **4d-f**), the reductions are less selective. Changing THF for apolar media (hexane, toluene) gave much lower degrees of selectivity, less than 20 %.



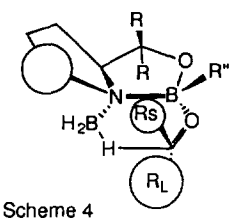
7a

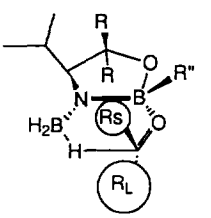


7b

Scheme 3

The admitted mechanism shown in scheme 4, was studied essentially in the case of prolinol induced reductions.[4] The ketonic oxygen binds to the intracyclic boron atom, and the hydride is delivered from the exocyclic BH_3 group to the carbonyl group placed in such a manner to minimize the repulsive interactions between the ligand and its appendages, and the bulkier group of the ketone.

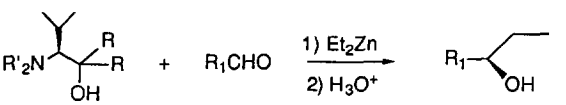




Scheme 4

The major steric hindrance originates from the proximity effects of the ketone substituents and the methylene group next to the nitrogen atom in the 5-membered ring. The validity of this model for valinol derivatives should be examined further. Our own results, for instance the difference in enantioselectivity in the reductions of acetophenone **6a** and acetylcyclohexane **6c**, seems difficult to accomodate with this picture. A similar statement, based on a study of the effect of substituents on the intracyclic boron atom, was previously formulated by the Merck group.[15] That attractive Van der Waals forces, in a first analysis, play a role in the actual transition states should probably be taken into account to obtain more accurate interpretations and predictions.

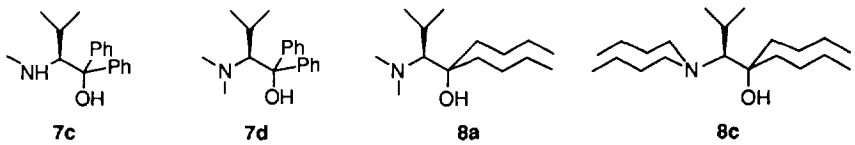
Despite the limited success in reduction reactions, the efficiency of the amino alcohols was tested in the addition of diethylzinc to aldehydes.



Scheme 5

With benzaldehyde (Scheme 5, R_1= Ph) as the model, the more promising inductors appeared to be those derived from amino alcohols **4a** and **4d** by N-methylation and butylation. Reaction in the presence of catalytic

amounts (10%) of **4a**, **7c**, **7d** and **7a** proceeded with (generally) increasing yields (58, 52, 80 and 88 % in this order) and e.e.'s (2, 53, 73 and 75 % respectively). Nitrogen disubstitution with aliphatic chains was shown to have positive effects with inductors derived from ephedrine.[7] This observation being confirmed by the above results, the efficiency of compounds **8**, totally aliphatic, was investigated. With **8a** and **c**, the expected alcohol is obtained quantitatively with e.e.'s of 93 and 97 % respectively and a (R) absolute configuration. Additions to various aldehydes with **8c** as the inductor were effected on aromatic aldehydes for the sake of comparison with published data, then on aliphatic aldehydes. Convenient yields and e.e.'s were obtained in these reactions (Table 2).



7c **7d** **8a** **8c**

Scheme 6

Table 2: Enantioselective Addition to Aldehydes in the Presence of Inductor **8c**

	This work[a]		Literature[b]	
Aldehyde	Yield %	e.e. %	Yield %	e.e. %
Benzaldehyde	100	97	99	99[c]
Cinnamaldehyde	95	88	81	96[d]
n-Heptanal	86	84	95	88[e]
Cyclohexanecarbaldehyde	75	82	90	97[f]
3-Methylbutanal	44	86	92	93[e]

[a] Isolated yields. e.e.'s were determined as mentionned above by NMR spectroscopy of Mosher's esters. [b] Literature data refer to the best yields and e.e.'s reported. [c] using ferrocene or borneol derived inductors; e.e. from HPLC analysis. Ref. 8. [d] using a borneol derived inductor; e.e. from HPLC analysis. Ref. 6. [e] using an ephedrine derived inductor; e.e. from NMR analysis. Ref. 7b. [f] using an ephedrine derived inductor; e.e. from VPC analysis. Ref. 7c.

Literature data mentionned in table 2 show that the more efficient inductors for addition to aromatic substrates are not the same as for aliphatic ones. In contrast, amino alcohol **8c**, even if giving slightly lower inductions, can be used in both cases, illustrating the favorable role of aliphatic substituents in the inductor's structure. An other conclusion of this work is the fact that a mechanism taking only into account the steric bulk of interacting groups seems unable to give an interpretation of all the data. Particularly, the disubstitution by identical groups, both on the nitrogen and carbinol carbon atoms, and the mobility of these saturated chains should "shield" the influence of the single stereodirecting isopropyl group. At last, the mechanisms proposed in literature for reductions on the one hand and for additions on the other hand offer strong similarities. If the same structural modifications in the inductors, replacement of aromatic substituents by aliphatic ones, lead to divergent results, a lower efficiency in reductions and an increased one in additions, the formulation of strongly related mechanisms in both cases could be hazardous.

Experimental Section

Borane (Me_2S complex or (1M) THF solution), diethyl zinc and Mosher's acid were obtained from Aldrich. Compounds **4** are prepared from methyl N-Boc L-valinate.[9] THF is distilled from benzophenone sodium. TLC chromatographies are effected on silica gel on aluminum plates (Merck), and column chromatographies, on silica gel (Merck, 70-230 mesh) with ethyl acetate in hexane (from 2 to 10% v:v) as eluents. Melting points, non corrected, are measured on a Büchi Tottoli apparatus. IR spectra are recorded as films or nujol suspensions on a Perkin-Elmer 357 spectrometer and ^1H NMR and ^{13}C NMR spectra, on Brucker 200 MHz and 50 MHz spectrometers respectively, in $CDCl_3$ solution with TMS as internal standard. Mass spectra are taken on a Nermag R-1010-C spectrometer (chemical ionisation using NH_3-isobutane, quadrupole detection). Optical rotations are taken on a Perkin-Elmer 241 polarimeter, in $CHCl_3$ solution at 25°C. After chromatographic purification, the alcohols are esterified to Mosher's esters. Combustion analyses were effected at the Service Central de Microanalyse du CNRS, Vernaison, France.

Standard procedure for reductions

Reagents **5** are prepared from 1 mmol of the inductor in 2 mL dry THF (0.5 M solution) and 2 mmol. of borane in THF, according to the published procedure.[7a] The ketone (1 equiv) is added via a syringe, and the mixture is stirred at room temperature. After 2 h (TLC monitoring), the flask is cooled to 0°C, aq. HCl (1N, 1 mL) is added dropwise and a white precipitate appears. THF is evaporated, and the residue is suspended in diethyl ether, filtered on celite and washed with the same solvent (3x10 mL). After drying (Na_2SO_4) and solvent removal, the alcohol is chromatographed. The pure alcohol (0.1 mmol) is esterified with Mosher's acid chloride (35 µL) in 400 µL CCl_4 and 100 µL pyridine. After completion of the reaction (TLC monitoring), the solvent is evaporated, THF (2 mL) and water (1 mL) are added and the mixture is stirred for 2 h. The mixture poured onto ethyl acetate (40 mL) is washed with aq. $CuSO_4$, then brine, and dried (Na_2SO_4). The crude is chromatographed to give the pure esters (yields > 92%), which are analyzed by ^1H and ^{19}F NMR (200 MHz). The measurement error on the e.e.'s is less than ±2%, giving figures identical to capillary column VPC analysis.The precipitate on celite is washed out with a sat. methanol solution of NH_3. After solvent removal, the residue is dissolved in CH_2Cl_2 and dried (Na_2SO_4). Evaporation of the solvent gives the recovered inductor in 80-90 % yields.

1(S)-α-(1-Butylamino-2-methylpropyl)-α-phenyl-benzenemethanol 7a.

4a (255 mg, 1 mmol.), 2 mL methanol, 460 µL butyl iodide (4 mmol., 4 equiv.) and 276 mg K_2CO_3 (2 mmol.) are refluxed for 24 h, then filtered on celite and the solvent evaporated. The residue is dissolved in CH_2Cl_2, dried (Na_2SO_4) and the solvent evaporated. Column chromatography yields **7a** (white solid, 191.2 mg, 0.614 mmol., 61%). mp 49-50°C. ^1H NMR: δ 0.64 (d, 3H, J = 6.9 Hz), 0.77 (t, 3H, J = 7.1 Hz), 1.01 (d, 3H, J = 7.1 Hz), 1.10-1.43 (m, 4H), 1.93-2.15 (m, 2H), 2.39-2.51 (m, 1H), 3.49 (d, 1H, J = 2.0 Hz), 7.1-7.7 (m, 10H). ^{13}C NMR: δ 13.7, 15.7, 20.0, 22.8, 28.7, 32.6, 50.3, 68.6, 78.2, 125.9, 126.0, 126.1, 126.2, 127.7, 127.8, 145.6, 148.9. IR (nujol): 3300, 3080, 1795, 1480, 1470 cm^{-1}. MS: m/e 312 (MH^+), 294, 128 (100%). $[\alpha]_D$ -46.5 ° (c 2.2). $C_{21}H_{29}NO$: Calcd.: C, 80.98; H, 9.38; N, 4.50. Found: C, 81.07; H, 9.30; N, 4.83.

1(S)-α-(1-Benzylamino-2-methylpropyl)-α-phenyl-benzenemethanol 7b.

4a (79.4 mg, 0.311 mmol), 216 µL NEt_3 and benzoyl chloride (39 µL, 48 mg, 0.342 mmol, 1.1 equiv.) are dissolved in 3 mL CH_2Cl_2. After 1h stirring at room temp. then solvent evaporation, the residue is dissolved in 30 mL ethyl acetate, washed with 2 mL of a 10 % NaOH solution, then sat. aq. NaCl. After drying and solvent removal, 110 mg (99 %) of a white solid are obtained, used as such in the following step. mp 228-9 °C dec.^1H

NMR: δ 0.97(d, 3H, *J* = 6.8 Hz), 0.99 (d, 3H, *J* = 6.7 Hz), 1.90-1.94 (m, 2H), 5.19 (dd, 1H, *J* = 9.9 and 2.3 Hz), 6.6 (br.d, 1H, *J* = 10.0 Hz), 7.1-7.5 (m, 10H). ^{13}C NMR: δ 17.9, 23.0, 29.2, 58.2, 82.4, 125.28, 125.33, 126.7, 126.9, 128.36, 128.43, 131.1, 145.5, 146.1, 167.0. IR (nujol): 3400, 1610, 1460, 1440, 1370, 1050 cm^{-1}. MS: m/e 342, 177, 105. 81 mg of this compound (0.22 mmol) and BH_3-Me_2S (70 µL, 3 equiv.) are refluxed in 2 mL toluene for 2 h, then hydrolyzed at 0 °C with a 2N aq. HCl. The solution is made alkaline with 10 % NaOH (3 mL), then extracted with ethyl acetate (2x20 mL). The organic phases are washed (sat. NaCl), dried and evaporated. The white solid (87 mg) is chromatographed to give the expected compound (60 mg, 0.176 mmol., 80%). mp 129-130 °C. ^1H NMR: δ 0.70 (d, 3H, J= 6.95 Hz), 0.96 (d, 3H, *J*= 6.95 Hz), 1.2 (br.s, 1H), 2.04 (hd, 1H, *J*= 6.91 and 1.84 Hz), 3.34 (ABq, 2H, J_{AB}= 12.3 Hz, δ_A-δ_B= 36.8 Hz), 3.63 (d, 1H, *J*= 2.0 Hz), 5.15 (br.s, 1H), 7.0-7.9 (m, 15H). ^{13}C NMR: δ 15.9, 22.6, 28.7, 55.0, 68.4, 78.5, 125.7, 126.0, 126.1, 126.4, 127.1, 127.8, 128.0, 128.2, 128.3, 140.1, 145.2, 148.8. IR (nujol): 3320, 3015, 1460, 1440, 1370, 1060 cm^{-1}·. MS: m/e 346 (MH^+, 100%), 328, 184, 162, 91. α_D -40.3 ° (c 1.1; CH_2Cl_2). $C_{24}H_{27}NO$. Calcd.: C, 83.44; H, 7.88; N, 4.05. Found: C, 83.34; H, 7.94; N, 4.11.

1(S)-α-(1-Methylamino-2-methylpropyl)-α-phenyl-benzenemethanol 7c and 1(S)-α-(1-dimethylamino-2-methylpropyl)-α-phenyl-benzenemethanol 7d.

Compound **4a** (510 mg, 2 mmol), K_2CO_3 (552 mg, 4 mmol) and methyl iodide (250 µL, 4 mmol) are refluxed in 8 mL EtOH for 24 h. The mixture is filtered on celite then the solvent is evaporated. The crude is chromatographed to give **7d** (oil, 212 mg, 0.75 mmol, 37 %) then the monomethyl product **7c** (white solid, 163 mg, 0.60 mmol., 30%). **7c**: mp 69-71 °C. ^1H NMR: δ 0.66 (d, 3H, *J* = 6.89 Hz), 1.01 (d, 3H, *J* = 7.08 Hz), 1.97 (hd, 1H, *J* = 6.98 and 1.87 Hz), 2.16 (s, 3H), 3.40 (d, 1H, *J*= 1.97 Hz), 7.1-7.7 (m, 10H). ^{13}C : δ 15.8, 22.9, 28.8, 38.0, 70.6, 78.6, 125.1, 126.1, 126.3, 127.8, 127.9, 145.5, 148.9. IR (nujol): 3350, 3070, 3050, 3010, 1595, 1480, 1440, 1380 cm^{-1}. MS: m/e 270 (MH^+, 100%), 252, 86. α_D -50.4 ° (c 2.1). $C_{18}H_{23}NO$. Calcd.: C, 80.26; H, 8.60; N, 5.20. Found: C, 80.55; H 8.35; N, 5.71. **7d**: ^1H NMR: δ 0.62 (d, 3H, *J* = 6.6 Hz), 0.97 (d, 3H, *J* = 6.4 Hz), 2.26 (s, 7H), 3.06 (d, 1H, *J* = 10.2 Hz), 7.1-7.7 (m, 10H). ^{13}C NMR: δ 23.0, 23.3, 29.4, 43.2, 78.8, 79.9, 126.7, 126.8, 127.5, 127.6, 128.1, 143.1, 146.3. IR (film): 3200, 3070, 3050, 3010, 1595, 1480, 1470, 1440, 1380 cm^{-1}. MS: m/e 284 (MH^+), 266, 183. α_D +10.3 ° (c 2). $C_{19}H_{25}NO$ Calcd.: C, 80.52; H, 8.89; N, 4.94. Found: C, 80.44; H, 8.96; N, 4.85.

3(S)-3-Dimethylamino-4-butyl-2-methyl-octane-4-ol 8a.

4d (416.6 mg, 1.93 mmol), dimethyl sulfate (1.8 mL, 10 equiv., *carcinogen*), and Na_2CO_3 (450 mg, 4 mmol.) are refluxed in 10 mL EtOH for 48 h. After filtration on celite, Et_2O (100 mL) is added and the organic phase is washed 3 times with a 10% NaOH solution. After drying (Na_2SO_4) and solvent removal, the crude oil (451.6 mg) is chromatographed to give **8a** (colorless oil, 347 mg, 1.42 mmol, 74 %) followed by the monomethyl product (non-fully characterized, colorless oil, 72 mg, 0.31 mmol, 18 %). **8a**: ^1H NMR: δ 0.91(t, 6H, *J* = 7.0 Hz), 1.01 (d, 3H, *J* = 6.6 Hz), 1.03 (d, 3H, *J* = 6.4 Hz), 1.1-1.6 (m, 12H), 2.0-2.2 (m, 1H), 2.26 (d, 1H, *J* = 10.2 Hz), 2.53 (s, 6H). ^{13}C NMR: δ 14.2, 22.2, 23.43, 23.49, 23.8, 25.6, 26.1, 28.4, 36.8, 37.2, 43.6, 72.9, 73.5. IR (film): 3450, 3200, 1470, 1460, 1380, 1370 cm^{-1}. MS: m/e 244 (MH^+, 100%), 100. α_D +10,3 ° (c 2.1). $C_{15}H_{33}NO$: Calcd.: C, 74.01; H, 13.66; N, 5.75. Found: C, 73.61; H, 13.44; N, 5.78.

3(S)-3-Dibutylamino-4-butyl-2-methyl-octane-4-ol 8c.

4d (249 mg, 1.15 mmol), butanoyl chloride (120 µL, 1.1 mmol) and 200 µL triethylamine in 6 mL CH_2Cl_2 are left to react at room temp. for 20 min. After evaporation of the solvent, ether (50 mL) is added, the

organic phase is washed with 3x3 mL of 10% aq. NaOH then worked up as usual to give the amide as an oil (330 mg, 1.15 mmol, 100 %). ^{1}H NMR: δ 0.8-1.1 (m, 15H), 1.1-1.6 (m, 12H), 1.70 (sextuplet, 2H, *J* = 7.4 Hz), 2.09 (hd, 1H, *J* = 6.8 and 2.3 Hz), 2.23 (t, 2H, *J* = 7.4 Hz), 3.87 (dd, 1H, *J* = 10.1 and 2.3 Hz), 5.93 (br. d, 1H, *J* = 10.1 Hz). ^{13}C NMR (20 MHz): δ 13.6, 13.80, 13.84, 17.0, 19.3, 22.3, 23.1, 23.2, 25.3, 25.8, 27.6, 35.4, 36.4, 38.8, 57.0, 76.8, 173.4. IR (nujol): 3400, 3300, 1640, 1540, 1460, 1370, 1360 cm^{-1}.MS : m/e 286 (MH^+, 100%), 268, 143. α_D -12.1 ° (c 0.8). $C_{17}H_{35}NO_2$: Calcd.: C, 71.52; H, 12.36; N, 4.91. Found: C, 71.34; H, 12.31; N, 4.94. This compound and BH_3-Me_2S (330 µL, 264 mg, 3.5 mmol., 3 equiv.) in 9 mL toluene are refluxed for 2 h. After hydrolysis under vigorous stirring by 2N aq. HCl, 10% NaOH is added until the pH is *ca.* 10. The aqueous phase is extracted with ethyl acetate then the organic layer worked up as usual. **8b** (302 mg, 1.11 mmol, 95 %) is obtained as a yellow oil. ^{1}H NMR: δ 0.8-1.0 (m, 12H), 1.03 (d, 3H, *J* = 7.1 Hz), 1.1-1.5 (m, 16H), 1.94 (hd, 1H, *J* = 6.9 and 2.3 Hz), 2.30 (d, 1H, *J* = 2.4 Hz), 2.5-2.6 (m, 1H), 2.8-2.9 (m, 1H). ^{13}C NMR (20 MHz): δ 14.00, 14.07, 14.14, 17.0, 20.3, 23.5, 23.7, 24.0, 25.8, 28.3, 33.3, 34.9, 37.1, 52.1, 67.7, 75.0. IR (film): 3400, 1460, 1380, 1370 cm^{-1}. MS: m/e 272 (MH^+-100%), 254, 214, 143. α_D +8.9 ° (c 1.7). $C_{17}H_{38}NO$. HRMS: Calcd. for MH^+: 272.2853. Found: 272.2938. The above process is repeated[16] from this compound (81.4 mg, 0.30 mmol), butanoyl chloride (60 µL, 0.57 mmol, 1.9 equiv.) and 200 µL triethylamine in 1.5 mL of CH_2Cl_2 at room temp. for 5 h. The mixture worked up as before gives the amide (102 mg, 0.299 mmol, 100 %) as an oil. ^{1}H NMR: δ 0.8-1.3 (m, 30H), 1.4-1.7 (m, 6H), 2.26 (td, 2H, *J* = 3.5 and 7.4 Hz), 2.5-2.7 (m, 1H), 2.75 (d, 1H, *J* = 5.2 Hz), 3.0-3.1 (m, 1H), 3.2-3.3 (m, 1H), 6.05 (s, 1H). ^{13}C NMR (100 MHz): δ 13.7, 14.01, 14.05, 14.11, 18.8, 20.1, 20.8, 23.1, 23.5, 25.0, 25.8, 26.7, 27.1, 31.1, 35.5, 36.2, 36.4, 54.2, 75.2, 174.7. IR (film): 3300, 1640, 1480, 1380 cm^{-1}. MS: m/e 342 (MH^+, 100%), 324, 284, 199. α_D +7.2 ° (c 0.8). $C_{21}H_{43}NO_2$: Calcd.: C, 73.84; H, 12.69; N, 4.10. Found: C, 73.89; H, 12.70; N, 4.40. N-butanoyl-N-butyl-1,1-dibutyl valinol (156 mg, 0.46 mmol) and BH_3-Me_2S (130 µL, 103 mg, 1.37 mmol, 3 equiv.) are refluxed in 5 mL toluene for 3 h, then the mixture is worked up to give after chromatography pure **8c** (144.5 mg, 0.44 mmol, 96 %) as a colorless oil. ^{1}H NMR: δ 0.70-0.85 (m, 12H), 0.9-1.0 (m, 6H), 1.1-1.6 (m, 20H), 1.9-2.1 (m, 1H), 2.34 (d, 1H, *J* = 10.5 Hz), 2.5-2.7 (m, 4H), 5.34 (s, 1H). ^{13}C NMR (75 MHz): δ 14.0, 14.12, 14.15, 20.4, 22.2, 23.47, 23.51, 23.8, 25.5, 25.9, 28.6, 32.9, 37.0, 37.9, 72.1, 72.3. IR (film): 3200, 1460, 1370 cm^{-1}. MS: m/e 328 (MH^+, 100%), 310, 270, 184. α_D +15.7 ° (c 2.5). $C_{21}H_{45}NO$: Calcd.: C, 76.99; H, 13.84; N, 4.28. Found: C, 77.25; H, 14.00; N, 4.25.

Standard procedure for alkylations.

In a 10 mL flask, N,N-dibutyl-1,1-dibutylvalinol (30.6 mg, 0.0936 mmol) and benzaldehyde (95 µL, 99.5 mg, 0.94 mmol) are dissolved in 1.5 mL dry toluene. Diethylzinc in hexane (1.2 mL, 1.2 mmol, 1.2 equiv) is added and the reaction is left to proceed at room temp. for 48 h *in the dark*. The mixture is then hydrolyzed with 1 mL 2N aq. HCl under strong stirring for 20 min. Conc. aq. NH_4OH is added to make the mixture alkaline (pH>10), the aqueous phase is extracted with diethyl ether (3x30 mL). The organic layer is dried and the solvent evaporated. The crude oil is chromatographed to provide **7c** (30.6 mg, 100 %) and 1-phenylpropanol (127.2 mg, 0.935 mmol, 99.5 %), which is distilled (Kugelrohr, 90°C, 2 torr) before esterification to Mosher's ester. Secondary alcohols obtained by this procedure have spectral and analytical data in accordance to published data.

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