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Catalytic enantioselective borane reduction of arylketones with pinene-derived amino alcohols

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Abstract

Both *cis*- and *trans*-1,2-amino alcohols **5** and their *N*-alkylated derivatives **6** were prepared from (−)-α-pinene **7** as chirality source and utilized in asymmetric borane reduction of arylketones **12** employing a one-pot multi-substrate screening. The oxazaborolidine catalysts were generated in situ from amino alcohols **5** and **6** and trimethyl borate.
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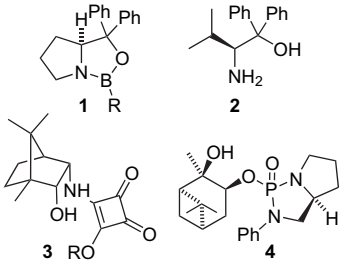
Keywords: Amino alcohols; Asymmetric catalysis; Boron; Pinene

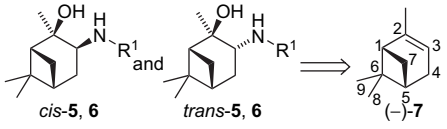
1. Introduction

Since the first report by Itsuno[1] and further development by Corey[2] that enantiomerically pure oxazaborolidines such as **1** efficiently catalyze the borane reduction of ketones to the corresponding secondary alcohols, the asymmetric CBS reduction has been grown into a reliable synthetic method,[3] which is amenable even to industrial scale production.[4] The majority of oxazaborolidines were either formed in situ or prepared separately from amino acid-derived amino alcohols (e.g., **2**). Terpenes such as camphor **3**, fenchone, or pinene **4** (Scheme 1) were used to a much lesser extent for this purpose.[5,6]

We have recently evaluated α-pinene as a versatile chiral scaffold for the synthesis of bisphosphinites and other phosphorus ligands.[7–9] In this context we also prepared *cis*- and *trans*-1,2-amino alcohols **5** and **6** from α-pinene (−)-**7** (Scheme 2) and investigated their behavior in the enantioselective borane-mediated reduction of prochiral ketones. The results toward this goal are reported below.



Scheme 1. Some potential catalysts in the asymmetric borane reduction of ketones developed by Itsuno,[1] Corey,[2,3] Xie,[5b] and Basavaiah.[5d]



Scheme 2.

2. Results and discussion

The synthetic approach to the amino alcohols **5** and their *N*-alkylated derivatives **6** is depicted in Scheme 3. Following a procedure by Pierce and Carlson[10] (−)-α-pinene **7** was treated with $KMnO_4$ to give the α-hydroxyketone **8**, which was converted into the crystalline oxime **9**[11a] in 97% yield.

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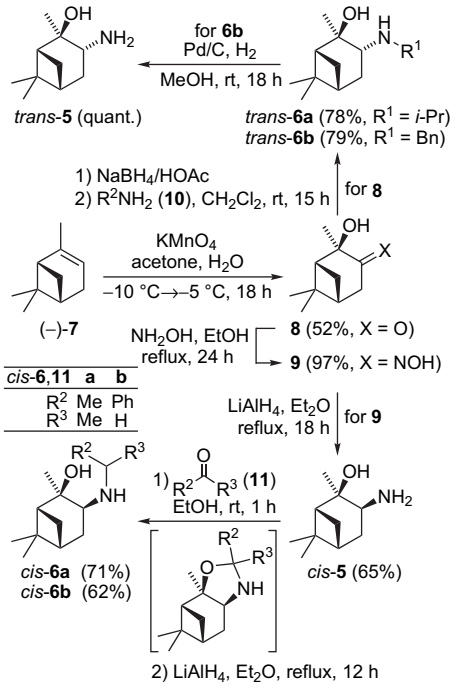


Scheme 3.

Reduction of **9** with $LiAlH_4$ in Et_2O yielded selectively *cis*-3-aminopinan-2-ol *cis*-**5**[11] in 65%. Following the reductive alkylation by Saavedra,[12] compound *cis*-**5** was treated with acetone (**11a**) or benzaldehyde (**11b**) in EtOH to give the corresponding intermediate oxazolidines, which were reduced with $LiAlH_4$ in Et_2O. After chromatographic purification on silica gel, *N*-isopropyl-[13] and *N*-benzyl-substituted *cis*-amino alcohols *cis*-**6a**,**b** were isolated in 71 and 62% yields, respectively. Derivative *cis*-**6a** was converted into the hydrochloride, which gave single crystals being suitable for X-ray crystal structure analysis (Fig. 1).[14] In this way, the absolute configuration of **6a** was determined to be 1*R*,2*R*,3*S*,5*R*.

Direct reductive amination[15] of α-hydroxyketone **8** with isopropyl- (**10a**) and benzylamine (**10b**) and $NaBH(OAc)_3$, which was formed in situ from $NaBH_4$ and HOAc, afforded the target amino alcohols *trans*-**6a** and *trans*-**6b** in 78 and 79% yields, respectively, and high diastereoselectivity (cis/trans=1:99). The 3-aminopinan-2-ol *trans*-**5** was obtained quantitatively by hydrogenation of *trans*-**6b** in MeOH (Scheme 3).

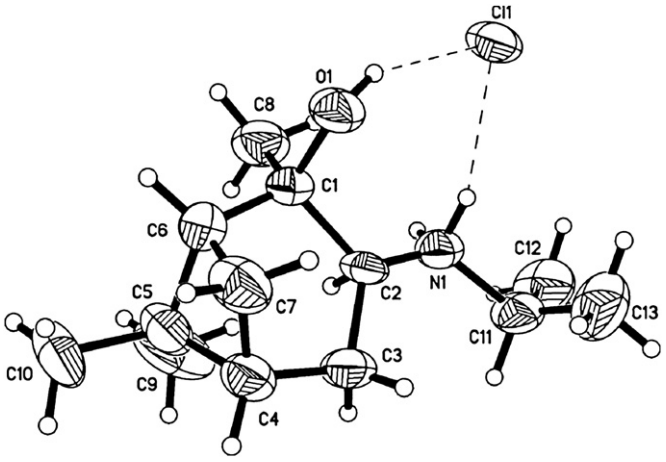


Figure 1. ORTEP plot of (1*R*,2*R*,3*S*,5*R*)-3-(isopropylamino)-2,6,6-trimethylbicyclo[3.1.1]heptan-2-ol hydrochloride (*cis*-**6a**·HCl).

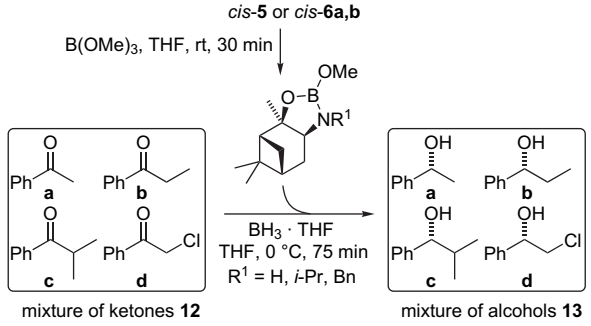
Prior to reduction of alkylarylketones **12** to secondary alcohols **13** (Table 1) using the chiral amino alcohols **5** and **6**, the racemic products *rac*-**13**, which were needed as a standard in GC analysis, were prepared from ketones **12** by treatment with $NaBH_4$ in MeOH at 0 °C.

For easier product analysis the 'one-pot multi-substrate screening' was used, which was originally introduced by Kagan.[16] As shown in Figure 2, the starting ketones **12a**–**d** and the resulting secondary alcohols **13a**–**d** were clearly separated in a single run on GC and unambiguously assigned.

Furthermore, as shown in Figure 3, a base line separation of the four pairs of enantiomers **13a**–**d** on a chiral stationary phase Bondex-unβ by capillary GC was achieved.

Thus, this methodology was applied to the asymmetric borane-catalyzed reduction of ketones **12** (Table 1). An equimolar mixture of the four substrates acetophenone (**12a**), propiophenone (**12b**), 2-methylpropiophenone (**12c**), and 2-chloroacetophenone (**12d**) (0.25 mmol each) was added over 75 min to a solution of the respective amino alcohols

Table 1
Catalytic borane reduction of a mixture of ketones **12** to alcohols **13** with *cis*-amino alcohols **5** and **6** using the one-pot multi-substrate screening[a]



Entry	Substrate **12**	Catalyst	Product **13**	Conv. [b,c] [%]	% ee[b,c]	Config.[d]
1	**a**	*cis*-**5**	**a**	100 (100)	96 (93)[e]	*R*
2	**b**	*cis*-**5**	**b**	100 (98)	93 (90)	*R*
3	**c**	*cis*-**5**	**c**	100 (100)	61 (57)	*R*
4	**d**	*cis*-**5**	**d**	100 (100)	91 (83)	*S*
5	**a**	*cis*-**6a**	**a**	100 (100)	6 (24)[f]	*R*
6	**b**	*cis*-**6a**	**b**	98 (100)	6 (20)	*R*
7	**c**	*cis*-**6a**	**c**	30 (100)	2 (2)	—
8	**d**	*cis*-**6a**	**d**	100 (100)	3 (22)	*S*
9	**a**	*cis*-**6b**	**a**	100 (100)	7 (3)	—
10	**b**	*cis*-**6b**	**b**	100 (100)	—	—
11	**c**	*cis*-**6b**	**c**	100 (100)	6 (—)	—
12	**d**	*cis*-**6b**	**d**	100 (100)	6 (2)	—

[a] Reaction conditions: ketone solution (1 mL), THF (1 mL), $B(OMe)_3$ (1 mL, 0.1 M solution), BH_3·THF (1 mL, 1 M solution), 0 °C→rt, 75 min.
[b] Conversions determined by capillary GC on an achiral phase and enantioselectivities on a chiral Bondex-unβ phase.
[c] Conversion and ee values of reactions without $B(OMe)_3$ additive in parenthesis.
[d] Assignment by comparison of optical rotation values with literature data.
[e] For comparison see Refs. 13 and 17.
[f] For comparison see Ref. 13.

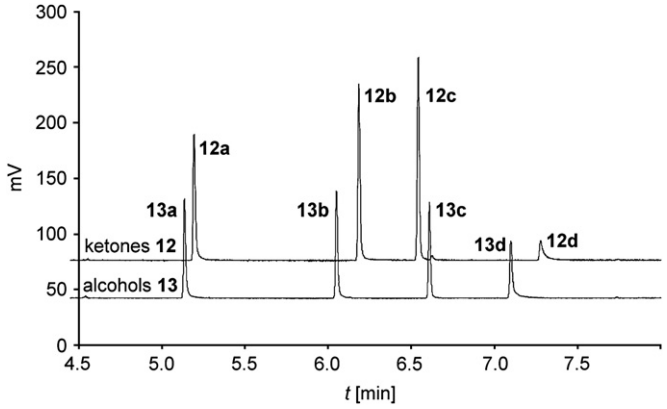


Figure 2. Capillary GC trace of a mixture of arylketones **12a–d** and the resulting alcohols **13a–d**.

cis-**5** or *cis*-**6a**,**b** (10 mol %) and $BH_3 \cdot THF$ (1 equiv) in abs THF at 0 °C. As catalytic borane reductions are known to be improved by the addition of trimethyl borate resulting in the in situ formation of an oxazaborolidine with a B–OMe rather than a B–H moiety,[3,17] reactions were also carried out in the presence of 10 mol % trimethyl borate in order to study the effect on our catalytic system. After workup, the product mixture was analyzed in a single run by capillary GC with regard to conversion and enantioselectivity (Table 1).

As shown in Table 1, in the case of *cis*-**5**, $B(OMe)_3$ addition led to higher enantiomeric excesses as compared to the results without additive with the highest effect for product **13d** (entry 4). The best ee values were achieved for alcohol **13a** (entry 1). This result is in good agreement with findings by Markowicz[13] and Shioiri[17] who obtained similar enantioselectivities for the enantiomeric ligand *ent-cis*-**5** from (+)-α-pinene. In contrast, $B(OMe)_3$ lowered the ee values when *cis*-**6a** was used (entries 5, 6, and 8). The *N*-benzylated amino alcohol *cis*-**6b**, however, was not effected, giving nearly racemic mixture in all cases despite of complete conversions (entries 9–12). Both the size of the substrate and the bulkiness of substituent R^1 in the oxazaborolidine influenced the enantioselectivity. The ee values of alcohol **13a** decreased from 93 (R^1=H) to 24% (R^1=*i*-Pr) and 3% (R^1=Bn) (entries 1, 5, and 9). Within the product mixture **13a–d** the lowest enantiomeric excess was found for the branched alcohol **13c** (entries 3 and 7) combined with low conversion in the case of *cis*-**6a** (entry 7). Markowicz[13] also reported a decrease of enantioselectivity upon using the antipode *ent-cis*-**6a** instead of *ent-cis*-**5**. However, the effect was much less pronounced as compared to our results.

The corresponding *trans*-amino alcohols *trans*-**5** and *trans*-**6a**,**b** did not show enantioselectivity, resulting not only in racemic products **13** but also in low conversions.

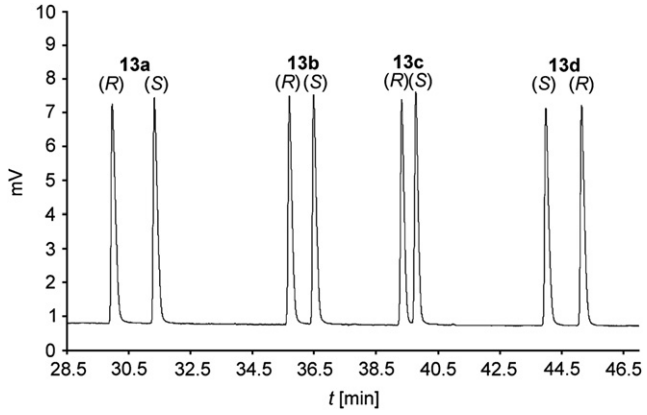


Figure 3. Capillary GC trace of a mixture of racemic secondary alcohols **13a–d** on a chiral stationary phase Bondex-unβ.

3. Conclusion

Starting from (−)-α-pinene **7** a series of *cis*- and *trans*-amino alcohols **5** and **6** were conveniently prepared. The in situ formed oxazaborolidines from compounds **5** and **6** and trimethyl borate and $BH_3 \cdot THF$ are capable of catalyzing the reduction of arylketones **12** to the secondary alcohols **13**. The used 'one-pot multi-substrate screening' allowed the analysis of the product mixture by GC in a single run on a chiral stationary phase. The reagent from *cis*-**5**/trimethyl borate afforded the secondary alcohols (*R*)-**13a–c** and (*S*)-**13d** in high enantiomeric excesses (up to 96% for (*R*)-1-phenylethanol **13a**), which are slightly higher than those obtained by Rao for related camphor-derived *endo*- and *exo*-amino alcohols.[5e] Furthermore, while Rao reported decreased enantioselectivities upon addition of trimethyl borate, we found improved selectivities for *cis*-**5** in the presence of trimethyl borate as compared to parent system without any additives. The *N*-alkylated amino alcohols *cis*-**6a**,**b** gave poor ee values thus indicating the deleterious effect of steric hindrance on the enantioselectivity. The oxazaborolidines from the corresponding *trans*-amino alcohols and trimethyl borate gave low conversion and only racemic products **13**.

4. Experimental section

4.1. General

Melting points (uncorrected) were determined on a Büchi 510 melting point apparatus. Optical rotations were determined with a Perkin–Elmer 241 LC polarimeter. IR spectra: Bruker Vektor 22 FT-IR spectrometer. Mass spectra: Finnigan MAT 95 and Varian MAT 711 spectrometers. NMR spectra: Bruker AC-250F and Bruker ARX 500 spectrometers. The spectra were recorded with TMS as an internal standard. ^{13}C NMR multiplicities were determined by DEPT experiments. Column chromatography: Macherey-Nagel Kieselgel 60 (230–400 mesh). GC: Hewlett Packard HP 5890 with capillary column HP-5MS (30 m×0.32 mm); temperature program: starting temperature 80 °C, then 8 °C min^{-1} gradient to 280 °C. GC condition for ee determination is given in the appropriate preparation. Derivatives **8**, **9**, *cis*-**5** were prepared according to the literature.[10,11]

4.2. (1R,2R,3S,5R)-3-(Isopropylamino)-2,6,6-trimethylbicyclo[3.1.1]heptan-2-ol (*cis*-**6a**) via benzoxazole

(a) To a solution of *cis*-**5** (338 mg, 2.0 mmol) in abs EtOH (5 mL) at room temperature was added acetone (**11a**)

(0.18 mL, 3.0 mmol). After 2 h, additional **11a** (0.18 mL, 3.0 mmol) was added and the reaction mixture stirred for a further 30 min. The solvent was removed under vacuum to give (3a*S*,5*R*,7*R*,7a*R*)-2,2,6,6,7a-pentamethyloctahydro-5,7-methano-1,3-benzoxazole as a colorless liquid (386 mg, 95%). $[\alpha]_D^{20}$ +18.4 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ=0.87 (s, 3H, 7a-CH_3), 1.28 (s, 3H, 9-H), 1.36 (d, *J*=10.9 Hz, 1H, 7-H), 1.37 (s, 3H, 8-H), 1.44 (s, 3H, C(CH_3)$_2$), 1.47 (s, 3H, C(CH_3)$_2$), 1.57 (dd, *J*=3.6, 1.0 Hz, 1H, 10-H), 2.01 (t, *J*=5.2 Hz, 1H, 4-H), 1.93 (m_c, 1H, 5-H), 2.15 (m_c, 1H, 4-H), 2.30 (dd, *J*=6.0, 8.7 Hz, 1H, 10-H), 3.41 (d, *J*=8.4 Hz, 1H, 3a-H), 7.28 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ=23.9 (7a-CH_3), 25.7 (C-4), 27.4 (C(CH_3)$_2$), 28.4 (C-8), 29.9 (C-9), 32.9 (C-10), 38.0 (C-6), 40.4 (C-5), 52.1 (C-7), 59.1 (C-3a), 84.8 (*C*(CH_3)$_2$), 93.6 (C-7a); IR (film) 3320 (br), 2977 (s), 2908 (s), 2870 (s), 1970 (br), 1455, 1428, 1373 (s), 1269, 1233, 1204, 1173, 1142, 1073, 1052, 1018, 993, 951, 931, 916, 872, 795 cm^{-1}; MS (EI): *m*/*z* (%)=210 (1) [M^++H^+], 209 (7) [M^+], 196 (1), 195 (14), 194 (100), 177 (1), 167 (1), 166 (6), 153 (3), 152 (25), 140 (1), 139 (14), 135 (34), 120 (2), 119 (5), 113 (11), 109 (18), 99 (2), 98 (32), 93 (51), 85 (10), 84 (64), 71 (16), 60 (61), 44 (41), 41 (33), 28 (9), 18 (17). Anal. Calcd for $C_{13}H_{23}NO$: C, 74.59; H, 11.07; N, 6.69. Found: C, 74.58; H, 11.03; N, 6.71.

(b) To a suspension of $LiAlH_4$ (759 mg, 20.0 mmol) in abs Et_2O (75 mL) at 0 °C was added dropwise a solution of the benzoxazole (2.09 g, 10.0 mmol) in abs Et_2O (10 mL) and the reaction mixture heated at reflux for 14 h. The reaction mixture was then hydrolyzed with EtOAc (2 mL) and 1 N NaOH solution (6 mL). The precipitate was filtered off and washed with Et_2O (3×50 mL). The combined organic layers were concentrated under vacuum to give *cis*-**6a** as a colorless liquid (1.91 g, 90%). ^1H NMR (250 MHz, $CDCl_3$) δ=0.98 (s, 3H, 2-CH_3), 1.10 (dd, *J*=4.6, 4.8 Hz, 6H, CH(CH_3)$_2$), 1.21 (s, 3H, 9-H), 1.23 (m_c, 2H, 4-H), 1.26 (s, 3H, 8-H), 1.85 (m_c, 1H, 5-H), 1.99 (t, *J*=5.7 Hz, 1H, 1-H), 2.13 (m_c, 1H, 7-H), 2.54 (m_c, 1H, 7-H), 2.83 (m_c, 1H, C*H*(CH_3)$_2$), 2.91 (m_c, 1H, 3-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ=23.3 (2-CH_3), 23.9 (C-9), 24.1 (C-8), 28.0 (CH(*C*H_3)$_2$), 31.2 (C-4), 38.4 (C-7), 39.6 (C-5), 40.5 (C-6), 48.9 (C-1), 53.7 (*C*H(CH_3)$_2$), 54.3 (C-3), 71.4 (C-2). The spectroscopic data were in accordance with those in the literature.[13]

*4.3. (1R,2R,3S,5R)-3-(Benzylamino)-2,6,6-trimethylbicyclo-[3.1.1]heptan-2-ol (cis-**6b**) via benzoxazole*

(a) Benzaldehyde (**11b**) (1.52 mL, 15.0 mmol) was added to a solution of *cis*-**5** (1.69 g, 10.0 mmol) in abs MeOH (15 mL) and the reaction mixture stirred for 1 h. The solvent was removed under vacuum, the residue dissolved in EtOH (25 mL) and adjusted to pH 5 with concd HCl. After removal of the solvent under vacuum, the residue was washed with acetone (3×10 mL). The obtained hydrochloride was dissolved in H_2O (50 mL) and alkalized with 10 N NaOH solution. The precipitate was extracted with EtOAc (3×50 mL), the combined organic layers successively washed with H_2O (2×50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated to give a diastereomeric mixture of 6,6,7a-trimethyl-2-phenyloctahydro-5,7-methano-1,3-benzoxazole as a pale yellow liquid (2.14 g, 83%). ^1H NMR (500 MHz, $CDCl_3$) δ=0.92 (s, 2.1H, 7a-CH_3*), 0.99 (s, 3.9H, 7a-CH_3), 1.32 (s, 6H, 9-H, 9*-H), 1.34 (s, 3.9H, 8-H), 1.42 (s, 2.1H, 8*-H), 1.44 (d, *J*=10.0 Hz, 1.3H, 4-H), 1.58 (m_c, 1.3H, 5-H), 1.76 (m_c, 0.7H, 5*-H), 1.95 (m_c, 2.0H, 7-H, 7*-H), 2.24 (m_c, 2.7H, 4*-H, 10-H, 10*-H), 2.42 (m_c, 2H, 4-H, 4*-H), 3.32 (dd, *J*=9.0, 1.7 Hz, 0.7H, 3a*-H), 3.57 (dd, *J*=9.5, 5.5 Hz, 1.3H, 3a-H), 5.38 (s, 0.7H, 2*-H), 5.69 (s, 1.3H, 2-H), 7.30–7.55 (m, 10H, aromat); ^{13}C NMR (125 MHz, $CDCl_3$) δ=23.9 (7a-CH_3*), 24.0 (7a-CH_3), 25.6 (C-4*), 26.3 (C-4), 27.3 (C-9*), 27.6 (C-9), 27.8 (C-8*), 29.5 (C-8), 33.8 (C-6*), 35.1 (C-6), 38.1 (C-10*), 39.4 (C-10), 40.4 (C-5*), 40.6 (C-5), 51.2 (C-7*), 52.9 (C-7), 59.3 (C-3a*), 59.5 (C-3a), 83.8 (C-7a*), 86.0 (C-7a), 89.3 (C-2*), 92.9 (C-2), 126.2 (C-4′*), 126.3 (C-4′), 128.2–134.5 (C-2′, C-2′*, C-3, C-3′*), 138.5 (C-1′*), 140.1 (C-1′) (* signal of the minor diastereomer); IR (film) 3314, 3061 (w), 2978, 2951, 2917 (s), 2865, 1953 (w), 1889 (w), 1809 (w), 1739 (w), 1704 (w), 1601 (w), 1547 (w), 1494, 1470, 1447, 1430, 1386, 1367, 1345, 1306, 1273, 1245, 1223, 1206, 1170, 1159, 1145, 1123, 1113, 1082, 1029, 1011, 998, 972, 945, 937, 918, 907, 883, 867, 838 cm^{-1}; MS (EI): *m*/*z* (%)=258 (14) [M^++H^+], 257 (78) [M^+], 242 (3), 214 (8), 187 (8), 180 (18), 161 (26), 145 (8), 144 (21), 132 (100), 119 (31), 105 (52), 94 (8), 93 (41), 79 (14), 77 (23), 67 (10), 55 (8), 43 (13), 41 (18), 28 (25).

(b) To an ice cold suspension of $LiAlH_4$ (759 mg, 20.0 mmol) in abs Et_2O (65 mL) was added dropwise a solution of benzoxazole (2.57 g, 10.0 mmol) in abs Et_2O (10 mL) and the reaction mixture heated at reflux for 18 h. It was then hydrolyzed with EtOAc (2 mL) and 1 N NaOH solution (4 mL). The precipitate was filtered off and washed with Et_2O (3×50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was chromatographed on SiO_2 (200 g) with CH_2Cl_2/MeOH/NH_3 (100:10:1) to give *cis*-**6b** as a light yellow liquid (2.10 g, 81%). $[\alpha]_D^{20}$ −41.1 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ=0.94 (s, 3H, 2-CH_3), 1.25 (s, 3H, 9-H), 1.26 (s, 3H, 8-H), 1.28 (m_c, 2H, 7-H), 1.87 (m_c, 1H, 5-H), 1.99 (t, *J*=5.8 Hz, 1H, 1-H), 2.14 (m_c, 1H, 4-H), 2.48 (m_c, 1H, 4-H), 2.96 (dd, *J*=9.8, 5.9 Hz, 1H, 3-H), 3.87 (d, *J*=12.8 Hz, 1H, CH_aH_bPh), 3.92 (d, *J*=12.8 Hz, 1H, CH_aH_bPh), 7.31 (m_c, 5H, aromat); ^{13}C NMR (125 MHz, $CDCl_3$) δ=24.1 (2-CH_3), 27.9 (C-9), 28.1 (C-4), 31.4 (C-8), 38.1 (C-7), 38.3 (C-6), 40.5 (C-5), 54.2 (C-1), 54.3 (*C*H_2Ph), 56.9 (C-3), 71.7 (C-2), 127.3 (C-4′), 128.2 (C-2′), 128.6 (C-3′), 139.9 (C-1′); IR (film) 3315 (br), 3063, 3028, 2985, 2905 (s), 2868, 1604, 1495, 1452, 1383, 1368, 1325, 1272, 1219, 1166, 1120, 1095, 1017, 949, 937, 922, 899, 859, 738, 697, 653 cm^{-1}; MS (EI): *m*/*z* (%)=259 (2) [M^+], 244 (2), 216 (8), 188 (3), 160 (4), 134 (25), 133 (100), 104 (3), 91 (68), 72 (8), 43 (6), 28 (14). Anal. Calcd for $C_{17}H_{25}NO$: C, 78.72; H, 9.71; N, 5.40. Found: C, 78.36; H, 9.68; N, 5.43.

*4.4. General procedure for the preparation of trans-amino alcohols (**6**) by reductive amination*

To a suspension of finely powdered $NaBH_4$ (980 mg, 26.0 mmol) in abs CH_2Cl_2 (60 mL) was added dropwise glacial

acetic acid (4.80 mL, 84.0 mmol) and the suspension heated at reflux for 30 min. The reaction mixture was cooled to room temperature and a solution of **8** (1.68 g, 10.0 mmol) in abs CH_2Cl_2 (10 mL) was added followed by a solution of isopropylamine (**10a**) (2.22 mL, 26.0 mmol) or benzylamine (**10b**) (2.84 mL, 26.0 mmol) in abs CH_2Cl_2 (10 mL). After stirring at room temperature for 15 h, the reaction mixture was hydrolyzed with 2 N NaOH solution (11 mL) and adjusted to pH 10 with 2 N NaOH solution. The layers were separated and the organic layer extracted with 1 N HCl (7×25 mL). The extracts were alkalized with NaOH, the precipitate filtered off and extracted with Et_2O (3×50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and concentrated under vacuum. The residue was chromatographed on SiO_2 with Et_2O/MeOH/NH_3.

*4.4.1. (1R,2R,3R,5R)-3-(Isopropylamino)-2,6,6-trimethylbicyclo[3.1.1]heptan-2-ol (trans-**6a**)*

Colorless liquid (1.65 g, 78%), cis/trans=1:99; $[\alpha]_D^{20}$ −23.4 (*c* 1.0, CH_2Cl_2); R_f (Et_2O/MeOH/NH_3=150:10:1)=0.52; ^{1}H NMR (500 MHz, $CDCl_3$) δ=0.87 (s, 3H, 2-CH_3), 1.07 (dd, *J*=6.2, 6.3 Hz, 6H, CH(CH_3)$_2$), 1.24 (s, 3H, 9-H), 1.32 (s, 3H, 8-H), 1.36 (m_c, 1H, 4-H), 1.60 (d, *J*=10.4 Hz, 1H, NH), 1.63 (m_c, 1H, 4-H), 1.87 (t, *J*=5.7 Hz, 1H, 1-H), 1.92 (m_c, 1H, 5-H), 2.27 (m_c, 1H, 7-H), 3.01 (m_c, 1H, 7-H), 3.02 (m_c, 1H, CH(CH$_3$)$_2$), 3.21 (t, *J*=9.1 Hz, 1H, 3-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=23.0 (2-CH_3), 23.2 (C-8), 23.2 (C-9), 24.7 (CH(CH_3)$_2$), 27.7 (C-4), 33.6 (C-7), 39.2 (C-5), 40.4 (C-6), 46.2 (C-1), 55.8 (CH(CH$_3$)$_2$), 57.2 (C-3), 78.1 (C-2); IR (film) 3411 (br, NH), 2956 (s), 2908 (s), 2867 (s), 2548 (br), 2361 (s), 2342, 2159, 1975, 1661, 1458, 1381, 1366, 1267, 1227, 1164, 1126, 1066 (s), 1030, 921, 891, 846 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{25}NO$ 212.2014 [M^+], found 212.2013 [M^++H^+]. Anal. Calcd for $C_{13}H_{25}NO$: C, 73.88; H, 11.92; N, 6.63. Found: C, 73.84; H, 11.83; N, 6.65.

*4.4.2. (1R,2R,3R,5R)-3-(Benzylamino)-2,6,6-trimethylbicyclo[3.1.1]heptan-2-ol (trans-**6b**)*

Colorless oil (2.05 g, 79%), cis/trans=1:99; $[\alpha]_D^{20}$ −42.6 (*c* 1.0, CH_2Cl_2); R_f (Et_2O/MeOH/NH_3=100:10:1)=0.73; ^{1}H NMR (500 MHz, $CDCl_3$) δ=0.91 (s, 3H, 2-CH_3), 1.24 (s, 3H, 9-H), 1.40 (s, 3H, 8-H), 1.48 (m_c, 1H, 5-H), 1.54 (d, *J*=10.4 Hz, 1H, 4-H), 1.87 (t, *J*=5.7 Hz, 1H, 1-H), 1.94 (m_c, 1H, 4-H), 2.11 (m_c, 1H, 7-H), 2.31 (m_c, 1H, 7-H), 3.14 (t, *J*=8.6 Hz, 1H, 3-H), 3.90 (d, *J*=12.6 Hz, 1H, CH_2Ph), 4.01 (d, *J*=12.6 Hz, 1H, CH_2Ph), 7.24 (m_c, 1H, 4′-H), 7.32 (m_c, 2H, 3′-H), 7.37 (m_c, 2H, 2′-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=23.1 (2-CH_3), 24.7 (C-9), 24.8 (C-8), 27.7 (C-4), 33.2 (C-7), 35.4 (CH_2Ph), 39.2 (C-6), 40.3 (C-5), 52.9 (C-1), 60.3 (C-3), 77.9 (C-2), 126.9 (C-4′), 128.1 (C-3′), 128.4 (C-2′), 140.9 (C-1′); IR (film) 3402 (br, NH), 3025, 2990, 2907 (s), 2866, 1603 (w), 1494, 1453, 1384, 1366, 1212, 1159, 1129, 1091, 1070, 1028, 921, 891, 732, 696 (s) cm^{-1}; MS (EI): *m/z* (%)=259 (2) [M^+], 254 (7), 216 (3), 188 (2), 160 (4), 135 (4), 134 (30), 133 (100), 118 (5), 104 (6), 92 (7), 91 (71), 65 (6), 43 (8), 28 (13). Anal. Calcd for $C_{17}H_{25}NO$: C, 78.72; H, 9.71; N, 5.40. Found: C, 78.38; H, 9.62; N, 5.44.

*4.5. (1R,2R,3R,5R)-3-Amino-2,6,6-trimethylbicyclo[3.1.1]heptan-2-ol (trans-**5**)*

To a solution of *trans*-**6b** (519 mg, 2.0 mmol) in abs MeOH (10 mL) at room temperature was added 10% Pd/C (20 mg) and the suspension stirred for 18 h under 1 atm of H_2. The catalyst was filtered through Celite and the solvent removed under vacuum to give *trans*-**5** as a crystalline powder (338 mg, quant.). Mp 72 °C (66–67 °C);[18] $[\alpha]_D^{20}$ −31.2 (*c* 1.0, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ=0.88 (s, 3H, 2-CH_3), 1.25 (s, 3H, 9-H), 1.30 (s, 3H, 8-H), 1.41 (q, *J*=5.2 Hz, 1H, 5-H), 1.58 (d, *J*=10.5 Hz, 1H, 1-H), 1.73 (br, 3H, NH_2, OH), 1.93 (sext, *J*=5.4 Hz, 2H, 4-H), 2.13 (m_c, 1H, 7-H), 2.31 (sept, *J*=5.0 Hz, 1H, 7-H), 3.33 (t, *J*=9.2 Hz, 1H, 3-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=23.2 (2-CH_3), 24.9 (C-8), 24.5 (C-9), 27.7 (C-4), 34.9 (C-7), 39.2 (C-5), 40.5 (C-6), 54.6 (C-1), 55.3 (C-3), 77.6 (C-2); IR (film) 3374 (NH), 3317 (NH), 3191 (br, NH), 2988, 2915 (s), 2902 (s), 2868, 1577 (s), 1459, 1382, 1372, 1325, 1268, 1240, 1156, 1108, 1061, 983, 929, 920, 895, 838, 739 (br), 698 (br), 659 (br), 578 cm^{-1}; MS (EI): *m/z* (%)=169 (1) [M^+], 151 (2), 136.1 (3), 127 (3), 126 (30), 112 (4), 111 (41), 99 (11), 93 (12), 71 (48), 58 (8), 56 (15), 44 (100), 30 (19).

*4.6. General procedure for the preparation of racemic alcohols (rac-**13**)*

To a stirred solution of the respective **12** (5.0 mmol) in abs MeOH (10 mL) at 0 °C was added $NaBH_4$ (95.0 mg, 2.50 mmol) over 15 min, and the reaction mixture was stirred for a further 2 h. After hydrolysis with a satd NH_4Cl solution (15 mL), the reaction mixture was extracted with EtOAc (3×15 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and the solvent was removed under vacuum. The enantiomers were separated by GC on a column Bondex-unβ (20 m×0.30 mm) and H_2 as carrier gas; temperature program: 5 min at 40 °C, then 2 °C min^{-1} gradient to 140 °C followed by 10 °C min^{-1} gradient to 200 °C.

*4.6.1. rac-1-Phenylethanol (rac-**13a**)*

$t_R(R)$=30.0 min, $t_R(S)$=31.3 min.

*4.6.2. rac-1-Phenylpropanol (rac-**13b**)*

$t_R(R)$=35.7 min, $t_R(S)$=36.5 min.

*4.6.3. rac-2-Methyl-1-phenylpropanol (rac-**13c**)*

$t_R(R)$=39.3 min, $t_R(S)$=39.8 min.

*4.6.4. rac-2-Chloro-1-phenylethanol (rac-**13d**)*

$t_R(R)$=45.1 min, $t_R(S)$=44.0 min.

4.7. General procedure for the one-pot multi-substrate screening

To a solution of the respective amino alcohol **5** or **6** (0.10 mmol) in abs THF (1 mL) at 0 °C were added 1 M BH_3·THF solution (1.0 mL, 1.00 mmol) in THF and 0.1 M

$B(OMe)_3$ solution (1.0 mL, 0.10 mmol) in THF followed by dropwise addition of the mixture of substrates **12** (1.0 mL, 1.00 mmol) [prepared from 2.50 mmol of each ketone **12** in 10 mL THF] over 75 min by syringe. The reaction mixture was hydrolyzed with H_2O (4 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. The crude product mixture was taken up in CH_2Cl_2 and directly analyzed by GC as described for the racemic mixture.

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