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One-Pot Synthesis of Trisubstituted 1,2-Amino Alcohols from Deprotonated α-Amino Nitriles

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A short synthesis of *N*,1,2-trisubstituted vicinal amino alcohols by 1,2-addition of deprotonated *N*-monosubstituted α-amino nitriles to aldehydes and subsequent one-pot reduction of the intermediates with borane–THF is described. This procedure leads to the predominant formation of the *anti*-configured products.

Introduction

Vicinal amino alcohols are prominent members of the large class of 1,2-difunctional compounds. They can be found in nature where they play for instance a role as neurotransmitters, hormones or constituents of enzyme inhibitors. Some synthetic 1,2-amino alcohols are used as antiretroviral or antimalarial[1] agents or as drugs that interfere with noradrenergic signal transmission.[2] Moreover, they can serve as useful synthetic intermediates for the preparation of heterocyclic compounds. Chiral vicinal amino alcohols are used as ligands in asymmetric catalysis as well as in the preparation of chiral auxiliaries.[3–5] Owing to their versatility in a range of applications, miscellaneous methods have been developed for the preparation of vicinal amino alcohols,[6] including the reduction of amino acids,[7,8] α-amino ketones[9–11] or nitro alcohols,[12] nucleophilic addition to α-amino aldehydes,[13] cyanohydrins[14] or α-hydroxyimines,[15] the opening of epoxides with nitrogen nucleophiles[16,17] and many more.

Methods for the formation of the central C–C bond of a 1,2-amino alcohol are also known, the most important one being the addition of nitronates to aldehydes.[18–20] This reaction can also be conducted in an asymmetric fashion but its scope is limited by the availability of suitably substituted nitroalkanes.[21] An alternative route is the 1,2-addition of α-metallated amines to aldehydes. In this case, however, protection of the amine nitrogen is required if products with a primary or secondary amino function are to be obtained.

Herein, we describe a short access to *N*,1,2-trisubstituted vicinal amino alcohols from *N*-monosubstituted α-amino nitriles and aldehydes that does not require protecting-group manipulations. Owing to the anion-stabilizing effect of the nitrile function, α-amino nitriles can serve as readily accessible α-amino carbanion equivalents.[22] Stork et al. used the addition of deprotonated Strecker products to aldehydes for the preparation of 1,2-amino alcohols.[23] In this case, however, an *N*-acyl protecting group was used to prevent the undesired elimination of HCN, that is, the retro-Strecker reaction, during the deprotonation of the pronucleophile.

Results and Discussion

We found that *N*-mono- and even *N*-unsubstituted α-amino nitriles can be quantitatively deprotonated without inducing the elimination of HCN if an aromatic, heteroaromatic or olefinic α-substituent is present. The resulting stabilized α-amino carbanions readily undergo 1,4-additions to α,β-unsaturated aldehydes, ketones and esters, whereas their 1,2-addition to imines furnishes enediamines.[24–26] The latter reaction can be understood by the intermediate formation of an amide anion followed by intramolecular elimination of HCN. In contrast, the addition of α-deprotonated Strecker products to non-enolizable aldehydes is not immediately accompanied by the retro-Strecker reaction. Presumably, the basicity of the resulting alkoxide is not sufficient to effect abstraction of the vicinal N–H proton. The resulting intermediates **4** can be isolated but decompose slowly at ambient temperature. To convert them to the 1,2-amino alcohols **5** without prior isolation (Scheme 1), we tested several reduction methods. Although the reductive decyanation of **4** with $NaCNBH_3$ and acetic acid, which gave the best results in other cases,[27] turned out to be sluggish and inefficient, we found, in particular, the borane–THF complex to be well suited for this purpose. In accordance with a chelate model for the transition state of the reduction of the α-hydroxyimine formed upon spon-

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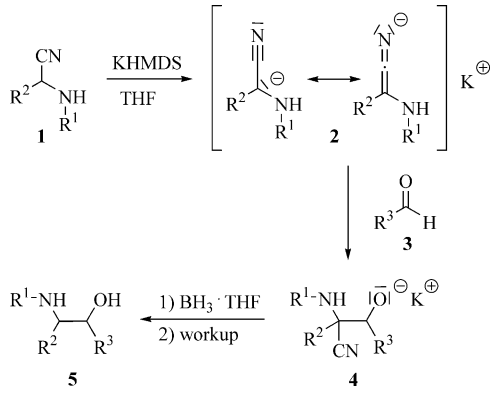
Table 1. Preparation of amino alcohols from α-amino nitriles.

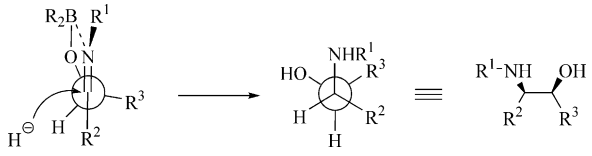
Nr.	Nitrile	R^1	R^2	Aldehyde	R^3	Product	% Yield[a]	*dr* (*anti*/*syn*)
1	**1a**	Ph_2CH	Ph	**3a**	Ph	**5a**	74	3.2:1
2	**1a**	Ph_2CH	Ph	**3b**	4-ClC_6H_4	**5b**	61	4.0:1
3	**1a**	Ph_2CH	Ph	**3c**	3,4-$(MeO)_2C_6H_3$	**5c**	68	3.0:1
4	**1a**	Ph_2CH	Ph	**3d**	4-pyridyl	**5d**	56	2.5:1
5	**1b**	Me	2-naphth	**3a**	Ph	**5e**	52	3.0:1
6	**1b**	Me	2-naphth	**3b**	4-ClC_6H_4	**5f**	58	2.4:1
7	**1b**	Me	2-naphth	**3c**	3,4-$(MeO)_2C_6H_3$	**5g**	48	3.1:1
8	**1c**	$Ph(CH_2)_2$	Ph	**3a**	Ph	**5h**	55	8.2:1
9	**1c**	$Ph(CH_2)_2$	Ph	**3b**	4-ClC_6H_4	**5i**	78	5.3:1
10	**1c**	$Ph(CH_2)_2$	Ph	**3c**	3,4-$(MeO)_2C_6H_3$	**5j**	63	2.9:1
11	**1c**	$Ph(CH_2)_2$	Ph	**3e**	3-furyl	**5k**	76	2.1:1
12	**1d**	*i*Pr	Ph	**3a**	Ph	**5l**	54	6.2:1
13	**1d**	*i*Pr	Ph	**3b**	4-ClC_6H_4	**5m**	47	4.7:1
14	**1d**	*i*Pr	Ph	**3c**	3,4-$(MeO)_2C_6H_3$	**5n**	32	7.3:1
15	**1e**	$PhCH_2$	2-thienyl	**3e**	3-furyl	**5o**	34	2.3:1

[a] Yield after purification by chromatography or crystallization.

taneous or induced elimination of HCN, the *anti*-configured products were predominantly formed (Scheme 2). The results of the one-pot synthesis of amino alcohols **5** from amino nitriles **1** are summarized in Table 1.



Scheme 1. Mechanism of the reaction of α-amino nitriles to form amino alcohols.



Scheme 2. Chelate model for the reduction step.

The diastereomeric products show characteristic ^1H and ^{13}C NMR chemical shifts. The signals of the 1-H and 2-H atoms of the *anti* compounds appear as comparatively sharp doublets with a coupling constant of around 5–6 Hz, whereas the corresponding signals of the *syn* isomers are broader, have coupling constants of around 8–9 Hz and are constantly found at a higher field. The C-1 and C-2 atoms of the *anti* products resonate at a higher field than their counterparts in the corresponding *syn* diastereomers. The X-ray crystallographic analysis of the major isomer of compound **5h** proved the *anti* arrangement of the substituents. Its crystal structure is shown in Figure 1.

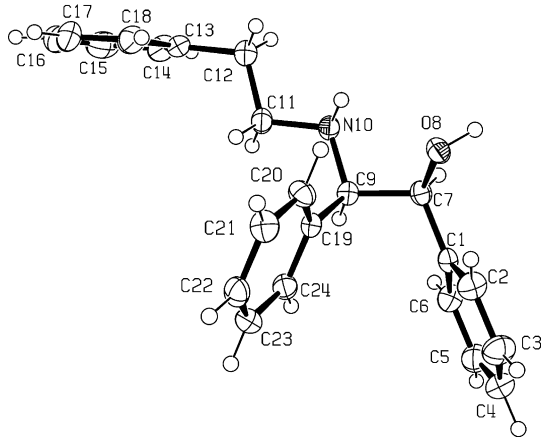


Figure 1. Crystal structure of *anti*-**5h** at 193 K (ORTEP). Thermal ellipsoids are drawn at the 50% probability level.

Remarkably, the presence of electron-donating substituents in the electrophile does not lead to a clear decrease in the overall yield, which is in sharp contrast to the observations made in the 1,2-addition of carbanions **2** to *N*-arylimines.[27] Although the reaction with pivalaldehyde led to low yields due to steric hindrance, the addition to enolizable aldehydes such as isobutyraldehyde was presumably hampered by concurrent α-deprotonation.

In summary, we have developed a one-pot synthesis of *N*,1,2-trisubstituted vicinal amino alcohols by the 1,2-addition of deprotonated *N*-monosubstituted α-amino nitriles to aldehydes followed by reductive decyanation. As the pronucleophiles can be readily obtained by the Strecker reaction from an aldehyde and an amine, the reaction is amenable to combinatorial variation of all three substituents.

Experimental Section

Methods: ^1H and ^{13}C NMR spectra were recorded with a Bruker AC-300 or Avance II-400 spectrometer; chemical shifts were referenced to the residual solvent signal ($CDCl_3$: δ_H = 7.24 ppm, δ_C =

77.0 ppm). ESI-HRMS spectra were measured with a Waters Q-TOF-Ultima 3 spectrometer equipped with a LockSpray interface (NaO_2CH or NaI/CsI as the external reference). IR spectra were recorded with a Perkin–Elmer 1760X FTIR spectrometer. Elemental analyses were performed with a Vario Micro Cube (Elementar Analysensysteme). The melting points were measured with a Dr. Tottoli apparatus (Büchi) and are uncorrected. α-Amino nitriles **1a**–**e** were synthesized by the Strecker reaction according to known procedures.[26,28–30]

Materials: THF was distilled from potassium/benzophenone immediately prior to use. Benzaldehyde (**3a**) was freshly distilled in vacuo. All other solvents and reagents were purchased from commercial suppliers and were used without further purification. TLC was performed on aluminium sheets coated with silica gel (60 F_{254}, E. Merck). Preparative TLC was performed on PSC glass plates (silica gel 60 F_{254}, 2 mm, 20 × 20 cm, Macherey–Nagel). Flash column chromatography was carried out on silica gel (35–70 μm, 60 Å, Acros).

General Procedure for the Synthesis of Amino Alcohols 5: A solution of KHMDS (184.3 mg, 0.92 mmol) in dry THF (1 mL) was added to a stirred solution of the amino nitrile **1** (0.84 mmol) in dry THF (1.0 mL) at –50 °C under argon. After 3 min, a solution of the aldehyde **3** (0.84 mmol) in dry THF (1 mL) was added and the reaction mixture was warmed to –20 °C within approx. 100 min. A solution of BH_3·THF (3.4 mL, 1 M in THF) was added, the mixture was warmed to room temperature and stirring was maintained for a further 15 h. After addition of diethanolamine/water (1:1 v/v, 2 mL), the mixture was stirred for 4 d at room temperature[31] and diluted with ethyl acetate. The organic layer was washed with HCl (0.5 M), sat. $NaHCO_3$ and brine, dried with Na_2SO_4 and the solvent was removed in vacuo.

2-(Benzhydrylamino)-1,2-diphenylethanol (5a): Preparation from amino nitrile **1a** and aldehyde **3a** according to the general procedure furnished a colourless oil (346.3 mg). A portion (205.2 mg) of the crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc, 10:1, + 1% $EtNMe_2$) to give amino alcohol **5a** (139.2 mg, 74%) as a colourless solid. Ratio of isomers: *anti*/*syn* = 3.2:1. R_f (cyclohexane/EtOAc 10:1 + 1% $EtNMe_2$) = 0.29. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–6.93 (m, 40 H), 4.78 (d, J = 6.3 Hz, 1 H, 1-H *anti*), 4.65–4.63 (m, 2 H, 1-H *syn*, Ph_2CH *syn*), 4.58 (s, 1 H, Ph_2CH *anti*), 3.78 (d, J = 6.3 Hz, 1 H, 2-H *anti*), 3.57 (d, J = 8.4 Hz, 1 H, 2-H *syn*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 144.1 (2 C), 142.6, 142.1, 140.9, 140.6, 139.6, 139.3, 128.8–126.9 (partly overlapping signals), 77.9 (C-1 *syn*), 77.3 (C-1 *anti*), 67.2 (C-2 *syn*), 65.8 (C-2 *anti*), 63.6 (Ph_2CH *syn*), 63.2 (Ph_2CH *anti*) ppm. IR (NaCl, film): $\tilde{\nu}$ = 3425 (m), 3061 (m), 3028 (m), 2921 (w), 1699 (w), 1493 (s), 1454 (vs), 1266 (w), 1191 (w), 1028 (s) cm^{-1}. ESI-MS: *m*/*z* (%) = 380.04 (100) $[M + H]^+$. $C_{27}H_{25}NO$ (379.49): calcd. C 85.45, H 6.64, N 3.69; found C 85.40, H 6.56, N 3.70.

2-(Benzhydrylamino)-1-(4-chlorophenyl)-2-phenylethanol (5b): Preparation from amino nitrile **1a** and aldehyde **3b** according to the general procedure furnished a colourless oil (417.7 mg). A portion (162.2 mg) of the crude product was purified by preparative TLC (SiO_2, cyclohexane/*tert*-butyl methyl ether, 2:1) to give amino alcohol **5b** (82.2 mg, 61%) as a colourless solid. Ratio of isomers: *anti*/*syn* = 4.0:1. R_f (cyclohexane/*tert*-butyl methyl ether, 2:1) = 0.52. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.17 (m, 23 H), 7.10–7.03 (m, 9 H), 7.01–6.87 (m, 6 H), 4.77 (d, J = 6.1 Hz, 1 H, 1-H *anti*), 4.63–4.58 (m, 3 H, 1-H *syn*, Ph_2CH), 3.76 (d, J = 6.1 Hz, 1 H, 2-H *anti*), 3.48 (d, J = 8.6 Hz, 1 H, 2-H *syn*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 143.8, 142.4, 139.1, 138.7, 133.3, 128.7–127.1 (partly overlapping signals), 76.8 (C-1 *syn*), 76.3 (C-1 *anti*), 67.3 (C-2 *syn*), 65.7 (C-2 *anti*), 63.6 (Ph_2CH *syn*), 63.3 (Ph_2CH *anti*) ppm. IR (NaCl, film): $\tilde{\nu}$ = 3430 (s), 3062 (m), 3028 (m), 2925 (w), 2854 (w), 1600 (m), 1493 (vs), 1454 (s), 1266 (s), 1092 (s), 1029 (s), 1014 (s) cm^{-1}. ESI-MS: *m*/*z* (%) = 273.97 (90) $[Ph_2CHNHCH_2Ph + H]^+$, 414.09 (100) $[M + H]^+$. $C_{27}H_{24}ClNO$ (413.94): calcd. C 78.34, H 5.84, N 3.38; found C 78.39, H 5.87, N 3.22.

2-(Benzhydrylamino)-1-(3,4-dimethoxyphenyl)-2-phenylethanol (5c): Preparation from amino nitrile **1a** and aldehyde **3c** according to the general procedure furnished a slightly yellow oil (377.6 mg). A portion (168.5 mg) of the crude product was purified by preparative TLC (SiO_2, cyclohexane/*tert*-butyl methyl ether, 1:1) to give amino alcohol **5c** (112.8 mg, 68%) as a colourless oil. Ratio of isomers: *anti*/*syn* = 3.0:1. R_f (cyclohexane/*tert*-butyl methyl ether, 1:1) = 0.45. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.13 (m, 26 H), 7.03–6.98 (m, 2 H), 6.98–6.93 (m, 2 H), 6.77 (s, 2 H, 5′-H *anti*, 6′-H *anti*), 6.61 (d, J = 8.1 Hz, 1 H, 5′-H *syn*), 6.56 (dd, J = 1.5, J = 8.1 Hz, 1 H, 6′-H *syn*), 6.48 (s, 1 H, 2′-H *anti*), 6.39 (d, J = 1.5 Hz, 1 H, 2′-H *syn*), 4.70 (d, J = 6.4 Hz, 1 H, 1-H *anti*), 4.64 (s, 1 H, Ph_2CH *syn*), 4.61–4.55 (m, 2 H, 1-H *syn*, Ph_2CH *anti*), 3.86 (s, 3 H, OCH_3 *anti*), 3.77 (s, 3 H, OCH_3 *syn*), 3.73 (d, J = 6.4 Hz, 1 H, 2-H *anti*), 3.66 (s, 3 H, OCH_3 *anti*), 3.60 (s, 3 H, OCH_3 *syn*), 3.51 (d, J = 8.6 Hz, 1 H, 2-H *syn*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 148.7, 148.6 (C-3′, C-4′ *anti*), 148.2, 148.1 (C-3′, C-4′ *syn*), 144.1, 142.7, 142.1, 139.7, 139.6, 133.4, 133.0, 128.6–126.9 (partly overlapping signals), 119.5 (C-6′ *anti*), 118.9 (C-6′ *syn*), 110.4 (2 C), 109.9, 109.7 (C-2′, C-5′), 77.5 (C-1 *syn*), 77.3 (C-1 *anti*), 67.3 (C-2 *syn*), 65.8 (C-2 *anti*), 63.6 (Ph_2CH *syn*), 63.0 (Ph_2CH *anti*), 55.9–55.6 (4 C, OCH_3) ppm. IR (NaCl, film): $\tilde{\nu}$ = 3506 (m), 3061 (m), 3027 (m), 3003 (m), 2935 (m), 2835 (m), 1596 (m), 1516 (s), 1494 (s), 1454 (s), 1265 (vs), 1236 (s), 1154 (s), 1029 (s) cm^{-1}. ESI-MS: *m*/*z* (%) = 440.06 (100) $[M + H]^+$. $C_{29}H_{29}NO_3$ (439.55): calcd. C 79.24, H 6.65, N 3.19; found C 79.30, H 6.54, N 3.12.

2-(Benzhydrylamino)-2-phenyl-1-pyridin-4-ylethanol (5d): Preparation from amino nitrile **1a** and aldehyde **3d** according to the general procedure furnished a yellow oil (334.8 mg). Purification by flash column chromatography (SiO_2, cyclohexane/EtOAc, 3:1) gave amino alcohol **5d** (180.0 mg, 56%) as a colourless solid. Ratio of isomers: *anti*/*syn* = 2.5:1. R_f (cyclohexane/EtOAc, 2:1) = 0.24. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.34 (AA′ part of AA′XX′ system, 2 H, 2′,6′-H *anti*), 8.27 (AA′ part of AA′XX′ system, 2 H, 2′,6′-H *syn*), 7.33–6.94 (m, 34 H), 4.93 (d, J = 5.3 Hz, 1 H, 1-H *anti*), 4.71–4.67 (m, 2 H, Ph_2CH *anti*, 1-H *syn*), 4.62 (s, 1 H, Ph_2CH *syn*), 3.82 (d, J = 5.3 Hz, 1 H, 2-H *anti*), 3.36 (d, J = 5.3 Hz, 1 H, 2-H *syn*), 2.50 (br. s, 4 H, OH, NH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 154.3 (C-4′ *syn*), 154.1 (C-4′ *anti*), 146.6 (2 C, C-2′,6′ *syn*), 146.5 (2 C, C-2′,6′ *anti*), 143.4, 143.1, 142.0, 141.3, 137.9 (C-1′′ *syn*), 137.1 (C-1′′ *anti*), 129.1–126.9 (partly overlapping signals), 123.3 (2 C, C-3′,5′ *anti*), 123.2 (2 C, C-3′,5′ *syn*), 75.9 (C-1 *syn*), 74.4 (C-1 *anti*), 66.7 (C-2 *syn*), 65.2 (C-2 *anti*), 63.8 (Ph_2CH *anti*), 63.7 (Ph_2CH *syn*) ppm. IR (NaCl, film): $\tilde{\nu}$ = 3456 (m), 3027 (m), 2364 (s), 1630 (s), 1494 (m), 1453 (s), 1436 (s), 1170 (m), 1072 (m) cm^{-1}. ESI-MS: *m*/*z* (%) = 381.04 (100) $[M + H]^+$. ESI-HRMS: calcd. for $[C_{26}H_{24}N_2O + Na]^+$ 403.1787; found 403.1796.

2-(Methylamino)-2-(2-naphthyl)-1-phenylethanol (5e): Preparation from amino nitrile **1b** and aldehyde **3a** according to the general procedure furnished a yellow oil (266.3 mg). The crude product was crystallized from cyclohexane/EtOAc to yield exclusively the *anti* isomer of amino alcohol **5e** as colourless crystals (121.2 mg, 52%). Ratio of isomers: *anti*/*syn* = 3.0:1. R_f (CH_2Cl_2/MeOH, 5:1) = 0.24.

Data for the *anti* Isomer: M.p. 136 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83–7.73 (m, 3 H), 7.64 (br. s, 1 H, 1′-H), 7.49–7.42 (m, 2 H), 7.32–7.16 (m, 6 H), 4.87 (d, J = 6.3 Hz, 1 H, 1-H), 3.91 (d, J = 6.3 Hz, 1 H, 2-H), 2.26 (s, 1 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 140.6 (C_6H_5–C-1), 136.6 (C-2′), 133.1, 133.1, 128.2–125.8 (partly overlapping signals), 76.7 (C-1), 71.2 (C-2), 34.4 (CH_3) ppm. IR (NaCl, film): $\tilde{\nu}$ = 3318 (m), 3058 (m), 2853 (m), 2798 (m), 2364 (w), 1600 (m), 1452 (s), 1124 (m), 1079 (m), 1056 (s) cm^{-1}. ESI-MS: m/z (%) = 277.96 (100) [M + H]$^+$. ESI-HRMS: calcd. for [$C_{19}H_{19}NO$ + H]$^+$ 278.1545; found 278.1551.

1-(4-Chlorophenyl)-2-(methylamino)-2-(2-naphthyl)ethanol (5f): Preparation from amino nitrile **1b** and aldehyde **3b** according to the general procedure furnished a yellowish oil (248.9 mg). A portion (187.9 mg) of the crude product was purified by preparative TLC (SiO_2, CH_2Cl_2/MeOH, 5:1) to give amino alcohol **5f** (115.1 mg, 58%) as a colourless solid. Ratio of isomers: *anti*/*syn* = 2.4:1. R_f (CH_2Cl_2/MeOH, 5:1) = 0.39. ^{1}H NMR, HSQC (400 MHz, $CDCl_3$): δ = 7.82–7.69 (m, 6 H), 7.58 (br. s, 2 H, 1′-H), 7.48–7.42 (m, 4 H), 7.22 (dd, J = 8.4, 1.8 Hz, 2 H), 7.17 (AA′ part of AA′BB′ system, 2 H, 3′′,5′′-H *anti*), 7.08–7.03 (m, 4 H, 3′′,5′′-H *syn*, 2′′,6′′-H *anti*), 6.98 (BB′ part of AA′BB′ system, 2 H, 2′′,6′′-H *syn*), 4.94 (d, J = 5.5 Hz, 1 H, 1-H *anti*), 4.70 (d, J = 8.8 Hz, 1 H, 1-H *syn*), 3.89 (d, J = 5.5 Hz, 1 H, 2-H *anti*), 3.60 (d, J = 8.8 Hz, 1 H, 2-H *syn*), 3.23 (br. s, 4 H, OH, NH), 2.30 (s, 3 H, CH_3 *syn*), 2.29 (s, 3 H, CH_3 *anti*) ppm. ^{13}C NMR, HSQC (100.6 MHz, $CDCl_3$): δ = 139.8 (C-1′′ *syn*), 139.2 (C-1′′ *anti*), 136.1 (C-2′ *syn*), 135.8 (C-2′ *anti*), 133.3, 133.1 (4 C), 133.0, 128.3–127.7 (partly overlapping signals), 126.2, 126.1, 126.0, 125.9, 125.4, 76.6 (C-1 *syn*), 75.6 (C-1 *anti*), 72.4 (C-2 *syn*), 70.9 (C-2 *anti*), 34.3 (CH_3 *anti*), 34.1 (CH_3 *syn*) ppm. IR (NaCl, film): $\tilde{\nu}$ = 3408 (s), 3055 (m), 2953 (m), 2853 (m), 1600 (s), 1490 (vs), 1407 (s), 1090 (vs), 1015 (s) cm^{-1}. ESI-MS: m/z (%) = 312.15 (100) [M + H]$^+$. ESI-HRMS: calcd. for [$C_{19}H_{18}ClNO$ + H]$^+$ 312.1155; found 312.1165.

1-(3,4-Dimethoxyphenyl)-2-(methylamino)-2-(2-naphthyl)ethanol (5g): Preparation from amino nitrile **1b** and aldehyde **3c** according to the general procedure furnished a yellow oil (311.7 mg). A portion (145.0 mg) of the crude product was purified by flash column chromatography (SiO_2, EtOAc/2-propanol, 4:1 + 1% $EtNMe_2$) to give amino alcohol **5g** (63.2 mg, 48%) as a colourless solid. Ratio of isomers: *anti*/*syn* = 3.1:1. R_f (EtOAc/2-propanol, 3:1 + 1% $EtNMe_2$) = 0.32, 0.23. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96–7.14 (m, 14 H), 6.84–6.74 (m, 2 H), 6.60–6.55 (m, 4 H), 4.81 (d, J = 6.3 Hz, 1 H, 1-H *anti*), 4.63 (d, J = 8.6 Hz, 1 H, 1-H *syn*), 3.88–3.81 (m, 4 H, 2-H *anti*, OCH_3 *anti*), 3.75 (s, 3 H, OCH_3 *syn*), 3.62–3.59 (m, 7 H, 2-H *syn*, 2 × OCH_3), 2.32 (s, 3 H, NCH_3 *syn*), 2.27 (s, 3 H, NCH_3 *anti*) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 148.7, 148.6 (C-3′, C-4′ *anti*), 148.4, 148.2 (C-3′, C-4′ *syn*), 137.1 (C-2′′ *syn*), 136.9 (C-2′′ *anti*), 133.7, 133.2, 133.1, 132.9, 128.0–125.5 (partly overlapping signals), 125.4, 125.1, 119.2 (C-6′ *anti*), 119.1 (C-6′ *syn*), 110.6 (C-2′ *anti*), 110.5 (C-2′ *syn*), 109.9 (C-5′ *anti*), 109.7 (C-5′ *syn*), 77.2 (C-1 *syn*), 76.6 (C-1 *anti*), 72.5 (C-2 *syn*), 71.3 (C-2 *anti*), 55.8 (2 C, OCH_3), 55.7 (OCH_3 *syn*), 55.6 (OCH_3 *anti*), 34.4 (NCH_3 *anti*), 34.3 (NCH_3 *syn*) ppm. IR (NaCl, film): $\tilde{\nu}$ = 3112 (m), 3054 (m), 2936 (m), 2836 (m), 2796 (m), 1646 (m), 1601 (m), 1515 (s), 1464 (s), 1418 (m), 1263 (s), 1235 (s), 1139 (s), 1064 (m), 1028 (s) cm^{-1}. ESI-MS: m/z (%) = 338.02 (100) [M + H]$^+$. ESI-HRMS: calcd. for [$C_{21}H_{23}NO_3$ + H]$^+$ 338.1756; found 338.1762.

2-(Phenethylamino)-1,2-diphenylethanol (5h): Preparation from amino nitrile **1c** and aldehyde **3a** according to the general procedure furnished a colourless solid (292.4 mg). A portion (176.8 mg) of the crude product was purified by preparative TLC (SiO_2, CH_2Cl_2/MeOH, 20:1) to give amino alcohol **5h** (89.4 mg, 55%) as a colourless solid. Ratio of isomers: *anti*/*syn* = 8.2:1. R_f (CH_2Cl_2/MeOH, 20:1) = 0.44. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24–6.98 (m, 30 H), 4.77 (d, J = 5.7 Hz, 1 H, 1-H *anti*), 4.48 (d, J = 8.5 Hz, 1 H, 1-H *syn*), 3.88 (d, J = 5.7 Hz, 1 H, 2-H *anti*), 3.57 (d, J = 8.5 Hz, 1 H, 2-H *syn*), 2.82–2.64 (m, 8 H, C_2H_4Ph), 2.21 (br. s, 4 H, OH, NH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 140.4, 139.7, 139.0, 128.7–126.7 (partly overlapping signals), 126.2, 126.1, 76.5 (C-1 *anti*), 70.5 (C-2 *syn*), 68.6 (C-2 *anti*), 48.5 (NH–CH_2 *syn*), 48.4 (NH–CH_2 *anti*), 36.4 ($PhCH_2$ *syn*), 36.2 ($PhCH_2$ *anti*) ppm. The signal of C-1 *syn* is obscured by the solvent signal. IR (NaCl, film): $\tilde{\nu}$ = 3355 (w), 3085 (m), 3061 (m), 3028 (s), 2861 (m), 2364 (w), 1491 (m), 1454 (s), 1428 (m), 1106 (m), 1087 (m), 1052 (s), 1029 (m) cm^{-1}. ESI-MS: m/z (%) = 318.08 (100) [M + H]$^+$. ESI-HRMS: calcd. for [$C_{22}H_{23}NO$ + H]$^+$ 318.1858; found 318.1854.

1-(4-Chlorophenyl)-2-phenethylamino-2-phenylethanol (5i): Preparation from amino nitrile **1c** and aldehyde **3b** according to the general procedure furnished a colourless solid (323.1 mg). A portion (168.2 mg) of the crude product was purified by preparative TLC (SiO_2, CH_2Cl_2/MeOH, 20:1) to give amino alcohol **5i** (120.5 mg, 78%) as a colourless solid. Ratio of isomers: *anti*/*syn* = 5.3:1. R_f (CH_2Cl_2/MeOH, 20:1) = 0.38. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–6.85 (m, 28 H), 4.75 (d, J = 5.4 Hz, 1 H, 1-H *anti*), 4.44 (d, J = 8.8 Hz, 1 H, 1-H *syn*), 3.83 (d, J = 5.4 Hz, 1 H, 2-H *anti*), 3.47 (d, J = 8.8 Hz, 1 H, 2-H *syn*), 2.84–2.67 (m, 8 H, C_2H_4Ph), 2.41 (br. s, 4 H, OH, NH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 139.6, 139.5, 139.3, 138.9, 138.6, 133.2 (C-4′ *anti*), 128.6–127.6 (partly overlapping signals), 126.2, 76.8 (C-1 *syn*), 75.6 (C-1 *anti*), 70.6 (C-2 *syn*), 68.5 (C-2 *anti*), 48.4 (NH–CH_2 *syn*), 48.3 (NH–CH_2 *anti*), 36.3 ($PhCH_2$ *syn*), 36.2 ($PhCH_2$ *anti*) ppm. IR (NaCl, film): $\tilde{\nu}$ = 3379 (m), 3062 (m), 3029 (m), 2928 (w), 2864 (m), 1600 (m), 1493 (vs), 1455 (vs), 1428 (s), 1113 (s), 1090 (s), 1058 (s), 1016 (s) cm^{-1}. ESI-MS: m/z (%) = 352.02 (100) [M + H]$^+$. ESI-HRMS: calcd. for [$C_{22}H_{22}ClNO$ + H]$^+$ 352.1468; found 352.1472.

1-(3,4-Dimethoxyphenyl)-2-(phenethylamino)-2-phenylethanol (5j): Preparation from amino nitrile **1c** and aldehyde **3c** according to the general procedure furnished a slightly yellow oil (344.3 mg). A portion (144.6 mg) of the crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc, 1:1 + 1% $EtNMe_2$) to give amino alcohol **5j** (83.1 mg, 63%) as a colourless solid. Ratio of isomers: *anti*/*syn* = 2.9:1. R_f (cyclohexane/EtOAc, 1:1 + 1% $EtNMe_2$) = 0.15. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.03 (m, 19 H), 6.91–6.87 (m, 2 H), 6.71 (d, J = 8.2 Hz, 1 H, 5′-H *anti*), 6.67 (dd, J = 8.2, 1.8 Hz, 6′-H *anti*), 6.62 (d, J = 8.2 Hz, 1 H, 5′-H *syn*), 6.56 (dd, J = 8.2, 1.8 Hz, 1 H, 6′-H *syn*), 6.49 (d, J = 1.8 Hz, 1 H, 2′-H *syn*), 6.39 (d, J = 1.8 Hz, 1 H, 2′-H *anti*), 4.17 (d, J = 5.7 Hz, 1 H, 1-H *anti*), 4.44 (d, J = 8.7 Hz, 1 H, 1-H *syn*), 3.83 (s, 3 H, OCH_3 *anti*), 3.82 (d, J = 5.7 Hz, 1 H, 2-H *anti*), 3.78 (s, 3 H, OCH_3 *syn*), 3.66 (s, 3 H, OCH_3 *syn*), 3.62 (s, 3 H, OCH_3 *anti*), 3.52 (d, J = 8.7 Hz, 1 H, 2-H *syn*), 2.86–2.64 (m, 8 H, C_2H_4Ph), 2.44 (br. s, 4 H, OH, NH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 148.4, 148.3 (C-3′, C-4′ *anti*), 148.3, 148.1 (C-3′, C-4′ *syn*), 139.6, 139.5, 139.2, 133.5 (C-1′ *syn*), 132.9 (C-1′ *anti*), 128.7–127.4 (partly overlapping signals), 126.2, 126.4, 118.9 (2 C, C-6′), 110.4 (2 C, C-5′), 109.8 (C-2′ *syn*), 109.7 (C-2′ *anti*), 77.2 (C-1 *syn*), 76.3 (C-1 *anti*), 70.7 (C-2 *syn*), 68.8 (C-2 *anti*), 55.8 (OCH_3 *anti*), 55.7 (OCH_3 *syn*), 55.6 (OCH_3 *syn*), 55.6 (OCH_3 *anti*), 48.4 (NH–CH_2 *syn*), 48.3 (NH–CH_2 *anti*), 36.3 ($PhCH_2$ *syn*), 36.1 ($PhCH_2$ *anti*) ppm. IR (NaCl, film): $\tilde{\nu}$ = 3318 (m), 3061 (m), 3027 (m), 2935 (s), 2835 (m), 1594 (m), 1516 (vs), 1454 (s), 1420 (m), 1264 (vs), 1236 (s), 1155 (s), 1139 (s), 1029 (vs) cm^{-1}. ESI-MS: m/z (%) = 378.05 (100) [M + H]$^+$. $C_{24}H_{27}NO_3$ (377.48): calcd. C 76.36, H 7.21, N 3.71; found C 76.35, H 7.16, N 3.65.

1-(3-Furyl)-2-(phenethylamino)-2-phenylethanol (5k): Preparation from amino nitrile **1c** and aldehyde **3e** according to the general procedure furnished a yellowish oil (276.3 mg). Purification by flash column chromatography (SiO_2, cyclohexane/EtOAc, 2.5:1) gave amino alcohol **5k** (195.9 mg, 76%) as a colourless wax. Ratio of isomers: *anti*/*syn* = 2.1:1. R_f (cyclohexane/EtOAc, 2:1) = 0.21. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.02 (m, 24 H), 6.01 (m_c, 1 H, 4′-H *syn*), 6.00 (m_c, 1 H, 4′-H *anti*), 4.74 (d, J = 5.5 Hz, 1 H, 1-H *anti*), 4.52 (d, J = 8.9 Hz, 1 H, 1-H *syn*) 3.86 (d, J = 5.5 Hz, 1 H, 2-H *anti*), 3.54 (d, J = 8.9 Hz, 1 H, 2-H *syn*), 2.84–2.69 (m, 8 H, C_2H_4Ph), 2.34 (br. s, 4 H, OH, NH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 142.8 (C-5′ *anti*), 142.7 (C-5′ *syn*), 140.1 (C-2′ *anti*), 139.9 (2 C, C-2′ *syn*), 139.7, 139.3, 128.6–127.6 (partly overlapping signals), 126.2 (2 C), 125.7 (C-3′ *syn*), 125.1 (C-3′ *anti*), 108.9 (C-4′ *anti*), 108.8 (C-4′ *syn*), 70.2 (C-1 *syn*), 69.9 (C-1 *anti*), 69.4 (C-2 *syn*), 67.7 (C-2 *anti*), 48.5 ($NHCH_2$ *syn*), 48.4 ($NHCH_2$ *anti*), 36.4 ($PhCH_2$ *syn*), 36.3 ($PhCH_2$ *anti*) ppm. IR (NaCl, film): $\tilde{\nu}$ = 3296 (m), 3027 (s), 2922 (m), 1602 (m), 1497 (s), 1454 (s), 1158, 1022 (s) cm^{-1}. ESI-MS: *m*/*z* (%) = 308.15 (100) $[M + H]^+$. ESI-HRMS: calcd. for $[C_{20}H_{21}NO_2 + H]^+$ 308.1650; found 308.1646.

2-(Isopropylamino)-1,2-diphenylethanol (5l): Preparation from amino nitrile **1d** and aldehyde **3a** according to the general procedure furnished a colourless solid (244.4 mg). A portion (144.2 mg) of the crude product was crystallized from cyclohexane/EtOAc to yield exclusively the *anti* isomer of amino alcohol **5l** as colourless crystals (68.6 mg, 54%). Ratio of isomers: *anti*/*syn* = 6.2:1. R_f (CH_2Cl_2/MeOH, 10:1) = 0.44.

Data for the *anti* Isomer: M.p. 139 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.16 (m, 6 H), 7.03–6.96 (m, 4 H), 4.82 (d, J = 5.2 Hz, 1 H, 1-H), 4.06 (d, J = 5.2 Hz, 1 H, 2-H), 2.68 [sept, J = 6.3 Hz, 1 H, C*H*(CH_3)$_2$], 2.55 (br. s, 2 H, OH, NH), 1.02–0.96 [m, 6 H, CH(C*H*$_3$)$_2$] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 140.4, 139.0 (C-1′, C-1′′), 128.1–126.7 (partly overlapping signals), 76.1 (C-1), 65.5 (C-2), 45.6 [*C*H(CH_3)$_2$], 23.9 [CH(*C*H$_3$)$_2$], 22.1 [CH(*C*H$_3$)$_2$] ppm. IR (NaCl, film): $\tilde{\nu}$ = 3388 (m), 3296 (m), 3024 (m), 2960 (m), 2869 (m), 1601 (m), 1452 (m), 1088 (m), 1056 (s), 1029 (m) cm^{-1}. ESI-MS: *m*/*z* (%) = 256.00 (100) $[M + H]^+$. ESI-HRMS: calcd. for $[C_{17}H_{21}NO + H]^+$ 256.1701; found 256.1698.

1-(4-Chlorophenyl)-2-(isopropylamino)-2-phenylethanol (5m): Preparation from amino nitrile **1d** and aldehyde **3b** according to the general procedure furnished a slightly yellow solid (269.4 mg). A portion (152.7 mg) of the crude product was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH, 20:1) to give amino alcohol **5m** (64.9 mg, 47%) as a colourless solid. Ratio of isomers: *anti*/*syn* = 4.7:1. R_f (CH_2Cl_2/MeOH, 20:1) = 0.25. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23–7.08 (m, 10 H), 7.01–6.84 (m, 8 H), 4.83 (d, J = 4.9 Hz, 1 H, 1-H *anti*), 4.47 (d, J = 9.0 Hz, 1 H, 1-H *syn*), 4.03 (d, J = 4.9 Hz, 1 H, 2-H *anti*), 3.53 (d, J = 9.0 Hz, 1 H, 2-H *syn*), 2.77–2.64 [m, 2 H, C*H*(CH_3)$_2$], 1.28–1.12 [m, 6 H, CH(C*H*$_3$)$_2$ *syn*], 1.06–0.96 [m, 6 H, CH(C*H*$_3$)$_2$ *anti*] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 138.9, 138.5, 133.0 (ClC_6H_4 C-4), 128.1–127.6 (partly overlapping signals), 75.2 (C-1 *anti*), 67.9 (C-2 *syn*), 65.3 (C-2 *anti*), 46.2 [*C*H(CH_3)$_2$ *syn*], 45.6 [*C*H(CH_3)$_2$ *anti*], 24.1 [CH(*C*H$_3$)$_2$ *syn*], 23.8 [CH(*C*H$_3$)$_2$ *anti*], 22.2 [CH(*C*H$_3$)$_2$ *anti*], 21.8 [CH(*C*H$_3$)$_2$ *syn*] ppm. The signal of C-1 *syn* is obscured by the solvent signal. IR (NaCl, film): $\tilde{\nu}$ = 3412 (s), 2965 (m), 2926 (w), 2871 (w), 2360 (m), 1637 (m), 1492 (m), 1455 (m), 1174 (m), 1090 (s), 1074 (s), 1015 (m) cm^{-1}. ESI-MS: *m*/*z* (%) = 289.95 (100) $[M + H]^+$. ESI-HRMS: calcd. for $[C_{17}H_{20}ClNO + H]^+$ 290.1311; found 290.1315.

1-(3,4-Dimethoxyphenyl)-2-(isopropylamino)-2-phenylethanol (5n): Preparation from amino nitrile **1d** and aldehyde **3c** according to the general procedure furnished a yellowish oil (269.4 mg). A portion (148.1 mg) of the crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc, 1:1 + 1% $EtNMe_2$) to give amino alcohol **5n** (84.4 mg, 32%) as a colourless solid. Ratio of isomers: *anti*/*syn* = 7.3:1. R_f (cyclohexane/EtOAc, 1:1 + 1% $EtNMe_2$) = 0.10. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.16 (m, 6 H), 7.05–7.01 (m, 2 H), 7.00–6.94 (m, 2 H), 6.72 (d, J = 8.2 Hz, 1 H, 5′-H *anti*), 6.66 (dd, J = 8.2, 1.8 Hz, 1 H, 6′-H *anti*), 6.63 (d, J = 8.2 Hz, 1 H, 5′-H *syn*), 6.58 (dd, J = 8.2, 1.8 Hz, 1 H, 6′-H *syn*), 6.47 (d, J = 1.8 Hz, 1 H, 2′-H *syn*), 6.30 (d, J = 1.8 Hz, 1 H, 2′-H *anti*), 4.75 (d, J = 5.1 Hz, 1 H, 1-H *anti*), 4.40 (d, J = 8.9 Hz, 1 H, 1-H *syn*), 4.00 (d, J = 5.1 Hz, 1 H, 2-H *anti*), 3.82 (s, 3 H, OCH_3 *anti*), 3.77 (s, 3 H, OCH_3 *syn*), 3.64 (s, 3 H, OCH_3 *syn*), 3.58 (s, 3 H, OCH_3 *anti*), 3.53 (d, J = 8.9 Hz, 1 H, 2-H *syn*), 2.72–2.61 [m, 2 H, C*H*(CH_3)$_2$], 0.10–0.95 [m, 12 H, CH(C*H*$_3$)$_2$] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 148.2 (4 C, C-3′, C-4′), 139.5, 132.9, 128.3–127.3 (partly overlapping signals), 118.9 (C-6′ *syn*), 118.8 (C-6′ *anti*), 110.4 (C-5′ *syn*), 110.3 (C-5′ *anti*), 110.0 (C-2′ *anti*), 109.9 (C-2′ *syn*), 77.1 (C-1 *syn*), 76.0 (C-1 *anti*), 68.1 (C-2 *syn*), 65.8 (C-2 *anti*), 55.8 (2 C, OCH_3), 55.6 (OCH_3 *syn*), 55.5 (OCH_3 *anti*), 46.0 [*C*H(CH_3)$_2$ *syn*], 45.4 [*C*H(CH_3)$_2$ *anti*], 24.3 [CH(*C*H$_3$)$_2$ *syn*], 24.0 [CH(*C*H$_3$)$_2$ *anti*], 22.2 [CH(*C*H$_3$)$_2$ *anti*], 22.1 [CH(*C*H$_3$)$_2$ *syn*] ppm. IR (NaCl, film): $\tilde{\nu}$ = 3365 (m), 2962 (s), 2835 (m), 1594 (w), 1516 (vs), 1466 (s), 1264 (vs), 1235 (s), 1138 (s), 1028 (s) cm^{-1}. ESI-MS: *m*/*z* (%) = 316.09 (100) $[M + H]^+$. ESI-HRMS: calcd. for $[C_{19}H_{25}NO_3 + H]^+$ 316.1912; found 316.1916.

2-(Benzylamino)-1-(3-furyl)-2-(2-thienyl)ethanol (5o): Preparation from amino nitrile **1e** and aldehyde **3e** according to the general procedure furnished a yellowish oil (246.3 mg). A portion (188.7 mg) of the crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc, 4:1) to give amino alcohol **5o** (66.3 mg, 34%) as a colourless amorphous solid. Ratio of isomers: *anti*/*syn* = 2.3:1. R_f (cyclohexane/EtOAc, 2:1) = 0.23. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.23 (m, 8 H), 6.99–6.93 (m, 3 H, 3′-H *anti*, 4′-H), 6.80 (br. d, J = 3.3 Hz, 1 H, 3′-H *syn*), 6.14 (m_c, 1 H, 4′′-H *anti*), 6.12 (s, 1 H, 4′′-H *syn*), 4.77 (d, J = 5.8 Hz, 1 H, 1-H *anti*), 4.65 (d, J = 8.4 Hz, 1 H, 1-H *syn*), 4.12 (d, J = 5.8 Hz, 1 H, 2-H *anti*), 3.93 (d, J = 8.4 Hz, 1 H, 2-H *syn*), 3.84 (d, J = 13.0 Hz, 1 H, CH_2Ph *syn*), 3.82 (d, J = 13.2 Hz, 1 H, CH_2Ph *anti*), 3.63 (d, J = 13.0 Hz, 1 H, CH_2Ph *syn*), 3.62 (d, J = 13.2 Hz, 1 H, CH_2Ph *anti*), 2.53 (br. s, 4 H, OH, NH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 143.8 (C-2′ *syn*), 143.5 (C-2′ *anti*), 143.2 (C-5′′ *anti*), 142.8 (C-5′′ *syn*), 140.6 (C-2′′ *anti*), 140.2 (C-2′′ *syn*), 139.6 (C-1′′′ *anti*), 139.4 (C-1′′′ *syn*), 128.5–124.8 (partly overlapping signals), 108.8 (C-4′′ *anti*), 108.7 (C-4′′ *syn*), 70.9 (C-1 *syn*), 70.0 (C-1 *anti*), 63.7 (C-2 *syn*), 62.9 (C-2 *anti*), 51.2 (2 C, CH_2Ph) ppm. ESI-MS: *m*/*z* (%) = 300.96 (100) $[M + H]^+$. ESI-HRMS: calcd. for $[C_{17}H_{17}NO_2S + H]^+$ 300.1058; found 300.1066. $C_{17}H_{17}NO_2S$ (299.39): calcd. C 68.20, H 5.72, N 4.68; found C 68.20, H 5.75, N 4.85.

Crystal Data for *anti*-5h: Formula $C_{22}H_{23}NO$, monoclinic, space group $P2_1/n$, a = 12.4405(5), b = 5.7873(1), c = 24.5948(5) Å, β = 92.697(2)°, V = 1768.80(6) Å^3, Z = 4, D = 1.192 g cm^{-3}, T = 193 K, R = 0.042, Rw = 0.1113.

CCDC-670570 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of all amino alcohols.

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