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Rearrangement of *N*-alkyl 1,2-amino alcohols. Synthesis of (*S*)-toliprolol and (*S*)-propanolol

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ABSTRACT

N-alkyl 1,2-amino alcohols were rearranged stereospecifically by using TFAA/Et_3N. This rearrangement has been used to synthesize *N*-isopropyl-3-(aryloxy)-2-hydroxypropylamines, β-adrenergic blocking agents such as (*S*)-toliprolol and (*S*)-propanolol.

1. Introduction

The 1,2-amino alcohol functionality is present in a wide variety of natural products and biologically active compounds.[1] Of particular importance, are the optically active *N*-isopropyl-3-(aryloxy)-2-hydroxypropylamines **A**. This family of more than 30 β-adrenergic antagonists is used in the therapy of hypertension, glaucoma, angina pectoris, anxiety, and obesity.[2,3] These *N*-isopropyl-3-(aryloxy)-2-hydroxypropylamines, such as (*S*)-toliprolol **I** and (*S*)-propanolol **II**, are mainly active as the (*S*)-enantiomers. For example, the (*S*)-propanolol **II** is 100-fold more active than the (*R*)-stereoisomer[4] (Fig. 1).

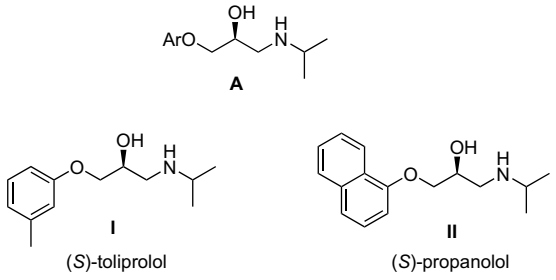
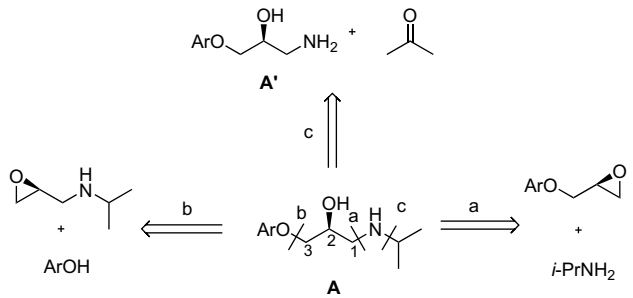


Figure 1.

Several syntheses of homochiral β-adrenergic blocking agents of type **A** have been achieved mainly through the formation of either the C1–N bond (pathway a) or the C3–O bond (pathway b). The third pathway (pathway c) corresponds to a reductive amination of **A'** (Scheme 1). The key chiral epoxides can be readily obtained via enzymatic resolution, nitroaldol reaction, asymmetric ring opening of aryl glycidyl ethers, Sharpless asymmetric epoxidation or asymmetric dihydroxylation. An asymmetric synthesis has also been achieved utilizing the chiral pool.[5,6]

Recently, we have shown that linear *N*,*N*-dialkyl 1,2-amino alcohols **C** were obtained by rearrangement of *N*,*N*-dialkyl β-amino alcohols **B**[7] by treatment with a catalytic amount of TFAA[8] or with



Scheme 1.

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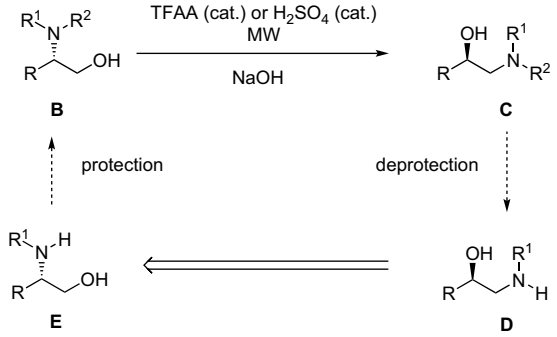
a catalytic amount of sulfuric acid.[9] The rearranged *N*,*N*-dialkylamino compounds **C** can be transformed to *N*-alkylamino alcohols **D**, but this strategy necessitates a deprotection step, which is not atom economical. In order to avoid these protection/deprotection steps, the direct rearrangement of *N*-alkyl 1,2-amino alcohols of type **E** has been considered (Scheme 2).[10]

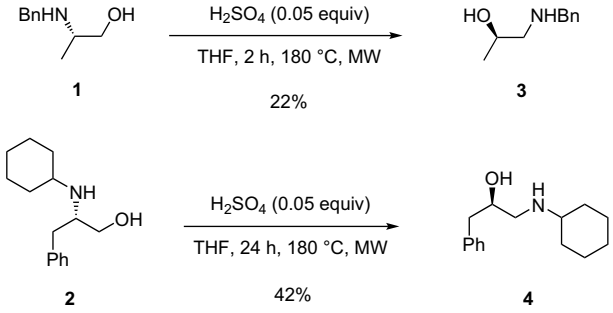


Scheme 2. General scheme.

Here, we would like to report our results concerning the rearrangement of *N*-alkyl 1,2-amino alcohols of type **E** and the application of this rearrangement to the synthesis of (*S*)-toliprolol **I** and (*S*)-propanolol **II**.

2. Rearrangement of *N*-alkyl 1,2-amino alcohols

At first, *N*-alkyl β-amino alcohols **1** and **2** were examined under the catalytic acidic conditions that were previously developed for the rearrangement of *N*,*N*-dialkyl β-amino alcohols.[9] Thus, when **1**[13] and **2** were treated with H_2SO_4 (0.05 equiv), respectively, for 2 h and 24 h, at 180 °C in THF under microwave irradiation, **3** (22%) and **4** (42%) were obtained in poor yields (Scheme 3).

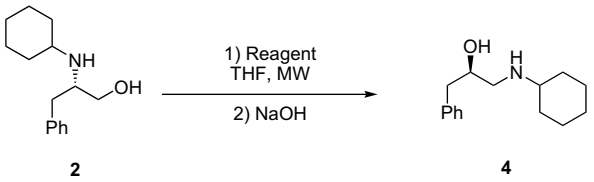


Scheme 3. Rearrangement of *N*-alkyl β-amino alcohols **1** and **2** with H_2SO_4.

Due to these results, rearrangement of compound **2** was examined under different conditions in order to improve the yields in the rearranged product **4**. Other reagents such as TFA and TFAA were used in catalytic amount to rearrange *N*-alkylamino alcohol **2** (THF, microwave irradiation, 24–30 h). However, the yields in the rearranged amino alcohol **4** were modest (54–57%) (Table 1, entries 1 and 2). The best yield in **4** (78%) was obtained by using a stoichiometric amount of TFAA and Et_3N at 120 °C for 12 h under microwave irradiation, followed by the addition of NaOH (Table 1, entry 3).

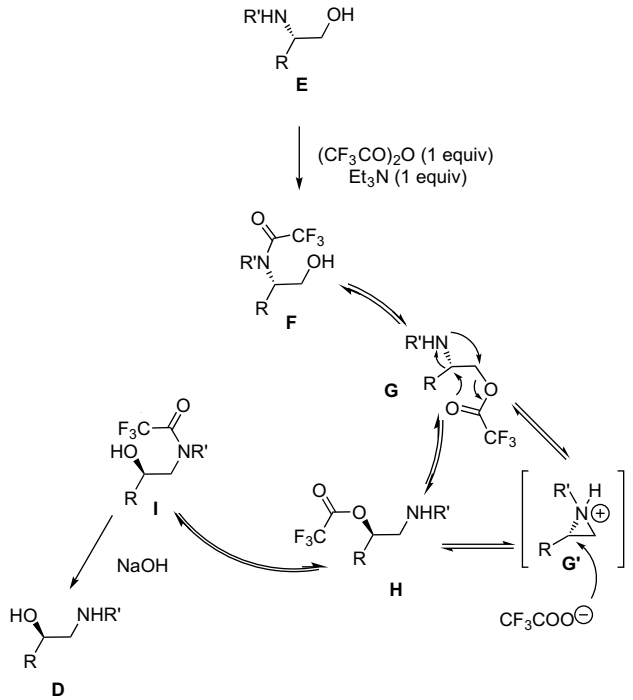
In order to explain these results, the mechanism of the rearrangement of β-amino alcohols **E** into β-amino alcohols **D** using a stoichiometric amount of TFAA and Et_3N has been considered. In this rearrangement, the first step is probably the trifluoroacetylation of the amino group in **E**, which would produce **F**. After a 1,4-migration of the trifluoroacetyl group from the amino group to the hydroxy group, **G** was produced and an intramolecular rearrangement could take place, leading to ester **H**.

Table 1
Rearrangement of *N*-cyclohexyl β-amino alcohol **2**



Entry	Reagent (equiv)	Conditions (h,°C)	Yield (%)
1	TFA (0.06 equiv)	24 h, 180 °C	57
2	TFAA (0.06 equiv)	30 h, 180 °C	54
3	TFAA (1 equiv), Et_3N (1 equiv), NaOH (20 equiv)	12 h, 120 °C	78

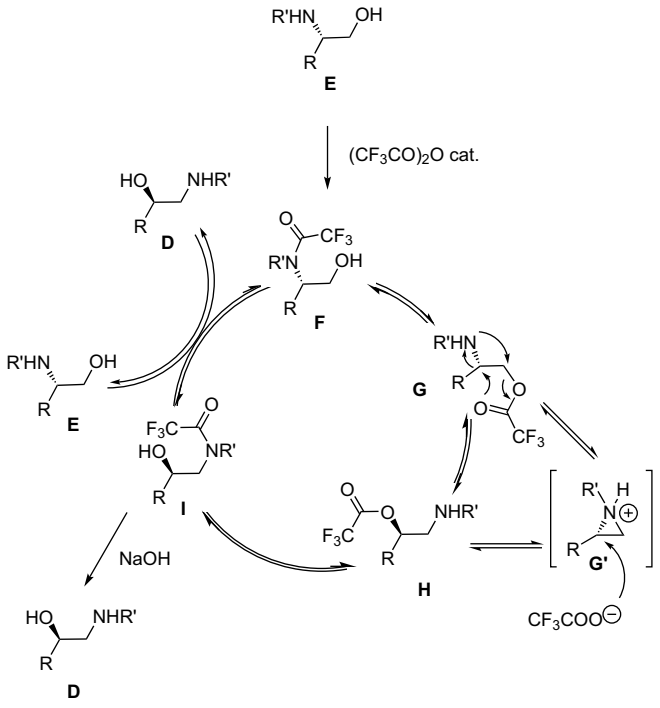
Ester **H** could also be formed via an aziridinium intermediate **G′**, which could be attacked by the trifluoroacetyl anion released in the reaction media. After a 1,4-migration of the trifluoroacetyl group from the hydroxy group to the amino group producing **I**, treatment with NaOH led to the rearranged amino alcohol **D** (Scheme 4). By analogy with our previous work,[11] we assume that compounds **F** and **I** are in equilibrium, and that trifluoroamide **I** is the thermodynamic product.



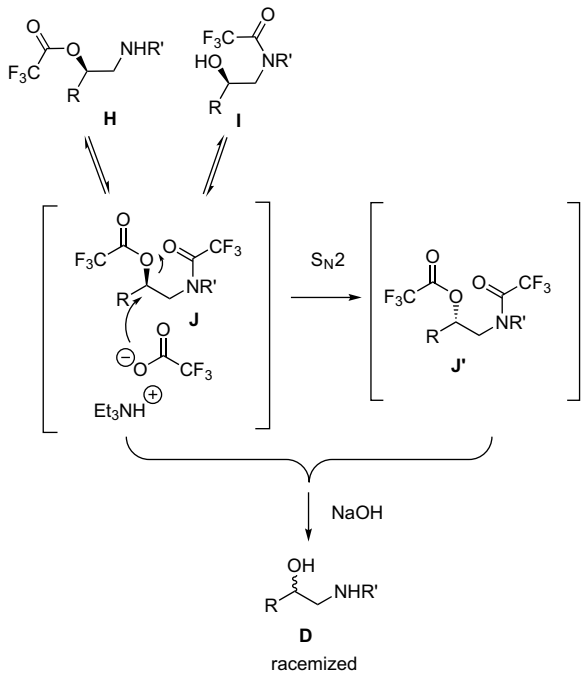
Scheme 4. Supposed mechanism for the rearrangement of **E** with a stoichiometric amount of TFAA and Et_3N.

Furthermore, if one considers the mechanism of the rearrangement of **E** into β-amino alcohol **D** using a catalytic amount of TFAA, the first steps will be identical to the rearrangement using a stoichiometric amount but an additional step, a transamidification between compound **I** and amino alcohol **E** can occur to complete the catalytic cycle by generating the rearranged amino alcohol **D** and the trifluoroamide **F**. This latter can be involved in the catalytic cycle (Scheme 5). By analogy with our previous work,[8] we assume that compounds **E**, **F**, **I**, and **D** are in equilibrium, and that compounds **D** and **I** are the thermodynamic products.

As the conditions of the rearrangement of *N*-alkyl β-amino alcohols are more drastic (higher temperature and longer reaction

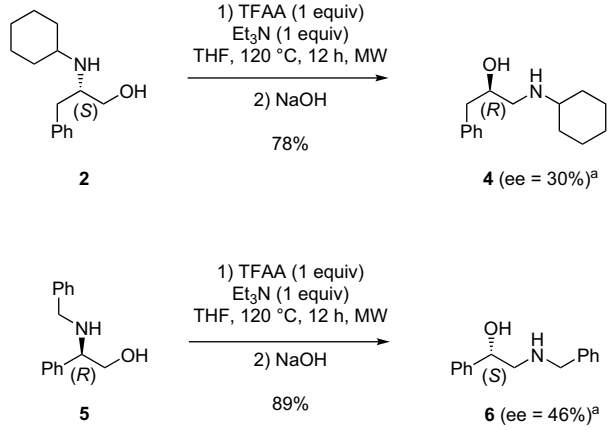


Scheme 5. Supposed mechanism of the rearrangement of **E** with a catalytic amount of TFAA.



Scheme 7. Supposed mechanism of racemization.

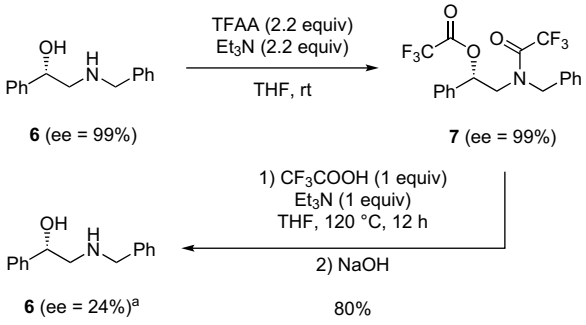
time) in utilizing a catalytic amount of TFAA than in utilizing a stoichiometric one, the use of 1 equiv of TFAA and 1 equiv of Et_3N in THF for 12 h at 120 °C followed by the addition of NaOH was chosen as conditions to study the rearrangement. When these conditions were applied to β-amino alcohol **2** and commercially available compound **5**, the corresponding rearranged compounds **4** and **6** were, respectively, obtained in good yields (> 78%) but, very disappointingly, the enantiomeric excesses were low, 30% for compound **4** and 46% for compound **6** (Scheme 6).



Scheme 6. Rearrangement of β-amino alcohols **2** and **5**. [a]Determined on the dibenzylated compound **19** and the benzylated compound **22** (cf. Scheme 10).

Based on the proposed mechanism, we would not expect to see this sort of epimerization. An hypothesis can be proposed to explain this racemisation. After the rearrangement, several species can be present in the reaction media such as **H**, **I**, and **J**, this latter can be formed from **H** and **I**. The epimerization can occur in species **J** according to an S_N2 mechanism involving a trifluoroacetyl anion that can be delivered from triethylammonium trifluoroacetate, which is present in the reaction media (Scheme 7).

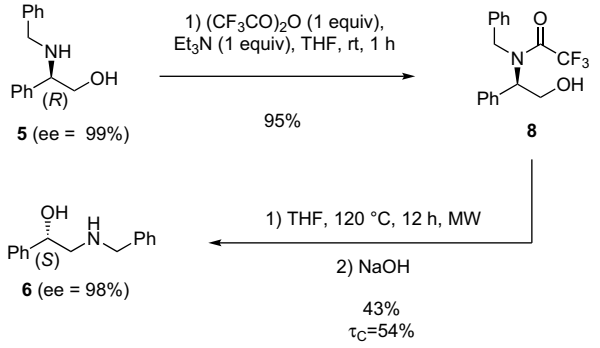
In order to verify this hypothesis, the rearranged β-amino alcohol **6** possessing an enantiomeric excess of 99% was transformed to amidoester **7** [TFAA (2.2 equiv), Et_3N (2.2 equiv), THF, rt]. This latter was then treated with 1 equiv of triethylammonium trifluoroacetate, in THF under microwave irradiation at 120 °C. After 12 h, the reaction media was treated with NaOH and **6** was isolated in 80% yield with an enantiomeric excess of 24%, demonstrating that the trifluoroacetate anion present in the reaction media can attack **7** according to an S_N2 mechanism leading to the racemization of **6** (Scheme 8).



Scheme 8. Racemization of optically pure β-amino alcohol **6**. [a]Determined on the dibenzylated compound **19** (cf. Scheme 10).

Furthermore, in order to prove that in the absence of the triethylammonium trifluoroacetate in the reaction media the racemization does not occur, trifluoroamide **8** was synthesized from **5** [TFAA (1 equiv), Et_3N (1 equiv), THF, rt] and then heated in THF under microwave irradiation at 120 °C for 12 h without triethylammonium trifluoroacetate. The reaction media was then treated with NaOH and **6** was isolated in 43% yield with an enantiomeric excess of 98%. These experiences demonstrated that triethylammonium trifluoroacetate was involved in the racemization process of **6**. Unfortunately, the lack of this ammonium salt entailed a moderate conversion in **6** (54%), demonstrating that triethylammonium trifluoroacetate is probably involved in the mechanism

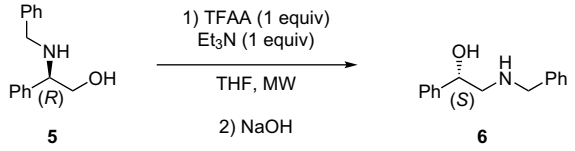
and/or the kinetic of the rearrangement (Scheme 9). Rising the temperature of the reaction to improve the conversion in **6** unfortunately came with the racemization of this latter.



Scheme 9. Synthesis and rearrangement of β-amido alcohol **8**.

In order to obtain the best yield and enantiomeric excess in **6**, the temperature and the reaction time were examined. The best conditions were 1 equiv of TFAA and 1 equiv of Et_3N at 100 °C under microwave irradiation for 15 h. It is worth noting that when heated at 110 °C under microwave irradiation for 6 h, **5** was transformed into **6** with a very good enantiomeric excess (94%) and with a good yield (72%). The results are reported in Table 2.

Table 2
Optimization of the temperature and reaction time for the rearrangement of **5**



Entry	Time (h)	Temperature (°C)	τ_C (%)	Yield (ee)[a][%]
1	12	120	100	89 (46)
2	6	120	95	78 (87)
3	1	180	100	72 (64)
4	6	110	91	72 (94)
5	15	100	84	63 (96)

[a] Determined on the dibenzylated compound **19** (cf. Scheme 10).

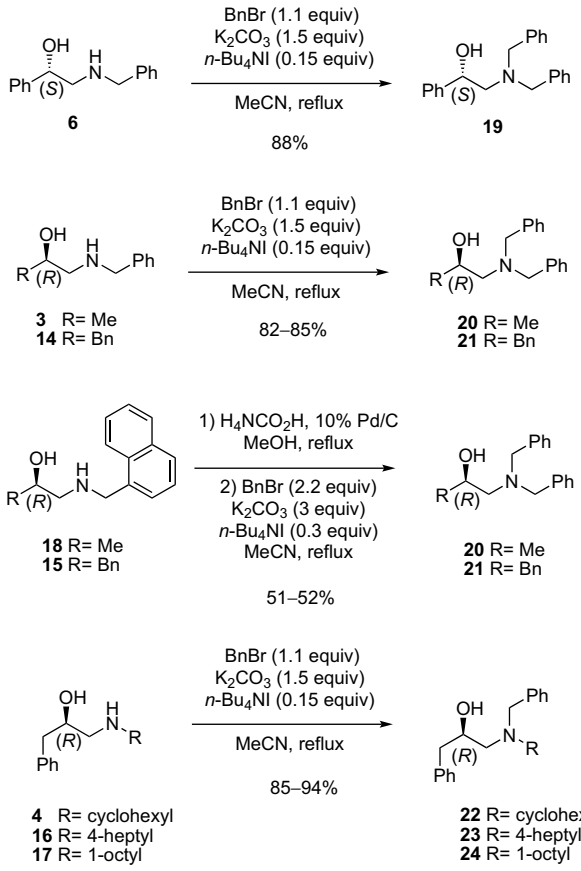
It is worth noting that for each substrate, the conditions have to be tuned up. The best conditions and results in obtaining **3**, **4**, **14**–**18** from, respectively, **1**, **2**, **9**–**13** are reported in Table 3.

The enantiomeric excesses of compounds **3**, **4**, **14**–**18** were found to be superior to 93% when amino alcohols **1**, **2**, **9**–**13** were heated at 110 °C or 120 °C for 6 h to 12 h.

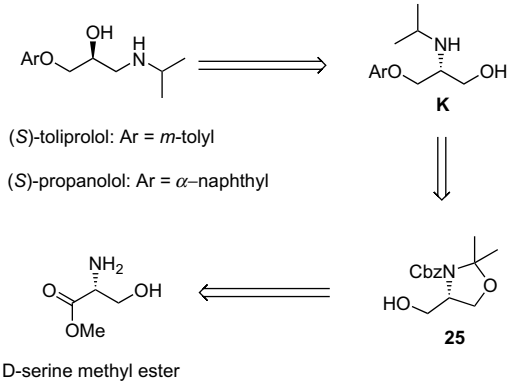
The enantiomeric excesses of compounds **3**, **4**, **6**, **14**–**18** were determined by measuring the enantiomeric excesses of either the dibenzyl β-amino alcohols **19**–**21** or the benzylalkyl β-amino alcohols **22**–**24**. Preparations of **19**–**24** are reported in Scheme 10.

3. Synthesis of (*S*)-toliprolol and (*S*)-propanolol

The rearrangement of *N*-alkyl β-amino alcohols was then applied to the synthesis of (*S*)-toliprolol and (*S*)-propanolol, two β-adrenergic blocking agents, which are active as the (*S*)-enantiomers. The synthesis of these *N*-isopropyl-3-(aryloxy)-2-hydroxypropylamines would be obtained by rearrangement of 1,2-amino alcohols **K** that would be synthesized from D-serine methyl ester via the protected amino alcohol **25**[12] (Scheme 11).



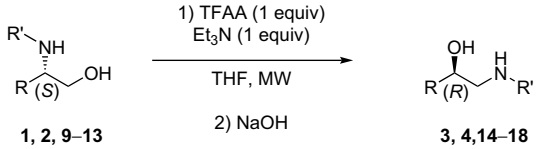
Scheme 10. Synthesis of β-amino alcohols **19**–**24**.



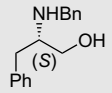
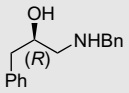
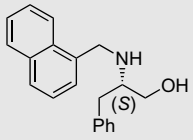
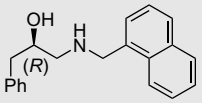
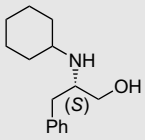
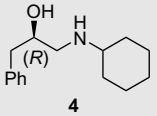
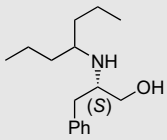
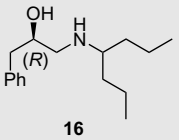
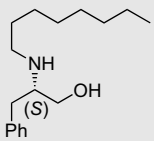
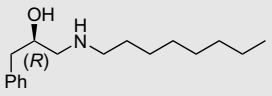
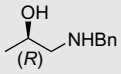
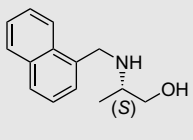
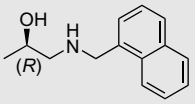
Scheme 11. Retrosynthetic approach to (*S*)-toliprolol and (*S*)-propanolol.

The common intermediate **25** was synthesized in three steps from D-serine methyl ester.[12] After carbamoylation [CbzCl (1.1 equiv), K_2CO_3 (3 equiv) in THF/H_2O 1/1], protection of the hydroxy carbamate [APTS, 2,2-dimethoxypropane] and reduction [$NaBH_4$, THF/MeOH], **25** was isolated in 59% yield. In order to synthesize (*S*)-toliprolol, **25** was treated with *m*-cresol under the Mitsunobu conditions (PPh_3, DEAD, toluene, 80 °C, 18 h) and the obtained aryl ether **26** (69%) was hydrogenated (H_2, Pd/C 10%, MeOH) producing amino alcohol **27** (77%). This latter was rearranged to (*S*)-toliprolol by treatment with TFAA (1 equiv), Et_3N (1 equiv) in THF under microwave irradiation at 110 °C for 12 h followed by the addition of NaOH. Under these conditions, (*S*)-toliprolol was isolated in 69% yield and with an enantiomeric excess of 92% (Scheme 12).

Table 3
Rearrangement of *N*-alkyl β-amino alcohols



1, 2, 9–13 → **3, 4,14–18**

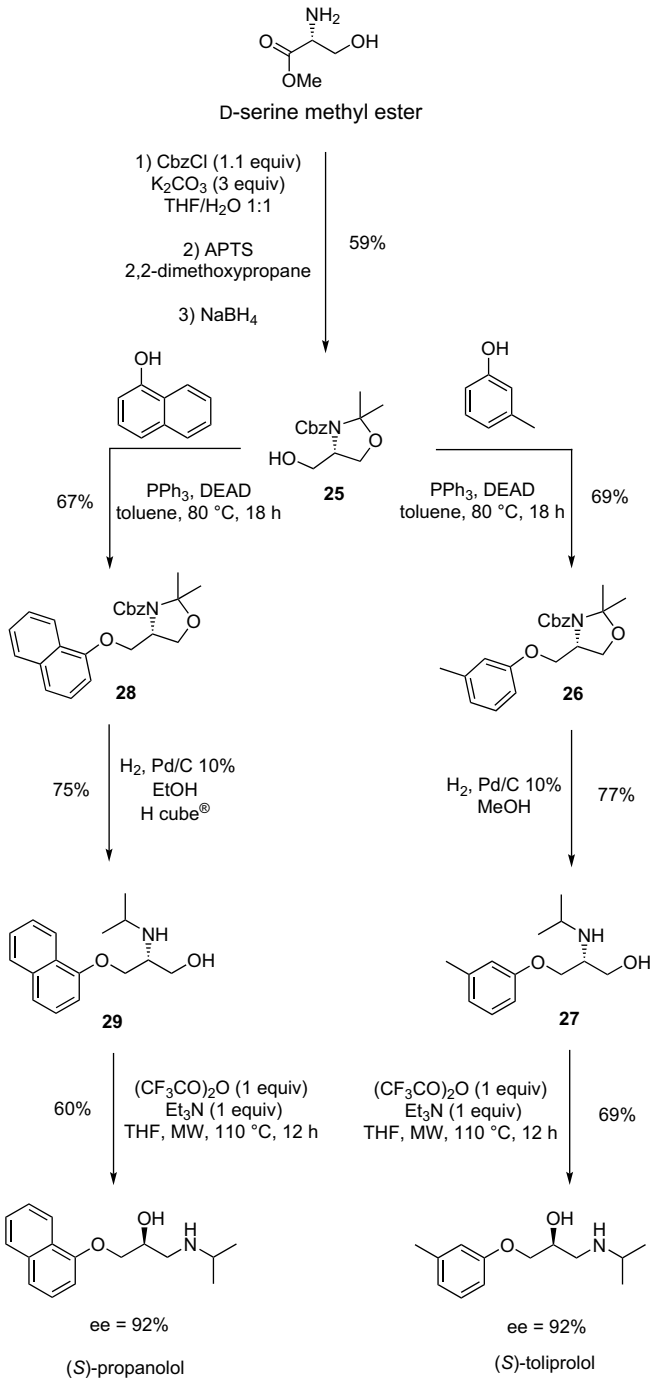
Entry	Starting material	Time (h)	Temperature (°C)	Product	Yield (ee) [%]
1	 **9**	12	120	 **14**	70 (98)[a]
2	 **10**	12	120	 **15**	80 (96)[a]
3	 **2**	6	110	 **4**	85 (94)[b]
4	 **11**	6	110	 **16**	91 (96)[b]
5	 **12**	12	120	 **17**	78 (93)[b]
6	 **1**	12 18	120 110	 **3**	88 (93)[a] 60 (96)[a]
7	 **13**	8	120	 **18**	74 (93)[a]

[a] Determined on the dibenzylated compounds **20**, **21** (cf. Scheme 10).
[b] Determined on the benzylalkyl β-amino alcohols **22**–**24** (cf. Scheme 10).

Similarly, (*S*)-propanolol was synthesized from **25**. After a Mitsunobu reaction with α-naphthol leading to the aryl ether **28** (67%), classical hydrogenation (H_2, Pd/C 10%, MeOH) of this latter produced the amino alcohol **29** in poor yield (33%). When the hydrogenation was conducted in a flow manner using H-Cube™ (Thales Nanotechnology Inc.), the amino alcohol **29** was isolated in a better yield of 75%. This latter was rearranged by treatment with TFAA (1 equiv), Et_3N (1 equiv) in THF under microwave irradiation at 110 °C for 12 h followed by the addition of NaOH leading to (*S*)-propanolol in 60% yield, with an enantiomeric excess of 92% (Scheme 12).

4. Conclusion

The rearrangement of optically active *N*-alkyl 1,2-amino alcohols can take place by treatment of these latter with TFAA, Et_3N (1 equiv). For each substrate, the temperature and the reaction time have to be controlled in order to obtain the best yield and enantiomeric excess in the rearranged products. This simple rearrangement can be applied to the synthesis of biologically active compounds in an efficient manner.



Scheme 12. Synthesis of (*S*)-toliprolol and (*S*)-propanolol.

5. Experimental

5.1. General

TLC was performed on Merck $60F_{254}$ silica gel plates and visualized with a UV lamp (254 nm), or by using a solution of $KMnO_4$/K_2CO_3/NaOH in water followed by heating. Column chromatography was performed with Merck Geduran Si 60 silica gel (40–63 μm). Infrared (IR) spectra were recorded on a Bruker TENSOR™ 27 (IRFT), wave numbers are indicated in cm^{-1}. ^1H NMR spectra were recorded on a Bruker AVANCE 400 at 400 MHz and data are reported as follows: chemical shift in parts per million from tetramethylsilane as internal standard, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, h=heptuplet, m=multiplet or overlap of non-equivalent resonances, integration). ^{13}C NMR spectra were recorded on a Bruker AVANCE 400 at 100 MHz and data are reported as follows: chemical shift in parts per million from tetramethylsilane with the solvent as internal standard ($CDCl_3$, δ 77.0 ppm), multiplicity with respect to proton (deduced from DEPT experiments, s=quaternary C, d=CH, t=CH_2, q=CH_3). Mass spectra with electronic impact (MS-EI) were recorded from a Hewlett-Packard tandem 5890A GC (12 m capillary column)–5971 MS (70 eV). All reactions were carried out under argon atmosphere. Commercially available reagents and solvents were used as received. Anhydrous solvents were distilled: tetrahydrofuran and diethyl ether were purified by distillation from sodium and benzophenone, methylene chloride and toluene were dried by distillation from CaH_2. Flash column chromatography was performed on silica gel (Merck-Kieselgel 60, 230–400 mesh). HRMS were performed by the Centre Régional de Microanalyses (Université Pierre et Marie Curie, Paris VI). Microwave irradiation experiments were performed using a single-mode Initiator TM EXP (0–300 W, 2.45 GHz) from Biotage.

5.2. Reductive amination: compounds 2, 9–13

*5.2.1. (S)-2-Cyclohexylamino-3-phenylpropan-1-ol (**2**)*

To a stirred suspension of (*S*)-2-amino-3-phenylpropan-1-ol (1.01 g, 6.6 mmol) and cyclohexanone (690 μL, 6.6 mmol, 1 equiv) in 1,2-dichloroethane (23 mL) were successively added $NaBH(OAc)_3$ (2.1 g, 9.9 mmol, 1.5 equiv) and AcOH (0.38 mL, 6.6 mmol, 1 equiv). After stirring at rt for 12 h, the reaction mixture was hydrolyzed by addition of an aqueous 1 M NaOH solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organic phases were washed with an aqueous 1 M NaOH solution, dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and the residue was purified by flash column chromatography on silica gel (EtOAc+0.5% Et_3N) to give **2** (1.33 g, 5.7 mmol, 85%). $[\alpha]_D^{25}$ +11.57 (*c* 0.55, $CHCl_3$); IR (neat) 3272, 3026, 2849, 1600, 1492, 1477, 1350, 1122, 1037, 805, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.32–7.15 (m, 5H), 3.54 (dd, *J*=10.4, 4.1 Hz, 1H), 3.23 (dd, *J*=10.4, 5.6 Hz, 1H), 3.0 (tdd, *J*=6.8, 5.7, 4.2 Hz, 1H), 2.78–2.67 (m, 2H), 2.45 (tt, *J*=10.2, 3.8 Hz, 1H), 2.12 (br s, 2H), 1.85 (m, 1H), 1.75–1.54 (m, 4H), 1.28–0.9 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7 (s), 129.2 (d, 2C), 128.5 (d, 2C), 126.3 (d), 63.1 (t), 56.8,(d), 53.7 (d), 38.7 (t), 34.3 (t), 33.9 (t), 26.0 (t), 25.0 (t), 24.9 (t); MS-EI *m*/*z* (relative intensity): 202 ($M^{+\bullet}-CH_2OH^{\bullet}$, 32), 142 (100), 132 (13), 120 (33), 105 (8), 91 (36), 83 (12), 60 (35), 55 (16); HRMS calcd for $C_{15}H_{24}NO$ (MH^+): 234.18524, found: 234.18539.

*5.2.2. (S)-2-Benzylamino-3-phenylpropan-1-ol (**9**)*[14]

To a suspension of molecular sieves 4 Å (1.3 g) in CH_2Cl_2 (13 mL) were successively added (*S*)-2-amino-3-phenylpropan-1-ol (1 g, 6.6 mmol) and benzaldehyde (670 μL, 6.6 mmol, 1 equiv). After 3 h at rt without stirring, the suspension was filtered and concentrated under reduced pressure. The residue was dissolved in EtOH (13 mL) and sodium borohydride was added (294 mg, 7.9 mmol, 1.2 equiv). After stirring at rt for 12 h, the reaction mixture was hydrolyzed by addition of a saturated aqueous solution of NH_4Cl and concentrated under reduced pressure. After addition of an aqueous 1 M NaOH solution followed by the extraction with CH_2Cl_2, the organic phase was dried over $MgSO_4$ and filtered. The solvent was removed in vacuo and the residue was purified by flash column chromatography on silica gel (EtOAc+0.5% Et_3N) to give **9** (1.274 g, 5.3 mmol, 80%).

*5.2.3. (S)-2-(Naphthalen-1-ylmethylamino)-3-phenylpropan-1-ol (**10**)*

To a suspension of molecular sieves 4 Å (1 g) in CH_2Cl_2 (7 mL) were successively added (*S*)-2-amino-3-phenylpropan-1-ol (500 mg, 3.3 mmol) and 1-naphthaldehyde (450 μL, 3.3 mmol, 1 equiv). After 3 h at rt without stirring, the suspension was filtered

and concentrated under reduced pressure. The residue was dissolved in EtOH (7 mL) and $NaBH_4$ was added (150 mg, 4 mmol, 1.2 equiv). After stirring at rt for 12 h, the reaction mixture was hydrolyzed by addition of a saturated aqueous solution of NH_4Cl and concentrated under reduced pressure. Basification of the aqueous residue with an aqueous 1 M NaOH solution was followed by the extraction with CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$ and filtered. The solvent was removed in vacuo and the residue was purified by flash column chromatography on silica gel (CH_2Cl_2/EtOAc 50/50+0.5% Et_3N) to give **10** (814 mg, 2.8 mmol, 84%). $[\alpha]_D^{25}$ −25.2 (*c* 1.0, $CHCl_3$); IR (neat) 3500–2600, 2334, 2114, 1596, 1495, 1460, 1353, 1229, 1116, 1054, 1028, 963, 881, 842, 777, 747, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (m, 1H), 7.83 (m, 1H), 7.75 (d, *J*=8.0 Hz, 1H), 7.48–7.32 (m, 4H), 7.29–7.13 (m, 5H), 4.21 (d, *J*=12.8 Hz, 1H), 4.16 (d, *J*=12.8 Hz, 1H), 3.71 (dd, *J*=10.8, 4.0 Hz, 1H), 3.38 (dd, *J*=10.8, 5.3 Hz, 1H), 3.06 (m, 1H), 2.83 (dd, *J*=13.8, 7.3 Hz, 1H), 2.79 (dd, *J*=13.6, 6.8 Hz, 1H), 1.98 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4 (s), 135.5 (s), 133.9 (s), 131.7 (s), 129.2 (d, 2C), 128.8 (d), 128.6 (d, 2C), 128.1 (d), 126.5 (d), 126.3 (d), 126.2 (d), 125.7 (d), 125.4 (d), 123.4 (d), 62.8 (t), 60.1 (d), 49.3 (t), 38.2 (t); MS-EI *m*/*z* (relative intensity): 273 ($M^{+\bullet}-H_2O$, 6), 260 (6), 200 (26), 141 (100), 132 (20), 115 (17), 91 (8); HRMS calcd for $C_{20}H_{22}NO$ (MH^+): 292.16959; found: 292.16905.

5.2.4. (*S*)-2-(Heptan-4-ylamino)-3-phenylpropan-1-ol (**11**)

To a stirred suspension of (*S*)-2-amino-3-phenylpropan-1-ol (500 mg, 3.3 mmol) and 4-heptanone (460 μL, 3.3 mmol, 1 equiv) in 1,2-dichloroethane (12 mL) were successively added $NaBH(OAc)_3$ (1.5 g, 7.1 mmol, 2.2 equiv) and AcOH (0.19 mL, 3.3 mmol, 1 equiv). After stirring at rt for 12 h, the reaction mixture was hydrolyzed by addition of an aqueous 1 M NaOH solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organic phases were washed with an aqueous 1 M NaOH solution, dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and the residue was purified by flash column chromatography on silica gel (EtOAc+0.5% Et_3N) to give **11** (416 mg, 1.7 mmol, 51%). $[\alpha]_D^{25}$ −5.8 (*c* 1.0, $CHCl_3$); IR (neat) 3500–2500, 1602, 1495, 1455, 1377, 1150, 1031, 907, 743, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.32–7.15 (m, 5H), 3.54 (dd, *J*=10.5, 4.0 Hz, 1H), 3.25 (dd, *J*=10.5, 4.5 Hz, 1H), 2.94 (m, 1H), 2.75 (dd, *J*=13.6, 7.0 Hz, 1H), 2.69 (dd, *J*=13.6, 7.3 Hz, 1H), 2.50 (tt, *J*=5.6, 5.6 Hz, 1H), 1.41–0.95 (m, 8H), 0.89 (t, *J*=6.9 Hz, 3H), 0.80 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8 (s), 129.2 (d, 2C), 128.5 (d, 2C), 126.4 (d), 62.9 (t), 60.4 (d), 57.5 (d), 39.1 (t), 37.3 (t), 36.4 (t), 18.9 (t), 18.3 (t), 14.4 (q), 14.3 (q); MS-EI *m*/*z* (relative intensity): 231 ($M^{+\bullet}-H_2O$, 16), 188 (81), 140 (64), 117 (60), 91 (100), 57 (24); HRMS calcd for $C_{16}H_{28}NO$ (MH^+): 250.21654; found: 250.21641.

5.2.5. (*S*)-2-(Octylamino)-3-phenylpropan-1-ol (**12**)

To a stirred suspension of (*S*)-2-amino-3-phenylpropan-1-ol (500 mg, 3.3 mmol) and octanal (516 μL, 3.3 mmol, 1 equiv) in 1,2-dichloroethane (12 mL) were successively added $NaBH(OAc)_3$ (1.05 g, 5 mmol, 1.5 equiv) and AcOH (0.20 mL, 3.3 mmol, 1 equiv). After stirring at rt for 48 h, the reaction mixture was hydrolyzed by addition of an aqueous 1 M NaOH solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organic phases were washed with an aqueous 1 M NaOH solution, dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and the residue was purified by flash column chromatography on silica gel (EtOAc+0.5% Et_3N) to give **12** (505 mg, 1.92 mmol, 58%). $[\alpha]_D^{25}$ −0.6 (*c* 1.15, $CHCl_3$); IR (neat) 3500–2500, 1496, 1453, 1351, 1120, 1037, 930, 834, 744, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.32–7.15 (m, 5H), 3.59 (dd, *J*=10.5, 4.0 Hz, 1H), 3.30 (dd, *J*=10.5, 5.5 Hz, 1H), 2.87 (m, 1H), 2.78 (dd, *J*=13.6, 6.8 Hz, 1H), 2.71 (dd, *J*=13.6, 7.0 Hz, 1H), 2.58 (m, 2H), 1.45–1.35 (m, 2H), 1.33–1.18 (m, 10H), 0.88 (t, *J*=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7 (s), 129.2 (d, 2C), 128.5 (d, $2C_{Ar}$), 126.4 (d), 62.5 (t), 60.1 (d), 47.0 (t), 38.2 (t), 31.8 (t), 30.3 (t), 29.4 (t), 29.2 (t), 27.2 (t), 22.6 (t), 14.1 (q); MS-EI *m*/*z* (relative intensity): 232 ($M^{+\bullet}-CH_2OH^{\bullet}$, 39), 172 (100), 154 (15), 146 (9), 120 (10), 91 (25), 60 (8); HRMS calcd for $C_{17}H_{30}NO$ (MH^+): 264.23219; found: 264.23196.

5.2.6. (*S*)-2-(Naphthalen-1-ylmethylamino)propan-1-ol (**13**)

To a suspension of molecular sieves 4 Å (1.5 g) in CH_2Cl_2 (7 mL) were successively added (*S*)-2-amino-propan-1-ol (500 μL, 6.4 mmol) and 1-naphthaldehyde (916 μL, 6.4 mmol, 1 equiv). After 3 h at rt without stirring, the suspension was filtered and concentrated under reduced pressure. The residue was dissolved in EtOH (7 mL) and $NaBH_4$ was added (240 mg, 6.5 mmol, 1.01 equiv). After stirring at rt for 12 h, the reaction mixture was hydrolyzed by addition of a saturated aqueous solution of NH_4Cl and concentrated under reduced pressure. Basification of the aqueous residue with an aqueous 1 M NaOH solution was followed by the extraction with CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$ and filtered. The solvent was removed in vacuo and the residue was purified by flash column chromatography on silica gel (EtOAc+0.5% Et_3N) to give **13** (965 mg, 4.5 mmol, 70%). $[\alpha]_D^{25}$ +31.9 (*c* 1.0, $CHCl_3$); IR (neat) 3500–2600, 2327, 1598, 1510, 1445, 1371, 1262, 1149, 1064, 879, 851, 790, 765, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, *J*=8.5 Hz, 1H), 7.86 (d, *J*=7.8 Hz, 1H), 7.77 (d, *J*=8.0 Hz, 1H), 7.55–7.39 (m, 4H), 4.31 (d, *J*=12.8 Hz, 1H), 4.19 (d, *J*=12.8 Hz, 1H), 3.63 (dd, *J*=10.5, 4.0 Hz, 1H), 3.29 (dd, *J*=10.8, 7.0 Hz, 1H), 2.95 (m, 1H), 1.91 (br s, 2H), 1.15 (d, *J*=6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.9 (s), 134.0 (s), 131.8 (s), 128.8 (d), 128.0 (d), 126.3 (d), 126.2 (d), 125.7 (d), 125.4 (d), 123.6 (d), 65.7 (t), 54.4 (d), 49.0 (t), 17.3 (q); HRMS calcd for $C_{14}H_{18}NO$ (MH^+): 216.13829; found: 216.13817.

5.3. Rearrangement: compounds 3, 4, 6, 14–18

5.3.1. Typical procedure

To a solution of β-aminoalcohol of type **E** in THF (0.5 M) was added dropwise trifluoroacetic anhydride (1 equiv) and then Et_3N (1 equiv). The reaction mixture was then heated under microwave irradiation in a sealed tube. After addition of an aqueous 2.5 M NaOH solution (2 mL), the mixture was stirred at rt for 2 h, extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel afforded β-amino alcohol of type **D**.

5.3.2. (*R*)-1-Benzylaminopropan-2-ol (**3**)[15]

Following the typical procedure (120 °C, 12 h, MW), the transformation of **1** (100 mg, 0.6 mmol) afforded an oil that was purified by flash column chromatography on silica gel (EtOAc/MeOH 90/10+0.5% Et_3N) to give **3** (88 mg, 0.53 mmol, 88%). $[\alpha]_D^{25}$ −25.0 (*c* 0.50, $CHCl_3$); IR (neat) 2825, 1673, 1495, 1453, 1374, 1201, 1136, 1028, 918, 841, 736, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.32–7.15 (m, 5H), 3.74 (d, *J*=13.3 Hz, 1H), 3.73 (m, 1H), 3.69 (d, *J*=13.3 Hz, 1H), 3.0 (br s, 2H), 2.60 (dd, *J*=10.7, 4.0 Hz, 1H), 2.35 (dd, *J*=10.7, 7.0 Hz, 1H), 1.07 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.7 (s), 128.5 (d, 2C), 128.3 (d, 2C), 127.2 (d), 65.5 (d), 56.2 (t), 53.5 (t), 20.7 (q).

5.3.3. (*R*)-1-Cyclohexylamino-3-phenylpropan-2-ol (**4**)

Rearrangement with a catalytic amount of H_2SO_4. To a solution of (*S*)-2-cyclohexylamino-3-phenylpropan-1-ol **2** (200 mg, 0.86 mmol, 1.0 equiv) in THF (1 mL) was added dropwise sulfuric acid (3 μL, 0.04 mmol, 0.05 equiv). The reaction mixture was then heated at 180 °C for 24 h under microwave irradiation in a sealed tube. After addition of a saturated aqueous $NaHCO_3$ solution, the mixture was extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (EtOAc+0.5% Et_3N) afforded **4** (84 mg, 0.36 mmol, 42%).

Rearrangement with a catalytic amount of TFA. To a solution of (*S*)-2-cyclohexylamino-3-phenylpropan-1-ol **2** (200 mg, 0.86 mmol, 1.0 equiv) in THF (1 mL) was added dropwise trifluoroacetic acid (4 μL, 0.05 mmol, 0.06 equiv). The reaction mixture was then heated at 180 °C for 24 h under microwave irradiation in a sealed tube. After addition of an aqueous 2.5 M NaOH solution (1 mL), the mixture was stirred at rt for 2 h, extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (CH_2Cl_2/EtOAc+0.5% Et_3N) afforded **4** (114 mg, 0.49 mmol, 57%).

Rearrangement with a catalytic amount of TFAA. To a solution of (*S*)-2-cyclohexylamino-3-phenylpropan-1-ol **2** (200 mg, 0.86 mmol, 1.0 equiv) in THF (1 mL) was added dropwise trifluoroacetic anhydride (7 μL, 0.05 mmol, 0.06 equiv). The reaction mixture was then heated at 180 °C for 30 h under microwave irradiation in a sealed tube. After addition of an aqueous 2.5 M NaOH solution (1 mL), the mixture was stirred at room temperature for 2 h, extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (CH_2Cl_2/EtOAc+0.5% Et_3N) afforded **4** (107 mg, 0.46 mmol, 54%).

Rearrangement with a stoichiometric amount of TFAA and Et_3N. Following the typical procedure (110 °C, 6 h, MW), the transformation of **2** (91 mg, 0.39 mmol) afforded an oil that was purified by flash column chromatography on silica gel (EtOAc+0.5% Et_3N) to give **4** (77 mg, 0.33 mmol, 85%).

$[\alpha]_D^{25}$ −20.2 (*c* 1.17, $CHCl_3$); IR (neat) 3290, 2922, 2850, 2347, 1602, 1451, 1338, 1081, 961, 739, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31–7.15 (m, 5H), 3.80 (dddd, *J*=9.0, 7.3, 5.7, 3.2 Hz, 1H), 2.82–2.68 (m, 3H), 2.47 (dd, *J*=12.0, 9.1 Hz, 1H), 2.36 (tt, *J*=10.4, 3.8 Hz, 1H), 2.16 (br s, 2H), 1.88–1.56 (m, 5H), 1.36–0.83 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5 (s), 129.4 (d, 2C), 128.4 (d, 2C), 126.3 (d), 70.9 (d), 56.6,(d), 51.8 (t), 41.8 (t), 34.0 (t), 33.6 (t), 26.1 (t), 25.0 (t), 25.0 (t); MS-EI *m*/*z* (relative intensity): 233 ($M^{+\bullet}$, 4), 190 (4), 117 (4), 112 (100), 91 (17), 55 (8); HRMS calcd for $C_{15}H_{24}NO$ (MH^+): 234.18524; found: 234.18509.

5.3.4. (*S*)-2-*N*-Benzylamino-1-phenylethanol (**6**)[16]

Following the typical procedure (110 °C, 6 h, MW), the transformation of **5** (54 mg, 0.24 mmol) afforded an oil that was purified by flash column chromatography on silica gel (EtOAc+0.5% Et_3N) to give **6** (39 mg, 0.17 mmol, 72%).

5.3.5. (*R*)-1-Benzylamino-3-phenylpropan-2-ol (**14**)[17]

Following the typical procedure (120 °C, 12 h, MW), the transformation of **9** (104 mg, 0.43 mmol) afforded an oil that was purified by flash column chromatography on silica gel (EtOAc+0.5% Et_3N) to give **14** (72 mg, 0.30 mmol, 70%). $[\alpha]_D^{25}$ −20.2 (*c* 1.0, $CHCl_3$); IR (neat) 3026, 2845, 1723, 1656, 1602, 1494, 1453, 1274, 1029, 740, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35–7.12 (m, 10H), 3.87 (m, 1H), 3.78 (d, *J*=13.2 Hz, 1H), 3.71 (d, *J*=13.2 Hz, 1H), 2.82–2.67 (m, 3H), 2.53 (dd, *J*=12.1, 9.0 Hz, 1H), 2.38 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.1 (s), 138.3 (s), 129.3 (d, 2C), 128.6 (d, 2C), 128.5 (d, 2C), 128.2 (d, 2C), 127.1 (d), 126.4 (d), 70.7 (d), 54.2 (t), 53.7 (t), 41.6 (t); MS-EI *m*/*z* (relative intensity): 223 ($M^{+\bullet}-H_2O$, 6), 120 (82), 91 (100), 65 (8).

5.3.6. (*S*)-2-(Naphthalen-1-ylmethylamino)-3-phenylpropan-1-ol (**15**)

Following the typical procedure (120 °C, 12 h, MW), the transformation of **10** (100 mg, 0.52 mmol) afforded an oil that was purified by flash column chromatography on silica gel (CH_2Cl_2/EtOAc 50/50+0.5% Et_3N) to give **15** (79 mg, 0.27 mmol, 80%). $[\alpha]_D^{25}$ −25.2 (*c* 1.0, $CHCl_3$); IR (neat) 3500–2500, 2336, 2116, 1597, 1510, 1494, 1453, 1340, 1124, 1099, 1046, 890, 849, 792, 774, 745, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J*=8.3 Hz, 1H), 7.83 (m, 1H), 7.75 (m, 1H), 7.53–7.42 (m, 2H), 7.41–7.35 (m, 2H), 7.30–7.16 (m, 5H), 4.20 (d, *J*=13.3 Hz, 1H), 4.12 (d, *J*=13.2 Hz, 1H), 3.87 (m, 1H), 2.81 (dd, *J*=12.0, 3.3 Hz, 1H), 2.76 (dd, *J*=13.6, 7.3 Hz, 1H), 2.69 (dd, *J*=13.8, 5.8 Hz, 1H), 2.60 (dd, *J*=12.0, 8.8 Hz, 1H), 2.39 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4 (s), 135.6 (s), 133.9 (s), 131.8 (s), 129.4 (d, 2C), 128.8 (d), 128.5 (d, 2C), 128.0 (d), 126.4 (d), 126.2 (d, 2C), 125.8 (d), 125.4 (d), 123.7 (d), 70.8 (d), 54.7 (t), 51.5 (t), 41.6 (t); MS-EI *m*/*z* (relative intensity): 291 ($M^{+\bullet}$, 1), 285 (4), 273 (6), 170 (21), 141 (100), 132 (12), 115 (15), 91 (13); HRMS calcd for $C_{20}H_{22}NO$ (MH^+): 292.16959; found: 292.16917.

5.3.7. (*R*)-1-(Heptan-4-ylamino)-3-phenylpropan-2-ol (**16**)

Following the typical procedure (110 °C, 6 h, MW), the transformation of **11** (81 mg, 0.33 mmol) afforded an oil that was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 50/50+0.5% Et_3N) to give **16** (74 mg, 0.30 mmol, 91%). $[\alpha]_D^{25}$ −23.7 (*c* 1.15, $CHCl_3$); IR (neat) 3500–2500, 1602, 1495, 1454, 1377, 1153, 1084, 1030, 904, 745, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.32–7.18 (m, 5H), 3.77 (m, 1H), 2.82–2.66 (m, 3H), 2.48–2.37 (m, 2H), 2.35 (br s, 2H), 1.37–1.23 (m, 8H), 0.97–0.84 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.6 (s), 129.3 (d, 2C), 128.4 (d, 2C), 126.3 (d), 70.9 (d), 57.0 (d), 51.8 (t), 41.7 (t), 36.8 (t), 36.6 (t), 19.0 (t), 18.9 (t), 14.3 (q, 2C); MS-EI *m*/*z* (relative intensity): 231 ($M^{+\bullet}-H_2O$, 3), 206 (88), 188 (81), 140 (14), 128 (41), 117 (37), 91 (100), 84 (35), 57 (28); HRMS calcd for $C_{16}H_{28}NO$ (MH^+): 250.21654; found: 250.21635.

5.3.8. (*R*)-1-(Octylamino)-3-phenylpropan-2-ol (**17**)

Following the typical procedure (120 °C, 12 h, MW), the transformation of **12** (81 mg, 0.31 mmol) afforded an oil that was purified by flash column chromatography on silica gel (EtOAc+0.5% Et_3N) to give **17** (69 mg, 0.26 mmol, 78%). $[\alpha]_D^{25}$ −8.9 (*c* 1.5, $CHCl_3$); IR (neat) 3500–2500, 1494, 1454, 1377, 1082, 1031, 911, 745, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.32–7.15 (m, 5H), 3.85 (m, 1H), 2.78 (dd, *J*=13.6, 7.3 Hz, 1H), 2.73–2.67 (m, 2H), 2.62–2.46 (m, 3H), 2.40 (br s, 2H), 1.50–1.38 (m, 2H), 1.36–1.20 (m, 10H), 0.88 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5 (s), 129.4 (d, 2C), 128.5 (d, 2C), 126.3 (d), 70.5 (d), 54.8 (t), 49.7 (t), 41.8 (t), 31.8 (t), 30.1 (t), 29.7 (t), 29.5 (t), 27.3 (t), 22.7 (t), 14.1 (q); MS-EI *m*/*z* (relative intensity): 231 ($M^{+\bullet}-H_2O$, 3), 218 (37), 206 (37), 188 (21), 158 (100), 140 (19), 120 (44), 105 (12), 91 (70), 72 (16), 60 (50); HRMS calcd for $C_{17}H_{30}NO$ (MH^+): 264.23219; found: 264.23203.

5.3.9. (*R*)-1-(Naphthalen-1-ylmethylamino)propan-2-ol (**18**)

Following the typical procedure (120 °C, 8 h, MW), the transformation of **13** (115 mg, 0.53 mmol) afforded an oil that was purified by flash column chromatography on silica gel (EtOAc+0.5% Et_3N) to give **18** (85 mg, 0.40 mmol, 74%). $[\alpha]_D^{25}$ −19.0 (*c* 1.45, $CHCl_3$); IR (neat) 3500–2600, 1655, 1597, 1509, 1450, 1373, 1325, 1074, 968, 791, 774, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.08 (m, 1H), 7.84 (m, 1H), 7.75 (dd, *J*=7.3, 2.2 Hz, 1H), 7.53–7.37 (m, 4H), 4.24 (d, *J*=13.3 Hz, 1H), 4.17 (d, *J*=13.3 Hz, 1H), 3.78 (m, 1H), 2.78 (dd, *J*=12.0, 3.3 Hz, 1H), 2.50 (dd, *J*=12.0, 9.3 Hz, 1H), 2.38 (br s, 2H), 1.13 (d, *J*=6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.7 (s), 134.0 (s), 131.8 (s), 128.8 (d), 128.0 (d), 126.2 (d), 126.1 (d), 125.7 (d), 125.4 (d), 123.6 (d), 65.8 (d), 56.9 (t), 51.4 (t), 20.5 (q); HRMS calcd for $C_{14}H_{18}NO$ (MH^+): 216.13829; found: 216.13817.

5.4. Benzylation: compounds 19–24

Method A. A mixture of *N*-benzyl or *N*-alkyl β-amino alcohol, benzyl bromide (1.1 equiv), K_2CO_3 (1.5 equiv), *n*-Bu_4NI (0.3 equiv) in acetonitrile (5 mL), was stirred at reflux for 4 h. The reaction media was concentrated under reduced pressure and the residue was dissolved in water (10 mL) and ethyl acetate (10 mL). The aqueous phase was extracted three times with ethyl acetate and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude residue by flash

chromatography on silica gel afforded *N*,*N*-dibenzyl or *N*,*N*-benzylalkyl β-amino alcohol.

Method B. A mixture of *N*-naphthyl β-amino alcohol, ammonium formate (10 equiv), and 10% Pd/C (25 mg) in MeOH (5 mL) was stirred at reflux for 4 h. The reaction media is filtered on Celite and concentrated under reduced pressure. The residue was mixed with benzyl bromide (2.2 equiv), K_2CO_3 (3 equiv), *n*-Bu_4NI (0.3 equiv) in acetonitrile (5 mL) and was stirred at reflux for 4 h. The reaction media was concentrated under reduced pressure and the residue was dissolved in water (10 mL) and ethyl acetate (10 mL). Aqueous phase was extracted three times with ethyl acetate and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude residue by flash chromatography on silica gel afforded *N*,*N*-dibenzyl β-amino alcohol.

5.4.1. (*S*)-2-N,N-Dibenzylamino-1-phenylethanol (**19**)[11]

Method A was used to prepare **19** from **6**. The transformation of **6** (29 mg, 0.13 mmol) led to an oil that was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 95/5) to give **19** (35 mg, 0.11 mmol, 88%); ee=94% determined by supercritical fluid chromatography on Daicel chiralpack OD-H column (MeOH 20%, flow rate 8 mL/min, t_R (major)=1.4 min, t_R (minor)=1.9 min).

5.4.2. (*R*)-1-N,N-Dibenzylaminopropan-2-ol (**20**)[11]

Method A was used to prepare **20** from **3**. The transformation of **3** (29 mg, 0.13 mmol) led to an oil that was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 95/5) to give **20** (35 mg, 0.11 mmol, 85%).

Method B was used to prepare **20** from **18**. The transformation of **18** (49 mg, 0.23 mmol) led to an oil that was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 90/10) to give **20** (30 mg, 0.12 mmol, 51%).

ee=93% determined by supercritical fluid chromatography on Daicel chiralpack OD-H column (MeOH 5%, flow rate 5 mL/min, t_R (major)=1.5 min, t_R (minor)=1.7 min).

5.4.3. (*R*)-1-N,N-Dibenzylamino-3-phenylpropan-2-ol (**21**)[11]

Method A was used to prepare **21** from **14**. The transformation of **14** (44 mg, 0.27 mmol) led to an oil that was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 90/10) to give **21** (56 mg, 0.22 mmol, 82%).

Method B was used to prepare **21** from **15**. The transformation of **15** (48 mg, 0.22 mmol) led to an oil that was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 90/10) to give **21** (29 mg, 0.11 mmol, 52%).

ee=98% (**21** from **14**) and 96% (**21** from **15**) determined by supercritical fluid chromatography on Daicel chiralpack OD-H column (MeOH 10%, flow rate 8 mL/min, t_R (major)=2.1 min, t_R (minor)=2.6 min).

5.4.4. (*R*)-1-(Benzylcyclohexylamino)-3-phenylpropan-2-ol (**22**)

Method A was used to prepare **22** from **4**. The transformation of **4** (42 mg, 0.18 mmol) led to an oil that was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 95/5) to give **22** (55 mg, 0.17 mmol, 94%). $[\alpha]_D^{25}$ −64.5 (*c* 1.57, $CHCl_3$); ee=94% determined by supercritical fluid chromatography on Daicel chiralpack OD-H column (MeOH 3%, flow rate 5 mL/min, t_R (major)=7.3 min, t_R (minor)=8.4 min); IR (neat) 3500–2500, 1601, 1493, 1449, 1349, 1093, 1076, 889, 748, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.24–7.08 (m, 10H), 3.63 (m, 1H), 3.60 (d, *J*=13.8, 1H), 3.49 (d, *J*=13.8, 1H), 3.38 (br s, 1H), 2.67 (dd, *J*=13.6, 7.3 Hz, 1H), 2.53 (dd, *J*=13.8, 5.5 Hz, 1H), 2.46 (dd, *J*=12.8, 3.5 Hz, 1H), 2.40 (m, 1H), 2.35 (dd, *J*=12.8, 10.0 Hz, 1H), 1.85 (m, 1H), 1.75–1.45 (m, 4H), 1.28 (dddd, *J*=12.0, 12.0, 12.0, 3.5 Hz, 1H), 1.15–0.90 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.1 (s), 138.8 (s), 129.2 (d, 2C), 128.6 (d, 2C), 128.5 (d, 2C), 128.3 (d, 2C), 127.0 (d), 126.2 (d), 68.1 (d), 59.3 (d), 55.9 (t), 55.0 (t), 41.3 (t), 31.4 (t), 26.6 (t), 26.3 (t), 26.2 (t), 26.0 (t); MS-EI *m*/*z* (relative intensity): 323 ($M^{+\bullet}$, 1), 278 (5), 202 (100), 146 (5), 120 (17), 91 (84), 65 (6), 55 (6); HRMS calcd for $C_{22}H_{30}NO$ (MH^+): 324.23219; found: 324.23220.

5.4.5. (*R*)-1-[Benzyl(heptan-4-yl)amino]-3-phenylpropan-2-ol (**23**)

Method A was used to prepare **23** from **16**. The transformation of **16** (55 mg, 0.22 mmol) led to an oil that was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 97.5/2.5) to give **23** (67 mg, 0.20 mmol, 90%). $[\alpha]_D^{25}$ −74.0 (*c* 1.05, $CHCl_3$); ee=96% determined by supercritical fluid chromatography on Daicel chiralpack OD-H column (MeOH 5%, flow rate 5 mL/min, t_R (major)=2.5 min, t_R (minor)=2.9 min); IR (neat) 3500–2500, 1602, 1495, 1454, 1376, 1258, 1147, 1072, 1028, 951, 908, 737, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.32–7.15 (m, 10H), 3.76 (m, 1H), 3.67 (d, *J*=13.3 Hz, 1H), 3.47 (br s, 1H), 3.44 (d, *J*=13.3 Hz, 1H), 2.72 (dd, *J*=13.8, 7.3 Hz, 1H), 2.61 (dd, *J*=13.6, 5.3 Hz, 1H), 2.49 (dd, *J*=12.8, 3.3 Hz, 1H), 2.45 (tt, *J*=4.5, 4.5 Hz, 1H), 2.38 (dd, *J*=13.1, 10.0 Hz, 1H), 1.59–1.48 (m, 1H), 1.47–1.07 (m, 7H), 0.87 (t, *J*=7.3 Hz, 3H), 0.78 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.9 (s), 138.8 (s), 129.2 (d, 2C), 129.1 (d, 2C), 128.4 (d, 2C), 128.3 (d, 2C), 127.1 (d), 126.1 (d), 68.3 (d), 59.2 (d), 55.7 (t), 54.6 (t), 41.3 (t), 33.7 (t), 31.4 (t), 20.7 (t), 20.3 (t), 14.3 (q), 14.1 (q); MS-EI *m*/*z* (relative intensity): 339 ($M^{+\bullet}$, 0.1), 321 (1), 296 (25), 278 (7), 218 (74), 162 (10), 120 (17), 117 (13), 91 (100), 65 (7); HRMS calcd for $C_{23}H_{34}NO$ (MH^+): 340.26349; found: 340.26333.

5.4.6. (*R*)-1-(Benzyloctylamino)-3-phenylpropan-2-ol (**24**)

Method A was used to prepare **24** from **17**. The transformation of **17** (38 mg, 0.14 mmol) led to an oil that was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 95/5) to give **24** (43 mg, 0.12 mmol, 85%). $[\alpha]_D^{25}$ −51.1 (*c* 1.0, $CHCl_3$); ee=93% determined by supercritical fluid chromatography on Daicel chiralpack OD-H column (MeOH 5%, flow rate 3 mL/min, t_R (major)=7.3 min, t_R (minor)=8.2 min); IR (neat) 3500–2500, 1671, 1601, 1495, 1453, 1374, 1075, 1028, 968, 910, 738, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33–7.17 (m, 10H), 3.86 (m, 1H), 3.77 (d, *J*=13.3 Hz, 1H), 3.39 (d, *J*=13.6 Hz, 1H), 2.78 (dd, *J*=13.6, 7.3 Hz, 1H), 2.62 (dd, *J*=13.8, 5.5 Hz, 1H), 2.52 (m, 1H), 2.43 (m, 2H), 2.34 (m, 1H), 1.63–1.42 (m, 2H), 1.39–1.13 (m, 12H), 0.87 (t, *J*=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8 (s), 138.6 (s), 129.3 (d, 2C), 129.0 (d, 2C), 128.4 (d, 2C), 128.3 (d, 2C), 127.2 (d), 126.2 (d), 68.1 (d), 59.9 (t), 58.8 (t), 54.1 (t), 41.4 (t), 31.9 (t), 29.5 (t), 29.3 (t), 27.3 (t), 27.0 (t), 22.7 (t), 14.1 (q); MS-EI *m*/*z* (relative intensity): 353 ($M^{+\bullet}$, 1), 252 (9), 232 (100), 134 (7), 120 (8), 117 (11), 91 (92), 65 (5); HRMS calcd for $C_{24}H_{36}NO$ (MH^+): 354.27914; found: 354.27917.

5.5. Synthesis of (*S*)-toliprolol and (*S*)-propanolol

5.5.1. (*S*)-Benzyl 4-(hydroxymethyl)-2,2-dimethyloxazolidine-3-carboxylate (**25**)[12,18]

To a solution of D-serine methyl ester hydrochloride (2 g, 12.9 mmol) and K_2CO_3 (5.33 g, 38.6 mmol, 3 equiv) in H_2O (10 mL) was added at 0 °C a solution of benzyl chloroformate (2.02 mL, 14.15 mmol, 1.1 equiv) in THF (10 mL). The two phases were stirred vigorously and warmed to rt. After 4 h, hexane (20 mL) was added. The aqueous layer was extracted with Et_2O (2×10 mL). The combined organic layers were washed with 5% citric acid (20 mL) and an aqueous saturated NaCl solution (20 mL), dried with $MgSO_4$, and evaporated. The crude oil was dissolved in 2,2-dimethoxypropane (35 mL, 285 mmol, 22 equiv) and $TsOH \cdot H_2O$ (350 mg, 1.8 mmol, 0.14 equiv) was added. The reaction mixture was refluxed for 4 h and then concentrated under reduced pressure. The residue was dissolved in EtOAc (100 mL) and washed with aqueous $NaHCO_3$ (2×50 mL). The organic layer was dried over $MgSO_4$ and evaporated in vacuo and the residue purified by flash chromatography (silica gel, petroleum ether/EtOAc 90/10) to afford (*S*)-3-benzyl-4-methyl-

2,2-dimethyloxazolidine-3,4-dicarboxylate[18] (3.13 g, 10.7 mmol, 83%). This latter was dissolved in THF (40 mL) and solid $NaBH_4$ (1.6 g, 42.3 mmol, 4 equiv) was added at −10 °C and the mixture was stirred at the same temperature for 30 min. MeOH (17 mL) was then added dropwise and the mixture was stirred at rt for 16 h. H_2O (5 mL) was added and the mixture stirred for 30 min. The organic solvent was evaporated under reduced pressure and brine (50 mL) was added. The mixture was extracted with EtOAc (3×100 mL) and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 60/40) to give **25**[12] (2.01 g, 7.6 mmol, 59%). $[\alpha]_D^{25}$ +20.2 (*c* 1.0, $CHCl_3$); IR (neat) 3428, 2879, 1679, 1406, 1349, 1257, 1208, 1152, 1069, 839, 737, 697 cm^{-1}; ^1H NMR (400 MHz, toluene-d^8, 100 °C): δ 7.22–7.00 (m, 5H), 5.06 (d, *J*=12.3 Hz, 1H), 5.01 (d, *J*=12.3 Hz, 1H), 3.84 (m, 1H), 3.68 (m, 2H), 3.60 (dd, *J*=10.6, 4.8 Hz, 1H), 3.43 (dd, *J*=10.8, 6.6 Hz, 1H), 2.25 (br s, 1H), 1.55 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) mixture of two rotamers: (major rotamer) δ 154.4 (s), 135.9 (s), 128.6 (d, 3C), 128.3 (d), 128.1 (d), 94.4 (s), 67.7 (t), 65.3 (t), 64.2 (t), 59.8 (d), 27.1 (q), 24.7 (q); (minor rotamer) δ=152.3 (s), 136.4 (s), 128.6 (d, 3C), 128.1 (d), 128.0 (d), 94.4 (s), 66.8 (t), 65.5 (t), 62.6 (t), 58.2 (d), 26.5 (q), 23.0 (q); MS-EI *m*/*z* (relative intensity): 234 ($M^{+\bullet}-CH_2OH^{\bullet}$, 7), 206 (4), 190 (5), 91 (100), 65 (6).

5.5.2. (S)-Benzyl 2,2-dimethyl-4-(m-tolyloxymethyl)oxazolidine-3-carboxylate (**26**)

To a solution of **25** (512 mg, 1.9 mmol), *m*-cresol (205 μL, 2.0 mmol, 1.1 equiv), and triphenylphosphine (560 mg, 2.13 mmol, 1.1 equiv) in toluene (4 mL) was added DEAD (40 wt % solution in toluene; 1 mL, 2.18 mmol, 1.1 equiv). The reaction mixture was stirred for 18 h at 80 °C in a sealed tube. The solvent was evaporated and the residue was dissolved in EtOAc (20 mL), washed with an aqueous 2.5 M NaOH solution (10 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 90/10) to give **26** (475 mg, 1.34 mmol, 69%). $[\alpha]_D^{25}$ +53.6 (*c* 1.0, $CHCl_3$); IR (neat) 2877, 1701, 1585, 1490, 1456, 1403, 1348, 1257, 1209, 1156, 1070, 839, 766, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) mixture of two rotamers (65/35): (major rotamer) δ 7.37–7.32 (m, 5H), 7.05 (dd, *J*=7.8, 7.8 Hz, 1H), 6.77–6.61 (m, 3H), 5.22–5.16 (m, 2H), 4.25 (m, 1H), 4.15–3.98 (m, 3H), 3.81 (dd, *J*=9.4, 9.4 Hz 1H), 2.28 (s, 3H), 1.66 (s, 3H), 1.56 (s, 3H); (minor rotamer) δ 7.37–7.32 (m, 5H), 7.15 (dd, *J*=8.0, 8.0 Hz, 1H), 6.77–6.61 (m, 3H), 5.22–5.16 (m, 2H), 4.35 (m, 1H), 4.25 (m, 1H), 4.15–3.98 (m, 2H), 3.88 (dd, *J*=9.3, 9.3 Hz 1H), 2.32 (s, 3H), 1.58 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): (major rotamer) δ 158.3 (s), 152.2 (s), 139.6 (s), 136.4 (s), 129.2 (d), 128.6 (d, 2C), 128.2 (d), 128.1 (d, 2C), 121.9 (d), 115.5 (d), 111.2 (d), 94.5 (s), 66.9 (t), 66.4 (t), 65.7 (t), 55.7 (d), 26.7 (q), 23.1 (q), 21.5 (q); (minor rotamer) δ 158.5 (s), 153.1 (s), 139.6 (s), 136.1 (s), 129.2 (d), 128.6 (d, 2C), 128.2 (d), 128.1 (d, 2C), 121.8 (d), 115.5 (d), 111.4 (d), 94.0 (s), 67.4 (t), 65.7 (t), 65.4 (t), 56.6 (d), 27.5 (q), 24.5 (q), 21.5 (q); MS-EI *m*/*z* (relative intensity): 355 ($M^{+\bullet}$, 3), 340 (6), 248 (14), 190 (10), 91 (100), 65 (5); HRMS calcd for $C_{21}H_{25}NO_4Na$ (MNa^+): 378.16758; found: 378.16751.

5.5.3. (R)-2-(Isopropylamino)-3-(m-tolyloxy)propan-1-ol (**27**)

To a solution of **26** (200 mg, 0.56 mmol) in MeOH (10 mL) was added Pd/C 10% (25 mg) and the mixture was vigorously stirred under an atmosphere of H_2 for 14 h. The suspension was filtered through Celite and the filtrate was concentrated in vacuo. Purification of the residue by flash chromatography on silica gel (EtOAc/MeOH 90/10+0.5% Et_3N) gave **27** (96 mg, 0.43 mmol, 77%). $[\alpha]_D^{25}$ +30.6 (*c* 1.0, $CHCl_3$); IR (neat) 2962, 2870, 1601, 1585, 1489, 1462, 1381, 1289, 1257, 1157, 1044, 769, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.19 (dd, *J*=7.8, 7.8 Hz, 1H), 6.83–6.77 (m, 1H), 6.76–6.71 (m, 2H), 4.03 (dd, *J*=9.5, 5.3 Hz, 1H), 3.95 (dd, *J*=9.4, 5.4 Hz, 1H), 3.73 (dd, *J*=10.7, 4.6 Hz, 1H), 3.55 (dd, *J*=10.7, 5.7 Hz, 1H), 3.14 (dddd, *J*=5.2, 5.2, 5.2, 5.2 Hz, 1H), 3.00 (qq, *J*=6.2, 6.2 Hz, 1H), 2.35 (s, 3H), 2.20 (br s, 2H), 1.12 (d, *J*=6.2 Hz, 3H), 1.11 (d, *J*=6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7 (s), 139.6 (s), 129.3 (d), 121.9 (d), 115.4 (d), 111.4 (d), 67.8 (t), 61.8 (t), 55.3 (d), 46.1 (d), 23.6 (q), 23.5 (q), 21.5 (q); MS-EI *m*/*z* (relative intensity): 192 ($M^{+\bullet}-CH_2OH^{\bullet}$, 40), 133 (22), 102 (100), 70 (12), 60 (31); HRMS calcd for $C_{13}H_{22}NO_2$ (MH^+): 224.16451; found: 224.16431.

5.5.4. (S)-Benzyl-2,2-dimethyl-4-[(naphthalen-1-yloxy)methyl]oxazolidine-3-carboxylate (**28**)

To a solution of **25** (418 mg, 1.6 mmol), α-naphthol (341 mg, 2.4 mmol, 1.5 equiv) and triphenylphosphine (621 mg, 2.4 mmol, 1.5 equiv) in toluene (4 mL) was added DEAD (40 wt % solution in toluene; 1.1 mL, 2.4 mmol, 1.5 equiv). The reaction mixture was stirred for 18 h at 80 °C in a sealed tube. The solvent was evaporated and the residue was dissolved in EtOAc (20 mL), washed with an aqueous 2.5 M NaOH solution (10 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 92/8) to give **28** (413 mg, 1.06 mmol, 67%). $[\alpha]_D^{25}$ +44.7 (*c* 0.9, $CHCl_3$); IR (neat) 2877, 1700, 1580, 1402, 1348, 1237, 1209, 1157, 1067, 837, 768, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) mixture of two rotamers (65/35): (major rotamer) δ 8.20 (d, *J*=7.8 Hz, 1H), 7.78 (d, *J*=8.3 Hz, 1H), 7.50–7.33 (m, 8H), 7.16 (dd, *J*=7.9, 7.9 Hz, 1H), 6.70 (d, *J*=7.5 Hz, 1H), 5.19 (m, 2H), 4.41 (m, 1H), 4.28 (m, 2H), 4.11 (m, 2H), 1.71 (s, 3H), 1.59 (s, 3H); (minor rotamer) δ 8.26 (d, *J*=8.0 Hz, 1H), 7.78 (d, *J*=8.3 Hz, 1H), 7.50–7.33 (m, 9H), 6.96 (d, *J*=7.5 Hz, 1H), 5.19 (m, 2H), 4.52 (m, 1H), 4.28 (m, 2H), 4.11 (m, 2H), 1.63 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): (major rotamer) δ 153.8 (s), 152.3 (s), 136.2 (s), 134.5 (s), 128.7 (d, 2C), 128.3 (d, 3C), 127.5 (d), 126.5 (d), 125.8 (d), 125.5 (s), 125.3 (d), 121.8 (d), 120.7 (d), 104.9 (d), 94.6 (s), 67.1 (t), 66.7 (t), 65.8 (t), 55.6 (d), 26.7 (q), 23.1 (q); (minor rotamer) δ 154.1 (s), 153.2 (s), 136.1 (s), 134.5 (s), 128.7 (d, 2C), 128.1 (d, 3C), 127.5 (d), 126.4 (d), 126.0 (d), 125.5 (s), 125.2 (d), 122.0 (d), 120.6 (d), 105.0 (d), 94.1 (s), 67.5 (t), 66.2 (t), 65.4 (t), 56.6 (d), 27.6 (q), 24.5 (q); MS-EI *m*/*z* (relative intensity): 391 ($M^{+\bullet}$, 6), 248 (13), 190 (12), 127 (6), 115 (6), 91 (100), 65 (3); HRMS calcd for $C_{24}H_{25}NO_4Na$ (MNa^+): 414.16758; found: 414.16829.

5.5.5. (R)-2-(Isopropylamino)-3-(naphthalen-1-yloxy)-propan-1-ol (**29**)

A solution of **28** (220 mg, 0.56 mmol) in EtOH (55 mL) was hydrogenated in a flow manner using the H-Cube (Thales Nanotechnology Inc.) operating at 10–15 bars of in situ H_2 pressure at rt with a flow rate of 1 mL/min. The catalyst bed (Cat-Cart™) Pd/C 10% used was available from Thales. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (EtOAc/MeOH 90/10+0.5% Et_3N) to give **29** (109 mg, 0.42 mmol, 75%). $[\alpha]_D^{25}$ +25.1 (*c* 1.5, $CHCl_3$); IR (neat) 3200–2500, 2327, 1578, 1506, 1455, 1403, 1272, 1241, 1099, 1046, 995, 870, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.23 (m, 1H), 7.84 (m, 1H), 7.55–7.46 (m, 3H), 7.40 (dd, *J*=7.9, 7.9 Hz, 1H), 6.85 (dd, *J*=7.5, 0.8 Hz, 1H), 4.22 (dd, *J*=9.5, 5.0 Hz, 1H), 4.14 (dd, *J*=9.3, 5.5 Hz, 1H), 3.83 (dd, *J*=10.8, 4.5 Hz, 1H), 3.68 (dd, *J*=10.8, 5.8 Hz, 1H), 3.32 (dd, *J*=5.3, 5.3, 5.3, 5.3 Hz, 1H), 3.08 (qq, *J*=6.2, 6.2 Hz, 1H), 2.43 (br s, 2H), 1.18 (d, *J*=6.5 Hz, 3H), 1.16 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3 (s), 134.5 (s), 127.6 (d), 126.5 (d), 125.9 (d), 125.5 (s), 125.4 (d), 121.6 (d), 120.7 (d), 104.7 (d), 68.0 (t), 61.8 (t), 55.5 (d), 46.3 (d), 23.7 (q), 23.5 (q); MS-EI *m*/*z* (relative intensity): 244 ($M^{+\bullet}-CH_3^{\bullet}$, 100), 165 (83), 152 (19), 115 (17), 56 (10); HRMS calcd for $C_{16}H_{22}NO_2$ (MH^+): 260.16451; found: 260.16489.

5.5.6. (S)-Toliprolol[5,6]

To a solution of **27** (27 mg, 0.12 mmol) in THF (1 mL) was added dropwise trifluoroacetic anhydride (17 μL, 0.12 mmol, 1 equiv) and

then Et_3N (17 μL, 0.12 mmol, 1 equiv). The reaction mixture was then heated at 110 °C for 12 h under microwave irradiation in a sealed tube. After addition of an aqueous 2.5 M NaOH solution (2 mL), the mixture was stirred at rt for 2 h, extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (EtOAc/MeOH 90/10+0.5% Et_3N) afforded (*S*)-toliprolol (19 mg, 0.08 mmol, 69%). $[\alpha]_D^{25}$ −7.6 (*c* 0.9, EtOH) (lit[6] $[\alpha]_D^{25}$ −9.9 (*c* 0.83, EtOH)); mp 52–54 °C; ee=92% determined by supercritical fluid chromatography on Daicel chiralpack OD-H column (MeOH/Et_3N 99.5/0.5 15%, flow rate 5 mL/min, t_R (major)=4.8 min, t_R (minor) =1.4 min); IR (neat) 3500–2500, 1611, 1584, 1487, 1457, 1377, 1293, 1256, 1051, 949, 867, 765, 687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.16 (dd, *J*=7.8, 7.8 Hz, 1H), 6.79–6.76 (m, 1H), 6.75–6.70 (m, 2H), 4.05–3.92 (m, 3H), 2.88 (dd, *J*=12.0, 3.8 Hz, 1H), 2.82 (h, *J*=6.3 Hz, 1H), 2.72 (dd, *J*=12.0, 7.0 Hz, 1H), 2.52 (br s, 2H), 2.32 (s, 3H), 1.09 (d, *J*=6.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7 (s), 139.6 (s), 129.2 (d), 121.9 (d), 115.4 (d), 111.4 (d), 70.4 (t), 68.4 (d), 49.4 (t), 49.0 (d), 23.0 (q), 22.9 (q), 21.5 (q); MS-EI *m*/*z* (relative intensity): 223 ($M^{+\bullet}$, 1), 208 (3), 179 (8), 91 (13), 72 (100), 56 (11); HRMS calcd for $C_{13}H_{22}NO$ (MH^+): 224.16451; found: 224.16481.

5.5.7. (S)-Propanolol[5,6]

To a solution of **29** (54 mg, 0.21 mmol) in THF (1 mL) was added dropwise trifluoroacetic anhydride (30 μL, 0.21 mmol, 1 equiv) and then Et_3N (30 μL, 0.21 mmol, 1 equiv). The reaction mixture was then heated at 110 °C for 12 h under microwave irradiation in a sealed tube. After addition of an aqueous 2.5 M NaOH solution (2 mL), the mixture was stirred at rt for 2 h, extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (EtOAc/MeOH 90/10+0.5% Et_3N) afforded (*S*)-propanolol (32 mg, 0.12 mmol, 60%). $[\alpha]_D^{25}$ −7.6 (*c* 1.25, EtOH) (lit[6] $[\alpha]_D^{25}$ −9.0 (*c* 0.5, EtOH)); mp 73–74 °C; ee=92% determined by supercritical fluid chromatography on Daicel chiralpack OD-H column (MeOH/Et_3N 99.5/0.5 15%, flow rate 3 mL/min, t_R (major)=7.4 min, t_R (minor) =4.7 min); IR (neat) 3200–2500, 1596, 1582, 1509, 1459, 1401, 1341, 1268, 1241, 1101, 1067, 1020, 941, 787, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.17 (m, 1H), 7.72 (m, 1H), 7.44–7.35 (m, 3H), 7.29 (dd, *J*=7.9, 7.9 Hz, 1H), 6.75 (d, *J*=7.5 Hz, 1H), 4.13–4.03 (m, 3H), 2.92 (dd, *J*=12.0, 3.3 Hz, 1H), 2.83–2.73 (m, 2H), 2.35 (br s, 2H), 1.03 (d, *J*=6.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3 (s), 134.5 (s), 127.6 (d), 126.5 (d), 125.9 (d), 125.6 (s), 125.3 (d), 121.9 (d), 120.7 (d), 104.9 (d), 70.7 (t), 68.5 (d), 49.5 (t), 49.0 (d), 23.2 (q), 23.1 (q); MS-EI *m*/*z* (relative intensity): 259 ($M^{+\bullet}$, 5), 215 (5), 144 (17), 127 (9), 115 (28), 72 (100), 56 (10); HRMS calcd for $C_{16}H_{22}NO_2$ (MH^+): 260.16451; found: 260.16479.

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