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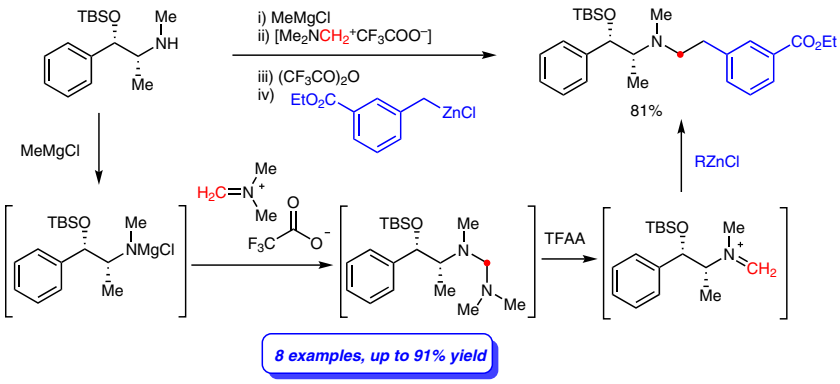
Synthesis and Bioactivity of Novel *N*-Benzylic and *N*-Phenethylic Ephedrine Derivatives

Mario Ellwart
Georg Höfner
Aaron Gerwien
Klaus T. Wanner
Paul Knochel*

Ludwig-Maximilians-Universität München, Department Chemie und Department Pharmazie, Butenandtstraße 5–13, Haus F, 81377 München, Germany
paul.knochel@cup.uni-muenchen.de



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Abstract A range of *N*-benzylic and *N*-phenethylic ephedrine derivatives were prepared in a one-pot procedure starting from the two enantiomers of ephedrine using the Potier reagent, and a polyfunctional aryl- or benzylic organozinc halide. The biological activity in indatraline MS Binding Assays addressing hDAT, hNET and hSERT was determined and discussed.

Key words organozinc halides, organomagnesium halides, iminium ion, ephedrine, binding assays

(–)-Ephedrine ((1*R*,2*S*)-(–)-ephedrine, **1**) and its stereoisomers ((1*S*,2*R*)-(+)-ephedrine, **2**; (1*R*,2*R*)-(–)-pseudoephedrine, **3**; (1*S*,2*S*)-(+)-pseudoephedrine, **4**; Figure 1) are used for a wide range of purposes, e.g. as bronchodilators, nasal decongestants, appetite suppressants or energizers, to name just a few.[1] They act as sympathomimetic agents at adrenergic receptors and are known to be substrates or inhibitors at monoamine transporters.[2,3] Recently we have developed a one-pot procedure, which allows the conversion of *N*,*N*,*N*′,*N*′-tetramethylmethanediamine (TMDAM) directly into a broad variety of tertiary amines.[4] This one-pot procedure is compatible with the use of a range of functionalized amines as well as a variety of benzylic organozinc reagents, leading selectively to the corresponding phenethylamines. We have shown that this homologative amination procedure furthermore allowed the conversion of (+)-ephedrine derivatives to the corresponding benzylic and phenethylic amines. Due to the importance of the potential biological properties of all ephedrine stereoisomers we found it worth to characterize the affinities of the prepared ephedrine derivatives at the dopamine transporter (DAT), at the norepinephrine transporter (NET) as well as at the serotonin transporter (SERT) in MS Binding Assays, and to compare these affinities with those determined for the enantiomers of ephedrine and pseudoephedrine.

Consequently, we report herein an efficient preparation of a range of (+)- and (–)-ephedrine derivatives and their activity in MS binding assays for the three monoamine transporters. Thus, the treatment of a THF solution of TBS-protected (+)-ephedrine derivative **5** with MeMgCl (1.1 equiv. 2.8 M in THF, –20 °C, 30 min) provided the corresponding magnesium amide (**6**), which was added to the *Potier*salt [$Me_2NCH_2^+CF_3COO^-$],[5] generated by the addition of trifluoroacetic anhydride (TFAA) (1.0 equiv.) to TMDAM (1.0 equiv., CH_2Cl_2, –20 °C, 15 min) (Scheme 1).[6,7] The addition of TFAA (1.0 equiv.) to the mixed aminal thus formed (**7**) led selectively after 15 min at –20 °C to the iminium salt **8**which was then treated with a variety of benzylic zinc reagents of type **9**[8] furnishing the expected tertiary amines of type **10** in 70-91% yield (Scheme 1 and Table 1).

(4-Methoxybenzyl)zinc chloride (**9a**) as well as the ester and trifluoromethyl containing benzylic zinc reagents **9b**

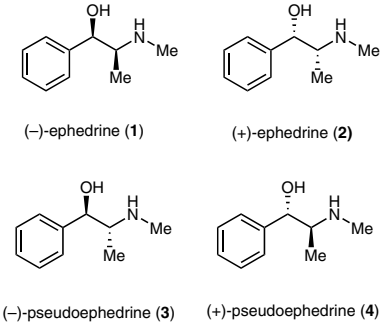
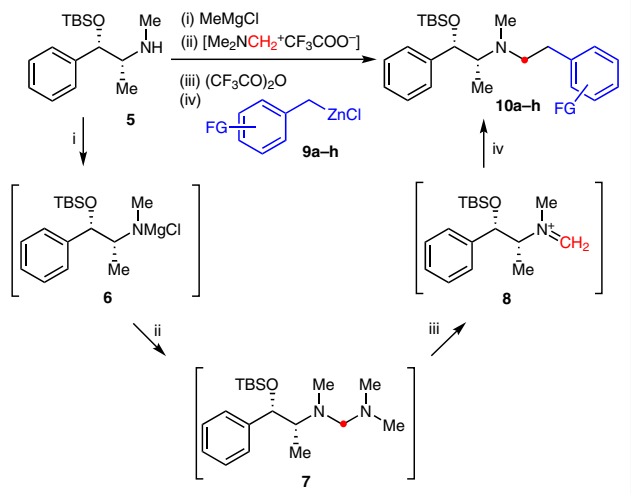


Figure 1 Chemical structures of ephedrine and pseudoephedrine stereoisomers.



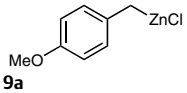
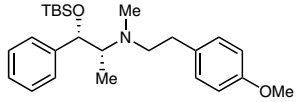
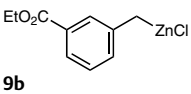
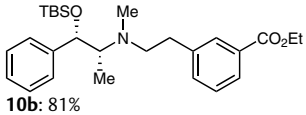
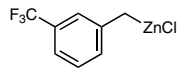
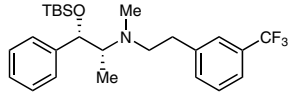
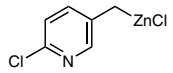
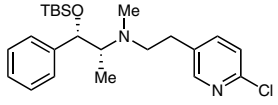
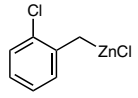
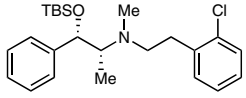
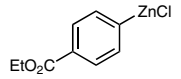
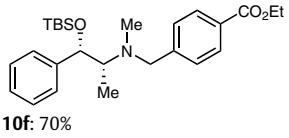
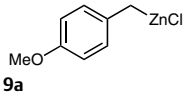
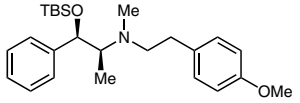
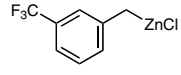
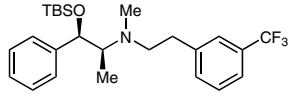
Scheme 1 Preparation of ephedrine derivatives containing a tertiary amine by cleavage of mixed aminals and subsequent reaction with benzylic zinc reagents. Conditions: i) MeMgCl (1.1 equiv.), –20 °C, 30 min; ii) $[Me_2NCH_2^+CF_3COO^-]$ (1.0 equiv.), –20 °C, 30 min; iii) $(CF_3CO)_2O$ (1.0 equiv.), –20 °C, 15 min; iv) benzylic zinc halide (1.1 equiv.), –78 °C to 25 °C, overnight.

and **9c** were added to the iminium ion **8** providing the phenethylamines **10a-c** in 81-85% yield (Table 1, Entries 1-3). Interestingly, the heterocyclic and the *ortho*-substituted zinc reagents **9d,e** showed a similar behavior and led selectively to the desired phenethylamines **10d,e** in 75% and 91% yield, respecively (Entries 4-5). Furthermore, the arylzinc reagent **9f** was used according to the same protocol and furnished the benzylic amine **10f** in 70% yield (Entry 6). In addition, the (–)-ephedrine derivatives **10g,h** were prepared from the corresponding TBS-protected (–)-ephedrine derivative using (4-methoxybenzyl)zinc chloride (**9a**) and (3-(trifluoromethyl)benzyl)zinc chloride (**9c**) (Entries 7-8).

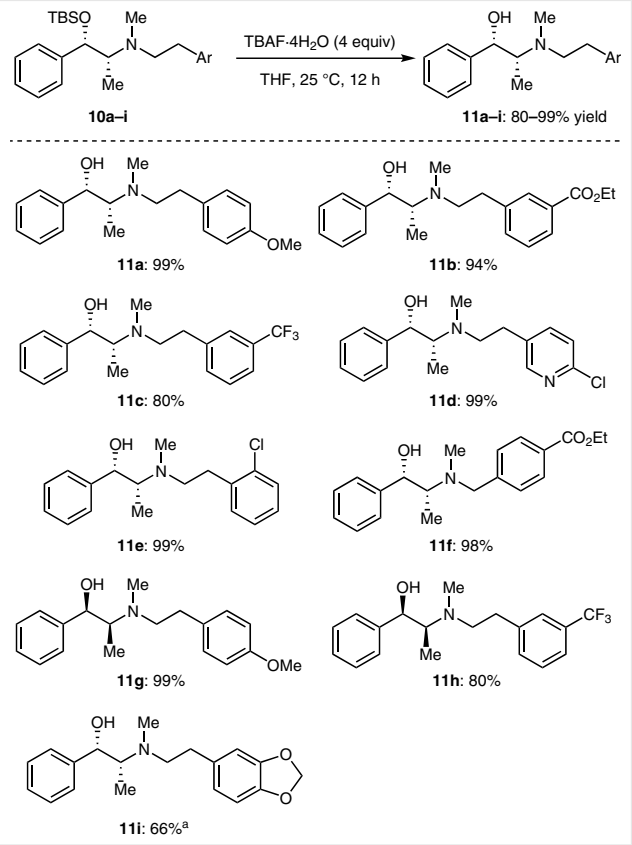
The smooth removal of the TBS-group was shown by the conversion of several TBS-protected phenethylamines to the corresponding alcohols using TBAF·$4H_2O$ (4 equiv., THF, 25 °C, 12 h). Thus, the (+)- and (–)-ephedrine derivatives **11a-h** were obtained in 80-99% yield (Scheme 2) after 12 h at ambient temperature. In addition, **11i** was produced in 66% yield starting directly from TBS-protected (+)-ephedrine without isolation of the intermediate TBS-deprotected phenethylamine. The functionalized tertiary amines of type **11** were converted into their corresponding HCl salts and their activity in MS binding assays for the three monoamine transporters was evaluated.

The results obtained for the ephedrine enantiomers (**1** and **2**) in MS Binding Assays addressing hDAT, hNET and hSERT, respectively, indicate that both enantiomers bind with moderate affinity at hNET and little less affinity at hDAT but – at least up to a concentration of 100 µM – almost not at hSERT. These results are roughly in agreement with those from [^{3}H]dopamine, [^{3}H]norepinephrine and [^{3}H]serotonin uptake assays employing rat brain synaptosomes.[2] For the enantiomers of pseudoephedrine results similar to those for the ephedrine enantiomers were obtained in MS Binding Assays addressing hDAT, hNET and hSERT. These binding profiles of the pseudoephedrine enantiomers (**3** and **4**) are in accordance with those known from radioligand binding experiments targeting DAT, NET and SERT in monkey brain as well.[3] The affinities of the prepared (+)-ephedrine derivatives of type **11** at hNET and

Table 1 Preparation of (+/–)-ephedrine derivatives of type **10** in a one-pot procedure

Entry	Zinc Reagent[a]	Product[b]
1	 **9a**	 **10a**: 85%
2	 **9b**	 **10b**: 81%
3	 **9c**	 **10c**: 85%
4	 **9d**	 **10d**: 75%
5	 **9e**	 **10e**: 91%
6	 **9f**	 **10f**: 70%
7	 **9a**	 **10g**: 85%
8	 **9c**	 **10h**: 85%

[a] Complexed LiCl is omitted for clarity.
[b] Yields refer to analytically pure products.



Scheme 2 TBS-deprotection of tertiary amines **10a-i** to the corresponding alcohols **11a-i** which were subjected to biological evaluation. [a] Yield over two steps starting from **5** without purification of the TBS-protected intermediate.

hDAT tend to be a little bit higher than those observed for (+)-ephedrine. Interestingly, the synthesized (+)-ephedrine derivatives showed also considerable affinity towards hSERT, in some cases (**11a** and **11i**) even with a more than tenfold selectivity vs NET and DAT. In the series of the (+)-ephedrine derivatives, the highest affinities for hSERT are in the high nM range and were observed for **11a** and **11i**. Regarding the affinity towards hSERT a clear enantioselectivity with the (+)-ephedrine derivative **11a** as eutomer and the (–)-ephedrine derivative **11g** as distomer was observed. In contrast, for the enantiomers **11c** and **11h,** only poor differences regarding their affinities at hDAT, hNET and hSERT were found.

In summary, we have prepared nine polyfunctional ephedrine derivatives via a one-pot homologative amination procedure which led after a TBS-deprotection directly to the corresponding benzylic and phenethylic amines. These new ephedrine derivatives were subjected to indatraline MS Binding Assays addressing hDAT, hNET and hSERT showing that affinities of the prepared ephedrine derivatives at all three transporters tend to be higher than those observed for the four stereoisomers of (pseudo-)ephedrine. Interestingly, in the series of the (+)-ephedrine derivatives, the highest affinities for hSERT are in the high nM-range while a poorer affinity was found for the corresponding (–)-ephedrine derivatives.

Melting points were measured on a Büchi B 540 apparatus and are uncorrected. Optical rotation values were determined on a P8000-P8100-T polarimeter from A. Krüss Optronic, running software V3.0 with 5 cm path length. IR spectra were recorded on a PERKIN ELMER Spectrum BX-59343 instrument. ^{1}H NMR and ^{13}C NMR spectra were measured on VARIAN Mercury 200, BRUKER AXR 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments in $CDCl_3$ or C_6D_6 and refer-

Table 2 Affinities (pKi-values as mean values ± S.E.M, n ≥ 3; or for less affine compounds specific binding in the presence of 100 µM test substance in %) toward the human transporters for serotonin (hSERT), noradrenaline (hNET) und dopamine (hDAT) determined in indatraline MS Binding Assays.

Compound	hSERT	hNET	hDAT
(1*R*,2*S*)-(–)-ephedrine·HCl (**1**)	81 %	4.61 ± 0.03	3.89 ± 0.02
(1*S*,2*R*)-(+)-ephedrine·HCl (**2**)	91 %	4.48 ± 0.11	4.04 ± 0.03
(1*R*,2*R*)-(–)-pseudoephedrine·HCl (**3**)	96 %	4.49 ± 008	3.96 ± 0.06
(1*S*,2*S*)-(+)-pseudoephedrine·HCl (**4**)	87 %	4.83 ± 0.10	3.58 ± 0.08
11a·HCl ($C_{19}H_{26}ClNO_2$)	6.63 ± 0.09	5.33 ± 0.13	4.79 ± 0.04
11b·HCl ($C_{21}H_{30}ClNO_4$)	6.00 ± 0.05	5.96 ± 0.12	5.24 ± 0.03
11c·HCl ($C_{19}H_{23}ClF_3NO$)	5.53 ± 0.01	5.07 ± 0.08	5.00 ± 0.11
11d·HCl ($C_{21}H_{30}ClNO_4$)	5.90 ± 0.05	52 %	61 %
11e·HCl ($C_{18}H_{23}Cl_2NO$)	6.14 ± 0.01	5.77 ± 0.05	5.57 ± 0.11
11f·HCl ($C_{20}H_{26}ClNO_3$)	4.78 ± 0.11	5.48± 0.14	4.88 ± 0.17
11g·HCl ($C_{19}H_{26}ClNO_2$)	5.09 ± 0.05	5.22 ± 0.05	5.17 ± 0.11
11h·HCl ($C_{19}H_{23}ClF_3NO$)	5.21 ± 0.03	5.65 ± 0.13	4.71 ± 0.09
11i·HCl ($C_{19}H_{24}ClNO_3$)	6.67 ± 0.01	5.07 ± 0.09	4.93 ± 0.03

enced to the solvent signal. Low resolution mass spectra were recorded on a HP 6890/MSD 5973 spectrometer fitted with a HP-5 column (30 m× 0.25 mm×0.25 µm). HR-MS EI spectra were recorded on a FINNIGAN MAT 95Q instrument with an electron energy of 70 eV. Flash chromatography was accomplished using Merck Kieselgel 60 (230–400 mesh ASTM).

Procedures

Typical Procedure for the Preparation of *N*-Phenethylic Ephedrine Derivatives of Type 10 (TP1):

A dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with *N,N,N',N'*-tetramethylmethanediamine (1.0 equiv) and anhydrous CH_2Cl_2 to obtain a 1 M solution. After cooling to −20 °C, trifluoroacetic anhydride (1.0 equiv) was added dropwise and the solution was allowed to stir for 15 min at −20 °C. A second dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with the TBS-protected ephedrine derivative (1.1 equiv) and THF to obtain a 0.2 M solution. After cooling to −20 °C, MeMgCl (1.1 equiv., 2.8 M in THF) was added dropwise and the solution was stirred for 30 min. Next, the magnesium amide was added over 15 min to the previously prepared methylene(dimethyl)iminium trifluoroacetate at −20 °C and stirring was continued for another 30 min. Then, trifluoroacetic anhydride (1.0 equiv) was added, resulting in the formation of a white precipitate. The mixture was stirred for 15 min before the desired organomagnesium/organozinc reagent (1.1 equiv) was added at −78 °C and the reaction mixture warmed to room temperature giving a clear solution. Sat. aq. $NaHCO_3$ was added and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried with $MgSO_4$, the solvent was removed *in vacuo* and purification by column chromatography afforded the expected products.

Typical Procedure for the Deprotection of *N*-Ethylaryl Ephedrine Derivatives of Type 11 (TP2):

A round bottom flask, equipped with a magnetic stirring bar and a septum, was charged with the tertiary ephedrine derivative (1.0 equiv), 5 mL dry $CH_2Cl_2$and TBAF·$3H_2O$ (4.0 equiv). The progress of the reaction was monitored by GC-analysis of the consumption of the starting material. Upon complete deprotection after 12 h, 5 mL sat. aq. $NaHCO_3$solution was added and the product was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried with $MgSO_4$, the solvent was removed *in vacuo* and purification by column chromatography afforded the expected products.

Preparation of *N*-Phenethylic Ephedrine Derivatives of Type 10

(1*S*, 2*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-*N*-(4-methoxyphenethyl)-*N*-methyl-1-phenylpropan-2-amine (10a)

Prepared according to **TP1** from (+)-**5**(306 mg, 1.10 mmol, 1.1 equiv) and (4-methoxybenzyl)zinc chloride (1.96 mL, 0.560 m in THF, 1.10 mmol, 1.1 equiv). Purification of the crude product by flash chromatography (SiO_2, *i*hexane/EtOAc = 20:1) afforded **10a** as a colorless oil (350 mg, 85% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.26–7.17 (m, 5H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.72 (d, *J* = 8.7 Hz, 2H), 4.57 (d, *J* = 5.9 Hz, 1H), 3.72 (s, 3H), 2.79–2.70 (m, 1H), 2.59–2.36 (m, 4H), 2.23 (s, 3H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.81 (s, 9H), -0.03 (s, 3H), -0.36 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 157.9, 145.1, 133.1, 130.0, 129.7, 127.7, 126.9, 113.8, 77.4, 65.4, 56.9, 55.4, 38.1, 34.2, 26.0, 18.3, 9.2, -4.2, -4.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$/cm^{-1} = 2953 (m), 2929 (m), 2865 (m), 1690 (w), 1612 (w), 1511 (s), 1462 (m), 1360 (w), 1300 (w), 1245 (vs), 1176 (m), 1110 (w), 1081 (s), 1060 (vs), 1039 (s), 1005 (m), 863 (s), 832 (vs), 774 (vs), 737 (m), 698 (s), 668 (m).

MS (EI, 70 eV): *m/z* (%) = 398.3 (1), 292.1 (5), 192.2 (100), 135.1 (30), 105.1 (6), 73.2 (10).

HRMS (EI): *m/z* calc. for $[C_{25}H_{38}NO_2Si]^+$: 412.2666; found 412.2674.

Ethyl 3-(2-(((1*S*, 2*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)(methyl)amino)ethyl)benzoate (10b)

Prepared according to **TP1** from (+)-**5**(158 mg, 0.550 mmol, 1.1 equiv) and (3-ethoxycarbonylbenzyl)zinc chloride (1.56 mL, 0.300 M in THF, 0.550 mmol, 1.1 equiv). Purification of the crude product by flash chromatography (SiO_2, *i*hexane/EtOAc = 20:1) afforded **10b** as a colorless oil (196 mg, 81% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.84 (d, *J* = 7.7), 7.80 (s, 1H), 7.30–7.16 (m, 7H), 4.60 (d, *J* = 6.0, 1H), 4.38 (q, *J* = 7.1, 2H), 2.83–2.77 (m, 1H), 2.66–2.51 (m, 4H), 2.30 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.05 (d, *J* = 6.7, 3H), 0.86 (s, 9H), 0.02 (s, 3H), -0.31 (s, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 167.0, 145.0, 141.3, 133.4, 130.5, 129.9, 128.3, 127.7, 127.2, 126.9, 77.2, 65.4, 61.0, 56.4, 38.0, 34.9, 26.0, 18.3, 14.5, 9.4, -4.2, -4.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$/cm^{-1} = 2955 (m), 2929 (m), 2856 (m), 1718 (vs), 1605 (w), 1587 (w), 1462 (m), 1366 (m), 1274 (vs), 1257 (s), 1194 (s), 1104 (s), 1082 (s), 1060 (vs), 1026 (s), 1005 (m), 863 (s), 834 (vs), 774 (vs), 749 (m), 697 (s), 669 (m).

MS (EI, 70 eV): *m/z* (%) = 440.3 (1), 410.3 (1), 234.2 (100) 177.1 (4), 149.1 (6), 131.1 (6), 105.1 (5), 73.1 (7)

HRMS (EI): *m/z* calc. for $[C_{26}H_{38}NO_3Si]^+$: 440.2621; found 440.2616.

((1*S*, 2*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-*N*-methyl-1-phenyl-*N*-(3-(trifluoromethyl)phenethyl)propan-2-amine (10c)

Prepared according to **TP1** from (+)-**5**(158 mg, 0.550 mmol, 1.1 equiv) and (3-(trifluoromethyl)benzyl)zinc chloride (0.350 mL, 1.43 M in THF, 0.550 mmol, 1.1 equiv). Purification of the crude product by flash chromatography (SiO_2, *i*hexane/EtOAc = 30:1) afforded **10c** as a colorless oil (187 mg, 83% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.41 (d, *J* = 7.9, 1H), 7.35 (s, 1H), 7.34–7.18 (m, 7H), 4.59 (d, *J* = 6.0 Hz, 1H), 2.80 (p, *J* = 6.5 Hz, 1H), 2.68–2.50 (m, 4H), 2.29 (s, 3H), 1.06 (d, *J* = 6.5 Hz, 3H), 0.86 (s, 8H), 0.02 (s, 3H), −0.31 (s, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 144.8, 141.8, 132.1, 130.3 (q, *J* = 31.8 Hz), 128.5, 127.6, 126.7, 125.3, 124.2 (q, *J* = 273.3 Hz) 122.6, 77.1, 65.3, 56.2, 37.8, 34.7, 25.8, 18.1, 9.2, −4.4, −5.0.

^{19}F-NMR (376 MHz, $CDCl_3$): δ / ppm = −62.48.

IR (Diamond-ATR, neat): $\tilde{\nu}$/cm^{-1} = 2955 (m), 2930 (m), 2857 (m), 1493 (w), 1471 (w), 1450 (m), 1326 (s), 1320 (s), 1256 (m), 1198 (m), 1163 (s), 1123 (vs), 1071 (s), 1061 (s), 1027 (w), 1005 (w), 908 (m), 863 (s), 833 (vs), 774 (vs), 737 (m), 699 (s), 669 (m).

MS (EI, 70 eV): *m/z* (%) = 436.4 (1), 320.3 (2), 230.2 (100), 173.1 (7), 153.1 (6), 133.1 (5), 73.1 (5).

HRMS (EI): *m/z* calc. for $[C_{24}H_{33}F_3N_2OSi]^+$: 436.2284; found 436.2282.

(1*S*, 2*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-*N*-(2-(6-chloropyridin-3-yl)ethyl)-*N*-methyl-1-phenylpropan-2-amine (10d)

Prepared according to **TP1** from (+)-**5**(306 mg, 1.10 mmol, 1.1 equiv) and (3-((6-chloropyridin-3-yl)methyl)zinc chloride (3.33 mL, 0.330 M in THF, 1.10 mmol, 1.1 equiv). Purification of the crude product by flash chromatography (SiO_2, *i*hexane/EtOAc = 20:1) afforded the title compound as a colorless oil (313 mg, 75% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.03 (dd, *J* = 2.5, 0.7 Hz, 1H), 7.29–7.16 (m, 5H), 7.11 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.04 (dd, *J* = 8.2, 0.7 Hz), 4.50 (d, *J* = 6.9 Hz), 2.77 (p, *J* = 6.7 Hz, 1H), 2.67–2.39 (m, 4H), 2.23 (s, 3H), 1.05 (d, *J* = 6.6 Hz, 3H), 0.84 (s, 9H), 0.00 (s, 3H), -0.33 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 149.7, 148.8, 144.8, 139.2, 135.3, 127.8, 127.0, 126.9, 123.7, 77.4, 65.5, 56.1, 37.1, 30.9, 26.0, 18.2, 9.5, -4.3, -4.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$/cm^{-1} = 2954 (m), 2928 (m), 2855 (m), 1585 (w), 1564 (w), 1458 (s), 1381 (m), 1360 (w), 1250 (s), 1209 (w), 1103 (s), 1082 (s), 1059 (vs), 1025 (s), 1005 (m), 863 (s), 833 (vs), 774 (vs), 737 (m), 699 (s), 669 (m).

MS (EI, 70 eV): *m/z* (%) = 403.2 (1), 287.1 (2), 197.1 (100), 140.1 (12), 104.1 (4), 73.1 (7), 56.1 (2).

HRMS (EI): *m/z* calc. for $[C_{23}H_{34}ClN_2OSi]^+$: 417.2123; found 417.2129.

(1*S*, 2*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-*N*-(2-chlorophenethyl)-*N*-methyl-1-phenylpropan-2-amine (10e)

Prepared according to **TP1** from (+)-**5** (279 mg, 1.0 mmol, 1.0 equiv) and 2-chlorobenzylzinc chloride (0.69 mL, 1.60 M in THF, 1.1 mmol, 1.1 equiv). Purification of the crude product by flash chromatography (Al_2O_3, *i*hexane/EtOAc = 49:1) afforded **10e**as a colorless oil (380 mg, 91% yield).

^{1}H-NMR (300 MHz, $CDCl_3$) δ/ ppm = 7.34-7.23 (m, 6H), 7.15-7.08 (m, 3H), 4.63 (d, *J* = 5.9 Hz, 1H), 2.81 (qi, *J* = 6.6 Hz, 1H), 2.71-2.61 (m, 4H), 2.32 (s, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.02 (s, 3H), –0.30 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ/ppm = 145.3, 138.7, 134.2, 131.2, 129.6, 127.9, 127.6, 127.1, 127.0, 127.0, 65.8, 54.6, 38.4, 33.0, 26.2, 18.4, 9.7, –4.0, –4.6.

IR (cm^{-1}): $\tilde{\nu}$= 2956, 2929, 2886, 2856, 2796, 1472, 1360, 1251, 1082, 1053, 1028, 1006, 863, 834, 816, 774, 747, 698, 680, 675.

MS (70 eV, EI) *m/z* (%) = 417 (1) [M$^+$], 402 (1), 198 (35), 197 (12), 196 (100), 139 (19), 103 (12), 73 (17).

HRMS (EI): *m/z* calc. for $C_{24}H_{36}{}^{35}ClNOSi$ (402.2025, [M–CH_3]$^+$): found: 402.2024.

Ethyl 4-((((1*S*, 2*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)(methyl)amino)methyl)benzoate (10f)

Prepared according to **TP1** from (+)-**5** (279 mg, 1.0 mmol, 1.0 equiv) and (4-(ethoxycarbonyl)phenyl)zinc chloride (1.7 mL, 0.65 M in THF, 1.1 mmol, 1.1 equiv). Purification of the crude product by flash chromatography (Al_2O_3, *i*hexane/EtOAc = 99:1) afforded the title compound as a colorless oil (309 mg, 70% yield).

^{1}H-NMR (300 MHz, $CDCl_3$) δ/ ppm = 7.80 (d, *J* = 8.4 Hz, 2H), 7.28-7.20 (m, 5H), 6.96 (d, *J* = 8.4 Hz, 2H), 4.56 (d, *J* = 7.2 Hz, 1H), 4.32 (q, *J* = 7.0 Hz, 2H), 3.60-3.46 (m, 2H), 2.79 (qi, *J* = 6.6 Hz, 1H), 2.12 (s, 3H), 1.35 (t, *J*= 7.0, 3H), 1.11 (d, *J* = 6.6 Hz, 3H), 0.83 (s, 9H), 0.00 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ/ ppm = 166.7, 145.8, 144.8, 129.2, 128.7, 128.1, 127.6, 126.9, 126.9, 64.9, 60.7, 58.7, 37.3, 25.8, 18.1, 14.4, 9.1, -4.4, -5.0.

IR (cm^{-1}): $\tilde{\nu}$= 2957, 2930, 2857, 2794, 1717, 1611, 1472, 1452, 1413, 1365, 1272, 1258, 1172, 1105, 1098, 1084, 1060, 1020, 863, 834, 775, 756, 699.

MS (70 eV, EI) *m/z* (%) = 441 (1) [M$^+$], 221 (15), 220 (100), 163 (28), 73 (7).

HRMS (EI): *m/z* calc. for $C_{26}H_{39}NO_3Si$ (440.2626, [M–H]$^+$): found: 440.2616.

(1*R*, 2*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-*N*-(4-methoxyphenethyl)-*N*-methyl-1-phenylpropan-2-amine (10g)

Prepared according to **TP1** from (+)-**5**(306 mg, 1.10 mmol, 1.1 equiv) and (4-methoxybenzyl)zinc chloride (1.96 mL, 0.560 M in THF, 1.10 mmol, 1.1 equiv). Purification of the crude product by flash chromatography (SiO_2, *i*hexane/EtOAc = 20:1) afforded **10g** as a colorless oil (350 mg, 85% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.26–7.17 (m, 5H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.72 (d, *J* = 8.7 Hz, 2H), 4.57 (d, *J* = 5.9 Hz, 1H), 3.72 (s, 3H), 2.79–2.70 (m, 1H), 2.59–2.36 (m, 4H), 2.23 (s, 3H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.81 (s, 9H), -0.03 (s, 3H), -0.36 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 157.9, 145.1, 133.1, 129.7, 127.7, 126.9, 126.4, 113.8, 77.4, 65.4, 56.9, 55.4, 38.1, 34.2, 26.0, 18.3, 9.2, -4.2, -4.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$/cm^{-1} = 2953 (m), 2929 (m), 2865 (m), 1690 (w), 1612 (w), 1511 (s), 1462 (m), 1360 (w), 1300 (w), 1245 (vs), 1176 (m), 1110 (w), 1081 (s), 1060 (vs), 1039 (s), 1005 (m), 863 (s), 832 (vs), 774 (vs), 737 (m), 698 (s), 668 (m).

MS (EI, 70 eV): *m/z* (%) = 398.3 (1), 292.1 (5), 192.2 (100), 135.1 (30), 105.1 (6), 73.2 (10).

HRMS (EI): *m/z* calc. for $[C_{25}H_{38}NO_2Si]^+$: 412.2666; found 412.2674.

((1*R*, 2*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-*N*-methyl-1-phenyl-*N*-(3-(trifluoromethyl)phenethyl)propan-2-amine (10h)

Prepared according to **TP1** from (+)-**5**(158 mg, 0.550 mmol, 1.1 equiv) and (3-(trifluoromethyl)benzyl)zinc chloride (0.350 mL, 1.43 M in THF, 0.550 mmol, 1.1 equiv). Purification of the crude product by flash chromatography (SiO_2, *i*hexane/EtOAc = 30:1) afforded **10h** as a colorless oil (187 mg, 83% yield).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.41 (d, *J* = 7.9, 1H), 7.35 (s, 1H), 7.34–7.18 (m, 7H), 4.59 (d, *J* = 6.0 Hz, 1H), 2.80 (p, *J* = 6.5 Hz, 1H), 2.68–2.50 (m, 4H), 2.29 (s, 3H), 1.06 (d, *J* = 6.5 Hz, 3H), 0.86 (s, 8H), 0.02 (s, 3H), -0.31 (s, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 144.8, 141.8, 132.1, 130.3 (q, *J* = 31.8 Hz), 128.5, 127.6, 126.7, 125.3, 124.2 (q, *J* = 273.3 Hz) 122.6, 77.1, 65.3, 56.2, 37.8, 34.7, 25.8, 18.1, 9.2, -4.4, -5.0.

^{19}F-NMR (376 MHz, $CDCl_3$): δ / ppm = -62.48.

IR (Diamond-ATR, neat): $\tilde{\nu}$/cm^{-1} = 2955 (m), 2930 (m), 2857 (m), 1493 (w), 1471 (w), 1450 (m), 1326 (s), 1320 (s), 1256 (m), 1198 (m), 1163 (s), 1123 (vs), 1071 (s), 1061 (s), 1027 (w), 1005 (w), 908 (m), 863 (s), 833 (vs), 774 (vs), 737 (m), 699 (s), 669 (m).

MS (EI, 70 eV): *m/z* (%) = 436.4 (1), 320.3 (2), 230.2 (100), 173.1 (7), 153.1 (6), 133.1 (5), 73.1 (5).

HRMS (EI): *m/z* calc. for $[C_{24}H_{33}F_3N_2OSi]^+$: 436.2284; found 436.2282.

Deprotection of the Silylated Ephedrine Derivatives of Type 10 Using TBAF

(1*S*, 2*R*)-2-((4-Methoxyphenethyl)(methyl)amino)-1-phenylpropan-1-ol (11a)

Prepared according to **TP2** from **10a**(290 mg, 0.700 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO_2, *i*hexane/EtOAc = 5:1) afforded **11a** as a white solid (208 mg, 99% yield).

[α]D19 = +4.65° (c = 0.90; CH_2Cl_2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.35–7.21 (m, 5H), 7.08 (d, *J* = 8.6 Hz), 6.84 (d, *J* = 8.6 Hz, 2H), 4.76 (d, *J* = 4.3 Hz, 1H), 3.79 (s, 3H), 2.92–2.80 (m, 1H), 2.75–2.62 (m, 4H), 2.34 (s, 3H), 0.87 (d, *J* = 6.9 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.1, 142.3, 132.4, 129.7, 128.2, 126.9, 126.2, 114.0, 73.1, 63.7, 57.1, 55.4, 39.3, 33.3, 10.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$/cm^{-1} = 2934 (m), 2834 (m), 2797 (m), 1611 (m), 1583 (w), 1511 (s), 1462 (m), 1451 (m), 1300 (m), 1244 (vs), 1176 (m), 1035 (w), 996 (w), 960 (w), 909 (m), 849 (w), 821 (s), 733 (s), 700 (s).

MS (EI, 70 eV): *m/z* (%) = 292.1 (4), 192.2 (100), 135.2 (40), 105.1 (4), 73.1 (8).

HRMS (EI): *m/z* calc. for $[C_{17}H_{20}NO_2]^+$: 254.1545; found 254.1586.

Ethyl 3-(2-(((1*S*, 2*R*)-1-Hydroxy-1-phenylpropan-2-yl)(methyl)amino)ethyl)benzoate (11b)

Prepared according to **TP2** from **10b**(156 mg, 0.340 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO_2, *i*hexane/EtOAc = 5:1) afforded **11b** as a colorless oil (110 mg, 94% yield).

[α]D19 = +13.25° (c = 0.20; CH_2Cl_2).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.90–7.79 (m, 2H), 7.37–7.14 (m, 7H), 4.74 (d, *J* = 4.3 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.57 (br, 1H), 2.91–2.82 (m, 1H), 2.82–2.65 (m, 4H), 2.34 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ / ppm = 166.7, 142.2, 140.5, 133.2, 130.6, 129.8, 128.4, 127.9, 127.4, 126.9, 126.1, 73.1, 63.6, 60.9, 56.5, 39.1, 33.8, 14.4, 10.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$/cm^{-1} = 2990 (w), 2937 (w), 2797 (w), 1714 (vs), 1604 (w), 1587 (w), 1449 (m), 1367 (m), 1273 (vs), 1195 (s), 1104 (s), 1083 (s), 1024 (m), 1000 (m), 909 (m), 864 (w), 817 (w), 749 (s), 731, (s), 698 (vs), 673 (m).

MS (EI, 70 eV): *m/z* (%) = 341.2 (1), 296.3 (6), 234.3 (100), 149.1 (10), 105.1 (10), 70.1 (8).

HRMS (EI): *m/z* calc. for $[C_{19}H_{22}NO_2]^+$: 296.1651 ([M–OEt]$^+$); found 296.1651.

(1*S*, 2*R*)-2-(Methyl(3-(trifluoromethyl)phenethyl)amino)-1-phenylpropan-1-ol (11c)

Prepared according to **TP2** from **10c**(157 mg, 0.350 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO_2, *i*hexane/EtOAc = 5:1) afforded **11c** as a colorless oil (94 mg, 80% yield).

[α]D19 = +2.00° (c = 0.15; CH_2Cl_2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.46–7.42 (m, 1H), 7.39–7.19 (m, 8H), 4.72 (d, *J* = 4.5 Hz, 1H), 3.22 (br, 1H), 2.85 (qd, *J* = 6.9, 4.5 Hz, 1H), 2.81–2.62 (m, 4H), 2.33 (s, 3H), 0.88 (d, *J* = 6.9 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 142.1, 141.1, 132.0, 130.7 (q, *J* = 32.0 Hz), 128.8, 127.8, 127.0, 126.1, 125.4 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 271.5 Hz), 123.0 (q, *J* = 3.8 Hz), 73.3, 63.8, 56.3, 39.2, 34.0, 10.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$/cm^{-1} = 2963 (w), 2856 (w), 2800 (w), 1598 (w), 1493 (w), 1450 (m), 1377 (w), 1369 (w), 1329 (vs), 1199 (m), 1161 (s), 1119 (vs), 1072 (s), 1026 (m), 1000 (m), 907 (m), 883 (w), 798 (m), 761 (w), 734 (m), 699 (vs), 661 (m).

MS (EI, 70 eV): *m/z* (%) = 318.3 (1), 230.3 (100), 173.2 (12), 153.1 (8), 77.1 (3), 58.9 (4).

HRMS (EI): *m/z* calc. for $[C_{19}H_{22}F_3NO]^+$: 336.1572; found 336.1569.

(1*S*, 2*R*)-2-((2-(6-Chloropyridin-3-yl)ethyl)(methyl)amino)-1-phenylpropan-1-ol (11d)

Prepared according to **TP2** from **10d**(253 mg, 0.600 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO_2, *i*hexane/EtOAc = 5:1) afforded **11d** as a colorless oil (183 mg, 99% yield).

[α]D1910.75° (c = 0.18; CH_2Cl_2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.16 (dd, *J* = 2.5, 0.7 Hz, 1H), 7.36 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.34–7.23 (m, 5H), 7.19 (dd, *J* = 8.2, 0.7 Hz, 1H), 4.73 (d, *J* = 4.8 Hz, 1H), 2.86 (qd, *J* = 6.8, 4.8 Hz), 2.73–2.60 (m, 4H), 2.34 (s, 3H), 0.92 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 149.7, 149.2, 142.2, 138.9, 134.5, 128.0, 127.1, 126.0, 123.8, 73.6, 63.8, 55.8, 38.8, 30.5, 9.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$/cm^{-1} = 2963 (w), 2933 (w), 2897 (w), 1585 (m), 1565 (m), 1455 (vs), 1382 (m), 1360 (w), 1285 (w), 1210 (w), 1135 (m), 1103 (s), 1051 (m), 1024 (s), 996 (m), 915 (w), 824 (m), 798 (w), 761 (m), 736 (s), 700 (vs), 698 (w).

MS (EI, 70 eV): *m/z* (%) = 197.2 (100), 140.1 (26).

HRMS (EI): *m/z* calc. for $[C_{17}H_{19}ClN_2]^+$: 286.1236; found 286.1227.

(1*S*,2*R*)-2-((2-Chlorophenethyl)(methyl)amino)-1-phenylpropan-1-ol (11e)

Prepared according to **TP2** from **10e**(100 mg, 0.239 mmol). Purification of the crude product by flash chromatography (SiO_2, *i*hexane/EtOAc = 20:1 + 2% NEt_3) afforded **11e** as a colorless oil (73 mg, 99% yield).

[α]D19 = +16.46° (c = 0.14; CH_2Cl_2).

^{1}H-NMR (600 MHz, $CDCl_3$): δ / ppm = 7.36–7.29 (m, 4H), 7.26–7.14 (m, 4H), 4.98 (s, 1H), 3.09–2.76 (m, 5H), 1.33–1.19 (m, 1H), 0.93 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ / ppm = 141.9, 137.4, 134.1, 131.2, 129.7, 128.2, 128.1, 127.2, 127.1, 126.1, 72.8, 64.2, 54.8, 39.1, 31.3, 29.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$/cm^{-1} = 3352 (w), 3062 (w), 3027 (w), 2933 (m), 2853 (w), 2799 (w), 1475 (m), 1450 (m), 1383 (w), 1248 (w), 1198 (w), 1156 (w), 1122 (m), 1052 (s), 1041 (m), 998 (m), 750 (vs), 701 (vs).

MS (EI, 70 eV): *m/z* (%) = 302 (M–H)$^+$, 285 (31), 260 (30), 258 (100).

HRMS (EI): *m/z* calc. for $[C_{18}H_{21}ClNO]^+$: 302.1317; found 302.1317 [(M–H)$^+$].

Ethyl 4-((((1*S*,2*R*)-1-Hydroxy-1-phenylpropan-2-yl)(methyl)amino)methyl)benzoate (11f)

Prepared according to **TP2** from **10f**(100 mg, 0.239 mmol). Purification of the crude product by flash chromatography (SiO_2, *i*hex-

ane/EtOAc = 20:1 + 2% NEt_3) afforded **11f** as a colorless oil (73 mg, 99% yield).

[α]D19 = +9.29° (c = 0.07; CH_2Cl_2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.92–7.86 (m, 2H), 7.35–7.26 (m, 3H), 7.26–7.16 (m, 4H), 4.79 (d, *J* = 5.2 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.59 (s, 2H), 3.35–2.94 (m, 1H), 2.87 (qd, *J* = 6.8, 5.2 Hz, 1H), 2.14 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 166.7, 145.1, 142.8, 129.7, 129.3, 128.5, 128.2, 127.2, 126.3, 74.2, 63.8, 61.0, 58.8, 38.8, 14.5, 9.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$/cm^{-1} = 2990, 2937, 2797, 1714, 1604, 1587, 1449, 1367, 1273, 1195, 1104, 1083, 1024, 1000, 909, 864, 817, 749, 731, 698, 673.

MS (EI, 70 eV): *m/z* (%) = 282 (4), 220 (100), 191 (3), 163 (59), 135 (11), 107 (12).

HRMS (EI): *m/z* calc. for $[C_{20}H_{24}NO_3]^+$: 326.1762 ($[M–H]^+$); found 326.1750.

(1*R*, 2*S*)-2-((4-Methoxyphenethyl)(methyl)amino)-1-phenylpropan-1-ol (11g)

Prepared according to **TP2** from **10g**(290 mg, 0.700 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO_2, *i*hexane/EtOAc = 5:1) afforded **11g** as a white solid (208 mg, 99% yield).

[α]D19 = –4.86° (c = 0.82; CH_2Cl_2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.35–7.21 (m, 5H), 7.08 (d, *J* = 8.6 Hz), 6.84 (d, *J* = 8.6 Hz, 2H), 4.76 (d, *J* = 4.3 Hz, 1H), 3.79 (s, 3H), 2.92–2.80 (m, 1H), 2.75–2.62 (m, 4H), 2.34 (s, 3H), 0.87 (d, *J* = 6.9 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 158.1, 142.3, 132.4, 129.7, 128.2, 126.9, 126.2, 114.0, 73.1, 63.7, 57.1, 55.4, 39.3, 33.3, 10.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$/cm^{-1} = 2934 (m), 2834 (m), 2797 (m), 1611 (m), 1583 (w), 1511 (s), 1462 (m), 1451 (m), 1300 (m), 1244 (vs), 1176 (m), 1035 (w), 996 (w), 960 (w), 909 (m), 849 (w), 821 (s), 733 (s), 700 (s).

MS (EI, 70 eV): *m/z* (%) = 292.1 (4), 192.2 (100), 135.2 (40), 105.1 (4), 73.1 (8).

HRMS (EI): *m/z* calc. for $[C_{17}H_{20}NO_2]^+$: 254.1545; found 254.1586.

(1*R*, 2*S*)-2-(Methyl(3-(trifluoromethyl)phenethyl)amino)-1-phenylpropan-1-ol (11h)

Prepared according to **TP2** from **10h**(157 mg, 0.350 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (SiO_2, *i*hexane/EtOAc = 5:1) afforded **11h** as a colorless oil (94 mg, 80% yield).

[α]D19 = –0.21° (c = 0.95; CH_2Cl_2).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.46–7.42 (m, 1H), 7.39–7.19 (m, 8H), 4.72 (d, *J* = 4.5 Hz, 1H), 3.22 (br, 1H), 2.85 (qd, *J* = 6.9, 4.5 Hz, 1H), 2.81–2.62 (m, 4H), 2.33 (s, 3H), 0.88 (d, *J* = 6.9 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ / ppm = 142.1, 141.1, 132.0, 130.7 (q, *J* = 32.0 Hz), 128.8, 127.8, 127.0, 126.1, 125.4 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 271.5 Hz), 123.0 (q, *J* = 3.8 Hz), 73.3, 63.8, 56.3, 39.2, 34.0, 10.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$/cm^{-1} = 2963 (w), 2856 (w), 2800 (w), 1598 (w), 1493 (w), 1450 (m), 1377 (w), 1369 (w), 1329 (vs), 1199 (m), 1161 (s), 1119 (vs), 1072 (s), 1026 (m), 1000 (m), 907 (m), 883 (w), 798 (m), 761 (w), 734 (m), 699 (vs), 661 (m).

MS (EI, 70 eV): *m/z* (%) = 318.3 (1), 230.3 (100), 173.2 (12), 153.1 (8), 77.1 (3), 58.9 (4).

HRMS (EI): *m/z* calc. for $[C_{19}H_{22}F_3NO]^+$: 336.1572; found 336.1569.

(1*S*, 2*R*)-2-((2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)(methyl)amino)-1-phenylpropan-1-ol Hydrochloride (11i)

Prepared according to **TP1** and **TP2** from (+)-**5** (279 mg, 1.0 mmol, 1.0 equiv) without the purification of the intermediate. Purification of the crude product by flash chromatography (SiO_2, *i*hexane/EtOAc = 10:1 → 5:1) and acidic extraction afforded **11i**·HCl as a white powder (236 mg, 67% yield). NMR spectra show both diastereoisomers at the nitrogen center in the ratio A/B = 10:9. Therefore the ^{1}H and ^{13}C atoms are indicated with A or B, if the chemical shift differs.

^{1}H-NMR (400 MHz, $DMSO_3$): δ / ppm = 10.90 (br, 1H, NH_A), 10.81 (br, 1H, NH_B), 7.48–7.41 (m, 2H, C*H*–C), 7.37 (td, *J* = 7.6, 1.3 Hz, 2H, C*H*–CH–C), 7.32–7.23 (m, 1H, C*H*–CH–CH–C), 6.94 (dd, *J* = 3.8, 1.7 Hz, 1H, C–C*H*–C–O), 6.87 (dd, *J* = 7.9, 5.1 Hz, 1H, C*H*–C–O), 6.78 (ddd, *J* = 7.9, 5.1, 1.7 Hz, 1H, C*H*–CH–C–O), 6.10 (br, 1H, OH_B), 6.06 (br, 1H, OH_A), 5.99 (s, 2H, O–C$H_{2,B}$–O), 5.98 (s, 2H, O–C$H_{2,A}$–O), 5.51 (br, 1H, CH_A–OH), 5.49 (br, 1H, CH_B–OH), 3.72 – 3.64 (m, 1H, N–C$H_{2,B}$), 3.56 – 3.45 (m, 1H, CH$_3$–C$H_{A,B}$), 3.42–3.31 (m, 1H, N–C$H_{2,A}$), 3.30–3.18 (m, 1H, N–C$H_{2,A}$), 3.12–3.00 (m, 2H, C–CH_2), 2.92 (d, *J* = 4.0 Hz, 3H, N–C$H_{3,B}$), 2.90 (d, *J* = 4.0 Hz, 3H, N–C$H_{3,A}$), 1.05 (d, *J* = 6.9 Hz, 3H, CH–C$H_{3,B}$), 1.03 (d, *J* = 6.9 Hz, 3H, CH–C$H_{3,A}$).

^{13}C-NMR (201 MHz, $CDCl_3$): δ / ppm = 147.8$_B$, 147.8$_A$, 146.5$_A$, 146.4$_B$, 142.8$_B$, 142.7$_A$, 131.4$_B$, 131.3$_A$, 128.5, 127.7$_A$, 127.7$_B$, 126.2, 122.3, 109.6, 108.8$_B$, 108.8$_A$, 101.3, 70.4, 69.6$_A$, 65.9$_B$, 65.4$_B$, 55.7$_A$, 53.6$_B$, 38.1$_B$, 36.4$_A$, 30.1, 6.8$_B$, 5.6$_A$.

IR (Diamond-ATR, neat): $\tilde{\nu}$/cm^{-1} = 3209, (s), 2900 (w), 2647 (m), 1605 (w), 1501 (s), 1489 (m), 1443 (s), 1417 (w), 1378 (w), 1337 (m), 1254 (vs), 1230 (s), 1198 (m), 1189 (m), 1111 (m), 1041 (vs), 1010 (m), 934 (m), 926 (m), 888 (w), 847 (m), 814 (m), 765 (w), 741 (vs), 698 (vs), 667 (m).

MS (EI, 70 eV): *m/z* (%) = 206.2 (100), 178.2 (18), 149.1 (68).

HRMS (ESI): *m/z* calc. for $[C_{19}H_{24}NO_3]^+$: 314.17507; found 314.17514.

Affinity Determination at DAT, NET and SERT:

MS Binding Assays at hDAT, hNET and hSERT were performed as previously described. [9,10]

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588523.

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