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Asymmetric synthesis of 1,2-diaryl-2-amino ethanols

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Abstract—A straightforward procedure for the asymmetric synthesis of 1,2-diaryl-2-amino ethanols is described. The key step relies on the diastereoselective electrophilic amination of the enolates derived from the corresponding (*S*,*S*)-(+)-pseudoephedrine arylacetamides with di-*tert*-butylazodicarboxylate, followed by a hydrolysis/hydrogenolysis procedure to yield α-amino amide derivatives with a very high degree of diastereoselection. These substrates were subsequently subjected to a non-racemizing 1,2-addition step with several aryllithium reagents to yield the corresponding α-amino ketones which, upon diastereoselective reduction with $NaBH_4$ afforded the desired β-amino alcohols as single enantiomers with 1,2-*anti* relative configuration.

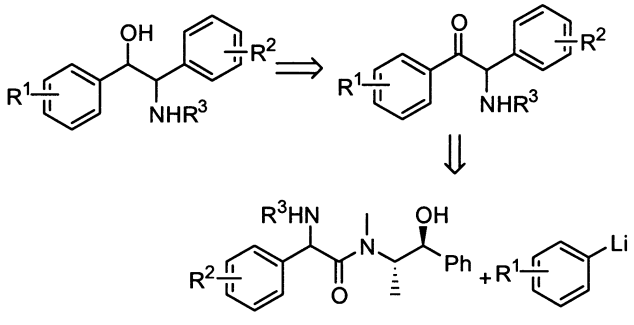
1. Introduction

The stereocontrolled synthesis of 1,2-diarylamino ethanols remains a challenging and worthwhile task in the field of organic synthesis,[1] since these compounds have shown very interesting applications as biologically active compounds,[2] chiral auxiliaries or ligands in asymmetric catalysis,[3] chiral stationary phases for HPLC applications[4] and also as building blocks for the preparation of natural products.[5] In this context, these interesting compounds have been obtained in non-racemic form using several different approaches like resolution,[6] modification of the corresponding chiral 1,2-diols,[7] stereocontrolled cyanohydrin formation/arylation,[8] asymmetric aminohydroxylation,[9] asymmetric reduction of 1,2-diaryl-2-alkoxyiminoethanones[10] or diastereoselective reductive amination of chiral non-racemic benzoins.[11]

In our group we have recently developed a procedure for the asymmetric synthesis of arylglycines in which the key step relied on the diastereoselective amination of (*S*,*S*)-pseudoephedrine-based arylacetamide enolates.[12] Myers et al.[13] and our group[14] have also shown that these pseudoephedrine amide adducts are suitable substrates to undergo reactions with organolithium reagents, affording the corresponding chiral nonracemic α-substituted ketones. In this context, and in connection with these previous studies, we decided to explore the possibility of preparing 1,2-diarylamino ethanols in a stereocontrolled way by addition of aryllithium reagents to the already mentioned (*S*,*S*)-(+)-pseudoephedrine-based α-amino substituted arylacetamides, followed by diastereoselective reduction of the so-obtained α-amino ketone derivatives (Scheme 1).

2. Results and discussion

We proceeded to perform the diastereoselective amination of (*S*,*S*)-(+)-pseudoephedrine arylacetamide enolates using the procedure already published by us,[12,15] which consisted of an initial deprotonation step of the starting arylacetamides **1a**–**c** with 2 equiv. of LDA in THF at –78°C, followed by treatment of the formed intermediate dianion with di-*tert*-butylazodicarboxylate



Scheme 1.

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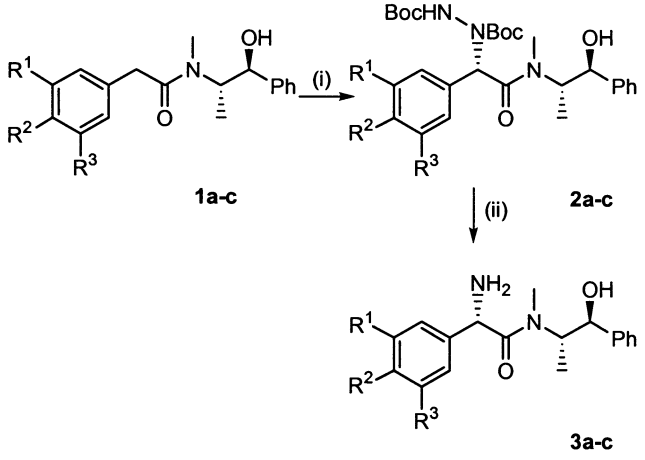
(BocN=NBoc) at –105°C (Scheme 2). The amination adducts **2a**–**c** were obtained cleanly in good yields and excellent diastereoselectivities, as could be checked by NMR and HPLC analysis of the crude reaction mixture (Table 1). These hydrazine derivatives **2a**–**c** were then subjected to hydrolysis with TFA in CH_2Cl_2 at rt followed by hydrogenation using Pd/C at catalyst affording the corresponding α-amino amides **3a**–**c** in excellent yields after column chromatography purification.

Next, we proceeded to perform the 1,2-addition reaction of an in situ formed aryllithium reagent across the C=O amide double bond, which would afford the corresponding 2-amino-1,2-diarylethanone derivatives.[16] When we tested the reaction using amides **2a**–**c** as starting materials and different reaction conditions, we observed only the formation of complicated mixtures of products and none of the desired α-amino ketone derivatives. However, when changing to the unprotected α-amino amides **3a**–**c** the addition proceeded cleanly under analogous conditions to those published by Myers et al. for the addition of organolithium reagents to pseudoephedrine amides (Scheme 3, Table 2).[13] Therefore, an alternative method was used: the reaction of amides **3a**–**c** with 3.5 equiv. of an aryllithium reagent prepared in situ at –78°C followed by warming to rt and subsequent acidic work-up afforded the desired α-amino ketone derivatives **4a**–**d** in good yields.

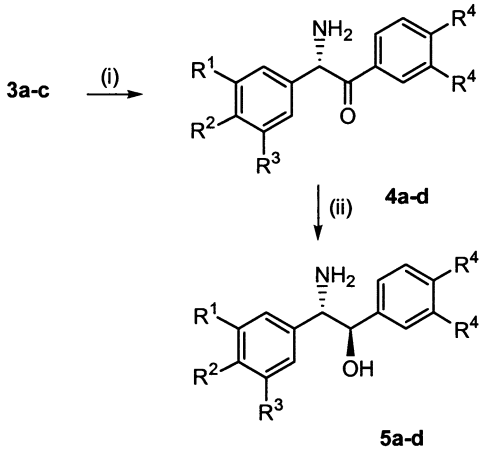
These α-amino ketone adducts **4a**–**d** were found to be rather unstable, as several reported data suggested.[16g,k] Therefore, they were directly reduced with $NaBH_4$ in THF, affording the desired 1,2-diarylamino ethanols in excellent yield. The reduction proceeded in a fully diastereoselective way, leading to the amino alcohols **5a**–**d** as single diastereoisomers with 1,2-*anti* relative configuration.

The 1,2-*anti* relative configuration was assigned according to the $J_{1,2}$ coupling constants found between both benzylic protons ($J=6.3$ Hz for **5d**) by comparison with data found in the literature.[4–11] However, for a more rigorous determination, we proceeded to prepare the corresponding cyclic oxazolidine derivative **6** starting from amino alcohol **5c**, by means of an *N*-methylation–cyclization sequence (Scheme 4).

The predominant 1,2-*anti* configuration of the products can be explained using Cram's cyclic model[17] in which an intermediate metal monoamidoborohydride species is formed by reaction of $NaBH_4$ with one of the acidic amine protons followed by coordination to the carbonyl oxygen. The reduction then would take place by intramolecular hydride delivery from the hydride reagent to the carbonyl moiety (Fig. 1). According to this arrangement, the hydride would attack from the *Si* face of the C=O bond thus leading to the formation of the 1,2-*anti* isomer as observed experimentally.



Scheme 2. *Reagents and conditions*: (i) 1. LDA, THF, –78°C, 2. BocN=NBoc, THF, –105°C; (ii) 1. TFA, CH_2Cl_2, rt; 2. H_2, Pd/C, CH_2Cl_2/EtOH.



Scheme 3. *Reagents and conditions*: (i) 1. ArLi, THF, –78→0°C; 2. *i*-Pr_2NH, 0°C; 3. AcOH/Et_2O; (ii) $NaBH_4$, THF, –20°C.

Table 1. Diastereoselective amination of (*S*,*S*)-(+)-pseudoephedrine arylacetamides **1a**–**c**

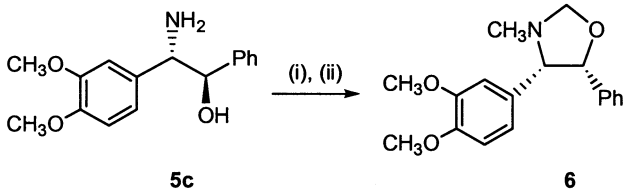
R^1	R^2	R^3	Prod.	Yield (%)[a]	D.r.[b]	Prod.	Yield (%)[a]
OMe	OMe	OMe	**2a**	90	>95/5	**3a**	78
OCH_2O		H	**2b**	91	>95/5	**3b**	79
OMe	OMe	H	**2c**	89	>95/5	**3c**	78

[a] Yield of pure product isolated after column chromatography.
[b] Determined by NMR analysis of the crude reaction mixture.

Table 2. 1,2-Addition/diastereoselective reduction sequence performed on α-amino amides **3a–c**

R^1	R^2	R^3	R^4	Prod.	Yield (%)[a]	Prod.	Yield (%)[b]	D.r.[c]
OMe	OMe	OMe	OMe	**4a**	82	**5a**	83	>95/5
OCH_2O		H	OMe	**4b**	72	**5b**	79	>95/5
OMe	OMe	H	H	**4c**	79	**5c**	89	>95/5
OMe	OMe	H	OMe	**4d**	77	**5d**	93	>95/5

[a] Yield of crude product.
[b] Yield of pure product isolated after column chromatography.
[c] Ratio of 1,2-*anti*/1,2-*syn* products determined by NMR analysis of the crude reaction mixture.



Scheme 4. *Reagents and conditions*: (i) 1. $HCONH_2$, 150°C, 2. LAH, THF, reflux; (ii) HCHO, 4 Å molecular sieves, benzene, rt.

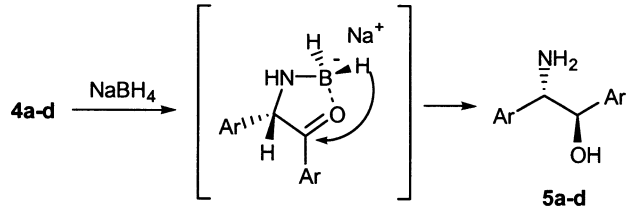
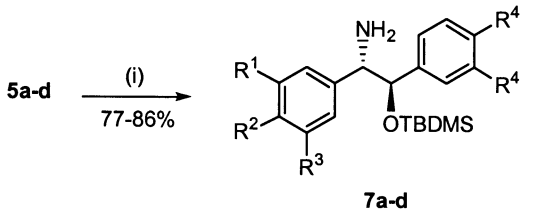


Figure 1.

For the determination of the enantiomeric excess of the 1,2-diarylamino ethanols **5a–d**, we could not find any conditions for the separation of the enantiomers by HPLC in a chiral stationary phase, mainly due to the fact that they are very highly polar compounds. Therefore, we resolved to convert them into the corresponding *O*-TBDMS protected analogues **7a–d** (Scheme 5) and in this case, separation of the enantiomers was possible by HPLC using a Chiracel OD® chiral column. The conditions for the separation were optimized working with racemic standards prepared by an alternative procedure also developed by us.[18] In all cases, the *O*-TBDMS protected 1,2-diarylamino ethanols **7a–d** showed to be in >99% ee. This also showed that all the transformations performed from hydrazines **2a–c** to the final compounds proceeded without racemization in the stereogenic centre that was obtained after the asymmetric amination step.



Scheme 5. *Reagents and conditions*: (i) TBDMSCl, imidazole, DMF, rt.

It should be pointed out that, to our surprise, even under such basic conditions during the 1,2-addition step of the aryllithium reagent to the amide moiety, the benzylic proton at the stereogenic centre remained untouched and no epimerization was observed. This is especially surprising considering the large excess of organometallic reagent necessary for the reaction to proceed. We believe that this is due to the possible deprotonation of the amino group which would generate an amide anion, substantially modifying the acidity of the benzylic proton and thus minimizing the possible epimerization of the stereogenic center. In the related work by Myers et al.,[13b] a similar 1,2-addition procedure was employed but in this case the amino functionality was protected as the *N*-Boc derivative and also in this case the addition proceeded without epimerization, which leads us to think that despite the high acidity of the benzylic proton of the α-amino amides **3a–c**, it is somehow well protected against attack by basic species.

3. Conclusions

A very efficient, high yielding procedure has been devised and carried out to prepare chiral non-racemic 1,2-diaryl-2-amino ethanols in a stereoselective way using (*S*,*S*)-(+)-pseudoephedrine as a chiral auxiliary. The procedure involves the reaction of stereodefined α-amino amides prepared by a procedure previously reported by us with aryllithium reagents, followed by diastereoselective reduction of the obtained α-amino ketones. The sequence proceeded cleanly and without racemization of the starting stereogenic center, affording the target compounds with 1,2-*anti* relative configuration.

Advantageous features of this procedure are that the chiral auxiliary, (*S*,*S*)-pseudoephedrine is inexpensive and commercially available in both enantiomeric forms. Additionally, using this methodology different substitution patterns can be introduced at both aryl rings of the 1,2-diarylaminoethanol moiety, thus allowing the preparation of a wide range of modified compounds, which could find applicability as chiral ligands in asymmetric synthesis or may show improved biological activities compared to other known derivatives.

4. Experimental

4.1. General procedures

Melting points were determined in unsealed capillary tubes and are uncorrected. IR spectra were obtained on KBr pellets (solids) or $CHCl_3$ solution (oils). NMR spectra were recorded at 20–25°C, running at 250 MHz for ^1H and 62.8 MHz for ^{13}C in $CDCl_3$ solution and resonances are reported in ppm relative to tetramethylsilane unless otherwise stated. Assignment of individual ^{13}C resonances are supported by DEPT experiments. ^1H–{^1H} NOE experiments were carried out in the difference mode by irradiation of all the lines of a multiplet.[19] Mass spectra were recorded under electron impact at 70 eV. TLC was carried out with 0.2 mm thick silica gel plates (Merck Kiesegel GF_{254}). Visualization was accomplished by UV light or by spraying with Dragendorff's reagent.[20] Flash column chromatography[21] on silica gel was performed with Merck Kiesegel 60 (230–400 mesh). Determination of enantiomeric excess was performed by chiral HPLC analysis of non crystallized samples using a Chiracel OD® column with a UV detector and the eluents and flow rates as indicated in each case. All solvents used in reactions were dried and purified according to standard procedures.[22] *n*-BuLi was titrated with diphenylacetic acid periodically prior to use. All air- or moisture-sensitive reactions were performed under argon. The glassware was oven dried (140°C) overnight and purged with argon. Amides **1a–c**, **2a–c**, and **3a–c** were prepared by already reported procedures.[15]

4.2. General procedure for the 1,2-addition of aryllithium reagents over the amides 3a–c. Synthesis of 1,2-diaryl-2-aminoethanones 4a–d

A solution of the organolithium reagent (3.50 mmol) was added dropwise over a cooled (−78°C) solution of the α-amino amide **3a–c** in dry THF (10 mL). After the addition was complete, the mixture was allowed to reach rt and after 25 min diisopropylamine (1.00 mmol) was added at once to avoid the excess of organolithium reagent. The reaction was quenched after additional 15 min by adding a 10% solution of AcOH in Et_2O. The mixture was basified with 10% NaOH, extracted with CH_2Cl_2 and the organic extracts were collected, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to afford crude α-amino ketones **4a–d** which were characterized and used in the next step without further purification.

4.2.1. (2*S*)-2-Amino-1-(3,4-dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethanone, 4a. The reaction of the amide **3a** (123 mg, 0.34 mmol) with $(3,4\text{-MeO})_2C_6H_3Li$ (prepared in situ by reaction of $(3,4\text{-MeO})_2C_6H_3Br$ (0.17 mL, 1.21 mmol) with *n*-BuLi (0.81 mL of a 1.5 M solution in hexanes, 1.21 mmol) in THF (15 mL) at −78°C for 2 h) following the general procedure afforded ketone **4a** (102 mg, 0.28 mmol) as a yellowish oil. Yield: 82%. IR ($CHCl_3$): 3350 (NH_2); 1655 (C=O). ^1H NMR (δ, ppm): 2.32 (bs, 2H); 3.59 (s, 3H); 3.72 (s, 6H); 3.74 (s, 3H); 3.79 (s, 3H); 5.36 (s, 1H); 6.50 (s, 2H); 6.61 (s, 1H); 7.31–7.39 (m, 2H). ^{13}C NMR (δ, ppm): 55.9; 56.0; 56.3; 56.5; 60.1; 110.0; 110.3; 111.5; 122.6; 128.2; 131.1; 148.3; 148.8; 149.2; 153.4; 198.5. MS (EI) *m*/*z* (rel. int.): 361 (M^+, 1), 346 (11), 207 (15), 165 (18), 142 (65), 127 (22), 115 (17), 111 (52), 97 (38), 91 (100), 85 (24), 77 (17), 69 (32), 65 (33), 57 (48).

4.2.2. (2*S*)-2-Amino-1-(3,4-dimethoxyphenyl)-2-(3,4-methylenedioxyphenyl)ethanone, 4b. The reaction of the amide **3b** (118 mg, 0.34 mmol) with $(3,4\text{-MeO})_2C_6H_3Li$ (prepared in situ by reaction of $(3,4\text{-MeO})_2C_6H_3Br$ (0.17 mL, 1.21 mmol) with *n*-BuLi (0.81 mL of a 1.5 M solution in hexanes, 1.21 mmol) in THF (15 mL) at −78°C for 2 h) following the general procedure afforded ketone **4b** (77 mg, 0.24 mmol) as a yellowish oil. Yield: 72%. IR ($CHCl_3$): 3345 (NH_2); 1665 (C=O). ^1H NMR (δ, ppm): 2.31 (bs, 2H); 3.45 (s, 3H); 3.71 (s, 3H); 5.28 (s, 1H); 5.98 (s, 2H); 6.60–6.69 (m, 4H); 7.41–7.46 (m, 2H). ^{13}C NMR (δ, ppm): 55.8; 56.3; 60.5; 98.6; 110.2; 110.6; 111.2; 111.9; 120.3; 122.5; 128.3; 133.5; 148.9; 150.1; 150.3; 153.2; 196.5. MS (EI) *m*/*z* (rel. int.): 315 (M^+, 1), 300 (8), 237 (2), 207 (15), 184 (12), 165 (23), 142 (55), 115 (19), 111 (53), 97 (22), 91 (100), 85 (17), 69 (49), 65 (63), 57 (43), 51 (29).

4.2.3. (2*S*)-2-Amino-2-(3,4-dimethoxyphenyl)-1-phenylethanone, 4c. The reaction of the amide **3c** (123 mg, 0.34 mmol) with PhLi (prepared in situ by reaction of PhBr (0.13 mL, 1.20 mmol) with *n*-BuLi (0.80 mL of a 1.5 M solution in hexanes, 1.20 mmol) in THF (15 mL) at −78°C for 2 h) following the general procedure afforded ketone **4c** (81 mg, 0.30 mmol) as a yellowish oil. Yield: 79%. IR ($CHCl_3$): 3360 (NH_2); 1680 (C=O). ^1H NMR (δ, ppm): 3.77 (s, 3H); 3.79 (s, 3H); 4.0–4.4 (bs, 2H); 5.55 (s, 1H); 6.70–6.84 (m, 2H); 7.21–7.48 (m, 5H); 7.87 (d, 1H, $J=7.0$ Hz). ^{13}C NMR (δ, ppm): 55.7; 55.8; 60.5; 110.3; 111.3; 120.3; 126.7; 126.8; 127.6; 133.2; 134.7; 148.8; 149.4; 198. MS (EI) *m*/*z* (rel. int.): 271 (M^+, 1), 256 (5), 211 (30), 151 (21), 134 (74), 127 (26), 111 (12), 105 (32), 97 (25), 91 (100), 85 (24), 77 (32), 65 (24), 57 (78), 51 (28).

4.2.4. (2*S*)-2-Amino-1,2-bis(3,4-dimethoxyphenyl)-ethanone, 4d. The reaction of the amide **3c** (110 mg, 0.31 mmol) with $(3,4\text{-MeO})_2C_6H_3Li$ (prepared in situ by reaction of the aryl bromide (0.16 mL, 1.08 mmol) with *n*-BuLi (0.72 mL of a 1.5 M solution in hexanes, 1.08 mmol) in THF (15 mL) at −78°C for 2 h) following the general procedure afforded ketone **4d** (79 mg, 0.24 mmol) as a yellowish oil. Yield: 77%. IR ($CHCl_3$): 3340 (NH_2); 1660 (C=O). ^1H NMR (δ, ppm): 2.28 (bs, 2H); 3.58 (s, 3H); 3.72 (s, 3H); 3.75 (s, 3H); 3.78 (s, 3H); 5.33 (s, 1H); 6.64–6.79 (m, 4H); 7.43–7.48 (m, 2H). ^{13}C NMR (δ, ppm): 55.9; 56.0; 60.4; 110.0; 110.4; 110.9; 111.5; 119.9; 122.6; 128.1; 133.6; 148.8; 148.9; 149.5; 153.3; 197.6. MS (EI) *m*/*z* (rel. int.): 331 (M^+, 1), 316 (8), 207 (20), 165 (22), 151 (12), 142 (68), 111 (41), 105 (9), 97 (31), 91 (100), 85 (12), 77 (25), 65 (61), 57 (58).

4.3. General procedure for the diastereoselective reduction of the α-amino ketones 4a–d: synthesis of 1,2-diaryl-2-amino ethanols 5a–d

A solution of $NaBH_4$ (1.00 mmol) in dry THF (5 mL) was added dropwise within 10 min over a cooled

(−20°C) solution of the α-amino ketone **4a–d** (1.00 mmol). The reaction was stirred for 2 h at this temperature then quenched with a saturated Na_2CO_3 solution (10 mL). The mixture was extracted with CH_2Cl_2 and the organic fractions were collected, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to afford pure β-amino alcohols **5a–d** after atmospheric pressure column chromatography purification (CH_2Cl_2/MeOH 9:1 as eluent).

4.3.1. (1*R*,2*S*)-(−)-2-Amino-1-(3,4-dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethanol, 5a. The reaction of the amino ketone **4a** (69 mg, 0.19 mmol) with $NaBH_4$ (8 mg, 0.19 mmol) according to the general procedure afforded β-amino alcohol **5a** (57 mg, 0.16 mmol) as a white solid. Yield: 83%. Mp: (as HCl salt) 176–177°C (MeOH). $[\alpha]_D^{20}$: −119.3 ($c=0.75$, EtOH). IR (KBr): 3340 (OH+NH_2). ^{1}H NMR (δ, ppm): 1.8–2.2 (bs, 3H); 3.78 (s, 3H); 3.79 (s, 3H); 3.80 (s, 6H); 3.81 (s, 3H); 4.01 (d, 1H, $J=6.4$ Hz); 4.59 (d, 1H, $J=6.4$ Hz); 6.50 (s, 2H); 6.73 (s, 1H); 6.79 (d, 1H, $J=8.2$ Hz); 6.84 (dd, 1H, $J=1.1$, 8.2 Hz). ^{13}C NMR (δ, ppm): 55.7; 55.8; 56.0; 60.7; 62.1; 78.2; 104.4; 109.7; 110.6; 119.3; 133.2; 137.2; 148.5; 148.8; 149.0; 153.0. MS (EI) m/z (rel. int.): 363 (M^+, 1), 345 (1), 196 (100), 180 (4), 169 (4), 154 (8), 115 (10), 106 (84), 95 (3), 79 (2), 77 (5), 51 (3). Anal. calcd for $C_{19}H_{26}ClNO_6$: C, 57.07; H, 6.55; N, 3.50. Found: C, 57.26; H, 6.34; N, 3.55%.

4.3.2. (1*R*,2*S*)-(−)-2-Amino-1-(3,4-dimethoxyphenyl)-2-(3,4-methylenedioxyphenyl)ethanol, 5b. The reaction of the amino ketone **4b** (63 mg, 0.20 mmol) with $NaBH_4$ (9 mg, 0.20 mmol) according to the general procedure afforded β-amino alcohol **5b** (50 mg, 0.16 mmol) as a white solid. Yield: 79%. Mp: 174–177°C (MeOH). $[\alpha]_D^{20}$: −118.3 ($c=0.72$, EtOH). IR (KBr): 3310 (OH+NH_2). ^{1}H NMR (δ, ppm): 1.6–2.0 (bs, 3H); 3.86 (s, 3H); 3.87 (s, 3H); 4.02 (d, 1H, $J=6.4$ Hz); 4.61 (d, 1H, $J=6.4$ Hz); 5.91 (s, 2H); 6.62–6.98 (m, 6H). ^{13}C NMR (δ, ppm): 55.7; 55.9; 61.4; 78.6; 100.5; 109.6; 110.5; 110.8; 111.2; 119.3; 119.9; 133.5; 134.8; 148.5; 148.6; 151.7; 152.3. MS (EI) m/z (rel. int.): 317 (M^+, 1), 299 (1), 252 (3), 167 (5), 139 (15), 115 (22), 106 (100), 91 (36), 79 (17), 77 (32), 51 (8). Anal. calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.54; H, 6.18; N, 4.43%.

4.3.3. (1*R*,2*S*)-(−)-2-Amino-2-(3,4-dimethoxyphenyl)-1-phenylethanol, 5c. Reaction of the amino ketone **4c** (73 mg, 0.27 mmol) with $NaBH_4$ (11 mg, 0.27 mmol) according to the general procedure afforded β-amino alcohol **5c** (66 mg, 0.24 mmol) as a white solid. Yield: 89%. Mp: 154–156°C (EtOH). $[\alpha]_D^{20}$: −110.9 ($c=0.70$, EtOH). IR (KBr): 3450 (OH+NH_2). ^{1}H NMR (δ, ppm): 2.1–2.6 (bs, 3H); 3.77 (s, 3H); 3.86 (s, 3H); 4.10 (d, 1H, $J=6.2$ Hz); 4.71 (d, 1H, $J=6.2$ Hz); 6.69 (s, 1H); 6.81 (m, 2H); 7.21–7.33 (m, 5H). ^{13}C NMR (δ, ppm): 55.7; 55.8; 61.5; 78.1; 110.3; 110.5; 119.7; 126.9; 127.7; 128.1; 133.4; 140.6; 148.3; 148.6. MS (EI) m/z (rel. int.): 273 (M^+, 1), 240 (1), 195 (1), 166 (18), 137 (15), 115 (18), 106 (100), 91 (22), 79 (13), 77 (11), 51 (5). Anal. calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.28; H, 6.95; N, 5.19%.

4.3.4. (1*R*,2*S*)-(−)-2-Amino-1,2-bis(3,4-dimethoxyphenyl)-ethanol, 5d. The reaction of the amino ketone **4d** (65 mg, 0.19 mmol) with $NaBH_4$ (8 mg, 0.19 mmol) according to the general procedure afforded β-amino alcohol **5d** (48 mg, 0.18 mmol) as a white solid. Yield: 93%. Mp: 155–160°C (MeOH). $[\alpha]_D^{20}$: −122.6 ($c=0.70$, EtOH). IR (KBr): 3320 (OH+NH_2). ^{1}H NMR (δ, ppm): 1.7–2.3 (bs, 3H); 3.80 (s, 3H); 3.83 (s, 3H); 3.87 (s, 6H); 4.07 (d, 1H, $J=6.3$ Hz); 4.63 (d, 1H, $J=6.3$ Hz); 6.66–6.92 (m, 6H). ^{13}C NMR (δ, ppm): 55.7; 55.8; 61.7; 78.4; 109.8; 110.4; 110.7; 110.8; 119.4; 119.9; 133.2; 134.0; 148.5; 148.6; 148.7; 148.9. MS (EI) m/z (rel. int.): 333 (M^+, 1), 315 (1), 254 (3), 166 (9), 139 (12), 115 (17), 106 (100), 91 (35), 79 (9), 77 (24), 51 (9). Anal. calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.75; H, 6.78; N, 4.12%.

4.4. General procedure for *O*-silylation of the β-amino alcohols, 5a–d

A solution of the β-amino alcohol **5a–d** (1.00 mmol), imidazole (2.20 mmol) and TBDMSCl (1.00 mmol) in dry DMF (10 mL) was stirred at rt for 90 min, after which AcOEt (15 mL) was added at once. The organic layer was washed twice with water and the organic fraction was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to afford the silylated alcohols **7a–d** after flash column chromatography purification (AcOEt as eluent).

4.4.1. (1*R*,2*S*)-(−)-2-[Dimethyl(2,2-dimethylethyl)-silyloxy] - 2 - (3,4 - dimethoxyphenyl) - 1 - (3,4,5 - trimethoxyphenyl)ethylamine 7a. Reaction of the amino alcohol **5a** (37 mg, 0.11 mmol) with imidazole (16 mg, 0.24 mmol) and TBDMSCl (16 mg, 0.11 mmol) according to the general procedure afforded *O*-silylated β-amino alcohol **7a** (40 mg, 0.08 mmol) as a yellowish oil. Yield: 77%. $[\alpha]_D^{20}$: −117.3 ($c=0.40$, CH_2Cl_2). IR ($CHCl_3$): 3410 (NH_2). ^{1}H NMR (δ, ppm): −0.36 (s, 3H); −0.21 (s, 3H); 0.83 (s, 9H); 2.11 (bs, 2H); 3.78 (s, 3H); 3.79 (s, 3H); 3.81 (s, 3H); 3.87 (s, 6H); 4.06 (d, 1H, $J=6.5$ Hz); 4.68 (d, 1H, $J=6.5$ Hz); 6.38 (s, 2H); 6.58–6.74 (m, 3H). ^{13}C NMR (δ, ppm): −5.7; −4.1; 18.2; 25.8; 55.6; 56.1; 56.9; 62.3; 77.8; 110.2; 110.7; 111.4; 112.9; 133.4; 139.1; 148.5; 148.9; 149.3; 151.1. MS (EI) m/z (rel. int.): 477 (M^+, 1), 386 (6), 372 (9), 282 (31), 281 (100), 195 (12), 167 (7), 106 (26), 91 (11), 79 (38), 77 (9), 73 (32), 51 (44). Anal. calcd for $C_{25}H_{39}NO_6Si$: C, 62.86; H, 8.23; N, 2.93. Found: C, 62.81; H, 8.18; N, 2.91%.

4.4.2. (1*R*,2*S*)-(−)-2-[Dimethyl(2,2-dimethylethyl)-silyloxy] - 2 - (3,4 - dimethoxyphenyl) - 1 - (3,4 - methylenedioxyphenyl)ethylamine, 7b. The reaction of the amino alcohol **5b** (60 mg, 0.19 mmol) with imidazole (29 mg, 0.43 mmol) and TBDMSCl (29 mg, 0.19 mmol) according to the general procedure afforded *O*-silylated β-amino alcohol **7b** (69 mg, 0.16 mmol) as a white solid. Yield: 84%. Mp: 159–162°C (Et_2O). $[\alpha]_D^{20}$: −133.8 ($c=0.50$, CH_2Cl_2). IR (KBr): 3410 (NH_2). ^{1}H NMR (δ, ppm): −0.30 (s, 3H); −0.21 (s, 3H); 0.71 (s, 9H); 2.12 (sa, 2H); 3.75 (s, 3H); 3.81 (s, 3H);

3.98 (d, 1H, $J=6.6$ Hz); 4.59 (d, 1H, $J=6.6$ Hz); 5.97 (s, 2H); 6.51 (d, 1H, $J=1.3$ Hz); 6.56 (dd, 1H, $J=1.3$, 8.6 Hz); 6.61–6.79 (m, 4H). ^{13}C NMR (δ, ppm): −5.6; −4.0; 18.2; 24.5; 55.7; 57.3; 62.4; 76.8; 101.6; 110.4; 110.5; 111.6; 112.4; 118.1; 118.6; 133.4; 136.9; 148.4; 148.7; 149.3; 150.8. MS (EI) m/z (rel. int.): 431 (M^+, 1), 386 (1), 384 (1), 372 (9), 282 (21), 281 (100), 195 (3), 167 (9), 106 (6), 91 (13), 79 (22), 77 (26), 73 (15), 51 (3). Anal. calcd for $C_{23}H_{33}NO_5Si$: C, 64.01; H, 7.71; N, 3.25. Found: C, 63.98; H, 7.67; N, 3.20%.

4.4.3. (1*R*,2*S*)-(−)-2-[Dimethyl(2,2-dimethylethyl)silyloxy]-1-(3,4-dimethoxyphenyl)-2-phenylethylamine, 7c. Reaction of the amino alcohol **5c** (53 mg, 0.19 mmol) with imidazole (29 mg, 0.43 mmol) and TBDMSCl (29 mg, 0.19 mmol) according to the general procedure afforded *O*-silylated β-amino alcohol **7c** (63 mg, 0.16 mmol) as a yellowish oil. Yield: 86%. $[\alpha]_D^{20}$: −137.2 ($c=0.50$, CH_2Cl_2). IR ($CHCl_3$): 3400 (NH_2). ^{1}H NMR (δ, ppm): −0.30 (s, 3H); −0.25 (s, 3H); 0.74 (s, 9H); 2.03 (bs, 2H); 3.75 (s, 3H); 3.85 (s, 3H); 3.99 (d, 1H, $J=6.6$ Hz); 4.63 (d, 1H, $J=6.6$ Hz); 6.56–6.75 (m, 3H); 7.22–7.36 (m, 5H). ^{13}C NMR (δ, ppm): −5.7; −5.0; 18.2; 25.1; 55.6; 55.9; 62.3; 78.9; 110.1; 110.3; 119.2; 126.8; 127.7; 128.3; 133.4; 142.6; 148.5; 148.7. MS (EI) m/z (rel. int.): 387 (M^+, 1), 315 (34), 282 (23), 272 (100), 167 (5), 106 (21), 91 (17), 79 (22), 77 (5), 73 (41), 51 (3). Anal. calcd for $C_{22}H_{33}NO_3Si$: C, 68.17; H, 8.58; N, 3.61. Found: C, 68.15; H, 8.53; N, 3.59%.

4.4.4. (1*R*,2*S*)-(−)-2-[Dimethyl(2,2-dimethylethyl)-silyloxy]-1,2-bis(3,4-dimethoxyphenyl)ethylamine, 7d. The reaction of the amino alcohol **5d** (48 mg, 0.14 mmol) with imidazole (21 mg, 0.31 mmol) and TBDMSCl (22 mg, 0.14 mmol) according to the general procedure afforded *O*-silylated β-amino alcohol **7d** (51 mg, 0.11 mmol) as a yellowish oil. Yield: 82%. $[\alpha]_D^{20}$: −126.9 ($c=0.50$, CH_2Cl_2). IR ($CHCl_3$): 3400 (NH_2). ^{1}H NMR (δ, ppm): −0.32 (s, 3H); −0.27 (s, 3H); 0.79 (s, 9H); 2.00 (bs, 2H); 3.77 (s, 3H); 3.79 (s, 3H); 3.85 (s, 6H); 4.03 (d, 1H, $J=6.5$ Hz); 4.66 (d, 1H, $J=6.5$ Hz); 6.48 (d, 1H, $J=1.5$ Hz); 6.54 (dd, 1H, $J=1.5$, 8.6 Hz); 6.67–6.83 (m, 4H). ^{13}C NMR (δ, ppm): −5.9; −4.6; 18.7; 24.6; 55.7; 56.2; 57.1; 62.5; 77.2; 110.2; 110.5; 111.2; 112.6; 117.4; 118.5; 133.6; 139.5; 148.3; 148.7; 148.9; 151.2. MS (EI) m/z (rel. int.): 447 (M^+, 1), 386 (1), 372 (12), 282 (18), 281 (100), 195 (5), 167 (3), 106 (12), 91 (23), 79 (33), 77 (6), 73 (52), 51 (12). Anal. calcd for $C_{24}H_{37}NO_5Si$: C, 64.39; H, 8.33; N, 3.13. Found: C, 64.31; H, 8.39; N, 3.09%.

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