A Method for the Selective Protection of Aromatic Amines in the Presence of Aliphatic Amines

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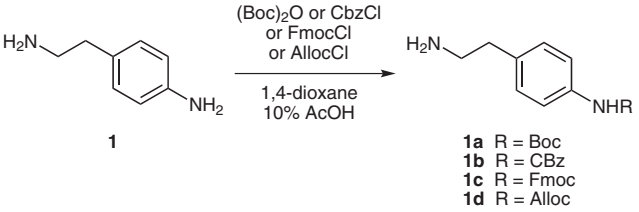
Abstract: A simple and efficient procedure has been developed for the regioselective protection of aromatic amines in the presence of aliphatic amines. The method is general for the preparation of mono-*N*-Boc, -*N*-Cbz, -*N*-Fmoc or -*N*-Alloc aromatic amines in high yield without affecting the aliphatic amines. This approach is applicable to substituted (aminoalkyl)aniline compounds with different functionalities and was employed to supply gram quantities of the protected aniline product.

Key words: amines, carbamates, protecting groups, protonations, regioselectivity



Scheme 1 Selective protection of the aromatic amine of 4-aminophenethylamine (**1**)

Selective protection and deprotection of functional groups are essential components of modern organic chemistry. Significant progress has been made in the development of suitable protecting groups for amines. Although a variety of these groups is available, little work has been undertaken on the monoprotection of diamines. These monoprotected compounds are of considerable synthetic importance. They are versatile intermediates in the synthesis of polyamines[1] and heteromacrocycles,[2] or in the construction of biologically active compounds.[3] Also, they are useful reagents that have found application in many synthetic procedures.[4] Several routes have been reported for the preparation of monoprotected alkanediamines.[4,5] For example, Lee and co-workers[5e] have described the mono-Boc protection of symmetrical and unsymmetrical aliphatic diamines by the sequential addition of one equivalent of hydrogen chloride and one equivalent of di-*tert*-butyl dicarbonate (Boc_2O); however, this procedure is not suitable for the selective protection of an aromatic amine when it is present with an aliphatic amine. King and co-workers[6a,b] studied the acetylation of 4-aminobenzylamine in water at specific pH values. Although a good selectivity was obtained at either of the two nucleophilic sites, the final monoprotected product was contaminated with the corresponding diacetate derivative.[6b] It was also reported[6a] that this procedure suffers from one or more drawbacks, including long reaction time, isolation of the starting materials, variable yields of the monoprotected aromatic amine and formation of the corresponding diprotected derivatives. Therefore, there is still a need for the development of a general and more facile method for the selective protection of aromatic amines in the presence of aliphatic amines. As part of our research, we required ready access to multigram quantities of mono-*N*-Boc-protected 4-aminophenethylamine **1a**. Reported herein is an efficient and general procedure for the selective protection of aromatic amines with a Boc, Cbz or Fmoc group when they are present with aliphatic amines (Scheme 1).

Our strategy to selectively protect an aromatic amine in the presence of an aliphatic amine was based on the difference of the pK_a value for each amino group. It has been reported[6] that the pK_a value of aromatic amines (aniline) is 4.25, while for aliphatic benzylamines, it is 9.3. Our initial experiments were carried out using 4-aminophenethylamine (**1**) as a model substrate. The reaction between diamine **1** and di-*tert*-butyl dicarbonate (Boc_2O) was studied at different pH values and in different solvents at room temperature in order to produce the corresponding mono-*N*-Boc derivative **1a**. The effect of the pH on the reaction was investigated using 1 N phosphate buffer or 1 N citrate buffer or 10% aqueous acetic acid at different acidic pH values (3–5.5) in 1,4-dioxane. Best results were obtained with the use of 10% aqueous acetic acid in 1,4-dioxane (pH 4.5). Replacement of 1,4-dioxane with tetrahydrofuran, or increasing the concentration of acetic acid, did not affect the yield of **1a**. Similar results were obtained when the temperature of the reaction was decreased to 0 °C during the addition of the Boc reagent.

Encouraged by these results and having established the optimized procedure, the generality of the method was investigated by probing an array of structurally diverse (aminoalkyl)aniline derivatives. The results are summarized in Table 1.

Under the optimized conditions, only aromatic amino groups react efficiently with Boc_2O (Table 1, first yield column), FmocCl (Table 1, second yield column) or CbzCl (Table 1, last yield column) to give the correspond-

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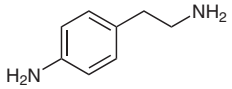
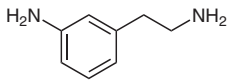
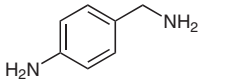
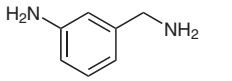
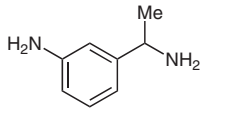
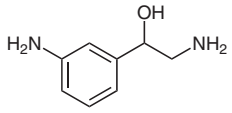
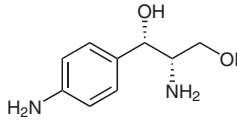
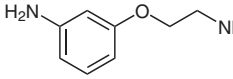
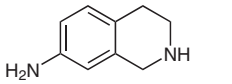
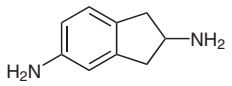
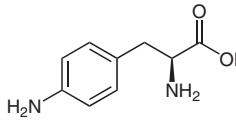
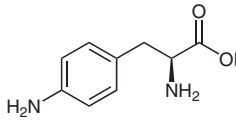
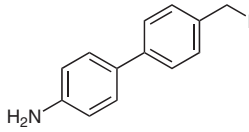
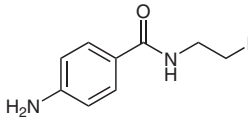
Table 1 Selective Protection of Aromatic Amines in the Presence of Aliphatic Amines

Entry	Substrate	Yield[a] (%) of protected aromatic amine		
		Boc	Fmoc[b]	Cbz
1		75	93	93
2[7a]		73	80	81
3		57[c]	93	97
4		60[c]	80	93
5		58	65	88
6[7b]		60	79	83
7[7b]		60	74	78
8[7c]		51	85	98
9		50[c]	78	73
10[7b]		71	81	76
11[7b]		67	80	84
12		53[c]	86	77
13[7d]		58[c]	94[c]	76
14[7e]		–[d]	87	61

[a] Isolated yield unless indicated otherwise.
[b] Isolated as the hydrochloride salt.
[c] % conversion by HPLC.
[d] Difficult to isolate.

ing protected aromatic amines in high yields. In the presence of a weak acid, such as acetic acid, the less reactive amino group was protected selectively. As expected, (2-aminoethyl)anilines (entries 1 and 2) and (aminomethyl)anilines (entries 3 and 4) showed regioselective protection of the aromatic amine; moving the amino group of the aniline portion of these compounds from the 3- to the 4-position did not alter the selectivity or the yield. The method is general and does not require heat or an inert atmosphere. The reaction conditions are very mild and, as a result, different functionalities (entries 5–8, 11, 12 and 14) are unaffected. The method also displays good chemoselectivity. In the presence of a hydroxy group, only the protected aromatic amino product was isolated and no protection of the oxygen atom was observed, according to ^{1}H NMR spectroscopy (entries 6 and 7). The procedure is also applicable to the protection of rigid aliphatic amines; only the aromatic amine was protected in high yield and not the cyclic primary (entry 10) or secondary (entry 9) aliphatic amine. The same result was also obtained when the substrate contained an acid (entry 12), ester (entry 11) or amide (entry 14) group; again, the aromatic amines were selectively protected under the reaction conditions. This method also constitutes a general approach for other protecting groups. For example, treatment of diamine **1** with allyl chloroformate under acidic conditions gave only **1d** in high yield (98%).

In summary, a practical and selective method has been developed for the protection of aromatic amines with a mono-*N*-Boc, -*N*-Cbz or -*N*-Fmoc group without affecting aliphatic amines. The procedure is amenable to scale-up and in most cases no chromatographic purification of the product is required. This method is applicable to substituted (aminoalkyl)aniline compounds with different functionalities. It offers the advantage of a general route with high yield which can be undertaken at ambient temperature and in environmentally acceptable conditions.

Solvents and reagents were obtained from commercial sources and used without purification. Melting points were determined on an Electrothermal melting point apparatus. NMR spectra were recorded on a Varian 400 spectrometer operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. The purity and identity of all the products were monitored by LC/MS at 210 or 250 nm (Agilent 1100) using an analytical C18 column (75 × 4.6 mm, 5 microns) with different gradients of MeCN–H_2O containing 0.01% TFA as the eluent. Compounds **1**, **3–5**, **9** and **12** are commercially available.

4-(2-Aminoethyl)-*N*-(*tert*-butoxycarbonyl)phenylamine (1a); Typical Procedure

To a soln of 4-aminophenethylamine (0.3 g, 2.3 mmol) in 10% aq AcOH (20 mL) was added a soln of Boc_2O (0.5 g, 2.4 mmol) in 1,4-dioxane (20 mL). After overnight stirring at r.t., H_2O (100 mL) was added and the mixture was washed with Et_2O (3 × 50 mL). The aqueous phase was basicified with 2 N NaOH to pH 14 and extracted with Et_2O (3 × 75 mL). The combined extract was washed with H_2O (2 × 40 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the expected product **1a**.

White solid; yield: 75% (98% conversion by HPLC); mp 89–91 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.32 (d, *J* = 8.4 Hz, 2 H), 7.09 (d, *J* = 8.6 Hz, 2 H), 2.80–2.83 (m, 2 H), 2.67 (t, *J* = 7.4 Hz, 2 H), 1.50 (s, 9 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 154.24, 137.60, 133.91, 128.88, 118.94, 79.53, 43.00, 38.08, 27.52.

MS (ESI): *m*/*z* = 259 [M + Na^+].

This procedure was scaled up using the following amounts: 4-aminophenethylamine (40.4 g, 310 mmol), 10% aq AcOH (2.5 L), Boc_2O (68.0 g, 311 mmol) and 1,4-dioxane (2.5 L). This gave the expected product **1a** in 65% yield.

Protection with Boc (Table 1, First Yield Column)
3-(2-Aminoethyl)-*N*-(*tert*-butoxycarbonyl)phenylamine (Entry 2)
Yellow oil; yield: 73%.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.28 (s, 1 H), 7.23 (d, *J* = 8.2 Hz, 1 H), 7.16 (t, *J* = 7.4 Hz, 1 H), 6.83 (d, *J* = 7.4 Hz, 1 H), 2.84 (t, *J* = 6.85 Hz, 2 H), 2.69 (t, *J* = 7.2 Hz, 2 H), 1.50 (s, 9 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 154.14, 140.35, 139.57, 128.75, 123.00, 118.99, 116.66, 79.60, 42.87, 38.89, 27.60.

MS (ESI): *m*/*z* = 259 [M + Na^+].

4-(Aminomethyl)-*N*-(*tert*-butoxycarbonyl)phenylamine (Entry 3)
Conversion by HPLC: 57%.

A portion of this material was isolated and characterized: pale yellow solid; mp 86–90 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.35 (d, *J* = 8.4 Hz, 2 H), 7.18–7.22 (m, 2 H), 3.69 (s, 2 H), 1.50 (s, 9 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 154.15, 138.26, 136.56, 128.30, 127.74, 118.72, 79.57, 45.00, 27.54.

MS (ESI): *m*/*z* = 245 [M + Na^+].

3-(Aminomethyl)-*N*-(*tert*-butoxycarbonyl)phenylamine (Entry 4)
Conversion by HPLC: 60%.

A portion of this material was isolated and characterized: pale yellow solid; mp 130–134 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.34 (s, 1 H), 7.27 (d, *J* = 8.0 Hz, 1 H), 7.20 (t, *J* = 7.6 Hz, 1 H), 6.97 (d, *J* = 7.4 Hz, 1 H), 3.73 (s, 2 H), 1.51 (s, 9 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 154.15, 143.18, 139.54, 128.77, 121.49, 117.60, 117.21, 79.62, 45.55, 27.52.

MS (ESI): *m*/*z* = 445 [M_2 + H^+].

(*RS*)-3-(1-Aminoethyl)-*N*-(*tert*-butoxycarbonyl)phenylamine (Entry 5)
Clear oil; yield: 58%.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.36 (s, 1 H), 7.25–7.27 (dd, *J* = 1.9, 8.2 Hz, 1 H), 7.15–7.22 (m, 1 H), 6.98 (dd, *J* = 1.4, 7.6 Hz, 1 H), 3.96 (q, *J* = 6.6 Hz, 1 H), 1.51 (s, 9 H), 1.35 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 154.16, 147.22, 139.56, 128.82, 120.00, 117.40, 116.23, 79.66, 51.12, 27.59, 23.75.

MS (ESI): *m*/*z* = 237 [M + H^+].

(*RS*)-2-Amino-1-[3-(*tert*-butoxycarbonylamino)phenyl]ethanol (Entry 6)
White solid; yield: 60%; mp 42–45 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.43 (s, 1 H), 7.21–7.30 (m, 2 H), 7.00 (d, *J* = 7.2 Hz, 1 H), 4.58 (t, *J* = 7.2 Hz, 1 H), 2.77–2.79 (m, 2 H), 1.51 (s, 9 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 154.14, 143.82, 139.50, 128.63, 120.19, 117.84, 116.40, 79.64, 74.54, 48.78, 27.56.

MS (ESI): *m*/*z* = 253 [M + H^+].

(1*S*,2*S*)-2-Amino-1-[4-(*tert*-butoxycarbonylamino)phenyl]propane-1,3-diol (Entry 7)
Pale yellow solid; yield: 60%; mp 138–140 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.38 (d, *J* = 8.6 Hz, 2 H), 7.28 (d, *J* = 8.6 Hz, 2 H), 4.60 (d, *J* = 8.8 Hz, 1 H), 3.73 (dd, *J* = 3.5, 11.9 Hz, 1 H), 3.59–3.65 (m, 1 H), 3.08–3.12 (m, 1 H), 1.50 (s, 9 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 154.09, 139.14, 134.18, 126.87, 118.64, 94.59, 80.32, 67.32, 58.21, 27.56.

MS (ESI): *m*/*z* = 283 [M + H^+].

3-(2-Aminoethoxy)-*N*-(*tert*-butoxycarbonyl)phenylamine (Entry 8)
Pale yellow solid; yield: 51%; mp 88–90 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.10–7.14 (m, 2 H), 6.91 (dd, *J* = 0.8, 1.8 Hz, 1 H), 6.89 (dd, *J* = 0.8, 1.8 Hz, 1 H), 3.96 (t, *J* = 5.3 Hz, 2 H), 2.96 (t, *J* = 5.1 Hz, 2 H), 1.50 (s, 9 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 159.63, 153.99, 140.65, 129.31, 111.03, 108.54, 104.94, 79.64, 69.21, 40.73, 27.52.

MS (ESI): *m*/*z* = 253 [M + H^+].

7-(*tert*-Butoxycarbonylamino)-1,2,3,4-tetrahydroisoquinoline (Entry 9)
Conversion by HPLC: 50%.

A portion of this material was isolated and characterized: pale yellow solid; mp 186–189 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.10–7.12 (m, 2 H), 6.97 (d, *J* = 8.0 Hz, 1 H), 3.87 (s, 2 H), 3.03 (t, *J* = 6.1 Hz, 2 H), 2.74 (t, *J* = 5.9 Hz, 2 H), 1.50 (s, 9 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 154.21, 137.12, 135.28, 129.23, 128.73, 117.09, 116.26, 79.51, 47.52, 43.38, 27.54.

MS (ESI): *m*/*z* = 249 [M + H^+].

5-(*tert*-Butoxycarbonylamino)indan-2-amine (Entry 10)
Pale yellow oil; yield: 71%.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.28 (br s, 1 H), 7.12–7.14 (m, 1 H), 7.04–7.07 (m, 1 H), 3.71–3.74 (m, 1 H), 3.10 (m, 2 H), 2.81 (m, 1 H), 2.78 (m, 1 H), 1.50 (s, 9 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 152.69, 140.86, 136.45, 134.48, 122.96, 115.86, 113.75, 77.86, 59.08, 51.37, 39.36, 37.90, 26.02.

MS (ESI): *m*/*z* = 249 [M + H^+].

Methyl (*S*)-2-Amino-3-[4-(*tert*-butoxycarbonylamino)phenyl]propionate (Entry 11)
White solid; yield: 67%; mp 108–110 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.36 (d, *J* = 8.6 Hz, 2 H), 7.11 (d, *J* = 8.6 Hz, 2 H), 3.98 (t, *J* = 6.8 Hz, 1 H), 3.73 (s, 3 H), 3.07 (dd, *J* = 6.1, 13.9 Hz, 1 H), 2.99 (dd, *J* = 7.0, 13.9 Hz, 1 H), 1.50 (s, 9 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 170.92, 152.49, 137.07, 128.10, 127.95, 117.30, 78.06, 53.22, 50.16, 36.34, 25.92.

MS (ESI): *m*/*z* = 295 [M + H^+].

(*S*)-2-Amino-3-[4-(*tert*-butoxycarbonylamino)phenyl]propionic Acid (Entry 12)
Conversion by HPLC: 53%.

A portion of this material was isolated and characterized: white solid; mp 198–200 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.36 (d, *J* = 8.4 Hz, 2 H), 7.20 (d, *J* = 8.6 Hz, 2 H), 3.71–3.74 (m, 1 H), 3.25 (dd, *J* = 4.1, 14.5 Hz, 1 H), 2.94 (dd, *J* = 8.8, 14.7 Hz, 1 H), 1.50 (s, 9 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 172.83, 154.18, 138.63, 130.13, 129.58, 119.12, 79.66, 56.38, 36.52, 27.48.

MS (ESI): *m*/*z* = 281 [M + H$^+$].

4′-(Aminomethyl)-*N*-(*tert*-butoxycarbonyl)-1,1′-biphenyl-4-ylamine (Entry 13)
Conversion by HPLC: 58%.

A portion of this material was isolated and characterized: yellow solid; mp 75–78 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.45–7.55 (m, 6 H), 7.36 (d, *J* = 8.4 Hz, 2 H), 3.80 (s, 2 H), 1.50 (s, 9 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 154.07, 140.59, 139.51, 138.79, 135.13, 127.81, 126.95, 126.51, 118.90, 79.72, 45.10, 27.60.

LRMS (ESI): *m*/*z* = 282 [M + H$^+$ – NH_3].

4-(2-Aminoethyl)-*N*-(9-fluorenylmethoxycarbonyl)phenylamine Hydrochloride (1b); Typical Procedure
To a soln of 4-aminophenethylamine (0.3 g, 2.3 mmol) in 10% aq AcOH (20 mL) was added FmocCl (0.6 g, 2.4 mmol) dissolved in 1,4-dioxane (20 mL). After overnight stirring at r.t., Et_2O (2 × 30 mL) was added to the reaction mixture to extract the nonpolar impurities. The reaction mixture was then acidified with 2 N HCl to pH 1. The precipitate was collected by filtration, washed with Et_2O (15 mL) and dried under reduced pressure overnight.

White solid; yield: 93% (99% conversion by HPLC); mp 207–209 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.68 (br s, 1 H), 7.92–8.05 (m, 2 H), 7.89 (d, *J* = 7.6 Hz, 2 H), 7.73 (d, *J* = 7.4 Hz, 2 H), 7.31–7.43 (m, 4 H), 7.13 (d, *J* = 8.2 Hz, 2 H), 4.45 (d, *J* = 6.7 Hz, 2 H), 4.28 (t, *J* = 6.5 Hz, 1 H), 2.93–2.97 (m, 2 H), 2.78–2.82 (m, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 154.23, 144.35, 141.42, 138.21, 131.99, 129.70, 128.44, 127.85, 125.80, 119.36, 66.24, 47.24, 40.81, 32.89.

MS (ESI): *m*/*z* = 359 [M + H$^+$].

Protection with Fmoc (Table 1, Second Yield Column)
3-(2-Aminoethyl)-*N*-(9-fluorenylmethoxycarbonyl)phenylamine Hydrochloride (Entry 2)
White solid; yield: 80%; mp 183–184 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.79 (d, *J* = 7.6 Hz, 2 H), 7.68 (t, *J* = 7.6 Hz, 2 H), 7.44 (br s, 1 H), 7.22–7.40 (m, 6 H), 6.95 (d, *J* = 6.8 Hz, 1 H), 4.46 (d, *J* = 6.8 Hz, 2 H), 4.24 (t, *J* = 6.8 Hz, 1 H), 3.15 (t, *J* = 8.0 Hz, 2 H), 2.92 (t, *J* = 8.0 Hz, 2 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 154.69, 144.05, 141.47, 139.54, 137.48, 129.31, 127.67, 127.02, 124.96, 123.29, 119.83, 119.07, 117.73, 66.55, 48.48, 40.70, 33.44.

MS (ESI): *m*/*z* = 359 [M + H$^+$].

4-(Aminomethyl)-*N*-(9-fluorenylmethoxycarbonyl)phenylamine Hydrochloride (Entry 3)
White solid; yield: 93%; mp >255 °C (dec).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.80 (br s, 1 H), 8.29 (br s, 2 H), 7.89 (d, *J* = 7.4 Hz, 2 H), 7.73 (d, *J* = 7.2 Hz, 2 H), 7.28–7.45 (m, 8 H), 4.48 (d, *J* = 6.7 Hz, 2 H), 4.29 (t, *J* = 6.7 Hz, 1 H), 3.91 (s, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 154.10, 144.44, 141.50, 139.91, 130.36, 128.60, 128.40, 127.83, 125.89, 120.94, 118.81, 66.33, 47.27, 42.40.

MS (ESI): *m*/*z* = 367 [M + Na$^+$].

3-(Aminomethyl)-*N*-(9-fluorenylmethoxycarbonyl)phenylamine Hydrochloride (Entry 4)
White solid; yield: 80%; mp 223–225 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.83 (d, *J* = 7.4 Hz, 2 H), 7.71 (d, *J* = 7.6 Hz, 2 H), 7.68 (m, 1 H), 7.32–7.44 (m, 6 H), 7.12–7.14 (m, 1 H), 4.53 (d, *J* = 6.5 Hz, 2 H), 4.30 (t, *J* = 6.5 Hz, 1 H), 4.08 (s, 2 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 154.58, 144.03, 141.49, 139.89, 133.97, 129.58, 127.69, 127.02, 124.97, 124.88, 123.10, 119.89, 119.78, 119.37, 66.55, 43.23.

MS (ESI): *m*/*z* = 345 [M + H$^+$].

(*RS*)-3-(1-Aminoethyl)-*N*-(9-fluorenylmethoxycarbonyl)phenylamine Hydrochloride (Entry 5)
Pale yellow solid; yield: 65%; mp 170–172 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.80 (d, *J* = 7.6 Hz, 2 H), 7.66–7.70 (m, 3 H), 7.30–7.42 (m, 6 H), 7.10–7.13 (m, 1 H), 4.51 (d, *J* = 6.5 Hz, 2 H), 4.39 (q, *J* = 6.7 Hz, 1 H), 4.28 (t, *J* = 6.4 Hz, 1 H), 1.61 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 154.57, 144.02, 141.46, 139.89, 139.16, 129.68, 127.71, 127.05, 125.02, 120.81, 119.90, 119.80, 116.98, 66.60, 51.20, 47.14, 19.51.

MS (ESI): *m*/*z* = 359 [M + H$^+$].

(*RS*)-2-Amino-1-[3-(9-fluorenylmethoxycarbonylamino)phenyl]ethanol Hydrochloride (Entry 6)
White solid; yield: 79%; mp 138–140 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.78 (d, *J* = 7.6 Hz, 2 H), 7.68 (d, *J* = 7.6 Hz, 2 H), 7.60 (br s, 1 H), 7.26–7.40 (m, 6 H), 7.10 (d, *J* = 7.6 Hz, 1 H), 4.85 (t, *J* = 7.2 Hz, 1 H), 4.45 (d, *J* = 6.8 Hz, 2 H), 4.24 (t, *J* = 6.8 Hz, 1 H), 3.14 (dd, *J* = 3.6, 13.0 Hz, 1 H), 2.99 (dd, *J* = 9.6, 12.4 Hz, 1 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 154.68, 144.05, 142.13, 141.46, 139.40, 129.08, 127.67, 127.02, 124.97, 120.41, 119.82, 118.65, 116.30, 69.68, 66.58, 48.50, 46.14.

MS (ESI): *m*/*z* = 375 [M + H$^+$].

(1*S*,2*S*)-2-Amino-1-[4-(9-fluorenylmethoxycarbonylamino)phenyl]propane-1,3-diol Hydrochloride (Entry 7)
White solid; yield: 74%; mp >246 °C (dec).

^{1}H NMR (400 MHz, CD_3OD): δ = 7.80 (d, *J* = 7.4 Hz, 2 H), 7.69 (d, *J* = 7.4 Hz, 2 H), 7.44 (m, 2 H), 7.34–7.39 (m, 2 H), 7.31 (m, 4 H), 4.69 (d, *J* = 9.0 Hz, 1 H), 4.48 (d, *J* = 6.7 Hz, 2 H), 4.27 (t, *J* = 6.5 Hz, 1 H), 3.54 (dd, *J* = 3.7, 11.7 Hz, 1 H), 3.39–3.43 (m, 1 H), 3.29–3.31 (m, 1 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 153.05, 142.49, 139.90, 137.75, 133.63, 126.10, 125.68, 125.45, 123.39, 118.27, 118.19, 117.31, 69.04, 64.99, 57.02, 45.59.

MS (ESI): *m*/*z* = 405 [M + H$^+$].

3-(2-Aminoethoxy)-*N*-(9-fluorenylmethoxycarbonyl)phenylamine Hydrochloride (Entry 8)
White solid; yield: 85%; mp 184–186 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.80 (d, *J* = 7.4 Hz, 2 H), 7.68 (d, *J* = 7.4 Hz, 2 H), 7.37–7.41 (m, 2 H), 7.31–7.33 (m, 3 H), 7.19 (t,

J = 8.2 Hz, 1 H), 6.93–6.96 (m, 1 H), 6.66–6.69 (m, 1 H), 4.46 (d, *J* = 6.8 Hz, 2 H), 4.26 (t, *J* = 6.8 Hz, 1 H), 4.19 (t, *J* = 4.9 Hz, 2 H), 3.34 (t, *J* = 5.1 Hz, 2 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 157.17, 152.97, 142.47, 139.88, 138.79, 128.01, 126.10, 125.45, 123.39, 118.26, 110.40, 107.36, 103.71, 64.99, 62.44, 45.57, 37.56.

MS (ESI): *m*/*z* = 375 [M + H$^+$].

7-(9-Fluorenylmethoxycarbonylamino)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (Entry 9)
Pale yellow solid; yield: 78%; mp >270 °C (dec).

^{1}H NMR (400 MHz, CD_3OD): δ = 7.79 (d, *J* = 7.6 Hz, 2 H), 7.68 (d, *J* = 7.4 Hz, 2 H), 7.39 (t, *J* = 7.4 Hz, 3 H), 7.28–7.33 (m, 3 H), 7.13 (d, *J* = 8.4 Hz, 1 H), 4.47 (br s, 2 H), 4.23–4.28 (m, 3 H), 3.46 (td, *J* = 3.3, 6.5 Hz, 2 H), 3.04 (t, *J* = 6.3 Hz, 2 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 154.54, 144.04, 141.47, 138.07, 129.39, 128.39, 127.67, 127.02, 125.73, 124.93, 119.83, 118.73, 116.32, 66.51, 44.71, 41.84, 24.29.

MS (ESI): *m*/*z* = 371 [M + H$^+$].

5-(9-Fluorenylmethoxycarbonylamino)indan-2-amine Hydrochloride (Entry 10)
White solid; yield: 81%; mp 208–210 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.81 (d, *J* = 7.4 Hz, 2 H), 7.69 (d, *J* = 7.4 Hz, 2 H), 7.42–7.52 (m, 1 H), 7.40 (t, *J* = 7.4 Hz, 2 H), 7.28–7.34 (m, 2 H), 7.15–7.23 (m, 2 H), 4.48–4.52 (m, 2 H), 4.27 (t, *J* = 6.5 Hz, 1 H), 4.04–4.10 (m, 1 H), 3.34–3.39 (m, 2 H), 2.92–3.01 (m, 2 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 153.15, 142.49, 139.87, 138.33, 136.90, 132.07, 126.11, 125.46, 123.41, 123.33, 118.28, 116.82, 113.78, 64.95, 50.12, 45.58, 36.13, 35.41.

MS (ESI): *m*/*z* = 371 [M + H$^+$].

Methyl (*S*)-2-Amino-3-[4-(9-fluorenylmethoxycarbonylamino)phenyl]propionate Hydrochloride (Entry 11)
White solid; yield: 80%; mp 203–205 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.79 (d, *J* = 7.4 Hz, 2 H), 7.68 (d, *J* = 7.4 Hz, 2 H), 7.37–7.46 (m, 4 H), 7.29–7.33 (m, 2 H), 7.15 (d, *J* = 8.4 Hz, 2 H), 4.48 (d, *J* = 6.5 Hz, 2 H), 4.24–4.29 (m, 2 H), 3.80 (s, 3 H), 3.21 (dd, *J* = 6.1, 14.5 Hz, 1 H), 3.11 (dd, *J* = 7.4, 14.5 Hz, 1 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 169.30, 154.63, 144.06, 141.47, 138.82, 129.72, 128.36, 127.67, 127.02, 125.00, 119.87, 119.76, 119.31, 66.53, 54.02, 52.50, 35.56.

MS (ESI): *m*/*z* = 417 [M + H$^+$].

(*S*)-2-Amino-3-[4-(9-fluorenylmethoxycarbonylamino)phenyl]propionic Acid Hydrochloride (Entry 12)
White solid; yield: 86%; mp 216–218 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.69 (br s, 1 H), 7.88 (d, *J* = 7.4 Hz, 2 H), 7.72 (d, *J* = 7.4 Hz, 2 H), 7.27–7.42 (m, 6 H), 7.15 (d, *J* = 8.4 Hz, 2 H), 4.44 (d, *J* = 6.8 Hz, 2 H), 4.26–4.29 (m, 1 H), 3.54–3.59 (m, 1 H), 3.07 (dd, *J* = 4.9, 14.3 Hz, 1 H), 2.89 (dd, *J* = 7.4, 14.3 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 170.87, 154.11, 144.45, 141.47, 138.36, 131.26, 130.46, 128.38, 127.81, 125.88, 120.93, 119.02, 66.17, 55.44, 47.30, 36.45.

MS (ESI): *m*/*z* = 403 [M + H$^+$].

4′-(Aminomethyl)-*N*-(9-fluorenylmethoxycarbonyl)-1,1′-biphenyl-4-ylamine Hydrochloride (Entry 13)
Conversion by HPLC: 94%; a portion of this material was isolated and characterized: pale yellow solid; mp >240 °C (dec).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.89 (br s, 1 H), 8.59 (br s, 2 H), 7.89 (d, *J* = 7.4 Hz, 2 H), 7.75 (d, *J* = 7.2 Hz, 2 H), 7.64 (d, *J* = 7.6 Hz, 2 H), 7.54–7.59 (m, 6 H), 7.41 (t, *J* = 7.2 Hz, 2 H), 7.33 (t, *J* = 7.2 Hz, 2 H), 4.48 (d, *J* = 6.3 Hz, 2 H), 4.30 (t, *J* = 6.7 Hz, 1 H), 4.01 (br s, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 154.10, 144.45, 141.50, 140.40, 139.47, 134.15, 133.39, 130.27, 128.40, 127.84, 127.67, 126.89, 125.86, 120.90, 119.34, 66.31, 47.30, 42.50.

LRMS (ESI): *m*/*z* = 404 [M + H$^+$– NH_3].

***N*-(2-Aminoethyl)-4-(9-fluorenylmethoxycarbonylamino)benzamide Hydrochloride (Entry 14)**
White solid; yield: 87%; mp 231–233 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.01 (br s, 1 H), 8.68 (t, *J* = 5.6 Hz, 1 H), 8.11 (br s, 2 H), 7.98 (d, *J* = 7.2 Hz, 2 H), 7.85 (d, *J* = 8.8 Hz, 2 H), 7.74 (d, *J* = 7.6 Hz, 2 H), 7.51 (br s, 2 H), 7.31–7.43 (m, 5 H), 4.49 (d, *J* = 6.8 Hz, 2 H), 4.30 (t, *J* = 6.4 Hz, 1 H), 3.47–3.51 (m, 2 H), 2.93–2.97 (m, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 166.90, 153.99, 144.39, 142.62, 141.50, 129.05, 128.41, 127.84, 125.82, 120.91, 117.91, 66.43, 47.24, 39.33, 37.74.

MS (ESI): *m*/*z* = 402 [M + H$^+$].

4-(2-Aminoethyl)-*N*-(benzyloxycarbonyl)phenylamine (1c); Typical Procedure
To a soln of 4-aminophenethylamine (0.32 g, 2.33 mmol) in 10% aq AcOH (20 mL) was added CbzCl (0.42 g, 2.44 mmol) dissolved in 1,4-dioxane (20 mL). The mixture was stirred overnight at r.t. H_2O (100 mL) was added and the mixture was washed with Et_2O (3 × 50 mL). The aqueous phase was made basic with 2 N NaOH to pH 14 and extracted with Et_2O (3 × 75 mL). The combined extract was washed with H_2O (2 × 40 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the expected product **1c**.

Pale yellow solid; yield: 93% (98% conversion by HPLC); mp 151–153 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.30–7.42 (m, 7 H), 7.13 (d, *J* = 8.6 Hz, 2 H), 5.16 (s, 2 H), 2.87 (t, *J* = 6.8 Hz, 2 H), 2.72 (t, *J* = 7.0 Hz, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 166.71, 154.08, 137.38, 135.37, 129.66, 129.12, 128.75, 118.85, 66.30, 53.28, 36.77, 29.42.

MS (ESI): *m*/*z* = 271 [M + H$^+$].

Protection with Cbz (Table 1, Last Yield Column)
3-(2-Aminoethyl)-*N*-(benzyloxycarbonyl)phenylamine (Entry 2)
White solid; yield: 81%; mp 79–81 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.40 (m, 5 H), 7.21–7.26 (m, 3 H), 6.87–6.90 (m, 1 H), 5.18 (s, 2 H), 2.94 (br s, 2 H), 2.70 (t, *J* = 6.8 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.70, 141.11, 138.34, 136.37, 129.34, 128.85, 128.57, 128.52, 124.17, 119.30, 116.81, 67.15, 43.56, 40.21.

MS (ESI): *m*/*z* = 271 [M + H$^+$].

4-(Aminomethyl)-*N*-(benzyloxycarbonyl)phenylamine (Entry 3)
White solid; yield: 97%.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.25–7.42 (m, 7 H), 7.20 (d, *J* = 8.4 Hz, 2 H), 5.13 (s, 2 H), 3.67 (s, 2 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 154.62, 137.88, 136.94, 128.43, 128.37, 127.95, 127.84, 118.75, 66.33, 54.24, 45.00.

MS (ESI): *m*/*z* = 257 [M + H$^+$].

3-(Aminomethyl)-*N*-(benzyloxycarbonyl)phenylamine (Entry 4)
Pale yellow solid; yield: 93%; mp 113–115 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.28–7.42 (m, 7 H), 7.23 (t, *J* = 7.6 Hz, 1 H), 7.00 (m, 1 H), 5.17 (s, 2 H), 3.73 (s, 2 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 154.63, 143.28, 139.19, 136.94, 128.91, 128.38, 127.97, 127.87, 121.86, 117.67, 117.28, 66.37, 45.53.

MS (ESI): *m*/*z* = 257 [M + H$^+$].

(*RS*)-3-(1-Aminoethyl)-*N*-(benzyloxycarbonyl)phenylamine (Entry 5)
Colorless oil; yield: 88%.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.28–7.42 (m, 7 H), 7.23 (t, *J* = 7.8 Hz, 1 H), 7.03 (d, *J* = 7.6 Hz, 1 H), 5.17 (s, 2 H), 3.98 (q, *J* = 6.7 Hz, 1 H), 1.36 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 153.09, 146.25, 137.60, 135.38, 127.35, 126.82, 126.41, 126.30, 118.80, 115.77, 114.69, 64.80, 49.56, 22.44.

MS (ESI): *m*/*z* = 271 [M + H$^+$].

(*RS*)-2-Amino-1-[3-(benzyloxycarbonylamino)phenyl]ethanol (Entry 6)
White solid; yield: 83%; mp 33–36 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.47 (s, 1 H), 7.23–7.41 (m, 7 H), 7.03 (d, *J* = 7.6 Hz, 1 H), 5.16 (s, 2 H), 4.52 (t, *J* = 5.6 Hz, 1 H), 2.70–2.83 (m, 2 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 154.65, 144.06, 139.12, 136.94, 128.71, 128.35, 127.94, 127.83, 120.58, 117.85, 116.44, 74.71, 66.34.

MS (ESI): *m*/*z* = 287 [M + H$^+$].

(1*S*,2*S*)-2-Amino-1-[4-(benzyloxycarbonylamino)phenyl]propane-1,3-diol (Entry 7)
Colorless oil; yield: 78%.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.26–7.45 (m, 9 H), 5.15 (s, 2 H), 4.50 (d, *J* = 6.8 Hz, 1 H), 3.44 (dd, *J* = 4.3, 10.8 Hz, 1 H), 3.29–3.33 (m, 1 H), 2.85–2.93 (m, 1 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 153.02, 137.19, 135.33, 133.10, 126.82, 126.42, 126.30, 125.39, 117.15, 93.21, 78.67, 65.74, 56.66.

MS (ESI): *m*/*z* = 317 [M + H$^+$].

3-(2-Aminoethoxy)-*N*-(benzyloxycarbonyl)phenylamine (Entry 8)
White solid; yield: 98%; mp 111–113 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.30–7.42 (m, 5 H), 7.13–7.17 (m, 2 H), 6.94–6.96 (m, 1 H), 6.61 (dd, *J* = 0.8, 2.5 Hz, 1 H), 5.16 (s, 2 H), 3.97 (t, *J* = 5.3 Hz, 2 H), 2.97 (t, *J* = 5.3 Hz, 2 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 159.64, 154.52, 140.26, 136.90, 129.47, 128.37, 127.97, 127.84, 111.17, 108.87, 105.08, 69.03, 66.34, 40.65.

MS (ESI): *m*/*z* = 287 [M + H$^+$].

7-(Benzyloxycarbonylamino)-1,2,3,4-tetrahydroisoquinoline (Entry 9)
Pale brown solid; yield: 73%; mp 171–173 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.28–7.41 (m, 5 H), 7.14–7.17 (m, 2 H), 6.99 (d, *J* = 8.2 Hz, 1 H), 5.15 (s, 2 H), 3.89 (s, 2 H), 3.04 (t, *J* = 6.1 Hz, 2 H), 2.75 (t, *J* = 6.1 Hz, 2 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 153.09, 135.40, 135.20, 133.82, 127.83, 127.76, 126.77, 126.35, 126.24, 115.54, 114.73, 64.70, 45.90, 41.75, 26.05.

MS (ESI): *m*/*z* = 283 [M + H$^+$].

5-(Benzyloxycarbonylamino)indan-2-amine (Entry 10)
Pale yellow solid; yield: 76%; mp 87–90 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.27–7.41 (m, 6 H), 7.16 (d, *J* = 8.0 Hz, 1 H), 7.09 (d, *J* = 8.0 Hz, 1 H), 5.15 (s, 2 H), 3.74–3.80 (m, 1 H), 3.10–3.17 (m, 2 H), 2.65–2.73 (m, 2 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 153.20, 140.50, 136.13, 135.43, 134.41, 126.77, 126.34, 126.23, 123.06, 116.01, 113.79, 64.70, 51.23, 39.82, 39.06.

MS (ESI): *m*/*z* = 283 [M + H$^+$].

Methyl (*S*)-2-Amino-3-[4-(benzyloxycarbonylamino)phenyl]propionate (Entry 11)[8a]
White solid; yield: 84%; mp 81–83 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.30–7.41 (m, 7 H), 7.13 (d, *J* = 8.6 Hz, 2 H), 5.16 (s, 2 H), 3.93 (t, *J* = 7.0 Hz, 1 H), 3.72 (s, 3 H), 3.06 (dd, *J* = 6.1, 13.9 Hz, 1 H), 2.97 (dd, *J* = 7.0, 13.9 Hz, 1 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 171.85, 154.62, 138.40, 136.90, 129.80, 129.70, 128.38, 127.98, 127.84, 119.02, 66.39, 54.55, 51.83, 37.42.

MS (ESI): *m*/*z* = 329 [M + H$^+$].

(*S*)-2-Amino-3-[4-(benzyloxycarbonylamino)phenyl]propionic Acid (Entry 12)[8b]
White solid; yield: 77%; mp 258–260 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.67 (br s, 1 H), 7.30–7.41 (m, 7 H), 7.13 (d, *J* = 8.6 Hz, 2 H), 5.12 (s, 2 H), 3.05 (dd, *J* = 4.3, 14.3 Hz, 1 H), 2.76 (dd, *J* = 8.4, 14.5 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 170.02, 154.06, 138.20, 137.34, 132.05, 130.36, 129.15, 128.76, 118.91, 66.32, 56.22, 36.89.

MS (ESI): *m*/*z* = 315 [M + H$^+$].

4′-(Aminomethyl)-*N*-(benzyloxycarbonyl)-1,1′-biphenyl-4-ylamine (Entry 13)
Beige solid; yield: 76%; mp 157–160 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.85 (br s, 1 H), 7.50–7.58 (m, 6 H), 7.27–7.44 (m, 7 H), 5.14 (s, 2 H), 3.37 (br s, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 154.03, 139.02, 138.39, 137.27, 134.87, 129.15, 128.84, 128.76, 128.29, 127.49, 126.58, 119.16, 66.47, 45.92, 43.00.

LRMS (ESI): *m*/*z* = 316 [M + H$^+$ – NH_3].

***N*-(2-Aminoethyl)-4-(benzyloxycarbonylamino)benzamide (Entry 14)**
White solid; yield: 61%; mp 154–156 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.79 (dd, *J* = 4.8, 2.0 Hz, 2 H), 7.55 (d, *J* = 8.8 Hz, 2 H), 7.31–7.43 (m, 5 H), 5.19 (s, 2 H), 3.46 (t, *J* = 6.4 Hz, 2 H), 2.86 (t, *J* = 6.0 Hz, 2 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 168.91, 154.25, 142.54, 136.76, 128.36, 128.21, 128.13, 127.89, 117.66, 66.52, 48.52, 41.80, 40.77.

MS (ESI): m/z = 314 [M + H$^+$].

***N*-(Allyloxycarbonyl)-4-(2-aminoethyl)phenylamine (1d)**
White solid; yield: 98%; mp 81–83 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.35 (d, J = 8.4 Hz, 2 H), 7.13 (d, J = 8.6 Hz, 2 H), 5.94–6.03 (m, 1 H), 5.35 (dd, J = 1.6, 17.2 Hz, 1 H), 5.21 (dd, J = 1.4, 10.6 Hz, 1 H), 4.61 (d, J = 5.5 Hz, 2 H), 2.84 (t, J = 7.6 Hz, 2 H), 2.70 (t, J = 7.4 Hz, 2 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 154.60, 137.30, 134.18, 133.12, 129.01, 119.01, 116.70, 65.23, 42.88, 37.84.

LRMS (ESI): m/z = 221 [M + H$^+$].

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