



# A short synthesis of (*S*)- $\alpha$ -(diphenylmethyl)alkyl amines from amino acids

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## Abstract

A range of (*S*)- $\alpha$ -(diphenylmethyl)alkyl amines were prepared from the corresponding (*S*)- $\alpha$ -amino acid ester hydrochlorides. These amines were derived by direct hydrogenation of their precursor oxazolidinones. © 1999 Elsevier Science Ltd. All rights reserved.

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## 1. Introduction

The synthesis of (*S*)- $\alpha$ -(diphenylmethyl)pyrrolidine **3** from (*S*)-proline **1** was recently described<sup>1</sup> as shown in Scheme 1. The key step in the route is the final one where the oxazolidinone **2**, when treated under standard hydrogenation conditions, delivered amine **3**, after removal of the elements of carbon dioxide. Amine **3** emerged as a good chiral solvating agent for enantiomeric analysis of chiral carboxylic acids and was also used to prepare the diamines **4** and **5**, potential bidentate ligands.<sup>1</sup>

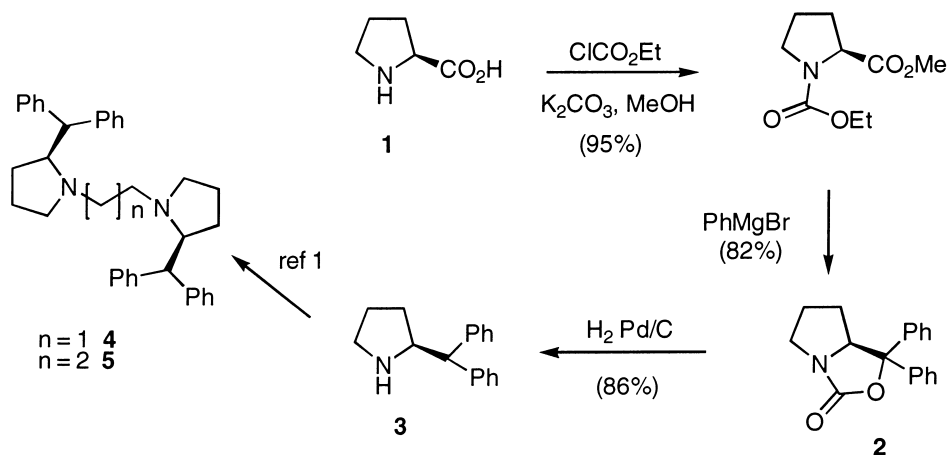
To develop this methodology further we now report the synthesis of the (*S*)- $\alpha$ -(diphenylmethyl)alkyl amines **11–15** from appropriate (*S*)-amino acids. The amines were delivered in a straightforward manner by an analogous hydrogenation to that of **2** on the corresponding oxazolidinones **6–10**.

## 2. Results and discussion

The general route to these amines is outlined in Scheme 2. Reaction of the ethyl ester ammonium HCl salts of the starting amino acids, with phenylmagnesium bromide has previously been described for all of the cases studied,<sup>2</sup> and similarly all of the oxazolidinones except **9** (derived from (*S*)-isoleucine) have previously been prepared by analogous routes.<sup>3</sup> In our case the amino alcohols were treated with diphosgene to generate the oxazolidinones **6–10** and generally the yields were good to excellent. The

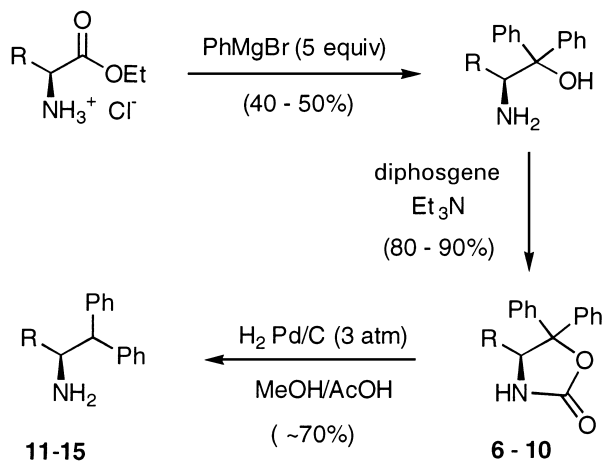
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Scheme 1.

hydrogenation of the oxazolidinones proved straightforward and the target amines were readily purified as detailed in the Experimental. Data for characterisation and physical properties of these novel amines are summarised in Table 1.

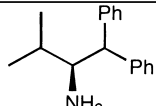
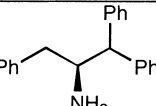
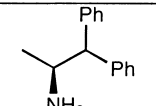
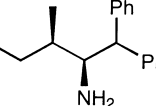
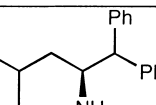


Scheme 2.

It was important to determine if the amines **11–15** were enantiomerically pure and that no racemisation had occurred during the hydrogen process. To this end amine **13** was prepared as a racemate from (*RS*)-alanine ethyl ester HCl salt and was then derivatised with (*S*)-Mosher's acid chloride<sup>4</sup> to generate the corresponding (*R*)-Mosher's amide derivatives **16** and **17**, a mixture of diastereoisomers. Fig. 1 illustrates a comparison of selected regions of the <sup>1</sup>H and <sup>19</sup>F NMR spectra (OMe and CF<sub>3</sub> signals, respectively), of the amide diastereoisomers **16** and **17**, and **16** generated by reaction of (*R*)-Mosher's acid chloride with (*S*)-**13**. It is clear that a single diastereoisomer is generated in the latter case and within the level of detection there is no indication of any racemisation. (*R*)-Mosher's amide derivatives were then prepared for the remaining amines (**11**, **12**, **14** and **15**) and in all cases the <sup>1</sup>H and <sup>19</sup>F NMR spectra indicated the presence of a single stereoisomer. Thus we are confident that the synthetic sequence outlined in Scheme 2 is not susceptible to racemisation.

These compounds offer a range of new chiral amines for applications in synthesis and as components for combinatorial libraries.

Table 1  
Physical properties and spectroscopic data for the (S) amines 11–15

 <p><b>11</b></p> <p>Yield: 72 %. M.p. 71–72 °C.</p>	<p><math>[\alpha]_D^{25} = -4.2</math> (c, 10.9 in <math>\text{CHCl}_3</math>). <math>\delta_{\text{H}}</math> 0.78 (3H, d, <math>J = 6.6</math> Hz, <math>\text{CH}_3</math>), 0.91 (3H, d, <math>J = 7.2</math> Hz, <math>\text{CH}_3</math>), 1.26 (2H, broad s, <math>\text{NH}_2</math>), 1.54–1.72 (1H, m, <math>\text{CHMe}_2</math>), 3.45 (1H, dd, <math>J = 10.5</math> and 2.4 Hz, <math>\text{CH-NH}_2</math>), 3.70 (1H, d, <math>J = 10.5</math> Hz, <math>\text{CH-Ph}_2</math>), 7.00–7.40 (10H, m, Ar-H). <math>\delta_{\text{C}}</math> 14.2 (<math>\text{CH}_3</math>), 21.5 (<math>\text{CH}_3</math>), 28.9 (<math>\text{CH-Me}_2</math>), 58.1 (<math>\text{CH}</math>), 58.9 (<math>\text{CH}</math>), 126.5, 126.7, 128.2, 128.5, 128.8, 129.0, 143.5 (Ar). Anal. Calc. for <math>\text{C}_{17}\text{H}_{21}\text{N}</math>: C 85.30; H 8.84; N 5.85. Found: C 85.12; H 8.91; N 5.96. m/e (CI-<math>\text{CH}_4</math>) 240 (<math>\text{MH}^+</math>, 8 %), 72 (100 %). Ir (<math>\nu</math>, <math>\text{cm}^{-1}</math>) 3361 (N-H), 3065, 3022 (Ar C-H), 2956, 2926, 2867, 1596, 1493, 1450 (Ar C=C).</p>
 <p><b>12</b></p> <p>Yield: 71 %. M.p. 71–72 °C.</p>	<p><math>[\alpha]_D^{25} = -8.0</math> (c, 10.5 in <math>\text{CHCl}_3</math>). <math>\delta_{\text{H}}</math> 1.21 (2H, broad s, <math>\text{NH}_2</math>), 2.29 (1H, dd, <math>J = 9.6</math> and 13.5 Hz, <math>\text{CH}_2</math>), 2.79 (1H, d, <math>J = 13.2</math> Hz, <math>\text{CH}_2</math>), 3.71 (1H, d, <math>J = 9.9</math> Hz, <math>\text{CH-Ph}_2</math>), 3.81 (1H, dt, <math>J = 2.7</math>, 9.6 Hz, <math>\text{CH-NH}_2</math>), 7.06–7.33 (15H, m, Ar-H). <math>\delta_{\text{C}}</math> 41.9 (<math>\text{CH}_2</math>), 55.7 (<math>\text{CH}</math>), 59.7 (<math>\text{CH}</math>), 126.3, 126.5, 126.6, 128.1, 128.2, 128.4, 128.7, 128.8, 129.1, 139.7, 142.6, 143.1 (Ar). m/e (CI-<math>\text{NH}_3</math>) 288 (<math>\text{MH}^+</math>, 100 %). HRMS (CI-<math>\text{NH}_3</math>): Found 288.175856; Calc. for (<math>\text{MH}^+</math>) <math>\text{C}_{21}\text{H}_{22}\text{N}</math> 288.175225 (-2.2 ppm). Ir (<math>\nu</math> <math>\text{cm}^{-1}</math>) 3383 (N-H), 3082, 3059, 3025 (Ar C-H), 2936, 2912, 1595, 1493, 1450 (Ar C=C).</p>
 <p><b>13</b></p> <p>Yield: 65 %. M.p. 76–77 °C.</p>	<p><math>[\alpha]_D^{25} = -19.3</math> (c, 10.8 in <math>\text{CHCl}_3</math>). <math>\delta_{\text{H}}</math> 1.04 (3H, d, <math>J = 6.3</math> Hz, <math>\text{CH}_3</math>), 1.31 (2H, s, <math>\text{NH}_2</math>), 3.55 (1H, d, <math>J = 9.9</math> Hz, <math>\text{CH-Ph}_2</math>), 3.66–3.80 (1H, m, <math>\text{CH-NH}_2</math>), 7.10–7.40 (10H, m, Ar-H). <math>\delta_{\text{C}}</math> 22.4 (<math>\text{CH}_3</math>), 50.3 (<math>\text{CH}</math>), 62.4 (<math>\text{CH}</math>), 126.5, 126.8, 128.2, 128.5, 128.7, 129.0, 143.3, 143.7 (<math>\alpha</math>-Ar). Anal. Calc. for <math>\text{C}_{15}\text{H}_{17}\text{NO}</math>: C 85.26; H 8.11; N 6.63. Found: C 85.10; H 8.08; N 6.36. m/e (CI-<math>\text{NH}_3</math>) 212 (<math>\text{MH}^+</math>, 100 %). Ir (<math>\nu</math> <math>\text{cm}^{-1}</math>) 3344 (N-H), 3083, 3027 (Ar C-H), 2976, 2958, 1597, 1493, 1449 (Ar C=C).</p>
 <p><b>14</b></p> <p>Yield: 71 %. M.p. 59–61 °C.</p>	<p><math>[\alpha]_D^{25} = -13.7</math> (c, 4.8 in <math>\text{CHCl}_3</math>). <math>\delta_{\text{H}}</math> 0.76 (3H, t, <math>J = 7.5</math> Hz, <math>\text{CH}_3</math>), 0.96 (3H, d, <math>J = 6.9</math> Hz, <math>\text{CH}_3</math>), 1.00–1.18 (3H, broad s and m, <math>\text{NH}_2</math> and <math>\text{CH}_2</math>), 1.28–1.42 (1H, m, <math>\text{CH-Me}</math>), 1.50–1.70 (1H, m, <math>\text{CH}_2</math>), 3.50 (1H, dd, <math>J = 10.5</math> and 2.40 Hz, <math>\text{CH-NH}_2</math>), 3.87 (1H, d, <math>J = 10.5</math> Hz, <math>\text{CH-Ph}_2</math>), 7.10–7.40 (10H, m, Ar-H). <math>\delta_{\text{C}}</math> 11.2 (<math>\text{CH}_3\text{-CH}_2</math>), 16.7 (<math>\text{CH}_3\text{-CH}</math>), 20.4 (<math>\text{CH}_2</math>), 34.8 (<math>\text{CH-Me}</math>), 56.4 (<math>\text{CH-Ph}_2</math>), 58.4 (<math>\text{CH-NH}_2</math>), 125.2, 125.4, 127.0, 127.4, 127.5, 127.7 (Ar). m/e (CI-<math>\text{NH}_3</math>) 254 (<math>\text{MH}^+</math>, 100 %). HRMS (CI-<math>\text{CH}_4</math>): Found 254.189998; Calc. for (<math>\text{MH}^+</math>) <math>\text{C}_{18}\text{H}_{24}\text{N}</math> 254.190875 (3.4 ppm). Ir (<math>\nu</math> <math>\text{cm}^{-1}</math>) 3355 (N-H), 3082, 3065, 3024 (Ar C-H), 2959, 2931, 2872, 1598, 1494, 1450 (Ar C=C).</p>
 <p><b>15</b></p> <p>Yield: 87 %. M.p. 46–48 °C.</p>	<p><math>[\alpha]_D^{25} = -31.6</math> (c, 4.1 in <math>\text{CHCl}_3</math>). <math>\delta_{\text{H}}</math> 0.86 (6H, dt, <math>J = 6.60</math> and 2.10 Hz, <math>\text{CH}_3</math>), 1.00–1.50 (4H, m and broad s, <math>\text{CH}_2</math> and <math>\text{NH}_2</math>), 1.66–1.86 (1H, m, <math>\text{CH}</math>), 3.61 (2H, s, <math>\text{CH-NH}_2</math> and <math>\text{CH-Ph}_2</math>), 7.10–7.40 (10H, m, Ar-H). <math>\delta_{\text{C}}</math> 21.8 (<math>\text{CH}_3</math>), 24.7 (<math>\text{CH}</math>), 25.5 (<math>\text{CH}_3</math>), 45.6 (<math>\text{CH}_2</math>), 52.4 (<math>\text{CH-NH}_2</math>), 61.6 (<math>\text{CH-Ph}_2</math>), 126.9, 127.1, 128.8, 129.0, 129.2, 129.4, 143.8, 144.0 (Ar). m/e (CI-<math>\text{NH}_3</math>) 254 (<math>\text{MH}^+</math>, 100 %). HRMS (CI-<math>\text{CH}_4</math>): Found 254.190200; Calc. for (<math>\text{MH}^+</math>) <math>\text{C}_{18}\text{H}_{24}\text{N}</math> 254.190875 (2.7 ppm). Ir (<math>\nu</math> <math>\text{cm}^{-1}</math>) 3368 (N-H), 3057, 3027 (Ar C-H), 2951, 2932, 2909, 2867, 1595, 1494, 1450 (Ar C=C) <math>\text{cm}^{-1}</math>.</p>

### 3. Experimental

#### 3.1. General hydrogenation method

To a suspension of the oxazolidinones 6–10 (15 mmol) in  $\text{MeOH}:\text{AcOH}$  (10:1) (100 ml) was added Pd (10%) on carbon (159 mg, 1.5 mmol) and the reaction was shaken for 2 days at 4–5 atm under hydrogen gas. The catalyst was filtered over Hyflo and the solvent removed under reduced pressure. The residue

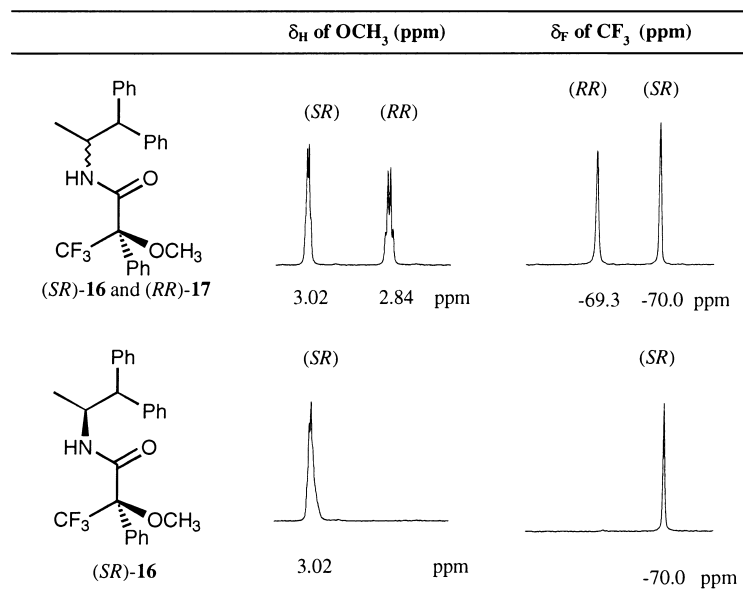


Figure 1. Selected regions of the  $^1\text{H}$  NMR and  $^{19}\text{F}$  NMR spectra of the (*R*)-Mosher's amides **16** and **17** prepared from either (*SR*)-**13** or (*S*)-**13**

was stirred with 2 M HCl (50 ml) and the acidic aqueous solution was washed with EtOAc (3×30 ml), and then made basic by addition of NaOH pellets. The amines were then extracted into ethyl acetate (3×100 ml), dried ( $\text{MgSO}_4$ ) and the solvent was removed under reduced pressure to give **11–15** as off-white amorphous solids (65–87%). When necessary, further purification was carried out by chromatography or recrystallisation from organic solvent. See Table 1 for characterisation.

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