Asymmetric Synthesis of Substituted Azetidine Type α- and β-Amino Acids

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Abstract: A versatile asymmetric synthesis of 3-substituted azetidine-2-carboxylic acids and 2-substituted azetidine-3-carboxylic acids via 1,3-amino alcohols with excellent stereoselectivities (de ≥ 96%, ee ≥ 96%) is reported. The high asymmetric inductions were achieved employing the SAMP/RAMP-hydrazone methodology. A phenyl moiety was used as a synthetic equivalent of the carboxylic acid function. In addition, the amino acids prepared were tested as organocatalysts in an asymmetric aldol reaction.

Key words: amino acids, amino alcohols, azetidines, organocatalysts, hydrazones

The plant growth inhibitor (S)-azetidine-2-carboxylic acid [L-aze, (S)-1] was the first known example for the occurrence of the uncommon azetidine motif in natural products.1 Since then only a few additional natural products containing this amino acid or substituted analogues have been isolated, such as the antifungal and antibiotic polyoxins,2 the phytosiderophores nicotianamine and mugineic acid,3 medicaine,4 and substituted azetidine-2,4-dicarboxylic acids.5 Although quite rarely found in nature, derivatives of 1 are of significant importance as active pharmaceutical ingredients, as for example the non-opioid analgesic agent ABT-594 [(R)-2]6 and the thrombin inhibitor melagatran (3)7 (Figure 1). Ligands derived from L-aze have also been successfully employed in asymmetric catalysis.8

Despite these promising applications of azetidine-2-carboxylic acid, limited progress has been made for the preparation of substituted analogues. Only a few general routes to non-racemic substituted azetidine-2-amino acids have been described so far. Very recently Lubell et al. reported the preparation of a 3-allyl substituted L-aze derivative from L-aspartic acid and the transformation of the allyl moiety into different heteroatom containing side chains.9 Hanessian et al. used Oppolzer’s sultam methodology for the preparation of 3-substituted L-aze analogues.10 Couty et al. converted 2-cyano azetidines derived from ephedrine, norephedrine and phenylglycine into the corresponding enantiopure 3-phenyl substituted amino acids.11 Apart from these general approaches only some specific examples of substituted non-racemic azetidine carboxylic acids have been prepared.3,12

We now wish to describe an efficient asymmetric synthesis of 3-substituted azetidine-2-carboxylic acids and 2-substituted azetidine-3-carboxylic acids employing the SAMP/RAMP-hydrazone methodology13,14 and extending our recently reported asymmetric synthesis of enantiopure substituted azetidines.15 Our synthetic approach comprises the synthesis of 1,3-amino alcohols by α-hydroxymethylation/1,2-addition of aldehyde SAMP/RAMP-hydrazones with subsequent N–N bond cleavage. Afterwards the 1,3-amino alcohols are cyclized to the corresponding azetidines. A phenyl substituent serves as a synthetic equivalent of the carboxylic acid function, easily obtained by oxidative cleavage.

The asymmetric synthesis of the azetidines 9 was carried out as depicted in Scheme 1. First the SAMP/RAMP-hydrazones16 4 were hydroxymethylated with excellent diastereoselectivities (de ≥ 96%, Table 1) by α-alkylation with (2-trimethylsilyl)ethoxy)methyl chloride (SEMC1) instead of benzyloxymethyl chloride as has been used in our previous procedure.15 This alteration meant a change of the O-protecting group from benzyl to TMS-ethyl, thus easily enabling the selective O-deprotection in the presence of the benzylic amine moiety generated in the next step of this synthesis.

A phenyl substituent was introduced by a nucleophilic 1,2-addition of a phenylcerium reagent to the C≡N double bond of the hydrazones 5.17 The phenylcerium reagent was generated in situ from phenyllithium following Imamoto’s procedure.18 The obtained crude hydrazines 6 were directly submitted to a reductive N–N bond cleavage to remove the chiral auxiliary.19 The corresponding O-protected amino alcohols were subsequently refluxed with tosyl chloride in the presence of K2CO3, yielding the differently N,O-protected amino alcohols 7 in good yields (58–64% over 3 steps) and excellent diastereomeric and enantiomeric excesses (de = 94–99%, ee ≥ 96–99%, Table 2). The de values were determined by GC or NMR.

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Preparation of the Protected Amino Alcohols 7 by 1,2-Addition, N–N Cleavage and N-Tosylation

Table 2 Preparation of the Protected Amino Alcohols 7 by 1,2-Addition, N–N Cleavage and N-Tosylation

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Yield (%)</th>
<th>de (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S,R)-7a</td>
<td>Me</td>
<td>64</td>
<td>99 (≥ 98)c</td>
<td>97d</td>
</tr>
<tr>
<td>(R,S)-7a</td>
<td>Me</td>
<td>58</td>
<td>99 (≥ 95)f</td>
<td>≥ 99d</td>
</tr>
<tr>
<td>(S,R)-7b</td>
<td>Et</td>
<td>61</td>
<td>96e</td>
<td>≥ 96</td>
</tr>
<tr>
<td>(S,R)-7c</td>
<td>i-Pr</td>
<td>59</td>
<td>96e</td>
<td>≥ 96</td>
</tr>
<tr>
<td>(S,R)-7d</td>
<td>n-Bu</td>
<td>58</td>
<td>99 (≥ 94)f</td>
<td>≥ 96</td>
</tr>
</tbody>
</table>

* Determined by GC.
* Based on the de values of the corresponding hydrazones. The following steps are racemization-free.
* Determined by HPLC on a chiral stationary phase.
* Determined by 13C NMR spectroscopy.

The relative configuration of the phenyl substituent and R was proven to be trans by NOE experiments on compound (S,S)-9a (Figure 2). The absolute configuration of the newly generated stereogenic centers was assigned according to the previously confirmed mechanisms for α-alkylations and 1,2-additions to SAMP-hydrazone.13,23

Figure 2 NOE enhancements as measured on (S,S)-9a

\[
\begin{align*}
\text{Scheme 1 Reagents and conditions:} & \quad \text{a) LDA, THF, 0 °C, then –100 °C, SEMCl;} \\
& \quad \text{b) PhLi, CCl₄, THF, –105 °C;} \\
& \quad \text{c) BH₃·THF, THF, reflux, then HCl;} \\
& \quad \text{d) TsCl, K₂CO₃, CH₂Cl₂, reflux;} \\
& \quad \text{e) LiBF₄, MeCN–H₂O (98:2), reflux;} \\
& \quad \text{f) DIAD, PPh₃, THF, r.t.}
\end{align*}
\]

The N-protected amino alcohols 8 were not purified, but cyclized under Mitsunobu conditions.22 The corresponding N-tosylated 2-phenylazetidines 9 were obtained in good yields (86–98% over 2 steps, Table 3) as one diastereomer (de ≥ 96%) and without racemization (ee ≥ 96–99%), as shown by HPLC on a chiral stationary phase for (S,S)-9a and (R,R)-9a.

Table 3 O-Deprotection and Cyclization to the Azetidines 9

<table>
<thead>
<tr>
<th>Azetidine</th>
<th>R</th>
<th>Yield (%)</th>
<th>de (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S,S)-9a</td>
<td>Me</td>
<td>86</td>
<td>≥ 96</td>
<td>97c</td>
</tr>
<tr>
<td>(R,R)-9a</td>
<td>Me</td>
<td>98</td>
<td>≥ 96</td>
<td>≥ 99c</td>
</tr>
<tr>
<td>(S,S)-9b</td>
<td>Et</td>
<td>91</td>
<td>≥ 96</td>
<td>≥ 96</td>
</tr>
<tr>
<td>(S,S)-9c</td>
<td>i-Pr</td>
<td>86</td>
<td>≥ 96</td>
<td>≥ 96</td>
</tr>
<tr>
<td>(S,S)-9d</td>
<td>n-Bu</td>
<td>94</td>
<td>≥ 96</td>
<td>≥ 96</td>
</tr>
</tbody>
</table>

* Determined by 13C NMR spectroscopy.
* Based on the de values of the corresponding hydrazones. The following steps are racemization-free.
* Determined by HPLC on a chiral stationary phase.
The preparation of the azetidines 9 was also tried without the use of a N-protecting group by direct O-deprotection of 6 and subsequent cyclization of the hydrazines to the corresponding \(N\)-amino azetidines. While the O-deprotection was easily achieved with \(LiBF_4\), the cyclization of the hydrazines failed under various conditions.

The conversion of the 2-phenylazetidines 9 to the corresponding azetidine type \(\alpha\)-amino acids was accomplished by catalytic oxidation with ruthenium tetroxide in a biphasic solvent system consisting of MeCN, \(H_2O\) and \(CCl_4\) as introduced by Sharpless et al. (Scheme 2).\(^{24}\) In order to achieve complete conversion, periodic acid had to be used as the stochiometric oxidant rather than sodium periodate which is usually applied in ruthenium tetroxide oxidations.\(^{25}\) N-Detosylation with sodium naphthalene gave the free \(\alpha\)-amino acids 10. In order to prepare an azetidine type \(\beta\)-amino acid, the same oxidation/deprotection sequence was applied for 3-phenylazetidine (\(R,S\))-12, which was prepared as reported previously.\(^{15}\)

![Scheme 2](https://via.placeholder.com/150)

**Scheme 2** Reagents and conditions: a) RuCl\(_3\), \(H_2IO_6\), MeCN, \(CCl_4\), \(H_2O\), r.t.; b) Na, naphthalene, DME, \(-78^\circ C\)

The Amino acids 10a-d and 13 were obtained after purification by ion exchange chromatography in 51–65\% yields (Table 4). Because no epimerization was detected by \(^{13}\)C NMR (de \(\geq 96\%\)), it was assumed that racemization also did not occur (ee \(\geq 96\%\)). This assumption was supported by comparison of the optical rotation of (\(S,S\))-10c with the optical rotation reported by Hanessian et al. ([\(\alpha\])\(_D\)\(^{22}\) = \(-9.4\) \(c = 0.20\), \(H_2O\)]. Lit.\(^{10}\); [\(\alpha\])\(_D\)\(^{10}\) = \(-9.5\) \(c = 0.11\), \(H_2O\)). However, long-term NMR experiments revealed that the \(\alpha\)-amino acids 10a-d contained small amounts of an impurity (5–8\%), which was identified as the acyclic \(\beta\)-amino acid 11a-d, respectively.\(^{26}\) This side product presumably resulted from a ring-opening followed by oxidation at the benzylic position.

As cyclic amino acids, especially proline, play a pivotal role as efficient organocatalysts,\(^{27}\) we were - apart from their biological activities - interested in the catalytic properties of the amino acids prepared. A screening of their catalytic activities, using the aldol reaction of acetone and \(p\)-nitrobenzaldehyde as a benchmark reaction (Scheme 3), showed good yields and moderate ee’s compared to proline and an increased performance compared to unsubstituted L-aze (\(L\)-1) for 3-substituted L-aze derivatives (Table 5).\(^{28}\) The \(\beta\)-amino acid 13 did not give an asymmetric induction worth mentioning.

![Table 4](https://via.placeholder.com/150)

**Table 4** Oxidation and Detosylation to the Free Acetidinic Amino Acids

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>R</th>
<th>Yield (%)</th>
<th>de (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>((S,S))-10a</td>
<td>Me</td>
<td>57</td>
<td>(\geq 96)</td>
<td>(\geq 96)</td>
</tr>
<tr>
<td>((R,R))-10a</td>
<td>Me</td>
<td>58</td>
<td>(\geq 96)</td>
<td>(\geq 96)</td>
</tr>
<tr>
<td>((S,S))-10b</td>
<td>Et</td>
<td>51</td>
<td>(\geq 96)</td>
<td>(\geq 96)</td>
</tr>
<tr>
<td>((S,S))-10c</td>
<td>i-Pr</td>
<td>65</td>
<td>(\geq 96)</td>
<td>(\geq 96)</td>
</tr>
<tr>
<td>((S,S))-10d</td>
<td>n-Bu</td>
<td>54</td>
<td>(\geq 96)</td>
<td>(\geq 96)</td>
</tr>
<tr>
<td>((R,S))-13</td>
<td>–</td>
<td>64</td>
<td>(\geq 96)</td>
<td>(\geq 96)</td>
</tr>
</tbody>
</table>

* A determined by \(^{13}\)C NMR spectroscopy.

In conclusion we have developed an efficient asymmetric synthesis of 3-substituted azetidine-2-carboxylic acids and 2-substituted azetidine-3-carboxylic acids with virtually complete control of the diastereo- and enantioselectivity.

All solvents were dried and purified by conventional methods prior to use. THF and dimethylethane were freshly distilled from lithium/lead alloy and benzophenone under Ar. All moisture-sensitive reactions were carried out under Ar using standard Schlenk techniques. Phenyllithium solution was purchased from Fluka and n-BuLi from Merck. Diisopropylamine was distilled from CaH\(_2\) under Ar and stored over molecular sieves. Flash column chromatography
was carried out with Merck silica gel 60 (0.040-0.063 mm particle size). Optical rotation values were measured on a Perkin-Elmer P241 polarimeter with solvents of Merck UVASOL quality. IR spectra were recorded on a Perkin-Elmer FT/IR spectrometer. NMR spectra were measured on Varian VXR 300, Varian Gemini 300 and Varian Inova 400 spectrometers, using TMS or DQO as internal standard. Mass spectra were measured on Varian MAT 212 and Finnigan SSQ 7000 instruments. Microanalyses were performed on Heraeus, CHN-O-Rapid instrument. Melting points were measured with a Büchi 510 apparatus and are uncorrected. Merck TLC plates with silica gel 60 F254 were used for analytical TLC.

Alkylation of Hydrazones with SEM Chloride; General Procedure (GP1)

A solution of LDA was freshly prepared by addition of n-BuLi (1.3 equiv) to a solution of diisopropylamine (1.3 equiv) in THF (1.4 mL/mmol) at 0 °C. After stirring for 15 min the SAMP- or RAMP-hydrazones (1 equiv) were added dropwise and the mixture was stirred for 2.5 h. The reaction vessel was then cooled to −100 °C and SEMCl (1.2 equiv) was added slowly. The mixture was allowed to warm to r.t. within 16 h and the pH 7 buffer solution (3 mL/mmol) was added. After extraction with Et2O and drying over MgSO4, the mixture was filtered through a pad of silica gel and the solvent was evaporated. Flash column chromatography was performed using the pure products 5a–d.

(E,2R)-3-[[2-(Trimethylsilyl)ethoxy]ethyl]-N-[[S]-(2-methoxymethyl)pyrrolidin-1-yl]-2-methylenepropan-1-imine ([R,R]-5a)

According to GP1, the alkylation of the SAMP-hydrazone (S)-4a (2.56 g, 15 mmol) gave (R,S)-5a after chromatography (n-pentane-EtOAc, 6:1); yield: 3.31 g (73%); colorless oil; de ≥ 96% (13C NMR); [α]D20 = −86.1 (c = 1.09, CHCl3); Rf 0.34 (n-pentane-EtOAc, 4:1).

IR (film): 2954 (s), 2874 (s), 1602 (m), 1457 (m), 1410 (w), 1353 (m), 1248 (s), 1197 (m), 1104 (s), 840 (m), 757 (m), 694 (m), 609 (w), 556 (w) cm⁻¹.

1H NMR (300 MHz, CDCl3): δ = 0.01 [s, 9 H, Si(CH3)3], 0.92 (t, J = 8.0 Hz, 2 H, CH2Si), 1.06 (d, J = 6.9 Hz, 3 H, CH3), 1.74–2.00 (m, 4 H, NCH2CH2CH2), 2.62 (m, 1 H, N=CHCH2), 2.71 (q, J = 8.4 Hz, 1 H, NCH2), 3.37 (s, 3 H, OCH3), 3.29–3.61 (m, 8 H, CH2OCH2CH2), 5.66 (d, J = 5.7 Hz, 1 H, N=CH).

13C NMR (75 MHz, CDCl3): δ = 14.9 (CH3), 19.1 (CH2Si), 23.1 (NCH2CH2), 27.6 (NCH2CH2), 38.5 (N=CHCH2), 51.0 (NCH2), 60.1 (OCH3), 64.3 (NCH), 69.0 (OCH2CH2), 75.2, 75.7 (N=CHCH2CH2), 140.2 (N=CH).

MS (EI, 70 eV): m/z (%) = 301 (11) [M]+, 255 (100), 183 (1), 169 (6), 139 (4), 73 (23), 70 (9).

Anal. Calc. for C16H34N2O2Si (314.54): C, 61.10; H, 10.90; N, 8.91.

Found: C, 61.25; H, 10.91; N, 9.16.

(E,2R)-2-[[2-(Trimethylsilyl)ethoxy]methyl]-N-[[S]-(2-methoxymethyl)pyrrolidin-1-yl]-3-methylenbutan-1-imine ([R,S]-5c)

According to GP1, the alkylation of the SAMP-hydrazone (S)-4c (1.98 g, 10 mmol) gave (R,S)-5c after chromatography (n-hexane-EtOAc, 30:1); yield: 2.16 g (66%); colorless oil; de ≥ 96% (13C NMR); [α]D20 = −83.0 (c = 1.04, CHCl3); Rf 0.79 (n-hexane-EtOAc, 1:1).

IR (film): 2955 (s), 2873 (s), 1601 (m), 1463 (m), 1357 (m), 1249 (m), 1198 (s), 1106 (s), 969 (m), 841 (s), 759 (m), 695 (m) cm⁻¹.

1H NMR (300 MHz, CDCl3): δ = 0.00 [s, 9 H, Si(CH3)3], 0.89 (d, J = 6.7 Hz, 3 H, CH3), 0.90 (t, J = 8.0 Hz, 2 H, CH2Si), 0.95 (d, J = 6.9 Hz, 3 H, CH3), 1.73–2.00 (m, 3 H, NCH2CH2CH2, CH2CH2), 2.28 (q, J = 6.4 Hz, 1 H, N=CHCH2), 2.75 (m, 1 H, NCH2), 3.36 (s, 3 H, OCH3), 3.29–3.60 (m, 8 H, CH2OCH2CH2), 5.67 (d, J = 7.2 Hz, 1 H, N=CH).

13C NMR (75 MHz, CDCl3): δ = −1.3 (SiCH3), 18.1 (CH3), 20.6 (CH2CH2), 22.1 (NCH2CH2), 24.3 (CH3CH2), 26.6 (NCH2CH2), 44.5 (N=CHCH2), 50.2 (NCH2), 59.2 (OCH3), 63.4 (NCH), 68.1 (OCH2CH2), 72.5 (N=CHCH2OCH3), 74.7 (OCH2CH2), 140.2 (N=CH).

MS (EL, 70 eV): m/z (%) = 314 (3) [M]+, 269 (100), 183 (5), 73 (26), 70 (12).

Anal. Calc. for C16H34N2O2Si (314.54): C, 61.10; H, 10.90; N, 8.91.

Found: C, 61.25; H, 10.91; N, 9.16.

(E,2R)-2-[[2-(Trimethylsilyl)ethoxy]methyl]-N-[[S]-(2-methoxymethyl)pyrrolidin-1-yl]-hexan-1-imine ([R,S]-5d)

According to GP1, the alkylation of the SAMP-hydrazone (S)-4d (3.19 g, 15 mmol) gave (R,S)-5d after chromatography (n-pentane-EtOAc, 20:1) yield: 3.95 g (77%); colorless oil; de ≥ 96% (13C NMR); [α]D20 = −82.2 (c = 1.39, CHCl3); Rf 0.53 (n-pentane-EtOAc, 4:1).

IR (film): 2953 (s), 2857 (s), 1602 (m), 1461 (m), 1353 (m), 1303 (w), 1248 (s), 1197 (m), 1108 (s), 1022 (w), 972 (m), 839 (s), 756 (m), 695 (m), 666 (w), 613 (w), 535 (w) cm⁻¹.

1H NMR (400 MHz, CDCl3): δ = 0.01 [s, 9 H, Si(CH3)3], 0.89 (t, J = 6.6 Hz, 3 H, CH3), 0.92 (t, J = 8.1 Hz, 2 H, CH2Si), 1.24–1.47 (m, 5 H, CH2CH2CH2), 1.53 (m, 1 H, CH2CH2CH2), 1.78–1.99 (m, 4 H, NCH2CH2CH2), 2.73 (q, J = 8.2 Hz, 1 H, NCH2), 3.37 (s, 3 H, OCH3), 3.30–3.60 (m, 8 H, CH2OCH2CH2, NCH2CH2OCH3), 6.51 (d, J = 6.6 Hz, 1 H, N=CH).

13C NMR (100 MHz, CDCl3): δ = −0.3 (SiCH3), 15.1 (CH3), 19.1 (CH2Si), 23.1 (NCH2CH2), 24.3 (CH3CH2), 27.5 (NCH2CH2).

Synthesis of the N-O-Protected 1,3-Amino Alcohols 7; General Procedure (GP2)

CeCl₃·7H₂O (4.0 equiv) was dehydrated for 2.5 h at 140 °C under reduced pressure (0.1 torr) and suspended in anhyd THF (17 mL/mmol) by sonification for 15 min and additional stirring for 12 h. The suspension was cooled to –78 °C and phenyllithium (4.0 equiv) was added. The mixture was refluxed for 4 h, cooled to –5 °C and hydrolyzed by addition of an aq 2 M HCl solution (10 mL/mmol). After heating the reaction mixture was then rinsed through a pad of silica gel with Et₂O. The aqueous phase was extracted with CH₂Cl₂ (3 ×), dried over Na₂SO₄ and filtered through a pad of silica gel. After removal of the solvent in vacuo, the crude hydrazones 5 were obtained.

N-N Cleavage was then performed by dissolving the product in CH₂Cl₂ (10 mL/mol), and Et₂O, 5:1. The mixture was refluxed for 4 h, cooled to –5 °C and hydrolyzed by addition of an aq 2 M HCl solution (10 mL/mmol). After heating at reflux for 2 h the mixture was removed under reduced pressure and the aqueous residue was neutralized with a sat. NaHCO₃ solution. The aqueous phase was extracted with CH₂Cl₂ (3 ×). Drying of the organic phase over Na₂SO₄ and removal of the solvent gave the crude amines, which were tosylated without further purification.

The pure tosylated amino alcohols 7 were obtained upon flash column chromatography; ee ≥ 98% (GC, CP-Sil-8, 160-10-100, 60 °C).

(1R,2S)-3-[2-(Trimethylsilyl)ethoxy]-2-methyl-1-phenyl-N-tosylpropan-1-amine ([R,S]-7a)

According to GP2 the hydrazone (R,S)-5a (1.40 g, 4.7 mmol) was converted into (R,S)-7a and purified by column chromatography (pentane–Et₂O, 5:1 → 4:1); yield: 992 mg (58% over 3 steps); colorless solid; de ≥ 95% (GC, CP-Sil-8, 160-10-100, ≥ 99% after chromatography); ee ≥ 99% (HPLC: Daicel AS, n-heptane–i-PrOH, 9:1); [α]D₂⁺ = 57.2 (c = 1.01, CHCl₃).

All other analytical data corresponded to those of (S,R)-7a.


According to GP2 the hydrazone (R,S)-5b (0.56 g, 1.78 mmol) was converted into (R,S)-7b and purified by column chromatography (pentane–Et₂O, 10:1 → 4:1); yield: 0.47 g (61% over 3 steps); colorless oil; de ≥ 96% (¹H NMR); mp 71 °C; [α]D₂⁺ = 49.2 (c = 1.17, CHCl₃); Rf = 0.76 (pentane–Et₂O, 1:1).

IR (KBr): 3298 (m), 3062 (w), 30 30 (m), 2956 (s), 2876 (s), 1600 (m), 1532 (m), 1436 (s), 1329 (m), 1249 (m), 1161 (s), 1096 (s), 1026 (m), 915 (m), 839 (m), 763 (m), 702 (s), 669 (s), 552 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 0.05 [s, 9 H, Si(CH₃)₃], 0.81 (t, J = 7.4 Hz, 3 H, CH₃), 1.21–1.52 (m, 5 H, CH₂CH₃), 1.50 (m, 2 H, CH₂CH₂), 1.65 (m, 2 H, CH₂CH₂), 2.13 (s, 3 H, CH₃). Rf = 0.22 (pentane–Et₂O, 2:1).

IR (KBr): 3274 (s), 3062 (w), 30 30 (m), 2956 (s), 2876 (s), 1600 (m), 1498 (m), 1442 (m), 1319 (s), 1250 (m), 1161 (s), 1097 (s), 1040 (m), 992 (w), 962 (m), 920 (m), 836 (s), 763 (m), 708 (s), 676 (s), 592 (s), 569 (s), 543 (m), 487 cm⁻¹.

¹C NMR (100 MHz, CDCl₃): δ = 0.3 [s, 9 H, Si(CH₃)₃], 11.6 (s, CH₃), 22.5 (C₂H₅), 22.6 (C₂H₅), 40.1 (NCH₃), 64.2 (NCH₃), 69.8 (OCH₂CH₂), 74.5 (CH₂OH), 127.9, 127.9, 128.1, 128.9, 129.9 (ArCH), 138.9, 141.5 (ArCH₂SO₂, ArCH), 143.3 (ArCH₃).

IR (film): 3293 (m), 3062 (w), 3030 (s), 2956 (s), 2876 (s), 1600 (m), 1494 (m), 1455 (m), 1419 (s), 1249 (m), 1161 (s), 1095 (s), 1028 (m), 939 (m), 839 (s), 755 (s), 700 (s), 664 (s), 549 cm⁻¹.

Anal. Calcd for C₂₆H₃₃NO₂SSi (419.65): C, 62.97; H, 7.93; N, 3.34. Found: C, 63.32; H, 7.59; N, 3.45.

(1R,2S)-3-[2-(Trimethylsilyl)ethoxy]-2-methyl-1-phenyl-N-tosylpropan-1-amine ([R,S]-7a)

According to GP2 the hydrazone (R,S)-5a (1.40 g, 4.7 mmol) was converted into (R,S)-7a and purified by column chromatography (pentane–Et₂O, 5:1 → 4:1); yield: 992 mg (58% over 3 steps); colorless solid; de ≥ 95% (GC, CP-Sil-8, 160-10-100, ≥ 99% after chromatography); ee ≥ 99% (HPLC: Daicel AS, n-heptane–i-PrOH, 9:1); [α]D₂⁺ = 57.2 (c = 1.01, CHCl₃).

All other analytical data corresponded to those of (S,R)-7a.


According to GP2 the hydrazone (R,S)-5b (0.56 g, 1.78 mmol) was converted into (R,S)-7b and purified by column chromatography (pentane–Et₂O, 10:1 → 4:1); yield: 476 mg (61% over 3 steps); colorless solid; de ≥ 96% (¹H NMR); mp 71 °C; [α]D₂⁺ = 49.2 (c = 1.17, CHCl₃); Rf = 0.76 (pentane–Et₂O, 1:1).

IR (KBr): 3298 (s), 3062 (w), 3031 (w), 2956 (s), 2877 (m), 1600 (m), 1493 (m), 1456 (m), 1420 (m), 1292 (m), 1249 (m), 1161 (s), 1096 (s), 1026 (m), 936 (m), 815 (m), 763 (m), 702 (s), 669 (s), 552 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 0.05 [s, 9 H, Si(CH₃)₃], 0.81 (t, J = 7.4 Hz, 3 H, CH₃), 0.91–1.07 (m, 2 H, CH₂Si), 1.34 (m, 2 H, CH₂CH₃), 1.60 (m, 1 H, NCH₂CH₂), 2.33 (s, 3 H, CH₃), 3.22 (dd, J = 4.7, 9.6 Hz, 1 H, CH₂CH₂), 3.31 (dd, J = 2.5, 9.6 Hz, 1 H, CH₂CH₂), 3.43 (m, 2 H, OCH₂CH₂), 4.46 (t, J = 6.1 Hz, 1 H, PhCH₂CH₂), 6.63 (d, J = 6.1 Hz, 1 H, NH), 7.07–7.19 (m, 7 H, CH₃arom.), 7.51 (d, J = 8.2 Hz, 2 H, SO₂CH₂CH₃).
Asymmetric Synthesis of Substituted Azetidine Amino Acids

PAPER

O-Deprotection of 7 and Cyclization to the Phenyl Azetidines 9; General Procedure (GP3)

The amino alcohols 7 (1 equiv) were dissolved in MeCN–H2O mixture (98:2, 20 mL/mmol) and LiBF4 (5 equiv) was added. The mixture was heated at reflux until complete conversion of the starting material was observed by TLC (22–72 h). The reaction mixture was worked up (pH 7 buffer, CH2Cl2, Na2SO4) and the solvent was evaporated, yielding the crude deprotected amino alcohols 8 as colorless solids.

Compound 8 and PPh3 (1.5 equiv) were then dissolved in anhyd THF (25 mL/mmol 8). Diisopropyl azodicarboxylate (DIAD, 1.5 equiv) was slowly added and the mixture was stirred for up to 24 h. After complete conversion of the starting material the reaction mixture was rinsed through a pad of silica gel with Et2O, evaporated and finally purified by flash column chromatography.

(2S,3S)-3-Methyl-2-phenyl-1-tosylazetidine ([S,S]-9a)

According to GP3 the azetidine ([S,S]-9a) was prepared from ([S,S]-7a (1.22 g, 2.9 mmol) and piperazine (1 equiv–Et2O, 6:1); yield: 753 mg (86% over 2 steps); colorless solid; de ≥ 96% ([H NMR]; ee ≥ 97% (HPLC, Daicel OD, n-heptane–i-PrOH, 4:1); mp 107 °C; [α]D23 = –92.5 (c = 0.2, CHCl3); Rf 0.53 (n-pentane–Et2O, 2:1).

IR (KBr): 3062 (m), 2953 (m), 1993 (s), 1808 (w), 1742 (s), 1656 (s), 1612 (s), 1573 (s), 1550 (s), 1392 (s), 1341 (s), 1319 (s), 1248 (s), 1204 (s), 1140 (m), 1091 (m), 1062 (s), 1024 (s), 931 (m), 912 (s), 810 (s), 742 (m), 702 (m), 664 (s), 595 (s), 547 (s), 494 (m) cm–1.

1H NMR (400 MHz, CDCl3): δ = 0.86 (d, J = 6.6 Hz, 3 H, CH2CH3), 2.43 (s, 3 H, CH3), 2.47 (m, 1 H, NCHCH), 3.33 (t, J = 7.6 Hz, 1 H, NCH2), 3.91 (t, J = 7.6 Hz, 1 H, NCH2), 4.34 (d, J = 7.4 Hz, 1 H, NCH), 7.24–7.39 (m, 7 H, CHarom), 7.68 (d, J = 8.2 Hz, 2 H, CHarom–SO2).

13C NMR (100 MHz, CDCl3): δ = 17.6 (CH2CH3), 21.5 (C3H3), 35.0 (NCHCH), 54.5 (NCH), 73.1 (NCH), 125.9, 127.8, 128.2, 128.3, 129.4 (ArCH), 131.9 (ArC=O), 139.7 (ArC=O), 143.7 (ArC=O).

MS (EI, 70 eV): m/z (%) = 301 (8) [M]+, 290 (9), 260 (5), 195 (4), 155 (71), 146 (100), 118 (52), 104 (16), 91 (61), 77 (6), 65 (7).

Anal. Calcd for C19H18NO2S (315.13): C, 68.54; H, 6.71; N, 4.44.

Found: C, 68.52; H, 6.52; N, 4.21.

(2S,3S)-3-Isopropyl-2-phenyl-1-tosylazetidine ([S,S]-9c)

According to GP3 the azetidine ([S,S]-9c) was prepared from ([S,S]-7e (0.97 g, 2.2 mmol) and piperazine by column chromatography (n-pentane–Et2O, 6:1); yield: 616 mg (86% over 2 steps); colorless solid; de ≥ 96% ([H NMR]; mp 78 °C; [α]D23 = –209.2 (c = 0.78, CHCl3); Rf 0.27 (n-pentane–Et2O, 4:1).

IR (KBr): 3062 (m), 2953 (m), 2898 (m), 1998 (s), 1802 (w), 1598 (m), 1494 (m), 1464 (m), 1392 (w), 1343 (s), 1300 (m), 1246 (w), 1164 (s), 1094 (m), 1049 (m), 1019 (m), 988 (m), 914 (s), 824 (m), 806 (m), 780 (m), 736 (m), 696 (m), 665 (s), 601 (s), 552 (s), 508 (m) cm–1.

1H NMR (300 MHz, CDCl3): δ = 0.69 [d, J = 6.7 Hz, 6 H, CH(CH3)2], 1.45 [m, 3 H, CH2CH3], 2.17 [m, 1 H, NCHCH], 2.43 (s, 3 H, CH3), 3.41 (d, J = 7.8 Hz, 1 H, NCH2), 3.86 (d, J = 7.8 Hz, 1 H, NCH), 4.49 (d, J = 7.2 Hz, 1 H, NCH), 7.24–7.35 (m, 5 H, CHarom), 7.41 (d, J = 7.9 Hz, 2 H, CHarom–SO2).

13C NMR (75 MHz, CDCl3); δ = 19.2, 19.4 [CH(CH3)2], 21.6 (C(CH3)2), 32.1 [CH(CH3)2], 46.7 (NCH-CH), 51.6 (NCH), 70.7 (NCH), 126.9, 128.0, 128.3, 128.4, 129.5 (ArCH), 132.6 (ArC=O), 140.4 (ArC=O), 143.8 (ArC=O).

MS (EL, 70 eV); m/z (δ) = 329 (7) [M+], 260 (29), 195 (3), 174 (100), 155 (70), 131 (25), 118 (8), 104 (12), 91 (52), 77 (3), 65 (5).


C9H12N2O3 was isolated by silica gel chromatography (n-pentane-CH2Cl2, 10:1). Yield: 96 mg (13C NMR); m.p. 128 °C (decomp.).

(2S,3S)-3-Butyl-2-phenyl-1-tosylazetidine ([S,S]-9d)
According to GP3 the azetidine ([S,S]-9d) was prepared from (S,R)-7d (1.39 g, 3.0 mmol) and purified by column chromatography (n-pentane-CH2Cl2, 10:1). Yield: 974 mg (94% over 2 steps); colorless oil; δ = 96% (13C NMR); δ = 1.21, CHCl3).

MS (EL, 70 eV); m/z (δ) = 116 (20) [M + 1]%, 115 (20) [M]+, 87 (20), 74 (12), 70 (100), 56 (12).

HRMS (EI); m/z [M]+ calcd for C19H23NO2S: 329.1364; found: 329.1363.

1H NMR (300 MHz, CDCl3); δ = 0.78 (t, J = 7.1 Hz, 4 H, CH2CH2), 1.04–1.43 (m, 6 H, CH2CH2CH2CH3), 2.38 (m, 18 H, NCH2), 2.42 (s, 3 H, C(CH3)3), 3.36 (t, J = 7.7 Hz, 1 H, NCH2), 3.89 (t, J = 7.7 Hz, 2 H, NCH2), 4.43 (d, J = 7.2 Hz, 2 H, NCH), 7.24–7.41 (m, 7 H, CHaryl), 7.67 (d, J = 8.2 Hz, 2 H, CHaryl, COSO2).

(1S,3S)-3,3-Dimethylazetidine-2-carboxylic Acid ([S,S]-10a)
According to GP4 the phenylazetidine ([S,S]-9a) (202 mg, 0.89 mmol) was converted into amino acid ([S,S]-10a); yield: 69 mg (51% over 2 steps); colorless solid; δ = 96% (13C NMR); δ = 0.23, H2O).

IR (KBr); 1550 cm–1.

HRMS (EI); m/z [M]+ calcd for C17H21NO2: 257.1518; found: 257.1513.

1H NMR (300 MHz, CDCl3); δ = 0.78 (t, J = 7.4 Hz, 3 H, CH3), 1.59 (m, 2 H, CH2CH2), 2.41 (m, 1 H, NCH), 3.60 (dd, J = 9.7, 10.4 Hz, 1 H, NCH2), 3.85 (dd, J = 8.9, 10.4 Hz, 1 H, NCH2), 4.26 (d, J = 7.7 Hz, 1 H, NCH).

13C NMR (75 MHz, CDCl3); δ = 13.8 [CH3CH2CH(CH3)2], 21.6 (C(CH3)2), 22.4, 28.6, 32.7 [CH3CH2CH(CH3)2], 39.9 (NCH), 53.3 (NCH), 71.8 (NCH), 126.4, 127.9, 128.4, 129.4, 129.5 (ArCH), 132.4 (ArC=O), 140.2 (ArC=O), 143.9 (ArC=O).

Synthesis of Azetidine Carboxylic Acids; General Procedure (GP4)
The tosylazetidines 9 and 12 (1 equiv) were dissolved in a mixture consisting of ClC2 (2 mL/mmol), MeCN (2 mL/mmol) and water (3 mL/mmol). H2O2 (15 equiv) and RuCl3-hydrate (0.05 equiv) were added to the vigorously stirred mixture and the reaction vessel was left open to the atmosphere. Whenever the orange color of the solution turned to black, additional small portions of H2O2 were added until complete conversion of the starting material was detected by TLC (24–72 h). The reaction mixture was diluted with Et2O and stirred for an additional 30 min. Water was added and the mixture was extracted with Et2O (3 ×), dried over MgSO4, filtered and concentrated in vacuo.

Sodium metal (6 equiv) and naphthalene (6 equiv) were dissolved in DME (20 mL/mmol azetidine) and stirred at 0 °C for 1 h and afterwards at r.t. for 1.5 h. A solution of the azetidine dissolved in a small amount of DME was then slowly added at −78 °C and the mixture was stirred for 30 min at this temperature. The reaction was stopped by addition of aq 2 M HCl solution. The aqueous phase was separated and the organic phase was extracted with 2 M HCl (3 ×). The combined aqueous phases were concentrated to a small volume at temperatures below 45 °C under high vacuum. The acidi solution of the amino acids was then submitted to ion exchange chromatography with Dowex 50X2-200 resin. The amino acids were isolated as colorless solids, which turned slightly yellow on storing at r.t.
(2S,3S)-3-Butylazetidine-2-carboxylic Acid [(2S,3S)-10d]
According to GP4 the phenylazetidine (2S,3S)-9d (384 mg, 1.1 mmol) was converted into amino acid (2S,3S)-10d; yield: 112 mg (54% over 2 steps); colorless solid; de ≥ 96% (1⁰C NMR); mp 178–181 °C (decomp.); [α]D 173.1 +14.0 (c = 0.16, H2O).

IR (KBr): 2957 (m), 2929 (m), 2854 (m), 1625 (s), 1462 (m), 1402 (m, 100), 98 (16), 74 (14), 70 (13), 56 (22).

1H NMR (300 MHz, D2O): δ = 0.68 (t, J = 6.6 Hz, 3 H, CH3), 1.10 (m, 4 H, CH2CH2CH2CH3), 1.52 (m, 2 H, CH2CH2CH2CH3), 2.64 (m, 1 H, NCHCH), 3.52 (dd, J = 8.2, 10.4 Hz, 1 H, NCH2), 3.79 (dd, J = 8.8, 10.4 Hz, 1 H, NCH2), 4.20 (d, J = 7.7 Hz, 1 H, NCH).

13C NMR (75 MHz, D2O): δ = 12.5 (CH2), 21.0, 27.1, 31.9 (CH2CH2CH3), 36.9 (NCHCH), 47.5 (NCH2), 64.0 (NCH), 173.1 (COOH).

HRMS (El): m/z: [M+] calcd for C14H15NO2: 231.1103; found: 158 (13) [M + 1 +], 157 (5) [M +], 112 (100), 98 (16), 74 (14), 70 (13), 56 (22).

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