Synthesis of 1,3-Diene-Containing alpha-Amino Acids and Peptides via N-Acyliminium Ions
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Chapter 5

Synthesis of 2-substituted piperazines via direct $\alpha$-lithiation$^\dagger$

5.1 Introduction

Piperazines are an often recurring motif in compounds displaying biological activity.$^{1,2}$ Whereas most of the pharmaceutically relevant piperazines only bear substituents at nitrogen, piperazines substituted in the carbon skeleton have also been reported such as farnesyl transferase inhibitor$^3$ L-745631 and neurokinin-1 (NK-1) antagonist FK-355$^4$ (Figure 5.1). For a discovery program towards NK-1 antagonists at Solvay Pharmaceuticals a set of structurally diverse 2-substituted piperazines was required. The most common way to synthesize 2-substituted piperazines is by reduction of the corresponding 2-substituted diketopiperazines. Diketopiperazines$^5,6$ in turn, can be obtained from suitable protected $\alpha$-amino acids (Scheme 5.1).

![Figure 5.1](image_url)

To avoid this and other lengthy syntheses$^7$ we looked for an alternative route, preferably one that was based on a common intermediate. In particular the work of Beak and Lee,$^8$ Dieter et al.$^9$ and others,$^{10-17}$ who reported the $\alpha$-lithiation of acyclic and cyclic $N$-Boc-functionalized amines, followed by trapping with several electrophiles, attracted our attention. Although this strategy has been thoroughly investigated starting from $N$-Boc-pyrrolidine,$^{18,19}$ $N$-Boc-piperidine$^{20}$ and $N$-Boc-hexahydropyrimidine,$^{21}$ to our surprise and to the best of our knowledge, no syntheses of 2-functionalised $N$-Boc-piperazines using the direct $\alpha$-lithiation method have been reported in the literature so far, except for an example in a recent patent to Solvay Pharmaceuticals.$^{22}$

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Functionalization at the 2 position of nitrogen heterocycles is greatly enhanced by the presence of a directed ortho metallating group\(^{23}\) (DOM-group) such as \(N\)-Boc, \(N\)-pivaloyl or \(N\)-benzenesulfonyl. After deprotonation of e.g. \(N\)-Boc-piperidine 1 (Scheme 5.2) the intermediate lithium salt 2 is stabilized by the carbonyl group. Because of resonance stabilization of the Boc-group the carbanion will be formed only at the equatorial position. Therefore, substitution of this class of compounds via the direct \(\alpha\)-lithiation method will only result in equatorially substituted products 3. After some initial test experiments the Boc group proved to be the best DOM-group for the \(\alpha\)-lithiation of piperazines.

In this chapter we disclose the successful synthesis of 2-functionalised piperazines via \(\alpha\)-lithiation of \(N\)-Boc-piperazines followed by trapping with a selected set of electrophiles.

5.2 Synthesis of 2-substituted piperazines

Starting from \(N\)-Boc-\(N'\)-benzylpiperazine 4, which can be easily made in large quantities from commercially available \(N\)-benzylpiperazine and di-\textit{tert}-butyl dicarbonate,\(^{24,25}\) several parameters were screened to find the optimal \(\alpha\)-lithiation conditions. For these initial experiments trimethylsilyl chloride was chosen as the electrophile (entry 1, Table 5.1) while the solvent, lithium base plus complexing additive and reaction temperature were evaluated. The best results were obtained using sec-BuLi/TMEDA (2.4 equiv) as the lithiation agents and ether as solvent at -78 °C. Using these conditions, 2-trimethylsilyl \(N\)-Boc-\(N'\)-benzylpiperazine 6 was isolated in a yield of 68% (entry 1A, Table 5.1). With these optimized conditions in hand several other electrophiles were screened. Although 2-tris-\textit{n}-butylstannylpiperazine 7 was isolated in a satisfactory 74% yield (entry 2A, Table 5.1), 2-allylpiperazine 8 and 2-naphthylpiperazine 9 were only obtained in a moderate 27% and 31% yield, respectively (entries 3A and 4A). The piperazines 10 and 11, bearing benzyl and \(n\)-butyl groups at the 2-position, were formed in trace amounts only (entries 5A and 6A).
Table 5.1

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>E</th>
<th>product</th>
<th>A yield (%)</th>
<th>B yield (%)</th>
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<tr>
<td>1</td>
<td>Bn</td>
<td>TMS</td>
<td>6</td>
<td>68</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>Bn</td>
<td>(n-Bu)_3Sn</td>
<td>7</td>
<td>74</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>Bn</td>
<td>allyl</td>
<td>8</td>
<td>27</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>Bn</td>
<td>Naph</td>
<td>9</td>
<td>31</td>
<td>72</td>
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<tr>
<td>5</td>
<td>Bn</td>
<td>Bn</td>
<td>10</td>
<td>trace</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>Bn</td>
<td>n-Bu</td>
<td>11</td>
<td>trace</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>Me</td>
<td>TMS</td>
<td>13</td>
<td>5</td>
<td>22(^a)</td>
</tr>
<tr>
<td>8</td>
<td>Me</td>
<td>(n-Bu)_3Sn</td>
<td>14</td>
<td>82</td>
<td>trace</td>
</tr>
<tr>
<td>9</td>
<td>Me</td>
<td>allyl</td>
<td>15</td>
<td>51</td>
<td>95</td>
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<td>Me</td>
<td>Bn</td>
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<td>60</td>
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<tr>
<td>11</td>
<td>Me</td>
<td>n-Bu</td>
<td>17</td>
<td>trace</td>
<td>72</td>
</tr>
</tbody>
</table>

\(^a\) 2,3-didehydro-N-Boc-N'-methyl piperazine 18 was isolated in 3.2% yield

A remarkable difference was found starting from the analogous N-Boc-N'-methylpiperazine 12\(^{25,26}\) with trimethylsilyl chloride as electrophile (entry 7A). Whereas the N'-benzyl analogue 4 gave 6 in 68% yield (entry 1A), the N'-methyl analogue 13 was obtained in a disappointing 5% yield for which we do not have an explanation yet. The yields obtained for compounds 14, 15, 16 and 17 (entries 8A–11A) were analogous to the results obtained for the lithiation of compound 4. It is clear that allylic or benzylic carbon electrophiles and those which contain a long aliphatic chain (n-butyl bromide) in particular fail to give satisfactory yields (entries 3A–6A and 9A–11A, Table 5.1).\(^{27}\) In some cases 3,4-dihydro-N-Boc-N'-methylpirazine 18\(^{28}\) and/or 2,2'-bipiperazine dimer 19 (Figure 5.2) could be isolated together with the desired compound.\(^{29}\)

![Figure 5.2](image-url)
Compound 18 was formed in particular when TMS-Cl was used as the electrophile. The mechanism of formation of these interesting byproducts has yet to be disclosed. However, the formation of the dimer 19 suggests a radical mechanism, which is supported by the recent findings of Gawley and co-workers.\textsuperscript{30}

During our investigation it was reported that the lithium/copper exchange strategy developed by Knochel and co-workers,\textsuperscript{31,32} was beneficial for the α-alkylation of cyclic aliphatic amines.\textsuperscript{9,33-36} Application of this methodology, i.e. transmetallation to a copper species by adding the CuCN·2LiCl complex before introduction of the electrophile, had a positive effect indeed and the allyl, naphthyl, benzyl and n-butyl groups could now be introduced at the 2-position in $N$-Boc-$N'$-benzylpiperazine 4 in isolated yields of 76%, 72%, 54% and 85%, respectively (entries 3B–6B, Table 5.1). Similar yields were obtained starting from $N$-Boc-$N'$-methylpiperazine 12 (entries 9B–11B). On the other hand, introduction of a tributylstannyl group (entries 2B and 8B), after transmetallation to the copper species, failed. By using trimethylsilyl chloride as the electrophile in combination with transmetallation $N$-Boc-$N'$-benzylpiperazine 4 gave 6 in a lower yield (14% vs. 68%, entries 1A and 1B) whereas $N$-Boc-$N'$-methylpiperazine 4 provided 13 in a slightly better yield (22% vs. 5%, entries 7A and B).

![Scheme 5.3](image)

**Scheme 5.3**

With two reliable methods available, two other sterically more demanding carbon-electrophiles were studied. We were delighted to see that addition of both 3-bromo-2-methylprop-1-ene and 2,3-dibromoprop-1-ene to the piperazine copper species gave the corresponding 2-substituted piperazines 20 and 21 in 70% and 69% yield, respectively (Scheme 5.3). Especially compound 21 provides useful handles for further derivatisation. Attempts to substitute the lithium salt of 12 for a boronate using trimethoxy-, triethoxy- or triisopropoxyborane were unsuccessful.\textsuperscript{37} The use of 1,2-dibromoethane as electrophile on both the lithium salt and the copper species of 12 did not give the desired 2-bromopiperazine derivative either.

### 5.3 Disubstitution of piperazines

Next, we wanted to extend this methodology to the 2,6-disubstituted piperazine series. To our surprise, after a 25-fold scale-up (2.5 g) of the synthesis of 8 in 71% yield, the bis-allyl
product 22 was also isolated in 15% yield (Scheme 5.4). This byproduct was only observed in trace amounts in the small scale (0.1 g) synthesis of 8 (Table 5.1). Although all reactions listed in Table 5.1 were carried out with an excess of sec-BuLi and electrophile (both 2.4 equiv), double substitution at both the 2 and the 6 positions had never been observed. Apparently, due to the excess sec-BuLi in the reaction mixture, a second proton abstraction of 8 did not occur at the 6-position on the piperazine-skeleton but on the ortho position of the phenyl substituent leading to compound 22. Most likely, the α-protons and the phenyl ortho protons have a similar acidity. Then, due to the steric repulsions introduced by the first allyl group, the second substitution takes place at the less hindered phenyl substituent. When bis-allyl compound 22 was subjected to Grubbs’ second generation ring closing metathesis (RCM) catalyst in toluene, the desired ring closed product 23 was obtained in 43% isolated yield.

Scheme 5.4

Gratifyingly, after lithiation of 2-allyl-N-Boc-N’-methylpiperazine 15 at the 6-position followed by transmetallation to the organocuprate and addition of allyl bromide, 2,6-diallyl-N-Boc-N’-methylpiperazine 24 was isolated in an excellent yield of 93% (Scheme 5.5). Unfortunately, subjection of 24 to ring closing metathesis conditions (5% Grubbs’ II, CH₂Cl₂, reflux), did not lead to the formation of the bicyclic product 26 (Scheme 5.5), neither did bishomoallyl derivative 25 (n = 3). The desired bridged piperazines are a recurring motif in medicinal chemistry. A new entry into this class of compounds would be a valuable addition to the toolbox of organic chemistry.

Scheme 5.5
A successful synthesis of cis-substituted bis-allyl N-heterocycles (29, Scheme 5.6) has been reported to start with the reduction of an allyl substituted lactam to the hydroxy lactam 28. Introduction of the second allyl group via a N-acyliminium ion addition\(^{41}\) to form cis-bis-allyl product 29 occurred in a cis/trans ratio of 24:1 for the piperidine series (\(n = 2\)).\(^{42,43}\) This method is less successful for the pyrrolidines (\(n = 1\)),\(^{44}\) but other more selective procedures have been developed.\(^{45,46}\) Both the bisallyl piperidines and pyrrolidines can be successfully converted into their corresponding bridged azabicyclic structures 30.\(^{42,45,47}\)

Because subjection of both 24 and 25 to RCM conditions did not lead to the desired bridged products, we thought to have the allyl groups in a trans-orientation.\(^{48}\) To verify this hypothesis, a solid derivative of 24 was required in order to obtain crystals for X-ray analysis. Therefore, the methyl group was removed (32, Scheme 5.7) in a two step process using ACE-Cl and methanol\(^{49}\) and a second Boc group was installed to give 33 in 79% over 3 steps.

To our delight 33 was isolated as a solid and after recrystallization from pentane, crystals were obtained suitable for X-ray determination. The X-ray structure, shown in Figure 5.3, clearly shows a trans configuration of the allyl substituents. A thorough literature screening revealed a paper by Beak and coworkers in which an explanation is given for the trans addition of the second electrophile.\(^{20}\) During formation of the equatorially positioned Li-chelate 36 (Scheme 5.8) the allyl substituent is forced to the axial position (34 \(\rightarrow\) 35) to avoid steric interactions with the bulky Boc tert-butyl moiety. Addition of the second electrophile then results in the trans product 37.
5.4 Conclusion

A novel synthetic approach has been developed to access pharmaceutically important 2-substituted piperazines via direct α-lithiation of N-Boc piperazines then followed by a lithiation/copper transmetallation reaction. These 2-substituted piperazines may be elaborated further to give trans-2,6-disubstituted products via a subsequent lithiation/transmetallation/electrophile introduction for the N-Boc-N'-methylpiperazine series. Remarkably, a second lithiation/transmetallation/allyl bromide introduction in the N-Boc-N'-benzylpiperazine series results in substitution at the benzyl group. This bis-allyl product successfully undergoes ring closure metathesis to an interesting and previously undescribed tricyclic product.

5.5 Acknowledgements

C. Sewing, L. van der Sluis, D. J. den Boer and F. Tavoni are gratefully acknowledged for their dedicated contributions to this chapter. A. van den Hoogenband, dr. J. W. Terpstra, dr. W. I. Iwema Bakker and dr. J. A. J. den Hartog (Solvay Pharmaceuticals, Weesp) are thanked for fruitful and stimulating discussions. Dr. R. de Gelder (Radboud Universiteit Nijmegen) is acknowledged for the determination of the X-ray structure of 33.
5.6 Experimental Section

General remarks

For general remarks see Chapter 2.

**tert-Butyl 4-benzylpiperazine-1-carboxylate (4).** A solution of 1-benzylpiperazine (4.40 g, 25.0 mmol) and di-tert-butyl dicarbonate (6.24 g, 28.4 mmol) in THF (60 mL) was stirred at room temperature for 1 h, after which all volatiles were removed in vacuo. The crude product was dissolved in EtOAc, washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. After column chromatography (PE/EtOAc 2:1) 4 was obtained as a white solid (6.81 g, 24.6 mmol, 99%). 1H-NMR (400 MHz, CDCl₃): δ = 7.10 (m, 5H), 3.51 (s, 2H), 3.42 (m, 4H), 2.38 (m, 4H), 1.45 (s, 9H) ppm; 13C-NMR (100 MHz, CDCl₃): δ = 156.12, 135.83, 129.01, 128.02, 127.33, 79.82, 62.87, 55.50, 44.34, 28.01 ppm, one NCH₂ not observed; HRMS(FAB): calculated for [C₁₆H₂₄N₂O₂+H]+: 277.1916, found: 277.1911; Rf (PE/EtOAc 2:1) = 0.28.

**tert-Butyl 4-methylpiperazine-1-carboxylate (12).** A solution of 1-methylpiperazine (15.0 g, 0.15 mol) and di-tert-butyl dicarbonate (35.0 g, 0.16 mol) in THF (400 mL) was stirred at room temperature for 1.5 h, after which all volatiles were removed in vacuo. The crude product was dissolved in EtOAc, washed with saturated aqueous NaHCO₃ solution and brine, dried over MgSO₄, filtered and concentrated in vacuo. After column chromatography (PE/EtOAc 2:1) 12 was obtained as a colorless oil (24.1 g, 0.12 mol, 80%). 1H-NMR (400 MHz, CDCl₃): δ = 3.42 (m, 4H), 2.33 (m, 4H), 2.27 (s, 3H), 1.44 (s, 9H) ppm; 13C-NMR (100 MHz, CDCl₃): δ = 154.56, 79.39, 54.72, 46.08, 28.29 ppm, NCH₂ not observed; HRMS(FAB): calculated for [C₁₀H₂₀N₂O₂+H]+: 201.1603, found: 201.1602; Rf (DCM/MeOH 9:1) = 0.24.

**General procedure A: Lithiation of N-Boc-piperazines.** N-Boc-N’-benzylpiperazine 4 or N-Boc-N’-methylpiperazine 12 and TMEDA (2.4 equiv) were dissolved in dry ether (0.03 M) in a flame dried three-necked flask. After cooling to -78 °C, sec-BuLi (2.4 equiv, 1.3 M in hexanes) was added slowly using a syringe. The reaction mixture was allowed to warm to -10 °C at which temperature it was stirred for 1 h. After cooling to -78 °C again, the electrophile (2.4 equiv) was slowly added and the resulting mixture was allowed to warm slowly to room temperature overnight. The reaction mixture was poured on saturated aqueous NH₄Cl solution and extracted with EtOAc three times. The organic layer was washed with saturated aqueous NaHCO₃ solution and brine, dried over MgSO₄, filtered and concentrated in vacuo. The crude product was purified by column chromatography.

**General procedure B: Lithiation and transmetallation to copper of N-Boc-piperazines.** N-Boc-N’-benzylpiperazine 4 or N-Boc-N’-methylpiperazine 12 and TMEDA (2.4 equiv) were dissolved in dry ether (0.03 M) in a flame dried three-necked flask. After cooling to -78 °C, sec-BuLi (2.4 equiv, 1.3 M in hexanes) was added slowly using a syringe. The reaction mixture was allowed to warm to -10 °C at which temperature it was stirred for 1 h. After cooling to -78 °C again, a freshly prepared solution of CuCN·2LiCl (CuCN 2.4 equiv and LiCl 4.8 equiv) in the minimum amount of THF was added and the resulting mixture was stirred at -50 °C for 0.5 h. The temperature was again lowered to -78 °C after which the electrophile (2.4 equiv) was slowly added and the resulting mixture was allowed to warm slowly to room temperature overnight. The reaction mixture was poured on saturated...
aqueous NH₄Cl solution and extracted with EtOAc three times. The organic layer was washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The crude product was purified by column chromatography.

**tert-Butyl 4-benzyl-2-(trimethylsilyl)piperazine-1-carboxylate (6).** According to general procedure A, 4 (138 mg, 0.5 mmol) was treated with TMSCl (130 mg, 1.2 mmol) to afford 6 (0.119 g, 0.34 mmol, 68%) as a slight yellow oil after column chromatography (PE/EtOAc 1:4). ¹H-NMR (500 MHz, DMSO, 125 °C): δ = 7.28 (m, 5H), 3.79 (d, J = 10.4 Hz, 1H), 3.47 (m, 3H), 2.95 (s, 2H), 2.80 (d, J = 11.2 Hz, 1H), 2.68 (d, J = 10.0 Hz, 1H), 2.25 (br s, 1H), 1.44 (s, 9H), 0.07 (s, 9H) ppm; ¹³C-NMR (125 MHz, DMSO, 125 °C): δ = 153.39, 128.43, 127.40, 126.35, 77.96, 61.91, 53.21, 52.26, 44.68, 41.97, 40.02, 27.58, -1.53 ppm; HRMS(FAB): calculated for [C₁₀H₁₂N₂O₂Si+H]+: 349.2311, found: 349.2297; Rₚ (PE/EtOAc 1:4) = 0.10.

**tert-Butyl 4-benzyl-2-(tributylstannyl)piperazine-1-carboxylate (7).** According to general procedure A, 4 (100 mg, 0.37 mmol) was treated with Sn(n-Bu)₃Cl (130 mg, 1.2 mmol) to afford 7 (0.155 g, 0.27 mmol, 74%) as a yellow oil after column chromatography (CH₂Cl₂/MeOH 98:2). ¹H-NMR (400 MHz, CDCl₃): δ = 7.27 (m, 5H), 4.17 (m, 1H), 3.47 (m, 3H), 2.74 (m, 1H), 2.65 (m, 1H), 2.47 (m, 1H), 2.04 (m, 1H), 1.64 (m, 1H), 1.44 (m, 15H), 1.32 (m, 9H), 0.90 (m, 18H) ppm; ¹³C-NMR (100 MHz, CDCl₃): δ = 156.45, 138.08, 129.28, 128.13, 127.05, 79.80, 63.20, 57.92, 52.73, 52.26, 33.05, 29.12, 28.40, 27.54, 13.67, 10.98 ppm; HRMS(FAB): calculated for [C₂₈H₅₀N₂O₂Sn+H]+: 567.2973, found: 567.2978; Rₚ (CH₂Cl₂/MeOH 98:2) = 0.10.

**tert-Butyl 2-allyl-4-benzylpiperazine-1-carboxylate (8).** According to general procedure B, 4 (100 mg, 0.37 mmol) was treated with allyl bromide (0.107 g, 0.89 mmol), to give 8 (89 mg, 0.28 mmol, 76%) as a yellow oil after column chromatography (CH₂Cl₂/MeOH 98:2). ¹H-NMR (500 MHz, CDCl₃): δ = 7.33 (m, 5H), 5.71 (td, J = 7.7, 17.2 Hz, 1H), 5.00 (m, 2H), 4.08 (br s, 1H), 3.87 (br s, 1H), 3.48 (m, 2H), 3.08 (t, J = 12.1 Hz, 1H), 2.75 (m, 2H), 2.49 (m, 2H), 2.05 (m, 2H), 1.46 (s, 9H) ppm; ¹³C-NMR (125 MHz, CDCl₃): δ = 155.06, 138.61, 135.70, 129.05, 128.42, 127.28, 117.18, 79.67, 63.07, 60.88, 54.96, 53.41, 34.83, 28.65 ppm, NCH missing; HRMS(EI): calculated for [C₁₉H₂₈N₂O₂]+: 316.2151, found: 316.2161; Rₚ (CH₂Cl₂/MeOH 98:2) = 0.10.

**tert-Butyl 4-benzyl-2-(naphthalen-2-ylmethyl)piperazine-1-carboxylate (9).** According to general procedure B, 4 (100 mg, 0.37 mmol) was treated with 2-(chloromethyl)naphthalene (0.157 g, 0.89 mmol), to give 9 (0.110 g, 0.26 mmol, 72%) as a yellow oil after column chromatography (CH₂Cl₂/MeOH 98:2). ¹H-NMR (400 MHz, CDCl₃): δ = 7.75 (d, J = 6.9 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.38 (m, 10H), 4.22 (br s, 1H), 3.95 (br s, 1H), 3.56 (d, J = 12.9 Hz, 1H), 3.36 (d, J = 12.9 Hz, 1H), 3.25 (dt, J = 12.6, 3.1 Hz, 2H), 2.98 (br d, J = 8.9 Hz, 1H), 2.87 (br d, J = 8.6 Hz, 1H), 2.67 (d, J = 11.4 Hz, 1H), 2.09 (dt, J = 12.0, 3.2 Hz, 1H), 1.97 (dd, J = 11.4, 3.3 Hz, 1H), 1.56 (s, 9H) ppm; ¹³C-NMR (100 MHz, CDCl₃): δ = 153.8, 136.3, 135.2, 131.6, 129.0, 128.2, 127.9, 127.5, 127.4, 127.2, 127.0, 126.7,
125.7, 124.8, 80.10, 59.4, 59.1, 55.9, 55.1, 48.7, 33.8, 28.2 ppm; HRMS(FAB): calculated for [C\textsubscript{27}H\textsubscript{32}N\textsubscript{2}O\textsubscript{2}+H]\textsuperscript{+}: 417.2542, found: 417.2549; R\textsubscript{f} (CH\textsubscript{2}Cl\textsubscript{2}/MeOH 98:2) = 0.10.

\textit{tert-Butyl 2,4-dibenzylpiperazine-1-carboxylate (10).} According to general procedure B, 4 (100 mg, 0.37 mmol) was treated with benzyl bromide (0.152 g, 0.89 mmol), to give 10 (73 mg, 0.20 mmol, 54%) as a yellow oil after column chromatography (CH\textsubscript{2}Cl\textsubscript{2}/MeOH 98:2). \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}): \(\delta = 7.28\) (m, 5H), 3.93 (br s, 1H), 3.47 (s, 2H), 3.20 (dt, \(J = 12.5, 3.2\) Hz, 1H), 3.03 (m, 1H), 2.64 (br d, \(J = 10.4\) Hz, 1H), 2.62 (d, \(J = 11.5\) Hz, 1H), 1.97 (m, 2H), 1.55 (d, \(J = 8.3\) Hz, 1H), 1.37 (s, 9H) ppm; \textsuperscript{13}C-NMR (100 MHz, CDCl\textsubscript{3}): \(\delta = 156.12, 138.73, 135.49, 129.98, 128.39, 128.17, 127.95, 127.30, 125.67, 80.10, 56.43, 56.04, 55.32, 52.90, 42.77, 31.91, 28.40\) ppm; R\textsubscript{f} (CH\textsubscript{2}Cl\textsubscript{2}/MeOH 98:2) = 0.10.

\textit{tert-Butyl 4-benzyl-2-butylpiperazine-1-carboxylate (11).} According to general procedure B, 4 (100 mg, 0.37 mmol) was treated with 1-iodobutane (0.163 g, 0.89 mmol), to give 11 (0.103 g, 0.31 mmol, 85%) as a yellow oil after column chromatography (CH\textsubscript{2}Cl\textsubscript{2}/MeOH 98:2). \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}): \(\delta = 7.26\) (m, 5H), 3.99 (br s, 1H), 3.85 (br s, 1H), 3.51 (m, 2H), 3.41 (m, 2H), 3.07 (m, 1H), 2.03 (m, 2H), 1.78 (m, 1H), 1.62 (m, 1H), 1.45 (s, 9H), 1.31 (m, 2H), 1.17 (m, 2H), 0.86 (m, 3H) ppm; HRMS(FAB): calculated for [C\textsubscript{20}H\textsubscript{33}N\textsubscript{2}O\textsubscript{2}+H]\textsuperscript{+}: 333.2542, found: 333.2539; R\textsubscript{f} (CH\textsubscript{2}Cl\textsubscript{2}/MeOH 98:2) = 0.13.

\textit{N\textsubscript{N}BnBoc tert-Butyl 4-methyl-2-(trimethylsilyl)piperazine-1-carboxylate (13).} According to general procedure B, 12 (100 mg, 0.50 mmol) was treated with TMSCl (0.130 g, 1.20 mmol), to give 13 (30 mg, 0.11 mmol, 22%) as a yellow oil after column chromatography (CH\textsubscript{2}Cl\textsubscript{2}/MeOH 98:2). \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}): \(\delta = 5.65\) (br s, 1H), 3.77 (br s, 1H) 3.30 (t, \(J = 11.7\) Hz, 1H), 2.78 (d, \(J = 10.8\) Hz, 2H), 2.26 (s, 3H), 2.17 (m, 2H), 0.86 (m, 3H) ppm; HRMS(FAB): calculated for [C\textsubscript{20}H\textsubscript{33}N\textsubscript{2}O\textsubscript{2}\textsubscript{120}Sn+H]\textsuperscript{+}: 491.2664, found: 491.2676; R\textsubscript{f} (CH\textsubscript{2}Cl\textsubscript{2}/MeOH 98:2) = 0.10.

\textit{N\textsubscript{N}MeBoc Sn(n-Bu)\textsubscript{3} tert-Butyl 4-methyl-2-(tributylstannyl)piperazine-1-carboxylate (14).} According to general procedure A, 12 (100 mg, 0.50 mmol) was treated with Sn(n-Bu)\textsubscript{3}Cl (0.391 g, 1.2 mmol), to give 14 (199 mg, 0.41 mmol, 82%) as a yellow oil after column chromatography (CH\textsubscript{2}Cl\textsubscript{2}/MeOH 98:2). \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}): \(\delta = 4.03\) (m, 1H), 3.47 (br s, 1H), 3.34 (br s, 2H), 2.68 (m, 2H), 2.26 (m, 1H), 2.21 (s, 3H), 1.60 (m, 3H), 1.46 (m, 12H), 1.35 (m, 6H), 0.88 (m, 15H) ppm; \textsuperscript{13}C-NMR (100 MHz, CDCl\textsubscript{3}): \(\delta = 153.69, 79.08, 59.35, 55.04, 54.95, 45.78, 31.65, 28.99, 28.15, 27.32, 13.43, 11.08\) ppm; HRMS(FAB): calculated for [C\textsubscript{22}H\textsubscript{47}N\textsubscript{2}O\textsubscript{2}\textsubscript{120}Sn+H]\textsuperscript{+}: 491.2664, found: 491.2676; R\textsubscript{f} (CH\textsubscript{2}Cl\textsubscript{2}/MeOH 98:2) = 0.10.

\textit{tert-Butyl 2-allyl-4-methylpiperazine-1-carboxylate (15).} According to general procedure B, 12 (100 mg, 0.50 mmol) was treated with allyl bromide (0.145 g, 1.2 mmol), to give 15 (0.114 g, 0.48 mmol, 95%) as a yellow oil after column chromatography (CH\textsubscript{2}Cl\textsubscript{2}/MeOH 98:2). \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}): \(\delta = 5.76\) (ddt, \(J = 7.3, 10.0, 17.3\) Hz, 1H), 5.06 (m, 2H), 4.11 (br s, 1H), 3.86 (br d, \(J = 12.7\) Hz, 1H), 3.05 (td, \(J = 2.7, 13.0\) Hz, 1H), 2.70 (t, \(J = 10.5\) Hz, 2H), 2.45 (m, 2H), 2.23 (s, 3H), 2.02 (dd, \(J = 4.0, 11.5\) Hz, 1H), 1.83 (m, 1H), 1.60 (m, 2H), 1.45 (s, 9H), 0.88 (m, 3H) ppm; HRMS(FAB): calculated for [C\textsubscript{22}H\textsubscript{47}N\textsubscript{2}O\textsubscript{2}\textsubscript{120}Sn+H]\textsuperscript{+}: 491.2664, found: 491.2676; R\textsubscript{f} (CH\textsubscript{2}Cl\textsubscript{2}/MeOH 98:2) = 0.10.
Synthesis of 2-substituted piperazines via direct α-lithiation

1.91 (td, J = 3.5, 11.9 Hz, 1H), 1.45 (s, 9H) ppm; 13C-NMR (100 MHz, CDCl3): δ = 154.48, 135.16, 116.75, 79.23, 56.85, 50.45, 46.13, 38.86, 34.37, 28.14 ppm; HRMS(FAB): calculated for [C13H24N2O2+H]+: 241.1916, found: 241.1920; Rf (CH2Cl2/MeOH 98:2) = 0.10.

**tert-Butyl 2-benzyl-4-methylpiperazine-1-carboxylate (16).** According to general procedure B, 12 (100 mg, 0.50 mmol) was treated with benzyl bromide (0.205 g, 1.2 mmol), to give 16 (87 mg, 0.30 mmol, 60%) as a yellow oil after column chromatography (CH2Cl2/MeOH 98:2). 1H-NMR (400 MHz, CDCl3): δ = 7.26 (m, 5H), 4.25 (br s, 1H), 3.90 (br s, 1H), 3.20 (dt, J = 12.5, 3.2 Hz, 1H), 3.03 (m, 1H), 2.88 (m, 1H), 2.61 (br d, J = 10.4 Hz, 1H), 2.62 (d, J = 11.5 Hz, 1H), 2.23 (s, 3H), 1.97 (m, 2H), 1.36 (s, 9H) ppm; 13C-NMR (100 MHz, CDCl3): δ = 154.64, 139.35, 129.42, 128.39, 126.15, 79.53, 55.13, 46.40, 28.30 ppm; 3x N-C phenyl and N-C phenyl not observed; HRMS(EI): calculated for [C17H26N2O2]+: 290.1994, found: 290.1988; Rf (CH2Cl2/MeOH 98:2) = 0.11.

**tert-Butyl 2-butyl-4-methylpiperazine-1-carboxylate (17).** According to general procedure B, 12 (100 mg, 0.50 mmol) was treated with 1-iodobutane (0.221 g, 1.2 mmol), to give 17 (92 mg, 0.36 mmol, 72%) as a yellow oil after column chromatography (CH2Cl2/MeOH 98:2). 1H-NMR (400 MHz, CDCl3): δ = 4.02 (br s, 1H), 3.86 (br d, J = 12.6 Hz, 1H), 3.02 (t, J = 12.6 Hz, 1H), 2.66 (m, 2H), 2.21 (s, 3H), 2.02 (dd, J = 4.0, 11.4 Hz, 1H), 1.88 (m, 1H), 1.73 (m, 1H), 1.61 (m, 1H), 1.44 (s, 9H), 1.28 (m, 4H), 0.84 (t, J = 7.2 Hz, 3H) ppm; 13C-NMR (100 MHz, CDCl3): δ = 154.80, 79.47, 57.99, 55.19, 46.49, 29.74, 28.64, 28.43, 22.55, 14.10 ppm, NCH2 and CH2-C6H5 not observed; HRMS(FAB): calculated for [C14H28N2O2+H]+: 257.2229, found: 257.2224; Rf (CH2Cl2/MeOH 98:2) = 0.10.

**tert-Butyl 4-methyl-2-(2-methylallyl)piperazine-1-carboxylate (20).** According to general procedure B, 12 (0.900 g, 4.49 mmol) was treated with 3-bromo-2-methylprop-1-ene (1.45 g, 10.8 mmol), to give 20 (0.796 g, 3.15 mmol, 70%) as a yellow oil after column chromatography (PE/EtOAc 4:1). 1H-NMR (500 MHz, CDCl3): δ = 4.19 (br s, 1H), 3.88 (br d, J = 10.7 Hz, 1H), 3.08 (t, J = 11.8 Hz, 1H), 2.71 (t, J = 13.1 Hz, 2H), 2.45 (dd, J = 8.1, 13.1, 1H), 2.36 (dd, J = 6.9, 13.1 Hz, 1H), 2.24 (s, 3H), 2.01 (dd, J = 3.9, 11.3 Hz, 1H), 1.93 (td, J = 3.2, 11.8 Hz, 1H), 1.79 (s, 3H), 1.46 (s, 9H) ppm; 13C-NMR (100 MHz, CDCl3): δ = 154.60, 142.59, 112.92, 79.39, 56.85, 54.98, 46.30, 38.18, 28.29, 22.77 ppm, NCH, NCH2 not observed; HRMS(FAB): calculated for [C14H28N2O2+H]+: 255.2073, found: 255.2065.

**tert-Butyl 2-(2-bromoallyl)-4-methylpiperazine-1-carboxylate (21).** According to general procedure B, 12 (0.100 g, 0.50 mmol) was treated with 2,3-dibromoprop-1-ene (0.240 g, 1.2 mmol), to give 21 (0.110 g, 0.35 mmol, 69%) as a yellow oil after column chromatography (PE/EtOAc 4:1). 1H-NMR (500 MHz, CDCl3): δ = 5.66 (s, 1H), 5.47 (d, J = 1.4 Hz, 1H), 4.41 (br s, 1H), 3.93 (br s, 1H), 3.03 (t, J = 12.1 Hz, 1H), 2.90 (dd, J = 8.0, 13.9 Hz, 1H), 2.73 (m, 3H), 2.24 (s, 3H), 2.06 (dd, J = 3.9, 11.7 Hz, 1H), 1.96 (td, J = 3.5, 11.9 Hz, 1H), 1.49 (s, 9H) ppm; 13C-NMR (100 MHz, CDCl3): δ = 154.53, 131.00, 119.06, 79.82, 56.17, 54.81, 49.58 (br), 46.22, 41.63 (br), 38.92 (br), 28.23 ppm; HRMS(FAB): calculated for [C13H279BrN2O2+H]+: 319.1021, found: 319.1025.
**tert-Butyl 2-allyl-4-(2-allylbenzyl)piperazine-1-carboxylate (22).** According to general procedure B, treatment of 4 (2.50 g, 9.05 mmol) with allyl bromide (2.63 g, 1.88 mL, 21.7 mmol), gave besides 8 (2.03 g, 6.43 mmol, 71%), side product 22 (0.484 g, 1.36 mmol, 15%) as a yellow oil after column chromatography (PE/EtOAc 4:1). $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ = 7.22 (m, 4H), 5.99 (m, 1H), 5.69 (td, $J$ = 7.4, 17.0 Hz, 1H), 5.02 (m, 4H), 4.08 (s, 1H), 3.84 (s, 1H), 3.57 (m, 2H), 3.44 (m, 2H), 3.01 (t, $J$ = 11.9 Hz, 1H), 2.73 (d, $J$ = 10.2 Hz, 2H), 2.45 (t, $J$ = 7.1 Hz, 2H), 2.10 (dd, $J$ = 3.6, 11.3 Hz, 1H), 1.99 (td, $J$ = 2.9, 11.7 Hz, 1H), 1.46 (s, 9H) ppm; $^{13}$C-NMR (125 MHz, DMSO): $\delta$ = 153.73, 138.91, 137.45, 135.67, 135.38, 130.06, 129.47, 127.28, 125.77, 116.83, 115.37, 78.57, 59.87, 54.62, 52.42, 36.16, 34.19, 27.97 ppm; HRMS (FAB): calculated for [C$_{22}$H$_{32}$N$_2$O$_2$+H$^+$]: 357.2542, found: 357.2543; R$_f$ (PE/EtOAc 19:1) = 0.19.

**1,14-Diaza-tricyclo[11.3.1.0$^{3,8}$]heptadeca-3(8),4,6,10-tetraene-14-carboxylic acid tert-butyI ester (23).** A flame dried 3-necked flask underwent three vacuum/Ar cycles, before it was charged with 22 (40 mg, 0.112 mmol), dry toluene (9 mL) and Grubbs’ II catalyst (4.8 mg, 0.0056 mmol). The resulting mixture underwent another 2 vacuum/Ar cycles and was stirred at 40 °C for 18 h, after which the slightly yellow solution was filtered over Celite®. The residue was washed with toluene two times and the combined organic fractions were concentrated in vacuo. The crude product was purified by column chromatography (PE/EtOAc 19:1) to afford 23 (16 mg, 0.048 mmol, 43%) and recovered 22 (20 mg, 0.056 mmol, 50%). $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ = 7.26 (m, 2H), 7.11 (m, 2H), 5.68 (m, 1H), 5.42 (m, 1H), 4.97 (t, $J$ = 11.9 Hz, 1H), 4.27 (d, $J$ = 13.8 Hz, 1H), 3.96 (m, 1H), 3.83 (d, $J$ = 12.3 Hz, 1H), 3.36 (m, 2H), 3.25 (m, 1H), 2.87 (m, 3H), 2.25 (td, $J$ = 3.5, 12.4 Hz, 1H), 1.89 (m, 1H), 1.70 (d, $J$ = 11.6 Hz, 1H), 1.49 (s, 4.5H), 1.48 (s, 4.5H) ppm; $^{13}$C-NMR (100 MHz, CDCl$_3$): (1:1 mixture of isomers) $\delta$ = 154.88, 154.61, 138.97, 138.89, 134.48, 134.38, 134.27, 133.88, 131.32, 130.25, 127.18, 125.67, 124.81, 124.41, 79.42, 79.34, 63.02, 53.37, 51.46, 50.07, 39.81, 38.77, 30.67, 28.31, 36.39, 25.75 ppm, NCH not observed; HRMS (FAB): calculated for [C$_{20}$H$_{38}$N$_2$O$_2$+H$^+$]: 329.2229, found: 329.2224; R$_f$ (PE/EtOAc 19:1) = 0.13.

**tert-Butyl trans-2,6-diallyl-4-methylpiperazine-1-carboxylate (24).** According to general procedure B, 8 (1.40 g, 5.83 mmol) was treated with allyl bromide (1.41 g, 1.0 mL, 11.7 mmol), to give 24 (1.51 g, 5.49 mmol, 93%) as a yellow oil after column chromatography (PE/EtOAc 2:1, 0.1% Et$_3$N). $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ = 5.78 (ddt, $J$ = 7.1, 10.1, 17.4 Hz, 2H), 5.07 (dd, $J$ = 1.1, 11.1, 13.6 Hz, 4H), 3.79 (m, 2H), 2.57 (m, 4H), 2.45 (dd, $J$ = 3.6, 11.5 Hz, 2H), 2.34 (dd, $J$ = 5.9, 11.5 Hz, 2H), 2.26 (s, 3H), 1.48 (s, 9H) ppm; $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ = 155.73, 135.35, 116.74, 79.47, 57.17, 52.64, 46.10, 36.26, 28.09 ppm; HRMS (FAB): calculated for [C$_{16}$H$_{28}$N$_2$O$_2$+H$^+$]: 281.2229, found: 281.2224; R$_f$ (PE/EtOAc 2:1, 0.1% Et$_3$N) = 0.34.

**tert-Butyl trans-2-allyl-4-methyl-6-(pent-4-enyl)piperazine-1-carboxylate (25).** According to general procedure B, 15 (0.160 g, 0.666 mmol) was treated with 5-iodopent-1-ene (easily prepared from its corresponding bromide) (0.261 g, 1.33 mmol), to give 25 (0.102 g, 0.331 mmol, 50%) as a yellow oil, and recovered 15 (40 mg, 0.167 mmol, 25%) after column chromatography (EtOAc). $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ = 7.26 (m, 4H), 5.09 (m, 1H), 4.08 (s, 1H), 3.84 (s, 1H), 3.57 (m, 2H), 3.44 (m, 2H), 3.01 (t, $J$ = 11.9 Hz, 1H), 2.73 (d, $J$ = 10.2 Hz, 2H), 2.45 (t, $J$ = 7.1 Hz, 2H), 2.10 (dd, $J$ = 3.6, 11.3 Hz, 1H), 1.99 (td, $J$ = 2.9, 11.7 Hz, 1H), 1.46 (s, 9H) ppm; $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ = 153.73, 138.91, 137.45, 135.38, 130.06, 129.47, 127.28, 125.77, 116.83, 115.37, 78.57, 59.87, 54.62, 52.42, 36.16, 34.19, 27.97 ppm; HRMS (FAB): calculated for [C$_{20}$H$_{38}$N$_2$O$_2$+H$^+$]: 329.2229, found: 329.2224; R$_f$ (PE/EtOAc 19:1) = 0.13.
MHz, CDCl₃): δ = 5.79 (m, 2H), 5.02 (m, 4H), 3.78 (m, 1H), 3.72 (m, 1H), 2.57 (m, 3H), 2.39 (m, 2H), 2.28 (m, 4H), 2.07 (m, 2H), 1.82 (m, 1H), 1.46 (s, 9H), 1.40 (m, 2H) ppm; ¹³C-NMR (100 MHz, CDCl₃): δ = 156.15, 138.94, 135.92, 117.06, 114.72, 79.82, 58.02, 57.77, 53.74, 53.03, 46.49, 36.66, 33.81, 31.27, 28.64, 26.11 ppm; HRMS(FAB): calculated for [C₁₈H₃₂N₂O₂+H]⁺: 309.2542, found: 309.2539.

**Di-tert-Butyl trans-2,6-diallylpiperazine-1,4-dicarboxylate (33).** To a solution of 24 (350 mg, 1.25 mmol) in 1,2-DCE (10 mL) was added ACE-Cl (0.35 mL, 2.50 mmol), and the solution was refluxed for 18 h after which al volatiles were removed in vacuo. The intermediate carbamate was dissolved in MeOH (9 mL) and the solution was refluxed for 54 h after which al volatiles were evaporated in vacuo. The salt was dissolved in CH₂Cl₂ (15 mL) after which Et₃N (0.40 ml) and Boc₂O (0.50 g, 2.29 mmol) were added. The solution was stirred for 18 h after which it was poured on saturated aqueous NH₄Cl and extracted with EtOAc 3 times. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by column chromatography (PE/EtOAc 19:1) to afford 33 (0.360 g, 0.982 mmol, 79%) as a white solid. Recrystallization from pentane at -20 °C gave 33 as colorless needles. Mp = 89 °C; X-ray structure data: C₂₀H₃₄N₂O₄; M = 366.49; T = 208 K; a = 0.71073 Å; monoclinic, P2₁; a = 6.4059(11) Å, b = 10.078(2) Å, c = 17.227(8) Å, α = 90°, β = 90.39(2)°, γ = 90°; V = 1112.1(6) Å³; 3867 observed unique reflections; R₁ = 0.1624, wR₂ = 0.4104 [I>2σ(I)]; ¹H-NMR (500 MHz, CDCl₃): δ = 5.77 (m, 2H), 5.09 (dd, J = 9.6, 13.8 Hz, 4H), 3.85 (m, 4H), 3.34 (dt, J = 4.4, 13.3 Hz, 2H), 2.47 (m, 2H), 2.16 (m, 2H), 1.50 (s, 9H), 1.49 (s, 9H) ppm; ¹³C-NMR (100 MHz, CDCl₃): δ = 156.06, 154.42, 134.84, 134.54, 118.33, 118.14, 80.22, 80.12, 52.15 (br); 42.83, 42.40, 39.52, 39.18, 28.62, 28.59 ppm.

### References

Chapter 5

27. In other experiments DMF and MeI also proved to be good carbon electrophiles.
29. Unpublished results, Solvay Pharmaceuticals, Weesp, the Netherlands.
48. These results are in contradiction with our previously published observations, which suggested cis-addition. See ref 40.
49. Intermediate 31 is stable and can be isolated.
50. Reactions with 5-iodopent-1-ene were proven to be superior to those with 5-bromopent-1-ene.
52. From spectral data of this intermediate was concluded that the Boc-group had been removed as well. Later on it was discovered that this can be avoided by addition of ACE-Cl at 0 °C.