Synthesis and applications of unsaturated non-proteinogenic a-H-a-amino acids.

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CHAPTER 5

PALLADIUM-CATALYZED CYCLIZATION REACTIONS OF ENANTIOPURE
2-AMINO-4,5-HEXADIENOIC ACID DERIVATIVES

5.1 Introduction

In Chapter 4, Pd-catalyzed coupling/cyclization reactions of acetylene-containing amino acids were described. This resulted predominantly in the synthesis of five-membered rings. Inspired by simultaneous research in our group on Pd-catalyzed cyclization reactions of allene-substituted lactams and because of the structural similarity between allenes and acetylenes, we set out to investigate the possibility of cyclizing allene-containing amino acids to the corresponding four- or six-membered rings, respectively.

Despite the fact that allenes have attracted increasing attention of organic chemists in recent years as electrophiles in metal-catalyzed cyclization reactions, in very few of such conversions amino acids were applied. In fact, the only amino acid example was published in 1993 by the group of Gallagher and is shown in Scheme 5.1. They developed useful conditions for the cyclization of the bishomoallenylglycine derivative 1 using Pd(PPh$_3$)$_4$ (10 mol%), iodobenzene (5 equiv) and K$_2$CO$_3$ (5 equiv) in DMF at 70 °C to obtain the pyrrolidine 4 in good yield as a 1:1 mixture of diastereoisomers.

Scheme 5.1

![Scheme 5.1](image)

The mechanism presumably involves initial reaction of the in situ generated phenylpalladium(II) species with the allene to give the π-allylpalladium complex 2. Intramolecular nucleophilic attack of the nitrogen, followed by release of Pd(0) then leads to the corresponding five-membered ring. Alternatively, it cannot be ruled out that a different,
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Wacker-type, mechanism is operating where the electrophilic phenylpalladium(II) species activates the internal double bond of the allene, which is then followed by nucleophilic attack of the nitrogen to give the vinyl-substituted Pd-complex 3. This intermediate can then undergo reductive elimination to the product with concomitant regeneration of Pd(0).

During the course of our work, several other cyclization reactions of allenes using nitrogen nucleophiles were published, which will be briefly summarized. Ibuka and coworkers demonstrated that subjecting sulfonamide 5 having a single carbon atom tether between the nitrogen nucleophile and the allene – to the Gallagher conditions resulted depending on the solvent in selective three- or five-membered ring formation (eq 5.1). In DMF, the pyrrolidine 6 was formed, whereas by changing to 1,4-dioxane aziridine 7 was formed exclusively in 80% yield (cis/trans 82:18).

\[
\begin{align*}
5 & \xrightarrow{\text{Pd(PPh}_3)_4, \text{Phl, K}_2\text{CO}_3} \text{Me} \quad \text{Ph} \\
\text{Mts} \quad \text{Mts} & \quad (5.1)
\end{align*}
\]

Cyclization reactions where the amine and the allene are separated by a two-carbon tether appeared more difficult. This was illustrated by the reluctance of 8 to cyclize under acidic conditions, leading instead to the conjugated diene 9 (eq 5.2). Inversely, five- and six-membered rings were obtained in good yields using allenes that were separated with a three or four carbon tether.

\[
\begin{align*}
8 & \xrightarrow{5 \text{ mol\% } [\eta^2\text{C}_2\text{H}_2\text{PdCl}]_2, 10 \text{ mol\% dppf}} 9 \\
\text{NHTs} & \quad \text{NHTs} \\
\text{THF, 70 °C, 5 h} & \quad (5.2)
\end{align*}
\]

Very recently, the first example of the formation of four- and six-membered azacycles starting from a β-amino allene appeared in the literature. In this case, instead of using phenyl iodide, a hypervalent iodonium salt was used as the phenyl source. The yield and the regioselectivity were moderate in this example (eq 5.3).
Cyclizations of allenes

\[
\begin{align*}
\text{NHTs} & \xrightarrow{\text{Pd(PPh}_3)_4, \text{PhI}, \text{BF}_4^-, \text{MeCN, 60 °C}} \text{Ts} \\
\text{Ph} & \quad \text{10 (36%)} \quad \text{Ph} \\
\end{align*}
\]

After our work was published, yet another example was published by the Ibuka group. Cyclization of the sulfonated β-amino allene 12 using again the Gallagher conditions in DMF gave the corresponding cis-substituted azetidinone 13 in excellent selectivity and yield (eq 5.4). In case 1,4-dioxane was used as the solvent, the trans-isomer was also formed to some extent.

\[
\begin{align*}
\text{N} & \xrightarrow{\text{Pd(PPh}_3)_4, \text{PhI, K}_2\text{CO}_3, \text{DMF, 70 °C, 2 h}} \text{Mts} \\
\text{Ph} & \quad \text{13 (98%)} \\
\end{align*}
\]

In all of these examples, the heteronucleophile attacks one of the sp²-carbon atoms of the allene. Interestingly, unprecedented alternative behavior was reported by our group, where five- rather than four- or six-membered rings were formed. This is illustrated in eq 5.5 with a representative example, where the lactam nitrogen atom (viz. 14) – note that there is again a two-carbon tether between the allene and the nitrogen atom – reacted at the sp-carbon atom of the allene to form the five-membered ring enamidone 15.

\[
\begin{align*}
\text{NH} & \xrightarrow{\text{Pd(PPh}_3)_4, \text{PhI, K}_2\text{CO}_3, \text{Bu}_4\text{NCl, MeCN, 3 h, reflux}} \text{Ph} \\
\text{14} & \quad \text{15 (64%)} \\
\end{align*}
\]

This chapter describes our efforts to obtain four- and six-membered ring heterocycles (cf. 16 and 17) using the Gallagher conditions from linear β-amino allene derivatives 18, where the allene and the amine are separated by a two-carbon tether (eq 5.6). The unsubstituted (R = H) and the substituted (R = CO₂Me) β-amino allenes are compared, both containing different protecting groups to tune the reactivity of the nitrogen atom.
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5.2 Preparation of the cyclization precursors

The unsubstituted β-amino allene 22 was obtained via a literature procedure. Starting from 3-butyn-1-ol (19) a Crabbé reaction was carried out to obtain 3,4-pentadien-1-ol (20) in modest yield \(^\text{11}\) (eq 5.7).

\[
\begin{align*}
\text{NH}^\text{Pr}_2 & \quad (\text{CH}_2\text{O})_n \\
\text{CuI, dioxane} & \quad \text{reflux}
\end{align*}
\]

The alcohol 20 was converted into the amine via tosylation of the alcohol with \(p\)-toluenesulfonyl chloride, followed by treatment with sodium azide and reduction with LiAlH\(_4\) \(^\text{12}\) (Scheme 5.2). The amine 22 was then protected using \(p\)-toluenesulfonyl chloride to give the sulfonamide 8 in 29% calculated over three steps. The somewhat moderate yield of 8 is probably due to the volatility of the amine 22.

Scheme 5.2

\[
\begin{align*}
\text{20} & \quad \text{a} & \quad \text{21} & \quad (76\%) & \quad \text{b, c} & \quad \text{22} & \quad \text{d} & \quad \text{8} & \quad (29\%) \\
\end{align*}
\]

Reagents and conditions: (a) \(p\)-toluenesulfonyl chloride (1.1 equiv), pyridine (5.0 equiv), \(\text{CH}_2\text{Cl}_2\), rt, 16 h (b) \(\text{NaN}_3\) (10 equiv), \(\text{DMF}, \text{H}_2\text{O}, 50^\circ\text{C}, 2\) h (c) \(\text{LiALH}_4\) (3 equiv), ether, reflux, 4 h (d) \(p\)-toluenesulfonyl chloride (1.3 equiv), pyridine, rt, 19 h

The corresponding \(p\)-nitrophenylsulfonyl (Ns)-protected amine (23) was obtained via a so-called Fukuyama-Mitsunobu reaction \(^\text{13}\). Thus, 3,4-pentadien-1-ol (20) was reacted with 4-nitrophenylsulfonamide (1 equiv), triphenylphoshine (1 equiv) and diethyl azodicarboxylate (1 equiv) in toluene to give 23 in a moderate yield (28%, eq 5.8).
To obtain the amino acid-derived cyclization precursors, the enantiopure (R)-amino acid 24 (Chapters 2 and 3) was protected as the corresponding methyl ester with different functional groups at the nitrogen atom. The conditions are summarized in Scheme 5.3. The amino acid was either first esterified (SOCl₂, MeOH) followed by functionalization of the nitrogen atom (viz. 25-27) using standard methods or via acetylation of the nitrogen followed by esterification (28).

Scheme 5.3

Reagents and conditions: 24→25 (a) p-toluenesulfonyl chloride (1.5 equiv), pyridine, rt, 16 h 24→26 (b) i) benzaldehyde (1.0 equiv), Et₃N (1.1 equiv), 4 Å molecular sieves, CH₂Cl₂, rt, 19 h ii) NaBH₄ (1.0 equiv), MeOH, 0 °C, 30 min, then quench with HCl 24→27 (c) ClCO₂CH₃ (1.5 equiv), Et₃N (2.5 equiv), CH₂Cl₂, 0 °C, 2 h

5.3 Coupling/cyclization reactions with Pd(0)

The cyclization results of the unsubstituted amino allenes 8 and 23 are shown in Table 5.1. Application of the Gallagher conditions (10 mol% Pd(PPh₃)₄, 5 equiv RX, 5 equiv K₂CO₃, DMF, 80 °C) onto allene 8 (entry 1) led in 30 min to complete conversion affording a 67:33 ratio of the four- and six-membered rings 33a and 33b, respectively, which is in line with the result of Kang et al. Upon prolonged reaction times, this ratio changed in favor of the six-membered ring (entry 2). Use of the pyridine-derived iodide 29 gave a similar result, with the six-membered ring being the major isomer (entry 3). When 2-bromopropene (30) was used complete selectivity was obtained with respect to the formation of the six-membered ring.
although in a moderate yield (entry 4). In contrast, reactions with the vinyl triflates 31\(^{15}\) and 32\(^{16}\) led to pleasing results. The azetidine 36a was formed selectively by using triflate 31 (entry 5), while reaction with triflate 32 gave a selectivity of 95:5 in favor of the four-membered ring 37a (entry 6). On the other hand, subjecting of amino allene 23 – protected with the more easily removable Ns-group – to these reaction conditions provided the tetrahydropyridine 38 selectively in 55% yield (entry 7).

Table 5.1

<table>
<thead>
<tr>
<th>entry</th>
<th>allene</th>
<th>RX</th>
<th>time</th>
<th>ratio (a:b)(^a)</th>
<th>product (yield)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8 (P = Ts)</td>
<td>PhI</td>
<td>0.5 h</td>
<td>67:33</td>
<td>33 (67%)</td>
</tr>
<tr>
<td>2</td>
<td>8 (P = Ns)</td>
<td>PhI</td>
<td>40 h</td>
<td>10:90</td>
<td>33 (34%)</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>Cl-Pyr</td>
<td>4 h</td>
<td>25:75</td>
<td>34 (55%)</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>t-Bu</td>
<td>2 h</td>
<td>0:100</td>
<td>35 (24%)</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>31</td>
<td>10 min</td>
<td>100:0</td>
<td>36 (34%)</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>n-Bu</td>
<td>15 min</td>
<td>95:5</td>
<td>37 (41%)</td>
</tr>
<tr>
<td>7</td>
<td>23</td>
<td>PhI</td>
<td>4 h</td>
<td>0:100</td>
<td>38 (55%)</td>
</tr>
</tbody>
</table>

\(^a\) Determined by analysis of the \(^1\)H NMR data of the crude mixture. \(^b\) Combined isolated yield after column chromatography.

To study the influence of the ester substituent, the enantiopure amino acid derivatives (25-28) were subjected to identical cyclization conditions (Table 5.2). Initially, 25 was treated with the Gallagher conditions (entry 1). These conditions resulted selectively in the piperolic acid derivative 39b in 78% yield. Closer examination of the conditions revealed that with shorter reaction times a considerable amount of the four-membered ring 39a was formed as a single cis-isomer. The best example is shown in entry 3: the reaction was finished in 10 min, with 39a being the major product. Surprisingly, the reaction also proceeded at room temperature, but did not show any selectivity (entry 2).

To improve the ratio in favor of the four-membered ring, different parameters (temperature, solvent and reaction time) were varied, resulting in a maximum selectivity of 120.
88:12 (THF, 60 °C, entry 4) albeit the yield was moderate (45%). Interesting results were obtained by using vinyl triflates 31 and 32 (entries 5 and 6). This led to fast reactions (finished in 10 to 15 min) and excellent yields of the four-membered amino acids 40a and 41a with only a small degree of formation of the six-membered rings.

Table 5.2

<table>
<thead>
<tr>
<th>entry</th>
<th>allene</th>
<th>RX</th>
<th>solvent</th>
<th>T (°C)</th>
<th>time</th>
<th>ratio (a:b)a</th>
<th>product (yield)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>PhI</td>
<td>DMF</td>
<td>80</td>
<td>4 h</td>
<td>0 : 100</td>
<td>39 (78%)</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>PhI</td>
<td>DMF</td>
<td>rt</td>
<td>4 h</td>
<td>50 : 50</td>
<td>39 (80%)</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>PhI</td>
<td>DMF</td>
<td>80</td>
<td>10 min</td>
<td>70 : 30</td>
<td>39 (84%)</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>PhI</td>
<td>THF</td>
<td>60</td>
<td>1.5 h</td>
<td>88 : 12</td>
<td>39 (45%)</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>31</td>
<td>DMF</td>
<td>80</td>
<td>15 min</td>
<td>88 : 12</td>
<td>40 (96%)</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>32</td>
<td>DMF</td>
<td>80</td>
<td>10 min</td>
<td>95 : 5</td>
<td>41 (77%)</td>
</tr>
<tr>
<td>7</td>
<td>26</td>
<td>PhI</td>
<td>DMF</td>
<td>70</td>
<td>3 h</td>
<td>0 : 100</td>
<td>42 (76%)</td>
</tr>
<tr>
<td>8</td>
<td>27</td>
<td>PhI</td>
<td>DMF</td>
<td>80</td>
<td>16 h</td>
<td>42 : 58</td>
<td>43 (33%)</td>
</tr>
<tr>
<td>9</td>
<td>28</td>
<td>PhI</td>
<td>DMF</td>
<td>80</td>
<td>2 h</td>
<td>67 : 33</td>
<td>44 (12%)</td>
</tr>
</tbody>
</table>

a Determined by analysis of the 'H NMR data of the crude mixture. b Combined isolated yield of a and b after column chromatography. In all entries, both products were obtained without loss of enantiopurity according to chiral HPLC (Chiralcel OD).

The benzylated precursor 26 led in a clean reaction to the unsaturated pipelicolic ester 42. This result is in accordance with previous reports on cyclizations of amines onto π-allylpalladium intermediates, where complete conversion into the thermodynamic product was encountered.\(^{17}\) Introduction of a methyl carbamate (entry 8) or an amide function (entry 9) did not lead to satisfactory results. Especially the low yields did not encourage further investigations into optimization of the product ratio. In all entries both products were obtained without loss of enantiopurity.
Interestingly, the carbamate-functionalized azetidine ester 43a was the only product that gave crystals that could be subjected to a crystal structure determination. Thus, the structure and absolute orientation of the substituents in the azetidine were unambiguously established. Note that this compound has the (2S, 4R) configuration, which is a result of using (S)-24 as the starting material.

![Figure 5.1 Crystal structure of 43a](image)

### 5.4 Mechanistic discussion

An explanation for the aforementioned results can be provided by considering the different pathways that play a role. Initially, reaction of the allene with the in situ formed organopalladium(II) species will give rise to the more stable syn-π-allylpalladium complex 45, which via π–σ–π isomerization can be converted into the more hindered anti-isomer. The syn-isomer can only cyclize in a 4-exo-trig-fashion to give the kinetic product 46. The four-membered ring, however, can undergo ring-opening under the influence of Pd(PPh₃)₄ to regenerate the π-allylpalladium complex, which eventually via the equilibrium with the anti-complex can isomerize to the thermodynamically more stable six-membered ring 47. The four- to six-membered ring isomerization was independently proven in a separate experiment via subjection of 39a to the cyclization conditions, resulting in complete conversion into the tetrahydropyridine 39b. Although the mechanism of the cyclization itself has not been proven – the earlier mentioned mechanism (Scheme 5.1) could also operate – it is highly probable that the isomerization mechanism proceeds via the π-allylpalladium complex.

Following this mechanistic hypothesis, the different results can be rationalized. With short reaction times, the kinetic product (the azetidine) is favored, since there is relatively little time for isomerization. The rate of the isomerization, in turn, will also depend on the substituents P and R. Probably, for R = alkenyl, the intermediate π-allylpalladium complex is somewhat less stable and therefore more difficult to form, so that isomerization does not rapidly occur and a relatively large amount of the four-membered ring is formed. On the other hand, improving the leaving group ability of the nitrogen (by going from Ts to Ns, for example) enhances the formation of the π-allylpalladium complex leading to a rapid
isomerization so that the four-membered ring is no longer observed. It is also clear from the results that the yield of the Pd-catalyzed cyclizations is enhanced by the ester substituent. This could well be a result of the ‘Thorpe-Ingold effect’ which predicts that ring-closing processes are enhanced by a growing number of substituents on the linear chain.

**Scheme 5.4**

\[
RX + \text{PdL}_4 \rightarrow \text{RPdXL}_2 + \text{K}_2\text{CO}_3 \rightarrow \begin{array}{c}
\text{PdL}_2 \text{HN} \\
\text{P} \hspace{1cm} \text{R} \hspace{1cm} \text{HN} \\
\text{P} \hspace{1cm} \text{CO}_2\text{Me} \\
\text{syn-45}
\end{array} \rightarrow \begin{array}{c}
\text{Pd}(0) \rightarrow \\
\text{Pd}(0) \rightarrow \\
\text{R} \hspace{1cm} \text{CO}_2\text{Me} \\
\text{4-exo-trig} \\
\text{R} \hspace{1cm} \text{CO}_2\text{Me} \\
\text{6-endo-trig}
\end{array}
\]

5.5 Cyclic nucleophiles

By changing different reaction parameters either four- or six-membered ring formation is observed resulting from attack of the nitrogen onto one of the sp²-allene carbon atoms. Most remarkably, a slight substrate modification – ester reduction followed by oxazolidinone formation – resulted in attack of the nitrogen on the central sp-allene carbon atom under similar reaction conditions, providing the corresponding five-membered ring 51 (Scheme 5.5).²¹

Thus, a linear allenic carbamate (viz. 27) led to the formation of four- and six-membered ring products, whereas a cyclic carbamate led to the five-membered ring product. The supposed mechanism for the five-membered ring formation is shown in Scheme 5.5.²² The initial step must be electrophilic activation of one of the two allene double bonds, followed by nucleophilic attack of the carbamate type nitrogen onto the activated double bond. This results in the allylic Pd²⁺-species 50, which actually might be in equilibrium with the corresponding π-allylpalladium complex. Reductive elimination of Pd(0) from 50 then leads to the 5-membered ring product. That means that in this case, the order of events is different. While in the acyclic substrates immediate reaction of the organopalladium(II)-species with the
allene takes place, in the cyclic structures nucleophilic attack of the carbamate NH onto the central carbon of the allene is a faster process.

Scheme 5.5

This difference might on the one hand be attributed to the conformational differences between the cyclic and the acyclic nucleophiles. On the other hand, a somewhat speculative reason could be that the cyclic carbamate, with the NH-CO-bond in the thermodynamically less favored s-cis configuration, is more prone to give nucleophilic attack than the more stable acyclic NH. Furthermore, neither variation of the N-substituents on the linear substrates (sulfonyl, acetate, benzyl), nor going from a cyclic carbamate to a lactam could change this behavior. This shows that the influence of the protecting group is apparently of less importance than the orientation of the nucleophile with respect to the allene.

5.6 Conclusions

In this chapter, it was shown that Pd-catalyzed coupling/cyclization reactions of β-amino allenes – the amine function separated from the allene by a two-carbon tether – can selectively lead to four- or six-membered nitrogen heterocycles without loss of enantiopurity and in high yields. In particular, vinyl triflates show a promising selectivity in the cyclization processes leading to the four-membered rings. In addition, it was shown that via conversion into the conformationally restricted oxazolidinone analogues, the corresponding five-membered rings were also accessible starting from the same amino acid.
5.7 Acknowledgements

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5.8 Experimental section

For general experimental details, see: Section 2.6.

N-(4-Toluenesulfonyl)-3,4-pentadienylamine (8). To a solution of alcohol 20 (1.20 g, 14.3 mmol) in CH₂Cl₂ (20 mL), pyridine (6.00 mL, 71.5 mmol) and p-toluenesulfonyl chloride (2.99 g, 15.7 mmol) were added. The reaction mixture was stirred for 19 h at ambient temperature. The reaction mixture was concentrated in vacuo. An aqueous solution of saturated CuSO₄ was added. The mixture was extracted with ether (3 × 20 mL). The combined organic layers were washed with H₂O, dried (MgSO₄) and concentrated. Unpurified 21 (2.60 g, 10.9 mmol, 76%) was obtained as a colorless oil. Rf = 0.86 (70% ether/PE), ¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, J = 8.3 Hz, 2H, Ar-H), 7.33 (d, J = 8.0 Hz, 2H, Ar-H), 4.99 (quin, J = 6.7 Hz, 1H, CH₂CH=C), 4.67-4.64 (m, 2H, C=CH₂), 4.07 (t, J = 6.7 Hz, 2H, OCH₂CH₂), 2.43 (s, 3H, Ts-CH₃), 2.36-2.30 (m, 2H, CH₂CH=C). To a solution of crude 21 (0.50 g, 2.10 mmol) in DMF (10.0 mL) a solution of sodium azide (1.37 g, 21.0 mmol) in H₂O (6 mL) was added. The reaction mixture was stirred at 50 °C for 2 h. Water was added (10 mL) and the reaction mixture was extracted with ether (3 × 15 mL). The combined organic layers were dried (MgSO₄) and concentrated. The crude product was slowly added to a solution of LiAlH₄ (0.24 g, 6.30 mmol) in ether (15 mL). After refluxing for 4 h, the reaction mixture was cooled to 0 °C and treated dropwise with water (10 mL). The reaction mixture was extracted with ether (2 ×15 mL) and the combined organic layers were extracted with H₂O (10 mL). The ether was carefully removed via distillation. The crude product (22) was dissolved in pyridine (10 mL) and p-toluenesulfonyl chloride (511 mg, 2.89 mmol) was added. After stirring for 19 h at ambient temperature, the reaction mixture was concentrated in vacuo. An aqueous solution of saturated CuSO₄ was added and extracted with ether (3 × 20 mL). The combined organic layers were washed with H₂O, dried (MgSO₄) and concentrated. After purification of the crude product by flash chromatography (50%, 70% ether/PE), 8 (136 mg, 0.61 mmol, 29%) was obtained as a yellow oil. Rf = 0.33 (70% ether/PE), ¹H NMR (400 MHz, CDCl₃) δ 7.73 (d, J = 8.3 Hz, 2H, Ar-H), 7.28 (d, J = 8.2 Hz, 2H, Ar-H), 4.97 (t, J = 6.7 Hz, 1H, NH), 4.85-4.83 (m, 1H, CH₂CH=C), 4.68-4.65 (m, 2H, C=CH₂), 3.02 (q, J = 6.6
Hz, 2H, NHCH₂CH₂), 2.42 (s, 3H, Ts-CH₃), 2.16-2.10 (m, 2H, CH₂CH=C), ¹³C NMR (100 MHz, CDCl₃) δ 209.50 (CH=C=CH₂), 143.24, 136.92, 129.46, 126.97 (Ar), 86.32 (CH=CH=CH₂), 75.77 (CH=CH₂CH₃), 42.18 (NHCH₂) 28.11 (CH₂CH=), 21.36 (CH₃), IR (film) ν 3276, 2962, 2924, 1955, 1598, 1325, 1158, 1094 cm⁻¹, HRMS (EI) calculated for C₁₄H₁₅NO₄S 237.0824, found 237.0820.

N-(4-Nitrobenzenesulfonyl)3,4-pentadienylamine (23). To a solution of 20 (50.0 mg, 0.59 mmol) in toluene (4.0 mL) triphenylphosphine (158 mg, 0.59 mmol) and diethyl azodicarboxylate (94.0 μL, 0.59 mmol) were added. After stirring for 5.5 h at ambient temperature an aqueous saturated solution of NH₄Cl was added (10 mL). The reaction mixture was extracted with ether (3 × 10 mL), dried (MgSO₄) and concentrated. After purification of the crude product by flash chromatography (20%, 50%, 70% ether/PE) 23 (45 mg, 0.17 mmol, 28%) was obtained as a colorless oil. Rₚ = 0.84 (100% ether), ¹H NMR (400 MHz, CDCl₃) δ 8.35 (d, J = 8.9 Hz, 2H, Ar-H), 8.05 (d, J = 8.9 Hz, 2H, Ar-H), 5.06-5.02 (m, 1H, NH), 4.98 (quin, J = 6.6 Hz, 1H, CH₂CH=C), 4.71-4.67 (m, 2H, C=CH₂), 3.02 (q, J = 6.5 Hz, 2H, NHCH₂CH₂), 2.20-2.14 (m, 2H, CH₂CH=C).

(R)-2-(Toluene-4-sulfonylamino)-hexa-4,5-dienoic acid methyl ester (25). To a solution of 24 (100 mg, 0.79 mmol) in MeOH (2.0 mL) thionyl chloride (112 μL, 1.57 mmol) was added. After refluxing at 70 °C for 5 h the reaction mixture was concentrated in vacuo. The crude methyl ester 24b was dissolved in pyridine (2.0 mL) treated with p-toluenesulfonyl chloride (225 mg, 1.18 mmol) and stirred for 16 h at ambient temperature. The pyridine was evaporated and aqueous saturated CuSO₄ (10 mL) was added. The reaction mixture was extracted with CH₂Cl₂ (3 × 10 mL) and the combined organic layers were washed with aqueous saturated sodium bicarbonate (10 mL) added by brine (10 mL), dried (MgSO₄) and concentrated. After purification of the crude product by flash chromatography (70 % ether/PE) 25 (112 mg, 0.80 mmol, 48%) was obtained as an amorphous solid. Rₚ = 0.51 (70% ether, PE), [α]D = -30 (c =1, CH₂Cl₂), ¹H NMR (400 MHz, CDCl₃) δ 7.72 (d, J = 8.3 Hz, 2H, Ar-H), 7.29 (d, J = 8.2 Hz, 2H, Ar-H), 5.21-5.10 (m, 1H, NH), 5.00-4.85 (m, 1H, CH₂CH=C), 4.70-4.66 (m, 2H, C=CH₂), 4.06-4.03 (m, 1H, NHCH₂CO₂Me), 3.55 (s, 3H, CO₂CH₃), 2.44-2.42 (m, 2H, CH₂CH₂CH=), 2.42 (s, 3H, Ts-CH₃), ¹³C NMR (100 MHz, CDCl₃) δ 209.61 (CH=C=CH₂), 171.07 (CO₂CH₃), 143.55, 136.73, 129.51, 127.11 (Ar), 83.61 (CH=CH=CH₂), 75.35 (CH=C=CH₂), 55.29 (CO₂CH₃), 52.35 (CH₂CH₃), 32.48 (CH₂CH₂), 21.39 (CH₃), IR (film) ν 1955, 1733, 1339, 1161 cm⁻¹, HRMS (EI) calculated for C₁₄H₁₅NO₄S 295.09, found 295.

(R)-2-Benzylaminohexa-4,5-dienoic acid methyl ester (26). To a solution of the crude methyl ester 24b (97.0 mg, 0.55 mmol) in CH₂Cl₂ (3.0 mL) triethylamine (84.0 μL, 0.61 mmol), benzaldehyde (56.0 μL, 0.55 mmol) and 4Å molecular sieves (200 mg) were added. After
stirring for 19 h at ambient temperature the reaction mixture was diluted with ether (5.0 mL), filtrated over Celite and concentrated. The crude residu was then dissolved in MeOH (3.0 mL), cooled to 0 °C and NaBH₄ (21.0 mg, 0.55 mmol) was added. After stirring for 30 min at 0 °C the reaction mixture was poured into 1M HCl (10 mL) and extracted with ether (3 × 10 mL). The pH was raised to 10 and the reaction mixture was extracted again with ether (3 × 10 mL), dried (MgSO₄), and concentrated. Without further purification 26 (82.0 mg, 0.35 mol, 65%) was obtained. ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.23 (m, 5H, Ar-H), 5.08 (quin, J = 7.0 Hz 1H, CH₂CH=C), 4.70-4.66 (m, 2H, C=CH₂), 3.72 (s, 3H, CO₂CH₃), 3.68 (d, J = 13.0 Hz, 1H, CH₂Ph), 3.39 (t, J = 6.3 Hz, 1H, NHCHCO₂Me), 2.43-2.36 (m, 2H, CHCH₂CH), ¹³C NMR (100 MHz, CDCl₃) δ 209.20 (CH₂CH=C=CH₂), 174.72 (CO₂CH₃), 139.58, 128.27, 128.13, 126.97 (Ar), 85.39 (CH=CH₂), 74.93 (CH=CH₂), 60.20 (CO₂CH₃), 51.85 (CH₂Ph), 51.63 (CHCH₂), 32.31 (CHCH₂), IR (film) ν 3028,2952,2842,1956,1729,1197 cm⁻¹.

(R)-2-(Methoxycarbonylamino)hexa-4,5-dienoic acid methyl ester (27). To a solution of methyl ester 24b (96.0 mg, 0.55 mmol) in CH₂Cl₂ (2.0 mL), CICO₂Me (64.0 μL, 0.83 mmol) and Et₃N (200 μL, 1.37 mmol) were added at 0 °C. After stirring for 2 h at 0 °C, the reaction mixture was poured into an aqueous saturated solution of NH₄Cl (10 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried (MgSO₄) and concentrated. After purification of the crude product by flash chromatography (70 % ether/PE), 27 (47.0 mg, 0.24 mmol, 43%) was obtained as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 5.32-5.20 (m, 1H, NH), 4.97 (quin, J = 7.0 Hz, 1H, CH₂CH=C), 4.71-4.68 (m, 2H, C=CH₂), 4.45-4.42 (m, 1H, NHCHCO₂Me), 3.73 (s, 3H, CO₂CH₃), 367 (s, 3H, CO₂CH₃), 2.53-2.43 (m, 2H, CHCH₂CH), IR (film) ν 3323,3001,2951,1956,1746,1699,1538,1218,1066 cm⁻¹.

(R)-2-Acetylamino-hexa-4,5-dienoic acid methyl ester (28). To a solution of 24 (100 mg, 0.61 mmol) in CH₂Cl₂ (2.0 mL), acetic anhydride (116 μL, 1.22 mmol) and pyridine (195 μL, 2.44 mmol) were added. After stirring for 16 h at ambient temperature the solvent was evaporated. The crude product was dissolved in MeOH (2.0 mL) and thionyl chloride (174 μL, 2.44 mmol) was added. After refluxing for 4 h, the mixture was concentrated and purified by flash chromatography (70 %, 100% ether/PE) to afford 28 (44.0 mg, 0.24 mmol, 44%) as a yellow amorphous solid. ¹H NMR (400 MHz, CDCl₃) δ 6.10-6.00 (bs, 1H, NH), 5.98 (quin, J = 6.9 Hz 1H, CH₂CH=C), 4.72-4.69 (m, 3H, C=CH₂, NHCHCO₂Me), 3.75 (s, 3H, CO₂CH₃), 2.61-2.52 (m, 1H, CHCH₂), 2.50-2.40 (m, 1H, CHCH₂), 2.02 (s, 3H, COCH₃).

General cyclization procedure A:
To a solution of the β-amino allene, RX (5 equiv) and K₂CO₃ (5 equiv) in DMF (0.1 M), Pd(PPh₃)₄ (10 mol%) was added under an inert atmosphere. The reaction was carried out
under the indicated conditions and quenched with saturated aqueous NH₄Cl. The mixture was extracted with ether (3 ×), dried with MgSO₄, and concentrated. The residue was purified with column chromatography to afford the pure products.

2-(1-Phenylvinyl)-1-(toluene-4-sulfonyl)azetidine (33a). Following the general procedure A, 8 (45.0 mg, 0.20 mmol) in DMF (2.0 mL) was reacted with K₂CO₃ (139 mg, 1.01 mmol), iodobenzene (113 µL, 1.01 mmol) and Pd(PPh₃)₄ (23.0 mg, 0.02 mmol) to give after flash column chromatography (50%, 70% ether/PE), a 2:1 mixture of 33a and 33b (42 mg, 0.14 mmol, 67%) as a colorless oil. 33a Rₐ = 0.6 (70% ether/PE), ¹H NMR (400 MHz, CDCl₃) δ 7.76 (d, J = 8.2 Hz, 2H, Ar-H), 7.36 (d, J = 8.0 Hz, 2H, Ar-H), 7.33-7.26 (m, 5H, Ar-H), 5.68 (t, J = 1.1 Hz, 1H, C=CH₂), 5.49 (s, 1H, C=CH₂), 4.80 (t, J = 8.3 Hz, 1H, C=CCHN), 3.77-3.72 (m, 2H, NCH₂), 2.46 (s, 3H, Ts-CH₃), 2.26-2.18 (m, 1H, CHCH₂CH₂), 2.05-1.98 (m, 1H, CH₂CH=), 13C NMR (100 MHz, CDCl₃) δ 146.03 (C=CH₂), 143.90, 137.98, 132.31, 129.61, 129.59, 128.40, 128.30, 127.72, 125.10 (Ar), 47.11 (NCH₂), 24.45 (CH₂), 21.47 (CH₃), IR (film) v 2922, 1597, 1345, 1163, 1094 cm⁻¹, HRMS (FAB): calculated for C₂₈H₂₂N₂O₂S (MH⁺) 314.1215, found 314.1223.

5-Chloro-2-{1-[1(toluene-4-sulfonyl)azetidine-2-yl]vinyl}pyridine (34a). Following the general procedure A, 8 (25.0 mg, 0.11 mmol) in DMF (1.0 mL) was reacted with K₂CO₃ (77.0 mg, 0.56 mmol), 2-chloro-4-iodopyridine (29) (135 mg, 0.56 mmol) and Pd(PPh₃)₄ (13.0 mg, 0.01 mmol) to give after flash column chromatography (20% ether/PE) a 1:3 mixture of 34a and 34b (12.0 mg, 0.04 mmol, 55%) as a yellow oil. Rₐ = 0.23 (70% ether/PE), ¹H NMR (400 MHz, CDCl₃) δ 8.27 (d, J = 2.4 Hz, 0.3H, Ar-H), 8.15 (d, J = 2.2 Hz, 1H, Ar-H), 7.74-7.66 (m, 2.6H, Ar-H), 7.42-7.21 (m, 5.2H, Ar-H), 6.69 (s, 1H, 34b C=CH), 5.72 (s, 0.3H, 34a C=CH₂), 5.49 (s, 0.3H, 34a C=CH₂), 4.69 (m, 0.3H, 34a =CCHN), 3.88-3.80 (m, 0.6H, 34a NCH₂), 3.70 (t, J = 6.8 Hz, 2H, 34b =CCH₂N), 2.68-2.58 (m, 0.6H, 34a NCH₂CH₂), 2.51-2.48 (m, 2H, 34b NCH₂), 2.44 (s, 1H, 34a Ar-H-CH₂), 2.42 (s, 3H, 34b Ts-CH₃), 2.20-2.13 (m, 0.6H, 34a NCH₂CH₂), 1.84 (quin, J = 7.0 Hz, 2H, 34b C=CHCH₂).

5-(1-Methylvinyl)-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydropyridine (35b). Following the general procedure A, 8 (25.0 mg, 0.11 mmol) in DMF (1.0 mL) was reacted with K₂CO₃ (77.0
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mg, 0.56 mmol), 2-bromopropene (50.0 µL, 0.56 mmol) and Pd(PPh$_3$)$_4$ (13.0 mg, 0.01 mmol) to give after column chromatography (20% ether/PE) 35b (7 mg, 0.03 mmol, 24%) as a yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.79 (d, $J = 8.35$ Hz, 2H, Ar-H), 7.31 (d, $J = 8.0$ Hz, 2H, Ar-H), 5.88-5.85 (m, 1H, C=CH), 4.86 (d, $J = 14.4$ Hz, 2H, C=CH$_2$), 3.77 (d, $J = 1.9$ Hz, 2H, NCH$_2$C=CH), 3.15 (t, $J = 5.8$ Hz, 2H, NCH$_2$CH$_2$), 2.42 (s, 3H, Ts-CH$_3$), 2.40-2.31 (m, 2H, CH$_2$CH$_2$C=CH), 1.55 (s, 3H, CH$_3$C=CH$_2$).

2-[1-(4-tert-Butylcyclohex-1-enyl)vinyl]-1-(toluene-4-sulfonyl)azetidin (36a). Following the general procedure A, 8 (25.0 mg, 0.11 mmol) in DMF (1.0 mL) was reacted with K$_2$CO$_3$ (77.0 mg, 0.56 mmol), vinyl triflate 31 (160 mg, 0.56 mmol) and Pd(PPh$_3$)$_4$ (13.0 mg, 0.01 mmol) to give after flash column chromatography (20% ether/PE) 36a (14 mg, 0.04 mmol, 34%) as a colorless oil. $R_f = 0.23$ (70% ether/PE), $^1$H NMR (400 MHz, CDCl$_3$) δ 7.73 (d, $J = 7.8$ Hz, 2H, Ar-H), 7.36 (d, $J = 8.0$ Hz, 2H, Ar-H), 5.54 (d, $J = 5.6$ Hz, 1H, C=CH$_2$), 5.46 (m, 1H, C=CH), 5.17 (s, 1H, C=CH$_2$), 4.75-4.68 (m, 1H, CH$_2$C=CHN), 3.74-3.70 (m, 2H, NCH$_2$C=CH), 2.46 (s, 3H, Ts-CH$_3$), 2.38-2.06 (m, 5H, CH$_2$), 1.93-1.88 (m, 3H, CH$_2$), 1.23-1.12 (m, 1H, CH$^t$Bu), 0.86 (s, 9H, t-Bu). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 146.04 (C=CH), 143.70 (C=CH$_2$), 133.23, 132.42, 129.53, 128.31 (Ar), 123.97 (C=CH), 110.58 (C=CH$_2$), 64.04 (CH$_2$=CCHN), 47.28 (NCH$_2$), 32.05 (C=CH$_2$), 27.37 (CH$_2$=CHC), 27.19 (CH$_3$), 27.01 (CH$_3$), 25.64 (C=CH$_2$), 25.26 (C=CH$_2$), 23.91 (CHCH$_3$), 21.47 (Ts-CH$_3$), IR (film) ν 2922, 1360, 1184, 1094 cm$^{-1}$, HRMS (FAB): calculated for C$_{30}$H$_{32}$NO$_2$S (MH$^+$) 373.2076, found 373.2088. The structure was proven with COSY, NOESY, CH correlation and NOE experiments.

2-(2-Butyl-1-methyleneallyl)-1-(toluene-4-sulfonyl)azetidin (37a). Following the general procedure A, 8 (25.0 mg, 0.11 mmol) in DMF (1.0 mL) was reacted with K$_2$CO$_3$ (77.0 mg, 0.56 mmol), vinyl triflate 32 (130 mg, 0.56 mmol) and Pd(PPh$_3$)$_4$ (13.0 mg, 0.01 mmol) to give after flash column chromatography (20% ether/PE) a 95:5 mixture of 37a and 37b (14.0 mg, 0.04 mmol, 41%) as a colorless oil. Data of the major isomer 37a: $R_f = 0.62$ (70% ether/PE), $^1$H NMR (400 MHz, CDCl$_3$) δ 7.82 (d, $J = 8.2$ Hz, 2H, Ar-H), 7.35 (d, $J = 8.2$ Hz, 2H, Ar-H), 5.69 (s, 1H, NCHC=CH$_2$), 5.30 (s, 1H, NCHC=CH$_2$), 4.88 (s, 1H, C=CH$_2$), 4.69 (s, 1H, C=CH$_2$), 3.75-3.70 (m, 2H, NCH$_2$), 4.65 (q, $J = 7.0$ Hz, 1H, NCHC=C), 2.44 (s, 3H, Ts-CH$_3$), 2.26-2.21 (m, 2H, CH$_2$C=C), 1.94-1.87 (m, 1H, CHCH$_2$CH$_2$), 1.50-1.16 (m, 2H, CH$_2$), 0.91 (t, $J = 7.2$ Hz, 3H, CH$_3$CH$_2$), $^{13}$C NMR (100 MHz, CDCl$_3$) δ 145.29 (n-BuC=CH$_2$), 144.81 (CHC=CH$_2$), 143.81, 132 (CqAr), 129.56, 128.31 (Ar), 112.56 (n-BuC=CH$_2$), 110.92 (C=CH$_2$), 64.08 (C=CH$_2$), 47.18 (NCH$_2$) 33.96 (CH$_2$C=CH$_2$), 30.65 (CH$_2$CH$_2$C=CH$_2$), 25.16 (CH$_2$CH$_3$), 22.42 (CH$_3$CH$_2$), 21.47 (Ts-CH$_3$), 13.82 (CH$_3$CH$_2$), IR (film) ν 2956, 2929, 2870, 1347, 1163, 1094 cm$^{-1}$. 129
1-(4-Nitrobenzenesulfonyl)-5-phenyl-1,2,3,6-tetrahydropyridine (38b). Following the general procedure A, 23 (45.0 mg, 0.17 mmol) in DMF (2.0 mL) was reacted with K$_2$CO$_3$ (116 mg, 0.84 mmol), iodobenzene (94.0 µL, 0.84 mmol) and Pd(PPh$_3$)$_4$ (19.0 mg, 0.02 mmol) to give after column chromatography (20% ether/PE) 38b (32.0 mg, 0.09 mmol, 55%) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.35 (d, J = 8.5 Hz, 2H, Ar-H), 8.02 (d, J = 8.5 Hz, 2H, Ar-H), 7.36-7.26 (m, 5H, Ar-H), 6.09-6.07 (m, 1H, C=CH), 4.05-4.04 (m, 2H, NCH$_2$C=CH), 3.37-3.30 (m, 2H, NCH$_2$CH$_2$), 2.39-2.38 (m, 2H, C=CHCH$_2$), 13C NMR (100 MHz, CDCl$_3$) δ 150.02, 143.01, 141.17. IR (film) ν 2836, 1529, 1349, 1169 cm$^{-1}$, HRMS (FAB): calculated for C$_{17}$H$_{16}$N$_2$O$_4$S (MH$^+$) 344.0831, found 344.0847.

(2R,4S)-4-(1-Phenyl-vinyl)-1-(toluene-4-sulfonyl)azetidine-2-carboxylic acid methyl ester (39a). Following the general procedure A, 25 (25.0 mg, 0.08 mmol) in DMF (1.0 mL) was reacted with K$_2$CO$_3$ (58.0 mg, 0.42 mmol), iodobenzene (47.0 µL, 0.42 mmol) and Pd(PPh$_3$)$_4$ (9.000 mg, 0.01 mmol) to give after column chromatography (20% ether/PE, Et$_3$N) a 70:30 mixture of 39a and 39b (26.0 mg, 0.07 mmol, 84%) as colorless oils. 39a; $\alpha$ = +4.0 (c = 1, CHCl$_3$), $^1$H NMR (400 MHz, CDCl$_3$) δ 7.81 (d, J = 8.3 Hz, 2H, Ar-H), 7.34-7.30 (m, 7H, Ar-H), 6.04-6.01 (m, 1H, C=CH), 4.70 (dd, J = 3.4, 5.1 Hz, 1H, NCH$_2$CO$_2$Me), 3.72 (s, 3H, CO.CH$_3$), 2.72-2.71 (m, 2H, C=CHCH$_2$), 2.45 (s, 3H, Ts-CH$_3$), 2.09 (dt, J = 7.7, 3.3 Hz, 1H, CH$_2$), 13C NMR (100 MHz, CDCl$_3$) δ 170.39 (C0$_2$CH$_3$), 146.03 (C=CH$_2$), 144.02, 137.68, 136.10, 129.46, 128.33, 128.86, 126.11 (Ar), 114.83 (C=CH$_2$), 61.62 (C=CH=CHN), 56.72 (NCH$_2$CO$_2$Me), 52.23 (CO$_2$CH$_3$), 28.38 (CH$_3$), 21.50 (Ts-CH$_3$), IR (film) ν 2967, 2923, 2853, 1747, 1457, 1340, 1163 cm$^{-1}$, HRMS (EI): calculated for C$_{20}$H$_{21}$NO$_4$S 371.1191, found 371.1195. (R)-5-Phenyl-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydro-pyridine-2-carboxylic acid methyl ester (39b); $\alpha$ = 0.37 (70% ether/PE), $[\alpha]_D$ = +4.0 (c = 1, CHCl$_3$), $^1$H NMR (400 MHz, CDCl$_3$) δ 7.71 (d, J = 8.3 Hz, 2H, Ar-H), 7.34-7.27 (m, 7H, Ar-H), 6.04-6.01 (m, 1H, C=CH), 4.93 (dd, J = 3.4, 5.1 Hz, 1H, NCH$_2$CO$_2$Me), 4.48 (dd, J = 2.0, 16.4 Hz, 1H, NCH$_2$C=CH), 4.15 (dd, J = 2.2, 16.4 Hz, 1H, NCH$_2$C=CH), 3.49 (s, 3H, CO$_2$CH$_3$), 2.72-2.71 (m, 2H, C=CHCH$_2$), 2.42 (s, 3H, Ts-CH$_3$), $^1$C NMR (100 MHz, CDCl$_3$) δ 170.70 (CO$_2$CH$_3$), 143.31, 138.17, 136.11, 133.67 (C=CH), 129.39, 127.18, 128.39, 127.74, 125.04 (Ar), 119.17 (C=CH), 52.13 (CO$_2$CH$_3$), 52.05 (NCH$_2$CO$_2$Me), 43.40 (NCH$_3$), 29.57 (C=CHCH$_2$), 21.41 (Ts-CH$_3$), IR (film) ν 2967, 2853, 1747, 1457, 1340, 1163 cm$^{-1}$, HRMS (EI): calculated for C$_{20}$H$_{21}$NO$_4$S 371.1191, found 371.1195.

(2R,4S)-4-[1-(4-tert-Butylcyclohex-1-enyl)vinyl]-1-(toluene-4-sulfonyl)azetidine-2-carboxylic acid methyl ester (40a). Following the general procedure A, 25 (25.0 mg, 0.08 mmol) in DMF (1.0 mL) was reacted with K$_2$CO$_3$ (58.0 mg, 0.42 mmol), 31 (121 mg, 0.42 mmol) and Pd(PPh$_3$)$_4$,
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(9.00 mg, 0.01 mmol) to give after column chromatography (20% 50% ether/PE, Et₂N) a 88:12 mixture of 40a and 40b (35.0 mg, 0.08 mmol, 96%) as colorless oils. Analytically pure samples were obtained after separation on a chiral HPLC (Chiralcel OD) column. HPLC ee >93%. Rf = 0.62 (70% ether/PE), [α]D = -15.0 (c = 0.5, CH₂Cl₂). 1H NMR (400 MHz, CDCl₃) δ 7.79 (d, J = 8.2 Hz, 2H, Ar-H), 7.32 (d, J = 8.0 Hz, 2H, Ar-H), 5.53-5.49 (m, 1H, C=CH), 5.33 (d, J = 10.6 Hz, 1H, C=CH₂), 5.07 (s, 1H, C=CH₂), 4.92-4.86 (m, 1H, C=CH₂), 4.63-4.68 (m, 1H, NCH₂CO₂Me), 3.70 (s, 3H, CO₂CH₃), 2.64-2.71 (m, 1H, CHCH₂CH₂), 2.44 (s, 3H, Ts-CH₂), 2.25-2.28 (m, 1H, CHCH₂(CH₂)₂), 2.12-2.00 (m, 2H, CH₂CH=), 1.99-1.96 (m, 2H, CH₂=C=CH₂), 1.80-1.84 (m, 2H, 'BuCH₂CH₂), 1.20-1.18 (s, 9H, t-Bu), 13C NMR (100 MHz, CDCl₃) δ 170.57 (CO₂Me), 145.42 (C=CH), 143.88 (Ar), 135 (C=CH₂), 133.14, 133.06, 129.40, 128.15 (Ar), 124.32 (C=CH₂), 110.07 (C=CH₂), 60.70 (NCH₂CO₂Me), 57.00 (NCH₂=CH₂), 52.18 (CO₂CH₂), 43.57 (CH₂Bu), 31.99 (Cq'Bu), 29.38 (CH=CH₂), 29.04 (CH₂CH=CH₂), 27.32 (CH₂CH₂CH₂), 27.26 (CH₂), 27.19 (CH₃), 27.12 (CH₃), 23.85 (CH₂CH₂CH₂), 21.49 (Ts-CH₂), IR (film) v 2954, 1749, 1338, 1159, cm⁻¹, HRMS (FAB): calculated for C₃H₅N₂O₃S (MH⁺) 432.2209, found 432.2207. (R)-5-(4-tet-Butylcyclohex-1-enyl)-1-(toluene-4-sulfonfonyl)-1,2,3,6-tetrahydropyridine-2-carboxylic acid methyl ester (40b). Rf = 0.62 (70% ether/PE), 1H NMR (400 MHz, CDCl₃) δ 7.68 (d, J = 8.3 Hz, 2H, Ar-H), 7.28-7.26 (m, 7H, Ar-H), 5.70-5.62 (m, 2H, C=CH, C=CH₂), 4.97-4.91 (m, 1H, NCH₂CO₂Me), 4.32-4.21 (m, 1H, CH=CH₂CH₂), 3.98-3.88 (m, 1H, CH₂=CH₂CH₂), 3.49 (s, 3H, CO₂CH₃), 2.70-2.60 (m, 2H, CHCH₂CH=), 2.41 (s, 3H, Ts-CH₂), 2.3-1.8 (m, 4H, CH₂, CH₃), 1.35-1.05 (m, 2H, CH₂), 0.85 (s, 9H, t-Bu).

(2R,4S)-4-(2-Butyl-1-methylenallyl)-1-(toluene-4-sulfonfonyl)azetidine-2-carboxylic acid methyl ester (41a). Following the general procedure A, 25 (25.0 mg, 0.08 mmol) in DMF (1.0 mL) was reacted with K₂CO₃ (58.0 mg, 0.42 mmol), 32 (98.0 mg, 0.42 mmol) and Pd(PPh₃)₄ (9.00 mg, 0.01 mmol) to give after column chromatography (20% ether/PE, Et₂N) a 95:5 mixture of 41a and 41b (20.0 mg, 0.05 mmol, 63%) as colorless oils. Data of the major isomer 41a: Rf = 0.53 (70% ether/PE), [α]D = -9.2 (c = 0.9, CH₂Cl₂). 1H NMR (400 MHz, CDCl₃) δ 7.78 (d, J = 8.2 Hz, 2H, Ar-H), 7.32 (d, J = 8.1 Hz, 2H, Ar-H), 5.49 (s, 1H, C=CH₂), 5.20 (s, 1H, C=CH₂), 4.90 (s, 1H, C=CH₂), 4.85-4.81 (m, 1H, =CCHN), 4.73 (s, 1H, C=CH₂), 4.65 (dd, J = 2.0, 7.6 Hz, 1H, NCH₂CO₂Me), 3.71 (s, 3H, CO₂CH₃), 2.70-2.63 (m, 1H, CHCH₂CH₂), 2.44 (s, 3H, Ts-CH₂), 2.18 (t, J = 7.3 Hz, 2H, CH₂=C=CH₂), 1.94-2.01 (m, 1H, CHCH₂CH₂), 1.42-1.25 (m, 2H, CH₂, CH₃), 0.92-0.85 (m, 3H, 3H, CH₃CO₂), 13C NMR (100 MHz, CDCl₃) δ 170.50 (CO₂Me), 144.80 (C=CH₂), 144.62 (C=CH₂), 143.99, 134.37, 129.44, 128.17 (Ar), 113.17 (nBuC=CH₂), 111.20 (C=CH₂), 60.87 (NCH₂CO₂Me), 56.89 (CH₂=CCHN), 52.21 (CO₂CH₃), 33.87 (CH₂C=CH₂), 30.44 (CH₂CH₂C=CH₂), 29.02 (CH₂CH₂CH₂), 22.38 (CH₂CH₂), 21.49 (Ts-CH₂), 13.80 (CH₂CH₂), IR (film) v 2955, 1752, 1336, 1159, 1093 cm⁻¹, HRMS (FAB): calculated for C₅H₉N₂O₃S (MH⁺) 378.1739, found 378.1743.
(R)-1-Benzyl-5-phenyl-1,2,3,6-tetrahydropyridine-2-carboxylic acid methyl ester (42b).

Following the general procedure A, 26 (40.0 mg, 0.17 mmol) in DMF (2.0 mL) was reacted with K$_2$CO$_3$ (119 mg, 0.86 mmol), iodobenzene (96.0 μL, 0.86 mmol) and Pd(PPh$_3$)$_4$ (20.0 mg, 0.02 mmol) to give after column chromatography (5% 20% ether/PE) 42b (40.0 mg, 0.13 mmol, 76%) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.41-7.23 (m, 10H, Ar-H), 6.12-6.09 (m, 1H, C=CH), 3.98 (q, $J = 13.4$ Hz, 2H, CH$_2$Ph), 3.83-3.82 (m, 1H, CH=CCH$_2$N), 3.68 (s, 3H, CO$_2$CH$_3$), 3.65 (dd, $J = 3.6, 6.2$ Hz, 1H, NCHCO$_2$Me), 3.62-3.52 (m, 1H, CH=CCH$_3$N), 2.70-2.64 (m, 2H, CH$_2$CH=CH$_2$), $^{13}$C NMR (100 MHz, CDCl$_3$) δ 173.3 (CQ,CH$_3$), 139.49 (C=CH), 138.39, 135.30, 128.78, 128.26, 128.18, 127.05, 124.84, (Ar), 119.55 (C=CH), 59.16 (CH$_2$Ph), 57.57 (CO$_2$CH$_3$), 51.24 (NCHCO$_2$Me), 50.11 (NCH$_2$), 28.53 (C=CHCH$_2$), IR (film) ν 3028, 2950, 2925, 1731, 1495, 1193, 1163 cm$^{-1}$.

(2R,4S)-4-(Phenylvinyl)azetidine-1,2-dicarboxylic dimethyl ester (43a). Following the general procedure A, 27 (47.0 mg, 0.24 mmol) in DMF (2.0 mL) was reacted with K$_2$CO$_3$ (163 mg, 1.18 mmol), iodobenzene (132 μL, 1.18 mmol) and Pd(PPh$_3$)$_4$ (27.0 mg, 0.02 mmol) to give after column chromatography (50% 70% ether/PE) a 42:58 mixture of 43a and 43b (24.0 mg, 0.08 mmol, 33%) as a white solid. The isomers 43a and 43b were separated via column chromatography (50% 70% ether/PE). 43a: Mp 90-91 °C, $^1$H NMR (400 MHz, CDCl$_3$) δ 7.35-7.26 (m, 5H, Ar-H), 5.69 (s, 1H, C=CH$_2$), 5.56 (s, 1H, C=CH$_2$), 5.08 (t, $J = 7.5$ Hz, 1H, CH$_2$CH=CH$_2$), 4.70 (dd, $J = 6.4, 9.7$ Hz, 1H, NCHCO$_2$Me), 3.76 (s, 3H, CO$_2$CH$_3$), 3.72 (s, 3H, CO$_2$CH$_3$), 2.94-2.87 (m, 1H, CH$_2$), 2.08-2.02 (m, 1H, CH$_2$).

Crystal structure was determined for (2S,4R)-43a obtained starting from (S)-27. Crystallographic data for (2S,4R)-43a monoclinic, P2$_1$, a = 8.080 (1), b = 6.0994 (5), c = 14.463 (1) Å, $b = 92.459 (8)^\circ$, $V = 712.1(1)$ Å$^3$, $Z = 2$, $D_x = 1.28$ gcm$^{-3}$, $\lambda$(Cu$\alpha$) = 1.5418 Å, $\mu$(Cu$\alpha$) = 7.33 cm$^{-1}$, F(000) = 292, -30 °C. Final R = 0.078 for 1554 observed reflections.

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<th>Table 5.3 Bond distances of the non-hydrogen atoms (Å) of 43a (standard deviations)</th>
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Table 5.4 Bond angles of the non-hydrogen atoms (Å) of 43a (standard deviations)

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<td>C(2)-C(3)-N</td>
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<td>C(14)-C(3)-N</td>
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<td>C(1)-C(4)-C(5)</td>
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<td>C(4)-C(6)-C(11)</td>
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<td>C(7)-C(6)-C(11)</td>
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<td>C(6)-C(7)-C(8)</td>
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(R)-5-Phenyl-3,6dihydro-2H-pyridine-1,2-dicarboxylic acid dimethyl ester (43b). 1H NMR (400 MHz, CDCl₃) δ 7.49-7.26 (m, 5H, Ar-H), 5.47 (s, 1H, C=CH), 5.38-5.34 (m, 2H, CH₂N), 4.61 (dd, J = 4.2, 9.0 Hz, 1H, NCHCO₂Me), 3.80 (s, 3H, CO₂CH₃), 3.70 (s, 3H, CO₂CH₂), 2.46-2.42 (m, 1H, CHCH₂CH), 2.31-2.25 (m, 1H, CHCH₂CH).

(2R,4S)-1-Acetyl-4-(1-phenylvinyl)azetidine-2-carboxylic acid methyl ester (44a). Following the general procedure A, 28 (18.0 mg, 0.10 mmol) in DMF (1.0 mL) was reacted with K₂CO₃ (75.0 mg, 0.55 mmol), iodobenzene (61.0 µL, 0.55 mmol) and Pd(PPh₃)₄ (13.0 mg, 0.01 mmol) to give after column chromatography (20% ether/PE) a 67:33 mixture of 44a and 44b (3.00 mg, 0.01 mmol, 12%) as colorless oils. Data of the major isomer 44a; 1H NMR (400 MHz, CDCl₃) δ 7.35-7.24 (m, 5H, Ar-H), 5.41 (m, 1H, C=CH₂), 5.28 (m, 1H, C=CH₂), 5.02-4.96 (m, 1H, CH₂=C(CH₃)₂), 4.72-4.67 (m, 1H, NCHCO₂Me), 3.74 (s, 3H, CO₂CH₃), 2.63-2.45 (m, 2H, CH₂), 2.03 (s, 3H, COCH₃). (R)-1-Acetyl-5-phenyl-1,2,3,6-tetrahydropyridine-2-carboxylic acid methyl ester (44b). 1H NMR (400 MHz, CDCl₃) δ 7.35-7.24 (m, 5H, Ar-H), 5.45 (s, 1H, C=CH₂), 5.18-5.19 (m, 1H, NCHCO₂Me), 4.24-4.19 (m, 1H, CH₂N), 4.12-4.09 (m, 1H, CH₂N), 3.80 (s, 3H, CO₂CH₂), 3.73 (s, 3H, CO₂CH₃), 2.86-2.79 (m, 1H, CHCH₂CH=C), 2.73-2.68 (m, 1H, CHCH₂CH=CH₂), 2.03 (s, 3H, COCH₃).

4-Buta-2,3-dienyloxazolidine-2-one (48). To a solution of 24 (150 mg, 0.85 mmol) in ether (10.0 mL) LiALH₄ (96.1 mg, 2.53 mmol) was added at 0 °C. The reaction mixture was allowed to
reach ambient temperature in 1 h. Then the reaction mixture was heated to reflux for 3 h. After cooling to 0 °C, KOH was added and the reaction mixture was extracted with EtOAc (3 \times 15 \text{ mL}). To the combined organic layers 1 M HCl (15 mL) was added, followed by washing with H$_2$O (3 \times 10 \text{ mL}). The combined organic layers were concentrated in vacuo. The crude alcohol (20.0 mg, 0.134 mmol, 16%) was obtained as a colorless oil. \textit{H} NMR (400 MHz, CD$_3$OD) $\delta$ 5.27 (quin, $J = 6.9$ Hz, 1H, CH$_2$CH=$C$), 4.83-4.80 (m, 2H, C=CH$_2$), 3.80 (dd, $J = 3.9$, 11.7 Hz, 1H, CH$_2$OH), 3.61 (dd, $J = 6.6$, 11.8 Hz, 1H, CH$_2$OH), 3.33-3.30 (m, 1H, NHCHCO$_2$Me), 2.41-2.32 (m, 2H, CHCH$_2$CH). To the solution of the crude alcohol in H$_2$O (1.0 mL), NaHCO$_3$ (11.7 mg, 0.139 mmol) was added and the reaction mixture was stirred for 10 min at ambient temperature. The reaction mixture was cooled to $-10$ °C and K$_2$CO$_3$ (20.0 mg, 0.142 mmol) was added. The reaction mixture was stirred for 2 h. Toluen (5 mL) and H$_2$O (5 mL) were added and the different layers were separated. The water layer was lyophilized. The white solid was extracted with CH$_2$Cl$_2$ (15 mL). The extract was dried and concentrated in vacuo to obtain 51 as a colorless oil. \textit{H} NMR (400 MHz, CDCl$_3$) $\delta$ 5.21 (bs, 1H, NH), 5.10 (quin, $J = 6.6$ Hz, 1H, CH$_2$CH=$C$), 4.82-4.78 (m, 2H, C=CH$_2$), 4.51 (t, $J = 8.5$ Hz, 1H, CH$_2$O), 4.10 (dd, $J = 5.6$, 8.6 Hz, 1H, CH$_2$O), 3.98-3.96 (m, 1H, NHCHCO$_2$Me), 2.30-2.26 (m, 2H, CHCH$_2$CH).

5-(Benzylidene)tetrahydropyrrolo[1,2-c]oxazo-3-one (51). A mixture of 48 (209 mg, 1.50 mmol), K$_2$CO$_3$ (799 mg, 6.00 mmol), iodobenzene (1.22 \mu L, 6.00 mmol), Bu$_4$NCl (624 mg, 2.25 mmol) and Pd(PPh$_3$)$_4$ (174 mg, 0.15 mmol) in MeCN (20 mL) was refluxed for 2 h. The mixture was cooled, diluted with water (25 mL) and extracted with ether (3 \times 25 mL). The combined ether layers were washed with water (25 mL) and brine (25 mL), dried (Na$_2$SO$_4$) and concentrated. Chromatography (EtOAc/PE 1:2) afforded 51 (195 mg, 0.90 mmol, 60%) as an oil. $R_f = 0.3$ (30% EtOAC/PE), \textit{H} NMR (400 MHz, CDCl$_3$) $\delta$ 7.31-7.21 (m, 5H, Ar), 4.81 (s, 1H, CH=C), 4.65-4.56 (m, 2H, OCH$_3$), 4.16-4.09 (m, 1H, NCH), 3.87 (d, $J = 16.0$ Hz, 1H, CH$_2$Ph), 3.78 (d, $J = 16.0$ Hz, 1H, CH$_2$Ph), 2.61-2.47 (m, 2H, =CHCH$_2$), $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 157.4 (CO$_2$), 142.7 (C=), 137.5, 129.1, 128.3, 126.4, (Ar), 109.6 (C=CH), 70.5 (OCH$_3$), 59.9 (NCH), 35.0, 33.5 (CH$_2$Ph, CHCH$_2$), IR (film) v 2964, 1758 cm$^{-1}$, HRMS (El) calculated for C$_{13}$H$_{15}$NO$_2$ 215.0946, found 215.0931.

5.9 References and notes

2. For a recent review of Pd-catalyzed reactions of allenes, see: Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. Chem. Rev. 2000, 100, 3067. For nitrogen nucleophiles see e.g.: (a)
Cyclizations of allenes


5. See for example: Kang, S. K.; Bai, T. G.; Kulak, A. N. Synlett 1999, 324.


10. More recently, similar regiochemistry was observed in lanthanide-catalyzed cyclizations of amino allenes: Arredondo, V. M.; McDonald, F. E.; Marks, T. J. Am. Chem. Soc. 1998, 120, 4871.


19. A similar ring expansion (from three- to five-membered rings) has been reported previously: Fugami, K.; Morizawa, Y.; Oshima, K.; Nozaki, H. Tetrahedron Lett. 1985, 26, 857.

