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Asymmetric Allylic Alkylation in Combination with Ring-Closing Metathesis for the Preparation of Chiral N-Heterocycles

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ABSTRACT

Asymmetric copper-catalyzed allylic substitution with methylmagnesium bromide is employed in combination with ring-closing olefin metathesis or ene-yne metathesis to achieve the synthesis of chiral, unsaturated nitrogen heterocycles. The resulting six- to eight-membered chiral heterocycles are accessible in high yields and with excellent enantioselectivities. Nitrogen-containing heterocycles are ubiquitous in naturally occurring compounds, such as alkaloids, but are also key structural features in many biologically active products. Among these, nitrogen heterocycles with various ring sizes bearing stereogenic centers are frequently observed. For example, poisonous frogs produce a variety of biologically active chiral piperidines featuring methyl substituents at the stereocenters. These structures represent interesting targets for synthesis, imposing particular challenges with regard to the construction of the stereogenic centers with high selectivity. One approach that has been frequently exploited is the use of ring-closing metathesis for the construction of N-heterocycles, which has among
We have developed the asymmetric Cu-catalyzed allylic substitution of allylic bromides with Grignard reagents, employing chiral ferrocene-based bishphosphine ligands (Scheme 1).22–26 This catalytic process is especially suited for the introduction of chiral methyl substituents, a structural motif frequently observed in naturally occurring compounds.27 One major advantage of this methodology is that it furnishes terminal olefinic bonds, which represent ideal starting points for further modifications. This concept has been successfully applied in the synthesis of chiral allylic esters, which are important building blocks for the preparation of chiral lactones.28 Similar approaches have been reported for the formation of the corresponding unsaturated piperidines, azepanes or azocanes. One important feature of this approach is the fact that the resulting compounds bearing olefins or dienes are well-suited chiral building blocks for further modifications.

When allyl bromides 1 with terminal olefin substituents were subjected to allylic alkylation conditions (3.0 mol % of CuBr·SMe2, 4.0 mol % of L1 (Taniaphos32–34), 1.2 equiv of MeMgBr in CH2Cl2 at −80 °C), the desired chiral products 2 were obtained in good yields and up to excellent enantioselectivities (reaching 99% ee, Table 1, entry 1). Furthermore, the product distribution of branched (2) to linear (3) was very good, exceeding 92:8 favoring the branched products. To reach full conversion of 1c (n = 3) (Table 1, entry 3), a higher catalyst loading of 6.0 mol % of CuBr·SMe2 and 8.0 mol % of L1 was required. Chiral compounds 2 were subsequently transformed to the corresponding N-heterocycles 4 by ring-closing metathesis (Table 2). With 5.0 mol % of Hoveyda–Grubbs second-generation catalyst,35 the six- to eight-membered rings were obtained in moderate to good yields. The best result was found for the eight-membered unsaturated azocene 4c (77%), which was transformed to the corresponding azocane 3c (Scheme 2).

### Table 1. Asymmetric Allylic Alkylation of Allylic Bromides 1

<table>
<thead>
<tr>
<th>entry</th>
<th>n</th>
<th>branched (2)/linear (3) yield (%) (for 2)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>95:5</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>98:2</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>92:8</td>
<td>72</td>
</tr>
</tbody>
</table>

When allyl bromides 1 with terminal olefin substituents were subjected to allylic alkylation conditions (3.0 mol % of CuBr·SMe2, 4.0 mol % of L1 (Taniaphos32–34), 1.2 equiv of MeMgBr in CH2Cl2 at −80 °C), the desired chiral products 2 were obtained in good yields and up to excellent enantioselectivities (reaching 99% ee, Table 1, entry 1). Furthermore, the product distribution of branched (2) to linear (3) was very good, exceeding 92:8 favoring the branched products. To reach full conversion of 1c (n = 3) (Table 1, entry 3), a higher catalyst loading of 6.0 mol % of CuBr·SMe2 and 8.0 mol % of L1 was required. Chiral compounds 2 were subsequently transformed to the corresponding N-heterocycles 4 by ring-closing metathesis (Table 2). With 5.0 mol % of Hoveyda–Grubbs second-generation catalyst,35 the six- to eight-membered rings were obtained in moderate to good yields. The best result was found for the eight-membered unsaturated azocene 4c (77%), which was transformed to the corresponding azocane 3c (Scheme 2).

### Table 2. Ring-Closing Metathesis of Olefinic Substrates 2

<table>
<thead>
<tr>
<th>entry</th>
<th>n</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>54 (4a)36</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>61 (4b)</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>77 (4c)</td>
<td>98</td>
</tr>
</tbody>
</table>
Table 2 entry 3). It is important to note that the ee of the desired product was not compromised during the reaction.

For the synthesis of chiral N-heterocycles carrying a diene motif, the synthesis started from allylic bromides 5 bearing terminal alkyne substituents of various chain lengths. Under standard allylic substitution conditions, the desired chiral products 6 were isolated in good yields (Table 3). In all cases, excellent regio- and enantioselectivities were achieved (6/7 >95:5, 99% ee). As in the case of the olefinic substrates 1 (Table 1), the longest spacer length (5c, n = 3) required a slightly higher catalyst loading to achieve full conversion (Table 3, entry 3).

For the ene-yne metathesis of compounds 6 to reach full conversion, 5.0 mol % Grubbs first generation catalyst under an ethene atmosphere was employed. The influence of ethene was found to be essential for the reaction to proceed to 8.38,39 The resulting six- and seven-membered nitrogen-containing rings with diene motifs 8a,b were isolated in good yields (Table 4). Again, no loss of ee was observed in this transformation, making this a viable pathway for the construction of chiral nitrogen-containing heterocycles with various ring sizes.

The reaction of 6c under the given conditions did not produce the desired eight-membered ring. The ene-yne metathesis proceeded to the linear product 8c in moderate yields (Scheme 2), where the alkyne moiety of 6c reacted in an intermolecular fashion with ethene instead of intramolecularly with the terminal olefin. Product 8c in turn did not react any further to the desired ring system under the reaction conditions.41

In summary, we have demonstrated that chiral unsaturated heterocycles are available in excellent enantiomeric excess and good yields via a combination of Cu-catalyzed allylic substitution and Ru-catalyzed ring-closing metathesis. Six- to eight-membered nitrogen-containing rings are easily available through this short synthetic pathway. By employing terminal olefins, singly unsaturated rings are accessible while terminal alkynes were transformed to the corresponding dienes in good yields and 99% ee. The obtained compounds are ideal chiral building blocks for further functionalization through the olefinic bonds.

Supporting Information Available: Experimental procedures and spectroscopic data for the reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(36) Reaction reaches full conversion; one unidentified side product is present in the reaction mixture.
(37) Reaction reaches 75% conversion; no side products were observed.
(39) In the absence of an ethene atmosphere, no turnover was observed.
(40) Reaction reaches 90% conversion; one unidentified side product observed.
(41) For optimization results, see the Supporting Information.

Table 3. Asymmetric Allylic Alkylation of Allylic Bromides 5

<table>
<thead>
<tr>
<th>entry</th>
<th>n</th>
<th>branched (6)/linear (7) yield (%) for 6 ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>5a:95 77 (6a) 99</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>5b:96 53 (6b) 99</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>5c:95 82 (6c) 99</td>
</tr>
</tbody>
</table>

* 6.00 mol % of CuBr(SMe)₂ and 8.00 mol % of L1 were used.

Table 4. Ene–Yne Metathesis of Alkyne Substrates 6

<table>
<thead>
<tr>
<th>entry</th>
<th>n</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>77 (8a) 99</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>65 (8b) 99</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>n.d. 99</td>
<td></td>
</tr>
</tbody>
</table>

Scheme 2. Ene–Yne Metathesis of 6c