Highly Enantioselective [3+2] Annulation of Cyclic Enol Silyl Ethers with Donor–Acceptor Cyclopropanes: Accessing 3α-Hydroxy [n.3.0]Carbobicycles

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Angewandte Communications

Asymmetric Catalysis

[n.3.0]Carbobicycles containing a tertiary alcohol moiety located at the ring junction are found as a key structure in a large number of biologically active and naturally occurring molecules such as botrydials, africanol, palustrols, lucinones, furoscrobiculins, etc. (Figure 1).

In the past decades, considerable effort has been focused on the synthesis of these molecules such as botrydials, africanols, palustrols, lucinones, furoscrobiculins, etc. (Figure 1).

In view of the prevalence of [5.3.0]bicyclic skeletons in natural products, we first commenced our study with the screening of BOX ligands using the cycloheptanone-derived enol silyl ether and PMP-substituted cyclopropane (Table 1). Cu(ClO4)2 was employed as the copper(II) source and dichloromethane as the solvent.

Table 1: Reaction optimization.

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>2</th>
<th>L</th>
<th>I [h]</th>
<th>Conv. [%]</th>
<th>d.r.</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2a</td>
<td>L1</td>
<td>24</td>
<td>88</td>
<td>80:20</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>2a</td>
<td>L2</td>
<td>24</td>
<td>92</td>
<td>85:15</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>2a</td>
<td>L3</td>
<td>24</td>
<td>&gt;99</td>
<td>86:14</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>2a</td>
<td>L4</td>
<td>24</td>
<td>&gt;99</td>
<td>84:16</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>2a</td>
<td>L5</td>
<td>24</td>
<td>&gt;99</td>
<td>85:15</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>1a</td>
<td>2a</td>
<td>L6</td>
<td>24</td>
<td>&gt;99</td>
<td>82:18</td>
<td>97</td>
</tr>
<tr>
<td>7</td>
<td>1a</td>
<td>2a</td>
<td>L7</td>
<td>11</td>
<td>&gt;99(83)</td>
<td>87:13</td>
<td>97</td>
</tr>
<tr>
<td>8</td>
<td>1a</td>
<td>2b</td>
<td>L7</td>
<td>42</td>
<td>&gt;99</td>
<td>80:20</td>
<td>88</td>
</tr>
<tr>
<td>9</td>
<td>1b</td>
<td>2a</td>
<td>L7</td>
<td>19</td>
<td>88(0)</td>
<td>–</td>
<td>(94)</td>
</tr>
<tr>
<td>10</td>
<td>1c</td>
<td>2a</td>
<td>L7</td>
<td>10</td>
<td>&gt;99(27)</td>
<td>68:32</td>
<td>90(96)</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: [Cu(ClO4)2·6 H2O] (0.02 mmol), Si/TBDPS (1a), TIPS (1b), TBS (1c), R = 2-Adamantyl (2a), CH2/8Bu (2b).
[b] Conversion and d.r. values (cis/trans) were determined by H NMR spectroscopy. The major isomer (d.r. > 20:1) of product is the cis products.
[c] The ee values within the parentheses are of the major isomer (d.r. > 20:1) of product 4. PMP = para-methoxyphenyl, TBDPS = tert-butyldiphenylsilyl, TBS = tert-butyldimethylsilyl, TIPS = trisopropylsilyl.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201300032.

[*] We are grateful for the financial support from the National Natural Sciences Foundation of China (20932008 and 21121062), the State Basic Research Development Program (Grant No. 2009CB825300), and the Chinese Academy of Sciences.

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bisoxazoline ligands unveiled that iPr-BOX gave the best enantioselectivity (entry 2),[8] and encouraged us to further elaborate this framework. To our delight, the sidearm strategy[9,10] of introducing a pendant group at the bridging carbon atom of the bisoxazoline ligand proved to be quite effective in this reaction, and the enantioselectivity of the reaction was gradually improved to 97% ee by increasing the steric hindrance at the para position of the aryl sidearm groups (entries 3–7). It is worth noting that the racemic D–A cyclopropanes 2a and 2b were used in this reaction, thus suggesting that the current reaction proceeds with a dynamic kinetic resolution[11–14] of the cyclopropanes. Reaction acceleration was consistently observed with the sidearm-modified ligands (entries 3–7 versus entries 1 and 2). In contrast, alteration of the ester group of 2 (4-MeOC6H4) is also important to the enantioselectivity with 2-adamantyl (Ad) being the best (entry 7 versus 8).[12] It is noteworthy that the TBDPS protecting group proved to be crucial to suppress the formation of the ring-opened product 4 and ensure a high yield of the desired [3+2] product (entries 9 and 10). For example, in the reactions of the TBDPS enol ether 1a, only a trace or a small (<10%) amount of the ring-opened product can be detected by proton NMR spectroscopy, which is in contrast to reaction of the TIPS-protected enol ether 1b which exclusively produced the ring-opened product (entry 9). The formation of 4 may result from the hydrolysis of the carboxoxybenzene intermediate before the ring closure or the abstraction of its α proton followed by desilylation.[5,6] In addition, other metal salts such as Cu(SbF6)2, Cu(OTf)2, CuBr2, Ni(ClO4)2, and Co(ClO4)3 were also examined. Only Cu(SbF6)2 and Cu(OTf)2 showed a good activity, but resulted in slightly lower enantioselectivities.[8]

Having the optimized reaction conditions, we moved to the investigation of the reaction scope. As shown in Table 2, apart from a PMP-substituted D–A cyclopropane, 2-thiophenyl- (2c), 3,4,5-trimethoxyphenyl- (TMP, 2d), and alkényl-substituted (2e) cyclopropanes also reacted well with 1a, thus giving the desired fused cyclic products in good to excellent enantiomeric excesses (entries 1–4). The reaction of the TMP-substituted cyclopropanes was slower, and could probably be ascribed to the steric hindrance of the TMP group or the competing bidentate coordination of the methoxy groups to the copper (entry 3). Notably, both conjugated and isolated dienol-ether-type substrates (1d and 1e) also react smoothly under the standard reaction conditions, thus affording carbon–carbon double-bond-containing [5,3,0] bicyclic products, with the potential for additional transformation of this functionality (entries 5 and 6). To our great pleasure, the current reaction works quite well with six- and five-membered substrates (entries 7–13). Thus, a range of [n,3.0] (n = 3–5) 3a-hydroxy bicycles in high enantiomeric purity are accessible by this reaction. Remarkably, in the reactions with five- and six-membered enol silyl ethers, perfect diastereoselectivities (>99:1) were consistently observed (entries 7–12). In fact, in these cases only one diastereoisomer was detected by 1H NMR analysis of the crude reaction mixture. In addition, the β-disubstituted enol silyl ether 1h is also a suitable substrate with high enantioselectivity, and notably the corresponding product (3ha) contains three contiguous quaternary centers, two of which are at the ring juncture (entry 13). The configurations of the products 3aa, 3da, and 3ge were determined by X-ray crystal structure analysis,[15] and the configurations of other products were assigned by analogy.

The success with monocyclic enol silyl ethers encouraged us to extend the current method to benzylicenol silyl ethers, which can deliver the benzene-fused cyclic products. As shown in Scheme 1, the reaction works extraordinarily well with these benzenefused substrates, such as 3,4-dihydronaphthalen-1-one and 1-indanone-derived silyl enol ethers (5a–f), and different substitution patterns such as 6-bromo, 6-fluoro, 7-methyl, and 5-methyl substituents are tolerated under the standard reaction conditions. In all cases high yield (80–98%) and complete diastereoselectivity...
(> 99:1) were obtained. The sterically demanding 4,7-dimethyl-substituted enol silyl ether 5f also reacted well under the current reaction conditions, thus giving the desired cycloaddition product 6fa in 91% yield and 93% ee.

For less reactive cyclopropanes, it is worth mentioning that the present reaction proceeds in a kinetic resolution fashion, though normally the reaction is slower. As exemplified in Scheme 2, a high selectivity factor (S = 152) was obtained with the phenyl-substituted cyclopropane 2g. Both the [3+2] cycloaddition product 6bg and the remaining cyclopropane (S)-2g were isolated in nearly quantitative yields and high optical purities (95% and 92% ee, respectively, Scheme 2).

With respect to the transformation of the [3+2] annulation products, manipulations on the silyl and ester groups in the product 3ga can be performed without erosion of enantiomeric purity (Scheme 3). The silyl protecting group can be readily removed with HF/pyridine. In contrast, the two ester groups can be selectively reduced. One ester can be reduced with LiAlH4 to give the diol 7, which accommodates four contiguous stereocenters. And both esters can be reduced with DIBAL-H/NaBH4 to give the desired cycloaddition product 6fa in 99:1 d.r., 94% ee.

**Scheme 1.** Extension to the syntheses of benzocycles.

**Scheme 2.** Concurrent kinetic resolution of the cyclopropane 2g.


