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Copper-Catalyzed Enantioselective Conjugate Addition of Grignard Reagents to Acyclic Enones

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The conjugate addition (CA) of organometallic reagents to enones is one of the most widely used synthetic methods for carbon–carbon bond formation. Enantioselective metal-catalyzed versions of this key transformation have been studied extensively with cyclic enones and chalcones using dialkylzinc, organoboron, and silicon reagents. However, despite the versatility and ready availability of Grignard reagents for organic synthesis, enantioselectivities in asymmetric CA reactions rarely reached the 90% ee level. Recently, we showed that enantioselective Cu-catalyzed CA of Grignard reagents to cyclic enones can be achieved using chiral ferrocenyl diphosphines. Here we report the Cu-catalyzed addition of Grignard reagents to the challenging class of acyclic aliphatic enone substrates with high regio- and enantioselectivity to provide optically active β-substituted ketones.

Aliphatic β-substituted linear ketones are common subunits in biologically active molecules and are important building blocks for natural product synthesis. However, highly enantioselective catalytic procedures for their preparation are rare, and enantioselectivities are usually substrate- and ligand-dependent. Notable exceptions are the Cu-catalyzed CA of dialkylzinc reagents using peptidic phosphate ligands described by Hoveyda and a complementary approach by Lipshutz that relies on a CuH-catalyzed asymmetric conjugate reduction of β,β-disubstituted enones. Nevertheless, despite more than two decades of intensive research, a general method based on asymmetric CA of organomagnesium reagents to acyclic enones is still lacking.

We started our investigation with the screening of TaniaPhos ligand recently found to be effective in the asymmetric addition of Grignard reagents to cyclic enones (Figure 1). In the present study, the catalyst prepared in situ from CuCl and CuCl provides good regioselectivity in the Cu-catalyzed addition of EtMgBr to the model substrate (E)-3-nonen-2-one (7a), although the product is obtained with low enantioselectivity (Scheme 1, Table 1, entries 1 and 2). Noteworthy is that the use of JosiPhos ligand dramatically enhanced the selectivity of the addition, providing 8a in 80% ee (entry 3). Optimization of solvent, Grignard halide, and copper source (entries 4–7) resulted in a further improvement in the selectivity of this process, providing 8a in 98% ee (entry 8). Interestingly, ligand 2 proved to be clearly superior to any of the structurally related ferrocenyl diphosphines studied (3–6), with different alkyl and aryl residues at phosphorus (entries 8–11).

Having established an optimal protocol, the addition of different Grignard reagents as well as a variety of aliphatic linear enones was examined. The results are summarized in Table 2. Gratifyingly, the optimal conditions found for EtMgBr and the model substrate 7a resulted in high selectivities when Grignard reagents with different linear alkyl chains were employed.

Thus, the CA of RMgBr reagents (R = Me, Et, n-Pr, n-Bu) to (E)-noneone, octenone, or heptenone (entries 1–7) occurred smoothly at −75 °C within 2 h to give the corresponding chiral β-substituted ketones with excellent yields (62–91%), regio- (>94% 6), and enantioselectivities (90–98%). High enantioselectivities were also observed in the formation of 8h,i despite the small β-Me substituent in enone 7d (entries 8–10). In all cases, the 1,2-addition products 9 were obtained as racemates. Particularly noteworthy is the addition of MeMgBr (e.g., to octenone and heptenone, entries 3 and 7), which provides 8d and 8g with 97–98% ee. The influence of the catalyst loading was examined for the addition of MeMgBr to heptenone. With only 1 mol % of catalyst, ketone 8g was obtained with good regioselectivity and in equal enantioselectivity (97% ee) (entry 17). To the best of our knowledge, these values constitute the highest enantioselectivities thus far reported in the addition of alkylmetals to acyclic aliphatic enones. Furthermore, the versatility of this procedure is illustrated by the fact that opposite enantiomers for a particular ketone can be obtained just by judicious selection of complementary enones and Grignard reagents, without changing the configuration of the chiral diphosphine (entries 3, 9 and 4, 5).

Figure 1. Chiral ferrocenyl-based diphosphines.

Table 1. Enantioselective CA of EtMgBr to (E)-3-Nonen-2-one 7a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>CuX</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>8a:9a</th>
<th>8a:9a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl</td>
<td>Et2O</td>
<td></td>
<td>0</td>
<td>84:16</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>CuCl</td>
<td>Et2O</td>
<td></td>
<td>−75</td>
<td>70:30</td>
<td>48 (R)</td>
</tr>
<tr>
<td>3</td>
<td>CuCl</td>
<td>Et2O</td>
<td></td>
<td>−75</td>
<td>86:14</td>
<td>80 (R)</td>
</tr>
<tr>
<td>4</td>
<td>Cu</td>
<td>Et2O</td>
<td></td>
<td>−75</td>
<td>83:17</td>
<td>72 (R)</td>
</tr>
<tr>
<td>5</td>
<td>CuBr:SMMe</td>
<td>Et2O</td>
<td></td>
<td>−75</td>
<td>91:9</td>
<td>86 (R)</td>
</tr>
<tr>
<td>6</td>
<td>CuBr:SMMe</td>
<td>BuOMe</td>
<td></td>
<td>−75</td>
<td>99:1</td>
<td>90 (R)</td>
</tr>
<tr>
<td>7</td>
<td>CuBr:SMMe</td>
<td>BuOMe</td>
<td></td>
<td>−75</td>
<td>77:23</td>
<td>74 (R)</td>
</tr>
<tr>
<td>8</td>
<td>CuBr:SMMe</td>
<td>BuOMe</td>
<td></td>
<td>−75</td>
<td>86:14</td>
<td>44 (R)</td>
</tr>
<tr>
<td>9</td>
<td>CuBr:SMMe</td>
<td>BuOMe</td>
<td></td>
<td>−75</td>
<td>95:5</td>
<td>57 (R)</td>
</tr>
<tr>
<td>10</td>
<td>CuBr:SMMe</td>
<td>BuOMe</td>
<td></td>
<td>−75</td>
<td>80:20</td>
<td>21 (R)</td>
</tr>
<tr>
<td>11</td>
<td>CuBr:SMMe</td>
<td>BuOMe</td>
<td></td>
<td>−75</td>
<td>71:29</td>
<td>27 (R)</td>
</tr>
</tbody>
</table>

* Conditions: EtMgBr (1.15 equiv) added to a solution of the enone (0.1 M), 5 mol % CuX, and 6 mol % ligand unless otherwise noted. All conversions >98% (GC–MS) after 2 h. Regio- and ee’s determined by chiral GC. 4 94% isolated yield (8a). 5 EMICl (1.15 equiv) was employed.
Enone 7g reacted smoothly with n-PrMgBr reagent to give the corresponding ketone (8s) with excellent yield and enantioselectivity (entry 4). Not unexpected, with the sterically hindered t-Bu ketone 7h a drastic decrease in enantioselectivity was observed (40% ee, entry 5).

The scope of the Cu-catalyzed asymmetric CA includes both β-substituted aliphatic and aromatic enones. Benzyldieneacetone (7f) and thienyl and furyl derivatives 7j and 7k react smoothly in BuOMe at ~75 °C with RMgBr reagents to give the corresponding enones in good yields and high regioselectivities and enantioselectivities of 90–97% (entries 6–9). It is noteworthy that the scope of the Cu-catalyzed CA reactions presented here is not limited to (E)-enones. The versatility of the present method is illustrated in the reactions of (Z)-4-furyl-3-en-2-one 7k, providing chiral ketones 8w and 8x in 80–89% yield with and excellent enantioselectivities (90–96% ee) (entries 8 and 9).

In summary, we have developed a general and efficient catalytic CA of Grignard reagents to achiral acyclic enones to provide optically active β-substituted acyclic ketones with high yields and enantioselectivities. Studies toward the elucidation of the mechanism of this transformation are currently in progress.

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

References

8. (a)刺激: //asmr//. (b) Other solvents (THF, BuOMe, EtOMe, toluene) and Cu sources (CuBr, CuCl) were evaluated provided lower selectivities. (c) See Supporting Information for more details.
9. (a) Standard conditions gave 8i in 62% ee (90:10 ratio). The use of BuOMe was crucial (the reaction in Et2O provided 8i with 42% ee, 78:22 ratio).