Highly Enantioselective Catalytic Conjugate Addition and Tandem Conjugate Addition - Aldol Reactions of Organozinc Reagents**

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Dedicated to Professor D. Seebach
on the occasion of his 60th birthday

Although efficient catalysts for a number of asymmetric carbon - carbon formations are known to date,[1] a highly enantioselective catalytic version of the conjugate addition of organometallic reagents to enones is lacking.[2] Recently chiral catalysts based on Cu, Ni, Zn, or Co complexes of a variety of ligands have shown enantioselectivities up to 90 % in 1,4-additions of Grignard, organolithium, or dialkylzinc reagents.[3] The results so far have not revealed, however, the key elements for realization of complete stereocontrol but do reveal the rather complex nature of some of these chiral catalytic systems.[4] Previously we have demonstrated that copper complexes of chiral phosphorus amidites show relatively high ee values for the 1,4-adducts of R₂Zn reagents and acyclic as well as cyclic enones.[5]

In this communication both the first catalytic asymmetric 1,4-addition reactions of organometallic reagents with complete

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stereocontrol and highly enantioselective tandem conjugate addition-aldol reactions are reported. In our design of a catalytic asymmetric 1,4-addition the following aspects were considered: a) Can very efficient ligand-accelerated catalysis \([8]\) be achieved? b) Is it possible to use an enone and an olefin \([\text{Eq. (a)}]\) as starting material? c) Are functional groups tolerated?

The remarkable ligand effect of binaphthol-derived phosphorus amides on the copper-catalyzed 1,4-addition of \(\text{Et}_2\text{Zn}\) to enones \([5]\) was explored by a modular variation of the phosphorus amidites on the copper-catalyzed 1,4-addition of \(\text{Et}_2\text{Zn}\) \([5, 16]\). The \(\text{R}_2\text{Zn}\) reagents were prepared from the corresponding alkenes by hydroboration and subsequent zinc exchange according to Knochel\([10, 11]\) or with the corresponding Grignard reagent (Table 1, entry 9). Again excellent enantioselectivities were achieved (Table 1, entries 8-13). It is particular noteworthy that the new catalyst tolerates ester and acetal functionalities. So far the catalyst based on \(\text{Cu(OTf)}_2/\text{ligand}\) (Table 1, entry 9) again excellent enantioselectivities were achieved (Table 1, entries 8-13). It is particular noteworthy that the new catalyst tolerates ester and acetal functionalities.

A possible pathway for the 1,4-addition could involve transfer of an alkyl fragment from \(\text{R}_2\text{Zn}\) to the copper complex\([11]\) followed by \(\pi\)-complexation of the resulting copper alkyl species to the double bond of the enone \([12]\) and on subsequent conjugate addition, might be trapped by an aldehyde in a subsequent aldol reaction \([13]\). The regio- and enantioselective catalytic three-component coupling was indeed achieved with

\[
\text{O} + \text{R}_2\text{Zn} \xrightarrow{\text{Cu(OTf)}_2 (2\%)} \text{R}_2\text{Zn} \xrightarrow{C_7H_8, 3h, -30^\circ C} 4a \quad 94\% > 98\% \text{ en ee}
\]

![Scheme 1. Enantioselective 1,4-addition of Et\(_2\)Zn to 2, catalyzed by Cu(OTf)_2/1. Tf = trifluoromethane sulfonate.](image)

(2 mol%) and \(\text{Cu(OTf)}_2/\text{ligand 1}\) \(1\) (4 mol%) provided \((S)-4a\) in 94% yield and an ee value greater than 98%. Excellent yields and enantioselective ratios ranging from 94 to greater than 98% are obtained for cyclohexenone and substituted cyclohexenones with a variety of zinc reagents (Table 1)\([9]\). Having realized complete stereocontrol in the formation of a number of 3-substituted cyclohexanones \(4\) (Table 1, entries 1, 4-7), we examined catalytic 1,4-additions of diisopropyl zinc \((3c)\) and functionalized dialkyllzinc reagents \((3e-3h)\)\([9]\). The \(\text{R}_2\text{Zn}\) reagents were prepared from the corresponding alkenes by hydroboration and subsequent zinc exchange according to Knochel\([10, 11]\) or with the corresponding Grignard reagent (Table 1, entry 9). Again excellent enantioselectivities were achieved (Table 1, entries 8-13). It is particular noteworthy that the new catalyst tolerates ester and acetal functionalities.

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![Scheme 2. Postulated catalytic cycle of the 1,4-addition.](image)

It is anticipated that the zinc enolate 5, resulting from the conjugate addition, might be trapped by an aldehyde in a subsequent aldol reaction \([13]\). The regio- and enantioselective catalytic three-component coupling was indeed achieved with
The synthetic versatility of the new catalytic enantioselective C-C bond formation is further illustrated by the 1,4-addition of Et₂Zn to highly symmetrical diene 10 readily obtained by oxidation of hydroquinone 9 (Scheme 3).[15] in view of the potential to use various zinc reagents, the multifunctional nature of 11, and the short, highly selective, and efficient route from hydroquinone, this new method may allow a versatile entry to a variety of optically active cyclohexenones.

### Experimental Section

1: The procedure for related phosphorus amidites [5] was followed except that nBuLi/THF was used instead of Et₃N/toluene in the second step. Chromatography (SiO₂, hexane:ethyl acetate mixture of 10% ethyl acetate and 90% hexanes) provided pure diketone 8a with 95% ee. The results shown in Table 2 indicate that other representative aldehydes undergo the tandem 1,4-addition - aldol reactions (in the presence or absence of Lewis acids) affording the corresponding trans-2,3-disubstituted cyclohexanones with enantioselectivities always exceeding 90%. In all cases small amounts of copper catalyst (1.2 mol %) lead to clean zinc enolate formation, fast and regioselective aldol reactions and trans-vinyl substituted cyclohexanones are exclusively obtained. The relative and absolute stereochemistry of (-)-trans-erythro-6b was established to be 2S,3S,1'S on the basis of single crystal X-ray analysis.[14] As far as we know this represents the first catalytic one-pot organozinc conjugate addition - enolate-trapping reaction that proceeds with high enantioselectivity.

![Scheme 3. Catalytic enantioselective 1,4-addition of Et₂Zn to the diene 10](image)

**Table 2. 1,4-Additions of dialkylzinc compounds and subsequent aldol reactions of the zinc enolate 5.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid[a]</th>
<th>t [min]</th>
<th>Products</th>
<th>erythro/thero</th>
<th>Yield [%][b]</th>
<th>ee [%][c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF₃·Et₂O</td>
<td>3 (-30)</td>
<td>6a/7a</td>
<td>68/32</td>
<td>88</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>BF₃·Et₂O</td>
<td>10 (-20)</td>
<td>6b/7b</td>
<td>38/62</td>
<td>68</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>BF₃·Et₂O</td>
<td>10 (-20)</td>
<td>6c/7c</td>
<td>38/62</td>
<td>68</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>BF₃·Et₂O</td>
<td>3 (-20)</td>
<td>6d/7d</td>
<td>54/46</td>
<td>64</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>BF₃·Et₂O</td>
<td>5 (-20)</td>
<td>6e/7e</td>
<td>52/48</td>
<td>68</td>
<td>&gt; 99</td>
</tr>
<tr>
<td>6</td>
<td>BF₃·Et₂O</td>
<td>6 (-30)</td>
<td>6f/7f</td>
<td>32/68</td>
<td>88</td>
<td>91</td>
</tr>
<tr>
<td>7</td>
<td>ZnCl₂·Et₂O</td>
<td>10 (-30)</td>
<td>6g/7g</td>
<td>46/54</td>
<td>64</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td>ZnCl₂·Et₂O</td>
<td>10 (-30)</td>
<td>6h/7h</td>
<td>65/35</td>
<td>81</td>
<td>91</td>
</tr>
<tr>
<td>9</td>
<td>ZnCl₂·Et₂O</td>
<td>10 (-30)</td>
<td>6i/7i</td>
<td>48/52</td>
<td>75</td>
<td>97</td>
</tr>
</tbody>
</table>

[a] 1.0 equiv of Lewis acid added. [b] Yields of isolated, pure aldols. [c] See Experimental Section for the determination of the ee values. [d] An unseparable mixture of aldols was obtained. [e] The relative configuration (erythro/threo) has not been established.

in situ generated enolate (Table 2). For example, when enolate 5, formed from 2 and diethylzinc in the presence of Cu(OTf)₂ (1.2 mol %) and ligand 1 (2.4 mol %), was treated with benzaldehyde at -30°C for 10 min, an approximately 3:7 mixture of trans,erythro-6a and trans,threo-7a was obtained in 88% isolated yield (Table 2, No. 1). The aldol products were readily separated by flash chromatography (SiO₂, 30% ethyl acetate, 70% hexanes) and oxidized to a single isomer of diketone 8a with 95% ee. The results shown in Table 2 indicate that other representative aldehydes undergo the tandem 1,4-addition - aldol reactions (in the presence or absence of Lewis acids) affording the corresponding trans-2,3-disubstituted cyclohexanones with enantioselectivities always exceeding 90%. In all cases small amounts of copper catalyst (1.2 mol %) lead to clean zinc enolate formation, fast and regioselective aldol reactions and trans-vinyl substituted cyclohexanones are exclusively obtained. The relative and absolute stereochemistry of (-)-trans-erythro-6b was established to be 2S,3S,1'S on the basis of single crystal X-ray analysis.[14] As far as we know this represents the first catalytic one-pot organozinc conjugate addition - enolate-trapping reaction that proceeds with high enantioselectivity.


[7] a) Mismatched ligand S,S,S-1 afforded 4a with 82 % yield and 75 % ee; b) the introduction of substituents at the 3,3'-positions of the binaphthol moiety only marginally affected the enantioselectivities.

[8] The spectral and analytical data for all new compounds were in agreement with the indicated structures.


[14] The X-ray structural analysis of compound 6b was performed by Dr. A. L. Spek (Utrecht University). Details will be reported separately.
