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 CuI, NiII, ZnII, or CoII 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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stereocenters 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 \(^{[6]}\) 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 amidites on the copper-catalyzed 1,4-addition of Et\(_2\)Zn to enones\(^{[5]}\) was explored by a modular variation of the stericly demanding \((R,R)\)-bis(1-phenylethyl)amine and unsubstated \((S,2,2\)'-binaphthol (as present in \(C_2\) symmetric ligand 1), resulted in a matched combination\(^{[7]}\) and a highly selective catalyst for the addition of Et\(_2\)Zn to cyclohexenone (Scheme 1). Thus the catalyst prepared from Cu(OTf)\(_2\)/

\[
\text{O} + \text{Et}_2\text{Zn} \rightarrow \text{Cu(OTf)}_2 \rightarrow \text{C}_7\text{H}_9\text{p} - 3\text{h}, -30^\circ \text{C} \rightarrow 4\text{a} > 98\% e\text{e}
\]

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

(2 mol %) and 1 (4 mol %) provided \((S)-4\)a in 94 % yield and an ee value greater than 98 %. Excellent yields and enantio-
meric excesses 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 dihexyl zinc \((3e)\) and functionalized dialkylzinc reagents \((3e-3h)\).\(^{[9]}\) The R\(_2\)Zn reagents were prepared from the corresponding alkynes by hydroboration and subsequent zinc exchange according to \(\text{Knochel}^{[10,11]}\) 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 Cu(OTf)\(_2\)/ligand 1 does not show satisfactory enantioselectivities for five- and seven-membered cyclic enones (Table 1, entries 2,3). For these substrates further ligand tuning is required.

A possible pathway for the 1,4-addition could involve transfer of an alkyl fragment from R\(_2\)Zn to the copper complex\(^{[12]}\) followed by \(\pi\)-complexation of the resulting copper alkyl species to the double bond of the enone \(2\) and o

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\]

Scheme 2. Postulated catalytic cycle of the 1,4-addition.

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] 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/Noeulene in the second step. 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 of Lewis acid) 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 disubstituted 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.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid[a]</th>
<th>t[min] (°C)</th>
<th>Products</th>
<th>erythro/threo</th>
<th>Yield (%)[b]</th>
<th>ee [%][c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 (-30)</td>
<td>6a/7a</td>
<td>6a + 7a</td>
<td>31:69</td>
<td>88</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>10 (-30)</td>
<td>6b/7b</td>
<td></td>
<td>38:62</td>
<td>85</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>3 (-30)</td>
<td>6c/7c</td>
<td></td>
<td>54:46</td>
<td>64</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>3 (-20)</td>
<td>6d/7d</td>
<td></td>
<td>38:62</td>
<td>67</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>3 (-20)</td>
<td>6e/7e</td>
<td></td>
<td>52:48</td>
<td>&gt;99</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>6h/7h</td>
<td>6f/7f</td>
<td></td>
<td>32:68[d,e]</td>
<td>88</td>
<td>91</td>
</tr>
<tr>
<td>7</td>
<td>6i/7i</td>
<td></td>
<td></td>
<td>45:55[e]</td>
<td>82</td>
<td>&gt;99</td>
</tr>
<tr>
<td>8</td>
<td>6j/7j</td>
<td></td>
<td></td>
<td>65:35[e]</td>
<td>81</td>
<td>97</td>
</tr>
<tr>
<td>9</td>
<td>6k/7k</td>
<td>6l/7l</td>
<td></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.

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]


[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.
