Highly enantioselective catalytic conjugate addition and tandem conjugate addition - Aldol reactions of organozinc reagents
Feringa, B.L.; Pineschi, M.; Arnold, L.A.; Imbos, R.; de Vries, A.H.M.

Published in:
Angewandte Chemie-International Edition in English

DOI:
10.1002/anie.199726201

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
1997

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Highly Enantioselective Catalytic Conjugate Addition and Tandem Conjugate Addition - Aldol Reactions of Organozinc Reagents**

Ben L. Feringa,* Mauro Pineschi, Leggy A. Arnold, Rosalinde Imbos, and André H. M. de Vries

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...
stereocenter 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 [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 Et₂Zn to enones [7] was explored by a modular variation of the sterically demanding (S)-2,2′-binaphthol (as present in C₂ symmetric ligand 1), resulting in a matched combination [8] and a highly selective catalyst for the addition of Et₂Zn to cyclohexenone (Scheme 1). Thus the catalyst prepared from Cu(OTf)₂ (2 mol %) and 1 (4 mol %) provided (5)-4a in 94 % yield and an ee value greater than 98 %. Excellent yields and enantiomeric 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 diheptyl zinc (3e) and functionalized dialkyl zinc reagents (3e-3h). [9] The R₂Zn 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 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 R₂Zn to the copper complex [12] followed by π-complexation of the resulting copper alkyl species to the double bond of the enone [13] and oxygenation and subsequent zinc exchange according to Knochel [10,11] or with the corresponding Grignard reagent (Table 1, entry 9).

Table 1. Enantioselective 1,4-additions of dialkyl zinc compounds to enones, catalyzed by Cu(OTf)₂/1 [a].

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enone R₂Zn</th>
<th>1,4-Adduct Yield [%] [b] ee [%] [c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a R₁=H, R₂=Et</td>
<td>4a 94 &gt; 98 [d]</td>
</tr>
<tr>
<td>2</td>
<td>2b R₁=H, R₂=Me</td>
<td>4b 75 10</td>
</tr>
<tr>
<td>3</td>
<td>2c R₁=H, R₂=2,2’-binaphthol</td>
<td>4c 82 53</td>
</tr>
<tr>
<td>4</td>
<td>2d R₁=H, R₂=2,3,4,5-tetramethylcyclohexene</td>
<td>4f 74 &gt; 98 [d]</td>
</tr>
<tr>
<td>5</td>
<td>2e R₁=H, R₂=4-tert-butylcyclohexene</td>
<td>4g 93 &gt; 98 [d]</td>
</tr>
<tr>
<td>6</td>
<td>2f R₁=H, R₂=3,4,5-trimethylcyclohexene</td>
<td>4h 73 &gt; 98 [d]</td>
</tr>
<tr>
<td>7</td>
<td>2g R₁=H, R₂=2,2’-binaphthol</td>
<td>4i 68 &gt; 98 [d]</td>
</tr>
<tr>
<td>8</td>
<td>2h R₁=H, R₂=2,3,4,5-tetramethylcyclohexene</td>
<td>4j 95 94</td>
</tr>
<tr>
<td>9</td>
<td>2i R₁=H, R₂=4-tert-butylcyclohexene</td>
<td>4k 53 95</td>
</tr>
<tr>
<td>10</td>
<td>2j R₁=H, R₂=3,4,5-trimethylcyclohexene</td>
<td>4l 77 95</td>
</tr>
<tr>
<td>11</td>
<td>2k R₁=H, R₂=2,2’-binaphthol</td>
<td>4m 91 97</td>
</tr>
<tr>
<td>12</td>
<td>2l R₁=H, R₂=2,3,4,5-tetramethylcyclohexene</td>
<td>4n 87 93</td>
</tr>
</tbody>
</table>

[a] Reaction conditions as in ref. [5]. [b] Yields of isolated products. [c] Determined by 13C NMR spectroscopy after derivatization with 1,2-diphenyl ethyl-enediamine [5, 16]. [d] (S)-4 could not be detected.

Scheme 1. Enantioselective 1,4-addition of Et₂Zn to 2, catalyzed by Cu(OTf)₂/1. Tf = trifluoroacetate anion.

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 [11]. 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 amides [5] was followed except that nBuLi/THF was used instead of Et3N/toluene in the second step. Chromatography (SiO2, 20% ethyl acetate and 80% hexanes) gave pure 37 (3.05 mmol) as a white solid (22.0 g, 75% yield).

To a mixture of 6b (0.1 g, 0.024 mmol) in toluene (5.0 mL) was added 1.0 equiv of Lewis acid ([a] Cu(OTf)2 (0.0045 g, 0.012 mmol) and ligand [b] threo-6a and erythro-6a at -30°C for 10 min, an approximately 3:7 mixture of aldols was obtained. [c] The relative configuration (erythro/threo) has not been established.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid[a]</th>
<th>t[min] (T[°C])</th>
<th>Products</th>
<th>Erythro/threo</th>
<th>Yield ee[}%[c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF3·Et2O</td>
<td>6b/7b</td>
<td>88%</td>
<td>6a - 7a - h</td>
<td>88%</td>
</tr>
<tr>
<td>2</td>
<td>BF3·Et2O</td>
<td>6b/7b</td>
<td>82%</td>
<td>6a - 7a - h</td>
<td>93%</td>
</tr>
<tr>
<td>3</td>
<td>ZnCl2·Et2O</td>
<td>6b/7b</td>
<td>78%</td>
<td>6a - 7a - h</td>
<td>89%</td>
</tr>
<tr>
<td>4</td>
<td>ZnCl2·Et2O</td>
<td>6b/7b</td>
<td>64%</td>
<td>6a - 7a - h</td>
<td>91%</td>
</tr>
<tr>
<td>5</td>
<td>ZnCl2·Et2O</td>
<td>6b/7b</td>
<td>67%</td>
<td>6a - 7a - h</td>
<td>91%</td>
</tr>
<tr>
<td>6</td>
<td>BF3·Et2O</td>
<td>6b/7b</td>
<td>82%</td>
<td>6a - 7a - h</td>
<td>&gt;99</td>
</tr>
<tr>
<td>7</td>
<td>ZnCl2·Et2O</td>
<td>6b/7b</td>
<td>88%</td>
<td>6a - 7a - h</td>
<td>91%</td>
</tr>
<tr>
<td>8</td>
<td>ZnCl2·Et2O</td>
<td>6b/7b</td>
<td>92%</td>
<td>6a - 7a - h</td>
<td>91%</td>
</tr>
</tbody>
</table>

The results shown in Table 2 indicate that other representative aldehydes undergo the tandem 1,4-addition - aldol reactions (in the presence of Lewis acids) affording the corresponding trans-2,3-disubstituted cyclohexenones 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-vicinal 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.

Keywords: 1,4-additions · aldol reactions · asymmetric synthesis · C-C coupling · homogeneous catalysis · zinc
COMMUNICATIONS

[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.