Enantioselective Conjugate Addition of Dialkylzinc Reagents to Cyclic and Acyclic Enones Catalyzed by Chiral Copper Complexes of New Phosphorus Amidites**

André H. M. de Vries, Auke Meetsma, and Ben L. Feringa*

Conjugate addition reactions of organometallic reagents to enones are among the most widely used methods for carbon-carbon bond formation in organic synthesis.[1] A number of successful methods for stereoselective 1,4-additions, based on chiral auxiliaries or stoichiometric organometallic reagents have been developed.[1, 2] Recently, catalytic, enantioselective conjugate additions of organometallic reagent (RMgX, RLi, or R2Zn) with chiral CuI, NiII, and ZnII complexes have been demonstrated.[3, 4] All these catalysts, however, show enantioselectivity for only one specific type of enone.[5] For example, complexes prepared in situ from [Ni(acac)2] (acac = acetylacetonate) and chiral amino alcohols are enantioselective for the addition of Et2Zn to acyclic enones, but for cyclic enones no enantioselectivity was found.[6] On the other hand, chiral Cu complexes with sulfonfurylarylazolone ligands are only effective in 1,4-addition reactions of Grignard reagents to cyclic enones.[3] We now report chiral copper catalysts, capable of facilitating conjugate addition of readily available dialkylzinc reagents to cyclic and acyclic enones in high yields and with ee values up to 90%.

Since trivalent phosphorus compounds are known as ligands for stoichiometric conjugate organo-copper additions,[6, 7] we examined the new chiral phosphorus amido complex 1, recently synthesized in our group from (S)-2,2'-binaphthol (2) and hexamethylphosphoramide (HMPT),[8] as ligand in the Cu-catalyzed addition of Et2Zn to cyclohexenone (3a) and chalcone (5a) [Eq. (a) and (b)].[9] Some remarkable results were observed: 1 Amidine represents a new class of chiral ligands, which proved to be essential for this catalytic system. Within 3 h both substrates are converted into the 1,4-product exclusively (GC

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Fig. 4. Expected melting point phase diagram of ST; T = melting point (temperature of the end of fusion), ee = enantiomeric excess.

compounds the reversal of chirality in the deposited crystals never occurs. It should be emphasized that spontaneous isomerization of one enantiomer to the other one never occurred under our recrystallization conditions. Although the mechanism of the enantiomeric resolution phenomenon of ST is yet under investigation, it may be related to the unique polymorphism of the ST crystals described above. If this is true, this enantiomeric resolution phenomenon might be extended and become a powerful general method for the resolution of organic racemates showing similar polymorphism, by which both the racemic crystals and the mixed crystals are simultaneously produced.

[11] X-ray data for a) the racemate: PI, Z = 2, a = 14.638(2), b = 15.681(2), c = 6.2281(6) Å, α = 100.321(1), β = 99.781(9), γ = 66.258(9), V = 1280(6) Å3, R = 0.052, Rw = 0.049; b) the (+)-isomer: PI, Z = 2, a = 15.651(2), c = 8.223(2) Å, α = 100.41(2), β = 108.95(2), γ = 85.732(2), V = 1289(1) Å3, R = 0.043, Rw = 0.044; c) a mixed crystal of ca. 1/3 ee: PI, Z = 2, a = 10.764(3), b = 15.618(3), c = 8.225(2) Å, α = 100.44(2), β = 108.47(3), γ = 85.62(3), V = 1289(6) Å3, R = 0.044, Rw = 0.042. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-179-107. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Telefax: Int. code + (1223) 336-033: e-mail: techdep@chemcrys.cam.ac.uk).

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yields greater than 95%), whereas without the ligand the copper-catalyzed reaction is very slow and many side products were found. When a larger amount of 1 (50 mol %) was employed, the reaction proceeds only at room temperature and was far less selective. These observations provide potentially striking advantages for a successful asymmetric catalysis. For both substrates moderate enantioselectivities were found (4a, 35 % (S) and 6a, 47 % (R)), which indicates that this chiral catalyst is not limited to one specific type of enone.

With this knowledge we set out to determine the structure of the complex of CuI and the ligand. Crystallization from benzene provided white needles (I) suitable for X-ray analysis. The molecular structure is shown in Figure 1. Three chiral ligands are bound to the copper center creating a C$_2$-symmetrical complex. Examination of the structure showed that crucial positions for ligand modifications are the amine moiety and the 3,3'-positions of the binaphthyl part of the ligand.

Therefore, starting from phosphoryl chloride (7), several new phosphorus amidites were prepared [Eq. (c)]. The complexes generated in situ of these ligands and CuI gave unsatisfactory results, presumably due to low solubility. However, homogeneous catalyst solutions were obtained with CuOTf (Tf = CF$_3$SO$_2$), and the influence of the structural modifications in 8 - 15 on the enantiomeric excess of 4a and 6a could be determined (Table 1). For both products significant improvement in ee was observed when sterically demanding substituents were introduced on the ligand’s nitrogen atom. The best results were obtained with the bis(iso-propyl)-substituted ligand 12. Products 4a and 6a were isolated in high yields (> 80%) and ee values of 60% and 83%, respectively. Ligands 13 and 14 (R' = CH$_3$) furnished the 1,4-products with comparable ee values. With ligand 15 (R' = Ph) lower enantioselectivities were found. Probably different clusters are formed with sterically demanding substituents on the 3- and 3'-position of the ligand creating less selective catalysts. In an effort to enhance the selectivity and realizing that Cu II salts are used as catalyst for conjugate addition, we investigated Cu(OTf)$_2$ together with Cu(SbF$_6$)$_2$ as catalyst. Under the same conditions 4a and 6a were isolated with higher ee values (Table 2). The actual chiral catalyst is probably a Cu' species, generated by in situ reduction of the CuII complex. The chiral copper complex of ligand 12 catalyzes the addition of Et$_2$Zn to various enones enantioselectively.

### Table 1. Enantioselective CuOTf-catalyzed addition of Et$_2$Zn to 3a and 5a [a].

<table>
<thead>
<tr>
<th>No.</th>
<th>Ligand</th>
<th>ee (4a) [%]</th>
<th>ee (6a) [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>50</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>53</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>55</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>43</td>
<td>79</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td>60</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>13, R = Me R' = Me</td>
<td>56</td>
<td>52</td>
</tr>
<tr>
<td>7</td>
<td>14, R = iPr R' = Me</td>
<td>59</td>
<td>81</td>
</tr>
<tr>
<td>8</td>
<td>15, R = Me R' = Ph</td>
<td>35</td>
<td>&lt;20</td>
</tr>
</tbody>
</table>

[a] Reaction conditions as in Equation (a). Yields of isolated products > 80 %. For ee determination see Experimental Procedure.

### Table 2. Enantioselective conjugate addition of Et$_2$Zn to enones, catalyzed by Cu(OTf)$_2$ 12 [a].

<table>
<thead>
<tr>
<th>No.</th>
<th>Enone</th>
<th>1,4-Adduct</th>
<th>Yield [%] [b]</th>
<th>ee [%] [c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>4a</td>
<td>78 (68) [d]</td>
<td>63 (71) [d]</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>4b</td>
<td>76</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>4c</td>
<td>76</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>5a</td>
<td>6a</td>
<td>88</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>5b</td>
<td>6b</td>
<td>84</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>5c</td>
<td>6c</td>
<td>85</td>
<td>80</td>
</tr>
</tbody>
</table>


Cyclic and acyclic enones gave the corresponding 1,4-products in 55-90% ee. The best results were obtained for 4,4-dimethyl-2-cyclohexen-1-one (3c) and 5a. Mechanistic studies on the enantioselective catalyst are under way, and at present we emphasize the following observations. 1) With the catalyst derived from bidentate ligand 16 and copper salt (1:1) we achieve the same ee values as found for ligand 1.
(2,1), which indicates that during reaction two ligands are bound to the copper ion. The remaining sites in the tetrahedral coordination sphere of the copper ion are likely to be occupied by π-complexation of the enone’s double bond,[16] and an ethyl fragment transferred from zinc.[16] 2) The pyridyl-substituted chalcone 3c gave the corresponding 1,4-product in only 29 % ee, presumably due to competitive binding of the copper catalyst to the enone’s pyridine moiety.

Preliminary experiments showed that diocylzinc, prepared directly from 1-ocetane by boron-zinc exchange,[16] can be used as well; it furnishes the 1,4-products with comparable ee values. This protocol can be extended to functionalized diorganozinc reagents. For instance, with the chiral catalyst derived from 12 and Cu(OtBu)2, 4-penten-1-yl acetate was added to 3a with 56 % ee. [Eq. (d)].

In conclusion a new highly efficient catalyst for asymmetric conjugate addition of diorganozinc reagents to enones has been developed. Remarkable features are the excellent chemoselectivity to give nearly pure 1,4-products, the effective ligand acceleration by new phosphorus amide ligands, the relatively high ee values for both cyclic and acyclic enones, the efficiency of a monodentate ligand in this asymmetric catalysis, and the fact that alkynes can be used as starting material.

Experimental Procedure

General procedure for ligands 8 - 16 (argen atmosphere): A warm solution (60 °C) of (S)-2,2' -binaphthyl (2) (800 mg, 3 mmol) in toluene (25 mL) was added in 5 minutes to a cooled solution (-60 °C) of PCl3 (270 µL, 3 mmol), Et3N (860 µL, 6 mmol), and toluene (5 mL). The reaction mixture was stirred for 2 h, warmed to room temperature, and filtered. The filtrate was treated with Et3N (410 µL, 2.9 mmol) and 2.9 mmol of the appropriate secondary amine at -40 °C. After 16 h at room temperature, the reaction mixture was filtered, concentrated, and purified by chromatography (SiO2; hexane:diethyl ether 5:1) to give the pure amide (yield 30 - 80%). (S)-12 [α]D = -591 (c = 0.68 in CHCl3), 1H NMR (200 MHz, CDCl3): δ = 7.99-7.89 (m, 4 H), 7.55-7.22 (m, 8 H), 3.42 (heptet, δ = 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H); 1.24 (d, δ = 6.84 Hz, 6 H). The reaction mixture was poured into 25 mL of 1 M HCl and extracted with diethyl ether (2 x 25 mL). The combined organic layers were washed with brine (25 mL), dried (MgSO4), filtered, and evaporated to give the crude 1,4-products. After purification by chromatography (SiO2; hexane:diethyl ether 5:1) the ee values were determined. Cyclic substrates were derivatized with optically pure 1,2-diphenyl ethylene diamine and analyzed by 1H NMR [20]. Acyclic substrates were studied by HPLC (Daicel OD or OJ column).

Keywords: asymmetric syntheses - carbon-carbon coupling - copper complexes - phosphorus compounds - zinc complexes -

A Catalyst-Specific, Stereocontrolled Ring-Closing Metathesis**
Christoph M. Huwe, Janna Velder, and Siegfried Blechert*

Ring-closing olefin metatheses have been used increasingly for the synthesis of unsaturated carbo- and heterocycles. To our knowledge, diastereoselective ring-closing metatheses have not been investigated to date. [2] We recently explored the synthesis of chiral, α-substituted heterocycles from amino acid derivatives, and used the chiral center for stereocontrolled secondary reactions of the double bond produced by the metathesis for the synthesis of natural products.

Natural products or biologically active compounds such as various pheromones and glycosidase inhibitors contain α,β-di-substituted pyrrolidine or piperidine units. To selectively ob-

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