



Copper-catalyzed enantioselective conjugate addition of diethylzinc to α,β -unsaturated carbonyl compounds using diphosponites as chiral ligands[†]

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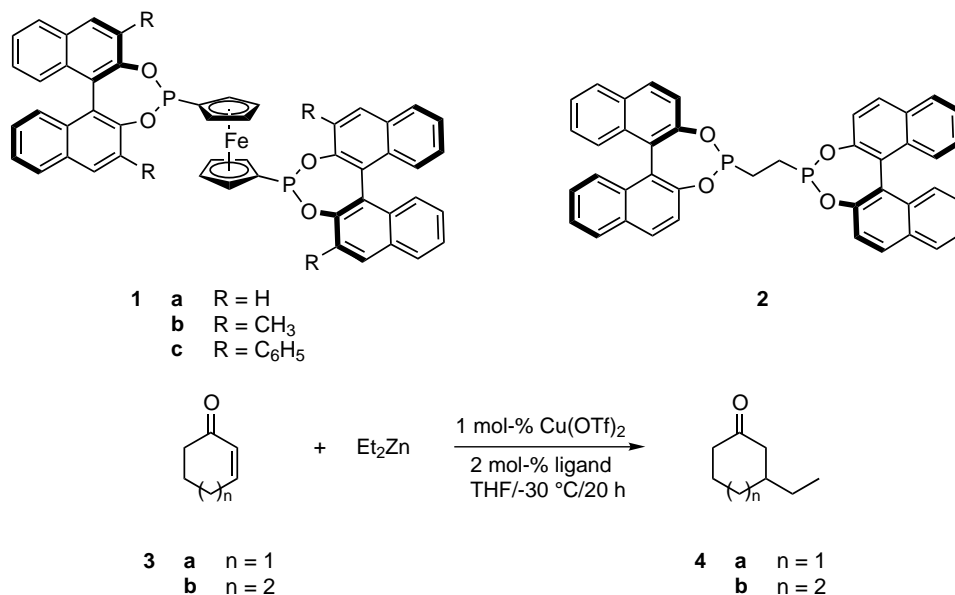
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Abstract—BINOL-based diphosponites in which ferrocene functions as the achiral backbone are excellent chiral ligands in the Cu(OTf)₂-catalyzed conjugate addition of Et₂Zn to enones, enantioselectivities of up to 99% being observed. © 2002 Elsevier Science Ltd. All rights reserved.

We have previously shown that BINOL-based diphosponites of type **1** and **2** are excellent bidentate ligands in the asymmetric Rh-catalyzed hydrogenation of prochiral olefins, enantioselectivity typically being in the range of 97–99% ee.¹ Since these results constitute the first cases of high asymmetric induction in catalytic hydrogenation using chiral diphosponites as ligands,² it was of interest to study the behavior of **1** and **2** in other types of transition metal-catalyzed reactions. We now show that these

ligands are also well suited for asymmetric conjugate addition of Et₂Zn to prochiral enones.^{3–5}

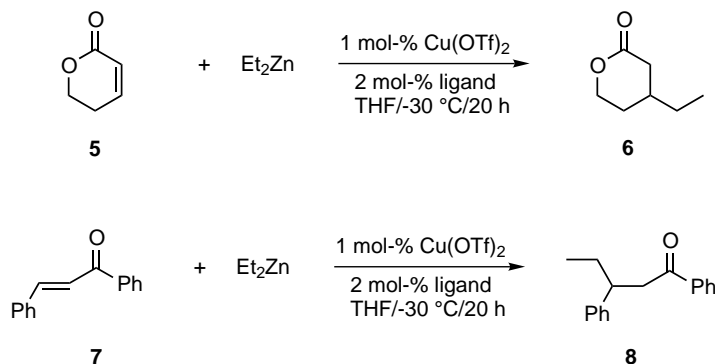
Upon adding Et₂Zn to a cooled (–30°C) mixture of cyclohexenone (**3a**) and catalytic amounts of Cu(OTf)₂ (1 mol%) in the presence of the chiral ligand **1a** (Cu:ligand = 1:2) and allowing the mixture to react for 20 h, an excellent conversion to the product **4a** was observed, enantioselectivity amounting to 95% ee (Table 1, entry



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**Table 1.** $\text{Cu}(\text{OTf})_2$ -catalyzed conjugate addition of Et_2Zn in the presence of chiral diphosphonites

Entry	Substrate	Ligand	Temperature ($^\circ\text{C}$)	Conversion (%)	% ee (abs. config.)
1	3a	1a	-30	89–94	95 (<i>R</i>) (+)
2	3a	1a	-20	100	92–94 (<i>R</i>) (+)
3	3a	1b	-30	72–88	93–99 (<i>R</i>) (+)
4	3a	1b	-20	100	95 (<i>R</i>) (+)
5	3a	1c	-20	100	38 (<i>R</i>) (+)
6	3a	2	-30	53–65	29–46 (<i>R</i>) (+)
7	3b	1a	-30	86–92	90–93 (+)
8	5	1a	-30	100	87 ^a
9	5	1a	-20	100	84 ^a
10	5	1b	-30	87	88 ^a
11	7	1a	-30	29–37	69–71 (<i>R</i>) (–)
12	7	1a	22	91–92	8 (<i>R</i>) (–)
13	7	1a	0	100	55 (<i>R</i>) (–)
14	7	1b	0	100	64 (<i>R</i>) (–)
15	7	1c	0	100	24 (<i>S</i>) (+)

^a Absolute configuration not determined.

1).⁶ At -20°C enantioselectivity turned out to be a little lower (entry 2). The use of the dimethyl-analog **1b** led to an increase in enantioselectivity, whereas the phenyl derivative **1c** resulted in only 38% ee (Table 1, entry 5). Surprisingly, the ethano-bridged diphosphonite **2** failed to afford acceptable results (Table 1, entry 6), which means that the nature of the achiral backbone is crucial.

Similar results were observed in the case of the pyranone **5**, enantioselectivity comparing well with the best results previously reported by Chan who used a chiral diphosphite⁷ (Table 1, entries 8–10). In contrast, chalcone **7** reacted with considerably lower asymmetric induction (ee=64–71%; Table 1, entries 11–15). Thus, the general trend that a given ligand system seldom works well for both cyclic and for acyclic substrates^{3–5} seems to pertain in our system as well.

The ligands described herein are easy to prepare and belong to the best systems currently available, although the chiral phosphoramidites described by Feringa^{5b} result in slightly higher enantioselectivities. The study of other transition metal-catalyzed reactions using our ligands is in progress.

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6. Typical experimental procedure: In a 30 mL Schlenk tube, 1 mL of a 10 mM solution of Cu(OTf)₂ in THF and 2 mL of a 10 mM solution of a chiral ligand (e.g. **1a**) in THF were added at room temperature. A green coloration was immediately observed. After 20 min of stirring the solution turned yellow and 0.5 mL of a 2 [M] solution of cyclohexenone (**3a**) in THF was added. 50 μL of *n*-decane was added as an internal standard for the determination of conversion. The temperature was cooled down to –30°C and after 20 min 0.5 mL of a 3 [M] solution of Et₂Zn in THF was added. The mixture is stirred at –30°C for 20 h. Then 10 mL of a 1.2 [M] solution of HCl are added at –30°C, the Schlenk tube was warmed up to room temperature and 20 mL of water and 30 mL of CH₂Cl₂ were added. The water phase was extracted three times with CH₂Cl₂. The organic phase was dried over MgSO₄. After evaporation of THF the crude product was purified on silica gel with a 9:1 mixture of hexane and ether as an eluant.
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