

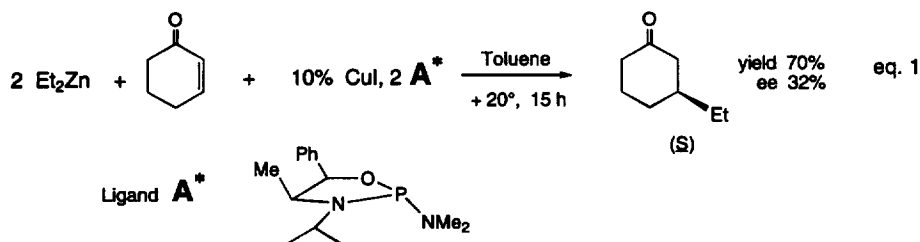
## Asymmetric conjugate addition of diethyl zinc to enones with tartrate chiral phosphite ligands

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**Abstract:** The asymmetric conjugate addition of diethyl zinc to cyclohexen-2-one occurs with 0.5% copper (II) triflate *and* 1% chiral phosphite. Cyclic phosphites derived from various tartrates gave a moderate enantiomeric excess. The nature of the exocyclic substituent of the dioxaphospholane ring is important, but the chiral induction is imposed by the tartrate framework. © 1997 Published by Elsevier Science Ltd

Many efforts are presently directed towards the asymmetric conjugate addition of organocopper reagents.<sup>1</sup> Although the stoichiometric version of this reaction is now well established using chiral covalent auxiliaries or chiral external ligands,<sup>1,2</sup> the catalytic version is still under investigation. Grignard reagents have most often been used with a catalytic amount of copper salt and chiral ligand.<sup>3</sup> In 1993 we pioneered the use of diorganozinc reagents as the main organometallic with a catalytic amount of a chiral phosphorus ligand.<sup>2f</sup>



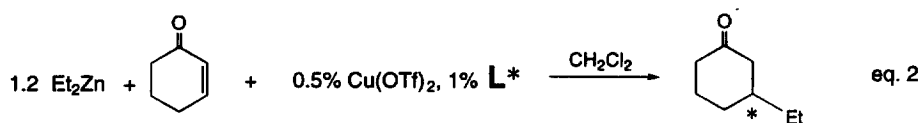
Although the ee was moderate, this study disclosed the best experimental conditions to achieve this transformation. The main point of further investigation was to find a better chiral ligand to improve the ee.<sup>4</sup>

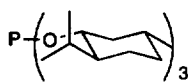
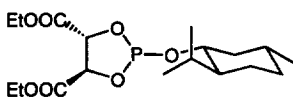
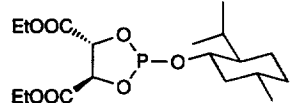
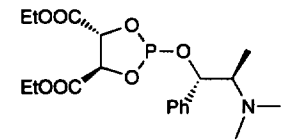
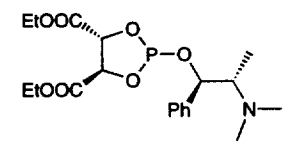
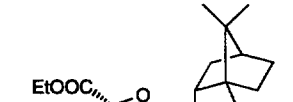
More recently, we found that 0.5%  $\text{Cu}(\text{OTf})_2$  associated with 1% of phosphites or aminophosphines gave excellent chemical yields and strongly enhanced the reaction rate.<sup>5</sup> This prompted us to examine chiral phosphorus ligands based on tartrate derivatives.<sup>6</sup> The main advantage of such phosphites lies in their stability towards moisture and oxidation in addition to the low cost of the chiral compound. We also found dichloromethane a more convenient solvent than toluene, with no detrimental effect on the enantiomeric excess (ee). Some of the most pertinent examples of the chiral C2 symmetric ligands are collected in Table 1.

Several trends may be drawn from these results:

- A simple ligand such as trimethyl phosphite (entry 1) compares well with the other ligands, for cyclohexen-2-one and chalcone. All other ligands have a dioxaphospholane ring formed with a C2 symmetric diol.

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**Table 1.** Variation of the chiral ligand in the asymmetric conjugate addition of diethyl zinc

Entry	Ligand	Enone	Conditions	Yield <sup>a</sup> %	ee <sup>b</sup>	Abs. Conf.
1a		cyclohexen-2-one	-20°, 15 min	98	36	R
1b		chalcone	-20°, 50 min	98	23	S
1c		benzalacetone	-20°, 3 h	57	4	R
2a		cyclohexen-2-one	-20°, 1 h	87	6	S
2b		chalcone	-20° to 0°, 6 h	86	6	S
2c		benzalacetone	-20° to r.t. 6 h	48	62	S
3a		cyclohexen-2-one	-20° to r.t. 1 h	99	3	S
3c		benzalacetone	0°, 5 h	60	63	S
4a		cyclohexen-2-one	-15°, 2 h	90	30	S
4b		chalcone	0°, 5 h	95	4	S
4c		benzalacetone	0°, 4 h	70	22	S
5a		cyclohexen-2-one	-15° to 0°, 1.5 h	97	28	S
6a		cyclohexen-2-one	-20° to 0°, 2 h	97	8	S
6b		chalcone	-20° to 0°, 5 h	78	16	S
6c		benzalacetone	-20° to 0°, 2 h	77	65	S

7a		cyclohexen-2-one	0°, 5 h	79	8	S
7b		chalcone	0° to r.t. 12 h	94	10	S
7c		benzalacetone	0° to r.t. 12 h	67	53	S
8a		cyclohexen-2-one	-5°, 1 h	99	40	R
8b		chalcone	-20° to 0°, 5 h	60	20	S
8c		benzalacetone	-20° to 0°, 5 h	98	28	S
9a		cyclohexen-2-one	-20°, 1 h	90	19	S
9b		chalcone	-10°, 3 h	90	10	R
9c		benzalacetone	0°, 6 h	52	4	R
10a		cyclohexen-2-one	-20° to -5°, 3 h	50	5	S
11a		cyclohexen-2-one	-20° to -5°, 3 h	58	7	S
11c		benzalacetone	-20° to -5°, 3 h	9	6	R
12a		cyclohexen-2-one	-20° to -5°, 1 h	84	10	S
12b		chalcone	-20°, 2 h	53	0	-
12c		benzalacetone	-20° to -5°, 3 h	74	11	S

a. Yield of isolated adduct.

b. *Ee* determined on G.C. with chiral capillary column (Lipodex E-0.2  $\mu$ m, 50m, 0.25 mm).

- Ligands with a simple diol such as 2,3-butanediol (entry 10), 2,4-pentanediol (entry 12), 1,2-diphenyl ethanediol (entry 11) or binaphthol (entry 9) gave low asymmetric induction with all three enones.
- Tartrate derivatives where the ester or amide functionality serves as a second chelation site gave more interesting results: 65% *ee* on benzalacetone (entry 6c) and 40% *ee* on cyclohexenone (entry 8a).
- The absolute configuration of the exocyclic substituent plays no role at all. (*R,R*)-Diethyl tartrate with *L*-menthol (entry 2) or *D*-menthol (entry 3) gave exactly the same result with respect to the *ee* and the absolute configuration. The same result was also observed with *D*- or *L*-ephedrine as the exocyclic substituent (entries 4 and 5).
- The nature of the exocyclic alcohol has some influence. If one compares menthol (entry 2 or

- 3), ephedrine (entry 4 or 5) and borneol (entry 6), the bulkiest substituent (borneol) is the most efficient for benzalacetone, but not for the two other enones.
- Both diethyl (entry 2 or 3) and diisopropyl (entry 7) tartrates give similar results.
  - A tartramide functionality (entry 8) shows increased selectivity for cyclohexenone (up to 40% ee). Coordination of the metal to an amide functionality is stronger than to an ester functionality. It should be noted that the absolute stereochemistry of the conjugate adduct is reversed as compared to diethyl tartrate (entry 2 or 3)!
  - The additional chelation site positioned on the exocyclic ephedrine derivatives (entries 4 and 5) alters the level of asymmetric induction, but this effect is small enough to be overruled by the chirality of the tartrate moiety.
  - Two groups of enones may be distinguished: benzalacetone on the one hand and, cyclohexenone and chalcone on the other. Improvement of the ee with one group usually brings a decrease of ee with the other group.

The above results are not among the best ones in the asymmetric conjugate addition of diethylzinc to enones. However, they allow a better understanding of the different factors which affect the efficiency of these chiral phosphite ligands.

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6. Typical procedure: A mixture of Cu(OTf)<sub>2</sub> (9 mg, 0.025 mmol), dichloromethane (3 mL) and chiral ligand (50 µL of a 1 M sol. in toluene, 0.05 mmol) was stirred for 30 min. After cooling to –20°C, Et<sub>2</sub>Zn (1M sol. in hexane, 7 mL, 7 mmol) was added followed by a solution of the enone (5 mmol) in dichloromethane (3 mL). The reaction was followed by GC until completion. Acidic work-up and chromatography gave the pure adduct.

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