

Asymmetric conjugate addition of diethyl zinc to enones with chiral phosphine ligands

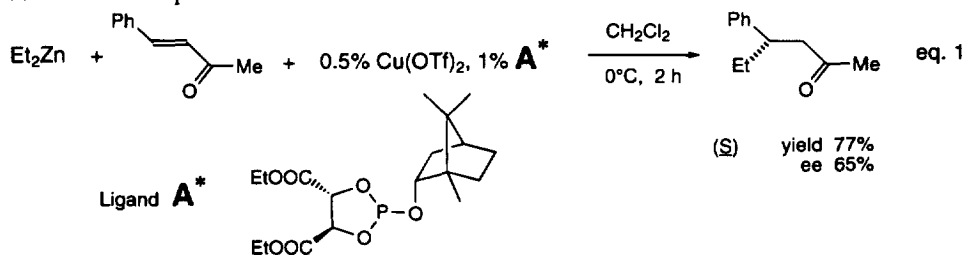
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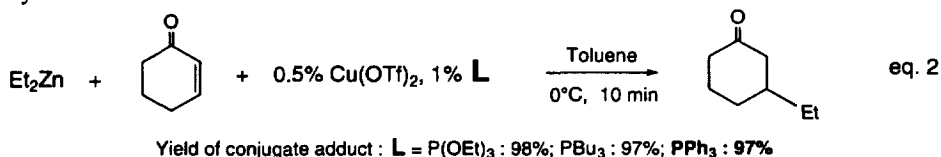
Abstract: Chiral bidentate aryl- and alkyl phosphines (0.5%) coordinated to copper(II) triflate (0.5%) are efficient catalysts for the asymmetric conjugate addition of diethyl zinc to cyclohexen-2-one, chalcone and benzalacetone. Among the chiral phosphines tested, (S)-Norphos, (S,S)-Chiraphos and (R)-Prophos gave the best enantiomeric excesses (44%, 44% and 36% respectively). © 1997 Elsevier Science Ltd. All rights reserved.

Asymmetric conjugate addition is a topic of very active research nowadays. Among the different ways to perform this synthetic transformation, the chiral organocopper approach seems the most attractive.¹ Successful stoichiometric systems have been described, but most efforts are presently directed towards catalytic use of chirally modified copper salts. Although Grignard reagents are usually used as the primary organometallic source,² diorganozinc reagents have been shown to be an attractive alternative.³

We recently found that 0.5% Cu(OTf)₂, associated with 1% of a trivalent phosphorus ligand, strongly accelerated the rate of the conjugate addition of diethyl zinc to enones.⁴ Moreover, we have shown that chiral phosphites derived from cheap tartrate esters or amides allow the chiral conjugate adduct to be obtained with up to 65% enantiomeric excess.^{3f}



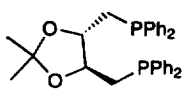
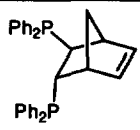
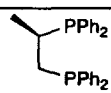
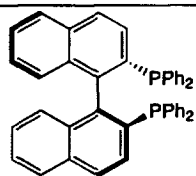
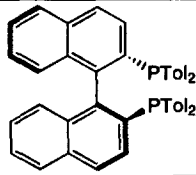
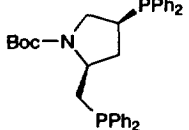
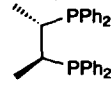
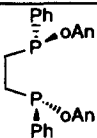
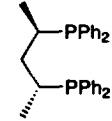
In addition to phosphites and aminophosphines, we found that tributyl as well as *triphenyl phosphine* are also efficient ligands for increasing the rate of the reaction. This last result is quite astonishing as *aryl phosphines* were always considered as far less efficient than trialkyl phosphines in organocopper chemistry.⁵



These findings open to investigation a whole range of chiral aryl phosphines usually employed in transition metal catalysis.⁶ We report herein some of our results with several commercially available chiral bidentate phosphines. The reactions were run under the same experimental conditions as those

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

		1.2 Et ₂ Zn + enone + 0.5% Cu(OTf) ₂ , 0.5% L*			CH ₂ Cl ₂ → conjugate adduct		
Entry		Ligand	Enone	Conditions	Yield ^a %	ee ^b %	Abs. Conf.
1	(+) DIOP		cyclohexen-2-one	0°, 1 h	84	8	S
2a	(S)- Norphos		cyclohexen-2-one	0°, 1.5 h	81	44	S
2b			same in <i>toluene</i>	0°, 3 h	75	28	S
2c			benzalacetone	0° to +20°, 12 h	86	6	S
3	(R)- Prophos		cyclohexen-2-one	0°, 2 h	72	36	S
4a	(S)-Binap		cyclohexen-2-one	0°, 1 h	80	24	S
4b			benzalacetone	0° to r.t. 12 h	6	rac	-
5	(S)-Tol-Binap		cyclohexen-2-one	0°, 2 h	67	26	S
6	(S,S)- BPPM		cyclohexen-2-one	0°, 2 h	83	rac	-
7a	(S,S)- Chiraphos		cyclohexen-2-one	0°, 1 h	98	44	S
7b			benzalacetone	0° to +20°, 12 h	51	16	R
8	(S,S)- Dipamp		cyclohexen-2-one	0°, 2 h	73	10	S
9	(R,R)- BDPP		cyclohexen-2-one	0°, 1 h	81	9	R

10	(S,S)- DIMPC		cyclohexen-2-one	0°, 3 h	93	8	S
11a	(R,R)- DuPhos		cyclohexen-2-one	0°, 5 h	82	16	S
11b			benzalacetone	-10° to 0°, 6 h	98	25	S
12a	(S,S)-Me BPE		cyclohexen-2-one	-10°, 10 min	99	14	R
12b			chalcone	-5°, 4 h	69	rac	-
12c			benzalacetone	-10°, 4 h	96	10	S
13a	(S,S)-Et BPE		cyclohexen-2-one	-15°, 10 min	98	6	R
13b			chalcone	-10° to 0°, 6 h	60	7	R
13c			benzalacetone	-10° to 0°, 6 h	96	8	S

a. Yield of isolated adduct.

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

with chiral phosphite ligands,^{3f} except that only one equivalent of diphosphine was used per equivalent of copper salt.⁷ In many cases both cyclic and acyclic enones were examined, as shown in Table 1.

In all the above reactions, the rate of the conjugate addition is strongly accelerated by the addition of 0.5% of the diphosphine ligands. In their absence, the reaction takes several hours at room temperature. No significant differences in rate were noted between alkyl- and aryl phosphines; the main differences concerned the degree of asymmetric induction.

Although all of these chiral phosphine ligands have proven their efficiency in many transition metal catalysed asymmetric transformations, none of them gave a very high asymmetric induction in the above copper catalysed asymmetric conjugate addition. The two *alkyl* phosphines, (S,S)-Me BPE and (S,S)-Et BPE (entries 12 and 13) were not among the best. It seems that the relative position of the two phosphorus atoms is more important, as well as the position of the stereogenic centres which have to be on the carbon backbone linking the two P atoms. Thus, (R)-Norphos (entry 2), (R)-Prophos (entry 3) and (S,S)-Chiraphos (entry 7) gave the highest enantiomeric excesses on cyclohexen-2-one (44%, 36% and 44% respectively). The fact that 1,3 and 1,4 diphosphines gave poor *ees* points, probably, to the ring size of the resulting metallacycle.

In summary, although the above chiral diphosphine ligands do catalyse the conjugate addition, they do not promote high asymmetric induction, despite the transition metal character of the copper atom.

Acknowledgements

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 - Typical procedure: a mixture of $\text{Cu}(\text{OTf})_2$ (9 mg, 0.025 mmol), dichloromethane (3 mL) and chiral ligand (0.025 mmol) was stirred for 30 min. After cooling to -20°C , Et_2Zn (1 M sol. in hexanes, 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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