Tetrahedron: Asymmetry Vol. 4, No. 12, pp. 2427-2430, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

Chiral Phosphorus Ligands for the Asymmetric Conjugate Addition of Organocopper Reagents

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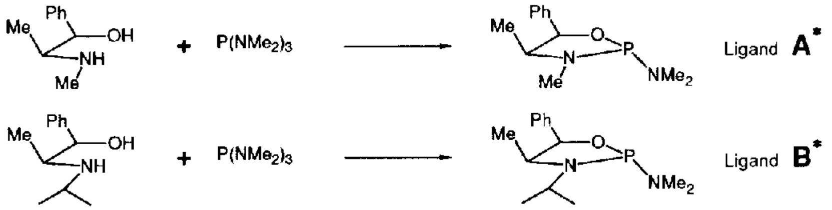
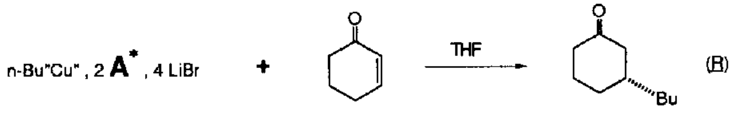
(*Received in UK* 4 *October* 1993)

Abstract : *The asymmetric conjugate addition of medium order alkyl cuprate reagents, $R_5Cu_3Li_2$, to 2-cyclohexen-1-one, 2-cyclopenten-1-one and 2-cyclohepten-1-one, with the help of phosphorus ligand B*, is described. 3-Alkyl substituted cyclohexanones are obtained in essentially optically pure form. The same chiral ligand, associated with CuI, in catalytic amount (10%), allows the asymmetric conjugate addition of Et_2Zn to 2-cyclohexen-1-one.*

The asymmetric conjugate addition reaction is, presently, a very active field of investigations, and organocopper reagents are among the best for such reactions.[1] We have recently disclosed a new family of chiral ligands for these organometallic reagents,[2] based on trivalent phosphorus derivatives easily obtained in homochiral form by reaction of an amino-alcohol with hexamethyl phosphorous triamide (HMPT) :



In the optimization study with n-butyl copper derivatives and 2-cyclohexen-1-one,[2] we have shown that the reaction had to be run in THF solvent, with two equivalents of chiral phosphorus ligand and four equivalents of lithium bromide. Reactions with n-BuCu gave steadily a moderate chemical yield (50-65%) of 1,4 adduct and a moderate ee (60-65%), whatever the CuI source or the quality of n-BuLi. In contrast, reactions run with n-Bu_2CuLi gave always a very high chemical yield but irreproducible ee values (0-76% !).



eq. 1

We have now explored this problem in more details by investigating cuprate reagents of various stoichiometry, and the results are summarized in Table 1. Although higher order cuprate (entry 4) or cyanocuprate (entry 3) gave excellent yield of the 1,4 adduct, they were completely inefficient as far as the ee is concerned. However, "medium order" cuprates having the stoichiometry $R_5Cu_3Li_2$, as described by Ashby,[3] gave both an excellent chemical yield and very good enantiomeric excess. This cuprate composition corresponds, in fact, to a

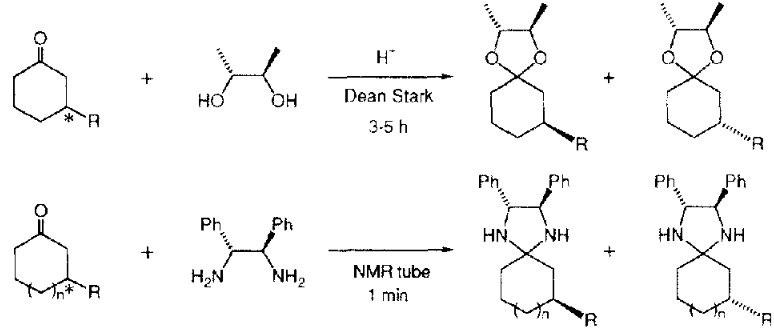
20% increase of the CuI salt as compared to the usual 2:1 (RLi:CuI) "normal" cuprate stoichiometry. We believe that this excess of copper salt serves, essentially, to prevent the formation of higher order heterocuprates arising from the variable amount of n-BuOLi contained in all commercial solutions of n-BuLi.

TABLE 1 : Optimization (eq. 1) according to the cuprate stoichiometry (with ligand A*)

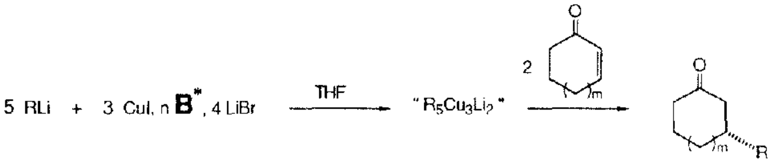
Entry	Stoichiometry of the organometallic reagent[a]	Chemical Yield %	Enantiomeric excess %
1	1 BuLi + 1 CuI → BuCu	62	62
2	2 BuLi + 1 CuI → Bu_2CuLi	90	0-76
3	2 BuLi + 1 CuCN → $Bu_2CuCNLi_2$	84	racemic
4	3 BuLi + 1 CuI → Bu_3CuLi_2	74	racemic
5	5 BuLi + 3 CuI → $Bu_5Cu_3Li_2$[b]	80	***81***

a) All reactions are run with 2 equivalents of ligand **A*** and 4 equivalents of LiBr per copper atom.
b) Two equivalents of enone per cuprate reagent.

Another point of concern was the fast determination of the enantiomeric purity of the resulting 1,4 adduct. This task was routinely accomplished by the formation of the diastereomeric ketals according to Wynberg's method.[4] We have now found that the formation of diastereomeric aminals, with commercialy available (R,R)-1,2-diphenyl ethylene diamine, is much faster and also very reliable :[5]



Having established the best conditions for the organometallic reagent and a simple way to determine the ee of the 1,4 adduct, we explored the generalization of this asymmetric conjugate addition to various organic groups and to various enones, according to the following equation :



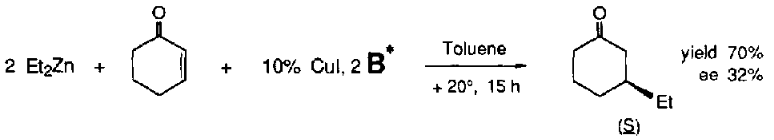
eq. 2

TABLE 2 : Reactions of "medium order" cuprates (eq. 2)with various enones (2 equiv. per cuprate).

Entry	RLi	n L*	enone m	Yield %	Ee %
1	n-Bu	2 **A***	1	80	81
2	"	1 **A***	"	65	63
3	"	2 **B***	"	82	>95
4	"	1 **B***	"	79	72
5	t-Bu-O-$(CH_2)_4$-	2 **A***	"	84	82
6	"	2 **B***	"	83	>95
7	Et	"	"	81	>95
8	Me	"	"	75	26
9	Ph	"	"	90	racemic
10	n-Bu	"	0	72	70
11	t-Bu-O-$(CH_2)_4$-	"	"	80	71
12	t-Bu-O-$(CH_2)_4$-	"	2	82	76

The results of this investigation are shown in Table 2. Both ligands **A*** and **B*** were tested and, as described previously, ligand **B***, having an intracyclic N-iPr group was more efficient than ligand **A*** with a N-Me group. Although the best result is attained with two equivalents of chiral ligand, a single equivalent affords quite good enantioselectivity.[6] The asymmetric transfer of n-alkyl groups occurs with an excellent selectivity on 2-cyclohexen-1-one. Thus, with ligand **B***, a single enantiomer could be detected (entries 3, 6 and 7). However, the transfer of the Methyl group occurs less selectively (entry 8) and the Phenyl group gives a racemic material. We have also briefly examined the behaviour of other 3-cyclenones. Both 2-cyclopenten-1-one (entries 10 and 11) and 2-cyclohepten-1-one (entry 12) gave high levels of enantioselection, although significantly lower than in the case of 2-cyclohexen-1-one. It should be noted that the same enantiomer is always observed.

The use of ligand **B*** complexed with copper iodide was also explored in catalytic reactions. With n-Butyl Grignard reagents only racemic material was obtained whatever the solvent used. However recent results with the combination *Et_2Zn / Ni catalyst / chiral ligand* have demonstrated their efficiency on s-cis enones, the most representative of which is chalcone.[7] We have found that copper salts also catalyze this reaction :[8]



In acetonitrile as solvent, only the racemic adduct was obtained, in 30% yield. On the other hand, under the above conditions, chalcone also gave racemic material (70% yield).

Unexpectedly, the sense of optical induction is the reversed as compared with stoichiometric lithium cuprates. This fact may be ascribed either to the different metal counterion (Zn instead of Li) or to the different solvent (toluene instead of THF). Although modest in ee, our result with Et_2Zn and 2-cyclohexen-1-one, a representative of s-trans enones, stands in contrast with the previous work on asymmetric conjugate addition of Et_2Zn, where only s-cis enones, such as chalcone, gave interesting levels of enantioselection.[7]

In summary, we have demonstrated that chiral trivalent phosphorus ligands can act as effective auxiliaries for the asymmetric conjugate additon of organocopper and dialkyl zinc reagent (with copper catalyst). Work is in progress to get more insight informations on the chiral organometallic species involved in these processes.

References and notes.

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5. See following letter.
6. It should be noted that ligand **B*** is not diastereomerically pure.[2] The 93:7 mixture used in the present experiments should not afford, in theory, a higher ee (we assume, by analogy to closely related ligands where the diastereomeric composition is much worse, that the minor diastereomer gives low or reverse asymmetric induction). However, n-alkyl "medium order" cuprates gave a single enantiomer, and the level of detection by diastereomeric aminal formation is well beyond the 93:7 value. The fact that organocopper reagents are, at least, dimeric aggregates should allow some kind of "diastereomeric amplification" (by analogy to the known "asymmetric amplification").
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