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Asymmetric conjugate addition of metal alkyl reagents catalyzed by copper complexes with BINPO: a hemilabile P,O-heterobidentate axially chiral ligand

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Abstract—We herein report the use of a new class of P,O-bidentate arylphosphine ligand for the asymmetric copper catalyzed conjugate addition of dialkylzinc and trialkylaluminium with the enantiomeric excesses reaching 91% while (*R*)-muscone was obtained with 77% ee.

1. Introduction

The formation of carbon–carbon bonds is one of the most important synthetic reactions in organic chemistry. In this context, the transition metal catalyzed conjugate addition is an excellent way to introduce hard nucleophiles to Michael acceptors.[1] In addition, it allows asymmetry to be induced in the formation of this new bond.

For this process, two metals hold a prominent position as catalysts, copper[2] and rhodium.[3] These systems provide complementary methods for the preparation of 1,4-adducts through alkyl or aryl/alkenyl group additions.

In the copper-catalyzed version, dialkylzinc reagents were the most frequently used.[2d] However, trialkylaluminium reagents were also reported to afford good results.[4] Amongst the >300 ligands screened in this reaction,[2d] quite a few were bidentate, however, the best results were consistently obtained with monodentate derivatives. Amongst these, phosphites and phosphoramidites perform better than phosphines.

In this context, we were interested to have an insight into the potential of hemilabile bidentate ligands in this reaction and for this reason we have addressed our attention towards 2-diphenylphosphinyl-2′-diphenylphosphino-1,1′-binaphtalene [(*R*)-BINPO] **L1**, a new type of ligand developed by Gladiali et al.[5] (Fig. 1). Due to the presence of a hard oxygen and a soft phosphorus as the donors, BINPO displays a pronounced propensity to act as a hemilabile ligand,[6] even if it can also bind the metal by chelate coordination. BINPO has been successfully employed as a chiral inducer in the Pd-catalyzed allylic alkylation[7] and in a range of addition reactions to styrene covering hydrosilylation,[5] hydroformylation[8] and Rh-catalyzed hydroboration.[9]

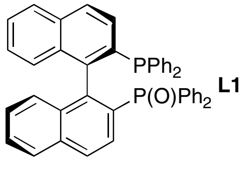

Figure 1.

2. Results and discussion

It was our hope that coordination of the soft phosphorus and of the hard oxygen to the copper and to the other metal (Zn or Al), respectively, could occur in a

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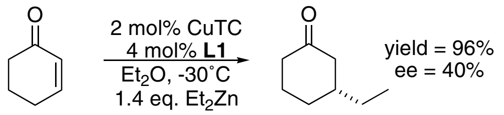
cooperative mode so as to build up a transition state of highly organized asymmetry.

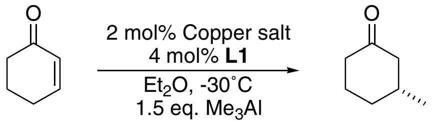
The first attempts were done with diethylzinc on 2-cyclohexenone but the results were not promising with only 40% ee (Scheme 1).



Scheme 1.

In contrast, when the reaction was carried out with trimethylaluminium the results were quite encouraging. A short list of copper salts was tested under the conditions we developed for other ligands and R_3Al reagents (Table 1). From this screening, $Cu(CH_3CN)_4PF_6$ turned out to be the best suited catalyst for the enantioselectivity of the reaction. This result is quite interesting because so far $Cu(CH_3CN)_4BF_4$ was consistently reported to be the best performer in this reaction.[4b,e]

Table 1. Copper salt optimization



Entry	Copper salt	Conv. (%)[a]	ee (%)
1	CuCl	>99	72
2	CuBr	nd	nd[b]
3	$Cu(OAc)_2 \cdot 2H_2O$	>99	70
4	$Cu(OTf)_2$	>99	29
5	CuTC	>99	69
6	$Cu(CH_3CN)_4BF_4$	>99	65
7	$Cu(CH_3CN)_4PF_6$	>99	77

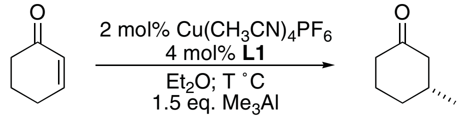
[a] GC conversions.

[b] Too many by-products.

In the Cu-catalyzed conjugate addition, it is known that the lowest reaction temperature is not always the best one for enantioselectivity.[10] Therefore, this parameter was checked (Table 2) and we observed that working at −45 °C, was the best temperature for the enantioselectivity.

Although at −65 °C we were able reach 91% ee, the conversion was incomplete. Therefore, we decided to perform the next screening at −45 °C, where a quantitative conversion of 2-cyclohexenone was obtained at the expense of a modest decrease of ee (89%).

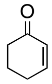
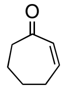
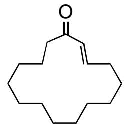
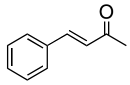
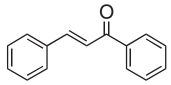
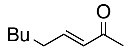
Table 2. Temperature optimization



Entry	Temp. (°C)	Conv. (%)[a]	ee (%)
1	−10	>99	66
2	−30	>99	77
3	−45	>99	89
4	−65	91	91

[a] GC conversions.

Table 3. Screening of enones with Me_3Al

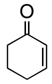
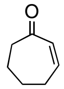
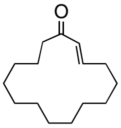
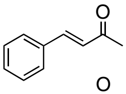
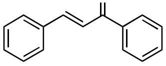
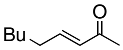
Entry	Substrates	Conv. (%)	Isolated yield (%)	ee (%)
1		>99	61	89 (*R*)
2		>99	57	89 (*R*)
3		>99	60	77 (*R*)
4		>99	31	71 (*S*)
5		>99	50	25 (*R*)
6		>99	15	74 (*R*)

A range of cyclic and acyclic enones were tested under standard conditions (Table 3). Cyclohexenone afforded 3-methyl cyclohexanone in 61% isolated yield (entry 1) in spite of the complete conversion. This result shows the importance of the competing polymerization that plagues the reaction of 2-cyclohexenone with organoaluminium reagents.[11] The polymer is produced via a Michael addition to the starting material of the aluminium enolate of 3-methyl cyclohexanone produced in the first Cu-catalyzed conjugate addition. Cycloheptenone gave similar results (entry 2) with 57% isolated yield and 89% ee.

Due to its ring size (15 membered) 2-cyclopentadecenone is generally considered to react like an acyclic enone.[12] The conjugate addition of the methyl group to this substrate (entry 3) affords the well-known fragrance (*R*)-Muscone[13] with 77% ee, one of the best reported for the asymmetric synthesis of this compound.[14] With the exception of chalcone (entry 5), which was a poor substrate for this reaction (25% ee), the two other tested acyclic enones (entries 4 and 6) gave comparable levels of enantioselectivity (71% and 74%, respectively).

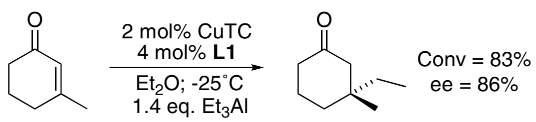
For the sake of comparison, the same work was carried out with triethylaluminium. Screening of the copper salt showed that, this time, $Cu(CH_3CN)_4BF_4$ was the best salt. Optimization of the temperature revealed, again, that −45 °C was the most favourable. Finally, the conjugate addition to the various cyclic and acyclic enones was performed (Table 4).

Table 4. Screening of enones with Et_3Al

Entry	Substrates	Conv. (%)	Isolated yield (%)	ee (%)
1		>99	61	86 (*R*)
2		>99	66	75 (*R*)
3		>99	n.d.	41 (*R*)
4		>99	40	20 (*S*)
5		>99	25	16 (*R*)
6		>99	27	51 (*R*)

In keeping with the usual trend, triethylaluminium did not afford results as appealing as the previous ones, with both yields and ees lower than the ones obtained with trimethylaluminium.[4] It should be stressed, however, that, from a synthetic point of view, the conjugate addition of an ethyl group is by far less important than that of a methyl group.

From these results, (*R*)-BINPO ligand **L1** does not suffer from comparison with other well-known phosphoramidite ligands.[2d] An additional support to this view is provided by the conjugate addition of triethylaluminium to 3-methyl cyclohexenone, which proceeds smoothly at −25 °C generating a quaternary stereocentre in 86% ee (Scheme 2).[4e] Although not working at full conversion, no heavier products were found due to the lower reactivity of the more substituted enone towards an aluminium enolate.



Scheme 2.

3. Conclusion

In summary, we have enlightened for the first time the potential of a chiral P,O-hemilabile ligand in the asymmetric Cu-catalyzed conjugate addition of trialkylaluminium to enones. This chiral inducer allowed us to achieve stereoselectivities up to 91% with trimethylaluminium and to produce a quaternary stereocentre in up to 86% ee. From these results, it follows that phosphine ligands should no more be neglected in this reaction. Our results also demonstrate that the heterobidentate nature of the P,O-ligand is essential for high stereoselections to be pursued in the conjugate addition. For instance, BINAP, the homobidentate close relative of BINPO, is a very poor chiral inducer in this process.[15] Whether the good performances of BINPO may be related or not to the hemilabile behaviour of this ligand currently remains a matter of speculation.[16]

Acknowledgements

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13. For a review, see: Ohloff, G. *Fortschr. Chem. Forsch.* **1969**, *12*, 185.
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16. Typical procedure: In a flame-dried flask, a solution of copper salt (0.01 mmol, 2.0 mol %) and ligand **L1** (0.02 mmol, 4.0 mol %) was made under argon in 1.5 mL dry diethyl ether. The mixture was stirred for 30 min at room temperature and then cooled to −45 °C. Trialkylaluminium (0.75 mmol, 1.5 equiv) was added dropwise and the solution stirred for 5 min. Then, the Michael acceptor (0.5 mmol) was added dropwise. The solution was stirred overnight at −45 °C. Then, the flask was removed from the cooling bath, warmed to room temperature and the reaction mixture was quenched by the addition of MeOH (05 mL) followed by aqueous HCl 2 M. The organic layer was separated and the aqueous phase extracted with ether. The combined organic phases were dried over anhydrous $MgSO_4$ and evaporated to afford the crude product. Purification by flash chromatography over silica gel afforded the pure product.