Tetrahedron: Asymmetry Vol. 2, No. 11, pp. 1097-1100, 1991
Printed in Great Britain

0957-4166/91 $3.00+.00
Pergamon Press plc

On the Way to Chiral Copper(I) Arenethiolate Catalysts for the Enantioselective Conjugate Addition of Methyl Lithium and Methyl Magnesium Iodide to Benzylideneacetone

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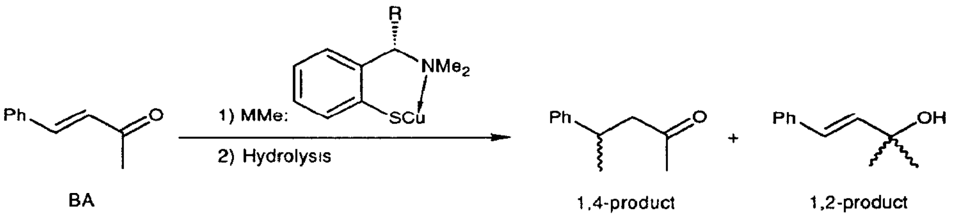
(*Received* 25 *September* 1991)

Abstract: Selective conjugate addition (0 % enantiomeric excess (e.e.)) of organo-arenethiolatocuprates (from methyl lithium and 2-[1-(*R*)-(dimethylamino)ethyl]phenyl-thiolatocopper(I), CuSAr*) to benzylideneacetone (BA) is found up to a LiMe/CuSAr* ratio of 2/1 indicating the potential of the chiral SAr*-anion as non-transferable group; at higher ratios only 1,2-addition occurs. Reactions of methyl magnesium iodide with BA in the presence of a catalytic amount of CuSAr* (9 mol%) result in exclusive conjugate addition with 57% e.e..

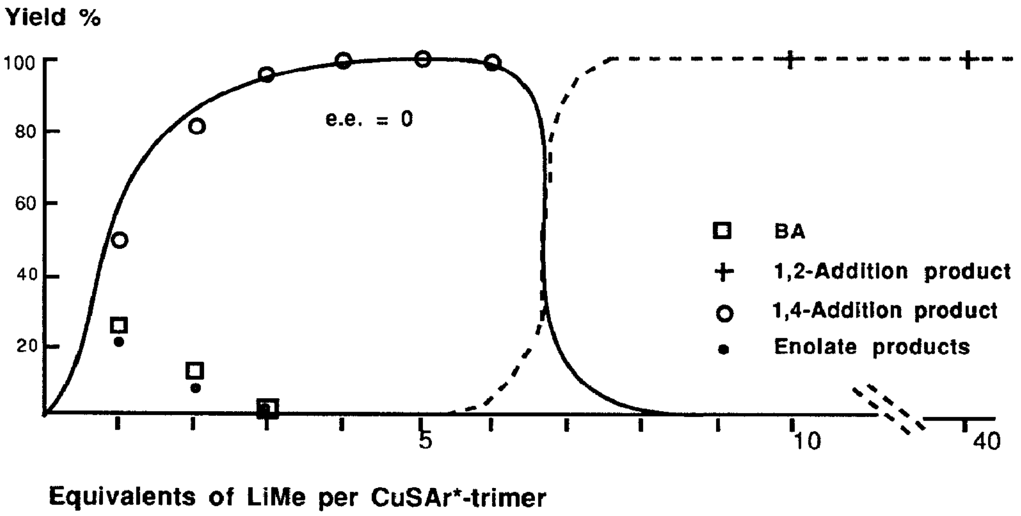
Recently, we reported the first examples of structurally characterized (chiral) organo-arenethiolatocuprates and -copper compounds which have been obtained from the reactions of organo-copper,[1] -lithium,[2] and -magnesium[3] compounds with newly developed (chiral) arenethiolatocopper(I) complexes (CuSAr*)[4]. Here we report a selective conjugate addition reaction of organo-lithium and -magnesium compounds to BA (see eqn. 1). Our choice of the arenethiolato group (SAr*) for the synthesis of (chiral) cuprate reagents is based on the fact that transferability decreases in the order alkyl>aryl>alkylthiolato>arenethiolato while stabilization of the resulting heterocuprate can be anticipated to decrease in the reverse order. Moreover, the *ortho*-amino group in [$CuSC_6H_4(CH(R)NMe_2)$-2] can be choosen to be either chiral (R = Me) or achiral (R = H) and may function both as an anchoring group that can bind Lewis acidic metal centres (*e.g.* Li^+ or Mg^{2+}) and as a ligand that stabilizes cuprate intermediates through coordination to reactive copper centres.[1,5] The successful use of chiral non-transferable groups in cuprate conjugate additions has been reported.[6] So far the use of chiral organothiolates has remained unexplored although the application of the simple benzenethiolato group in cuprate reagents is known.[7] We report here two observations that are to the best of our knowledge unprecedented; *i*, the formation in reaction mixtures of methyl lithium and CuSAr* of a distinct (methyl)arenethiolato lithiumcuprate which does not exchange with excess methyl lithium, and *ii*, the use of a catalytic amount of CuSAr* in a conjugate addition reaction of methyl magnesium iodide to benzylideneacetone (BA) which proceeds with enantioselectivity.



eqn. 1

Figure 1 summarizes the results of reactions of the organo-arenethiolatocuprate reagents, derived from methyl lithium and 2-[1-(*R*)-(dimethylamino)ethyl]phenylthiolatocopper(I) (CuSAr*),[8] in molar ratios varying from 1/3 to 40/1, with BA. These reactions were carried out at 0 °C by adding a solution of 1 equivalent of BA in diethyl ether to a preformed solution of 1 equivalent (based on LiMe) of the organo-arenethiolatocuprate reagent in THF/Et_2O.

Figure 1.



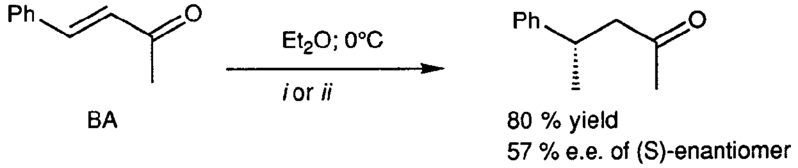
The following observations have been made:

-At low LiMe/CuSAr* ratios of 1/3 and 2/3 the reaction is slow and as well as the conjugate addition product, 4-phenylpentan-2-one, enol reaction products are also formed.[9] The reaction becomes fast at LiMe/CuSAr* ratios higher than 1/1. Up to a LiMe/CuSAr* molar ratio of 2/1 an almost exclusive formation of the 1,4-addition product occurs; when this ratio is increased above 6/3 (c.f. ref. 8) the reaction switches to the formation of the 1,2-addition product, *trans*-2-methyl-4-phenylbut-3-en-2-ol. Comparative ^{13}C NMR studies (in THF-d_8) of free LiMe and solutions of two LiMe/CuSAr* mixtures (5/3 and 5/1, respectively) showed the absence of free LiMe and the presence of [CuSAr*]$_3$[LiMe]$_n$)-aggregates in the first mixture, and the presence of a small amount of free LiMe in the second mixture.

-Attempts to isolate [CuSAr*][LiMe]$_n$ (n = 1 or 2) in Et$_2$O resulted invariably in the isolation of yellow [CuSAr*][LiMe],[10] whose structure is now under investigation.

These results indicate that the arenethiolato group even in the presence of excess of methyl lithium still strongly binds to copper(I) and that copper-lithium exchange under these conditions, that would lead to the formation of the kinetically highly reactive homocuprate, CuLiMe$_2$, *i.e.* to the formation of the 1,4-addition product irrespective of the LiMe/CuSAr* molar ratio, does not take place.

Two different reaction procedures were followed for reactions of BA with methyl magnesium iodide in the presence of catalytic amounts of CuSAr*. Method A comprises the addition of a solution of BA in Et$_2$O to a preformed solution of methyl magnesium iodide and 9 mol% of CuSAr* at 0 °C in toluene/Et$_2$O. This afforded quantitatively, the 1,4-addition product and this result indicates that a cuprate reagent rather than free MgIMe is involved in the reaction. The low e.e. of the product (3%: (S)-enantiomer) points to a low selectivity of the chiral cuprate in the presence of excess MgIMe. In contrast to this lack of enantioselectivity the reverse addition (method B): i.e. slow addition of MgIMe to a preformed Et$_2$O-solution of BA (0.06 M) and 9 mol% CuSAr* at 0 °C afforded the (S)-enantiomer of the 1,4-product in 57% e.e. (yield 80%).[9,11] This procedure is designed to keep a low excess of MgIMe with respect to the reactive magnesium cuprate. The correctness of this approach is confirmed by the fact that the addition of an Et$_2$O-solution of BA to a solution of preformed [CuSAr*][MgIMe] (method C) gave exactly the same result as found with method B (see eqn. 2).



eqn. 2

i: 3 mol % [CuSAr*]: MgIMe added slowly *ii*. [CuSAr*][MgIMe]: BA added slowly

Experimental

Synthesis of [CuSC$_6$H$_4$((R)-CH(Me)NMe$_2$-2]$_3$. The catalyst was prepared in accordance with the procedure described in *Inorg. Chem.* (in press).[12]

Acknowledgements

This work was partly supported (to F.L.) by EC-grant "Stimulation Action" No.: ST2000107.

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8. CuSAr* exists both in the solid state and in solution as a well-defined trinuclear aggregate [CuSAr*]$_3$. However, for clarity it will be considered as a monomer in this report .
9. At these ratios (order of addition of the reagents) the enolate formation is competitive with the addition reactions of organocuprate reagents, in particular with the more acidic methylketones (cf. G. Hallnemo and C. Ullenius, *Tetrahedron Lett.* **39** (1983) 1621; B. Christenson, and C. Ullenius, *Tetrahedron*, **47** (1991) 4739). In a recent study we found that subsequent condensation of benzylideneacetone with two equivalents of its lithium enolate, results in the formation of a tri-Michael product (15% yield, unique stereochemistry established by an X-ray crystallographic study); F. Lambert, A.L. Spek, J. Boersma, and G. van Koten, to be published.
10. [CuSAr*][LiMe] is soluble but unstable in THF whereas this cuprate is insoluble in Et_2O, toluene and hexane. Hydrolyses of this cuprate with water and measurement of the amount of methane evolved confirmed the proposed 1/1 molar ratio.[5]
11. With smaller amounts of [CuSAr*] catalyst lower selectivities for 1,4- vs. 1,2-addition were found, above 9 mol % the e.e. values remain the same.
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