

Asymmetric Synthesis Using Organocopper Reagents

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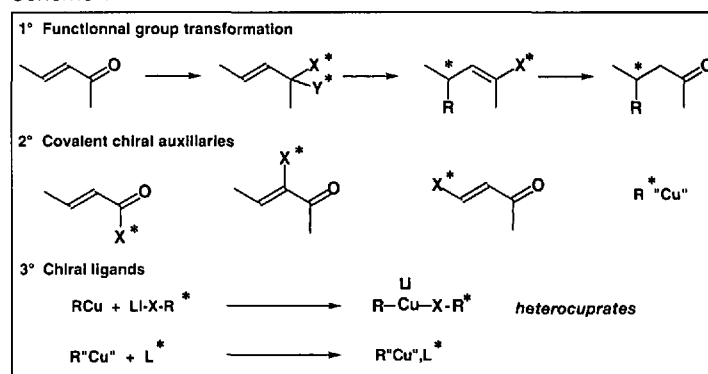
Organocopper reagents emerged as useful synthetic tools in the early sixties and have since then enjoyed standing popularity among organic chemists [1]. By far the most popular reaction is conjugate addition, which can be performed either with a stoichiometric organocopper reagent or under copper (I) catalysis, with, most often, a Grignard reagent as the main organometallic. In conjugate addition, the substrate has usually a double (or triple) bond to which an electron-withdrawing group (most often a carbonyl group) is attached. Conceptually, there are several ways to tackle this problem in an asymmetric sense [2] (Scheme 1): Although very successful [2], the covalent chiral auxiliary approach requires, by definition, a stoichiometric amount of the chiral auxiliary. The last approach uses an external chiral moiety. The amount of chiral ligand should therefore reflect the amount of copper metal used. Two different ways have been explored. The discovery of 'heterocuprates' by Posner *et al.* in 1973 [3], gave an immediate strong impetus to the heterocuprate approach. Some stoichiometric *lithium* heterocuprates have been shown to be efficient [2], but a catalytic (5–10%) use of the chiral copper complex cannot be accomplished with organolithium reagents necessitating the use of Grignard reagents. Such systems were developed more recently [4], although the ee's do not yet match those obtained in the stoichiometric cases.

More attention is currently given to the non-covalently bound ligands. Early reports with (–)-sparteine [5] or chiral solvents [6] and lithium diorganocuprate gave disappointingly low ee's. The first successful example was described by Leyendecker *et al.* with a ligand **1** derived from hydroxy proline [7]. Ee's up to 90% were obtained with acyclic enones. In 1991, we introduced a new class of ligands based on trivalent phosphorus derivatives [8]. In this case the phosphorus atom is itself a stereogenic center. These ligands are easily available from cheap ephedrine or its derivatives. Ligand **2** (Scheme 2) was very efficient with primary lithium diorganocuprates and cyclic enones, giving ee's in the 70–95% range [9].

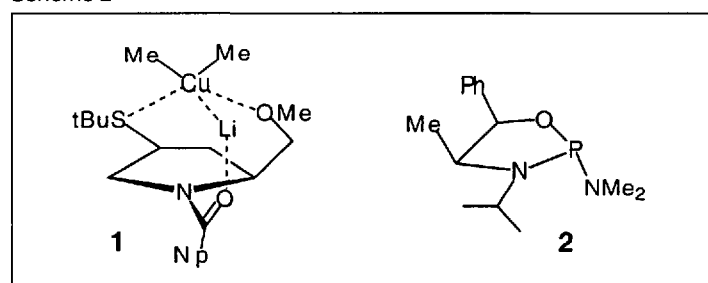
More recently, copper catalysis has also been shown to be effective in the conjugate addition of organozinc reagents [9]. In 1993, we reported [10] the first enantioselective result with a catalytic amount of the chiral copper complex **2** and diethyl zinc (Scheme 3). The best solvent appeared to be a non-polar one such as toluene.

Although the ee was moderate (32%) with cyclic enones, the asymmetric copper catalyzed conjugate addition of *dialkyl zinc* seemed to us to be the most promising way to do this synthetic transformation. A most important discovery was the fact that a ligand-accelerating effect was observed when the copper source was changed from CuI to Cu(OTf)₂ [11]. The scope of the reaction under these new conditions is quite wide and the catalyst loading (0.5%) among the lowest in organocopper chemistry. Some typical substrates are shown in Scheme 4.

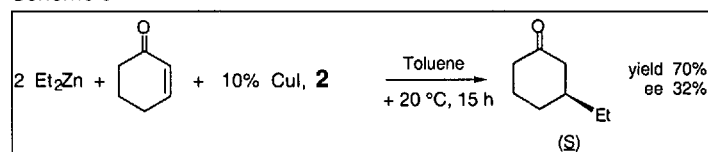
Scheme 1



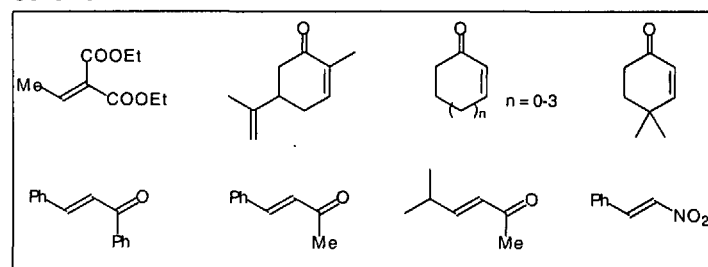
Scheme 2



Scheme 3

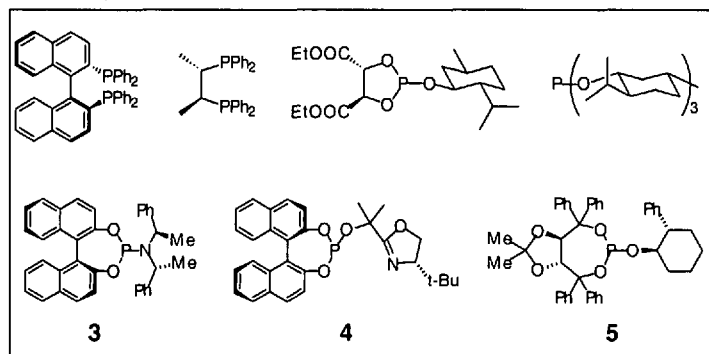


Scheme 4

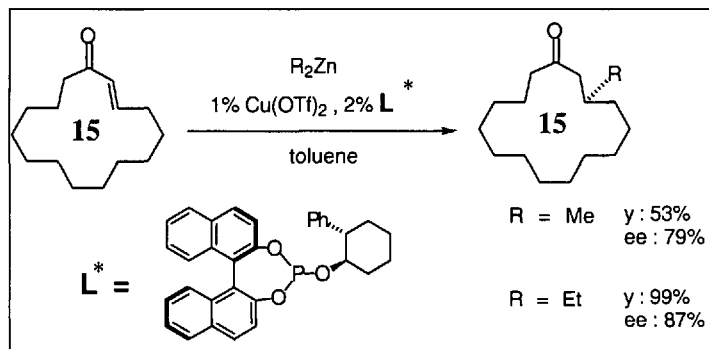


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Scheme 5



Scheme 6



We have investigated several phosphorus ligands, in both toluene and CH_2Cl_2 (the latter being somewhat better), with as little as 0.5% $\text{Cu}(\text{OTf})_2$ and 0.5–1% chiral ligand [12]. Some of them are shown below, but so far the best ligands for cyclic enones, such as cyclohexenone, are the phosphoramidate **3** [13] or the phosphites **4** [14] and **5** [15] based on binaphthol or TADDOL (Scheme 5):

However, there is no 'universal' ligand in the sense that each substrate has an optimized ligand. Acyclic enones, which exist as *s-cis* and *s-trans* conformers, as well as macrocyclic ones give good results even with other ligands. The synthesis of (–)-muscone is shown in Scheme 6 [16].

Although considerable progress has been made in designing new efficient chiral ligands, there is a real need for new, more general catalysts. As for other possible asymmetric transformations, the field remains wide open for investigation in the future.

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