Copper-Catalyzed Enantioselective Michael Additions: Recent Progress with New Phosphorus Ligands

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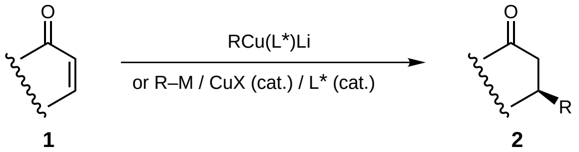
Enantioselective Michael addition of a chiral organometallic reagent to a prochiral substrate is an attractive method for creating a center of chirality in an organic molecule.[1] For this purpose chirally modified organocopper compounds of composition RCu(L*)Li can be used; the chiral nontransferable ligand L* controls the stereochemical course of the transfer of group R to the substrate **1**. By using stoichiometric amounts of these "chiral cuprates", the groups of Bertz, Corey, Dieter, Rossiter, and Tanaka obtained the 1,4-adducts **2** with good enantioselectivities (over 90% *ee* in some cases). Naturally occuring alcohols and amines were used as chiral ligands L* (e.g., ephedrine and proline derivatives).[1] However, these investigations also revealed two fundamental problems of enantioselective Michael additions:



1) In solution organocopper compounds show dynamic behavior with equilibria between several species. If this leads to the formation of achiral, but more reactive cuprates, a loss of enantioselectivity is unavoidable. Therefore, it is crucial to develop chiral reagents which react so rapidly with the substrate that undesired competing reactions are suppressed.
2) Many chiral organocopper reagents exhibit high substrate specificity; that is, they give good stereoselectivities with only one or very few Michael acceptors.

Both problems may be solved by taking advantage of the concept of *ligand-accelerated catalysis*,[2] which involves catalytic reactions characterized by dynamic ligand-exchange processes. The presence of a suitable ligand can lead to the formation of a highly reactive and selective catalyst by self-assembly. If a chiral ligand is used, a stereoselective reaction may be favored over a nonselective one. Other advantages of catalytic transformations compared to their stoichiometric counterparts are the more efficient use of the metal and the chiral ligand, as well as the minimization of waste production.

Michael additions of organolithium, Grignard, and diorganozinc reagents to enones and other α,β-unsaturated carbonyl compounds are catalyzed inter alia by copper, nickel, and cobalt salts. The best results are obtained with copper(I) catalysts, especially those in which copper is bound to a "soft", readily polarizable center (sulfur or phosphorus).

The first reaction of this type was reported by Lippard et al. in 1988: the reaction of 2-cyclohexenone (**3**) with Grignard reagents in the presence of the chiral aminotroponeimine copper complex **5** as catalyst gave the 1,4-adducts **4** with 4–14% *ee*.[3a] The selectivity was increased to 74% *ee* by addition of hexamethylphosphoric triamide (HMPA) and silyl halides.[3b] Spescha et al.[4] used the copper complex **6**, which was obtained from a thioglucofuranose derivative, as catalyst for 1,4-additions of Grignard reagents to **3**, and observed enantioselectivities of up to 60% *ee*. The dihydrooxazolylthiophenolato copper complex **7** was employed by Pfaltz et al.[5] for the enantioselective catalysis of Michael additions to cyclic enones; the best results were obtained with tetrahydrofuran as solvent and HMPA as additive. There was a pronounced dependence of the stereoselectivity on the ring size of the substrate: 16–37% *ee* for 2-cyclopentenone, 60–72% *ee* for **3**, and 83–87% *ee* for 2-cycloheptenone. Alexakis et al.[6] used the heterocycle **8**, which is readily accessible from ephedrine, as chiral ligand for the copper(I)-catalyzed addition of diethylzinc to **3**, and obtained ketone **4** (R = Et) with 32% *ee*. Another neutral phosphorus ligand is the proline derivative **9**, with which Kanai and Tomioka[7] obtained 67–90% *ee* in the Cu(I)-catalyzed 1,4-addition of Grignard reagents to 2-cyclohexenone (**3**). Recently, Feringa et al.[8] reported the use of phosphorus amidites of type **10** in Michael additions of diethylzinc to enones. These reactions are catalyzed by copper(I) salts and by copper(II) triflate; when **3** was used as substrate, stereoselectivities of 60% *ee* (with CuOTf) and 63% *ee* (with $Cu(OTf)_2$) were obtained (a much higher value of 81% *ee* resulted with 4,4-dimethyl-2-cyclohexenone in the presence of **10**. Even when $Cu(OTf)_2$ is employed, the actual chiral catalyst is probably a copper(I) species which is formed by in situ reduction of the copper(II) complex. In all these cases, the regioselectivities (1,4- vs. 1,2-addition) and chemical yields are acceptable or good.

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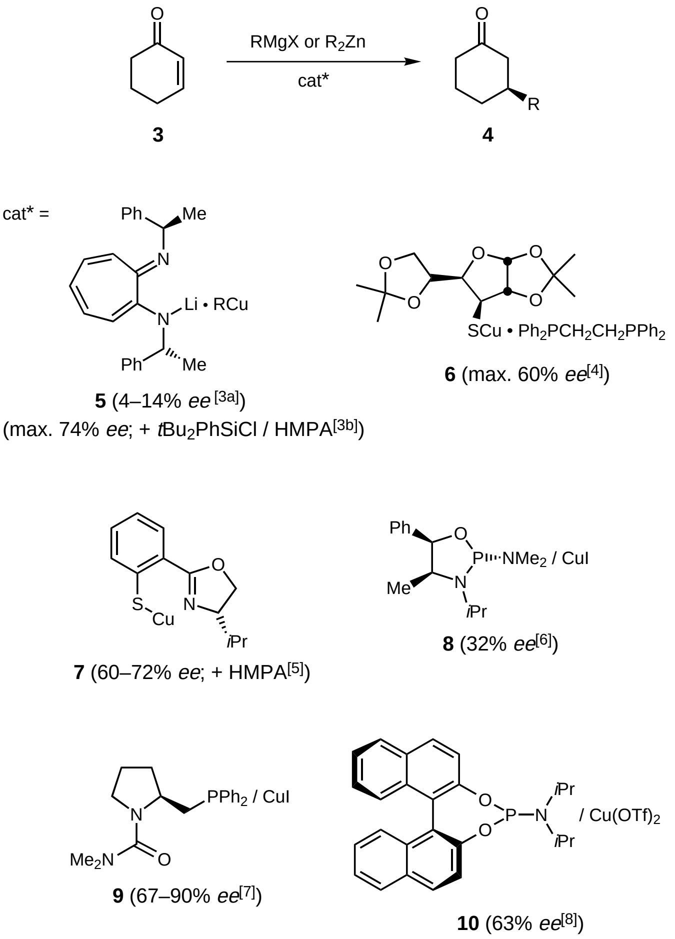


3 **4**

5 (4–14% *ee*[3a])
(max. 74% *ee*; + *t*Bu$_2$PhSiCl / HMPA[3b])

6 (max. 60% *ee*[4])

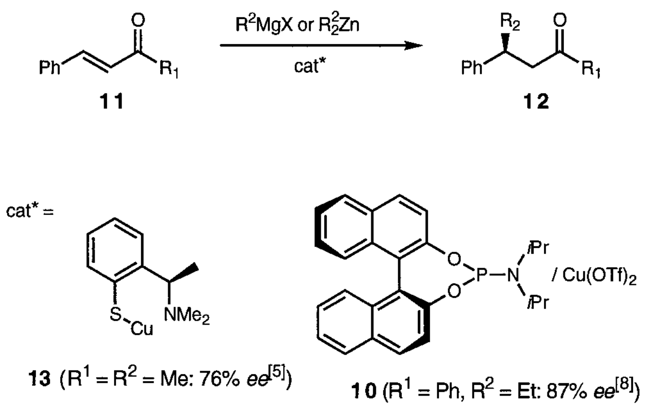
7 (60–72% *ee*; + HMPA[5])

8 (32% *ee*[6])

9 (67–90% *ee*[7])

10 (63% *ee*[8])

As these examples show, cyclic enones are normally used as substrates for copper-catalyzed enantioselective Michael additions. In some cases, however, good stereoselectivities were also attained with acyclic enones of type **11**. Thus van Klaveren, van Koten et al.[9] employed the copper arenethiolate **13** as catalyst for the 1,4-addition of methylmagnesium iodide to benzylideneacetone and obtained adduct **12** ($R^1 = R^2 =$ Me) with 76% *ee*. Interestingly, this catalyst is not suitable for analogous additions to cyclic enones; similarly, the structurally related copper thiolate **7** does not catalyze enantioselective Michael additions of Grignard reagents to acyclic enones of type **11**. With **7** and **13**, complicated nonlinear relationships between the enantiomeric excesses of the catalyst and the product were observed, indicating that the product is formed via different organocopper intermediates in several reaction pathways. Progress with regard to this undesired substrate specificity was achieved with the phosphorous amidite **10**, which catalyzes not only Michael additions of organozinc reagents to cyclic enones but also to chalcone (**11**, $R^1 =$ Ph) and related acyclic substrates. In the case of the addition of diethylzinc to chalcone, a good stereoselectivity of 87% *ee* was observed.[8]

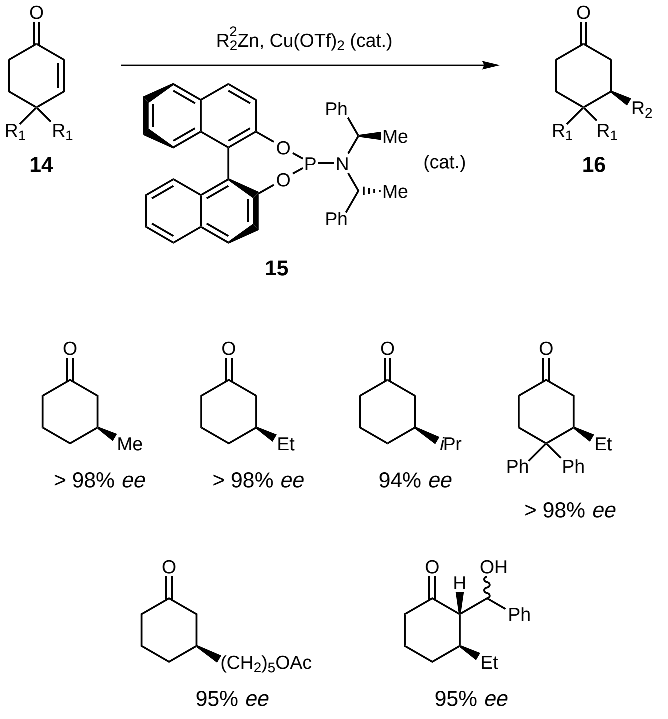


11 **12**

13 ($R^1 = R^2 =$ Me: 76% *ee*[5])

10 ($R^1 =$ Ph, $R^2 =$ Et: 87% *ee*[8])

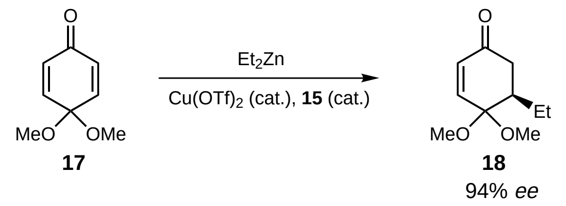
The last example shows that neutral binaphthol phosphorus ligands are particularly well suited for enantioselective Michael additions. On the basis of this structural feature, Feringa et al.[10] achieved a breakthrough. By combining C_2-symmetrical axially chiral binaphthol with C_2-symmetrical bis(1-phenylethyl)amine through a phosphorus center, they obtained the new ligand **15**, which can be used in highly enantioselective copper-catalyzed Michael additions of diorganozinc reagents to numerous cyclic enones. Here the steric properties of the substrate and the reagent are unimportant, since the transfer of methyl, ethyl, and isopropyl groups to 2-cyclohexenone takes place with high enantioselectivities ($\geq$94% *ee*) and good chemical yields (72–95%), as does the transfer of an ethyl group to 4,4-diphenyl-2-cyclohexenone. Additional functional groups can be introduced into the addition product in several ways without affecting the stereo-



14 **15** **16**

> 98% *ee* > 98% *ee* 94% *ee* > 98% *ee*

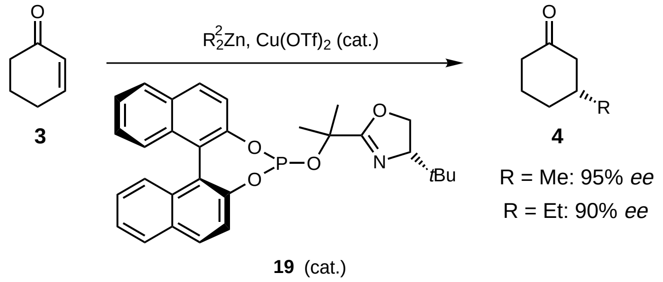
95% *ee* 95% *ee*



17 **18**
94% *ee*

chemical course of the reaction. Thus the addition of diethylzinc to 4,4-dimethoxy-2,5-cyclohexadienone (**17**), catalyzed by **15** und $Cu(OTf)_2$, gives adduct **18** with 94% *ee*. The functionalized zinc reagent $[AcO(CH_2)_5]_2Zn$, prepared by hydroboration of the corresponding alkene and transmetalation according to Knochel's method, can be added to 2-cyclohexenone with excellent selectivity of 95% *ee*. Finally, the zinc enolates formed in these transformations can also be treated with more complex electrophiles instead of protons. For example, the three-component coupling of 2-cyclohexenone, diethylzinc, and benzaldehyde in the presence of **15** and $Cu(OTf)_2$ furnishes the expected hydroxyketone with 95% *ee*; however, the diastereoselectivities of these transformations are not yet satisfactory.[10]

With the combination of phosphorus amidite **15** and $Cu(OTf)_2$, a catalyst has been developed for the first time which can be applied with confidence to almost any combination of Michael acceptor and organozinc reagent. This system apparently exploits the pinciple of ligand-accelerated catalysis. However, an important limitation has to taken into account: Only enones with six-membered rings give high stereoselectivities (the analogous reactions of diethylzinc with 2-cyclopentenone and 2-cycloheptenone gave the adducts with 10 and 53% *ee*, respectively). Another recent report by Pfaltz et al.[11] underlines that the bridging of binaphthol and a chiral amine through a phosphorus center is a general feature of catalysts which are suitable for highly enantioselective Michael additions. In the presence of the phosphite **19** with oxazoline structure, the 1,4-additions of dimethyl- and diethylzinc to **3** also give stereoselectivities of 95 and 90% *ee*, respectively. Hopefully, this major progress will trigger further investigations leading to new chiral copper catalysts which can be applied even more generally to cyclic Michael acceptors with different ring sizes as well as to acyclic substrates.



German version: *Angew. Chem.* **1998**, *110*, 295–297

Keywords: asymmetric catalysis · biaryls · enantioselectivity · ligand-accelerated catalysis · Michael additions

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