Conjugate Addition

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Copper-Catalyzed Asymmetric Michael Addition of Magnesium, Zinc, and Aluminum Organometallic Reagents: Efficient Synthesis of Chiral Molecules**

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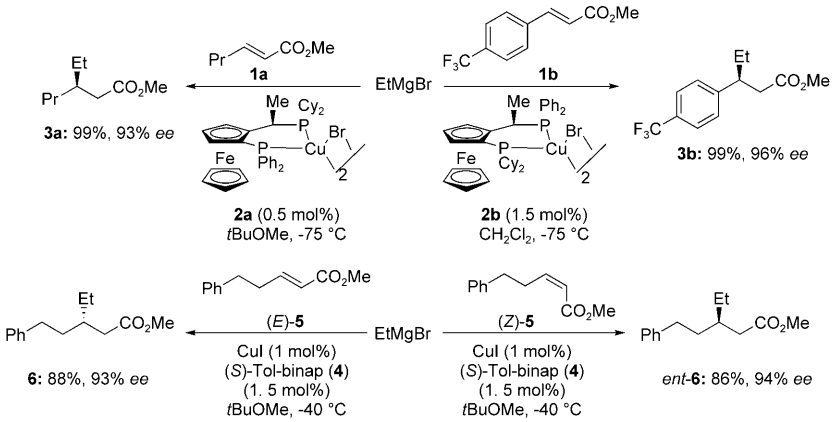
asymmetric catalysis · copper · homogeneous catalysis · Michael addition

Copper-catalyzed asymmetric conjugate addition reactions of organometallic reagents to Michael acceptors have been an important research topic for two decades. New procedures developed by careful tuning of the reaction conditions, the organometallic reagent, and the chiral ligand provide the conjugate adducts with very high enantioselectivities.[1] This brief overview of copper-catalyzed asymmetric conjugate addition reactions highlights some of the most important recent contributions.

Copper-catalyzed enantioselective conjugate addition reactions were first studied with Grignard reagents.[2] With chiral ferrocene ligands, such as taniaphos[3] or josiphos,[4] EtMgBr underwent Michael addition to unsaturated esters, such as **1a** and **1b**. In the presence of the regioisomeric copper–ligand complex **2a** (0.5 mol%) or **2b** (1.5 mol%), the expected adducts **3a** and **3b** were formed in 99% yield with 93 and 96% *ee*, respectively (Scheme 1).[5] Interestingly, the use of (*S*)-Tol-binap (**4**) in combination with CuI (1 mol%) enables stereoselective addition reactions to *E*- and *Z*-unsaturated esters to be carried out. For example, (*E*)-**5** and (*Z*)-**5** were converted into the two enantiomeric Michael adducts **6** and *ent*-**6** in 93 and 94% *ee*, respectively.[6] No isomerization of the sensitive unsaturated ester (*Z*)-**5** was observed during the reaction.



Scheme 1. Conjugate addition to acyclic unsaturated esters. Cy = cyclohexyl, Tol-binap = 2,2′-bis(di-*p*-tolylphosphanyl)-1,1′-binaphthyl.

This methodology could be used directly for the addition of MeMgBr to the α,β-unsaturated ester **7** in the presence of (*S*)-Tol-binap (**4**) and CuI. The conjugate adduct **8** was formed in 68% yield with 96% *ee* (Scheme 2). By using an iterative reaction sequence, it was possible to synthesize both *anti*-**9** (obtained with (*R*)-binap) and *syn*-**9** (obtained with (*S*)-binap) with d.r. > 95:5. Remarkably, the stereoselectivity of the addition is not affected by the stereogenic center already present in the substrate. Further iterations provided a straightforward route to the marine natural product siphonarienal (**10**).[7] When (*R*,*S*)-josiphos[4] is used as the chiral ligand, the addition of MeMgBr proceeds most efficiently with unsaturated thioesters, rather than methyl esters, as substrates. Thus, the Michael adduct **12** was formed in 92% yield with 96% *ee* from **11**. Compound **12** was converted readily in two steps into the chiral unsaturated thioester **13** (81%), which was transformed in a further asymmetric conjugate addition step into either *syn*-**14** or *anti*-**14** with d.r. ≥ 95:5, depending on the configuration of the josiphos catalyst. This iterative method was applied to the synthesis of the insect pheromone (−)-lardolure (**15**).[8]

To extend the scope of the 1,4-addition of organomagnesium reagents,[9] a new modular phosphine–phosphite ligand **16** was prepared from inexpensive 2-*tert*-butylphenol (**17**) and taddol.[10,11] This type of ligand enables the conjugate addition of a broad range of Grignard reagents to 2-cyclohexenone. The use of a nonpolar, weakly coordinating ether, such as 2-methyltetrahydrofuran,[12] as the solvent proved essential for high enantioselectivity to be attained. Thus, the addition of 2-propenylmagnesium bromide (**18**) to cyclohexenone furnish-

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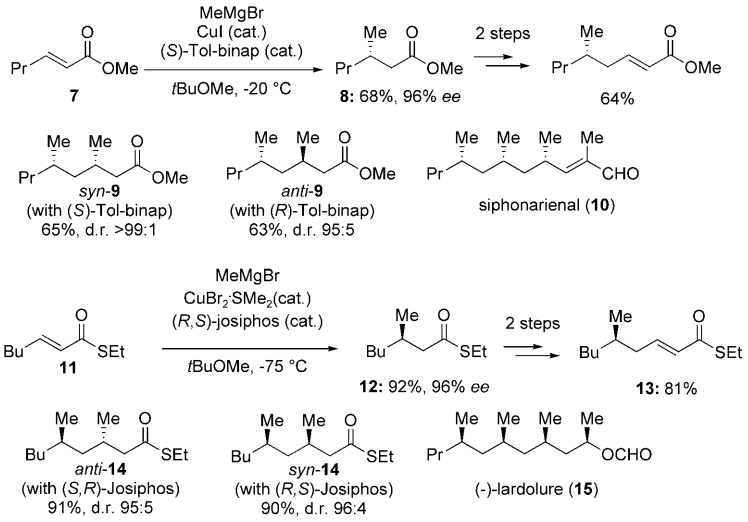
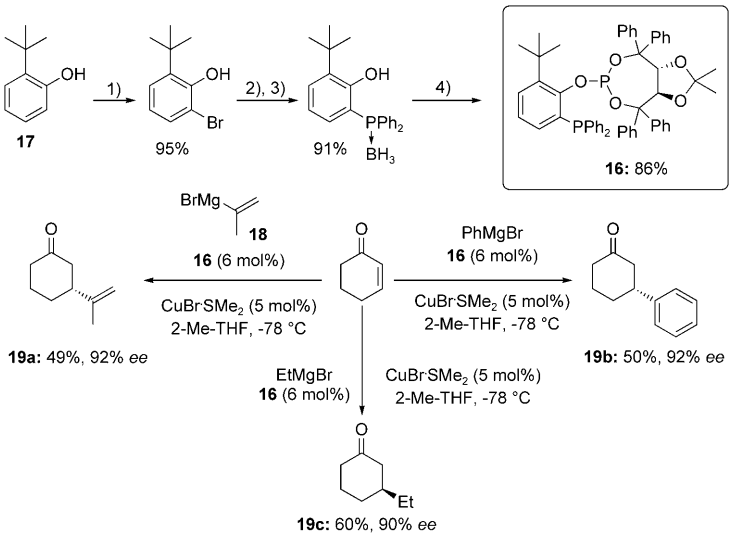


Scheme 2. Iterative conjugate addition of MeMgBr.

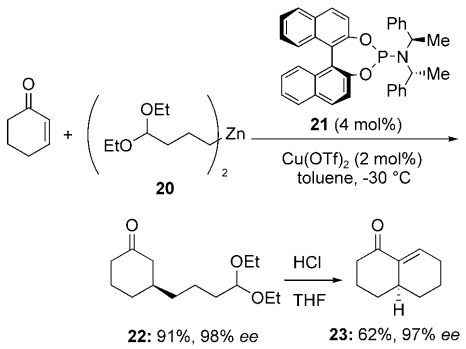
ed the 1,4-adduct **19a** with 92% *ee*. Similarly, the addition of PhMgBr provided the cyclic ketone **19b** with 92% *ee*. When EtMgBr was used, the ketone **19c** was obtained with an equally high *ee* value, but with the opposite configuration, which results in this case from the addition of the nucleophile to the *Si* face of cyclohexenone (Scheme 3).

In 1993, it was shown that the highly reactive Grignard reagents could be replaced advantageously with diorganozinc reagents, which exhibit greater functional-group compatibility.[13,14] Thus, the addition of the functionalized diorganozinc reagent **20** to cyclohexenone in toluene at −30 °C in the presence of the phosphoramidite ligand **21** provided the Michael adduct **22** in 91% yield with 98% *ee*. The treatment of **22** with an acid provided the useful chiral bicyclic enone **23**



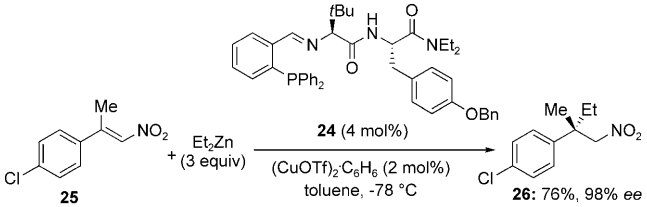
Scheme 3. A modular ligand for the addition of alkenyl, alkyl, and aryl magnesium reagents to cyclohexenones: 1) NBS, iPr_2NH (cat.), CH_2Cl_2, reflux; 2) $ClPPh_2$, dabco, CH_2Cl_2, 0 °C→RT, then BH_3·THF, 0 °C→RT; 3) *n*BuLi, THF, 0 °C; 4) PCl_3, dabco, CH_2Cl_2, room temperature, then taddol, room temperature. dabco = 1,4-diazabicyclo[2.2.2]octane, NBS = *N*-bromosuccinimide, taddol = 1,1,4,4-tetraphenyl-2,3-*O*-isopropylidene-L-threitol.

in 62% yield with 97% *ee* (Scheme 4). This sequence of asymmetric conjugate addition and cyclization also proceeded well with seven- and eight-membered cyclic enones.[15]



Scheme 4. Conjugate addition of a functionalized dialkyl zinc reagent. Tf = trifluoromethanesulfonyl.

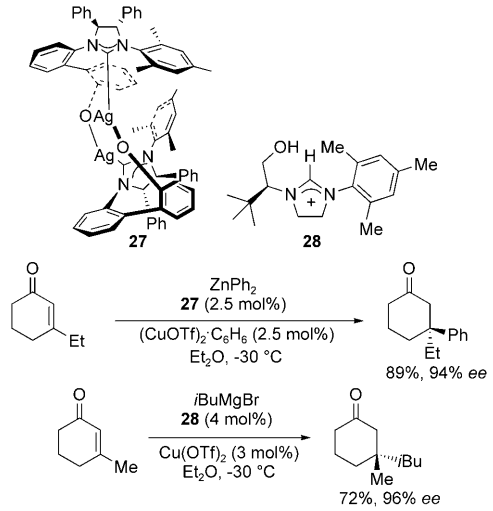
The construction of configurationally pure all-carbon quaternary centers is an important synthetic goal,[16] which can be achieved by the conjugate addition of organozinc and organomagnesium reagents to β-disubstituted Michael acceptors. In the presence of peptide ligands, such as **24**, diorganozinc reagents underwent enantioselective addition to nitroolefins, such as **25**. Thus, the nitro compound **26** was obtained from **25** with 98% *ee* (Scheme 5).[17,18]



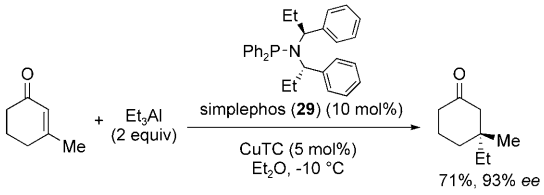
Scheme 5. Creation of a quaternary all-carbon stereogenic center through the addition of diethylzinc to a nitroolefin.

Alternatively, N-heterocyclic carbene (NHC) ligands, such as **27** and **28**, can be used for the construction of quaternary centers with excellent enantioselectivity through the addition of organozinc[19] and Grignard[20] reagents to β-disubstituted cycloalkenones (Scheme 6). Remarkably, activated cyclopentenones[19b] with an ester group at the β position also underwent conjugate addition with high enantioselectivity. The use of ligands of the simplephos family, such as **29**, enables highly enantioselective addition reactions to be carried out with aluminum organometallic reagents with the generation of quaternary stereogenic centers (Scheme 7).[21]

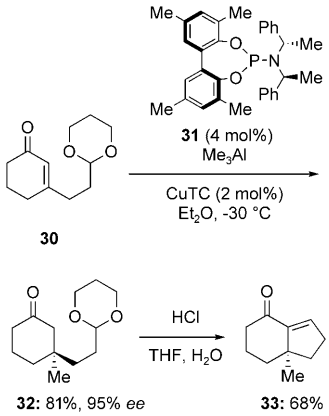
Functionalized enones, such as **30**, undergo stereoselective copper-catalyzed conjugate addition with organoaluminum reagents in the presence of the phosphoramidite ligand **31**. Thus, **30** was converted by treatment with Me_3Al into the chiral enone **32** (95% *ee*), which was transformed into the bicyclic product **33** under acidic conditions (Scheme 8). This method is also suitable for the generation of quaternary stereogenic centers at the β position of cyclopentanones.[22]



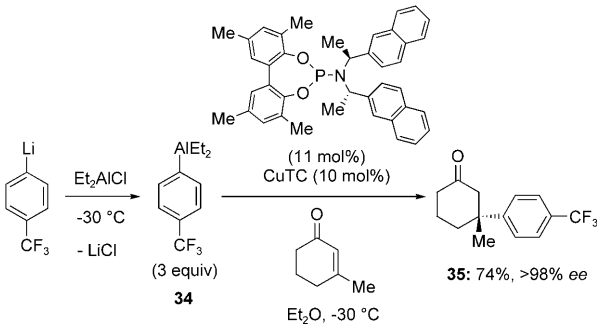
Scheme 6. NHC ligands for the generation of quaternary stereogenic centers through conjugate addition.



Scheme 7. Conjugate addition of a trialkyl aluminum reagent with a simple phos ligand. CuTC = copper(I) thiophenecarboxylate.



Scheme 8. Creation of a stereogenic all-carbon quaternary center with a trialkyl aluminum reagent.



Scheme 9. Synthesis of aryl aluminum reagents and subsequent conjugate addition.

A new method for the synthesis of aryl aluminum organometallic reagents, such as **34**, has made it possible to prepare enones such as **35** with a functionalized aryl moiety at the quaternary stereogenic center (Scheme 9).[23] 3-Alkenyl cyclohexen-2-ones such as **36** contain two conjugated C–C double bonds, both of which may undergo conjugate addition. Whereas the use of trialkyl aluminum and dialkyl zinc reagents in combination with the phosphoramidite **37**–copper(II) catalyst system leads to the 1,6-addition products (e.g. **38** from **36**), Grignard reagents in combination with the NHC ligand **28** provide the 1,4-adducts (e.g. **39** from **36**).[24] A combination of the last reaction to form **39** with a metathesis reaction afforded the chiral spiro compound **40** (Scheme 10).

We have shown herein that the copper-catalyzed conjugate addition of organometallic reagents (organozinc, organomagnesium, and organoaluminum reagents) has become a reliable method for the synthesis of chiral molecules with high enantioselectivity. Moreover, it offers a direct, general, and highly stereoselective approach to the construction of chiral quaternary stereocenters: one of the most important and most challenging tasks in asymmetric catalysis.[16a]

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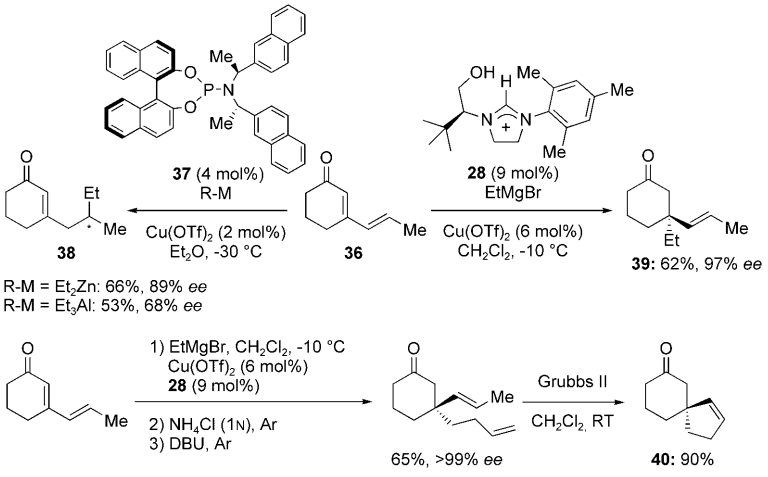

Scheme 10. Regiodivergent conjugate 1,4- and 1,6-addition. DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, Grubbs II = Grubbs second-generation catalyst.

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