The conjugate addition reaction

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1. Introduction.

Conjugate addition is among the basic carbon-carbon bond forming reactions [1]. An organometallic reagent is required with, most often, a transition metal in stoichiometric or catalytic amount. The substrate is usually a double (or triple) bond to which an electron-withdrawing group (most often a carbonyl group) is attached.

\[
\text{R-met.} + \text{EWG} \rightarrow \text{R} \text{EWG}
\]

Traditionally, organocopper derivatives were the reagent of choice to undergo this synthetic transformation. Several books and review articles deal with the various aspects of his reaction: reactivity, stereochemistry, mechanism [2]. This last aspect is still somewhat controversial as well as the exact nature of the reagent itself [3].

This chapter deals with some of the most recent developments put in the context of reactivity and, particularly, enantioselectivity.

2. General aspects of reactivity

Historically, the conjugate addition reaction was first performed with Grignard reagents and catalytic amounts of copper (I) salts [4]. Later developments used lithium diorganocuprate reagents, which were more reliable, and of much wider applicability, since the parent organolithium reagent [5] could be generated in several ways. Nowadays, many other organometallics may also be used such as organozinc, organotin, organoaluminium, organoboron, organozirconium reagents, organosamarium, etc. [6]. By varying the amount of copper (I) salt, several types of reagents are available.

\[
\begin{align*}
\text{R-met.} + \text{CuX} & \rightarrow \text{R-met (cat. CuX)} & 1 \\
\text{R-met.} + 1 \text{ equiv. CuX} & \rightarrow \text{R-Cu} & 2 \\
2 \text{ equiv. R-met.} + 1 \text{ equiv. CuX} & \rightarrow \text{R}_2\text{Cu,met} & 3 \\
3 \text{ equiv. R-met.} + 1 \text{ equiv. CuX} & \rightarrow \text{R}_3\text{Cu,met} & 4
\end{align*}
\]

Stoichiometric organocopper reagents (Eq. 2) are usually poorly soluble and of low reactivity. The 2:1 reagent (Eq. 3) usually called cuprate reagent, or Gilman reagent, is
the most commonly applied, whereas the 3:1 reagent (Eq. 4), called higher order cuprate [7], is of increased reactivity, but also of increased basicity.

As the substrate is concerned, there is a notable difference according to the nature of the electron-withdrawing group and the substitution pattern of the double bond. Substitution in the β-position strongly slows down the reaction rate. When the electron-withdrawing group is an ester or amide functionality the reaction is also sternly slowed down. Ketones represent the most common carbonyl group. As for aldehydes, the main problem deals with the competition between the conjugate addition (1,4 addition) and the direct carbonyl attack (1,2 addition).

Among the different classes of R group to be transferred, there are some general trends observed whatever the stoichiometry of Cu(I) salt. Alkynyl groups react by direct carbonyl attack (1,2 addition). Alkenyl and aryl groups are normally transferred in conjugate fashion, albeit at a somewhat slower rate than alkyl groups do. The main problem deals with the thermal stability of the alkenyl copper reagent (in contrast, aryl copper reagents are extremely stable). In the class of alkyl groups, the methyl group (which lacks β hydrogens) is of exceptional stability but also of very low reactivity.

In general, other type of organometallic reagents, than those of copper, are of more moderate reactivity. Their use is mainly restricted to chemo- and stereoselective processes and will be discussed below.

In order to increase the reactivity for conjugate addition Yamamoto [8] studied the compatibility of stoichiometric organocopper reagents (considered as soft) with strong (and hard) Lewis acids. He observed that the combination R\text{Cu}/BF_3 is a suitable alternative to R_2CuLi for the transfer of the methyl group to sterically hindered enones.

\[
\text{Me-Cu} + \text{BF}_3 \longrightarrow \text{Me-CO-R}
\]

This R\text{Cu}/BF_3 combination was even more successful in other typical organocopper reactions, such as S_N2' substitutions, cleavage of epoxides [9] or asymmetric cleavage of chiral acetals [10]. In all these reactions, it is believed that the activation mainly arises from coordination of the Lewis acid to the oxygen atom of the carbonyl group.

Organomanganese reagents, catalyzed by copper(I) salts, were also reported to be of increased reactivity towards sterically hindered enones, although the exact role of manganese was not clarified [11].

Several groups reported independently the beneficial effect of added Me_3SiCl (TMSCl) to the reaction mixture prior to the addition of the enone [12]. Stoichiometric organocopper reagents are totally unreactive towards Me_3SiCl, and even Me_3SiI ! [13].
Organocuprate reagents are also compatible with Me$_3$SiCl, at least below $-50^\circ$C in THF. Even Grignard reagents may be used with catalytic copper(I) salts [12c], provided HMPA is added as cosolvent. The dramatic rate enhancement of the conjugate addition, and the experimental simplicity, has made this method very popular. However, care should be taken in stereoselective processes, as cases of total inversion of selectivity were reported [12a][14].

$$\text{R}_2\text{CuLi} + \text{CO-R'} + \text{Me}_3\text{SiCl} \rightarrow \text{R-CO-R'}$$

In general, in the presence of Me$_3$SiCl $\alpha,\beta$-ethylenic aldehydes react cleanly in conjugate fashion, with negligible amounts of the competing direct carbonyl attack [15]. Amides and esters [12b] react at a convenient rate, as well as sterically hindered enones. Me$_3$SiCl is also needed for the conjugate addition of organozinc-copper reagents, which may bear additional functionalities [16].

The use of Me$_3$SiI (TMSI) with copper acetylides allows this class of R groups to be transferred in conjugate fashion [17].

$$\text{R-C=C-Cu} + \text{CO-R'} + \text{Me}_3\text{Si} \rightarrow \text{R-C≡C-CO-R'}$$

Previously other organometallic combinations such as (R = alkynyl) RAlMe$_2$/Ni cat. [18], RAl(Li)Me$_3$/TMSOTf [19], RZnBr/TMSOTf [20] and RB(9-BBN)/BF$_3$ [21] have been known to undergo alkynylation.

The exact role of TMSCl on the acceleration of the conjugate addition is still unclear. It was first believed that TMSCl traps the Cu(III) intermediate as a silyl enol ether, thus increasing the rate of the reductive elimination step [12a]. However, recent kinetic studies revealed that conjugate addition sometimes occurs prior to the silylation of the resulting enolate [22]. It was also reported that TMSCl may act as a Lewis acid [23], although it does not accelerates typical Lewis assisted reactions such as epoxide opening or acetal cleavage. Whatever the exact mechanism, the synthetic result seems wider in scope since a recent report reveals rate enhancement in the conjugate addition of stabilized organolithium reagents [24].

3. Enantioselectivity

Most often, the conjugate addition results in the creation of a new stereogenic center. This point was already noticed in the late 1950s and several reports deal with this
topic. A complete review covers this topic until 1991 [25a]. More recently, decisive advances have been made in the copper-[26] and the rhodium-catalyzed [27] versions of the reaction, resulting in an explosive growth of articles dealing with the subject.

There are several ways to tackle this problem of asymmetry:

1° Functionnal group transformation

\[
\begin{align*}
\text{RCu} + \text{Li-X-R}^* & \rightarrow \text{Li} \quad R=\text{Cu}=X-R^* \\
\text{R"Cu"} + \text{L}^* & \rightarrow \text{R"Cu"-L}^*
\end{align*}
\]

2° Covalent chiral auxiliaries

3° Chiral ligands

One approach is to transform the sp2 carbon of the carbonyl into another functionality with an sp3 carbon. The reaction is now a γ allylic substitution. Chiral acetals are the typical example of this class [28], resulting in the formal asymmetric conjugate addition of organolithiums to α,β-ethylenic aldehydes.

Very successful results were obtained by the covalent chiral auxiliary approach, which allow the purification of the major diastereomer thus affording ultimately a pure enantiomer. The chiral covalent auxiliary may be attached at different positions of the substrate. There are several examples in the literature describing such an approach:

Chiral esters or amides of various chiral alcohols or amines allow a very large array of chiral auxiliaries [25]. Several of the most popular ones take advantage of the camphor framework. Although the reactivity of such substrates is usually rather low, good chemical yields may be obtained using the various ways to increase the reactivity. Some representative examples are listed below:
The third approach uses an external chiral moiety. Early studies dealt with heterocuprates where the chirality is brought by a chiral alcoholate, thiolate or amide [25, 37]. However, the success came from the external ligand approach, the best one to allow a catalytic use of transition metal and ligand. Cu, Ni and Rh are the most appropriate metals.

Historically, Cu was the metal of choice. Early reports with (-) sparteine [38] or chiral solvents [39] and lithium diorganocuprate or triorganozincates gave disappointingly low ee’s. The first successful example was described by Leyendecker et al with a ligand derived from hydroxy proline [40]. More recently, Alexakis [41] and Tomioka [42] introduced a new class of ligands based on the concept of chiral trivalent phosphorus derivatives. These ligands were efficient in stoichiometric amounts, or very high catalyst loading.

The breakthrough in catalysis came with the replacement of organolithium or Grignard reagent, as primary organometallics, by diorganozinc reagents. Although some organozinc species undergo conjugate addition [43], Ni [44] or Cu [45] catalysis is helpful. An even stronger acceleration is found when Cu salts are coordinated by a ligand [46]. The combination of \( \text{R}_2\text{Zn} + \text{Cu salt} + \text{phosphorus ligand} \) is presently the most widely used. A recent review [26g], covering this exact topic, shows that, in just 4-5 years, >350 chiral ligands have been developed, just for the asymmetric conjugate addition of diethyl zinc to cyclohexenone!
Et₂Zn + \begin{array}{c}
\text{O} \\
\text{O}
\end{array} + 0.5-2\% \text{ CuX, } 2 \text{ L}^* \rightarrow \begin{array}{c}
\text{O} \\
\text{O}
\end{array} \text{Et}

This reaction is wide in scope, allowing very high (>99\%) enantioselectivities for a range of substrates and alkyl groups. Even functionalized diorganozincs can be added. Representative Michael acceptors are shown below:

\[
\begin{array}{c}
\text{O} \\
\text{O}
\end{array} \quad \text{R}^1 \text{R}^2 \\
\text{n} = 0, 1, 3, 4 \\
\begin{array}{c}
\text{O} \\
\text{O}
\end{array} \quad \text{R}^1 \text{R}^2 \\
\text{R}^1 \text{NO}_2 \\
\text{R}^1 \text{COOEt}
\]

The experimental conditions for all these substrates are rather similar: CuOTf or Cu-thiophene carboxylate or CuOAc or CuBF\(_4\)[CH\(_3\)CN]\(_4\), as Cu source; toluene or Et\(_2\)O as solvent. The Cu : chiral ligand ratio is usually 2 : 1. Several structural types of chiral ligands are, now, known, most of them having a phosphorus atom [see ref 26g for the complete list of ligands]. Representative efficient ligands are shown below:

\[
\begin{array}{c}
\text{Ph} \\
\text{Me} \\
\text{Ar}
\end{array} \\
\text{P} \\
\text{N} \\
\text{Me} \\
\text{Ph}
\]

More recently, trialkyl aluminum were also good candidates for the Cu-catalyzed conjugate addition [53]. All these reactions lead ultimately to a zinc (or Al) enolate, which may be trapped with other electrophiles than simple water. Aldehydes react readily [54], but not ketones, to afford the aldol product. Acetals, chiral and achiral ones, need the
assistance of a strong Lewis acid such as BF$_3$:Et$_2$:O [55]. Alkylation is feasible with HMPA and excess alkylating agent [52], as well as allylation with Pd catalysis and allyl acetate [47, 54]. Silylation of the enolate allows the obtention of the very versatile silyl enol ethers for further elaboration [56, 57].

Nickel catalysis, with R$_2$:Zn is also known, but limited in scope. Only chalcone type enones (Ar-CH=CH-CO-Ar’) react with some successful enantioselectivities. Representative examples of ligands are shown below:

In contrast to Cu and Ni, Rh catalysis uses ArB(OH)$_2$ as primary organometallics. Therefore, for the introduction of aryl and alkenyl groups it is more appropriate to shift to Rh catalysis [27, 58]. Since the first report by Miyaura [59], Hayashi et al has developed the asymmetric version very successfully (ee’s >95%), both on cyclic and acyclic enones. Other Michael acceptors are also possible, as for copper.

Alkenyl boranes, resulting from hydroboration of alkynes, can also be transferred. An alternative to boronic acids are potassium tetrafluoroborate [60]. The chiral ligand is a diphosphine [27], or a diphosphite [61], or even a monodentate phosphorus ligand [62].
Finally, by analogy to zinc enolates, boron (or titanium) enolates have been trapped by silylation [63], allylation [64] or aldol condensation [65].

4. References and Notes.


