2
Transmetalation Reactions Producing Organocopper Reagents

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2.1
Introduction

Organocopper reagents constitute a key class of organometallic reagents, with numerous applications in organic synthesis [1]. Their high reactivities and chemoselectivities have made them unique intermediates. Most reports use organocopper reagents of type 1 or 2, which are prepared from organolithiums. This transmetalation procedure confers optimal reactivity, but in many cases it permits only the preparation of relatively unfunctionalized organocopper reagents. More recently, substantial developments have been taking place in transmetalations to organocopper reagents starting from organometallic species that tolerate the presence of functional groups [2], while synthetic methods permitting the preparation of functionalized organolithiums and organomagnesium compounds have also been developed. All organometallics in which the metal M is less electronegative than copper, and all organometallic species of similar electronegativity but with weaker carbon-metal bonds, are potential candidates for transmetalation reactions [3]. Thus, reaction conditions allowing the transmetalation of organo-boron, -aluminium, -zinc, -tin, -lead, -tellurium, -titanium, -manganese, -zirconium and -samarium compounds have all been found, resulting in a variety of new organocopper reagents of type 3. Their reactivity is dependent on the nature of the original metal M, which in many cases is still intimately associated with the resulting organocopper reagent (Scheme 2.1) [3–5].

In this chapter, we will emphasize these recent developments, especially those that allow the preparation of organocopper species not accessible through the standard procedures involving organolithiums as precursors and their use in reactions with organic electrophiles.

2.2
Transmetalation of Functionalized Organolithium and Organomagnesium Reagents

Many functional groups are incompatible with organolithium reagents. Execution of transmetalations at very low temperatures, however, enables functionalized
alkenyllithiums and aryllithiums to be prepared, and subsequent further transmetalation at low temperatures provides the corresponding copper reagents [6]. Thus, treatment of 4-bromobenzonitrile 4 with \( n \)BuLi at \(-100 \) °C in a THF/ether/pentane mixture provides the corresponding aryllithium within 5 min. (Scheme 2.2), and subsequent treatment with the THF-soluble copper salt CuCN·2LiCl [7] then affords the functionalized arylcopper compound 5. Treatment of this with 2-cyclohexene in the presence of TMSCl [8] furnishes the expected Michael adduct 6 in 93% yield.

In some cases it can be advantageous first to transmetalate the functionalized aryllithium reagent to the corresponding zinc reagent and then to perform a second transmetalation to afford the corresponding organocopper species. Thus, 2-iodo-1-nitrobenzene 7 is converted into the corresponding lithium reagent by treatment with phenyllithium [9]. Subsequent transmetalation, firstly with ZnI₂ at
−80 °C and then with CuCN-2LiCl [7] at −30 °C, provides the arylcopper 8. This reacts with 3-iodo-2-cyclohexenone to give the expected addition-elimination product 9 in 70% yield.

This method can be extended to the preparation of alkenylcopper compounds. Thus, treatment of the iodoalkenyl azide 10 with nBuLi at −100 °C (Scheme 2.3), followed by transmetalation with ZnI2 in THF and then by a second transmetalation with CuCN-2LiCl, produces the copper species 11. This then effects a cis-selective carbocupration of ethyl propiolate to furnish the (E, E) diene 12 in 81% yield.

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\text{Scheme 2.3. Preparation of an azido-alkenylcopper reagent from an alkenyl iodide.}
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In general, the preparation of functionalized organolithiums is difficult, although direct lithiation with lithium powder in the presence of a catalytic amount of 4,4′-di-t-butylbiphenyl (DTBB) as introduced by Yus [10] is a very general approach to a broad range of polyfunctional organolithiums [11–16], which may be converted into the corresponding organocopper compounds by treatment with CuCN-2LiCl [6]. Organomagnesium compounds are less reactive than organolithiums and tolerate a wider range of functional groups. Mild methods are required for their preparation and excellent results have been obtained by insertion of highly reactive “Rieke-magnesium” into alkyl or aryl halides [17]. Unfortunately, the presence of such important electron-withdrawing functional groups as esters or cyano functions inhibits the formation of Grignard reagents [18]. Complementarily, halogen-magnesium exchange [19] has proven to be an excellent method for preparation of functionalized organomagnesium compounds. Thus, treatment of 4-iodobenzonitrile 13 with iPrMgBr or iPr2Mg in THF at −25 °C furnishes the corresponding organomagnesium reagent, which is transmetalated to produce the desired functionalized organocopper 14. Treatment of 14 with allyl bromide produces the allylated product 15 in 75% yield (Scheme 2.4) [20].

This iodine-magnesium exchange can also be performed with heterocyclic iodides, such as the functionalized pyridine 16 [21] or the iodouracil derivative 17 (Scheme 2.5) [22]. In both cases, the intermediate organomagnesium reagent can

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\text{Scheme 2.4. Preparation of functional arylcoppers from functionalized arylmagnesium compounds.}
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be converted into the corresponding organocopper compound (18 and 19, respectively) and then treated with several electrophiles such as allyl bromide or benzylic chloride, resulting in the expected products 20 and 21 in good yields.

The preparation of polyfunctional 5-membered heterocycles can be achieved in the same manner. The ester-substituted imidazole 22 undergoes a smooth iodine-magnesium exchange at \(-40^\circ\text{C}\) within 1 h (Scheme 2.6). After transmetalation with CuCN·2LiCl, the copper reagent 23 is obtained. Treatment of this with benzylic chloride furnishes the benzyliclated imidazole 24 in 67\% yield [23]. In the case of the 2,3-iodoindole derivative 25, it is possible to perform a selective iodine-magnesium exchange at position 2, furnishing the 3-iodo-2-indolylcopper reagent 26 after transmetalation with CuCN·2LiCl. Treatment of 26 with allyl bromide provides the monoallylated indole derivative 27 in 92\% yield [24].
Remarkably, halogen-magnesium exchange can also be extended to aryl and heteroaryl bromides [24, 25]. Thus, the functionalized aryl bromides 28 and 29 (Scheme 2.7) were converted, at 0 °C and at −30 °C, respectively, into the corresponding Grignard reagents. After treatment with CuCN, the copper derivative 30 and 31 were obtained. Subsequent treatment with typical electrophiles such as benzoyl bromide or allyl bromide furnished the products 32 and 33, in 70 and 80% yields.

The rate of bromine-magnesium exchange largely depends on the electron density on the aromatic ring, although also being accelerated by the presence of chelating groups [25]. In the case of polyhalogenated heterocycles, these effects enable selective exchange reactions to be accomplished. Thus, the tribromoimidazole 34 (Scheme 2.8) can be successfully converted first into the magnesium derivative and then into the copper reagent 35, by treatment with iPrMgBr followed by...
CuCN-2LiCl. This can then be selectively allylated with allyl bromide to provide the dibromoimidazole 36, which can now be magnesiated by treatment with a further equivalent of iPrMgBr, providing the ester-substituted imidazole 37 in 55% yield after carboxylation with ethyl cyanoformate [25].

The halogen-magnesium reaction can be extended to electron-poor hetero-aryl chlorides. Thus, tetrachlorothiophene 38 (Scheme 2.9) undergoes chlorine-magnesium exchange at 25 °C, providing the corresponding Grignard reagent in 2 h. Treatment with CuCN-2LiCl gives the copper reagent 39, and allylation with ethyl (2-bromomethyl)acrylate produces the functionalized thiophene 40 in almost quantitative yield.

All the allylation reactions can be performed using only catalytic amounts of CuCN-2LiCl, with yields the same as those obtained when a stoichiometric amount of the copper salt is deployed. The halogen-magnesium exchange reaction can also be extended to the solid phase, allowing a variety of polyfunctional copper species to be generated on a resin. Thus, various aryl or heteroaryl iodides or bromides can be attached to Wang resins and treated with an excess of iPrMgBr (3–8 equiv.) at –30 °C to –15 °C to provide the expected functionalized Grignard reagent. Transmetalation with CuCN-2LiCl then gives, as expected, the corresponding copper reagent, which can react with various electrophiles such as acid chlorides or allylic halides. After cleavage from the resin, a range of functionalized products may be obtained. Use of the resin-bound bromothiophene 41 as starting material furnishes the copper reagent 42, which produces the carboxylic acid 43 after allylation and cleavage from the resin (Scheme 2.10) [19, 24].
Functionalized organocopper reagents also undergo 1,4-additions. Thus, the alkylcopper 45, prepared from the corresponding Grignard reagent 44, reacts with cyclohexenone at $-78\,^\circ\text{C}$ to give the expected product 46 [26]. Arylcopper compounds such as 47 add to 2-enones in the presence of TMSCl and CuCN-2LiCl [27] (Scheme 2.11).

It is also possible to perform copper-catalyzed alkylation of arylmagnesium compounds. Thus, the copper reagent 48 undergoes a selective cross-coupling [28] with ethyl 4-iodobutyrate to furnish the desired product 49 in 69% yield (Scheme 2.12) [29].

2.3 Transmetalation of Organoboron and Organoaluminium Reagents

Direct transmetalation of organoboranes to organocopper reagents is not a general reaction. Because of their similar bond energies and electronegativities, this transmetalation is limited to the preparation of alkenylcopper and unfunctionalized...
alkylcopper compounds. In the latter case, the reaction is favored by the formation of an ate-complex [30]. Thus, treatment of tripropylborane with MeLi produces the lithium organoboronate 50, which is converted into the copper boronate 51. Treatment of 51 with benzoyl chloride is not selective, since both the methyl group and the propyl group are transferred, affording a mixture of two ketones (Scheme 2.13).

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\begin{array}{c}
\text{Pr}_3\text{B} \xrightarrow{\text{MeLi}} \text{Pr}_3(\text{Me})\text{B} \xrightarrow{\text{CuCl(COD), ether, 0 °C, 5 min}} \text{Pr}_3(\text{Me})\text{B} \xrightarrow{\text{PhCOCl}} \\
\end{array}
\]

Scheme 2.13. Acylation of organocopper reagents derived from organoboranes.

The transmetalation of dialkenylchloroboranes of type 52 with methylcopper (3 equiv.) provides an alkenylcopper compound 53, which undergoes cross-coupling with allylic halides to produce mixtures of $S_N2$ and $S_N2'$ products. Interestingly, this method is also useful for the preparation of functionalized alkenylcoppers such as 54 (Scheme 2.14) [31].

Better results can be obtained by generating the boronate species with the aid of sodium methoxide. In this case, satisfactory transmetalation occurs on treatment with CuI. Thus, the functionalized copper reagent 55 can be alkynylated with 1-bromo-1-hexyne at $-40^\circ\text{C}$, furnishing the enyne 56 in 75% yield (Scheme 2.15) [32].

In the presence of a polar cosolvent such as hexamethylphosphoric triamide (HMPA), it is possible to generate the fluorine-substituted copper compound 57,
obtained through a 1,2-migration of a butyl group. After acylation, this provides useful unsaturated ketones such as \(58\) (Scheme 2.16) [33].

Thus, direct transmetalation of organoboranes to form organocopper compounds is a capricious reaction, not really generally applicable. Much more general access to organocopper compounds can, on the other hand, be achieved by prior conversion of the organoboranes into organozinc compounds. After addition of CuCN-2LiCl [7], the desired copper compounds are then cleanly generated and can be treated with a broad range of electrophiles, giving excellent yields (Scheme 2.17; see also Sect. 2.4) [34].

A smoother transmetalation procedure should be ensured by the more electronegative character of aluminium, as first demonstrated by Wipf and Ireland [35]. Thus, hydroalumination of 1-hexyne with DIBAL-H, followed by addition of the cuprate \(59\), bearing non-transferable alkynyl groups, provides the copper intermediate \(60\). This adds smoothly to 2-cyclohexenone to produce the Michael adduct \(61\), in 72% yield (Scheme 2.18) [36].
Alternatively, by performing a zirconium-catalyzed Negishi methylalumination on 1-hexyne, it is possible to produce stereochemically pure alkenylcopper species 62, which adds to enones in a 1,4-fashion, to give compounds such as 63 (Scheme 2.18) [35, 36].

Wipf has shown that this method is quite general and tolerates several functional groups, such as ethers, thioethers, silanes, halides, aromatic rings, and olefins. The iodoalkyne 64 is readily carbometalated and after treatment with the dialkynylcuprate 59 furnishes the functionalized copper reagent 65, which smoothly undergoes 1,4-addition reactions with enones. Thus, in the case of 2-cyclohexenone, the functionalized ketone 66 is produced in 85% yield (Scheme 2.19) [2, 36].

The scope of this transmetalation is very much a function of the availability of interesting alkenylaluminium species [37]. Stannylalumination of alkynes also proceeds through a stannylcopper intermediate 68, obtained by transmetalation of the stannylated aluminium precursor 67. This reaction enables regioselective stannylation of alkynes to be accomplished (Scheme 2.20) [38].

2.4 Transmetalation of Functionalized Organozinc Reagents

2.4.1 Preparation of Organozinc Reagents

Organozinc compounds have been known for more than 150 years, but their application in organic synthesis was formerly rather limited [39], due to their
moderate reactivity. Only when it was realized that organozincs undergo smooth transmetalations to give a broad range of organometallics did their synthetic applications begin to increase exponentially. Transmetalation of organozinc reagents to give organopalladium intermediates [40] and their transmetalation to organocopper compounds proved to be particularly important [7, 34, 41, 42]. Since it is possible to prepare organozinc compounds bearing a large range of organic functional groups, this methodology broadens the scope of organocopper chemistry considerably. This high functional group compatibility is a function of the pronounced covalent character of the carbon-zinc bond, while the excellent transmetalation capability of organozincs for production of other organometallics is a consequence of the presence of low-lying empty $p$-orbitals. Especially useful for this transmetalation are THF-soluble copper salts of the type CuCN·2LiX [7, 41]. After transmetalation, the resulting copper species, tentatively represented as $\text{RCu(CN)ZnX}$, reacts with most of those electrophiles $E^+$ that also react with the more classical diorgano lithium cuprates ($\text{R}_2\text{CuLi}$), to afford products of type $\text{R-E}$ (Scheme 2.21).

$$\text{RZnX} + \text{CuCN} \cdot 2\text{LiX} \xrightarrow{\text{THF}} \text{RCu(CN)ZnX} \xrightarrow{E^+} \text{R-E}$$

Scheme 2.21. Preparation of zinc-copper reagents.

Notable exceptions are epoxides and alkyl halides, which do not react directly with $\text{RCu(CN)ZnX}$, although reaction conditions for performing alkylation reactions are available [43]. There are two classes of organozinc compounds: organozinc halides ($\text{RZnX}$) and diorganozincs ($\text{R}_2\text{Zn}$). The reactivity of diorganozincs is slightly higher, but the major difference relevant to this second class of organozinc compounds is the absence of zinc salts ($\text{ZnX}_2$), which is highly important for applications in asymmetric addition reactions [44]. The preparation methods are different. Whereas organozinc halides are obtained either by transmetalation reactions or by direct insertion of zinc dust into alkyl halides, diorganozincs are best prepared by means either of an iodine-zinc exchange reaction or of a boron-zinc exchange reaction (Scheme 2.22).

$$\text{R-ZnX} + \text{ZnX}_2 \xrightarrow{\text{Zn}} \text{R-ZnX} + \text{ZnX}_2 \xrightarrow{\text{Zn}} \text{R-ZnX} + \text{ZnX}_2 \xrightarrow{\text{Zn}} \text{R-ZnX} + \text{ZnX}_2 \xrightarrow{\text{Zn}} \text{R-ZnX} + \text{ZnX}_2 \xrightarrow{\text{Zn}} \text{R-ZnX} + \text{ZnX}_2 \xrightarrow{\text{Zn}} \text{R-ZnX} + \text{ZnX}_2 \xrightarrow{\text{Zn}} \text{R-ZnX} + \text{ZnX}_2$$

Scheme 2.22. Preparation of organozinc reagents.
2.4.1.1 Preparation of Organozinc Halides

Functionalized organozinc halides are best prepared by direct insertion of zinc dust into alkyl iodides. The insertion reaction is usually performed by addition of a concentrated solution (approx. 3 M) of the alkyl iodide in THF to a suspension of zinc dust activated with a few mol% of 1,2-dibromoethane and Me₃SiCl [7]. Primary alkyl iodides react at 40 °C under these conditions, whereas secondary alkyl iodides undergo the zinc insertion process even at room temperature, while allylic bromides and benzylic bromides react under still milder conditions (0 °C to 10 °C). The amount of Wurtz homocoupling products is usually limited, but increases with increased electron density in benzylic or allylic moieties [45]. A range of polyfunctional organozinc compounds, such as 69–72, can be prepared under these conditions (Scheme 2.23) [41].

Insertion of zinc dust into aryl or heteroaryl iodides is also possible, but polar co-solvents are required in some cases [48, 49]. The use of highly activated zinc (Rieke zinc) prepared by reduction of zinc halides with lithium results in faster insertion (Scheme 2.24) [50–52].
Crucially, this allows organozinc reagents to be prepared from less reactive aryl bromides and secondary or tertiary alkyl bromides. Alternatively, organozinc iodides can be prepared by means of a palladium(0)-catalyzed reaction between alkyl iodides and Et₂Zn (Scheme 2.25) [53–56].

The palladium(0)-catalyzed insertion proceeds through a radical insertion mechanism, allowing radical cyclizations to be performed. This procedure constitutes a new, stereoselective preparation of cyclic zinc reagents from unsaturated, open-chain compounds. Since the cyclization is radical in nature, the relative stereochemistry of the starting alkyl iodide does not need to be controlled. Thus, the unsaturated iodide 73, used as a 1:1 mixture of diastereomers, produces a cyclic organozinc reagent after Pd(0)-catalyzed iodine-zinc exchange, by way of the transition state 74. This then, after transmetalation with CuCN·2LiCl, gives the stereomerically pure organocopper 75. Allylation with ethyl 2-{bromomethyl}acrylate affords the cyclopentane derivative 76 almost as a single stereoisomer (Scheme 2.26) [54].

This reaction can also be applied to the preparation of heterocyclic organocopper reagents such as 77 from readily available secondary alkyl iodides. Ring-closure in this case is catalyzed by Ni(acac)₂ rather than by Pd(0), affording new heterocyclic molecules such as 78 (Scheme 2.26) [55]. These cyclization reactions are key steps in the preparation of such natural products as (−)-methylenolactocin 79 [57] and methyl epijasmonate 80 [58] (Scheme 2.27).
Various other less general methods for the preparation of organozinc halides are available, transmetalation from organomagnesium compounds being of interest. Thus, iodine-magnesium exchange in ethyl 2-iodobenzoate 81 produces a magnesium intermediate, which is transmetalated with ZnBr₂ to give the corresponding zinc reagent 82. This undergoes smooth Ni(0)-catalyzed cross-coupling with functionalized alkyl iodides (Scheme 2.28) [59].
Finally, the use of homoallylic zinc alcohohates as masked allylic zinc reagents has been described [60]. Thus, the ketone 83 was treated with nBuLi, producing a highly sterically hindered lithium alkoide that, after conversion to the corresponding zinc alkoide, underwent a fragmentation reaction to form the allylic zinc reagent 84. After transmetalation with CuCN-2LiCl, this organozinc species underwent an intermolecular addition to the double bond, furnishing the spiroorganometallic compound 85. Benzoylation of this produced the ketone 86, in a diastereomeric ratio of >98:2 and in 60% yield (Scheme 2.29) [61].

![Scheme 2.28](image)

Scheme 2.28. Preparation of a functionalized arylic halide by transmetalation of an organomagnesium compound.

![Scheme 2.29](image)

Scheme 2.29. Organozinc reagent prepared by an ene reaction.

### 2.4.1.2 Preparation of Diorganozinc Reagents

Other than transmetalation reactions from organolithium and organomagnesium compounds, there are two general methods for preparing diorganozincs. These are boron-zinc exchange and iodine-zinc exchange [42]. The iodine-zinc exchange reaction is catalyzed by the presence of copper(I) salts and is radical in nature. It is best performed with Et$_2$Zn [62, 63], and usually takes place within 12 h at 50 °C. It is also possible to perform the exchange under irradiation conditions [64]. Provided that the presence of metal salts does not perturb the further course of the reaction, iodine-zinc exchange can be performed by using iPr$_2$Zn generated in situ by treat-
ment of iPrMgBr with ZnBr₂ (0.5 equiv.). With this reagent, the exchange reaction occurs very rapidly (25 °C, 1 h), allowing complex secondary diorganozincs to be prepared (Scheme 2.30) [65].

Because of the radical character of the exchange, it is not possible to prepare chiral diorganozinc reagents in this way [66]. The most general and practical preparation of diorganozincs is the boron-zinc exchange reaction, which has several advantages. It tolerates various functional groups and, since the starting organoboranes used for the exchange are prepared from olefins, numerous functionalized olefins are available as starting materials. More importantly, boron-zinc exchange proceeds with retention of configuration. Thus, chiral organoboranes are excellent precursors for chiral secondary alkylzinc reagents (Scheme 2.31) [42].

In the case of primary organoboranes, the exchange reaction is best performed with Et₂Zn, whereas less reactive secondary organoboranes require the use of iPr₂Zn. Thus, a wide variety of terminal olefins have been converted into primary diorganozincs such as 87–89 (Scheme 2.32).
Remarkably, this reaction sequence permits the preparation of diorganozincs bearing acidic hydrogen atoms in the molecule. The unsaturated nitroalkane and the unsaturated alkylidenemalonate are smoothly converted into the corresponding diorganozinc reagents by the sequence shown in Scheme 2.33. Transmetalation with CuCN$\cdot$2LiCl provides the expected organocopper reagents and . After allylation with an excess of allyl bromide, the desired products and are obtained in excellent yields [70].

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\text{Scheme 2.33. Preparation of organocopper reagents bearing acidic hydrogens.}
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As mentioned above, chiral diorganozincs can be prepared by this procedure. Thus, treatment of 1-phenylcyclopentene with $(-)$-IpcBH$_2$ provides a chiral organoborane (99% ee after recrystallization). Treatment of this with Et$_2$BH at 60 °C for 16 h gives a diethylorganoborane, which undergoes transmetalation with iPr$_2$Zn to afford the chiral organozinc reagent. After further transmetalation with CuCN$\cdot$2LiCl, the chiral secondary organocopper reagent is formed. Allylation of this with allyl bromide gives the cyclopentane 99 in 44% overall yield (94% ee and 98:2 trans: cis ratio; Scheme 2.34) [71].

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\text{Scheme 2.34. Preparation of chiral alkylcopper reagents (Ipc = isopinocampheyl).}
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The same method can be applied to the preparation of chiral acyclic organocopper reagents of somewhat lower configurational stability [72]. Chiral cyclic organocopper compounds can also be prepared by diastereoselective hydroboration of prochiral allylic ethers [73]. Mixed secondary organozinc reagents of the type FG$\cdot$ZnCH$_2$SiMe$_3$ (FG = functional group; CH$_2$SiMe$_3$: non-transferable group) can also be prepared [74–76].
2.4.2 Substitution Reactions with Copper-Zinc Reagents

Organocopper reagents prepared from organozinc species undergo \( S_N2' \) reactions with allylic halides or allylic phosphates in high yields. These reactions display excellent \( S_N2' \) regioselectivity. The polyfunctional organozinc species 100, obtained from the corresponding olefin by a hydroboration/boron-zinc exchange sequence, can be smoothly allylated in the presence of the THF-soluble salt CuCN \( \cdot \) LiCl [7, 70] to give the polyfunctional quinoline derivative 101. Selective double \( S_N2' \) reaction is observed with 1,3-dichloropropene reagent 102, producing the unsaturated selenide 103 in 89% yield and with high regioselectivity (Scheme 2.35) [77].

In most allylation reactions, only a catalytic amount of CuCN \( \cdot \) LiCl is required [41]. Use of the chiral ferrocenylamine 104 as a catalyst makes enables asymmetric allylation of diorganozinc reagents to be effected with allylic chlorides (Scheme 2.36) [78]. Related electrophiles such as propargylic bromides [79] and unsaturated epoxides [80] also undergo \( S_N2' \)-substitution reactions (Scheme 2.37).

Scheme 2.35. Copper(I)-mediated allylation reactions.

Scheme 2.36. Enantioselective allylation with diorganozinc reagents.
Substitution reactions also proceed well with cationic η⁵-cycloheptadienyliiron complexes such as 105 [81] and related chromium complexes [82], and have found applications in natural product synthesis (Scheme 2.38).

Scheme 2.37. Substitution reactions of propargylic bromides and unsaturated epoxides with organozinc reagents.

Alkyl iodides do not react with zinc-copper reagents. However, use of copper species R₂Cu(CN)₃MgX₂-Me₂Zn, obtained by treatment of the cuprate Me₂Cu(CN)₃(MgCl)₂ with a diorganozinc compound R₂Zn, results in a cross-coupling reaction at 0 °C in DMPU. The reaction tolerates a number of functional groups, as well as alkyl iodides containing acidic hydrogens, such as 106. The desired cross-coupling product 107 is produced in good yield (Scheme 2.39) [43].

Scheme 2.38. Reactions between copper-zinc reagents and cationic metal complexes.

Scheme 2.39. Cross-coupling between copper-zinc reagents and alkyl iodides.
Cross-coupling between functionalized zinc-copper reagents and 1-iodoalkynes or 1-bromoalkynes is very fast [83]. This smooth cross-coupling occurs at low temperatures (−55 °C) and offers high stereoselectivity in reactions with chiral secondary organozinc-copper reagents such as 108 (obtained by a hydroboration/boron-zinc exchange sequence), producing the alkyne 109 in 42% overall yield (Scheme 2.40) [73].

Alkynylation of zinc-copper compounds has been used for the synthesis of polyfunctional acetylenic ethers [84] and for the preparation of building blocks for pharmaceutically active compounds [85]. Whereas cross-coupling between non-activated iodoalkenes and zinc-copper reagents only proceeds at elevated temperatures and in polar solvents such as NMP or DMPU (60 °C, 12 h) [86], alkenyl iodides conjugated with electron-withdrawing groups react under milder conditions. Thus, 3-iodo-2-cyclohexenone undergoes the addition-elimination reaction with the zinc-copper reagent 110 at −30 °C within 1 h, affording the functionalized enone 111 in excellent yield (Scheme 2.41) [46].

The same mechanism is operative for the preparation of squaric acid derivatives of type 112. Treatment of 3,4-dichlorocyclobutene-1,2-dione with two different zinc-copper reagents provides the double addition-elimination product 112 in 67% yield (Scheme 2.41) [87].
The reaction between zinc-copper reagents and acid chlorides is very general and provides a useful synthesis of ketones [7, 34, 41, 42]. This acylation has also been used to prepare various indoles substituted in position 2 (Scheme 2.42) [88].

![Scheme 2.42. Synthesis of 2-substituted indoles by acylation of functionalized organozinc reagents.](image)

Zinc-copper compounds readily undergo Michael addition reactions in the presence of TMSCl, selectively affording 1,4-adducts [7, 34, 41, 42]. In the case of β-disubstituted enones, the 1,4-addition proceeds well in the presence of BF₃·OEt₂ (Scheme 2.43) [89].

![Scheme 2.43. Michael additions of copper-zinc reagents to enones.](image)

Prostaglandin derivatives may be prepared by the addition of copper-zinc reagents to substituted cyclopentenones [90–92]. In the presence of a copper(I)-monosubstituted sulfonamide, dialkylzincs also add to enones [93]. The addition of zinc-copper compounds to unsaturated esters is difficult, and only efficient if a leaving group is present in the β-position. Alkylidenemalonates, on the other hand, readily undergo Michael additions [94]. The β-phenylsulfonylalkylidenemalonate 113 undergoes an addition-elimination process to provide functionalized alkylidenemalonates such as 114 in excellent yields [95]. Similarly, the β-phenylsulfonylnitroolefin 115 readily reacts with copper-zinc organometallics to provide nitro compounds such as 116, which readily undergo intramolecular Diels-Alder reactions (Scheme 2.44) [96].
In general, copper-zinc compounds, unlike organolithium-derived organocopper reagents, undergo clean addition reactions to nitroolefins. After Michael addition, the resulting zinc nitronates can be oxidatively converted into polyfunctional ketones, such as 117 (Scheme 2.45) [96].

Addition to unsaturated aldehydes results either in the 1,2- or in the 1,4-addition product, depending on the reaction conditions. Thus, in the case of cinnamaldehyde, the 1,2-addition product is produced in the presence of BF₃·OEt₂ and the 1,4-addition product is obtained in the presence of Me₃SiCl (Scheme 2.46) [97].

Acetylenic esters react well with copper-zinc compounds. Propiolic esters are especially reactive [83], but other acetylenecarboxylic acid derivatives such as dimethyl acetylenedicarboxylate or propiolamide 118 undergo highly stereoselective cis addition (Scheme 2.47) [46].
Finally, zinc-copper exchange by treatment of FG−RZnI with Me$_2$Cu(CN)Li$_2$ provides copper species that add smoothly to various alkynes and which can also be used to perform cyclization reactions (Scheme 2.48) [98].

Scheme 2.47. Addition of zinc-copper compounds to propiolic acid derivatives.

\[
\text{EtO}_2\text{C} \text{Cu} \text{Zn} \text{I} + \text{H} = \text{CONH}_2 \xrightarrow{\text{THF, -30 °C}} \text{EtO}_2\text{C} \text{Cu} \text{ZnI} \text{CONH}_2
\]

118 53 %, 100 % $E$

Scheme 2.48. Intermolecular and intramolecular carbometalation of alkynes with copper-zinc reagents.

Organozinc copper reagents have very broad synthetic potential and a number of typical experimental procedures have recently been published [99, 100].

2.5 Transmetalation of Organotin, Organosulfur, and Organotellurium Reagents

Transmetalations of alkenylstannanes with copper salts are reversible if they are performed with CuCl in polar solvents [101]. This has found application in cyclization reactions (Scheme 2.49) [102].

Scheme 2.49. Cyclization of alkenylcopper compounds generated from organostannanes.
Transmetalation of this type has also been used to assist palladium(0)-catalyzed cross-coupling reactions in sterically congested substrates. Transmetalation of stannanes into alkenylcopper intermediates considerably accelerates subsequent palladium(0)-catalyzed cross-coupling with arylsulfonates (Scheme 2.50) [103].

These transmetalations may be performed not only with copper(I) halides in DMF [104], but also by using Me2CuLi/C1LiCN. This transmetalation has been used in the synthesis of prostaglandin derivatives (Scheme 2.51) [105].

As well as alkenylstannanes [106–108], other classes such as α-heteroatom-substituted alkyltributylstannanes [109] and, more importantly, allylic stannanes [110, 111] also undergo these Sn–Cu transmetalations. Otherwise difficult to prepare, allylic copper reagents may, however, be obtained by treatment of allylic stannanes (produced in turn from organolithium, magnesium, or zinc organometallics) with Me2CuLi/C1LiCN. They enter into cross-coupling reactions with alkyl bromides [110] or vinyl triflates (Scheme 2.52) [111].

Michael additions [112] and other reactions typical of organocopper species can also be performed with silylcopper reagents such as TBDMSCu, prepared by Sn/Cu exchange [113] between Me3SnSiMe2(tBu) and Bu(Th)CuLi·LiCN (Th = 2-thienyl) (Scheme 2.53) [113, 114].

Transmetalation of thioethers to organocopper compounds can also be performed in some special cases. Thus, treatment of the ester 119 with Me2CuLi·LiCN provides the copper reagent 120, which can be treated successfully with several electrophiles such as allyl bromide or acid chlorides to afford the expected products such as 121 (Scheme 2.54) [115, 116].

This reaction can be extended to cyanoketone dithioacetals [117]. Alkenyltellu-
Tellurium species also undergo exchange with Me₂CuLi/LiCN. The synthetic importance of this exchange is due to the easy availability of (Z)-alkenyltellurium species by reduction of alkynyl tellurides such as 122 (Scheme 2.55) [118].

Scheme 2.52. Cross-coupling of allylic copper compounds.

Scheme 2.53. Preparation of silylcuprates by Sn/Cu-transmetalation.

Scheme 2.54. Sulfur/copper exchange reaction.

Scheme 2.55. Te/Cu exchange reactions of (Z)-alkenyltellurium species.
Transmetalation of Organotitanium and Organomanganese Reagents

Transmetalations with first row transition metal elements such as titanium or manganese have produced useful synthetic applications. Organotitanate species of type 123 show the advantage of high $S_N2'$ selectivity in the anti stereochemistry of the resulting copper(I) intermediates (Scheme 2.56) [119, 120].

![Scheme 2.56. Copper(I)-catalyzed anti-$S_N2'$ substitution of allylic phosphates.](image)

Organomanganese reagents are very useful organometallics, reacting with high chemoselectivity with acid chlorides [121] and several other classes of electrophiles [122]. The scope of organomanganese reagents can be greatly increased by use of copper(I) catalysis. Especially impressive is the performance of Michael additions [123–128]. Thus, the Michael addition between BuMnCl and pulegone 124, furnishing 125, proceeds in excellent yield in the presence of Li$_2$CuCl$_4$ (3 mol%) (Scheme 2.57) [128].

![Scheme 2.57. Copper-catalyzed Michael addition reactions between organomanganese reagents and pulegone.](image)

Acylation reactions can also be greatly improved in this way, with $t$-alkyl- or sec-alkyl-manganese reagents reacting with acid chlorides in excellent yields [123]. The related addition-elimination to 3-ethoxy-2-cyclohexenone is also improved, resulting after acidic aqueous workup in 3-methyl-2-cyclohexenone [125]. The perilla-ketone 126 was prepared in an improved yield using copper(I) catalysis (Scheme 2.58) [129].
Alkylation of organomanganese reagents with alkyl bromides can also be improved by addition of CuCl (3 mol%). The reactions proceed at room temperature and are complete within a few hours [123, 130]. The opening of epoxides is also improved under these conditions. The reaction also features good chemoselectivity, tolerating the presence of sensitive functions such as ketones (Scheme 2.59) [130].

Benzylic organomanganese reagents prepared by direct insertion of activated manganese metal display the same behavior (Scheme 2.60) [131]. Excellent results are also obtained for 1,4-additions of organomanganese reagents to unsaturated esters in the presence of CuCl (3 mol%) [127].

Transmetalation reactions of organozirconium reagents were pioneered by Schwartz [130–132], with improved procedures developed more recently by Lipshtutz [133] and Wipf [134]. The hydrozirconation of 1-hexene with H(Cl)ZrCp₂ at 25 °C under sonication conditions produces the n-hexylzirconium complex 127, which adds to cyclohexenone in the presence of CuBr-Me₂S (10 mol%) to afford the desired product 128 in 79% isolated yield (Scheme 2.61) [134].
Similarly, alkenylzirconium species prepared by the hydrozirconation of alkynes add in a conjugated fashion to enones. Formation of an intermediate zincate prior to transmetalation to the copper species facilitates the Michael addition (Scheme 2.62) [135]. This methodology has been applied to the preparation of protected misoprostol 129 (Scheme 2.63) [136, 137].

The mechanism and the nature of the reaction intermediates have been carefully studied by Wipf, revealing an activation of the carbonyl group of the enone by the zirconium complex. Remarkably, a variety of primary and secondary alkylzirconium complexes can be added to enones in 1,4-fashion under mild conditions [134, 138]. Interestingly, treatment of zirconocyclopentadienes such as 130 with alkynes such as dimethyl acetylenedicarboxylate in the presence of CuCl gives benzene derivatives such as 131 [136, 137]. A transmetalation from Zr to Cu has been postulated in this reaction. Annelation reactions involving a similar transmetalation of 130 and cross-coupling with 1,2-diodobenzene proceeds in high yield to afford 132 (Scheme 2.64) [139, 140].
Cross-coupling reactions between alkenylzirconocenes such as 133 and aryl or alkenyl iodides occur readily in the presence of CuCl and Pd(PPh₃)₄, producing tetrasubstituted olefins such as 134 in good yields (Scheme 2.65) [141, 142].

![Scheme 2.64. Copper-catalyzed reactions of zirconocyclopentadienes.](image)

Carbocupration of alkynes by zirconacyclopentane derivatives can be performed according to the same procedure. Thus, the zirconacyclopentane 135, obtained by treatment of Bu₂ZrCp₂ with 1,6-heptadiene, reacts at room temperature with phenylacetylene to afford the adduct 136 through a carbocupration-reductive elimination mechanism. Cross-coupling followed by intramolecular carbocupration takes place in the case of the reaction with 1-bromohexyne, producing 137 (Scheme 2.66) [143].

![Scheme 2.65. Cross-coupling between alkenylzirconocene complexes and aryl iodides.](image)

![Scheme 2.66. Copper-catalyzed reactions of zirconacyclopentane derivatives.](image)
Finally, spiro-compounds such as \(138\) can be prepared by treatment of zirconacyclopentadienes such as \(139\) with 3-iodo-2-cyclohexenone in the presence of CuCl (2 equiv.) (Scheme 2.67) [144].

\[
\begin{array}{c}
\text{Cp}_2\text{Zr} & \xrightarrow{\text{CuCl (2 equiv)}} & \text{Cp}_2\text{Zr} \\
\text{Ph} & \text{Ph} & \text{Ph} \\
\end{array}
\]

Scheme 2.67. Spirometalation of zirconacyclopentadienes.

Very few transmetalations between organolanthanides and organocopper reagents have been reported. Organosamarium(III) reagents, prepared by treatment of SmI\(_2\) with alkyl halides in THF/HMPA, undergo easy conjugate addition to unsaturated ketones and nitriles in the presence of TMSI, producing the corresponding Michael adducts. Functionalized alkyl bromides such as \(140\) react chemo-selectively with cyclohexenone in the presence of TMSI and CuBr-\(\text{Me}_2\text{S}\) (0.1 equiv.) to afford the polyfunctional ketone \(141\) in 60% yield (Scheme 2.68) [145].

\[
\begin{array}{c}
\text{Ph} & \text{N(Me)COPh} & \xrightarrow{\text{1. SmI}_2, \text{THF} / \text{HMPA, 22 °C}} & \text{Ph} & \text{N(Me)COPh} \\
\text{Br} & \text{Ph} & \xrightarrow{\text{2. CuBr, Me}_2\text{S (0.1 equiv), TMSI (4 equiv), -78 °C, 10 min}} & \text{Ph} & \text{N(Me)COPh} \\
\end{array}
\]

Scheme 2.68. Copper-catalyzed 1,4-addition of organosamarium reagents.

2.8 Conclusion

Transmetalations of various organometallic species with copper salts have been found to produce highly useful organocopper reagents of great synthetic interest. Many different organometallic precursors have proved valuable, depending on the functionality present in the copper reagent. The scope of organocopper chemistry has been greatly enhanced by these new transmetalation reactions and these reagents have found many applications in organic synthesis.
References

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