LECTURE TEXT

Transmetalation: a fundamental organometallic reaction critical to synthesis and catalysis

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Abstract

A number of critical reactions form the foundation of organometallic chemistry. One such fundamental reaction of organometallic chemistry is transmetalation, a general term that in its modern meaning describes the transfer of carbon ligands (i.e., alkyl, aryl, alkynyl, allyl, etc.) from one metal to another. Transmetalation has a very long history and the reaction dates back to the early beginnings of organometallic chemistry with the work of the English chemist Edward Frankland (1825–1899) in the 1860s. Since its introduction, transmetalation has found significant utility in synthetic chemistry, allowing the generation of a wide variety of organometallic compounds of both main group and transition metal elements, and has been identified as a critical step in many synthetic organic reactions catalyzed by transition metal complexes. Regardless of the long history of this reaction and its significant applications, transmetalation is not covered in the same depth as other fundamental reactions in organometallic chemistry and is rarely given serious treatment in organometallic textbooks. Thus, the aim of the current work is to supplement current textbooks by presenting the basics of what is currently known about the details and parameters of this important reaction.

Keywords Organometallics · Metal–carbon bonds · Transition metals · Main group metals

Introduction

The study of organometallic chemistry involves a number of critical reactions that form the foundation of this subdiscipline. In addition to simple substitution, such reactions include oxidative addition, reductive elimination, α- and β-elimination, oxidative coupling, as well as 1,1-, 1,2-, and 1,4-migratory insertion [1–8]. Another fundamental reaction of organometallic chemistry is *transmetalation* (or *transmetallation*), a general term that in its modern meaning describes the transfer of carbon ligands (i.e., alkyl, aryl, alkynyl, allyl, etc.) from one metal to another [9–13]. Of course, it should be pointed out that the term transmetalation has referred to a number of different processes over time. In addition to the definition given here, transmetalation has also been used at times to refer to the transfer of a metal from one organic moiety to another [14], the exchange of

one metal for another in polymetallic species [15], as well as the transfer of a main group organometallic species (i.e., trialkylstannyl, trialkylsilyl, etc.) onto a transition metal [16].

Transmetalation in the modern sense has a very long history and the reaction dates back to the early beginnings of organometallic chemistry with the work of the English chemist Edward Frankland (1825–1899, Fig. 1) [17, 18]. In 1849, Frankland reported the preparation of ethylzinc species from zinc metal and ethyl iodide, as shown in Eq. (1) (R = ethyl, methyl) [19, 20]:

$$3\,RI\ +\ 3\,Zn \rightarrow ZnR_2\ +\ RZnI\ +\ ZnI_2 \tag{1}$$
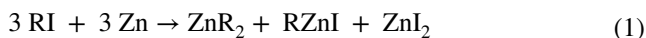
This was followed quickly with the analogous methyl compounds, as well as evidence showing that phosphorus reacted with organic iodides in a similar fashion [21, 22]. By 1852, Frankland had expanded the scope of his efforts to include the analogous reactions of tin, antimony, arsenic, and mercury, for which he coined the term "*organo-metallic*" to describe the products [23]. In addition, he showed that amyl iodide gave similar results to the previous methyl and ethyl iodides, and proposed that other organic iodides (propyl, butyl, phenyl, etc.) would do the same.

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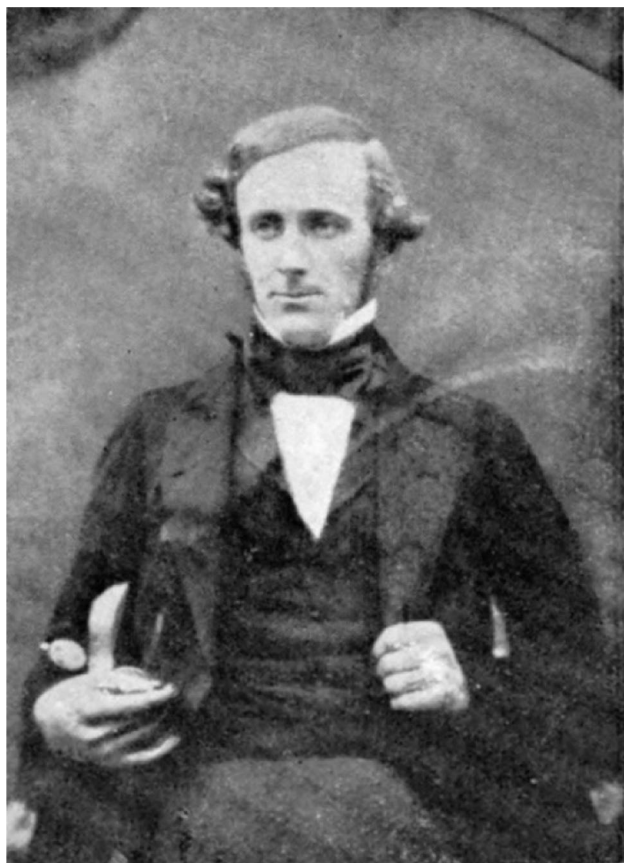
Fig. 1 Edward Frankland (1825–1899) at ca. age 26, about 1 year before he coined the term *organometallic* [Edgar Fahs Smith Memorial Collection. Kislak Center for Special Collections, Rare Books and Manuscripts. University of Pennsylvania]

Later, in 1861, Frankland reported that the organozinc compounds could be used to transfer the alkyl groups to a second metal via reaction with the corresponding metal halide, as outlined in Eq. (2) (R = methyl, ethyl; M = Hg, Sn, Pb, Sb, As) [24]:

$$n\,ZnR_2 + 2\,MX_n \rightarrow n\,ZnX_2 + 2\,MR_n \qquad (2)$$
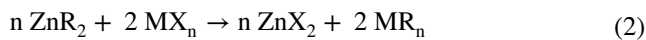
Frankland felt that this method was the most convenient approach to the generation of organometallic species and capable of the most general application. However, attempts to apply this to the halides of copper, silver, and platinum were unsuccessful.

Frankland followed this with a report in 1864 that showed that the original zinc compounds could be made more easily by reacting the previous organomercury compounds with metallic zinc, as outlined in Eq. (3) (R = methyl, ethyl, amyl) [25, 26]:

$$HgR_2 + Zn \rightarrow ZnR_2 + Hg \qquad (3)$$
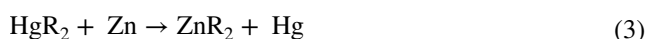
This allowed the isolation of the dialkylzinc species in higher yield, as this bypassed the previous alkylzinc iodide

intermediate, and also allowed the isolation of analogues for which the direct reaction of the organic iodide with zinc was problematic. In addition, it was found that this process was also successful with either cadmium or bismuth, although attempts to replace zinc with transition metals were all unsuccessful.

Of course, the processes given in Eqs. (2) and (3) are the first examples of transmetalation, although Frankland described it as a "transformation" [25] and the modern term for the reaction was not introduced until later. With further development and expansion in scope, this general organometallic reaction allowed the transfer of intact organic species to and from metal centers in a fashion quite similar to inorganic species [17]. While it is now understood that some such organometallic species can be highly toxic (e.g., dimethylmercury), the general application of transmetalation has found significant utility in synthetic chemistry and has allowed the generation of a wide variety of organometallic compounds of both main group and transition metal elements [10], including the development of less toxic reagents for various applications. In addition, transmetalation from main group elements to transition metals has been identified as a critical step in many synthetic organic reactions catalyzed by transition metal complexes. This is particularly true in the various named cross-coupling reactions (Fig. 2) commonly applied throughout organic and polymer chemistry, all of which primarily differ only in the transmetalation reaction [27–32]. Furthermore, transmetalation is also often the rate-limiting step of these catalytic processes.

Regardless of the long history of this reaction and its critical role in the mechanistic details of various transition-metal-catalyzed processes of significant importance, transmetalation is not covered in the same depth as other fundamental reactions in organometallic chemistry [10] and is rarely given serious treatment in organometallic textbooks. In fact, it is often invoked with little explanation or discussion. Why this is the case is unclear, but it could be the result of authors viewing it as just a simple metathesis or double decomposition reaction, and thus a topic already covered in lower-level courses, or may be simply due to a lack of significant understanding of the factors involved. Whatever the reason, the aim of the following presentation is to supplement current textbooks by presenting the basics of what is currently known about the details and parameters of this important reaction.

Transmetalation from organometallic compounds to neutral metals

This first form of transmetalation can be considered the simplest and typically occurs between two main group metals (here including group 12 elements), as illustrated by the initial example of Hg and Zn reported by Frankland
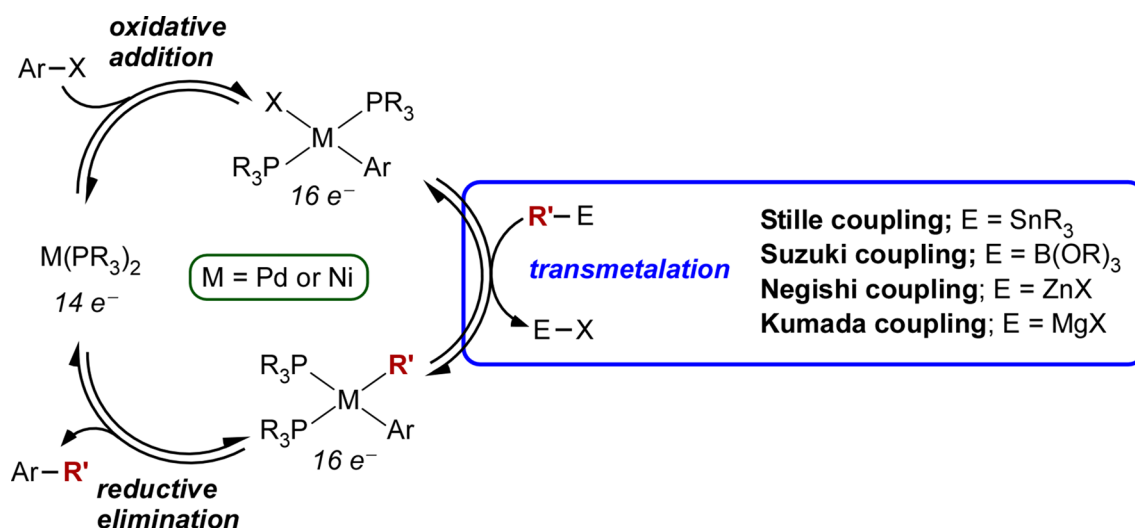
Fig. 2 Basic mechanistic processes of several important named cross-coupling reactions involving transmetalation

in 1864 [25, 26]. The process can be described as an intermolecular ligand transfer accompanied by reduction of the transferring metal and oxidation of the receiving metal [10]. Overall, this can be represented by the following general reaction given in Eq. (4):

$$M + M'{-}R \rightleftharpoons M{-}R + M' \tag{4}$$

This form of transmetalation has also been referred to as oxidative-reductive transmetalation [33] or redox transmetalation [10].

The reaction given in Eq. (4) bears some resemblance to inner-sphere electron transfer processes involving halide-containing transition metal complexes, where it is believed that electron transfer occurs via direct atom transfer of the halide through an activated halide-bridged intermediate (Fig. 3) [34–36]. Thus, in the same way, it is believed that such transmetalations occur via carbon-bridged bimetallic intermediates resulting in electron transfer coupled with

transfer of the carbon ligand [10], which makes it distinct from most other reactions of organometallic compounds. While one could also envision direct metal–metal interactions in such organometallic intermediates, the majority of known alkyl-bridged binuclear complexes do not display metal–metal bonds [37]. Of course, since most known transmetalations of this type are not simple one-electron processes and include the transfer of multiple carbon ligands, it is unclear if each ligand and electron transfer occur in sequential steps or if the mechanism is more complex than represented by the simple process outlined in Fig. 3.

This general method may be applied to neutral metals of the *s*-block, as well as metals and metalloids of groups 12–16. Overall, the thermodynamics are thought to be influenced by the relative stability of the metal–carbon bonds of the organometallic species consumed (M'–R) and produced (M–R) [10]. As such, on the basis of the bond dissociation enthalpies given in Table 1 [38], it is not surprising that organomercury species are especially facile for the transfer of organic ligands to other metals in this manner.

Of course, the decisive factor in the reaction feasibly is ultimately the difference in their free energies of formation ΔG_f° [39]:

$$\Delta G^\circ = \Delta G_f^\circ(M{-}R) - \Delta G_f^\circ\!\left(M'{-}R\right) \tag{5}$$

However, because of the non-availability of accurate ΔG_f° values for organometallic compounds, one has to rely on the known standard enthalpies of formation (ΔH_f°, Table 2) [33, 40, 41], making due allowance for plausible estimates for the contributions of the entropy term $T\Delta S$ [42]. Thus, $\Delta H_f(M'{-}R)$ should be more positive (or less negative)
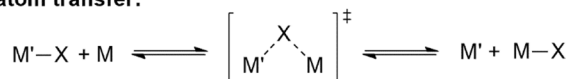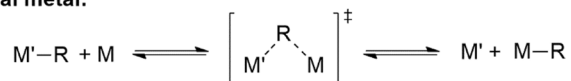

Fig. 3 Comparative mechanistic pathways for halide-mediated inner-sphere electron transfer and transmetalation between an organometallic compound and a neutral metal

than $\Delta H_f(M-R)$ [33], which is most likely when $\Delta H_f(M-R)$ is either weakly exothermic ($\Delta H_f < 0$) or, preferentially, endothermic ($\Delta H_f > 0$) [39]. Thus, from the ΔH_f° values of R_2Hg and R_2Zn given in Table 2, the reaction given in Eq. (3) would be thermodynamically favorable, assuming similar contributions of $T\Delta S$.

Transmetalation from organometallic compounds to metal halides via metathesis

This type of transmetalation involves a ligand transfer from an organometallic compound and a metal complex containing a halide or pseudohalide (i.e., cyanides, isocyanides, etc.) ligand. This is the most common type of transmetalation and most often occurs between an organometallic complex of main group metals (here including group 12 elements) and a transition metal halide. However, it can also occur between two main group metal species as illustrated by the examples involving organozinc compounds and main group halides initially reported by Frankland in 1861 [24]. In addition, the intermolecular exchange of alkyl or aryl ligands between two organometallic compounds also falls under this category [10]. As shown in Eq. (6), this involves the exchange of both the carbon ligand and the halide/pseudohalide and thus is often described as a metathesis reaction:

$$M-R + M'-X \rightleftharpoons M-X + M'-R \qquad (6)$$

Unlike the transmetalation discussed above, this type of transmetalation does not result in any change in the oxidation state of the two metals involved [33]. In addition, this reaction involves no changes in either the coordination number or electron count of either metal compound. As well as being characterized as a metathesis, this type of transmetalation has been referred to as either alkylation or metal exchange transmetalation [10, 16, 39].

Although this reaction has been described as a nucleophilic attack on the metal halide by an anionic carbon ligand (alkyl, aryl, etc.) [12], the metal–carbon bond of the

Table 2 Gas-phase enthalpies of formation for select methyl and ethyl compounds

Compound	ΔH_f° (kJ/mol)	Compound	ΔH_f° (kJ/mol)
Me_2Zn	52.9	Me_4Ge	− 107.5
Et_2Zn	57.0	Et_4Ge	− 156.8
Me_2Cd	104.8	Me_4Sn	− 20.0
Et_2Cd	105.3	Et_4Sn	− 42.0
Me_2Hg	92.4	Me_4Pb	136.1
Et_2Hg	90.0	Et_4Pb	109.6
Me_3Al	− 86.5	Me_3Sb	32.0
Et_3Al	− 114.1	Et_3Sb	49.0
Me_3Ga	− 36.0	Me_3Bi	194.0
Et_3Ga	− 62.0	Et_3Bi	216.0
Me_3In	208.6		

Experimental values collected from [40]

Me methyl, *Et* ethyl

organometallic reagent should not be considered ionic and pre-dissociation of the carbon-bonded ligand does not readily occur [9]. Metal alkyls of group 1 and 2 elements, as well as Al and Zn, are correctly described as polar covalent, in which the M−C bond exhibits quite strong polarity. As a consequence, the alkyl group retains much of the nucleophilic and basic character of the free anion [43], even though the formal generation of the free anion is unlikely. Thus, transmetalation reactions are believed to take place via an associative process in which the metal–carbon unit adds to the second metal to form a bimetallic species with a bridging carbon ligand (Fig. 4) [9, 10]. The bimetallic intermediate or transition states are often further stabilized by a bridging halide, although alternative pathways via cationic forms have also been proposed [10, 13].

The formation of a bimetallic intermediate and its dissociation in a concerted pathway suggest a reversible intermolecular exchange of the two ligands. Most transmetalation reactions, however, occur smoothly and are seemingly irreversible in nature [10]. This is largely because the forward reaction is usually highly favored as a result of both thermodynamic and kinetic reasons. In terms of kinetics, the reaction is favored if an empty orbital is available on both metals, thus allowing facile formation of the doubly bridged bimetallic intermediate shown in Fig. 4 [10, 13]. In addition, the bimetallic intermediate could be expected to form more rapidly for ligands more capable of forming stable carbon bridges. For example, vinylic bridges are more stable than analogous alkyl bridges [9] and aryl bridges can be stabilized via contributing π-bonding interactions [37, 44]. A final kinetic rationalization for the directionality of some transmetalations has been attributed to the greater nucleophilic nature of alkyl compounds of *s*-block elements, which

Table 1 Select M–CH$_3$ bond dissociation enthalpies

Compound	D_{M-Me} (kJ/mol)	Compound	D_{M-Me} (kJ/mol)
Me_2Zn	186.4	Me_4Ge	258.2
Me_2Cd	148.5	Me_4Sn	226.4
Me_2Hg	130.0	Me_4Pb	161.1
Me_3Al	283.3	Me_3Sb	223.5
Me_3Ga	256.4	Me_3Bi	150.5
Me_3In	169.4		

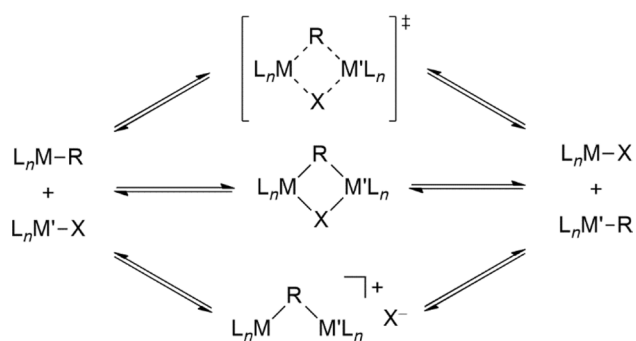Values collected from [38]

Me methyl

Fig. 4 Proposed mechanistic pathways for transmetalation between an organometallic compound and a metal halide

favors alkyl transfer from these species relative to *p*-block elements or transition metals [10].

In terms of thermodynamics, transmetalation is determined by the relative stabilities of the two metal–carbon bonds and two metal–halogen (or pseudohalogen) bonds involved in the reaction [10, 38], which results in the general trend that the equilibrium favors the forward reaction if the metal transferring the carbon ligand is more electropositive than that receiving the carbon ligand [10, 11, 13, 33, 39]. This general trend can be conceptualized by considering the changing bonds involved during transmetalation relative to the hard-soft acid-base (HSAB) principle [45–48].

The HSAB principle was introduced by Ralph G. Pearson (b. 1919) in 1963 in an attempt to provide a unified explanation of reaction trends in organic and inorganic chemistry [46]. In the process, Lewis acids and bases were classified as either "hard" or "soft" (Table 3) and the general rule was proposed that *hard acids bind strongly to hard bases, and soft acids bind strongly to soft bases* [45–47]. It should be noted, however, that the HSAB principle is not something that can be measured, but rather is a simple rule of thumb based on observation [45, 48].

One of the most important properties in determining relative hardness or softness is the Pauling electronegativity. In comparing the electronegativities of hard acid–hard base pairings, large differences are observed that favor bonds with strong ionic character. In a similar manner, soft acid–soft base pairings have similar electronegativities characteristic of nonpolar covalent bonds. On the other hand, hard–soft pairs combine relative electronegativities that are not optimal for either ionic or covalent bonding and are thus typically characteristic of polar covalent bonds. As such, the HSAB principle is consistent with the observation that polar covalent species tend to be rather reactive if more stable ionic and nonpolar covalent products can be produced [46, 48].

For optimal cases involving an alkyl ligand (classified as a soft Lewis base [47]) bound to an electropositive metal

(a hard Lewis acid) that undergoes reaction with a less-electropositive metal halide (a soft acid–hard base combination), this mismatch in hard–soft combination will be relieved by the transmetalation and thus provide the driving force of the apparently irreversible reaction [10]. It should be highlighted, however, that while the thermodynamics of transmetalation can be viewed through HSAB principles and this allows some prediction of favorable transmetalations, it does not correlate directly with the relative thermodynamic stability of the M–C and M–X bonds of the metal complexes involved [10]. Nevertheless, this accounts for why transmetalation is especially applicable to organometallic compounds of alkali or alkaline earth metals (i.e., LiR, RMgX, etc.), as the formation of the corresponding metal halides (a hard acid–borderline/hard base combination) makes a large contribution to the driving force [10, 33, 39]. Despite this, compounds of Li and Mg still have limitations in terms of functional group tolerance, as these compounds tend to react with electrophilic functional groups. As such, compounds of Zn or Al can be more favorable when utilizing functional groups of this type [33].

Based on these trends, a transmetalation reactivity series can be constructed for metal alkyls in which this sequence can be used to predict transmetalation to other metals important in organic synthesis [9, 39]:

$$\text{Li} < \text{Mg} < \text{Zn, Al} < \text{Cd} < \text{In, Ga} < \text{Sn} < \text{Cu, Ni} < \text{Ir, Pd, Rh, Ru}$$

Here, metals low on the series (i.e., Li, Mg) can be used to transfer organic species to any metal listed higher on the series. In contrast, metals highest in the series (i.e., Ir, Pd, etc.) are too stable and thus typically are only products of transmetalation. However, as transmetalation is an equilibrium process, the transfer of organic ligands to more electropositive metals can still occur. Such cases usually involve the irreversible consumption of the more electropositive organometal species, thus shifting the equilibrium to compensate and permitting the synthetic use of transmetalation processes not normally favored by equilibrium [11, 13, 33].

Table 3 Properties of hard and soft acids and bases

|	Acids	Bases
Hard	Small size; high positive oxidation state; low polarizability; bond to halides in the order: $I < Br < Cl \ll F$	High electro negativity; low polarizability; hard to oxidize
Soft	Large size; low or zero oxidation state; high polarizability; bond to halides in the order: $F < Cl < Br \ll I$	Less electronegative; high polarizability; easier to oxidize

Compiled from [45–48]

Transmetalation from organometallic compounds to form ate complexes

The final type of transmetalation is the least likely to be included in discussions of such reactions and, as shown in Eq. (7), involves the transfer of a formally anionic organic ligand from a neutral organometallic species to a neutral metal compound.

$$M-R + M'-L \rightleftharpoons M^+\left[L-M'-R\right]^- \tag{7}$$
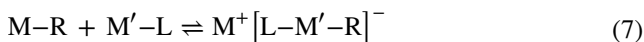
As no other ligand transfers are involved in this process, this results in the formation of a cationic species (from the loss of the anionic ligand) and an anionic organometallic compound (following the addition of the anionic ligand), the combination of which constitutes a bimetallic salt often referred to as an *ate complex* [10]. Here, the transmetalation does not change the oxidation states of either metal involved, although the coordination number and electron count of both metals are affected.

The high reactivity of alkyllithium species often causes multiple alkylation of transition metal halides during transmetalation. Although initial alkylation proceeds via metathesis as discussed above, alkylation continues after the loss of the final halide ligand to ultimately produce an ate complex containing multiple alkyl ligands, as shown in Eq. (8):

$$L-MX_n + (n+1)\,LiR \rightleftharpoons Li^+[L-MR_{(n+1)}]^- + n\,LiX \tag{8}$$
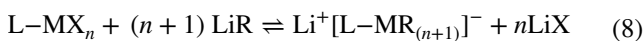
The reactions forming such ate complexes are of significant interest in organic and organometallic chemistry, with organocuprates ($Li[CuR_2]$) representing the most common and important examples of these compounds [10, 49–51]. However, alkyl or aryl ate complexes of other transition metals, including Pt, Rh, and Au, have also been obtained via reaction of the corresponding organolithium species with various halide complexes of these metals [10].

Organocuprates were first reported by Henry Gilman (1893–1986) in 1952 [52] and are thus sometimes referred to as *Gilman reagents* [49–51]. Such organocuprates are less nucleophilic than the parent organolithium species and thus react more selectively with organic substrates [51]. Although the most common organocuprates are homoleptic species in which all anionic ligands on the copper are identical, more complex organocuprates are also known. Other common variants also include the use of Grignard reagents, rather than organolithium as the transfer agent, thus resulting in magnesium organocuprates of the form $[MgX]^+[CuR_2]^-$ [49, 50].

Sequential transmetalation in applications of catalytic cross-coupling

As introduced above, transmetalation plays a critical role in a number of cross-coupling reactions (Fig. 2) commonly applied throughout organic and polymer chemistry, which differ primarily in the nature of the specific transmetalation reaction applied [27–32]. Such a statement, however, still does not fully acknowledge the full role of transmetalation in the real-world application of common cross-coupling methods. In general, these methods utilize a transmetalation step in which a main group organometallic reagent transfers an alkyl or aryl group to the transition metal catalyst. In turn, the main group organometallic species applied is also typically generated via transmetalation, usually from an initial organolithium reagent. In the case of Zn and Mg species (for Negishi and Kumada cross-coupling, respecitvely), the needed organometallic reagent can be prepared in some cases directly from the corresponding organic halide [32], although the use of organolithium precursors is still the more prevalent approach. This overall sequential transmetalation can thus be generalized as outlined in Fig. 5.

Of course, as the initial organolithium reagent could simply be used in transmetalation directly to the transition catalyst, one could question the need for the various intermediate main group species. Here, the less reactive main group intermediate is necessary to prevent multiple transmetalations to the catalyst and thus the formation of the corresponding ate complexes as discussed above. The primary differences in the various intermediates possible for the controlled transmetalation to the transition metal are the corresponding nucleophilicity and reactivity of the selected

I. Synthesis of main group organometallic reagent:

$$LiR + E-X \rightleftharpoons \textbf{E-R} + LiX$$

II. Transmetalation to transition-metal catalyst:

$$\textbf{E-R} + L_nArM-X \rightleftharpoons E-X + \textbf{L}_n\textbf{ArM-R}$$

Stille coupling: E = SnR'$_3$
Suzuki coupling: E = B(OR')$_n$
Negishi coupling: E = ZnX
Kumada coupling: E = MgX

Fig. 5 Sequential transmetalation in common catalytic cross-coupling methods

main group reagent, with increased reactivity generally coupled with reduced selectivity and lower tolerance for various functional groups [31]. Furthermore, as transmetalation is often the rate-limiting step of these catalytic processes, the reactivity of the main group intermediate can drive the overall kinetics of the cross-coupling reaction.

Conclusion

As can be seen from the above discussion, the transfer of organic ligands from one metal to another is an important organometallic process with wide practical applications. At the same time, transmetalation cannot be simplified to a single chemical reaction, with at least three primary classes of transmetalation processes known, each with its own specific parameters and characteristics. Considering that transmetalation dates back to 1861, and is thus one of the oldest known organometallic reaction types, the mechanistic and energetic aspects of these reactions are still not completely understood and further study is required to reveal the full details of these processes. Still, it is hoped that the above discussion offers a useful overview of our current knowledge of these reactions, while providing insight into their general application in organic and organometallic chemistry.

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