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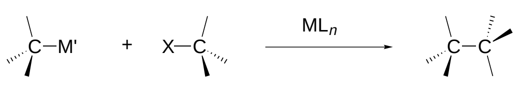
Towards Efficient and Wide-Scope Metal-Catalyzed Alkyl – Alkyl Cross-Coupling Reactions**

Diego J. Cárdenas*

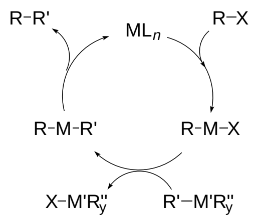
Cross-coupling between organic electrophiles and main group organometallic derivatives constitutes the most direct approach for the formation of carbon – carbon bonds. During the last two decades a great number of methods based mainly on Pd and Ni complexes have been reported.[1, 2] Many different organometallic compounds can be employed as the nucleophile, ranging from the most reactive organolithium and Grignard reagents to the more functional group tolerant tin,[3] boron,[4] and even silicon derivatives.[5] In general C(sp^3), C(sp^2), and C(sp) substituents may be coupled with suitable electrophiles. Diverse organic electrophiles such as those containing alkynyl, aryl, alkenyl, allyl, benzyl, and acyl groups as well as alkyl halides and pseudohalides have also been used as coupling partners.

Nevertheless, not all the reactions leading to the possible types of carbon – carbon bonds whose formation can be envisaged by crossing all the different nucleophiles and electrophiles have been equally developed. Whereas, for example, coupling between different kinds of C(sp^2) centers can be achieved with a variety of reagents and substrates, the development of catalytic methods for the formation of C(sp^3)–C(sp^3) bonds between alkyl derivatives (Scheme 1) has been much less successful. Cross-couplings between unactivated alkyl halides and organomagnesium compounds catalyzed by Cu salts are probably the most studied of such reactions.[6, 7] Recently it has been demonstrated that alkylcopper – zinc reagents, exhibiting a higher functional group tolerance, can be coupled with primary and benzyl halides.[8]



Scheme 1. A general metal-catalyzed alkyl – alkyl cross-coupling reaction. M' = Li, Mg, Zn, Al, Sn, B, Si, etc.; X = halide, OTf, etc.

However, a general metal-catalyzed cross-coupling reaction of unactivated alkyl halides and alkyl nucleophiles less reactive than organomagnesium compounds, and hence compatible with more functional groups, has not been developed yet. This is due to several possible drawbacks which can be rationalized on the basis of the general mechanism for metal-catalyzed cross-coupling reactions (Scheme 2). A coupling reaction usually starts with the oxidative addition of the electrophile to a coordinatively unsaturated low-valent metal complex, yielding an organometallic compound to which the second organic group is transferred from the nucleophile (transmetalation) in a second step. The resulting diorganometal complex finally gives rise to the coupling product by reductive elimination, regenerating the catalytically active species.[9]



Scheme 2. General mechanism for a metal-catalyzed cross-coupling reaction between an organic electrophile and an organometallic nucleophile.

Difficulties are present in all these steps when unactivated alkyl halides and alkyl electrophiles are employed:

1) Alkyl halides (even CH$_3$I) react slowly with Pd^0 complexes, in contrast with the behavior observed for allyl, benzyl, alkenyl, and aryl bromides and iodides.[10] The reaction of CH$_3$I with phosphane – Ni^0 complexes is about 10^7 faster and follows a complex pathway in which radical species may be involved.[11]

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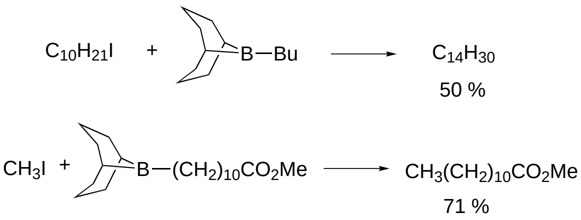
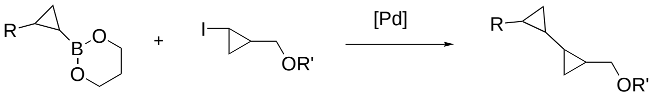
2) Once the alkyl – Pd^{II} complex has been formed, there should exist the possibility of decomposition by a fast β-elimination of hydrogen, which competes with the usually slower transmetalation. β-Elimination requires several conditions such as the existence of a vacant coordination site and the feasibility of arranging the M-C-C-H atoms in the same plane. This undesirable process may not be a problem in carbonylative couplings of $C(sp^3)$ centers since the fast CO insertion prevents decomposition of the alkyl – Pd intermediate.[12]
3) Reductive elimination is slow for σ-alkyl-π-allyl – Pd^{II} and di-π-allyl – Pd^{II} complexes.[13] In many cases this process can be accelerated by the addition of species capable of stabilizing the low-valent state of the metal, typically ligands with π-acceptor properties. Thus the choice of an additive with suitable coordinating properties could facilitate this step.

In spite of these problems, some examples of alkyl – alkyl coupling reactions have been reported. Suzuki et al. described some years ago the interesting Pd-catalyzed cross-coupling between alkyl halides and alkylboranes, although yields were not high (Scheme 3).[14]



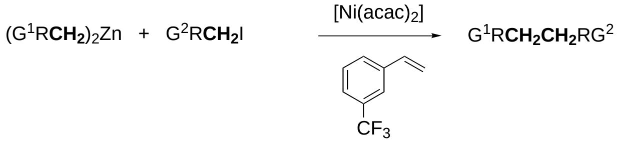
Scheme 3. Coupling of alkylboranes with iodoalkanes studied by Suzuki et al.[14]

More recently, dicyclopropanes have been synthesized by Pd-catalyzed reaction of cyclopropylboronic acids and boronates with iodocyclopropanes (Scheme 4).[15] In this case the instability of the cyclopropene that would be formed as well as the impossibility for the M-C-C-H atoms to reach a coplanar arrangement prevent decomposition by β-elimination of hydrogen.



Scheme 4. Suzuki-type cross-coupling between cyclopropyl derivatives. R = alkyl, alkoxy; R′ = H, benzyl.

The results presented above[12–15] show that the oxidative addition of primary and secondary alkyl iodides actually takes place on Pd^0 complexes. These derivatives are by no means the only possible catalysts for alkyl – alkyl cross-coupling. Knochel et al. have reported an efficient Ni-catalyzed cross-coupling reaction for the formation of $C(sp^3)$–$C(sp^3)$ bonds that employs organozinc compounds as nucleophiles.[16] This work has important features; an efficient alkyl – alkyl cross-coupling has been attained for the first time in the presence of different functional groups (thioacetal, thiophene, ketone, ester, amide; Scheme 5).



Scheme 5. A functional group tolerant Ni-catalyzed cross-coupling between iodoalkanes and functionalized dialkyl – Zn reagents. Functional group G^1 = alkyl, ester; G^2 = amide, ester, thioacetal, ketone.

Although only the use of primary alkyl iodides has been reported, the usual reactivity of other types of electrophiles with Ni complexes[17] suggests that a wider scope may be discovered. A suitable cocatalyst is necessary to promote reductive elimination (or oxidative addition). It has been demonstrated that C–C reductive elimination in square-planar diorgano – Ni^{II} complexes follows an associative pathway that is accelerated by the addition of a suitable ligand.[18] Among the reagents assayed, *m*-trifluoromethylstyrene afforded the cleanest and fastest reactions, although electron-deficient aromatic compounds and ketones were also effective. The presence of thioether or thioacetal moieties on the electrophile also makes the process favorable, probably by coordination to the metal. Nickel complexes react faster with alkyl iodides than their Pd analogues, and thus are of some advantage for reactions with such electrophiles.[19] Knochel et al. point out that the oxidative addition may involve a radical pathway in this case since *p*-dinitrobenzene completely inhibits the reaction.[20] On the other hand, β-elimination does not seem to be a problem here, which may be due to the occurrence of fast transmetalation and reductive elimination steps, although mechanistic studies would be necessary to ascertain this point.

The use of a coordinating cocatalyst may prevent the formation of vacant coordination sites necessary for β-elimination to occur, or it may simply accelerate the reductive elimination step. As far as the scope of the reaction in terms of the nucleophile is concerned, the coupling has been extended more recently to polyfunctional arylzinc derivatives.[21] The possibility of preparing organozinc derivatives from metallic Zn and alkyl iodides means that the use of Grignard reagents or organolithium compounds can be avoided, thus allowing a greater functional group tolerance in the preparation of the nucleophiles.

In summary, the above-mentioned results show that the problems usually encountered in catalytic alkyl – alkyl cross-couplings can be overcome. Oxidative addition and reductive elimination can be tuned by the careful choice of additives. The ubiquitous β-elimination process can be avoided. The Ni-catalyzed reaction of alkyl halides with alkylzinc derivatives opens a new way for the formation of $C(sp^3)$–$C(sp^3)$ bonds in the presence of different functional groups. A conceivable extension of this process to nucleophiles with higher functional group tolerance such as organotin, organoboron, or organosilicon compounds might widen the field of alkane

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fragment coupling and solve one of the pending problems in synthetically useful organometallic chemistry.

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