Cross-Coupling Reactions

Catalysts for Cross-Coupling Reactions with Non-activated Alkyl Halides

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Despite the problems inherent to metal-catalyzed cross-coupling reactions with alkyl halides, these reactions have become increasingly important during the last few years. Detailed mechanistic investigations have led to a variety of novel procedures for the selective cross-coupling of non-activated alkyl halides bearing β hydrogen atoms with a variety of organometallic nucleophiles under mild reaction conditions. This Minireview highlights selected examples of metal-catalyzed coupling methods and is intended to encourage chemists to exploit the potential of these approaches in organic synthesis.

1. Introduction

C–C coupling reactions are among the most important transformations in organic synthesis, as they make it possible to build up complex structures from readily available components in diverse ways. As a result of the development of a large number of metal-catalyzed coupling reactions of various C–X-containing compounds (X = Cl, Br, I, OTf, OMs, N_2^+, etc.; Tf = trifluoromethanesulfonyl, Ms = methanesulfonyl) over the last three decades, efficient methods are now available for the direct formation of bonds between of sp^3-, sp^2-, and sp-hybridized carbon atoms.[1]

Not all C–C coupling reactions have been thoroughly examined and developed. The intensively used reactions with aryl and vinyl electrophiles play a prominent role in organic synthesis because of the ready availability of substrates, their general applicability, and their high selectivities (comparatively simple oxidative addition, no β-hydride elimination). The relatively mild reaction conditions of such processes, as well as the high tolerance of functional groups under palladium, nickel, and copper catalysis, contributed substantially to the advancement of these reactions and paved the way for their abundant use in natural product syntheses.[2] Furthermore, numerous metal-catalyzed cross-coupling reactions are applied in the industrial synthesis of fine and agrochemicals, pharmaceuticals, and polymers.[3]

Alkyl halides R_{alkyl}–X, especially those with β hydrogen atoms, represent a more difficult class of electrophiles for cross-coupling reactions than the corresponding vinyl or aryl halides. Although industrial processes that involve the activation of methyl iodide or 2-chloroacetates are well known (e.g. acetic acid and malonic ester synthesis), until recently no efficient and general metal-catalyzed cross-coupling methodologies existed for non-activated alkyl electrophiles (i.e. compounds with β hydrogen atoms).[4] The reluctance of these compounds to undergo oxidative addition and their tendency to participate in competitive side reactions (elimination, hydrodehalogenation) were the largest hurdles in the development of selective cross-coupling reactions with alkyl halides. A new era of cross-coupling methodology dawned when pioneering work by Kochi and Tamura[5] in the 1970s and by Suzuki and co-workers[6] and Knochel and co-workers[7] in the 1990s proved the general feasibility of metal-catalyzed cross-coupling reactions with non-activated alkyl halides.

A simplified general catalytic cycle for metal-catalyzed cross-coupling reactions with alkyl halides is shown in Scheme 1. The underlying mechanism involves the usual sequence of oxidative addition to a coordinatively unsaturated metal complex, transmetalation of the organometallic nucleophile to the catalyst species, and reductive elimination of the functionalized alkane. As the $C(sp^3)$–X bond in alkyl halides is more electron rich than the $C(sp^2)$–X bond in aryl and vinyl halides, the propensity of alkyl halides to undergo oxidative addition to a low-valent transition-metal complex (i.e. formal reduction of $C(sp^3)$–X) is much lower than that of aryl and vinyl halides. The resulting alkyl–metal complex is

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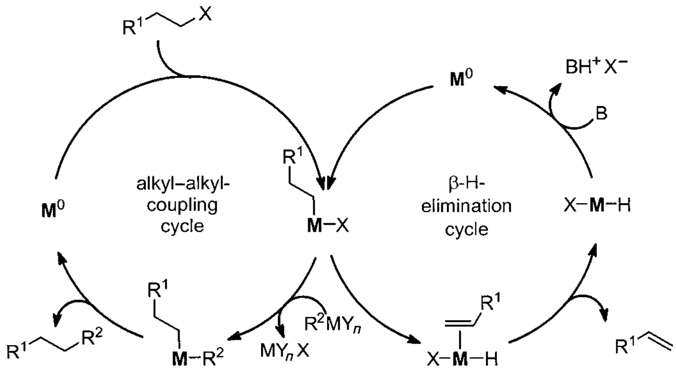


Scheme 1. Postulated mechanism of the alkyl–alkyl cross-coupling and the β-H elimination as a side reaction.

highly reactive owing to the absence of stabilizing electronic interactions with the metal d orbitals. The fast and thermodynamically favored β-hydride elimination leads to the predominant formation of olefinic by-products with most catalyst systems. The relatively slow reductive elimination of the cross-coupling product from the catalyst (aryl–aryl > aryl–alkyl > alkyl–alkyl) makes side reactions even more likely. Therefore, the design of new, more active catalyst systems and the development of suitable reaction conditions for cross-coupling reactions of alkyl halides have generally been aimed at facilitating the oxidative-addition and reductive-elimination steps and preventing the competing β-hydride elimination.

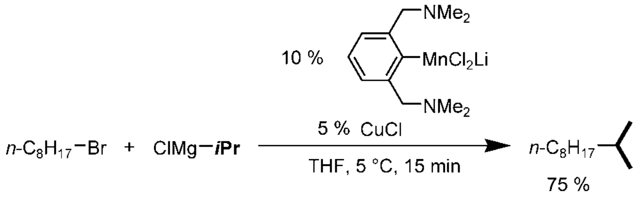
In the last three years, the development of cross-coupling reactions of alkyl halides with β hydrogen atoms has undergone remarkable progress. A variety of highly selective and practicable transition-metal-catalyzed methods have been introduced. Herein the most important recent developments in this area are summarized to provide the reader with a concise overview of the impressive scope of these methods. Emphasis is placed on direct cross-coupling reactions of organometallic nucleophiles with non-activated alkyl halides and related electrophiles in the presence of metal catalysts. Reactions of activated[4] alkyl halides, electrochemically initiated coupling reactions, and reactions with stoichiometric quantities of the metal reagent are not treated.[8] The reaction classes are organized by nucleophile type; in schemes and tables the nucleophilic component is shown in **bold**.

2. Cross-Coupling with Alkyl Nucleophiles

2.1. Alkyl–MgX (Kumada Coupling)

In the early 1970s, Kochi and Tamura reported on a series of kinetic and thermodynamic investigations into cross-coupling reactions with alkyl halides.[5] Subsequently, individual examples of metal-catalyzed coupling reactions with primary alkyl halides were published, although yields were modest and no general applications were demonstrated.[9] The first, if controversial, preparative work on the cross-coupling of alkyl iodides with alkyl Grignard reagents was reported by Castle and Widdowson in 1986.[10] Primary and secondary alkyl iodides were shown to react with alkyl magnesium bromides in the presence of [Pd(dppf)] (formed in situ from [$PdCl_2$(dppf)] and diisobutylaluminum hydride (DIBAL); dppf = 1,1′-bis(diphenylphosphanyl)ferrocene) in very good yields. Later these results were called into question by Scott and co-workers, who observed predominant reductive dehalogenation under identical conditions.[11]

In 1998, van Koten, Cahiez, and co-workers described the coupling of primary, secondary, and tertiary alkyl magnesium chlorides with *n*-alkyl bromides in the presence of a Mn/Cu catalyst mixture (Scheme 2). The reaction seems to involve transmetalation to give a heteroleptic diorganomanganese compound, which undergoes efficient coupling at 5 °C within 15 min in the presence of copper catalysts. α-Branched alkyl bromides, which are not suitable substrates for purely manganese-[12] or copper-catalyzed[13] reactions, can be coupled by applying the Mn/Cu protocol.[14]



Scheme 2. Manganese-catalyzed coupling (van Koten and co-workers).

Cahiez et al. reported an improved copper-catalyzed Kumada protocol with alkyl halides in 2000 (Scheme 3). In the presence of Li_2CuCl_4 (3 mol %), functionalized alkyl

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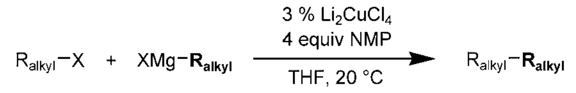
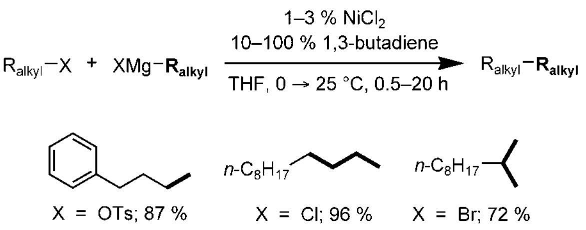


Scheme 3. Copper-catalyzed cross-coupling (Cahiez and co-workers).

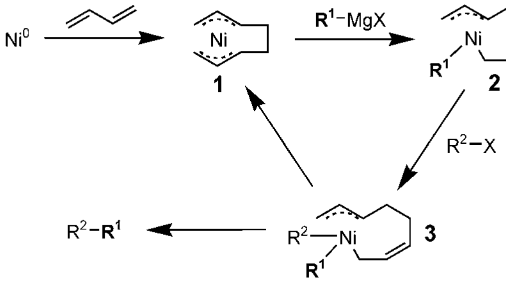
bromides react in good yields at room temperature. Key to success was the use of the solvent *N*-methylpyrrolidinone (NMP), which greatly accelerates the coupling reaction and thus prevents possible side reactions. However, secondary and tertiary halides, as well as the commercially more attractive alkyl chlorides, proved to be unreactive.[15]

As an extension of the protocol developed by Kumada and co-workers[16] as well as Corriu and Masse[17] for nickel-catalyzed cross-coupling with Grignard reagents, Kambe and co-workers reported similar reactions of alkyl bromides, chlorides, and tosylates in 2002 (Scheme 4).[18] Interestingly, the addition of 1,3-butadiene instead of phosphine ligands proved necessary to stabilize the active catalyst and accelerate the reductive elimination of the product. With alkyl bromides and tosylates, the products were obtained in almost quantitative yield at 0 °C in the presence of $NiCl_2$ (1–3 mol %) and butadiene (10–100 mol %). In the absence of a diene, reduction and/or elimination of the electrophile were mainly observed.



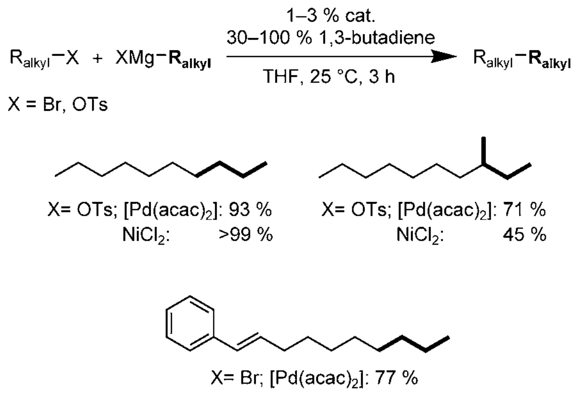
Scheme 4. Nickel–butadiene catalyst in Kumada cross-coupling reactions (Kambe and co-workers). Ts = toluenesulfonyl.

The postulated mechanism of the reaction is shown in Scheme 5. The actual catalyst **1** results from the reduction of $NiCl_2$ with R^1MgX and subsequent reaction of the Ni^0 formed with 2 equivalents of 1,3-butadiene. This catalyst is unreactive towards R^2X and undergoes transmetalation with R^1MgX to form the anionic alkyl nickel(II) complex **2**. Subsequent alkylation with R^2X and reductive elimination give the cross-coupled alkane product with regeneration of the active catalyst. The postulation of a Ni^{IV} intermediate, however, contradicts the mechanistic interpretations of similar nickel-catalyzed cross-coupling reactions with aryl or vinyl halides.

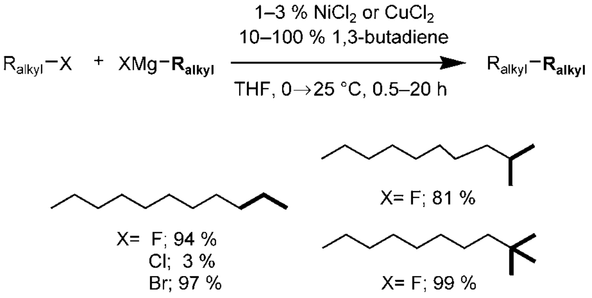


Scheme 5. Mechanism postulated by Kambe and co-workers for the nickel-catalyzed Kumada coupling.

In 2003, Kambe and co-workers also reported the palladium-catalyzed coupling of alkyl tosylates and bromides with alkyl magnesium reagents in the presence of 1,3-butadiene and $[Pd(acac)_2]$ (Scheme 6).[19] The palladium catalyst[20] exhibited higher chemoselectivity for tosylates and led to significantly improved yields with secondary alkyl magnesium compounds.[19] In the same year, nickel- and copper-catalyzed alkyl–alkyl coupling reactions with otherwise unreactive alkyl fluorides were reported to proceed under similar reaction conditions (Scheme 7). The best reactivities were found in the presence of $CuCl_x$ (3 mol %; $x = 1,2$) and 1,3-butadiene (20 mol %) additives. Surprisingly, the reactivities of the alkyl halides increased in the order Cl < F < Br, a trend that can not be explained by the bond energies of the alkyl halides and the magnesium salts formed.[21]



Scheme 6. Palladium- or nickel-catalyzed variant of the Kumada coupling (Kambe and co-workers). acac = acetylacetonate.

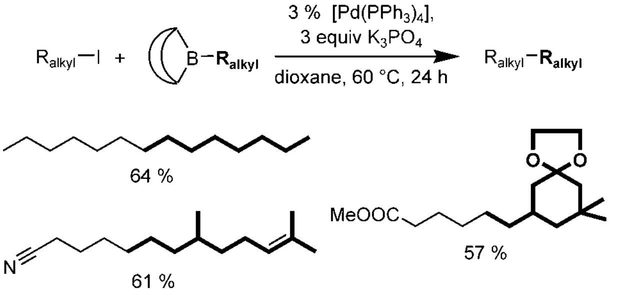


Scheme 7. Alkyl fluorides in Kumada cross-coupling reactions.

2.2. *Alkyl–BX₂ (Suzuki–Miyaura Coupling)*

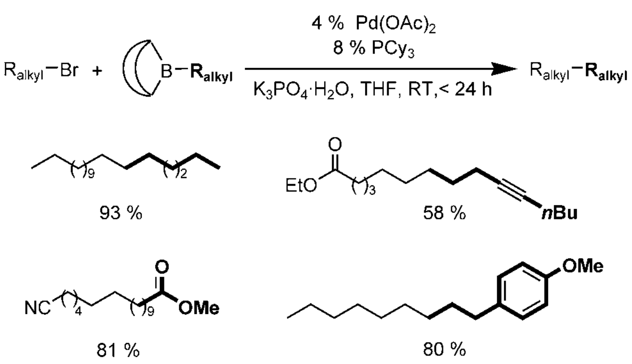
In 1992, Suzuki and co-workers reported the first palladium-catalyzed alkyl–alkyl cross-coupling of primary alkyl iodides with alkyl boranes and thereby paved the way for the development of this general method.[6] In the presence of

$[Pd(PPh_3)_4]$ (3 mol %) and K_3PO_4 (3 equiv) as a base, cross-coupling reactions of functionalized nucleophiles R_{alkyl}–9-BBN were effected in moderate yields (< 64 %; 9-BBN = 9-borabicyclononane; Scheme 8). A variety of functional groups are tolerated, and β-hydride elimination is largely suppressed. However, significant hydrodehalogenation of the electrophile is observed, and neither alkyl bromides nor secondary alkyl iodides react under these conditions.



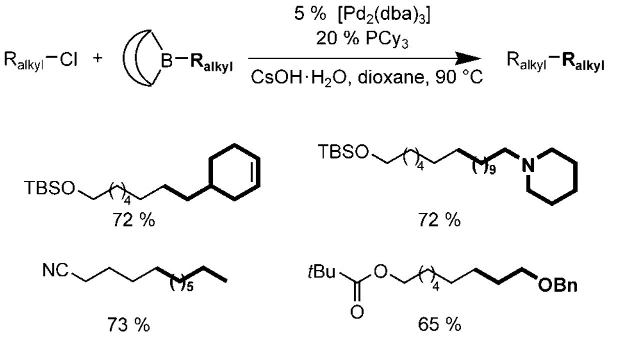
Scheme 8. Suzuki coupling with alkyl iodides.

The most important general method for alkyl–alkyl cross-coupling reactions was developed by Fu and co-workers and is based on the Suzuki reaction. Over the last few years, numerous examples of the palladium-catalyzed cross-coupling of alkyl boranes with primary alkyl bromides, chlorides, and tosylates in the presence of catalysts with bulky electron-rich phosphane ligands have demonstrated the broad scope of the reaction.[22] Because of the mild reactivity of organoboron nucleophiles, many functional groups of particular importance for organic synthesis are tolerated (e.g. ester, nitrile, amide, and ether functionalities, as well as double and triple bonds; Scheme 9). Generally, individual fine-tuning of the ligand and base employed is required to assure high selectivity in the cross-coupling reaction and suppression of competitive β-hydride elimination.



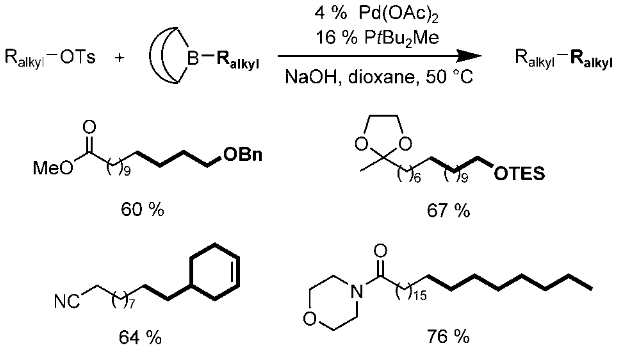
Scheme 9. Optimized palladium-catalyzed Suzuki coupling with alkyl bromides.

After extensive ligand screening, Fu and co-workers reported that the ligand PCy_3 (Cy = cyclohexyl) gave the highest selectivity and yield in the cross-coupling of primary alkyl bromides and chlorides with nucleophiles R_{alkyl}–9-BBN. Interestingly, the sterically and electronically similar ligands $P(c\text{-}C_5H_9)_3$ and $PiPr_3$ were significantly less effective. Furthermore, the choice of the precatalyst (RBr: $Pd(OAc)_2$;[22a] RCl: $[Pd_2(dba)_3]$[22b]) and the base is of special importance. The nature of the latter has a crucial influence on the nucleophilicity of the alkyl borane and on the tolerance of functional groups. Tripotassium phosphate monohydrate ($K_3PO_4{\cdot}H_2O$) was demonstrated to be superior to various other inorganic bases for the cross-coupling of alkyl bromides at room temperature.[22a] Alkyl chlorides, however, require higher catalyst loadings and reaction temperatures, as well as the use of hydroxide bases, such as $CsOH{\cdot}H_2O$ and NaOH (Scheme 10).[22b]



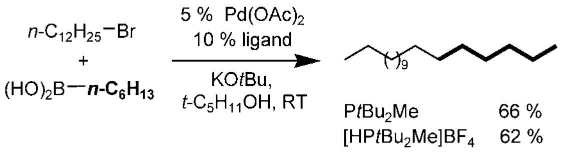
Scheme 10. Alkyl chlorides in the Suzuki reaction (Fu and co-workers). Bn = benzyl, dba = dibenzylideneacetone, TBS = *tert*-butyldimethylsilyl.

In contrast to reactions with alkyl bromides and chlorides, $PtBu_2Me$ was found to be the best ligand for Suzuki reactions with alkyl tosylates (Scheme 11). The results of mechanistic investigations suggest that the oxidative addition of the alkyl tosylate and the reductive elimination proceed with inversion of the configuration at the α carbon atom.



Scheme 11. Suzuki coupling with alkyl tosylates. TES = triethylsilyl.

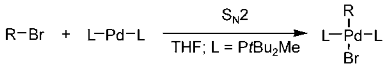
The same catalyst system ($Pd(OAc)_2/PtBu_2Me$) was used successfully in Suzuki cross-coupling reactions of alkyl bromides with alkyl boronic acids (Scheme 12). The nearly quantitative oxidative addition of an alkyl bromide to $[PdL_2]$ ($L = PtBu_2Me$) at 0 °C demonstrates the high activity of this catalyst system. The resulting alkyl–palladium complex was shown to resist β-hydride elimination and was characterized crystallographically.

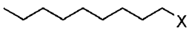
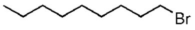
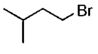
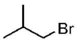
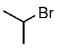


Scheme 12. Ligand-free Suzuki coupling with alkyl boronic acids.

Extensive mechanistic studies on the model reaction with *n*-nonylbromide in THF revealed the activation parameters for the oxidative addition to $[Pd(PtBu_2Me)_2]$: $\Delta G^* = 20.8\ \text{kcal mol}^{-1}$; $\Delta H^* = 2.4\ \text{kcal mol}^{-1}$; $\Delta S^* = -63$ eu. An increase in the solvent polarity (in the order THF < t-$C_5H_{11}OH$ < NMP < *N*,*N*-dimethylformamide (DMF)) was shown to lead to a decrease in the activation barrier, as expected for an S_N2-type nucleophilic attack of $[PdL_2]$ onto RX. Branching at the β or γ position in the electrophile resulted in significantly lower reactivities, and α-branched electrophiles are inert towards oxidative addition under the reaction conditions (Table 1).[23] The substantially lower reactivity of complexes $[PdL_2]$ with L = $PtBu_2Et$ or $PtBu_3$ is attributed to conformational restriction and resulting steric shielding of the palladium center.

Table 1: Kinetic investigations of oxidative addition to $[PdL_2]$.

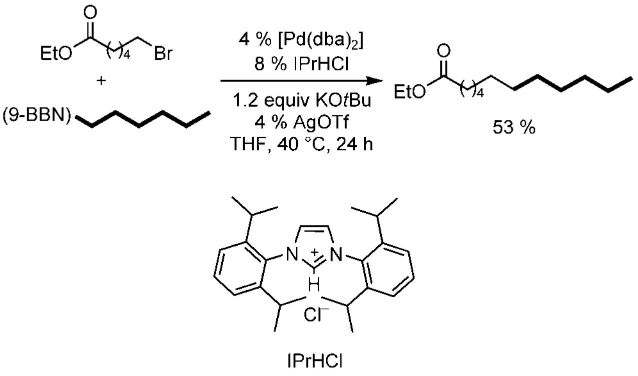


R–X	X	$t_{1/2}$ (*T*)
	I	2.2 h (–60 °C)
	Br	2.3 h (0 °C)
	Cl	2.0 days (60 °C)
	F	[a]
	OTs	10.4 h (40 °C)
R–Br		k_{rel} at 0 °C
		1.0
		0.19
		0.054
		< 0.0001

[a] Yield: < 2% after 43 h at 60 °C.

By virtue of the mildness of the reaction conditions and the broad functional-group tolerance, this palladium-catalyzed cross-coupling of alkyl bromides with alkyl boranes qualifies as a general method for selective C–C bond formation suitable for application in natural product synthesis. The required alkyl boranes can be accessed readily through the hydroboration of alkenes on a multigram scale. The restriction to primary alkyl halides has somewhat impeded a more general application of this reaction. Until very recently, no efficient catalyst system had been developed for the conversion of secondary and tertiary alkyl halides.

N-Heterocyclic carbene ligands have also been used successfully in alkyl–alkyl cross-coupling reactions with alkyl boranes (Scheme 13). However, Cloke and co-workers obtained the products of palladium-catalyzed reactions of primary alkyl bromides with alkyl–9-BBN derivatives in the presence of IPrHCl (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) as the ligand precursor in only moderate yields (28–56 %).[24]



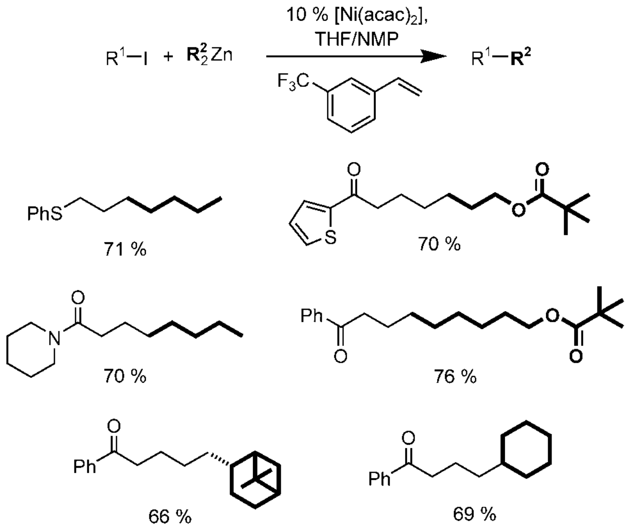
Scheme 13. First alkyl–alkyl Suzuki coupling with carbene ligands.

2.3. *Alkyl$_x$–ZnX$_y$ (Negishi Coupling)*

Early investigations by Tucker and Knochel focused on reactions of alkyl iodides with dialkyl zinc reagents in the presence of stoichiometric quantities of $[Cu(CN)Me_2(MgCl_2)]$.[25] Shortly afterwards, Knochel and co-workers reported a nickel-catalyzed cross-coupling between $C(sp^3)$ centers. The introduction of a double bond at the 4- or 5-position of the alkyl iodide made possible this first efficient purely nickel-catalyzed alkyl–alkyl cross-coupling reaction. The reductive elimination of the coupling product is facilitated by intramolecular coordination of the double bond and can be further enhanced by electron-withdrawing substituents on the double bond.[7] The reaction proceeds in the presence of $[Ni(acac)_2]$ (7 mol %) in a THF/NMP solvent mixture. However, the generality of this method is clearly limited by the structural requirements.

A few years later, Knochel and co-workers extended the scope of this methodology with a similar protocol that exploits intermolecular olefin coordination at the nickel catalyst (Scheme 14). In this case the $[Ni(acac)_2]$-catalyzed coupling of alkyl iodides, which now no longer require a pendant double bond for coordination to the metal center, could be effected by adding a π-acceptor ligand, such as acetophenone, benzophenone, or a styrene derivative. A screening of different ligands identified 3-trifluoromethylstyrene as the most effective cocatalyst.[26] The optimized reaction conditions tolerate ester and amide functionalities in the alkyl iodides. The presence of a thioether or thioacetal group leads to a significant increase in the reaction rate, presumably as a result of complexation by the sulfur atom to the metal center. The reaction is generally limited to primary alkyl iodides.

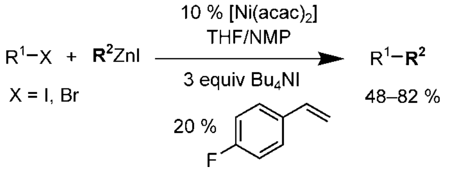
An extension of this method to secondary dialkyl zinc nucleophiles allowed the conversion of ω-functionalized alkyl iodides in good yields.[27] Knochel and co-workers also described the boron–zinc exchange as a selective route to



Scheme 14. Nickel-catalyzed alkyl–alkyl Negishi coupling with diorganozinc nucleophiles (Knochel and co-workers).

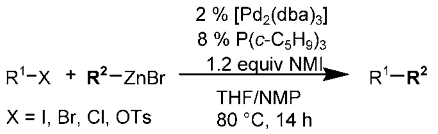
secondary diorganozinc compounds through a hydroboration–transmetalation sequence.[28] Retention of configuration was observed for both the B–Zn transmetalation and the reductive elimination, thus permitting the synthesis of stereoisomerically pure coupling products. The required chiral boranes are readily accessible by the stereoselective hydroboration of olefins.

Under optimized conditions, the less reactive alkyl zinc iodides, which tolerate a wider variety of functional groups, can also be used in coupling reactions (Scheme 15). The presence of tetrabutylammonium iodide (3 equiv) and 4-fluorostyrene (20 mol %) is required for the cross-coupling with primary alkyl iodides and bromides. By using this protocol, secondary alkyl zinc iodides could be used for the first time. Ether, keto, nitrile, and amide groups are compatible with the reaction conditions.[27]



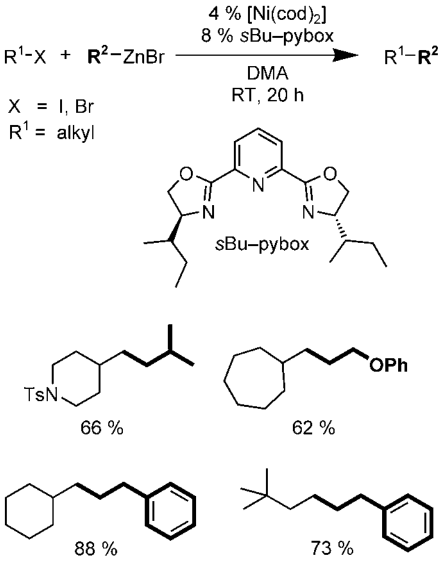
Scheme 15. Negishi coupling with secondary alkyl zinc iodides.

Zhou and Fu recently described a powerful catalyst system for alkyl–alkyl Negishi coupling reactions. A variety of non-activated primary alkyl iodides, bromides, chlorides, and tosylates underwent cross-coupling with alkyl zinc nucleophiles in the presence of the catalyst system $[Pd_2(dba)_3]/P(c\text{-}C_5H_9)_3/NMI$ at 80 °C (Scheme 16). Alkene, ether, nitrile, amide, and ester functionalities are tolerated in both reactants, but the reaction is limited to primary alkyl halides and alkyl zinc iodides. The presence of NMI facilitates the transmetalation to palladium and leads to improved yields. In analogy with the results of Knochel and co-workers, an NMP/THF mixture proved to be the optimal solvent. Interestingly, the corresponding air- and moisture-stable phosphonium salt can be used instead of the trialkyl phosphine ligand.[29]



Scheme 16. Palladium/phosphine-catalyzed Negishi coupling by Zhou and Fu. NMI = *N*-methylimidazole.

The first cross-coupling reaction of non-activated secondary alkyl bromides and iodides was possible with nickel catalysts in the presence of bis(oxazolinyl)pyridine (pybox) ligands (Scheme 17). The fine-tuning of the substituents on the ligand revealed the best catalyst activities with *s*-butyl groups; significantly lower activities were observed with larger or smaller groups (*i*Pr, *t*Bu, Ph). However, many nickel–phosphine catalyst mixtures were shown to be inactive under the test conditions. The cross-coupling reaction proceeds at room temperature within 20 h in moderate to good yields, but requires an excess of the nucleophile (1.6 equiv).[30] This protocol constitutes a milestone in the development of efficient alkyl–alkyl cross-coupling methodology, as the use of secondary alkyl halides is an indispensable requirement for the development of stereoselective coupling reactions.



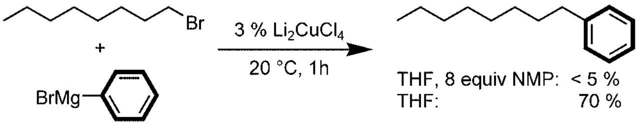
Scheme 17. First nickel-catalyzed Negishi coupling with secondary alkyl bromides and iodides. DMA = *N*,*N*-dimethylacetamide.

3. Cross-Coupling with Aryl Nucleophiles

Aryl nucleophiles are generally less reactive in cross-coupling reactions with electrophiles R_{alkyl}–X because of the lower nucleophilicity of the sp^2-hybridized carbon atom. However, they also undergo fewer side reactions owing to the lack of β hydrogen atoms. The large number of known palladium- or nickel-catalyzed inverse cross-coupling reactions (alkyl–MX with aryl–X)[16,17,31] suggests that the oxidative addition of the electrophile in the first step, rather than the nature of the nucleophile, is crucial for good reactivity. Considerably fewer examples exist of cross-coupling reactions between an aryl metal species and an alkyl halide.

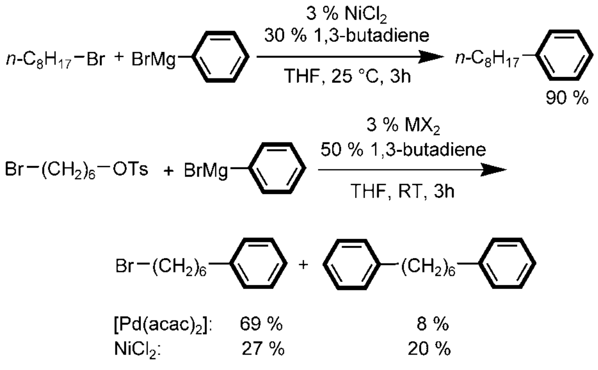
3.1. Alkyl–MgX (Kumada Coupling)

Fuchikami and co-workers reported copper-catalyzed cross-coupling reactions of β-perfluoroalkyl-substituted alkyl bromides with aryl magnesium compounds under mild conditions as early as 1996.[32] In 2000, Cahiez et al. documented a copper-catalyzed cross-coupling reaction of aryl magnesium compounds with alkyl bromides at room temperature (Scheme 18). Interestingly, the reaction is inhibited by NMP, which was added as an activator in the related alkyl–alkyl cross-coupling protocol.[15] A similar effect was also observed in reactions with aryl manganese compounds.[12]



Scheme 18. The Cahiez variant of the alkyl–aryl Kumada coupling.

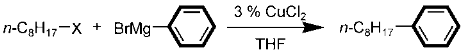
Kambe and co-workers described the application of the $NiCl_2$/butadiene catalyst system they developed for cross-coupling reactions of R_{alkyl}–X with R_{alkyl}–MgX to two reactions with phenyl magnesium bromide (Scheme 19). With primary alkyl tosylates and bromides the products were obtained in moderate yields at 0–25 °C.[18] Similar yields and chemoselectivity were observed for alkyl tosylates with $[Pd(acac)_2]$ as the precatalyst.[19]



Scheme 19. Alkyl–aryl cross-coupling (Kambe and co-workers).

Kambe and co-workers also reported copper-catalyzed reactions analogous to their alkyl–alkyl cross-coupling protocol with various nucleophiles ArMgX. Interestingly, the reactivities of alkyl fluorides and bromides were similar or even higher in the absence of 1,3-butadiene than with the additive (Table 2).[21]

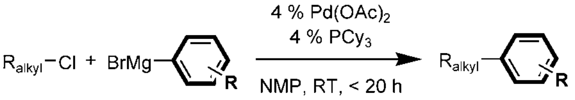
Table 2: Copper-catalyzed Kumada coupling according to Kambe and co-workers.



X	*T* [°C]	*t* [h]	Yield [%]
F	25	6	38[a]
F	25	6	53
F	67	1	99
Cl	67	1	42
Br	67	1	99

[a] In the presence of 1,3-butadiene (0.2 mmol).

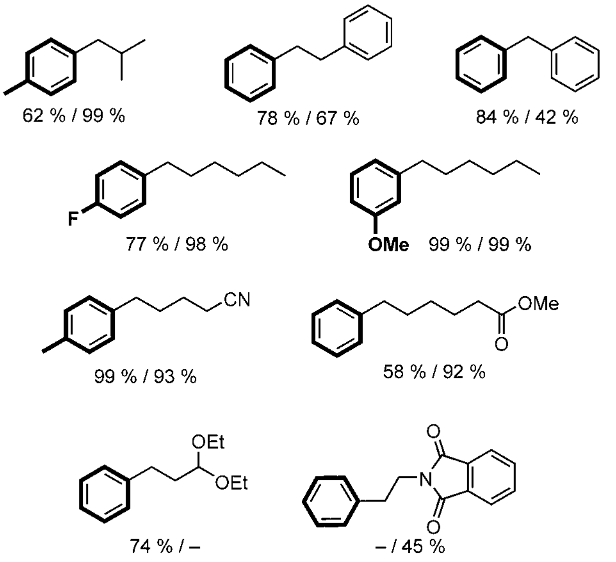
In our laboratory, a general method was developed for the palladium-catalyzed Kumada cross-coupling of aryl magnesium halides with inexpensive alkyl chlorides at room temperature in the presence of a catalytic amount of $Pd(OAc)_2$ (Scheme 20).[33] The choice of the solvent (NMP) and ligand (PCy_3) proved to be crucial for high yields and selectivities to be attained. In the presence of PCy_3 or P*i*Pr_3, the coupling products were obtained in good yields. However, secondary and tertiary alkyl chlorides do not react under these conditions. In contrast to reactions with alkyl bromides,[34] an optimal palladium/ligand ratio of 1:1 was established for reactions in NMP. It is assumed that the presence of a large excess of weakly coordinating NMP inhibits the competitive β-hydride elimination by coordinative saturation of the palladium atom. Reactions with the sterically more demanding P*t*Bu_3 ligand or the aromatic phosphines PPh_3 and P(*o*-Tol)$_3$ (Tol = tolyl) were found to be less strongly dependent on the Pd/L ratio, but gave the cross-coupling products in only moderate yields (< 30 %).



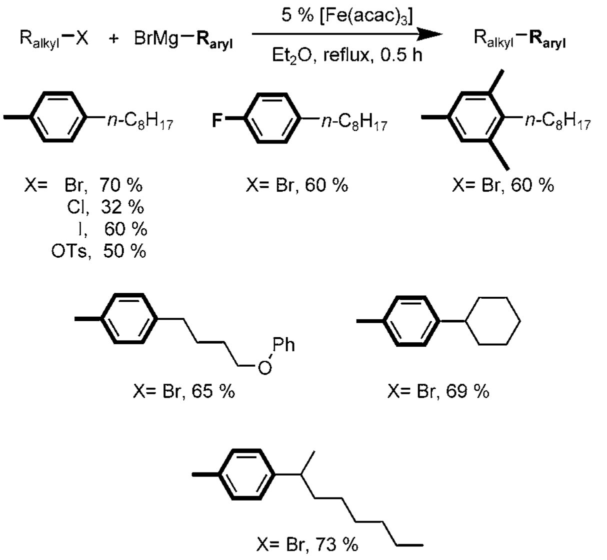
Scheme 20. Palladium-catalyzed Kumada coupling with alkyl chlorides at room temperature.

We also investigated similar cross-coupling reactions in the presence of N-heterocyclic carbene ligands.[35] A significant increase in selectivity and activity was observed with the monocarbene palladium dimer $[\{Pd(IMes)(NQ)\}_2]$ (IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene; NQ = naphthoquinone). The generality of the new procedure was demonstrated in reactions of a variety of functionalized alkyl chlorides (Scheme 21). This Kumada cross-coupling of alkyl chlorides with aryl magnesium reagents at room temperature constitutes a robust method for practicable access to functionalized alkanes in good yields and under mild conditions.

Very recently, iron-catalyzed coupling reactions of secondary alkyl halides were described independently by the research groups of Hayashi and Nakamura (Schemes 22 and

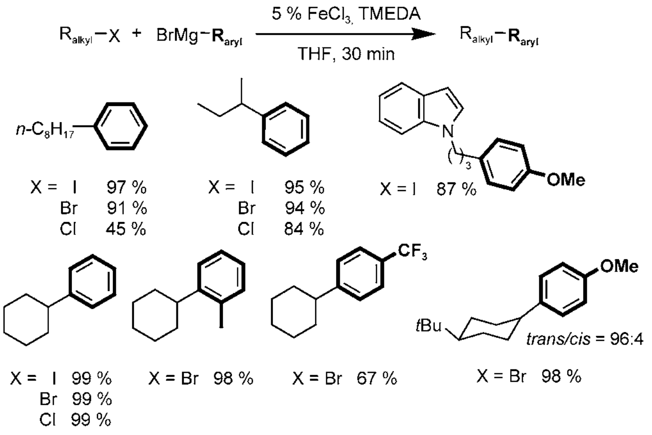


Scheme 21. Selected products of the Kumada coupling with alkyl chlorides. Left-hand yields: with $Pd(OAc)_2/PCy_3$; right-hand yields: with $[\{Pd(IMes)(NQ)\}_2]$.



Scheme 22. Iron-catalyzed coupling with secondary alkyl halides (Nagano and Hayashi).

23). Nagano and Hayashi reported the use of $[Fe(acac)_3]$ as an efficient catalyst for cross-coupling reactions of diversely substituted reagents ArMgBr (2 equiv).[36] The best results were obtained with secondary alkyl bromides under mild reaction conditions (Et_2O, 35 °C). When THF or solvent mixtures with NMP were used, significant quantities of elimination and homocoupling products were obtained.

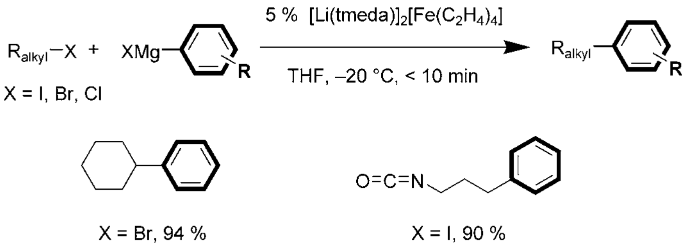


Scheme 23. Iron-catalyzed coupling (Nakamura and co-workers).

Nakamura and co-workers reported a $FeCl_3$-catalyzed reaction with secondary alkyl bromides and iodides,[37] which were substantially more reactive than primary halides under these conditions. The addition of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) led to significantly higher selectivities and largely suppressed competitive elimination and hydrodehalogenation. Tertiary alkyl halides are converted faster than secondary, but give predominantly undesired by-products. The reactivity of the electrophile follows the expected pattern and decreases from the alkyl iodide to the alkyl chloride.

Secondary alkyl chlorides generally require slightly higher temperatures (up to 40 °C) and an excess of the Grignard reagent (1.5 equiv) for successful coupling. Electron-rich aryl groups on the Grignard reagent accelerate the reaction. Cyclic and acyclic secondary alkyl halides gave similar results. The reactions seem to involve radical intermediates, as complete epimerization was observed with alkyl halides with α stereocenters.

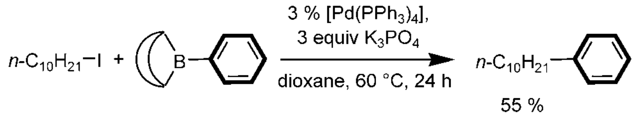
A further contribution to the art of iron-catalyzed alkyl–aryl cross-coupling reactions was made by Martin and Fürstner. They postulated that the active catalysts were Fe/Mg clusters of the formal composition $[Fe(MgX)_2]_n$ formed in situ, and carried out iron-catalyzed Kumada-type reactions with the tetrakis(ethylene)ferrate(II) compound $[Li(tmeda)]_2[Fe(C_2H_4)_4]$ (5 mol %; Scheme 24).[38] In the presence of this well-defined precatalyst, primary and secondary alkyl bromides and iodides as well as propargyl and allyl halides react smoothly to afford the desired arylated products in good to very good selectivity. The mechanism seems to involve radical species, as racemization has been observed with enantiomerically pure substrates and cyclization with 5-haloalkenes.



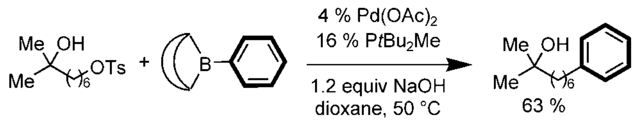
Scheme 24. Iron-catalyzed coupling (Martin and Fürstner).

3.2. Aryl–BX$_2$ (Suzuki Coupling)

The first palladium-catalyzed coupling of an aryl borane with an alkyl iodide was reported by Suzuki and co-workers in 1992 (Scheme 25).[6] The reactions were carried out in the presence of [Pd(PPh$_3$)$_4$] (3 mol%) and K$_3$PO$_4$ (3 equiv) as a base in dioxane at 60 °C. Ten years later, Fu and co-workers presented an optimized set of conditions for palladium-catalyzed coupling reactions of alkyl tosylates with 9-BBN derivatives (Scheme 26). The catalyst is formed in situ from Pd(OAc)$_2$ (4 mol%) and an excess of the basic and sterically demanding ligand P*t*Bu$_2$Me.[22c]

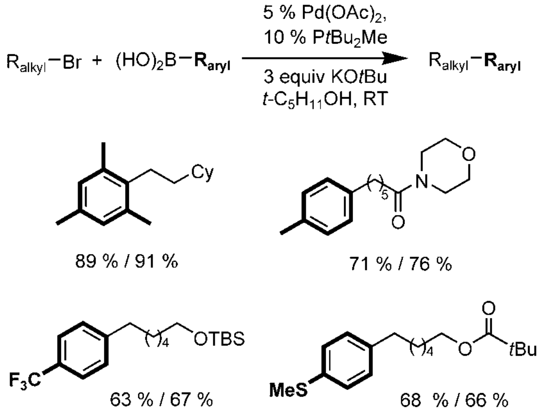


Scheme 25. First efficient alkyl–aryl Suzuki coupling.



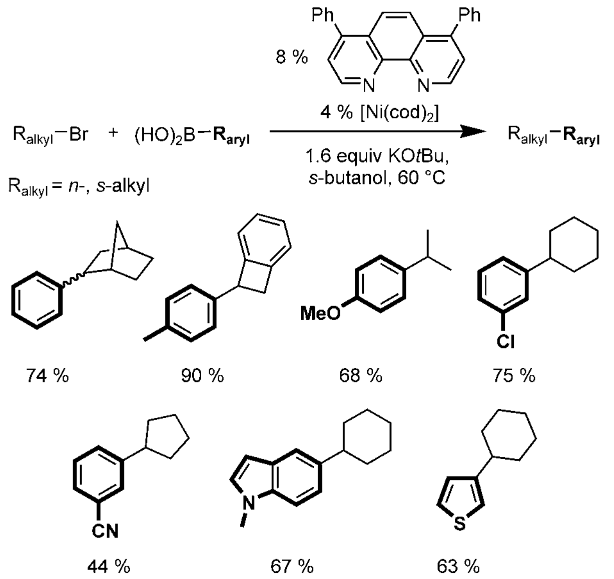
Scheme 26. Suzuki reaction of alkyl tosylates with aryl 9-BBN derivatives.

These reaction conditions for the coupling of alkyl tosylates with 9-BBN derivatives were shown to be ineffective for the more practical, commercially available aryl boronic acids. However, conditions were found for the cross-coupling of aryl boronic acids with alkyl bromides at room temperature with *t*-amyl alcohol as the solvent and KO*t*Bu as the base (Scheme 27). The catalyst system Pd(OAc)$_2$/P*t*Bu$_2$Me tolerates a large number of functional groups, such as ester, ether, thioether, amide, nitrile, and acetal functionalities. Deactivated (4-CF$_3$C$_6$H$_4$–B(OH)$_2$) and sterically demanding (*o*-tolyl–B(OH)$_2$) aryl boronic acids can also be coupled in good to very good yields under these reaction conditions.[22d] The stable alkyl palladium(II) complex formed at 0 °C through the oxidative addition of an alkyl bromide to [Pd(P*t*Bu$_2$Me)$_2$] was characterized crystallographically and identified as an intermediate in the catalytic cycle.



Scheme 27. Aryl boronic acids as coupling partners in the presence of palladium catalysts. Left-hand yields: with P*t*Bu$_2$Me; right-hand yields: with [HP*t*Bu$_2$Me]BF$_4$.

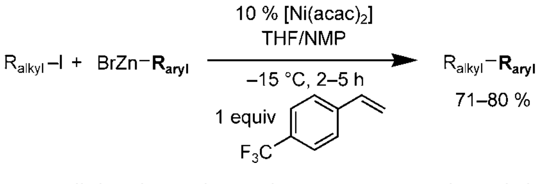
In 2004, Zhou and Fu described the first efficient protocol for the cross-coupling of non-activated secondary alkyl bromides and iodides with aryl boronic acids (Scheme 28). A similar catalyst system to that for the alkyl–alkyl Negishi reaction was used. Although in the presence of the *s*Bu–pybox ligand only marginal activity was observed, the coupling products were obtained in moderate to good yields with the chelating dinitrogen ligand bathophenanthroline. Interestingly, reasonable selectivities were observed only with [Ni(cod)$_2$] as the precatalyst.[39]



Scheme 28. First nickel-catalyzed Suzuki coupling of secondary alkyl bromides with the ligand bathophenanthroline. cod = 1,5-cyclooctadiene.

3.3. Aryl$_x$–ZnX$_{2-x}$ (Negishi Coupling)

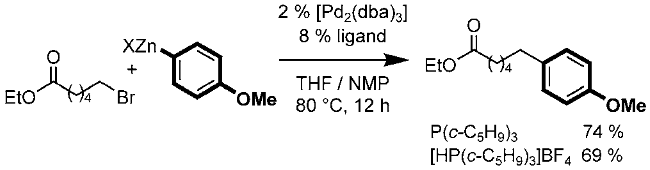
In 1998, Giovannini and Knochel reported nickel-catalyzed Negishi reactions with aryl zinc derivatives and alkyl iodides (Scheme 29). As in the related alkyl–alkyl coupling protocol, an olefin is required as a coligand to accelerate the reductive elimination of the cross-coupling product from the



Scheme 29. Alkyl–aryl Negishi coupling (Giovannini and Knochel).

Ni^{II} intermediate. In the absence of the coligand 4-trifluoromethylstyrene, substantial quantities of homocoupling and iodine–zinc-exchange products were formed. With $[Ni(acac)_2]$ (10 mol %) and 1 equivalent of the activator in an NMP/THF mixture at −15 °C, primary alkyl iodides coupled with aryl zinc bromides in good yields (71–80 %). These reaction conditions tolerate keto, ester, amide, nitrile, ether, and thioether substituents on both substrates, as well as chlorine substituents on the aryl zinc substrate.[40]

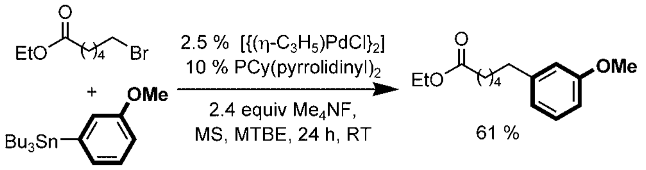
During their studies of the palladium-catalyzed alkyl–alkyl Negishi coupling, Zhou and Fu established $[Pd_2(dba)_3]$/$P(c\text{-}C_5H_9)_3$ as a suitable catalyst system for alkyl–aryl cross-coupling reactions of aryl zinc compounds with alkyl bromides and iodides.[29] As shown in Scheme 30, instead of the air-sensitive phosphine, the corresponding phosphonium salt $[HP(c\text{-}C_5H_9)_3]BF_4$ can be used advantageously as the ligand precursor.



Scheme 30. Palladium/phosphine-catalyzed Negishi coupling (Zhou and Fu).

3.4. *Aryl–SnX$_3$ (Stille Coupling)*

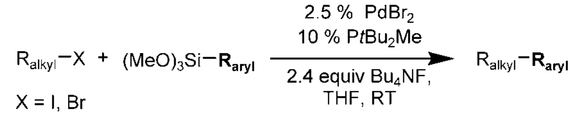
Arylations of β-perfluoroalkyl-substituted alkyl iodides with aryl tin reagents under $[PdCl_2(PPh_3)_2]$ catalysis have been reported. However, only moderate yields were observed and high catalyst loadings (up to 50 mol %) were required.[41] In contrast, Stille cross-coupling reactions of aryl stannanes can generally be effected in good yields with palladium/phosphine catalyst systems. A screening of ligands resulted in optimal yields for electron-rich alkyl diaminophosphines, whereas simple trialkyl phosphines, such as $PtBu_2Me$, showed only low activities. In the presence of tetramethylammonium fluoride, molecular sieves, and a large excess of cyclohexyldi(pyrrolidinyl)phosphane ($PCy(pyrr)_2$) as the ligand, ω-functionalized primary alkyl bromides reacted smoothly with electron-rich and, albeit in slightly lower yields, electron-deficient aryl tributylstannanes at room temperature (Scheme 31).[42]



Scheme 31. Palladium-catalyzed alkyl–aryl Stille reaction (Fu and coworkers). MS = molecular sieves, MTBE = *tert*-butyl methyl ether.

3.5. *Aryl–SiX$_3$ (Hiyama Coupling)*

$PtBu_2Me$ is also a suitable ligand for palladium-catalyzed Hiyama cross-coupling reactions of primary alkyl iodides and bromides with aryl silanes. Under identical conditions to those for related Suzuki reactions, no conversion was observed with aryl silanes. However, the addition of Bu_4NF as an activator led to the in situ generation of a more nucleophilic hypervalent silicate species, which reacted cleanly with alkyl bromides, even at room temperature (Scheme 32). In the presence of $PdBr_2$ (4 mol %) and $PtBu_2Me$ (10 mol %), coupling products were obtained in moderate to good yields with ω-functionalized alkyl bromides and iodides. Significantly lower activities were observed with electron-deficient aryl silanes and when the air-stable phosphonium salt $[HPtBu_2Me]BF_4$ was used in place of the phosphine ligand.[43]

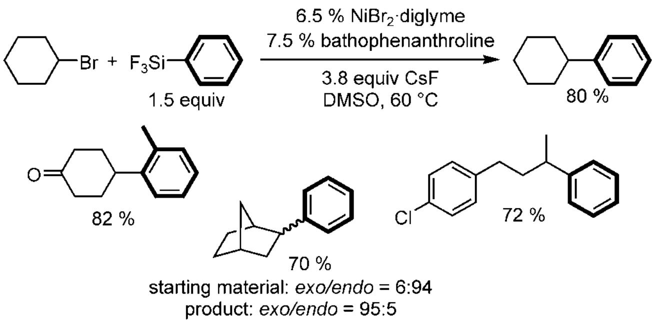


$$\mathrm{R_{alkyl}{-}X} + \mathrm{(MeO)_3Si{-}\mathbf{R}_{aryl}} \xrightarrow[\text{2.4 equiv } Bu_4NF,\ \text{THF, RT}]{\text{2.5 \% } PdBr_2,\ \text{10 \% } PtBu_2Me} \mathrm{R_{alkyl}{-}\mathbf{R}_{aryl}}$$

X = I, Br

Scheme 32. Palladium-catalyzed Hiyama reaction with aryl siloxanes.

Good yields were also described in the Hiyama coupling of secondary alkyl bromides in the presence of the convenient catalyst system $NiBr_2$·diglyme/bathophenanthroline (Scheme 33). Only slightly lower yields were observed with $NiBr_2$ or $[Ni(cod)_2]$ as metal sources and the structurally related dinitrogen ligands 1,10-phenanthroline and 2,2′-bipyridine.[44] However, the reaction was limited to aryl trifluorosilanes and required a large excess of the promotor cesium fluoride (4 equiv). Again, the conditions for Suzuki and Negishi coupling reactions of secondary alkyl bromides proved to be rather inefficient for these cross-coupling reactions.



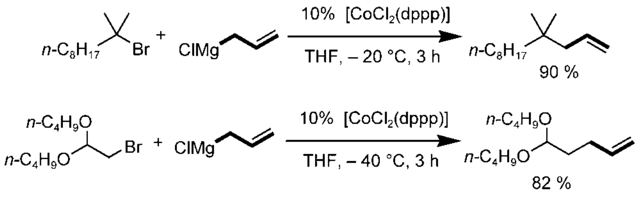
Scheme 33. Nickel-catalyzed Hiyama coupling of secondary alkyl bromides with $ArSiF_3$. diglyme = diethyleneglycol dimethyl ether, DMSO = dimethyl sulfoxide.

4. Cross-Coupling with Other Nucleophiles

Besides the cross-coupling reactions of alkyl electrophiles with alkyl and aryl metal nucleophiles, a few protocols for similar reactions with allyl, vinyl, and alkynyl nucleophiles have been reported more recently. Furthermore, sparse examples of direct carbonylation reactions of non-activated alkyl halides are known.

4.1. Allyl–MX$_n$

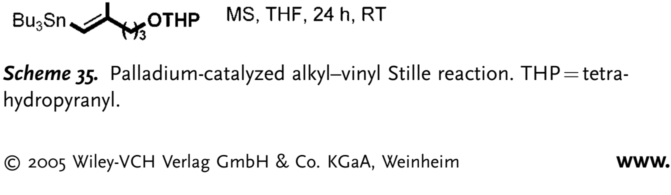
Oshima and co-workers reported the first cobalt-catalyzed cross-coupling reactions of allyl magnesium compounds with alkyl iodides, bromides, and chlorides at low temperatures (−40 to 0°C). Interestingly, tertiary alkyl halides also underwent successful cross-coupling (Scheme 34). A radical mechanism was proposed for this reaction, with the oxidative addition involving single-electron transfer (SET) from the electron-rich allyl–cobalt complex to the alkyl halide. π-Allyl ligands can block free coordination sites at the cobalt center and thus enable the allylation of tertiary and secondary alkyl halides as well as alkyl halides with β-alkoxy substituents without significant β-hydride or β-alkoxy eliminination.[45]



Scheme 34. Cobalt-catalyzed allylation of secondary and tertiary alkyl bromides. dppp = 1,3-bis(diphenylphosphanyl)propane.

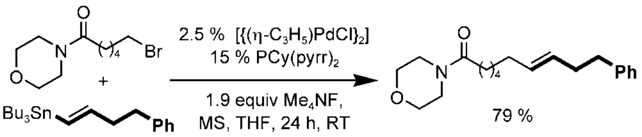
4.2. Vinyl–MX$_n$

Shimizu and Fuchikami reported palladium-catalyzed Stille reactions of β-perfluoroalkyl-substituted alkyl iodides with vinyl and alkynyl stannanes at elevated temperatures.[41] The palladium-catalyzed Stille coupling of primary alkyl bromides with alkenyl tin reagents is also known to proceed at room temperature (Scheme 35). With PtBu$_2$Me as the ligand, substituted olefins were formed in good to very good yields in the presence of [{Pd(η-C_3H_5)Cl}$_2$] (2.5 mol%) and Me_4NF (1.9 equiv).[46]



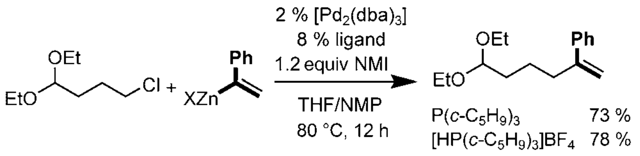
Scheme 35. Palladium-catalyzed alkyl–vinyl Stille reaction. THP = tetrahydropyranyl.

Furthermore, alkyl diaminophosphines were shown to be active ligands under similar reaction conditions (Scheme 36). Although the yields were comparable to those observed for the system with PtBu$_2$Me, aryl stannanes can also be used as substrates with this modified catalyst system.[42]



Scheme 36. The diaminophosphine ligand PCy(pyrr)$_2$ in the Stille reaction (Fu and co-workers).

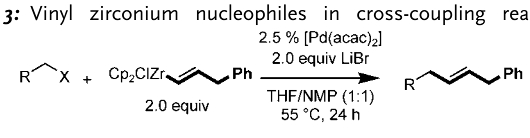
A general procedure for palladium-catalyzed Negishi cross-coupling reactions of alkyl electrophiles (RI, RBr, RCl, ROTs) with alkenyl zinc reagents in good yields (53–98%) was described by Zhou and Fu.[29] In the presence of P(c-C_5H_9)$_3$ or its stable phosphonium salt, good reactivities were observed even with sterically hindered geminal or *cis*-substituted vinyl zinc halides (Scheme 37). A one-pot hydrozincation–cross-coupling sequence constitutes an interesting extension of this methodology: Vinyl zinc halides formed in situ through the titanium-catalyzed reduction of alkynes react with primary alkyl electrophiles under palladium catalysis in moderate yields.

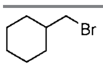
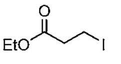
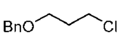
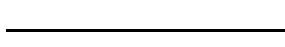


Scheme 37. Alkyl–vinyl Negishi coupling and domino hydrometalation–cross-coupling.

[Pd(acac)$_2$] was used as a catalyst for reactions of alkyl halides with alkenyl zirconium reagents under mild conditions (Table 3). With this ligand-free catalyst system, primary alkyl bromides, iodides, and tosylates react in good yields. However, β-branched alkyl bromides could only be coupled in moderate yields, and alkyl chlorides also exhibit lower reactivities.[47]

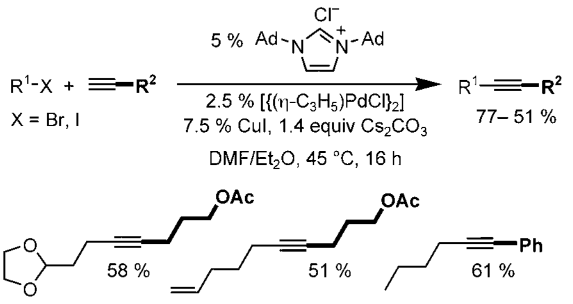
Table 3: Vinyl zirconium nucleophiles in cross-coupling reactions.



Alkyl halide	Yield [%]
	60
	82
	83
	46

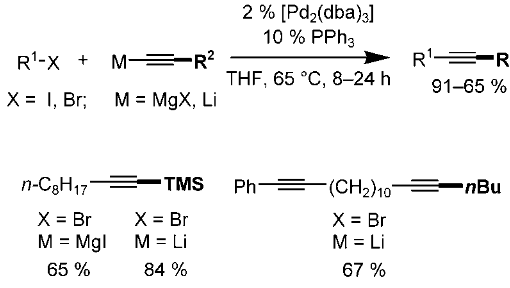
4.3. Alkynyl–MX$_n$

Surprisingly, to date no example of the palladium/copper-catalyzed Sonogashira coupling of primary alkyl bromides and iodides with terminal alkynes in the presence of phosphine ligands has been reported. However, in the presence of N-heterocyclic carbene ligands, the reaction proceeds in moderate yields (Scheme 38). A multitude of functional groups (ester, nitrile, and acetal functionalities, double bonds, and unprotected hydroxy groups) are tolerated in this process. Variations in the substitution pattern on the alkyne have a significant influence on the reactivity. Thus, the reaction conditions (temperature, catalyst loading) must be adjusted for each substrate. As alkyl chlorides do not react, chemoselective transformations with halochloroalkanes are possible.[48]



Scheme 38. Palladium/carbene-catalyzed Sonogashira coupling (Eckhardt and Fu).

[Pd$_2$(dba)$_3$]/PPh$_3$ constitutes another viable catalyst system for alkyl–alkynyl coupling reactions. In this Kumada–Corriu-type reaction of primary alkyl bromides and iodides with alkynyl lithium compounds or the corresponding Grignard reagents, the coupling products were obtained in good yields (Scheme 39). In general, yields with the alkynyl lithium compounds were slightly better. PPh$_3$ proved to be a superior ligand to electron-rich trialkyl phosphines. This effect suggests that the reductive elimination may be rate determining. The choice of the palladium source was shown to influence the amount of homocoupling product formed.[49]

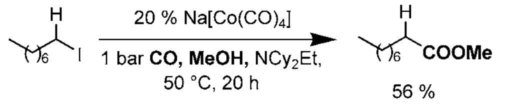


Scheme 39. Palladium-catalyzed alkynylation (Luh and co-workers).

4.4. Carbonylations of Alkyl Electrophiles

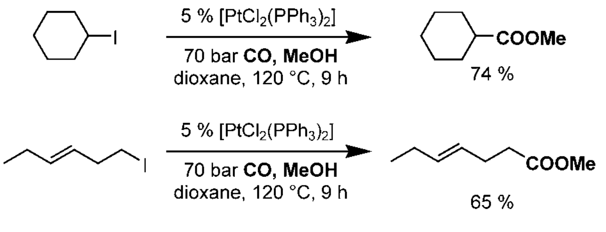
Beside cross-coupling reactions with organometallic nucleophiles, the carbonylation of alkyl halides ranks among the most important C–C coupling reactions on an industrial scale, and therefore deserves a brief discussion in the context of this Minireview. Radical carbonylations of alkyl iodides[50] will not be dealt with.

The carbonylation of alkyl halides enables the direct synthesis of aldehydes, ketones, esters, and amides. The industrial importance of such syntheses is underlined by the carbonylation of methanol to give acetic acid (Monsanto, Cativa processes),[51] which involves the rhodium- or iridium-catalyzed activation of methyl iodide. The efficient transition-metal-catalyzed carbonylation of alkyl halides is generally limited to activated substrates, such as methyl, benzyl, or allyl halides.[4] Thus, the carbonylation of alkyl halides with β hydrogen atoms at a C(sp^3) center still presents a synthetic challenge, although Heck and Breslow reported a cobalt-catalyzed carbonylation of alkyl iodides under basic conditions as early as 1963 (Scheme 40).[52] Because of the formation of a stoichiometric quantity of HX as a by-product, the addition of a stoichiometric amount of a base is required.



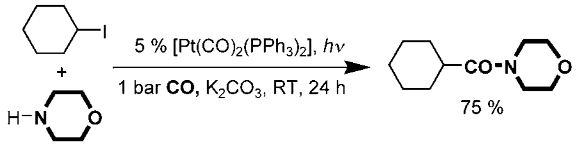
Scheme 40. First cobalt-catalyzed carbonylation of alkyl iodides.

In the mid 1980s Alper and co-workers showed that [Pd(PPh$_3$)$_4$][53] and the bimetallic mixture [Pd(PPh$_3$)$_4$]/[{RhCl(hd)}$_2$] (hd = 1,5-hexadiene)[54] are active catalysts for the carbonylative synthesis of alkyl esters (Scheme 41). Later, platinum catalysts were used in the carbonylation of alkyl halides under thermal[55] as well as photochemical[56] conditions. For most thermal carbonylations, K$_2$CO$_3$ is the base of choice.



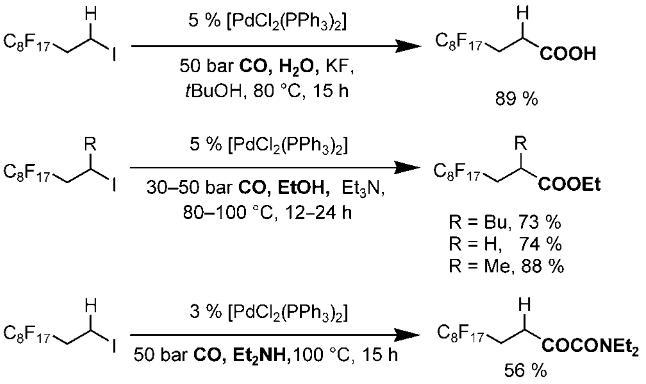
Scheme 41. Platinum-catalyzed thermal carbonylation of alkyl halides.

The carbonylation of alkyl iodides in the presence of 2–5 mol% of different metal carbonyl compounds ([Mn$_2$(CO)$_{10}$], [Co$_2$(CO)$_8$], [Ru$_3$(CO)$_{12}$], [Re$_2$(CO)$_{10}$], and [Os$_3$(CO)$_{12}$]) under UV irradiation is possible at room temperature and 1 bar CO (Scheme 42).[56] A radical mechanism was excluded, since reactions also proceed in the presence of radical inhibitors.



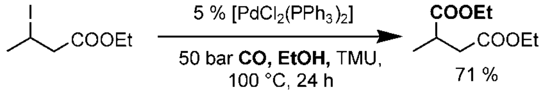
Scheme 42. Platinum-catalyzed photoinduced carbonylation.

Carboxylic acids and esters with perfluoroalkyl substituents were obtained by the thermal carbonylation of the corresponding iodides in the presence of KF or Et_3N as a base (Scheme 43).[57] Interestingly, double carbonylation to give α-ketoamides occurred when secondary amines were used as nucleophiles.[58]



Scheme 43. Palladium-catalyzed carbonylation of alkyl iodides.

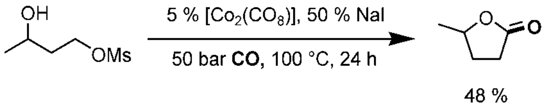
Unfortunately, the aforementioned carbonylation conditions are not suitable for the conversion of base-sensitive halides. In this context, the base-free carbonylations of Fuchikami and co-workers[59] in polar aprotic solvents[60] or with molecular sieves[61] as HX sponges are interesting (Scheme 44).



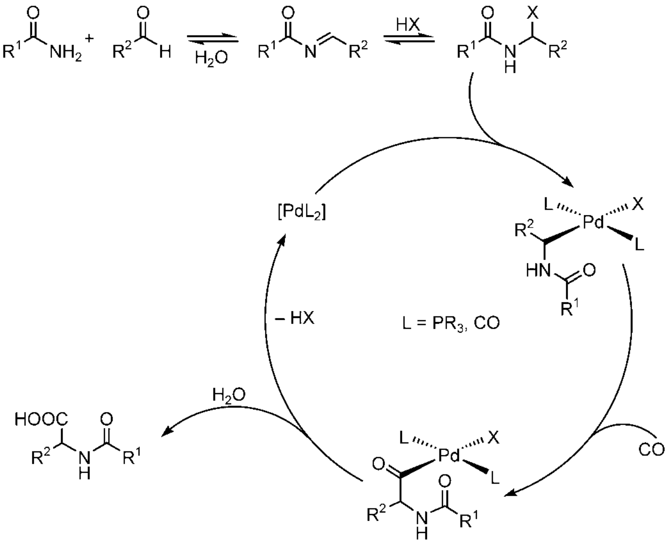
Scheme 44. Base-free carbonylation.

Alkyl sulfonates can be carbonylated in a similar manner.[62] As shown in Scheme 45, lactones are generated directly from alkyl sulfonates under cobalt catalysis.

Most industrial-scale syntheses of acetic acid derivatives involve the in situ generation of the more reactive methyl iodide from methanol. A related approach was utilized in the palladium-catalyzed amidocarbonylation of aldehydes, which constitutes an interesting three-component reaction for the synthesis of *N*-acyl α-amino acids (Scheme 46).[63] Model studies with *N*-(chloromethyl)phthalimides revealed the palladium-catalyzed activation of an intermediate α-halo *N*-acyl amine.[64] Subsequent carbonylation of the resulting alkyl palladium species leads directly to a wide range of amino acids, such as aryl glycines and hydantoins.[65]



Scheme 45. Carbonylation of alkyl sulfonates.



Scheme 46. Amidocarbonylation of aldehydes.

5. Summary

Metal-catalyzed cross-coupling reactions of alkyl halides with organometallic compounds have been developed to an advanced stage and provide synthetic organic chemists with a versatile arsenal of C–C bond-forming methods. The most important synthetic variations are summarized in Table 4.

Combinations of palladium sources and phosphine ligands, which are the most prevalent type of catalyst system, allow for mild reaction conditions and a large range of applications owing to their functional-group tolerance. Thus, general protocols for Kumada, Suzuki, Negishi, Stille, and Hiyama cross-coupling reactions with alkyl, vinyl, and aryl metal nucleophiles in the presence of bulky, electron-rich trialkyl phosphines have been developed. However, the sluggishness of the reactions of secondary and β-branched electrophiles still prevents an even broader use of these palladium/phosphine-catalyzed methods in organic chemistry. Nickel and iron catalysts address this challenge and lead to excellent yields with secondary alkyl halides and a wide variety of organometallic nucleophiles.

Future research will certainly be aimed at the further optimization of reaction conditions to attain higher catalyst productivity (< 1 mol% catalyst) and greater tolerance towards sensitive functional groups. Further mechanistic studies are required to establish the often unpredictable effects of specific solvents and additives. With regard to efficiency criteria, improvements in the atom economy of most processes are necessary, as most of the known procedures require nucleophiles (organometallic unit) of high

Table 4: Important cross-coupling methods with alkyl electrophiles.

R	X	Nucleophile	Catalyst	Conditions	Ref.
n	Br, I	*n*-, *s*-, *t*-RMgX	Li_2CuCl_4	NMP, RT	[15]
n	Cl, Br, OTs	*n*-, *s*-, *t*-RMgX	$NiCl_2$, 1,3-butadiene	RT	[18]
n	Br, OTs	*n*-, *s*-RMgX	$[Pd(acac)_2]$, 1,3-butadiene	RT	[19]
n	F, Br	*n*-, *s*-RMgX	$NiCl_2$ or $CuCl_2$, 1,3-butadiene	below RT	[21]
n	Br	*n*-, *s*-RMgX	$Pd(OAc)_2/PCy_3$	$K_3PO_4 \cdot H_2O$, RT	[22a]
n	Cl	*n*-R-(9-BBN)	$[Pd_2(dba)_3]/PCy_3$	$CsOH \cdot H_2O$, 90 °C	[22b]
n	OTs	*n*-R-(9-BBN)	$Pd(OAc)_2/PtBu_2Me$	NaOH, 50 °C	[22c]
n	I	*n*-R_2Zn	$[Ni(acac)_2]$, 3-CF_3-styrene	THF/NMP, −35 °C	[26]
n	Br, I	*n*-, *s*-R_xZnX_{2-x}	$[Ni(acac)_2]$, 4-F-styrene	Bu_4NI	[27]
n	Cl, Br, I, OTs	*n*-RZnX	$[Pd_2(dba)_3]/P(c\text{-}C_5H_9)_3$	NMI, NMP/THF, 80 °C	[29]
s	Br, I	*n*-RZnX	$[Ni(cod)_2]$/sBu–pybox	RT	[30]
n	Cl	ArMgX	$Pd(OAc)_2/PCy_3$	RT	[33]
n	Cl	ArMgX	$[\{Pd(IMes)(NQ)\}_2]$	RT	[35]
n, *s*	Cl, Br, I	ArMgX	$FeCl_3$	TMEDA, below RT	[37]
n	Br	$ArB(OH)_2$	$Pd(OAc)_2/PtBu_2Me$	KO*t*Bu, RT	[22d]
n, *s*	Br, I	$ArB(OH)_2$	$[Ni(cod)_2]$/bathophenanthroline	KO*t*Bu, 60 °C	[39]
n	I	ArZnX	$[Ni(acac)_2]$, 4-CF_3-styrene	THF/NMP	[40]
n	Br, I	$ArSi(OMe)_3$	$PdBr_2/PtBu_2Me$	Bu_4NF, RT	[43]
n, *s*	Br, I	$ArSiF_3$	$NiBr_2 \cdot$diglyme/bathophenanthroline	CsF, 60 °C	[44]
n	Br	$ArSnBu_3$, vinyl–$SnBu_3$	$[\{Pd(\eta\text{-}C_3H_5)Cl\}_2]/PCy(pyrr)_2$	Me_4NF, MS, RT	[46]
n	Cl, Br, I, OTs	vinyl–Zn	$[Pd_2(dba)_3]/P(c\text{-}C_5H_9)_3$	NMI, THF/NMP, 80 °C	[29]
n	Cl, Br, I, OTs	vinyl–Zr	$[Pd(acac)_2]$	LiBr, THF/NMP, 55 °C	[47]
n	Br, I	alkynyl–Cu	$[\{Pd(\eta\text{-}C_3H_5)Cl\}_2]$/CuI/IAdHCl	Cs_2CO_3, DMF/Et_2O, 45 °C	[48]
s	Cl, Br	CO	$PdBr_2$ (or $Pd(OAc)_2$, $[Pd_2(dba)_3]$) /PPh_3	NMP, LiBr, 80–120 °C, 20–100 bar	[63]

[a] IAd = 1,3-bis(adamantyl)imidazol-2-ylidene.

molecular mass, an excess of one reaction partner, and several additives. The progress made in the last few years in metal-catalyzed cross-coupling reactions of alkyl electrophiles with β hydrogen atoms makes us optimistic that the development of more efficient catalysts and reaction conditions might be expected in the near future. Furthermore, if selective (and even stereospecific) reactions with sterically hindered secondary and tertiary alkyl halides become possible, these cross-coupling methods will undoubtedly become part of the standard repertoire of synthetic organic chemistry for use in the synthesis of more complex molecules.

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