Nickel-Catalyzed Cross-Couplings of Unactivated Alkyl Halides and Pseudohalides with Organometallic Compounds

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Abstract: Until recently, there had been a widespread perception that unactivated, β-hydrogen-containing alkyl halides/pseudohalides are not suitable partners for nickel-catalyzed coupling reactions. During the past several years, a number of reports have dispelled this misconception by demonstrating that a diverse array of electrophiles and organometallic reagents can in fact be efficiently cross-coupled.

Keywords: alkyl halides; C–C coupling; homogeneous catalysis; nickel; synthetic methods

1 Introduction

Transition metal-catalyzed cross-coupling reactions have matured into powerful, selective, and high-yielding methods for the synthesis of organic compounds.[1] For example, C–C bond-forming processes, which are generally achieved through nickel or palladium catalysis, are now ubiquitous in both academia and industry. While remarkable advances have been described for couplings of aryl and alkenyl electrophiles (i.e., C_{sp^2}–X), as well as for certain activated alkyl (e.g., allylic, benzylic, and α-halocarbonyl) electrophiles, until recently, couplings of unactivated, β-hydrogen-containing alkyl electrophiles were rare.[2]

The comparative lack of success in cross-coupling alkyl electrophiles is often attributed to two problematic steps in the catalytic cycle (Figure 1).[2] First, oxidative addition of an alkyl electrophile to a metal catalyst is believed to generally be slower than the addition of an aryl or alkenyl electrophile. Second, if oxidative addition does indeed occur, the alkylmetal intermediate may undergo intramolecular β-hydride elimination more rapidly than intermolecular transmetalation.

For many years, these concerns appear to have strongly discouraged the pursuit of palladium- or nickel-catalyzed methods for cross-coupling alkyl electrophiles. Recently, however, a number of studies have clearly demonstrated that these potential problems are in fact surmountable.

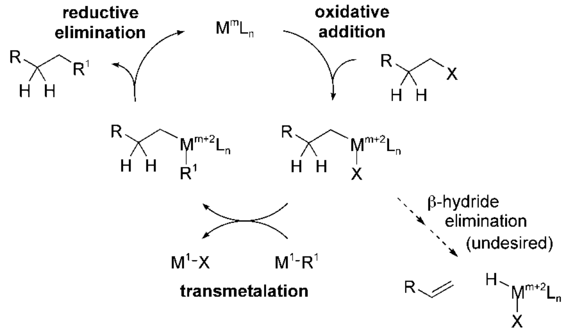

Figure 1. A possible pathway for a metal-catalyzed cross-coupling reaction of an alkyl electrophile.

Suzuki[3] provided the first examples of palladium- or nickel-catalyzed cross-couplings of unactivated, β-hydrogen-containing alkyl electrophiles. Specifically, he established that $Pd(PPh_3)_4$ catalyzes couplings of primary alkyl iodides with alkyl-, alkenyl-, and aryl-9-BBN reagents [Eq. (1)].

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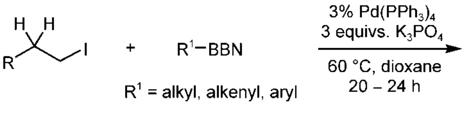
A native of Cobourg, Ontario, Canada, *Matthew Netherton* received his B.Sc. (Hons. Chemistry) in 1995 from the University of Western Ontario. Following this, he pursued his Ph. D. in organic chemistry at the University of British Columbia under the supervision of Prof. John Scheffer where he studied the relationship between the solid-state structure and photochemical reactivity of organic crystals, especially reactions involving asymmetric induction. In 2001, he moved to the Massachusetts Institute of Technology and began work as an NSERC postdoctoral fellow in the laboratory of Prof. Gregory Fu. His work at MIT included developing methods for the cross-coupling of alkylboranes with alkyl halides and tosylates, and the use of phosphonium salts as air-stable replacements for trialkylphosphine ligands in metal-catalyzed reactions. Dr. Netherton is currently a Senior Scientist in the Department of Medicinal Chemistry at Boehringer Ingelheim Pharmaceuticals in Ridgefield Connecticut.

Gregory C. Fu received a B. S. degree from MIT in 1985, where he worked in the laboratory of Prof. Barry Sharpless. After earning a Ph. D. from Harvard in 1991 under the guidance of Prof. David Evans, he spent two years as a postdoctoral fellow with Prof. Robert Grubbs at Caltech. In 1993, he returned to MIT, where he is currently a Professor of Chemistry. Professor Fu's research program has recently been focused on the chemistry of boron heterocycles, palladium- and nickel-catalyzed coupling processes, and the development of applications of planar-chiral heterocycles as enantioselective nucleophilic catalysts and as chiral ligands for transition metals.



(1)

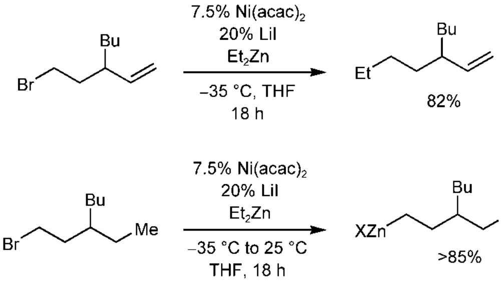
Since Suzuki's pioneering study, a variety of groups have described additional methods for cross-coupling alkyl electrophiles with the aid of palladium,[4–10] nickel, or other transition metal catalysts.[11–13] This review will focus specifically on nickel-based catalysts, highlighting the evolution of the methodology and its scope and limitations.

2 Negishi Couplings

2.1 Couplings of Primary Alkyl Halides

2.1.1 Key Initial Studies

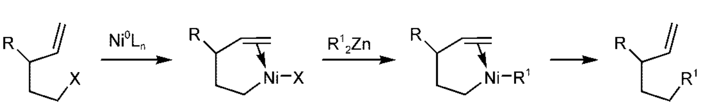
During studies of radical cyclizations using Et_2Zn, Knochel discovered that $Ni(acac)_2$/LiI serves as an efficient catalyst for C_{sp^3}–C_{sp^3} bond formation (Scheme 1, top).[14] A control experiment that employed the saturated analogue of the alkyl halide resulted only in bromine-zinc exchange (Scheme 1, bottom), thereby implicating the remote C=C double bond as a critical element for this new cross-coupling process.



Scheme 1. Divergent reactivity for an unsaturated *versus* a saturated alkyl bromide.

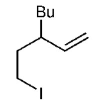
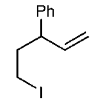
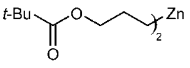
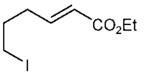
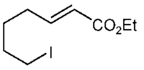
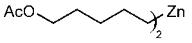
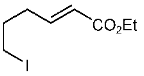
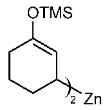
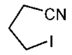
Knochel suggested that the divergence in reactivity is due to the formation of an intermediate Ni(II)-olefin complex that is amenable to transmetalation and reductive elimination (Scheme 2).[15] Furthermore, he postulated that the π-acidity of the olefin removes electron density from nickel and thereby facilitates reductive elimination.

Knochel demonstrated that $Ni(acac)_2$ serves as an effective cross-coupling catalyst for an array of unsaturated primary alkyl iodides with diorganozinc reagents [Eq. (2); Table 1]. Couplings can proceed in good-to-excellent yields both for three- and for four-carbon tethers



Scheme 2. Putative role of the olefin in Knochel's nickel-catalyzed cross-couplings of alkyl halides with alkylzinc reagents.

Table 1. Cross-couplings of primary alkyl iodides with diorganozinc reagents [Eq. (2)].

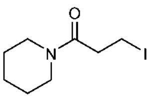
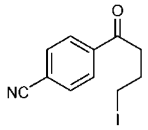
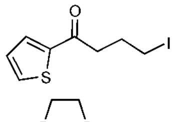
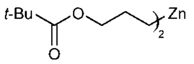
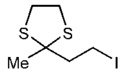
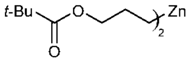
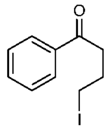
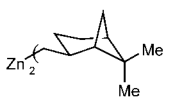
Entry	Alkyl Iodide	Diorganozinc	Yield [%]
1		n-pentyl$_2$Zn	72
2			90
3		n-pentyl$_2$Zn	83
4			78
5			65[a]
6		n-pentyl$_2$Zn	52[b]

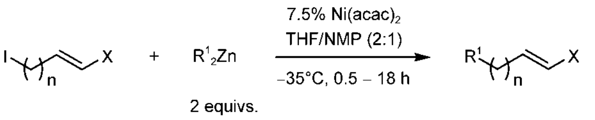
[a] The isolated product is the 3-substituted cyclohexanone, not the TMS enol ether.

[b] The reaction was carried out at −25 °C for 48 h.

between the iodide and the olefin. Functional groups such as esters and nitriles are compatible with the reaction conditions (entries 2–6), and secondary allylic zinc reagents are suitable cross-coupling partners (entry 5). For the reaction of 4-iodobutyronitrile that is illustrated in entry 6, the nitrile presumably fills a role analogous to that of the olefin in Scheme 2.

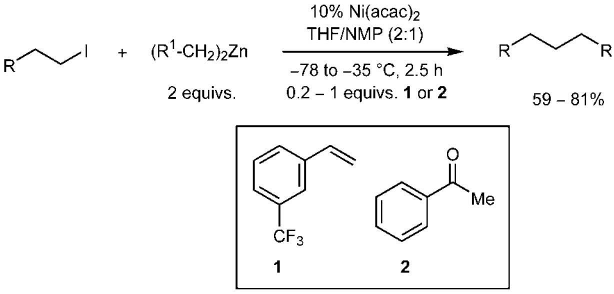
Table 2. Cross-coupling of primary alkyl iodides with primary diorganozinc reagents in the presence of a promoter [Eq. (3)].

Entry	Alkyl Iodide	Diorganozinc	Promoter (equivs.)	Yield [%]
1		n-pentyl$_2$Zn	**2** (1.0)	70
2		n-pentyl$_2$Zn	**1** (0.3)	81
3			**2** (0.5)	70
4			**1** (0.5)	70
5			**2** (1.0)	66



(2)

In order to expand the scope of these nickel-catalyzed couplings to alkyl iodides that lack a pendant olefin or nitrile, Knochel surveyed the effect of a variety of electron-poor arene, styrene, and ketone additives, anticipating that they might serve as substitutes for the olefin/nitrile, binding to nickel and activating it toward reductive elimination.[16] He found that additives such as 3-(trifluoromethyl)styrene or acetophenone (20–100 mol %) do indeed promote the cross-coupling of a variety of primary alkyl iodides with primary diorganozinc reagents in moderate to good yield [Eq. (3) and Table 2].

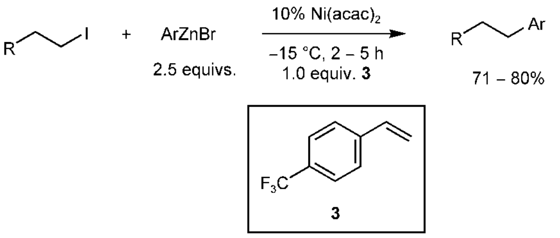


(3)

The method tolerates functionality such as tertiary amides (entry 1), ketones (entries 2, 3, and 5), esters (entries 3 and 4), and sulfur-containing groups (thiophenes: entry 3; 1,3-dithianes: entry 4). In addition, β-branched primary organozinc reagents can be cross-coupled (entry 5).

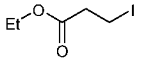
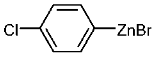
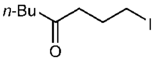
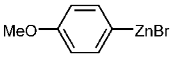
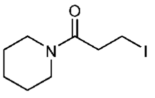
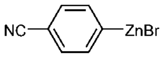
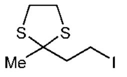
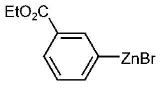
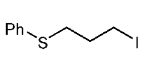
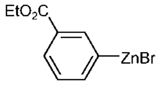
2.1.2 Subsequent Methods Development

While there are a number of examples of transition metal-catalyzed formation of C_{sp^2}–C_{sp^3} bonds through the coupling of an aryl/alkenyl halide with an alkylmetal compound,[1,17] there are few reports of the complementary transformation, coupling of an alkyl halide with an aryl-/alkenylmetal reagent. Building on the work described in the preceding section, Knochel developed a method that achieves cross-couplings of primary alkyl iodides with arylzinc bromides in good yield [Eq. (4), Table 3].[18]



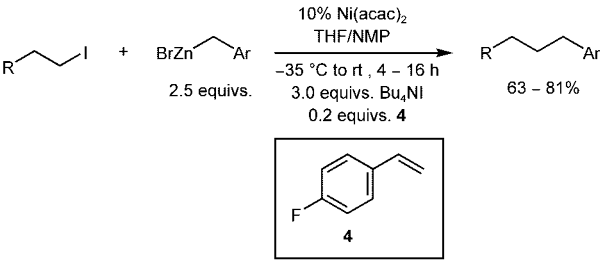
(4)

Table 3. Cross-coupling of primary alkyl iodides with arylzinc bromides in the presence of 4-(trifluoromethyl)styrene [Eq. (4)].

Entry	Alkyl Iodide	Arylzinc Bromide	Yield [%]
1			71
2			72
3			71
4			72
5			75

A stoichiometric quantity of an electron-deficient promoter [4-(trifluoromethyl)styrene] is required. As illustrated in Table 3, both electron-rich and electron-poor arylzinc species are suitable cross-coupling partners. The catalyst displays good functional-group compatibility, effecting coupling in the presence of esters (entries 1, 4, and 5), aryl chlorides (entry 1), ketones (entry 2), tertiary amides (entry 3), nitriles (entry 3), 1,3-dithianes (entry 4), and thioethers (entry 5).

In Knochel's early studies, he was unable to achieve cross-couplings of benzylzinc reagents with alkyl iodides. In 1999, while exploring palladium-catalyzed couplings of aryl and alkenyl triflates with organozinc halides, he discovered that the addition of Bu$_4$NI greatly enhances reaction efficiency.[19] By applying this promoter to nickel, Knochel could effect cross-couplings of primary alkyl iodides with benzylzinc bromides in good yield [Eq. (5), Table 4].



(5)

In a subsequent paper, Knochel established that Ni(acac)$_2$/4-fluorostyrene/Bu$_4$NI also achieves Negishi cross-couplings of secondary organozinc reagents and of primary alkyl bromides [Eq. (6) and Table 5].[20]

Table 4. Cross-coupling of primary alkyl iodides with benzylzinc bromides in the presence of 4-fluorostyrene and Bu$_4$NI [Eq. (5)].

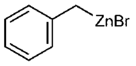
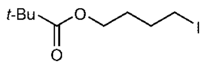
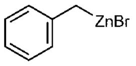
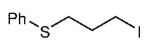
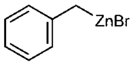
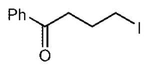
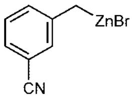
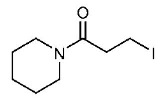
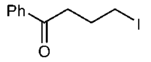
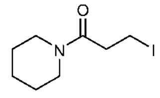
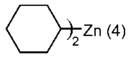
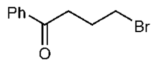
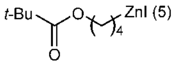
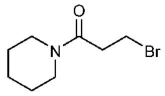
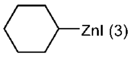
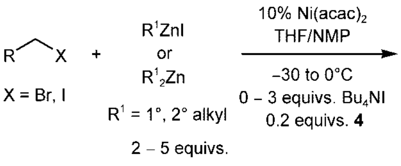
Entry	Alkyl Iodide	Benzylzinc Bromide	Yield [%]
1	*n*-octyl-I		77
2			81
3			63
4			74

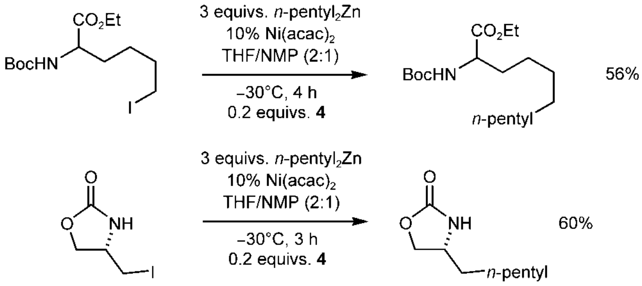
Table 5. Cross-coupling of primary alkyl bromides and iodides with primary and secondary organozinc reagents [Eq. (6)].

Entry	Alkyl Halide	Organozinc Reagent (equivs.)	Conditions (time; temp; Bu$_4$NI)	Yield [%]
1		*n*-pentylZnI (3)	30 h; 0 °C; 3 equivs.	62
2		*n*-pentylZnI (5)	30 h; 0 °C; 3 equivs.	71
3		*i*-Pr$_2$Zn (2)	3 h; -30 °C; 0 equivs.	63
4			16 h; -15 °C; 0 equivs.	73
5			20 h; -5 °C; 3 equivs.	73
6			16 h; -5 °C; 3 equivs.	63



(6)

The mechanism by which Bu$_4$NI enhances reactivity has not been fully elucidated. Knochel has suggested that coordination of iodide to the organozinc halide may lead to the formation of an 'ate' complex, which may be a more reactive transmetalating species, or that the rate acceleration may be due to an increase in the ionic strength of the medium. In any case, Knochel only employs Bu$_4$NI for couplings that involve organozinc hal-



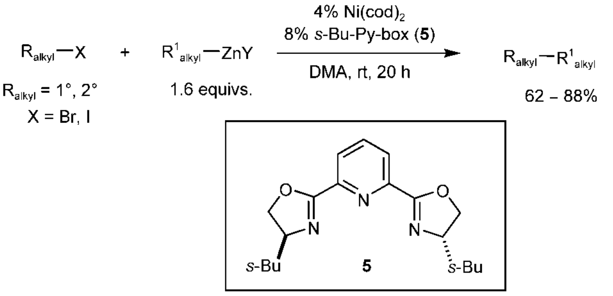
Scheme 3. Applications of Negishi cross-couplings of alkyl halides to generate C_{sp^3}–C_{sp^3} bonds.

ides, which are less reactive coupling partners than diorganozinc reagents.

Finally, Knochel has demonstrated the utility of nickel-catalyzed Negishi cross-couplings of alkyl halides in the preparation of amino acid and oxazolidinone derivatives (Scheme 3).

2.2 Couplings of Secondary Alkyl Halides

Through the work described above on Negishi reactions of primary alkyl halides, Knochel clearly established that nickel-catalyzed cross-couplings of unactivated, β-hydrogen-containing alkyl electrophiles can indeed be achieved. A next critical objective was to expand the scope of such processes to include *secondary* alkyl electrophiles. In 2003, Fu reported that Ni(cod)$_2$/(*s*-Bu-Py-box) catalyzes the room-temperature cross-coupling of a range of secondary (and primary) alkyl bromides and iodides with alkylzinc halides in moderate to good yield [Eq. (7), Table 6].[21]

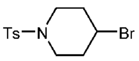
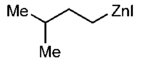
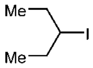
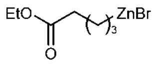
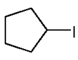
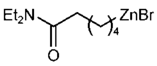
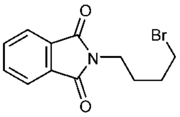
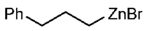
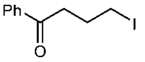
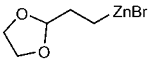
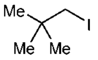
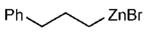


(7)

Among the ligands that were surveyed, only Py-box-based compounds were effective; a range of phosphines, as well as an N-heterocyclic carbene, failed to generate any product. The *s*-butyl-substituted Py-box provided a higher yield than Py-box ligands bearing larger (e.g., *t*-Bu) or smaller (e.g., *i*-Pr) groups. Fu has suggested that the chelating nature of the Py-box ligand may suppress ß-hydride elimination, which presumably requires a vacant coordination site on the alkylnickel intermediate. Nickel(II) complexes furnish lower yields than Ni(cod)$_2$, and Pd(0) or Pd(II) complexes afford no carbon-carbon bond formation.

As illustrated in Table 6, the reaction conditions are compatible with sulfonamides (entry 1), esters (entry 2), tertiary amides (entry 3), imides (entry 4), ketones (entry 5), and acetals (entry 5). Although neopentyl iodide does not possess ß hydrogen atoms, its reactivity is nonetheless noteworthy, due to its steric demand (entry 6).

Table 6. Cross-coupling of primary and secondary alkyl bromides and iodides with primary alkylzinc halides [Eq. (7)].

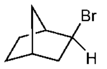
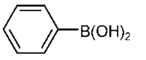
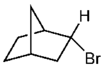
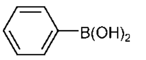
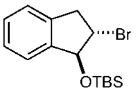
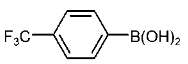
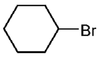
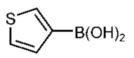
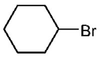
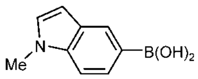
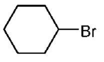
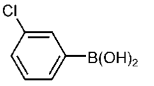
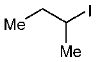
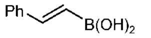
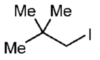
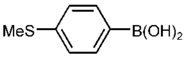
Entry	Alkyl Halide	Alkylzinc Halide	Yield [%]
1			66
2			62
3			78
4			65
5			74
6			73

3 Suzuki Couplings of Primary and Secondary Alkyl Halides with Unsaturated Boronic Acids

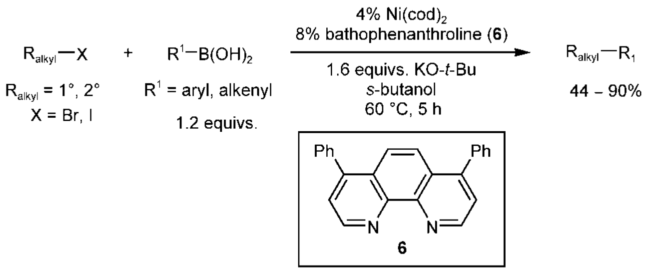
Among cross-coupling processes, Suzuki reactions are particularly widely used, as a consequence of attractive attributes such as the commercial availability of a broad array of functionalized boronic acids, the ease of use afforded by their stability to air and moisture, and their non-toxic nature.[1] Progress has recently been described for *palladium*-catalyzed Suzuki cross-couplings of unactivated primary, but not secondary, alkyl halides/pseudohalides.[4]

Fu has very recently reported that a nickel-based catalyst can achieve efficient couplings of secondary alkyl bromides and iodides with a variety of functionalized, unsaturated boronic acids in moderate to excellent yield [Eq. (8), Table 7].[22] Among the metal/ligand combinations that were examined, Ni(cod)$_2$/bathophenanthroline provided the most effective catalyst. In contrast to nickel-catalyzed Negishi couplings of secondary alkyl electrophiles (Section 2.2), Py-box ligands were ineffective for these Suzuki reactions, as were phosphines and Pd complexes.

Table 7. Suzuki cross-coupling of primary and secondary alkyl bromides and iodides with unsaturated boronic acids [Eq. (8)].

Entry	Alkyl Halide	Boronic Acid	Yield [%]
1			74[a] *exo* isomer
2			71[a] *exo* isomer
3			63[b] *trans* isomer
4			63
5			67
6			75
7			65
8			75

[a] The *exo* product is formed (>20:1 selectivity).
[b] The *trans* product is formed (>20:1 selectivity).

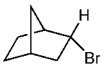
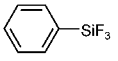
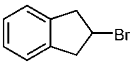
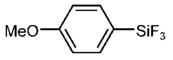
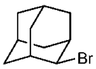
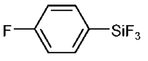
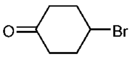
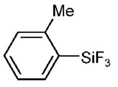
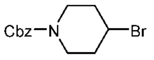
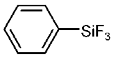
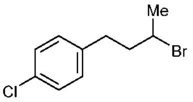
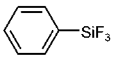
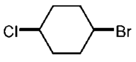
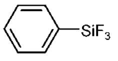
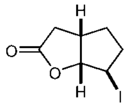
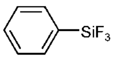
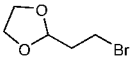
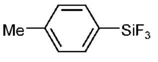
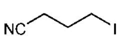
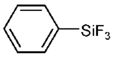


(8)

The boronic acid coupling partner can bear a wide range of functional groups (thiophenes, indoles, aryl chlorides, and sulfides) (Table 7); in contrast, Fu noted that the use of functionalized alkyl halides leads to lower yields. Under the reaction conditions described in Eq. (8), neither primary alkyl bromides nor alkylboronic acids undergo cross-coupling.

From a mechanistic standpoint, it is interesting that Suzuki reactions of *exo*- and *endo*-2-bromonorbornane (entries 1 and 2) both provide exclusively (>20:1) the *exo* product. These results are consistent with the formation of a radical intermediate during oxidative addition.[23–25] Similarly, in the case of entry 3, steric hindrance likely favors formation of a *trans* organonickel compound from the presumed radical precursor.

Table 8. Hiyama cross-coupling of primary and secondary alkyl bromides and iodides with trifluoroarylsilanes [Eq. (9)].

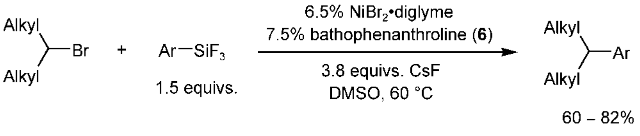
Entry	Alkyl Bromide	Aryl Silane	Yield [%]
1			70[a] *exo* isomer
2			71
3			68[b]
4			82
5			63
6			72
7			60[c] *cis/trans* mixture
8			60[d] *exo* isomer
9			80
10			73

[a] Starting material: *exo/endo* = 6/94; product: *exo/endo* = 95/5.
[b] 9% NiBr$_2$·diglyme, 10% bathophenanthroline.
[c] Starting material: *cis/trans* = 95/5; product: *cis/trans* = 55/45.
[d] 9% NiBr$_2$·diglyme, 10% bathophenanthroline; the starting material and the product are exclusively the *exo* isomer (>20:1).

4 Hiyama Couplings of Primary and Secondary Alkyl Halides with Trifluoroarylsilanes

Organosilanes are attractive substrates for cross-coupling reactions, for many of the same reasons mentioned above for organoboron reagents (ready availability, low toxicity, and high functional-group tolerance).[1] As for Suzuki reactions, previous work has established that palladium-based catalysts can achieve certain Hiyama couplings of primary, but not secondary, alkyl electrophiles.[8]

Fu has recently demonstrated that a nickel/bathophenanthroline-based catalyst can effect Hiyama reactions of trifluoroarylsilanes (which are easily prepared from trichloroarylsilanes)[26] with primary and secondary alkyl bromides and iodides [Eq. (9), Table 8].[27] Ligands that are structurally similar to bathophenanthroline, such as 1,10-phenanthroline and 2,2′-bipyridine, also furnish the desired cross-coupling product, albeit in lower yield. Importantly, in contrast to the Ni(cod)$_2$-based catalysts that have been described for Negishi and Suzuki couplings of secondary alkyl electrophiles, for Hiyama reactions, an air-stable Ni(II) complex, NiBr$_2$·diglyme, is used.



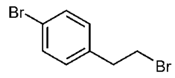
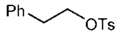
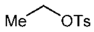
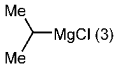
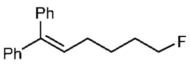
(9)

A variety of functional groups are compatible with the cross-coupling conditions, including ketones (entry 4), carbamates (entry 5), aryl chlorides (entry 6), alkyl chlorides (entry 7), lactones (entry 8), acetals (entry 9), and nitriles (entry 10). Interestingly, highly hindered 2-bromoadamantane (entry 3) is a suitable reaction partner. This result, along with the stereochemical data for several other cyclic alkyl halides (entries 1, 7, and 8), is consistent with the intervention of a radical intermediate during the oxidative addition step of the catalytic cycle.

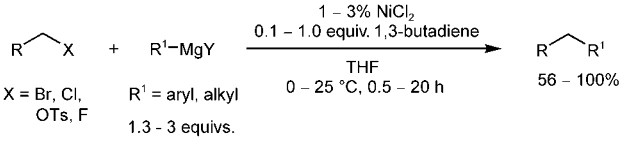
5 Kumada Couplings of Primary Alkyl Halides and Tosylates with Grignard Reagents

Two recent reports by Kambe describe nickel-catalyzed cross-couplings of alkyl- and aryl-Grignard reagents with primary alkyl bromides, chlorides, tosylates,[28] and fluorides[11c] [Eq. (10), Table 9]. The substrates are largely unfunctionalized, perhaps due to the high reactivity of Grignard reagents.[29] Entry 1 illustrates an interesting coupling of an alkyl bromide in preference to an aryl bromide.

Table 9. Kumada cross-coupling of primary alkyl bromides, chlorides, tosylates, and fluorides with Grignard reagents [Eq. (10)].

Entry	Alkyl Electrophile	Grignard Reagent (equivs.)	Conditions (% NiCl$_2$; % diene)	Yield [%][a]
1		*n*-BuMgCl (1.3)	1; 10	100
2		EtMgBr (1.3)	3; 30	87
3		PhMgBr (1.3)	3; 100	56
4	*n*-octyl-Br		3; 30	72
5	*n*-octyl-Cl	*n*-BuMgCl (2)	3; 50	96
6		*n*-PrMgBr[b]	3; 100	72

[a] Yield determined by GC.
[b] Amount of Grignard reagent not reported.



(10)

NiCl$_2$/1,3-butadiene furnishes the most effective catalyst. Other Ni(II)/diene combinations provide less of the cross-coupling product and more of compounds derived from ß-hydride elimination or disproportionation of an alkylnickel intermediate. Kambe has proposed that the catalytic cycle proceeds through Ni(II) and Ni(IV) species.

6 Conclusions and Future Outlook

During the past decade, noteworthy advances have been made toward the objective of developing general methods for metal-catalyzed cross-couplings of unactivated alkyl electrophiles. The perceived stumbling blocks of sluggish oxidative addition and relatively slow transmetalation have proved to be surmountable. At the present time, nickel-based catalysts have been shown to be effective for certain Negishi, Suzuki, Hiyama, and Kumada couplings of primary and secondary alkyl electrophiles. The recent rapid rate of progress is tremendously exciting; on the other hand, important challenges remain, including increasing the scope of these processes and developing asymmetric variants. Finally, in addition to investigations directed at methods development, it will be important to pursue studies that will furnish a better understanding of the mechanism(s) of these reactions.

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