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Direct $C(sp^2)$–$C(sp^3)$ Cross-Coupling of Diaryl Zinc Reagents with Benzylic, Primary, Secondary, and Tertiary Alkyl Halides[**]

*Jay J. Dunsford, Ewan R. Clark, and Michael J. Ingleson**

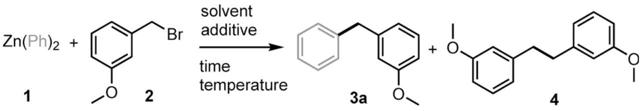
Abstract: *The direct $C(sp^2)$–$C(sp^3)$ cross-coupling of diaryl zinc reagents with benzylic, primary, secondary, and tertiary alkyl halides proceeded in the absence of coordinating ethereal solvents at ambient temperature without the addition of a catalyst. The $C(sp^2)$–$C(sp^3)$ cross-coupling showed excellent functional-group tolerance, and products were isolated in high yields, generally without the requirement for purification by chromatography. This process represents an expedient, operationally simple method for the construction of new $C(sp^2)$–$C(sp^3)$ bonds.*

The efficient construction of new carbon–carbon bonds is of the utmost importance for contemporary molecular synthesis.[1] In particular, the generation of new $C(sp^2)$–$C(sp^3)$ bonds is of great significance for the preparation of complex molecules.[2,3] Current state-of-the-art methods for the generation of $C(sp^2)$–$C(sp^3)$ bonds typically involve the use of alkyl electrophiles, organometallic nucleophiles, and palladium-[4–8] or nickel-based[9–13] (pre)catalysts. Complementary transition-metal-free approaches to $C(sp^2)$–$C(sp^3)$ bond formation have also emerged.[14] Despite these notable advances, challenges in cross-coupling still remain, including the development of a single system applicable to the cross-coupling of benzylic, primary, secondary, and tertiary alkyl halides with electron-rich, electron-deficient, and sterically hindered aryl nucleophiles.

In recent years there has been a conscious move towards the development of new cross-coupling methodologies with cheaper and more environmentally benign (pre)catalysts. Impressive advances have been made in this area with iron catalysts, particularly in the cross-coupling of alkyl electrophiles with organometallic nucleophiles.[15–20] Zinc systems for the generation of $C(sp^2)$–$C(sp^3)$ bonds from alkyl halides and aryl nucleophiles would also be particularly attractive owing to the low cost, low toxicity, and environmentally benign nature of zinc.[21] Although the utility of organozinc reagents in certain catalytic and stoichiometric carbon–carbon bond-forming reactions is well-established,[21,22] zinc systems that can activate alkyl halide electrophiles for subsequent cross-coupling are extremely limited. A recent study showed that zinc compounds are viable for the cross-coupling of alkyl halides with activated diboron reagents in the absence of additional catalysts in a radical-mediated process.[23] However, the direct, or zinc-catalyzed, coupling of aryl zinc nucleophiles with alkyl halides to form new $C(sp^2)$–$C(sp^3)$ bonds is to the best of our knowledge unknown beyond examples with allyl and propargyl halides.[24,25] Herein, we report on the solvent-dependent direct $C(sp^2)$–$C(sp^3)$ cross-coupling of diaryl zinc reagents with a wide range of benzylic, primary, secondary, and tertiary alkyl halides in an operationally simple manner.

During ongoing investigations into iron-catalyzed $C(sp^2)$–$C(sp^3)$ cross-coupling transformations and in particular the hydrocarbyl transmetalation step,[26] we became interested in the roles of additives, such as diaryl zinc reagents, in these transformations.[27,28] Control experiments examining the influence of diaryl zinc additives included the stoichiometric addition of diphenylzinc (**1**) to a prototypical electrophile, 3-methoxybenzyl bromide (**2**), in [D$_6$]benzene without a transition-metal catalyst. The outcome of this reaction was unexpected: within 5 min at ambient temperature, a colorless precipitate had separated from solution (presumably PhZnBr), and analysis of the soluble components by ^{1}H and ^{13}C{^{1}H} NMR spectroscopy revealed the complete consumption of **2** and the formation of a single new species, consistent with the $C(sp^2)$–$C(sp^3)$ cross-coupling product **3a** (Table 1, entry 1). The assignment of perprotio-**3a**, formed from **1** and

Table 1: Direct arylation of **2** with **1** in the presence/absence of additives.[a]



Entry	Solvent	T [°C]	t	Additive (equiv)	2	3a	4
1	C_6D_6	20	5 min	–	0	>99	0
2	C_6D_6	20	20 h	THF (10)	78	19	3
3	C_6D_6	60	20 h	THF (10)	11	65	24
4	C_6D_6	20	20 h	Et_2O (10)	50	50	0
5	C_6D_6	20	20 h	MTBE (10)	21	79	0
6	C_6D_6	20	1 h	THF (1)	85	14	1
7	C_6H_5Cl	20	20 min	–	0	>99	0

[a] Standard reaction conditions: diphenylzinc (99%; 22.0 mg, 0.1 mmol), 3-methoxybenzyl bromide (14.0 µL, 0.1 mmol), solvent (0.8 mL), ± additive (1 or 10 equiv).

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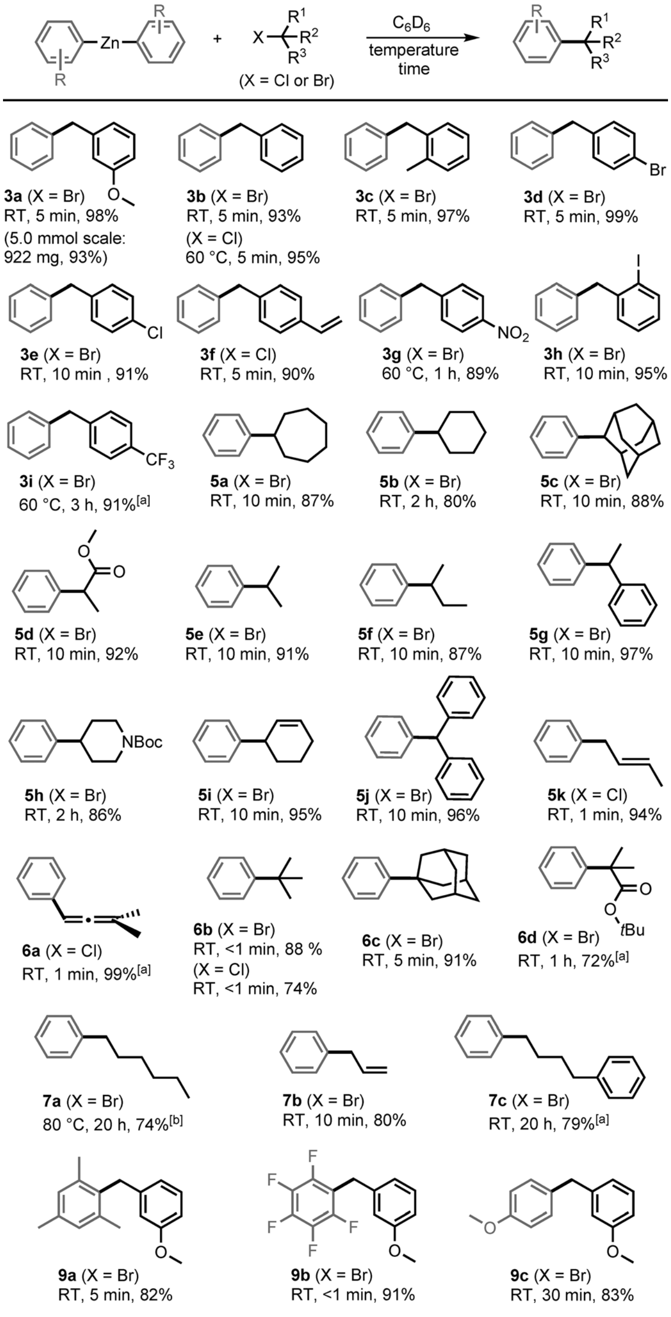
2, was also confirmed by GC–MS, thus ruling out any Friedel–Crafts benzylation of the [D$_6$]benzene solvent.[29] This outcome was extremely surprising, as in previous investigations of the stoichiometric arylation of 3-methoxybenzyl bromide with **1** in dioxane, essentially no cross-coupling product (3 %) was observed after 16 h at 60 °C.[30]

The influence of the solvent, particularly the use of an excess amount of a coordinating ethereal solvent, was subsequently investigated as the likely cause of the disparity between outcomes. The reaction between **1** and **2** in [D$_6$]benzene with the addition of THF (10 equiv) resulted in the drastic suppression of reactivity (Table 1, entry 2). After 20 h, only 19 % of the cross-coupling product **3a** was observed along with **2** (78 %) and 1,2-bis(3-methoxyphenyl)ethane (**4**; 3 %). An increase in the reaction temperature to 60 °C did lead to increased conversion into the cross-coupling and homocoupling products **3a** and **4** (65 and 24 %, respectively, after 20 h; Table 1, entry 3), but the reaction was still extremely slow relative to the analogous THF-free reaction. These observations suggest a strong solvent dependence, reinforced through reactivity suppression on the addition of either diethyl ether (10 equiv; Table 1, entry 4) or *tert*-butyl methyl ether (MTBE, 10 equiv; entry 5), albeit to a lesser extent. Remarkably, even the addition of a stoichiometric quantity of THF was sufficient to significantly retard the rate of the reaction (Table 1, entry 6). When the reaction was conducted in [D$_8$]toluene, the desired cross-coupled product **3a** (69 %) was formed along with two isomers derived from Friedel–Crafts benzylation of the [D$_8$]toluene solvent (31 %).[31] In contrast, use of the less nucleophilic aromatic solvent chlorobenzene led to only **3a** with comparable reactivity to that observed for the reaction in [D$_6$]benzene (Table 1, entries 1 and 7). However, owing to solubility issues the use of aliphatic hydrocarbon solvents was not possible. Notably, a decrease in the diphenylzinc concentration to 0.5 equivalents led to the generation of **3a** in 89 % yield in [D$_6$]benzene within 10 min; thus, both aromatic groups on **1** can be utilized for cross-coupling.[31] Furthermore, the employment of reagent-grade "wet" [D$_6$]benzene led to no decrease in the observed overall yield.

We were mindful of the fact that trace amounts of highly active late-transition-metal impurities can result in apparent "catalyst-free" cross-coupling protocols.[32] To probe the influence of trace impurities, we used diphenylzinc obtained from multiple sources and of varying purity; these reagents promoted comparable rapid cross-coupling.[31] Further analysis of the starting materials for trace metal impurities by inductively coupled plasma mass spectrometry (ICP-MS) revealed exceedingly low concentrations of common non-innocent trace impurities.[31] These results gave us confidence that trace metal impurities were not accountable for the observed reactivity; nevertheless, we examined this possibility further by the addition of palladium-, nickel-, copper-, and iron-based additives to a number of model systems under the standard conditions. All these transition-metal additives could be excluded as catalysts on the basis of either observed relative rates and/or product distribution relative to the additive-free protocol.[31] The observed reactivity is thus attributed to an uncatalyzed or zinc-catalyzed process, in line with a recent study of the use of zinc catalysis for the borylation of alkyl halides.[23]

Satisfied that the reactivity observed in the model reaction (Table 1, entry 1) was not impurity-driven, we evaluated the scope of this transformation with respect to the electrophile (Scheme 1). These reactions were all performed in [D$_6$]benzene simply to facilitate rapid analysis by in situ NMR spectroscopy. The heterocoupling of a range of benzylic

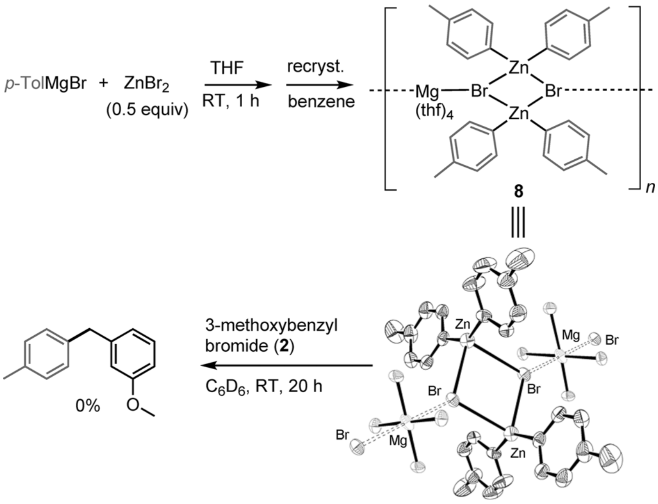


Scheme 1. Scope of the C(sp^2)–C(sp^3) cross-coupling of benzylic, primary, secondary, and tertiary alkyl halides with diaryl zinc reagents. Typical reaction conditions: diaryl zinc (0.25 mmol), alkyl halide (0.25 mmol), C$_6$D$_6$ (1 mL), ambient temperature, < 10 min. Yields reported are for the isolated product unless otherwise indicated. [a] The yield was determined by ^{1}H NMR spectroscopy. [b] The yield was determined by GC–MS. Boc = *tert*-butyloxycarbonyl.

halides (bromides or chlorides) with diphenylzinc (**1**) in [D$_6$]benzene led to diaryl methanes **3a**–**i** incorporating halide (Cl, Br, or I), ether, nitro, vinyl, and trifluoromethyl substituents in good to excellent yields (70–99 %). Remarkably, in the majority of cases short reaction times were sufficient (< 10 min) for complete conversion at ambient temperature, with reaction completion indicated by the precipitation of PhZnX (X = Br or Cl). After this time, simple filtration of the crude reaction mixture typically afforded the pure diaryl methane (as judged by GC–MS and NMR spectroscopy) without the necessity for chromatography or any further purification. It was also possible to scale up the synthesis of **3a** to 5.0 mmol without any significant erosion of the yield of the isolated product (93 %). In contrast to the addition of even a stoichiometric amount of an aliphatic ether, no significant reactivity suppression was observed with aryl ethers, as indicated by the comparable rates for the formation of **3a** and **3b**.

A range of secondary alkyl halide (bromide or chloride) substrates could also be effectively coupled with **1** at ambient temperature to generate compounds **5a**–**i** incorporating ester, vinyl, and *tert*-butyloxycarbonyl-protected amine functionalities in 86–97 % yield. Product **5j** was also isolated in excellent yield (96 %, < 10 min at ambient temperature), thus demonstrating the utility of this method for the generation of triaryl methanes, which are ubiquitous motifs in medicinal/biological chemistry.[33] The use of a secondary allylic electrophile, 3-chlorobut-1-ene, and a tertiary propargylic electrophile, 3-chloro-3-methyl-1-butyne, both led to S$_N$2′ products, with the formation of **5k** and **6a**, respectively. Although the latter two classes of electrophile have been previously coupled with aryl zinc reagents in THF, it is notable that under these etherate-free conditions cross-coupling with **1** requires only a stoichiometric amount of the electrophile and is complete within minutes versus 16 h with zincates in THF.[25] Tertiary alkyl halides were also readily coupled with **1** at ambient temperature in exceedingly short reaction times (< 5 min) to afford compounds **6b**–**d** bearing new quaternary centers in good to excellent yields (72–91 %). These results are remarkable, as C(sp^2)–C(sp^3) cross-coupling with tertiary alkyl halides is extremely challenging even using state-of-the-art transition-metal-catalyzed procedures.[34] Finally, we examined the propensity of primary alkyl halide substrates to undergo heterocoupling transformations with **1**. 1-Bromohexane could be coupled with **1** to afford **7a** in 74 % yield, but this transformation required heating at 80 °C for 20 h. After 20 h the complete consumption of 1-bromohexane was observed with the remaining mass balance (26 %) made up by internal isomerization cross-coupled products.[31] These reactions were all performed in [D$_6$]benzene. Clearly, the use of less toxic solvents is highly desirable, and we re-emphasize that chlorobenzene is also a viable solvent for this process (for example, **3a**, **5a**, and **6c** were all isolated in high yields when chlorobenzene was used as the solvent with the reaction carried out on a 1 mmol scale and at the higher concentration of 1 M).[31]

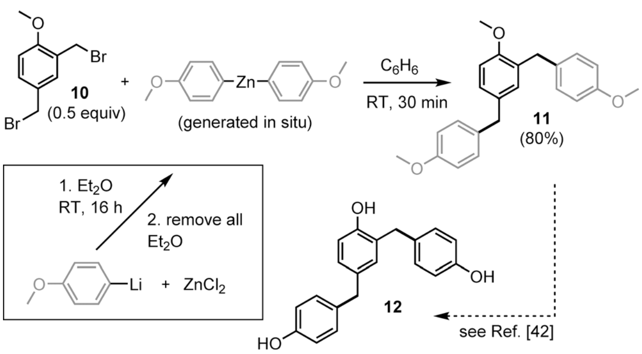
We next sought to extend the range of nucleophilic diaryl zinc reagents for this reaction by using 3-methoxybenzyl bromide (**2**) as the model electrophile. We initially attempted to form diaryl zinc reagents in THF from Grignard reagents, and in our hands this approach resulted in the isolation of ionic zincates. For example, attempts to form di(*p*-tolyl)zinc from *p*-TolMgBr (1 M in THF) and ZnBr$_2$ in THF led instead to the isolation of the zincate species **8** (identified by X-ray crystallography, Scheme 2). In [D$_6$]benzene, **8** exists as a single species displaying one set of THF and *p*-tolyl resonances in the ^{1}H NMR spectrum, which is comparable to that previously reported for [Zn(*p*-tolyl)$_3$]$^-$[(Mg$_2$(μ-Cl)$_3$(THF)$_6$]$^+$ by Hevia et al.[35] Although there is growing evidence that zincates are active (and possibly crucial)[36–38] nucleophiles in transition-metal-catalyzed cross-coupling in more polar solvents (including THF), the combination of 3-methoxybenzyl bromide (**2**; 2 equiv, 1 equiv per Zn atom) and **8** in [D$_6$]benzene led to no cross-coupling even after extended periods (20 h). This outcome is significant given that the generation of diaryl zinc reagents from Grignard reagents in situ in THF is a standard process.



Scheme 2. Synthesis of zincate species **8** and its reactivity with **2** under the standard cross-coupling conditions. An ORTEP representation of part of the extended solid-state structure of **8** is shown with ellipsoids at 50% probability. Hydrogen atoms and solvent molecules (benzene) have been omitted for clarity; THF molecules have also been simplified to oxygen atoms for clarity.

The lack of cross-coupling using zincate **8** led us to target bona-fide examples of etherate-free diarylzinc reagents, a family of compounds that are relatively scarce within the literature.[39,40] Dimesitylzinc had been generated previously in an etherate-free form from mesitylmagnesium bromide and ZnCl$_2$ in THF.[41] Pleasingly, the combination of dimesitylzinc with **2** in [D$_6$]benzene led to rapid cross-coupling to form **9a** in high yield (82 %), with the rate of reaction not appreciably diminished for this sterically hindered diaryl zinc reagent (Scheme 1). Other etherate-free diaryl zinc reagents could be generated by lithium/halogen exchange (with *n*BuLi) and subsequent zincation with ZnCl$_2$ in diethyl ether; all diethyl ether was subsequently removed in vacuo (5×10^{-2} mbar, ambient temperature, 2–5 h). Etherate-free diaryl zinc reagents incorporating aromatic groups with electron-withdrawing and electron-donating substituents also underwent cross-coupling cleanly to afford the desired products **9b** and **9c** in high yields (91 and 83 %, respectively). In each case the aryl zinc halide by-product precipitated from benzene, thus enabling facile assessment of reaction completion.

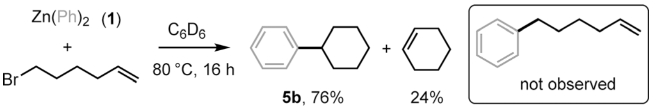
To further demonstrate the utility of this protocol, we synthesized, without the aid of a glove box, a precursor to naturally occurring 2,4-bis(4-hydroxybenzyl)phenol (**12**; Scheme 3).[42] Compound **12** was recently reported to be an inhibitor of heat shock transcription factor 1 and enhance the effectiveness of conventional anticancer agents (e.g., cisplatin and paclitaxel).[43] Di(*p*-anisole)zinc was generated in situ by lithium/halogen exchange of 4-bromoanisole with *n*BuLi in anhydrous diethyl ether followed by zincation with $ZnCl_2$. After filtration and removal of all volatiles in vacuo (5×10^{-2} mbar, ambient temperature, 3 h), the resultant white microcrystalline solid was taken up in anhydrous benzene prior to the addition of 2,6-di(bromomethyl)anisole (**10**; 0.5 equiv). Compound **11** was formed as the major product within 30 min at ambient temperature.



Scheme 3. Glove-box-free synthesis of a precursor to naturally occurring 2,4-bis(4-hydroxybenzyl)phenol.

Regarding the mechanism of this novel cross-coupling protocol, we made a number of preliminary observations. The degree of cross-coupling suppression on the addition of ethereal solvents increased as the ether became more nucleophilic (with THF having the most pronounced effect of the ethers studied to date). This trend suggests that coordination of the alkyl halide with the diaryl zinc reagent is a key step, whereby ethers are more nucleophilic towards diaryl zinc reagents than alkyl halides, thus disfavoring the formation of a $Ph_2Zn(X{-}alkyl)_n$-type species. This hypothesis is supported by calculations (at the M06-2X/6-311G + (d,p)/PCM(benzene) level), which indicate that the coordination of THF to **1** is energetically 5.3 kcal mol^{-1} more favored than the binding of the benzyl bromide to **1**. Qualitative comparison of the relative rates of cross-coupling for various diaryl zinc reagents is also informative. The employment of di(pentafluorophenyl)zinc led to complete conversion into the corresponding diaryl methane **9b** within 1 min at ambient temperature, whereas di(*p*-anisole)zinc gave a reduced rate of reaction (30 min), and diphenylzinc displayed intermediate reactivity (5 min). This observation is consistent with an increase in the relative Lewis acidities of the diaryl zinc reagents from Zn(*p*-anisole)$_2$ to $ZnPh_2$ to $Zn(C_6F_5)_2$. This trend was confirmed by the increased magnitude of the downfield shift in the ^{31}P NMR signal ($\Delta\delta$) on the coordination of Et_3PO to the diaryl zinc reagent, which also followed the expected order of increasing Lewis acidity: $Zn(C_6F_5)_2 > ZnPh_2 >$ Zn(*p*-anisole)$_2$.[31] As previously mentioned, the less coordinating aryl ethers (relative to aliphatic ethers) did not display any appreciable rate retardation. An increase in Lewis acidity at zinc can be expected to favor the formation of adducts of the type $(aryl)_2Zn(X{-}alkyl)_n$ and is also consistent with the observed coupling suppression with the halide-bridged zincate species **8**. Attempts to observe any $(aryl)_2Zn(X{-}alkyl)_n$ species in solution by multinuclear NMR spectroscopy and DOSY NMR spectroscopy upon the treatment of 1-bromohexane with **1** or $Zn(C_6F_5)_2$ at ambient temperature were, however, inconclusive.[31]

The recent zinc-catalyzed borylation of alkyl halides was proposed to be mediated by radical intermediates.[23] This $C(sp^2){-}C(sp^3)$ cross-coupling protocol also appears to be mediated by radical intermediates, as indicated by the observation of the bibenzyl homocoupling product as a minor product (8 %) in the formation of **3i**.[31] The use of the radical probe 6-bromo-1-hexene in cross-coupling with **1** in benzene further supported the intermediacy of radical species in this process, with the major product being phenylcyclohexane (**5b**) derived from an *endo* radical cyclization of a radical intermediate (Scheme 4). No linear cross-coupling product or (cyclopentylmethyl)benzene derived from an *exo* radical cyclization were observed. It is, however, interesting to note that the attempted trapping of radical intermediates in the model reaction with 9,10-dihydroanthracene (8 equiv)[23] failed, and quantitative cross-coupling was observed within 10 min at ambient temperature.[31] Radical-mediated alkylation reactions with zinc reagents are documented, including examples initiated by the coordination of Lewis bases to ZnR_2.[44–46] Thus, it is feasible that $R_2Zn(X{-}alkyl)_n$ intermediates result in a related radical alkylation pathway. Additional mechanistic studies are currently under way to examine this process further.



Scheme 4. Preliminary mechanistic experiment consistent with radical-mediated reactivity.

In summary, from the initial unexpected discovery of cross-coupling between diphenylzinc and 3-methoxybenzyl bromide in [D$_6$]benzene, we have developed an operationally simple and efficient method for the direct $C(sp^2){-}C(sp^3)$ cross-coupling of diaryl zinc reagents with benzylic, primary, secondary, and tertiary alkyl halides. Reactivity was found to be highly solvent dependent, with the presence of even one equivalent of a coordinating ethereal solvent being exceedingly detrimental to subsequent reactivity. Preliminary mechanistic studies suggest Lewis acidity at zinc is important, and that the coupling involves radical species. Investigations are ongoing in our laboratory with regard to mechanism elucidation as well as the extension of the reaction to a broader range of substrates.

Keywords: alkyl halides · cross-coupling · organozinc reagents · synthetic methods · zinc

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