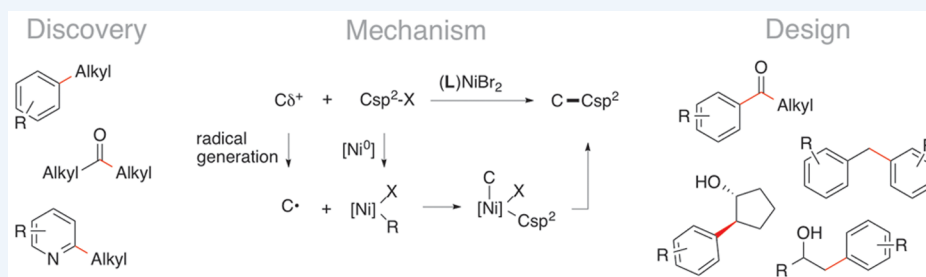# Methods and Mechanisms for Cross-Electrophile Coupling of Csp^2 Halides with Alkyl Electrophiles

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CONSPECTUS: Cross-electrophile coupling, the cross-coupling of two different electrophiles, avoids the need for preformed carbon nucleophiles, but development of general methods has lagged behind cross-coupling and C−H functionalization. A central reason for this slow development is the challenge of selectively coupling two substrates that are alike in reactivity. This Account describes the discovery of generally cross-selective reactions of aryl halides and acyl halides with alkyl halides, the mechanistic studies that illuminated the underlying principles of these reactions, and the use of these fundamental principles in the rational design of new cross-electrophile coupling reactions.

Although the coupling of two different electrophiles under reducing conditions often leads primarily to symmetric dimers, the subtle differences in reactivity of aryl halides and alkyl halides with nickel catalysts allowed for generally cross-selective coupling reactions. These conditions could also be extended to the coupling of acyl halides with alkyl halides. These reactions are exceptionally functional group tolerant and can be assembled on the benchtop.

A combination of stoichiometric and catalytic studies on the mechanism of these reactions revealed an unusual radical-chain mechanism and suggests that selectivity arises from (1) the preference of nickel(0) for oxidative addition to aryl halides and acyl halides over alkyl halides and (2) the greater propensity of alkyl halides to form free radicals. Bipyridine-ligated arylnickel intermediates react with alkyl radicals to efficiently form, after reductive elimination, new C−C bonds. Finally, the resulting nickel(I) species is proposed to regenerate an alkyl radical to carry the chain.

Examples of new reactions designed using these principles include carbonylative coupling of aryl halides with alkyl halides to form ketones, arylation of epoxides to form β-aryl alcohols, and coupling of benzyl sulfonate esters with aryl halides to form diarylmethanes. Arylnickel(II) intermediates can insert carbon monoxide to form acylnickel(II) intermediates that react with alkyl halides to form ketones, demonstrating the connection between the mechanisms of reactions of aryl halides and acid chlorides with alkyl halides. The low reactivity of epoxides with nickel can be overcome by the use of either titanium or iodide cocatalysis to facilitate radical generation and this can also be extended to enantioselective arylation of *meso*-epoxides. The high reactivity of benzyl bromide with nickel, which leads to the formation of bibenzyl in attempted reactions with bromobenzene, can be overcome by using a benzyl mesylate along with cobalt phthalocyanine cocatalysis to convert the mesylate into an alkyl radical.
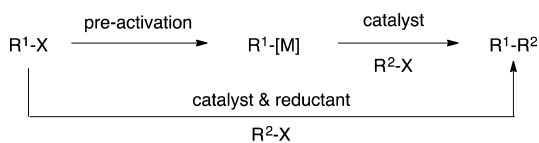
■ INTRODUCTION

While the synthesis of molecules has been made easier by the advent of the cross-coupling of carbon nucleophiles with carbon electrophiles, there are fewer carbon nucleophiles listed as commercially available than carbon electrophiles. As a consequence, the development of improved methods for the synthesis of organometallic reagents and cross-coupling methods that avoid preformed organometallic reagents have become important research areas. One method that avoids the need for carbon nucleophiles is the direct coupling of two different carbon electrophiles: cross-electrophile coupling

(Figure 1).[1−3] Although reductive dimerizations of electrophiles were among the earliest reactions known with metals (Wurtz;[4] Ullman and Bielecki[5]), general methods for the cross-coupling of electrophiles have lagged far behind cross-couplings of nucleophiles with electrophiles or even C−H functionalization.

One of the reasons for this slow development is the challenge of selectively forming the cross-product over the two possible

Figure 1. Cross-electrophile coupling (bottom) versus cross-coupling (top).

Figure 3. Generally selective cross-electrophile reactions were envisioned to be possible between Csp^2-X and Csp^3-X bonds because the mechanisms of oxidative addition are different.

symmetric dimers (Figure 2).[1] Unlike in cross-coupling of nucleophiles with electrophiles, where one component favors oxidative addition and the other favors transmetalation, in cross-electrophile coupling the two electrophiles must always compete for oxidative addition at the catalyst. In cases where the electrophiles are very alike, this results in statistical mixtures of products. In cases where one electrophile is much more reactive, the more reactive substrate will rapidly be converted to the symmetric dimer first, followed by slow conversion of the less reactive substrate to its symmetric dimer.
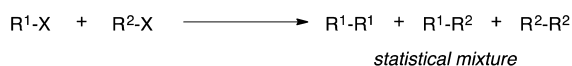
While some reports had already appeared toward this goal, and the cross-coupling of nucleophiles with electrophiles had been routine for decades, cross-electrophile coupling was still nascent when our studies began in 2008.[1–3,6–9] This Account will focus on our studies of one class of cross-electrophile coupling reaction, the coupling of Csp^2 halides with Csp^3 halides. The development from discovery of general conditions, to understanding of the origin of the cross-selectivity, to applying that understanding to design new reactions serves as a road map for future studies.

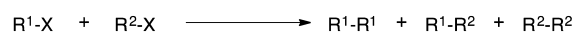## ■ INITIAL DISCOVERY OF THE COUPLING OF ARYL IODIDES WITH ALKYL IODIDES

As an initial target, we examined the coupling of unactivated alkyl halides with aryl halides. This choice was a consequence of two observations: (1) the formation of Csp^2-Csp^3 bonds remains a challenge[10,11] and (2) the mechanism of oxidative addition differs for Csp^2-X bonds and for Csp^3-X bonds (Figure 3).[12] The different mechanisms of oxidative addition seemed especially important if the reaction was going to tolerate a wide range of substrate electronics and sterics.

Initial studies focused on nickel and palladium catalysts as well as combinations of the two catalysts. This was because previous studies had shown that both metals were effective catalysts for the formation of Csp^2-Csp^3 bonds and that their selectivity for oxidative addition appeared to be different. Palladium prefers Csp^2-X bonds in most cases[10,13,14] while nickel has been shown to couple alkyl halides efficiently.[15,16] A mixed Pd/Ni system provided a starting point yield (~10% of cross product) and follow-up studies showed that omitting the palladium led to similar results (Scheme 1).[17]
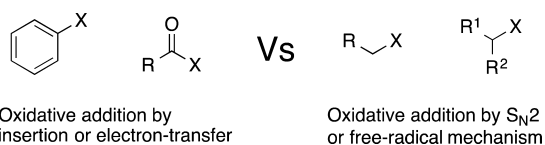
Scheme 1. Early Stoichiometric and Catalytic Results

Refinement of these initial results into a catalytic system required a number of adjustments, including the discovery that the synergistic combination of a bipyridine nickel catalyst and a bisphosphine nickel catalyst resulted in improved yields.[18] While bipyridine-ligated nickel alone could achieve high yields in select cases, cross-selectivity was generally lower. The bisphosphine nickel catalyst diminished the amount of aryl dimer observed substantially through an unknown mechanism, but was a poor catalyst by itself. The major challenge in this new two-ligand nickel system was not cross-selectivity, which was generally high, but β-hydride elimination. This was substantially diminished by the addition of pyridine as a coligand. The reaction was tolerant of protic substrates, and C–B bonds were not reactive under these conditions. Not only unhindered primary, but secondary and neopentyl alkyl halides could also be coupled with aryl iodides (Scheme 2).

Scheme 2. Substrate Scope of the Coupling of Aryl Halides with Alkyl Halides

Equal reactivity of substrates

R^1-X + R^2-X ⟶ R^1-R^1 + R^1-R^2 + R^2-R^2

statistical mixture

R^1-X more reactive than R^2-X
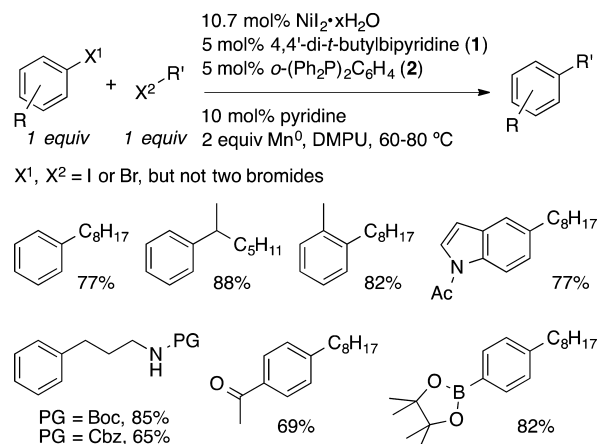
R^1-X + R^2-X ⟶ R^1-R^1 + R^1-R^2 + R^2-R^2

R^1-R^1 formed first
R^2-R^2 formed second
incidental R^1-R^2 formed

**Figure 2.** Challenges of cross-electrophile coupling.

■ COUPLING OF ARYL BROMIDES WITH ALKYL BROMIDES

Adjustment of the catalyst and conditions were required to enable the coupling of aryl bromides, vinyl bromides, and activated aryl chlorides with alkyl bromides because our original conditions were poorly selective for the coupling of two organic bromides. Although we did not yet understand the mechanism of the reaction, it was evident that alkyl bromides were slower to react than alkyl iodides, resulting in the formation of biaryl from disproportionation of a supposed arylnickel intermediate. Based on this hypothesis, we added iodide to the reaction to convert the recalcitrant alkyl bromide into a more reactive alkyl iodide.[19,20] In addition, we found that zinc was the better-performing reducing agent and a single nickel bipyridine or phenanthroline catalyst would suffice at a catalyst loading of 5−10 mol %.[21] A wide variety of functional groups were tolerated, but functional groups prone to reduction, such as a nitro group or an azide, were not tolerated (Scheme 3).

Under the optimized conditions in Scheme 3, we found that zinc was superior to manganese (77% yield vs 39% yield). This contrasts with our original results with organic iodides, where manganese was superior (Scheme 2).[18] This difference is not attributable to the reductant alone, because before optimization with zinc the advantage was smaller (~15% yield). In general, a variety of electron-sources work, even an organic reductant (vide infra), suggesting that reducing power of the reductant alone is not the only important factor. A decisive role may be played by the different MX_2 salts (ZnX_2, MnX_2, and $[TDAE]^{2+}X_2$) formed in the reactions, which have been shown to have profound effects in other cross-coupling reactions.[22]

In addition to aryl bromides, activated aryl chlorides could be coupled with alkyl bromides, but only if the additional iodide was omitted (eq 1). In these reactions, it appeared that in situ formation of an alkyl iodide was not beneficial, likely because
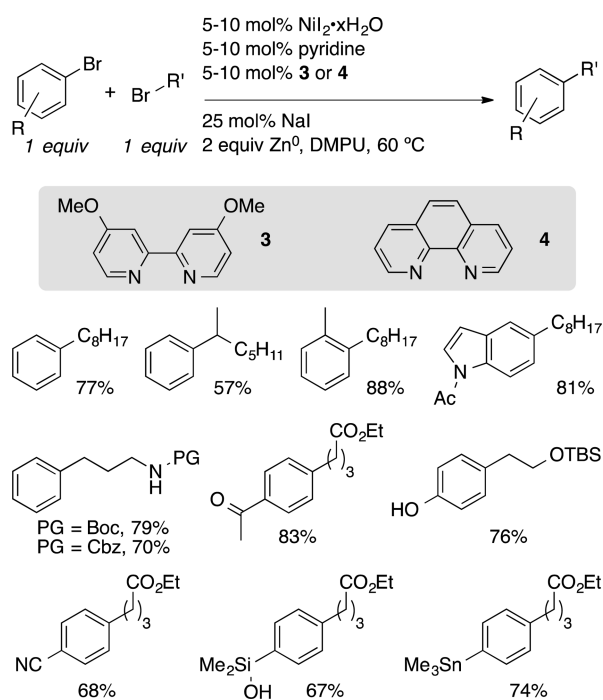
(1)
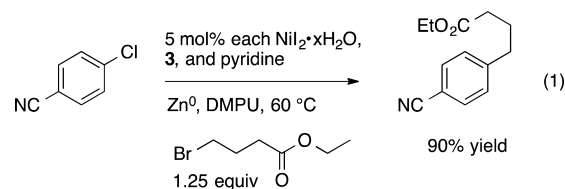
alkyl iodides are more reactive than aryl chlorides (see mechanism discussion below). In some cases, activated aryl chlorides provided higher yields than the corresponding reactions with aryl bromides (eq 1 versus Scheme 3).

The state and activation of the reducing agent was also examined for the first time. While a variety of commercial zinc sources were satisfactory (zinc dust, zinc powder, zinc flake), we found that some, presumably older, zinc led to sluggish reactions. Activity could be restored by mild activation with HCl or by activation with TMS-Cl and dibromoethane.[23] These results suggested that reduction of nickel needed to be relatively fast for the cross-coupling to take place with high efficiency. It was possible, however, to "over-activate" the zinc through extended washing with HCl. In these reactions, we observed increased amounts of hydrodehalogenation, suggesting that direct insertion of zinc into C−X bonds was detrimental.

While examining the scale-up of this reaction (eq 2),[24] we noticed that the reactions were resilient to water and oxygen. Up to 1000 ppm of water in the DMPU solvent did not change the yield or selectivity of the reaction.[21] While the presence of some oxygen in the headspace of reactions did not prevent high yields or selectivity, it did result in long induction periods. Excessive amounts of oxygen led to incomplete conversion. These results suggested that the nickel catalyst reacts with oxygen before it participates in the cross-coupling reaction, but that this process does not destroy the catalyst.

A comparison of the two published sets of conditions is illuminating: while the conditions in Scheme 3 are superior for the coupling of two bromides or couplings with aryl chlorides, the conditions in Scheme 2 are superior for couplings involving at least one organic iodide (Table 1).

## ■ COUPLING OF ACYL HALIDES AND THIOESTERS WITH ALKYL IODIDES

While several reports on the coupling of acid chlorides with benzylic halides[25−27] and alkyl iodides with pyridyl carboxylates[28] were already in the literature, a general method for coupling carboxylic acid derivatives with unactivated alkyl halides had not been reported. Building from our success with aryl halides, we found general conditions that tolerated a wide array of functional groups and steric hindrance on the carboxylic acid (Scheme 4).[29] Unlike the previous reactions, couplings with acid chlorides proceeded even at 0 °C, possibly due to activation of the manganese by the acid chloride or liberated HCl.

Scheme 3. Scope of the Coupling of Aryl Bromides with Alkyl Bromides

(2)
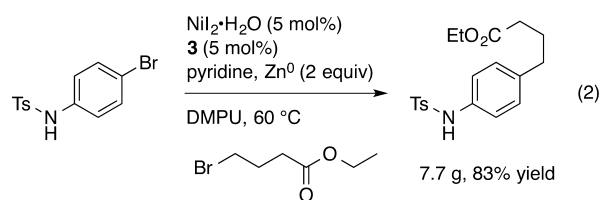
Table 1. Comparison of Conditions for Coupling Aryl Halides with Alkyl Halides[18,21]

entry	substrates	yield (%) as in Scheme 2[a]	yield (%) as in Scheme 3[b]
1	Ar–I + I–alkyl	**88**	49
2	Ar–Br + Br–alkyl	65	77
3	Ar–Br + I–alkyl	77	45
4	Ar–I + Br–alkyl	**85**	61

[a]Conditions as in Scheme 2. Yield is corrected GC yield. [b]Conditions as in Scheme 3. Yield is corrected GC yield.

Scheme 4. Nickel-Catalyzed Coupling of Acid Chlorides with Alkyl Iodides
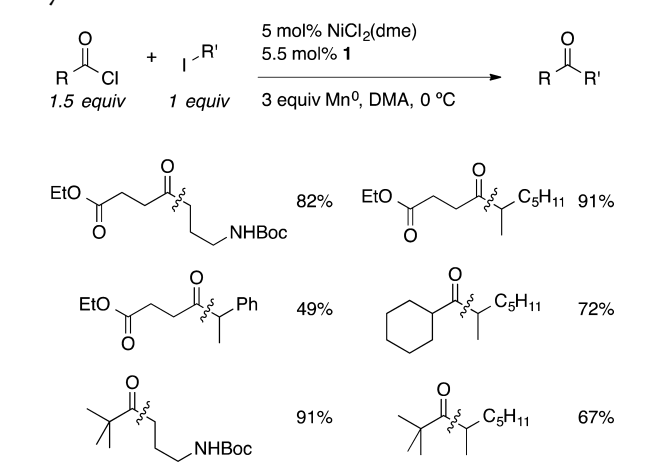
While acyl halides are convenient and affordable, a coupling partner that could be made directly from a functionalized carboxylic acid and is stable to chromatography would be synthetically useful. After a survey of several candidates, we found that 2-pyridyl thioesters were a convenient solution to this challenge.[30] The key change to the conditions was the use of zinc instead of manganese as the reductant to minimize *S*-alkylation of the liberated thiolate. As an example of the utility of 2-pyridyl thioesters, we were able to couple free biotin to an alkyne-containing alkyl iodide to form a highly functionalized biotin conjugate in just two steps (Scheme 5).

Scheme 5. Nickel-Catalyzed Coupling of 2-Pyridyl Thioesters with Alkyl Iodides
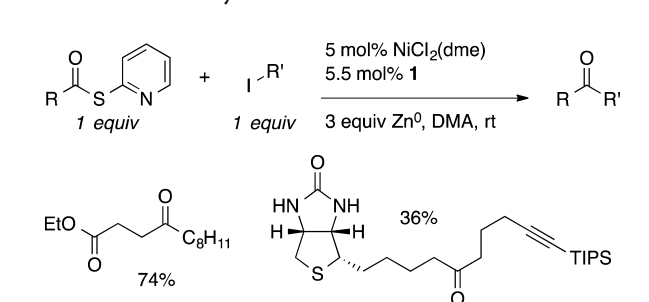


COUPLING OF 2-CHLOROPYRIDINES WITH ALKYL HALIDES

At the time we started examining the coupling of nitrogen heteroarenes with alkyl halides, relatively few examples of the coupling of 2-halopyridines with alkyl halides had been published[31] and our published conditions produced a low yield of product (one example, 26% yield).[21] After an examination of several different ligands, we found that bathophenanthroline enhanced the yield of product formed from 2-chloropyridines and alkyl bromides (Scheme 6).[32] Intriguingly, the very slow coupling of 2-chloro-4-trifluoromethylpyridine with an alkyl bromide could be dramatically accelerated by adding 10 mol % AIBN (from 48 to 19 h). This experiment had been informed by our ongoing mechanistic studies (vide infra) and is consistent with a radical initiation process.
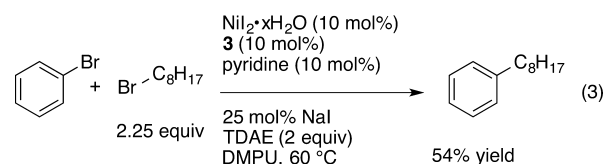
MECHANISM OF THE COUPLING OF ARYL HALIDES WITH ALKYL HALIDES

While the reactions reported above were general and selective in many cases, some substrates were not selective, such as the couplings of unactivated aryl chlorides (e.g., chlorobenzene), benzylic bromides, and epoxides. Furthermore, the discovery of improved conditions or new reactions remained largely Edisonian. Mechanistic studies were undertaken based upon the conviction that an understanding of the principles underlying selective cross-electrophile coupling reactions would enable us to design new reactions.

Early mechanistic studies established that the coupling could be conducted with the organic reductant tetrakis-(dimethylamino)ethylene (TDAE) in place of zinc or manganese, suggesting that organozinc or organomanganese reagents were not playing a major role in the observed chemistry (eq 3).[18,21] The yield of 54% compares favorably to analogous reactions with zinc (77%) and manganese (39%). A larger amount of alkyl bromide was needed because some of it appears to be lost to a side reaction with dimethylamine liberated by decomposition of TDAE.

Later experiments led us to formulate a radical chain mechanism (Scheme 7) inspired by a proposal by Hegedus and Miller for the stoichiometric reactivity of allylnickel reagents[33] and consistent with one of two mechanisms proposed by Durandetti et al. for closely related chemistry.[34] While our initial study focused on the coupling of aryl iodides with alkyl

**Scheme 6. Coupling of 2-Chloropyridines with Alkyl Bromides**

(3)
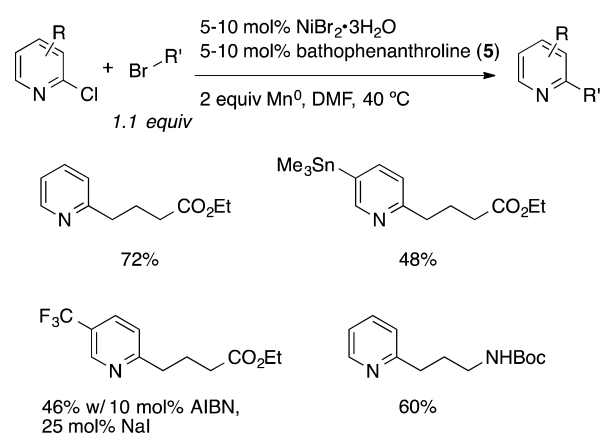
Scheme 7. Proposed Mechanism for the Cross-Coupling of Csp^2−X and Csp^3−X
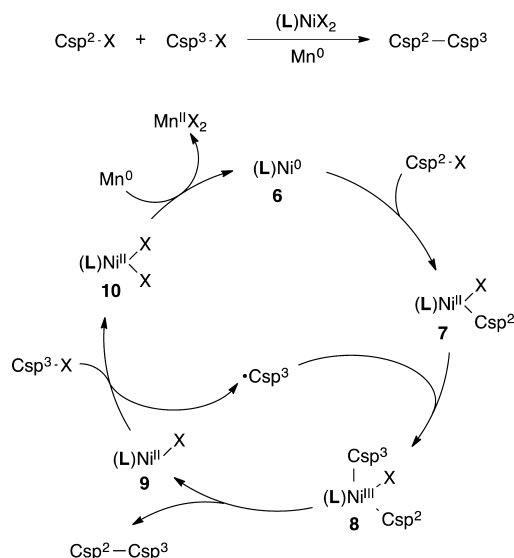
iodides,[35] subsequent studies by our group[36] and Gong et al.[37] have suggested that reactions with acyl halides proceed by the same mechanism. Starting from the nickel precatalyst **10**, reduction with Mn (or Zn or TDAE) forms reactive nickel(0) intermediate **6**. Complex **6** selectively reacts with Csp^2 halides (aryl halides[35] and acyl halides[38]) in preference to Csp^3 halides (alkyl halides) to form organonickel(II) **7**. This is the first selectivity determining step and explains why poor results are obtained with unreactive aryl halides like chlorobenzene.[21]

Stoichiometric studies established that **7a** reacts with alkyl halides to form nickel(II) dihalide **10** and cross-coupled product without the need for any added reductant (eq 4, L = **1**).[35,36] In addition, we found that alkylnickel(II) complexes did not react with iodobenzene to form product. Similarly, acylnickel(II) complexes, like **7b**, reacted with alkyl halides and benzylic halides to form ketone products without any added reductant, suggesting intermediate reduction was not needed (eq 5, L = **1**).

The intermediacy of an alkyl radical intermediate could be deduced from the observation that (R)-ethyl 3-bromobutyrate (98% ee) formed only racemic product (eq 6) and reactions of cyclopropylmethyl bromide with either isolated **7a** or under catalytic conditions formed only the rearranged product.

(4)

(5)

(6)
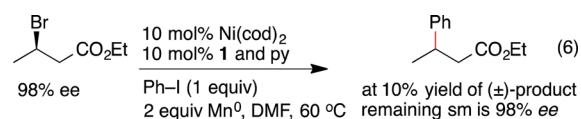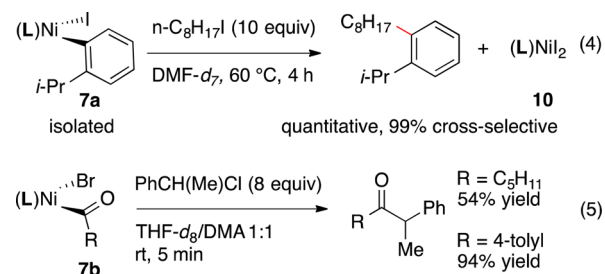
Finally, a radical clock study modeled after the work of Bergman et al.[39] demonstrated that the amount of rearranged product varied with nickel concentration (Scheme 8). This result is consistent with our proposed radical chain mechanism because the radical must be formed and consumed at different nickel centers (**9** and **7** in Scheme 7) rather than formed and consumed at the same nickel center. Gong recently used a similar study to demonstrate the radical chain nature of the coupling of acyl electrophiles with alkyl halides.[37]

Finally, **7** appears to be the resting state of the catalyst based upon quenching studies of catalytic reactions. Indeed, for a selective reaction to take place, the concentration of **7** must be higher than the concentration of the reactive alkyl radical.[40,41] Although similar reactions have been catalyzed by cobalt,[42] it is not clear at this time if the cobalt reactions proceed by a radical chain mechanism.

CONSEQUENCES OF THE RADICAL CHAIN MECHANISM

With the discovery of a unified radical chain mechanism for cross-electrophile coupling of aryl and acyl halides with alkyl halides, many previous results could now be explained and the design of new reactions became possible. The key observation was that an arylnickel(II) or acylnickel(II) species will couple with an alkyl radical to form the cross-coupled product in high yield (Figure 4). The design of new reactions requires (1) selective formation of the aryl or acylnickel(II) intermediate; (2) relatively slow disproportionation of the organonickel(II) intermediate; (3) selective generation of an alkyl radical. It immediately became clear that these conditions could be met by nonreductive mechanisms, that not only electrophiles could serve as radical precursors, and that the use of two different catalysts might allow for a broader range of substrates to participate.

SECOND-GENERATION METHODS: CARBONYLATIVE CROSS-COUPLING

With the realization that the mechanisms for the coupling of aryl halides and acyl halides were so closely related, we considered that an arylnickel(II) intermediate could be converted to an acylnickel(II) intermediate by insertion of carbon monoxide.[36] While Troupel et al. had demonstrated carbonylative dimerization and cross-coupling of aryl halides and CO with benzylic halides, the use of unactivated alkyl halides had resulted in lower yields. We were able to find improved conditions based upon our earlier cross-coupling work (Scheme 9).

COUPLING OF EPOXIDES WITH ARYL HALIDES

While nickel-mediated methods have been published for the coupling of epoxides with nucleophiles, and the oxidative addition of nickel to an epoxide is known, early attempts to couple epoxides with aryl halides or alkyl halides had met with little success, forming primarily hydrodehalogenated aryl halide and biaryl. Our mechanistic studies suggested an obvious reason: the epoxide was not being efficiently converted into an alkyl radical (Figure 5).

Scheme 8. Plot of the Fraction of Rearranged Product Observed at Different Nickel Concentrations
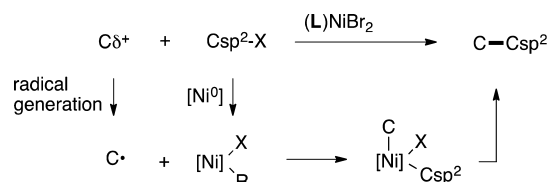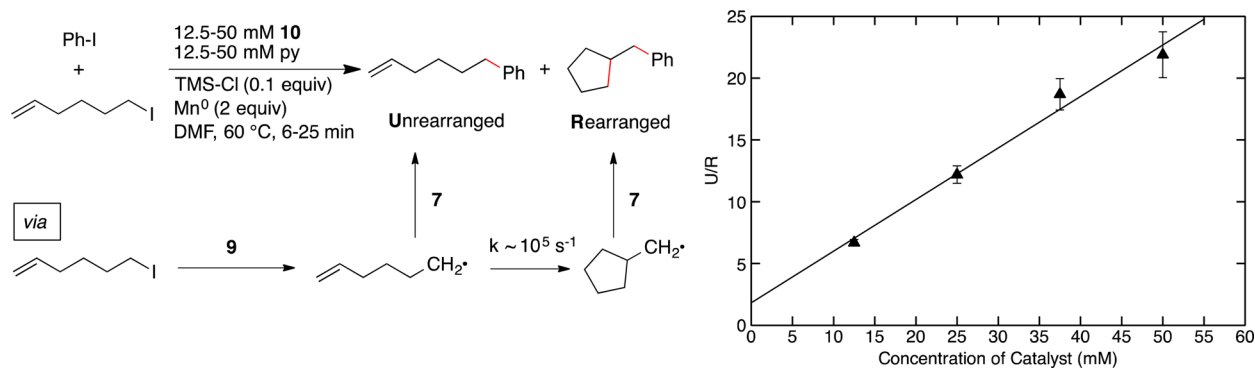
Figure 4. Generalized cross-coupling of Csp^2–X with radicals.
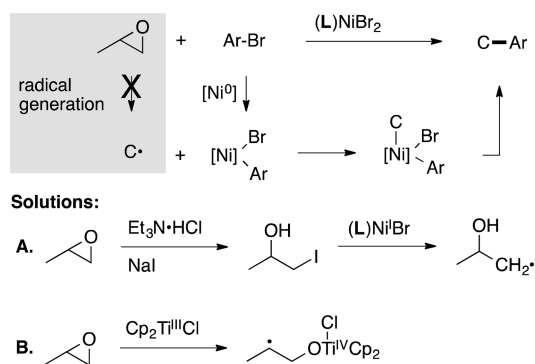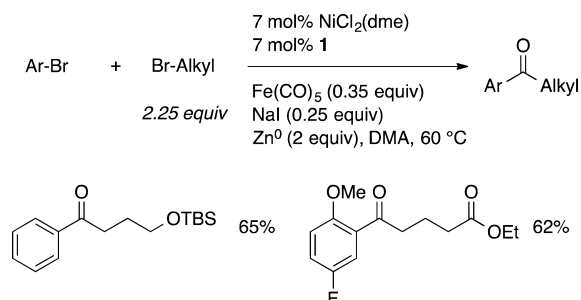
Scheme 9. Carbonylative Cross-Coupling

Figure 5. Epoxide coupling problem and mechanism-based solutions.

We considered two solutions for this problem. First, the addition of an HI equivalent to the reaction would form an iodohydrin, which could then be coupled according to our general mechanism. Second, RajanBabu and Nugent's reagent has been demonstrated to form alkyl radicals from epoxides[43] and Gansäuer and co-workers have demonstrated that this can be made catalytic in titanium[44] and even enantioselective.[45] If the resulting β-titanoxy radical could be captured by arylnickel-(II), then the opposite regiochemistry could be obtained. Both of these approaches were realized recently by our group (Scheme 10).[46] While the regiochemistry for the iodide-

**Scheme 10. Regiodivergent Arylation of Epoxides**
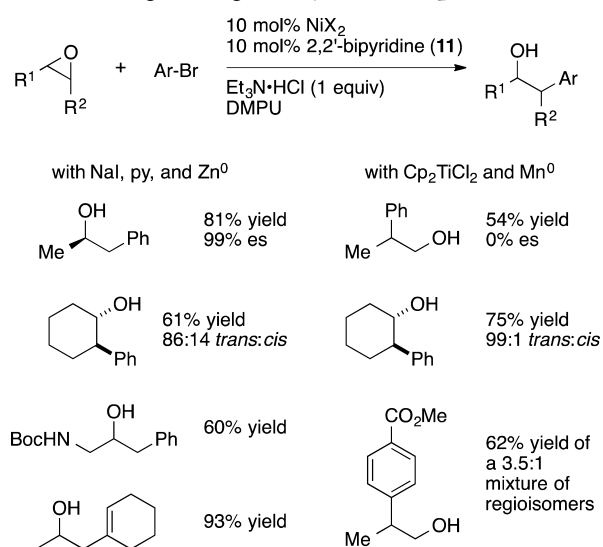
mediated chemistry is usually high (>10:1), the regiochemistry for the titanium chemistry is more modest at this time (3.3:1). As expected, enantioenriched propylene oxide is coupled enantiospecifically in the iodide mediated reactions and with loss of stereochemistry for titanium-mediated reactions.

Building upon this result and the high enantioselectivities observed by Gansäuer and co-workers for the opening of *meso*-epoxides by Kagan's chiral titanocene catalysts, we have also realized the first enantioselective arylation of epoxides with aryl halides. A variety of epoxides couple with enantioselectivities ranging from 78 to 95% ee (Scheme 11).[47]

COUPLING OF BENZYL MESYLATES WITH ARYL HALIDES

In contrast to the low reactivity of epoxides under our standard conditions, benzyl halides were too reactive in coupling reactions with aryl halides. The attempted coupling of bromobenzene with benzyl bromide rapidly formed dibenzyl along with small amounts of diphenylmethane. We interpreted this observation as the result of benzyl halides reacting with the nickel catalyst faster than aryl bromides or even aryl iodides. The formed benzylnickel(II) halide[48] reacts further to form bibenzyl, but does not form the diarylmethane cross-product (Figure 6).

Our solution to this challenge[49] was to make two simultaneous changes to the reaction that would (1) ensure that arylnickel(II) was formed and not benzylnickel(II) and (2)

Scheme 11. Enantioselective Arylation of *meso*-Epoxides
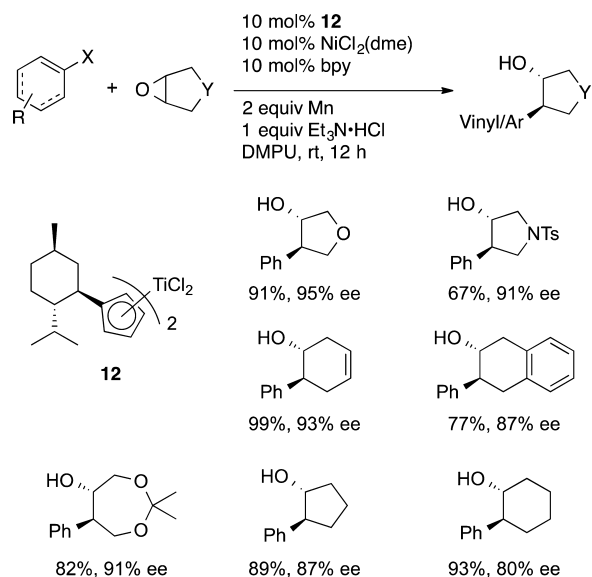
Scheme 12. Synthesis of Diarylmethanes by Nickel and Cobalt Cocatalysis
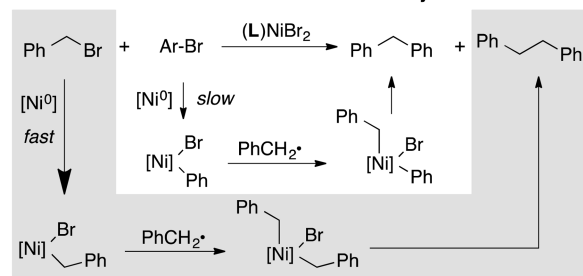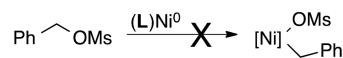
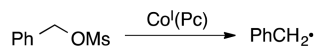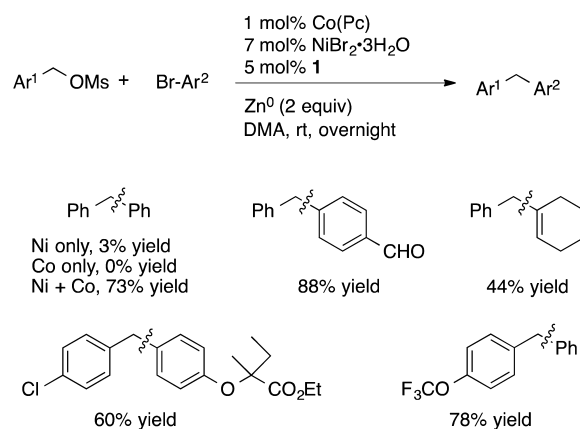**Figure 6.** Challenge of diarylmethane synthesis and mechanism-based solution.

generate a benzyl radical (Figure 6). The first change was to use benzyl mesylates instead of benzyl bromides or chlorides. We found that benzyl mesylates were not reactive with nickel under reducing conditions. The second change was the addition of a cocatalyst, cobalt phthalocyanine (Co(Pc)), that could form a benzyl radical from a benzyl mesylate.[50] The resulting reaction is highly selective for cross-product over dimeric products and the scope is similar to our previous cross-electrophile coupling reactions (Scheme 12). The benzyl mesylates could be generated in situ from readily available benzyl alcohols, making the procedure more convenient. Finally, we reported a preliminary result for the enantioselective synthesis of a diarylethane from the coupling of 1-chloroethylbenzene with 4-bromoacetophenone.

CONCLUSIONS

Selective cross-coupling methods for the synthesis of alkylated arenes from aryl halides and alkyl halides have seen rapid development in the past 5 years. Already, researchers in both academics and industry are utilizing this chemistry to address

synthetic challenges that were difficult using more established cross-coupling methods.[51−56] Our description of the first radical chain mechanism for nickel-catalyzed cross-coupling has been followed by reports of two other radical chain mechanisms.[37,57,58] One of these examples is a nickel-catalyzed cross-coupling of organozinc reagents with propargylic halides, suggesting that radical chain mechanisms may be common even outside cross-electrophile coupling. The understanding that bipyridine-ligated arylnickel complexes react with radicals to form cross-coupled product has not only enabled the rational design of new cross-electrophile coupling reactions, but entirely new processes that combine nickel catalysis with radical generation by photoredox catalysis.[59−61] The application of these concepts to new nickel-catalyzed cross-electrophile coupling reactions as well as the development of new mechanistic concepts for achieving selectivity are ongoing in our laboratories.

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Notes

The authors declare no competing financial interest.

Biography

Daniel Weix was raised in Oak Creek, Wisconsin, received his BA from Columbia University conducting research with Thomas Katz, obtained his PhD from UC Berkeley with Jonathan Ellman, and was an NIH postdoctoral fellow under John Hartwig at both Yale University and the University of Illinois. In 2008, he began his independent career at the University of Rochester and was promoted to associate professor in 2014. In addition to the coupling of aryl halides and acyl halides with alkyl electrophiles, he has also developed cross-electrophile coupling reactions of allylnickel(II) intermediates with a variety of electrophiles and collaborated with Patrick Holland of Yale University on the development of cobalt catalyzed reactions.

■ REFERENCES

(1) Everson, D. A.; Weix, D. J. Cross-Electrophile Coupling: Principles of Reactivity and Selectivity. *J. Org. Chem.* **2014**, *79*, 4793−4798.

(2) Knappke, C. E. I.; Grupe, S.; Gärtner, D.; Corpet, M.; Gosmini, C.; Jacobi von Wangelin, A. Reductive Cross-Coupling Reactions between Two Electrophiles. *Chem.—Eur. J.* **2014**, *20*, 6828−6842.

(3) Moragas, T.; Correa, A.; Martin, R. Metal-Catalyzed Reductive Coupling Reactions of Organic Halides with Carbonyl-Type Compounds. *Chem.—Eur. J.* **2014**, *20*, 8242−8258.

(4) Wurtz, A. Ueber eine neue Klasse organischer Radicale. *Ann. Chem. Pharm.* **1855**, *96*, 364−375.

(5) Ullmann, F.; Bielecki, J. Ueber Synthesen in der Biphenylreihe. *Chem. Ber.* **1901**, *34*, 2174−2185.

(6) Chaussard, J.; Folest, J.-C.; Nedelec, J.-Y.; Perichon, J.; Sibille, S.; Troupel, M. Use of Sacrificial Anodes in Electrochemical Functionalization of Organic Halides. *Synthesis* **1990**, 369−381.

(7) Nédélec, J.-Y.; Périchon, J.; Troupel, M. Organic electroreductive coupling reactions using transition metal complexes as catalysts: Electrochemistry VI Electroorganic Synthesis: Bond Formation at Anode and Cathode. *Top. Curr. Chem.* **1997**, *185*, 141−173.

(8) Jutand, A. Contribution of Electrochemistry to Organometallic Catalysis. *Chem. Rev.* **2008**, *108*, 2300−2347.

(9) Klein, A.; Budnikova, Y.; Sinyashin, O. Electron transfer in organonickel complexes of α-diimines: Versatile redox catalysts for C-C or C-P coupling reactions - A review. *J. Organomet. Chem.* **2007**, *692*, 3156−3166.

(10) Frisch, A. C.; Beller, M. Catalysts for Cross-Coupling Reactions with Non-activated Alkyl Halides. *Angew. Chem., Int. Ed.* **2005**, *44*, 674−688.

(11) Rudolph, A.; Lautens, M. Secondary Alkyl Halides in Transition-Metal-Catalyzed Cross-Coupling Reactions. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656−2670.

(12) Hartwig, J. F. *Organotransition Metal Chemistry: From Bonding to Catalysis*; University Science Books: Sausalito, CA, 2009.

(13) Mollar, C.; Besora, M.; Maseras, F.; Asensio, G.; Medio-Simón, M. Competitive and Selective Csp³−Br versus Csp²−Br Bond Activation in Palladium-Catalysed Suzuki Cross-Coupling: An Experimental and Theoretical Study of the Role of Phosphine Ligands. *Chem.—Eur. J.* **2010**, *16*, 13390−13397.

(14) Ariafard, A.; Lin, Z. Understanding the Relative Easiness of Oxidative Addition of Aryl and Alkyl Halides to Palladium(0). *Organometallics* **2006**, *25*, 4030−4033.

(15) Gonzalez-Bobes, F.; Fu, G. Amino Alcohols as Ligands for Nickel-Catalyzed Suzuki Reactions of Unactivated Alkyl Halides, Including Secondary Alkyl Chlorides, with Arylboronic Acids. *J. Am. Chem. Soc.* **2006**, *128*, 5360−5361.

(16) Jones, G. D.; McFarland, C.; Anderson, T. J.; Vicic, D. A. Analysis of key steps in the catalytic cross-coupling of alkyl electrophiles under Negishi-like conditions. *Chem. Commun.* **2005**, 4211−4213.

(17) Everson, D. A.; Weix, D. J. Unpublished results from thesis work.

(18) Everson, D. A.; Shrestha, R.; Weix, D. J. Nickel-Catalyzed Reductive Cross-Coupling of Aryl Halides with Alkyl Halides. *J. Am. Chem. Soc.* **2010**, *132*, 920−921.

(19) Takahashi, H.; Inagaki, S.; Nishihara, Y.; Shibata, T.; Takagi, K. Novel Rh Catalysis in Cross-Coupling between Alkyl Halides and Arylzinc Compounds Possessing ortho-COX (X = OR, NMe2, or Ph) Groups. *Org. Lett.* **2006**, *8*, 3037−3040.

(20) Prinsell, M. R.; Everson, D. A.; Weix, D. J. Nickel-Catalyzed, Sodium Iodide-Promoted Reductive Dimerization of Alkyl Halides, Alkyl Pseudohalides, and Allylic Acetates. *Chem. Commun.* **2010**, *46*, 5743−5745.

(21) Everson, D. A.; Jones, B. A.; Weix, D. J. Replacing Conventional Carbon Nucleophiles with Electrophiles: Nickel-Catalyzed Reductive Alkylation of Aryl Bromides and Chlorides. *J. Am. Chem. Soc.* **2012**, *134*, 6146−6159.

(22) McCann, L. C.; Organ, M. G. On The Remarkably Different Role of Salt in the Cross-Coupling of Arylzincs From That Seen With Alkylzincs. *Angew. Chem., Int. Ed.* **2014**, *53*, 4386−4389.

(23) Sase, S.; Jaric, M.; Metzger, A.; Malakhov, V.; Knochel, P. One-Pot Negishi Cross-Coupling Reactions of In Situ Generated Zinc Reagents with Aryl Chlorides, Bromides, and Triflates. *J. Org. Chem.* **2008**, *73*, 7380−7382.

(24) Everson, D. A.; George, D. T.; Weix, D. J.; Buergler, J. F.; Wood, J. L. Nickel-Catalyzed Cross-Coupling of Aryl Halides with Alkyl Halides: Ethyl 4-(4-(4-methylphenylsulfonamido)-phenyl)butanoate. *Org. Synth.* **2013**, *90*, 200−214.

(25) d'Incan, E.; Sibille, S.; Perichon, J.; Moingeon, M.-O.; Chaussard, J. Electrosynthesis of ketones from organic halides and anhydrides. *Tetrahedron Lett.* **1986**, *27*, 4175−4176.

(26) Marzouk, H.; Rollin, Y.; Folest, J. C.; Nédélec, J. Y.; Périchon, J. Electrochemical synthesis of ketones from acid chlorides and alkyl and aryl halides catalysed by nickel complexes. *J. Organomet. Chem.* **1989**, *369*, C47−C50.

(27) Amatore, C.; Jutand, A.; Périchon, J.; Rollin, Y. Mechanism of the Nickel-Catalyzed Electrosynthesis of Ketones by Heterocoupling of Acyl and Benzyl Halides. *Monatsh. Chem.* **2000**, *131*, 1293−1304.

(28) Onaka, M.; Matsuoka, Y.; Mukaiyama, T. A Convenient Method for the Direct Preparation of Ketones from 2-(6-(2-Methoxyethyl)-Pyridyl)Carboxylates and Alkyl Iodides by Use of Zinc Dust and a Catalytic Amount of Nickel Dichloride. *Chem. Lett.* **1981**, *10*, 531−534.

(29) Wotal, A. C.; Weix, D. J. Synthesis of Functionalized Dialkyl Ketones from Carboxylic Acid Derivatives and Alkyl Halides. *Org. Lett.* **2012**, *14*, 1476−1479.

(30) Kobayashi, S.; Iimori, T.; Izawa, T.; Ohno, M. Ph₃P-(PyS)₂-CH₃CN as an excellent condensing system for.beta.-lactam formation from.beta.-amino acids. *J. Am. Chem. Soc.* **1981**, *103*, 2406−2408.

(31) Wang, S.; Qian, Q.; Gong, H. Nickel-Catalyzed Reductive Coupling of Aryl Halides with Secondary Alkyl Bromides and Allylic Acetate. *Org. Lett.* **2012**, *14*, 3352−3355.

(32) Everson, D. A.; Buonomo, J. A.; Weix, D. J. Nickel-catalyzed cross-electrophile coupling of 2-chloropyridines with alkyl bromides. *Synlett* **2014**, *25*, 233−238.

(33) Hegedus, L. S.; Miller, L. L. Reaction of π-allylnickel bromide complexes with organic halides. Stereochemistry and mechanism. *J. Am. Chem. Soc.* **1975**, *97*, 459−460.

(34) Durandetti, M.; Nédélec, J.-Y.; Périchon, J. Nickel-Catalyzed Direct Electrochemical Cross-Coupling between Aryl Halides and Activated Alkyl Halides. *J. Org. Chem.* **1996**, *61*, 1748−1755.

(35) Biswas, S.; Weix, D. J. Mechanism and Selectivity in Nickel-Catalyzed Cross-Electrophile Coupling of Aryl Halides with Alkyl Halides. *J. Am. Chem. Soc.* **2013**, *135*, 16192−16197.

(36) Wotal, A. C.; Ribson, R. D.; Weix, D. J. Stoichiometric Reactions of Acylnickel(II) Complexes with Electrophiles and the Catalytic Synthesis of Ketones. *Organometallics* **2014**, *33*, 5874−5881.

(37) Zhao, C.; Jia, X.; Wang, X.; Gong, H. Ni-Catalyzed Reductive Coupling of Alkyl Acids with Unactivated Tertiary Alkyl and Glycosyl Halides. *J. Am. Chem. Soc.* **2014**, *136*, 17645−17651.

(38) Yin, H.; Zhao, C.; You, H.; Lin, K.; Gong, H. Mild ketone formation via Ni-catalyzed reductive coupling of unactivated alkyl halides with acid anhydrides. *Chem. Commun.* **2012**, *48*, 7034−7036.

(39) Kinney, R. J.; Jones, W. D.; Bergman, R. G. Synthesis and reactions of (η⁵-cyclopentadienyl)tricarbonylhydridovanadate. A comparative mechanistic study of its organic halide reduction reactions with those of tri-n-butyltin hydride. *J. Am. Chem. Soc.* **1978**, *100*, 7902−7915.

(40) Fischer, H. The Persistent Radical Effect: A Principle for Selective Radical Reactions and Living Radical Polymerizations. *Chem. Rev.* **2001**, *101*, 3581−3610.

(41) Studer, A. The Persistent Radical Effect in Organic Synthesis. *Chem.—Eur. J.* **2001**, *7*, 1159−1164.

(42) Amatore, M.; Gosmini, C. Direct Method for Carbon-Carbon Bond Formation: The Functional Group Tolerant Cobalt-Catalyzed Alkylation of Aryl Halides. *Chem.—Eur. J.* **2010**, *16*, 5848−5852.

(43) RajanBabu, T. V.; Nugent, W. A. Selective Generation of Free Radicals from Epoxides Using a Transition-Metal Radical. A Powerful New Tool for Organic Synthesis. *J. Am. Chem. Soc.* **1994**, *116*, 986−997.

(44) Gansäuer, A.; Pierobon, M.; Bluhm, H. Catalytic, Highly Regio- and Chemoselective Generation of Radicals from Epoxides: Titanocene Dichloride as an Electron Transfer Catalyst in Transition Metal Catalyzed Radical Reactions. *Angew. Chem., Int. Ed.* **1998**, *37*, 101−103.

(45) Gansäuer, A.; Lauterbach, T.; Bluhm, H.; Noltemeyer, M. A Catalytic Enantioselective Electron Transfer Reaction: Titanocene-Catalyzed Enantioselective Formation of Radicals from meso-Epoxides. *Angew. Chem., Int. Ed.* **1999**, *38*, 2909−2910.

(46) Zhao, Y.; Weix, D. J. Nickel-Catalyzed Regiodivergent Opening of Epoxides with Aryl Halides: Co-Catalysis Controls Regioselectivity. *J. Am. Chem. Soc.* **2014**, *136*, 48−51.

(47) Zhao, Y.; Weix, D. J. Enantioselective Cross-Coupling of meso-Epoxides with Aryl Halides. *J. Am. Chem. Soc.* **2015**, *137*, 3237−3240.

(48) Hipler, B.; Uhlig, E. Benzylnickel(II)-Komplexe und ihre Reaktionen. *Z. Anorg. Allg. Chem.* **1984**, *510*, 11−15.

(49) Ackerman, L. K. G.; Anka-Lufford, L. L.; Naodovic, M.; Weix, D. J. Cobalt co-catalysis for cross-electrophile coupling: diaryl-methanes from benzyl mesylates and aryl halides. *Chem. Sci.* **2015**, *6*, 1115−1119.

(50) Takai, K.; Nitta, K.; Fujimura, O.; Utimoto, K. Preparation of alkylchromium reagents by reduction of alkyl halides with chromium-(II) chloride under cobalt catalysis. *J. Org. Chem.* **1989**, *54*, 4732−4734.

(51) Molander, G. A.; Traister, K. M.; O'Neill, B. T. Reductive Cross-Coupling of Nonaromatic, Heterocyclic Bromides with Aryl and Heteroaryl Bromides. *J. Org. Chem.* **2014**, *79*, 5771−5780.

(52) Molander, G. A.; Wisniewski, S. R.; Traister, K. M. Reductive Cross-Coupling of 3-Bromo-2,1-borazaronaphthalenes with Alkyl Iodides. *Org. Lett.* **2014**, *16*, 3692−3695.

(53) Singh, R.; Bordeaux, M.; Fasan, R. P450-Catalyzed Intra-molecular sp3 C−H Amination with Arylsulfonyl Azide Substrates. *ACS Catal.* **2014**, *4*, 546−552.

(54) Morofuji, T.; Shimizu, A.; Yoshida, J.-i. Direct C−N Coupling of Imidazoles with Aromatic and Benzylic Compounds via Electro-oxidative C−H Functionalization. *J. Am. Chem. Soc.* **2014**, *136*, 4496−4499.

(55) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. Catalytic Asymmetric Reductive Acyl Cross-Coupling: Synthesis of Enantien-riched Acyclic α,α-Disubstituted Ketones. *J. Am. Chem. Soc.* **2013**, *135*, 7442−7445.

(56) Cherney, A. H.; Reisman, S. E. Pd-catalyzed Fukuyama cross-coupling of secondary organozinc reagents for the direct synthesis of unsymmetrical ketones. *Tetrahedron* **2014**, *70*, 3259−3265.

(57) Choi, J.; Martín-Gago, P.; Fu, G. C. Stereoconvergent Arylations and Alkenylations of Unactivated Alkyl Electrophiles: Catalytic Enantioselective Synthesis of Secondary Sulfonamides and Sulfones. *J. Am. Chem. Soc.* **2014**, *136*, 12161−12165.

(58) Schley, N. D.; Fu, G. C. Nickel-Catalyzed Negishi Arylations of Propargylic Bromides: A Mechanistic Investigation. *J. Am. Chem. Soc.* **2014**, *136*, 16588−16593.

(59) Tellis, J. C.; Primer, D. N.; Molander, G. A. Single-electron transmetalation in organoboron cross-coupling by photoredox/nickel dual catalysis. *Science* **2014**, *345*, 433−436.

(60) Zuo, Z.; Ahneman, D.; Chu, L.; Terrett, J.; Doyle, A. G.; MacMillan, D. W. C. Merging photoredox with nickel catalysis: Coupling of α-carboxyl sp3-carbons with aryl halides. *Science* **2014**, *345*, 437−440.

(61) For an early example of the combination of palladium catalysis with photoredox-generated radicals, see: Kalyani, D.; McMurtrey, K. B.; Neufeldt, S. R.; Sanford, M. S.; Room-Temperature, C−H Arylation: Merger of Pd-Catalyzed C−H Functionalization and Visible-Light Photocatalysis. *J. Am. Chem. Soc.* **2011**, *133*, 18566−18569.