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Transition-Metal (Pd, Ni, Mn)-Catalyzed C–C Bond Constructions Involving Unactivated Alkyl Halides and Fundamental Synthetic Building Blocks

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CONSPECTUS:

The catalytic construction of C–C bonds between organo-halide or -pseudohalide electrophiles and fundamental building blocks such as alkenes, arenes, or CO are widely utilized metal-catalyzed processes. The use of simple, widely available unactivated alkyl halides in these catalytic transformations has significantly lagged behind the use of aryl or vinyl electrophiles. This difference is primarily due to the relative difficulty in activating alkyl halides with transition metals under mild conditions. This account details our group's work towards developing a general catalytic manifold for the construction of C–C bonds using unactivated alkyl halides and a range of simple chemical feedstocks. Critical to the strategy was the implementation of new modes of hybrid organometallic-radical reactivity in catalysis. Generation of carbon-centered radicals from alkyl halides using transition metals offers a solution to challenges associated with the application of alkyl electrophiles in classical two-electron reaction modes.

A major focus of this work was the development of general, palladium-catalyzed carbocyclizations and intermolecular cross-couplings of unactivated alkyl halides (alkyl-Mizoroki-Heck-type reactions). Initial studies centered on the use of alkyl iodides in these processes, but subsequent studies determined that the use of an electron-rich, ferrocenyl bisphosphine (dtbpf) enables the palladium-catalyzed carbocyclizations of unactivated alkyl bromides. Mechanistic studies of these reactions revealed interesting details regarding a difference in mechanism between reactions of alkyl iodides and alkyl bromides in carbocyclizations. These studies were consistent with alkyl bromides reacting via an auto-tandem catalytic process involving atom-transfer radical cyclization (ATRC) followed by catalytic dehydrohalogenation. Reactions of alkyl iodides, on the other hand, involved metal-initiated radical chain pathways.

Recent studies have expanded the scope of alkyl-Mizoroki-Heck-type reactions to the use of a first-row metal. Inexpensive nickel precatalysts, in combination with the bisphosphine ligand Xantphos, efficiently activate alkyl bromides for both intra- and intermolecular C–C bond-forming reactions. The reaction scope is similar to the palladium-catalyzed system, but in addition, alkene regioisomeric ratios are dramatically improved over those in reactions with palladium, solving one of the drawbacks of our previous work. Initial mechanistic studies were consistent with a hybrid organometallic-radical mechanism for the nickel-catalyzed reactions.

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The novel reactivity of the palladium catalysts in the alkyl-Mizoroki-Heck-type reactions have also paved the way for the development of other C–C bond-forming processes of unactivated alkyl halides, including aromatic C–H alkylations as well as low pressure alkoxy-carbonylations. Related hybrid organometallic-radical reactivity of manganese has led to an alkene dicarbofunctionalization using alkyl iodides.

Graphical Abstract

INTRODUCTION

The catalytic construction of C–C bonds is invaluable to the synthesis and discovery of industrially- and medically-relevant compounds. Classical transition-metal-catalyzed cross-couplings such as the Suzuki-Miyaura, Negishi, and Mizoroki-Heck reactions are indispensable methodologies of this class.¹ Despite the synthetic utility of these processes, applications have traditionally been limited to the use of activated, or sp^2 -hybridized aryl or vinyl electrophiles. Modern studies in transition metal catalysis have extended organometallic cross-couplings to reactions with unactivated alkyl electrophiles.^{2–4} However, at the outset of our studies, there were few general examples of catalytic C–C bond-forming reactions of unactivated alkyl halides with non-organometallic building blocks such as alkenes, arenes, or CO.

Alkyl halides are ubiquitous chemical building blocks which are widely commercially available and easily synthesized from simple and abundant starting materials. The use of unactivated alkyl halides in transition-metal-catalyzed C–C bond-forming reactions has posed a significant synthetic challenge, however, owing to (1) the relative reluctance of electron-rich, sp^3 -hybridized electrophiles to undergo oxidative addition with low-valent metal complexes^{5,6} and (2) the susceptibility of alkylmetal intermediates toward rapid β -hydride elimination rather than desired C–C bond formation (Figure 1).^{7,8}

These limitations of two-electron activation mechanisms must be overcome for successful C–C construction. In cases involving organometallic cross-coupling, this has been accomplished via the judicious selection of ligands.^{9,10} However, with rare exceptions,¹¹ this approach has not translated to other C–C constructions involving non-organometallic coupling partners (e.g., alkenes). We viewed an alternative activation method as holding potential in mitigating these problems. Many transition metal complexes are known to participate in single-electron activation modes with alkyl electrophiles through either an inner-sphere atom abstraction or outer-sphere single-electron transfer pathway to yield a carbon-centered radical intermediate (Figure 1).¹² The carbon-centered radical thus formed is capable of participating in any of a number of C–C bond-forming reactions. This type of

single-electron manifold offers a solution to the slow oxidative addition associated with two-electron reactivity, while minimizing the formation of putative alkylmetal intermediates which could lead to deleterious, premature β -hydride elimination.

The use of hybrid organometallic-radical pathways in alkene additions had significant precedent at the start of our studies, most notably in atom-transfer radical additions.^{13,14} Applications involving unactivated alkyl electrophiles were rare, however, and required the use of superstoichiometric amounts of reactive alkylmetal reagents.^{15–17} In this account, we detail our work focused on developing general alkyl-Mizoroki-Heck-type reactions under mild conditions and the revealing mechanistic studies involved. These studies subsequently led to our group developing several other C–C constructions in the hybrid organometallic-radical manifold, which will also be discussed.

PALLADIUM-CATALYZED CARBOCYCLIZATIONS OF UNACTIVATED ALKYL IODIDES

We began our studies with the goal of developing a carbonylative Mizoroki-Heck-type reaction of unactivated alkyl iodides.¹⁸ Our decision to use alkyl iodides as substrates was guided by the higher inherent reactivity of alkyl iodides over other alkyl halides in single-electron manifolds.¹⁹ We hypothesized that the CO involved in the reaction would limit undesired dehydrohalogenation owing to either the known addition of carbon-centered radicals to CO—avoiding the production of an alkylpalladium(II) intermediate—or to fast CO migratory insertion if such an intermediate did indeed form.²⁰ Important precedent for this work was Ryu's application of a palladium/light system for a cascade radical cyclization in a multi-carbonylation sequence.²¹ This prior work demonstrated the ability of a palladium catalyst to successfully form five-membered cyclic ketones via radical cyclization.

Representative examples of successful carbonylative ring formations are shown in Table 1. These reactions were successfully catalyzed using simple $\text{Pd}(\text{PPh}_3)_4$, albeit under relatively high pressure (50 atm) and temperature (130 °C). A variety of cyclic enones were prepared from both primary and secondary alkyl iodides. Both monocyclic and bicyclic structures were easily accessible via 5-exo and 6-endo modes of cyclization.

While studying the substrate scope of this carbocyclization, we obtained an exciting and unexpected result which led our investigations down a new avenue.²² The reaction of a hexenyl iodide was anticipated to produce a six-membered enone via a carbonylative 6-exo cyclization (Scheme 1). This product was not observed, however, and instead the sole product was that of a non-carbonylative 5-exo cyclization to give a methylene cyclopentane product in 86% yield as a single alkene regioisomer. We were intrigued by the potential for this process, as such a palladium-catalyzed carbocyclization of unactivated alkyl halides was unknown with the exception of a single report limited to five-membered ring synthesis involving terminal alkenes.¹¹

As CO is not incorporated in the reaction, the next experiment was to perform the carbocyclization in its absence. Unexpectedly, while this modification in reaction conditions did not influence reaction efficiency to a large extent, the production of another alkene

regioisomer was observed (Scheme 2). While we were able to decrease the CO pressure from 50 atm to 10 atm, lowering pressure further to 2 atm CO led to a significant amount of this undesired regioisomer. This effect was observed with other primary alkyl iodides as well, and in addition these conditions led to a decrease in the production of reductive byproducts. Therefore, these carbocyclizations were performed under 10 atm CO. Interestingly, our studies of substrate scope revealed that reactions of secondary alkyl iodides did not benefit from a CO atmosphere and proceeded efficiently when performed under argon (see below).

The carbocyclization succeeded with a range of primary and secondary alkyl iodides containing diverse alkene substitution patterns, enabling the synthesis of 5- and 6-membered carbo- and heterocycles (Table 2). The reaction also efficiently constructed products containing all-carbon quaternary centers. Several bicyclic structures were prepared in good yield, although a mixture of alkene regioisomers formed in certain instances. Notably, the carbocyclization was not limited to the formation of 5-membered rings, as 6-exo cyclization was also possible. As previously mentioned, carbocyclizations of secondary alkyl iodides did not benefit from a CO atmosphere; reactions of this substrate class were performed under Ar with good efficiency. We speculate that the carbocyclizations of primary iodides performed in this study benefited from the CO atmosphere owing to modification of the reactivity profile of the palladium catalyst, although detailed mechanistic studies have not been performed. This issue is resolved in later generations of the reaction, which avoid CO altogether (*vide infra*).^{23,24}

With respect to the reaction mechanism, our early studies sought to determine whether the carbocyclizations proceeded via single- or two-electron mechanisms. Prior studies have demonstrated that both pathways potentially proceed in reactions of low-valent palladium and alkyl iodides.^{25,26} Carbonylative and non-carbonylative cyclizations were performed in the presence of 1 equiv of the persistent radical TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl), and in both cases, the TEMPO-trapped adducts were observed (Scheme 3). These results are consistent with the intermediacy of carbon-centered radicals in these reactions involving single-electron mechanisms. Subsequent studies shed light on other mechanistic details of the reactions (*vide infra*).²⁴

INTERMOLECULAR PALLADIUM-CATALYZED MIZOROKI-HECK-TYPE CROSS-COUPPLINGS OF UNACTIVATED ALKYL IODIDES

Following our carbocyclization studies, we targeted a complementary method involving the intermolecular cross-couplings of unactivated alkyl iodides.²⁷ At the time of our studies, general methods for intermolecular alkyl-Mizoroki-Heck-type reactions required the use of reactive reductants (i.e. stoichiometric alkylmetal reagents) and were limited to cross-couplings involving styrene.^{15,16,28–30} Using palladium catalysis, we were able to overcome these limitations and develop an alkyl-Mizoroki-Heck-type cross-coupling using non-styrenyl substrates. We began our studies with the catalytic cross-coupling of iodocyclohexane with acrylonitrile (Scheme 4). Initially, a significant amount of a reductive addition product was observed along with the desired cross-coupling product. We

determined that switching to a solvent lacking abstractable hydrogen atoms (PhCF_3) and the use of an inorganic base instead of an amine base (K_3PO_4 instead of Cy_2NMe) minimized this byproduct. Further studies indicated that the optimal base was dependent on the identity of the alkene coupling partner; Cy_2NMe proved to be superior in reactions with styrenes.

With respect to substrate scope, a number of non-styrenyl alkenes were amenable to the cross-coupling—a distinct advantage over existing intermolecular alkyl-Mizoroki-Heck-type processes (Scheme 5). Moreover, both primary and secondary alkyl iodides performed well in the reaction. In addition, the reaction of a substrate containing a β -stereogenic center proceeded without epimerization, indicating that reversible β -hydride elimination does not occur prior to coupling.

Mechanistic studies supported a hybrid organometallic-radical pathway similar to the catalytic carbocyclizations. For example, the reaction of acrylonitrile with a diastereomerically pure, cyclohexyl substrate produced a cross-coupling product in 50:50 dr. Furthermore, the reaction of styrene with a radical-clock (6-iodohex-1-ene) led to exclusive formation of the cyclopentyl product with no linear cross-coupling product observed, consistent with the presence of a carbon-centered radical intermediate which undergoes fast 5-exo cyclization (Scheme 6).

PALLADIUM-CATALYZED MIZOROKI-HECK-TYPE CARBOCYCLIZATIONS OF UNACTIVATED ALKYL BROMIDES

Following our initial studies, we sought to develop new protocols for the alkyl-Mizoroki-Heck-type carbocyclizations which addressed important drawbacks that limited the practicality of our approach.²⁴ Firstly, the use of heat- and light-sensitive alkyl iodides in these reactions was less attractive than more stable unactivated alkyl bromides. Applying our previously-developed system to the transformation of alkyl bromides gave little product, however; such substrates are inherently more difficult to activate using metal catalysis.³¹ Furthermore, as mentioned previously, carbocyclizations of primary alkyl halides required the use of CO atmosphere which was suboptimal. A survey of electron-rich, bidentate ferrocenyl ligands led to a catalytic system which addressed both of these issues (Scheme 7). As with our intermolecular coupling, the use of PhCF_3 instead of PhMe was important to limit the formation of reductive byproducts.

Our studies applying this second-generation catalytic system to reactions of alkyl bromides demonstrated increased reaction efficiencies over our previous carbocyclizations of alkyl iodides in nearly all cases (Table 3, entries 1–5). Importantly, these carbocyclizations avoided the use of a CO atmosphere. This catalytic system also expanded the scope of the carbocyclization to include substrates that were not well-tolerated in our reactions of alkyl iodides. For example, substrates with styrenyl and terminal olefins worked well, and we successfully expanded capabilities in accessing 6-membered heterocycles (Table 3, entries 8–9).

Following our synthetic studies, we sought to gain a detailed understanding of the reaction mechanism. We began by determining if any reaction intermediates could be found at partial

conversion. Surprisingly, after 10 minutes we observed an atom-transfer radical cyclization (ATRC) product in addition to the expected alkyl-Mizoroki-Heck-type product (Scheme 8). We were able to select for these bromine ATRC products by slight modification of the reaction conditions. Existing methods for the ATRC of alkyl bromides require highly activated substrates.³² While Mitani and co-workers have demonstrated intermolecular atom-transfer radical addition (ATRA) reactions of unactivated alkyl halides,³³ our studies disclosed the first examples of ATRC involving unactivated alkyl bromides. With respect to mechanism, it became clear that direct production of the desired carbocyclization product was not the sole reaction pathway.

Our next major focus was on identifying the role of palladium in the radical cyclization step—specifically, whether palladium served as a simple radical chain initiator or as a true catalyst, and whether reactions of alkyl bromides and iodides proceeded via the same mechanism. We began by comparing the carbocyclizations of an alkyl bromide substrate and its corresponding iodide in the absence and presence of the single-electron inhibitor 1,4-dinitrobenzene (Table 4). Under standard reaction conditions, the reactions of the alkyl bromide and alkyl iodide proceeded in 77% and 48% yield, respectively. The reaction of the alkyl bromide in the presence of 10 mol % 1,4-dinitrobenzene resulted in low yield and conversion, however. Surprisingly, reaction of the corresponding iodide in the presence of 10 mol % 1,4-dinitrobenzene still gave the expected product in high yield.

We next studied the dehydrohalogenation of the ATRC intermediates observed in these reactions. In preparation for these studies, we determined that the ATRC of alkyl iodides are also fast; the reaction of the alkyl iodide in Table 4 provided the ATRC product in 68% yield after only 1 minute. Resubjection of the alkyl bromide or iodide ATRC products to the standard reaction conditions provided the expected alkyl-Mizoroki-Heck-type products (Table 5). We next studied the dehydrohalogenations in the presence of 1,4-dinitrobenzene. The reaction of the alkyl bromide was significantly inhibited, while the reaction of the alkyl iodide was unaffected. Furthermore, in the absence of metal or ligand, no dehydrohalogenation of the alkyl bromide was observed, while in the case of the alkyl iodide, a significant amount of base-mediated elimination occurred.

The results of these studies are consistent with an auto-tandem catalytic mechanism^{34,35} for the carbocyclizations of unactivated alkyl bromides (Scheme 9). Single-electron activation of the alkyl bromide substrate provides a carbon-centered radical intermediate which undergoes addition to the pendant alkene. Following cyclization, bromine atom transfer delivers the ATRC alkyl bromide. Subsequent single-electron activation of this product followed by addition to palladium and β -hydride elimination gives the carbocyclization product and regenerates the catalyst.

Interestingly, we hypothesize that reactions involving unactivated alkyl iodides proceed via a different mechanism, namely through a metal-initiated, rather than metal-catalyzed, radical chain process (Scheme 10). As further support of this hypothesis, we examined the reactions of representative alkyl bromide and iodide substrates with a more traditional radical initiator, AIBN, in the absence of a metal catalyst. Alkyl iodides are well known to participate in ATRC reactions via innate chain processes,³⁶ and our studies above indicated that simple

base-mediated deiodination was possible (Table 5). While the reaction of the bromide depicted in Scheme 7 proceeded with low conversion in the presence of AIBN, the reaction of the corresponding iodide furnished the carbocyclization product in moderate yield, indicating that the palladium is simply serving as a radical initiator in the reactions of alkyl iodides.

NICKEL-CATALYZED ALKYL-MIZOROKI-HECK-TYPE REACTIONS OF UNACTIVATED ALKYL BROMIDES

Extending the palladium-catalyzed carbocyclizations to unactivated alkyl bromides significantly increased the scope of our approach, yet upon critical examination, we identified two major limitations that remained. The transformations often proceeded with modest alkene regioselectivity, and the requirement of a precious metal precatalyst was also suboptimal. Given the versatility of inexpensive nickel catalysts in the activation of alkyl halides for a variety of cross-couplings and other synthetically useful transformations,^{37–39} we hypothesized that a nickel-catalyzed method for alkyl-Mizoroki-Heck-type carbocyclizations could be developed. A potential challenge we envisioned was the documented higher energy barrier for β -hydride elimination of alkylnickel(II) species versus their palladium counterparts.⁴⁰ At the start of our studies, existing methods for such nickel-catalyzed carbocyclizations were limited to the use of activated substrates, or alkyl iodides in reactions that produced both alkene regioisomers and reductive cyclization byproducts.^{29,41,44} We sought a nickel catalytic system that used unactivated alkyl bromides as substrate and minimized the production of alkene regioisomers to enhance the utility of this manifold.

Initial attempts towards a nickel-catalyzed alkyl-Mizoroki-Heck-type reaction of alkyl bromides using bipyridine-type ligands typical of related nickel-catalyzed transformations produced large amounts of the reductive cyclization byproduct in addition to the desired product. An extensive ligand screen uncovered that by switching to the bisphosphine ligand 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos), we were able to both minimize the formation of any reductive cyclization byproducts and facilitate the alkyl-Mizoroki-Heck-type process in excellent yields and alkene regioisomeric ratios (Scheme 11). Furthermore, the use of an air-stable nickel precatalyst ($\text{NiBr}_2\cdot\text{glyme}$) allowed for reaction setup without a glovebox, another distinct advantage over the palladium-catalyzed reactions described above.

We applied our catalytic system to the carbocyclizations of a range of substrates (Table 6). While yields were generally comparable to those in our palladium-catalyzed work, alkene regioisomeric ratios were significantly improved. Carbocyclizations involving di- and trisubstituted pendant alkenes, styrenes, or terminal alkenes all proceeded in good yield and with excellent alkene regioselectivity. Applications to the synthesis of bicyclic frameworks and six-membered rings was also possible. The new catalytic system also extended the scope to products that were previously inaccessible using our Pd/dtbpf conditions, such as the spirocyclic compound formed in entry 6.

In concert with our cyclization studies, we also explored the possibility for nickel-catalyzed intermolecular alkenylations. Our studies indicated that acyclic or cyclic secondary alkyl bromides were viable substrates in cross-couplings with acrylonitrile or methyl acrylate (Table 7). On the other hand, primary alkyl bromides were poor substrates, and cross-couplings with styrene were also unsuccessful, as styrene dimers predominated.

We performed several experiments to further understand the mechanism of the nickel-catalyzed reactions (Scheme 12). Under standard conditions, the addition of 10 mol % of the single-electron inhibitor 1,4-dinitrobenzene led to complete recovery of unreacted starting material, consistent with the presence of radical intermediates. In contrast to the palladium-catalyzed transformation, no ATRC product was observed at partial conversion, consistent with a direct alkyl-Mizoroki-Heck-type carbocyclization not involving auto-tandem catalysis. We hypothesize that the excellent regioisomeric ratios observed in the reaction are a result of alkene isomerization occurring over the course of the reaction, as low selectivity was observed at short reaction times (see Scheme 11 for the minor regioisomer).

PALLADIUM-CATALYZED AROMATIC C–H ALKYLATIONS WITH UNACTIVATED ALKYL HALIDES

Building upon our successes in the development of alkyl-Mizoroki-Heck-type processes, we sought to capitalize on the catalytic hybrid organometallic-radical reactivity to enable C–C bond constructions involving unsaturated units other than alkenes. We viewed aromatic C–H alkylation as a particularly interesting goal, owing to the limitations in substrate scope of canonical Friedel-Crafts alkylations⁴³ and radical-mediated homolytic aromatic substitutions.⁴⁴ The use of simple Pd(PPh₃)₄ as catalyst—similar to our early alkyl-Mizoroki-Heck studies—led to a general palladium-catalyzed, ring-forming aromatic C–H alkylation using unactivated alkyl halides.⁴⁵ Primary and secondary alkyl iodides and bromides were competent substrates for the construction of a diverse array of polycyclic carbocycles and heterocycles (Table 8).

As with the alkyl-Mizoroki-Heck-type reactions, mechanistic studies of the C–H alkylation were consistent with a single-electron activation pathway. Once again, a reaction conducted under standard conditions in the presence of persistent radical TEMPO provided the TEMPO-trapped adduct while no C–H alkylation was observed. Furthermore, reaction of an enantioenriched iodide substrate stopped at partial conversion yielded racemic product. Interestingly, the recovered starting material was completely racemic as well, supporting a reversible single-electron activation of the alkyl halide prior to cyclization (Scheme 13).

A mechanistic proposal consistent with our studies is depicted in Scheme 14. Following reversible, single-electron activation of the alkyl halide substrate, we propose that a carbon-centered radical then adds to the aromatic ring to form a cyclohexadienyl radical intermediate. Single-electron transfer with a putative palladium(I) intermediate and subsequent deprotonation with base produces the final product. An alternative mechanistic pathway is possible in which addition of the cyclohexadienyl radical to palladium(I) followed by β -hydride elimination of the resulting alkylmetal species gives the product.

MANGANESE-CATALYZED CARBOACYLATIONS OF ALKENES WITH ALKYL IODIDES

We also sought to extend the hybrid organometallic-radical reactivity to alkene dicarbofunctionalizations. In contrast to the many examples of alkene difunctionalizations involving the addition of two heteroatoms, alkene dicarbofunctionalizations, involving the formation of two C–C bonds, were rare when we began our studies in this area.⁴⁶ We hypothesized that following the cyclization of the carbon-centered radical as in the alkyl-Mizoroki-Heck work, carbonylation instead of β -hydride elimination would lead to a ring-forming carboacylation process. Early studies indicated that palladium catalysis would not prove suitable for the development of such a transformation, and we became interested in the attractive possibility of using cheaper and more earth-abundant first row transition metals in these reactions. Manganese catalysts are known to participate in both single-electron activation and carbonylation of unactivated alkyl halides and thus appeared suitable for this purpose.^{47–49} Indeed, simple and commercially available $\text{Mn}_2\text{CO}_{10}$ efficiently catalyzed a ring-forming carboacylation of alkenes with alkyl iodides under mild conditions and low CO pressures for the synthesis of a variety of carbocyclic and heterocyclic products (Table 9).⁵⁰

Primary and secondary alkyl iodides underwent successful reactions to form a variety of carbo- and heterocycles via 5-exo, 6-exo, and 7-endo cyclization processes. Both alcohols and amines could be used to intercept putative acylmanganese intermediates in the termination step, delivering ester and amide products in high yield.

PALLADIUM-CATALYZED ALKOXYCARBONYLATIONS OF UNACTIVATED ALKYL BROMIDES

The hybrid organometallic-radical activation mode of palladium catalysis used to generate radical intermediates from alkyl halides has utility in other valuable C–C bond-forming reactions beyond alkene (or arene) addition processes. Carbonylations of aryl and vinyl electrophiles have found widespread use in a range of synthetic contexts.⁵¹ Applications to unactivated alkyl electrophiles are much less precedented, typically requiring high CO pressures, specialized light irradiation, or the use of relatively unstable alkyl iodides as substrates.⁵² We hypothesized that the application of the modes of catalysis described herein would enable a mild, low pressure palladium-catalyzed alkoxy carbonylation of alkyl bromides, constituting the first examples of catalytic carbonylations of unactivated alkyl bromides. Upon identification of a suitable catalytic system featuring 5 mol % $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ as precatalyst and 10 mol % IMes as ligand, a general alkoxy carbonylation was developed.⁵³ A diverse range of aliphatic, heterocyclic, and complex substrates were efficiently transformed using a variety of alcohols as nucleophiles (Scheme 15).

Mechanistic studies of the alkoxy carbonylation are consistent with an activation step involving an irreversible bromine atom abstraction to generate a carbon-centered radical intermediate. The C–C bond-forming step may involve either outer-sphere addition to a carbonyl ligand, or recombination with the palladium center and migratory insertion to

provide an acyl palladium intermediate. Subsequent nucleophilic attack of alkoxide on the acylpalladium intermediate furnishes the product (Scheme 16).

CONCLUSIONS

In recent years, creative applications of hybrid organometallic-radical catalysis by many research groups has led to unique transformations for organic synthesis. Our studies in this area have featured new modes of reactivity in this class using palladium, nickel, and manganese catalysis to develop several valuable C–C bond-forming reactions of unactivated alkyl halides. The transformations developed used widely available and synthetically accessible alkyl iodides and bromides in reactions with ubiquitous chemical building blocks such as alkenes, arenes, and carbon monoxide. Current work continues to develop new reaction platforms for C–C bond construction using unactivated alkyl electrophiles and first-row transition metal catalysts.

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BIOGRAPHICAL INFORMATION

Megan R. Kwiatkowski completed her B.S. in biochemistry in 2015 at the University of Michigan where she conducted undergraduate research with Professor Masato Koreeda. In 2015, she moved to the University of North Carolina at Chapel Hill and began her graduate studies with Professor Erik Alexanian. Her research has focused on the development of metal-catalyzed reactions using unactivated alkyl electrophiles.

Erik J. Alexanian was born in Boston, Massachusetts, in 1979. He earned his A.B. in chemistry in 2001 from Harvard University where he worked in the laboratory of Prof. Amir Hoveyda at Boston College. He obtained his Ph.D. from Princeton University under the direction of Professor Erik Sorensen, and carried out postdoctoral studies with Professor John Hartwig at Yale University and the University of Illinois at Urbana-Champaign. In 2008, he joined the faculty at the University of North Carolina at Chapel Hill and was promoted to associate professor in 2014. Research in the Alexanian laboratory focuses on the development of novel transformations using fundamental synthetic building blocks.

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■ Challenges of two-electron, catalytic activation of alkyl electrophiles.

■ Alternative approach: single-electron activation via inner- or outer-sphere pathways.

Figure 1.

Two- and single-electron activation of unactivated alkyl electrophiles.

Scheme 1.

Non-Carbonylative Pathway Favored in Attempted 6-Exo Carbonylative Carbocyclization.

Scheme 2.

Unexpected Effect of Carbon Monoxide on the Efficiency of the Non-Carbonylative Carbocyclization.

Scheme 3.

Initial Mechanistic Studies Involving Persistent Radical TEMPO.

Scheme 4.
Palladium-Catalyzed Alkyl-Mizoroki-Heck-Type Cross-Coupling.

Scheme 5.

Representative Examples of Palladium-Catalyzed, Intermolecular Alkyl-Mizoroki-Heck-Type Cross-Couplings.

Scheme 6.
Mechanistic Probes for Palladium-Catalyzed Cross-Couplings.

Scheme 7.

Palladium-Catalyzed Carbocyclization of Unactivated Alkyl Bromides.

Scheme 8.

Palladium-Catalyzed Carbocyclization at Short Reaction Time.

Scheme 9.
Proposed Mechanism for the Carbocyclization of Alkyl Bromides Involving Auto-Tandem Catalysis.

Scheme 10.

Proposed Mechanism for the Carbocyclization of Alkyl Iodides Involving an Innate Chain Reaction.

Scheme 11.

Nickel-Catalyzed Alkyl-Mizoroki-Heck-Type Reaction of Unactivated Alkyl Bromides.

Reaction in the Presence of SET Inhibitor 1,4-dinitrobenzene:

Reaction Stopped at Partial Conversion:

Scheme 12.

Mechanistic Studies of the Nickel-Catalyzed Alkyl-Mizoroki-Heck-Type Reaction.

Reaction in the Presence of Persistent Radical TEMPO: *Reaction of Enantioenriched Iodide Stopped at Partial Conversion:* **Scheme 13.**

Mechanistic Studies of the Palladium-Catalyzed C–H Alkylation.

Scheme 14.
Proposed Mechanism of the Palladium-Catalyzed C-H Alkylation.

Scheme 15.

Palladium-Catalyzed Alkoxy carbonylations of Unactivated Alkyl Bromides.

Scheme 16.

Proposed Mechanism for the Catalytic Alkoxy carbonylation.

Table 1.Representative Palladium-Catalyzed Carbonylative Carbocyclizations.^a

entry	substrate	product	yield (%)
1			77 10:1 <i>E:Z</i>
2			55 >25:1 <i>E:Z</i>
3			63 1.3:1 <i>rr</i>
4			74 7.1:1 <i>rr</i>
5			91 1.2:1 <i>dr</i>
6			69
7			90

^aReactions performed with [substrate]₀ = 0.5 M in PhMe at 130 °C under 50 atm CO with 10 mol % Pd(PPh₃)₄ and 2 equiv *i*Pr₂EtN.

Table 2.Representative Palladium-Catalyzed Carbocyclizations of Unactivated Alkyl Iodides.^a

entry	substrate	product	yield (%)
1			80
2			70
3			74 9:1.2:1 rr
4 ^b			73 83:17 dr
5			70 2.3:1 rr
6 ^c			66 >95:5 dr

^aReactions performed with [substrate]₀ = 0.5 M in PhH at 110 °C under 10 atm CO with 10 mol % Pd(PPh₃)₄ and 2 equiv PMP (1,2,2,6,6-pentamethylpiperidine).

^b Reaction temperature 130 °C.

^c Reaction performed under Ar.

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Table 3.Alkyl-Mizoroki-Heck-Type Carbocyclizations of Unactivated Alkyl Bromides.^a

entry	substrate	product	yield (%)
1			90
2			80
3			77 7.2:3:1 rr
4			82 4.3:1 rr
5			93 >95:5 dr
6			65 1:1 <i>E:Z</i>
7 ^b			65

entry	substrate	product	yield (%)
8 ^c			92 1.9:1 rr
9			75 >95:5 dr 1.5:1 E:Z

^aReactions performed with [substrate]₀ = 0.25 M in PhCF₃ at 100 °C with 5 mol % [Pd(allyl)Cl]₂, 20 mol % dtbpf, and 2 equiv Et₃N as base.

^bDBU used as base instead of Et₃N.

^cReaction performed at 120 °C with 5 mol % [Pd(allyl)Cl]₂, 20 mol % dtbpf, and 2 equiv Cy₂NMe as base.

Table 4.

Carbocyclizations of an Alkyl Bromide and Corresponding Iodide in the Presence of a Single-Electron Inhibitor.

entry	conditions	conversion (%) ^a	yield (%) ^a
1	X = Br, no additive	100	77
2	X = I, no additive	100	48
3	X = Br, with 10 mol % dinitrobenzene	<2	<2
4	X = I, with 10 mol % dinitrobenzene	100	78

^aDetermined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.

Table 5.

Dehydrohalogenation Studies of Alkyl Bromide and Iodide ATRC Intermediates.

entry	conditions	conversion (%) ^a	yield (%) ^a
1	X = Br, no additive	100	100
2	X = I, no additive	100	97
3	X = Br, with 10 mol % dinitrobenzene	22	9
4	X = I, with 10 mol % dinitrobenzene	100	100
5	X = Br, no metal or ligand	<2	<2
6	X = I, no metal or ligand	56	37

^aDetermined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.

Table 6.Substrate Scope for Nickel-Catalyzed Alkyl-Mizoroki-Heck-Type Carbocyclizations.^a

entry	substrate	product	yield (%)
1			86 1.1:1 <i>E:Z</i>
2			84 >25:1 rr
3			82 15:1 rr
4			86 1.6:1 <i>E:Z</i>
5			70 >25:1 rr
6 ^b			80 3.1:1 rr
7			64 >25:1 rr

^aReactions performed with [substrate]₀ = 0.25 M in MeCN at 80 °C with 10 mol % NiBr₂·glyme, 10 mol % Xantphos, 3 equiv Mn, and 3 equiv Et₃N as base.

^b Reaction performed with [substrate]₀ = 0.25 M in DMSO.

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Table 7.Substrate Scope for Cross-Couplings of Alkyl Bromides.^a

entry	substrate	product	yield (%)
1			64 5.7:1 <i>Z:E</i>
2 ^{b,c}		Ar = 4-(MeO)-C ₆ H ₄	36 ^d
3			50 7.3:1 <i>Z:E</i>
4			47 5.6:1 <i>Z:E</i>

^aReactions performed with [substrate]₀ = 0.5 M in DMF at 70 °C with 10 mol % Ni(COD)₂, 10 mol % Xantphos, 3 equiv alkene, 3 equiv Mn, and 3 equiv Et₃N as base.

^bReaction performed with [substrate]₀ = 0.5 M in MeCN.

^cNa₂CO₃ used as base instead of Et₃N.

^dYield determined by ¹H NMR spectroscopy of crude reaction mixture using an internal standard.

Table 8.Representative Examples of Palladium-Catalyzed, Ring-Forming C–H Alkylations.^a

entry	substrate	product	yield (%)
1	X = Br		91
2	X = I		85
3 ^b	X = Br		89
4	X = I		51
5 ^b	X = Br		54
6	X = I		82
7	R = H	R = H	70 ^c
8	R = Me	R = Me	90 ^c

^aAll reactions were performed with [substrate]₀ = 0.5 M and 10 mol % Pd(PPh₃)₄ as catalyst. The reactions of alkyl bromides were performed in Ph₃Bu at 130 °C with 2 equiv PMP (1,2,2,6,6-pentamethylpiperidine) as base. The reactions of alkyl iodides were performed in dioxane at 100 °C with 2 equiv K₃PO₄ as base.

^bK₃PO₄ used as base.

^cYield determined by ¹H NMR spectroscopy of crude reaction mixture using an internal standard.

Table 9.Representative Manganese-Catalyzed Carboacylations.^a

entry	substrate	product	yield (%)
1			83 2:1 dr
2		R = OEt 77, 10:1 dr R = NMePh ^b 73, 10:1 dr	
3 ^c			79 1:1 dr
4 ^c			64
5 ^c			78 3:1 dr
6			89 7:1 dr

^a All reactions were performed with [substrate]₀ = 0.13 M in EtOH with 2.5 mol % Mn₂(CO)₁₀, 1 equiv KHCO₃, and 10 atm CO at rt.^b 2 equiv amine and KHCO₃ used.

^c 5 mol % Mn₂(CO)₁₀ used.

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