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Tutorial

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Cross-Coupling and Related Reactions: Connecting Past Success to the Development of New Reactions for the Future

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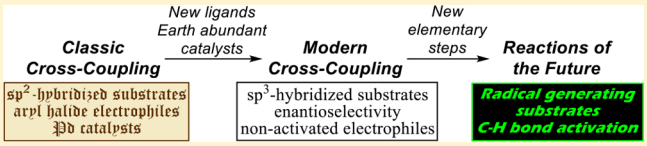
ABSTRACT: Cross-coupling reactions, which were discovered almost 50 years ago, are widely used in both industry and academia. Even though cross-coupling reactions now represent mature technology, there is still a significant amount of research in this area that aims to improve the scope of these reactions, develop more efficient catalysts, and make reactions more practical. In this tutorial, a brief background to cross-coupling reactions is provided, and then the major advances in cross-coupling research over the last 20 years are described. These include the development of improved ligands and precatalysts for cross-coupling and the extension of cross-coupling reactions to a much wider range of electrophiles. For example, cross-coupling reactions are now common with sp^3-hybridized electrophiles as well as ester, amide, ether, and aziridine substrates. For many of these more modern substrates, traditional palladium-based catalysts are less efficient than systems based on first-row transition metals such as nickel. Conventional cross-coupling reactions have also inspired the development of a range of related reactions, such as cross-electrophile and decarboxylative couplings as well as couplings based on metallaphotoredox chemistry. The development of these new reactions is probably at the same stage as traditional cross-coupling reactions 30 years ago, and this tutorial highlights how many of the same strategies used to improve cross-coupling reactions may also be applicable to making the new reactions more practical.



1. INTRODUCTION

Cross-coupling, which traditionally involves the metal-catalyzed coupling of an sp^2-hybridized aryl halide electrophile with an organometallic nucleophile, is an important synthetic method (Figure 1a).[1] Classical cross-coupling reactions are named on the basis of the type of nucleophile used. For example, a reaction that utilizes an organoborane nucleophile is known as a Suzuki–Miyaura reaction, while a reaction that involves an organozinc nucleophile is called a Negishi reaction. The discovery of cross-coupling reactions was facilitated by the observation in the 1940s that simple first-row transition metal salts, such as $FeCl_3$, $CoCl_2$, $NiCl_2$, $CuCl_2$, or $CrCl_2$, act as catalysts for the homocoupling of Grignard reagents using alkyl or aryl halides as oxidizing agents.[2] This led to seminal studies by Kochi in the 1970s describing the use of iron salts for the cross-coupling of alkenyl halides with Grignard reagents.[3] Kochi's reports inspired further studies, and over time, because of its bench stability and high activity, palladium became the metal of choice for catalyzing cross-coupling reactions, which are now used in almost all areas of synthetic chemistry.

The power of cross-coupling reactions can be illustrated through two observations. First, the advent of these methods has enabled the development of expedient synthetic routes for the preparation of molecules with valuable industrial applications.[1] For instance, the synthesis of the blood pressure drug losartan involves a late-stage Suzuki–Miyaura reaction (Figure 1b).[4] Second, and perhaps even more significantly, cross-coupling reactions have inspired novel designs for molecules that would not otherwise have been imagined. This is demonstrated through a comparison of the use of the Suzuki–Miyaura reaction, which was discovered in 1981, in medicinal chemistry in 1984 and 2014. In 1984 there were almost no examples of Suzuki–Miyaura reactions, while in 2014 it was the second most common reaction.[5] The dramatic shift toward cross-coupling reactions such as the Suzuki–Miyaura reaction was also likely partially responsible for the well documented "flattening" of pharmaceuticals in this period toward planar structures.[6] This lends support to the theory that advances in reliable synthetic methods can inspire molecular design and further highlights the incredible impact of cross-coupling. The impact was recognized in 2010 when the Nobel Prize in Chemistry was awarded for the development of palladium-catalyzed cross-coupling reactions.

A major factor in the widespread use of cross-coupling reactions is their reliability and reproducibility compared with many other synthetic methods.[7] In particular, the high success rates of Suzuki–Miyaura reactions are remarkable.[5] Undoubtedly, our detailed understanding of the mechanism of cross-coupling reactions, including knowledge about the nature of the organometallic intermediates and catalyst decomposition

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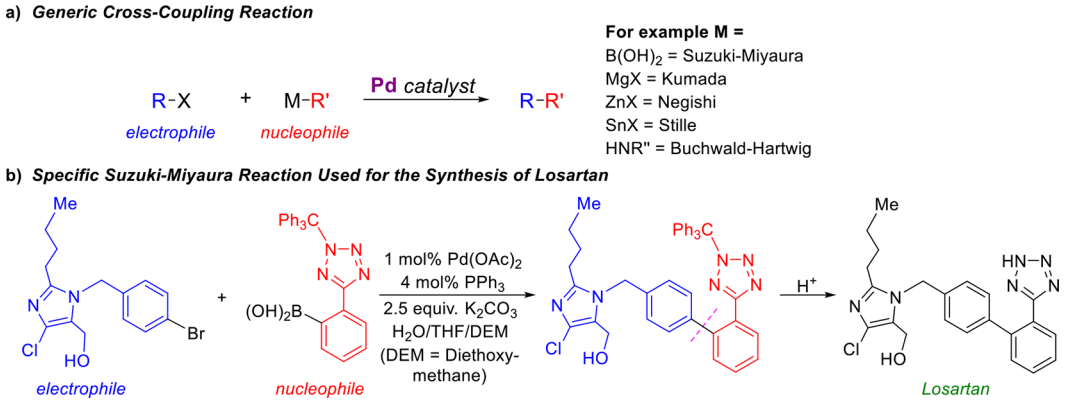

Figure 1. (a) Depiction of a generic cross-coupling reaction. (b) Depiction of the Suzuki−Miyaura reaction used in the synthesis of losartan.

pathways, has contributed to the dependability of these reactions.[1] In general, the mechanism of palladium-catalyzed cross-coupling is proposed to involve a palladium(0)/palladium(II) catalytic cycle (Figure 2). The elementary

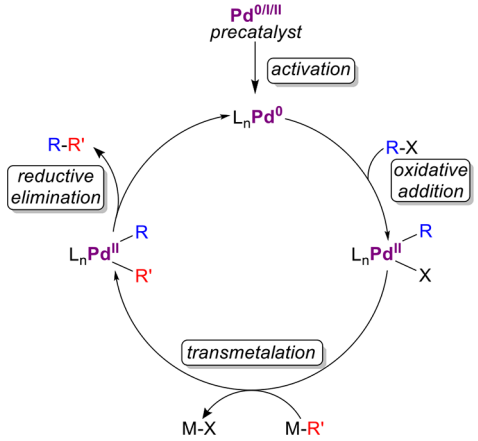

Figure 2. Proposed mechanism for traditional palladium-catalyzed cross-coupling reactions.

steps involved in catalysis are oxidative addition of the electrophile to the coordinatively unsaturated palladium(0) catalyst, transmetalation of the nucleophile, and reductive elimination to form the product and regenerate the palladium(0) catalyst. There is now extensive experimental and computational evidence to support this pathway, and the factors that are important in each of the elementary steps have been elucidated. This has enabled the rational design of highly active and stable catalysts.

Even though palladium-catalyzed cross-coupling is now a mature field, a considerable amount of research is still being performed.[1] This research aims to improve the scope of the reaction, develop more efficient catalysts, and make the reaction more practical. Additionally, over the last 20 years, a major focus has been to extend the reaction to a much broader range of electrophiles than the conventional sp^2-hybridzed aryl halides. For example, there is ongoing research on cross-coupling reactions with less-activated sp^2-hybridized electrophiles, such as amides and esters,[8] as well as sp^3-hybridized substrates.[9] Often these substrates utilize catalysts that are based on metals other than palladium, such as nickel, copper, or iron, and as a consequence, there is a significant amount of current research exploring the development of catalysts for cross-coupling based on more sustainable first-row transition metals.[10] Finally, traditional cross-coupling reactions have directly inspired more modern types of reactions, such as cross-electrophile coupling,[11] conjunctive coupling,[12] and metallaphotoredox chemistry.[13] All of these reactions are likely to greatly expand the scope of cross-coupling, but additional research is still required.

In this tutorial, our goal is to educate the community about recent advances in cross-coupling reactions. We do not aim to thoroughly educate the reader about conventional palladium-catalyzed cross-coupling reactions involving sp^2-hybridized aryl halide electrophiles, as there are already many excellent reviews about this topic.[1] Instead, we provide selected highlights from the last 20 years and then connect the traditional cross-coupling reactions with more modern reactions. We discuss how the strategies that were successful in making cross-coupling practical may also be applicable to these new reactions and how they may inspire solutions to current challenges in synthetic chemistry.

2. RECENT ADVANCES IN TRADITIONAL PALLADIUM-CATALYZED CROSS-COUPLING REACTIONS

In view of the fact that palladium-catalyzed cross-coupling reactions are performed extensively in industry, small improvements in catalyst efficiency can lead to significant economic savings.[1] Therefore, there is always a desire for cheaper and more efficient catalysts, especially in the fine chemical and agrochemical industries, where profit margins are low. Additionally, for both industrial and academic applications it is desirable to use catalytic systems that are not air-sensitive and can easily be handled on the benchtop. Surprisingly, despite the extensive research on palladium-catalyzed cross-coupling, there are still a variety of sp^2-hybridized substrates that are difficult to couple. For example, under basic conditions boronic acids containing fluorinated aromatics or ortho heteroatoms are prone to undergo protodeborylation (Figure 3a), which means that extremely active catalysts are required so that coupling occurs before decomposition.[14] Sterically bulky substrates are also often challenging to couple, and the generation of tetra-ortho-substituted biaryl products requires harsher conditions compared with less sterically bulky substrates (Figure 3b).[15] In the following sections we describe recent advances that are designed to solve some of these problems.

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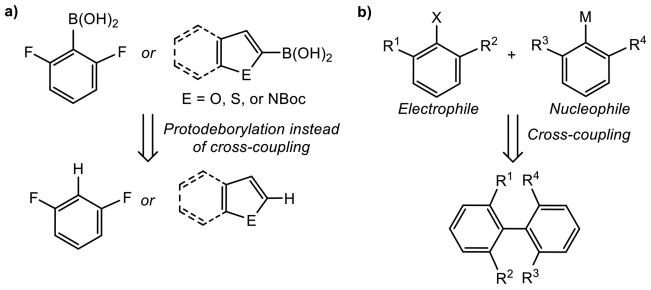

Figure 3. Examples of selected challenges in cross-coupling: (a) protodeborylation of boronic acids; (b) generation of tetra-ortho-substituted biaryl products.

2.1. New Ligands for Cross-Coupling. One of the biggest advances in palladium-catalyzed cross-coupling methodology over the last 20 years has been the development of specialized ligands that enhance the rates of the elementary steps in catalysis, such as oxidative addition and reductive elimination.[16] Historically, simple triarylphosphine ligands were used in cross-coupling, but seminal work from the Buchwald group showed that sterically bulky dialkylbiarylphosphine ligands generated catalytic systems with increased scope and efficiency (Figure 4).[16e] For example, the development of these ligands was in part responsible for the discovery of catalytic systems capable of room-temperature Suzuki–Miyaura reactions involving unactivated aryl chloride substrates[17] and has been crucial to improvements in the scope of Buchwald–Hartwig reactions.[1g] Currently a wide variety of Buchwald-type dialkylbiarylphosphine ligands are commercially available, and the general design principles for promoting both the elementary steps in catalysis and the formation of the active monoligated palladium(0) species are well-understood (Figure 4a). In general, it is also possible to predict which class of ligand, although not a specific ligand, will be best for a certain type of reaction, for example, a Suzuki–Miyaura or Buchwald–Hartwig reaction. It is unlikely that there will ever be a "universal" ligand that is optimal for all cross-coupling reactions, but instead, researchers will be able to choose from a suite of specialized ligands, with the "best" ligand depending on the specific reaction and conditions. Although research into more advanced phosphine ligands for specialized applications continues, it seems likely that these will result in only small improvements in efficiency for traditional cross-coupling reactions. The main improvement that can be made to dialkylbiarylphosphine ligands is probably to make them less expensive or to design new ligands that give comparable activity but are cheaper.

Over the past decade, N-heterocyclic carbene (NHC) ligands have become increasingly popular in cross-coupling reactions.[16f,g,k] NHC ligands are typically better σ donors than phosphines, and in an analogous fashion to phosphine ligands, their steric bulk can be tuned (Figure 5). Initially, simple NHC ligands such as IPr and IMes were primarily used in catalysis,[16f,g] but an array of NHCs with increased steric bulk have recently been prepared.[16k] These specialized ligands are often particularly efficient for coupling of sterically bulky substrates,[18] but like the recently developed phosphine ligands, they are expensive. Unfortunately, at the moment there is often relatively little understanding about whether a phosphine or NHC ligand will be more effective for a particular reaction, and experimental testing is generally required to optimize the ancillary ligand for a particular reaction. We suggest that computational chemistry has a large role to play in

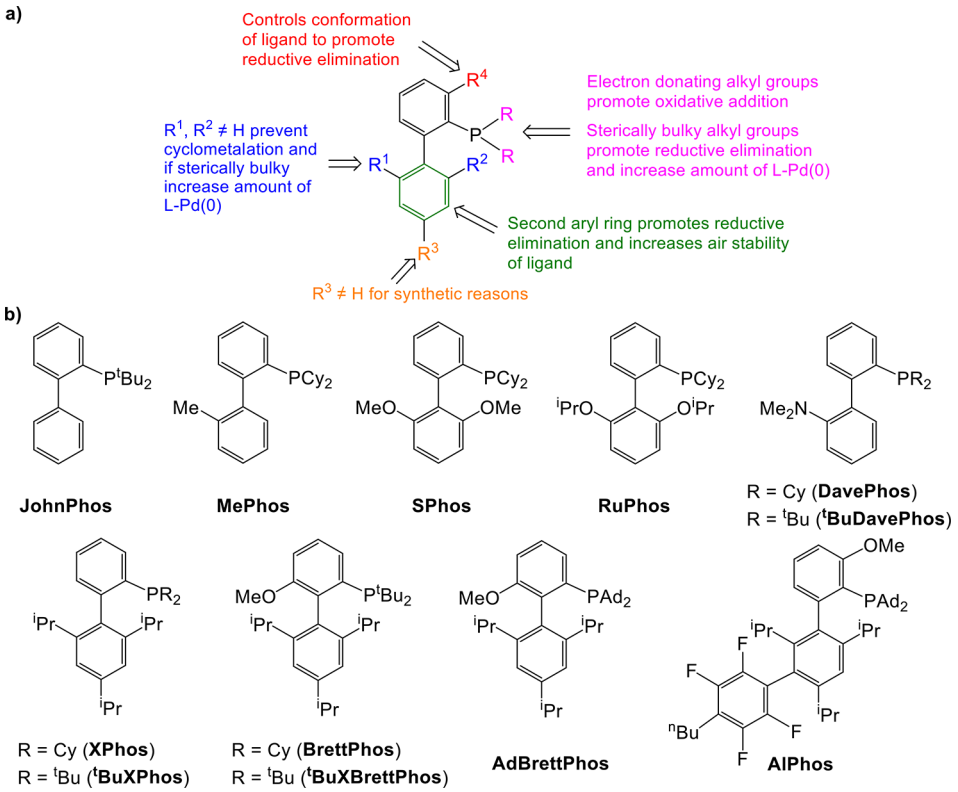

Figure 4. (a) Generic advantages and design principles of Buchwald-type dialkylbiarylphosphine ligands. (b) Specific examples of common dialkylbiarylphosphine ligands.

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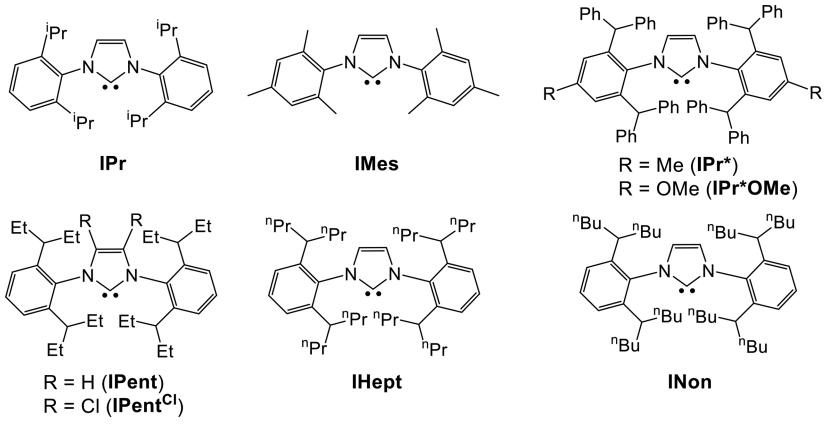

Figure 5. Examples of NHC ligands that are commonly used in cross-coupling reactions.

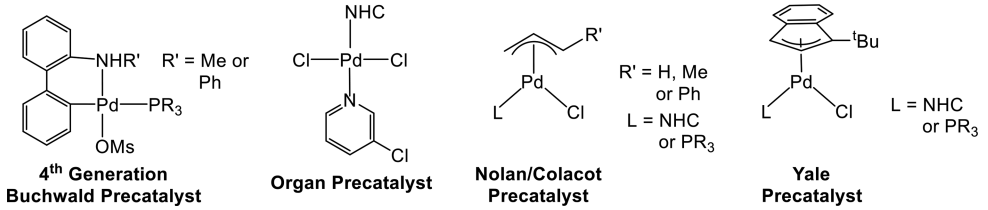

Figure 6. Selected examples of commercially available bench-stable palladium(II) precatalysts for cross-coupling.

understanding ligand effects in cross-coupling reactions, in part because of the instability of the key intermediates, which makes experimental studies challenging.

2.2. The Development of Precatalysts for Cross-Coupling. The specialized phosphine and NHC ligands described in the previous section often have comparable expense with respect to the palladium precursors employed in catalysis. This means that the traditional route for generating the active species, addition of excess ligand to a palladium(0) precursor, is no longer attractive. Furthermore, in many cross-coupling reactions the optimal palladium to ligand ratio is 1:1 and the active species is proposed to be monoligated palladium(0),[1h,19] so it is not desirable to have excess ligand present. As a result, a number of well-defined bench-stable palladium(II) precatalysts with a 1:1 palladium to ligand ratio have been developed and are now commercially available (Figure 6).[1h,19] These precatalysts can be divided into classes that have different strengths and weaknesses. Buchwald has designed a series of precatalysts based on a palladacycle framework that feature an aminobiphenyl ligand.[14a,20] Four generations of precatalysts have now been developed, with each generation improving on weaknesses in earlier systems. The Buchwald-based precatalysts are especially active with phosphine ligands but to date have not been utilized with NHC ligands. A highly active class of precatalysts that are compatible with NHC ligands are Organ's PEPPSI-based precatalysts.[21] The efficiency of these systems is related to the speed at which they activate to the monoligated palladium(0) active species. An alternative to PEPPSI-based systems are precatalysts which feature an allyl, crotyl, or cinnamyl ligand.[22] These systems were initially used exclusively with NHC ligands by Nolan,[16f] but recent work from Colacot has demonstrated that they are also compatible with state-of-the-art Buchwald phosphines.[23] By studying the mechanism of activation of Nolan-type precatalysts, researchers at Yale designed a related system featuring a 1-^{t}BuIndenyl ligand.[24] Precatalysts incorporating a 1-^{t}BuIndenyl ligand are compatible with both NHC and phosphine ligands and are even more efficient than allyl-, crotyl-, or cinnamyl-based precatalysts for a variety of different cross-coupling reactions. Apart from providing highly efficient catalytic systems, precatalysts are also useful for ligand screening. The Buchwald, Nolan, and Yale systems all have ligand-free precursors, (2-aminobiphenyl)$_2$(μ-OMs)$_2$Pd$_2$, (η^3-cinnamyl)$_2$(μ-Cl)$_2$Pd$_2$, and (η^3-1-^{t}BuIndenyl)$_2$(μ-Cl)$_2$Pd$_2$ respectively, which can be converted into the ligated precatalyst through treatment with a ligand in situ. These ligand-free precursors allow rapid screening of a variety of different ligands for a reaction without the need for the synthesis or isolation of a family of well-defined precatalysts. This is important because, as described above, it is often difficult to predict which ligand system will be optimal for a particular cross-coupling reaction. Similarly, predicting which precatalyst will be the "best" for a particular reaction is not straightforward, and the best precatalyst will vary depending on both the reaction and the conditions. In fact, for most cross-coupling reactions, some empirical optimization of the precatalyst and ligand will be necessary to find the optimal conditions. At this stage, despite overwhelming evidence that precatalysts lead to improved activity over conventional systems like Pd(PPh$_3$)$_4$ or Pd(dba)$_2$ (dba = dibenzylideneacetone) and free ligand and are often easier to use, their potential has not been fully exploited by synthetic chemists, especially in academia. Because of their widespread benefits we expect there will be increased use of precatalysts over the next decade.

2.3. Practical Improvements in Cross-Coupling Methodology. Given the synthetic power of cross-coupling reactions, it is not surprising that researchers have developed methods to perform and optimize these reactions in a variety of innovative ways. In this tutorial we provide details about two modern strategies for performing cross-coupling reactions that have found relatively widespread use, especially in

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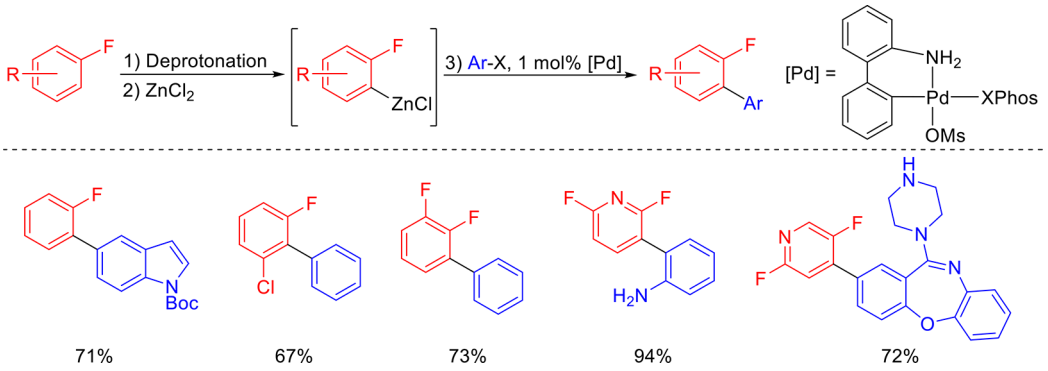

Figure 7. Flow cross-coupling of fluorinated aromatics and heteroaromatics.

industry. We note, however, that research into the development of methods to make cross-coupling more practical is ongoing, and there are recent strategies, such as the incorporation of air-sensitive catalysts in waxes,[25] that may become more common over the next decade.

High-Throughput Experimentation Methods. The use of high-throughput experimentation to perform cross-coupling reactions is a prime example of an innovative strategy to make research more practical.[26] Historically, the two main challenges preventing widespread adoption of high-throughput experimentation were (1) analysis (i.e., could the desired output be measured fast enough to be useful?) and (2) miniaturization (i.e., could small-scale screening be easily performed and reproduced upon scaling of reactions to conventional reaction setups?). Improvements in the range of equipment and instruments available to synthetic chemists has largely solved the first challenge.[27] For example, autosamplers alone can alleviate a significant amount of the burden associated with analyzing experiments. Additionally, improved analytical techniques, such as supercritical fluid chromatography (SFC) and ultraperformance liquid chromatography (UPLC), with their short analysis times, have dramatically improved researchers' ability to evaluate their experiments. Furthermore, the combination of these techniques with protocols for rapid analysis, such as MISER chromatography, can greatly accelerate the screening of catalysts or reaction conditions.[28]

The second challenge, miniaturization, has required more experimentation and involved solving many individual problems. First, because each reaction discovery/optimization array tends to require a unique design, automation of their assembly was historically often cumbersome and slow. Improvements in software have made the process of setting up high-throughput experiments more facile, and at this point a person with minimal training outside of conventional organic synthesis can easily conduct these experiments. Second, most cross-coupling reactions are performed under inert conditions. This obstacle was overcome by setting up experiments in gloveboxes or glovebags. Third, a convenient method for the generation of the active species in catalysis was required. Mixtures of palladium(II) precursors and ligands cannot be stored together for extended periods, as they can react even in the solid state. Therefore, a key breakthrough for high-throughput experimentation methods was the development of robust palladium precatalysts that enable the rapid generation of palladium(0) under the reaction conditions (vide supra) and often enable facile ligand screening. These stable precatalysts have facilitated a large amount of research using high-throughput experimentation, in part because they result in fewer false negatives. Precatalysts can also be directly utilized for scale-up, which avoids any reproducibility issues associated with a specialized experimental setup for precatalyst activation. Fourth, many cross-coupling reactions are heterogeneous, which means that mixing the solutions is important. For very small volume reactions (<100 μL) or larger arrays (96-well plates), tumble stirring has overcome this problem. In contrast, reactions in smaller arrays of 24-well plates using >100 μL of solvent can usually be performed on a standard hot plate. All of these advances have led to the development of nanomole-scale screening using robotics to control dosing of solutions, a truly remarkable demonstration of miniaturization.[29] Overall, the benefits of high-throughput experimentation for the development and optimization of cross-coupling reactions are evident by the widespread use of this technology in industry. We anticipate that the recent development of more user-friendly technology that requires minimal capital investment should drive more academic institutions to start investing in high-throughput experimentation tools in the near future.

Flow Chemistry. Performing cross-coupling reactions using flow chemistry instead of in batch mode can improve reaction rates, yields, and selectivities and allow for integration into an existing sequence of reactions in flow.[30] Packed-bed reactors with immobilized palladium catalysts have been successfully applied to cross-coupling reactions. Because of the large amount of catalyst present in the reactor, this approach can accelerate reactions and in principle should prevent product contamination with the catalyst. However, there is strong evidence that soluble palladium species leach from these immobilized systems, leading to the eventual deactivation of the catalyst bed and contamination of the reaction products. Consequently, in the absence of another driving force for flow reactors, these packed-bed reactors are usually not a superior option to homogeneous systems, and further research into immobilized systems that are less prone to leaching is required. One potential driver for the use of flow reactors is in integrated systems to handle reactive or unstable intermediates. For example, the presence of fluorinated aryl groups in a molecule can be beneficial in medicinal chemistry, but fluorinated aryl nucleophiles are often unstable, making them difficult to use as coupling partners. To solve this problem, Buchwald and co-workers generated thermally unstable fluorinated arylzinc species in flow and used them directly in Negishi couplings (Figure 7).[31] This procedure was used to generate a range of important fluorinated biaryls in

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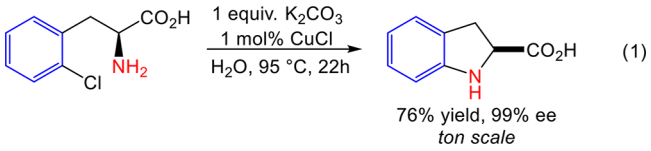
high yields, which would have been difficult using a batch reactor.

2.4. Base Metal Catalysts as Alternatives to Palladium. Palladium-based systems are used in the vast majority of industrial processes involving conventional cross-coupling reactions with sp^2-hybridized substrates because of their high activity and bench stability.[1] Nevertheless, there are disadvantages to using palladium-based catalysts. Palladium is not an abundant metal, and as a consequence, for both environmental and economic reasons it would be desirable to find alternative catalysts, particularly for large-scale transformations. Additionally, for pharmaceutical applications, the amount of palladium that is permissible in drugs must be tightly controlled at low (ppm) levels.[32] It can be expensive to reduce the palladium content to such levels, especially if cross-coupling is used at a late stage in the synthesis of an active pharmaceutical ingredient. To circumvent these issues, there has been considerable research, especially in the last 10 years, into the development of more abundant first-row transition metal catalysts for cross-coupling.[10] Research into first-row transition metal complexes has focused primarily on iron-, nickel-, and copper-based systems, although recently cobalt-based catalysts have also been developed.[10] Despite intensive recent research, these first-row systems generally give lower activity than palladium for traditional cross-coupling reactions and require significantly higher catalyst loadings and harsher reaction conditions.

One reason that palladium systems may operate under milder conditions in comparison to first-row transition metal systems is that researchers have been exploring palladium-catalyzed cross-coupling for approximately 50 years. Over this time there has been a significant amount of optimization of ancillary ligands, palladium sources, and reaction conditions. Often this optimization is based on detailed mechanistic studies, which have elucidated the nature of the fundamental steps in catalysis. In contrast, research into the development of first-row transition metal based systems is in its infancy, with sustained research having been performed in only the last 15 years. Typically, conditions and ligands that have been optimized for palladium have been employed in the development of systems using first-row transition metals. However, in view of the different reactivity of first-row transition metal complexes compared with palladium (e.g., first-row transition metal complexes are significantly more likely to access odd-electron oxidation states), it is unlikely that the optimal ligands and reaction conditions for palladium are also the best for first-row transition metal systems. A noteworthy example where reaction conditions have been optimized independently of palladium are copper-based systems for Buchwald–Hartwig reactions (eq 1).[10g,33]



This optimization led to systems that are now used on a large scale, which is unusual for first-row transition metal catalysts. The different reactivity of first-row transition metals compared with palladium can be an advantage in cross-coupling reactions that do not use traditional sp^2-hybridized substrates and in the development of new reactions related to cross-coupling. Specific examples that highlight this point are provided in later sections of this tutorial. At this stage, it is still too early to determine whether it will be possible to develop first-row transition metal systems for traditional cross-coupling reactions that will rival or surpass palladium catalysts. Nevertheless, if first-row transition metal catalysts are to replace palladium systems, many of the same improvements that have occurred for palladium systems, such as the development of specialized ligands and precatalysts, are required. An increase in mechanistic understanding, including knowledge about catalyst decomposition pathways, will likely facilitate this process. Overall, in our opinion, given the high efficiency of palladium-based systems and the opportunity to recycle the catalyst at the end of reactions, researchers should concentrate on developing new reactions using systems based on first-row transition metals rather than replacing palladium in conventional reactions.

3. NEW SUBSTRATES FOR TRADITIONAL CROSS-COUPLING REACTIONS

The extension of cross-coupling to substrates other than standard sp^2-hybridized aryl halide or pseudo-halide electrophiles is a major focus of contemporary cross-coupling research. The aims of this research are to increase the range of potential substrates that can be used in cross-coupling reactions and to make cross-coupling reactions more versatile, sustainable, and atom-efficient. Significant progress has been made, and a vast number of electrophiles can now be utilized. For many of these reactions it has proven beneficial to use metal catalysts that are not based on palladium. In the following sections we summarize cross-coupling reactions involving nontraditional electrophiles.

3.1. Cross-Coupling Reactions Using sp^3-Hybridized Substrates. For many years cross-coupling reactions were almost exclusively limited to sp^2-hybridized substrates. Although C–C bonds between two sp^2-hybridized carbon atoms are common in organic molecules, C–C bonds between two sp^3-hybridized carbon atoms are even more abundant.[9] Therefore, there is great value in synthetic methods that can controllably form alkyl–alkyl bonds. Historically, when sp^3-hybridized substrates were utilized in cross-coupling reactions, rapid β-hydride elimination was observed before any productive coupling (Figure 8). Another challenge was that oxidative addition of sp^3-hybridized electrophiles was often considerably slower than that of sp^2-hybridized substrates. In a seminal paper in 2001, Fu and co-workers reported room-

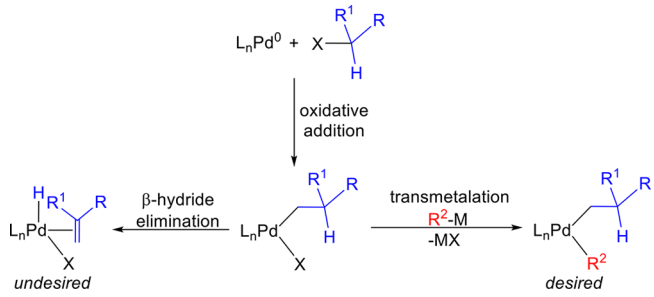


Figure 8. Competition between β-hydride elimination and transmetalation in cross-coupling with sp^3-hybridized substrates. After oxidative addition, β-hydride elimination is an undesired side reaction when alkyl substrates are used. If the nucleophile contains a β-hydride, reductive elimination is also in competition with β-hydride elimination (not shown in the figure).

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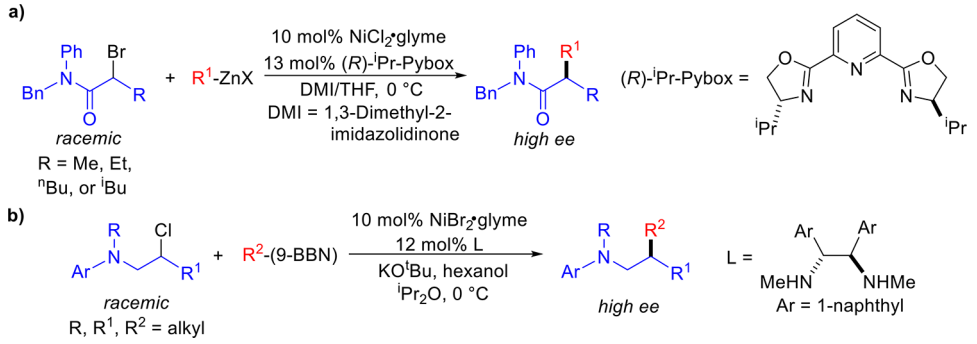


Figure 9. Selected examples of stereoconvergent (a) Negishi and (b) Suzuki–Miyaura reactions using racemic alkyl electrophiles.

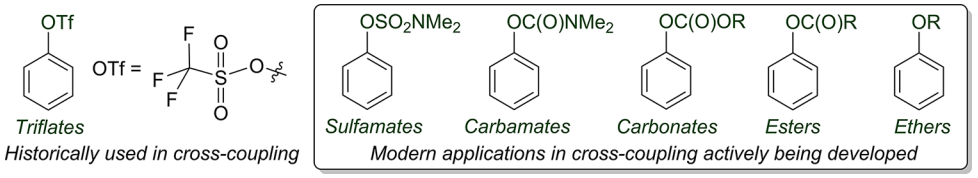
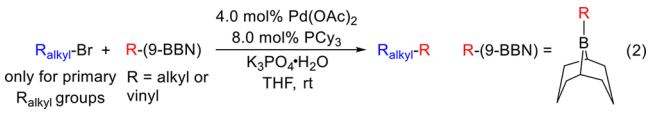


Figure 10. Phenol derivatives that are used as electrophiles in cross-coupling.

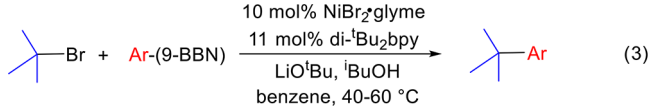
temperature palladium-catalyzed alkyl–alkyl Suzuki–Miyaura reactions using alkyl bromides as the electrophile (eq 2).[34]

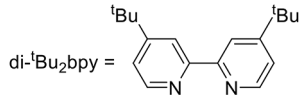


Unlike most previous examples of sp^3-hybridized cross-coupling, the reaction was compatible with substrates that contained a β-hydrogen. Furthermore, previous cross-coupling reactions had generally required harsh nucleophiles, such as Grignard reagents, whereas this reaction could be performed using organoboranes, which are compatible with a greater variety of functional groups. This methodology has been utilized in the synthesis of a number of natural products.[9b] However, the reaction is limited to primary alkyl bromides, as the oxidative addition is proposed to proceed through an S_N2 reaction, and secondary and tertiary alkyl halides are less likely to undergo S_N2 reactions.

Nickel is more likely to undergo one-electron redox reactions compared with palladium because of its lower ligand field splitting, which for square-planar nickel(II) complexes means that it is easier to add an electron to the antibonding $d_{x^2-y^2}$ orbital or move to a tetrahedral geometry.[35] A consequence of the greater tendency for one-electron chemistry is that nickel catalysts more readily undergo oxidative addition via a radical pathway than analogous palladium systems. Building on work by Knochel for primary alkyl halide electrophiles,[36] Fu developed nickel-based catalysts for Negishi and Suzuki–Miyaura reactions involving secondary alkyl halide electrophiles.[37] Mechanistic studies suggest that these reactions do indeed proceed via radical pathways. The use of secondary alkyl substrates also adds another dimension to the reaction, as in principle enantiomeric products can be formed. As the oxidative addition involves the formation of a radical, the stereochemical information in the electrophile is ablated. The use of a chiral nickel catalyst makes it possible to generate a single enantiomer of the product starting from a racemic starting material. Both unactivated and activated racemic mixtures of alkyl halides have now been utilized in stereoconvergent Suzuki–Miyaura and Negishi cross-coupling reactions (Figure 9).[38] Generally, chiral bidentate nitrogen-containing ligands are sufficient to promote enantioselectivity, but in some cases a directing group on the electrophile is also required in order to obtain high enantioselectivites.[39] The reverse reaction, in which a racemic mixture of a nucleophile is enantioselectively coupled with an electrophile, has also been demonstrated,[40] but to date there are no examples of racemic mixtures of both the electrophile and nucleophile being coupled to generate a single diastereomer.

The number of examples of cross-coupling reactions utilizing tertiary alkyl electrophiles to generate quaternary carbon centers is much lower than reactions involving either primary or secondary electrophiles.[41] A notable example was described in 2013 when unactivated tertiary alkyl bromides were used in nickel-catalyzed Suzuki–Miyaura reactions (eq 3).[42]





Nevertheless, general methods involving tertiary electrophiles remain elusive, and enantioselective approaches still need to be developed. In general, there is still room for significant improvement in the catalyst loadings for cross-coupling reactions using sp^3-hybridized substrates, and at this stage, specialized ligands have not been designed. Additionally, the functional group tolerance of cross-coupling reactions involving two sp^3-hybridized substrates is significantly lower than for two sp^2-hybridized substrates, especially when acidic functional groups are present. This challenge needs to be addressed to make these reactions more synthetically valuable. Finally, examples of C–N and C–O bond formation using alkyl electrophiles are rare, and this is an area where further catalyst development is required.[43]

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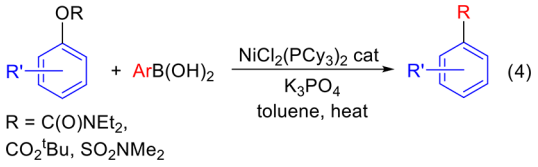
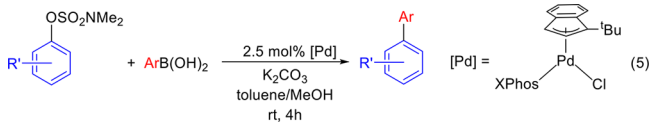
3.2. Cross-Coupling Reactions Using Phenol Derivatives. Phenolic derivatives, such as those shown in Figure 10, are robust and easy to synthesize from ubiquitous phenols,[44] and they offer unique advantages for cross-coupling compared with aryl halides.[45] For example, phenol-containing moieties are intermediates in many target-oriented syntheses and can be used as coupling partners after activation when analogous halides would be difficult to access.[46] Additionally, in some cases phenol derivatives can act as directing groups for prefunctionalization of the aromatic backbone of the electrophile through directed ortho-metalation prior to cross-coupling.[47] Although simple phenol derivatives such as aryl sulfonates (e.g., triflates, mesylates, and tosylates) are often used in cross-coupling,[45b,48] these moieties are not useful directing groups.[49] The reactivity of aryl sulfonates in cross-coupling is well-established, and therefore, in this tutorial we focus on the development of methods for cross-coupling involving less reactive phenol derivatives, such as sulfamates, carbamates, esters, and ethers. We note that the reactivity of phenol derivatives in cross-coupling is also often orthogonal to that of aryl halides, which enables selective sequential coupling at each site. This concept was elegantly utilized by Garg in the synthesis of the anti-inflammatory drug flurbiprofen[50] but still has not been fully explored. In general, the development of synthetic methods for the coupling of phenol derivatives that are compatible with aryl halides will be advantageous for synthesis, and this should be a goal of research in this area.

Sulfamates, Carbamates, and Carbonates. In independent reports in 2009, both Garg[50] and Snieckus[51] described Suzuki–Miyaura reactions involving aryl carbamates using nickel precatalysts with monodentate phosphine ligands. This discovery was noteworthy because carbamates are excellent directing groups for C–H functionalization via ortho-metalation reactions. The reaction conditions developed by the two groups were similar, although Snieckus and co-workers used boronic esters while Garg and co-workers utilized boronic acids. Garg demonstrated that the reaction conditions developed for coupling of aryl carbamates could also be utilized to couple aryl sulfamates and carbonates (eq 4).



In general, Suzuki–Miyaura reactions using aryl sulfamates, which can also be used as directing groups for C–H functionalization, give higher yields than those involving either aryl carbamates or carbonates. Mechanistic studies suggest a standard mechanism involving initial oxidative addition of the aryl sulfamate, carbamate, or carbonate followed by turnover-limiting transmetalation and reductive elimination of the product.[52] The initial reaction conditions required high temperature (>100 °C), high catalyst loadings, and large numbers of equivalents of boronic acid and base. Subsequent optimization of the precatalyst and ancillary ligand has resulted in systems for the coupling of activated naphthyl sulfamates that operate at room temperature with catalyst loadings of 2.5 mol % and lower numbers of equivalents of boronic acid and base.[53] It was also demonstrated that aryl carbamates and sulfamates could be used as substrates in Buchwald–Hartwig reactions using nickel catalysts supported by NHC ligands.[54] It is unclear why phosphine ligands are preferred for Suzuki–Miyaura reactions and NHC ligands are better for Buchwald–Hartwig reactions.

The first reports of cross-coupling reactions involving aryl sulfamates, carbonates, and carbamates all utilized nickel catalysts. It was suggested that nickel outperformed palladium for these substrates because they do not readily undergo oxidative addition, and oxidative addition is kinetically more facile with nickel. Recently, however, the use of Buchwald-type ligands with palladium systems for Suzuki–Miyaura reactions involving aryl sulfamates was reported (eq 5).[55]



The conditions for these reactions are milder than those typically used for nickel. In fact, the best palladium systems for Suzuki–Miyaura reactions involving aryl sulfamates are almost as efficient as those that utilize aryl chlorides, demonstrating how readily these substrates can now be coupled. However, these reactions are not compatible with aryl halides. In contrast, no palladium systems for the coupling of aryl carbonates or carbamates have been developed, and there is a need for systems that operate under milder conditions and use a lower number of equivalents of boronic acids for these substrates to be practical in synthesis.

Esters. Unactivated aryl esters are valuable substrates for cross-coupling because they are often readily synthesized from phenols[44] or carboxylic acids,[56] are bench-stable, and are common intermediates in organic synthesis. Additionally, because they are relatively unreactive, they can be installed early in a synthesis, carried through numerous steps, and then functionalized at a late stage. The first reports of the use of esters in reactions related to cross-coupling appeared around 2000, and these initial studies facilitated the large amount of research that has been performed in this area over the past decade.[45e,57] When aryl esters are used as electrophiles in cross-coupling, three different reactions have been observed depending on the reaction conditions (Figure 11):[8b–d] either

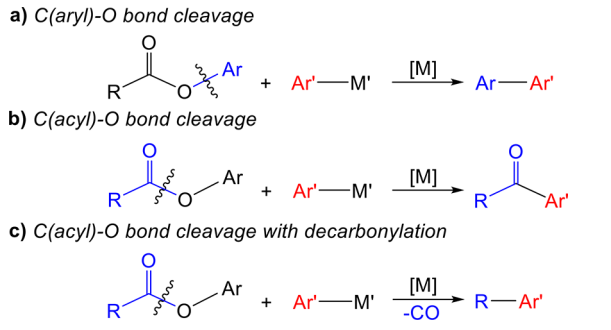


Figure 11. Generic representations of the different types of cross-coupling reactions involving aryl ester electrophiles.

the C(aryl)–O bond or the C(acyl)–O bond can be cleaved, and activation of the C(acyl)–O bond can be followed by decarbonylation, providing another alternative pathway. Catalysts that are selective for all three possible reactions are known, and there is some mechanistic understanding about the factors that are important in promoting one pathway over another.[8b–d] In general, the conditions required for aryl ester cross-coupling are harsh (in terms of both catalyst loading and

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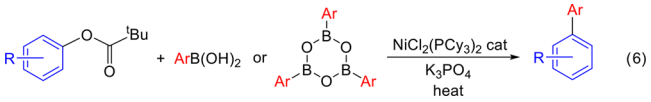
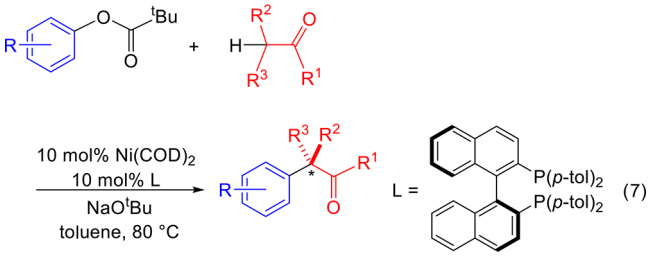
temperature), and improvements are required to provide more practical systems. To date, the development of catalysts for the coupling of esters has utilized many of the major advances outlined in section 2 for the improvement of traditional palladium-catalyzed cross-coupling reactions, including the use of ligands tailor-made for cross-coupling and the use of well-defined precatalysts.

In independent reports in 2008, Garg[58a] and Shi[58b] reported nickel-catalyzed Suzuki−Miyaura reactions to form biaryls involving aryl esters in which the C(aryl)−O bond is cleaved (eq 6).



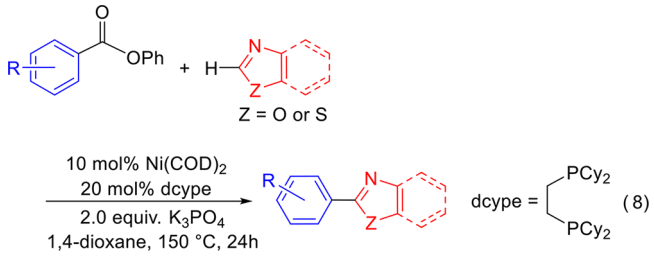
(6)

This is noteworthy because the C(aryl)−O bond is significantly stronger than the C(acyl)−O bond. Computational studies suggest that the barrier for oxidative addition of the C(acyl)−O bond is lower than the corresponding barrier for cleavage of the C(aryl)−O bond but that oxidative addition of the C(aryl)−O bond is thermodynamically preferred.[59] However, experimental studies on the oxidative addition of the C(aryl)−O bond in esters to low-valent nickel complexes are rare, and there is still a need for fundamental information to understand all of the factors that are important in this process compared with more traditional electrophiles such as aryl halides.[60] The next step in the catalytic cycle is transmetalation, which is turnover-limiting. As a result, the oxidative addition step is under thermodynamic control (reversible), and cleavage of the C(aryl)−O bond is observed. Sterically bulky aryl pivalates are optimal for Suzuki−Miyaura reactions involving aryl esters, as they are less likely to undergo hydrolysis compared with acetates, although the reaction conditions are still harsh. Additionally, naphthyl-based pivalates are significantly more reactive than phenyl-based pivalates because they more readily undergo oxidative addition. Since the initial discovery of Suzuki−Miyaura reactions with aryl pivalates, nickel-catalyzed Negishi,[61] Buchwald−Hartwig,[62] silylation,[63] and Heck[64] reactions featuring aryl pivalates have all been developed. Martin[65] reported a nickel-catalyzed enantioselective reaction involving coupling of aryl pivalates with prochiral ketone enolates (e.g., 2-methyl-1-indanone) (eq 7), demonstrating the potential for aryl esters to be used as electrophiles for a diverse range of reactions. In order for these reactions to be more widely used, it is crucial to find milder reaction conditions that still allow the oxidative addition step to be under thermodynamic control and to extend the substrate scope, especially for non-naphthyl-based pivalates.



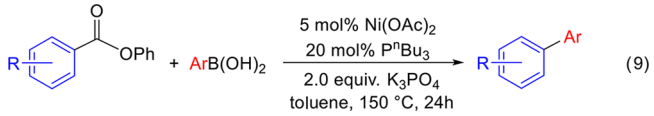
(7)

The first examples of cross-coupling reactions involving cleavage of the C(acyl)−O bond in esters or related substrates predominantly involved decarbonylation.[8b−d] These reactions typically used reactive acid anhydrides as substrates, as opposed to unactivated aryl esters. In 2012, Yamaguchi and Itami reported the nickel-catalyzed decarbonylative coupling of phenyl esters with azoles (eq 8).[66]



(8)

This reaction, which involved both a base metal catalyst and a simple unactivated ester, prompted significant research into decarbonylative coupling reactions using phenyl esters. Subsequently, in 2015, Yamaguchi, Itami, and Musaev[67a] and Love[67b] independently described nickel-catalyzed decarbonylative Suzuki−Miyaura reactions involving phenyl esters (eq 9).



(9)

Yamaguchi, Itami, and Musaev demonstrated that the reaction was compatible with a large number of substrates (more than 50) and could be performed on a gram scale. Phenyl esters have now been used as electrophiles for decarbonylative metal-catalyzed Sonogashira[68] and Buchwald−Hartwig reactions[69] as well as related reactions that generate ethers,[70] aromatic silanes,[71] and boranes.[71b] Most of these reactions are nickel-catalyzed, as nickel can undergo both oxidative addition of the C(acyl)−O bond and relatively rapid decarbonylation of the oxidative addition product. The reactions are typically performed well above the boiling point of the solvent, presumably to drive the release of CO and possibly prevent catalyst poisoning. The development of reactions that can be performed at lower temperatures would be advantageous and may require the development of reaction vessels that allow gas to be constantly removed from solution. To date, standard ligands have been utilized, such as simple monodentate or bidentate phosphine ligands, and there may be benefits associated with the rational design of specialized ligands for these transformations.

Metal-catalyzed cleavage of the C(acyl)−O bond in esters, followed by transmetalation and reductive elimination without decarbonylation, can lead to the formation of ketones or amides depending on the nucleophile utilized (Figure 12). The first example of this type of reaction was described by Chatani and co-workers.[72] Using a palladium catalyst, they demonstrated Suzuki−Miyaura reactions using 2-pyridyl esters to generate a range of ketones. The pyridyl group was proposed to assist in oxidative addition to the metal center through chelation of the nitrogen atom. In 2017, Newman utilized a palladium precatalyst supported by an NHC ligand to perform Suzuki−Miyaura reactions using a variety of unactivated phenyl esters.[73] The use of unactivated phenyl esters dramatically increases the scope of this reaction and is an improvement in terms of chemoselectivity, functional group tolerance, and atom economy compared with standard stoichiometric routes for the synthesis of aryl ketones, such as the addition of organometallic nucleophiles to Weinreb amides. Subsequently, with the Yale precatalyst, ketone

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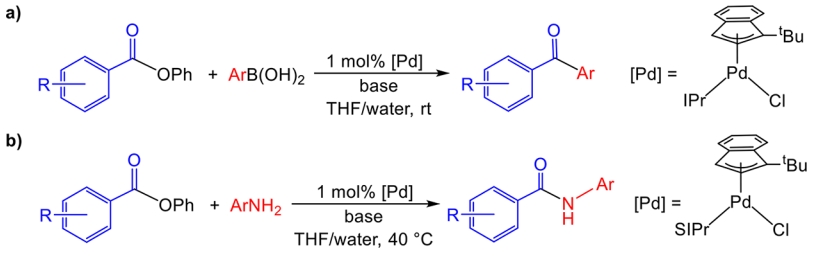
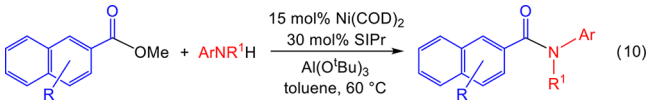


Figure 12. Examples of (a) Suzuki–Miyaura and (b) Buchwald–Hartwig reactions involving cleavage of the C(acyl)–O bond in phenyl esters.

formation at room temperature with a low catalyst loading was reported.[74] The conditions required for Suzuki–Miyaura reactions involving C(acyl)–O bond cleavage of phenyl esters are now comparable to those utilized for aryl halides. Similarly, using well-defined precatalysts, efficient systems for the formation of amides through the coupling of esters with amines have been developed.[74b,75]

For the formation of both ketones and amides through coupling reactions involving C(acyl)–O bond cleavage in esters, NHC ligands give vastly superior performance compared with phosphine ligands, although the reasons behind this are unclear. It is also noteworthy that although nickel catalysts are predominantly used for decarbonylative coupling reactions, palladium systems have been mainly used for ketone or amide formation. Palladium systems presumably undergo transmetalation more rapidly and/or decarbonylation less rapidly than nickel systems. One notable exception to the almost exclusive use of palladium systems for ketone or amide formation is Garg's report that a catalytic system generated by in situ reaction of $Ni(COD)_2$ and SIPr can cleave the C(acyl)–O bond in methyl esters and facilitate coupling with amines to form amides (eq 10).[76]



This reaction is a rare example of coupling using methyl esters, which are more synthetically valuable than phenyl esters (because of their increased stability), but it requires the addition of an excess of the strong Lewis acid $Al(O^tBu)_3$. Additionally, only substrates with extended aromatic groups, such as methyl 1-naphthoate, can be successfully used as the electrophile, likely because extended aromatic groups help with oxidative addition. Newman recently reported a system that does not require a Lewis acid and has a greater substrate scope, but high temperatures are still required.[77] The development of milder methods to couple methyl (or other alkyl) esters would greatly enhance this methodology and should be a goal of future research.

Ethers. Aryl ethers are ubiquitous and stable functional groups that do not suffer from the selectivity problems associated with aryl esters in cross-coupling reactions. The first report of the use of aryl ethers as electrophiles in cross-coupling reactions occurred in 1979, when Wenkert described nickel-catalyzed Kumada–Corriu couplings (Figure 13).[78] The reaction was only compatible with naphthyl ethers, and the functional group tolerance was poor. As a consequence, little research was performed into cross-coupling reactions using aryl ethers for more than 25 years. In 2004, Dankwardt[79] increased the scope of Kumada–Corriu couplings using aryl ethers by changing the ancillary phosphine ligand on the nickel

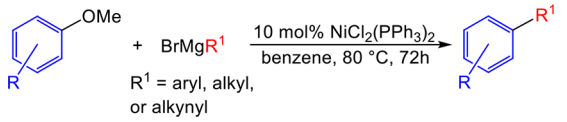
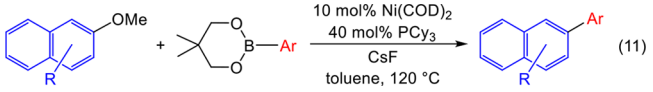
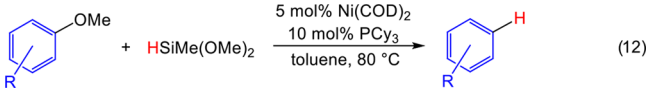


Figure 13. General scheme for nickel-catalyzed Kumada–Corriu couplings involving aryl ethers.

catalyst. Subsequently, Chatani and co-workers described nickel-catalyzed Suzuki–Miyaura reactions using naphthyl ethers in the presence of a cesium fluoride additive, which assisted with transmetalation (eq 11).[80]



These results, along with a report from Shi describing improved substrate scope and conditions for the Kumada–Corriu coupling pioneered by Wenkert,[81] provided the impetus for numerous studies of cross-coupling using ether substrates in the past decade. Initially, the Suzuki–Miyaura reaction was extended to include alkenyl methyl ether electrophiles.[82] Subsequently, as with many other cross-coupling methodologies, the scope of the reaction was broadened to include Buchwald–Hartwig aminations.[62] In an important breakthrough, Chatani and co-workers solved the limitation that naphthyl ethers were privileged substrates in Suzuki–Miyaura reactions by changing to a nickel catalyst featuring an NHC ligand.[83] In this case the cesium fluoride additive was no longer required, and anisole derivatives were successfully coupled. On the basis of density functional theory calculations it was proposed that the NHC ligand makes the nickel center sufficiently electron-rich to promote oxidative addition of the anisole C–O bond.[84] However, complementary studies on a related nickel-catalyzed reaction suggest that the mechanism may not involve oxidative addition of the C–O bond to a nickel(0) intermediate but instead may involve nickel(I) species.[85] Improvements have also been made to Kumada–Corriu couplings involving aryl ethers, specifically, alkynyl, aryl, and alkyl Grignard reagents, including alkyl Grignards that contain β-hydrogens, which can all now be utilized as substrates.[86] In a reaction related to cross-coupling, the groups of Martin[87a] and Chatani[87b] independently demonstrated that with a nickel catalyst aryl ethers could be coupled with hydrosilanes, resulting in the replacement of the methoxy group with a hydrogen atom (eq 12).



The formation of C–heteroatom bonds from aryl ethers has also been explored, and amination,[88] borylation,[89] and

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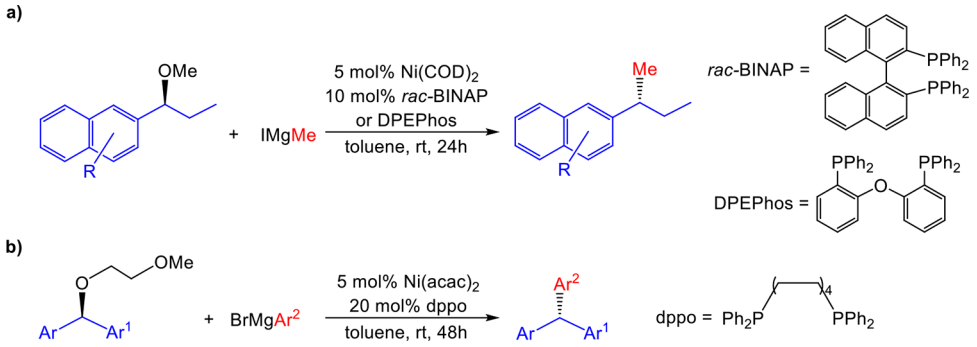

Figure 14. Selected examples of stereospecific Kumada−Corriu couplings involving secondary benzylic ethers.

silylation[90] reactions have all been reported, but this area is less well explored than C−C bond formation.

The scope of the ether substrate used as the electrophile in cross-coupling reactions has been extended beyond aryl ethers. Initially, Shi and co-workers demonstrated nickel-catalyzed Kumada−Corriu couplings using primary benzylic methyl ethers.[91] This work provided the foundation for Jarvo and co-workers to develop a series of stereoselective reactions involving secondary benzylic ethers (Figure 14a).[92] Initially, they reported stereospecific reactions involving benzylic ethers and methyl Grignard reagents,[93] before broadening the reaction to alkyl Grignard reagents with β-hydrogen atoms.[94] Currently, the reactions are compatible only with ethers containing extended aromatic groups, such as 2-naphthyl-substituted ethers. The reactions proceed with inversion of stereochemistry, which is proposed to occur as a result of inversion in the oxidative addition step followed by stereoretentive transmetalation. Subsequently, they coupled aryl Grignard reagents with diaryl-substituted benzylic ethers to stereoselectively form triarylmethanes (Figure 14b).[95] In this case, a traceless chelating directing group is appended to the benzylic ether to promote oxidative addition with the nickel catalyst. The use of the directing group also allows ethers without extended aromatic groups (such as naphthyl substituents) to be more readily coupled and has been used as a strategy to promote Negishi couplings, which are more functional-group-tolerant.[96] At this stage, nickel catalysts have been used almost exclusively for cross-coupling reactions involving ethers, but the exact reasons why they promote these reactions are unclear. Major challenges that still need to be addressed in this area include limitations on the scope of these reactions and the lack of systems that can effectively perform stereodivergent reactions of racemic benzyl ethers or couple unactivated C(sp^3)−O(alkyl) bonds. Greater mechanistic understanding may facilitate the development of catalysts to address these problems, as on a molecular level the nature of the C−O bond cleavage is relatively poorly understood.

3.3. Cross-Coupling Reactions Using Twisted Amides.

Amides are common functional groups in synthetic chemistry that are noted for their stability. The use of amides as electrophiles in cross-coupling reactions through initial cleavage of the C−N bond has many of the same advantages as cross-coupling reactions involving breaking of the C(acyl)−O bond in unactivated esters, and in many cases these two reactions are developed in parallel.[8a,b] Traditionally, because of resonance stabilization, cleavage of the C−N bond of amides requires either harsh conditions, strong acids or bases, or pyrophoric reagents. Resonance stabilization is also relevant in coupling reactions, as the resonance structure involving C═N double bond character is a greater contributor in planar amides, and as a consequence, only coupling reactions using twisted amides (which have weaker C−N bonds) as substrates have been reported.[97] In 2015, Garg and co-workers reported the first coupling reaction involving amides.[98] Specifically, they were able to couple amides and alcohols into esters (Figure 15a). The proposed mechanism involves initial turnover-

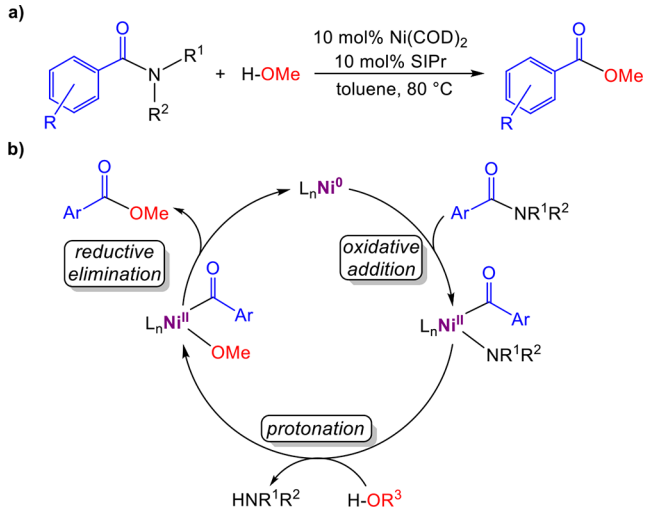

Figure 15. (a) Generic example of a nickel-catalyzed conversion of an amide and alcohol into an ester and (b) proposed mechanism.

limiting oxidative addition of the C−N bond of the amide to a low-valent nickel center, protonation of the resultant nickel(II) amide with alcohol to form a free amine and a nickel(II) alkoxide, and reductive elimination of the alkoxide group with the acyl fragment to form an ester (Figure 15b). The scope of this reaction includes both alkyl and aryl amides.[99] Subsequently, this chemistry was extended to facilitate transamidation reactions, which provide a convenient route for preparing amides but are often problematic because equilibrium mixtures of products are formed.[100] The route involving transition-metal-catalyzed cleavage of the C−N bond of amides requires two steps and proceeds to completion because the amine that is released is less nucleophilic than the amine involved in transamidation (eq 13).

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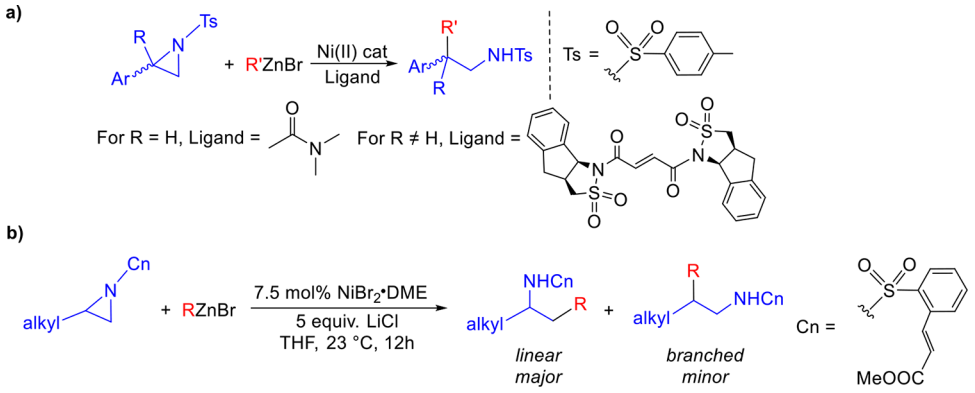
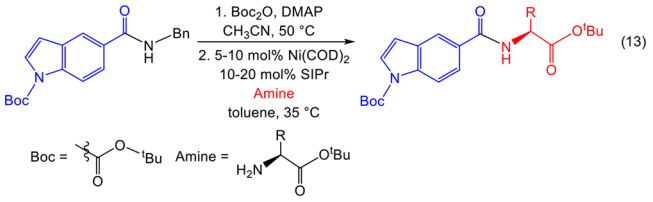


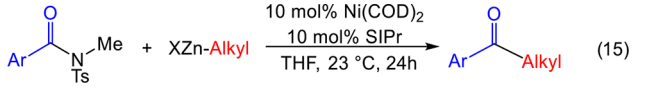
Figure 16. Examples of nickel-catalyzed Negishi reactions involving (a) 2-styrenylaziridines and (b) 2-alkylaziridines.



In the first step, a secondary amide is activated by conversion into a Boc-protected amide, which then undergoes oxidative addition via cleavage of the C−N bond of the amide to a nickel(0) catalyst, protonation of the nickel amide bond with a different amine, and reductive elimination to generate a new amide. A palladium-based version of this reaction has also been reported,[101] demonstrating that both nickel and palladium systems can activate amides.

Methods for the formation of C−C bonds after cleavage of the C−N bonds in amides complement the reactions for the preparation of C−heteroatom bonds described above. Initially, Garg and co-workers described nickel-catalyzed Suzuki−Miyaura reactions of Boc-protected amides to furnish ketones in high yields (eq 14).[102]

This work was extended independently by the groups of Zou[103a] and Szostak,[103b] who reported that palladium systems could also perform these reactions. Subsequently, Szostak and co-workers demonstrated that the Yale precatalyst is capable of performing Suzuki−Miyaura reactions involving amide C−N bond cleavage at room temperature.[74a] In related studies, Negishi reactions involving cleavage of the C−N bond of amides have also been developed.[104] In one version of this reaction, alkyl Negishi reagents can be used to generate mixed alkyl/aryl ketones that cannot be prepared using Suzuki−Miyaura reactions (eq 15).[105]



Overall, there are many similarities between cross-coupling reactions using amides as substrates and those that utilize esters. This is exemplified by a report of a nickel-catalyzed decarbonylative Suzuki−Miyaura reaction involving amide substrates to form biaryls, which is directly comparable to the decarbonylative reactions involving esters described in eq 9.[106] Catalyst and reaction development in cross-coupling using esters is also likely to be relevant to amides, as many of the same problems need to be solved. Additionally, the inability of current systems to activate planar amides is a major limitation, and the development of catalysts for these substrates would be transformative.

3.4. Cross-Coupling Reactions of Aziridines. Cross-coupling reactions involving aziridines provide a pathway for the preparation of β-substituted amines. This type of amine is valuable because compounds containing 2-arylphenethylamines are dopamine receptor agonists and could be useful for the production of drugs for the treatment of schizophrenia and Parkinson's disease.[107] Amines of this nature are typically prepared through ring opening of the aziridines with organometallic nucleophiles, such as cuprates, in the presence of strong Lewis acids.[108] The functional group compatibility is limited by both the cuprate and Lewis acid, and alternative methods that operate under milder conditions would be beneficial. In 2012, Huang and Doyle[109] used 1-sulfonyl-2-styrenylaziridines in Negishi reactions catalyzed by a nickel(II) salt in the presence of dimethyl fumarate (Figure 16a). Originally, only monosubstituted aziridines were coupled, but the development of a new electron-deficient ligand facilitated the coupling of protected 2,2-disubstituted aziridines.[110] In related chemistry, the Doyle group was able to couple 2-alkylaziridines utilizing a nickel catalyst when a novel protecting group was used on the aziridine (Figure 16b).[111] Whereas in the case of protected 2-styrenylaziridines only branched products were obtained, in this case both linear and branched products were observed, with the linear products preferred. Subsequently, through careful optimization of the ancillary ligand, Jamison and co-workers developed a nickel-based system that could catalyze Negishi reactions involving alkylzinc reagents and protected 2-alkylaziridines with essentially complete selectivity for the linear product.[112]

Whereas nickel-based catalysts have been exclusively used for Negishi reactions involving aziridines, only palladium-based systems have been used for Suzuki−Miyaura reactions. Duda and Michael[113] reported that the reaction of protected 2-alkylaziridines with arylboronic acids catalyzed by $Pd(dba)_2$ in the presence of a phosphine ligand generates linear amines with regioselectivity greater than 20:1 (Figure 17a). In a fashion analogous to results from nickel-catalyzed Negishi reactions, Takeda and Minakata showed that branched amine products are generated when protected 2-arylaziridines are used in Suzuki−Miyaura reactions (Figure 17b).[107] A notable feature of this reaction is the high stereospecificity, with one enantiomer being formed with high selectivity. In this case, a well-defined palladium(II) precatalyst with an NHC ligand is

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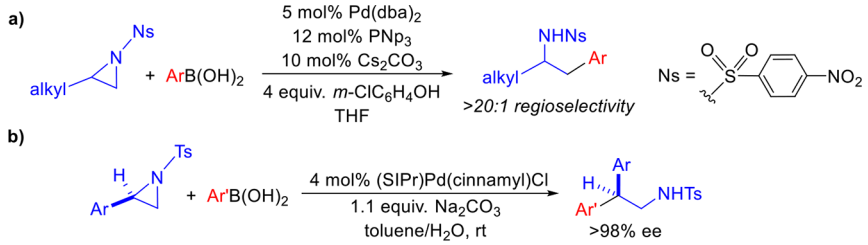
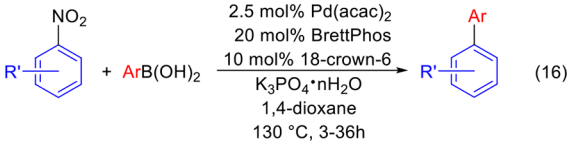


Figure 17. Examples of palladium-catalyzed Suzuki–Miyaura reactions involving (a) 2-alkylaziridines and (b) 2-arylaziridines.

utilized. Overall, coupling reactions involving protected aziridines are noteworthy because they represent significantly different substrates compared with sp^2-hybridized aryl halides. If the methodology could be extended to include nonprotected aziridines, this would be beneficial. Although a protonation step is required in cross-coupling reactions involving aziridines, they are otherwise proposed to have similar elementary steps as a typical cross-coupling reaction and demonstrate that if there is a pathway for an electrophile to undergo oxidative addition, coupling chemistry may be plausible. This emphasizes that there are still many electrophiles that may be compatible with coupling chemistry that have not yet been utilized as substrates.

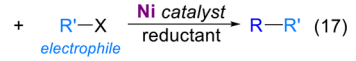
3.5. Cross-Coupling Reactions Using Nitroarenes. A common method to prepare aryl halides involves nitration of a parent unfunctionalized arene followed by reduction to an aniline and a Sandmeyer reaction to form the desired aryl halide. These reactions are often not very selective but are practiced because chemical manufacturers are able to sell all of the individual isomers from the mixtures that are generated. Therefore, the direct use of nitroarenes in cross-coupling reactions could reduce waste and increase overall atom efficiency. In 2017, the first examples of Suzuki–Miyaura reactions using nitroarenes were reported (eq 16).[114]



This was followed shortly afterward by the discovery of Buchwald–Hartwig reactions with nitroarenes.[115] Both reactions require high temperatures and catalyst loadings and often extended times, but they represent an important proof of principle. In Suzuki–Miyaura reactions, the oxidative addition of the nitroarene to the palladium(0) active species is proposed to be the turnover-limiting step in catalysis. It is possible that with ligand optimization to lower the barrier to oxidative addition and the development of precatalysts that increase the amount of palladium that is in the active form, the conditions required for these reactions could be improved. Nevertheless, the development of cross-coupling reactions that use more sustainable starting materials is likely to be a focus of research in the next decade.

4. NEW TYPES OF REACTIONS RELATED TO CROSS-COUPLING

4.1. Cross-Electrophile Coupling Reactions. The nucleophile (the organometallic component) in many cross-coupling reactions is often synthesized from the corresponding electrophile, such as an alkyl or aryl halide. In view of the benefits of developing more sustainable and atom-economical methods for synthesis, it is unsurprising that cross-electrophile coupling reactions, in which the substrates are two electrophiles (eq 17),



are attracting significant interest.[11] By coupling two electrophiles, one obviates the additional step required to preactivate one coupling partner, and in some cases significant reductions in waste can be achieved, although this can be offset by the reagents used in the single step cross-electrophile protocol, such as a stoichiometric reductant. Cross-electrophile coupling can also be advantageous in coupling reactions where the organometallic component is unstable and needs to be generated in situ. Operationally, cross-electrophile coupling reactions are usually simple to set up in a single operation, enabling practioners to couple easily synthesized or commercially available fragments, and as result, cross-electrophile coupling is an increasingly popular method in medicinal chemistry.

The reductive homocoupling of electrophiles has been known for well over a century, as exemplified by the Wurtz homocoupling of alkyl halides using sodium as the reductant.[116] Nevertheless, historically cross-electrophile couplings were limited to the formation of statistical mixtures, and the most significant advances in the field have only appeared in the past decade.[11c] The recent breakthroughs in cross-electrophile coupling were guided by our increased mechanistic understanding of the reactions of different electrophiles with transition metal complexes, which provided a basis for developing new retrosynthetic disconnections. For example, in order to design a direct synthesis of ketones from aroyl chloride electrophiles and alkyl iodides (and some activated alkyl bromides/chlorides), Gong and co-workers proposed that the reaction could proceed via an oxidative addition–reduction–oxidative addition–reductive elimination sequence (Figure 18a,b).[117] In this case, one electrophile (the aroyl chloride) selectively reacts with a nickel(0) species to generate a nickel(II) species, which can then be reduced by the stoichiometric reductant to a nickel(I) species. This nickel(I) species then reacts preferentially with the other electrophile (the alkyl iodide) to generate a nickel(III) complex, which can undergo reductive elimination, yielding the product and a nickel(I) species that is reduced again by the stoichiometric reductant to re-enter the catalytic cycle as nickel(0). It should be noted that a related transformation was concurrently published by Wotal and Weix[118] in which alkyl acid chlorides and thioesters were coupled with alkyl iodides. They proposed a different catalytic cycle where no intermediate reduction takes place and instead a ligand metathesis event at nickel(II) after the first oxidative addition results in a reactive bis(alkyl)nickel(II) complex that reacts with the acyl electro-

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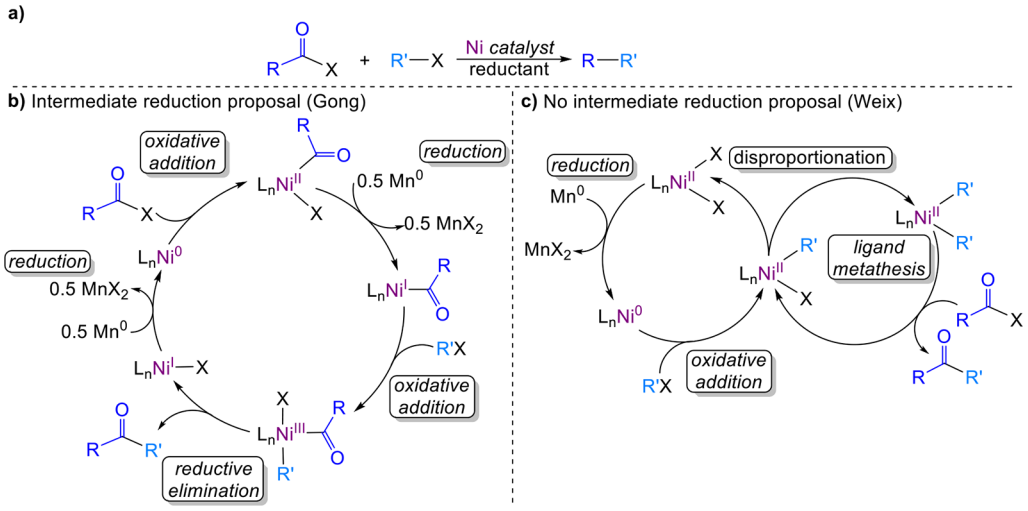

Figure 18. (a) Cross-electrophile coupling reactions between alkyl halides and acyl electrophiles and (b, c) mechanisms proposed by (b) Gong and (c) Weix.

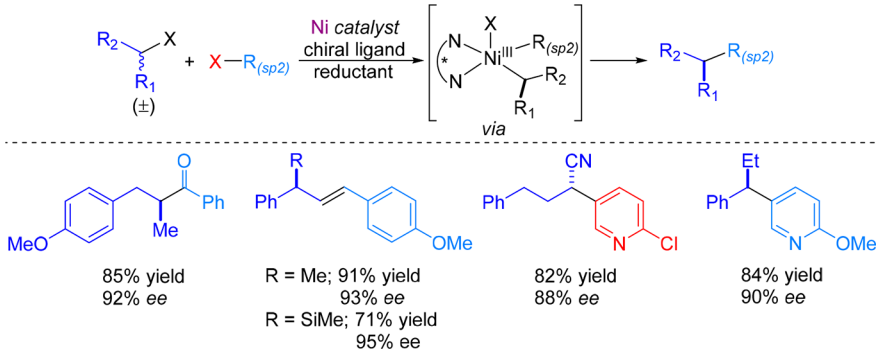

Figure 19. Examples of asymmetric nickel-catalyzed cross-electrophile coupling reactions.

phile (Figure 18c). To date, nickel has been almost exclusively used for cross-electrophile coupling reactions, likely because of its ability to undergo one-electron redox processes and disproportionation reactions, both of which are uncommon for palladium. Additionally, bidentate nitrogen-based ligands are most commonly used to facilitate the reaction. As these types of ligands can be redox-active, it is possible that they act as electron reservoirs during catalysis. However, there is little experimental evidence to support this possibility, and further work is required to fully understand ligand effects in cross-electrophile coupling.

An exciting feature of the cross-electrophile coupling reaction between aroyl chlorides and alkyl iodides is that it potentially involves organometallic intermediates similar to those proposed in nickel-catalyzed enantioconvergent alkyl cross-coupling reactions (vide supra). Reisman and co-workers hypothesized that it should therefore be possible to realize the enantioconvergent acylation of benzyl chlorides as electrophiles (Figure 19).[119] The reaction provides a new retrosynthetic disconnection for enantioenriched acyclic α,α-disubstituted ketone synthesis. This concept was extended to a wide variety of electrophiles to access chiral products such as vinyl bromides,[120] α-chloronitriles,[121] α-chlorobenzylsilanes,[122] and simple secondary benzyl chlorides to access 1,1-diarylalkanes.[122]

At this stage it is unclear whether a common mechanism exists for cross-electrophile coupling reactions or if subtle substrate and catalyst variations lead to different pathways. Unfortunately, mechanistic and kinetic studies of cross-electrophile couplings are difficult because the reactions are heterogeneous and likely involve air-sensitive intermediates. Potentially, the use of online analytical tools as well as machine learning algorithms for predicting reactivity could result in an increase in understanding and the development of new reactions. A further complication is that some substrates likely react via a radical-chain process. This pathway has been proposed by Weix and co-workers for the coupling of aryl halides with primary and secondary alkyl halides,[123] which is a highly desirable transformation (Figure 20). The reaction is scalable,[124] and the scope of the aryl halide partner includes

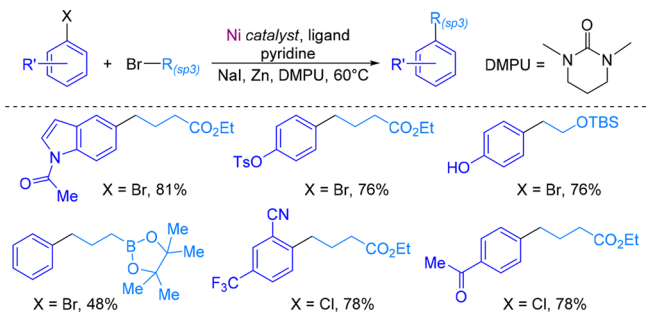

Figure 20. General reaction and functional group tolerance of nickel-catalyzed cross-electrophile coupling reactions between aryl and heteroaryl halides and alkyl bromides.

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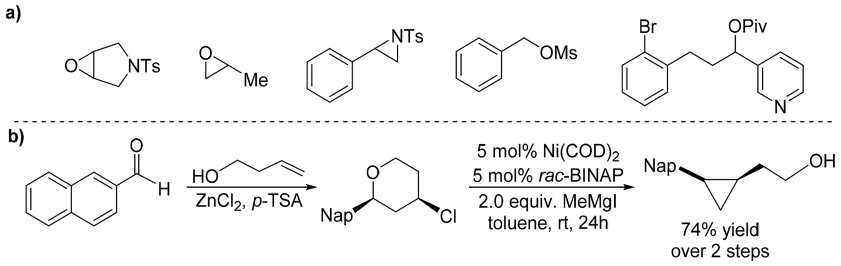

Figure 21. (a) Examples of other electrophiles successfully used in nickel-catalyzed cross-electrophile coupling reactions with aryl and/or heteroaryl halides. (b) Sequential Prins cyclization and cross-electrophile coupling to generate a cyclopropane.

activated and unactivated bromo- and iodoarenes, vinyl bromides and iodides, and activated chloroarenes, while that of the alkyl halide partner includes bromo- and iodoalkanes.[125] The functional group tolerance of these reactions is also impressive and is superior to those of the corresponding reactions involving organozinc or organomagnesium reagents, which can be used to form the same products in conventional cross-coupling reactions. For example, several base-sensitive functional groups or acidic functionalities are tolerated, such as esters, labile amides, sulfonyl esters, phenols, silyl-protected alcohols, boronic esters, ketones, and benzonitriles.[125] A variant of this reaction that allows all-carbon quaternary centers to be generated through the coupling of aryl bromides with tertiary alkyl halides has also been developed,[126] along with a related reaction involving the coupling of alkyl acids with tertiary alkyl and glycosyl halides to generate quaternary centers.[127] Recently, cross-electrophile couplings using a variety of other alkyl electrophiles have been reported, including reactions of epoxides,[128] aziridines,[129] benzyl mesylates,[130] benzylic esters,[131] and even ethers for the interesting rearrangement of Prins cyclization adducts into cyclopropanes (Figure 21).[132]

Recent research in nickel-catalyzed cross-electrophile coupling reactions has also focused on the discovery and design of novel ligand scaffolds to promote increased reactivity. The impact of ligand design in palladium-catalyzed cross-coupling cannot be understated (vide supra). Similarly, innovations in ligand design for precious-metal-based asymmetric hydrogenations have greatly expanded the applicability of these reactions.[133] In fact, access to large ligand libraries has become an integral part of catalytic reaction development in both academia and industry, and coupling these libraries with high-throughput experimentation (vide supra) has transformed the application of catalysis in synthesis. In contrast, there has been considerably less ligand development for catalysis based on first-row transition metals. Additionally, existing phosphine ligand libraries designed for palladium, ruthenium, rhodium, and other precious metal catalysts have largely been ineffective.[134] This is unfortunate because there are far more commercially available phosphine ligands compared with the nitrogen-based ligands predominantly utilized in cross-electrophile coupling. A recent collaborative effort between the Weix group and Pfizer sought to find new bidentate nitrogen ligands for cross-electrophile coupling.[135] Their hypothesis was that screening of nitrogen-rich heterocyclic compounds in the Pfizer library using the same methodology typically employed in focused screening campaigns for drug discovery would enable the identification of new scaffolds, which could provide starting points for new ligand classes. Compounds in the library were first screened in silico to identify bidentate ligands containing the privileged 2-pyridyl motif. A subset of these compounds were screened against two challenging cross-electrophile coupling reactions (Figure 22). A new class of

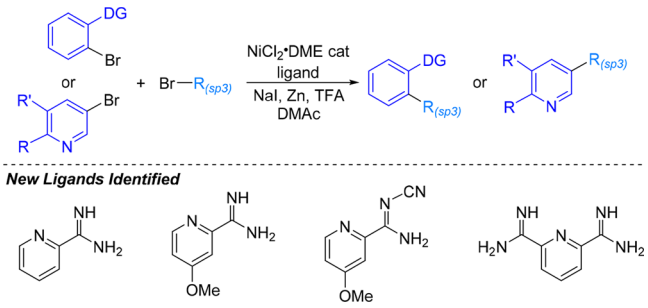

Figure 22. New bidentate ligands for challenging cross-electrophile coupling reactions identified through screening of the Pfizer library.

pyridyl carboxamidine ligands was identified for cross-electrophile couplings. With this new class of ligands, several challenging coupling reactions that failed or gave low yields with conventional bipyridyl ligands could be performed. Additionally, the synthesis of analogues of pyridyl carboxamidine is facile compared with functionalization of bipyridines given the ready availability of 2-cyanopyridines.

As mechanistic understanding of cross-electrophile coupling reactions evolves and more of the organometallic intermediates involved are identified and studied, we expect that the design of tailor-made new ligands will enable even more developments in this burgeoning area. This process may be accelerated by the new technologies of today, including high-throughput experimentation approaches, parallel library synthesis, mass-directed purification, computational modeling, informatics, and machine learning. Fully elucidating the mechanism of these reactions will be challenging because of the likely presence of highly reactive paramagnetic intermediates, but it is almost certainly required for the reaction to be improved. Key problems that need to be addressed include the use of amide-based solvents for many cross-electrophile coupling reactions and the use of heterogeneous metal reductants, which can lead to complicated kinetics causing problems in scale-up.

4.2. Photoredox Reactions Involving Cross-Coupling.

Since its resurgence in 2007, the number of synthetic methods that involve photoredox catalysis has increased dramatically. In fact, the ability of photoredox catalysts to turn photonic energy into electrochemical potential has facilitated a revival in radical-based synthetic methods. Although many new transformations that are directly facilitated by photoredox catalysts have been discovered, it is the inclusion of photoredox steps in multicatalytic cascades that has largely driven the rapid

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expansion in the use of photoredox chemistry.[136] This includes the combination of transition metal catalysts with photoredox catalysts.[13,137] Early examples of this strategy were the use of $[Ru(bpy)_3]^{2+}$ (bpy = 2,2′-bipyridine) in conjunction with a palladium catalyst by Osawa[138] and later with palladium or copper catalysts by Sanford.[139] These transformations are related to the types of dual-catalytic approaches that were employed between organocatalysts and photoredox catalysts.[140] The general concept involves the photoredox catalyst generating a species that enters another catalytic cycle. One example, outlined in Figure 23, is the copper-catalyzed

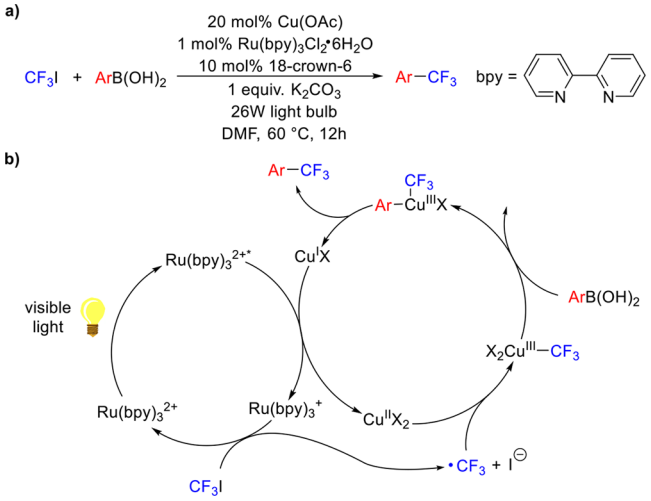

Figure 23. (a) Generic reaction scheme and (b) proposed catalytic cycle for metallaphotoredox-catalyzed trifluoromethylation of boronic acids.

trifluoromethylation of boronic acids reported by Sanford.[139b] In this case, $[Ru(bpy)_3]^{2+}$ is reduced to $[Ru(bpy)_3]^{+}$, which generates a trifluoromethyl radical from trifluoromethyl iodide, in the process reoxidizing $[Ru(bpy)_3]^{+}$ to $[Ru(bpy)_3]^{2+}$. Once generated, the trifluoromethyl radical is involved in a second catalytic cycle involving copper, reacting with a copper(II) species to form a copper(III) trifluoromethyl complex. Transmetalation of the copper(III) trifluoromethyl complex with the arylboronic acid, which results in a new Cu−aryl bond, precedes reductive elimination of the organic product and the generation of a copper(I) species. The excited state of $[Ru(bpy)_3]^{2+}$ then oxidizes the copper(I) intermediate to the copper(II) complex to complete the copper cycle.

The use of photoredox chemistry to generate reactive organometallic intermediates via single-electron processes has provided a new manifold for reactivity with late transition metals, which more commonly operate via two-electron processes. After the initial reports by Sanford and Osawa, a large number of transformations that use photoredox chemistry in combination with catalytic cycles related to cross-coupling have been reported. The rapid growth in research using this approach was no doubt catalyzed by simultaneous reports by Molander[141a] and MacMillan and Doyle[141b] on the use of photoredox/nickel catalytic systems to enable $C(sp^2)-C(sp^3)$ bond-forming reactions using alkyl radical precursors (Figure 24). Molander and co-workers demonstrated that an iridium photoredox catalyst is capable of oxidizing an alkyl trifluoroborate, resulting in the generation of a stabilized radical.[141a] The radical reacts with an organometallic nickel(II) intermediate to form a reactive nickel(III) species which quickly reductively eliminates to form the new C−C bond. A similar concept using amino acid carboxylates or tertiary anilines to generate α-amino radicals was applied by MacMillan and Doyle.[141b] This method is attractive because it uses substrates with readily available functional groups as coupling partners and generates products with pharmaceutically relevant motifs.

A notable feature of early metallaphotoredox chemistry is that in addition to generating a reactive radical, the photoredox catalyst usually plays a role in adjusting the oxidation state of an organometallic intermediate so it can participate in two-electron chemistry with the other coupling partner. In the Molander and MacMillan and Doyle cases, it reduces a nickel(I) intermediate to a nickel(0) species, which can participate in two-electron oxidative addition, and in the case of the copper-catalyzed trifluoromethylation, it oxidizes a copper(II) intermediate to a copper(III) species, which can subsequently undergo transmetalation and two-electron reductive elimination. There are now many examples of metallaphotoredox chemistry in which the photocatalyst plays these dual roles. A noteworthy extension is to reactions involving gold-catalyzed additions of nucleophiles to π systems (Figure 25).[142] Traditionally, in these reactions a Au−aryl species undergoes protodeauration, but when a photoredox catalyst oxidizes the metal, reductive elimination can occur. In this case, the photoredox catalyst promotes a different type of reactivity from gold than what is conventionally observed.

The above reactions highlight the use of photoredox catalysts to generate radical species that react with an organometallic intermediate. A recent innovation in metallaphotoredox catalysis was the use of a photoredox catalyst solely to modulate the oxidation state of the transition metal catalyst to facilitate reactivity of otherwise unreactive organometallic intermediates. This approach was first utilized by

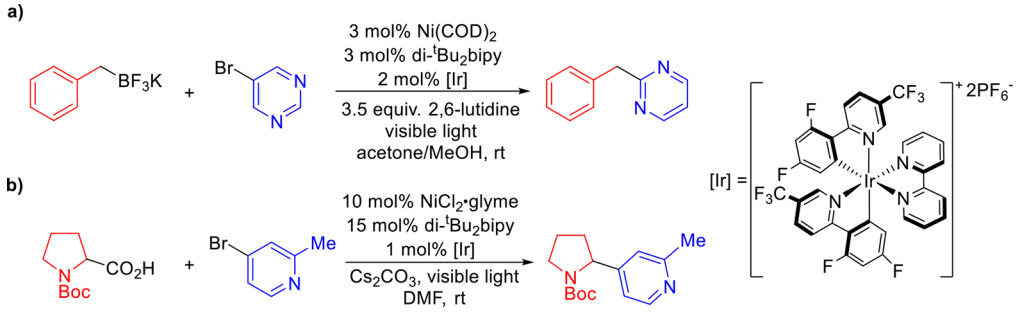

Figure 24. Examples of arylations mediated by nickel metallaphotoredox catalysis with (a) tetrafluoroborates and (b) carboxylic acids.

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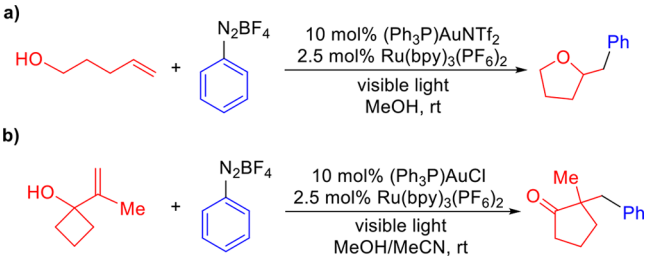


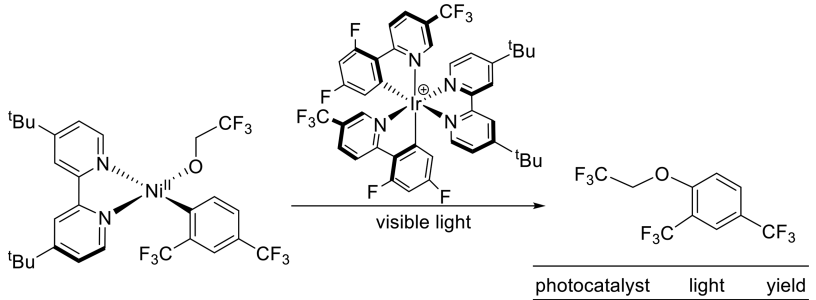
Figure 25. Examples of arylative functionalization mediated by gold metallaphotoredox catalysis with (a) homoallylic alcohols and (b) allylic cyclobutanols.

MacMillan and co-workers to perform nickel-catalyzed C−O arylation reactions using an iridium photoredox catalyst.[143] Hillhouse previously showed that nickel(II) alkoxide complexes do not undergo reductive elimination but that nickel(III) alkoxides do form aryl ethers after reductive elimination.[144] The mechanistic hypothesis proposed by MacMillan is that the photoredox catalyst enables the oxidation of a nickel(II) organometallic intermediate to a nickel(III) complex, which results in reductive elimination of the product and the formation of a nickel(I) complex. In a key control experiment, they showed that a nickel(II) aryl oxide would not undergo reductive elimination unless both light and a photoredox catalyst were present (Figure 26). This concept has since been extended to other coupling reactions with nickel, such as C−S,[145] C−P,[146] and C−N bond-forming reactions.[147] It is noteworthy that the nickel/iridium metallaphotoredox aryl amination reaction published by MacMillan and Buchwald in collaboration with Merck[148] afforded the highest success rate of any amination reaction studied using the informer library set method.[147] As described in the amination reaction, originally the photocatalysts in nickel-catalyzed photoredox reactions were based on expensive ruthenium and iridium polypyridyl complexes, but recently it has been demonstrated that these photosensitizers can be replaced with considerably less expensive organic molecules that can absorb light and transfer electrons.[149]

The study and optimization of metallaphotoredox reactions is challenging because of the need to consider two connected catalytic cycles as well as the possibility of radical chain mechanisms. The relative catalyst loadings of the two components must often be adjusted to enable productive catalysis, which means that optimization strategies need to be carefully performed. This is further complicated by variability in experimental setup, and it was only recently that a standardized reaction vessel for photoredox chemistry was proposed.[150] Additionally, when a reaction is operating in a light-limited regime because of either the experimental setup or the photoredox catalyst loading, it creates complications for studying the reaction kinetics and establishing the order in each component. For example, small-scale experiments in high throughput can often exhibit faster kinetics than larger-scale reactions (in vials) because of this effect. The recent application of light-emitting diode (LED)-based NMR tools to calculate quantum yields is an important advance, but more work needs to be done to develop methods to study these reactions.[151] As researchers converge on standardized platforms for visible-light catalysis, the opportunity for further study of the connections between the two catalytic cycles and the organometallic intermediates involved should lead to novel reactivity, and a more robust understanding of mechanism should result in better outcomes for practitioners.

4.3. Conjunctive Cross-Coupling. Conjunctive cross-coupling is a new class of reaction that was first described by Morken and co-workers in 2016.[12] The reaction involves an electrophile and two nucleophiles (Figure 27a). In the seminal example, an initial reaction between an organolithium and an organoboronic ester produces a vinyl boronate containing either an alkyl or aryl group directly bound to the boron. A chiral palladium catalyst then couples the vinyl boronate with an aryl or alkenyl triflate to generate an organoboronic ester in high yield and enantioselectivity (Figure 27b). The organoboronic ester is not typically isolated but rather is treated with NaOH and H_2O_2 in situ to generate the corresponding chiral alcohols. The key step in conjunctive cross-coupling is a metal-mediated 1,2-rearrangement of the vinyl boronate in which the alkyl or aryl group bound to boron migrates to an adjacent carbon atom, which in a concerted reaction creates a new C−C bond and a new Pd−C σ bond. This elementary step replaces transmetalation in a conventional cross-coupling reaction. A generic mechanism for conjunctive cross-coupling, shown in Figure 27c, indicates that the other major steps in the postulated pathway, namely, oxidative addition and reductive elimination, are similar to those proposed in traditional cross-coupling reactions. The key vinyl boronate compounds in conjunctive cross-coupling can be generated either by addition of an organolithium to a vinylboron species or by addition of a vinyllithium to an organoborane.

The Morken group has reported two extensions to conjunctive cross-coupling. In the first, they demonstrated



photocatalyst	light	yield
no	yes	n.r.
yes	no	n.r.
yes	yes	59%

Figure 26. Mechanistic probe for nickel metallaphotoredox chemistry involving C−O coupling.

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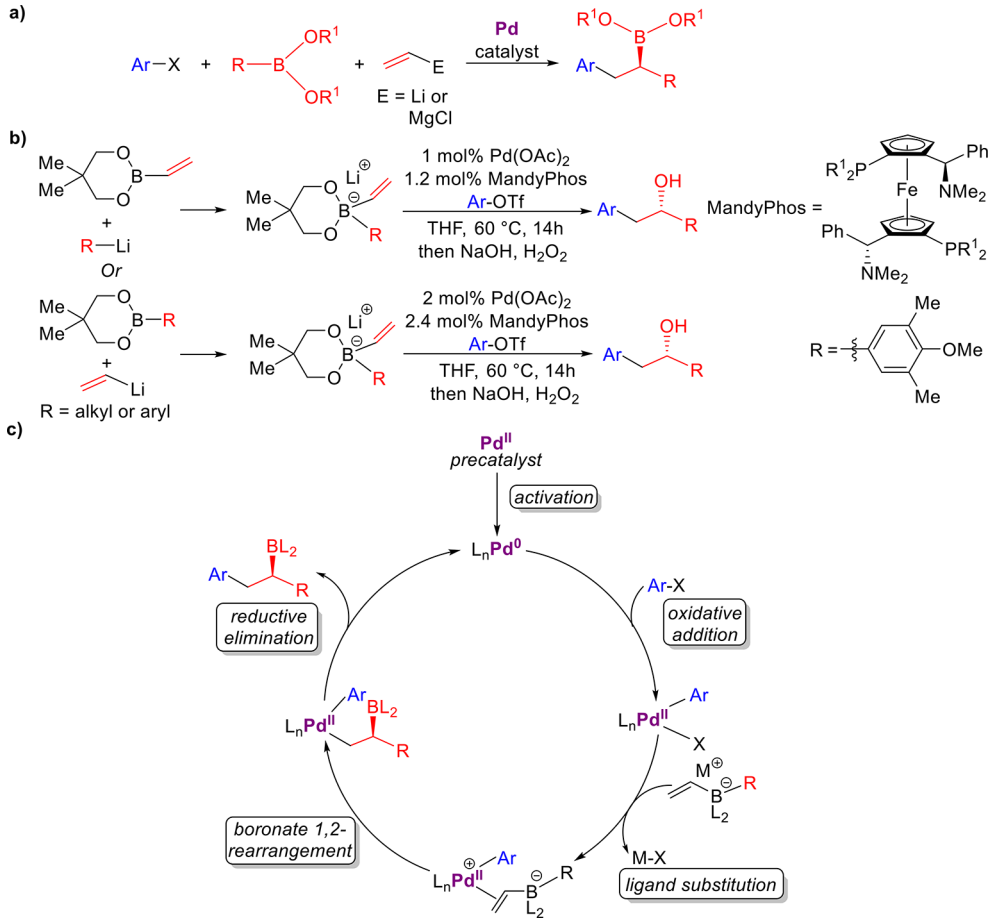
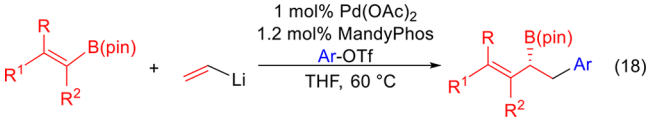
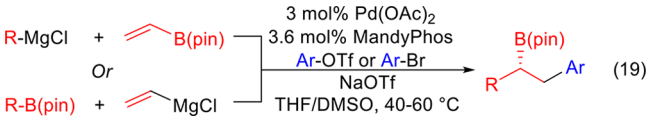


Figure 27. (a) Generic scheme, (b) seminal example, and (c) proposed mechanism for conjunctive cross-coupling.

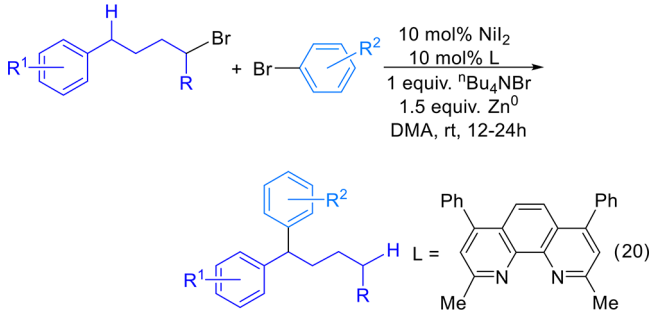
that alkenyl boronates could be used as substrates with vinyllithiums and aryl or alkenyl triflates to generate enantioenriched allylboron reagents (eq 18).[152]



This was a significant finding because allylboron reagents are important synthetic intermediates. In the second, they showed that vinyl Grignard reagents could be used instead of vinyllithiums (eq 19).[153]



Grignard reagents are less reactive than organolithiums, so this finding increased the functional group tolerance of the reaction. Additionally, the use of Grignard reagents allows aryl bromides to be used as the electrophile, provided that sodium triflate is also present. At this stage, research into conjunctive cross-coupling is in its infancy, and it is not clear whether this reaction will become a common synthetic method. Nevertheless, the development of conjunctive cross-coupling reactions demonstrates how changing an elementary step in the standard cross-coupling sequence can lead to new reactions, and it may be possible to use this strategy to develop other novel transformations. To this end, recent examples where "chain-walking" is an additional elementary step in cross-electrophile coupling reactions have allowed remote functionalization in reactions between aryl halides and alkyl halides,[154] highlighting the power of adding additional elementary steps in cross-coupling reactions to build complex fragments (eq 20).[155]



4.4. Decarboxylative Cross-Coupling. Carboxylic acids are readily available and straightforward to store and handle, and they can be prepared on a large scale.[156] Therefore, there are advantages to cross-coupling reactions that utilize carboxylic acids (or carboxylates).[157] Interestingly, depending on the transformation, carboxylic acids can be used as either the electrophilic or nucleophilic partner in cross-coupling reactions. In either case, the key step typically involves metal-catalyzed decarboxylation of the carboxylic acid to generate a metal–aryl bond and subsequent coupling with an electrophile or nucleophile to generate a new C–C bond. The general

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strategy used when a carboxylic acid-containing substrate is the electrophile is shown in Figure 28. Catalytic systems based

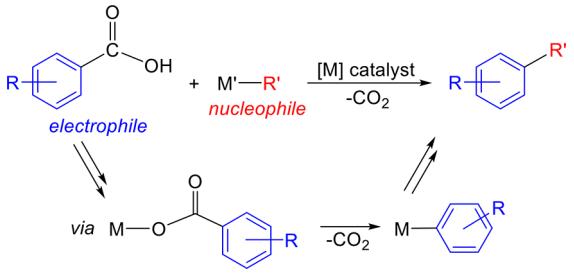

Figure 28. Generic depiction of decarboxylative cross-coupling, including the proposed metal intermediates that facilitate decarboxylation.

on either palladium or copper complexes or a combination of palladium and copper or palladium and silver catalysts have been used to facilitate these reactions, which generally involve two sp^2-hybridized substrates. In the systems requiring two metal catalysts, the different elementary steps of the reaction typically occur at distinct metal centers. At this stage, decarboxylative cross-coupling reactions involving sp^2-hybridized substrates are not widely used in synthesis because the reaction conditions are typically quite harsh, involving both temperatures above 100 °C and highly polar solvents. Additionally, for reactions where the carboxylic acid is the electrophile, the substrate scope is limited, as, for example, 2-nitro substituents are often required on the arene. A significant amount of further research is required before these reactions are widely applicable.

In 2016, Baran and co-workers pioneered a nickel-catalyzed approach to sp^2–sp^3 Negishi reactions involving the use of alkyl carboxylic acids as the electrophiles.[158] Initially, either in situ or in a step prior to cross-coupling, the alkyl carboxylic acid electrophile is converted into a redox-active *N*-hydroxyphthalimide ester (Figure 29a). This involves treatment of the carboxylic acid with *N*-hydroxyphthalimide in the presence of a stoichiometric amount of *N*,*N*′-diisopropylcarbodiimide (DIC) and a catalytic quantity of base (4-dimethylaminopyridine). In the cross-coupling component of the reaction, a nickel complex catalyzes the reaction of the *N*-hydroxyphthalimide ester with an aryl Negishi reagent (Figure 29b). The reaction is compatible with a broad substrate scope, uses a bench stable catalyst, and can be performed on a large scale. The key step in the proposed mechanism is the reduction of the *N*-hydroxyphthalimide ester by a arylnickel(I) species (Figure 29c). The reduction causes the fragmentation of the *N*-hydroxyphthalimide to generate CO_2, the phthalimide anion, and an alkyl-based radical. The radical then reacts with the oxidized arylnickel(II) to form a nickel(III) species. Reductive elimination generates the cross-coupled product and

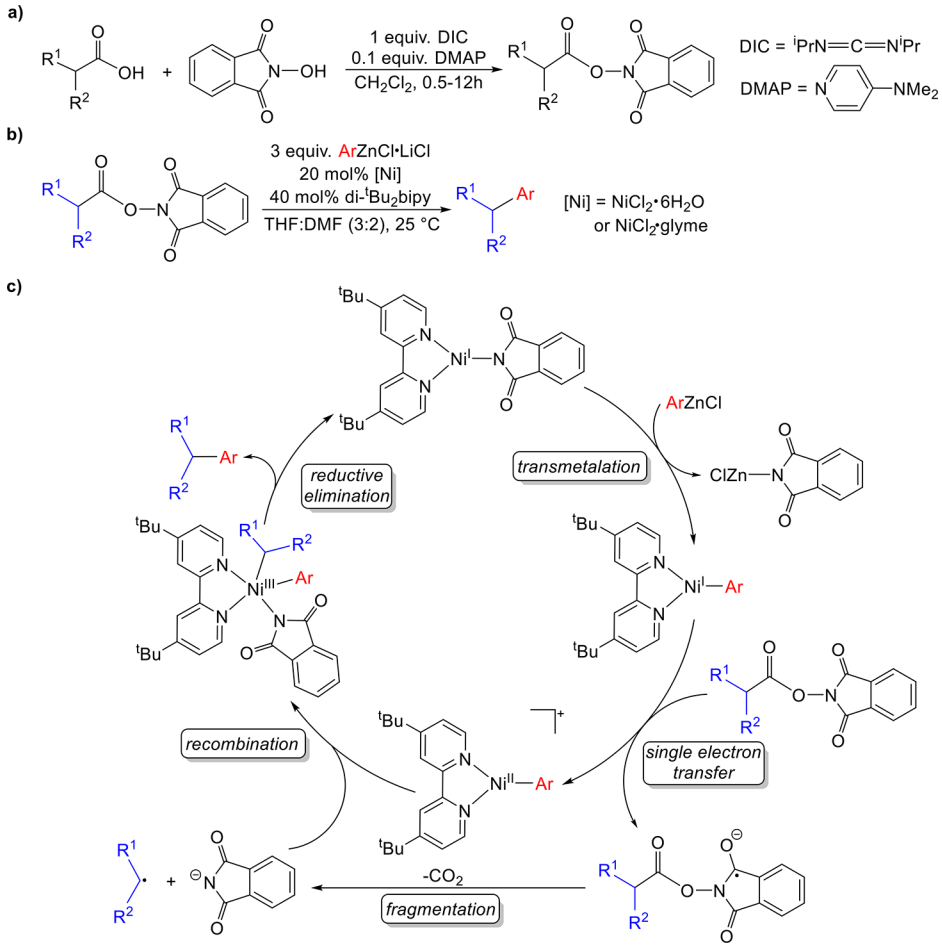

Figure 29. (a) Generic scheme for the preparation of *N*-hydroxyphthalimide esters. (b) Generic example of Ni-catalyzed Negishi reactions involving *N*-hydroxyphthalimide esters. (c) Proposed mechanism.

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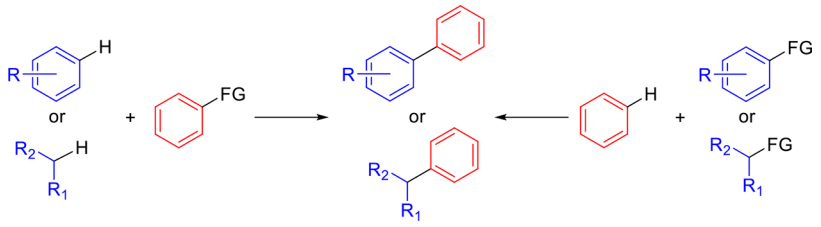
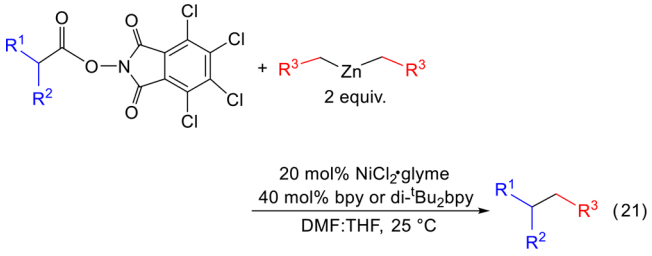


Figure 30. General disconnections in direct arylation reactions.

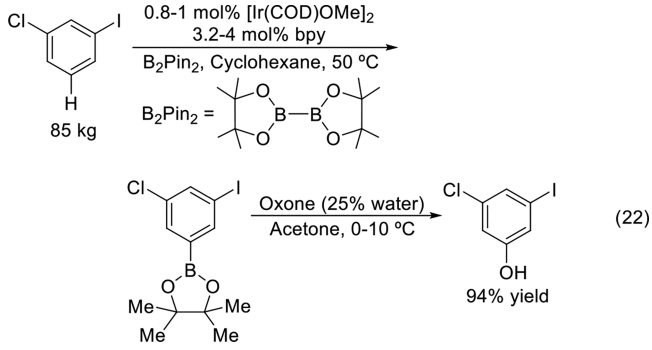
a nickel(I) phthalimide, which undergoes transmetalation with the arylzinc reagent to regenerate the arylnickel(I) complex. Although this mechanism is speculative and a significant amount of further work is required to establish its veracity, it provides a template for the design of improved catalysts for this novel reaction. We note that the types of nickel(I) intermediates proposed in these decarboxylative cross-coupling reactions are related to species proposed in cross-electrophile coupling and that an increased understanding of the chemistry of nickel(I) complexes,[159] which are not commonly studied, could prove vital to improving both reactions.

Since their initial report, the Baran group has described several extensions and advances relating to decarboxylative cross-coupling. They developed a nickel-catalyzed version of the reaction that uses boronic acids as the nucleophile instead of arylzinc reagents and increases the functional group tolerance.[160] Additionally, they demonstrated that an iron catalyst could be used as an alternative to nickel-based systems to facilitate the types of decarboxylative sp^2-sp^3 Negishi reactions shown in Figure 29.[161] The major advantages of the iron system are that it can couple redox-active esters derived from tertiary carboxylic acids, including cubane derivatives, and that the reaction is much faster than with nickel catalysts. Furthermore, the iron catalysts allow the use of nucleophilic Grignard reagents as the coupling partner. However, arguably the Baran group's most significant extension was to apply their methodology to sp^3-sp^3 couplings.[162] Specifically, they demonstrated that redox-active tetrachloro-*N*-hydroxyphthalimide esters, which can be readily generated from the corresponding free carboxylic acids, can be coupled with alkylzinc reagents using a nickel catalyst (eq 21).



Over 70 examples were demonstrated, including reactions conducted on a solid phase, which are compatible with methods for peptide synthesis.[162] Despite the recent development of nickel-catalyzed decarboxylative cross-coupling reactions, they have yet to be widely applied in synthetic chemistry, but the number of potential applications is high. We expect these reactions to be widely used in both academia and industry over the next decade and to influence the types of molecules that are made for drug discovery. It may also be possible to incorporate *N*-hydroxyphthalimide esters as substrates in other types of cross-coupling reactions, such as cross-electrophile coupling. An increased understanding of the mechanism will assist in this process.

4.5. Cross-Coupling Reactions Involving C−H Activation. As synthetic chemists continue to strive for more streamlined and sustainable synthetic methods, it is unsurprising that over the last 20 years a large number of direct functionalization reactions have emerged. These have ranged from the conceptually interesting to the truly practical. For example, the direct borylation of arenes is an integral component of many synthetic strategies because of its relatively broad substrate scope and the versatility of the boronic ester products, which enable a multitude of transformations, including Suzuki−Miyaura cross-coupling reactions.[163] Borylation reactions are now a workhorse of direct functionalization methods, with applications in medicinal[164] and process chemistry.[165] An example from Merck[148] is provided in eq 22.



In this tutorial, which has an emphasis on reactions related to cross-coupling, we will focus our discussions regarding C−H activation on direct arylation reactions that feature the replacement of a C−H bond with a C−C bond to form either a biaryl or substituted benzyl derivative (Figure 30). The naming of these reactions has ranged widely over the years, and they are often broadly termed C−H activation or C−H functionalization reactions. Here we have elected to use the term direct arylation for two reasons: (i) to indicate that an arylation occurs and (ii) to place the emphasis on the bond being formed rather than the group being replaced. Additionally, this nomenclature does not provide any biases about the mechanism that the reaction follows. Direct arylation reactions for the synthesis of biaryl products are attractive because they can obviate the need to prefunctionalize at least one of the reactive components (Figure 30). Similarly, arylations of alkanes are desirable replacements for cross-coupling reactions involving sp^3-hybridized organometallic reagents. Direct arylation reactions are typically catalyzed by palladium complexes, although there have been examples with many other transition metals, notably ruthenium and several recent reports of rhodium-catalyzed direct functionalization of arenes.[166]

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In palladium-catalyzed direct arylation reactions, the mechanism for the "activation" of the C−H bond has been the subject of much speculation since this elementary organometallic step was first observed (Figure 31). Various

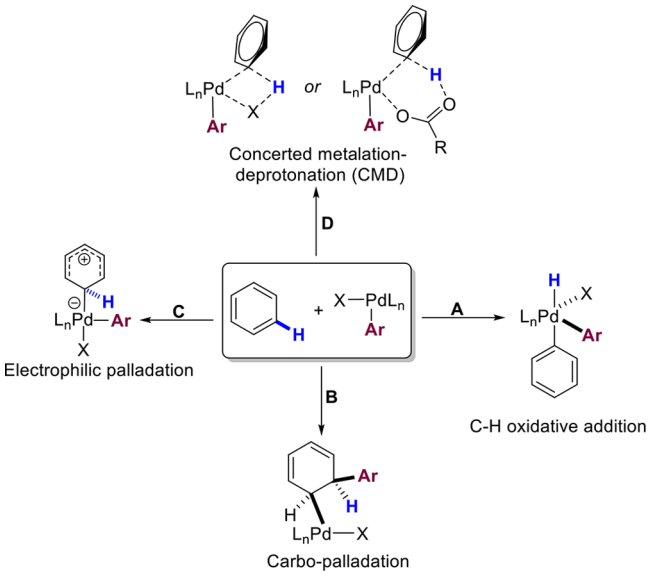
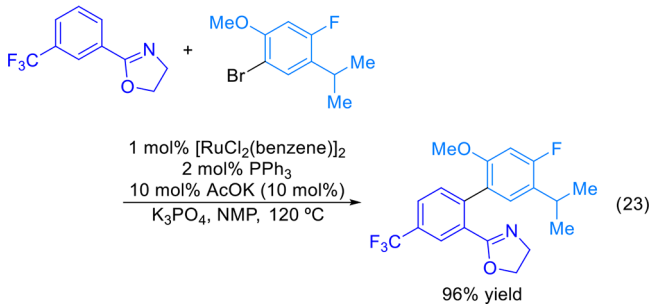


Figure 31. Proposed mechanisms for the C−H "activation" step in palladium-catalyzed direct arylation. reactions.

pathways have been proposed, including true C−H oxidative addition (pathway A), α,β-migratory insertion (carbopalladation) across aromatic systems (pathway B), and electrophilic aromatic substitution of the palladium center (pathway C). However, in the last 10−15 years, the field has coalesced around concerted metalation−deprotonation (CMD) (pathway D) as the likely pathway for the formation of the Pd−C bond and breaking of the C−H bond.[167] In the 1960s, on the basis of stoichiometric reactions, Ryabov proposed a mechanism for C−H "activation" that involves the concerted formation of a Pd−C bond and cleavage of the C−H bond with assistance from coordinated acetate.[168] Despite this precedent, much of the work on direct arylation in the 1980s and 1990s focused on the arylation of electron-rich heterocycles, which were proposed to act as π nucleophiles via an S_EAr pathway. In these reactions, the heterocycle replaced the organometallic reagent in conventional cross-coupling. The S_EAr mechanism was used to guide the development of many early direct arylation reactions. Conversely, in the early 2000s, as research focused on expanding direct arylation reactions to unactivated arenes, mechanistic experiments suggested that these reactions did not follow an S_EAr pathway. Both Echavarren[169] and Fagnou[170] analyzed kinetic isotope effects (KIEs) in intramolecular direct arylations of simple arenes and demonstrated that the C−H bond cleavage step was kinetically significant, which is consistent with a pathway involving CMD. Further mechanistic experiments across a wide range of palladium-catalyzed reactions have also been in agreement with a CMD mechanism, and similar proposals have now also been made for ruthenium-[171] and rhodium-catalyzed[172] processes.

The first catalytic examples of direct arylation reactions featured substrates containing a Lewis basic group, which could bind to the metal and provide chelation assistance for some of the elementary steps.[173] For example, it is typically more facile to activate a C−H bond in substrates that can chelate to the metal (a process often called cyclometalation) compared with substrates that cannot chelate. These early studies led to significant advances in understanding and, in cases where the directing group is required in the substrate, the development of processes that are practiced on a large scale. A classic example is the use of a ruthenium-based direct arylation reaction in the synthesis of anacetrapib (eq 23).[174]



In this example, an oxazoline is used as a directing group and is subsequently transformed into the required side chain of the molecule. An additional feature of this reaction is that a carboxylate additive is utilized because it was noticed that a trace amount of a carboxylate was required for reliable reactions. This reaction is one of the earliest examples of the deliberate use of a soluble proton shuttle to induce CMD in a direct arylation process.

Recent advances in directed arylation have focused on the design of moieties that are effective directing groups but bind more weakly to the metal, thus limiting unproductive binding events that can decrease the catalyst lifetime.[175] This phenomenon is often a problem for palladium-based systems. The Yu group has made significant contributions in this area, starting with their work using weakly coordinating groups, such as carboxylates, as directing groups.[176] A notable example of this strategy is shown in Figure 32, where benzoic acid can

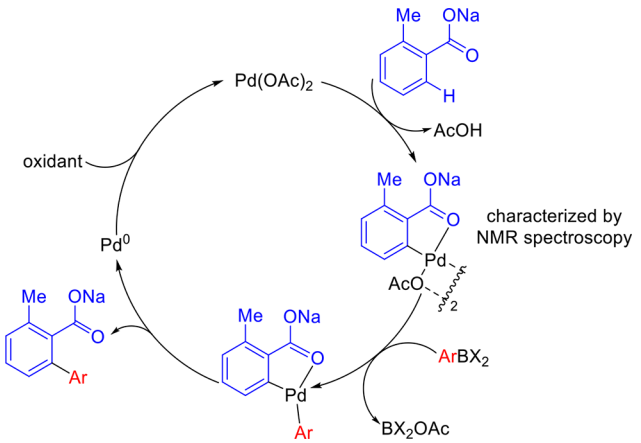


Figure 32. Proposed mechanism for arylation of benzoic and phenylacetic acids with arylboron reagents.

be arylated using arylboron reagents.[177] This method was extended to phenylacetic acids.[178] In these reactions, as in many examples of directed functionalization, the metalation is proposed to occur first, followed by transmetalation, reductive elimination, and reoxidation of palladium(0) to palladium(II) to regenerate the active species. Subsequently, the Yu group has explored the use of traceless directing groups, which can

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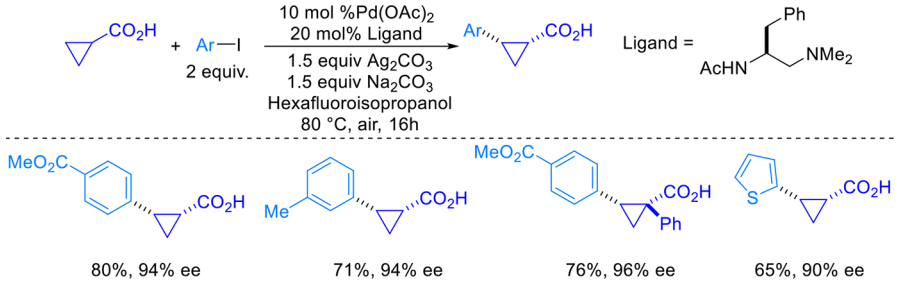
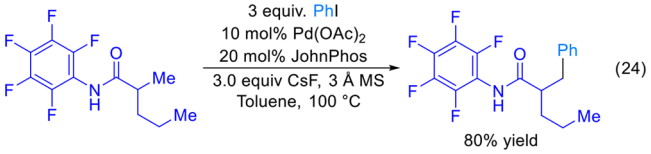


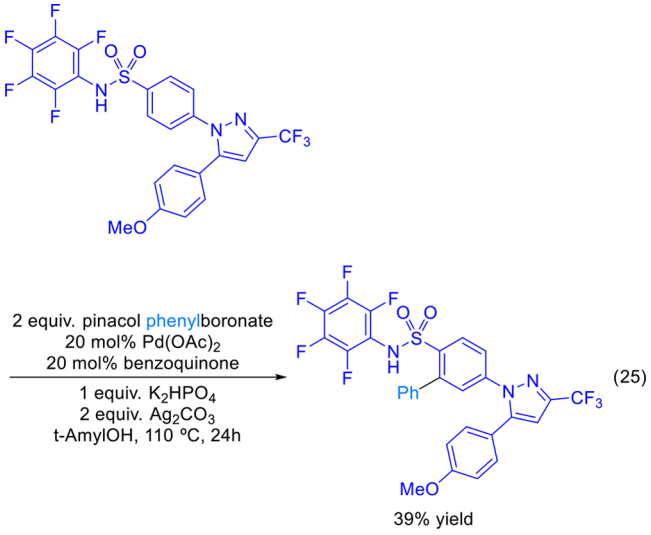
Figure 33. Direct arylation of cyclopropyl carboxylic acids using aryl iodides.

be installed, facilitate a reaction, and then be removed. These designed auxiliaries are particularly useful for reactions in which the native functional group does not yield the desired arylation product. For instance, in several cases transformation of the carboxylate directing groups to pentafluorophenyl amides has enabled arylation at several sp^3 and sp^2 C−H bonds (eq 24).[179]



(24)

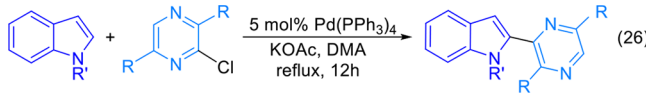
Sulfonamides can also be used as directing groups and have been applied to the synthesis of advanced drug intermediates such a celecoxib analogue (eq 25).[180]



(25)

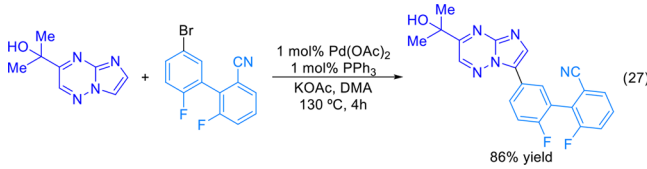
In 2011, Yu and co-workers discovered that it was possible to significantly accelerate some directed arylations using very simple mono-N-protected amino acids as ligands.[181] In fact, the use of amino acids as simple and readily available ligands has facilitated the discovery of many novel arylation reactions, including asymmetric variants.[182] An important recent application of this method was in the enantioselective direct arylation of cyclopropyl carboxylic acids, which involves an sp^3-hybridzed C−H bond (Figure 33).[183] Because of the prevalence of cyclopropanes in drug discovery, they have previously been a target in both intramolecular[184] and intermolecular arylation reactions.[185] However, intermolecular reactions had required the use of perfluorinated amides as directing groups.[185] In this latest example, a simple ligand derived from phenylalanine was used to desymmetrize the cyclopropane yielding high enantioselectivity for the cis diastereomer.[183] The reaction scope included a large number of aryl iodides as well as 1,1-substituted cyclopropanes, and the reaction was extended to desymmetrize 1,1-dimethylglycine derivatives to give chiral α-methyl phenylalanines. The reaction could be improved, as currently it requires the use of stoichiometric silver additives and heterocycles bearing Lewis basic groups are not part of the substrate scope. Unfortunately, at this stage it is common for carboxylate-directed reactions to be incompatible with Lewis basic groups, which are common in medicinal chemistry, as the Lewis base can presumably interfere with binding events at the metal.

A large number of heterocycles have been used in direct arylation reactions that do not require a directing group. Privileged substrates include electron-rich five-membered heterocycles, with one of the first examples being the direct arylation of *N*-methylindole reported by Otha and co-workers (eq 26).[186]



(26)

Since then, a variety of coupling reactions between heteroarenes and aryl halides have been described. These have been extensively reviewed and will not be discussed here.[166a,176,187] Most of these reactions, however, use relatively simple substrates and require high reaction temperatures in the presence of base, which limits their applicability to the complex systems encountered in many practical applications. It is noteworthy that a review focused on the application of these methods to biologically active unnatural compounds (those used in medicinal chemistry) had only applications of these transformations to known compounds in academic settings and no examples from the discovery phase of medicinal chemistry.[166b] In contrast, there a number of examples from process chemistry groups, where researchers are seeking the shortest route from true commodity chemicals. For example, the Merck[148] process group demonstrated the direct arylation of an imidazo[1,2-*b*][1,2,4]triazine with an aryl bromide as a key step in the synthesis of a GABA agonist (eq 27).[188]



(27)

More recently, Bristol-Myers Squibb (BMS) demonstrated an intramolecular direct arylation of an indole in the synthesis of beclabuvir (eq 28).[189]

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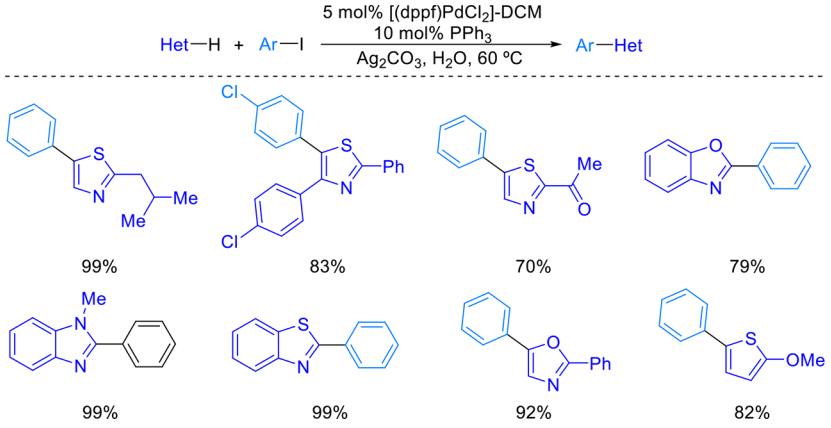


Figure 34. Greaney's "on-water" direct arylation of heterocycles.

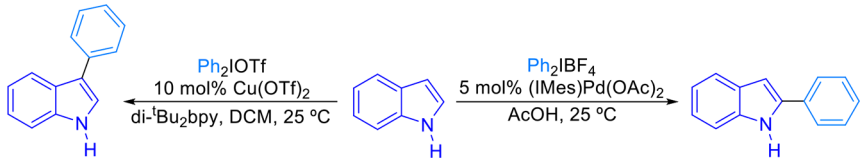
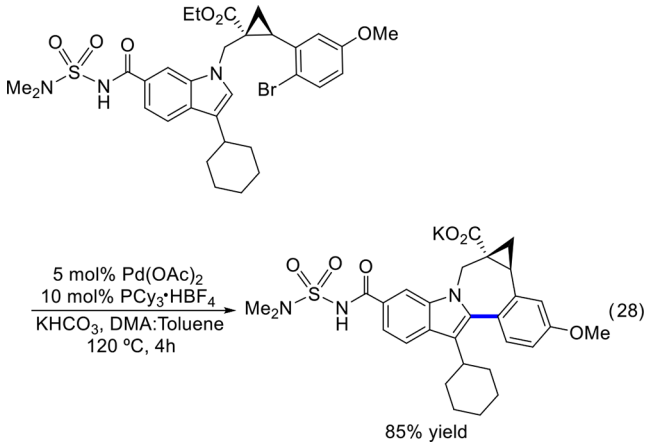
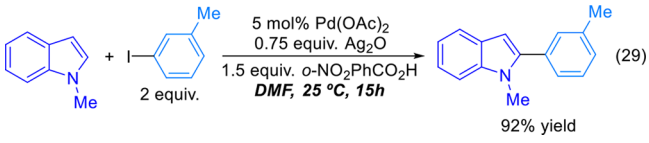


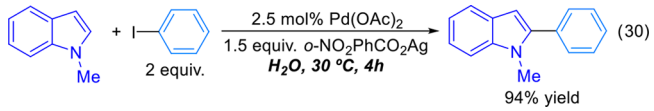
Figure 35. Divergent arylation of indoles using aryl iodonium salts.



At this stage, milder reaction conditions and expanded substrate scopes will be required for direct arylation reactions between heteroarenes and aryl halides to be more commonly used in drug discovery. In particular, these reactions could be valuable in cases where the corresponding organometallic reagents are unstable or not readily available. Recent work by the Larrosa group has started to address the limitations of these transformations. For example, they demonstrated that by addition of silver oxide, arylation reactions between indoles and aryl iodides can be performed at close to room temperature using a palladium(II) catalyst and a benzoic acid additive (eq 29).[190]



The silver additive is proposed to abstract an iodide ligand from palladium(II) and as a consequence make the intermediates more electrophilic and reactive. Additionally, there is an inverse correlation between the pK_a of the carboxylate additive and the reaction performance. This suggests that it is important to limit carboxylate binding to key metal intermediates, but the requirement for some kind of carboxylate additive is consistent with a CMD-based pathway. Larrosa and co-workers subsequently discovered that when these arylations were performed "on water", a silver carboxylate could be used as a base, which greatly accelerated the reaction and resulted in reactions times of 1−4 h at lower catalyst loadings (eq 30).[191]



The rate acceleration observed for "on-water" reaction conditions was first reported by Greaney and co-workers in 2007 for arylation reactions between thiazoles and aryl iodides at 60 °C (Figure 34).[192] In their initial report, Greaney also showed that other heterocycles could also be arylated "on water" using silver carbonate as the base.

The use of stoichiometric silver salts in direct arylation reactions is an obvious limitation. In some cases it may even obviate the advantages of removing the organometallic cross-coupling partner with respect to waste and sustainability. Nevertheless, this remains a viable option for heterocycles whose organometallic equivalent is hard to prepare or unstable. Recently, Larrosa reported an alternative to silver salts.[193] In some carboxylate-directed arylation reactions a tetramethylammonium additive can be used in place of silver. The additive is proposed to abstract a halide from palladium in a similar fashion to silver salts. Although this strategy has not yet been extended to a wide substrate scope, it should be explored for cases where the sole role of the silver additive is to abstract a halide.

An alternative strategy that has been successfully used to perform direct arylations of indoles at room temperature is to change the mechanism by which the reaction proceeds from a palladium(0)−palladium(II) cycle to a palladium(II)−palladium(IV) cycle.[194] In these cases, a palladium(II)

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carboxylate is capable of metalating the indole at room temperature, but oxidation of this intermediate to form a palladium(IV)−aryl complex requires the use of strong oxidants such as iodonium salts. Subsequent reductive elimination generates the arylated product (Figure 35). It is interesting that the use of a copper catalyst instead of a palladium catalyst results in C-3 versus C-2 arylation.[195] In general, iodonium salts have potential for use in drug discovery. However, better methods for their synthesis at the late stage of drug discovery and greater commercially availability are likely required for increased use.

Finding systems for the catalytic nondirected arylation of simple arenes was significantly more difficult than for heteroarenes. Through the study of intramolecular reactions, both Fagnou[170,196] and Echavarren[169] demonstrated that electron-deficient arenes were not only competent substrates but in fact were even sometimes better substrates than heteroarenes in direct arylation reactions. These observations along with further mechanistic work (already discussed above) led to the investigation of intermolecular reactions of electron-deficient substrates that lack the typical Lewis basic directing groups. It was discovered that electron-deficient arenes, such as nitrobenzene[197] and perfluorobenzenes,[198] could be arylated. Even benzene could be arylated through addition of a catalytic pivalic acid additive, which is proposed to act as a soluble proton shuttle and facilitate the CMD transition state (Figure 36).[199] In this reaction, two pathways are possible for

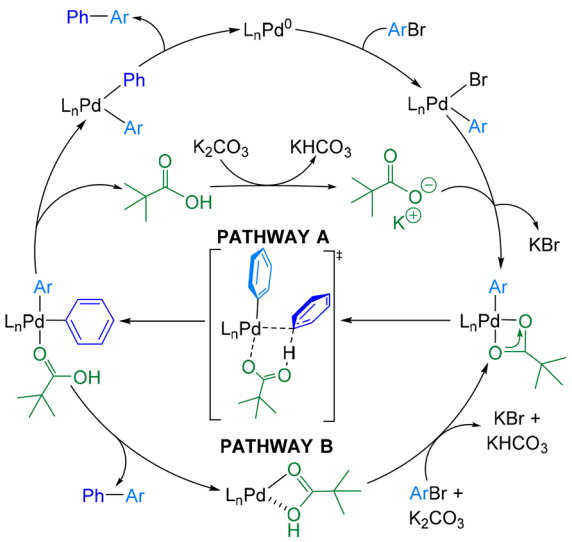
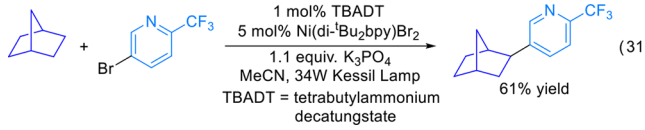


Figure 36. Proposed mode of action of the pivalic acid cocatalyst in the direct arylation of benzene.

reductive elimination of the product and regeneration of the catalyst, which differ depending on the role that the carboxylate plays. Despite the slight mechanistic ambiguity, carboxylate additives are now common in many arylation reactions, including those with ruthenium.[171,200]

Overall, in recent years there have been few significant breakthroughs in the arylation of simple sp^2-hybridized C−H bonds in arenes. In fact, for these transformations the reaction conditions are generally harsh, undesirable additives such as stoichiometric silver are commonly utilized, substrate scopes are limited, and often the arene being functionalized is used as a solvent or in large excess. Even though these reactions have the potential to be highly impactful in synthetic chemistry, novel ways of generating and using the key organometallic intermediates are required to move the field forward. In contrast, there have been numerous significant results in arylation reactions involving sp^3-hybridized C−H bond activation, and several new mechanistic pathways have been described. For example, several laboratories have developed direct arylation reactions at sp^3-hybridized C−H bonds that involve using metallaphotoredox reactions to facilitate hydrogen atom transfer chemistry.[201] Most recently, in a collaborative effort involving the MacMillan group and Merck,[148] tetrabutylammonium decatungstate (TBADT) was utilized in conjunction with nickel catalysis to enable the direct arylation of strong aliphatic C−H bonds (eq 31).[202]



TBADT acts as both the hydrogen atom transfer catalyst and a single-electron relay, which enables turnover of the nickel catalyst. The mild conditions required for these reactions suggest that they will likely be useful for the preparation of synthetically valuable molecules. In general, applying the mechanistic lessons learned from cross-coupling and related reactions to direct arylation reactions could result in new paradigms for this important class of reactions.

5. CONCLUSIONS, FUTURE DIRECTIONS, AND OUTLOOK

Our tutorial highlights both the importance of cross-coupling reactions and the wide range of research that is still being performed exploring cross-coupling and related reactions. Given the maturity of research into traditional palladium-catalyzed cross-coupling reactions involving sp^2-hybridized substrates, we expect activity in this area to continue to decrease while work exploring the use of nontraditional substrates grows. In many cases, the reaction conditions for the coupling of nontraditional substrates such as nitroarenes or esters are harsh, and the reactions are not compatible with the types of functional groups often encountered in medicinal chemistry. Thus, significant improvements are required for these substrates to be used in synthesis. Unfortunately, in the majority of cases after an academic group discovers a reaction, the relative benefits (in relation to funding and impact of publication) for improving the transformation further are small. Industry, in contrast, wants reactions that are robust and relatively mature. Therefore, there is a gap between the two communities. Finding methods to bridge this divide would be useful for the more rapid development of methods that are practical. An important step to solve this problem would be for academic groups to more often provide information about substrates that do not work in their scope and for industry to inform academic groups about the challenges they face when trying to apply a new methodology.

Analysis of the new reactions described in this work indicates that there is a strong movement toward the development of reactions involving sp^3-hybridized substrates. This includes not only traditional Suzuki−Miyaura or Negishi reactions involving sp^3-hybridized substrates but also metallaphotoredox and C−H activation reactions. Continued investigation of these reactions to make them more functional-group-tolerant and practical will likely have transformative implications for the types of molecules that are

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used in drug discovery, as the availability of synthetic methods influences the types of compounds that are designed. It will also help with an escape from "flatland".[6] Similarly, the incorporation of another elementary step into traditional cross-coupling reactions, such as what has been achieved in conjunctive cross-coupling, could also facilitate the movement of cross-coupling reactions away from biaryl products. In fact, it is likely that there are opportunities for the discovery of many new reactions by incorporation of new elementary reactions into the traditional cross-coupling sequence.

We anticipate that the improvement of new coupling reactions will follow a closely related path to that for traditional palladium-catalyzed cross-coupling. That is, in many cases, mechanistic understanding will guide the rational development of more efficient catalysts and more practical reactions. For example, precatalysts now play an important role in the application of traditional palladium-catalyzed cross-coupling reactions, but their development was facilitated by an understanding of the mechanism of these reactions and the nature of the active species. Since in many new reactions the identity of the active species is unclear, precatalysts are unlikely to be developed until mechanistic ambiguities have been clarified. An additional complication in this regard is that many new cross-coupling reactions utilize first-row transition metal catalysts, which are more likely to form paramagnetic species. Mechanistic studies involving these systems are complicated and will require greater cooperation between synthetic organic and physical inorganic chemists with expertise in areas such as EPR spectroscopy. In an analogous fashion, the understanding of metallaphotoredox reactions is difficult and will require cooperation between communities who traditionally have had limited overlap. An additional feature in designing improved catalysts is to understand off-cycle processes. This includes both precatalyst activation and catalyst decomposition. Large improvements in performance can be achieved if these often neglected processes are well-understood.

Improvements in instrumentation such as high-throughput experimentation could increase the speed at which advances in cross-coupling and related reactions occur. It may even be possible to combine the data from high-throughput experimentation with machine learning to assist in the process of optimizing current reactions and developing new reactions. In fact, the types of large data sets generated from high-throughput experiments make them excellent candidates to be coupled with machine learning. Industry, perhaps because of its greater resources, has been able to integrate high-throughput experimentation into its research much more rapidly than academia, and this is an area where there are significant opportunities for growth. There are several examples of successful collaborations between industry and academia involving high-throughput experimentation, and continued investment in this area will benefit both groups.

This tutorial demonstrates how in addition to the plethora of practical applications of palladium-catalyzed cross-coupling reactions involving sp^2-hybridzed substrates, cross-coupling has also directly contributed to the discovery of many new transformations. This profound fundamental impact of cross-coupling appears likely to persist for many years to come and will drive the discovery of more sustainable and economical processes. There is still a significant amount to learn, and the results are likely to continue to have a large impact on society.

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Notes

The authors declare no competing financial interest.

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