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Palladium- and Copper-Catalyzed Arylation of Carbon−Hydrogen Bonds

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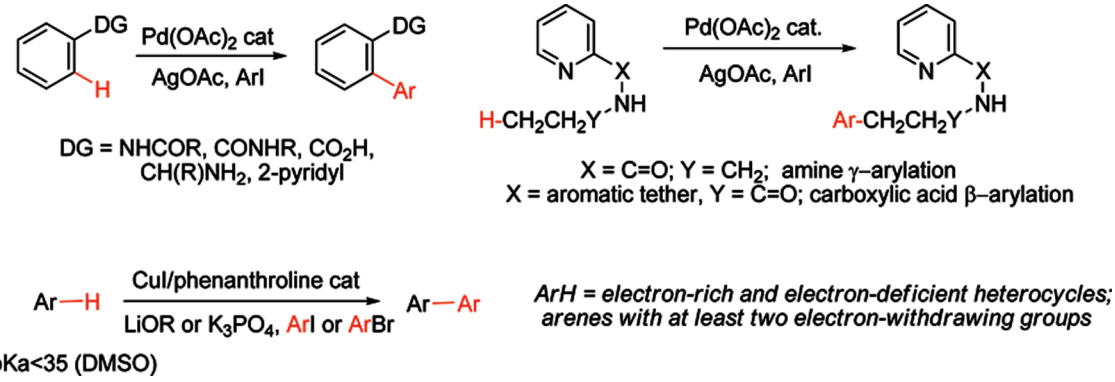
CONSPECTUS



The transition-metal-catalyzed functionalization of C−H bonds is a powerful method for generating carbon−carbon bonds. Although significant advances to this field have been reported during the past decade, many challenges remain. First, most of the methods are substrate-specific and thus cannot be generalized. Second, conversions of unactivated (i.e., not benzylic or α to heteroatom) sp^3 C−H bonds to C−C bonds are rare, with most examples limited to *t*-butyl groups, a conversion that is inherently simple because there are no β-hydrogens that can be eliminated. Finally, the palladium, rhodium, and ruthenium catalysts routinely used for the conversion of C−H bonds to C−C bonds are expensive. Catalytically active metals that are cheaper and less exotic (e.g., copper, iron, and manganese) are rarely used.

This Account describes our attempts to provide solutions to these three problems. We have developed a general method for directing-group-containing arene arylation by aryl iodides. Using palladium acetate as the catalyst, we arylated anilides, benzamides, benzoic acids, benzylamines, and 2-substituted pyridine derivatives under nearly identical conditions. We have also developed a method for the palladium-catalyzed auxiliary-assisted arylation of unactivated sp^3 C−H bonds. This procedure allows for the β-arylation of carboxylic acid derivatives and the γ-arylation of amine derivatives. Furthermore, copper catalysis can be used to mediate the arylation of acidic arene C−H bonds (i.e., those with pK_a values <35 in DMSO). Using a copper iodide catalyst in combination with a base and a phenanthroline ligand, we successfully arylated electron-rich and electron-deficient heterocycles and electron-poor arenes possessing at least two electron-withdrawing groups. The reaction exhibits unusual regioselectivity: arylation occurs at the most hindered position. This copper-catalyzed method supplements the well-known C−H activation/borylation methodology, in which functionalization usually occurs at the least hindered position.

We also describe preliminary investigations to determine the mechanisms of these transformations. We anticipate that other transition metals, including iron, nickel, cobalt, and silver, will also be able to facilitate deprotonation/arylation reaction sequences.

1. Introduction

It can be argued that the goal of any methodology project is to increase the efficiency of the desired chemical transformation. This goal may be achieved either by optimization of the current synthetic methods or by introduction of new transformations that allow synthesis of the desired substances to be carried out in fewer steps or in higher yield. Increased efficiency results in labor and energy savings and is usually environmen-

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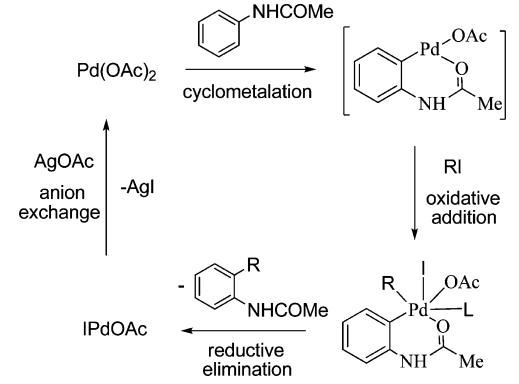
tally beneficial by decreasing the amount of disposable reaction waste such as byproducts and solvents. In this context, employing the C−H bond as a functional group for direct functionalization is advantageous.[1] Most of the starting materials that are obtained in large scale from petrochemical sources contain only carbon−carbon and carbon−hydrogen bonds. Thus, the C−H or C−C bonds in these compounds need to be converted into other functional groups. However, selective one-step conversion of C−H bonds to most functional groups usually is not possible and several steps are required to obtain the desired products. Consequently, methods for selective functionalization of C−H bonds may result in shorter synthetic schemes. While the advantages of such procedures were recognized some time ago, formidable difficulties have prevented development of user-friendly, viable, and general methods in this field until the past decade. The majority of the transition-metal-catalyzed C−H bond functionalization examples involve regioselective arylation of sp^2 C−H bonds in directing-group-containing arenes[2] or electron-rich heterocycles such as azoles or indoles.[3] However, these methods often are not general and are usually applicable to only a few substrate classes. Different reaction conditions and catalysts are required even for closely related structures. Formation of carbon−carbon bonds from unactivated (not benzylic or α to heteroatom) sp^3 C−H bonds is rare,[4] and most of the examples described in literature involve functionalization of *t*-butyl groups, which is a particularly easy case due to entropic considerations and lack of β-hydride elimination from metalated intermediates. Additionally, catalysts that are employed for arylation usually are complexes of rhodium, palladium, platinum, and ruthenium. Less expensive metals such as copper or iron only rarely have been used for functionalization of C−H bonds.[5]

Thus, three major problems can be formulated for C−H bond arylation reactions. First, reactions are not general and that may be a reason why such reactions have only rarely been used in synthetic regimes or for industrial applications. Second, unactivated (alkane) sp^3 C−H bond conversion to C−C bonds is rare. Third, expensive late transition metals with relatively high catalyst loadings are generally employed. Our efforts described in this Account are directed toward addressing these issues.

2. Discussion

2.1. Directing-Group-Containing Arene Arylation. 2.1.1. Anilides. Our interest in this area was spurred by Tremonts' seminal paper describing palladium acetate-promoted anilide alkylation by alkyl iodides.[6] Tremont suggested

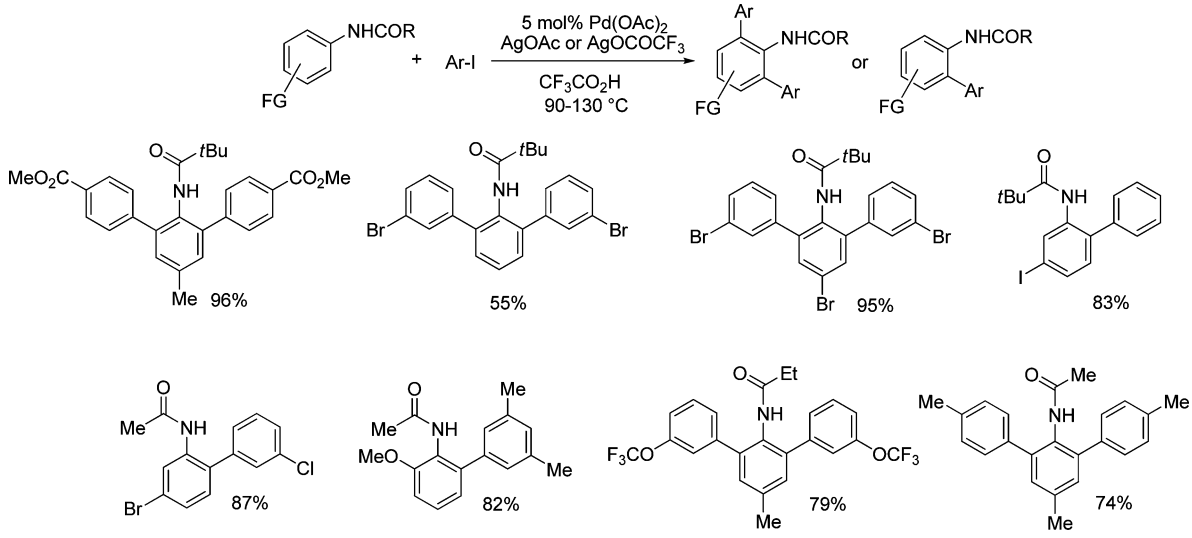
SCHEME 1. Catalytic Cycle



that the reaction proceeds by either a Pd(II)−Pd(IV) catalytic cycle or a σ-bond metathesis mechanism.[6a] The former is more likely due to the well-established mechanism for the Catellani reaction where intermediacy of Pd(IV) is not disputed.[7] The Pd(II)−Pd(IV) catalytic cycle is presented in Scheme 1. Cyclometalation of the directing-group-containing arene is followed by oxidative addition of aryl or alkyl iodide to Pd(II) species affording a high-energy Pd(IV) intermediate. Fast reductive elimination and anion exchange affords the product and regenerates the catalyst. Inspection of the scheme allows several conclusions. Since Catellani has shown that both alkyl and aryl iodides participate in Pd(II)−Pd(IV) catalytic cycles,[7] it should be possible to employ aryl iodides in the reactions. Arylations can be rendered catalytic because ArI is compatible with silver salts used for iodide removal from the palladium coordination sphere. It has been shown that Pd(IV) complexes possessing hard ligands are isolable in some cases;[8a] hence, if arene contains a hard directing group and can be cyclopalladated, we should be able to arylate it. Palladacycles have been studied extensively;[8b] however, alternative mechanistic pathways for C−H activation by iridium complexes have also been proposed.[8c]

The initial targets were anilides since they are known to be reactive under Tremont conditions. We were pleased to discover that a combination of aryl iodide, silver acetate, and catalytic palladium acetate efficiently arylates pivalanilides (Scheme 2).[9a] The reactions proceed in trifluoroacetic acid at elevated temperatures affording the *ortho*-arylated products in good to excellent yields. Interestingly, bromide is tolerated on both the aryl iodide and pivalanilide coupling partners. As a result, scaffolds amenable for further functionalization by using Pd(0)−Pd(II) coupling processes can be obtained. While the pivaloylated anilines afford the cleanest results, it is difficult to remove the acyl group from the arylation product. Use of removable directing groups such as acetyl, propionyl, or trifluoroacetyl would allow a short synthesis of 2-aminobiphe-

SCHEME 2. Anilide Arylation



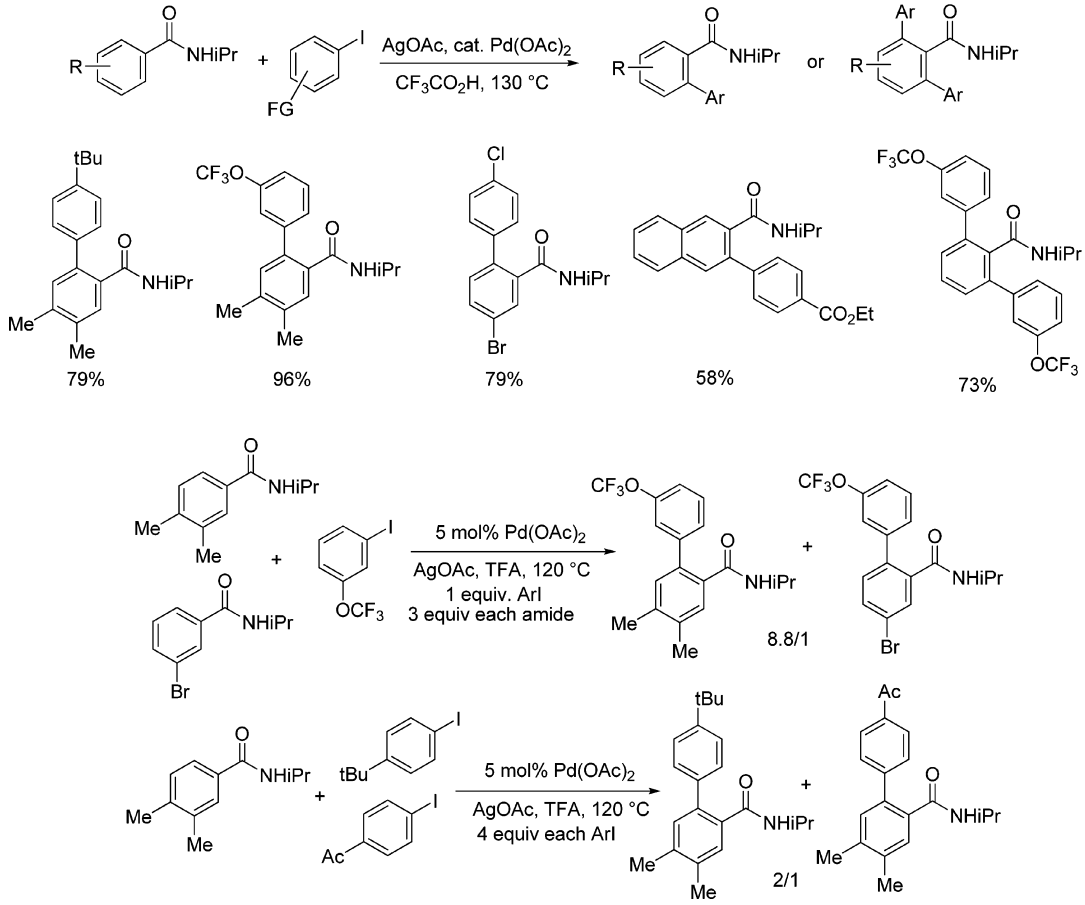
nyl or terphenyl derivatives. After a short optimization, we showed that also acetanilides and propionanilides can be efficiently arylated under conditions similar to the ones for pivalanilide arylation (Scheme 2).[9b] After deprotection, *ortho*-amino biphenyl or terphenyl derivatives are obtained in excellent yields. Access to these compounds requires multiple step syntheses from starting materials that may not be readily available. Direct arylation methodology allows for the short and convenient synthesis of such materials. Sanford has reported arylation of anilides by iodonium salts.[10] Boronic acids have been employed in arylation of anilides.[11]

2.1.2. Benzamides. According to Scheme 1, if an arene contains a hard directing group and can be palladated, we should be able to arylate it provided the mechanistic considerations are valid. Miura has demonstrated that benzamide derivatives can be arylated under Pd(0)−Pd(II) catalytic cycle conditions.[12] We reasoned that the arylation of benzamide derivatives should be possible also under Pd(II)−Pd(IV) couple conditions. Gratifyingly, conditions that were developed for anilide arylation worked well for benzamide arylation (Scheme 3).[13] The best results were obtained with *n*-propylamide and isopropylamide derivatives. Benzamide derivatives can be arylated by both electron-rich and electron-poor aryl iodides and good functional group tolerance is observed. A competition experiment was carried out by reacting a mixture of an electron-rich and electron-poor benzamide with aryl iodide. The electron-rich benzamide was shown to react preferentially (8.8/1). The faster reaction of electron-rich benzamide can be explained by its preferential coordination to Pd(II) before the metalation step as shown by Sanford.[14] More interestingly, electron-rich aryl iodides react faster than electron-poor ones (Scheme 3).

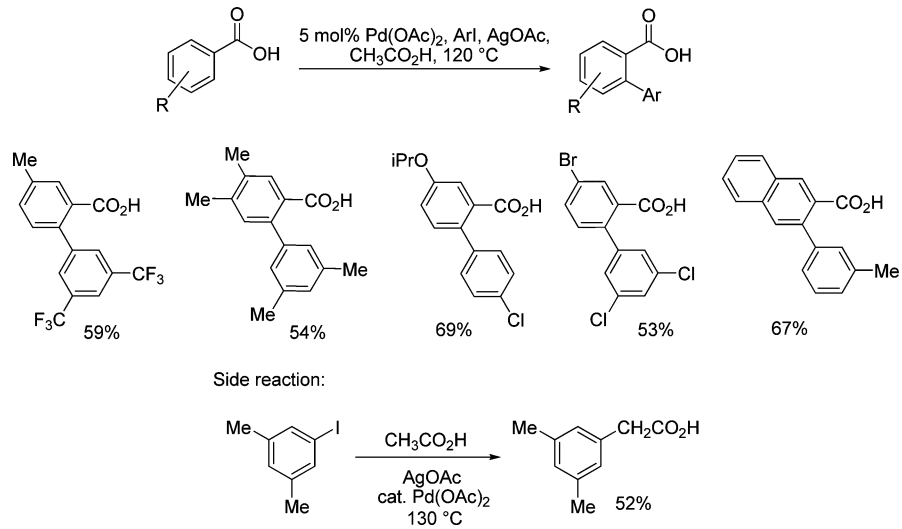
The aryl iodide enters the catalytic cycle at the stage of oxidative addition to Pd(II), which is most likely the rate-determining step since arylation rate depends on ArI and reductive elimination from Pd(IV) is expected to be fast.[8a] The oxidative addition step must be faster for electron-rich aryl iodides, which is different from the usual Pd(0)−Pd(II) coupling cycle where electron-deficient aryl halides are more reactive.[15] In general, 2- or 3-substituted benzamides are monoarylated, presumably due to steric interference of the substituent. It is well-known that the palladation of sterically hindered positions is unfavorable.[8b,d]

2.1.3. Benzoic Acid Arylation. *ortho*-Arylation of benzoic acids is often preferable to *ortho*-arylation of benzamides if conversion of the amide moiety to another functional group is desired. However, only a few reports have dealt with the *ortho*-functionalization of free benzoic acids.[4e,16a,b] Direct functionalization of C−H bonds in carboxylic acids is challenging. The reactions can be complicated by decarboxylation of the product, the starting material, or both. If successful, direct arylation of aromatic carboxylic acids would allow one-step synthesis of 2-arylbenzoic acids. Amides of such acids are potent MTP and ApoB inhibitors.[16c] We were pleased to discover that benzoic acid arylation under Pd(II)−Pd(IV) catalytic cycle conditions proceeds under conditions that are similar to the conditions for benzamide and anilide arylation; however, the optimal solvent for the arylation reaction is acetic acid. One can employ from electron-rich to moderately electron-deficient benzoic acids and from electron-rich to electron-deficient aryl iodides (Scheme 4).[17] Reactions generally proceed in lower yields than amide or anilide arylations due to competing solvent arylation (Scheme 4). Thus, temperature needs to be controlled carefully for achieving optimal results. Use of

SCHEME 3. Benzamide Arylation



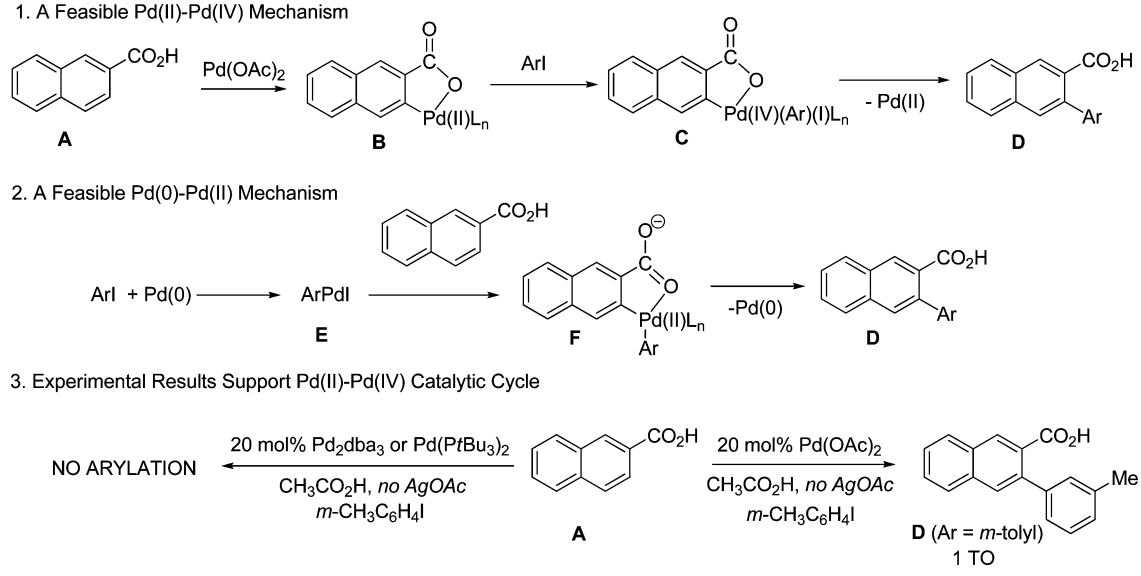
SCHEME 4. Benzoic Acid Arylation



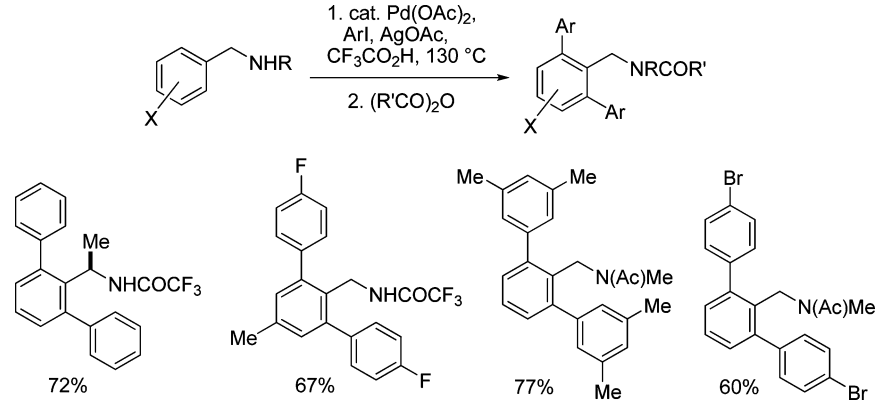
trifluoroacetic acid solvent often results in product or starting material decarboxylation.

Several mechanistic pathways are possible for benzoic acid arylation (Scheme 5). The reaction may proceed via a Pd(II)−Pd(IV) catalytic cycle (Scheme 5.1). Cyclometalation of naphthoic acid, **A**, followed by oxidative addition of aryl iodide would afford a high-energy Pd(IV) intermediate, **C**. Reductive elimination would produce the arylated carboxylic acid **D**. Alternatively, a Pd(0)−Pd(II) catalytic cycle may be operative. The catalytically active Pd(0) is produced by an in situ reduction of Pd(II). Oxidative addition of aryl iodide would afford an arylpalladium iodide **E**. Cyclometalation followed by

SCHEME 5. Mechanistic Considerations



SCHEME 6. Benzylamine Arylation

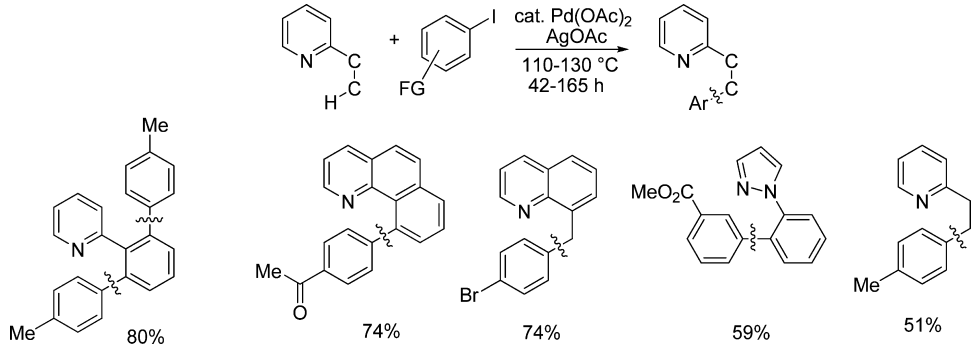


reductive elimination would produce the arylated carboxylic acid **D** and regenerate the Pd(0) catalyst. β-Naphthoic acid was reacted with 3-iodotoluene in the presence of a 20 mol % palladium source. If palladium acetate was used, one turnover to the arylated product **D** was observed. Reactions in the presence of Pd(0) complexes did not afford tolylnaphthoic acid **D**. Instead, formation of 3,3′-dimethylbiphenyl was observed. This result suggests a Pd(II)−Pd(IV) catalytic cycle. However, a σ-bond metathesis mechanism suggested by Tremont cannot be rigorously excluded.

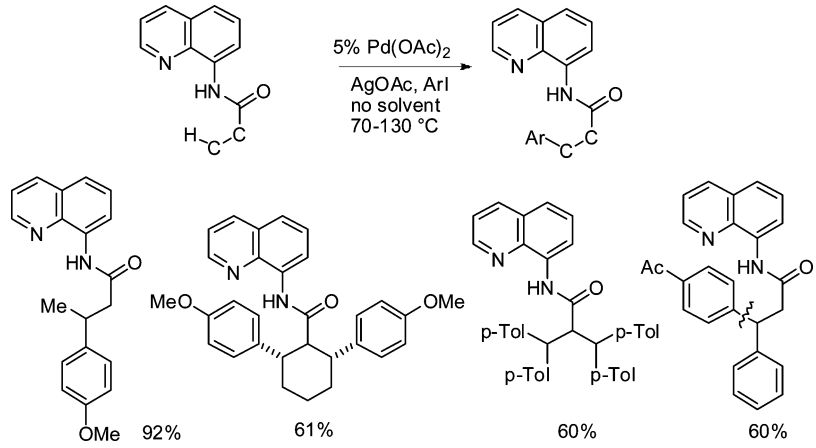
2.1.4. Benzylamine Arylation. Palladium-catalyzed *ortho*-arylation is often complementary to the existing lithiation/boronation/cross-coupling methodologies. However, there are cases where *ortho*-lithiation strategies are not likely to be successful. Examples include functionalization of compounds containing aryl−bromine or −iodine bonds or substances possessing multiple acidic protons such as benzylamines. Furthermore, it is known that even unsubstituted benzylamines can be palladated.[18] According to mechanistic considerations of Scheme 1, benzylamine arylation should be feasible. The palladation of benzylamines in strong acid might be retarded due to protonation of the directing amino group. Employing a limited amount of trifluoroacetic acid solvent allowed to achieve efficient benzylamine arylation. Specifically, the benzylamine arylation reactions are the fastest if about 5 equiv of trifluoroacetic acid solvent is used. A number of benzylamines and *N*-methylbenzylamines were shown to be reactive under these conditions (Scheme 6).[19] The products are acylated after the reaction to facilitate isolation.

2.1.5. Arylation of 2-Substituted Pyridines. Ruthenium-catalyzed 2-substituted pyridine C−H bond arylation by aryl halides was reported by Oi and Inoue in 2001.[20a] We were interested in developing a complementary palladium-catalyzed method that would expand the scope of our arylation protocol (Scheme 7).[20b] Acetic acid solvent is usually employed, and extended reaction times, typically several days,

SCHEME 7. Pyridine and Pyrazole Derivative Arylation

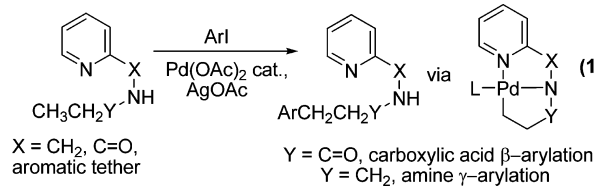


SCHEME 8. Carboxylic Acid Derivative Arylation



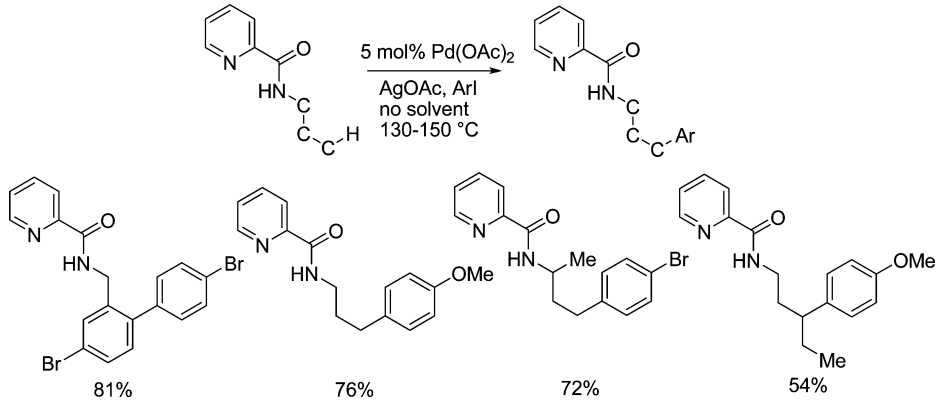
are required. Interestingly, the most reactive substrate is 8-methylquinoline showing that arylation of benzylic sp^3 C−H bonds is more facile than the arylation of sp^2 C−H bonds. The most interesting arylation example is the *p*-tolylation of 2-ethylpyridine. This is one of the first examples of palladium-catalyzed C−C bond formation from an unactivated sp^3 C−H bond that is not a part of a *t*-butyl group. Unfortunately, the arylation of other 2-alkyl-substituted pyridines results in product mixtures. Furthermore, requirement for the pyridine directing group limits the generality of the reaction. The generality issue is addressed in section 2.2. Aryliodonium salts have also been used for 2-substituted pyridine functionalization under Pd(II)−Pd(IV) catalytic cycle.[10]

2.2. Auxiliary-Directed Arylation of sp^2 and sp^3 C−H Bonds. The development of a general method for the arylation of directing-group containing arenes is described in section 2.1. If the directing group is pyridine, even sp^3 C−H bonds can be arylated. The generality of the method could be improved by employing pyridine as a part of a removable auxiliary ligand. Several issues were considered while contemplating attachment of the auxiliary ligand. The reaction mechanism involves a C−H activation step and, most likely, a step where Pd(II) is converted to Pd(IV). An additional pyridine ligand should stabilize a high-energy Pd(IV) species and presumably increase its rate of formation.[8a] It is likely that the Pd(II) to Pd(IV) transformation is the rate-determining step in the catalytic cycle. The C−H activation step will also most likely be facilitated by an additional coordination site. β-Hydride elimination should be retarded by saturating the coordination sites on palladium. The logical auxiliary structures are pyridines linked to the group to be arylated by an amide linkage. After the arylation step, the auxiliary could be removed by acid or base hydrolysis. The arylation of both carboxylic acid and amine derivatives should be possible, depending on how the auxiliary is attached (eq 1). The arylation regiochemistry is dictated by five-membered palladated chelate formation.



Auxiliary-assisted sp^3 C−H bond arylation results are presented in Schemes 8 and 9.[21] As expected, carboxylic acid derivatives are arylated in β-positions (Scheme 8). Aliphatic

SCHEME 9. Amine Derivative Arylation



C−H bonds are arylated extremely easily in this case. The butyramide of 8-aminoquinoline undergoes *p*-methoxylation in the methylene group in less than 5 min at 110 °C. Cyclohexanecarboxylic acid amide is diarylated. The reaction proceeds at 70 °C and is diastereoselective (8:1) for the formation of the all-cis product. For a Pd-catalyzed functionalization of secondary aliphatic C−H bonds, these are exceptionally mild conditions. Interestingly, secondary C−H bonds react faster than primary bonds, allowing the tetraarylation of isobutyric amide. This method was recently used for the synthesis of modified amino acid derivatives.[22] The transposition of the amide group allows arylation of benzyl- and alkylamine derivatives by employing picolinic acid as a removable directing group (Scheme 9). This is an unprecedented remote functionalization reaction that allows selective arylation of the γ-position of an aliphatic amine. The reaction conditions are harsher than those for aminoquinoline derivatives, showing that the role of the auxiliary ligand is quite important.

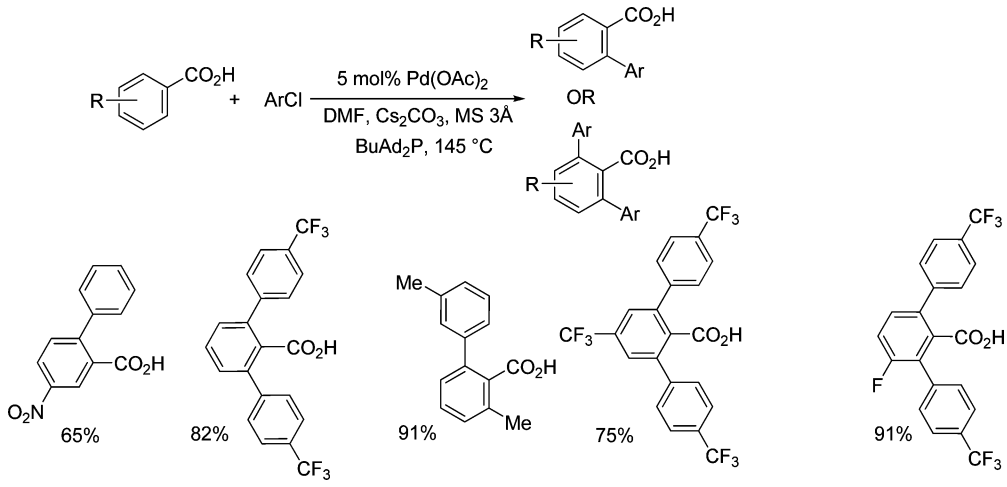
Remote functionalizations resulting in the formation of C−C bonds are rare.[23] Most of these methods involve radical reactions. While it is relatively easy to functionalize the enolizable α-position of the carboxylic acid derivatives, the selective functionalization of β-positions is substantially more difficult.[24] In a somewhat related case, Sen has described the Pt-catalyzed oxidation of the terminal methyl group in propionic acid; however, in the next homologue, butyric acid, the γ-position is reactive.[24a] Du Bois has described Rh-catalyzed β- and γ-amination of alcohol and amine derivatives.[25]

Selective γ-arylation of aliphatic amine chains is unique. The reactions shown above are also the first examples of palladium-catalyzed unactivated sp^3 C−H bond transformation into C−C bonds with no adjacent tertiary centers.[4]

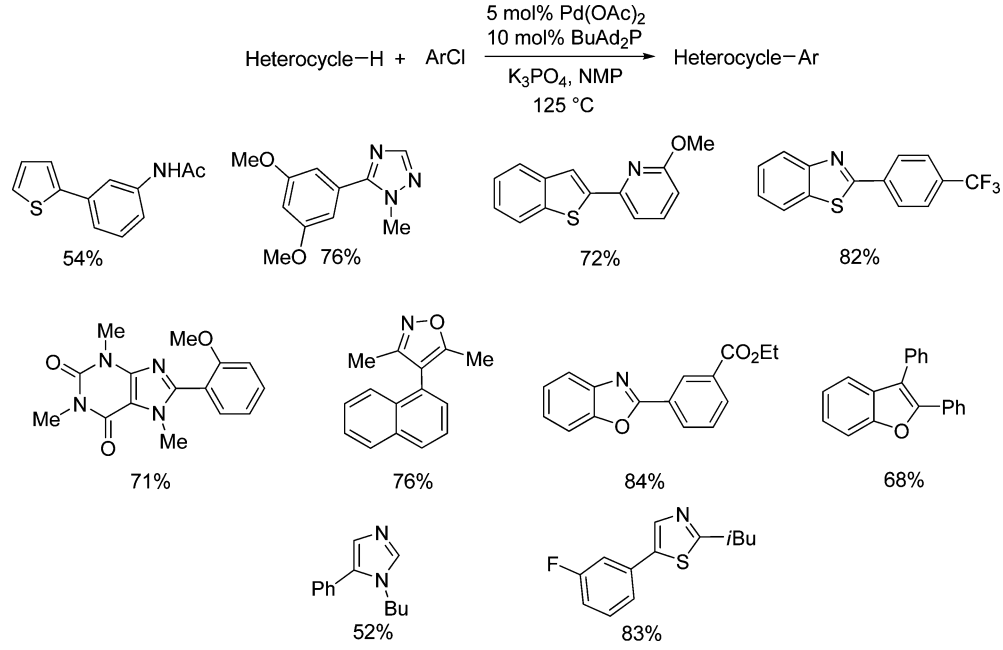
2.3. Arylation by Aryl Chlorides: A Pd(0)−Pd(II) Catalytic Cycle. 2.3.1. Benzoic Acid Arylation. While the Pd(II)−Pd(IV) catalytic cycle conditions allow for the arylation of a wide variety of directing-group-containing arenes, use of comparatively expensive aryl iodides is required. Aryl chlorides are now routinely used for C−C bond creation under Pd(0)−Pd(II) catalytic cycle conditions.[26] As a consequence, use of cheaper ArCl in C−H bond functionalization should also be possible if appropriate ligands are used and catalytic cycle for the arylation is changed from Pd(II)−Pd(IV) to Pd(0)−Pd(II) couple. Ohta published a method for palladium-catalyzed indole arylation by activated pyrazinyl chlorides in the 1980s.[27] Fagnou and Ackermann have previously reported C−H bond arylation by unactivated ArCl.[28] We were interested in developing the method for benzoic acid arylation by aryl chlorides. During the optimization, substantial conversions to product were observed with many electron-rich, bulky phosphine ligands. The best conversions were observed by employing *n*-butyl-di-1-adamantylphosphine ligand in combination with cesium carbonate base and palladium acetate precatalyst.[17] Benzoic acids of any electronic properties are reactive (Scheme 10). However, the combination of an electron-rich aryl chloride and an electron-rich benzoic acid is occasionally problematic due to decarboxylation of either product or reactant benzoic acid. Halogens other than fluorine are not compatible with the reaction conditions in contrast with the ArI/AgOAc method.

2.3.2. Electron-Rich Heterocycles. While aryl bromides are widely used for direct arylation of electron-rich heterocycles,[1,3] use of aryl chlorides in such reactions has been rare.[3e,27,29] A simple optimization of conditions that were successful for benzoic acid arylation afforded a method for electron-rich heterocycle arylation.[30] The ligand of choice that afforded the best combination of arylation scope, price, and operational simplicity is *n*-butyl-di-1-adamantylphosphine. Thiophene, benzothiophene, isoxazole and thiazole derivatives, benzoxazole, benzothiazole, imidazole, alkyltriazoles, and caffeine can all be efficiently arylated (Scheme 11).

SCHEME 10. Benzoic Acid Arylation by Aryl Chlorides



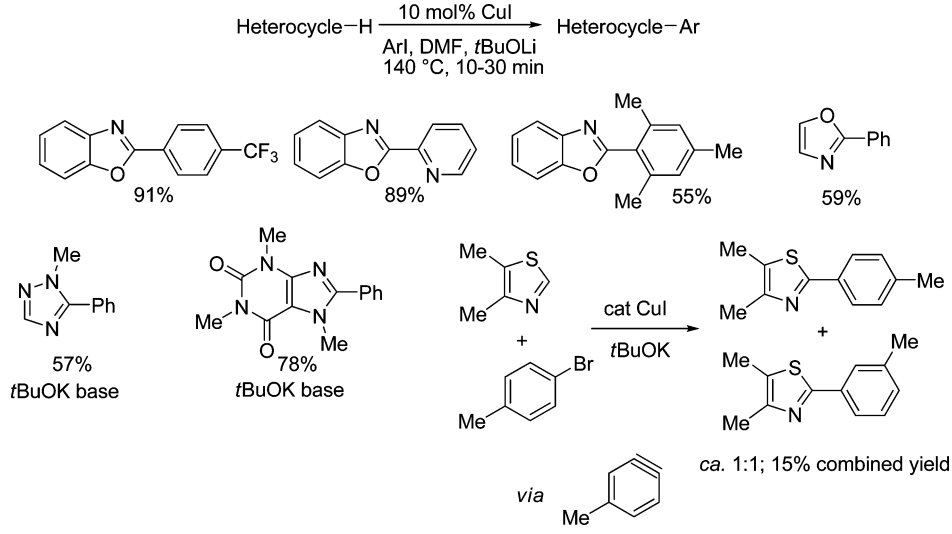
SCHEME 11. Heterocycle Arylation by Aryl Chlorides



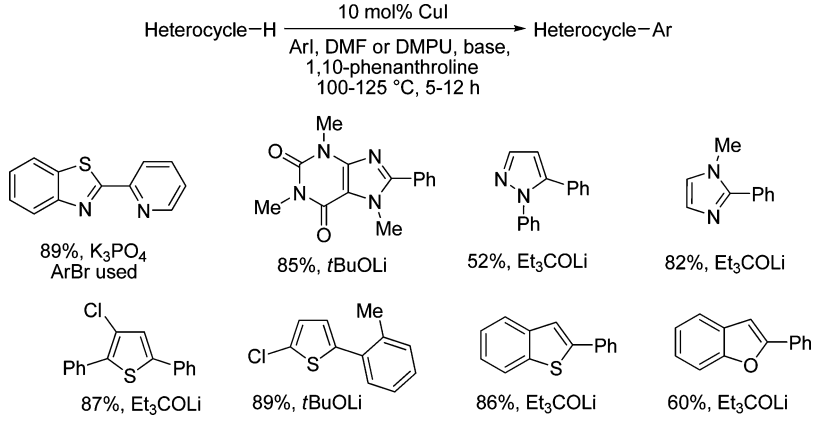
While the method is very general, additional optimization may be required to maximize reaction yields, since the heterocycles that can be arylated are very structurally different. For example, the optimized procedure for the phenylation of isobutylthiazole involves a decreased amount of phosphine ligand, added sodium acetate reagent, and DMA instead of NMP solvent.[31]

2.4. Copper Catalysis. The palladium catalysis allows for the arylation of a wide variety of directing-group-containing arenes and unactivated sp^3 C−H bonds. Aryl chlorides can be used in some of the arylations. However, it would be advantageous to employ cheaper catalysts for such transformations. Copper is underutilized as a catalyst for C−H bond functionalization even though it was the first transition metal shown to promote carbon−hydrogen bond arylation.[32] Our attention was drawn to the observation that copper salts can affect the regioselectivity of palladium-catalyzed electron-rich heterocycle arylation,[3a] and that both electron-poor arenes, such as trinitrobenzene, and electron-rich heterocycles, such as thiophene, can be arylated under harsh conditions by employing stoichiometric copper(I) oxide reagent.[32] These observations can be explained by invoking an organocopper intermediate. Arylated benzene or heterocycle would be formed by the reaction of the arylcopper with aryl iodide. If the presumed arylcopper intermediate could be generated efficiently, a copper-catalyzed method for the carbon−hydrogen bond arylation would be achieved. A logical approach to organocopper species generation involves employing a relatively

SCHEME 12. Copper-Catalyzed Arylation of Acidic Heterocycles



SCHEME 13. Electron-Rich Heterocycle Arylation

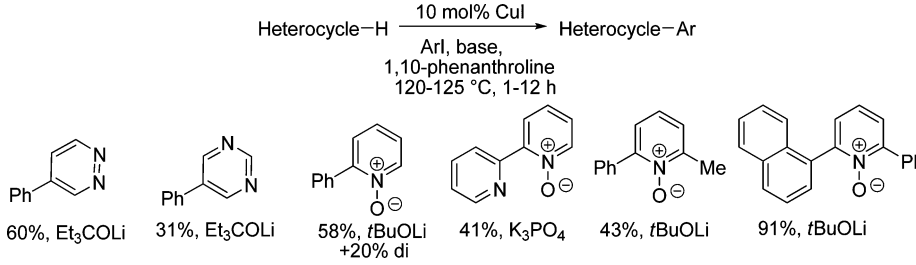


strong base. This approach was successful as described in the following sections.

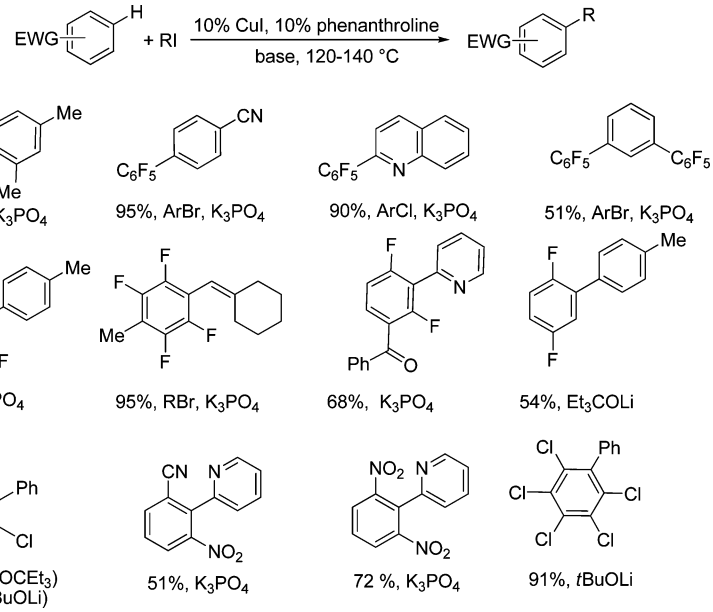
2.4.1. Electron-Rich Heterocycle Arylation. Two sets of conditions have been developed for electron-rich heterocycle arylation. More acidic heterocycles such as benzoxazole or benzothiazole may be arylated by employing *t*BuOLi base, aryl iodide, and DMF solvent. These reactions proceed at 140 °C in minutes. However, for less acidic imidazole, 1,2,4-triazole, and caffeine derivatives, a stronger *t*BuOK base is required, and the reaction proceeds by a benzyne-type mechanism.[33a] Formation of regioisomer mixtures was observed if substituted aryl halides were used in combination with *t*BuOK base (Scheme 12).

Several other issues had to be considered for developing a more widely applicable procedure. For slower reactions, formation of *tert*-butyl aryl ether by the reaction of *tert*-butoxide base with aryl iodide was observed, resulting in decreased conversion to the arylation products. Copper catalyst is relatively unstable at the temperature required for the arylation, and only fast reactions were successful. Therefore, a second set of conditions was developed. Employing phenanthroline ligand should allow for a more efficient heterocycle arylation by stabilizing the copper catalyst and facilitating the halide displacement step. Replacing *t*BuOK with a weaker lithium alkoxide or K_3PO_4 base should shut down the benzyne mechanism ensuring arylation regioselectivity. Employing hindered Et_3COLi base instead of *t*BuOLi should slow down the nucleophilic substitution of aryl iodide while not influencing the arylation rate. We were pleased to discover that addition of a phenanthroline ligand[34] allows *t*BuOLi or Et_3COLi base to be used for less acidic heterocycle arylation avoiding the problems associated with the benzyne mechanism.[33c] The modified reaction conditions allow for the arylation of heterocycles that were not reactive under our previous conditions (Scheme 13). It is possible to employ K_3PO_4 base in the arylation of the most acidic heterocycles possessing DMSO pK_a's below 27. Thiophenes, caffeine, alkylimidazoles, alkyltriazoles, benzothiophene, and benzofuran can be arylated by employing

SCHEME 14. Electron-Deficient Heterocycle Arylation



SCHEME 15. Electron-Deficient Benzene Arylation



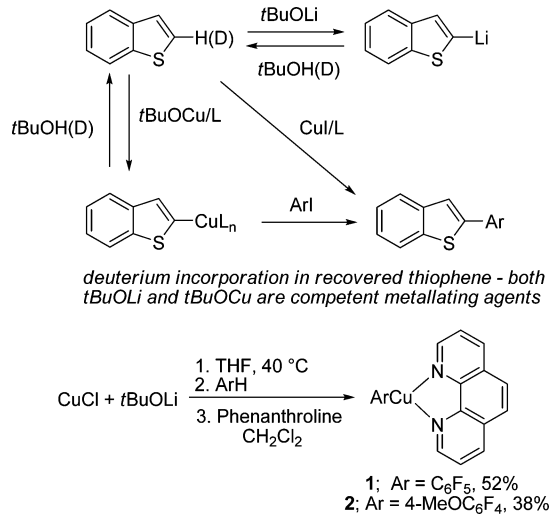
either *t*BuOLi or Et_3COLi base. The limitations of the method are as follows. Furans and N-substituted indoles are unreactive, while heterocycles possessing acidic N−H bonds are arylated on the nitrogen. The following DMSO pK_a's of heterocycle C−H bonds have been reported: *N*-alkylindoles, about 37; furan, 35; *N*-methylimidazole, 33.[35] It can be concluded that copper-catalyzed electron-rich heterocycle arylation is successful for compounds possessing pK_a's below 35.

2.4.2. Electron-Deficient Heterocycles and Benzene Derivatives. If the mechanistic considerations are valid, arylation of any arenes with C−H bond DMSO pK_a's below 35 should be possible. The reaction conditions developed for electron-rich heterocycles were applied for electron-deficient heterocycle and benzene arylation. Pyridine oxides, pyrimidine, and pyridazine can be efficiently functionalized (Scheme 14).[33c] The most acidic position of the heterocycle is selectively arylated.

Arylation of electron-deficient benzene derivatives proceeds smoothly (Scheme 15).[33b,c] All polyfluorobenzenes are arylated efficiently. The reactivity parallels the acidity of C−H bonds with the most acidic C−H bonds, those flanked by two electron-withdrawing groups, arylated most efficiently. Potassium phosphate can be used as a base if an arene contains more than two fluorine substituents or two fluorine substituents and an additional electron-withdrawing group. Penta-, tetra-, 1,3,5-tri-, and 1,3-dichlorobenzenes can be arylated in excellent to reasonable yield. 1,3-Dinitrobenzene and 3-nitrobenzonitrile are also reactive affording the arylation products in moderate yields. Arenes possessing only one electron-withdrawing group, such as nitro-, chloro-, fluoro-, and cyanobenzene, are unreactive.

2.4.3. Mechanistic Considerations. The arylation reaction can be divided into three parts: metalation, transmetalation with copper halide, and reaction of arylcopper with a haloarene. Both *t*BuOLi and *t*BuOCu are competent metalating agents under the reaction conditions (Scheme 16). Intermediacy of an arylcopper species was proven by in situ NMR studies. The reaction of copper iodide, potassium phosphate, pentafluorobenzene, and phenanthroline in DMF under the conditions of the catalytic process affords pentafluorophenylcopper−phenanthroline complex **1** as determined by ^{19}F NMR of the crude reaction mixture. Furthermore, 4-methoxy-

SCHEME 16. Mechanistic Considerations



2,3,5,6-tetrafluorophenylcopper−phenanthroline complex **2** was prepared by reacting *t*BuOCu with 2,3,5,6-tetrafluoroanisole followed by addition of phenanthroline ligand (Scheme 16). The structures of **1** and **2** have been verified by X-ray crystallographic analysis.[33c] Complex **1** reacts with aryl iodides affording the coupling products. Consequently, the reaction mechanism parallels that of copper-catalyzed heteroatom arylation.[36]

3. Summary and Outlook

This Account details our progress in developing direct, transition-metal-catalyzed carbon−hydrogen bond arylation procedures. By building on early observations of Tremont and Liebeskind,[6] we were able to develop a very general method that allows conversion of directing-group-containing arene C−H bonds into carbon−carbon bonds. Anilides, benzamides, benzoic acids, benzylamines, and 2-substituted pyridine derivatives can be arylated by aryl iodides under very similar reaction conditions thus attesting to the generality of the method. Others have shown that arylation of imines and heterocyclic substrates are possible under nearly identical conditions.[37] Furthermore, extension of the method to the arylation of unactivated sp^3 C−H bonds has been achieved by incorporating a removable, pyridine-based auxiliary. Highly regioselective arylation of β-positions of carboxylic acid derivatives and γ-positions of amine derivatives is thus possible. For several classes of substrates, such as benzoic acids and electron-rich heterocycles, aryl chloride coupling partners can be employed under Pd(0)−Pd(II) catalytic cycle conditions. For the arylation of acidic (DMSO pK_a below 35) arene C−H bonds, copper catalysis can be employed. Electron-rich and electron-deficient heterocycles as well as electron-poor arenes possessing at least two electron-withdrawing groups can be arylated by using copper catalyst in combination with a base and phenanthroline ligand. The most acidic position, which usually is the most hindered one, is arylated. The copper-catalyzed method complements the C−H activation/borylation methodology where functionalization usually occurs at the least hindered position.[38] It is interesting to consider differences between the palladium- and copper-catalyzed arylations. Mechanistically, palladium complexes are intimately involved both in the C−H activation and the subsequent C−C bond formation steps. This feature allows a greater scope of substrates to be functionalized by virtue of many substrate classes that can be palladated. On the other hand, mechanistic details are quite complicated and synthetic procedures are often developed by a trial-and-error method. The copper-catalyzed C−H bond arylation, in contrast, involves a simple acid−base reaction followed by a Cu-catalyzed C−C bond formation. Only relatively acidic (pK_a below 35) substrates can be functionalized; however, the simple mechanistic picture allows for an easy and predictable development of synthetic procedures. Since the transition metal is involved only in the C−C bond formation, copper-catalyzed arylation is conceptually similar to Kumada, Negishi, and Castro cross-couplings. It is likely that other transition metals such as iron, nickel, cobalt, or silver can be employed in deprotonation/arylation reaction sequences.

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BIOGRAPHICAL INFORMATION

Olafs Daugulis received an undergraduate degree in Chemical Engineering from Riga Technical University, Latvia. After earning a Ph.D. from University of Wisconsin under the guidance of Prof. Edwin Vedejs in 1999, he spent three years as a postdoctoral associate with Prof. Maurice Brookhart at University of North Carolina at Chapel Hill. He joined the chemistry faculty at the University of Houston in 2003. He is interested in the application of organometallic chemistry to organic chemistry problems.

Hien-Quang Do received his B.S. in chemistry from the University of Natural Sciences at Ho Chi Minh City in Vietnam. A few years after obtaining a Masters degree from the same University in 2003, he came to the University of Houston where he currently is a third-year graduate student in Prof. Daugulis' group. He developed the method for copper-catalyzed arylation of acidic sp^2 C−H bonds and is currently working on expanding the arylation scope.

Dmitry Shabashov obtained his B.S. degree in Chemical Engineering from Riga Technical University in 2001 followed by a M.S. degree in 2004. He is currently a fourth-year graduate student at the University of Houston in Prof. Daugulis' group. His research involves auxiliary-directed arylation of sp^3 carbon−hydrogen bonds.

FOOTNOTES

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