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A General Method for Copper-Catalyzed Arene Cross-Dimerization

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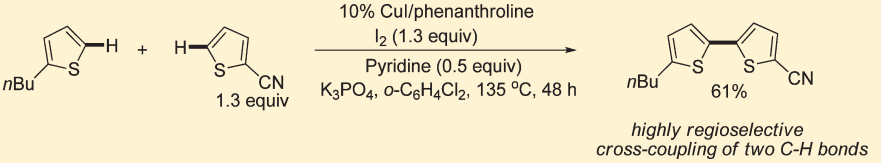
Supporting Information

ABSTRACT:



highly regioselective cross-coupling of two C-H bonds

A general method for a highly regioselective copper-catalyzed cross-coupling of two aromatic compounds using iodine as an oxidant has been developed. The reactions involve an initial iodination of one arene followed by arylation of the most acidic C−H bond of the other coupling component. Cross-coupling of electron-rich arenes, electron-poor arenes, and five- and six-membered heterocycles is possible in many combinations. Typically, a 1/1.5 to 1/3 ratio of coupling components is used, in contrast to existing methodology that often employs a large excess of one of the arenes. Common functionalities such as ester, ketone, aldehyde, ether, nitrile, nitro, and amine are well-tolerated.

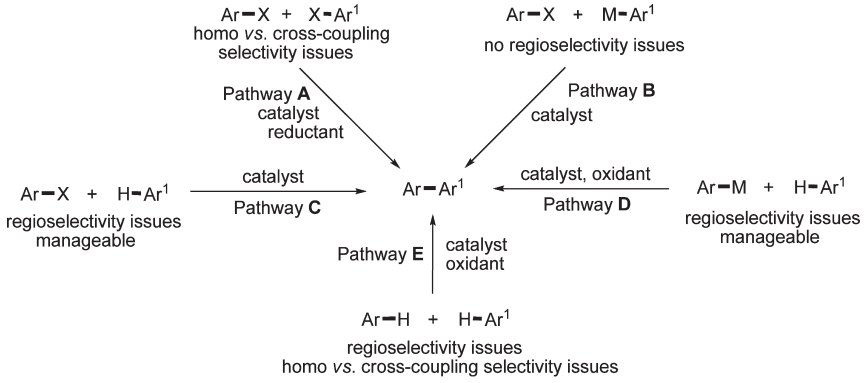
1. INTRODUCTION

The biaryl moiety is a ubiquitous structural motif in natural products, pharmaceuticals, and functional materials.[1] As a consequence, formation of aryl−aryl bonds has interested chemists since Ullmann reported a copper-catalyzed method for biaryl synthesis more than a century ago.[2a] The following methods can be used for creating an aryl−aryl bond (Scheme 1). Ullmann coupling is an example of the coupling of two aryl halides to give a biaryl (pathway A). A stoichiometric reducing agent is necessary, and achieving selective cross-coupling is difficult for most intermolecular cases.[2] Presently, the most widely used method for aryl−aryl bond formation is the coupling of an arylmetal with an aryl halide (pathway B). Reactions such as Stille, Suzuki, Kumada, Negishi, and others allow for a highly controlled synthesis of biaryls possessing virtually any structural motif.[3] However, this methodology requires functionalized starting materials that may not be readily available, resulting in longer synthetic sequences. Coupling of an aryl halide with an arene C−H bond is also possible (pathway C). Reoxidation is not required. Excellent regioselectivity with respect to the arene C−H bond-coupling component has been achieved for arylation of heterocycles[4,5] and directing-group-containing arenes[4,6] as well as deprotonative arylation that includes functionalization of polyfluorobenzenes.[4,7] However, for many simple substrates, the regioselectivity of the arylation is still problematic. Often only symmetric arenes such as benzene or *p*-xylene are employed as C−H coupling components because of the formation of regioisomeric mixtures.[4] Pathway D involves the coupling of an arylmetal or carboxylic acid with an arene C−H bond.[4,8] The regioselectivity issues for this pathway are similar to the ones observed for pathway C. Additionally, a stoichiometric oxidant, typically a transition-metal salt, is required. Direct dehydrogenative arene coupling (pathway E) is perhaps the most efficient method for biaryl synthesis.[4,9] Functionalized starting materials are not required, and a stoichiometric oxidant is needed. However, this pathway presents the most formidable difficulties with respect to regioselectivity and selectivity for cross-coupling over homocoupling. Often up to 100 equiv of one of the coupling components is required to achieve a good yield of the cross-coupling product. A few recent reports have shown that in special cases, a minimal excess of one of the coupling components can be used.[9d,m,n] Achieving good coupling regioselectivity is also problematic unless five-membered-ring heterocycles, directing-group-containing arenes, or polyfluorobenzenes are employed. Besides the above-mentioned issues, in most of the published cases palladium catalysts are used in conjunction with several equivalents of heavy-metal (silver or copper) reoxidants. However, oxygen can sometimes be used as the stoichiometric oxidant, avoiding the generation of heavy-metal waste.[10]

The generality of direct dehydrogenative arene coupling is relatively low. Success has been achieved either in the arylation of electron-rich heterocycles and directing-group-containing arenes with simple benzenes or cross-coupling of five-membered-ring heterocycles. Therefore, the development of a new, general catalytic system for dehydrogenative cross-coupling would be quite appealing. In view of the existing limitations, the new reaction system should deliver highly efficient cross-coupling with good regioselectivity while involving a readily available copper catalyst and a transition-metal-free oxidant. Additionally, the method should be highly general, allowing for cross-coupling of many arene types.

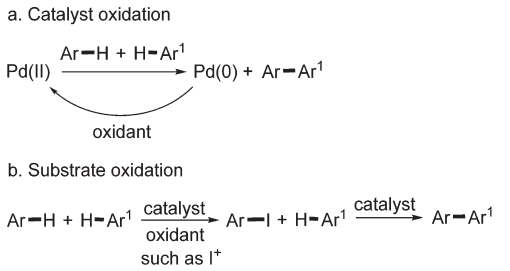
Received: May 24, 2011
Published: August 08, 2011

Scheme 1. Methods for Aryl−Aryl Bond Formation



X = halogen, OSO_2R; M = SnR_3, $B(OR)_2$, CO_2H, etc.

Scheme 2. Reaction Development Considerations



Issues: *1. chemo- and regioselectivity of oxidation*
2. oxidation step compatibility with cross-coupling step

We report here a method for highly regioselective copper-catalyzed cross-coupling of arene C−H bonds that employs iodine as the terminal oxidant.

2. METHOD DEVELOPMENT CONSIDERATIONS

As mentioned above, most of the existing dehydrogenative arene cross-coupling methods are palladium-catalyzed, and the scope of the published reactions is rather limited. The explanation for the lack of generality can be inferred from the proposed mechanisms, in which the palladium catalyst governs both the arylation selectivity and the available substrate scope. The oxidant reoxidizes Pd(0) to Pd(II) and must be inert with respect to the substrates and reaction products. Alternatively, one can envision reaction conditions under which one of the coupling partners instead of the catalyst would be oxidized, affording a functionalized intermediate that could participate in further reaction to form a cross-coupling product (Scheme 2).

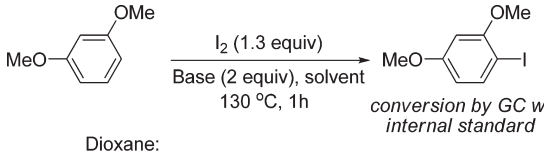
The oxidative direct arylation can be dissected into two consecutive in situ processes: oxidation and direct arylation. This approach may result in several advantages if the substrate oxidation step is designed correctly. Fast and selective oxidation of only one of the coupling components should result in minimization of the amount of the homodimerization byproduct. Additionally, a large excess of one of the coupling components should not be necessary. Regioselective oxidation would result in selective activation of only one of the many C−H bonds in the substrate. Consequently, diverse and nonsymmetric coupling partners could be employed. The oxidant must be able to functionalize a broad range of aromatic compounds regioselectively, affording intermediates that are reactive toward subsequent copper-catalyzed direct arylation.[7b−j] Iodination usually occurs with high regioselectivity.[11,12] Electron-rich and electron-poor arenes can be iodinated under electrophilic and deprotonative reaction conditions, respectively.[11,12] Aryl iodides can be employed as substrates in highly regioselective copper-catalyzed arylation of C−H bonds, which has been found to be successful in the arylation of a variety of heterocycles and electron-deficient arenes.[7b−j] The combination of a copper-catalyzed direct arylation reaction with an in situ iodination should allow the creation of a general method for oxidative cross-coupling of two arenes. The iodinating reagent must be compatible with the copper(I) catalyst. Strong oxidants must be avoided, since they efficiently convert catalytically active Cu(I) to inactive Cu(II). We have reported a sequential iodination/cross-coupling method that employs ICl as the oxidant.[7i] However, because ICl is incompatible with the Cu(I) catalyst, the reaction must be carried out in two steps. With those considerations in mind, we chose to use I_2, since it is a weaker oxidant than ICl and delivers an C(sp^2)−I functionality that is reactive under copper catalysis.

3. RESULTS

3.1. Optimization of the Iodination Step. The method for oxidative arene cross-coupling consists of iodination followed by direct arylation, which should be mutually compatible. The conditions for direct arylation employing copper catalysis have been investigated extensively.[7] The iodination method and its compatibility with the arylation step had to be investigated, taking into account that iodination may proceed by different mechanisms for various arene types. Iodinations of electron-rich arenes, electron-deficient arenes, five-membered-ring heterocycles, and six-membered-ring heterocycles are discussed below according to the mechanisms by which these halogenations occur.

The iodination of electron-rich arenes proceeds through electrophilic aromatic substitution.[11] Our initial attempts were directed toward developing optimized conditions for the iodination of electron-rich arenes by iodine that would be compatible with the subsequent cross-coupling step. 1,3-Dimethoxybenzene was

Scheme 3. Optimization of Iodination Conditions for Electron-Rich Arenes



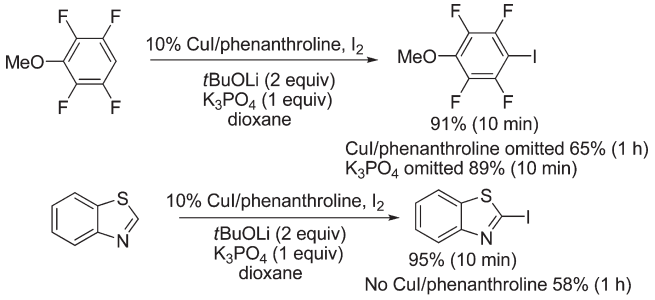
Dioxane:

K_3PO_4	32%
K_3PO_4 + Pyridine (0.5 equiv)	40%
Na_3PO_4	45%
Na_3PO_4 + Pyridine (0.5 equiv)	65%

1,2-$C_6H_4Cl_2$:

K_3PO_4 + Pyridine (0.5 equiv)	**90%**
Na_3PO_4 + Pyridine (0.5 equiv)	88%

Scheme 4. Influence of Copper Catalyst on Iodination of Electron-Poor Arenes and Acidic Heterocycles



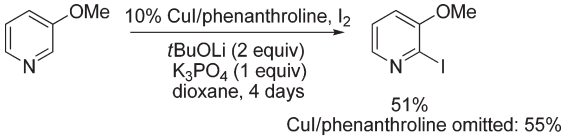
conversions by GC with internal standard

used as the model substrate for iodination. A number of bases and additives were screened in dioxane and 1,2-dichlorobenzene solvent (Scheme 3).

The best conversion in dioxane was obtained when Na_3PO_4 was used as a base in the presence of 0.5 equiv of pyridine as an additive. However, the use of excess pyridine resulted in lower conversions. Unfortunately, Na_3PO_4 is not an efficient base for the subsequent cross-coupling step, and thus, the reaction was examined in 1,2-dichlorobenzene. To our delight, the conversion was improved to 90% when K_3PO_4 was employed as the base in the presence of pyridine as an additive. Thus, the conditions for iodination of electron-rich aromatic compounds involve K_3PO_4 as the base, I_2, dichlorobenzene as the solvent, and pyridine as an additive. For more reactive substrates, iodination can be performed in dioxane. These conditions can be used for iodination of electron-rich arenes such as methoxy- or aminobenzenes as well as five-membered-ring heterocycles such as thiophenes, indoles, pyrazoles, pyrroles, furans, and indolizines.

In contrast, iodination of electron-deficient arenes by electrophilic pathways requires harsh reaction conditions that are incompatible with the subsequent cross-coupling step.[13] Consequently, a deprotonative halogenation pathway should be employed.[12] As reported previously, use of dioxane as the solvent in combination with an alkoxide base and iodine proved to be efficient for regioselective iodination of the most acidic arene C−H bond (Scheme 4).[14] The reaction conditions are applicable to the iodination of electron-poor arenes that contain several electron-withdrawing groups as well as the most acidic heterocycles, such as oxazoles and thiazoles. Interestingly, the best results were obtained in the presence of the copper catalyst that is

Scheme 5. Pyridine Iodination



conversion by GC with internal standard

required in the cross-coupling step and by employing a mixture of *t*BuOLi and K_3PO_4 as the base. Huang and co-workers have reported that in nonpolar solvents, the acidity of five-membered-ring heterocycles is increased by copper complexation, thus facilitating the deprotonation step.[15]

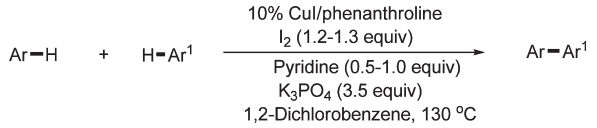
Finally, a method was developed for iodination of pyridines at the 2-position. Conditions similar to the ones used for the iodination of electron-poor arenes afforded reasonable conversions to 2-iodopyridines. Only pyridines possessing electron-donating substituents or halogens are reactive (Scheme 5). Interestingly, in this case the CuI/phenanthroline additive slightly decreases the conversion, in contrast to the iodination of electron-poor arenes.

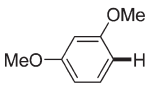
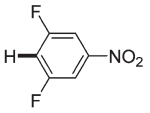
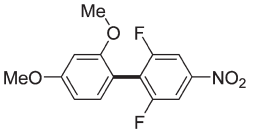
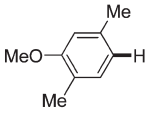
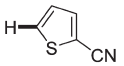
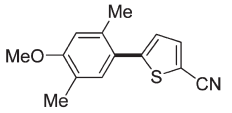
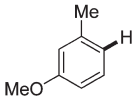
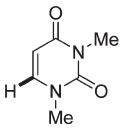
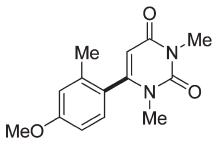
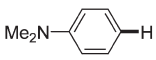
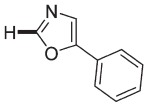
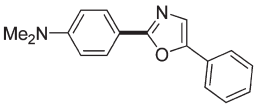
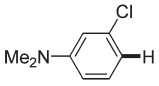
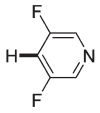
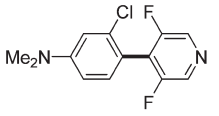
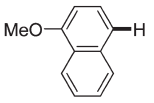
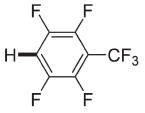
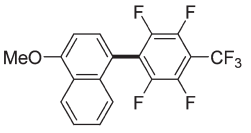
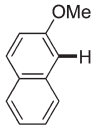
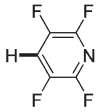
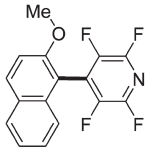
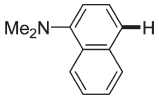
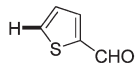
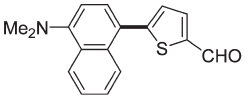
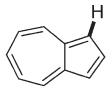
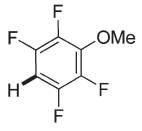
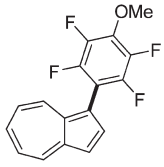
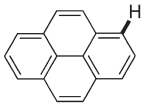
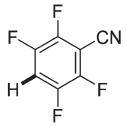
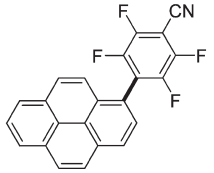
3.2. Oxidative Arene Cross-Dimerization. The wide scope of iodination combined with the generality of copper-catalyzed C−H bond arylation results in a very general method that allows the cross-coupling of many arene types. For example, by employing this methodology, one can cross-couple electron-rich arenes with electron-poor arenes as well as five- and six-membered-ring heterocycles. Any combinations of cross-coupling of electron-poor arenes, five-membered-ring heterocycles, and six-membered-ring heterocycles should also be possible. The types of cross-coupling reactions that are not possible with this methodology include cross-coupling of electron-rich arenes. Additionally, electron-neutral arenes such as benzene cannot be used as either of the coupling components because of the requirement of a relatively acidic C−H bond with a DMSO pK_a of 35−37 or below[16] for the copper-catalyzed arylation step and their lack of reactivity in the iodination step. For convenience, the cross-coupling examples below are classified according to arene type rather than the iodination mechanism.

3.2.1. Coupling of Electron-Rich Arenes with Heterocycles and Electron-Poor Arenes. The reaction between 1,3-dimethoxybenzene and 3,5-difluoronitrobenzene was performed under the conditions developed for iodination of electron-rich arenes. The arenes were cross-coupled using 10 mol % CuI/phenanthroline as the catalyst, K_3PO_4 as the base, iodine as the oxidant, and pyridine as an additive in 1,2-dichlorobenzene, and an excellent yield of the product was obtained (Table 1, entry 1). When the CuI/phenanthroline catalyst was omitted, the cross-coupling product was not formed. A number of electron-rich arenes were then cross-coupled with five- and six-membered-ring heterocycles as well as electron-poor arenes. Typically, an arene ratio of 1/1.5 to 1/3 was used, and no homocoupling products were observed. A single product regioisomer was obtained in each case. Electron-rich arenes possessing either one dialkylamino or alkoxy substituent with an additional electron-donating group were reactive. 2,5-Dimethylanisole was coupled with 2-cyanothiophene, affording the coupling product in a good yield (entry 2). The coupling of 3-methylanisole with a uracil derivative gave the product in 61% yield (entry 3). Dimethylaniline derivatives were arylated with phenyloxazole (entry 4), 3,5-difluoropyridine (entry 5), and thiophene-2-carbaldehyde (entry 8). Couplings

dx.doi.org/10.1021/ja2047717 |*J. Am. Chem. Soc.* 2011, 133, 13577–13586

Table 1. Arylation of Electron-Rich Arenes[a]

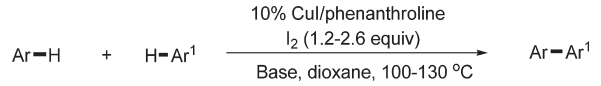


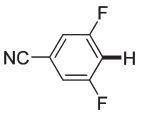
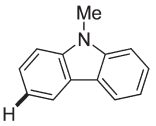
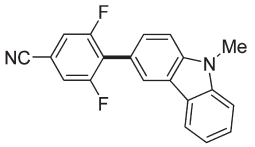
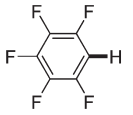
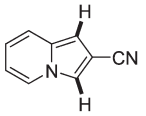
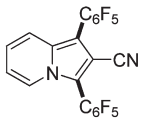
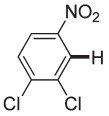
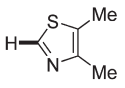
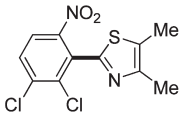
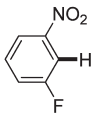
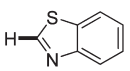
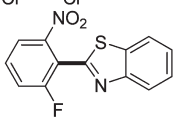
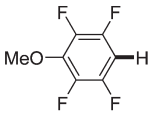
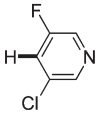
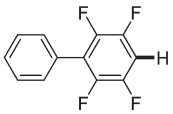
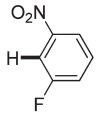
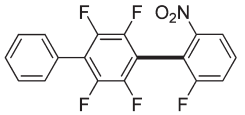
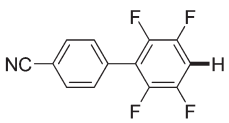
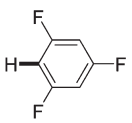
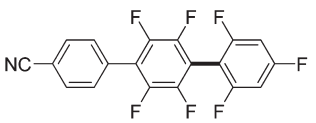
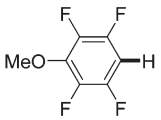
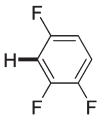
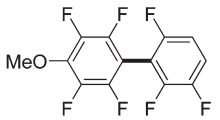
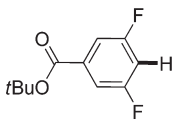
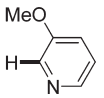
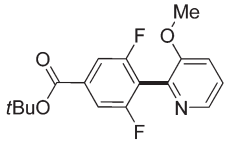
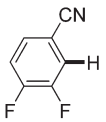
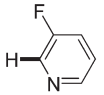
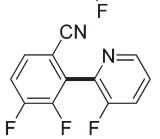
Entry	Electron-rich arene	Coupling partner	Product	Time	Yield
1				5 days	82%
2				5 days	72%
3[b]				2 days	61%
4[c]				4 days	57%
5				4 days	80%
6[d]				2 days	85%
7				4 days 3 days	55% 75%[b]
8				6 days	64%
9[c]				1 day	49%
10				7 days	53%

[a] Conditions: copper(I) iodide (0.1 mmol), phenanthroline (0.1 mmol), electron-rich arene (1−3 mmol), coupling partner (1−2 mmol), iodine (1.2−1.3 mmol), 1,2-dichlorobenzene solvent (0.7−1.0 mL), pyridine additive (0.5−1.0 mmol), 1−7 days. Yields are isolated yields. See the Supporting Information for details. [b] Sequential iodination/cross-coupling. [c] Dioxane solvent. [d] Less than 3% of perfluoro-4,4′-bitolyl was also formed.

dx.doi.org/10.1021/ja2047717 |J. Am. Chem. Soc. 2011, 133, 13577–13586

Table 2. Arylation of Electron-Deficient Arenes[a]



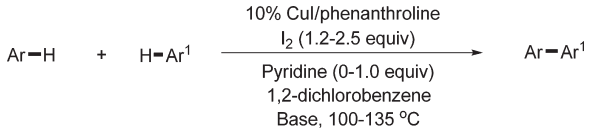
Entry	Electron-deficient arene	Coupling partner	Product	Time	Yield
1[b]				3 days	52%
2[c]				3 days	78%
3[d]				12 hours	55%
4[e]				5 hours	65%
5[f]				6 hours	69%
6[g]				12 hours	60%
7[h]				12 hours	68%
8[i]				12 hours	48%
9				4 days	50%
10				5 days	56%

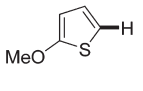
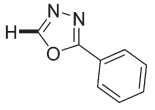
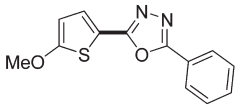
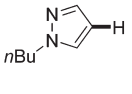
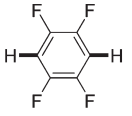
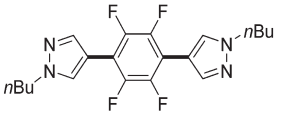
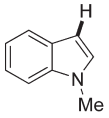
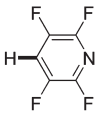
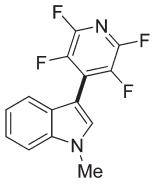
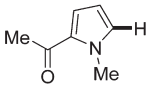
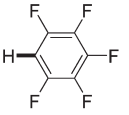
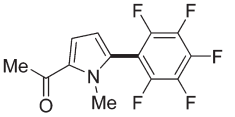
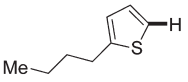
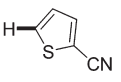
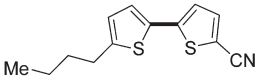
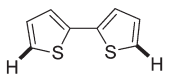
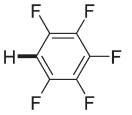
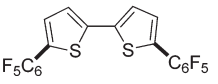
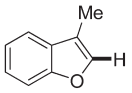
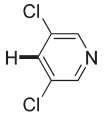
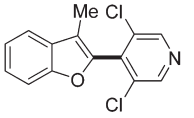
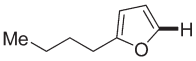
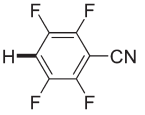
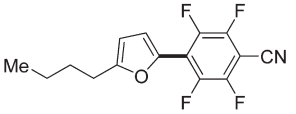
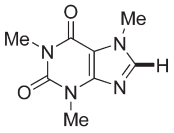
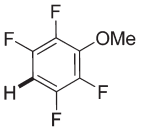
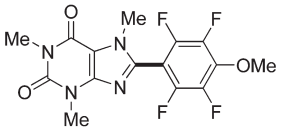
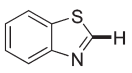
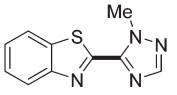
[a] Conditions: copper(I) iodide (0.1 mmol), phenanthroline (0.1 mmol), electron-poor arene (1−4 mmol), coupling partner (1−3 mmol), iodine (1.2−2.6 mmol), dioxane solvent (0.8−2.0 mL), K_3PO_4 or *t*BuOLi/K_3PO_4 base, 5 h−5 days. Yields are isolated yields. See the Supporting Information for details. [b] Pyridine additive (0.5 mmol), 1,2-dichlorobenzene solvent. [c] Pyridine additive (1.0 mmol), 20 mol % CuI/phenanthroline. [d] 4,4′,5,5′-Tetramethyl-2,2′-bithiazole byproduct (13%) was formed. [e] 2,2′-Bibenzothiazole byproduct (15%) was formed. [f] 2,2′,3,3′,5,5′,6,6′-Octafluoro-4,4′-dimethoxybiphenyl byproduct (12%) was formed. [g] 2′,2″,3′,3″,5′,5″,6′,6″-Octafluoro-*p*-quaterphenyl byproduct (8%) was formed. [h] 2,3,5,6-Tetrafluoro-4′-cyanobiphenyl dimer byproduct (12%) was formed. [i] 2,2′,3,3′,5,5′,6,6′-Octafluoro-4,4′-dimethoxybiphenyl byproduct (18%) was formed.

of 1- and 2-methoxynaphthalene with a polyfluorinated arene and 2,3,5,6-tetrafluoropyridine, respectively, were also successful (entries 6 and 7). Some polycyclic hydrocarbons such as azulene and pyrene were arylated with polyfluorinated arenes (entries 9 and 10). The method appears to have good functional group tolerance, with nitro, cyano, amide, chloro, and aldehyde substituents being compatible with the reaction conditions. In all of these examples, the reactions proceeded

dx.doi.org/10.1021/ja2047717 |*J. Am. Chem. Soc.* 2011, 133, 13577–13586

Table 3. Arylation of Five-Membered Ring Heterocycles[a]



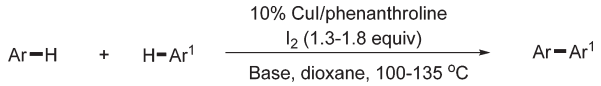
Entry	Five-membered-ring heterocycle	Coupling partner	Product	Time	Yield
1[b]				2 days	60%
2[c]				9 days	80%
3[d,e]				1 day	82%
4[f]				2.5 days	55%
5				2 days	61%
6[g]				5 days	62%
7				2 days	50%
8				2 days	61%
9[h]				7 hours	73%
10[i]				2 hours	51%

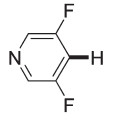
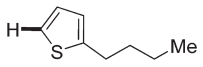
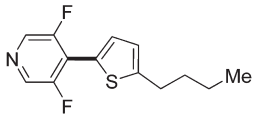
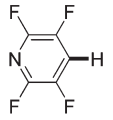
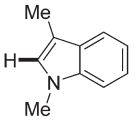
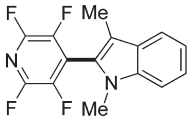
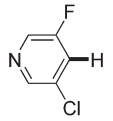
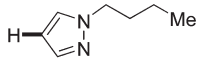
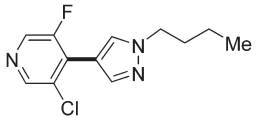
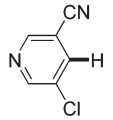
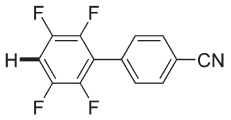
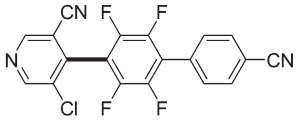
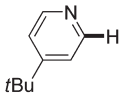
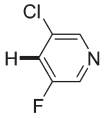
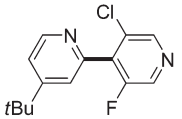
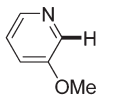
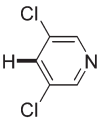
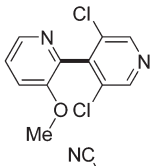
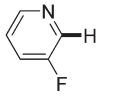
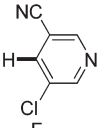
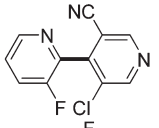
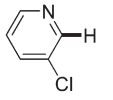
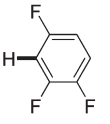
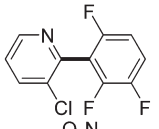
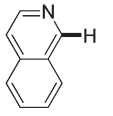
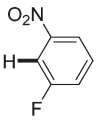
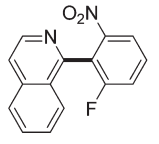
[a] Conditions: copper(I) iodide (0.1 mmol), phenanthroline (0.1 mmol), heterocycle (1−3 mmol), coupling partner (1−4 mmol), iodine (1.2−2.5 mmol), 1,2-dichlorobenzene solvent (0.7−1.0 mL), K_3PO_4 or *t*BuOLi/K_3PO_4 base, 2 h−9 days. Yields are isolated yields. See the Supporting Information for details. [b] Dioxane solvent. Less than 5% of 2-phenyloxazole dimer was formed. [c] 20 mol % CuCl/phenanthroline. [d] Dioxane/DMF mixed solvent (9/1). [e] Sequential iodination/cross-coupling. [f] A minor amount of regioisomer (<5%) was formed. [g] 20 mol % CuCl/phenanthroline catalyst. Decafluorobiphenyl byproduct (<3%) was formed. [h] Dioxane solvent. 2,2′,3,3′,5,5′,6,6′-Octafluoro-4,4′-dimethoxybiphenyl byproduct (16%) was formed. [i] Dioxane solvent. 2,2′-Bibenzothiazole byproduct (15%) was formed.

by initial iodination of the electron-rich arene followed by copper-catalyzed cross-coupling. In only one case was the formation of a minor amount of a homocoupling byproduct observed: 1-methoxynaphthalene arylation by heptafluorotoluene (entry 6) afforded <3% of perfluoro-4,4′-bitolyl in addition to the cross-coupling product.

3.2.2. Arylation of Electron-Deficient Arenes. A wide range of aromatic compounds bearing at least two electron-withdrawing

Table 4. Pyridine Arylation[a]



Entry	Pyridine	Coupling partner	Product	Time	Yield
1[b]				7 days	79%
2[c]				1 day	71%
3[d]				2 days	79%
4				5 hours	67%
5				3 days	42%
6				3 days	47%
7				3 days	51%
8				5 days	53%
9[e]				3 days	32%

[a] Conditions: copper(I) iodide (0.1 mmol), phenanthroline (0.1 mmol), pyridine substrate (1.5−3.0 mmol), coupling partner (1.0 mmol), iodine (1.3−1.8 mmol), dioxane solvent (0.9−1.6 mL), K_3PO_4 or *t*BuOLi/K_3PO_4 base, 5 h−7 days. Yields are isolated yields. See the Supporting Information for details. [b] 1,2-Dichlorobenzene solvent. [c] Mixed 1,2-dichlorobenzene/DMF solvent (9.5/0.5). [d] 1,2-Dichlorobenzene solvent, pyridine additive (0.5 mmol). [e] 2,2′-Difluoro-6,6′-dinitrobiphenyl byproduct (16%) was formed.

groups such as chloro, fluoro, nitro, cyano, and ester were selectively arylated at the most acidic C−H bond (Table 2). The entries are arranged with respect to the mechanism of iodination pathway involved in the coupling. The iodination occurred by electrophilic aromatic substitution (entries 1 and 2), deprotonation/iodination (entries 3−8), and iodination of six-membered ring heterocycles (entries 9 and 10). In entries 5−8, the electron-deficient arene was iodinated. In all other cases, the coupling partner was iodinated. Only one regioisomer of the coupling product was observed.

3,5-Difluorobenzonitrile was coupled with *N*-methylcarbazole in an acceptable yield (entry 1). Coupling of pentafluorobenzene and several halogenated nitrobenzenes with five-membered-ring heterocycles such as cyanoindoline (entry 2), dimethylthiazole (entry 3), and benzothiazole (entry 4) were successful. Interestingly, selective cross-coupling of two electron-deficient arenes was possible when there was a sufficient C−H bond acidity difference between the coupling partners. For example, tetrafluorobiphenyl could be coupled with 1-fluoro-3-nitrobenzene (entry 6). Coupling of a cyanated tetrafluorobiphenyl with 1,3,5-trifluorobenzene delivered the cross-coupling product selectively (entry 7). Finally, coupling of an arene possessing four fluorine substituents with an arene possessing three fluorines occurred in a moderate yield (entry 8). The cross-coupling product can be

dx.doi.org/10.1021/ja2047717 |*J. Am. Chem. Soc.* 2011, 133, 13577–13586

obtained because the iodination step requires electron-deficient arenes possessing at least four fluorine substituents. The more acidic arene is converted to an aryl iodide, which then couples with the less acidic arene to afford the cross-coupling product. Arylation of pyridine derivatives with electron-deficient arenes affords 2-arylpyridines in moderate yields (entries 9 and 10). In cases where the deprotonation/iodination pathway was operative, homocoupling byproduct formation was observed (entries 3−8).

3.2.3. Arylation of Five-Membered-Ring Heterocycles. The reaction scope for the arylation of five-membered-ring heterocycles is summarized in Table 3. The entries are arranged with respect to the mechanism of the iodination pathway involved in the cross-coupling. The iodination occurred by electrophilic aromatic substitution (entries 1−8) or deprotonation/iodination (entries 9 and 10). In all cases except entry 9, the five-membered-ring heterocycle was iodinated.

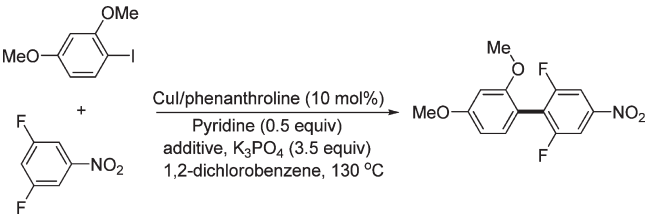
Thiophenes were arylated by other five-membered-ring heterocycles, such as 2-phenyloxadiazole (entry 1) and 2-cyanothiophene (entry 5), as well as electron-deficient arenes (entry 6). Especially interesting is the cross-coupling of two electronically different thiophenes (entry 5). This reaction proceeded with an excellent cross-coupling selectivity, and no homocoupling products were observed in the crude reaction mixture. Double arylation of 1,2,4,5-tetrafluorobenzene with *N*-butylpyrazole afforded the coupling product in an excellent yield (entry 2). Arylations of *N*-methylindole and 1-methyl-2-acetylpyrrole with electron-deficient arenes were successful (entries 3 and 4). Furan derivatives were arylated with electron-deficient arenes (entries 7 and 8). Caffeine was functionalized in a good yield (entry 9). Benzothiazole was coupled with *N*-methyl-1,2,4-triazole, and the product was obtained in a moderate yield. Two examples in Table 3 show a fourfold C−H bond functionalization wherein the substrate was diarylated (entries 2 and 6). In some cases, minor amounts of arene homodimerization products were observed (entries 1, 6, 9, and 10).

3.2.4. Pyridine Arylation by Heterocycles and Electron-Deficient Arenes. Table 4 summarizes the scope for arylation of pyridine derivatives. The data are arranged according to the mechanism of the iodination pathway involved in the cross-coupling. The iodination occurred by electrophilic aromatic substitution (entries 1−3), deprotonation/iodination (entry 4), and pyridine iodination (entries 6−9). In entries 1−4, the coupling partner was iodinated. In all other cases, the pyridine derivative was iodinated. Only one product isomer was observed in each case.

Polyfluoropyridines were arylated with 2-butylthiophene (entry 1), 1,3-dimethylindole (entry 2), and *N*-butylpyrazole (entry 3). 3-Chloro-5-cyanopyridine was also reactive and could be coupled with tetrafluorocyanobiphenyl (entry 4). Pyridine itself was not reactive toward iodination/cross-coupling. However, pyridine derivatives possessing a halogen, methoxy, or alkyl substituent at the 3- or 4-position could be iodinated/cross-coupled under the general conditions with moderate yields and high selectivities (entries 5−8). Only monoarylation was observed even in the presence of excess iodine. Interestingly, isoquinoline was arylated regioselectively with 3-fluoronitrobenzene, albeit in a moderate yield (entry 9). The low efficiency of isoquinoline iodination was responsible for the diminished yield in the latter case. The 2,2′-difluoro-6,6′-dinitrobiphenyl byproduct was formed in entry 9.

3.2.5. General Considerations. Copper-catalyzed arene cross-dimerization required reaction times anywhere from a few hours to 9 days. Both the iodination and subsequent copper-catalyzed cross-coupling[7d] proceeds on a time scale of hours. For the methodology to be useful and predictable, the factors causing the long reaction times must be understood. Several control experiments were run to determine which components of the reaction mixture inhibit the reaction (Table 5).

Table 5. Influence of Additives



Entry	Additive	Time (h)	Conversion (%)[a]
1	none	5	68
2	none	12	>98
3	LiI (1 equiv)	12	88
4	I_2 (0.5 equiv)	5	<1
5	I_2 (0.5 equiv)	24	<1
6	I_2 (0.5 equiv) + LiI (1 equiv)	5	<1
7	I_2 (0.5 equiv) + LiI (1 equiv)	24	12

[a] Determined by GC using an internal standard.

The cross-coupling of 1,3-dimethoxybenzene with 3,5-difluoronitrobenzene required 5 days to achieve an 82% yield (Table 1, entry 1). In contrast, 3,5-difluoronitrobenzene arylation of 2,4-dimethoxyiodobenzene proceeded to complete conversion in 12 h (Table 5, entry 2). Iodination of 1,3-dimethoxybenzene to produce the intermediate 2,4-dimethoxyiodobenzene required 1 h to achieve 90% conversion (Scheme 3). Clearly, one of the reaction components inhibits the copper-catalyzed cross-coupling of 1,3-dimethoxybenzene with 3,5-difluoronitrobenzene. Addition of LiI somewhat slowed the reaction (entry 3). However, addition of 0.5 equiv of I_2 shut the reaction down completely (entries 4 and 5). Interestingly, when both LiI and I_2 were added to the reaction mixture, some activity was restored (entries 6 and 7). The mechanism of inhibition most likely involves oxidation of catalytically active Cu(I) to inactive Cu(II).[7i,17] Analysis of the data in Tables 1−4 allows us to conclude that the reaction time depends on the efficiency of the iodination process. If iodination is either slow or inefficient, resulting in the presence of residual iodine in the reaction mixture, the reactions are slow. Diarylation examples such as those shown in entries 2 and 6 of Table 3 were among the slowest reactions. The shortest reaction times were generally observed for examples where the acidic heterocycle or polyfluoroarene coupling component was iodinated.

4. SUMMARY

An operationally simple and general method for copper-catalyzed cross-coupling of two aromatic compounds that employs iodine as the oxidant has been developed. The reactions proceed by iodination of one of the coupling components followed by arylation of the most acidic C−H bond of the other coupling component. Electron-rich arenes can be coupled with electron-poor arenes as well as five- and six-membered-ring heterocycles. Additionally, any combinations of five- and six-membered-ring heterocycles and electron-poor arenes can also

be cross-coupled. In many cases, formation of homocoupling products is not observed. The coupling components are used in a ratio of 1/1.5 to 1/3, in contrast to existing methodology that often employs one of the arenes as the solvent. Most common functionalities, such as ester, ketone, aldehyde, ether, nitrile, nitro, and amine, are well-tolerated. For arenes containing multiple active C−H bonds, polyfunctionalization is possible.

4. EXPERIMENTAL SECTION

General Procedure for Coupling Reactions. Outside the glovebox, a 1 dram vial equipped with a magnetic stir bar was charged with 1,10-phenanthroline (10 mol %), CuI (10 mol %), iodine (1.2−2.6 equiv), the arene substrates in the indicated ratio, pyridine (0−1.0 equiv), and 1,4-dioxane or 1,2-dichlorobenzene solvent. The vial was flushed with nitrogen, capped, and placed inside the glovebox. To this mixture was added base (K_3PO_4 or a *t*BuOLi/K_3PO_4 mixture). The sealed vial was then taken out of the glovebox and stirred at the appropriate temperature. After the completion of the reaction, the mixture was cooled to room temperature, diluted with CH_2Cl_2 (1.0 mL), and subjected to column chromatography on silica gel in hexanes followed by an appropriate solvent to elute the products. After concentration of the fractions containing the product, the residue was dried under reduced pressure to yield the pure product.

■ ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

We thank the Welch Foundation (Grant E-1571), the National Institute of General Medical Sciences (Grant R01GM077635), the Alfred P. Sloan Foundation, the Camille and Henry Dreyfus Foundation, and the Norman Hackerman Advanced Research Program for supporting this research.

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