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Direct Arylation of Simple Arenes with Aryl Bromides by Synergistic Silver and Palladium Catalysis

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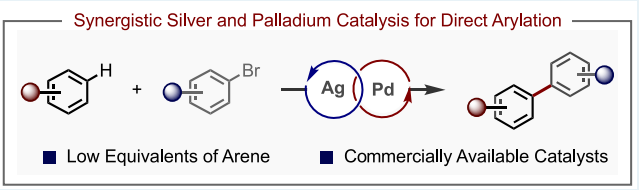
ABSTRACT: The direct, catalytic arylation of simple arenes in small excess with aryl bromides is disclosed. The developed method does not require the assistance of directing groups and relies on a synergistic catalytic cycle in which phosphine-ligated silver complexes cleave the aryl C−H bond, while palladium catalysts enable the formation of the biaryl products. Mechanistic experiments, including kinetic isotope effects, competition experiments, and hydrogen-deuterium exchange, support a catalytic cycle in which cleavage of the C−H bond by silver is the rate-determining step.



KEYWORDS: *direct arylation, C−H activation, palladium and silver catalysts, synergistic catalysis, aryl bromides*

The functionalization of carbon−hydrogen bonds enables the construction of carbon−carbon and carbon−heteroatom bonds from readily available starting materials.[1] The direct arylation of arenes with aryl electrophiles is a process by which an sp^2 C−H bond is transformed into a C−aryl linkage in biaryl structures, which are common motifs in pharmaceuticals, agrochemicals, and organic materials (Scheme 1a).[2] Despite the many reported catalytic methods for direct arylation, the intermolecular arylation of simple arenes, which do not contain strongly coordinating functional groups that accelerate and control the site of C−H activation, remains a longstanding synthetic challenge. Existing methods for direct arylation in the absence of directing groups with transition-metal catalysts either require a large excess of arene[3] or require activated substrates containing several electron-donating or electron-withdrawing groups that facilitate C−H activation (Scheme 1b, left).[4]

A strategy for the direct arylation of simple arenes was published recently by Larrosa and co-workers. In this work, the coordination of $Cr(CO)_3$ to the arene π-system facilitated the activation of aryl C−H bonds (Scheme 1b, right).[5] However, these methods require the separate installation of the $Cr(CO)_3$ unit prior to the direct arylation and removal of this unit after the arylation process. A few reports describe conditions for direct arylation without such activation of the arene, but these reactions lacking an excess of the arene include a specific functional group that directs the C−H activation step,[6] even if the reaction occurs beyond the position ortho to this group.[7] The most efficient undirected reactions occur with a diimine ligand on palladium, but even these reactions have been demonstrated to occur only with three arenes and only at the positions ortho to a fluoro, a nitro, or a cyano group.[8]

We report a method for the direct arylation of a series of arenes containing one or more substituents with commercially available aryl bromides and transition-metal catalysts with a small excess of the arene (1.5 to 5 equiv). This process stems from our previous report of the direct allylation of simple arenes with palladium and silver;[9] a series of mechanistic data, including kinetic isotope effects, competition experiments and H/D exchange reactions, imply that this direct arylation reaction occurs by a synergistic combination of a silver complex that cleaves the C−H bond of the arene and a palladium system that forms the biaryl product by transmetalation with an arylsilver intermediate and subsequent reductive elimination (Scheme 1c).[10]

Our initial efforts to increase the efficiency of direct arylation reactions focused on conditions comprising a combination of silver and palladium for the reaction of 1-fluoronaphthalene (**1a**) with 3-bromotoluene (**2a**) under conditions with just 1.5 equiv of the arene. We examined a series of reaction parameters, including a range of silver- and palladium-catalysts, ligands, bases, and solvents (see SI for details). These experiments demonstrated that the biaryl product **3aa** formed selectively in 81% yield in the presence of 0.5 mol % of $Pd(OAc)_2$ and 5 mol % of commercially available Cy_2PtBu as ligand with Ag_2O and Cs_2CO_3 as the silver component and base (Table 1, entry 1).

The effect of reaction parameters on the direct arylation of **2a** with **1a** is shown in Table 1. The yields for the formation of **3aa** decreased when the arylation reaction was catalyzed by

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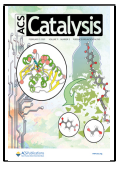

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Scheme 1. Biaryls in Bioactive Compounds and Strategies for their Synthesis via Direct Arylation

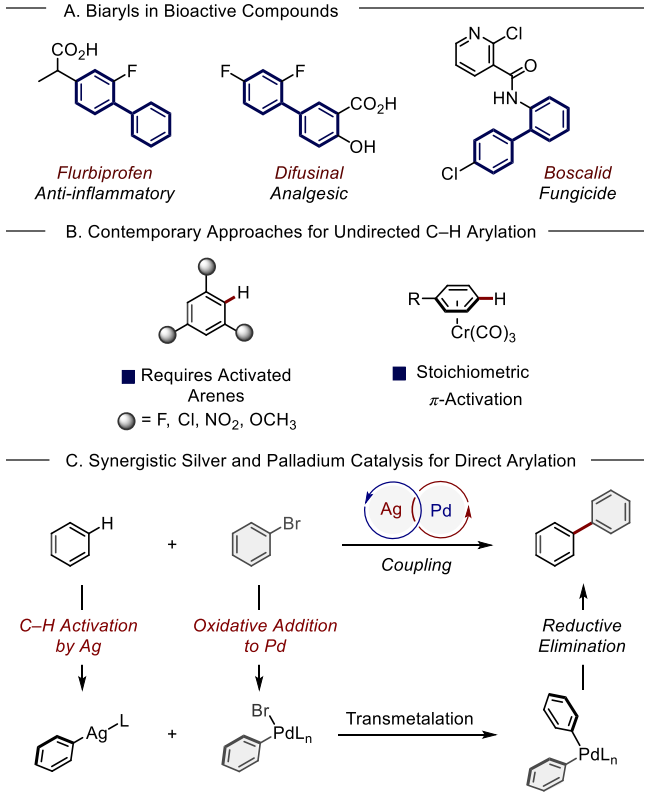
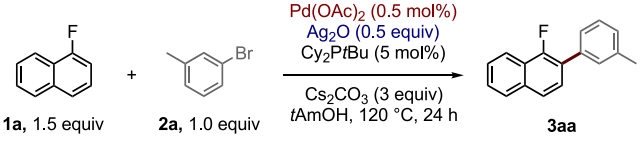


Table 1. Evaluation of Reaction Conditions for the Direct Arylation of 1-Fluoronaphthalene (1a)



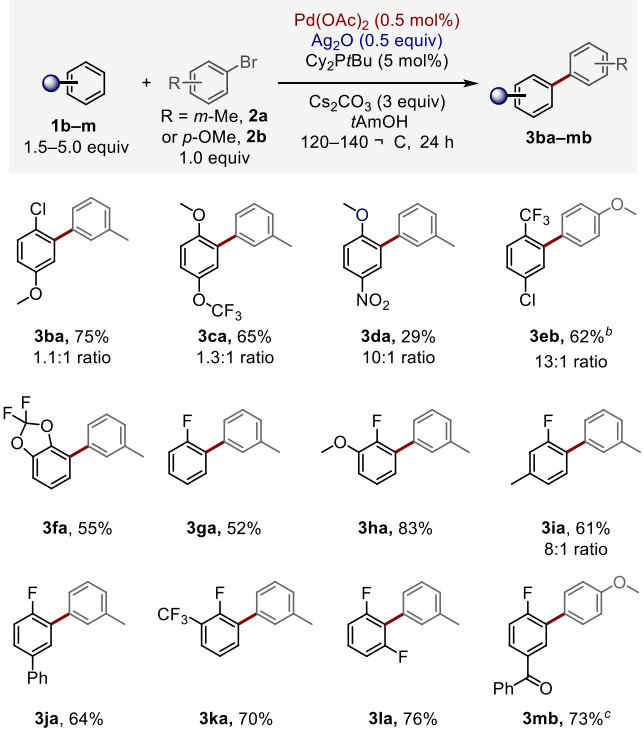
entry	deviation on reaction conditions	yield (%)[a]
1	none	81
2	Cy_3P, instead of tBuPCy$_2$	50
3	Cy_2PPh, instead of tBuPCy$_2$	41
4	tBu$_3$P, instead of tBuPCy$_2$	35
5	Ph_3P, instead of tBuPCy$_2$	10
6	(o-Tolyl)$_3$P, instead of tBuPCy$_2$	<5
7	AgOAc (1 equiv), instead of Ag_2O	38
8	Ag_2CO_3, instead of Ag_2O	43
9	$AgNO_3$, instead of Ag_2O	56
10	K_2CO_3, instead of Cs_2CO_3	24
11	Na_2CO_3, instead of Cs_2CO_3	20
12	without Pd(OAc)$_2$	<5
13	without tBuPCy$_2$	<5
14	without Ag_2O	<5

[a]Determined by ^{19}F NMR in $CDCl_3$ with C_6H_5F as internal standard.

complexes bearing ligands other than Cy$_2$PtBu, including aromatic and trialkylphosphines (Table 1, entries 2−6). Reactions conducted with stoichiometric silver additives and bases other than Ag_2O and Cs_2CO_3 gave **3aa** in yields that were lower than those obtained under the standard conditions (Table 1, entries 7−11). Reactions conducted without the palladium catalyst, the silver additive, or Cy$_2$PtBu formed **3aa** in only trace amounts (Table 1, entries 12−14).

Having established conditions for the direct arylation of aryl bromides in which the arene is used in small excess, the scope of reactions with a variety of substituted arenes was investigated. As shown in Scheme 2, 4-substituted anisoles

Scheme 2. Scope of Arenes that Underwent Direct Arylation[a]



[a]See SI for experimental details. [b]Performed with 4-bromoanisole. [c]Performed with 4-bromoanisole for 48 h.

containing chloro and trifluoromethoxy groups underwent arylation with 3-bromotoluene. These reactions formed biaryls **3ba**−**3ca** in a nearly equimolar mixture of constitutional isomers in good yield. A reaction with 1,4-nitroanisole led to the formation of **3da** in high selectivity, albeit in moderate yield. Notably, 4-chlorobenzotrifluride and 2,2-difluorobenzodioxole reacted smoothly under the developed reaction conditions to form biaryls **3eb** and **3fa** in good yield and excellent selectivity.

Biaryls containing a single fluorine atom are common motifs in pharmaceuticals and agrochemicals,[11] but methods to prepare these structures by direct arylation with low equivalents of arene have been limited to monofluorobenzenes containing additional electron-withdrawing groups or fluoroarenes containing directing groups.[6d−g,12] In contrast, our developed method enables the direct arylation of several substituted anisoles and of both electron-rich and electron-poor fluorobenzenes selectively at the position ortho to the fluorine atom (Scheme 2). Fluorobenzene (**1g**) itself has been a challenging substrate with which to achieve C−H arylation previously, often requiring this arene to be solvent.[13] However, our method enabled the synthesis of **3ga** with just 5 equiv of arene in 52% yield at 140 °C. Electron-donating functional groups at the 2-, 3-, and 4-positions (**1h**−**1j**) were tolerated, although reactions of such arenes required 5 equiv of arene. A

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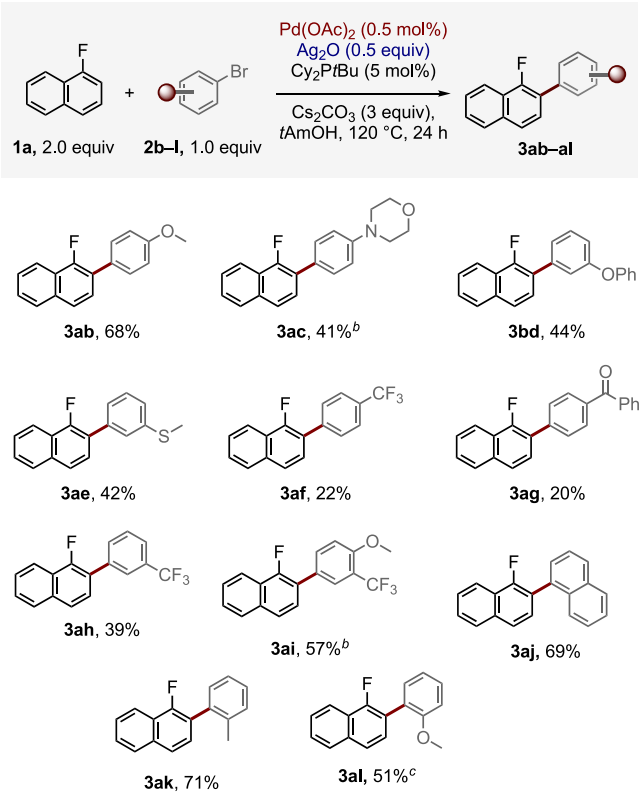
range of fluorobenzenes bearing electron-withdrawing groups at the 2-, 3-, and 4-positions, including trifluoromethyl, fluorine, and benzoyl moieties also reacted. In this case, the reactions occurred in high yields (**3ka**−**3mb**) with low equivalents of arene (1.5−2 equiv).

The scope of aryl bromides that underwent direct arylation with 1-fluoronaphthalene (**1a**) is shown in Scheme 3. Aryl

Scheme 3. Scope of Aryl Bromides that Underwent Direct Arylation with 1a[a]

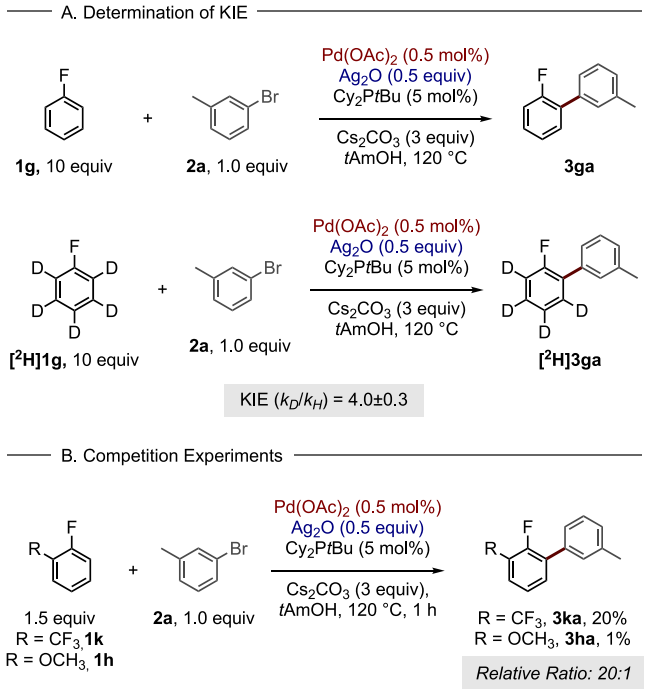


[a]See SI for experimental details. [b]With 1.0 mol % of $Pd(OAc)_2$, 10 mol % of *t*BuPCy$_2$, and 4 equiv of **1a** for 48 h. [c]Reaction performed at 140 °C for 48 h.

bromides containing electron-donating groups (**2b**−**e**) at the para and meta positions, such as methoxy, morpholinyl, phenoxy, and thiomethoxy, were tolerated, providing biaryl products in good yields. The reactions of aryl halides containing electron-withdrawing groups at the 4- and 3-positions gave only moderate yields of their corresponding biaryls (**3af**−**3ah**). A 3,4-dibustituted aryl bromide and 1-bromonaphthalene reacted smoothly, leading to the synthesis of **3ai** and **3aj** in good yields. The developed direct arylation also allowed the synthesis of biaryls in high yield from sterically demanding 2-substituted bromobenzenes, as shown for **3ak** and **3al**.

Having stablished that the efficiency of this direct arylation process is higher than that of the direct arylations published previously, we performed a series of experiments to gain insights into its reaction mechanism. To investigate if C−H bond cleavage at the arene is rate determining, we compared the initial rates of the direct arylation of 2-bromotoluene (**2a**) with fluorobenzene (**1g**) and its deuterated analogue [^{2}H]**1g** in separate vessels (Scheme 4a). These experiments gave a primary kinetic isotope effect with a value of 4.0 ± 0.3, a value

Scheme 4. Determination of KIE and Competition Experiment[a]

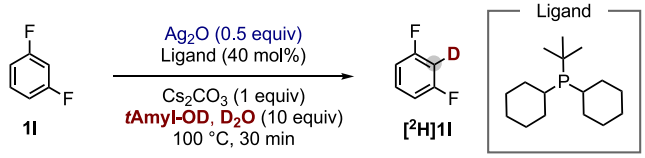


[a]See SI for experimental details.

that is consistent with a mechanism in which C−H bond cleavage is rate determining. To gain further insight into the mechanism of the C−H bond cleavage, we conducted a competition experiment between **1k** and **1h**. As shown in Scheme 4b, the electron-poor arene **1k** was the more reactive substrate, which is consistent with a mechanism in which C−H bond cleavage proceeds by a concerted metalation deprotonation step.[14]

A series of experiments summarized in Table 2 probed our initial mechanistic hypothesis that silver-complexes cleave the

Table 2. Evaluation of Reaction Conditions for the Deuteration of 1l



entry	deviation from above conditions	yield (%)[a]
1	none	83
2	with $Pd(OAc)_2$ (5 mol %) and Ag_2O	71
3	without Ag_2O	<5
4	without ligand	<5
5	with $Pd(OAc)_2$ (5 mol %) without Ag_2O	<5

[a]Determined by ^{19}F and ^{1}H NMR in $CDCl_3$.

aryl C−H bond during the arylation process (Scheme 1c). To do so, we conducted H/D exchange reactions with 1,3-difluorobenzene (**1l**) and 10 equiv of D_2O in *tert*-amyl alcohol-d_1. In the presence of 0.5 equiv of Ag_2O, 40% mol of *t*BuPCy$_2$, and stoichiometric Cs_2CO_3, [^{2}H]**1l** formed with 84% incorporation of deuterium into the 2-position (entry 1). A

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lower degree of deuterium incorporation in **1l** was observed in the presence of $Pd(OAc)_2$ (entry 2). Reactions conducted in the absence of Ag_2O or ligand led to only trace levels of H/D exchange (entries 3−4). Moreover, $Pd(OAc)_2$ in the presence of ligand without silver additive did not catalyze H/D exchange with **1l**. These results imply that a phosphine-ligated silver complex, instead of a palladium-species, cleaves the C−H bond during the rate-determining step of the arylation reaction.

In summary, we have developed a catalytic method for the direct arylation of simple arenes with commercially available aryl bromides and a catalyst system comprising a combination of silver and palladium that react synergistically. This method does not require directing groups and allows the arylation reaction to proceed with one of the smallest excesses of arene for any direct arylation with arenes lacking a directing group. Mechanistic experiments imply that C−H bond cleavage occurs by a phosphine-ligated silver complex, presumably by a concerted metalation-deprotonation step, and that this step of the catalytic cycle is rate determining. Current work in our laboratory is being conducted to fully understand the mechanism of the proposed catalytic cycle involving reactions of both Ag and Pd and to use this knowledge for the development of further improved, undirected, C−H bond functionalization reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c05254.

Experimental procedures and spectroscopic data on the reaction products (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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