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Catalytic Direct Arylation with Aryl Chlorides, Bromides, and Iodides: Intramolecular Studies Leading to New Intermolecular Reactions

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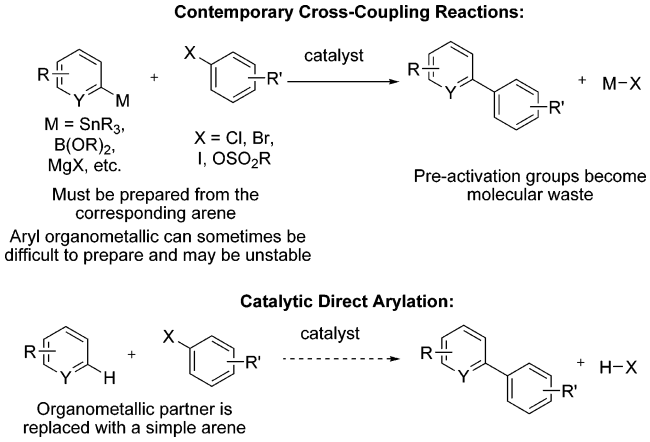
Abstract: A catalyst for the intramolecular direct arylation of a broad range of simple and heterocyclic arenes with aryl iodides, bromides, and chlorides has been developed. These reactions occur in excellent yield and are highly selective. Studies with aryl iodides substrates revealed that catalyst poisoning occurs due to the accumulation of iodide in the reaction media. This can be overcome by the addition of silver salts which also permits these reactions to occur at lower temperature. The utility of the methodology is illustrated by a rapid synthesis of a carbazole natural product and by the synthesis of sterically encumbered tetra-ortho-substituted biaryls via ring-opening reactions of the direct arylation products. Mechanistic investigations have provided insight into the catalyst's mode of action and show the presence of a kinetically significant C−H bond cleavage in palladium-catalyzed direct arylation of simple arenes. Knowledge garnered from these studies has led to the development of new intermolecular arylation reactions with previously inaccessible arenes, opening the door for the development of other new direct arylation processes.

Introduction

The utility of the biaryl structural motif has prompted intense research directed at discovering efficient and high-yielding methods for its preparation. Transition metal catalysis has featured prominently in these efforts, leading to the establishment of a range of useful cross-coupling reactions.[1] A common element in all of these processes is the need for two activated arenes that can react selectively with the metal catalyst. While high yields can be achieved with preactivated substrates, the need for dual preactivation is inherently wasteful since these groups may require multiple steps for their installation and none of the preactivation groups appear in the final product. Furthermore, not all regioisomers of the organometallic or aryl halide are readily available making some biaryl compounds difficult to access. In some instances the preactivated species may not be stable thus complicating application of this methodology.

In recent years, direct arylation reactions have emerged as attractive alternatives to these more commonly employed cross-coupling reactions.[2] These reactions substitute one of the preactivated arenes with a simple arene (Scheme 1). Importantly, it is typically the more expensive and difficult to prepare organometallic coupling partner that is replaced. Several electron-rich heteroarenes such as imidazoles, indoles, pyrroles, thiazole, and imidazo[1,2-a]pyrimidines can now be employed,[3] and progress has been made in the use of the more challenging unactivated simple arenes[4,8] and π-electron deficient heterocycles.[5] Despite these advances, several important challenges remain. For example, the predominance of direct arylation

Scheme 1. Cross-Coupling Methods for the Preparation of Biaryl Molecules



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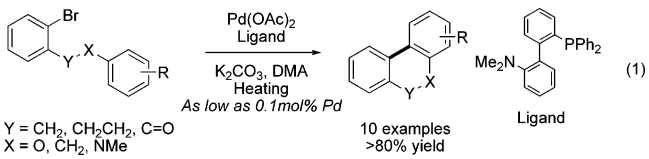
reactions employs aryl iodides as coupling partners.[3a,4e,4j,22] Even with electron-rich heterocyclic arenes, use of aryl chlorides is rare despite the fact that aryl chlorides are more readily available and less expensive.[6] Furthermore, no single catalyst has been shown to be capable of achieving catalytic arylation with simple arenes and aryl iodides, bromides, and chlorides.

In this account we report (1) the development of an operationally simple catalyst system for direct intramolecular arylation processes exhibiting broad scope for aryl chlorides, bromides, and iodides including previously incompatible sterically encumbered aryl chlorides and bromides; (2) evidence that, despite their widespread use, aryl iodides exhibit inferior reactivity compared to that of aryl bromides and chlorides in the direct arylation reactions studied; (3) insight into catalyst poisoning with aryl iodides leading to new reaction conditions showing increased reactivity; (4) application of these processes to the synthesis of a carbazole natural product, Mukonine, in three steps from simple starting materials; (5) conditions for the efficient formation of tetra-ortho-substituted biaryls and their conversion to acyclic tetra-ortho-substituted biaryls; (6) mechanistic studies pointing to a kinetically significant C−H bond cleavage step in the direct arylation of simple arenes; (7) the development of the first intermolecular direct arylation reactions of a simple arene with aryl chlorides and bromides thus setting the stage for further expansion in these previously inaccessible processes.

Results and Discussion

As part of a research program targeted at the development of new direct arylation reactions we sought to develop catalyst systems that enable efficient reaction with unactivated arenes. As a first step into the development of these processes we explored an intramolecular variant. Although intramolecular direct arylations with unactivated arenes were known prior to our work, they typically suffered from low selectivity and very low catalyst turnover numbers; indeed very high catalyst loadings of greater than 20 mol % were frequently employed.[7] Initial investigations revealed a catalyst system that enabled selective functionalization of unactivated arenes with aryl bromides exhibiting high catalyst activity and selectivity (eq 1).[8] Encouraged by this initial discovery, the scope of this



(1)

catalyst system with other aryl halides was investigated. While good outcomes were obtained in the direct arylation of bromoarenes, inferior results were obtained with aryl chlorides. Intriguingly, poor outcomes were also obtained with aryl iodide substrates, despite the fact that aryl iodides are typically regarded as providing greater reactivity in cross-coupling reactions.

Aryl Chlorides as Substrates. Significant progress has been made in the use of aryl chlorides as substrates in palladium-mediated cross-coupling reactions, and many reactions with aryl chlorides can now be performed under very mild conditions.[9] In contrast, direct arylation reactions rarely employ aryl chloride substrates.[6] In an initial report we described the use of *N*-heterocyclic carbene (NHC) ligands for the direct arylation of aryl chlorides.[10] In subsequent studies, we discovered that these catalysts failed to induce complete reaction when more sterically encumbered substrates were employed.[11] This limitation prompted a reinvestigation of the potential catalysts capable of performing direct arylation with aryl chlorides. Catalyst screens were performed with aryl chloride **1** in the presence of 1 mol % $Pd(OAc)_2$, 2 mol % ligand, and 2 equiv of K_2CO_3 in dimethylacetamide (DMA) at 130 °C. Results are outlined in Scheme 2. Triarylphosphines (**3**−**6**) as well as ortho-biaryl phosphines (**7**−**11**) gave inferior reactivity in the direct arylation of aryl chlorides. Better results were obtained with some trialkylphosphines (**13**−**15**) as well as *N*-heterocyclic carbenes (**12**). Tricyclohexylphosphine and di-*tert*-butylmethylphosphine

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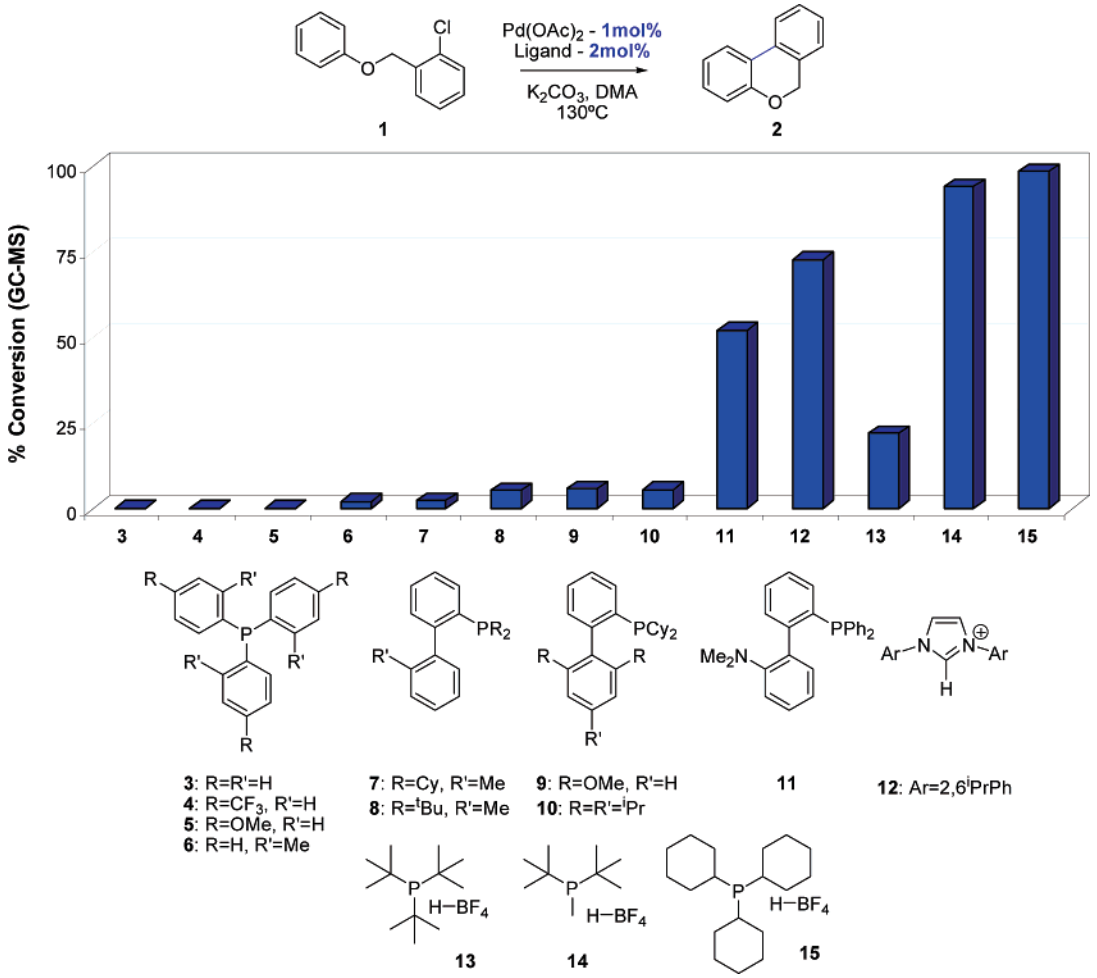
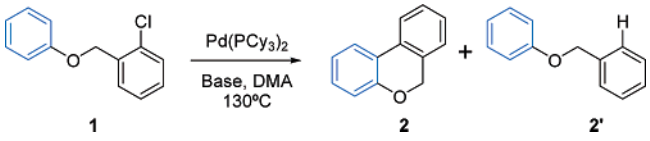
Scheme 2. Screen of Various Ligands for Direct Arylation of **1**[a]



[a] Conditions: substrate **1**, $Pd(OAc)_2$ (1 mol %), ligand (2 mol %), and K_2CO_3 (2 equiv) are dissolved in DMA (0.2 M) and heated to 130 °C until catalyst deactivation has occurred.

Table 1. Base Effects in Direct Arylation of Aryl Chlorides[a]



entry	base	conversion (%)	ratio **2**:**2'**[b]
1	Na_2CO_3	11	20:1
2	K_2CO_3	100	>99:1
3	Cs_2CO_3	25	15:1
4	KO^{t}Bu	84	2.3:1
5	K_3PO_4	13	5:1
6	KOAc	81	>99:1
7	NaOAc	41	28:1
8	Et_3N	3	2:1
9	DIPEA	2	1.8:1
10	Cy_2MeN	4	3:1

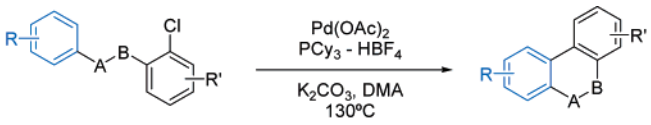
[a] Conditions: substrate, $Pd(PCy_3)_2$, and base (2 equiv) are dissolved in DMA (0.2 M) and heated to 130 °C until catalyst deactivation has occurred. [b] Determined by GC−MS.

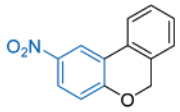
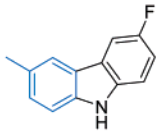
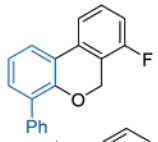
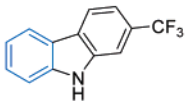
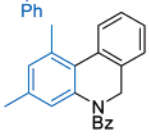
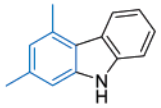
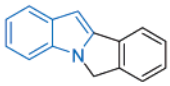
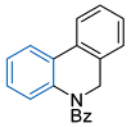
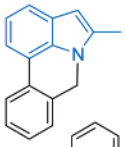
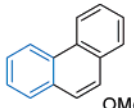
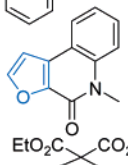
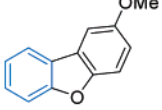
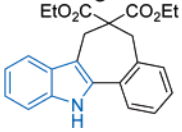
(added as the air-stable HBF_4 salts[12]) showed increased reactivity and robustness compared to those of the NHC system, affording complete conversion with only 1 mol % $Pd(OAc)_2$.

The influence of base was also examined (Table 1). The nature of the base and its counterion have a significant impact on catalyst reactivity and selectivity. For example, while K_2CO_3 gives optimal results (entry 2), both Na_2CO_3 and Cs_2CO_3 are ineffective, giving low conversion and leading to inferior ratios of coupling versus hydrodechlorination (entries 1 and 3). Alkoxide bases such as KO^{t}Bu also lead to increased amount of dehalogenation (entry 4). KOAc gives good selectivity but lower conversion (entry 6). The same base counterion effect is also observed with acetate bases since NaOAc gives lower conversion and selectivity than KOAc (entries 6 and 7). Organic bases such as Et_3N, Cy_2MeN, and diisopropylethylamine (DIPEA) lead to hydrodechlorination as the major product and very low conversion (entries 8−10).

To probe the origin of the base counterion effect, we compared the relative solubility of sodium, potassium, and cesium carbonate. Mimicking the reaction conditions, we heated the base in DMA at 100 °C for 30 min, then filtered the hot solution. Distillation of the DMA from the filtrate revealed that in all three cases, only trace amounts (1−2%) of the carbonate base is dissolved. In light of the dramatic halide effect observed with the use of aryl iodide substrates (vide infra), we also evaluated the relative solubility of sodium, potassium, and cesium chloride, which would be generated as a byproduct of the reaction as it progressed. Again all of the salts were effectively insoluble under the reaction conditions indicating that this cannot account for the observed base counterion effect.

Table 2. Scope of Intramolecular Direct Arylation of Aryl Chlorides[a]



Entry	Product	mol% Pd	Yield[b]	Entry	Product	mol% Pd	Yield[b]
1		1	97	8		3	88
2		1	92	9		3	87
3		5	89	10		5	78
4		3	94	11		3	91
5		3	97	12		3	82
6		3	87	13		3	83
7		5	81	14		10	80

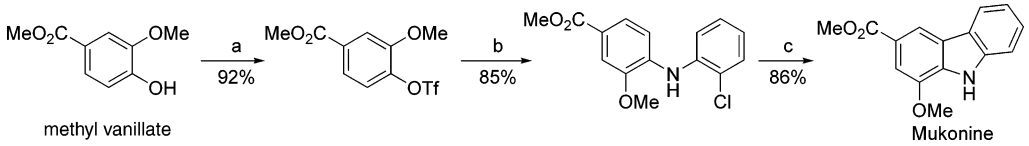
[a] Conditions: substrate, $Pd(OAc)_2$, ligand (2 equiv per Pd), and K_2CO_3 (2 equiv) are dissolved in DMA (0.2 M) and heated to 130 °C for 8−16 h. [b] Isolated yields. Ms = CH_3SO_2-, Bz = PhC(O)-.

While the reason for the base effect remains elusive when aryl chlorides are employed, the observation that potassium bases provide superior reaction outcomes should be of use in the development of other arylation processes.

Various palladium sources such as $PdBr_2$, $PdCl_2$, $Pd(acac)_2$, $Pd(TFA)_2$, and $Pd_2(dba)_3$ were also examined. These studies reconfirmed that $Pd(OAc)_2$ is the optimal palladium catalyst source. The optimal reaction concentration remained 0.2 M and heating to temperatures lower than 130 °C necessitated an increase in catalyst loading with certain substrates. These conditions, $Pd(OAc)_2$, $PCy_3 \cdot HBF_4$ (2 equiv per Pd), and 2 equiv of K_2CO_3 in DMA (0.2 M) at 130 °C were therefore selected for further study.

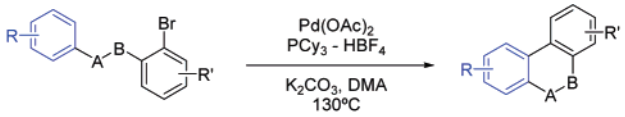
The scope of the reaction with aryl chlorides is outlined in Table 2. Typically reactions were left to react overnight but in some cases were done within 8 h. Various tethers including carbon (entries 6, 11, 12, and 14), oxygen (entries 1, 2, and 7), and nitrogen (entries 3−5, 8−10, and 13) can be effectively employed in these transformations. In the formation of six-membered rings with a nitrogen atom in the tether, an amide or a sulfonamide protecting group can be employed (entries 3−5). Five-membered ring carbazole products can be obtained without the installation of a nitrogen protecting group (entries 8−10). The synthesis of hindered biaryls is also facilitated by this catalyst as demonstrated by entries 3 and 10 which is an improvement over our previously reported conditions which fail to induce complete reactions.[10,11] *Z*-Alkenes undergo intramolecular direct arylation with complete selectivity over a possible competitive intermolecular Heck pathway (entry 6). Substitution is also tolerated on the aryl halide moiety with fluoro (entries 2 and 8) and trifluoromethyl (entry 9) aryl chlorides reacting readily. Additional catalyst is needed in the case of deactivated aryl chlorides as illustrated with methoxy-substituted substrate (entry 7). This catalyst system also allows the use of heterocycles in these processes (entries 11−14). *N*-alkyl indole reacts at the 2-position to afford the biaryl product in high yield (entry 11). When the 2-position is blocked with a methyl group arylation occurs on the adjacent phenyl ring of indole to afford the pyrrolophenanthridine-like class of natural products[13] (entry 12). Furans can also be arylated as illustrated by the synthesis of a furoquinolinone product (entry 13). Unprotected indoles also react (entry 14), in this case to form

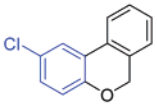
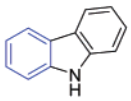
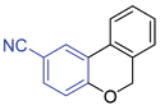
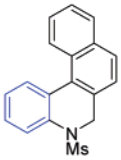
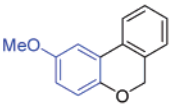
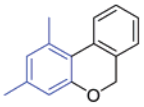
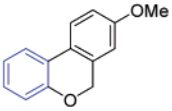
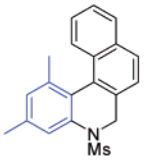
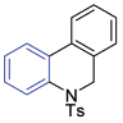
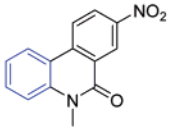
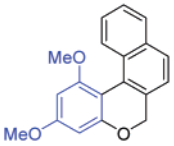
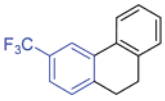
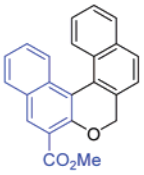
Scheme 3. Synthesis of Mukonine[a]



[a] Conditions: (a) Tf_2O (1.1 equiv), DIPEA (2 equiv), THF −78 °C to 0 °C; (b) $Pd_2(dba)_3$ (2.5 mol %), 2-(di-*tert*-butylphosphino)-2′-methylbiphenyl (10 mol %), K_3PO_4 (1.4 equiv), 2-chloroaniline (1.2 equiv), DME 80 °C; (c) $Pd(OAc)_2$ (3 mol %), $PCy_3{-}HBF_4$ (6 mol %), K_2CO_3 (2 equiv), DMA 130 °C.

Table 3. Scope of Intramolecular Direct Arylation of Aryl Bromides[a]



Entry	Product	mol% Pd	Yield[b]	Entry	Product	mol% Pd	Yield[b]
1		1	90	8		3	94
2		1	99	9		5	98
3		1	92	10		5	86
4		5	75	11		5	97
5		3	97				
6		3	84	12		5	90
7		5	87[c]	13		5	85

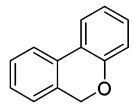
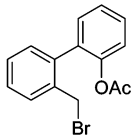
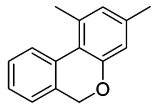
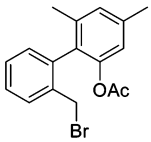
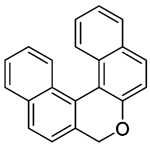
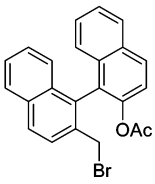
[a] Conditions: substrate, $Pd(OAc)_2$, ligand (2 equiv per Pd), and K_2CO_3 (2 equiv) are dissolved in DMA (0.2 M) and heated to 130 °C for 8−16 h. [b] Isolated yields. [c] Heated to 145 °C. Ts = 4-$MePhSO_2$-, Ms = CH_3SO_2-, Bz = PhC(O)-.

a seven-membered ring which has been scarcely explored in direct arylation reactions.[14]

Carbazole alkaloids have attracted significant interest due to their structural features and biological activity.[15] Scheme 3 shows a short and high-yielding route to Mukonine. Triflation of methyl vanillate proceeds smoothly to afford aryl triflate in 92% yield, and Buchwald−Hartwig amination with 2-chloroaniline affords diarylamine in 85% yield.[16] Direct arylation without protection of the nitrogen moiety proceeds smoothly using 3 mol % palladium to afford Mukonine in three steps with a 75% overall yield.

Aryl Bromides as Substrates. Direct arylation of aryl bromides can be achieved without modification to the protocol developed for aryl chlorides. The scope of reactions employing aryl bromides is outlined in Table 3. Selective arylation in the presence of a chloride functionality is possible, providing a useful handle for further cross-coupling reactions (entry 1). Electron-rich as well as electron-poor arenes are compatible (entries 2 and 3). Deactivated aryl bromides can be used although increased catalyst loading is required for the reaction to complete (entry 4). Tosyl protecting groups are compatible when a nitrogen atom is in the tether (entry 5). Activated aryl

Table 4. Scope of Ring-Opening Reactions[a]

Entry	Starting	Product	Yield[b]
1			83
2			84
3			85

[a] Conditions: (1) biaryl, BBr_3 1.0 M solution in heptane (1 equiv), DCM, room temperature; (2) crude benzyl bromide from step 1, Ac_2O (excess), 2,6-lutidine (2 equiv), PhH, 0 °C to room temperature. [b] Isolated yields.

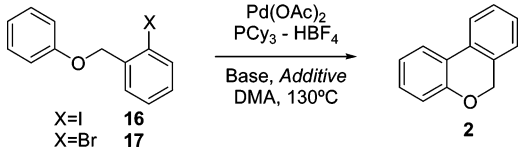
bromides react to yield the corresponding phenanthredinone product in good yield (entry 6).

Recent advances in catalyst development for biaryl synthesis have been directed at the formation of sterically hindered biaryls.[17] In the context of these challenging cross-coupling reactions, we were interested in determining whether this catalyst system could achieve direct arylation reactions of more sterically demanding substrates such as tetra-ortho-substituted substrates. We were pleased to find that under our optimized conditions, the synthesis of tri- (entries 9 and 10) and tetra-ortho-substituted (entries 11−13) biaryls was feasible. A mesylate protecting group can be used when a nitrogen atom is in the tether (entries 9 and 11). Ester groups also remain intact under reaction conditions (entry 13).

To grant access to acyclic biaryl molecules, we also explored ring-opening reactions in the context of hindered biaryl synthesis. Treatment of the direct arylation products with 1.1 equiv of BBr_3 in CH_2Cl_2 at room temperature followed by trapping with acetic anhydride yields the acyclic biaryl products in good yield (Table 4).[18] This sequence of direct arylation/ring cleavage is a complimentary entry point to these challenging biaryl substrates and may offer an attractive alternative to cross-coupling protocols in some cases.

Aryl Iodides as Substrates. The use of aryl iodides in direct arylation is well precedented.[3a,4e,4j,19,22] The disproportionate attention focused on the use of aryl iodides compared to aryl bromides and especially aryl chlorides may be rationalized, at least in part, by the desire to reduce catalytic demand. It is well precedented that oxidative insertion into a C−X bond is most facile for aryl iodides,[20] so use of aryl iodides can permit the chemist to focus their reaction/catalyst development efforts on the challenging arylation step of the catalytic cycle. Given the strong precedent for the use of aryl iodides in direct arylation

Table 5. Halide Effect in Direct Arylation Reactions[a]



entry	halide	base	additive	yield[b]
1	Br	K_2CO_3	none	99
2	I	K_2CO_3	none	64[c]
3	Br	K_2CO_3	KI[d]	<5
4	I	Cs_2CO_3	none	89[e]
5	I	K_2CO_3	AgOTf[d]	99
6	I	K_2CO_3	Ag_2CO_3[f]	99

[a] Conditions: substrate, $Pd(OAc)_2$ (1 mol %), ligand (2 equiv per Pd), and K_2CO_3 (2 equiv) are dissolved in DMA (0.2 M) and heated to 130 °C for 12 h. [b] GC−Ms yields. [c] **2**:**2′** = 8:1. [d] 1 equiv. [e] **2**:**2′**=8.5:1. [f] 0.5 equiv.

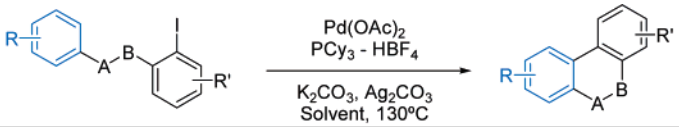
reactions, we were surprised to find that aryl iodides reacted very poorly under our optimized conditions. For example, reaction of aryl iodide **16** under the conditions optimized for aryl chlorides and bromides gave only 64% conversion, even after prolonged reaction times.[21] We have established that this poor reactivity is due to the accumulation of iodide anions in the reaction mixture and that this catalyst poisoning may be overcome. Although bromide **17** and iodide **16** react at similar rates at early conversions, the conversion of iodide **16** reaches a plateau at 64% conversion (Table 5, entries 1 and 2). Furthermore, if 1 equiv of KI is added to a reaction of bromide **17**, the arylation reaction is completely inhibited (Table 5, entry 3).

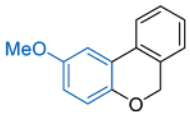
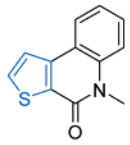
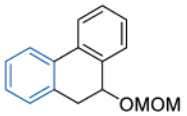
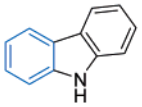
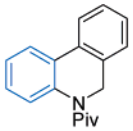
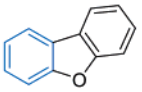
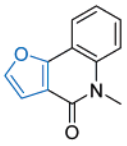
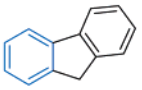
To sequester iodide, we explored the use of different bases and silver additives. In some cases, superior results can be achieved by using Cs_2CO_3 instead of K_2CO_3.[22] With the reaction of **16**, the use of Cs_2CO_3 was ineffective, resulting in an erosion of selectivity for cyclization to hydrodehalogenation from greater than 99:1 with K_2CO_3 to 8.5:1 with Cs_2CO_3. (Table 5, entry 4). Of the silver sources tested, AgOTf and Ag_2CO_3 gave the best results (Table 5, entries 5 and 6). We opted to use silver carbonate because of its increased ease of handling and lower cost.[23] We also found that addition of silver additives accelerated reaction times and that reactions could be carried out at temperatures as low as 80 °C with 5 mol % catalyst. These observations warn against the presumption of the increased reactivity of aryl iodides in catalyst/reaction development efforts in direct arylation processes and indicate that catalyst and substrate screens in the search for new reactions may best be performed with aryl bromides and/or chlorides, and not with aryl iodides as is commonly the case.

With these new reaction conditions, other reaction parameters were reinvestigated including solvent and temperature. Use of Ag_2CO_3 provides complete conversion of aryl iodide **16** with 5 mol % catalyst in refluxing dioxane. In contrast no reaction is observed in dioxane in the absence of Ag_2CO_3. It is also possible to achieve good conversion in refluxing THF if 2 equiv of HMPA are used as an additive. The scope of direct arylation with aryl iodides is outlined in Table 6. Pivaloyl (entries 4 and 5) and MOM ethers (entry 3) can be used as protecting groups for amine and alcohol functional groups. Thiophenes are suitable

(23) Ag_2CO_3 (272CAD$/100 g, Aldrich 2005) 377CAD$/mol Ag; AgOTf (196CAD$/25 g, Aldrich 2005) 2008CAD$/mol Ag.

Table 6. Scope of Intramolecular Direct Arylation of Aryl Iodides[a]



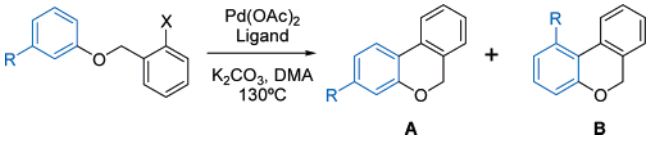
Entry	Product	Solvent	mol% Pd	Yield[b]	Entry	Product	Solvent	mol% Pd	Yield[b]
1		THF[c]	5	86	7		DMA	5	88
2		Dioxane	5	93					
3		DMA	5	85	8		DMA	3	83
4		DMA	3	94	9		DMA	3	99
5		Dioxane	5	86					
6		DMA	5	81	10		DMA	3	81

[a] Conditions: substrate, $Pd(OAc)_2$, ligand (2 equiv per Pd), Ag_2CO_3 (0.5 equiv), and K_2CO_3 (2 equiv) are dissolved in solvent (0.2 M) and heated (DMA, 130 °C; dioxane, 100 °C; THF, 70 °C) for 8−16 h. [b] Isolated yields. [c] 2 equiv HMPA added. MOM = $MeOCH_2$-, Piv = $^tBuC(O)$-.

reaction partners for the transformation (entry 7). Five-membered ring biaryls can also be formed to afford the carbazole (entry 8), benzopyrane (entry 9), and fluorene (entry 10) products.

Regioselectivity and Selectivity in Direct Arylation Reactions. While regioselectivity is an important factor when considering the application of a methodology in synthesis, regioselectivity issues in direct arylation have been scarcely studied.[24,25] Consequently, various ether substrates were synthesized to study the influence of sterics and electronics on arylation regioselectivity of nonsymmetrical arenes (Table 7). In general, we have determined that arylation occurs at the most sterically accessible site to give regioisomer **A** preferentially. In the case of large alkyl substituents (entries 3 and 4) only one product is detected by NMR. Diminished but still synthetically useful selectivity is obtained when using a smaller alkyl substituent such as a methyl group (entry 2) or a methoxy group[26] (entry 1). In the case of electron-withdrawing groups (entries 5−7), arylation is very selective, giving only one product by NMR. Halide substituents give poorer regioselectivities. For example, a chlorine substituent gives a 3.2:1 ratio in favor of isomer **A**. Interestingly, when the arene is substituted with a fluorine atom, isomer **B** is produced as the major product in a 1:4.3 ratio.[27] The reason for this reversal in selectivity is under investigation.

Table 7. Catalyst Selectivity in Direct Arylation[a]



A **B**

entry	substituent	halide	ligand	ratio **A**:**B**[b]
1	OMe	Br	PCy_3-HBF_4	10:1
2	Me	Br	PCy_3-HBF_4	15:1
3	*i*-Pr	Br	PCy_3-HBF_4	>30:1
4	*t*-Bu	Br	PCy_3-HBF_4	>30:1
5	CF_3	Br	PCy_3-HBF_4	>30:1
6	NO_2	Br	PCy_3-HBF_4	>30:1
7	CO_2Me	Br	PCy_3-HBF_4	>30:1
8	Cl	Br	PCy_3-HBF_4	3.2:1
9	F	Br	PCy_3-HBF_4	1:4:3
10	F	Cl	PCy_3-HBF_4	1:8.3
11	F	Br	$P^tBu_3-HBF_4$	1:1.3
12	F	Br	$P^tBu_2Me-HBF_4$	1:6.9

[a] Conditions: aryl halide, $Pd(OAc)_2$ (3 mol %), ligand (6 mol %), and K_2CO_3 (2 equiv) are dissolved in DMA (0.2 M) and heated to 130 °C for 8−16 h. [b] Ratio determined by ^1H NMR. All reactions reached 100% conversion as determined by crude ^1H NMR analysis.

It is worth noting that this reversal contrasts recent reports in palladium-catalyzed C−H activation/oxygenation reactions.[24]

The regioselectivity is also affected by the halide functionality on the substrate. For example, a ratio of **A**:**B** of 1:8.3 is obtained from the reaction of fluoro-substitued aryl chloride (entry 10) compared to a ratio of 1:4.3 when the corresponding aryl bromide is used (entry 9). This indicates that the halide may

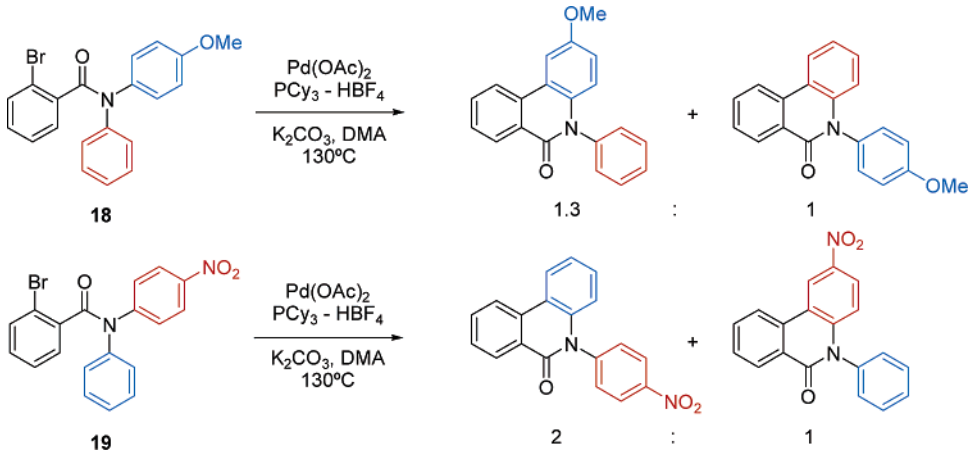
(24) For examples of such studies in other types of arene functionalization reactions, see: Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149 and references therein.

(25) For stoichiometric studies dealing with palladacycle formation, see: (a) Teijido, B.; Fernandez, A.; Lopez-Torres, M.; Castro-Juiz, S.; Suarez, A.; Ortigueira, J. M.; Vila, J. M.; Fernandez, J. J. *J. Organomet. Chem.* **2000**, *598*, 71. (b) Gutierrez, M. A.; Newkome, G. R.; Selbin, J. *J. Organomet. Chem.* **1980**, *202*, 341. (c) Holton, R. A.; Davis, R. G. *J. Am. Chem. Soc.* **1977**, *99*, 4175.

(26) We had previously reported a ratio of 20:1 for this substrate which might be an indication of the increased reactivity of this system; see ref 8.

(27) This type of effect with fluorine has also been observed in direct borylation of aromatic C−H bonds (a) and ruthenium-catalyzed C−H/olefin coupling (b): (a) Chotana, G. A.; Rak, M. A.; Smith, M. R., III. *J. Am. Chem. Soc.* **2005**, *127*, 10539. (b) Sonoda, M.; Kakiuchi, F.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 3117.

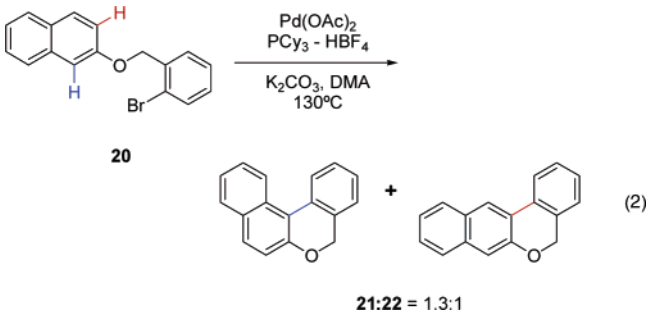
Scheme 4. Electronic Preference in Direct Arylation



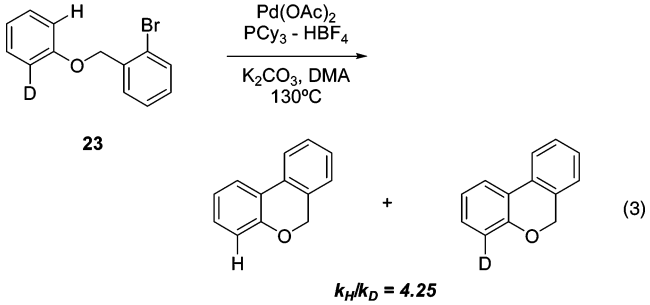
interact with the metal during the arylation step of the catalytic cycle. We also observe an effect of the phosphine ligand on product ratio as illustrated by entries 9, 11, and 12 where the ratio changes from 1:4.3 with PCy_3·HBF_4, to 1:6.9 with P^tBu_2Me·HBF_4, to 1:1.3 when P^tBu_3·HBF_4 is used.

Mechanistic Investigations. To probe for the presence of an electronic bias in the direct arylation reaction, competition experiments were devised to ascertain if the catalyst would selectively react with an electron-rich or electron-poor aromatic ring. Two amide substrates were synthesized. With amide **18**, reaction could occur with an "activated" ring bearing a methoxy substituent or at an unactivated ring. With amide **19**, the catalyst could select for reaction at an unactivated ring or a "deactivated" ring that is substituted with a nitro functionality. With both substrates, small selectivity is obtained for reaction at the more electron-rich ring (Scheme 4).

Reaction of naphthyl substrate **20** is also informative. In this case, two regioisomeric products are possible. It is well documented that electrophilic additions to naphthalenes occurs preferentially at the 1-position.[28] When **20** is reacted under the standard arylation conditions, a 1.3:1 ratio of **21**:**22** is obtained. While it is important not to over interpret the reaction preference when such low selectivities are obtained, the fact that such low selectivities are observed is informative since this is not a characteristic outcome of electrophilic aromatic substitutions on this substrate class (eq 2).



The presence of kinetic isotope effects can provide valuable information about the rate-determining steps in complex chemical processes. In our initial communication we reported a primary intramolecular kinetic isotope effect (KIE) of 3.5.[8] With the new conditions described in this account, a larger primary kinetic isotope effect of 4.25 is observed (eq 3). This value does not change in the presence of a silver additive.



Several mechanistic scenarios have been proposed for direct arylation reactions. The pathway with the strongest experimental support is electrophilic palladation.[29,30] Oxidative C−H insertion to palladium (IV) has also been proposed[4e] as has a carbopalladation (Heck-type) pathway requiring a formal anti β-hydride elimination.[31] Carbene intermediates have been demonstrated with other metals such as rhodium,[32] but analogous reactivity in palladium arylations has not appeared.

While it cannot be definitively ruled out, the carbopalladation or Heck-type route is unlikely. It is reasonable to assume that the mechanism of these processes should parallel that involved in the preparation of palladacycles.[33] In these cases, there exists ample evidence pointing to an electrophilic metalation or C−H oxidative insertion. The oxidative C−H insertion pathway fits with our experimental observations, but recently reported

(28) For a discussion on the preferred site of attack of many ring systems, see: de la Mare, P. B. D.; Ridd, J. H. *Aromatic Substitution Nitration and Halogenation*; Academic Press: New York, 1959; p 169.

(29) With simple arenes: (a) Martin-Matute, B.; Matea, C.; Cardenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2001**, *7*, 234. (b) Echavarren, A. M.; Gòmez-Lor, B.; Gonzàlez, J. J.; de Fruto, O.; *Synlett* **2003**, *5*, 585. (c) Gonzalez, J. J.; Garcia, N.; Gomez-Lor, B.; Echavarren, A. M. *J. Org. Chem.* **1997**, *62*, 1286. (d) Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003** *125*, 12084. (e) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586. (f) Shue, R. S. *J. Am. Chem. Soc.* **1971**, *93*, 7116. (g) Parshall, G. W. *Acc. Chem. Res.* **1970**, *3*, 139.

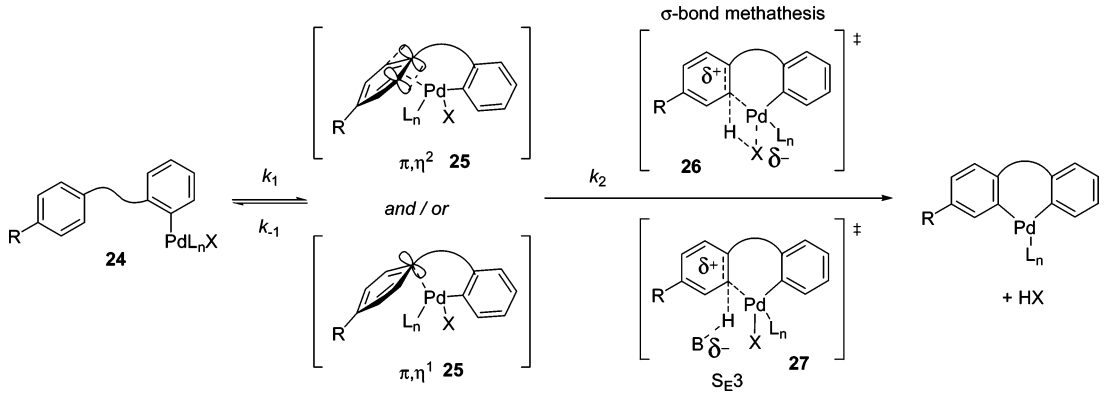
(30) With heteroaromatics: (a) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. (b) Ref 3d. (c) Trauner, D.; Hughes, C. C.; *Angew. Chem., Int. Ed.* **2002**, *41*, 1569. (d) Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. F. *Org. Lett.* **2003**, *5*, 301.

(31) This pathway has been proposed as a possibility before: (a) Toyata, M.; Ilangovan, A.; Okamoto, R.; Masaki, T.; Arakawa, M.; Ihara, M. *Org. Lett.* **2002**, *4*, 4293. (b) Ref 30. (c) Proposed but dismissed: ref 29d.

(32) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 3203.

(33) For a review, see: Ryabox, A. D. *Chem. Rev.* **1990**, *90*, 403.

Scheme 5. Plausible Pathways for Direct Arylation



computational studies indicate that C−H insertion is higher in energy and less favorable than an alternative σ-bond methathesis pathway that does not require the intermediacy of a palladium(IV) species.[34] Furthermore, there is growing evidence for the implication of an electrophilic-type pathway in the direct arylation of heterocyclic arenes.[30] Thus, while a C−H insertion pathway cannot be definitively ruled out, evidence points away from its involvement.

On the other hand, an electrophilic aromatic substitution pathway can rationalize the current experimental observations and has significant mechanistic support in the direct arylation of other classes of arene. Many electrophilic−aromatic substitution reactions do not exhibit KIEs because deprotonation is fast relative to the formation of the arenium σ-complex.[35] In some cases, however, electrophilic aromatic substitution reactions do exhibit significant KIEs, as exemplified by electrophilic mercurations for which KIEs of up to 6 have been documented.[36] The presence of a primary kinetic isotope effect in palladium-catalyzed direct arylation[37] can be rationalized by considering the relative rates for the formation of π,η^2-**25** and/or π,η^1-**25**[38] from the palladium(II) arene intermediate **24** (k_1 and k_{-1}) and deprotonation (k_2) (Scheme 5). The presence of a KIE implies that k_1 and k_{-1} are fast and reversible compared to k_2. As a consequence, [π-**25**]k_2 becomes kinetically significant and would result in the observed KIE. Either an S_E3 process, where an external base deprotonates the arene as the palladium−carbon bond is being formed,[35] or a σ-bond metathesis mechanism,[39] where it is a ligand on the palladium metal that serves as the base for the deprotonation, could be occurring.[29d,40]

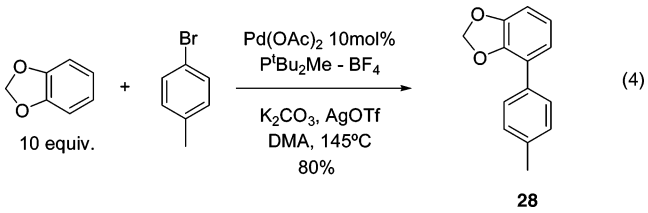
In this mechanism, it is reasonable to anticipate that the electronic properties of the arene ring will influence k_1, k_{-1}, and k_2. Our competition experiments (Scheme 4) as well as reactions with 2-naphthol derived substrates (eq 2) reveal a small but reproducible bias for the more electron-rich arene (or site), which is in accord with the qualitative kinetics reported by Echavarren and co-workers who found no strong electronic bias in direct arylation.[29a] The small electronic bias may point to a lack of cationic areneium character at the rate-determining step which may be anticipated in a concerted palladium−carbon/carbon−hydrogen bond formation/cleavage process.

New Intermolecular Direct Arylation Processes. In addition to advancing the use of intramolecular direct arylation reactions with aryl chlorides, bromides, and iodides, these studies were also conducted with the desire to learn more about the necessary catalyst, substrate, and reaction parameters necessary to achieve high levels of reactivity. Our hope was that knowledge garnered from these efforts would ultimately lead to the establishment of new intermolecular reactions with previously unknown substrate classes and open new doors in the direct arylation methodology. These goals are beginning to be achieved as illustrated by the first examples of intermolecular direct arylation of benzodioxole with aryl bromides and chlorides (vide infra). To achieve the substrate−catalyst interactions necessary to induce intermolecular direct arylation, researchers have previously employed very basic directing groups such as phenols,[41] amides,[42] and pyridyl[43] groups (in the absence of which no reaction occurs). The examples reported below constitute the first time that such reactivity has been achieved with an ether directing group on a simple arene. From a synthetic perspective, these reactions generate products that are regio-complementary to those readily accessible from commercially available aryl-halides and organometallics with traditional cross-coupling techniques.[44] Importantly, these results lay the foundation for the establishment of direct arylation reactions with significantly improved scope, which is a focus of continued study in our group.

To validate the intermolecular reactivity of benzodioxole, reactions were performed with 10 mol % $Pd(OAc)_2$, 10−30 mol

(34) Mota, A. J.; Dedieu, A.; Bour, C.; Suffert, J. *J. Am. Chem. Soc.* **2005**, *127*, 7171.
(35) Zollinger, H. *Adv. Phys. Org. Chem.* **1964**, *2*, 162.
(36) Kresge, A. J.; Brennan, J. F. *J. Org. Chem.* **1967**, *32*, 752.
(37) (a) Ref 29e. (b) Shue, R. S. *J. Am. Chem. Soc.* **1971**, *93*, 7116. (c) Ref 27d.
(38) (a) Càmpora, J.; Gutiérrez-Puebla, E.; Lòpez, J. A.; Monge, A.; Palma, P.; del Rýó, D.; Carmona, E. *Angew. Chem., Int. Ed.* **2001**, *40*, 3641. (b) Càmpora, J.; Lòpez, J. A.; Palma, P.; Valerga, P.; Spillner, E.; Carmona, E. *Angew. Chem., Int. Ed.* **1999**, *38*, 147.
(39) During the submission of this manuscript a paper appeared suggesting this type of process for cyclometalation with palladium acetate: Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754.
(40) This type of mechanistic dichotomy has been proposed before with Hg (ref 36) and Rh (ref 3a).
(41) For examples, see: (a) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M.; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740. (b) Satoh, T.; Inoh, J.-I.; Kawamura, Y.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239. (c) Kawamura, Y.; Satoh, T.; Miura, M.; Nomura, M. *Chem. Lett.* **1999**, 961. (d) Kawamura, Y.; Satoh, T.; Miura, M.; Nomura, M. *Chem. Lett.* **1998**, 931.
(42) For examples, see: (a) Kametani, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2000**, *41*, 2655. (b) Ref 4a.
(43) For examples, see: (a) Ref 4a. (b) Oi, S.; Fukita, S.; Hirata, N.; Watanuki, N.; Miyano, S.; Inoue, Y. *Org. Lett.* **2001**, *3*, 2579. (c) Ref 4b.
(44) For recent the use of 1,3-benzodioxl-5-yl boronic acid in Suzuki coupling, see: (a) Gurjar, M. K.; Cherian, J.; Ramana, C. V. *Org. Lett.* **2004**, *6*, 317. (b) Savarin, C.; Liebeskind, L. S. *Org. Lett.* **2004**, *3*, 2149. Cross-coupling reactions with 4-bromo-1,3-benzodioxle (c) or 4-(1,3-benzodioxolyl)-boronic acid (d) are exceedingly rare. See: (c) Thibonnet, J.; Abarbri, M.; Parrain, J.-L.; Duchêne, A. *Tetrahedron* **2003**, *59*, 4433. (d) Wu, T. Y. H.; Schultz, P. G. *Org. Lett.* **2002**, *4*, 4033.

% of either $P^tBu_2Me{\cdot}HBF_4$ or $PCy_3{\cdot}HBF_4$, 1 equiv of AgOTf, and 2 equiv of K_2CO_3 in DMA at 145 °C. While Ag_2CO_3 performed well in intramolecular reactions, its use led to more homocoupling of aryl bromide in these intermolecular processes compared to that with AgOTf. A total of 10 equiv of benzodioxole were employed, and initial screens were executed with 4-bromotoluene. Reaction concentration was also evaluated ranging from 0.1 to 0.8 M. From these initial screens, a 3:1 ligand to palladium ratio was deemed optimal with the $P^tBu_2Me{\cdot}HBF_4$ preligand performing slightly better than the tricyclohexylphosphine salt. Optimal results are also achieved under very concentrated conditions. Reactions are typically performed at 0.7 M. Under these conditions, we were gratified to find that an 80% isolated yield of **28** can be obtained as exclusively one regioisomer (eq 4).



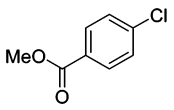
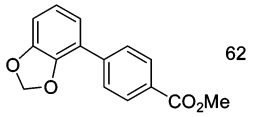
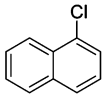
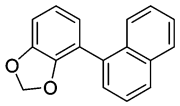
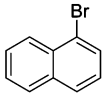
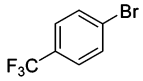
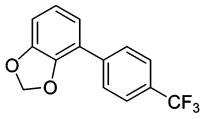
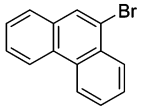
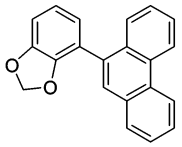
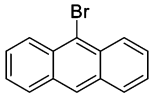
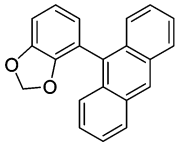
(4)

These reaction conditions were used to investigate the intermolecular direct arylation of benzodioxle (Table 8) with a range of aryl chlorides and bromides. Both activated and nonactivated aryl chlorides can be employed (entries 1 and 2). More sterically encumbered aryl bromides can also be employed with good yield as illustrated by reaction with bromoanthracene (entry 6). Interestingly, no cross-coupled direct arylation product is obtained when these reactions are run with iodobenzene. In this case, the major product as determined by GC−MS analysis of the crude reaction mixture is biphenyl arising from homocoupling of the iodobenzene. This result underlines our findings that aryliodides can frequently exhibit inferior reactivity in direct arylation reaction with simple arenes and that they should not be used exclusively as model substrates in the development of new direct arylation processes.

Conclusion

In conclusion, we have established a broadly applicable catalyst for direct intramolecular arylation reactions with aryl chlorides, bromides, and iodides including sterically encumbered aryl chlorides and bromides. We have also found that, despite their widespread use, aryl iodides exhibit inferior reactivity compared to that of aryl bromides and chlorides in the direct arylation reactions studied. The inferior reactivity of aryl iodides was noted in both intramolecular and intermolecular reactions and warns against the exclusive use of aryl iodides in the development of other new direct arylation reactions. We have determined that catalyst poisoning associated with aryl iodides in intermolecular reactions is due to an accumulation of KI in the reaction media which can be overcome through the addition of silver additives. Mechanistic studies revealed a kinetically significant C−H bond cleavage step during arylation that may be rationalized by a mechanism proceeding via electrophilic metalation involving either a σ-bond metathesis or an S_E3 C−H functionalization step. Finally, these studies enabled the development of a new intermolecular direct arylation reaction of benzodioxole with aryl chlorides and bromides, which is the first time such reactions are possible with these substrates.

Table 8. Direct Arylation of 1,3-Benzodioxle[a]

Entry	Aryl Halide	Product	Yield[b]
1			62
2			78
3			83
4			86
5			81
6			80

[a] Conditions: dioxane (10 equiv), aryl halide, $Pd(OAc)_2$ (10 mol %), ligand (30 mol %), AgOTf (1 equiv), and K_2CO_3 (2 equiv) are dissolved in DMA (0.7 M) and heated to 145 °C for 8−16 h. [b] Isolated yield.

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

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