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Palladium-Catalyzed Intra- and Intermolecular C−H Arylation Using Mesylates: Synthetic Scope and Mechanistic Studies

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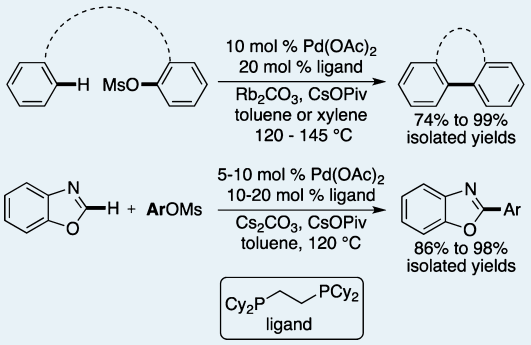
Supporting Information

ABSTRACT: This paper describes the development of Pd-catalyzed inter- and intramolecular direct arylation using mesylates. Furthermore, a sequential mesylation/arylation protocol using phenols as substrates is described. These transformations are general with respect to the electronics of the C−H substrates and allow for the synthesis of diverse heterocyclic motifs in good yields. Both arenes and heteroarenes efficiently participate in these reactions. Preliminary mechanistic studies are presented for both inter- and intramolecular arylations.



KEYWORDS: *homogeneous catalysis, palladium, arylation, C−H activation, mesylates*

INTRODUCTION

Transition-metal-catalyzed direct arylation is a well-established method for the construction of biaryl bonds.[1] The products of these reactions find widespread applications in a variety of industries including pharmaceutical, agrochemical, and material science.[1] As such, there is a continuous desire for the development of arylation methods with enhanced scope, generality, and cost effectiveness. Considerations of atom-economy, step-economy, and the environmental impacts of these methods are also important.

The vast majority of currently known direct arylations use aryl halides (or their derivatives) as electrophiles.[1] Recently, there has been an increasing interest toward employing phenolic electrophiles in place of aryl halides in these transformations to broaden the scope of C−H arylations.[2] Furthermore, the use of phenolic electrophiles avoids the production of undesirable halide-containing byproducts.[3]

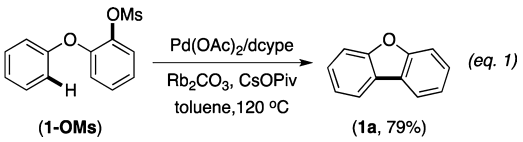
In this context, a number of sulfonate electrophiles including triflates[4] and tosylates[5] have been successfully employed for direct arylation.[6] In contrast, reports on the use of mesylates as electrophiles are primarily limited to specific substrate classes: perfluoroarenes,[7a,b] *N*-oxides, [5d] and azoles.[5b,7c] Mesylates are attractive electrophiles because they are more atom economical than tosylates. Additionally, they are less expensive and more stable than triflates.[2a] Despite these advantages, the relatively few examples of direct arylations using mesylates can be partially attributed to the poorer leaving ability of the mesylate group.[2a,8]

Careful examination of the reported methods (mentioned above) for C−H arylations using mesylates reveals several avenues that are either unexplored or underdeveloped. These include the following: (1) the direct arylation of unactivated arenes, a reaction for which no examples have been reported, (2) the coupling of azoles with electron-rich mesylate electrophiles, a transformation which thus far provides arylation products in only low yields,[7c] and (3) a mesylation/arylation sequence that provides arylated products without purification of the intermediate mesylates, a protocol which has not yet been described.

We report herein the development of a palladium-catalyzed method for the direct arylation of arenes and heteroarenes using mesylates. The experiments detailed below seek to address the limitations described above. The synthetic scope and a preliminary mechanistic study for both the inter- and intramolecular arylations are discussed.

RESULTS AND DISCUSSION

Preliminary Results. As part of our program on the use of C−O electrophiles for C−H arylation, we recently reported the first example of palladium-catalyzed intramolecular arylation of unactivated arenes with aryl mesylates.[9] As a representative example, the Pd-catalyzed reaction of **1-OMs** led to **1a** in 79% isolated yield (eq 1). Importantly, dcype (1,2-bis (dicyclo-



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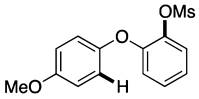
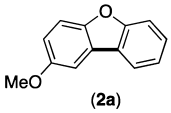
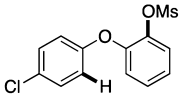
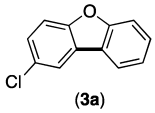
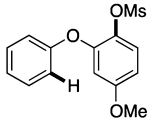
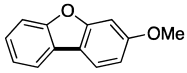
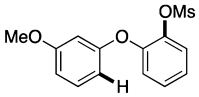
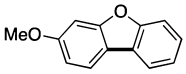
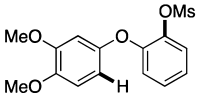
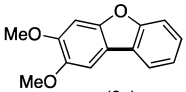
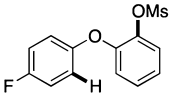
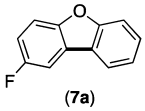
hexylphosphino)ethane) is the optimal ligand for this reaction. Other commonly employed ligands for Pd-catalyzed C−H arylation of heteroaromatic substrates with sulfonate electrophiles (e.g., XPhos,[5d] SPhos,[7a] CM-Phos[7b,c]) did not afford the desired product. Although the products were obtained in good yields using the $Pd(OAc)_2$/dcype catalyst system, only four examples of C−H/C−mesylate coupling were reported by us in 2012 (eq 1 and Table 1, entries 1−3, vide infra).[9] Notably, these examples were limited to the synthesis of dibenzofurans.

Table 1. Dibenzofurans via Intramolecular Arylation

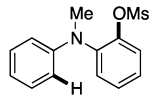
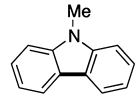
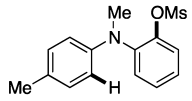
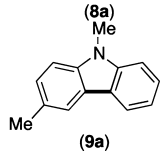
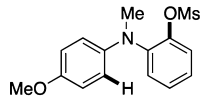
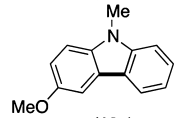
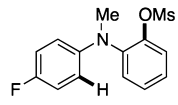
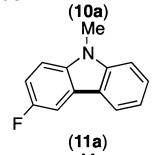
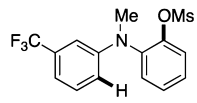
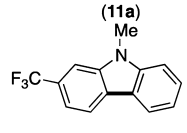
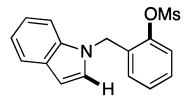
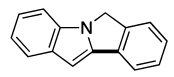
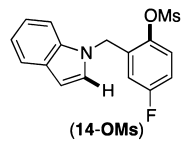
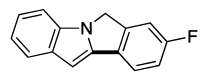
entry	substrate	product	yield[a,b]
1	 (2-OMs)	 (2a)	96%
2	 (3-OMs)	 (3a)	76%
3[c]	 (4-OMs)	 (4a)	92%
4[d]	 (5-OMs)	 (5a)	90%
5[d]	 (6-OMs)	 (6a)	89%
6[c]	 (7-OMs)	 (7a)	74%

[a]General conditions: substrate (1.0 equiv), $Pd(OAc)_2$ (0.1 equiv), dcype (0.2 equiv), Rb_2CO_3 (1.5 equiv), CsOPiv (1.0 equiv), toluene, 120 °C. [b]Isolated yields. [c]General conditions but with xylene as solvent at 140 °C. [d]General conditions but without CsOPiv.

Herein, we detail a more complete development of the arylation using mesylate electrophiles. Specifically, the current work (1) broadens the scope of the intramolecular arylation of unactivated arenes, (2) demonstrates the intermolecular coupling of azoles with electronically diverse mesylates to obtain the arylated products in excellent yields, (3) enhances the step-economy of the arylations through the achievement of the sequential mesylation/arylation using phenols, and (4) provides preliminary insight into the mechanism of the C−H activation step.

Scope of Intramolecular Arylations. As shown in Table 1, the optimal conditions for Pd-catalyzed intramolecular arylation of **1-OMs** could be applied toward the cyclization of a number of electronically differentiated aryloxy ether substrates. Nitrogen-containing heterocyclic motifs including carbazoles and indoles could also be accessed by this method in good to excellent yields (Table 2).[10] Importantly, these heterocycles are widely prevalent in bioactive molecules.[1]

Table 2. Scope of Heterocycle Synthesis via Arylation

entry	substrate	product	yield[a,b]
1	 (8-OMs)	 (8a)	94%
2	 (9-OMs)	 (9a)	95%
3	 (10-OMs)	 (10a)	92%
4	 (11-OMs)	 (11a)	99%
5	 (12-OMs)	 (12a)	95%
6[c]	 (13-OMs)	 (13a)	73%
7[d]	 (14-OMs)	 (14a)	77%

[a]General conditions: substrate (1.0 equiv), $Pd(OAc)_2$ (0.1 equiv), dcype (0.2 equiv), Rb_2CO_3 (1.5 equiv), CsOPiv (1.0 equiv), toluene, 120 °C. [b]Isolated yields. [c]General conditions but with xylene as solvent at 145 °C. [d]General conditions but with CsOPiv (0.5 equiv) and xylene as solvent at 145 °C.

As illustrated in Tables 1 and 2, the reactions are tolerant toward a number of functional groups including ethers, benzylic C−H bonds, and aryl halides. Notably, product **3a** contains an aryl chloride and could be further elaborated using cross-coupling reactions of aryl chlorides (Table 1, entry 2). Substrates containing electron-rich and electron-deficient groups on the C−H bearing aromatic ring participate efficiently. The site-selectivity for the reaction of substrates bearing two chemically distinct *ortho* C−H bonds is consistent with similar Pd-catalyzed transformations reported previously.[9,11] In these systems, the product is obtained via the selective functionalization of the less sterically hindered C−H bond (Table 1, entries 4−5; Table 2, entry 5).

Intermolecular Arylations. We next turned toward applying our optimized reaction conditions toward intermolecular couplings. We were particularly interested in exploring the efficiency for the coupling of azoles with electron-rich mesylates because this reaction class (e.g., using benzoxazole

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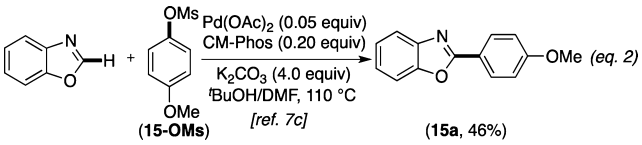
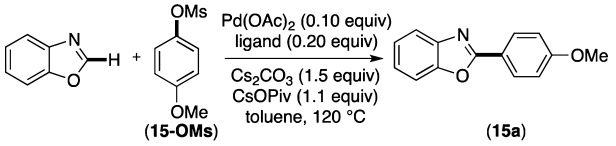
and **15-OMs**, eq 2) has been reported previously to provide only low yields of the arylated products.[7c]



On the basis of the observation that the electron-rich mesylate **4-OMs** underwent intramolecular arylation in high yield under our conditions (Table 1, entry 3), we hypothesized that our reaction protocol might prove more effective for generation of **15a** from **15-OMs**. Gratifyingly, subjection of benzoxazole and **15-OMs** to our optimized $Pd(OAc)_2$/dcype reaction conditions provided the biaryl product in quantitative yield (Table 3, entry 1). Unlike the intramolecular reactions of

Table 3. Ligand Optimization for Intermolecular Arylation



entry	ligand	yield[a]
1	**dcype**	**100%**
2	CM-phos	52%
3	Ru-Phos	14%
4	S-Phos	06%
5	X-Phos	50%

[a]Calibrated GC yields against hexadecane as the internal standard.

unactivated arenes discussed above, the coupling of the activated heteroarene, benzoxazole, with **15-OMs** could be accomplished with varying efficiency using a number of phosphine ligands. Importantly, XPhos, SPhos, and CMPhos are ligands that have been previously employed for the coupling of mesylates with heteroaromatic C–H bonds.[7] Nevertheless, the $Pd(OAc)_2$/dcype catalyst system still outperformed these other ligands for the formation of product **15a**.

Similarly, high yields of the arylated products were obtained by the reaction of other azoles with **15-OMs** (Table 4, entries 5–7). The use of other electron-rich mesylates such as **16-OMs**, **17-OMs**, and **18-OMs** also led to the desired products in excellent yields (entries 2–4).

Sequential Mesylation/Arylation. Having explored both inter- and intramolecular arylations with mesylates, we next desired to develop a protocol for generating the biaryl products from phenols without the necessity for isolation and purification of the intermediate mesylates. These studies began with the investigation of the reaction sequence depicted in eq 3 below. This two-step method involved the mesylation of

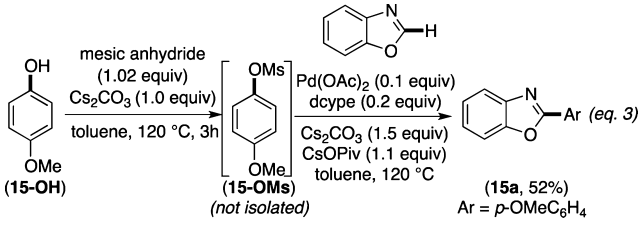
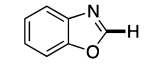
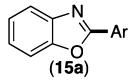
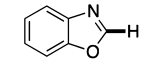
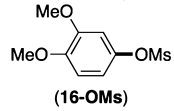
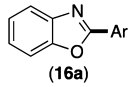
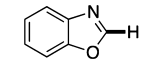
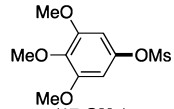
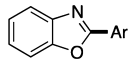
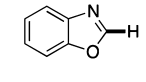
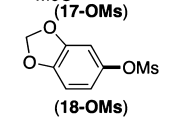
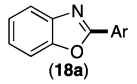
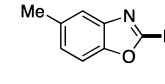
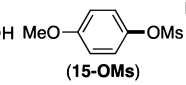
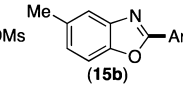
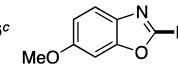
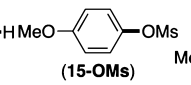
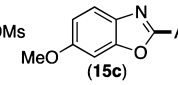
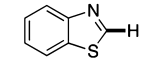
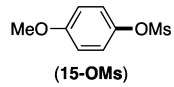
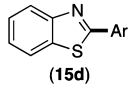


Table 4. Scope of Electron-Rich Mesylates for Arylation

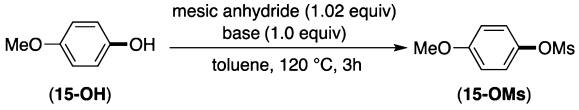
entry	substrate	Ar-OMs	product	yield[a,b]
1		 (15-OMs)	 (15a)	97%
2		 (16-OMs)	 (16a)	94%
3		 (17-OMs)	 (17a)	96%
4		 (18-OMs)	 (18a)	97%
5		 (15-OMs)	 (15b)	98%
6[c]		 (15-OMs)	 (15c)	86%
7		 (15-OMs)	 (15d)	86%

[a]General conditions: azole (1.0 equiv), Ar-OMs (1.5 equiv), $Pd(OAc)_2$ (0.05 equiv), dcype (0.1 equiv), Cs_2CO_3 (1.5 equiv), CsOPiv (1.1 equiv), toluene, 120 °C. [b]Isolated yields. [c]General conditions but with $Pd(OAc)_2$ (0.1 equiv), dcype (0.2 equiv).

15-OH with mesic anhydride, followed by the subjection of the crude mesylate solution to the Pd-catalyzed arylation conditions to afford the desired product **15a**, albeit in modest yield (52%). Importantly, Cs_2CO_3 has been employed as the base in sequential tosylation/arylation reactions previously.[9]

We hypothesized that the low yield of this reaction could be in part due to incomplete conversion of phenol **15-OH** to mesylate **15-OMs** in the first step. Indeed, analysis of the crude reaction mixture after the first step showed the presence of both **15-OMs** and **15-OH** in 42% and 51% GC yields, respectively (Scheme 1). The use of alternative carbonate and phosphate

Scheme 1. Base Optimization for Mesylation Step



Base:	K_2CO_3	Rb_2CO_3	Cs_2CO_3	K_3PO_4	2,4,6-collidine
GC Yield of 15-OMs:	20%	36%	42%	31%	97%
GC Yield of 15-OH:	81%	60%	51%	60%	4%

bases also led to low yields of the desired mesylate **15-OMs**. This result was not too surprising because inorganic bases are not standardly used for mesylation of alcohols with mesic anhydride.[12] However, more commonly used pyridine bases are good ligands for palladium and could interfere with catalysis in the next step.[13] As such, we hypothesized that a sterically hindered pyridine-like 2,4,6-collidine could serve as an effective base for the first step without significantly affecting the

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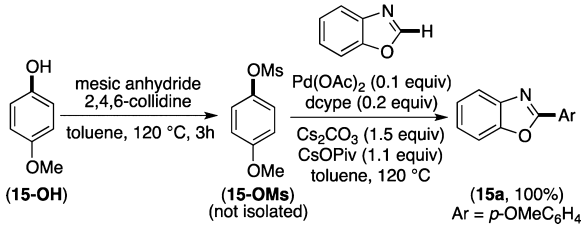
subsequent coupling step. As shown in Scheme 1 below, the use of 2,4,6-collidine led to the desired mesylate **15-OMs** in near quantitative yield as determined by GC analysis of the crude reaction mixture.

The newly developed two-step sequential mesylation/arylation afforded **15a** in quantitative GC yields (Scheme 2).

Scheme 2. Optimized Sequential Mesylation/Arylation



To the best of our knowledge, this is the first report of such a sequential mesylation/arylation sequence without isolation of the mesylate intermediate. Notably, the use of mesic anhydride as the mesylating reagent avoids the production of any halide waste. This is an advance over previously reported sulfonation/arylation methods that generally employ sulfonyl chlorides for the synthesis of the electrophiles in the first step.[4,5,7]

The generality of the optimal conditions for the sequential mesylation/arylation sequence depicted in Scheme 2 above was next explored (Table 5). A number of electron-rich (entries 1−4), electron-neutral (entry 5), electron-deficient (entry 6), and *ortho*-substituted phenols (entry 7) efficiently coupled with benzoxazole to afford the products in excellent yields. Substituted benzoxazoles, thiazole, and oxadiazole substrates coupled with **15-OH** to afford the arylated products effectively (entries 9−12).

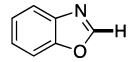
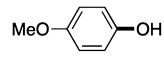
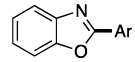
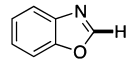
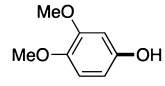
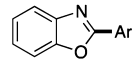
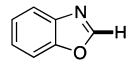
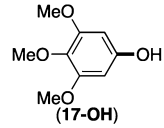
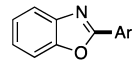
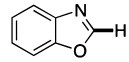
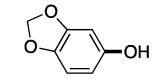
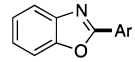
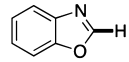
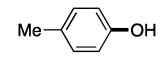
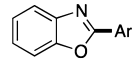
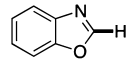
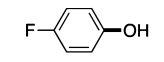
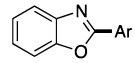
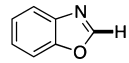
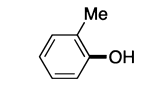
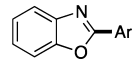
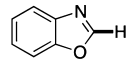
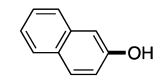
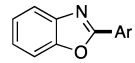
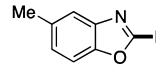
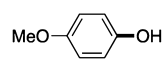
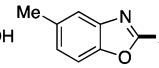
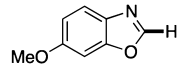
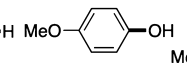
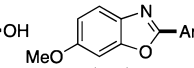
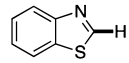
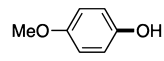
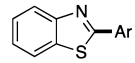
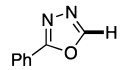
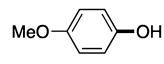
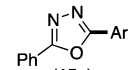
The sequential mesylation/arylation protocol was also applied to the synthesis of dibenzofurans from 2-phenoxyphenols. As shown in Table 6 below, the mesylation/intramolecular arylation reactions provided the desired biaryl products in good yields comparable to those shown in Table 1 above.

Preliminary Mechanistic Considerations. Having explored the synthetic scope of inter- and intramolecular arylations using mesylates, we conducted preliminary studies to gain insight into the mechanism of these reactions. On the basis of literature reports[1,11a] on Pd-catalyzed direct arylations, a plausible mechanism for the transformations described here is shown in Scheme 3. It involves (i) oxidative addition of the C−OMs bond into Pd(0), (ii) C−H activation, and (iii) reductive elimination to afford the product and regenerate the Pd(0) catalyst. The C−H activation step has been proposed to be turnover-limiting in similar Pd-catalyzed direct arylations with aryl halides. Furthermore, C−H activation is often thought to be a two-step process involving a π-complexation event followed by C−H bond-breaking.[11a,14]

We conducted kinetic isotope effect (KIE) studies to gain insight into the nature of the C−H activation step. As shown below in Scheme 4a, an intermolecular primary k_H/k_D of 2.3 was obtained from the competition reaction of an equimolar amount of **26-OMs** and **26-OMs-d_5**. Furthermore, the reaction of the monodeuterated substrate **1-OMs-*d*** exhibited an intramolecular k_H/k_D of 3.9 (Scheme 4b).[14] Although initial rate kinetic studies are needed to determine whether C−H cleavage is rate-determining, the observed intermolecular 1° isotope effect suggests against π-complexation as the product-determining step.[15−17] Furthermore, the KIE data are similar to previously reported direct arylations involving a concerted-metalation-deprotonation (CMD) type mechanism for C−H cleavage. The CMD pathway for C−H cleavage is proposed to involve simultaneous C−Pd bond making and base-assisted C−H bond breaking events in the transition state.[11a,14,18]

We next turned toward gaining insight into the electronic demands of the C−H activation step. As such, we explored the arylation of the amine substrate **27-OMs** bearing two electronically differentiated aryl rings that could undergo C−

Table 5. Scope of Alcohols for Sequential Mesylation/Arylation

entry	substrate	Ar-OH	product	yield[a,b]
1		 (15-OH)	 (15a)	96%
2		 (16-OH)	 (16a)	95%
3		 (17-OH)	 (17a)	88%
4		 (18-OH)	 (18a)	93%
5		 (19-OH)	 (19a)	92%
6		 (20-OH)	 (20a)	95%
7		 (21-OH)	 (21a)	94%
8		 (22-OH)	 (22a)	87%
9		 (15-OH)	 (15b)	97%
10		 (15-OH)	 (15c)	90%
11		 (15-OH)	 (15d)	84%
12		 (15-OH)	 (15e)	91%

[a]General conditions: 1. Ar−OH (1.5 equiv), mesic anhydride (1.52 equiv), 2,4,6-collidine (1.5 equiv), toluene, 120 °C, 3 h; 2. azole (1.0 equiv), $Pd(OAc)_2$ (0.1 equiv), dcype (0.2 equiv), Cs_2CO_3 (1.5 equiv), CsOPiv (1.1 equiv), toluene, 120 °C. [b]Isolated yields.

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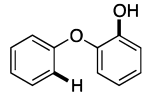
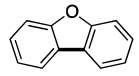
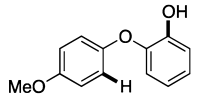
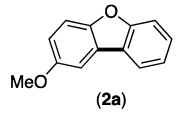
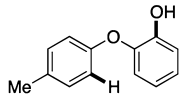
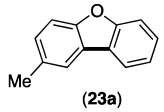
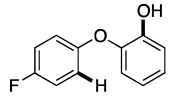
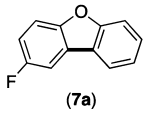
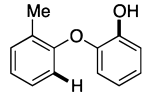
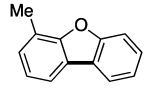
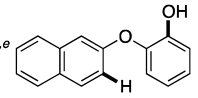
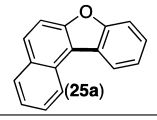
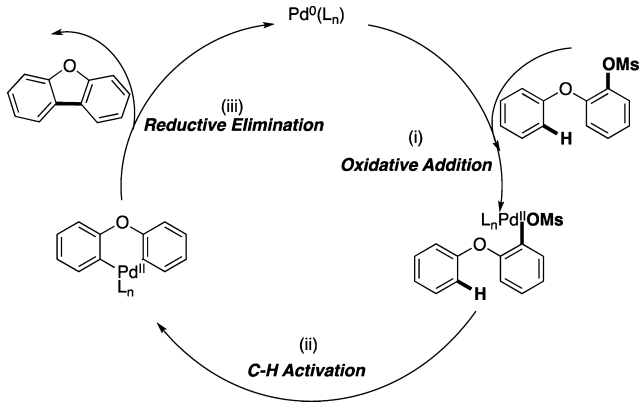
Table 6. Intramolecular Sequential Mesylation/Arylation

entry	substrate	product	yield[a,b]
1	 (1-OH)	 (1a)	74%
2	 (2-OH)	 (2a)	70%
3[c]	 (23-OH)	 (23a)	71%
4	 (7-OH)	 (7a)	82%
5	 (24-OH)	 (24a)	84%
6[d,e]	 (25-OH)	 (25a)	81%

[a]General conditions: 1. substrate (1.0 equiv), mesic anhydride (1.02 equiv), 2,4,6-collidine (1.0 equiv), xylene, 120 °C, 3 h; 2. $Pd(OAc)_2$ (0.1 equiv), dcype (0.2 equiv), Rb_2CO_3 (1.5 equiv), xylene, 120 °C. [b]Isolated yields. [c]General conditions with toluene instead of xylene. [d]General conditions at 140 °C. [e]Total yield of mixture of regioisomers (1.5:1 ratio favoring 25a).

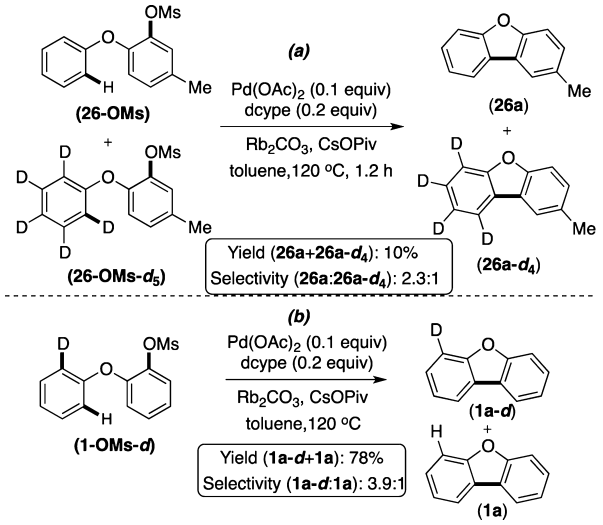
Scheme 3. Plausible Mechanism



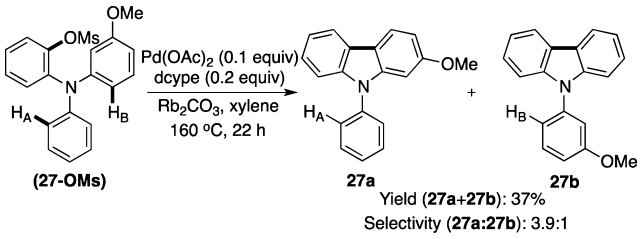
H functionalization.[19] As illustrated in Scheme 5, the reaction of **27-OMs** proceeded to afford a mixture of carbazoles **27a** and **27b** in a 3.9:1 ratio. The modest selectivity for the arylation of the electron-rich aryl rings is similar to that observed with Pd-catalyzed arylation using aryl halides[11a] and tosylates[9] involving a CMD electrophilic palladation step.[14]

Next, we sought to undertake a brief mechanistic exploration of the intermolecular reactions. Specifically, we explored the electronic demands of both the C−H substrate and the mesylate electrophile. As shown in Scheme 6, the reaction of an

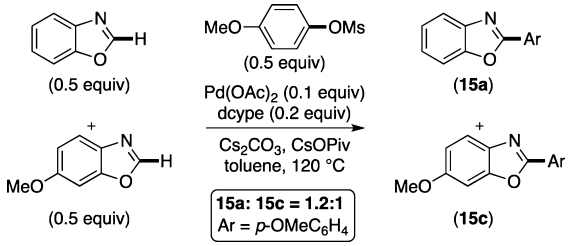
Scheme 4. Kinetic Isotope Effect Studies



Scheme 5. Electronic Effects in the Intramolecular Arylation



Scheme 6. Azole Competition Study



equimolar amount of benzoxazole and 6-methoxy benzoxazole with **15-OMs** led to a 1.2:1 mixture of **15a**/**15c**. Such selectivity (albeit very modest in this case) for preferential arylation of electron-deficient arenes has been observed for the direct arylation of acidic arenes. However, the selectivity for the reaction is significantly attenuated compared to selectivities reported previously for related *N*-oxide arylations.[20]

Next, we explored relative rates of arylations with electronically varied mesylates. A series of competition studies were conducted involving the treatment of benzoxazole with an equimolar amount of two electronically differentiated mesylates in the same reaction vessel. As shown in Scheme 7 below, in each case the major product was derived from the reaction of benzoxazole with the electron-deficient mesylate. These results are likely reflecting the electronic requirements of the oxidative addition step because this step is expected to be faster with electron-deficient aryl electrophiles.[20−22] Although the competition studies detailed herein provide some preliminary insight into the electronic demands of these arylations, detailed kinetic analysis is essential to elucidate the rate-determining step in these intermolecular reactions.[20−22]

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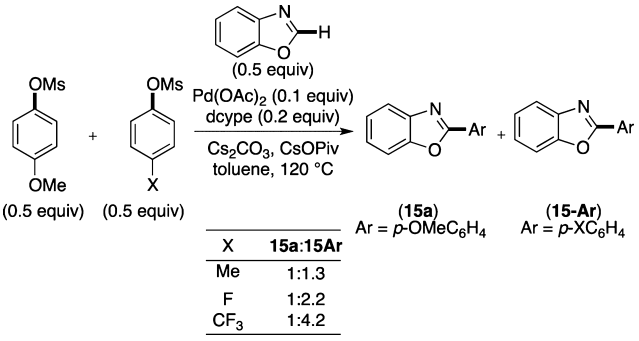
Scheme 7. Mesylate Competition Study



X	15a:15Ar
Me	1:1.3
F	1:2.2
CF_3	1:4.2

In summary, this paper describes the development of Pd-catalyzed intra- and intermolecular arylations using mesylates. The intramolecular reactions are applied toward the synthesis of heterocycles including dibenzofurans, carbazoles, and indoles. The intermolecular arylations are efficient for the coupling of azoles with electronically diverse mesylates. Preliminary mechanistic studies are presented for both the intra- and intermolecular arylations. However, more detailed kinetic studies are needed to elucidate the mechanistic intricacies of these transformations.

■ ASSOCIATED CONTENT

Supporting Information

This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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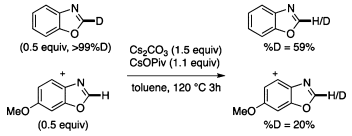
(21) The kinetic isotope effect studies for azole arylations have thus far been inconclusive because of the following base-mediated H/D scrambling. Furthermore, the H/D scrambling also suggests that a mechanism involving (i) base-mediated reversible deprotonation of the C−H bond, (ii) transmetalation of the azole anion onto the oxidative addition adduct, and (iii) reductive elimination to release the product and regenerate the catalyst, cannot be excluded at this time.



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