ORGANIC LETTERS

2012
Vol. 14, No. 18
4838–4841

Palladium-Catalyzed Intramolecular C−H Arylation of Arenes Using Tosylates and Mesylates as Electrophiles

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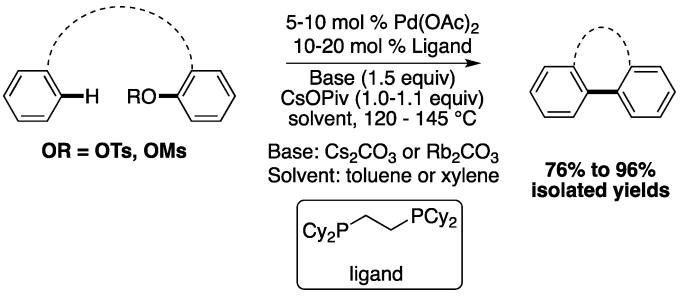
Received August 3, 2012

ABSTRACT



This paper describes a method for the palladium catalyzed intramolecular C−H arylation using tosylates and mesylates as electrophiles. The transformation is efficient for the synthesis of various heterocyclic motifs including furans, carbazoles, indoles, and lactams. Additionally, a protocol for the one-pot sequential tosylation/arylation of phenol derivatives is presented.

Transition metal catalyzed C−H arylation reactions are now well established for the construction of C−C bonds.[1] A vast majority of these reactions utilize aryl halides and their derivatives as electrophiles. Recently, however, there has been an increasing demand for the use of phenolic electrophiles in place of aryl halides.[2] This is because such electrophiles are readily available from inexpensive phenol derivatives. However, the development of C−H arylation protocols using C−O electrophiles has been relatively slow. Initial reports toward achieving this goal employed aryl triflates as electrophiles.[3] While this represents a significant advancement, these reactions are not ideal for use in long synthetic sequences due to the sensitive and expensive nature of triflates.[4] The use of tosylates and mesylates for C−H arylation would constitute a more robust methodology because these sulfonates are easy to handle and are generally stable to hydrolysis. Additionally, these electrophiles can be accessed using inexpensive sulfonating reagents. However, the increased stability of tosylates and mesylates render them less reactive electrophiles. Nonetheless, over the past six years a few sporadic reports have described their use as substrates for transition metal catalyzed C−H arylations. These methods have accomplished the direct arylations of heteroarenes[5,6] (azoles and azine *N*-oxides) as well as fluorinated aromatics.[7] To date, however, there is no general report on the C−H arylation of

[§] These authors contributed equally to this work.

(1) For representative reviews on C−H arylation, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (c) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447. (d) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (e) Ackermann, L.; Vincente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (f) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269. (g) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (h) Daugulis, O. *Top. Curr. Chem.* **2010**, *292*, 57. (i) Chiusoli, G. P.; Catellani, M.; Costa, M.; Motti, E.; Della Ca', N.; Maestri, G. *Coord. Chem. Rev.* **2010**, *254*, 456.

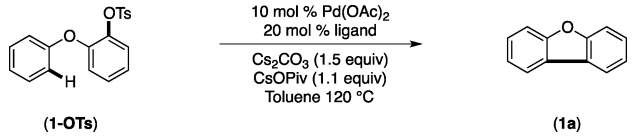
(2) (a) Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Acc. Chem. Res.* **2010**, *43*, 1486. (b) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346. (c) Li, B.-J.; Yu, D.-G.; Sun, C.-L.; Shi, Z.-J. *Chem.—Eur. J.* **2011**, *17*, 1728.

(3) For some representative recent reports, see: (a) Brenner, M.; Mayer, G.; Terpin, A.; Steglich, W. *Chem.—Eur. J.* **1997**, *3*, 70. (b) Kametani, K.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2000**, *41*, 2655. (c) Hara, O.; Nakamura, T.; Sato, F.; Makino, K.; Hamada, Y. *Heterocycles* **2006**, *68*, 1. (d) Cruz, A. C. F.; Miller, N. D.; Willis, M. C. *Org. Lett.* **2007**, *9*, 4391. (e) Roger, J.; Doucet, H. *Org. Biomol. Chem.* **2008**, *6*, 169. (f) Schipper, D. J.; El-Salfiti, M.; Whipp, C. J.; Fagnou, K. *Tetrahedron* **2009**, *65*, 4977.

(4) Goossen, L. J.; Rodriguez, N.; Lange, P. P.; Linder, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 1111.

10.1021/ol302166n
Published on Web 09/13/2012

Table 1. Optimization of the Intramolecular C−H Arylation Reaction of **1-OTs**



(**1-OTs**) (**1a**)

entry	ligand	Cs_2CO_3 (equiv)	CsOPiv (equiv)	GC yield[a,b]
1	none	1.5	1.1	3%
2	X-Phos	1.5	1.1	12%
3	S-Phos	1.5	1.1	4%
4	Ru-Phos	1.5	1.1	4%
5	dcype	1.5	1.1	92%
6	dcype	none	1.1	0%
7	dcype	1.5	none	96%
8[c]	dcype	1.5	1.1	0%
9[d]	dcype	1.5	1.1	86%

[a] General conditions: **1-OTs** (1 equiv), $Pd(OAc)_2$ (0.10 equiv), dcype (0.20 equiv), Cs_2CO_3 (1.5 equiv), CsOPiv (1.1 equiv), toluene (0.25 M in **1-OTs**), 120 °C. [b] Calibrated GC yields against hexadecane as the internal standard. [c] General conditions with no $Pd(OAc)_2$. [d] General conditions, but with $Pd(OAc)_2$ (0.05 equiv), dcype (0.10 equiv).

simple arenes using tosylates and mesylates as electrophiles.[5a] We report herein a general method for the palladium-catalyzed intramolecular arylation of diverse arenes with aryl tosylates as electrophiles. Furthermore, a preliminary scope for the use of more atom-economical mesylates for C−H arylations is also presented.

Our investigations commenced with the optimization of conditions for the intramolecular arylation of substrate **1-OTs** (Table 1). These studies began with the use of some reaction parameters (e.g., carbonate base and pivalate salt) known to be essential for Pd-catalyzed C−H arylations using aryl halides.[8] The initial choice of ligands included those that have been used in the context of Pd-catalyzed C−H arylations using C−O electrophiles (e.g., X-Phos, Ru-Phos, S-Phos, Table 1, entries 2−4).[5−7] The desired product **1a** was obtained in all three cases albeit in low yields. Further ligand screening revealed that the use of 1,2-bis(dicyclohexylphosphino)ethane (dcype) led to product **1a** in excellent yield (92%) (entry 5).[9] Notably, the use of ligand, Cs_2CO_3, and $Pd(OAc)_2$ is each essential for catalysis (entries 1, 6, and 8). With substrate **1-OTs**, a slightly higher yield of product was obtained in the absence of CsOPiv (entry 7). However, the conditions were more broadly applicable and reproducible in the presence of CsOPiv. Finally, the catalyst loading could be lowered (5 mol % $Pd(OAc)_2$, 10 mol % dcype, 1.5 equiv of Cs_2CO_3, 1.1 equiv of CsOPiv, toluene, 120 °C) to afford

Table 2. Substrate Scope for the Pd-Catalyzed C−H Arylation for Synthesis of Furans

entry	substrate	product	isolated yield[a]
1	(**1-OTs**)	(**1a**)	88%
2	(**2-OTs**)	(**2a**)	95%
3	(**3-OTs**)	(**3a**)	90%
4	(**4-OTs**)	(**4a**)	83%
5[b]	(**5-OTs**)	(**5a**)	80%
6	(**6-OTs**)	(**6a**)	87%
7	(**7-OTs**)	(**7a**)	89%
8	(**8-OTs**)	(**8a**)	90%
9[c-e]	(**9-OTs**)	(**9a**)	84%
10[e]	(**10-OTs**)	(**6a**)	84%
11[e]	(**11-OTs**)	(**7a**)	81%

[a] General conditions: substrate (1 equiv), $Pd(OAc)_2$ (0.05 equiv), dcype (0.10 equiv), Cs_2CO_3 (1.5 equiv), CsOPiv (1.1 equiv), toluene (0.25 M in substrate), 120 °C. [b] General conditions but with 7.5 mol % $Pd(OAc)_2$ and 15 mol % dcype. [c] Isolated as a 1.5:1 mixture of isomers favoring **9a** as determined by gas chromatographis analysis of the crude reaction mixture. [d] General conditions but with xylene at 140 °C. [e] General conditions but with 10 mol % $Pd(OAc)_2$ and 20 mol % dcype.

(5) (a) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 2619. (b) Ackermann, L.; Mulzer, M. *Org. Lett.* **2008**, *10*, 5043. (c) Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 201. (d) Ackermann, L.; Barfuesser, S.; Pospech, J. *Org. Lett.* **2010**, *12*, 724. (e) Ackermann, L.; Pospech, J.; Potukuchi, H. K. *Org. Lett.* **2012**, *14*, 2146. (f) Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 169.

(6) (a) Ackermann, L.; Fenner, S. *Chem. Commun.* **2011**, *47*, 430.

(7) (a) Fan, S.; Yang, J.; Zhang, X. *Org. Lett.* **2011**, *13*, 4374. (b) Chang, J. W. W.; Chia, E. Y.; Chai, C. L. L.; Seayad *J. Org. Biomol. Chem.* **2012**, *10*, 2289.

(8) (a) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (b) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315.

(9) Other bidentate phosphine ligands such as dppf and dppe were ineffective in these transformations. See Supporting Information (Table S1) for details.

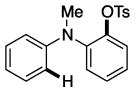
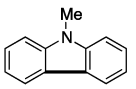
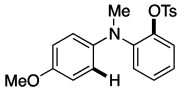
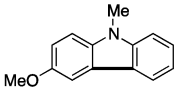
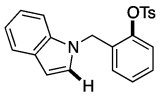
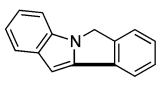
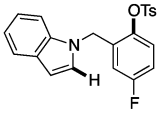
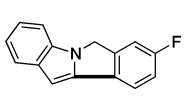
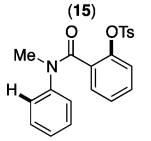
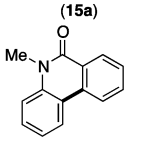
the product (**1a**) in good yield (86%) as determined by gas chromatographic analysis of the crude reaction mixture (entry 9).[10]

Having the optimal conditions in hand for the arylation of **1-OTs**, we next examined the generality of this transformation with respect to varied substitution patterns on the tethered aryl rings. As shown in Table 2, the method is compatible with electron-donating (entries 3, 6, and 10) and -withdrawing substituents (entries 7 and 11) on both aryl rings to afford the corresponding furan products in good to excellent yields. Substrates bearing benzylic methyl groups (entries 2 and 8) as well as halides (entries 4 and 5) effectively participated in these reactions.[11] Importantly, product **5a** is amenable to further structural elaboration by transition metal catalyzed cross-couplings of aryl chlorides.[12] Substrates such as **6-OTs**, **7-OTs**, and **9-OTs** bear two different aromatic C−H bonds that could undergo arylation (entries 6, 7, and 9). While products **6a** and **7a** form via functionalization of the less sterically hindered C−H bond, a 1.5:1 mixture of isomers was obtained from the reaction of naphthyl substrate **9-OTs**. These selectivities are consistent with those previously documented for known Pd-catalyzed C−H arylation reactions.[8a,13]

We next explored the scope of these arylations toward the synthesis of diverse heterocycles. As shown in Table 3, carbazoles, fused indoles, and lactams could be obtained in good yields from the palladium-catalyzed reaction of substrates **12**−**16**. Importantly, these heterocyclic motifs are widely prevalent in bioactive molecules and pharmaceutical targets.[8a]

Our next efforts focused on the development of reaction conditions for the one-pot sequential tosylation/arylation starting from phenol derivatives.[5b,c] We were pleased to find that this could be accomplished using a sequence involving (1) the reaction of phenolic substrates such as **1-OH** with Cs_2CO_3 (1.5 equiv) and TsCl (1.02 equiv) in toluene for 1 h at 120 °C and (2) the addition of $Pd(OAc)_2$ (10 mol %), dcype (20 mol %), and CsOPiv (1.1 equiv) to the reaction mixture. This procedure allowed the reaction of **1-OH** to lead to the desired product **1a** in good yield (Table 4, entry 1). As depicted in Table 4, the one-pot tosylation/arylation sequence was general with respect to different substrates and led to products in good isolated yields. Importantly, the sequential arylation obviates the isolation and purification of the intermediate tosylates and effectively leads to the desired products from readily accessible phenol derivatives.

Table 3. Scope of Pd-Catalyzed C−H Arylation for Synthesis of Diverse Heterocycles

Entry	Substrate	Product	Isolated Yield[a]
1	 (12)	 (12a)	82%
2	 (13)	 (13a)	81%
3[b]	 (14)	 (14a)	85%
4[b]	 (15)	 (15a)	87%
5[c,d]	 (16)	 (16a)	92%

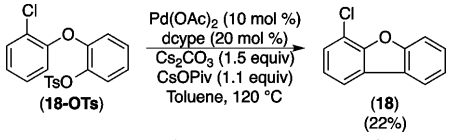
[a] General conditions: substrate (1 equiv), $Pd(OAc)_2$ (0.10 equiv), dcype (0.20 equiv), Cs_2CO_3 (1.5 equiv), CsOPiv (1.1 equiv), toluene (0.25 M in substrate), 120 °C. [b] General conditions but at 145 °C in xylene. [c] Substrate (1 equiv), $Pd(OAc)_2$ (0.15 equiv), dcype (0.30 equiv), Rb_2CO_3 (1.5 equiv), xylene (0.25 M in **16**), 140 °C. [d] The isolated product contained a small amount of protodeoxygenated substrate (16:1).

In order to gain preliminary insight into the mechanism of the C−H activation step of the newly developed intramolecular arylation, we conducted the reaction with substrate **17**. As illustrated in Scheme 1, this reaction proceeded to afford a mixture of products **17a** and **17b** in 61% isolated yield. Importantly, the major product **17a** was obtained via the preferential functionalization of the electron-rich aryl ring. Although further studies are needed to elucidate the detailed mechanism, the modest selectivity for **17a** is consistent with the C−H activation step proceeding via a concerted metalation−deprotonation (CMD) pathway.[8b,14,15]

(10) Although the reaction was optimized with Cs_2CO_3, other bases (e.g., K_3PO_4 and K_2CO_3) also lead to good yields of product **1a** (see Supporting Information for details).

(11) Gas chromatographic analysis of the crude reaction mixture obtained from the reaction of **5-OTs** did not show any trace of products derived from intermolecular arylation.

(12) Upon a reviewers suggestion, the reaction of **18-OTs** was also conducted to study the direct competition between the reaction of aryl chloride versus aryl tosylate. The reaction of **18-OTs** afforded product **18** via selective oxidative addition into the C−O bond albeit in a low yield (22%). The mass balance is accounted for by the low conversion of subtrate **18-OTs** and trace protodechlorination.



(13) For some representative recent reports on furan synthesis via C−H activation, see: (a) Wang, C.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194. (b) Xiao, B.; Gong, T.-J.; Liu, Z.-J.; Liu, J.-H.; Luo, D.-F.; Xu, J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 9250.

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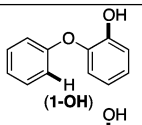
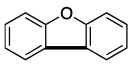
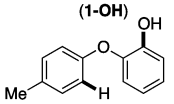
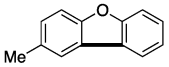
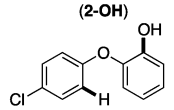
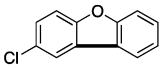
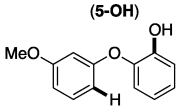
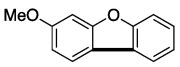
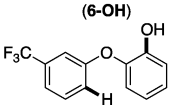
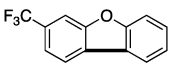
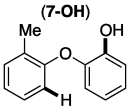
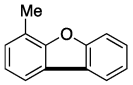
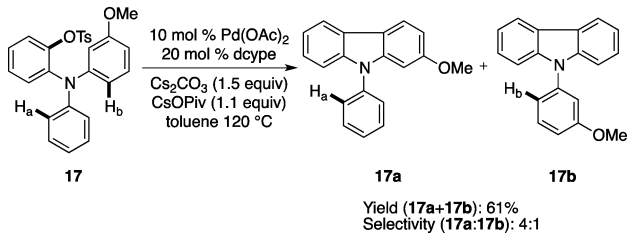
(15) (a) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496. (b) Garcia-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880. (c) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Org. Chem.* **2012**, *77*, 658.

Table 4. Scope of Sequential Tosylation/Arylation

Entry	Substrate	Product	Isolated Yield[a,b]
1	 (1-OH)	 (1a)	73%
2	 (2-OH)	 (2a)	83%
3	 (5-OH)	 (5a)	76%
4	 (6-OH)	 (6a)	87%
5	 (7-OH)	 (7a)	73%
6	 (8-OH)	 (8a)	80%

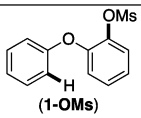
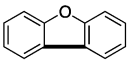
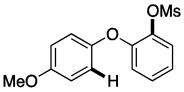
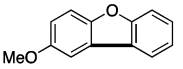
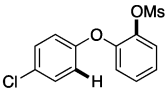
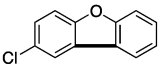
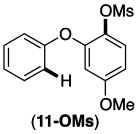
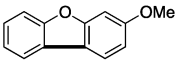
[a] General conditions: (1) substrate (1 equiv), Cs_2CO_3 (1.5 equiv), TsCl (1.02 equiv), toluene (0.25 M in substrate), 1 h, 120 °C; (2) $Pd(OAc)_2$ (0.10 equiv), dcype (0.20 equiv), CsOPiv (1.1 equiv), toluene (0.25 M in substrate), 120 °C. [b] The isolated products contained trace amounts of protodeoxygenated substrate. The ratio of desired product to the protodeoxygenated substrate was generally >20:1.

Scheme 1. Electronic Effect for Pd-Catalyzed C−H Arylation



The successful achievement of the Pd-catalyzed intramolecular arylation using tosylates set the stage for the use of more challenging mesylates as electrophiles. The optimized conditions for the C−H arylation using tosylates led to significant hydrolysis of the mesylates. We were pleased to find, however, that the use of less soluble Rb_2CO_3 as the base in place of Cs_2CO_3 significantly attenuated the hydrolysis and led to the desired products in good yields. The results in Table 5 depict a preliminary scope of the arylations using mesylate substrates.

Table 5. Pd-Catalyzed Intramolecular Arylation Using Mesylates

Entry	Substrate	Product	Isolated Yield[a,c]
1	 (1-OMs)	 (1a)	79%
2	 (3-OMs)	 (3a)	96%
3	 (5-OMs)	 (5a)	76%
4[b]	 (11-OMs)	 (6a)	92%

[a] General conditions: substrate (1 equiv), $Pd(OAc)_2$ (0.10 equiv), dcype (0.20 equiv), Rb_2CO_3 (1.5 equiv), CsOPiv (1.0 equiv), toluene, (0.25 M in substrate), 120 °C. [b] General conditions but with xylene at 140 °C. [c] The isolated products contained trace amounts of protodeoxygenated substrate. The ratio of the desired product to the protodeoxygenated substrate was generally >20:1.

In summary, this paper describes the development of palladium-catalyzed intramolecular C−H arylation of arenes and heteroarenes using tosylates and mesylates as electrophiles. The transformation is general and efficient with respect to diverse substrates. Further studies will focus on broadening the scope of the current transformation. Additionally, detailed mechanistic studies will be conducted and reported in due course.

Acknowledgment. This work was supported by St. Olaf College. The authors would also like to thank the CURI (Collaborative Undergraduate Research and Inquiry) program at St. Olaf College for financial support of this work.

Supporting Information Available. Experimental details and spectroscopic and analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.