J|A|C|S ARTICLES

Published on Web 04/01/2010

# Palladium-Catalyzed *Ortho*-Arylation of *O*-Phenylcarbamates with Simple Arenes and Sodium Persulfate

Xiaodan Zhao, Charles S. Yeung, and Vy M. Dong*

*Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario, Canada M5S 3H6*

Received January 28, 2010; E-mail: vdong@chem.utoronto.ca

***Abstract:*** By palladium catalysis, the C−H bond functionalization of *O*-phenylcarbamates with simple arenes has been achieved using sodium persulfate ($Na_2S_2O_8$), an inexpensive, easy-to-handle, and environmentally friendly oxidant. This oxidative cross-coupling involves two aromatic C−H bonds undergoing concomitant oxidation to furnish a new biaryl C−C linkage. Excellent reaction efficiencies and regioselectivities were observed with a range of electron-rich, electron-neutral, and electron-deficient arenes; minimal homocoupling of either component was observed. When two reactive C−H bonds are present on the *O*-phenylcarbamate, selective diarylation can be achieved via quadruple C−H bond functionalization. This work represents a rare example of using *O*-carbamates as directing groups for catalytic C−H bond activation. Additionally, a palladacycle obtained from an *O*-phenylcarbamate was prepared and fully characterized. This trifluoroacetate-bridged bimetallic Pd complex exhibits clean conversion to the *ortho*-arylation product upon treatment with simple arenes. The addition of trifluoroacetic acid (TFA) was found to be critical for successful cyclopalladation of *O*-phenylcarbamates. We propose this oxidative arene cross-coupling occurs via two discrete C−H bond activations, namely cyclopalladation and electrophilic metalation, within a Pd(0/II) catalytic cycle.

## Introduction

The 2-arylphenol is a structural motif found in important natural products, medicinal targets,[1] and privileged ligands.[2] Snieckus and co-workers have developed a widespread and popular strategy for accessing elaborate phenol derivatives via directed *ortho*-metalation (D*o*M) of *O*-phenylcarbamates.[3] Notably, the *O*-carbamate not only serves as a useful protecting group but also acts as a functional handle for further transformations, including anionic Fries rearrangements[3,4] and cross-couplings (Figure 1).[5] Using D*o*M to form a C−C biaryl linkage, however, requires multiple steps and valuable prefunctionalized reagents involving distinct metalation, halogenation, and cross-coupling steps (Figure 2).

Catalytic C−H bond functionalization of phenol derivatives is a promising alternative synthetic strategy. Direct access to 2-arylphenol derivatives has thus far been limited to oxidative phenolic homo- and heterocoupling,[6] anodic phenol/arene cross-coupling,[7] and transition metal-catalyzed arylation with aryl iodides with either unprotected phenols[8] in the presence of phosphites or phosphoramidites,[9] or benzodioxoles.[10] Considering their synthetic utility, the use of *O*-phenylcarbamates in catalytic C−H bond functionalization warrants further explora-

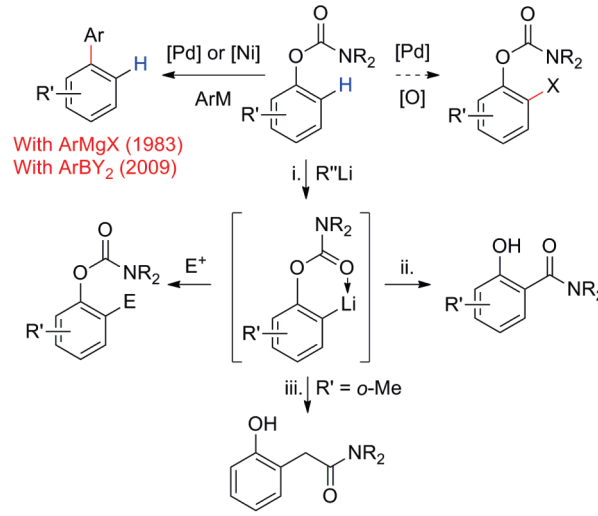



***Figure 1.*** *O*-Phenylcarbmates: A versatile functional group with unrealized potential for catalytic C−H functionalization. C−X = C−C, C−N, C−O, C−S, C−F, C−Cl, C−Br, C−I.

(1) (a) He, X.; Alian, A.; Stroud, R.; Ortiz de Montellano, P. R. *J. Med. Chem.* **2006**, *49*, 6308–6323. (b) Jeong, T.-S.; Kim, K. S.; An, S.-J.; Cho, K.-H.; Lee, S.; Lee, W. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2715–2717. (c) Jeong, T.-S.; Kim, K. S.; Kim, J.-R.; Cho, K.-H.; Lee, S.; Lee, W. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2719–2723. (d) Million, M.-E.; Boiziau, J.; Parker, F.; Tocque, B.; Roques, B. P.; Garbay, C. *J. Med. Chem.* **1995**, *38*, 4693–4703.

(2) For reviews on BINOL, see: (a) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857–898. (b) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155–3212.

(3) For a review, see: Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933.

(4) Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935–1937.

(5) (a) Sengupta, S.; Leite, M.; Raslan, D. S.; Quesnelle, C.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 4066–4068. (b) Quasdorf, K. W.; Riener, M.; Petrova, K. V.; Garg, N. K. *J. Am. Chem. Soc.* **2009**, *131*, 17748–17749. (c) Antoft-Finch, A.; Blackburn, T.; Snieckus, V. *J. Am. Chem. Soc.* **2009**, *131*, 17750–17752. (d) Xu, L.; Li, B.-J.; Wu, Z.-H.; Lu, X.-Y.; Guan, B.-T.; Wang, B.-Q.; Zhao, K.-Q.; Shi, Z.-J. *Org. Lett.* **2010**, *12*, 884–887.

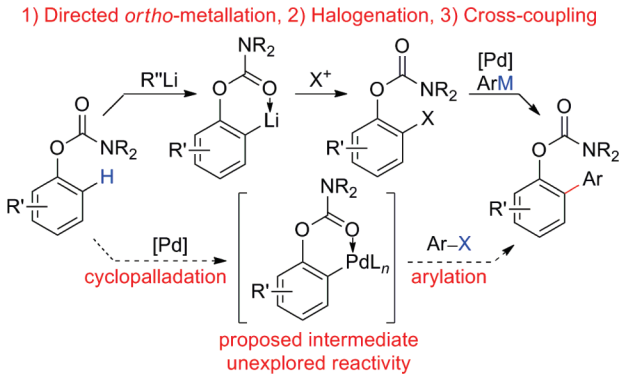


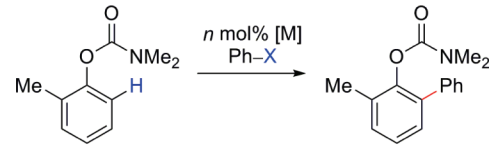

***Figure 2.*** Proposed catalytic arylation of *O*-phenylcarbamates.

tion.[11] Arylation of *O*-phenylcarbamates with aryl iodides and hypervalent iodonium salts ($Ph_2IOTf$) has only recently been achieved.[12]

Cross-coupling of simple arenes has emerged as a green strategy for making biaryl linkages.[13] This arylation involves two aromatic C−H bonds (Ar−H and Ar′−H) undergoing concomitant functionalization to form a new biaryl C−C bond (Ar−Ar′). Despite recent advances, known oxidative arylations remain limited to *N*-protected indoles,[13a,b] *N*-protected pyrroles,[13b] pyridines,[13c,d] anilides,[13e,f] pyridine *N*-oxides,[13g] and benzofurans.[13h] As such, developing oxidative cross-coupling with broader substrate scope and studying the mechanistic underpinning of these processes remains an important challenge in catalysis.

Herein, we report a complementary Pd-catalyzed *ortho*-arylation of *O*-phenylcarbamates using simple arenes (e.g., benzene or *o*-dichlorobenzene) as coupling partners for the formation of 2-arylphenol derivatives. In contrast to known methods, our oxidative arene cross-coupling allows for direct C−H bond arylation while avoiding the need for highly functionalized coupling partners such as aryl iodides and hypervalent iodine reagents.

***Table 1.*** Screen of Known Direct Arylation Conditions to *O*-Phenylcarbamates




| entry | *n* | X | M | conditions | 2a[a] (%) |
|---|---|---|---|---|---|
| 1 | 5 | I | $Pd(OAc)_2$ | AgOAc, AcOH, 130 °C[16] | 0 |
| 2 | 5 | I | $Pd(OAc)_2$ | $Cs_2CO_3$, xylene, 100 °C[17] | 0 |
| 3 | 2.5 | Br | $[Ru(p\text{-cymene})Cl_2]_2$ | $PPh_3$, $K_2CO_3$, NMP, 120 °C[18] | 0 |
| 4 | 2.5 | Cl | $[Ru(p\text{-cymene})Cl_2]_2$ | $ArCO_2H$, toluene, 120 °C[b19] | 0 |
| 5 | 5 | $IPhBF_4$ | $Pd(OAc)_2$ | AcOH, 100 °C[16] | 89 |

[a] GC yield with dodecane as an internal standard. [b] Ar = $2,4,6\text{-}Me_3C_6H_2$.

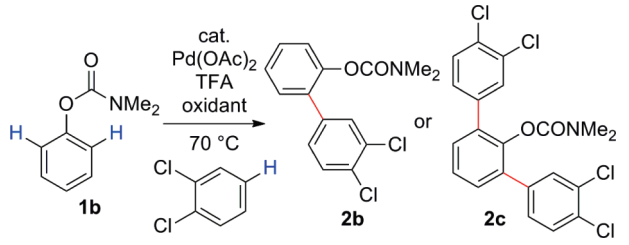
## Results and Discussion

**Initial Studies.** We imagined that *ortho*-arylation would be possible in a one-step process from an *O*-phenylcarbamate. On the basis of known cyclopalladations,[12,14] we proposed that *O*-phenylcarbamates could undergo C−H bond activation with Pd to produce a novel palladacycle that could be isolated and characterized (Figure 2). In addition, we reasoned this palladacycle intermediate could react with an arene coupling partner (Ar−X) to produce 2-aryl and/or 2,6-diaryl *O*-phenylcarbamates. Using *o*-tolyl dimethylcarbamate (**1a**), we considered various arene coupling partners including aryl halides and hypervalent iodonium salts (e.g., $Ph_2IBF_4$)[15] (Table 1). Our preliminary studies revealed that while aryl halides were ineffective oxidants (entries 1−4), $Ph_2IBF_4$ showed promising results (entry 5), in agreement with Fu and Liu's recent report.[12b] Our results demonstrated that *O*-carbamates are effective directing groups for C−H activation in the presence of strong oxidants. With these initial experiments, we concentrated our efforts on cross-coupling with simple arenes to overcome the need for valuable arylating agents.[13]

Toward achieving a new oxidative cross-coupling, we focused on identifying conditions for the arylation of *O*-phenylcarbamate

(6) (a) Grandbois, A.; Mayer, M.-E.; Bédard, M.; Collins, S. K.; Michel, T. *Chem.—Eur. J.* **2009**, *15*, 9655–9659. (b) Yan, P.; Sugiyama, Y.; Takahashi, Y.; Kinemuchi, H.; Temma, T.; Habaue, S. *Tetrahedron* **2008**, *64*, 4325–4331. (c) Habaue, S.; Temma, T.; Sugiyama, Y.; Yan, P. *Tetrahedron Lett.* **2007**, *48*, 8595–8598. (d) Temma, T.; Hatano, B.; Habaue, S. *Tetrahedron* **2006**, *62*, 8559–8563. (e) Hon, S.-W.; Li, C.-H.; Kuo, J.-H.; Barhate, N. B.; Liu, Y.-H.; Wang, Y.; Chen, C.-T. *Org. Lett.* **2001**, *3*, 869–872.
(7) Kirste, A.; Schnakeburg, G.; Stecker, F.; Fischer, A.; Waldvogel, S. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 971–975.
(8) Kawamura, Y.; Satoh, T.; Miura, M.; Nomura, M. *Chem. Lett.* **1999**, 961–962.
(9) (a) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 112–114. (b) Bedford, R. B.; Limmert, M. E. *J. Org. Chem.* **2003**, *68*, 8669–8682. (c) Oi, S.; Watanabe, S.-i.; Fukita, S.; Inoue, Y. *Tetrahedron Lett.* **2003**, *44*, 8665–8668.
(10) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581–590.
(11) For a related Boc-directed C−H bond activation, see: Wang, D.-H.; Hao, X.-S.; Wu, D.-F.; Yu, J.-Q. *Org. Lett.* **2006**, *8*, 3387–3390.
(12) During preparation of this manuscript, the following accounts of *ortho*-arylation of phenolic esters and *O*-phenylcarbamates with hypervalent iodonium salts was reported: (a) Bedford, R. B.; Webster, R. L.; Mitchell, C. J. *Org. Biomol. Chem.* **2009**, *7*, 4853–4857. (b) Xiao, B.; Fu, Y.; Xu, J.; Gong, T.-J.; Dai, J.-J.; Yi, J.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 468–469.
(13) (a) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172–1175. (b) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072–12073. (c) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904–11905. (d) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 9651–9653. (e) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115–1118. (f) Brasche, G.; García-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207–2210. (g) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254–9256. (h) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137–3139. (i) Potavathri, S.; Dumas, A. S.; Dwight, T. A.; Naumiec, G. R.; Hammann, J. M.; DeBoef, B. *Tetrahedron Lett.* **2008**, *49*, 4050–4053. (j) Xia, J.-B.; You, S.-L. *Organometallics* **2007**, *26*, 4869–4871.
(14) For a review on palladacycles, see: Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527–2572.
(15) (a) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330–7331. (b) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972–4973. (c) Deprez, N. R.; Sanford, M. S. *Inorg. Chem.* **2007**, *46*, 1924–1935. (d) Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234–11241.
(16) Shabashov, D.; Daugulis, O. *Org. Lett.* **2005**, *7*, 3657–3659.
(17) Kametani, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2000**, *41*, 2655–2658.
(18) Oi, S.; Fukita, S.; Hirata, N.; Watanuki, N.; Miyano, S.; Inoue, Y. *Org. Lett.* **2001**, *3*, 2579–2581.
(19) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299–2302.

***Table 2.*** Optimization of Reaction Conditions for Selective Mono- and Diarylation of *O*-Phenylcarbamates[a]




| entry | oxidant/equiv | **2b**[b] (%) | **2c**[b] (%) |
|---|---|---|---|
| 1 | $Cu(OAc)_2$/3 | 3 | 0 |
| 2 | AgOAc/3 | 0 | 0 |
| 3 | $Ag_2CO_3$/3 | 0 | 0 |
| 4 | 1 atm of $O_2$, DMSO/0.2 | 27 | 0 |
| 5 | Oxone/3 | 1 | 0 |
| 6 | $Na_2S_2O_8$/1.5 | 73 (62) | 18 |
| 7 | $Na_2S_2O_8$/3 | 15 | 83 (76) |

[a] Conditions: substrate, 0.2 mmol; *o*-dichlorobenzene, 1 mL; Pd $(OAc)_2$, 10 mol %; TFA, 5 equiv; 48 h. [b] GC yield with dodecane as an internal standard; isolated yield in parentheses.

**1b** with electron-deficient arenes such as *o*-dichlorobenzene (Table 2). This model system would help us probe issues of both reactivity and selectivity, as competing mono- and diarylation can take place. We decided to focus on using electron-deficient arenes because they represent a challenging class of substrates for oxidative coupling. For example, related arylations of anilides are relatively inefficient with electron-deficient arenes.[13f] Neither biaryl **2b** nor **2c** was formed in the absence of Pd catalysts; the presence of trifluoroacetic acid (TFA) was also found to be critical.[20] Oxidants reported for previous *ortho*-arylations were not optimal: $Cu(OAc)_2$, AgOAc, and $Ag_2CO_3$ were ineffective (Table 2, entries 1−3). The use of $O_2$ as an oxidant, which is known to be effective in related anilide arylations,[13f] liberated product **2b** in only a modest 27% yield (entry 4). In comparison, when benzene was used as the simple arene, $O_2$[13e,f] was sufficient in promoting the desired C−H bond arylation (cf. 85% GC yield for **1a**). Because $Ph_2IBF_4$[15] was found to be effective in preliminary studies, we chose to explore stronger metal salt oxidants for our oxidative arene cross-coupling. While we found that Oxone resulted in decreased yields (entry 5), we discovered that $Na_2S_2O_8$ was an efficient oxidant (entries 6 and 7).[21] Furthermore, by simply controlling the stoichiometry of the oxidant, we could select for either the 2-arylated product **2b** (62%, entry 6) or the 2,6-diarylated product **2c** (76%, entry 7).[22]

**Synthetic Scope.** With this protocol in hand, we were able to rapidly access 21 different 2-arylcarbamates in 44−98% yields (Table 3). *O*-Phenylcarbamates bearing substitution at the *ortho* or *meta* positions underwent regioselective monoarylation to form products **2d**−**w**. Significant variation on the aromatic ring of the masked phenol was tolerated, including electron-donating groups (e.g., Me, Et, $^i$Pr, $^t$Bu, Ph, OMe) and electron-withdrawing groups (e.g., F, Cl, COOMe). Substrates bearing a stronger electron-withdrawing group (e.g., $CF_3$), however, gave the desired *ortho*-arylation product with poor efficiency (<20%). In contrast to anilide arylations,[13e,f] *O*-phenylcarbamate arylation occurs with high efficiency using electron-deficient arenes, including *o*-dichlorobenzene (**2d**−**n**) and *o*-difluorobenzene (**2o**−**s**). With these simple *o*-disubstituted arenes, exclusive functionalization was observed at the 4-position. Benzene (**2a**,**t**,**u**, 71−98%) and electron-rich arenes, including *o*-dimethyl- and *o*-dimethoxybenzene (**2v**−**w**, 47−76%), were also suitable coupling partners.

Rather than consuming a valuable aryl halide or boronic acid and producing stoichiometric amounts of waste byproducts in the process, this approach uses an inexpensive arene as the reagent and formally liberates one equivalent of $H_2$. Furthermore, while boronic acids are known to homocouple, the analogous arene dimerization to form polyhalogenated biphenyls is minimal under our conditions (i.e., only trace homocoupling products could be observed with *o*-dichloro- and *o*-difluorobenzene). The use of electron-rich arenes as coupling partners, however, resulted in competitive homocoupling, thus reducing the reaction efficiency (**2w**, 47%). Homocoupling with benzene also occurs, but phenylation of **1a** remains competitive; benzene generates the corresponding biphenyl side product with a catalyst TON = 8.5.

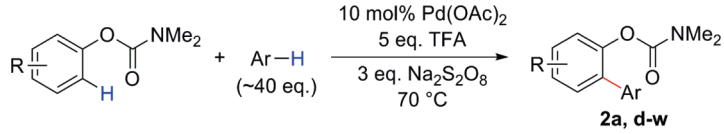
The 2,6-diarylphenol motif is found in molecules that have demonstrated promising activities in various enzymatic inhibition studies.[1] Our work provides access to these structures using simple arenes as coupling partners (Table 4, entries 2−5). Notably, we demonstrate rare examples of oxidative diarylation and 4-fold C−H bond functionalization with unprecedented efficiency.[13b] A range of 2,6-diaryl-*O*-phenylcarbamates (**2c**,**x**−**z**) were prepared (68% to 78%). The reaction tolerates electron-neutral and -donating substituents at the *para* position. However, substitution with electron-withdrawing groups resulted in selective monoarylation to yield 2-aryl-*O*-phenylcarbamates as the major products (**2aa**−**ab**, 66%).

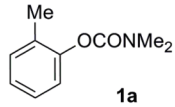
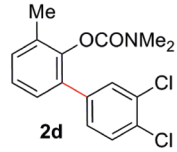
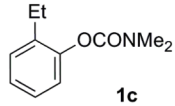
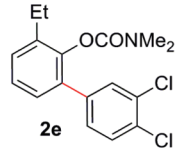
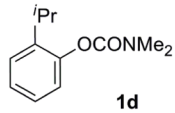
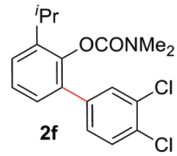
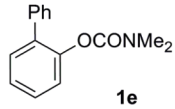
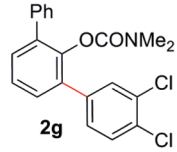
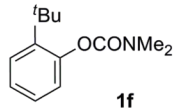
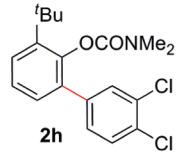
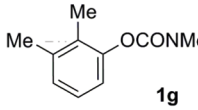
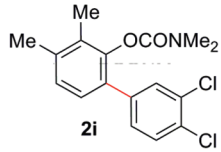
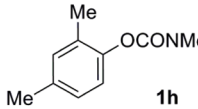
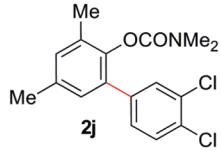
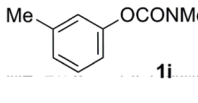
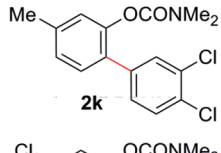
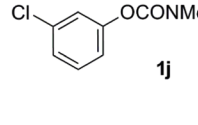
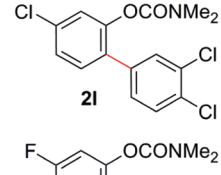
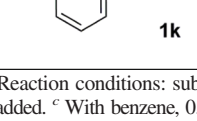
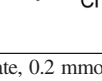
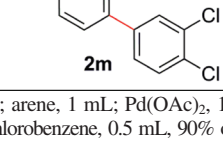
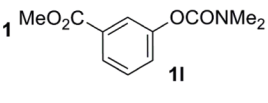
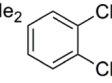
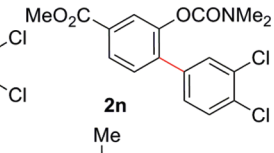
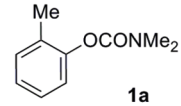
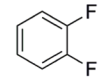
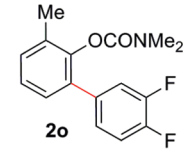
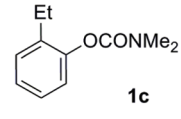
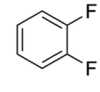
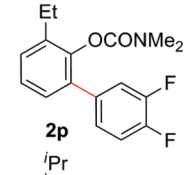
**Mechanistic Proposal.** Few mechanistic studies have been reported for oxidative arene cross-coupling via tandem C−H bond functionalization.[13d] Herein, we present studies that support a distinct mechanistic proposal shown in Figure 3. Our oxidative cross-coupling occurs via a Pd(0/II) catalytic cycle involving (1) C−H bond activation by carbamate-assisted cyclopalladation, (2) C−H bond functionalization by electrophilic metalation, (3) reductive elimination, and finally, (4) reoxidation of Pd(0) to an active Pd(II) catalyst with sodium persulfate.

**Role of TFA and $Na_2S_2O_8$.** Both TFA and sodium persulfate were found to be critical in achieving high efficiency for our oxidative cross-coupling of *O*-phenylcarbamates. A recent computational study by Davies and Macgregor suggests that acetate anions can facilitate intramolecular H-transfer through a six-membered transition state.[23] In addition to this role, we propose that TFA enhances the electrophilicity of the Pd center and aids electrophilic metalation.[20,24] Dissociation of a trifluoroacetate anion and concurrent generation of a cationic Pd species has been proposed in the literature (Figure 4).[24b,25] Substitution of TFA with the less acidic acids (e.g., trichloro-

(20) Li, R.; Liang, L.; Lu, W. *Organometallics* **2006**, *25*, 5973–5975.
(21) (a) Wang, G.-W.; Yuan, T.-T.; Wu, X.-L. *J. Org. Chem.* **2008**, *73*, 4717–4720. (b) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141–1144.
(22) The use of phenol esters under our oxidative arylation conditions yielded no desired product. See ref 12b.
(23) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754–13755.
(24) TFA is known to facilitate the formation of Pd(II) $\sigma$-aryl intermediates. Our results suggest that TFA can also promote direct C−H activation by palladacycle formation. (a) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992–1995. (b) Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fujiwara, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7252–7263.

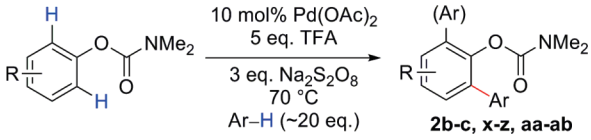
***Table 3.*** Pd-Catalyzed Oxidative Arylation of *O*-Phenylcarbamates[a]

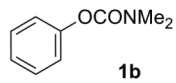
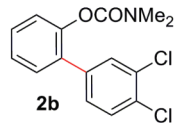
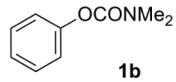
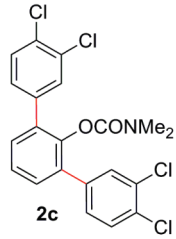
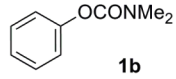
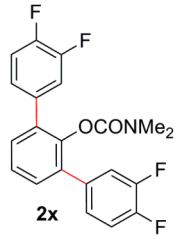
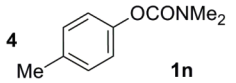
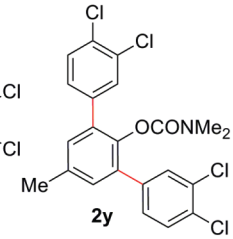
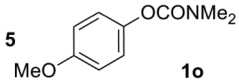
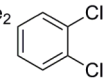
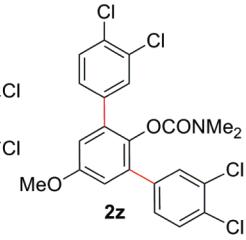
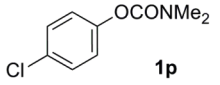
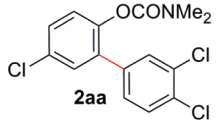
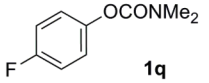
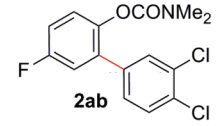



| entry | substrate | arene | product | yield |
|---|---|---|---|---|
| 1 |  **1a** |  |  **2d** | 80% |
| 2 |  **1c** |  |  **2e** | 82% |
| 3 |  **1d** |  |  **2f** | 55% |
| 4 |  **1e** |  |  **2g** | 73% |
| 5 |  **1f** |  |  **2h** | 76% |
| 6 |  **1g** |  |  **2i** | 75% |
| 7 |  **1h** |  |  **2j** | 81% |
| 8 |  **1i** |  |  **2k** | 85% |
| 9 |  **1j** |  |  **2l** | 76% |
| 10 |  **1k** |  |  **2m** | 84% |
| 11 |  **1l** |  |  **2n** | 44% |
| 12 |  **1a** |  |  **2o** | 79% |
| 13 |  **1c** |  |  **2p** | 69% |
| 14 |  **1d** |  |  **2q** | 71% |
| 15 |  **1e** |  |  **2r** | 87% |
| 16 |  **1f** |  |  **2s** | 82% |
| 17 |  **1a** |  |  **2a** | 90%[a] |
| 18 |  **1i** |  |  **2t** | 98%[a,b] |
| 19 |  **1m** |  |  **2u** | 71%[a] |
| 20 |  **1m** |  |  **2v** | 76%[a] |
| 21 |  **1m** |  |  **2w** | 47%[c] |

[a] Reaction conditions: substrate, 0.2 mmol; arene, 1 mL; $Pd(OAc)_2$, 10 mol %; $Na_2S_2O_8$, 3 equiv; TFA, 5 equiv; 30−68 h. [b] After 24 h, 5 mol % of $Pd(OAc)_2$ was added. [c] With benzene, 0.5 mL, and *o*-dichlorobenzene, 0.5 mL, 90% of **2t** was isolated. [d] *o*-Dimethoxybenzene, 0.5 mL.

***Table 4.*** Pd-Catalyzed Oxidative Mono- and Diarylation of *O*-Phenylcarbamates[a]




| entry | substrate | arene | product | yield |
|---|---|---|---|---|
| 1 |  **1b** |  |  **2b** | 62%[a] |
| 2 |  **1b** |  |  **2c** | 76% |
| 3 |  **1b** |  |  **2x** | 78% |
| 4 |  **1n** |  |  **2y** *major:minor = 18:1* | 77% |
| 5 |  **1o** |  |  **2z** *major:minor = 5.5:1* | 68% |
| 6 |  **1p** |  |  **2aa** | 66% |
| 7 |  **1q** |  |  **2ab** | 66% |

[a] Reaction conditions: substrate, 0.2 mmol; arene, 1 mL; $Pd(OAc)_2$, 10 mol %; $Na_2S_2O_8$, 3 equiv; TFA, 5 equiv; 48−72 h.

acetic acid, tribromoacetic acid, or acetic acid) leads to a decrease in reaction efficiencies. Triflic acid, which is known

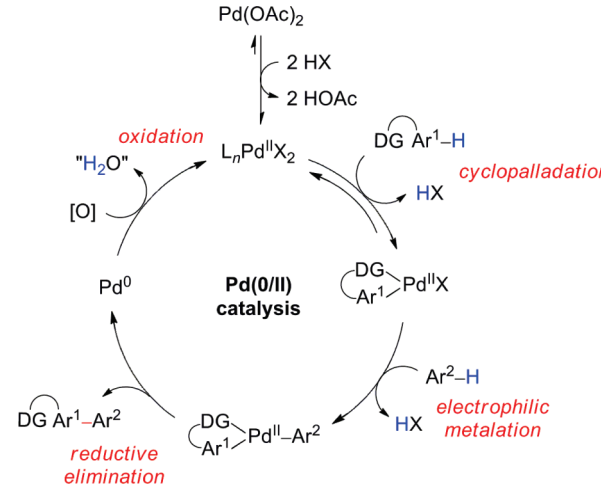



***Figure 3.*** Proposed mechanism for Pd-catalyzed oxidative arylation of *O*-phenylcarbamates. X = $CO_2CF_3$.

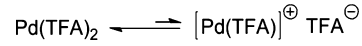



***Figure 4.*** Proposed dissociation of trifluoroacetate anion from $Pd(TFA)_2$.[24b,25]

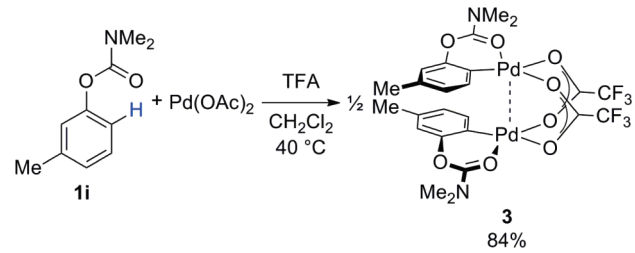



***Figure 5.*** Preparation of dimeric Pd complex **3**.

to be a useful additive in C−H bond activations,[12b] led to decomposition products under our reaction conditions.

The strong oxidant $Na_2S_2O_8$ promotes reoxidation of Pd(0) to Pd(II). Because both strong oxidants such as $Na_2S_2O_8$[21] and hypervalent iodonium salts ($Ph_2IBF_4$)[15] are effective in our oxidative *ortho*-arylation, alternative mechanistic proposals involving Pd(II/III)[26] and/or Pd(II/IV)[27] catalytic cycles are also reasonable to consider. Based on the studies described below, however, we favor a mechanism involving two discrete C−H bond activations via Pd(0/II) catalysis.

**Support for the First C−H Bond Activation by Cyclopalladation.** As previously mentioned, directed C−H bond activation of *O*-phenylcarbamates was unknown until recently.[12] Fu and Liu demonstrated that monomeric Pd·HOTf complexes were competent catalysts for the *ortho*-arylations of phenylcarboxylates with hypervalent iodine reagents.[12b] However, isolation and characterization by X-ray crystallography of the proposed palladacycle intermediate derived from an *O*-phenylcarbamate had not been achieved. We prepared Pd complex **3** by combining *m*-tolyl dimethylcarbamate with $Pd(OAc)_2$ in the presence of TFA as characterized by $^1$H, $^{13}$C, and $^{19}$F NMR spectroscopy (Figure 5); following recrystallization, we were able to deduce the molecular geometry of **3** by X-ray crystallography (Figure 6). The *O*-phenylcarbamate ligands are oriented in a head-to-

(25) (a) Tunge, J. A.; Foresee, L. N. *Organometallics* **2005**, *24*, 6440–6444. (b) Swang, O.; Blom, R.; Ryan, O. B.; Fægri, K., Jr. *J. Phys. Chem.* **1996**, *100*, 17334–17336.

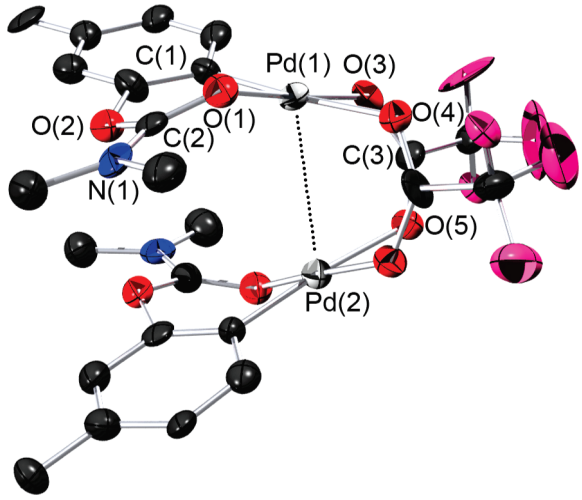



***Figure 6.*** ORTEP plot of dimeric Pd complex **3**. All H atoms have been omitted for clarity. Anisotropic displacement ellipsoids are shown at the 50% probability level. Selected bond lengths (Å) and angles (deg) for **3**: Pd(1)−Pd(2) = 2.9163(10), Pd(1)−O(1) = 2.012(6), Pd(1)−C(1) = 1.957(8), C(2)−O(1) = 1.249(10), C(2)−N(1) = 1.338(11), O(2)−C(2) = 1.320(10), Pd(1)−O(3) = 2.072(6), Pd(1)−O(4) = 2.160(6), N(1)−C(2)−O(1) = 120.1(8), O(2)−C(2)−N(1) = 114.3(8), O(2)−C(2)−O(1) = 125.1(7), C(1)−Pd(1)−O(1) = 83.3(3), C(1)−Pd(1)−O(3) = 94.8(3), O(3)−Pd(1)−O(4) = 87.5(2), O(4)−Pd(1)−O(1) = 89.3(2), O(3)−C(3)−O(5) = 133.2(9).

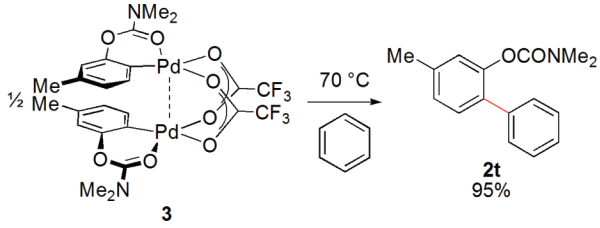



***Figure 7.*** Direct phenylation of dimeric Pd complex **3**.

tail fashion. Notably, the formed Pd complex **3** is dimeric in nature, exhibiting bridging trifluoroacetate ligands and a weak interaction between two Pd nuclei.[28]

This molecular structure confirms that *O*-carbamate is a suitable directing group for C−H bond activation. Furthermore, this structure supports the feasibility of a palladacycle intermediate in our proposed mechanism. Indeed, subjecting Pd complex **3** to benzene resulted in smooth conversion to the phenylated product **2t** in excellent yield at elevated temperatures (Figure 7). Moreover, an oxidant or external additives is not required to promote the desired *ortho*-arylation of complex **3**. Thus, the second C−H bond activation can occur via a Pd(II) intermediate.

**Support for Second C−H Bond Activation by Electrophilic Metalation via Pd(II).** A number of mechanisms can be considered for the second C−H bond activation, including Fagnou's concerted metalation deprotonation[29] or Sanford's proposed $\sigma$-bond metathesis.[13d] Our experimental results suggest, however, that arene activation occurs by a variant of the classical electrophilic aromatic substitution mechanism ($S_EAr$),[30] namely electrophilic metalation.[31]

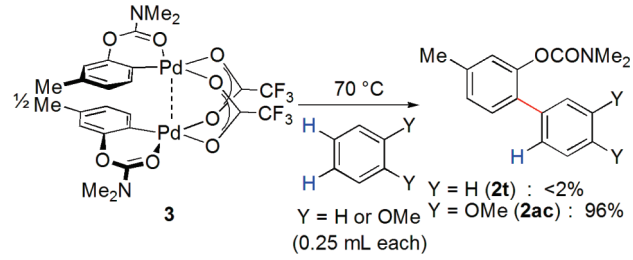



***Figure 8.*** Competition study between electron-rich and electron-neutral arenes for oxidative arylation.

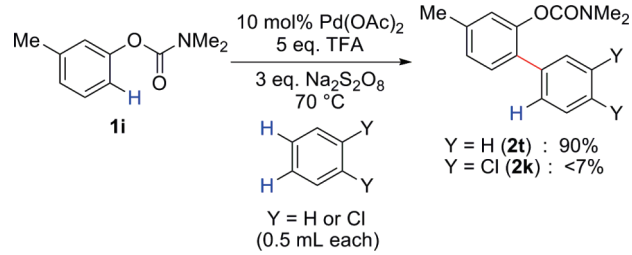



***Figure 9.*** Competition study between electron-neutral and electron-deficient arenes for oxidative arylation.

With palladacycle **3** in hand, we performed a series of competition experiments to study the second C−H bond activation step in our oxidative cross-coupling. Treatment of **3** with a 1:1 mixture of benzene and *o*-dimethoxybenzene resulted in 96% conversion to the *o*-3,4-dimethoxyphenyl product (**2ac**) (Figure 8). In comparison, the phenylation product with benzene (**2t**) was observed in <2% yield. Thus, more electron-rich arenes appear to undergo arylation at a faster reaction rate than less electron-rich arenes. Indeed, a second competition study between benzene and *o*-dichlorobenzene supports this reactivity trend (Figure 9). Our earlier experiments, however, revealed that oxidative *ortho*-arylation of 3-methoxyphenyl dimethylcarbamate (**1m**) with benzene (**2u**, 71%) was more efficient than *o*-dimethoxybenzene (**2w**, 47%) (see Table 2, entries 20, 21). To explain this apparent contradiction, we propose that electron-

(26) For seminal work on catalytic oxidations involving Pd(III) intermediates, see: (a) Powers, D. C.; Ritter, T. *Nat. Chem.* **2009**, *1*, 302–309. (b) Powers, D. C.; Geibel, M. A. L.; Klein, J. E. M. N.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 17050–17051.

(27) Arylation at Pd(IV) has been proposed: (a) Rosewall, C. F.; Sibbald, P. A.; Liskin, D. V.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 9488–9489. (b) Sibbald, P. A.; Rosewall, C. F.; Swartz, R. D.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 15945–15951.

(28) The internuclear distance between the two Pd atoms was determined to be 2.9163(10) Å, slightly longer than known bimetallic complexes containing acetate bridging ligands.[26a] In comparison to other Pd complexes bearing bridging trifluoroacetate ligands, our bimetallic Pd complex **3** exhibits slightly shorter Pd−Pd bonds: (a) Ruddock, P. L.; Williams, D. J.; Reese, P. B. *Steroids* **2004**, *69*, 193–199. (b) Stromnova, T. A.; Paschenko, D. V.; Boganova, L. I.; Daineko, M. V.; Katser, S. B.; Chukarov, A. V.; Kuz'mina, L. G.; Howard, J. A. K. *Inorg. Chim. Acta* **2003**, *350*, 283–288. (c) Schwarz, I.; Rust, J.; Lehmann, C. W.; Braun, M. *J. Organomet. Chem.* **2000**, *605*, 109–116. (d) Goddard, R.; Krüger, C.; Mynott, R.; Neumann, M.; Wilke, G. *J. Organomet. Chem.* **1993**, *454*, C20−C25. For a Pd·TFA complex exhibiting a similar Pd−Pd bond distance, see: (e) Stromnova, T. A.; Orlova, S. T.; Kazyul'kin, D. N.; Stolyarov, I. P.; Eremenko, I. L. *Russ. Chem. Bull.* **2000**, *49*, 150–153.

(29) (a) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754–8756. (b) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848–10849.

(30) For a discussion on classical $S_EAr$, see: Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part B: Reactions and Synthesis*, 5th ed.; Springer: New York, 2007; pp 1004−1025.

(31) For a discussion on electrophilic metalation, see: (a) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part B: Reactions and Synthesis*, 5th ed.; Springer: New York, 2007; p 1026. (b) Ryabov, A. D. *Chem. Rev.* **1990**, *90*, 403–424. (c) Davidson, J. M.; Triggs, C. *J. Chem. Soc. A* **1968**, 1324–1330.

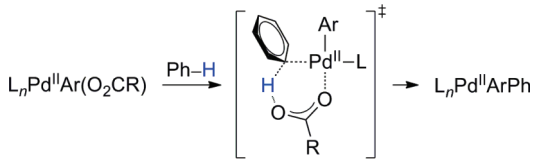



***Figure 10.*** Transition state for a concerted metalation deprotonation mechanism supported by Fagnou and Woo's computational and mechanistic studies.[29]

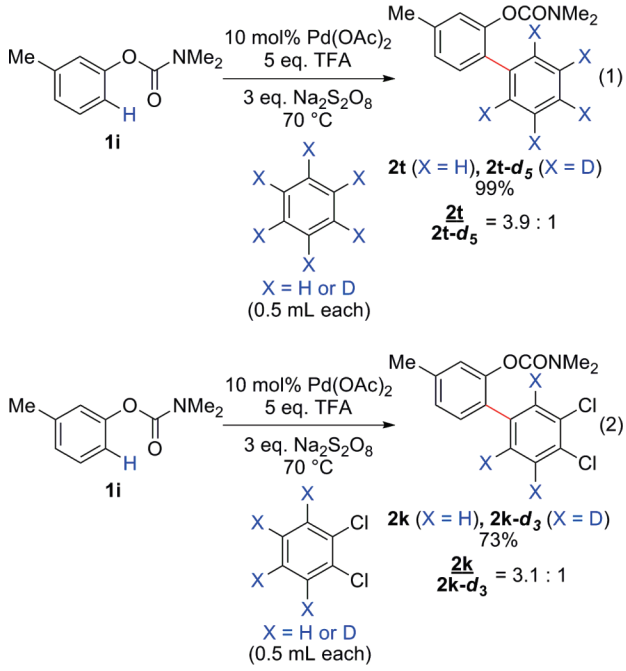



***Figure 11.*** Competition study between deuterated and undeuterated arenes for oxidative arylation.

rich arenes undergo competitive homodimerization, leading to lower yields of the desired 2-phenylcarbamate products. (Attempted arylation of *m*-tolyl dimethylcarbamate (**1i**) with *o*-dimethoxybenzene resulted in homocoupling of the simple arene solely to generate the corresponding biaryl byproduct with a catalyst TON = 7.8; no desired 2-aryl-*O*-phenylcarbamate product was produced.)

The significant differences in arene reactivity observed (i.e., *o*-dichlorobenzene ≪ benzene ≪ *o*-dimethoxybenzene) leads us to favor an $S_EAr$ mechanism[30,31] over both concerted metalation deprotonation[29] and the $\sigma$-bond metathesis[13d] pathways. In a concerted metalation deprotonation mechanism, electron-deficient arenes usually undergo arylation faster due to enhanced acidity (see Figure 10).[29a] However, recent computational studies reveal that acidity is not the only critical parameter.[29b] In Sanford's oxidative coupling involving $\sigma$-bond metathesis, electron-rich arenes (e.g., ArOMe) and electron-deficient arenes (e.g., $ArNO_2$) showed comparable reactivity (1.3:1).[13d]

Next, we investigated the relative reactivity of isotopically labeled arenes under catalytic conditions. Based on a competition experiment, the observed product distributions suggest that both benzene (**2t**:**2t-*d*$_5$** = 3.9:1) and *o*-dichlorobenzene (**2k**:**2k-*d*$_5$** = 3.1:1) undergo the second C−H bond activation faster than their deuterated analogues (Figure 11). Although most aromatic substitutions involve a rate-limiting electrophilic attack, primary kinetic isotope effects suggesting slow H-abstraction have been reported for acylations, sulfonations, nitrosations, and amination.[32] Moreover, in electrophilic metalations using stoichiometric amounts of Hg and Pd complexes,[31] kinetic isotope effects were also observed.[20,31] Thus, our results are consistent with an $S_EAr$ mechanism via two elementary steps: electrophilic attack of Pd on the simple arene to yield a Wheland intermediate followed by rate-limiting proton abstraction to form the aryl Pd $\sigma$-complex (Figure 12).[31] However, both concerted metalation deprotonation[29] and $\sigma$-bond metathesis[13d] remain viable pathways and further mechanistic studies are underway.

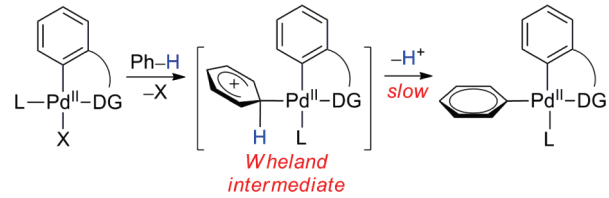



***Figure 12.*** Proposed electrophilc metalation mechanism for functionalization of the second arene.

## Conclusion

In conclusion, we have developed an *ortho*-arylation of *O*-phenylcarbamates using simple arenes as the cross-coupling partner and sodium persulfate as a convenient oxidant. Further, we demonstrate a rare use of *O*-carbamates in directing group assisted catalytic C−H bond activation. The first cyclopalladate derived from an *O*-phenylcarbamate as a bimetallic Pd species containing a weak Pd−Pd interaction has been isolated and characterized. Arylation of this Pd(II) complex is demonstrated in the absence of external oxidants and/or additives. Based on data obtained from competition experiments, we propose a mechanism whereby two C−H bond activations occur via cyclopalladation and electrophilic metalation, respectively, within a Pd(0/II) catalytic cycle. We expect that insights gained from our present study will aid future advances in oxidative cross-coupling, including developing new coupling partners, oxidants, catalysts, and strategies for controlling chemoselectivity.

## Experimental Section

**General Procedure for Oxidative Arylation.** To a 1-dram vial equipped with a Teflon cap were added the *O*-phenylcarbamate (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol, 10 mol %), $Na_2S_2O_8$ (0.6 mmol), and the simple arene (1 mL). Subsequently, trifluoroacetic acid (1 mmol) was added. The vial was stirred on a heating block at 70 °C for the indicated length of time. The reaction mixture was cooled to room temperature, diluted in EtOAc, and washed with satd $NaHCO_3$. The aqueous phase was re-extracted with EtOAc. The combined organic extracts were dried over $Na_2SO_4$ and concentrated in vacuo, and the resulting residue was purified by silica gel column chromatography or preparative thin-layer chromatography (eluent: hexanes/EtOAc) to afford the pure arylation products as single regioisomers. For more details, see the Supporting Information.

**Synthesis of Bimetallic Palladacycle 3 with *m*-Tolyl Dimethylcarbamate (1i).** To a 1-dram vial were added *m*-tolyl dimethylcarbamate (**1i**) (21.5 mg, 0.12 mmol), $Pd(OAc)_2$ (22.4 mg, 0.1 mmol), and dichloromethane (1 mL). Trifluoroacetic acid (11.4 mg, 0.1 mmol) was subsequently added into the vial, and the resulting solution was heated at 40 °C for 30 min. After being cooled to ambient temperature, the reaction mixture was concentrated in

(32) (a) Vougioukalakis, G. C.; Chronakis, N.; Orfanopoulos, M. *Org. Lett.* **2003**, *5*, 4603–4606. (b) Challis, B. C.; Higgins, R. J.; Lawson, A. J. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1831–1836. (c) Olah, G. A.; Lukas, J.; Lukas, E. *J. Am. Chem. Soc.* **1969**, *91*, 5319–5323. (d) Zollinger, H. *Adv. Phys. Org. Chem.* **1964**, *2*, 163–200.

vacuo, and the resulting residue was redissolved in hexanes (2 mL). After 2 h, precipitation of the desired complex occurred. The suspension was filtered through Celite and washed with 2 × 0.3 mL hexanes. The residue was washed with dichloromethane, and the wash solution was subsequently collected and concentrated in vacuo to afford the bimetallic palladacycle **3** as a yellow solid (33.2 mg, 84%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.86 (d, $J$ = 8.1 Hz, 1H), 6.78 (d, $J$ = 8.0 Hz, 1H), 6.51 (s, 1H), 2.70 (s, 3H), 2.32 (s, 3H), 2.31 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 166.0 (q, $J$ = 38.1 Hz), 154.4, 148.27, 135.8, 132.7, 124.7, 115.3, 115.0 (q, $J$ = 287.5 Hz), 107.5, 36.5, 36.4, 20.4; $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −74.5. Recrystallization from dichloromethane and hexanes gave a single crystal suitable for X-ray analysis. For crystallographic data, see the Supporting Information.

**Reaction of Bimetallic Palladacycle 3 with Benzene.** In a 1-dram vial was stirred a solution of palladacycle **3** (33.2 mg, 0.042 mmol) and benzene (0.5 mL) on a heating block at 70 °C for 18 h. After the solution was cooled to ambient temperature, GC-FID analysis was conducted using dodecane (23 $\mu$L, 0.1 mmol) as an internal standard. Target product **2t** was afforded in >99% GC yield. The reaction mixture was concentrated in vacuo, and the resulting residue was purified by preparative thin-layer chromatography (eluent: hexanes/EtOAc = 3:1, v/v) to afford the phenylated product **2t** as a colorless oil (20.3 mg, 95%).

**Competitive Arylation of Bimetallic Palladacycle 3 with Benzene and *o*-Dimethoxybenzene.** In a 1-dram vial was stirred a solution of palladacycle **3** (31.6 mg, 0.040 mmol), benzene (0.25 mL), and *o*-dimethoxybenzene (0.25 mL) on a heating block at 70 °C for 18 h. After the solution was cooled to ambient temperature, GC-FID analysis was conducted using dodecane (23 $\mu$L, 0.1 mmol) as an internal standard. The target products **2t** and **2ac** were afforded in 2% and 98% GC yields, respectively. The reaction mixture was concentrated in vacuo, and the resulting residue was purified by preparative thin-layer chromatography (eluent: hexanes/EtOAc = 3:1, v/v) to afford the product arising from arylation with *o*-dimethoxybenzene **2ac** as a yellow viscious oil (96%). 3′,4′-Dimethoxy-4-methylbiphenyl-2-yl dimethylcarbamate (**2ac**): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.25 (d, $J$ = 7. Hz, 1H), 7.07 (d, $J$ = 7.7 Hz, 1H), 7.01 (s, 1H), 6.96 (m, 2H), 6.90 (d, $J$ = 8.7 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 2.92 (s, 3H), 2.91 (s, 3H), 2.38 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 154.9, 148.3, 148.1, 148.1, 138.2, 131.7, 130.7, 130.3, 126.5, 123.9, 121.3, 112.3, 110.8, 55.8, 55.7, 36.6, 36.3, 21.0; HRMS (ESI) $m/z$ calcd for $C_{18}H_{22}NO_4$ [M + H]$^+$ 316.1543, found 316.1543.

**Acknowledgment.** Dedicated to the memory of Professor Keith Fagnou for his contributions to C−H bond functionalization. Funding is provided by the University of Toronto, Canada Foundation for Innovation, Ontario Research Fund, Boehringer Ingelheim Ltd. Canada, and the Natural Sciences and Engineering Research Council (NSERC) of Canada. V.M.D. is grateful for an Alfred P. Sloan Fellowship and C.S.Y. for an NSERC André Hamer Award and a Canada Graduate Scholarship. We thank Mengzhou Li for helpful experiments and Yang Li and Serge Gorelsky for helpful discussions.

**Supporting Information Available:** Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

JA100783C