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Regioselectivity in Palladium-Catalyzed C–H Activation/Oxygenation Reactions

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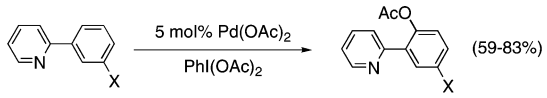
ABSTRACT



X = OMe, OMOM, CH_3, Br, F, CF_3, Ac, oxime, NO_2

6:1 to >20:1 selectivity for oxygenation of less sterically hindered ortho-C–H bond

Palladium-catalyzed directed C–H activation/oxygenation reactions have been explored in a series of *meta*-substituted aryl pyridine and aryl amide derivatives. These transformations tolerate a diverse array of electron-donating and electron-withdrawing *meta*-substituents and generally proceed with high levels of regioselectivity for functionalization of the less sterically hindered *ortho*-C–H bond.

The development of mild methods for the selective functionalization of carbon−hydrogen bonds in complex molecules remains a significant challenge in organic synthesis.[1−5] Such reactions can facilitate the construction of diverse compounds, including organic materials, natural products, and pharmacophores. Recently, we[2] and others[3] have reported Pd^{II}-catalyzed methods for the heteroatom-directed functionalization of arene and alkane C−H bonds. These transformations offer the advantages that (i) they generally do not require the use of strong acids/bases or expensive ancillary ligands, (ii) they are tolerant of ambient air and moisture, (iii) they can be used to install carbon−oxygen,[2b,c] carbon−halogen,[2c,3b] and carbon−carbon bonds,[2a,3a,c−f] and (iv) they proceed with very high levels of *ortho*-regioselectivity.

Despite significant recent advances in this area,[2−4] fundamental questions concerning the selectivity of these Pd^{II}-catalyzed transformations remain. In particular, the functionalization of *meta*-substituted arenes (which contain two different *ortho*-C−H bonds) has not been systematically explored (Scheme 1).[2−4,6] The ability to achieve high and predictable levels of regioselectivity in the *ortho*-function-

(1) For a recent review, see: Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077.

(2) (a) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (b) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542. (c) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300.

(3) For additional recent examples of Pd^{II}-catalyzed ligand-directed C−H activation/functionalization reactions, see: (a) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046. (b) Giri, R.; Chen, X.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112. (c) Daugulis, O.; Zaitsev, V. G. *J. Am. Chem. Soc.* **2005**, *127*, 4156. (d) Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Tokuda, M. *J. Am. Chem. Soc.* **2004**, *126*, 14342. (e) Sezen, B.; Franz, R.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 13372. (f) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586.

(4) For other examples of regioselectivity in Pd^{II}-catalyzed C−H activation/C−C bond-forming reactions of *meta*-substituted arenes, see: (a) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186. (b) Zhang, H.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6144. (c) Huang, Q.; Campo, M. A.; Yao, T.; Tian, Q.; Larock, R. C. *J. Org. Chem.* **2004**, *69*, 8251. (d) Buchwald, S. L.; Hennessy, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 12084.

(5) For other recent examples of the metal-catalyzed oxidative functionalization of C−H bonds, see: (a) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970. (b) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968. (c) Espino, C. G.; Fiori, K. M.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378. (d) Lawrence, J. D.; Takahashi, M.; Bae, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 15334. (e) Hamilton, C. W.; Laitar, D. S.; Sadighi, J. P. *Chem. Commun.* **2004**, 1628. (f) Diaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Perez, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 12078. (g) Maleczka, R. E.; Shi, F.; Holmes, D.; Smith, M. R., III. *J. Am. Chem. Soc.* **2003**, *125*, 7792. (h) Dangel, B. D.; Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2001**, *123*, 8149.

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

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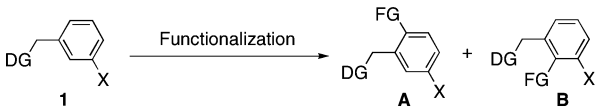
Scheme 1. Possible Products from C−H Activation/Functionalization of *meta*-Substituted Arenes



DG = Directing Group, FG = Functional Group

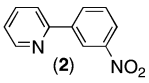
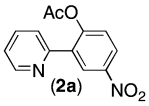
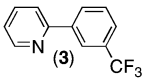
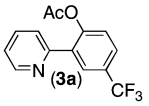
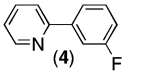
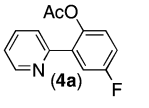
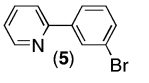
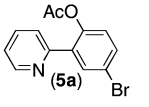
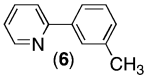
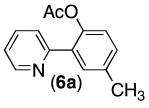
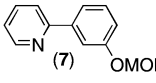
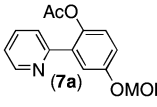
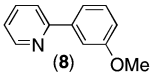
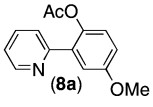
X = OMe, OMOM, CH_3, Br, F, CF_3, Ac, oxime, NO_2, etc.

alization of **1** (a commonly encountered structural motif) would significantly expand the synthetic utility of these methods. Sporadic reports have suggested that isomer **A** is often favored in Pd^{II}-catalyzed reactions; however, the data are difficult to generalize because of the very limited set of *meta*-substituents that have been examined.[2−4,6] We report herein the first detailed, systematic study of regioselectivity in the Pd^{II}-catalyzed C−H activation/functionalization of *meta*-substituted arenes. We demonstrate that these transformations typically proceed with high (>20:1) selectivity and serve as a potentially valuable complement to widely practiced directed *ortho*-lithiation.[7]

The effect of *meta*-substitution on the regioselectivity of *ortho*-lithiation reactions of **1** has been well documented in the literature.[7] In general, substituents that can act as secondary chelating groups to a Li cation (e.g., OMe, OMOM, F, Cl) lead to highly selective formation of regioisomer **B**, whereas noncoordinating substituents (e.g., CH_3) afford the less sterically hindered product **A**.[7] The regioselectivity of Ru^0-catalyzed C−H activation/olefin addition reactions of *meta*-substituted aryl ketones has also been systematically explored and shown to proceed with selectivity similar to that of *ortho*-lithiation.[8] For example, when X is a potential ligand for Ru (e.g., X = OMe, F, OCH_2O), isomer **B** is obtained with modest to good regioselectivity, whereas when X is a noncoordinating substituent, **A** is the major product.[8−11] In contrast, as detailed above, analogous systematic studies of regioselectivity in the Pd^{II}-catalyzed C−H activation/functionalization of **1** have not been reported.[2−4,6]

Our initial studies in this area focused on the $Pd(OAc)_2$-catalyzed acetoxylation of a series of *meta*-substituted 2-phenylpyridine derivatives **2**−**8**. These substrates reacted cleanly with 5 mol % $Pd(OAc)_2$ and 1−3 equiv of $PhI(OAc)_2$ to produce mono-oxygenated products in good to excellent yields (Table 1). Notably, these reactions proceeded to completion in similar times (0.5−4 h) with electron-donating and electron-withdrawing *meta*-substituents; furthermore, comparable yields were obtained regardless of the electronic nature of X. In addition, a variety of functional groups, including aryl halides, ethers, benzylic hydrogens, nitro groups, and enolizable ketones, oximes, and amides (vide infra) were well-tolerated in these transformations.

Table 1. Palladium-Catalyzed Acetoxylation of 2-Arylpyridines[a]

entry	starting material	major product	yield	ratio of **A**:**B**
1	 (**2**)	 (**2a**)	60%	>20:1[b]
2	 (**3**)	 (**3a**)	81%	>20:1[b]
3	 (**4**)	 (**4a**)	59%	6:1[c]
4	 (**5**)	 (**5a**)	83%	>20:1[b]
5	 (**6**)	 (**6a**)	77%	27:1[d]
6	 (**7**)	 (**7a**)	76%	>20:1[b]
7	 (**8**)	 (**8a**)	78%	60:1[d]

[a] Conditions: 5 mol % $Pd(OAc)_2$, 1.1−3.0 equiv of $PhI(OAc)_2$, AcOH, C_6H_6, or C_6H_6/Ac_2O, 100 °C, 0.5−4 h. [b] A single regioisomer was observed by GC and ^1H NMR spectroscopy. [c] Ratio of **A**:**B** determined by ^1H NMR. [d] Ratio of **A**:**B** determined by GC.

The regioselectivity of acetoxylation was assessed using ^1H NMR spectroscopy and gas chromatography.[12] As summarized in Table 1, regioisomer **A** was obtained as the major product in synthetically useful ratios ranging from 6:1 (entry 3) to >20:1 (entries 1, 2, and 4−7). The electronic nature of the substituent did not have an appreciable effect on regioselectivity, and both electron-donating and electron-withdrawing groups afforded comparable preference for **A**. Furthermore, in contrast to directed *ortho*-lithiation[7] and to Ru-catalyzed C−H activation/olefin addition reactions,[8]

(7) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(8) Sonoda, M.; Kakiuchi, F.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 3117.

(9) Ru^0-catalyzed C−H activation/carbonylation generally shows higher selectivity for **A** [**A**:**B** > 20:1 except when X = F (2.5:1) and OCH_2O (1:5.5)]. This preference for **A** (in comparison to the analogous C−H activation/olefin additions) may be due to the high CO pressures (5−20 atm) used in these experiments, which are expected to limit the open sites at Ru for weak secondary coordination interactions. (a) Asaumi, T.; Matsuo, T.; Fukuyama, T.; Ie, Y.; Kakiuchi, F.; Chatani, N. *J. Org. Chem.* **2004**, *69*, 4433. (b) Ie, Y.; Chatani, N.; Ogo, T.; Marshall, D. R.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2000**, *65*, 1475. (c) Fukuyama, T.; Chatani, N.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **1997**, *62*, 5647. (d) Chatani, N.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **1997**, *62*, 2604.

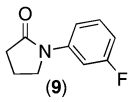
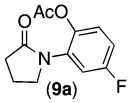
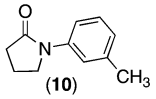
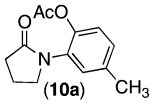
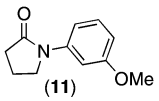
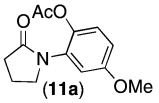
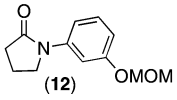
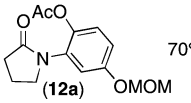
(10) Rh-catalyzed C−H activation/alkylation of aldimines proceeds to afford **A** as the major regioisomer with good selectivity except when X = F (**A**:**B** = 1:3). Lim, Y.-G.; Han, J.-S.; Koo, B. T.; Kang, J.-B. *J. Mol. Catal. A* **2004**, *209*, 41.

(11) For Ru-catalyzed pyridine-directed C−H activation/arylation, see: Oi, S.; Fukita, S.; Hirata, N.; Watanuki, N.; Miyano, S.; Inoue, Y. *Org. Lett.* **2001**, *3*, 2579.

(12) Authentic samples of a number of the products were prepared (particularly for **4a** and **18a/b**, where the regioselectivity was difficult to assess by ^1H NMR spectroscopy). See Supporting Information for full details.

substituents such as OMe, OMOM, and F did not exhibit secondary directing effects, and all resulted in clean and selective formation of **A**. Comparable levels of selectivity were also observed when the directing group was changed from a pyridine to a pyrrolidinone (Table 2); furthermore,

Table 2. Palladium-Catalyzed Acetoxylation of Aryl Pyrrolidinones[a]

entry	starting material	major product	yield	ratio of **A**:**B**
1	 (**9**)	 (**9a**)	88%[b]	14:1[c]
2	 (**10**)	 (**10a**)	74%	>20:1[d]
3	 (**11**)	 (**11a**)	73%	>20:1[d]
4	 (**12**)	 (**12a**)	70%	>20:1[d]

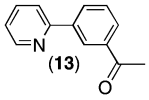
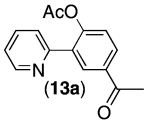
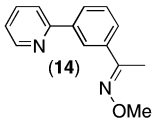
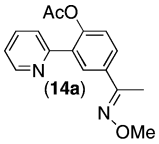
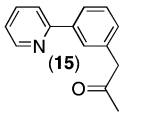
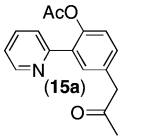
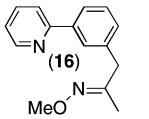
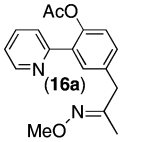
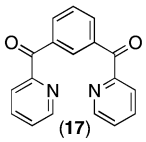
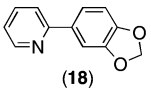
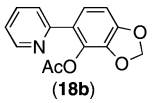
[a] Conditions: 5 mol % $Pd(OAc)_2$, 1.1−2.2 equiv of $PhI(OAc)_2$ in AcOH or $AcOH/Ac_2O$, 100 °C, 3−12 h. [b] Oxidant = $PhI(TFA)_2$ in $AcOH/Ac_2O$. [c] Ratio of **A**:**B** determined by GCMS. [d] A single regioisomer was observed by ^1H NMR and GC.

similar results have been reported for the C−H activation/oxidative arylation of related substrates.[2a] This preliminary data suggests that selectivity for **A** may be general over many classes of directing groups and types of Pd^{II}-catalyzed C−H activation/oxidative functionalization reactions.

We were intrigued by the lack of secondary directing effects with OMe, MOM, and halide substituents and felt that this could be due to (i) the poor ligand abilities of these groups for Pd^{II} and/or (ii) the unfavorable ring sizes (fused 4,5 ring systems) required for secondary coordination in these systems. As such, we next examined phenylpyridine derivatives **13**−**16** (Table 3), which (i) contain *meta*-ketone and oxime ether substituents (significantly better ligands for Pd^{II})[2b,13] and (ii) can form more favorable 5,5 or 5,6 ring systems upon coodination of the two directing groups. However, treatment of **13**−**16** with 5 mol % $Pd(OAc)_2$ and 1.5−1.8 equiv $PhI(OAc)_2$ afforded regioisomer **A** in >20:1 selectivity, indicating no coopertivity between the two potential ligands. Interestingly, a single regioisomeric product was detected even in substrates containing a pyridine and an oxime ether, which are each independently competent as directing groups (Table 3, entries 2 and 4). In both cases, the acetoxy group was installed adjacent to the pyridine moiety, suggesting that this ligand out-competes the oxime

(13) For representative examples of ketones acting as L-type ligands for Pd^{II}, see: (a) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360. (b) Nozaki, K.; Sato, N.; Takaya, H. *J. Am. Chem. Soc.* **1995**, *117*, 9911.

Table 3. Palladium-Catalyzed Acetoxylation of Substrates with Potential Dual Chelating Groups[a]

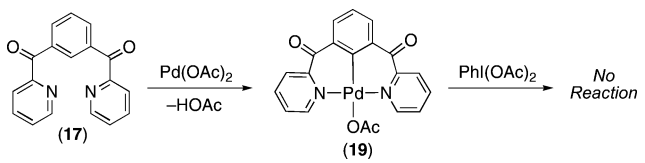
entry	starting material	major product	yield	ratio of **A**:**B**
1	 (**13**)	 (**13a**)	82%	>20:1[b]
2	 (**14**)	 (**14a**)	81%	>20:1[b]
3	 (**15**)	 (**15a**)	83%	>20:1[b]
4	 (**16**)	 (**16a**)	78%	>20:1[b]
5	 (**17**)	***No Reaction***		
6	 (**18**)	 (**18b**)	29%[d]	1:2[c]

[a] Conditions: 5 mol % $Pd(OAc)_2$, 1.5−1.8 equiv of $PhI(OAc)_2$, C_6H_6/Ac_2O, or C_6H_6, 100 °C. [b] A single regioisomer was observed by ^1H NMR and GC. [c] Ratio of **A**:**B** determined by GC. [d] Reaction carried out at 60 °C.

for binding the Pd^{II} catalyst. This result provides promising precedent that highly selective C−H bond oxygenation can be achieved in complex molecules containing multiple basic sites.

In a further attempt to obtain selectivity for isomer **B**, we explored substrate **17** (Table 3, entry 5), which contains two symmetrically disposed, strongly coordinating pyridine ligands. As shown in Scheme 2, **17** is known to undergo clean

Scheme 2. Synthesis and Stoichiometric Reaction of **19** with $PhI(OAc)_2$



stoichiometric C−H activation at $Pd(OAc)_2$ to afford regioisomer **B** in high yield.[14] However, treatment of **17** with catalytic $Pd(OAc)_2$ and 1.5 equiv of $PhI(OAc)_2$ returned

unreacted starting material as the sole organic product. In addition, no acetoxylated product was obtained when palladacycle **19** was subjected to stoichiometric oxidation with $PhI(OAc)_2$ (Scheme 2). These results suggest that dual chelation of the pyridine ligands (which is necessary for the selective formation of isomer **B**) effectively prevents the functionalization step required for catalyst turnover.

In a final effort to bias C−H activation/acetoxylation to the formation of isomer **B**, we examined *meta*-methylenedioxy substrate **18** (Table 3, entry 6). This cyclic acetal substituent has been shown to afford isomer **B** preferentially in some[3d] (but not all)[4b] related Pd^{II}-catalyzed C−H activation/C−C bond-forming reactions.[6a,15] When **18** was subjected to 5 mol % $Pd(OAc)_2$ and 1.2 equiv of $PhI(OAc)_2$, the acetoxylated product was obtained as a 2:1 mixture of regioisomers in favor of isomer **B**. The yield of **18a/b** was low (29%), but attempts at further optimization afforded significant amounts of the corresponding diacetoxylated product.[16] Nonetheless, to date substrate **18** remains a unique example of the selective formation of isomer **B** in $Pd(OAc)_2$-catalyzed C−H activation/acetoxylation.

The data presented above are generally consistent with a strong preference for Pd^{II}-mediated C−H activation to proceed at the less sterically congested site of *meta*-substituted substrates.[17] This steric effect appears to dominate in the presence of diverse substituents (including those that exert both resonance and inductive electron withdrawing and electron donating effects) and also typically overrides intramolecular secondary coordination by most ether, halide, ketone, and even oxime groups. The results obtained with substrates **4** and **9**, which show ≥6:1 preference for reaction adjacent to H versus F, are particularly remarkable, as these two atoms are sterically quite similar.[18] It appears that Pd^{II} is very sensitive to even minor steric perturbations in these systems. This steric preference can be overcome by the use of substrate **17**, which contains two strongly donating pyridine ligands; however, the tight chelation required to achieve selectivity prevents catalyst turnover.

Arylpyridine **18** is the only catalytically viable substrate that affords selectivity (albeit modest) for isomer **B**. Similar regioselectivity has been reported in the literature for the C−H activation of other *meta*-methylene dioxy-substituted arenes and has been rationalized on the basis of a secondary coordination interaction between the ether oxygen and the metal center.[3d,6a,15] The accessibility of this oxygen is proposed to be enhanced by the cyclic nature of the ether moiety, which decreases the effective size of the *meta*-substituent and may also render the oxygen lone pair more available.[3d] Current efforts are aimed at obtaining direct evidence for this secondary interaction to gain further insights into this unusual regioselectivity.

In conclusion, this paper describes Pd-catalyzed chelate-directed acetoxylation of *meta*-substituted arene substrates. These reactions show remarkably broad scope and functional group tolerance with respect to the *meta*-substituent on the arene. Additionally, they generally exhibit high levels of regioselectivity for functionalization at the less sterically hindered *ortho*-position. Ongoing studies in our laboratories aim to expand the scope and elucidate the mechanism of these reactions, and will be reported in due course.

Acknowledgment. We are grateful to the University of Michigan, the Arnold and Mabel Beckman Foundation, and the Camille and Henry Dreyfus Foundation for financial support of this research.

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

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(14) Canty, A. J.; Minchin, N. J.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Dalton Trans.* **1987**, 1477.

(15) This substituent also gives selectivity for **B** in Ru^0-catalyzed reactions and similar arguments have been invoked in these systems (see refs 8 and 9).

(16) The two regioisomers of **18a** react with 5 mol % $Pd(OAc)_2$ and $PhI(OAc)_2$ to form the diacetoxylated product at similar rates. Therefore, the observed selectivity appears to be inherent to the C−H activation reaction of **18** (rather than resulting from selective consumption of one of the regioisomers after it is formed).

(17) The regioselectivity of transition metal-mediated C−H activation reactions is frequently dominated by steric effects. For example, see ref 5d,g and refs 8−10.

(18) *Chemistry of Organofluorine Compounds 2*; Hudlicky, M., Pavlath, A. E., Eds.; American Chemical Society: Washington, DC, 1995.