ORGANIC LETTERS

2013
Vol. 15, No. 21
5428–5431

Steric Control of Site Selectivity in the Pd-Catalyzed C−H Acetoxylation of Simple Arenes

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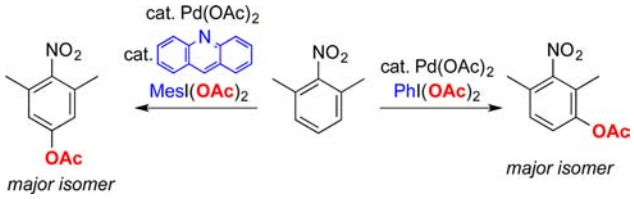
Received August 22, 2013

ABSTRACT



This report describes the use of an oxidant and a ligand to control site selectivity in the $Pd(OAc)_2$-catalyzed C−H acetoxylation of simple arenes. The use of $MesI(OAc)_2$ as the terminal oxidant in combination with acridine as the ligand results in primarily sterically controlled selectivity. In contrast, with $Pd(OAc)_2$ as the catalyst and $PhI(OAc)_2$ as the oxidant, electronic effects dominate the selectivity of arene C−H acetoxylation.

The ability to oxidatively transform carbon−hydrogen bonds into carbon−heteroatom bonds is highly desirable for the late-stage derivatization of complex molecules. Such transformations have the potential to greatly expedite the discovery and optimization of biologically active molecules including pharmaceuticals and agrochemicals.[1] However, the full potential of this strategy has not yet been realized, in large part due to the difficulty of controlling site selectivity.[2] For example, while many advances have been made in Pd-catalyzed ligand-directed C−H oxidation,[1−3] analogous nonchelate assisted transformations remain relatively poorly developed.[1−4] For example, the Pd-catalyzed C−H oxygenation of simple arenes is typically characterized by the formation of complex mixtures of isomers.[4,5] In many of these systems, the selectivity is governed by electronic factors, with C−H oxidation occurring preferentially at the more electron rich site(s) in the substrate.[4−6]

We recently reported that pyridine dramatically accelerates the $Pd(OAc)_2$-catalyzed C−H acetoxylation of simple arenes.[7−9] Pyridine is believed to serve as a ligand for Pd during this process, and the ratio of pyridine:Pd was found to be critical to high activity (an approximately 1:1 ratio was optimal). We hypothesized that, in addition to accelerating the rate of C−H acetoxylation, the ancillary ligand could also be used to influence the site selectivity of

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(6) Throughout this manuscript, discussions of selectivity governed by electronic factors refer to selectivity similar to that observed in electrophilic aromatic substitution reactions.

(7) (a) Gary, J. B.; Cook, A. K.; Sanford, M. S. *ACS Catal.* **2013**, *3*, 700. (b) Emmert, M. H.; Cook, A. K.; Xie, Y. J.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 9409.

(8) For similar effects of pyridine in oxidative C−H olefination, see: Kubota, A.; Emmert, M. H.; Sanford, M. S. *Org. Lett.* **2012**, *14*, 1760.

(9) For the use of substituted pyridine ligands in the *meta*-selective C−H olefination of electron-deficient arenes, see: (a) Zhang, Y. H.; Shi, B. F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072. (b) Zhang, S.; Shi, L.; Ding, Y. *J. Am. Chem. Soc.* **2011**, *133*, 20218.

10.1021/ol4024248
Published on Web 10/14/2013

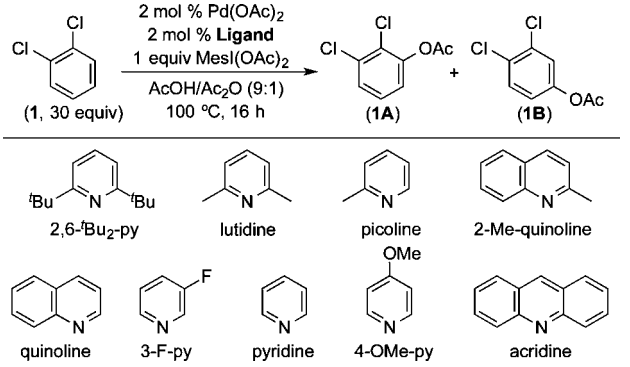
the reaction. Such ligand-modulated selectivity would provide opportunities for accessing different isomeric products by simply changing the catalyst structure.[2] Herein we report the realization of this strategy in the development of pyridine-based ligands that impart sterically controlled selectivity[10,11] in Pd-catalyzed C−H acetoxylation.

Our initial studies probed the effect of a series of pyridine-based ligands on the selectivity of the C−H acetoxylation of 1,2-dichlorobenzene (**1**) with $MesI(OAc)_2$.[12] Pyridine and its derivatives are highly attractive ligands for this chemistry, because: (1) they are generally not susceptible to oxidation by hypervalent iodine reagents, (2) they are known to increase the rate of C−H acetoxylation,[7b] and (3) they possess highly modular structures. The test substrate **1** was selected because it has two inequivalent arene C−H bonds that are electronically similar, but sterically dissimilar.[6] Furthermore, electron-deficient arenes such as **1** are traditionally difficult to functionalize via Pd-catalyzed C−H acetoxylation.[5,7b,13]

In the absence of added ligand, the $Pd(OAc)_2$-catalyzed reaction of **1** with $MesI(OAc)_2$ proceeded in low yield (19%) after 16 h at 100 °C (Table 1, entry 1). Acetoxylation at the less sterically hindered 4-position was weakly preferred under these ligand-free conditions (**1A**:**1B** = 29:71). A similar yield and selectivity were obtained in the presence of 2 mol % of 2,6-di-*tert*-butylpyridine (entry 2), suggesting that the very sterically hindered nitrogen atom does not bind to the Pd center. In contrast, other pyridine derivatives, including lutidine, picoline, quinoline, 3-fluoropyridine, 2-methylquinoline, pyridine, 4-methoxypyridine, and acridine (entries 3−10), all afforded large increases in yield and enhancements in selectivity for acetoxylation at the sterically less hindered 4-position.[14] Under these conditions, the best selectivity was obtained with acridine as the ligand (**1A**:**1B** = 5:95, entry 8).[15]

We next evaluated the influence of the acridine:Pd ratio on the reaction yield and site selectivity. As shown in Table 2, the addition of up to 6 mol % of acridine (3 equiv relative to Pd) led to further enhancements in selectivity (**1A**:**1B** = 2:98) with minimal deleterious effect on the overall reaction yield (entry 4). Further increases in acridine loading resulted in even better selectivity (> 1:99 at 20 mol % acridine, entry 7); however, the product yield was significantly lower under these conditions. Notably,

Table 1. Effect of Pyridine Ligands on Site Selectivity and Yield for the C−H Acetoxylation of 1,2-Dichlorobenzene[a]



entry	ligand	yield (%)	selectivity (**1A**:**1B**)
1	none	19	29:71
2	2,6-^{t}Bu$_2$-py	28	27:73
3	2,6-lutidine	76	11:89
4	2-picoline	84	8:82
5	quinoline	82	7:93
6	2-Me-quinoline	77	7:93
7	3-F-py	55	6:94
8	pyridine	71	6:94
9	4-OMe-py	59	6:94
10	acridine	78	5:95

[a] Yield and selectivity were determined by GC using a calibration curve based on PhCl as a standard.

the results with acridine stand in striking contrast to the effects observed upon increasing the loading of pyridine. As shown in entries 8−11 (Table 2), increasing the pyridine loading to 6 mol % led to a precipitous drop-off in yield. Overall, an acridine:Pd ratio of 3:1 provided the best balance of yield and selectivity and was thus used in all further experiments exploring the substrate scope.

Further studies revealed that the site selectivity of $Pd(OAc)_2$/acridine catalyzed C−H acetoxylation is substantially influenced by the nature of the oxidant.[7b,12] For instance, a significant erosion in selectivity is observed when $MesI(OAc)_2$ is replaced with $PhI(OAc)_2$. With 2 mol % of acridine and 2 mol % of $Pd(OAc)_2$, the **1A**:**1B** ratio was 5:95 with $MesI(OAc)_2$ and 19:81 with $PhI(OAc)_2$ as the oxidant. These results implicate a synergistic effect between the hypervalent iodine oxidant and the ligand.[16]

We next optimized the catalyst loading using trifluorotoluene (**2**). This was selected because it is a challenging substrate that typically shows low reactivity in Pd-catalyzed C−H oxidations.[7b,8,9] Thus, we anticipated that the trends observed in this system should be transferrable to a wide variety of other substrates. Varying the catalyst loading from 6 to 0.2 mol % $Pd(OAc)_2$ while keeping the

(10) For a recent example of Pd-catalyzed C−H amination where selectivity is dictated by substrate sterics, see: Shrestha, R.; Mukherjee, P.; Tan, Y.; Litman, Z. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 8480.

(11) For a review on sterically controlled selectivity in C−H borylation reactions, see: Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890.

(12) For preliminary studies of the influence of $MesI(OAc)_2$ [versus $PhI(OAc)_2$] on the site selectivity of C−H aectoxyation with the $Pd(OAc)_2$/pyridine catalyst system, see ref 7b.

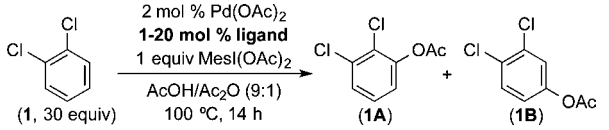
(13) Emmert, M. H.; Gary, J. B.; Villalobos, J. M.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 5884.

(14) Pyridine, 4-methoxypyridine, and 3-fluoropyridine afforded identical selectivity, suggesting that there is minimal ligand electronic effect on this reaction.

(15) A recent report by Hartwig and co-workers demonstrated sterically controlled selectivity in Pd-catalyzed C−H aminations of simple arenes (see ref 10). However, the supporting ligand had no effect on the site selectivity of the reaction in this system.

(16) Similar effects were seen with pyridine as the ligand. For example, with 2 mol % $Pd(OAc)_2$ and 2 mol % pyridine, the selectivity (**1A**:**1B**) using substrate **1** was 19:81 with $PhI(OAc)_2$ and 6:94 with $MesI(OAc)_2$. See Supporting Information Table S1B for more details.

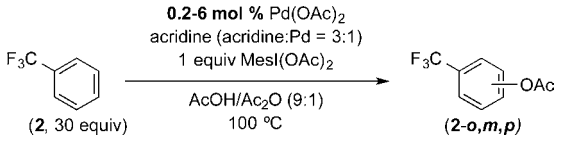
Table 2. Optimization of $Pd(OAc)_2$/Acridine-Catalyzed C−H Acetoxylation of 1,2-Dichlorobenzene



entry	ligand	ligand loading (mol %)	yield[a] (%)	selectivity[b] (1A: 1B)
1	acridine	1	79	10:90
2	acridine	2	78	5:95
3	acridine	3	78	5:95
4	acridine	6	76	2:98
5	acridine	8	68	1:99
6	acridine	10	66	1:99
7	acridine	20	29	>1:99
8	pyridine	1	62	9:91
9	pyridine	2	71	6:94
10	pyridine	3	56	7:93
11	pyridine	6	3	–[b]

[a] Yield and selectivity were determined by GC using a calibration curve based on PhCl as a standard. [b] The yield was too low for accurate determination of the selectivity.

Table 3. Optimization of Catalyst Loading[a]



entry	mol % Pd	yield (%)	TON
1[b]	6	21	3.5
2[b]	4	30	7.4
3[c]	2	35	18
4[b]	1	36	36
5[d]	0.5	44	88
6[e]	0.2	38	188

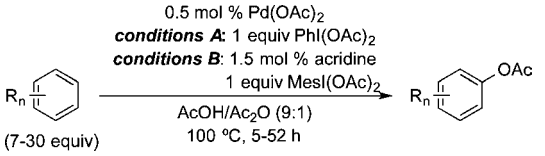
[a] Yields determined by GC using a calibration curve based on PhCl as a standard. In all cases, the *o*:*m*:*p* selectivity was 1:76:23. Reactions were generally stopped upon observation of Pd black, as our previous studies[7,8] have shown that this is indicative of the reaction cessation. [b] 22 h. [c] 21 h. [d] 49 h. [e] 120 h.

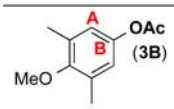
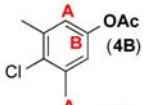
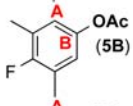
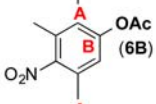
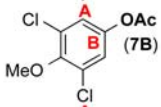
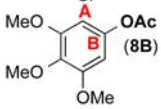
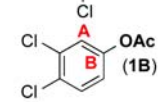
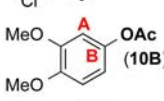
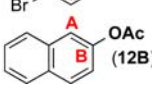
acridine:Pd ratio constant at 3:1 revealed that the reaction yield is highest at 0.5 mol % Pd (44% yield, corresponding to a TON of 88; Table 3, entry 5). As such, this catalyst loading was selected for subsequent experiments.[17]

With these optimized conditions in hand, we next explored the C−H acetoxylation of a variety of mono-, di-, and trisubstituted arene substrates (Tables 4 and 5). For each substrate we compared the ligand-free conditions

(17) Similar trends of ligand sterics, metal-to-ligand ratio, and catalyst loading were observed for all of the other substrates examined in these studies (see Supporting Information, Tables S4−S7 for details).

Table 4. $Pd(OAc)_2$/Acridine-Catalyzed C−H Acetoxylation of Tri- and Disubstituted Arenes[a]



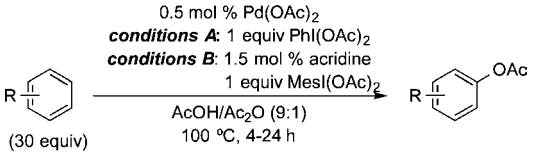
product (B shown)	yield (A:B selectivity) *conditions A*	yield (A:B selectivity) *conditions B*	isolated yield (A:B selectivity) *conditions B*
 (3B)	44% (47:53)	64% (17:83)	55% (19:81)
 (4B)	42% (65:35)	71% (22:78)	60% (5:95)
 (5B)	42% (59:41)	55% (24:76)	28% (22:78)
 (6B)	36% (81:19)	38% (39:61)	25% (41:59)
 (7B)	29% (61:39)	49% (8:92)	53% (2:98)
 (8B)	26% (87:13)	42% (28:72)	38% (<1:99)
 (9B)	17% (83:17)	56% (17:83)	42% (<1:99)
 (1B)	16% (44:56)	82% (4:96)	64% (2:98)
 (10B)	35% (17:83)	66% (4:96)	62% (<1:99)
 (11B)	51% (16:84)	82% (5:95)	38% (2:98)
 (12B)	69% (53:47)	88% (20:80)	60% (19:81)

[a] Yields and selectivities in columns 2 and 3 were determined by calibrated GC using PhCl or $PhCH_2C(CH_3)_3$ as a standard. ***Conditions A:*** 0.5 mol % $Pd(OAc)_2$, 1 equiv of $PhI(OAc)_2$. ***Conditions B:*** 0.5 mol % $Pd(OAc)_2$, 1.5 mol % acridine, 1 equiv of $MesI(OAc)_2$.

with $PhI(OAc)_2$ as the oxidant (***conditions A***) to the conditions with acridine as the ligand and $MesI(OAc)_2$ as the oxidant (***conditions B***).[18] In general, ***conditions A*** provided modest yields and poor site selectivities. With a few exceptions, the selectivity under ***conditions A*** was dominated by

(18) Reactions were also run using no ligand and $MesI(OAc)_2$ (see Supporting Information, Table S8 for details), and the resulting selectivities are intermediate between those observed in ***conditions A*** and ***conditions B***.

Table 5. $Pd(OAc)_2$/Acridine-Catalyzed C−H Acetoxylation of Monosubstituted Arenes[a]



product (major product shown)	yield (*o*:*m*:*p* selectivity) ***conditions A***	yield (*o*:*m*:*p* selectivity) ***conditions B***	isolated yield (*o*:*m*:*p* selectivity) ***conditions B***
OAc (**13**)	12%	94%	38%
MeO, OAc (**14*p***)	54% (46:6:51)	94% (12:40:48)	61% (13:24:63)
^{t}Bu, OAc (**15*m***)	51% (0:16:84)	99% (0:62:38)	68% (0:60:40)
Cl, OAc (**16*m***)	18% (26:27:47)	77% (5:52:43)	54% (3:49:48)
F_3C, OAc (**2*m***)	5% (3:74:23)	65% (3:75:22)	50% (<1:77:23)

[a] Yields and selectivities in columns 2 and 3 were determined by calibrated GC using PhCl or $PhCH_2C(CH_3)_3$ as a standard. ***Conditions A:*** 0.5 mol % $Pd(OAc)_2$, 1 equiv of $PhI(OAc)_2$. ***Conditions B:*** 0.5 mol % $Pd(OAc)_2$, 1.5 mol % acridine, 1 equiv of $MesI(OAc)_2$.

electronic factors,[6] with preferential functionalization at the most electron-rich sites in the molecule. In contrast, ***conditions B*** generally provided higher product yields. Furthermore, the selectivity was typically enhanced in favor of acetoxylation at the least sterically hindered C−H bond. In many cases (*e.g.*, **4**−**8** and **12**), a reversal in the favored isomer was observed upon moving from ***conditions A*** to ***conditions B***. For example, the C−H bond at the A-position of **8** is electronically activated, and acetoxylation is favored at this site in the absence of acridine (**8A**:**8B** = 81:19, ***conditions A*** of Table 4). In contrast, this electronic bias is overridden with the Pd/acridine system, and the major product is the B-isomer (**8A**:**8B** = 39:61, ***conditions B*** of Table 4).

Although the product ratios using Pd/acridine/$MesI(OAc)_2$ typically reflect a preference for acetoxylation at the least hindered site, this catalyst system does not effectively distinguish between the *meta*- and *para*-positions of monosubstituted arenes. For example, *ortho*-acetoxylation of anisole (**14**) and chlorobenzene (**16**) was dramatically suppressed under ***conditions B***, but a nearly 1:1 ratio of *meta* and *para* substituted products was formed (Table 5).

In conclusion, this report demonstrates the use of acridine as an ancillary ligand to control site selectivity in the $Pd(OAc)_2$-catalyzed C−H acetoxylation of simple arenes. In combination with $MesI(OAc)_2$ as the terminal oxidant, the $Pd(OAc)_2$/acridine system overrides the substrate electronic bias that dominates the site selectivity observed using ligand-free $Pd(OAc)_2$ as the catalyst and $PhI(OAc)_2$ as the oxidant. Instead, the site selectivity of acetoxylation using the $Pd(OAc)_2$/acridine/$MesI(OAc)_2$ system is primarily dictated by sterics for a variety of different substrates. Overall, catalyst-controlled selectivity through the use of ancillary ligands provides exciting new prospects for the field of Pd-catalyzed C−H oxidation.

Acknowledgment. This work was supported by the NSF under the CCI Center for Enabling New Technologies through Catalysis (CENTC) Phase II Renewal, CHE-1205189. We thank Professors Karen Goldberg (University of Washington), Bill Jones (University of Rochester), Mike Heinekey (University of Washington), Elon Ison (NCSU), and Tom Cundari (University of North Texas) for valuable discussions and input. A.K.C. thanks the Rackham Graduate School for a predoctoral fellowship.

Supporting Information Available. Experimental procedures 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.