ORGANIC LETTERS

2006
Vol. 8, No. 12
2523−2526

A Simple Catalytic Method for the Regioselective Halogenation of Arenes

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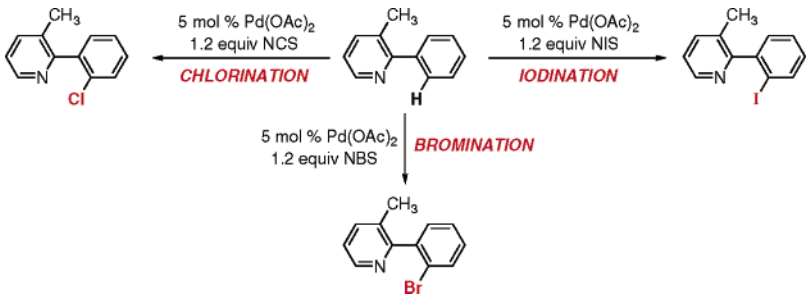
Received March 27, 2006

ABSTRACT



This paper describes a mild palladium-catalyzed method for the regioselective chlorination, bromination, and iodination of arene C–H bonds using *N*-halosuccinimides as oxidants. These transformations have been applied to a wide array of substrates and can provide products that are complementary to those obtained via conventional electrophilic aromatic substitution reactions.

Selectively halogenated arenes [halogen (X) = Cl, Br, or I] are extremely valuable starting materials for synthetic elaboration. Classically, these functional groups have been used as precursors to organolithium[1] and Grignard reagents[2] as well as in benzyne generation[3] and nucleophilic aromatic substitution.[4] More recently, aryl halides have also found widespread utility as substrates for Pd-, Ni-, and Cu-catalyzed cross-coupling reactions to form diverse C−C, C−N, C−O, and C−S bonds.[5,6] In addition, aryl chlorides, bromides, and iodides serve as important components of a wide array of biologically active molecules.[7]

The most common synthetic approach to halogenated arenes is electrophilic aromatic substitution (EAS),[8] using reagents such as *N*-halosuccinimides,[9a−c] X_2,[9d] peroxides/HX,[9e,f] peroxides/MX,[9g−j] or hypervalent iodine reagents/MX (M = Li, Na, K, or TMS).[9k,l] While these transformations are widely used, they suffer from several notable disadvantages, such as the following: (i) the substrate scope is often

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(2) *Handbook of Grignard Reagents*; Silverman, G. S., Rakita, P. E., Eds.; Dekker: New York, 1996.
(3) Levin, R. H. *React. Intermed. (Wiley)* **1985**, *3*, 1.
(4) Crampton, M. R. *Organic Reaction Mechanisms*; Wiley: New York, 2003; p 275.
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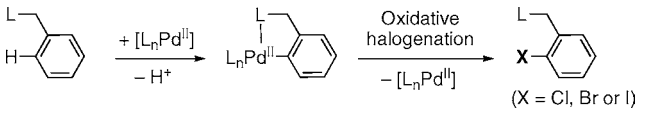
10.1021/ol060747f CCC: $33.50
Published on Web 05/19/2006

limited to activated arenes, (ii) side reactions including benzylic halogenation and overhalogenation of the arene are common, (iii) only a limited set of arene substitution patterns can be accessed, and (iv) multiple regioisomeric products are frequently obtained, resulting in decreased yields and the requirement for tedious separations.[8,9] Another important route to selectively halogenated arenes involves directed *ortho*-lithiation (DoL) followed by a halogen quench.[10] DoL reactions have found application in the construction of a variety of complex molecules;[11] however, their broad utility remains limited by the requirement for strong bases (which results in reduced functional group tolerance) and by the relatively narrow scope of suitable directing groups.

Due to the clear limitations of current methods, the development of new, simple, and complementary transition metal-catalyzed reactions for the selective halogenation of arenes would be highly desirable. In general, examples of the metal-catalyzed formation of arene C−X bonds remain rare, predominantly because carbon−halogen bond-forming reductive elimination is thermodynamically disfavored relative to aryl halide oxidative addition at most metal centers.[12] However, a number of reports have shown that stoichiometric C−X coupling can be achieved at Pd^{II} centers under oxidizing conditions, using oxidants such as X_2,[13a−d] CuX_2,[13e,f] peroxides/[TEBA]Cl (TEBA = triethylbenzylammonium chloride),[13g] or $PhICl_2$.[13h] In addition, several groups have demonstrated that Pd^{II}-catalyzed reactions can be terminated with an oxidative carbon−halogen bond-forming step.[14d,15] We sought to exploit such C−X couplings in the development of a general, Pd-catalyzed method for the halogenation of arene carbon−hydrogen bonds. As summarized in Scheme 1, we hoped to couple Pd-mediated ligand-directed C−H activation (a well-precedented transformation at Pd^{II} centers)[14] with oxidative halogenation of the resulting Pd^{II} carbon bond to release an aryl chloride, bromide, or iodide product.[14d,15a] We report herein that a variety of commercially available electrophilic halogenating reagents — particularly *N*-chloro-, *N*-bromo-, and *N*-iodosuccinimide—effectively mediate Pd-catalyzed arene halogenation; furthermore, these transformations can provide complementary products to those of classical EAS reactions.

Scheme 1. Pd-Catalyzed Ligand-Directed C−H Bond Halogenation



We began our studies by screening a series of electrophilic reagents for the Pd-catalyzed halogenation of 3-methyl-2-phenylpyridine (**1**) in two different solvents—AcOH and CH_3CN.[16] Importantly, control reactions (in the absence of palladium) were first carried out with each reagent and generally did not yield any halogenated products in AcOH or CH_3CN.[17] In contrast, in the presence of catalytic $Pd(OAc)_2$, most of these reagents afforded at least traces of **1-Cl**, **1-Br**, and **1-I**, with GC yields ranging from 0% to 87%. Interestingly, $PhICl_2$ (entry 5) afforded low conversion to the chlorinated product **1-Cl**; in contrast, similar iodine(III) reagents have served as highly effective oxidants in Pd-catalyzed C−H activation/acetoxylation and C−H activation/arylation reactions.[14,18] This surprising result is likely due to the instability of $PhICl_2$ under the reaction conditions.[19] The best overall yields in all cases were obtained using commercially available and inexpensive *N*-halosuccinimides as terminal oxidants.[20,21] Notably, NIS (entry 13) afforded a yield of **1-I** comparable to that of $I_2/PhI(OAc)_2$ (entry 14)—conditions recently reported for the Pd-catalyzed C−H activation/iodination of oxazoline derivatives.[15a] In general, similar results were obtained in MeCN and AcOH, although the yield of iodinated product **1-I** was reproducibly higher in MeCN. While the yields shown in Table 1 were obtained with 5 mol % of $Pd(OAc)_2$, reactions of **1** with *N*-halosuccinimides proceeded in comparable reaction times and GC yields (71%, 54%, and 90% for **1-Cl**, **1-Br**, and **1-I**, respectively) using as little as 1% catalyst loading.[22]

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

(11) For some recent examples, see: (a) Young, D. W.; Comins, D. L. *Org. Lett.* **2005**, *7*, 5661. (b) McCulloch, M. W. B.; Barrow, R. A. *Tetrahedron Lett.* **2005**, *46*, 7619. (c) Pradhan, T. K.; De, A.; Mortier, J. *Tetrahedron* **2005**, *61*, 9007.

(12) For example, K_{eq} for direct reductive elimination of haloarenes from Pd^{II} ranges from $\sim 10^{-5}$ (for Ar-I) to $\sim 10^{-2}$ (for Ar-Cl). See: Roy, A. H.; Hartwig, J. F. *Organometallics* **2004**, *23*, 1533 and references therein.

(13) (a) van Belzen, R.; Elsevier: C. J.; Dedieu, A.; Veldman, N.; Spek, A. L. *Organometallics* **2003**, *22*, 722. (b) Alsters, P. L.; Engel, P. F.; Hogerheide, M. P.; Marinus, P. H.; Copijn, M.; Spek, A. L.; van Koten, G. *Organometallics* **1993**, *12*, 1831. (c) Kubota, M.; Boegeman, S. C.; Keil, R. N.; Webb, C. G. *Organometallics* **1989**, *8*, 1616. (d) Wong, P. K.; Stille, J. K. *J. Organomet. Chem.* **1974**, *70*, 121. (e) Bäckvall, J. *Acc. Chem. Res.* **1983**, *16*, 335. (f) Bäckvall, J. *Tetrahedron Lett.* **1977**, *18*, 467. (g) Alsters, P. L.; Boersma, J.; van Koten, G. *Organometallics* **1993**, *12*, 1629. (h) Lagunas, M.-C.; Gossage, R. A.; Spek, A. L.; van Koten, G. *Organometallics* **1998**, *17*, 731.

(14) (a) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141. (b) Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, 7, 4149. (c) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542. (d) Dick, A. R.; Hull, K. L. Sanford, M. S. *J. Am Chem. Soc.* **2004**, *126*, 2300. (e) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330.

(15) (a) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112. (b) Lei, A.; Lu, X.; Liu, G. *Tetrahedron Lett.* **2004**, *45*, 1785. (c) Manzoni, M. R.; Zabawa, T. P.; Kasi, D.; Chemler, S. R. *Organometallics* **2004**, *23*, 5618. (d) El-Qisairi, A. K.; Qaseer, H. A.; Katsigras, G.; Lorenzi, P.; Trivedi, U.; Tracz, S.; Hartman, A.; Miller, J. A.; Henry, P. M. *Org. Lett.* **2003**, *5*, 439 and references therein. (e) Zhu, G.; Lu, X. *J. Organomet. Chem.* **1996**, *508*, 83 and references therein. (f) Henry, P. M. *J. Org. Chem.* **1971**, *36*, 1886. (g) Fahey, D. R. *J. Organomet. Chem.* **1971**, *27*, 283.

(16) An initial screen of the reaction of 2-phenylpyridine with NCS in 11 different solvents revealed that the highest yields were obtained in MeCN and AcOH. As a result, further investigations focused on these two solvents.

(17) The control reaction with $PhICl_2$ in AcOH afforded traces (5% by GC) of a monochlorinated product.

(18) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046.

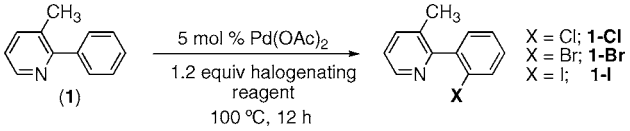
(19) Togo, H.; Sakuratani, K. *Synlett* **2002**, 1966.

(20) Notably, bromination of **1** with NBS (and bromination reactions in general) proceeded in lower yield than the analogous chlorinations or iodinations. The yield was independent of the source or quality (recrystallized versus nonrecrystallized) of the NBS. The predominant side products appeared to be traces of the corresponding dibrominated product along with mixtures of oxidatively coupled arylpyridines (dimers of **1**, heterodimers of **1** with **1-Br**, etc.). Interestingly, no acetoxylated side products were observed with NBS, even in AcOH.

(21) Low yields with some oxidants may be due to the formation PdX_2, which is both less soluble and less electrophilic than $Pd(OAc)_2$. See ref 15a.

(22) The use of 0.5 mol % of $Pd(OAc)_2$ in the reaction of **1** with NXS resulted in somewhat lower yields of **1-Cl**, **1-Br**, and **1-I** (60%, 41%, and 77% GC yield, respectively).

Table 1. Palladium-Catalyzed Halogenation of 2-Methyl-3-Phenylpyridine with Diverse Oxidants



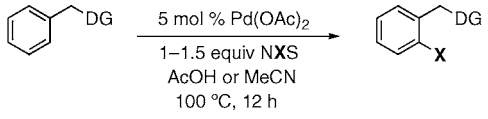
entry	halogenating reagent	product	GC yield in AcOH (%) (isolated yield, %)	GC yield in MeCN (%) (isolated yield, %)
1	NCS	**1-Cl**	60 (65)[b]	56
2	$Pb(OAc)_4/LiCl$[c]	**1-Cl**	63	51
3	Chloramine-T	**1-Cl**	56	36
4	$K_2Cr_2O_7/LiCl$[c]	**1-Cl**	42	0
5	$PhICl_2$	**1-Cl**	32	15
6	$CuCl_2$	**1-Cl**	21[a]	30[a]
7	NBS	**1-Br**	53 (56)[b]	44
8	$Br_2/PhI(OAc)_2$	**1-Br**	39	24
9	$Pb(OAc)_4/LiBr$[c]	**1-Br**	32	42
10	$K_2Cr_2O_7/LiBr$[c]	**1-Br**	15	8
11	Br_2	**1-Br**	0	26
12	$CuBr_2$	**1-Br**	0[a]	15[a]
13	NIS	**1-I**	64	87 (79)
14	$I_2/PhI(OAc)_2$	**1-I**	64	71
15	$K_2Cr_2O_7/LiI$[c]	**1-I**	44	0
16	$Pb(OAc)_4/LiI$[c]	**1-I**	37	0
17	I_2	**1-I**	0	40

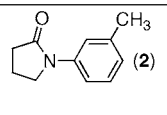
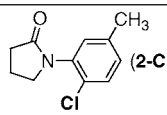
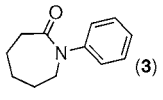
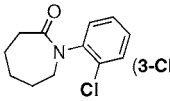
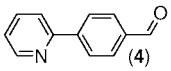
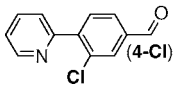
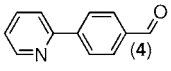
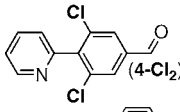
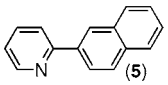
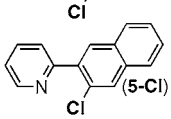
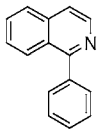
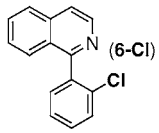
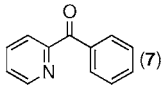
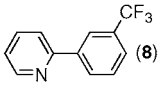
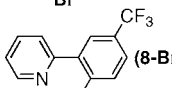
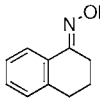
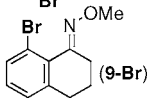
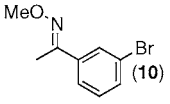
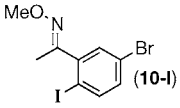
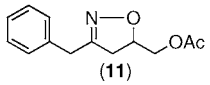
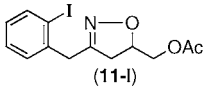
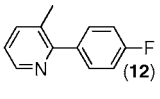
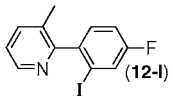
[a] With 2.4 equiv of halogenating reagent. [b] Isolated yield obtained from reaction conducted at 120 °C. [c] With 2 equiv of LiX.

As summarized in Table 2, the Pd-catalyzed chelate-directed halogenation of arenes with *N*-halosuccinimides could be extended to a variety of substrates. In general, these halogenation reactions exhibited scope and functional group tolerance comparable to analogous Pd-catalyzed C−H activation/acetoxylation[14a−d] and C−H activation/arylation[14e,18] reactions. Pyridines (entries 3−5, 7, 8, 12), oxime ethers (entries 9, 10), isoquinolines (entry 6), amides (entries 1, 2), and isoxazolines (entry 11) were successfully employed as directing groups. Additionally, the reactions were tolerant of aryl halides (entries 10, 12), enolizable oxime ethers (entries 9, 10), and esters (entry 11), as well as oxidizable functionalities, such as aromatic aldehydes (entries 3, 4) and benzylic methylene groups (entries 9, 11). Importantly, these reactions were readily scalable; for example, a 15 g (82 mmol) scale reaction of substrate **7** with NBS afforded a yield of **7-Br** (56%) comparable to that obtained on the 1.4 mmol scale (entry 7).

In substrates containing two readily accessible *ortho*-C−H bonds, only modest yields of the monohalogenated products were obtained (e.g., Table 2, entry 3), due to competitive formation of the corresponding di-*ortho*-halogenated compound. These di-*ortho*-halogenated products could be isolated cleanly and in good yields by the use of excess (∼2.5 equiv) oxidant under otherwise identical conditions (for example, Table 2, entry 4). The tendency for facile bis-*ortho*-halogenation could be attenuated in several ways. For example, placing a *meta* substituent on the arene ring resulted

Table 2. $Pd(OAc)_2$-Catalyzed Directed Halogenation of Arenes



entry	starting material	product	yield
1	 (**2**)	 (**2-Cl**)	81%[a]
2	 (**3**)	 (**3-Cl**)	77%[a]
3	 (**4**)	 (**4-Cl**)	57%[b,c]
4	 (**4**)	 (**4-Cl$_2$**)	72%[b–d]
5	 (**5**)	 (**5-Cl**)	82%[b]
6	 (**6**)	 (**6-Cl**)	53%[a]
7	 (**7**)	 (**7-Br**)	56%[a,c]
8	 (**8**)	 (**8-Br**)	63%[a,c]
9	 (**9**)	 (**9-Br**)	62%[a]
10	 (**10**)	 (**10-I**)	57%[a]
11	 (**11**)	 (**11-I**)	54%[a]
12	 (**12**)	 (**12-I**)	70%[a]

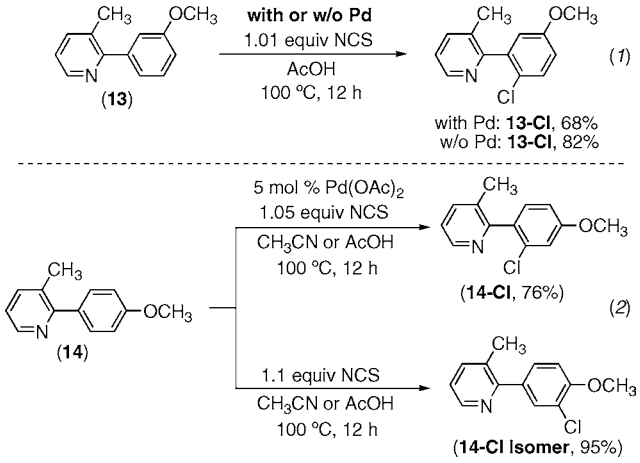
[a] In AcOH. [b] In MeCN. [c] At 120 °C. [d] With 2.5 equiv of NCS.

in selective monohalogenation at the less sterically hindered *ortho* position (entries 1, 8, 10).[14b] The second *ortho*-halogenation was slowed dramatically in these systems, presumably due to unfavorable steric interactions during palladation of the more hindered *ortho*-C−H bond. Similar results were obtained with the naphthyl-substituted substrate **5**, in which chlorination occurs at the less hindered 3′ position despite the fact that the 1′ position is more nucleophilic. This high sensitivity to the steric environment of the aromatic ring

appears to be general for a variety of Pd-catalyzed directed C−H activation/oxidative functionalization reactions.[14a,b,e]

In biaryl systems, dihalogenation could also be controlled by placing a substituent adjacent to the biaryl junction (for example, the 3-methyl group of pyridine substrates **1** and **12** or the fused phenyl ring of isoquinoline substrate **6**). After the first C−H activation/halogenation reaction takes place, this substituent experiences unfavorable steric interactions with the halogen, making it energetically unfavorable for the two aryl rings to achieve coplanarity (which is required for palladation to take place).[23] As a result, a second C−H activation/halogenation reaction is dramatically slowed or completely inhibited. This is exemplified by the fact that the isolated monohalogenated products **1-Cl**, **1-Br**, and **1-I** showed very low reactivity toward a second functionalization; in fact, even under forcing conditions (5 mol % of $Pd(OAc)_2$, 2 equiv of NXS, AcOH, 120 °C), these reactions afforded <35% conversion to the corresponding dihalogenated compounds. The lowest conversion (<5%) was obtained with **1-I**, consistent with the large size of this substituent exacerbating the unfavorable steric interactions at the biaryl junction.[23]

An important feature of these palladium-catalyzed directed C−H activation/halogenation reactions is that they can frequently outcompete alternative and more conventional uncatalyzed transformations. As shown in eq 1, the electron-rich substrate **13** reacts with NCS under our standard reaction conditions to afford product **13-Cl**[24] with or without the $Pd(OAc)_2$ catalyst. This is because both electrophilic aromatic substitution and pyridine-directed halogenation favor the same product. However, in substrate **14**, there is a mismatch in the products favored by the catalyzed versus the uncatalyzed reactions. Under the uncatalyzed conditions, electrophilic aromatic substitution predominates, leading to the selective formation of product **14-Cl isomer** (eq 2). However, in the presence of $Pd(OAc)_2$, the relative rate of catalytic C−H activation/halogenation is significantly faster than that of the corresponding uncatalyzed EAS reaction. As a result, chlorinated product **14-Cl** is obtained cleanly as a single isomer (eq 2). This further augments the utility of this methodology because it allows access to halogenated products that are complementary to those obtained using traditional synthetic methods.



In summary, we have shown that Pd-catalyzed chelate directed C−H activation/halogenations proceed efficiently using simple, inexpensive, and readily available *N*-halosuccinimides as terminal oxidants. These transformations provide access to a wide array of selectively chlorinated, brominated, and iodinated arenes. Further exploration of the full scope of these reactions, as well as their extension to alkane and alkene substrates is underway and will be reported in due course.

Acknowledgment. We thank the NIH NIGMS (RO1-GM073836-01), the University of Michigan, the Camille and Henry Dreyfus Foundation, and the Arnold and Mabel Beckman Foundation for support. Unrestricted support from Amgen, Boehringer Ingelheim, Eli Lilly, and Merck Research Laboratories is also gratefully acknowledged. Additionally, A.R.D. thanks Eli Lilly for a graduate fellowship, and W.Q.A. is grateful for a Margaret and Henry Sokol undergraduate summer research fellowship.

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.

OL060747F

(23) (a) Oi, S.; Fukita, S.; Hirata, N.; Watanuki, N.; Miyano, S.; Inoue, Y. *Org. Lett.* **2001**, *3*, 2579 and references therein; (b) Chatani, N.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **1998**, *62*, 2604.

(24) GC analysis of the isolated product showed ~10% of a regioisomeric product both with and without Pd.