ORGANIC LETTERS

2009
Vol. 11, No. 6
1357−1360

Site-Selective Azaindole Arylation at the Azine and Azole Rings via *N*-Oxide Activation

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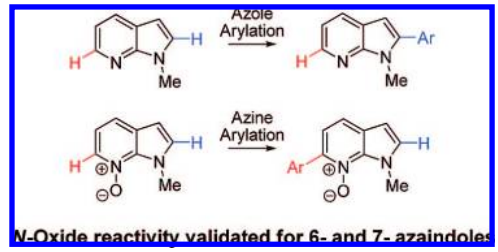
Received January 23, 2009

ABSTRACT



Subjection of *N*-methyl 6- and 7-azaindole *N*-oxides to a $Pd(OAc)_2$/DavePhos catalyst system enables regioselective direct arylation of the azine ring. Following deoxygenation, 7-azaindole substrates undergo an additional regioselective azole direct arylation event in good yield.

In the past decade, direct arylation has emerged as an increasingly viable alternative to traditional cross-coupling techniques.[1] In these reactions, the organometallic reagent of traditional cross-coupling reactions is replaced by a simple arene (Ar-H), thus minimizing the number of synthetic manipulations prior to cross-coupling. A number of arenes have been shown to participate in these transformations, including electron-rich[2] and electron-deficient heterocycles,[3] as well as simple benzenes.[4] As the opportunities for reactivity grow, a greater emphasis on understanding and controlling site-selectivity will become possible. Such advances are of particular value because they can enable a rapid increase in molecular complexity with a minimal amount of synthetic expenditure. As part of a program dedicated to the development of novel direct arylation reactions, we became interested in the use of azaindole compounds. Azaindoles, which possess the same [4.3]-bicyclic indene architecture as indoles but with a second nitrogen in the azine ring (Figure 1),

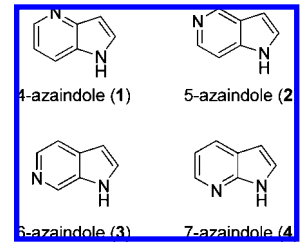


Figure 1. Azaindoles (pyrrolo[2,3]pyridines).

have demonstrated importance in medicinal chemistry.[5] Compared to indoles, however, they are far more challenging

(1) Recent reviews on direct arylation: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35. (c) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (d) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (e) Lewis, J. C.; Bergman, R. C.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (f) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949. (g) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2007**, 3382. (h) Pascual, S.; de Mendoza, P.; Echavarren, A. M. *Org. Biomol. Chem.* **2007**, *5*, 2727. (i) Catellani, M.; Motti, E.; Della Ca', N.; Ferraccioli, R. *Eur. J. Org. Chem.* **2007**, 4153.

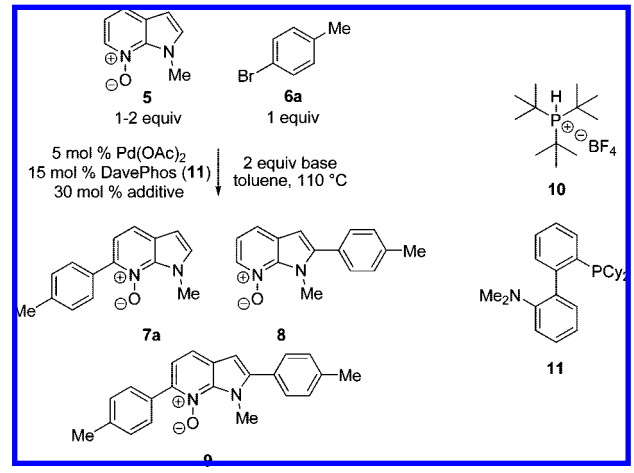
10.1021/ol900150u CCC: $40.75
Published on Web 02/18/2009

to prepare, especially in highly functionalized form.[6] In the context of direct arylation, a C2 arylation of 7-azaindole has been described,[7] but methods for the direct functionalization of the azine ring have not been forthcoming.

Because azaindoles have electron-rich azole and electron-deficient azine ring systems, we wondered if it might be possible to capitalize on recent advances in direct arylation methods to selectively functionalize both rings in a controlled fashion. Herein, we describe that, by employing *N*-oxide azine activation,[8] both 7- and 6-azaindoles undergo regioselective direct arylation at the azine ring. We have also found that, by modifying the Larrosa arylation protocol[9] slightly (heating to 80 °C), highly selective C2 arylation can be induced, offering a divergent method for the preparation of polyaromatic compounds based on an azaindole core. These studies point to new opportunities for the site-selective functionalization of useful organic building blocks and may find application in the preparation of novel medicinal compounds.

Initial optimization studies were performed with *N*-methyl-7-azaindole *N*-oxide **5** and 4-bromotoluene **6a** as cross-coupling partners. Under previously reported conditions for azine *N*-oxides,[8f] only 5% NMR yield was obtained favoring the formation of regioisomer **7a** (Table 1, entry 1). In subsequent work, particularly promising results were obtained when utilizing palladium(II) acetate, Buchwald phosphine ligands,[10] and carbonate bases. For example, by employing DavePhos **11**[11] in a 3:1 ligand-to-metal ratio, the NMR yield of **7a** could be increased to 24% (entry 2). The use of cesium carbonate instead of potassium carbonate as base was found to further increase the yield to 37% (entry 3). Increasing the concentration from 0.3 to 0.5 M also provided an improvement to 52% NMR yield (entry 4), and a 57% yield could be reached by the addition of 30 mol %

Table 1. Optimization of Azine Arylation on *N*-Methyl-7-azaindole *N*-Oxide **5**[a]



entry	base	additive	equiv of **5**	molarity	yield (**7a**:**8**:**9**)[b]
1	K_2CO_3	none	1	0.3	5:1:0[c]
2	K_2CO_3	none	1	0.3	24:2:1
3	Cs_2CO_3	none	1	0.3	37:4:6
4	Cs_2CO_3	none	1	0.5	52:4:5
5	Cs_2CO_3	PivOH	1	0.5	57:1:4
6	Cs_2CO_3	none	2	0.5	65:6:4
7	Cs_2CO_3	PivOH	2	0.5	87:7:0[d]

[a] Conditions: aryl halide (1 equiv), *N*-oxide (1 or 2 equiv), base (2 equiv), $Pd(OAc)_2$ (5 mol %), ligand (15 mol %), and PivOH (0 or 30 mol %) were weighed into a vial, purged with argon, charged with toluene (0.3 or 0.5 M), and stirred at 110 °C overnight. [b] Determined by NMR analysis relative to 1,3,5-trimethoxybenzene as an internal standard. [c] Compound **10** used as ligand. [d] Isolated yields, 35% recovered **5**.

(2) For recent examples, see: (a) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (b) Lewis, J. C.; Berman, A. M.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 2493. (c) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. (d) Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *Tetrahedron* **2008**, *64*, 6073. (e) Ackermann, L.; Vicente, R.; Born, R. *Adv. Synth. Catal.* **2008**, *350*, 741. (f) Bellina, F.; Cauteruccio, S.; Rossi, R. *Eur. J. Org. Chem.* **2006**, 1379. (g) Bellina, F.; Benelli, F.; Rossi, R. *J. Org. Chem.* **2008**, *73*, 5529. (h) Flegeau, E. F.; Popkin, M. E.; Greaney, M. F. *Org. Lett.* **2008**, *10*, 2717. (i) Martin, T.; Verrier, C.; Hoarau, C.; Marsais, F. *Org. Lett.* **2008**, *10*, 2909. (j) Ban, I.; Sudo, T.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 3607. (k) Wang, X.; Gribkov, D. V.; Sames, D. *J. Org. Chem.* **2007**, *72*, 1476. (l) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972. (m) Wang, J. X.; McCubbin, J. A.; Jin, M.; Laufer, R. S.; Mao, Y.; Crew, A. P.; Mulvihilland, M. J.; Snieckus, V. *Org. Lett.* **2008**, *10*, 2923. (n) Yang, S.-D.; Sun, C.-L.; Fang, Z.; Li, B.-J.; Li, Y.-Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2007**, *47*, 1473. (o) Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 201.

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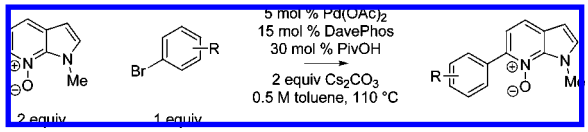
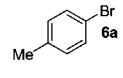
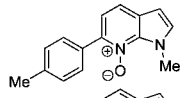
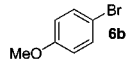
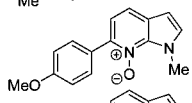
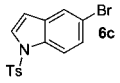
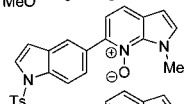
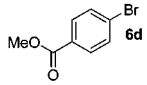
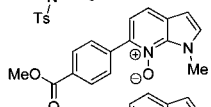
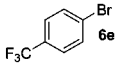
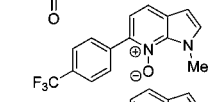
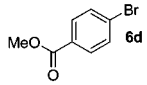
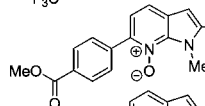
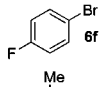
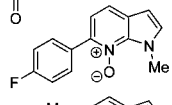
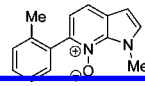
(11) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.

pivalic acid[12] (entry 5). With these conditions in hand, the influence of reagent stoichiometry was evaluated. These studies revealed that through the use of 2 equiv of *N*-oxide **5** a 65% NMR yield could be obtained (entry 6). Finally, if 30 mol % pivalic acid is added to the reaction mixture, **7a** can be obtained in 87% isolated yield (Table 1, entry 7).

Illustrative examples of the scope for C6 arylation of *N*-methyl-7-azaindole *N*-oxide **5** under standard reaction conditions are included in Table 2. In each case, no

Table 2. Scope of *N*-Methyl-7-azaindole *N*-Oxide **5** Azine Arylation[a]



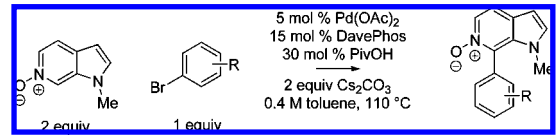
entry	aryl bromide	product	% yield
1	 **6a**	 **7a**	87%
2	 **6b**	 **7b**	54%[b]
3	 **6c**	 **7c**	68%
4	 **6d**	 **7d**	53%[b]
5	 **6e**	 **7e**	65%
6	 **6d**	 **7f**	56%[c]
7	 **6f**	 **7g**	62%
8	 **6g**	 **7h**	46%

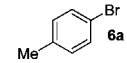
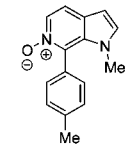
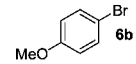
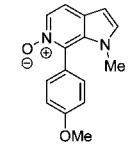
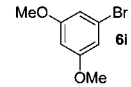
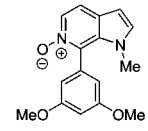
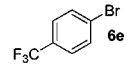
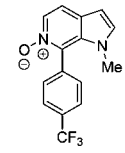
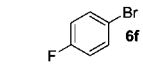
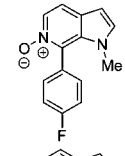
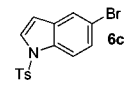
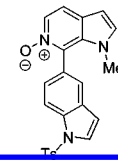
[a] Conditions: aryl halide (1 equiv), *N*-oxide (2 equiv), Cs_2CO_3 (2 equiv), $Pd(OAc)_2$ (5 mol %), DavePhos (15 mol %), and PivOH (30 mol %) were weighed into a vial, purged with argon, charged with toluene (0.5 M), and stirred at 110 °C overnight. [b] Three equivalents of *N*-oxide used. [c] *N*-Oxide reactant was compound **8** (see Table 1).

re-optimization of the reaction conditions was performed, which may result in improved yields in each instance if carried out. The transformation is equally compatible with electron-donating and electron-withdrawing substituents (entries 2 and 4−7). 4-Bromoanisole can be cross-coupled in 54%, while methyl 4-bromobenzoate results in 53% yield (entries 2 and 4). Entries 5 and 7 demonstrate that the reaction works well with fluorinated aryl bromides (65% for *p*-CF_3 and 62% for *p*-F). Sterically encumbered aryl halides are compatible, albeit in lower yield (46%, entry 8). A bis-indole compound could also be assembled in 68% yield (entry 3), providing access to polycyclic heteroaromatic compounds.

The remaining three isomeric *N*-methyl azaindole *N*-oxide[13] coupling partners were also synthesized and evaluated under the conditions established for the 7-azaindole substrate. Although those derived from 4- and 5-azaindole (**1** and **2**) displayed minimal reactivity under the newly reoptimized conditions, *N*-methyl-6-azaindole *N*-oxide **12** and *p*-tolyl bromide **6a** reacted to give the C7 cross-coupled product in 62% yield (Table 3, entry 1).

Table 3. Scope of *N*-Methyl-6-azaindole *N*-Oxide **12** Azine Arylation[a]



entry	aryl bromide	product	% yield
1	 **6a**	 **13a**	62%[b]
2	 **6b**	 **13b**	68%
3	 **6i**	 **13i**	70%
4	 **6e**	 **13e**	57%
5	 **6f**	 **13g**	60%
6	 **6c**	 **13c**	55%

[a] Conditions: aryl halide (1 equiv), *N*-oxide (2 equiv), Cs_2CO_3 (2 equiv), $Pd(OAc)_2$ (5 mol %), DavePhos (15 mol %), and PivOH (30 mol %) were weighed into a vial, purged with argon, charged with toluene (0.4 M), and stirred at 110 °C overnight. [b] No PivOH added.

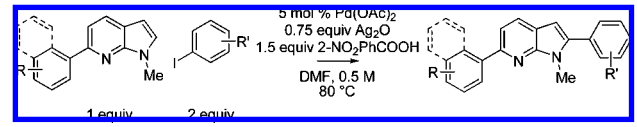
As with the 7-azaindole analogue, electron-donating (Table 3, entries 2 and 3) and inductively withdrawing substituents

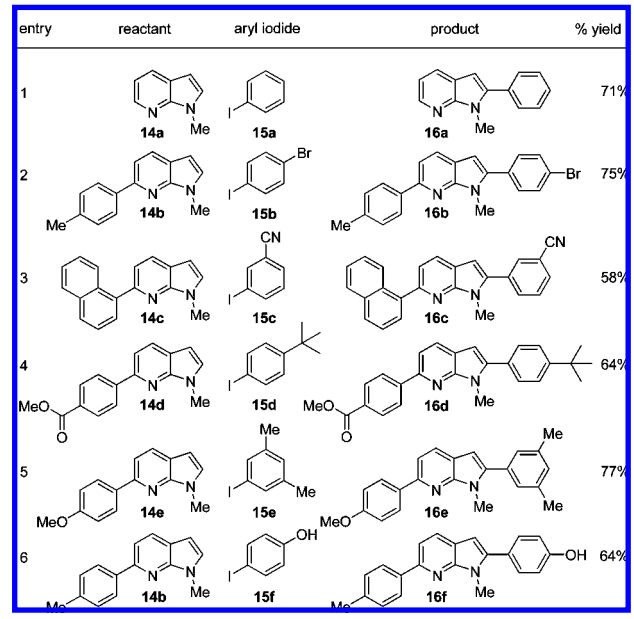
(entries 4−6) are compatible. Aryl halides possessing methoxy substituents were particularly reactive, giving yields of 68% and 70% for 4-methoxy and 3,5-dimethoxy aryl bromides, respectively (entries 2 and 3). As exemplified by entries 4 and 5, fluorinated aryl halides readily participate in direct arylation, furnishing 57% yield for *p*-CF_3 and 60% yield for *p*-F (entries 4 and 5). Again, a 5-bromoindole could be cross-coupled in acceptable yield (55%, entry 6). It is important to note that in addition to other modes of reactivity that the *N*-oxide moiety enables, it may also be easily cleaved by zinc dust[14] to afford the arylated azaindoles in yields ranging from 84% to quantitative.[15]

Drawing from direct arylation reaction conditions that have been shown to functionalize the conventional indole nucleus, we then explored arylation of the azole ring of azaindoles. In preliminary screens, unsatisfactory outcomes were obtained with *N*-oxide substrates. Consequently, *N*-methyl-7-azaindole **14a** was investigated as the coupling partner, in conjunction with the use of palladium(II) catalysts and boronic acids,[2n] palladium(0) catalysts with aryl iodides,[7,9] and palladium(II)[2l] or copper(II)[2c] catalysts with iodine(III) reagents. In no case was arylation detected at the azine ring, with varying reactivity being observed at C2/C3 of the azole moiety. For example, reactions using copper gave no conversion to product,[16] while those with Pd(0) and boronic acids gave low conversions upon heating (∼30% by GCMS). On the other hand, good conversion was seen with no modification to the originally reported conditions for reaction with Pd(0) and aryl iodides[7] (75% by GCMS), but an inseparable mixture of C2/C3 isomers (10:1) was obtained. Similarly, at 110 °C, Pd(II) and iodine(III) reagents[2l] provided exclusively the C2 arylated product, using 10 mol % Pd catalyst and 3 equiv of iodine(III) reagent. While the conditions described by Larrosa[9] initially provided only 6% conversion by GCMS, a survey of the reaction components revealed that by simply heating the reaction mixture to 80 °C with no other modifications, arylation of *N*-methyl-7-azaindole was achieved in 71% isolated yield with complete C2 regioselectivity (Table 4, entry 1).

The Larrosa arylation conditions are robust and exhibit broad scope as illustrated in Table 4. Yields of up to 77% were obtained with electron-neutral aryl iodides (entries 4 and 5). We were also able to employ arenes possessing cyano

Table 4. Scope of *N*-Methyl-7-azaindole Azole Arylation[a]





[a] Conditions: Azaindole (1 equiv), aryl iodide (2 equiv), $Pd(OAc)_2$ (5 mol %), silver(I) oxide (0.75 equiv), and 2-nitrobenzoic acid (1.5 equiv) were weighed into a vial, purged with argon, charged with DMF (0.5 M), and stirred at 80 °C overnight.

(58%) and phenolic (64%) functional groups (entries 3 and 6, respectively). Furthermore, 1-bromo-4-iodobenzene was selective for reaction at the iodo functional group, preserving the aryl bromide handle intact in the product (entry 2).

In conclusion, the regioselective direct arylation of the azaindole core can be achieved by making use of both the *N*-oxide activation strategy and the Larrosa arylation protocol. Validation of this reactivity should prompt a consideration of the direct arylation method with other substrate classes, where multiple reaction sites may be available for diversification.

Acknowledgment. NSERC, the University of Ottawa, the Sloan Foundation, the Research Corporation, Merck-Frosst, Amgen, Eli Lilly, Astra Zeneca, and Boehringer Ingelheim are thanked for financial support.

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

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(12) (a) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826−1834. (b) Liégault, B.; Fagnou, K. *Organometallics* **2008**, *27*, 4841. (c) Liégault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008**, *73*, 5022–5028. (d) Lafrance, M.; Lapointe, D.; Fagnou, K. *Tetrahedron* **2008**, *64*, 6015. (e) Watanabe, T.; Oishi, S.; Fujii, N; Ohno, H. *Org. Lett.* **2008**, *10*, 1759. (f) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570. See also refs 2o, 3c, and 4b.

(13) Standard IUPAC names: 1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (**5**), 1-methyl-1*H*-pyrrolo[2,3-*c*]pyridine 6-oxide (**12**), 1-methyl-1*H*-pyrrolo[3,2-*c*]pyridine 5-oxide, 1-methyl-1*H*-pyrrolo[3,2-*b*]pyridine 4-oxide.

(14) Aoyagi, Y.; Abe, T.; Ohta, A. *Synthesis* **1997**, 891.

(15) See Supporting Information for examples and experimental procedures.

(16) We postulate that catalyst inhibition may be occuring via substrate binding through the azine nitrogen atom.