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Palladium-Catalyzed Benzylic Arylation of 2-Methyl Azaarenes

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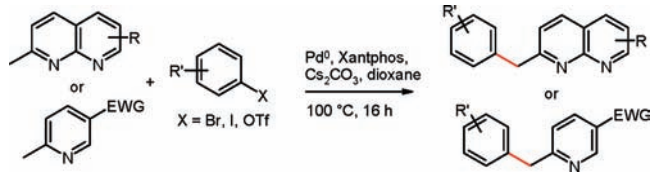
ABSTRACT



A palladium-catalyzed benzylic sp^3 direct arylation of electron-deficient heterocycles is reported. The method described enables the introduction of electron-rich and -poor aromatics at the benzylic position of heterocycles without the need for preactivation or the use of directing groups.

Naphthyridine derivatives show an exceptionally broad range of biological activities, ranging from the treatment of human diseases to their use as pesticides.[1a] Of the many isomeric pyridopyridines, the 1,8-naphthyridines have been by far the most studied subclass (Figure 1).[1] Synthetic methodologies that allow the rapid and late-stage derivatization of this class of molecule are thus highly attractive in research and optimization of new pharmaceuticals and agrochemicals.

Transition-metal-catalyzed direct arylation of C−H bonds is now a well-established method for the formation of sp^{2}C−sp^{2}C bonds and enjoys a broad reaction scope.[2] In contrast, the direct arylation of sp^{3}C−H bonds is less widely established. Examples are generally limited to either chelation-assisted sp^{3}C−H arylation[3] or preactivation of heteroaromatic systems through the use of *N*-oxides[4] or *N*-imino ylides.[5]

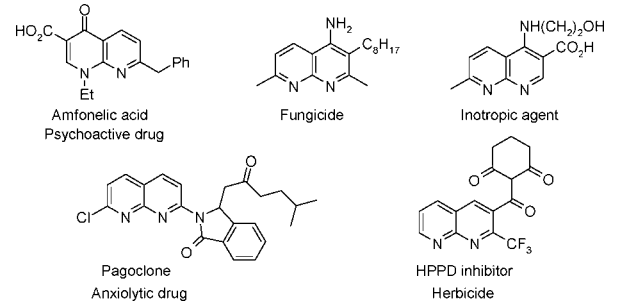


Figure 1. Bioactive 1,8-naphthyridines.

Due to our ongoing interest in naphthyridines,[1d] we sought to prepare 2-benzyl-1,8-naphthyridine analogues by a route amenable to 2-methyl-arylation at a late stage in the synthesis. To this end, we report herein a general palladium-catalyzed direct arylation of 2-methyl naphthyridines which can be extended to sp^{3}C−H arylation in other electron-deficient heteroaryl scaffolds.

Exploratory studies for the coupling of substituted 2-methyl-1,8-naphthyridines with aryl halides under palladium catalysis were promising. We established dioxane to be the preferred solvent and found cesium carbonate to be a suitable

(1) (a) Litvinov, V. P. *Adv. Heterocycl. Chem.* **2006**, *91*, 189–300. (b) Atack, J. R. *Curr. Drug Target CNS Neurol. Disord.* **2003**, *2*, 213–232. (c) Fuller, R. W.; Bymaster, F. P.; Perry, K. W.; Wong, D. T. *J. Pharm. Pharmacol.* **1978**, *30*, 464–466. (d) Mitchell, G.; Salmon, R.; Bacon, D. P.; Aspinall, I. H.; Briggs, E.; Avery, A. J.; Morris, J. A.; Russell, C. J. W.O. Patent No. 2009/115788, 2009.

(2) For selected reviews in this area, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (b) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074–1086. (c) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792–9826. (d) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169.

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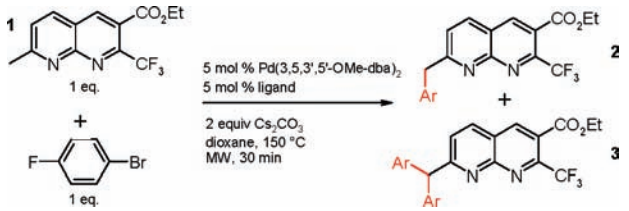
and mild base.[6] The use of stronger bases such as potassium *t*-butoxide gave a complex mixture of products.

We initiated a ligand screen employing equimolar amounts of the naphthyridine **1**[1d] and 1-bromo-4-fluorobenzene as model coupling partners (table 1). For these exploratory experiments, we employed a 5 mol % catalyst loading and performed the reactions under microwave irradiation (30 min at 150 °C). The nature of the ligand on palladium had a significant effect on the ratio of mono- to bisarylation. Xantphos[7] (entry 1) clearly showed the highest combination of reactivity and selectivity for monoarylation and was used for all subsequent studies. One can postulate that the second arylation, reacting with a more acidic C−H bond than the starting material, would be favored electronically but disfavored by steric factors.[8] As expected, when an excess of the aryl bromide was used, the selectivity for monoarylation diminished in favor of bisarylation. However, employing equimolar amounts of the coupling partners is particularly attractive when one or both substrates are valuable late-stage intermediates. We found the desired monoarylation adduct to be readily separable by chromatography from both unreacted starting material and any bisarylated product that may have formed.

Table 1. Effect of the Palladium Ligand on the Ratio of Mono- to Bisarylation[a]



entry	ligand	product ratio (**1**:**2**:**3**)[b]
1	Xantphos	11:83:6
2	BINAP	94:6:0
3	S-Phos	19:53:28
4	*t*-Bu-XPHOS	92:8:0
5	P(*t*-Bu)$_3$·HBF$_4$	49:14:37
6	DPPF	43:49:8
7	dicyclohexyl JohnPhos	38:46:16

[a] All reactions performed in a sealed tube under microwave irradiation. [b] Determined by analysis of the crude ^{1}H NMR spectra.

The nature of the palladium source was found to be less vital, with similar results found for $Pd_2(dba)_3$, Pd(dba-3,5,3′,5′-OMe)$_2$, $Pd(OAc)_2$, and $(MeCN)_2PdCl_2$ for most substrates. The commercially available Fairlamb catalyst, Pd(dba-3,5,3′,5′-OMe)$_2$,[9] was selected due to a marginally higher selectivity for the desired monoarylation product when coupling with the most electron-deficient aryl halides. Reducing the catalyst/ligand loading to 2.5 mol % had no detrimental effect, and switching from microwave irradiation to thermal conditions gave a cleaner, higher-yielding reaction. Our optimum conditions were thus found to be 1 equiv each of the methyl naphthyridine and aryl bromide, 2 equiv of Cs_2CO_3, 2.5 mol % of Pd(dba-3,5,3′,5′-OMe)$_2$, and 2.5 mol % of Xantphos, heated to reflux for 16 h in dioxane. The reaction is experimentally simple and does not require strict anhydrous conditions, with reagents and solvents used as purchased.[10]

The scope of the reaction with respect to the aryl coupling partner was then investigated by subjecting 2-methyl-1,8-naphthyridine **4**[11] and a range of commercially available aryl halides and triflates to our optimum reaction conditions (Table 2). Both electron-rich (entries 1−5) and -deficient (entries 6−13) aryl bromides were found to couple well. However, a lower selectivity for monoarylation was observed with the strongly mesomerically withdrawing *p*-cyano group (entry 10). The tolerance of the reaction to ortho substituents (entries 3 and 4), esters (entries 6 and 9), nitriles (entry 11), and even aliphatic ketones (entry 12) was demonstrated. The latter was particularly interesting because no α-arylation of the ketone was observed.[12] Aryl iodides and triflates could also be successfully reacted (entries 15 and 16). Employing an aryl chloride as the coupling partner failed to afford any product (entry 17), which we used to our advantage to chemoselectively functionalize an aryl bromide with chloride substituents (entry 8).

(3) For selected examples of chelation-assisted arylation of sp^{3}C−H bonds, see: (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154–13155. (b) Shabashov, D.; Daugulis, O. *Org. Lett.* **2005**, *7*, 3657–3659. (c) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965–3972. (d) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330–7331. (e) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510–3511. (f) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 9886–9887. (g) Niwa, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 2634–2645. (h) Shang, R.; Yang, Z.-W.; Wang, Y.; Zhang, S.-L.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 14391–14393.

(4) (a) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266–3267. (b) Schipper, D. J.; Campeau, L.-C.; Fagnou, K. *Tetrahedron* **2009**, *65*, 3155–3164.

(5) Mousseau, J. J.; Larivée, A.; Charette, A. B. *Org. Lett.* **2008**, *10*, 1641–1643.

(6) At least 2 equiv of base was necessary for the reaction to go to completion. For a discussion on the role of base in the palladium-catalyzed arylation of carbanions, see: Mitin, A. V.; Kashin, A. N.; Beletskaya, I. P. *J. Organomet. Chem.* **2004**, *689*, 1085–1090.

(7) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *14*, 3081–3089.

(8) Arylation of aryl(azaaryl)methanes: Niwa, T.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 2373–2375.

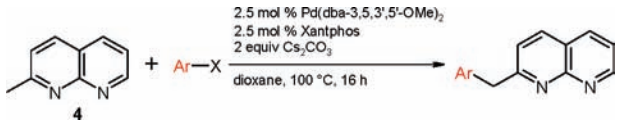
(9) Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F. *Org. Lett.* **2004**, *6*, 4435–4438.

(10) Typical procedure: A 25 mL RBF or a carousel tube was charged with the methyl heterocycle (1.00 mmol), caesium carbonate (650 mg, 2.00 mmol), Pd(3,5,3′,5′-OMe-dba)$_2$ (20 mg, 0.025 mmol), and Xantphos (15 mg, 0.025 mmol). 1,4-Dioxane (8 mL) was then added, followed by the aryl bromide, iodide or triflate (1.00 mmol), and a stirrer bar. A reflux condenser was fitted; the atmosphere was replaced with nitrogen; and the reaction was heated to 100 °C (reflux) and left overnight. After 16 h, the reaction was allowed to cool and then filtered, washing with EtOAc. The filtrate was then concentrated under reduced pressure onto silica, then purified by chromatography.

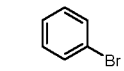
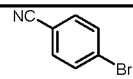
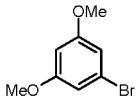
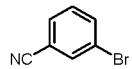
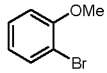
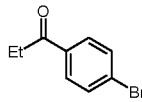
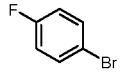
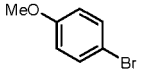
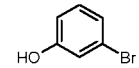
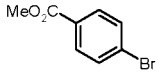
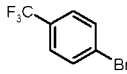
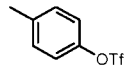
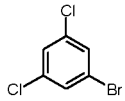
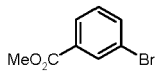
(11) Prepared by the piperidine-catalyzed Friedlander condensation of 2-aminonicotinaldehyde with acetone: Hawes, E. M.; Wibberley, D. G. *J. Chem. Soc. (C)* **1966**, 315–321.

(12) Selected examples of α-arylation of carbonyls: (a) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473–1478. (b) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360–1370. (c) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234–245. (d) For a review, see: Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676–707.

Table 2. Pd-Catalyzed sp^3 C−H Arylation of 2-Methyl-[1,8]-naphthyridine: Scope of ArX[a]

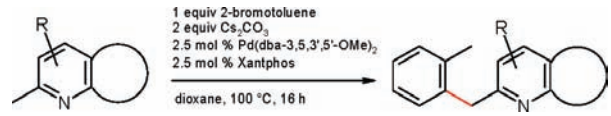


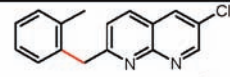
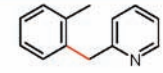
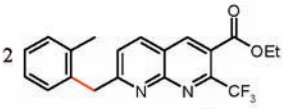
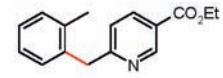
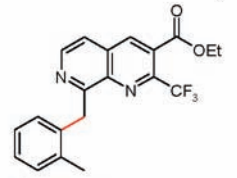
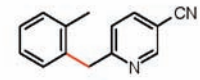
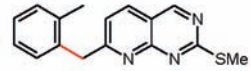
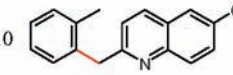
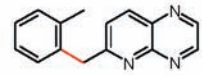
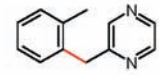
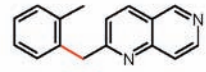
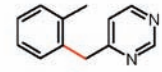
4

entry	ArX	yield (%)[b]	entry	ArX	yield (%)[b]
1		81	10		35
2		78	11		70
3		78	12		60
4		92	13		64
5		83	14		0
6		63	15		81
7		81	16		83
8		80	17		0
9		65			

[a] All reactions performed on a 1.0 mmol scale in 8 mL of solvent. [b] Isolated yield of product after chromatography.

Table 3. Pd-Catalyzed sp^3 C−H Arylation of Electron-Deficient Heterocycles[a]



entry	product	yield (%)	entry	product	yield (%)
1		83	7		0
2		76	8		75
3		78[b]	9		81
4		65	10		56[b]
5		65	11		trace
6		51[b]	12		81

[a] All reactions performed on a 1.0 mmol scale in 8 mL of solvent. [b] 5 mol % of Pd(dba-3,5,3′,5′-OMe)$_2$ and Xantphos used.

With a broad scope of electrophiles established, we were particularly interested in extending the direct arylation to other methyl heteroaromatics (Table 3). Ester, trifluoromethyl, and chloride substituents on the 1,8-naphthyridine core had no detrimental effect on the arylation (entries 1−3). Isomeric 1,6- and 1,7-naphthyridines (entries 3 and 6) and the addition of core nitrogens in the form of pyridopyrimidines and pyridopyrazines (entries 4 and 5) were also coupled successfully. Unsubstituted 2-methylpyridine failed to give any of the desired product (entry 7), but the introduction of an electron-withdrawing group to the 5-position allowed the reaction to proceed well (entries 8 and 9).[13] These results suggest the acidity of the methyl C−H is crucial to the success of the reaction, with the successful arylation of 6-cyanoquinaldine and 4-methylpyrimidine further illustrating this point (entries 10 and 12).[14,15]

In conclusion, we have developed a new direct arylation procedure for benzylic sp^3C−H's adjacent to electron-deficient heteroaromatics, with the mild conditions allowing for a wide functional group tolerance. The application of this methodology to the discovery of novel agrochemicals is ongoing within our laboratories.

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

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(13) However, no reaction occurred for 2-methyl pyridines with electron-withdrawing groups (e.g., esters) in the 3-position. Potentially, the 3-substituent would in this case be twisted out of conjugation with the pyridine ring due to steric factors, thereby limiting its ability to acidify the methyl C−H bonds.

(14) For the sp^3 bisarylation of 4-methylpyrimidine, see: Inoh, J.-I.; Satoh, T.; Pivsa-Art, S.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1998**, *39*, 4673–4676.

(15) On the other hand, 2-methylpyrimidine derivatives gave no reaction.