ORGANIC LETTERS

2013
Vol. 15, No. 9
2302–2305

Mild Palladium-Catalyzed C−H Alkylation Using Potassium Alkyltrifluoroborates in Combination with MnF_3

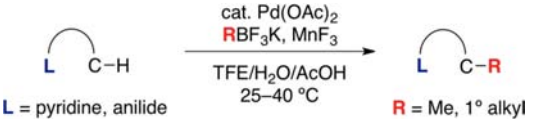
Sharon R. Neufeldt, Cydney K. Seigerman, and Melanie S. Sanford*

Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, Michigan 48109, United States

mssanfor@umich.edu

Received April 1, 2013

ABSTRACT



A Pd-catalyzed method for ligand-directed C−H alkylation with organoboron reagents is described. The combination of potassium organotrifluoroborates, MnF_3, and a Pd^{II} catalyst effects pyridine and amide-directed C−H alkylation. These reactions proceed under mild conditions (25−40 °C in weakly acidic media), are effective for installing methyl and 1° alkyl groups, and do not require promoters such as benzoquinone.

Palladium-catalyzed C−H functionalization is an atom-economical alternative to more traditional cross-coupling reactions for the formation of C−C bonds.[1] Numerous reports have demonstrated Pd-catalyzed ligand-directed C−H arylation using diaryliodonium salts, aryl halides, and arylboronic acids.[1] In contrast, examples of analogous Pd-catalyzed ligand-directed C−H alkylations remain much more limited.[2−6]

Organoboron compounds are particularly attractive reagents for C−H alkylation due to their low toxicity, low cost, and synthetic accessibility.[7] Seminal work by Yu established the feasibility of $Pd^{II/0}$-catalyzed C−H alkylation with alkylboronic acids.[2] However, these transformations have limitations with respect to generality, practicality, and efficiency.[2] For example, relatively few directing groups are effective, and extensive optimization of additives, solvent, and oxidant is typically required for each substrate class. In addition, these transformations generally require high temperatures (≥100 °C), along with bases, silver salts, and other additives/promoters. In particular, stoichiometric quantities of benzoquinone (BQ) are used in all such reactions reported to date.

These limitations are due, in large part, to the reaction mechanism, which is believed to involve (i) ligand-directed C−H activation at Pd^{II}, (ii) transmetalation from boron to Pd^{II}, (iii) C−C reductive elimination from Pd^{II}, and (iv)

(1) (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (c) McGlacken, G. P.; Bateman, L. *Chem. Soc. Rev.* **2009**, *38*, 2447. (d) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (e) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (f) Daugulis, O. *Top. Curr. Chem.* **2010**, *292*, 57. (g) Chiusoli, G. P.; Catellani, M.; Costa, M.; Motti, E.; Ca', N. D.; Maestri, G. *Coord. Chem. Rev.* **2010**, *254*, 456.

(2) (a) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634. (b) 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. (c) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190. (d) Dai, H.-X.; Stepan, A. F.; Plummer, M. S.; Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7222. (e) Romero-Revilla, J. A.; Garcia-Rubia, A.; Arrayas, R.; Fernandez-Ibanez, M. A.; Carretero, J. C. *J. Org. Chem.* **2011**, *76*, 9525. (f) Wasa, M.; Engle, K. M.; Lin, D. W.; Yoo, E. J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19598. (g) Wasa, M.; Chan, K. S. L.; Yu, J.-Q. *Chem. Lett.* **2011**, *40*, 1004.

(3) C−H alkylation with alkylstannanes: Chen, X.; Li, J.-J.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 78.

(4) C−H methylation with MeI: Tremont, S. J.; Rahman, H. U. *J. Am. Chem. Soc.* **1984**, *106*, 5759.

(5) C−H alkylation with alkyl halides: (a) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed.* **1997**, *36*, 119. (b) Rudolph, A.; Rackelmann, N.; Lautens, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1485. (c) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 6097. (d) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. (e) Zhao, Y.; Chen, G. *Org. Lett.* **2011**, *13*, 4850. (f) Tran, L. D.; Daugulis, O. *Angew. Chem., Int. Ed.* **2012**, *51*, 5188. (g) Zhang, S. Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 2124.

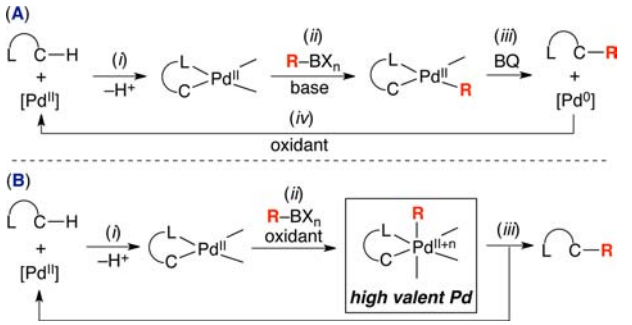
(6) C−H methylation with TBHP: Zhang, Y.; Feng, J.; Li, C.-J. *J. Am. Chem. Soc.* **2008**, *130*, 2900.

(7) (a) Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, *108*, 288. (b) Molander, G. A.; Sandrock, D. L. *Curr. Opin. Drug Discovery Dev.* **2009**, *12*, 811.

10.1021/ol400888r
Published on Web 04/19/2013

oxidation of Pd^0 to Pd^{II} by Cu^{II} or Ag^I (Scheme 1A). In this sequence, the reductive elimination (step iii) is typically slow, thus requiring BQ as a promoter.[2] The oxidation of Pd^0 (step iv) can also be challenging, since aggregation of Pd black is a competing side reaction. As a result, extensive optimization and complex mixtures of additives are often required to facilitate this step.[8]

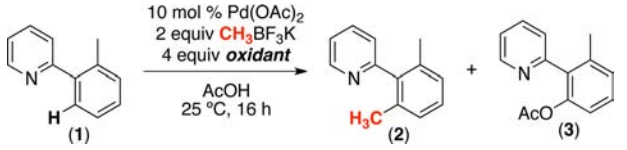
Scheme 1. Potential Pathways for Pd-Catalyzed C−H Alkylation with Alkyl Boron Reagents



We sought to address these challenges by targeting a complementary pathway for Pd-catalyzed C−H alkylation with organoboron reagents (Scheme 1B). The proposed sequence would involve the use of strong oxidants that are capable of oxidizing Pd^{II} intermediates to high-valent Pd species. Under these conditions C−C coupling should occur at a Pd^{III} or Pd^{IV} center, where it is known to proceed under mild conditions without the requirement for promoters such as benzoquinone.[9,10] This pathway also circumvents the intermediacy of Pd^0, thereby avoiding the challenging oxidation of Pd^0 to Pd^{II}.

We first evaluated the $Pd(OAc)_2$-catalyzed methylation of **1** with CH_3BF_3K in AcOH at room temperature in the presence of oxidants that are capable of oxidizing Pd^{II} to high valent Pd (Table 1).[9] While *ortho*-acetoxylation to form **3** was a major side product in some cases, a number of these oxidants provided modest to good yields of **2** after 16 h (entries 4−7). The highest yield of **2** was obtained with MnF_3 (entry 7). Further optimization of the solvent

Table 1. Oxidant Screen for Methylation of **1**[a]



entry	oxidant	yield **2** (%)	yield **3** (%)
1	$PhI(OAc)_2$	≤2	4
2	$PhI(O_2CCF_3)_2$	≤2	16
3	*N*-chlorosuccinimide	4	nd[b]
4	$K_2S_2O_8$	7	≤2
5	$Mn(OAc)_3$	20	≤2
6	*t*-BuOOH	33	≤2
7	MnF_3	60	3
8[c]	MnF_3	80	nd
9[c,d]	MnF_3	89	nd
10[c,d,e]	MnF_3	51	nd
11[c,d,f]	MnF_3	nd	nd
12	benzoquinone	≤2	nd
13	$Cu(OAc)_2$	≤2	nd
14	Ag_2O	≤2	nd
15	AgOAc	≤2	nd
16	Ag_2CO_3	≤2	nd

[a] Yields determined by GC analysis of the crude reaction mixture; nd = not detected. [b] C−H chlorination product (~7%) formed. [c] In TFE/H_2O/AcOH (8:1:1), 6 h. [d] 40 °C [e] With 1 equiv of CH_3BF_3K and 2 equiv of MnF_3. [f] Control reaction without Pd.

[changing to TFE/H_2O/AcOH (8:1:1)] and temperature (moving to 40 °C) resulted in an 89% yield of **2** in just 6 h (entry 9).[11,12] Importantly, no methylation occurred in the absence of Pd (entry 11). Further, only traces (≤2%) of **2** were detected with $Pd^{II/0}$ oxidants such as benzoquinone, $Cu(OAc)_2$, Ag_2O, AgOAc, or Ag_2CO_3 under these conditions.

The optimal conditions were next applied to the C−H methylation of diverse arylpyridine and anilide substrates (Figure 1). Products derived from the *ortho*-C−H methylation of acetanilide (**5**−**8**), pyrrolidinone (**9**), acetylindoline (**10**), and tetrahydroacetylquinoline (**11**) derivatives were all obtained in good to excellent yields. Notably, the presence of an aryl iodide was well tolerated (**8**).

Other 1° alkyl groups were installed using the corresponding alkyltrifluoroborates (Figure 2). Alkylation of both arylpyridine **1** and 3′-methylacetanilide with ethyl, *n*-butyl, and *n*-hexyl groups proceeded efficiently to afford **12**, **13**, **14**, and **21**. The sterically hindered neopentyl group was introduced in 40% yield (**16**), and alkyl chains bearing phenyl, ester, ketone, and trifluoromethyl substituents were compatible with the reaction conditions. The major current limitation of this method is that 2° alkyl trifluoroborates afford low yields (typically ≤10%).

We envisioned at least two possible roles for MnF_3 in these reactions, both of which would lead to the formation of high valent Pd intermediates. The first would involve Mn^{III} oxidizing RBF_3K to an alkyl radical (R•); subsequent reaction of R• with palladacycle **I** would then form Pd^{III} intermediate **II** (Scheme 2A). A number of recent

(8) Engle, K. M.; Thuy-Boun, P. S.; Dang, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 18183.

(9) Reviews on high valent Pd: (a) Muñiz, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9412. (b) Canty, A. J. *Dalton Trans.* **2009**, *47*, 10409. (c) Xu, L.-M.; Li, B.-J.; Yang, Z.; Shi, Z.-J. *Chem. Soc. Rev.* **2010**, *39*, 712. (d) Hickman, A. J.; Sanford, M. S. *Nature* **2012**, *484*, 177.

(10) C−C reductive elimination from high valent Pd is well-known to be facile. For examples, see: (a) Lanci, M. P.; Remy, M. S.; Kaminsky, W.; Mayer, J. M.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 15618. (b) Canty, A. J.; Ariaford, A.; Sanford, M. S.; Yates, B. F. *Organometallics* **2013**, *32*, 544.

(11) Methylboronic acid and trimethylboroxine performed nearly as well as $MeBF_3K$ (80 and 83% yield, respectively); however, these reagent classes are not as convenient to prepare and handle as trifluoroborate salts (see ref 7).

(12) The composition of the reaction vessel (glass vs PTFE) and the size of the reaction vessel (4 mL vs 20 mL) did not have a significant influence on the yield of the reaction at an early time point (see Supporting Information for details). Lennox, A. J. J.; Lloyd-Jones, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 7431.

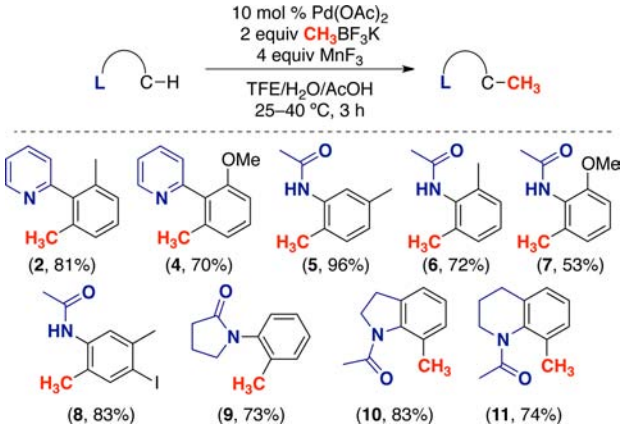


Figure 1. Substrate scope for C−H methylation. Conditions: Substrate (1 equiv), $Pd(OAc)_2$ (0.10 equiv), CH_3BF_3K (2 equiv), MnF_3 (4 equiv), TFE/H_2O/AcOH (0.067 M in substrate), 25−40 °C, 3 h. Yields are of isolated products.

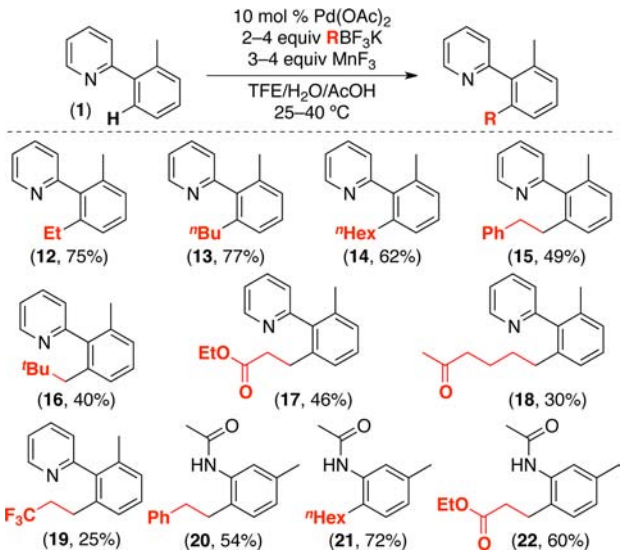


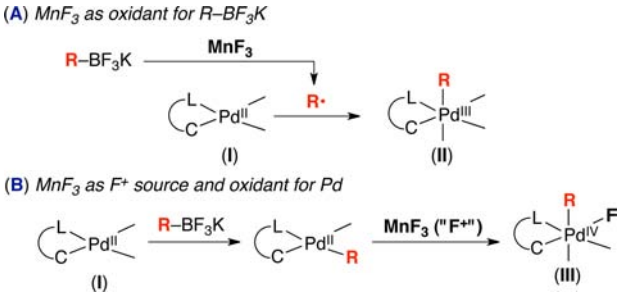
Figure 2. Scope of alkyl trifluoroborates. General conditions: **1** or 3′-methylacetanilide (1 equiv), $Pd(OAc)_2$ (0.10 equiv), alkyl−BF_3K (2−4 equiv), MnF_3 (3−4 equiv), TFE/H_2O/AcOH, 25−40 °C, 3−6 h. Yields are of isolated products.

reports have shown the feasibility of both the oxidation of organoboron compounds with Mn^{III} to generate radicals[13] and the oxidation of palladacycles by radicals.[14]

A second potential pathway would involve oxidation of a Pd^{II} intermediate by Mn^{III}. This oxidation could occur by F^+ transfer from MnF_3 to Pd^{II} either after (shown in Scheme 2B) or before transmetalation from boron to palladium. Importantly, MnF_3 is a known F^+ source for

(13) (a) Demir, A. S.; Reis, Ö.; Emrullahoglu, M. *J. Org. Chem.* **2003**, *68*, 578. (b) Guchhait, S. K.; Kashyap, M.; Saraf, S. *Synthesis* **2010**, 1166. (c) Dickschat, A.; Studer, A. *Org. Lett.* **2010**, *12*, 3972. (d) Molander, G. A.; Colombel, V.; Braz, V. A. *Org. Lett.* **2011**, *13*, 1852.

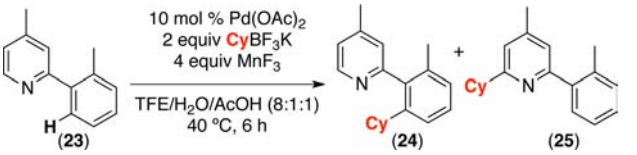
Scheme 2. Two Possible Roles for MnF_3



fluorination of organic substrates.[15] Furthermore, recent publications have demonstrated $Pd^{II/IV}$ catalysis with other electrophilic fluorinating reagents.[16]

We initially favored the free radical mechanism in Scheme 2A based on several pieces of circumstantial evidence. First, Minisci-type radical aromatic substitution products were detected in several of the pyridine alkylation reactions.[17] For example, the reaction of **23** with $CyBF_3K$ afforded alkylated pyridine **25** in 5% yield, along with 9% of the desired product **24** (Table 2, entry 1). Formation of **25** did not require Pd (entry 2) but did require MnF_3 (entry 3), consistent with a Mn-promoted radical pathway to this product.

Table 2. Products Obtained with $CyBF_3K$[a]



entry	conversion (%)	yield **24** (%)	yield **25** (%)
1	42	9	5
2[b]	35	nd	6
3[c]	18	nd	nd

[a] Determined by GC analysis of the crude reaction mixture. [b] Control reaction without Pd; nd = not detected. [c] Control reaction without Mn.

A second piece of circumstantial evidence consistent with a radical pathway is the observation of dose-dependent inhibition of C−H methylation by the radical inhibitor galvinoxyl (Table 3).

(14) Selected examples: (a) Yu, W.-Y.; Sit, W. N.; Lai, K.-M.; Zhou, Z.; Chan, A. S. C. *J. Am. Chem. Soc.* **2008**, *130*, 3304. (b) Yu, W.-Y.; Sit, W. N.; Zhou, Z.; Chan, A. S.-C. *Org. Lett.* **2009**, *11*, 3174. (c) Kalyani, D.; McMurtrey, K. B.; Neufeldt, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 18566. (d) Neufeldt, S. R.; Sanford, M. S. *Adv. Synth. Catal.* **2012**, *354*, 3517.

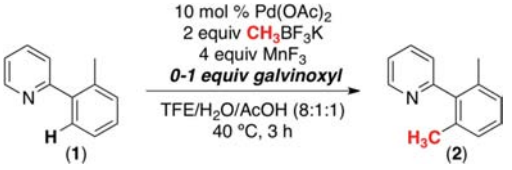
(15) Selected examples: (a) Fowler, R. D.; Anderson, H. C.; Hamilton, J. M.; Burford, W. B.; Spadetti, A.; Bitterlich, S. B.; Litant, I. *Ind. Eng. Chem.* **1947**, *39*, 343. (b) Boltalina, O. V.; Borschevskii, A. Ya.; Sidorov, L. N.; Street, J. M.; Taylor, R. *Chem. Commun.* **1996**, 529.

(16) Vigalok, A. *Organometallics* **2011**, *30*, 4802.

(17) Minisci, F.; Bernardi, R.; Bertini, F.; Galli, R.; Perchinummo, M. *Tetrahedron* **1971**, *27*, 3575.

We reasoned that if MnF_3 and CH_3BF_3K react directly to generate $CH_3\bullet$ (Scheme 2A), then prestirring these two reagents with **1** for 3 h prior to the addition of $Pd(OAc)_2$ should lead to a dramatically diminished yield of product **2**. However, as shown in eq 1, this prestirring protocol resulted in only a minor drop in the yield of **2** (83% compared to 89% without the prestir). *This strongly suggests against the direct oxidation of CH_3BF_3K by Mn^{III} to generate $CH_3\bullet$ in this transformation.* Thus, the results in Tables 2 and 3 appear to be 'red herrings'. They may reflect radical side reactions that are not mechanistically connected to the Pd-catalyzed conversion of **2** to **3** (Table 2) and/or the interaction of galvinoxyl with the oxidant or some other intermediate in the catalytic cycle (Table 3).

Table 3. Inhibition by Galvinoxyl[a]

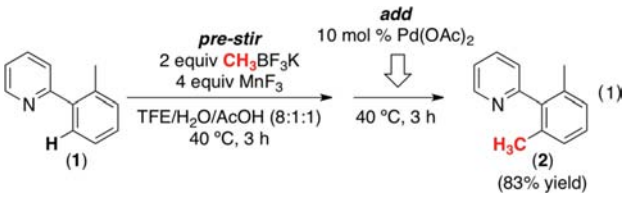


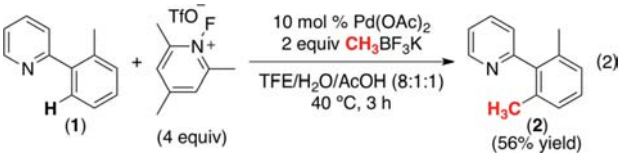
entry	galvinoxyl (equiv)	conversion (%)	yield **2** (%)
1	0	94	87
2	0.5	76	67
3	1	13	3

[a] Yields determined by GC analysis of the crude reaction mixture.

We next sought to probe whether the MnF_3 is serving as an F^+ oxidant in this system (Scheme 2B). To preliminarily test this possibility, we substituted MnF_3 with *N*-fluoro-2,4,6-trimethylpyridinium triflate (NFTPT), a reagent that has been used as a F^+ source to generate high valent Pd intermediates.[16] As shown in eq 2, NFTPT provided a 56% yield of **2** under the optimal conditions.[18] While further studies will be required to fully elucidate the details of the reaction mechanism, the observed efficacy of NFTPT is consistent with the feasibility of a 'F^+'-mediated pathway such as that shown in Scheme 2B.

(18) All other oxidants screened under the optimized reaction conditions afforded ≤10% yield; see Supporting Information for details.





In summary, this manuscript describes a new approach to Pd-catalyzed ligand-directed C−H alkylation that uses MnF_3 in conjunction with potassium organotrifluoroborates. This method has enabled us to address several of the key limitations of prior C−H alkylation processes. The current transformations proceed under mild conditions (25−40 °C in weakly acidic media) and are effective for the installation of methyl and 1°-alkyl substituents into substrates bearing both pyridine and amide directing groups. The detailed mechanism remains to be elucidated, but preliminary studies suggest that the MnF_3 likely serves to oxidize a Pd^{II} intermediate, rather than the organotrifluoroborate. Ongoing investigations are focused on gaining a deeper mechanistic understanding of this transformation, as well as expanding the scope with respect to both C−H substrate and alkyl groups.

Acknowledgment. This work was supported by the NIH NIGMS (GM073836).

Supporting Information Available. Experimental details 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.