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Mild Palladium-Catalyzed C–H Alkylation Using Potassium Alkyltrifluoroborates in Combination with MnF₃

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Abstract

A Pd-catalyzed method for ligand-directed C–H alkylation with organoboron reagents is described. The combination of potassium organotrifluoroborates, MnF₃, 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 like 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.^{2,3,4,5,6}

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) oxidation of Pd⁰ 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 Pd⁰ (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

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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>.

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 like benzoquinone.^{9,10} This pathway also circumvents the intermediacy of Pd⁰, thereby avoiding the challenging oxidation of Pd⁰ to Pd^{II}.

We first evaluated the Pd(OAc)₂-catalyzed methylation of **1** with CH₃BF₃K 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 MnF₃ (entry 7). Further optimization of the solvent [changing to TFE/H₂O/AcOH (8:1:1)] and temperature (moving to 40 °C) resulted in 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 like benzoquinone, Cu(OAc)₂, Ag₂O, AgOAc, or Ag₂CO₃ 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.

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 MnF₃ in these reactions, both of which would lead to the formation of high valent Pd intermediates. The first would involve Mn^{III} oxidizing RBF₃K 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 reports have shown the feasibility of both the oxidation of organoboron compounds with Mn^{III} to generate radicals¹³ 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 MnF₃ to Pd^{II} either after (shown in Scheme 2B) or before transmetalation from boron to palladium. Importantly, MnF₃ is a known F⁺ source for 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 CyBF₃K 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 MnF₃ (entry 3), consistent with a Mn-promoted radical pathway to this product.

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

We reasoned that if MnF_3 and $\text{CH}_3\text{BF}_3\text{K}$ react directly to generate $\text{CH}_3^\bullet$ (Scheme 2A), then pre-stirring these two reagents with **1** for 3 h prior to the addition of $\text{Pd}(\text{OAc})_2$ should lead to a dramatically diminished yield of product **2**. However, as shown in eq. 1, this pre-stirring protocol resulted in only a minor drop in the yield of **2** (83% compared to 89% without the pre-stir). This strongly suggests against the direct oxidation of $\text{CH}_3\text{BF}_3\text{K}$ by Mn^{III} to generate $\text{CH}_3^\bullet$ 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 some other intermediate in the catalytic cycle (Table 3).

(1)

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 an F^+ source to generate high valent Pd intermediates.¹⁶ As shown in eq 2, NFTPT provided 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 an ‘ F^+ ’-mediated pathway like that in Scheme 2B.

(2)

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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

Figure 1. Substrate Scope for C–H Methylation ^{a,b}

^a Conditions: substrate (1 equiv), Pd(OAc)₂ (0.10 equiv), CH₃BF₃K (2 equiv), MnF₃ (4 equiv), TFE/H₂O/AcOH (0.067 M in substrate), 25–40 °C, 3 h. ^b Yields are of isolated products.

Figure 2. Scope of Alkyl Trifluoroborates ^{a,b}

^a General conditions: 1 or 3'-methylacetanilide (1 equiv), Pd(OAc)₂ (0.10 equiv), alkyl-BF₃K (2–4 equiv), MnF₃ (3–4 equiv), TFE/H₂O/AcOH, 25–40 °C, 3–6 h. ^b Yields are of isolated products.

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

(A) MnF_3 as oxidant for $\text{R-BF}_3\text{K}$

(B) MnF_3 as F^+ source and oxidant for Pd

Scheme 2.

Two Possible Roles for MnF_3

Table 1

Oxidant Screen for Methylation of **1** ^a

entry	oxidant	yield 2 (%)	yield 3 (%)
1	PhI(OAc) ₂	2	4
2	PhI(O ₂ CCF ₃) ₂	2	16
3	<i>N</i> -chlorosuccinimide	4	nd ^b
4	K ₂ S ₂ O ₈	7	2
5	Mn(OAc) ₃	20	2
6	<i>t</i> -BuOOH	33	2
7	MnF ₃	60	3
8 ^c	MnF ₃	80	0
9 ^{c,d}	MnF ₃	89	0
10 ^{c,d,e}	MnF ₃	51	0
11 ^{c,d,f}	MnF ₃	nd	nd
12	benzoquinone	2	nd
13	Cu(OAc) ₂	2	nd
14	Ag ₂ O	2	nd
15	AgOAc	2	nd
16	Ag ₂ CO ₃	2	nd

^aYields determined by GC analysis of the crude reaction mixture; nd = not detected.

^bC–H chlorination product (~7%) formed.

^cIn TFE/H₂O/AcOH (8:1:1), 6 h.

^d40 °C ^eWith 1 equiv CH₃BF₃K and 2 equiv MnF₃.

^eWith 1 equiv CH₃BF₃K and 2 equiv MnF₃.

^fControl reaction without Pd.

Table 2Products Obtained with CyBF₃K^a

entry	conversion (%)	yield 24 (%)	yield 25 (%)
1	42	9	5
2 ^b	35	0	6
3 ^c	18	0	0

^aDetermined by GC analysis of the crude reaction mixture.^bControl reaction without Pd.^cControl reaction without Mn.

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

^aYields determined by GC analysis of the crude reaction mixture.