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Published on Web 02/13/2008

Palladium-Catalyzed Methylation of Aryl C−H Bond by Using Peroxides

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Transition-metal-catalyzed activation of aryl C−H bonds followed by C−C bond formation provides a promising alternative to the standard coupling reactions using preformed organometallic reagents. In this area of research, various functional groups containing heteroatoms such as acetyl, acetoamino, oxazolyl, pyridyl, and imino groups can provide an anchor for either stoichiometric or catalytic *ortho*-metalation of aromatic rings, which leads to subsequent regioselective formation of C−C bonds for synthetic purposes.[1] Ru and Rh complexes are the hors d'oeuvres of effective catalysts which have succeeded in performing carbo-functionalization of aryl C−H bonds by reacting with olefins or aryl organometallic reagents.[1a,2]

Recently, Pd-catalyzed direct functionalizations of aryl C−H to form C−C bonds have been investigated intensively (Scheme 1). Among them, alkenylation of aryl C−H bonds via Pd(II)/Pd(0) catalysis generated Heck-type reaction[3] products (route a).[4] For alkylation of aryl C−H bonds, recently Yu and co-workers reported the aryl methylation with methylboronic acids (analogous to the Suzuki-type reaction[5]) and organotin reagents catalyzed by Pd together with an oxidizing reagent (route b).[6] Alternatively, a Pd-catalyzed aryl−aryl coupling via aryl C−H bond by using arylsilanes has been achieved,[7] analogous to the Corriu−Kumada−Hiyama coupling.[8] Herein, we wish to report an unprecedented palladium-catalyzed methylation of arenes by using peroxides, serving as both a novel methylating reagent and the hydrogen acceptor (route c).

To begin our study, we discovered that the reaction of 2-phenylpyridine (**1a**) with *tert*-butyl peroxide (**2a**) catalyzed by Pd(OAc)$_2$ at 140 °C under an atmosphere of nitrogen generated 20% of 2-*o*-tolylpyridine (**3a**) (Table 1, entry 1) (*Caution: heating large amounts of peroxide at high temperature is potentially dangerous*). Further optimization showed that 40% of **3a** and 5% of 2-(2,6-dimethylphenyl)pyridine **4a** (a bismethylation product) could be obtained when *tert*-butylbenzene was used as solvent (Table 1, entry 2). Interestingly, no reaction was observed when *tert*-butyl hydroperoxide instead of *tert*-butyl peroxide was used. On the other hand, *tert*-butyl peroxybenzoate, *tert*-butyl cumyl peroxide, and di(*tert*-butyl peroxyisopropyl)benzene were also found to be effective in generating the desired product without any solvent (Table 1, entries 4−6), with dicumyl peroxide providing the best results under the neat conditions (Table 1, entry 7). It should be mentioned that the remaining unreacted phenylpyridine can be recovered nearly quantitatively and no other significant product could be detected in the reaction. Subsequently, various palladium catalysts were examined under these conditions (Table 1, entries 8−13). $PdCl_2$ and $(CH_3CN)_2PdCl_2$ also gave good yields of the methylation product (Table 1, entries 8 and 9), whereas $Pd(CF_3CO_2)_2$, $Pd(PPh_3)_4$, $Pd(C_5H_7O_2)_2$, and $(PPh_3)_2PdCl_2$ were less effective (Table 1, entries 10−13) as catalysts for this transformation. When 1 equiv of the peroxide **2f** was used, only a small amount of the double methylation product was observed (Table 1, entry 14). With 4 equiv of the peroxide **2f**, the double methylation product **4a** was the only product, obtained in 70% yield (Table 1, entry 15). Raising the reaction temperature slightly increases the product yield (Table 1, entry 16). Lowering the reaction temperature or reducing the amount of catalyst markedly decreases the product yield (Table 1, entries 17 and 18). No product was detected in the absence of $Pd(OAc)_2$ (Table 1, entry 19).

Under the optimized reaction conditions, various 2-phenylpyridine derivatives were examined (Table 2, entries 4−10). With benzo[*h*]quinoline (**1d**), only one reactive site being available for the reaction, as the substrate, 76% of the monomethylation product **3d** was obtained (Table 2, entry 7). The electronic effect does not affect the reaction significantly (compare entries 5, 8, and 9). The

Scheme 1. Pd-Catalyzed Functionalization of Aryl C−H Bond

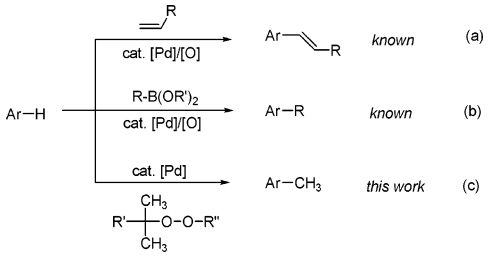
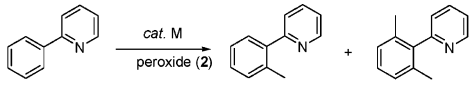
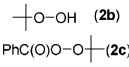
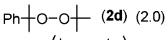
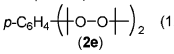
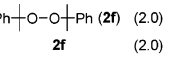
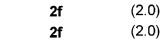


Table 1. Optimization of Reaction Conditions[a]



entry	catalyst (mol %)	2 (equiv)		T (°C)	yields of 3 + 4 (%)[b]
1[c]	$Pd(OAc)_2$ (10)	 **(2a)**	(5.0)	140	20 + 0
2[d]	$Pd(OAc)_2$ (10)	**2a**	(5.0)	150	40 + 5
3	$Pd(OAc)_2$ (10)	 **(2b)**	(2.0)	130	0[e]
4	$Pd(OAc)_2$ (10)	 **(2c)**	(2.0)	130	5 + 0[f]
5	$Pd(OAc)_2$ (10)	 **(2d)**	(2.0)	130	50 + 10
6	$Pd(OAc)_2$ (10)	 **(2e)**	(1.0)	130	50 + 10
7	$Pd(OAc)_2$ (10)	 **(2f)**	(2.0)	130	50 + 40
8	$PdCl_2$ (10)	**2f**	(2.0)	130	65 + 10
9	$(CH_3CN)_2PdCl_2$ (10)	**2f**	(2.0)	130	55 + 7
10	$Pd(CF_3COO)_2$ (10)	**2f**	(2.0)	130	30 + 10
11	$Pd(PPh_3)_4$ (10)	**2f**	(2.0)	130	30 + 0[f]
12	$Pd(C_5H_7O_2)_2$ (10)	**2f**	(2.0)	130	20 + 5
13	$(PPh_3)_2PdCl_2$ (10)	**2f**	(2.0)	130	20 + 0[f]
14	$Pd(OAc)_2$ (10)	**2f**	(1.0)	130	50 + 10
15	$Pd(OAc)_2$ (10)	**2f**	(4.0)	130	0[f] + 70
16	$Pd(OAc)_2$ (10)	**2f**	(2.0)	150	50 + 45
17	$Pd(OAc)_2$ (10)	**2f**	(2.0)	100	40 + 5
18	$Pd(OAc)_2$ (5)	**2f**	(2.0)	130	60 + 20
19	-------	**2f**	(2.0)	130	0[e]

[a] Conditions: all reactions were carried out with **1a** (0.2 mmol), 12 h under N_2 in a closed reaction vessel, unless otherwise noted. [b] ^{1}H NMR yields determined by using 1,4-dioxane as an internal standard. [c] Reaction time: 5 h. [d] *tert*-Butylbenzene (0.1 mL) as solvent. [e] Not detected by ^{1}H NMR; 90% of **1a** remained. [f] Not detected by ^{1}H NMR.

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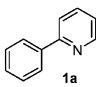
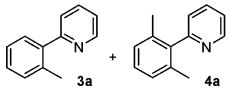
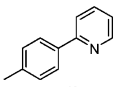
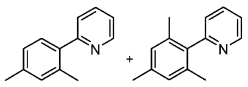
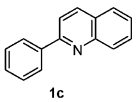
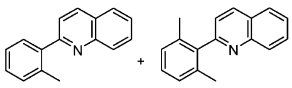
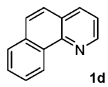
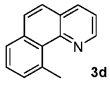
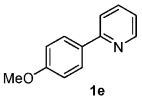
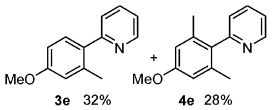
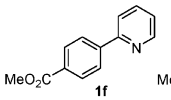
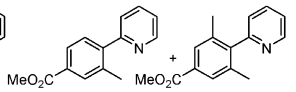
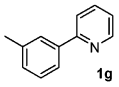
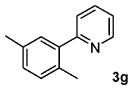
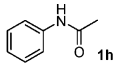
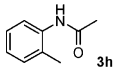
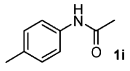
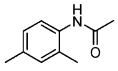
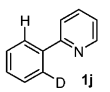
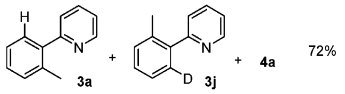
10.1021/ja0775063 CCC: $40.75

Table 2. Methylation of sp^2 C−H Bonds with **2f**[a]

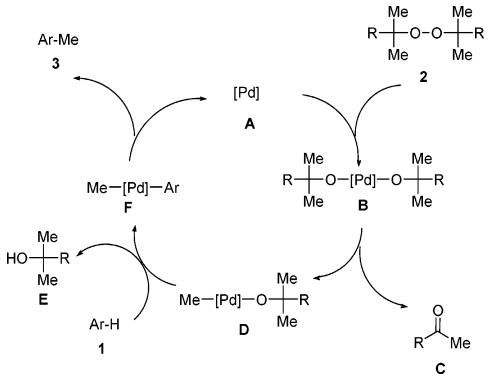
entry	substrate (**1**)	product and yields[b]	overall yield
1[c]	 **1a**	 **3a** 54% + **4a** 18%	72%
2[d]		**3a** 45% + **4a** 28%	73%
3[e]		**3a** + **4a** 63%	63%
4	**3a**	**3a** + **4a** 55%	55%
5	 **1b**	 **3b** 35% + **4b** 24%	59%
6	 **1c**	 **3c** 55% + **4c** 13%(NMR)	68%
7[f]	 **1d**	 **3d**	76%
8	 **1e**	 **3e** 32% + **4e** 28%	60%
9	 **1f**	 **3f** 55% + **4f** 8%	63%
10	 **1g**	 **3g**	63%
11	 **1h**	 **3h**	42%
12	 **1i**	 **3i**	33%
13	 **1j**	 **3a** + **3j** + **4a** Total yield of **3a** and **3j** = 42% ^{1}H NMR ratio of **3a**:**3j** = 1:1	30%

[a] Conditions: all reactions were carried out with **1** (0.5 mmol), dicumyl peroxide **2f** (1.0 mmol), 12 h under N_2, unless otherwise noted. [b] Isolated yields. [c] **1a** (0.5 mmol), dicumyl peroxide (0.75 mmol). [d] **1a** (0.5 mmol), dicumyl peroxide (1.0 mmol). [e] **1a** (0.5 mmol), dicumyl peroxide (2.0 mmol). [f] **1d** (0.5 mmol), dicumyl peroxide (0.75 mmol).

reaction of 2-(3-methylphenyl)pyridine (**1g**) gave **3g** exclusively (Table 2, entry 10). It is interesting to note that acetanilides are also effective in this transformation, generating the methylation product in moderate yields under these conditions (Table 2, entries 11 and 12).

A tentative mechanism to rationalize this novel palladium catalyzed methylation of aryl C−H bond is illustrated in Scheme 2. Palladium species **A**, at a lower oxidation state, inserts into the weak O−O bond of peroxide **2** to generate a higher oxidation state intermediate **B**. Heterolytic β-methyl elimination[9] of **B** leads to ketone **C** and the methylpalladium intermediate **D**. Reaction of **D** with arenes generates alcohol **E** and intermediate **F**, which leads to methylation product **3** via reductive elimination, and regenerates the active palladium species **A**.[10] In support of this proposed mechanism, nearly stoichiometric amounts of both ketone **C** and alcohol **E** were detected in the crude reaction mixture by ^{1}H NMR and could be isolated nearly quantitatively by column chromatography. On the other hand, no significant isotope effect was observed in an intramolecular competition experiment using 2-(2-deuterophenyl)pyridine as a substrate (Table 2, entry 13), which suggests a possible alternative (e.g., radical) mechanism.

Scheme 2. Tentative Mechanism for the Palladium-Catalyzed Methylation of Arenes with Peroxides, [Pd] = Pd(0) or Pd(II)



In summary, we have developed a novel method for the direct methylation of aryl C−H bonds by using peroxide compounds as both methylating reagents and hydrogen acceptor. The study provides a new avenue for the direct alkylation of aryl C−H bonds by using alkyl radicals rather than organometallic reagents. Further investigations including the scope, mechanism, and synthetic application of this reaction are in progress.

Acknowledgment. We are grateful to the Canada Research Chair (Tier I) Foundation (to C.J.L.), the NSF-EPA Joint Program for a Sustainable Environment, and NSERC for support.

Supporting Information Available: Representative experimental procedure and characterization of all new compounds (PDF). This material is available free of charge via the Internet at http:/pubs.acs.org.

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JA0775063