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Palladium-Catalyzed Decarboxylative Arylation of C−H Bonds by Aryl Acylperoxides

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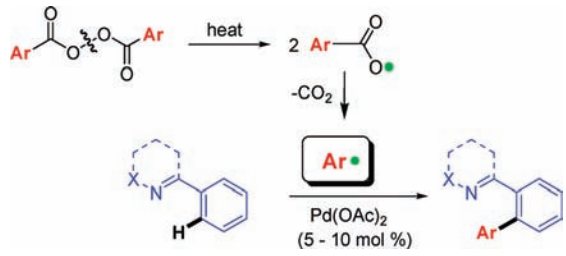
ABSTRACT



A $Pd(OAc)_2$-catalyzed protocol for decarboxylative arylation of aromatic C−H bond was developed using aryl acylperoxides as inexpensive aryl sources. Substrates containing pyridyl, oxime, and oxazoline groups undergo effectively *ortho*-selective C−H arylation with excellent functional group tolerance. This arylation should begin by directing-group-assisted cyclopalladation, followed by the reaction of the palladacycle with aryl radicals generated in situ by thermal decomposition of the peroxides.

Transition-metal-catalyzed biaryl cross-coupling reactions involving C−H activation are attracting current interest.[1] Without using prefunctionalized substrates, direct arylation of C−H bonds would streamline the synthetic process and reduce formation of byproduct. Extensive studies showed that Rh,[2] Ru,[3] Pd,[4] and Cu[5] are effective catalysts for direct arylation of aromatic C−H bonds using diaryliodonium(III) salts,[4o] organoboron compounds,[4a,c,k] and aryl halides.[4b,d,g,j,n,5b] However, the relatively high price and limited availability of the organoboron/iodonium reagents would hamper the general uses of the protocols for practical synthesis. With aryl halides as coupling partners, problems of functional group compatibility arise if substrates or the aryl halides contain pre-installed halogen substituents designed for later coupling reactions.

The use of carboxylic acids for decarboxylative arylation reactions constitutes a new development in catalytic cross-coupling reactions.[6] Notable examples are the Heck-type coupling reaction developed by Myers and co-workers[7] and the coupling reactions of benzoic acids with aryl halides developed by Goossen and co-workers.[8] Recently, an intramolecular direct C−H arylation reaction by tandem decarboxylation/C−H activation has been reported in the literature.[9] This process involves the use of readily available and inexpensive benzoic acids as aryl sources, and handling of sensitive organometallic coupling reagents is avoided. However, high reaction temperature (140−170 °C) and long reaction time (14−20 h) remain major shortcomings for the decarboxylative coupling reactions. As part of our program to explore new cross-coupling reactions via C−H activation,[10] we described earlier direct C−H ethoxycarbonylation of 2-arylpyridines by coupling of the palladacycle intermediate with the ethoxyacyl [EtOC(O)•] radical.[10b] Inspired by this discovery, we envisaged that direct C−H arylation

(1) (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (c) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

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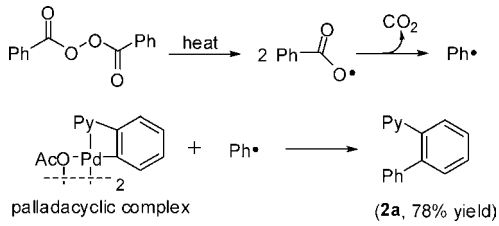
reactions could be achieved by coupling of aryl radicals with organopalladium complexes (Scheme 1). Here we describe

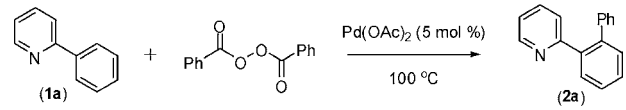
Scheme 1. Reaction of Palladacycle with Benzoyl Peroxide



the $Pd(OAc)_2$-catalyzed decarboxylative arylation of arene C−H bonds using aryl acylperoxides. During the course of our investigation, Li and co-workers reported direct arene C−H methylation using cumyl peroxide.[11] It is accepted that aryl radicals can be generated by decarboxylation of aryl-carboxyl radicals, produced by the homolytic O−O cleavage of the peroxides.[12] In this work, the decarboxylative direct arylation can be achieved in good yield and selectivity in 10 min to 2 h.

As a proof-of-concept study, we were gratified that treatment of a 2-phenylpyridine-derived palladacyclic complex with benzoyl peroxide (2 equiv) in a MeCN/AcOH (1:1 v/v) mixture at 100 °C for 2 h afforded **2a** in 78% yield (Scheme 1). With this favorable result, we turned to develop a catalytic direct C−H arylation protocol using 2-phenylpyridine (**1a**) as model substrate. When **1a** reacted with benzoyl peroxide (4 × 0.5 equiv/0.5 h) and $Pd(OAc)_2$ (5 mol %) in a MeCN/AcOH mixture (1:1 v/v) at 100 °C for 2 h, **2a** was formed in 80% yield [Table 1, entry 1 (method A)].[13] Slower

Table 1. Optimization of Reaction Conditions[a]



entry	solvent	% convn	% yield[a]
1	AcOH/CH_3CN = 1:1	92	80
2[b]	AcOH/CH_3CN = 1:1	92	80
3[c]	DCE	43	38
4	CH_3CN	46	64
5	CH_3CN (2 mL) + AcOH (0.1 mL)	68	77
6	AcOH/DMF = 1:1	43	56
7	AcOH/DMSO = 1:1	56	61
8[d]	AcOH/CH_3CN = 1:1	86	80

[a] The reactions were carried out on a 0.5-mmol scale of **1a**. Conversion and yield were determined by GC/FID. The percentage yield is based on conversion. [b] Reaction at 100 °C for 4 h, peroxide (4 × 0.5 equiv/1 h). [c] Dimer of **1a** (yield 12%) and chlorinated product (trace) were detected by GC−MS. [d] Method B.

addition rate of the peroxide (4 × 0.5 equiv/1 h) gave similar results (entry 2). In the absence of $Pd(OAc)_2$, only a trace amount of **2a** was formed.[14] Performing the Pd-catalyzed reaction in MeCN or DCE alone (i.e., without AcOH) resulted in lower product yield and substrate conversion (entries 3 and 4). Furthermore, using a MeCN/AcOH (20:1 v/v) mixture as solvent for the arylation reaction also gave less satisfactory results (entry 5). Employing DMF or DMSO as co-solvent failed to produce better results (entries 6 and 7). Notably, when **1a** reacted with benzoyl peroxide (2 equiv) and $Pd(OAc)_2$ (5 mol %) at 160 °C in MeCN/AcOH (1:1

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(3) (a) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 2619. (b) Kakiuchi, F.; Matsuura, Y.; Kan, S.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 5936. (c) Oi, S.; Aizawa, E.; Ogino, Y.; Inoue, Y. *J. Org. Chem.* **2005**, *70*, 3113.
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(5) (a) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. (b) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185.
(6) For reviews, see: (a) Goossen, L. J.; Rodriguez, N.; Goossen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100. (b) Bonesi, S. M.; Fagnoni, M.; Albini, A. *Angew. Chem., Int. Ed* **2008**, *47*, 10022. For recent examples: (c) Bi, H.-P.; Zhao, L.; Liang, Y.-M.; Li, C.-J. *Angew. Chem., Int. Ed.* **2009**, *48*, 792. (d) Becht, J.-M.; Drian, C. L. *Org. Lett.* **2008**, *10*, 3161.
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(9) Wang, C.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194.
(10) (a) Yu, W.-Y.; Tsoi, Y.-T.; Zhou, Z.; Chan, A. S. C. *Org. Lett.* **2009**, *11*, 469. (b) Yu, W.-Y.; Sit, W. N.; Lai, K.-M.; Zhou, Z.; Chan, A. S. C. *J. Am. Chem. Soc.* **2008**, *130*, 3304. (c) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (d) Choi, M. K.-W.; Yu, W.-Y.; Che, C.-M. *Org. Lett.* **2005**, *7*, 1081. (e) Cheung, W.-H.; Zheng, S.-L.; Yu, W.-Y.; Zhou, G.-C.; Che, C.-M. *Org. Lett.* **2003**, *5*, 2535.
(11) Zhang, Y.; Feng, J.; Li, C.-J. *J. Am. Chem. Soc.* **2008**, *130*, 2900.
(12) (a) Moad, G.; Solomon, D. H. *The Chemistry of Free Radical Polymerization*; Elsevier: Boston, 2006. (b) Moody, C. J.; Whitham, G. H. *Reactive Intermediates*; Oxford University Press: New York, 1992.

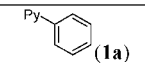
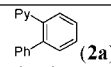
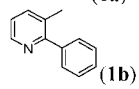
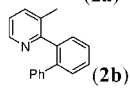
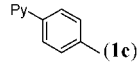
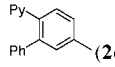
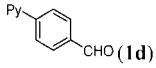
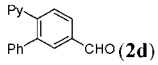
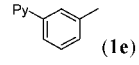
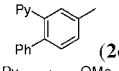
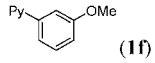
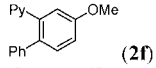
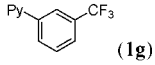
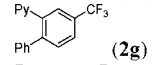
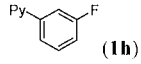
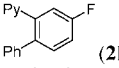
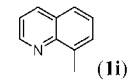
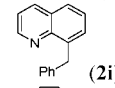
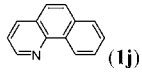
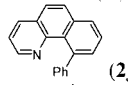
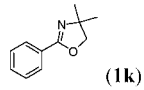
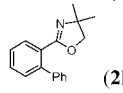
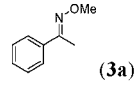
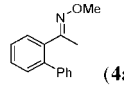
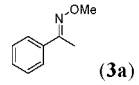
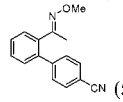
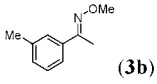
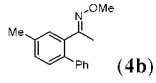
(13) **Experimental Procedure.** Method A: A mixture of substrate (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol, 5 mol %), and benzoyl peroxide (1 mmol; addition interval 4 × 0.5 equiv/0.5 h) in acetonitrile (1 mL) and acetic acid (1 mL) was sealed in a 8 mL vial with a Teflon-lined cap. The mixture was heated at 100 °C (oil bath temperature) for 2 h. Method B: A mixture of substrate (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol, 5 mol %), and benzoyl peroxide (1 mmol) in acetonitrile (1 mL) and acetic acid (1 mL) was sealed in a 8 mL vial with a Teflon-lined cap. The mixture was heated at 160 °C (oil bath temperature) for 10 min. Method C: A mixture of substrate (0.5 mmol), $Pd(OAc)_2$ (0.05 mmol, 10 mol %), and benzoyl peroxide (1 mmol) in acetonitrile (2 mL) was sealed in a 8 mL vial with a Teflon-lined cap. The mixture was heated at 160 °C (oil bath temperature) for 10 min. *Caution*: Aryl acylperoxides are potentially explosive and should be handled with care and in small quantities.

(14) Without $Pd(OAc)_2$ catalyst, **1a** (87%) was recovered with trace quantities of isomeric *o*-, *m*-, and *p*-arylated products being observed by GC−MS.

v/v) solvent, **2a** was obtained in 80% yield in 10 min. Prolonged reaction (30 min) at 160 °C had little effect on the product yield (76%). However, addition of further equivalents of the peroxide led to lower product yield (41%).

Table 2 depicts the scope of the decarboxylative arylation reaction; the arylpyridines were converted to their biaryls in

Table 2. Pd-Catalyzed Decarboxylative Arylation of Aromatic C−H Bonds[a]

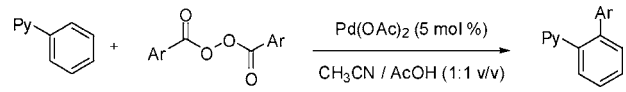
entry	substrate	product	method	% convn	% yield[b]
1	 (**1a**)	 (**2a**)	A	87	79
2	 (**1b**)	 (**2b**)	A	91	82
3	 (**1c**)	 (**2c**)	A	80	75
4	 (**1d**)	 (**2d**)	A	65	80
5	 (**1e**)	 (**2e**)	A	87	73
6	 (**1f**)	 (**2f**)	A	68	71
7	 (**1g**)	 (**2g**)	A	88	69
8	 (**1h**)	 (**2h**)	A	87	77
9	 (**1i**)	 (**2i**)	A	65	81
10	 (**1j**)	 (**2j**)	B	52	78
11	 (**1k**)	 (**2k**)	C	72	79
12	 (**3a**)	 (**4a**)	C	71	80
13	 (**3a**)	 (**5**)	C	63	85
14	 (**3b**)	 (**4b**)	C	62	81

[a] Reaction conditions: substrate (0.5 mmol), peroxide (2 equiv), $Pd(OAc)_2$ [5 mol % (for entries 1−10); 10 mol % (for entries 11−14)]. [b] Isolated yield based on conversion.

good yields with excellent functional group (F, OMe, CF_3, CHO) tolerance (entries 1−8). Using our Pd-catalyzed protocol, 8-methylquinoline (**1i**) would undergo facile arylation at the sp^3 C−H bond, and **2i** was furnished in 81% yield (entry 9). For **1j** as substrate, our initial catalytic protocol [i.e., method A, $Pd(OAc)_2$ (5 mol %), benzoyl peroxide (4 × 0.5 equiv/0.5 h), 100 °C, MeCN/AcOH (1:1) mixture] failed to effect any conversion of the substrate. However, when the analogous reaction was conducted at 160 °C for 10 min (method B), **2j** was produced in 78% yield (entry 10). Yet, the arylations of oxazoline (**1k**) and oximes (**3a**, **3b**) with benzoyl peroxide (2 equiv) and $Pd(OAc)_2$ (10 mol %) were best performed at 160 °C in MeCN for 10 min (method C), and the expected biaryls were formed in ca. 80% yield (entries 11−14).[15]

Various aryl acylperoxides have been examined for the Pd-catalyzed direct C−H arylations. The acylperoxides were prepared from their carboxylic acid precursors. As shown in Table 3, the halongenated (Cl, Br, F) and other functionalized (Me, ^{t}Bu, CF_3, CN, and NO_2) peroxides can effect the biaryl formation (**6a**−**6k**) regioselectively.[16] Yet, the coupling reaction with sterically crowded 2,3,6-trimethylbenzene acylperoxide was unsuccessful (entry 12). Nevertheless, our results are comparable to other reported protocols using diaryliodonium salts, organoborons, and aryl halides as reagents.

Table 3. Reaction with Various Aryl Acylperoxides[a]



entry	Ar	% convn	% yield[b]
1	2-Cl-C_6H_4	70	84
2	3-Cl-C_6H_4	87	83
3	4-Cl-C_6H_4	85	83
4	4-F-C_6H_4	78	84
5	4-Br-C_6H_4	84	75
6	2-Me-C_6H_4	65	82
7	4-Me-C_6H_4	76	81
8	4-CF_3-C_6H_4	88	84
9	4-^{t}Bu-C_6H_4	70	81
10	4-CN-C_6H_4	63	80
11	4-NO_2-C_6H_4	90	54
12[c]	2,4,6-$(Me)_3$-C_6H_2		

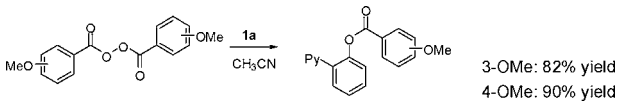
[a] Reaction conditions: **1a** (0.5 mmol), $Pd(OAc)_2$ (5 mol %), 100 °C for 2 h in CH_3CN (1 mL), AcOH (1 mL), peroxide (4 × 0.5 equiv/0.5 h). [b] Isolated yield based on conversion. [c] Methods A and B were employed, but no arylation products were detected.

However, the methoxy-substituted aryl acylperoxides were found to be poor reagents for the decarboxylative C−H arylations. When **1a** was treated with the methoxy-substituted peroxides using either method A or B, no arylation products were formed with 90% substrate recovery. When method C was employed, arylcarboxylation products were obtained exclusively in ca. 85% yield (Scheme 2). We hypothesized that the electron-releasing OMe group may stabilize the aryl carboxyl radicals, thereby retarding the decarboxylation reaction. The observed carboxylation should be mediated by the reaction of the aryl carboxyl radical with the palladacycle.[18]

(15) Performing the arylation of oximes in MeCN/AcOH medium produced a complicated mixture, and extensive hydrolysis of the oximes was observed (see Table S10 in Supporting Information for results).

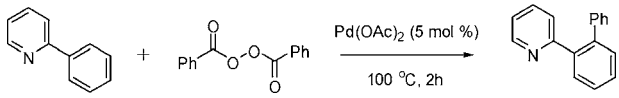
(16) See Supporting Information for details.

Scheme 2. Arylcarboxylation of **1a**[17]



In this work, the catalytic C−H arylation is probably initiated by cyclometalation of 2-arylpyridines to form a palladacycle, which would subsequently react with aryl radicals to afford the biaryl products.[19] The aryl radicals were produced by the thermal decomposition of aryl acylperoxides. Consistent with a radical mechanism, radical scavengers such as ascorbic acid were found to reduce the substrate conversion in a dose-dependent manner (Table 4).

Table 4. The Effect of Radical Scavengers[a]



entry	ascorbic acid (mol %)	% convn	% yield
1		92	80
2	10	82	78
3	25	62	80
4	50	44	78

[a] The reactions were carried out on a 0.5-mmol scale of **1a** at 100 °C for 2 h in CH_3CN (1 mL) and AcOH (1 mL), peroxide (4 × 0.5 equiv/0.5 h). Conversion and yield were determined by GC/FID. The percentage yield is based on conversion.

In closing, we have developed a Pd-catalyzed protocol for decarboxylative arene C−H arylation using aryl acylperoxides as reagents. While the aryl acylperoxides are an inexpensive source of aryl groups and readily prepared from diverse carboxylic acids, CO_2 was produced as an innocuous byproduct. Our results demonstrate a new approach for biaryl formation based on the cross-coupling reactions of organopalladium complexes with aryl radicals. While pursuing a wider application of the biaryl coupling reactions, we are exploring coupling reactions with other carboradicals or heteroatom radicals.

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

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(17) With 2-methoxylbenzoyl peroxide as reagent, no arylation but carboxylation products formation was observed with recovery of **1a**.

(18) A plausible alternative route to arylcarboxylation is via oxidative addition of the peroxide to Pd(II) to give a reactive Pd(IV) species, which would subsequently undergo reductive elimination; see: Canty, A. J.; Jin, H.; Skelton, B. W.; White, A. H. *Inorg. Chem.* **1998**, *37*, 3975.

(19) Ritter and co-workers disclosed a radical mechanism for the $Pd(OAc)_2$-catalyzed heteroatom C-H functionalization, and formation of a Pd(III) −Pd(III) intermediate was proposed; see: Powers, D. C.; Ritter, T. *Nat. Chem.* **2009**, *1*, 302–309.