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Pd-Catalyzed Arylation/Oxidation of Benzylic C–H Bond

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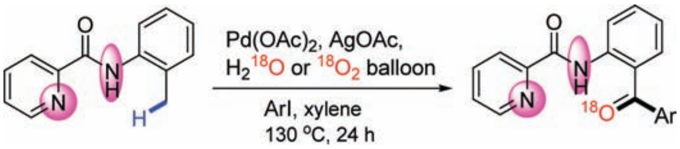
ABSTRACT



A palladium-catalyzed benzylic C–H arylation/oxidation reaction leading to diaryl ketones has been accomplished. The indispensable role of the bidentate system is disclosed for this sequential process. This chemistry offers a direct new access to a range of diarylketones.

Transition-metal-catalyzed selective C–H bond activation has attracted considerable attention because it provides an unprecedented disconnection strategy for constructing carbon–carbon and carbon–heteroatom bonds.[1] Recently, significant progresses in the development of metal-catalyzed sp^2 C–H activations have been approached.[2] However, attempts to establish metal-catalyzed direct functionalization of sp^3 C–H bonds have met with great difficulty for both kinetic and thermodynamic reasons.[3] The benzyl group is an important motif of organic synthesis, and the benzylic C–H bond belongs to a relatively active sp^3 C–H bond due to the proximity of the aromatic system. However, the relevant examples of such direct functionalizations have thus far remained scarce. A pioneering work by Daugulis and co-workers describes the method by employing bidentate systems for the direct arylation of aliphatic sp^3 C–H bonds.[4] Their strategy has been utilized in the synthesis of natural product (+)-obafluorin.[5] Recently, Chatani's group presented important studies by the use of ruthenium catalyst and bidentate systems for the cyclocarbonylation of aromatic[6a] and aliphatic amides.[6b] These breaking discoveries provide promising routes for the activation of sp^3 C–H bond. Herein, we report our findings on palladium-catalyzed benzylic C–H arylation/oxidation that offers the useful diarylmethanones by employing aryl iodides as coupling partners. Importantly, the presence of a bidentate system is essential for this sequential arylation/oxidation process. The monodentate directing groups failed to achieve the transformation (Scheme 1).

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(1) (a) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (b) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (c) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (d) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (e) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (f) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (g) Ashenhurst, J. A. *Chem. Soc. Rev.* **2010**, *39*, 540. (h) Lei, A.; Liu, W.; Liu, C.; Chen, M. *Dalton Trans.* **2010**, *39*, 10352. (i) Daugulis, O. *Top. Curr. Chem.* **2010**, *292*, 57. (j) Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 11212. (k) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (l) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2009**, *110*, 624. (m) Bellina, F.; Rossi, R. *Chem. Rev.* **2009**, *110*, 1082. (n) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (o) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949. (p) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173.

(2) (a) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (b) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (c) Wang, D.-H.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 17676. (d) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115. (e) Deng, G.; Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6278. (f) Tsai, A. S.; Tauchert, M. E.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 1248. (g) García-Rubia, A.; Urones, B.; Gómez Arrayás, R.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 10927.

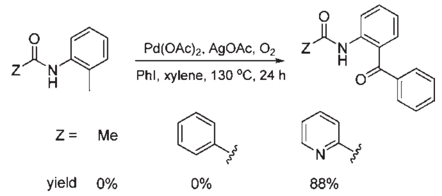
(3) (a) Chatani, N.; Asaumi, T.; Ikeda, T.; Yorimitsu, S.; Ishii, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2000**, *122*, 12882. (b) Dangel, B. D.; Godula, K.; Youn, S. W.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 11856. (c) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542. (d) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882.

(4) (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965.

(5) He, G.; Chen, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 5192.

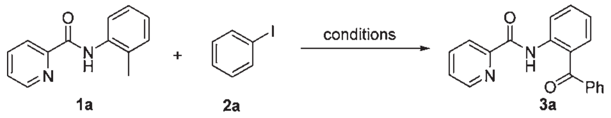
10.1021/ol300037p

Scheme 1. Control Experiments



Amides are potential directing groups in the reactions of C−H activation. We initially employed acetamide and benzamide as directing groups for the arylation of benzylic C−H bond with iodobenzene in the presence of palladium catalysts and AgOAc (Scheme 1). After extensive screening of the reaction conditions, the arylation failed. In light of the remarkable success of Daugulis and Chatani,[4−6] we explored the bidentate systems. To our delight, we obtained a new product, diarylmethanone **3a**, resulting from palladium-catalyzed arylation and oxidation. The reaction took place under argon or air, but dioxygen atmosphere was superior (Table 1, entries 1−3). Screening of the additives indicated that AgOAc gave the best yield (see the Supporting Information). Other palladium catalysts such as PdCl$_2$, Pd(CH$_3$CN)$_2$Cl$_2$, and Pd(PPh$_3$)$_2$Cl$_2$ also worked in this transformation but delivered lower yields (Table 1, entries 4−6). Control experiments confirmed that the palladium catalyst and silver additive were necessary in this process. No reaction was observed in the absence of silver salts or palladium catalysts (Table 1, entries 7−8).

Table 1. Optimization of Reaction Conditions[a]

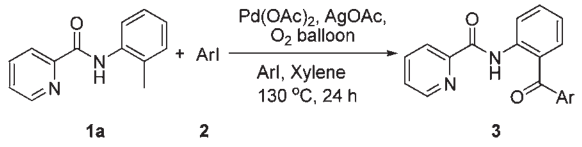


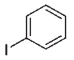
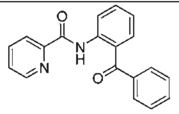
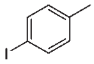
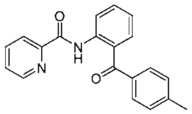
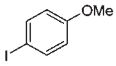
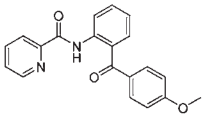
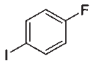
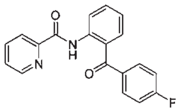
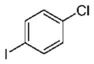
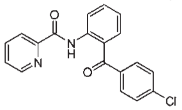
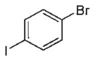
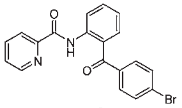
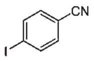
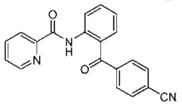
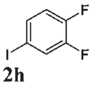
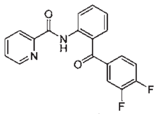
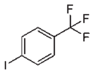
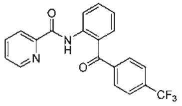
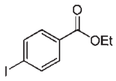
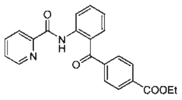
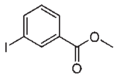
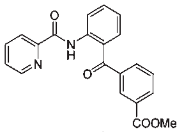
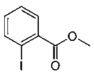
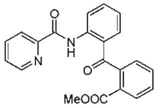
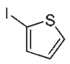
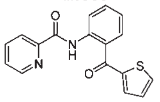
entry	catalyst	additive	atm	yield (%)[b]
1	Pd(OAc)$_2$	AgOAc	Ar	38
2	Pd(OAc)$_2$	AgOAc	Air	51
3	Pd(OAc)$_2$	AgOAc	O$_2$	88
4	PdCl$_2$	AgOAc	O$_2$	83
5	Pd(CH$_3$CN)$_2$Cl$_2$	AgOAc	O$_2$	86
6	Pd(PPh$_3$)$_2$Cl$_2$	AgOAc	O$_2$	47
7	Pd(OAc)$_2$	none	O$_2$	n. r.
8	none	AgOAc	O$_2$	n. r.

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (1.2 mmol), Pd(OAc)$_2$ (0.03 mmol), additive (1.2 mmol), xylene (2 mL), 130 °C, 24 h. [b] Isolated yields.

We next examined the scope of aryliodide as shown in Table 2. Aryliodides with both electron-withdrawing and electron-donating groups presented good compatibility with the reaction conditions (Table 2, entries 1−11).

Table 2. Scope of Aryl Iodides[a]



entry	aryl iodide	product	yield (%) [b]
1	 **2a**		88(**3a**)(71) [c]
2	 **2b**		57(**3b**)
3	 **2c**		60(**3c**)
4	 **2d**		75(**3d**)
5	 **2e**		69(**3e**)
6	 **2f**		57(**3f**)
7	 **2g**		41(**3g**)
8	 **2h**		64(**3h**)
9	 **2i**		64(**3i**)
10	 **2j**		76(**3j**)
11	 **2k**		62(**3k**)
12	 **2l**		n. r. (**3l**)
13	 **2m**		47(**3m**)

[a] Reaction conditions: **1a** (0.3 mmol), aryl iodides (1.2 mmol), Pd(OAc)$_2$ (0.03 mmol), AgOAc (1.2 mmol), xylene (2 mL), 24 h. [b] Isolated yields. [c] 71% of **3a** was obtained on 2 mmol scale.

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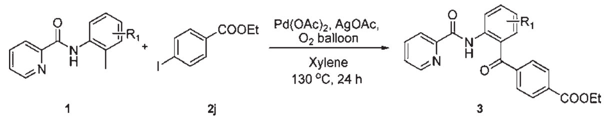
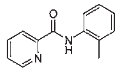
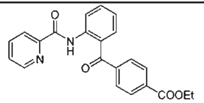
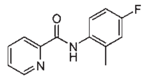
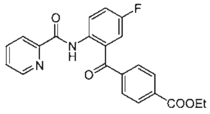
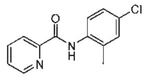
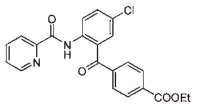
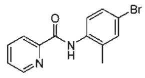
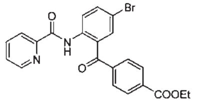
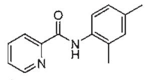
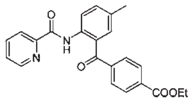
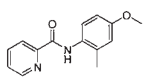
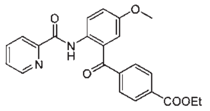
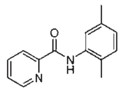
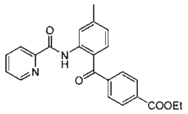
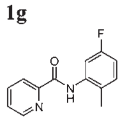
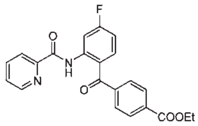
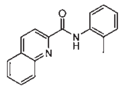
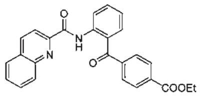
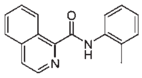
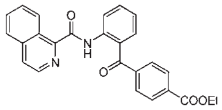
(6) (a) Inoue, S.; Shiota, H.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 6898. (b) Hasegawa, N.; Charra, V.; Inoue, S.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 8070.

Table 3. Scope of Substrate 1[a]

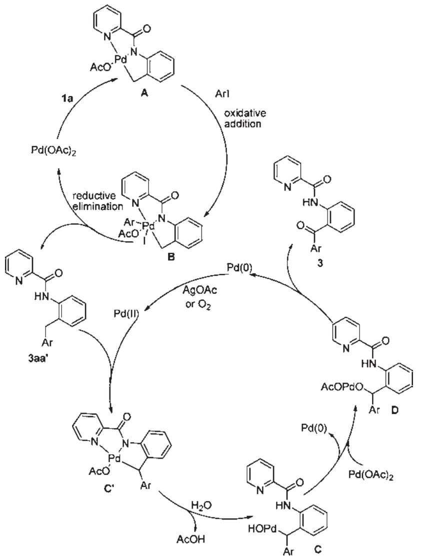


entry	aryl iodide	product	yield (%) [b]
1	 **1a**		76 (**3j**)
2	 **1b**		78 (**3n**)
3	 **1c**		70 (**3o**)
4	 **1d**		63 (**3p**)
5	 **1e**		60 (**3q**)
6	 **1f**		55 (**3r**)
7	 **1g**		70 (**3s**)
8	 **1h**		86 (**3t**)
9	 **1i**		67 (**3u**)
10	 **1j**		62 (**3v**)

[a] Reaction conditions: **1** (0.3 mmol), **2j** (1.2 mmol), Pd(OAc)$_2$ (0.03 mmol), AgOAc (1.2 mmol), xylene (2 mL), 24 h, isolated yield. [b] Isolated yields.

A larger scale of the reaction afforded 71% yield for **3a** (Table 2, entry 1). Notably, introducing functional groups such as F, Cl, Br, CN, and COOEt adds flexibility to further elaborate the ketone products. As for substitution pattern, *meta*-substituted aryliodide also worked in the reaction to give the desired product in 62% (Table 2, entry 11), but an attempt to employ *ortho*-substituted aryliodide failed to yield the expected product, showing that the steric effect plays the role in the reaction (Table 2, entry 12). 2-Iodothiophene also participated in the reaction to give the corresponding ketone product (Table 2, entry 13).

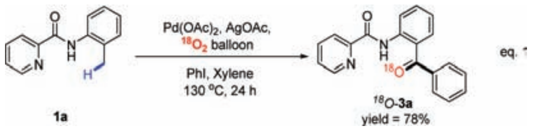
Scheme 2. Plausible Reaction Mechanism

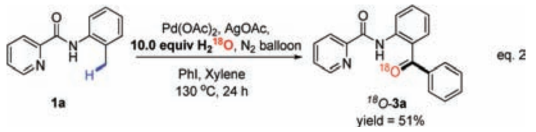


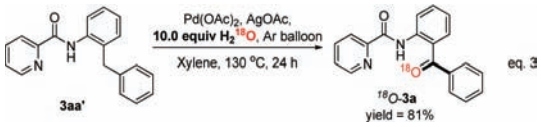
Various arenes were then evaluated as shown in Table 3. The arenes with both electron-withdrawing substituents (F, Cl, and Br) and electron-donating substituents (OMe and Me) on the *para*-position of the phenyl ring underwent this novel transformation to form the corresponding products in moderate to good yields (Table 3, entries 2–6). The introduction of substituents on the *meta*-position of arenes had a negligible effect on the reactions, offering the desired products with minimal variation in yields compared with their *para*-substituted analogues (Table 3, entries 7–8). Moreover, by replacing the pyridine moiety in the substrate with quinoline and isoquinoline, the reaction worked well to give the expected products (Table 3, entries 9–10).

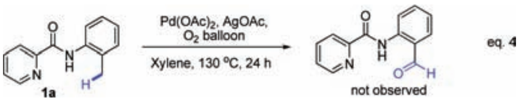
GC–MS analysis of the reaction mixture after 1 h revealed the formation of arylated product **3aa′** (see the Supporting Information), suggesting that the reaction proceeded through a sequential arylation/oxidation process. A plausible mechanism was proposed as depicted in Scheme 2. The coordination of the substrate **1a** with Pd(OAc)$_2$ and subsequent C–H bond cleavage led to the formation of intermediate **A**, which underwent oxidative addition with aryliodide to produce intermediate **B** involving a Pd(IV) center.[4] The subsequent reductive elimination gave the arylation product **3aa′** (detected by GC–MS, see the Supporting Information), which can complex with Pd(OAc)$_2$ followed by ligand exchange with H$_2$O to form the intermediate **C**. The subsequent oxidation of **3aa′** generated the final ketone product.

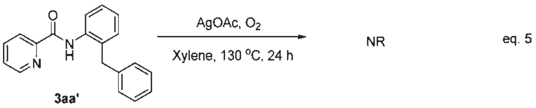
The reaction of **1a** with iodobenzene under $^{18}O_2$ atmosphere delivered ^{18}O-labeled product ^{18}**O-3a** (see the Supporting Information), indicating that the oxygen in the diaryl ketones originated from molecular oxygen (eq 1). We subjected **1a** under the reaction conditions in the presence of $H_2{}^{18}O$ under argon, and the ^{18}O-labeled product ^{18}O-**3a** was indeed isolated in 51% (eq 2). However, the oxidation product **3a** was also produced in good yield when the arylated product **3aa′** was employed as substrate under argon under the reaction conditions. Moreover, ^{18}O-labeled product ^{18}O-**3a** was isolated in 81% yield when the reaction proceeded in the presence of $H_2{}^{18}O$ (eq 3). This result suggested that the oxygen in the ketone also possibly came from water. No oxidation was observed prior to arylation under the standard conditions (eq 4). The ketone was not detected in the absence of palladium catalysts (eq 5). One possible explanation for this result is that $^{18}O_2$ may serve as the oxidant for Pd(0) to Pd(II) and generate $H_2{}^{18}O$, which would participate in the catalytic cycle to yield the ^{18}O-labeled product. The oxidation of **3aa′** possibly occurred by the reductive elimination of intermediate **C** followed by ligand exchange with $Pd(OAc)_2$ to give intermediate **D**, which underwent β-hydrogen elimination to liberate **3** product. The resulting Pd(0) was oxidized by dioxygen or silver salt to Pd(II) to furnish the cycle. Under the dioxygen atmosphere, the direct oxidation of **3aa′** by oxygen in the presence of palladium catalyst to form the ketones was also possible under the reaction conditions.[7]





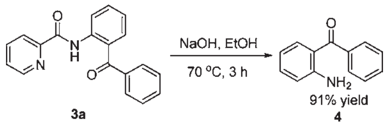






Further experiments showed that the directing group can be removed by hydrolysis under basic conditions to afford 2-aminobenzophenone derivatives (Scheme 3), which are key starting materials for the synthesis of bioactive agents, such as proquazone[8] and amfenac.[9]

Scheme 3. Hydrolysis of Amide **3a**



In conclusion, we have developed a new protocol for Pd-catalyzed arylation/oxidation of benzylic C–H bonds by employing a bidentate system. This new transformation tolerates a broad range of substrates, providing an alternative for the synthesis of diarylketones. Further efforts for direct functionalization of the benzylic C–H bond by using bidentate systems are going on in our laboratory.

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Supporting Information Available. The experimental procedures and spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS) for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.