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Versatile Pd(II)-Catalyzed C−H Activation/Aryl−Aryl Coupling of Benzoic and Phenyl Acetic Acids

Dong-Hui Wang, Tian-Sheng Mei, and Jin-Quan Yu*

Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

Received August 23, 2008; E-mail: yu200@scripps.edu

Despite the development and progress of Pd-catalyzed C−H activation/C−C coupling reactions with organometallic reagents,[1,2] improving the practicality of Pd(II)/Pd(0) catalysis[3] and expanding the substrate scope remain significant challenges. In this regard, the highly versatile Pd-catalyzed cross-coupling reactions using organohalides and other surrogates have two principal advantages:[4,5] (1) an exogenous oxidant is not required, and (2) rationally designed ligands that promote these reactions and modulate the reactivity with a wide range of substrates are available. Herein we disclose a new catalytic system for C−H activation/C−C coupling that offers a greatly improved scope and practicality by using aryltrifluoroborates[6] as the coupling partners and O_2 or air as the oxidant. These new conditions made possible, for the first time, the *ortho*-C−H coupling of highly electron-deficient arenes and phenyl acetic acids, a class of broadly useful starting materials. Importantly, the presence of acidic α-hydrogens is tolerated. This method provides a general preparative route for compounds that are not accessible via the widely used ortho-metalation/iodination/cross-coupling sequence (Figures 1 and 2).[7]

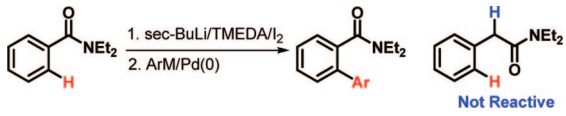


Figure 1. Directed *ortho*-metalation (DOM).

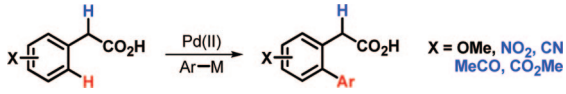
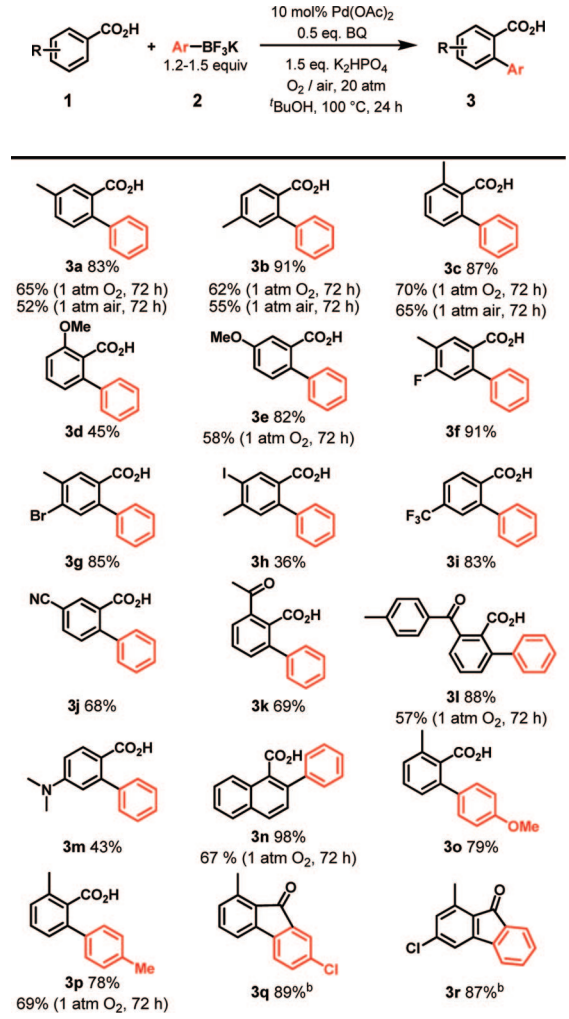


Figure 2. C−H activation/aryl−aryl Coupling.

We have previously reported Pd-catalyzed *ortho*-coupling of benzoic acids with phenylboronate using Ag_2CO_3 as the oxidant.[1c] This arylation protocol is limited to only a handful of benzoic acids. Poor yields (<40%) are obtained with electron-deficient arenes. No coupling products are observed with phenyl acetic acid substrates due to the sluggish six-membered cyclopalladation directed by the carboxyl group. From the viewpoint of synthetic applications, development of C−H activation reactions for phenyl acetic acids would substantially improve the versatility and usefulness of this reaction. Therefore, we extensively screened reaction parameters and coupling partners, using benzoic acids as substrates, in an effort to accelerate the C−H activation step. We found the replacement of the Ag_2CO_3 oxidant by air or O_2 and the use of aryltrifluoroborates together greatly improve the yield and scope of the ortho-coupling of benzoic acids (Table 1). Since the κ^2 coordination of carboxylate with the K^+ is essential for C−H activation,[1c] Ag^+ or Cu^{2+} apparently retards the reaction by binding to the carboxyate. The influence of $ArBF_3K$ on the C−H activation reaction deserves further study.

Although, the use of 20 atm of air or O_2 was needed to shorten the reaction time, we were pleased to find that use of 1 atm of O_2 or air

Table 1. Coupling of Benzoic Acids with Potassium Aryltrifluoroborate[a]



[a] **3b**−**3d**, **3f**−**3p** were isolated as their methyl esters formed by reacting with CH_2N_2. [b] Treatment of the coupling products with oxalyl chloride afforded **3q** and **3r**.

gave the desired products in 60−70% yields after 72 h (**3a**–**3c**). Especially noteworthy are the excellent yields obtained with the highly electron-deficient substrates containing fluoride, bromide, trifluoromethyl, cyano, and acetyl groups (**3f**, **3g**, **3i**, **3j**, **3k**), the presence of which is crucial for further synthetic manipulations. Excellent regioselectivity in favor of the less hindered C−H bonds was observed with *meta*-substituted substrates (**3a**, **3f**, **3g**). The isolation of the coupling products **3o**, **3p**, and **3q** also demonstrated the compatibility of this reaction with other aryltrifluoroborates. Ketones **3q** and **3r** were readily formed by treating the initially formed coupling products with

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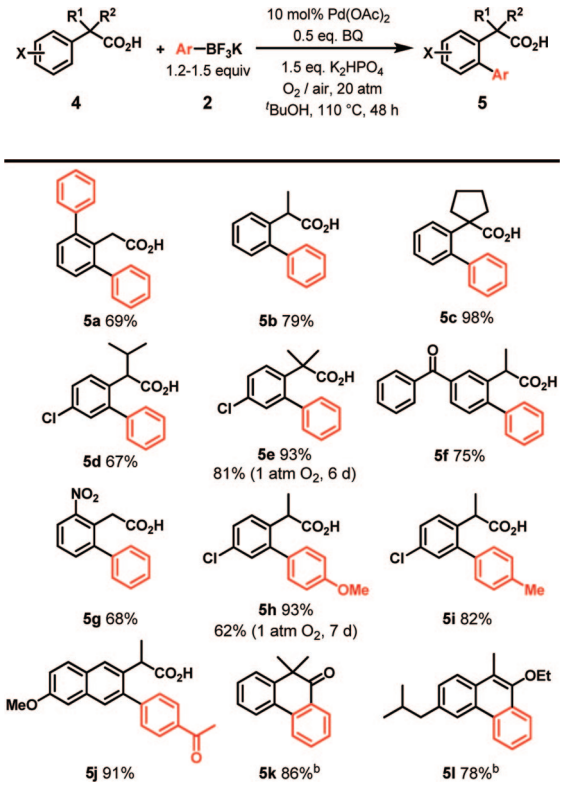
oxalyl chloride, illustrating potential applications for the synthesis of biologically interesting fluoren-9-ones.[8]

The efficiency of this reaction protocol encouraged us to test the coupling of phenyl acetic acids. Notably, our previous approach using an oxazoline as the auxiliary for the *ortho*-coupling failed with substrates containing α-hydrogens.[1a] Another existing protocol using *O*-methyl hydroxamic acids as a directing group, unfortunately, is not applicable to sp^2 C−H activation/C−C coupling.[1e] We were pleased to find that the coupling of phenyl acetic acid with $PhBF_3K$ using O_2 as the oxidant proceeded effectively to give the diarylated product **5a** in 69% yield. Interestingly, the presence of Ag^+ oxidant results in a complete loss of the reactivity. The presence of an α-substituent provides sufficient steric hindrance to induce the monoselectivity (**5b**, **5c**). Both strongly electron-withdrawing (**5d**−**5g**) and electron-donating (**5j**) groups are compatible with this reaction. Aryltrifluoroborates containing either electron-donating or electron-withdrawing groups were also effective (**5h**−**j**)

Table 2. Coupling of Arylacetic Acids with Potassium Aryltrifluoroborates[a]

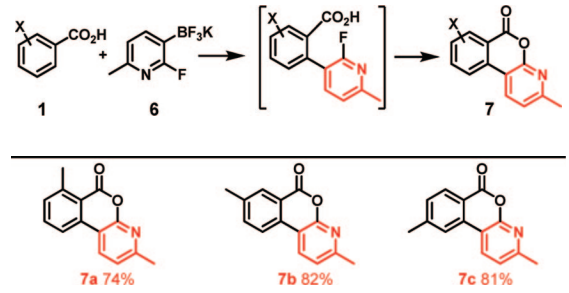


[a] **5a**, **5c**, **5e**−**5j** were isolated as their methyl esters formed by treating with CH_2N_2. [b] Treatment of the coupling products with oxalyl chloride afforded **5k** and **5l**.

In general, phenyl acetic acids are a class of broadly useful starting materials for synthetic chemistry. For example, the reduction of the nitro group in the methyl ester of **5g** to the corresponding amine simultaneously triggers lactamization to give a synthetically useful lactam. Treating the coupling products with oxalyl chloride readily gave the cyclized ketone (**5k**), and the coupling product from a drug, ibuprofen, was also converted to a tricyclic enoether **5l** by treatment with oxalyl chloride in the presence of trace ethanol.

Considering the importance of heterocycles in medicinal chemistry, we attempted to introduce a pyridyl group into benzoic acid via this newly developed coupling protocol. While coupling of benzoic acids with 3-pyridyltrifluoroborate gave the desired products

Table 3. Coupling with Potassium Pyridyltrifluoroborate[a]



[a] Reaction conditions: **1** (0.5 mmol), **6** (0.7 mmol), $Pd(OAc)_2$ (0.05 mmol), BQ (0.25 mmol), K_2HPO_4 (1 mmol), O_2 or air (20 atm), *t*-BuOH (2 mL), 110 °C, 36 h.

in only ∼10% yield, pyridyltrifluoroborate bearing 2-substitution proved to be effective. Surprisingly, the coupling products underwent a further intramolecular fluoro-displacement by the carboxyl groups to give the tricyclic lactones in a one-pot process.

In summary, we have developed a versatile protocol for C−H activation/aryl−aryl coupling using aryltrifluoroborates. This new protocol substantially expands the scope of reactions involving benzoic acids and made possible, for the first time, the *ortho*-C−H coupling of phenyl acetic acids containing α-hydrogens, and electron-deficient arenes. We are currently investigating a possible effect of $ArBF_3K$ on C−H activation reactions and improving the efficiency of this reaction under 1 atm of air.

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

References

(1) (a) Chen, X.; Li, J.-J.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 78. (b) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634. (c) 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. (d) Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 6066. (e) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190.

(2) For recent examples of Pd-catalyzed arylation of C−H bonds involving other types of catalysis, see: (a) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (b) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046. (c) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020.

(3) For recent reviews on Pd(II)/Pd(0) catalysis, see: (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400. (b) Stoltz, B. *Chem. Lett.* **2004**, *33*, 362. (c) Gligorich, K. M.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 6612. (d) Piera, J.; Backvall, J.-E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3506.

(4) For reviews, see: (a) Diederich, F., Stang, P. J., Eds. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: New York, 1998. (b) Hiyama, T. *J. Organomet. Chem.* **2002**, *653*, 58. (c) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442. (d) Negishi, E.; Hu, Q.; Huang, Z.; Qian, M.; Wang, G. *Aldrichimica Acta* **2005**, *38*, 71.

(5) (a) Old, D. W.; Wolf, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722. (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387. (c) Herrmann, W. A.; Reisinger, C.-P.; Spiegler, M. *J. Organomet. Chem.* **1998**, *557*, 93. (d) Beller, M.; Riermeier, T. H. *Eur. J. Inorg. Chem.* **1998**, 29. (e) Shaughnessy, K. H.; Kim, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 2123. (f) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804.

(6) (a) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020. (b) Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393. (c) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275. (d) Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, *108*, 288.

(7) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306.

(8) Zhao, J.; Yue, D.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2007**, *129*, 5288.

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