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Palladium-Catalyzed Methylation and Arylation of sp^2 and sp^3 C−H Bonds in Simple Carboxylic Acids

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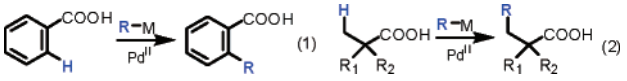
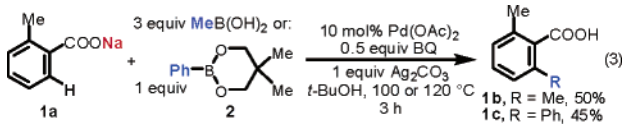
Palladium-catalyzed cross-coupling reactions are among the most widely used carbon−carbon bond-forming reactions in organic synthesis.[1] Extensive development of a wide range of ligands has allowed the use of ArCl,[2a−c] alkyl halides,[2d] and sterically hindered 2,6-substituted ArX[2e] as coupling partners. The decarboxylative Heck or Suzuki coupling using ArCOOH is another practically appealing approach since carboxylic acids are readily available.[3] The potential of Pd-catalyzed C−H activation reactions for developing synthetically useful carbon−carbon bond forming reactions prompted our initial efforts to couple sp^2 and sp^3 C−H bonds in oxazoline and pyridine substrates with organotin and organoboron reagents.[4,5] However, these types of substrates seriously restrict the substrate scope since the oxazolines require installation and removal and pyridines lack versatility for further synthetic manipulations.

Considering the broad utility of hydroxyl and carboxyl functionalities as directing groups in asymmetric catalysis,[6] the use of simple functional groups to direct C−H activation/C−C coupling processes could prove fruitful in developing C−C bond forming reactions.[7] Carboxyl-directed lactonization of sp^3 C−H bonds catalyzed by K_2PtCl_4 has been previously observed by Sen, Sames, and others.[8] Ortho alkenylation of benzoic acid catalyzed by Pd(OAc)$_2$ has been reported by Miura.[9] Despite these significant advances, Pd-catalyzed C−H activation/C−C coupling reactions using a carboxyl group (eqs 1,2) have not been developed. In particular, Pd-catalyzed coupling of sp^3 β-C−H bonds in aliphatic acids with organometallic reagents is an unanswered challenge and yet a significant goal from the viewpoint of synthetic applications. Herein, we report the first catalytic protocol for the coupling of both *o*-C−H bonds in benzoic acids and β-C−H bonds in aliphatic acids with organoboron reagents via Pd^{II}/Pd^0 catalysis. The generality of this newly observed Pd-insertion into β-C−H bonds was further demonstrated by β-arylation of aliphatic acids using ArI in which Pd^{II}/Pd^{IV} catalysis is likely responsible.[10−11]



The formation of phenoxide in the presence of Cs_2CO_3 accelerates both intra-[12a] and intermolecular[12b] ortho arylation of phenols using a combination of Pd^0 and ArI. This effect was attributed to either an increase of the electron density of the phenyl ring or an enhanced binding of the ArPdI species to the phenoxide. Inspired by these observations, we focused on the development of Pd(OAc)$_2$-catalyzed C−H functionalization processes directed by carboxyl groups. If successful, these types of processes could be applicable to a wide range of simple substrates containing acidic protons. On the basis of the Pd-catalyzed coupling protocols recently developed in our laboratory,[4b] we began to search for coupling conditions using simple carboxylic acids as substrates. Extensive screening of conditions (see Supporting Information) led us to discover that the use of sodium carboxylates as substrates was effective for the desired transformation. Thus, stirring sodium toluate **1a** with 0.5 equiv of benzoquinone, 1 equiv of Ag_2CO_3,[13] 3 equiv of MeB(OH)$_2$ and 10 mol % Pd(OAc)$_2$ in *tert*-amyl alcohol or *tert*-BuOH at 100 °C for 3 h affords ortho methylated product **1b** in 50% isolated yield (eq 3). Arylation of **1a** using a phenylboronate **2** as the coupling partner proceeds under similar conditions at 120 °C to give ortho arylated product **1c** in 45% isolated yield (eq 3). Based on our previous studies,[4b] this catalytic reaction most likely proceeds via a Pd^{II}/Pd^0 catalysis. *Although the role of sodium counterions remains to be elucidated, we have shown that the preformed palladium toluate*[14] *in the absence of sodium counterions is not reactive.* This led us to hypothesize that the electronically enriched carbonyl instead of the O-anion of the sodium carboxylate binds the Pd^{II} in the C−H cleavage step.



Guided by the mechanism of the Suzuki coupling reaction, we reasoned that the yield could be further improved by employing a suitable base to enhance the transmetalation step in the coupling reaction. We screened a wide range of bases and found that K_2HPO_4 increases the yields of **1b** and **1c** to 75% and 63%, respectively (Table 1, entries 1, 3). Since the presence of K_2HPO_4 leads to the in situ formation of carboxylates, benzoic acids instead of sodium carboxylates are used as substrates under these new conditions.

Although the arylation of benzoic acid gives a mixture of mono- and diarylated compounds in 50% yield (3:2 ratio), we found that the meta substituted benzoic acids lead to regioselective arylation, albeit in lower yields (Table 1, entries 4−6). The tolerance of OMe and CO_2Me groups allows for the preparation of a wide range of 1,2,4-substituted arenes.

Encouraged by these results, we attempted the coupling of β-C−H bonds in aliphatic acids with **2**. The sodium carboxylate of **6** was subjected to the arylation conditions in eq 3 to give

Table 1. Ortho Methylation and Arylation of Benzoic Acids[a]

entry	substrate	product	yield(%)	entry	substrate	product	yield(%)
1			75[b]	4			50
2			71[b]	5			46
3			63	6			40

[a] Conditions: 10 mol % Pd(OAc)$_2$, 0.5 equiv of benzoquinone, 1 equiv of Ag_2CO_3, 1.5 equiv of K_2HPO_4, 2 equiv of MeB(OH)$_2$ or 1 equiv of **2**, *tert*-BuOH, 120 °C, 3 h. [b] Yield at 100 °C.

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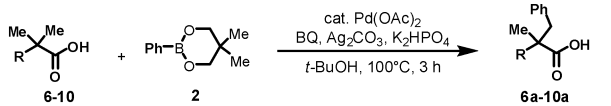
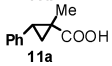
Table 2. β-Arylation of Aliphatic Acids Using Ph−B(OR)$_2$[a]

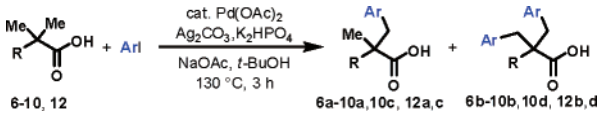


6-10 + 2 → 6a-10a

entry	product	yield (%)[b]	entry	product	yield (%)[b]
1	R = Me **6a**	38	4	R = $(CH_2)_3OBn$ **9a**	30
2	R = Et **7a**	30	5	R = $(CH_2)_2CO_2Me$ **10a**	30
3	R = ^{n}Bu **8a**	28	6	 **11a**	20

[a] Conditions: 10 mol % Pd(OAc)$_2$, 1 equiv of **2**, 0.5 equiv of benzoquinone, 1 equiv of Ag_2CO_3 and 1.5 equiv of K_2HPO_4. [b] Yields of their methyl esters. Less than 2% diarylated products were observed in **6**−**10**.

Table 3. β-Arylation of Aliphatic Acids Using ArI[a]



6-10, 12 → 6a-10a,10c, 12a,c + 6b-10b,10d, 12b,d

entry	product	yield (%)[b]	entry	product	yield (%)[b]
1	R = Me, Ar = Ph **6a/6b**, 5:2	70	5	R = ^{t}Bu,, Ar = Ph **8a/8b**, 4:1	62
2	R = Et, Ar = Ph **7a/7b**, 4:1	72	6	R = $(CH_2)_3OBn$, Ar = Ph **9a/9b**, 5:1	45
3	R = ^{i}Pr, Ar = *p*MePh **12a/12b**, 3:1	60	7	R = $(CH_2)_2CO_2Me$, Ar = Ph **10a/10b**, 5:1	42[c]
4	R = ^{n}Pr, Ar = *p*-BrPh **12c/12d**, 3:1	63	8	R = $(CH_2)_2CO_2Me$, Ar = *p*-MePh **10c/10d**, 5:1	43

[a] Conditions: 10 mol % Pd(OAc)$_2$, 2 equiv of aryl iodide, 2 equiv of Ag_2CO_3, 1 equiv of K_2HPO_4, and 2 equiv of NaOAc. [b] Yields of their methyl esters. [c] **10b** was not isolated. The yield is based on **10a**.

predominantly the monoarylated product **6a** in 30% isolated yield. The use of Ag_2O or AgOAc in place of Ag_2CO_3 as an oxidant afforded less than 5% of **6a**. The presence of Na_2CO_3 results in a complete loss of reactivity with aliphatic acids. However, the potassium carboxylate of **6** generated in situ using K_2HPO_4 affords **6a** in 38% isolated yield (Table 2, entry 1).

While the catalytic turnover remains to be improved, the observed mono-selectivity is a highly desirable advantage. Benzylethers and esters were also tolerated (Table 2, entries 4−5), thus making this protocol potentially applicable to organic synthesis. The preferential arylation of the cyclopropyl C−H bond is worth noting since examples of Pd insertion into methylene C−H bonds are still rare (entry 6).[15]

Importantly, this coupling reaction provides the first example for carboxyl-directed Pd-insertion into sp^3 β-C−H bonds in simple aliphatic acids. To demonstrate the generality of this C−H cleavage reactivity in C−C bond forming reactions, we carried out arylation reactions using ArI as the arylating reagents.[15−17] We found that alteration of our coupling protocol by omitting the benzoquinone and using PhI as the coupling partner led to mono- and diarylation of aliphatic acid **6** in 40% combined yield (**6a**/**6b** = 5:2). We further discovered that the use of 2 equiv of NaOAc as an additive substantially increases the combined yield of **6a** and **6b** to 70% (Table 3).[18]

This arylation reaction most likely involves a COOH directed Pd insertion into C−H bonds and subsequent oxidation of the RPd^{II}-complex to (R)(Ar)Pd^{IV}I intermediate by ArI. The formation of diarylated products (Table 3) is consistent with the Pd^{II}/Pd^{IV} pathway in which the Pd^{II}, unlike the Pd^0 in the cross-coupling protocol, remains bound to the carboxylate and results in further arylation. Ag_2CO_3 is mainly responsible for the catalytic turnover by converting PdI_2 into the reactive Pd^{II} species.[16a] The excess AcO$^-$ could also displace the iodide from the (R)(Ar)Pd^{IV}I intermediate and increase the turnover number as observed.

In summary, we have observed the first example of Pd-insertion into sp^3 β-C−H bonds in simple aliphatic acids. A promising protocol for the coupling of sp^2 and sp^3 C−H bonds in simple carboxylic acids with organoboron reagents has been established. The potential of carboxyl-directed C−H activation in developing C−C bond-forming reactions is also demonstrated by the arylation of β-C−H bonds in aliphatic acids using ArI. We are currently optimizing the conditions to improve the yields of these reactions.

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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) For reviews see: (a) Diederich, F., Stang, P. J., Eds. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: New York, 1998. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442.
(2) (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2411. (b) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413. (c) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473. (d) Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099. (e) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.
(3) (a) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250. (b) Goo*β*en, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662.
(4) (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.
(5) For a Rh-catalyzed ortho arylation of 2-phenylpyridine using tetraaryltin see: Oi, S.; Fukita, S.; Inoue, Y. *Chem. Commun*. **1998**, 2439.
(6) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Brown, J. M. *Chem. Soc. Rev.* **1993**, *22*, 25. (c) Halpern, J. *Science* **1982**, *217*, 401.
(7) (a) For a remarkable Ru-catalyzed ortho arylation of acetophenone using a phenylboronate see: Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698. (b) For an example of Rh-catalyzed alkenylation of aryl C−H bonds directed by imine see: Thalji, R. K.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2004**, *126*, 7192. (c) For a Pd-catalyzed arylation of sp^3 C−H bonds in 2,4,6-tri-*tert*-butylbromobenzene with PhB(OH)$_2$ see: Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685. (d) For a Pd-catalyzed arylation of vinylic C−H bonds with PhB(OH)$_2$ see: Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 15076.
(8) (a) Kao, L.-C.; Sen, A. *J. Chem. Soc., Chem. Commun*. **1991**, 1242. (b) Dangel, B. D.; Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2001**, *123*, 8149. (c) Lee, J. M.; Chang, S. *Tetrahedron Lett.* **2006**, *47*, 1375.
(9) Miura, M.; Tsuda, T.; Satoh, T.; Pivsa-Art, S.; Nomura, M. *J. Org. Chem.* **1998**, *63*, 5211.
(10) For arylation of sp^3 C−H bonds using an amide-pyridine directing group and ArI as the arylating reagent see: Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154.
(11) For arylation of aryl and benzylic C−H bonds using [Ph$_2$I]BF$_4$ or [Ph$_2$I]-PF$_6$ 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.
(12) (a) Hennings, D. D.; Iwasa, S.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 2. (b) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 1740.
(13) Ag_2CO_3 releases Ag^+ and CO_3^{2-} slowly during the reaction which appears to be important for the catalysis.
(14) Hermans, S.; Wenkin, M.; Devillers, M. *J. Mol. Catal. A: Chem.* **1998**, *136*, 59.
(15) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391.
(16) For examples of Pd-catalyzed methylation or arylation of sp^2 C-H bonds using MeI or ArX see: (a) Tremont, S. J.; Rahman, H. U. *J. Am. Chem. Soc.* **1984**, *106*, 5759. (b) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1985**, *286*, C13. (c) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed.* **1997**, *36*, 119. (d) Campo, M. A.; Huang, Q.; Yao, T.; Tian, Q.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 11506. (e) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148.
(17) For arylation of sp^3 C−H bonds in 1-*tert*-butyl-2-iodobenzene see: Dyker, G. *Angew. Chem., Int. Ed.* **1992**, *31*, 1023.
(18) The arylation of toluic acid **1** under the same conditions gives the ortho arylated product in 95% yield.

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