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Regioselective *ortho*-acetoxylation/methoxylation of *N*-(2-benzoylphenyl)benzamides via substrate directed C–H activation

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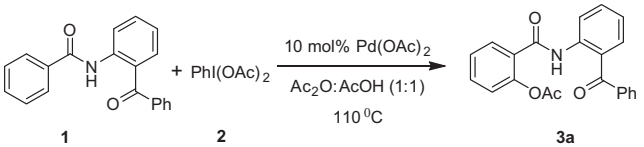
ABSTRACT

A highly regioselective *ortho*-acetoxylation of *N*-(2-benzoylphenyl)benzamides has been achieved using a catalytic amount of $Pd(OAc)_2$ (10 mol %) and a stoichiometric amount of $PhI(OAc)_2$ in a mixture of acetic anhydride and acetic acid via C–H activation to produce the corresponding 2-acetoxybenzamides in good yields. *ortho*-Methoxylation has been accomplished using methanol under similar conditions.

The transition metal catalyzed C–H activation has become a powerful tool for the functionalization of unactivated carbon–hydrogen bonds to construct carbon–carbon or carbon–heteroatom bonds.[1–5] However, direct functionalization of substrates with similar C–H bonds tends to require a directing group.[6] Generally, the directing group possesses a lone pair which coordinates to the transition metal catalyst to direct *ortho* functionalization via a five- or six-membered metallacycle.[7] In particular, the oxidation of aromatic C–H bonds is a challenging task in organic synthesis.[8] The concept of dual activation in the acetoxylation of amides possessing a pyridine or 8-aminoquinoline directing group has recently been reported.[9] However, there are no reports on the oxidative functionalization of carboxamide amides via dual activation of both amide NH and *ortho*-chelating carbonyl group.

In continuation of our interest on the functionalization of arenes via C–H activation,[10] herein, we report a direct method for the acetoxylation/methoxylation of benzamides activated by both amide NH and *ortho*-carbonyl group. Initially, we attempted the acetoxylation of simple benzamide derived from benzoic acid and aniline with Ac_2O using a catalytic amount of $Pd(OAc)_2$ and a stoichiometric amount of $PhI(OAc)_2$ in acetic acid at 100 °C. The reaction was very slow and the desired product was obtained in 40% yield after 24 h. Next, we attempted the acetoxylation of *N*-(2-benzoylphenyl)benzamide (**1**) under similar conditions. Interestingly, mono-acetoxylated product **3a** was obtained in 80% yield after 5 h (Scheme 1).

The acetoxylation was highly *ortho*-selective to the amide group. In acetoxylation reaction, $Pd(OAc)_2$ acts as a catalyst to activate aromatic C–H bond via an oxidative insertion. $PhI(OAc)_2$ acts as a co-oxidant to reoxidize Pd(0) to Pd(II). Ac_2O acts as an acetoxylating agent. The efficiency of various co-oxidants such as $PhI(OAc)_2$, AgOAc, $Cu(OAc)_2$, $Mn(OAc)_3$, and benzoquinone was tested for this reaction. Of these, $PhI(OAc)_2$ was found to be effective in terms of conversion. The acetoxylation was also performed using various amounts of $Pd(OAc)_2$. Though the reaction proceeds with 5 mol % of $Pd(OAc)_2$, the reaction requires long reaction time, about 12 h, to furnish comparable yield. Under optimized conditions, the acetoxylation typically requires 10 mol % $Pd(OAc)_2$ and a stoichiometric amount of $PhI(OAc)_2$ to achieve good conversions. Next we have performed the reaction at various temperatures in various solvents. The reaction was sluggish either in toluene or in 1,4-dioxane. The reaction proceeds smoothly at 100–110 °C in acetic acid. Notably, sterically hindered substrates also participated effectively in acetoxylation (Table 1, entry f). No acetoxylation was observed on remote sp^3 C–H bond in case of methyl substituted benzamides (Table 1, entries g, l, and m).



1 2 3a

Scheme 1. Acetoxylation of *N*-(2-benzoylphenyl)benzamide.

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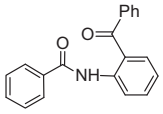
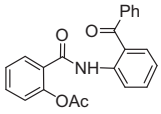
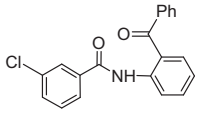
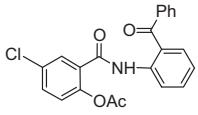
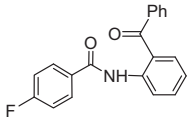
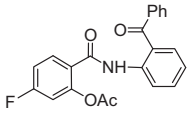
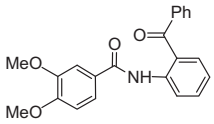
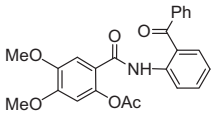
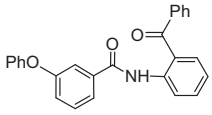
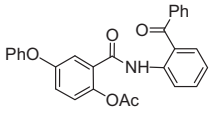
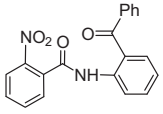
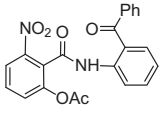
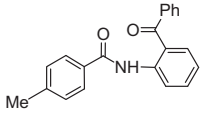
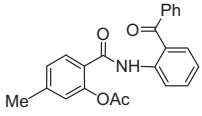
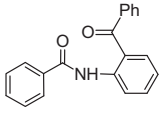
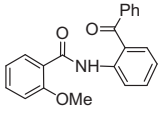
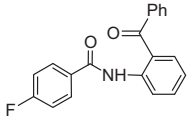
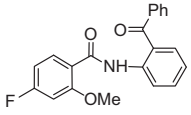
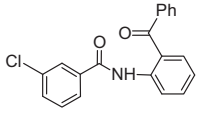
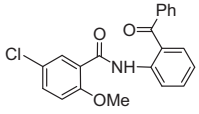
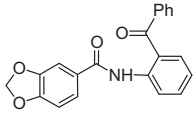
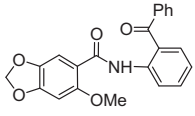
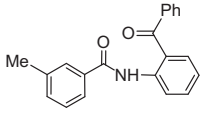
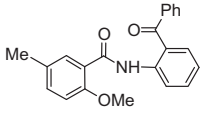
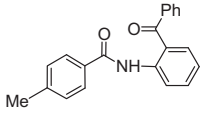
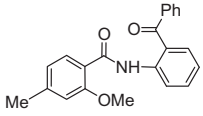
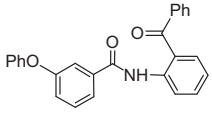
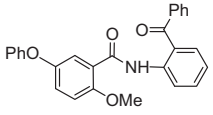
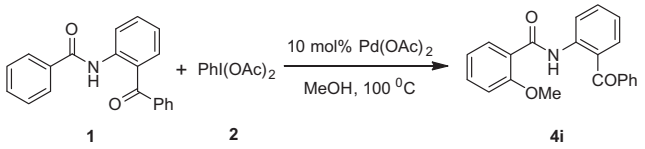
Table 1
Pd(II)-catalyzed acetoxylation/methoxylation of aromatic carboxamides via C–H activation

Entry	Substrate	Nucleophile	Product[a]	Time (h)	Yield[b] (%)
a		Ac_2O	 **3a**	5.0	80
b		Ac_2O	 **3b**	4.0	85
c		Ac_2O	 **3c**	4.0	82
d		Ac_2O	 **3d**	6.0	90
e		Ac_2O	 **3e**	5.0	85
f		Ac_2O	 **3f**	10	30
g		Ac_2O	 **3g**	6.0	70
h		MeOH	 **4h**	6.0	85
i		MeOH	 **4i**	6.0	80
j		MeOH	 **4j**	6.0	82
k		MeOH	 **4k**	8.0	70
l		MeOH	 **4l**	8.0	73
m		MeOH	 **4m**	8.0	75
n		MeOH	 **4n**	5.0	85

[a] All products were characterized by ^{1}H NMR, IR, and mass spectrometry.
[b] Yield refers to pure products after chromatography.



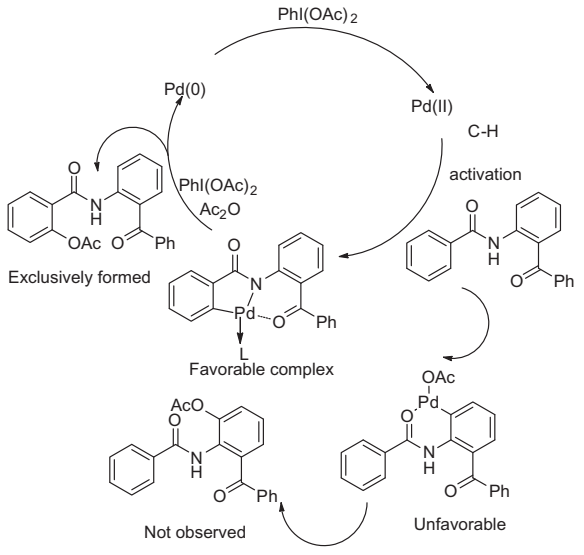
Scheme 2. Methoxylation of *N*-(2-benzoylphenyl)benzamide.

Next, we extended this method to study the methoxylation of benzamides under similar conditions. Accordingly, we attempted the methoxylation of *N*-(2-benzoylphenyl)benzamide (**1**) in methanol using $Pd(OAc)_2$/$PhI(OAc)_2$. By simply changing the solvent from acetic acid to methanol, the methoxylated product **4i** was obtained in 85% yield over 6 h (Scheme 2).

Interestingly, a variety of aromatic carboxamides bearing substitutions at *ortho-*, *meta-*, and *para*-positions participated well in this reaction (Table 1). No dehalogenation was obtained in case of halogenated substrates (Table 1, entries b, c, i, and j). Notably, various functional groups such as amide, ketone, halides, ethers, and methyl functionalities are well tolerated under the reaction conditions. No acetoxylation was observed in the absence of either $Pd(OAc)_2$ or $PhI(OAc)_2$. Among various oxidants such as AgOAc, $Mn(OAc)_3$, and $Cu(OAc)_2$, $PhI(OAc)_2$ was found to be effective in terms of conversion. In all cases, the reactions were clean and the products were obtained in excellent yields. The products were characterized by NMR, IR, and mass spectroscopy. The scope and generality of this process are illustrated with respect to various benzamides bearing electron-rich as well as electron-deficient substituents on aromatic ring and the results are presented in Table 1.[11]

We assume that the reaction proceeds via the formation of five-membered transition state by an oxidative insertion of Pd(II) into aromatic C–H bond as depicted in Scheme 3. Thus formed palladacyle might be stabilized with carbonyl group to induce the *ortho*-acetoxylation. The resulting Pd(0) could be converted into Pd(II) by $PhI(OAc)_2$ to complete the catalytic cycle.

In summary, we have developed a novel protocol for the oxidative functionalization of benzamides bearing *ortho*-chelating carbonyl group via C–H activation. The method is very useful not only for acetoxylation but also for methoxylation of aromatic systems. It works for both electron-rich as well as electron-deficient substrates.



Scheme 3. A plausible reaction pathway.

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References and notes

1. (a) Dyker, G. *Handbook of C–H Transformations: Applications in Organic Synthesis*; Wiley-VCH: Weinheim, 2005; (b) Chatani, N. In *Directed Metallation*; Springer: Berlin, 2008; Vol. 24,; (c) Beccalli, E M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318; (d) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013; (e) Goj, L. A.; Gunnoe, T. B. *Curr. Org. Chem.* **2005**, *9*, 671; (f) Li, B.; Yang, S.; Shi, Z. *Synlett* **2008**, 949; (g) Diaz-Requejo, M. M.; Perez, P. J. *Chem. Rev.* **2008**, *108*, 3379; (h) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242; (i) Daugulis, O.; Do, J.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074.
2. (a) Shi, Z.; Li, B.; Wan, X.; Cheng, J.; Fang, Z.; Cao, B.; Qin, C.; Wang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 5554; (b) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449; (c) Wakui, H.; Kawasaki, S.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2004**, *126*, 8658; (d) Ueda, S.; Nagasawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6411; (e) Roy, A. H.; Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **2007**, *129*, 2082; (f) Ozdemir, I.; Demir, S.; Cetinkaya, B.; Gourlaouen, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156; (g) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897; (h) Wang, D.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190; (i) Ko, S.; Kang, B.; Chang, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 455.
3. (a) Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. *J. Am. Chem. Soc.* **2006**, *128*, 7416; (b) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112; (c) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134.
4. (a) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542; (b) Desai, L. V.; Stowers, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 13285.
5. (a) Thu, H. Y.; Yu, W. Y.; Che, C. M. *J. Am. Chem. Soc.* **2006**, *128*, 9048; (b) Inamoto, K.; Saito, T.; Katsuno, M.; Sakamoto, T.; Hiroya, K. *Org. Lett.* **2007**, *9*, 2931.
6. (a) Desai, L. V.; Ren, D. T.; Rosner, T. *Org. Lett.* **2010**, *12*, 1032; (b) Chernyak, N.; Dudnik, A. S.; Huang, C.; Gevorgyan, V. *J. Am. Chem. Soc.* **2010**, *132*, 8270; (c) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 2925; (d) Zhao, X.; Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 5837; (e) Gu, S.; Chen, C.; Chen, W. *J. Org. Chem.* **2009**, *74*, 7203.
7. (a) Shabashov, D.; Daugulis, O. *Org. Lett.* **2005**, *7*, 3657; (b) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439; (c) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2006**, 3382; (d) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094; (e) Wasa, M.; Worrell, B. T.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 1275.
8. (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300; (b) Wang, G.-W.; Yuan, T.-T.; Wu, X.-L. *J. Org. Chem.* **2008**, *73*, 4717; (c) Wang, G.-W.; Yuan, T.-T. *J. Org. Chem.* **2010**, *75*, 476; (d) Stowers, K. J.; Sanford, M. S. *Org. Lett.* **2009**, *11*, 4584; (e) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141; (f) Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149.
9. Gou, F.-R.; Wang, X.-C.; Huo, P. F.; Bi, H.-P.; Guan, Z.-H.; Liang, Y.-M. *Org. Lett.* **2009**, *11*, 5726.
10. (a) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391; (b) Reddy, B. V. S.; Ramesh, K.; Yadav, J. S. *Synlett* **2011**, 169.
11. *General procedure for acetoxylation*: A mixture of *N*-(2-benzoylphenyl)benzamide (361 mg, 1 mmol), $PhI(OAc)_2$ (322 mg, 1 mmol), $Pd(OAc)_2$ (22 mg, 0.1 mmol), in AcOH (0.5 mL) and Ac_2O (0.5 mL) was heated at 110 °C for the appropriate time under N_2 atmosphere. Upon completion of the reaction as indicated by TLC, the mixture was quenched with water followed by neutralization with saturated $NaHCO_3$ (20 mL) and then extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent followed by purification on silica gel (ethyl acetate/*n*-hexane, 3:7) gave the pure acetoxy arene. *Methoxylation*: A mixture of *N*-(2-benzoylphenyl)benzamide (361 mg, 1 mmol), $PhI(OAc)_2$ (322 mg, 1 mmol), $Pd(OAc)_2$ (22 mg, 0.1 mmol), in MeOH (0.5 mL) was heated at 100 °C for the appropriate time under N_2 atmosphere. Upon completion of the reaction as indicated by TLC, the mixture was diluted with water and then extracted with dichloromethane. Removal of the solvent followed by purification on silica gel (ethyl acetate/*n*-hexane, 3:7) gave the pure methoxyarene. *Spectroscopic data for selected products: Compound* ***3b****: 2-(2-Benzoylphenylcarbamoyl)-4-chlorophenyl acetate*: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 11.39 (br s, 1H), 8.75 (d, J = 9.0 Hz, 1H), 7.92 (d, J = 2.6 Hz, 1H), 7.76–7.69 (m, 2H), 7.65–7.53 (m, 3H), 7.52–7.42 (m, 3H), 7.16–7.09 (m, 2H), 2.32 (s, 3H), ^{13}C NMR ($CDCl_3$, 75 MHz): δ 199.2, 168.9, 162.7, 146.7, 139.6, 138.1, 134.1, 133.3, 132.7, 132.2, 131.8, 130.1, 130.0, 129.4, 128.3, 124.9, 124.3, 122.8, 122.2, 21.0; IR (KBr): ν 3421, 2923, 2853, 1773, 1640, 1598, 1448, 1166, 805, 701; ESI-MS: m/z = 416 [M+Na]$^+$ HRMS calcd for $C_{22}H_{16}NO_4NaCl$: 416.0665, found: 416.0665.
Compound ***3d****:* 2-2(-Benzoylphenylcarbamoyl)-3,4-dimethoxyphenylacetate: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.91 (br s, 1H), 8.76 (d, J = 8.3 Hz, 1H), 7.82–7.70 (m, 2H), 7.64–7.51 (m, 3H), 7.50–7.41 (m, 2H), 7.14–7.06 (m, 1H), 6.96–6.80 (m, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 2.16 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.5,

167.6, 162.5, 150.8, 148.5, 141.3, 139.6, 133.8, 133.0, 132.6, 130.0, 128.2, 124.9, 122.5, 122.0, 118.4, 113.8, 61.9, 56.2, 20.8; IR (KBr): ν 3344, 2923, 1765, 1678, 1644, 1581, 1479, 1441, 1296, 1268, 1200, 1049, 814, 754, 703; ESI-MS: m/z = 420 [M+H]. HRMS calcd for $C_{24}H_{22}NO_6$: 420.1447, found: 420.1455.

Compound ***4i***: *N*-(2-Benzoylphenyl)-4-fluoro-2-methoxy benzamide: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 11.76 (br s, 1H), 8.79 (d, J = 9.0 Hz, 1H), 8.29–8.23 (m, 1H), 7.77 (d, J = 6.7 Hz, 2H), 7.61–7.40 (m, 5H), 7.12–7.01 (m, 1H), 6.81–6.64 (m, 2H), 4.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.9, 167.5, 164.1, 163.2, 139.2, 138.3, 134.6, 134.4, 133.1, 132.6, 132.0, 130.1, 128.2, 126.3, 123.1, 122.2, 108.1, 107.8, 99.5, 99.1, 56.1; IR (KBr): ν 3417, 2924, 1653, 1578, 1442, 1255, 1153, 1106, 1022, 952, 829, 756, 702, 635; ESI-MS: m/z = 372 [M+Na]. HRMS calcd for $C_{21}H_{16}NO_3FNa$: 372.1011, found: 372.1009.

Compound ***4j***: *N*-(2-Benzoylphenyl)-5-chloro-2-methoxy benzamide: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 11.89 (br s, 1H), 8.78 (d, J = 8.9 Hz, 1H), 8.20 (d, J = 2.9 Hz, 1H), 7.78 (d, J = 6.7 Hz, 2H), 7.53–7.58 (m, 2H), 7.46 (t, J = 6.7 Hz, 3H), 7.38 (dd, J = 8.6 and 2.9 Hz, 1H), 7.09 (t, J = 7.7 Hz, 1H), 6.92 (d, J = 9.6 Hz, 1H), 4.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.8, 162.8, 156.2, 139.0, 138.2, 133.1, 132.8, 132.7, 132.0, 130.1, 128.3, 126.4, 126.3, 123.2, 123.1, 122.4, 112.7, 56.1; IR (KBr): ν 3449, 2924, 1646, 1577, 1514, 1448, 1259, 1025, 806, 754; ESI-MS: m/z = 388, [M+Na]. HRMS calcd for $C_{21}H_{16}NO_3NaCl$: 388.0716, found: 388.0707.