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Pd(II)-Catalyzed *o*-C−H Acetoxylation of Phenylalanine and Ephedrine Derivatives with MeCOOO^{t}Bu/Ac_2O

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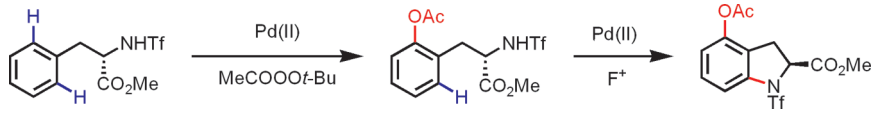
ABSTRACT



Pd(II)-catalyzed ortho C−H acetoxylation of triflate protected phenethyl- and phenpropylamines has been achieved with *tert*-butyl peroxyacetate as the stoichiometric oxidant and either DMF or CH_3CN as the promoter. The reaction was found to tolerate a large variety of functional groups and could be combined with subsequent intramolecular amination to afford functionalized indoline derivatives.

Pd(II)- and Cu(II)-catalyzed C−H activation/C−O bond forming reactions have received increased attention recently, and major efforts have been directed toward discovering new oxidants and conditions that enhance catalytic turnover.[1−5] Consequentially, a number of new oxidation systems with Pd and Cu catalysts for activation of inert C−H bonds have been reported during the past decade, namely, Pd(II)/$K_2S_2O_8$,[6] Pd(II)/PhI(OAc)$_2$,[7] Pd(II)/MeCOOO^{t}Bu/Ac_2O,[8a] Pd(II)/IOAc,[8b] Pd(II)/O_2,[9] and Cu(II)/O_2.[10] In contrast to the rapid improvement of Pd-catalyzed C−H activation/C−C bond forming reactions,[11] in terms of both practicality and scope, oxidation of C−H bonds by Pd(II) and Cu(II) catalysts remains underdeveloped, which has limited the application of these potentially powerful reactions in making molecules that are relevant to medicinal chemistry or total synthesis. Herein, we report a new transformation that effects ortho-acetoxylation of C−H bonds in phenethyl- and phenpropyltriflamide substrates (including amino acid derivatives)[12] using palladium acetate as the catalyst, *tert*-butyl peroxyacetate as the stoichiometric oxidant, and either DMF or

(1) For reviews, see: (a) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (b) Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041.

(2) For recent examples of Pd-catalyzed allylic peroxidation, see: (a) Yu, J.-Q.; Corey, E. J. *Org. Lett.* **2002**, *4*, 2727. (b) Yu, J.-Q.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 3232. For a recent example on Rh-catalyzed allylic peroxidation, see: (c) Catino, A. J.; Forslund, R. E.; Doyle, M. P. *J. Am. Chem. Soc.* **2004**, *126*, 13622. For a new development of Pd-catalyzed allylic acetoxylation of terminal olefins, see: (d) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970.

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(4) For a single example of oxaziridine-promoted C−H oxidation, see: Litvinas, N. D.; Brodsky, B. H.; Du Bois, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 4513.

(5) For benzylic C−H acetoxylation, see: (a) Zhang, J.; Khaskin, E.; Anderson, N. P.; Zavalij, P. Y.; Vedernikov, A. N. *Chem. Commun.* **2008**, 3625. (b) Vedernikov, A. N. *Chem. Commun.* **2009**, 4781.

(6) (a) Gretz, E.; Oliver, T. F.; Sen, A. *J. Am. Chem. Soc.* **1987**, *109*, 8109. (b) Muehlhofer, M.; Strassner, T.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1745. (c) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141. (d) Wang, G.-W.; Yuan, T.-T.; Wu, X.-L. *J. Org. Chem.* **2008**, *73*, 4717.

(7) (a) Yoneyama, T.; Crabtree, R. H. *J. Mol. Catal. A: Chem.* **1996**, *108*, 35. (b) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300. (c) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542.

(8) (a) Giri, R.; Liang, J.; Lei, J.-G.; Li, J.-J.; Wang, D.-H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420. (b) Wang, D.-H.; Hao, X.-S.; Wu, D.-F.; Yu, J.-Q. *Org. Lett.* **2006**, *8*, 3387.

(9) Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 14654.

(10) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790.

(11) (a) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094.

(12) For an example of acetoxylation of amino acids, see: Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391.

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CH_3CN additive as the crucial promoter. The reaction was found to proceed under relatively mild temperatures (70 °C) and could be used with a variety of functional groups, such as alcohols and ketones, as well as with both electron-rich and electron-deficient arenes. A sequential *o*-C−H activation/intramolecular amination of the products was also carried out to synthesize 4-oxygenated indolines, demonstrating additional synthetic utilities. Another attractive feature of this method is its potential application toward the derivation of natural amino acids tyrosine and phenylalanine as well as other biologically active molecules such as ephedrine, which together with its analogues comprise a family of important hormones and neurotransmitters in biological systems[13] (Figure 1).

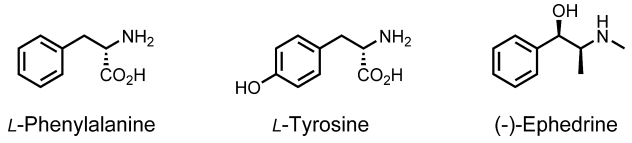


Figure 1. Examples of biologically active molecules that can be modified by this method.

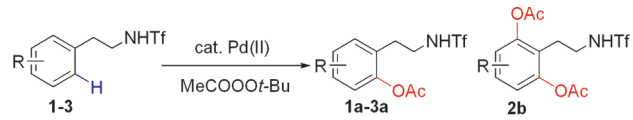
We have previously developed a Pd(II)-catalyzed C−H oxidation reaction using MeCOOO*t*Bu as the stoichiometric oxidant and Ac_2O as the crucial promoter.[8] Since MeCOOO*t*-Bu is inexpensive and easy to use ($37 per mol), we began our study by investigating whether this oxidation system can be applied to the oxidation of phenethyltriflamide substrates.[14] Through extensive screening and optimization, we discovered new conditions to effect ortho-acetoxylation of this type of substrates (Table 1).

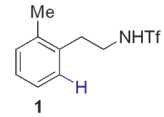
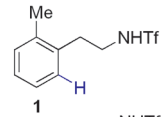
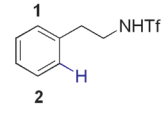
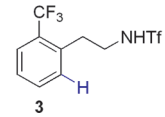
A number of important observations are worth noting. First, the use of 6 equiv of DMF or CH_3CN as an additive increases the yields significantly (Table 1, entries 1 and 2). The highest reactivity was achieved when CH_3CN was used; thus these conditions were useful with ortho-substituted or electron-poor substrates (entries 2 and 4). However, in the case of substrates lacking ortho-substitution, the high reactivity proved to be detrimental to the mono-/diselectivity (entry 3). Thus, in cases where substrates are electron-rich or lack ortho-substitution, DMF was found to offer better control and higher overall yields. Second, the presence of 1 equiv of HOAc was found to increase the yield further by ∼15%. Finally, it is important to note that running the oxidation reaction under relatively dilute conditions results in the formation of indolines (∼25%) via the intramolecular C−H amination pathway[14c] along with ∼35% of the desired products.

(13) For studies on the biochemical role of ephedrine, see: (a) Astrup, A.; Lundsgaard, C.; Madsen, J.; Christensen, N. J. *Am. J. Clin. Nutr.* **1985**, *42*, 83. (b) Vansal, S. S.; Feller, D. R. *Biochem. Pharmacol.* **1999**, *58*, 807. (c) Rothman, R. B.; Vu, N.; Partilla, J. S.; Roth, B. L.; Hufeisen, S. J.; Compton-Toth, B. A.; Birkes, J.; Young, R.; Glennon, R. A. *J. Pharmacol. Exp. Ther.* **2003**, *307*, 138.

(14) For triflamide-directed *o*-C−H activation, see: (a) Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452. (b) Wang, X.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520. (c) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806.

Table 1. DMF versus CH_3CN as an Additive



entry	substrate	additive	% yield (mono)[a]	% yield (di)[a]
1	 1	—	11	—
2	 1	CH_3CN[b]	98	—
		DMF[c]	73	
3	 2	CH_3CN[b]	58	21
		DMF[c]	63	7
4	 3	CH_3CN[b,d,e]	79	—
		DMF[c,d,e]	48	

[a] Substrate (0.5 mmol), $Pd(OAc)_2$ (10 mol %), *tert*-butyl peroxyacetate (1.0 mmol), Ac_2O (1.0 mmol), AcOH (0.5 mmol), $ClCH_2CH_2Cl$ (0.19 mL), 70 °C, 24 h. The yields were determined by ^1H NMR analysis of the crude reaction mixture with CH_2Br_2 as the internal standard. [b] As in footnote a, but with CH_3CN (3.0 mmol). [c] As in footnote a, but with DMF (3.0 mmol), $ClCH_2CH_2Cl$ (0.32 mL), 70 °C, 48 h. [d] 48 h. [e] *tert*-Butyl peroxyacetate (1.25 mmol), Ac_2O (1.25 mmol).

With the established reaction conditions, we proceeded to examine the substrate scope (Figure 2). The acetoxylation of unsubstituted and para-substituted substrates are best performed with DMF as the additive to avoid significant formation of diacetoxylated products (**2a**, **5a**). DMF is also the additive of choice when substrates contain electron-rich arene rings (**6a**, **7a**, **8a**). Ortho- and meta-substituted substrates work well in the presence of 6 equiv of CH_3CN, giving yields of 93% and 63%, respectively (**1a**, **4a**). The tolerance of a wide range of halides on the arenes is a synthetically useful feature (**9a**−**14a**). Substrate **3** containing an electron-withdrawing CF_3 group is also acetoxylated to give **3a** in 72% yield; however, NO_2 and acetyl groups decrease the yields significantly (**15a**, **16a**).

As anticipated from our previous understanding based on the Thorpe−Ingold effect,[15] substitutions at the benzylic position, or the α-position of the triflamide enhance the reactivity (**17a**−**23a**). Notably, a wide range of functional groups at these positions are tolerated, such as ketal, OTBS, triflate, and ester groups (**17a**, **19a**−**21a**). This versatile reactivity has allowed acetoxylation of a number of biologically important compounds such as derivatives of phenylalanine, tyrosine, and ephedrine. By using our more reactive CH_3CN conditions, the acetoxylation of phenpropyltriflamide derivative **23** was also possible, albeit in relatively low yield

(15) Bachrach, S. M. *J. Org. Chem.* **2008**, *73*, 2466.

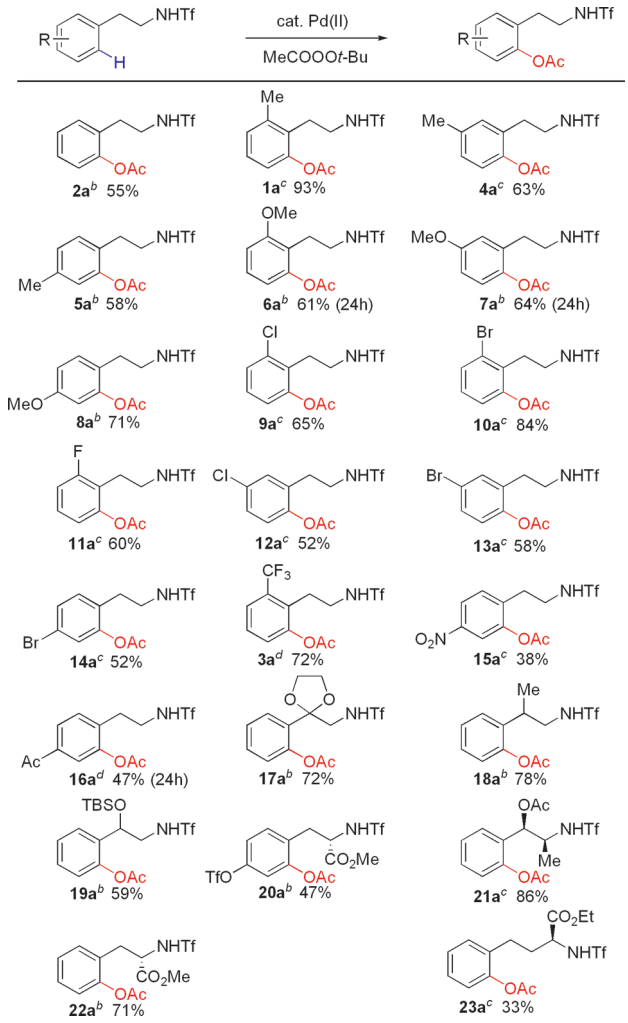


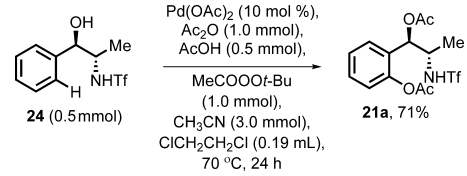
Figure 2. C−H acetoxylation of phenethyltriflamides: (a) isolated yields; (b) substrate (0.5 mmol), $Pd(OAc)_2$ (10 mol %), Ac_2O (1.0 mmol), AcOH (0.5 mmol), *tert*-butyl peroxyacetate (1.0 mmol), DMF (3.0 mmol), $ClCH_2CH_2Cl$ (0.32 mL), 70 °C, 48 h; (c) as in b, but with CH_3CN (3.0 mmol), $ClCH_2CH_2Cl$ (0.19 mL), 24 h; (d) as in b, but with Ac_2O (1.25 mmol), *tert*-butyl peroxyacetate (1.25 mmol), 48 h.

(**23a**). Notably, this reaction presumably proceeds through a seven-membered palladacycle intermediate and as such represents a rare example of remote directed C−H activation.[16] A hydroxyl-containing substrate was also smoothly acetoxylated under the standard conditions. It is possible that the free hydroxyl is acetylated by Ac_2O in situ prior to the C−H oxidation reaction (Scheme 1).

This method also lends itself to the preparation of 4-acetoxyindoline derivatives using a transformation recently described by our group to cyclize the phenethyltriflamide

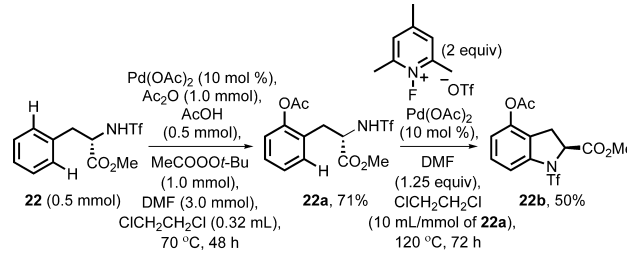
(16) For a definition of remote C−H functionalizations, see: Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170.

Scheme 1. Acetoxylation of Hydroxyl-Containing Substrate



moiety via intramolecular C−H amination to form a new indoline ring system that can subsequently be oxidized to the corresponding indole.[14c] In principle, this two-step C−H acetoxylation/C−H amination sequence could be used to synthesize an array of indolines and indoles adorned with diverse substitution patterns. To demonstrate this approach, we converted one of the acetoxylated products (**22a**) to **22b** (Scheme 2). All told, this represents a net conversion of phenylalanine to 4-acetoxy-2-carbomethoxyindoline derivative (**22b**) in three steps: amine triflation, ortho-acetoxylation, and intramolecular amination.

Scheme 2. Tandem C−H Acetoxylation/Indoline Formation



In summary, we have developed a mild protocol for *o*-C−H acetoxylation of a wide range of phenyethyltriflamides with varying electronic and steric properties on the aryl rings. This technology enables the site-specific oxidation of biologically important amines, using a synthetically versatile directing group capable of undergoing further synthetic manipulations, including intramolecular C−H amination to give 4-acetoxyindolines.

Acknowledgment. We thank The Scripps Research Institute and the U.S. National Science Foundation (NSF CHE-0910014), Amgen, and Lilly for financial support.

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.

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