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# Palladium-Catalyzed Oxidation of *Boc*-Protected *N*-Methylamines with IOAc as the Oxidant: A *Boc*-Directed sp$^3$ C–H Bond Activation

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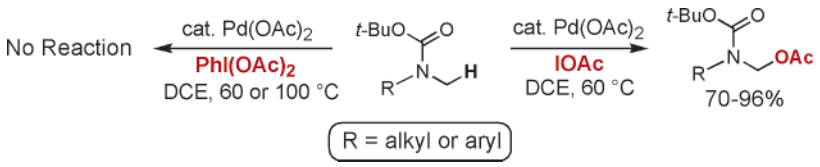
## ABSTRACT




**Pd-catalyzed selective oxidation of *Boc*-protected *N*-methylamines with IOAc as the oxidant is described. Evidence for the involvement of a *Boc*-directed C–H activation process is provided.**

Selective functionalization of C−H bonds adjacent to a nitrogen atom in simple amines and amides is of great importance for the synthesis of nitrogen-containing compounds and understanding enzymatic oxidations.[1] Murahashi's pioneering work on the oxidation of 3° amines using $Pd^0$ and $Ru^{II}$ catalysts mimics amine oxidase type (eq 1) and cytochrome P-450 type (eq 2) reactivity.[2] Transition metal-catalyzed oxidation of *N*,*N*-dialkylanilines to iminium ions[3] (eq 3) followed by nucleophilic capture has been utilized by Murahashi and Li to form C−C bonds with selected substrates.[4]

$$R_1R_2N{-}CHR_3R_4 \overset{Pd^0}{\rightleftharpoons} R_1R_2N^+{=}CR_3R_4 + PdH^- \quad (1)$$

$$R_1R_2N{-}CHR_3R_4 \overset{Ru^V{=}O}{\rightleftharpoons} R_1R_2N^+{=}CR_3R_4 + Ru^{III}(OH) \quad (2)$$

$$ArR_1N{-}CHR_2R_3 \overset{\text{Cu(I), Ru(II)}}{\underset{\text{peroxides}}{\rightleftharpoons}} ArR_1N^+{=}CR_2R_3 \quad (3)$$

Recently, Doyle described an efficient alkylation of C−H bonds adjacent to nitrogen atoms with a wide range of *N*,*N*-dialkylanilines using dirhodium caprolactamate.[5] The electrochemical oxidation of cyclic amides to provide α-oxygenated compounds as precursors for N-acyliminium ions has been widely used in natural product synthesis.[6] A novel method of generating *N*-sulfonyliminium ions by a nitriene insertion into C−H bonds adjacent to an oxygen atom was also reported.[7]

In our effort to enhance the efficiency and practicality of directed C−H activation reactions, we have strategically selected to develop C−H functionalizations directed by synthetically useful protecting groups. Herein, we describe

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(1) (a) For a minireview on activation of sp$^3$ C−H bonds in the α-position to a nitrogen atom see: Doye, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3351. (b) Nugent, W. A.; Ovenall, D. W.; Holmes, S. J. *Organometallics* **1983**, *2*, 161. (c) Chatani, N.; Asaumi, T.; Ikeda, T.; Yorimitsu, S.; Ishii, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2000**, *122*, 12882. (d) Yi, C. S.; Yun, S. Y. *Organometallics* **2004**, *23*, 5392. (e) Li, Z.; Li, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 11810.

(2) (a) Murahashi, S.-I. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2443. (b) Murahashi, S.-I.; Naota, T.; Kuwabara, T.; Saito, T.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1990**, *112*, 7820.

(3) Lu, C. C.; Peters, J. C. *J. Am. Chem. Soc.* **2004**, *126*, 15818.

(4) (a) Murahashi, S.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312. (b) Li, Z.; Li, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 11810. (c) Li, Z.; Li, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 3672.

(5) Catino, A. J.; Nichols, J. M.; Nettles, B. J.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 5648.

(6) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527.

(7) Fleming, J. J.; Fiori, K. W.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 2028.

a $Pd^{II}$-catalyzed highly selective acetoxylation of α-methyl groups in a wide range of aliphatic and aromatic *Boc* -protected 2° *N*-methylamines using IOAc as the stoichiometric oxidant. The exclusive selectivity toward methyl groups is a characteristic feature of our catalytic system in contrast to the previously reported iminium ion pathway.[3−5] The observed isotope effect, regioselectivity, and stereoselectivity are consistent with an unusual *Boc*-directed Pd insertion into $sp^3$ C−H bonds.

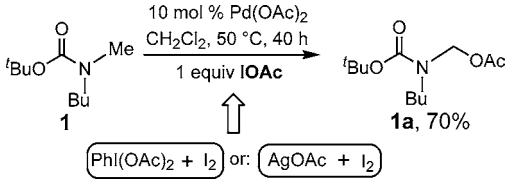
Amide-directed palladation of $sp^2$ C−H bonds has been extensively explored to develop C−C bond and C−heteroatom bond-forming reactions since the early examples reported by Horino and Tremont using $Pd^{II}/Pd^{IV}$ catalysis.[8] Remarkably, Buchwald achieved an amide-directed C−H activation/C−N bond-forming sequence involving $Pd^{II}/Pd^0$ catalysis in which practically useful oxidants ($Cu^{II}$/air) were employed.[9] However, *Boc*-directed activation of $sp^3$ C−H bonds ajacent to the nitrogen atom has not been achieved despite the potential synthetic utility due to the low coordination ability of the *Boc* group.[10] Inspired by Beak's carbamate-directed lithiation reactions,[11] Crabtree's carbonyl-directed cycloiridation of aryl C−H bonds[12] and the early efforts from Murai, Chatani, and Kakiuchi,[10] we decided to identify conditions that would oxidize *Boc*-protected *N*-methylamines via a *Boc*-directed C−H activation catalyzed by $Pd(OAc)_2$.

*Boc*-protected *N*-methylbutan-1-amine **1** was used to screen for a catalytic oxidation system. We have previously shown that Pd−alkyl or Pd−aryl complexes react with $I_2$ to give the iodinated products and $PdI_2$.[13a,b] Unfortunately, stirring **1** with 1 equiv of $Pd(OAc)_2$ and $I_2$ in $CH_2Cl_2$ at room temperature or 50 °C led to a full recovery of the starting material. We further tested various inexpensive peroxide oxidants that were recently used in our C−H bond oxidation reactions.[13c] No significant reaction was observed under these reaction conditions. We were pleased to find that the use of 1 equiv of IOAc as the oxidant generated in situ by reacting AgOAc with $I_2$ gave the actoxylated product **1a** in 90% yield in the presence 1 equiv of $Pd(OAc)_2$. Following a procedure reported by Lusztyk,[14] IOAc is more efficiently produced by reacting $I_2$ with $PhI(OAc)_2$ (eq 4).

$$I_2 + PhI(OAc)_2 \rightarrow PhI + IOAc \quad (4)$$

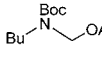
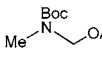
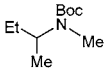
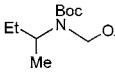
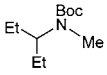
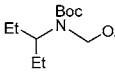
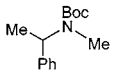
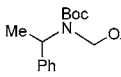
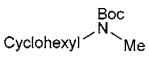
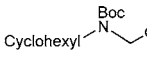
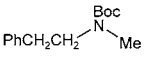
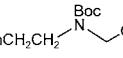
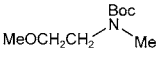
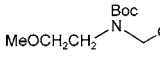
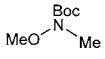
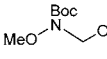
Thus, stirring **1** with 1 equiv of $PhI(OAc)_2$ and $I_2$ in the presence of 10 mol % of $Pd(OAc)_2$ in $CH_2Cl_2$ at 50 °C in a sealed tube for 40 h gives the acetoxylated product **1a** in 70% yield (Scheme 1).

**Scheme 1.** Selective Acetoxylation of *N*-Methylcarbamates with IOAc as a Crucial Oxidant




$PhI(OAc)_2$ has been previously used as a stoichiomertic oxidant in Pd-catalyzed acetoxylation of C−H bonds.[15] However, control experiments showed that no reaction was observed when $PhI(OAc)_2$ or $I_2$ was used alone. This result suggests that IOAc is critical for the *Boc*-directed oxidation of the C−H bonds. It is worth noting that our previously reported Pd-mediated iodination reaction directed by oxazolines can occur in the presence of either $I_2$ alone or IOAc,[13a,b] which made it difficult to determine whether the oxidation of the Pd−C bonds involves $I_2$ or IOAc.

**Table 1.** Pd-Catalyzed Acetoxylation of *Boc*-Protected *N*-Methylamines[a]

| entry | substrate | | product | | yield% |
|---|---|---|---|---|---|
| 1 |  | **1** |  | **1a** | 83 |
| 2 |  | **2** |  | **2a** | 78 |
| 3 |  | **3** |  | **3a** | 74 |
| 4 |  | **4** |  | **4a** | 92 |
| 5 |  | **5** |  | **5a** | 85 |
| 6 |  | **6** |  | **6a** | 91 |
| 7 |  | **7** |  | **7a** | 86 |
| 8 |  | **8** |  | **8a** | 69 |
| 9 |  | **9** |  | **9a** | 96 |

[a] 10 mol % of $Pd(OAc)_2$, 1.6 equiv of $I_2$, 1.6 equiv of $PhI(OAc)_2$, DCE, 60 °C, 40 h.

(8) (a) Horino, H.; Inoue, N. *J. Org. Chem.* **1981**, *46*, 4416. (b) Tremont, S. J.; Rahman, H. U. *J. Am. Chem. Soc.* **1984**, *106*, 5759. (c) Kametani, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2000**, *41*, 2655. (d) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586. (e) Zaitsev, V. G.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 4156.

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(12) Li, X.; Chen, P.; Faller, J. W.; Crabtree, R. H. *Organometallics* **2005**, *24*, 4810.

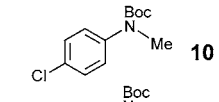
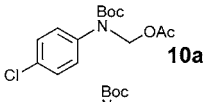
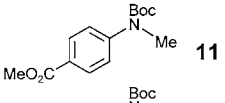
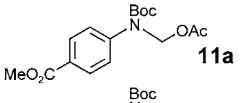
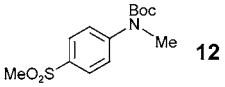
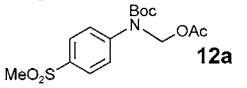
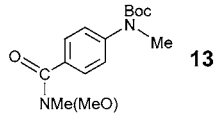
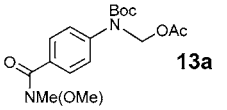
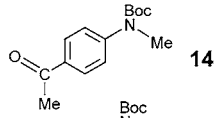
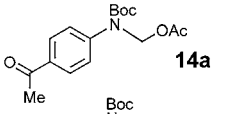
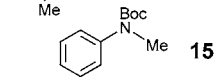
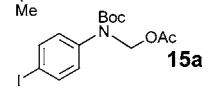
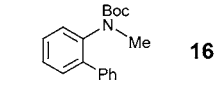
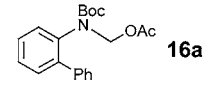
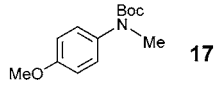
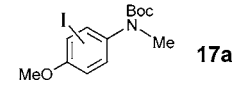
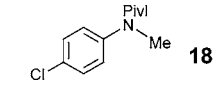
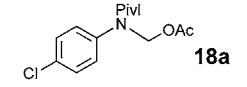
(13) (a) Giri, R.; Chen, X.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112. (b) Giri, R.; Chen, X.; Hao, X. S.; Li, J. J.; Fan, Z. P.; Yu, J. Q. *Tetrahedron*: *Asymmetry* **2005**, *16*, 3502. (c) Giri, R.; Liang, J.; Lei, J. G.; Li, J. J.; Wang, D. H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420.

(14) Courtneidge, J. L.; Lusztyk, J.; Page, D. *Tetrahedron Lett.* **1994**, *35*, 1003.

Screening of the reaction conditions identified $CH_2ClCH_2Cl$ (DCE) as a better solvent. The yield of the acetoxylation of **1** was increased to 83% at 60 °C (Table 1, entry 1). Pd loading was reduced to 5 mol % by extending the reaction time to 72 h. The substrate scope was tested by using a variety of *N*-methylamines. The *N*-methyl groups are oxidized highly selectively to give the acetoxylated products in good yields (Table 1). The successful acetoxylation of substrate **9** also provides a potential means for functionalization of primary amines as both the Boc and OMe can be readily deprotected to release the primary amine.

This oxidation protocol was successfully applied to a wide range of *Boc*-protected *N*-methylanilines (Table 2). Functional groups such as amides, ketones, esters, and sulfonates are tolerated and good yields are consistently obtained. In the absence of a para-substituent, electrophilic iodination by IOAc took place simultaneously to give the *p*-iodinated acetoxylation product **15a** (Table 2, entry 6). By carrying out the reaction at room temperature, the *p*-iodination of substrate **16** was prevented (Table 2, entry 7). However, the *p*-iodination of **15** cannot be prevented completely at room temperature. Intriguingly, no *N*-methyl oxidation was observed with substrates containing an electron-donating group on the para-position (Table 2, entry 8).[16] Notably, we also found that the pivaloyl group is as effective as the *Boc* group for this reaction (Table 2, entry 9), although the less hindered acetyl group displayed poor reactivity.

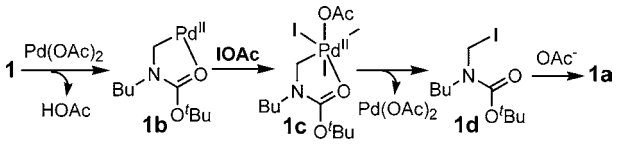
**Table 2.** Pd-Catalyzed Acetoxylation of *Boc*-Protected *N*-Methylanilines[a]

| entry | substrate | | product | | yield% |
|---|---|---|---|---|---|
| 1 |  | **10** |  | **10a** | 87 |
| 2 |  | **11** |  | **11a** | 89 |
| 3 |  | **12** |  | **12a** | 84 |
| 4 |  | **13** |  | **13a** | 84 |
| 5 |  | **14** |  | **14a** | 83 |
| 6 |  | **15** |  | **15a** | 77 |
| 7 |  | **16** |  | **16a** | 86[b] |
| 8 |  | **17** |  | **17a** | 50 |
| 9 |  | **18** |  | **18a** | 93 |

[a] 10 mol % of $Pd(OAc)_2$, 1 equiv of $I_2$, 1 equiv of $PhI(OAc)_2$, DCE, 60 °C, 40 h. [b] 24 °C, 72 h.

On the basis of characterizations of a number of $Pd^{IV}$ complexes obtained by oxidizing $Pd^{II}$ with MeI (X-ray),[17] $(PhCO_2)_2$ ($^1$HNMR),[18] and $PhI(O_2CPh)$ (X-ray)[19] and our recently developed C−H bond iodination reaction using $Pd^{II}/Pd^{IV}$ catalysis,[12a] we propose an unusual *Boc*-directed C−H insertion pathway to account for the acetoxylation of the *N*-methyl groups (Scheme 2). The IOAc serves as a stoichiometric oxidant to oxidize the unstable $Pd^{II}$ complex **1b** to a $Pd^{IV}$ complex **1c**.[20] Our previous iodination reaction prompts us to assume a preferential reductive elimination of the iodide other than the acetate. It is also possible that the reductive elimination of the acetate occurs to give the acetoxylated product directly.

**Scheme 2.** Proposed Reaction Pathway




A number of mechanistic observations support our hypothesis. First, the high selectivity for primary C−H bonds and lack of reactivity of benzylic C−H bonds in **19** and **20** and secondary C−H bonds in **21** (Figure 1) cannot be explained by the reaction pathways proposed for amine oxidations (eq 1−3) or a radical pathway.[21]

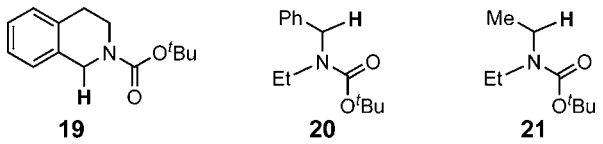



**Figure 1.** Unreactive substrates.

Second, the acetoxylation of a mixture of diastereomers **22** in 1:1 ratio gave **22a** in 2:1 ratio at 40% conversion

(15) For the direct involvement of $PhI(OAc)_2$ in C−H bond oxidation see: (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.

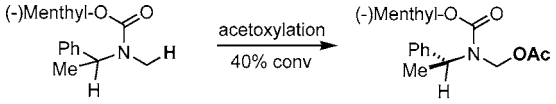
(16) The formation of a mixture of both *o*- and *m*-iodinated products is most likely due to an electrophilic substitution. The lack of reactivity of the *N*-methyl group in **17** could be explained by a bisdentate coordination from the *Boc* and the electron-rich aryl ring, which positions the *N*-methyl group away from the Pd(II) center. The presence of a *p*-methyl group also inhibits the *N*-methyl oxidation.

(17) Byers, P. K.; Canty, A. J.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Chem. Commun.* **1986**, 1722.

(18) Canty, A. J.; Denney, M. C.; Skelton, B. W.; White, A. H. *Organometallics* **2004**, *23*, 1122.

(19) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790.

**Scheme 3.** Diastereoselective Acetoxylation

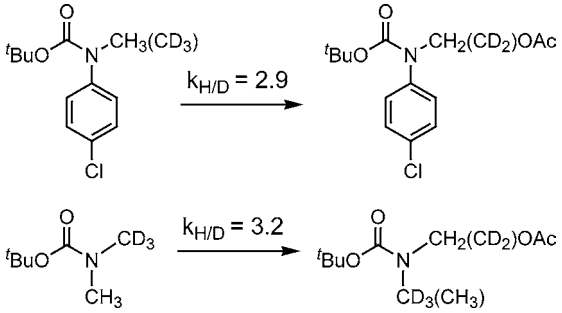



**22** **22a**, 67:33 d.r

(Scheme 3). The diastereoselectivity obtained is consistent with a cyclic transition state formed via the coordination of the *Boc* group to the Pd center.

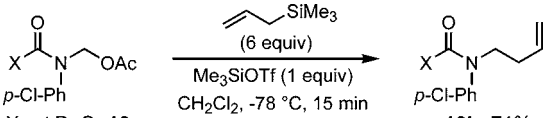
The isotope effects observed in both intermolecular ($k_{H/D}$ = 2.9) and intramolecular ($k_{H/D}$ = 3.2) competition experiments are consistent with the C−H cleavage being the rate-limiting step (Scheme 4).

**Scheme 4.** Isotope Effects




Finally, the synthetic utility of both *Boc*- and pivaloyl-protected products is demonstrated by allylation with allyltrimethylsilane, using a literature procedure (Scheme 5).[4]

**Scheme 5.** Synthetic Applications




X = *t*-BuO, **10a** **10b**, 71%
X = *t*-Bu, **18a** **18b**, 95%

In summary, we have developed a Pd-catalyzed acetoxylation of a wide range of *N*-methylamines directed by a *Boc* or pivaloyl group. Mechanistic data obtained are consistent with a $\sigma$-chelation-assisted $sp^3$ C−H insertion. The acetoxylated products are useful building blocks for further synthetic transformations.

**Acknowledgment.** We thank Brandeis University for financial support and the Camille and Henry Dreyfus Foundation for a New Faculty Award. D.F.W is grateful to Pfizer for a Fellowship.

**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.

OL061384M

(20) For a *Boc*-coordinated alkylpalladium complex formed from the Heck reaction see: Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323.

(21) For nonselective radical oxidation of tertiary amines with peroxide oxidants see: Ochiai, M.; Kajishima, D.; Sueda, T. *Heterocycles* **1997**, *46*, 71.