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# *O*-Acetyl Oximes as Transformable Directing Groups for Pd-Catalyzed C−H Bond Functionalization

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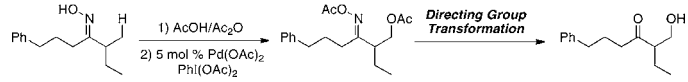
## ABSTRACT




***O*-Acetyl oximes serve as effective directing groups for Pd-catalyzed $sp^2$ and $sp^3$ C−H functionalization reactions. The C−H functionalization products can be subsequently transformed into *ortho*- or *β*-functionalized ketones, alcohols, amines, and heterocycles.**

Over the past decade, palladium-catalyzed ligand-directed C−H functionalization has been extensively exploited to convert unactivated carbon−hydrogen bonds into carbon−heteroatom and carbon−carbon bonds.[1] Despite the rapidly growing arsenal of methods in the field, the synthetic utility of these transformations is limited by the requirement that a directing group be built into the substrate. In particular, many effective directing groups are nitrogen-containing heterocycles that are not easily transformed or removed following the C−H functionalization event.[1]

The ideal directing ligand would be sufficiently robust to tolerate C−H activation/functionalization conditions but then readily converted into diverse functional groups. Instances of such directing groups in Pd-catalyzed reactions are relatively rare. Yu and Shi have independently demonstrated C−H functionalization of triflamide[2a]- and dimethyl[2b]-protected benzyl amines followed by nucleophilic displacement or reduction of the amine directing group. Oxazolines have been used for Pd-catalyzed C−I bond forming reactions followed by $H_2SO_4$-catalyzed hydrolysis to afford carboxylic acids.[3] Carboxylic acids have also been directly employed in Pd-catalyzed C−H arylation and then removed by decarboxylation.[4] Finally, amides have proven effective for directing Pd-catalyzed C−C and C−halogen bond formation and have been subsequently transformed into nitriles[5a] or carboxylic acids.[5b]

Ketones are particularly versatile and widely used synthetic intermediates.[6] However, ketones are poor ligands for $Pd^{II}$ and thus are generally ineffective directing groups for Pd-catalyzed C−H functionalization.[7,8] We thus sought to temporarily mask ketones as more coordinating imine or oxime derivatives during C−H functionalization and then

(1) For reviews, see: (a) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (b) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q. N.; Lazareva, A. *Synlett* **2006**, 3382. (c) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (d) Li, B. J.; Yang, S. D.; Shi, Z. J. *Synlett* **2008**, 949. (e) Deprez, N. R.; Sanford, M. S. *Inorg. Chem.* **2007**, *46*, 1924. (f) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094.

(2) (a) Wang, X.; Mei, T. S.; Yu, J. Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520. (b) Cai, G.; Fu, Y.; Li, Y.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 7666.

(3) Giri, R.; Wasa, M.; Breazzano, S. P.; Yu, J. Q. *Org. Lett.* **2006**, *8*, 5685.

(4) Chiong, H. A.; Pham, Q. N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879.

(5) (a) Shabashov, D.; Maldonado, J. R. M.; Daugulis, O. *J. Org. Chem.* **2008**, *73*, 7818. (b) Wasa, M.; Engle, K. M.; Yu, J. Q. *J. Am. Chem. Soc.* **2009**, *131*, 9886.

(6) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; John Wiley & Sons, Inc.: New York, 1999; pp 1197−1620.

(7) For rare examples of ketones or aldehydes serving as directing groups at Pd, see: (a) Terao, Y.; Kametani, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron* **2001**, *57*, 5967. (b) Gürbüz, N.; Özdemir, I.; Çetinkaya, B. *Tetrahedron Lett.* **2005**, *46*, 2273.

(8) For reviews on ketone-directed C−H alkylation and arylation reactions catalyzed by metals other than Pd, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* [Online early access]. DOI: 10.1021/cr900005n. Published Online: May 13, 2009. http://pubs.acs.org/doi/pdf/10.1021/cr900005n (accessed December 10, 2009).

10.1021/ol902720d 
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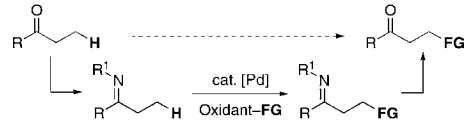
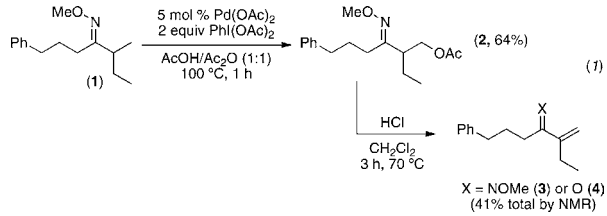
subsequently remove this group to reveal the ketone functionality (Scheme 1). This communication describes the

**Scheme 1.** Approach to $\beta$-C−H Functionalization of Ketones

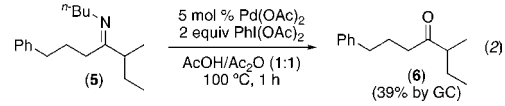


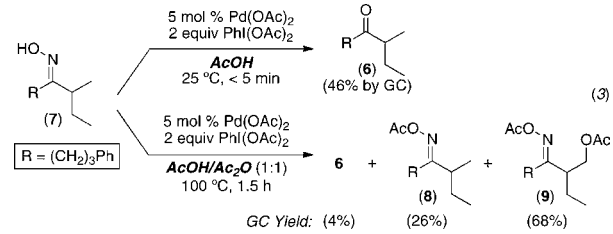

development of *O*-acetyl oximes as versatile and readily transformable directing groups for Pd-catalyzed C−H functionalization.

Two key challenges exist in the design of a ketone surrogate for Pd-catalyzed C−H functionalization. First, the protecting group must be stable to the catalytic conditions. Second, the group must be readily removed in high yield *without affecting the newly installed functional group*. Previous studies have shown that oxime ethers such as **1** (eq 1) are effective directing groups for Pd-catalyzed $sp^2$ and $sp^3$ C−H acetoxylation reactions with $PhI(OAc)_2$.[9,10] However, removal of the oxime ether protecting group from $\beta$-functionalized products like **2** is problematic. Acid-catalyzed hydrolysis[11] is sluggish and produces significant quantities of elimination products **3** and **4** (eq 1).[12] The use of superstoichiometric $Ti^{III}Cl_3$ is effective in some cases,[13] but this expensive, air-sensitive reagent is not practical for general application.




Imines would be a versatile alternative to oxime ethers, as they are readily hydrolyzed under mild conditions. Pd-catalyzed imine-directed acetoxylation of an $sp^2$ C−H bond has been reported;[9a] however, imines have proven too labile for analogous $sp^3$ C−H functionalizations. For example, reaction of **5** under standard acetoxylation conditions affords the hydrolyzed ketone **6** as the major identifiable product (39% yield, eq 2).




Simple hydroxyl (OH) oximes are another attractive ketone surrogate. These readily available, stable, often crystalline starting materials are known to direct stoichiometric cyclopalladation at both $sp^2$ and $sp^3$ C−H sites[14] and are much more readily cleaved than their oxime ether counterparts.[15] In addition, they are prepared from $NH_2OH$•HCl, which is nearly 100-fold less expensive than $NH_2OMe$•HCl.[16] Despite these advantages, oximes are known to undergo rapid oxidative cleavage in the presence of oxidants like $PhI(OAc)_2$.[17] For example, subjecting oxime **7** to $Pd(OAc)_2$ and $PhI(OAc)_2$ in AcOH resulted in a nearly instantaneous color change from colorless to blue-green, concomitant with regeneration of the parent ketone **6**. However, encouragingly, a similar color change was *not* observed when the solvent was changed from AcOH to $AcOH/Ac_2O$ (1:1). Under these conditions, only traces of ketone **6** (4% by GC) were formed; instead the major product (68% by GC) was the O-acetylated/C−H acetoxylated compound **9** (eq 3).

This initial result suggested that the in situ reaction of **7** with $Ac_2O$ affords a stable *O*-acetyl oxime (**8**) that can direct C−H acetoxylation. Further study showed that this in situ O-acetylation occurred quantitatively upon stirring the oxime starting material in $AcOH/Ac_2O$ for 2 h at 25 °C. Subsequent addition of Pd catalyst and oxidant, followed by heating the reaction mixture at 100 °C for 12 h, afforded **8** in 70% GC yield (49% isolated).

As summarized in Table 1, a number of dialkyl oximes underwent in situ acetylation/$\beta$-acetoxylation in modest to

(9) (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300. (b) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542. (c) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 3387. (d) Desai, L. V.; Stowers, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 13285.

(10) For related C−H acetoxylation reactions of other substrates, see: (a) Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149. (b) Giri, R.; Liang, J.; Lei, J. Q.; 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. (c) Wang, D. H.; Hao, X. S.; Wu, D. F.; Yu, J. Q. *Org. Lett.* **2006**, *8*, 3387. (d) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391. (e) Wang, G. W.; Yuan, T. T.; Wu, X. L. *J. Org. Chem.* **2008**, *73*, 4717. (f) Zhang, J.; Khaskin, E.; Anderson, N. P.; Zavalij, P. Y.; Vedernikov, A. N. *Chem. Commun.* **2008**, 3625. (g) Stowers, K. J.; Sanford, M. S. *Org. Lett.* **2009**, *11*, 4584.

(11) For example, see: Shipe, W. D.; Sorensen, E. J. *Org. Lett.* **2002**, *4*, 2063.

(12) Conversion of oxime ethers to ketones has been reported using Amberlyst 15 at temperatures ranging from 25 to 110 °C. See: (a) Sakamoto, T.; Kikugawa, Y. *Synthesis* **1993**, 563. (b) Mears, R. J.; Sailes, H. E.; Watts, J. P.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3250. In our hands, **2** and derivatives were unreactive to the reported conditions at room temperature. At elevated temperatures (80 °C), **2** reacted to form a complex mixture of products that did not include the expected $\beta$-acetoxy or $\beta$-hydroxy ketone.

(13) (a) Desai, L. V. Palladium-Catalyzed Functionalization of C-H Bonds and Alkenes. *Ph.D. Thesis*, University of Michigan, April 2008. (b) Corey, E. J.; Niimura, K.; Konishi, Y.; Hashimoto, S.; Hamada, Y. *Tetrahedron Lett.* **1986**, *27*, 2199.

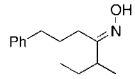
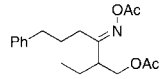
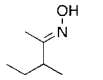
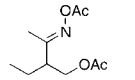
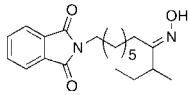
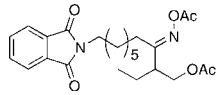
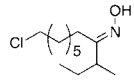
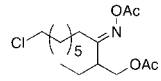
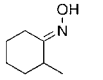
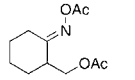
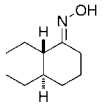
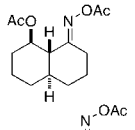
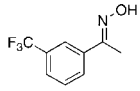
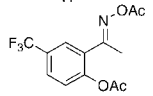
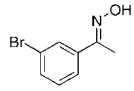
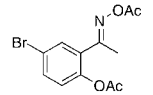
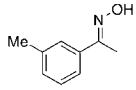
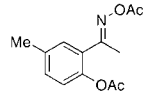
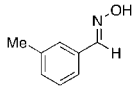
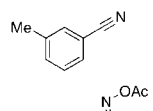
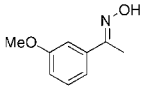
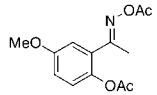
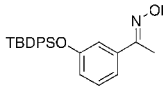
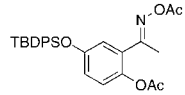
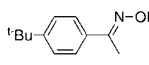
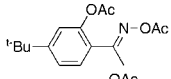
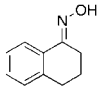
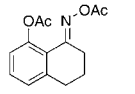
(14) For selected examples, see: (a) Baldwin, J. E.; Jones, R. H.; Nájera, C.; Yus, M. *Tetrahedron* **1985**, *41*, 699. (b) Baldwin, J. E.; Nájera, C.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1985**, 126. (c) Carr, K.; Saxton, H. M.; Sutherland, J. K. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1599.

(15) Corsaro, A.; Chiacchio, U.; Pistarà, V. Synthesis **2001**, 1903.

(16) Cost calculated on a molar basis using: *Aldrich Catalog Handbook of Fine Chemicals*; Aldrich Chemical: Milwaukee, WI, 2009.

(17) Moriarty, R. M.; Prakash, O.; Vavilikolanu, P. R. *Synth. Commun.* **1986**, *16*, 1247.

**Table 1.** *O*-Acetyl Oxime-Directed Acetoxylation of C−H Bonds[a]

| entry | starting material | product | yield[b] |
|---|---|---|---|
| 1[c] |  |  | 49% (70%)[d] |
| 2[c] |  |  | 61% |
| 3[c] |  |  | 65% |
| 4[c] |  |  | 33% |
| 5[c] |  |  | 66% |
| 6 |  |  | 41% |
| 7[e] |  |  | 61% |
| 8[e] |  |  | 86% |
| 9[e] |  |  | 72% |
| 10 |  |  | 77%[d] |
| 11[e] |  |  | 77% |
| 12[c] |  |  | 79% |
| 13[e] |  |  | 80% |
| 14 |  |  | 55% |

[a] Conditions: 0.12 M in AcOH/$Ac_2O$ (1:1), 2 h, 25 °C; then 5 mol % $Pd(OAc)_2$, 1−3 equiv of $PhI(OAc)_2$, 80 or 100 °C, 4−12 h. [b] The remaining mass balance (as determined by GC of the crude reaction mixtures) was generally unreacted *O*-acetyloxime (analogous to **8** in eq 3). [c] Starting material and product consisted of a mixture of oxime *E*/*Z* stereoisomers. [d] GC yield. [e] Product consisted of a mixture of oxime *E*/*Z* stereoisomers.

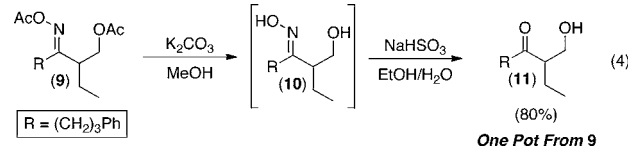
good yields (entries 1−6). The observed trends in reactivity and selectivity were similar to those in $sp^3$ C−H functionalization reactions of related oxime ethers.[9b] For example, oxidation occurred selectively at 1° $\beta$-$sp^3$ C−H bonds versus the analogous 2° sites (entries 1−4). Acetoxylation of a 2° C−H bond could be achieved in modest yield in the rigid *trans*-decalone system (entry 6). The reaction conditions were compatible with a number of functional groups, including alkyl chlorides (entry 4) and protected amines (entry 3); furthermore, remote benzylic C−H bonds were well tolerated under the oxidizing reaction conditions (entries 1, 9, and 14).[18]

*O*-Acetyl ketoximes were also effective directing groups for Pd-catalyzed acetoxylation at $sp^2$ C−H sites. Both electron-poor and electron-rich aryl rings underwent mono-*ortho*-oxygenation in high yields (entries 7 and 11). Further, aryl bromides (entry 8) and silyl-protected phenols (entry 12) were compatible with the reaction conditions. One notable limitation of this method is that *O*-acetyl aldoximes (for example, entry 10) were susceptible to elimination of AcOH to generate nitriles.[19]

The C−H acetoxylation products in Table 1 were obtained in yields comparable to those previously reported with oxime ether derivatives.[9b,d] However, the *O*-acetyl oxime directing group is significantly more readily deprotected. In general, $\beta$-hydroxy ketones are accessible via alcoholysis of both acetate groups (to afford $\beta$-hydroxy oximes) followed by removal of the oxime functionality. The first step can be accomplished by treatment of starting materials like **9** with $K_2CO_3$ in MeOH to afford **10** in 91% isolated yield.

While numerous methods exist for the second step (conversion of an oxime to a ketone), many of our substrates are susceptible to competing formation of side products (e.g., via alcohol oxidation, isoxazoline formation, or elimination). After extensive experimentation, we identified the use of $NaHSO_3$ in EtOH/$H_2O$[20] as the most general and high yielding method to transform these oximes into $\beta$-hydroxy ketones while circumventing undesired side reactions and persistent byproducts. Under these conditions, substrate **10** was converted cleanly to **11** in 80% yield. Compound **11** was obtained in pure form by a simple extraction, obviating the need for chromatography.

The two deprotection steps could also be combined to provide an operationally simple, high-yielding, one-pot route from *O*-acetyl oxime C−H oxidation products to $\beta$-hydroxy ketones (eq 4). For example, treatment of **9** with $K_2CO_3$ in MeOH, followed by addition of $NaHSO_3$ and $H_2O$, provided **11** in 80% yield after a simple extractive workup (eq 4). As shown in Table 2, this one-pot deprotection could also be achieved with other substrates. Under these conditions, elimination products were not observed, and isoxazoline formation was limited to ≤5%.



(4)

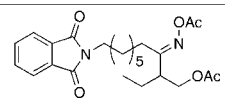
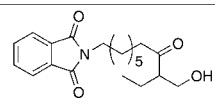
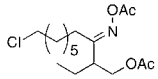
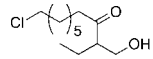
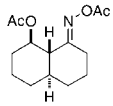
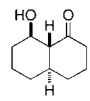
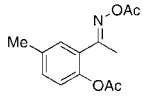
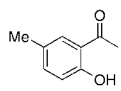
An important characteristic of the *O*-acetyl oxime directing group is that it enables access to a variety of additional

(18) The acetoxylated products were typically isolated as mixtures of *E*/*Z* oxime stereoisomers, which rapidly interconvert under the catalytic reaction conditions.

(19) For an example under similar conditions, see: Waring, P. *Aust. J. Chem.* **1988**, *41*, 667.

(20) Pines, S. H.; Chermerda, J. M.; Kozlowski, M. A. *J. Org. Chem.* **1966**, *31*, 3446.

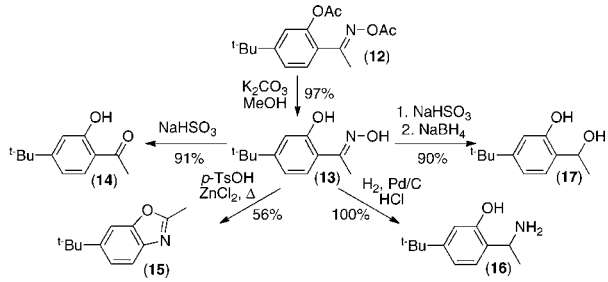
**Table 2.** Deprotection to $\beta$- and *ortho*-Hydroxy Ketones[a]

| entry | starting material | product | yield |
|---|---|---|---|
| 1 |  |  | 80% |
| 2 |  |  | 56% |
| 3 |  |  | 83% |
| 4 |  |  | 89% |

[a] Conditions in entries 1−3 (one pot): $K_2CO_3$ (3 × 0.15 equiv/2.5 h), MeOH, 25 °C, then 3.5 equiv of $NaHSO_3$, $H_2O$, 80 °C, 3 h. Conditions in entry 4 (two steps): (i) 0.15 equiv of $K_2CO_3$, MeOH, 25 °C, 1 h, then (ii) 3.5 equiv of $NaHSO_3$, $H_2O$, EtOH, 90 °C, 12 h.

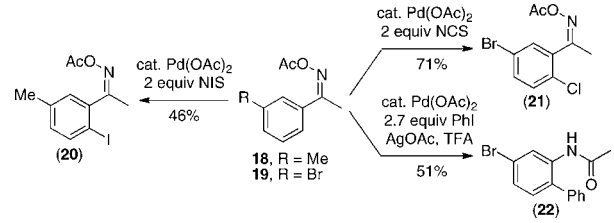
structural motifs from a common synthetic intermediate. As exemplified with **12** in Scheme 2, $K_2CO_3$-catalyzed methanolysis of the acetyl groups provided oxime **13** in quantitative yield. Product **13** could then be converted to the corresponding acetophenone **14**, to oxazoline **15** (via Beckmann rearrangement[21] followed by intramolecular condensation), to amino phenol **16** (via reduction),[22] and to diol **17** (via oxime hydrolysis followed by reduction).[23]

**Scheme 2.** Diverse Transformations on C−H Functionalization Product **12**




Preliminary results indicate that these *O*-acetyl oximes are also effective directing groups for other Pd-catalyzed C−H functionalization reactions. For example, as shown in Scheme 3, the Pd-catalyzed iodination of **18** and chlorination of **19** proceeded to form aryl halides **20** and **21** in modest to good yields.[24] Interestingly, under standard Pd-catalyzed C−H arylation conditions with PhI and AgOAc in TFA,[25] **19** underwent in situ Beckmann rearrangement/C−H phenylation to afford acetamide **22**.

**Scheme 3.** Other Pd-Catalyzed C−H Functionalization Reactions of *O*-Acetyl Oximes




In conclusion, this letter describes the use of in situ generated *O*-acetyl oximes as effective directing groups in Pd-catalyzed C−H functionalization reactions. These directing groups are stable under the catalytic reaction conditions but can then be readily manipulated to afford ketones, alcohols, amines, and heterocycles.

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**Supporting Information Available:** Experimental details and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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