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

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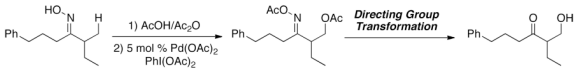
## Abstract




*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 sought to temporarily mask ketones as more coordinating imine or oxime derivatives during C–H functionalization and then subsequently remove this group to reveal the ketone functionality (Scheme 1). This communication describes the development of *O*-acetyl oximes as versatile and readily transformable directing groups for Pd-catalyzed C–H functionalization.

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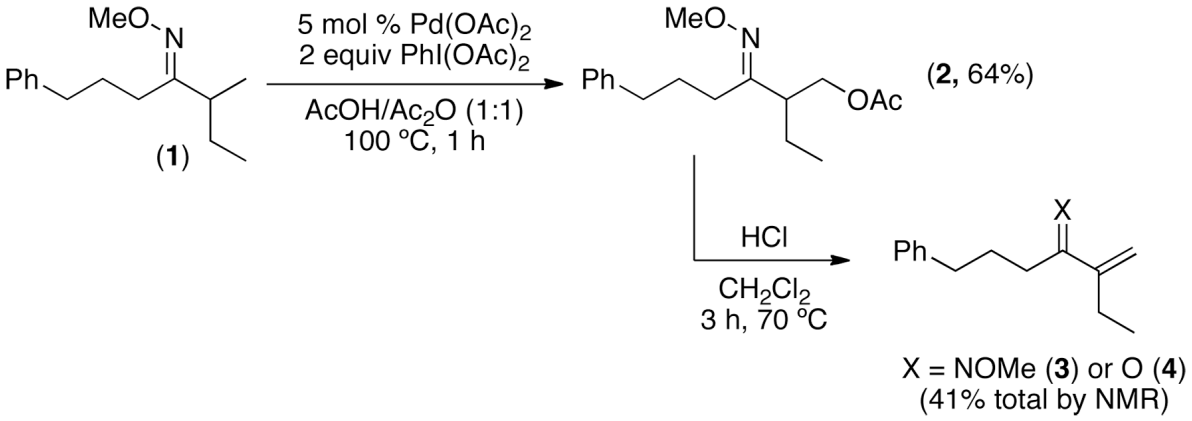
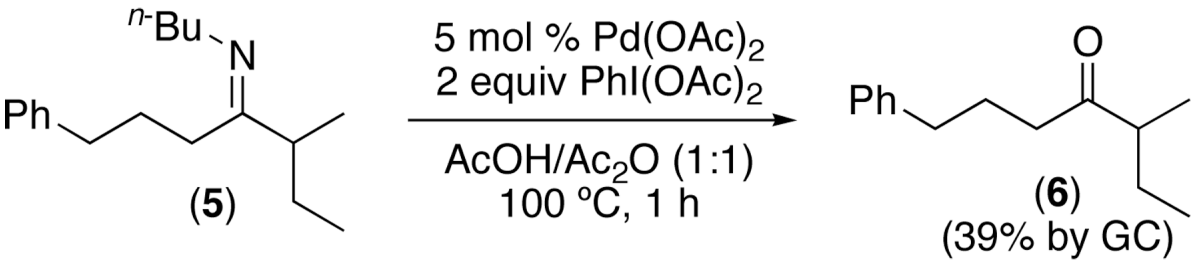
**Supporting Information Available.** Experimental details and spectroscopic data for new compounds. This material is available free of charge via the internet at http://pubs.acs.org.

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 β-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 super-stoichiometric $Ti^{III}Cl_3$ is effective in some cases,[13] but this expensive, air sensitive reagent is not practical for general application.

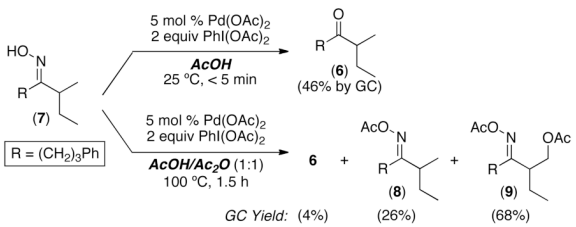



(*1*)

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 acetoxylations. For example, reaction of **5** under standard acetoxylation conditions affords the hydrolyzed ketone **6** as the major identifiable product (39% yield, eq 2).




(*2*)




(*3*)

Simple hydroxyl (OH) oximes are another attractive ketone surrogate. These are readily available, stable, often crystalline starting materials, are known to direct stoichiometric cyclopalladation of both $sp^2$ and $sp^3$ C–H bonds,[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).

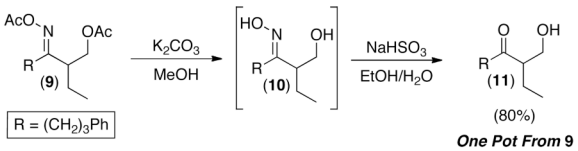
As summarized in Table 1, a number of dialkyl oximes underwent in situ acetylation/β-acetoxylation in modest to good yields (entries 1–6). The observed trends in reactivity and selectivity were similar to those in $sp^3$ C–H functionalization reactions of related oxime ethers.[9b] For example, oxidation occurred selectively at 1° β-$sp^3$ 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, 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, β-hydroxy ketones are accessible via alcoholysis of both acetate groups (to afford β-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 β-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 β-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 work-up (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 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]

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**.

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.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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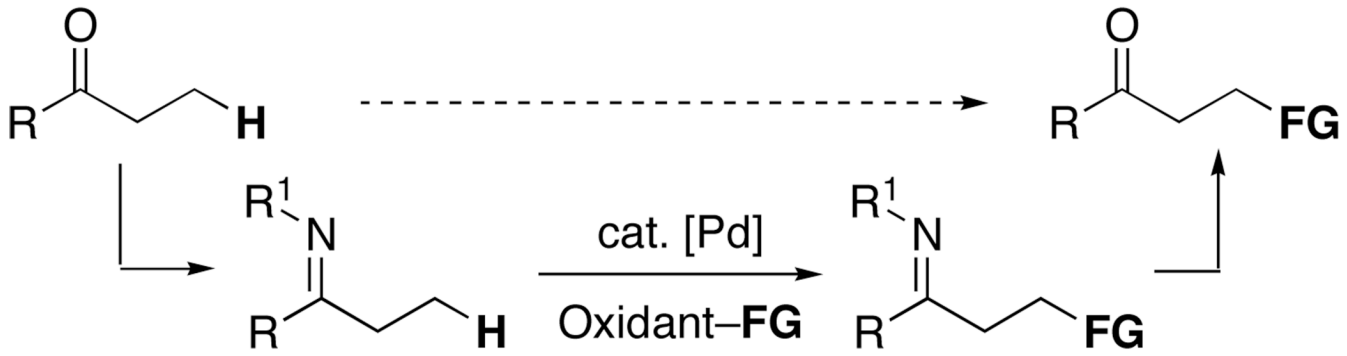
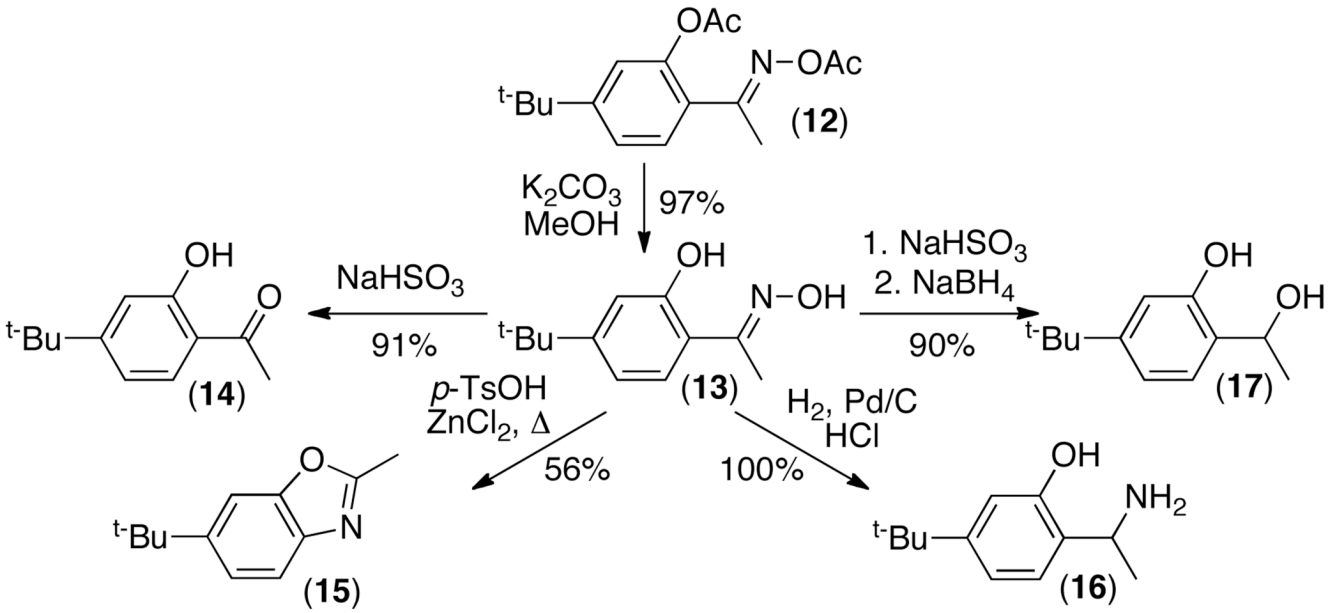
## References


1. For reviews, see (a) Dick AR, Sanford MS. Tetrahedron 2006;62:2439. (b) Daugulis O, Zaitsev VG, Shabashov D, Pham QN, Lazareva A. Synlett 2006:3382. (c) Alberico D, Scott ME, Lautens M. Chem. Rev 2007;107:174. [PubMed: 17212475] (d) Li BJ, Yang SD, Shi ZJ. Synlett 2008:949. (e) Deprez NR, Sanford MS. Inorg. Chem 2007;46:1924. [PubMed: 17348723] (f) Chen X, Engle KM, Wang DH, Yu JQ. Angew. Chem., Int. Ed 2009;48:5094..
2. (a) Wang X, Mei TS, Yu JQ. J. Am. Chem. Soc 2009;131:7520. [PubMed: 19435367] (b) Cai G, Fu Y, Li Y, Wan X, Shi Z. J. Am. Chem. Soc 2007;129:7666. [PubMed: 17530847]
3. Giri R, Wasa M, Breazzano SP, Yu JQ. Org. Lett 2006;8:5685. [PubMed: 17134247]
4. Chiong HA, Pham QN, Daugulis O. J. Am. Chem. Soc 2007;129:9879. [PubMed: 17649995]
5. (a) Shabashov D, Maldonado JRM, Daugulis O. J. Org. Chem 2008;73:7818. [PubMed: 18763824] (b) Wasa M, Engle KM, Yu JQ. J. Am. Chem. Soc 2009;131:9886. [PubMed: 19580277]
6. Larock, RC. Comprehensive Organic Transformations. 2nd ed. New York: John Wiley & Sons, Inc.; 1999. p. 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 ME, Lautens M. Chem. Rev 2007;107:174. [PubMed: 17212475] (b) Colby DA, Bergman RG, Ellman JA. Chem. Rev. [Online early access]. DOI: 10.1021/cr900005n. Published Online: May 13, 2009. http://pubs.acs.org/doi/pdf/10.1021/cr900005n.
9. (a) Dick AR, Hull KL, Sanford MS. J. Am. Chem. Soc 2004;126:2300. [PubMed: 14982422] (b) Desai LV, Hull KL, Sanford MS. J. Am. Chem. Soc 2004;126:9542. [PubMed: 15291549] (c) Desai LV, Malik HA, Sanford MS. Org. Lett 2006;8:3387. [PubMed: 16836412] (d) Desai LV, Stowers KJ, Sanford MS. J. Am. Chem. Soc 2008;130:13285. [PubMed: 18781752]
10. For related C–H acetoxylation reactions of other substrates, see: (a) Kalyani D, Sanford MS. Org. Lett 2005;7:4149. [PubMed: 16146374] (b) Giri R, Liang J, Lei JQ, Li JJ, Wang DH, Chen X, Naggar IC, Guo C, Foxman BM, Yu JQ. Angew. Chem., Int. Ed 2005;44:7420. (c) Wang DH, Hao XS, Wu DF, Yu JQ. Org. Lett 2006;8:3387. [PubMed: 16836412] (d) Reddy BVS, Reddy LR, Corey EJ. Org. Lett 2006;8:3391. [PubMed: 16836413] (e) Wang GW, Yuan TT, Wu XL. J. Org. Chem 2008;73:4717. [PubMed: 18484772] (f) Zhang J, Khaskin E, Anderson NP, Zavalij PY, Vedernikov AN. Chem. Commun 2008:3625. (g) Stowers KJ, Sanford MS. Org. Lett 2009;11:4584. [PubMed: 19754074] .
11. For example, see: Shipe WD, Sorensen EJ. Org. Lett 2002;4:2063. [PubMed: 12049518] .
12. Conversion of oxime ethers to ketones has been reported using Amberlyst 15 at temperatures ranging from 25 °C to 110 °C. See: (a) Sakamoto T, Kikugawa Y. Synthesis 1993:563. (b) Mears RJ, Sailes HE, Watts JP, Whiting A. J. Chem. Soc., Perkin Trans. 1 2000:3250.. In our hands, **2** and derivatives were stable 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 β-acetoxy or β-hydroxy ketone.
13. (a) Desai, LV. Ph.D. Thesis. University of Michigan; 2008 Apr. Palladium-Catalyzed Functionalization of C–H Bonds and Alkenes. (b) Corey EJ, Niimura K, Konishi Y, Hashimoto S, Hamada Y. Tetrahedron Lett 1986;27:2199.
14. For selected examples, see: (a) Baldwin JE, Jones RH, Nájera C, Yus M. Tetrahedron 1985;41:699. (b) Baldwin JE, Nájera C, Yus M. J. Chem. Soc., Chem. Commun 1985:126. (c) Carr K, Saxton HM, Sutherland JK. 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. Milwaukee, WI: Aldrich Chemical; 2009.
17. Moriarty RM, Prakash O, Vavilikolanu PR. Synth. Commun 1986;16:1247.
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..

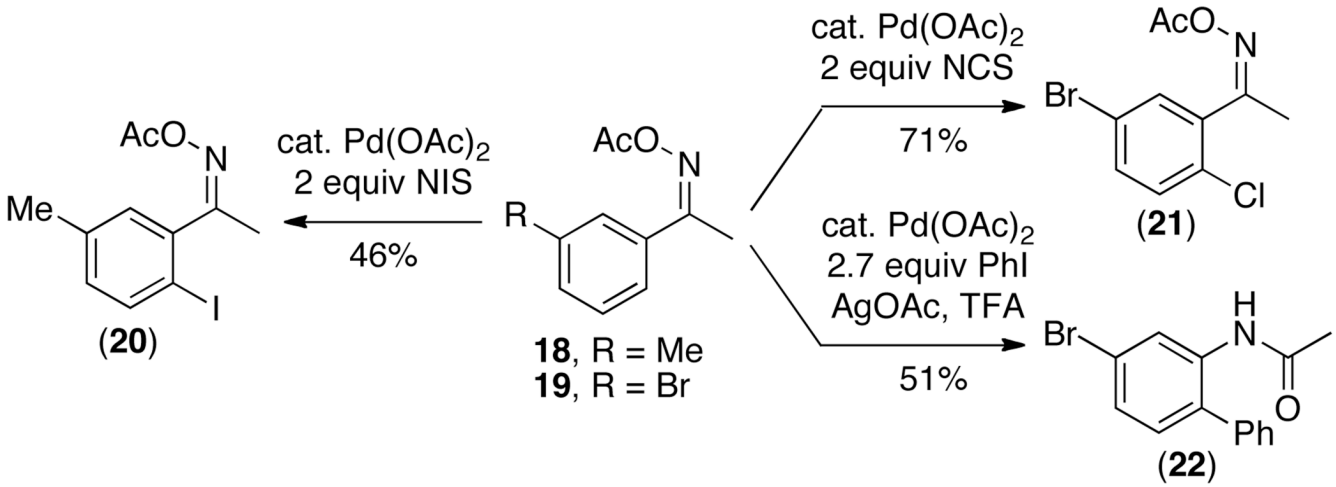
20. Pines SH, Chermerda JM, Kozlowski MA. J. Org. Chem 1966;31:3446.
21. Xiao LF, Xia CG, Chen J. Tetrahedron Lett 2007;48:7218.
22. Chung JU, Kim SY, Lim JO, Choi HK, Kang SU, Yoon HS, Ryu H, Kang DW, Lee J, Kang B, Choi S, Toth A, Pearce LV, Pavlyukovets VA, Lundberg DJ, Blumberg PM. Bioorg. Med. Chem 2007;15:6043. [PubMed: 17629487]
23. Prein M, Maurer M, Peters EM, Peters K, von Schnering HG, Adam W. Chem. Eur. J 1995;1:89.
24. (a) Kalyani D, Dick AR, Anani WQ, Sanford MS. Org. Lett 2006;8:2523. [PubMed: 16737304] (b) Kalyani D, Dick AR, Anani WQ, Sanford MS. Tetrahedron 2006;62:11483.
25. Daugulis O, Zaitsev VG. Angew. Chem. Int. Ed 2005;44:4046.




**Scheme 1.**
Approach to β-C–H Functionalization of Ketones




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




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

**Table 1**

*O*-Acetyl Oxime-Directed Acetoxylation of C–H Bonds[a]

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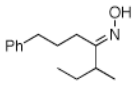
| 1[c] |  |

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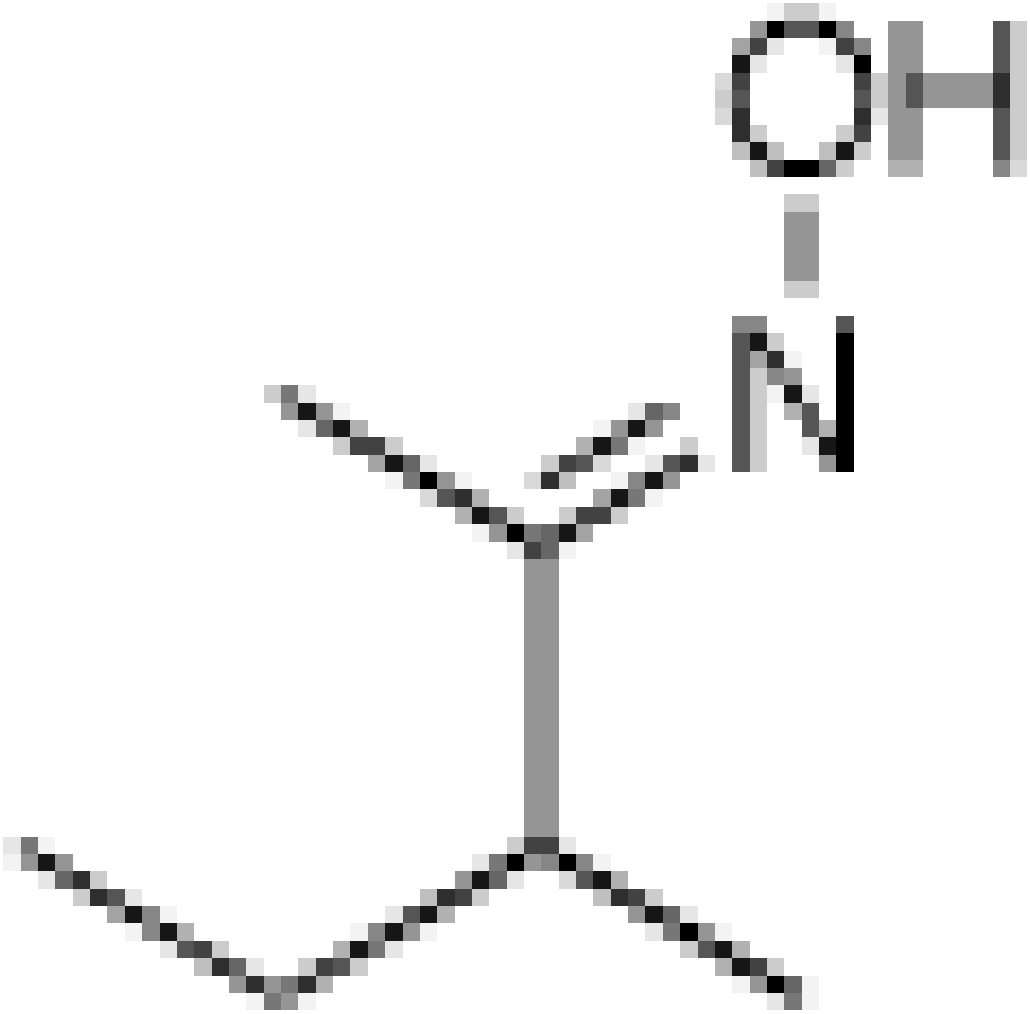
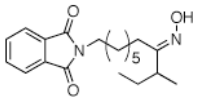
| 2[c] |  |
| 3[c] |  |

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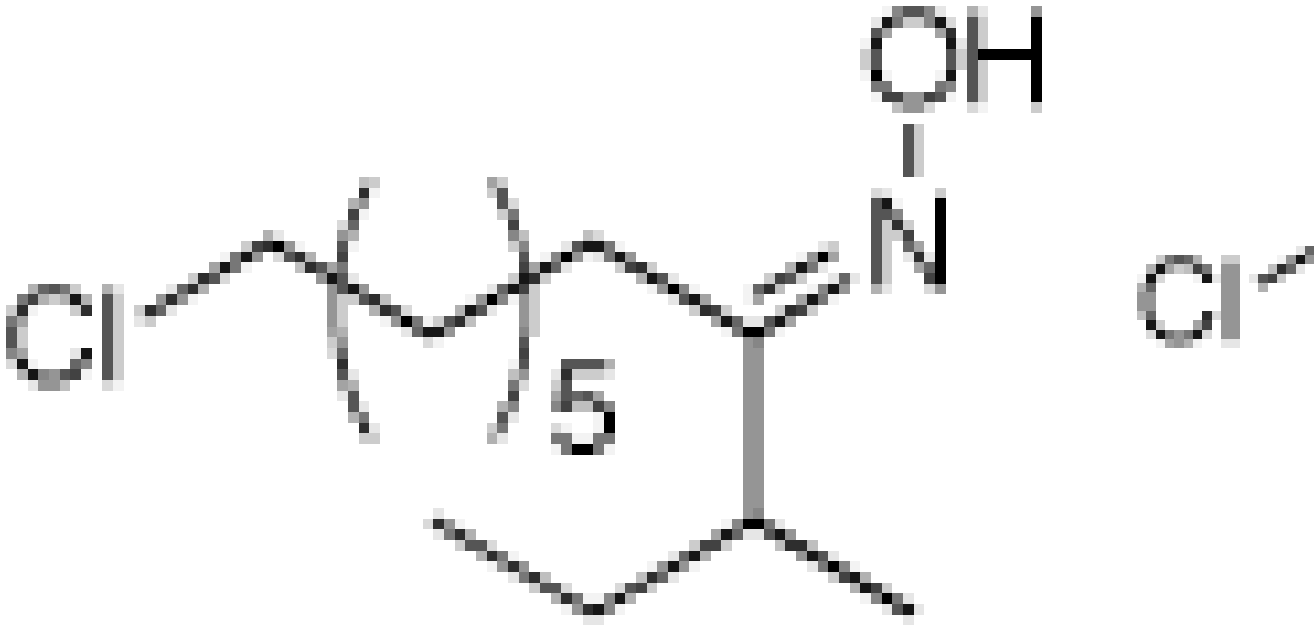
| 4[c] |  |

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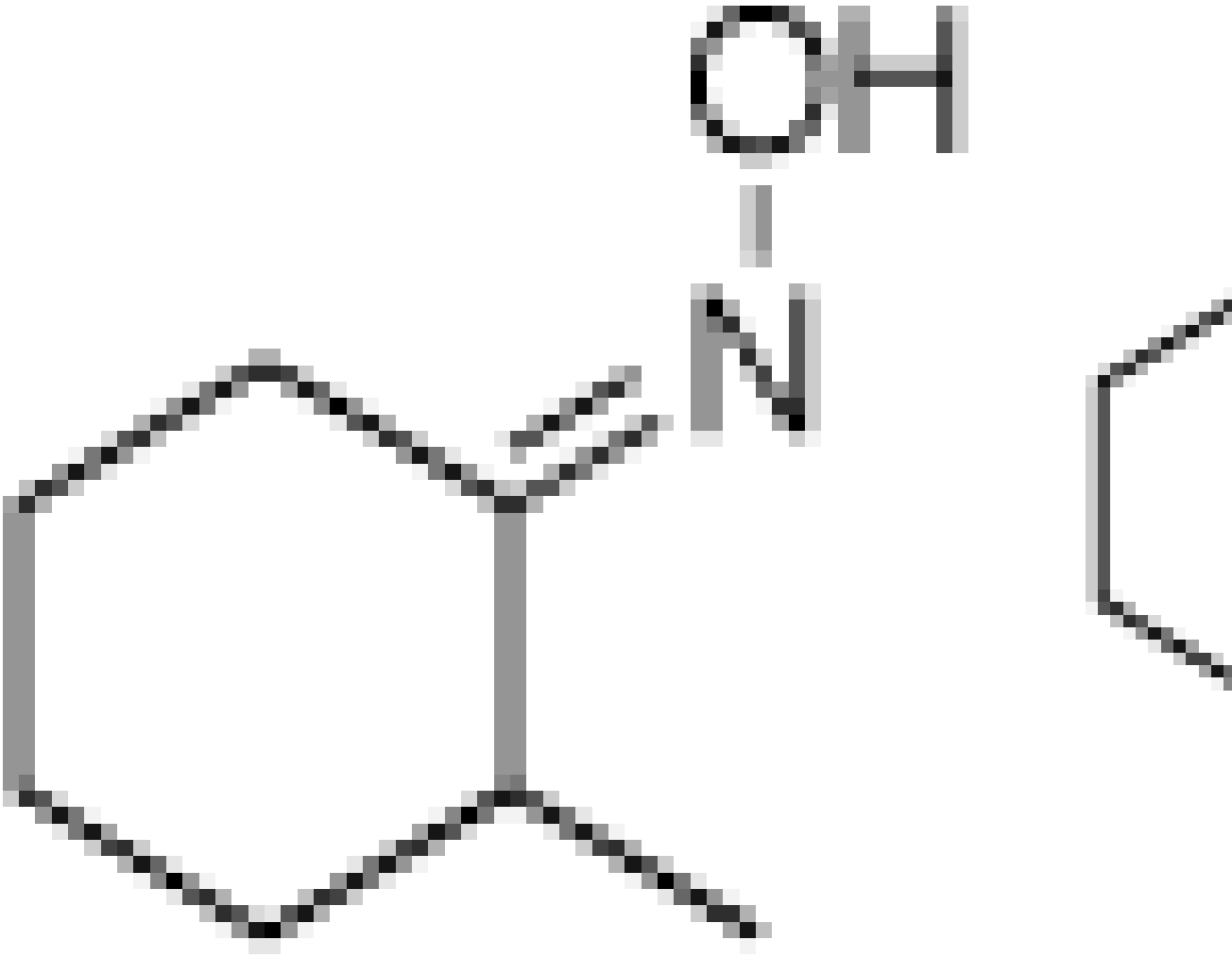
| 5[c] |  |

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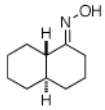
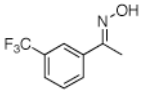
| **6** |  |
| **7**[e] |  |

| entry | starting material |
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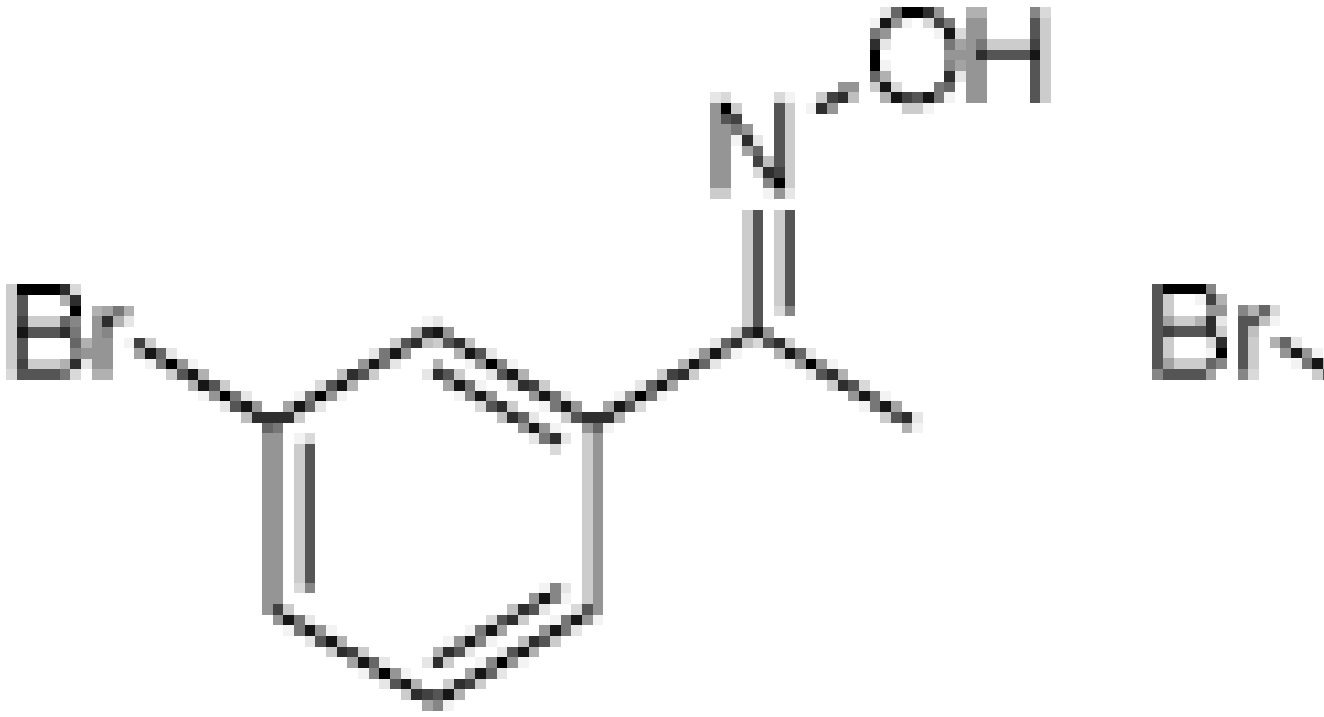
| 8[e] |  |

| entry | starting material |
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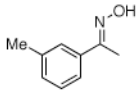
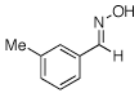
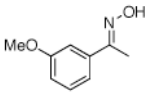
| **9**[e] |  |
| **10** |  |
| **11**[e] |  |

| entry | starting material |
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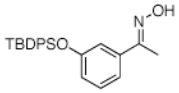
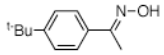
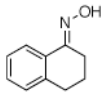
| **12**[e] |  |
| **13**[e] |  |
| **14** |  |

[a] Conditions: 0.12 M in $AcOH/Ac_2O$ (1:1), 2 h, 25 °C; then 5 mol % $Pd(OAc)_2$, 1–3 equiv $PhI(OAc)_2$, 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).

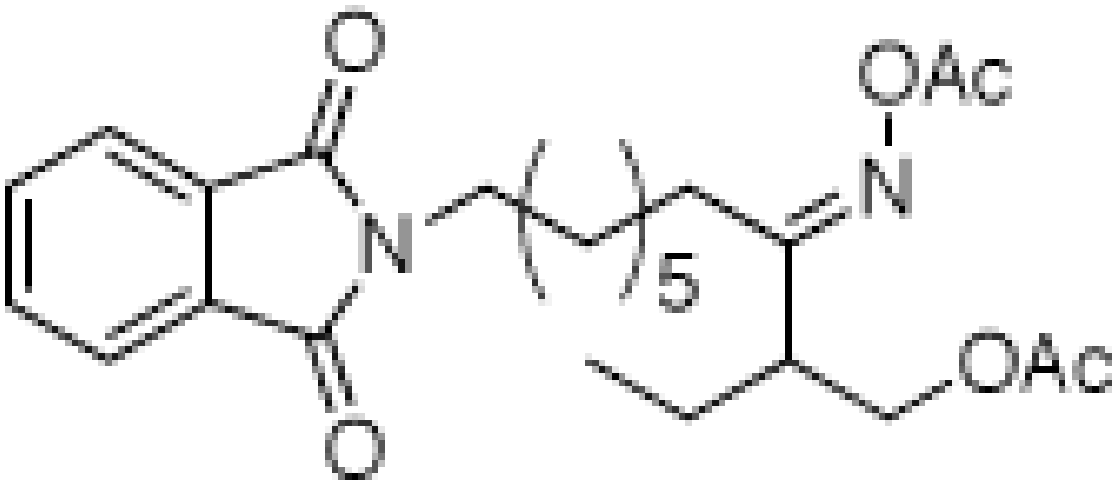
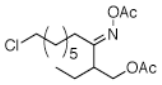
[c] Starting material and product consisted of a mixture of oxime E/Z stereoisomers.

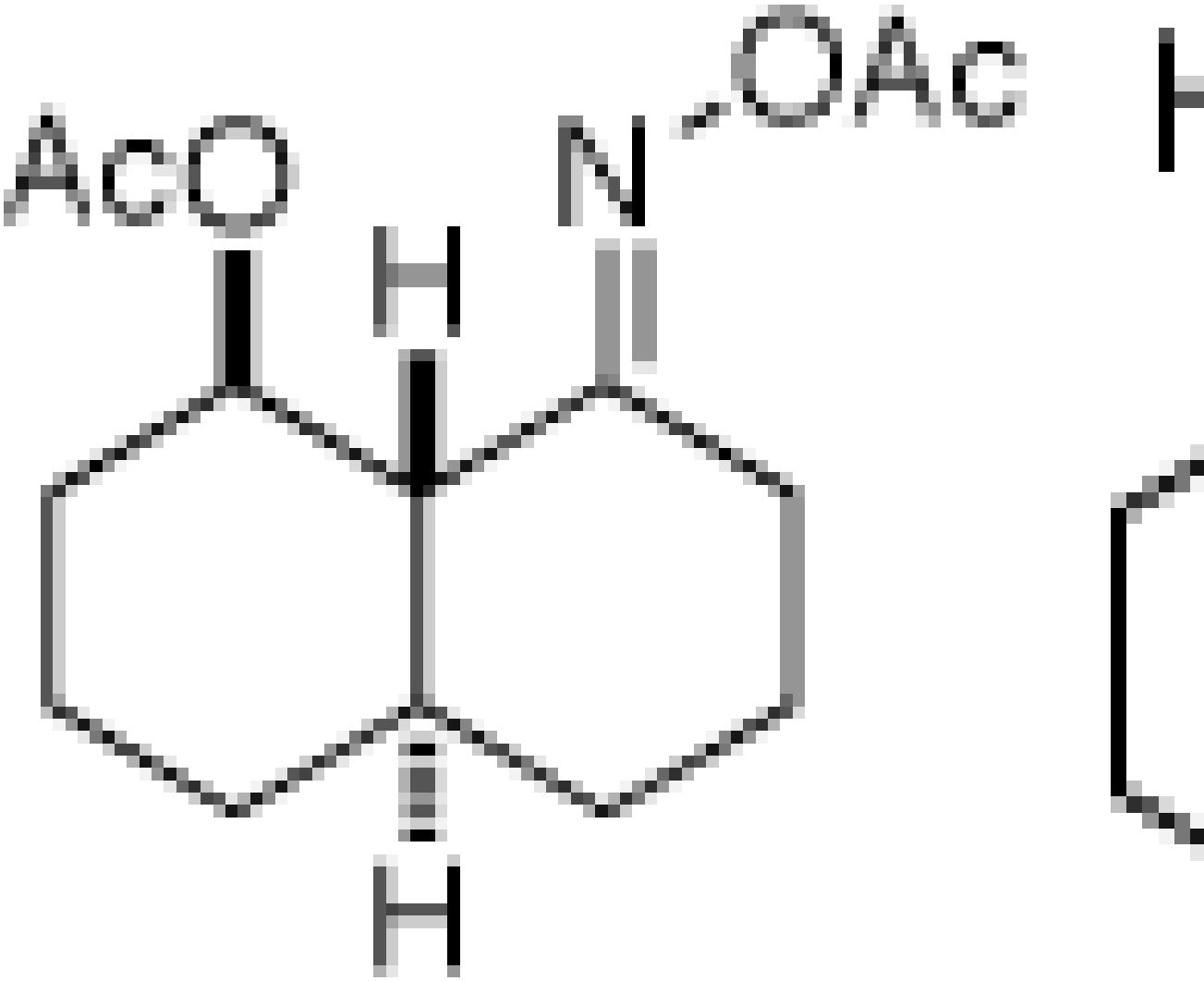
[d] GC yield.

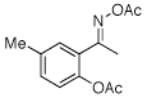
[e] Product consisted of a mixture of oxime E/Z stereoisomers.

**Table 2**

Deprotection to β- and *ortho*-Hydroxy Ketones[a]

| entry | starting material |
|---|---|
| 1 |  |
| 2 |  |

| entry | starting material |
|---|---|
| 3 |  |

| entry | starting material |
|---|---|
| **4** |  |



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