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Pd(II)-Catalyzed Primary-C(sp^3)−H Acyloxylation at Room Temperature

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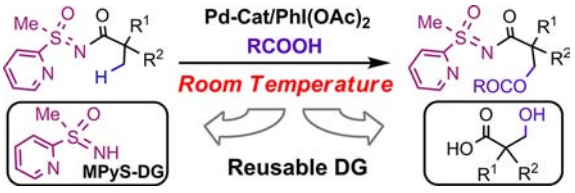
ABSTRACT



With the aid of a novel *S*-methyl-*S*-2-pyridyl-sulfoximine (MPyS) directing group (DG), the unactivated primary β-C(sp^3)−H bond of MPyS-*N*-amides oxidizes at room temperature. The catalytic conditions are applicable to the diacetoxylation of primary β,β'-C(sp^3)−H bonds, and the carboxylic acid solvent is pivotal in the formation of the C−O bond. The MPyS-DG cleaves from the oxidation products and is recovered. This method provides convenient access to α,α'-disubstituted-β-hydroxycarboxylic acids.

Transition-metal-catalyzed, directing-group (DG) assisted oxidation of an unactivated C(sp^3)−H bond has emerged as an elegant and powerful tool for the construction of chemo- and regioselective C−O bonds in aliphatic chains.[1] This unique strategy allows the creation of a hydroxy functional group within a complex molecule, therefore giving it broad application in synthetic chemistry.[2] However, owing to the high bond dissociation energy of the C(sp^3)−H bond and lack of π-participation, direct oxidation of an unactivated alkane C−H bond is a challenging problem.[1b] Among the known processes for C−H bond oxidation,[3−5] the inherently reactive and relatively weaker alkane C−H bonds are more amenable to oxidation.[6] Sanford and co-workers demonstrated an elegant approach for the transformable oximes or pyridine-directed 1°/2°-C(sp^3)−H oxidation of alkanes (eq 1).[5e,j] The Yu group employed a chiral oxazoline to accomplish the otherwise challenging diastereoselective oxidation of a methyl group (eq 1).[5i] However, the use of nonremovable and nonmodifiable DGs limit the applications of alkane C−H oxidation methods to synthetic chemistry.[7] Therefore, the development of a new synthetic pathway for the direct oxidation of C(sp^3)−H bonds with the aid of reusable DG under mild catalytic conditions is highly desirable.[1b,8]

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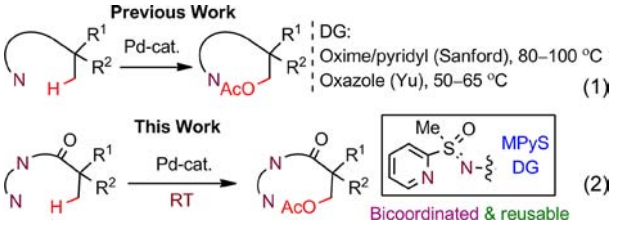
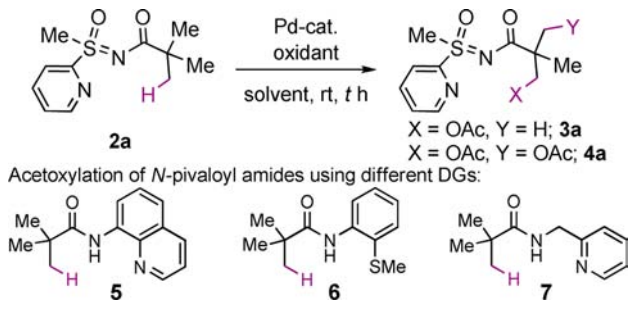


A recent report by Simmons and Hartwig describes a conceptually interesting method for the primary γ-C−H functionalization of aliphatic alcohols/ketones in the presence of an iridium-phenanthroline catalyst and a dihydridosilane reagent at 120 °C.[9] We recently reported our preliminary observation on the Pd-catalyzed direct 1°-β-C(sp^3)−H acetoxylation of *S*-methyl-*S*-phenylsulfoximine-*N*-amide at 100 °C.[10] This result inspires us to envision a new *S*-methyl-*S*-2-pyridylsulfoximine (MPyS)[11] bidented reusable DG to carry out the oxidation of an alkane C−H bond. Presumably the facile coordination of pyridyl[12] and sulfoximine nitrogens of MPyS-DG to a Pd-catalyst would trigger activating the β-C(sp^3)−H bond of MPyS-N-amides with the involvement of a [5,5]-fused-Pd-bridged system (eq 2), a concept that was first reported by Daugulis.[12c] Moreover, the oxidation of C(sp^3)−H bonds of amides and the use of a bicoordinated DG for the C−H oxidation of alkane are rare.[5f] Recently, Chen et al. demonstrated the picolinamide-directed alkoxylation of a C(sp^3)−H bond at 110 °C.[13] We report herein a Pd-catalyzed highly selective direct acetoxylation of a 1°-β-C(sp^3)−H bond of MPyS-*N*-amides at room temperature (rt).

Scheme 1. Acetoxylation of *N*-Pivaloyl-MPyS



To probe this hypothesis, compound **2a** was exposed to catalytic conditions comprising of various combinations of Pd-catalysts, oxidants, and solvents.[14] The reaction of **2a** (0.5 mmol) in the presence of $Pd(OAc)_2$ (5 mol %) and $PhI(OAc)_2$ (0.75 mmol) in AcOH (1.50 mL) was found to be optimal.[14] Other *N*,*N*- or *N*,*S*-bicoordinated directing groups,[16] such as 8-aminoquinoline (8-AQ),[16a,b,e] 2-methylthioaniline (2-MTA),[16e] and 2-pyridin-ylmethylamine (2-PMA)[16c] in **5**, **6**, and **7**, were found to be ineffective under the optimized conditions (Scheme 1).

To investigate the effect of the MPyS-DG for the unactivated primary β-C(sp^3)−H oxidation, a wide variety of MPyS-*N*-amides having a 1°-β-C−H bond were subjected to the optimized catalytic conditions at rt. Table 1 summarizes the scope and limitations of these studies. The desired monoacetoxylation product **3a** was obtained in 80% yield from **2a** in 14 h. The β-C(sp^3)−H bond was exclusively oxidized leaving the γ-C(sp^3)−H unaffected,[15] producing **3b** in 82% yield. Interestingly, chloro and bromo substitutions on an aliphatic chain survived, delivering **3c** and **3d** effectively; in contrast oxidation of β,β'-dichloro containing amide **2e** proceeded sluggishly even at 60 °C. The 2°-benzylic β-C(sp^3)−H bonds and the more reactive aromatic C−H bonds were inert to the reaction conditions; the desired oxidation products **3f**−**j** were furnished in good yields. Functional groups on the aromatic ring, including nitro (**3g**), bromo (**3h**), and ether (**3i**), were unaffected. Amides derived from 2-methylcyclohexane carboxylic acids underwent β-acetoxylation successfully (**3k**). The ester functional group did not affect the reaction productivity, furnishing **3l** in an appreciable yield in Ac_2O. Pleasingly, a good amount of β,β'-diacetoxylation product **4a** resulted from **3a**, when the reaction was performed in an AcOH and Ac_2O mixture.

The catalytic conditions were next surveyed to examine the oxidation of β-C(sp^3)−H bonds of MPyS-*N*-amides bearing α-C−H bonds. In general, the α-C−H is prone to undergo the β−H elimination with the involvement of either the Saegusa-type process or the cyclopalladated intermediates.[17] However, the decrease in α-substitutions causing a sluggish reaction and poor product yield was observed. To overcome this problem, oxidations of **2m**−**2o** were therefore conducted at 60 °C. Moderate to good yields of the desired β-C−H acetoxylated products **3m**−**3o** were isolated. The β-H elimination products, possibly obtained from the cyclopalladated intermediates, were not detected.[17a]

The β,β'-dihydroxycarboxylic acids are valuable precursors to the functionalized cyclic carbonates.[18a] These cyclic carbonate monomers are used for the production of

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(14) For more details, see the Supporting Information.
(15) Oxidations of the 1°-acidic-α-H of **8** and the 1°-γ-H of **9** were unsuccessful.

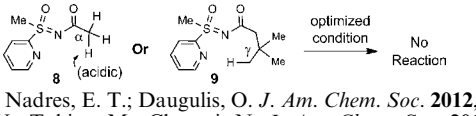

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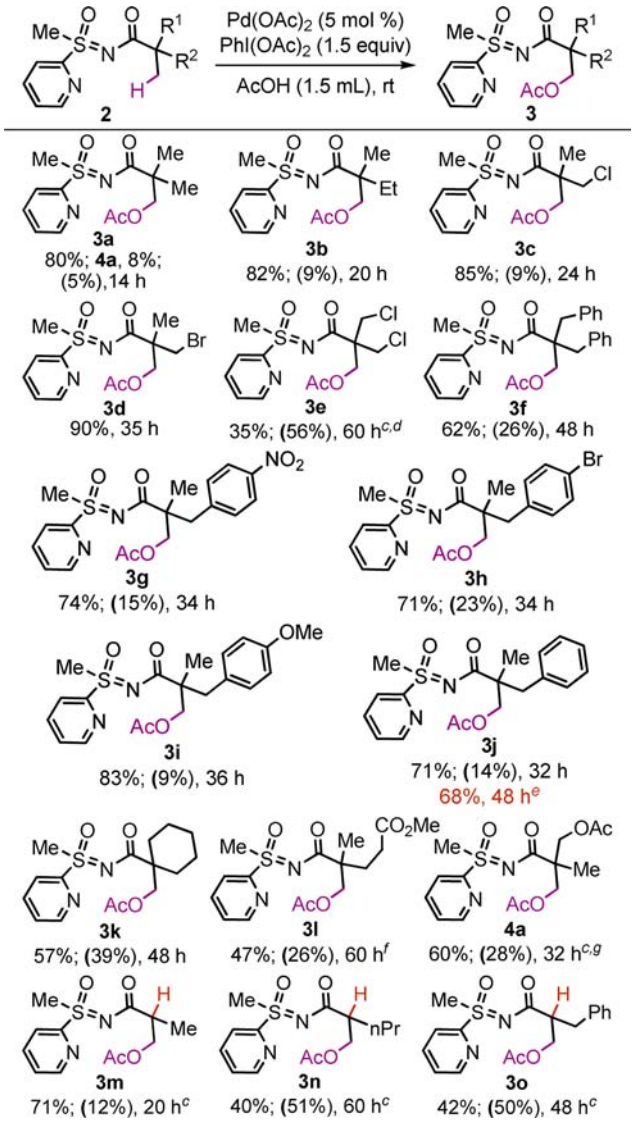
Table 1. Acetoxylation of 1°-β-C(sp^3)−H Bonds of Amides[a,b]

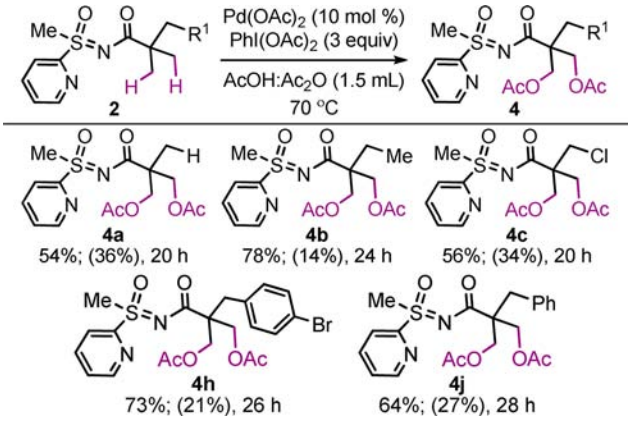


[a] Reaction conditions: **2** (0.5 mmol), $Pd(OAc)_2$ (5 mol %), $PhI(OAc)_2$ (0.75 mmol), AcOH (1.5 mL) at rt. [b] Isolated yields. Recovered starting material is indicated in parentheses. [c] Reaction was carried out at 60 °C. [d] **2e** (100 mg) was employed. [e] Bulk scale reaction of **2j** (1.50 g) was performed. [f] 10 mol % of $Pd(OAc)_2$ was introduced; Ac_2O was used as solvent. [g] Mixture of AcOH and Ac_2O (1:1) was used.

biodegradable and biocompatible polymers.[18b] Hydrolysis of **4a** would generate β,β'-dihydroxycarboxylic acids. To obtain **4a** from **2a**, the diacetoxylation of the primary β,β'-C(sp^3)−H bonds of amides was therefore investigated. Excellent conversion of **2a** to **3a** and **4a** was observed under the modified conditions [$Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (3.0 equiv) in AcOH/Ac_2O at 70 °C] as shown in Table 2. Following this method, **4b**, **4c**, **4h**, and **4j** were isolated in 56−78% yields.

It was speculated that the acetate moiety from the $PhI(OAc)_2$ or AcOH was involved in the formation of the C−O bond. To study the role of the oxidant in this transformation, **2a** was reacted with $PhI(OPiv)_2$ in the

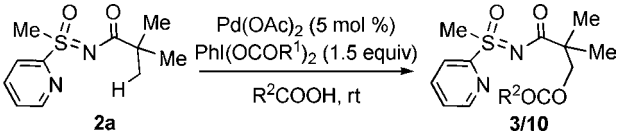
Table 2. Direct β,β'-Di-acetoxylation of Primary β,β'-C(sp^3)−H Bonds of Amides[a,b]



[a] Reaction conditions: **2** (0.25 mmol), $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (0.75 mmol), AcOH/Ac_2O (1:1, 1.5 mL) at 70 °C. [b] Isolated yields. Yield of the monoacetoxylation product is given in parentheses.

presence of $Pd(OAc)_2$ in AcOH. No trace of the −OPiv containing C−H oxidation product was detected by ^1H NMR; rather **3a** was exclusively formed in 81% yield (entry 1, Table 3). In contrast, this reaction did not proceed in the absence of oxidant.[14] The effect of various carboxylic acid solvents was next examined. The carboxylate groups

Table 3. Acyloxylation of 1°-β-C(sp^3)−H Bond of Amides[a]



entry	R^1	R^2	t (h)	R^2 (major)	3/10	yield (%)[b]
1	*t*-Bu	CH_3	30	CH_3	**3a**	81(13)
2	CH_3	CD_3[c]	12	CD_3	**10a**	68(20)
3	CH_3	Et	32	Et	**10b**	59(26)
4	CH_3	*n*-Pr	30	*n*-Pr	**10c**	58(21)[d,e]
5	CH_3	*iso*-Pr	26	*iso*-Pr	**10d**	54(30)[d,e]

[a] Reaction conditions: **2a** (100 mg, 0.42 mmol), $Pd(OAc)_2$ (5 mol %), $PhI(OAc)_2$ (0.63 mmol), R^2COOH (1.25 mL) at rt. [b] Isolated yields. Yield of the recovered **2a** shown in parentheses. [c] CD_3COOD was used as solvent. [d] Reaction performed at 65 °C. [e] Yield of the nonseparable mixture of **10** and **2a**.

CD_3COO−, EtCOO−, *n*-PrCOO−, and *iso*-PrCOO− from the corresponding carboxylic acids were successfully incorporated into the oxidation products, producing **10a**−**d** in good yields (entries 2−5).[5d,i] It appeared that the

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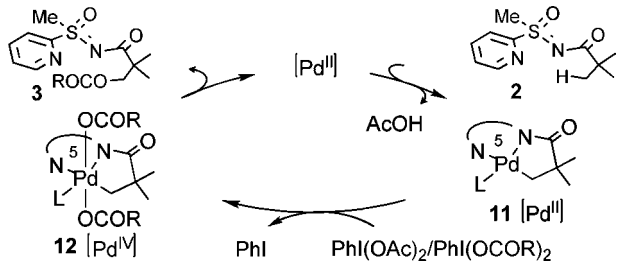
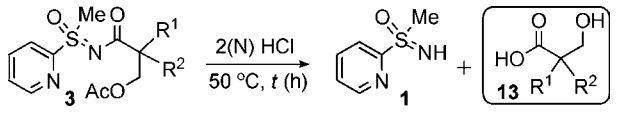
Scheme 2. Proposed Catalytic Cycle



carboxylic acid solvent was responsible for the C−O bond formation, while the oxidant kept the catalytic cycle active.

Based on the discussed Pd-catalyzed alkane C−H oxidation and the results of the β-C(sp^3)−H acyloxylation shown in Table 3, the catalytic cycle in Scheme 2 is proposed with the involvement of the Pd^{II} and Pd^{IV} species.[19] The bichelated Pd^{II} species, generated in situ via the chelation of pyridine and the sulfoximine N-atom to Pd(OAc)$_2$, activates the 1°-β-C(sp^3)−H of MPyS-*N*-amide at rt and produces the [5,5]-fused bicyclic cyclopalladated intermediate **11**. Following this, oxidation of the Pd^{II}-species of **11** with PhI(OAc)$_2$ or PhI(OCOR)$_2$, obtained through the ligand exchange between PhI(OAc)$_2$ and carboxylic acid, delivers the Pd^{IV} species **12**.[20,21] Finally reductive elimination of **12** delivers the desired β-acyloxylated product **3** and the active Pd^{II} species. Alternatively the oxidation could also proceed with the involvement of a Pd(III) intermediate.[22]

Table 4. Recovery of the MPyS Directing Group[a,b]



entry	3	*t* (h)	yield of **1**	yield of **13**
1	**3a**, $R^1 = R^2 = Me$	3	87	88 ($215/1 g)
2	**3j**, $R^1 = Bn$, $R^2 = Me$	6	87	90
3	**3k**, R^1--R^2 = cyclohexyl	5	89	91

[a] Reaction conditions: **3** (0.25 mmol), 1 mL of 2 N HCl at 50 °C. [b] Isolated yields. Bn = benzyl.

Facile cleavage of the directing group from the oxidation products and the successful recovery of the MPyS-moiety would broaden the synthetic versatility of this strategy.[16b,23] Pleasingly, the MPyS-containing amide **3a** was hydrolyzed with HCl (2 N) at 50 °C in 3 h (entry 1, Table 4). The desired 3-hydroxy-2,2-dimethyl-propanoic acid **13a** (215 $/1 g; Aldrich)[24] was extracted from the crude reaction mixture in 88% yield. Following this procedure, various β-hydroxycarboxylic acids **13j** and **13k** were obtained with ease (entries 2 and 3). The precious MPyS-DG was readily isolated from the acidic mother liquor in excellent yields.[14]

Finally, potential synthetic application of this strategy was demonstrated performing Pd-catalyzed unactivated primary β-C(sp^3)−H acetoxylation of drug derivatives (Figure 1). The fibrate-based drugs gemfibrozil and clofibrate are effective in reducing the cardiovascular risk factors associated with type 2 diabetics.[25] Gratifyingly, reaction of MPyS-bearing amides derived from gemfibrozil and clofibrate, under the optimized conditions, furnished the desired β-C(sp^3)−H acetoxylation products **14** and **15** in 66% and 51% yield, respectively.[14]

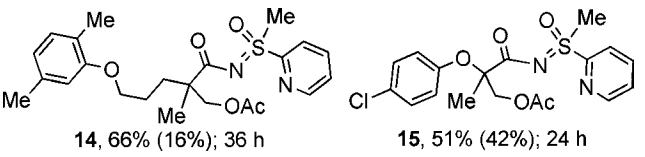


Figure 1. 1°-β-C(sp^3)−H Acetoxylation of drug derivatives.

In conclusion, we have developed a novel MPyS directing group that is functional in the highly selective acetoxylation of the unactivated 1°-β-C(sp^3)−H of MPyS-*N*-amides at rt. The catalytic conditions are able to tolerate various functional groups with a broad reaction scope, making them suitable for use in the synthesis of drug derivatives. The process also allows the formation of the β,β'-diacetoxylation products. The facile cleavage and easy recovery of the robust MPyS-DG makes the present protocol highly useful. Generalization of MPyS-DG for other C−H functionalizations, unraveling of mechanistic details, diastereoselective C(sp^3)−H functionalizations, and investigation of the novel synthetic applications are being actively pursued.

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Supporting Information Available. Detailed experimental procedures, spectra, and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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