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Catalytic Functionalization of Unactivated sp^3 C–H Bonds via *exo*-Directing Groups: Synthesis of Chemically Differentiated 1,2-Diols

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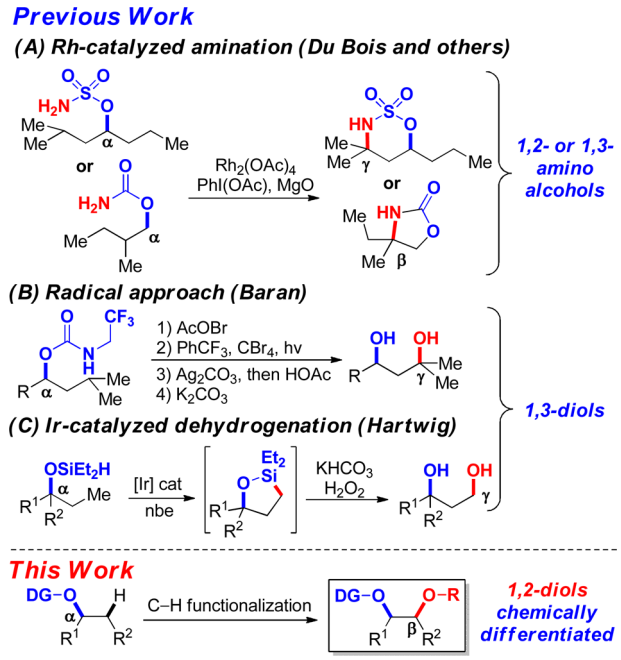
Supporting Information

ABSTRACT: We describe a Pd-catalyzed site-selective functionalization of unactivated aliphatic C–H bonds, providing chemically differentiated 1,2-diols from monoalcohol derivatives. The oxime was employed as both a directing group (DG) and an alcohol surrogate for this transformation. As demonstrated in a range of substrates, the C–H bonds β to the oxime group are selectively oxidized. Besides activation of the methyl groups, methylene groups (CH_2) in cyclic substrates and methine groups (CH) at bridge-head positions can also be functionalized. In addition, an intriguing oxidative skeleton rearrangement was observed using the menthol-derived substrate. The use of *exo*-directing groups in C–H activation, as illustrated in this work, would potentially open doors for the discovery of new transformations and new cleavable DGs.

Site selectivity represents one of the grand challenges for catalytic functionalization of aliphatic C–H bonds.[1] Elegant approaches have been developed for selective activation of specific C–H bonds based on intrinsic reactivity;[2] to date, directing groups (DGs), broadly defined, still serve as highly effective tools for controlling which sp^3 C–H bond to activate.[3] Among various DGs, those derived from alcohols or masked alcohols are particularly attractive due to the ubiquity of hydroxyl groups. Using alcohols or masked alcohols as DGs for activation of more reactive aryl and allylic C–H bonds has been demonstrated by Yu,[4] Hartwig,[5] and White;[6] however, limited success has been made with unactivated sp^3 C–H bonds.[7] It is well documented that the C–H bonds at the δ-position of alcohols can be functionalized through a 1,5-H shift using an oxygen-centered radical approach.[8] Du Bois et al. have developed carbamate- and sulfamate-directed nitrene insertions to access 1,2 or 1,3 amino alcohol moieties (Scheme 1A).[9] Recently, Baran disclosed an efficient four-step one-pot sequence to convert a trifluoromethyl carbamate to a 1,3-diol using a Hofmann–Lőffler reaction-like approach (Scheme 1B).[10] Most recently, Hartwig reported a powerful approach to convert monoalcohols to 1,3-diols using Ir-catalysts (Scheme 1C).[1c]

We have been interested in *1,2-diol synthesis directly from monoalcohols or masked alcohols via catalytic activation of unactivated sp^3 C–H bonds*, which, to our knowledge, has not been realized previously.[11] The challenge is twofold: (1) compared to the γ-position that gives 1,3-diols, the β-position of an alcohol is relatively electron-deficient due to the inductive effect of the oxygen and is, thus, less reactive toward electrophilic C–H activation (such as metal-oxo insertion);[2] (2) designing DGs for such a site-selective reaction is nontrivial because, aside from serving as a good ligand for transition-metal catalysts, the DG should be easily removable to restore the alcohol. To address these challenges, here, we report our development of a Pd-catalyzed functionalization of the unactivated β sp^3 C–H bonds, where oximes are employed as unusual *exo*-DGs.

Scheme 1. Alcohol or Masked-Alcohol Directed C–H Bond Functionalization (Ac, Acetate)



We postulated that properly designed oximes would likely serve as both an alcohol surrogate and a DG for metal-catalyzed site-selective functionalization of β C–H bonds. Oxime-directed catalytic C–H activation was first reported by Sanford, where oximes serve as a carbonyl equivalent directing oxidation of the sp^3 C–H bonds on the nitrogen side (eq 1).[12] In this case, an *endo*-palladacycle is formed through coordination with the oxime nitrogen. In contrast to the *endo*-metallocycles (π-bond of the DG inside the metallocycle), formation of the *exo*-metallocycles (π-bond of the DG outside the metallocycle) is rare in catalytic reactions[13] and often less competitive when formation of an *endo*-cycle is possible (Figure 1).[14] However, *we hypothesized*

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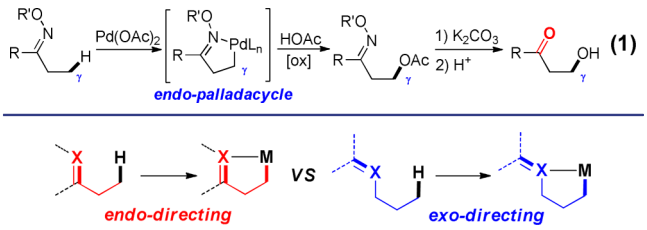
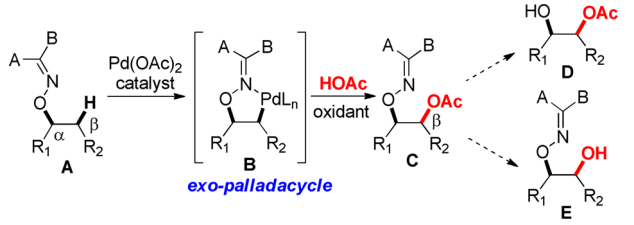


Figure 1. *endo*-Metalation *vs exo*-Metalation.

that, by blocking or obviating potential reaction sites on the nitrogen site of oximes, selective activation of the C−H bonds on the alcohol site should become feasible (Scheme 2). Thus, using such an oxime

Scheme 2. Our Strategy Design

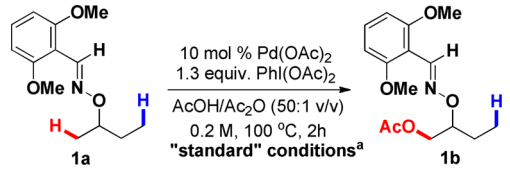


as a DG, a five-membered *exo*-palladacycle (intermediate **B**) is expected to be generated via metalation of the β C−H bond. Subsequent oxidation of intermediate **B** would provide the desired 1,2-diol motif (**C**). Note that the resulting diols would be chemically differentiated, because removal of the acetate group and cleavage of the oxime N−O bond can be operated under orthogonal reaction conditions (*vide infra*).

To test our hypothesis, oxime-derived 2-butanol (**1a**) was employed as the initial substrate. Having optimized the reaction conditions, we were delighted to find that the desired protected 1,2-diol (**1b**) was obtained in 67% yield with excellent site selectivity; oxidation at the γ-position was not observed (entry 1, Table 1). A number of control experiments were conducted to provide further insight of this reaction. Not surprisingly, without the Pd catalyst or the oxidant, no desired product was formed (entries 2 and 4). Use of less catalyst (5 mol %) gave incomplete conversion on a small scale (0.1 mmol, *vide infra*, eq 2) (entry 3). The yield was slightly diminished in the absence of Ac_2O (entry 5),[15] while addition of a small amount of water led to a significant reduction of the yield, suggesting water may hamper the desired reaction pathway (entry 6).

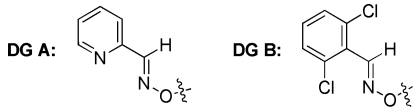
Use of other solvents, such as chlorobenzene, toluene, and 1,2-dichloroethane, proved to be less efficient (entries 7−9). When $K_2S_2O_8$ was employed as the oxidant, a significant amount of the elimination product (2,6-dimethoxybenzonitrile) was formed (entry 10). Addition of LiOAc did not affect the reaction yield (entry 11). Control of the reaction concentration seems to be critical: at higher concentration decomposition products were formed, while at lower concentration incomplete conversion was observed (entries 12 and 13). Finally, 2,6-dimethoxybenzyl oxime proved an optimal DG because use of either the 2-pyridyl (**DG A**) or 2,6-dichlorobenzyl (**DG B**) analogue is much less efficient (entries 14 and 15).[16] It is likely that the pyridine-derived oxime chelates strongly with the Pd and consequently inhibits catalyst turnover, while the 2,6-dichlorobenzyl oxime has relatively weak coordination ability compared to the 2,6-dimethoxybenzyl oxime.

Table 1. Selected Optimization of Reaction Conditions[a]



entry	variation from the "standard" conditions	yield[b,d]
1	none	**67%** (**61%**[c])
2	no $Pd(OAc)_2$	0%
3	5 mol % $Pd(OAc)_2$	50%
4	no $PhI(OAc)_2$	0%
5	no Ac_2O	61%
6	H_2O instead of Ac_2O	50%
7	chlorobenzene instead of HOAc	7%
8	toluene instead of HOAc	7%
9	1,2-dichloroethene instead of HOAc	10%
10	$K_2S_2O_8$ instead of $PhI(OAc)_2$	24%
11	add 0.1 equiv of LiOAc	**67%**
12	0.25 mL of HOAc	53%
13	1 mL of HOAc	52%
14	use "**DG A**"	0%
15	use "**DG B**"	31%

[a]Reaction conditions: all the reactions were run on a 0.1 mmol scale with 0.5 mL of solvents in 2 h. [b]NMR yield determined using 1,1,2,2-tetrachloroethane as internal standard. [c]Isolated yield. [d]Product **1b** consisted of a mixture of oxime *E*/*Z* stereoisomers; see SI.



The substrate scope is depicted in Table 2. All the substrates were prepared from the corresponding alcohols via first conversion to the corresponding *N*-alkoxyphthalimides using a Mitsunobu (for 1° and 2° alcohols) or S_N1 (for 3° alcohols)-type reaction, followed by a one-pot deprotection/condensation with 2,6-dimethoxybenzaldehyde (for a summary and details, see Supporting Information (SI)). Substrates derived from primary, secondary, and tertiary alcohols all reacted smoothly under the optimized conditions, and the corresponding vicinal diols were afforded in good yields (entries 1−9). Substrates with different steric properties were examined, and it seems that increasing sterics on one side of the alcohol does not have a significant impact on the overall reactivity (entries 5−7); however, it seems clear that the secondary alcohol-derived substrates generally give higher reactivity (conversion) than the tertiary ones (entries 8 and 9). The oxidation occurred site selectively on the β-position (X-ray crystal structure of product **9b** was obtained, see SI), and in the presence of a methyl and a nonmethyl alkyl group at the β-position, reaction with the methyl group is generally preferred (entries 3−7).

In addition to methyl groups, cyclic methylene groups (CH_2) also react. In the case of a cyclopentanol-derived substrate, both the mono- and bis-oxidation products (diol **10b** and triol **10c**) were obtained (entry 10).[17] It is interesting to note that the reaction gave a *trans*-isomer for diol **10b** but a *cis*/*trans*-isomer for triol **10c**. This suggests the first metalation occurs selectively on the opposite side of the DG, but the second takes place on the same side. Such selectivity is likely dictated by the inherently preferred conformation of these substrates in the transition states (for details, see SI).

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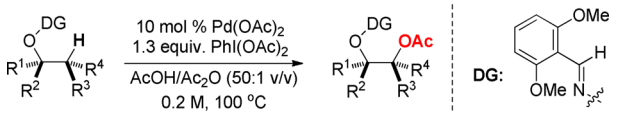
Table 2. Summary of the Substrate Scope

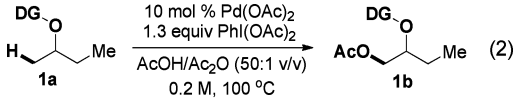


Entry	Substrate	Product	Yield[a]/Reaction Time
1	2a	2b	65%[d]/1.5h
2	3a	3b + 3c	79%[b]/1h (3b: 3c= 2.6:1)
3	1a	1b	61%[b,d]/1h
4	4a	4b	86%[b]/1h
5	5a	5b	72%[b]/1h
6	6a	6b	74%[b]/1h
7	7a	7b	68%[b]/2h
8	8a	8b + 8c	50%[b,d]/2.5h (8b: 8c= 1.4:1)
9	9a	9b	44%[b,c]/2h (79% brsm)
10	10a	10b + 10c	62%[e]/1.5h (10b:10c= 2.1:1)
11	11a	11b	78%[b]/1.5h
12	12a	12b	75%[b]/1.5h

[a]Isolated yields. [b]Product consisted of a mixture of oxime *E*/*Z* stereoisomers; see SI. [c]Starting material and product consisted of a mixture of oxime *E*/*Z* stereoisomers; see SI. [d]1 equiv of $PhI(OAc)_2$ was used. [e]3 equiv of $PhI(OAc)_2$ were used.

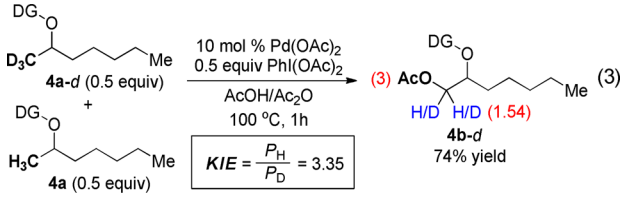
Furthermore, it is surprising to find that in the cases of norbornyl-derived alcohols, both the *endo*- and *exo*-substrates directed the C−H functionalization at the *β*-methine (CH) group, instead of the less hindered *β*-methylene group (entries 11 and 12). The structures of the products (**11b** and **12b**) were determined by removal of both the DG and Ac groups to give the known diols (*vide infra*, Scheme 4).[18] *To our knowledge, Pd-catalyzed C−H functionalization of tertiary carbon centers is extremely rare;*[19] *thus this finding might shed light on the unique reactivity of bridge-head C−H bonds in these reactions.* Although functional group compatibility is not a focus of this communication, we envision this reaction should tolerate a range of functionalities, such as ether, ester, oxime, and aryl groups given that the DG contains aryl methyl ether and oxime groups and that the products contain acetate groups.[20]

Reactions on different scales have also been examined with substrate **1a** (eq 2). On larger scales, the yield was significantly higher and less catalyst was required. For example, the yield increased from 61% on a 0.1 mmol scale to 80% on a 5 mmol (gram) scale. In addition, on a 2 mmol scale, use of 2 mol % $Pd(OAc)_2$ provided a 74% yield of the product.



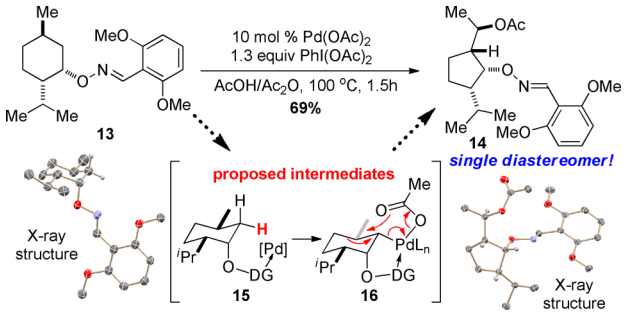
Scale	Isolated yields
0.1 mmol	61%
0.3 mmol	68%
2 mmol (2 mol % catalyst)	74%
5 mmol (Gram Scale)	**80%**

The kinetic isotope effect (KIE) was determined to briefly explore the reaction mechanism. The KIE observed in the intermolecular competition experiments ($k_{H/D}$ = 3.35) is consistent with C−H cleavage being the rate-determining step (eq 3).[21]



An unusual skeleton rearrangement was observed when menthol-derived oxime **13** was used as the substrate (Scheme 3). A five-membered ring product (**14**) with 1,3-diol moieties was isolated as a single diastereomer in good yield.[22] Both the starting material (**13**) and product (**14**) were unambiguously identified by ^1H and ^{13}C NMR, IR, HRMS, and X-ray crystallography. The mechanism for this rearrangement is unclear[23] but likely involves an intermediate such as **16** formed via *cis*-palladation. Detailed mechanistic studies and extension of this transformation to other substrates will be provided in a later report.

Scheme 3. An Unusual Oxidative Rearrangement



Finally, we demonstrated the DG and Ac groups can be removed in excellent yields using orthogonal chemical methods (Scheme 4). Thus, the diols can be easily differentiated, which shows great potential for use in syntheses of complex natural products.

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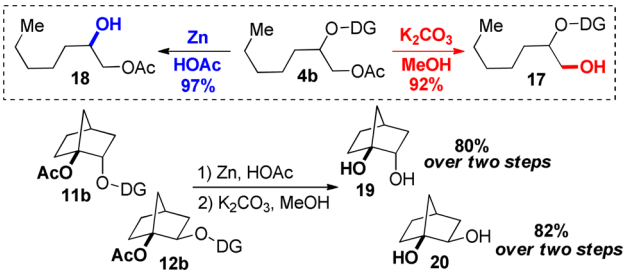
Scheme 4. Orthogonal Protecting Groups



In summary, we have developed a new strategy for the Pd-catalyzed site-selective functionalization of unactivated aliphatic C−H bonds, which allows access to chemically differentiated 1,2-diols from monoalcohol derivatives. The oxime was employed as both a DG and an alcohol surrogate for this transformation. The use of *exo*-DGs in C−H activation, as illustrated in this work, would potentially open doors for the discovery of new transformations and new cleavable DGs. On the basis of these preliminary results, efforts toward enhancing the efficiency of the DG for higher reactivity and easier installation, expanding the substrate/reaction scope, and a detailed mechanistic study are currently ongoing.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(22) Compound **14** was isolated as a mixture of oxime *E*/*Z* isomers. Cleavage of the DG revealed the corresponding alcohol as a single diastereomer.

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