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# Cyclic Ether Synthesis via Palladium-Catalyzed Directed Dehydrogenative Annulation at Unactivated Terminal Positions

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Supporting Information

**ABSTRACT:** Here, a palladium-catalyzed functionalization of unactivated $sp^3$ C−H bonds with internal alcohol nucleophiles is described. Directed by an oxime-masked alcohol, annulation chemoselectively occurs at the $\beta$ position, leading to a range of aliphatic cyclic ethers with four- to seven-membered rings. Tethered primary, secondary, and tertiary free hydroxyl groups can all react to give the corresponding cyclized products. In addition, benzyl and silyl protected alcohols can also be directly coupled. An $sp^3$ C−H activation/intramolecular $S_N2$ pathway was proposed.

Cyclic ethers are commonly found in a variety of biologically important molecules (Figure 1).[1] While numerous efficient

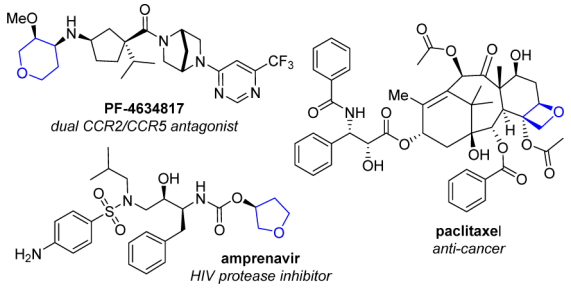
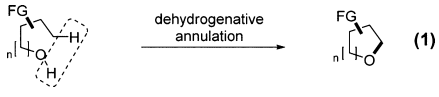



**Figure 1.** Examples of Bioactive Compounds Containing Cyclic Ether Moieties.

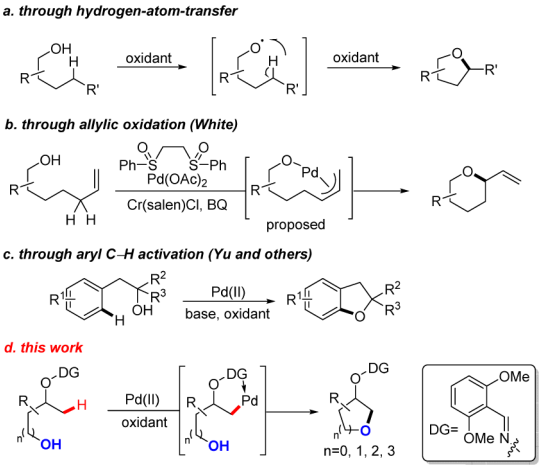
methods (e.g., various $S_N2$ reactions) have been introduced to synthesize this moiety from an alcohol nucleophile with a tethered electrophile,[2] the dehydrogenative coupling between an O−H bond and an unactivated $sp^3$ C−H bond arguably represents the most attractive approach since preactivation can be avoided at the position to be cyclized eq 1.




(1)

Preparation of aliphatic cyclic ethers via dehydrogenative annulation can first be traced back to a hydrogen-atom-transfer strategy mediated by a highly reactive oxygen-centered radical (Scheme 1a);[3] however, chemo- and site-selective breaking of stronger terminal (unactivated) C−H bonds is generally nontrivial. Recently, White et al. reported an elegant method for the efficient preparation of six-membered cyclic ethers

**Scheme 1. Dehydrogenative Annulation for Cyclic Ether Synthesis**




through allylic C−H oxidation (Scheme 1b).[4] During the past decade, C−O bond formation via activation of inert $sp^3$ C−H bonds has been greatly advanced by palladium catalysis.[5] While ether synthesis through directed activation of aromatic C−H bonds has been extensively studied by Sanford,[5a,6] Yu,[7] Liu,[8] Yoshikai,[9] Wang,[10] and others,[11] $sp^3$ C−H alkoxylation with alcohols remains a significant challenge.[12,13] The Chen group reported the first intermolecular alkoxylation of unactivated $sp^3$ C−H bonds using a picolinamide directing group (DG).[14] Later, Shi and Rao independently reported amide-directed linear ether syntheses through activation of methyl and methylene groups.[15] To the best of our knowledge, intramolecular $sp^3$ C−H alkoxylation at unactivated terminal positions has yet been developed. Herein, we describe a Pd-catalyzed masked-alcohol-directed method for preparing various sized cyclic ethers through activation of a methyl group.

Our laboratory has been interested in masked alcohol-directed C−H functionalization due to the prevalence of hydroxyl groups in organic molecules.[16] Oximes, first demonstrated by Sanford et al. in directed catalytic C−H activation,[17] are employed here as alcohol surrogates and DGs for $\beta$ $sp^3$-C−H functionalization involving an *exo*-metallocycle. Instead of relying on attacks by external reagents, a strategy of using a pendant alcohol as an internal nucleophile was conceived for cyclic ether formation via $sp^3$ C−H alkoxylation. This approach would allow for a new

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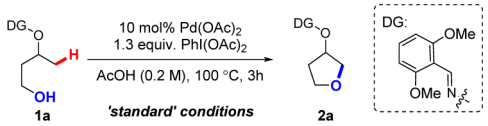
disconnection strategy to construct cyclic ethers. While the proximity effect in an intramolecular setting should accelerate the reaction rate, three challenges can nevertheless exist: (1) Pd-mediated alcohol dehydrogenation to aldehydes/ketones is well-known,[18] thus substrate stability represents a major concern; (2) intermolecular reactions, such as $\beta$-acetoxylation[16] and esterification with the free −OH ( *vide infra*), can compete; (3) compared to the intermolecular reaction[14,15] that can possibly use excess alcohols, only a stoichiometric quantity of alcohol is available in an intramolecular setting, thus any side reactions aforementioned with the free −OH would lead to a lower yield.

Stimulated by these challenges, we started with monoprotected diol (2,6-dimethoxybenzaldoxime) **1a** as the initial substrate. After optimizing the reaction conditions, to our delight, the tetrahydrofuran product (**2a**) was formed in 64% yield simply with 10 mol % $Pd(OAc)_2$ and 1.3 equiv $PhI(OAc)_2$ in HOAc at 100 °C for 3h (Table 1, entry 1). Interestingly,

**Table 1. Optimization with Substrate 1a**[a]



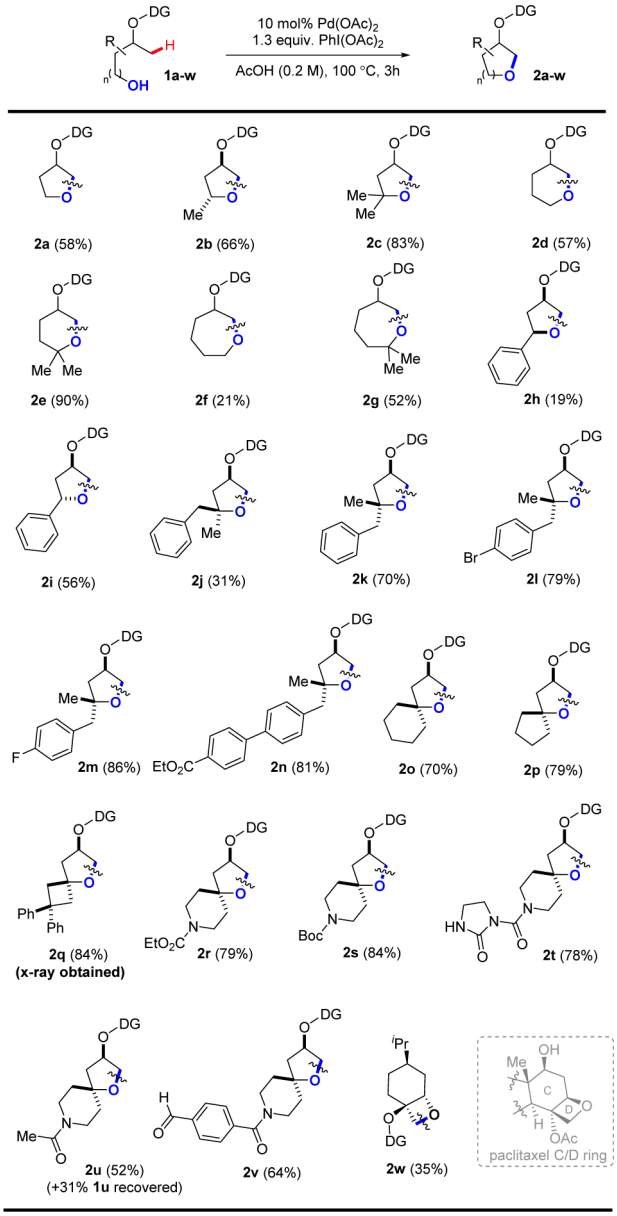

| entry | deviation from standard conditions | yield (%) |
|---|---|---|
| 1 | none | 64(58)[b] |
| 2 | no $Pd(OAc)_2$ | 0 |
| 3 | no $PhI(OAc)_2$ | 0 |
| 4 | $AcOH/Ac_2O$ (50:1 v/v) | 27 |
| 5 | add 4 Å M.S. | 39 |
| 6 | add 5 $\mu$L $H_2O$ | 54 |
| 7 | TFA instead of AcOH | 28 |
| 8 | DCE/AcOH (20:1 v/v) instead of AcOH | <1 |
| 9 | PhCl/AcOH (20:1 v/v) instead of AcOH | 0 |
| 10 | DCE/AcOH (1:1 v/v) instead of AcOH | 23 |
| 11 | oxone instead of $PhI(OAc)_2$ | 52 |
| 12 | 80 °C instead of 100 °C | 49 |

[a]All the reactions were run on a 0.1 mmol scale. The yield was determined by $^1$H NMR using 1,1,2,2-tetrachloroethane as the internal standard. [b]Isolated yield.

oxidation of the alcohol to the corresponding aldehyde was not observed.[19] Control experiments showed that in the absence of either the palladium catalyst or oxidant, no cyclized product was observed (entries 2 and 3). Use of acetic anhydride led to more acylation of the free alcohol (entry 4). Addition of molecular sieves or water reduced the yield to 39% and 54%, respectively (entries 5 and 6). The reaction also proceeded in TFA albeit in a lower yield (entry 7). Attempts to use less acetic acid with other organic cosolvents were unfruitful, causing sluggish reactions (entries 8−10). Replacing $PhI(OAc)_2$ with oxone was also effective; however, a significant amount of 2,6-dimethoxylbenzaldehyde was formed as the byproduct, indicating more decomposition of the oxime substrate (entry 11). Finally, lowering the reaction temperature to 80 °C gave a lower conversion but still provided the desired product (entry 12).

The substrate scope was then explored (Scheme 2, for details of substrate preparation, see Supporting Information). Gratifyingly, substrates possessing a primary, secondary, or tertiary hydroxyl group all cyclized to give the corresponding cyclic ethers under the standard conditions in moderate to high yields. It is interesting to note that the yield increased significantly in the order of primary < secondary < tertiary alcohol nucleophiles

**Scheme 2. Substrate Scope**[a]




[a]Isolated yields. Product consists of a mixture of oxime *E*/*Z* stereoisomers (for details, see Supporting Information).

(e.g., **2a**−**c**), despite increasing steric congestion. It is likely that tertiary alcohols are less prone to undergo esterification with HOAc, and the Thorpe−Ingold effect[20] should also help the annulation. Besides five-membered rings, a number of six- and seven-membered cyclic ethers were also formed in moderate to high yields.[21]

It is not surprising to note that the efficiency of the dehydrogenative annulation reaction is closely related to the relative stereochemistry of the substrates. For example, the *anti* diol derivative (**2i**) resulted in 56% yield, while its *syn* diastereomer (**2h**) only gave 19% yield. This trend was further confirmed in a pair of tertiary hydroxyl substrates (**2j** vs **2k**). While the reaction mechanism remains to be better understood, these observations are consistent with the proposed C−H activation/intramolecular $S_N2$ pathway[22] (for a mechanistic discussion, *vide infra*). In addition, similar substrates with



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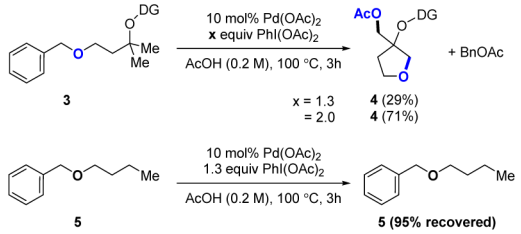
bromide and fluoride substitution on the arene gave satisfactory yields (**2l** and **2m**).

With the success of tertiary alcohols participating in the cyclization, forming spirocyclic ethers was next investigated. Indeed, 6,5-, 5,5- and 4,5-spiroethers can be efficiently accessed (**2o**–**v**). Moreover, protected piperidine (**2r**–**v**) was also found compatible under the reaction conditions. Besides aryl bromides and fluorides, a number of functional groups were found compatible under the reaction conditions, such as ester (**2n**), carbamates (**2r** and **2s**), urea (**2t**), amide (**2u**), and aryl aldehyde (**2v**). Furthermore, this dehydrogenative annulation approach can also be applied to synthesize oxetane rings. Oxetanes, four-membered cyclic ethers, are widely found in pharmaceutically interesting compounds, e.g., paclitaxel (Taxol).[23,24] Using this approach, a 6/4-fused oxetane product (**2w**), exhibiting a structural motif mimicking the Taxol D-ring, can be successfully afforded in a moderate yield.[25]

For the substrate containing a tertiary DG and a benzyl-protected alcohol (**3**), an unexpected transformation was observed (Scheme 3). Under the standard reaction conditions,

**Scheme 3. Cyclization with a Benzyl-Protected Alcohol**




a highly functionalized tetrahydrofuran compound (**4**) was isolated, and the yield can be improved to 71% simply by employing 2 equiv of $PhI(OAc)_2$. Two interesting aspects can be noted: (1) the *gem*-dimethyl groups can both be functionalized and differentiated via double C–H activation; (2) benzyl-protected alcohols can be directly used as the annulation precursor. To gain insight into this transformation, a control experiment showed that a regular benzyl ether (e.g., **5**) was not deprotected under these reaction conditions. In addition, a significant amount of benzyl acetate was isolated during the C–H activation/cyclization reaction (see Supporting Information). These observations indicated that the ether oxygen may have acted as a nucleophile for the annulation reaction, instead of a free hydroxyl group.

While the exact mechanism remains to be defined, a plausible reaction pathway is proposed (Figure 2). After a directed C–H palladation followed by oxidation of the palladium to a high oxidation state (e.g., $Pd^{IV}$), an intramolecular $S_N2$ reaction[26] can

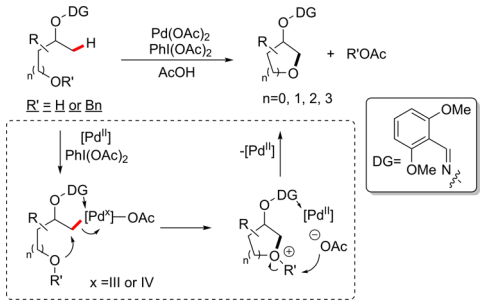
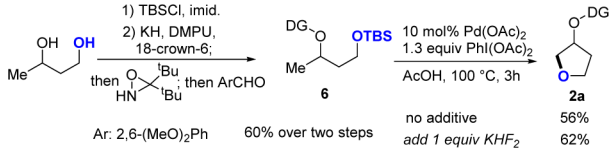



**Figure 2.** Plausible reaction pathway.

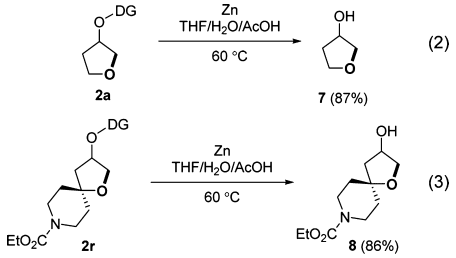
occur to give an oxonium intermediate and meanwhile reduce the palladium to $Pd^{II}$. Subsequently, an acetate ion would undergo a net deprotonation or debenzylation to afford the cyclic ether product.

Besides benzyl-protected alcohols, silyl-protected alcohol substrate **6**, available in two steps from commercially available 1,3-buta-diol,[27] also successfully cyclized to tetrahydrofuran **2a** albeit through a different mechanism (Scheme 4). Control

**Scheme 4. Cyclization of Silyl Protected Alcohols**




experiments have shown that the TBS group was deprotected *in situ* under the reaction conditions. Hence, the yield was comparable to the reaction of unprotected alcohol **1a** (*vide supra*, Scheme 2). Addition of a fluoride source slightly improved the yield to 62%. Given the ready availability of 1,3-diols, this approach is expected to be useful for streamlining synthesis of functionalized tetrahydrofurans.[28] Finally, the DG in the products can be easily removed through zinc-mediated N–O bond cleavage eqs 2 and 3.[16]




In summary, we developed a Pd-catalyzed masked alcohol-directed site-selective C–H annulation approach, which provides rapid access to a variety of cyclic ethers of different ring sizes. The oxidative cyclization chemoselectively occurs at an inert terminal position, thus complementary to other existing ether-synthesis methods. The reaction can tolerate air and moisture and is operationally simple. Free primary, secondary, tertiary alcohols, and even protected alcohols can be employed as the internal nucleophile, suggesting a promising substrate scope. In particular, the feasibility of directly using benzyl ethers as the coupling partner should have a broad implication (e.g., use of masked nucleophiles) beyond this work. Detailed mechanistic study and expansion of the reaction scope to methylene C–H bonds and other internal nucleophiles are under investigation in our laboratory.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b07384.

Experimental procedures; spectral data (PDF)
Crystallization data (CIF)
Crystallization data (CIF)
Crystallization data (CIF)



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### Notes

The authors declare no competing financial interest.

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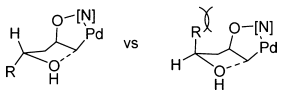
(22) The *syn* diol substrate is expected to have a lower activation energy than the *anti* one. For a proposed model, see:

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