Organic LETTERS

Letter

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Access to Diverse Oxygen Heterocycles via Oxidative Rearrangement of Benzylic Tertiary Alcohols

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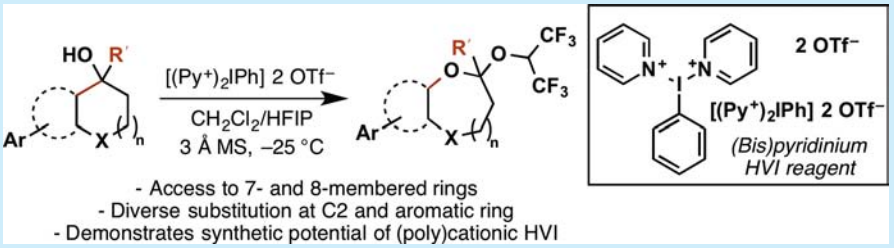
Supporting Information



ABSTRACT: A facile method for the synthesis of challenging medium-sized cyclic ethers has been developed via a novel oxidative rearrangement of benzylic tertiary alcohols. The reaction provides access to cyclic acetals with diverse substitution at both C2 and the aromatic ring. The unique reactivity is enabled by poly(cationic) hypervalent iodine reagents and represents the first synthetic application of this underexplored class of compounds.

Medium-sized cyclic ethers, such as oxepines and oxecanes, are commonly encountered structural motifs in natural products (**1**−**3**) (Figure 1). As such, methods for the synthesis of these diverse scaffolds have prompted a long-standing pursuit.[1−3]

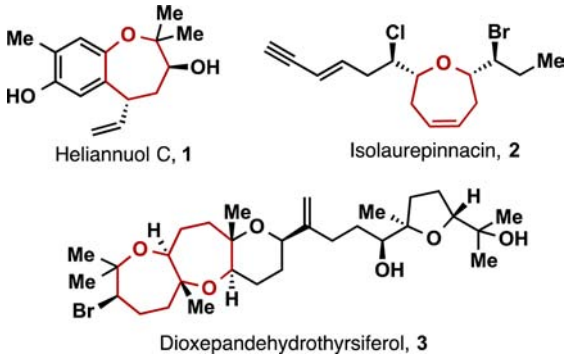


Figure 1. Diverse medium-sized oxacyclic natural products.

Unlike the corresponding furan and pyran derivatives, the synthesis of medium-sized ethers is problematic due to unfavorable entropic penalties and transannular interactions associated with their formation.[4,5] Common methods include ring closing metathesis,[6] lactone formation with subsequent reduction,[7] Prins-type cyclizations,[8,9] regioselective epoxide opening,[10] and cyclopropane fragmentation.[11] While these approaches have been widely utilized, the discovery of new, readily available precursors and novel disconnections to access such valuable ring systems is of continued interest.[3] We approached this problem with the realization that there are currently no methods to directly transform commonly encountered alcohol substrates into cyclic ethers (Figure 2).

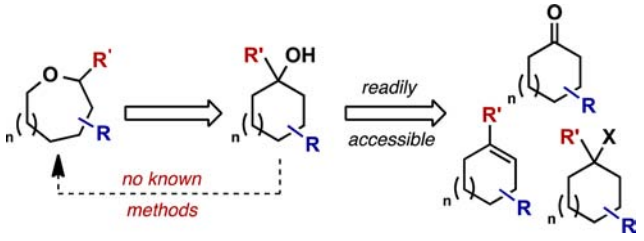


Figure 2. Readily available tertiary alcohols would serve as useful precursors to medium-size oxacycles.

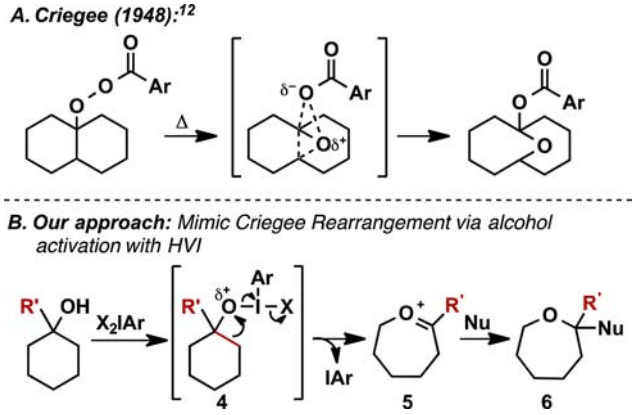
In principle, the ubiquity and relative ease of synthesis make tertiary alcohols very attractive precursors to much more challenging medium-sized heterocycles. Such a method could provide access to an array of structural diversity, including different ring sizes (by varying *n*), substitution at C2 (by varying R′), and remote ring functionality (by varying R).

In developing such a method, we took inspiration from the Criegee rearrangement of activated alkyl peroxides, wherein the O−O bond is labilized via reaction with an anhydride, promoting C-to-O migration (Scheme 1A).[12,13] We envisioned an analogous transformation in the context of simple alcohols via electrophilic activation with a hypervalent iodine reagent (Scheme 1B).[14−17] Attack of the alcohol on the iodine center would generate an activated intermediate (**4**) wherein the oxygen is now electrophilic. This sets the stage for a carbon-to-

Received: March 8, 2016
Published: March 29, 2016

DOI: 10.1021/acs.orglett.6b00672
Org. Lett. 2016, 18, 1896−1899

Scheme 1. (A) Criegee Rearrangement of Tertiary Peroxides; (B) Proposed Rearrangement of Tertiary Alcohols via Activation with Hypervalent Iodine

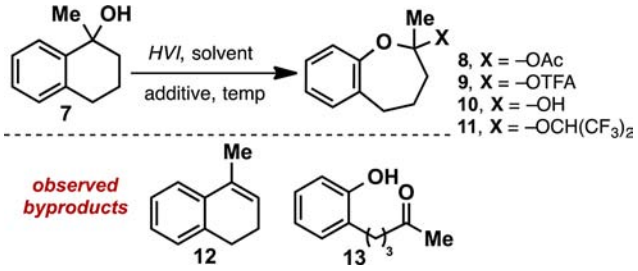


oxygen alkyl migration, driven by the loss of iodine in its normal valency (IAr), and the resultant oxonium ion (**5**) could be trapped by a nucleophile to give the functionalized ether scaffold (**6**). Hypervalent iodine (HVI) reagents are ideal for this transformation due to their low cost, low toxicity, ease of handling, and excellent leaving group ability.[18] HVI reagents have been utilized in numerous electrophilic rearrangements, including Hoffman rearrangements[19,20] and carbocyclic ring expansions;[21] however, there are no reports employing an alcohol functionality. Their application in the context of alcohols has primarily been limited to simple oxidations, either via two- or one-electron processes, to generate the carbonyl or oxygen-centered radicals, respectively.[22,23]

Herein, we report the oxidative rearrangement of benzylic tertiary alcohols, which provides access to a variety of aromatic fused oxepane and oxecane derivatives, with diverse substituents at C2 as well as the aromatic ring. The obtained acetals are readily functionalized using known methods, giving rise to an array of structural diversity. This unique reactivity is enabled by (poly)cationic hypervalent iodine reagents and represents the first systematic report on a synthetic application of this class of reagents.

We began our studies with alcohol **7** and screened HVI reagents with varied electronics about both the aryl iodide and the ligands (Table 1) (for a full list of reagents screened, see Supporting Information). We anticipated the formation of the rearranged acetal wherein the terminal nucleophile (**X**) would be derived from the respective iodine ligands or nucleophilic solvent (**8**–**11**) (Table 1). Traditional reagents including phenyliodine diacetate (PIDA), phenyliodine bis(trifluoroacetate) (PIFA), Koser's reagent, and derivatives thereof failed to give any of the desired rearranged acetals, leading instead to elimination (**12**) or recovered starting material (Table 1, entires 1–3). In an attempt to suppress elimination, we then buffered the reaction (Table 1, entries 4–5); however, this led to only elimination or recovered starting material.[22] Switching from oxygen to chloride ligands with the use of iodobenzene dichloride (Table 1, entry 6) also failed to give any desired product, giving only dehydration (**12**). At this stage we hypothesized that the alcohol oxygen was not developing sufficient partial positive charge to promote the desired alkyl migration. As such we needed to identify HVI reagents with significantly more electron-deficient iodine centers, in an effort to more closely mimic the O–O bond of

Table 1. Optimization of Oxidative Rearrangement[a]

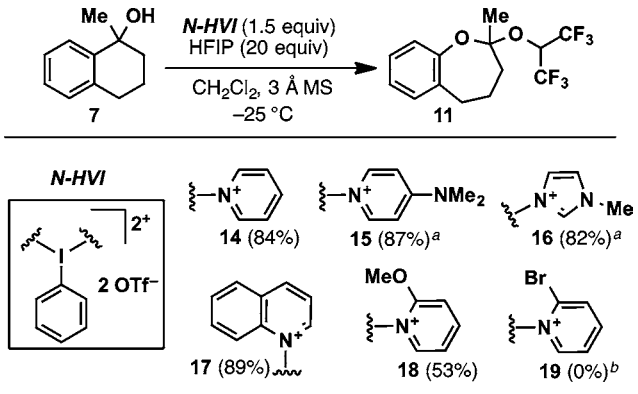


entry	conditions	product (yield)
1	PIDA, CH_2Cl_2, rt	**7**
2	PIFA, CH_2Cl_2, rt	**12**
3	PhI(OH)OTs, CH_2Cl_2, rt	**12**
4	PIFA, K_2CO_3, EtOAc, rt	**12**
5	PIFA, base,[b] CH_2Cl_2, rt	**12**
6	$PhICl_2$, CH_2Cl_2, rt	**12**
7	**14**, CH_2Cl_2, rt	**13** (33%)[c]
8	**14**, HFIP, 0 °C	**11** (55%)[c,d]
9	**14**, HFIP,[e] CH_2Cl_2, −25 °C	**11** (68%)[c,d]
10	**14**, HFIP,[e] 3 Å MS, CH_2Cl_2, −25 °C	**11** (84%)[c]

[a]Reaction conditions: HVI (1.5 equiv), solvent (0.2 M). [b]Base: pyridine, triethylamine, dimethylaminopyridine. [c]Isolated yield. [d]5–10% ketone **13** observed over several trials. [e]20 equiv.

an activated peroxide. With this in mind, it was then that we discovered a report by Weiss from 1994, describing the electrostatic activation of HVI compounds via the use of positively charged nitrogen ligands.[24] Since this initial report, these reagents have received very little attention from the synthetic community.[25−27] Recent reports have shown them to be effective oxidants to access high-valent transition metals,[28−31] but no attention has been paid to their synthetic utility.

Scheme 2. Screening of Cationic HVI Reagents with Varied Heterocyclic Nitrogen Ligands



[a]Reactions required warming to rt and 18 h to reach completion. [b]Starting material decomposition.

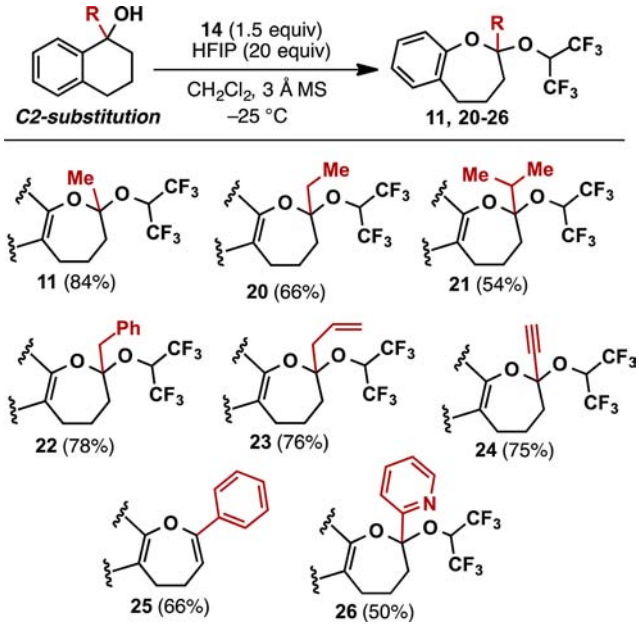
We began our exploration into these cationic reagents with a known pyridine derivative[24] (**14**) (Scheme 2), and to our delight, the desired rearrangement was observed for the first time, albeit giving the product as open chain ketone **13**, resulting from rearrangement with adventitious water as a terminal nucleophile and subsequent ring opening (Table 1, entry 7). It is worth noting that, while formation of **13** is a result of the desired rearrangement, its formation should be avoided as the resulting phenol can also undergo competitive

DOI: 10.1021/acs.orglett.6b00672
Org. Lett. 2016, 18, 1896–1899

subsequent oxidation, leading to decreased yields. With this promising result in hand, a solvent screen revealed that the use of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) at 0 °C gave rise to the desired cyclic acetal as the HFIP adduct (**11**) in 55% yield, through addition of HFIP to the intermediate oxonium (Table 1, entry 8). The yield of **11** could be improved to 68% by using 20 equiv of HFIP in CH_2Cl_2 and lowering the reaction temperature to −25 °C; however, variable amounts of ketone were still observed over multiple trials (Table 1, entry 9). The inclusion of 3 Å MS eliminated any ketone formation, and finally the addition of **14** in HFIP to a precooled (−25 °C) solution of substrate in CH_2Cl_2 gave **11** as the exclusive product in 84% yield (Table 1, entry 10).

Having established effective conditions for the rearrangement using pyridine-reagent **14**, we wanted to investigate the effect of altering the nitrogen ligands on the hypervalent iodine (**15**−**19**) (Scheme 2). It was found that tuning of either the electronic or steric parameters had an effect on the reaction efficiency; more electron-rich DMAP and *N*-Me imidazole reagents **15** and **16** gave comparable yields to **14**, but required prolonged reaction times, whereas *o*-substituted reagents **18** and **19** led to decreased yields or complete decomposition. Given these results, we continued with reagent **14** for further study in this report; however, the ability to modulate the reactivity of these unique reagents is a key feature that will likely prove vital to the further development of synthetic applications.

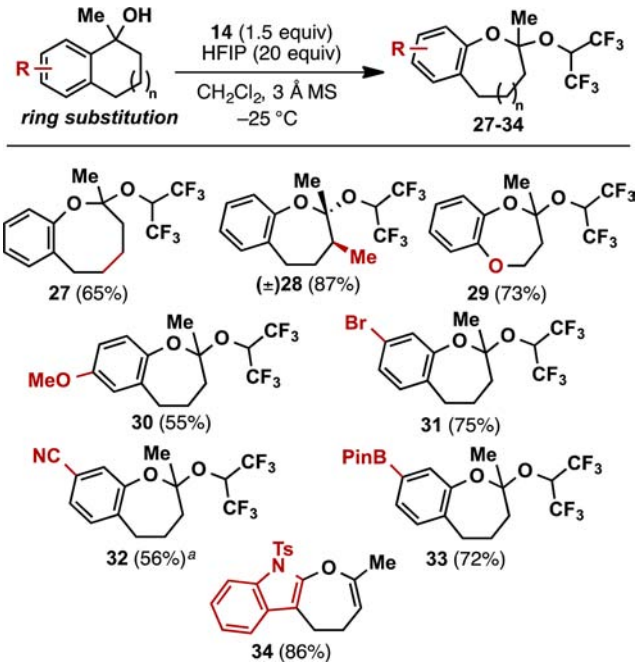
Scheme 3. Substrate Scope with Varied Substitution at Tertiary Alcohol



With the optimized conditions in hand, we examined the scope of the reaction. A variety of substitutions at the tertiary alcohol were well tolerated, including alkyl (**11**, **20**−**22**), unsaturated (**23** and **24**), and both electron-neutral and -deficient aryl groups (**25** and **26**) (Scheme 3). All products were isolated as their HFIP-acetals, with the exception of **25**, wherein elimination gave the corresponding dihydrooxepin.[32] Gratifyingly, benzyl acetal **22** was highly crystalline, allowing us to confirm the structure of the HFIP-acetal products via X-ray crystallography (see Supporting Information). The reactions to give unsaturated products **23** and **24** are noteworthy as traditional HVI reagents are known to activate π-bonds via formation of iodonium intermediates, and in the presence of tertiary alcohols, electrophilic cyclizations have been reported.[33,34] This further highlights the unique reactivity and chemoselectivity of the (poly)cationic HVI reagents.

We then examined substitution at both the aromatic and alkyl ring (Scheme 4). In addition to oxepines, the rearrangement was found to be effective for accessing 8-membered oxecanes, with a benzosuberone-derived substrate reacting smoothly to give **27**. Substitution adjacent to the tertiary alcohol was well tolerated, giving **28** as exclusively the *cis*-diastereomer. Both electron-donating (**29** and **30**) and electron-withdrawing (**32**) aromatic substituents performed well, although **32** required prolonged heating. Halogens as well as boronic esters were also compatible (**31**, **33**), providing valuable functional handles for subsequent derivatization. Somewhat surprisingly, even an oxidatively labile indole performed well, giving enol ether **34** in high yield.[32]

Scheme 4. Substrate Scope with Respect to Substitution at Both the Alkyl and Aryl Ring



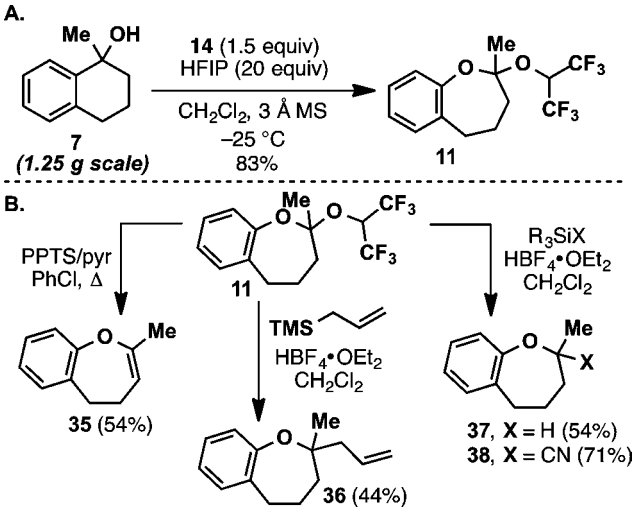
[a]Reaction ran at 35 °C for 48 h.

The rearrangement was found to be highly scalable, with a gram scale reaction producing **11** in 83% yield (Scheme 5A). Conveniently, the obtained HFIP-derived acetals are amenable to a variety of subsequent derivatizations (Scheme 5B). Acetal **11** was readily eliminated to give enol ether **35** with exposure to mild acid and heat, allylated to give **36** with TMS allyl silane under Bronsted acid catalysis, or substituted upon exposure to Bronsted acid and various silylated nucleophiles, including Et_3SiH and TMSCN to give **37** and **38**, respectively. Notably, traditional Lewis acid catalysis was not effective for these transformations, consistently giving selective cleavage of the endocyclic C−O bond resulting in formation of undesired ketone **13** with a range of catalysts.

In conclusion, we have developed a novel method for the synthesis of 7- and 8-membered oxygen heterocycles via the

DOI: 10.1021/acs.orglett.6b00672
Org. Lett. 2016, 18, 1896−1899

Scheme 5. (A) Gram-Scale Reaction; (B) Derivatization of HFIP-Acetals



rearrangement of tertiary alcohols. The reaction is tolerant of a range of substitutions at both the tertiary alcohol and the aromatic ring, allowing access to products with diverse scaffolds and functional handles. The resulting acetals are readily derivatized allowing for further functionalization of the ether moiety. The reaction is enabled by the unique reactivity of (poly)cationic hypervalent iodine reagents, and this represents the first synthetic application of this underexplored class of reagents. Studies to extend this reaction to other heteroatoms as well as secondary alcohols are ongoing in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00672.

Experimental procedures; characterization for all new compounds (PDF)
Crystallographic data for **18** (CIF)
Crystallographic data for **22** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was conducted with the generous financial support of Temple University. J.C.W. was supported by a Temple University Future Faculty Fellowship. We would like to thank Prof. Michael Zdilla and Michael Gau (Temple University) for their assistance in acquiring X-ray structures. We would also like to thank Susan Gramlich (Temple University) for her work on the synthesis of various hypervalent iodine reagents.

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DOI: 10.1021/acs.orglett.6b00672
Org. Lett. 2016, 18, 1896–1899