EurJOC
European Journal of Organic Chemistry

A Journal of
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Accepted Article

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Authors: Jennifer C. Walters, Anthony F. Tierno, Aimee H. Dubin, and Sarah E. Wengryniuk

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201800118

Link to VoR: http://dx.doi.org/10.1002/ejoc.201800118

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10.1002/ejoc.201800118

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(Poly)cationic λ³–Iodane Mediated Oxidative Ring Expansion of Secondary Alcohols

Jennifer C. Walters,‡ Dr. Anthony F. Tierno,‡ Aimee H. Dubin, and Prof. Dr. Sarah E. Wengryniuk*[a]

Abstract: Herein, we report a simplified approach to the synthesis of medium-ring ethers through the electrophilic activation of secondary alcohols with (poly)cationic λ³-iodanes (*N*-HVI). Excellent levels of selectivity are achieved for C–O bond migration over established α-elimination pathways, enabled by the unique reactivity of a novel 2-OMe-pyridine-ligated *N*-HVI. The resulting HFIP-acetals are readily derivatized with a range of nucleophiles, providing a versatile functional handle for subsequent manipulations. The utility of this methodology for late-stage natural product derivatization was also demonstrated, providing a new tool for diversity-oriented synthesis and complexity-to-diversity (CTD) efforts. Preliminary mechanistic investigations reveal a strong effect of alcohol conformation on reactive pathway, thus providing a predictive power in the application of this approach to complex molecule synthesis.

Medium-ring cyclic ethers (7-11 atoms) are commonly encountered structural motifs in bioactive natural products (**1**-**3**, Figure 1); however, their synthesis remains a preeminent challenge in organic chemistry due to the high strain energy associated with these systems (i.e. entropic penalties, transannular and angle strain).[1] Current approaches include ring-closing metathesis, cycloadditions, pericyclic reactions, epoxide openings, cross-couplings, and ring fragmentations,[2] however, these methods are not general and often require multi-step sequences and highly engineered starting materials, decreasing the efficiency and practicality of total syntheses. Additionally, while medium-ring ethers are commonly encountered in Nature, they are relatively scarce in *de novo* medicinal chemistry libraries, where synthetic design is reliant on robust methods that allow for rapid structural diversification.[3] Recent reports highlighting the lack of structural diversity in pharmaceutical screening platforms emphasize the importance of accessing complex architectures which possess drastically altered three-dimensional topography and increased structural flexibility.[4] The development of new methodologies to directly access medium-ring ethers from simple, readily-accessible precursors would enable more efficient total syntheses of complex molecules as well as enable these scaffolds to be viewed as viable platforms for small molecule library synthesis.

[a] J. C. Walters, Dr. A. F. Tierno, A. H. Dubin, Prof. Dr. S. E. Wengryniuk
Department of Chemistry
Temple University
1901 N. 13th St. Philadelphia, PA 19122
E-mail: sarahw@temple.edu; wengryniuklab.weebly.com
‡ These authors contributed equally to the results disclosed in this manuscript.

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To address these challenges, we recognized that the ability to leverage the venerable hydroxyl group as a handle to directly access medium-ring ethers would be highly enabling (Figure 1). Alcohols are among the most readily synthesized and commonly encountered intermediates in synthetic sequences. Additionally, they are ubiquitous in bioactive natural product scaffolds (**4**-**5**, Figure 1) and, thus, would provide a novel approach for accessing medium-ring analogues in "complexity-to-diversity" (CTD) type derivatizations.[5] In devising such a method, we drew inspiration from the Criegee rearrangement of alkyl peroxides[6] and hypothesized that treatment of an alcohol with a λ³-hypervalent iodine reagent (HVI)[7] would provide a similar electrophilic oxygen intermediate (**7**), enabling a carbon-to-oxygen ring expansion (driven by loss of aryl iodide) to give functionalized medium-ring ethers (**8**) in a single step (Scheme 1).

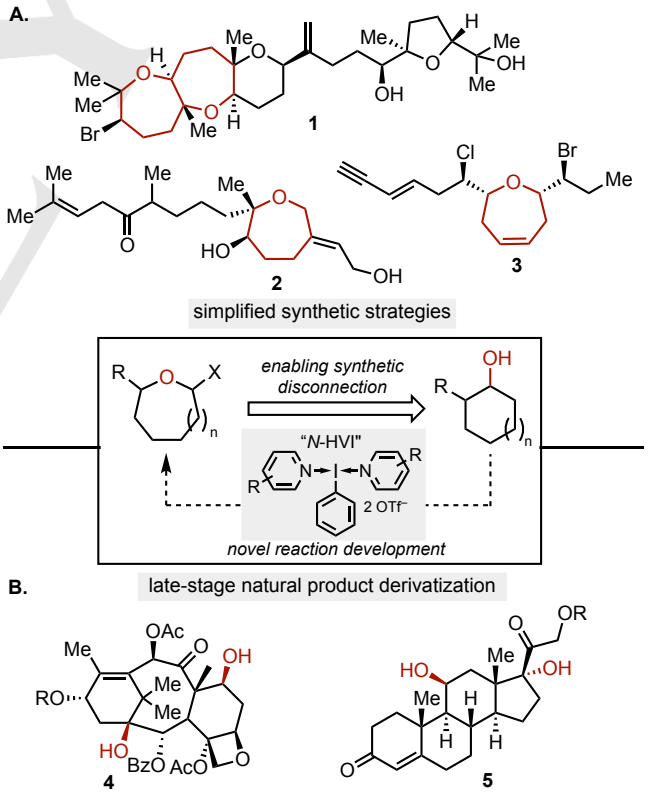
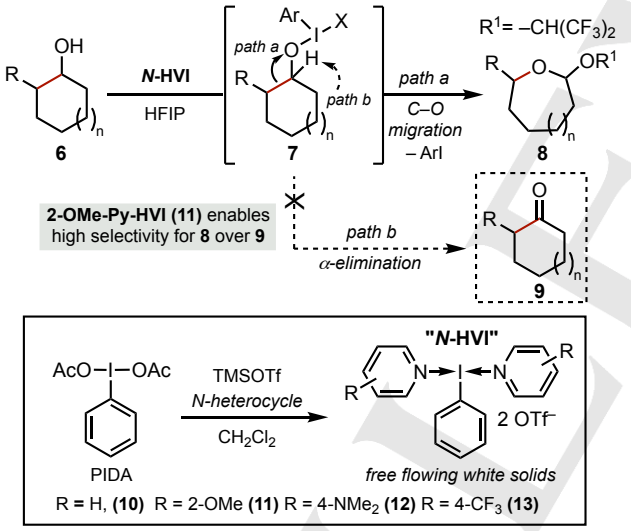


Figure 1. A. Medium ring ether scaffolds in bioactive natural products. **B.** Hydroxyl groups provide a ubiquitous functional handle in bioactive natural products.

A preliminary report from our laboratory[8] described the application of this electrophilic alcohol ring expansion approach

to tertiary, benzylic alcohols to give diverse benzofused ether scaffolds. These efforts revealed that (poly)cationic λ^3-iodanes (*N*-HVIs), possessing two heterocyclic nitrogen ligands datively bonded to the central iodine, were uniquely effective as electrophilic activators in this transformation (Scheme 1, inset). Readily synthesized from commercially available phenyliodine diacetate (PIDA), *N*-HVIs are a potentially powerful class of λ^3-iodanes whose utility as synthetic reagents has gone relatively unexplored since their discovery over 20 years ago.[9]

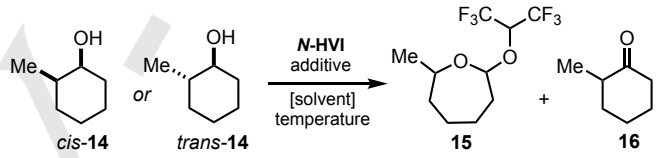
Herein, we describe the application of *N*-HVIs to the electrophilic ring expansion of secondary, aliphatic alcohols (**6**) to give diverse cyclic ether scaffolds (Scheme 1). The inherent challenge to utilizing secondary alcohols is achieving selective rearrangement (path a) over direct oxidation via α-elimination (path b), reactivity well-established with traditional hypervalent iodine reagents.[7,10] In this regard, it was found that both the electronics of the *N*-HVI as well as the use of hexafluoroisopropanol (HFIP) as a hydrogen-bonding solvent were critical to achieving high levels of selectivity. The secondary alcohol ring expansion was also explored in CTD applications, producing several complex, medium-ring scaffolds via late-stage natural product derivatization. The resulting HFIP-acetals are readily functionalized with a range of nucleophiles, providing a highly general approach to diverse medium-ring ether scaffolds from simple starting materials.



Scheme 1. Synthesis of medium-ring ethers from secondary alcohols via electrophilic activation with (poly)cationic λ^3-iodanes (*N*-HVIs).

We began our studies with both *cis*- and *trans*-2-Me-cyclohexanol (**14**) as model substrates in order to probe any potential effects of ring stereochemistry on selectivity for rearrangement over oxidation (Table 1). Subjecting both *cis*-**14** and *trans*-**14** to our previously optimized conditions[8] gave exclusively oxidation after prolonged reaction times (entry 1); however, increasing the temperature to 40 °C gave full conversion after ~2 days, with *cis*-**14** giving an encouraging 20:80 ratio of desired HFIP-acetal (**15**) to ketone (**16**) (entry 2). In contrast, *trans*-**14** gave exclusively **16**, with none of acetal **15** (entry 3), showing a clear divergence between the two stereoisomers, and thus, *cis*-**14** was selected for continued optimization. We then examined the effect of the electronics of the *N*-heterocycle on the *N*-HVI and found that a more electron-rich heterocyclic ligand (**12**, entry 4) showed extremely low reactivity, whereas the electron-deficient **13** gave an improved ratio to 47:53 and significantly shortened reaction time (entry 5). Interestingly, the use of 2-OMe-Py-HVI **11** gave a ratio favoring acetal **15** for the first time (59:41) after prolonged reaction times (entry 6), and subsequently increasing the temperature to 60 °C led to increased reaction efficiency without affecting product ratios (entry 7). Increasing the concentration from to 0.3 M gave a slight improvement in ratio (entry 8); however, any further increases in either temperature or concentration led to significant amounts of byproduct formation and decomposition. After an extensive screening effort, it was found that pre-mixing the substrate with a 1:1 ratio of DCE:HFIP was crucial, followed by addition of **11** in a solution of HFIP, which gave a 91:9 ratio of **15**:**16** after just 1 h (entry 9).[11]

Table 1. Optimization of electrophilic ring expansion.

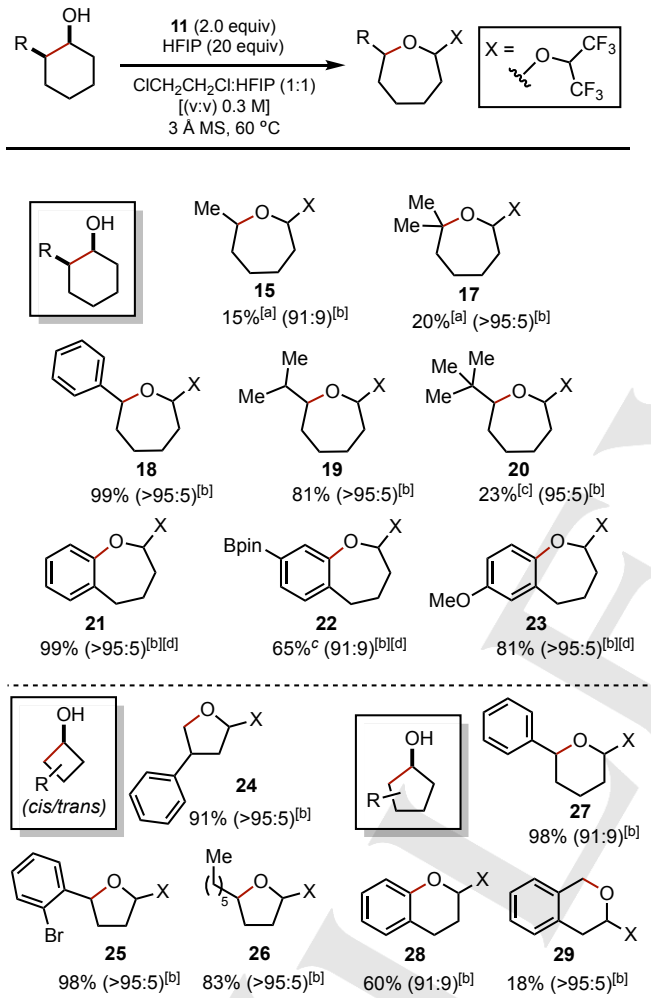


entry	conditions[a]	time (h)	product ratio (**15**:**16**)[b]
1	**10**, *cis*-**14** or *trans*-**14**, DCM (0.2 M), –25 °C to rt	>72	0:100
2	**10**, *cis*-**14**, DCE (0.2 M), 40 °C	58	20:80
3	**10**, *trans*-**14**, DCE (0.2 M), 40 °C	10	0:100
4	**12**, *cis*-**14**, DCE (0.2 M), 40 °C	>72	n.r.
5	**13**, *cis*-**14**, DCE (0.2 M), 40 °C	3	47:53
6	**11**, *cis*-**14**, DCE (0.2 M), 40 °C	54	59:41[c]
7	**11**, *cis*-**14**, DCE (0.2 M), 60 °C	4	59:41[c]
8	**11**, *cis*-**14**, DCE (0.3 M), 60 °C	3.5	67:37[c]
9	**11**, *cis*-**14**, DCE:HFIP (1:1)[d] (0.3 M), 60 °C	1	**91:9**[c]

[a] Reaction conditions: DCM = dichloromethane, DCE = 1,2-dichloroethane, *N*-HVI (2.0 equiv), HFIP (20.0 equiv), 3 Å MS. [b] Ratio based on integration of crude ^{1}H-NMR. [c] Combined mixture of diastereomers of HFIP-acetal. [d] (v:v).

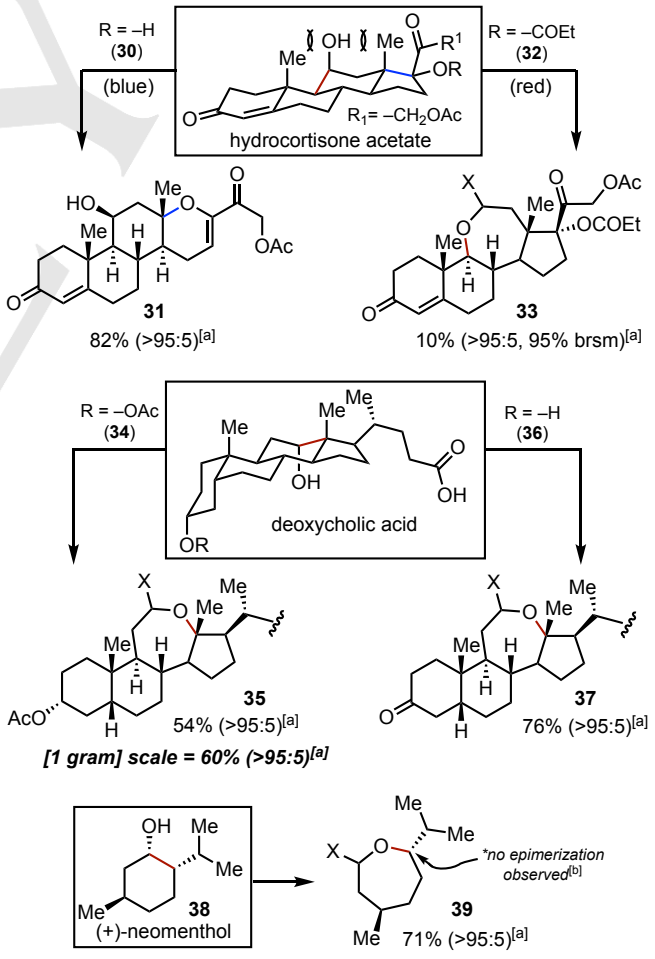
With selective conditions in hand, a range of C2–substituted *cis*-alcohols were examined, with R-groups selected to be representative of varied migratory aptitude and sterics (Scheme 2). Substrates possessing 2–Me, 2,2-dimethyl, 2–Ph, and 2–*i*Pr (**15**, **17**-**19**), all underwent rearrangement to the desired HFIP-acetals with excellent selectivity and yield. The low isolated yields of **15** and **17** are due to volatility of the acetal products with both TLC and crude ^{1}H-NMR showing clean conversion to desired products (see SI for details). *t*-Butyl derivative **20** proceeded with high selectivity for rearrangement but low

isolated yield, due to significant amounts of open chain aldehyde products. Benzylic alcohol derivatives with either electron neutral (**21, 22**) or electron-rich (**23**) aromatic rings also proceeded in good to excellent yield to the corresponding benzoxepanes, notably including an aryl boronic ester. The ring expansion was also applicable to the synthesis of substituted tetrahydrofurans from the corresponding *cis*- or *trans*-cyclobutanols, giving **24**-**26** in excellent yield. The rearrangement of cyclopentanols to the corresponding pyrans could also be achieved, however this was restricted to the use of aryl-substituted alcohols (**27**-**28**) and rearrangement of 2-indanol to give **29** proceeded in low yield along with significant formation of unidentified byproducts.



Scheme 2. Scope of electrophilic ring expansion of secondary alcohols. [a] Low yield due to volatility of acetal products. [b] Ratio of HFIP-acetal to ketone by ^{1}H-NMR. [c] Formation of open chain aldehyde products. [d] Reaction run using *N*-HVI **10** (1.5 equiv), DCM, –25 °C.

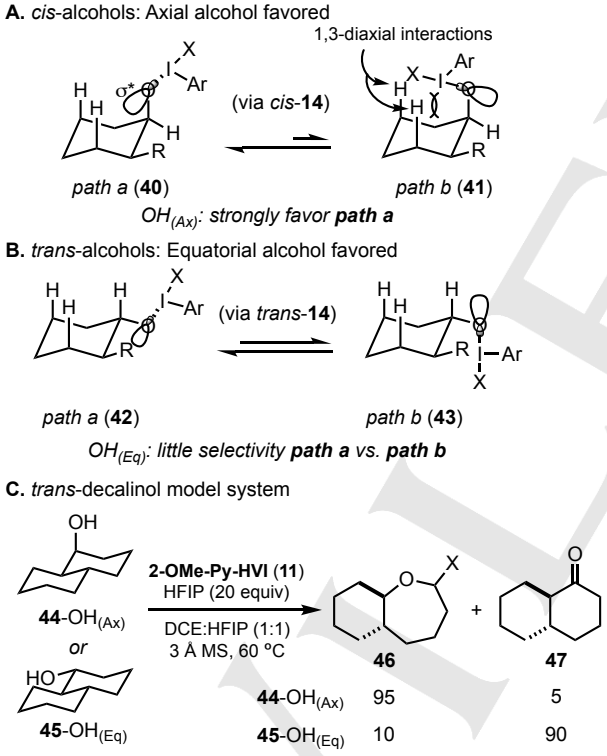
We then explored the ring expansion of several natural product scaffolds, to probe the utility of our approach as a tool for late-stage CTD manipulations (Scheme 3). Hydrocortisone acetate (**30**), which possesses both a C-ring and D-ring alcohol, underwent selective rearrangement of the D-ring to give dihydropyran **31**, without affecting the A-ring enone. We hypothesized the lack of reactivity of the C-ring alcohol was due to steric hinderance from two axial methyl groups. We therefore protected the D-ring alcohol as the carbonate (**32**) and this resulted in clean rearrangement of the C-ring to oxepane **33**, albeit in low yield, despite use of a more reactive *N*-HVI **13** and prolonged reaction times. In contrast, acetyl deoxycholic acid (**34**), with a sterically unencumbered α-OH on its C-ring, underwent clean rearrangement to give analogue **35** in 54%, with no loss of yield on 1-gram scale, even in the presence of a free carboxylic acid. Deoxycholic acid (**36**) with an unprotected A-ring alcohol gives a 76% yield of the double oxidation product (**37**) when 4 equiv. of **11** are used. Finally, the ring expansion of (+)-neomenthol (**38**) proceeded in excellent yield to give chiral oxepane **39** with no erosion of chirality on the migrating bond. In contrast, rearrangement of (+)-menthol, with a *trans*-alcohol, gave only a 31% yield, giving a 1:2 ratio of acetal to (+)-menthone (not shown); this result further supported our preliminary finding that the relative alcohol stereochemistry had a dramatic effect on selectivity (see Table 1). These examples show the promise of our alcohol ring expansion approach for producing medium-ring analogues of bioactive molecules that would be highly impractical to access via *de novo* synthetic strategies.



Scheme 3. Application to complex scaffold derivatization. X= HFIP [a] Ratio of HFIP-acetal to ketone by ^{1}H-NMR. [b] ^{1}H-NMR of **39** shows only two

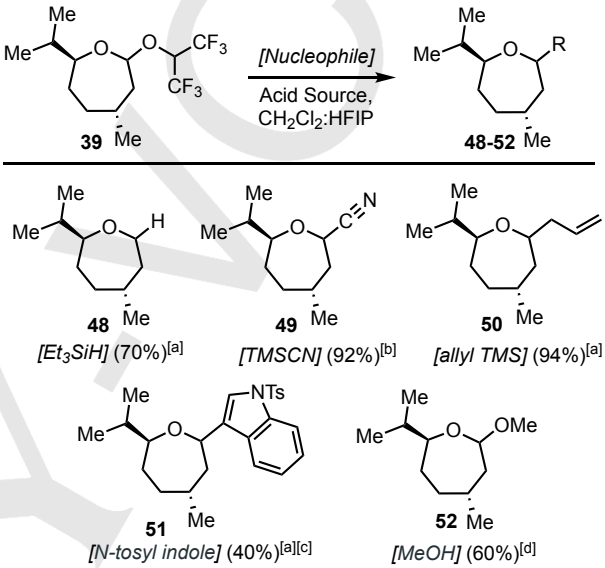
diastereomers, resulting from HFIP-acetal. Lack of epimerization further established after reduction of **39**. See SI for details.

At this stage, we wished to better understand the observation that *cis*-**14** displayed high selectivity for rearrangement whereas *trans*-**14** gave exclusively oxidation (see Table 1). We hypothesized that this could be a result of differences in the conformational equilibria of the cyclohexanols (Scheme 4). In the *cis*-alcohols, the alcohol would exist preferentially in the axial position, and FMO analysis reveals this would strongly favor desired path a via reactive conformer **40**, due to significant 1,3-diaxial interactions disfavoring conformer **41** (Scheme 4A). In contrast, the same analysis on the *trans*-alcohols (Scheme 4B) predicts low levels of selectivity. To test this hypothesis, conformationally locked *cis*- and *trans*-decalinol (**44**, **45**) were subjected to rearrangement (Scheme 4C) and as predicted, **44** (OH_{ax}) favored acetal **46** in a 95:5 ratio, whereas **45** (OH_{eq}) gave almost exclusively ketone **47**. Thus, extrapolating from these findings, one could conclude that any substrate or complex natural product that is either conformationally locked or would have a preferentially axial alcohol would react with high selectivity to give medium-ring ether products.



Scheme 4. Role of alcohol conformation on reaction pathway.

Significantly, the HFIP-acetals can be readily functionalized under mild conditions, providing a versatile handle for subsequent derivatizations (Scheme 5). Under optimized conditions, treatment of **39** with Lewis acid in CH_2Cl_2:HFIP allows for facile reduction with Et_3SiH (**48**) or C–C bond formation with TMSCN (**49**) or allyl silane (**50**). The addition of N-tosyl indole gave **51** in 40% yield, a notable result considering the highly activated nature of **51** is known to result in competitive double addition products.[12] Simple exchange to the methyl acetal (**52**) could be accomplished using HCl in a 14:1 mixture of MeOH:HFIP. Conveniently, **52** can also be accessed in a one-pot fashion simply by quenching the crude rearrangement reaction with MeOH after removal of the molecular sieves (Ssee SI for details). Conditions to access **48**-**50** were also found to be readily applicable to deoxycholanoic acid acetal **35**, thus providing conditions for derivatization of both simple and complex HFIP-acetal scaffolds (see SI for details).



Scheme 5. Functionalization of HFIP-acetals. Lewis Acid: [a] TMSOTf [b] BF_3•OEt_2. [c] Et_2O used in place of DCM [d] Conditions: HCl, 14:1 MeOH:HFIP.

In conclusion, we report a method for the direct conversion of readily available secondary, aliphatic alcohols to medium-ring ethers. The reaction proceeds via electrophilic oxygen activation by a novel (poly)cationic λ^3-iodane, with exquisite selectivity for C–O bond migration over prototypical α-elimination pathways, further demonstrating the unique reactivity of this reagent class. The reaction is applicable to the synthesis of 5-7 membered ethers with diverse substitution at the *C2*-position, including migration of chiral centers with no observed epimerization, and the resulting HFIP-acetals can be readily derivatized. The ubiquity of secondary alcohols in bioactive molecules makes this method a valuable tool for CTD and diversity-oriented synthesis efforts, and its utility was demonstrated through the synthesis of several novel medium-ring natural product analogues. Future studies including more detailed mechanistic investigations as well as targeted CTD efforts on several natural product classes are underway and will be reported in due course.

Acknowledgements

The authors are grateful to the National Institutes of Health (R01GM-123098-01) for the financial support of this work and would also like to acknowledge the Donors of the American Chemical Society Petroleum Research Fund for partial support of this research (DNI-56603). J. C. W. was supported in part by

a Temple University Future Faculty Fellowship. We thank Dr. Charles DeBrosse (Temple University) for NMR spectroscopic assistance and Dr. Charles W. Ross III, Director: Automated Synthesis and Characterization at University of Pennsylvania Chemistry for providing chromatographic and mass spectral method development, analyses, and data interpretation.

Keywords: medium-ring; cyclic ethers; hypervalent iodine; ring expansion

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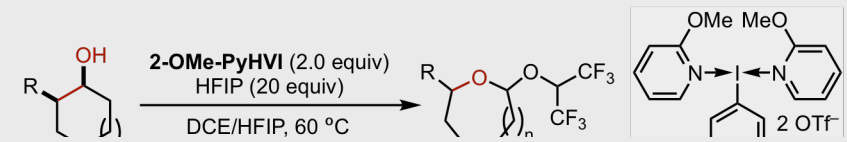

The unique reactivity of poly(cationic) λ^3-iodanes (*N*-HVIs) enables a simplified approach to cyclic ethers through the oxidative ring expansion of secondary alcohols. The method can be applied to the synthesis of 5-, 6-, and 7-membered rings as well as the late-stage derivatization of natural product scaffolds. The obtained HFIP-acetals are readily functionalized, providing a versatile approach to the synthesis of valuable cyclic ether scaffolds.

*Jennifer C. Walters,[‡] Dr. Anthony F. Tierno,[‡] Aimee H. Dubin, and Prof. Dr. Sarah E. Wengryniuk**

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