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Chemoselective Oxidation of Equatorial Alcohols with N-Ligated λ^3-Iodanes

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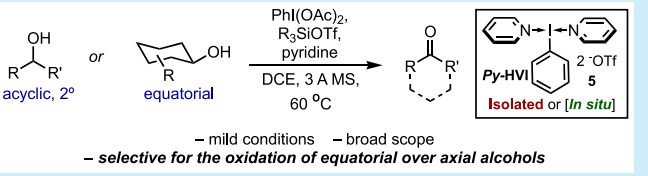
Supporting Information

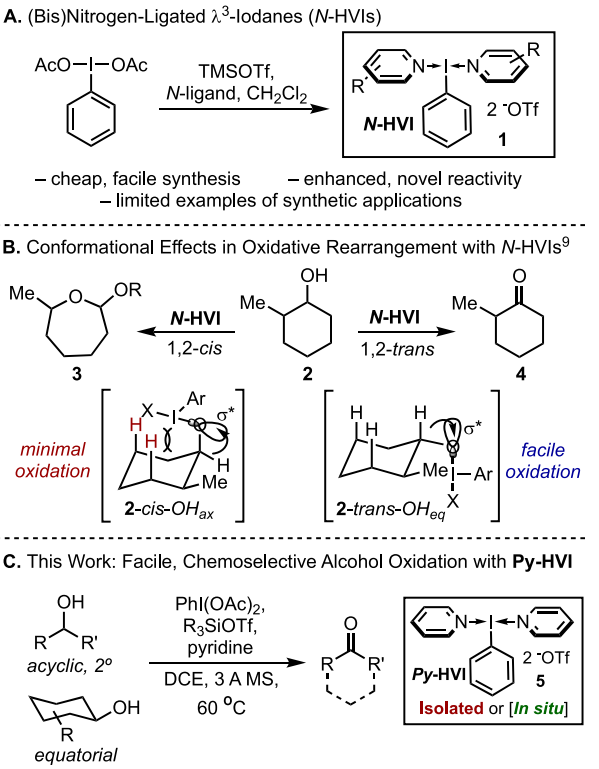
ABSTRACT: The site-selective and chemoselective functionalization of alcohols in complex polyols remains a formidable synthetic challenge. Whereas significant advancements have been made in selective derivatization at the oxygen center, chemoselective oxidation to the corresponding carbonyls is less developed. In cyclic systems, whereas the selective oxidation of axial alcohols is well known, a complementary equatorial selective process has not yet been reported. Herein we report the utility of nitrogen-ligated (bis)cationic λ^3-iodanes (*N*-HVIs) for alcohol oxidation and their unprecedented levels of selectivity for the oxidation of equatorial over axial alcohols. The conditions are mild, and the simple pyridine-ligated reagent (**Py-HVI**) is readily synthesized from commercial $PhI(OAc)_2$ and can be either isolated or generated in situ. Conformational selectivity is demonstrated in both flexible 1,2-substituted cyclohexanols and rigid polyol scaffolds, providing chemists with a novel tool for chemoselective oxidation.



The chemoselective and site-selective modification of complex molecular scaffolds persists as a formidable synthetic challenge. One area of particular interest is the selective reaction of one hydroxyl group among numerous sterically similar sites on a polyol scaffold. Whereas significant advancements have been made toward derivatization at oxygen,[1] selective reaction at the α-carbon through oxidation to the corresponding carbonyls is less developed. In a significant advancement, the Hartwig laboratory recently disclosed an elegant approach to the selective oxidation of hindered secondary alcohols in the presence of primary sites via rhodium-catalyzed transfer hydrogenation.[2] In cyclic systems, conformational effects can drive selectivity; Cr(VI) oxidants such as PCC will selectively oxidize axial alcohols due to steric relief driving the breakdown of the intermediate chromate ester.[3,4] Whereas equatorial alcohols are more sterically accessible,[5] to the best of our knowledge, a broadly selective method for the preferential oxidation of equatorial over axial alcohols has not been reported. Thus, the development of such a method would provide chemists with a powerful new tool in the chemoselective oxidation of complex molecules.

Recently, our laboratory has reported on the synthetic applications of (bis)cationic nitrogen-ligated λ^3-iodanes [PhI-(het)$_2$]2OTf$^-$, or *N*-HVIs (**1**) (Scheme 1).[6−9] Whereas *N*-HVIs have been known for over 20 years, reports on the synthetic utility of these reagents are scarce.[6,10,11] *N*-HVIs possess two datively bound heterocyclic nitrogen ligands on the central iodine, resulting in significantly enhanced oxidation potentials relative to traditional λ^3-iodanes and opening up new modes of reactivity to this reagent class.[11,12] Adding to their appeal, *N*-HVIs are readily synthesized from commercially available $PhI(OAc)_2$ using just TMSOTf and the desired heterocycle (Scheme 1A), leading to free-flowing white solids.[6]

Scheme 1. *N*-HVIs: Synthesis and Reactivity



During our recent efforts to develop an electrophilic ring expansion of secondary alcohols with *N*-HVIs (**2** → **3**, Scheme

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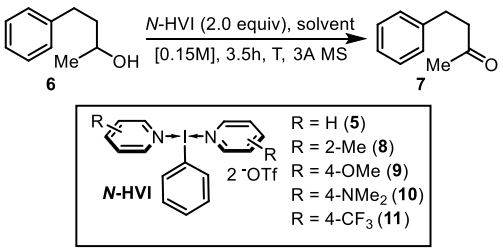
1B),[9] we observed that the relative alcohol stereochemistry had a significant effect on the reaction pathway. In using model substrate 2-Me-cyclohexanol (**2**), *cis*-**2** gave a clean rearrangement to cyclic ether **3**, whereas *trans*-**2** led to significant amounts of competitive ketone formation (**4**). We rationalized this divergent reactivity through differences in the conformational equilibria of the two substrates. The *trans*-**2** placed the alcohol equatorial in the major conformer, resulting in an intermediate iodate ester that could readily achieve the necessary antiperiplanar orbital alignment with the α-hydrogen (**2**-*trans*-OH_{eq}), enabling facile oxidation. In contrast, the *cis*-**2** was biased toward an axial alcohol conformer, wherein significant steric clash with the 1,3-diaxial hydrogens inhibited access to the necessary orbital alignment, thus leading to rearranged products (**2**-*cis*-OH_{ax}). On the basis of this model, we recognized that if the *N*-HVI reactivity could instead be tuned to favor oxidation, this could lead to the first general method for the chemoselective oxidation of equatorial over axial alcohols. Furthermore, this would provide a rare example of broad-scope alcohol oxidation with a λ^3-iodane reagent as the sole oxidant,[13] providing practical advantages over the current λ^5-iodane oxidants.[12,14,15]

Herein we report the successful development of two practical protocols for alcohol oxidation using simple pyridine-ligated *N*-HVI, **Py-HVI** (**5**), and its utility in the chemoselective oxidation of equatorial alcohols. The oxidation can be performed either with isolated **Py-HVI** or via its in situ generation, enabling a one-pot procedure from commercial $PhI(OAc)_2$ (Scheme 1C). The oxidation shows a broad substrate scope and functional group tolerance. In cyclic substrates, **Py-HVI** displays excellent selectivity for equatorial alcohols in both conformationally flexible 1,2-substituted cyclohexanols and rigid polyol scaffolds, providing chemists with a general approach to the chemoselective oxidation of equatorial alcohols for the first time.

To begin our study, efficient conditions for direct alcohol oxidation with *N*-HVIs needed to be established. Using 4-phenyl-2-butanol (**6**) as a model substrate, treatment with 2.0 equiv of **Py-HVI** in 1,2-dichloroethane (DCE) at room temperature gave a modest 37% yield of the corresponding ketone (**7**) (Table 1, entry 1). Increasing the temperature to 60 °C resulted in near-quantitative oxidation in just 2.5 h, producing **7** in 96% isolated yield (entry 2). Decreasing the equivalents of **Py-HVI** to either 1.0 or 1.5 (entries 3 and 4) also gave high conversion but with decreased efficiency, taking 8 and 12 h to reach completion, respectively, and thus 2.0 equiv of **Py-HVI** was used for the remainder of our studies. A brief solvent screen found that acetonitrile was equally effective (entry 5), obviating the need for a halogenated solvent if so desired. To gain more insight into the role of the nitrogen ligand, a small library of electronically and sterically diverse *N*-HVIs was screened. The use of ortho-substituted (**8**) or more electron-rich (**9**, **10**) *N*-HVIs also gave excellent yields (entries 7−9), whereas the highly reactive *p*-CF_3-Py-HVI (**11**) was not as effective (entry 10).

We then wished to further simplify our method by developing a one-pot protocol via the in situ generation of **Py-HVI**, avoiding the need for its isolation and storage. This would also benefit the broader application of *N*-HVIs because these reagents can be moisture-sensitive and prone to degradation upon prolonged storage.[9] The initial application of our standard conditions for *N*-HVI synthesis using TMSOTf, followed by the addition of the substrate, resulted

Table 1. Oxidation with Isolated *N*−HVI

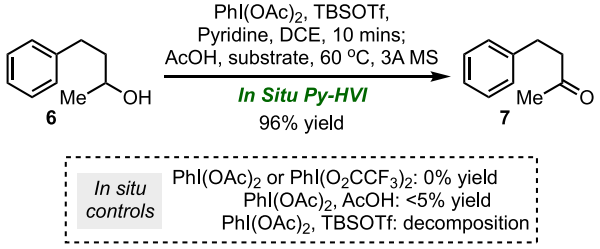


entry	*N*-HVI	solvent	*T* (°C)	yield (%)
1	Py-HVI (**5**)	DCE	r.t.	37[a]
2	Py-HVI (**5**)	DCE	60	96
3	Py-HVI (**5**)[b]	DCE	60	84 (95)[c]
4	Py-HVI (**5**)[d]	DCE	60	52 (84)[e]
5	Py-HVI (**5**)	ACN	60	97
6	Py-HVI (**5**)	THF	60	45
7	2-MePy (**8**)	DCE	60	97[a]
8	4-OMe (**9**)	DCE	60	89[a]
9	4-NMe_2 (**10**)	DCE	60	75[a]
10	4-CF_3 (**11**)	DCE	60	63[a]

[a]NMR yield with CH_2Br_2 as an internal standard [b]1.5 equiv of Py-HVI. [c]Yield after 8 h. [d]1.0 equiv of Py-HVI. [e]Yield after 12 h.

in variable yields of **7** along with significant amounts of silyl-protected **6**. The use of the bulkier TBSOTf as the silyl activator suppressed alcohol protection, and a screen of hydrogen bonding and Brønsted acid additives[8,9,16−18] found that the use of AcOH gave a consistently excellent yield of **7** (Scheme 2). (See the Supporting Information for additional

Scheme 2. Oxidation with in-Situ-Generated Py-HVI



optimization details.) Several control reactions were conducted to determine if **Py-HVI** was, in fact, the active oxidant under these in situ conditions (Scheme 2, inset). Neither $PhI(OAc)_2$ nor $PhI(O_2CCF_3)_2$ alone produced any oxidation product, and $PhI(OAc)_2$/AcOH gave only trace oxidation, indicating that Brønsted acid activation alone was insufficient. Finally, the exclusion of pyridine from the reaction resulted in significant substrate decomposition, likely through the reaction of highly reactive [PhI(OAc)]OTf, formed upon the treatment of $PhI(OAc)_2$ with R_3SiOTf.[7b,17]

The scope of the oxidation was then examined using both in-situ-generated (condition A) and isolated **Py-HVI** (**5**) (condition B) and was found to be quite general (Scheme 3). A variety of acyclic, cyclic, and benzylic alcohols (**6**, **12**−**19**) gave good to excellent yields. The excellent yield of cyclopropyl substrate **14** provides evidence that the reaction does not proceed through a radical pathway. More functionalized substrates, including those with halogens (**20**, **26**), acetate (**21**), alkyne (**28**), and saturated heterocycles (**22**, **23**), all proceeded in high yield. We were pleased to see that an

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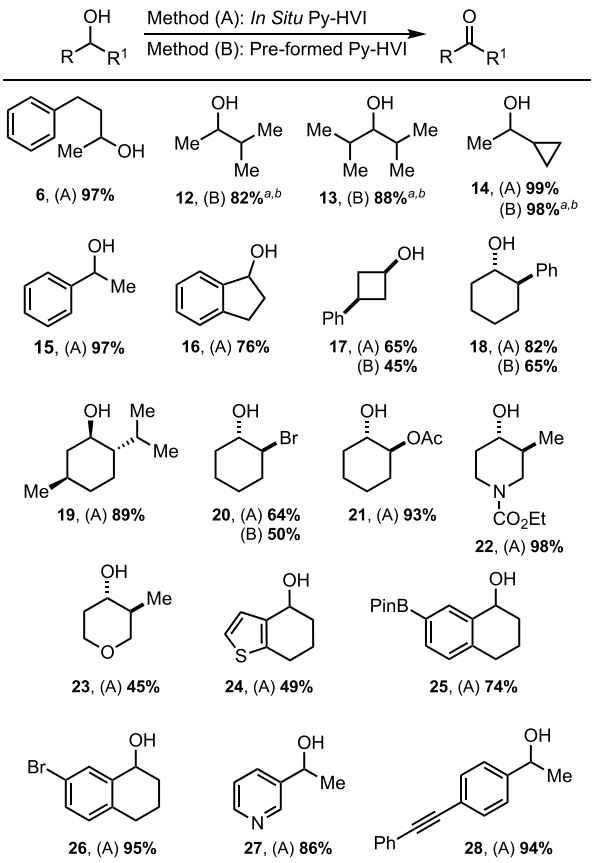
Scheme 3. Alcohol Oxidation Scope[c]

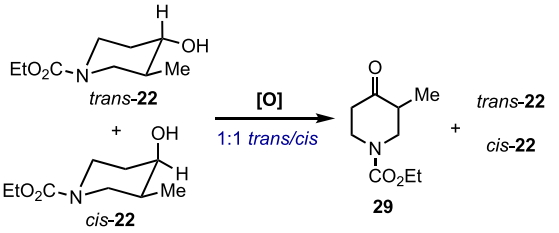


[a]Run in ACN-d_3. [b]NMR yield, CH_2Br_2 internal standard. No isolated yield obtained due to volatility of products. [c]Method (A): $PhI(OAc)_2$ (2.0 equiv), TBSOTf (4.0 equiv) pyridine (4.0 equiv), DCE, 10 min rt; then AcOH (1.0 equiv), ROH substrate, 3A MS, 60 °C. Method (B): Py-HVI (2.0 equiv), DCE, 60 °C.

oxidatively sensitive thiophene and boronic ester were both well tolerated (**24**, **25**) as well as a pyridine substrate (**27**), which underwent smooth oxidation rather than ligand exchange with the *N*-HVI.

With robust oxidation conditions in hand, we returned to the intriguing question of effecting equatorial-selective alcohol oxidation. Our scope studies revealed that the newly optimized conditions exhibited significantly enhanced reactivity for 1,2-*trans*-substituted cyclic substrates over the corresponding 1,2-*cis* isomers, in line with findings from our prior studies.[6] We therefore chose to begin our selectivity studies by examining if this divergent reactivity could be leveraged to achieve selective oxidation between two conformationally flexible molecules. Thus a 1:1 mixture of *cis*- and *trans*-**22** was treated with in-situ-generated **Py-HVI** under our standard conditions (Scheme 4). The reaction displayed exquisite levels of selectivity for the oxidation of *trans*-**22**; ketone **29** was produced in 46% yield, along with only 2% recovered *trans*-**22** and the near-quantitative recovery of *cis*-**22** (entry 1). In fact, the reaction of pure *cis*-**22** produced no ketone products, even upon prolonged heating, eventually producing small amounts of nonspecific degradation products. To further establish the novelty of this cis/trans chemoselectivity, the same mixture was subjected to a panel of common oxidants including Swern oxidation, pyridinium chlorochromate (PCC), Dess–Martin periodinane, and $PhI(OAc)_2$/TEMPO,[13i] wherein the λ^3-iodane acts only as a co-oxidant. As expected, no cis/trans selectivity was observed with Swern or Dess–Martin periodinane. $PhI(OAc)_2$/TEMPO and PCC, on the contrary, showed slight selectivity, however, favoring the consumption of *cis*-**22**, likely arising from *cis*-**22** slightly favoring the more rapidly oxidized axial alcohol conformation.

Scheme 4. Chemoselective Oxidation of 1,2-*trans* versus 1,2-*cis* Cyclic Alcohols



	29	*trans*-22	*cis*-22	*trans*:*cis*[d]
In situ Py-HVI[a]	**46%**	**2%**	**45%**	**>20 : 1**
Swern[a]	84%	4%	6%	1.5 : 1
DMP[a]	99%	n/a	n/a	n/a
PCC[b,c]	62%	27%	11%	1 : 2.4
$PhI(OAc)_2$/TEMPO[b,c]	67%	26%	7%	1 : 3.7

Percentages based on total starting mmol *cis*/*trans*-**22**. [a]Isolated yields. [b]NMR yields only. CH_2Br_2 internal standard. [c]Percentages after 4 to 5 h of reaction time. [d]Selectivity ratio based on the percentage remaining of *trans*/*cis*-**22** starting from 50% maximum yield.

Next, we examined the oxidation of conformationally locked scaffolds, wherein the reactivity of equatorial versus axial alcohols could be clearly established. Three *trans*-decalinol model substrates, **30**, **31**, and **32**, were selected to examine the effect of both alcohol conformation and two-substitution on the reaction rate (Scheme 5). As predicted, equatorial alcohol **30** gave near-quantitative oxidation in only 30 min, producing **33** in 91% isolated yield (Scheme 5A). In marked contrast, axial alcohol **31** reacted sluggishly, producing only trace ketone after 1 h and only reaching 78% conversion after prolonged heating (Scheme 5B). Interestingly, alcohol **32**, wherein the equatorial alcohol was flanked by a syn angular methyl group, analogous to equatorial alcohols in the 1,2-*cis*-cyclic alcohols (see Scheme 4), also displayed low reactivity, giving only 34% yield at 4 h.

Finally, to demonstrate this novel chemoselectivity in a complex setting, deoxycholic acid (**35**), possessing both an equatorial A-ring alcohol and an axial C-ring alcohol, was subjected to oxidation with isolated **Py-HVI** (Scheme 5, inset). As expected, we observed an exclusively A-ring ketone **36** in 75% yield, with no products arising from either selective C-ring oxidation or double oxidation, even in the presence of excess **Py-HVI**. (See the Supporting Information for details.)

Taken together, these results demonstrate the ability of *N*-HVIs to effect the chemoselective oxidation of equatorial over axial alcohols for the first time. Given our findings, we now present a more comprehensive predictive model for the application of *N*-HVIs in conformationally selective oxidation (Scheme 6). In cyclic alcohols, chair conformations in which the alcohol is oriented axial suffer significant steric clash with the 1,3-diaxial hydrogens in the necessary conformation (**37**), thereby significantly inhibiting oxidation. In contrast, equatorial alcohols will undergo facile oxidation because the reactive

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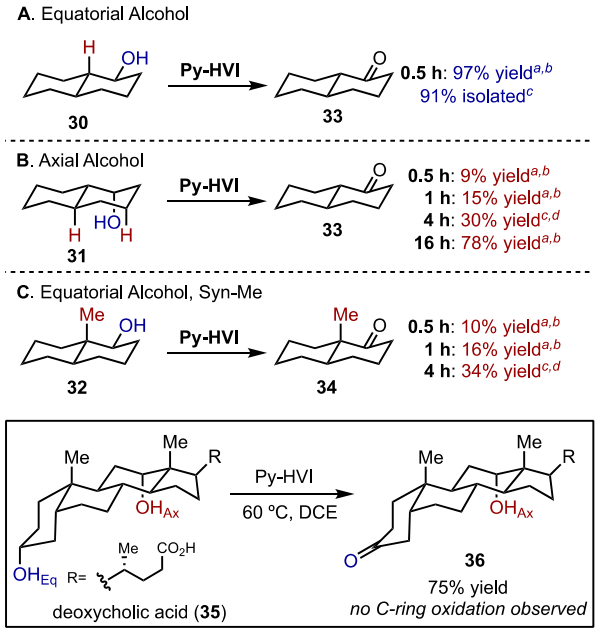
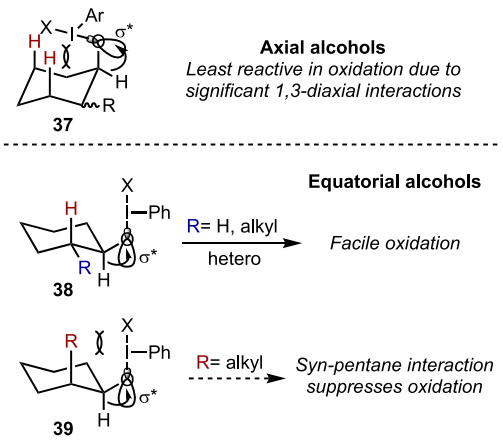
Scheme 5. Chemoselective Oxidation of Conformationally Locked Scaffolds



[a]Following Method B (premade **Py-HVI**) in $CDCl_3$. [b]NMR yields using CH_2Br_2 internal standard. [c]Following Method A (in situ **Py-HVI**) [d]Isolated yield.

Scheme 6. Predictive Model for Conformational Selectivity in *N*-HVI-Mediated Oxidation



iodate ester conformation is readily accessible (**38**). An exception exists in equatorial cases wherein an axial syn substituent at the two-position (e.g., angular methyl) results in a significant *syn*-pentane interaction between the equatorial iodate ester and the two-substituent (**39**), again leading to low reactivity. This final data point explains the general lack of reactivity in 1,2-*cis*-cyclic alcohols, whereby no active conformation for oxidation is readily accessible.

In conclusion, we report a facile approach to the alcohol oxidation with a pyridine-ligated (bis)cationic λ^3-iodane, **Py-HVI**, which is readily synthesized from commercial $PhI(OAc)_2$ and can be either presynthesized or generated in situ. The enhanced reactivity of *N*-HVI reagents enables a rare example of oxidation with the λ^3-iodane, avoiding the cost and safety concerns associated with Cr(VI)- and I(V)-based oxidants. In addition to its operational simplicity and broad substrate scope, the method displays exquisite selectivity for the oxidation of equatorial over axial alcohols, providing a powerful new tool with highly predictable reactivity for the chemoselective derivatization of complex scaffolds. *N*-HVI-mediated oxidation offers a general solution to a long-standing selectivity challenge in organic synthesis and should find widespread utility in total synthesis, particularly in the derivatization of complex polyols.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02018.

Experimental details, analytical data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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