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Catalytic Regio- and Enantioselective Haloazidation of Allylic Alcohols

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Abstract

Herein we report a highly regio- and stereoselective haloazidation of allylic alcohols. This enantioselective reaction uses readily available materials and can be performed on a variety of alkyl-substituted alkenes and can incorporate either bromine or chlorine as the electrophilic halogen component. Both halide and azido groups of the resulting products can be transformed into valuable building blocks with complete stereospecificity. The first example of an enantioselective 1,4-haloazidation of a conjugated diene is reported as well as its application to a concise synthesis of an aza-sugar.

Graphical Abstract

Vicinal difunctionalization of alkenes is a powerful way to rapidly build complexity into small molecules from readily available starting materials.¹ However, adding two functional groups across alkenes with regio-, diastereo-, and enantiocontrol is a challenging task. Taking advantage of the inherent reactivity of olefins, halofunctionalization^{2,3} is among the most direct ways to react unactivated alkenes without resorting to π -bond activation by late-transition metals.^{1b,1c,1g} Nevertheless, due to the highly reactive nature of most commonly employed halogen sources and the potential issue of configurational instability⁴ of haliranium ions, successful enantioselective halofunctionalizations have largely relied on the intramolecular capture of haliranium ion intermediates; this substantially limits their substrate scope and synthetic utility. Our group has recently developed an enantioselective titanium-mediated dihalogenation of allylic alcohols. Selectivity is achieved through the addition of substoichiometric amounts of simple chiral Schiff base (*R,S*)-**1** that is available in one step from commercial materials (Figure 1A).⁵ This method has been used strategically to achieve enantioselective total syntheses of over 11 structurally diverse

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ASSOCIATED CONTENT

Experimental procedures, characterizations, spectral data, and CIF files. This material is available free of charge via the Internet at <http://pubs.acs.org>.

halogenated natural products.^{5h} Due to the importance of nonracemic chiral amines in small molecules,^{6a} we next sought to extend this system to C–N bond formation. For this, we envisioned a combination of halogen electrophiles with a titanium-bound nitrogen nucleophile to render this a more general platform for the selective 1,2-difunctionalization of allylic alcohols. Herein we describe the enantioselective haloazidation of allylic alcohols as an illustration of this process.

Since the first preparation of iodine azide by Hantsch^{6b} in 1900, alkene haloazidation has seen use in synthetic chemistry.⁷ Given the utility of organic azides⁸ and alkyl halides,⁹ the haloazide motif serves as an obvious precursor to valuable chiral amines and potentially to a handful of aminochlorinated natural products (Figure 1B).¹⁰ For electron-deficient alkenes, conjugate 1,4-addition of azide followed by trapping with electrophilic halogen sources provides substrate-controlled regioselective access to α -halo- β -azides (Figure 1C). Using this strategy to control regioselectivity, Feng¹¹ recently reported a highly enantioselective Lewis acid-catalyzed haloazidation of enones as the first and only enantioselective example of such a reaction. The haloazidation of electron-neutral or rich olefins typically uses preformed or in situ generated haloazide reagents, however, enantioselective variants are still unknown, presumably because these highly reactive and unstable reagents render the control of selectivity challenging. In addition, free radical^{7b,7d,7r,7s} and ionic addition pathways have been proposed under different conditions, further complicating the design of a system for asymmetric catalysis. We thus set out to determine if our titanium–Schiff base combination would be amenable to such a selective alkene functionalization.

To apply our titanium-based system to selective alkene haloazidation, we posited that a titanium azide species would be Lewis acidic enough to activate an electrophilic halogen source (bracketed intermediate, Table 1) for intramolecular transfer of Br⁺ or Cl⁺ to form a transient bromonium or chloronium ion. Azide could then add to the transient halonium to deliver a haloazide product. In accord with the seminal work of Sharpless and others on the ring opening of epoxides by Ti(N₃)₂(O*i*-Pr)₂ and TiN₃(O*i*-Pr)₃,¹² we observed formation of solid TiN₃(O*i*-Pr)₃ by IR (2076 cm^{−1}) upon combining stoichiometric amounts of TMSN₃ and Ti(O*i*-Pr)₄. A mild exotherm was observed in combining these two reagents (see Supporting Information). We obtained calorimetry/thermogravimetric analysis data on TiN₃(O*i*-Pr)₃ and observed an onset temperature of decomposition of 230 °C (see Supporting Information). The resulting TiN₃(O*i*-Pr)₃ can then be dissolved in hexanes and directly employed in enantioselective haloazidations. With *N*-bromosuccinimide (NBS) as the halogen source, the bromoazidation is highly selective for a variety of allylic alcohols. Cinnamyl alcohol (Table 1, entry 1), geminal disubstituted alkenes (entries 2, 3 and 4), 1,2-disubstituted allylic alkenes (entries 5 and 6), linear trisubstituted alkene (entry 7) and cyclic alkenes (entry 8) are all suitable substrates, and the resulting vicinal bromo azides can be obtained in good yields, excellent enantioselectivities, and good to moderate constitutional isomer ratios (cr). C-3 disubstitution, including tetrasubstitution, is not tolerated. Evidence for a similar reaction pathway with our dihalogenation is provided by identical observed regioselectivities.^{5c} With the exception of cinnamyl alcohols (entry 1) and *trans*-disubstituted allylic alcohols (entry 5), C-2 azide products are obtained as the major isomer. High chemoselectivity for allylic alcohol haloazidation is demonstrated on a doubly unsaturated substrate (entry 4). When substituting NBS with *t*-BuOCl, the corresponding

vicinal chloroazides are produced with similarly high selectivities. A collection of allylic alcohols is well tolerated (entries 9 to 13), although higher Schiff base loadings are necessary, likely due to the more reactive nature of *t*-BuOCl and intermediate chloronium ions. Density functional theory calculations (M06-2X/6-31g(d), pcm = *n*-hexane) comparing N-1 with N-3 azide addition show an energetic preference for the distal N-3 serving as the nucleophile (Figure 2).

In order to further demonstrate the utility and stereointegrity of the product haloazides, several derivatizations were investigated. *All derivatizations occur with complete stereospecificity* (Scheme 1). LiAlH₄ is known to reduce haloazides to the corresponding aminohalides which spontaneously collapse to aziridines,^{7g} and this proceeded smoothly in 82% yield to give hydroxy *N*-H aziridine **2**.¹³ Selective reduction of the azide to the primary amine without aziridine formation was also achieved. It was found that a combination of Ac₂O, tri-*n*-butylphosphonium tetrafluoroborate,¹⁴ and base was capable of reducing the azide and trapping the incipient iminophosphorane to provide diacyl bromoaminoalcohol **3** in 70% yield. Bromides can be selectively substituted by pyrrolidine, piperidine, or sodium azide to provide **4**, **5**, and **6/8**, respectively, demonstrating efficiency in simple nucleophilic displacements.¹⁵ In addition, an azide-alkyne cycloaddition¹⁶ proceeds under mild conditions in the presence of a copper catalyst without interference of the secondary alkyl bromide to produce triazole **7** in 84% yield.

Lastly, in an interesting display of regiochemistry, 2,4-hexadien-1-ol is functionalized in a 1,4-manner, giving rise to selective formation of unsaturated 1,4-bromoazide **9** (Scheme 2). This method represents the first example of an enantioselective intermolecular 1,4-halofunctionalization of a conjugated diene¹⁷ and sets two remote stereocenters. Here it is likely that the N-3 nitrogen of the azide serves as the nucleophilic atom, however we propose that this pathway involves diene 1,2-addition followed by [3,3] allylic azide rearrangement (Scheme 2, top).¹⁸ Such rearrangements are known to have a first order rate constant of at least $4.9 \times 10^5 \text{ sec}^{-1}$.^{18a} Seeing potential for such products in the construction of highly substituted chiral pyrrolidines we targeted aza-sugar **11** (Scheme 2); such monosaccharide mimics have served as therapeutic agents in a variety of diseases including diabetes and viral infection as glycosidase inhibitors.¹⁹ Following TBS protection of alcohol **9**, the internal alkene undergoes a stereoselective Sharpless dihydroxylation to give diol **10**. Without the (DHQD)₂PHAL ligand, a 1:1 mixture of diastereomers was observed. The diol is subsequently protected as the acetonide, and the azide can then be reduced by LiAlH₄ to give the primary amine. After global deprotection with HCl, clean cyclization is achieved under basic conditions at elevated temperatures to provide target **11**. This application paves the way for the synthesis of other enantioenriched pyrrolidines utilizing this haloazidation technology.

In summary, we have developed a highly practical method for the catalytic enantioselective haloazidation of electronically-unbiased alkenes with catalyst-controlled regio- and enantioselectivity. We have also used this system in the first example of an enantioselective 1,4-haloazidation of a 1,3-conjugated diene. The obtained products have been demonstrated as precursors to chiral nitrogen-containing small molecules including an aza-sugar. The

continuing development of our titanium-based catalytic system in other difunctionalizations of π -systems is ongoing in our lab.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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A Ti-based regio- and enantioselective halofunctionalization: *catalyst-controlled regioselectivity***B Select aminochloride natural products** **C Prior regio- and enantioselective haloazidation** **Figure 1.**

Selective Haloazidation and Aminochloride Natural Products

Figure 2. Computed isomeric transition state structures for N-1 versus N-3 nucleophilic addition; M06-2X/6-31g(d) level of theory (PCM = *n*-hexane); relative uncorrected electronic energies.

Scheme 1.
Bromoazide Derivatizations

Scheme 2.
Diene 1,4-Bromoazidation and Application to the Synthesis of Aza-Sugars

Table 1.

Haloazidation Substrate Scope

Reaction scheme: $R^1-CH(R^2)-CH(R^3)-OH \xrightarrow[\text{hexanes, } -20^\circ\text{C}]{\text{NBS or } t\text{-BuOCl, Ti(O}^i\text{Pr)}_4, \text{TMSN}_3, 10\text{--}30 \text{ mol } \% (R,S)\text{-1}}$ $\left[\begin{array}{c} \text{N}_3 \\ | \\ \text{L}_n-\text{Ti}-\text{O}-\text{CH(R}^1\text{)-CH(R}^2\text{)-CH(R}^3\text{)-OH} \\ | \\ \text{R} \end{array} \right] \rightarrow \begin{array}{c} \text{R}^1-\text{CH(R}^2\text{)-CH(R}^3\text{)-OH} \\ | \\ \text{X} \end{array} \text{ or } \begin{array}{c} \text{R}^1-\text{CH(R}^2\text{)-CH(R}^3\text{)-OH} \\ | \\ \text{N}_3 \end{array}$ $\text{X} = \text{Br, Cl}$

entry	substrate	product	mol % (R,S)-1	yield (%) ^a	ee (%)	cr ^b
1			10	79	94	>20:1
2 ^f			20	97	93	>20:1
3			10	44	94	>20:1
4 ^c			10	69	90	>20:1
5			10	83	95	4:1
6			30	75	87	5:1
7			10	87	96	>20:1
8			20	92	86	>20:1
9 ^f			20	84	95	>20:1
10			20	89	99	5:1
11			30	78	87	4:1
12			20	79	94	>20:1 ^d
13			20	87	91	>20:1 ^e

Conditions unless otherwise noted: 1.0 mmol allylic alcohol, 1.3 equiv of NBS or 2.0 equiv of *t*-BuOCl, 1.2 equiv Ti(O^{*i*}Pr)₄, 1.1 equiv TMSN₃, 10–30 mol % (*R,S*)-1, hexanes, –20 °C, 12–18 h;

^a reported isolated yields are for the sum of constitutional isomers;

^b cr = constitutional isomer ratio;

^c reaction run at 0 °C;

^d 10:1 ratio of product to dichlorinated alkene;

^e 5:1 ratio of product to dichlorinated alkene;

^f. See Supporting Information for X-ray structures of ferrocene triazole derivatives.

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