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Brønsted Acid-Promoted Olefin Aziridination and Formal *anti*-Aminohydroxylation

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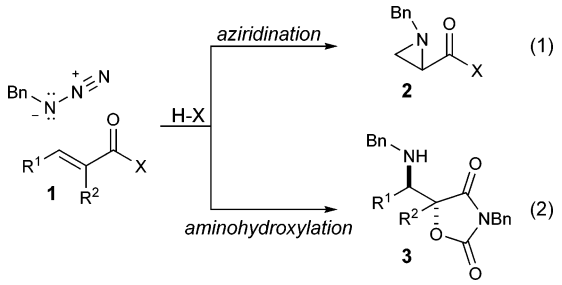
The stereocontrolled functionalization of olefins with heteroatoms provides direct entry to functionalized carbon chains used as small-molecule feedstocks in organic synthesis. For example, olefin aziridination and subsequent ring-opening reactions often form the basis for more complex target synthesis.[1] Aminohydroxylation of unsaturated esters provides entry to both α- and β-amino acid derivatives.[2]

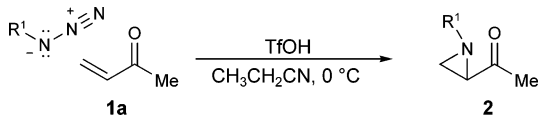
We envisioned the design of an acid-promoted nucleophilic azide addition to an electrophilic enone. The use of acid would catalyze both cycloaddition and nitrogen extrusion steps and would be driven by the evolution of N_2 as a relatively benign coproduct.[3] This approach favors the use of an electron-rich alkyl azide as a nucleophilic nitrene equivalent,[4,5] a behavior synthetically developed in recent years largely by the groups of Aubé[6] (carbonyl electrophiles) and Pearson[7] (carbenium ion electrophiles). Extensive studies of the [3+2] cycloaddition chemistry of azides with alkenes have led to protocols for thermal[8,9] and photochemical[10] decomposition of the resulting triazolines.[11] Triazoline decomposition by acid also leads to aziridine, but the overall efficiency is typically low and the scope narrow at present.[12] Azide cycloadditions and addition/rearrangement reactions are more general in an intramolecular setting (cyclizations) since azides decompose in various ways upon binding to Lewis acids and transition metals.[4]

We report here a new Brønsted acid-promoted addition of azides to activated olefins that delivers the corresponding aziridines in good yield under relatively mild, non-redox conditions (eq 1). Furthermore, active ester derivatives bearing a Lewis basic oxygen readily participate in a tandem process to deliver both α- and β-substituted *threo*-α-hydroxy β-amino acids in orthogonally protected form (eq 2).



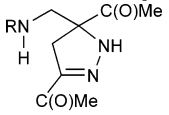
When benzyl azide and methyl vinyl ketone (**1a**) are stirred at room temperature, the 2:1 ketone−azide adduct **4a** is formed cleanly in 66% yield (Table 1).[9] Subsequent treatment of **4a** with triflic acid provides only the derived salt. That a Brønsted acid might be effective, if not uniquely so, in the desired aziridination was based on the predictions that (1) protonation of the azide would be reversible, perhaps even disfavored, (2) decomposition of the azide with solvent-bound proton would be relatively slow,[13] (3) the presence of a protic acid might favor an intermediate aminodiazonium ion (**A**, *vide infra*) over the concerted [3+2] cycloaddition to produce triazoline, and (4) collapse of an intermediate enol to triazoline would be slow relative to aziridine formation. A Lewis acid screen was executed in a generally nonparticipating solvent with low polarity (dichloromethane), as well as in a solvent that is both a competent Lewis base and polar (acetonitrile).[14] The unique effectiveness of trimethylsilyl triflate and triflic acid, a representative Brønsted acid, in the transformation emerged. The higher yields and ease of product purification led to exclusive use of triflic acid in subsequent experiments. Acetonitrile was identified from a broad solvent screen as the most effective medium for the aziridination (CH_3CN, 79%; Et_2O, 58%; CH_2Cl_2, 49%; THF, 35%; $CHCl_3$, 33%; CH_3OH and DMF, 0%).

Table 1. Bronsted Acid-Promoted Azirdinations: Azide Scope[a]



entry	R^1		% yield
1[c]	Bn	**2a**	79
2	Bn	**2a**	92[d]
3	Ph_2CH	**2b**	88
4	Ad	**2c**	93
5	*p*-$MeOC_6H_4$	**2d**	43[e]
6	$^tBuO_2CCH_2$	**2e**	66
7	$MeOCCH{=}CHCH_2$	**2f**	76
8	$Me_2C{=}CHCH_2$	**2g**	68

[a] All reactions were 0.30 M in substrate and proceeded to complete conversion. [b] Isolated yield after chromatography. [c] The thermal reaction (no TfOH) produces **4a** and **4b** in 66% and quantitative yield, respectively.



4a,R=Bn
4b, R=PMP

[d] Yield of the crystalline **2a** triflic acid salt. [e] Reaction run in CH_2Cl_2 at 78 °C to minimize azide decomposition.

Electron-rich alkyl azides are generally effective donors (Table 1). Benzyl azide engages the olefin to produce the *N*-benzyl-protected terminal aziridine in 79% isolated yield after flash chromatography (Table 1, entry 1). Alternatively, the aziridine may be isolated in slightly higher yield (92%) by direct crystallization of the triflic acid salt (Table 1, entry 2). More hindered azides are also effective, including diphenylmethyl azide (Table 1, entry 3) and adamantyl azide (Table 1, entry 4). Electron-rich azides derived from aniline produce the desired aziridine but competitively form what appears to be the azide dimer or trimer (Table 1, entry 5). Azides such as *tert*-butyl glycinyl azide can be smoothly converted to the aziridine without identifiable ester hydrolysis (Table 1, entry 6). Finally, a variety of allylic azides formed their derived aziridines in good yield (Table 1, entries 7 and 8).

The ease with which the aziridine triflic acid salt **2a**·HOTf could be formed and isolated led us to consider the possibility that an oxygen nucleophile might be internally delivered by an activated ester heteroatom. The acrylate derivative of *N*-benzyl methyl

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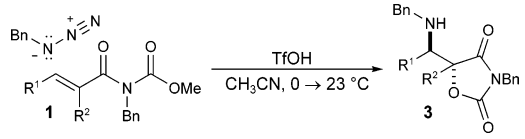
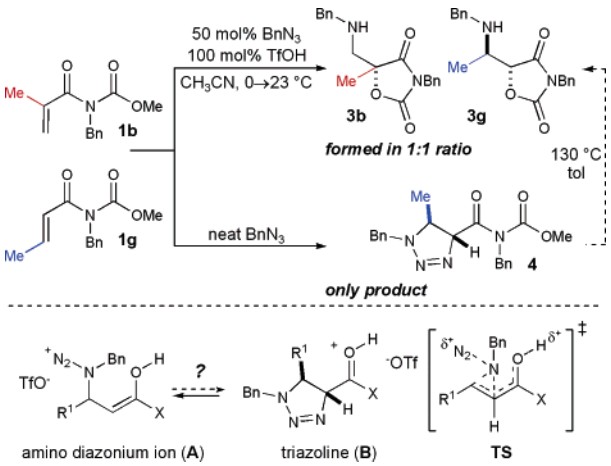
Table 2. Regiospecific, Stereoselective Formal *anti*-Aminohydroxylation of Activated Olefins[a]



entry	R^1	R^2		dr[b]	% yield[c]
1	H	H	**3a**		84
2	H	Me	**3b**		88
3	H	Et	**3c**		61
4	H	^{n}Pr	**3d**		60
5	H	Bn	**3e**		46
6	H	Ph	**3f**		86
7	Me	H	**3g**	>20:1	94
8	Et	H	**3h**	15:1	82
9	^{i}Pr	H	**3i**	>20:1	61

[a] All reactions were 0.25 M in substrate and proceeded to complete conversion. [b] Diastereomeric ratio determined by ^{1}H NMR spectroscopy. Relative configuration of **3g** assigned by X-ray analysis of a derivative. [c] Isolated yield after chromatography.

Scheme 1. Competition Experiments for Catalyzed Aminohydroxylation and Thermal [3+2] Cycloaddition



carbamate (**1a**) was prepared and subjected to the standard aziridination conditions to deliver oxazolidine dione **3a** as a single regioisomer (>20:1, ^{1}H NMR). Use of α-substituted acrylates led to generally high yields of the expected oxazolidine diones **3b**−**f** (Table 2, entries 2−6).[15] Of these substrates, the α-benzyl-substituted acrylate was noticeably more sluggish and required warming to achieve complete conversion (Table 2, entry 5). A series of *β*-substituted imides were then subjected to the aminohydroxylation conditions with very similar results. Crotonyl imide **1g** formed the desired *β*-amino α-acyloxy acid in protected form in 94% yield (Table 2, entry 7). Spectroscopic analysis of the crude reaction mixture (^{1}H NMR) suggested that a single regio- and stereoisomer was formed in this transformation. *β*-Substituents with increasing size were generally tolerated (Table 2, entries 7−9).

Throughout the course of these studies, substantial effort was applied toward the identification and isolation of the potential triazoline intermediate (e.g., **B** in Scheme 1), since the literature implicates it without exception as the intermediate to aziridine. It was not until imide **1g** was stirred in neat benzyl azide that the triazoline could be formed, isolated, and characterized. This triazoline failed to thermally convert to aziridine or oxazolidinedione, but its exposure to triflic acid led to clean low-temperature (−20 °C) conversion to **3g**. However, a competition experiment between **1b** and **1g** revealed a pronounced substituent effect in the cycloaddition not observed in the aminohydroxylation (Scheme 1).

We speculate that the triazoline need not be an intermediate and that rate acceleration and selective formation of the aziridine intermediate might also be explained by **TS**. This proposal not only departs from conventional wisdom but also presents significant implications for the design of new reactions based on azides, as well as their stereoselective variants.[16] We do not rule out triazoline intermediacy in all cases, since Brønsted acid clearly promotes the conversion of triazoline **B** to aminodiazonium ion **A**.[12]

In summary, the addition of electron-rich azides to electron-deficient olefins is promoted by Brønsted acids. Our present findings suggest that catalysis is achieved by either providing access to **TS** or promoting the formation of the aminodiazonium ion intermediate **A** by either direct conjugate addition or triazoline fragmentation. The aminohydroxylation variant is stereocomplementary to traditional metal-mediated aminohydroxylations that provide *syn*-amino alcohols from *E*-olefins.

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Supporting Information Available: General experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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