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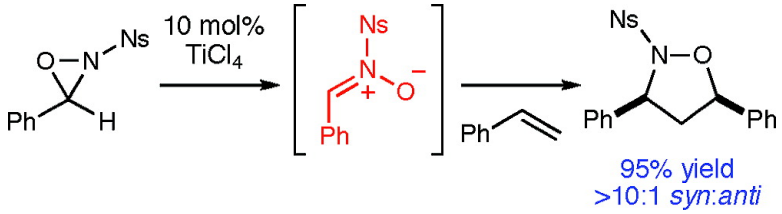

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Cycloadditions of *N*-Sulfonyl Nitrones Generated by Lewis Acid Catalyzed Rearrangement of Oxaziridines

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The weak N−O bond of 1,2-isoxazolidines can undergo facile reductive cleavage to furnish 1,3-aminoalcohols. Due to the ease with which isoxazolidines can be processed into these synthetically valuable structures, considerable effort has been invested toward the development of methods for [3 + 2] nitrone cycloadditions.[1] This enormous body of work, however, has focused primarily upon *N*-alkyl nitrones that produce 1,2-isoxazolidines whose *N*-substituents cannot be removed without concomitant cleavage of the sensitive N−O bond;[2] cycloadditions of nitrones bearing easily hydrolyzed electron-withdrawing *N*-substituents are almost completely unexplored.[3] Recently, 1,2-isoxazolidines have begun to attract significant attention as nucleoside analogues[4] and synthetic transcriptase activators.[5] Exploration of the biological activity of this class of heterocycles would be facilitated by new methods to access the parent *N*-unsubstituted isoxazolidines for diversification into libraries of *N*-modified analogues. Herein, we report a novel method for Lewis acid catalyzed formation and cycloaddition of otherwise inaccessible *N*-nosyl nitrones, which produce 1,2-isoxazolidines that can be deprotected under mild conditions without accompanying ring cleavage.

Our group has been developing new synthetic methods based upon activation of oxaziridines with exogenous catalysts. We recently reported a new aminohydroxylation procedure in which *N*-sulfonyl oxaziridine **1** reacts with styrenes in the presence of $Cu(TFA)_2$ to provide 1,3-oxazolidines.[6] In an unusual example of divergent, catalyst-controlled reactivity, we have discovered that the isomeric 1,2-isoxazolidine **3** is produced when styrene reacts with **1** in the presence of $Sc(OTf)_3$ (Scheme 1). This heterocycle presumably arises from rearrangement of the oxaziridine to a transient *N*-sulfonyl nitrone (**2**) that undergoes [3 + 2] cycloaddition with styrene. While the corresponding rearrangement of *N*-alkyl oxaziridines to nitrones is precedented,[7] we are unaware of any previous studies describing the Lewis acid catalyzed rearrangement of *N*-sulfonyl oxaziridines to nitrones.[8]

Careful analysis of the $Sc(OTf)_3$-catalyzed reaction revealed that benzaldehyde oxime, *O*-sulfonyl oxime **4**, and polystyrene are significant byproducts. We speculated that these compounds could arise upon heterolytic decomposition of the *N*-sulfonyl nitrone (Scheme 1);[9] the sulfonyl cation could either recombine with the oxime anion to produce **4** or initiate the cationic polymerization of styrene. This mechanistic hypothesis suggests that the efficiency of the desired cycloaddition would be improved by decreasing the propensity of the nitrone to undergo ionic fragmentation. Indeed, optimized reaction conditions for this novel transformation utilized toluene as a nonpolar solvent, which disfavors formation of ionic intermediates, as well as oxaziridines bearing *N*-4-nitrobenzenesulfonyl groups that would further destabilize the problematic sulfonyl cation (*vide infra*).

The effect of various Lewis acids on the cycloadditions of *N*-nosyl oxaziridine **5** in toluene is summarized in Table 1. A wide range of oxophilic Lewis acids afford the desired 1,2-isoxazolidine. The diastereoselectivity of the cycloaddition shows a dependence

Scheme 1

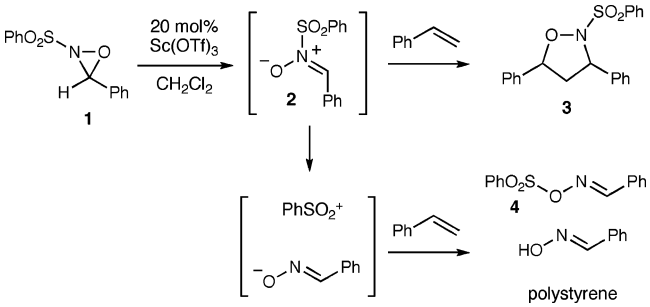
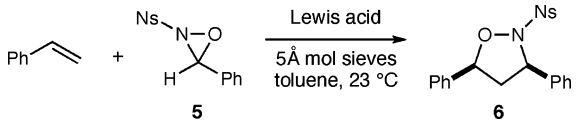


Table 1. Effect of Oxophilic Lewis Acids on the Efficiency and Diastereoselectivity of 1,2-Isoxazolidine Formation[a]



entry	catalyst	loading mol %	time h	yield[b]	d.r.[c] (*syn*/*anti*)
1	$Sc(OTf)_3$	20	6	23%	1.2:1
2	$BF_3{\cdot}OEt_2$	20	6	58%	>10:1
3	$SnCl_4$	20	6	80%	6:1
4	$TiCl_4$	20	1	93%	>10:1
5	$TiCl_4$	10	4	95%	>10:1

[a] Ns = 4-nitrobenzenesulfonyl. [b] Isolated yields. [c] Diastereomer ratio determined by ^{1}H NMR.

on the nature of the Lewis acid, which suggests that the catalyst is intimately involved in both the isomerization and cycloaddition steps. Of the catalysts screened, $TiCl_4$ provided the optimal yield and selectivity, and we found that the catalyst loading could successfully be reduced to 10 mol %.

A variety of olefins are successful dipolarophiles in this reaction (Table 2). Styrenes bearing electron-withdrawing substituents are excellent reaction partners (entries 2−4), although substrates that react slowly require stoichiometric quantities of $TiCl_4$ to proceed to completion. Conversely, electron-rich styrenes and olefins particularly prone to cationic polymerization require slow addition to achieve good yields (entries 5−9). In all reactions of simple monosubstituted alkenes investigated, the cycloaddition shows very high diastereoselectivity, affording the *cis* isomer with >10:1 selectivity. Both α- and *trans*-*β*-methylstyrene are also good substrates for this process (entries 9 and 10). Finally, while primary aliphatic olefins react sluggishly, 1,3-dienes and 1,1-disubstituted aliphatic olefins are suitable dipolarophiles for this transformation (entries 11 and 12).

The scope of this reaction with respect to the oxaziridine is somewhat more limited (Table 3). Oxaziridines bearing only aliphatic *C*-substituents do not undergo rearrangement to the nitrone, and aryl oxaziridines bearing strongly electron-donating *para* substituents are unstable and cannot be isolated.[10] Within these

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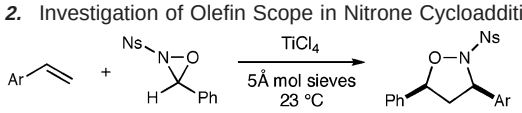
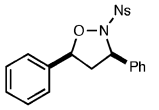
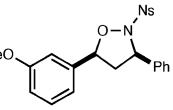
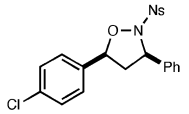
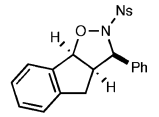
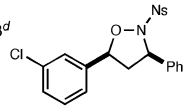
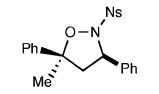
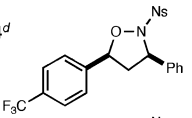
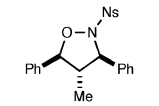
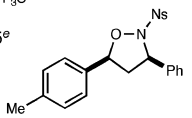
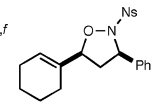
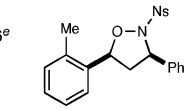
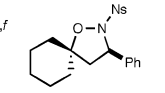
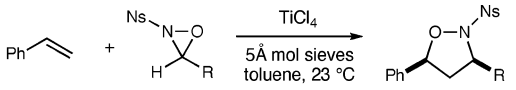
Table 2. Investigation of Olefin Scope in Nitrone Cycloadditions

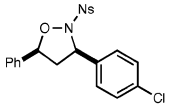
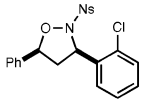
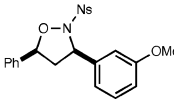
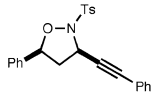


entry[a]	product	mol% $TiCl_4$ yield,[b] d.r.[c]	entry[a]	product	mol% $TiCl_4$ yield,[b] d.r.[c]
1		10 mol% 95% yield >10:1 d.r.	7[e]		10 mol% 87% yield >10:1 d.r.
2		10 mol% 87% yield >10:1 d.r.	8[e]		10 mol% 65% yield >10:1 d.r.
3[d]		100 mol% 93% yield >10:1 d.r.	9[e]		10 mol% 83% yield 3:1 d.r.
4[d]		100 mol% 69% yield >10:1 d.r.	10[d]		100 mol% 81% yield >10:1 d.r.
5[e]		10 mol% 92% yield >10:1 d.r.	11[e,f]		20 mol% 86% yield 10:1 d.r.
6[e]		10 mol% 89% yield >10:1 d.r.	12[d,f]		100 mol% 55% yield

[a] Reactions performed using 1 equiv of oxaziridine and 1.5−2 equiv of olefin in toluene unless otherwise noted. [b] Isolated yields. [c] Diastereomer ratio determined by ^{1}H NMR. [d] Reaction performed in CH_2Cl_2. [e] Alkene added by syringe pump over 2−3 h. [f] Used 3−4 equiv of alkene.

Table 3. Investigation of Oxaziridine Scope in Nitrone Cylcoadditions

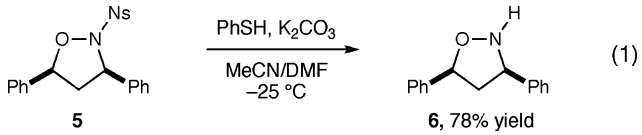


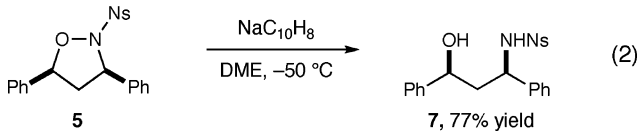
entry[a]	product	mol% $TiCl_4$ yield,[b] d.r.[c]	entry[a]	product	mol% $TiCl_4$ yield,[b] d.r.[c]
1		10 mol% 95% yield >10:1 d.r.	3		10 mol% 80% yield 10:1 d.r.
2		10 mol% 94% yield >10:1 d.r.	4		10 mol% 91% yield 5:1 d.r.

[a] Reactions performed using 1 equiv of oxaziridine and 1.5 equiv of olefin. [b] Isolated yields. [c] Diastereomer ratio determined by ^{1}H NMR.

constraints, however, electron-donating and -withdrawing substituents can be accommodated on the nitrone precursor (entries 1−3), and other oxaziridines bearing electron-stabilizing moieties such as alkynes undergo facile rearrangement and cycloaddition under our optimized conditions (entry 4).

Synthetic manipulation of the nitrone cycloadducts can be accomplished under mild conditions. Treatment of *N*-nosyl isoxazolidine **5** with thiophenol and potassium carbonate[11] reveals the *N*-unsubstituted isoxazolidine **6** in 78% yield (eq 1). Importantly, no products resulting from ring opening of the 1,2-isoxazolidine could be observed upon ^{1}H NMR analysis of the unpurified reaction mixture. In contrast, treatment of **5** using sodium napthalenide results in selective cleavage of the N−O bond of the isoxazole without reduction of the nosyl moiety (eq 2). Thus, our new method for generation and cycloaddition of *N*-sulfonyl nitrones enables access to either unprotected 1,2-isoxazolidine heterocycles or *N*-protected 1,3-aminoalcohols under orthogonal conditions.





This new method for the synthesis of *N*-nosyl 1,2-isoxazolidines involves the first Lewis acid catalyzed cycloaddition of *N*-sulfonyl nitrones. Efforts to understand the divergent reactivity of *N*-sulfonyl oxaziridines in the presence of titanium and copper catalysts and to develop enantioselective methods based upon these reactions are the focus of current investigations in our lab.

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

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