Heterocycles

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Carbonyl Imines from Oxaziridines: Generation and Cycloaddition of N–O=C Dipoles**

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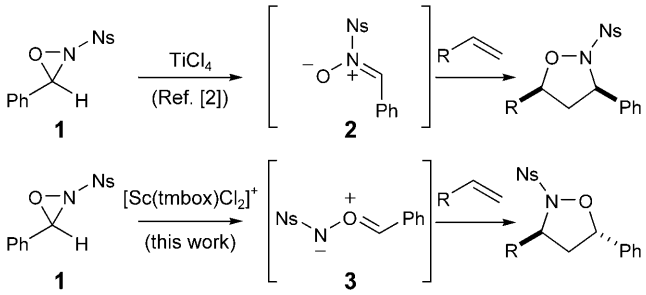
Cycloaddition reactions of nitrones,[1] azides,[2] and related 1,3-dipolar species[3] are recognized as powerful tools for the construction of compounds with great utility in organic synthesis, chemical biology, and materials science. The conceptual model that underpins our understanding of this broad class of reactions was first formalized by Huisgen in 1963.[4] This seminal contribution to organic chemistry provided chemists with a unified framework for understanding the structure and reactivity of 1,3-dipolar compounds, and also predicted the structures of several elementary 1,3-dipoles that were unknown at that time. Subsequent research has identified cycloaddition reactions of many of these predicted 1,3-dipolar species;[5] however, carbonyl imines (e.g., **3**; Scheme 1) have remained elusive since Huisgen's initial prediction. Although these unusual dipoles have been postulated to be intermediates in the photochemical decomposition of nitroarenes,[6] the synthesis of dipolar cycloaddition products of carbonyl imines has not yet been reported. Herein, we demonstrate that carbonyl imines can be efficiently generated by the Lewis acid catalyzed rearrangement of *N*-sulfonyl oxaziridines, and trapped by cycloaddition with a variety of dipolarophiles.

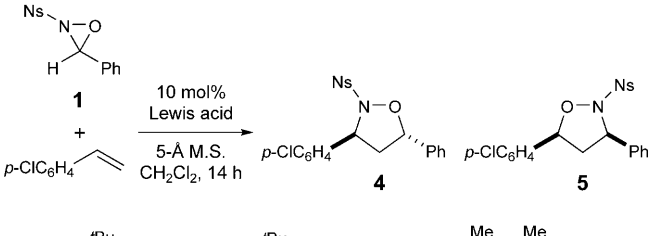


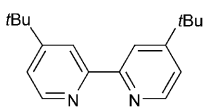
Scheme 1. Lewis acid dependent formation of nitrones or carbonyl imines from *N*-sulfonyl oxaziridines. Ns = 4-nitrobenzenesulfonyl.

We recently reported the $TiCl_4$-catalyzed rearrangement of *N*-sulfonyl oxaziridines[7] ("Davis oxaziridines", e.g. **1**) to produces a new class of electron-deficient *N*-sulfonyl nitrones **2** (Scheme 1).[8] These highly unstable nitrones can efficiently undergo in situ cycloaddition with a variety of styrenic olefins to afford 1,2-isoxazolidines with very high *cis* selectivity (**5**; Table 1, entry 1). During the course of investigating this novel reactivity, we made the surprising observation that a variety of other Lewis acid catalysts (Table 1, entries 2–5) produce a side product that we identified as the regio- and diastereomeric 1,2-isoxazolidine **4**.[9] The production of **4** suggested that the Lewis acid catalyzed rearrangement of **1** could be used to generate either *N*-sulfonyl nitrones or *N*-sulfonyl carbonyl imines, and that the partitioning between these two 1,3-dipoles could be controlled by the identity of the catalyst. Intrigued by this observation, we sought to develop conditions that would result in exclusive formation of carbonyl imine cycloadduct **4**, which would enable us to explore this reactivity in greater detail.

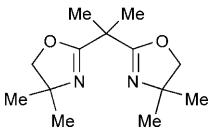
Noting that the sterically demanding lanthanide triflate Lewis acids favored formation of **4**, albeit in poor yields, we

Table 1: Lewis acid optimization for carbonyl imine cycloaddition.[a]





4,4'-*t*Bu-bipy (**6**)



tmbox (**7**)

Entry	Catalyst	*T* [°C]	Yield [%][b]	**4**/**5**[b]
1[c]	$TiCl_4$	23	69	1:>10
2	$BF_3{\cdot}OEt_2$	23	32	1:5
3	$Sc(OTf)_3$	23	65	1:2
4	$Yb(OTf)_3$	23	40	8:1
5	$La(OTf)_3$	23	26	9:1
6	$Sc(OTf)_3$·**6**	23	30	>10:1
7	$Sc(OTf)_3$·**7**	23	38	>10:1
8	$(ScCl_2)SbF_6$·**7**	23	41	>10:1
9	$(ScCl_2)SbF_6$·**7**	40	80	>10:1

[a] 10 mol% catalyst and 4 equiv oxaziridine unless otherwise noted. [b] Yields and product ratios were determined by ^1H NMR analysis using a calibrated internal standard. [c] 2 equiv oxaziridine.

Noting that the sterically demanding lanthanide triflate Lewis acids favored formation of **4**, albeit in poor yields, we

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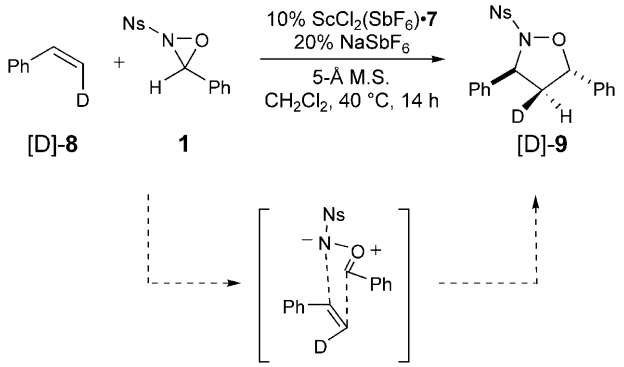
speculated that the coordination of a bulky ligand to a more reactive, but poorly selective, transition metal salt (e.g., $Sc(OTf)_3$; Table 1, entry 3) might reverse the selectivity. Indeed, coordination of either bipyridyl ligand **6** or bis(oxazoline) ligand tmbox (**7**)[10] resulted in the exclusive formation of carbonyl imine cycloadduct **4**, although the reactivity of these complexes was attenuated (Table 1, entries 6 and 7). The scandium complex, $[Sc(tmbox)Cl_2]SbF_6$, proved to be a more reactive catalyst (Table 1, entry 8),[11] and afforded good yields of the desired cycloadduct at elevated temperatures without loss of selectivity (Table 1, entry 9). These conditions for the formation of **4** were then used to further investigate this rearrangement–cycloaddition sequence.

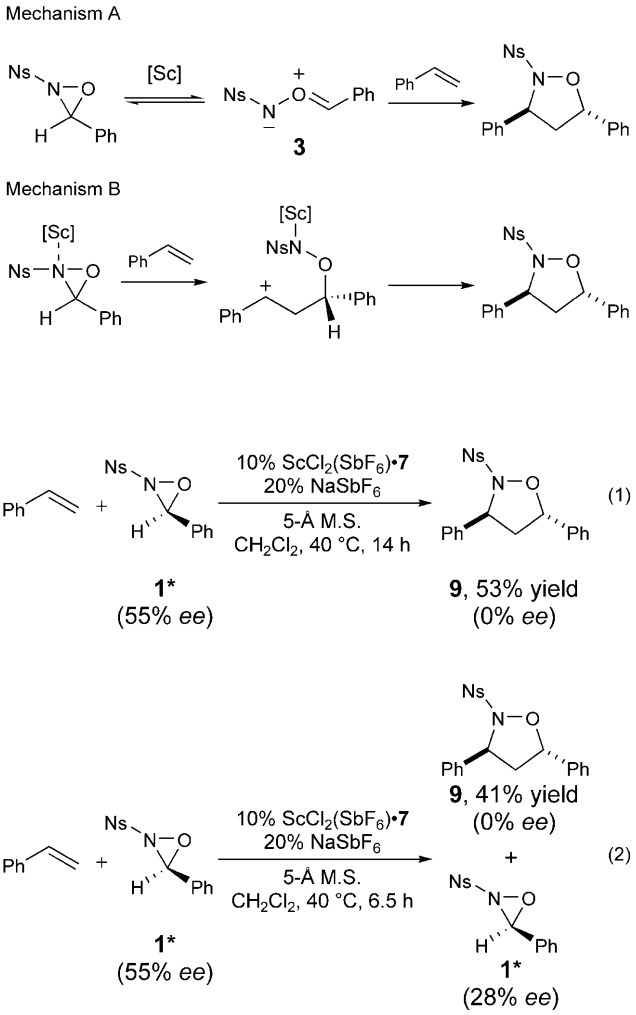
Both theoretical and experimental data support the postulated formation of carbonyl imine intermediate **3** in these reactions. The rearrangement of oxaziridines into carbonyl imines was first proposed in a series of computational studies reported by Rzepa et al.[12] Those studies characterized the oxaziridine rearrangement to carbonyl imines as a thermally allowed, conrotatory electrocyclic ring opening, and predicted that the presence of electron-withdrawing N substituents would significantly stabilize and increase the lifetime of the carbonyl imines. Given this theoretical support, we felt that the formation of *N*-nosyl carbonyl imine intermediate **3** was a reasonable explanation to account for the formation of **4**.

The intermediacy of a carbonyl imine is also supported by the stereospecificity of the cycloaddition (Scheme 2). The reaction of **1** with *cis*-β-deuterostyrene [D]-**8** (96 atom % [D])[13] afforded isoxazolidine [D]-**9** without any detectable loss of stereochemical fidelity of the deuterium label. This result is what would be expected from a stereospecific *syn* addition of a carbonyl imine with an olefin in a concerted cycloaddition process.



Scheme 2. Cycloaddition of deuterium-labeled styrene.

Finally, to distinguish between the proposed carbonyl imine mechanism (Scheme 3, Mechanism A) and an alternate mechanism involving the direct nucleophilic attack of the dipolarophile on the Lewis acid activated oxaziridine (Scheme 3, Mechanism B), we investigated the cycloaddition of enantioenriched oxaziridine **1***.[14] The cycloaddition of **1*** (55 % *ee*) with styrene afforded only the racemic cycloadduct **9** [Eq. (1)], which is consistent with reaction via an achiral

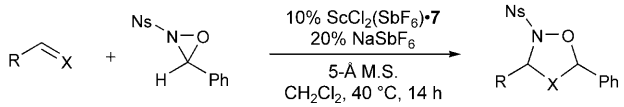


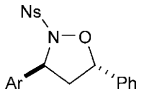
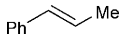
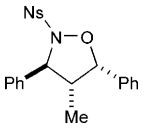
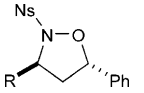
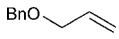
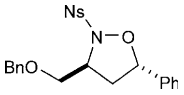
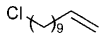
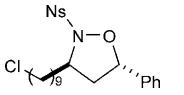
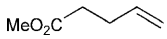
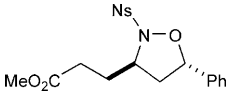
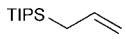
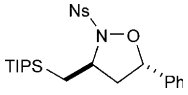
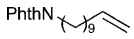
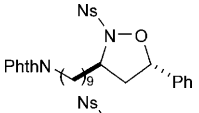
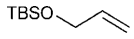
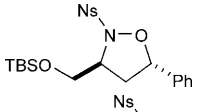
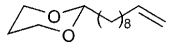
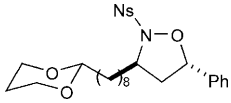
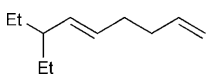
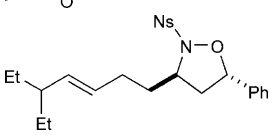
Scheme 3. Stereochemical probe in support of carbonyl imine intermediate **3** (Mechanism A) over Mechanism B.

intermediate such as **3**, and is not consistent with the stereospecific nucleophilic attack suggested by Mechanism B. We can also exclude the alternate possibility that this result arises from rapid Lewis acid catalyzed racemization of oxaziridine **1***; when the reaction is halted before completion, the remaining oxaziridine can be re-isolated in enantioenriched form, albeit with reduced *ee*, along with the racemic cycloadduct [Eq. (2)]. This result indicates that the rate of formation of racemic cycloadduct **9** is faster than the rate of racemization of **1***, which is not consistent with Mechanism B but is fully consistent with the slow, reversible Lewis acid catalyzed rearrangement of **1** to **3** followed by rapid cycloaddition with styrene, as proposed in Mechanism A.

Table 2 summarizes the range of dipolarophiles that were used to investigate the scope of the carbonyl imine cycloaddition.[15] Styrenes are very good substrates for this process, and substitution at the *para* (Table 2, entries 2–5), and *meta* (Table 2, entries 6–8) positions have little impact on the efficiency of the reaction. Conversely, large *ortho* substituents diminish the efficiency and diastereoselectivity of the reaction (Table 2, entries 9–11), and styrenes that have substituents on

Table 2: Dipolarophile scope in carbonyl imine cycloadditions.[a]



Entry	Dipolarophile	Product	Yield [%][b,d]	*trans*/*cis*[c,d]
				
1	Ar = Ph		65	>10:1
2	Ar = 4-$AcOC_6H_4$		66	>10:1
3	Ar = 4-ClC_6H_4		74	>10:1
4	Ar = 4-BrC_6H_4		69	>10:1
5	Ar = 4-$MeO_2CC_6H_4$		70	>10:1
6	Ar = 3-$MeOC_6H_4$		69	>10:1
7	Ar = 3-FC_6H_4		52	>10:1
8	Ar = 3-ClC_6H_4		55	>10:1
9	Ar = 2-ClC_6H_4		19[e]	7:1
10	Ar = 2-MeC_6H_4		56	9:1
11	Ar = 2-FC_6H_4		62	>10:1
12			26	>10:1
				
13	R = *n*Hex		78	>10:1
14	R = Bn		68	>10:1
15	R = cyclohexyl		60	>10:1
16	R = 1-adamantyl		24[e]	>10:1
17			74	>10:1
18			79	>10:1
19			78	>10:1
20			65	>10:1
21			73	>10:1
22			72	>10:1
23			79	>10:1
24			73	>10:1

the olefin do not undergo cycloaddition in synthetically useful yields (Table 2, entry 12).

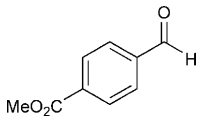
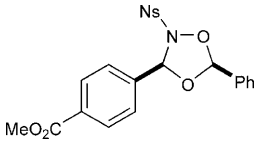
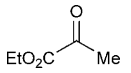
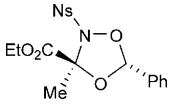
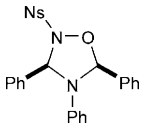
Monosubstituted aliphatic alkenes are also excellent substrates for this cycloaddition reaction. Olefins bearing both linear and branched alkyl substituents react smoothly (Table 2, entries 13–15), although tertiary alkyl substituents diminish the yield of the cycloadduct (Table 2, entry 16). A variety of functional groups are successfully tolerated, including ethers, halides, esters, silanes, and protected amines and alcohols (Table 2, entries 17–22). Notably, despite the Lewis acidity of the cationic scandium(III) complex, the reaction conditions tolerate the presence of sensitive acetal functional groups (Table 2, entry 23). We found that internal aliphatic alkenes are unreactive using this methodology; therefore, the highly chemoselective cycloaddition of terminal olefins is observed in substrates bearing multiple olefinic bonds (Table 2, entry 24).

The highest occupied molecular orbital (HOMO) and lowest energy molecular orbital (LUMO) energies of these highly electron-deficient carbonyl imines are presumably to be quite low, and are likely poorly matched to electron-deficient dipolarophiles. Indeed, fumarates, succinimides, and acrylates fail to produce the desired cycloadducts. Conversely, heteroatom-containing dipolarophiles are good substrates for cycloaddition; the reaction of aldehydes, ketones, or imines (Table 2, entries 25–27) all proceed in good yields, and with good diastereoselectivity.[16]

Although the scope of the dipolarophile is quite broad, the scope of the oxaziridine is somewhat more limited (Table 3). Oxaziridines that have aliphatic substituents at carbon do not successfully undergo this reaction (Table 3, entries 1 and 2), and the use of N-sulfonyl groups that have electron-withdrawing substituents is critical to the success of the rearrangement–cycloaddition process (Table 3, entries 3–5). This observation is fully consistent with the computation studies reported by Rzepa and co-workers,[12] which suggested that the introduction of electron-withdrawing N-substituents would significantly increase the propensity of the oxaziridine to rearrange to the isomeric carbonyl imine. A variety of C-aromatic *N*-nosyl oxaziridines are excellent carbonyl imine precursors; experiments using *para* or *meta* substituents proceeded smoothly (Table 3, entries 6–8), although diminished yields were observed using *ortho*-substituted oxaziridines (Table 3, entry 9). Electron-donating substituents increased the propensity of the oxaziridine to react; however, *N*-nosyl oxaziridines bearing even weakly electron-donating groups at the *para* position (such as methyl groups) are very unstable and can decompose violently.[17]

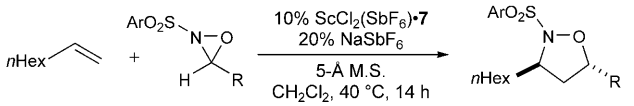
The superior reactivity of oxaziridines that have electron-deficient N-sulfonyl groups confers an

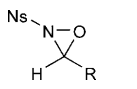
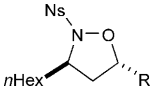
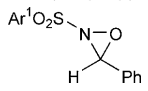
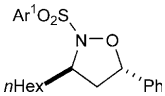
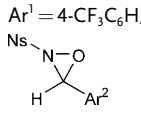
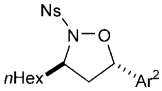
Table 2: (Continued)

Entry	Dipolarophile	Product	Yield [%][b,d]	*trans*/*cis*[c,d]
25			75	1:>10
26			85	4:1
27			89	1:>10

[a] TIPS = triisopropylsilyl; Phth = phthalimido; TBS = *tert*-butyldimethylsilyl; See the Supporting Information for experimental details. [b] Yield of isolated product unless otherwise noted. [c] Diastereomeric ratios were determined by ^{1}H NMR analysis. [d] These yields and diastereomeric ratios represent the averaged results of two experiments. [e] Yield determined by ^{1}H NMR analysis using a calibrated internal standard.

Table 3: Variation of oxaziridine structure.[a]

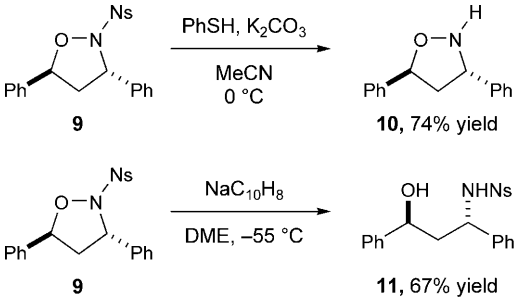


Entry	Oxaziridine	Product	Yield [%][b,d]	*trans*/*cis*[c,d]
				
1	R = *t*Bu		0	–
2	R = cyclopropyl		0	–
				
3	Ar^1 = Ph		0	–
4	Ar^1 = 4-ClC_6H_4		18	>10:1
5	Ar^1 = 4-$CF_3C_6H_4$		45	>10:1
				
6	Ar^2 = 4-FC_6H_4		83	>10:1
7	Ar^2 = 3-$MeOC_6H_4$		81	>10:1
8	Ar^2 = 3,5-$Me_2C_6H_3$		90	>10:1
9	Ar^2 = 2-ClC_6H_4		50	10:1

[a] See the Supporting Information for experimental details. [b] Yield of isolated product. [c] Diastereomeric ratios were determined by ^{1}H NMR analysis. [d] Yields and diastereomeric ratios represent the averaged results of two experiments.

additional practical benefit to this methodology (Scheme 4). The N-nosyl moiety can be removed from *trans*-1,2-isoxazolidine cycloadduct **9** using mild deprotection conditions reported by Fukuyama et al. (PhSH, K_2CO_3);[18] no unwanted cleavage of the sensitive N–O bond is observed in the reaction, and the N-unsubstituted isoxazolidine **10** is isolated in good yields [Eq. (3)]. Alternatively, the heterocycle can be ring-opened upon reduction of **9** with sodium naphthalenide to afford N-nosyl-protected *anti*-1,3-aminoalcohol **11** in high diastereomeric purity [Eq. (4)]. Importantly, the isomeric *cis*-1,2-isoxazolidines that are formed from our previously reported $TiCl_4$-catalyzed nitrone cycloadditions, are also amenable to these synthetic manipulations.[8] Therefore, using two complementary sets of conditions, the reaction of *N*-sulfonyl oxaziridines with olefins can provide access to deprotected *cis*- and *trans*-*N*-isoxazolidines and *syn* and *anti* 1,3-aminoalcohols with high levels of control over the chemoselectivity and the stereoselectivity of the two-step processes.

In conclusion, we have found that oxaziridines undergo highly stereoselective cycloaddition with a variety of dipolarophiles in the presence of a bulky scandium(III) catalyst. This reactivity suggests the formation of a carbonyl imine intermediate, and this study is the first report of cycloaddition products arising from this long-elusive class of 1,3-dipoles. As a procedure for the synthesis of structurally complex heterocycles, this transformation is a valuable complement to the TiCl-catalyzed nitrone cycloadditions previously reported by our laboratory. *Cis*- or *trans*-*N*-sulfonyl-1,2-isoxazolidines can be selectively produced from the reaction of *N*-sulfonyl oxaziridines and olefins, and the sense of diastereoselectivity can be controlled by the choice of Lewis acid catalyst utilized. An enantioselective variant of these reactions would be a powerful tool for the synthesis of complex molecules. Whilst we have not yet observed good levels of enantioinduction using a variety of chiral bis(oxazoline) ligands that are commonly used in asymmetric catalysis[19] in place of **7**, studies towards this goal are currently ongoing in our laboratory.



Scheme 4. Conversion of *N*-isoxazolidines into either deprotected *N*-isoxazolidines [Eq. (3)] or 1,3-aminoalcohols [Eq. (4)] under complementary conditions.

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