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Use of comparative triazolinium triflate fragmentation rates as a tool to assay relative competency of Brønsted bases in N→N proton transfer

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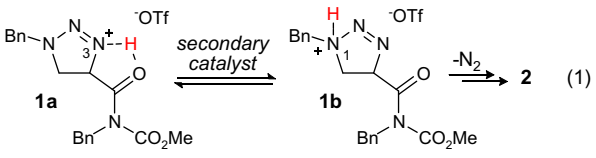
ABSTRACT

Brønsted acid-induced fragmentation of a triazoline is used as a tool to identify Brønsted base additives capable of playing the role of a proton shuttle. Relative to water, dimethyl formamide accelerates proton transfer substantially under these conditions. A series of alcohols and ethers were also used to demonstrate that the Brønsted basicity of additive functionality, not their Brønsted acidity, is responsible for their ability to accelerate proton transfer from triazoline N3 to N1. This knowledge was then used to develop a convenient two step protocol for the synthesis of oxazolidine diones from benzyl azide and an unsaturated imide that employs a substoichiometric additive for triazolinium fragmentation.

Proton transfer between *heteroatoms* is a key aspect of countless organic reactions, but is not often characterized as a slow, rate-limiting step.[1] Exceptions do exist, and acceleration of proton transfer(s) is perhaps most commonly invoked in enzymology, where a solvent-restricted cavity lined with amino acid side chains provides a unique context to study individual proton transfer steps.[2–5] Unfortunately, the complexity of this venue demands the use of specialized techniques to probe the proton transfer phenomenon.[5,6]

We recently characterized a triazolinium fragmentation[7,8] reaction in which water functions as a *secondary catalyst* to accelerate an otherwise slow proton transfer (N3 to N1) at low temperature (Eq. 1, Scheme 1).[9,10] This step can be followed using in situ IR spectroscopy to monitor the disappearance of triazolinium **1** (1711 cm^{-1}) and/or the appearance of oxazolidine dione **2** (as the salt, 1830 cm^{-1}), concomitant with the evolution of N_2. Herein we describe the use of this system as a tool to identify additional additives, both protic and aprotic, that might similarly function as proton shuttles. A number of additives, particularly those containing the amide functional group, provide a more effective agent for proton transfer to convert the intermediate triazoline to product oxazolidine dione.

Our benchmark system used either temperature (−20→25 °C) or a stoichiometric amount of water (−20 °C, isothermal) to promote the formation of oxazolidine dione **2** (as its triflic acid salt prior to reaction quench),[11] and was used here to screen additives that might provide a similar function—that of a proton transfer agent (Scheme 1, Eq. 2). For example, the polar aprotic additive dimethyl formamide (DMF) was found to accelerate triazolinium fragmentation at −20 °C, and following a low temperature quench, oxazolidine dione **2** was retrieved in 75% isolated yield (Scheme 1, Eq. 2). By analogy, this suggested that water's Brønsted basicity at oxygen might be more important than its Brønsted acidity in the proton transfer step.



additive	yield (%)	additive	yield (%)
thermal (→25 °C)	53	H_2O	87
		DMF	75

Scheme 1. Additive-accelerated fragmentation of triazolinium triflates.

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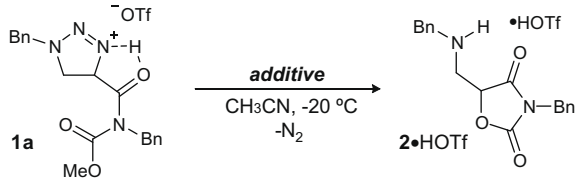
Table 1
Additive effects in the conversion of triazolinium to oxazolidine dione[a]



Entry	Additive	$t_{1/2}$[b] (min)
1	H_2O	33
2	D_2O	58
3	CH_3OH	2
4	$(CH_3CH_2)_2O$	—[c]
5	CF_3CH_2OH	—[c]
6	AcOH	—[c]
7	DMF	2
8	$CH_3C(O)NH_2$	1
9	*N*-Me-oxazolidinone	46
10	*N*-Me-imidazole	3
11	Imidazole	2
12	Pyridine	2
13	DBU	2
14	$^{i}PrNH_2$	3

[a] The intermediate triazolinium salt was prepared in situ using 200 mol % TfOH, and maintained for >20 min to establish its stability in the absence of additive. See Supplementary data for complete experimental details and data sets. Complete conversion was observed at 210–230 min for entries 1, 2 and 9, and at 5 min or less for entries 3, 7, 8 and 10–14.

[b] Times were measured from the point of addition of the additive. When conversion was observed by IR, nitrogen evolution was also noted. Entries 8, 10, 11, 13 and 14 monitored the decomposition of the triazoline using the absorption at 1711 cm^{-1}. Entries 1–3, 7, 9 and 12 monitored the growth of the oxazolidine dione absorption at 1830 cm^{-1}.

[c] Changes in the IR spectrum occurred at the addition point, but no gas (nitrogen) evolution was observed.

An attempt to more definitively identify the 'business end' of water is summarized by the experiments in Table 1 (entries 1–5), in which a series of water derivatives were evaluated by their ability to promote the conversion of **1** to **2**·**HOTf**. Under standard experimental conditions for this series,[12] our benchmark additive—water—promoted the conversion with a triazolinium half-life of 33 min, and apparent completion at 210 min (Table 1, entry 1). Deuterated water appeared to behave similarly, with a half-life of 58 min and time to completion at approximately 231 min (Table 1, entry 2). The behavior is consistent with the attenuated Brønsted basicity (and increased Brønsted acidity) of D_2O relative to H_2O.[13] By comparison, methanol promotes the proton transfer more efficiently, leading to a triazolinium half-life of 2 min, and time to completion of 4 min (Table 1, entry 3). If the oxygen bears two alkyl groups as in diethyl ether, the triazolinium stability appears unaffected (Table 1, entry 4). Similarly, trifluoroethanol failed to promote the conversion (Table 1, entry 5). Finally, acetic acid caused seemingly characteristic changes in the IR spectrum, but nitrogen evolution was not observed (Table 1, entry 6). These behaviors suggest that the Brønsted basicity of the oxygen in these additives (not their Brønsted acidity) is the most important determinant of triazolinium stability. Moreover, the Brønsted basicity can be modulated using both steric (ether) and inductive effects (trifluoroethanol, acetic acid).

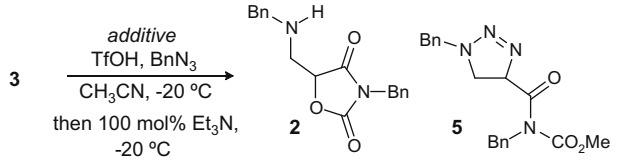
We expanded our search for effective proton transfer agents based on the observation that methanol was superior to water (cf. entries 1 and 3, Table 1), and that polar aprotic additives such as DMF did not adversely affect the overall reaction (Scheme 1, Eq. 2). Our goal here was twofold: (1) explore a greater variety of functionality, particularly nitrogen bases, that might promote the formation of oxazolidine dione, and (2) identify an additive that not only catalyzed the triazolinium conversion, but could be employed in substoichiometric amount.

This series continued with Brønsted basic oxygen donors (Table 1, entries 7–9). The immediate evolution of nitrogen, appearing as a gaseous eruption, was a characteristic of the most effective additives, and continued with other oxygen donors such as dimethyl formamide and acetamide (Table 1, entries 7 and 8). *N*-Methyl oxazolidinone, however, exhibited only moderate activity that was on par with the behavior of water (cf. entries 9 and 1, Table 1).

We next turned to Brønsted basic nitrogen donors. The behavior of all of these places them in the class of most effective additives and is again consistent with their ability to function as a proton shuttle (Table 1, entries 10–14). It is important to note that the fragmentation rate, which requires positive charge generation at N1, increases when Brønsted basic nitrogen additives are employed, despite the fact that these same additives would attenuate Brønsted acidity of the system. This knowledge can be used to effect the overall conversion of **3** to **2** in a two step procedure for substrates that require the full Brønsted acidity provided by triflic acid to promote triazoline formation; once its formation is complete, the triazoline can then be converted to oxazolidine dione in a manner that requires both Brønsted acid and a proton transfer agent at low temperature. The effectiveness of amine additives under conditions of excess Brønsted acid also suggests their role as kinetically labile ligands for the proton.[12]

As a final examination of additive performance in the outcome of these transformations, we investigated whether additive turnover is possible. We were guided by our knowledge of mechanism insofar as the penultimate intermediate in the production of **2** is oxonium **4**.[9] When water is the additive, hydrolysis of **4** occurs rapidly. We first evaluated the effect of 20 mol % DMF and found that nitrogen evolution was again vigorous, and that all triazoline had been converted to oxazolidine dione (**2**) upon inspection of the crude reaction mixture by ^1H NMR (see Supplementary data). This establishes the ability of DMF to turn over in the proton transfer step. The isolated yield, however, was only 41% (Table 2, entry 1). This could be attributed to the minimization of a means at −20 °C for **4**—a competent methylating agent—to convert to oxazolidine dione **2** through a controlled, efficient pathway; the acetonitrile solvent competitively demethylates **4**, but only at warmer

Table 2
Comparison of stoichiometric and substoichiometric additive effects in the conversion of triazolinium to oxazolidine dione[a]

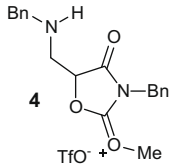


Entry	Additive	mol %	**2**:**5**[b]	Yield[b] (%)
1	DMF	20	>95:5	41
2	PhSMe	100	<5:95	—
3	PhSMe/DMF	60/20	>95:5	51
4	DMF	100	>95:5	70

[a] The additive was introduced 30 min following the combination of azide, olefin, and 100 mol % TfOH at −20 °C. Following a 6 h reaction time, Et_3N (100 mol %) was introduced, and the reaction was warmed to ambient temperature, concentrated, and analyzed by ^1H NMR prior to purification (see Supplementary data for details). Nitrogen evolution was observed at the point of additive addition for entries 1, 3, and 4 but not at reaction quench or beyond. See Supplementary data for additive drying procedures.

[b] Ratio estimated by ^1H NMR analysis of the crude reaction mixture. Yields represent isolated, analytically pure material.

temperatures.[9,14] We therefore turned to thioanisole as a methyl scavenger, one that does not itself promote triazolinium fragmentation (Table 2, entry 2). Using a combination of 60 mol% PhSMe and 20 mol% DMF, a slight improvement was observed both spectroscopically and in the isolated yield (Table 2, entry 3). When used in a stoichiometric amount, DMF may either stabilize **4** until reaction quench, or become methylated itself, leading to an improved yield of **2** (Table 2, entry 4). The ability to form reactive intermediate **4** using a substoichiometric amount of Brønsted base additive might provide the opportunity to sequence an additional intra- or intermolecular reaction in order to further increase the overall structural complexity generated during the olefin functionalization.



It is interesting to note that the behavior of these additives in bulk solvent parallels observations of the role of peptide side chain functionality performing a similar function, but in the shielded environment of a protein's active site.[1,3–5] Although the reaction and conditions here bear little resemblance to biological contexts where proton transfer is rate-limiting, some of the additives examined might be considered reasonable surrogates: acetamide∼Gln/Asn, $^{i}Pr_2NH$∼Lys, imidazole∼His, DBU∼Arg, MeOH∼Ser, and AcOH∼Asp/Glu. In contrast to studies involving enzymes, where the presence of water is inherent to the system, the triazolinium fragmentation reaction can be considered a tool to evaluate an N→N proton transfer under anhydrous conditions.

In summary, a range of Brønsted basic additives have been classified by their ability to facilitate a proton transfer leading to irreversible triazoline fragmentation. In this comparison, a variety of Brønsted basic reagents are highly effective proton transfer agents. In cases of polar protic oxygen acids, relative to water, Brønsted basicity is clearly more important than Brønsted acidity. Nitrogen Brønsted bases are highly effective promoters in general, and this behavior is revealed here despite the ability of these additives to simultaneously attenuate the Brønsted acidity important for triazoline fragmentation. The use of additives to manipulate triazoline intermediates for synthetic advantage will be the subject of future reports.

Acknowledgments

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Supplementary data

Supplementary data (general experimental details and IR reaction plots for all additive experiments) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.07.067.

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12. The experimental protocol for Table 1 employed 200 mol % TfOH (instead of 100 mol %), as we have previously demonstrated that this merely slows the fragmentation to a measurable level, but does not otherwise affect reaction outcome. See Ref. 9 for details.
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