# The Brønsted Acid-Catalyzed Direct Aza-Darzens Synthesis of *N*-Alkyl *cis*-Aziridines

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The proton is arguably the most abundant and least expensive of the Lewis acids.[1] Brønsted acids are also readily removed from an organic reaction—an attractive feature with substantial strategic and practical implications. We turned to Brønsted acid catalysis to extend the scope of Lewis acid-catalyzed aza-Darzens reactions[2,3] and facilitate construction of the more Lewis basic and functionally diverse *N*-alkyl aziridines (eq 1).[4] This objective requires not only

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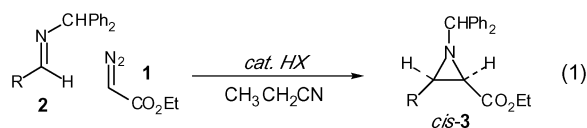
a latent enolate that resists direct protonation,[5] but also generation of a stoichiometric base product in the presence of a catalytic amount of Brønsted acid. Whereas electronic (orbital)[6] and steric effects[7] are exerted through the ligands of conventional Lewis acids to influence turnover and their direct reaction[8] with latent enolates, a proton would appear to lack these strategic elements.[9] We report here the first examples of the use of diazo compounds in carbon–carbon bond-forming reactions with a Schiff base and *Brønsted acid* (the aza-Darzens reaction) (eq 1).[10,11] The protocol is catalytic in protic acid despite the basic nature of the *N*-alkylamine products. Moreover, the alkylation (eq 2) and homocoupling (eq 3) reaction pathways expected upon treatment of a diazo compound with Brønsted acid are slow relative to aziridine ring formation.[12]

$$(2)$$

$$(3)$$
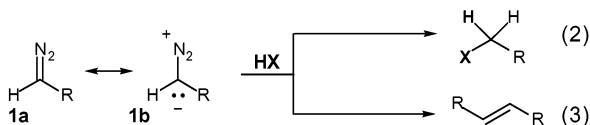
The screening of various Brønsted acids with Schiff base **2a**[13] revealed both improved generality and rate acceleration versus the thermal addition[14] (Table 1). In all of these experiments, no evidence of triazoline formation was observed spectroscopically. The background reaction and an attempt to promote the reaction with acetic acid produced trace amounts of aziridine (Table 1, entries 1−2), whereas trifluoroacetic acid effectively promoted formation of the aziridine product in 63% yield as a single diastereomer. Importantly, nearly equimolar amounts (1:1.2) of Schiff base **2** and ethyl diazoacetate (**1**) are employed in all reactions described. Brønsted acids with decreasing pK_a provided decreasing reaction times (Table 1, entries 4−6). Triflic acid was found to be both particularly convenient (distillable liquid) and effective (complete conversion at −78 °C after 5 h) (Table 1, entry 6).[15] A solvent screen revealed that less polar solvents (toluene, dichloromethane) exhibited diminished overall reaction rates but otherwise indistinguishable reaction characteristics (yield, turnover, diastereoselectivity).

Both Lewis acid and late transition metal catalysis of alkyl diazo additions to azomethines often produce several enamide products

Table 1. Protic Acid-Catalyzed Aza-Darzens Reaction[a]

entry	acid	T(°C)	*t*(h)[b]	yield (%)[c]
1	none	25	24	<5
2	CH₃CO₂H	25	24	<5
3	CF₃CO₂H	25	18	63
4	CSA	25	18	74
5	HCl	0	2.5	58
6	TfOH	−78	5	67

[a] All reactions were equimolar in Schiff base and ethyl diazoacetate, and proceeded to completion. All entries exhibited >95:5 *cis:trans* aziridine **4a**. See Supporting Information for complete experimental details. [b] Approximate time to completion except for entries 1−2. [c] Isolated yield after chromatography.

**Table 2.** Protic Acid-Catalyzed Aza-Darzens Reaction (eq 4)[a]

$$(4)$$

entry	R		T (°C)	*cis:trans*[d]	yield (%)[e]
1	MeO₂C	a	-78	>95:5	86
2	*t*BuO₂C	b	-78	>95:5	89
3[b]	*t*BuO₂C	b	-78	>95:5	75
4[c]	*t*BuO₂C	b	25	>95:5	62
5	Cy	c	25	80:20	42
6	*t*Bu	d	25	60:40	45
7	Ph	e	0	82:18	42
8	2-py	f	-78	90:10	73
9	(cyclopropyl)	g	25	82:18	40
10	EtO₂C—	h	-78	>95:5	53

[a] All reactions were 0.3 M in substrate. [b] Five-gram scale reaction using 7 mol % TfOH; isolated yield after recrystallization from diethyl ether. [c] Solvent used: 1:1 THF:H₂O. [d] Measured by ¹H NMR (400 MHz). [e] Isolated yield after chromatography.
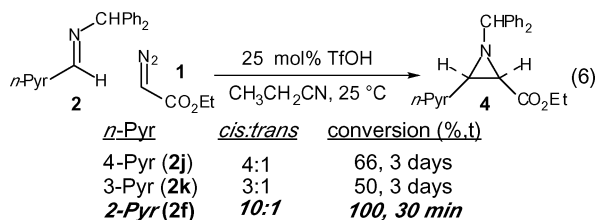
in addition to the desired aziridine, yet these studies have almost entirely focused on simple aliphatic and substituted benzaldimines.[16] Our initial examination of the substrate generality revealed those factors important for selective aziridine formation, a high level of *cis*-diastereoselectivity, and efficient turnover (Table 2). Additions to α-imino glyoxalates provide the differentiated *cis*-aziridino succinate derivatives in analytically pure form after straightforward neutralization. Catalyst loading at 7 mol % on 5-g scale provided

4b as a single diastereomer in 75% yield after recrystallization from ether. This transformation was also efficient when the propionitrile solvent was substituted with 1:1 H$_2$O:THF (Table 2, entry 4).[2b]

Aldimines derived from simple aliphatic aldehydes provided low isolated yields (41−45%, Table 2, entries 5−6) of the *cis*-aziridine. These substrates produced substantial amounts of the *trans*-diastereomer but posed a greater problem insofar as the derived enamides constituted the mass balance. Hypothesizing that an electronic difference was responsible for the success of imino glyoxalate substrates, we examined increasingly electron-deficient aldimines that also contained functionality useful for subsequent reactions. Cyclopropyl aldimine **2g** gave slight, but noticeable, improvement of selectivity. Benzaldehyde imine was comparably selective, but notably more reactive by proceeding to completion at 0 °C (Table 2, entry 7). A dramatic improvement came by employing pyridine 2-carbaldehyde imine (Table 2, entry 8), which provided the desired *cis*-aziridine **4f** (90:10 ds) in 73% isolated yield. Moreover, α,β-unsaturated aldimine **2h** (Table 2, entry 10) furnished aziridine *cis*-**4h** in >95:5 ds and 53% isolated yield.[17] Finally, the isolation of a single diastereomer in 83% yield from the glyceraldehyde-derived aldimine **2i** (eq 5) both supported our hypothesis regarding the need for an electron-deficient alkyl aldimine and demonstrated the stereochemical complexity that can be generated in a single step using this mild protocol. In an otherwise identical experiment, BF$_3$·OEt$_2$ provided only 30% conversion of **2i** to *cis*-**4i**.

$$\text{(5)}$$
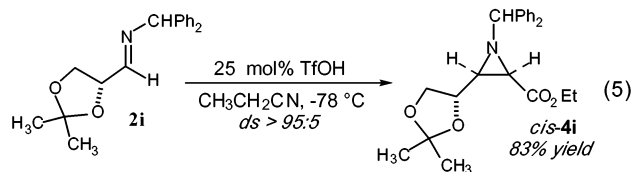
Although the Lewis basicity of the *N*-alkyl aziridine nitrogen is attenuated relative to the prototypical tertiary trialkylamine, the efficient turnover observed here was unexpected. The differential behavior of pyridine carboxaldehyde derivatives (eq 6) illustrates this point. Whereas the 2-substituted derivative **2f** proceeds to

$$\text{(6)}$$

n-Pyr	*cis:trans*	conversion (%,t)
4-Pyr (**2j**)	4:1	66, 3 days
3-Pyr (**2k**)	3:1	50, 3 days
2-Pyr (**2f**)	*10:1*	*100, 30 min*

completion in 30 min, the 3- and 4-substituted variants (**2j**−**k**) are at 50 and 66% conversion, respectively, after 3 days. The absence of diethyl fumarate formation in all of these experiments, the greater *cis*-selectivity for electron-deficient aldimines, and the more rapid overall reaction rates characteristic of bidentate aldimines, when considered collectively, suggest that chelation may be an important design principle for Brønsted acid-catalyzed processes.

In summary, we have developed a Brønsted acid-catalyzed amine synthesis that is unusually mild, extends the scope of Lewis acid-catalyzed [2 + 1] annulations, and demonstrates for the first time that a diazo compound can be used as an acetate enolate synthon

without decomposition during a Brønsted acid-catalyzed carbon−carbon bond-forming reaction (eq 1 vs eqs 2−3). Significantly, no products resulting from acid-promoted aziridine ring-opening were observed in any instance. The method is competitive with its metal and Lewis acid-catalyzed counterparts by measures of selectivity and turnover yet is considerably more economical and environmentally benign.[18] Extension of the approach to other ylides that might be similarly activated is currently underway.[19]

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

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(14) The failure of ethyl diazoacetate to react directly with imines more electron deficient than **2** has been noted by others: Aggarwal, V. K.; Alonso, E.; Ferrara, M.; Spey, S. E. *J. Org. Chem.* **2002**, *67*, 2335.

(15) The low boiling point of **1** notwithstanding, 50% conversion to diethylfumarate (TfOH) was observed in CDCl$_3$ after 5 min at 25 °C (in NMR tube), whereas 30% conversion was observed after 1 h in CH$_3$CH$_2$CN at −78 °C.

(16) Enamides of the type R(NRH)C=CHCO$_2$Et and H(NHR)C=CPhCO$_2$Et (both olefin isomers) are most common. See ref 2 for additional details.

(17) The depressed yield is due to noticeable decomposition of aziridine **4h** during purification.

(18) For a special issue of reviews on "Green Chemistry", see: *Chem. Rev.* **2002**, *102*. For efforts toward "green" aziridinations: Kubo, T.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **2000**, 625.

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