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Amphoteric Amino Aldehydes Reroute the Aza-Michael Reaction

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A kinetically stable molecule containing both nucleophilic and electrophilic nodes constitutes an amphoteric entity.[1] Such molecules are of significant interest, as their participation in both reversible and irreversible polar reactions can offer a wide palette of bond-forming options. While the opposing nucleophilic and electrophilic centers render such molecules capable of forging multiple bonds in a single transformation, it is the orthogonality between these centers that ensures high chemoselectivity.[2] Although a limited number of amphoteric molecules are known, their synthetic value is substantial, most notably because of their participation in multicomponent and domino processes.[3] Two of the widely used multicomponent processes, the Passerini and Ugi reactions, hinge upon the isocyanide functional group. Isocyanides can be viewed as (1,1) amphoteric molecules because the same atom (the α-carbon) establishes a connection with *both* the nucleophile (carboxylic acid) and electrophile (aldehyde or imine). Our continuing efforts to expand the scope of synthetically useful amphoteric molecules have led us to examine systems in which the electrophilic and nucleophilic nodes of reactivity are separated by one or more atoms. Of particular interest are (1,3) systems, exemplified by the unprotected α-amino aldehydes in which NH aziridine, a well-established precursor to complex amines, plays an integral role.[4] When employed as electrophiles in the Pictet−Spengler process, amphoteric aziridine aldehydes have enabled nucleophilic interception of the electrophilic iminium ion intermediate. As a result, a novel reaction pathway has been established.[4a] A notable feature characterizing this domino process is the initiation step, which is triggered by nucleophilic attack at the aldehyde center. This *nucleophile-initiated process* represents only half of the reaction dichotomy characterizing amphoteric molecules. The reactivity profile can be reduced into two canonical representations: a nucleophile-initiated mechanism and an electrophile-initiated mechanism (Figure 1).

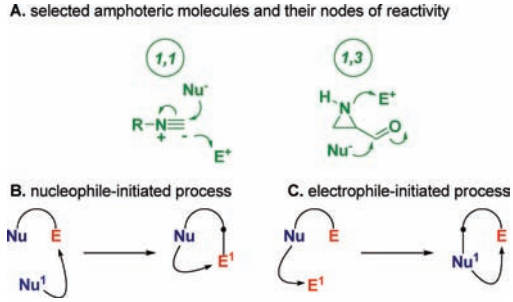
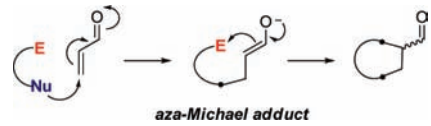


Figure 1. Amphoteric molecules and their reactivity profiles.

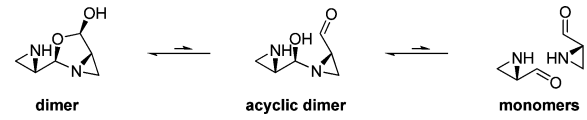
We sought to determine the feasibility of an electrophile-initiated domino process. Our initial efforts focused on investigating reactions between amphoteric amino aldehydes and Michael acceptors (Scheme 1).

Scheme 1. General Scheme for a Domino Aza-Michael/Aldol Reaction



While the general pathway of a domino hetero-Michael/aldol process has been demonstrated elsewhere,[5] we recognized that our system presented some notable differences. Particularly important is the fact that amphoteric amino aldehydes exist as stable dimers, with the equilibrium strongly favoring the dimeric species in a variety of solvents (Scheme 2). We recently established that collapse of the hemiacetal of the dimer to yield the acyclic dimer is kinetically slow.[6] It was important to determine whether similar rate-limiting kinetics might be operative during an aza-Michael/aldol reaction.

Scheme 2. Amphoteric Amino Aldehydes: Dimer/Monomer Equilibrium



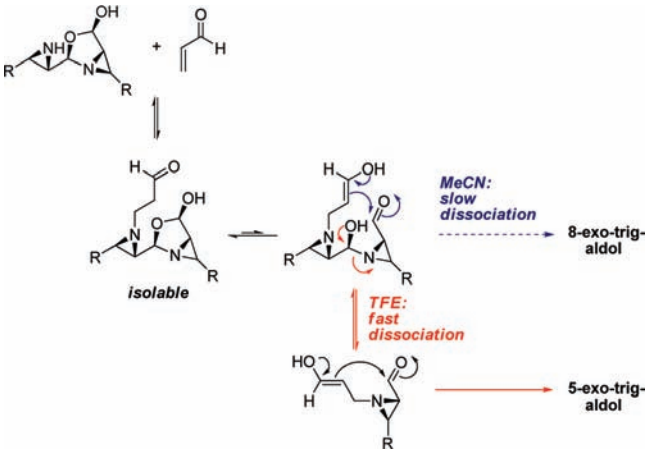
When **2a** was reacted with methyl acrylate in acetonitrile at 40 °C, only the rather uninteresting aza-Michael adduct containing the *undissociated dimer* was isolated (Scheme 3, R = *i*-Bu). This apparent lack of monomeric aldehyde reactivity contrasts that observed during thio- or oxa-Michael/aldol reactions involving thio or hydroxyl ketones, which also exist in dimeric form.[5b] As opposed to the sluggish kinetics governing the dissociation of α-amino aldehyde dimers, the α-thio ketone dimers readily dissociate, conferring favorable kinetics onto thio-Michael/aldol domino reactions.

We hypothesized that this difference in dissociation kinetics might provide an opportunity to establish a previously inaccessible pathway in domino aza-Michael/aldol reactions. While fast dimer dissociation would produce an intermediate capable of undergoing a conventional 5-(enolendo)-exo-trig cyclization,[7] slow dimer dissociation might present the possibility of an 8-(enolendo)-exo-trig pathway, whereby aldol addition occurs prior to dimer dissociation (Scheme 3).

To increase the chemoselectivity of the aldolization step, we focused on reaction conditions that *increase* the rate of the aldol cyclization while *decreasing* the rate of dimer dissociation. Since dimer dissociation is slow in polar aprotic solvents, we chose to react aziridine aldehyde dimer **1a** with cinnamaldehyde **2a** in acetonitrile using a secondary amine[8]/Brønsted acid catalyst combination (Table 1). Gratifyingly, aminohydroxyaldehyde **3a** was

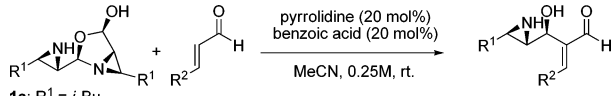
10.1021/ja9072194 CCC: $40.75

Scheme 3. Influence of Dimer Dissociation Kinetics on Reaction Outcome



isolated in >20:1 diastereoselectivity and 89% yield. No byproducts from the 5-(enolendo)-exo-trig cyclization pathway were observed.

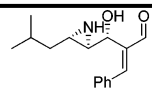
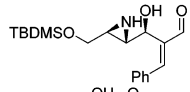
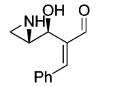
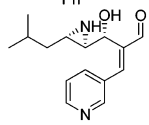
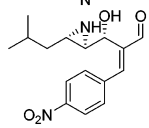
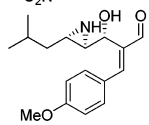
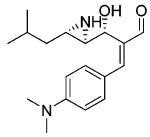
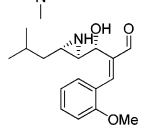
Table 1. Scope of the Aza-Michael/Aldol Reaction[a]



1a: R^1 = *i*-Bu
1b: R^1 = H
1c: R^1 = $CH_2OTBDMS$

2

3a-h

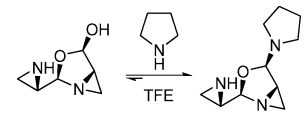
Entry	R^1	R^2	Product[b]	Time	Yield[c]
1	1a	Ph		5h	89% dr>20:1
2	1e	Ph		5h	90% dr>20:1
3	1b	Ph		4h	86% dr>20:1
4	1a	*m*-pyr		8h	86% dr>20:1
5	1a	*p*-NO_2-Ph		6h	81% dr>20:1
6	1a	*p*-MeO-Ph		15h	85% dr>20:1
7	1a	*p*-Me_2N-Ph		48h	80% dr>20:1
8[d]	1a	*o*-MeO-Ph		12h	87%(3:1) dr>20:1

[a] Reaction conditions: 0.2 mmol of **1a**−**c**, 0.4 mmol of **2**, 20 mol % pyrrolidine/benzoic acid, 0.25 M in MeCN, room temperature. [b] Product identities were determined using 1D and 2D ^{1}H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry (HRMS). [c] dr was determined by crude ^{1}H NMR analysis; % yield is of purified product. [d] *E/Z* ratio was determined by crude ^{1}H NMR analysis.

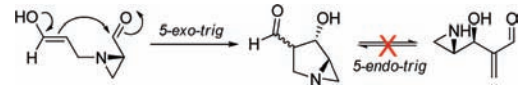
Benzoic acid was necessary to promote the reaction; its absence resulted in less than 30% conversion over a 48 h period. Stronger acids such as HCl and trifluoroacetic acid resulted in decreased yields and byproduct formation, while reactions catalyzed by acetic acid were sluggish. The substrate scope of substituted cinnamaldehydes **2** shows that the reaction tolerates both electron-donating and electron-withdrawing substituents on the aromatic ring, with all cases delivering high yields and diastereoselectivities (Table 1). Substrates containing electron-donating groups required longer reaction times, whereas those with electron-withdrawing substituents were found to react with efficiencies comparable to that of cinnamaldehyde.

A solvent screen established acetonitrile as the most effective medium. Other aprotic solvents delivered reduced yields and longer reaction times, while protic solvents such as trifluoroethanol (TFE) resulted in quantitative recovery of the starting material. Interestingly, our earlier studies identified TFE as the only medium in which appreciable levels of monomeric amino aldehyde were formed. One could expect the 5-(enolexo)-trig aldol pathway to operate on the monomeric species (Scheme 3). However, the only reaction seen in TFE was that between pyrrolidine and amino aldehyde dimer **1** (Scheme 4), with no evidence for the 5-(enolexo)-trig pathway. The 5-(enolexo)-trig pathway is also not likely to be responsible for product formation in MeCN, as the product would have had to be formed through collapse of the bicyclic aziridine intermediate (Scheme 5). As 5-endo-trig addition of the aziridine to the α,β-unsaturated system in **3** is unlikely because of orthogonal orbital geometries, so too is the microscopic reverse of the process, rendering the 5-exo-trig pathway highly improbable. It therefore appears that the monomeric aziridine aldehyde is not the reactive aza-Michael donor.

Scheme 4. Catalyst Consumption through Hemiaminal Ether Formation

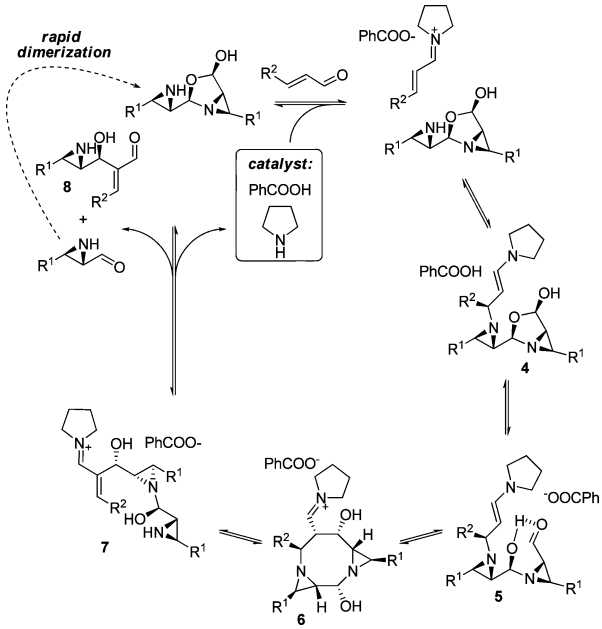


Scheme 5. The 5-Exo-Trig Pathway Is Inoperative



In contrast to TFE, aprotic solvents such as MeCN disfavor dimer dissociation but preclude the sequestration of pyrrolidine, thus creating a possibility to control the aziridine aldehyde equilibrium. We believe that this is precisely what is behind the observed reaction outcome. Importantly, in situ analysis of the reaction mixture using electrospray ionization mass spectrometry showed the production of an adduct between **2a** and aldehyde *prior* to product formation, suggesting that aza-Michael addition of the dimer to the α,β-unsaturated aldehyde occurs before dimer dissociation. This observation supports a reaction pathway operating through the mechanism defined in Scheme 6. Upon iminium activation, aza-Michael addition of the dimer to the α,β-unsaturated aldehyde affords aza-Michael adduct **4**, which, following hemiacetal collapse, undergoes an intramolecular 8-(enolendo)-exo-trig aldolization to afford intermediate **6**. Transformation of **6** into **7** is expected to be straightforward, driven by the excellent leaving-group ability of protonated aziridine (pK_{aH} = 8.0 in water). Hydrolysis of the enamine and elimination of monomeric aziridine aldehyde gives the product aminohydroxyaldehyde **8**. The monomeric amino

Scheme 6. Proposed Mechanism for the Aza-Michael/8-Exo-Trig Aldol Reaction



aldehyde rapidly redimerizes and re-enters the reaction, which is why the reaction stoichiometry is 1:1.[9a]

The high diastereoselectivity of this process is likely a result of the rigid stereochemical environment assumed by the dimeric intermediate **5** (Scheme 6).[9b] To better understand the origin of the selectivity for the intramolecular aldol addition, an ab initio computation at the Hartree−Fock level of theory was used to locate the transition state for the process (Figure 2). The transition state exhibits an intramolecular hydrogen bond between the aldehyde oxygen and the hemiaminal hydrogen, which governs the facial selectivity for enamine attack on the aldehyde. This transition state assembly correctly predicts the observed diastereoselectivity.

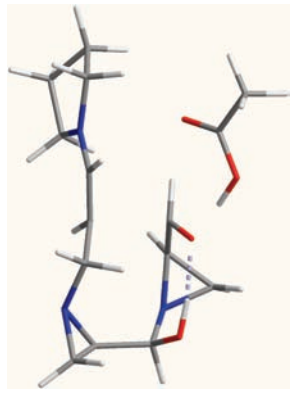


Figure 2. Intramolecular aldolization of **5**. The calculated transition state exhibits an aldehyde/hemiaminal hydrogen bond (for simplicity, acetic acid was modeled in place of benzoic acid).

In conclusion, the reactivity profile of amphoteric amino aldehydes now includes electrophile-initiated domino processes. This mode of reactivity was demonstrated through a novel aza-Michael/aldol pathway, which furnished aminohydroxy α,β-unsaturated aldehydes in high yields and with excellent diastereocontrol. These products cannot be easily accessed by the conventional Baylis−Hillman reaction because of the substitution pattern of the olefin. We also note that the products contain unprotected amine functionality. The overall reaction efficiency has been attributed to solvent-dependent control over the dissociation kinetics of aziridine aldehyde dimers. Disfavoring dimer dissociation directs the aza-Michael/aldol domino process toward a novel 8-(enolendo)-exo-trig cyclization. The products of this reaction are significant in that they extend the orthogonal amine/aldehyde relationship to (1,5) systems. As opposed to the (1,3) systems, the (1,5) variants are not dimeric, but one can anticipate their participation in a range of nucleophile- and electrophile-initated processes, delivering useful templates for complex amine synthesis via aziridine ring opening. As reversible dimerization is a salient feature of aziridine aldehydes, our study should facilitate investigations aimed at probing the reaction dichotomy of amphoteric molecules and synthesis of complex chiral amines.

Acknowledgment. We thank NSERC for financial support.

Supporting Information Available: Experimental procedures and chemical characterizations of compounds **3a**−**j** (^{1}H and ^{13}C NMR and HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) For instance, the rate-limiting step of reductive conjugation (ref 4b) occurs prior to hydride delivery.
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(9) (a) Rapid re-dimerization is one of the salient features of monomeric aziridine aldehydes (see refs 4a−c). (b) Partial dimer dissociation was previously implicated in indium-promoted allylation reactions (see ref 4b for details).

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