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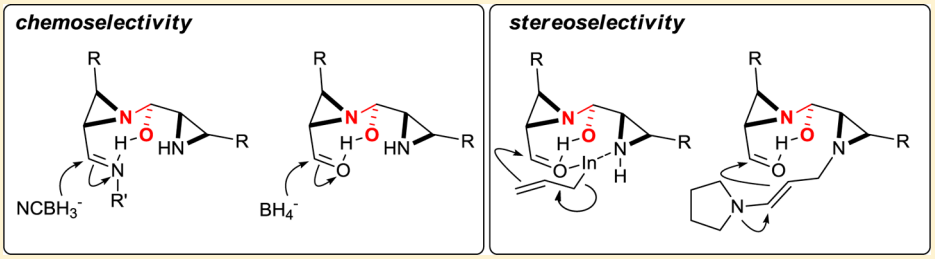
Role of Reversible Dimerization in Reactions of Amphoteric Aziridine Aldehydes

Naila Assem, Ryan Hili, Zhi He, Takahito Kasahara, Brittany L. Inman, Shannon Decker, and Andrei K. Yudin*

Davenport Research Laboratories, Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario, Canada M5S 3H6

Supporting Information



ABSTRACT: Unprotected aziridine aldehydes belong to the amphoteric class of molecules by virtue of their dual nucleophilicity/electrophilicity. The dimeric nature of these molecules, brought together by a weak and reversible aminal "connection", was found to be an important element of reactivity control. We present evidence that reversible dimer dissociation is instrumental in aziridine aldehyde transformations. We anticipate further developments that will unveil other synthetic consequences of remote control of selectivity through forging reversible covalent interactions.

INTRODUCTION

The challenges of chemo- and stereoselectivity continue to stimulate the development of new strategies for chemical synthesis.[1] Catalysts and reagents that are being designed to meet the stringent demands of modern synthesis are subject to continuous scrutiny. The value of a new chemo- and/or stereoselective process depends on many factors that range from operational simplicity to the amount of waste generated. The mode in which substrate activation is achieved by a given reagent or catalyst relies on an interplay of both covalent and noncovalent interactions. Our inroads in the area of chemoselective transformations have led us to view functional group interrelationships as the overarching theme of our research. We have been particularly intrigued by the possibility of accessing amphoteric molecules that incorporate an amine and an aldehyde in their structures. Typically, an amine and an aldehyde cannot coexist for a prolonged period of time without undergoing inter- or intramolecular condensation or decomposition. Glycinal, the simplest α-amino aldehyde, was first synthesized by Fischer but was only characterized through degradation studies (Figure 1).[2] Fischer did succeed in the synthesis of D-glucosamine, a δ-amino aldehyde.[3] In this case, the aldehyde functionality was autoprotected through hemiacetal formation; however, the ring−chain equilibrium that unveiled the aldehyde group of glucosamine made it vulnerable to self-condensation. In their seminal work, Myers *et al.* used autoprotection of the aldehyde functionality in α-amino aldehydes by trifluoroacetic acid (TFA) in methanol. The resulting amphoteric molecules were found to be susceptible to self-condensation above pH 5.[4] Maruoka's studies suggest that self-condensation of amino aldehydes can be suppressed but only if the α-carbon is quaternary.[5] These notable examples aside, amino aldehydes have been mainly employed in their *N*- or *C*-protected forms.[6] Despite the effectiveness of protecting groups, α-amino aldehydes are still regarded as relatively unstable both chemically and configurationally.[7−12]

In 2006, we disclosed a new family of molecules that contain a counterintuitive combination of an aldehyde and an unprotected secondary amine in the form of an NH aziridine.[13] These NH aziridine aldehydes exist as homochiral dimers that belong to the amphoteric class of molecules by virtue of their dual nucleophilicity/electrophilicity.[14] Driven by the utility of aziridines in complex amine synthesis, we have pursued a range of applications involving these building blocks[15−21] and searched for other molecules that belong to the exciting class of kinetically amphoteric molecules.[22,23]

Aziridine aldehyde dimers can be prepared from readily accessible starting materials. The most common routes employ inexpensive chiral pool inputs (Scheme 1). The aziridine ring closure is most commonly accomplished by intramolecular S_N2 chemistry, whereas the aldehyde functionality is typically derived from ester reduction using diisobutyl aluminum hydride (DIBAL-H).[24] The ester is either attached to the corresponding aziridine carbon at the very beginning of the synthesis or is

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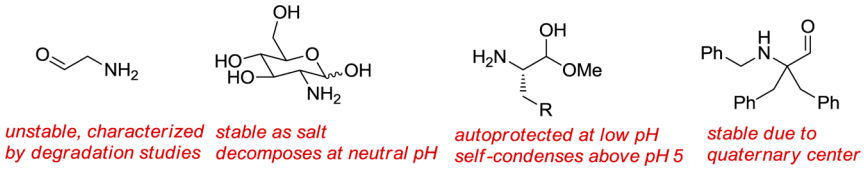
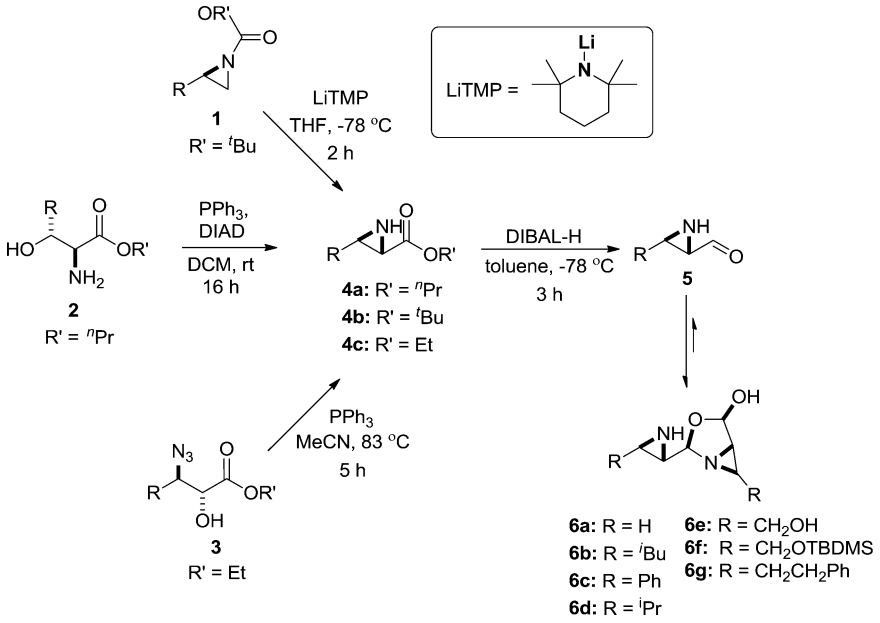


Figure 1. Selected examples of unprotected amino aldehydes.

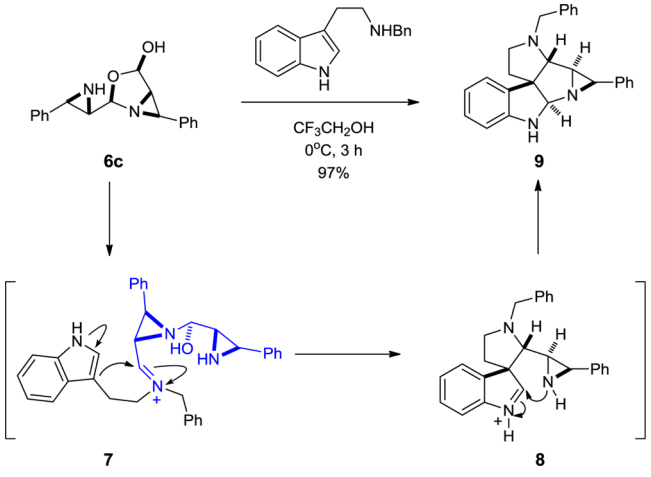
Scheme 1. Three Synthetic Routes toward Dimeric Aziridine Aldehydes



transferred from nitrogen to carbon using the lithiation protocol developed by Hodgson.[25]

From the outset, we became aware of the synthetic potential of aziridine aldehyde dimers. In one of the first applications reported by our lab, *N*-benzyltryptamine was transformed into a complex pentacyclic alkaloid core **9** through a cascade transformation upon exposure to 2-phenylaziridine aldehyde dimer **6c** in trifluoroethanol (TFE) (Scheme 2).[13] The structure of the product implied that a disrupted Pictet–Spengler reaction took place. During this process, the aziridine nucleophile had attacked the intermediate iminium ion **8** before the Wagner–Meerwein shift occurred. This outcome suggested

Scheme 2. Disrupted Pictet–Spengler Reaction Using 6c



to us that other reactions in which cationic intermediates are generated by way of condensation with the aldehyde group could provide attractive design opportunities. Recently, we succeeded in diverting the Ugi four-component condensation from its normal linear outcome to a cyclic product.[16] The dimeric aziridine aldehydes were also found to alter the course of the aza-Michael aldol process.[17] Instead of the expected cyclic product **14**, aldehyde **12** was produced in the reaction between an aziridine aldehyde and an α,β-unsaturated aldehyde in the presence of pyrrolidine and benzoic acid (Scheme 3).

The rerouted aza-Michael reaction was a pivotal point in suggesting a possible involvement of a dimeric aziridine aldehyde species in the mechanism.[17] Upon careful examination, we deduced that the reaction product must have originated from a sequence in which the dimeric nature of the starting material was preserved throughout the transformation (Scheme 3). At that point, we started to suspect that dimer-based reactivity may be the *modus operandi* in the majority of aziridine aldehyde transformations, signaling a distinct aldehyde activation modality. In this paper, we explore the relevance of open-dimer intermediates **15** to aziridine aldehyde reactivity (Scheme 4). The open-dimer intermediates are assembled through reversible covalent bonds: the aminal carbon and the NH aziridine of the open dimer are the main control elements that influence both chemo- and stereoselectivity of downstream transformations. We postulate that the unprotected aziridine[26] and the nearby hydroxyl group lead to the emergence of stabilizing interactions in the vicinity of the aldehyde carbonyl group. Our study should encourage the search for other systems that derive selectivity from an interplay of reversible covalent interactions.[27−30] With the growing list of

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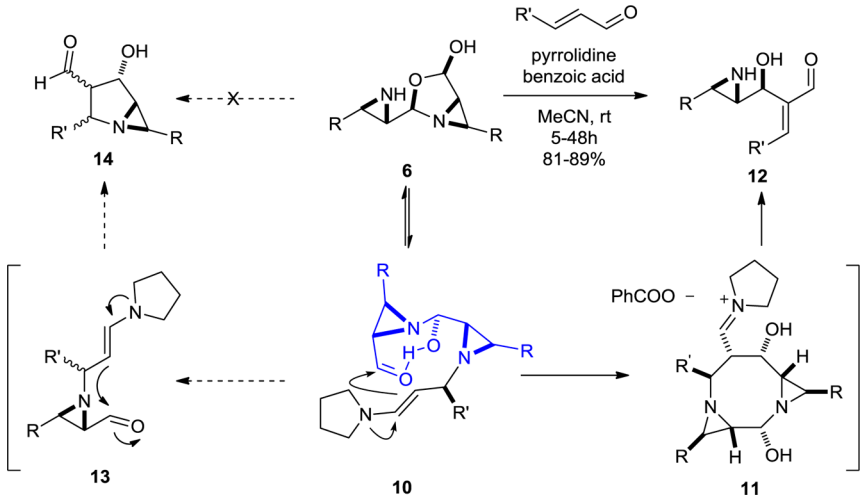
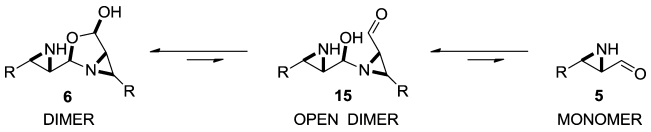
Scheme 3. Disrupted Aza-Michael Aldol Reaction with Dimeric Aziridine Aldehydes



Scheme 4. Aziridine Aldehyde Dimer/Monomer Equilibrium



amphoteric molecules,[22] the prospects of finding new reactivity trends are encouraging.

RESULTS

Properties of Unprotected Aziridine Aldehydes. Our study commenced by addressing the fundamental question of the possible coexistence between a secondary amine and an aldehyde in the same molecule. We turned to NH aziridines as iminium ion precursors and hypothesized that a thermodynamic driving force to undergo amine/aldehyde condensation could be offset by a high kinetic barrier imposed on this process by the aziridine ring strain. Although there have been observations to suggest that intermolecular imine formation is possible between NH aziridines and aldehydes,[31] its barrier was projected to be higher than that of a regular secondary amine-derived ion. This kinetic barrier appeared to be a compelling hypothesis and we proceeded to prepare unprotected aziridine aldehydes through a sequence of well-known reactions (Scheme 1). The products were isolated as dimers. Crystallographic data (Figure 2A)[2] of dimer **6c** revealed that the dimerization was stereoselective: the *S* enantiomer was found to preferentially associate with another *S* enantiomer (Figure 2B). This stereoselectivity is due to a combination of destabilizing steric and stabilizing hydrogen bonding interactions.

Although 6-membered hemiacetal ring formation is also feasible, its absence in spectra suggests that the dimerization to the 5-membered ring is both kinetically and thermodynamically favored. During dimerization, the intermediate hemiaminal is trapped by attack of the hydroxyl functionality at the aldehyde (Scheme 5). This process is faster than formation of the exocyclic iminium ion which would have formed during condensation. A comparison to glycolaldehyde, another noteworthy α-heteroatom-containing aldehyde, can be made. Crystalline glycolaldehyde is known to rest as the dimer **17**. In polar media, glycolaldehyde is a dynamic mixture of 5- and 6-membered ring dimers (Scheme 6). In contrast, the kinetically formed 5-membered heterocycle is also the product of thermodynamic control in the case of aziridine aldehydes.[32]

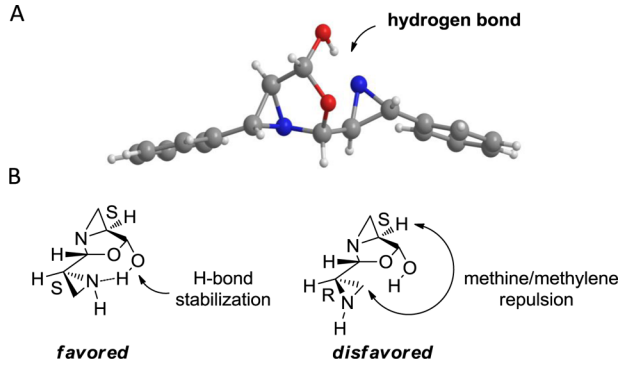
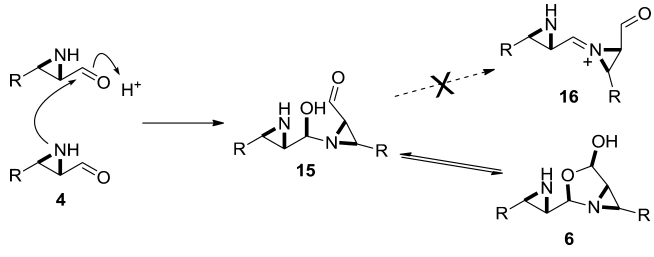
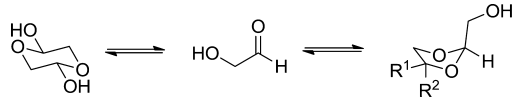


Figure 2. (A) Crystal structure of phenyl-substituted aziridine aldehyde dimer **6c**. (B) Difference in stability between homochiral and heterochiral aziridine aldehyde dimers (phenyl substituents have been omitted for clarity).

Scheme 5. Aziridine Aldehyde Dimerization through Hemiaminal Trapping



Scheme 6. Glycolaldehyde: an Equilibrium between Monomer and 5-/6-Membered Ring Dimers



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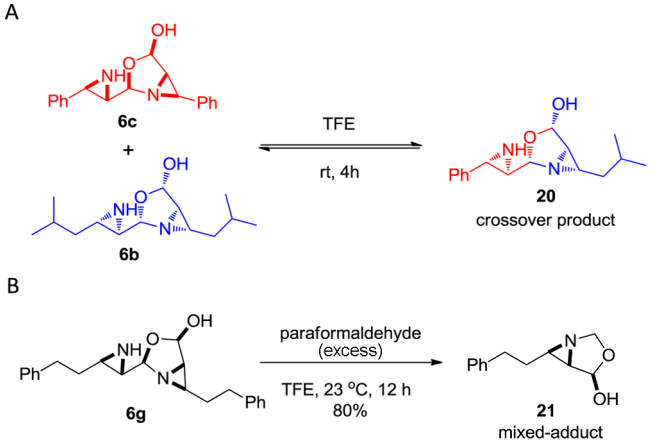
In terms of synthetic application of aziridine aldehyde dimers, our original objectives were based on an assumption that one must achieve access to the corresponding monomeric aziridine aldehyde species. However, in every aziridine aldehyde dimer we have synthesized, the ^{1}H NMR spectrum did not contain a characteristic aldehyde resonance. To get a better understanding of dissociation, we ran crossover studies between two structurally different aziridine aldehyde dimers (Scheme 7A). The reaction was monitored by ESI/MS, and attention

Scheme 7. (A) Crossover between Dimers 6c and 6b. (B) Reaction of Dimer 6g with Paraformaldehyde



was paid to the emergence of an adduct with an averaged molecular mass (see the Supporting Information). The use of organic solvents such as dichloromethane, methanol, tetrahydrofuran, acetonitrile, and toluene, resulted in small amounts of crossover after 1 h. Fluorinated alcohols such as TFE were the exception to this trend, consistently generating crossover products within 5 min, regardless of the pair of aziridine aldehyde dimers under consideration. We also questioned the possibility of crossover in the presence of monofunctional aldehydes. Intriguingly, mixed adducts such as **21** were formed in TFE.

The detection of crossover in TFE made it the solvent of choice for probing aziridine aldehyde reactivity. To investigate the role of TFE in aziridine aldehyde dimer dissociation, the ^{1}H NMR spectrum of **6b** was measured in TFE-d_3. At room temperature, a broad peak at 8.8 ppm began to emerge. When the temperature was raised to 50 °C, the peak at 8.8 ppm became more prominent. We assigned this resonance to free aldehyde of the open dimer **15b** after HSQC analysis confirmed its correlation to the aldehyde carbon at 200 ppm. The broad nature of this peak is consistent with chemical exchange between the aldehyde in open dimer **15b** and the hemiacetal in dimer **6b**. A thorough literature search for monomeric and *N*-unprotected aziridine aldehydes returned one publication from 1983. In this work, Reinhoudt and coworkers reported the aziridine aldehyde **22** (Figure 3), which

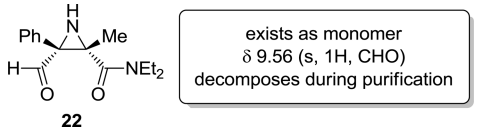
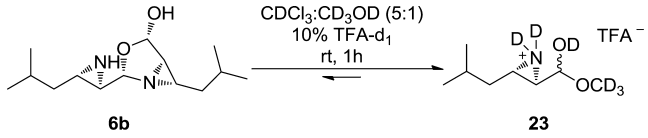


Figure 3. Monomeric aziridine aldehyde reported by Reinhoudt *et al.*

was described as an unstable oil that decomposed during purification but did possess a clear aldehyde peak in its ^{1}H NMR.[33] The ^{13}C NMR spectrum was not reported, presumably due to the short half-life of **22**. This observation stands in stark contrast to our findings of stable and often crystalline aziridine aldehyde dimers. On the basis of this data, one can conclude that the monomeric species are not expected to be isolable.

In order to find conditions for in situ monomerization of aziridine aldehyde dimers, we focused our efforts on producing hemiacetals. Stabilization of the monomer through hemiacetalization and aziridinium salt formation using methanol and trifluoroacetic acid were tested. When **6b** was dissolved in a $CDCl_3/CD_3OD$ (5:1 v/v) mixture containing 10% TFA-d_1 (v/v), the hemiacetal **23** was formed within minutes (Scheme 8).

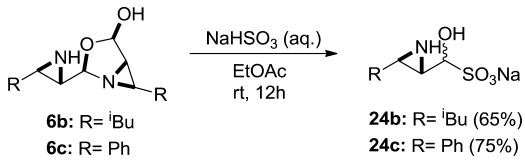
Scheme 8. Monomerization of Dimer 6b through Hemiacetal Formation



The NMR analysis of the aziridinium hemiacetal/TFA salt revealed that the aziridine ring remained intact with aziridine methine proton shifts at 3.02 and 3.09 ppm. The hemiacetal can be transformed back to the aziridine aldehyde dimer upon addition of base. While this experiment confirms that hemiacetals can be selectively formed from aziridine aldehyde dimers, the strongly acidic conditions required to form the monomeric species limit their potential in organic synthesis.

We subsequently turned our attention to influencing the monomer/dimer equilibrium under conditions closer to neutral pH. Sodium bisulfite ($NaHSO_3$) is known to react with aldehydes to give bisulfite adducts, often isolable as stable solids. Sodium bisulfite adducts are attractive candidates that serve as aldehyde surrogates in organic synthesis.[34] When aziridine aldehyde dimers **6b** and **6c** were mixed with a 3 M aqueous $NaHSO_3$ solution and ethyl acetate overnight, bisulfite adducts **24b** and **24c** (1:1 mixture of diastereoisomers), respectively, precipitated as white solids (Scheme 9). These

Scheme 9. Synthesis of Bisulfite Adducts from Aziridine Aldehyde Dimers



compounds underwent dissociation and reversal to the corresponding aziridine aldehyde dimers when stirred at room temperature with one equivalent of sodium hydroxide. We also subjected bisulfite adduct **24b** to crossover conditions with the phenyl substituted aziridine aldehyde dimer **6c**. Interestingly, only traces of crossover product **20** were detected in TFE, whereas no crossover was observed in acetonitrile.

In efforts to further understand the monomer/dimer equilibrium, we reacted aziridine aldehyde dimer **6b** with Boc_2O and base. Boc dimer **25** was isolated with no evidence of the monomeric Boc species (eq 1). The Boc dimer was found to be stable in TFE and did not dissociate to give any aziridine

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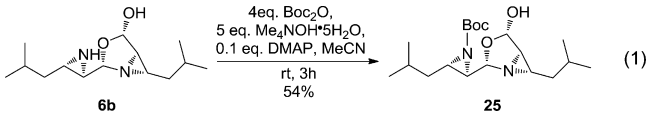
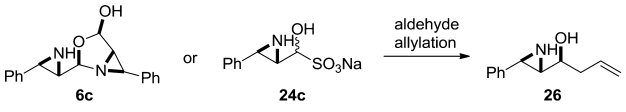


(1)

aldehyde dimer and/or monomeric Boc species. Importantly, no crossover was detected while mixing dimer **6c** and **25** in TFE.

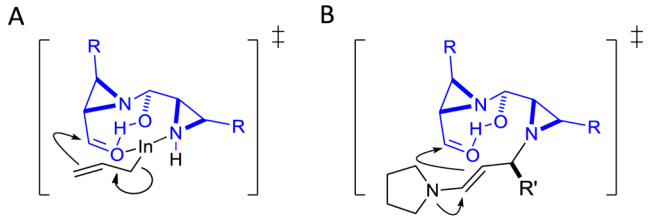
Reactivity of Aziridine Aldehyde Dimers. *Amino Alcohol Synthesis.* Based on the preference of aziridine aldehydes to exist as dimers, we hypothesized that the high diastereoselectivity observed during indium-promoted allylation of aziridine aldehydes might be attributed to a dimeric nature of the reactive species.[4] To further probe this hypothesis, we compared the reactivity of the aziridine aldehyde dimer **6c** to the corresponding bisulfite adduct **24c** in allylation reactions (Scheme 10). While typical reaction times for the indium-mediated allylation of aziridine aldehyde dimers are around 2 h, full conversion to the homoallylic alcohol was observed within minutes when the corresponding bisulfite adduct was used as the starting material. However, the diastereoselectivity of 20:1, observed with dimeric aziridine aldehydes, was eroded to 3:1 when the corresponding bisulfite adduct was used. Alternatively, when **6c** was subjected to the more reactive allylmagnesium bromide in THF at room temperature, only poor diastereoselectivety (dr = 3:1) was obtained (Scheme 10). Unlike what was seen with indium-mediated allylation, reactions with highly basic nucleophiles such as organolithium and Grignard reagents did not yield encouraging results. The reaction between the dimer **6c** and the Grignard reagent never reached completion, even with significant excess of the organometallic reagent (10 equiv) and prolonged reaction times (24 h). Akin to indium-mediated allylation, we observed further erosion of the diastereoselectivity (dr = 1:1) when the corresponding bisulfite adduct **24b** was treated with allylmagnesium bromide.

Scheme 10. Comparison of Reactivity and Selectivity between Aziridine Aldehyde 6c and Bisulfite Adduct 24c in Indium-Mediated Allylation and Grignard Addition



starting material	reagents and conditions	reaction time	conv. (%)	dr
6c	Br, In H_2O:THF (1:1), rt	2 hours	100	20:1
24c	Br, In H_2O:THF (1:1), rt	minutes	100	3:1
6c	BrMg THF, 0°C→rt	12 hours	60	3:1
24c	BrMg THF, 0°C→rt	4 hours	100	1:1

Our DFT analysis of the transition state assembly in indium-mediated allylation revealed a pocket made out of two nitrogen and two oxygen atoms surrounding the indium center (Figure 4A).[4] This arrangement of heteroatoms features a capacity to serve as a general template for controlling aldehyde reactivity. We surmised that such open dimer assembly could serve as a general mode of reactivity. We were able to show that aziridine aldehydes reroute the aza-Michael reaction to a Baylis–Hillman product. In polar aprotic solvents, such as acetonitrile, the aza-Michael aldol reaction gave aminohydroxyl aldehyde **12** with a 20:1 diastereoselectivity. High levels of diastereoselectivity observed in the aza-Michael aldol reaction are predicated upon an open dimer in which an enamine participates in a face-selective attack on the aldehyde (Figure 4B), akin to the proficiency seen in the indium-mediated allylation.



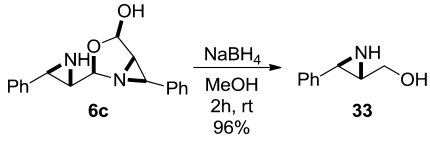
27
Indium-mediated allylation

10
aza-Michael aldol reaction

Figure 4. (A) Calculated transition state of the indium-mediated allylation.[4] (B) Calculated transition state of the disrupted aza-Michael aldol reaction.[6]

To further expand the reaction scope of aziridine aldehyde reactivity, we examined their participation in phosphine-catalyzed annulations.[35] Dimer **6c** was treated with ethyl allenoate **28** in the presence of a catalytic amount of Ph_3P in nonpolar solvents such as benzene, toluene, dichloromethane, or chloroform. Interestingly, amino alcohol **29** with a 7-membered ring was isolated in good yield from the reaction (Scheme 11). The 7-membered ring product was likely formed via the nucleophilic attack of the ylide intermediate **30**, generated from the interaction of ethyl allenoate **28** and Ph_3P, at the open dimer species **15c**. This step was then followed by the intramolecular Michael-type reaction and subsequent elimination of Ph_3P. Trapping the open dimer species with the phosphorus ylide demonstrates that aziridine aldehydes can give rise to products that preserve the dimeric scaffold, which further supports the involvement of partial dissociation.

We also subjected aziridine aldehyde dimers to reduction with sodium borohydride in efforts to obtain amino alcohol templates (eqs 2 and 3). This chemistry is instructive: at no point did we ever observe *N*-alkylated aziridine species. Once again, this speaks against the possibility of intermolecular iminium ion formation in the case of aziridine aldehydes. This behavior stands in contrast to the apparent intermediacy of aziridine-based iminium ions reported by Poulter and co-workers (Scheme 12)[31] and others.[36]



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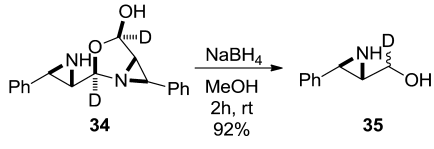

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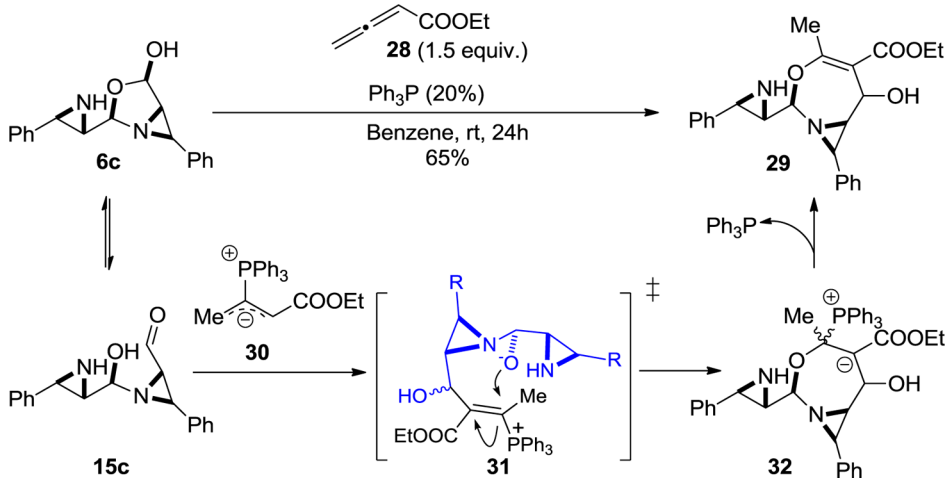
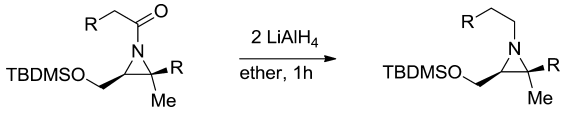
Scheme 11. Trapping of the Open-Dimer Species Using Ylides



Scheme 12. Poulter's Reduction of Acyl Aziridine: Indirect Evidence for Iminium Ion Formation

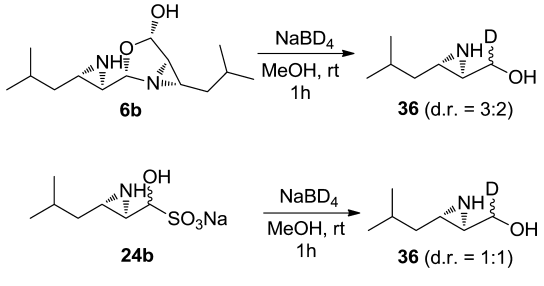


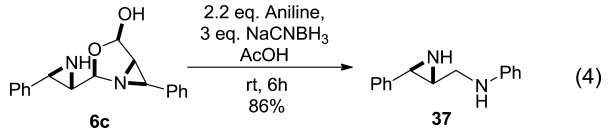
We monitored the reduction of aziridine aldehyde **6c** using sodium borohydride by ^{1}H NMR (500 MHz) at 25 °C. The reduction was carried out under pseudo-first-order conditions in aziridine aldehyde dimer **6c** and gave a k_{obs} of $(5.7 \times 10^{-3}) \pm (1 \times 10^{-4})$ s^{-1}. Using the same conditions with deuterated dimer **34**, we observed a k_{obs} of $(4.7 \times 10^{-3}) \pm (1.0 \times 10^{-3})$ s^{-1}. A secondary kinetic isotope effect was calculated to be 1.2, which is consistent with an sp^3 to sp^2 transformation on the carbon adjacent to the hydroxyl group.[37]

We also subjected the isobutyl substituted aziridine aldehyde dimer **6b** to 1 equiv of sodium borodeuteride in methanol. We observed a small diastereoselectivity of 3:2 which was not seen when the corresponding bisulfite adduct was subjected to the same reduction conditions (Scheme 13). Interestingly, when we subjected the Boc-protected dimer **25** to reduction conditions with sodium borohydride, no reaction was observed.

Diamine Synthesis. To further evaluate the kinetic importance of dimer dissociation, we ran studies on reductive amination with aziridine aldehyde **6c** (eq 4).[38] Under pseudo-first-order conditions in aziridine aldehyde dimer, kinetic analysis revealed that the reaction proceeded with a k_{obs} of $(2.4 \times 10^{-3}) \pm (5 \times 10^{-4})$ s^{-1} and was unaffected by varying

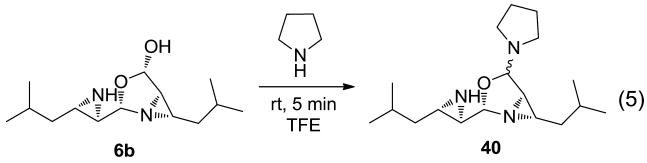
Scheme 13. Comparison of Reactivity and Selectivity between Aziridine Aldehyde 6b and Bisulfite Adduct 24b in the Reduction Using Sodium Borodeuteride



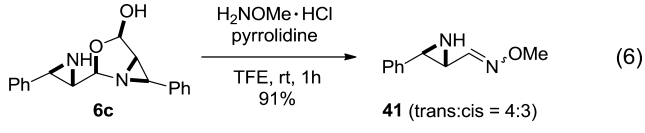


concentrations of aniline or cyanoborohydride. This finding implies that dimer dissociation must be the rate-determining step in reductive amination.

While aziridine aldehyde dimers undergo reductive amination, we have not been able to isolate or detect the corresponding imine species. A number of different routes were tested toward the synthesis of aziridine imines, but none of them were successful to date. Our initial attempt was to perform a condensation of a primary amine and an aziridine aldehyde dimer in TFE. Imine synthesis through an aza-Wittig approach was also tested but was equally unsuccessful. Although imines were not isolable, we did find that the iminium ion could be trapped using cysteine ester (Scheme 14) to give the corresponding thiazolidine **38**, a useful building block for heterocycle synthesis. Analogous to what is observed with pyochelin,[39] compound **38** is in equilibrium with the imine **39**, affording two sets of diastereomers. Noticeably, when we turned our attention from primary to secondary amines, we did observe interesting reactivity. Upon addition of pyrrolidine to a solution of **6b** in TFE, the pyrrolidine adduct **40** was detected by ESI/MS (eq 5).



Oximes stand alone as the only imine-like species that we have been able to prepare. Rapid formation of aziridine oxime **41** was observed when **6c** and *O*-methylhydroxylammonium chloride were mixed in the presence of pyrrolidine (eq 6).



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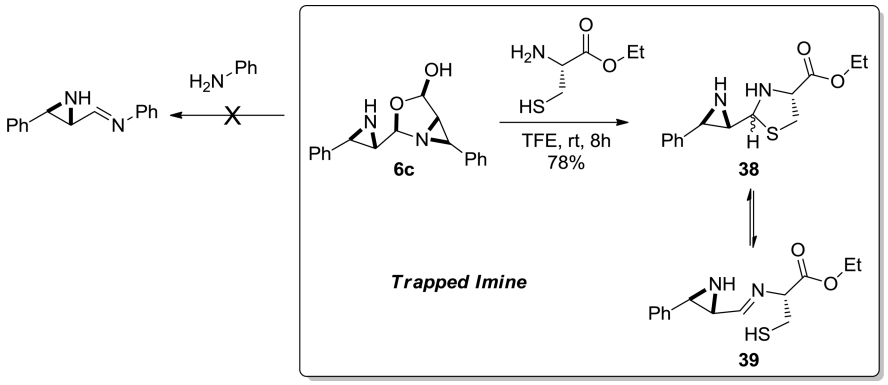
Scheme 14. Imine Trapping Using Cysteine Ethyl Ester



Negligible formation of oxime was recorded in the absence of pyrrolidine. The reaction did not occur when either aniline or triethylamine were employed but proceeded exceptionally fast when pyrrolidine was used as an additive. It is interesting that a secondary amine accelerates the reaction, whereas aniline, typically used to accelerate oxime formation, has no effect.[40]

DISCUSSION

From the beginning, our working hypothesis was that the lack of *intermolecular* iminium ion formation would be the main contributor toward aziridine aldehyde stability. To the best of our knowledge, there is only one report in the literature wherein an unprotected monomeric aziridine aldehyde has been mentioned (Figure 3). Because of its unstable nature, the corresponding molecule has eluded isolation and complete characterization.[33] We conclude that the sterically encumbered substitution pattern around the aziridine ring in **22** impedes dimerization but does not prevent unwanted decomposition from occurring. Aminal-initiated dimerization of aziridine aldehydes plays a key stabilizing role in the case of our molecules. The analysis of the relative stereochemistry of the aminal stereocenter in open dimer **15** suggests that the facial selectivity of dimer formation is the same as the one observed in the course of C−C bond formations seen in our studies (Scheme 4).

The fact that we do not observe any free aldehyde by NMR ($CDCl_3$ at 25 °C) implies that even if present, the monomeric species accounts for less than 5% of the overall population. Solvents that encourage aziridine aldehyde dimer crossover show open dimer formation in NMR (TFE-d_3 at 50 °C). Crossover in TFE suggests possible monomer involvement, yet it does not exclude open dimer participation (Figure 5). Slow crossover between bisulfite adducts and aziridine aldehydes again points toward the significance of accessing the open dimer intermediates. It is also true, however, that lack of full dissociation does not imply lack of reactivity: our previous studies show that full conversion can be achieved in toluene.[2,9]

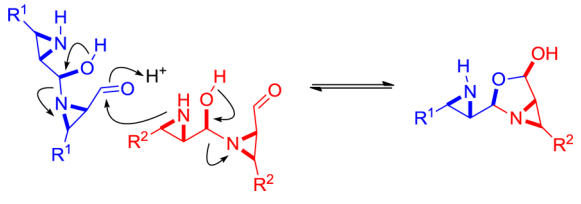


Figure 5. Possible crossover between two open dimers.

However, an investigation of Boc-protected aziridine aldehyde dimer **25** revealed that the blockage of intramolecular hydrogen bonding in aziridine aldehyde dimers completely eliminates crossover and reactivity. The lack of reactivity suggests that the aziridine NH functionality plays an important role in aziridine aldehyde dimer dissociation.

The monomer/dimer equilibration in our system stands in stark contrast to the well-known monomerization of glycoladehyde dimer in solution. The rate of monomerization of glycolaldehyde is solvent-dependent and is known to be catalyzed by either acid or base. The monomerization is sluggish in both DMSO and acetone as evidenced by the lack of the aldehyde signal in ^{1}H NMR. However, upon addition of a Brønsted acid, the aldehyde peak becomes observable.[41]

To emulate monomer reactivity, we prepared aziridine bisulfite adducts **24**. Reactions that employ bisulfite adducts show high reactivity but uniformly lower levels of diastereoselectivity, suggesting that monomeric species do not react selectively. In the case of indium-mediated allylation, we observed a sharp difference in both reaction time and diastereoselectivity when comparing the monomeric bisulfite adduct to the dimeric aziridine aldehyde. A possibility that low diastereoselectivity is due to some detrimental effect of sodium bisulfite has been ruled out: the addition of sodium bisulfite to indium-mediated allylation of dimer **6c** did not erode the diastereoselectivity. The poor diastereoselectivity seen with the monomeric bisulfite adduct implies that, in indium-mediated allylation, the dimeric intermediate holds the key to facial selectivity.

The products of the aza-Michael aldol reactions using aziridine aldehydes (Scheme 3) highlight the significance of slow dimer dissociation kinetics in attaining high levels of selectivity. The reaction was first tested in TFE, but the only product observed was the pyrrolidine dimer adduct **40** (eq 5). On the other hand, in acetonitrile, the amino hydroxyl aldehyde **12** was formed. In acetonitrile, a solvent that does not favor aziridine aldehyde dimer dissociation, the pyrrolidine no longer reacts with the dimer and instead preferentially performs its role as catalyst through iminium ion formation with the *α,β*-unsaturated aldehyde. The product **12** may appear, at first glance, to derive from structure **14** via a ring-opening process (Scheme 15). Upon closer inspection, the microscopic reverse of **14** to intermediate **12** would necessitate an unfavorable 5-*endo-trig* pathway. As a result, the most probable route to the observed product is through intramolecular 8-*exo-trig* cyclization of intermediate **11** before its collapse to the final product. The high diastereoselectivity seen in the aza-Michael aldol

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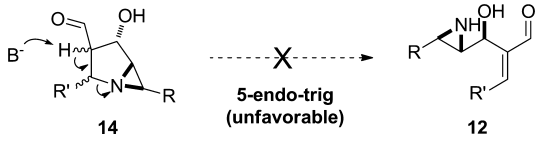
Scheme 15. Unfavorable 5-*Endo-Trig* Pathway for the Formation of Amino Hydroxyl Aldehyde 12



reaction is likely a result of stabilizing factors that emerge in intermediate **10**. Importantly, the preservation of the dimeric scaffold was captured in the reaction with phosphorus ylides. This process delivered 7-membered ring product **29** in benzene, a solvent that does not favor dimer dissociation.

To further solidify the relevance of aziridine aldehyde dimer dissociation, we ran kinetic studies on reduction and reductive amination. The fact that the rate of reductive amination was not perturbed by the change in concentration of hydride or amine suggests that neither k_2 nor k_3 are kinetically important, thus leaving k_1 to be rate-determining in this reaction (Figure 6).

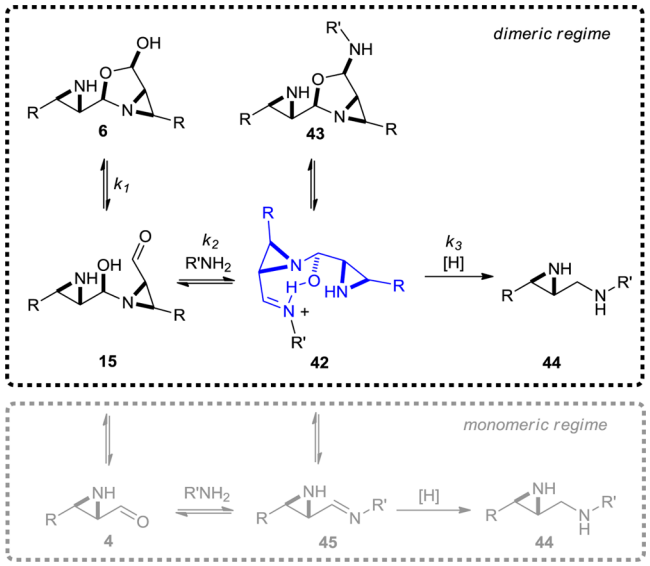


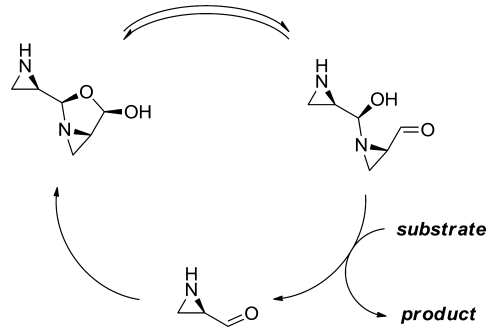
Figure 6. Possible pathways for reductive amination.

This finding does not establish the molecularity of the process following the rate-determining step. However, in indium-mediated allylation, when one compares the diastereoselectivity of aziridine aldehyde dimer with monomeric bisulfite adduct-mediated transformations, a dimeric pathway is strongly supported. To further confirm our proposal of rate-determining aziridine aldehyde dimer dissociation, we synthesized deuterated phenyl-substituted aziridine aldehyde **34** and performed kinetic studies on its $NaBH_4$-mediated reduction. A secondary kinetic isotope effect of 1.2 was obtained, which is consistent with a sp^3 to sp^2 transformation. If the reduction step were rate-determining, the kinetic isotope effect would have been much closer to 1 due to the averaging effect of the sp^2 to sp^3 transformation.[42] A value of 1.2 is again consistent with our hypothesis that aziridine aldehyde dimer dissociation is rate-determining.

The sodium borohydride reduction of dimer **6c** (eq 2) gave a k_{obs} that is 2.3 times larger than that of reductive amination (eq 4). One explanation is that $NaBH_4$ could be involved in catalyzing the aziridine aldehyde redimerization via general base catalysis. With reductive amination this effect is not observed due to the diminished reactivity of sodium cyanoborohydride and the addition of acetic acid to neutralize the pH.

Aziridine aldehyde dimerization is an important aspect of our system that sets it apart from other reactions: once a product is formed, the remaining monomer redimerizes, providing feedback to the starting material pool (Scheme 16). Our

Scheme 16. Monomer Redimerization: A Feedback Mechanism



kinetic analysis of reductive amination did not show a simple first order relationship in the dimeric aziridine aldehyde. Using COPASI (COmplexPAthwaysSImulator),[43] we were able to model the reaction with the consideration of the redimerization process, which resulted in proper curve fitting (see the Supporting Information). Upon aldehyde conversion, a weak aminal functionality is the only link that connects the product with the remaining half of the original aziridine aldehyde dimer. Our inability to detect monomeric aziridine aldehydes suggests an extremely favorable redimerization process in our reactions. The balance of relative rates between a desired aziridine aldehyde transformation and monomer redimerization is a likely contributor to the high diastereoselectivity observed.

Interesting parallels can be drawn with some metal-based processes that depend on higher order aggregates. The field of autocatalysis has been exemplified by Soai's studies of remarkable enantioselectivities observed in reactions of pyrimidine-5-carbaldehyde with diisopropylzinc.[44] In this nucleophilic addition chemistry, the product promotes its own formation, acting as an autocatalyst. Very instructive examples that employ higher order aggregates can be found in organolithium chemistry. Collum and co-workers have provided ample evidence in favor of deaggregation of lithium dialkylamide-solvated dimers en route to open-dimer-based transition-state structures. Maximum rates in this chemistry were attained by optimizing the open-dimer-based pathways.[45] The aforementioned examples highlight important reactivity preferences that result from reversible covalent interactions.

Collectively, our data suggest that the kinetically competent species in aziridine aldehyde dimer-based transformations is dimeric in nature. We postulate that in the majority of useful reactions mediated by this class of amphoteric molecules, a glovelike heteroatom pocket that is capable of catalyzing bond-forming events in its cavity, is being established.[46]

The well-known glycolaldehyde, thioglycolaldehyde, and derivatives thereof, also contain a nucleophilic heteroatom in the α-position relative to the aldehyde center, but do not offer any enabling reactivity opportunities based on their dimeric nature. We hypothesize that catalysts operating on the basis of our findings may someday be designed.

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CONCLUSIONS

In summary, in aziridine aldehyde transformations the evidence points to open dimer **15** as a critical component along the reaction pathway. The kinetic data obtained for key processes show dependence on aziridine aldehyde dimer dissociation and highlights the importance of partial dissociation for achieving high levels of stereoselectivity. The dimeric nature of aziridine aldehydes appears to be significant for both stability and reactivity. We anticipate further developments will unveil other important synthetic consequences of remote control of selectivity by forging reversible covalent interactions.

EXPERIMENTAL SECTION

(*5S,6R*)-6-Phenethyl-3-oxa-1-azabicyclo[3.1.0]hexan-4-ol (21). To a solution of 4-phenylbutene aziridine aldehyde dimer **6g** (1.0 g, 1.86 mmol) in 2,2,2-trifluoroethanol (TFE) (16 mL) was added paraformaldehyde (856 mg, 28.6 mmol) under N_2 at room temperature. The reaction was allowed to stir at room temperature for 16 h, at which point it was concentrated to give an orange/yellow oil. The crude oil was purified by flash chromatography eluting from a gradient of hexanes/EtOAc (0−80% EtOAc) to give the title compound as a white solid: yield 940 mg (80%); R_f = 0.5 (8:2, EtOAc/hexanes); mp = 81−84 °C; IR ν 3118.9, 2895.1, 1453.6, 1081.3, 974.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.16 (m, 5H), 5.39 (d, J = 4.5 Hz, 1H), 4.61 (d, J = 5.5 Hz, 1H), 4.45 (d, J = 5.5 Hz, 1H), 3.60 (d, J = 4.5 Hz, 1H), 2.74 (dtd, J = 21.5, 13.8, 7.5 Hz, 2H), 2.43 (d, J = 2.7 Hz, 1H), 1.78−1.72 (m, 2H), 1.49 (dt, J = 6.3, 2.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 128.7, 126.3, 95.4, 84.9, 49.1, 38.7, 33.6, 32.7 ppm; HRMS (ESI+) $[M + H]^+$ calcd for $C_{12}H_{16}NO_2$ 206.1175, found 206.1177

Sodium Hydroxy((*2R,3S*)-3-isobutylaziridin-2-yl)-methanesulfonate (24b). The aziridine aldehyde dimer **6b** (254.4 mg, 1.0 mmol) was dissolved in 5 mL of ethyl acetate. Separately, $NaHSO_3$ (228.8 mg, 2.2 mmol) was dissolved in 0.6 mL of water. The sodium bisulfite aqueous solution was then added to the aziridine aldehyde solution and was stirred vigorously. A solid precipitated within 1 h, but the reaction was stirred continuously overnight. The solid was then filtered and washed with 5 mL ethanol and twice with 5 mL of diethyl ether to afford a white solid: yield 150.3 mg (65%); ^{1}H NMR (400 MHz, D_2O) δ 4.26−4.22 (d, J = 5.8 Hz, 0.36H), 4.12−4.05 (d, J = 6.7 Hz, 0.5H), 2.28−2.19 (m, 2H), 1.87−1.72 (dt, J = 13.5, 6.7 Hz, 1H), 1.59−1.43 (m, 1H), 1.33−1.22 (m, 1H), 1.03−0.89 (d, J = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, D_2O) δ 84.6, 83.5, 41.0, 40.9, 37.1, 36.4, 34.9, 33.6, 26.9, 26.9, 22.1, 22.0, 21.9, 21.9; IR ν 3494, 3284, 2959, 2868, 2517, 1621, 1467, 1185, 1052

Sodium Hydroxy(*trans*-3-phenylaziridin-2-yl)-methanesulfonate (24c). The aziridine aldehyde dimer **6c** (294.4 mg, 1.0 mmol) was dissolved in 5 mL of ethyl acetate. Separately, $NaHSO_3$ (228.8 mg, 2.2 mmol) was dissolved in 0.6 mL of water. The sodium bisulfite aqueous solution was then added to the aziridine aldehyde solution and was stirred vigorously. A solid precipitated within 1 h, but the reaction was stirred continuously overnight. The solid was then filtered and washed with 5 mL of ethanol and twice with 5 mL of diethyl ether to afford a white solid: yield 188.4 mg (75%); ^{1}H NMR (400 MHz, D_2O) δ 7.52−7.28 (m, 5H) 4.60−4.37 (d, J = 5.4 Hz, 0.45H), 4.39−4.27 (d, J = 6.4 Hz, 0.58H), 3.30−3.26 (d, J = 3.2 Hz, 0.48H), 3.26−3.22 (d, J = 3.2 Hz, 0.58H), 2.70−2.63 (td, J = 6.5, 6.0, 3.3 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 138.2, 137.8, 128.9, 128.9, 128.0, 127.9, 126.5, 126.5, 84.2, 82.8, 39.8, 39.2, 37.2, 35.6; IR ν 3586, 3239, 3219, 2536, 1630, 1497, 1456, 1427, 1183, 1058

(2*R*,3*S*)-*tert*-Butyl 2-((2*S*,4*S*,5*R*,6*S*)-4-Hydroxy-6-isobutyl-3-oxa-1-azabicyclo[3.1.0]hexan-2-yl)-3-isobutylaziridine-1-carboxylate (25). Aziridine aldehyde **6b** (254.4 mg, 1 mmol) was dissolved in 12.5 mL of acetonitrile. $Me_4NOH{\cdot}5H_2O$ (906.2 mg, 5 mmol), Boc anhydride (877.0 mg, 4 mmol), and DMAP (12.2 mg,0.1 mmol) were all subsequently added to the reaction mixture. A few drops of water were then added. The reaction was allowed to stir at room temperature and was monitored by TLC and LCMS. After a few hours, the dimer was completely consumed and a new spot appeared. The product was purified by flash silica gel column chromatography. A gradient of 0−50% ethyl acetate in hexanes was used to afford a clear colorless oil: yield 191.4 mg (54%); R_f = 0.6 (100% EtOAc); IR ν 2955.4, 1746.6, 1467.1, 1368.2, 1253.2, 1277.2^{1}H NMR (300 MHz, $CDCl_3$) δ 6.17 (d, J = 6.8 Hz, 1H), 4.62 (d, J = 4.4 Hz, 0.57H), 4.51 (d, J = 5.9 Hz, 0.34H), 2.56 (t, J = 3.1 Hz, 1H), 2.06 (dd, J = 6.8, 3.8 Hz, 1H), 1.94−1.87 (m, 3H), 1.85−1.65 (m, 3H), 1.49 (s, 9H), 1.43−1.21 (m, 3H), 1.14 (dt, J = 14.0, 7.6 Hz, 1H), 1.03−0.85 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 152.3, 97.7, 83.2, 82.9, 49.3, 47.5, 40.0, 39.8, 39.6, 38.6, 34.6, 27.9, 27.9, 27.4, 27.2, 27.1, 23.1, 22.9, 22.8, 22.5; HRMS (ESI+) $[M + H]^+$ calcd for $C_{19}H_{35}N_2O_4$ 355.2597, found 355.2605

Ethyl 6-Hydroxy-4-methyl-8-phenyl-2-(*trans*-3-phenylaziridin-2-yl)-3-oxa-1-azabicyclo[5.1.0]oct-4-ene-5-carboxylate (29). To the solution of phenylaziridine aldehyde dimer **6c** (100 mg,0.34 mmol) in 5 mL of benzene were added ethyl allenoate (122 mL,10.2 mmol) and triphenylphosphine (18 mg, 0.068 mmol). The reaction mixture was stirred at room temperature for 24 h. After benzene was removed in vacuo, the residue was purified by silica gel chromatography (hexanes/EtOAc 9:1 → 1:1) to afford the desired product as a yellowish oil: yield 88.4 mg (65%); NMR analysis showed the formation of only one diastereomer; R_f = 0.2 (2:8 EtOAc/hexanes); IR ν 2979.4, 1709.2, 1627.8, 1256.3, 1133.8, 1004.7; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.23 (m, 10H), 5.86 (s, 1H), 5.43 (s, 1H), 5.09 (bs, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.18 (d, J = 2.7 Hz, 1H), 3.00 (d, J = 2.6 Hz, 1H), 2.58 (d, J = 2.7 Hz, 1H), 2.37 (bs, 1H), 2.16 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 167.5, 139.4, 136.5, 128.7, 128.6, 128.1, 127.4, 126.6, 126.3, 98.8, 95.8, 59.8, 52.4, 43.6, 41.2, 18.6, 14.5; HRMS (ESI) $[M + H]^+$ calcd for $C_{24}H_{27}N_2O_4$ 407.197, found 407.197

Phenyl-Substituted Deuterium-Labeled Aziridine Aldehyde (34). *trans*-Ethyl 3-phenylaziridine-2-carboxylate (994.4 mg,5.2 mmol) was dissolved in methanol (5 mL) and water (2 mL), and lithium hydroxide (113.8 mg,4.75 mmol) was added. The reaction was allowed to stir for 3 h. The product, lithium 3-phenylaziridine-2-carboxylate **45**, was precipitated with ethyl acetate, and the white solid was filtered off: yield 694.3 mg (79%); ^{1}H NMR (400 MHz, D_2O) δ 7.56−7.18 (m, 5H), 3.23 (s, 1H), 2.57 (s, 1H), 1.93 (s, 1H); ^{13}C NMR (100 MHz, D_2O) δ 177.6, 138.2, 128.6, 127.7, 126.2, 40.7, 38.6.

The aziridine carboxylate **45** (2 mmol, 338.2 mg) and *N,O*-dimethyl hydroxylamine (2.12 mmol, 206.8 mg) were dissolved in 12 mL of DMF (anhydrous). The reaction was then cooled to 0 °C, and DPPA (2.2 mmol, 474 μL) was added. The triethylamine (4.04 mmol, 564 μL anhydrous) dissolved in 4 mL of DMF was then slowly added to the reaction mixture over 10 min. The reaction was stirred at 0 °C for the next 6 h and was then warmed to room temperature and left to stir for another 12 h under nitrogen. The reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with 7:3 chloroform/methanol mixture and washed three times with water, once with 5% sodium bicarbonate, and twice with brine. The organic layers were then combined, dried over sodium sulfate, and evaporated in vacuo. The residue was then purified by flash silica gel column chromatography to afford *N*-methoxy-*N*-methyl-3-phenylaziridine-2-carboxamide **46** as a clear colorless oil: yield 309.4 mg (75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.01 (m, 5H), 3.54 (s, 3H), 3.15 (s, 3H), 3.01 (dd, J = 8.9, 1.8 Hz, 1H), 2.92 (s, 1H), 2.12−1.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 137.5, 127.4, 126.5, 125.1, 60.9, 38.9, 36.6, 31.7; HRMS (ESI+) $[M + H]^+$ calcd for $C_{11}H_{15}N_2O_2$ 207.1134, found 207.1138

The Weinreb amide **46** (150.6 mg,0.73 mmol) was first dissolved in 7.5 mL of THF and cooled to 0 °C. The lithium aluminum deuteride (39.5 mg,0.94 mmol) was then suspended in a minimal amount of THF and slowly added to the reaction mixture. Once the reaction had gone to completion it was diluted with ether at 0 °C. A 40 μL portion of water was added followed by 100 μL of 15% NaOH followed by another 20 μL of water. The reaction was warmed to room temperature and stirred for 15 min. An extra 60 μL of 15% NaOH was then added and allowed to stir for an additional 2 h. The organic layer was then washed with 10% NaOH followed by brine (twice).

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The organic layer was then dried over sodium sulfate and solvent removed in vacuo. The product, phenyl-substituted deuterium-labeled aziridine aldehyde **34**, was isolated as a white solid. The title compound was then recrystallized in methanol: yield 70.3 mg (65%); mp = 140−142 °C; IR 3037.0, 1605.9, 1494.2, 1453.6, 1197.5, 1162.0, 1108.8, 967.0 ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.07 (m, 10H), 3.12−3.01 (bdd, J = 6.0, 3.3 Hz, 1H), 2.87−2.79 (d, J = 2.8 Hz, 1H), 2.50−2.44 (d, J = 2.8 Hz,1H), 1.30−1.16 (bd, J = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 129.1, 128.6, 128.6, 128.2, 127.7, 126.5, 126.5, 125.8, 53.2, 40.9, 40.9, 40.5, 36.6; HRMS (ESI+) $[M + H]^+$ calcd for $C_{18}H_{27}D_2N_2O_2$ 297.1572, found 297.1573.

(4*R*)-Ethyl 2-((2*S*,3*R*)-3-Phenylaziridin-2-yl)thiazolidine-4-carboxylate (38). The phenylaziridine aldehyde **6c** (29.4 mg, 0.1 mmol) was dissolved in 250 μL of trifluoroethanol and cooled to 0 °C. Separately, the cysteine ethyl ester (30 mg, 0.2 mmol) was dissolved in 250 μL of trifluorethanol. The cysteine ethyl ester solution was then added to the cooled aziridine aldehyde solution and allowed to stir under nitrogen atmosphere for 1 h. The reaction was allowed to stir at room temperature for another 8 h under nitrogen atmosphere. The reaction was monitored by TLC. Once completed, the solvent was removed under reduced pressure and the diastereomers were separated by flash silica gel column chromatography (gradient 0−100% ethyl acetate in hexanes): R_f = 0.45(1:1, EtOAc/hexanes): yield 23.7 mg (85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49−6.95 (m, 5H), 5.06−4.62 (d, J = 4.6 Hz, 1H), 4.28−4.18 (dd, J = 7.2, 1.8 Hz, 2H), 4.18−4.08(m, 1H), 3.40−3.24 (dd, J = 10.4, 6.7 Hz, 1H), 3.11−2.79 (m, 2H), 1.35−1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 139.1, 128.6, 127.3, 125.8, 70.0, 65.7, 64.6, 61.7, 37.9, 14.2; R_f = 0.35, 1:1 ethyl acetate/hexanes); HRMS (ESI+) $[M + H]^+$ calcd for $C_{14}H_{19}N_2O_2S$ 279.1167, found 279.1166

3-Phenylaziridine-2-carbaldehyde *O*-Methyloxime (41). To a solution of *O*-methyl hydroxylamine salt (10.7 mg, 0.11 mmol) dissolved in 0.5 mL of TFE was added pyrrolidine (15.6 mg, 0.22 mmol) at rt and the mixture stirred for 5 min. Aziridine aldehyde dimer **6c** (14.8 mg, 0.05 mmol) was added in one portion and stirred until disappearance of dimer was observed by TLC (~30 min). The reaction was concentrated and coevaporated with MeOH to give an amber oil. Purification by column (1:1 EA/Hex) eluted *cis* isomer (9 mg) followed by *trans* isomer (7 mg), total yield of 16 mg (91%). *Cis* isomer: ^{1}H (400 MHz, $CDCl_3$) δ 7.43−7.04 (m, 6H), 3.85 (s, 3H), 3.10 (br d, 1H), 2.53 (br s, 1H), 1.77 (br s, 1H); ^{13}C (100 MHz, $CDCl_3$): 148.2, 138.5, 128.4, 127.4, 125.9, 61.8, 41.2, 39.2. *Trans* isomer ^{1}H (400 MHz, $CDCl_3$) δ 7.39−7.15 (m, 5H), 6.32 (br d, 1H), 3.89 (s, 3H), 3.48 (br s, 0.5H), 3.21 (br d, 0.5H), 3.10 (br s, 0.5H), 2.97 (br s, 0.5H), 1.42 (br s, 0.5H), 1.13 (br s, 0.5H). *Cis* + *trans* isomer: ^{13}C (100 MHz, $CDCl_3$) 150.7, 149.2, 138.0, 128.8, 128.4, 127.8, 127.5, 125.9, 125.3, 62.1, 40.2, 38.7, 36.2, 33.7; HRMS (ESI+) $[M + H]^+$ calcd for $C_{10}H_{13}N_2O$ 177.1028, found 177.1023

Kinetics. Kinetic measurements by ^{1}H NMR were taken using an Agilent VNMRS 500 MHz spectrometer at 25 °C. All data were obtained in triplicate.

Reduction (eq 2). Pseudo-first-order conditions were run on the phenyl-substituted aziridine aldehyde dimer. A 13.3 mg (0.0452 mmol) portion of phenyl-substituted aziridine aldehyde **6c** was dissolved in 1.5 mL of $CDCl_3$ followed by the addition of 7.8 μL of phenyltrimethylsilane (internal standard). Into two separate NMR tubes was added 0.6 mL of the dimer solution with internal standard. To one of the NMR tubes was added 0.2 mL of CD_3OD, and this was used as the control NMR. The control NMR was taken first. Then afterward to monitor the reaction, 17.08 mg (0.27 mmol) of $NaBH_4$ was added to 0.5 mL of CD_3OD. A 0.2 mL portion of this solution was then quickly added to the second NMR tube. NMR spectra were then promptly taken at 159 s intervals for the first 20 NMRs and then at 167 s intervals for the last 10 NMRs. Each NMR took 8 scans with a 10 s delay. A total of 30 NMRs were taken. Both disappearance of dimer and appearance of product were monitored. To measure the kinetic isotope effect the same procedure was followed using deuterated aziridine aldehyde dimer **34**.

Reductive Amination (eq 4). Pseudo-first-order conditions were run on the phenyl-substituted aziridine aldehyde dimer **6c**. A 13.3 mg (0.0452 mmol) portion of phenyl-substituted aziridine aldehyde was dissolved in 1.5 mL of CD_3OD followed by the addition of 7.6 mg of 1,3,5-trimethoxybenzene (internal standard). Into two separate NMR tubes was added 0.6 mL of the dimer solution with internal standard. To one of the NMR tubes was added 0.2 mL of CD_3OD, and this was used as the control NMR. The control NMR was taken first. Separately, 5.2 μL (0.0904 mmol) of acetic acid and 82.4 μL (0.90 mmol) of aniline were added to 0.5 mL of CD_3OD. Right before the NMR was taken 28.4 mg (0.452 mmol) of sodium cyanoborohydride was added to the aniline solution. A 0.2 mL portion of the aniline and hydride solution was then quickly added to the second NMR tube. NMRs were then promptly taken at 159 s intervals for the first 30 NMRs and at 737 s intervals for the last 50 NMRs. Each NMR took 8 scans with a 10 s delay. A total of 80 NMRs were taken. Both disappearance of dimer and appearance of product were monitored.

Order in Aniline. The same procedure as above was followed, but the following various amounts of aniline were added, 10×, 30×, and 40× excess: 10×, 41.2 μL of aniline was added; 30×, 123.6 μL of aniline was added; 40×, 164.8 μL of aniline was added.

Order in Hydride. The same procedure as above was followed but the following various amounts of sodium cyanoborohydride were added, 10×, 20×, and 40× excess of hydride: 10×, 9.5 mg of $NaCNBH_3$ was added; 20×, 18.9 mg of $NaCNBH_3$ was added; 40×, 37.9 mg of $NaCNBH_3$ was added.

Determination of k_{obs} in Reduction and Reductive Amination. Since both reactions did not demonstrate typical first order kinetics, we turned to COPASI, a complex reaction simulation program. The rate constants were all determined using time versus concentration data measured experimentally using the "Parameter Estimation" protocol with the assumption that all reactions were irreversible. To ensure the estimated parameters were not a local minima each rate was randomly varied and the simulation was repeated.

■ ASSOCIATED CONTENT

Supporting Information

Experimental detail and characterization of new compounds along with a copy of their ^{1}H and ^{13}C spectra provided. Details on kinetic data and COPASI simulations of reduction and reductive amination. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ayudin@chem.utoronto.ca.

Notes

The authors declare no competing financial interest.

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