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Ring Expansion of Bicyclic Methyleneaziridines via Concerted, Near-Barrierless [2,3]-Stevens Rearrangements of Aziridinium Ylides

Steven C. Schmid[†], **Ilia A. Guzei**[†], **Israel Fernández**[*,‡], and **Jennifer M. Schomaker**[*,†]

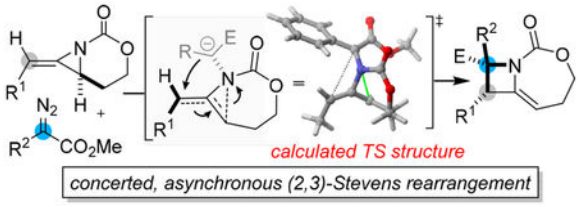
[†]Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706, United States

[‡]Departamento de Química Organica I and Centro de Innovacioń en Química Avazanda (ORFEO −CINQA), Facultad de Ciencias Químicas, Universidad Complutense de Madrid, 28040 Madrid, Spain

Abstract

The synthesis of densely functionalized azetidinesin a highly stereocontrolled manner is challenging, but interest in the bioactivities of these small heterocycles has stimulated methods for their preparation. We recently reported a one-carbon ring expansion of bicyclic methylene aziridines under dirhodium catalysis capable of delivering enantioenriched azetidines. This work explores this ring expansion using computational and experimental studies. DFT computations indicate that the reaction proceeds through formation of an aziridinium ylide, which is precisely poised for concerted, asynchronous ring-opening/closing to deliver the azetidines in a [2,3]-Stevens-type rearrangement. The concerted nature of this rearrangement is responsible for the stereospecificity of the reaction, where axial chirality from the initial allene substrate is transferred to the azetidine product with complete fidelity. The computed mechanistic pathway highlights the key roles of the olefin and the rigid structure of the methylene aziridine in differentiating our observed ring expansion from competing cheletropic elimination pathways noted with ylides derived from typical aziridines.

Graphical Abstract



[*]Corresponding Authors: schomakerj@chem.wisc.edu (J.M.S.)., israel@quim.ucm.es (I.F.).

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b02206. Experimental procedures, computational details, and characterization data for all new compounds (PDF) Crystallographic information for (**S**)-**3bb** (CIF)

The authors declare no competing financial interest.

Keywords

azetidine; methylene aziridines; [2,3]-Stevens rearrangement; aziridinium ylides

INTRODUCTION

Substituted azetidines occur in several natural products and medicinal chemistry libraries generated through diversity-oriented synthesis (Scheme 1A).[1] However, methods to access highly functionalized, enantioenriched azetidines that are not comprised of β-lactam cores are surprisingly rare. The Schomaker group recently reported an efficient ring expansion of carbamate-derived bicyclic methylene aziridines (MAs) to methylene azetidines using substituted α-diazoacetates under dirhodium catalysis (Scheme 1B).[2] This transformation was synthetically impressive in its ability to efficiently set adjacent functionalized stereocenters, as well as forge new C−C and C− N bonds. The transformation displayed an unexpected ability to transfer chirality from the initial allene substrate to the azetidine products and represents a rare example of a successful catalytic, intermolecular one-carbon ring expansion reaction involving a three-membered nitrogen heterocycle and a metal-supported carbene.[3,4] In this paper, we explore the mechanistic details of this unusual ring expansion using both experimental and computational studies and provide important insight that may expand the scope and utility of these types of useful ring expansions.

The formation and controlled reactivity of onium ylides, including ammonium, sulfonium, and oxonium ylides, continue to be a powerful approach for transforming simple precursors into stereochemically rich, densely functionalized products, often with high levels of diastereo- and enantiocontrol.[5] For example, onium ylides are key intermediates in 1,3-dipolar cycloadditions,[6] 1,2- and 2,3-rearrangements,[7] 1,2-ring closures, and various multicomponent reactions, among other useful transformations.[8] Catalytic reactions of heteroatoms with metal-supported carbenes are a subset of this class of reactions that provide a convenient entry point to onium ylides.[5e,9,10] Insight into the factors responsible for the reactivity and stereocontrol in these systems has been critical for advancing the scope and versatility of these classes of reactions.

Despite their potential utility, onium ylides derived from aziridines and epoxides have seen limited use in synthesis due to their propensity to undergo retro [2 + 1] cycloadditions. In 1972, Watanabe disclosed the first attempted ring expansion of an aziridine to an azetidine through in situ formation of an aziridinium ylide using a copper-bound carbene (Scheme 2).[11] Instead of the productive C−C bond formation that was noted with azetidine precursors, the utilization of aziridine substrates led to cheletropic extrusion to form ethylene and the α-imino ester. In 2004, Rowlands attempted to bypass this cheletropic extrusion process through an intramolecular [2,3]-Stevens rearrangement of a vinyl aziridine.[12] Even after extensive optimization of the substrate and the reaction conditions, the highest yield of the substituted piperidine that could be obtained was 21%. The low yield was attributed to the dependence of the rearrangement on the configuration of the nitrogen lone pair; that is, effective ring expansion required a syn orientation between the nitrogen lone pair and the

alkene upon formation of the ylide. If this condition was not met, decomposition of the aziridinium ylide intermediate occurred through a [1,5]-hydrogen shift.

RESULTS AND DISCUSSION

On the basis of our understanding of the unusual features of carbamate-derived methylene aziridines[13] and the literature of rhodium-bound carbenes,[14] we initially proposed that ring expansion proceeds through formation of an aziridinium ylide, **4.2**, followed by a stepwise ring-opening, ring-closing sequence to deliver the functionalized azetidine **4.5** (Scheme 3, red). Despite the precedent for the formation of this type of aziridinium ylide, the difference in the observed reactivity of our system, compared to that of the Watanabe and Rowlands systems, suggested that a better understanding of the factors responsible for controlling the ring expansion was required. Such insight could have broad implications for controlling the reactivity of aziridinium ylides and significantly expand the utility and substrate scope of these types of ring expansions. With the goal of ascertaining the most likely mechanistic pathway, detailing the factors responsible for successful ring expansion, and increasing the reactivity profile of our methylene aziridines, we initiated a more rigorous mechanistic study of this unusual reaction.[2]

In addition to our initial proposed mechanism (Scheme 3a red, **4.1**−**4.5**), several other pathways were considered, as highlighted in Scheme 3. In contrast to the stepwise ring-opening/closing path, we recognized the possibility that a concerted [2,3]-type rearrangement proceeding through transition state **4.6** could, in principle, deliver azetidine **4.5** and account for the enantioretention observed previously (Scheme 3b, orange). Ylide **4.2** could diverge to a pathway invoking a cheletropic extrusion similar to that observed by Watanabe and would generate both allene and imine functionality in **4.8**, which could be envisaged to undergo a [2 + 2] cycloaddition to furnish **4.5** (Scheme 3c, green). However, no product from cycloaddition with the proximal allene double bond to give **4.9** was noted, seeming to argue against this pathway. Finally, dinuclear Rh catalysts are well-known to promote alkene cyclopropanation reactions; such a scenario applied to **4.1** would lead to the azaspiropentane intermediate **4.10** (Scheme 3d, blue) that could undergo rearrangement to yield **4.5**.

Studies sought to answer the following questions: (a) What is the full reaction pathway, as supported by both computational and experimental evidence? (b) What is the source of the high diastereoselectivity and enantioretention that is observed in this ring expansion process? and (c) What specific features enable this rare transformation and how can a better understanding of these factors be utilized to expand the scope of similar reactions?

Previous mechanistic studies of the ring expansion concluded that a radical pathway was not likely as both inter- and intramolecular radical traps, in the form of added TEMPO and a vinyl cyclopropane substrate, respectively, did not affect the observed reactivity.[2] Control reactions demonstrated the necessity of forming the rhodium-bound carbene prior to ring expansion. Due to the constraints associated with carrying out kinetic analyses on reactions that require slow addition, we felt that density functional theory (DFT) calculations would

be an excellent tool to help elucidate the reaction pathway, with experimental evidence serving as a control on the calculations.

DFT calculations were performed at the dispersion-corrected SMD(CH_2Cl_2)-B3LYP-D3/def2-SVP level (see Computational Details in the Supporting Information) beginning from the methyl-substituted MA 1a and dirhodium-bound carbene **2a-Rh$_2$**, derived from phenyl diazoacetate (Figure 1).[15,16] Formation of aziridinium ylide **INT1** proceeded through transition state **TS1** with a low barrier of 3.2 kcal mol^{-1} in a moderately exergonic transformation (ΔG_R = −7.6 kcal mol^{-1}). In contrast, the potentially competing cyclopropanation pathway had a notably higher transition state energy of 11.3 kcal mol^{-1} (**TS1′**), supporting the literature consensus that ylide formation generally outcompetes cyclopropanation.[5a] Taken together, these results argue against the pathway shown in Scheme 3d, which can be safely ruled out.

Dissecting the fate of rhodium-bound aziridinium ylide **INT1** proved to be nontrivial. Attempted ring-opening of the strained, allylic **C−N** bond of **INT1** via **TS2** was 12.5 kcal mol^{-1} uphill in energy. However, dissociation of the dirhodium center from the rhodium-bound ylide to produce ylide **INT2**, followed by a similar ring-opening via **TS3**, was found to be favored over the process involving **TS2** (9.2 kcal mol^{-1} from **INT1**). Despite the energetic cost associated with the initial dissociation of the transition metal fragment (relaxed scans performed at different Rh···C distances starting from **INT1** indicates that this dissociation is essentially a barrierless process), this metal-free ylide route is believed to be the dominant pathway. In addition, this early dissociation of the dirhodium catalyst is consistent with studies on the fates of rhodium and copper ylides in **O−H** insertion chemistry.[17]

In contrast to our previous proposed stepwise pathway from the ylide **INT1** to the product **3aa**, **TS3** suggests an asynchronous, concerted ring-opening, ring-closing cascade to deliver azetidine **3aa**, formally considered a [2,3]-Stevens-type rearrangement.[18] Zwitterion **INT3** could not be identified as a minimum on the potential energy surface. Indeed, intrinsic reaction calculations (IRCs) starting from **TS3** demonstrated that the final closing of the C−C bond to form the azetidine exists on a plateau-like energy pathway, where ring closure only begins to occur following completion of the C−N bond rupture and initial planarization of the pseudoallyl cation (Figure 2). The transformation from the ylide **INT2** to **3aa** merits further discussion. The relief of methylene aziridine ring strain drives the reactivity captured in this final step, which is highly exergonic and releases nearly 60 kcal mol^{-1} of energy, despite forming congested adjacent stereocenters. Additionally, the low barrier associated with accessing **TS3** reflects the lability of the strained aziridinium C−N bond. Despite the exergonicity and near-barrierless nature of **TS3**, the C−N bond length in **TS3** (2.332 Å) resembled the analogous bond length in the product azetidine **3aa** (2.507 Å) more closely than that of the ylide **INT2** (1.577 Å), highlighting that some degree of positioning for ring closure occurs following aziridinium opening. Interestingly, the distance between the two reactive carbon atoms remains nearly unchanged, 3.512 Å in **INT2** and 3.241 Å in **TS3**, consistent with the IRC depiction of C−N bond breakage, followed by pseudoallyl cation planarization and the final C−C bond formation. In comparison to Singleton's work on the transition state of acyclic [2,3]-Stevens rearrangements,[18] the longer C−C bond distance in

TS3 appears to highlight how the constrained structure of the MA can allow for a looser rearrangement transition state.

The concerted nature of **TS3** has important repercussions for the diastereoselectivity of the ring expansion reaction. Figure 1 shows calculations of the energies for the full pathways leading to both possible diastereomeric azetidine products **3aa** and **3aa-iso**. The lower barrier of **TS3** compared to **TS1** indicated that ylide formation is slow relative to the rearrangement step. As such, ylide formation operates under kinetic rather than thermodynamic control. Our computations (see the SI for further details) suggest that there is no interconversion between **INT2** and **INT2**-iso through rotation about the N−C bond as the rotation barrier was much higher ($\Delta G^{\ddagger}$ = 24.7 kcal mol^{-1}) than that for the process involving **TS3**. Thus, the stereochemical outcome of the reaction is set during the initial formation of the aziridinium ylide, with the diastereoselectivity of the final ring closure originating from the facial differentiation of the rhodium-bound ylide in its approach to the methylene aziridine. The 3.5 kcal mol^{-1} difference noted between **TS1** and **TS1-iso** (Figure 1) is in part due to the occurrence of stabilizing noncovalent interactions (NCIs) in **TS1** that are not present in **TS1-iso**. These weak but significant interactions can be readily visualized by means of the NCIPLOT method.[19] As clearly shown in Figure 3a, there are two genuine stabilizing NCIs (green surfaces) in **TS1**, namely, the n···π* interaction involving the carbamate moiety and the carbene ester and the CH···π interaction involving the alkene CH and the carbene phenyl group. Obviously, these interactions cannot be accommodated in **TS1-iso**, as shown in Figure 3b, which is translated into the lower stability computed for this saddle point.

Additional evidence for the selectivity of the ylide formation controlling the overall diastereoselectivity of the reaction and the key role of the NCIs can be found from the lower experimental *dr* values observed for substrates such as methyl or styrenyl α-diazoacetates (7:1 and 4:1, respectively, vs 19:1 for the Ph-substituted counterpart).[7] These particular systems lack the phenyl group responsible for the stabilizing CH···π interaction in the corresponding **TS1** saddle points, which is reflected in the lower *dr* values observed experimentally.

As noted earlier, we previously discovered that subjecting enantioenriched methylene aziridines to the reaction conditions transferred chirality to the product azetidine (Scheme 4a). As an additional check of our computations, the absolute configuration of the enantioenriched chlorinated derivative **3bb** was determined by single-crystal X-ray diffraction, which indicated that the precursor **(S)-1b** delivers the **(S,S)-3bb** azetidine, a result consistent with our computations (see the SI for full details).

The transfer of chirality observed in Scheme 4a agrees with our proposed concerted ring-opening, ring-closing pathway proceeding through **TS3**. The concavity of the methylene aziridine **(S)-1b**, combined with the barrierless ring-closing process suggested by computations, necessitates that ring closure occur from the back side of **(S)-1**.[20] We were curious whether this observation would hold true with other carbene precursors; thus, we separately subjected both the symmetric iodonium ylide **2c** and the phenyl diazonitrile **2d** to the reaction conditions with enantioenriched **1b** (Scheme 4b). In both cases, enantioretention

in the azetidine products **3bc** and **3bd** was observed. Although it is possible that reactions of these carbene precursors do not proceed through the same concerted pathway, these results strongly support the stereo-specificity of the rearrangement. We found that the **TS3-E** directly evolves to the final azetidine **3bc′**, a situation similar to that found for the analogous phenyl-substituted **INT2** in Figure 1 (see Figure 4). The corresponding intrinsic reaction coordination is included in the Supporting Information as Figure S9.

With an understanding of the reaction pathway and the origin of the observed diastereoselectivity and enantioretention, we sought to understand the factors differentiating the fate of our methylene aziridinium ylides, as compared to the simpler aziridinium ylides described by Watanabe and Rowlands.[11,12] Thus, saturated bicyclic carbamate aziridines **5a** and **5b** were synthesized from aziridination of the corresponding homoallylic carbamates and exposed to the ring expansion conditions (Scheme 5).

The trans isomer **5a** showed no conversion, even under forcing conditions. In contrast, the cis isomer **5b** yielded the imine alkene **5c** in moderate yield as the sole product of the reaction, highlighting that ready access to the nitrogen lone pair is necessary for reaction with the metal-supported carbene. The product 5c results from the same stereospecific cheletropic extrusion noted by Watanabe as only the *cis*-alkene isomer was observed. DFT calculations (Figure 5) indicate that the cheletropic extrusion path involving **5b** can proceed either directly from the rhodium ylide **INT1-b** via **TS4-b** or from the corresponding nonmetallic ylide **INT2-b** via **TS5-b**, with feasible activation barriers of 9.9 and 7.2 kcal mol^{-1}, respectively. This is a significantly higher barrier as compared to **TS3** (Figure 1) and suggests that the presence of the olefin in the MA is the key difference between the retro [2 + 1] and the ring expansion fates of the aziridinium ylide. Although the computed barrier for the analogous chelotropic extrusion from alkene ylide **INT2** is lower ($\Delta G^{\ddagger}$ = 5.1 kcal mol^{-1}), it is still higher than that computed for the process involving **TS3**, which makes this alternative pathway kinetically unfavored.

We propose that the alkene in the MA substrate, compared to a typical aziridine, alters two key parameters that combine to lower the energy barrier for ring expansion, as opposed to cheletropic extrusion. The additional alkene in **INT2** increases the ring strain of the methylene aziridine by roughly 4.5 kcal mol^{-1} (see section VII in the Supporting Information for the ring strain calculations); this serves to differentiate the bond strengths of the two aziridine C−N bonds in **INT2**, effectively biasing which C−N bond breaks first. Indeed, the computed NBO-Wiberg bond indices (WBIs) nicely agree with this hypothesis. Thus, whereas rather similar N−C WBIs were computed for **INT2-b** (0.78 and 0.79, respectively), the corresponding N−C bond strengths in the alkene-substituted counterpart **INT2** are markedly different (0.82 and 0.75, respectively). Therefore, in contrast to saturated bicylic aziridine **INT2-b**, where the equivalent C−N bond strengths facilitate concerted extrusion, the discrepancy between the bond strengths of the allylic and vinylic C−N bonds in **INT2** favors complete rupture of the allylic C−N bond first, effectively leading to subsequent ring expansion.

CONCLUSIONS

Through evidence obtained through combined computational and experimental studies, we have demonstrated that the ring expansion of MAs with rhodium-bound carbenes proceeds through an aziridinium ylide that undergoes a concerted, near-barrierless [2,3]-Stevens rearrangement to deliver substituted azetidines. The concerted nature of this rearrangement confers stereospecificity to the transformation. In comparison to the corresponding saturated bicyclic carbamate aziridines, the olefin of the MA plays a key role in the success of this chemistry, channeling the aziridinium ylide toward ring expansion processes vs the competing cheletropic extrusions. These studies provide a mechanistic basis for expanding our MA chemistry and point to important factors that must be considered in developing further approaches toward more general heterocyclic ring expansion reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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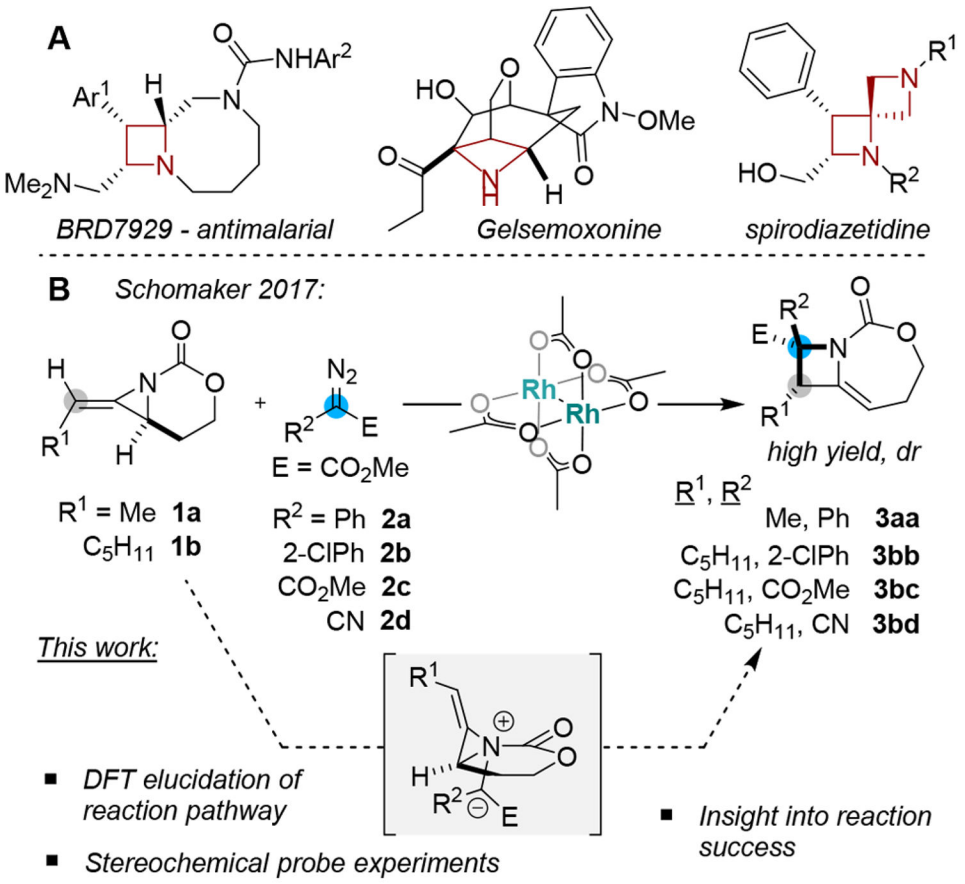
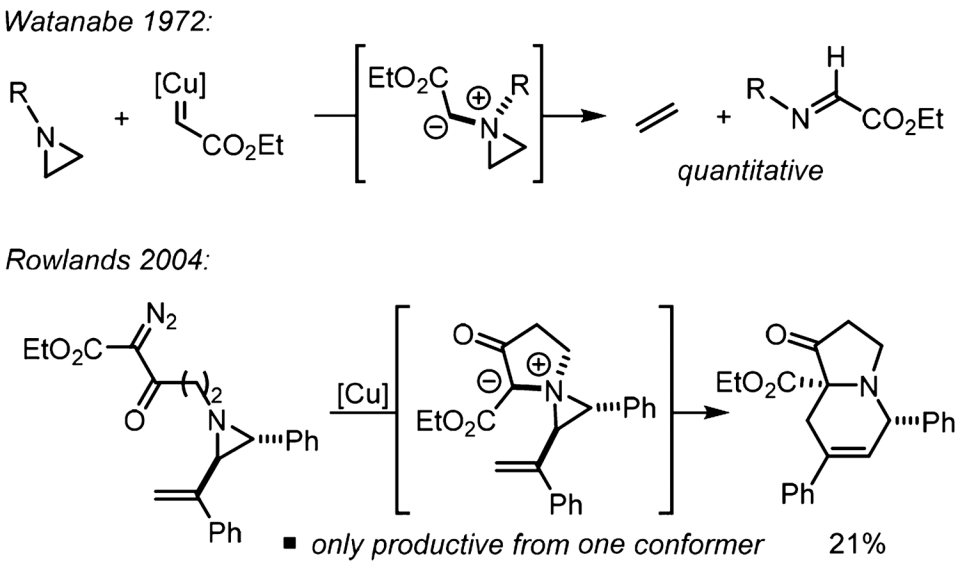
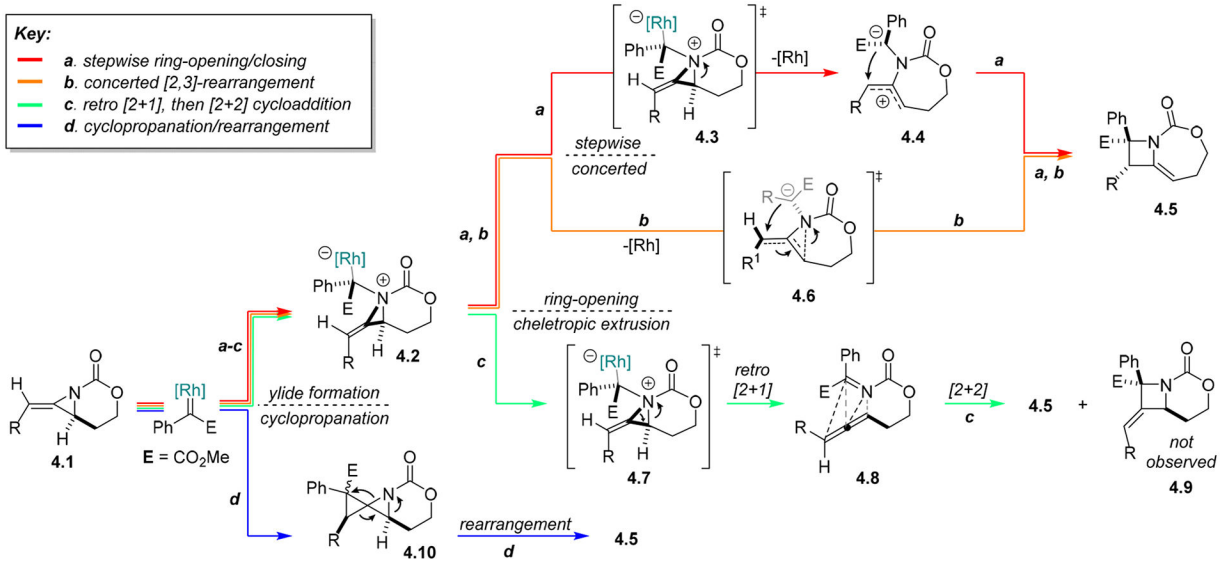
(20). The concavity of the methylene aziridines and the corresponding ylides discussed is reflective of the chirality at nitrogen that is present in these species. To the best of our knowledge, these bicyclic aziridines cannot undergo nitrogen inversion and thus contain nitrogen stereocenters; however, for the sake of simplicity in the text, we refer to the bowl-shaped structure of the MA and resulting ylides synonymously in place of nitrogen chirality.



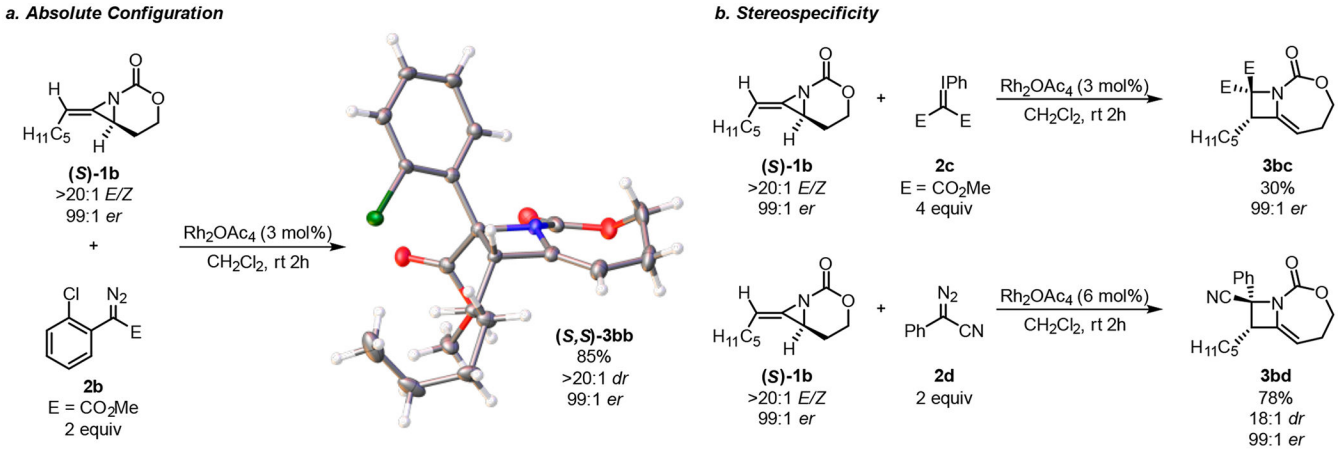
Scheme 1.
Bioactive Azetidines and Stereocontrolled Synthesis via Aziridine Ring Expansion



Scheme 2.
Reactivity of Typical Aziridinium Ylides

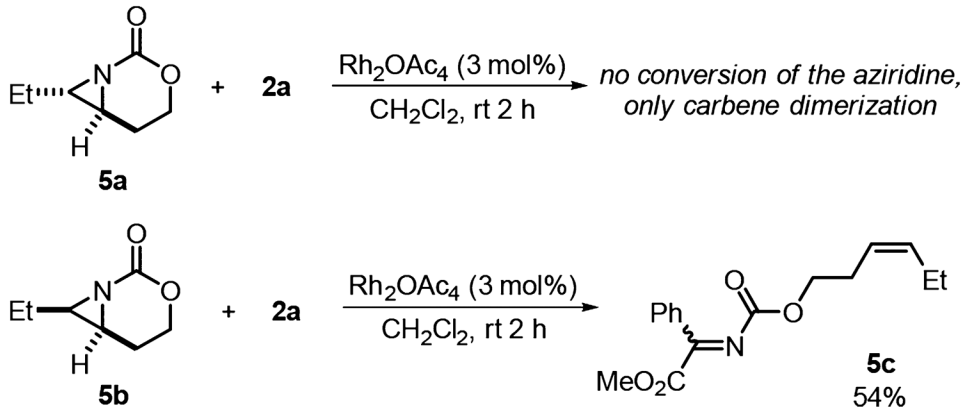


Scheme 3.
Potential Mechanisms for Aziridine Ring Expansion



Scheme 4.

Stereochemical Probes for the Ring Expansion of MAs to Methylene Azetidines



Scheme 5.
Fate of Bicyclic Aziridinium Ylides

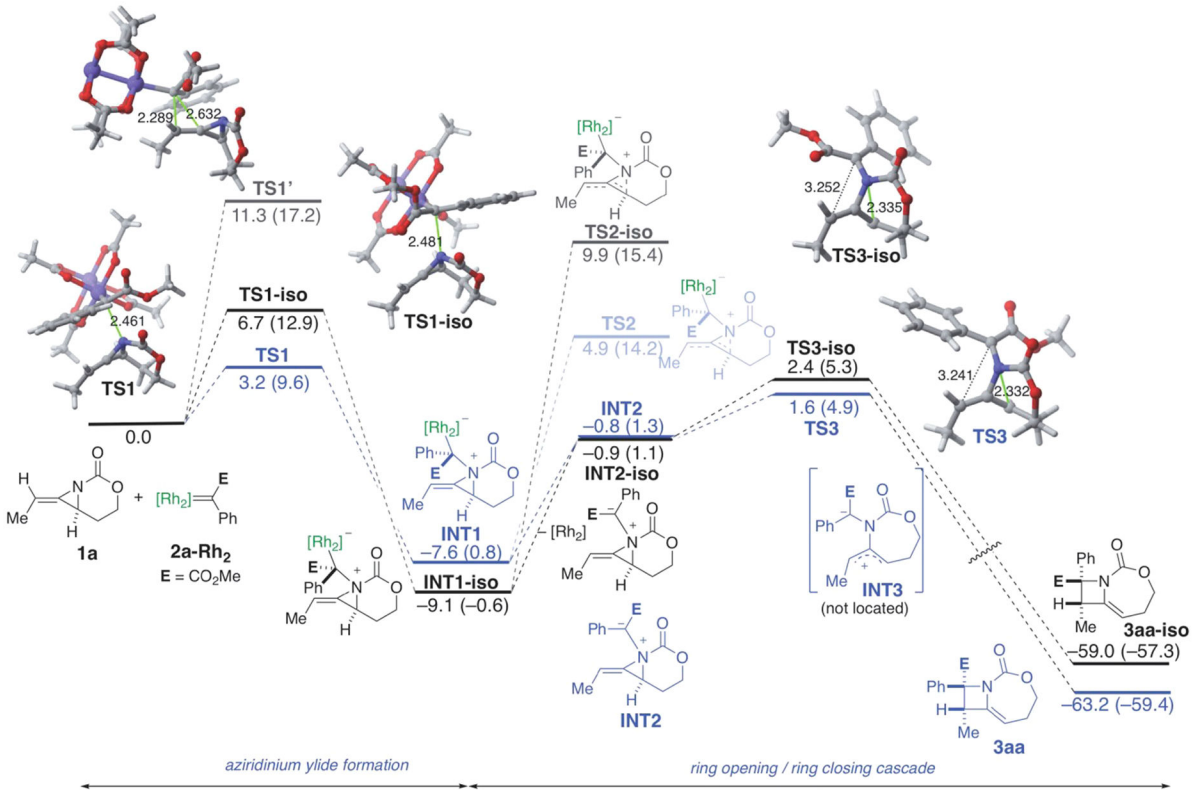


Figure 1.

Computed reaction profile for the process involving methyl-substituted MA **1a** and dirhodium-bound carbene **2a-Rh$_2$**. Relative free energies (ΔG, computed at 298.15 K and 1 M) and bond distances are given in kcal/mol and angstroms, respectively. All data have been computed at the SMD(CH_2Cl_2)-B3LYP-D3/def2-SVP level. Values within parentheses were computed at the SMD(CH_2Cl_2)-B3LYP-D3/def2-TZVPP//SMD(CH_2Cl_2)-B3LYP-D3/def2-SVP level.[16]

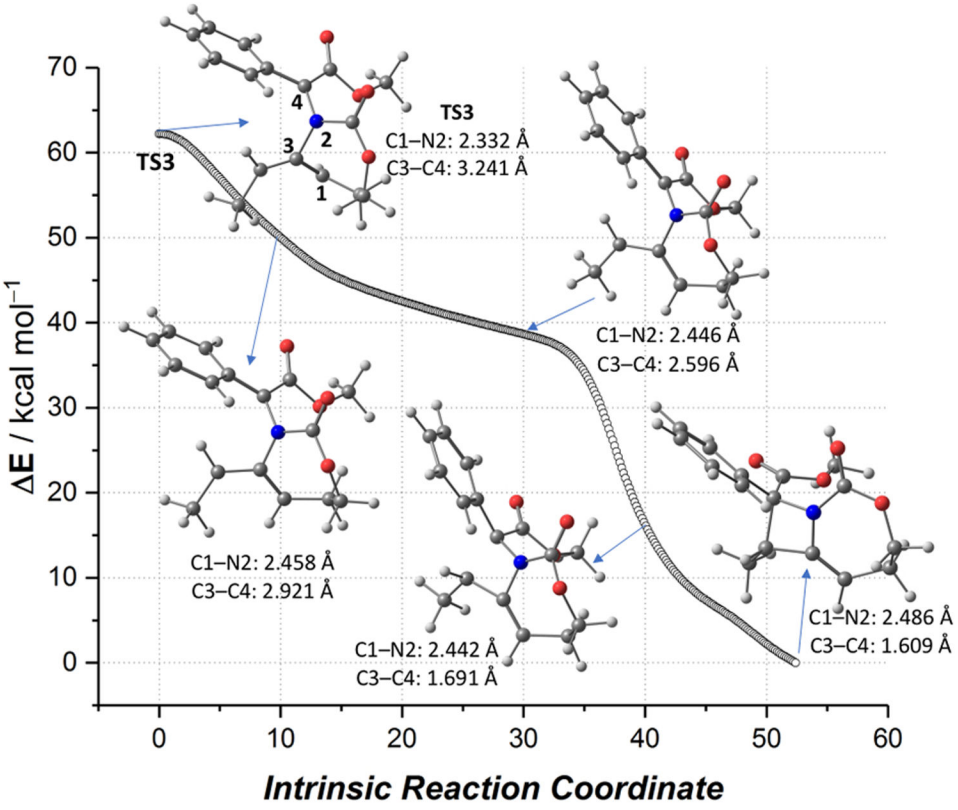


Figure 2.

Computed intrinsic reaction coordinate at the reference SCM(CH_2Cl_2)-B3LYP-D3/def2-SVP level for the transformation of **TS3** into **3aa**.

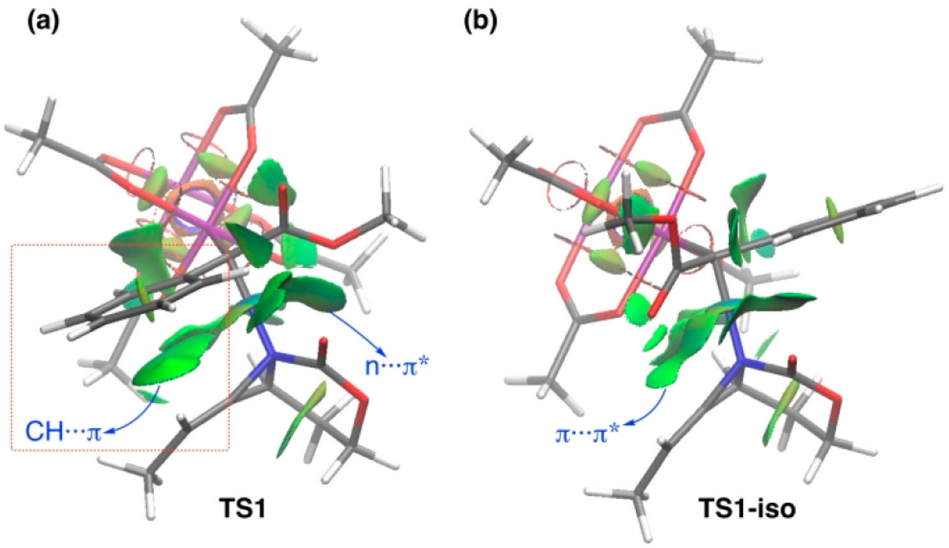


Figure 3.

Contour plots of the reduced density gradient isosurfaces (density cutoff of 0.03 au) for **TS1** (a) and **TS1-iso** (b). The green surfaces indicate attractive NCIs.

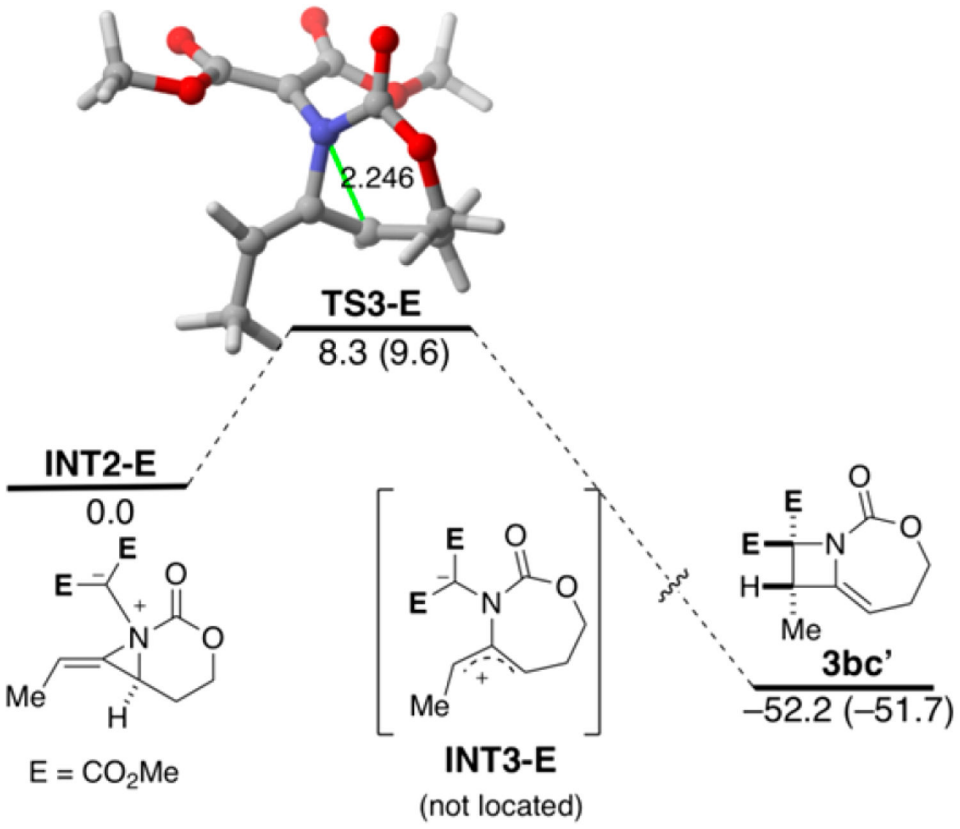


Figure 4.
Computed reaction profile for the **INT2-E** → **3bc′** transformation. See Figure 1 for additional caption details.

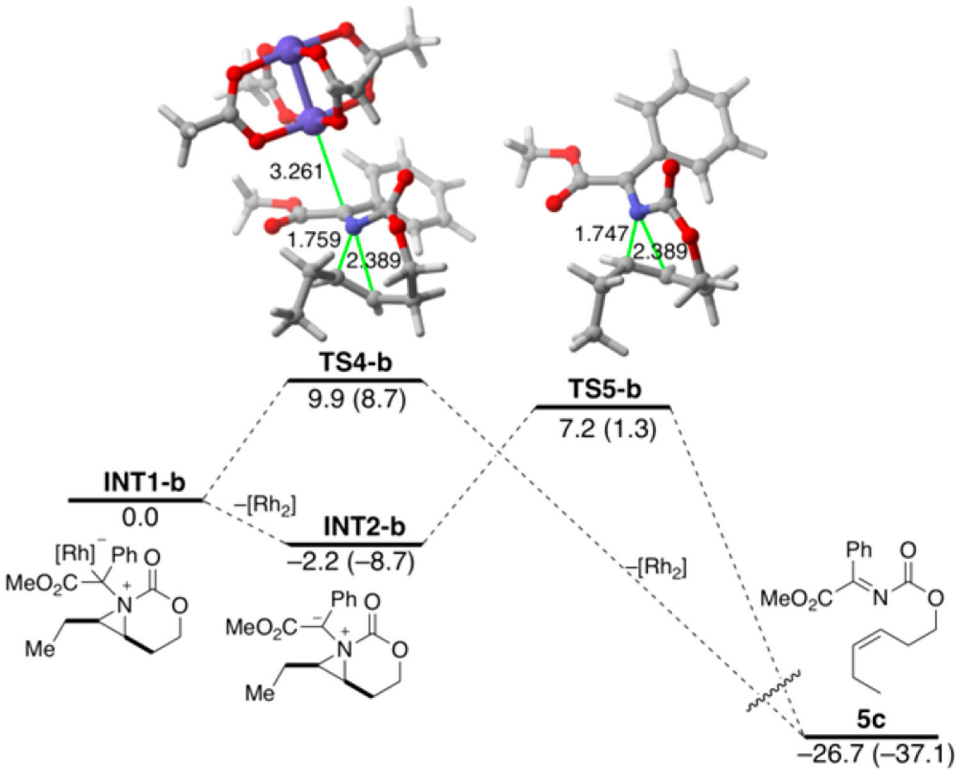


Figure 5.

Computed chelotropic extrusion from the aziridinium ylide formed in the reaction of **5b** and dirhodium-bound carbene **2a-Rh$_2$**. See Figure 1 for additional caption details.