Intermolecular [3+3] Ring-Expansion of Aziridines to Dehydropiperidines through the Intermediacy of Aziridinium Ylides

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ABSTRACT: Bicyclic aziridines undergo formal [3+3] ring expansion reactions when exposed to rhodium-bound vinyl carbenes to form complex dehydropiperidines in a highly stereocontrolled rearrangement. Mechanistic studies and DFT computations indicate the reaction proceeds through the formation of a vinyl aziridinium ylide; this reactive intermediate undergoes a concerted, asynchronous, pseudo-[1,4]-sigmatropic rearrangement to directly furnish the heterocyclic products with net retention at the new C-C bond. In combination with an asymmetric silver-catalyzed aziridination developed in our group, this method quickly delivers enantioenriched scaffolds with up to three contiguous stereocenters. The mild reaction conditions, functional group tolerance, and high stereochemical retention of this method are especially well-suited for appending piperidine motifs to natural product and complex molecules. Ultimately, our work establishes the value of underutilized aziridinium ylides as key intermediates in strategies to convert small, strained rings to larger *N*-heterocycles.

The importance of nitrogenated heterocycles in pharmaceuticals, natural products, and fine chemicals continues to drive innovative strategies for their efficient syntheses from readily available precursors.[1-8] The ability to improve upon existing preparations of known compounds, enable alternate retrosynthetic approaches to useful building blocks, and increase opportunities to explore novel chemical space outside of 'flatland' are compelling reasons to develop new approaches to *N*-heterocycles.[9] Piperidines rank as the most prominent *N*-heterocyclic pharmacophore in current drugs on the market, appearing in ~55% of all FDA-approved drugs containing at least one *N*-heterocycle, as well as in numerous bioactive natural products.[2a] Convergent methods that unite multiple reactive fragments, particularly hetero-[4+2] cycloadditions (Figure 1a, left), deliver substituted dehydropiperidines in enantioenriched form;[10,11] however, critical substrate and/or catalyst control over regio- and stereoselectivity is challenging and often results in narrow scope. Traditional preparations of stereodefined piperidines using intramolecular S_N2-type reactions require selective installation of functional groups prior to ring closure, resulting in lower efficiency, modularity, and step economy as the desired target's complexity increases.[2a] Herein, we report an attractive and surprisingly underexplored strategy to assemble stereochemically complex and densely substituted heterocycles via an intermolecular ring expansion between aziridines and Rh-supported vinyl carbenes. This chemistry enables rapid, convergent access to enantioenriched dehydropiperidines (Figure 1a), with the potential for flexible introduction of additional groups on the *N*-heterocycle. The strain and charge

of the bicyclic aziridinium ylide intermediate drives reaction under mild conditions, rendering it ideal for late-stage functionalization of biomolecules.

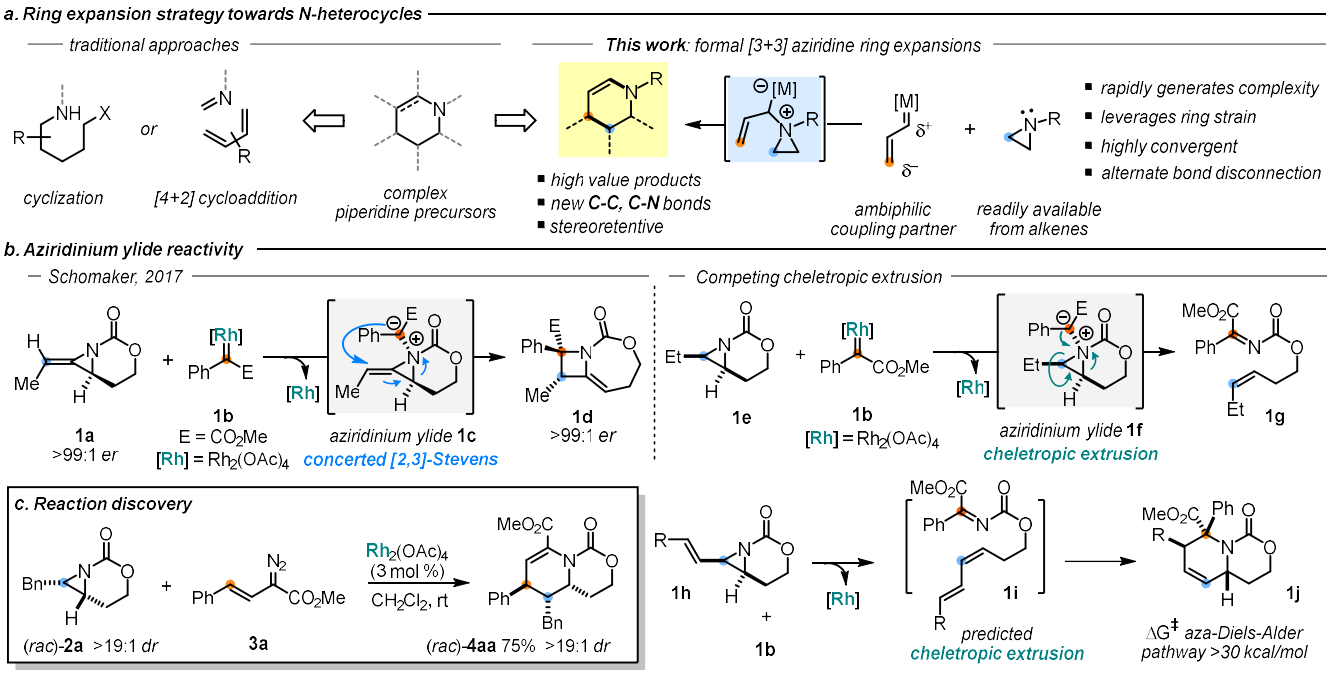
Aziridines are an ideal starting material for conversion to larger nitrogenated heterocycles. They are easily accessible from a variety of alkenes by nitrene transfer or from simple manipulations of epoxides; methods for asymmetric aziridination enable these strained rings to be prepared with substantial stereochemical and substitutional complexity.[12] One of the most attractive features of aziridines is their ~26 kcal mol^{-1} of ring strain, ensuring a favorable thermodynamic driving force for ring-opening reactions. Indeed, methods to transform aziridines to azetidines and pyrrolidines initiated by initial nucleophilic attack are well-established in the literature.[13] However, from a kinetic perspective, aziridines can often require highly engineered substrates to achieve effective ring expansions. For example, the inclusion of a vinyl group in an aziridine precursor may provide kinetic impetus to drive successful metal-mediated isomerizations and other functionalizations.[13d,e] However, utilizing unbiased aziridines for stereocontrolled expansions to larger *N*-heterocycles can be challenging, as epimerization or racemization of the aziridine must be avoided in order to relay stereochemical information at sp^3 stereocenters to the product with excellent fidelity.[14] Despite these difficulties, the ease of aziridine preparation and their strain-loaded reactivity make them attractive scaffolds for the discovery of new reactivity.[12]

We previously leveraged the unusual strain (~42 kcal/mol) in methyleneaziridine **1a** to achieve a formal [3+1] reaction to furnish azetidine **1d** upon exposure to rhodium-supported carbene **1b** (Figure 1b, left).[15,16] Mechanistic studies support initial formation of the aziridinium ylide **1c**, which subsequently undergoes a highly asynchronous, concerted [2,3]-Stevens rearrangement to directly form **1d**.[17] The complete transfer of the *ee* in **1a** to **1d** provided further experimental evidence to support this mechanism. The efficiency of this transformation, involving stereospecific formation of two C-C and C-N bonds and two adjacent stereocenters in an intermolecular two-fragment coupling, prompted further studies of aziridinium ylides, particularly efforts to extend this reactivity to simpler, unbiased aziridines containing less strain than **1a**. Unfortunately, removing the key exocyclic alkene of **1a** in **1e** (Figure 1b) gave only cheletropic extrusion with **1b** to furnish **1g**. Extending the conjugation in vinylaziridine **1h** was also calculated to result in cheletropic extrusion to **1i**, with the subsequent aza-Diels-Alder requiring high temperatures to form racemic **1j**. Both these examples highlight the difficulty in controlling the reactivity of aziridinium ylides, an observation that has likely hampered their broader utility as reactive intermediates for the syntheses of *N*-heterocycles.

We hypothesized incorporating additional unsaturation into an ampiphilic metal-supported carbene precursor (Figure 1a) instead of the aziridine might preclude cheletropic extrusion; sequential ring-opening and ring-closing of the aziridinium ylide would furnish a dehydropiperidine, a net [3+3] annulation of a vinyl carbenoid and an aziridine. One other report in the scant literature on aziridinium ylides details productive C-C bond formation. In 2004, Rowlands demonstrated a single example of a dehydropiperidine in 21% yield via intramolecular formation of a vinyl aziridinium ylide, followed by [2,3]-rearrangement.[18] The low yield was ascribed to the required coplanarity of the anion and the vinyl group; if the ylide formed with the opposite stereochemistry at nitrogen, hydride transfer and other decomposition pathways, such as cheletropic extrusion,[19] competed with the productive ring expansion.

To our delight, reaction of *cis*-alkene-derived aziridine **2a** with Davies' styrenyl diazoacetate[20] **3a** under dirhodium catalysis produced **4aa** in 75% yield and in excellent >19:1 diastereoselectivity (Figure 1c). Three note-worthy features of this strategy that contribute to its success

Figure 1. Background and reaction design.



include: 1) invoking ambiphilic reactivity of the aziridine, where the ring nitrogen behaves as a nucleophile towards the electrophilic metal-supported carbenoid, then the resultant aziridinium ylide functions as an electrophile, 2) effective leveraging of the conformation of the bicyclic aziridine, which minimizes pyramidal inversion of the nitrogen and delivers only one diastereomer of the intermediate aziridinium ylide, and 3) harnessing the zwitterionic character of the ylide to drive reaction under mild conditions and retain the stereochemical information present in the aziridine precursor.

The difficulty of studying carbene transfer using traditional kinetics, particularly when slow addition is required, led us to turn to DFT calculations[21] to gain more insight into the mechanism of the ring expansion (Figure 2). The pathway involving the reaction of the methyl-substituted aziridine **2b** and the [Rh_2]-carbenoid derived from diazoacetate **3a** to furnish piperidine **4ba** was explored. Nucleophilic attack of the aziridine nitrogen atom on the carbon of the Rh-supported carbenoid occurs as the first step, forming aziridinium ylide **INT1** *via* transition state **TS1**.[16,17] A saddle point was associated with dissociation of the dirhodium catalyst from the nitrogen to produce zwitterion **INT2**, where the negative charge is fully delocalized into the allylic system (see inset in Figure 2). Two fates were envisaged for this species, one involving a cheletropic extrusion/aza-Diels-Alder reaction and the other a ring-opening/ring-closing sequence to furnish the observed **4ba**. In the former case, **INT2** forms azadiene **INT3** through a cheletropic extrusion reaction (*via* **TS2**), followed by a concerted aza-Diels-Alder cycloaddition (*via* **TS3**). Experimentally, we found that subjecting enantioenriched (*S,R*)-**2a**[22] to the standard reaction conditions resulted in transfer of the *ee* to unsaturated piperidine (*R,R,S*)-**4aa** with good fidelity (Figure 2, bottom). Thus, the cheletropic extrusion path does not account for the observed enantioretention in the reaction of (*S,R*)-**2a** to (*R,R,S*)-**4aa**; in addition, the height of the barrier of **TS3** relative to **INT3** argues against the aza-Diels-Alder reaction proceeding at room temperature. Based on these observations, a pathway involving a pseudo-[1,4]- sigmatropic rearrangement of **INT2** *via* **TS2'**, is favored as: (i) it proceeds with a lower barrier than the alternative

cheletropic extrusion ($\Delta\Delta G^{\neq}$ = 5.3 kcal/mol), (ii) enables delocalization of the negative charge of the ylide through the vinyl group to produce the observed dehydropiperidine, and (iii) directly parlays absolute and relative stereochemical information from the aziridine into the product.[23,24] Most importantly, computational studies support our experimental observations of chirality transfer from aziridine (*S,R*)-**2a** to the product (*R,R,S*)-**4aa**.[16,17]

Finally, it is important to highlight that the unique carbamate tether is critical to the high *dr* associated with **4ba**. As the stereochemistry is set during the initial formation of the aziridinium ylide is subsequently transferred to **4ba**, it is imperative that **2b** does not undergo pyramidal inversion following attack of the aziridine on the Rh-supported carbene. While the electron-withdrawing carbamate in the tether may contribute to the lack of pyramidal inversion, the bicyclic nature of the substrate is likely to play the key role in restricting conformational flexibility.[25] Ongoing investigations in our lab are exploring other strategies to avoid mixtures of invertomers in the formation of the aziridinium ylide to eliminate the requirement for a bicyclic aziridine substrate; these results will be reported in due course.

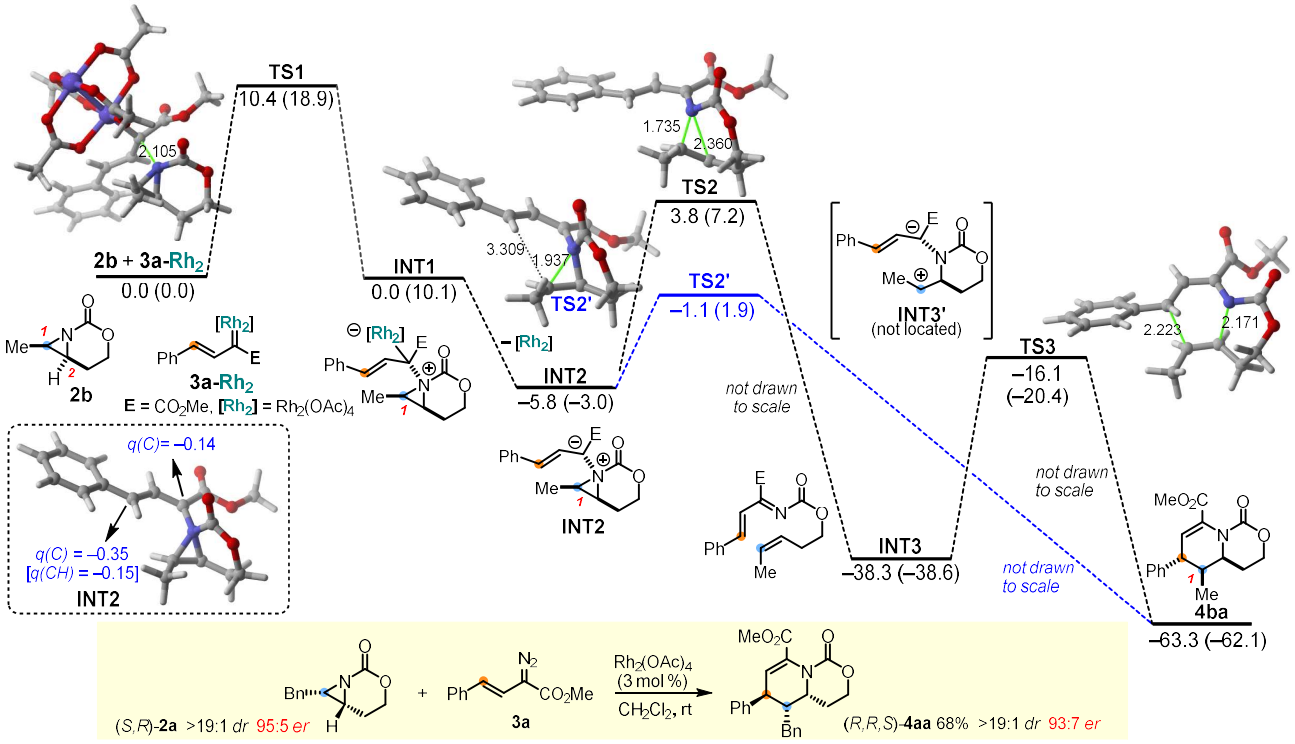


Figure 2. Computed reaction profile for the process involving aziridine **2b** and Rh$_2$-bound carbene **3a**-Rh$_2$. Relative free energies (ΔG, computed at 298.15 K and 1 M) and bond distances are given in kcal/mol and Å, respectively. All data have been computed at the SMD(CH_2Cl_2)-B3LYP-D3/def2-SVP 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 of theory.

The retention of stereochemistry at the internal aziridine carbon C1 of **2b** in the heterocycle product bears further comment; it may be tempting to invoke an intramolecular S_N2 attack to close the ring. However, even if the charge is placed on the benzylic carbon, this orbital π cannot overlap effectively with the σ* of the aziridinium ylide. Computations shed insight into this unusual stereoretentive S_N1-like

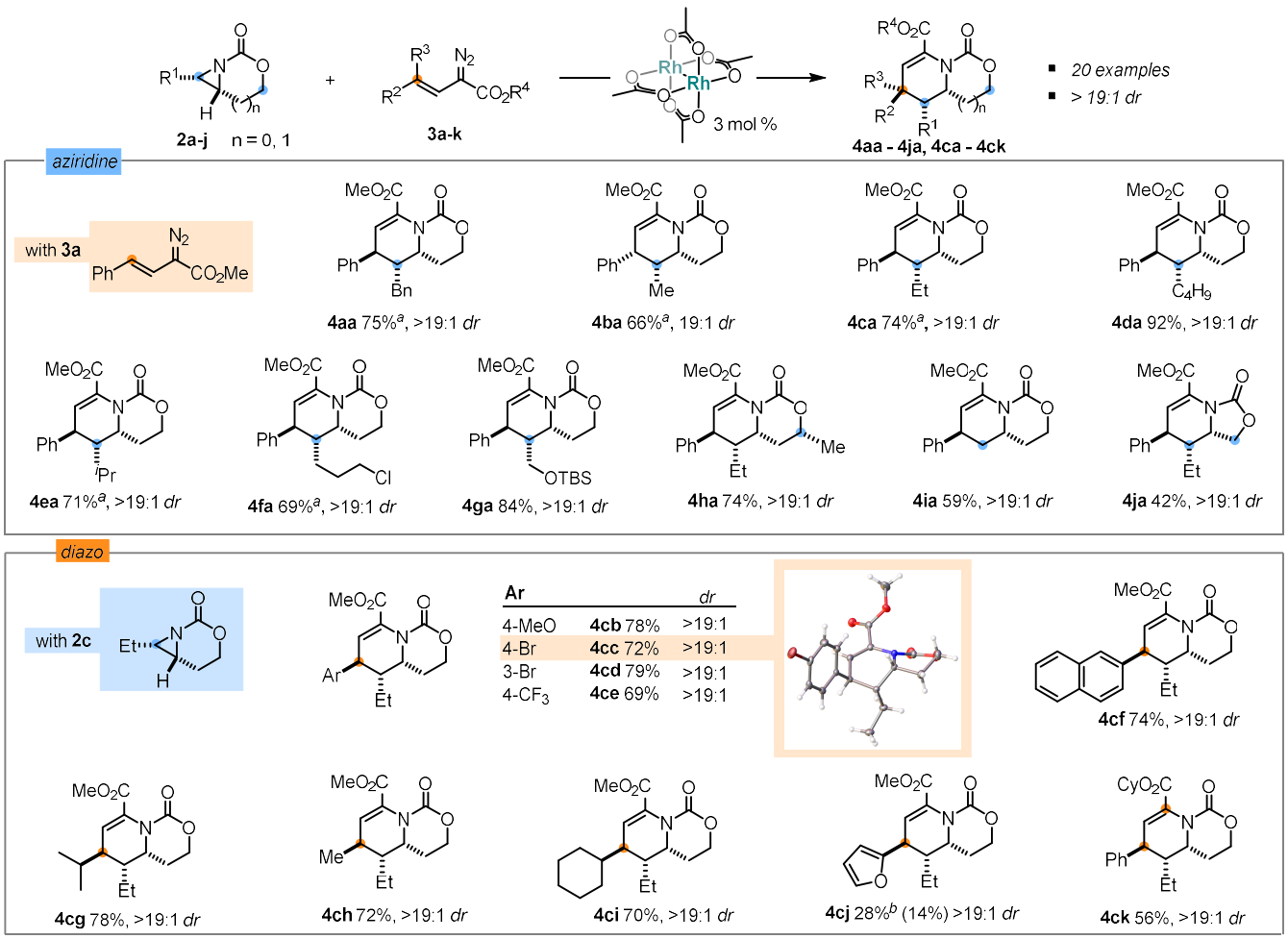
mechanism. Firstly, **TS2'** is comprised mainly of C-N bond breakage at the external C1-N bond, which elongates to 1.937 Å. This contrasts to the bond-breaking sequence in **TS2**, where the internal bicyclic C2-N bond shows more elongation at 2.360 Å, as compared to the C1-N bond (1.735 Å). Thus, even though both **TS2** and **TS2'** can be described as relatively low-barrier, early transition states, the extent to which the C-N bond breaks appears biased. Secondly, consistent with our experimental results, **TS2'** predicts that ring-opening of the C1-N aziridine bond and subsequent C-C bond formation proceeds with retention, due to the stereochemical relationship established between the nitrogen and the carbon substituents on the aziridine during formation of the aziridinium ylide. The Me-bearing C1 of the original aziridine **2b** is essentially a full carbocation, with nearly complete C-N rupture in **TS2'** just prior to the ring closure. We are unaware of any other non-metal induced aziridine substitutions of this type that occur with retention of configuration, highlighting the unique nature of tethered aziridine opening of the bicyclic aziridinium ylide intermediate.

Optimization of conditions for the [3+3] aziridine ring expansion showed that the simple dirhodium paddlewheel complex $Rh_2(OAc)_4$ was the superior catalyst using slow addition of the vinyl diazoacetate (see the SI for further details). With these conditions in hand, the aziridine scope was explored (Table 1, top) using **3a** as the vinyl carbene precursor. Linear alkyl groups on the aziridines **2a-d**, including benzyl, methyl, ethyl, and *n*-butyl, gave good yields of the products **4aa-4da** in high *dr*. ^{1}H NMR spectroscopy indicated a *dr* of at least >19:1 for the unsaturated piperidine products; minor amounts of the presumed diastereomers were noted. In select cases, SPC was used to more accurately quantify the *dr*. Increasing the bulk of the substituent on the aziridine to an isopropyl group in **2e** furnished **4ea** in 71% yield and excellent *dr*. Alkyl chloride and ether functionalities were also well-tolerated to deliver piperidines **4fa** and **4ga**. Alkyl substitution α to the carbamate tether in **2h** (*dr* >19:1) gave a 74% yield of **4ha** as a single diastereomer. Aziridine **2i**, unsubstituted at the terminal carbon, gave **4ia** in 59% yield and >19:1 *dr*. Finally, it was not necessary to have the carbamate contained in a six-membered ring, as the [5.3]-bicyclic aziridine **2j** (R^1 = Et, n = 0) gave the [5.6]-bicyclic ring **4ja** in 42% yield and in >19:1 *dr*.

We next examined the scope of the carbene precursor using ethyl-substituted aziridine **2c** (Table 2, bottom). The impact of the electronics of a series of phenyl-substituted diazo acetates **3a-3f** was investigated first. Similar yields were obtained for **4ca** and **4cb-4cc**, irrespective of whether the diazoester carbene precursor contains electron-donating or neutral substituents, suggesting there is little effect of the electronics of the styrene on the reaction outcome. A single crystal X-ray structure of **4cc** established the relative stereochemical configuration in the heterocycle product (see expansion for **4cc** and the SI for further details), confirming earlier nOe studies. Moving the Br to the *meta* position in **3d** resulted in a similar 79% yield of **4cd**. Diazoester **3e**, bearing a strongly electron-withdrawing trifluoromethyl group, gave a 69% yield of **4ce**, also in good *dr*, providing a convenient way to introduce valuable fluorine into the piperidine product.

Carbene transfer of the naphthyl-substituted **3f** provided **4cf** in similar yield and *dr* as compared to **4ca**. It was not necessary to employ a styrenyl-derived diazoester, as a series of β-alkyl-substituted diazoesters **3g-i** all resulted in good yields of unsaturated piperidines **4cg**-**4ci** as single diastereomers as determined by ^{1}H NMR. The furan-substituted **3j** gave **4cj** in only 14% isolated yield, as these oxygen heterocycles have been reported to be reactive in the presence of metal-supported carbenoids.[26,27] Bulking up the methyl ester on the diazoester to a cyclohexyl ester was also successful, producing **4ck** in 56% yield and >19:1 *dr*.

Table 1. Scope of the aziridine and diazoester in Rh-catalyzed ring expansions to unsaturated piperidines.



[a] Conditions: 3 mol % $Rh_2(OAc)_4$, 0.05 M CH_2Cl_2, rt, slow addition of diazocetate as a solution in CH_2Cl_2. [b] NMR yield.

The synthetic utility of the sequential nitrene/carbene transfer reaction could be amplified by running it in tandem with asymmetric alkene aziridination to form enantioenriched piperidines over two steps. In 2017, we disclosed an asymmetric aziridination protocol using silver bisoxazoline (BOX) complexes to enact intramolecular aziridination of homoallylic carbamate esters to achieve high enantioselectivities with a cost-effective catalyst.[22] Application of our asymmetric aziridination to the carbamate of (3Z)-3-penten-5-phenyl-1-ol gave enantioenriched (*S,R*)-**2a**[22] in 95:5 *er* (bottom of Figure 2 and Figure 3a). Treatment of (*S,R*)-**2a** under the standard reaction conditions gives (*R,R,S*)-**4aa** with minimal loss of *ee*. Alternatively, a single catalyst could be used to accomplish the sequential nitrene/carbene transfer. Preparation of the allylic *N*-tosyloxycarbamate ester **5**, according to the method described by Lebel and coworkers,[28] followed by treatment with $Rh_2(OAc)_4$ and K_2CO_3 generated the intermediate [5.3]-bicyclic aziridine. Filtration and solvent exchange, followed by slow addition of **3a**, gave the unsaturated piperidine **4ja** in 54% and >19:1 *dr*. Efforts to identify chemo- and enantioselective Rh-catalyzed aziridination catalysts are underway to secure access to these valuable heterocycles in one pot with good *ee*.

Further functionalization of the unsaturated piperidine **4ca** provides fully substituted, stereochemically rich piperidines in just two steps from the bicyclic aziridine. Indeed, treatment of **4ca** with a higher order cuprate furnished **6** in 57% yield and >19:1 *dr* through a

diastereoselective conjugate addition reaction; the relative stereochemistry was verified by both NOE and ^{1}H NMR coupling constants (Figure 3b, see the Supporting Information for more details).[29] In an initial effort to expand the conjugate addition reaction to include other heteroatom nucleophiles, we found treatment of **4ca** with DBU and various nucleophiles did not furnish a conjugate addition product, but rather produced styrene **7** in 71% yield and excellent *dr* (Figure 3b*)*. Further treatment of **7** with *m*CPBA yielded epoxide **8** in equally good yield and *dr* (Figure 3b). Furthermore, inspired by MacMillan and co-workers,[30] **4ca** was found to undergo a radical Michael addition with Boc-protected tryptophan **9** to yield fully elaborated piperidine **10** in 32% yield as a single diastereomer. Although the yield was modest, this transformation rapidly builds complexity in two steps from a simple aziridine.

Finally, the mild reaction conditions and the transfer of the stereochemical information in the aziridine (*S,R*)-**2a** to (*R,R,R*)-**4aa** with good fidelity promoted us to explore the potential of this chemistry to append biomolecules to our unsaturated piperidine scaffolds. D-Phenylalanine and cholic acid were transformed into suitable diazoesters **11a** and **11b** (Figure 3c), then subjected to treatment with (*S,R*)-**2a** (94% *ee*) under the standard reaction conditions. The products **12a** and **12b** were obtained in good yields, with excellent diastereoselectivities and enantiomeric ratios. We envisage this strategy could be effectively applied to explorations of new bioactive chemical space uncovered through fragment-based screening approaches.

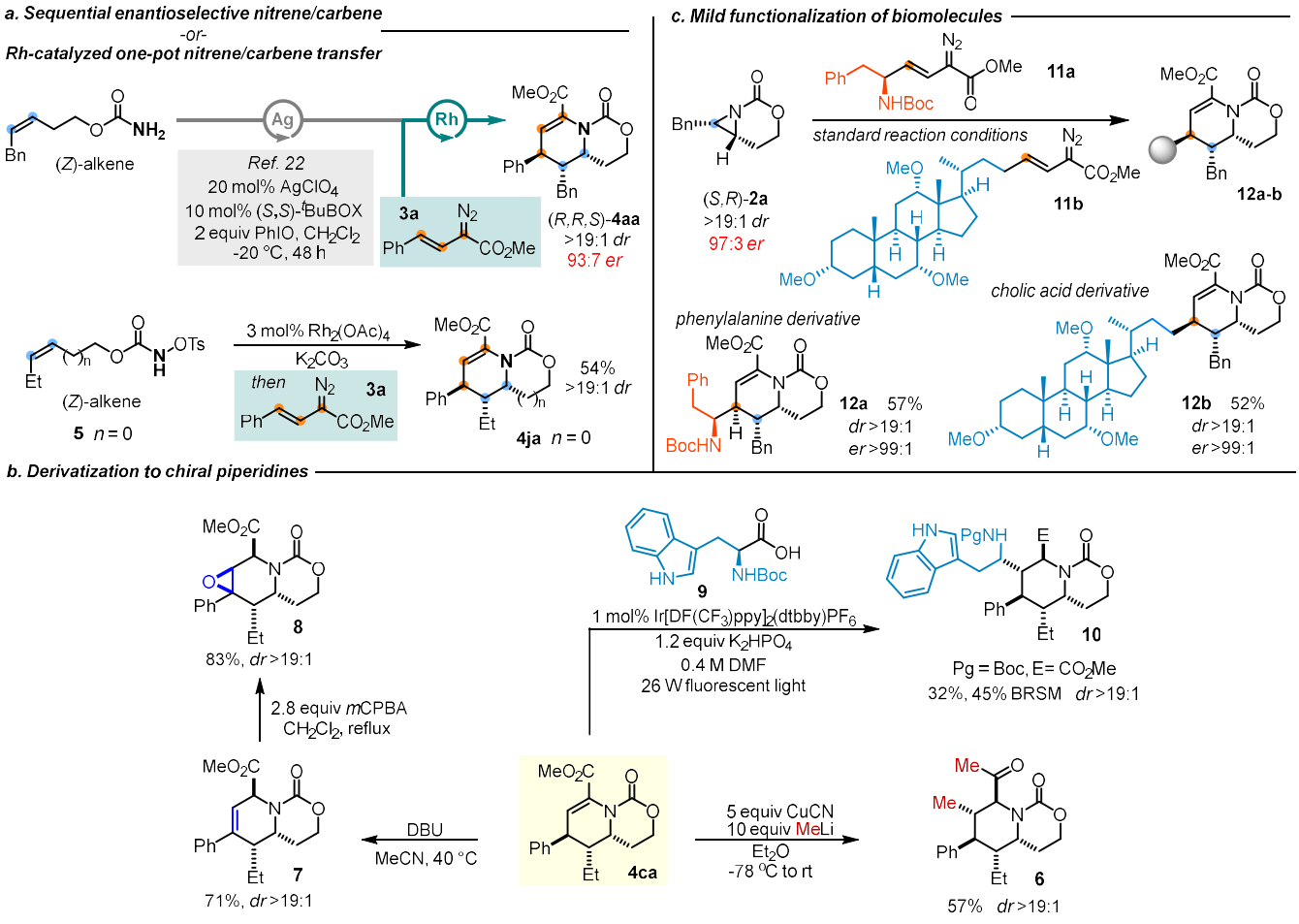


Figure 3. Tandem nitrene/carbene chemistry and derivatization of products.

In conclusion, aziridinium ylides, accessed in high diastereoselectivity from the intermolecular reaction of simple aziridines with metal-bound vinyl carbenes, are shown to be efficient intermediates for the conversion of small ring heterocycles to complex piperidines, a privileged motif in bioactive compounds. DFT computations, in tandem with transfer of chirality experiments, revealed that the ylides undergo a concerted, asynchronous, pseudo-[1,4]-sigmatropic rearrangement to yield products in high diastereoselectivity and with retention of *ee* installed in the aziridine precursor. Surprisingly, this chemistry is the first to bypass deleterious cheletropic extrusion using unbiased aziridines, suggesting that rearrangements of other strained ylides can likewise be controlled in a productive fashion. Additionally, this mechanism proceeds with retention at the C-C bond, a unique consequence of the S_N1-like closing of the vinyl anion tether. We anticipate this report will spur further research into the reactivity of both aziridinium ylides and other onium ylides derived from small ring heterocycles, thus expanding the utility of these species for the synthesis of valuable azetidines, pyrrolidines, piperidines, pyrazines, and other *N*-heterocycles.[31]

Supporting Information

Experimental procedures, computational details, and characterization data for all new compounds are available in the Supporting Information.

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Notes

The authors declare no competing financial interests.

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