

Rhodium-Catalyzed One-Carbon Ring Expansion of Aziridines with Vinyl-*N*-trifosylhydrazones for the Synthesis of 2-Vinyl Azetidines

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Abstract: Azetidines, being four-membered *N*-heterocycles, possess significant potential in contemporary medicinal chemistry owing to their favorable pharmacokinetic properties. Regrettably, the incorporation of functionalized azetidines into pharmaceutical lead structures has been impeded by the absence of efficient synthetic methods for their synthesis. In this study, a Rh-catalyzed one-carbon ring expansion of aziridines with vinyl-*N*-trifosylhydrazones is presented, which facilitates the synthesis of high value-added 2-alkenyl azetidine products. This research represents the first example of ring expansion of aziridines enabled by vinyl carbenes. Additionally, a one-pot two-step protocol, initiated from cinnamaldehyde, was successfully achieved, offering a step-economical and facile approach for the synthesis of these compounds. The pivotal aspect of this successful transformation lies in the in situ formation of an alkenyl aziridinium ylide intermediate. Experimental investigations, coupled with computational studies, suggest that a diradical pathway is involved in the reaction mechanism.

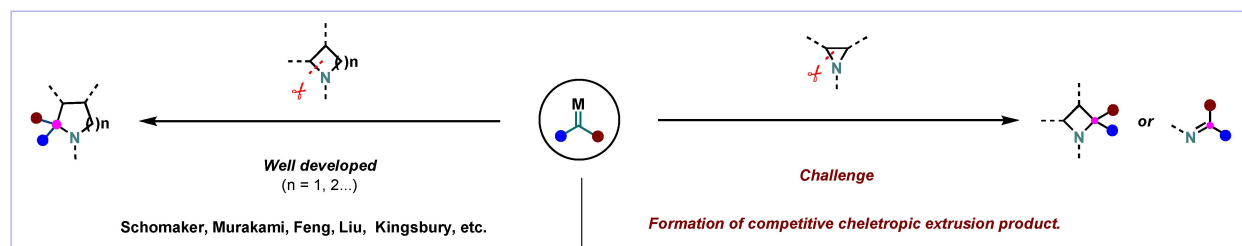
Introduction

Saturated compounds play a prominent role in the field of medicinal chemistry and are considered essential building blocks in drug discovery. In fact, they constitute over 59 % of U.S. FDA-approved drugs.^[1,2] The well-defined, three-dimensional structure of these sp³-rich scaffolds not only grants access to unique chemical space, but is also associated with improved pharmacokinetic properties, bioavailability, and metabolic stability.^[3,4] Consequently, the precise synthesis and manipulation of ring systems hold paramount significance in the field of organic chemistry. Skeletal ring enlargement presents a potent approach to transform common starting materials into structurally intricate frame-

works, resulting in substantial modifications to the chemical and biological properties of the initial compounds.^[5–7] Recently, there has been a resurgence of interest in the one-carbon ring expansion of cyclic molecules through carbene insertion. This methodology allows for the conversion of readily available cyclic structures into ring-expanded compounds.^[8–14] In the context of skeletal editing of saturated *N*-heterocycles via one-carbon insertion, one potential mechanism for achieving ring expansion involves the sequential formation of an ammonium ylide and subsequent [1,2]-stevens rearrangement, enabling efficient one-carbon ring expansion. The pioneering works of multiple research groups have demonstrated the application of this approach for achieving 4- to 5-membered ring expansions through reacting with an azetidine with a diazo compound, leading to the formation of the corresponding pyrrolidine product (Figure 1A, left).^[15–19] Considering the widespread usage of nitrogen heterocycles in various sectors of the chemical industry, particularly in the pharmaceutical field, the extension of this concept to other saturated *N*-heterocycles would be of immense value.

Azetidines represent crucial structural motifs found in a diverse range of medicinally significant compounds, including Cobimetinib, Tebanicline, Penaresidin A and L-azetidine-2-carboxylic acid (Figure 1B).^[20,21] However, existing synthetic approaches for the preparation of azetidines typically necessitate the use of prefunctionalized starting materials and involve multistep sequences.^[22–25] A question arises as to whether readily available aziridines, which serve as ideal starting materials for the synthesis of larger *N*-heterocycles,^[26–28] could provide a more expedient pathway to azetidines through [1,2]-stevens rearrangement via the formation of aziridinium ylides. However, due to the inherent reactivity of the aziridinium ylides, they often undergo highly favorable cheletropic extrusion of olefins. This characteristic poses a significant challenge in the development of ring-expansion from aziridine to azetidines (Figure 1A, right).^[29] Despite multiple attempts in 1972,^[30–32] one example successful example was realized by Arnold et al. in 2022, which employed enzyme as catalysts to circumvent competing pathways and enable the [1,2]-stevens rearrangement of aziridinium ylides.^[33] However, this reaction exhibited significantly lower yields and demonstrated limited substrates scope and functional group tolerance (nine examples, 75 %, 18 %–38 % yields) using the current P411-AzetS lineage performs. Moreover, the carbene source is restricted to less readily available diazo compounds in this method, thereby severely limiting their broader applications and molecular flexibility.^[34] Consequently, there is a high

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A. The state-of-the-art one carbon ring expansion of saturated *N*-heterocycles

B. Examples of bioactive molecules containing an azetidines motif

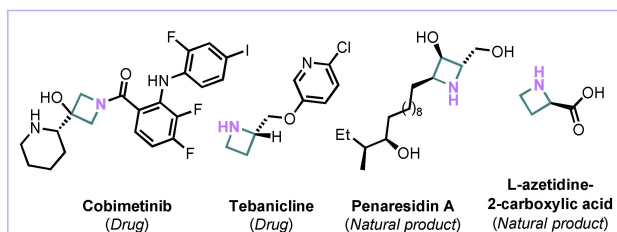
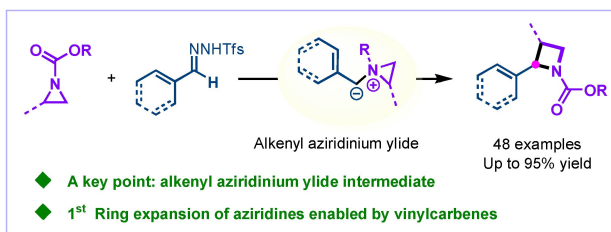
C. One-carbon ring expansion of aziridines with vinyl-*N*-trifosylhydrazones

Figure 1. A. One-carbon ring expansion of saturated *N*-heterocycles via carbene insertion process: drawbacks and solutions. B. Examples of bioactive molecules containing an azetidines motif. C. One-carbon ring expansion of aziridines with vinyl-*N*-trifosylhydrazones (this work).


demand for conceptually distinct approaches in this field. In recent years, the reactivity of aziridinium ylides, as demonstrated by Schomaker, and other researcher, has shown promise in [2,3]-stevens rearrangements and other ring-opening reactions when employing rigid bicyclic aziridines as precursors.^[35–38] Considering the significance of azetidines in organic synthesis and medicinal chemistry, coupled with the recent advancements in the chemistry of *N*-trifosylhydrazones,^[39–43] a novel strategy is presented herein for the achievement of one-carbon ring expansion from aziridines to azetidines (Figure 1C). The successful transformation relies on the in situ formation of an alkenyl aziridinium ylide intermediate. This study presents the first documented instance of ring expansion of aziridines through the utilization of vinyl carbenes.^[44,45]

Results and Discussion

Initially, the model substrates selected for investigation in this study were vinyl-*N*-trifosylhydrazone **1a** and benzyl aziridine 1-carboxylate **2** (Table 1). These substrates were chosen to examine the feasibility of the single-atom ring expansion of aziridines. Under the reaction conditions involving K_2CO_3 and $Rh_2(Oct)_4$ in dichloromethane (DCM) at 60 °C, the model reaction successfully afforded the desired 2-vinyl azetidine **3** in a high yield of 90%. Notably, this transformation occurred without the occurrence of cheletropic extrusion of olefin and the formation of α -imino ester by-products. Various Rhodium catalysts, such as $Rh_2(esp)_2$, $Rh_2(OAc)_4$ and $Rh_2(TFA)_2$ were examined, and all gave the ring-expansion product **3** in high yield (entries 2–4). $Rh_2(OAc)_4$ exhibited the highest yield of 95%, making it the optimal catalyst for this transformation (entry 3). In contrast, other well-known carbene insertion catalysts such as $Cu(acac)_2$,^[20] $AgOTf$,^[43] $Tp^{Br3}Ag$ ^[40] and $FeTPPCL$, yielded

lower product yields or were found to be ineffective for this transformation (entries 5–8). The reaction temperature was found to be a crucial parameter, as both increasing and decreasing it resulted in a decrease in product yield (entries 9 and 10). Furthermore, the choice of vinyl diazo surrogate had a notable impact on the efficiency of the reaction. When vinyl-*N*-trisylhydrazone (**1b**) or vinyl-*N*-tosylhydrazone (**1c**) were used as substitutes for **1a**, lower yields were obtained (entries 11–12).^[46,47] Consequently, entry 3, which corresponds to the use of $Rh_2(OAc)_4$ as the catalyst, was selected as the optimal condition for the subsequent investigations regarding the scope reaction.

Having established the optimized conditions, the scope of the one-carbon ring expansion of aziridines was investigated, focusing on the utilization of different vinyl-*N*-trifosylhydrazone substrates. As depicted in Figure 2A, the single-atom ring expansion reaction proved to be an applicable to a range of β -aryl substituted vinyl-*N*-trifosylhydrazones, featuring diverse substituents on the benzene ring. This led to the formation of the desired 2-vinyl azetidine products (**4–17**) with yields ranging from 73 % to 95 %. In particular, the reaction proceeded smoothly with various substituents on the *para*-position of aryl ring in vinyl-*N*-trifosylhydrazones resulting in the formation of products **4–13** with yields ranging from 73 % to 95 %. Encouragingly, common functional groups such as alkoxy, alkyl, aryl, halogen (F, Cl and Br), cyano, trifluoromethyl, oxytrifluoromethyl and ester were all well tolerated in the reaction. Likewise, ortho-, meta-, disubstituted and trisubstituted β -aryl vinyl-*N*-trifosylhydrazones did not hinder the reaction, resulting in the formation of the desired 2-alkenyl azetidine products **14–21** with high yields ranging from 78 % to 92 %. Vinyl-*N*-trifosylhydrazones derived from fused ring cinnamaldehydes were also successfully subjected to the reaction, providing compounds **22** and **23** in yields of 87 % and 91 %, respectively. Vinyl-*N*-trifosylhydrazones contain-

Table 1: Optimization of the reaction conditions.^[a]


Entry	Cat. (xx mol %)	T (°C)	Yield of 3 (%) ^[b]
1	Rh ₂ (Oct) ₄ (2.5 mol %)	60	90
2	Rh ₂ (esp) ₂ (2.5 mol %)	60	93
3	Rh₂(OAc)₄ (2.5 mol %)	60	95
4	Rh ₂ (TFA) ₂ (2.5 mol %)	60	50
5	Cu(acac) ₂ (10 mol %)	60	20
6	AgOTf (10 mol %)	60	15
7	Tp ^{Br3} Ag (5 mol %)	60	30
8	FeTPPCL (2 mol %)	60	0
9	Rh ₂ (OAc) ₄ (2.5 mol %)	25	40
10	Rh ₂ (OAc) ₄ (2.5 mol %)	80	62
11 ^[c]	Rh ₂ (OAc) ₄ (2.5 mol %)	60	80
12 ^[d]	Rh ₂ (OAc) ₄ (2.5 mol %)	60	Trace
13 ^[e]	Rh ₂ (OAc) ₄ (2.5 mol %)	60	40

[a] Reaction conditions: **1a** (0.45 mmol), **2** (0.3 mmol), K₂CO₃ (0.66 mmol), Cat. (xx mol %) in DCM (3 mL) at 60 °C under N₂ for 6 h. [b] Isolated yields. [c] **1b**. [d] **1c**, with 80% pyrazole was obtained. [e] **1d**.

ing a medically relevant heteroaromatic moieties, such as benzofuran, pyridine and furan were also found to be compatible with the reaction conditions. This enabled the synthesis of the corresponding products (**24–26**) with good yields ranging from 55 % to 80 %.

Vinyl-*N*-triflylhydrazones containing an unsaturated group were also successfully subjected to this transformation, leading to the formation of the corresponding azetidine products. The use of 1, 3-diene, 1, 3, 5-triene, and 1, 3-alkyne functionalities resulted in yields ranging from 58 % to 78 % for the synthesis of products **27–30**. These compounds are valuable building blocks in synthetic chemistry.^[48] Gratifyingly, β -alkyl substituted vinyl-*N*-triflylhydrazones, which were prone to self-cyclization to pyrazoles,^[49] were also found to be suitable for this C–N bond insertion reaction to afford the products **31** and **32** successfully. Moreover, β , β -diaryl substituted vinyl-*N*-triflylhydrazones were found to be suitable substrate, leading to the formation of β , β -diaryl vinyl substituted azetidine **33** in 70 % yield.

Continuing the investigation, the use of α , β -disubstituted vinyl-*N*-triflylhydrazones as starting materials led to the synthesis of multi-substituted or functionalized 2-vinyl azetidine products **34–37** with yields ranging from 62 % to 80 %. Notably, the presence of a halogen atoms in the products provided a convenient handle for subsequent coupling reactions. Finally, the reaction scope was also examined regarding the aziridine component in reactions

involving vinyl-*N*-triflylhydrazone **1a**. As depicted in Figure 2B, aziridine possessing carbamate protecting groups with primary alkyl, secondary alkyl, or tertiary alkyl moieties underwent smooth conversion to yield products **38–42** with high yields ranging from 91 % to 93 %. Moreover, aziridine featuring functional groups on the terminal carbon of the alkyl chain (e.g., chloro and trichloromethyl groups) also proved to be suitable substrates. These substrates yielded products **43** and **44** in high yields of 88 % and 95 %, respectively. Additionally, an aziridine with a carbamate protecting group containing an allyl group was also compatible with the reaction conditions, affording the desired product **45** in a yield of 85 %. In addition, aziridine substrates containing a methyl group on the carbon backbone of the ring were also suitable for this reaction, leading to the formation of 2, 3-disubstituted azetidine product **46** with a yield of 65 %. It should be noted that the aforementioned aziridine substrates were unable to undergo ring expansion using enzyme as catalysts in the previous studies.^[33] Regrettably, *N*-alkyl, *N*-aryl, and other nitrogen protecting groups such as amides and sulfonamides were found to be unsuitable for ring expansion due to their increased susceptibility to ring opening through hydrolysis, which was more pronounced compared to unsubstituted aziridine rings.

Given the accessibility of vinyl-*N*-triflylhydrazones from their corresponding cinnamaldehyde derivatives, the

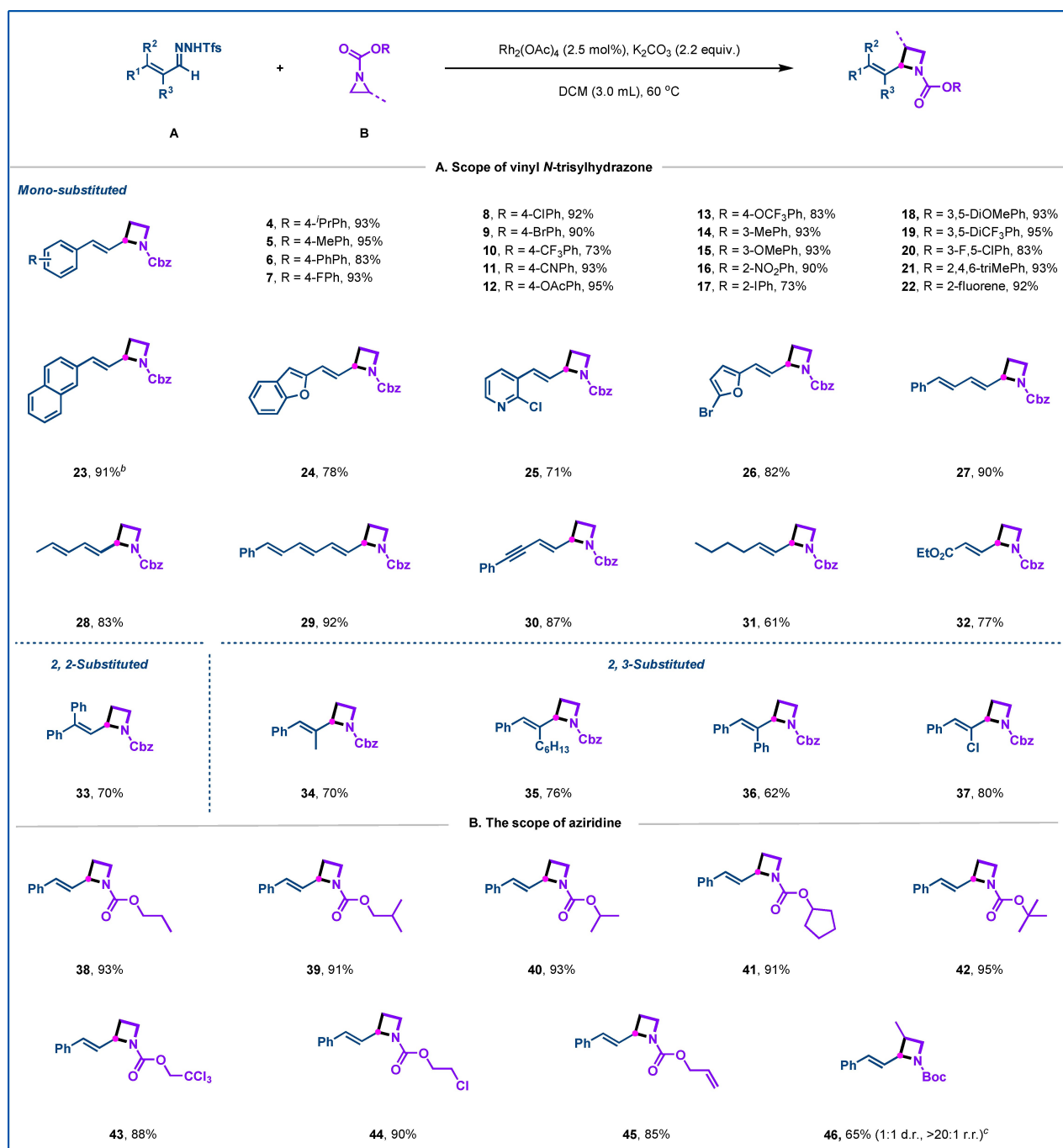


Figure 2. Scope of one-carbon ring expansion of aziridines.^[a] Reaction conditions: **A** (0.45 mmol, 1.5 equiv.), **B** (0.3 mmol, 1 equiv.), K₂CO₃ (0.66 mmol, 2.2 equiv.) and Rh₂(OAc)₄ (2.5 mol %) in DCM (3 mL) at 60 °C for 6–12 h. ^b **A** (0.45 mmol, 1.5 equiv.), **2** (0.3 mmol, 1 equiv.), K₂CO₃ (0.66 mmol, 2.2 equiv.) and Rh₂(esp)₂ (2.5 mol %) in DCM (3 mL) at 60 °C for 6–12 h. ^c Diastereoselectivity (d.r.) and regioisomeric ratios (r.r.) were determined by analysis crude ¹H NMR analysis.

focus was directed towards exploring the feasibility of directly accessing the target products from cinnamaldehydes through a one-pot sequence involving a tandem hydrazone synthesis/C–N bond insertion reaction. As depicted in Figure 3A, it was satisfying to confirm that aryl, and alkenyl-substituted alkenyl azetidines (**3**, **27** and **30**) could be synthesized with yields of 63–91 %, by employing vinyl-*N*-trifosylhydrazones generated in situ from the correspond-

ing cinnamaldehydes. This was achieved through the subsequent insertion of vinylcarbenes into C–N bonds. Furthermore, other carbamate protecting groups, such as alkyl and Boc groups, were also found to be suitable for this “one-pot” tandem protocol, leading to the formation of products **38** and **42** with yields of 88 % and 92 %, respectively. Overall, this tandem process provides a step-economical and straightforward method for the preparation of 2-vinyl

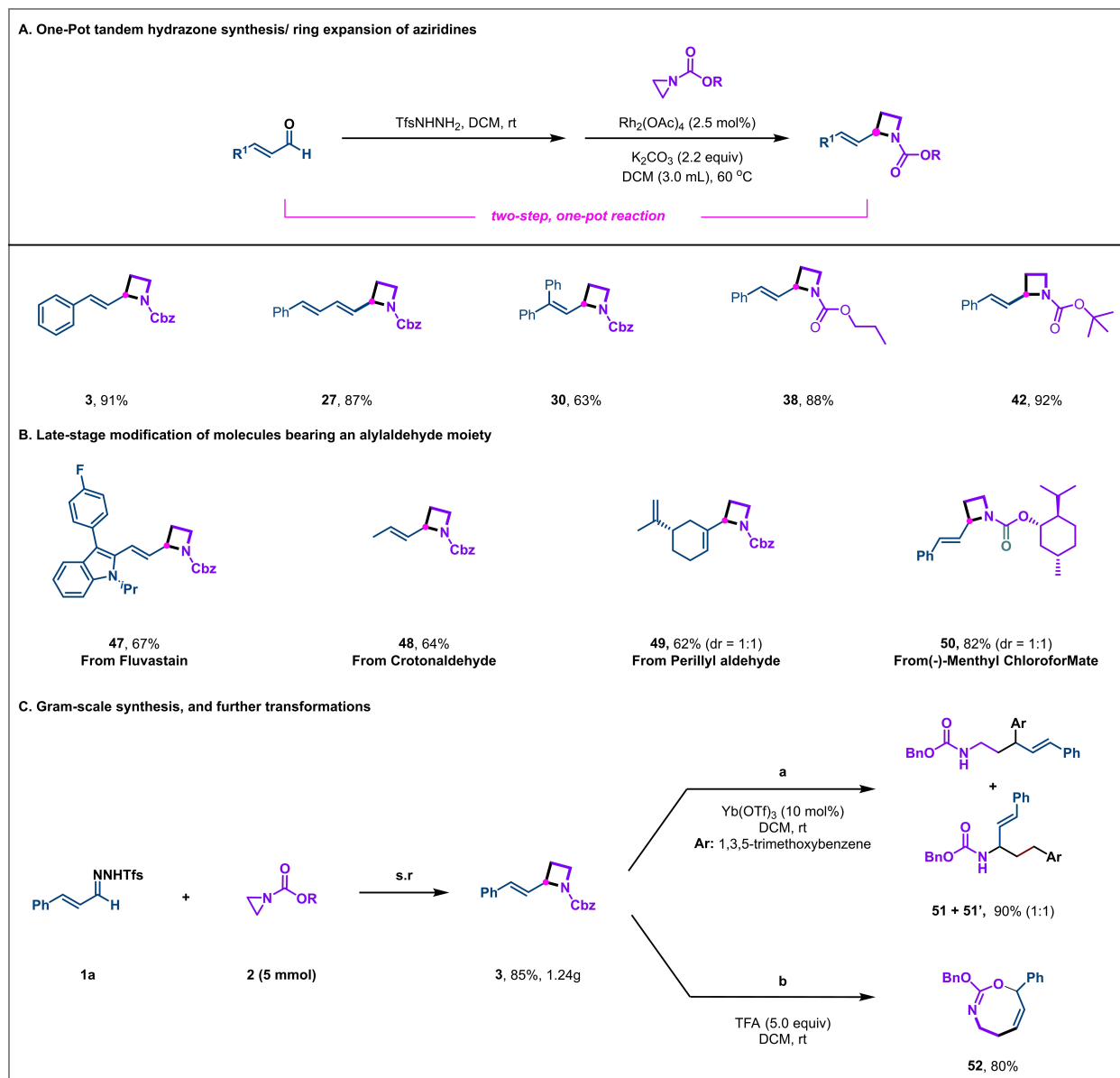


Figure 3. One-Pot tandem hydrazone synthesis/ring expansion of aziridines, late-stage modification of molecules, gram-scale synthesis, and further transformations. Reaction conditions for further transformations: a. **3** (0.2 mmol), 1,3,5-trimethoxybenzene (2.0 equiv) and Yb(OTf)₃ (10 mol%) in DCM (2.0 mL) at room temperature for 1 h; b. **3** (0.2 mmol) and TFA (5.0 equiv) in DCM (2.0 mL) at room temperature for 1 h.

aziridine products. Additionally, considering the pharmaceutical significance of the aziridine moiety in various medicinal scaffolds, the late-stage diversification of certain biologically active cinnamaldehydes, such as Fluvastatin, Crotonaldehyde, Perillyl aldehyde and (–)-Menthyl Chloroformate were subjected to the reaction conditions and successfully furnished the desired products (**47–50**) with yields ranging from 51 % to 84 % (Figure 3B). To showcase the synthetic utility of this novel method, a gram-scale reaction was performed, resulting in the desired product **3** with a yield of 85 % (1.75 g). Two transformations were performed on the 2-vinyl azetidine according to Figure 3C. A noteworthy observation was made during the nucleophilic ring opening of 2-vinyl azetidine with 1, 3, 5-trimethoxybenzene, resulting in the formation of a mixture of compounds **51** and **51'** in 90 % yield.^[50] Interestingly, ring expansion of 2-vinyl azetidine could be achieved using TFA to form 5, 8-dihydro-4H-1, 3-oxazocine product **52**. This is in contrast to a previous report where 2, 2-disubstituted azetidine was employed to produce disubstituted 1,3-oxazinan-2-ones.^[51]

To gain a deeper understanding of the reaction mechanism, mechanistic experiments were performed (Figure 4). In the absence of Rh₂(OAc)₄, no reaction occurred, indicating the essential role of forming the rhodium-bound carbene prior to the ring expansion step (Figure 4A, 1). Furthermore, the investigation of other substituted *N*-trifosylhydrazones, including those with aryl, and alkyl groups, under-

oxybenzene, resulting in the formation of a mixture of compounds **51** and **51'** in 90 % yield.^[50] Interestingly, ring expansion of 2-vinyl azetidine could be achieved using TFA to form 5, 8-dihydro-4H-1, 3-oxazocine product **52**. This is in contrast to a previous report where 2, 2-disubstituted azetidine was employed to produce disubstituted 1,3-oxazinan-2-ones.^[51]

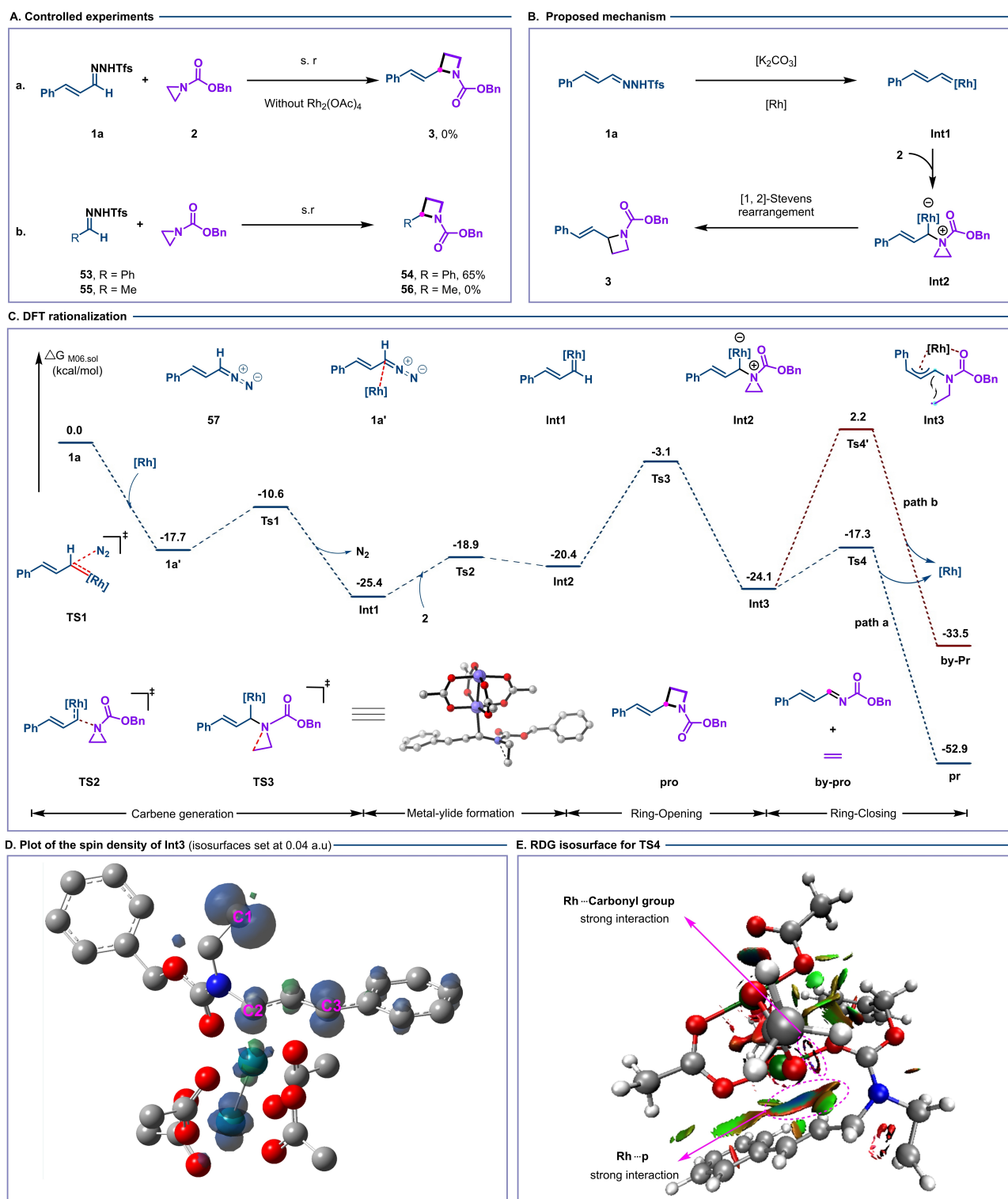


Figure 4. Mechanistic study and proposal for the ring expansion of aziridines. The energy profile was obtained by DFT calculations at freq SMD(DCM)-M06/6-31G (d, p)/SDD(Rh) at 333.1 K.

standard reaction conditions were carried out (Figure 4A, 2). It was observed that only *N*-trifosylhydrazones derived from benzaldehyde provided the desired 2-phenyl substituted azetidines **54** with a yield of 65%. This result suggests that both the aryl and alkenyl groups play a crucial

role in the formation of the aziridinium ylides and the subsequent rearrangement process. A proposed mechanism for the ring expansion of aziridines is shown in Figure 4B. Initially, decomposition of *N*-trifosylhydrazone under K_2CO_3 and $Rh_2(OAc)_4$ generated rhodium carbene Int1.

Subsequently, the aziridine nitrogen atom undergoes a nucleophilic attack on the carbon atom of the rhodium-carbene, leading to the formation of aziridinium ylide Int2. Finally, the Int2 could undergo the desired [1,2]-Stevens rearrangement preferentially over cheletropic extrusion of ethylene, liberating the desired product and regenerating the rhodium catalyst.

In order to study the subsequent processes in this work, the calculations were initiated directly with the vinyl diazo species **57** (Figure 4C). Initially, the vinyl diazo species **57** interacted with $\text{Rh}_2(\text{OAc})_4$, leading to the formation of **1a'**. Subsequently, through the transition state TS1, nitrogen was eliminated to generate the alkenyl rhodium carbene Int1 ($\Delta G = 7.1$ kcal/mol). The energy barrier for generation of Rh-coordinated aziridinium ylides Int2 through the reaction between benzyl aziridine 1-carboxylate **2** and the rhodium carbene is relatively low (6.5 kcal/mol). Subsequently, the Rh-coordinated aziridinium ylides undergo ring opening to form the diradical Int3 through the transition state TS3, with an energy barrier of 17.3 kcal/mol.^[52] This step is considered to be the rate-determining step of the entire reaction. Notably, the presence of the alkenyl group is essential for the stabilization of TS3. Indeed, the spin density in the diradical species of Int3 is primarily concentrated at the C_1 atoms, with an additional contribution at the C_2 and C_3 atoms of alkenyl carbene (Figure 4D).^[53] Lastly, the diradical species Int3 undergoes ring closure, preferably at the C_2 atoms through a formal 1,2-migration, rather than at the C_4 atoms via a pseudo-[1,4]-sigmatropic rearrangement. This process occurs through the transition state TS4 ($\Delta G^\ddagger = 6.8$ kcal/mol) and results in the formation of the final ring-expanded product **3** (path a). A competitive reaction involving cheletropic extrusion of olefins from Int3 was also investigated and evaluated. However, the calculated energy barrier for the aforementioned reaction is very high, at 22 kcal/mol. This is significantly higher than the energy barrier for the ring expansion process and therefore is excluded as a viable pathway (path b). Furthermore, an investigation was conducted to explore a potential concerted pathway from Rh-coordinated aziridinium ylides Int2 to form final product **3**. The color-filled reduced density gradient (RDG) iso-surface further confirmed the existence of Rh and vinyl group interaction (Figure 4E).

Conclusion

Conclusively, a novel one-carbon ring expansion of aziridines enabled by vinyl carbenes has been developed. This method utilizes easily decomposable vinyl-*N*-trifosylhydrazones as the source of the vinyl carbene, enabling efficient and selective ring expansion reactions. The straightforward reaction protocol presented in this study can be successfully applied to various vinyl-*N*-trifosylhydrazones containing diverse functional groups. This versatile method enables the synthesis of 2-vinyl azetidines with good to excellent yields. Moreover, the resulting products obtained from the ring expansion reactions can easily undergo further ring-opening and expansion processes. The combination of experimental

and computational studies provides insights into the mechanistic aspects of this ring expansion, indicating that it proceeds via a diradical mechanism.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: vinyl carbenes • ring expansion • aziridines • 2-vinyl azetidines

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