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Ring expansion of unsubstituted aziridinium ylides to trifluoromethylated dehydropiperidines†

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The first rhodium-catalyzed [3 + 3] ring expansion of unsubstituted aziridines was achieved using trifluoroalkenyl *N*-triftosylhydrazones as vinylcarbene precursors to afford a series of structurally diverse 2-trifluoromethylated dehydropiperidines under mild conditions. DFT calculations supported a scheme involving aziridinium ylide formation followed by a [1,4] sigmatropic rearrangement sequence. Notably, the reaction shows broad scope and functional group tolerance, which enables the translation of routine olefination of unsubstituted aziridinium ylides into a strategy for heterocyclic ring syntheses. Beyond enabling access to valuable dehydropiperidines from easily prepared starting materials, we also demonstrated the synthetic utility of this approach in the late-stage modification of bioactive compounds.

Nitrogen ylides are the third most common type of onium ylides and have been widely employed as intermediates for the preparation of diverse amine scaffolds for decades.[1–7] Given the importance of nitrogen in pharmaceuticals and natural products[8,9] the chemistry of nitrogen ylides is highly attractive. Among nitrogen ylides,[1,3,7,10–12] aziridinium ylides (which are generated by the reaction between an aziridine and metal-supported carbene) are a subclass of ammonium ylides that are useful synthetic intermediates (Fig. 1A).[12] In this context, Schomaker *et al*. made significant contributions using aziridinium ylides generated from rigid bicyclic aziridines and Rh-bound carbenes, allowing diverse ring expansion reactions to afford a variety of heterocycles such as azetidines,[13,14] dehydropiperidines,[15] dehydromorpholines,[16] and [3,9]-bicyclic aziridines (Fig. 1A, left).[17] Despite these significant advances, the chemistry of aziridinium ylides generated from unsubstituted aziridines remains poorly understood and underexplored (Fig. 1A, right). The fundamental reason why aziridinium ylides are under-investigated is their innate reactivity, which leads them to undergo cheletropic extrusion of olefins. In 1972, Watanabe observed formation of ethylene and an α-imino ester attempting to convert an unsubstituted aziridinium ylide to an azetidine.[18] In 2004, Rowlands suppressed cheletropic extrusion in favor of a [2,3]-Stevens rearrangement of an aziridinium ylide. Unfortunately, a competing [1,5]-H shift led to only a 21% yield of the heterocycle.[19] So far, only two examples have described the transformations of unsubstituted aziridinium ylides to azetidines *via* one-carbon homologation of aziridines by enzyme- and Rh-catalyzed carbene insertion processes (Fig. 1B).[20,21] Therefore, creatively altering the reactivity of unsubstituted aziridinium ylides to form other heterocycles with suitable metal-supported carbenes controlling the chemo-, regio-, and stereochemistry is highly desirable.

Trifluoromethylated piperidines are key structural motifs in a variety of medicinally important compounds.[22–26] For example, they exhibit anti-inflammatory properties[27] and act as Janus kinase inhibitors.[28,29] However, the efficient synthesis of these heterocyclic scaffolds is relatively rare due to the lack of trifluoromethylated substrates.[30,31] We questioned whether readily available aziridines, which serve as ideal starting materials for the synthesis of larger N-heterocycles,[32,33] could provide a more expedient pathway to azetidines through [1,4]-sigmatropic rearrangement *via* the formation of aziridinium ylides with vinyl carbenes.[15] Considering the significance of trifluoromethylated piperidines in organic synthesis and medicinal chemistry, coupled with the recent advancements in the chemistry of *N*-triftosylhydrazones,[21,34–39] we here report a [3 + 3] ring expansion strategy for the direct conversion of *N*-substituted aziridines into trifluoromethylated dehydropiperidines in a single step. The reaction is based on using trifluoroalkenyl carbenes derived from trifluoroalkenyl *N*-triftosylhydrazones (Fig. 1C). Notably, this chemoselective approach could completely avoid the competitive side reac-

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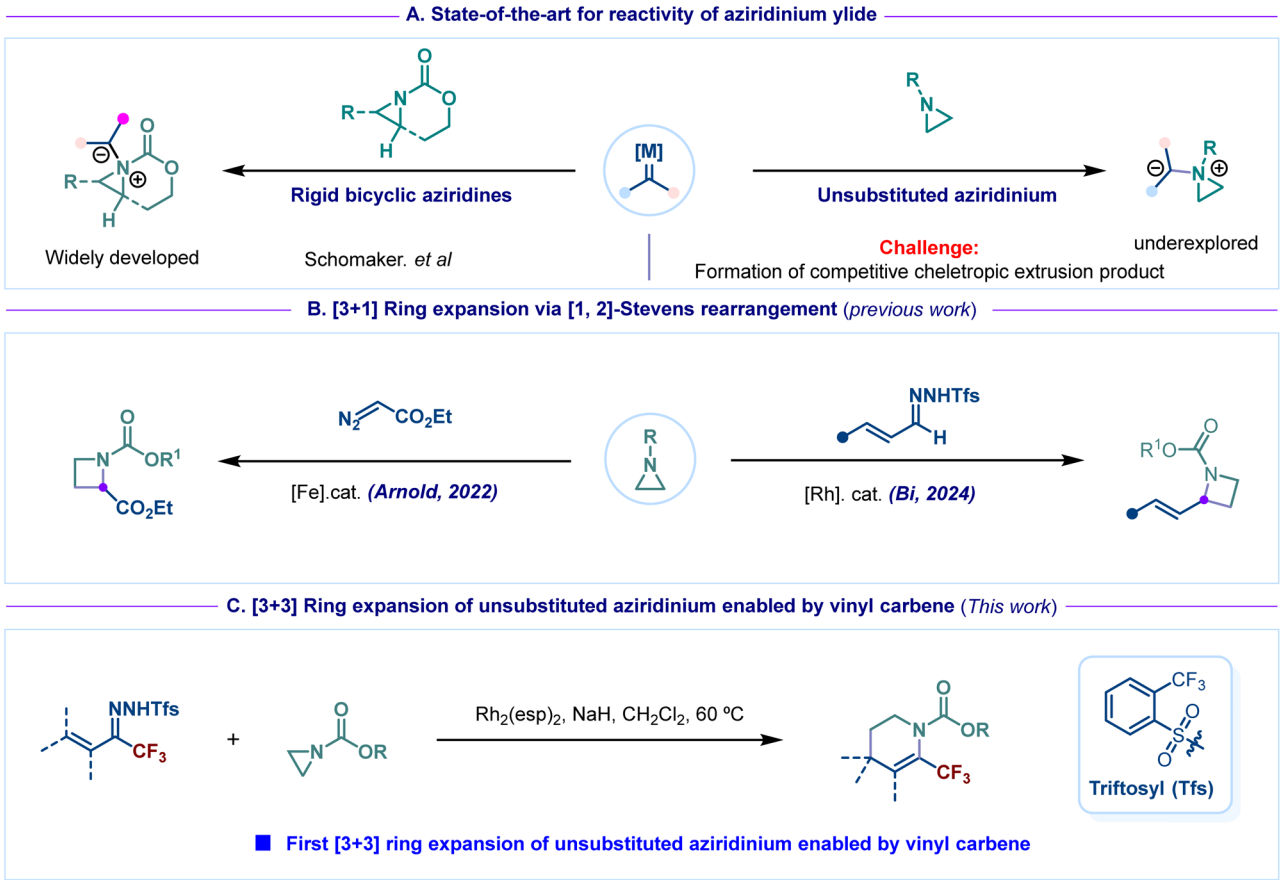
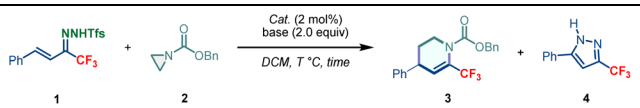


Fig. 1 Background and motivations for the development of [3 + 3] ring expansion of unsubstituted aziridinium ylides. (A) State-of-the-art for reactivity of aziridinium ylides. (B) The [3 + 1] ring expansion of unsubstituted aziridinium ylides (previous work). (C) [3 + 3] ring expansion of *N*-substituted aziridines with fluoroalkenyl *N*-triftosylhydrazones (this work).

tions, including cheletropic extrusion of olefins, alkenyl carbene insertion into C–N bonds, and self-cyclization of *N*-triftosylhydrazones to form pyrazoles. To the best of our knowledge, this was the first [3 + 3] ring expansion of unsubstituted aziridiniums enabled by vinyl carbenes.

To test our hypothesis, we initiated our studies by screening the optimal transition metal catalyst for the model reaction of *N*-Cbz aziridine (**2**) with trifluoromethyl vinyl *N*-triftosylhydrazone (**1**) as the carbene precursor (Table 1). Using $Tp^{Br_3}Ag(thf)$ (10 mol%) as a catalyst and NaH as a base in dichloromethane (DCM) at 60 °C the expected tetrahydropyridine **3** was isolated in 48% yield (entry 1). The reaction with $Tp^{(CF_3)_2}Ag(thf)$ also gave the desired product, albeit in a much lower yield, while AgOTf failed to provide the desired product (entries 2 and 3). The use of other transition metals for vinylcarbene transfer reactions, such as $Pd(OAc)_2$, FeTPPCl, and $Cu(acac)_2$ did not afford the desired tetrahydropyridine **3** (entries 4–6). However, pyrazole **4** was observed as the major side product in all these cases. Pyrazole **4** is probably formed through the competitive cyclization of vinyl *N*-triftosylhydrazone. We were pleased to find that rhodium catalysts (*e.g.*, $Rh_2(OAc)_4$, $Rh_2(Oct)_4$, and $Rh_2(esp)_2$) completely suppressed the formation of the self-cyclization product **4** (entries 7–9) and the expected

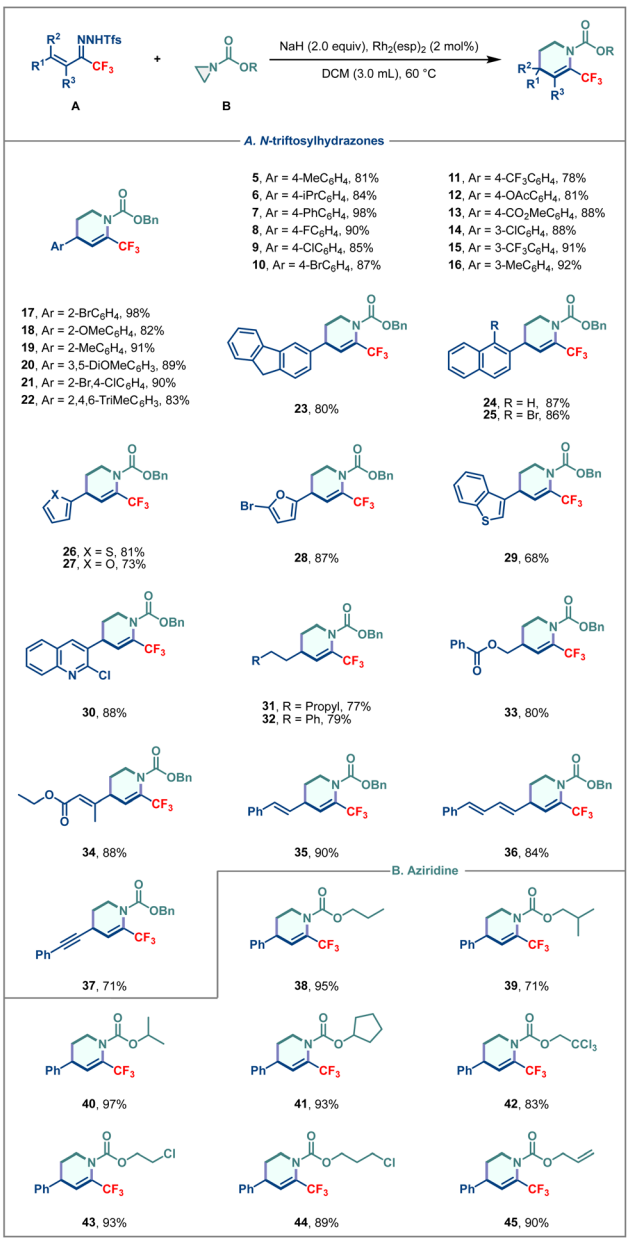
Table 1 Optimization of the reaction conditions[a]



Entry	Cat. (*x* mol%)	*T* (°C)	Yield of **3**	Yield of **4**
1	$Tp^{Br_3}Ag(thf)$ (10)	60	48%	50%
2	$Tp^{(CF_3)_2}Ag(thf)$ (10)	60	19%	78%
3	AgOTf (10)	60	Trace	88%
4	$Pd(OAc)_2$ (5)	60	Trace	32%
5	FeTPPCl (5)	60	Trace	52%
6	$Cu(acac)_2$ (5)	60	Trace	Trace
7	$Rh_2(OAc)_4$ (2)	60	11%	Trace
8	$Rh_2(Oct)_4$ (2)	60	23%	Trace
9	**$Rh_2(esp)_2$ (2)**	60	97%	Trace
10	$Rh_2(esp)_2$ (2)	80	89%	Trace
11	$Rh_2(esp)_2$ (2)	60	72%	Trace
12	$Rh_2(esp)_2$ (2)	60	Trace	13%
13	$Rh_2(esp)_2$ (2)	60	37%	Trace

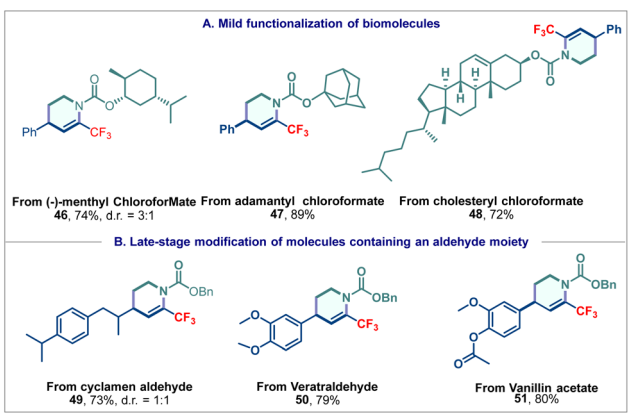
[a] Reaction conditions: **1** (0.3 mmol, 1.0 equiv.), **2** (0.6 mmol, 2.0 equiv.), NaH (0.6 mmol, 2.0 equiv.), and cat. (5–10 mol%) in CH_2Cl_2 (3.0 mL) at 60 °C under an argon atmosphere for 12 h. Yields refer to isolated products.

ring expansion product **3** was obtained in 97% yield using the sterically demanding $Rh_2(esp)_2$ catalyst (entry 9). A decrease of yield was observed when the reaction was performed at 80 °C (entry 10). This result indicated that *N*-triftosylhydrazones are more susceptible to decomposition at low temperatures. A quick screening of various solvents (DCM, $PhCF_3$, DMSO, and THF) indicated that DCM is the solvent of choice to produce **3** in the highest yield (entries 11–13). Overall, the optimized conditions were obtained as the following: **1** (1.0 equiv.), **2** (2.0 equiv.), NaH (2.0 equiv.), and $Rh_2(esp)_2$ (2 mol%), heating under argon in DCM at 60 °C for 12 h.



Scheme 1 Substrate scope of synthesis of trifluoromethyl tetrahydropyridines. Reaction conditions: **A** (0.3 mmol, 1.0 equiv.), **B** (0.6 mmol, 2.0 equiv.), NaH (0.6 mmol, 2.0 equiv.), $Rh_2(esp)_2$ (2.0 mol%) in CH_2Cl_2 (3.0 mL) at 60 °C under an argon atmosphere for 12 h. Yields of the isolated products are given.

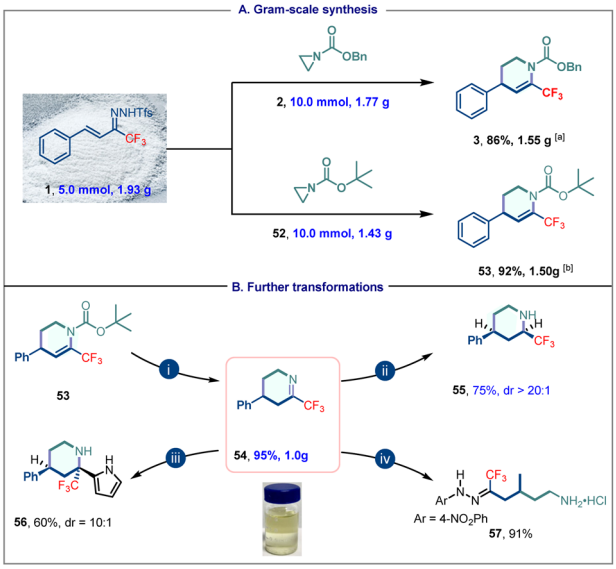
Using the optimized conditions, we then investigated the generality of the new synthetic approach (Scheme 1). First, the scope of various trifluoromethylated vinyl *N*-triftosylhydrazones in combination with aziridine-1-carboxylic acid benzyl ester was explored (Scheme 1A). A series of aryl-substituted vinyl *N*-triftosylhydrazones bearing electron-rich, electron-deficient, and halogen substituents at various positions were well tolerated, affording the corresponding dehydropiperidines (**5–22**) in good yields. Substrates with electron-deficient groups (*e.g.*, fluoro, bromo, chloro, trifluoromethyl, acetyl, and ester) produced slightly higher yields than electron-rich hydrazones (*e.g.*, methyl, isopropyl, and methoxy). This is probably due to an enhanced electrophilicity of the carbene that increases its reactivity. Aside from *meta*- and *para*-substituted aryl vinyl *N*-triftosylhydrazones, *ortho*- and multi-substituted aryl vinyl *N*-triftosylhydrazones were also proven to be efficient in the synthesis of the desired products (**17–22**). To our delight, polyaromatic (*e.g.*, fluorenyl and naphthyl) and heterocyclic (*e.g.*, thienyl, furyl, benzo[*b*]thiophene, and quinoline) fluoroalkenyl *N*-triftosylhydrazones were also suitable substrates for the reaction. The expected fluoroalkylated tetrahydropyridines (**23–30**) were successfully obtained in moderate to good yields. The tolerance of the heteroatomic systems opens up new possibilities for the construction of pharmaceutically relevant polyheterocyclic molecular modules. Under the optimized conditions, alkyl-substituted fluoroalkenyl *N*-triftosylhydrazones were proven to be viable substrates, furnishing the desired alkyl-substituted dehydropiperidines (**31–33**) in high yield. Methyl substitution at the α-position of trifluoromethyl vinyl *N*-triftosylhydrazones still gave the desired methylated dehydropiperidine (**34**) in good yield. Interestingly, *N*-triftosylhydrazones derived from 1,3-dienyl-, 1,3,5-trienyl-, 1,3-enynyl ketones could be converted smoothly into the corresponding alkenyl-, dienyl-, and alkynyl-substituted dehydropiperidines (**35–37**) in good yield, products amenable to synthetic manipulation by exploiting the alkene/alkyne handle.[40] Subsequently, we focused on the aziridine scope in combination with trifluoromethylstyryl ketone-derived *N*-triftosylhydrazone (**1**). As shown in Scheme 1B, various car-



Scheme 2 The late-stage modifications of natural products and biorelevant compounds.

bamate-protected aziridines bearing chain alkyl, branched alkyl, cycloalkyl, and allyl groups could undergo smooth chemoselective ring expansion, liberating the desired products (**38–41** and **45**) in good to excellent yields. Chlorine substitutions on the carbamate-protected aziridines were also tolerated to furnish **42–44** with high efficiency. These halogenated heterocycles may have the potential to be a powerful synthetic handle for late-stage functional group transformations and cross-coupling processes.

The mild reaction conditions and high functional group tolerance of the process could facilitate the late-stage modifications of natural products and bio-relevant compounds. The intermolecular [3 + 3] ring expansion strategy could also be applied for aziridines derived from natural products, such as (–)-menthyl chloroformate (**46**), adamantyl chloroformate (**47**), and cholesteryl chloroformate (**48**), providing the corresponding dehydropiperidines in 72–89% yield (Scheme 2A). Similarly, trifluoroalkenyl *N*-triftosylhydrazones prepared from cyclamen aldehyde, veratraldehyde, and vanillin acetate all are tolerated under these conditions, giving the desired trifluoromethyl dehydropiperidines **49–51** in 73–80% yield (Scheme 2B). As a result, this efficient protocol can be used to open the way for late-stage functionalization of drug molecules, and improve drug discovery efficiency.



Scheme 3 Gram-scale synthesis and further transformations. Reaction conditions: [a] Trifluoromethyl vinyl *N*-triftosylhydrazone **1** (5.0 mmol, 1.0 equiv., 1.93 g), NaH (2.0 equiv.), $Rh_2(esp)_2$ (2.0 mol%), *N*-Cbz aziridine **2** (10.0 mmol, 2.0 equiv., 1.77 g) in CH_2Cl_2 at 60 °C under an argon atmosphere for 12 h. [b] Trifluoromethyl vinyl *N*-triftosylhydrazone (0.3 mmol, 1.0 equiv.), NaH (0.6 mmol, 2.0 equiv.), $Rh_2(esp)_2$ (2.0 mol%), *N*-Boc aziridine **52** (0.6 mmol, 2.0 equiv., 1.43 g) in CH_2Cl_2 (3.0 mL) at 60 °C under an argon atmosphere for 12 h. Yields of the isolated products are given.

In order to explore the synthetic practicability of this protocol, the reaction of **1** and **2** at the 5.0 mmol scale was carried out. Product **3** was isolated in 86% yield (1.55 g), which was comparable to the results of the 0.3 mmol scale reaction. On the other hand, the 5.0 mmol scale reaction of **1** with *N*-Boc-protected aziridine (**52**) produced a 92% (1.50 g) yield of dehydropiperidine product **53** (Scheme 3A). The *tert*-butoxycarbonyl group in **53** could be removed by treatment with silica gel, affording trifluoromethylated 2,3,4,5-tetrahydropyridine (**54**) in 95% yield (Scheme 3B(i)). To further highlight the versatility of 2,3,4,5-tetrahydropyridines, the derivatization of **54** was investigated. The imino group in **54** could be reduced to the corresponding trifluoromethylated piperidine (**55**), which is a common structural motif in a variety of pharmaceuticals and bioactive molecules, with sodium cyanoborohydride (Scheme 3B(ii)).[41] Note that imines are valuable synthetic intermediates for the attachment of alkaloid-like pyrroles to trifluoromethylated aza rings in the α-position.[42] Lewis acid mediated Friedel–Crafts type heteroarylation of **54** with pyrroles gave rise to the desired 2-pyrrolyl piperidine **56** in 60% yield with a 10 : 1 dr (Scheme 3B(iii)). In addition, trifluoromethylated 2,3,4,5-tetrahydropyridine could undergo a Fischer-type ring-opening reaction with arylhydrazine hydrochloride to afford the corresponding hydrazone **57** in excellent yield (Scheme 3B(iv)).[43] These product derivatization experi-

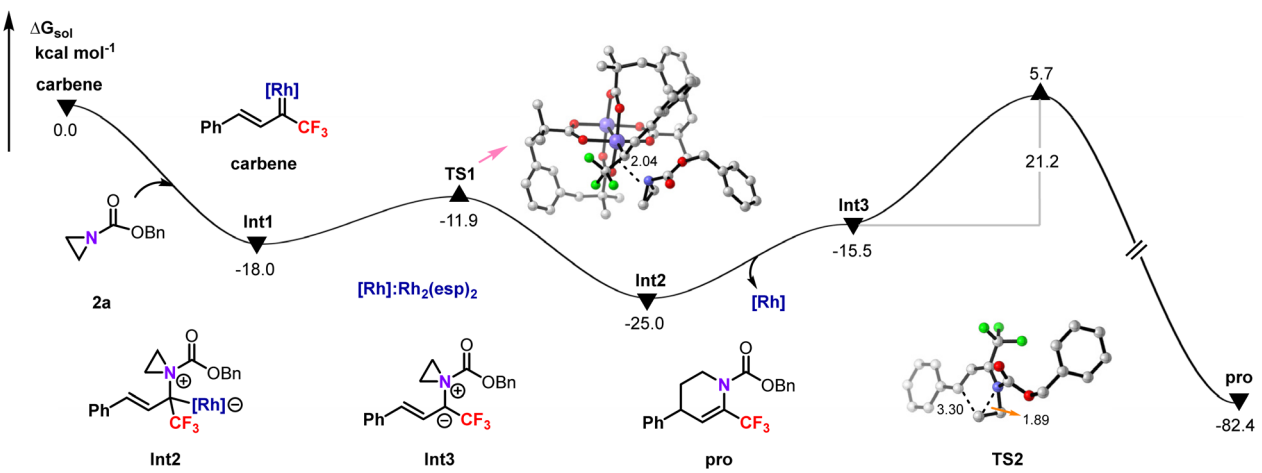


Fig. 2 Gibbs free energy profile (in kcal mol^{-1}) of [3 + 3] ring expansion reaction of fluoroalkenyl *N*-triftosylhydrazones with aziridines.

ments demonstrate that this strategy is highly practical and offers a novel approach to the synthetic organic transformation of tetrahydropyridines.

To gain a deeper understanding of the mechanism and origin of the chemoselectivity of this ring expansion, density functional theory (DFT) calculations were performed at the B3LYP/def2-SVP-GD3BJ level (Fig. 2, see the ESI† for more details). The reaction of *N*-Cbz-aziridine and the rhodium carbenoid derived from trifluoromethylstyryl ketone *N*-triftosylhydrazone (Fig. S1, see the ESI† for details) to furnish **3** was explored computationally. First, nucleophilic attack of the nitrogen atom of *N*-Cbz-aziridine **2a** on the carbon atom of the Rh-bound carbenoid occurs to form a transient aziridine–rhodium complex **Int1**, which then generates aziridinium rhodium ylide **Int2** *via* transition state **TS1** with an energy barrier of 6.1 kcal mol^{-1}. Subsequent coordination of another molecule of *N*-Cbz-aziridine with rhodium gives metal-free aziridinium ylide **Int3** with the regeneration of the rhodium catalyst. **Int3** then undergoes a 1,4-sigmatropic rearrangement *via* **TS2** (ΔG = 21.2 kcal mol^{-1}) to afford the ring expansion product **3**. A competitive reaction involving vinylcarbene insertion into the aziridine C–N bond for azetidine synthesis was also evaluated. However, this competitive reaction has a very high calculated activation barrier (nearly 27.8 kcal mol^{-1}, which is 6.6 kcal mol^{-1} higher than that of the [3 + 3] ring expansion process) for the one-carbon insertion step *via* the aziridinium ylide and is thus excluded (Fig. S2, see the ESI† for details).

Conclusions

In conclusion, we developed an efficient ring expansion strategy for the synthesis of fluoroalkylated dehydropiperidines *via* the rhodium-catalyzed reaction of *N*-carbamate aziridines and fluoroalkenyl *N*-triftosylhydrazones. This process represents the first example of highly efficient ring expansion of unsubstituted aziridinium ylides *via* [1,4]-sigmatropic rearrangement. Moreover, it also exhibits unprecedented selectivity for aziridinium ylides over cheletropic extrusion of ethylene and carbene insertion into C–N bonds. The developed protocol allows high-yielding, scalable synthesis that occurs with wide functional group tolerance under mild conditions, enabling the extension of this methodology to bioactive complex frameworks. DFT calculations support that the formation of aziridinium ylides is a key step in the reaction.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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