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Brønsted acid-promoted aziridination of electron-deficient olefins

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ABSTRACT

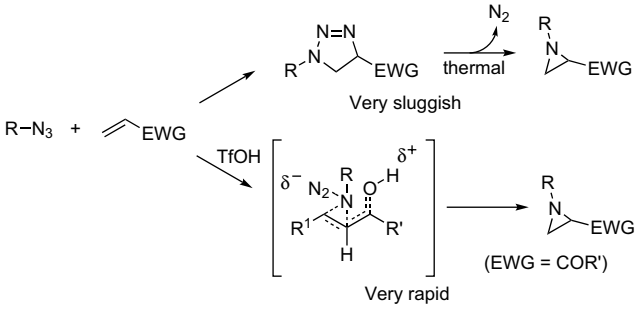
A combined theoretical and experimental approach was used to systematically study the Brønsted acid-promoted aziridination of electron-deficient olefins. It was found that Brønsted acid-promoted aziridination of electron-deficient olefins proceeded through the attack of the internal nitrogen of the azide to the terminal carbon of protonated olefin, which afforded an acyclic adduct that subsequently discharged N_2 to produce the aziridine ring. The basicity of the electron-deficient olefins is an important parameter to determine the efficiency of Brønsted acid-promoted aziridination. More basic carbonyl compounds including vinyl ketones and acrylamides were predicted to be readily activated by Brønsted acid such as TfOH, whereas less basic carbonyl compounds were predicted to be poor substrates. Significantly, all these theoretical predictions were demonstrated to be consistent with the experimental data. Furthermore, a systematic evaluation of TfOH-promoted aziridination of acrylamides was performed, which established a new, single-step method for the preparation of a number of aziridine-2-carboxamides.

1. Introduction

Organic azides are energy-rich and flexible intermediates that present a broad range of chemical reactivity.[1] The utilization of these azides in organic synthesis has enjoyed considerable interest over the past few decades, where they play the role of either electrophile or nucleophile. Previous groundbreaking efforts of Sharpless,[2] Aubé,[3] and several other groups have allowed the synthesis of a variety of nitrogen-containing heterocycles from organic azides. In particular, the [3+2] cycloaddition reaction of azides with olefins has been intensively studied for the preparation of triazolines,[4] which can be subsequently converted to synthetically more valuable intermediates, i.e., aziridines, through thermal[5] or photochemical[6] decomposition (Scheme 1). Nonetheless, a bottleneck problem of this olefin aziridination method is that the [3+2] cycloaddition reaction tends to be extremely sluggish, which may take weeks, or even months, at room temperature to get only partial completion.[7]

To overcome the efficiency problem in the olefin aziridination reaction, Johnston et al. reported in 2005 a highly interesting finding that a Brønsted acid (namely, TfOH) could promote addition of azides to electrophilic olefins, delivering the corresponding aziridines in good yield under relatively mild, non-redox conditions.[8] The significance of this discovery is manifested by the fact that olefin aziridination and subsequent ring-opening reactions can form the basis for more complex target synthesis.[9] Meanwhile, because of the difficulty encountered in the isolation of reaction intermediates, it raises a serious question as to how the Brønsted acid accelerates the aziridination. In their study, Johnston et al. proposed that the triazoline did not need to be an intermediate and that rate acceleration and selective formation of the aziridine might be explained by an unprecedented transition state (Scheme 1).[8] However, since almost nothing has been known about the possible occurrence of such a triangular transition state in the chemistry of organic azides, more mechanistic examinations on this newly discovered aziridination reaction remain necessary.

In the present study, we sought to study the mechanism of the Brønsted acid-promoted olefin aziridination reaction using a combined theoretical and experimental approach. Our major question is how a Brønsted acid could dramatically accelerate the olefin aziridination reaction. To answer this question, we carefully compared the reaction pathway that involved the conventional



Scheme 1.

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triazoline intermediate with the one that involved the unusual triangular transition state. In this way, we established the first theoretical model that could interpret the experimental behavior for the olefin aziridination reactions. To further corroborate our theoretical model, we next examined the scope of Johnston's aziridination reaction by considering the effects of substitution on the azide and olefin substrates. To our satisfaction, we found that the substituent effects predicted by the theoretical model were consistent with the experimental results previously reported as well as newly obtained by us, thereby providing further support for the mechanism discussed in the present work. Furthermore, we systematically evaluated the efficiency of the Brønsted acid-promoted aziridination reactions of acrylamides for the first time.

2. Results and discussion

2.1. General mechanism

To simplify the calculation, we firstly studied the reaction between azidomethane (**1**) and 3-butenone (**2**) to produce 1-(1-methylaziridin-2-yl)ethanone (**8**) in acetonitrile solution (Fig. 1). Two reaction pathways were considered to be different from each other due to the presence or absence of TfOH. In the first pathway under the neutral condition, a bimolecular collision between **1** and **2** might take place to produce either a cyclic adduct (**4**) or an acyclic one (**5**). Through B3LYP/6-31+G(p,d) optimizations, it was found that **5** was not a local minimum (i.e., **5** cannot be obtained through the optimization). Thus we ruled out the possible involvement of **5** as an intermediate.

As to the triazoline intermediate **4**, a classical [3+2] cycloaddition transition state (**TS1**) can be readily located (Fig. 2), where 3-butenone acted as a dipolarophile and azidomethane acted as the dipole. The solution-phase activation free energy associated with **TS1** was +29.4 kcal/mol in acetonitrile (Fig. 3). The formation of **4** in acetonitrile had a negative free energy of −4.8 kcal/mol. From **4**, we then successfully located the transition state (**TS2**) for the opening of triazoline through nitrogen extrusion to produce the final product **8**. The solution-phase activation free energy associated with the nitrogen extrusion step was +30.4 kcal/mol in acetonitrile.

For the second pathway under the acidic condition, it was found that the protonation of 3-butenone by TfOH had a positive free energy of +4.6 kcal/mol in acetonitrile. Surprisingly, from **1** and protonated 3-butenone (**3**) all attempts failed to locate the classical [3+2] cycloaddition transition state for the formation of a protonated triazoline **6**. Besides, we could not find the triangular transition state (Scheme 1) proposed by Johnston et al.[8] Nonetheless, we eventually discovered an interesting transition state (**TS3**) where the internal nitrogen of the azide **1** attacked the terminal carbon of protonated 3-butenone (**3**) nucleophilically. In this transition state, the N–N–N angle (167.8°) remained close to 180°, as opposed to 140.4° observed in the [3+2] transition state **TS1**. The IRC analysis from **TS3** led to an acyclic adduct **7** (a zwiterionic intermediate) as a local minimum on the potential energy surface (see Fig. 2). The solution-phase activation free energy associated with **TS3** was +13.4 kcal/mol in acetonitrile from **1**+**3**. The formation of **7** in acetonitrile had a positive free energy of +11.6 kcal/mol calculated from **1**+**3**.

From intermediate **7**, we next successfully located the transition state (**TS4**) for the extrusion of nitrogen. The IRC analysis from this transition state to the two associated minima, **7** and **9**, indicated that the nitrogen extrusion and the aziridine-ring formation took place through a concerted process. The solution-phase activation free energy associated with **TS4** was +11.3 kcal/mol in acetonitrile from **7**. The formation of **9** in acetonitrile had a large negative free energy of −39.3 kcal/mol calculated from **1**+**3**. Finally, intermediate **9** should undergo a rapid proton exchange reaction with the medium to produce the final product **8**.

Comparing the reaction free energy profiles (Fig. 3), we found that pathway I had two high barriers to overcome, i.e., the formation of the triazoline intermediate (+29.4 kcal/mol) and the extrusion of nitrogen from the triazoline (+30.4 kcal/mol). Because the triazoline intermediate has a lower free energy than the starting material, the observed kinetics should be mainly determined by the second step with a barrier of +30.4 kcal/mol. In comparison, pathway II includes two relatively facile steps, i.e., the formation of an acyclic adduct (+13.4 kcal/mol) and the extrusion of nitrogen (+11.3 kcal/mol). Because all the intermediates before the nitrogen extrusion step had higher energies than the starting material, the observed kinetics should be determined by an overall barrier of +27.5 kcal/mol.

Evidently, the difference between +30.4 and +27.5 kcal/mol by ca. 3 kcal/mol means that pathway II should be faster than pathway I by about 10^2 fold. This result is in good agreement with the experimental observations. On the basis of the above results, we can finally draw the general mechanism for olefin aziridination under the neutral or Brønsted acid-promoted condition, respectively (Fig. 4).

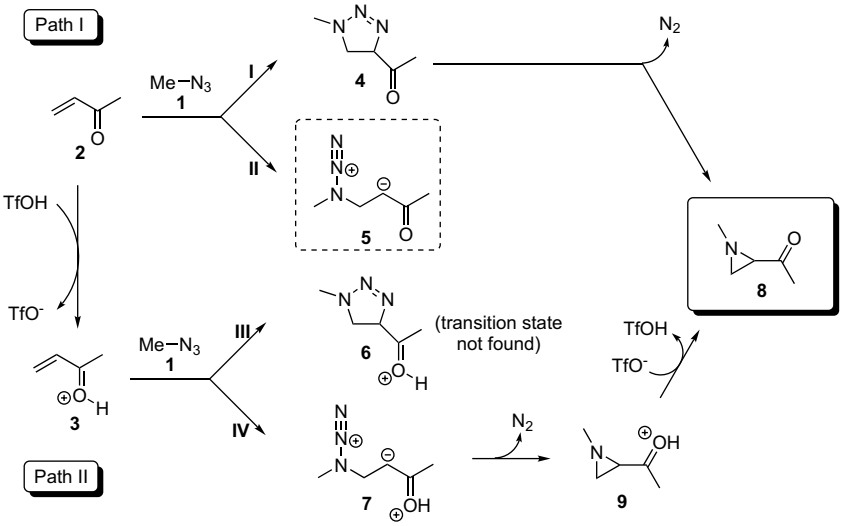


Figure 1. Possible pathways for the reaction between azidomethane and 3-butenone.

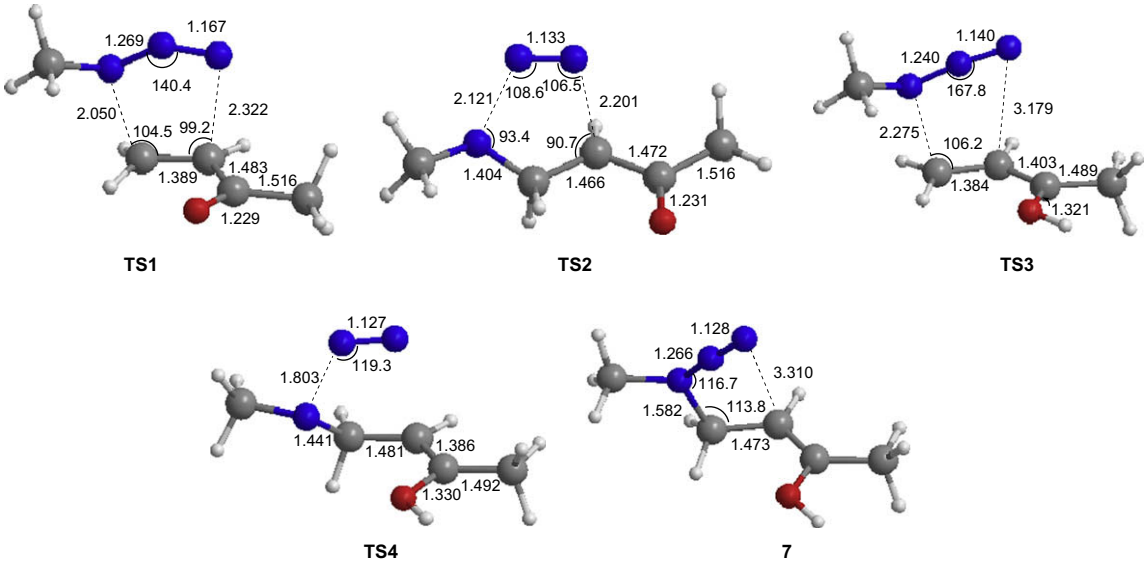


Figure 2. Three-dimensional structures for **TS1**–**TS4** and **7**. The bond lengths directly involved in the reaction are given in angstrom.

2.2. Effects of substituents on azides

Having studied the general mechanism for the Brønsted acid-promoted olefin aziridination reaction, we then examined the effects of substituents on its efficiency. The results from such substituent effect studies may not only help us to understand the scope of the reaction, but also test whether or not our proposed mechanism is valid.

First, we fixed the olefin as 3-butenone. Three types of organic azides, namely, azidomethane, azidobenzene, and benzyl azide, were selected to represent alkyl, aryl, and benzylic azide, respectively. It was found that for the formation of the olefin–azide adduct through **TS3**, methyl azide had a much lower free energy barrier than phenyl azide by about 8 kcal/mol (Fig. 5). This observation can be readily explained by the fact that the internal nitrogen of methyl azide is more nucleophilic than the internal nitrogen of phenyl azide, presumably because of the better electron-donating ability of methyl group than that of phenyl. On the other hand, the better electron-donating ability of the methyl group also makes the extrusion of nitrogen from adduct **7** more difficult than the phenyl case. Thus, the overall effect is that the free energy barrier for the olefin aziridination by azidomethane (i.e., 27.5 kcal/mol) is only slightly lower than that for azidobenzene (i.e., 28.7 kcal/mol), whereas benzyl azide has an intermediate value, 28.2 kcal/mol.

The above calculations indicate that the effect of substitution on the azide is not significant for the Brønsted acid-promoted olefin aziridination reaction (1 kcal/mol difference in barrier means ca. 10-fold difference in rate). Noteworthy, Johnston et al. reported yields of 93%, 79%, and 43% for the aziridination by adamantyl azide, benzyl azide, and 1-azido-4-methoxybenzene, respectively.[8] Thus, the experiments also showed that differently substituted azides could be converted to the desired products under the same reaction conditions, where alkyl azide was slightly more reactive than benzyl azide and aryl azide.

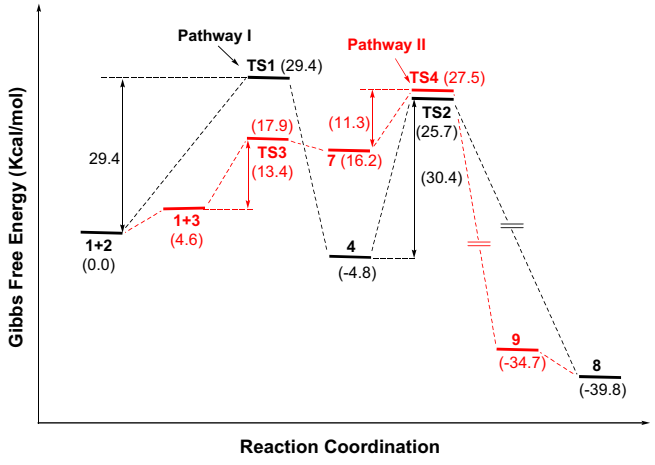


Figure 3. Free energy profiles (in kcal/mol) for the two proposed pathways.

2.3. Effects of substituents on olefins

Johnston et al. reported the Brønsted acid-promoted addition of organic azides to methyl vinyl ketone.[8] It remains unclear whether or not the other electron-deficient olefins (e.g., acrylate esters, acrylonitriles, and acrylamides) can also participate in this reaction. To solve this problem, we use theoretical method as discussed above to model the reactions of benzyl azide with methyl acrylate, acrylonitrile, and acrylamide in acetonitrile in the presence or absence of TfOH.

As to the reaction of benzyl azide with methyl acrylate, it is found that the un-catalyzed reaction in the absence of TfOH has an almost identical free energy profile as compared to the reaction of 3-butenone (pathway I in Fig. 6). The rate-limiting step is the [3+2] cycloaddition step to form the triazoline intermediate, which has a free energy barrier of 31.3 kcal/mol (as compared to 30.4 kcal/mol for 3-butenone). On the other hand, we are very surprised to find that the reaction of benzyl azide with methyl acrylate in the presence of TfOH has a dramatically different free energy profile as compared to the reaction of 3-butenone (pathway II in Fig. 6). Firstly, it is found that the aziridination of methyl acrylate in the presence of TfOH has a much higher free energy barrier (i.e., 42.0 kcal/mol) as compared to that for 3-butenone (i.e., 27.5 kcal/mol). Secondly, the aziridination of methyl acrylate in the presence of TfOH actually has a much higher free energy barrier (42.0 kcal/mol) than that in the absence of TfOH (31.3 kcal/mol). This means that TfOH cannot promote the aziridination of methyl acrylate, despite the fact that methyl acrylate is a typical electron-deficient olefin!

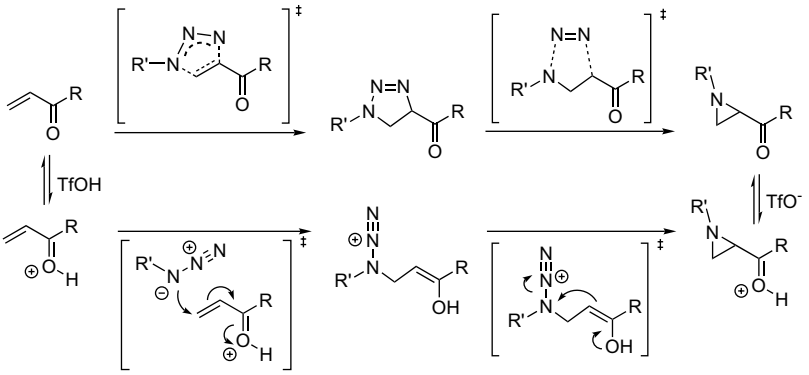


Figure 4. General mechanism for olefin aziridination under the neutral or Brønsted acid-promoted condition.

The above surprising observation requires an explanation. To this end, we pay attention to the individual steps in pathway II of Figure 6. It is then recognized that the protonation of methyl acrylate in acetonitrile by TfOH requires a free energy change of +13.3 kcal/mol, whereas the protonation of 3-butenone requires a free energy change of +4.6 kcal/mol. The ca. 9 kcal/mol difference in the protonation free energy means that methyl acrylate is much less basic than 3-butenone (at their carbonyl oxygens). Because of the highly unfavorable free energy cost in the protonation step, Brønsted acid as strong as TfOH cannot promote the aziridination of methyl acrylate in acetonitrile. A stronger Brønsted acid might be able to promote this reaction, or the solvent should be re-optimized.

As to the reaction of benzyl azide with acrylonitrile, observations similar to the methyl acrylate case have been obtained for the free energy profiles in the absence or presence of TfOH. For the aziridination in the absence of TfOH (pathway I in Fig. 7), the rate-limiting step is again the [3+2] cycloaddition, which has a free energy barrier of 31.3 kcal/mol. On the other hand, the reaction of benzyl azide with acrylonitrile in the presence of TfOH (pathway II in Fig. 7) has a much higher free energy barrier of 41.3 kcal/mol. Thus, TfOH cannot promote the aziridination of acrylonitrile, despite the fact that acrylonitrile is also a typical electron-deficient olefin. The explanation of this observation is again associated with the protonation free energy, which amounts to +11.2 kcal/mol for acrylonitrile (at its terminal nitrogen atom) as compared to +4.6 kcal/mol for 3-butenone.

Finally, for the reaction of benzyl azide with acrylamide, it is found that the rate-limiting step in the absence of TfOH (pathway I in Fig. 8) is the [3+2] cycloaddition, which has a free energy barrier of 32.7 kcal/mol. Interestingly, it is also found that the reaction of benzyl azide with acrylamide in the presence of TfOH (pathway II in Fig. 8) has a lower free energy barrier of 27.8 kcal/mol. These results indicate that: (1) TfOH can promote the aziridination of acrylamide by accelerating the reaction by ca. 10^3- to 10^4-fold in rate (or 4.9 kcal/mol in free energy barrier); (2) TfOH-promoted aziridination of acrylamide (barrier=27.8 kcal/mol) is only slightly slower than TfOH-promoted aziridination of 3-butenone (barrier=27.5 kcal/mol). Noteworthy, the high reactivity of acrylamide as compared to methyl acrylate and acrylonitrile can be readily attributed to the good basicity of the amidyl carbonyl, whose protonation by TfOH in acetonitrile has a negative free energy of −4.8 kcal/mol (Fig. 8).

Our above calculations show that Brønsted acid-promoted aziridination of electron-deficient olefins has a dramatic dependence on the substituents in the olefins. More basic carbonyl compounds including vinyl ketones and acrylamides are easier to be activated by the Brønsted acids, whereas less basic carbonyl compounds including acrylate esters and acrylonitriles are not good substrates in the reaction. To validate the theoretical predictions, we have examined the TfOH-promoted aziridination reactions of different electron-deficient olefins (Table 1). Through the product analysis, we are able to identify the aziridine products for all the olefin substrates. However, good yields are obtained only for 3-butenone and acrylamide,[10] whereas the yields for acrylonitrile

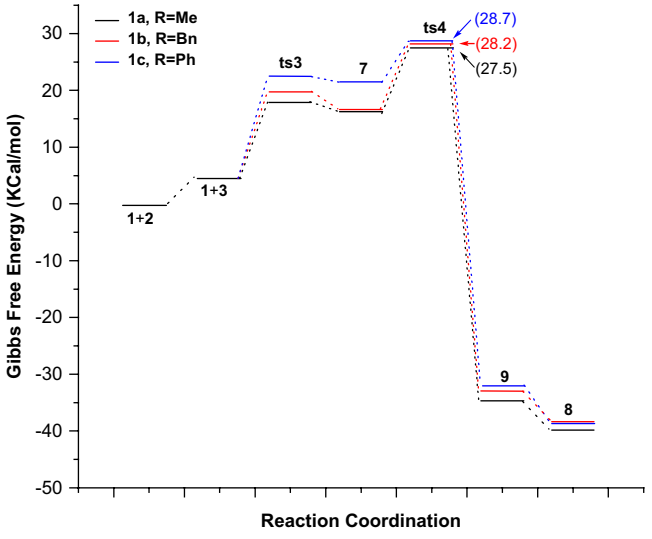


Figure 5. Free energy profiles (in kcal/mol) for olefin aziridination by methyl, phenyl, and benzyl azides under Brønsted acid-promoted condition.

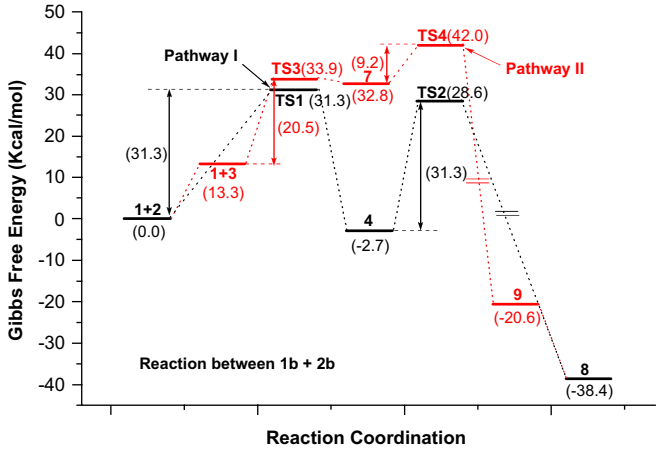


Figure 6. Free energy profiles (in kcal/mol) for olefin aziridination between methyl acrylate and benzyl azide in the absence (pathway I) or presence (pathway II) of TfOH in acetonitrile.

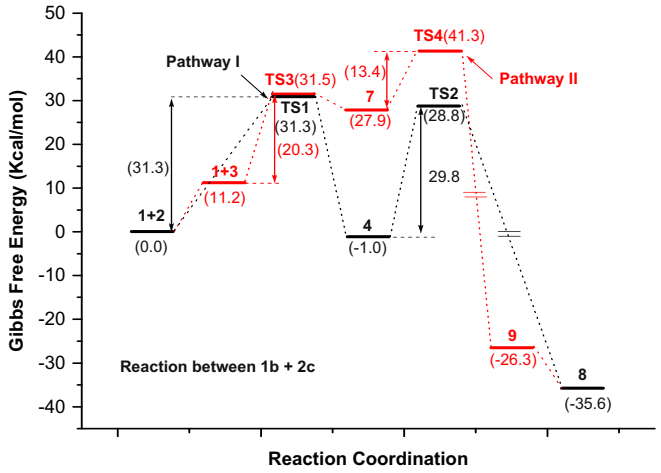


Figure 7. Free energy profiles (in kcal/mol) for olefin aziridination between acrylonitrile and benzyl azide in the absence (pathway I) or presence (pathway II) of TfOH in acetonitrile.

and methyl acrylate are considerably lower.[11,12] These experiments are consistent with our theoretical analyses.

2.4. Brønsted acid-promoted aziridination of acrylamides

Johnston et al. reported the Brønsted acid-promoted reaction of organic azides with methyl vinyl ketone and methyl acryloyl(benzyl)carbamate.[8] The former substrate gave aziridines as the products, whereas the later substrate produced oxazolidine diones. They have not studied the aziridination of acrylamides, which, however, was predicted by the above calculations to be a relatively facile reaction. Because this reaction can produce aziridine-2-carboxamides as highly interesting intermediates in organic synthesis through their regio- and stereo-selective ring openings,[13] we decided to systematically evaluate this reaction in the present study. Noteworthy, the previous syntheses of aziridine-2-carboxamides normally required the preparation of the corresponding aziridine esters or nitriles at first followed by their aminolysis or hydrolysis.[14] Compared to the previous two-step methods, the current one-step synthesis from readily available starting materials (organic azide and acrylamides) is evidently an appealing approach.

Shown in Table 2 are the detailed isolated yields for the TfOH-promoted reactions of various organic azides with different acrylamides affording aziridine-2-carboxamides as the main products. It is

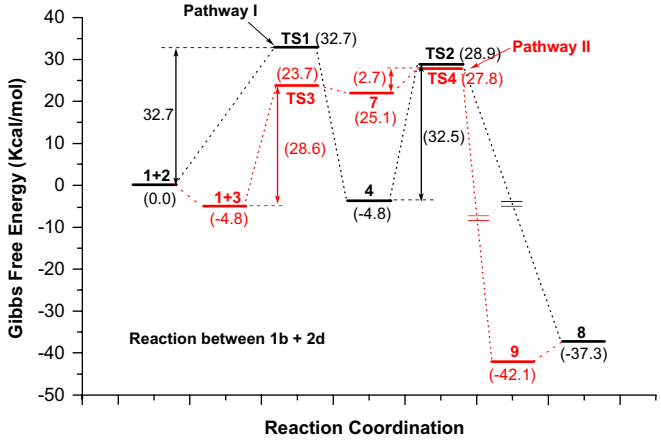


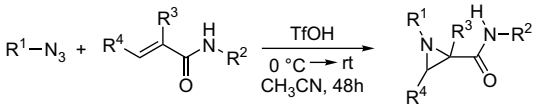
Figure 8. Free energy profiles (in kcal/mol) for olefin aziridination between acrylamide and benzyl azide in the absence (pathway I) or presence (pathway II) of TfOH in acetonitrile.

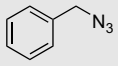
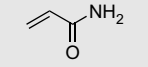
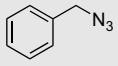
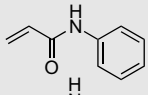
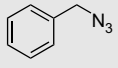
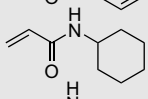
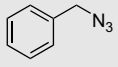
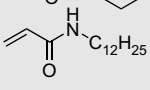
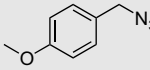
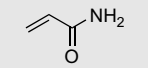
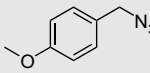
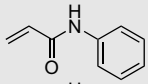
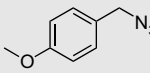
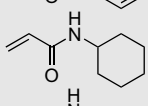
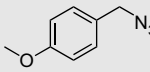
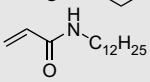
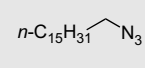
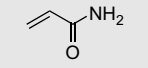
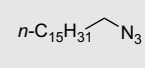
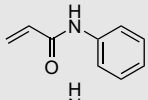
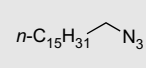
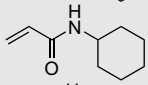
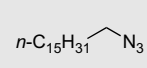
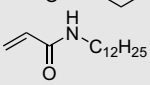
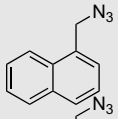
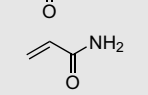
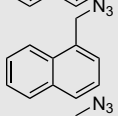
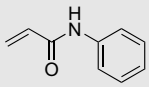
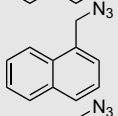
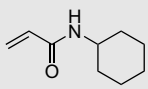
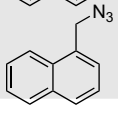
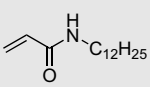
Table 1
Brønsted acid-promoted aziridination of different electron-deficient olefins[a]

Entry	Olefin	Isolated yield (%)
1	3-Butenone	76 (79[b])
2	Acrylamide	72
3	Acrylonitrile	10
4	Methyl acrylate	20

[a] General reaction conditions: organic azide (4.5 mmol), olefin (3.0 mmol), TfOH (3.6 mmol), CH_3CN (10 mL), 0 °C to room temperature, 48 h.
[b] Yield previously reported in Ref. 8.

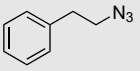
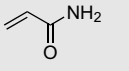
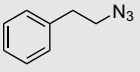
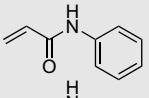
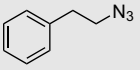
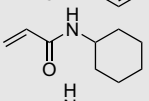
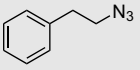
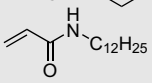
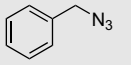
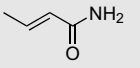
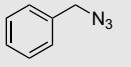
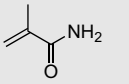
Table 2
Brønsted acid-promoted olefin aziridination of acrylamides[a]



Entry	Azide	Amide	Compound	Isolated yield (%)
1			**10**	72
2			**11**	53
3			**12**	64
4			**13**	54
5			**14**	48
6			**15**	41
7			**16**	54
8			**17**	43
9			**18**	60
10			**19**	40
11			**20**	56
12			**21**	40
13			**22**	43
14			**23**	31
15			**24**	42
16			**25**	40

(*continued on next page*)

Table 2 (*continued*)

Entry	Azide	Amide	Compound	Isolated yield (%)
17			**26**	59
18			**27**	47
19			**28**	50
20			**29**	56
21			—	0
22			—	0

[a] General reaction conditions: organic azide (4.5 mmol), acrylamide (3.0 mmol), TfOH (3.6 mmol), CH_3CN (10 mL), 48 h.

found that both benzylic and normal alkyl azides can smoothly react with unsubstituted acrylamides to give the desired products as white solid in ca. 50–70% isolated yields (entries 1, 5, 9, 13, and 17). Substituted acrylamides carrying substituents at the nitrogen atom can also participate in the reaction, albeit with slightly lower yields (ca. 30–60%). Furthermore, 2- or 3-substituted acrylamides cannot afford the desired aziridine-2-carboxamides under the TfOH conditions (entries 21 and 22). Noteworthy, the reported yields for TfOH-promoted aziridination of 3-butenones were mostly around 70%,[8] which are relatively higher than the yields for the aziridination of acrylamides. A possible explanation is that acrylamides are more reactive than 3-butenone toward some yet unclear side reactions under the TfOH conditions, as we observe significant amounts of highly polar byproduct mixtures in the aziridination of acrylamides.

3. Conclusions

In the present work, we have utilized both the theoretical and the experimental methods to systematically study the Brønsted acid-promoted aziridination reaction of electron-deficient olefins. We have the following major conclusions:

(1) Brønsted acid-promoted aziridination reaction of electron-deficient olefins does not undergo the classical [3+2] cycloaddition mechanism. It proceeds through the attack of the internal nitrogen of the azide to the terminal carbon of protonated electron-deficient olefin, which affords an acyclic adduct that subsequently discharges N_2 to produce the aziridine ring.
(2) The basicity of the electron-deficient olefins is an important parameter to determine the efficiency of Brønsted acid-promoted aziridination. More basic carbonyl compounds including vinyl ketones and acrylamides are predicted to be readily activated by Brønsted acid as strong as TfOH, whereas less basic carbonyl compounds including acrylate esters and acrylonitriles are predicted to be poor substrates under the TfOH conditions.
(3) The theoretical predictions are consistent with all the available experimental results previously reported or newly obtained in the present study. In particular, our systematic evaluation of TfOH-promoted aziridination of acrylamides establishes a new, single-step method for the preparation of a number of aziridine-2-carboxamides from acrylamides and organic azides.

4. Experimental

4.1. Theoretical method

All calculations were carried out with the Gaussian 03 suite of programs.[15] Density functional theory (DFT) calculations were carried out using the B3LYP exchange-correlation functional, together with the standard 6-31+G(p,d) (for geometry optimization) and 6-311++G(d,p) (for single-point energy calculation) basis sets. The potential energy surface was explored in detail to ensure that all relevant stationary points were located and properly characterized. Berny analytical gradient optimization routines were used for the geometry optimization. The stationary points were characterized by frequency calculations in order to verify that the transition states had one and only one imaginary frequency. The intrinsic reaction coordinate (IRC) path was traced to obtain and check the energy profiles connecting each transition state to the two associated minima of the proposed mechanism by using the second order Gónzalez–Schlegel integration method. Relative enthalpies (ΔH), entropies (ΔS), and free energies (ΔG) were calculated with the standard statistical thermodynamics at 298.15 K. The solvent effects, modeled as a continuum medium, were considered by performing single-point B3LYP/6-311++G(d,p) calculations using the self-consistent reaction field (SCRF) based on the polarizable continuum model (PCM) of Tomasi's group.[16,17] Acetonitrile was used as solvent. Note that a number of recent studies have shown that it is sufficiently reliable to use the B3LYP method augmented with appropriate basis sets to investigate the mechanism of the [3+2] cycloaddition reactions.[18]

4.2. Aziridination of acrylamides

4.2.1. Typical experimental procedure

A solution of the acrylamide (3.0 mmol) in acetonitrile (10 mL) was cooled to 0 °C and treated with triflic acid (3.6 mmol). Organic azide (4.5 mmol) was then added in one portion and the reaction mixture was allowed to stir for 48 h while attaining room temperature. The reaction mixture was then diluted with ethyl acetate and washed with 1 M aqueous NaOH. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified on a silica gel column with petroleum ether/ethyl acetate as the eluent to provide the desired product.

*4.2.2. 1-Benzylaziridine-2-amide (**10**)*

Prepared as a white solid. IR (KBr) 3405, 3207, 3031, 2926, 2853, 1671, 1636, 1498, 1450, 738, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.29 (m, 5H), 6.40 (br, 1H), 5.19 (br, 1H), 3.56 (d, J=13.5 Hz, 1H), 3.50 (d, J=13.5 Hz, 1H), 2.18 (dd, J=7.2, 2.7 Hz, 1H), 2.06 (d, J=2.7 Hz, 1H), 1.80 (d, J=7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 173.7, 138.0, 128.6, 128.0, 127.6, 63.1, 39.0, 35.3; HRMS (EI) exact mass calcd for $C_{10}H_{12}N_2O$ $[M]^+$ 176.0950, found 176.0938.

*4.2.3. 1-Benzylaziridine-2-(N-phenyl)amide (**11**)*

Prepared as a white solid. IR (KBr) 3435, 3286, 3134, 3059, 2933, 2844, 1661, 1601, 1539, 1499, 1444, 1310, 754, 721, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.36 (br, 1H), 7.50 (d, J=7.5 Hz, 2H), 7.40–7.25 (m, 7H), 7.08 (t, J=7.3 Hz, 1H), 3.66 (d, J=13.3 Hz, 1H), 3.55 (d, J=13.3 Hz, 1H), 2.34 (dd, J=6.9, 3.0 Hz, 1H), 2.11 (d, J=3.0 Hz, 1H), 1.88 (d, J=6.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 168.3, 137.6, 137.4, 128.9, 128.6, 128.0, 127.6, 124.1, 119.5, 62.7, 39.4, 35.2; HRMS (EI) exact mass calcd for $C_{16}H_{16}N_2O$ $[M]^+$ 252.1263, found 252.1256.

*4.2.4. 1-Benzylaziridine-2-(N-cyclohexyl)amide (**12**)*

Prepared as a white solid. IR (KBr) 3274, 3086, 3030, 2926, 2851, 1648, 1558, 1448, 1424, 1267, 1026, 733, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.28 (m, 5H), 6.41 (br, 1H), 3.69–3.66 (m,

1H), 3.56 (d, *J*=13.5 Hz, 1H), 3.47 (d, *J*=13.5 Hz, 1H), 2.17 (dd, *J*=6.9, 3.0 Hz, 1H), 1.93 (d, *J*=3.0 Hz, 1H), 1.86–1.81 (m, 2H), 1.75 (d, *J*=6.9 Hz, 1H), 1.69–1.56 (m, 2H), 1.36–1.06 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 169.3, 138.0, 128.5, 127.9, 127.4, 62.9, 47.3, 39.3, 35.2, 32.9, 25.5, 24.7; HRMS (EI) exact mass calcd for $C_{16}H_{22}N_2O$ $[M]^+$ 258.1732, found 258.1736.

*4.2.5. 1-Benzylaziridine-2-(N-n-dodecyl)amide (**13**)*

Prepared as a white solid. IR (KBr) 3427, 3299, 3061, 2920, 2851, 1645, 1549, 1466, 726, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.32 (m, 5H), 6.53 (br, 1H), 3.55 (d, *J*=13.5 Hz, 1H), 3.49 (d, *J*=13.5 Hz, 1H), 3.23–3.12 (m, 2H), 2.21 (dd, *J*=6.7, 2.8 Hz, 1H), 1.95 (d, *J*=2.8 Hz, 1H), 1.77 (d, *J*=6.7 Hz, 1H), 1.45–1.43 (m, 2H), 1.31–1.20 (m, 18H), 0.88 (t, *J*=6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.3, 138.1, 128.6, 128.1, 127.6, 63.1, 39.3, 38.9, 35.3, 32.0, 29.7, 29.6, 29.4, 26.9, 22.8, 14.2; HRMS (EI) exact mass calcd for $C_{22}H_{36}N_2O$ $[M]^+$ 344.2828, found 344.2819.

*4.2.6. 1-(p-Methoxybenzyl)aziridine-2-amide (**14**)*

Prepared as a white solid. IR (KBr) 3405, 3206, 2933, 2842, 1632, 1515, 1461, 1443, 1340, 1257, 1029, 819 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J*=8.4 Hz, 2H), 6.87 (d, *J*=8.4 Hz, 2H), 6.38 (br, 1H), 5.26 (br, 1H), 3.80 (s, 3H), 3.49 (d, *J*=12.9 Hz, 1H), 3.43 (d, *J*=12.9 Hz, 1H), 2.16–2.14 (m, 1H), 2.02 (d, *J*=2.7 Hz, 1H), 1.78 (d, *J*=7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 173.8, 159.0, 130.0, 129.3, 114.0, 62.5, 55.3, 38.8, 35.1; HRMS (EI) exact mass calcd for $C_{11}H_{14}N_2O_2$ $[M]^+$ 206.1055, found 206.1051.

*4.2.7. 1-(p-Methoxybenzyl)aziridine-2-(N-phenyl)amide (**15**)*

Prepared as a white solid. IR (KBr) 3431, 3288, 3134, 3062, 2926, 2840, 1662, 1604, 1513, 1443, 1311, 1248, 1032, 823, 755, 692 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (br, 1H), 7.49 (d, *J*=8.1 Hz, 2H), 7.32–7.25 (m, 4H), 7.07 (t, *J*=7.2 Hz, 1H), 6.89 (d, *J*=8.4 Hz, 2H), 3.80 (s, 3H), 3.58 (d, *J*=12.9 Hz, 1H), 3.50 (d, *J*=12.9 Hz, 1H), 2.33–2.31 (m, 1H), 2.08 (d, *J*=2.7 Hz, 1H), 1.88–1.85 (m, *J*=7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 168.5, 159.3, 137.5, 129.9, 129.5, 129.1, 124.3, 119.6, 114.2, 62.3, 55.4, 39.5, 35.3; HRMS (EI) exact mass calcd for $C_{17}H_{18}N_2O_2$ $[M]^+$ 282.1368, found 282.1370.

*4.2.8. 1-(p-Methoxybenzyl)aziridine-2-(N-cyclohexyl)amide (**16**)*

Prepared as a white solid. IR (KBr) 3277, 3087, 2931, 2851, 1647, 1613, 1557, 1512, 1251, 1026, 811 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J*=8.5 Hz, 2H), 6.87 (d, *J*=8.5 Hz, 2H), 6.42–6.39 (br, 1H), 3.81 (s, 3H), 3.73–3.68 (m, 1H), 3.50 (d, *J*=13.2 Hz, 1H), 3.39 (d, *J*=13.2 Hz, 1H), 2.15 (dd, *J*=6.9, 3.0 Hz, 1H), 1.90 (d, *J*=3.0 Hz, 1H), 1.87–1.80 (m, 2H), 1.74 (d, *J*=6.9 Hz, 1H), 1.68–1.56 (m, 2H), 1.39–1.05 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 169.5, 159.0, 130.2, 129.2, 113.9, 62.4, 55.3, 47.4, 39.2, 35.2, 33.0, 25.5, 24.8; HRMS (EI) exact mass calcd for $C_{17}H_{24}N_2O_2$ $[M]^+$ 288.1838, found 288.1838.

*4.2.9. 1-(p-Methoxybenzyl)aziridine-2-(N-n-dodecyl)amide (**17**)*

Prepared as a white solid. IR (KBr) 3425, 3301, 2955, 2919, 2849, 1645, 1615, 1549, 1515, 1467, 1252, 1034, 828 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J*=8.4 Hz, 2H), 6.87 (d, *J*=8.4 Hz, 2H), 6.49 (br, 1H), 3.80 (s, 3H), 3.47 (d, *J*=13.2 Hz, 1H), 3.41 (d, *J*=13.2 Hz, 1H), 3.18 (d, *J*=6.9 Hz, 1H), 3.13 (d, *J*=6.9 Hz, 1H), 2.18 (dd, *J*=6.9, 3.0 Hz, 1H), 1.91 (d, *J*=3.0 Hz, 1H), 1.74 (d, *J*=6.9 Hz, 1H), 1.44–1.42 (m, 2H), 1.31–1.20 (m, 18H), 0.88 (t, *J*=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.4, 159.1, 130.2, 129.4, 114.0, 62.6, 55.4, 39.3, 38.9, 35.3, 32.0, 29.7, 29.6, 29.4, 26.9, 22.8, 14.2; HRMS (EI) exact mass calcd for $C_{23}H_{38}N_2O_2$ $[M]^+$ 374.2933, found 374.2936.

*4.2.10. 1-n-Hexadecylaziridine-2-amide (**18**)*

Prepared as a white solid. IR (KBr) 3380, 3171, 2918, 2850, 1667, 1628, 1467 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.37 (br, 1H), 5.19 (br, 1H), 2.35–2.26 (m, 2H), 1.95–1.93 (m, 2H), 1.65–1.49 (m, 5H), 1.30–1.20 (m, 24H), 0.87 (t, *J*=6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 174.1, 60.0, 38.9, 35.3, 32.0, 29.8, 29.7, 29.6, 29.5, 27.4, 22.8, 14.2; HRMS (EI) exact mass calcd for $C_{19}H_{38}N_2O$ $[M]^+$ 310.2984, found 310.2979.

*4.2.11. 1-n-Hexadecylaziridine-2-(N-phenyl)amide (**19**)*

Prepared as a white solid. IR (KBr) 3432, 3250, 3197, 3139, 3080, 2919, 2850, 1658, 1603, 1550, 1501, 1468, 1444, 1315, 753, 721, 690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (br, 1H), 7.51 (d, *J*=7.8 Hz, 2H), 7.32–7.24 (m, 2H), 7.06 (t, *J*=7.3 Hz, 1H), 2.44–2.29 (m, 2H), 2.09 (dd, *J*=6.9, 2.8 Hz, 1H), 1.98 (d, *J*=2.8 Hz, 1H), 1.67 (d, *J*=6.9 Hz, 1H), 1.61–1.53 (m, 4H), 1.29–1.20 (m, 24H), 0.86 (t, *J*=6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 168.8, 137.6, 129.0, 124.1, 119.4, 59.6, 39.5, 35.3, 32.0, 29.8, 29.7, 29.6, 29.5, 29.4, 27.4, 22.7, 14.2; HRMS (EI) exact mass calcd for $C_{25}H_{42}N_2O$ $[M]^+$ 386.3297, found 386.3304.

*4.2.12. 1-n-Hexadecylaziridine-2-(N-cyclohexyl)amide (**20**)*

Prepared as a white solid. IR (KBr) 3277, 3088, 2923, 2843, 1651, 1559, 1469 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.41–6.39 (br, 1H), 3.72–3.68 (m, 1H), 2.37–2.30 (m, 1H), 2.26–2.20 (m, 1H), 1.95 (dd, *J*=6.7, 2.8 Hz, 1H), 1.90–1.86 (m, 1H), 1.80–1.76 (m, 2H), 1.69–1.62 (m, 2H), 1.56–1.42 (m, 5H), 1.25–1.05 (m, 30H), 0.87 (t, *J*=6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 169.9, 59.9, 47.3, 39.3, 35.3, 33.1, 32.0, 29.8, 29.7, 29.6, 29.5, 27.4, 25.6, 24.9, 24.8, 22.8, 14.2; HRMS (EI) exact mass calcd for $C_{25}H_{48}N_2O$ $[M]^+$ 392.3767, found 392.3772.

*4.2.13. 1-n-Hexadecylaziridine-2-(N-n-dodecyl)amide (**21**)*

Prepared as a white solid. IR (KBr) 3428, 3282, 2956, 2918, 2849, 1645, 1553, 1469 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (br, 1H), 3.22–3.13 (m, 2H), 2.35–2.24 (m, 3H), 1.99–1.98 (m, 1H), 1.84–1.83 (m, 1H), 1.58–1.45 (m, 6H), 1.31–1.20 (m, 42H), 0.87 (t, *J*=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.7, 59.9, 39.2, 38.9, 35.3, 32.0, 29.8, 29.7, 29.6, 29.4, 27.4, 26.9, 22.8, 14.2; HRMS (EI) exact mass calcd for $C_{31}H_{62}N_2O$ $[M]^+$ 478.4862, found 478.4861.

*4.2.14. 1-(2-Naphthalenemethyl)aziridine-2-amide (**22**)*

Prepared as a white solid. IR (KBr) 3398, 3201, 2923, 1640, 1510, 1441, 799, 771 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J*=7.8 Hz, 1H), 7.89–7.86 (m, 1H), 7.83–7.80 (m, 1H), 7.57–7.42 (m, 4H), 6.34 (br, 1H), 5.36 (br, 1H), 3.96 (s, 2H), 2.25 (dd, *J*=6.9, 3.0 Hz, 1H), 2.09 (d, *J*=3.0 Hz, 1H), 1.87 (d, *J*=6.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 173.8, 133.8, 133.7, 131.6, 128.8, 128.4, 126.3, 126.0, 125.9, 125.5, 123.8, 61.2, 39.1, 35.7; HRMS (EI) exact mass calcd for $C_{14}H_{14}N_2O$ $[M]^+$ 226.1106, found 226.1104.

*4.2.15. 1-(2-Naphthalenemethyl)aziridine-2-(N-phenyl)amide (**23**)*

Prepared as a white solid. IR (KBr) 3430, 3265, 3134, 3064, 2959, 2924, 2851, 1664, 1599, 1542, 1499, 1444, 1308, 1260, 797, 779, 755, 691 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (br, 1H), 8.29 (d, *J*=8.7 Hz, 1H), 7.90 (d, *J*=8.1 Hz, 1H), 7.84–7.81 (m, 1H), 7.62–7.50 (m, 3H), 7.44–7.43 (m, 2H), 7.38–7.32 (m, 2H), 7.28–7.22 (m, 1H), 7.04 (t, *J*=7.5 Hz, 1H), 4.12 (d, *J*=13.5 Hz, 1H), 3.96 (d, *J*=13.5 Hz, 1H), 2.40 (dd, *J*=7.0, 2.8 Hz, 1H), 2.17 (d, *J*=2.8 Hz, 1H), 1.97 (d, *J*=7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 168.4, 137.4, 134.0, 133.5, 131.7, 129.1, 129.0, 128.7, 126.4, 126.3, 126.0, 125.5, 124.2, 123.9, 119.5, 61.0, 39.5, 35.9; HRMS (EI) exact mass calcd for $C_{20}H_{18}N_2O$ $[M]^+$ 302.1419, found 302.1412.

*4.2.16. 1-(2-Naphthalenemethyl)aziridine-2-(N-cyclohexyl)-amide (**24**)*

Prepared as a white solid. IR (KBr) 3282, 3061, 2930, 2852, 1648, 1553, 1445, 1269, 1256, 1013, 776, 687 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, *J*=8.7 Hz, 1H), 7.89–7.86 (m, 1H), 7.82–7.79 (m, 1H), 7.55–7.50 (m, 2H), 7.43–7.41 (m, 2H), 6.42–6.40 (br, 1H), 4.03 (d, *J*=13.6 Hz, 1H), 3.88 (d, *J*=13.6 Hz, 1H), 3.67–3.56 (m, 1H), 2.23 (dd, *J*=6.9, 3.0 Hz, 1H), 1.99 (d, *J*=3.0 Hz, 1H), 1.84 (d, *J*=6.9 Hz, 1H),

1.74–1.49 (m, 4H), 1.32–0.94 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 169.3, 133.8, 133.7, 131.6, 128.7, 128.3, 126.1, 126.0, 125.8, 125.4, 123.8, 61.0, 47.0, 39.2, 35.9, 32.6, 25.5, 24.4; HRMS (EI) exact mass calcd for $C_{20}H_{24}N_2O$ $[M]^+$ 308.1889, found 308.1886.

4.2.17. 1-(2-Naphthalenemethyl)aziridine-2-(N-n-dodecyl)-amide (**25**)

Prepared as a white solid. IR (KBr) 3317, 3055, 2923, 2851, 1653, 1531, 1464, 796, 772 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, J=8.1 Hz, 1H), 7.88–7.85 (m, 1H), 7.81–7.78 (m, 1H), 7.54–7.40 (m, 4H), 6.44 (br, 1H), 4.00 (d, J=13.5 Hz, 1H), 3.87 (d, J=13.5 Hz, 1H), 3.15–3.02 (m, 2H), 2.25 (dd, J=6.9, 3.0 Hz, 1H), 1.98 (d, J=3.0 Hz, 1H), 1.83 (d, J=6.9 Hz, 1H), 1.30–1.11 (m, 20H), 0.87 (t, J=6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.1, 133.8, 131.6, 128.7, 128.3, 126.1, 126.0, 125.8, 125.4, 123.8, 61.1, 39.3, 38.7, 35.7, 31.9, 29.7, 29.6, 29.5, 29.4, 29.2, 26.7, 22.7, 14.1; HRMS (EI) exact mass calcd for $C_{26}H_{38}N_2O$ $[M]^+$ 394.2984, found 394.2987.

4.2.18. 1-Phenethylaziridine-2-amide (**26**)

Prepared as a white solid. IR (KBr) 3300, 3153, 3028, 2940, 2891, 2847, 1689, 1633, 1497, 1433, 1340, 732, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.19 (m, 5H), 6.27 (br, 1H), 5.51 (br, 1H), 2.87 (t, J=6.8 Hz, 2H), 2.71–2.63 (m, 1H), 2.55–2.47 (m, 1H), 1.95–1.93 (m, 2H), 1.59 (d, J=6.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 174.0, 139.5, 128.7, 128.4, 126.3, 61.1, 38.8, 36.0, 35.0; HRMS (EI) exact mass calcd for $C_{11}H_{14}N_2O$ $[M]^+$ 190.1106, found 190.1113.

4.2.19. 1-Phenethylaziridine-2-(N-phenyl)amide (**27**)

Prepared as a white solid. IR (KBr) 3324, 3060, 3028, 2929, 2840, 1682, 1595, 1525, 1496, 1442, 1311, 757, 696, 640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (br, 1H), 7.46 (d, J=7.8 Hz, 2H), 7.36–7.22 (m, 7H), 7.08 (t, J=7.2 Hz, 1H), 2.94–2.82 (m, 3H), 2.57–2.51 (m, 1H), 2.11 (dd, J=6.9, 3.0 Hz, 1H), 1.98 (d, J=3.0 Hz, 1H), 1.70 (d, J=6.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 168.5, 139.5, 137.5, 129.0, 128.8, 128.6, 126.5, 124.1, 119.4, 60.7, 39.5, 36.0, 35.3; HRMS (EI) exact mass calcd for $C_{17}H_{18}N_2O$ $[M]^+$ 266.1419, found 266.1422.

4.2.20. 1-Phenethylaziridine-2-(N-cyclohexyl)amide (**28**)

Prepared as a white solid. IR (KBr) 3431, 3272, 3088, 3025, 2920, 2851, 1647, 1559, 1449, 1270, 750, 695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.19 (m, 5H), 6.32–6.29 (br, 1H), 3.72–3.66 (m, 1H), 2.86–2.76 (m, 3H), 2.45–2.35 (m, 1H), 2.17 (dd, J=6.9, 3.0 Hz, 1H), 1.79 (d, J=3.0 Hz, 1H), 1.77–1.62 (m, 4H), 1.57 (d, J=6.9 Hz, 1H), 1.35–1.31 (m, 3H), 1.16–0.98 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 169.4, 139.5, 128.6, 128.3, 126.2, 60.9, 47.2, 39.1, 35.9, 35.1, 32.9, 25.4, 24.7; HRMS (EI) exact mass calcd for $C_{17}H_{24}N_2O$ $[M]^+$ 272.1889, found 272.1885.

4.2.21. 1-Phenethylaziridine-2-(N-n-dodecyl)amide (**29**)

Prepared as a white solid. IR (KBr) 3281, 3063, 2921, 2851, 1644, 1550, 1466, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.18 (m, 5H), 6.39 (br, 1H), 3.18–3.11 (m, 2H), 2.88–2.83 (m, 2H), 2.72–2.70 (m, 1H), 2.47–2.43 (m, 1H), 1.99 (dd, J=6.9, 3.0 Hz, 1H), 1.82 (d, J=3.0 Hz, 1H), 1.57 (d, J=6.9 Hz, 1H), 1.46–1.41 (m, 2H), 1.31–1.20 (m, 18H), 0.88 (t, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.3, 139.5, 128.7, 128.4, 126.3, 61.0, 39.1, 38.8, 36.0, 35.1, 31.9, 29.6, 29.5, 29.3, 26.8, 22.7, 14.1; HRMS (EI) exact mass calcd for $C_{23}H_{38}N_2O$ $[M]^+$ 358.2984, found 358.2982.

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Supplementary data

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