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# Nucleophile-Dependent Regio- and Stereoselective Ring Opening of 1-Azoniabicyclo[3.1.0]hexane Tosylate

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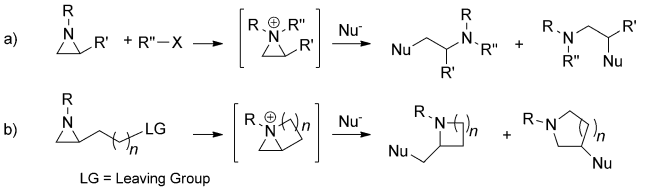
*Dedicated to Professor Tae Young Lee on the occasion of his 90th birthday*

**Abstract:** 1-[(1*R*)-(1-Phenylethyl)]-1-azoniabicyclo[3.1.0]hexane tosylate was generated as a stable bicyclic aziridinium salt from the corresponding 2-(3-hydroxypropyl)aziridine upon reaction with *p*-toluenesulfonyl anhydride. This bicyclic aziridinium ion was then treated with various nucleophiles including halides, azide, acetate, and cyanide in $CH_3CN$ to afford either piperidines or pyrrolidines through regio- and stereoselective ring opening, mediated by the characteristics of the applied nucleophile. On the basis of DFT calculations, ring-opening reactions under thermodynamic control yield piperidines, whereas reactions under kinetic control can yield both piperidines and pyrrolidines depending on the activation energies for both pathways.

**Keywords:** aziridines · density functional theory calculations · heterocycles · nucleophilic substitution · ring expansion · ring opening

## Introduction

The versatile chemistry of aziridines as nitrogen-containing three-membered ring systems is based on their propensity to undergo ring-opening reactions with various nucleophiles owing to the favorable release of ring-strain energy.[1] As compared to cyclopropane and oxirane, the aziridine unit has an additional bonding site located at the ring nitrogen atom, which controls its reactivity toward ring-opening reactions. Aziridines are quite stable when decorated with an electron-donating group, such as a benzyl substituent, at the ring nitrogen.[2] These systems are rather inert and are thus referred to as "non-activated aziridines".[3] Prior to further synthetic elaborations, they have to be activated as aziridinium ions or their equivalents, the structures of which have been shown to retain the characteristics of quaternary ammonium ions on the basis of spectroscopic and X-ray crystallographic structural studies.[2,4] This implies that the ring nitrogen of non-activated aziridines is nucleophilic enough to react with a proper electrophile or a Lewis acid, thereby resulting in the formation of highly electrophilic aziridinium ion intermediates. In that respect, the use of benzyl bromide and methyl triflate has been documented to result in synthetically interesting aziridinium ions, and subsequent nucleophilic ring openings with various nucleophiles have furnished acyclic compounds in a regio- and stereospecific manner (Scheme 1 a).[4b,5] Instead of applying an external electrophile, aziridinium ions can also be generated as bicyclic structures through displacement of a suitable leaving group within the aziridine side chain. The subsequent ring-opening reactions will then generate cyclic products, thus rendering this a convenient approach toward the construction of different types of azaheterocyclic scaffolds (Scheme 1 b). This approach of handling internal electrophiles within the aziridine side chain has found already ap-




Scheme 1. Formation of a) monocyclic and b) bicyclic aziridinium ions and their subsequent ring-opening reactions by nucleophiles.

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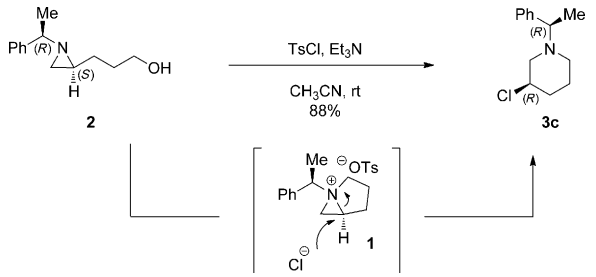
plications in the synthesis of pyrrolidines and piperidines, as well as synthons of pharmaceutical products and alkaloids.[6e]

Herein, we describe the preparation of a stable bicyclic aziridinium ion, 1-azoniabicyclo[3.1.0]hexane tosylate (**1**), and its nucleophile-controlled regiochemical ring opening is described. Although 1-azoniabicyclohexanes have been reported as transient intermediates from 2-(halomethyl)pyrrolidines and 3-halopiperidines,[6] this is the first report on its isolation and characterization by means of cyclization of 2-(3-hydroxypropyl)aziridines.

## Results and Discussion

In continuation of our interest in the use of 2-substituted 1-benzylaziridines for the preparation of nitrogen-containing cyclic and acyclic target compounds,[7] (2*S*)-2-(3-hydroxypropyl)-1-[(1*R*)-(1-phenylethyl)]aziridine (**2**)[8] was treated with *p*-toluenesulfonyl chloride and triethylamine in $CH_3CN$ at room temperature to synthesize the corresponding 2-(3-tosyloxypropyl)aziridine. However, this approach only provided (3*R*)-3-chloro-1-[(1*R*)-(1-phenylethyl)]piperidine (**3c**) in 88% yield without any detectable amount of the anticipated tosylated aziridine (Scheme 2). This unexpected result

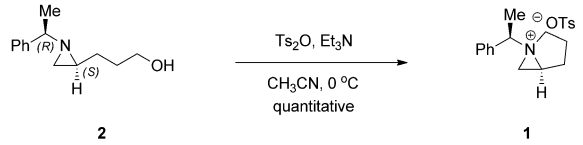



Scheme 2. Reaction of **2** with *p*-toluenesulfonyl chloride and triethylamine in $CH_3CN$.

pointed to the presumable participation of 1-azoniabicyclo-[3.1.0]hexane ion **1** as an intermediate, followed by nucleophilic ring opening by chloride in a regio- and stereospecific manner.

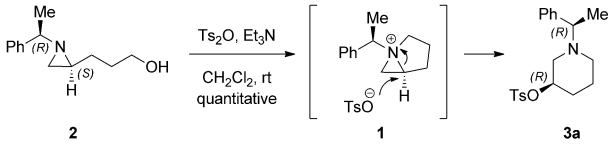
Inspired by the observation above, we turned our attention to the preparation of a stable 1-azoniabicyclo-[3.1.0]hexane ion (**1**) to study its ring-opening reactions with various nucleophiles. Considering earlier investigations on 1-methylaziridinium ions as suitable synthetic intermediates,[6] we anticipated the preparation of a stable 1-azoniabicyclo[3.1.0]hexane salt starting from an appropriate aziridine precursor. It is evident that the presence of good in situ formed nucleophiles in the reaction medium is undesirable, and thus the counteranion should not be prone to induce aziridinium ion ring opening.

The formation of 1-azoniabicyclo[3.1.0]hexane tosylate **1** was accomplished by means of the treatment of 2-(3-hydroxypropyl)aziridine **2** with *p*-toluenesulfonyl anhydride




Scheme 3. Preparation of the stable 1-azoniabicyclo[3.1.0]hexane tosylate (**1**).

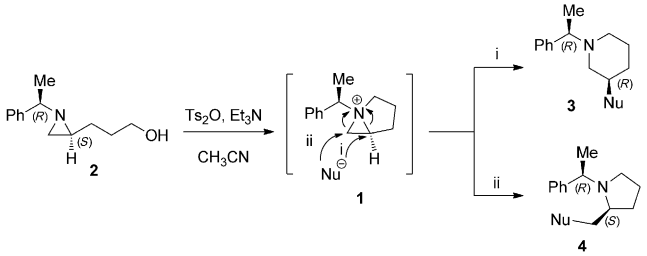
(1.1 equiv) in $CH_3CN$ in the presence of triethylamine (1.1 equiv; Scheme 3), and its structure was acknowledged by means of $^1H$ NMR spectroscopic analysis ($CD_3CN$). Surprisingly, this bicyclic aziridinium ion **1** was found to be remarkably stable in $CH_3CN$ upon prolonged storage for 5 days at room temperature. However, aziridinium ion **1** underwent quantitative conversion into 1-[(1*R*)-(1-phenylethyl)]-(3*R*)-3-tosyloxypiperidine (**3a**) after 2 h at room temperature by changing the solvent from $CH_3CN$ to $CH_2Cl_2$, $CHCl_3$, and THF (Scheme 4). In addition, the ring-opened




Scheme 4. Formation of **3a** in $CH_2Cl_2$.

product (i.e., 3-tosyloxypiperidine **3a**) was again transformed into the bicyclic aziridinium salt **1** by redissolving this compound in $CH_3CN$ without the assistance of any external reagent.[9] Apparently, acetonitrile provides an ideal environment for the formation and preservation of this aziridinium tosylate **1**.

In the next phase, the stable aziridinium ion **1**, prepared from aziridine **2** using *p*-toluenesulfonyl anhydride and $Et_3N$ in $CH_3CN$, was evaluated as an eligible substrate for ring-opening reactions with various nucleophiles. As shown in Scheme 5, these ring openings can proceed through two different pathways to yield either piperidines **3** (Scheme 5, pathway i) or pyrrolidines **4** (pathway ii) by means of ring opening at the more or less hindered aziridinium carbon atom, respectively. The results of these experiments are summarized in Table 1.




Scheme 5. Possible pathways in the ring opening of 1-azoniabicyclo-[3.1.0]hexane salt (**1**).

Table 1. Ring-opening reactions of 1-azoniabicyclo[3.1.0]hexane tosylate **1** by means of different nucleophiles in $CH_3CN$.

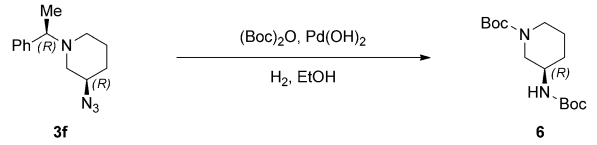
| Entry | Nucleophile | Yield [%][a] | **3**/**4** (ratio)[b] |
|---|---|---|---|
| 1 | CsF | 83 | **3b**/**4b** (54:46) |
| 2 | TsCl | 88 | **3c**/**4c** (100:0) |
| 3 | $n$Bu$_4$N$^+$Br$^-$ | 42 | **3d**/**4d** (100:0) |
| 4 | $I_2$ | 75 | **3e**/**4e** (100:0) |
| 5 | $NaN_3$ | 89 | **3f**/**4f** (36:64) |
| 6 | NaOAc | 65 | **3g**/**4g** (35:65) |
| 7 | $n$Bu$_4$N$^+$AcO$^-$ | 92 | **3g**/**4g** (32:68) |
| 8 | NaCN | 11 | **3h**/**4h** (0:100)[c] |
| 9 | KCN | 10 | **3h**/**4h** (0:100)[c] |
| 10 | $n$Bu$_4$N$^+$CN$^-$ | 89 | **3h**/**4h** (0:100) |

[a] The yield of the isolated mixture of **3** and **4**. [b] The ratios were determined by $^1$H NMR spectroscopy. [c] Starting material was mostly recovered.

When halide nucleophiles were used, chloride, bromide, and iodide were found to induce selective ring opening of substrate **1** along pathway i to yield the corresponding 3-halogenated piperidines **3c–e** in 88, 42, and 75% yields, respectively (Table 1, entries 2–4), whereas fluoride participated both in pathways i and ii to furnish a mixture of the corresponding 3-fluoropiperidine **3b** and 2-(fluoromethyl)pyrrolidine **4b** in a ratio of 54:46 in 83% yield (Table 1, entry 1). This result parallels previous findings that deal with the ring-opening reactions of 2-substituted monocyclic aziridinium ions by halogens.[10] Furthermore, azide and acetate were investigated as possible nucleophiles, thereby resulting in the formation of pyrrolidine derivatives **4f** and **4g** as the major reaction products along with minor amounts of piperidines **3f** and **3g** in good yields and **3**/**4** ratios of 36:64 ($NaN_3$), 35:65 (NaOAc), and 32:68 ($n$Bu$_4$NOAc), respectively (Table 1, entries 5–7). Apparently, these nucleophiles mainly, but not exclusively, induce attack at the less hindered position (pathway ii). Surprisingly, application of cyanide ions afforded 2-(cyanomethyl)pyrrolidine **4h** as the sole reaction product through exclusive ring opening at the nonsubstituted aziridinium carbon atom (pathway ii). The most efficient conversion in that respect was obtained from the reaction with $n$Bu$_4$NCN to afford only pyrrolidine **4h** in 89% yield (Table 1, entry 10).

A similar behavior was observed when using the diastereomeric counterpart of aziridine **2** (i.e., (2*R*)-2-(3-hydroxypropyl)-1-[(1*R*)-(1-phenylethyl)]aziridine). The ring-opening reactions with $NaN_3$ and $n$Bu$_4$OAc gave inseparable mixtures of piperidine and pyrrolidine ring compounds in 91 and 72% yield in ratios of 46:54 and 48:52, respectively, as determined by $^1$H NMR spectroscopic analysis. As was the case for (2*S*)-aziridine **2**, the corresponding 2-(cyanomethyl)pyrrolidine was obtained as the sole product from the reaction of (2*R*)-2-(3-hydroxypropyl)-1-[(1*R*)-(1-phenylethyl)]aziridine with $n$Bu$_4$NCN in 81% yield.

The stereochemical pathway to form the bicyclic aziridinium ion **1** and its ring-opening reactions was elucidated by the conversion of (3*R*)-3-azido-1-[(1*R*)-1-phenylethyl]piperidine **3f** obtained from entry 5 in Table 1 to the known compound *N*,*N*′-di-*tert*-butoxycarbonyl-(3*R*)-3-aminopiperidine **6**

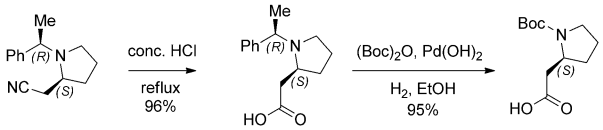



3f 6

Scheme 6. Preparation of *N*,*N*′-di-*tert*-butoxycarbonyl-(3*R*)-3-aminopiperidine **6** from 3-azidopiperidine **3f**.

(Scheme 6). Hydrogenation of 3-azidopiperidine was performed with $Boc_2O$ (Boc = *tert*-butyloxycarbonyl) in the presence of a catalytic amount of $Pd(OH)_2$, which effected debenzylation and reduction of the azido group followed by double *N*-*tert*-butoxycarbonylation, thus yielding *N*,*N*′-di-*tert*-butoxycarbonyl-(3*R*)-3-aminopiperidine **6** with an $[\alpha]_D$ value of +2.5 ($c$ = 0.95 in $CHCl_3$). By comparison of this observed $[\alpha]_D$ with the reported value of *N*,*N*′-di-*tert*-butoxycarbonyl-(3*S*)-3-aminopiperidine ($[\alpha]_D = -2.4$ ($c$ = 1.50, $CHCl_3$)),[11] the absolute configuration of the 3-aminopiperidine **3f** obtained in this work could be assigned to be 3*R*. Consequently, the configuration of 3-azidopiperidine **3f** resulted from a complete inversion of stereochemistry during the ring-opening reaction of the stable bicyclic aziridinium ion **1**, thus pointing to a clean $S_N2$ process.

(2*S*)-2-Cyanomethyl-1-[(1*R*)-(1-phenylethyl)]pyrrolidine (**4h**), derived from the ring-opening reaction of bicyclic aziridinium ion **1** by cyanide (Table 1, entry 10), was used for further elaboration into *N*-Boc-β-homoproline **8** (Scheme 7).




4h 7 8

Scheme 7. Synthesis of *N*-Boc-β-homoproline **8**.

The cyano group of 2-(cyanomethyl)pyrrolidine **4h** was first converted to the corresponding carboxylic acid through hydrolysis by utilizing concentrated HCl under reflux conditions. Finally, *N*-Boc-β-homoproline **8**, which is of interest considering the biological importance of β-amino acids,[12] was prepared by hydrogenation of pyrrolidine **7** by applying $H_2$ (atmospheric pressure) over $Pd(OH)_2$ in EtOH in the presence of $(Boc)_2O$. The $[\alpha]_D$ of the latter constrained amino acid **8** was measured to be −28.9 ($c$ = 0.67, $CHCl_3$), thus confirming the 2*S* configuration of the reaction product **4h** with the authentic sample prepared from the commercial (*S*)-β-homoproline (Table 1, entry 10).[13]

Thus, the ring opening of 1-azoniabicyclo[3.1.0]hexane tosylate **1** by different nucleophiles yields either piperidines **3** through ring opening at the more hindered aziridinium carbon atom or pyrrolidines **4** through ring opening at the less hindered aziridinium carbon atom (Scheme 5, pathway i and ii, respectively).

To better understand the factors that govern this experimentally observed nucleophile-dependent regioselectivity, density functional theory (DFT) calculations were performed on the ring-opening reaction of **1** with chloride, cyanide, and azide nucleophiles, thus leading exclusively to piperidine **3c**, pyrrolidine **4h**, and a mixture of **3f** and **4f**, respectively (Table 2).

Table 2. Relative Gibbs free energies [kJ mol$^{-1}$] for the ring opening of bicyclic ammonium ion **1** with different nucleophiles (M06-2X/6-311++G(d,p)//B3LYP/6-31++G(d,p), 298 K and 1 atm).[a]

| $Nu^-$ | PRC | Pathway i | | Pathway ii | | Exptl **3**/**4** |
|---|---|---|---|---|---|---|
| | | TS-i | Piperidine **3** | TS-ii | Pyrrolidine **4** | |
| CN | 0.0 | 48.7 | −212.7 | 35.2 | −209.3 | 0:100 |
| $N_3$ | 0.0 | 53.2 | −127.3 | 50.0 | −109.7 | 36:64 |
| Cl | 0.0 | 47.2 | −76.9 | 40.4 | −59.3 | 100:0 |

[a] Two explicit acetonitrile molecules. All energies relative to the pre-reactive complex (PRC) of pathway ii of the corresponding nucleophile (Scheme 5).

It has been shown that solvent effects cannot be underestimated in the regioselective ring opening of aziridinium ions **1**.[2,5a,10,14–16] Therefore, the pathways under study were modeled with a proper solvent environment. Since the reactions at hand take place in acetonitrile, which can interact explicitly with the reactive substrate, discrete solvent molecules were placed around the chemically active species. Two explicit acetonitrile molecules were taken into account. (The influence of the number of acetonitrile molecules was tested, and the results are given in the Supporting Information.) The tosylate ion and the counterions of the nucleophiles were not taken into account since they will most likely diffuse away from the bicyclic ammonium ion owing to the high polarity of the solvent and do not play a significant role in the ring opening.

It might be anticipated that the six-membered ring compound, that is, piperidines **3**, are more stable than the five-membered ring compound (i.e., pyrrolidines **4**). Indeed this is confirmed by the stability of the products from the ring opening of **1** (Table 2). Piperidines **3** are always more stable than pyrrolidines **4**. Table 2 shows the relative Gibbs free energies for both ring-opening pathways of **1** (Scheme 5) for azide, cyanide, and chloride ions. The free energies of activation for both pathways are also tabulated in Table 2. All values are referred to the pre-reactive complex of pathway ii. A complete list of all free energies along the reaction pathway for both pathways is given in the Supporting Information. All transition states that correspond to the formation of pyrrolidines have a lower free energy of activation. For the azide ion, the difference is, however, very small between pathways i and ii ($\Delta G^{\ddagger}=53.2$ or 50.0 kJ mol$^{-1}$ for pathways i or ii, respectively). However, since piperidines **3** were found to be more stable than pyrrolidines **4**, thermal equilibration could lead to piperidine **3** provided the activation barrier for the reverse reaction (ring closure) is feasible.

The free energies of activation for the reverse reaction are feasible for the chloride ion ($\Delta G^{\ddagger}=99.7$ kJ mol$^{-1}$ for pathway ii), but not for the cyanide ($\Delta G^{\ddagger}=244.6$ kJ mol$^{-1}$ for pathway ii) and azide ions ($\Delta G^{\ddagger}=180.6$ and 159.7 kJ mol$^{-1}$ for pathways i and ii, respectively). Our results show that the ring opening of the bicyclic ammonium ion **1** is under kinetic control for cyanide and azide ions and under thermodynamic control for chloride ions. Gibbs free-energy profiles for the ring opening of the three nucleophiles under study can be found in Figure 1. Transition-state structures for the reactions under kinetic control are shown in Figure 2, and product structures for the reaction under

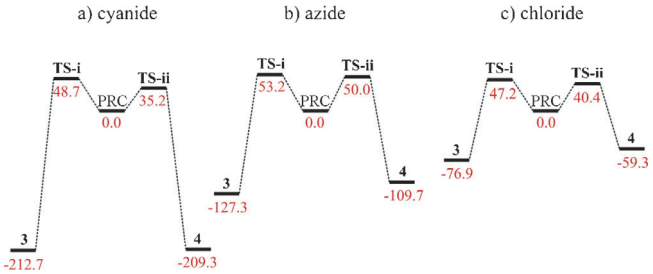



Figure 1. Gibbs free-energy profiles for the ring opening of bicyclic ammonium ion **1** with different nucleophiles [kJ mol$^{-1}$] (M06-2X/6-311++G(d,p)//B3LYP/6-31++G(d,p), 298 K and 1 atm, two explicit acetonitrile molecules).

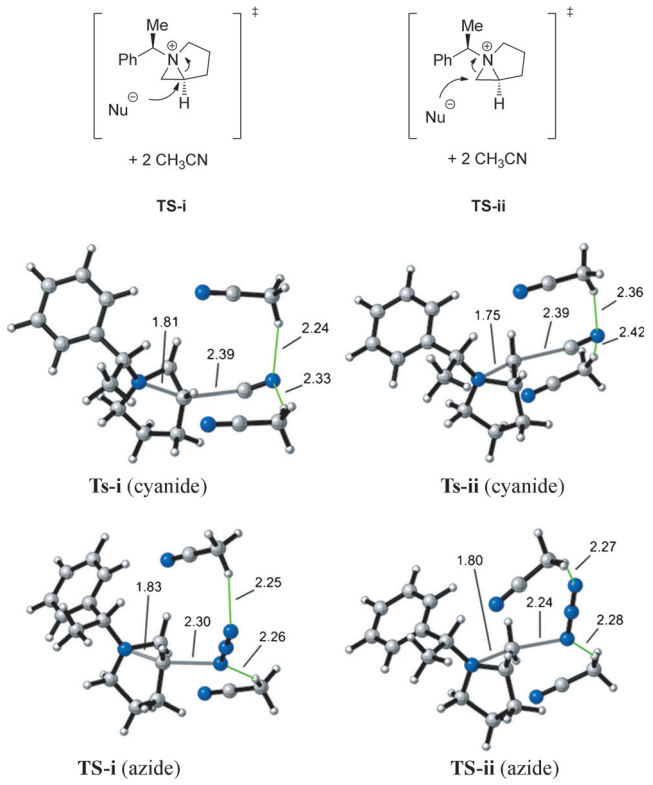



Figure 2. Transition-state structures for the kinetically controlled ring opening of bicyclic ammonium ion **1** with cyanide (top) and azide (bottom) nucleophiles (B3LYP/6-31++G(d,p), two explicit acetonitrile molecules); critical distances in Å.

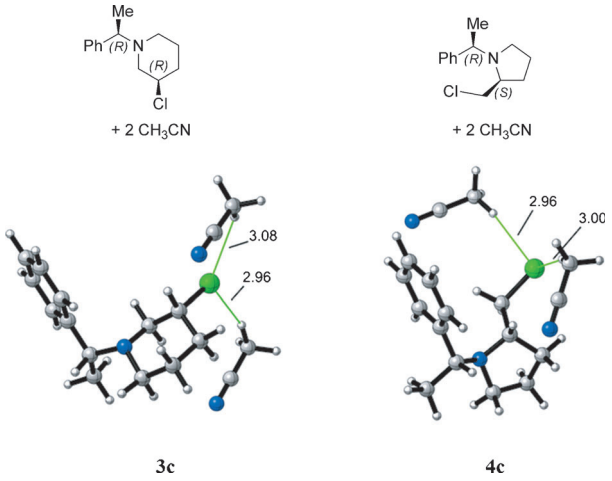



Figure 3. The most stable conformations of **3c** and **4c** (B3LYP/6-31++G(d,p), two acetonitrile molecules); critical distances in Å

thermodynamic control are shown in Figure 3. Additional 3D figures of all localized transition-state and product structures can be found in the Supporting Information (see additional structures). The observed stereochemistry that involves a back-side nucleophilic attack and subsequent Walden inversion is present in all transition-state structures.

To summarize, pyrrolidines **4** are initially formed from the ring opening of bicyclic ammonium ion **1** with cyanide or chloride nucleophiles, since pathway ii is the kinetically preferred route. For cyanide ions, pyrrolidines **4** are also the final product due to the high activation energy of the reverse reaction. For chloride ions, however, the activation energy of the reverse reaction is much lower, and thermal equilibration yields piperidines **3** (the most stable product).[10c] In the case of an azide nucleophile, both piperidines **3** and pyrrolidines **4** are formed initially, since there is no significant difference in activation energy between both pathways. Thermal equilibration with full conversion to piperidines **3** is not feasible for the azide ion, because the activation energy for the reverse reaction is relatively high.

## Conclusion

In conclusion, 1-[(1*R*)-(1-phenylethyl)]-1-azoniabicyclo-[3.1.0]hexane tosylate was generated as a stable bicyclic aziridinium ion from (2*S*)-2-(3-hydroxypropyl)-1-[(1*R*)-1-phenylethyl]aziridine upon treatment with *p*-toluenesulfonyl anhydride and $Et_3N$ in $CH_3CN$. This bicyclic aziridinium tosylate was shown to rearrange spontaneously into the corresponding ring-opened 3-(*p*-toluenesulfonyloxy)piperidine upon changing the solvent to $CH_2Cl_2$, $CHCl_3$, or THF. The latter piperidine also served as the precursor to regenerate the same bicyclic aziridinium ion by changing the solvent back to $CH_3CN$. The obtained 1-azoniabicyclo[3.1.0]hexane tosylate was further subjected to ring-opening reactions with various nucleophiles to afford either piperidines or pyrrolidines in a regio- and stereoselective manner depending on the characteristics of the applied nucleophiles. As shown by DFT calculations, ring-opening reactions under thermodynamic control yield piperidines, whereas reactions under kinetic control can yield both piperidines and pyrrolidines depending on the activation energies for both pathways.

## Experimental Section

*General Information*

All commercially available compounds were used as received unless stated otherwise. All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm E. Merck precoated silica gel plates (60 F254). Visualization was accomplished with either UV light, or by immersion in solutions of ninhydrin, *p*-anisaldehyde, or phosphomolybdic acid (PMA) followed by heating on a hot plate for about 10 s. Purification of reaction products was carried out by column chromatography using Kieselgel 60 Art 9385 (230–400 mesh). $^1H$ and $^{13}C$ NMR spectra were obtained with a Varian 200 (200 MHz for $^1H$, and 50.3 MHz for $^{13}C$) spectrometer or Varian Unity Inova 400WB (400 MHz for $^1H$) and Bruker Advance III NMR spectrometers (400 MHz for $^1H$ and 100 MHz for $^{13}C$). Chemical shifts are reported relative to chloroform ($\delta = 7.26$ ppm) for $^1H$ NMR spectroscopy and chloroform ($\delta = 77.2$ ppm) for $^{13}C$ NMR spectroscopy. Coupling constants are given in hertz. Ambiguous assignments were resolved on the basis of standard one-dimensional proton decoupling experiments. Optical rotations were obtained with a Rudolph Autopol IV digital polarimeter and optical rotation data was reported as follows: $[\alpha]_D$ ($c$ = g per 100 mL, solvent). High-resolution mass spectra were recorded with 4.7 Tesla IonSpec ESI-FOFMS and JEOL (JMS-700) instruments.

*Synthesis of (2S)-2-(3-Hydroxypropyl)-1-[(1R)-(1-phenylethyl)]aziridine (**2**)*

$LiAlH_4$ (287 mg, 7.57 mmol) was added to a solution of methyl (3*S*)-[(1*R*)-1-phenylethylaziridin-2-yl]propanoate (1.178 g. 5.05 mmol)[8,14] in THF (25 mL) at 0 °C. The reaction mixture was stirred at RT for 1 h. After the reaction was completed (monitoring by TLC) it was quenched by saturated $KHSO_4$ (5 mL). The reaction mixture was filtered with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under vacuum. The crude reaction product was purified by column chromatography. Yield = 92 %; $[\alpha]_D = +42.9$ ($c = 1.326$ in $CHCl_3$); $^1H$ NMR (200 MHz, $CDCl_3$): $\delta = 7.39$–$7.15$ (m, 5H), 3.61 (t, $J = 6.4$ Hz, 2H), 2.53 (q, $J = 6.6$ Hz, 1H), 1.85–1.50 (m, 5H), 1.44 (d, $J = 6.6$ Hz, 3H), 1.48–1.40 ppm (m, 2H); $^{13}C$ NMR (50 MHz, $CD_3OD$): $\delta = 144.9$, 129.3, 129.2, 127.9, 70.5, 62.6, 42.0, 33.9, 31.6, 30.2, 23.0 ppm; HRMS: *m*/*z* calcd for $C_{15}H_{28}N_2O_4$: 228.1358 $[M+Na]^+$; found: 228.1355.

*Synthesis of (2R)-2-(3-Hydroxypropyl)-1-[(1R)-(1-phenylethyl)]aziridine*

The reduction reaction was carried out by following the same procedure as for **2** with methyl (3*R*)-[(1*R*)-1-phenylethylaziridin-2-yl]propanoate as the starting material instead of (3*S*)-[(1*R*)-1-phenylethyl-aziridin-2-yl]propanoate. Yield = 90 %; $[\alpha]_D = +37.6$ ($c = 0.68$ in $CHCl_3$); $^1H$ NMR (200 MHz, $CDCl_3$): $\delta = 7.34$–$7.09$ (m, 5H), 3.21 (m, 2H), 2.44 (q, $J =$ 6.4 Hz, 1H), 1.63 (m, 1H), 1.55–1.43 (m, 2H), 1.34 (d, $J = 6.4$ Hz, 3H), 1.30–1.07 ppm (m, 4H); $^{13}C$ NMR (50 MHz, $CD_3OD$): $\delta = 145.2$, 129.4, 128.4, 128.0, 70.9, 62.1, 40.0, 35.0, 31.2, 29.9, 22.2 ppm; HRMS: *m*/*z* calcd for $C_{15}H_{28}N_2O_4$: 228.1358 $[M+Na]^+$; found: 228.1353.

*Synthesis of 1-[(1R)-(1-Phenylethyl)]-1-azoniabicyclo[3.1.0]hexane tosylate (**1**)*

TEA (0.37 mL, 0.268 mmol) and *p*-toluenesulfonic anhydride (87.4 mg, 0.268 mmol) were added to a solution of **2** (51 mg, 0.244 mmol) in $CD_3CN$ (1.2 mL) at 0 °C. More details are described in the Supporting Information. $^1H$ NMR (200 MHz, $CD_3CN$): $\delta = 7.68$–$7.56$ (d, $J = 8.1$ Hz, 2H), 7.50 (br s, 5H), 7.15 (d, $J = 8.1$ Hz, 2H), 4.50 (q, $J = 7.1$ Hz, 1H),

4.02 (m, 1H), 3.39 (ddd, $J$=11.1, 8.2, 1.3 Hz, 1H), 3.23 (dd, $J$=8.2, 4.3 Hz, 1H), 3.06 (m, 2H), 2.33 (s, 3H), 2.15–1.72 (m, 4H) 1.70 ppm (d, $J$=7.1 Hz, 3H).

*General procedure for the preparation of piperidines and pyrrolidines*

TEA (1.1 equiv) and *p*-toluenesulfonic anhydride (1.1 equiv) were added to a solution of **2** (51 mg, 0.244 mmol) in $CH_3CN$ (1.2 mL) at 0°C. After 10 min, the reaction mixture was stirred at RT for 30 min before adding the corresponding nucleophile (3 equiv) at RT. The reaction mixture was stirred for 24 h and quenched by the addition of ice water (10 mL) and $CH_2Cl_2$ (40 mL). The mixture was washed with water (30 mL) and brine (40 mL) consecutively. The reaction product was extracted with $CH_2Cl_2$ (3×30 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification by silica gel flash chromatography ($CH_2Cl_2$/EtOAc/*n*-hexane 1:1:4) provided the analytically pure product.

*Data for 1-[(1R)-(1-Phenylethyl)]-(3R)-3-tosyloxypiperidine (**3a**)*

$[\alpha]_D$=−6.8 ($c$=1.21 in $CHCl_3$); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$=7.72 (d, $J$=8.3 Hz, 2H), 7.40–7.10 (m, 7H), 4.46 (m, 1H), 3.46 (q, $J$=6.8 Hz, 1H), 2.68 (m, 2H), 2,43 (s, 3H), 2.16–1.91 (m, 2H), 1.89–1.30 (m, 4H), 1.27 ppm (d, $J$=6.8 Hz, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$=144.3, 134.3, 129.6, 128.0, 127.4, 127.3, 126.8, 125.8, 78.3, 63.6, 54.2, 49.2, 30.6, 23.0, 21.5, 18.2 ppm; HRMS: $m/z$ calcd for $C_{20}H_{25}NO_3S$: 360.1627 $[M+H]^+$; found: 360.1630.

*Data for (3R)-3-Fluoro-1-[(1R)-1-phenylethyl]piperidine (**3b**)*

$[\alpha]_D$=+8.6 ($c$=0.22 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.33–7.21 (m, 5H), 4.69–4.51 (dtt, $J$=48.4, 7.9, 3.8 Hz, 1H), 3.51 (q, $J$=6.8 Hz, 1H), 2.86 (dd, $J$=19.8, 7.8 Hz, 1H), 2.44 (m, 1H), 2.33 (dt, $J$=10.9, 7.2 Hz, 1H), 2.23 (dt, $J$=8.9, 2.7 Hz, 1H), 1.80 (m, 2H), 1.51 (m, 2H), 1.37 ppm (d, $J$=6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=143.1, 128.1, 127.6, 126.9, 88.7 (d, $J$=171.4 Hz), 64.1, 54.4 (d, $J$=23.8 Hz), 50.1, 30.4 (d, $J$=19.1 Hz), 22.3 (d, $J$=8.0 Hz), 18.7 ppm; HRMS $m/z$ calcd for $C_{13}H_{18}FN$: 208.1496 $[M+H]^+$; found: 208.1494.

*Data for (2S)-2-Fluoromethyl-1-[(1R)-1-phenylethyl]pyrrolidine (**4b**)*

$[\alpha]_D$=−1.2 ($c$=1.69 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.37–7.19 (m, 5H), 3.83 (dd, $J$=47.5, 1.7 Hz, 1H), 3.82 (d, $J$=47.5 Hz, 1H), 3.70 (q, $J$=6.6 Hz, 1H), 3.03 (m, 2H), 2.53 (m, 1H), 1.74 (m, 4H), 1.39 ppm (d, $J$=6.6 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=145.1, 128.2, 127.7, 127.1, 85.5 (d, $J$=170.3 Hz), 62.8, 60.5 (d, $J$=21.5 Hz), 51.5, 27.7 (d, $J$=2.7 Hz), 23.7, 19.6 ppm; HRMS: $m/z$ calcd for $C_{13}H_{18}FN$: 208.1496 $[M+H]^+$; found: 208.1494.

*Data for (3R)-3-Chloro-1-[(1R)-1-phenylethyl]piperidine (**3c**)*

$[\alpha]_D$=+20.5 ($c$=0.38 in $CHCl_3$); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$=7.46–7.17 (m, 5H), 4.14–3.96 (m, 1H), 3.59 (q, $J$=6.8 Hz, 1H), 3.18 (dd, $J$=10.9, 3.7 Hz, 1H), 2.70 (d, $J$=11.3 Hz, 1H), 2.25 (dd, $J$=17.8, 7.2 Hz, 1H), 2.20–2.03 (m, 2H), 1.88–1.49 (m, 3H), 1.43 ppm (d, $J$=6.8 Hz, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$=143.0, 128.1, 127.4, 126.8, 63.9, 58.2, 56.8, 49.9, 35.0, 24.9, 18.5 ppm; HRMS: $m/z$ calcd for $C_{13}H_{18}ClN$: 224.1200 $[M+H]^+$; found: 224.1195.

*Data for (3R)-3-Bromo-1-[(1R)-1-phenylethyl]piperidine (**3d**)*

$[\alpha]_D$=+20.0 ($c$=0.43 in $CHCl_3$); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$=7.53–7.22 (m, 5H), 4.20 (m, 1H), 3.58 (q, $J$=6.8 Hz, 1H), 3.21 (m, 1H), 2.72 (d, $J$=11.3 Hz, 1H), 2.40 (dd, $J$=9.6, 11.0 Hz, 1H), 2.32–2.04 (m, 2H), 1.91–1.54 (m, 3H), 1.44 ppm (d, $J$=6.8 Hz, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$=143.0, 128.1, 127.5, 126.8, 64.0, 58.7, 49.9, 49.3, 35.8, 26.1, 18.6 ppm; HRMS $m/z$: calcd for $C_{13}H_{18}BrN$: 268.0695 $[M+H]^+$; found: 268.0690.

*Data for (3R)-3-Iodo-1-[(1R)-1-phenylethyl]piperidine (**3e**)*

$[\alpha]_D$=+1.0 ($c$=0.70 in $CHCl_3$); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$=7.45–7.19 (m, 5H), 4.48–4.24 (m, 1H), 3.57 (q, $J$=6.8 Hz, 1H), 3.14 (d, $J$=9.9 Hz, 1H), 2.76 (d, $J$=11.3 Hz, 1H), 2.57 (t, $J$=11.3 Hz, 1H), 2.20 (m, 2H), 1.85 (m, 1H), 1.77–1.58 (m, 2H), 1.41 ppm (d, $J$=6.8 Hz, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$=142.8, 128.1, 127.5, 126.9, 63.9, 60.5, 49.9, 37.6, 28.3, 27.4, 18.6 ppm; HRMS: $m/z$ calcd for $C_{13}H_{18}IN$: 316.1627 $[M+H]^+$; found: 316.1622.

*Data for (3R)-3-Azido-1-[(1R)-1-phenylethyl]piperidine (**3f**)*

$[\alpha]_D$=+2.9 ($c$=0.82 in $CHCl_3$); $^1$H NMR (200 MHz, $CD_3OD$): $\delta$=7.45–7.11 (m, 5H), 3.6–3.4 (m, 1H), 3.51 (q, $J$=6.8 Hz, 1H), 2.88 (m, 1H), 2.52 (m, 1H), 2.25–2.00 (m, 2H), 1.90–1.61 (m, 2H), 1.60–1.40 (m, 2H), 1.37 ppm (d, $J$=6.8 Hz, 3H); $^{13}$C NMR (50 MHz, $CD_3OD$): $\delta$=143.5, 129.2, 128.8, 128.1, 65.8, 58.5, 55.6, 54.7, 30.4, 24.1, 19.1 ppm; HRMS: $m/z$ calcd for $C_{13}H_{18}N_4$: 231.1604 $[M+H]^+$; found: 231.1600.

*Data for (2S)-2-Azidomethyl-1-[(1R)-1-phenylethyl]pyrrolidine (**4f**)*

$[\alpha]_D$=−20.2 ($c$=0.83 in $CHCl_3$); $^1$H NMR (200 MHz, $CD_3OD$): $\delta$=7.53–7.14 (m, 5H), 3.64 (q, $J$=6.6 Hz, 1H), 3.09 (m, 1H), 2.93 (m, 1H), 2.65 (d, $J$=5.5 Hz, 2H), 2.48 (m, 1H), 2.03 (s, 2H), 1.99–1.57 (m, 4H), 1.39 ppm (d, $J$=6.6 Hz, 3H); $^{13}$C NMR (50 MHz, $CD_3OD$): $\delta$=146.0, 129.4, 129.0, 128.4, 64.9, 62.7, 56.2, 53.4, 30.0, 24.6, 20.4 ppm; HRMS: $m/z$ calcd for $C_{13}H_{18}N_4$: 231.1604 $[M+H]^+$; found: 231.1610.

*Data for (3R)-3-Acetoxy-1-[(1R)-1-phenylethyl]piperidine (**3g**)*

$[\alpha]_D$=+42.1 ($c$=0.46 in $CHCl_3$); $^1$H NMR (200 MHz, $CD_3OD$): $\delta$=7.48–7.01 (m, 5H), 4.88–4.67 (m, 1H), 3.49 (q, $J$=6.8 Hz, 1H), 2.88 (m, 1H), 2.53 (m, 1H), 2.23–2.02 (m, 2H), 2.01 (s, 3H), 1.89–1.48 (m, 4H), 1.37 ppm (d, $J$=6.8 Hz, 3H); $^{13}$C NMR (50 MHz, $CD_3OD$): $\delta$=172.2, 143.6, 129.2, 128.8, 128.2, 71.3, 65.9, 55.4, 51.2, 30.6, 23.7, 21.1, 19.4 ppm; HRMS: $m/z$ calcd for $C_{15}H_{21}NO_2$: 270.1464 $[M+Na]^+$; found: 270.1460.

*Data for (2S)-2-Acetoxymethyl-1-[(1R)-1-phenylethyl]pyrrolidine (**4g**)*

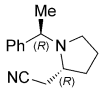
$[\alpha]_D$=−19.1 ($c$=1.905 in $CHCl_3$); $^1$H NMR (200 MHz, $CD_3OD$): $\delta$=7.55–7.06 (m, 5H), 3.70 (q, $J$=6.7 Hz, 1H), 3.64–3.46 (m, 2H), 3.16–2.93 (m, 2H), 2.68–2.45 (m, 1H), 1.97 (s, 3H), 1.90–1.54 (m, 4H), 1.39 ppm (d, $J$=6.7 Hz, 3H); $^{13}$C NMR (50 MHz, $CD_3OD$): $\delta$=172.5, 145.8, 129.3, 128.8, 128.2, 67.8, 64.1, 61.0, 52.5, 29.3, 24.3, 20.7, 19.9 ppm; HRMS: $m/z$ calcd for $C_{15}H_{21}NO_2$: 270.1464 $[M+Na]^+$; found: 270.1458.

*Data for (2S)-2-Cyanomethyl-1-[(1R)-(1-phenylethyl)]pyrrolidine (**4h**)*

$[\alpha]_D$=−20.3 ($c$=1.453 in $CHCl_3$), $^1$H NMR (200 MHz, $CD_3OD$): $\delta$=7.45–7.25 (m, 5H), 3.66 (q, $J$=6.7 Hz, 1H), 3.15–2.97 (m, 2H), 2.50 (m, 1H), 2.16–1.95 (m, 2H) 1.95–1.59 (m, 4H), 1.37 ppm (d, $J$=6.7 Hz, 3H); $^{13}$C NMR (50 MHz, $CD_3OD$): $\delta$=146.1, 129.4, 128.7, 128.4, 120.0, 63.5, 59.6, 52.4, 31.8, 24.4, 24.1, 19.8 ppm; HRMS: $m/z$ calcd for $C_{14}H_{18}N_2$: 215.1543 $[M+H]^+$; found: 215.1545.

*Data for (2R)-2-Cyanomethyl-1-[(1R)-(1-phenylethyl)]pyrrolidine (**Dia-4h**)*

$[\alpha]_D$=+64.4 ($c$=0.97 in $CHCl_3$); $^1$H NMR (200 MHz, $CD_3OD$): $\delta$=7.32–7.17 (m, 5H), 3.79 (q, $J$=6.8 Hz, 1H), 3.12–2.97 (m, 1H), 2.91–2.79 (m, 1H), 2.54–2.41 (m, 3H), 2.03–1.57 (m, 4H), 1.41 ppm (d, $J$=6.8 Hz, 3H); $^{13}$C NMR (50 MHz, $CD_3OD$): $\delta$=144.1, 129.3, 128.7, 128.1, 120.1, 61.9, 57.3, 51.6, 31.8, 24.2, 23.8, 22.3 ppm; HRMS: $m/z$ calcd for $C_{14}H_{18}N_2$: 215.1543 $[M+H]^+$; found: 215.1540.



**Dia-4h**

*Synthesis of N,N′-Di-tert-butoxycarbonyl-(3R)-3-aminopiperidine (**6**)*

Piperidine **3f** was dissolved in EtOH (0.1 M) before $Pd(OH)_2$ (10 mol%) was added. The reaction mixture was stirred at room temperature under atmospheric pressure of $H_2$ gas. After 2 h, $(Boc)_2O$ (3 equiv) was added to the reaction flask at room temperature. The reaction mixture was stirred for one hour, filtered with EtOH, and concentrated under vacuum. Purification by silica gel flash chromatography provided analytically pure target product **6**. Yield=85%; $[\alpha]_D$=+2.5 ($c$=0.95 in $CHCl_3$); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$=4.63 (m, 1H), 3.50 (m, 4H), 1.95–1.4 (m, 4H), 1.48 ppm (s, 18H); $^{13}$C NMR (50 MHz, $CD_3OD$): $\delta$=157.4, 156.3,

80.9, 79.9, 71.5, 47.9, 44.6, 31.3, 28.8, 28.7, 24.5 ppm; HRMS: *m*/*z* calcd for $C_{15}H_{28}N_2O_4$: 323.1941 $[M+Na]^+$; found: 323.1940.

*Synthesis of (2S)-1-[(1R)-1-Phenylethyl)pyrrolidin-2-yl]acetic acid (**7**)*

Pyrrolidine **4h** (121.9 mg, 0.569 mmol) in concentrated HCl (5.7 mL) was heated to reflux for 5 h. The reaction mixture was neutralized with aqueous NaOH (3 M) to pH 7.0. Water (5 mL) was added and the aqueous layer was extracted with diethyl ether (3×10 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum to yield **7** (127.3 mg, 0.546 mmol) as colorless liquid in 96% yield. $[\alpha]_D = -75.7$ ($c = 1.47$ in $CHCl_3$); $^1$H NMR (200 MHz, $CDCl_3$): $\delta =$ 7.58–7.38 (m, 5H), 4.57 (q, $J = 6.8$ Hz, 1H), 3.85–3.70 (m, 1H), 3.45–3.24 (m, 1H), 2.35–2.10 (m, 3H), 2.10–1.85 (m, 2H), 1.85–1.75 (m, 2H), 1.69 ppm (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (50 MHz, $CD_3OD$): $\delta = 177.5$, 137.8, 130.7, 130.3, 129.5, 64.2, 63.0, 51.7, 36.5, 31.5, 23.7, 16.2 ppm; HRMS: *m*/*z* calcd for $C_{14}H_{19}NO_2$: 234.1488 $[M+H]^+$; found: 234.1482.

*Synthesis of (2S)-2-[1-(tert-Butoxycarbonyl)pyrrolidin-2-yl]acetic acid (**8**)*

Compound **7** (127.3 mg, 0.546 mmol) was dissolved in EtOH (0.2 M), and $Pd(OH)_2$ (76.7 mg, 0.546 mmol) was added. The reaction mixture was stirred at RT under atmospheric pressure of $H_2$ gas. After 2 h, $(Boc)_2O$ (178.8 mg, 0.819 mmol) was added to the reaction flask at room temperature. The reaction mixture was stirred for 2 h, filtered, and EtOH was added. The filtrate was concentrated under vacuum to yield the crude reaction product, which was further purified by column chromatography (EtOAc, $R_f = 0.43$) to give analytically pure **8** (118.9 mg, 0.519 mmol) as a white solid in 95% yield. $[\alpha]_D = -28.9$ ($c = 0.67$ in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta =$ 4.24–4.05 (m, 1H), 3.46–3.25 (m, 2H), 3.10–2.75 (m, 1H), 2.35 (dd, $J = 15.4$, 9.3 Hz, 1H), 2.16–2.01 (m, 1H), 1.94–1.78 (m, 3H), 1.46 ppm (s, 9H); HRMS: *m*/*z* calcd for $C_{11}H_{19}NO_4$: 252.1206 $[M+Na]^+$; found: 252.1202.

*Computational Methods*

The B3LYP/6-31++G(d,p) level of theory was used for geometry optimizations.[17] The B3LYP functional was shown to provide good geometries, but is less reliable for energy calculations.[18] Therefore, energies were refined at the M06-2X/6-311++G(d,p) level of theory,[19] which is able to account for dispersion effects. Intrinsic reactions coordinate (IRC) calculations[20] followed by full geometry optimizations were used to connect transition states (TS) with the corresponding ground states (GS). Stationary points were verified as minima (GS) or as first-order saddle points (TS) through frequency calculations. Thermal free-energy corrections were obtained from B3LYP/6-31++G(d,p) optimizations at 1 atm and 298 K. The Gaussian 09 program package was used for all calculations.[21]

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