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Scope and Mechanism of Intramolecular Aziridination of Cyclopent-3-enyl-methylamines to 1-Azatricyclo[2.2.1.0^{2,6}] heptanes with Lead Tetraacetate

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Abstract

A series of seven cyclopent-3-en-1-ylmethylamines bearing one, two, or three methyl substituents at the C2, C3, C4, or C_α positions, including the unsubstituted parent, was accessed by ring-closing metatheses of α,α-diallylacetonitrile (or methallyl variants) and α,α-diallylacetone followed by hydride reductions, or by Curtius degradations of α,α-dimethyl- and 2,2,3-trimethylcyclopent-3-enylacetic acids. Oxidation of the primary amines with $Pb(OAc)_4$ in CH_2Cl_2, $CHCl_3$ or benzene in the presence of K_2CO_3 effected efficient intramolecular aziridinations, in all cases except the α-methyl analogue (**16**), to form the corresponding 1-azatricyclo[2.2.1.0^{2,6}]heptanes, including the novel monoterpene analogues, 1-azatricyclene and the 2-azatricyclene enantiomers. The cumulative rate increases of aziridination reactions observed by ^{1}H NMR spectroscopy in $CDCl_3$ resulting from the presence of one or two methyl groups on the cyclopentene double bond, in comparison to the rate of the unsubstituted parent amine (1 : 17.5 : >280), indicate a highly electrophilic intermediate as the nitrene donor and a symmetrical aziridine-like transition state. A mechanism is outlined in which the amine displaces an acetate ligand from $Pb(OAc)_4$ to form a lead(IV) amide intermediate $RNHPb(OAc)_3$ proposed as the actual aziridinating species.

Introduction

Protonated aziridines (pK_a 8.0)[1] are nitrogen analogues of protonated cyclopropanes and protonated epoxides (Fig. 1), species commonly invoked as initiating groups in polyene cyclizations, or in the former case as carbocation intermediates in biosynthetic mechanisms leading to isoprenoid natural products.[2,3] The obvious structural similarities have stimulated the synthesis and evaluation of many isoprenoid aziridines as inhibitors of terpene biosynthesis. For example, 2,3-epiiminosqualene, the aziridine analogue of 2,3-oxidosqualene, is an effective inhibitor of oxidosqualene cyclases.[4] Sterol analogues bearing an aziridine ring in the side chain at the 24, 25 position are potent inhibitors of cholesterol biosynthesis in rat hepatoma cells,[5a] and they block sterol methyl transferase activity essential for plant development[5b] and fungal cell growth.[5c,5d] The epiimino analogue of 24,28-epoxyfucosterol, an intermediate in phytosterol side chain cleavage, retards the growth and development of the

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Supporting Information Available: General aspects, instrumentation, preparative procedures, and characterization data for cyanocyclopentenes, cyclopentenylmethylamines, and related intermediates (**4–6** and **8–16**); *N*-(cyclopentenyl)methylhydroxylamines (**33 – 35**); cyclopentenyl tosylate (**17**) and α,α-dimethylcyclopentenylacetic acid (**18**); and campholenic acids **22** and **23**; and ^{1}H and ^{13}C NMR spectra of most compounds reported. This material is available free of charge via the Internet at http://pubs.acs.org

silk worm, *Bombyx mori*.[5e] Aziridine analogues of the Cecropea juvenile hormones (JH) potentiate the JH activity of the natural epoxide metamorphosis regulators.[6]

The cyclopropane rings frequently found in terpene natural products[7] (eg presqualene diphosphate and cycloartenol) and marine steroid side chains (eg gorgosterol)[8] are presumably formed by proton eliminations from various types of protonated cyclopropanes or related bridged carbocation intermediates. In accord with this analogy, aziridine analogues of presqualene diphosphate were found to be inhibitors of squalene synthase at low micromolar concentrations.[9] The pentacyclic aziridine aza-trachylobane in the presence of inorganic pyrophosphate is a potent competitive inhibitor (IC_{50} 0.02 μM) of recombinant kaurene synthase from *Arabidopsis thaliana*.[10] These isoprenoid aziridines presumably exert their inhibitory effects by selective binding in the active sites and by specific interactions with catalytic residues. Since aziridinium ions are potential electrophiles, they may also undergo covalent reactions with active site residues. These transition state mimics have applications as active site probes and aids to assist crystallization of recombinant terpene synthases and to locate the active sites in co-crystals with these enzymes.[11]

We became interested in the synthesis of 1-azatricyclo[2.2.1.$0^{2,6}$]heptanes[12] as aziridinium analogues of bridged ions in Wagner-Meerwein rearrangements that occur in biosynthetic mechanisms leading to bicyclic and tricyclic monoterpenes (Fig 2),[2b, 13] and in the evaluation of the bridged aziridines as active site probes for monoterpene synthases. In this paper we explore the scope of the intramolecular aziridination of methyl-substituted cyclopent-3-enylmethylamines to the corresponding methyl-bearing 1-azatricyclo[2.2.1.$0^{2,6}$]heptanes, including the aza-tricyclenes, by means of lead tetraacetate oxidations.[14] The rates of the cyclizations afford insights into the mechanism and structure of the nitrenoid intermediate in the reactions.

Considerable current interest in the synthesis, reactions, and applications of aziridines is evident from numerous recent reviews[15, 16] and a monograph on aziridines and epoxides.[17] In principle bicyclic aziridines might be accessible by intramolecular reactions of unsaturated nitrenes or nitrenium ions.[18,19] However, a more practical approach for intramolecular aziridination involves the cyclization of nitrene equivalents bearing electron-withdrawing groups generated by oxidation of amides and sulfonamides, either presence or absence of Cu and Rh mediators.[20] Although oxidations of *N*-amino quinazolones and *N*-amino phthalimide with $Pb(OAc)_4$ or $PhI(OAc)_2$ generate nitrenoids capable of intermolecular aziridination of C=C double bonds,[15,21,22] these approaches are not readily adaptable to intramolecular aziridinations. A homologue of azatricylene **2** (1,3,3-trimethyltricyclo[2.2.2.$0^{2,6}$]octane) was prepared by reaction of terpinylamine with NBS in acetone.[23] We decided to apply Nagata's direct synthesis of bridged, polycyclic aziridines by $Pb(OAc)_4$ oxidation of unsaturated primary amines,[14] as reported previously by Portoghese and Sepp for the parent 1-aza-nortricyclene, [12] and employed previously in the synthesis of azatrachylobane.[10]

Synthesis of Cyclopentenylmethylamines

The parent amine (**6**)[12] was obtained from diallylacetonitrile (**4**)[24] by ring-closing metathesis (RCM) using Grubbs' 1st-generation ruthenium catalyst,[25a] followed by $LiAlH_4$ reduction of cyclopentenyl nitrile **5** as summarized in Scheme 1. Similar metatheses of α-allyl-α-methallylacetonitrile and bis-(α-methallyl)acetonitrile using the Grubbs 2nd-generation ruthenium catalyst (**8** → **9** and **11** → **12**)[25b] and subsequent hydride reductions afforded the homologues bearing one and two methyl groups on the cyclopentene double bond (**10** and **13**). The modest 31% yield of **12** reflects the slower, incomplete ring-closing metathesis at the low concentration necessary to minimize the competing polymerization. The two methallyl acetonitrile derivatives (**8** and **11**) were prepared by alkylations of the corresponding

cyanoacetate precursors (ethyl α-allylcyanoacetate (**7**) and ethyl cyanoacetate) with methallyl chloride followed by chloride-induced de-ethylation-decarboxylations (NaCl, DMSO, 150 °C).[26]

The syntheses of substrates bearing one or two methyl substituents on the exocyclic aminomethyl position (**16** and **20**) are outlined in Scheme 2. De-ethylation-decarboxylation (LiCl, DMF, reflux) of α,α-diallylacetoacetate gave α,α-diallylacetone (**14**, 44%) which underwent metathesis and reductive amination[27] to 1-(cyclopenten-3-yl)ethylamine (**15** → **16**). The low purity of the crude product necessitated purification by conversion to the t-Boc derivative followed by TFA hydrolysis-decarboxylation (35% over 3 steps). Alkylation of the lithium enolate of methyl isobutyrate with homoallylic cyclopentenyl tosylate **17**[28] in THF and subsequent hydrolysis of the resulting methyl ester intermediate gave α-cyclopentenyl isobutyric acid **18** in high overall yield. Curtius rearrangement with diphenylphosphoryl azide,[29] conversion of the resulting isocyanate to the carbamate **19** (An = *p*-anisyl) with *p*-methoxybenzyl alcohol, and alkaline hydrolysis afforded geminal dimethyl analogue **20**.

The long known retro-Prins fragmentation of (*S*)-(+)-camphorsulfonic acid (**21**) by KOH fusion at 200–220 °C for 5 min afforded (+)-α-campholenic acid **22**, in accord with the literature procedures[30] (Sch 3). The intermediacy of the expected exocyclic isomer (+)-isocampholenic acid (**23**), observed as a trace impurity (ca 2%) in **22**, was verified by interrupting the fusion reaction after 1 min, at which time mixtures of **22** and **23** were present. Selective epoxidation of the former in a 2:1 isomer mixture and chromatographic separation of the relatively polar epoxide enabled isolation of pure **23** having optical rotation and NMR spectral data matching the literature values.[31] The exo/endo ratios varied from 1:1 to 1:9 (yields 75–90%) in 10 runs differing in the proportion of water (0–30%) added to 85% KOH in preparation of the fusion reagent. Nor-campholenyl amine **25** was obtained by Curtius rearrangement[29] of acid **22**, carbamate derivatization (**24**, An = *p*-anisyl), and alkaline hydrolysis as described previously for the α,α-dimethyl amine **20** in Scheme 2. The same reaction sequence with (*R*)-(−)-camphorsulfonic acid (*ent*-**21**) provided (−)-α-campholenic acid (*ent*-**22**), the related carbamate intermediate *ent*-**24**, and the enantiomeric nor-campholenyl amine *ent*-**25** bearing the three ring methyl groups.

Intramolecular Aziridinations

The preparative aziridination reactions with the seven cyclopentenylmethylamines were conducted with 1–2 equivalents of $Pb(OAc)_4$ in CH_2Cl_2 at room temp in the presence of anhydrous K_2CO_3 as base to neutralize the acetic acid released according to similar procedures described by Nagata, Portoghese and their co-workers. (See Sch 4 and Table 1).[10,12,14] The reactions were terminated by addition of satd aq K_2CO_3, and the aziridines were extracted into ether and converted to the stable trifluoroacetate (TFA) salts, at which point yields were calculated. The free aziridine bases were later liberated as needed for characterization by reactions with solid K_2CO_3 in CH_2Cl_2, $CDCl_3$, or other solvents. The aziridines proved to be stable in dilute solutions (CH_2Cl_2, $CDCl_3$, frozen benzene) at −20 °C. However, as noted previously,[10,12,14] the strained heterocycles decomposed readily as pure liquids, presumably undergoing polymerization to insoluble, uncharacterized material.

The proton and carbon-13 NMR chemical shifts for the aziridine ring protons and carbons, the C-7 N-CH_2, and C-CH_3 attached to the aziridines in the free base and TFA salt forms are collected in Table 2. The assignments are based on chemical shift trends, and in some cases on the carbon multiplicities from DEPT experiments.

Some interesting trends are apparent from the data in Table 2. The chemical shifts for the aziridine ring C-H protons are consistently in the range 2.03 to 2.22 ppm, and they are shifted downfield ($\Delta\delta$ = +1.48 to +1.63 ppm) in the protonated forms, reflecting the positive charge

and hybridization changes in the internal C-N bonds. The values for the C-7 N-CH_2 moieties are spread over a considerable range, δ2.11–2.80 ppm. A shift to lower field is evidently caused by CH_3 substitution on the aziridine ring carbons. In contrast downfield shifts arising from N-protonation are reasonably consistent at Δδ = 0.49–0.74 ppm. The higher field position of aziridine C-CH_3 in aza-tricyclene **32** (δ_H 1.16) as compared to the aziridine ring methyl derivatives **27** and **28** (δ_H 1.35 and 1.38) is attributable to C-C bond anisotropy arising from the adjacent CH_3 groups. The protonation shifts for the ring CH_3 vary from Δδ +0.36 (**27**) to Δδ +0.27 ppm (**28**).

The ^{13}C NMR chemical shifts for the aziridine ring carbons (C-2 and C-6) move from 31.8 (**26**) to 38.4 or 39.1 for one CH_3 (**27**) and to 45.1 for the dimethyl case (**28**), and they undergo downfield shifts by Δδ +5.5 to + 10.7 ppm in the corresponding TFA salts. In contrast the aziridine ring methyl resonances (δ_C 16.0 and 12.5 ppm) appear at higher field positions in the TFA salts (Δδ −4.2 to −2.9 ppm for **27** and **28**). Similar protonation shieldings for carbons β to nitrogen in acyclic amines (generally Δδ −3 to −5 ppm) are attributed to "electric field effects and C-H bond polarizations."[32b,c]

First-order rates for the aziridinations reactions were determined by integration of ^1H NMR spectra carried out in NMR tubes with the free amines and 2 equivalents of $Pb(OAc)_4$ in $CDCl_3$ (Table 1). An initial "burst phase" apparent in the slower reactions is attributed to warming resulting from the exothermic interactions of the amines with $Pb(OAc)_4$. The proton NMR peaks for the α-methyl groups of **16** and **20** immediately moved somewhat downfield upon addition of $Pb(OAc)_4$ ($\Delta\delta_H$ +0.118 and +0.156 ppm, respectively). Reaction progress was monitored by the consistent decrease in the vinyl proton integrations, or in the case of **13** by the integration changes accompanying conversion of the vinyl CH_3 to aziridine CH_3. Log plots (Fig 3 below) were linear over approximately 0.5 to 1 half-lives.

The proton NMR spectra acquired during oxidation of α-methylamine **16** showed extraneous peaks considered to be impurities formed competitively with aziridine **29**. We suppose that these byproducts arise from competing dehydrogenation to the ketimine and its subsequent condensation and/or oxidations of the enamine tautomers.[33a] Although the presence of aziridine **29** was evident from its characteristic ^1H NMR signals (eg new methyl peak δ_H 1.18 (d, J = 6.5 Hz, 3H)), the numerous impurities present after high conversions prevented isolation of the aziridine TFA salt in pure form, and the isolated yield was not determined in this case. The intramolecular aziridination of amine **13** bearing two CH_3 groups on the double bond was essentially complete within 4 min, and the half-life in this case could only be estimated to be < 1 min. The half-lives varied approximately ± 15 % in duplicate runs, and were independent of the amount of $Pb(OAc)_4$ reagent added.

The rates of several aziridinations in the same heterogeneous medium used in the preparative reactions, ie TFA salts in the presence of 5 equivalents of solid K_2CO_3, were also measured by NMR analyses. The reactions of the TFA amine salts bearing methyl groups on the cyclopentene double bond proceeded considerably more slowly (**13**·TFA $t_{1/2}$ 9 min vs < 1 min, and **10**·TFA 95 min vs 16 min), whereas the rate of the parent cyclopentenylmethylamine (**6**) TFA salt was unchanged. Evidently liberation of the free amines **13** and **10** from the TFA salts becomes the rate-limiting step under these heterogeneous conditions.

The oxidative aziridination with α,α-dimethyl amine **20** was also effected with 2 equivalents of $PhI(OAc)_2$ 21 in CH_2Cl_2 with a half-life of 6 h, ie about 3 times more slowly than the reaction with $Pb(OAc)_4$. In this case the methyl singlet shifted from 1.058 to 1.176 and then to 1.252 over 30 min, and remained at 1.252 as the peaks for the aziridine grew more intense.

The solubility and stability of $Pb(OAc)_4$ in many organic solvents[33] provided an opportunity to evaluate the effects of additives and medium on the aziridination process. No reaction

occurred with 2 equiv of $Pb(OAc)_4$ and α, α-dimethylamine **20** in CD_3CN after 10 days or in CD_3CO_2H after 2 days, and the aziridination was very slow in CD_3OH. The aziridination with **20** proceeded ca 4 times more slowly in benzene-d_6 ($t_{1/2}$ 530 min vs 125 min in $CDCl_3$). No aziridine formation was observed when 2 equiv of the sterically hindered tertiary amine base diisopropylethylamine was present in $CDCl_3$, although shifts of the NMR peaks for the *N*-isopropyl and *N*-ethyl groups were noticeable. The aziridination rate with the TFA salt of **10** was about the same ($t_{1/2}$ 16 and 15 min) when effected by 1.1 or 2.0 equivalents of $Pb(OAc)_4$, 2 equiv of pyridine, and 3 equiv of K_2CO_3. Much faster rates were observed in aziridinations conducted with free amines **6**, **10**, and **20** and 2 equiv of $Pb(OAc)_4$ in pyridine-d_5 ($t_{1/2}$ <15 min vs 280 min, ca 6 min vs 16 min, and <2 min vs 125 min, respectively). However, the product from the unsubstituted amine **6** was a 1:1 mixture of aziridine **26** and nitrile **5** resulting from double dehydrogenation. The oxidation of primary amine to nitriles with $Pb(OAc)_4$ has been reported.[34]

Scope and Mechanism of Aziridinations

The intramolecular aziridinations proceeded in satisfactory to high yields (65 – 88%) with all amines except α-methyl amine **16**, despite the large ring strain of the 1-azatricyclo[$2.2.1.0^{2,6}$] heptane products estimated to be in the neighborhood of 47 kcal/mol. This figure is based on the known strain energy of nortricyclene (47.0 kcal/mol)[35a] together with the very similar values recorded for cyclopropane (27.5 and 28.13 kcal/mol)[35a] and aziridine (27.1 kcal/mol).[35b] We presume that our inability to isolate aziridine **29** is attributable to competing dehydrogenation to a labile ketimine and its relatively rapid oxidation and/or self-condensation to a mixture of amine by-products having properties similar to those of the aziridine. The various tricyclo[$3.2.1.0^{2,7}$]octanes prepared in Nagata's pioneering investigation of aziridinations with $Pb(OAc)_4$ are further indications of the scope of this little used reaction.[14]

The increased rates (k_{rel} 2.8 and 2.2) observed with amines bearing one or two α-methyl groups (**16** and **20**) clearly indicates the insensitivity of the aziridination reaction to steric hindrance around the nitrogen center. In fact the cyclization reactions of all methyl-substituted derivatives proceeded faster than that of the parent amine **6**. The rates of these formal [2+1] heterocycloadditions increased dramatically and cumulatively with one or two methyl groups situated on the cyclopentenyl double bond (**10** k_{rel} 17.5 and **13** k_{rel} 280), demonstrating that aziridination is the slow step in the mechanism, and revealing the highly electrophilic nature of the nitrenoid intermediate and the apparent symmetry of the transition state.

A wide range of mechanisms and types of nitrenoid intermediates has been considered for the well-known aziridinations of olefins with N-amino heterocycles (primarily *N*-aminophthalimides and *N*-aminoquinazolones).[21a, 22] Plausible intermediates include *N*-acetoxyamines, nitrenes, nitrenium ions, aminyl radicals, hypervalent iodine (III) species (amino- or imino-iodinanes) with $PhI(OAc)_2$ as oxidant, and in the case of $Pb(OAc)_4$ lead (IV) species (lead amides or lead imines). Although Atkinson advocated the intermediacy of *N*-acetoxyamino heterocycles,[22] the selectivity variations with $Pb(OAc)_4$ and $PhI(OAc)_2$ as oxidant are considered inconsistent with a common intermediate.[21a,21b]

We decided to test the possibility of an *N*-acetoxy intermediate by independent synthesis of the hydroxylamino ester **35** from the parent cyclopentenylmethylamine **6** as shown in Scheme 5.[36] However, the reaction of **35** with $Pb(OAc)_4$ under the usual conditions with monitoring by ^1H NMR spectroscopy proceeded slowly with the development of numerous peaks, of which none were the characteristic signals of aziridine **26**. No evidence for a detectable buildup of the characteristic NMR absorptions for **35** could be seen in spectra taken during the kinetic runs of **6** with $Pb(OAc)_4$. Furthermore the 3-fold faster aziridination of α,α-dimethylamine

20 observed with $Pb(OAc)_4$ as oxidant ($t_{1/2}$ 125 min) compared to that with $PhI(OAc)_2$ ($t_{1/2}$ 360 min) is inconsistent with a common intermediate.

It seems reasonable to expect the amines to undergo ligand substitution with $Pb(OAc)_4$ to generate lead(IV) amides (**36**) or possibly lead imines (**37** and **38**) by the equilibrations shown in Scheme 6. One driving force for the exchange would be the subsequent formation of an acetate salt between the remaining amine and the equivalent of acetic acid released. The slight exotherm observed upon adding $Pb(OAc)_4$ to the amine as well the slight downfield of the proton NMR signals for the geminal methyls in **20** are attributable to the exchange process. Although the Pb(IV)-N bond is very weak (E_D Pb-N ~ 20–30 kcal/mol),[37] many trialkyllead amides (eg Et_3PbNEt_2) and tritylllead amides and imides were reported in the literature by 1980.[37] A similar exchange equilibrium was proposed as the first step in the Steglitz rearrangement of tritylamine to benzophenone *N*-phenylimine ($Pb(OAc)_4$, benzene, reflux).[38]

We propose that the aziridinations effected with $Pb(OAc)_4$ occur by intramolecular electrophilic attack of lead(IV) amides onto the ring double bonds with simultaneous formation of the aziridinium acetate salt (**41**) and $Pb(OAc)_2$ as depicted in the mechanism **39** → **40** → **41** (Sch 7). The large and cumulative rate-accelerating effects of methyl groups on the double bonds (**10** k_{rel} 17.5 and **13** k_{rel} > 280, $k_{\mathbf{10}}/k_{\mathbf{13}}$ >16) clearly signify substantial and symmetrical positive charge accumulation at carbon in the transition state. Major driving forces for this formal [2+1]cycloaddition are the exchange of the weak Pb-N bond and for the stronger C-N bonds in the product, as well as the exothermic Pb(IV) → Pb(II) 2-electron reduction ($E°$ at 25 °C, $Pb^{+4} + 2\ e^- = Pb^{+2}$ 1.65*V*).[39] This mechanism is similar to that proposed by Richardson et al[21a] for intermolecular aziridinations of olefins with *N*-aminoheterocycles and aryl iodinanes $ArI(OAc)_2$ in the absence of transition metal catalysts. Transition state [**40**] bears a resemblance to one proposed for the $Pb(OAc)_4$-induced Steglitz rearrangement of tritylamines mentioned above.[38]

The transition state proposed for the intramolecular aziridinations [**40**] is similar to those associated with peroxy acid epoxidations of C=C double bonds (**42** → [**43**] → **44**)[40, 41] and with the solvolytic cyclizations of cyclopentenylethyl sulfonates to symmetrically-bridged norbornyl carbonium ions (**45** → [**46**] → **47**)[42] as illustrated in Scheme 7. The cumulative, rate-enhancing effects of alkyl substituents on olefin epoxidations (ca 10–20 times per alkyl substituent),[43] and the accelerating influence of one and two methyl groups on the cyclopentenyl double bond of **45** (increases of 7 and 38.5 times)[42] are taken to indicate analogous transition structures [**43**] and [**46**] having substantial positive charge accumulation simultaneously at both C=C carbons.

Transition state **40** may be likened to an intramolecular S_N2 reaction taking place at nitrogen, with the C=C double bond as nucleophile and $Pb(OAc)_2$ as the leaving group. This analogy suggests aziridination via lead imine **38** would be disfavored by the presumed sp^2 hybridization at the C=N nitrogen, in accord with the highly suppressed rates of S_N2 substitutions at vinylic carbon. Furthermore, to our knowledge lead(IV) imines of this type are unknown in the literature.

The solvent effects observed on the aziridinations seem generally consistent with the mechanism and transition state in Scheme 6 and Scheme 7. The somewhat faster rates observed in $CDCl_3$ compared to those in C_6D_6 are attributable to transition state stabilization by the dipole of the former. However, the slower rates in CD_3CN and CD_3OH can be rationalized by competing ligation of Pb(IV) with the excess solvents. The rate suppression observed in CD_3CO_2H is probably caused by formation of an ammonium acetate salt and the resulting reduced concentration of free amine. Similarly the faster rates in pyridine probably arise from

the scavenging of acetic acid, and the resulting higher concentrations of free amine and key intermediate **36**.

Conclusion

This work has established the generality of the $Pb(OAc)_4$-induced intramolecular aziridination of cyclopentenylmethylamines to 1-azatricyclo[2.2.1.$0^{2,6}$]heptanes[12] and has provided evidence indicating the highly electrophilic nature of the key nitrene donor **39** and a symmetrical aziridine-like transition state **40**. The strained, bridged aziridine products, or their *N*-alkyl or *N*-acyl aziridinium derivatives, and others available by analogous intramolecular aziridinations of related types of unsaturated primary amines,[14] would undergo predictable nucleophilic and electrophilic ring cleavage reactions,[12, 15–17,44] affording access to various heterocyclic structures. A noteworthy distinction of the intramolecular aziridinations with $Pb(OAc)_4$ 12,[14] is the use of unsaturated primary amines lacking the commonly employed *N*-acyl or *N*-sulfonyl linkages.[15–17, 45] The compatibility of $Pb(OAc)_4$ with a wide range of functional groups and solvents,[33] together with the many synthetic approaches to unsaturated amines, point to a broad generality for the intramolecular aziridination-ring opening route to nitrogen heterocycles.

The azatricyclenes reported are novel aza analogues of the bridged bornyl carbonium ion (Fig 2) and potentially useful transition state inhibitors and active site probes for monoterpene cyclases. The enantiomeric 2-aza-tricyclenes ((+)-**32** and (−)-**32**) provide a means to evaluate the stereoselectivity of interactions with the biosynthetic enzymes that produce enantiomeric monoterpenes, eg (+)- and (−)-bornyl diphosphate synthases, and (+)- and (−)-pinene cyclases.[2b,13] Furthermore, ring opening reactions of the azatricyclenes afford a simple route to aza-monoterpenes such as 6-azaborneol and 2-azacamphane.[46]

Experimental Section

4-Methoxybenzyl 2-(Cyclopent-3-en-1-yl)prop-2-ylcarbamate (19)

In the same manner as described below for urethane **24**, compound **19** was prepared from acid **18** (2.8 g, 18.18 mmol). Carbamate **19** (4.2 g, 80%) was obtained as an oil: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.30 (d, 2H, *J* = 8.8 Hz), 6.89 (d, 2H, *J* = 8.8 Hz), 5.65 (s, 2H), 4.97 (br s, 2H), 4.64 (br s, 1H), 3.81 (s, 3H), 2.70 (app quintet, 1H, J_{app} = 8.4 Hz),[47] 2.36 (br dd, 2H, *J* = 14.8, 9.6 Hz), 2.18 (br dd, 2H, *J* = 14.8, 8.5 Hz), 1.30 (br s, 6H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 159.7, 159.3, 130.2 129.6, 128.9, 114.1, 71.6, 66.0, 55.5, 46.5, 34.1, 24.6; HRMS (ESI) *m/z* calcd for $C_{17}H_{27}NO_3$ $(M + H)^+$ 290.1756, found: 290.1752.

2-(Cyclopent-3-en-1-yl)propan-2-amine (20)

As described below for amine **25**, carbamate **19** (4.2 g, 14.53 mmol) was hydrolyzed by refluxing in 40% methanolic KOH (25 mL). Amine **20** (1.75 g, 98%) was obtained as a colorless liquid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.66 (s, 2H), 2.40–2.26 (m, 3H), 2.16 (br dd, 2H, *J* = 13.5, 8. Hz), 1.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 129.6, 50.9, 49.5, 34.0, 28.6; HRMS (ESI) *m/z* calcd for $C_8H_{15}N$ $(M + H)^+$ 125.1205, found: 125.1202.

(+)-(1*S*)-4-Methoxybenzyl (2,2,3-Trimethylcyclopent-3-enyl)methylcarbamate ((+)-24)

Yamada's modified procedure[29] for the Curtius rearrangement was followed. A solution of acid (+)-**22** (3.0 g, 17.9 mmol) and Et_3N (4.2 mL, 3.0 g, 30.1 mmol) in 1,2-dichloroethane (40 mL) was stirred under N_2 as neat diphenylphosphoryl azide (3.9 mL, 5.0 g, 18.1 mmol) was added. The solution was heated at reflux for 100 min, *p*-methoxybenzyl alcohol (3.7 mL, 4.1 g, 30.0 mmol) was added *via* syringe, and heating was resumed for 12 h. The solution was concentrated under reduced pressure, and the resulting yellow, oily residue was purified by

flash chromatography using a gradient of 5–10% EtOAc/hexane to give 4.5 g (83%) of urethane (+)-**24** as a colorless oil, which crystallized at −15 °C. Data for crystalline (+)-**24**: TLC R_f 0.75 (10% EtOAc-hexane); mp 43–44 °C; $[\alpha]^{25}{}_{D}$ +5.67° (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) as a 5:2 mixture of two rotamers: δ 7.30 (d, 2H, *J* = 8.5 Hz), 6.88 (d, 2H, *J* = 8.5 Hz), 5.20 (s, 1H), 5.03 (s, 2H), 4.68 (br s, 1H), 3.80 (s, 3H,), 3.36 (m, 1H), 3.15 (m, 1H), 2.30 (m, 1H), 1.94 (m, 2H), 1.58 (s, 3H), 1.03 (s, 3H,), 0.83 (s, 3H,); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.7(s), 156.7(s), 148.5 (s), 130.2 (d, 2C), 128.9 (s), 121.4 (d), 114.1 (d, 2C), 66.6 (t), 55.4 (q), 49.7 (d), 46.6 (s), 42.4 (t), 34.3 (t), 26.5 (q), 19.9 (q), 12.5 (q); HRMS (ESI) *m/z* calcd for $C_{18}H_{26}NO_3$ $(M + H)^+$ 304.1913, found: 304.1910.

(−)-(1*R*)-4-Methoxybenzyl (2,2,3-Trimethylcyclopent-3-enyl)methylcarbamate ((−)-24)

Crystalline urethane *ent*-**22** (6.2 g, 84%) was prepared as described above for (+)-**22** starting from (−)-α-campholenic acid (−)-*ent*-**22** (4.1 g, 24.4 mmol): mp 42–44 °C; $[\alpha]^{25}{}_{D}$ −5.23° (*c* 2.9, $CHCl_3$); the ^{1}H and ^{13}C NMR spectra of (−)-**24** were identical to those previously recorded for carbamate (+)-**24**; HRMS (ESI) *m/z* calcd for $C_{18}H_{26}NO_3$ $(M + H)^+$ 304.1913, found: 304.1912.

(±)-4-Methoxybenzyl (2,2,3-Trimethylcyclopent-3-enyl)methylcarbamate ((±)-24)

Urethane (±)-**24** (oil, 2.7 g, 83%) was prepared as described above for (+)-**24** starting from (±)-α-campholenic acid (±)-**22** (1.8 g, 10.7 mmol). The ^{1}H and ^{13}C NMR spectra of compound (±)-**24** were identical to those previously recorded for carbamate (+)-**24**; HRMS (ESI) *m/z* calcd for $C_{18}H_{26}NO_3$ $(M + H)^+$ 304.1913, found: 304.1910.

(+)-(1*S*)-(2,2,3-Trimethylcyclopent-3-enyl)methylamine ((+)-25)

Hydrolysis of the (*S*)-carbamate (+)-**24** was accomplished following a literature procedure.[48] A solution of (+)-**24** (4.0 g, 13.20 mmol) and KOH (10.0 g, 178.6 mmol) in 30 mL of 95% EtOH (4% H_2O) was heated at reflux for 2.5 h, cooled to 0 °C, and acidified with concd HCl. The solution was partially concentrated under reduced pressure, diluted with water (150 mL), and extracted with CH_2Cl_2 (2 × 25 mL). The aq phase was cooled again to 0 °C, basified with KOH pellets, and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried (K_2CO_3) and evaporated at atmospheric pressure to yield 1.7 g (93%) of amine (+)-**25** as a clear oil: TLC R_f 0.24 (alumina, 1% MeOH-$CHCl_3$); $[\alpha]^{25}{}_{D}$ +9.11° (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.21 (br s, 1H), 2.84 (dd, 1H, *J* = 12, 4.5 Hz), 2.62 (dd, 1H, *J* = 12, 10 Hz), 2.37 (m, 1H), 1.93-1.79 (m, 2H), 1.58 (br s, 3H), 1.49 (br s, 2H), 1.02 (s, 3H), 0.77 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 48.7, 121.5, 53.6, 46.6, 43.3, 34.5, 26.6, 19.9, 12.5.

(−)-(1*R*)-[2,2,3-Trimethylcyclopent-3-enyl)]methylamine ((−)-25)

Hydrolysis of urethane (−)-**24** (4.2 g, 13.86 mmol) following the procedure described above for (+)-**25**, gave the enantiomeric amine *ent*-**25** (1.8 g, 93%). Data for (−)-**25**: $[\alpha]^{25}{}_{D}$ −9.16° (*c* 3.8, $CHCl_3$). The ^{1}H and ^{13}C NMR spectra of (−)-**25** were identical to those previously recorded for (+)-**25**.

(±)-[2,2,3-Trimethylcyclopent-3-enyl)]methylamine ((±)-25)

Hydrolysis of urethane (±)-**24** (2.2 g, 7.26 mmol) following the procedure described above for (+)-**25**, gave the racemic amine (±)-**25** (0.91 g, 89%). The ^{1}H and ^{13}C NMR spectra of (±)-**25** were identical to those previously recorded for (+)-**25**.

Aziridination Reactions

1-Azatricyclo [2.2.1.0^{2,6}]heptane (26)

A suspension of anhyd K_2CO_3 (460 mg, 3.33 mmol) in a solution of amine **6** as its trifluoracetic acid (TFA) salt (129 mg, 0.611 mmol) in 40 mL of dry CH_2Cl_2 was stirred magnetically as 580 mg (1.27 mmol) of solid $Pb(OAc)_4$ was added according to literature procedures[10, 12, 14] except that CH_2Cl_2 was used as solvent instead of benzene. TLC analyses ($CHCl_3$: MeOH = 10 : 1) showed complete reaction after 13 h. Satd aq K_2CO_3 (20 mL) was added, and the product was extracted with ether (2 × 15 mL). The organic layers were combined, dried with $MgSO_4$, and treated with TFA (90 mg, 0.79 mmol). Evaporation of the solvent provided the pure TFA salt of 1-azatricyclo [2.2.1.0^{2,6}]-heptane (**26**) as a yellow oil: yield, 83.0 mg (0.406 mmol, 67%); ^{1}H NMR ($CDCl_3$, 400 MHz)[47] δ 10.30–11.30 (m, 1H), 3.70 (s, 2H), 2.92 (s, 2H), 2.72 (s, 1H), 1.89 (app d, 2H, J_{app} = 12.4 Hz), 1.74 (app dd, 2H, J_{app} = 13.2, 1.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.0 (q, J = 38.4 Hz), 115.8 (q, J = 286.6 Hz), 51.0, 38.1, 31.0, 29.1. Free aziridine: ^{1}H NMR ($CDCl_3$, 400 MHz)[47] δ 2.22 (s, 2H), 2.18 (s, 2H), 2.08 (s, 1H), 1.34 (app d, 2H, J_{app} = 11.2 Hz), 1.21 (app dd, 2H, J_{app} = 11.2, 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.8, 31.8, 31.5, 28.5; IR (NaCl): 3027, 2924, 1446, 1393; HRMS (ESI-HRMS) *m/z* calcd for (M + H$^+$) 96.0813, found 96.0717.

The following preparative aziridinations were conducted as described above for the unsubstituted 1-azatricyclo [2.2.1.0^{2,6}]heptane (**26**).

2-Methyl-1-azatricyclo [2.2.1.0^{2,6}]heptane (27)

Amine **10** as the TFA salt (105 mg, 0.47 mmol), K_2CO_3 (350 mg, 2.5 mmol), CH_2Cl_2 (20 mL), $Pb(OAc)_4$ (440 mg, 1.00 mmol), time (2 h), TFA (70 mg, 0.61 mmol), yield of aziridine **27** TFA salt (81 mg, 78%): ^{1}H NMR ($CDCl_3$, 400 MHz)[47] δ 10.50–11.00 (m, 1H), 3.63 (s, 1H), 3.05 and 2.91 (ABdd, J_{AB} = 9.2 Hz, 2H), 2.67 (s, 1H), 1.90 (app ABd1, J_{app} = 12.4 Hz, 1H), 1.85 (app ABXdd1, J_{app} = 12.4, 1.2 Hz, 1H), 1.78 (app ABd2, J_{app} = 12.4 Hz, 1H), 1.71 (app ABXdd2, J_{app} = 12.4, 1.2 Hz, 1H), 1.71 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.5 – 162.0 (m), 112.0 – 123.0 (m), 112.0 – 123.0 (m), 51.6, 49.8, 43.9, 36.4, 32.4, 31.1, 11.8. Free aziridine: ^{1}H NMR ($CDCl_3$, 500 MHz)[47] δ 2.39 and 2.25 (app ABdd, J_{app} = 9.9 Hz, 2H), 2.00–2.11 (br m, 1H), 2.08 (s, 1H), 1.32–1.40 (m, 2H), 1.35 (s, 3H), 1.16–1.24 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 56.7, 39.1, 38.5, 37.0, 33.1, 31.6, 16.0; IR (NaCl): 3289, 2960, 1557, 1455, 1377; HRMS (ESI-HRMS) *m/z* calcd for (M + H$^+$) 110.0970, found: 110.0968.

2,6-Dimethyl-1-Azatricyclo [2.2.1.0^{2,6}]heptane (28)

Amine **13** TFA salt (100 mg, 0.42 mmol), K_2CO_3 (310 mg, 2.24 mmol), CH_2Cl_2 (20 mL), $Pb(OAc)_4$ (380 mg, 0.84 mmol), time 1 h, TFA (60 mg, 0.53 mmol), yield of aziridine **28** TFA salt (80 mg, 81 %): ^{1}H NMR ($CDCl_3$, 500 MHz)[47] δ 10.30–10.70 (m, 1H), 3.01 (s, 2H), 2.60 (s, 1H), 1.83 (app dd, J_{app} = 13.0, 1.0 Hz, 2H), 1.79 (app dd, J_{app} = 12.5, 1.5 Hz, 2H), 1.65 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.9 (q, J = 38.1 Hz), 116.0 (q, J = 287.9 Hz), 53.2, 52.2, 37.8, 31.4, 9.6. Free aziridine: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.53 (s, 2H), 2.16 (s, 1H), 1.35–1.44 (m, 4H), 1.38(s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 56.3, 45.1, 38.4, 32.3, 12.5; IR (NaCl): 3252, 2949, 1557, 1455, 1386; HRMS (ESI-HRMS) *m/z* calcd for (M + H$^+$) 124.1126, found: 124.1121.

7,7-Dimethyl-1-azatricyclo[2.2.1.0^{2,6}]heptane (30) and its Methiodide Salt (31)

Following Nagata's procedure for the synthesis of bridged aziridines.[14] To a stirred suspension of primary amine **20** (894 mg, 7.3 mmol) and anhyd K_2CO_3 (4.02 g, 29 mmol) in 150 mL of CH_2Cl_2 was added $Pb(OAc)_4$ (6.45 g, 14.5 mmol) in 2-g portions. After 20 h, the solids were filtered, and the resulting filtrate was passed through a small column of basic alumina (Aldrich,

50.0 g, 150 mesh, 58 Å) under vacuum. The column was washed using a gradient of 1–2% MeOH/CH_2Cl_2 as eluent. Fractions containing the aziridine (TLC alumina, 1% MeOH/CH_2Cl_2 single spot at R_f 0.7 when visualized with I_2 vapors) were combined and washed with 10% aq HCl. The aq layer was cooled to 0 °C, basified with NaOH pellets, extracted with Et_2O (total volume 250 mL), and dried over anhyd K_2CO_3. For characterization purposes, a small portion of this solution was evaporated (0 °C) using a stream of nitrogen to give aziridine **30** as a colorless and highly volatile liquid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.19 (s, 2H), 1.79 (d, 2H, *J* = 11 Hz), 1.59 (s, 1H), 1.13 (d, 2H, *J* = 11 Hz), 1.02 (s, 6H). Methyl iodide (905 μL, 14.5 mmol) was added to the above dry ethereal solution. After 20 h at room temp, the white crystals that formed were filtered, washed with ether, and recrystallized from EtOH-Et_2O to afford the methiodide salt **31** (1.3 g, 68% over two steps). Data for recrystallized **31**: mp 278–280 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.51 (s, 2H), 3.34 (s, 3H,), 2.45 (d, 2H, *J* = 13 Hz), 2.34 (s, 1H), 1.77 (d, 2H, *J* = 13 Hz), 1.40 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 49.3, 39.8, 34.7, 30.7, 19.8, 8.7; HRMS (ESI) calcd for *m/z* $C_9H_{16}N$ 138.1283, found, 138.1282.

(+)-2,3,3-Trimethyl-1-azatricyclo[2.2.1.0^{2,6}]heptane ((+)-2-Azatricyclene, (+)-32)

A suspension of primary amine (+)-**25** (308 mg, 2.2 mmol) and K_2CO_3 (1.23 g, 8.9 mmol) in 150 mL of CH_2Cl_2 was stirred and cooled in an ice bath as $Pb(OAc)_4$ (1.97 g, 4.44 mmol) was added in 0.5-g portions over 5 min. After 20 min, the solids were removed by filtration, and the resulting filtrate was passed through basic alumina (Aldrich, 50.0 g, 150 mesh, 58 Å) under vacuum using a gradient of 1–2% MeOH/CH_2Cl_2 as eluent. Fractions containing aziridine (+)-**32** (TLC alumina R_f 0.6, using 1% MeOH-$CHCl_3$, single yellow spot when visualized with I_2 vapors) were combined and washed with 10% aq HCl (3 × 25 mL). The aq layer (containing the HCl salt of the aziridine) was cooled at 0 °C, basified with NaOH pellets, extracted with Et_2O (3 × 100 mL), and dried over anhyd K_2CO_3. For characterization purposes, a small portion of this solution was evaporated using a steam of nitrogen to give aziridine (+)-**32** as a colorless and volatile liquid: $[\alpha]^{25}{}_D$ +3.67° (*c* 0.33, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.80 (d, 1H, *J* = 10 Hz), 2.11 (d, 1H, *J* = 10 Hz), 2.03 (s, 1H), 1.74 (dt, 1H, *J* = 12, 1.6 Hz), 1.62 (s, 1H), 1.24 (d, 1H, *J* = 12 Hz), 1.16 (s, 3H), 0.93 (s, 3H), 0.91 (s, 3H); ^{1}H-NMR (D_2O, 500 MHz) δ 2.64 (d, 1H, *J* = 10 Hz), 2.10 (s, 1H), 1.96 (d, 1H, *J* = 10 Hz), 1.67 (d, 1H, *J* = 12 Hz), 1.60 (s, 1H), 1.11 (d, 1H, *J* = 12 Hz), 0.99 (s, 3H), 0.74 (s, 3H), 0.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 54.1, 45.2, 42.4, 41.2, 40.0, 30.1, 19.7 (2C), 10.5. HRMS (ESI) *m/z* calcd for $C_9H_{16}N$ $(M + H)^+$ 138.1283, found: 138.1281. The dry ethereal solution thus obtained was filtered and kept at −20 °C for storage. The aziridine readily polymerizes when stored as a neat liquid.

(+)-2,3,3-Trimethyl-1-azatricyclo[2.2.1.0^{2,6}]heptane ((+)-2-Azatricyclene, (+)-32), Trifluoroacetate Salt

To a cold (0 °C) and stirred solution of aziridine (+)-**32** (152.1 mg, 1.1 mmol) in 150 mL of ether was added TFA (122.8 mg, 83 μL, 1.11 mmol). Removal of the solvents under reduced pressure afforded the aziridinium TFA salt of (+)-**32** (246 mg, 88% for two steps) as an oil. A small sample was crystallized from ether/pentane. Data for the recrystallized salt: mp 117–118 °C; $[\alpha]^{25}{}_D$ +1.26° (*c* 1.35, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.66 (1H, s), 3.43 (d, 1H, *J* = 10 Hz), 2.85 (d, 1H, *J* = 10 Hz), 2.22 (s, 1H), 2.17 (d, 1H, *J* = 13.2 Hz), 1.79 (d, 1H, *J* = 13.2 Hz), 1.55 (s, 3H), 1.14 (s, 3H), 1.05 (s, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 160.6 (q, *J* = 39.6 Hz), 115.4 (q, *J* = 288.2 Hz), 55.3, 49.6, 45.5, 43.6, 40.1, 29.5, 18.4, 18.3, 7.0; ^{19}F NMR (376 MHz) δ −76.01 (br s).

(−)-2,3,3-Trimethyl-1-azatricyclo[2.2.1.0^{2,6}]heptane ((−)-2-Azatricyclene, (−)-32)

$Pb(OAc)_4$ oxidation of amine (−)-**25** (540 mg, 3.88 mmol) following the procedure given above for (+)-**25** gave the bridged aziridine *ent*-**32**, $[\alpha]^{25}{}_D$ −3.52° (*c* 0.8, $CHCl_3$). The ^{1}H and ^{13}C

NMR spectra of (−)-**32** were identical to those previously recorded for the enantiomer (+)-**32**. HRMS (ESI) *m/z* calcd for $C_9H_{16}N$ $(M + H)^+$ 138.1283, found: 138.1280.

(−)-2,3,3-Trimethyl-1-azatricyclo[2.2.1.0^{2,6}]heptane [(−)-2-Azatricyclene] TFA Salt

The TFA salt of *ent*-**25** (386 mg, 80% for two steps), prepared as described for (+)-**32**, showed mp 116–117 °C; $[\alpha]^{25}{}_D$ −1.31° (*c* 1.6, $CHCl_3$). The ^1H, ^{13}C and ^{19}F NMR spectra of the TFA salt were identical to those previously recorded for the salt of the enantiomeric (+)-**32**.

(±)-2,3,3-Trimethyl-1-azatricyclo[2.2.1.0^{2,6}]heptane ((±)-2-Azatricyclene, (±)-32) and its Picrate Salt

$Pb(OAc)_4$ oxidation of racemic amine (±)-**25** (122 mg, 0.86 mmol) following the procedure given above for (+)-**25** gave the bridged aziridine (±)-**32**. The ^1H and ^{13}C NMR spectra of (±)-**32** were identical to those previously recorded for aziridine (+)-**32**. HRMS (ESI) *m/z* calcd for $C_9H_{16}N$ $(M + H)^+$ 138.1283, found: 138.1282.

The picrate salt of (±)-2-azatricyclene ((±)-**32**) was prepared by adding a solution of amine (±)-**32** (55.1 mg, 0.40 mmol) in 1 mL of 95% ethanol to a warm solution of picric acid (91.0 mg, 0.40 mmol) in 1 mL of 95% EtOH. Recrystallization from absolute ethanol gave the picrate salt (133 mg, 93%): mp 234–236 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.88 (s, 2H), 3.49 (s, 1H), 3.48 (d, 1H, *J* = 10 Hz), 2.93 (d, 1H, *J* = 10 Hz), 2.23 (s, 1H), 2.19 (d, 1H, *J* = 13.5 Hz), 1.81 (d, 1H, *J* = 12 Hz), 1.59 (s, 3H), 1.17 (s, 3H), 1.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.5, 141.8, 126.5 (4C), 54.4, 49.9, 44.8, 43.7, 40.2, 29.7, 18.9, 18.6, 7.3.

(±)-2,3,3-Trimethyl-1-azatricyclo[2.2.1.0^{2,6}]heptane ((±)-2-Azatricyclene) TFA Salt

The TFA salt of (±)-**32** (18.5 mg, 83% over two steps), prepared as described for (+)-**32**, showed mp 111–113 °C. The ^1H, ^{13}C and ^{19}F NMR spectra were identical to those previously recorded for TFA salt of (+)-**32**.

Representative Procedures and Data for Kinetic Runs

3-Methylcyclopent-3-enylmethylamine (**10**) was liberated from its TFA salt (15.8 mg, 0.0702 mmol) by reaction with excess anhyd K_2CO_3 in $CDCl_3$ (0.70 mL), the supernatant solution was transferred to an NMR tube, and solid $Pb(OAc)_4$ (60.0 mg, 0.138 mmol) was added. The progress of the aziridination reaction (**10** → **27**) was monitored by integration of the vinyl CH_3 signal in ^1H NMR spectra taken at 5- and 3-minute intervals. Figure 3 (orange circles) shows a plot of -ln [(integral **10**)/(integral **10** + **27**)] at each time point. The half-life for this run was 19 min. Spectra taken at shorter times indicate faster conversion to the aziridine owing to warming of the solution caused by the initial exothermic reaction of $Pb(OAc)_4$ with the amine.

The kinetics of the other aziridination reactions were conducted similarly by NMR monitoring of CH_3 signals, or in the case of the unsubstituted amine (**6**), by integration of the vinyl protons. The plots from three other kinetic run are shown in Figure 3. No peaks for side products were observed in the NMR spectra, except after extended time in aziridination **16** → **29**. The half-lives and relative rates are collected in Table 1.

Supplementary Material

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45. The intramolecular aziridination (77%) of a *t*-alkyl primary amine with 1 equiv of NBS in acetone has been reported (see Introduction).[23] However the scope of this potential alternative method is unclear

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47. The abbreviation "app" (apparent) in NMR data means that the interpretation was based on a first-order analysis of the multiplet in question, and the data give the appearance, positions, and spacings of the signals. If the multiplet is actually part of a second-order spin system, the “apparent” chemical shift(s), multiplicity, and J values reported may be different than the true values

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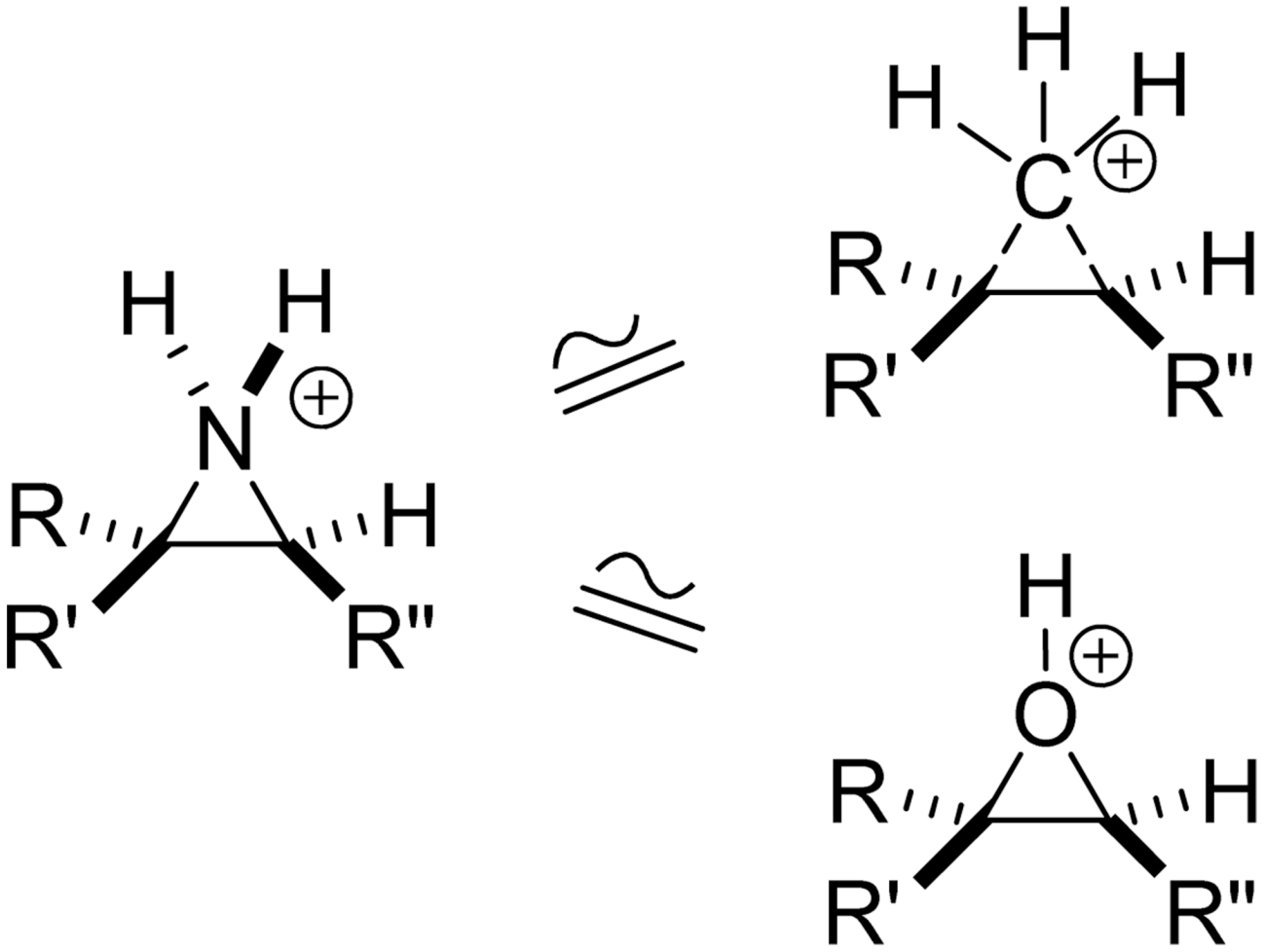


Figure 1.
Illustration of the structural similarity of a generic protonated aziridine to protonated cyclopropanes and protonated epoxides.

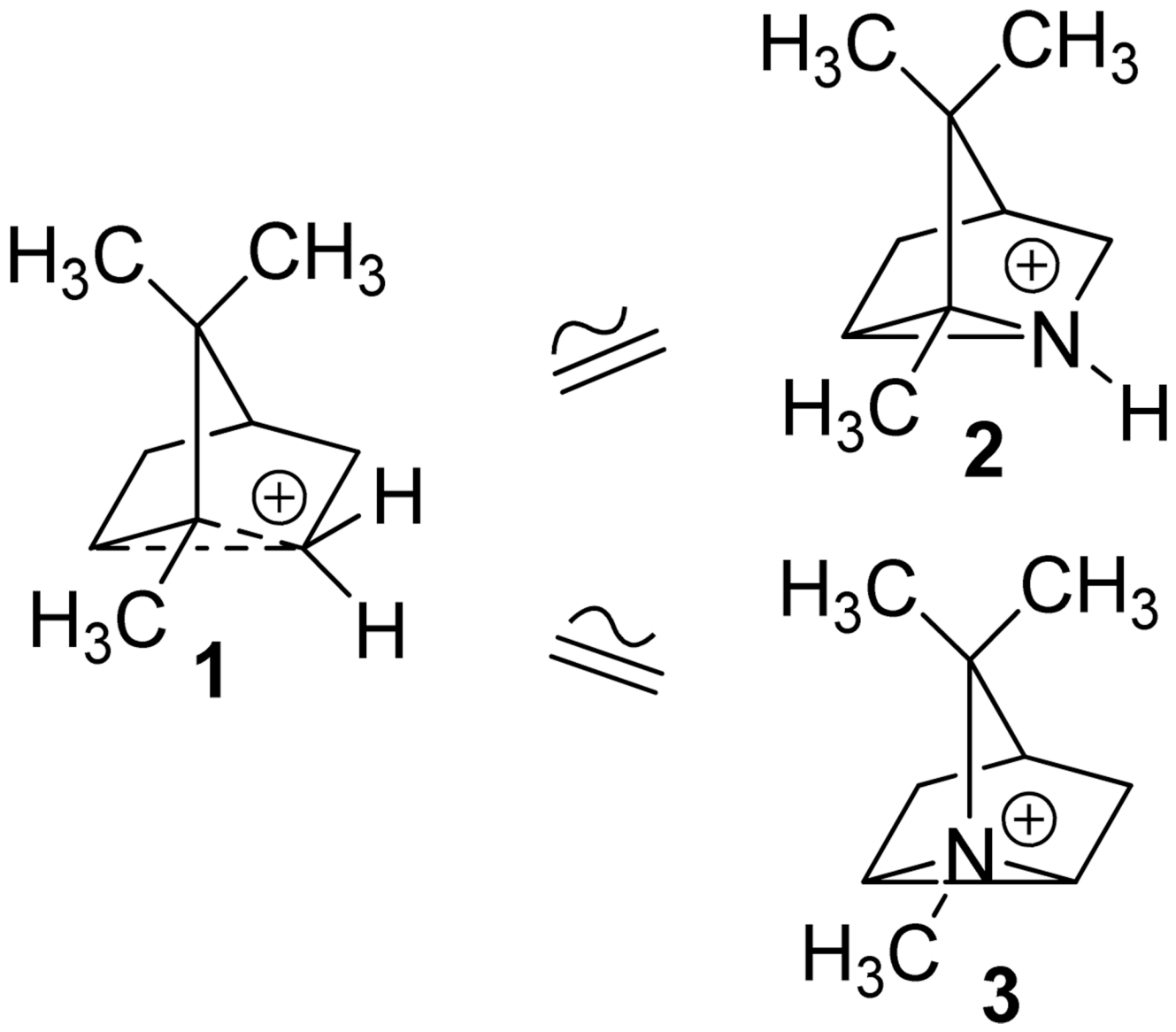


Figure 2.
Non-classical bridged bornyl carbonium (**1**) and its azatricyclo[2.2.1.$0^{2,6}$]heptane (azatricyclene) analogues **2** and **3**.

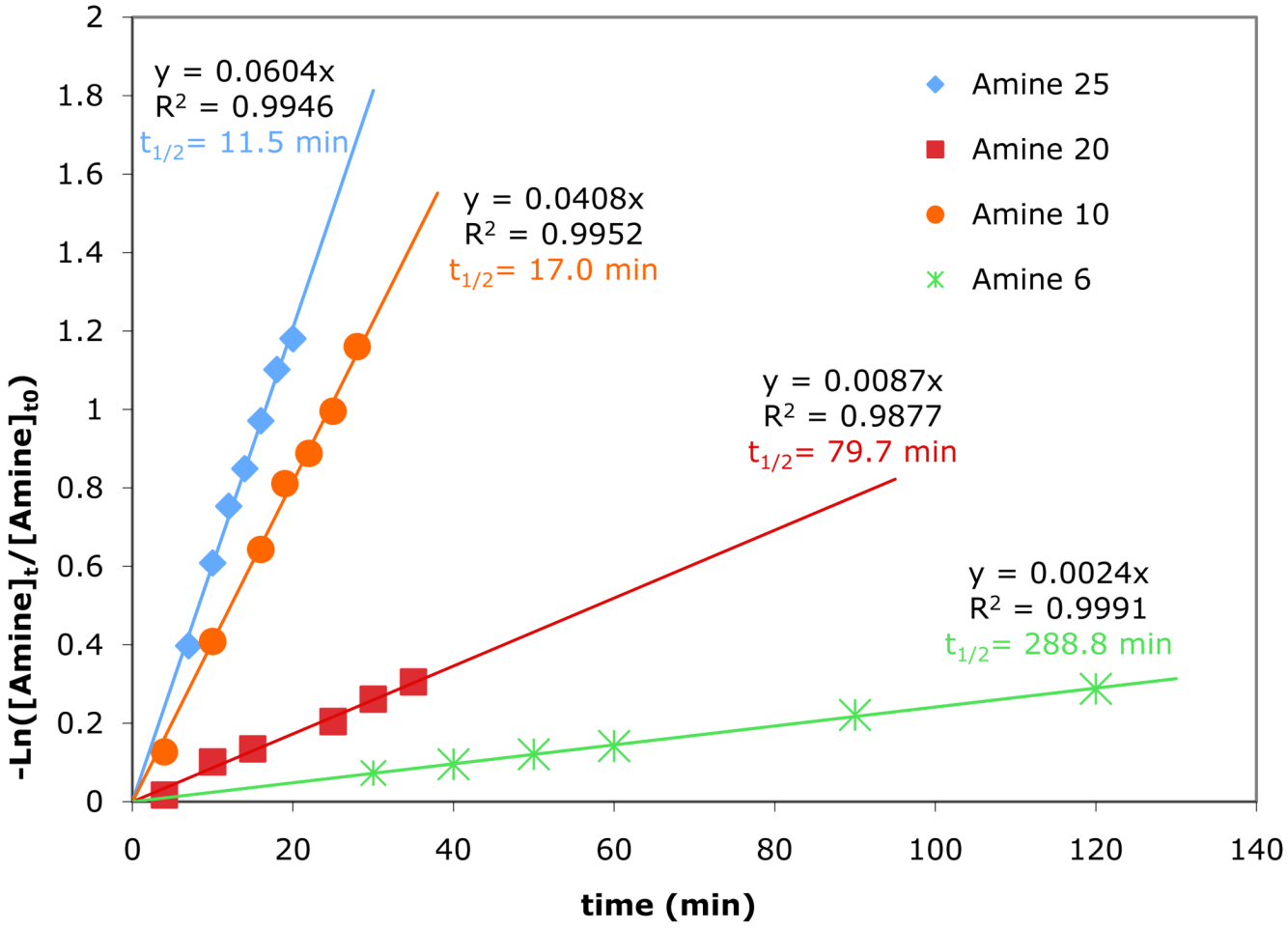
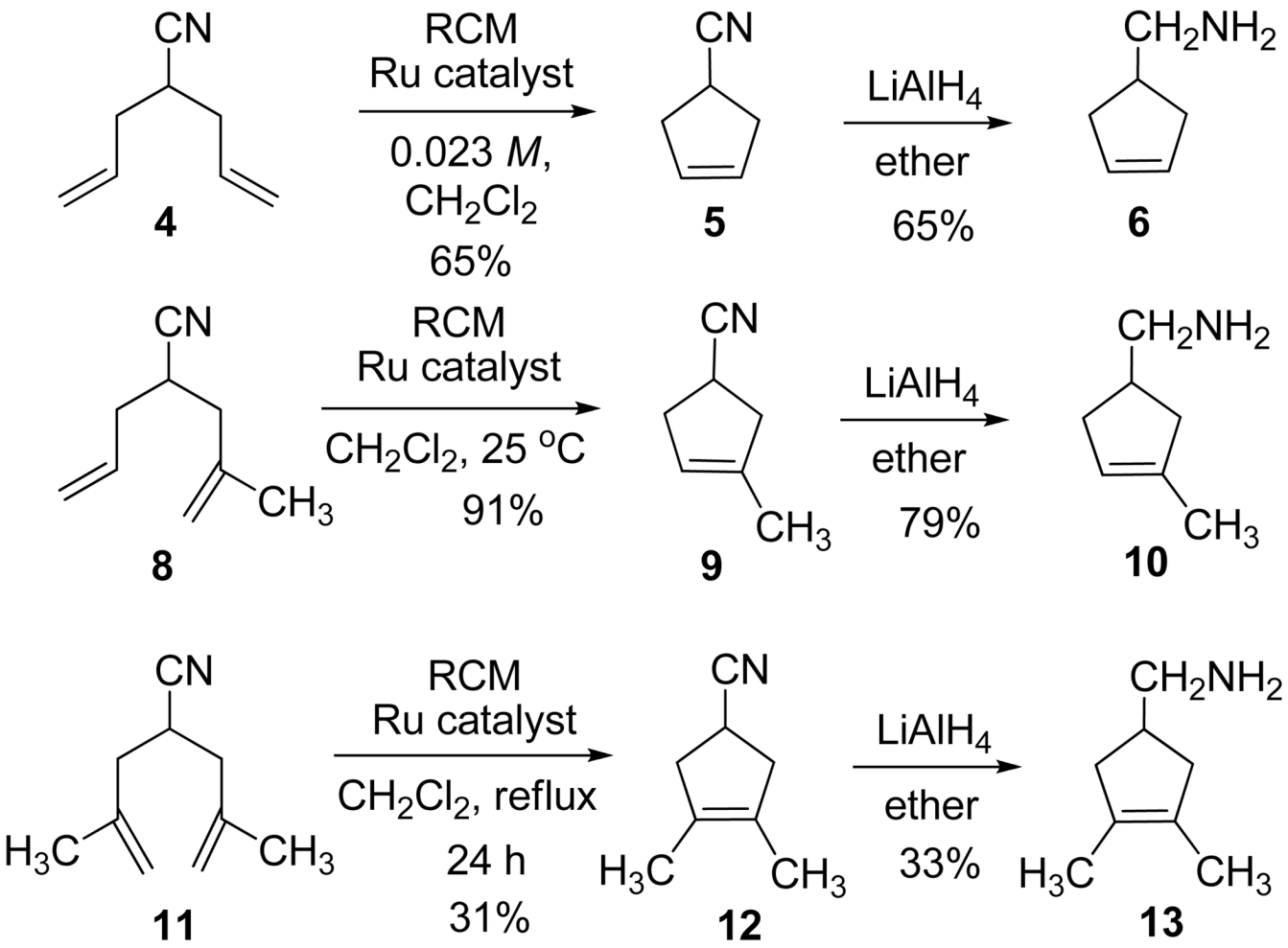
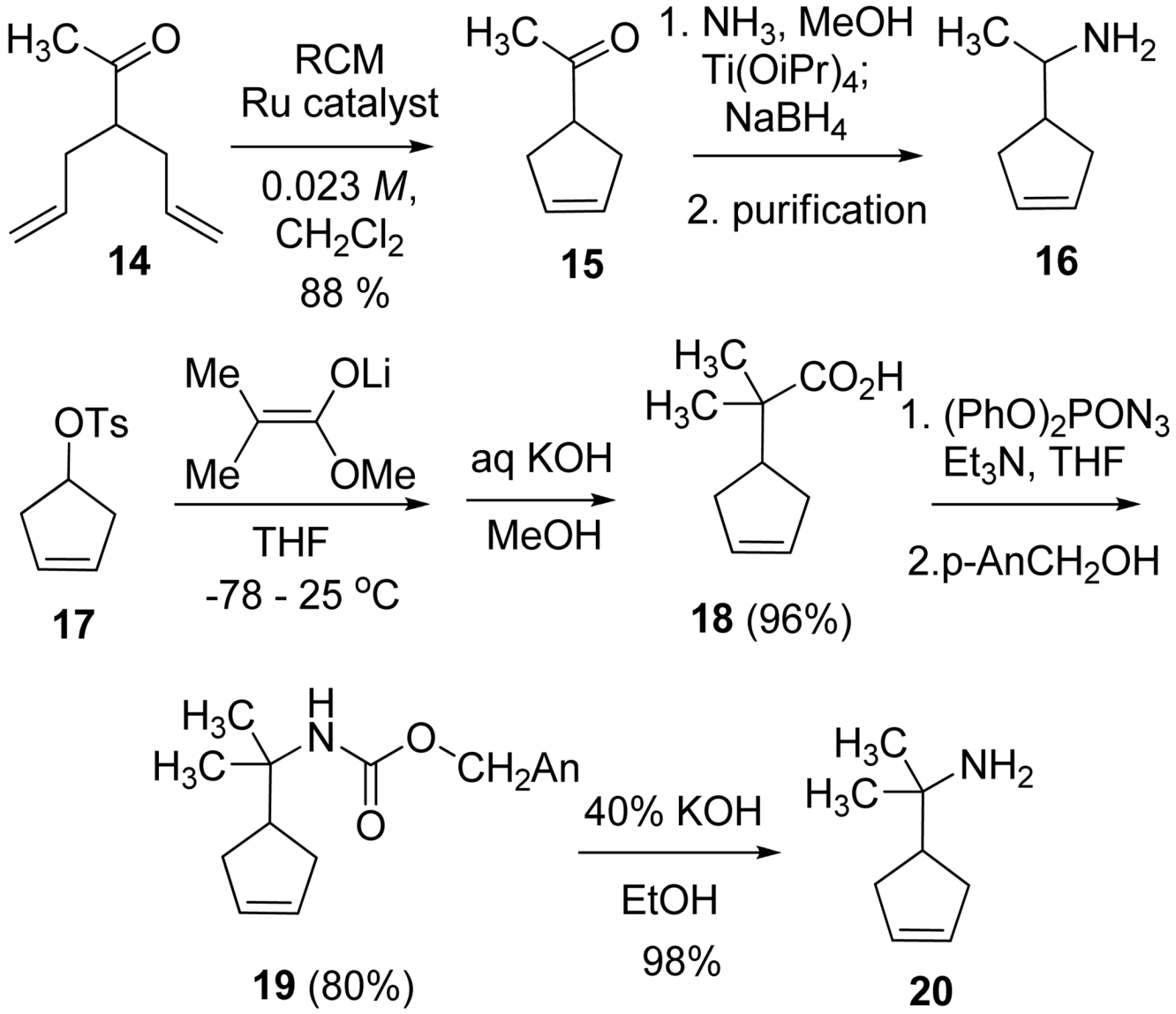


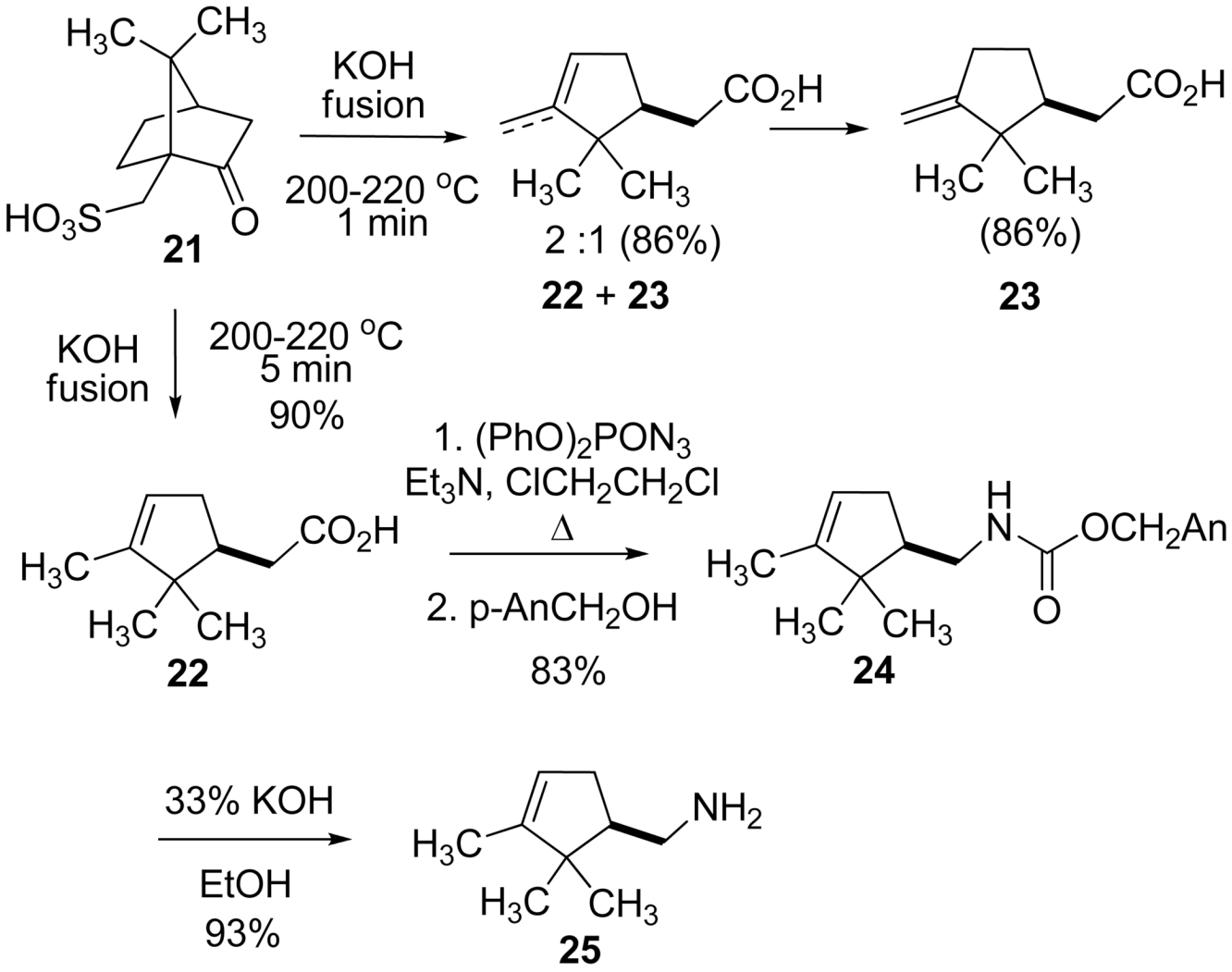
Figure 3.
Pseudo first-order kinetic plots ($t_{1/2} - \ln(2)/k$) for $Pb(OAc)_4$ oxidations of cyclopentenyl amines **6**, **10**, **20**, and **24** by ^1H NMR integrations of peaks for the corresponding aziridine products **26**, **27**, **30**, and **32**.



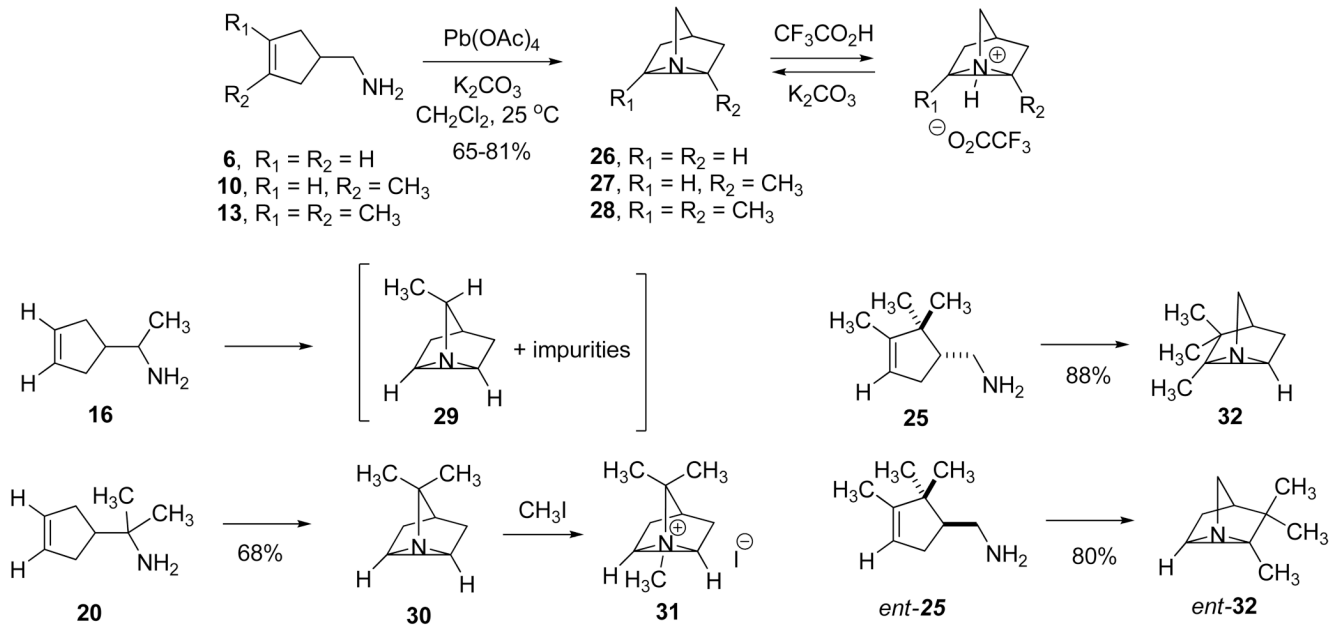
scheme 1.



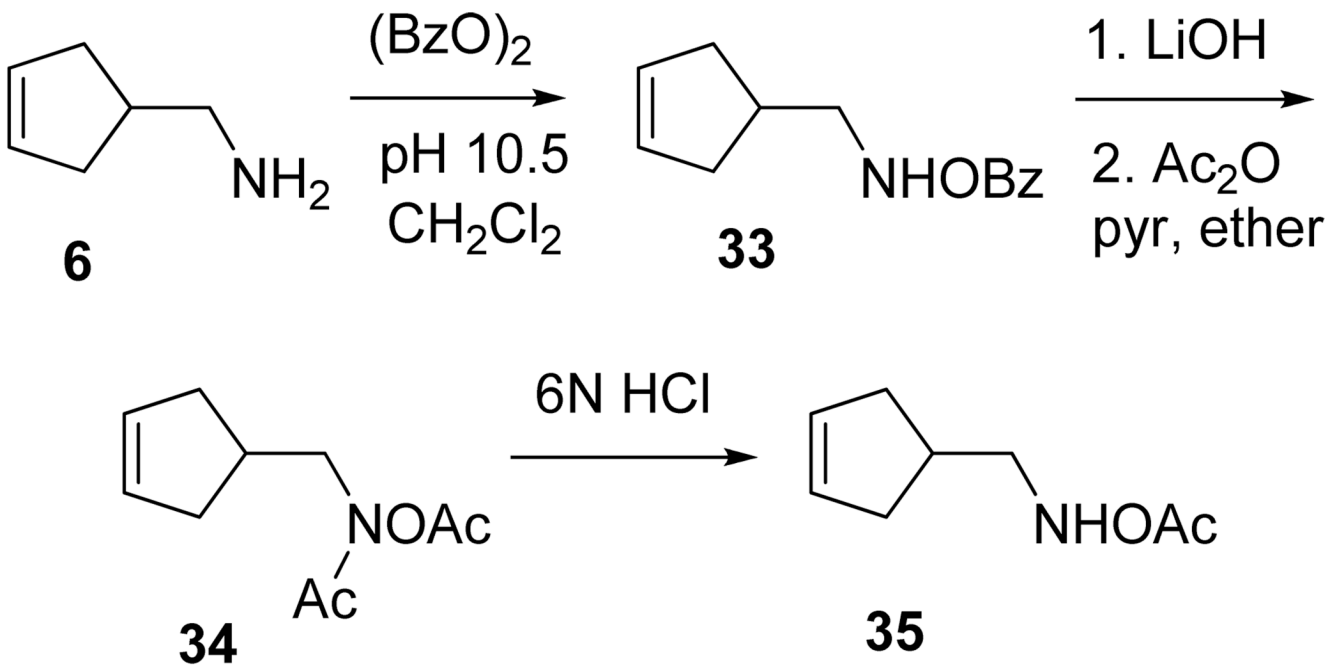
scheme 2.



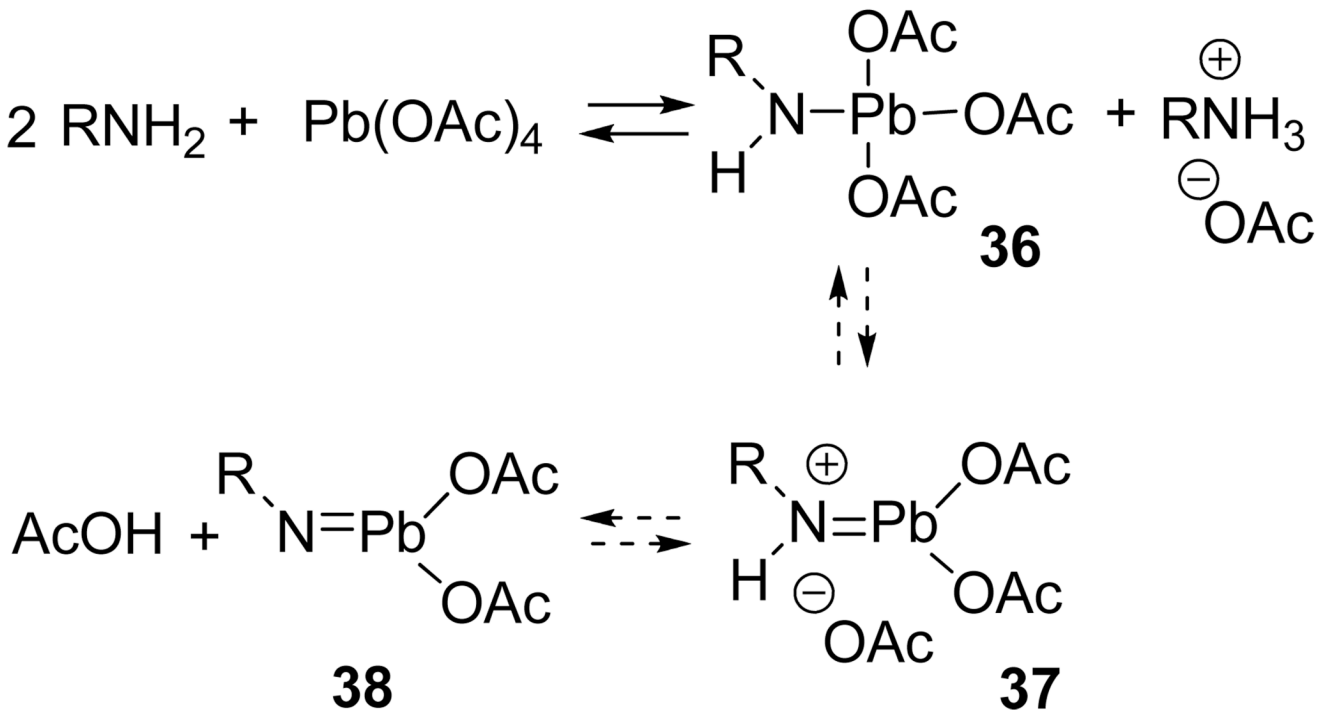
scheme 3.



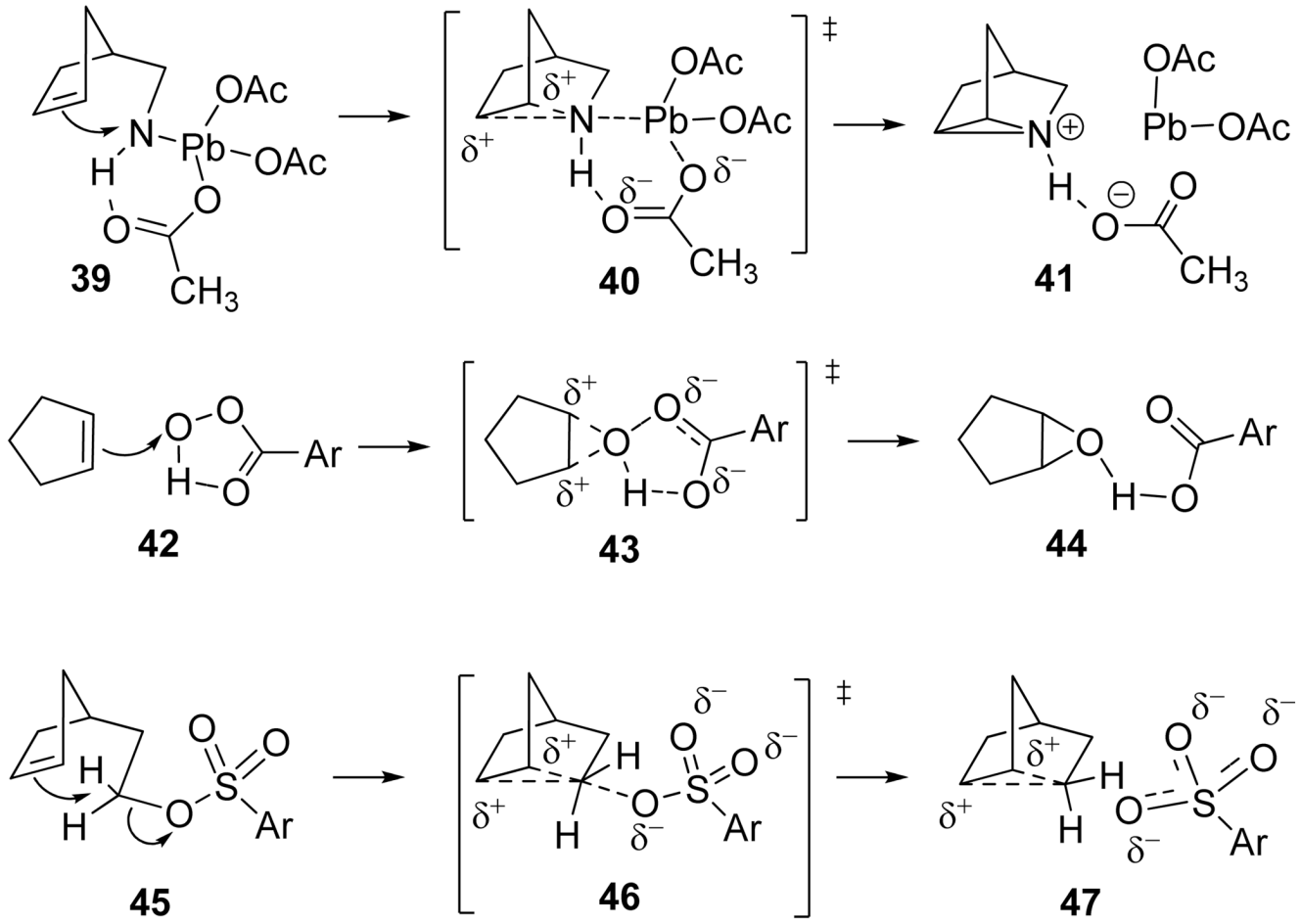
scheme 4.



scheme 5.



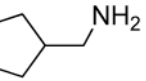
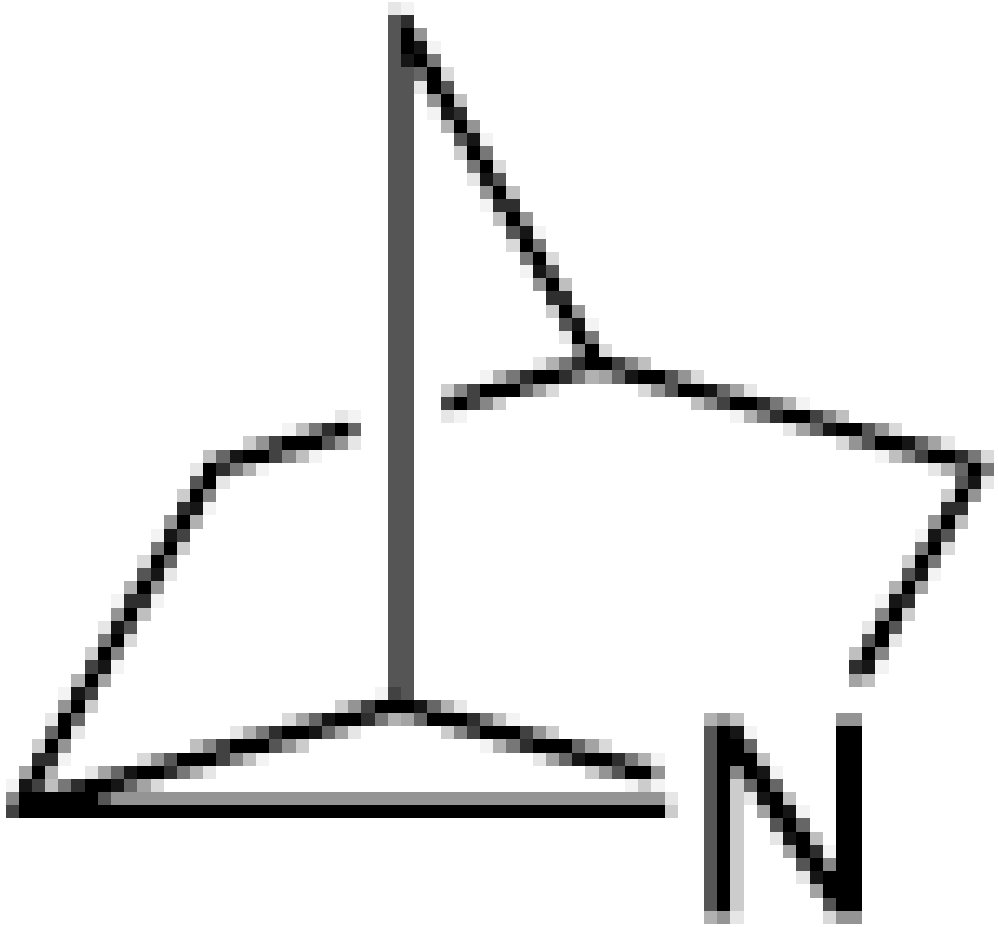
scheme 6.



scheme 7.

Table 1

es of Intramolecular Aziridination of 3-Cyclopentenylmethylamine (**6**) and its Methyl Derivatives
ve Runs) or $CDCl_3$ (kinetic Runs) at 25 °C.

Amine No.	Aziridine No.	Yield[a] (%)	$t_{1/2}$ (min, ave)	k_{rel}
 **6**	 **26**	65	280	(1.0)

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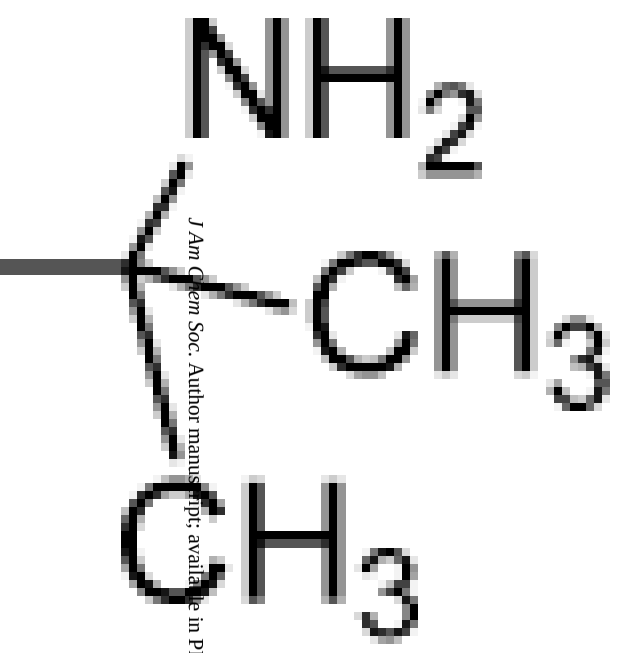
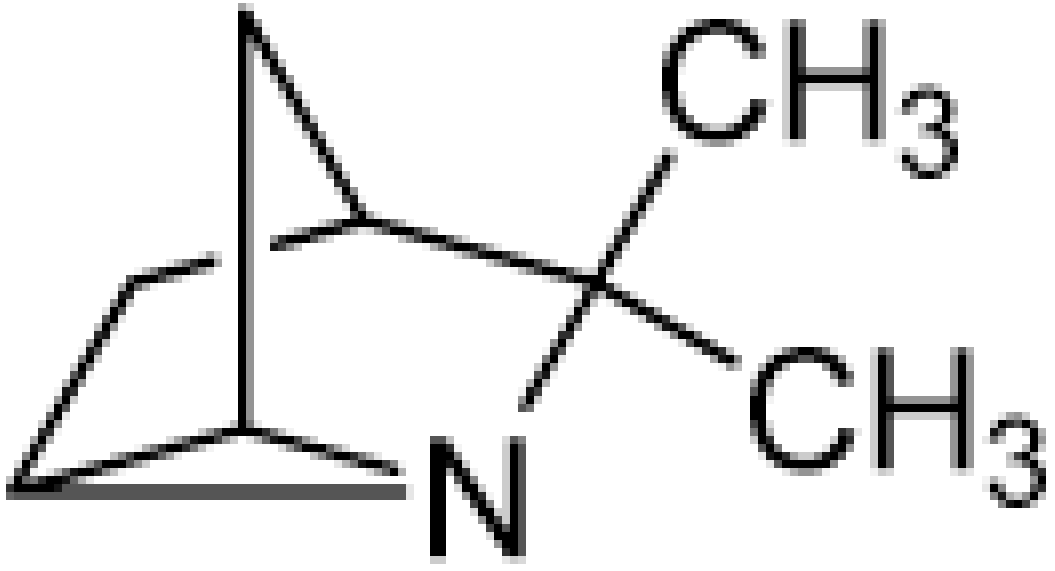
Amine No.		Aziridine No.	Yield[a] (%)	$t_{1/2}$ (min, ave)	k_{rel}
10		27	78	16, 19 (17.5)	17.5

Amine No.		Aziridine No.	Yield[a] (%)	$t_{1/2}$ (min, ave)	k_{rel}
13		**28**	81	< 1[b]	> 280

Amine No.		Aziridine No.	Yield[a] (%)	$t_{1/2}$ (min, ave)	k_{rel}
		29	ND[c]	100[e]	2.8

Amine No.	Aziridine No.	Yield[a] (%)	$t_{1/2}$ (min, ave)	k_{rel}
	 **30**	68[d]	125	2.2

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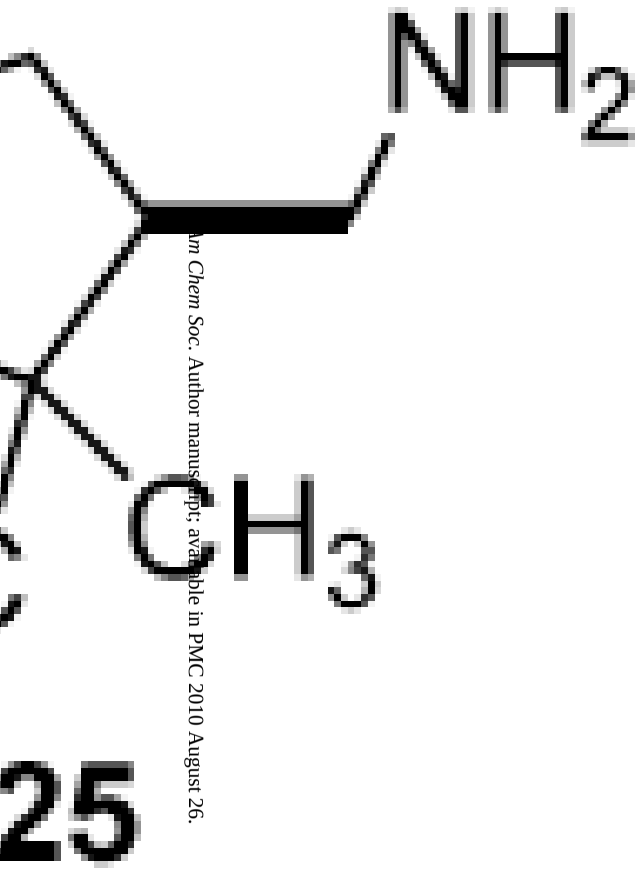
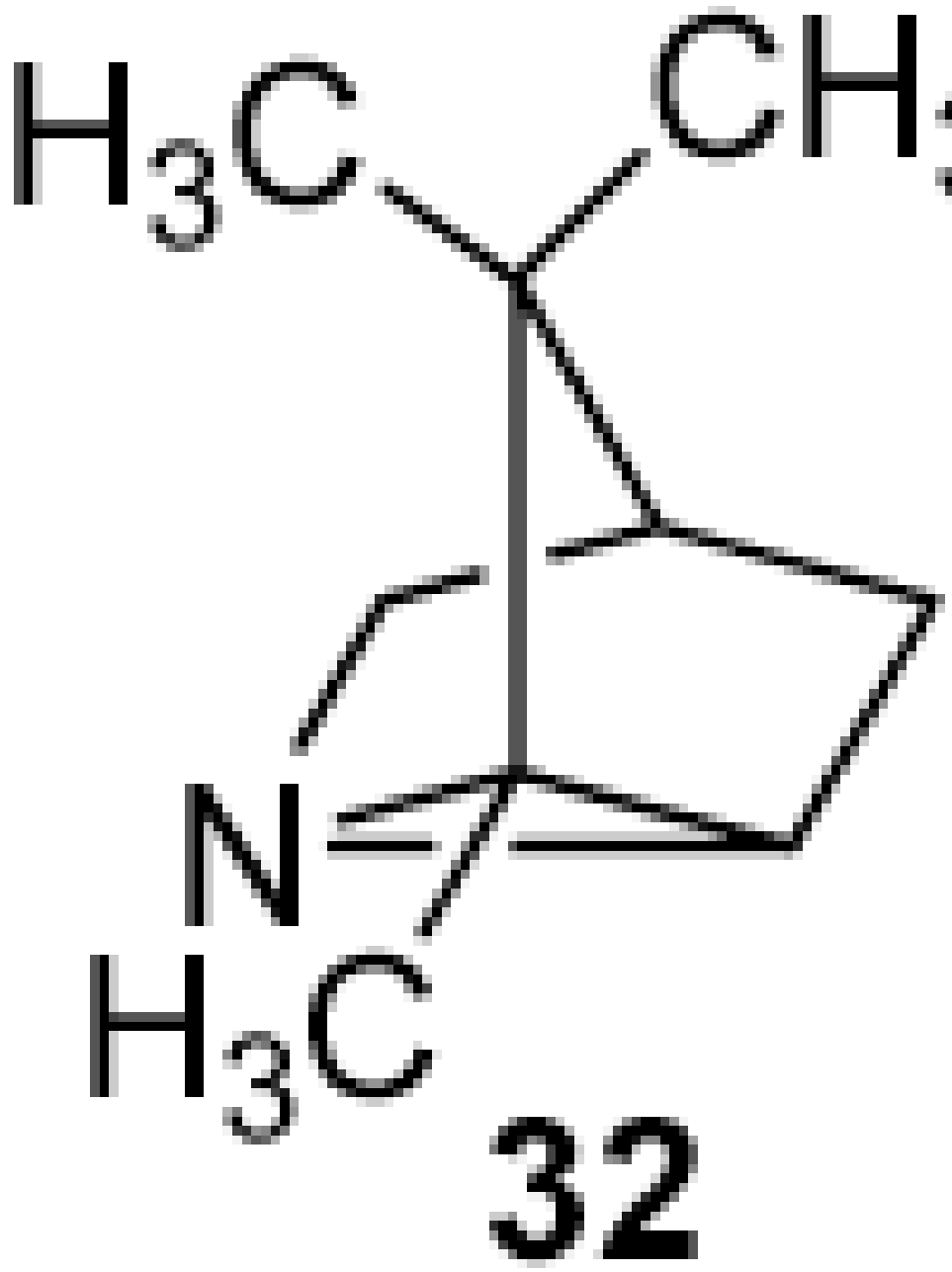
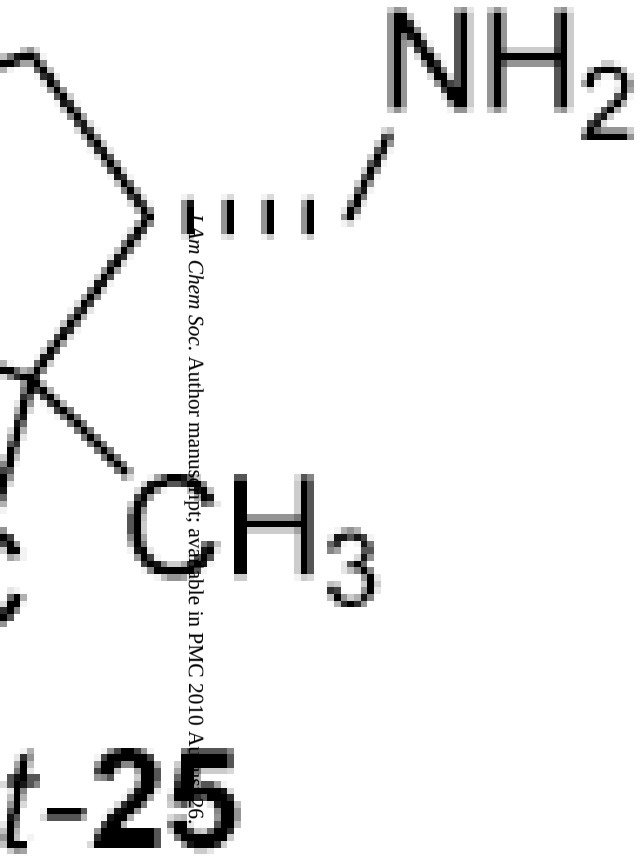
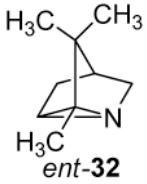
Amine No.	Aziridine No.	Yield[a] (%)	$t_{1/2}$ (min, ave)	k_{rel}
 25	 32	88	8, 11 (9.5)	29

Amine No.	Aziridine No.	Yield[a] (%)	$t_{1/2}$ (min, ave)	k_{rel}
		80	ND[c]	ND[c]

ent-**25**

ent-**32**

Table 2

Selected Proton and Carbon-13 NMR Chemical Shifts for 1-Azabicyclo[2.2.1.$0^{2,6}$]heptanes and Their Trifluoroacetate (TFA) Salts in $CDCl_3$.

Aziridine No.	CH_3 substituents	Aziridine N-C-H	Aziridine N-C-CH_3	C-7 N-CH_2(CH)	C-8 N-C-CH_3
26	none	δ_H 2.22		2.18	
		δ_C 31.8	—	55.8	—
26 • TFA	none	δ_H 3.70		2.92	
		δ_C 38.1	—	51.0	—
27	2-CH_3	δ_H 2.10	1.35	2.25,2.39	
		δ_C 38.4, 39.1	16.0	56.7	—
27 • TFA	2-CH_3	δ_H 3.63	1.71	2.92, 3.05	
		δ_C 43.9, 49.8	11.8	51.6	—
28	2,6-$(CH_3)_2$	$\delta_{H—}$	1.38	2.53	
		δ_C 45.1	12.5	56.3	—
28 • TFA	2,6-$(CH_3)_2$	$\delta_{H—}$	1.65	3.01	
		δ_C 53.2	9.6	52.2	—
30[a]	7,7-$(CH_3)_2$	δ_H 2.19	—	45.4	1.02
		δ_C 36.8			22.9
30 • TFA[a]	7,7-$(CH_3)_2$	δ_H 3.72	—	—	1.37
		δ_C 39.1		45.2	20.6
32	2,3,3-$(CH_3)_3$	δ_H 2.03	1.16	2.11, 2.80	
		δ_C 41.2, 45.2	19.7	52.2	—
32 • TFA	2,3,3-$(CH_3)_3$	δ_H 3.66	1.55	2.85, 3.43	
		δ_C 45.5, 49.6	7.0	55.3	—

[a]Peaks from impurities appear in the ^{13}C NMR spectrum.