Addition, Elimination, and Rearrangement Reactions of Cyclopropyl-Substituted Nitrenium Ions: A Computational and Experimental Investigation

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Abstract. Two cyclopropyl substituted nitrenium ions were generated through photolysis of their corresponding N-aminopyridinium ion photoprecursors. In the case of N-biphenyl-N-cyclopropyl nitrenium ion (**5**). Stable products are derived from a combination of cyclopropyl ring expansion, forming N-biphenylazetium ion, and ethylene elimination, forming biphenylisonitrilium ion. When present in high concentrations, methanol can add to the cyclopropyl ring forming N-3-methoxypropyl-N-biphenyl iminium ion. In contrast, the only detectable product from N-benzyl-N-cyclopropyl nitrenium ion (**6**) is benzylisonitrile, resulting from elimination of ethylene. DFT calculations predict the product distributions from the more stable biphenyl system **5** with reasonable accuracy. However product distributions from the less stable benzyl system **6** are forecast with less accuracy.

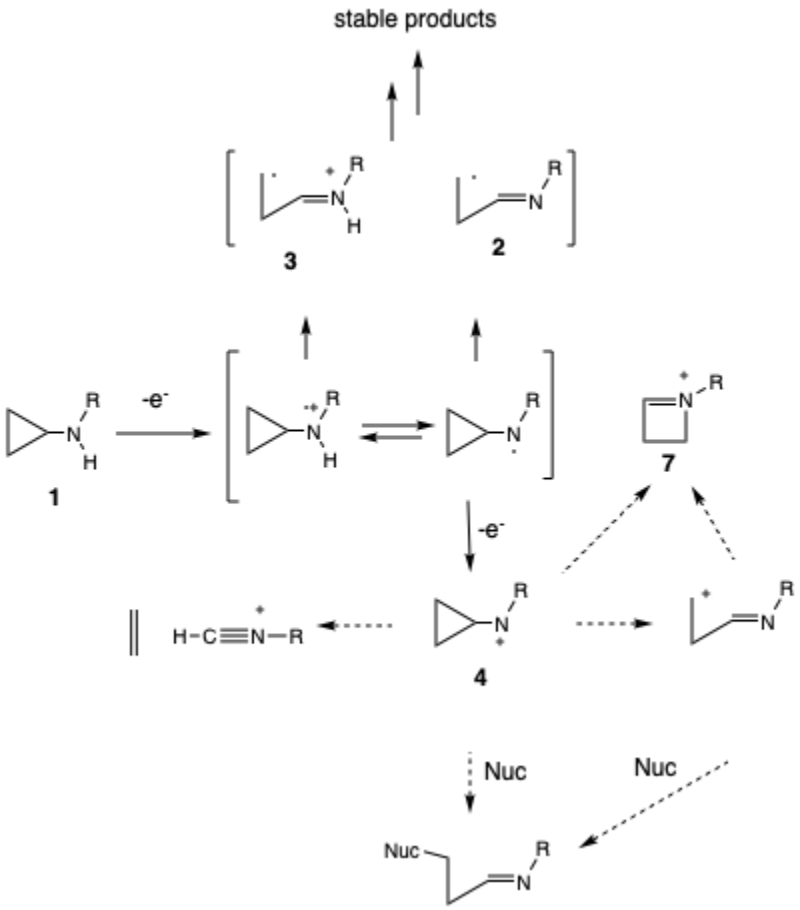
Nitrenium ions are reactive intermediates characterized by a di-coordinate nitrogen atom bearing a formal positive charge.[1–5] These species can be derived from a net two-electron oxidation of amines or through a net 4-electron reduction of nitro compounds. Detailed understanding of nitrenium ion behavior is needed in order to identify, or exclude, the involvement of these species in chemical and biological processes that entail oxidation or reduction of nitrogen-containing compounds.

In particular, the oxidation of cyclopropyl amines, **1** is involved in a surprising variety of important reactions, including synthetic transformations,[6–8] the treatment of depression through the inactivation of monoamine oxidases,[9–13] and has been used as a mechanistic probe.[14–16] It is generally accepted that radical or radical cation formation on the nitrogen triggers a ring-opening reaction that produces a radical (**2**) or ion radical species (**3**). These intermediates are then captured in secondary processes to form various stable products. Biosynthesis of the plant hormone, ethylene, also involves oxidation of a cyclopropylamine derivative— in this case aminocyclopropane carboxylate.[17–21] This process leads to elimination of the two distal CH2 groups from the cyclopropane ring, forming ethylene and cyanoformate ion.[22] Over the years a number of ethylene-generating intermediates have been suggested for this process, including the corresponding nitrenium ion (**4**) and various radical species. More recent studies favor concerted elimination via a complex wherein the amine nitrogen is bound to a Fe(IV)-oxo species, rather than via a free nitrenium ion.[23]

Previous experimental and computational studies have revealed some general trends in nitrenium ion properties and behavior.For example, arylnitrenium ions (i.e. PhNH+ and its simple derivatives) are generally ground-state singlets having triplet states that are ca. 10-25

kcal/mol higher in energy.[24–30] Conjugation with the aromatic ring results in significant positive charge delocalization onto the ring carbons. Indeed, nucleophiles tend to add to the aryl ring carbons in preference to the nitrogen. There is significantly less information about alkyl nitrenium ions. The simplest examples seem to rearrange without barrier through 1,2 shifts of H or alkyl groups to form iminium ions. However even modestly pi-donating substituents (vinyl, alkoxy groups) on the nitrogen result in significant barriers to rearrangement and cause the nitrenium ion to have a discrete existence and singlet ground state.[31]

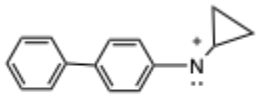
Scheme 1. Oxidation of Cyclopropylamines.



Cyclopropyl-substituted nitrenium ions deviate from the general behavior of alkylnitrenium ions.[32] Cyclopropyl groups donate electron density to the electron-deficient nitrogen center by forming a non-classical structure that is analogous to its well-studied hydrocarbon analog, the cyclopropylcarbinyl cation.[33–36] This sigma donation is remarkably effective. In fact, on the basis of calculated N-hydration enthalpies, cyclopropyl groups provide more stabilization to a nitrenium center than a phenyl group.

To provide a comprehensive picture of possible pathways that could accompany cyclopropylamine oxidation, we examined the behavior of of two cyclopropyl nitrenium ions, one

where the other substituent was an aromatic ring capable of delocalizing charge through pi-conjugation, N-biphenyl-N-cyclopropylnitrenium ion **5**, and another where the remaining substituent was an alkyl group incapable of delocalizing significant positive charge, the N-benzyl-N-cyclopropylnitrenium ion **6**. In order to distinguish between products from concerted reactions and those from nitrenium ion intermediates, the target intermediates were generated from photolysis of N-aminopyridinium ions. Experiments and calculations described herein demonstrate cyclopropyl nitrenium ions decay through a combination of ethylene elimination and expansion of the cyclopropyl ring carbon to form an azetium ion. The former process predominates in the alkyl-substituted system, whereas the aryl-substituted example shows a mixture of the two pathways.



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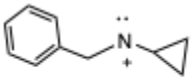

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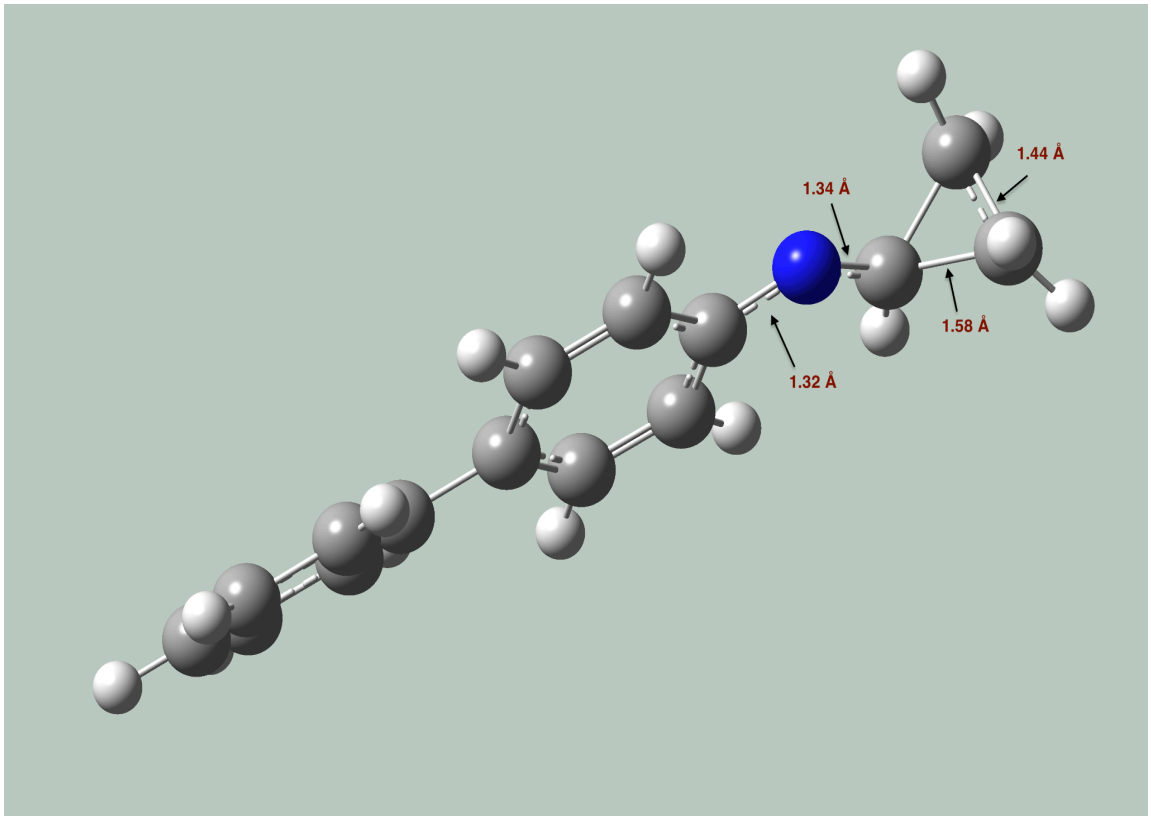
Results and Discussion.

DFT Calculations. Shown in Figure 1 are DFT calculated geometries of the conjugated biphenylcyclopropyl nitrenium ion **5** and the non-conjugated benzyl cyclopropyl nitrenium ion **6**. As seen in the previous study on the parent cyclopropyl nitrenium ion, the non-conjugated example **6** adopts a non-classical structure that allows positive charge to localize into the cyclopropyl ring. This delocalization has the effect of elongating the proximal C–C bonds (1.70 Å and 1.72 Å) and shortening the distal C–C bond (1.40 Å). Additionally the cyclopropyl C-N bond is shortened to almost a C=N double bond distance of 1.28 Å. This contrasts with **5** where the conjugated biphenyl ring competes with the cyclopropyl ring for the positive charge, In this case the C–N bond distances to the two substituents are nearly identical (1.32 Å to the biphenyl group and 1.34 Å to the cyclopropyl). Additionally, the cyclopropyl group shows a more classical structure having proximal C–C bond distances of 1.58 Å and a distal C–C distance of 1.44 Å.



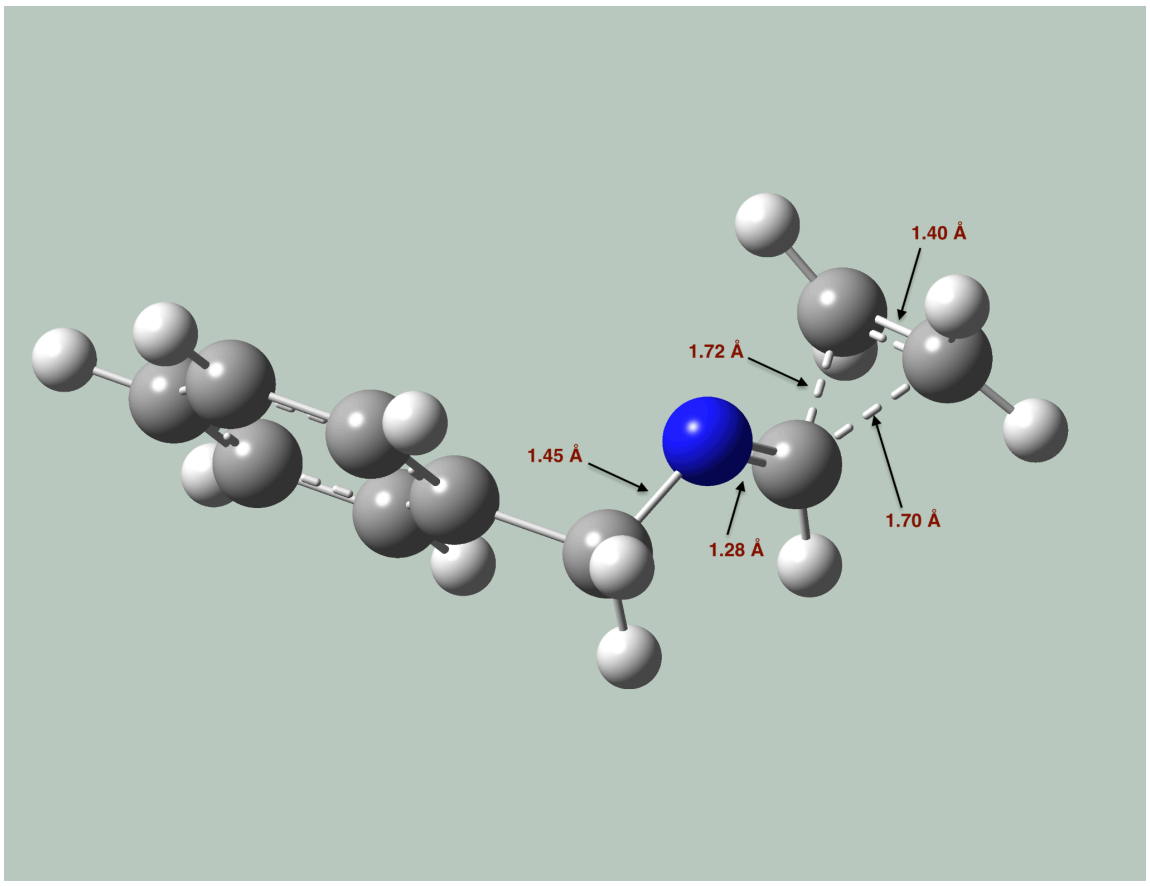


Figure 1. Geometries and selected bond distances for nitrenium ions **5** (top) and **6** (bottom) from DFT (B3LYP-d3/def2SVP) calculations.

Figure 2 illustrates relative energies (kcal/mol, from DFT calculations) for stationary points on the potential energy surface for various unimolecular decay processes anticipated for the biphenyl cyclopropyl nitrenium ion **5**. These calculations identify two low barrier reactions. The first is a cheleotropic elimination of ethylene to produce biphenylisonitrilium ($E^{‡}$= +18.3 kcal/mol) . Of comparable or slightly lower energy ($E^{‡}$= +14.2 kcal/mol) is a transition state (**9‡**) connecting the nitrenium ion **5** to its ring expansion product, N-biphenylazetium ion **10**. Hydride migration from the cyclopropyl group to the nitrogen leading to iminium ion **11** is predicted to have a substantially larger barrier ($E^{‡}$ = 44.7 kcal/mol) , and is thus unlikely to be chemically significant.

When a molecule of methanol is included in the calculations, a significantly lower energy transition state (**13‡** $E^{‡}$ = +3.6 kcal/mol) is located wherein the methanol adds to the cyclopropyl group, resulting in a ring-opened iminium ion **14** (via **15‡** and **16**). The latter product could also be derived from opening the azetium isomer. However, this pathway would entail surmounting two barriers (**9‡** and **17‡**) that are substantially larger than the one for direct addition to the cyclopropyl group. Thus, direct addition to the nitrenium ion is favored.

Lacking competing pi-conjugation, the benzyl cyclopropyl nitrenium ion **6** is predicted to be significantly more reactive. The potential energy diagram describing potential decay, provided in Figure 3, is consistent with this prediction. Three reactions are expected to have very low barriers: (a) cyclopropyl ring expansion via transition state **19‡** to form a N-benzylazetium ion **20** , (b) elimination of ethylene to form benzylisonitrilium ion **21**, and (c) 1,2-phenyl migration forming N-cyclopropyl-N-methylenebenzaminium ion **23**. In the gas phase, phenyl migration is expected to predominate. However, barriers computed with implicit (SMD) methanol solvation predict that ring expansion **19‡** and elimination **22‡** will predominate, with the former having an activation energy of 4.5 kcal/mol vs. 8.0 kcal/mol for elimination. However, given that both barriers are very small and the approximations associated with DFT-calculated kinetic barriers, both of these reactions should be considered kinetically feasible. The actual product distributions will likely be determined by explicit solvent interactions and other nuances not captured by DFT calculations. Also modeled were two H shift pathways providing iminium ions **28** and **30**. These pathways are predicted to be even less kinetically favorable (E, and were not examined in detail.

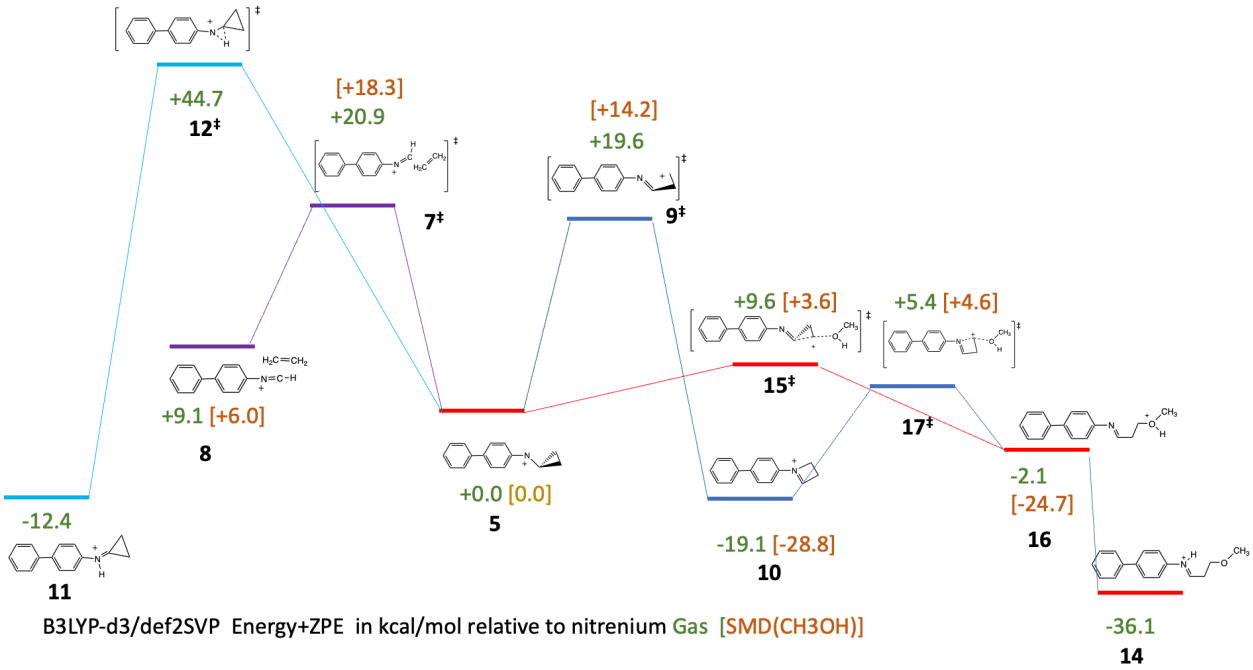


Figure 2. Potential energy surface showing selected stationary points for reactions of nitrenium ion **5** derived from DFT (B3LYP-d3/def2SVP) calculations. Energies are in kcal/mol relative to **5.**

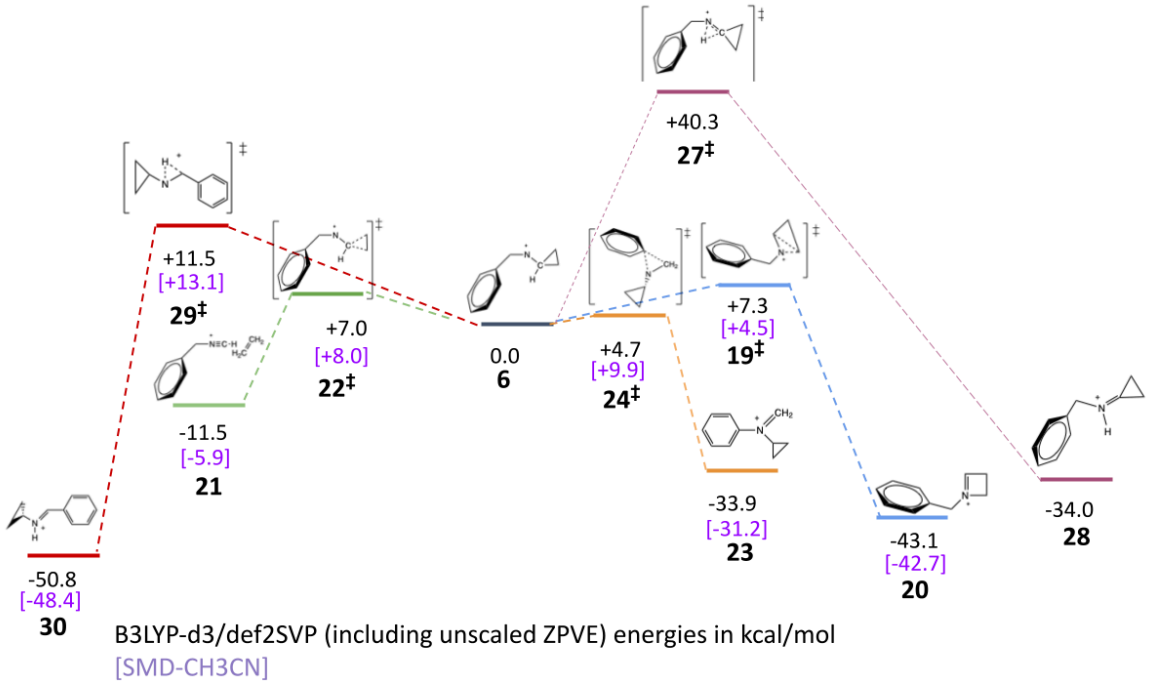
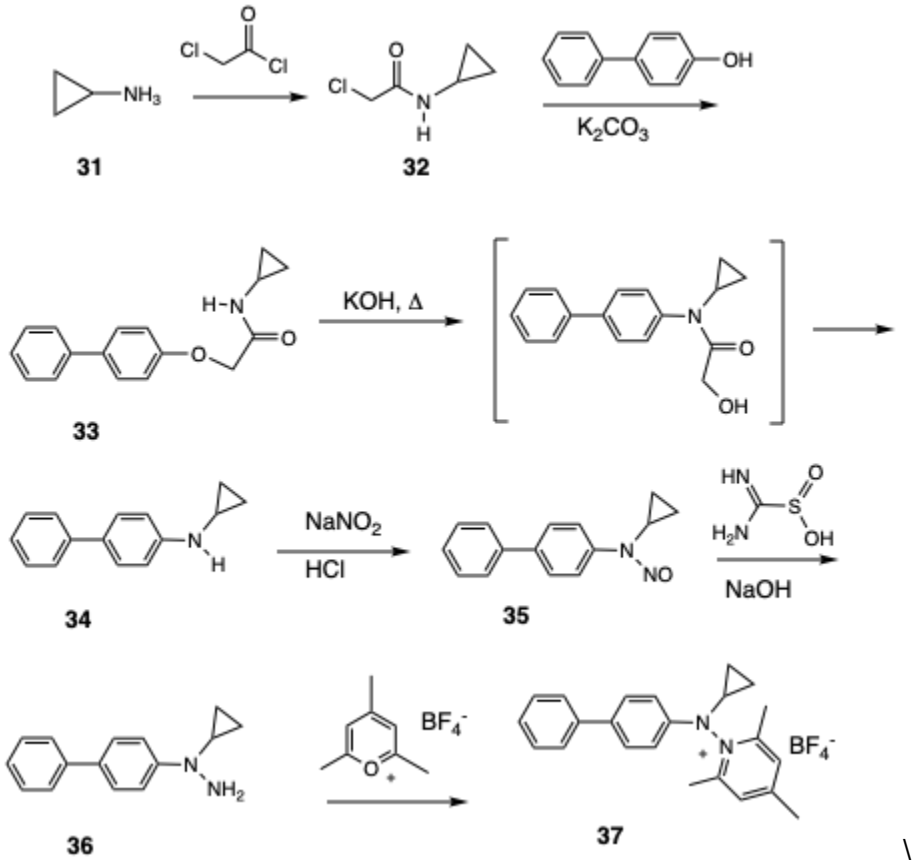


Figure 3. Potential energy diagram for N-benzyl-N-cyclopropylnitrenium **6** showing stationary points for unimolecular decay reactions. Energies are from DFT (B3LYP-d3/def2SVP) calculations. Values in brackets include implicit (SMD) MeOH solvation.

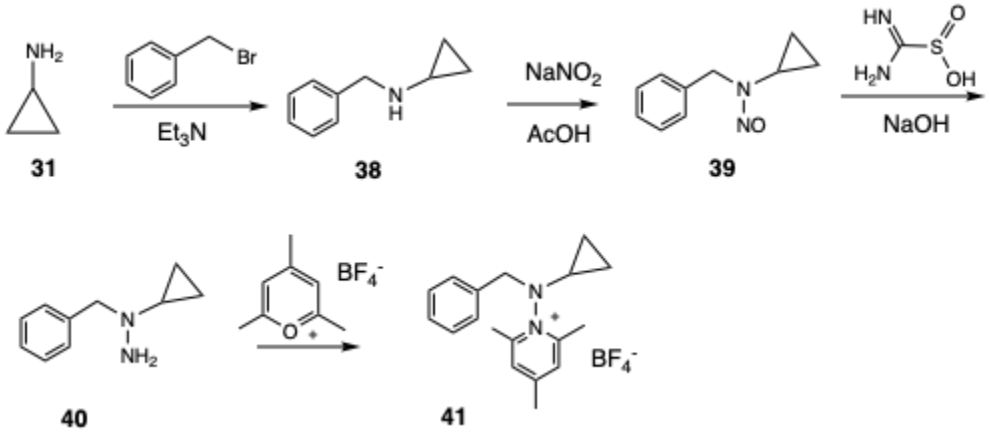
Generation of CyclopropylNitrenium ions and Characterization of Stable Products. Nitrenium ions can be produced through several methods, including solvolysis of N-chloramines[37] and oxidation of amines using hypervalent iodonium salts.[38–41] However, these routes can also produce stable products from concerted reactions in addition to those from true nitrenium intermediates. Therefore, a photochemical route was chosen for the present study. Several previous studies have demonstrated that photolysis of N-aminopyridinium salts provides nitrenium ions cleanly via heterolysis of the N–N bond.[42–44] Thus, stable products detected from this procedure can confidently be attributed to reactions of free nitrenium ions.

Scheme 2 describes preparation of the corresponding N-aminopyridinium ion precursors (**37** and **41)** to cyclopropyl nitrenium ions **(6** and **5,** respectively). In both cases the corresponding amines, **34** and **38**) are N-nitrosated and then reduced to provide 1,1-disubstituted hydrazines **40** and **36**. The latter an be condensed with 2,4,6-trimethylpyrillium ion to give the desired photoprecurors. For benzyl derivative **41**, the amine **38** can be obtained from a simple alkylation of cyclopropylamine **31**, For the biphenyl derivative **37**, the corresponding amine **34** was prepared via a Smiles rearrangement starting with 4-phenylphenol and 2-chloro-N-cyclopropylacetamide **32**.

Scheme 2

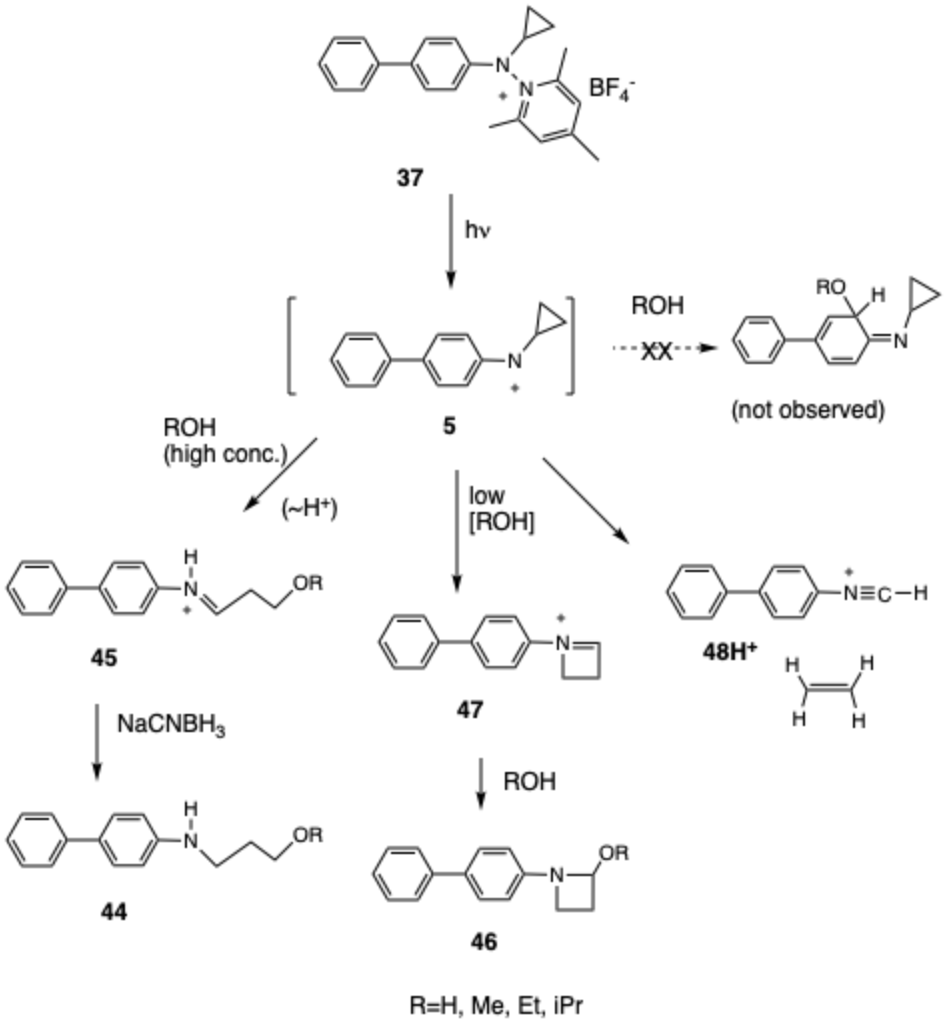


Scheme 3



Arylnitrenium ions typically react with alcohols and water (ROH) to form ortho and para adducts. Surprisingly, this is not the case with biphenylcyclopropylnitrenium ion . Product analysis experiments were carried out by irradiating the photoprecursor in the indicated solvent using a 390 nm LED light source. Solvent was removed under low pressure and the photolysate was dissolved in a deuterated solvent and analyzed using ^{1}H NMR spectroscopy. Photolysis of **37** in methanol, ethanol or i-PrOH generates a complex mixture of products. However when a reducing agent, $NaCNBH_3$, is included, the major product is the corresponding N-biphenyl-N-3-alkoxypropane **44**. This product is attributed to direct addition of ROH to the cyclopropyl ring, rather than the aryl ring. Initially this process provides an iminium ion **45**, which upon reduction with hydride is converted to the more stable product **44**. Absent the reducing agent, the iminium ion **45** appears to be unstable, eventually forming a complex mixture of products. Product **44**, therefore, is consistent with the DFT calculations in Fig 2, which predict a low barrier (<4 kcal/mol) for addition of methanol to the cyclopropyl ring.

Scheme 4

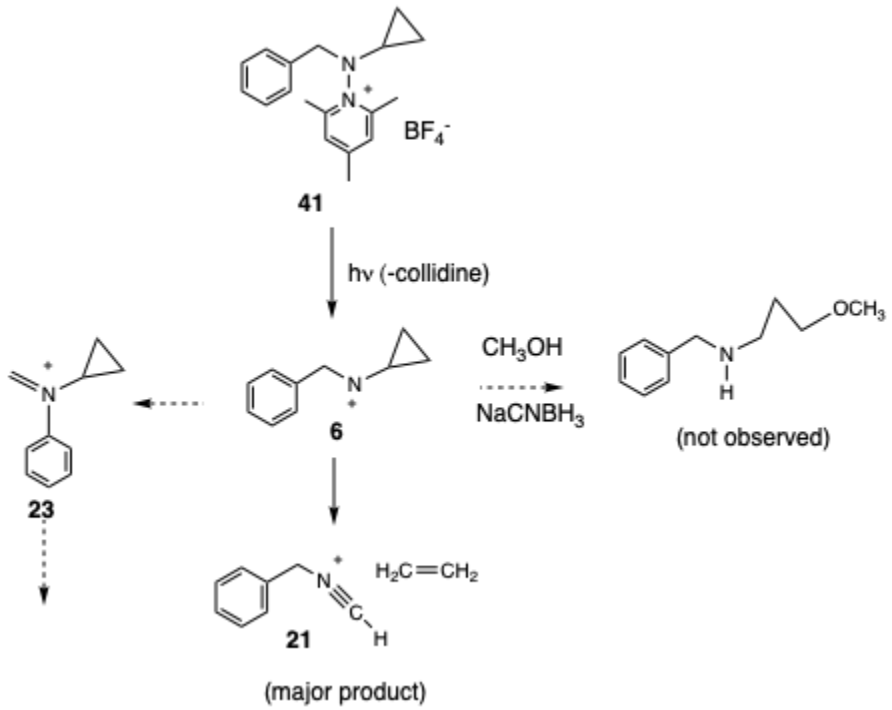


If the nucleophilic traps (ROH) are diluted with CH_3CN, then unimolecular decay processes compete with ring addition. Photolysis of **37** in CH_3CN with 15% methanol was examined by ^1H NMR spectroscopy. In addition to the collidine leaving group, two products were detected. The predominant route produces 2-alkoxy biphenylazetidine **46**. The major product under these conditions originates from 1,2–shift of a cyclopropyl CH_2 group to the nitrenium ion center forming an azetium ion **47**. The latter in turn combines with either water or alcohols to form the alkoxy- or hydroxysubstituted azetidine. The isopropoxy derivative of **46** was isolated by column chromatography and characterized by ^1H NMR and MS.

A minor, but significant, product was ethylene which could be easily detected when photolyses were carried out in CD_3CN and the product mixture was analyzed directly by ^1H NMR. The co-product from the latter process, biphenylisonitrile **48**, could not be confidently identified in the ^1H NMR spectrum of the photolysis mixture due to overlap of peaks in the aromatic region However, its formation was confirmed after it was isolated from the photolysis mixture by column chromatography and verified through its ^1H NMR spectrum.

In contrast, N-benzyl-N-cyclopropylnitrenium ion decays primarily through ethylene elimination. When the pyridinium ion precursor **41** is photolyzed (350 nm) in CD3CN the 1H NMR spectrum shows decay of the precursor and formation of benzylisonitrile **21** and ethylene, along with the collidine leaving group. No products from the expected ring expansion reaction **(20**) or phenyl migration (**23**) were identified in these experiments.

Scheme 5



To see if addition of methanol to the cyclopropyl ring would be competitive, similar photolyses were carried out in CD_3OD. Again only ethylene and benzylisonitrile were detected. Some weak signals were observed in the region (Xxx-yyy ppm) that could be consistent with the corresponding alkoxy azetidine. However, these could not be definitively attributed to this adduct. Even if these were associated with this product, the latter would constitute less than 6% of the product mixture.

Finally benzylcyclopropylnitrenium ion was also generated in a $CH_3OH/NaCHBH_3$ mixture in an attempt to trap the iminium ion product from methanol addition to the cyclopropyl group (analogous to product **44** from the biphenyl system). The anticipated addition/reduction product had been previously characterized, but it was not evident in the ^1H NMR from photolysis of **41** under these conditions.

Given the low (<10 kcal/mol) barriers predicted for elimination and isomerization of benzylcyclopropylnitrenium ion **6**, the lack of methanol addition is not surprising. However, less clear is why elimination is favored over ring expansion and phenyl migration. In the gas phase, the phenyl migration is predicted to have the lowest barrier for all of the unimolecular decay reactions. However, no evidence for this product is seen. When an implicit solvation model is

used, the order of the barriers change. In methanol, phenyl migration is projected to have a slightly higher barrier (9.9 kcal/mol) than elimination (8.0 kcal/mol), and ring expansion (4.5 kcal/mol) is expected to provide the major product. Experimentally, however, elimination is the major pathway and ring expansion, is at best, a minor pathway.

It's possible that the DFT and solvation models employed here are too approximate to distinguish between such small barriers. Alternatively, the DFT barriers may be accurate, but the short-lived nitrenium ion intermediate might not reach thermal equilibrium after its photochemical generation. In that case the approximations of transition state theory would not be valid. It is becoming increasingly clear that high energy intermediates such as carbenium ions, diradicals and carbenes often fail to produce stable product distributions that would follow from a straightforward comparison of barrier heights.[45–50] Nitrenium ion **6** may be another example of this situation. However additional calculations and experiments would be necessary to definitively establish that this is the case for nitrenium ion **6**.

Conclusions. Earlier calculations on cyclopropylnitrenium ions indicated that these species would differ from simple alkylnitrenium ions due to the non-classical delocalization of the positive charge into the sigma bonds of the cyclopropyl ring.[32] Products from **5** and **6** support this idea. The more stable biphenyl-substituted cyclopropylnitrenium ion **5** decays through a combination of cyclopropyl ring expansion and ethylene elimination. However the barriers to these unimolecular processes are high enough that bimolecular trapping by alcohols is competitive when these traps are available in high concentrations. Interestingly these nucleophiles add to the cyclopropyl ring, rather than to the aromatic ring. In contrast, the benzyl cyclopropyl nitrenium **6** eliminates ethylene under all conditions examined.

Experimental Section

General Information. All reagents and solvents were obtained from commercial sources and used without purification. Thin layer chromatography was performed on precoated silica plates. Yields of product refer to purification by silica-gel column chromatography and/or vacuum filtration. Photolysis of compounds was done using a 390 nm Kessil Lamp or 350 nm Rayonet. ^{1}H NMR were recorded at ambient temperatures on a 400MHz Bruker AV NEO, 400MHz Bruker-AVIII HD NanoBay, or a 600MHz Bruker-AVIII. ^{13}C nuclear magnetic spectra were recorded at ambient temperature on a 100MHz Bruker-AVIII HD NanoBay. High-Resolution Mass Spectrometry (HRMS) were recorded on a JEOL AccuTOF-CS mass spectrometer using electro-spray ionization (ESI).

General NMR Photolysis Experiment. Pyridinium salt is dissolved in deuterated solvent and added into an NMR tube. An NMR experiment was then performed to obtain an NMR spectrum at time T=0 hour. The NMR tube is then placed in front of the irradiation source (390 nm Kessil Lamp or 350 nm Rayonet) and the contents are photolyzed for 1-3 hours. Afterwards, an NMR spectrum is obtained of the photolysis products after 1-3 hours and compared to synthesized products.

General Preparative Photolysis Procedure. Into a 20 mL scintillation vial equipped with a stir bar was added the pyridinium salt along with acetonitrile or alcohol. The solution is then placed in front of a 390 nm Kessil Lamp or into a 350 nm Rayonet and was photolyzed for 3-4 hours. Afterwards, the solution is added to a separatory funnel and washed with a 10% NaOH solution followed by an extraction using methylene chloride (3x20 mL). The organic layers are collected, dried using magnesium sulfate, and then concentrated on the rotovap. The resulting products are then isolated via flash column chromatography.

2,4,6-Trimethylpyrilium tetrafluoroborate[51] This compound was synthesized following a literature procedure. To a 250 mL round bottom flask equipped with a magnetic stir was added acetic anhydride (530 mmol, 54 g, 50 mL) and tert-butyl alcohol (43.2 mmol, 3.1 g, 4.0 mL). Then 48% tetrafluoroboric acid (44.8 mmol, 3.94 g, 6 mL) is slowly added to the stirred mixture in 0.2 mL portions such that the temperature of the reaction does not exceed 100℃. The mixture is left to stir for 30 minutes, before being cooled to 5°C in an ice bath. The product is precipitated out from upon addition of 100 mL of diethyl ether and isolated via vacuum filtration (4.20g, 46.4%). The product matched known literature values and was used without further purification. ^{1}H NMR (400 MHz, CD_3CN) δ 7.69 (s, 2H), 2.80 (s, 6H), 2.65 (s, 3H).

(isocyanomethyl)benzene (21). The compound was isolated following

2-Chloro-N-cyclopropylacetamide (32)[52] The compound was synthesized using a modified literature procedure. To a stirred solution of cyclopropylamine (**31**, 2eq, 87.6 mmol, 5.00g) in dichloromethane (25 mL) in a 100 mL round bottom flask at 0°C is added 2-chloroacetyl chloride (1eq, 43.6 mmol, 4.92g) dropwise by addition funnel. The resulting mixture is then stirred for 2 hours at 0℃ before being vacuumed filtered through a pad of celite. The filtrate is further concentrated to a yellow-orange solid, slurried in hexane, and then refiltered. The yellow-orange solid is further dried under house vacuum for 30 min to give the desired product **32** (5.40 g, 92.7%). The product matched known literature values and was used without further purification in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (s, 1H), 4.03 (s, 2H), 2.77-2.73 (m, 1H), 0.860-0.812 (m, 2H), 0.599-0.559 (m, 2H).

2-([1,1'-Biphenyl]-4-yloxy)-N-cyclopropylacetamide (33)[52] **(cite Arava Synthesis 2013, 45, 1039-1044).** The compound was synthesized using a modified literature procedure. To a 250 round bottom flask equipped with a stir bar was added **32** (1 eq, 17.7 mmol, 2.36g), 4-phenylphenol (2.5 eq, 44.3 mmol, 7.53g), K_2CO_3 (2.5eq, 44.3 mmol, 6.12g), and Toluene (60 mL). The resulting mixture is heated to 110℃ and stirred overnight. Solvent is evaporated under vacuum and the solid precipitate is stirred with 500 mL of 10% aqueous NaOH solution at RT for 2 hours. The precipitate is isolated by filtration and further stirred with H_2O for an additional 2 hours before being filtered again to give an off-white solid **33** (3.77g, 79.9%). The solid matched known literature values and was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.54 (d, 4H), 7.45-7.42 (t, 2H), 7.35-7.32 (t, 1H), 6.99-9.97 (t, 2H), 6.66 (s, 1H), 4.52 (s, 2H), 2.83-2.79 (m, 1H), 0.867-0.835 (m, 2H), 0.614-0.587 (m, 2H).

N-Cyclopropyl-[1,1'-biphenyl]-4-amine (34)[52] The compound was synthesized using a modified literature procedure. Acetamide **33** (1 eq, 11.22 mmol, 3.00g) is added to a 100 mL round bottom flask equipped with a magnetic stir bar. Then, potassium hydroxide (2 eq, 22.4 mmol, 1.26g), anhydrous n-methyl-2-pyrrolidone (15 mL) and toluene (55 mL) is added into the flask at room temperature. The mixture is then heated to 130℃ and stirred overnight. Afterwards, the mixture is cooled to room temperature and 200 mL of H_2O was added with stirring. The layers were then separated and the aqueous layer was extracted with toluene (3x100mL). The organic layers were then combined and washed with H_2O (2x100ml), dried with magnesium sulfate, and then concentrated to give a yellow oil. The oil was then purified via column chromatography (30:1 Hexanes: Ethyl Acetate) to yield a yellow solid **34** (1.9189g, 81.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.54 (d, 2H), 7.48-7.45 (d, 2H), 7.42-7.38 (t, 2H), 7.29-7.25 (t, 1H), 6.89-6.86 (d, 2H), 2.51-2.46 (m, 1H), 0.794-0.760 (m, 2H), 0.576-0.540 (m, 2H).

N-([1,1'-Biphenyl]-4-yl)-N-cyclopropylnitrous amide (35)[30] The nitrosamine was synthesized following a known literature procedure. Amine **34** (1eq, 5.30 mmol, 1.11g), was added to a 100 mL round bottom flask equipped with a stir bar and dissolved in 25 mL of dimethylformamide. Then $NaNO_2$ (1.1eq, 5.83 mmol, 0.402 g) is added and the mixture is cooled to 0℃. Upon cooling, 12 mL of a 2 M HCl solution is added dropwise to the mixture which is then stirred for an additional hour to allow for the precipitate to form. The precipitate is collected by vacuum filtration and washed with 100 mL of water to yield nitrosamine **35** (1.06g, 84.2%). The crude precipitated was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.61 (m, 6H), 7.50-7.46 (t, 2H), 7.41-7.37 (t, 1H), 3.02-2.96 (m, 1H), 1.21-1.16 (m, 2H), 0.658-0.614 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.46, 140.15, 140.09, 129.04, 127.85, 127.75, 127.12, 121.16, 27.09, 8.27. HRMS (ESI) *m/z* calcd for $C_{15}H_{15}N_2O^+$ $[M+H]^+$ 239.1179, found 239.1193.

1-([1,1'-Biphenyl]-4-yl)-1-cyclopropylhydrazine (36)[53] The hydrazine was synthesized using a modified literature procedure. To a 250 mL round bottom flask equipped with a magnetic stir bar was added 30 mL of methanol and nitrosamine **35** (1eq, 2.29 mmol, 0.784 g) and stirred at 50℃ for five minutes. Next, 30 mL of a 2M NaOH solution was added to the stirred mixture and the resulting solution was stirred for an additional five minutes at 50℃. Afterwards, thiourea dioxide (10eq, 32.9 mmol, 3.56g) is added to the heated mixture and the solution is stirred overnight to generate a light yellow precipitate. The precipitate is then isolated via vacuum filtration to yield hydrazine **36** (0.658 g, 89.0%). The product was used in the next synthetic step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.54 (m, 4H), 7.45-7.38 (m, 4H), 7.33-7.27 (t, 1H), 2.55-2.50 (m, 1H), 0.943-0.898 (m, 2H), 0.819-0.781 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.45, 141.27, 132.19, 128.78, 127.49, 126.66, 126.42, 115.11, 36.79, 8.70. HRMS (ESI) *m/z* calcd for $C_{15}H_{17}N_2^+$ $[M+H]^+$ 225.1387, found 225.1389.

1-([1,1'-Biphenyl]-4-yl(cyclopropyl)amino)-2,4,6-trimethylpyridin-1-ium tetrafluoroborate (37) The pyridinium salt was synthesized following a literature procedure.[54] To a 100 mL round bottom flask equipped with a magnetic stir bar was added hydrazine **38** (1.5eq, 2.72 mmol, 0.610 g), 2,4,6-trimethylpyrilium tetrafluoroborate (1eq, 1.81 mmol, 0.380 g), and 25 mL of ethanol. The mixture was then stirred at 70°C for 1 hour and cooled to room temperature. Ethyl

ether is then added to the mixture to crash out the pyridinium salt which is then isolated by vacuum filtration to yield salt **37** (0.493g, 65.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 2H), 7.57-7.50 (m, 4H), 7.43-7.39 (t, 2H), 7.34-7.31 (t, 1H), 6.66 (b.s., 2H), 3.29-3.26 (m, 1H), 2.68 (s, 3H), 2.60 (s, 6H), 1.19-1.14 (m, 2H), 0.888-0.848 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.70, 157.61, 142.86, 139.79, 135.97, 130.31, 129.12, 129.01, 127.42, 126.80, 112.59, 34.07, 22.17, 19.88, 9.13. HRMS (ESI) *m/z* calcd for $C_{23}H_{25}N_2^+$ $[M+H]^+$ 329.2012, found 329.2009.

N-Benzylcyclopropanamine (38)[55] The compound was synthesized following a literature procedure. To a stirred solution of cyclopropylamine (1eq, 144 mmol, 8.2 g) in tetrahydrofuran (0.8 M) was added triethylamine (1.5 eq, 215 mmol, 21.8 g). Benzyl bromide (1.2 eq, 172 mmol, 29.5 g) was then carefully added in dropwise to the solution and the resulting mixture is stirred overnight at room temperature. Afterwards, the reaction mixture is partitioned between ethyl acetate and water. The aqueous layer was extracted twice with ethyl acetate (50 mL) and the combined organic layers were washed with brine, dried over $NaSO_4$, filtered, and then concentrated to dryness. The recovered oil matched known literature values and was purified via column chromatography (10:1 hexanes: ethyl acetate) to give amine **38** (9.36 g, 44.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.25 (m, 5H), 3.85 (s, 2H), 2.19-2.14 (m, 1H), 0.464-0.394 (m, 4H).

N-Benzyl-N-cyclopropylnitrous amide (39)[56] The compound was synthesized following a literature procedure. To a stirred solution of amine **38** (1eq, 58.4 mmol, 8.60 g) in glacial acetic acid (3 mL of HOAc/mmol of substrate) at 0°C was added dropwise $NaNO_2$ (2 mmol of $NaNO_2$/mmol of substrate) dissolved in H_2O (2 mL/mmol of $NaNO_2$). The reaction is stirred at 0°C for 1 hour before being neutralized with an aqueous solution of saturated K_2CO_3. After neutralization, the solution was extracted using Et_2O (10mL/mmol). The ether layer was then washed three times with H_2O and once with a saturated solution of sodium chloride. The aqueous washes were combined and back extracted with diethyl ether. The organic layers were then combined, dried over $MgSO_4$, and then concentrated to yield a yellow-orange oil. The oil is purified via column chromatography (12% ethyl acetate in hexanes) which yielded nitrosamine **39** (8.37 g,81.3%) as an inseparable mixture of two geometric isomers that matched known literature values. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (m, 4H), 7.18-7.16 (d, 2H), 4.82 (s, 2H), 3.26-3.21 (m, 1H), 1.16-1.12 (m, 2H), 1.01-0.978 (m, 2H).

1-Benzyl-1-cyclopropylhydrazine (40) The compound was synthesized using a modified literature procedure.[53] In a 50 mL round bottom flask equipped with a magnetic stir bar was added nitrosamine **39 (**1eq, 3.66 mmol, 0.645 g) and 10 mL of methanol. The mixture was stirred at 50°C to allow for the nitrosamine to dissolve. Then, 11 mL of a 2M NaOH solution was added to the stirred solution which resulted in a cloudy solution. The cloudy solution was stirred for an additional five minutes before thiourea dioxide (3 eq, 10.9 mmol, 1.19 g) is added in and the mixture is stirred for an additional 3-6 hours while being monitored by TLC. Upon completion of the reaction, the mixture is diluted with chloroform and the organic layer is separated. The aqueous layer is further extracted with chloroform (3x50 mL) and the combined organic layers are washed with H_2O, dried with $MgSO_4$, and concentrated to give hydrazine **40** as a light yellow oil (0.4028 g, 67.8%). A mass of the compound could not be obtained due to how unstable the

compound is; the oil was used immediately without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.24 (m, 5H), 3.87 (s, 2H), 1.99-1.94 (m, 1H), 0.582-0.567 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.27, 129.69, 128.39, 127.38, 64.62, 41.42, 7.12.

1-(Benzyl(cyclopropyl)amino)-2,4,6-trimethylpyridin-1-ium tetrafluoroborate (41) The compound was synthesized following a literature procedure.[54] Hydrazine **40** (1.5 eq, 2.48 mmol, 0.403 g) and 2,4,6-trimethylpyrilium tetrafluoroborate (1 eq, 1.66 mmol, 0.348 g) are combined in a 50 mL round bottom flask along with 20 mL of ethanol. The resulting mixture is stirred at 70°C for 30 min before being allowed to cool to room temperature. Once cooled, 20 mL of ethyl ether is added and the round bottom flask is placed in an ice bath to promote precipitation of the product. Pyridinium ion **41** is obtained as a light yellow precipitate/crystal (0.136 g, 23.1%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 2H), 7.32-7.29 (m, 3H), 7.21-7.19 (m, 2H), 4.57 (s, 2H), 3.16-3.11 (m, 1H), 2.68 (s, 6H), 2.54 (s, 3H), 0.801-0.751 (m. 2H), 0.527-0.489 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.21, 157.43, 133.94, 130.19, 129.79, 129.10, 128.97, 60.59, 36.82, 21.64, 21.21, 9.29. HRMS (ESI) *m/z* calcd for $C_{18}H_{23}N_2^+$ $[M+H]^+$ 267.1856, found 267.1869.

N-(3-methoxypropyl)-[1,1'-biphenyl]-4-amine (44) The compound was obtained following a modified general preparatory photolysis procedure. Into a 20 mL scintillation vial equipped with a stir bar was added pyridinium salt **37** (1eq, 1.20 mmol, 0.500g), sodium cyanoborohyride (10eq, 12 mmol, 0.755g), and 10 mL of methanol. The mixture is placed in front of a 390 nm Kessil lamp, that is turned on to full intensity, and stirred/photolyzed for 2-3 hours. Afterwards, the mixture is added to a separatory funnel, neutralized with 10% NaOH, and extracted with dichloromethane (3x20 mL). The organic extracts are then combined, washed with water, and then dried with $MgSO_4$ before being concentrated using a rotovap. Compound **44** is then isolated as a clear oil (0.121 g, 41.9%) via flash column chromatography with the mobile phase being 4:1 hexanes: ethyl acetate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.54 (d, 2H), 7.47-7.45 (d, 2H), 7.42-7.38 (t, 2H), 7.29-7.24 (m, 1H), 6.71-6.69 (d, 2H), 3.56-3.53 (t, 2H), 3.38 (s, 3H), 3.31-3.28 (t, 2H), 1.96-1.90 (p, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.97, 141.44, 130.20, 128.76, 128.06, 126.40, 126.11, 113.12, 71.38, 58.93, 42.05, 29.47. HRMS (ESI) *m/z* calcd for $C_{16}H_{20}NO^+$ $[M+H]^+$ 242.1540, found 242.1542

1-([1,1'-biphenyl]-4-yl)-2-isopropoxyazetidine (46) The compound was obtained following a modified general preparation photolysis procedure. Into a 20 mL scintillation vial equipped with a stir bar was added pyridinium salt **37** (1.20 mmol, 0.500g) and 20 mL of an 85:15 v:v mixture of acetonitrile:isopropyl alcohol. The mixture is stirred/photolyzed for 3 hours in front of a 390 nm Kessil lamp set at maximum intensity. Afterwards, the mixture is added to a separatory funnel and washed with saturated bicarbonate solution before being extracted with methylene chloride (3x20 mL). The organic extracts are combined, dried over magnesium sulfate, and then concentrated on the rotovap. The resulting oil is then purified via flash column chromatography (9:1 hexanes:ethyl acetate) to isolate **46** as a red precipitate (0.167g, 52.0%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.22 (m, 9H), 4.93 (s, 1H), 3.81-3.53 (m, 3H), 2.41-2.31 (m, 2H), 1.12-1.11 (d, 3H), 0.958-0.943 (d, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.19, 138.73, 129.17, 127.90,

127.27, 126.42, 114.04, 84.86, 72.46, 68.46, 31.07, 22.89, 22.19. HRMS (ESI) *m/z* calcd for $C_{20}H_{25}N_2O^+$ [M+CH_3CN+H] 309.1962, found 309.1942.

4-isocyano-1,1'-biphenyl (48) The compound was isolated from the photolysis mixture via column chromatography following the general preparatory photolysis procedure. The ^{1}H NMR spectrum of the isolated product matched that previously reported for isonitrile **48 [Adv. Synth.Catal.2020,362, 376–3]**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.60 (d, 2H), 7.58-7.56 (d, 2H), 7.49-7.39 (m, 5H).

Computational Methods. Structures and relative energies for the nitrenium ions, decay products, and the transition states that connect them were calculated with the Gaussian 16 software suite,[57] using density functional theory (DFT). The notation B3LYP-d3 designates calculations that use Becke's[58] three parameter exchange functional, the LYP correlation functional of Lee, Yang, and Parr,[59] and an empirical dispersion correction developed by Grimme, et al.[60] The basis set def2SVP refers to the split-valence with polarization basis set developed by Ahlrichs et al.[61] All geometries were optimized to stationary points and a subsequent vibrational frequency analysis showed that they had either zero (for products and intermediates) or one (for transition states, denoted with the superscript ‡) imaginary frequency. Transition states were connected to the corresponding reactants and products either through intrinsic reaction coordinate (IRC) calculations or visualizations of the single imaginary frequency. Solvent effects were evaluated using the SMD implicit continuum solvation model with density developed by Truhlar et al.[62]

(1) Gassman, P. G. Nitrenium Ions. *Acc. Chem. Res.* **1970**, *3* (1), 26–33. https://doi.org/10.1021/ar50025a004.
(2) Falvey, D. E. Nitrenium Ions. In *Reactive Intermediate Chemistry*; John Wiley & Sons, Ltd, 2003; pp 593–650. https://doi.org/10.1002/0471721492.ch13.
(3) Falvey, D. E. Electronic Properties of Nitrenium Ions. In *Nitrenes and Nitrenium Ions*; John Wiley & Sons, Ltd, 2013; pp 191–216. https://doi.org/10.1002/9781118560907.ch6.
(4) Novak, M.; Wang, Y.-T. Aryl Nitrenium Ions in Aqueous Solution. In *Nitrenes and Nitrenium Ions*; John Wiley & Sons, Ltd, 2013; pp 117–165. https://doi.org/10.1002/9781118560907.ch4.
(5) Borodkin, G. I.; Shubin, V. G. Nitrenium Ions: Structure and Reactivity. *Russ. Chem. Rev.* **2008**, *77* (5), 395–419. https://doi.org/10.1070/RC2008v077n05ABEH003760.
(6) Blackburn, A.; Bowles, D. M.; Curran, T. T.; Kim, H. Air Oxidation of N-Cyclopropylanilines. *Synth. Commun.* **2012**, *42* (12), 1855–1863. https://doi.org/10.1080/00397911.2010.545166.
(7) Sokolova, O. O.; Bower, J. F. Selective Carbon–Carbon Bond Cleavage of Cyclopropylamine Derivatives. *Chem. Rev.* **2021**, *121* (1), 80–109. https://doi.org/10.1021/acs.chemrev.0c00166.
(8) Luo, Z.; Cao, B.; Song, T.; Xing, Z.; Ren, J.; Wang, Z. Visible-Light Organophotoredox-Mediated [3 + 2] Cycloaddition of Arylcyclopropylamine with Structurally Diverse Olefins for the Construction of Cyclopentylamines and Spiro[4.n] Skeletons. *J. Org. Chem.* **2022**, *87* (22), 15511–15529. https://doi.org/10.1021/acs.joc.2c02061.
(9) Tipton, K. F. 90 Years of Monoamine Oxidase: Some Progress and Some Confusion. *J.*

Neural Transm. **2018**, *125* (11), 1519–1551. https://doi.org/10.1007/s00702-018-1881-5.
(10) Silverman, R. B. Radical Ideas about Monoamine Oxidase. *Acc. Chem. Res.* **1995**, *28* (8), 335–342. https://doi.org/10.1021/ar00056a003.
(11) Silverman, R. B. Mechanism of Inactivation of Monoamine Oxidase by Trans-2-Phenylcyclopropylamine and the Structure of the Enzyme-Inactivator Adduct. *J. Biol. Chem.* **1983**, *258* (24), 14766–14769. https://doi.org/10.1016/S0021-9258(17)43725-2.
(12) Malcomson, T.; Yelekci, K.; Borrello, M. T.; Ganesan, A.; Semina, E.; De Kimpe, N.; Mangelinckx, S.; Ramsay, R. R. Cis-Cyclopropylamines as Mechanism-Based Inhibitors of Monoamine Oxidases. *FEBS J.* **2015**, *282* (16), 3190–3198. https://doi.org/10.1111/febs.13260.
(13) Ramsay, R. R.; Albreht, A. Kinetics, Mechanism, and Inhibition of Monoamine Oxidase. *J. Neural Transm.* **2018**, *125* (11), 1659–1683. https://doi.org/10.1007/s00702-018-1861-9.
(14) Li, X.; Grimm, M. L.; Igarashi, K.; Neal Castagnoli, J.; Tanko, J. M. The First Calibration of an Aminiumyl Radical Ion Clock: Why N-Cyclopropylanilines May Be Poor Mechanistic Probes for Single Electron Transfer. *Chem. Commun.* **2007**, No. 25, 2648–2650. https://doi.org/10.1039/B702157G.
(15) Cooksy, A. L.; King, H. F.; Richardson, W. H. Molecular Orbital Calculations of Ring Opening of the Isoelectronic Cyclopropylcarbinyl Radical, Cyclopropoxy Radical, and Cyclopropylaminium Radical Cation Series of Radical Clocks. *J. Org. Chem.* **2003**, *68* (24), 9441–9452. https://doi.org/10.1021/jo035085b.
(16) Grimm, M. L.; Suleman, N. K.; Hancock, A. N.; Spencer, J. N.; Dudding, T.; Rowshanpour, R.; Castagnoli, N. Jr.; Tanko, J. M. Stereoelectronic and Resonance Effects on the Rate of Ring Opening of N-Cyclopropyl-Based Single Electron Transfer Probes. *J. Am. Chem. Soc.* **2020**, *142* (5), 2640–2652. https://doi.org/10.1021/jacs.9b12617.
(17) Adams, D. O.; Yang, S. F. Ethylene the Gaseous Plant Hormone: Mechanism and Regulation of Biosynthesis. *Trends Biochem. Sci.* **1981**, *6*, 161–164. https://doi.org/10.1016/0968-0004(81)90059-1.
(18) Houben, M.; Poel, B. V. de. 1-Aminocyclopropane-1-Carboxylic Acid Oxidase (ACO): The Enzyme That Makes the Plant Hormone Ethylene. *Front. Plant Sci.* **2019**, *10*. https://doi.org/10.3389/fpls.2019.00695.
(19) Pirrung, M. C. Ethylene Biosynthesis from 1-Aminocyclopropanecarboxylic Acid. *Acc. Chem. Res.* **1999**, *32* (8), 711–718. https://doi.org/10.1021/ar960003+.
(20) Adams, D. O.; Yang, S. F. Ethylene Biosynthesis: Identification of 1-Aminocyclopropane-1-Carboxylic Acid as an Intermediate in the Conversion of Methionine to Ethylene. *Proc. Natl. Acad. Sci.* **1979**, *76* (1), 170–174. https://doi.org/10.1073/pnas.76.1.170.
(21) Peiser, G. D.; Wang, T.-T.; Hoffman, N. E.; Yang, S. F.; Liu, H.; Walsh, C. T. Formation of Cyanide from Carbon 1 of 1-Aminocyclopropane-1-Carboxylic Acid during Its Conversion to Ethylene. *Proc. Natl. Acad. Sci.* **1984**, *81* (10), 3059–3063. https://doi.org/10.1073/pnas.81.10.3059.
(22) Murphy, L. J.; Robertson, K. N.; Harroun, S. G.; Brosseau, C. L.; Werner-Zwanziger, U.; Moilanen, J.; Tuononen, H. M.; Clyburne, J. A. C. A Simple Complex on the Verge of Breakdown: Isolation of the Elusive Cyanoformate Ion. *Science* **2014**, *344* (6179), 75–78. https://doi.org/10.1126/science.1250808.
(23) Bassan, A.; Borowski, T.; Schofield, C. J.; Siegbahn, P. E. M. Ethylene Biosynthesis by 1-Aminocyclopropane-1-Carboxylic Acid Oxidase: A DFT Study. *Chem. – Eur. J.* **2006**, *12* (34), 8835–8846. https://doi.org/10.1002/chem.200501459.
(24) Favley, D. E.; Cramer, C. J. Aryl- and Alkylnitrenium Ions: Singlet-Triplet Gaps via AB Initio and Semi-Empirical Methods. *Tetrahedron Lett.* **1992**, *33* (13), 1705–1708. https://doi.org/10.1016/S0040-4039(00)91711-8.

(25) Cramer, C. J.; Dulles, F. J.; Falvey, D. E. Ab Initio Characterization of Phenylnitrenium and Phenylcarbene: Remarkably Different Properties for Isoelectronic Species. *J. Am. Chem. Soc.* **1994**, *116* (21), 9787–9788. https://doi.org/10.1021/ja00100a069.
(26) McIlroy, S.; Cramer, C. J.; Falvey, D. E. Singlet−Triplet Energy Gaps in Highly Stabilized Nitrenium Ions: Experimental and Theoretical Study of 1,3-Dimethylbenzotriazolium Ion. *Org. Lett.* **2000**, *2* (16), 2451–2454. https://doi.org/10.1021/ol006106g.
(27) Srivastava, S.; Ruane, P. H.; Toscano, J. P.; Sullivan, M. B.; Cramer, C. J.; Chiapperino, D.; Reed, E. C.; Falvey, D. E. Structures of Reactive Nitrenium Ions: Time-Resolved Infrared Laser Flash Photolysis and Computational Studies of Substituted N-Methyl-N-Arylnitrenium Ions. *J. Am. Chem. Soc.* **2000**, *122* (34), 8271–8278. https://doi.org/10.1021/ja001184k.
(28) Sullivan, M. B.; Brown, K.; Cramer, C. J.; Truhlar, D. G. Quantum Chemical Analysis of Para-Substitution Effects on the Electronic Structure of Phenylnitrenium Ions in the Gas Phase and Aqueous Solution. *J. Am. Chem. Soc.* **1998**, *120* (45), 11778–11783. https://doi.org/10.1021/ja982542a.
(29) Du, L.; Wang, J.; Qiu, Y.; Liang, R.; Lu, P.; Chen, X.; Phillips, D. L.; Winter, A. H. Generation and Direct Observation of a Triplet Arylnitrenium Ion. *Nat. Commun.* **2022**, *13* (1), 3458. https://doi.org/10.1038/s41467-022-31091-z.
(30) Chinn, E. S.; Falvey, D. E. Photochemical Generation and Characterization of the 5-Endo-10,11-Dihydrodibenzoazepine Nitrenium Ion. *Photochem. Photobiol. Sci. Off. J. Eur. Photochem. Assoc. Eur. Soc. Photobiol.* **2022**, *21* (11), 1907–1914. https://doi.org/10.1007/s43630-022-00267-3.
(31) Falvey, D. E. Discrete Existence of Singlet Nitrenium Ions Revisited: Computational Studies of Non-Aryl Nitrenium Ions and Their Rearrangements. *ACS Omega* **2018**, *3* (8), 10418–10432. https://doi.org/10.1021/acsomega.8b01038.
(32) Falvey, D. E. Nitrenium Ion Analogues of Nonclassical Carbocations: Cyclopropylnitrenium, Allylnitrenium, and Azetidenium Ions and Mechanisms for Their Interconversion. *Org. Lett.* **2015**, *17* (3), 484–487. https://doi.org/10.1021/ol503488b.
(33) Brown, H. C. The Cyclopropylcarbinyl Cation. In *The Nonclassical Ion Problem*; Brown, H. C., Ed.; Springer US: Boston, MA, 1977; pp 69–82. https://doi.org/10.1007/978-1-4613-4118-5_5.
(34) Olah, G. A.; Surya Prakash, G. K.; Rasul, G. Ab Initio/GIAO-CCSD(T) Study of Structures, Energies, and 13C NMR Chemical Shifts of C4H7+ and C5H9+ Ions: Relative Stability and Dynamic Aspects of the Cyclopropylcarbinyl vs Bicyclobutonium Ions. *J. Am. Chem. Soc.* **2008**, *130* (28), 9168–9172. https://doi.org/10.1021/ja802445s.
(35) Casanova, J.; Kent, D. R.; Goddard, W. A.; Roberts, J. D. Quantum-Mechanical Calculations of the Stabilities of Fluxional Isomers of C4H\documentclass[12pt]{minimal} \usepackage{amsmath} \usepackage{wasysym} \usepackage{amsfonts} \usepackage{amssymb} \usepackage{amsbsy} \usepackage{mathrsfs} \setlength{\oddsidemargin}{-69pt} \begin{document} \begin{equation*}{\mathrm{_{7}^{+}}}\end{equation*}\end{document} in Solution. *Proc. Natl. Acad. Sci.* **2003**, *100* (1), 15–19. https://doi.org/10.1073/pnas.0136820100.
(36) Mazur, R. H.; White, W. N.; Semenow, D. A.; Lee, C. C.; Silver, M. S.; Roberts, J. D. Small-Ring Compounds. XXIII. The Nature of the Intermediates in Carbonium Ion-Type Interconversion Reactions of Cyclopropylcarbinyl, Cyclobutyl and Allylcarbinyl Derivatives1a. *J. Am. Chem. Soc.* **1959**, *81* (16), 4390–4398. https://doi.org/10.1021/ja01525a073.
(37) Gassman, P. G.; Dygos, D. K.; Trent, J. E. Chemistry of Nitrenium Ions. X. Solvolysis of 1-Chloroaziridines. *J. Am. Chem. Soc.* **1970**, *92* (7), 2084–2090. https://doi.org/10.1021/ja00710a048.
(38) Maiti, S.; Alam, M. T.; Bal, A.; Mal, P. Nitrenium Ions from Amine-Iodine(III) Combinations. *Adv. Synth. Catal.* **2019**, *361* (19), 4401–4425. https://doi.org/10.1002/adsc.201900441.

(39) O'Neil, L. G.; Bower, J. F. Electrophilic Aminating Agents in Total Synthesis. *Angew. Chem.* **2021**, *133* (49), 25844–25870. https://doi.org/10.1002/ange.202102864.
(40) Wardrop, D. J.; Bowen, E. G. Nitrenium Ion-Mediated Alkene Bis-Cyclofunctionalization: Total Synthesis of (−)-Swainsonine. *Org. Lett.* **2011**, *13* (9), 2376–2379. https://doi.org/10.1021/ol2006117.
(41) Pichette, S.; Aubert-Nicol, S.; Lessard, J.; Spino, C. Photochemical and Thermal Ring-Contraction of Cyclic Hydroxamic Acid Derivatives. *J. Org. Chem.* **2012**, *77* (24), 11216–11226. https://doi.org/10.1021/jo3023507.
(42) Takeuchi, H.; Hayakawa, S.; Tanahashi, T.; Kobayashi, A.; Adachi, T.; Higuchi, D. Novel Generation of Parent, Alkyl, Dialkyl and Alicyclic Nitrenium Ions in Photolyses of Pyridinium, Quinolinium, Bipyridinium and Phenanthrolinium Salts and Aromatic N-Substitution by Nitrenium Ions. *J. Chem. Soc. Perkin Trans. 2* **1991**, No. 6, 847–855. https://doi.org/10.1039/P29910000847.
(43) McIlroy, S.; Moran, R. J.; Falvey, D. E. Photogenerated Nitrenium Ions: A Search for Triplet-State Reactivity in the Chemistry of the Diphenylnitrenium Ion. *J. Phys. Chem. A* **2000**, *104* (47), 11154–11158. https://doi.org/10.1021/jp002756q.
(44) Phillips, D. L. Time-Resolved Resonance Raman Spectroscopic Studies of Aryl Nitrenium Ions and Their Chemical Reactions. In *Nitrenes and Nitrenium Ions*; John Wiley & Sons, Ltd, 2013; pp 217–272. https://doi.org/10.1002/9781118560907.ch7.
(45) Carpenter, B. K. Intramolecular Dynamics for the Organic Chemist. *Acc. Chem. Res.* **1992**, *25* (11), 520–528. https://doi.org/10.1021/ar00023a006.
(46) Carpenter, B. K. Energy Disposition in Reactive Intermediates. *Chem. Rev.* **2013**, *113* (9), 7265–7286. https://doi.org/10.1021/cr300511u.
(47) Bailey, J. O.; Singleton, D. A. Failure and Redemption of Statistical and Nonstatistical Rate Theories in the Hydroboration of Alkenes. *J. Am. Chem. Soc.* **2017**, *139* (44), 15710–15723. https://doi.org/10.1021/jacs.7b07175.
(48) Feng, Z.; Guo, W.; Kong, W.-Y.; Chen, D.; Wang, S.; Tantillo, D. J. Analogies between Photochemical Reactions and Ground-State Post-Transition-State Bifurcations Shed Light on Dynamical Origins of Selectivity. *Nat. Chem.* **2024**, 1–9. https://doi.org/10.1038/s41557-023-01410-y.
(49) Tantillo, D. J. Dynamic Effects on Organic Reactivity—Pathways to (and from) Discomfort. *J. Phys. Org. Chem.* **2021**, *34* (6), e4202. https://doi.org/10.1002/poc.4202.
(50) Roytman, V. A.; Singleton, D. A. Solvation Dynamics and the Nature of Reaction Barriers and Ion-Pair Intermediates in Carbocation Reactions. *J. Am. Chem. Soc.* **2020**, *142* (29), 12865–12877. https://doi.org/10.1021/jacs.0c06295.
(51) Balaban, A. T.; Boulton, A. J. 2,4,6-TRIMETHYLPYRYLIUM TETRAFLUOROBORATE. *Org. Synth.* **1969**, *49*, 121. https://doi.org/10.15227/orgsyn.049.0121.
(52) Arava, V. R.; Bandatmakuru, S. R. An Efficient Synthesis of N-Cyclopropylanilines by a Smiles Rearrangement. *Synthesis* **2013**, *45* (8), 1039–1044. https://doi.org/10.1055/s-0032-1318389.
(53) Chaudhary, P.; Gupta, S.; Sureshbabu, P.; Sabiah, S.; Kandasamy, J. A Metal Free Reduction of Aryl-N-Nitrosamines to the Corresponding Hydrazines Using a Sustainable Reductant Thiourea Dioxide. *Green Chem.* **2016**, *18* (23), 6215–6221. https://doi.org/10.1039/C6GC02444K.
(54) Thomas, S. I.; Falvey, D. E. N,N-Di(4-Halophenyl)Nitrenium Ions: Nucleophilic Trapping, Aromatic Substitution, and Hydrogen Atom Transfer. *J. Org. Chem.* **2007**, *72* (13), 4626–4634. https://doi.org/10.1021/jo062578i.
(55) Huang, Y.-Q.; Song, H.-J.; Liu, Y.-X.; Wang, Q.-M. Dehydrogenation of N-Heterocycles by Superoxide Ion Generated through Single-Electron Transfer. *Chem. – Eur. J.* **2018**, *24* (9), 2065–2069. https://doi.org/10.1002/chem.201705202.
(56) Loeppky, R. N.; Elomari, S. N-Alkyl-N-Cyclopropylanilines as Mechanistic Probes in the

Nitrosation of N,N-Dialkyl Aromatic Amines. *J. Org. Chem.* **2000**, *65* (1), 96–103. https://doi.org/10.1021/jo991104z.
(57) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A. Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian16, 2016.
(58) Becke, A. D. Density-functional Thermochemistry. III. The Role of Exact Exchange. *J. Chem. Phys.* **1993**, *98* (7), 5648–5652. https://doi.org/10.1063/1.464913.
(59) Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti Correlation-Energy Formula into a Functional of the Electron Density. *Phys. Rev. B* **1988**, *37* (2), 785–789. https://doi.org/10.1103/PhysRevB.37.785.
(60) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. A Consistent and Accurate Ab Initio Parametrization of Density Functional Dispersion Correction (DFT-D) for the 94 Elements H-Pu. *J. Chem. Phys.* **2010**, *132* (15), 154104. https://doi.org/10.1063/1.3382344.
(61) Weigend, F.; Ahlrichs, R. Balanced Basis Sets of Split Valence, Triple Zeta Valence and Quadruple Zeta Valence Quality for H to Rn: Design and Assessment of Accuracy. *Phys. Chem. Chem. Phys.* **2005**, *7* (18), 3297–3305. https://doi.org/10.1039/B508541A.
(62) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B* **2009**, *113* (18), 6378–6396. https://doi.org/10.1021/jp810292n.

Graphical Abstract: