Migratory aptitudes in rearrangements of destabilized vinyl cations

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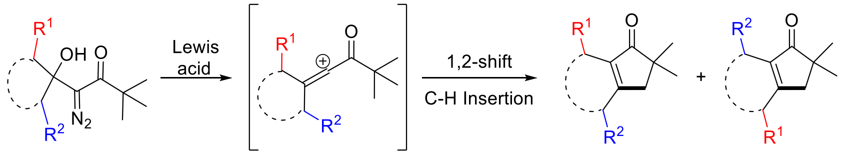
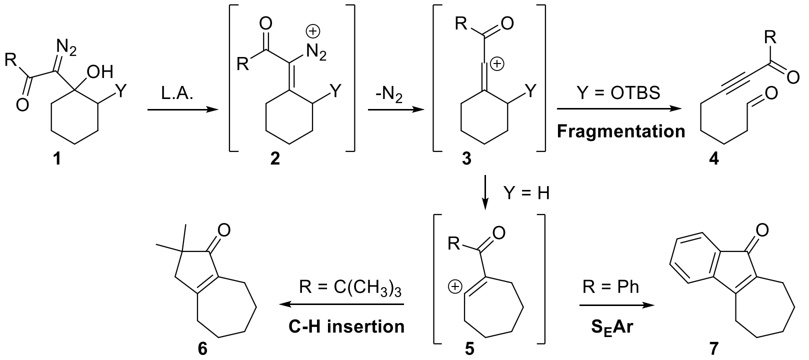
Abstract

The Lewis acid-promoted generation of destabilized vinyl cations from β-hydroxy diazo ketones leads to an energetically favorable 1,2-shift across the alkene followed by an irreversible C-H insertion to give cyclopentenone products. This reaction sequence overcomes typical challenges of counter ion trapping and rearrangement reversibility of vinyl cations and has been used to study the migratory aptitudes of non-equivalent substituents in an uncommon $C(sp^2)$ to C(sp) vinyl cation rearrangement. The migratory aptitude trends were consistent with those observed in other cationic rearrangements; the substituent that can best stabilize a cation more readily migrates. However, DFT calculations show that the situation is more complex. Selectivity in the formation of one conformational isomer of the vinyl cation, and facial selective migration across the alkene due to an electrostatic interaction between the vinyl cation and the adjacent carbonyl oxygen work in concert to determine which group migrates. This study provides valuable insight for predicting migration preferences when applying this methodology to the synthesis of structurally complex cyclopentenones that are differentially substituted at the α and β positions.



Introduction

Although vinyl cations have been studied for over 60 years, a lack of methods to generate these highly reactive intermediates has hindered the development of general, synthetically useful reactions.[1,2] However, the recent realization of milder ways to form vinyl cations has led to renewed interest in their reactivity.[3-10] For example, our group has taken advantage of vinyl cations to develop a ring fragmentation reaction,[11-14] as well as methods to form cyclopentenones[15,16] and indenones[17] (Scheme 1). These reactions take advantage of Padwa and Pellicciari's finding that vinyl cations are formed when β-hydroxy-α-diazo carbonyl compounds are treated with a Lewis acid.[4] As shown in Scheme 1, the Lewis acid facilitates the loss of the β-hydroxy group to give vinyl diazonium **2**, which spontaneously loses molecular nitrogen to yield exocyclic vinyl cation **3**. If an electron releasing group is present in the γ-position (e.g. **3**, Y = OTBS), a Grob-like fragmentation ensues which leads to an aldehyde tethered ynone (**4**).[18] Compounds that lack an electron releasing group do not fragment, but instead undergo a 1,2-shift across the alkene to give a second vinyl cation (**5**). This rearrangement is energetically favorable because the electron withdrawing carbonyl group destabilizes cation **3**.[4,16] Depending on the structure of the ketone, vinyl cation **5** can then participate in an intramolecular C-H insertion reaction to give a cyclopentenone (**6**), or an electrophilic aromatic substitution reaction to give an indenone (**7**).



Scheme 1. Reactions of vinyl cations.

Cyclopentenones, indanones, and their derivatives are important motifs found in biologically active compounds and natural products, which tend to be structurally complicated molecules (Figure 1).[19,20] In order for these vinyl cation reaction sequences to be useful strategies for complex molecule synthesis, it is important to be able to predict the migratory aptitude of different groups in the 1,2-shift in systems that are not symmetric (e.g. **3**, Y = alkyl, aryl). While many studies have looked at the migratory aptitudes of various groups in cationic rearrangements that involve migrations from sp^3 centers to sp^3 centers, migrations across the alkene of vinyl cations are unique in that they involve $C(sp^2)$ and C(sp) centers and should show different stereoelectronic effects. To date, the majority of studies involving vinyl cation rearrangements have focused on the migratory aptitude of aryl rings,[21] and few have involved destabilized vinyl cations such as **3**.[22]

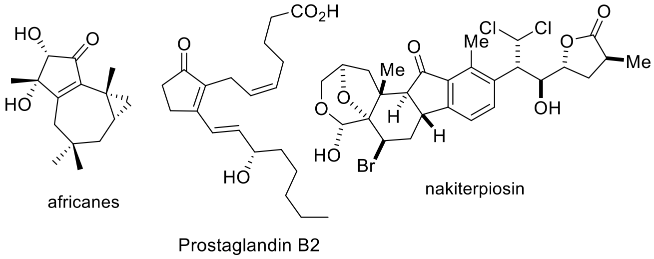
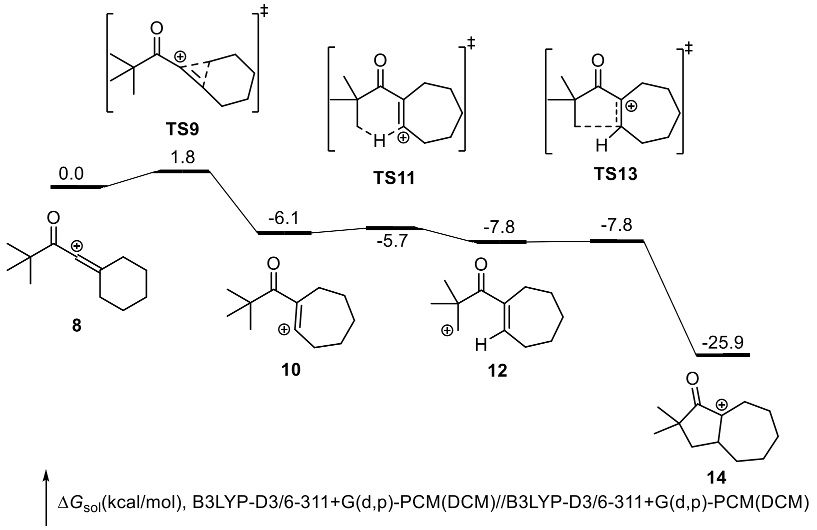


Figure 1. Representative examples of biologically active cyclopentenones and indanones

We recently reported DFT calculations of the energy profile of the transition metal-free rearrangement and C-H insertion reaction of vinyl cations.[16] As shown in Scheme 2, the energy barrier for the 1,2-shift of vinyl cation **8** to vinyl cation **10** is only 1.8 kcal/mol, and **10** is 6.1 kcal/mol lower in energy than **8**. The subsequent C-H insertion has an energy barrier of only 0.4 kcal/mol leading to a product that is 19.8 kcal/mol more stable. In view of these low energy barriers, the rearrangement and insertion steps are likely kinetically controlled and irreversible. As such, this reaction sequence constitutes a good platform to study the migratory aptitude of nonequivalent groups across the alkene of destabilized vinyl cations. Herein we report results of experimental and computational studies that define the relative migratory aptitudes of various alkyl and aryl groups in this rearrangement step.

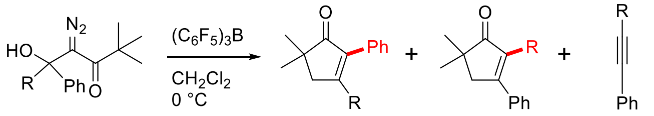


Scheme 2. Calculated energy profile of the rearrangement and C-H insertion of a vinyl cation

Results and discussion

We began our studies by comparing the migratory aptitude of aryl rings to alkyl groups. In optimizing the conversion of diazo ketones to cyclopentenones, we determined that treating the diazo ketone with 1 equiv of tris(pentafluorophenyl)borane (BCF; $(C_6F_5)_3B$) in CH_2Cl_2 at 0 °C gave good results,[15] and these conditions were used for our present studies without further attempts at optimization. Product ratios of the regioisomeric cyclopentenones were determined from isolated yields of the products, or by ^{1}H NMR of the crude reaction mixtures using 1,3,5-trimethoxybenzene as an internal standard.

The initial vinyl cation precursor we targeted was β-hydroxy-α-diazoketone **15a** (Scheme 3), which we prepared by adding lithiated 1-diazo-3,3-dimethylbutan-2-one to acetophenone. Treating **15a** with BCF gave the known[23] regioisomeric cyclopentenones **16a** and **17a** in 16% and 2% yield respectively, as determined by NMR spectroscopy of the crude reaction mixture. The 8 : 1 product ratio favoring phenyl group migration is consistent with the Baeyer-Villiger and pinacol-pinacolone rearrangements, and can be rationalized by the intermediacy of a phenonium species.[24] It is not clear why the cyclopentenone products are formed in such low yields in this case, but 1-phenyl-1-propyne (**18a**) was also observed in the crude reaction mixture in 7% yield. This latter product, which is fairly volatile and may have been produced in higher quantities, could form from the vinyl cation intermediate by bond fragmentation giving the alkyne and an acylium ion, which is the reverse of the first step of the Friedel-Crafts acylation of an alkyne. Cyclic systems, such as those we have previously studied, are unlikely to suffer this side reaction as it would lead to a highly strained cycloalkyne. Ethyl analog **15b** gave phenyl migration product **16b** in 30% yield, with an additional 27% yield of alkyne **18b**. The product of ethyl migration (**17b**) was not identified in the crude reaction mixture.



15a, R = Me
15b, R = Et

16a; 16%[a]
16b; 30%[a]

17a; 2%[a]
17b; Not Observed

18a; 7%[a]
18b; 27%[a]

[a] Determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.
Group that migrated is colored red.

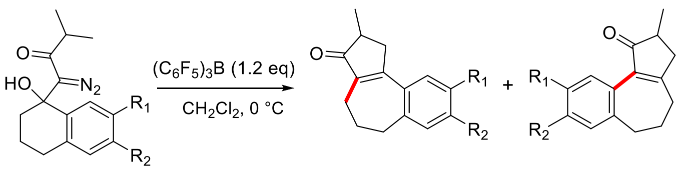
Scheme 3. Migratory competition between phenyl and alkyl groups.

We next turned our attention to tetralone systems. The Baeyer-Villiger oxidation of tetralone results in selective migration of the aryl ring.[25,26] However, Baeyer-Villiger oxidation involves migration between adjacent sp^3 centers, whereas the vinyl cation rearrangement involves migration from an sp^2 center to an sp center. Because the vinyl cation is coplanar with the migrating group, the stereoelectronic arrangement is different than that of the Baeyer-Villiger reaction; the tetralone aromatic π system would be nearly perpendicular to the vacant p-orbital of the vinyl cation and a phenonium intermediate should not form. As such the reaction would be a more direct comparison of the migratory aptitude of an sp^2 center vs an sp^3 center.

Adding a lithiated diazo ketone to tetralone was not trivial; the standard reaction conditions gave no desired product. After extensive optimization, we found that addition product **19a** could be isolated when lithiated 1-diazo-3-methylbutan-2-one was added to tetralone in a 3.5 : 1 mixture of hexane and THF as solvent. Interestingly, treating this material with BCF gave exclusive migration of the alkyl carbon to give cyclopentanone **20a** as the major product in 27% yield as determined by NMR spectroscopy of the crude complex reaction mixture. The regioisomeric product derived from aryl ring migration (**21a**) was not observed. In migrations to cationic centers, the group that can better stabilize a cation tends to migrate more readily.[27] In this case, preferential migration of the methylene carbon may be rationalized by considering the differing electronegativities of

sp^2 and sp^3 hybridized atoms. Centers that are sp^2 hybridized are more electronegative and, unless they can form a stabilized intermediate such as a phenonium ion, should be less likely to migrate.

We continued these studies by preparing the substituted tetralone derivatives shown in Scheme 4. In each case, Lewis acid treatment returned complex mixtures. Proton NMR spectroscopy of the crude reaction mixtures revealed that the tricyclic cyclopentenone compounds were the major products formed, and the yields shown in Scheme 4 are isolated yields. Not surprisingly, aryl rings with electron withdrawing substituents gave only products of methylene migration (Scheme 4, **19b-d**). However, an electron donating methoxy group para to the migrating atom promoted migration of the aryl ring. Substrate **20e** gave a 2.6 to 1 ratio of aryl to methylene migration products, showing that electron donating substituents can increase the migratory aptitude of sp^2 centers.



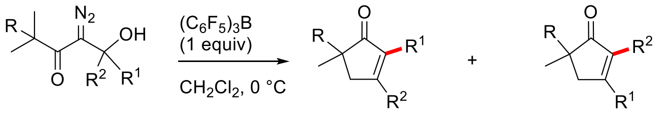
19a, R_1,R_2 = H	**20a**, 27%[a]	**21a**, Not Observed
19b, R_1 = H; R_2 = NO_2	**20b**, 37%[b]	**21b**, Not Observed
19c, R_1 = NO_2; R_2 = H	**20c**, 29%[b]	**21c**, Not Observed
19d, R_1 = H; R_2 = Br	**20d**, 26%[b]	**21d**, Not Observed
19e, R_1 = H; R_2 = OMe	**20e**, 14%[b]	**21e**, 37%[b]

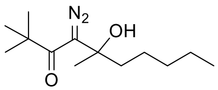
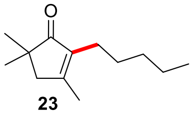
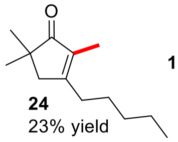
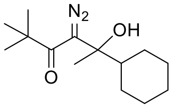
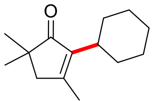
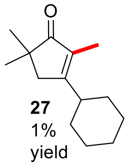
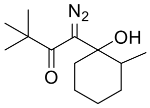
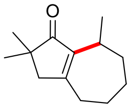
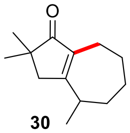
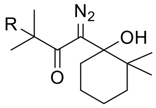
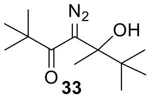
[a] Determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard; [b] isolated yield
Group that migrated is colored red.

Scheme 4. Migratory competition studies of tetralone based systems.

We next focused on comparing the migratory aptitude of various alkyl groups. The substrates shown in Table 1 were prepared for these competition experiments and were subjected to the standard C-H insertion conditions. In the competition between methyl and a 1° alkyl chain (**22**, pentyl, entry 1), migration of the alkyl chain was favored by 1.7 to 1 as determined by the NMR spectrum of the crude reaction mixture. However, cyclopentenone **23** proved difficult to purify and nearly equal quantities of **23** and **24** were isolated. Increasing the substitution to a 2° alkyl group (**25**, cyclohexyl, entry 2) led to an increase in relative migratory aptitude compared with methyl. In this case, the product of cyclohexyl migration (**26**) was formed in 16% yield while the product of methyl migration (**27**) was formed in only trace amounts (<5%). The major product of this reaction was prop-

1-yn-1-ylcyclohexane, which forms by fragmentation of the vinyl cation similar to compounds **15a** and **15b** (Scheme 3). To compare the relative migratory aptitude of 1° and 2° alkyl groups, we prepared diazo **28** from 2-methylcyclohexanone (entry 3). Treating this compound with BCF gave cyclopentenone **29**, formed by migration of the 2° alkyl group, in 50% yield with an additional 11% yield of a 1:1 mixture of **29** and **30** (entry 4). Attempts to isolate and characterize the minor isomer (**30**) from this reaction failed. However, **30** was isolated cleanly and fully characterized when $SnCl_4$ was used as the Lewis acid. With **30** characterized, we were able to determine by ^{1}H NMR spectroscopy of the crude mixture that $(C_6F_5)_3B$ gave **29** and **30** in a 4.4 : 1 ratio. All of these results are consistent with other cationic 1,2-rearrangements, wherein alkyl substituents that can best stabilize a positive charge in the transition state have higher migratory aptitudes.



Entry	α-diazo ketone	Product **a** isolated yield	Product **b** isolated yield	NMR ratio[a] **a : b**
1	 **22**	 **23** 21% yield	 **24** 23% yield	**1.7 : 1**
2	 **25**	 **26** 16% yield	 **27** 1% yield	**~16 : 1**
3	 **28**	 **29** 50% yield	 **30** 6% yield	**4.4 : 1**
4	 **31** R = Me **32** R = H	no reaction		
5	 **33**	no reaction		

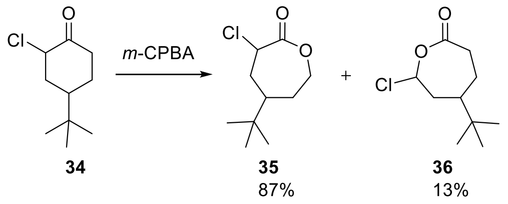
[a] Regiomeric ratio, determined from ^{1}H NMR integrations of crude reaction.
Group that migrated is colored red.

Table 1. Migratory competition between alkyl groups.

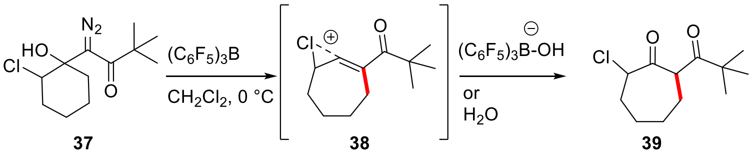
With these results in mind, we would expect a 3° alkyl group to migrate more readily than a 1° alkyl group. However, diazo ketones **31** and **32** (entry 4), and the slightly less sterically hindered **33** (entry 5), did not react with $(C_6F_5)_3B$. As only starting material was returned from these reactions, it appears that steric crowding around the β-hydroxy group may prevent Lewis acid coordination and vinyl cation formation. Less bulky Lewis acids ($SnCl_4$ and BF_3•OEt_2) were tested, but these also failed to promote a reaction.

α-Chloro ketones are known to exhibit a strong preference for migration of the non-halogenated alkyl group in the Baeyer-Villiger reaction. For example, **34** reacted with *m*-CPBA to give α-chlorolactone **35** as the major product (87%, Scheme 5a).[28] To test if a similar trend holds for the rearrangement of vinyl cations, γ-chloro-β-hydroxy-α-diazo ketone **37** was prepared and treated with $(C_6F_5)_3B$. In this case, we were surprised to isolate dione **39** as the major product (45% yield, Scheme 5b) in place of the expected cyclopentenone products that would form by the C-H insertion sequence. Diketone **39** could form directly from **37** by an acid catalyzed rearrangement, but this seems unlikely as we have only observed that type of reactivity when protic acids are present.[17] Alternatively, if diazo **37** reacts with BCF to give the destabilized vinyl cation and the non-halogenated carbon migrates as expected, then vinyl cation **38** would be formed. This cation could be stabilized by the adjacent chlorine via a chloronium-type intermediate, which should slow the C-H insertion reaction and allow competitive addition of water to give dione **39**.

a. Baeyer-Villiger oxidation reported by Grein *et al.*[28]



b. Vinyl cation rearrangement (this work)



Group that migrated is colored red.

Scheme 5. Migratory aptitude of a chloro-containing substituent.

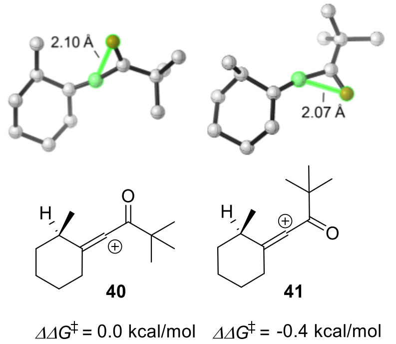


Figure 2. DFT-optimized structures of the vinyl cation conformational isomers **40** and **41**. All hydrogens are omitted for clarity.

To gain a better understanding of what factors control the selectivity of the migration step, we studied the reaction of diazo ketone **28** computationally. The vinyl cation derived from **28** can adopt two conformational isomers (**40** and **41**, Figure 2) that have nearly identical energies and that benefit from an electrostatic interaction between the carbonyl oxygen and the cationic carbon. From these intermediates, the migration step could occur from the group that is either cis or trans to the carbonyl, or both. Importantly, for the unsubstituted cyclohexane based system we observed that the group that is cis to the carbonyl oxygen migrates irreversibly across the alkene via **TS2** (Figure 3), with an energy barrier that is 6.9 kcal/mol lower than that for the group trans to the carbonyl oxygen (**TS1**).

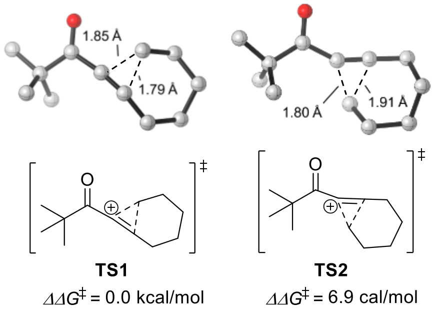
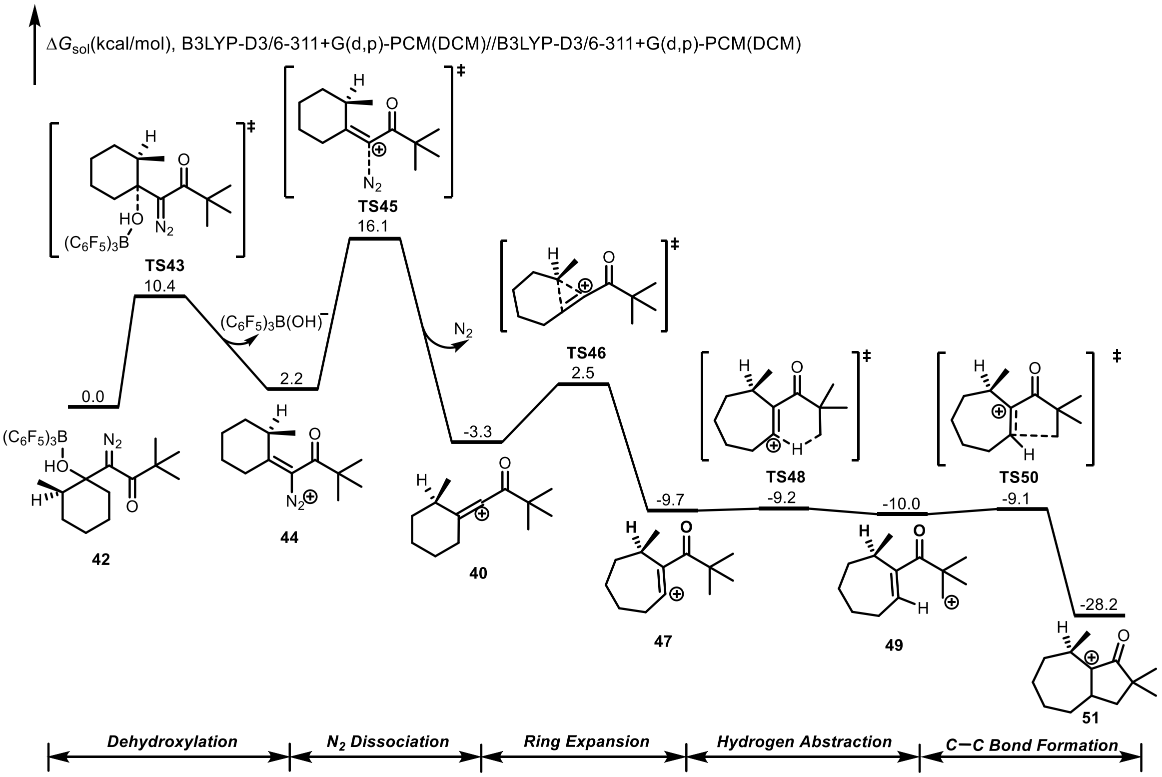
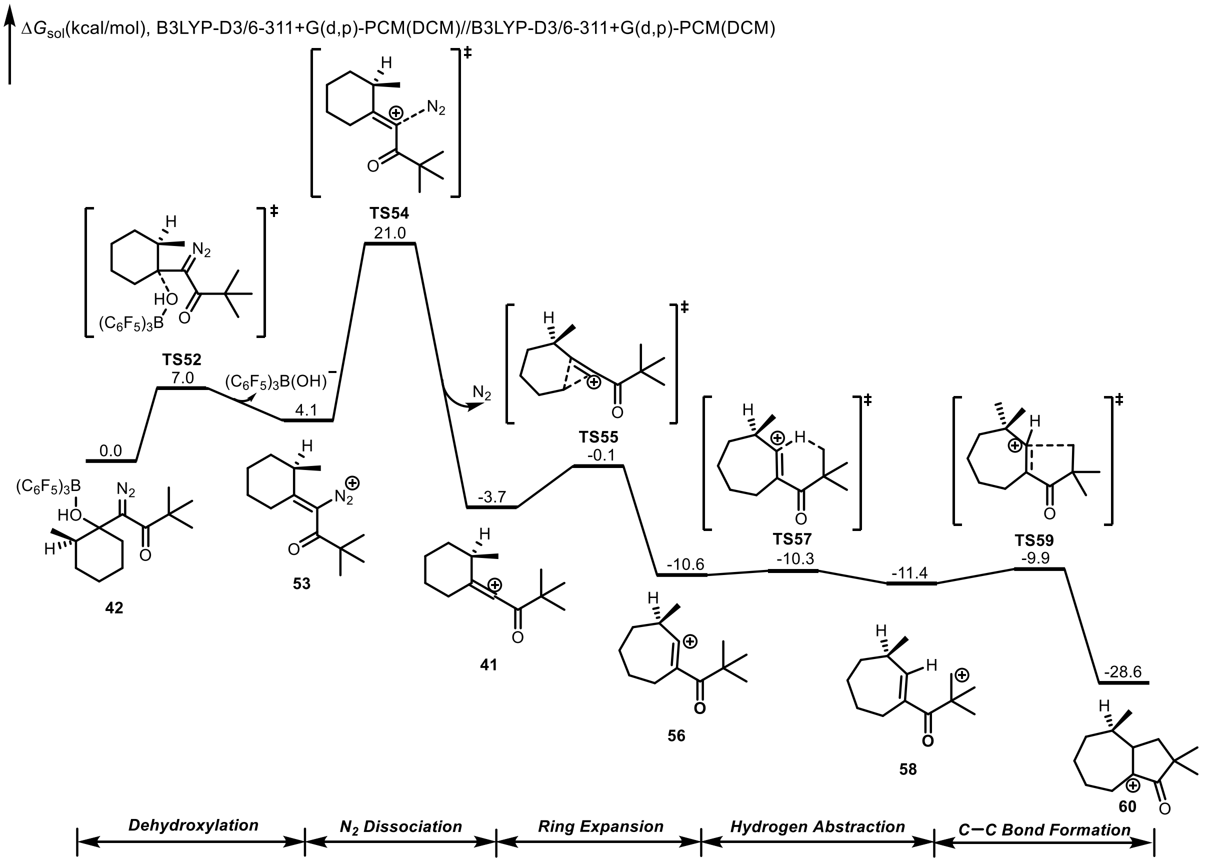


Figure 3. DFT-calculated transitions states for migration across the alkene in cyclohexane based system. All hydrogens are omitted for clarity.

This large energy difference, which is presumably due to the electrostatic interaction, means that the vinyl cation isomers **40** and **41** would react to give different products; isomer **40** would give **29** while isomer **41** would give **30**. Our initial supposition was that the isomerization between isomers **40** and **41** would have a low energy barrier and the outcome of the reaction would be controlled by the energy barriers of the competitive irreversible migrations. However, computational modeling showed that the less substituted group migrates with a lower energy barrier than the more substituted group (3.6 kcal/mol for **41** to **56** and 5.8 kcal/mol for **40** to **47**, Schemes 6 and 7). The difference in energy is presumably due to a steric interaction between the carbonyl oxygen and the bulkier migrating group in **TS46** (Scheme 6). Based on these results, the major product of the reaction would be expected to be **30** rather than the observed **29**. With this in mind, we performed a more comprehensive computational study of the reaction paths leading to cyclopentenones **29** and **30**.



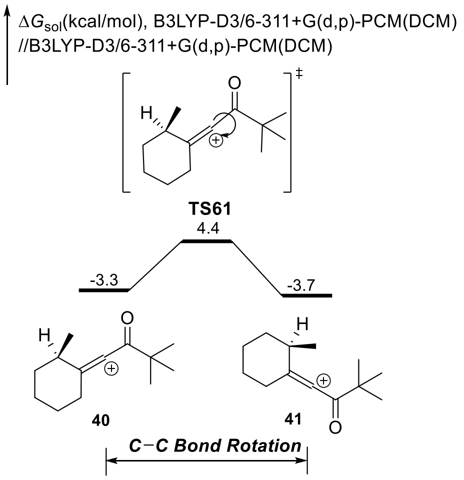
Scheme 6. DFT-computed Gibbs free energy barriers for the reaction pathway leading to the major product.



Scheme 7. DFT-computed Gibbs free energy barriers for the reaction pathway leading to the minor product.

The initial step of this sequence, the Lewis acid mediated loss of the β-hydroxy group from **42**, leads to two diastereomeric vinyl diazonium salts (**44** and **53**, Schemes 6 and 7), which cannot isomerize by direct rotation. However, this dehydroxylation step is reversible and thus **44** and **53** are in equilibrium. The (*E*)-isomer (**44**) is 1.9 kcal/mol lower in energy than the (*Z*)-isomer (**53**). This difference in stability is presumably due to allylic 1,3-strain between the linear diazo group and the methyl in **53**. Loss of nitrogen to form the vinyl cations is the rate limiting step in these sequences. Importantly, the energy barrier for N_2 loss is 4.9 kcal/mol lower for the (*E*)-isomer of the vinyl diazonium salt (**44**) than (*Z*)-isomer **53** (**TS45** vs. **TS54**). This energy difference would lead to the preferential formation of vinyl cation conformational isomer **40**. Importantly, as shown in Scheme 8, isomerization of **40** to **41** via **TS61** has a higher energy barrier (7.7 kcal/mol) than irreversible migration across the alkene via **TS46** (5.8 kcal/mol) to give vinyl cation **47**. Once **47** is formed, it would undergo a fast insertion to give cyclopentenone **29**. The competing formation of the minor product (**30**) suggests that a small portion of vinyl cation

40 isomerizes to **41**, which would rearrange and insert. Thus cyclopentenone **29** is formed as the major product because diazonium salt **44** loses nitrogen to give vinyl cation **40** more easily than the alternative isomer that suffers from allylic 1,3-strain. At this point, it is not clear if linear or tetralone based systems have similar control elements, and further computational studies will be needed to clarify this point.



Scheme 8. DFT-computed Gibbs free energy barrier for interconversion of vinyl cation isomers.

Conclusion

The relative migratory aptitudes of various alkyl and aryl groups in the 1,2-shift across the alkene of destabilized vinyl cations has been assessed. Qualitatively, the substituent that best stabilizes the cation had the higher aptitude for migration. However, DFT calculations show that in cyclohexanone based systems the observed migratory aptitude is due to conformational biases rather than transition state stabilization. An aryl ring migrated in preference to an alkyl group if a phenonium intermediate could form. Conversely, in tetralone systems that have electron neutral or electron poor aryl rings, the alkyl group migrated in preference to the aryl ring. In these cases, the vacant orbital of the vinyl cation is coplanar with the migrating group, which prevents the formation of a phenonium intermediate, and the less electronegative sp^3 hybridized atom migrated in preference to the more electronegative sp^2 center. However, incorporating an electron releasing methoxy group at the para position of the tetralone aryl ring increased the migratory aptitude of the aryl group, and in this case both the product of aryl migration and alkyl migration were isolable with a preference for aryl migration. Further computational studies will determine if steric interactions play a role in these outcomes. In the migratory competition between two alkyl groups, the more electron-rich group migrated with a higher aptitude. For example, a 1° or 2° alkyl group migrated in preference to methyl, and a 2° alkyl group migrated in preference to a 1° alkyl group. Systems that contained a 3° alkyl group adjacent to the β-hydroxy group failed to react, presumably because of steric hindrance. Finally, incorporating a halogen adjacent to the β-hydroxy group led to a dione product. In this case, after migration of the unsubstituted side, neighboring group participation may slow the C-H insertion step, allowing water to capture the vinyl cation. Systems where the product of rearrangement was an endocyclic vinyl cation led to higher yields of insertion products. This is due to the tendency of linear β-keto vinyl cations to fragment giving alkyne products prior to insertion. These migratory aptitude studies provide further insight into the reactivity of destabilized vinyl cations and will facilitate the use of these electron deficient intermediates in more complex molecule synthesis.

EXPERIMENTAL SECTION

General Information. All reactions were performed under an atmosphere of nitrogen in flame-dried glassware. Solvents were removed in vacuo using a rotary evaporator attached to a dry vacuum pump. Tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were dried via a solvent dispensing system, hexane was distilled before use, and when used as a reaction solvent it was also dried over 4 Å molecular sieves. Diisopropylamine (*i*Pr_2NH) was freshly distilled from CaH_2 prior to use. 1-Diazo-3,3-dimetylbutan-2-one[29] and 1-diazo-3-methylbutan-2-one[30] were prepared following known procedures. All other commercially available reagents were used without further purification. Flash column chromatography was performed on a CombiFlash Rf 150 system using silica columns. TLC analysis was carried out using silica on glass plates. Visualization of TLC plates was achieved using ultraviolet light and ceric ammonium molybdate. ^1H, $^{13}C\{^1H\}$, $^1H{-}^{13}C$ HMBC, and ^1H NOE NMR spectroscopic data was collected at room temperature on a 500 MHz spectrometer in $CDCl_3$. ^1H NMR chemical shifts are reported in ppm (δ units) downfield from tetramethylsilane, and $^{13}C\{^1H\}$ NMR spectra are referenced to the $CDCl_3$ signal at 77.0 ppm. Exact mass analysis was performed on a Waters Xevo G2-XS LCMS-QTOF operated in positive ESI mode.

General Procedure A: Preparation of β-hydroxy-α-diazo ketones. A –78 °C solution of LDA (1.5 equiv) [prepared by adding *n*-butyllithium in hexanes (1.5 equiv) to a solution of *i*Pr$_2$NH (1.7 equiv) in THF (3 mL per mmol of *n*-butyllithium)] was added dropwise over 30 min down the side of a chilled (–78 °C) flask containing a solution of ketone (1 equiv) and α-diazo ketone (1.6 equiv) in THF (3 mL per mmol of ketone) under an atmosphere of nitrogen. The mixture was maintained at –78 °C until complete conversion was achieved as monitored by TLC (typically 30 min). AcOH (0.5M in THF, 1.6 equiv.) was added, the reaction flask was removed from the cold bath and water (10 mL) was added. The layers were separated and the aqueous layer was extracted three times with EtOAc (15 mL). The organic layers were combined, washed with saturated aqueous NaHCO$_3$ (50 mL), brine (50 mL), and dried over anhydrous CaCl$_2$. The solvent was removed in vacuo to give an oily residue that was subjected to flash silica gel chromatography to afford the desired β-hydroxy-α-diazo ketone.

General Procedure B: Preparation of β-hydroxy-α-diazo ketones of tetralone derivatives. A –78 °C solution of LDA (1.5 equiv) [prepared by adding *n*-butyllithium in hexanes (1.5 equiv) to a solution of *i*Pr$_2$NH (1.7 equiv) in dry hexanes (3 mL per mmol of *n*-butyllithium)] was added dropwise over 10 min down the side of a chilled flask containing a cold (–78 °C) solution of ketone (1 equiv) and α-diazo ketone (1.6 equiv) in dry hexanes (3 mL per mmol of *n*-butyllithium) and dry THF (2.5 mL per mmol of ketone) under an atmosphere of nitrogen. The mixture was maintained at –78 °C for 45 minutes. One equiv. of AcOH in hexanes (16.4 mL per mmol AcOH) was added to the dark red reaction at -78 °C under nitrogen at which point the mixture became yellow. The reaction flask was removed from the cold bath and allowed to warm to room temperature. The reaction mixture was poured into a separatory funnel containing water (50 mL), the layers were separated, and the aqueous layer was extracted three times with EtOAc (15 mL). The organic layers were combined, washed with saturated aqueous NaHCO$_3$ (50 mL), brine (50 mL), and dried over anhydrous CaCl$_2$. The solvent was removed in vacuo to provide an oily residue that was subjected to flash silica gel chromatography to afford the desired β-hydroxy-α-diazo ketone.

4-Diazo-5-hydroxy-2,2-dimethyl-5-phenylhexan-3-one (15a): Prepared from acetophenone (80 µL, 0.69 mmol) and 1-diazo-3,3-dimetylbutan-2-one (136 mg, 1.08 mmol) following General Procedure A with the modification that dry hexanes were used in place of THF as the solvent. Unreacted acetophenone was removed under high vacuum overnight. Further purification of the crude material using silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) afforded 53 mg (31% yield) of the title compound as a yellow solid: $R_f = 0.62$ (4:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, $J = 7.5$ Hz, 2H), 7.33 (t, $J = 7.4$ Hz, 2H), 7.25 (t, $J = 7.6$ Hz, 1H), 5.24 (s, 1H), 1.61 (s, 3H), 1.22 (s, 9H); $^{13}C\{^1H\}$ (125 MHz, $CDCl_3$): δ 202.1, 147.1, 128.4, 127.4, 124.3, 75.1, 69.4, 44.6, 28.9, 26.3. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{18}N_2O_2Na$ 269.1266; Found: 269.1263.

4-Diazo-5-hydroxy-2,2-dimethyl-5-phenylheptan-3-one (15b): Prepared from propiophenone (240 µL, 1.80 mmol) and 1-diazo-3,3-dimethylbutan-2-one (363 mg, 2.88 mmol) following General Procedure A with the modification that the reaction was quenched with 1 equiv of AcOH in THF (16.4 mL per mmol AcOH). The crude yellow oil was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 15% EtOAc), the desired compound was isolated, then resubjected to silica gel flash chromatography (hexanes/CH_2Cl_2, gradient elution 0 to 30% CH_2Cl_2) to give 158 mg (34% yield) of the title compound as a bright yellow oil which solidified upon standing in freezer: $R_f = 0.61$ (4:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41-7.37 (m, 2H), 7.35-7.30 (m, 2H), 7.27-7.23 (m, 1H), 5.34 (s, 1H), 1.98 (dq, $J = 14.7$, 7.4 Hz, 1H), 1.77 (dqd, $J = 14.8$, 7.4, 1.2 Hz, 1H), 1.20 (s, 9H), 0.86 (t, $J = 7.3$ Hz, 3H); ^{13}C $\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 202.6 145.6, 128.2, 127.3, 125.0, 77.2, 69.4, 44.7, 33.4, 26.3, 7.6. HRMS (ESI-TOF) m/z: $[M + K]^+$ Calcd for $C_{15}H_{20}N_2O_2K$ 299.1162; Found 299.1147.

1-Diazo-1-(1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methylbutan-2-one (19a): Prepared from tetralone (150 µL, 1.13 mmol) and 1-diazo-3-methyl-2-butanone (203 mg, 1.81 mmol) following General Procedure B. The crude orange solid was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 9% EtOAc), the desired compound was isolated, then resubjected to silica gel flash chromatography (hexanes/CH_2Cl_2, gradient elution 0 to 100% CH_2Cl_2) to give 144 mg (43% yield) of the title compound as a bright yellow solid: R$_f$ = 0.50 (4:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.65 (d, *J* = 7.8 Hz, 1H), 7.27-7.18 (m, 2H), 7.10 (d, *J* = 7.2 Hz, 1H), 5.26 (s, 1H), 2.88-2.73 (m, 3H), 2.51-2.40 (m, 1H), 2.07 (td, *J* = 11.9, 2.8 Hz, 1H) 2.03-1.93 (m, 1H), 1.77-1.64 (m, 1H), 1.15 (d, *J* = 6.8 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 200.6, 137.4, 136.4, 129.1, 128.5, 127.4, 126.8, 74.1, 72.9, 37.6, 36.7, 29.1, 20.4, 18.8, 18.4. HRMS (ESI-TOF) m/z: [M + K]$^+$ Calcd for $C_{15}H_{18}N_2O_2K$ 297.1005; Found 297.0991.

1-Diazo-1-(1-hydroxy-6-nitro-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methylbutan-2-one (19b): Prepared from 6-nitro tetralone (262 mg, 1.37 mmol) and 1-diazo-3-methyl-2-butanone (246 mg, 2.19 mmol) following General Procedure B. The crude orange solid was purified using silica gel flash chromatography (hexanes/CH$_2$Cl$_2$, gradient elution 0 to 100% CH$_2$Cl$_2$) to give 161 mg (39% yield) of the title compound as a bright yellow solid: R$_f$ = 0.29 (3.7:1 hexane/EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.07 (dd, *J* = 8.7, 2.3 Hz, 1H), 8.00 (d, *J* = 2.0 Hz, 1H), 7.86 (d, *J* = 8.7 Hz, 1H), 5.32 (s, 1H), 2.95-2.89 (m, 2H), 2.83 (hept, *J* = 6.8 Hz, 1H), 2.51 (ddd, *J* = 13.2, 6.6, 2.3 Hz, 1H), 2.13-2.02 (m, 2H), 1.83-1.72 (m, 1H), 1.17 (d, *J* = 6.8 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 200.5, 147.7, 143.5, 139.4, 129.0, 124.2, 121.7, 73.5, 72.0, 36.9, 29.1, 19.9, 18.8, 18.4. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{15}H_{17}N_3O_4Na$ 326.1117; Found 326.1119.

1-Diazo-1-(1-hydroxy-7-nitro-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methylbutan-2-one (19c): Prepared from 7-nitro tetralone (229 mg, 1.20 mmol) and 1-diazo-3-methyl-2-butanone (216 mg, 1.93 mmol) following General Procedure B. The crude orange brown oil was purified using silica gel flash chromatography (hexanes/CH$_2$Cl$_2$, gradient elution 0 to 90% CH$_2$Cl$_2$), the desired compound was isolated, then resubjected to silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 14% EtOAc) to give 90.5 mg (25% yield) of the title compound as a bright yellow solid: R$_f$ = 0.28 (3.7:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.55 (d, *J* = 2.3 Hz, 1H), 8.07 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 5.34 (s, 1H), 2.94-2.89 (m, 2H), 2.84 (hept, *J* = 6.8 Hz, 1H), 2.51 (ddd, *J* = 13.1, 6.5, 2.5 Hz, 1H), 2.12-2.02 (m, 2H), 1.82-1.72 (m, 1H), 1.17 (app t, *J* = 6.5 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 200.5, 147.1, 145.2, 138.5, 130.4, 123.2, 73.4, 72.1, 36.9, 36.9, 29.2, 19.8, 18.9, 18.4. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{17}N_3O_4Na$ 326.1117; Found 326.1111.

1-(6-Bromo-1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-1-diazo-3-methylbutan-2-one (19d): Prepared from 6-bromo tetralone (90.9 mg, 0.40 mmol) and 1-diazo-3-methyl-2-butanone (75.8 mg, 0.68 mmol) following General Procedure B. The crude orange solid was purified using silica gel flash chromatography (hexanes/CH_2Cl_2, gradient elution 0 to 50 to 60% CH_2Cl_2) to give 67.8 mg (50% yield) of the title compound as a bright yellow solid: $R_f = 0.53$ (100% CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): δ 7.53 (d, J = 8.4 Hz, 1H), 7.37 (dd, J = 8.5, 2.1 Hz, 1H), 7.28 (d, J = 2.0 Hz, 1H), 5.27 (s, 1H), 2.87-2.70 (m, 3H), 2.49-2.41 (m, 1H), 2.08-1.95 (m, 2H), 1.75-1.62 (m, 1H), 1.16 (d, J = 6.8 Hz, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 200.7, 139.8, 135.7, 132.0, 130.2, 129.4, 122.7, 73.8, 37.4, 36.9, 28.9, 20.3, 18.9, 18.5. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{17}BrN_2O_2Na$ 359.0371; Found 359.0365.

1-Diazo-1-(1-hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methylbutan-2-one (19e): Prepared from 6-methoxy tetralone (150 mg, 0.85 mmol) and 1-diazo-3-methyl-2-butanone (156 mg, 1.39 mmol) following General Procedure B. The crude orange brown oil was purified using silica gel flash chromatography (hexanes/CH_2Cl_2, gradient elution 0 to 75% CH_2Cl_2) to give 58.5 mg (24% yield) of the title compound as a bright yellow solid: $R_f = 0.42$ (3.7:1 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$): δ 7.56 (d, J = 8.7 Hz, 1H), 6.81 (dd, J = 8.8, 2.7 Hz, 1H), 6.60 (d, J = 2.4 Hz, 1H), 5.22 (s, 1H), 3.79 (s, 3H), 2.86-2.70 (m, 3H), 2.44 (ddd, J = 13.1, 6.5, 2.5 Hz, 1H), 2.05 (td, J = 12.6, 2.8 Hz, 1H), 2.02-1.93 (m, 1H), 1.74-1.63 (m, 1H), 1.16 (d, J = 6.8 Hz, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 200.6, 159.4, 139.1, 128.9, 113.3, 113.2, 73.9, 73.1, 55.3, 37.9, 36.8, 29.5, 20.6, 18.9, 18.4. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{20}N_2O_3Na$ 311.1372; Found 311.1370.

4-Diazo-5-hydoxy-2,2,5-trimethyldecan-3-one (22): Prepared from 2-heptanone (110 μL, 0.79 mmol) and 1-diazo-3,3-dimetylbutan-2-one (163 mg, 1.29 mmol) following General Procedure A. Purification of the crude material using silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 15% EtOAc) afforded 131 mg

(69% yield) of the title compound as a yellow solid: *R_f* = 0.58 (5:1 hexanes/ EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.92 (s, 1H), 1.80 (ddd, *J* = 13.8, 11.1, 4.7 Hz, 1H), 1.69 (ddd, *J* = 13.8, 11.0, 4.8 Hz, 1H), 1.38 (s, 3H), 1.36-1.25 (m, 6H), 1.23 (s, 9H), 0.88 (t, *J* = 6.7 Hz, 3H); $^{13}C\{^1H\}$ (125 MHz, $CDCl_3$): δ 202.8, 73.1, 67.5, 44.8, 41.4, 31.9, 26.5, 25.1, 24.2, 22.5, 14.0. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{24}N_2O_2Na$ 263.1735; Found 263.1732.

5-Cyclohexyl-4-diazo-5-hydroxy-2,2-dimethylhexan-3-one (25): Prepared from 1-cyclohexylethanone (140 μL, 1.00 mmol) and 1-diazo-3,3-dimetylbutan-2-one (243 mg, 1.64 mmol) following General Procedure A. Purification of the crude material using silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) afforded 121 mg (48% yield) of the title compound as a yellow solid: R_f = 0.63 (4:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.99 (s, 1H), 1.92-1.85 (m, 1H), 1.78 (tt, *J* = 12.2, 3.3 Hz, 1H), 1.77-1.69 (m, 2H), 1.65-1.53 (m, 2H), 1.22 (s, 3H), 1.19 (s, 9H), 1.17-1.11 (m, 2H), 1.10-0.89 (m, 3H); $^{13}C\{^1H\}$ (125 MHz, $CDCl_3$): δ 202.7, 75.8, 67.4, 47.9, 44.7, 28.6, 27.0, 26.6, 26.5, 26.42, 26.36, 20.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{25}N_2O_2$ 253.1916; Found 253.1923.

1-Diazo-1-(1-hydroxy-2-methylcyclohexyl)-3,3-dimethylbutan-2-one (28): Prepared from 2-methylcyclohexanone (100 μL, 0.82 mmol) with 1-diazo-3,3-dimethyl-2-butanone (165 mg, 1.31 mmol) following General Procedure A. Unreacted 2-methylcyclohexanone was removed under high vacuum to give the title compound in 33% yield as a yellow solid: R_f = 0.54 (5:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, CDCl3): δ 5.00 (s, 1H), 2.06-2.01 (m, 1H), 1.73-1.64 (m, 2H), 1.59-1.47 (m, 5H), 1.23 (s, 9H), 1.28-1.18 (m, 1H), 0.93 (d, *J* = 6.0 Hz, 3H); $^{13}C\{^1H\}$ (125 MHz, CDCl3): δ 203.1, 74.1, 67.8, 44.9, 37.8, 37.7, 30.0, 26.5, 25.5, 21.5, 16.1. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{22}N_2O_2Na$ 261.1579; Found 261.1576.

1-Diazo-1-(1-hydroxy-2,2-dimethylcyclohexyl)-3,3-dimethylbutan-2-one (31): Prepared from 2,2-dimethylcyclohexanone[3] (73 mg, 0.58 mmol) and 1-diazo-3,3-dimetylbutan-2-one (122 mg, 0.97 mmol) following General Procedure A. Silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 5% EtOAc) afforded 28 mg (19% yield) of the title compound as a yellow oil: R_f = 0.29 (5:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.53 (s, 1H), 1.86-1.62 (m, 4H), 1.53 (t, J = 17.6 Hz, 2H), 1.47-1.35 (m, 1H), 1.24 (s, 9H), 1.11 (d, J = 12.0 Hz, 1H), 0.95 (s, 3H), 0.85 (s, 3H); ^{13}C{^{1}H} (125 MHz, $CDCl_3$): δ 203.9, 44.9, 43.2, 36.1, 32.1, 26.5, 23.3, 21.4, 20.7. HRMS (ESI-TOF) m/z: [M]$^+$ Calcd for $C_{14}H_{23}O$ 207.1749; Found 207.1755

1-Diazo-1-(1-hydroxy-2,2-dimethylcyclohexyl)-3-methylbutan-2-one (32): Prepared from 2,2-dimethylcyclohexanone[3] (81 mg, 0.64 mmol) and 1-diazo-3-methylbutan-2-one (108 mg, 0.96 mmol) following General Procedure A. Unreacted 2,2-dimethylcyclohexanone was removed under high vacuum. Silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) afforded 26 mg (17% yield) of the title compound as a yellow oil: R_f = 0.59 (5:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.21 (s, 1H), 2.86 (hept, J = 6.8 Hz, 1H), 1.87-1.65 (m, 5H), 1.58-1.48 (m, 2H), 1.48-1.35 (m, 1H), 1.17 (d, J = 6.8 Hz, 3H), 1.12 (d, J = 6.8 Hz, 3H), 0.96 (s, 3H), 0.89 (s, 3H); ^{13}C{^{1}H} (125 MHz, $CDCl_3$): 202.1, 76.1, 68.8, 42.7, 36.5, 35.9, 32.3, 26.2, 23.3, 21.3, 20.6, 19.1, 18.2. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{13}H_{22}N_2O_2Na$ 261.1579; Found 261.1570.

4-Diazo-5-hydroxy-2,2,5,6,6-pentamethylheptan-3-one (33): Prepared from pinacolone (210 μL, 1.68 mmol) and 1-diazo-3,3-dimetylbutan-2-one (340 mg, 2.69 mmol) following General Procedure A. Purification of the crude material using silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) afforded 43 mg (11% yield) of the title compound as a yellow oil: R_f = 0.14 (5:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.43 (s, 1H), 1.40 (s, 3H), 1.25 (s, 9H), 0.95 (s, 9H); ^{13}C{^{1}H} (125 MHz, $CDCl_3$): δ 203.6, 78.1, 66.2, 45.0, 43.7, 26.6, 25.7, 21.9. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{12}H_{23}N_2O_2$ 227.1760; Found 227.1768.

1-(2-Chloro-1-hydroxycyclohexyl)-1-diazo-3,3-dimethylbutan-2-one (37): Prepared from 2-chlorocyclohexanone (95 mg, 0.70 mmol) and 1-diazo-3,3-dimetylbutan-2-one (143 mg, 1.13 mmol) following General Procedure A. Purification of the crude material using silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10%

EtOAc) afforded 143 mg (79% yield) of the title compound as a yellow solid: $R_f = 0.45$ (5:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.72 (dd, J = 11.9, 4.9 Hz, 1H), 3.36 (s, 1H), 2.10-1.94 (m, 4H), 1.79-1.72 (m, 1H), 1.68 (tt, J = 13.1, 4.0 Hz, 1H), 1.54-1.50 (m, 1H), 1.39 (qt, J = 13.1, 4.1 Hz, 1H), 1.22 (s, 9H); ^{13}C{^{1}H} (125 MHz, $CDCl_3$): δ 200.0, 72.9, 70.6, 64.9, 44.5, 35.1, 32.3, 26.5, 25.5, 20.6. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{19}ClN_2O_2Na$ 281.1033; Found 281.1029.

General Procedure C: Tris(pentafluorophenyl)borane-promoted cyclopentenone formation. A –15 °C solution of 0.1M diazo ketone (1 equiv) in CH_2Cl_2 was rapidly added to a –15 °C solution of 0.1M tris(pentafluorophenyl)borane (1 equiv) in CH_2Cl_2. The reaction mixture was kept at –15 °C for 10 min as gas evolved and the solution's color diminished. Saturated aqueous $NaHCO_3$ (20 mL) was added, and the biphasic layers were stirred for 30 minutes. The mixture was transferred to a separatory funnel with the aid of CH_2Cl_2 (10 mL). The layers were separated, and the aqueous layer was extracted three times with Et_2O (10 mL). The organic layers were combined, washed with water and brine, dried over $MgSO_4$ and filtered. If quantitative NMR was used to calculate yield, the internal standard was added to the filtrate and the solvent was removed under vacuum that did not exceed 125 mmHg. An NMR of the crude reaction mixture was taken, and the material was then purified by silica gel flash column chromatography.

General Procedure D: Tin(IV) chloride-promoted cyclopentenone formation. A 1M solution of $SnCl_4$ in CH_2Cl_2 (1 equiv) was added quickly as a stream to a –20 °C solution of diazo ketone (1 equiv) in CH_2Cl_2 (20 mL/mmol of diazo ketone). The bright yellow reaction mixture was stirred at –20 °C for 10 min while gas evolved and the solution's color diminished. Saturated aqueous $NaHCO_3$ (20 mL) was added and the mixture was transferred to a separatory funnel with the aid of 10 mL CH_2Cl_2. The layers were separated, and the aqueous layer was extracted three times with Et_2O (10 mL). The organic layers were combined, washed with water and brine, dried over $MgSO_4$ and filtered. If quantitative NMR was used to calculate yield, a known quantity of the internal standard was added to the filtrate and the solvent was removed under a vacuum that did not exceed 125 mmHg. An NMR of the crude reaction mixture was taken, and the material was then purified by silica gel flash column chromatography.

3,5,5-Trimethyl-2-phenylcyclopent-2-enone (16a),[23] 2,5,5-trimethyl-3-phenylcyclopen-2-enone (17a),[23] and **prop-1-yn-1-ylbenzene (18a):[31]** Prepared by subjecting diazo ketone **15a** to 1 equivalent of tris(pentafluorophenyl)borane following General Procedure C. Yields of the title compounds (16%, 2 %, and 7%, respectively) were determined using quantitative ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. ^{1}H NMR values for **16a**, **17a** and **18a** matched those previously reported.[23,31]

*3-Ethyl-5,5-dimethyl-2-phenylcyclopent-2-en-1-one **(16b)** and but-1-yn-1-ylbenzene **(18b)***: Prepared by subjecting β-hydroxy-α-diazo ketone **15b** (64.8 mg, 0.25 mmol) to General Procedure C with the modification that the aqueous layer was extracted 4 times with CH_2Cl_2 (10 mL) instead of Et_2O. The yield of the title compounds was determined using quantitative ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene (41.8 mg, 0.25 mmol) as an internal standard. Cyclopentenone **16b** was formed in 30% yield and alkyne **18b** was formed in 27% yield.

3-Ethyl-5,5-dimethyl-2-phenylcyclopent-2-en-1-one (16b): R_f = 0.51 (4:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (t, J = 7.6 HZ, 2H), 7.31 (tt, J = 7.4, 1.3 Hz, 1H), 7.28-7.26 (m, 2H), 2.55 (q, J = 7.6 Hz, 2H), 2.54 (s, 2H), 1.19 (s, 6H), 1.16 (t, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 212.1, 173.4, 137.1, 132.4, 129.3, 128.3, 127.6, 45.9, 43.3, 25.5, 24.8, 12.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{19}O$ 215.1436; Found 215.1431.

But-1-yn-1-ylbenzene (18b): R_f= 0.76 (4:1 hexanes:EtOAc); ^{1}H NMR values matched those previously reported.[32]

2-Methyl-1,4,5,6-tetrahydrobenzo[e]azulen-3(2H)-one (20a): Prepared by subjecting β-hydroxy-α-diazo ketone **19a** (66.5 mg, 0.27 mmol) to General Procedure C with the modification that 1.2 equiv of tris(pentafluorophenyl)borane was used and the aqueous layer was washed 4 times with CH_2Cl_2 (10 mL) instead of Et_2O during the workup. The yield of cyclopentenone **20a** was 27% as determined using quantitative ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene (45.4 mg, 0.27 mmol) as an internal standard.

In a separate experiment, **20a** was isolated by silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to provide a pale yellow solid: R*f* = 0.53 (4:1 hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (dd, *J* = 6.9, 2.1 Hz, 1H), 7.34-7.27 (m, 2H), 7.21 (dd, *J* = 6.7, 2.3 Hz, 1H), 3.23 (ddt, *J* = 17.1, 6.9, 2.5 Hz, 1H), 2.87-2.76 (m, 2H), 2.59 (dq, *J* = 17.1, 2.6 Hz, 1H) 2.56-2.50 (m, 3H), 2.10-1.93 (m, 2H), 1.27 (d, *J* = 7.4, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 212.6, 162.5, 144.3, 140.0, 134.5, 130.0, 129.9, 127.7, 126.5, 39.1, 38.5, 36.0, 26.7, 26.4, 16.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{17}O$ 213.1279; Found 213.1272.

2-Methyl-8-nitro-1,4,5,6-tetrahydrobenzo[e]azulen-3(2H)-one (20b): Prepared by subjecting β-hydroxy-α-diazo ketone **19b** (65.8 mg, 0.22 mmol) to General Procedure C with the modification that 1.2 equiv of tris(pentafluorophenyl)borane was used and the reaction mixture was concentrated under vacuum without workup. The crude oil was subjected to silica gel flash chromatography (hexanes/CH_2Cl_2, gradient elution 0 to 100% CH_2Cl_2) to give 20.8 mg (37% yield) of the title compound as a pale brown solid: R*f* = 0.22 (3.7:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (dd, *J* = 8.5, 2.3 Hz, 1H), 8.08 (d, *J* = 2.3 Hz, 1H), 7.69 (d, *J* = 8.6 Hz, 1H), 3.29-3.20 (m, 1H), 2.98-2.85 (m, 2H), 2.66-2.55 (m, 4H), 2.15-1.97 (m, 2H), 1.30 (d, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 211.8, 159.2, 147.9, 145.6, 143.2, 140.8, 128.4, 124.5, 121.5, 39.2, 38.5, 35.8, 26.7, 26.1, 16.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{16}NO_3$ 258.1130; Found 258.1125.

2-Methyl-9-nitro-1,4,5,6-tetrahydrobenzo[e]azulen-3(2H)-one (20c): Prepared by subjecting β-hydroxy-α-diazo ketone **19c** (60.5 mg, 0.20 mmol) to General Procedure C with the modification that 1.2 equiv of tris(pentafluorophenyl)borane was used and the reaction mixture was concentrated under vacuum without workup. The crude oil was subjected to silica gel flash chromatography (hexanes/ CH_2Cl_2, gradient elution 0 to 94% CH_2Cl_2) to give 14.8 mg (29% yield) of the title compound as a pale brown solid: R*f* = 0.24 (4:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.41 (d, *J* = 2.3 Hz, 1H), 8.14, (dd, *J* = 8.3, 2.3 Hz, 1H), 7.38 (d, *J* = 8.4, 1H), 3.28 (ddt, *J* = 17.0, 7.0, 2.6 Hz, 1H), 3.01-2.86 (m, 2H), 2.67 (dq, *J* = 17.0, 2.8 Hz, 1H), 2.62-2.55 (m, 3H), 2.13-1.94 (m, 2H), 1.30 (d, *J* = 7.4, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 212.0, 159.2, 151.3, 146.9, 142.1, 135.8, 130.9, 124.3, 122.6, 39.1, 38.5, 36.0, 26.9, 25.5, 16.7. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{15}H_{16}NO_3$ 258.1130; Found 258.1122.

8-Bromo-2-methyl-1,4,5,6-tetrahydrobenzo[e]azulen-3(2H)-one (20d): Prepared by subjecting β-hydroxy-α-diazo ketone **19d** (71.7 mg, 0.21 mmol) to General Procedure C with the modification that 1.2 equiv of tris(pentafluorophenyl)borane was used and the reaction mixture was concentrated under vacuum without workup. The crude oil was subjected to silica gel flash chromatography (hexanes/CH_2Cl_2, gradient elution 0 to 75% CH_2Cl_2), the desired compound was isolated with impurities and was further purified by silica gel flash chromatography (8:1 hexanes/EtOAc) to give 15.9 mg (26% yield) of the title compound as a colorless solid: R_f = 0.50 (100% CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43-7.39 (m, 2H), 7.37 (s, 1H), 3.22-3.14 (m, 1H), 2.84-2.72 (m, 2H), 2.59-2.43 (m, 4H), 2.09-1.89 (m, 2H), 1.27 (d, *J* = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 212.1, 161.0, 146.1, 140.5, 133.4, 132.7, 129.5, 129.1, 124.2, 39.0, 38.4, 35.8, 26.8, 25.9, 16.8. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{15}H_{16}BrO$ 291.0385; Found 291.0385.

8-Methoxy-2-methyl-1,4,5,6-tetrahydrobenzo[e]azulen-3(2H)-one (20e) and 8-methoxy-2-methyl-3,4,5,6-tetrahydrobenzo[e]azulen-1(2H)-one (21e): Prepared by subjecting β-hydroxy-α-diazo ketone **19e** (57.5 mg, 0.20 mmol) to General Procedure C with the modification that 1.2 equiv of tris(pentafluorophenyl)borane was used and the reaction mixture was concentrated under vacuum without workup. The crude oil was subjected to silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 11% EtOAc) to give 18.1 mg (37% yield) of **20e** and 6.7 mg (14% yield) of **21e** as pale orange solids:

8-Methoxy-2-methyl-1,4,5,6-tetrahydrobenzo[e]azulen-3(2H)-one (20e): R_f = 0.30 (3.7:1 hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (d, *J* = 8.7 Hz, 1H), 6.80 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.74 (d, *J* = 2.7 Hz, 1H), 3.85 (s, 3H), 3.23-2.16 (m, 1H), 2.86-2.78 (m, 2H), 2.59-2.47 (m, 4 H), 2.07-1.89 (m, 2H), 1.26 (d, *J* = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 212.5, 162.1, 160.9, 146.4, 138.0, 129.6, 127.2, 115.5, 111.4, 55.4, 38.9, 38.7, 36.6, 27.2, 25.6, 17.0. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{16}H_{19}O_2$ 243.1385; Found 243.1384.

8-Methoxy-2-methyl-3,4,5,6-tetrahydrobenzo[e]azulen-1(2H)-one (21e): R_f = 0.20 (8:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.7 Hz, 1H), 6.80 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.71 (d, *J* = 2.8 Hz, 1H), 3.81 (s, 3H), 2.88 (dd, *J* = 18.5, 7.0 Hz, 1H), 2.65 (t, *J* = 5.5 Hz, 2H), 2.61 (t, *J* = 7.0 Hz, 2H), 2.53 (app pd, *J* = 7.4, 2.8 Hz, 1H), 2.25 (dd, *J* = 18.5, 2.7 Hz, 1H), 2.16-2.05 (m, 2H) 1.25 (d, *J* = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 210.7, 172.4, 158.9, 144.2, 135.7, 130.3, 123.6, 114.9, 110.7, 55.3, 40.6, 40.5, 34.4, 33.6, 28.8, 16.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{19}O_2$ 243.1385; Found 243.1386.

3,5,5-Trimethyl-2-pentylcyclopen-2-enone (23) and **2,5,5-trimethyl-3-pentylcyclopent-2-enone (24):** Prepared by subjecting diazo ketone **22** (43 mg, 0.18 mmol) to General Procedure C. ^{1}H NMR of the crude mixture showed a 1.7:1 ratio of **23** and **24**. Purification by silica gel flash column chromatography (hexanes/Et_2O, gradient elution 0 to 10% Et_2O) returned 7.3 mg (21% yield) of **23** and 8.0 mg (23% yield) of **24** as oils: R_f = 0.25 and 0.19, respectively (5:1 hexanes/EtOAc).

3,5,5-Trimethyl-2-pentylcyclopent-2-enone (23): ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.35 (s, 2H), 2.15 (t, *J* = 7.6 Hz, 2H), 2.01 (s, 3H), 1.37-1.20 (m, 6H), 1.07 (s, 6H), 0.87 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^1H\}$ (125 MHz, $CDCl_3$): δ 213.7, 166.3, 100.0, 48.7, 42.7, 31.7, 28.0, 25.1, 23.1, 22.5, 17.0, 14.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{23}O$: 195.1749; Found 195.1747.

2,5,5-Trimethyl-3-pentylcyclopent-2-enone (24): ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.38 (t, *J* = 8.1, 2H), 2.35 (s, 2H), 1.69 (s, 3H), 1.51 (p, *J* = 7.6, 2H), 1.40-1.25 (m, 4H), 1.08 (s, 6H), 0.90 (t, *J* = 7.0, 3H); $^{13}C\{^1H\}$ (125 MHz, $CDCl_3$): δ 214.3, 170.6, 133.2, 46.4, 42.7, 31.7, 30.9, 26.9, 25.2, 22.4, 14.0, 8.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{23}O$: 195.1749; Found 195.1747.

2-Cyclohexyl-3,5,5-trimethylcyclopent-2-enone (26) and **3-cyclohexyl-2,5,5-trimethylcyclopent-2-enone (27):** Prepared by subjecting diazo ketone **25** (61.0 mg, 0.24

mmol) to 1 equivalent of tris(pentafluorophenyl)borane following General Procedure C with the modification that the aqueous layer was extracted 4 times with CH_2Cl_2 (10 mL) instead of Et_2O. Purification by centrifugal thin-layer chromatography (2:1, hexanes/CH_2Cl_2) provided 8.2 mg (16% yield) of **26** and trace quantities of **27**. In a different run, **27** was isolated by gravity column chromatography (19:1, pentane/Et_2O) to afford a 1% yield: R_f = 0.60 and 0.27, respectively (100% CH_2Cl_2).

2-Cyclohexyl-3,5,5-trimethylcyclopent-2-enone (26): ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.40 (tt, *J* = 12.1, 3.7 Hz, 1H), 2.31 (s, 2H), 2.04 (s, 3H), 1.82-1.63 (m, 5H), 1.49-1.42 (m, 2H), 1.32-1.20 (m, 3H), 1.04 (s, 6H); $^{13}C\{^1H\}$ (125 MHz, $CDCl_3$): δ 213.7, 166.7, 141.3, 49.1, 42.6, 35.5, 30.1, 27.0, 26.2, 25.2, 17.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{23}O$ 207.1749; Found 207.1750.

3-Cyclohexyl-2,5,5-trimethylcyclopent-2-enone (27): ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.71-2.62 (m, 1H), 2.33 (s, 2H), 1.85-1.79 (m, 2H), 1.78-1.72 (m, 1H), 1.69 (s, 3H), 1.67-1.61 (m, 2H), 1.42-1.27 (m, 4H), 1.27-1.15 (m, 1H), 1.07 (s, 6H); $^{13}C\{^1H\}$ (125 MHz, $CDCl_3$): δ 214.7, 174.8, 132.0, 43.4, 42.5, 39.9, 30.5, 26.2, 26.1, 25.4, 8.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{23}O$ 207.1749; Found 207.1754.

2,2,8-Trimethyl-2,3,5,6,7,8-hexahydroazulen-1(4H)-one (29) and **2,2,4-trimethyl-2,3,5,6,7,8-hexahydroazulen-1(4H)-one (30)**: Prepared by treating diazo ketone **28** (60 mg, 0.25 mmol) with 1 equivalent of tris(pentafluorophenyl)borane following General Procedure C. ^{1}H NMR of the crude mixture showed a 4.4:1 ratio of **29** and **30**. Purification by silica gel flash column chromatography (hexanes/Et_2O, gradient elution 0 to 5% Et_2O) returned 24 mg (50% yield) of pure **29** as an oil, and 5 mg of a mixture of **29** and **30** (11% yield of both isomers). Alternatively, subjecting diazo ketone **28** to 1 equivalent of $SnCl_4$ following General Procedure D gave **29** in 39% isolated yield and **30** in 6% isolated yield: R_f = 0.32 and 0.26, respectively (9:1 hexanes/Et_2O).

2,2,8-Trimethyl-2,3,5,6,7,8-hexahydroazulen-1(4H)-one (29): ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.93 (qt, *J* = 7.4, 3.8 Hz, 1H), 2.46 (dddd, *J* = 15.2, 12.1, 3.4, 1.4 Hz, 1H), 2.37 (td, *J* = 5.7, 5.0, 2.0 Hz, 1H), 2.35 (s, 1H), 2.34 (s, 1H), 1.93-1.86 (m, 1H), 1.85-1.71 (m, 3H), 1.55-1.46 (m, 1H), 1.44-1.34 (m, 1H), 1.08 (s, 3H), 1.05 (s, 3H), 1.00 (d, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ (125 MHz, CDCl$_3$): δ 213.2, 171.1, 143.3, 49.3, 42.9, 33.1, 32.9, 28.0, 27.0, 25.2, 25.0, 24.8, 17.5. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{20}ONa$ 215.1412; Found 215.1413.

2,2,4-Trimethyl-2,3,5,6,7,8-hexahydroazulen-1(4H)-one (30): ^1H NMR (500 MHz, CDCl$_3$): δ 2.65 (td, *J* = 7.4, 2.8 Hz, 1H), 2.43 (d, *J* = 18.4 Hz, 1H), 2.32 (d, *J* = 17.6 Hz, 1H), 2.36-2.24 (m, 2H), 1.93-1.86 (m, 1H), 1.78-1.66 (m, 2H), 1.61-1.44 (m, 3H), 1.15 (d, *J* = 7.2 Hz, 3H), 1.08 (s, 3H), 1.07 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, CDCl$_3$): δ 211.7, 177.0, 138.4, 46.6, 42.7, 37.3, 33.7, 27.6, 26.6, 25.3, 25.1, 23.3, 17.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{21}O$ 193.1592; Found 193.1588.

2-Chloro-7-pivaloylcycloheptanone (39): Prepared by subjecting diazo ketone **37** (46 mg, 0.18 mmol) to General Procedure C with the modification that 30 mol% of tris(pentafluorophenyl)borane was used. ^1H NMR of the crude mixture showed **39** was the major product. Silica gel flash column chromatography (hexanes/Et$_2$O, gradient elution 0 to 10% Et$_2$O) provided 18 mg (45% yield, 92 : 8 dr) of the title compound: R_f = 0.30 (9:1 hexanes/Et$_2$O); HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{19}ClO_2Na$ 253.0971. Found: 253.0967. *Major diastereomer*: ^1H NMR (500 MHz, CDCl$_3$): δ 4.80 (dd, *J* = 11.1, 3.7 Hz, 1H), 4.32 (dd, *J* = 10.5, 6.0 Hz, 1H), 2.32-2.24 (m, 1H), 2.00-2.09 (m, 1H), 1.99-1.78 (m, 4H), 1.58-1.44 (m, 1H), 1.38-1.27 (m, 1H), 1.17 (s, 9H); $^{13}C\{^1H\}$ (125 MHz, CDCl$_3$): δ 211.1, 202.2, 62.6, 57.8, 45.7, 35.9, 29.1, 27.3, 26.8, 25.9. *Minor diastereomer*: ^1H NMR (500 MHz, CDCl$_3$): δ 4.75 (dd, *J* = 7.1, 4.5 Hz, 1H), 4.16 (dd, *J* = 9.1 Hz, 4.0 Hz, 1H), 2.54 (td, *J* = 13.7, 4.1 Hz, 1H), 2.07-1.78 (m, 4H), 1.77-1.70 (m, 2H), 1.67-1.59 (m, 1H), 1.26 (s, 9H).

Computational Details.

All DFT calculations were conducted with the Gaussian 16 software package.[33] Geometry optimizations of all the minima and transition states were performed using B3LYP[34,35] functional with 6-311+G(d,p) basis set, including solvation energy corrections and Grimme's D3 empirical dispersion corrections with BJ-damping.[36,37] To confirm whether each optimized stationary point is an energy minimum or a transition state, as well as evaluate the zero-point vibrational energy and thermal corrections at 298 K, the vibrational frequencies were computed at the same level of theory as for the geometry optimizations. The solvation energies were evaluated by a self-consistent reaction field (SCRF) using the PCM model[38-40] with dichloromethane as the solvent. Extensive conformational searches for the intermediates and transition states have been conducted to ensure that the lowest energy conformers were located. The 3D diagrams of molecules were generated using CYLView.[41]

SUPPORTING INFORMATION

The Supporting Information is available free of charge on the ACS Publications website at DOI:

- Copies of ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra for all new compounds and ^{1}H-^{13}C HMBC spectra showing key correlations for **23**, **24**, **26** and **29** and ^{1}H NOE spectrum of compound **20c.**

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Notes

The authors declare no competing financial interests.

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