Graphical Abstract

Abstract:

We report an improved two-step reaction sequence that gives tricyclic protonated azomethine imine products containing a 1,2,3,4-tetrahydrocinnoline scaffold in high yield. This sequence involves the oxidation of aryl hydrazones with TFAA-activated DMSO to give the corresponding α -trifluoroacetoxyazo products, which react readily with TMSOTf to give 1-aza-2-azoniaallene salt intermediates that undergo intramolecular (4+2) cycloadditions with pendent alkenes. This reaction sequence is more general, more practical and more environmentally friendly than our initially reported method. The cycloaddition provides exceptionally sterically-hindered products in high yield.

Keywords:

(4+2) Cycloaddition

1-Aza-2-azoniaallene salt

Heteroallene

Azomethine imine

Oxidation

Hydrazone

Intramolecular (4 + 2) cycloaddition of aryl-1-aza-2-azoniaallene salts: A practical approach to highly sterically-congested polycyclic protonated azomethine imines

Ram C. Dhakal and Matthias Brewer*

Department of Chemistry, The University of Vermont, 82 University Place, Burlington, VT 05405, United States

This paper is dedicated to Professor Neil Garg on the occasion of his receipt of the 2016 Tetrahedron Young Investigator Award

Email: Matthias.Brewer@uvm.edu; rdhakal@uvm.edu

1. Introduction

Cationic 1-aza-2-azoniaallene salts (e.g. **2**, Scheme 1) can undergo a variety of mechanistically-distinct transformations that lead to an assortment of structurally unique products. These heteroallene species, which are oxidized derivatives of hydrazones, are highly electrophilic and readily react at carbon with weak nucleophiles to form the corresponding azo products.^{1,2} For instance, aryl hydrazones are oxidized with chloro(dimethyl)sulfonium chloride at low temperature to give 1-aza-2-azoniaallene salt intermediates that are captured by the chloride counter ion to give the corresponding α -chloroazo products in high yield.³ This addition is reversible and 1-aza-2-azoniaallene salts are commonly prepared by treating an α -chloroazo compound with a halophilic Lewis acid (SbCl_5 or AlCl_3), which facilitates chloride elimination.⁴ Once formed, these cationic heteroallenes, which are 1,3-monopols, can react in concerted (3+2) cycloadditions with alkenes to give bicyclic diazenium salt products (Scheme 1, **1** $\rightarrow$ **3**).⁵⁻⁷ In addition, we have shown that these species, which can be thought of as imino-nitrenium cations, can react in C-H insertion reactions to give pyrazolines through a bonding stepwise but energy concerted amination process (Scheme 1, **4** $\rightarrow$ **6**).^{8,9}

1,3-Dipolar Cycloaddition:

C-H Insertion:

(4 + 2) Cycloaddition:

Scheme 1. Known reactions of 1-aza-2-azoniaallene salts.

More recently we reported that aryl-1-aza-2-azoniaallene systems can also react in an unprecedented (4+2) cycloaddition reaction with a pendent alkene to give tricyclic protonated azomethine imine products that containing a 1,2,3,4-tetrahydrocinnoline scaffold (Scheme 1, **7** $\rightarrow$ **9**).¹⁰ We studied the mechanism of this reaction computationally and showed that it occurs by a concerted (4+2) cycloaddition in which one aromatic π -bond of the heteroallene and the azo bond serve as the 4- π component.¹¹ This concerted mechanism is consistent with our experimental results that showed that the transformation is stereospecific with respect to the stereochemistry of the alkene; the heteroallenes derived from (*Z*)- and (*E*)-hept-5-en-2-one led to diastereomeric cycloaddition products without crossover.¹⁰ Importantly, the scope of this reaction is fairly general in terms of electronic and steric changes to the alkene portion of the molecule. A variety of alkene substitution patterns were well tolerated including di- and trisubstituted olefins, which led to products containing sterically congested nitrogen-bearing and all-carbon quaternary centers in high yield.¹⁰ We have continued to study this cycloaddition experimentally, and in this paper we describe substrate scope studies with respect to substitution on the N-aryl ring. We also report an improved route to the cycloaddition products that is more practical, more environmentally friendly, and provides remarkably sterically hindered products in high yield.

2. Results and Discussion

2.1 Scope of the SbCl_5 mediated (4+2) cycloaddition from α -chloroazo precursors

With a better understanding of the mechanism of this (4+2) cycloaddition in hand,¹¹ we were interested to determine what affect substitution on the aromatic ring would have on the

outcome of the cycloaddition process. With this in mind, we prepared hydrazones **10a-e** (Scheme 2) and subjected them to oxidation with chloro(dimethyl)sulfonium chloride to give the corresponding α -chloroazo products. While the electron rich aryl hydrazones (**10a-c**) reacted in high yield, the nitro derivatives (**10d-e**) did not react to completion — a useless mixture of desired product and hydrazone starting material was returned. Treating the clean α -chloroazo products (**11a-c**) with SbCl_5 gave good yields of the cycloaddition products when the N-aryl ring was substituted with methyl (**12a-b**), but gave a mixture of products for methoxy aryl derivative **12c**. Attempts to isolate **12c** from this mixture failed.

Scheme 2. Scope and limitations of the SbCl_5 mediated (4+2) cycloaddition.

In prior work we observed that the intramolecular cycloaddition proceeded in high yield with tri-substituted alkenes, and we were interested to see if a more highly hindered alkene would react productively. With this in mind we prepared the α -chloroazo product of the phenyl hydrazone of dihydro- β -ionone (**14**, Scheme 3). Unfortunately, this substrate also failed to give clean cycloaddition product when treated with SbCl_5 under the standard cycloaddition conditions and all attempts to purify the desired product failed.

Scheme 3. Attempted (4+2) cycloaddition of a highly hindered alkene substrate.

These results highlight several problems with this cycloaddition procedure. Namely, hydrazones that do not react cleanly with chloro(dimethyl)sulfonium chloride are unsuitable for the reaction sequence, and α -chloroazos with a methoxy substituted aromatic ring or substrates with highly hindered alkenes, failed to undergo clean cycloaddition. This procedure was also not ideal from an environmental or practical standpoint, with one notable drawback being that the SbCl_6 iminium ion salt products were difficult to purify. With this in mind, we set our sights on developing a greener and more practical procedure to effect this (4+2) cycloaddition reaction.

2.2 TMSOTf mediated (4+2) cycloaddition from α -chloroazo precursors

Our first goal was to identify an alternative Lewis acid that could generate the requisite heteroallene from an α -chloroazo compound and facilitate the cycloaddition reaction. We were pleased to discover that treating α -chloroazo **7** (Scheme 1) with trimethylsilyl trifluoromethanesulfonate (TMSOTf) at room temperature for 24 hours in hexane gave the desired cycloaddition product (**9**) as the triflate salt in 84% yield. This procedure offered several practical and environmental advantages over the prior procedure — the reaction is conducted at room temperature rather than $-78\text{ }^{\circ}\text{C}$, heavy metal salts are avoided, and the solvent is non-halogenated. Importantly, the triflate counter ion made the iminium salt product significantly more crystalline than the corresponding SbCl_6 salts, which allowed for purification by recrystallization. Subjecting α -chloroazos **11a** and **11b** (Scheme 2) to these new reaction conditions provided the desired cycloaddition products (**19a** and **19b**, Scheme 7) in 85% and 83% yield respectively after a 12h reaction time. Importantly, the methoxyphenyl α -chloroazo (**11c**) gave clean cycloaddition product **19c** (Scheme 7) in 85% yield, and dihydro- β -ionone derivative **14** (Scheme 3) gave **18a** (Scheme 6) in 45% yield after purification by recrystallization. The high steric congestion in this later product is noteworthy; over the course of the reaction two quaternary centers form adjacent to a third to give three contiguous quaternary centers in the product. In all cases the salt products were highly crystalline and could be easily purified by recrystallization from a mixture of methanol and diethyl ether. More careful crystallization of **18a** from this solvent mixture gave crystals suitable for x-ray diffraction and x-ray crystallography provided the crystal structure shown in Figure 1, which confirmed the structure of this salt.¹²

Figure 1. Crystal structure of protonated azomethine imine **18a**.

2.3 Preparation of α -trifluoroacetoxyazo compounds

Although the TMSOTf mediated cycloaddition procedure described in Section 2.2 addressed several of the limitations of the original cycloaddition procedure, it still depended on the production of clean α -chloroazo intermediates, which was not always possible. With this in mind, we sought to identify an alternate, more readily formed, α -substituted azo species that could act as a heteroallene salt progenitor. A variety of sulfonium salt oxidants are easily formed from DMSO by treatment with different activating agents,¹³ and we attempted to oxidize hydrazone **13a** (Scheme 3) with dimethylsulfonium diacetate. Unfortunately, this reaction did not provide any of the desired α -acetoxyazo product. However, treating hydrazone **13a** with DMSO that had been activated with trifluoroacetic anhydride (TFAA) gave α -

trifluoroacetoxyazo **16a** in 87% yield (Scheme 4). This transformation could also be conducted in THF in comparable yield (84%).

To test the scope of this procedure we subjected the hydrazones shown in Schemes 4 and 5 to these oxidation conditions. In all cases good yields of the azo product were obtained, even when nitro substituents were present on the aryl ring (**17d** and **17e**). With further experimentation, we have recently discovered that a hexane solution of hydrazone **10h**, DMSO, and Et₃N can be treated with TFAA at 0 °C to give azo product **17h** in 87% yield. This modified procedure, which is operationally simpler than low-temperature conditions, is notable because DMSO activated with TFAA typically decomposes above -30 °C.¹³ In this case, the low polarity of the solvent likely slows the decomposition of the activated DMSO species allowing the hydrazone to react with the in situ generated oxidant. Under these higher temperature conditions, unsubstituted and alkyl-, nitro-, and methoxy-substituted N-aryl hydrazones (**13a**, **10b**, **10e**, **13d**) give the corresponding azo products in 82%, 62%, 79%, and 57% yield respectively.

Scheme 4. Formation of α -trifluoroacetoxyazo compounds **16a-e**.

Scheme 5. Formation of α -trifluoroacetoxyazo compounds **17a-h**.

2.4 TMSOTf mediated (4+2) cycloaddition from α -trifluoroacetoxyazo precursors

With a new and general route to α -substituted azo compounds in hand, we were keen to see if these α -trifluoroacetoxyazo compounds would serve as heteroallene and cycloaddition precursors. In the event, treating dihydro- β -ionone derived α -trifluoroacetoxyazo **16a** (Scheme 6) with TMSOTf for 12 h in hexane at room temperature returned cycloaddition product **18a** in 55% yield, which is a slight improvement over the results obtained from the corresponding α -chloroazo precursor. In attempts to optimize the procedure we observed that changing the solvent to CH_2Cl_2 gave comparable yield, whereas THF polymerized under the reaction conditions giving no desired product. Importantly, raising the reaction temperature to 40 °C gave substantially improved product yield (72%) in a shorter reaction time (4 h), and these became our conditions of choice. Attempts to conduct the oxidation/cycloaddition sequence in one pot gave the desired cycloaddition product, but we were unable to separate it from the triethyl ammonium salt generated during the oxidation step.

Subjecting the 5-hexen-2-one derived α -trifluoroacetoxyazos **17a-h** to these optimized cycloaddition conditions gave the expected cycloaddition products **19a-h** in uniformly high yields independent of the electronic character of the aryl ring (Scheme 7). As might be expected, the meta-substituted aromatic derivative (**17e**) gave a mixture of regioisomeric cycloaddition products in a 6:4 ratio. The more sterically demanding dihydro- β -ionone derived α -trifluoroacetoxyazos **16a-e** (Scheme 6) also reacted smoothly under these conditions, to give the highly sterically congested cycloaddition products in impressive yield.

Scheme 6. TMSOTf mediated (4+2) cycloaddition of α -trifluoroacetoxyazos **16a-e**.

Scheme 7. TMSOTf mediated (4+2) cycloaddition of α -trifluoroacetoxyazos **17a-h**.

3. Conclusions

We have developed an improved two step reaction sequence for the synthesis of tricyclic protonated azomethine imine products that contain a 1,2,3,4-tetrahydrocinnoline scaffold. This sequence is based on our discovery that aryl hydrazones react readily with DMSO activated with TFAA to give the corresponding α -trifluoroacetoxyazo products. These materials react efficiently with TMSOTf in hexane at 40 °C to give 1-aza-2-azoniaallene salt intermediates that undergo intramolecular (4+2) cycloadditions with pendent alkenes. This cycloaddition is a general process that can lead to exceptionally sterically congested products. The new reaction sequence reported here is more environmentally friendly, more practical, higher yielding and has a broader substrate scope than the SbCl₅ mediated process we previously reported.¹⁰

4. Experimental

4.1 General Experimental Information

All reactions were performed under an atmosphere of nitrogen in flame-dried glassware. All solvents were removed *in vacuo* using a rotary evaporator attached to a self-cleaning dry vacuum pump, and further dried under reduced pressure on a high vacuum line. Tetrahydrofuran (THF) and dichloromethane (CH₂Cl₂) were dried via a solvent dispensing system. Triethylamine was freshly distilled from CaH₂ before use. Oxalyl chloride, trimethylsilyl trifluoromethanesulfonate and antimony(V)chloride, purchased from Acros Organics, were freshly distilled before use. Anhydrous aluminum(III)chloride (98.5%), purchased from Acros Organics, was used as received and stored in a dry glovebox under an atmosphere of nitrogen. Extra dry DMSO stored over molecular sieves was purchased from Acros Organics and was used as received. All hydrazones were freshly prepared before use as these materials could not be stored and underwent facile auto oxidation on standing in air. Molecular sieves (4 Å) were activated by heating overnight at 120 °C in a vacuum oven.

Reactions were cooled to –78 °C by immersion in dry-ice acetone baths and were maintained at –60 °C with the aid of an immersion cooler. Silica gel flash column chromatography was performed using silica gel (230-400 mesh) and TLC analysis was carried out using silica on glass plates. Visualization of TLC plates was achieved using ultraviolet light, polyphosphomolybdic acid and cerium sulfate in EtOH with H₂SO₄, ceric ammonium molybdate, or iodine.

¹H and ¹³C NMR data was collected at room temperature on a 500 MHz spectrometer in CDCl₃ or CD₃CN. ¹H NMR chemical shifts are reported in ppm (δ units) downfield from tetramethylsilane. Solvent peaks were used as internal references for all ¹³C NMR. Accurate mass data was acquired in ESI mode using an orbitrap mass analyzer. X-Ray diffraction data were collected on a Bruker APEX 2 CCD platform (MoK α , λ = 0.71073 Å) at set temperature of 135 K. A suitable crystal was mounted in a nylon loop under Paratone-N cryoprotectant oil. Direct methods and standard difference map techniques were used for solution structure followed

by refinement using full-matrix least squares procedures on F2 via SHELXTL (version 6.14; Sheldrick, G. M., *Acta Cryst.* **2008**, *A64*, 112-122). Non-hydrogen atoms were refined anisotropically. The hydrogen atom on N(2), H(1), was located in the Fourier difference map and refined semi-freely using a distance restraint.

4.2 General experimental procedure 1: Preparation of aryl hydrazones.

A ketone (1.0 equiv, 1.0 mmol) was added to a room temperature solution of aryl hydrazine (1.2 equiv, 1.2 mmol) in CH₂Cl₂ (8 mL) containing 4Å molecular sieves under a nitrogen atmosphere. After stirring at room temperature for three hours, the solution was filtered and the filtrate was concentrated. The residue was dissolved in hexane (12 mL), was passed through a plug of basic alumina and was concentrated *in vacuo* to provide a diastereomeric mixture of the hydrazone as a yellow oil.

1-(hex-5-en-2-ylidene)-2-(*p*-tolyl)hydrazine (10a): Yield = 75% (152 mg); *E/Z* 1:0.14; major diastereomer: ¹H NMR (500 MHz, CDCl₃) δ = 7.04 (d, *J* = 8.1, 2H), 6.97 – 6.92 (m, 2H), 6.78 (s, broad, 1H), 6.01 – 5.78 (m, 1H), 5.10 (dd, *J* = 26.6, 16.4, 1H), 4.98 (d, *J* = 12.1, 1H), 2.45 – 2.30 (m, 4H), 2.27 (s, 3H), 1.85 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 145.4, 143.7, 138.1, 129.6, 128.7, 114.8, 113.0, 38.2, 30.8, 20.5, 14.5. Observable resonances for minor diastereomer: ¹H NMR (500 MHz, CDCl₃) δ = 5.12 (dd, *J* = 17.1, 1.4, 1H), 2.02 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 137.1, 115.9, 29.1, 28.7, 23.2. MS (ESI) calcd for [C₁₃H₁₈N₂H]⁺: 203.1548, found: 203.1552.

1-(hex-5-en-2-ylidene)-2-(*o*-tolyl)hydrazine (10b): Yield = 83% (168 mg); *E/Z* 1:0.18; major diastereomer: ¹H NMR (500 MHz, CDCl₃) δ = 7.46 (d, *J* = 8.1, 1H), 7.18 (t, *J* = 7.7, 1H), 7.06 (d, *J* = 7.4, 1H), 6.77 (t, *J* = 7.4, 1H), 6.7-6.9 (s, broad, 1H), 5.98 – 5.77 (m, 1H), 5.08 (dq, *J* = 5.9, 1.5, 1H), 4.99 (ddt, *J* = 10.2, 1.9, 1.1, 1H), 2.47 – 2.36 (m, 4H), 2.19 (s, 3H), 1.89 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 143.5, 138.0, 130.1, 127.2, 120.2, 119.1, 116.2, 114.9, 112.5, 38.2, 30.7, 16.9, 14.5. Observable resonances for minor diastereomer: ¹H NMR (500 MHz, CDCl₃) δ = 7.42 (d, *J* = 8.1, 2H), 5.14 (dd, *J* = 17.1, 1.5, 1H), 2.17 (s, 3H), 2.07 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 34.7. MS (ESI) calcd for [C₁₃H₁₈N₂H]⁺: 203.1548, found: 203.1548.

1-(hex-5-en-2-ylidene)-2-(4-methoxyphenyl)hydrazine (10c): Yield = 64% (140 mg); *E/Z* 1:0.18; major diastereomer: ¹H NMR (500 MHz, CDCl₃) δ = 7.00 (d, *J* = 8.9, 2H), 6.83 (d, *J* = 8.9, 2H), 6.68 (s, broad, 1H), 5.93 – 5.80 (m, 1H), 5.07 (dd, *J* = 17.1, 1.5, 1H), 4.98 (dd, *J* = 10.2, 0.8, 1H), 3.77 (s, 3H), 2.55 – 2.23 (m, 4H), 1.85 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 153.5, 145.7, 140.2, 138.1, 124.4, 114.6, 114.3, 55.7, 38.2, 30.8, 14.5. Observable resonances for minor diastereomer: ¹H NMR (500 MHz, CDCl₃) δ = 5.12 (d, *J* = 17.2, 1H), 3.88 (s, 3H), 2.02 – 1.99 (m, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 137.1, 115.9, 55.6, 34.7, 23.1, 19.5. MS (ESI) calcd for [C₁₃H₁₈N₂OH]⁺: 219.1497, found: 219.1503.

1-(hex-5-en-2-ylidene)-2-(4-nitrophenyl)hydrazine (10d): Yield = 65% (151 mg); *E/Z* 1:0.13; major diastereomer: ¹H NMR (500 MHz, CDCl₃) δ = 8.14 (d, *J* = 9.3, 2H), 7.44 (s, broad, 1H), 7.05 (d, *J* = 9.2, 2H), 5.88 (ddt, *J* = 16.6, 10.1, 6.4, 1H), 5.09 (dd, *J* = 17.1, 1.7, 1H), 5.01 (dd, *J* = 10.2, 1.8, 1H), 2.54 – 2.19 (m, 4H), 1.92 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 150.3, 149.7, 139.97, 137.5, 126.1, 115.2, 111.6, 38.2, 30.4, 14.79. ¹³C NMR (126 MHz, CDCl₃) δ 144.6, 136.5, 129.0, 129.0, 127.6, 123.9, 114.0, 39.8, 39.5, 35.0, 32.7, 28.6, 25.5, 19.8, 19.5, 14.7.

Observable resonances for minor diastereomer: ^1H NMR (500 MHz, CDCl_3) δ = 5.15 (dd, J = 17.1, 1.5, 1H), 2.07 (s, 3H).

1-(hex-5-en-2-ylidene)-2-(3-nitrophenyl)hydrazine (10e): Yield = 78 % (182 mg); E/Z 1:0.19; major diastereomer: ^1H NMR (500 MHz, CDCl_3) δ = 7.88 (dd, J = 4.8, 2.7, 1H), 7.69 – 7.61 (m, 1H), 7.36 – 7.29 (m, 2H), 7.12 (s, broad, 1H), 5.88 (ddt, J = 16.5, 10.1, 6.3, 1H), 5.09 (dd, J = 17.1, 1.7, 1H), 5.01 (dd, J = 10.1, 1.6, 1H), 2.48 – 2.32 (m, 4H), 1.90 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 149.3, 148.1, 146.7, 137.7, 129.7, 118.5, 115.1, 114.0, 107.4, 38.1, 30.6, 14.7. Observable resonances for minor diastereomer: ^1H NMR (500 MHz, CDCl_3) δ = 5.15 (dd, J = 17.1, 1.4, 1H), 2.06 (s, 3H). MS (ESI) calcd for $[\text{C}_{12}\text{H}_{15}\text{N}_3\text{O}_2\text{H}]^+$: 234.1243, found: 234.1246.

1-(4-chlorophenyl)-2-(hex-5-en-2-ylidene)hydrazine (10f): Yield = 68% (152 mg); E/Z 1:0.17; major diastereomer: ^1H NMR (500 MHz, CDCl_3) δ = 7.18 (d, J = 8.8, 2H), 6.98 (d, J = 8.8, 2H), 6.87 (s, broad, 1H), 5.88 (ddt, J = 16.4, 10.2, 6.3, 1H), 5.07 (dd, J = 17.1, 1.5, 1H), 4.98 (d, J = 10.0, 1H), 2.46 – 2.25 (m, 4H), 1.85 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 146.6, 144.5, 137.9, 129.0, 124.0, 114.9, 114.0, 38.1, 30.6, 14.6. Observable resonances for minor diastereomer: ^1H NMR (500 MHz, CDCl_3) δ = 5.14 (d, J = 17.2, 1H), 2.04 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 136.9, 129.4, 123.8, 116.0, 114.0, 25.2, 15.5. MS (ESI) calcd for $[\text{C}_{12}\text{H}_{15}\text{ClN}_2\text{H}]^+$: 223.1002, found: 223.1008.

1-(2,4-dichlorophenyl)-2-(hex-5-en-2-ylidene)hydrazine (10g): Yield = 74% (190 mg); E/Z 1:0.13; major diastereomer: ^1H NMR (500 MHz, CDCl_3) δ = 7.43 (d, J = 8.8, 1H), 7.33 (s, broad, 1H), 7.25 (d, J = 2.3, 1H), 7.18 – 7.13 (m, 1H), 5.88 (ddt, J = 16.4, 10.2, 6.3, 1H), 5.08 (ddd, J = 17.1, 3.3, 1.6, 1H), 4.99 (ddd, J = 10.2, 3.0, 1.2, 1H), 2.45 – 2.40 (m, 2H), 2.40 – 2.34 (m, 2H), 1.90 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 148.7, 140.4, 137.7, 128.4, 127.9, 123.3, 117.3, 115.0, 114.8, 38.1, 30.5, 14.7. Observable resonances for minor diastereomer: ^1H NMR (500 MHz, CDCl_3) δ = 5.14 (dd, J = 17.1, 1.5, 1H), 2.04 (s, 3H). MS (ESI) calcd for $[\text{C}_{12}\text{H}_{14}\text{Cl}_2\text{N}_2\text{H}]^+$: 257.0612, found: 257.0616.

1-(hex-5-en-2-ylidene)-2-phenylhydrazine (10h): Yield = 71% (133 mg); E/Z 1:0.14; major diastereomer: ^1H NMR (500 MHz, CDCl_3) δ = 7.26 – 7.20 (m, 2H), 7.04 (dt, J = 3.2, 1.7, 2H), 6.87 (s, broad, 1H), 6.84 – 6.79 (m, 1H), 6.05 – 5.77 (m, 1H), 5.07 (d, J = 17.1, 1H), 4.98 (d, J = 10.2, 1H), 2.46 – 2.25 (m, 4H), 1.85 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 145.9, 138.0, 129.1, 119.6, 114.8, 112.9, 112.9, 38.2, 30.7, 14.5. Observable resonances for minor diastereomer: ^1H NMR (500 MHz, CDCl_3) δ = 5.13 (dd, J = 17.1, 1.3, 1H), 2.03 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 122.5, 115.9, 29.1, 23.2.

1-phenyl-2-(4-(2,6,6-trimethylcyclohex-1-en-1-yl)butan-2-ylidene)hydrazine (13a): Yield = 72% (204 mg); E/Z 1:0.25; major diastereomer: ^1H NMR (500 MHz, CDCl_3) δ = 7.24 (dd, J = 8.6, 7.4, 2H), 7.06 (dd, J = 8.6, 1.1, 2H), 6.88 (s, broad, 1H), 6.86 – 6.75 (m, 1H), 2.36 (ddd, J = 7.3, 6.5, 2.9, 2H), 2.31 – 2.25 (m, 2H), 1.94 (dd, J = 14.1, 7.7, 2H), 1.89 (s, 3H), 1.64 (s, 3H), 1.62 – 1.53 (m, 2H), 1.47 – 1.42 (m, 2H), 1.03 (s, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 146.8, 146.0, 136.6, 129.1, 127.5, 119.5, 112.9, 39.8, 39.5, 35.0, 32.8, 28.6, 25.6, 19.8, 19.5, 14.6. Observable resonances for minor diastereomer: ^1H NMR (500 MHz, CDCl_3) δ = 7.01 (d, J = 7.5, 2H), 1.70 (s, 3H), 1.05 (s, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 136.2, 131.2, 128.5, 122.5, 112.8, 35.6, 30.2, 23.6, 23.2, 21.8, 20.0, 19.4. MS (ESI) calcd for $[\text{C}_{19}\text{H}_{28}\text{N}_2\text{H}]^+$: 285.2331, found: 285.2335.

1-(*p*-tolyl)-2-(4-(2,6,6-trimethylcyclohex-1-en-1-yl)butan-2-ylidene)hydrazine (13b): Yield = 76% (227 mg); E/Z 1:0.24; major diastereomer: ^1H NMR (500 MHz, CDCl_3) δ = 7.04 (d, J = 8.4,

2H), 6.97 (d, $J = 8.4$, 2H), 6.78 (s, broad, 1H), 2.37 – 2.24 (m, 7H), 1.98 – 1.82 (m, 5H), 1.66 – 1.53 (m, 5H), 1.48 – 1.38 (m, 2H), 1.03 (s, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 143.8, 136.7, 129.6, 128.7, 127.5, 113.0, 39.8, 39.5, 35.0, 32.8, 28.6, 25.6, 20.5, 19.8, 19.5, 14.6. Observable resonances for minor diastereomer: ^1H NMR (500 MHz, CDCl_3) δ = 6.91 (d, $J = 8.4$, 2H), 2.42 (s, 3H), 2.05 (s, 3H), 1.69 (s, 3H), 1.05 (s, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 31.6. MS (ESI) calcd for $[\text{C}_{20}\text{H}_{30}\text{N}_2\text{H}]^+$: 299.2487, found: 299.2491.

1-(*o*-tolyl)-2-(4-(2,6,6-trimethylcyclohex-1-en-1-yl)butan-2-ylidene)hydrazine (13c): Yield = 85% (254 mg); *E/Z* 1:0.18; major diastereomer: ^1H NMR (500 MHz, CDCl_3) δ = 7.49 (d, $J = 8.1$, 1H), 7.18 (t, $J = 7.4$, 1H), 7.06 (d, $J = 7.2$, 1H), 6.76 (t, $J = 7.4$, 1H), 6.71 (s, broad, 1H), 2.41 – 2.27 (m, 4H), 2.19 (d, $J = 5.3$, 3H), 1.97 – 1.84 (m, 5H), 1.65 (s, 3H), 1.59 (ddd, $J = 9.0$, 7.3, 2.5, 2H), 1.48 – 1.40 (m, 2H), 1.04 (s, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 147.6, 143.7, 136.6, 130.1, 127.5, 127.2, 120.23, 119.0, 112.5, 39.8, 39.6, 35.0, 32.8, 28.6, 25.6, 19.8, 19.5, 17.0, 14.5. Observable resonances for minor diastereomer: ^1H NMR (500 MHz, CDCl_3) δ = 7.46 (d, $J = 8.0$, 1H), 2.08 (s, 3H), 1.71 (s, 3H), 1.06 (s, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 136.0, 112.4, 39.6, 35.8, 30.3, 28.4, 25.3, 17.2, 15.4. MS (ESI) calcd for $[\text{C}_{20}\text{H}_{30}\text{N}_2\text{H}]^+$: 299.2487, found: 299.2481.

1-(4-methoxyphenyl)-2-(4-(2,6,6-trimethylcyclohex-1-en-1-yl)butan-2-ylidene)hydrazine (13d): Yield = 57% (180 mg); *E/Z* 1:0.19; major diastereomer: ^1H NMR (500 MHz, CDCl_3) δ = 7.02 (d, $J = 9.0$, 2H), 6.83 (d, $J = 9.0$, 2H), 6.67 (s, broad, 1H), 3.77 (s, 3H), 2.38 – 2.20 (m, 4H), 1.93 (dd, $J = 13.6$, 7.0, 2H), 1.87 (s, 3H), 1.64 (s, 3H), 1.62 – 1.52 (m, 2H), 1.47 – 1.39 (m, 2H), 1.03 (s, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 153.4, 146.7, 140.4, 136.7, 127.5, 114.6, 114.2, 55.7, 39.8, 39.5, 35.0, 32.8, 28.6, 25.7, 19.8, 19.5, 14.6. Observable resonances for minor diastereomer: ^1H NMR (500 MHz, CDCl_3) δ = 6.99 (d, $J = 5.5$, 2H), 3.81 (s, 3H), 1.69 (s, 3H), 1.05 (s, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 124.4, 44.5, 39.7, 28.4, 22.3. MS (ESI) calcd for $[\text{C}_{20}\text{H}_{30}\text{N}_2\text{OH}]^+$: 315.2436, found: 315.2431.

1-(4-chlorophenyl)-2-(4-(2,6,6-trimethylcyclohex-1-en-1-yl)butan-2-ylidene)hydrazine (13e): Yield = 55% (175 mg); *E/Z* 1:0.25; major diastereomer: ^1H NMR (500 MHz, CDCl_3) δ = 7.21 (d, $J = 8.5$, 2H), 7.02 (d, $J = 8.6$, 2H), 6.88 (s, 1H), 2.41 – 2.22 (m, 4H), 2.01 – 1.85 (m, 5H), 1.68 – 1.54 (m, 5H), 1.49 – 1.44 (m, 2H), 1.05 (s, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 144.6, 136.5, 129.0, 129.0, 127.6, 123.9, 114.0, 39.8, 39.5, 35.0, 32.7, 28.6, 25.5, 19.8, 19.5, 14.7. Observable resonances for minor diastereomer: ^1H NMR (500 MHz, CDCl_3) δ = 6.96 (d, $J = 8.2$, 2H) δ = 1.71 (s, 3H), 1.10 (s, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 129.42, 113.90. MS (ESI) calcd for $[\text{C}_{19}\text{H}_{27}\text{ClN}_2\text{H}]^+$: 319.1941, found: 319.1937.

4.3 Representative experimental procedure 2: Preparation of α -chloroazo compounds:

A solution of DMSO (2.5 equiv) in THF (10 mL) was stirred and cooled to $-55\text{ }^\circ\text{C}$ in a flame-dried flask under a nitrogen atmosphere at which point oxalyl chloride (2.0 equiv) was added in a dropwise manner. The reaction was maintained at $-55\text{ }^\circ\text{C}$ until gas evolution ceased (~ 20 min) at which point the reaction was cooled further to $-78\text{ }^\circ\text{C}$. A mixture of Et_3N (2.5 equiv) and hydrazone (1 equiv) in THF (3 mL) was added in a dropwise manner *via* cannula to give a white precipitate. The reaction mixture was maintained at $-78\text{ }^\circ\text{C}$ for 30 min and was then allowed to warm to room temperature at which point the solid was removed by filtration through a medium porosity sintered-glass funnel. The filtrate was concentrated by rotary evaporation and the residue was dissolved in pentane (~ 15 mL). The pentane solution was filtered through a plug of

cotton in a Pasteur pipette to remove insoluble solids. The pentane was removed *in vacuo* to provide the clean α -chloroazo product as a yellow oil.

(E)-1-(2-chlorohex-5-en-2-yl)-2-(p-tolyl)diazene (11a): The title α -chloroazo compound **11a** was prepared in 94% yield (206 mg) as described in representative experimental procedure 2 using hydrazone **10a** (1 equiv, 188 mg, 0.93 mmol), oxalyl chloride (2.0 equiv, 0.16 mL, 1.86 mmol), DMSO (2.5 equiv, 0.17 mL, 2.33 mmol), and TEA (2.5 equiv, 0.32 mL, 2.33 mmol). ^1H NMR (500 MHz, CDCl_3) δ = 7.68 (d, J = 8.3, 2H), 7.27 (d, J = 8.0, 2H), 5.86 – 5.75 (m, 1H), 5.04 (dd, J = 17.1, 1.7, 1H), 4.97 (dd, J = 10.2, 1.7, 1H), 2.42 (s, 3H), 2.38 (d, J = 12.9, 1H), 2.35 – 2.22 (m, 2H), 2.20 – 2.09 (m, 1H), 1.90 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 149.0, 141.9, 137.4, 129.6, 122.9, 115.0, 96.1, 42.0, 28.8, 28.5, 21.4.

(E)-1-(2-chlorohex-5-en-2-yl)-2-(o-tolyl)diazene (11b): The title α -chloroazo compound **11b** was prepared in 95% yield (169 mg) as described in representative experimental procedure 2 using hydrazone **10b** (1 equiv, 152 mg, 0.75 mmol), oxalyl chloride (2.0 equiv, 0.13 mL, 1.5 mmol), DMSO (2.5 equiv, 0.13 mL, 1.87 mmol), and TEA (2.5 equiv, 0.26 mL, 1.87 mmol). ^1H NMR (500 MHz, CDCl_3) δ = 7.40 – 7.27 (m, 3H), 7.22 (t, J = 7.4, 1H), 5.82 (ddt, J = 16.5, 10.2, 6.2, 1H), 5.01 (dd, J = 34.8, 13.7, 2H), 2.64 (s, 3H), 2.48 – 2.03 (m, 4H), 1.91 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 149.2, 137.6, 137.4, 131.2, 131.0, 126.3, 116.2, 115.1, 96.7, 41.9, 28.8, 28.5, 17.2.

(E)-1-(2-chlorohex-5-en-2-yl)-2-(4-methoxyphenyl)diazene (11c): The title α -chloroazo compound **11c** was prepared in 95% yield (134 mg) as described in representative experimental procedure 2 using hydrazone **10c** (1 equiv, 122 mg, 0.56 mmol), oxalyl chloride (2.0 equiv, 0.10 mL, 1.12 mmol), DMSO (2.5 equiv, 0.10 mL, 1.4 mmol), and TEA (2.5 equiv, 0.20 mL, 1.4 mmol). ^1H NMR (500 MHz, CDCl_3) δ = 7.78 (d, J = 9.0, 2H), 6.97 (d, J = 9.0, 2H), 5.88 – 5.70 (m, 1H), 5.04 (dd, J = 17.1, 1.6, 1H), 4.97 (d, J = 10.1, 1H), 3.87 (s, 3H), 2.43 – 2.09 (m, 4H), 1.90 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 162.2, 145.1, 137.5, 124.9, 115.0, 114.12, 96.0, 55.5, 42.1, 28.9, 28.6.

(E)-1-(2-chloro-4-(2,6,6-trimethylcyclohex-1-en-1-yl)butan-2-yl)-2-phenyldiazene (14): The title α -chloroazo compound **14** was prepared in 95% yield (209 mg) as described in representative experimental procedure 2 using hydrazone **13a** (1 equiv, 196 mg, 0.69 mmol), oxalyl chloride (2.0 equiv, 0.12 mL, 1.38 mmol), DMSO (2.5 equiv, 0.12 mL, 1.72 mmol), and TEA (2.5 equiv, 0.24 mL, 0.17 mmol). ^1H NMR (500 MHz, CDCl_3) δ = 7.84 – 7.72 (m, 2H), 7.59 – 7.37 (m, 3H), 2.42 – 2.30 (m, 1H), 2.24 (ddd, J = 12.6, 7.7, 3.7, 2H), 2.04 (d, J = 4.1, 1H), 1.94 – 1.84 (m, 5H), 1.61 – 1.51 (m, 5H), 1.44 – 1.36 (m, 2H), 0.99 (s, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 151.0, 135.7, 131.2, 129.0, 128.1, 122.8, 96.9, 42.7, 39.7, 35.1, 32.7, 28.7, 28.6, 28.5, 23.1, 19.8, 19.4.

4.4 Representative experimental procedure 3: Preparation of α -trifluoroacetoxyazo compounds at -78 °C:

A solution of DMSO (1.2 equiv) in CH_2Cl_2 (1 mL) was added in a dropwise manner to a -78 °C solution of trifluoroacetic anhydride (TFAA) (1.1 or 1.2 equiv) in 10 mL of CH_2Cl_2 under a nitrogen atmosphere. The mixture was stirred for 10 min at -78 °C at which point a solution of hydrazone (1 equiv) in CH_2Cl_2 (5 mL) was added dropwise to the mixture via cannula. After 1 min, TEA (1.15 equiv) was added in a dropwise manner. The mixture was stirred for 10 min at -

78 °C and was then allowed to warm to room temperature (~20 min) at which point the mixture was concentrated. The residue was dissolved in hexane (~15 mL), filtered through a plug of basic alumina to remove triethylammonium salt, and the hexane was removed *in vacuo* to provide the α -trifluoroacetoxyazo product as a yellow oil.

4.5 Representative experimental procedure 4: Preparation of α -trifluoroacetoxyazo compounds at 0 °C:

TFAA (1.1 or 1.2 equiv) was added dropwise to a 0 °C solution of hydrazone (1.0 equiv), DMSO (1.2 equiv), TEA (1.15 equiv), and hexane under a nitrogen atmosphere. The mixture was stirred for 5 min at 0 °C and for 15 min at room temperature at which point it was filtered through a plug of basic alumina to remove triethylammonium salt. The hexane was removed *in vacuo* to provide the α -trifluoroacetoxyazo product as a yellow oil.

(E)-2-(phenyldiazenyl)-4-(2,6,6-trimethylcyclohex-1-en-1-yl)butan-2-yl 2,2,2-trifluoroacetate (16a): The title α -trifluoroacetoxyazo **16a** was prepared in 87% (595 mg) yield as described in representative experimental procedure 3 using hydrazone **13a** (1 equiv, 490 mg, 1.72 mmol), TFAA (1.1 equiv, 0.27 mL, 1.89 mmol), DMSO (1.2 equiv, 0.15 mL, 2.06 mmol), and TEA (1.15 equiv, 0.28 mL, 1.98 mmol). Alternatively, the title α -trifluoroacetoxyazo **16a** was prepared in 82% yield (267 mg) as described in the representative experimental procedure 4 using hydrazone **13a** (1 equiv, 233 mg, 0.82 mmol), TFAA (1.2 equiv, 0.14 mL, 0.98 mmol), DMSO (1.2 equiv, 0.07 mL, 0.98 mmol), and TEA (1.2 equiv, 0.13 mL, 0.94 mmol). ¹H NMR (500 MHz, CDCl₃) δ = 7.74 – 7.64 (m, 2H), 7.52 – 7.45 (m, 3H), 2.29 – 1.97 (m, 4H), 1.94 – 1.86 (m, 5H), 1.60 – 1.49 (m, 5H), 1.42 – 1.37 (m, 2H), 0.96 (d, *J* = 2.6, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 150.7, 135.4, 131.5, 129.1, 128.3, 122.8, 107.6, 39.7, 38.6, 35.0, 32.7, 28.5, 28.4, 21.7, 21.4, 19.6, 19.4.

(E)-2-(p-tolyldiazenyl)-4-(2,6,6-trimethylcyclohex-1-en-1-yl)butan-2-yl 2,2,2-trifluoroacetate (16b): The title α -trifluoroacetoxyazo **16b** was prepared in 76% yield (204 mg) as described in representative experimental procedure 3 using hydrazone **13b** (1 equiv, 193 mg, 0.65 mmol), TFAA (1.1 equiv, 0.10 mL, 0.71 mmol), DMSO (1.2 equiv, 0.06 mL, 0.78 mmol), and TEA (1.15 equiv, 0.10 mL, 0.75 mmol). ¹H NMR (500 MHz, CDCl₃) δ = 7.61 (d, *J* = 8.3, 2H), 7.26 (d, *J* = 8.0, 2H), 2.41 (s, 3H), 2.29 – 2.15 (m, 1H), 2.15 – 2.08 (m, 2H), 2.07 – 1.96 (m, 1H), 1.90 (s, 3H), 1.92 – 1.83 (m, 2H), 1.55 (s, 3H), 1.58 – 1.51 (m, 2H), 1.43 – 1.37 (m, 2H), 0.99 – 0.94 (m, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 148.8, 142.0, 135.5, 129.6, 128.3, 122.8, 107.5, 39.7, 38.7, 35.0, 32.7, 28.5, 28.4, 28.4, 21.7, 21.4, 19.6, 19.4.

(E)-2-(o-tolyldiazenyl)-4-(2,6,6-trimethylcyclohex-1-en-1-yl)butan-2-yl 2,2,2-trifluoroacetate (16c): The title α -trifluoroacetoxyazo **16c** was prepared in 83% yield (344 mg) as described in representative experimental procedure 3 using hydrazone **13c** (1 equiv, 303 mg, 1.01 mmol), TFAA (1.1 equiv, 0.16 mL, 1.12 mmol), DMSO (1.2 equiv, 0.09 mL, 1.21 mmol), and TEA (1.15 equiv, 0.16 mL, 1.2 mmol). ¹H NMR (500 MHz, CDCl₃) δ = 7.35 (dd, *J* = 11.6, 7.6, 2H), 7.30 (d, *J* = 7.4, 1H), 7.22 (t, *J* = 7.6, 1H), 2.55 (s, 3H), 2.28 – 2.17 (m, 1H), 2.17 – 2.11 (m, 2H), 2.04 – 1.94 (m, 4H), 1.92 – 1.85 (m, 2H), 1.59 – 1.54 (m, 5H), 1.43 – 1.36 (m, 2H), 0.97 (d, *J* = 3.5, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 149.0, 137.6, 135.4, 131.3, 131.2, 128.3, 126.4, 115.9, 107.4, 39.7, 38.8, 35.0, 32.7, 28.5, 28.4, 28.4, 21.96, 21.3, 19.6, 19.4, 17.2.

(E)-2-((4-methoxyphenyl)diazenyl)-4-(2,6,6-trimethylcyclohex-1-en-1-yl)butan-2-yl 2,2,2-trifluoroacetate (16d): The title α -trifluoroacetoxyazo **16d** was prepared in 76% yield (287 mg) as described in representative experimental procedure 3 using hydrazone **13d** (1 equiv, 281 mg, 0.89 mmol), TFAA (1.2 equiv, 0.15 mL, 1.07 mmol), DMSO (1.2 equiv, 0.08 mL, 1.07 mmol), and TEA (1.15 equiv, 0.14 mL, 1.02 mmol). Alternatively, the title α -trifluoroacetoxyazo **16d** was prepared in 57% yield (360 mg) as described in representative experimental procedure 4 using hydrazone **13d** (1 equiv, 465 mg, 1.48 mmol), TFAA (1.2 equiv, 0.31 mL, 2.2 mmol), DMSO (1.2 equiv, 0.16 mL, 2.2 mmol), and TEA (1.15 equiv, 0.24 mL, 1.7 mmol). ¹H NMR (500 MHz, CDCl₃) δ = 7.71 (d, J = 9.1, 2H), 6.95 (d, J = 9.0, 2H), 3.87 (s, 3H), 2.31 – 2.17 (m, 1H), 2.17 – 2.07 (m, 2H), 2.07 – 1.96 (m, 1H), 1.97 – 1.83 (m, 5H), 1.63 – 1.49 (m, 5H), 1.44 – 1.35 (m, 2H), 0.96 (d, J = 2.3, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 162.3, 144.93, 135.5, 128.26, 124.7, 114.1, 107.4, 55.58, 39.7, 38.7, 35.0, 32.7, 28.5, 28.4, 21.8, 21.4, 19.6, 19.4.

(E)-2-((4-chlorophenyl)diazenyl)-4-(2,6,6-trimethylcyclohex-1-en-1-yl)butan-2-yl 2,2,2-trifluoroacetate (16e): The title α -trifluoroacetoxyazo **16e** was prepared in 86% yield (422 mg) as described in representative experimental procedure 3 using hydrazone **13e** (1 equiv, 363 mg, 1.14 mmol), TFAA (1.1 equiv, 0.18 mL, 1.25 mmol), DMSO (1.2 equiv, 0.10 mL, 1.37 mmol), and TEA (1.15 equiv, 0.18 mL, 1.13 mmol). ¹H NMR (500 MHz, CDCl₃) δ = 7.66 (d, J = 8.8, 2H), 7.45 (d, J = 8.8, 2H), 2.29 – 2.17 (m, 1H), 2.16 – 2.07 (m, 2H), 2.07 – 1.95 (m, 1H), 1.92 – 1.85 (m, 5H), 1.60 – 1.49 (m, 5H), 1.45 – 1.35 (m, 2H), 0.96 (d, J = 3.1, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 149.03, 137.61, 135.34, 129.38, 128.44, 124.12, 107.52, 39.68, 38.65, 34.99, 32.75, 28.52, 28.45, 21.68, 21.39, 19.61, 19.41.

(E)-2-(p-tolyldiazenyl)hex-5-en-2-yl 2,2,2-trifluoroacetate (17a): The title α -trifluoroacetoxyazo **17a** was prepared in 69% yield (340 mg) as described in representative experimental procedure 3 using hydrazone **10a** (1 equiv, 318 mg, 1.58 mmol), TFAA (1.1 equiv, 0.24 mL, 1.73 mmol), DMSO (1.2 equiv, 0.13 mL, 1.88 mmol), and TEA (1.15 equiv, 0.25 mL, 1.81 mmol). ¹H NMR (500 MHz, CDCl₃) δ = 7.61 (d, J = 8.3, 2H), 7.26 (d, J = 6.7, 2H), 5.85 – 5.72 (m, 1H), 5.04 (dd, J = 17.1, 1.5, 1H), 4.98 (dd, J = 10.2, 1.5, 1H), 2.41 (s, 3H), 2.36 – 2.04 (m, 4H), 1.88 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 148.6, 142.2, 137.0, 129.7, 122.8, 115.3, 107.0, 37.6, 27.0, 22.09, 21.4.

(E)-2-(o-tolyldiazenyl)hex-5-en-2-yl 2,2,2-trifluoroacetate (17b): The title α -trifluoroacetoxyazo **17b** was prepared in 65% yield (137 mg) as described in representative experimental procedure 3 using hydrazone **10b** (1 equiv, 136 mg, 0.67 mmol), TFAA (1.1 equiv, 0.10 mL, 0.74 mmol), DMSO (1.2 equiv, 0.06 mL, 0.80 mmol), and TEA (1.15 equiv, 0.10 mL, 0.77 mmol). Alternatively, the title α -trifluoroacetoxyazo **17b** was prepared in 62% yield (180 mg) as described in representative experimental procedure 4 using hydrazone **10b** (1 equiv, 186 mg, 0.92 mmol), TFAA (1.1 equiv, 0.14 mL, 1.01 mmol), DMSO (1.2 equiv, 0.08 mL, 1.10 mmol), and TEA (1.15 equiv, 0.15 mL, 1.06 mmol). ¹H NMR (500 MHz, CDCl₃) δ = 7.36 (t, J = 7.7, 2H), 7.30 (d, J = 7.4, 1H), 7.22 (t, J = 7.6, 1H), 5.79 (dd, J = 17.1, 10.2, 1H), 5.05 (dd, J = 17.1, 1.6, 1H), 4.99 (dd, J = 10.3, 1.6, 1H), 2.54 (s, 3H), 2.34 – 2.03 (m, 4H), 1.93 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 148.9, 137.7, 136.9, 131.4, 131.3, 126.4, 116.0, 115.4, 107.0, 37.6, 26.9, 22.2, 17.2.

(E)-2-((4-methoxyphenyl)diazenyl)hex-5-en-2-yl 2,2,2-trifluoroacetate (17c): The title α -trifluoroacetoxyazo **17c** was prepared in 74% yield (143 mg) as described in representative

experimental procedure 3 using hydrazone **10c** (1 equiv, 130 mg, 0.59 mmol), TFAA (1.1 equiv, 0.09 mL, 0.66 mmol), DMSO (1.2 equiv, 0.05 mL, 0.72 mmol), and TEA (1.15 equiv, 0.10 mL, 0.09 mmol). ¹H NMR (500 MHz, CDCl₃) δ = 7.71 (d, *J* = 9.1, 2H), 6.96 (d, *J* = 9.1, 2H), 5.85 – 5.72 (m, 1H), 5.04 (dd, *J* = 17.1, 1.6, 1H), 4.98 (dd, *J* = 10.2, 1.6, 1H), 3.87 (s, 3H), 2.35 – 2.02 (m, 4H), 1.87 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 162.45, 144.81, 137.10, 124.85, 115.33, 114.14, 106.96, 55.61, 37.68, 27.07, 22.14.

(*E*)-2-((4-nitrophenyl)diazenyl)hex-5-en-2-yl 2,2,2-trifluoroacetate (17d): The title α-trifluoroacetoxyazo **17d** was prepared in 82% yield (298 mg) as described in representative experimental procedure 3 using hydrazone **10d** (1 equiv, 244 mg, 1.05 mmol), TFAA (1.1 equiv, 0.16 mL, 1.15 mmol), DMSO (1.2 equiv, 0.09 mL, 1.26 mmol), and TEA (1.15 equiv, 0.17 mL, 1.21 mmol). ¹H NMR (500 MHz, CDCl₃) δ = 8.35 (d, *J* = 9.0, 2H), 7.83 (d, *J* = 9.1, 2H), 5.78 (dd, *J* = 17.1, 10.2, 1H), 5.03 (ddd, *J* = 13.7, 11.7, 1.5, 2H), 2.33 – 2.08 (m, 4H), 1.92 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 153.6, 149.3, 136.5, 124.7, 123.5, 115.7, 107.2, 37.4, 26.9, 21.9.

(*E*)-2-((3-nitrophenyl)diazenyl)hex-5-en-2-yl 2,2,2-trifluoroacetate (17e): The title α-trifluoroacetoxyazo **17e** was prepared in 88% yield (207 mg) as described in representative experimental procedure 3 using hydrazone **10e** (1 equiv, 159 mg, 0.68 mmol), TFAA (1.1 equiv, 0.11 mL, 0.75 mmol), DMSO (1.2 equiv, 0.06 mL, 0.82 mmol), and TEA (1.15 equiv, 0.11 mL, 0.78 mmol). Alternatively, the title α-trifluoroacetoxyazo **17e** was prepared in 79% yield (209 mg) as described in representative experimental procedure 4 using hydrazone **10e** (1 equiv, 180 mg, 0.77 mmol), TFAA (1.2 equiv, 0.13 mL, 0.92 mmol), DMSO (1.2 equiv, 0.07 mL, 0.92 mmol), and TEA (1.15 equiv, 0.89 mL, 0.12 mmol). ¹H NMR (500 MHz, CDCl₃) δ = 8.53 (t, *J* = 2.0, 1H), 8.36 (ddd, *J* = 8.2, 2.3, 1.1, 1H), 8.06 (ddd, *J* = 7.9, 1.9, 1.1, 1H), 7.69 (t, *J* = 8.1, 1H), 5.78 (ddt, *J* = 16.5, 10.2, 6.3, 1H), 5.03 (ddq, *J* = 21.4, 10.1, 1.3, 2H), 2.39 – 2.04 (m, 4H), 1.94 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 150.9, 148.9, 136.5, 130.1, 129.1, 125.8, 117.3, 115.7, 107.0, 37.5, 26.9, 22.0.

(*E*)-2-((4-chlorophenyl)diazenyl)hex-5-en-2-yl 2,2,2-trifluoroacetate (17f): The title α-trifluoroacetoxyazo **17f** was prepared in 80% yield (428 mg) as described in representative experimental procedure 3 using hydrazone **10f** (1 equiv, 353 mg, 1.59 mmol), TFAA (1.1 equiv, 0.25 mL, 1.75 mmol), DMSO (1.2 equiv, 0.14 mL, 1.91 mmol), and TEA (1.15 equiv, 0.25 mL, 1.83 mmol). ¹H NMR (500 MHz, CDCl₃) δ = 7.66 (d, *J* = 8.8, 2H), 7.45 (d, *J* = 8.8, 2H), 5.77 (ddt, *J* = 13.4, 10.2, 6.2, 1H), 5.04 (dd, *J* = 17.1, 1.6, 1H), 4.99 (dd, *J* = 10.2, 1.5, 1H), 2.33 – 2.03 (m, 4H), 1.89 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 148.9, 137.7, 136.8, 129.3, 124.1, 115.5, 107.0, 37.5, 27.0, 22.0.

(*E*)-2-((2,4-dichlorophenyl)diazenyl)hex-5-en-2-yl 2,2,2-trifluoroacetate (17g): The title α-trifluoroacetoxyazo **17g** was prepared in 80% yield (186 mg) as described in representative experimental procedure 3 using hydrazone **10g** (1 equiv, 161 mg, 0.63 mmol), TFAA (1.1 equiv, 0.10 mL, 0.69 mmol), DMSO (1.2 equiv, 0.06 mL, 0.76 mmol), and TEA (1.15 equiv, 0.10 mL, 0.72 mmol). ¹H NMR (500 MHz, CDCl₃) δ = 7.55 (d, *J* = 2.1, 1H), 7.39 (d, *J* = 8.6, 1H), 7.28 (dd, *J* = 8.7, 2.2, 1H), 5.78 (ddt, *J* = 16.4, 10.2, 6.3, 1H), 5.05 (dd, *J* = 17.1, 1.6, 1H), 5.00 (dd, *J* = 10.3, 1.5, 1H), 2.46 – 2.05 (m, 4H), 1.91 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 145.4, 137.9, 136.7, 135.9, 130.4, 127.7, 118.8, 115.6, 107.2, 37.5, 26.9, 22.1.

(*E*)-2-(phenyldiazenyl)hex-5-en-2-yl 2,2,2-trifluoroacetate (17h): The title α-trifluoroacetoxyazo **17h** was prepared in 80% yield (171 mg) as described in representative experimental procedure 3 using hydrazone **10h** (1 equiv, 336 mg, 0.71 mmol), TFAA (1.1 equiv,

0.11 mL, 0.78 mmol), DMSO (1.2 equiv, 0.06 mL, 0.85 mmol), and TEA (1.15 equiv, 0.11 mL, 0.82 mmol). Alternatively, the title α -trifluoroacetoxyazo **17h** was prepared in 87% yield (391 mg) as described in representative experimental procedure 4 using hydrazone **10h** (1 equiv, 281 mg, 1.5 mmol), TFAA (1.1 equiv, 0.23 mL, 1.65 mmol), DMSO (1.2 equiv, 0.13 mL, 1.65 mmol), and TEA (1.15 equiv, 0.24 mL, 1.71 mmol). ^1H NMR (500 MHz, CDCl_3) δ = 7.73 – 7.66 (m, 2H), 7.50 – 7.43 (m, 3H), 5.90 – 5.62 (m, 1H), 5.11 – 4.90 (m, 2H), 2.31 – 2.02 (m, 4H), 1.90 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 150.6, 136.9, 131.6, 129.1, 122.8, 115.4, 107.0, 37.58, 2.02, 22.0.

4.6 Representative experimental procedure 5: SbCl_5 mediated $[4^\oplus + 2]$ -cycloaddition:

SbCl_5 (0.95 equiv) was added in a dropwise manner to a solution of an α -chloroazo compound (1 equiv) in CH_2Cl_2 under a nitrogen atmosphere at -78°C . The mixture was stirred for 30 min at -78°C and then warmed to room temperature. The solvent was removed *in vacuo* to give a thick foam that was triturated with petroleum ether 3 times and dried under high vacuum to give the cycloaddition product as a powder. To determine yields, the solid material was fully dissolved in CD_3CN , 1,3,5-trimethoxybenzene (0.95 equiv) was added as an internal standard, and an aliquot of this homogeneous mixture was analyzed by ^1H NMR.

3,8-dimethyl-2,5,10,10a-tetrahydro-1H-pyrrolo[1,2-b]cinnolin-4-ium hexachlorostibate(V) (12a): The title $[4^\oplus + 2]$ cycloaddition product **12a** was prepared in 86% yield as determined by ^1H NMR (crude product 95%, 444 mg) as described in representative experimental procedure 5 by reacting α -chloroazo **11a** (206 mg, 0.87 mmol), SbCl_5 (2 M in CH_2Cl_2 , 0.42 mL, 0.83 mmol), and CH_2Cl_2 (15 mL). Mp 92.6°C . ^1H NMR (500 MHz, Acetone- d_6) δ = 7.05 (d, J = 7.1, 1H), 7.05 (s, 1H), 7.01 (d, J = 8.9, 1H), 4.81 – 4.59 (m, 1H), 3.42 – 3.25 (m, 3H), 3.05 (dt, J = 17.2, 8.6, 1H), 2.86 – 2.73 (m, 1H), 2.63 (s, 3H), 2.27 (s, 3H), 2.16 (ddd, J = 18.9, 12.9, 9.2, 1H). ^{13}C NMR (126 MHz, Acetone- d_6) δ 168.9, 135.9, 132.7, 130.2, 129.5, 119.4, 114.9, 67.6, 36.4, 33.4, 25.9, 20.6, 16.3; IR (film) ν_{max} : 3200, 3003, 2970, 2947, 1738, 1724, 1504, 1423, 1366, 1275, 1227, 1217, 1157, 1032, 816 cm^{-1} . MS (ESI) calcd for $[\text{C}_{13}\text{H}_{17}\text{N}_2]^+$: 201.1392, found: 201.1387.

3,6-dimethyl-2,5,10,10a-tetrahydro-1H-pyrrolo[1,2-b]cinnolin-4-ium hexachlorostibate(V) (12b): The title $[4^\oplus + 2]$ cycloaddition product **12b** was prepared in 80% yield as determined by ^1H NMR (crude product 89%, 341 mg) as described in representative experimental procedure 5 by reacting α -chloroazo **11b** (170 mg, 0.72 mmol), SbCl_5 (2 M in CH_2Cl_2 , 0.34 mL, 0.68 mmol), and CH_2Cl_2 (15 mL). Mp 96.8°C . ^1H NMR (500 MHz, Acetone- d_6) δ = 7.11 (dd, J = 17.7, 7.5, 2H), 6.97 (t, J = 7.5, 1H), 4.72 (d, J = 6.1, 1H), 3.50 – 3.31 (m, 3H), 3.11 (dd, J = 15.6, 12.6, 1H), 2.90 – 2.77 (m, 1H), 2.73 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (126 MHz, Acetone- d_6) δ 176.6, 136.5, 130.4, 127.8, 125.0, 123.6, 120.1, 66.6, 36.6, 34.0, 25.4, 17.3, 17.0; IR (film) ν_{max} : 3200, 3014, 2970, 2941, 1738, 1724, 1474, 1435, 1366, 1269, 1229, 1217, 1206, 1090, 1032 cm^{-1} . MS (ESI) calcd for $[\text{C}_{13}\text{H}_{17}\text{N}_2]^+$: 201.1392, found: 201.1386.

4.7 Representative experimental procedure 6: TMS-OTf mediated $[4^\oplus + 2]$ -cycloaddition:

Freshly distilled trimethylsilyl trifluoromethanesulfonate (1.05 equiv or 1.5 equiv) was added dropwise *via* syringe to a stirred solution of α -chloroazo or α -trifluoroacetoxyazo compound (1.0 equiv) in hexane or CH_2Cl_2 under a nitrogen atmosphere at room temperature. The resulting

mixture was stirred at room temperature for 12 h or at 40 °C for 4 h at which point a light-brown precipitate was collected by filtration, and washed with diethyl ether to give a solid product. In some cases the product was recrystallized using a very small amount of methanol with diethyl ether to provide very fine crystals.

rel-(4aR,13bR)-4,4,7,13b-tetramethyl-1,2,3,4,5,6,9,13b-octahydrobenzo[c]pyrrolo[1,2-b]cinnolin-8-ium trifluoromethanesulfonate (18a): The title $[4^{\oplus}+2]$ cycloaddition product **18a** was prepared in 45% yield (519 mg) as described in representative experimental procedure 6 by reacting α -chloroazo **14** (1 equiv, 851 mg, 2.66 mmol), TMS-OTf (1.05 equiv, 0.51 mL, 2.8 mmol), and hexane (20 mL) for 12 h at room temperature. Alternatively, treating α -trifluoroacetoxyazo compound **16a** (1 equiv, 595 mg, 1.5 mmol) with TMSOTf (1.5 equiv, 0.41 mL, 2.25 mmol) in hexane (12 mL) for 4 h at 40 °C returned 467 mg of **18a** (72% yield). Mp 189.4 °C (recrystallized from MeOH/Et₂O). ¹H NMR (500 MHz, CD₃CN) δ = 9.30 (s, 1H), 7.34 (d, J = 7.8, 1H), 7.26 (t, J = 7.1, 1H), 7.10 (t, J = 7.1, 1H), 6.89 (d, J = 8.1, 1H), 3.21 – 3.01 (m, 1H), 2.54 (s, 3H), 2.53 – 2.43 (m, 3H), 1.72 – 1.43 (m, 4H), 1.35 – 1.27 (m, 1H), 1.06 (s, 3H), 0.95 (s, 3H), 0.62 (s, 3H). ¹³C NMR (126 MHz, CD₃CN) δ 171.6, 137.6, 128.7, 128.2, 124.8, 124.3, 114.4, 85.4, 42.3, 41.5, 39.4, 36.4, 32.2, 29.8, 27.2, 25.6, 24.9, 18.6, 16.6; IR (film) ν_{max} : 3188, 3003, 1591, 1497, 1445, 1344, 1285, 1242, 1225, 1151, 1028 cm⁻¹. MS (ESI) calcd for [C₁₉H₂₇N₂]⁺: 283.2174, found: 283.2173.

rel-(4aR,13bR)-4,4,7,12,13b-pentamethyl-1,2,3,4,5,6,9,13b-octahydrobenzo[c]pyrrolo[1,2-b]cinnolin-8-ium trifluoromethanesulfonate (18b): The title $[4^{\oplus}+2]$ cycloaddition product **18b** was prepared in 25% yield (46 mg) as described in representative experimental procedure 6 by reacting α -trifluoroacetoxyazo **16b** (1 equiv, 173 mg, 0.42 mmol), TMS-OTf (1.05 equiv, 0.08 mL, 0.44 mmol), and hexane (10 mL) for 12 h at room temperature. Alternatively, this product was prepared in 70% yield (531 mg) as described in representative experimental procedure 6 by reacting α -trifluoroacetoxyazo **16b** (1 equiv, 697 mg, 1.7 mmol), TMS-OTf (1.5 equiv, 0.46 mL, 2.54 mmol), and hexane (15 mL) for 4 h at 40 °C. Mp 211.5 °C (recrystallized from MeOH/Et₂O). ¹H NMR (500 MHz, Acetone-*d*₆) δ = 10.36 (s, 1H), 7.24 (s, 1H), 7.07 (dd, J = 8.1, 1.0, 1H), 6.89 (d, J = 8.2, 1H), 3.49 – 3.20 (m, 2H), 2.72 (s, 3H), 2.70 – 2.57 (m, 3H), 2.33 (s, 3H), 1.76 (td, J = 13.1, 4.1, 1H), 1.69 – 1.54 (m, 2H), 1.50 (ddd, J = 10.9, 6.5, 3.4, 1H), 1.40 – 1.31 (m, 1H), 1.13 (s, 3H), 1.04 (s, 3H), 0.72 (s, 3H). ¹³C NMR (126 MHz, CD₃CN) δ 171.0, 135.3, 134.0, 129.2, 128.1, 125.2, 114.5, 85.4, 42.3, 41.5, 39.4, 36.43, 32.2, 29.9, 27.2, 25.6, 24.9, 20.9, 18.6, 16.5; IR (film) ν_{max} : 3204, 2978, 2870, 1713, 1645, 1614, 1506, 1279, 1242, 1223, 1155, 1028, 827 cm⁻¹. MS (ESI) calcd for [C₂₀H₂₉N₂]⁺: 297.2331, found: 2297.2332.

rel-(4aR,13bR)-4,4,7,10,13b-pentamethyl-1,2,3,4,5,6,9,13b-octahydrobenzo[c]pyrrolo[1,2-b]cinnolin-8-ium trifluoromethanesulfonate (18c): The title $[4^{\oplus}+2]$ cycloaddition product **18c** was prepared in 33% yield (111 mg) as described in representative experimental procedure 6 by reacting α -trifluoroacetoxyazo **16c** (1 equiv, 307 mg, 0.75 mmol), TMS-OTf (1.05 equiv, 0.14 mL, 0.79 mmol), and hexane (12 mL) for 12 h at room temperature. Alternatively, this product was prepared in 70% yield (262 mg) as described in representative experimental procedure 6 by reacting α -trifluoroacetoxyazo **16c** (1 equiv, 343 mg, 0.84 mmol), TMS-OTf (1.5 equiv, 0.23 mL, 1.3 mmol), and hexane (12 mL) for 4 h at 40 °C. Mp 216.4 °C (recrystallized from MeOH/Et₂O). ¹H NMR (500 MHz, Acetone-*d*₆) δ = 9.38 (s, 1H), 7.28 (d, J = 7.8, 1H), 7.14 (dd, J = 7.4, 0.4, 1H), 7.05 (t, J = 7.6, 1H), 3.43 – 3.33 (m, 2H), 2.82 (s, 3H), 2.76 – 2.54 (m, 3H), 2.31 (s, 3H), 1.80 – 1.45 (m, 4H), 1.35 (ddd, J = 13.6, 4.9, 3.1, 1H), 1.12 (s, 3H), 1.07 (s, 3H).

^{13}C NMR (126 MHz, CD_3CN) δ 177.3, 135.8, 130.1, 128.4, 124.3, 123.9, 122.5, 84.1, 42.2, 41.6, 39.5, 36.4, 32.3, 30.0, 26.9, 25.5, 24.7, 18.6, 17.2, 17.1; IR (film) ν_{max} : 3208, 3015, 2970, 2941, 2870, 1740, 1728, 1464, 1423, 1369, 1283, 1254, 1225, 1217, 1150, 1032 cm^{-1} . MS (ESI) calcd for $[\text{C}_{20}\text{H}_{29}\text{N}_2]^+$: 297.2331, found: 2297.2328.

rel-(4aR,13bR)-12-methoxy-4,4,7,13b-tetramethyl-1,2,3,4,5,6,9,13b-

octahydrobenzo[c]pyrrolo[1,2-b]cinnolin-8-ium trifluoromethanesulfonate (18d): The title $[4^{\oplus}+2]$ cycloaddition product **18d** was prepared in 53% yield (330 mg) as described in representative experimental procedure 6 by reacting α -trifluoroacetoxyazo **16d** (1 equiv, 578 mg, 1.35 mmol), TMS-OTf (1.05 equiv, 0.26 mL, 1.42 mmol), and hexane (20 mL) for 12 h at room temperature. Alternatively, this product was prepared in 40% yield (143 mg) as described in representative experimental procedure 6 by reacting α -trifluoroacetoxyazo **16d** (1 equiv, 326 mg, 0.76 mmol), TMS-OTf (1.5 equiv, 0.21 mL, 1.15 mmol), and hexane (15 mL) for 4 h at 40 $^{\circ}\text{C}$. The final product was recrystallized using the smallest amount of methanol with diethyl ether to provide golden crystals. Mp 191.5 $^{\circ}\text{C}$ (recrystallized from MeOH/Et₂O). ^1H NMR (500 MHz, CD_3CN) δ = 9.24 (s, 1H), 6.87 (s, 1H), 6.84 (d, J = 2.1, 2H), 3.78 (s, 3H), 3.20 – 2.98 (m, 2H), 2.52 (s, 3H), 2.51 – 2.42 (m, 3H), 1.70 – 1.42 (m, 4H), 1.35 – 1.28 (m, 1H), 1.12 (t, J = 7.0, 1H), 1.06 (s, 3H), 0.95 (s, 3H), 0.64 (s, 3H). ^{13}C NMR (126 MHz, CD_3CN) δ 170.6, 157.2, 131.3, 129.7, 115.8, 114.1, 110.3, 85.3, 56.3, 42.4, 41.7, 39.3, 36.4, 32.2, 29.6, 27.1, 25.6, 25.0, 18.7, 16.5; IR (film) ν_{max} : 3196, 3005, 2874, 1713, 1645, 1592, 1501, 1423, 1362, 1277, 1246, 1223, 1155, 1030, 872, 816 cm^{-1} . MS (ESI) calcd for $[\text{C}_{20}\text{H}_{29}\text{N}_2\text{O}]^+$: 313.228, found: 313.2277.

rel-(4aR,13bR)-12-chloro-4,4,7,13b-tetramethyl-1,2,3,4,5,6,9,13b-

octahydrobenzo[c]pyrrolo[1,2-b]cinnolin-8-ium trifluoromethanesulfonate (18e): The title $[4^{\oplus}+2]$ cycloaddition product **18e** was prepared in 35% yield (160 mg) as described in representative experimental procedure 6 by reacting α -trifluoroacetoxyazo **16e** (1 equiv, 422 mg, 0.98 mmol), TMS-OTf (1.05 equiv, 0.19 mL, 1.03 mmol), and hexane (20 mL) for 12 h at room temperature. Alternatively, this product was prepared in 42% yield (71 mg) as described in representative experimental procedure 6 by reacting α -trifluoroacetoxyazo **16e** (1 equiv, 157 mg, 0.36 mmol), TMS-OTf (1.5 equiv, 0.10 mL, 0.55 mmol), and hexane (15 mL) for 4 h at 40 $^{\circ}\text{C}$. Mp 230.0 $^{\circ}\text{C}$ (recrystallized from MeOH/Et₂O). ^1H NMR (500 MHz, CD_3CN) δ = 9.73 (s, 1H), 7.28 (dd, J = 26.5, 24.9, 2H), 6.91 (d, J = 8.6, 1H), 3.26 – 2.93 (m, 2H), 2.56 (s, 3H), 2.53 – 2.37 (m, 3H), 1.72 – 1.23 (m, 5H), 1.06 (s, 3H), 0.96 (s, 3H), 0.66 (s, 3H). ^{13}C NMR (126 MHz, CD_3CN) δ 172.7, 136.5, 130.1, 128.7, 128.6, 124.8, 116.0, 84.9, 42.3, 41.7, 39.2, 36.5, 32.0, 29.6, 27.0, 25.5, 24.8, 18.5, 16.7; IR (film) ν_{max} : 3177, 3015, 2970, 2947, 1740, 1728, 1493, 1435, 1366, 1279, 1225, 1217, 1161, 1028, 824 cm^{-1} . MS (ESI) calcd for $[\text{C}_{19}\text{H}_{26}\text{ClN}_2]^+$: 317.1785, found: 317.1781.

3,8-dimethyl-2,5,10a-tetrahydro-1H-pyrrolo[1,2-b]cinnolin-4-ium

trifluoromethanesulfonate (19a): The title $[4^{\oplus}+2]$ cycloaddition product **19a** was prepared in 85% yield (113 mg) as described in representative experimental procedure 6 by reacting α -chloroazo **11a** (1 equiv, 89 mg, 0.38 mmol), TMS-OTf (1.05 equiv, 0.07 mL, 0.39 mmol), and hexane (10 mL) for 12 h at room temperature. Alternatively, this product was prepared in 86% yield (325 mg) as described in representative experimental procedure 6 by reacting α -trifluoroacetoxyazo **17a** (1 equiv, 340 mg, 1.1 mmol), TMS-OTf (1.05 equiv, 0.21 mL, 1.15 mmol), and hexane (7 mL) for 4 h at room temperature. Mp 152.7 $^{\circ}\text{C}$ (recrystallized from

MeOH/Et₂O). ¹H NMR (500 MHz, CD₃CN) δ = 9.08 (s, 1H), 7.08 (d, *J* = 8.2, 1H), 7.03 (s, 1H), 6.90 (d, *J* = 8.2, 1H), 4.48 (qd, *J* = 12.3, 10.4, 1H), 3.24 (dd, *J* = 16.0, 4.3, 1H), 3.16 – 3.00 (m, 2H), 2.92 (dd, *J* = 15.8, 12.6, 1H), 2.63 (dtd, *J* = 12.1, 8.1, 3.9, 1H), 2.38 (s, 3H), 2.28 (s, 3H), 2.01 – 1.95 (m, 1H). ¹³C NMR (126 MHz, CD₃CN) δ 168.4, 135.7, 133.4, 130.4, 129.8, 119.5, 114.7, 67.6, 36.2, 33.2, 25.7, 20.6, 15.9; IR (film) ν_{max}: 3198, 3024, 2970, 1740, 1728, 1501, 1427, 1366, 1294, 1233, 1217, 1148, 1030, 833 cm⁻¹. MS (ESI) calcd for [C₁₃H₁₇N₂]⁺: 201.1392, found: 201.1387.

3,6-dimethyl-2,5,10,10a-tetrahydro-1*H*-pyrrolo[1,2-*b*]cinnolin-4-ium

trifluoromethanesulfonate (19b): The title [4[⊕]+2] cycloaddition product **19b** was prepared in 83% yield (40 mg) as described in representative experimental procedure 6 by reacting α-chloroazo **11b** (1 equiv, 33 mg, 0.14 mmol), TMS-OTf (1.05 equiv, 0.03 mL, 0.15 mmol), and 6 mL hexane (6 mL) for 12 h at room temperature. Alternatively, this product was prepared in 83% yield (296 mg) as described in representative experimental procedure 6 by reacting α-trifluoroacetoxyazo **17b** (1 equiv, 320 mg, 1.02 mmol), TMS-OTf (1.05 equiv, 0.20 mL, 1.07 mmol), and hexane (15 mL) for 12 h at room temperature. This product was also prepared in 90% yield (181 mg) as described in representative experimental procedure 6 by reacting α-trifluoroacetoxyazo (1 equiv, 180 mg, 0.57 mmol), TMS-OTf (1.5 equiv, 0.16 mL, 0.86 mmol), and hexane (12 mL) for 4 h at 40 °C. Mp 149.1 °C (recrystallized from MeOH/Et₂O). ¹H NMR (500 MHz, CD₃CN) δ = 8.22 (s, 1H), 7.13 (d, *J* = 7.4, 1H), 7.06 (d, *J* = 7.6, 1H), 6.97 (t, *J* = 7.5, 1H), 4.54 – 4.36 (m, 1H), 3.30 (dd, *J* = 16.0, 4.4, 1H), 3.23 – 3.05 (m, 2H), 2.97 (dd, *J* = 15.9, 12.5, 1H), 2.72 – 2.62 (m, 1H), 2.50 (s, 3H), 2.27 (s, 3H), 1.98 (ddd, *J* = 9.7, 8.9, 4.9, 1H). ¹³C NMR (126 MHz, CD₃CN) δ 176.1, 136.4, 130.6, 128.0, 124.9, 123.8, 120.0, 66.6, 36.4, 33.8, 25.3, 16.9, 16.6; IR (film) ν_{max}: 3219, 2995, 1713, 1668, 1601, 1479, 1425, 1391, 1362, 1281, 1254, 1234, 1223, 1148, 1030 cm⁻¹. MS (ESI) calcd for [C₁₃H₁₇N₂]⁺: 201.1392, found: 201.1386.

8-methoxy-3-methyl-2,5,10,10a-tetrahydro-1*H*-pyrrolo[1,2-*b*]cinnolin-4-ium

trifluoromethanesulfonate (19c): The title [4[⊕]+2] cycloaddition product **19c** was prepared in 85% yield (137 mg) as described in representative experimental procedure 6 by reacting α-chloroazo **11c** (1 equiv, 111 mg, 0.44 mmol), TMS-OTf (1.05 equiv, 0.08 mL, 0.46 mmol), and hexane (5 mL) for 12 h at room temperature. Alternatively, the title [4[⊕]+2] cycloaddition product was prepared in 81% yield (267 mg) as described in representative experimental procedure 6 by reacting α-trifluoroacetoxyazo **17c** (1 equiv, 300 mg, 0.9 mmol), TMS-OTf (1.05 equiv, 0.17 mL, 0.95 mmol), and hexane (20 mL) for 12 h at room temperature. Mp 146.2 °C (recrystallized from MeOH/Et₂O). ¹H NMR (500 MHz, CD₃CN) δ = 8.95 (s, 1H), 6.94 (d, *J* = 8.8, 1H), 6.88 – 6.82 (m, 1H), 6.79 (d, *J* = 2.5, 1H), 4.53 – 4.44 (m, 1H), 3.76 (s, 3H), 3.25 (dd, *J* = 16.1, 4.3, 1H), 3.17 – 2.99 (m, 2H), 2.93 (dd, *J* = 16.0, 12.5, 1H), 2.63 (dtd, *J* = 12.2, 8.1, 3.9, 1H), 2.37 (s, 3H), 2.02 – 1.95 (m, 1H). ¹³C NMR (126 MHz, CD₃CN) δ 168.3, 156.4, 131.7, 121.1, 116.1, 115.1, 114.9, 67.5, 56.2, 36.2, 33.3, 25.6, 15.8; IR (film) ν_{max}: 3229, 3015, 2970, 1740, 1503, 1435, 1369, 1277, 1227, 1217, 1155, 1029 cm⁻¹. MS (ESI) calcd for [C₁₃H₁₇N₂O]⁺: 217.1341, found: 217.1337.

3-methyl-8-nitro-2,5,10,10a-tetrahydro-1*H*-pyrrolo[1,2-*b*]cinnolin-4-ium

trifluoromethanesulfonate (19d): The title [4[⊕]+2] cycloaddition product **19d** was prepared in 86% yield (324 mg) as described in representative experimental procedure 6 by reacting α-trifluoroacetoxyazo **17d** (1 equiv, 298 mg, 0.99 mmol), TMS-OTf (1.05 equiv, 0.19 mL, 1.04

mmol), and hexane (20 mL) for 12 h at room temperature. Alternatively, this product was prepared in 96% yield (268 mg) as described in representative experimental procedure 6 by reacting α -trifluoroacetoxyazo **17d** (1 equiv, 253 mg, 0.732 mmol), TMS-OTf (1.5 equiv, 0.20 mL, 1.1 mmol), and hexane (15 mL) for 4 h at 40 °C. Mp 209.6 °C (recrystallized from MeOH/Et₂O). ¹H NMR (500 MHz, CD₃CN) δ = 10.05 (s, 1H), 8.27 – 7.83 (m, 2H), 7.16 (d, J = 8.7, 1H), 4.64 – 4.33 (m, 1H), 3.45 (dd, J = 16.2, 4.3, 1H), 3.23 – 3.07 (m, 2H), 3.03 (dd, J = 16.2, 12.5, 1H), 2.73 – 2.62 (m, 1H), 2.45 (s, 3H), 2.05 – 1.96 (m, 1H). ¹³C NMR (126 MHz, Acetone-*d*₆) δ 172.1, 143.4, 143.0, 125.8, 124.9, 119.9, 114.6, 67.0, 36.7, 33.2, 25.7, 16.0; IR (film) ν_{max} : 3186, 3003, 1618, 1593, 1504, 1344, 1287, 1240, 1223, 1153, 1030, 937, 826 cm⁻¹. MS (ESI) calcd for [C₁₂H₁₄N₃O₂]⁺: 232.1086, found: 232.1084.

3-methyl-7-nitro-2,5,10,10a-tetrahydro-1H-pyrrolo[1,2-*b*]cinnolin-4-ium

trifluoromethanesulfonate and 3-methyl-9-nitro-2,5,10,10a-tetrahydro-1H-pyrrolo[1,2-*b*]cinnolin-4-ium trifluoromethanesulfonate (19e): The title [4⁺+2] cycloaddition products was prepared as a 6:4 mixture in 87% yield (200 mg) as described in representative experimental procedure 6 by reacting α -trifluoroacetoxyazo **17e** (1 equiv, 209 mg, 0.61 mmol), TMS-OTf (1.5 equiv, 0.16 mL, 0.91 mmol), and hexane (15 mL) for 12 h at room temperature. Alternatively, this mixture was prepared in quantitative yield (467 mg) as described in representative experimental procedure 6 by reacting α -trifluoroacetoxyazo **17e** (1 equiv, 468 mg, 1.23 mmol), TMS-OTf (1.5 equiv, 0.33 mL, 1.85 mmol), and hexane (15 mL) for 4 h at 40 °C. The minor isomer was less soluble in chloroform than the major isomer and filtration of a chloroform solution provided pure minor isomer (**19e**) in 20% yield (15 mg from 75 mg of the mixture).

Minor Isomer: 3-methyl-9-nitro-2,5,10,10a-tetrahydro-1H-pyrrolo[1,2-*b*]cinnolin-4-ium trifluoromethanesulfonate: Mp 191.7 °C (recrystallized from MeOH/Et₂O). ¹H NMR (500 MHz, CD₃CN) δ = z (d, J = 21.2, 1H), 7.66 (d, J = 8.1, 1H), 7.47 (t, J = 8.2, 1H), 7.34 (d, J = 8.2, 1H), 4.47 – 4.36 (m, 1H), 3.66 (dd, J = 17.2, 4.3, 1H), 3.21 – 3.00 (m, 3H), 2.66 (dtd, J = 12.5, 8.3, 4.0, 1H), 2.43 (s, 3H), 2.04 (ddd, J = 18.4, 13.2, 9.1, 1H). ¹³C NMR (126 MHz, CD₃CN) δ 171.2, 150.2, 139.8, 129.7, 119.7, 119.3, 114.7, 65.7, 36.4, 30.5, 25.4, 16.0; IR (film) ν_{max} : 3144, 2994, 2947, 1713, 1678, 1618, 1584, 1533, 1358, 1277, 1238, 1225, 1177, 1153, 1177, 1153, 1030, 853, 804 cm⁻¹. MS (ESI) calcd for [C₁₂H₁₄N₃O₂]⁺: 232.1086, found: 232.1082. **Major Isomer: 3-methyl-7-nitro-2,5,10,10a-tetrahydro-1H-pyrrolo[1,2-*b*]cinnolin-4-ium trifluoromethanesulfonate:** ¹H NMR (500 MHz, CD₃CN) δ = 9.74 (s, 1H), 7.85 (s, 1H), 7.86 – 7.81 (m, 1H), 7.43 (d, J = 8.3, 1H), 4.58 – 4.47 (m, 1H), 3.45 (dd, J = 16.6, 4.3, 1H), 3.18 – 2.99 (m, 3H), 2.73 – 2.61 (m, 1H), 2.45 (s, 3H), 2.08 – 1.95 (m, 1H). ¹³C NMR (126 MHz, CD₃CN) δ 171.4, 148.8, 138.8, 131.4, 126.6, 117.8, 109.5, 66.7, 36.5, 33.2, 25.5, 16.1.

8-chloro-3-methyl-2,5,10,10a-tetrahydro-1H-pyrrolo[1,2-*b*]cinnolin-4-ium

trifluoromethanesulfonate (19f): The title [4⁺+2] cycloaddition product **19f** was prepared in 72% yield (106 mg) as described in representative experimental procedure 6 by reacting α -trifluoroacetoxyazo **17f** (1 equiv, 134 mg, 0.4 mmol), TMS-OTf (1.05 equiv, 0.07 mL, 0.42 mmol), and hexane (12 mL) for 12 h at room temperature. Alternatively, this product was prepared in 84% yield (361 mg) as described in representative experimental procedure 6 by reacting α -trifluoroacetoxyazo **17f** (1 equiv, 427 mg, 1.16 mmol), TMS-OTf (1.5 equiv, 0.31 mL, 1.73 mmol), and hexane (15 mL) for 4 h at 40 °C. Mp 142.0 °C (recrystallized from MeOH/Et₂O). ¹H NMR (500 MHz, CD₃CN) δ = 9.35 (s, 1H), 7.26 (d, J = 8.1, 2H), 7.00 (d, J = 8.4, 1H), 4.48 (dd, J = 4.5, 2.0, 1H), 3.29 (dd, J = 16.1, 4.2, 1H), 3.18 – 3.03 (m, 2H), 2.94 (dd, J

= 15.9, 12.6, 1H), 2.69 – 2.57 (m, 1H), 2.40 (s, 3H), 2.05 – 1.95 (m, 1H). ¹³C NMR (126 MHz, CD₃CN) δ 169.8, 136.9, 129.7, 129.0, 127.8, 121.5, 116.2, 67.0, 36.3, 32.9, 25.5, 15.9; IR (film) ν_{max}: 3204, 3003, 1713, 1678, 1610, 1491, 1433, 1420, 1283, 1237, 1223, 1152, 1026, 864, 804 cm⁻¹. MS (ESI) calcd for [C₁₂H₁₄ClN₂]⁺: 221.0846, found: 221.0842.

6,8-dichloro-3-methyl-2,5,10,10a-tetrahydro-1H-pyrrolo[1,2-b]cinnolin-4-ium

trifluoromethanesulfonate (19g): The title [4⁺+2] cycloaddition product **19g** was prepared in 59% yield (120 mg) as described in representative experimental procedure 6 by reacting α-trifluoroacetoxyazo **17g** (1 equiv, 186 mg, 0.5 mmol), TMS-OTf (1.05 equiv, 0.10 mL, 0.53 mmol), and hexane (15 mL) for 12 h at room temperature. Alternatively, this product was prepared in 73% yield (178 mg) as described in representative experimental procedure 6 by reacting α-trifluoroacetoxyazo **17g** (1 equiv, 233 mg, 0.6 mmol), TMS-OTf (1.5 equiv, 0.16 mL, 0.86 mmol), and hexane (15 mL) for 4 h at 40 °C. Mp 169.9 °C (recrystallized from MeOH/Et₂O). ¹H NMR (500 MHz, CD₃CN) δ = 8.60 (s, 1H), 7.46 (dd, *J* = 2.2, 0.9, 1H), 7.26 (s, 1H), 4.46 (ddd, *J* = 8.1, 3.8, 1.9, 1H), 3.34 (dd, *J* = 16.3, 4.4, 1H), 3.29 – 3.09 (m, 2H), 2.99 (dd, *J* = 16.3, 12.4, 1H), 2.69 (dddd, *J* = 13.3, 9.9, 8.3, 3.5, 1H), 2.51 (s, 3H), 2.06 – 1.96 (m, 1H). ¹³C NMR (126 MHz, CD₃CN) δ 178.9, 133.9, 129.0, 128.9, 128.3, 123.8, 121.0, 66.0, 36.7, 33.4, 24.9, 17.0; IR (film) ν_{max}: 3208, 2974, 1713, 1678, 1576, 1479, 1414, 1277, 1244, 1223, 1148, 1028, 856 cm⁻¹. MS (ESI) calcd for [C₁₂H₁₃Cl₂N₂]⁺: 255.0456, found: 255.0453.

3-methyl-2,5,10,10a-tetrahydro-1H-pyrrolo[1,2-b]cinnolin-4-ium trifluoromethanesulfonate

(19h): The title [4⁺+2] product **19h** was prepared in 96% yield (258 mg) as described in representative experimental procedure 6 by reacting α-trifluoroacetoxyazo **17h** (1 equiv, 240 mg, 0.8 mmol), TMS-OTf (1.5 equiv, 0.22 mL, 1.2 mmol), and hexane (15 mL) for 4 h at 40 °C. Mp 136.0 °C (recrystallized from MeOH/Et₂O). ¹H NMR (500 MHz, CDCl₃) δ = 9.83 (s, 1H), 7.19 (t, *J* = 7.7, 1H), 7.08 (d, *J* = 7.6, 1H), 7.02 (d, *J* = 7.9, 1H), 6.97 (td, *J* = 7.5, 0.9, 1H), 4.47 (dd, *J* = 5.0, 2.2, 1H), 3.28 – 3.14 (m, 2H), 3.08 (dd, *J* = 19.5, 9.7, 1H), 2.94 (dd, *J* = 15.8, 12.6, 1H), 2.75 – 2.64 (m, 1H), 2.50 (s, 3H), 1.98 (dq, *J* = 13.1, 9.4, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 169.3, 137.0, 129.0, 128.7, 123.0, 117.3, 114.8, 66.1, 35.4, 33.3, 25.2, 16.0. MS (ESI) calcd for [C₁₉H₂₇N₂]⁺: 187.1235, found: 187.1231.

Acknowledgements

We are grateful to the National Scientific Foundation for financial support of this research through grant CHE-1362286 and through instrumentation grants CHE-1039436, CHE-1126265 and CHE-0821501. Mass spectrometry data was acquired by Bruce O'Rourke on instruments purchased through instrumentation grants provided by the NIH (S10 OD018126). We thank Prof. Rory Waterman for X-ray data collection and structure determination.

References Cited

- (1) Huisgen, R.; Koch, H.-J. *Justus Liebigs Ann. Chem.* **1955**, 591, 200.
- (2) Gladstone, W. A. F.; Norman, R. O. C. *J. Chem. Soc.* **1965**, 3048.

- (3) Wyman, J. M.; Jochum, S.; Brewer, M. *Synth. Commun.* **2008**, 38, 3623.
- (4) Wang, Q. R.; Jochims, J. C.; Kohlbrandt, S.; Dahlenburg, L.; Altalib, M.; Hamed, A.; Ismail, A. E. H. *Synthesis* **1992**, 710.
- (5) Wirschun, W. G.; Al-Soud, Y. A.; Nusser, K. A.; Orama, O.; Maier, G.-M.; Jochims, J. C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4356.
- (6) Wyman, J.; Javed, M. I.; Al-Bataineh, N.; Brewer, M. *J. Org. Chem.* **2010**, 75, 8078.
- (7) Javed, M. I.; Wyman, J. M.; Brewer, M. *Org. Lett.* **2009**, 11, 2189.
- (8) Bercovici, D. A.; Brewer, M. *J. Am. Chem. Soc.* **2012**, 134, 9890.
- (9) Hong, X.; Bercovici, D. A.; Yang, Z. Y.; Al-Bataineh, N.; Srinivasan, R.; Dhakal, R. C.; Houk, K. N.; Brewer, M. *J. Am. Chem. Soc.* **2015**, 137, 9100.
- (10) Bercovici, D. A.; Ogilvie, J. M.; Tsvetkov, N.; Brewer, M. *Angew. Chem., Int. Ed. Engl.* **2013**, 52, 13338.
- (11) Hong, X.; Liang, Y.; Brewer, M.; Houk, K. N. *Org. Lett.* **2014**, 16, 4260.
- (12) CCDC 1444718 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.
- (13) Tojo, G.; Fernández, M. *Oxidation of alcohols to aldehydes and ketones : a guide to current common practice*; Springer: New York, NY, 2006.

***Graphical Abstract**