Copies of Publications

Copies of selected recent publications are provided in the following section. These are organized by research area and are presented in chronological order.

***Please Note**: Links are imbedded in this PDF. Click the article title to navigate to the article within this PDF.*

Formation and reactivity of 1-aza-2-azoniaallene salts:

1. Wyman, J.; Javed, M.I.; Al-Betaineh, N.; Brewer, M. "Synthetic Approaches to Bicyclic Diazenium Salts", *The Journal of Organic Chemistry*, **2010**, *75*(23), 8078-8087. (*DOI: 10.1021/jo101706h*)

Brief summary: This full paper details our studies on the intramolecular 1,3-dipolar cycloaddition of 1-aza-2-azoniaallene salts with alkenes. A new method to form the 1-aza-2-azoniaallene salts from hydrazones is also described.

2. Bercovici, D.A.; Brewer, M. "Stereospecific intramolecular C–H amination of 1–aza–2–azoniaallene salts", *Journal of the American Chemical Society*, **2012**, *134*(24) 9890-9893. (*DOI: 10.1021/ja303054c*)

Brief summary: This manuscript documents our finding that aryl 1-aza-2-azoniaallene salts can insert into C–H bonds to give pyrazoline or pyrazole products, which are common substructures in medicines. Importantly, this type of reactivity had never been documented before for these salts.

3. Al Bataineh, N.Q.; Brewer, M. " Iodine(III)-mediated bicyclic diazenium salt formation", *Tetrahedron Letters*, **2012**, *53*, 5411-5413. (*DOI: 10.1016/j.tetlet.2012.07.116*)

Brief summary: A new method to form bicyclic diazenium salts directly from hydrazones via oxidation with hypervalent iodine is described.

4. Bercovici, D.A.; Ogilvie, J.M.; Tsvetkov, N.; Brewer, M. "Intramolecular Polar [$4^{\oplus}$ + 2]-Cycloadditions of Aryl-1-aza-2-azoniaallene Salts: Unprecedented Reactivity Leading to Polycyclic Protonated Azomethine Imines" *Angewandte Chemie, International Edition*, **2013**, *52*(50), 13338-13341. (*DOI*: *10.1002/anie.201306553*)

Brief summary: This manuscript documents our finding that aryl 1-aza-2-azoniaallene salts can react in (4 + 2)-cycloadditions to give polycyclic protonated azomethine imine products. This type of reactivity had never been documented before, and provides synthetically useful and structurally complex products in very good yield from simple starting materials.

5. Hong, X.; Liang, Y.; Brewer, M.; Houk, K.N. "How Tethers Control the Chemo- and Regio-Selectivities of Intramolecular Cycloadditions between Aryl-1-Aza-2-Azoniaallenes and Alkenes" *Organic Letters* **2014**, *16*(16), 4260-4263. (*DOI: 10.1021/ol501958s*)

Brief summary: This paper describes computational studies that explain how tethers control the reactivity of 1-aza-2-azoniaallene salts in intramolecular reactions. This computational work also highlights the concerted nature of the bond forming reactions.

6. Hong, X.; Bercovici, D.; Yang, Z.; Al-Bataineh, N.; Srinivasan, R.; Dhakal, R.; Houk, K.N.; Brewer, M. "Mechanism and Dynamics of Intramolecular C-H Insertion Reactions of 1-Aza-2-azoniaallene Salts" *Journal of the American Chemical Society*, **2015**, *137*(28), 9100-9107. (*DOI*: *10.1021/jacs.5b04474)*

Brief summary: This full paper describes experimental and computational mechanistic studies which show that the C–H insertion reaction of 1-aza-2-azoniaallene salts occurs by a bonding stepwise but energy concerted mechanism. This mechanism is unique to this insertion and highlights the reactivity of these salts as aza-nitrenium cations.

Development and synthetic applications of a ring fragmentation reaction:

7. Tsvetkov, N.P.; Bayir, A.; Schneider, S.; Brewer, M. "A Ring Fragmentation Approach to Medium-Sized Cyclic 2-Alkynones", *Organic Letters*, **2012**, *14*(1), 264-267. (*DOI: 10.1021/ol2030422*)

Brief summary: This paper details our findings that bicyclic γ-silyloxy-β-hydroxy-α-diazoketones can fragment in good yields to provide medium-sized sized rings containing an ynone functionality.

8. Jabre, N.D.; Brewer, M.; "Stereoelectronic Effects in the Fragmentation of γ -Silyloxy- β -hydroxy- α -diazocarbonyl Compounds", *The Journal of Organic Chemistry* **2012**, *77*(21), 9910-9914. *(DOI: 10.1021/jo301944t)*

Brief summary: This paper describes experimental studies that probe the mechanism of the fragmentation reaction. Specifically, we show how the relative stereochemistry of groups on a ring effect the outcome of the fragmentation reaction based on the stereoelectronic requirements of the fragmentation process.

9. Zhang, Z.; Giampa, G.M.; Draghici, C.; Huang, Q; Brewer, M. "Synthesis of demissidine by a ring fragmentation/1,3-dipolar cycloaddition approach", *Organic Letters*, **2013**, *15*(9), 2100-2103. (*DOI: 10.1021/ol4004993*)

Brief summary: This paper describes our total synthesis of the steroid alkaloid demissidine. Our synthetic route took advantage of the ring fragmentation / 1,3-dipolar cycloaddition methodology we developed in our laboratories. This was the first total synthesis we accomplished using this methodology, and it is an important achievement because it

demonstrates that our methodology is robust enough to be used in complex molecule synthesis as a way to quickly build structural complexity.

10. Jabre, N.D.; Watanabe, T.; Brewer, M. "Formal and Total Synthesis of (±)-Cycloclavine" *Tetrahedron Letters,* **2014**, *55*(1), 197-199. (*DOI: 10.1016/j.tetlet.2013.10.152*)

Brief summary: This paper describes our total synthesis of the indole alkaloid cycloclavine. Our synthetic route took advantage of the ring fragmentation / 1,3-dipolar cycloaddition methodology and it is an important achievement because it further demonstrates that this methodology is robust enough to be used in complex molecule synthesis.

11. Bayir, A.; Brewer, M. "The fragmentation of bicyclic γ-silyloxy-β-hydroxy-α-diazolactones as an approach to ynolides" *The Journal of Organic Chemistry,* **2014**, *79*(13), 6037-6046. *(DOI: 10.1021/jo500634d)*

Brief summary: This full paper details our findings that bicyclic γ-silyloxy-β-hydroxy-α-diazolactones can fragment in good yields to provide medium-sized lactones that contain an alkyne functional group within the ring (i.e. an ynolide). Medium-sized lactones are important scaffolds in drug discovery programs, but are difficult to prepare. This synthetic approach to these systems not only helps to fill a void in synthetic methodology, but also provides products that are functional group rich and thus useful synthetic intermediates.

Miscellaneous:

12. Collins, N.; Brewer, M. "Development of a Clinically Applicable Protocol for Assessment of Hypoxic Response Through Measurement of the Endogenous Gasotransmitter Hydrogen Sulfide in Human Plasma" *Journal of Neurosurgical Anesthesiology,* **2015**, *27*(3), 257-261 *(DOI: 10.1097/ana.0000000000000150).*

Brief summary: This paper describes the use of danzyl azide for hydrogen sulfide detection in human plasma.

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Synthetic Approaches to Bicyclic Diazenium Salts

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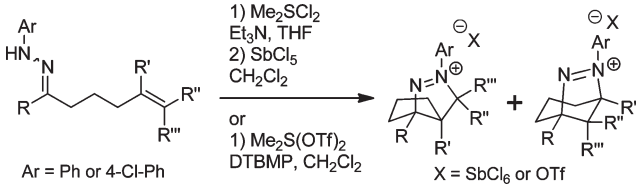
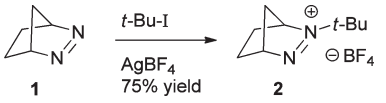


Bicyclic diazenium salts have been prepared from α-chloroazo species via a Lewis acid-mediated intramolecular cycloaddition. An alternative, more direct, route to these salts by the reaction of hydrazones with dimethylsulfonium ditriflate is also described. Terminal olefins provided mixtures of fused and bridged bicyclic diazenium salts. The ratio of the fused and bridged species was observed to depend on the electronics of the N-aryl substituent, which is explained by considering a concerted asynchronous cycloaddition mechanism.

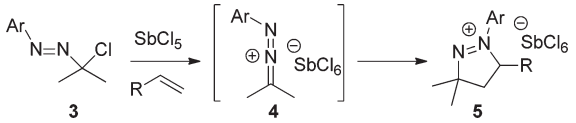
Introduction

Cyclic trisubstituted diazenium salts (e.g., **2**, Scheme 1) are cationic heterocycles that contain a reactive nitrogen−nitrogen double bond.[1] Although these species are potentially useful synthetic intermediates, they have received less attention from the synthetic community than most classes of nitrogen-containing heterocycles and few methods exist for their preparation. Nelsen and co-workers[2−5] have prepared bridged bicyclic diazenium salts by alkylation of the corresponding diazene (Scheme 1), and have studied the redox properties, structure, and charge distribution of these salts; Nelsen and co-workers also observed that protonated bicyclic azo compounds act as dienophiles in [4 + 2] cycloaddition reactions.[6,7]

SCHEME 1. Nelsen's Preparation of Bridged Bicyclic Diazenium Salts



SCHEME 2. Jochims' Preparation of Diazenium Salts



More recently, Jochims and colleagues[8−10] reported that α-chloroazo compounds (e.g., **3**, Scheme 2) react with halophilic Lewis acids to provide 1-aza-2-azoniaallene cation intermediates (e.g., **4**), which display reactivity reminiscent of Huisgen-type 1,3-dipolar compounds[11] and undergo intermolecular [3 + 2] cycloaddition with alkenes to provide diazenium salt heterocycles (e.g., **5**). We recently reported the preparation of more structurally complex bicyclic diazenium salts by rendering this Lewis acid-mediated process intramolecular.[12] The success of this intramolecular cycloaddition

(1) Kuznetsov, M. A. *Russ. Chem. Rev.* **1979**, *48*, 1054.
(2) Nelsen, S. F.; Landis, R. T. *J. Am. Chem. Soc.* **1974**, *96*, 1788.
(3) Nelsen, S. F.; Landis, R. T. *J. Am. Chem. Soc.* **1973**, *95*, 2719.
(4) Nelsen, S. F.; Blackstock, S. C. *J. Org. Chem.* **1984**, *49*, 1134.
(5) Nelsen, S. F.; Chang, H.; Wolff, J. J.; Powell, D. R. *J. Org. Chem.* **1994**, *59*, 6558.
(6) Nelsen, S. F.; Blackstock, S. C.; Frigo, T. B. *J. Am. Chem. Soc.* **1984**, *106*, 3366.
(7) Nelsen, S. F.; Blackstock, S. C.; Frigo, T. B. *Tetrahedron* **1986**, *42*, 1769.
(8) 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.
(9) Wang, Q. R.; Amer, A.; Mohr, S.; Ertel, E.; Jochims, J. C. *Tetrahedron* **1993**, *49*, 9973.
(10) Al-Soud, Y. A.; Wirschun, W.; Hassan, N. A.; Maier, G. M.; Jochims, J. C. *Synthesis* **1998**, 721.
(11) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565.
(12) Javed, M. I.; Wyman, J. M.; Brewer, M. *Org. Lett.* **2009**, *11*, 2189.

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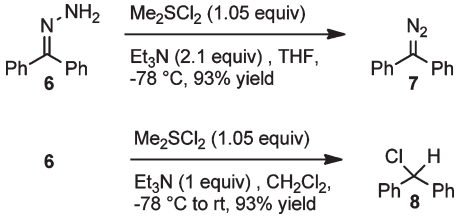
in providing structurally complex heterocyclic products from simple starting materials encouraged us to explore the formation of bicyclic diazenium salts further and we present our results here. We also report our discovery that bicyclic diazenium salts can be formed directly from hydrazones by reaction with dimethylsulfonium ditriflate.

Results and Discussion

Reactions of Hydrazones with Sulfonium Salts. The work described herein stems from our recent studies on reactions of hydrazones with sulfonium salts, which we have discovered can provide a variety of useful products. For example, we have observed that unsubstituted hydrazones react readily at low temperature with chlorodimethylsulfonium chloride (Me_2SCl_2) in the presence of 2 equiv of triethylamine to provide diazo products (Scheme 3).[13,14] This method of forming diazo compounds is more environmentally friendly than the well-established dehydrogenation procedures mediated by lead or mercury salts,[15−18] and it is particularly useful for the formation of aryl diazomethanes. Unstabilized aliphatic diazo compounds appear to form readily under these reaction conditions, but these more reactive species are unstable in the presence of the triethylammonium chloride that is generated over the course of the reaction.

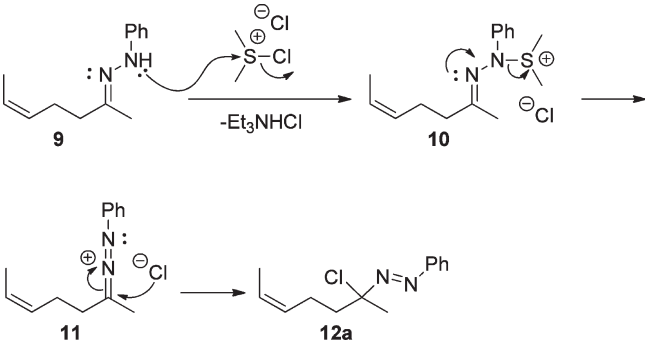
SCHEME 3. Sulfonium Salt-Mediated Formation of Diazos and Alkyl Chlorides



Changing the reaction conditions so that equimolar quantities of triethylamine and hydrazone are used in the reaction results in the formation of alkyl chloride products rather than diazo species (Scheme 3).[19] This latter transformation is unique in that the hydrazone starting material undergoes a net reduction under standard oxidizing conditions.

Aryl-substituted hydrazones (e.g., **9**, Scheme 4), on the other hand, reacted with Me_2SCl_2 to provide α-chloroazo products[20] (e.g., **12a**). This transformation is general and we were pleased to find that Me_2SCl_2 smoothly converted hydrazones containing a pendent alkene into the corresponding α-chloroazo species with no modification of the olefin. α-Chloroazo compounds had been prepared previously by reacting substituted hydrazones with either chlorine gas or *tert*-butyl hypochlorite,[21,22] and these products are useful synthetic precursors to azoalkenes,[23] tetrahydropyridazines,[23] 1,2,4-triazolium salts,[24,25] *N*-(azoalkyl)iminium salts,[26] 1,2,4,5-tetrazinium salts,[26] 1*H*-pyrazolium salts,[9] diazenium salts,[9] and pyrazoles.[9]

SCHEME 4. Proposed Mechanism of α-Chloroazo Formation



We hypothesize that Me_2SCl_2 reacts with hydrazones to provide α-chloroazo products by the mechanism shown in Scheme 4. Nucleophilic attack of the hydrazone on the electrophilic sulfonium salt would provide azasulfonium salt **10** after deprotonation with Et_3N. Lone pair donation by the α-nitrogen would result in elimination of dimethyl sulfide to provide the cationic heteroallene **11**, which could in turn be captured by the chloride counterion to provide α-chloroazo **12a**.[27]

Lewis Acid-Mediated Diazenium Salt Formation. With a convenient route to aryl-α-chloroazo alkenes in hand, we have begun to study the formation of bicyclic diazenium salts via intramolecular Lewis acid-mediated cycloaddition.[12] For example, treating phenyl-α-chloroazo **12a** with antimony pentachloride resulted in an intramolecular cycloaddition to provide fused bicyclic diazenium salt **13a** as a single diastereomer in 88% isolated yield (entry 1, Table 1). This transformation efficiently builds structural complexity and over the course of the reaction new carbocyclic and new heterocyclic rings form. The diastereoselectivity of this reaction further supports the notion that the cycloaddition occurs by a concerted process.[8] To assess the scope of this intramolecular cycloaddition reaction we prepared phenyl-α-chloroazo compounds **12a**−**g** (Table 1) and subjected these to the Lewis acid-mediated cyclization. Most of these substrates reacted smoothly to provide the diazenium salt products in good to excellent yield after purification by trituration from diethyl ether. Of note, electron-deficient alkene **12c** reacted with $SbCl_5$ to provide the desired diazenium salt **13c** (entry 3, Table 1) in 83% yield. This result is significant because electron-deficient alkenes do not participate in intermolecular cyclizations of this type[8] and this result broadens the useful substrate range of this

(13) Javed, M. I.; Brewer, M. *Org. Lett.* **2007**, *9*, 1789.
(14) Javed, M. I.; Brewer, M. *Org. Synth.* **2008**, *85*, 189.
(15) Regitz, M.; Maas, G. *Diazo Compounds Properties and Synthesis*: Academic Press, INC.: Orlando, FL, 1986.
(16) Heydt, H. In *Science of synthesis Houben-Weyl methods of molecular transformations: Heteroatom Analogues of Aldehydes and Ketones*, 5th ed.; Thieme: Stuttgart, Germany, 2004; Vol. 27, p 843.
(17) Holton, T. L.; Shechter, H. *J. Org. Chem.* **1995**, *60*, 4725.
(18) For a summary of other oxidants that effect this conversion but find less use see ref 16.
(19) Brewer, M. *Tetrahedron Lett.* **2006**, *47*, 7731.
(20) Wyman, J. M.; Jochum, S.; Brewer, M. *Synth. Commun.* **2008**, *38*, 3623.
(21) Moon, M. W. *J. Org. Chem.* **1972**, *37*, 383.
(22) Moon, M. W. *J. Org. Chem.* **1972**, *37*, 386.
(23) Gaonkar, S. L.; Rai, K. M. L. *Tetrahedron Lett.* **2005**, *46*, 5969.
(24) Wang, Q. R.; Jochims, J. C.; Kohlbrandt, S.; Dahlenburg, L.; Altalib, M.; Hamed, A.; Ismail, A. E. H. *Synthesis* **1992**, 710.
(25) Wang, Q. R.; Liu, X. J.; Li, F.; Ding, Z. B.; Tao, F. G. *Synth. Commun.* **2002**, *32*, 1327.
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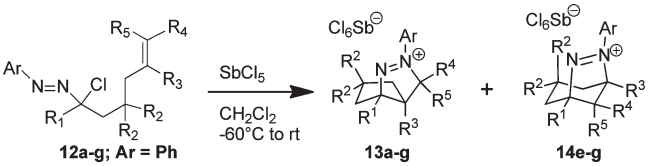
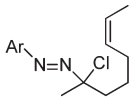
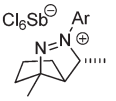
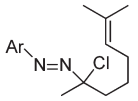
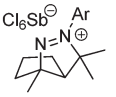
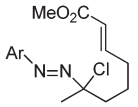
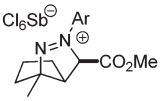
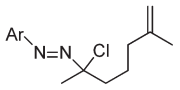
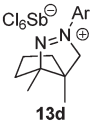
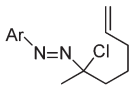
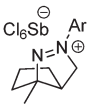
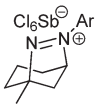
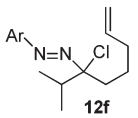
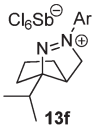
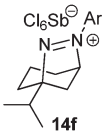
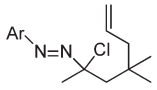
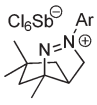
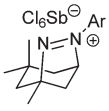
(27) Alternatively, the chloride ion could react directly with azasulfonium salt **10** by an SN_2' mechanism.

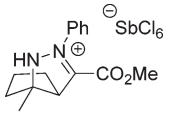
TABLE 1. Results of Intramolecular Lewis Acid-Mediated Diazenium Salt Formation



Entry	α-chloroazo	Product	Yield Ratio **13**:**14**[a]	
1				
	12a	**13a**[b]	88%	---
	12a'	**13a'**	87%	---
2				
	12b	**13b**	71%	---
	12b'	**13b'**	---[c]	---
3				
	12c	**13c**[b]	83%	---
	12c'	**13c'**	69%[d]	---
4				
	12d	**13d**	0%	---
5		 		
	12e	**13e**	**14e**	87% 1: 0.2
	12e'	**13e'**	**14e'**	92% 1: 0.3
6		 		
	12f	**13f**	**14f**	88% 1 : 0.05
	12f'	**13f'**	**14f'**	80% 1 : 0.1
7		 		
	12g	**13g**	**14g**	75% 1: 0.1
	12g'	**13g'**	**14g'**	89% 1: 0.2

[a]Diazenium salts **13g'**−**g**/**e'**−**g'** and **14e**−**g**/**e'**−**g'** were isolated as mixtures. [b]Diazenium salts **13a** and **13c** were formed as single diastereomers and their relative configurations were assigned by nOe experiments. [c]Product was formed as an intractable mixture. [d]After titration the only observable product was the minimum tautomer.

transformation. On handling, diazenium salt **13c** readily tautomerized to hydrazonium salt **15**. Disubstituted terminal alkene **12d** did not provide any of the expected diazenium salt product. In this case, the expected product would contain adjacent quaternary centers and steric encumbrance may inhibit cyclization.



15

Terminal alkene **12e** reacted with $SbCl_5$ to provide a mixture of ring-fused diazenium salt **13e** and bridged diazenium salt **14e** in a 1 to 0.2 ratio (entry 5, Table 1). Mixtures of bridged and fused bicyclic diazenium salts were obtained for other terminal alkenes as well (entries 6 and 7) and the ratio of these products appears to be affected by steric factors. For example, Lewis acid-induced cyclization of isopropyl derivative **12f** provided a 1 to 0.05 ratio of fused (**13f**) to bridged (**14f**) products, while incorporation of a gem-dimethyl group within the chain (**12g**) provided the fused (**13g**) and bridged (**14g**) products in a 1 to 0.1 ratio. Formation of the fused and bridged products can be explained by considering two alternative orientations by which the alkene can approach the heteroallene intermediate. These alternate approaches would lead to transition states **16** and **17** shown in Figure 1, which would in turn provide the fused and bridged bicyclic products, respectively.

To more fully explore the scope of this transformation we prepared the 4-chlorophenyl-α-chloroazo compounds **12a′**−**g′** (Table 1) and subjected these to Lewis acid-mediated intramolecular cycloaddition as well. Modification of the aryl substituent from phenyl to 4-chlorophenyl had little effect on the outcome of this reaction and the corresponding diazenium salts **13a′**,**c′**,**e′**−**g′** and **14e′**−**g′** were formed in good to excellent yield. For reasons we do not fully understand, reactions of trisubstituted alkene **12b′** consistently provided complex mixtures that were intractable and could not be resolved to pure diazenium salt **13b′**. Another notable effect of this modification was that the terminal alkene substrates **12e′**−**g′** reacted to provide bridged and fused products in different ratios than was observed for the corresponding phenyl derivatives. In each case, the 4-chlorophenyl substrates provided a modest increase in the relative proportion of the 6,5-bridged diazenium salt product.

To further assess how the electronics of the aryl ring affect the outcome of the cycloaddition reaction, we prepared the aryl-α-chloroazo compounds shown in Table 2 and subjected these compounds to Lewis acid-mediated intramolecular cycloaddition. The ratio of the fused to bridged bicyclic diazenium salt products was determined by proton NMR analysis of the crude reaction mixtures. From these results, it is clear that the electronic nature of the aromatic ring substituent on nitrogen affects the reaction outcome; an increase in the electron-withdrawing character of the aryl ring resulted in an increase in the proportion of the 6,5-bridged bicyclic product that was formed. Conversely, a more electron-rich aryl ring provided the 5,5-fused product to an even greater extent (Table 2). A Hammett plot of these results (Figure 2) shows a linear correlation between the ratio of the products formed and the Hammett constants for the aryl ring substituents.[28−30]

(28) Hammett, L. P. *J. Am. Chem. Soc.* **1937**, *59*, 96.
(29) Hammett, L. P. *Chem. Rev.* **1935**, *17*, 125.

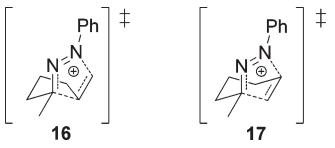
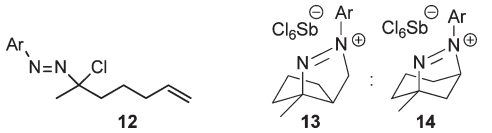


FIGURE 1. Proposed transition states leading to diazenium salts **13** and **14**.

TABLE 2. Dependence of Product Ratio on the Electronics of Aryl Substituent



Ar substituent	product ratio[a]
12e	1 : 0.2 (13e : 14e)
12e'	1 : 0.3 (13e' : 14e')
12h'	1 : 0.8 (13h' : 14h')
12i'	1 : 0.1 (13i' : 14i')

[a]Product ratio determined by proton NMR of the crude reaction mixture..

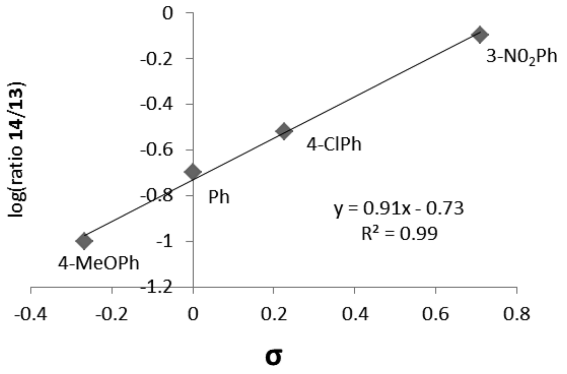


FIGURE 2. Hammett plot of log(ratio **14/13**) data vs σ for reaction of **12e**, **12e′**, **12h′**, and **12i′**.

The observation that the electronics of the hydrazone aryl substituent biases the product distribution is consistent with a concerted but asynchronous mechanism in which C−C bond formation to the highly electrophilic carbon atom of heteroallene **18** (Figure 3) is more advanced at the transition state than N−C bond formation to the heteroallene nitrogen.[10,31] If this is the case, then on route to the transition state a partial positive charge would build on the carbon

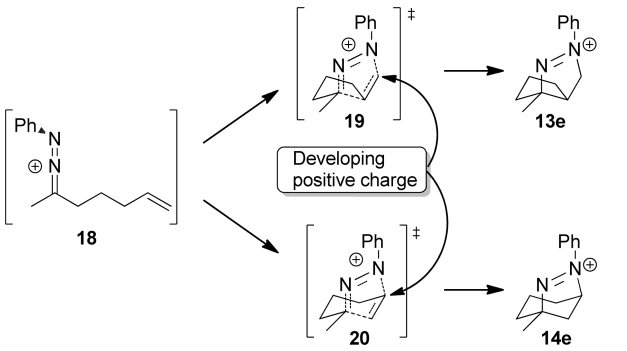


FIGURE 3. Location of charge in the asynchronous cycloaddition mechanism.

atom that forms a new bond with nitrogen. Transition state **20** (Figure 3), leading to the 6,5-bridged product **14e**, would have a partial positive charge develop on a secondary carbon atom, whereas proposed transition state **19**, leading to the 5,5-fused product **13e**, would have a partial positive charge develop on a primary carbon. While cationic charge buildup on a primary carbon would make transition state **19** higher in energy, we suspect that this transition state is entropically favored, which explains why the fused diazenium salt **13e** is always the dominant species formed (Tables 1 and 2). However, as the aryl substituent becomes more electron withdrawing, C−N bond formation should be further delayed and the amount of partial positive charge developed at the transition state would increase. If this is the case, then the amount of bridged diazenium salt (**14**) formed would be expected to increase as the aryl ring becomes more electron withdrawing, which is consistent with our observations (Table 2). In the case of terminal dimethyl substrate **12b′** (Table 1), a more stepwise process resulting in the formation of a tertiary carbocation intermediate could explain the observed formation of complex product mixtures.[31]

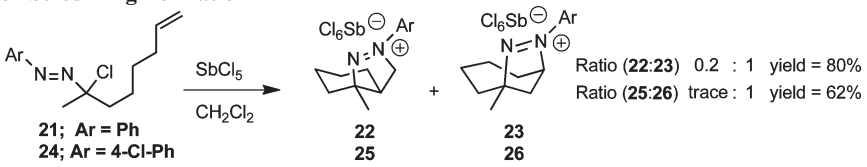
Subjecting α-chloroazo substrate **21** (Scheme 5) to intramolecular cyclization could provide either 6,5-fused (**22**) or 7,5-bridged (**23**) bicyclic diazenium salts. In this case, formation of the seven-membered carbocyclic ring was favored over formation of the six-membered ring; the 7,5-bridged diazenium salt **23** was formed as the major product in a 1 to 0.2 ratio with the 6,5-fused system. This result is important because methods to prepare carbocyclic 7-membered rings are generally lacking. As would be expected, changing the aryl ring to the more electron-withdrawing 4-chlorophenyl derivative increased the relative proportion of the 7,5-bridged product (**26**), and in this case only traces of the 6,5-fused product were observed.

Preferential formation of the 7,5-bridged products (**23** or **26**) is likely due to the fact that the reactive orbitals of the 1-aza-2-azoniaallene intermediate (i.e., the heteroallene and the alkene) cannot productively overlap to form the 6,5-fused product (**22** or **25**) when the heteroallene adopts a conformation in which the 6-membered ring that forms is in a chairlike conformation (e.g., **27**, Figure 4). To obtain reasonable orbital overlap leading to the 6,5-fused products, the 1-aza-2-azoniaallene intermediate would need to adopt an unfavorable conformation in which the 6-membered ring that forms is in a boat-like conformation (e.g., **28**). The longer tether length seems to provide sufficient flexibility in the system to allow the reacting centers to align in a conformation

(30) The log of the ratio of products obtained was used for these plots because (assuming the reaction is irreversible under the reaction conditions) these values are directly related to the free energy difference between the regioisomeric transition states. This relationship is analogus to using log(er) for Hammett plots of results obtained for enantioselective reactions. For an example of the use of log(er) in Hammett plots see: Constantine, R. N.; Kim, N.; Bunt, R. C. *Org. Lett.* **2003**, *5*, 2279.

(31) Wei, M. J.; Fang, D. C.; Liu, R. Z. *J. Org. Chem.* **2002**, *67*, 7432.

SCHEME 5. Seven-Membered Ring Formation



(e.g., **29**) leading to the formation of the seven-membered ring carbocycle without major energetic penalties. In addition, as discussed above, an asynchronous concerted mechanism would also favor the formation of 7,5-bridged bicyclic products **23** and **26**.

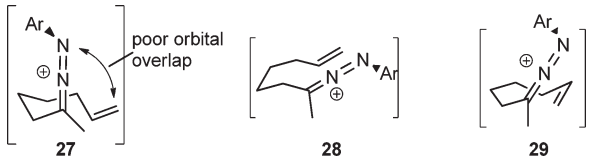
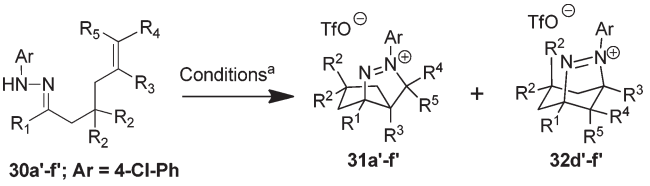


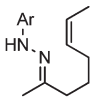
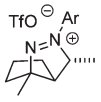
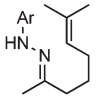
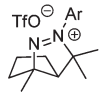
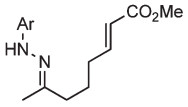
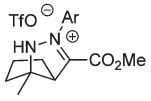
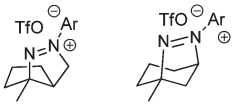
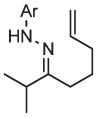
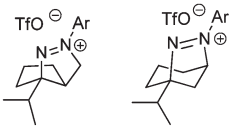
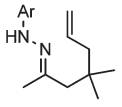
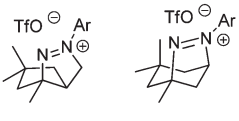
FIGURE 4. Proposed conformations leading to observed products.

Sulfonium Salt-Mediated Conversion of Hydrazones to Diazenium Salts. The mechanism we propose in Scheme 4 for Me_2SCl_2-mediated α-chloroazo formation invokes a 1-aza-2-azoniallene salt intermediate (**11**), which is subsequently captured by a chloride counterion. With this in mind, we hypothesized that a sulfonium salt bearing a non-nucleophilic counterion might react with aryl hydrazones to provide heteroallene intermediates that could then undergo intramolecular cycloadditions to provide diazenium salt products. In this way, hydrazones would be directly converted into diazenium salts avoiding the need to prepare and isolate α-chloroazo compounds as intermediates.

Dimethyl sulfide ditriflate ($Me_2S(OTf)_2$) seemed a logical sulfonium salt to use for this transformation; it is known to have similar reactivity to Me_2SCl_2,[32] but has a poorly nucleophilic counterion that we thought unlikely to capture the heteroallene intermediate. Upon treating hydrazone **30e′** (Table 3, entry 4) with $Me_2S(OTf)_2$ and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), we were pleased to observe that the expected fused and bridged bicyclic diazenium salts (**31e′** and **32e′**) were indeed present in the proton NMR spectrum of the crude reaction mixture, along with small quantities of what appeared to be an aryldimethyl sulfonium salt presumably formed by electrophilic aromatic substitution.[33] In an effort to optimize this transformation, sulfonium salts derived by activation of dimethyl sulfoxide with acetic anhydride, trifluoroacetic anhydride, or sulfur trioxide/pyridine complex were tested for their ability to facilitate diazenium salt formation. Unfortunately, none of these activated DMSO species provided any of the diazenium salt products. Substituting pyridine, proton sponge, or 2,6-dichloropyridine as base in place of DTBMP provided notably less product, and deprotonating the hydrazone with *n*-butyllithium prior to adding $Me_2S(OTf_2)$ also failed to provide the desired product. Interestingly, a small amount of diazenium salt formed when no external base was added; in this case it seems likely that another equivalent of hydrazone starting material could be acting as base to facilitate the transformation.

TABLE 3. Results of $Me_2S(OTf)_2$-Mediated Diazenium Salt Formation[a]



Entry	Hydrazone	Product	Yield[b]	Ratio **30**:**31**[c]
1	 **30a'**	 **31a'**	61%	---
2	 **30b'**	 **31b'**	---%[d]	---
3	 **30c'**	 **31c'**	44%	---
4	 **30e'**	 **31e'** **32e'**	67%	1: 0.4
5	 **30f'**	 **31f'** **32f'**	66%	1 : 0.1
6	 **30g'**	 **31g'** **32g'**	54%	1: 0.2

[a]Conditions: $Me_2S(OTf)_2$ (1.1 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (1.2 equiv) CH_2Cl_2 (0.02 M), −78 °C (20 min), −78 °C to rt (35−40 min), added benzyl ether (0.5 equiv), solvent removed in vacuo. [b]Yield determined by NMR vs an internal standard. [c]Diazenium salts **31e'**−**g'** and **32e'**−**g'** were formed as mixtures. [d]Product formed in low yield as an intractable mixture.

(32) Hendrickson, J. B.; Schwartzman, S. M. *Tetrahedron Lett.* **1975**, *16*, 273.

(33) Nenajdenko, V. G.; Vertelezkij, P. V.; Balenkova, E. S. *Sulfur Lett.* **1996**, *20*, 75.

To check the reaction time, several reactions were allowed to proceed at low temperature (−78 °C) for prolonged periods (up to 48 h). These runs led to inconsistent results; reaction time did not correlate to reaction outcome, which indicated to us that reaction temperature might be an important parameter. To better understand temperature effects on the course of the reaction we monitored the processes by variable-temperature NMR. When a −78 °C solution of the hydrazone and DTBMP in CD_2Cl_2 was added to a −78 °C solution of $Me_2S(OTf_2)$ in CD_2Cl_2, a significant change in the proton NMR signals of the hydrazone occurred, indicating that a reaction had occurred between these two compounds. However, at this low temperature no diazenium salt product was observed to form. The temperature of the NMR probe was raised by 10 °C increments and spectra were recorded at each stop along the way. Raising the temperature caused no change in the spectrum until the temperature reached −40 °C, at which point traces of diazenium salt appeared. Increasing the temperature to −30 °C provided only slightly more diazenium salt. However, a critical temperature was reached between −30 and −20 °C, and the reaction proceeded to completion over this temperature range; no changes were noted in the spectrum above −20 °C. On the basis of these data, we hypothesize that $Me_2S(OTf_2)$ reacts rapidly with the hydrazone at low temperature to provide an aza-sulfonium intermediate (e.g., **10**, Scheme 4) that appears to be stable until the temperature is increased above −30 °C. At this higher temperature, formation of the heteroallene and subsequent intramolecular cycloaddition with the alkene would provide the diazenium salt products. With these data in mind, it is not surprising that allowing the −78 °C reaction mixture to warm to room temperature 20 min after mixing the reagents consistently provided cleaner products and this became the procedure of choice.

To determine the scope of this one-step diazenium salt-forming reaction, hydrazones **30a′**−**g′** were subjected to the reaction conditions and the results from these studies are shown in Table 3. The diazenium salt products (**31a′**−**g′** and **32e′**−**g′**) formed in these reactions are highly polar and labile compounds and our attempts to purify these products from the reaction mixtures have not yet been fruitful; all standard purification techniques (e.g., extraction, chromatography, HPLC, ion exchange chromatography) failed to return clean product. However, the NMR spectra of compounds **13a′**−**g′**·$SbCl_6$ and **14e′**−**g′**·$SbCl_6$ (Table 1) were identical to those of the triflate salts shown in Table 3 and thus identifying the desired products in the product mixtures was trivial. Yields for these transformations were established by integration of the NMR spectra by adding a known quantity of benzyl ether to the reaction mixture to serve as an internal standard.

Treating hydrazone **30a′** with $Me_2S(OTf_2)$ and DTBMP provided diazenium salt **31a′** in 61% yield. Only a single diastereomer of **31a′** was observed and the diastereoselectivity of this process is consistent with the selectivity observed for the $SbCl_5$-mediated reaction, which supports the notation that the $Me_2S(OTf_2)$-mediated reaction also proceeds through a heteroallene intermediate.

Hydrazone **30b′**, which has a pendent trisubstituted olefin, provided diazenium salt **31b′** as a complex mixture in less than 30% yield. The low yield in this case is not surprising in view of the poor results obtained for the corresponding Lewis acid-mediated cyclization of α-chloroazo **12b′**. Hydrazone **30c′**, bearing a pendant enoate, was also a competent reactant and after trituration returned iminium ion **31c′** in 44% yield. As noted earlier, iminium ion **31c′** results from isomerization of the corresponding diazenium salt.

Hydrazones **30e′**−**g′**, each bearing a terminal olefin, all reacted with $Me_2S(OTf_2)$ to provide mixtures of fused and bridged bicyclic diazenium salts in 67%, 66%, and 54% yield, respectively. In each case, the ratio of bridged to fused product is comparable to the ratio obtained by the Lewis acid-mediated cycloaddition, which again supports our supposition that these two transformations occur via a common heteroallene intermediate.

Conclusions

The studies described here indicate that reactions between hydrazones and sulfonium salts are versatile and useful for the preparation of a variety of products. Unsubstituted hydrazones react efficiently at low temperature with Me_2SOCl_2 to provide either alkyl chlorides or diazo compounds depending on the quantity of base present, whereas aryl-substituted hydrazones react with Me_2SOCl_2 to provide α-chloroazo compounds in good yield. Importantly, when aryl-substituted hydrazones that contain a pendent alkene are converted into α-chloroazo compounds the olefin is untouched and these products readily participate in Lewis acid-mediated intramolecular cycloadditions to provide bicyclic diazenium salt products. Our data support the supposition that this cycloaddition occurs by a concerted[8] but asynchronous mechanism. Aryl hydrazones that bear a pendent alkene could be directly converted into diazenium salt products by reaction with $Me_2S(OTf_2)$. These latter transformations result in the formation of a new carbon−carbon bond under mild conditions and provide two new rings: a carbocycle and a cyclic diazenium salt. The reactivity and synthetic utility of cyclic diazenium salts is currently under investigation and results from these studies will be reported in due course.

Experimental Section

I. Representative Experimental Procedure for the Preparation of 4-Chlorophenyl Hydrazones:[34]. 1-(4-Chlorophenyl)-2-(hept-6-en-2-ylidene)hydrazine (30e′). 4-Chlorophenyl hydrazine (0.636 g, 4.46 mmol, 1 equiv) was added to a mixture of hept-6-en-2-one (0.50 g, 4.46 mmol, 1 equiv) and 4-Å molecular sieves in CH_2Cl_2 (4 mL). After 1.5 h of stirring the sieves were removed by filtration and the solvent was removed in vacuo to provide 1-(4-chlorophenyl)-2-(hept-6-en-2-ylidene)hydrazine (**30e′**) in 89% yield as a 1:0.17 ratio of *E* and *Z* hydrazone diastereomers. The highly air-sensitive[35] product was typically of sufficient purity to use in subsequent

(34) (i) O'Connor, R. *J. Org. Chem.* **1961**, *26*, 4375. (ii) Yao, H. C.; Resnick, P. *J. Org. Chem.* **1965**, *30*, 2832. (iii) Harej, M.; Dolenc, D. *J. Org. Chem.* **2007**, *72*, 7214. (iv) Tiecco, M.; Testaferri, L.; Marini, C. S.; Bagnoli, L.; Temperini, A. *Tetrahedron* **1997**, *53*, 7311. (v) The hydrazones could also be prepared by mixing the ketone, 4-chlorophenyl hydrazine hydrochloride, and sodium acetate in ethanol under an atmosphere of nitrgen. The mixture was stirred at room temperature or heated to reflux (for sterically encumbered ketones) and the progress of the reaction was monitored by TLC. Upon completion, the solvent was removed in vacuo to provide the hydrazone, which could be further purified by dissolving the residue in pentane and passing the mixture through a short plug of basic alumina.

(35) Harej, M.; Dolenc, D. *J. Org. Chem.* **2007**, *72*, 7214.

reactions without further purification. Small quantities of α-azohydroperoxide could be removed by dissolving the impure hydrazone in pentane and passing the mixture through a short plug of basic alumina. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, J = 8.9 Hz, 2H), 6.97 (d, J = 8.9 Hz, 2H), 6.84 (br s, 1H), 5.84 (ddt, J = 16.9, 10.4, 6.8 Hz, 1H), 5.03 (app dq, J = 17.3, 1.6 Hz, 1H), 4.96−4.99 (m, 1H), 2.31 (t, J = 7.5 Hz, 2H), 2.11 (q, J = 7.1 Hz, 2H), 1.85 (s, 3H), 1.68 (p, J = 7.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.2, 144.5, 138.4, 128.9, 123.9, 114.8, 114.0, 38.2, 33.3, 25.7, 14.4; MS (ESI) calcd for $[C_{13}H_{17}ClN_2H]^+$ 237.1158, found 237.1158. Observable resonances for the minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (d, J = 8.9 Hz, 2H), 5.06−5.11 (m, 2H), 2.24 (t, J = 8.3 Hz, 2H), 2.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.1, 144.4, 137.7, 115.8, 113.9, 28.4, 24.2, 23.1.

II. Characterization Data for 4-Chlorophenyl Hydrazones. (*E*)-1-(4-Chlorophenyl)-2-((*Z*)-oct-6-en-2-ylidene)hydrazine (30a′). Yield 83%; *E*/*Z* 1:0.1; major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, J = 8.9 Hz, 2H), 6.96 (d, J = 8.7 Hz, 2H), 6.83 (br s, 1H), 5.41−5.44 (m, 1H), 5.33−5.44 (m, 1H), 2.32 (t, J = 7.6 Hz, 2H), 2.04−2.15 (m, 2H), 1.85 (s, 3H), 1.64 (p, J = 7.8 Hz, 2H), 1.60 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.4, 144.6, 130.1, 129.0, 124.3, 123.9, 114.1, 38.4, 26.4, 14.4, 12.7; observable resonances for minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.94 (d, J = 8.8 Hz, 2H), 5.53−5.62 (m, 2H), 2.24 (app t, J = 7.5, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 129.4, 125.6, 123.9, 113.9, 28.6, 26.5, 24.9, 23.1, 12.9; MS (ESI) calcd for $[C_{14}H_{19}ClN_2H]^+$ 251.1315, found 251.1313.

(*E*)-1-(4-Chlorophenyl)-2-(7-methyloct-6-en-2-ylidene)hydrazine (30b′). Yield 94%; *E*/*Z* 1:0.3; major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, J = 8.9 Hz, 2H), 6.96 (d, J = 8.7 Hz, 2H), 5.13 (tp, J = 7.2, 1.5 Hz, 1H), 2.30 (t, J = 7.7 Hz, 2H), 2.00−2.08 (m, 3H), 1.84 (s, 3H), 1.70 (s, 3H), 1.60 (s, 3H), 1.50−1.66 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.7, 144.6, 131.9, 129.0, 124.2, 114.1, 38.5, 27.6, 26.7, 25.7, 17.7, 14.4; observable resonances for minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (d, J = 8.7 Hz, 2H), 5.06−5.11 (m, 1H), 2.23 (t, J = 7.4 Hz, 2H), 2.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 123.9, 113.9, 17.8; MS (ESI) calcd for $[C_{15}H_{21}ClN_2H]^+$ 265.1472, found 265.1475.

(2*E*,7*E*)-Methyl 7-(2-(4-chlorophenyl)hydrazono)oct-2-enoate (30c′). Yield 84%; major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, J = 8.7 Hz, 2H), 6.99 (dt, J = 15.6, 7.1 Hz, 1H), 6.97 (d, J = 9.2 Hz, 2H), 6.87 (br s, 1H), 5.85 (dt, J = 15.6, 1.6 Hz, 1H), 3.73 (s, 3H), 2.33 (t, J = 7.5 Hz, 2H), 2.28 (qd, J = 7.5, 1.6 Hz, 2H), 1.84 (s, 3H), 1.77 (p, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 149.0, 146.2, 144.4, 128.9, 123.9, 121.3, 114.0, 77.3, 77.0, 76.8, 51.3, 38.0, 31.6, 24.6, 14.5; MS (ESI) calcd for $[C_{15}H_{19}ClN_2O_2H]^+$ 295.1213, found 295.1209.

(*Z*)-1-(4-Chlorophenyl)-2-(2-methyloct-7-en-3-ylidene)hydrazine (30f′). Yield 92%; *E*/*Z* 1:4.7; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, J = 8.5 Hz, 2H), 6.99 (br s, 1H), 6.96 (d, J = 8.8 Hz, 2H), 5.80−5.95 (ddt, J = 16.6, 10.2, 6.6 Hz, 1H), 5.07−5.12 (m, 2H), 2.53 (sept, J = 6.9 Hz, 1H), 2.2−2.32 (m, 2H), 2.14 (q, J = 7.2 Hz, 2H), 1.62−1.65 (m, 2H), 1.14 (d, J = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5 144.7, 137.7, 128.9, 123.7, 116.0, 113.9, 35.6, 33.7, 26.2, 24.4, 20.4; observable resonances for minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01−5.06 (m, 1H), 4.96−5.00 (m, 1H), 2.87 (sept, J = 6.8 Hz, 1H), 1.11 (d, J = 6.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8, 138.8, 114.6, 33.5, 31.0, 26.9, 25.5, 18.8; MS (ESI) calcd for $[C_{15}H_{21}ClN_2H]^+$ 265.1472, found 265.1479.

(*E*)-1-(4-Chlorophenyl)-2-(4,4-dimethylhept-6-en-2-ylidene)hydrazine (30g′). Yield 90%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, J = 9.2 Hz, 2H), 6.97 (d, J = 9.0 Hz, 2H), 6.87 (br s, 1H), 5.89 (ddt, J = 17.5, 10.2, 7.4 Hz, 1H), 5.00−5.08 (m, 2H), 2.22 (s, 2H), 2.05 (d, J = 7.5 Hz, 2H), 1.89 (s, 3H), 0.96 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.4, 144.4, 135.4, 129.0, 123.9, 117.2, 114.0, 50.1, 46.8, 34.5, 27.3, 17.2; observable resonances for minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (d, 8.6 Hz, 2H), 5.09−5.17 (m, 2H), 2.18 (s, 3H), 2.09 (d, 6.9 Hz, 2H), 1.03 (s, 6H); MS (ESI) calcd for $[C_{15}H_{21}ClN_2H]^+$ 265.1472, found 265.1470.

(*E*)-1-(Hept-6-en-2-ylidene)-2-(3-nitrophenyl)hydrazine (30h′). Yield 74%; *E*/*Z* 1:0.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.60−7.65 (m, 1H), 7.28−7.37 (m, 2H), 7.14 (br s, 1H), 5.84 (ddt, J = 16.9, 10.3, 6.9 Hz, 1H), 5.02−5.07 (m, 1H), 5.00 (br d, J = 10.1 Hz, 1H), 2.34 (t, J = 7.4 Hz, 2H), 2.13 (q, J = 7.0 Hz, 2H), 1.89 (s, 3H), 1.70 (p, J = 7.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.2, 148.9, 146.8, 138.3, 129.7, 118.5, 114.9, 113.9, 107.4, 38.2, 33.3, 25.7, 14.6; observable resonances for minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (s, 1H), 2.27 (t, J = 7.7 Hz, 2H), 2.04 (s, 3H); MS (ESI) calcd for $[C_{13}H_{17}N_3O_2H]^+$ 248.1399, found 248.1402.

(*E*)-1-(Hept-6-en-2-ylidene)-2-(4-methoxyphenyl)hydrazine (30i′). Yield 92%; *E*/*Z* 1:0.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (d, J = 8.9 Hz, 2H), 6.82 (d, J = 8.9, 2H), 6.69 (br s, 1H), 5.84 (ddt, J = 17.0, 10.3, 6.6 Hz, 1H), 4.93−5.06 (m, 2H), 3.76 (s, 3H), 2.30 (t, J = 7.3 Hz, 2H), 2.08−2.16 (m, 2H), 1.84 (s, 3H), 1.68 (p, J = 7.6, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5, 146.4, 140.3, 138.6, 114.7, 114.7, 114.3, 77.3, 77.0, 76.8, 55.7, 38.3, 33.3, 25.9, 14.4; observable resonances for minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05−5.11 (m, 2H), 2.24 (t, J = 8.0 Hz, 2H), 2.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 115.7, 114.2, 28.5, 24.2, 23.1; MS (ESI) calcd for $[C_{14}H_{20}N_2OH]^+$ 233.1654, found 233.1652.

(*E*)-1-(4-Chlorophenyl)-2-(oct-7-en-2-ylidene). Yield 87%; *E*/*Z* 1:0.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, J = 8.9 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 6.83 (br s, 1H), 5.82 (ddt, J = 17.6,10.7, 6.9 Hz, 1H), 4.93−5.04 (m, 2H), 2.30 (t, J = 7.8 Hz, 2H), 2.06−2.13 (m, 2H), 1.84 (s, 3H), 1.56−1.62 (m, 2H), 1.41−1.47 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.6, 144.6, 138.8, 129.0, 124.0, 114.5, 114.1, 38.7, 33.6, 28.5, 26.0, 14.4; observable resonances for minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.23 (t, J = 7.7 Hz, 2H), 2.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.5, 25.1; MS (ESI) calcd for $[C_{14}H_{19}ClN_2H]^+$ 251.1315, found 251.1317.

III. Representative Experimental Procedure for the Preparation of Aryl-α-chloroazoalkanes:[36] 1-(2-Chlorohept-6-en-2-yl)-2-(4-chlorophenyl)diazene (12e′). Oxalyl chloride (5.15 mmol, 0.44 mL, 1.2 equiv) was added in a dropwise manner to a stirred solution of DMSO (5.58 mmol, 0.40 mL, 1.3 equiv) in THF (30 mL) at −55 °C under a nitrogen atmosphere. The reaction was maintained at −55 °C until gas evolution ceased (∼20 min) at which point the reaction was cooled further to −78 °C. A mixture of Et_3N (6.43 mmol, 0.90 mL, 1.5 equiv) and hydrazone **30e′** (1.02 g, 4.29 mmol, 1 equiv) in THF (5 mL) was added in a dropwise manner via cannula. An immediate

(36) The aryl-α-chloroazoalkane products were moderately stable, but decomposed on standing. Attempts to send the sample for exact mass determination failed to provide useful data.

color change and a concomitant formation of a white precipitate were noted. The reaction mixture was maintained at −78 °C for 30 min and was then removed from the cold bath and warmed to room temperature at which point the solids were removed by filtration through a medium porosity sintered-glass funnel. The filtrate was concentrated by rotary evaporation and the residue was dissolved in pentane (∼20 mL) and decanted away from an insoluble red oil. The pentane was removed in vacuo to provide 1-(2-chlorohept-6-en-2-yl)-2-(4-chlorophenyl)diazene (**12e′**) in 80% yield. This material was used in the subsequent step without further purification. Residual DMSO could be removed by washing the pentane solution with water before concentrating, but this step was not routinely performed as it lowered product recovery and was not necessary for the subsequent transformation. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (dm, J = 8.6, 1.9 Hz, 2H), 7.48 (dm, J = 8.6, 1.9 Hz, 2H), 5.78 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.01 (app dq, J = 17.0, 1.6 Hz, 1H), 4.95−4.98 (m, 1H), 2.28 (ddd, J = 14.0, 12.0, 4.7 Hz, 1H), 2.17 (ddd, J = 14.0, 12.0, 4.6 Hz, 1H), 2.09 (q, J = 7.3 Hz, 2H), 1.89 (s, 3H), 1.60−1.70 (m, 1H), 1.44−1.53 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 138.0, 137.3, 129.3, 124.2, 115.1, 96.5, 42.2, 33.4, 28.7, 23.4.

IV. Characterization Data for 4-Chlorophenyl-α-chloroazo Alkanes. (*E*)-1-((*Z*)-2-Chlorooct-6-en-2-yl)-2-(4-chlorophenyl)-diazene (12a′). Yield 83%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 8.6 Hz, 2H), 7.45 (d, J = 8.6 Hz, 2H), 5.44−5.50 (m, 1H), 5.32−5.38 (m, 1H), 2.28 (ddd, J = 14.1, 11.9, 4.7 Hz, 1H), 2.17 (ddd, J = 14.1, 11.9, 4.7 Hz, 1H), 2.08 (q, J = 7.3 Hz, 2H), 1.89 (s, 3H), 1.54−1.68 (m, 1H), 1.59 (d, J = 6.7 Hz, 3H), 1.41−1.50 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 137.3, 129.7, 129.3, 124.6, 124.2, 96.5, 42.3, 28.7, 26.5, 24.1, 12.8.

1-(2-Chloro-7-methyloct-6-en-2-yl)-2-(4-chlorophenyl)diazene (12b′). Yield 87%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 8.6 Hz, 2H), 7.45 (d, J = 8.6 Hz, 2H), 5.08 (t, J = 7.1 Hz, 1H), 2.25 (ddd, J = 14.0, 11.8, 4.5 Hz, 1H), 2.16 (ddd, J = 14.0, 11.8, 4.6 Hz, 1H), 2.01 (q, J = 7.3 Hz, 2H), 1.89 (s, 3H), 1.68 (s, 3H), 1.58 (s, 3H), 1.55−1.65 (m, 1H), 1.40−1.47 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 137.2, 132.0, 129.2, 124.2, 123.8, 96.5, 42.4, 28.6, 27.7, 25.6, 24.4, 17.7.

(*E*)-Methyl 7-Chloro-7-((*E*)-(4-chlorophenyl)diazenyl)oct-2-enoate (12c′). Yield 69%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 8.6 Hz, 2H), 7.45 (d, J = 8.6 Hz, 2H), 6.94 (dt, J = 15.7, 7.0, Hz, 1H), 5.83 (dt, J = 15.7, 1.5 Hz, 1H), 3.72 (s, 3H), 2.30 (ddd, J = 14.0, 11.8, 4.6 Hz, 1H), 2.25 (qd, J = 7.3, 1.4 Hz, 2H), 2.18 (ddd, J = 14.1, 12.9, 4.6 Hz), 1.89 (s, 3H),1.68−1.78 (m, 2H), 1.51−1.63 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 149.6, 148.6, 137.8, 129.7, 124.6, 121.9, 96.4, 51.8, 42.9, 42.5, 32.1, 31.7, 30.3, 29.1, 23.0, 22.2.

1-(3-Chloro-2-methyloct-7-en-3-yl)-2-(4-chlorophenyl)diazene (12f′). Yield 95%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 8.6 Hz, 2H), 7.45 (d, J = 8.6 Hz, 2H), 5.74 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 4.95 (app dq, J = 17.1, 1.7 Hz, 1H), 4.92−4.96 (m, 1H), 2.65 (septet, J = 6.71 Hz, 1H), 2.37 (ddd, J = 14.1, 11.8, 4.6 Hz, 1H), 2.20 (ddd, J = 14.0, 12.0, 4.4 Hz, 1H), 2.05 (q, J = 7.2 Hz, 2H), 1.55−1.64 (m, 1H), 1.21−1.30 (m, 1H), 1.15 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 138.0, 137.1, 129.3, 124.1, 115.0, 104.2, 39.3, 37.7, 33.5, 22.9, 17.5, 17.4.

1-(2-Chloro-4,4-dimethylhept-6-en-2-yl)-2-(4-chlorophenyl)-diazene (12g′). Yield 86%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 8.6 Hz, 2H), 7.48 (d, J = 8.6 Hz, 2H), 5.81 (ddt, J = 17.1, 9.79, 7.5 Hz, 1H), 4.96−5.07 (m, 2H), 2.50 (d, J = 15.5 Hz, 1H), 2.30 (d, J = 15.5 Hz, 1H), 1.96−2.1 (m, 2H), 1.91 (s, 3H), 0.95 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.2, 137.4, 135.0, 129.4, 124.3, 117.6, 96.6, 53.7, 48.5, 34.8, 31.6, 28.5, 28.4.

1-(2-Chlorohept-6-en-2-yl)-2-(3-nitrophenyl)diazene (12h′). Yield 75%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.34 (d, J = 8.2 Hz, 1H), 8.14 (d, J = 8.2 Hz, 1H), 7.70 (t, J = 8.2 HZ, 1H), 5.80 (ddt, J = 17.0, 10.2, 6.9 Hz, 1H), 4.95−5.06 m (2H), 2.31 (ddd, J = 14.1, 11.8, 4.7 Hz, 1H), 2.21 (ddd, J = 14.4, 11.9, 4.6 Hz, 1H), 2.09 (q, J = 6.9 Hz, 2H), 1.93 (s, 3H), 1.59−1.71 (m, 1H), 1.44−1.55 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3, 148.9, 137.8, 130.1, 129.4, 125.4, 117.0, 115.2, 96.5, 42.0, 33.3, 28.7, 23.4.

1-(2-Chlorohept-6-en-2-yl)-2-(4-methoxyphenyl)diazene (12i′). Yield 82%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 5.78 (ddt, J = 17.1, 10.2, 6.7 Hz, 1H), 5.01 (app d, J = 17.2 Hz, 1H), 4.93−4.98 (app d, J = 10.4 Hz, 1H), 3.87 (s, 3H), 2.27 (ddd, J = 14.2, 12.0, 4.7 Hz, 1H), 2.16 (ddd, J = 14.1, 11.9, 4.7 Hz, 1H), 2.09 (q, J = 7.0 Hz, 2H), 1.88 (s, 3H), 1.58−1.70 (m, 1H), 1.46−1.57 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2, 145.1, 138.2, 124.9, 115.0, 114.1, 96.5, 55.6, 42.4, 33.5, 28.8, 23.5.

(*E*)-1-(2-Chlorooct-7-en-2-yl)-2-(4-chlorophenyl)diazene (24). Yield 60%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 8.7 Hz, 2H), 7.45 (d, J = 8.6 Hz, 2H), 5.78 (ddt, J = 16.9, 10.1, 6.8 Hz, 1H), 4.90−5.04 (m, 2H), 2.24−2.32 (m, 1H), 2.13−2.20 (m, 1H), 2.01−2.10 (m, 2H), 1.89 (s, 3H), 1.51−1.59 (m, 1H), 1.37−1.46 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 138.8, 137.7, 129.7, 124.6, 115.0, 96.9, 43.0, 33.8, 29.1, 29.0, 24.0.

V. Representative Experimental Procedures for the Formation of Bicyclic Diazenium Salts. Method A: Lewis acid-mediated formation of bicyclic diazenium salts from α-chloroazo compounds:

6a-Methyl-2-(4-chlorophenyl)-3,3a,4,5,6,6a-hexahydrocyclopenta[*c*]pyrazol-2-ium Hexachlorostibate(V) (13e′). Antimony pentachloride (3.56 mmol, 0.455 mL, 1 equiv) was added dropwise to a stirred solution of the α-chloroazoalkane **12e′** (3.56 mmol, 0.965 g, 1 equiv) in CH_2Cl_2 (40 mL) at −60 °C under a nitrogen atmosphere. The cooling bath was allowed to warm slowly to 0 °C (∼45 min) and the reaction was maintained at that temperature for 1 h. The mixture was allowed to stir at room temperature for 10 min at which point the solvent was removed in vacuo to provide a dark oil or foam. This crude material was analyzed by proton NMR (CD_3CN) to determine the ratio of fused to bridged diazenium salt products. The NMR sample was recombined with the crude reaction mixture, the solvent was removed in vacuo, and the residue was triturated with Et_2O to provide the desired diazenium salt as a powder in 92% yield: ^{1}H NMR (500 MHz, CD_3CN) δ 8.09 (d, J = 9.1 Hz, 2H), 7.76 (d, J = 9.3 Hz, 2H), 5.54 (dd, J = 17.2, 9.2 Hz, 1H), 5.13 (dd, J = 17.2, 4.5 Hz, 1H), 2.92−2.97 (m, 1H), 2.45−2.54 (m, 1H), 2.03−2.17 (m, 2H), 1.80 (s, 3H), 1.72−1.82 (m, 2H), 1.45−1.56 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 139.1, 131.7, 126.7, 101.2, 78.0, 43.2, 39.8, 33.7, 25.1, 23.8; observable resonances for minor isomer: 6-(4-chlorophenyl)-1-methyl-6,7-diazabicyclo[3.2.1]oct-6-en-6-ium hexachlorostibate(V) (**14e′**): ^{1}H NMR (500 MHz, CD_3CN) δ 8.09 (d, J = 6.6 Hz, 2H), 7.79 (d, J = 6.1 Hz, 2H), 6.05 (app t, J = 5.1 Hz, 1 H), 1.87 (s, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 144.6, 132.3, 87.5, 83.7, 29.4, 22.9, 22.6, 18.4; IR (ATR, cm^{-1}) 1586, 1529, 1413, 1095, 831; MS (ESI) calcd for $[C_{13}H_{16}ClN_2]^+$ 235.1002, found 235.0998.

Method B: Dimethyl sulfide ditriflate mediated formation of bicyclic diazenium salts from hydrazones:

6a-Methyl-2-(4-chlorophenyl)-3,3a,4,5,6,6a-hexahydrocyclopenta[*c*]pyrazol-2-ium Triflate (31e′). Trifilic anhydride (0.82 mmol, 0.14 mL, 1.1 equiv) was added dropwise to a −78 °C solution of DMSO (0.86 mmol, 0.06 mL, 1.15 equiv) in CH_2Cl_2 (32 mL). After 20 min a solution of 4-chlorophenyl hydrazone (0.75 mmol, 0.18 g, 1 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (0.89 mmol, 0.18 g, 1.2 equiv) in CH_2Cl_2 (5 mL) was added. The resulting bright yellow solution was stirred for 20 min during which time a fine precipitate often formed. The dry ice dewar was removed and the solution was allowed to warm to room temperature over 30 min during which time the silky precipitate dissolved and an orange solution resulted. Upon warming to room temperature, a known quantity of dibenzyl ether (0.37 mmol, 0.07 mL, 0.5 equiv) was added to the reaction mixture as an internal NMR standard and the solvent was removed in vacuo at 60 Torr to provide an orange powder. The ratio of diazenium salt to dibenzyl ether was determined by proton NMR analysis (CD_3CN), which showed the desired product had formed in 67% yield. Spectroscopic data matched that of hexachlorostibate salts **13e′** and **14e′**.

VI. Characterization Data for the Diazenium Salt Products. 2-(4-Chlorophenyl)-3,6a-dimethyl-3,3a,4,5,6,6a-hexahydrocyclopenta[*c*]pyrazol-2-ium Hexachlorostibate(V) (13a′) or Triflate (31a′). Method A yield 87%; Method B yield 61%; ^{1}H NMR (500 mHz, CD_3CN) δ 7.95 (d, J = 9.1 Hz, 2H), 7.76 (d, J = 9.1 Hz, 2H), 5.94 (dq, J = 9.3, 7.2 Hz, 1H), 2.96−3.00 (m, 1H), 2.45−2.53 (m, 1H), 2.18−2.25 (m, 1H), 1.76−1.92 (m, 3H), 1.79 (s, 3H), 1.58 (d, J = 7.2 Hz, 3H), 1.42−1.53 (m, 1H); ^{13}C NMR (125 MHz, CD_3CN) δ 142.8, 138.1, 131.5, 127.3, 99.8, 84.6, 46.9, 39.7, 28.6, 25.6, 24.1, 15.7; IR (ATR, cm^{-1}) 1518, 1441, 1409, 1095, 832; MS (ESI) calcd for $[C_{14}H_{18}ClN_2]^+$ 249.1158, found 249.1153.

2-(4-Chlorophenyl)-3-(methoxycarbonyl)-6a-methyl-1,3a,4,5,6,6a-hexahydrocyclopenta[*c*]pyrazol-2-ium Hexachlorostibate(V) (13c′) or Triflate (31c′). Method A yield 69%; Method B yield 44%; ^{1}H NMR (500 MHz, CD_3CN) δ 8.07 (s, 1H), 7.60−7.66 (m, 4H), 3.93 (dd, J = 9.8, 5.0 Hz, 1H), 3.79 (s, 3H), 2.27−2.37 (m, 2H), 2.09−2.18 (m, 1H), 1.76−1.88 (m, 3H), 1.57 (s, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 157.2, 151.0, 139.7, 134.5, 130.78, 127.5, 73.8, 58.8, 55.0, 42.9, 34.2, 26.0, 25.9; IR (ATR, cm^{-1}) 1746, 1515, 1436, 1096, 838, 829; MS (ESI) calcd for $[C_{15}H_{18}O_2ClN_2]^+$ 293.1057, found 293.1056.

6a-Isopropyl-2-(4-chlorophenyl)-3,3a,4,5,6,6a-hexahydrocyclopenta[*c*]pyrazol-2-ium Hexachlorostibate(V) (13f′) or Triflate (31f′). Method A yield 80%; Method B yield 66%; ^{1}H NMR (500 MHz, CD_3CN) δ 8.12 (d, J = 9.2 Hz, 2H), 7.76 (d, J = 9.2 Hz, 2H), 5.53 (dd, J = 17.5, 9.8 Hz, 1H), 5.14 (dd, J = 17.5, 4.4 Hz, 1H), 3.11−3.16 (m, 1H), 2.43 (septet, J = 6.5 Hz, 1H), 2.37−2.40 (m, 1H), 2.23−2.29 (m, 1H), 1.90−1.98 (m, 1H), 1.74−1.81 (m, 2H), 1.41−1.50 (m, 1H), 1.16 (d, J = 6.9 Hz, 3H), 1.12 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 144.0, 139.0, 131.8 (t), 127.0 (m), 108.7, 78.0, 40.1, 37.2, 35.4, 33.8, 24.6, 18.6, 18.3; observable resonances for minor isomer: 6-(4-chlorophenyl)-1-isopropyl-6,7-diazabicyclo[3.2.1]oct-6-en-6-ium hexachlorostibate(V) (**14f′**) or triflate (**32f′**): ^{1}H NMR (500 MHz, CD_3CN) δ 8.19 (d, J = 9.3 Hz, 2H), 7.79 (d, J = 9.3 Hz, 2H), 6.04−6.10 (m, 1H); ^{13}C NMR (125 MHz, CD_3CN) δ 38.8, 34.5, 25.4, 22.9, 18.4, 17.9; IR (ATR, cm^{-1}) 1530, 1414, 1092, 828; MS (ESI) calcd for $[C_{15}H_{20}ClN_2]^+$ 263.1315, found 263.1319.

5,5,6a-Trimethyl-2-(4-chlorophenyl)-3,3a,4,5,6,6a-hexahydrocyclopenta[*c*]pyrazol-2-ium Hexachlorostibate(V) (13g′) or Triflate (31g′). Method A yield 89%; Method B yield 54%; ^{1}H NMR (500 MHz, CD_3CN) δ 8.11 (d, J = 9.1 Hz, 2H), 7.76 (d, J = 9.3 Hz, 2H), 5.41 (dd, J = 16.2, 7.9 Hz, 1H), 5.23 (dd, J = 16.2, 2.3 Hz, 1H), 3.12 (qd, J = 8.0, 2.3 Hz, 1H), 2.26 (d, J = 13.9 Hz, 1H), 2.20 (dd, J = 14.3, 1.7 Hz, 1H), 2.05 (ddd, J = 13.1, 8.3, 1.6 Hz, 1H), 1.75 (s, 3H), 1.47 (ddd, J = 13.1, 9.3, 1.6 Hz, 1H), 1.13 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 143.9, 139.2, 131.8, 127.0, 101.0, 77.0, 51.2, 47.6, 43.2, 39.8, 28.5, 28.3, 25.0; observable resonances for minor isomer: 6-(4-chlorophenyl)-1,3,3-trimethyl-6,7-diazabicyclo[3.2.1]-oct-6-en-6-ium hexachlorostibate(V) (**14g′**) or triflate (**32g′**): ^{1}H NMR (500 MHz, CD_3CN) δ 8.18 (d, J = 9.1 Hz, 2H), 7.82 (d, J = 9.3 Hz, 2H), 5.94−5.96 (m, 1H), 1.89 (s, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 132.7, 126.7, 87.6, 81.7, 43.0, 36.4, 31.7, 23.2; IR (ATR, cm^{-1}) 1524, 1412, 1094, 831; MS (ESI) calcd for $[C_{15}H_{20}ClN_2]^+$ 263.1315, found 263.1312.

6a-Methyl-2-(3-nitrophenyl)-3,3a,4,5,6,6a-hexahydrocyclopenta[*c*]pyrazol-2-ium Hexachlorostibate(V) (13h′). Method A yield 81%; proton NMR resonances assignable to **13h′**: ^{1}H NMR (500 MHz, CD_3CN) δ 8.87 (t, J = 2.1 Hz, 1H), 8.68 (dd, J = 8.3, 1.7 Hz, 1H), 8.46 (dd, J = 8.3, 2.2 Hz, 1H), 8.01 (t, J = 8.3 Hz, 1H), 5.61 (dd, J = 17.3, 9.7 Hz, 1H), 5.23 (dd, J = 17.3, 4.2 Hz, 1H), 2.97−3.05 (m, 1H), 1.86 (s, 3H); proton NMR resonances assignable to 1-methyl-6-(3-nitrophenyl)-6,7-diazabicyclo[3.2.1]oct-6-en-6-ium hexachlorostibate-(V) (**14h′**): ^{1}H NMR (500 MHz, CD_3CN) δ 8.93 (t, J = 2.1 Hz, 1H), 8.71 (dd, J = 8.3, 1.7 Hz, 1H), 8.54 (dd, J = 8.3, 2.4 Hz, 1H), 8.04 (t, J = 8.4 Hz, 1H), 6.17 (t, J = 5.2 Hz, 1H), 2.38 (d, J = 11.8 Hz, 1H), 1.93 (s, 3H), 0.92−1.04 (m, 1H); proton NMR resonances assignable to **13h′** and **14h′**: 2.52−2.62 (m, 2H), 1.74−2.22 (m, 10 H); carbon NMR resonances assignable to **13h′** and **14h′**: ^{13}C NMR (125 MHz, CD_3CN) δ 150.1, 149.6, 140.6, 139.2, 133.3, 132.8, 131.8, 131.2, 130.5, 130.4, 120.2, 120.1, 101.7, 88.5, 84.5, 78.5, 43.1, 43.0, 39.7, 33.4, 29.1, 24.7, 23.6, 22.6, 22.0, 18.0; IR (ATR, cm^{-1}) 1529, 1454, 1349, 803, 735; MS (ESI) calcd for $[C_{13}H_{16}N_3O_2]^+$ 246.1243, found 246.1248.

6a-Methyl-2-(4-methoxyphenyl)-3,3a,4,5,6,6a-hexahydrocyclopenta[*c*]pyrazol-2-ium Hexachlorostibate(V) (13i′). Method A yield 92%; ^{1}H NMR (500 MHz, CD_3CN) δ 8.09 (d, J = 8.9 Hz, 2H), 7.20 (d, J = 8.9 Hz, 2H), 5.47 (dd, J = 16.7, 9.7 Hz, 1H), 5.07 (dd, J = 16.7, 4.1 Hz, 1H), 3.97 (s, 3H), 2.86−2.93 (m, 1H), 2.41−2.47 (m, 1H), 2.03−2.08 (m, 2H), 1.76 (s, 3H), 1.98−2.03 (m, 1H), 1.41−1.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 132.2, 126.6 (br), 115.5, 98.1, 75.8, 56.1, 41.8, 38.4, 32.4, 23.7, 22.5; IR (ATR, cm^{-1}) 1580, 1513, 1429, 1246, 1171, 1097, 1021, 835; MS (ESI) calcd for $[C_{14}H_{19}N_2O]^+$ 231.1497, found 231.1498.

7-(4-Chlorophenyl)-1-methyl-7,8-diazabicyclo[4.2.1]non-7-en-7-ium Hexachlorostibate(V) (26). Method A yield 62%; ^{1}H NMR (500 MHz, CD_3CN) δ 8.14 (d, J = 8.9 Hz, 2H), 7.79 (d, J = 8.9 Hz, 2H), 6.08−6.10 (m, 1H), 2.67 (d, J = 13.3 Hz, 1H), 2.36−2.41 (m, 2H), 2.02−2.21 (m, 3H), 1.86 (s, 3H), 1.68−1.77 (m, 2H), 1.24−1.32 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.0, 137.2, 132.2, 126.9 (br), 90.7,85.2, 41.2, 35.6, 33.5, 25.7, 24.6, 23.9; IR (ATR, cm^{-1}) 1519, 1411, 1094, 829; MS (ESI) calcd for $[C_{14}H_{18}ClN_2]^+$ 249.1158, found 249.1153.

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Supporting Information Available: General experimental details and copies of ^{1}H and ^{13}C NMR spectra for compounds **12a′**−**c′**, **12e′**−**i′**, **13a′**, **13c′**, **13e′**−**i′**, **14e′**−**h′**, **24**, **26**, **30a′**−**c′**, **30e′**−**i′**, **31a′**, **31c′**, **31e′**−**g′**, **32e′**−**g′**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Stereospecific Intramolecular C−H Amination of 1-Aza-2-azoniaallene Salts

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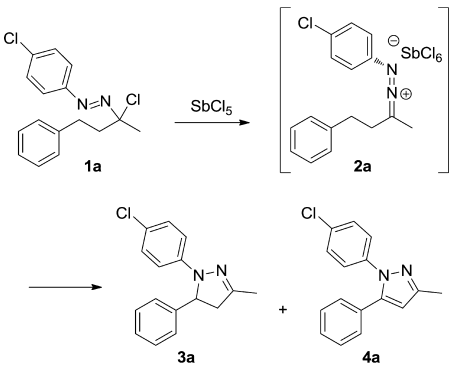
Supporting Information

ABSTRACT: We report that 1-aza-2-azoniaallene salts, generated from α-chloroazo compounds by treatment with halophilic Lewis acids, participate in intramolecular C−H amination reactions to provide pyrazoline products in good to excellent yield. This intramolecular amination occurs readily at both benzylic and tertiary aliphatic positions and proceeds at an enantioenriched chiral center without loss of enantiomeric excess. A competition reaction shows that insertion occurs more readily at an electron-rich benzylic position than an electron-deficient one. These observations are consistent with the 1-aza-2-azoniaallene intermediate reacting as a nitrenium-like ion by a concerted insertion mechanism.

Reactions that result in direct functionalization of unactivated C−H bonds are powerful transformations because they provide new synthetic strategies that can be more efficient and simpler to execute than traditional synthetic sequences.[1] For example, Rh-catalyzed carbene insertion reactions, wherein Rh complexes selectively functionalize C−H bonds, have become an important strategy for C−C bond formation.[2] Similarly, since Breslow and Gellman's[3,4] seminal demonstration that (imidoiodo)benzene derivatives react with alkanes in the presence of a transition metal to provide amine products, transition-metal-catalyzed C−H amination reactions have become important ways to prepare organic amines.[5−9] These techniques are powerful because they allow for the selective installation of N atoms both inter- and intramolecularly at a late stage in a synthetic sequence and provide fundamentally new approaches to the preparation of N heterocycles, which are prevalent in bioactive molecules.[10−12] The significant advances that have been made over the past decade in transition-metal-mediated amination were made possible in part by the discoveries by Che[13] and Du Bois[14] that metal nitrenoid species could be prepared in situ from amine derivatives, iodine(III) reagents, and a transition metal catalyst. Recently, amination reactions have been used elegantly in natural product synthesis[15,16] and have been rendered stereoselective.[17−20] Here we report our discovery that 1-aza-2-azoniaallene salts[21] (e.g., **2a**, Scheme 1) undergo intramolecular C−H insertion reactions to provide pyrazoline products without the formation of a metal nitrenoid intermediate.

Recent work in our group has focused on investigating 1-aza-2-azoniaallene salts as reactive intermediates for the synthesis of N heterocycles.[22,23] We have demonstrated that these heteroallene salts, which can be generated by reaction of α-chloroazo compounds with halophilic Lewis acids,[21] productively react with pendant alkenes to provide bicyclic diazenium salts via intramolecular 1,3-dipolar cycloaddition reactions similar to the intermolecular cycloadditions described by Jochims et al.[24,25] The requisite α-chloroazo compounds are easily prepared by reaction of hydrazones with chlorodimethylsulfonium chloride.[26] We became interested in exploring the reactivity of these cationic heteroallenes in systems that cannot participate in 1,3-dipolar cycloadditions because they lack a pendant alkene.[27] To this end, we prepared heteroallene **2a** (Scheme 1) by treating the α-chloroazo compound **1a** with $SbCl_5$, and upon purifying this reaction we were surprised to isolate pyrazoline **3a** in good yield as well as traces of pyrazole **4a**. This unexpected result is, to our knowledge, the first example of heteroallenes such as **2a** reacting by a nitrene-like manifold to provide the product of an intramolecular C−H amination reaction. Although pyrazolines can be readily prepared by reaction of hydrazines with α,β-unsaturated aldehydes and ketones or by 1,3-dipolar cycloaddition of diazoalkanes with alkenes,[28,29] the development of new methods to prepare these compounds is still of interest[30−36] due to their prevalence in biologically active compounds.[30,37,38] The novelty of this C−H amination reaction encouraged us to examine this new reactivity more thoroughly.

Scheme 1. Preparation of a Pyrazoline from an α-Chloroazo Compound



Upon repeating this transformation several times, we noted that the ratio of pyrazoline **3a** and pyrazole **4a** varied significantly between trials, and we reasoned that the pyrazole likely formed by a precedented $SbCl_6^-$-mediated oxidation of the pyrazoline.[39] This secondary oxidation reaction proved

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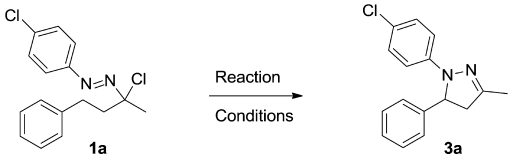
Table 1. Optimization of Reaction Conditions for Pyrazoline Formation



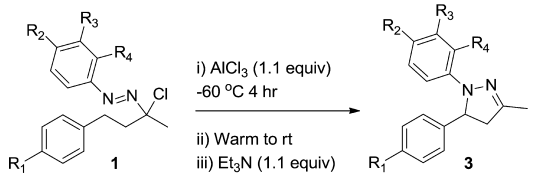
entry	MCl_X	equiv	solvent	time (h)	temp (°C)	yield (%)[a]
1	$SbCl_5$	1.1	CH_2Cl_2	2	−60	53
2	$AlCl_3$	1.1	CH_2Cl_2	2	−60	51
3	$AlCl_3$	1.1	CH_2Cl_2	4	−60	61
4	$AlCl_3$	1.1	CH_2Cl_2	6	−60	62
5	$AlCl_3$	1.1	CH_2Cl_2	32	−60	59
6	$AlCl_3$	1.1	CH_2Cl_2	48	−60	38
7	$AlCl_3$	1.1	CH_2Cl_2	34	−40	56
8	$AlCl_3$	1.1	CH_2Cl_2	24	25	49
9	$AlCl_3$	1.1	THF	24	−60	0
10	$AlCl_3$	2.2	CH_2Cl_2	24	−60	36

[a]Yields determined by ^{1}H NMR integration relative to an internal standard.

difficult to control, but we were pleased to find that changing the Lewis acid from $SbCl_5$ to $AlCl_3$ eliminated formation of pyrazole **4a** while providing comparable yields of the desired pyrazoline (Table 1, entry 2).[21] We next evaluated the effect of reaction time on the reaction outcome. Increasing the reaction time from 2 to 4 h resulted in increased product yield (entries 2 and 3), but further extending the reaction time added no benefit (entries 4−6). We also evaluated the temperature dependence of the reaction and observed the best results at −60 °C; higher temperatures resulted in slightly lower yields (entries 7 and 8). Changing the solvent from CH_2Cl_2 to THF inhibited the reaction altogether (entry 9), and increasing the equivalents of $AlCl_3$ decreased the pyrazoline yield (entry 10).

To gain insight into the role that electronic effects might play in this reaction, we prepared a series of substrates having either electron-donating or -withdrawing groups on the N-aryl or the pendant aryl ring (Table 2). Electron-rich N-aryl rings facilitated the reaction, and changing the N-aryl ring from 4-chlorophenyl to phenyl, 4-methylphenyl, or 4-methoxyphenyl

Table 2. Effect of Aryl Ring Electronics on the Intramolecular Amination

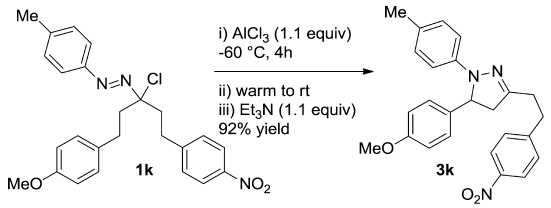


entry	α-chloroazo	R_1	R_2	R_3	R_4	yield (%)
1	**1a**	H	Cl	H	H	61
2	**1b**	H	H	H	H	74
3	**1c**	H	CH_3	H	H	79
4	**1d**	H	OCH_3	H	H	76
5	**1e**	H	H	NO_2	H	<20
6	**1f**	H	H	H	CH_3	80
7	**1g**	OCH_3	Cl	H	H	79
8	**1h**	CH_3	Cl	H	H	65
9	**1i**	Cl	Cl	H	H	62
10	**1j**	NO_2	Cl	H	H	65

resulted in an increase in yield of ∼15%. The 3-nitrophenyl derivative (entry 5), in contrast, returned product in at most 20% yield.[40] A moderate increase in steric hindrance adjacent to the amine was well tolerated; 2-methylphenyl derivative **1f** provided the expected product in 80% yield (entry 6). Changing the electronics of the pendant aryl ring from marginally electron-rich (entry 8) to electron-neutral (entry 1) to electron-poor (entries 9 and 10) had surprisingly little influence on the reaction outcome; in each case a similar quantity of pyrazoline product was formed (61−65% yield). In contrast, a strong electron-donating group on the pendant aryl ring (entry 7) appeared to activate the benzylic C−H bond toward amination and gave a significantly higher product yield (79%).

To test this finding more directly, we devised a competition experiment in which the heteroallene intermediate has equal opportunity to react at an electron-rich or -deficient benzylic position. For this experiment, we prepared α-chloroazo substrate **1k** (Scheme 2), which contains both electron-poor

Scheme 2. Competition Experiment



and -rich pendant aryl rings. The heteroallene generated from this substrate reacted with complete selectivity at the more electron-rich benzylic C−H bond to provide pyrazoline **3k** as the only product in 92% yield.[41] The high yield obtained for this reaction is likely due to the electron-rich nature of both the N-aryl and pendant aryl ring. It is accepted that, over the course of carbenoid and nitrenoid C−H insertion reactions, positive charge builds at the C undergoing the C−H insertion, and sites adjacent to electron-donating groups react more quickly.[2,42] The result of the competition study supports the notion that heteroallene intermediate **2**, which could exist in nitrenium ion form **5** (Figure 1), may be reacting similarly to a nitrenoid via a

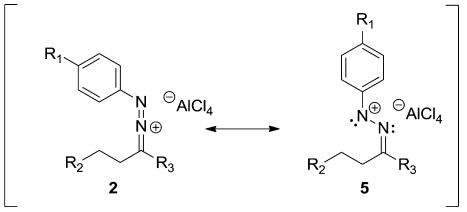


Figure 1. Nitrenium ion resonance form.

C−H amination reaction. Theoretical studies support the ability of 1-aza-2-azoniaallene cations to react by a nitrenium ion manifold.[43] Nitrenium ions are isoelectronic with carbenes, but despite the plethora of research in carbene chemistry, nitrenium ions have been far less studied,[44−46] although recently aryl nitrenium ions[47−49] have received more attention due to their proposed role in mutagenesis and carcinogenesis. Additionally, nitrenium ions are known to undergo concerted addition to alkenes to provide aziridinium products,[50−53] and they can act as hydride acceptors.[54] The increased yields of

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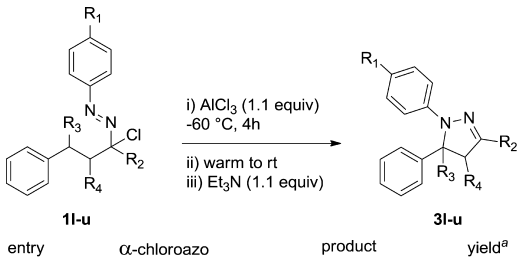
pyrazoline we obtained for electron-rich N-aryl substrates (Table 2, entries 3 and 4, and Table 3, all entries) are also consistent with a nitrenium ion-type reaction intermediate since electron-rich aryl rings and adjacent heteroatoms are known to stabilize the nitrenium ion singlet state,[55] which should undergo insertion reactions more readily than the triplet state.

We next examined the effect of adding substituents on the C chain of the α-chloroazo substrate (Table 3) on the reactions leading to tri- or tetrasubstituted pyrazolines. Adding a substituent adjacent to the chloroazo center and between the reacting centers returned a single diastereomer[56] of product; however, in these cases yields suffered (entries 3 and 4). The reduction in yield is likely due to an increase in steric interactions that make pyrazoline formation less facile, and not a subtle electronic effect imparted by the extra substituent since adding a group adjacent to the chloroazo center on the side opposite the aryl ring provided the expected product in good yield (entry 1). Adding a substituent in the benzylic position was well tolerated when the N-aryl ring was electron-rich to provide 5,5-disubstituted pyrazoline **3o** (entry 2).[57] For reasons that we do not fully understand, this transformation consistently failed when the N-aryl ring was electron-deficient (entry 2, **1n**). In this latter case, substantial quantities of the starting ketone were isolated upon workup.

Table 3. Substrate Scope



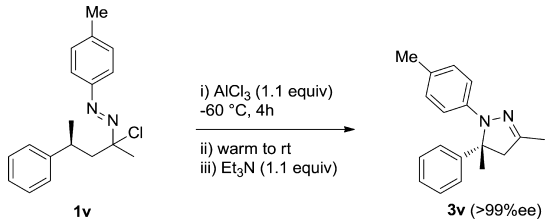
entry	α-chloroazo	product	yield[a]
1	**1l** / **1m**	**3l**; R_1 = Cl / **3m**; R_1 = Me	64% / 79%
2	**1n** / **1o**	**3n**; R_1 = Cl / **3o**; R_1 = Me	~6% / 66%
3	**1p** / **1q**	**3p**; R_1 = Cl / **3q**; R_1 = Me	12% / 35%[b]
4	**1r** / **1s**	**3r**; R_1 = Cl / **3s**; R_1 = Me	44%[c] / 67%[d]
5	**1t** / **1u**	**3t**; R_1 = Cl / **3u**; R_1 = Me	59%[e] / 62%[f]

[a]Isolated yield. [b]^{1}H NMR yield, 40%. [c]^{1}H NMR yield, 56%. [d]^{1}H NMR yield, 71%. [e]^{1}H NMR yield, 75%. [f]^{1}H NMR yield, 66%.

Successful insertion into a tertiary benzylic center led us to examine the potential of the heteroallene to react at a tertiary non-benzylic site. Importantly, subjecting isopropyl derivative **1t** or **1u** to the reaction conditions returned pyrazoline **3t** or **3u** (Table 3, entry 5) in 59% and 62% isolated yield, respectively. Unfortunately, attempts to insert into a secondary aliphatic position were not fruitful; the heteroallene derived from 2-pentanone returned a complex mixture.

Mechanisms that could account for pyrazoline formation include the concerted C−H insertion of a singlet-state nitrenium ion-type intermediate, a radical abstraction of a benzylic H by a triplet-state nitrenium ion-type intermediate followed by a radical recombination to form the new C−N bond, or a 1,5-hydride shift followed by nucleophilic attack of N onto the newly formed benzylic cation. To give some indication of which of these mechanisms might be operative, we prepared substrate **1v** (Scheme 3) in enantioenriched form.

Scheme 3. Stereospecific C−H Amination



Subjecting this material to the reaction conditions provided pyrazoline **3v** with complete stereochemical fidelity, as determined by HPLC analysis on a chiral stationary phase. This result favors a concerted C−H insertion reaction since the other two mechanistic possibilities would proceed through achiral intermediates. However, these latter two mechanisms cannot be ruled out entirely since the recombination steps could, in principle, occur faster than bond rotation; further studies are planned to more fully probe the operative mechanism.

In summary, 1-aza-2-azoniaallene salts have been observed to participate in unprecedented amination reactions at benzylic and tertiary aliphatic centers to provide pyrazoline products. A substrate that contained an enantioenriched tertiary benzylic center reacted without erosion of stereopurity. The results gathered thus far support the hypothesis that the amination reaction occurs via a concerted C−H insertion of a singlet-state nitrenium ion intermediate. Further studies on the scope and mechanism of this transformation are underway.

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■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, spectral data for all compounds, and HPLC traces for **3o** and **3v**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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Iodine(III)-mediated bicyclic diazenium salt formation

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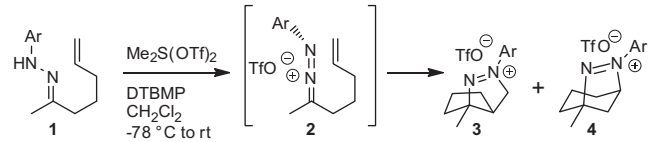
ABSTRACT

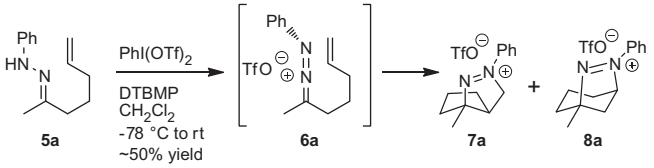
The hypervalent iodine(III) reagent $PhI(OTf)_2$ has been shown to be an effective oxidant for the conversion of linear aryl-hydrazones bearing a pendant alkene into bicyclic diazenium salts. This oxidative cyclization presumably occurs by the iodine(III) mediated formation of a 1-aza-2-azoniaallene salt intermediate that undergoes a subsequent intramolecular 1,3-dipolar cycloaddition with the pendant alkene.

The development of new methods to prepare N heterocycles is important because of the prevalence of these structures in biologically active compounds.[1,2] Recent work in our group has focused on investigating highly reactive 1-aza-2-azoniaallene salts (e.g. **2**, Scheme 1) as precursors to nitrogen heterocycles.[3–5] 1-Aza-2-azoniaallene salts are a class of hetero-cumulene that can participate in a diverse set of reactions. For example, we have recently shown that these species can participate in intramolecular amination reactions to provide pyrazoline products[5] Gladstone et al.[6,7] have shown that 1-aza-2-azoniaallene salts derived from aryl ketones undergo electrophilic aromatic substitution to provide indazole products, and Jochims et al.[8–10] have shown that these hetero-cumulenes react readily via 1,3-dipolar cycloaddition with a variety of different π-systems. In this latter regard, we rendered the 1,3-dipolar cycloaddition reaction of 1-aza-2-azoniaallene salts with alkenes intramolecular as a way to form bicyclic diazenium salts.[3] In each of the above cases, the heteroallene intermediate was generated by the Lewis acid-mediated deoxygenation or dehalogenation of an α-functionalized azo precursor. More recently, we discovered that bicyclic diazenium salts could also be formed directly from aryl hydrazones bearing a pendant alkene by reaction with dimethyl sulfide ditriflate ($Me_2S(OTf)_2$; Scheme 1).[4] This latter transformation presumably occurs via sulfonium salt-mediated oxidation of the hydrazone to a 1-aza-2-azoniaallene salt intermediate that undergoes a subsequent intramolecular cycloaddition and we became interested in the prospect of identifying other oxidants that could mediate this same transformation.

Hypervalent iodine(III) reagents are versatile oxidants[11–13] that can mediate a variety of transformations including the oxidation of alcohols to carbonyl compounds,[14,15] the α-hydroxylation of ketones,[16,17] and the oxidative dearomatization of phenols.[18,19] In addition, iodine(III) reagents can dehydrogenate hydrazodicarbonyls to azodicarbonyls[20] and Lutz and Thomson[21] recently reported that allyl hydrazones react with hypervalent iodine reagents to give products derived from the 3,3-sigmatropic rearrangement of a presumed 1-aza-2-azoniaallene salt intermediate. With this in mind, we became interested in the prospect of using iodine(III) reagents as oxidants for the conversion of hydrazones to bicyclic



Scheme 1.



Scheme 2.

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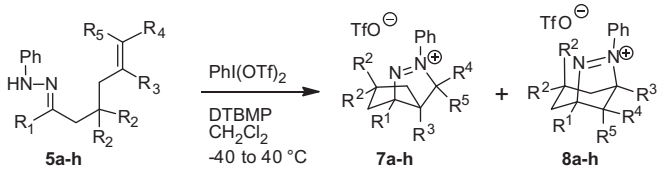
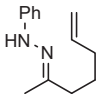
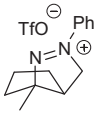
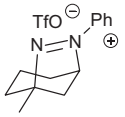
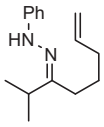
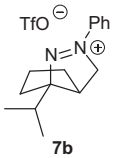
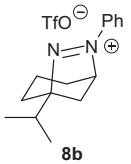
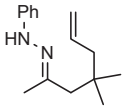
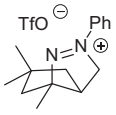
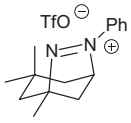
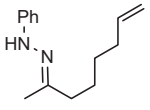
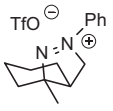
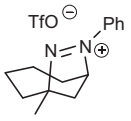
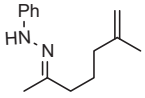
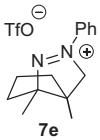
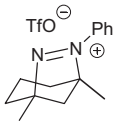
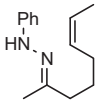
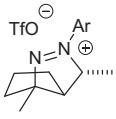
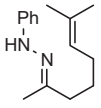
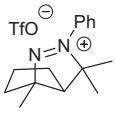
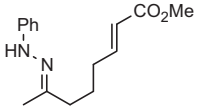
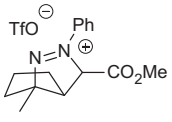
Table 1
$PhI(OTf)_2$ mediated bicyclic diazenium salt formation



Entry	Hydrazone	Product		Yield[a] (%)	Ratio **7:8**[b]
1	 **5a**	 **7a**	 **8a**	78	1:0.4
2	 **5b**	 **7b**	 **8b**	70	1:0.10
3	 **5c**	 **7c**	 **8c**	79	1:0.10
4	 **5d**	 **7d**	 **8d**	22	Trace:1
5	 **5e**	 **7e**	 **8e**	0	–
6	 **5f**	 **7f**		68	–
7	 **5g**	 **7g**		26	–
8	 **5h**	 **7h**		0	–

[a] Yield determined by NMR vs. an internal standard.
[b] Diazenium salts **7a–d** and **8a–d** were formed as mixtures.

diazenium salts and here we report that $PhI(OTf)_2$ can effectively facilitate this transformation.

Iodosobenzene diacetate ($PhI(OAc)_2$) and iodosylbenzene are stable, storable compounds that can be easily modified to other iodine(III) reagents[11] and we focused our studies on these oxidants. Unfortunately, treating hydrazone **5a** (Scheme 2) with $PhI(OAc)_2$ in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) did not provide any of the desired diazenium salt product. Barton et al. have reported that $PhI(OAc)_2$ reacts with phenyl hydrazones to give α-acetoxy azo products.[23] Changing the oxidant to $PhI(OTFA)_2$ led to a complex mixture of products that did not contain any of the expected fused diazenium salt (**7a**). However, a small amount of the bridged diazenium salt (**8a**) was observed in the NMR spectrum of the crude reaction mixture and it is possible that the more labile fused salt **7a** was also formed but subsequently degraded under the reaction conditions. In our earlier studies using

sulfonium salts as oxidants for these intramolecular cycloadditions we observed that a highly non-nucleophilic counterion was necessary for success. With this in mind we turned our attention to $PhI(OTf)_2$ as a potential oxidant and we were pleased to observe that treating hydrazone **5a** with freshly generated $PhI(OTf)_2$ in the presence of DTBMP at −78 °C for 2 h and then warming the mixture to room temperature provided the expected 5,5-fused (**7a**) and 6,5-bridged (**8a**) bicyclic diazenium salts in ~50% combined yield. Using a large excess of oxidant (2.5 equiv) reduced the yield of the desired products, as did changing the base from DTBMP to Et_3N. Extending the reaction time at low temperature also resulted in decreased yield of the diazenium salt products, whereas allowing the reaction to warm soon after mixing appeared to improve the reaction outcome. After some experimentation we discovered that consistently good results were obtained when the hydrazone and DTBMP were added to the oxidant at −40 °C and the reaction was then immediately transferred to a 40 °C bath and concentrated in vacuo.[22] Under these conditions bicyclic diazenium salts **7a** and **8a** were formed in a 2.5:1 ratio in 78% combined yield (Table 1).

To test the generality of this transformation we subjected a series of hydrazones bearing pendent alkenes to the optimized cyclization conditions and the results of these studies are presented in Table 1. Mono-substituted terminal olefins reacted easily to provide mixtures of fused and bridged bicyclic products in good yield (entries 1–3). Extending by one carbon the tether length joining the reacting centers resulted in a significant decrease in product yield; hydrazone **5d** (entry 4) provided predominantly bridged salt **8d** in only 22% yield. In our prior work, we observed that di-substituted terminal olefin **5e** failed to provide any of the desired diazenium salts, which is the case here as well (entry 5). Conversely, hydrazone **5f**, which contains a 1,2-disubstituted olefin, reacted smoothly to yield 5,5-fused diazenium salt **7f** as a single diastereomer in 68% yield. Hydrazone **5g** (entry 7), which contains a trisubstituted olefin, provided the desired diazenium salt product in low yield (26%), whereas the hydrazone **5h** (entry 8), which contains an electron deficient olefin, failed to provide any desired product.

In summary, $PhI(OTf)_2$ is an effective oxidant for the direct formation of bicyclic diazenium salts from a variety of linear hydrazone precursors. This oxidative cyclization presumably occurs by the iodine(III) mediated formation of a 1-aza-2-azoniaallene salt intermediate that undergoes a subsequent intramolecular 1,3-dipolar cycloaddition with the pendent alkene. These studies provide further evidence that iodine(III) reagents react with hydrazones to yield synthetically versatile heteroallene salt intermediates.

Acknowledgments

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22. *Representative experimental procedure*: Trimethylsilyl triflate (0.353 g, 1.59 mmol) was added dropwise to a stirred 0 °C solution of iodosobenzene (0.175 g, 0.79 mmol) in CH_2Cl_2 (2 mL). After 5 min the reaction was cooled to −40 °C and a solution of hydrazone **5a** (0.107 g, 0.53 mmol) and DTBMP (0.130 g, 0.64 mmol) in CH_2Cl_2 (1 mL) was added in one portion. The reaction vessel was transferred to a 40 °C water bath and solvents were removed in vacuo. The residue was dissolved in CH_2Cl_2 (2 mL) and a 1 M solution of 3,5-dinitrobenzonitrile in CH_2Cl_2 (0.53 mL, 0.53 mmol) was added as an internal standard to determine yield by NMR spectroscopy. The mixture was carefully concentrated under moderately reduced pressure and analyzed by ^1H NMR spectroscopy which showed the formation of **7a** and **8a** in 57% and 21% yield, respectively.
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Heterocycles

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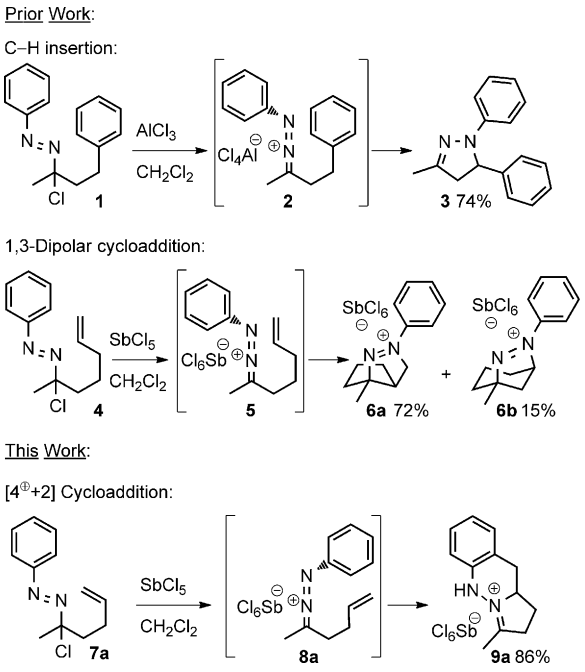
Intramolecular Polar [4⊕+2] Cycloadditions of Aryl-1-aza-2-azoniaallene Salts: Unprecedented Reactivity Leading to Polycyclic Protonated Azomethine Imines**

*Daniel A. Bercovici, Jodi M. Ogilvie, Nikolay Tsvetkov, and Matthias Brewer**

Polar cycloadditions, in which one of the reacting partners is ionic, are less common than cycloadditions involving uncharged or dipolar components, but often occur more readily.[1] For example, whereas [4+2] cycloaddition reactions that involve styrene subunits as the 4π component generally require reactive dienophiles or harsh reaction conditions to proceed,[2] the Povarov reaction, which is the stepwise[3] [4⊕+2] cycloaddition of N-aryliminium ions with electron-rich olefins, occurs readily at or below room temperature.[4,5] The charge that is present in the ionic partner of polar cycloadditions is often due to the presence of a heteroatom and these systems can provide useful routes to heterocyclic products,[1a] which are prevalent scaffolds in biologically active molecules.[6] Although uncharged heteroallenes have been used extensively in the preparation of heterocyclic compounds,[7] cationic heteroallenes have received less attention. To this end, we have been exploring the use of 1-aza-2-azoniaallene cations (e.g. **2**, Scheme 1) in intramolecular reactions as a means of preparing a variety of aza-heterocycles. Herein we report our discovery that aryl-1-aza-2-azoniaallene cations can react by an unprecedented intramolecular [4⊕+2] cycloaddition with pendant alkenes wherein the azo bond and one aromatic π bond make up the 4π component.

1-Aza-2-azoniaallene cations are known to react by several different pathways, thus leading to a variety of products. For example, these species can add nucleophiles at the carbon atom to provide azo products,[8] can undergo 3,3-sigmatropic rearrangements,[9] and can react in stereospecific intramolecular C–H amination reactions to provide pyrazolines by what appears to be a concerted nitrenoid-type insertion (e.g. **2** to **3**, Scheme 1).[10] In addition, these cationic heteroallenes can act as 1,3-dipoles in [3+2] cycloaddition reactions with a variety of π systems to provide five-membered-ring heterocycles.[11] We have taken advantage of this latter reactivity to prepare bicyclic diazenium salts (e.g. **6a** and **6b**, Scheme 1).[12]



Scheme 1. Varied reactivity of aryl-1-aza-2-azoniaallene salts.

While continuing our studies on intramolecular reactions of 1-aza-2-azoniaallene cations we recently prepared the heteroallene **8a** (Scheme 1), which could in principle form a 5,5-bridged bicyclic diazenium salt similar to **6b**. However, orbital alignment in the transition state leading to that product would not be ideal; this asynchronous ring closure would be Baldwin-disfavored in the same way that 5-(enolendo)-*exo*-trig aldol condensations are disfavored.[13] We were interested to observe that **8a** in fact did not undergo intramolecular [3+2] cycloaddition, but instead reacted by an unprecedented intramolecular [4⊕+2] cycloaddition to provide a tricyclic protonated azomethine imine containing a 1,2,3,4-tetrahydrocinnoline scaffold (**9a**, Scheme 1). Cinnoline derivatives, including 1,2,3,4-tetrahydrocinnolines, show diverse biological activity[14] and although tetrahydrocinno-

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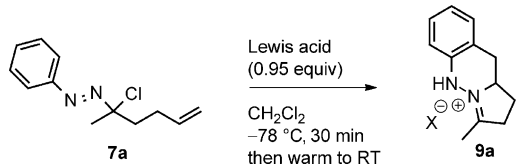
lines can be prepared by several classical methods,[15] the development of new methods to prepare this useful scaffold continues to be an active area of research.[16] The unprecedented nature of this reaction, the uniqueness of the protonated azomethine imine products,[17] and the potential that these products will have diverse reactivity, and thus be useful synthetic intermediates, encouraged us to examine this polar cycloaddition in more detail. Our preliminary results are presented here.

Our first task was to optimize the reaction conditions for the conversion of **7a** into **9a** (Table 1) . Our initial results were obtained by adding 1.2 equivalents of $SbCl_5$ to a solution

Table 1: Assessment of Lewis acids.



Entry	Lewis acid	Yield [%][a]
1	$SbCl_5$	86
2	$AlCl_3$	84
3	AgOTf[b,c]	70
4	TMSOTf[c,d]	84

[a] Yield determined by ^{1}H NMR spectroscopy using an internal standard, and based on the limiting reagent. [b] Reaction conducted at room temperature for 2 h. [c] 1 equiv of Lewis acid was used. [d] Reaction conducted at room temperature for 24 h. Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

of **7a** in CH_2Cl_2 at −78 °C, with warming to room temperature. After some experimentation, we discovered that using a slight deficiency of $SbCl_5$ (0.95 equiv) resulted in cleaner crude reaction mixtures. Alternative Lewis acids were screened and while we were pleased to see that $AlCl_3$, AgOTf, and TMSOTf could each mediate the reaction, they did not improve the yield or product purity compared to the use of $SbCl_5$. However, the triflate counter ion did give a product that was more crystalline, and allowed us to confirm the structure of **9a** by X-ray crystallography.[18] Factoring in both cost and the simplicity of using a liquid Lewis acid caused us to select $SbCl_5$ as the Lewis acid of choice for further studies.

With optimized reaction conditions in hand, we next explored the scope of this intramolecular cycloaddition (Table 2).[19] We were pleased to note that increased substitution adjacent to the heteroallene carbon atom was well tolerated. The more sterically hindered isopropyl derivative **7b** (entry 2) provided the desired product in 88% yield, whereas the cyclohexanone-derived α-chloroazo **7c** (entry 3) provided the tetracycle **9c** in 83% yield as a 2:1 mixture of diastereomers.[20] Incorporation of a silyloxy group adjacent to the heteroallene carbon atom was also well tolerated and the silyl ether **7d** provided the more-heteroatom-rich product **9d** in 71% yield (entry 4). In this case, one could envision the cationic heteroallene intermediate undergoing a competitive 1,2-hydride migration to the electrophilic carbon atom facilitated by the adjacent oxygen center, but this product was not observed.

We next examined the scope of this reaction with respect to alkene substitution. We were pleased to observe that the α-chloroazo compounds **7e** and **7f** (Table 2, entries 5 and 6), which contained a di- and trisubstituted olefin respectively, provided excellent yields (97% and 98%, respectively) of the desired product. Importantly, these examples show that this transformation can efficiently form nitrogen-bearing and all-carbon quaternary centers.

In an effort to gain some understanding of the concerted nature of the bond-forming events, we prepared *trans* and *cis* alkenes **7g** and **7h**, respectively (Table 2, entries 7 and 8) and subjected each to the cyclization conditions. The cycloaddition reaction proved to be stereospecific. Each substrate led to a unique diastereomer of the product, thus suggesting that the cycloaddition process is concerted.[21]

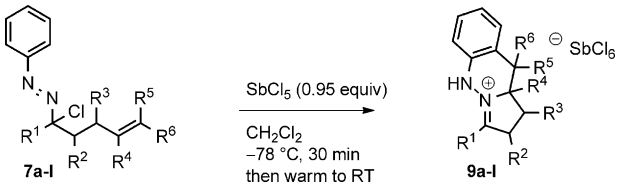
Incorporation of the alkene component into a ring provided the tetracyclic products **9i** and **9j** (Table 2, entries 9 and 10) as single diastereomers in high yield. These results highlight the ability of this transformation to provide structurally complex products from structurally simple starting materials.

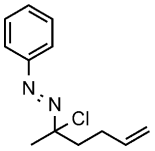
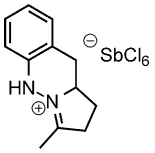
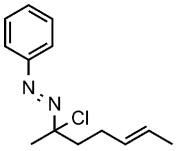
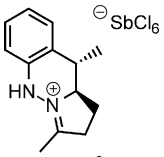
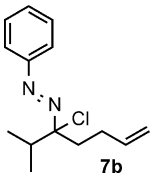
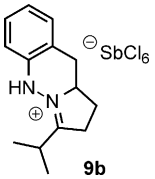
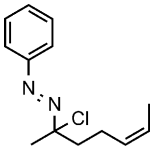
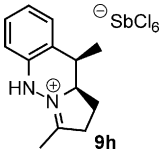
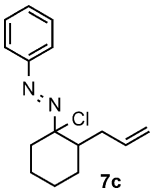
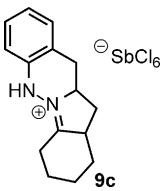
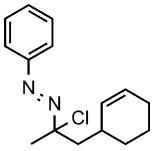
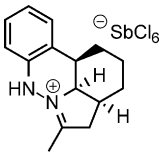
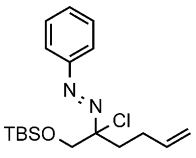
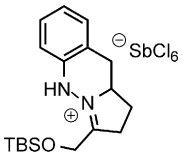
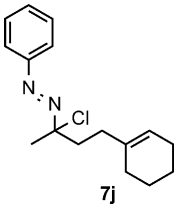
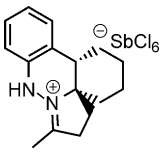
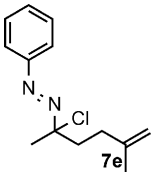
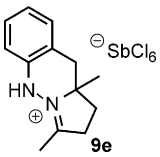
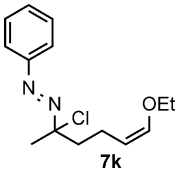
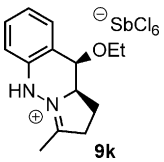
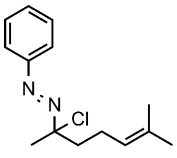
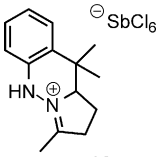
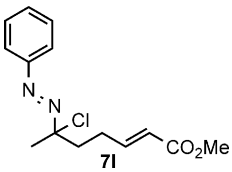
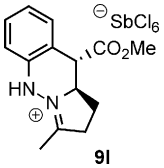
The electronic nature of the dienophile can have a dramatic effect on the efficiency of polar cycloadditions. For example, the Povarov reaction fails when the dienophile is electron deficient.[4d] To test the scope of this reaction with respect to the electronics of the pendant dienophile we prepared the cyclization precursors **7k** and **7l** (Table 2, entries 11 and 12) which contain electron-rich and electron-deficient olefins, respectively. The electron-rich olefin (**7k**) was surprisingly difficult to prepare as both it and the hydrazone precursor decomposed readily. Treating **7k** under the reaction conditions provided the cycloaddition product **9k** in a modest 33% yield. We suspect that this low yield is not due to the cycloaddition step itself, but rather to the instability of **7k** which became noticeably dark in color while setting up the reaction. It is interesting to note that this highly electron-rich olefin reacted to provide a single diastereomer of product. In view of the cationic nature of the heteroallene intermediate, we expected an electron-deficient alkene to be a poor reaction partner. We were surprised to observe that **7l** (entry 12) provided the cycloadduct **9l** in 93% yield. This high yield further demonstrates the broad scope of this reaction.

In view of the similarity between **5** and **8a** (Scheme 1), which are identical except for the length of the tether that separates the heteroallene from the pendent alkene, it is interesting that **5** provides only the diazenium salt product and none of the corresponding protonated azomethine imine. In addition, intermolecular cycloadditions of 1-aza-2-azoniaallene cations proceed by the [3$^{\oplus}$+2] manifold[11a–g] and taken together these facts indicate that the [3$^{\oplus}$+2] pathway is intrinsically more favorable than the alternative [4$^{\oplus}$+2] cycloaddition described here. It seems likely that this latter reaction occurs in the cases described here because of the orbital alignment constraints discussed above, which stem from the intramolecular nature of these reactions.

In conclusion, we have discovered an unprecedented reactivity of aryl-1-aza-2-azoniaallene salts. The [4$^{\oplus}$+2] cyclo-

Table 2: Substrate scope.



Entry	Substrate	Product	Yield [%][a]	Entry	Substrate	Product	Yield [%][a]
1	 **7a**	 **9a**	86	7	 **7g**	 **9g**	81
2	 **7b**	 **9b**	88	8	 **7h**	 **9h**	82
3	 **7c**	 **9c**	83 (2:1 d.r.)	9	 **7i**	 **9i**	89
4	 **7d**	 **9d**	71	10	 **7j**	 **9j**	85
5	 **7e**	 **9e**	97	11	 **7k**	 **9k**	33
6	 **7f**	 **9f**	98	12	 **7l**	 **9l**	93

[a] Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

addition reaction described herein is likely concerted and provides high yields of protonated azomethine imine products which contain a 1,2,3,4-tetrahydrocinnoline core. This reaction occurs at low temperature, is quite general with respect to alkene substitution, and delivers products which contain all-carbon or nitrogen-bearing quaternary centers in high yield. Further studies on the scope and mechanism of this transformation including computational studies and application of this cycloaddition in natural product synthesis are planned.

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[18] CCDC 952450 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[19] The crude reaction mixtures were triturated with petroleum ether to provide products with minimal impurities. Attempts to further purify the products by chromatography or crystallization failed. The yields reported in Tables 1 and 2 are based on the limiting reagent (Lewis acid) and were determined by proton NMR spectoscopy using 1,3,5-trimethoxybenzene as an internal standard.

[20] The diastereomers were not separable and the relative configuration of the major and minor component was not determined.

[21] The relative configuration of **9g–l** were determined by evaluation of the coupling constants between the benzylic proton and the proton adjacent to the positively charged amine. This is more fully described in the Supporting Information.

Organic LETTERS

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How Tethers Control the Chemo- and Regioselectivities of Intramolecular Cycloadditions between Aryl-1-aza-2-azoniaallenes and Alkenes

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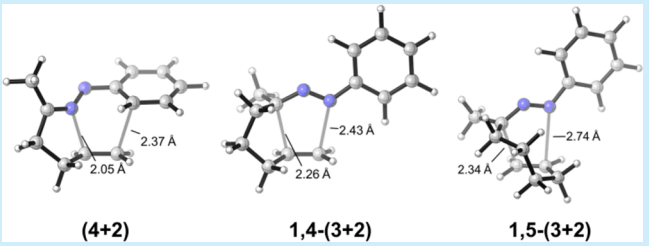
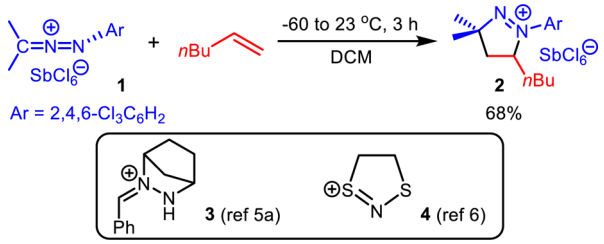
Supporting Information

ABSTRACT: Cationic 1-aza-2-azoniaallenes react intermolecularly with terminal alkenes to give 1,5-substituted (3 + 2)-cycloadducts, but intramolecular reactions lead to either 1,5- or 1,4-substituted (3 + 2)-cycloadducts or (4 + 2)-cycloadducts, depending on the tether length. DFT calculations and distortion/interaction analyses show that the $(CH_2)_3$ tether prevents the reacting partners from aligning efficiently to give 1,5-substituted (3 + 2)-cycloadducts, and the 1,4-regioselectivity dominates. With the $(CH_2)_2$ tether, the (3 + 2) cycloaddition is disfavored due to the forming four-membered ring in the transition state, and the (4 + 2) cycloaddition prevails.



The 1,3-dipolar cycloaddition reactions involve formally dipolar or zwitterionic molecules that add 1,3 to alkenes or alkynes to form five-membered heterocycles.[1] The identification and development of novel cycloaddition partners that lead to new heterocyclic scaffolds is an important area of ongoing research.[2] Jochims and co-workers reported that cationic aryl-1-aza-2-azoniaallenes can undergo intermolecular (3 + 2) cycloaddition reactions with alkenes to provide cationic diazenium products (Scheme 1).[3,4] This transformation has hitherto been

Scheme 1. Intermolecular (3 + 2) Cycloaddition between 1-Aza-2-azoniaallene Salt 1 and 1-Hexene and Examples of Other Experimentally Reported 1,3-Monopoles, Protonated Azomethine Imine 3 and Dithionitronium Cation 4

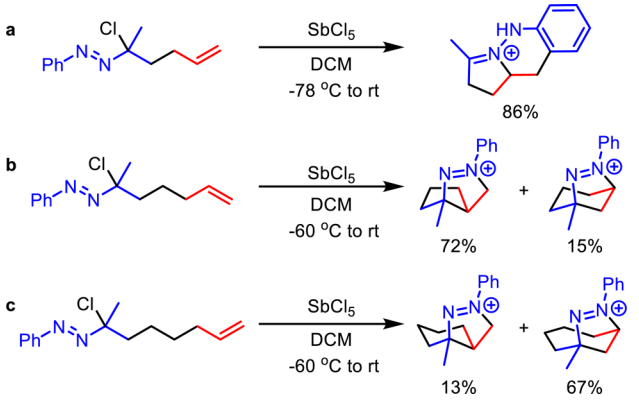


described as a polar 1,3-dipolar cycloaddition,[3,4] but we now suggest that these heteroallene salts are more accurately described as 1,3-monopoles, since they are cations and add 1,3 to alkenes.

Other 1,3-monopoles that participate in cycloaddition reactions include protonated azomethine imines[5] and dithionitronium cations[6] (Scheme 1). Reactions of these species with alkenes represent an unrecognized class of cycloadditions, which we term 1,3-monopolar cycloadditions.

Recently, Brewer and co-workers studied the intramolecular reactions between aryl-1-aza-2-azoniaallene cations and alkenes (Scheme 2), which lead to either normal (3 + 2) cycloadditions[7]

Scheme 2. Chemo- and Regioselectivities of Intramolecular Cycloadditions between Aryl-1-aza-2-azoniaallenes and Alkenes



or (4 + 2) cycloadditions[8] using the azo bond and one aromatic π-bond of a 1-aryl substituent. All of these cycloadditions proceed efficiently and selectively at low temperature with unactivated alkenes (Scheme 2). The only factor that controls chemo- and regioselectivities is the length of the tether that connects the reacting partners.[9] To determine origins of the tether-controlled reaction selectivity, we have undertaken a

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computational study at the B3LYP-D3/6-311+G(d,p)//B3LYP/6-31G(d) level of theory.[10,11]

We first studied the reactions of a simple 1,3-monopole **5**,[12] the result of hydride abstraction from the phenylhydrazone of acetone. Both (3 + 2) and (4 + 2) cycloadditions of **5** and propene were investigated. As shown in Figure 1, the concerted

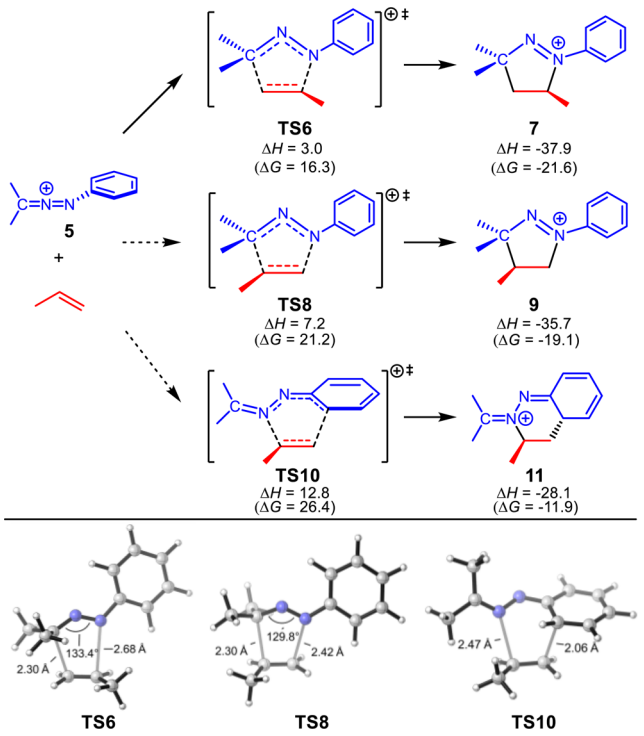
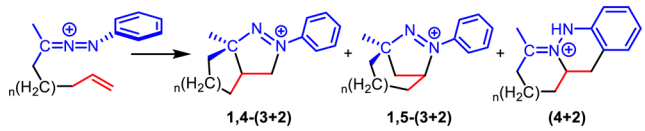


Figure 1. DFT-computed energetics (in kcal/mol) and transition-state structures for the (3 + 2) and (4 + 2) cycloadditions between 1-aza-2-azoniaallene **5** and propene.

(3 + 2) cycloaddition can occur with the methyl group of propene proximal to the forming C−N bond (via **TS6**) or distal to the C−N bond (via **TS8**). The free energy barrier for (3 + 2) cycloaddition via **TS6** is only 16.3 kcal/mol, and this reaction leads to a very stable five-membered ring product **7**. The alternative (3 + 2) transition state **TS8** is calculated to be 4.9 kcal/mol higher in free energy than **TS6**. The carbon terminus of **5** is highly electrophilic, and the LUMO+1 orbital coefficient of C3 in phenyl-1-aza-2-azoniaallene is much larger than that of N1.[13] This indicates that C3 reacts with the nucleophilic terminal carbon of propene, which has the larger HOMO orbital coefficient. The (3 + 2) cycloaddition via **TS6** (Figure 1) is the most favorable, consistent with the exclusive 1,5-regioselectivity reported for intermolecular reactions (Scheme 1).[3] The competing (4 + 2) cycloaddition via **TS10** leading to the bicyclic product **11** has a barrier of 26.4 kcal/mol. The (4 + 2) cycloaddition barrier is significantly higher than that of the (3 + 2) cycloaddition; the (4 + 2) cycloaddition pathway involves breaking the aromaticity of the phenyl ring in **5**.[14] Indeed, the (4 + 2) cycloadditions have not been observed in any intermolecular reactions of aryl-1-aza-2-azoniaallenes. While each of these cycloadditions is concerted, with a single transition state, the most favorable pathway is highly asynchronous, dominated by the C−C bond formation.

We also studied the intramolecular cycloadditions between aryl-1-aza-2-azoniaallenes and alkenes with tether lengths of n = 0−2 (Scheme 3). The barriers computed for various processes

Scheme 3. Possible Intramolecular (3 + 2) and (4 + 2) Cycloadditions between Aryl-1-aza-2-azoniaallenes and Alkenes



are shown in Figure 2. When n = 0, only (3 + 2) cycloaddition transition state **TS13** can be located. The regioisomeric (3 + 2) transition state could not be located, because the tether is too short. The barrier for the (3 + 2) cycloaddition (ΔG = 19.8 kcal/mol) is much higher than that for the alternative (4 + 2) cycloaddition via **TS14** (ΔG = 13.0 kcal/mol), in line with the experimental finding that only (4 + 2) cycloadditions occur for this system (Scheme 2a).[8] The tether introduces minimal strain to the (4 + 2) transition state, and the entropy penalty is small for this intramolecular process. When n = 1, one (4 + 2) and two regioisomeric (3 + 2) transition states were located. The activation free energy required for the (4 + 2) cycloaddition via **TS18** is about 5 kcal/mol higher than those for the (3 + 2) cycloadditions. These results align well with the experimental finding that only (3 + 2) products are formed in this reaction.[7] Comparing the two regioisomeric (3 + 2) cycloaddition transition states **TS16** and **TS17**, there is a 0.3 kcal/mol advantage for the formation of the 1,4-substituted (3 + 2)-cycloadduct via **TS16**, which is consistent with the experimental observation of a mixture of products (Scheme 2b). When n = 2, the (4 + 2) cycloaddition is even less favorable. The regioselectivity of the (3 + 2) cycloaddition, which prefers the 1,5-substituted (3 + 2)-cycloadduct via **TS21**, is like the selectivity observed in intermolecular reactions.

To understand the role of the tether on the reaction barriers, we have separated the electronic energy barrier (ΔE) into two terms (Scheme 4): (1) a term ($\Delta E'$) representing energy

Scheme 4. Representative Distortion/Interaction Model for the Transition State of an Intramolecular Cycloaddition

contributions stemming from the structurally distorted reacting fragments (in this case a cationic 1-aza-2-azoniaallene [blue] and ethylene [red] fragment) amd (2) a term (ΔE_{tether}) representing energy contributions stemming from the tether. We previously applied this type of distortion/interaction analysis to other intramolecular cycloadditions.[9,15] To obtain the contribution of the reacting fragments, the optimized transition structure for the intramolecular reaction of interest was modified by replacing the tether with hydrogen atoms appended at a C−H distance of 1.09 Å. This provides a distorted version of an intermolecular TS for the reaction of a model 1-aza-2-azoniaallene cation with ethylene. The $\Delta E'$ term represents the difference in energy between this distorted intermolecular TS and the separated reactants. The energy associated with distorting the 1-aza-2-azoniaallene cation and ethylene to their transition-state geometries is the distortion energy (ΔE_{dist}), and the energy stemming from interactions between the two fragments is the interaction energy

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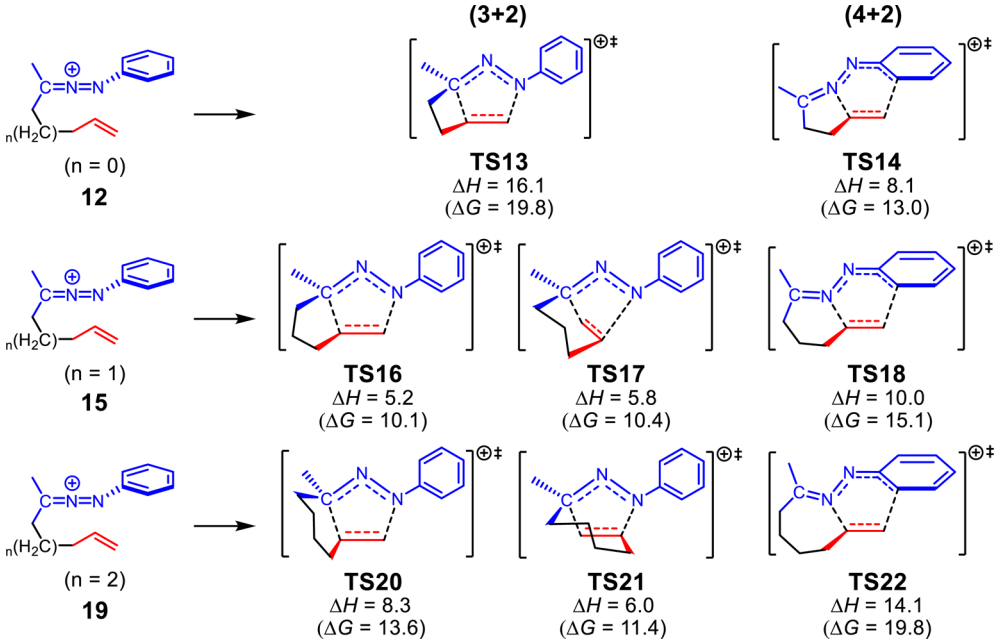

Figure 2. DFT-computed activation enthalpies and free energies (in kcal/mol) for the intramolecular (3 + 2) and (4 + 2) cycloadditions between 1-aza-2-azoniaallenes and alkenes with different tether lengths.

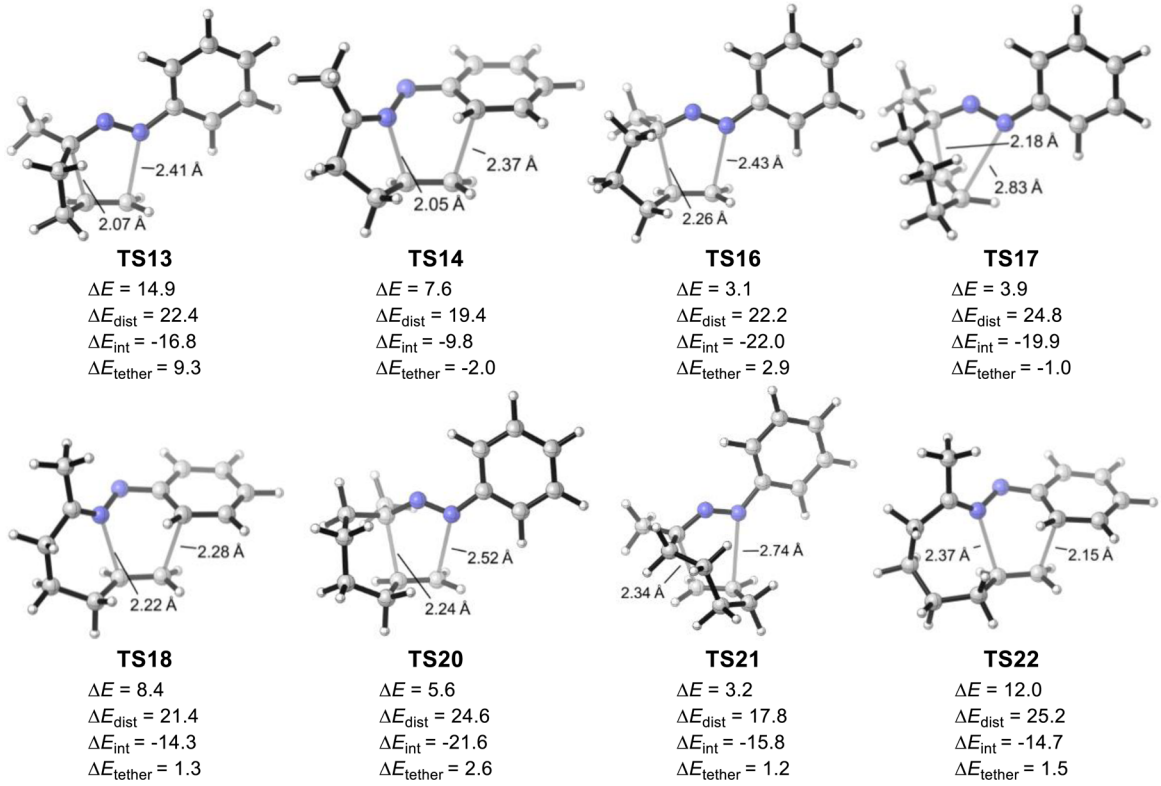

Figure 3. DFT-optimized transition structures, electronic energy barriers, distortion and interaction energies, and energy contributions from the tether for the intramolecular (3 + 2) and (4 + 2) cycloadditions with different tethers. Energies are in kcal/mol.

(ΔE_{int}).[16−18] Because $\Delta E'$ represents the reaction barrier for the two fragments to undergo an "intramolecular reaction" without the tether, the difference between ΔE and $\Delta E'$ quantitatively shows how the tether affects the energetics of the reaction ($\Delta E_{tether} = \Delta E - \Delta E'$).

We first analyzed the effects of the shortest tether in the (3 + 2) transition state **TS13** and the (4 + 2) transition state **TS14** (Figure 3). The tether in **TS13** significantly increases the barrier (ΔE_{tether} = 9.3 kcal/mol) due to the partial formation of a strained four-membered ring. By contrast, the tether stabilizes the (4 + 2) transition state **TS14** by 2.0 kcal/mol.[19] The difference in energy imparted by the tether for these two reactions prevents the intrinsically more favorable (3 + 2) cycloaddition from occurring, and the unique (4 + 2)

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cycloaddition is realized. When a longer tether (n = 1) is applied, the longer tether imparts similarly small energies to the (3 + 2) and (4 + 2) transition states **TS16** and **TS18** (2.9 and 1.3 kcal/mol, respectively), and thus the innate (3 + 2) chemoselectivity is observed in this case. In considering the regioselectivity of the (3 + 2) cycloaddition, we note that it is opposite to the intrinsic 1,5-regioselectivity observed for the intermolecular (3 + 2) cycloaddition (Scheme 1). This is attributable to the fact that while the reacting partners in **TS16** have similar geometries and orientations as the intermolecular reaction (**TS8**, Figure 1), the reacting partners in **TS17** must distort more severely than in **TS6** (Figure 1) to achieve C−C and C−N bond formation. In this case, the tether controls the regioselectivity by dictating how the reacting partners can align. Lengthening the tether by one more methylene unit (n = 2), the computed tether effects are all small and similar. Therefore, this intramolecular cycloaddition has very similar chemo- and regioselectivities as compared to the intermolecular reaction.

These calculations have identified the origins of tether control of the chemo- and regioselectivities of intramolecular cycloadditions between aryl-1-aza-2-azoniaallenes and alkenes. The (3 + 2) cycloaddition is intrinsically more favorable than the competing (4 + 2) cycloaddition because it maintains the aromaticity of the aryl substituent. The high regioselectivity of intermolecular (3 + 2) cycloadditions is due to the better orbital interactions between the C3 in aryl-1-aza-2-azoniaallene and the terminal olefinic carbon. The chemo- and regioselectivities of intramolecular reactions depend on the length of the tether connecting the reacting partners. When the tether is sufficiently long (n = 2), the chemo- and regioselectivities of intramolecular reactions are similar to the selectivities observed for intermolecular reactions. Shortening the tether by one methylene unit (n = 1) prevents the reacting partners from aligning efficiently in the normally preferred orientation of the (3 + 2) cycloaddition, and thus the regioselectivity of the process changes. Finally, the shortest tether (n = 0) significantly destabilizes the (3 + 2) cycloaddition transition state because of unfavorable interactions within the forming four-membered ring; the (4 + 2) transition state is stabilized by the same tether and becomes preferred, leading to a reversal in chemoselectivity as compared to the intermolecular reactions.

■ ASSOCIATED CONTENT

Supporting Information

Computational details and complete ref 10. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(19) Alkyl-substituted alkenes are more reactive than ethylene in cycloadditions with the electrophilic aryl-1-aza-2-azoniaallene. Therefore, the negative ΔE_{tether} values are observed in transition states **TS14** and **TS17**.

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Mechanism and Dynamics of Intramolecular C−H Insertion Reactions of 1-Aza-2-azoniaallene Salts

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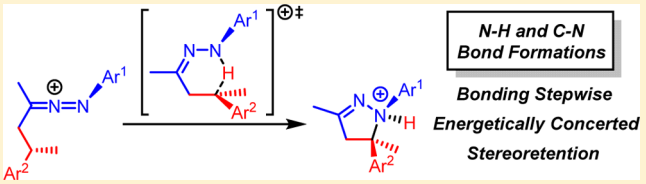
Supporting Information

ABSTRACT: The 1-aza-2-azoniaallene salts, generated from α-chloroazo compounds by treatment with halophilic Lewis acids, undergo intramolecular C−H amination reactions to form pyrazolines in good to excellent yields. This intramolecular amination occurs readily at both benzylic and tertiary aliphatic positions and proceeds at an enantioenriched chiral center with retention of stereochemistry. Competition experiments show that insertion occurs more readily at an electron-rich benzylic position than it does at an electron-deficient one. The C−H amination reaction occurs only with certain tethers connecting the heteroallene cation and the pendant aryl groups. With a longer tether or when the reaction is intermolecular, electrophilic aromatic substitution occurs instead of C−H amination. The mechanism and origins of stereospecificity and chemoselectivity were explored with density functional theory (B3LYP and M06-2X). The 1-aza-2-azoniaallene cation undergoes C−H amination through a hydride transfer transition state to form the N−H bond, and the subsequent C−N bond formation occurs spontaneously to generate the heterocyclic product. This concerted two-stage mechanism was shown by IRC and quasi-classical molecular dynamics trajectory studies.



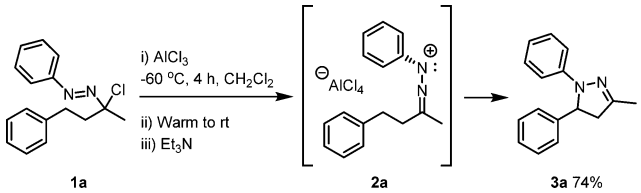
INTRODUCTION

C−H insertions of nitrogen-centered radicals,[1] nitrenes,[2] and, most notably, transition metal nitrenoids[3] are valuable synthetic reactions. On the basis of Breslow and Gellman's seminal work,[4] Che,[5] Du Bois,[6] Driver,[7] Davies,[8] Lebel,[9] and Shi[10] have made C−H insertions of transition metal nitrenoids practical and stereoselective processes for natural product synthesis. Mechanistic studies indicate that both concerted and stepwise radical rebound processes can be operative in these transformations.[11]

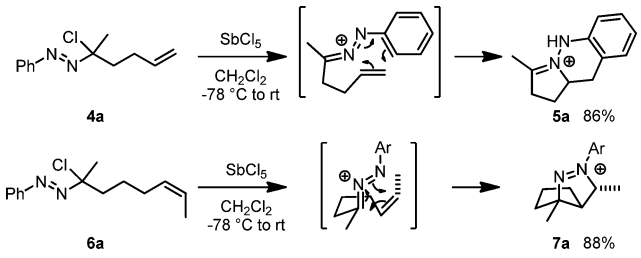
The Brewer group has studied the reactivities of aryl 1-aza-2-azoniaallene salts in intramolecular reactions leading to nitrogen heterocycles.[12] These heteroallene species can be prepared directly from N-aryl hydrazones by oxidation or through the reaction of α-chloroazo compounds with halophilic Lewis acids. As shown in Scheme 1, these species, which can also be considered to be imino-nitrenium cations, undergo direct insertion into pendant benzylic C−H bonds to afford pyrazolines.[12d]

These 1-aza-2-azoniaallene salts are also known to react with pendant alkenes in (3 + 2) or [4 + 2] cycloadditions to provide various heterocycles, as shown in Scheme 2.[12a−c,e] The chemo- and regioselectivity of the cycloaddition reactions were found to be controlled by the length of the tether that connects the reacting components. We recently studied these cycloaddition reactions computationally to understand the origins of these substrate-dependent reactivities.[13] We have now studied the scope of the insertion reaction experimentally and established the mechanism and determined the origins of selectivities in the insertion process through computation.

Scheme 1. Intramolecular Benzylic C−H Insertion of a 1-Aza-2-azoniaallene



Scheme 2. Intramolecular Cycloadditions of 1-Aza-2-azoniaallenes



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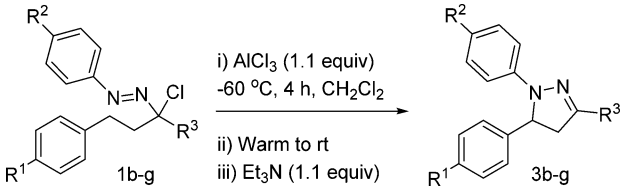
RESULTS AND DISCUSSION

Experimental Results. Our initial report of the C−H insertion reactivity of aryl 1-aza-2-azoniaallene salts (Table 1)

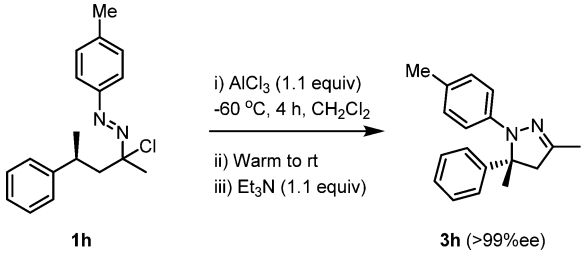
Table 1. Intramolecular C−H Insertions of 1-Aza-2-azoniaallenes with Electron-Rich and -Poor N-Aryl Substituents



entry	α-chloroazo	R^1	R^2	R^3	yield
1	**1b**	H	Cl	CH_3	61%
2	**1c**	H	CH_3	CH_3	79%
3	**1d**	OCH_3	Cl	CH_3	79%
4	**1e**	CH_3	Cl	CH_3	65%
5	**1f**	NO_2	Cl	CH_3	65%
6	**1g**	OCH_3	CH_3	$-(CH_2)_2$-(4-NO_2)Ph	92%

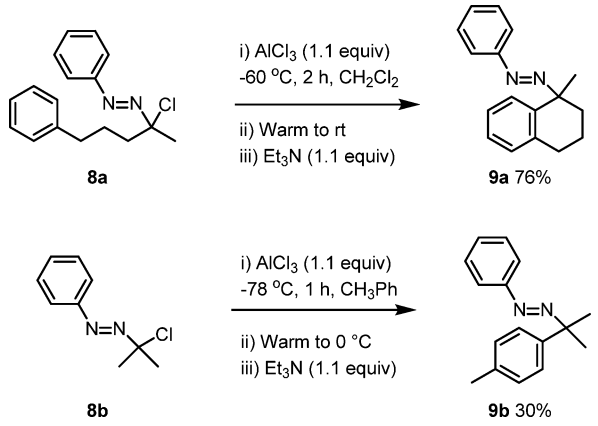
indicated that heteroallenes with electron-rich N-aryl groups provided higher yields of insertion products than those with electron-poor N-aryl groups (entry 1 vs 2, Table 1).[12d] The electronic properties of the pendant aryl group also affected the C−H insertion (entries 3−6, Table 1). Electron-rich methoxy derivatives gave notably higher yields of insertion, but there was little difference in yield between substrates with neutral and electron-deficient aryl rings (entries 4 and 5). A competition experiment showed that the insertion occurred more readily adjacent to an electron-rich aryl ring than it did adjacent to an electron-deficient one (entry 6). No insertion was observed at a secondary aliphatic center, but insertion did occur at a tertiary aliphatic center. The reaction in Scheme 3 showed that insertion at a chiral tertiary benzylic position occurs with retention of stereochemical purity.

Scheme 3. Stereospecific C−H Insertion of a 1-Aza-2-azoniaallene at a Tertiary Benzylic Position



We have now obtained further experimental data that define the scope and mechanism of this insertion reaction. We explored the effect of tether length on intramolecular C−H insertions. α-Chloroazo **8a** was treated with Lewis acid, $AlCl_3$, to generate the corresponding 1-aza-2-azoniaallene salt. This heteroallene, which has a tether that is one methylene unit longer than the tether in **1a**, does not undergo the C−H insertion but instead reacts with the pendant aryl group in an electrophilic aromatic substitution reaction to give azotetralin **9a** in 76% yield (Scheme 4). This reactivity highlights the electrophilic nature of heteroallene salts and shows that tether

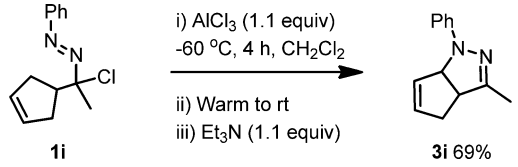
Scheme 4. Effect of Tether Length on Intramolecular Reactions of 1-Aza-2-azoniaallenes



length plays an important role in determining the result of these reactions. This Friedel−Crafts-type reactivity is not limited to intramolecular reactions; the heteroallene derived from acetone reacted with toluene to give azo-cymene **9b** in 30% yield (Scheme 4).

Unlike the well-established allylic C−H aminations with transition metal catalysts, the linear 1-aza-2-azoniaallene salts, such as **4a** and **6a**, undergo [4 + 2] or 1,3-monopolar[14] cycloadditions with pendant alkenes (Scheme 2). In order to achieve allylic C−H amination, we prepared a heteroallene salt of cyclopentene derivative **1i**, which would undergo [4 + 2] cycloaddition only with difficulty due to conformational constraints. Indeed, this substrate underwent allylic insertion instead of cycloaddition to give pyrazoline **3i** in 69% yield (Scheme 5).

Scheme 5. Intramolecular C−H Insertion of a 1-Aza-2-azoniaallene at an Allylic Position



We also studied competition between C−H insertion at benzylic and tertiary aliphatic positions. As a point of comparison, previous studies show that rhodium nitrenoids insert more readily at tertiary aliphatic centers than at benzylic positions,[15] whereas ruthenium[6h] and iron[16] based catalysts select for benzylic or allylic positions, and the selectivity of silver catalysts is ligand-dependent.[17] To assess the chemoselectivity of 1-aza-2-azoniaallene salt insertions, we prepared the heteroallene salt derived from 5-methyl-1-phenylhexan-3-one (**1j**); insertion occurred almost exclusively at the benzylic position (Scheme 6).

We also conducted a kinetic isotope effect (KIE) study using an internal competition experiment. The requisite deuterium-enriched ketone precursor of α-chloroazo **1k** was prepared by the conjugate reduction procedure described by Keinan and Greenspoon.[18] Subjecting **1k** to the C−H amination reaction conditions provided an average 4.3:1 ratio of deuterated to nondeuterated insertion products (**3k** and **3k′**), as determined by ^{1}H NMR integration of duplicate experiments (Scheme 7). Changing the N-aryl ring to *p*-tolyl had no effect on the

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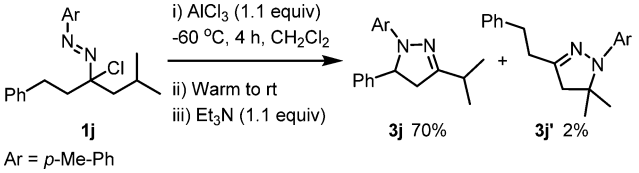
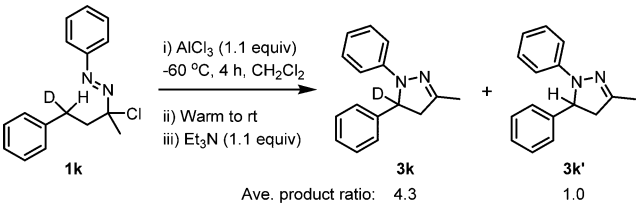
Scheme 6. Competition between Intramolecular C−H Insertions at Benzylic and Tertiary Aliphatic Positions of 1-Aza-2-azoniaallene



Scheme 7. Experimental Kinetic Isotope Effect



selectivity. KIE studies have been widely applied in mechanistic investigations of other C−H amination reactions. Typically, aminations that occur by a radical rebound mechanism have high KIEs (in the range of 6−12),[5a] since the transition state involves mainly hydrogen atom transfer. By contrast, aminations that proceed through concerted insertion mechanisms show significantly lower KIEs (typically, 1−3).[15,6h] KIEs between 3 and 6 seem to indicate rapid radical rebound mechanisms[17,19] or highly asynchronous concerted insertions.[6h,9c,20,21] The relatively high primary isotope effect of 4.3 suggests the latter mechanism.

Computational Methods. DFT calculations were performed with Gaussian 09.[22] Geometry optimizations were carried out with B3LYP functional and the 6-31G(d) basis set. The vibrational frequencies were computed at the same level to check whether each optimized structure is an energy minimum or a transition state and to evaluate its zero-point vibrational energy (ZPVE) and thermal energies at 298 K. Single-point energies were computed with the M06-2X functional[23] and the 6-311+G(d,p) basis set. Solvation energy corrections for dichloromethane were evaluated by a self-consistent reaction field (SCRF) using the SMD[24] model under the same level of theory as the single-point energy calculation (M06-2X/6-311+(d,p)).

The reaction mechanism and timing of bond formations were studied by quasi-classical trajectories at 298 K, with B3LYP and the 6-31G* basis set. All dynamics calculations were performed with Progdyn,[25] with which the classical equations of motion are integrated with the velocity Verlet algorithm. Energies and derivatives were computed on the fly using Gaussian 09 with a 1 fs integration step size. Trajectories were initialized, from the structure of the transition state **TS11**, by TS normal mode sampling and were then propagated in both reactants and products directions.[26]

Computational Results. *Reaction Mechanism.* We first studied the insertion reaction mechanism for the 1-aza-2-azoniaallene cation **10** (Figure 1). The optimized structures of transition states and the free energy changes on the singlet and triplet pathways are shown in Figure 1. From the singlet species **10**, C−H amination can occur through transition state **TS11**, with a free energy barrier of 20.0 kcal/mol, leading to the protonated heterocyclic product **12**.

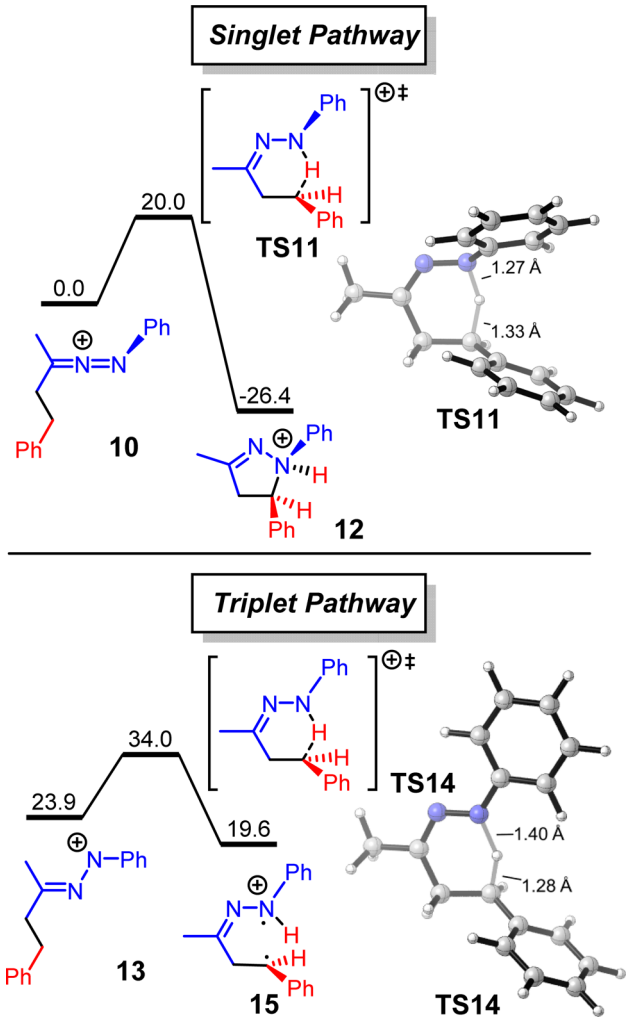


Figure 1. Optimized structures of transition states and free energy changes of singlet and triplet C−H amination pathways of aryl-1-aza-2-azoniallene **10**. Gibbs free energies are in kcal/mol.

Azoniaallene **10** has two moieties that can react: the cationic heterocumulene part and the pendant benzylic C−H bond. In the singlet transition state **TS11**, the major orbital interaction between the reacting fragments occurs between the LUMO of the 1,3-monopolar heterocumulene fragment and the HOMO of the benzylic C−H bond. This suggests that a hydride abstraction occurs initially to the electron-deficient heterocumulene, forming a N−H bond and a benzyl carbocation. This benzyl carbocation then forms a C−N bond with the remaining lone pair on nitrogen to give the insertion product.

Alternatively, **10** could undergo a spin transition to generate the triplet diradical species, **13**, which could react through a triplet C−H amination pathway.[27] However, triplet **13** is 23.9 kcal/mol less stable than **10**, making the triplet pathway much less favorable as compared with the singlet pathway.

Origins of Stereospecificity of the Singlet C−H Amination Pathway. The bonding stepwise process of the C−H amination seems to be at odds with the stereoselectivity observed for insertion at a chiral benzylic position (Scheme 3). The origin for the stereospecificity is, however, explained by the intrinsic reaction coordinate (IRC) of **TS11**, shown in Figure 2. Starting from the substrate (point 1), the benzylic hydride gradually moves to the electron-deficient terminal nitrogen via the transition state (point 21) to form the N−H bond (points

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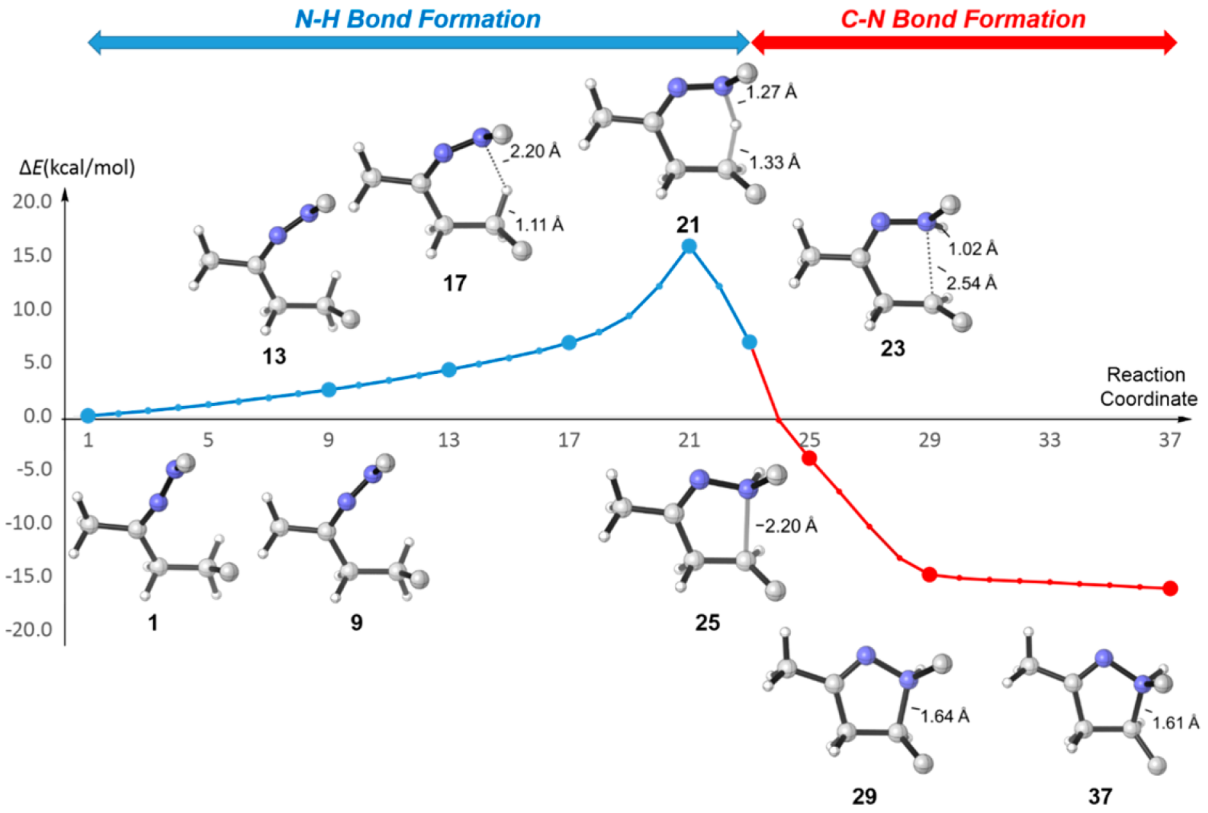

Figure 2. IRC of transition state **TS11**;only the α-carbons of the phenyl groups are shown for simplicity, and the boundary between N−H and C−N bond formations is chosen based on the N−H bond distance.

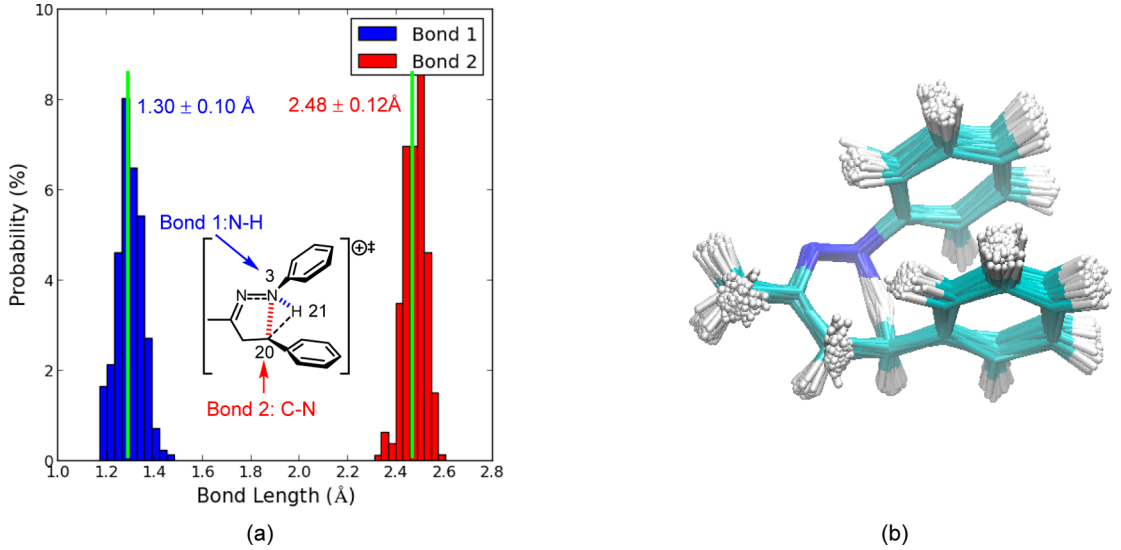

Figure 3. (a) Distribution of N−H and C−N bonding lengths in the transition state region of the singlet C−H amination pathway at 298 K. (b) Superposition of the 256 sampled transition state geometries.

1−23). At point 23, the N−H bond is fully formed with a distance of 1.02 Å, but the C−N distance is still 2.54 Å. The subsequent C−N bond formation then occurs spontaneously, leading to the heterocyclic product (points 23−37). This IRC trajectory indicates that while the singlet C−H amination process is bonding stepwise it is energetically concerted. That is, from substrate to product there is only one saddle point and, after the hydride transfer, there is no stable intermediate; the two consecutive bond formations are energetically concerted and occur via one transition state. This is a nitrogen rebound, in analogy to the oxygen rebound, which is well-known for cytochrome P-450[28] and other related oxidations, like that of dioxirane.[29]

In order for the insertion to occur at a chiral center without stereomutation, C−N bond formation must occur much faster than C−C bond rotation, which would erode the stereoselectivity, by allowing bond formation with inversion of configuration. To test whether the proposed mechanism accounts for the experimentally observed stereoselectivity, we also studied the insertion pathway through quasi-classical

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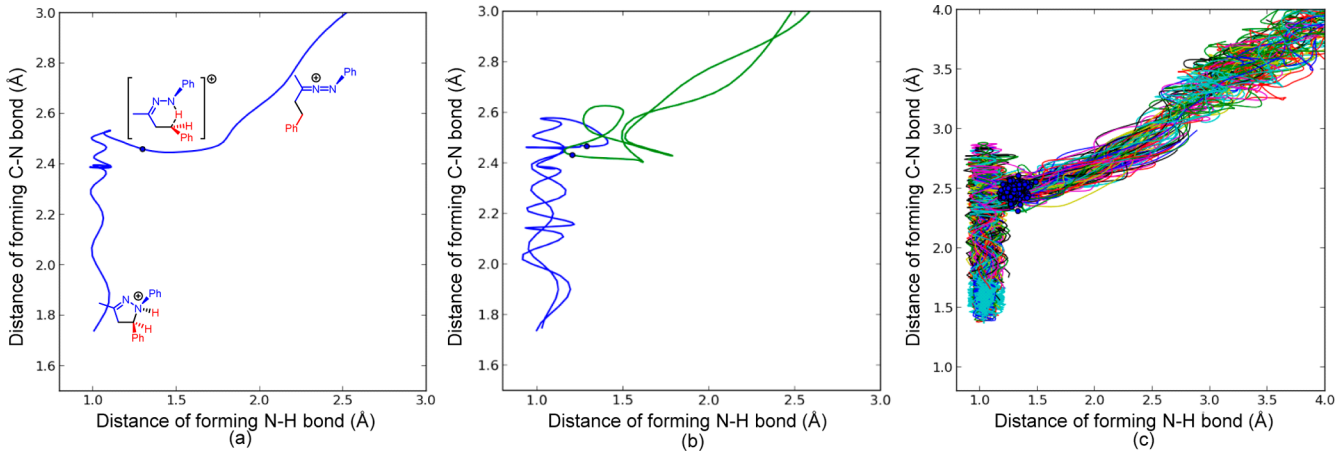

Figure 4. Quasi-classical molecular dynamics trajectories for the singlet C−H amination of aryl-1-aza-2-azoniaallene **10**: (a) A productive trajectory. The duration of the trajectory is 110 fs. (b) Two unproductive trajectories. The green trajectory recrosses at reactant side, and the blue trajectory recrosses at the product side. (c) Overlay of 256 trajectories at 298 K.

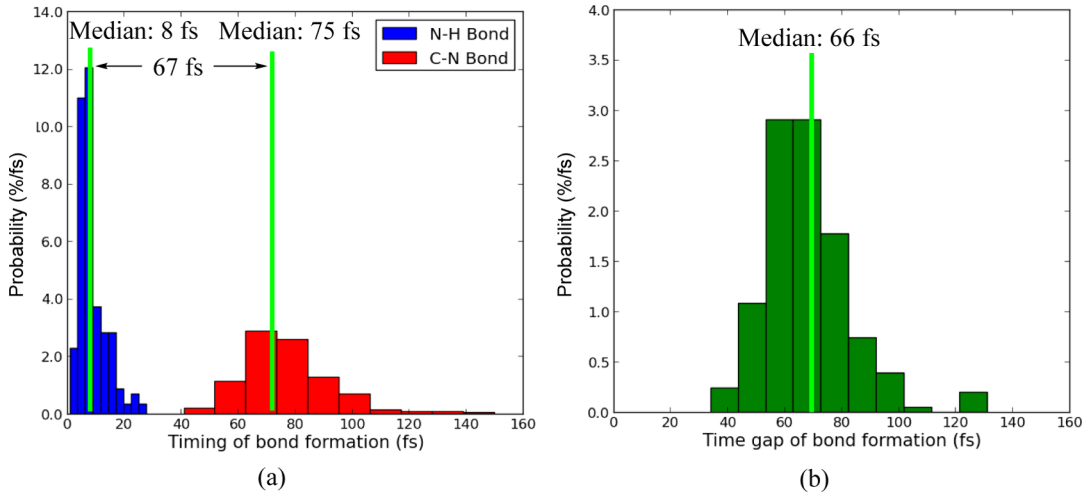

Figure 5. (a) Distribution of timing of C−N and N−H bond formations at 298 K. The starting point (time zero) is each sampled transition state geometry. (b) Distribution of the time gap between C−N and N−H bond formations.

molecular dynamics trajectories to provide information about the timing of bond formations. Quasi-classical trajectories were initialized by transition state normal mode sampling with the Progdyn program developed by Singleton.[25] An ensemble of transition states was sampled on the basis of Boltzmann distributions. These form a dividing surface intersecting the saddle point on the potential energy surface. The overlay of sampled transition state geometries and the corresponding C−N and N−H bond length distributions is shown in Figure 3. Both C−N and N−H bond lengths are distributed symmetrically with respect to the bond lengths of the saddle point (marked with green lines in Figure 3). This distribution of bond length is Gaussian, and we define the transition zone as the 98% confidence interval of the Gaussian distribution. The transition zones for the C−N and N−H bonds are 2.48 ± 0.12 and 1.30 ± 0.10 Å, respectively. This means that 98% of the C−N and N−H bond lengths sampled are within ±0.12 and ±0.10 Å of the respective bond lengths at the saddle point.

Sampled transition states were propagated forward and backward by Newtonian equations of motion until they reached reactants or products. The fully formed bond length is defined as 1.10 Å for N−H and 1.80 Å for C−N. The corresponding distances in the reactant are 3.00 Å for both bonds. Trajectories were terminated after 500 fs if they had not reached reactant or product in that period. A total of 256 trajectories was computed, and 95% of these were productive. Figure 4a illustrates one typical productive trajectory: starting from the substrate, the benzylic hydride moves to the terminal nitrogen until the N−H bond is about 1.1 Å, but at this time point, the C−N distance is still around 2.5 Å. The subsequent C−N bond formation occurs spontaneously, accompanied by some residual vibration of the just-formed C−H bond, with the formation of the heterocyclic product. Figure 4b shows two typical unproductive trajectories, which recross in the reactant or product side, and Figure 4c shows the overlay of all 256 trajectories.

Figure 5a shows the distribution of timing of bond formations for all productive trajectories. Starting from the sampled transition state starting geometries, the median time for N−H bond formation (reaching 1.10 Å) is 8 fs, and the median time for C−N bond formation (reaching 1.80 Å) is 75 fs; the timing of C−N bond formation is, on average, 67 fs later than that of N−H bond formation, essentially within a C−N vibrational period. This indicates that the N−H bond forms almost immediately after the transition state saddle point, which is in line with the IRC calculations (Figure 2), and that

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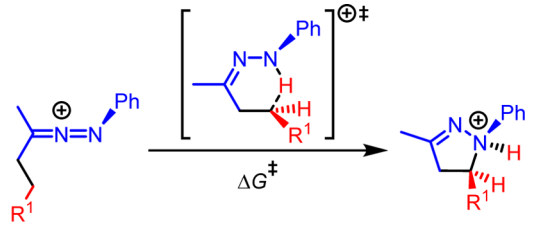
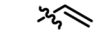
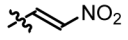
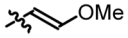
the C−N bond forms spontaneously afterward within a short period of time. We also calculated the time gap between the formation of the C−N and N−H bonds for each productive trajectory. The distribution of time gaps is shown in Figure 5b. The time gap of bond formation ranges only from 35 to 130 fs, with the median located at 66 fs. This indicates that there is a short time window between bond formation. Because the time scale of C−C bond rotation is generally longer than 1 ps, there is insufficient time for a C−C bond rotation to occur between the N−H and C−H bond forming events.

Substituent Effect on the Reactivity of C−H Amination. We have also studied the reaction barriers for substrates with a variety of substitutions on the β-phenyl (R^1) or in place of this group; results are shown in Table 2. The α-methylene of R^1 in the substituted 1-aza-2-azoniaallene salt is a hydride donor, and substituents that stabilize the forming carbocation increase the C−H amination reactivities. Replacing the phenyl group (entry 1) by hydrogen (entry 2) increases the barrier dramatically from 20.0 kcal/mol with phenyl to 31.4 kcal/mol with hydrogen. Substitution by alkyl groups (entries 3−6) does not stabilize the forming carbocation as much as the phenyl group, and the reaction barrier increases to 21−23 kcal/mol. The electronic effect has a strong effect on the barrier. The reaction barrier increases significantly with electron-withdrawing substituents (entries 7−11), whereas electron-donating groups reduce the barrier dramatically (entries 12 and 13). Various electron-rich vinyl and aryl substituents have achievable amination barriers (entries 14, 16, and 20−22). The energy barriers computed for the *p*-NO_2-Ph and *p*-MeO-Ph derivatives (entries 19 and 22) are consistent with the selectivity observed in the competition experiment (Table 1, entry 6). We also computed amination at a tertiary C−H using the 1-aza-2-azoniaallene cation generated from substrate **1j** as a model, and the barrier is 17.2 kcal/mol.[30] The additional alkyl substituent lowers the barrier of amination by stabilizing the forming carbon cation in the transition state, making it competitive with benzylic C−H amination.

Tether Effect on the Competition between C−H Amination and Electrophilic Aromatic Substitution. We also explored the tether effect on the competition between the C−H amination and electrophilic aromatic substitution (Table 3). When there is one methylene between the heteroallene component and the benzylic hydride donor (n = 1), the C−H amination transition state is 1.3 kcal/mol more stable than the electrophilic aromatic substitution transition state because of the proximity of the reacting partners in **TS16** and the strain in **TS17**. This preference is also in line with the experimental results that this tether causes the C−H amination. With longer tethers (n = 2, 3), the chemoselectivity is reversed, and the aromatic substitution is significantly more favorable than C−H amination.[31] A similar preference is also found in intermolecular reactions; the C−H amination between the corresponding 1-aza-2-azoniaallene and toluene has a barrier of 34.4 kcal/mol, whereas the barrier of electrophilic aromatic substitution is only 26.5 kcal/mol. Therefore, the electrophilic aromatic substitution is intrinsically much more favorable than the C−H amination. Only with the short tether (n = 1) does the ring strain of the two competing transition states significantly favor the C−H amination, leading to the reversed chemoselectivity.

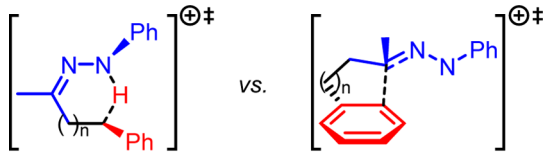
Table 2. C−H Amination Barriers of Substituted Aryl 1-Aza-2-azoniallene Cations[a]



entry	R^1	$\Delta G^{\ddagger}$	entry	R^1	$\Delta G^{\ddagger}$
1	Ph	20.0	12	OH	15.6
2	H	31.4	13	NH_2	11.7
3	Me	21.2	14		20.4
4	Et	21.7	15		25.6
5	*i*Pr	22.8	16		16.3
6	*t*Bu	22.9	17	*o*-NO_2-Ph	24.0
7	F	27.2	18	*m*-NO_2-Ph	21.3
8	Cl	29.4	19	*p*-NO_2-Ph	22.6
9	CN	33.9	20	*o*-OMe-Ph	19.2
10	CF_3	38.6	21	*m*-OMe-Ph	19.8
11	NO_2	35.3	22	*p*-OMe-Ph	17.9

[a]Gibbs free energies are in kcal/mol.

Table 3. Gibbs Free Energy Barriers of C−H Amination and Electrophilic Aromatic Substitution of Aryl 1-Aza-2-azoniallene Cations with Different Tethers[a]



TS16 **TS17**

n	TS16	TS17
1	20.0	21.3
2	23.8	14.2
3	32.5	20.1
intermolecular	34.4	26.5

[a]Gibbs free energies are in kcal/mol.

CONCLUSIONS

The scope, mechanism, and dynamics of C−H amination reactions of 1-aza-2-azoniaallene salts have been studied experimentally and computationally. The facility of this C−H amination relies heavily on the tether that connects the heteroallene cation component and the pendant aryl groups. While the insertion occurs readily at benzylic and tertiary aliphatic positions when the tether is two methylene units, a longer tether or intermolecular reaction gives electrophilic aromatic substitution, the intrinsically favored reaction, rather than C−H amination.

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This C−H amination proceeds through a hydride transfer transition state to form a N−H bond initially, and the subsequent C−N bond formation occurs spontaneously afterward to generate the heterocyclic product. IRC trajectory indicates that the two consecutive bond formation processes, N−H and C−N, are energetically concerted, and this concerted mechanism is further proved by quasi-classical molecular dynamics trajectory studies. The C−N bond formation occurs much faster than C−C bond rotation, which explains the stereospecificity in the C−H amination. In line with the hydride transfer transition state, electron-rich aryl substituents that stabilize the forming carbon cation facilitate the amination significantly, whereas alkyl and electron-poor aryl-substituted substrates have higher reaction barriers.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full characterization of the products and spectra. Coordinates, absolute electronic energies, and free energies in solution of DFT-computed stationary points. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b04474.

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Notes

The authors declare no competing financial interest.

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(26) The criteria to terminate trajectories were as follows: C20−N3 < 1.60 and H21−N3 < 1.10, or C20−H21 < 1.10 and C20−N3 > 5.00 (the atom index is shown in Figure 3). If none of the above criteria were met, then a trajectory was terminated after 500 fs. About 10% of trajectories recross the transition state region to form the same species in the forward and reverse directions, and these trajectories are not discussed.
(27) The possible singlet diradical transition state cannot be located; all optimizations for the corresponding singlet diradical intermediate led to the stable close-shell species **10**. The energy of the singlet species based on the optimized structure of triplet **13** is 29.2 kcal/mol less stable than **10**.
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(30) The calculated chemoselectivity of substrate **1j** is different than the experimental value (Scheme 6) because the tertiary C−H amination transition state is overstabilized by the solvation energy corrections. In gas phase calculations, benzylic C−H amination is favored by 2.6 kcal/mol. With the CPCM model (Radii = UA0), the chemoselectivity is 1.4 kcal/mol in favor of tertiary C−H amination.
(31) When n = 3, the electrophilic aromatic substitution appears to be attainable. However, neither reaction occurred experimentally, and the only identifiable product of this reaction was the corresponding ketone, which presumably forms by hydrolysis during workup.

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A Ring Fragmentation Approach to Medium-Sized Cyclic 2-Alkynones

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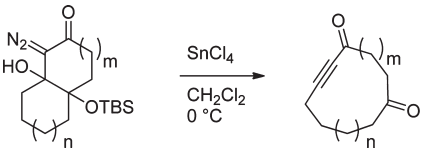
ABSTRACT



Bicyclic γ-silyloxy-β-hydroxy-α-diazoketones, in which the Cβ–Cγ bond is the ring fusion bond, productively fragment when treated with tin(IV) chloride to provide medium-sized cyclic 2-alkynones. This method provides good to excellent yields of 10-, 11-, and 12-membered alkynone products.

In view of the synthetic utility of ynones, and the fact that medium-sized rings are an underexplored[1] but important[2] structural motif in biologically active compounds, medium-sized cyclic 2-alkynones should be decidedly useful synthetic intermediates. However, these types of compounds have rarely been used in synthetic sequences;[3−7] a fact that can undoubtedly be attributed to a lack of available methods to prepare this structural motif. While functional group manipulations on medium-sized cycloalkynes[8−12] or medium sized cycloalkenes[13] have on occasion been used to prepare cyclic 2-alkynones, methods to directly prepare these compounds from precursors that do not contain a medium-sized ring are limited to the aluminum trichloride promoted intramolecular cyclization of silylalkynes and acid chlorides developed by Utimoto and co-workers.[14] Unfortunately, this strategy suffers from the common limitation of macrocyclization strategies, namely the requirement of high dilution conditions. With this in mind, we became interested in determining whether the Lewis acid promoted fragmentation of cyclic γ-silyloxy-β-hydroxy-α-diazocarbonyls (e.g., **1** to **2**, Figure 1) we recently discovered[15,16] could be applied to the direct formation of medium-sized cyclic 2-alkynones.

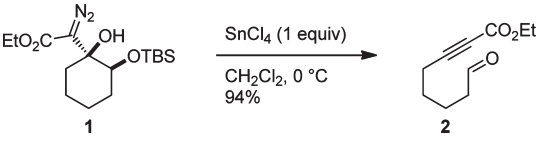


Figure 1. Fragmentation of cyclic γ-silyloxy-β-hydroxy-α-diazoesters yields aldehyde tethered ynoates.

In this letter we wish to report that bicyclic γ-silyloxy-β-hydroxy-α-diazoketones, in which the C_β–C_γ bond is the ring fusion bond, productively fragment to provide medium-sized cyclic 2-alkynones in good to excellent yields.[17]

To test our hypothesis that bicyclic diazoketones could be precursors to medium-sized cyclic 2-alkynones we

(1) Greve, B.; Imming, P.; Laufer, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1221.
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(12) Bodenmann, B.; Keese, R. *Tetrahedron Lett.* **1993**, *34*, 1467.
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(15) Bayir, A.; Draghici, C.; Brewer, M. *J. Org. Chem.* **2010**, *75*, 296.
(16) Draghici, C.; Brewer, M. *J. Am. Chem. Soc.* **2008**, *130*, 3766.

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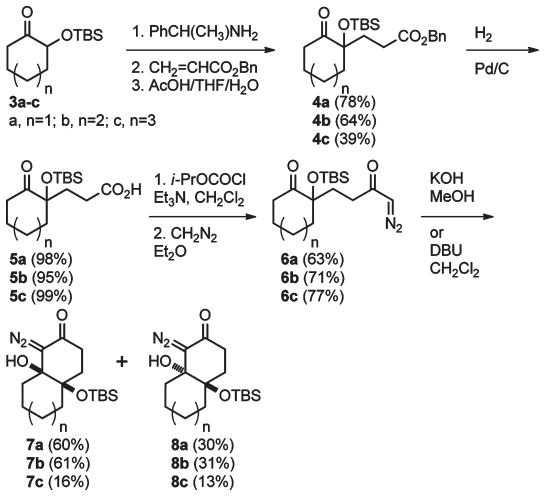
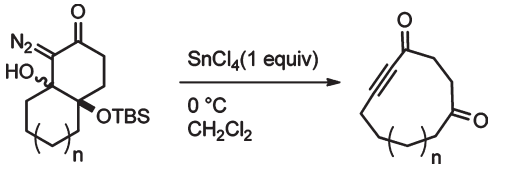
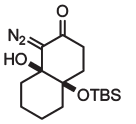
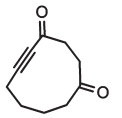
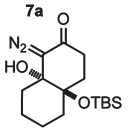
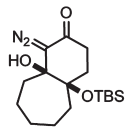
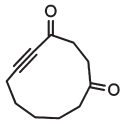
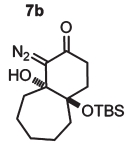
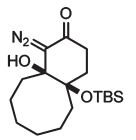
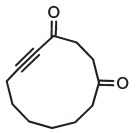
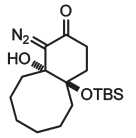
Scheme 1. Preparation of Bicyclic Fragmentation Substrates



prepared the diastereomeric bicyclo[4.4.0]decane diazo compounds **7a** and **8a** by the route shown in Scheme 1. d'Angelo-type[18] conjugate addition provided ester **4a** in 78% yield, and subsequent hydrogenolysis provided the free acid **5a** in 98% yield. The requisite diazo carbonyl **6a** was then formed in 63% yield over two steps from acid **5a** via the corresponding mixed anhydride. It was interesting to note the facility by which the pendant diazo ketone (**6a**) underwent intramolecular aldol-type addition to provide bicycles **7a** and **8a**; this intramolecular reaction was achieved with the mild base DBU over the course of 12 h. Intermolecular aldol-type additions of diazo carbonyl compounds to ketones require the generation of a lithiated diazo species, which is most often formed by deprotonation of the corresponding diazo carbonyl with either *n*-butyl lithium or LDA.[19,20] Due to their greater electrophilicity, aldehydes do react with diazo carbonyl compounds in the presence of DBU,[21] and in our case the proximity of the reacting partners likely makes the aldol-type addition more favorable. Potassium hydroxide in methanol induced the ring closure[22] more efficiently and

Table 1. Fragmentation of Fused Bicyclic Substrates



substrate	product	yield
 7a	 9	80%
 8a	9	71%
 7b	 10	99%
 8b	10	93%
 7c	 11	93%
 8c	11	80%

provided bicycles **7a** and **8a** as a separable mixture of diastereomers in 60% and 30% yield respectively after only 15 min.[23]

With the requisite fragmentation precursors in hand, we turned our attention to the fragmentation reaction. Treating the cis-fused bicyclo[4.4.0]decane diazo **7a** with 1 mol equiv of $SnCl_4$ at 0 °C resulted in observable gas evolution and provided essentially pure cyclodec-5-yne-1,4-dione (**9**, Table 1) in near-quantitative yield as determined by ^1H and

(17) The Eschenmoser–Tanabe fragmentation has been used to generate cyclic alkynes: Reese, C. B.; Sanders, H. P. *Synthesis* **1981**, 276. Tanabe, M.; Crowe, D. F.; Dehn, R. L. *Tetrahedron Lett.* **1967**, 3943. Tanabe, M.; Crowe, D. F.; Dehn, R. L.; Detre, G. *Tetrahedron Lett.* **1967**, 3739. Eschenmoser, A.; Felix, D.; Ohloff, G. *Helv. Chim. Acta* **1967**, *50*, 708. Schreiber, J.; Felix, D.; Eschenmoser, A.; Winter, M.; Gautschi, F.; Schulte-Elte, K. H.; Sundt, E.; Ohloff, G.; Kalovoda, J.; Kaufmann, H.; Wieland, P.; Anner, G. *Helv. Chim. Acta* **1967**, *50* (7), 2101. Lange, G. L.; Hall, T.-W. *J. Org. Chem.* **1974**, *39*, 3819. Gordon, D. M.; Danishefsky, S. J.; Schulte, G. K. *J. Org. Chem.* **1992**, *57* (26), 7052. Dudley and Tummatorn have recently extended the vinylogous acyl triflate fragmentation strategy to the preparation of cycloalkynes: Tummatorn, J.; Dudley, G. B. *Org. Lett.* **2011**, *13* (6), 1572.

(18) d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3* (4), 459.

(19) Schöllkopf, U.; Frasnelli, H. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 301.

(20) Pellicciari, R.; Natalini, B.; Sadeghpour, B. M.; Marinozzi, M.; Snyder, J. P.; Williamson, B. L.; Kuethe, J. T.; Padwa, A. *J. Am. Chem. Soc.* **1996**, *118*, 1.

(21) Jiang, N.; Wang, J. *Tetrahedron Lett.* **2002**, *43*, 1285.

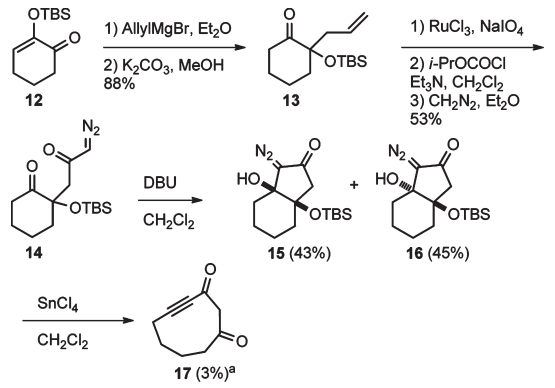
(22) Burkoth, T. L. *Tetrahedron Lett.* **1969**, *10*, 5049.

(23) The relative stereochemistry of diastereomer **7a** and **8a** were easily distinguishable by NMR. The conformational flexibility of cis-fused bicyclic **7a** led to broad signals in the ^1H and ^{13}C NMR spectra, which sharpened upon warming. Trans-fused diastereomer **8a**, on the other hand, had sharp signals in the ^1H and ^{13}C NMR spectra at room temperature. The structures of the other diastereomers were assigned by analogy based on the following consistent observations: (a) the hydroxyl proton appeared further downfield in each bicyclic structure assigned as cis-fused, presumably due to intramolecular hydrogen bonding with the adjacent silyl ether; (b) the methyl groups of the silyl ether showed a greater difference in chemical shift for the bicycles assigned as trans-fused compared to the cis-fused diastereomers.

^{13}C NMR analysis. Purification resulted in some compound loss, and isolation by chromatography returned cyclic ynone **9** in 80% yield. The trans-fused diastereomer **8a** also productively fragmented to give alkyne **9** in 71% yield.

Applying the same sequence of reactions shown in Scheme 1 to the corresponding 2-silyloxycycloheptanone (**3b**) and 2-silyloxycyclooctanone (**3c**) provided the diazo bicyclo[5.4.0]undecane and bicyclo[6.4.0]dodecane systems (**7b**, **8b** and **7c**, **8c**; Table 1) respectively. While the intramolecular cyclization of diazo compound **6b** occurred in high yield (92%) to give the expected diastereomeric aldol-products **7b** and **8b**, the cyclization of diazo compound **6c** did not go to completion. Under the reaction conditions this latter system existed as an equilibrium mixture of the starting material **6c** and the two diastereomeric products (**7c** and **8c**) in a 4.6 to 1.2 to 1 ratio. Separating these compounds was trivial, and the isolated bicyclic products were stable once removed from the basic reaction conditions. However, resubjecting bicycle **7c** to the cyclization reaction conditions provided the same equilibrium mixture of starting material and diastereomeric products, which highlights the reversibility of this aldol-type addition reaction. Attempts to shift the equilibrium toward the ring closed products by changing the solvent or base, or by trapping the bicyclic products as the silyl protected tertiary alcohols, failed. It seems likely that transannular interactions in the bicyclo[6.4.0]dodecane system make the ring closed form less favorable at equilibrium.

Scheme 2. Preparation of Bicyclo[4.3.0]nonane Fragmentation Precursor

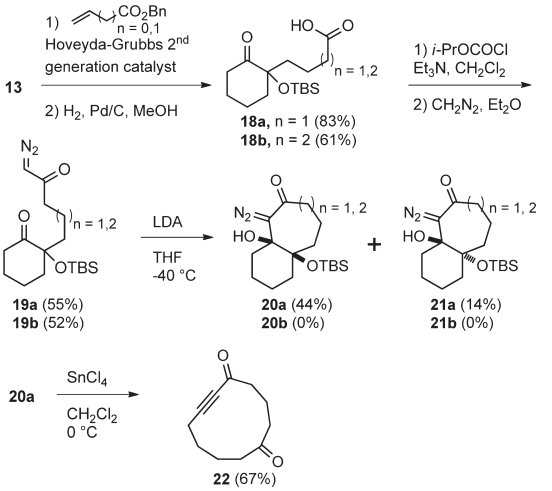


[a] Compound **17** appears to decompose during purification. Based on NMR analysis of crude reaction mixture, the initial yield was estimated at 40%.

Both the cis (**7b**) and trans (**8b**) diastereomers of the bicyclo[5.4.0]undecane system productively fragmented to provide cycloundec-5-yne-1,4-dione (**10**) in 99% and 93% yield respectively after purification. The larger bicyclo-[6.4.0]dodecane systems (**7c** and **8c**) were also competent fragmentation substrates and provided cyclododec-5-yne-1,4-dione (**11**) in 93% and 80% yield respectively after purification.

In order to extend the utility of this transformation we examined the possibility of varying the size of the diazo containing ring, which would allow a variety of different medium-sized rings to be formed from a common 5- or 6-membered ring precursor. Our synthetic routes to the bicyclo[4.3.0]nonane systems **15** and **16** and bicyclo-[5.4.0]undecane systems **20a** and **21a**, in which the diazo functional group resides on a 5- and 7-membered ring respectively, are shown in Schemes 2 and 3. The known[24] 2-silyloxycyclohex-2-enone (**12**) was converted in two steps to α-silyloxy ketone **13** by Grignard addition followed by base catalyzed silyl migration.[25] The olefin was oxidatively cleaved to the carboxylic acid, which was subsequently converted to diazo ketone **14** under standard conditions. Diazo compound **14** smoothly cyclized to diastereomeric bicycles **15** and **16** in 43 and 45% yield respectively. Fragmentation of **15** and **16** provided complex mixtures which appeared to contain ynone **17** in up to 40% yield, but the desired product was isolated in at most 3% yield. Ynone **17** proved to be unstable and upon standing decomposed to an intractable mixture of products. It is not clear at this point if the low yield obtained of ynone **17** is due to an unproductive fragmentation or the inherent instability of **17**.

Scheme 3. Preparation and Fragmentation of Bicyclo-[5.4.0]undecane Ring System



Diazo compounds **20a** and **21a** were prepared from ketone **13** by cross metathesis[26,27] to incorporate the requisite side chain functionality and subsequent simultaneous reduction of the alkene and hydrogenolysis of the benzyl ester to provide acid **18a**. Incorporation of the diazo functionality under standard conditions proceeded as expected to provide diazo ketone **19a**. Subsequent intramolecular aldol-type cyclization to form the 7-membered ring failed in the presence of DBU and KOH in methanol, but diazo compound **19a** did provide the expected cis- and trans-fused bicycles **20a** and **21a** in 44% and 14% yield

(24) Kadow, J. F.; Saulnier, M. G.; Tun, M. M.; Langley, D. R.; Vyas, D. M. *Tetrahedron Lett.* **1989**, *30*, 3499.
(25) Gulías, M.; Rodríguez, J. R.; Castedo, L.; Mascareñas, J. L. *Org. Lett.* **2003**, *5*, 1975.
(26) BouzBouz, S.; Simmons, R.; Cossy, J. *Org. Lett.* **2004**, *6* (20), 3465.
(27) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

respectively upon treatment with LDA. Fragmentation of bicycle **20a** with $SnCl_4$ returned cycloundec-6-yne-1,5-dione (**22**) in 67% yield. Ynone **22** differs from ynone **10** by the relative positions of the carbonyls. Attempts to apply this same sequence to the preparation of the bicyclo-[6.4.0]dodecane system (**20b** and **21b**), in which the diazo resides on an 8-member ring, were also made. Although the linear diazo precursor **19b** was formed without incident, all attempts to induce cyclization failed to yield any of the desired bicyclic products. We suspect that in this case the unfavorable equilibrium noted above for the closure of diazo compound **6c** is compounded by the fact that 8-member rings are inherently more difficult to form,[28] which prevents a productive cyclization from occurring.

The preliminary results presented here demonstrate that bicyclic γ-silyloxy-β-hydroxy-α-diazoketones are competent fragmentation substrates that can provide access to 10-, 11-, and 12-membered cyclo 2-alkynone products in good to excellent yields. It is not clear if the low yield obtained for the 9-membered cyclo 2-alkynone (**17**) is an inherent limitation of this method to form 9-membered ynones, or if this low yield is due to the instability of **17** under the reaction conditions. Further studies of this medium-sized ring forming reaction and applications of this method toward the synthesis of medium-ring containing natural products are underway and will be disclosed in future publications.

(28) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.

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Supporting Information Available. Experimental details and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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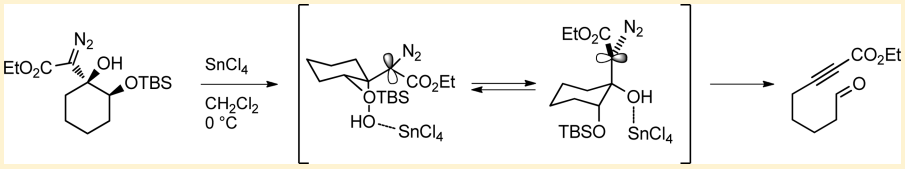
Stereoelectronic Effects in the Fragmentation of γ-Silyloxy-β-hydroxy-α-diazocarbonyl Compounds

Nitinkumar D. Jabre and Matthias Brewer*

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

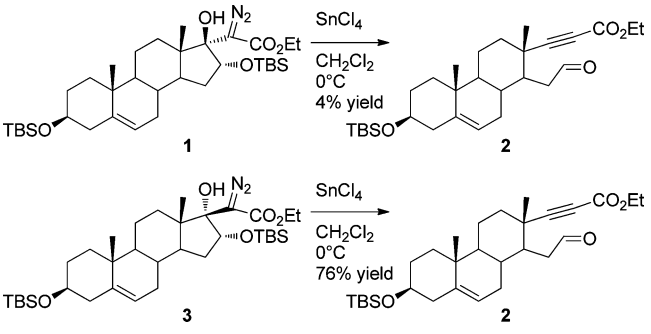
Supporting Information



ABSTRACT: A series of γ-silyloxy-β-hydroxy-α-diazocarbonyl compounds were prepared as fragmentation substrates to probe the hypothesis that steric interactions between the diazo ester and adjacent silyloxy group can play an important role in determining the success of fragmentations. Proper stereoelectronic alignment of the diazo ester and the departing hydroxyl group is necessary for productive fragmentation to occur.

Reactions that result in the cleavage of a carbon−carbon bond are important transformations because they can directly provide synthetic intermediates that are difficult to prepare by other routes and can unmask latent functional groups under chemoselective reaction conditions.[1−10] We recently reported that cyclic γ-silyloxy-β-hydroxy-α-diazocarbonyl compounds fragment in the presence of Lewis acids to provide aldehyde-tethered ynoates or ynones in high yield.[11,12] The fragmentation precursors were easily prepared for these studies by the aldol-type addition of ethyl lithiodiazoacetate to an α-silyloxy ketone.[13,14] Although high-yielding, this Aldol-type addition can result in the formation of two diastereomers, which is generally inconsequential because both stereoisomers typically fragment in similar yields. However, in the case of a more structurally complex steroid-based fragmentation substrate, a *trans*-diol diastereomer (**1**, Scheme 1) fragmented in dramatically lower yields (4%) than a *cis*-diol diastereomer (**3**, 76% yield). In this Note we describe results from a study we undertook to better understand the dependence of the fragmentation reaction on the stereochemistry of the fragmentation precursor.

Scheme 1. Unique Example of the Importance of Stereochemistry on Fragmentation Reaction Outcome



A proposed mechanism for the fragmentation of γ-silyloxy-β-hydroxy-α-diazocarbonyl compounds is shown in Scheme 2. The first step of this process is thought to be a Lewis acid assisted elimination of the β-hydroxy group to provide a vinyl diazonium intermediate (**6**),[15,16] which undergoes a Grob-type fragmentation with subsequent loss of the silyl protecting group. Alternatively, **6** may lose nitrogen to provide a vinyl cation prior to fragmentation. Loss of the β-hydroxyl group in the first step of this sequence would convert diazos **1** and **3** into a common intermediate, so the difference in reactivity observed for these compounds must arise during this initial elimination step. In order for the elimination of the β-hydroxyl to occur, the diazo and ester groups must lie in a plane that is perpendicular to the leaving group. Steric interactions that develop when the diazoester moiety is in the correct stereoelectronic orientation could account for the difference in observed reactivity for diastereomers **1** and **3**. That is, in the case of *cis*-diol isomer **3**, steric interactions involving the diazo ester should not be significant when it is oriented correctly for elimination to occur (**9**, Figure 1). Conversely, in the case of *trans*-diol diastereomer **1** significant steric interactions between the diazo ester and the adjacent silyloxy group would be expected, which may prevent the diazo ester from adopting the necessary conformation for the necessary elimination to occur (**10**, Figure 1).

The *cis*-diol diastereomer of fragmentation precursors derived from α-silyloxy cyclohexanone (e.g., **11**, Figure 2) should have steric interactions similar to those shown for structure **10** in Figure 1, yet the cyclohexanone-based systems fragment without issue. To rationalize these observations, we hypothesize that the cyclohexyl systems undergo ring inversion

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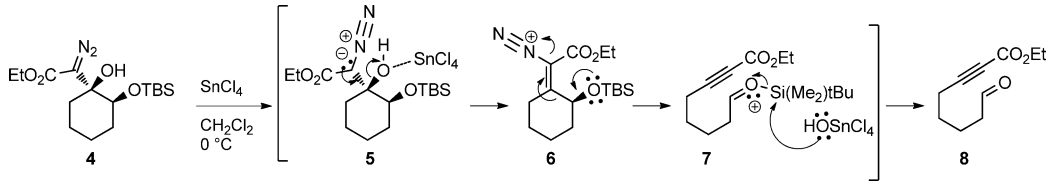
Scheme 2. Proposed Mechanism for the Fragmentation of γ-Silyloxy-β-hydroxy-α-diazocarbonyls



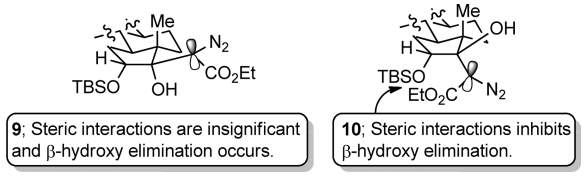


Figure 1. Steric interactions that could affect elimination of β-hydroxyl.

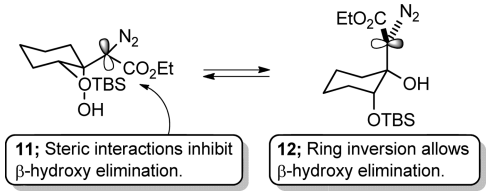


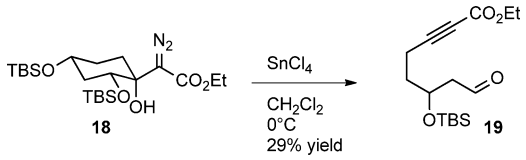
Figure 2. Ring inversion relieves steric interactions and facilitates elimination of β-hydroxyl.

to provide conformer **12** (Figure 2), in which the diazo ester adopts the stereochemical alignment necessary for elimination of the β-hydroxyl to occur. Alternatively, a twist boat conformation could also alleviate the steric interaction between the diazo ester and silyloxy group in cyclohexanone-based systems.

To test this hypothesis we have prepared several cyclohexyl-based fragmentation precursors that should be resistant to ring inversion, and we have assayed their ability to fragment. The first fragmentation precursor we prepared for these studies was γ-silyloxy-β-hydroxy-α-diazoester **13** (Scheme 3) derived from 4-*tert*-butyl cyclohexanone. In this case, the *tert*-butyl group should inhibit diazo **13** from undergoing a ring flip. In the event, treating diazo **13** under standard fragmentation conditions provided a complex mixture of products that contained only traces of the desired fragmentation product. This result supports the idea that ring inversion is necessary for fragmentation to occur since **13** should be able to adopt a twist boat conformation but did not fragment productively. In this case, a ring expansion and elimination sequence appears to be more favorable, and β-keto ester **17** was isolated in 55% yield. This ring expansion is interesting because while protic acids cause cyclic β-hydroxy-α-diazo esters to undergo ring expansion,[17,18] Lewis acids usually do so only when used in substoichiometric quantities; when used stoichiometrically, Lewis acids typically promote elimination of the hydroxy group leading to a vinyl diazonium species.[16,19] In the case of substrate **13**, a slow elimination step could result in a Lewis acid facilitated proton transfer to the diazo, which could lead to ring expansion as shown in Scheme 3. Importantly, diazo **13** was the first cyclohexyl-based fragmentation substrate we observed to not fragment productively.

To further probe the hypothesis that steric interactions between the diazo ester and an adjacent group affect the course of the reaction, we prepared two fragmentation substrates based on a 2,4-dihydroxycyclohexanone scaffold. The first, diazo ester **18** (Scheme 4) derived from 2,4-bis((*tert*-butyldimethylsilyl)-

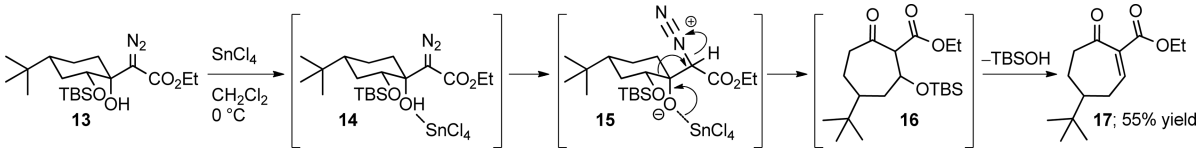
Scheme 4. Low-Yielding Ring Fragmentation



oxy)cyclohexanone,[20] should be resistant to ring inversion and should thus fragment poorly. Treating diazo ester **18** under the standard fragmentation conditions provided a complex mixture from which the desired product (**19**) was isolated in only 29% yield.[21] Although modest, this yield is higher than the yield obtained for the fragmentation of *tert*-butyl derivative **13**, which may be a reflection of the fact that OTBS has a smaller *A*-value than *tert*-butyl (1.06 vs >4.5 kcal/mol)[22,23] and thus **18** may undergo ring inversion to a greater extent than **13**. Coordination of the silyl ethers in **18** by the Lewis acid could also help facilitate ring inversion.

We prepared diazo **24** as a final substrate for these studies by the route shown in Scheme 5.[24] Diazo **24** is closely related to diazo **18** but has the alcohols tethered together by a silyl bridge. This bridge causes the diazo ester to be in an axial position on the ring, which allows it to adopt the stereoelectronic alignment needed for elimination of the β-hydroxyl without steric hindrance, and thus we expected **24** to fragment easily. When diazo **24** was treated with $SnCl_4$, copious gas evolution was noted, and when the reaction was stopped after 15 min, the NMR of the crude reaction mixture appeared to show a mixture of the expected aldehyde (**25**) and the dimeric acetal (**26**). When the fragmentation reaction was allowed to proceed for 12 h, the initially formed compounds reacted further to provide enal **27** in 83% isolated yield.

Scheme 3. First Example of a Cyclohexyl-Based Fragmentation Substrate That Failed To Fragment Productively



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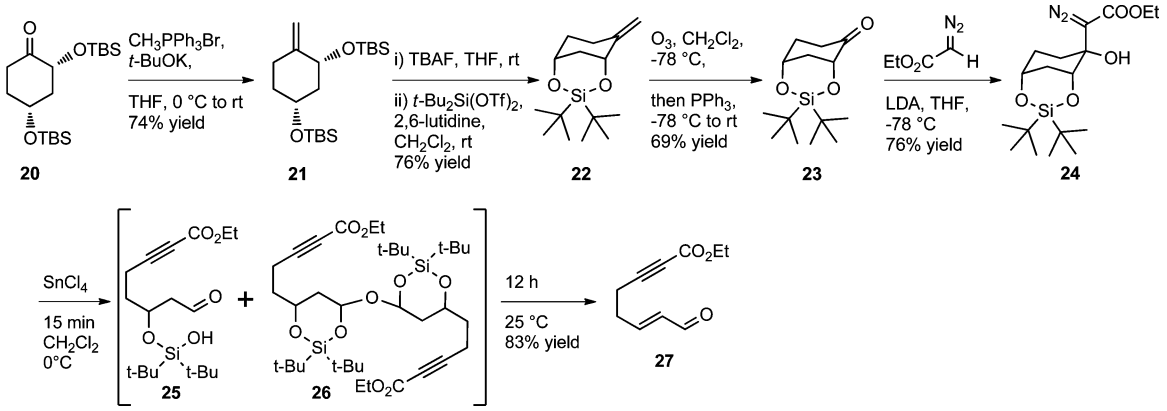
Scheme 5. Successful Ring Fragmentation



The studies presented here are consistent with our hypothesis that steric interactions involving the diazo ester play an important role in determining the success of fragmentations of γ-silyloxy-β-hydroxy-α-diazocarbonyl compounds. Proper stereoelectronic alignment of the diazo ester and the departing hydroxyl appears to be a necessary requirement for productive fragmentation, and steric interactions that inhibit this alignment from occurring are detrimental to the fragmentation process. This stereoelectronic requirement should be considered when applying this fragmentation in more complex systems.

EXPERIMENTAL SECTION

General Experimental Information. All reactions were carried out under an atmosphere of nitrogen using flame-dried glassware. Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), and diethyl ether (Et_2O) were dried via a solvent dispensing system. $SnCl_4$ was distilled twice from P_2O_5 under inert atmosphere conditions and stored in sealed tubes under an atmosphere of nitrogen as a 1 M solution in CH_2Cl_2. Flash column chromatography was performed using silica gel (230−400 mesh), and TLC analysis was carried out using Merck 60F-254 silica on glass plates. Visualization of TLC plates was achieved using ultraviolet light, polyphosphomolybdic acid, and cerium sulfate in EtOH with H_2SO_4, ceric ammonium molybdate, or iodine. Accurate mass data was acquired in ESI mode using an orbitrap mass analyzer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$. ^1H chemical shifts are reported in ppm (δ units) downfield from tetramethylsilane. Solvent peaks were used as internal references for all ^{13}C NMR.

Ethyl 2-(4-(*tert*-Butyl)-2-((*tert*-butyldimethylsilyl)oxy)-1-hydroxycyclohexyl)-2-diazoacetate (13). A solution of LDA (0.67 mmol) in THF (3.2 mL) was added dropwise via cannula over a period of 15 min to a −78 °C solution of *cis*-4-(*tert*-butyl)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexanone[25] (160 mg, 0.56 mmol) and ethyl diazo acetate (83.5 mg, 0.73 mmol) in THF (3.2 mL). The resulting brown solution was maintained at −78 °C for 2 h at which point an aqueous saturated solution of NH_4Cl (5 mL) was added. The mixture was warmed to room temperature, additional saturated NH_4Cl (40 mL) was added, and the mixture was extracted with EtOAc (20 mL × 3). The organic layers were combined, dried over anhydrous Na_2SO_4, and evaporated to provide a yellow viscous oil that was purified by silica gel column chromatography (100:0 to 98:2 hexanes/EtOAc) to give 205 mg (89% yield) of the title compound; TLC R_f = 0.4 (96:4 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 4.24 − 4.00 (m, 3H), 3.09 (d, J = 2.1 Hz, 1H), 2.06−1.95 (m, 1H), 1.89 (dt, J = 14.1, 3.2 Hz, 1H), 1.72 (ddt, J = 12.1, 4.9, 2.4 Hz, 1H), 1.53−1.45 (m, 1H), 1.39−1.26 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H), 1.15−1.07 (m, 1H), 0.85 (s, 9H), 0.83 (s, 9H), 0.03 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.8, 72.5, 70.8, 63.6, 60.0, 45.5, 33.6, 32.2, 32.1, 27.4, 25.6, 21.8, 17.7, 14.5, −4.5, −5.4; IR (thin film) 3529, 2093, 1684, 1094, 1082 cm^{-1}; HRMS (ESI) calcd for $[C_{20}H_{38}N_2O_4SiNa]^+$ 421.2493, found 421.2493.

Ethyl 4-(*tert*-Butyl)-7-oxocyclohept-1-enecarboxylate (17). A 1 M solution of $SnCl_4$ (414 μL, 0.41 mmol) was added as a single stream to a 0 °C solution of diazoester **13** (165 mg, 0.41 mmol) in CH_2Cl_2 (8.5 mL). The reaction mixture was maintained at 0 °C until gas evolution ceased (∼10 to 15 min). The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ (1.5 mL), stirred for 5 min at 0 °C, and transferred into a separatory funnel containing additional saturated aqueous $NaHCO_3$ (30 mL). The aqueous layer was extracted with pentane (10 mL × 3), the organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (98:2 hexanes/EtOAc) to provide 54 mg (55% yield) of **17** as a colorless oil; TLC R_f = 0.9 (80:20 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 6.97 (d, J = 4.6 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 2.53 (d, J = 16.0 Hz, 1H), 2.37 (d, J = 19.4 Hz, 1H), 2.11−1.98 (m, 2H), 1.93 (d, J = 12.7 Hz, 1H), 1.34 (t, J = 7.1 Hz, 3H), 1.31−1.24 (m, 1H), 1.10 (ddd, J = 24.9, 12.4, 5.0 Hz, 1H), 0.87 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.0, 164.7, 149.8, 135.9, 61.8, 43.2, 32.1, 28.4, 27.0, 23.4, 22.8, 14.0; IR (thin film) 2871, 1736, 1671, 1638, 1185, 1157, 1022 cm^{-1}; HRMS (ESI) calcd for $[C_{14}H_{23}O_3]^+$ 239.1642, found 239.1643.

Ethyl 2-(2,4-Bis((*tert*-butyldimethylsilyl)oxy)-1-hydroxycyclohexyl)-2-diazoacetate (18). Diazo ester **18** was prepared from 2,4-bis((*tert*-butyldimethylsilyl)oxy)cyclohexanone (**20**)[20] (1.45 g, 4.05 mmol) using the procedure described for the synthesis of diazo ester **13**. The product was purified by silica gel column chromatography (100:0 to 92:8 hexanes/EtOAc) to give 1.26 g (66% yield) of **18** as a yellow solid. A 100 mg sample of this material was crystallized from MeOH (3 mL) to provide 65 mg of analytically pure product (mp = 113−114 °C). TLC R_f = 0.5 (96:4 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 4.26−4.06 (m, 3H), 3.69−3.07 (m, 1H), 3.07 (d, J = 2.3 Hz, 1H), 2.03 (tdd, J = 13.5, 4.8, 2.4 Hz, 1H), 1.94−1.82 (m, 2H), 1.74−1.60 (m, 3H), 1.26 (t, J = 7.1 Hz, 3H), 0.881 (s, 9H), 0.876 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.002 (s, 3H), 0.001 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7, 70.2, 70.0, 68.4, 63.4, 60.2, 40.6, 30.3, 30.2, 25.8, 25.6, 18.1, 17.7, 14.5, −4.6, −4.67, −4.72, −5.4; IR (thin film) 3486, 2095, 1676, 1098, 1070 cm^{-1}; HRMS (ESI) calcd for $[C_{22}H_{44}N_2O_5Si_2Na]^+$ 495.2681, found 495.2675.

Ethyl 6-((*tert*-Butyldimethylsilyl)oxy)-8-oxooct-2-ynoate (19). Aldehyde **19** was obtained from diazo ester **18** (400 mg, 0.85 mmol) by the procedure described for the synthesis of **17**. The crude product was purified by silica gel column chromatography (98:2 to 75:25 hexanes/EtOAc) to provide 78 mg (29% yield) of **19** as a viscous oil. TLC R_f = 0.3 (92:8 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 9.80 (t, J = 2.2 Hz, 1H), 4.34−4.27 (app. p, J = 5.7 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 2.57 (dd, J = 5.6, 2.2 Hz, 2H), 2.42 (t, J = 7.3 Hz, 2H), 1.82 (t, J = 6.8 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H), 0.87 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.1, 153.6, 88.1, 73.6, 66.4, 61.8, 50.6, 35.1, 25.7, 17.9, 14.6, 14.0,

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−4.7; IR (thin film) 2858, 2237, 1712, 1254 cm^{-1}; HRMS (ESI) calcd for $[C_{16}H_{29}O_4Si]^+$ 313.1830, found 313.1831.

((4-Methylenecyclohexane-1,3-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) (21). A mixture of $Ph_3P^+CH_3Br^-$ (13.6 g, 38.1 mmol) and THF (142 mL) was cooled to 0 °C, and potassium *tert*-butoxide (4.3 g, 38.1 mmol) was added in a single portion. The resulting yellow mixture of ylide was maintained at 0 °C for 20 min. A solution of 2,4-bis((*tert*-butyldimethylsilyl)oxy)cyclohexanone (**20**)[20] (5.06 g, 14.1 mmol) in THF (51 mL) was added to the ylide solution. The reaction mixture was maintained at 0 °C for 10 min and then at room temperature for 3 h at which point water (300 mL) was added, and the aqueous layer was extracted with Et_2O (50 mL × 3). The organic layers were combined, dried over anhydrous Na_2SO_4, and evaporated to a residue that was purified by column chromatography (98:2 hexanes/EtOAc) to give 3.74 g (74% yield) of **21** as a viscous oil; TLC R_f = 0.6 (98:2 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.00 (s, 1H), 4.74 (s, 1H), 3.97 (d, J = 7.1 Hz, 1H), 3.78−3.66 (m, 1H), 2.33 (dd, J = 14.7, 4.2 Hz, 1H), 2.18−2.07 (m, 1H), 1.95−1.82 (m, 2H), 1.40 (dd, J = 23.0, 11.5 Hz, 1H), 1.34−1.22 (m, 1H), 0.92 (s, 9H), 0.89 (s, 9H), 0.07 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.4, 105.6, 70.5, 69.7, 46.8, 36.6, 30.2, 25.9, 18.4, 18.2, −4.6, −4.9, −5.0; IR (thin film) 1662, 1470, 1077, 835 cm^{-1}; HRMS (ESI) calcd for $[C_{19}H_{41}O_2Si_2]^+$ 357.2640, found 357.2639.

3,3-Di-*tert*-butyl-6-methylene-2,4-dioxa-3-silabicyclo[3.3.1]nonane (22). A 1 M solution of tetrabutyl ammonium fluoride (23.3 mL, 23.3 mmol) was added to a solution of **21** (3.7 g, 10.4 mmol) in THF (93 mL), and the mixture was maintained at room temperature for 1 h. After the starting material was fully consumed as judged by TLC analysis, silica gel was added, and the reaction mixture was evaporated to dryness to give the crude product mixture on silica gel. This solid was loaded onto a prepacked column of silica gel, and the product was eluted with hexanes/EtOAc (gradient elution 50:50 to 0:100; TLC 100% EtOAc, R_f = 0.1) to obtain 1.34 g of impure diol as a viscous oil that was used without further purification. A mixture of the diol (610 mg, 4.76 mmol), CH_2Cl_2 (98 mL), and distilled 2,6-lutidine (2.2 mL, 19.0 mmol) was maintained under a nitrogen atmosphere, and t-$Bu_2Si(OTf)_2$ (1.7 mL, 5.23 mmol) was added dropwise within 2 min. The reaction mixture was maintained at room temperature for 24 h at which point saturated aqueous NH_4Cl (100 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (30 mL × 3). The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, and evaporated to provide a residue that was purified by column chromatography (100:0 to 96:4 hexanes/EtOAc) to give 975 mg (76% yield) of **22** as a viscous oil. *Note:* Best results were obtained when the silica gel column was packed with 100% hexanes containing 0.5% Et_3N prior to loading the crude product; the mobile phase used for elution did not contain Et_3N; TLC R_f = 0.9 (96:4 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.86 (s, 1H), 4.75 (s, 1H), 4.51 (s, 1H), 4.36 (s, 1H), 3.13−3.04 (m, 1H), 2.67 (ddd, J = 14.7, 6.8, 3.7 Hz, 1H), 2.13 (dd, J = 15.3, 6.3 Hz, 1H), 2.09−2.02 (m, 1H), 1.64−1.51 (m, J = 6.9 Hz, 2H), 1.07 (s, 9H), 1.05 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.4, 110.3, 73.6, 67.8, 37.1, 33.4, 29.1, 28.4, 24.8, 21.6, 21.4; IR (thin film) 1652, 1480, 1106 cm^{-1}; HRMS (ESI) calcd for $[C_{15}H_{29}O_2Si]^+$ 269.1931, found 269.1928.

3,3-Di-*tert*-butyl-2,4-dioxa-3-silabicyclo[3.3.1]nonan-6-one (23). In a two-necked RBF, a solution of **22** (950 mg, 3.54 mmol) in CH_2Cl_2 (50 mL) was cooled to −78 °C, and ozone gas was bubbled through the solution in an efficient fume hood until the solution became blue (~5−10 min) at which point the solution was purged with N_2 until it became colorless. Triphenylphosphine (4.60 g, 17.7 mmol) was added, and the reaction mixture was warmed to room temperature. After maintaining the reaction mixture at room temperature for 3 h, the solvent was evaporated, and the crude product was purified by column chromatography (100:0 to 90:10 hexanes/EtOAc) to provide 662 mg (69% yield) of **23** as a white waxy solid. *Note:* Best results were obtained when the silica gel column was packed with 100% hexanes containing 0.5% Et_3N prior to loading the crude product; the mobile phase used for elution did not contain Et_3N. TLC R_f = 0.5 (92:8 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.44 (d, J = 1.1 Hz, 1H), 4.21 (d, J = 3.8 Hz, 1H), 3.27 (ddd, J = 16.8, 10.5, 8.8 Hz, 1H), 2.88 (ddd, J = 15.5, 7.8, 3.9 Hz, 1H), 2.34 (dd, J = 15.2, 7.7 Hz, 2H), 2.03−1.92 (m, 1H), 1.79 (d, J = 15.6 Hz, 1H), 1.09 (s, 9H), 1.05 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.9, 74.6, 66.5, 35.6, 33.0, 32.9, 28.7, 27.8, 21.3, 21.2; IR (thin film) 1720, 1121 cm^{-1}; HRMS (ESI) calcd for $[C_{14}H_{27}O_3Si]^+$ 271.1724, found 271.1721.

Ethyl 2-(3,3-Di-*tert*-butyl-6-hydroxy-2,4-dioxa-3-silabicyclo-[3.3.1]nonan-6-yl)-2-diazoacetate (24). Diazo ester **24** was prepared from **23** (618 g, 2.28 mmol) using the procedure described for the synthesis of diazo ester **13**. The reaction mixture was purified by silica gel column chromatography (96:4 to 85:15 hexanes/EtOAc) to give 665 mg (76% yield) of diazo ester **24** as a yellow amorphous solid. *Note:* Best results were obtained when the silica gel column was packed with 96:4 hexanes/EtOAc containing 0.5% Et_3N prior to loading the crude product; the mobile phase used for elution did not contain Et_3N. TLC R_f = 0.5 (88:12 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.74 (d, J = 4.3 Hz, 1H), 4.27 (s, 1H), 4.26−4.18 (m, 2H), 3.38 (s, 1H), 2.72−2.58 (m, 2H), 1.99 (d, J = 11.8 Hz, 1H), 1.81 (dd, J = 15.1, 4.9 Hz, 1H), 1.71 (d, J = 15.4 Hz, 1H), 1.51 (tdd, J = 14.4, 5.1, 3.0 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H), 1.12 (s, 9H), 1.11 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.4, 73.4, 71.4, 66.4, 61.2, 60.7, 32.4, 30.5, 29.1, 28.6, 27.2, 21.6, 21.5, 14.4; IR (thin film) 3520, 2089, 1700, 1128, 1015 cm^{-1}; HRMS (ESI) calcd for $[C_{18}H_{32}N_2O_5SiNa]^+$ 407.1973, found 407.1970.

(*E*)-Ethyl 8-Oxooct-6-en-2-ynoate (27). Aldehyde **27** was synthesized from diazo ester **24** (100 mg, 0.26 mmol) using the procedure described for the synthesis of **17** except the reaction was allowed to warm to room temperature and was then maintained at room temperature for 12 h. The crude reaction mixture was purified by silica gel column chromatography (100% CH_2Cl_2) to provide 39 mg (83% yield) of aldehyde **27** as a viscous oil. TLC R_f = 0.1 (92:8 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.49 (d, J = 7.7 Hz, 1H), 6.81 (dt, J = 15.7, 6.4 Hz, 1H), 6.13 (ddt, J = 15.6, 7.7, 1.4 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 2.61−2.55 (m, 2H), 2.55−2.45 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.3, 154.0, 153.3, 133.8, 86.2, 74.1, 61.8, 30.2, 17.2, 13.8; IR (thin film) 2826, 2749, 2238, 1706, 1691, 1640, 1253, 1126, 1070 cm^{-1}; HRMS (ESI) calcd for $[C_{10}H_{13}O_3]^+$ 181.0859, found 181.0859.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(21) What appears to be the ring expansion product was observed in the proton NMR spectrum of the crude reaction mixture in only small quantities (~15%); it is not clear if the complexity of the mixture is the result of decomposition of the ring expansion product, which would be an allylic silyl ether.
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Synthesis of Demissidine by a Ring Fragmentation 1,3-Dipolar Cycloaddition Approach

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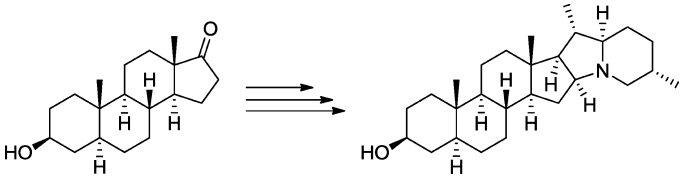
ABSTRACT



A synthesis of the steroidal alkaloid demissidine from epiandrosterone is reported. A ring fragmentation reaction that efficiently ruptured the D-ring of a diazo ester derivative of epiandrosterone to provide an aldehyde tethered ynoate product was key to this sequence. Incorporation of the indolizidine framework was achieved by an azomethine ylide 1,3-dipolar cycloaddition.

The *Solanum* alkaloids are steroidal glycoalkaloids isolated from potatoes and other Solanaceous plants. These toxic alkaloids are known to act as natural insect deterrents,[1] have antimicrobial properties,[2,3] can inhibit acetylcholinesterase,[4] and can disrupt cell membranes.[5] Demissine, commersonine (Figure 1), and their aglycon steroidal alkaloid demissidine (Scheme 1) are the principal alkaloids isolated from several wild potato species including *Solanum demissum*[6] and *Solanum acaule*.[7] Demissidine is structurally similar to solanidine (5-dehydrodemissidine), the steroidal alkaloid aglycon of solanine, the principal alkaloid isolated from *Solanum tuberosum*, the crop potato.

Demissidine was prepared by Kuhn et al.[8] in 1952 and later by Sato and Latham[9] by semisynthesis from the related steroidal alkaloid dihydrotomatidine. In 1963

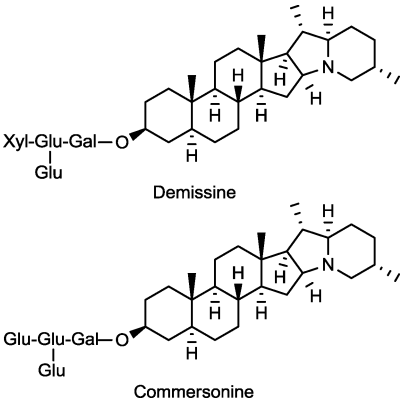


Figure 1. Structure of demissine and commersonine. Abbreviations: Gla = galactose; Glu = glucose; Xyl = xylose.

Adam and Schreiber[10] prepared demissidine in low yields from pregnenolone acetate by addition of 2-lithio-5-methylpyridine followed by unselective hydrogenation and a Hofmann–Löffler–Freytag cyclization. In this letter we report an efficient synthesis of demissidine from epiandrosterone by a sequence that involves a ring

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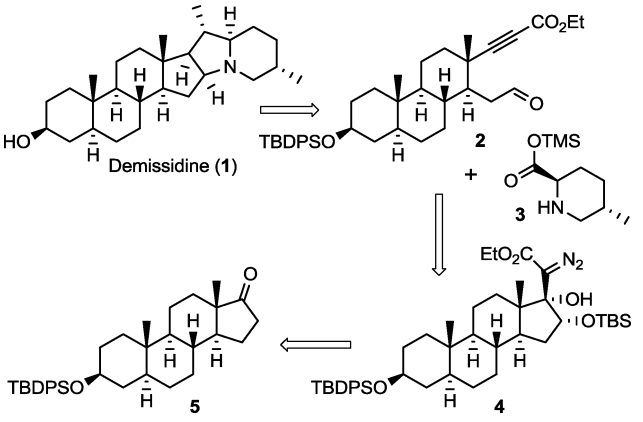
fragmentation and a 1,3-dipolar cycloaddition as key steps.

Our synthetic approach to demissidine takes advantage of our discovery that γ-silyloxy-β-hydroxy-α-diazocarbonyls undergo efficient rupture of the Cγ−Cβ bond in the presence of a Lewis acid to provide tethered aldehyde ynoates or ynones in high yield.[11,12] These bifunctional molecules are excellent precursors for intramolecular azomethine ylide 1,3-dipolar cycloadditions and give polycyclic 2,5-dihydropyrrole products in high yield.[13] As shown in Scheme 1, we envisioned using this sequence of reactions to create the indolizidine framework contained in demissidine. The requisite steroid-based tethered aldehyde ynoate (**2**) would be formed by fragmentation of γ-silyloxy-β-hydroxy-α-diazoester **4**, which in turn could be prepared from epiandrosterone.

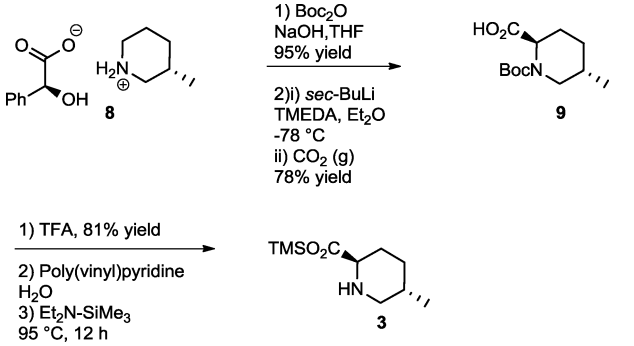
Our synthetic route started from epiandrosterone (**6**), which was converted into α-hydroxy ketone **7** (Scheme 2) by a modification of the procedure reported by Numazawa and Nagaoka[14] for the conversion of epiandrosterone to 16-hydroxy epiandrosterone. This sequence involved a $CuBr_2$ mediated bromination α to the ketone followed by protection of the secondary alcohol as the *tert*-butyldiphenylsilyl ether and subsequent displacement of bromide with hydroxide to provide alcohol **7**. Protection of the free alcohol as the TBS ether and subsequent aldol type addition of ethyl lithiodiazoacetate to the carbonyl provided *syn*-diol **4** in 61% yield over the two steps. Treating diazo **4** with $SnCl_4$ resulted in fragmentation of the steroid's D-ring to provide aldehyde tethered ynoate **2** in 75% yield.

With the requisite dipolar cycloaddition precursor in hand we turned our attention to preparing (5*S*)-5-methylpipecolic acid (Scheme 3). This was most conveniently achieved by resolution of racemic 3-methylpiperidine by cocrystallization with (*S*)-mandelic acid as described by Wong et al.[15] to provide (*S*)-3-methylpiperidine•(*S*)-mandelate in 98% ee.[16] Boc protection of the amine followed by α-lithiation[17−19] and trapping with CO_2 provided *N*-Boc-(2*R*,5*S*)-5-methylpipecolic acid (**9**) in 78% yield as a single diastereomer.[20] Subsequent TFA mediated Boc removal provided the TFA salt of (2*R*,5*S*)-5-methylpipecolic acid in 81% yield. In prior studies[13] we had noted that aldehyde tethered ynoates reacted with amino acids via a decarboxylative intramolecular azomethine ylide 1,3-dipolar cycloaddition more productively when the amino acid component was protected as the trimethylsilyl ester. With this in mind, the TFA salt of the amino acid was passed

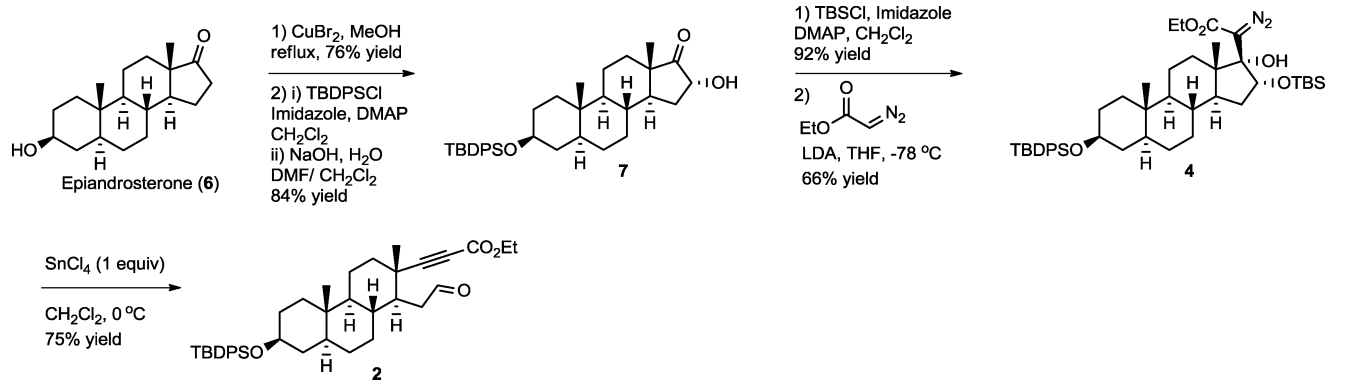
Scheme 1. Retrosynthetic Analysis of Demissidine



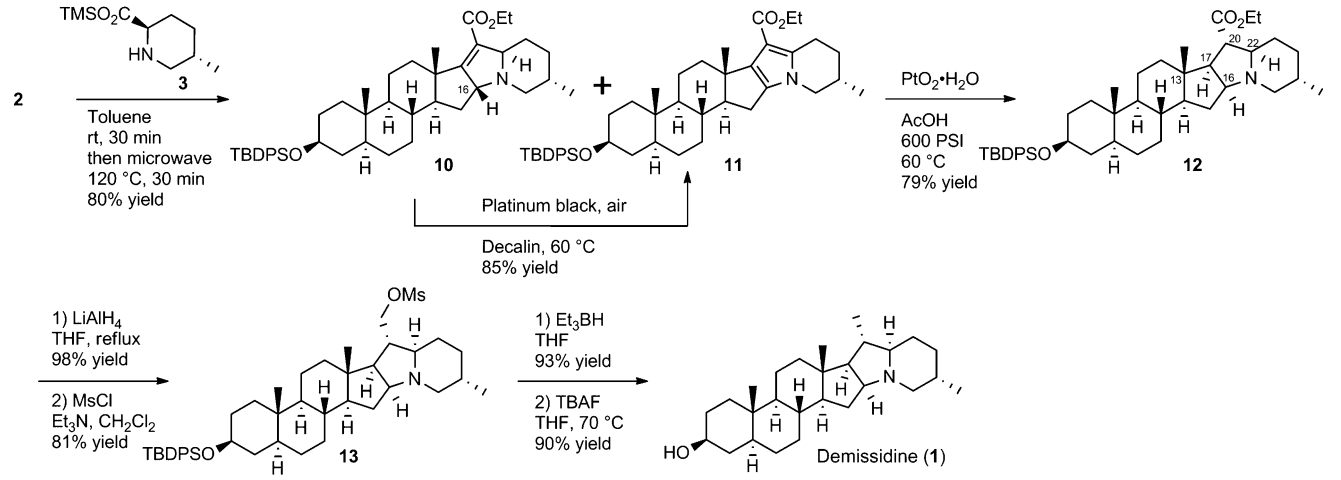
Scheme 3. Preparation of (5*S*)-5-Methylpipecolic Acid



Scheme 2. Preparation of Steroid-Based Tethered Aldehyde Ynoate



Scheme 4. Synthesis of Demissidine



through poly(vinylpyridine) to provide the free base,[21] which was treated with *N,N*-diethyltrimethylsilylamine to give the requisite amino acid silyl ester (**3**).

The key azomethine ylide 1,3-dipolar cycloaddition of aldehyde ynoate **2** and silyl ester **3** proceeded smoothly to provide an easily separable mixture of dihydropyrrole **10** and pyrrole **11** in a combined 80% yield in a ratio that varied from 2:1 to 1:1 (Scheme 4).[22] The formation of dihydropyrrole **10** was exquisitely diastereoselective, but unfortunately provided the product with incorrect stereochemistry at the C_{16} position.[23] Attempts to epimerize the C_{16} vinylogous ester position via deprotonation failed. We reasoned that hydrogenation of the fortuitously formed pyrrole **11** might lead to the corresponding pyrrolidine with the correct stereochemistry at C_{16}, C_{17}, and C_{22} if the angular methyl were to prevent the catalyst from approaching the methyl bearing face. In the event, hydrogenation of pyrrole **11** over PtO_2 in acetic acid at 60 °C and 600 psi provided the pyrrolidine product in a uniquely diastereoselective manner in which all of the protons were delivered from the face opposite the C_{13} angular methyl. We were pleased to note that extending the reaction time led to in situ epimerization at C_{20} and provided the desired pyrrolidine product **12** in which all the stereocenters were set correctly. Although pyrrole **11** is presumably formed by air oxidation of dihydropyrrole **10** during the 1,3-dipolar cycloaddition reaction, attempts to increase the yield of pyrrole **11** by extending the reaction time in the presence of oxygen failed. However, platinum black[24] dehydrogenated dihydropyrrole **10** to provide pyrrole **11** in 85% yield.

To complete the synthesis of demissidine, the ethyl ester was reduced by lithium aluminum hydride to the corresponding primary alcohol in 98% yield, which was in turn converted to mesylate **13** in 81% yield. Reductive cleavage of the mesylate by lithium triethylborohydride proceeded in 93% yield to give the requisite methyl at position C_{20} of the steroid. Removal of the silyl protecting group occurred in 90% yield to provide demissidine.

In summary, demissidine has been synthesized from epiandrosterone. This synthetic approach takes advantage of a Lewis acid mediated fragmentation of a γ-silyloxy-β-hydroxy-α-diazoester to provide a tethered aldehyde ynoate. This key intermediate was successfully used in a subsequent azomethine ylide 1,3-dipolar cycloaddition to provide the indolizidine framework present in the natural product.

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(23) The relative stereochemistry at C16 was assigned based on the oberservation of a positive NOE between the C16 proton and the angular methyl at C13.
(24) Platinum black was formed by suspending platinum oxide in decalin under an atmosphere of hydrogen gas for 2 h. The dark black solid was isolated by filtration, placed under vacuum overnight, and then exposed to air for 1 h before use.

of Vermont) for assistance with NMR characterization. This work was financially supported by the NIH (National Institute of General Medical Sciences Award Number R01GM092870) and was made possible by use of a facility supported by the Vermont Genetics Network through Grant Number 8P20GM103449 from the INBRE Program of the National Institute of General Medical Sciences (NIGMS), a component of the National Institutes of Health (NIH). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIGMS or NIH. The National Science Foundation supported this work through instrumentation grants CHE-1126265 and CHE-0821501.

Supporting Information Available. Experimental procedures, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Formal and total synthesis of (±)-cycloclavine

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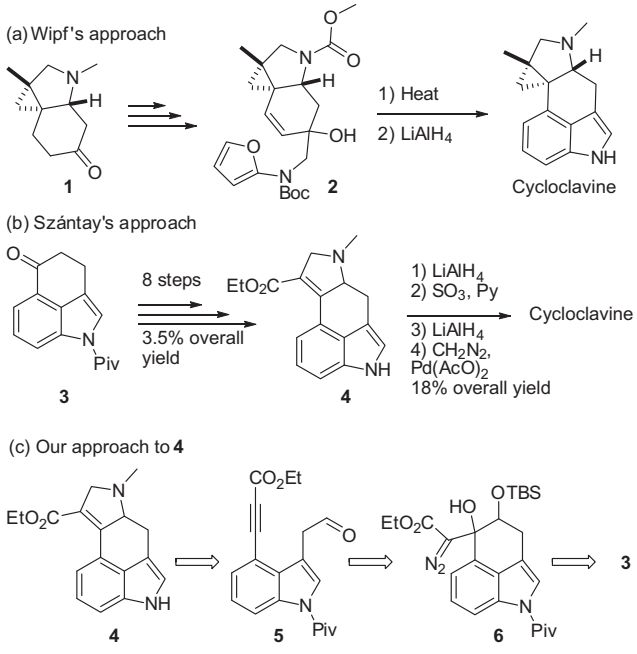
ABSTRACT

A ring fragmentation and intramolecular azomethine ylide 1,3-dipolar cycloaddition sequence of reactions was successfully used in the preparation of a known (±)-cycloclavine precursor in good overall yield. Results of efforts to incorporate the tetrasubstituted cyclopropane ring present in cycloclavine are also discussed.

Cycloclavine, an indole alkaloid first isolated in 1969 from seeds of *ipomoea hildebrandtii* by Hofmann and co-workers,[1] is a member of the ergot alkaloid family. The unique tetracyclic core of cycloclavine contains a tetrasubstituted cyclopropane moiety and has garnered interest from the synthetic community; to date two total syntheses of cycloclavine have been reported.[2] Most recently, Petronijevic and Wipf[2b] prepared (±)-cycloclavine in 14 linear steps with 1.2% overall yield by an elegant and unconventional approach in which the aromatic indole portion of the molecule was formed at a late stage in the synthesis by their intramolecular Diels–Alder cycloaddition of furan (IMDAF reaction) approach.[2b] Prior to this synthesis, Szántay and co-workers[2a] reported a more traditional approach to (±)-cycloclavine starting from pivalate protected Uhle's ketone (**3**)[3] (Scheme 1), which was advanced to tetracycle **4** in 8 steps. Reduction of the ethyl ester of **4** to the corresponding methyl group and Pd catalyzed cyclopropanation with diazomethane provided the target molecule. While this is a nice straightforward approach to (±)-cycloclavine, the route to tetracycle **4** was hampered by several low yielding steps and provided **4** in only 3.5% overall yield.

We recently reported an efficient synthetic approach to polycyclic 2,5-dihydropyrroles[4] that we have applied in the synthesis of the steroidal alkaloid demissidine.[5] This strategy is based on our report that cyclic γ-siloxy-β-hydroxy-α-diazocarbonyl compounds fragment when treated with $SnCl_4$ to provide tethered aldehyde ynoates,[6] which are excellent substrates for intramolecular azomethine ylide 1,3-dipolar cycloadditions, which in turn provide the desired 2,5-dihydropyrrole products. The fragmentation cycloaddition sequence appears to be fairly general, and we recognized that this reaction sequence might provide an efficient route to Szántay's tetracyclic 2,5-dihydropyrrole intermediate **4**. In this Letter we report our results on the formation of **4** and provide details about our efforts to advance **4** to (±)-cycloclavine.



Scheme 1. Synthetic approaches to cycloclavine.

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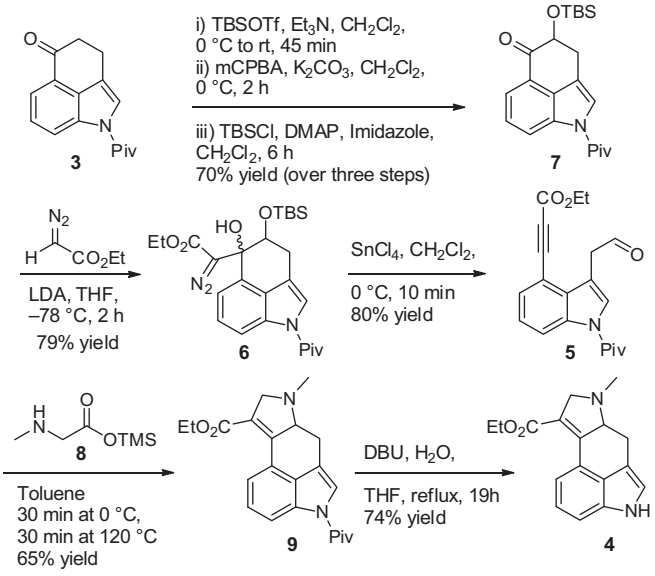
Our synthetic efforts, shown in Scheme 2, also began with pivalate protected Uhle's ketone (**3**),[3] which was converted into the corresponding enoxy silane by treatment with TBSOTf and Et_3N. This enoxy silane proved to be unstable to silica gel chromatography and after extractive workup it was subjected directly to Rubottom oxidation[7] under biphasic conditions containing aqueous base.[8] The oxidation proceeded efficiently but provided the α-hydroxy ketone as a mixture of the free and silyl protected alcohols. Treating the crude reaction mixture with TBSCl provided the desired α-silyloxy ketone (**7**) in 70% yield over the three steps. Aldol type addition of ethyl lithiodiazoacetate to ketone **7** furnished the corresponding γ-silyloxy-β-hydroxy-α-diazo ester derivative **6** as an inseparable mixture of diastereomers in 79% yield. We were pleased to observe that treating the diastereomeric mixture of **6** with $SnCl_4$ resulted in efficient rupture of the C_β–C_γ bond to provide tethered aldehyde ynoate **5** in 80% isolated yield. Reacting aldehyde ynoate **5** with the trimethylsilyl ester of sarcosine (**8**) resulted in the expected intramolecular azomethine ylide 1,3-dipolar cycloaddition to give the tetracyclic core of cycloclavine as 2,5-dihydropyrrole **9** in 65% yield. We attribute the moderate yield of this reaction to the instability of the sarcosine silyl ester which tended to dimerize under the reaction conditions. While optimizing this fragmentation cycloaddition sequence we observed that purifying the fragmentation product by chromatography prior to cycloaddition was not necessary. In fact, when the crude fragmentation product was used the overall yield for the two step sequence increased to 62%. We attribute this 10% increase in yield to losses of aldehyde ynoate **5** during chromatography. DBU mediated pivaloyl cleavage[9] from **9** provided tetracycle **4**, which intersects with Szántay's prior synthesis and thus completes a formal synthesis of cycloclavine. Overall, this ring fragmentation/cycloaddition approach provided Szántay's intermediate in seven steps and 25% overall yield.

With efficient access to protected indole intermediate **9** in place, we assessed various alternative strategies to incorporate the tetrasubstituted cyclopropane ring present in cycloclavine. Pyrazolines are well known cyclopropane precursors[10] and we envisioned converting enoate **9** into the corresponding pyrazoline via 1,3-dipolar cycloaddition with diazomethane. Unfortunately, enoate **9** failed to react with diazomethane even after prolonged reaction times. We next attempted to incorporate the cyclopropane moiety by a Corey–Chaykovsky cyclopropanation reaction.[11]



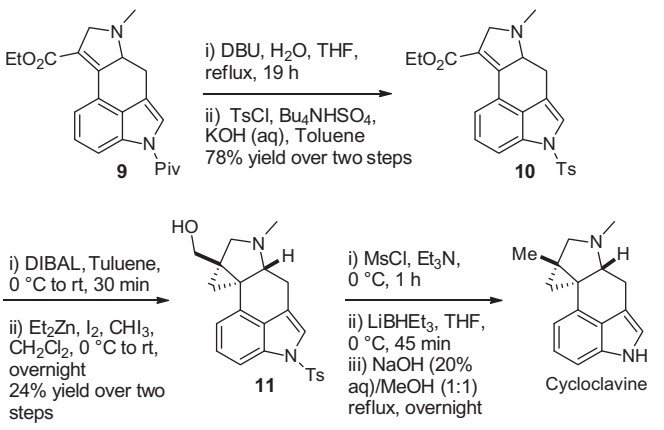
Scheme 2. Formal synthesis of cycloclavine.

However, the pivaloyl protecting group proved to be too labile for these nucleophilic conditions and only N-deprotected indole **4** was returned. To circumvent this problem, we exchanged the pivaloyl group with a more stable tosyl group via a two-step sequence (Scheme 3).[9,12] Unfortunately, Corey–Chaykovsky cyclopropanation of tosyl derivative **10** also failed to furnish any cyclopropane product; only starting material and decomposition products were returned. These results were surprising to us because Corey–Chaykovsky cyclopropanation of similar systems has been reported.[13]

Allylic hydroxyl groups are well known to act as directing groups in metal mediated cyclopropanation reactions.[14] With this in mind we subjected **10** to DIBALH reduction to generate the corresponding allylic alcohol and subjected this material to various metal carbenoid cyclopropanation reactions. Unfortunately, cyclopropanation reactions mediated by Zn,[15] Sm,[16] Pd,[17] Mg,[18] and Cr[19] all failed to provide any of the desired cyclopropane product. Ultimately, we observed that the gem-dizinc carbenoid conditions developed by Charette and co-workers[20] provided the desired cyclopropane (**11**), albeit in low and variable yields. For reasons we do not understand, this reaction was only successful when the allylic alcohol used was a crude material isolated from the preceding DIBALH reduction after aqueous workup, in which case cyclopropane **11** was formed in up to 24% yield over the two steps. When the allylic alcohol was purified by chromatography, the cyclopropanation consistently failed to provide any desired cyclopropane product.

With small quantities of cyclopropane intermediate **11** in hand we were able to complete the total synthesis of (±)-cycloclavine. This was achieved by mesylation of the primary alcohol followed by nucleophilic displacement with hydride to give the requisite methyl, and subsequent hydrolysis of the sulfonamide. Unfortunately, due to limited and inconsistent access to cyclopropyl intermediate **11** these final steps were not optimized.

In summary, a ring fragmentation/intramolecular azomethine ylide 1,3-dipolar cycloaddition route to 2,5-dihydropyrroles was successfully used in the preparation of (±)-cycloclavine. Attempts to incorporate the cyclopropane moiety of cycloclavine through a directed cyclopropanation reaction were moderately successful, but did not represent an improvement over Szántay's prior work. However, this route to known cycloclavine precursor **4** was significantly higher yielding (25% overall yield) than the published route to **4**, and increases the overall yield of the prior synthesis of (±)-cycloclavine to 4%. These results further highlight the synthetic utility of the fragmentation/cycloaddition sequence for the construction of polycyclic 2,5-dihydropyrroles in natural product synthesis.



Scheme 3. Synthesis of cycloclavine.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.152.

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Fragmentation of Bicyclic γ-Silyloxy-β-hydroxy-α-diazolactones as an Approach to Ynolides

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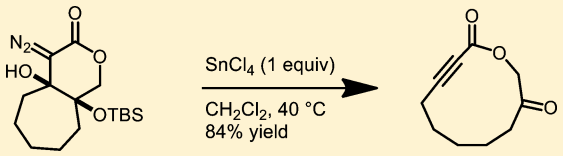
Supporting Information

ABSTRACT: Medium-sized ynolides were prepared by the Lewis acid-mediated fragmentation of bicyclic γ-silyloxy-β-hydroxy-α-diazolactones in which the Cβ−Cγ bond is the ring fusion bond. Although these lactone fragmentation substrates reacted somewhat less efficiently than their carbocyclic counterparts, the fragmentation provided 11-membered ynolides in up to 84% yield. Unlike prior fragmentations of similar substrates, elevated temperatures were required to obtain optimum yields of the ynolide products. The ynolides reported herein have ring sizes of 10 or 11, which are the smallest reported to date.

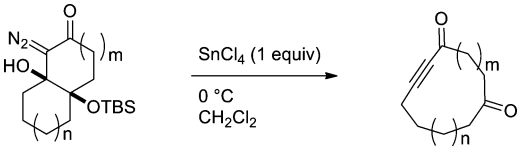


INTRODUCTION

Medium and large rings are common scaffolds in biologically active compounds, and there is growing interest in exploring macrocycles in therapeutic drug discovery programs.[1−4] Thus, the development of methods to prepare these structures is an important and ongoing area of research.[2,3] Large-ring lactones that contain an alkyne within the ring (i.e., ynolides[5,6]) are not common species but have proven to be useful synthetic intermediates in a number of macrolide natural product syntheses. For example, Smith and Malamas[7] subjected an ynolide intermediate to partial reduction as a way to stereoselectively form a *cis*-alkene in their synthesis of *cis*-normethyljatropholactone. Macrolactonization of alkynoates followed by partial reduction has also been used in the syntheses of phorboxazole B[8−10] and laulimalide[11−20] as a way to circumvent isomerization of the requisite *cis*-enoate during the macrolactonization step. In addition, Danishefsky and co-workers took advantage of ynolides as Diels−Alder dienophiles in their approach to resorcinylic fused macrolides.[5,6] These useful synthetic intermediates have been typically prepared through conventional macrocycle formation techniques, namely, macrolactonization and alkene or alkyne ring-closing metathesis.[21] In addition, Ogasawara and co-workers[22] reported a Pd-catalyzed carbomacrolactonization procedure that provides moderate yields of ynolides that are 15-membered or larger. Unfortunately, all of these strategies suffer from the common limitation of macrocyclization strategies, namely, the requirement of high-dilution conditions. To the best of our knowledge, no ynolides having a ring size smaller than 14 have been reported.

We recently disclosed that bicyclic γ-silyloxy-β-hydroxy-α-diazoketones in which the Cβ-Cγ bond is the ring fusion bond fragment in the presence of a Lewis acid to provide 10-, 11-, and 12-membered cyclic 2-alkynones in good to excellent yields (Scheme 1).[23] In view of the fact that γ-silyloxy-β-hydroxy-α-diazoesters fragment as efficiently as their ketone analogues,[24,25] we sought to extend this methodology to the preparation of the corresponding medium- and large-ring ynoates by fragmentation of bicyclic diazo lactones. While ultimately successful in delivering 10- and 11-membered ynolides, the fragmentation of these bicyclic lactones was not as straightforward as the fragmentation of the corresponding ketone species, and we describe our results herein.

Scheme 1. Formation of Medium- and Large-Ring Ynones



1a; n=1, m=1 — **2a**; 80%
1b; n=2, m=1 — **2b**; 99%
1c; n=3, m=1 — **2c**; 93%
1d; n=1, m=0 — **2d**; 3%
1e; n=1, m=2 — **2e**; 67%

RESULTS AND DISCUSSION

Our initial target for these studies was 10-membered ynolide **9** that we envisioned would come from fragmentation of diazo lactone **8**, which we prepared as shown in Scheme 2. Formylation of cyclohexanone with the Vilsmeier reagent[26] followed by reduction with sodium borohydride[27] gave allylic alcohol **4** in 75% yield over the two steps. Subsequent dihydroxylation with osmium tetroxide provided 1,2-ketodiol **5** in an unoptimized yield of 34%. Reaction of **5** with *p*-toluenesulfonylhydrazone glyoxylic acid chloride (**6**)[28] provided diazoester **7**, which was then treated with DBU to effect an intramolecular aldol addition providing the requisite bicyclic diazo lactone **8** in 37% yield over two steps.[29] Unfortunately, subjecting diazo **8** to the standard fragmentation conditions led only to the formation of an insoluble precipitate; none of the desired fragmentation product was observed. All of the

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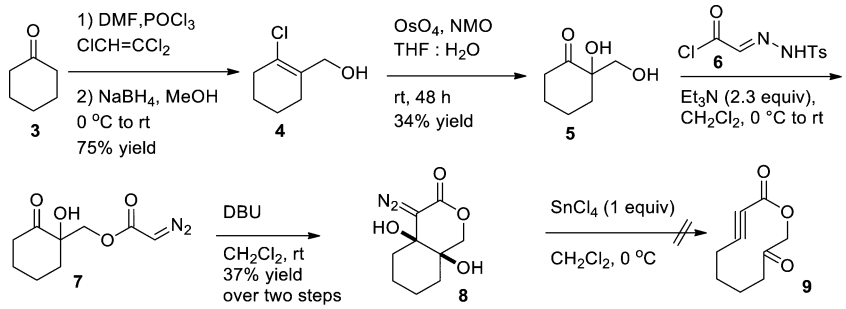
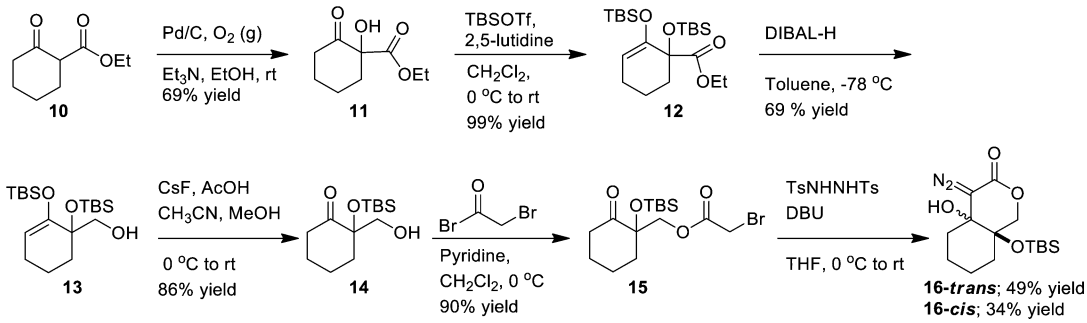
Scheme 2. Synthetic Route to Bicyclic β,γ-Dihydroxy-α-diazolactone 8



Scheme 3. Synthesis of Bicyclic Diazo Lactone Fragmentation Precursors 16



fragmentation substrates we previously studied had the γ-oxygen protected as a silyl ether, and with this in mind we attempted to convert diol **5** into the bis(*tert*-butyldimethylsilyl) ether and then selectively deprotect the primary alcohol. Unfortunately, these attempts were not successful.

Ultimately, we prepared γ-silyloxy-β-hydroxy-α-diazolactone **16** by the route shown in Scheme 3. Pd-mediated α-oxygenation[30] of commercially available ethyl 2-oxocyclohexanecarboxylate (**10**) gave α-hydroxy-β-keto ester **11**, which was converted into bis(silyl ether) **12** in which the ketone is conveniently protected as the silyl enol ether. Reduction of the ester with DIBAL-H and subsequent selective cleavage of the silyl enol ether with CsF in acetic acid provided keto alcohol **14**, and acylation of the primary alcohol with bromoacetyl bromide gave bromoacetate **15**. Treatment of **15** with *N,N′*-ditosylhydrazine[31] in the presence of DBU provided the corresponding diazo ester, which spontaneously cyclized to give diazo lactones **16-*trans*** and **16-*cis*** as separable diastereomers.[32]

In view of the high yields we observed for the fragmentation of bicyclic diazo ketones (Scheme 1) and acyclic diazo esters,[25] we were surprised to observe that subjecting diazo lactones **16-*trans*** and **16-*cis*** to the standard fragmentation conditions (i.e., 1 equiv of $SnCl_4$ at 0 °C) provided cyclic ynoate **9** (Figure 1) in only 10% and 12% yield, respectively. We thought that hydrolysis of the strained ynoate might be a facile reaction that would complicate isolation, but carrying out the fragmentation in the presence of molecular sieves did not improve the reaction outcome. We next assessed the ability of other Lewis acids to mediate the fragmentation and found that zinc chloride provided no reaction while indium triflate gave a mixture of epoxide **17** in 5% yield and diene **18** in 31% yield (Figure 1). Treating the fragmentation precursor with $BF_3\cdot OEt_2$ in acetonitrile at 0 °C provided the desired product **9** in only 6% isolated yield. To buffer against any acid that might be formed over the course of the $BF_3\cdot OEt_2$-mediated reaction, we included a proton sponge in the mixture, but this did not provide an increase in the yield. Interestingly, when $BF_3\cdot OEt_2$ was added to a −78 °C solution of the fragmentation precursor in dichloromethane, none of the desired product was formed. Instead, desilylated diene **19**, which had not been observed previously, was formed as the major product. With this in mind, we attempted the fragmentation with $SnCl_4$ at both −78 °C and room temperature. At low temperature the desired product was formed only as a minor component of a complex mixture, but treating the *cis*-fused fragmentation precursor **16-*cis*** with 1 equiv of $SnCl_4$ at room temperature provided the desired lactone product in 21% yield. Ultimately, we discovered that adding **16-*trans*** or **16-*cis*** to a refluxing solution of $SnCl_4$ in dichloromethane provided the desired product in 17% or 33% yield, respectively. Crystallization of **9** from cold methanol provided crystalline material, and the structure of **9** was further confirmed by single-crystal X-ray diffraction, which showed the alkyne to be distorted from linearity by approximately 10°.[33] This distortion is consistent with values computed for cyclodecyne.[34]

In considering why diazo lactone **16-*cis*** fragmented in lower yields than its carbocyclic counterpart **1a** (Scheme 1), we hypothesized that the proximity of the inductively electron-withdrawing ester to the bond that breaks might slow the bond-breaking step and increase the likelihood of competitive side reactions. To evaluate this supposition, we prepared diazoacetate **21** (Scheme 4),[35] which has the ester and the breaking bond in the same relative position as in **16**. Subjecting this

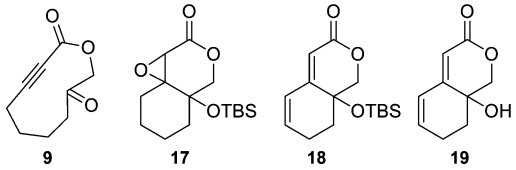


Figure 1. Products observed in various attempts to fragment diazo **16**.

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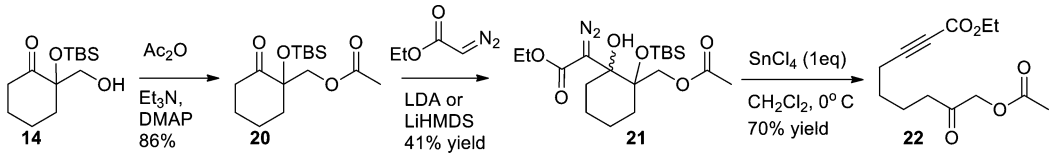
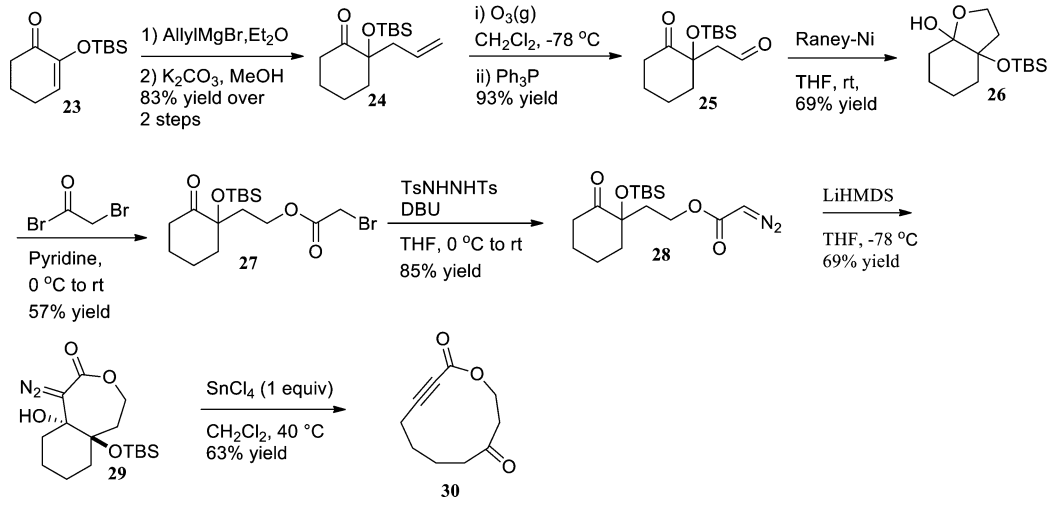
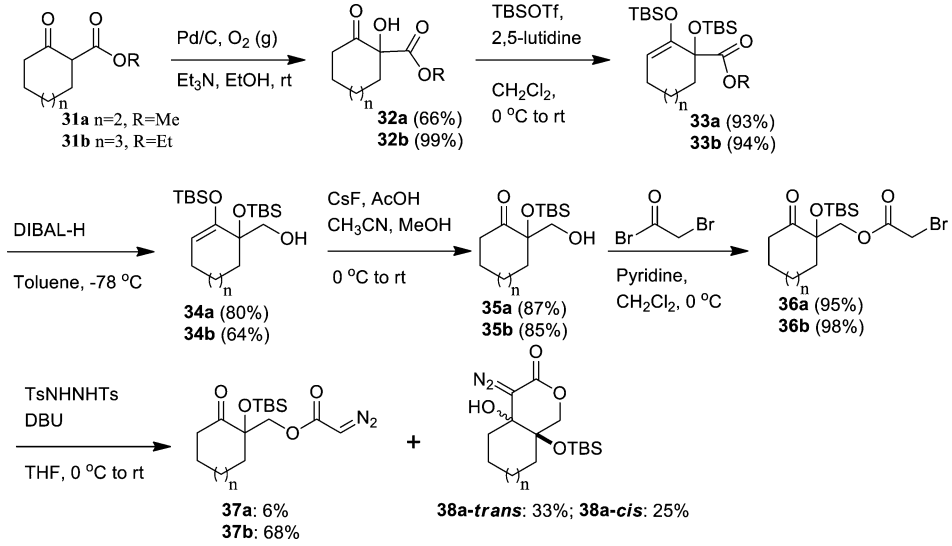
Scheme 4. Preparation of Acetate Diazo Ester 21 and Its Fragmentation



Scheme 5. Preparation and Fragmentation of Diazo Lactone 29



Scheme 6. Preparation of Diazo Lactone 38a and Diazo Ester 37b



compound to the standard fragmentation conditions resulted in a smooth transformation to give ynoate **22** in 70% isolated yield. This result indicates that the low yields observed in the fragmentation of **16** are most likely not due to the position of the electron-withdrawing ester.

To see whether the ring size affected the outcome of the fragmentation reaction, we envisioned preparing homologues of diazo lactone **16** in which either the carbocyclic ring or the ring containing the diazo ester was enlarged. With this in mind, we prepared diazo lactone **29** (Scheme 5), in which the ring bearing the diazo group has been enlarged by one methylene unit. Addition of allylmagnesium bromide to the known 2-silyloxycyclohex-2-enone **23** provided a tertiary alcohol that was converted into ketone **24** via a base-catalyzed silyl transfer reaction.[36] Ozonolysis of alkene **24** provided aldehyde **25** in high yield, and selective reduction of the aldehyde with Raney nickel[37] provided the primary alcohol as hemiacetal **26**. The hemiacetal was converted into diazo ester **28** by acylation and subsequent diazotization as described for the preparation of **16** (Scheme 3), but in this case cyclization did not spontaneously occur. However, treatment of **28** with LiHMDS under dilute conditions at low temperatures effected the ring closure and gave a single diastereomer (tentatively assigned as *trans*) of the desired bicyclic fragmentation precursor **29** in 69% yield. Upon treatment with 1 equiv of $SnCl_4$ at 0 °C, diazo **29** fragmented to provide the 11-membered cyclic ynoate **30** in 50% yield. The yield of **30** increased to 63% when the reaction was run at reflux temperature. The higher yields obtained for this enlarged ring

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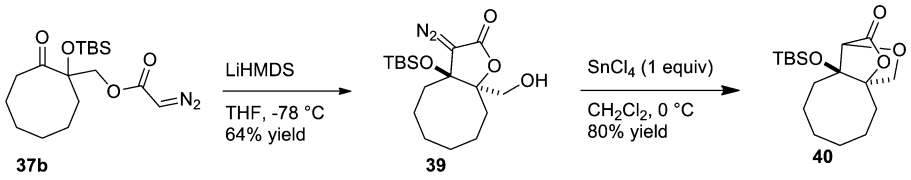
Scheme 7. Base-Mediated Formation and Subsequent Reaction of Diazo Ester 39



37b 39 40

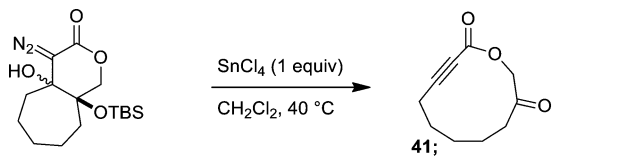
system seem to indicate that ring size does indeed play a role in the fragmentation outcome.

We next focused on preparing homologues of **16** (Scheme 3) in which the carbocyclic ring was expanded by one or two methylene units by routes analogues to that used for the preparation of **16**. While diazotization of **36a** (n = 2; Scheme 6) led directly to the diastereomeric bicyclic fragmentation precursors **38a-*trans*** and **38a-*cis***, diazotization of **36b** (n = 3) provided the linear diazo species **37b**. Interestingly, in our prior work with the carbocyclic derivatives of these diazo compounds[23] we noted a similar difficulty in forming the bicyclo-[4.6.0] ring system (**1c**, Scheme 1) and observed that at equilibrium the system exists predominantly in the ring-opened form. Attempts to convert **37b** to its ring-closed form by treatment with DBU failed to yield any desired product.

In an attempt to drive the ring closure under more strongly basic and nonequilibrating conditions, we treated **37b** with LiHMDS to provide a material we initially assigned as the homologue of **38a-*cis*** in 64% yield. However, attempts to fragment this latter material did not provide any desired ynolide product, which was surprising in view of the fact that the carbocyclic variant **1c** (Scheme 1) had fragmented in 93% yield.[23] Ultimately, full characterization of the cyclization product revealed that it was in fact the spectroscopically similar diazo lactone **39** (Scheme 7). Although the desired ring closure had occurred, the initially formed alkoxide product apparently underwent a subsequent silyl migration and translactonization. We have never encountered silyl migration in any of our prior work with similar substrates, and it is unclear why it occurred in this case. However, considering that the ring-closure step itself is unfavorable, it seems likely that in this case silyl migration is promoted by unfavorable steric interactions in the ring-closed form. This rearrangement is an unanticipated complication that is not possible in the carbocyclic series. Unfortunately, attempts to circumvent this rearrangement have not been fruitful. Subjecting diazo lactone **39** to the standard ring-fragmentation conditions returned cyclic ether **40** in 80% yield.

We were pleased to find that upon treatment with $SnCl_4$ at 0 °C, diazo lactone **38a-*cis*** productively fragmented to give 11-membered cyclic ynoate **41** in 64% yield, while **38a-*trans*** provided the desired product in 57% yield. At 40 °C these yields increased to 84% and 67%, respectively (Scheme 8). These results further support the notion that ring size is an important factor affecting the fragmentation outcome.

Scheme 8. Reactions of Bicyclic Diazo Lactones 38a and 38b



38a-*cis*
38a-*trans*

41;
84% yield from **38a-*cis***
67% yield from **38a-*trans***

CONCLUSIONS

While bicyclo[5.4.0] and -[4.5.0] diazo systems **29** and **38a-*cis*** fragmented to provide the corresponding 11-membered ynolides in 63% and 84% yield respectively, the bicyclo[4.4.0] homologue **16-*cis*** provided the 10-membered ynolide in at best 33% yield; as observed in our prior studies,[23] the corresponding *trans*-fused bicyclic diazo lactones consistently fragmented in slightly lower yields. Attempts to form the bicyclo[4.6.0] diazo lactone system failed because of an unexpected silyl migration and translactonization event. At this point it is clear that the fragmentation of bicyclic diazo lactones to provide ynolide products is not as straightforward or high-yielding as the fragmentation of their carbocyclic counterparts, which gives large-ring ynones (Scheme 1). It is unclear why these systems behave differently, and computational studies to shed light on this interesting reactivity trend are planned. It is noteworthy that the ynolides presented here have the smallest ring size reported to date; all prior examples of this structural motif are 14-membered[2] or larger.

EXPERIMENTAL SECTION[38]

(2-Chlorocyclohex-1-en-1-yl)methanol (4). $POCl_3$ (9.32 mL, 0.1 mmol) was added slowly to a 0 °C solution of DMF (10.84 mL, 0.14 mmol) in trichloroethylene (20 mL) at such a rate as to maintain the reaction temperature below 10 °C. The mixture was allowed to warm to room temperature, and cyclohexanone (11.4 mL, 0.11 mmol) in trichloroethylene (25 mL) was added at such a rate as to maintain the reaction temperature below 60 °C; the reaction mixture was then maintained at 55−60 °C for 3 h. The mixture was cooled in an ice bath, and a solution of NaOAc (40 g) in water (94 mL) was added slowly over 1 h, keeping the reaction temperature below 35 °C. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The organic layers were combined, washed with brine (2 × 200 mL) and water (200 mL), and dried over anhydrous Na_2SO_4. Anhydrous NaOAc (1 g) was added to the dried organic layer, and the solvent was reduced in vacuo. The residue was dissolved in 50 mL of MeOH, and the pH was adjusted to 8 by addition of a 10% aqueous NaOH solution at ice-bath temperature. $NaBH_4$ powder (3.78 g, 0.1 mmol) was added in small portions, and the mixture was stirred overnight at room temperature. The mixture was treated with 90 mL of water and extracted with EtOAc (3 × 90 mL). The organic layers were combined, washed with brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated, and the crude product was purified via flash silica gel chromatography (hexanes/EtOAc 20:1 to 5:1; R_f = 0.62 in hexanes/EtOAc 2:1) to afford the title compound in 75% yield (10.99 g). The ^1H and ^{13}C NMR data for this material matched previously reported values.[26,27]

2-Hydroxy-2-(hydroxymethyl)cyclohexanone (5). OsO_4 (2.78 g, 0.27 mmol) was added to a room-temperature solution of (2-chlorocyclohex-1-en-1-yl)methanol (**4**) (2 g, 13.67 mmol) and NMO (3.20 g, 27.33 mmol) in a mixture of THF (46 mL) and water (23 mL), and the mixture was stirred for 48 h. Then Na_2SO_3 (10 g) was added, and the mixture was stirred for an additional hour. The mixture was filtered through a pad of silica gel, which was then washed with EtOAc (150 mL). The solvents were removed in vacuo to provide an oily residue that was purified by silica gel flash chromatography (hexanes/EtOAc 2:1; R_f = 0.23 in hexanes/EtOAc 1:1) to afford the known compound 2-hydroxy-2-(hydroxymethyl)cyclohexanone as a

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colorless oil (0.66 g, 34%). The ^{1}H and ^{13}C NMR data for this material matched previously reported values.[39,40]

(1-Hydroxy-2-oxocyclohexyl)methyl 2-Diazoacetate (7). 2-Hydroxy-2-(hydroxymethyl)cyclohexanone (**5**) (0.15 g, 1.03 mmol) in CH_2Cl_2 (1 mL) was added to a 0 °C solution of *p*-toluenesulfonylhydrazone glyoxylic acid chloride (**6**)[28,41] (0.29 g, 1.14 mmol) in CH_2Cl_2 (10 mL) to provide a light-yellow solution. Et_3N (0.35 mL, 2.30 mmol) in CH_2Cl_2 (0.7 mL) was added dropwise, causing the color of the reaction mixture to become deep yellow. The reaction mixture was allowed to warm in the ice bath to room temperature over a period of 4 h, at which point the solvent was removed in vacuo. The solid residue was suspended in toluene (10 mL) and mixed with Florisil (1 g), and the solids were removed by filtration and rinsed with toluene (75 mL). The filtrate was concentrated under reduced pressure, and the crude product was used in the next step for the formation of **8** without further purification (R_f = 0.50 in hexanes/EtOAc 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.76 (bs, 1H), 4.72 (d, J = 11.65 Hz, 1H), 4.21 (d, J = 11.72 Hz, 1H), 4.12 (s, 1H), 2.60−2.58 (m, 2H), 2.26−2.22 (m, 1H), 2.16−2.12 (m, 1H), 1.85−1.84 (m, 1H), 1.71−1.65 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.8, 166.6, 78.2, 67.9, 46.5, 38.4, 38.1, 27.7, 22.7; IR (film) 3500 (br), 2940.1, 2866.2, 2111.7, 1692.9, 1453.2, 1389.7, 1337.9, 1246.2, 1175.2, 1128.1, 1050.7, 1008.1, 851.2, 738.6 cm^{-1}.

***rel*-(4a*S*,8a*R*)-4-Diazo-4a,8a-dihydroxyhexahydro-1*H*-isochromen-3(4*H*)-one (8).** DBU (0.15 mL, 0.97 mmol) was added dropwise to a solution of diazoester **7** (0.14 g, 0.65 mmol) in CH_2Cl_2 (13 mL) at room temperature, and the mixture was stirred for 12 h, at which point saturated aqueous NH_4Cl (15 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and filtered. The filtrate was evaporated under reduced pressure to give an orange-red oily residue. Flash column chromatography (hexanes/EtOAc 3:1; R_f = 0.21 in hexanes/EtOAc 1:1) on a Davisil solid support provided the title bicyclic diazo lactone as a yellow solid in 37% yield (0.081 g) over two steps starting from **5**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.29 (d, J = 11.4 Hz, 1H), 4.17 (bs, 1H), 3.90 (d, J = 10.3 Hz, 1H), 3.15 (s, 1H), 1.96 (t, J = 11.6 Hz, 1H), 1.82−165 (m, 5H), 1.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 71.5, 70.9, 68.2, 63.0, 32.6, 30.8, 22.4, 20.5; IR (film) 3371.6, 2935.9, 2106.1, 1659.4, 1392.3, 1298.60 cm^{-1}; MS (ESI) calcd for $[C_9H_{12}N_2O_4H]^+$ 213.08698, found 213.08715.

4-Oxacyclodecyne-3,6-dione (9). *Representative Experimental Procedure 1: Fragmentation Reactions Conducted at 0 °C and at Room Temperature.* A 1 M solution of $SnCl_4$ in CH_2Cl_2 (0.25 mL, 0.25 mmol) was added in a steady stream to a solution of bicyclic diazo lactone ***16-cis*** (0.0826 g, 0.25 mmol) in dry CH_2Cl_2 (6.3 mL) at 0 °C. The yellow solution initially turned colorless and then became deep yellow in color. After 30 min, 5% aqueous $NaHCO_3$ (12 mL) was added, and the mixture was transferred with the aid of CH_2Cl_2 (10 mL) into a separatory funnel. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined and dried over anhydrous $NaSO_4$. The solvents were removed in vacuo, and the residue was subjected to flash column chromatography on Davisil (hexanes/EtOAc 10:1, 6:1, 1:1; R_f = 0.13 in hexanes/EtOAc 1:1) to afford pure cyclic ynoate **9** in 12% yield (0.005 g). The yield increased to 21% (0.0089 g) when the same procedure was followed at room temperature. According to the same procedure at 0 °C, diazo lactone ***16-trans*** provided the title compound in 10% yield as determined via NMR analysis using mesitylene as an internal standard. Crystallization from cold methanol provided crystals suitable for X-ray crystallography (mp 95 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.85 (s, 2H), 2.53−2.50 (m, 2H), 2.39 (t, J = 6.0 Hz, 2H), 2.04−1.99 (m, 2H), 1.86−1.82 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.5, 153.5, 99.9, 74.7, 72.2, 41.0, 25.5, 24.6, 19.7; IR (film) 2923.3, 2854.8, 2229.8, 1734.1, 1558.6, 1454.4, 1376.3, 1280.8, 1194.9, 1124.6, 1078.3, 1037.7, 985.7, 922.0, 738.8 cm^{-1}; MS (ESI) calcd for $[C_9H_{10}O_3H]^+$ 167.07027, found 167.07016.

Representative Experimental Procedure 2: Fragmentation Reactions Conducted at 40 °C. A 1 M solution of $SnCl_4$ in CH_2Cl_2 (0.25 mL, 0.25 mmol) was added to refluxing CH_2Cl_2 (4 mL), and bicyclic diazo lactone ***16-cis*** (0.0818 g, 0.25 mmol) in dry CH_2Cl_2 (1 mL) was then added in one portion. The vial containing the bicyclic diazo lactone was rinsed with 1.3 mL of CH_2Cl_2, and this too was added to the refluxing reaction mixture. The mixture was held at reflux for 10 min and then cooled in an ice bath, at which point 5% aqueous $NaHCO_3$ (8 mL) was added and the mixture was transferred with the aid of CH_2Cl_2 (10 mL) into a separatory funnel. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined and dried over anhydrous Na_2SO_4. The solvents were removed in vacuo, and the residue was subjected to flash column chromatography on Davisil (hexanes/EtOAc 10:1, 6:1, 1:1; R_f = 0.13 in hexanes/EtOAc 1:1) to afford pure cyclic ynoate **9** in 33% yield (0.0134 g). According to the same procedure, diazo lactone ***16-trans*** provided the title compound in 17% yield as determined by NMR analysis using mesitylene as an internal standard.

Ethyl 1-Hydroxy-2-oxocyclohexanecarboxylate (11). A mixture of commercially available ethyl 2-oxocyclohexanecarboxylate (**10**) (4.69 mL, 29.4 mmol), 10% Pd/carbon (1.5 g), and Et_3N (4.5 mL, 32.3 mmol) in EtOH (150 mL) was attached to a balloon of O_2 via a three-way stopcock. The air in the reaction flask was evacuated via an aspirator and replaced with oxygen three times, and the reaction mixture was stirred under O_2 overnight. The mixture was filtered through Celite, and the solids were rinsed with EtOH (100 mL). The filtrate was concentrated in vacuo, and the oily residue was purified by silica gel flash column chromatography (hexanes/EtOAc 6:1; R_f = 0.35 in hexanes/EtOAc 5:1) to give the α-oxygenated product as a colorless oil in 69% yield (3.77 g). The ^{1}H and ^{13}C NMR spectral data matched previously reported values.[30]

Ethyl 1,2-Bis(*tert*-butyldimethylsilyloxy)cyclohex-2-enecarboxylate (12).[42] 2,5-Lutidine (0.35 g, 3.25 mmol) and TBSOTf (0.86 g, 3.25 mmol) were added sequentially to a 0 °C solution of α-hydroxy-β-ketoester **11** (0.20 g, 1.08 mmol) in CH_2Cl_2 (5 mL). The mixture was allowed to warm to room temperature overnight and was then cooled to 0 °C before the addition of saturated aqueous $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and filtered. Upon removal of the solvent, the filtrate gave an oily residue that was purified by silica gel flash column chromatography (hexanes/Et_2O 40:1; R_f = 0.78 in hexanes/EtOAc 5:1) to give the bis(silyl ether) as a colorless oil in 99% yield (0.44 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.89 (dd, J = 4.9, 3.2 Hz, 1H), 4.19 (qd, J = 10.8, 7.1 Hz, 1H), 4.09 (qd, J = 10.8, 7.2 Hz, 1H), 2.09 (m, 2H), 1.95 (dt, J = 13.2, 3.2 Hz, 1H), 1.85 (dt, J = 13.2, 3.4 Hz, 1H), 1.77−1.68 (m, 1H), 1.62−1.56 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 149.6, 105.9, 78.0, 61.0, 37.0, 26.1, 25.9, 24.1, 18.8, 18.3, 17.8, 14.3, −2.9, −3.0, −4.4, −4.5; MS (ESI) calcd for $[C_{21}H_{42}O_4Si_2Na]^+$ 437.25138, found 437.25164.

(1,2-Bis(*tert*-butyldimethylsilyloxy)cyclohex-2-enyl)methanol (13).[43] DIBAL-H (44.4 mL, 52.97 mmol) was added dropwise to a −78 °C solution of **12** (9.98 g, 24.08 mmol) in toluene (240 mL), and the resulting mixture was stirred for 1 h at −78 °C, transferred to a 0 °C bath, and quenched with 150 mL of saturated potassium sodium tartrate tetrahydrate. The mixture was allowed to warm to room temperature overnight with efficient stirring. The reaction mixture was extracted with EtOAc (3 × 150 mL), and the organic layers were combined, washed with water and brine, and dried over anhydrous $MgSO_4$. The mixture was filtered and concentrated in vacuo to give an oily residue that was purified via silica gel flash column chromatography (hexanes/Et_2O 20:1; R_f = 0.68 in hexanes/EtOAc 5:1) to afford the title compound as a colorless oil in 69% yield (6.19 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.91 (t, J = 3.7 Hz, 1H), 3.59 (dd, J = 10.4, 4.5 Hz, 1H), 3.51 (dd, J = 10.5, 8.6 Hz, 1H), 2.10−1.96 (m, 2H), 1.85−1.65 (m, 4H), 1.58−1.51 (m, 1H), 0.94 (s, 9H), 0.87 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9, 107.5, 75.5, 68.1, 34.6, 26.13, 26.1, 24.5, 18.9, 18.6, 18.4, −2.78, −2.8, −4.2, −4.4; MS (ESI) calcd for $[C_{19}H_{40}O_3Si_2Na]^+$ 395.24082, found 395.24092.

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2-(*tert*-Butyldimethylsilyloxy)-2-(hydroxymethyl)-cyclohexanone (14).[44] Acetic acid (0.45 g, 0.53 mL, 7.42 mmol) and CsF (0.56 g, 3.7 mmol) were added sequentially to a 0 °C solution of **13** (0.55 g, 1.48 mmol) in a mixture of CH_3CN (21.4 mL) and MeOH (8.6 mL). The mixture was allowed to warm to room temperature overnight and was then recooled to 0 °C and diluted with 20 mL of EtOAc, and saturated $NaHCO_3$ solution was added. The resulting white precipitate was separated via vacuum filtration, and the layers in the filtrate were separated. The aqueous layer was extracted with Et_2O (3 × 30 mL), and the organic layers were combined, washed with saturated $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. The solvents were evaporated, and the oily residue was purified by silica gel flash column chromatography (hexanes/EtOAc 8:1; R_f = 0.41 in hexanes/EtOAc 5:1) to give the title compound as an oil in 86% yield (0.33 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67 (d, J = 7 Hz, 2H), 2.73 (ddd, J = 13.6, 8.8, 5.5 Hz, 1H), 2.36 (t, J = 7.4 Hz, 1H), 2.30 (dt, J = 7.2, 7.0 Hz, 1H), 1.98−1.87 (m, 3H), 1.85−1.73 (m, 2H), 1.66−1.59 (m, 1H), 0.90 (s, 9H), 0.18 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.7, 81.4, 67.4, 39.3, 37.8, 27.7, 26.1, 21.4, 18.7, −2.4, −3.1; MS (ESI) calcd for $[C_{13}H_{26}O_3SiNa]^+$ 281.15434, found 281.15428.

(1-(*tert*-Butyldimethylsilyloxy)-2-oxocyclohexyl)methyl 2-Bromoacetate (15). Bromoacetyl bromide (0.57 mL, 6.51 mmol) was added dropwise to a 0 °C solution of alcohol **14** (0.56 g, 2.17 mmol) and pyridine (0.44 mL, 5.43 mmol) in dry CH_2Cl_2 (21 mL), and the resulting white suspension was stirred at room temperature for 5 h. The mixture was cooled to 0 °C, and MeOH (0.7 mL) was added, at which point the white suspension became a clear solution. Saturated aqueous NH_4Cl (20 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the organic layers were combined and dried over anhydrous $MgSO_4$. The solvents were removed in vacuo, and the resulting oily residue was purified by flash silica gel column chromatography (hexanes/EtOAc 8:1; R_f = 0.47 in hexanes/EtOAc 5:1) to provide the desired bromoacetate as an oil in 90% yield (0.74 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.34 (d, J = 11.6 Hz, 1H), 4.31 (d, J = 11.7 Hz, 1H), 3.81 (s, 2H), 2.72 (ddd, J = 15.4, 9.9, 5.6 Hz, 1H), 2.32 (td, J = 13.5, 5.6 Hz, 1H), 1.98−1.86 (m, 3H), 1.80−1.74 (m, 2H), 1.68−1.62 (m, 1H), 0.88 (s, 9H), 0.13 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.1, 166.9, 79.5, 68.9, 38.9, 38.1, 27.6, 25.9, 25.6, 21.2, 18.6, −2.4, −3.1; MS (ESI) calcd for $[C_{15}H_{27}BrO_4SiH]^+$ 379.09347, found 379.09340.

8a-(*tert*-Butyldimethylsilyloxy)-4-diazo-4a-hydroxyhexahydro-1*H*-isochromen-3(4*H*)-one (16-*cis* and 16-*trans*).[31] *N*,*N*′-Ditosylhydrazine (3.81 g, 11.19 mmol) was added to a 0 °C solution of bromoacetate **15** (2.12 g, 5.59 mmol) in THF (56 mL), at which point DBU (5.19 mL, 34.6 mmol) was added dropwise. The mixture was stirred at room temperature for 8 h and then cooled to 0 °C, and saturated aqueous $NaHCO_3$ (60 mL) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL). The organic layers were combined and dried over anhydrous $CaCl_2$, and the solvents were removed by evaporation to give a crude solid product. The crude product was purified via flash column chromatography (hexanes/EtOAc 8:1, 6:1, 4:1, 2:1, 1:1) on a Davisil solid support to provide the bicyclic diazo lactone as two separated diastereomers that had the following spectral data:

*rel-(4aS,8aR)-8a-(tert-Butyldimethylsilyloxy)-4-diazo-4a-hydroxyhexahydro-1H-isochromen-3(4H)-one (**16-cis**).* Yield 0.62 g, 34%; R_f = 0.31 in hexanes/EtOAc 5:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.23 (d, J = 10.2 Hz, 1H), 4.12 (bs, 1H), 2.95 (bs, 1H), 1.98 (bs, 1H), 1.91−1.86 (m, 1H), 1.83−1.73 (m, 2H), 1.71−1.65 (m, 2H), 1.42 (bs, 2H), 0.92 (s, 9H), 0.20 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 72.4, 72.1, 69.7, 63.1, 34.5 (b), 32.0, 25.9, 21.8 (b), 18.4, −2.2, −2.5 (b); IR (film) 2928.1, 2857.7, 2102.5, 1690.7, 1471.7, 1391.7 cm^{-1}; MS (ESI) calcd for $[C_{15}H_{26}N_2O_4SiH]^+$ 327.17346, found 327.17385.

*rel-(4aR,8aR)-8a-(tert-Butyldimethylsilyloxy)-4-diazo-4a-hydroxyhexahydro-1H-isochromen-3(4H)-one (**16-trans**).* Yield 0.90 g, 49%; R_f = 0.45 in hexanes/EtOAc 5:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.23 (d, J = 10.9 Hz, 1H), 3.76 (d, J = 10.9 Hz, 1H), 2.64 (d, J = 1.7 Hz, 1H), 1.94 (dt, J = 14.7, 4.4 Hz, 1H), 1.80−1.67 (m, 5H), 1.61−1.55 (m, 1H), 1.22−1.12 (m, 1H), 0.90 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.9, 75.2, 70.9, 68.4, 61.6, 32.4, 30.0, 25.9, 22.7, 19.5, 18.1, −2.7, −3.2; IR (film) 3538.6, 2952.2, 2859.6, 2103.5, 1699.4, 1465.0, 1388.8, 1302.9 cm^{-1}; MS (ESI) calcd for $[C_{15}H_{26}N_2O_4SiH]^+$ 327.17346, found 327.17401.

Reaction of Diazo Lactone 16-*cis* with Indium Triflate To Provide 17 and 18. A solution of diazo lactone **16-*cis*** (0.100 g, 0.31 mmol) in CH_2Cl_2 (4 mL) was added to a −78 °C suspension of $In(OTf)_3$ (0.173 g, 0.31 mmol, dried in a vacuum oven at 180 °C for 16 h before use) in CH_2Cl_2 (4 mL). The mixture was allowed to warm to room temperature over 2 h, at which point water (8 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and filtered, and the solvent was evaporated to give an oily residue that was purified by flash column chromatography on Davisil (hexanes/EtOAc 8:1, 5:1, 3:1) to provide epoxide **17** (R_f = 0.46 in hexanes/EtOAc 5:1) in 5% yield (0.005 g) and diene **18** (R_f = 0.21 in hexanes/EtOAc 5:1) in 31% yield (0.027 g) with the following spectral data:

*rel-(11S,5aR,8aR)-5a-(tert-Butyldimethylsilyloxy)-hexahydrooxireno[2,3-d]isochromen-8(8aH)-one (**17**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.30 (d, J = 12.3 Hz, 1H), 3.93 (d, J = 11.9 Hz, 1H), 3.43 (s, 1H), 2.38 (dt, J = 13.7, 4.2 Hz, 1H), 1.84−1.69 (m, 5H), 1.50−1.43 (m, 2H), 0.90 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 72.6, 71.9, 64.6, 55.9, 32.5, 27.3, 25.9, 23.0, 20.1, 18.5, −2.5, −3.0; IR (film) 2950.3, 2933.9, 2848.9, 1753.4, 1635.7, 1462.1, 1295.3, 1263.4, 1179.5, 1074.4, 957.7, 909.5, 838.1, 778.3, 735.9 cm^{-1}; MS (ESI) calcd for $[C_{15}H_{26}O_4SiH]^+$ 299.16731, found 299.16731.

*8a-(tert-Butyldimethylsilyloxy)-8,8a-dihydro-1H-isochromen-3(7H)-one (**18**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.38 (ddd, J = 9.7, 6.0, 1.9 Hz, 1H), 6.20 (dd, J = 9.9, 2.8 Hz, 1H), 5.69 (s, 1H), 4.31 (d, J = 12.1 Hz, 1H), 4.18 (d, J = 12.1 Hz, 1H), 2.59−2.51 (m, 1H), 2.27 (dt, J = 18.9, 5.4 Hz, 1H), 1.87 (dd, J = 13.2, 4.6 Hz, 1H), 1.47 (ddd, J = 12.9, 11.6, 5.1 Hz, 1H), 0.84 (s, 9H), 0.11 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 151.2, 140.0, 124.6, 113.9, 76.0, 66.4, 32.0, 25.6, 22.2, 18.5, −3.4, −3.9; IR (film) 2956.0, 2929.0, 2856.7, 1725.4, 1631.9, 1472.7, 1462.1, 1290.4, 1250.9, 1250.9, 1222.9, 1201.7, 1161.2, 1114.9, 1060.9, 1028.1, 892.1, 828.5, 777.4 cm^{-1}; MS (ESI) calcd for $[C_{15}H_{24}O_3SiH]^+$ 281.15675, found 281.15654.

8a-Hydroxy-8,8a-dihydro-1*H*-isochromen-3(7*H*)-one (19). $BF_3{\cdot}OEt_2$ (0.045 mL, 0.36 mmol) was added in a steady stream to a solution of bicyclic diazo lactone **16-*trans*** (0.12 g, 0.36 mmol) in dry CH_2Cl_2 (7 mL) at −78 °C. After 1.5 h, distilled water (7 mL) was added at 0 °C, and the mixture was transferred with the aid of CH_2Cl_2 (10 mL) into a separatory funnel. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined and dried over anhydrous $MgSO_4$, and the solvents were removed in vacuo. The residue was subjected to flash column chromatography on Davisil (hexanes/EtOAc 2:1, 1:1; R_f = 0.45 in CH_2Cl_2/EtOAc 1:1) to afford **19** in 26% yield (0.0153 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.44 (ddd, J = 11.3, 6.3, 2.2 Hz, 1H), 6.24 (dd, J = 10.3, 2.9 Hz, 1H), 5.71 (s, 1H), 4.34 (d, J = 11.9 Hz, 1H), 4.25 (d, J = 11.8 Hz, 1H), 2.65−2.57 (m, 1H), 2.53 (bs, 1H), 2.33 (dtt, J = 18.8, 5.8, 1.3 Hz, 1H), 1.93 (ddt, J = 13.4, 5.1, 0.8 Hz, 1H), 1.51 (ddd, J = 13.4, 11.6, 5.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 151.8, 140.7, 124.1, 113.3, 76.3, 64.5, 29.5, 21.9; IR (film) 3394.9 (b), 2920.4, 2854.8, 1720.6, 1694.5, 1681.0, 1624.1, 1455.4, 1288.5, 1248.9, 1229.7, 1101.4, 1057.1, 877.7, 734.9, 710.8 cm^{-1}; MS (ESI) calcd for $[C_9H_{10}O_3H]^+$ 167.07027, found 167.06980.

(1-(*tert*-Butyldimethylsilyloxy)-2-oxocyclohexyl)methyl Acetate (20).[45] Acetic anhydride (0.43 mL, 4.58 mmol), DMAP (0.0023 g, 0.02 mmol), and Et_3N (0.71 mL, 5.08 mmol) were added sequentially to a 0 °C solution of alcohol **14** (0.26 g, 1 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 2 h at 0 °C, and then water (5 mL) was added. The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organics were combined, dried (Na_2SO_4), and concentrated. The product was purified by silica gel flash column chromatography (hexanes/EtOAc

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10:1; R_f = 0.42 in hexanes/EtOAc 5:1) to give the keto acetate in 86% yield (0.26 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.26 (d, J = 11.7 Hz, 1H), 4.23 (d, J = 11.7 Hz, 1H), 2.72 (ddd, J = 13.7, 9.5, 5.4 Hz, 1H), 2.33 (ddd, J = 12.7, 6.8, 5.7 Hz, 1H), 2.06 (s, 3H), 1.96−1.85 (m, 3H), 1.82−1.74 (m, 2H), 1.68−1.61 (m, 1H), 0.89 (s, 9H), 0.14 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.3, 170.6, 79.7, 67.4, 38.9, 38.4, 27.6, 25.9, 21.3, 20.9, 18.6, −2.6, −3.2; MS (ESI) calcd for $[C_{15}H_{28}O_4SiH]^+$ 301.18296, found 301.18300.

Ethyl 2-(2-(Acetoxymethyl)-2-(*tert*-butyldimethylsilyloxy)-1-hydroxycyclohexyl)-2-diazoacetate (21). Lithium bis(trimethylsilyl)amide (1 M in THF/ethylbenzene, 0.75 mL, 0.75 mmol) was added dropwise over 1.5 h to a −78 °C solution of ketone **20** (0.20 g, 0.65 mmol) and ethyl diazoacetate (0.08 g, 0.72 mmol) in THF (12 mL). After the mixture was stirred for 30 min at −78 °C, saturated aqueous NH_4Cl (12 mL) was added. The mixture was allowed to warm to room temperature, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 15 mL), and the organic layers were combined, washed with brine, and dried over anhydrous $CaCl_2$. The solvents were evaporated, and the crude yellow oily residue was purified via silica gel flash column chromatography (hexanes/Et_2O 7:1, 5:1, 3:1) on a Davisil support to provide the acetate diazoester as two separate diastereomers. Both diastereomers were isolated together with an inseparable unknown impurity. The major diastereomer was obtained in 41% yield (0.14 g) as determined by NMR analysis using mesitylene as an internal standard (R_f = 0.42 in hexanes/EtOAc 5:1), and the minor diastereomer was obtained in 8% yield (0.030 g) as determined by NMR analysis using mesitylene as an internal standard (R_f = 0.26 in hexanes/EtOAc 5:1).

Data for the major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.46 (d, J = 12.2 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H, overlapped with peaks from the impurity), 3.97 (d, J = 12.2 Hz, 1H), 2.24−2.17 (m, 1H), 2.09 (s, 3H), 1.93−1.89 (m, 2H), 1.71 (apparent tt, J = 13.3, 3.9 Hz, 3H), 1.62 (m, 2H), 1.54−1.51 (m, 1H), 1.26 (t, J = 7.11 Hz, 3H), 0.87 (s, 9H), 0.18 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 166.6, 81.9, 73.3, 66.7, 62.2, 60.7, 32.8, 32.7, 26.2, 22.8, 21.1, 20.3, 18.6, 14.6, 1.9, 2.2; IR (film) 3505.8, 2930.9, 2893.4, 2094.8, 1747.6, 1693.6, 1471.7, 1464.0, 1388.8, 1367.6, 1297.2, 1251.9, 1234.5 cm^{-1}; MS (ESI) calcd for $[C_{19}H_{34}N_2O_6SiNa]^+$ 437.20783, found 437.20797.

Data for the minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.28 (d, J = 11.8 Hz, 1H), 4.21 (q, J = 7.0 Hz, 2H, overlapped with peaks from the impurity), 4.08 (d, J = 11.8 Hz, 1H), 2.09 (s, 3H), 1.94−1.85 (m, 2H), 1.72−1.52 (m, 7H, overlapped with peaks from the impurity), 1.27 (t, J = 7.1 Hz, 3H), 0.93 (s, 9H), 0.15 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 169.7, 79.1, 75.7, 68.9, 64.1, 61.2, 33.7, 30.4, 26.5, 26.2, 22.7, 21.0, 18.8, 14.6, −1.8, −1.9; IR (film) 3481.7, 2954.1, 2860.6, 2096.7, 1746.6, 1696.5, 1471.7, 1389.8, 1367.6, 1293.3, 1253.8, 1111.1, 1033.9 cm^{-1}; MS (ESI) calcd for $[C_{19}H_{34}N_2O_6SiNa]^+$ 437.20783, found 437.20810.

Ethyl 9-Acetoxy-8-oxonon-2-ynoate (22). According to representative experimental procedure 1 that was used to prepare **9**, the major diastereomer of diazoester **21** (0.060 g, 0.14 mmol) reacted at 0 °C to give tethered ketone ynoate **22** in 70% yield (0.024 g) after purification via flash chromatography on Davisil (hexanes/EtOAc 10:1, 8:1, 6:1, 4:1, 3:1, 2:1, 1:1; R_f = 0.11 in hexanes/EtOAc 5:1); the yield was determined to be 83% via NMR analysis using mesitylene as an internal standard. Under the same experimental conditions, the minor diastereomer of diazoester **21** (0.049 g, 0.12 mmol) provided the title compound in 54% isolated yield (0.012 g); the yield was determined to be 61% via NMR analysis using mesitylene as an internal standard. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.63 (s, 2H), 4.20 (q, J = 7.1 Hz, 2H), 2.45 (t, J = 7.1 Hz, 2H), 2.34 (t, J = 7.1 Hz, 2H), 2.16 (s, 3H), 1.73 (tt, J = 7.9, 7.0 Hz, 2H), 1.60 (tt, J = 7.6, 7.1 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.4, 170.4, 153.8, 88.5, 73.7, 68.1, 61.9, 38.1, 26.9, 22.4, 20.6, 18.6, 14.2; IR (film) 2900.1, 2233.7, 1751.4, 1730.2, 1705.2, 1419.7, 1367.6, 1251.9, 1234.5, 1076.3, 1026.2, 910.4, 858.4, 753.2, 735.9 cm^{-1}; MS (ESI) calcd for $[C_{13}H_{18}O_5Na]^+$ 277.10464, found 277.10486.

2-Allyl-2-(*tert*-butyldimethylsilyloxy)cyclohexanone (24). Freshly prepared allylmagnesium bromide (2.40 g, 19.88 mmol) in Et_2O (20 mL) was added dropwise to a 0 °C solution of 2-silyloxycyclohex-2-enone (**23**) (3.0 g, 13.25 mmol) in Et_2O (24 mL). 2-Silyloxycyclohex-2-enone[36] was made according to the literature procedure. During the addition the colorless solution became yellow in color. After 3 h of stirring at 0 °C, the reaction mixture was quenched with 50 mL of aqueous NH_4Cl solution, and the resulting mixture was warmed to room temperature. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 50 mL). The organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated to give an oily residue. This residue, which contained the crude tertiary alcohol (2.72 g, 10.13 mmol), was dissolved in 50 mL of dry MeOH and cooled to 0 °C. K_2CO_3 (0.07 g, 0.5 mmol) was added, and the mixture was stirred at room temperature for 1 h. The mixture was concentrated to give an oily residue, which was dissolved in 50 mL of Et_2O and washed with brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated down to an oily residue. Purification via flash silica gel chromatography (hexanes/Et_2O 50:1; R_f = 0.45 in hexanes/EtOAc 40:1) provided the title compound in 83% yield (2.95 g). The ^{1}H and ^{13}C NMR spectral data were identical to the reported values.[46]

2-(1-(*tert*-Butyldimethylsilyloxy)-2-oxocyclohexyl)-acetaldehyde (25).[47] A solution of allyl ketone **24** (1.27 g, 4.73 mmol) in CH_2Cl_2 (50 mL) was cooled to −78 °C, and ozonized oxygen gas was passed through the solution at a rate of 1 L/min until the solution became blue in color, at which point the solution was purged with nitrogen until the blue color disappeared. Then triphenylphosphine (2.48 g, 9.46 mmol) was added, and after 30 min the mixture was allowed to warm to room temperature over a period of 2 h. The solvent was removed, and the crude product was purified via flash column chromatography on a Davisil support (hexanes/EtOAc 10:1, 2:1; R_f = 0.23 in hexanes/EtOAc 8:1) to afford the title aldehyde in 93% yield (1.19 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73 (t, J = 2.4 Hz, 1H), 2.76 (dd, J = 15.4, 2.5 Hz, 1H), 2.78−2.73 (m, 1H, overlapped with dd at 2.76), 2.61 (dd, J = 15.4, 2.4 Hz, 1H), 2.36 (ddd, J = 13.6, 6.2, 5.7 Hz, 1H), 2.02−1.87 (m, 4H), 1.82−1.73 (m, 1H), 1.68−1.61 (m, 1H), 0.90 (s, 9H), 0.17 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.8, 200.6, 80.1, 50.5, 41.1, 38.7, 27.5, 25.9, 21.5, 18.6, −2.1, −2.7; MS (ESI) calcd for $[C_{14}H_{26}O_3SiNa]^+$ 293.15434, found 293.15429.

3a-(*tert*-Butyldimethylsilyloxy)octahydrobenzofuran-7a-ol (26).[37] An aqueous suspension of Raney nickel (5.67 g of the suspension) was transferred with THF (20 mL) to a solution of aldehyde **25** (0.87 g, 3.21 mmol) in THF (10 mL). The suspension was stirred at room temperature for 30 min, diluted with Et_2O (50 mL), and filtered through Celite, and the solvent was evaporated to yield an oily residue. The crude product was purified via silica gel flash column chromatography (hexanes/EtOAc 20:1, 10:1; 15:1; 5:1; R_f = 0.40 in hexanes/EtOAc 4:1) to afford the hemiacetal in 69% yield (0.60 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.10 (ddd, J = 8.9, 8.5, 4.6 Hz, 1H), 3.84 (dt, J = 8.4, 6.9 Hz, 1H), 3.29 (s, 1H), 2.14 (ddd, J = 11.2, 10.0, 6.9 Hz, 1H), 1.91 (ddd, J = 12.4, 8.3, 4.1 Hz, 1H), 1.86 (dt, J = 14.3, 4.4 Hz, 1H), 1.79−1.74 (m, 1H), 1.67−1.60 (m, 2H), 1.54−1.47 (m, 2H), 1.44−1.37 (m, 2H), 0.91 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 102.7, 80.3, 64.3, 36.1, 35.5, 33.6, 25.9, 22.9, 21.7, 18.2, −2.5, −2.6; IR (film) 3438.2 (b), 2933.9, 2857.7, 1471.75, 1360.8, 1295.26, 1252.8 cm^{-1}; MS (ESI) calcd for $[C_{14}H_{28}O_3SiNa]^+$ 295.16999, found 295.17049.

2-(1-(*tert*-Butyldimethylsilyloxy)-2-oxocyclohexyl)ethyl 2-Bromoacetate (27). Pyridine (0.47 mL, 5.81 mmol) and bromoacetyl bromide (0.61 mL, 6.98 mmol) were added sequentially to a 0 °C solution of hemiacetal **26** (0.63 g, 2.33 mmol) in CH_2Cl_2 (23 mL), and the resulting heterogeneous mixture was stirred overnight at room temperature. The mixture was cooled to 0 °C, and then MeOH (0.25 mL) was added, at which point the white suspension became a clear solution. Saturated aqueous NH_4Cl (25 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL), and the organic layers were combined, dried over anhydrous $MgSO_4$, and filtered. The solvents were removed in vacuo, and the resulting oily residue was purified by flash silica gel column chromatography (hexanes/EtOAc 20:1; R_f = 0.48 in hexanes/EtOAc

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4:1) to provide the desired bromoacetate as an oil in 57% yield (0.52 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.26−4.23 (m, 2H), 3.77 (s, 2H), 2.56−2.45 (m, 2H), 2.30 (dt, J = 21.5, 7.2 Hz, 1H), 1.98−1.93 (m, 3H), 1.86−1.79 (m, 2H), 1.74−1.65 (m, 2H), 0.87 (s, 9H), 0.18 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.9, 167.1, 80.7, 62.3, 42.1, 39.6, 37.1, 27.7, 26.1, 25.8, 22.7, 18.7, −2.4, −2.7; MS (ESI) calcd for $[C_{16}H_{29}BrO_4SiH]^+$ 393.10913, found 393.10952.

2-(1-(*tert*-Butyldimethylsilyloxy)-2-oxocyclohexyl)ethyl 2-Diazoacetate (28). Diazo ester **28** was prepared from bromoacetate **27** by the same procedure used to make ***16-cis***. The product was purified via filtration through a pad of Davisil using an 8:1 hexanes/EtOAc mixture as the eluent to provide the title compound (R_f = 0.28 in hexanes/EtOAc 4:1) in 85% yield (0.51 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.57 (bs, 1H), 4.29−4.19 (m, 2H), 2.53−2.44 (m, 2H), 2.31 (ddd, J = 14.4, 7.3, 7.0 Hz, 1H), 1.99−1.93 (m, 2H), 1.91 (dd, J = 6.1, 5.3 Hz, 1H), 1.87−1.77 (m, 2H), 1.74−1.63 (m, 2H), 0.88 (s, 9H), 0.19 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.7, 166.3 (b), 80.6, 60.6, 45.9 (b), 42.2, 39.4, 37.5, 27.6, 25.9, 22.6, 18.5, −2.6, −2.9; IR (film) 2928.1, 2855.73, 2112.14, 1724.4, 1697.4, 1472.7, 1394.6, 1394.6, 1359.8, 1248.0 cm^{-1}; MS (ESI) calcd for $[C_{16}H_{28}N_2O_4SiNa]^+$ 363.17106, found 363.17147.

***rel*-(5a*R*,9a*S*)-5a-(*tert*-Butyldimethylsilyloxy)-1-diazo-9a-hydroxyoctahydrobenzo[*d*]oxepin-2(1*H*)-one (29).** A solution of diazo ester **28** (0.05 g, 0.15 mmol) in THF (3 mL) was added dropwise over 16 h by a syringe pump to a stirred −78 °C solution of lithium bis(trimethylsilyl)amide (1 M in THF/ethylbenzene, 0.20 mL, 0.18 mmol) in THF (30 mL). After 1 h, saturated aqueous NH_4Cl solution (24 mL) was added to the reaction mixture at −78 °C, and the mixture was allowed to warm to room temperature. The mixture was extracted with EtOAc (3 × 70 mL), and the organic layers were combined, washed with brine, dried over anhydrous $CaCl_2$, filtered, and concentrated to a solid residue. Flash column chromatography of the crude product over Davisil (hexanes/EtOAc 4:1, 2:1, 1:1; R_f = 0.21 in hexanes/EtOAc 3:1) afforded a single diastereomer of the title product in 69% yield (0.035 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.37 (ddd, J = 12.8, 9.8, 1.8 Hz, 1H), 4.26 (ddd, J = 12.8, 6.1, 2.8 Hz, 1H), 2.34 (ddd, J = 15.8, 9.8, 2.8 Hz, 1H), 1.97 (s, 1H), 1.93 (dt, J = 12.6, 4.9 Hz, 1H), 1.80 (dt, J = 13.9, 4.3 Hz, 1H), 1.72−1.55 (m, 6H), 1.52−1.48 (m, 1H), 0.92 (s, 9H), 0.16 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 75.6, 74.0, 67.9, 65.4, 38.6, 35.3, 32.8, 26.1, 20.4, 20.2, 18.8, −1.7, −1.9; IR (film) 3358.2 (b), 2927.1, 2855.7, 2106.4, 1727.3, 1635.7, 1471.7, 1398.5, 1305.9, 1259.6 cm^{-1}; MS (ESI) calcd for $[C_{16}H_{28}N_2O_4SiH]^+$ 341.18911, found 341.18924.

4-Oxacycloundecyne-3,7-dione (30). According to representative experimental procedure 1 or 2 used to prepare **9**, diazo lactone **29** provided 11-membered cyclic ynoate **30** in 50% yield (0.022 g) at 0 °C and 63% yield (0.0063 g) at 40 °C. The title compound was isolated via flash column chromatography on Davisil (hexanes/EtOAc 4:1, 3:1, 2:1, 1:1; R_f = 0.16 in hexanes/EtOAc 2:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.65−4.63 (m, 2H), 2.79−2.77 (m, 2H), 2.76−2.73 (m, 2H), 2.42−2.39 (m, 2H), 1.92 (tt, J = 5.9, 4.0 Hz, 2H), 1.76−1.72 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.8, 154.4, 97.9, 73.1, 65.5, 44.4, 41.7, 25.0, 20.9, 18.2; IR (film) 2922.3, 2851.9, 2229.8, 1714.8 (b), 1463.1, 1387.8, 1282.7, 1228.7, 1079.2, 740.7 cm^{-1}; MS (ESI) calcd for $[C_{10}H_{12}O_3H]^+$ 181.08592, found 181.08584.

Methyl 1-Hydroxy-2-oxocycloheptanecarboxylate (32a). The title compound was prepared from commercially available methyl 2-oxocycloheptanecarboxylate (**31a**) (2.01 g, 11.8 mmol) by the method described for the preparation of **11**. Purification of the crude product via flash silica gel chromatography (hexanes/EtOAc 8:1; R_f = 0.25 in hexanes/EtOAc 5:1) afforded the title compound in 66% yield (1.44 g). The ^{1}H and ^{13}C NMR spectral data matched previously reported values.[48]

Ethyl 1-Hydroxy-2-oxocyclooctanecarboxylate (32b). The title compound was prepared from commercially available ethyl 2-oxocyclooctanecarboxylate (**31b**) (4.88 g, 24.8 mmol) by the method described for the preparation of **11**. Purification of the crude product via flash silica gel chromatography (hexanes/EtOAc 6:1; R_f = 0.27 in hexanes/EtOAc 5:1) afforded the title compound in 99% yield (5.26 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.35 (d, J = 1.6 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.05 (dd, J = 12.4, 3.9 Hz, 1H), 2.74−2.68 (m, 1H), 2.40−2.36 (m, 1H), 2.15 (dt, J = 15.3, 3.9 Hz, 1H), 1.98−1.93 (m, 1H), 1.82−1.63 (m, 4H), 1.47−1.32 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H), 0.90−0.86 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.1, 170.4, 83.0, 62.0, 36.8, 30.4, 30.1, 25.4, 24.1, 22.2, 13.9. MS (ESI) calcd for $[C_{11}H_{18}O_4Na]^+$ 237.1103, found 237.1105.

Methyl 1,2-Bis(*tert*-butyldimethylsilyloxy)cyclohept-2-enecarboxylate (33a). Compound **33a** was prepared from **32a** (0.15 g, 0.79 mmol) by the method described for the preparation of **12**. Purification by silica gel flash column chromatography (hexanes/Et_2O 50:1; R_f = 0.75 in hexanes/EtOAc 5:1) provided the title compound as a colorless oil in 93% yield (0.30 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.02 (dd, J = 6.9, 5.6 Hz, 1H), 3.68 (s, 3H), 2.14 (ddd, J = 14.5, 11.6, 4.7 Hz, 1H), 2.10−2.02 (m, 2H), 1.94−1.86 (m, 1H), 1.76 (td, J = 14.6, 3.9 Hz, 2H), 1.67−1.52 (m, 2H), 0.91 (s, 9H), 0.89 (s, 9H), 0.16 (s, 6H), 0.15 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 152.9, 110.5, 83.0, 51.9, 35.7, 26.7, 26.3, 26.1, 23.3, 22.4, 19.2, 18.4, −2.7, −2.8, −4.3, −4.6; MS (ESI) calcd for $[C_{21}H_{42}O_4Si_2H]^+$ 415.26944, found 415.26939.

(*E*)-Ethyl 1,2-Bis(*tert*-butyldimethylsilyloxy)cyclooct-2-enecarboxylate (33b). Compound **33b** was prepared from **32b** (0.20 g, 0.91 mmol) by the method described for the preparation of **12**. Purification by silica gel flash column chromatography (hexanes/Et_2O 30:1; R_f = 0.72 in hexanes/EtOAc 5:1) provided the title compound as a colorless oil in 94% yield (0.38 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.74 (dd, J = 9.8, 8.5 Hz, 1H), 4.19 (qd, J = 10.8, 7.2 Hz, 1H), 4.05 (qd, J = 10.8, 7.1 Hz, 1H), 2.42 (tdd, J = 14.2, 9.7, 7.0 Hz, 1H), 2.21 (dt, J = 14.5, 7.3 Hz, 1H), 2.16−2.03 (m, 2H), 1.76−1.64 (m, 3H), 1.58−1.48 (m, 3H), 1.26 (t, J = 7.2 Hz, 3H), 0.89 (two s, 18H), 0.17 (s, 3H), 0.14 (s, 3H), 0.137 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 152.7, 105.6, 82.7, 60.9, 37.0, 27.4, 26.3, 26.1, 23.7, 23.3, 22.6, 19.2, 18.5, 14.2, −2.5, −2.6, −4.3, −4.4; MS (ESI) calcd for $[C_{23}H_{46}O_4Si_2H]^+$ 443.30074, found 443.30074.

(1,2-Bis(*tert*-butyldimethylsilyloxy)cyclohept-2-enyl)-methanol (34a). The title compound was prepared from **33a** (2.84 g, 6.85 mmol) according to the same procedure as used to prepare **13**. Purification by silica gel flash column chromatography (hexanes/Et_2O 40:1; R_f = 0.80 in hexanes/EtOAc 5:1) provided compound **34a** as a colorless oil in 80% yield (2.13 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06 (dd, J = 7.9, 5.6 Hz, 1H), 3.58 (s, 1H), 3.56 (d, J = 1.6 Hz, 1H), 2.20 (dqd, J = 16.2, 5.3, 2.5 Hz, 1H), 2.00 (dd, J = 7.4, 6.2 Hz, 1H), 1.94 (dq, J = 7.8, 2.3 Hz, 1H), 1.88−1.83 (m, 3H), 1.74−1.68 (m, 1H), 1.65−1.61 (m, 1H), 1.48−1.40 (m, 1H), 0.94 (s, 9H), 0.89 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 111.1, 80.0, 68.8, 34.4, 26.9, 26.2, 26.19, 23.6, 23.1, 18.8, 18.5, −2.6, −2.7, −4.1, −4.4; MS (ESI) calcd for $[C_{20}H_{42}O_3Si_2Na]^+$ 409.25647, found 409.25635.

(*E*)-(1,2-Bis(*tert*-butyldimethylsilyloxy)cyclooct-2-enyl)-methanol (34b). The title compound was prepared from **33b** (0.27 g, 0.61 mmol) according to the same procedure as used to prepare **13**. Purification by silica gel flash column chromatography (hexanes/Et_2O 40:1; R_f = 0.79 in hexanes/EtOAc 5:1) provided compound **34b** as a colorless oil in 64% yield (0.16 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.79 (dd, J = 9.9, 8.6 Hz, 1H), 3.76 (dd, J = 11.0, 3.9 Hz, 1H), 3.47 (dd, J = 10.9, 10.0 Hz, 1H), 2.84 (dddd, J = 14.0, 12.2, 9.9, 5.6 Hz, 1H), 2.18 (dd, J = 9.9, 3.8 Hz, 1H), 1.99−1.88 (m, 2H), 1.80−1.74 (m, 1H), 1.63−1.57 (m, 4H), 1.49−1.37 (m, 2H), 0.94 (s, 9H), 0.89 (s, 9H), 0.21 (s, 3H), 0.18 (s, 3H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1, 107.5, 80.6, 68.8, 37.0, 28.1, 26.3, 26.1, 24.1, 22.8, 22.4, 18.8, 18.4, −2.6, −3.7, −4.6; MS (ESI) calcd for $[C_{21}H_{44}O_3Si_2H]^+$ 401.29017, found 401.29030.

2-(*tert*-Butyldimethylsilyloxy)-2-(hydroxymethyl)-cycloheptanone (35a). Compound **35a** was prepared from **34a** (0.15 g, 0.40 mmol) by the method described for the preparation of **14**. The title compound was obtained in 87% yield (0.09 g) after purification by silica gel flash column chromatography (hexanes/EtOAc 8:1; R_f = 0.36 in hexanes/EtOAc 5:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.70 (dd, J = 11.4, 7.2 Hz, 1H), 3.60 (dd, J = 11.4, 6.4 Hz, 1H), 2.77−2.72 (m, 1H), 2.44 (ddd, J = 13.7, 12.5, 4.8 Hz, 1H), 2.29 (dd, J = 7.1, 6.5 Hz, 1H), 1.78−1.71 (m, 5H), 1.63−1.56 (m, 2H),

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1.47−1.38 (m, 1H), 0.90 (s, 9H), 0.21 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.5, 84.5, 68.5, 40.1, 36.0, 29.3, 26.1, 25.3, 23.9, 18.8, −2.3, −2.8; MS (ESI) calcd for $[C_{14}H_{28}O_3SiNa]^+$ 295.16999, found 295.17004.

2-(*tert*-Butyldimethylsilyloxy)-2-(hydroxymethyl)-cyclooctanone (35b). Compound **35b** was prepared from **34b** (0.16 g, 0.39 mmol) by the method described for the preparation of **14**. The title compound was obtained in 85% yield (0.10 g) after purification by silica gel flash column chromatography (hexanes/EtOAc 8:1; R_f = 0.31 in hexanes/EtOAc 5:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.75 (dd, J = 11.4, 7.2 Hz, 1H), 3.57 (dd, J = 11.4, 6.4 Hz, 1H), 2.69 (ddd, J = 12.1, 7.9, 4.0 Hz, 1H), 2.39 (ddd, J = 12.3, 9.3, 4.2 Hz, 1H), 2.15 (dd, J = 6.5, 7.1 Hz, 1H), 2.04 (dd, J = 14.6, 3.4 Hz, 1H), 1.94−1.80 (m, 3H), 1.74−1.66 (m, 1H), 1.63−1.44 (m, 3H), 1.39−1.34 (m, 2H), 0.91 (s, 9H), 0.21 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.9, 84.4, 68.6, 37.8, 34.1, 28.9, 26.3, 26.2, 25.3, 22.3, 18.9, −2.3, −2.7; MS (ESI) calcd for $[C_{15}H_{30}O_3SiH]^+$ 287.20370, found 287.20376.

(1-(*tert*-Butyldimethylsilyloxy)-2-oxocycloheptyl)methyl 2-Bromoacetate (36a). The title compound was prepared from **35a** (1.38 g, 5.08 mmol) according to the same procedure as used to prepare **15**. The crude product was purified via flash silica gel column chromatography (hexanes/EtOAc 10:1; R_f = 0.56 in hexanes/EtOAc 5:1) to provide compound **36a** in 95% yield (1.91 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.34 (d, J = 11.2 Hz, 1H), 4.15 (d, J = 11.3 Hz, 1H), 3.82 (s, 2H), 2.70 (ddd, J = 11.7, 7.1, 4.7 Hz, 1H), 2.52 (ddd, J = 12.8, 10.6, 4.1 Hz, 1H), 1.86−1.75 (m, 4H), 1.68−1.61 (m, 2H), 1.59−1.50 (m, 1H), 1.47−1.38 (m, 1H), 0.88 (s, 9H), 0.19 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.4, 166.8, 82.6, 69.9, 40.3, 35.7, 29.3, 25.9, 25.6, 25.5, 23.6, 18.6, −2.4, −2.9; MS (ESI) calcd for $[C_{16}H_{29}BrO_4SiH]^+$ 393.10913, found 393.10927.

(1-(*tert*-Butyldimethylsilyloxy)-2-oxocyclooctyl)methyl 2-Bromoacetate (36b). The title compound was prepared from **35b** (0.11 g, 0.38 mmol) according to the same procedure as used to prepare **15**. The crude product was purified via flash silica gel column chromatography (hexanes/EtOAc 8:1; R_f = 0.68 in hexanes/EtOAc 5:1) to provide compound **36b** in 98% yield (0.15 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.41 (d, J = 11.6 Hz, 1H), 4.15 (d, J = 11.6 Hz, 1H), 3.80 (s, 2H), 2.63 (ddd, J = 12.3, 7.6, 3.6 Hz, 1H), 2.45 (ddd, J = 12.3, 10.2, 4.0 Hz, 1H), 2.09 (ddd, J = 14.5, 11.2, 3.5 Hz, 1H), 1.95−1.80 (m, 3H), 1.74−1.66 (m, 1H), 1.64−1.57 (m, 1H), 1.52−1.44 (m, 2H), 1.40−1.29 (m, 2H), 0.89 (s, 9H), 0.18 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.8, 166.8, 82.5, 70.2, 37.6, 33.7, 29.1, 26.3, 26.0, 25.4, 24.8, 22.2, 18.8, −2.4, −2.8; MS (ESI) calcd for $[C_{17}H_{31}BrO_4SiNa]^+$ 429.10672, found 429.10707.

(1-(*tert*-Butyldimethylsilyloxy)-2-oxocyclooctyl)methyl 2-Diazoacetate (37b). Diazo ester **37b** was prepared from the corresponding bromo ester **36b** (2.64 g, 6.48 mmol) by the method used to make **16-*cis***. Purification of the crude product by flash chromatography on a Davisil support (hexanes/EtOAc 10:1, 8:1, 6:1, 4:1, 2:1, 1:1; R_f = 0.46 in hexanes/EtOAc 5:1) provided diazoester **37b** in 68% yield (1.57 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.72 (bs, 1H), 4.38 (d, J = 11.5 Hz, 1H), 4.16 (d, J = 11.5 Hz, 1H), 2.57 (ddd, J = 12.3, 6.8, 3.9 Hz, 1H), 2.46 (dt, J = 11.2, 4.3 Hz, 1H), 2.08 (ddd, J = 14.3, 11.6, 3.3 Hz, 1H), 1.92−1.78 (m, 3H), 1.75−1.67 (m, 1H), 1.65−1.58 (m, 1H), 1.51−1.35 (m, 3H), 1.32−1.24 (m, 1H), 0.88 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.0, 166.2 (b), 82.8, 69.1, 46.3 (b), 37.7, 33.6, 29.2, 26.3, 25.9, 24.8, 22.2, 18.8, −2.5, −2.8; IR (film) 3125.8, 2946.4, 2857.7, 2114.1, 1701.3, 1471.8, 1388.8, 1351.2, 1249.9, 1156.4 cm^{-1}; MS (ESI) calcd for $[C_{17}H_{30}N_2O_4SiNa]^+$ 377.18671, found 377.18683.

9a-(*tert*-Butyldimethylsilyloxy)-4-diazo-4a-hydroxyoctahydrocyclohepta[*c*]pyran-3(1*H*)-one (38a-*cis* and 38a-*trans*). Diazo lactones **38a-*cis*** and **38a-*trans*** were prepared from bromoester **36a** (0.16 g, 0.40 mmol) by the same method as used to make **16-*cis***. Purification of the crude product by flash chromatography on a Davisil support (hexanes/EtOAc 12:1, 10:1, 5:1, 3:1) provided the bicyclic diazo lactones as two separated diastereomers with the following spectral data:

38a-*cis*: Yield 0.034 g, 25%; R_f = 0.19 in hexanes/EtOAc 5:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.01 (d, J = 12.3 Hz, 1H), 3.96 (d, J = 12.3 Hz, 1H), 3.60 (d, J = 1.7 Hz, 1H), 2.02−1.90 (m, 3H), 1.87−1.73 (m, 3H), 1.59−1.46 (m, 3H), 1.37−1.28 (m, 1H), 0.92 (s, 9H), 0.20 (s, 3H), 0.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 75.5, 75.2, 70.1, 65.9, 35.9, 34.7, 28.9, 25.9, 21.6, 20.2, 18.6, −2.6, −2.9; IR (film) 3503.8, 2929.0, 2857.7, 2102.5, 1693.57, 1464.0, 1392.7, 1287.5, 1128.4 cm^{-1}; MS (ESI) calcd for $[C_{16}H_{28}N_2O_4SiH]^+$ 341.18911, found 341.18928.

38a-*trans*: Yield 0.045 g, 33%; R_f = 0.36 in hexanes/EtOAc 5:1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.18 (d, J = 10.8 Hz, 1H), 3.73 (d, J = 10.7 Hz, 1H), 2.99 (d, J = 2.2 Hz, 1H), 2.14−2.04 (m, 2H), 1.84 (tt, J = 13.9, 1.7 Hz, 1H), 1.78−1.69 (m, 3H), 1.68−1.52 (m, 3H), 1.39−1.31 (m, 1H), 0.90 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 79.8, 73.3, 70.8, 62.8, 33.9, 29.9, 25.9, 25.3, 19.9, 18.2, 17.4, −2.6, −3.1; IR (film) 3515.4 (b), 2952.2, 2932.9, 2859.6, 2102.5, 1699.4, 1465.9, 1383, 1302.9, 1264.4 cm^{-1}; MS (ESI) calcd for $[C_{16}H_{28}N_2O_4SiH]^+$ 341.18911, found 341.18915.

***rel*-(3a*S*,9a*R*)-3a-((*tert*-Butyldimethylsilyl)oxy)-3-diazo-9a-(hydroxymethyl)octahydrocycloocta[*b*]furan-2(3*H*)-one (39).** Lithium bis(trimethylsilyl)amide (1 M in THF/ethylbenzene, 1.90 mL, 1.89 mmol) was added to THF (142 mL) at −78 °C. A solution of diazo ester **37b** (0.50 g, 1.42 mmol) in THF (10 mL) was added dropwise via a syringe pump over 24 h while maintaining the temperature at −78 °C. The reaction mixture was then quenched with saturated aqueous NH_4Cl (70 mL) and allowed to warm to room temperature. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 70 mL). The organic layers were combined, washed with brine, dried over anhydrous $CaCl_2$, and concentrated to give a solid residue. Flash column chromatography (hexanes/EtOAc 6:1, 4:1, 2:1, 1:1) afforded 0.32 g (64% yield) of the title compound as an oil (R_f = 0.16 in hexanes/EtOAc 5:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.99−3.94 (m, 1H), 3.88−3.84 (m, 1H), 2.33 (dt, J = 13.3, 2.5 Hz, 1H), 2.04−1.74 (m, 9H), 1.46−1.35 (m, 2H), 1.13−1.05 (m, 1H), 0.98 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 96.4, 81.4, 65.1, 62.6, 33.7, 29.5, 28.6, 28.4, 26.5, 26.3, 25.3, 18.8, −2.9, −3.1; IR (film) 3490.9 (b), 2930.9, 2857.7, 2095.75, 1743.7, 1471.8, 1464.0, 1371.5, 1255.7 cm^{-1}; MS (ESI) calcd for $[C_{17}H_{30}N_2O_4SiH]^+$ 355.20476, found 355.20539.

***rel*-(3a*S*,9a*R*)-3a-((*tert*-Butyldimethylsilyl)oxy)octahydro-2*H*-3,9a-(epoxymethano)cycloocta[*b*]furan-2-one (40).** According to representative experimental procedure 1 that was used to prepare **9**, diazo lactone **39** (0.027 g, 0.075 mmol) reacted at 0 °C to give 0.020 g (80% yield) of ether **40** after purification via flash column chromatography on Davisil (hexanes/EtOAc 10:1; R_f = 0.57 in hexanes/EtOAc 2:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 (d, J = 8.9 Hz, 1H), 3.91 (s, 1H), 3.74 (d, J = 9.0 Hz, 1H), 2.16−2.10 (m, 1H), 2.06−1.93 (m, 5H), 1.86−1.81 (m, 1H), 1.78−1.71 (m, 1H), 1.63−1.55 (m, 1H), 1.31−1.22 (m, 2H), 1.13−1.06 (m, 1H), 0.91 (m, 9H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 95.6, 84.9, 83.4, 70.9, 33.1, 31.1, 29.2, 25.8, 25.7, 23.8, 22.5, 18.4, −2.3, −2.4; IR (film) 2929.0, 2857.7, 1791.9, 1472.7, 1454.4, 1362.8, 1255.7, 1199.8, 1174.7, 1133.2, 1087.9, 1067.7, 1007.9, 907.6, 837.1, 809.2, 778.3, 675.1 cm^{-1}; MS (ESI) calcd for $[C_{17}H_{30}O_4SiH]^+$ 327.19861, found 327.19871.

4-Oxacycloundecyne-3,6-dione (41). According to representative experimental procedure 1 or 2 used to prepare **9**, diazo lactone **38a-*cis*** provided 11-membered cyclic ynoate **39** in 64% yield (0.056 g) at 0 °C and 84% yield (0.089 g) at 40 °C. Diazo lactone **38a-*trans*** provided **39** in 57% yield (0.0093 g) at 0 °C and 67% yield (0.074 g) at 40 °C. The product was purified via flash chromatography on Davisil (hexanes/EtOAc 8:1, 6:1, 4:1, 2:1, and 1:1; R_f = 0.22 in hexanes/EtOAc 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.90 (s, 2H), 2.54−2.51 (m, 2H), 2.45 (t, J = 6.3 Hz, 2H), 1.84 (dtd, J = 12.6, 7.0, 3.5 Hz, 2H), 1.67−1.62 (m, 2H), 1.59 (ddt, J = 19.5, 7.1, 1.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.2, 153.5, 97.2, 72.8, 71.7, 37.7, 24.1, 23.0, 22.9, 18.3; IR (film) 2946.4, 2876.9, 2224.0, 1726.4, 1554.7, 1464.0, 1430.3, 1371.5, 1280.8, 1209.4, 1192.1, 1162.2, 1128.4, 1092.7, 1028.1, 1011.7, 954.8, 738.8 cm^{-1}; MS (ESI) calcd for $[C_{10}H_{12}O_3H]^+$ 181.08592, found 181.08585.

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■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org. CCDC 992222 contains the supplementary crystallographic data for this paper.

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Notes

The authors declare no competing financial interest.

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Development of a Clinically Applicable Protocol for Assessment of Hypoxic Response Through Measurement of the Endogenous Gasotransmitter Hydrogen Sulfide in Human Plasma

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Background: Gasotransmitters are endogenously made, biologically active gases with unique physiological properties. In addition to participation in the hypoxic respiratory reflex of the carotid body, the gasotransmitter hydrogen sulfide (H_2S) is thought to play a role in more localized vasodilatory hypoxic tissue responses. This pilot project describes a methodology suitable to the clinical environment that allows for H_2S gas capture in human plasma utilizing the fluorescent trapping agent dansyl azide.

Methods: Under an IRB-approved pilot project, 10 healthy male volunteers were spontaneously ventilated on room air, hypoxic (15% oxygen, 85% nitrogen), and hyperoxic (100%) gas mixtures through a nonrebreather system. Venous whole-blood samples were collected at both internal jugular and antecubital sites following 7 minutes of exposure to the tested oxygen environments. Resultant plasma aliquots were treated with dansyl azide and submitted to fluorescence reading (excitation 340 nm, emission 517 nm).

Results: Compiled mean data from volunteer plasma samples demonstrated statistically significant findings ($P < 0.05$) in measurement of increased fluorescent intensity between those samples collected under mildly hypoxic conditions compared with normoxic and hyperoxic samples submitted to the same laboratory criteria.

Conclusions: To study the role of H_2S as a marker of hypoxic response in humans, a reliable, robust, and safe protocol amenable to standard hospital laboratory procedures is needed. Through modification to methodologies described in the biochemistry literature, this pilot project demonstrates the feasibility of utilizing a fluorescent H_2S gas trapping agent for assessment of hypoxic response in humans within the confines of a typical clinical collection and analysis environment.

Key Words: gasotransmitter, hydrogen sulfide, translational research, protocol development, hypoxia, hypoxic response, endogenous gas

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Gasotransmitters are a group of endogenous gases with biochemical activity. Whereas the physiological and therapeutic properties of nitric oxide (NO) have been investigated for decades, the newer gasotransmitters, hydrogen sulfide (H_2S) and carbon monoxide (CO), have only more recently been appreciated as biochemical gases synthesized with specific physiological intentions.[1–3] In particular, the role these gases play in the hypoxic respiratory reflex is well documented with CO thought to function as a tonic vasoconstrictor and gatekeeper to the H_2S hypoxic vasodilatory and ventilatory responses.[4–9] A similar system of regulation seems to play out in the peripheral vascular[10,11] and central nervous system tissues[12] when exposure to low oxygen concentrations is experienced. Tissues that experience profound detrimental effects under hypoxic stress, such as the nervous and cardiovascular systems, are areas of particular perioperative interest where autonomic regulation and therapeutic modification of the human subject is of concern.[13–16]

The very properties that allow for the discrete synthesis, site of action, and catabolism of the gasotransmitters are also the characteristics that make them difficult to measure. H_2S in particular is a potent reductive agent in the in vivo system and is readily oxidized in most tissue environments, particularly in the presence of mitochondria,[17] and has a half-life of seconds to minutes depending upon binding and tissue environment. It is suspected that the permeable free gas itself is the biological initiator in the vasodilatory limb of the hypoxic response and as such would be the ideal target for monitoring and therapeutic intervention.[18–20] Its short half-life as a native molecule and

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low endogenous concentrations (variable by collection techniques but typically reported as 0.1 to 200 μM), however, mean that indirect capturing methods of measurement are favored for analytic purposes.[3]

Although there has been substantial development in analytical techniques for measurement of H_2S in the research environment, there is a dearth of described methodologies suitable for translation into the hospital environment.[21–30] At the bench level, any chemical reagent used must provide for easy synthesis, stable storage, acceptable solubility, and be robust enough to reliably interact with the complex chemical environment of a human specimen. At the systems level to achieve rapid result turnover, variables to be considered include staff fluency with collection method and supply use, equipment availability, technician familiarity with the measurement technique, and accommodation of the human subject. For our moderate-sized academic hospital facility, it was deemed that use of human blood samples treated with the fluorescent H_2S trapping agent dansyl azide (DnAz) would provide for the most reproducible experimental model.[31]

MATERIALS AND METHODS

DnAz Synthesis

A turbid solution of dansyl chloride (1.00 g, 3.71 mmol) in acetone (2 mL) was added to a stirring mixture of sodium azide (265 mg, 4.08 mmol) in water (1.1 mL) and acetone (1.85 mL); the dansyl chloride flask was rinsed once with acetone (0.3 mL) and added to the NaN_3 solution. During addition a slight exotherm was noted. A bright yellow reaction mixture was observed, which formed 2 layers that were stirred rapidly to effect mixing; after 15 minutes the reaction color faded to pale yellow. Stirring was continued for 3 hours at which point the acetone was removed at room temperature in vacuo. The residual aqueous layer was diluted with water (10 mL) and extracted with ether (3 × 15 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated at room temperature in vacuo to give 0.89 g (87% yield) of DnAz as a bright yellow oil that solidified upon storage. This material was deemed sufficiently pure to use without further processing. (Of note, change of the DnAz from oil to solid substantially altered solubility of the agent and resulted in changes to reagent preparation as described below. Repeat NMR spectroscopy of the solid DnAz material demonstrated retained purity of the azide, results not shown.)

Reagent Preparations

To address solubility concerns, either a 100 mM DnAz in EtOH (DnAz-EtOH) or 50 mM DnAz in EtOH (DnAz-EtOHdil) solution was prepared fresh daily. Sodium sulfide nonahydrate (> 98%, Na_2S-$9H_2O$, CAS 1313-84-4; Sigma-Aldrich) in normal saline (H_2S-Stan) was made as a 1 mM stock solution before each collection and stored in a sealed plastic container at room temperature.

Internal Standards

DnAz-EtOH(dil) stock solution was added to 20 mM phosphate/0.5% Tween 20 buffer in polyurethane eppendorf tubes for a final concentration of 200 μM DnAz. The eppendorf samples were then spiked with H_2S-Stan to final concentrations of 0, 1, 5, 10, 20, 40, and 80 μM. Samples were sealed and stored at room temperature. Human plasma standard samples were collected as described below and internal standard curves were obtained through spiking of H_2S-Stan to final concentrations of 0, 5, 10, 20, 40, and 80 μM.

Human Plasma Studies

A study involving whole-blood samples collected from healthy human volunteers exposed to variable oxygen conditions was approved by our hospital ethics committee (CHRMS: M13-010). Twelve healthy adult male subjects were recruited and gave written informed consent before participation in the study. Laboratory inclusion criteria for these volunteers incorporated at least 1 of 2 successful runs of the prepared DnAz-EtOH(dil) in buffer with a resultant trendline correlation coefficient (R^2) ≥ 0.95. Ten of the 12 subjects met inclusion criteria as described. The 2 subjects who failed inclusions criteria were treated with the DnAz-EtOH as a 100 mM solution immediately following change of the DnAz from an oil to a solid and before decreasing to a 50 mM base solution (DnAz-EtOHdil); it is likely that the DnAz precipitated before reaction in these samples. Lastly, 1 recurrent subject (subject V) donated PIV samples only under the tested conditions but did not contribute IJ samples at that time; this brought the PIV collections to a higher sample total.

Volunteer subjects were placed in a reclined position and had an 18 g 1¾ inch catheter introduced into their right internal jugular (IJ) vein under ultrasound guidance, and a 20 g 1¼ inch catheter placed into a right antecubital vein (PIV). Venipuncture sites were accessed through a 3-way stockcock with 6 cm tubing and a saline flush/waste port. End-tidal oxygen concentration and ventilation cycles were monitored through a nonbreather anesthetic system (Narkomed 2B) through a self-applied tight-fitting face mask. Measurements of oxygen concentration, oxygen saturation, and end-tidal carbon dioxide served to ensure equilibration to the tested oxygen concentrations and maintenance of normocarbia. Oxygen exposure conditions and sample collection for test subjects occurred in the order of room air (RA), 15% oxygen and 85% nitrogen (15%O_2), and then 100% oxygen (100%O_2). RA samples were taken before ventilation of specialized gas mixtures and occurred without mask application.

After 7 minutes each of exposure to the 15% O_2 and then 100% O_2 gas mixtures, 3 mL samples of whole blood were drawn from the PIV and IJ sites and immediately placed into heparinized vacuum collection vials (Greiner Bio-One 3 mL Lithium Heparin Separation Vacuette, Ref#454247); PIVRA (n = 16), IJRA (n = 10), PIV15%O_2 (n = 15), IJ15%O_2 (n = 10), PIV100%O_2 (n = 16), IJ100%O_2 (n = 9). All samples were inverted gently before

addition of the DnAz-EtOH(dil) to a final concentration of 200 μM. Treated vials were stored at room temperature until all collections for each subject were completed; this resulted in six 3 mL samples per subject (except for subject V).

Collection vials were then transported to the hospital laboratory and plasma separated by centrifugation at 3000 rpm for 5 minutes. The first 4 study subjects were treated with DnAz-EtOH(dil) at whole-blood stage only. Solubility concerns for the fluorescent trapping agent led to later study subjects being treated with 200 μM DnAz-EtOHdil at both time of whole-blood collection and then subsequently again immediately after plasma separation; this was done to ensure adequate levels of DnAz for the last step of internal standard capture and trendline verification. Integrity of trendlines in both buffer and plasma samples with sequential addition versus single addition of DnAz was verified before initiation of this change in test subjects. Aliquots (200 μL) of DnAz-treated plasma were separated into individual eppendorf containers, where H_2S-Stan was added to final concentrations of 0, 5, 10, 20, 40, and 80 μM. Samples were sealed and stored at room temperature until analyzed.

Measurement of Fluorescence

Aliquots (150 μL) of buffer and plasma samples were placed in a 96-well plate reader (Synergy H4, BioTek; excitation 340 nm, emission 517 nm). Intensity readings were recorded and transferred as raw data to a Microsoft Office Excel 2007 spreadsheet for further analysis.

Statistics

Statistical analyses and graph design were conducted using Microsoft Office Excel 2007 and JMP 11 (SW) for Windows.

RESULTS

NMR Spectroscopy of DnAz

Rf = 0.5(4:1 Hexane:EtOAc): ^{1}H NMR (500 MHz, $CDCl_3$) δ8.67 (dt, J = 8.5,1.1 Hz,1 H), 8.34 (dd, J = 7.4,1.3 Hz,1 H), 8.20 (dt, J = 8.7,0.8 Hz,1 H), 7.64 (dd, J = 8.6,7.6 Hz,1 H), 7.58 (dd, J = 8.5,7.4 Hz,1 H), 7.24 (dd, J = 7.6,0.7 Hz,1 H), 2.90 (s,6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ152.1, 133.7, 132.6, 130.1, 130.0, 129.6, 129.2, 122.9, 118.7, 115.8, 77.3, 77.0, 76.8, 45.4.

Human Volunteer Response to Variable Oxygen Conditions

Overall trends in fluorescence show an increase in intensity in hypoxic samples compared with normoxic and hyperoxic samples obtained from both the PIV and IJ sites. Separate PIV and IJ sampling was initially undertaken due to concerns for differential H_2S-producing enzyme expression in the central nervous and peripheral vascular systems; this proved to be insignificant under our collection parameters and so PIV and IJ sample data were pooled by oxygen exposure type for analysis. Samples included: RA (n = 26, average fluorescence: 17107, SD: 5937), 15% O_2 (n = 25, average fluorescence: 19932, SD: 5642), 100% O_2 (n = 25, average fluorescence: 15467, SD: 6002) (Fig. 1).

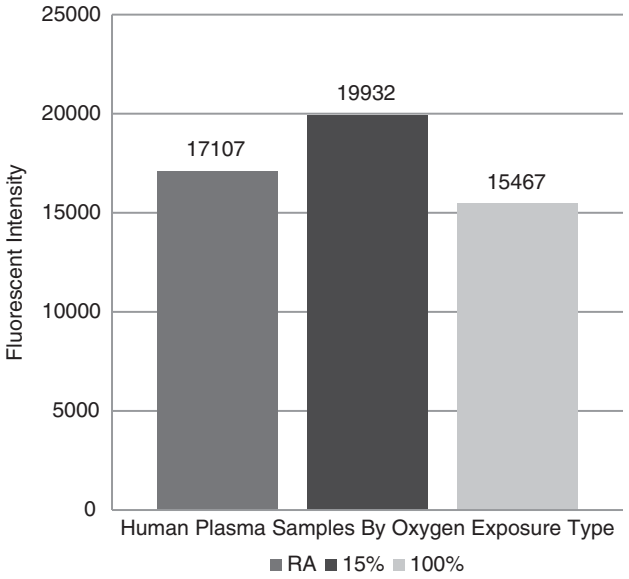

FIGURE 1. Mean fluorescent activity of human plasma samples collected under the tested oxygen conditions without internal standard addition (RA: room air, 15%: 15% O_2/85% N_2, 100%: 100% O_2).

Matched t test analysis was utilized to calculate the statistical significance ($P < 0.05$) in change between samples collected under the tested oxygen condition (RA, 15% O_2, or 100% O_2) such that each of the 10 study subjects had 3-sample set combinations collected in 6 vials (volunteer V contributed PIV samples only). Matched t test analyses were made in 2 ways: from intensity data taken from DnAz-treated plasma without addition of an internal standard ("zero-point" data), or from the mean derived from recombined internal standard samples ("internal standard" data) in a given set (eg, the mean from combined IJ and PIV plasma samples taken under 100%O_2 conditions). The combined internal standard data set was made at the suggestion of laboratory staff to evaluate the integrity of a pooled sample from trendline aliquots in the event larger sample volumes were needed. Statistically significant results were found when comparing PIV obtained samples under 15% O_2 versus hyperoxic and normoxic conditions (data not shown). When data were pooled by oxidative exposure type (PIV and IJ combined for each oxidative exposure type), all changes between all oxygen states became significant (Table 1).

Further supplemental materials related to volunteer subject data and pilot project equipment and reagent comparisons are available (Supplemental Digital Content, http://links.lww.com/JNA/A21).

DISCUSSION

Conditions of chronic and acute hypoxia are encountered with great frequency in the clinical environment

TABLE 1. Combined *t* Test by Oxygen Exposure

P	PIV&IJ: RA vs. 15%	PIV&IJ: 15% vs. 100%	PIV&IJ: RA vs. 100%
Zero-point means data	0.007	0.001	0.013
Internal standard means data	0.005	0.002	0.036

with their management often falling to the anesthesiologist in the perioperative period. Chronic obstructive pulmonary disease and sleep apnea, commonly encountered conditions of chronic hypercarbia that lead to a greater reliance upon hypoxic chemosensors, represent a conundrum for the physician with regard to the monitoring of a patient who is in a state of compensated dysautonomia.[32–34] Patients with diffuse neuronal injury, such as that seen in traumatic brain injury, also experience abnormalities in autonomic response, which can result in secondary damage to tissues following an initial hypoxic insult.[35–37] At present our ability to monitor subtle and acute physiological changes to hypoxia in these types of patients is limited and relies primarily upon observations that we use as a surrogate for the physiological change we are most interested in. How would our prognostic abilities as a physician to these types of patients change if we had the ability to quickly and specifically assess the integrity of their response to hypoxia?

Gasotransmitters are still early in their research paradigm and as such their potential for practical application in the clinical realm for monitoring and therapeutic management is unknown. Considering this unknown, the initial goal of our pilot project was not one of attempting to calculate quantitative changes in response to hypoxia, but rather was one of seeing whether significant variation within individuals could even be assessed using the materials and system available. Through use of a H_2S-specific fluorescent gas trapping agent, we were able to demonstrate in this small pilot study the significant increases in H_2S upon acute subject exposure to mildly hypoxic conditions, and a rapid return to near-baseline values upon subsequent application of hyperoxic gas.

Numerous equipment, solvent, concentration, temporal, and collection methodologies were investigated before initiation of the described human subject study; these data were not included for discussion but was nonetheless integral to successful translation of described literature techniques into the clinical environment (Supplemental materials available, Supplemental Digital Content, http://links.lww.com/JNA/A21). Weaknesses of this pilot project include a small sample size, relative insolubility of the hydrophobic fluorescent agent in human blood, and a collection timepoint that may not represent an optimal hypoxic response profile for H_2S capture in human plasma. With regard to the DnAz utilized for this study, newer fluorescent moieties have since been described and are likely to prove more amenable to whole human blood application[28,29]; this in turn would allow for better sequential analysis of H_2S production and development of response profiles for this gas in humans. It is anticipated that further work on the topic utilizing clinically applicable methodologies similar to the one described will help to elucidate the practicality of using gasotransmitters as a monitor of hypoxic response in human subjects.

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Figure 2: Human Serum Following Alternative Dosing Interval of DnAz
Legend: *Differing levels of hemolysis was noted with variation of order in addition of the DnAz to human whole blood and serum samples.*

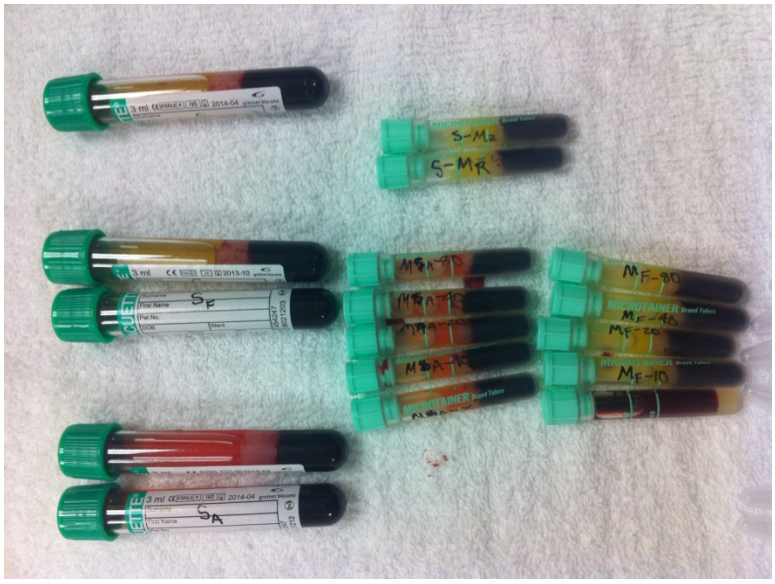

Figure 3: Mean Fluorescent Activity of Human Serum Collected at Variable Oxygen Condition

Legend: *Mean fluorescence of human volunteer serum exposed to variable oxygen conditions. (PIV: antecubital intravenous catheter collection site, IJ: intrajugular intravenous catheter collection site, RA: room air, 15%: 15% oxygen and 85% nitrogen, 100%: 100% oxygen).*

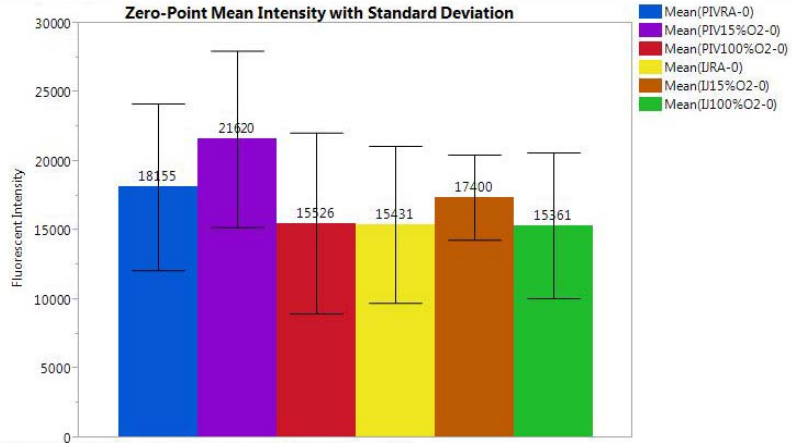

Table 1: Assessment of Dansyl Azide

Sample ID	R^2	Notes
Solvent Trials for DnAz		
Buffer $DnNH_2$-DMSO	0.281	$DnNH_2$-DMSO (250μM) standard
Buffer DnAz-DMSO	0.977	DnAz-DMSO (100mM)
Buffer DnAz-EtOH	1.000	DnAz-EtOH (100mM)
Buffer DnAz-EtOH filter	1.000	DnAz-EtOH (100mM) dissolved and filtered; added to WB
Serum EtOH (no DnAz)	0.089	EtOH added to WB, no DnAz
Serum DnAz-DMSO	0.554	DnAz-DMSO (100mM) added to WB
Serum DnAz-EtOH	0.039	DnAz-EtOH (100mM) added to WB
Serum DnAz-EtOH (pure solv)	0.864	DnAz-EtOH (100mM) to WB, purified EtOH
Serum DnAz-EtOH dilute	0.869	DnAz-EtOH (50mM standard) added to WB vial
Serum DnAz-EtOH filter	0.200	DnAz-EtOH (100mM) dissolved and filtered; added to WB
Solubility/Dilution Trials of DnAz		
Buffer	0.962	DnAz-EtOH (100mM) to buffer
Buffer	0.998	DnAz-EtOH (50mM) to buffer
Serum: PIVRA concentrated	0.025	DnAz-EtOH (100mM) to WB vial
Serum: PIVRA dilute	0.037	DnAz-EtOH (50mM) to WB vial
Serum: PIV15% concentrated	0.083	DnAz-EtOH (100mM) to WB vial
Serum: PIV15% dilute	0.315	DnAz-EtOH (50mM) to WB vial
Serum: PIV100% concentrated	0.906	DnAz-EtOH (100mM) to WB vial
Serum: PIV100% dilute	0.983	DnAz-EtOH (50mM) to WB vial

**DnAz-EtOH (xmM) listed as stock solution; added as 200μM to WB*

Abbreviations: ethanol (EtOH), dimethylsulfoxide (DMSO), dansyl azide (DnAz), dansyl amide ($DnNH_2$), peripheral intravenous catheter (PIV)

Table 2: Assessment of $ZnCl_2$ as Quenching Agent

Sample ID	R^2 (-)ZnCl	R^2 (+)ZnCl	Notes
Buffer	0.908	0.902	$ZnCl_2$>baseline ("zero-point")
Buffer	0.893	0.914	
Buffer	0.990	0.992	
Buffer	0.983	0.980	$ZnCl_2$>baseline ("zero-point")
Serum-MT	0.981	0.917	
DnAzpure-MT	0.226	0.182	$ZnCl_2$>baseline ("zero-point")

Serum-MT	0.967	0.968	$ZnCl_2$>baseline ("zero-point")
Serum-vial	0.967	0.575	

Abbreviations: microtainer (MT)

Table 3: Assessment of Solvents for Na_2S x $9H_2O$

Sample ID	R^2	Notes
Buffer	0.983	DnAz (100mM)
Serum-water	0.983	DnAz (100mM) added to MT after spin
Serum-NS	0.990	DnAz (100mM) added to MT after spin
WB-water	0.271	DnAz (100mM) added to WB in MT
WB-D5	0.344	DnAz (100mM) added to WB in MT
WB-D5NS	0.439	DnAz (100mM) added to WB in MT
WB-NS	0.521	DnAz (100mM) added to WB in MT
WB-LR	0.420	DnAz (100mM) added to WB in MT
D5-vial	0.949	DnAz added to serum in eppendorf tubes
D5NS-vial	0.836	DnAz added to serum in eppendorf tubes
LR-vial	*N/A*	*clotting noted upon addition to serum*

Abbreviations: 0.9% normal saline (NS), 5% dextrose (D5), 5%dextrose/ 0.9%NS (D5NS), lactated ringers (LR)

Table 4: Correlation Coefficients of Human Serum Fluorescence Following Internal Standard Addition

Subject ID	Buffer R^2	Internal Standard Intensity R^2			Mean Intensities
		RA	15%O_2	100%O_2	15%O_2>100%O_2
DnAz-EtOH: whole blood only[†]					
V - PIV	0.98	0.37	0.03	0.75	Yes
V - PIV		0.78	0.68	0.85	Yes
V - PIV		0.91	0.89	1.00	Yes
V - PIV	0.96	0.02	0.08	0.91	Yes
A - PIV[a]	0.99	0.98	*n/a*	0.96	*n/a*
A - IJ		0.98	0.99	*n/a*	Yes
B - PIV[b]	0.97	1.00	0.84	1.00	Yes
B - IJ		1.00	0.08	0.99	Yes
C - PIV/IJ	0.91				
E - PIV/IJ	0.94				

DnAz-EtOHdil: whole blood only[††c]					
V - PIV	0.96	0.04	0.31	0.98	Yes
F - PIV	0.97	0.04	0.49	0.25	Yes
F - IJ		0.08	0.10	0.93	Yes
G - PIV	1.00	0.21	0.02	0.71	Yes
G - IJ		0.27	0.33	0.92	Yes
DnAz-EtOHdil: whole blood and serum[†††]					
G - PIV	1.00	0.99	0.99	0.91	Yes
H - PIV	0.99	0.91	0.87	0.85	Yes
H - IJ		0.94	0.86	0.97	Yes
I - PIV	0.99	0.82	0.91	0.04	Yes
I - IJ		0.09	0.64	0.65	No
J - PIV	1.00	0.95	0.97	0.74	No
J - IJ		0.90	0.99	0.98	Yes
K - PIV	0.99	0.94	0.98	0.99	No
K - IJ		0.95	0.97	0.95	Yes
L - PIV	0.99	0.80	0.94	0.95	Yes
L - IJ		0.98	0.91	0.82	Yes
D - PIV	1.00	0.99	0.98	1.00	Yes
D - IJ		0.85	0.98	0.95	Yes

[†] *100mM DnAz-EtOH: 200µM to whole blood only*

[††] *50mM DnAz-EtOHdil: 200µM to whole blood only*

[†††] *50mM DnAz-EtOHdil: 200µM to whole blood and then 200µM to serum*

[a] *Unclear labeling: samples A-PIV15%02 and A-IJ100%O2 discarded from data set*

[b] *Trending suggests complete consumption of DnAz-EtOH (200µM) in 15%O_2 samples*

[c] *DnAz-EtOH (200µM)shows initial gas but not internal standard capturing*

Table 5: Assessment of Plates, Pipette Tips, and Reagents

Sample ID	R^2	Notes
Buffer: old Tween	0.997	old buffer solution
Buffer: new Tween	0.999	new buffer solution
New Plate:PIV RA 200µM	0.366	DnAz (200µM) added to WB only
New Plate:PIV 15% 200µM	0.030	DnAz (200µM) added to WB only
New Plate:PIV 100% 200µM	0.754	DnAz (200µM) added to WB only
Old Plate:PIV RA 200µM	0.775	DnAz (200µM) added to WB only
Old Plate:PIV 15% 200µM	0.678	DnAz (200µM) added to WB only
Old Plate:PIV 100% 200µM	0.851	DnAz (200µM) added to WB only
Old Plate:PIV RA 400µM	0.912	DnAz (400µM) added to WB only

Old Plate:PIV 15% 400µM	0.894	DnAz (400µM) added to WB only
Old Plate:PIV 100% 400µM	0.995	DnAz (400µM) added to WB only
Serum old pip-200µM	0.985	DnAz (200µM); old pipette tips and eppendorfs
Serum new pip-200µM	0.988	DnAz (200µM); old pipette tips and eppendorfs
Serum old pip-400µM	0.975	DnAz (400µM); old pipette tips and eppendorfs
Serum new pip-400µM	0.976	DnAz (400µM); old pipette tips and eppendorfs

**All DnAz-EtOH from 100mM stock solution*

Table 6: Combined t-Test by Site and Oxygen Exposure

p-values from Zero-Point Means Data

	PIVRA	PIV15%O2	PIV100%O2	IJRA	IJ15%O2	IJ100%O2
PIVRA		0.025	0.032	0.145	0.229	0.047
PIV15%O2	0.014		0.005	0.0496	0.043	0.022
PIV100%O2	0.076	0.006		0.265	0.082	0.066
IJRA	0.073	0.026	0.397		0.084	0.1
IJ15%O2	0.287	0.034	0.117	0.099		0.053
IJ100%O2	0.034	0.015	0.082	0.094	0.067	

p-values from Internal Standard Means Data

**p<0.05 shaded in purple*

Table 7: Combined t-Test by Oxygen Exposure

p-values from Zero-Point Means Data

	RA-PIV&IJ	15%O2-PIV&IJ	100%O2-PIV&IJ
RA-PIV&IJ		0.007	0.013
15%O2-PIV&IJ	0.005		0.001
100%O2-PIV&IJ	0.036	0.002	

p-values from Internal Standard Means Data

**p<0.05 shaded in purple*

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