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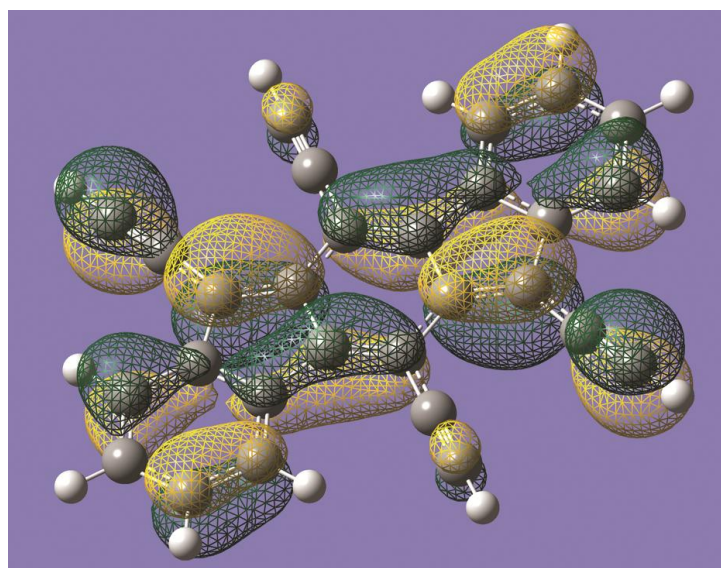
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Coarctate cyclization reactions: a primer†

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The cleavage of five-membered heterocycles possessing an exocyclic carbene or nitrene to form conjugated ene–ene–yne systems has been documented for over 40 years; however, the reverse reaction, using a conjugated “ene–ene–yne” precursor to form a heterocycle is a relatively new approach. Over the past decade, the Haley and Herges groups have studied computationally and experimentally the cyclization of the “hetero–ene–ene–yne” motif *via* an unusual class of concerted reactions known as *coarctate* reactions. This feature article details our synthetic and mechanistic work involving triazene–arene–alkynes and structurally-related systems to generate heterocycles using coarctate chemistry.

1. Introduction

Louis Pasteur is attributed for saying that “chance favours the prepared mind”. Chance, luck, serendipity—call it whatever you wish. Science, especially chemistry, is replete with examples where interesting and important discoveries have been made less by design and more by happenstance. This story, our discovery of the coarctate cyclizations of conjugated “azo–ene–yne” molecules to generate heterocycles, is no different. In this Feature Article we will define “coarctate” reactions, highlight

the key findings from our 12+ years of experimental and computational studies, and illustrate more than once that serendipity has played an important role in this line of research.

1.1 Surprising outcomes

Since the mid-1990s, the Haley lab at Oregon has been studying the synthesis and optoelectronic properties of a class of carbon-rich molecules known as dehydrobenzo[*n*]annulenes ([*n*]DBAs).^{1–4} Our initial targets were the triangular-shaped [18]DBAs, *e.g.*, **1**.^{5,6} In general, the assembly of these compounds (Scheme 1) involved triynes such as **2** prepared from triazene intermediates like **3**, which in turn started from commercially available or easily synthesized aniline derivatives. An important step in this overall sequence was the MeI-promoted conversion of the triazene unit into the corresponding aryl iodide.⁷ This transformation, developed by Jeff Moore’s group

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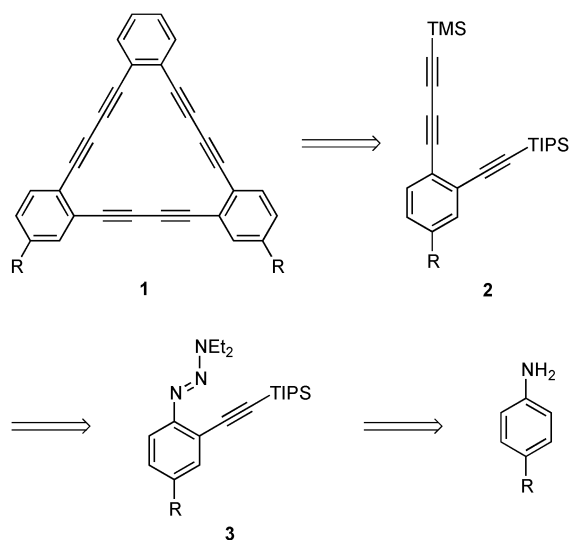
Brian S. Young was born in Seattle, WA, USA in 1981. He received his BS in biochemistry from the University of New Mexico in 2003. In 2008, he joined the University of Oregon where he is currently working toward his PhD under the supervision of Prof. Haley. His research focuses on the synthetic and computational investigations of the coarctate cyclizations of conjugated hetero–ene–ene–yne systems.



Rainer Herges

Rainer Herges studied chemistry at the University of Saarland and received his doctorate at the Technical University of Munich. After a postdoctoral stay at the University of Southern California, Los Angeles with George Olah, he joined the group of Paul v. R. Schleyer at the University of Erlangen for his habilitation. In 1996, he received a C3 position as Professor at the Technical University of Braunschweig, and in 2001 he was appointed as Full Professor

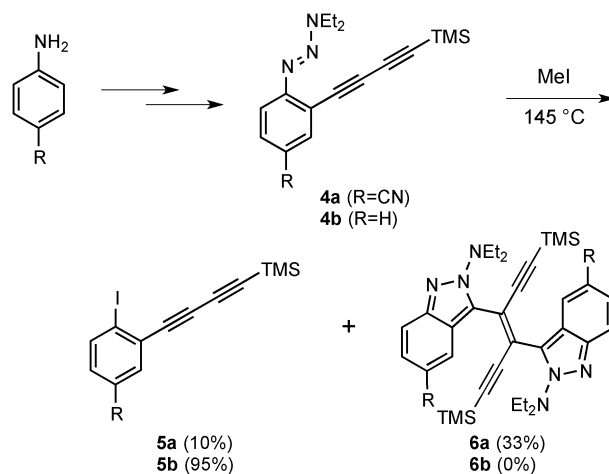
at the University of Kiel. His main interests are supramolecular chemistry, coarctate reactions, computational chemistry, and Moebius aromaticity.



Scheme 1 DBA formation *via* triazene-ene-yne intermediates.

for their phenyl-acetylene macrocycle work,^{8,9} has been successfully performed in our group hundreds of times.

In spring 2000, graduate student Dave Kimball uncovered an example where the MeI reaction failed spectacularly. As illustrated in Scheme 2, Dave had decided to reverse the order with which he attached the alkyne groups, electing to first put on the (trimethylsilyl)butadiyne unit such that it was *ortho* to the triazene (*e.g.*, **4**), instead of the usual (triisopropylsilyl)-acetylene unit as in **3**. Surprisingly, the desired aryl iodide **5a** was produced from **4a** in an abysmal 10% yield, along with a considerably more polar compound as the major product. To his credit, Dave did not discard the undesired molecule, but instead obtained copious spectral data to attempt to elucidate the structure of this mystery compound. From the data three things were certain: (1) the $-\text{NEt}_2$ group was still intact, (2) the azo linkage must be either locked or missing as the proton signal for the methylenes of the $-\text{NEt}_2$ unit was now a broad featureless resonance and not the sharp quartet typically



Scheme 2 Unanticipated dimer formation.

found in triazenes, and (3) the mass of the molecule was exactly twice that of starting material **4a**. “What did I make?” Dave wondered aloud. Admittedly, we had little clue. While we scribbled out a number of possible dimeric structures, most seemed implausible. An X-ray structure determination provided the answer—the major product was isoindazole **6a**, where the central nitrogen of the triazene had attacked the proximal carbon of the first alkyne unit and the distal carbon simply dimerized with a second molecule to generate the *trans*-enediyne.¹⁰ For a group whose most exciting experience with heterocycles was using THF as a solvent, this result came as a big surprise!

Dave next examined triazene **4b** and found that in this instance aryl iodide **5b** was produced in excellent yield with *no evidence* of the corresponding heterocycle **6b** (Scheme 2).¹⁰ Repeating these reactions at both lower and higher temperatures revealed an interesting temperature window and substituent preference. No reaction occurred below 110 °C. As noted above, **4a** formed isoindazole dimer **6a** along with the corresponding iodoarene as a minor product at 145 °C, whereas cyclization/dimerization of **4b** failed since triazene decomposition/iodoarene formation occurred well below 145 °C. If **4a** was heated above 160 °C, however, iodoarene **5a** was obtained in excellent yield. These results indicated that for cyclization/dimerization to occur in MeI, strong electron-withdrawing substituents must be present to deactivate the dialkylamino-nitrogen in the triazene toward nucleophilic attack.

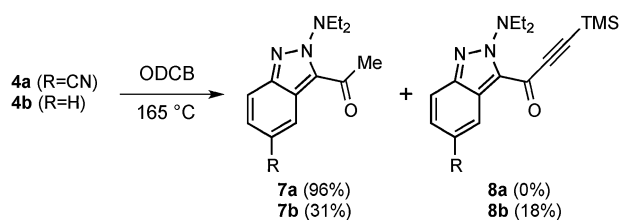
Given the extreme volatility, alkylation reactivity, and toxicity of MeI, Dave investigated other common solvents. Heating triazene **4a** to 160–170 °C for 48 h resulted either in no reaction (EtOAc, CHCl_3 , benzene, toluene, MeCN) or a complex mixture of by-products (DMF, DMSO). Since the reaction consistently afforded **6a** at 145 °C, he then focused on *ortho*-dichlorobenzene (ODCB), which boils at 180 °C yet has polarity similar to MeI. While heating **4a** in ODCB successfully gave an isoindazole product in high yield, it was not the expected dimer but instead acyl-2*H*-indazole **7a** (Scheme 3). Repeating this experiment with compound **4b** gave the corresponding indazole **7b** along with the likely intermediate in the acyl isoindazole formation, propioloyl compound **8b**.¹⁰ NMR and mass spectral analysis corroborated the structure of the



Michael M. Haley

Michael M. Haley received both his BA (1987) and PhD degrees (1991) from Rice University studying with W. E. Billups. After a two-year period as an NSF Postdoctoral Fellow working with Peter Vollhardt at the University of California, Berkeley, Haley joined the faculty at the University of Oregon in 1993 where he is currently a Professor of Chemistry and Head of the department. He was recently named a Fellow of the American Association

for the Advancement of Science (2011). Haley's current research focuses on coarctate reactions, pi-electron-rich organics for electronic applications, and the supramolecular chemistry of phenyl-acetylene scaffolding.



Scheme 3 Acylisoindazole formation from diynes **4a–b**.

oxygen-incorporated products. The loss of the SiMe₃ protecting group as well as one methine unit from **7a–b** was not readily explainable. As a whole, our results thus far suggested that we needed to simplify matters considerably.

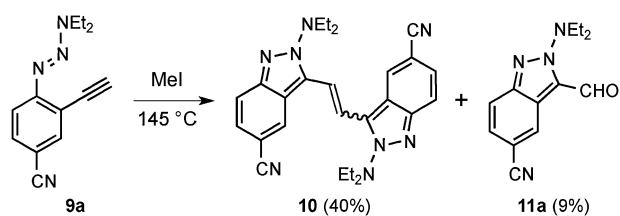
1.2 Monoynes cyclizations made easy

Starting material “simplification” was an easy process—exchange the (trimethylsilyl)butadiyne moiety for an ethyne unit to generate *ortho*-ethynylphenyltriazenes like **9**. Would that result in product mixture simplification? The answer for **9a** was “no” using MeI as solvent. Once more, Dave isolated an isoindazole dimer, now alkene-linked as a 2 : 1 *trans* : *cis* mixture (**10**), along with a low yield of isoindazolecarbaldehyde **11a**, where once again an oxygen atom was incorporated (Scheme 4).¹⁰

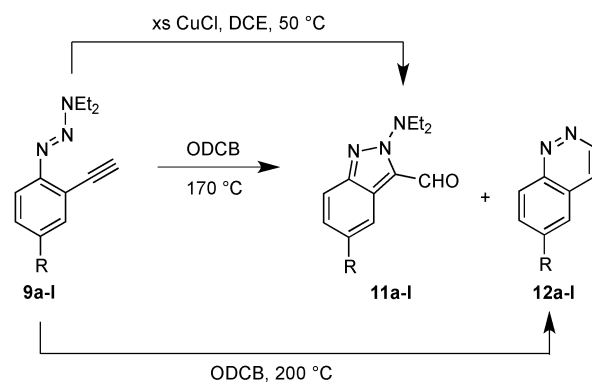
Things began to improve upon switching solvent. When heated to 170 °C in ODCB, monoynes **9a** gave a mixture of two different heterocycles—once again isoindazole aldehyde **11a** and a new 6-membered ring compound, cinnoline **12a** (Scheme 5). Although produced as roughly a 1 : 1 mixture, the combined isolated yield was a respectable 95% (Table 1). Interestingly, in ODCB the previously observed dimeric species were either not produced or obtained only in trace amounts. For the series of 12 substituents studied (**a–l**), mixtures of 5-substituted 3-formyl-2-diethylamino-2H-indazoles (**11**) and 6-substituted cinnolines (**12**) typically were generated; the electronic nature of the para substituent did affect the ratio of isoindazole to cinnoline, though not in a predictable fashion (Table 1). The sole exceptions were strongly-donating monoynes **9k** and **9l**, which furnished only the corresponding aldehydes **11k** and **11l**. Heating to 200 °C gave exclusively the cinnoline heterocycle for entries **a–j** in excellent yields (Table 1). Under the same conditions **9k** and **9l** once again resulted in no observable cinnoline formation. Satisfied with the thermal results, we finished the initial story and off it went to *Organic Letters* at the end of August 2000,¹¹ just in time for a three month sabbatical in Germany.

1.3 Talking shop in Braunschweig

Most of the sabbatical that fall was spent writing papers, crafting an NSF renewal proposal, giving lectures at



Scheme 4 Dimer and aldehyde formation from monoynes **9a**.



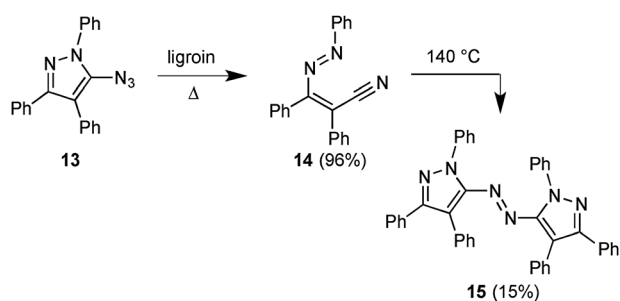
Scheme 5 Cyclizations of triazene-ene-yne **9**.

Table 1 Yields of isoindazoles **11** and cinnolines **12** from monoynes **9**

Entry	R	Isoindazole ^{a,b}	Cinnoline ^{a,c}
a	CN	50% [85%] ^d	45% (98%)
b	H	55% [95%]	35% (99%)
c	Me	20% [90%]	51% (97%)
d	^t Bu	22% [96%]	61% (98%)
e	CCH	36% [91%]	39% (83%)
f	Br	15% [98%]	70% (98%)
g	Cl	14% [95%]	58% (97%)
h	F	25% [94%]	35% (90%)
i	CO ₂ Me	63% [83%]	28% (96%)
j	NO ₂	60% [78%] ^e	25% (93%)
k	OMe	85% [98%]	0% (0%) ^f
l	OAc	89% [96%]	0% (0%) ^f

^a Yield at 170 °C. ^b Yield of CuCl-promoted reactions at 50 °C in brackets. ^c Yield at 200 °C in parentheses. ^d Reaction run at rt; reaction at 50 °C gave 60% yield of **11a** and 34% of **10**. ^e Reaction run at rt; reaction at 50 °C gave 54% yield of **11j** and 37% of NO₂-analogue of **10**. ^f Only isoindazole was generated under all reaction conditions.

universities and fighting with a continually crashing hard drive. While presenting the beginnings of this new work in lectures, we were convinced, erroneously at the time, that cinnoline formation proceeded *via* an “aza-Bergman” cyclization, and thus we were less interested in the isoindazoles. That all changed in late November. While many an evening had been spent in Rainer’s basement consuming wine and talking politics, we never really “talked shop” that much. During the last week in Germany, we finally got around to discussing the new heterocycle work. In addition to laying out the (incorrect) mechanistic case for the cinnolines, I mentioned in passing that we often obtained “unwanted” isoindazoles in low to modest yields. Without saying a word, Rainer retrieved a copy of a review he published in 1994.¹² With a huge grin on his face, he asked, “Does it look like this?” At the top of page 264 was the reaction sequence shown below in Scheme 6.¹³ It was immediately obvious that monoynes **9** could map topologically onto **14** and that similarly **11** and **10** onto **13** and **15**, respectively. I had forgotten that Rainer was the main proponent of “coarctate” reactions, a new reaction classification that had been hotly debated at the 1999 Physical Organic Gordon Research Conference. While examples of coarctate ring-opening reactions had been known since the mid-1960s,^{14,15} examples of the analogous ring-closing process were rare.



Scheme 6 Reactivity of azidopyrazole **13**.

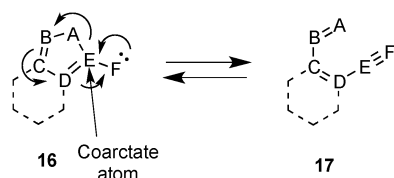
With the isoindazoles we had unknowingly discovered the first general example of a coarctate cyclization. Rainer was so excited by these results that he stopped all the jobs on his computers and calculated the reaction energy profile in less than four days—thus began our long-standing collaboration examining the experimental and theoretical details of “hetero-ene-yne” coarctate cyclizations.

2. The coarctate reaction

2.1 Classification by Herges

As noted above, the key clue for the mechanism of isoindazole formation came from two 1994 reviews written by Rainer. The *Angew. Chem.* article described a computer-aided classification of more than 80 000 chemical reactions from reaction databases, which indicated three topologies of electron redistribution.¹² Two of these reflected common ways of thinking about chemical reactions with the linear topology corresponding to mechanisms such as addition, substitution, and elimination, and with the cyclic topology corresponding to pericyclic reactions. However, Rainer found a third topology having a more complicated electron redistribution pattern that belonged to a distinct class of concerted reactions that had previously not been described. Rainer named these reactions “coarctate”, derived from the Latin *coarctare*, meaning compressed or constricted. In addition to numerous fragmentation reactions, these coarctate reactions included the cleavage of five-membered rings bearing exocyclic carbenes or nitrenes, depicted in Scheme 7. Although coarctate reactions are concerted, they cannot be considered pericyclic because of the involvement of the exocyclic carbene (atom F in **16**).

Coarctate reactions can be identified by so-called “coarctations”, an atom or linear sequence of atoms in which two bonds are broken and two bonds are formed in a single step. These coarctations are bound by “terminators”, which consist of an atom with a lone pair, two atoms complementing the electron shift to a three-membered ring, four atoms complementing the shift to a five-membered ring, *etc.*



Scheme 7 A generic coarctate ring-opening/-closing reaction.

In the *J. Chem. Inf. Comput. Sci.* paper,¹⁶ 74 conceivable reactions of the latter type were listed. Some of these reactions were known, most were predicted as possible candidates for future discovery. Our isoindazole cyclization turned out to fit reaction #71 in the list; thus, a new coarctate reaction was found!

2.2 Ring-opening reactions

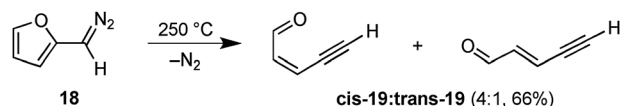
Aside from ring fragmentations, a significant majority of coarctate reactions in the literature are the ring-opening variety to generate conjugated “ene-ene-yne” such as **17**. Two classical and salient examples are presented here. Beginning in 1964, Smith and coworkers investigated the reactivity of azidotriazoles and azidopyrazoles in an attempt to synthesize a stabilised nitrene.¹⁴ Unbeknownst to them, their work represented the first examples of coarctate ring-opening reactions. For instance, pyrazole **13** decomposed at 50 °C, losing molecular nitrogen to afford azo-ene-nitrile **14** in excellent yield (Scheme 6).¹³ Heating **14** to 140 °C furnished dimer **15** in low yield, demonstrating that the ring-opened and ring-closed forms could readily interconvert.

Perhaps the most thoroughly studied coarctate reaction is the ring-opening of 2-furfurylcarbenes.^{17–20} For the parent system, Hoffman and Schechter found that thermal decomposition of **18** afforded a 4 : 1 mixture of *cis/trans*-2-penten-4-ynal (**19**) in 66% yield (Scheme 8). Additional experiments using cyclooctane and styrene generated C–H insertion and [2 + 1] cycloaddition products, respectively, strongly implicating a carbene intermediate.

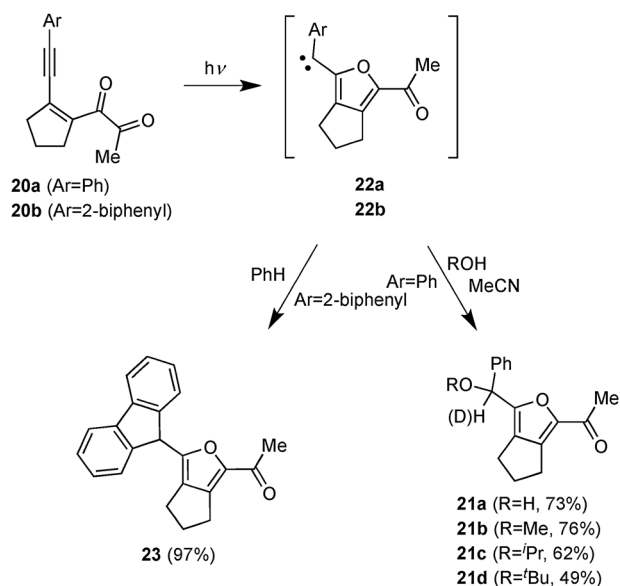
2.3 Ring-closing reactions

Whereas ring-opening reactions dominate the coarctate literature, considerably fewer ring-closing reactions have been reported. In 1995, Saito and coworkers discovered that an α -diketone in conjugation with an ene-yne moiety (**20a–b**) photolytically cyclizes under aqueous conditions to form O–H insertion product **21a** (Scheme 9).²¹ Optimization led to both water- and alcohol-trapped furan products (**21a–d**) in good yields *via* carbene **22a**. Photolysis in deuterated solvents gave only products with deuterium incorporated in the benzylic position. When a biphenyl moiety was used as in **20b**, insertion of carbene **22b** into an aryl C–H bond gave fluorene **23** in almost quantitative yield.

The catalytic use of transition metal complexes to afford more stable carbene/carbenoid intermediates has expanded the synthetic viability of ketone-ene-yne cyclizations. Initially championed by Herndon^{22–24} and later by Casey,²⁵ among others, this methodology has led to a variety of furan derivatives. Transition metal-catalyzed cyclizations of imine-ene-yne to generate pyrroles are also known,²⁶ but are much more limited in scope. Aside from these few examples, additional evidence for coarctate cyclization reactions is scarce.



Scheme 8 Ring-opening of diazo **18**.



Scheme 9 Photolytic coarctate cyclization of ene-yne-diones **20**.

3. Computational analysis of cyclizations

3.1 DFT calculations

To further understand these unique cyclizations, and to be able to predict whether or not potential systems could be successfully prepared, we examined these cyclizations computationally before attempting them in the lab. Reaction coordinate diagrams are calculated to compare potential systems of interest with previous successfully cyclized systems. Fig. 1

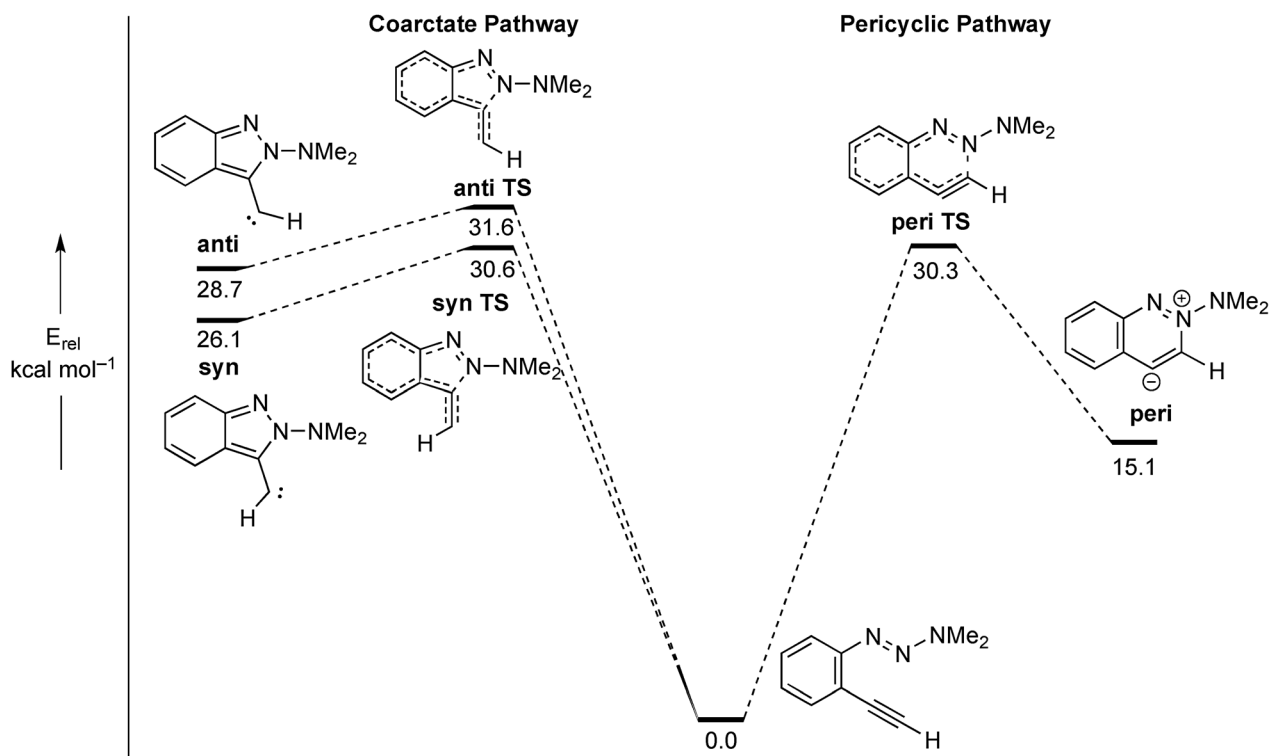


Fig. 1 DFT(B3LYP/6-31G*+ZPE) calculated energies of the reactant, transition states, and intermediates for the cyclization of the NMe₂ analogue of **9b** to form isoindazole carbenes and cinnoline zwitterion.

shows a representative DFT-calculated reaction coordinate diagram of the triazene-ene-yne system **7b** along with transition states and reactive intermediates for both the coarctate and pericyclic reaction pathways.²⁷ Energies here are typical for these systems, with transition states at approximately 30 kcal mol⁻¹ above the reactive conformation of the starting material. The calculations also showed that the zwitterionic intermediate along the pericyclic pathway is lower in energy than the carbene intermediate along the coarctate pathway. This is in agreement with experimental results in which the cinnoline could be formed exclusively at higher temperatures as the thermodynamic product. Both the pericyclic and the coarctate ring closures are concerted reactions, with no polar or diradicaloid intermediates involved. The coarctate reaction entails the simultaneous breaking of two bonds between two atoms; *viz.* the triple bond in the ethynylphenyl-triazene precursor is converted into a single bond in a single step, in agreement with the definition of a concerted coarctate reaction.

3.2 ACID calculations

In addition to reaction coordinate diagrams, the ACID (Anisotropy of Induced Current Density) method has been used to learn about the transition state of the coarctate cyclization pathway.^{28,29} The ACID scalar field is interpreted as the density of delocalized electrons. Pericyclic reactions exhibit a cyclic topology of delocalized electrons that resembles the delocalized system of electrons in aromatic compounds. This is consistent with the theory of aromatic transition states of Dewar³⁰ and Zimmerman.³¹ Current density

vectors plotted on top of the ACID surface of pericyclic transition states reveal a diamagnetic ring current and thus additionally confirm the analogy of aromatic π systems with the system of delocalized electrons in pericyclic reactions. ACID plots of coarctate transition states are clearly distinct from pericyclic transition states. The ACID surface of coarctate transition states is not purely cyclic but includes a linear part. Close inspection of the current density vectors reveals a ring current that corresponds to the electron pushing arrows if the reaction were written in the conventional mechanistic way. The linear part of the ACID surface defines a coarctation of the ring current.

The ACID method has also proved to be a valuable and intuitive tool to distinguish between pericyclic and pseudo-pericyclic reactions and similarly between coarctate and pseudo-coarctate reactions.^{32–35} Pseudopericyclic transition states exhibit a disconnection in their otherwise cyclic system of delocalized electrons.³⁶ In ACID plots this is nicely reflected by a disconnection in the ACID surface. Consequently, there is no ring current, because the density of mobile electrons is interrupted.

Very much like (pseudo)pericyclic reactions, many reactions that look coarctate at a first glance turn out to be pseudo-coarctate upon close inspection of their transition states. Again, ACID plots can be used to discriminate. Coarctate transition states exhibit a contiguous surface, whereas

pseudocoarctate systems include a disconnection. Unfortunately, discrimination is not clear-cut in several cases. There is a continuum between “normal” and “pseudo” transition states in pericyclic as well as coarctate reactions. There are weak and strong disconnections in these transition states, and it is somewhat arbitrary what to name a “true” disconnection, and hence where to draw the line between “normal” and “pseudo”. The ACID method allows to quantify the extent of delocalization or conjugation. A critical isosurface value (CIV) can be assigned to weak points in a linear, cyclic or coarctate system of delocalized electrons. A high CIV corresponds to a strong conjugation, and a low CIV to a weak delocalization at a critical point. We propose that a pericyclic or coarctate reaction should be called pseudo if the CIV of the weakest point in the delocalized system of electrons is < 0.02 , genuine pericyclic or coarctate if $\text{CIV} > 0.03$, and a borderline case for CIVs between 0.02–0.03.

Fig. 2a shows the ACID isosurface for the 5-membered ring cyclization to the isoindazole.³⁷ As a reference, the transition state for the all-carbon analogue is shown in Fig. 2b. The delocalized electrons in the transition state of the ethynyl-phenyltriazene involve the carbene center that is exocyclic to the 5-membered ring and is therefore not pericyclic. There is a disconnection, however, in the coarctate topology of the transition state between the N- and C-atom where the new bond is formed (Fig. 2a). This is due to the fact that the π

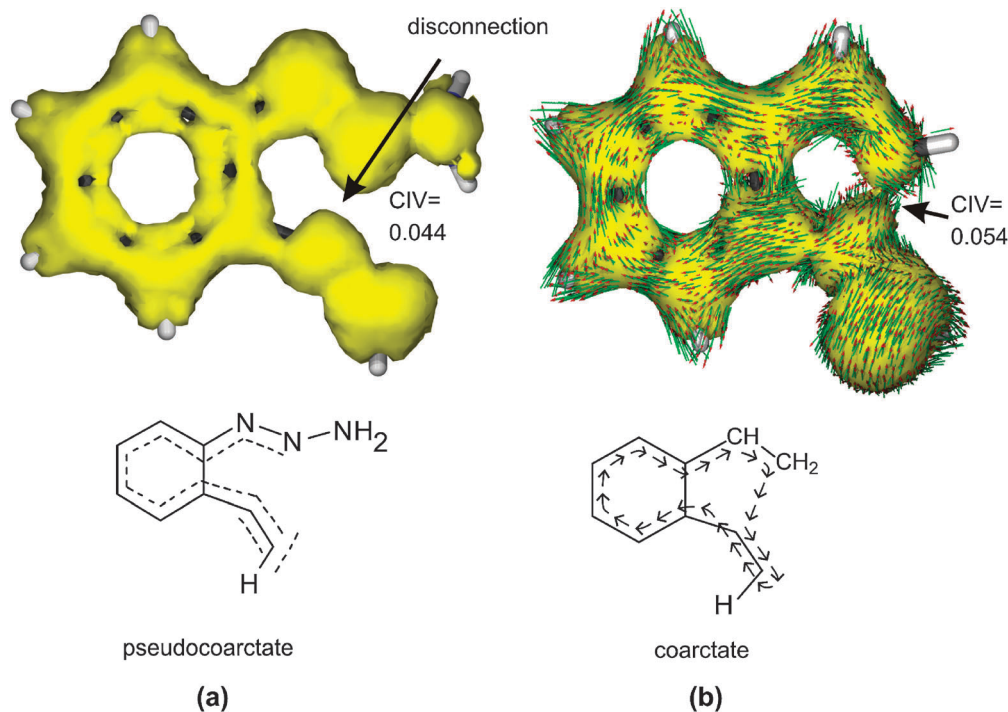


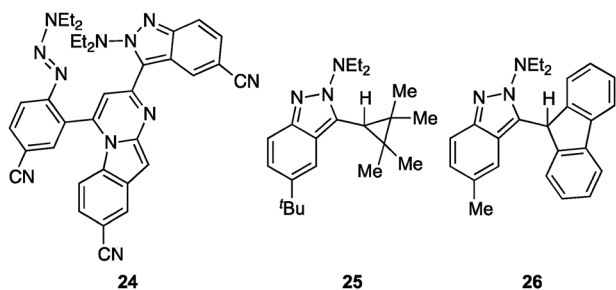
Fig. 2 (a) ACID plot (isosurface value = 0.05) of the transition state of the cyclization of (2-ethynylphenyl)triazene to 2-amino-3-methylidene-2H-indazole. The topology of delocalized electrons exhibits a disconnection between the C and N atoms at which the new C–N bond is formed; thus, the transition state is pseudocoarctate in contrast to the all-carbon analogue in panel b. (b) ACID plot (isosurface value = 0.05) of the transition state of the cyclization of 2-ethynylstyrene to 1-methylidene-2H-indene, the all-carbon analogue of the title isoindazole cyclization. The current density vectors on the ACID isosurface indicate the coarctate nature of the transition state. The ring current forms an exocyclic loop involving the carbon atom that becomes the carbene center in the product; thus, the topology of the delocalized system of electrons corresponds to a constricted or coarctate cycle. The CIV of 0.054 between the two carbon atoms at which the new bond is formed indicates that there is no disconnection; hence, the reaction is genuine coarctate in contrast to the isoindazole cyclization (panel a) that is pseudocoarctate.

system of the N=N and the π orbital of the alkyne that is involved in the bond formation are orthogonal to one another; therefore, the reaction is pseudocoarctate. The transition state of the all-carbon analogue (Fig. 2b) does not exhibit a disconnection, and therefore is true coarctate. A similar trend is seen in the six-membered ring cyclizations of the ethynylphenyltriazene and its all-carbon analogue. The transition states for both systems exhibit a cyclic topology and are thus pericyclic; however, the bond-forming atoms in the ethynylphenyltriazene exhibit a rather weak connection when compared to the all-carbon analogue, much like the transition states of the five-membered ring cyclizations.

4. Uncovering the mechanistic details

4.1 Isoindazole formation *via* carbenes

Having at last identified isoindazole formation as a coarctate reaction, this then meant that carbene intermediates were most likely involved. The products obtained so far supported this assumption, as carbenes are known both to dimerize to alkenes (*e.g.*, **6** and **10**) and to trap molecular oxygen (*e.g.*, **8** and **11**). Transition metal complexes as well as simple metal salts help stabilise carbenes; thus, we investigated numerous metal catalysts under a variety of conditions and eventually settled on Cu salts.¹⁰ Dave's first attempts with CuI in ODCB at 110 °C did afford higher isoindazole yields, but also furnished another by-product. The structure of this compound (**24**), a trimer of **9a** that was confirmed by X-ray crystallography, cannot be readily explained without again invoking carbene intermediate(s).³⁷ Eventually, optimization led to the use of 5 equiv. of CuCl as the carbene stabiliser, 1,2-dichloroethane (DCE) as solvent, and a 50 °C reaction temperature (Scheme 5). Under these conditions, complete conversion to isoindazolecarbaldehydes **11a–l** was attained in 12–36 h in excellent isolated yields (Table 1).¹⁰

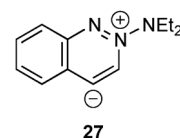


Having determined ideal conditions for the exclusive, high-yield production of isoindazoles, Dave performed two trapping experiments to provide additional evidence of carbene/carbenoid intermediates.³⁸ First, cyclization of triazene **9d** in the presence of 2,3-dimethyl-2-butene and CuCl gave cyclopropane **25** in 65% yield. This product undoubtedly resulted from carbene/carbenoid formation and intermolecular cycloaddition with the electron-rich alkene. Second, after appending a biphenyl unit to the end of **9c**, cyclization in the presence of CuCl produced fluorene **26** in 55% yield. Similar to Saito's work on **20b**,²¹ the intermediate carbene was trapped by an intramolecular C–H insertion. As a whole, there is little doubt about the intermediacy of carbenes/carbenoids.

4.2 Cinnoline formation *via* zwitterions

Unlike the formation of the isoindazole, the structure of the cinnoline did not readily suggest a mechanism responsible for its generation. The most common method for cinnoline synthesis is a von Richter cyclization, which gives 4-substituted products as the result of a Michael-type nucleophilic attack of an alkyne *ortho* to a diazonium functionality.³⁹ No such products were observed even when a hydroxide source was present. Simply heating the starting triazenes **9** in ODCB to 200 °C in a pressure tube gave cinnolines **12** in excellent yield.¹⁰

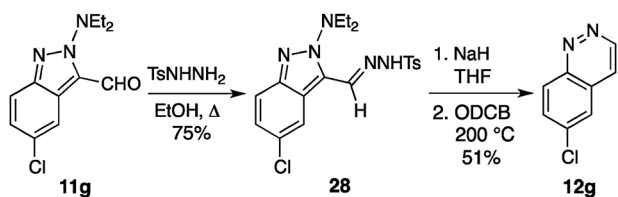
As mentioned earlier, our first inclination was that cinnoline production occurred by means of a Bergman-type cyclization to give a 1,4-diradical species; however, experiments performed in the presence of radical donors allowed Dave to discount this mechanistic pathway. Subsequent results with benzhydrol containing one or two deuterium atoms suggested that C4 in the intermediate in cinnoline formation had a propensity for proton/deuterium abstraction from the strong but rather acidic O–H(D) bond.³⁸ These results corroborated the calculations in Fig. 1, which predicted a pericyclic pathway to generate a zwitterionic dehydrocinnolinium intermediate such as **27**. The subsequent mechanism of Et₂N[–] loss as the corresponding imine took us a great deal of additional experimental and computational effort to figure out; however, because the focus of this article is on coarctate reactions, we refer the reader to the full paper that lays out the cinnoline mechanistic case in greater detail.³⁷



4.3 Proof of coarctate reaction reversibility

As predicted in Fig. 1, the zwitterionic dehydrocinnolinium is lower in energy than the carbene intermediate, which agreed well with the experimental results. Cyclizations at 170 °C gave a prototypical kinetic/thermodynamic product distribution of isoindazole and cinnoline.¹⁰ This also explained why the cinnoline formed exclusively in high yield when the cyclization was done at higher temperatures. An essential piece of evidence for our proposed pathways, however, was the demonstration of reversibility of the coarctate process. If the isoindazole carbene intermediate was in equilibrium with the starting material and zwitterionic dehydrocinnolinium, then independent generation of this carbene at 200 °C should ultimately provide the corresponding neutral cinnoline. This indeed proved to be the case. Heating the Na salt of tosylhydrazone **28**, prepared from aldehyde **11g**, in ODCB at 200 °C resulted in good conversion to the corresponding cinnoline **12g** (Scheme 10).³⁷ This presumably occurred through regeneration of triazene **9g** by coarctate ring-opening of the carbene, analogous to furfurylcarbene in Scheme 8, followed by pericyclic ring-closing to the cinnolinium zwitterion and finally imine loss.

It is worth noting that the *ortho*-ethynylphenyltriazenes, *i.e.*, **9**, are the *only* “hetero-ene-ene-yne” compounds where products are derived from both coarctate and pericyclic mechanisms.



Scheme 10 Cinnoline formation by coarctate ring-opening of **28**.

In every other system studied to date, we only isolate molecules arising *via* coarctate ring-closure. While calculations often suggest that the pericyclic reaction remains the thermodynamic pathway and therefore might be operational, in order to generate neutral (and thus isolable) molecules would often require elimination of high-energy species such as benzyne, which does not occur.

4.4 Making isoindazole formation the thermodynamic pathway

With the dual mechanistic pathways for cyclization of **9** solved, we wondered if it was possible to have the coarctate reaction as the thermodynamically-preferred route. To accomplish this, we hypothesized that it would be necessary to stabilise internally the carbene intermediate, such as inclusion of a methyl ester on the terminus of the conjugated azo-ene-yne unit, *e.g.*, **29**. Finally in summer 2008 did we get around to answering this question. By that time Dave Kimball had long since graduated with his PhD; thus, the task fell to Sean McClintock, the third graduate student to work on the project.

Sean travelled to Kiel, Germany where Rainer had since moved to explore this possibility computationally. As desired, incorporating the $-\text{CO}_2\text{Me}$ group (*e.g.*, **29e**) lowered the coarctate reaction energies significantly (Fig. 3) compared to parent system **9b** in Fig. 1.²⁷ The *syn* and *anti* intermediates were lowered by 6.8 and 8.7 kcal mol⁻¹, respectively, and the transition states dropped by 6.3 and 8.3 kcal mol⁻¹, respectively. Unexpectedly for the pericyclic reaction, the cinnolinium energy was raised by 6.7 kcal mol⁻¹ and the TS increased by 3.2 kcal mol⁻¹, thus indicating that we could stabilise the coarctate pathway while simultaneously destabilise the pericyclic pathway. Incorporation of the carbomethoxy group therefore makes the coarctate cyclization, rather than the pericyclic cyclization, the thermodynamically favored reaction.

Back in Eugene, Sean was quickly able to capitalize on the promising computational results. The desired precursors **29** were easily prepared in good yield by deprotonation of the terminal alkynes **9** and then treatment with methyl chloroformate. Similar to previous studies, Sean found that CuCl was optimal for cyclization, in this case to afford the isoindazole-substituted α -ketoesters **30** (Scheme 11) in good to excellent yields.²⁷ As suggested by the calculations, we observed a decrease in the reaction time, indicating a lower energy pathway. While **9** required a reaction time of 16 h (or more) at 50 °C, only 4 h were needed for the ester-functionalized triazenes **29**. Interestingly, when $[\text{Rh}(\text{OAc})_2]_2$ was used as the catalyst, α -hydroxyesters **31** were isolated rather than the expected α -ketoesters, showing that the carbenes had inserted into the O-H bond of a water molecule. The yields of **31** could

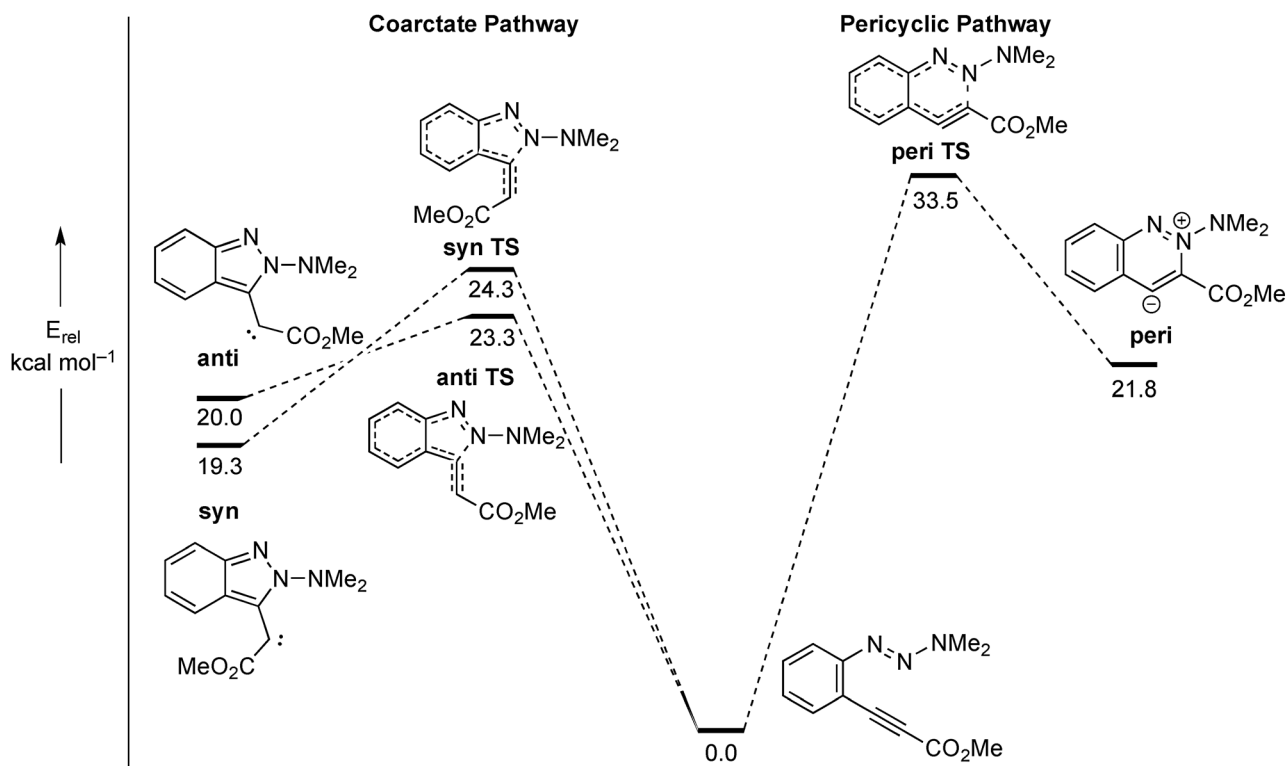
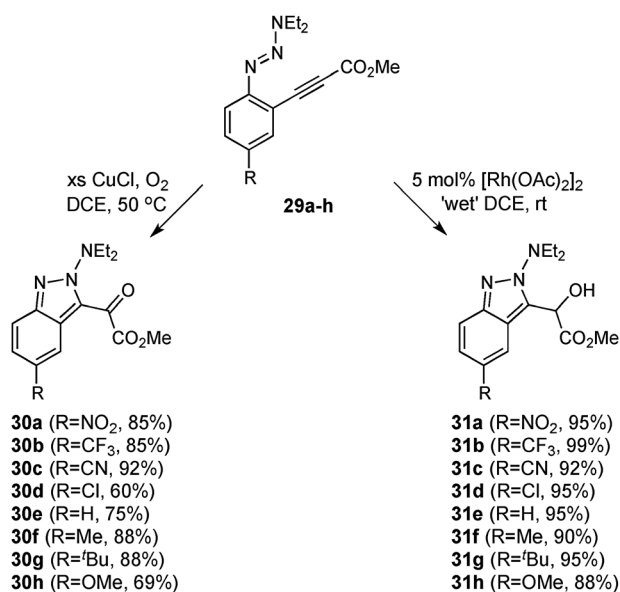


Fig. 3 DFT(B3LYP/6-31G* + ZPE) calculated relative energies of the reactants, transition states, and intermediates for the cyclization of the NMe₂ analogue of **29e** to isoindazole carbenes and cinnoline zwitterion.



Scheme 11 CuCl-mediated and [Rh(OAc)₂]₂-catalyzed thermodynamic coarctate cyclizations of esters **29**.

be maximized by intentionally adding a small amount of water to the reaction.

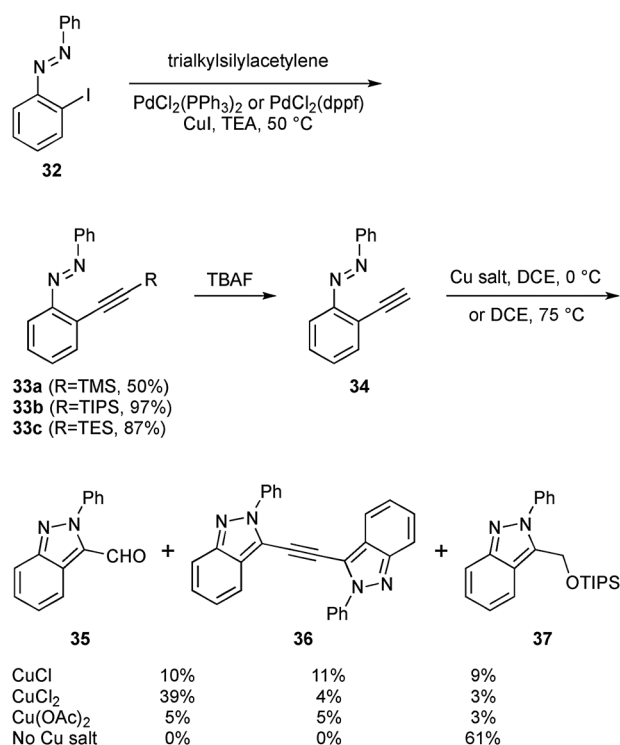
5. Structural variation of the conjugated hetero-ene-ene-yne unit

To further explore the mechanism and scope of our coarctate cyclizations, we systematically varied the atoms in the hetero-ene-ene-yne scaffold. Given their success in our initial studies, we again utilized DFT calculations as a predictive tool to evaluate the potential for successful cyclization. Laura Shirtcliff, Dave's successor, travelled to Kiel and examined a large number of structures computationally.⁴⁰ Synthetic access to many of these was not readily apparent; thus, Laura focused her laboratory efforts on those molecules that were computationally promising yet synthetically viable.

5.1 Diazene in place of triazene

After Dave's triazene work, the first system Laura studied experimentally contained an aryldiazene unit in place of the dialkyltriazene.⁴¹ Computationally, the diazene cyclizations were interesting for two reasons. First, the transition state energies for both pathways were more than 7 kcal mol⁻¹ lower in energy compared to the parent triazenes; therefore, we expected that cyclization would occur at a lower temperature. Second, the transition state of the coarctate cyclization was not planar, leading to the question of whether the cyclization was a pseudocoarctate or a true coarctate reaction. An ACID calculation showed that all the C-C and C-N bonds were conjugated, thus indicating a true coarctate transition state.

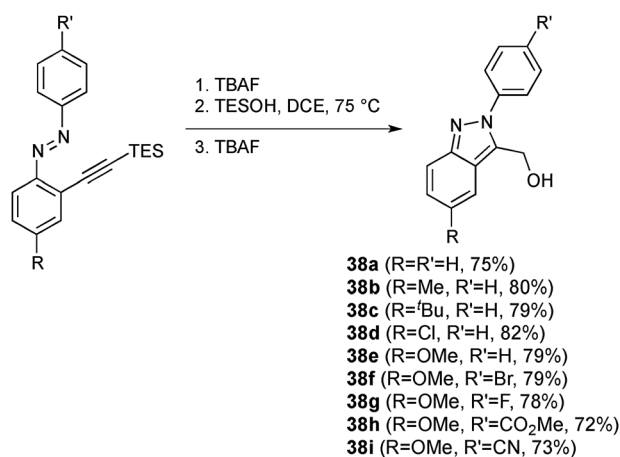
Initial synthetic attempts toward a phenyldiazene analogue were discouraging. Sonogashira cross-coupling of (trimethylsilyl)acetylene to iododiazene **32** gave at best a 50% yield of **33a** (Scheme 12). Unlike triazene **9**, this alkyne degraded upon workup due to the lability of the TMS group and the instability of free alkyne **34**. While use of bulkier acetylenes



Scheme 12 Initial products from coarctate cyclization of diazene **34**.

with triisopropylsilyl and triethylsilyl caps did furnish **33b** and **33c** in 97% and 87% yield, respectively, protodesilylation afforded **34** along with degradation products. Undeterred, Laura explored multiple metal salts to promote the coarctate reaction. Standard triazene cyclization conditions (5 equiv. CuCl in DCE at 50 °C) gave a low yield of the desired aldehyde **35** along with two other unidentified products. CuCl₂ gave an increased yield of **35**, while Cu(OAc)₂ as well as other Cu and Rh salts furnished equally disappointing results. X-ray crystallography elucidated the structure of the first unknown as dimer **36**. The most likely explanation for its formation is that **34** underwent Cu-catalyzed homocoupling followed by tandem coarctate cyclizations (*vide infra*).

The structure of the second unknown took a bit longer to solve, and once again serendipity played a key role. We envisioned that the carbene resulting from coarctate cyclization of **34** could potentially insert into a C-H bond of the pendant phenyl group giving a tetracyclic compound. To accomplish this, the reaction mixture must be devoid of any potential carbene traps. Diazene **33b** was desilylated with TBAF, subjected to aqueous workup, and concentrated without heat. The crude material was dissolved in DCE and subjected to four freeze-pump-thaw cycles to remove O₂. Heating the reaction mixture to 75 °C overnight followed by workup yielded a single aromatic compound which we initially thought was the tetracyclic contaminated with residual triisopropylsilylanol (TIPSOH). This product's NMR spectra, however, were consistent with that of unknown **37**. X-ray structural analysis revealed an unexpected result: rather than inserting into a phenyl C-H bond, the carbene had inserted into the O-H group of the residual TIPSOH giving **37** in 61% yield. The low volatility of TIPSOH makes its removal by



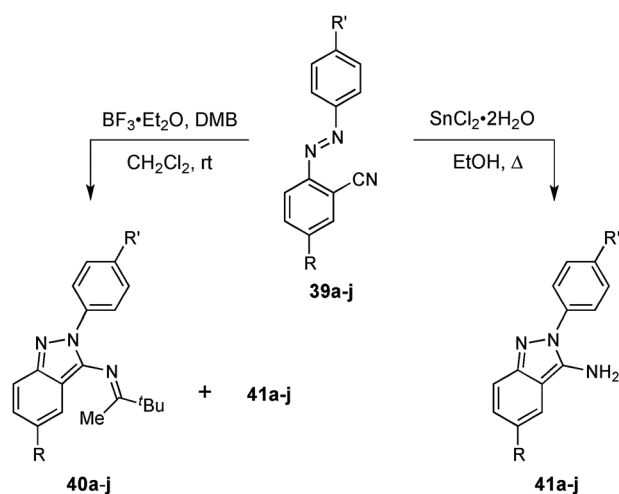
Scheme 13 Optimized diazene cyclization conditions.

evaporation impractical when dealing with unstable **34**. Given that this was Laura's best yield of an isoindazole from a phenyldiazene, we decided that trapping the carbene with a silanol would be the best option. Subjecting **33c** to the same stringent O₂-free conditions and then adding an excess of more volatile triethylsilanol (TESOH) gave the corresponding silyl ether in a satisfying 77% yield. Scheme 13 depicts the optimized conditions for isoindazole formation—deprotection, cyclization and subsequent removal of the TES group afforded the free alcohols **38** in very good overall yield.⁴¹

The diazene system is noteworthy in that it required no transition metal catalyst, only heat, to undergo the coarctate cyclization. This implies that these reactions proceed through free carbenes rather than transition metal-stabilised carbenoids such as those found in the cyclization of triazenes. This was confirmed experimentally—addition of 2,3-dimethyl-2-butene (DMB) as carbene trap in place of TESOH in the second step of Scheme 13 generated a cyclopropane similar to **25** in 75% yield.⁴¹

5.2 Nitrile in place of alkyne

We next examined replacing the alkyne portion of the conjugated system with a nitrile unit, as Laura's calculations suggested that these molecules too would readily undergo coarctate reaction. Synthetically, the diazene-ene-nitriles **39** were more accessible than the triazenes. Reacting the corresponding iodides with CuCN in ^tPrOH *via* nucleophilic aromatic substitution gave **39a–j**. In turn these were treated with DMB along with a number of Lewis acids (*e.g.*, CuCl, ZnCl₂, AlCl₃), with the highest yields of isoindazole obtained using BF₃·OEt₂ (Scheme 14).⁴² Interestingly, the aziridine expected from [2+1] cycloaddition of the presumed nitrene to the alkene was not the major product; instead, imine **40** was isolated as the main product along with low yields of amino-isoindazole **41** (Table 2). The use of dry solvent was essential to maximize the yield of **40**, with the yield of **41** increasing when water was present in small amounts, likely *via* hydrolysis of **40**. Alternatively, amine **41** was isolated as the sole product in 74–95% yield when using SnCl₂ in refluxing EtOH, with the SnCl₂ functioning both as Lewis acid and as a sacrificial two-electron source.⁴²



Scheme 14 Formation of imine **40** and amine **41**.

Table 2 Yields of isoindazoles **40** and **41** from nitrile **39**^a

Entry	R	R'	40 ^b	41 ^b	41 ^c
a	^t Bu	H	94%	NA ^d	87%
b	CH ₃	H	90%	5%	89%
c	H	H	84%	16%	95%
d	Cl	H	95%	NA ^d	94%
e	OMe	H	72%	27%	74%
f	OMe	Br	79%	9%	76%
g	OMe	F	70%	25%	79%
h	OMe	CO ₂ Me	89%	4%	84%
i	OMe	CN	63%	30%	94%
j	OMe	NO ₂	78%	22%	80%

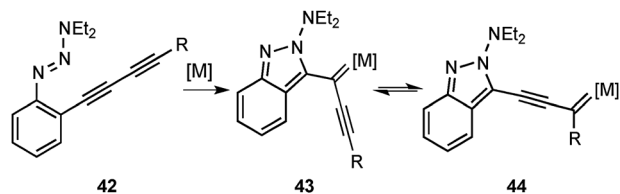
^a Isolated yield. ^b BF₃·OEt₂ reaction. ^c SnCl₂·H₂O reaction. ^d The amine was not isolated if imine yield was >90%.

While it is unlikely that **40** is formed through a free nitrene intermediate, it seems plausible that the isoindazole imine is generated formally *via* a coarctate pathway. One possible mechanism might involve activation of the nitrile by the Lewis acid (LA) followed by attack of a diazene nitrogen on the electron deficient “coarctate carbon”, forming a stabilised nitrenium. The LA-stabilised nitrene is then attacked by the alkene and a 1,2-methyl shift on the alkyl chain gives the imine.⁴²

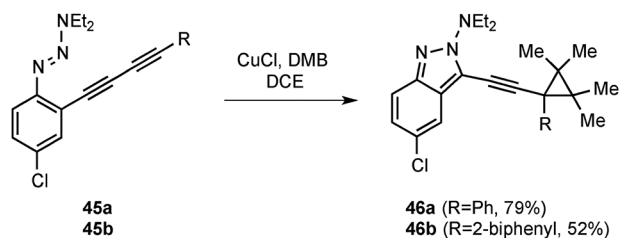
5.3 Butadiynylphenyltriazenes revisited

With a number of successful studies under our belt, we decided to go back to the beginning and re-examine the coarctate reactivity of triazenes substituted with an arylbutadiynyl unit (**42**, Scheme 15).⁴³ Whereas the initial TMS-terminated diynes **4** dimerized (**6**) and/or afforded products that had lost the TMS group (**7**), we anticipated that these new diynes would be more stable and that it might be possible to observe migration of the resultant metal carbenoid along the extended π-system (**43** → **44**). If migration indeed occurred, we anticipated that a 2-biphenyl derivative would undergo C–H insertion to generate a fluorene derivative similar to **26**.

Attempts at cyclization without metal salts were unsuccessful. Heating **45a–b** to 200 °C in the presence of DMB led to complete recovery of starting material, while temperatures



Scheme 15 Metal salt-induced cyclization of **42** affording carbenoid **43** and isomer **44**.



Scheme 16 Synthesis of cyclopropanes **46a-b**.

above 200 °C led to degradation of the starting material. Cyclization of **45a** and **45b** with CuCl and DMB each afforded a single product in 79% and 52% yield, respectively (Scheme 16).⁴³ X-ray crystal structures of both compounds confirmed that the carbenoid had migrated down the alkyne chain, forming cyclopropanes **46a** and **46b** via a [2+1] cycloaddition with DMB. Surprisingly though, in the absence of DMB, **45b** failed to generate the desired fluorene derivative and instead degraded via other deleterious pathways. Although not definitive proof, the X-ray structure of **45b** showed the biphenyl moiety in an unfavourable orientation for C–H insertion.

5.4 Beyond benzo-fused arenes

Until recently, all of our cyclizations utilized a fused benzene as the second “ene” within the ene–ene–yne motif. Inspired by the widespread use of PAHs and their heteroatom-containing counterparts in the field of organic electronics, we decided to investigate the cyclizations of naphthalene⁴⁴ and phenanthrene-based⁴⁵ triazene–ene–ynes. While expecting to form isoindazoles and cinnolines with extended conjugation, these studies also marked the return of unwanted coarctate cyclization dimers.

The most logical route to increase the size of our ring systems was to start with the appropriate “ortho-haloamino” naphthalenes and phenanthrene; thus, triazene–ene–ynes **47a–c** were prepared via the usual three-step route. While the thermal cyclizations to afford cinnolines **48a–c** were uneventful, we obtained some curious results along the way (Scheme 17). First, our standard CuCl-mediated coarctate reaction protocol failed to cleanly produce aldehydes **49**. We found that it was necessary to saturate the reaction mixture with O₂ prior to CuCl addition to produce angular aldehydes **49a** and **49b** in good yields. Unfortunately, this modification still resulted in low yields of **49c** accompanied by dimer **50c**; however, use of diphenylsulfoxide (DPSO) as the oxygen atom source afforded only **49c** in good yield.⁴⁶ Second, the unanticipated *trans*-dimers **50a–c** were also the sole products when

using [Rh(OAc)₂]₂ as the carbene/carbenoid stabiliser, in contrast to our earlier studies where [Rh(OAc)₂]₂ did not yield dimers. Whereas **50a** is stable, **50b** isomerizes completely to *cis*-dimer **50b'** and **50c** isomerizes to a 2 : 1 *trans* : *cis* mixture. Our calculations revealed that the carbenes are strongly stabilised through “coarctate conjugation”, thus suggesting a stationary concentration of the reactive intermediates high enough for dimerization.⁴⁵

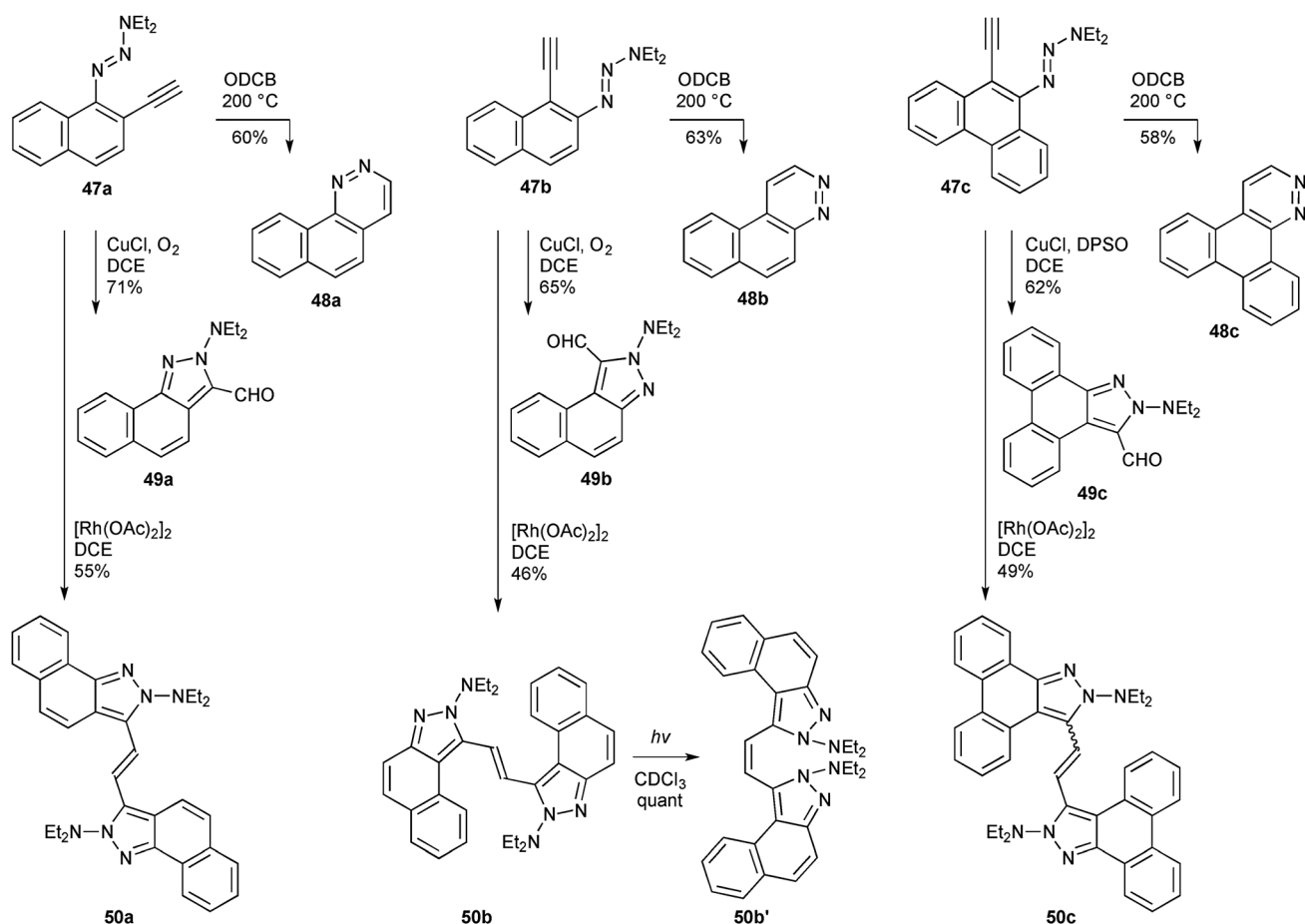
Noticeably absent from Scheme 17 are Sean’s attempts to cyclize the linear naphthalene-fused triazene–ene–yne **47d**. After its protracted synthesis, we were disappointed by the cyclization results—both the pericyclic and coarctate reactions afforded unidentifiable polymeric products.⁴⁴ Given that longer acenes such as anthracene and pentacene are known to dimerize and/or polymerize via cycloaddition reactions, Sean repeated the cyclizations in the presence of dimethyl acetylenedicarboxylate (DMAD) so as to intercept possible reactive species. Once again the pericyclic reaction afforded polymer, but more surprising was the clean isolation of linear isoindazole aldehyde **49d** via the coarctate pathway (Scheme 18) with no cycloaddition product(s) detected.⁴⁴ While this finding was indeed serendipitous, to this day we are at a loss for a reasonable explanation of this outcome.

It was up to Sean’s successor, Brian Young, to find a workable solution for preparing linear diaza-acenes. The answer, shown in Scheme 19, was to disrupt the conjugation in the cyclization precursor and instead form the aromatic diaza-acenes as the final step.⁴⁷ Starting from triazene **51**, which could be prepared from 2-aminoanthraquinone in five steps, pericyclic and coarctate reactions furnished cinnoline **52** and isoindazole **53**, respectively. Taking a page out of the John Anthony playbook,⁴⁸ alkynylation with (triisopropylsilyl)-acetylene (TIPSA) followed by reductive aromatization gave diazatetracene **54** in modest yield. Given that the aldehyde moiety of **53** would also react with the acetylide nucleophile, Brian deactivated/protected it as ether **55**. In a similar manner, alkynylation/reductive aromatization afforded **56**.

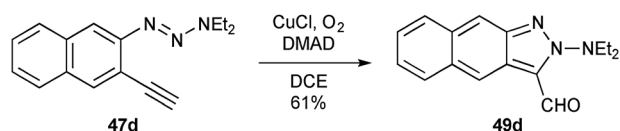
Initially we were disappointed by the optical properties of the fully aromatized molecules—**54** and **56** have essentially the same absorption and emission wavelengths, suggesting similar energy gaps.⁴⁷ It was the cyclic voltammetry data that clearly illustrated the fundamental difference between the molecular scaffolds. Similar to other nitrogen-containing heterocycles, cinnoline **54** with its six-membered rings is electron accepting, whereas the five-membered ring in **56** imparts electron-donating character. What made this study unique was our ability to prepare tetracene-like diaza-acenes with either an electron-poor cinnoline or an electron-rich isoindazole from a shared synthetic intermediate.

5.5 Cyclization of 2-nitrosobenzonitrile (or lemonade out of lemons)

Just because the computations suggest that a coarctate reaction is possible does not necessarily mean the molecule will react as planned. A case in point—the DFT calculations of the cyclization of 2-nitrosobenzonitrile suggested that the energies of the transition states and intermediates would have similar energies to those of our azo–ene–yne and azo–ene–nitrile systems.



Scheme 17 Formation of cinnolines **48**, isoindazole aldehydes **49** and isoindazole dimers **50**.



Scheme 18 Coarctate cyclization of linear ene-ene-yne **47d**.

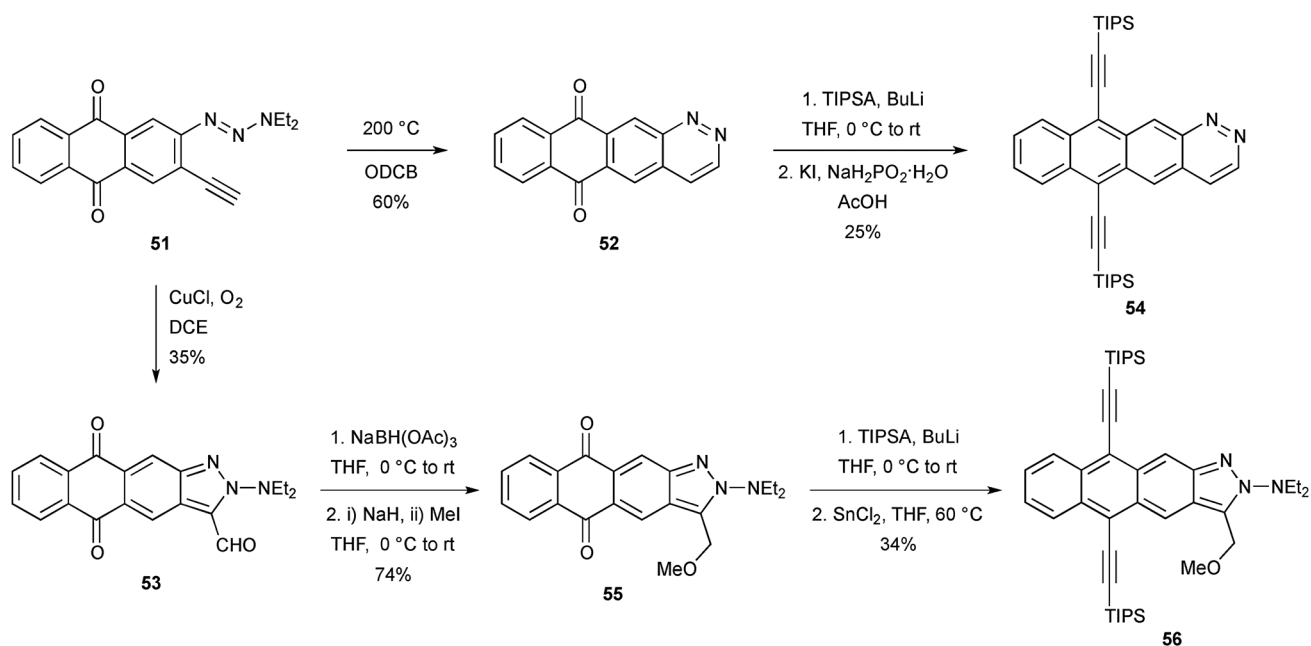
Naively, we expected that 2-nitrosobenzonitrile (**57**) would undergo facile coarctate cyclization to generate a nitrene intermediate that could potentially be trapped by an alkene such as DMB, as in many of our prior studies. Given the unusual reactivity of diazene-nitrile **39** with DMB (*vide supra*), we should have known that this study too would be a bit of a mystery.

It was undergraduate Jenna Jeffrey, working with Sean, who took on the task of studying the reactivity of **57**. While at first we were unsure as to the exact structure of the product that Jenna obtained, 1D and 2D NMR experiments suggested the benzisoxazole skeleton. Jenna decided to protonate the compound with HBF_4 in order to facilitate crystallization. While this strategy did indeed produce crystals, X-ray analysis showed the molecule to be the unusual U-shaped aza-propenylium salt **58** and not the molecule that we would have predicted as a result of coarctate cyclization (Scheme 20). Based on this structure, we inferred the structure of **59** and reasoned that acid-induced dimerization/condensation was responsible for the formation of **58**.⁴⁹

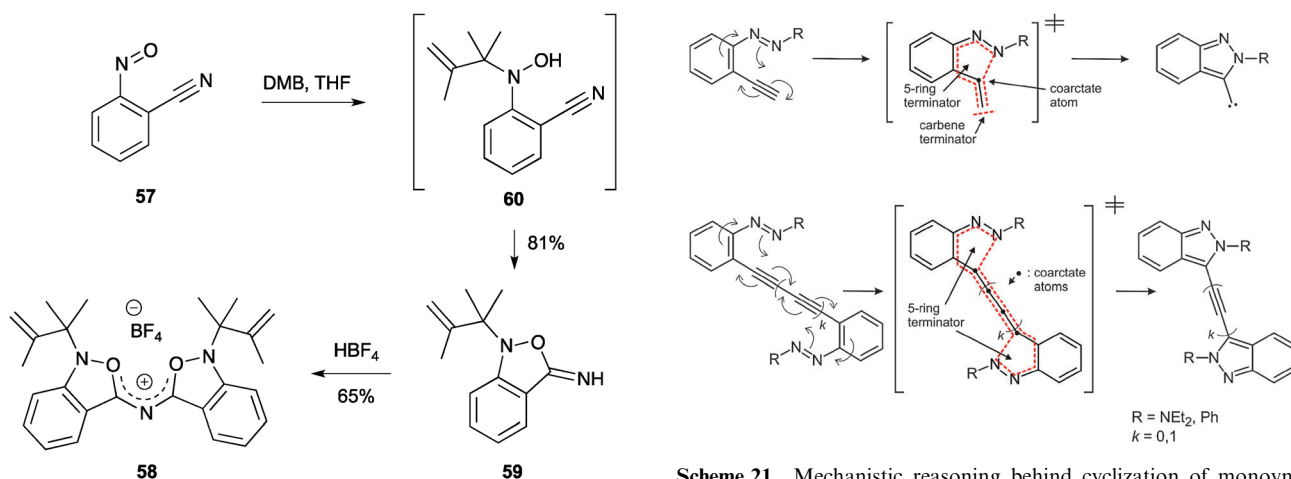
These results clearly indicated that the anticipated coarctate cyclization had not occurred. Instead, precursor **57** underwent a tandem nitroso-ene reaction/intramolecular cyclization to form **59**. The nitroso functionality is one of the most reactive enophiles and electron-rich alkenes such as DMB are the most reactive alkenes in the nitroso-ene reaction. This route would generate intermediate hydroxylamine **60**. The resultant nucleophilic hydroxyl group then quickly cyclizes with the electrophilic nitrile to yield **59**. While our calculations suggested that the coarctate cyclization was energetically favourable, the nitroso-ene reaction clearly represents a more favourable, lower-energy pathway. Nonetheless, Jenna was able to react **57** with several additional electron-rich alkenes to furnish a series of benzisoxazoles, thus turning a mediocre result into a nice story.⁴⁹

5.6 Even more surprises – butadiynyl- and ethynyl-linked bisdiazenes and bistriazenes

Having shown that several hetero-ene-ene-yne motifs could undergo coarctate cyclization with the resulting carbenes either dimerizing or reacting with a number of carbene traps, we sought to develop molecules that cyclise without forming these highly reactive intermediates. Until this time, all of our systems involved both a five-membered ring terminator as well as a carbene terminator (Scheme 21, top), as required in order



Scheme 19 Cyclization of quinone-fused ene-ene-yne **51** to ultimately generate diazatetracene analogues **54** and **56**.



Scheme 20 Cyclization of nitroso nitrile **57**.

Scheme 21 Mechanistic reasoning behind cyclization of mono- and diene-linked diazenes and triazenes.

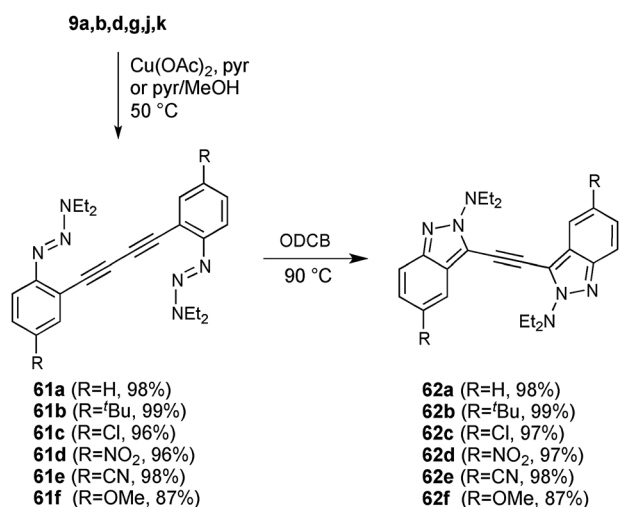
to be classified as coarctate. By combining two symmetrical five-ring cyclizations linked by one or two alkynes, we designed molecules with two five-ring terminators (Scheme 21, bottom). These molecules should in principle cyclise at low temperatures and likely without the need of carbene-stabilising transition metal salts.

We had uncovered this reactivity early on in our studies. Undergraduate Austin Hayes spent summer 2000 exploring alternative routes to isoindazole formation as Dave Kimball had not yet uncovered the CuCl-mediated method described in Section 4.1. Dave had found, however, that Eglinton homocoupling of **9a** with Cu(OAc)₂ furnished dimer **61a** in high yield (Scheme 22). More surprising, upon re-examination of the product after four months, was the fact that the bistriazene had doubly cyclised in the solid-state to afford mono-ene-linked bisoindazole **62a** in essentially quantitative yield. Austin's task that summer was to make a series of dimers,

optimize their cyclization, and if possible, determine the best method to cleave the triple bond oxidatively. Although all of Austin's attempts to accomplish the final transformation failed, Scheme 22 illustrates that he was quite successful in the first two objectives as both reactions proceeded in excellent yield. More important, Austin showed that the double cyclization occurred cleanly at 90 °C in ODCB and afforded only the bisoindazoles; cinnolines were never detected.⁵⁰

Monoene **63** could cyclize to the corresponding bisoindazole **64**, but required higher temperatures and/or carbene stabilisers to induce cyclization (Scheme 23).⁵⁰ Interestingly, heating **61** and **63** in excess DMB or protic solvents produced only **62** and **64**; as we initially hoped, carbene-trapped products were not observed.

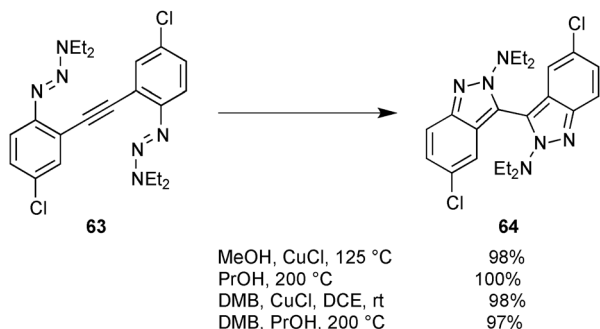
As noted in Section 5.1, we had unintentionally synthesized monoene-linked bisoindazole **36** while trying to optimize the reaction conditions for diazene cyclization, presumably *via* the



Scheme 22 Formation and double cyclization of diyne **61**.

corresponding butadiyne-linked bisdiazene;⁴¹ however, all attempts to deliberately prepare this diyne through a variety of homocoupling methods always yielded doubly cyclized **36** in moderate yields.⁵⁰ Given the high degree of reactivity of the diyne bisdiazene, we did not even attempt to prepare the monoene derivative.

The bisdiazene and bistriazene cyclization studies illustrated two important concepts with regard to coarctate reactions. Much like pericyclic reactions, there is a homologation principle to coarctate reactions termed “ethynylogation”.⁵¹ The series of coarctate atoms can be extended by an even number of additional sp-hybridized carbon atoms, as postulated in Scheme 21 and experimentally demonstrated in Schemes 22 and 23. The double cyclizations also confirmed the stereochemical rules postulated for coarctate reactions. Coarctate reactions with $[4n + 2]$ π -electrons (requiring an odd number of electron pushing arrows) exhibit a coarctate Hückel aromatic transition state with two co-planar terminators, whereas those with $[4n]$ π -electrons (and thus an even number of electron pushing arrows as depicted in Scheme 21) possess a coarctate Möbius aromatic transition state with two orthogonal terminators.⁵² Whereas DFT computations suggested that both bistriazene systems cyclize *via* two-step processes, with relatively low activation barriers and short-lived carbene intermediates, the bisdiazenes were predicted to proceed *via* concerted, synchronous, coarctate mechanisms with 12 (monoene, ACID CIV = 0.027) or 16 (diyne, CIV = 0.037)



Scheme 23 Double cyclization of monoene **63**.

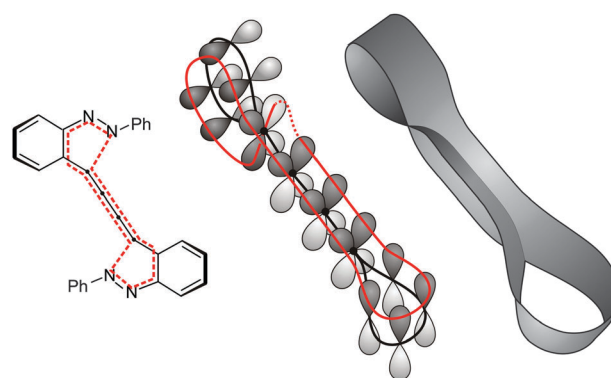
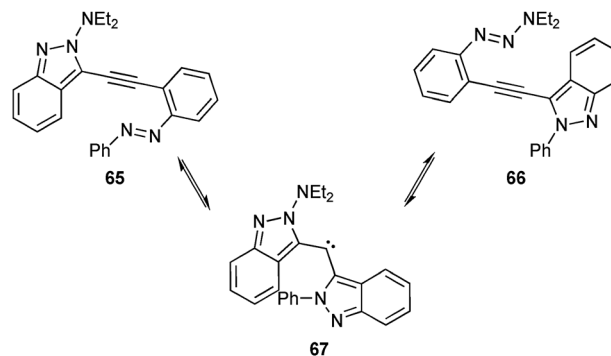


Fig. 4 Coarctate Möbius topology of the diazene biscyclization (left). There are 16 electrons (or 24 if the fused benzene rings are included) delocalized in the transition state. The Möbius topology and orthogonality of the forming isoindazole rings are reflected by the mutual overlap of the basis orbitals (center). There is a cyclic overlap (red line) and one sign inversion (dashed red line), indicative of a Möbius topology. Note that the red line passing the origin of a *p* orbital is not a sign inversion (this is not an overlap of two different basis orbitals with opposite phase).



Scheme 24 Doubly coarctate stabilised carbene **67**.

bonds being made and broken simultaneously. As $[4n]$ π -systems, these reactions obey the stereochemical rules, leading to a Möbius transition state and two isoindazole terminators that are nearly perpendicular with respect to each other, shown pictorially in Fig. 4.

Current studies in the lab focus on one last alkyne-linked system. We are examining the ease with which cyclized and uncyclized ene–ene–yne motifs joined by an ethyne unit interconvert (*e.g.*, **65** and **66**), presumably *via* a carbene intermediate such as **67** that is doubly coarctate stabilised (Scheme 24). Preliminary experimental and computational results suggest that compound **66** is highly favoured over **65**.⁵³

6. Conclusions

Looking back over the past 12 years, it is fascinating that the aberrant results in Scheme 2 could lead to a whole new area of research in one lab and result in close collaboration between the Oregon and Kiel groups. As we often joke, who would have thought the original botched iodination reaction would directly and indirectly yield 20 published papers to date? Certainly not us! While this has been an interesting journey—full of twists, turns and numerous surprise outcomes—two

things are clear. (1) The combined experimental and computational approach to our studies has been far more productive and mutually beneficial than either of these approaches would have been if conducted alone. (2) Accidental discoveries such as these unexpected results are often times more interesting and important than what one might expect to happen in the first place! While it is hard to predict where the coarctate reactions story will lead next, the multitude of unanticipated results and the excitement, dare we say fun, we have had figuring out the intriguing chemistry encourages to continue travelling on this productive road.

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References

- M. M. Haley, *Synlett*, 1998, 557–565.
- J. A. Marsden, G. J. Palmer and M. M. Haley, *Eur. J. Org. Chem. Soc.*, 2003, 2355–2369.
- E. L. Spittler, C. A. Johnson and M. M. Haley, *Chem. Rev.*, 2006, **106**, 5344–5386.
- M. M. Haley, *Pure Appl. Chem.*, 2008, **80**, 519–532.
- M. M. Haley, S. C. Brand and J. J. Pak, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 836–838.
- J. J. Pak, T. J. R. Weakley and M. M. Haley, *J. Am. Chem. Soc.*, 1999, **121**, 8182–8192.
- J. S. Moore, E. J. Weinstein and Z. Wu, *Tetrahedron Lett.*, 1991, **32**, 2465–2466.
- J. S. Moore, *Acc. Chem. Res.*, 1997, **30**, 402–413.
- W. Zhang and J. S. Moore, *Angew. Chem., Int. Ed.*, 2006, **45**, 4416–4439.
- D. B. Kimball, T. J. R. Weakley and M. M. Haley, *J. Org. Chem.*, 2002, **67**, 6395–6405.
- D. B. Kimball, A. G. Hayes and M. M. Haley, *Org. Lett.*, 2000, **2**, 3825–3827.
- R. Herges, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 255–276.
- P. A. S. Smith, G. J. W. Breen, M. K. Hajek and D. V. C. Awang, *J. Org. Chem.*, 1970, **35**, 2215–2221.
- P. A. S. Smith, L. O. Krbecek and W. Resemann, *J. Am. Chem. Soc.*, 1964, **86**, 2025–2033.
- H. H. Takimoto and G. C. Denault, *Tetrahedron Lett.*, 1966, 5369–5373.
- R. Herges, *J. Chem. Inf. Comput. Sci.*, 1994, **34**, 91–102.
- R. V. Hoffman and H. Shechter, *J. Am. Chem. Soc.*, 1971, **93**, 5940–5941.
- R. V. Hoffman and H. Shechter, *J. Org. Chem.*, 1974, **39**, 2939–2940.
- R. V. Hoffman, G. G. Orphanides and H. Shechter, *J. Am. Chem. Soc.*, 1978, **100**, 7927–7933.
- R. V. Hoffman and H. Shechter, *J. Am. Chem. Soc.*, 1978, **100**, 7934–7940.
- K. Nakatani, S. Maekawa, K. Tanabe and I. Saito, *J. Am. Chem. Soc.*, 1995, **117**, 10635–10644.
- B. K. Ghorai, J. W. Herndon and Y.-F. Lam, *Org. Lett.*, 2001, **3**, 3535–3538.
- Y. Zhang and J. W. Herndon, *J. Org. Chem.*, 2002, **67**, 4177–4185.
- Y. Zhang and J. W. Herndon, *Tetrahedron Lett.*, 2006, **47**, 5303–5306.
- C. P. Casey, N. A. Strotman and I. A. Guzei, *Organometallics*, 2004, **23**, 4121–4130.
- Y. Zhang and J. W. Herndon, *Org. Lett.*, 2003, **5**, 2043–2045.
- S. P. McClintock, N. Forster, R. Herges and M. M. Haley, *J. Org. Chem.*, 2009, **74**, 6631–6636.
- D. Geuenich and R. Herges, *J. Phys. Chem. A*, 2001, **105**, 3214–3220.
- D. Geuenich, K. Hess, F. Koehler and R. Herges, *Chem. Rev.*, 2005, **105**, 3758–3772.
- M. J. S. Dewar, *Angew. Chem., Int. Ed. Engl.*, 1971, **10**, 761–776.
- H. E. Zimmerman, *Acc. Chem. Res.*, 1971, **4**, 272–280.
- A. Peña-Gallego, J. Rodríguez-Otero and E. M. Cabaleiro-Lago, *J. Org. Chem.*, 2004, **69**, 7013–7017.
- A. Peña-Gallego, J. Rodríguez-Otero and E. M. Cabaleiro-Lago, *J. Phys. Chem. A*, 2007, **111**, 2935–2940.
- J. Rodríguez-Otero, E. M. Cabaleiro-Lago, J. M. Hermida-Ramon and A. Peña-Gallego, *J. Org. Chem.*, 2003, **68**, 8823–8830.
- M. M. Montero-Campillo, J. Rodríguez-Otero and E. M. Cabaleiro-Lago, *J. Phys. Chem. A*, 2004, **108**, 8373–8377.
- C. Cárdenas, E. Chamorro and R. Notario, *J. Phys. Chem. A*, 2005, **109**, 4352–4358.
- D. B. Kimball, T. J. R. Weakley, R. Herges and M. M. Haley, *J. Am. Chem. Soc.*, 2002, **124**, 13463–13473.
- D. B. Kimball, R. Herges and M. M. Haley, *J. Am. Chem. Soc.*, 2002, **124**, 1572–1573.
- V. von Richter, *Ber. Dtsch. Chem. Ges.*, 1883, **17**, 677–683.
- S. P. McClintock, L. D. Shirlcliff, R. Herges and M. M. Haley, *J. Org. Chem.*, 2008, **73**, 8755–8762.
- L. D. Shirlcliff, T. J. R. Weakley, M. M. Haley, F. Koehler and R. Herges, *J. Org. Chem.*, 2004, **69**, 6979–6985.
- L. D. Shirlcliff, J. Rivers and M. M. Haley, *J. Org. Chem.*, 2006, **71**, 6619–6622.
- L. D. Shirlcliff, R. Herges and M. M. Haley, *J. Org. Chem.*, 2007, **72**, 2411–2418.
- S. P. McClintock, L. N. Zakharov, R. Herges and M. M. Haley, *Chem.–Eur. J.*, 2011, **17**, 6798–6806.
- B. S. Young, F. Koehler, R. Herges and M. M. Haley, *J. Org. Chem.*, 2011, **76**, 8483–8487.
- C. A. Witham, P. Mauleón, N. D. Shapiro, B. D. Sherry and F. D. Toste, *J. Am. Chem. Soc.*, 2007, **129**, 5838–5839.
- B. S. Young, J. L. Marshall, E. MacDonald, C. L. Vonnegut and M. M. Haley, *Chem. Commun.*, 2012, **48**, 5166–5168.
- J. E. Anthony, J. S. Brooks, D. L. Eaton and S. R. Parkin, *J. Am. Chem. Soc.*, 2001, **123**, 9482–9483.
- J. L. Jeffrey, S. P. McClintock and M. M. Haley, *J. Org. Chem.*, 2008, **73**, 3288–3291.
- L. D. Shirlcliff, A. G. Hayes, M. M. Haley, F. Koehler, K. Hess and R. Herges, *J. Am. Chem. Soc.*, 2006, **128**, 9711–9712.
- R. Herges, D. Geuenich, G. Bucher and C. Tonshoff, *Chem.–Eur. J.*, 2000, **6**, 1224–1228.
- C. Berger, C. Bresler, U. Dilger, D. Geuenich, R. Herges, H. Roettele and G. Schoeder, *Angew. Chem., Int. Ed.*, 1998, **37**, 1850–1853.
- B. S. Young and M. M. Haley, work in progress.