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Deciphering the Mechanistic Dichotomy in the Cyclization of 1-(2-Ethynylphenyl)-3,3-dialkyltriazenes: Competition between Pericyclic and Pseudocoarctate Pathways

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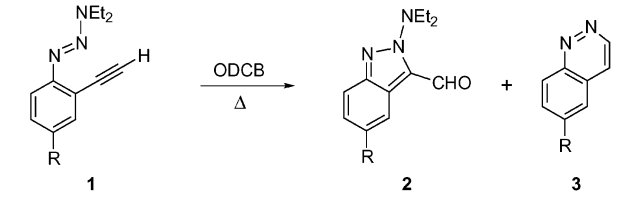
Abstract: The mechanistic aspects of the cyclization of (2-ethynylphenyl)triazenes under both thermal and copper-mediated conditions are reported. For cyclization to an isoindazole, a carbene mechanistic pathway is proposed. The carbene intermediate can react with oxygen, dimerize to give an alkene, or be trapped either intermolecularly (using 2,3-dimethyl-2-butene to generate a cyclopropane) or intramolecularly (using a biphenyl moiety at the terminus of the acetylene to form a fluorene). Density-functional theory (DFT) calculations support a *pseudocoarctate* pathway for this type of cyclization. Thermal cyclization to give a cinnoline from (2-ethynylphenyl)triazenes is proposed to occur through a *pericyclic* pathway. DFT calculations predict a zwitterionic dehydrocinnolinium intermediate that is supported by deuterium trapping studies as well as cyclizations performed using a 2,2,6,6-tetramethylpiperidine moiety at the 3-position of the triazene.

Introduction

The chemistry of triazenes has received considerable attention in the recent literature.[1] These compounds are useful as linkers to solid supports,[2] as protecting groups for amines,[3] and as precursors to haloarenes.[4] Among these and numerous other uses,[5] our group recently reported a new method for the synthesis of heterocycles via the cyclization of 1-(2-ethynylphenyl)-3,3-dialkyltriazenes (e.g., **1**, Scheme 1).[6] Heating **1** to 170 °C in *o*-dichlorobenzene (ODCB) gave both an isoindazole (**2**) and a cinnoline (**3**), both of which could be generated independently in good to excellent yields by either adding CuCl or heating **1** to 200 °C, respectively.[6c] These reactions are tolerant of a wide variety of functional groups.

Scheme 1



1 **2** **3**

The mechanistic aspects of these unusual cyclizations are atypical of more traditional syntheses of isoindazoles and cinnolines. The concurrent production of both heterocycles from the same triazene in the same pot is unique. Neutral conditions and halocarbon solvents do not favor the vast majority of isoindazole syntheses, which usually require mineral acids and activated hydrazines.[7] These types of reactions can be explained through ionic transitions states as well as electrophile−nucleophile interactions. No examples of cyclization between two fairly unreactive functional groups (a triazene and a phenylacetylene) without preactivation[8] (conversion to a diazonium, substitution on the acetylene) have been reported. Cinnoline formation also usually requires a diazonium species ortho to an activated methylene.[9] In cases where an acetylene is used,[10] a halogen or

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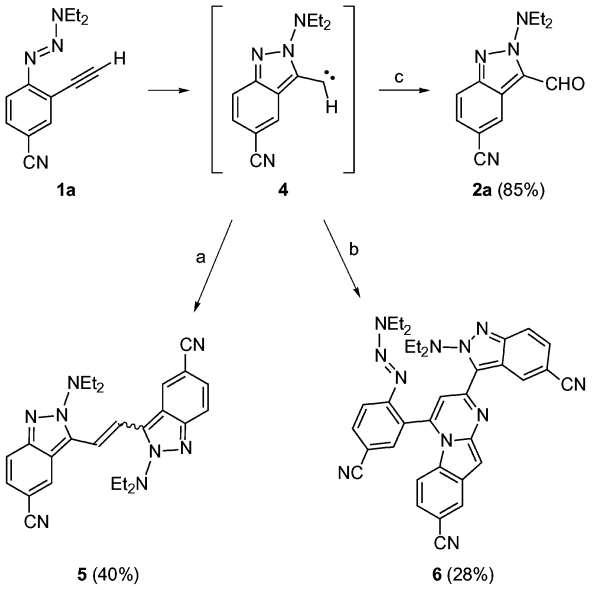
Scheme 2 [a]



[a] Reagents and conditions: (a) MeI, 145 °C; (b) CuI, ODCB, 110 °C; (c) CuCl, DCE, rt.

hydroxide ion is needed to cyclize in typical Richter fashion[11] (i.e., simultaneous attack of the nucleophile on the alkyne carbon proximal to the phenyl ring and cyclization of the distal alkyne carbon with the diazonium group in a pseudo-Michael-type fashion). To study the generality of our new cyclizations for the practical synthesis of these and other heterocycles, we needed to determine the mechanisms for both transformations. The following represents the full experimental and theoretical details of our efforts to delineate the mechanistic pathways responsible for the formation of isoindazoles and cinnolines from 1-(2-ethynylphenyl)-3,3-dialkyltriazenes.

Results and Discussion

Isoindazole Production. Of the several possible types of mechanisms responsible for the formation of an isoindazole from the cyclization of 1-(2-alkynylphenyl)-3,3-dialkyltriazenes, the one that produced a carbene intermediate (**4**, Scheme 2) was most supported by the products obtained. Carbenes are known to both dimerize to alkenes (e.g., **5**) and trap molecular oxygen (e.g., **2**). Copper salts have been widely known to stabilize carbene intermediates and to help generate products at reasonable temperatures.[12] Our first attempts at cyclization in the presence of copper salts gave higher yields of isoindazole but with several new byproducts. These reactions were done at 110 °C, using CuI, triazene **1a** (R = CN), and ODCB as the solvent (Scheme 2). The major byproduct was isolated, and a crystal structure was obtained (Figure 1; see Supporting Information for structure details). This new compound (**6**) contained a central tricyclic structure that was formed by the cyclization of three ethynylphenyltriazene units. Again, the connectivity that resulted could not readily be explained without involving a carbene intermediate(s).

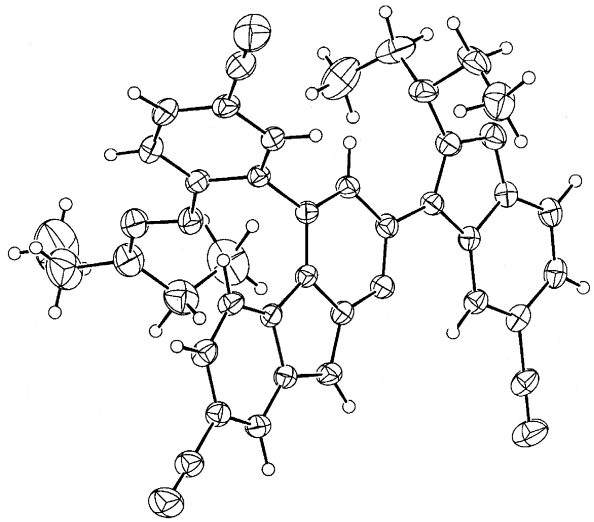


Figure 1. Molecular structure of trimer **6**; ellipsoids are drawn at the 30% probability level.

When the temperature was lowered to 50 °C or to ambient temperature, cyclization in the presence of CuI resulted in much higher yields of isoindazole. Although a number of Cu salts (as well as Zn and Rh salts) were examined, optimal conditions were found to be 1,2-dichloroethane as the solvent, CuCl as the carbene stabilizer, and a temperature of 50 °C. These conditions gave excellent yields of isoindazole for every compound studied.[6c] Although using 2−3 equiv of CuCl results in complete, exclusive production of isoindazole, the reaction can be done in the presence of catalytic amounts of CuCl (10 mol %) using a longer reaction time (ca. 3−4 days).

With ideal conditions for the exclusive, high yielding production of isoindazoles, we turned our attention to the use of trapping agents to provide additional evidence of a carbene intermediate. Cyclization of triazene **1b** (R = *t*-Bu) in the presence of 2,3-dimethyl-2-butene and CuCl gave isoindazole cyclopropane **7** in 65% yield (Scheme 3). This product undoubtedly resulted from carbene (carbenoid) formation and intermolecular trapping by the electron-rich alkene.

To lend further evidence to the carbene intermediate, we attempted cyclization to the isoindazole with a starting compound that could trap the carbene intramolecularly. Saito and co-workers[13] have shown that the use of a biphenyl moiety

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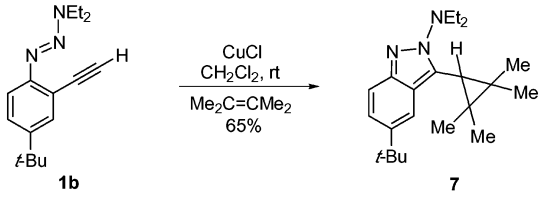
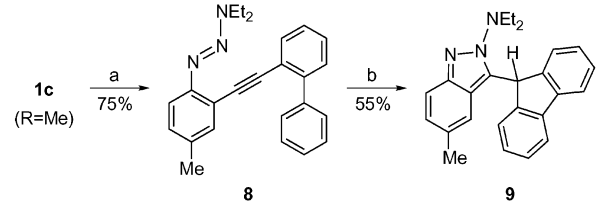
Scheme 3



Scheme 4 [a]



[a] Reagents and conditions: (a) 2-iodobiphenyl, $PdCl_2(PPh_3)_2$, CuI, Et_3N, 50 °C; (b) CuCl, DCE, 90 °C.

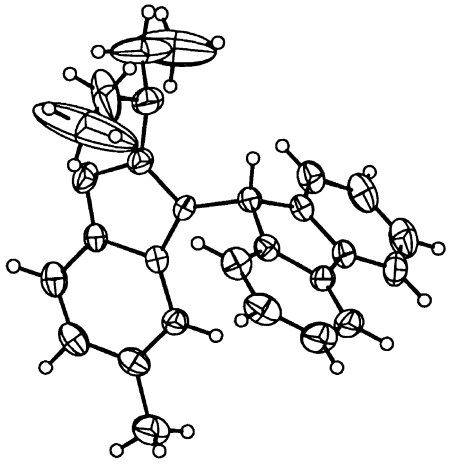


Figure 2. Molecular structure of fluorene **9**; ellipsoids are drawn at the 30% probability level.

allows carbenes to be trapped as fluorenes. Ethynylphenyltriazene **1c** (R = Me) was coupled to 2-iodobiphenyl[14] under Sonogashira conditions to give **8** in 75% yield (Scheme 4). Cyclization of **8** in the presence of CuCl produced fluorene **9** in 55% yield. The structure of **9** was confirmed by X-ray crystallography (Figure 2). These results strongly support a carbene intermediate in the formation of the isoindazole.

To better understand the reaction energetics and mechanisms, the stationary points (reactants, transition states, and products) for the cyclization of 1-(2-ethynylphenyl)-3,3-dialkyltriazenes to isoindazoles and cinnolines were calculated using DFT (Figure 3). In the calculated model system, the NEt_2 group was replaced by NH_2 to save computational costs and to reduce the complexity of the energy hypersurface. The energy barrier for isoindazole formation was calculated to be ca. 2.0 kcal mol^{-1} lower than that for the cinnoline. The cinnoline intermediate, however, was predicted to be much lower in energy than the isoindazole carbene. This agreed well with experimental results: cyclizations at 170 °C gave a prototypical kinetic−thermodynamic product distribution of isoindazole and cinnoline. This also explains why the cinnoline product could be obtained exclusively in high yield when the cyclization was done at higher temperatures. An alternative pathway leading to the cinnoline involving an ethyne−vinylcarbene rearrangement was calculated to have a much higher barrier (46.1 kcal mol^{-1}; see Supporting Information).

Key to providing evidence for our proposed pathways, however, was the demonstration of reversibility. If the isoindazole carbene intermediate was in equilibrium with the starting material, then independent generation of this carbene at 200 °C should provide the corresponding cinnoline species. The sodium salts of tosylhydrazones are known to eliminate N_2 readily to generate carbenes at temperatures close to 200 °C.[15] We thus prepared the tosylhydrazone of isoindazole **2d** (R = Cl, Scheme 5). Heating the salt resulting from treatment of hydrazone **10** with NaH to 200 °C in ODCB resulted in good conversion to the corresponding cinnoline **3d** (R = Cl), presumably through regeneration of the ethynylphenyltriazene from the carbene.

Experimental and theoretical results indicate that the formation of the carbene intermediate in the cyclization of ethynylphenyltriazenes (**1**) proceeds via a concerted *pseudocoarctate* pathway and that the cinnoline cyclization follows a pericyclic mechanism. Since there is some confusion in the literature, the terms *pericyclic*, *pseudopericyclic*, *coarctate*, and *pseudocoarctate* should be clarified at this point. Pericyclic reactions, by definition, exhibit a cyclic (aromatic) transition state of delocalized electrons.[17−19] Bond making and bond breaking occur simultaneously in a cyclic array.[20] Bond making and breaking in coarctate reactions[21] do not follow a cyclic path. As opposed to pericyclic reactions, there is at least one atom at which two bonds are made and two bonds are broken simultaneously. For the five-membered ring cyclization (Scheme 6), the coarctate atom is the carbon neighboring the carbene center. At this carbon, two bonds are broken (triple bond→single bond) and two bonds are made (new C−N bond and C=C double bond in five-membered ring) simultaneously; thus, there is an exocyclic part in the bond formation process. The reaction is therefore not electrocyclic since this term is reserved only for pericyclic reactions.

As Lemal et al. stated as early as 1976,[22] within pericyclic reactions there are special cases. Even though a reaction (e.g., Diels−Alder) from a formal point of view may look like a pericyclic reaction and follow a concerted mechanism, it does not necessarily have to exhibit a cyclic, aromatic transition state. Lemal termed these reactions pseudopericyclic. Numerous experimental and theoretical investigations have been performed on such systems,[16,23] some of them controversial.[24] In pseudopericyclic reactions, the cyclic delocalization of electrons in the

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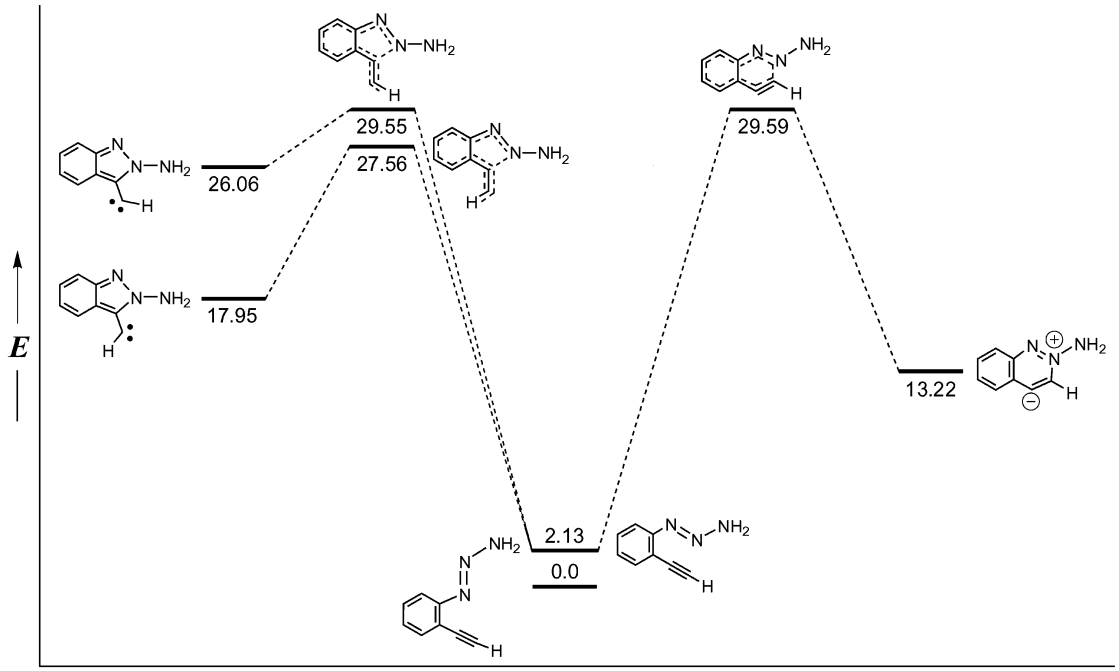
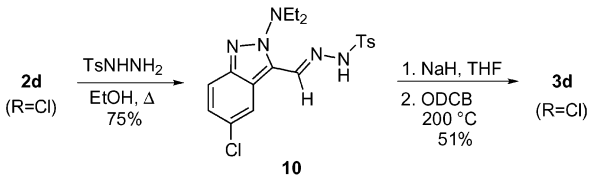
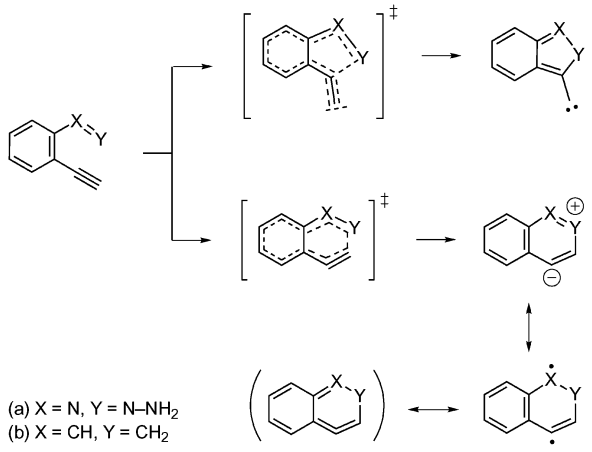


Figure 3. DFT (B3LYP/6-31G* + ZPE) calculated relative energies of reactants, transition states, and products of the cyclization to the isoindazole carbene and the cinnolinium zwitterion.

Scheme 5



Scheme 6. Theoretically (B3LYP/6-31G*, ACID) Investigated Cyclization Reactions



transition state is interrupted (disconnected) because the orbitals involved in the delocalized system are orthogonal at these points. Consequently, these reactions do not follow the Woodward–Hoffmann rules and in some cases nevertheless have surprisingly low activation barriers. Birney[16] recently discovered that such disconnections can also occur in coarctate reactions. In analogy to the pseudopericyclic reactions, we term these reactions pseudocoarctate.

Our ACID method (anisotropy of induced current density)[25] is an excellent tool to distinguish between pericyclic/pseudopericyclic and coarctate/pseudocoarctate reactivity. The ACID scalar field is interpreted as the density of delocalized electrons. A cyclic topology in an ACID plot indicates a pericyclic reaction, and a noncyclic but contiguous delocalized system (constricted or coarctate cycle) indicates a coarctate system. Disconnections that are characteristic for pseudopericyclic and pseudocoarctate systems are immediately visible by a disconnection in the (otherwise) contiguous system of the ACID boundary surface.

Figure 4a presents the ACID isosurface of the five-membered ring cyclization of the parent ethynylphenyltriazene. For comparison, the ACID plot of the all-carbon analogue of the transition state of the five-ring cyclization is shown in Figure 4b. The delocalized system of electrons in the transition state of the isoindazole cyclization (Figure 4a) is not pericyclic because it involves the carbene center that is exocyclic to the five-membered ring. The coarctate topology of the transition state, however, is disconnected between the N- and the C-atom at which the new bond is formed. It is worth noting that the current density vectors do not describe a circle (ring current) in the forming heterocyclic ring. The π system of the N=N and the π orbital of the triple bond that is involved in the bond formation are orthogonal with respect to each other; thus, the reaction is pseudocoarctate. Interestingly, similar to many pseudopericyclic systems, the all-carbon analogue (Figure 4b)

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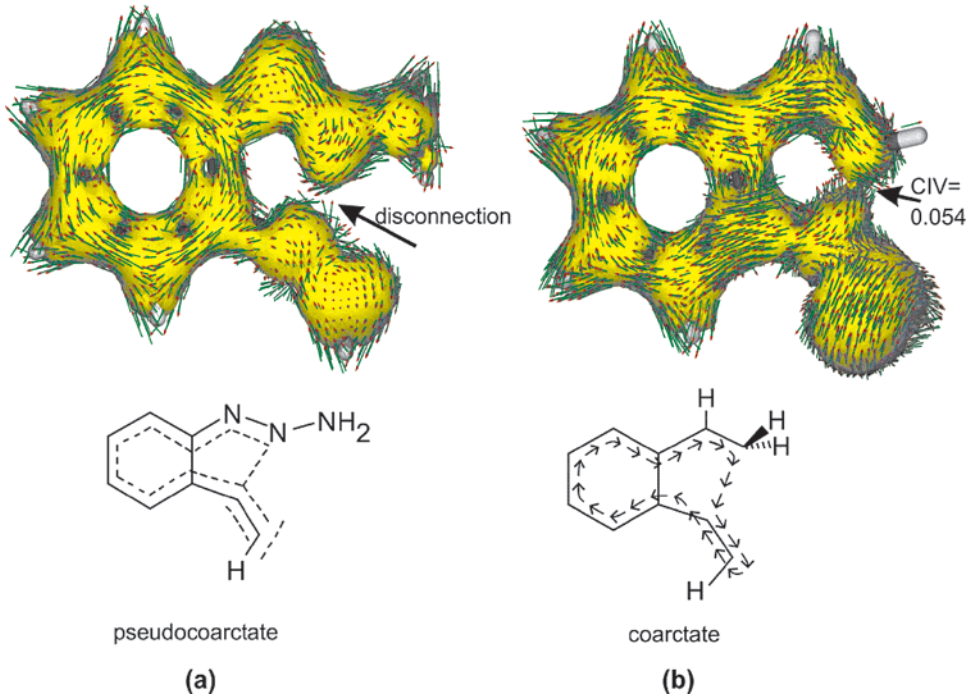


Figure 4. (a) ACID plot of the transition state of the cyclization of (2-ethynylphenyl)triazene to 2-amino-3-methylideneisoindazole. The topology of delocalized electrons exhibits a disconnection between the C and N atoms at which the new C−N bond is formed. The current density vectors (green arrows with red tips) do not exhibit a closed circle in the five-membered ring. Therefore, the transition state is pseudocoarctate in contrast to the all-carbon analogue in panel b. (b) ACID plot of the transition state of the cyclization of 2-ethynylstyrene to 1-methylidene-*2H*-indene, the parent all-carbon analogue of the title isoindazole cyclization. The current density vectors, which are plotted onto 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 title isoindazole cyclization (panel a) that is pseudocoarctate.

of the isoindazole cyclization does not exhibit a disconnection in the transition state and thus is a true coarctate reaction. In contrast to the nitrogen system (Figure 4a), the transition state (Figure 4b) is nonplanar, and the orbitals involved are not orthogonal. To gain further insight into the electronic structure, we plotted the current density vectors onto the ACID isosurface. If one follows the current density vectors, the coarctate nature of the delocalized system in Figure 4b becomes immediately evident. The diatropic ring current forms a hairpin loop involving the C-atom that becomes the carbene center in the product. The delocalized system corresponds to a constricted cycle, hence the name coarctate.[21b]

The ACID plot of the transition state of the six-membered ring cyclization (Figure 5a) exhibits a cyclic topology of delocalized electrons and thus is a pericyclic system. The connection between the two bond-forming centers, however, is rather weak. To quantify the degree of conjugation, we defined the critical isosurface value (CIV). In the case of the six-ring cyclization, the CIV value in forming the C−N bond is 0.045. Compared to the corresponding CIV value of the parent Diels−Alder reaction (0.069), this indicates that the aromaticity in the transition state is rather weak and that the reaction is a borderline case between pericyclic and pseudopericyclic. Similar to the five-ring cyclization, the all-carbon analogue (Figure 5b) exhibits a strong cyclic, aromatic, and thus pericyclic transition state (CIV = 0.072). The current density vectors plotted onto the ACID isosurface reveal a strong diatropic ring current as expected for an aromatic system.

Cinnoline Production. Unlike the formation of the isoindazole, no products from the cyclization of 1-(2-alkynylphenyl)-3,3-dialkyltriazenes readily suggested a mechanism responsible for the generation of a cinnoline species. The most common methods for cinnoline synthesis give 4-substituted products as the result of a Michael-type nucleophilic attack of an alkyne ortho to a diazonium functionality.[9] No such products were observed even when a hydroxide source was present. No source of H^+ or H^- was present to induce cyclization nor to aid in the elimination of Et_2NH. Simply heating the starting alkynylphenyltriazenes in ODCB to 200 °C in a sealed glass pressure tube gave the cinnoline products in excellent yield.[6c] NMR scale experiments confirmed that proton or hydride abstraction was not obtained from the solvent.

Our first inclination was that cinnoline production occurred by means of a Bergman-type[26] reaction to give a 1,4-diradical species. Bergman has shown that these systems can scavenge $H^\bullet$ from the glass reaction flasks. Reactions performed in the presence of radical donors such as dihydroanthracene-d_4[27] and 1,4-cyclohexadiene-d_4[26] gave neither deuterated products nor materials that incorporated the dihydroanthracene or cyclohexadiene structure. We also synthesized several triazenes with R groups at N3 capable of intramolecularly trapping a radical at N1 of the cinnoline. Triazene **11** provides a representative example (Scheme 7). The diazonium salt of iodoaniline was treated with amine **12**[28] and K_2CO_3 to generate triazene **13** in 91% yield. Reaction of **13** with TMSA under Sonogashira

(26) (a) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660−661. (b) Johnson, G. C.; Stofko, J. J., Jr.; Lockhart, T. P.; Brown, D. W.; Bergman, R. G. *J. Org. Chem.* **1979**, *44*, 4215−4218.
(27) Gleiter, R.; Weigl, H.; Haberhauer, G. *Eur. J. Org. Chem.* **1998**, 1447−1453.
(28) Lewis, F. D.; Reddy, G. D.; Schneider, S.; Gahr, M. *J. Am. Chem. Soc.* **1991**, *113*, 3498−3506.

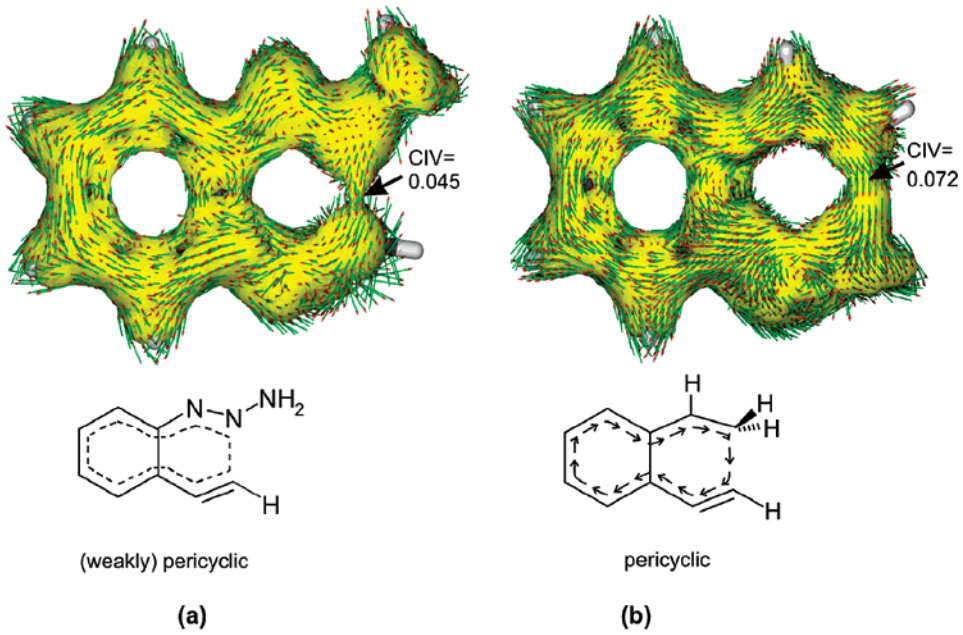
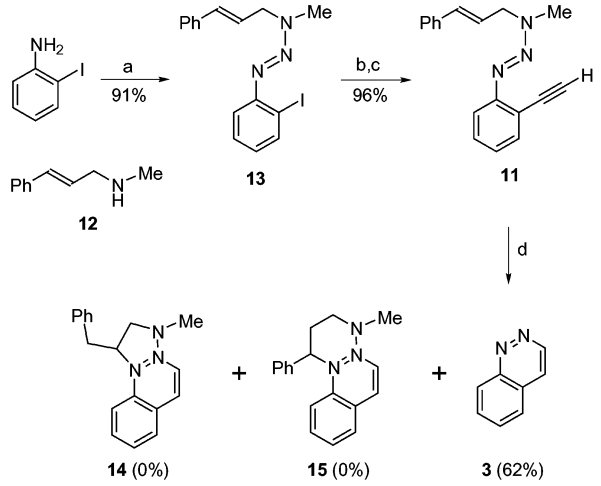


Figure 5. (a) ACID plot of the transition state of the cyclization of (2-ethynylphenyl)triazene to the cinnolinium zwitterion. The topology of delocalized electrons corresponds to a closed cycle and thus is pericyclic. The CIV value of 0.045 between the two carbon atoms at which the new bond is formed, however, is rather weak; thus, the reaction can be viewed as a borderline case between pericyclic and pseudopericyclic. (b) ACID plot of the transition state of the cyclization of 2-ethynylstyrene to isonaphthalene, the parent all-carbon analogue of the title cinnoline cyclization. Current density vectors that are plotted onto the ACID isosurface indicate a strong diatropic ring current and thus an aromatic, pericyclic transition state. The rather high CIV value of 0.072 between the two carbon atoms at which the new bond is formed confirms that the transition state is pericyclic.

Scheme 7 [a]



[a] Reagents and conditions: (a) (i) HCl, $NaNO_2$, MeCN, H_2O, −5 °C; (ii) **12**, K_2CO_3; (b) $Me_3SiC{\equiv}CH$, $PdCl_2(PPh_3)_2$, CuI, Et_3N; (c) K_2CO_3, MeOH, THF; (d) ODCB, 200 °C.

Scheme 8

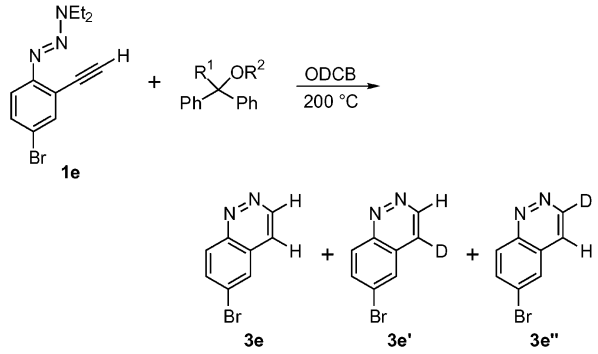


Table 1. Yields of **3e**, **3e′**, and **3e″** from **1e** in the Presence of Deuterated Benzhydrol

R^1	R^2	3e (%)	3e′ (%)	3e″ (%)
D	D	0	58	38
H	D	0	59	35
D	H	97	0	0

conditions, followed by cleavage of the trimethylsilyl group with K_2CO_3 in MeOH/THF, gave **11** in 96% yield. Heating **11** in ODCB to 200 °C gave, after workup, cinnoline (**3**, R = H) in 62% yield along with a complex mixture of byproducts. No products corresponding to the structures of **14** or **15** were isolated however.

Results obtained using benzhydrol-d_2 as the deuterium source suggested a different mechanism. Heating ethynylphenyltriazene **1e** (R = Br) in the presence of an excess of benzhydrol-d_2 (Scheme 8) generated the cinnoline compound that had incorporated deuterium predominantly at C4 (**3e′**, Table 1). Although benzophenone was generated in identical quantities to the resulting cinnoline, a radical mechanism was unlikely since no incorporation of benzhydrol was observed. Also, when cyclizations were performed in the presence of benzhydrol species that were selectively deuterated at either the alcohol or the methylene position, the cinnoline species showed deuterium incorporation only when the alcohol was deuterated.

These results showed that C4 in the intermediate in cinnoline formation had a propensity for proton/deuterium abstraction from the strong but rather acidic O−H bond. Natural bond order (NBO) calculations corroborated this type of reactivity. As the ethynylphenyltriazene cyclizes to the cinnoline intermediate, NBO analysis shows a partial negative charge developing at C4 (Figure 6). The calculated singlet/triplet gap, which can be interpreted as a measure of the diradical character, is 13.6 kcal mol^{-1}. This indicated that the intermediate in the formation of the cinnoline compound was likely a zwitterionic cinnolinium with rather low diradical character. Such a species could abstract

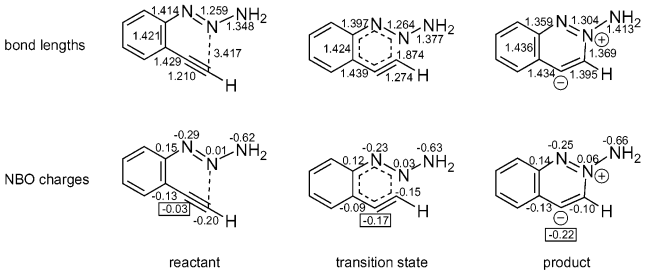
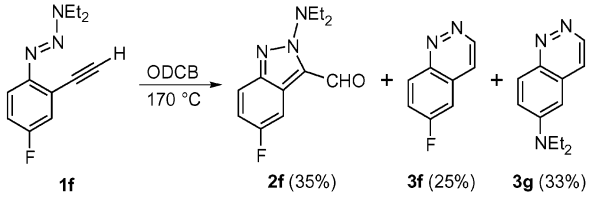


Figure 6. Bond lengths (Å, top) and NBO charges (bottom) of the reactant (left), transition state (middle), and product (right) of the pericyclic cinnoline cyclization reaction.

Scheme 9

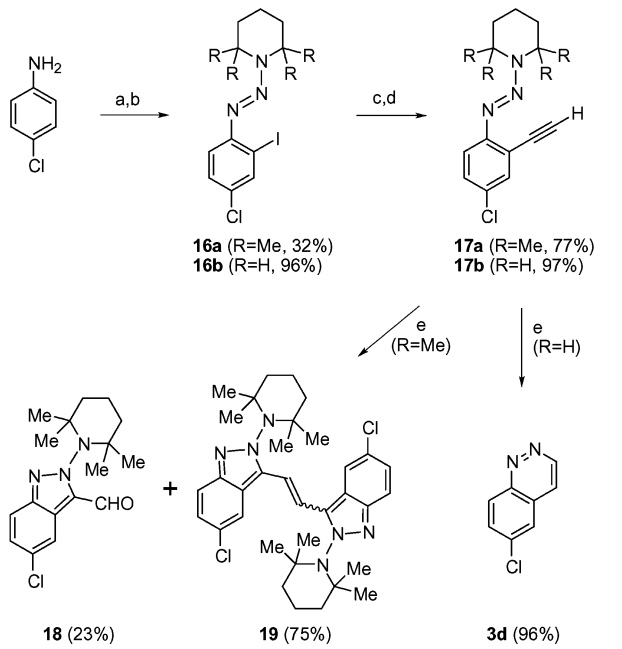


a hydrogen/deuterium from an −OH source after cyclization produced an anion at C4. Further electrocyclic rearrangement through a six-membered transition state would be consistent with a pericyclic pathway. This reactivity would give the zwitterion directly rather than a Hopf-type allene[29] that was not found to be a minimum on the energy hypersurface; however, the cyclic allene structure is the predominant valence bond configuration in the all-carbon analogue (Scheme 6). Shevlin and co-workers[30] have recently reported similar zwitterionic systems produced at low temperatures in inert matrixes.

Calculations for the cyclization of ethynylphenyltriazenes to cinnolines using a pericyclic pathway are consistent with our observed results. The subsequent mechanism of Et_2N- loss, however, remained in question. NMR scale experiments suggested that Et_2NH was generated during the reaction, and in one example this nucleophile reacted with the cinnoline species during the cyclization of a fluoroarene (Scheme 9). Presumably, 6-fluorocinnoline (**3f**) reacted in a nucleophilic aromatic substitution to generate the 6-diethylaminocinnoline (**3g**).

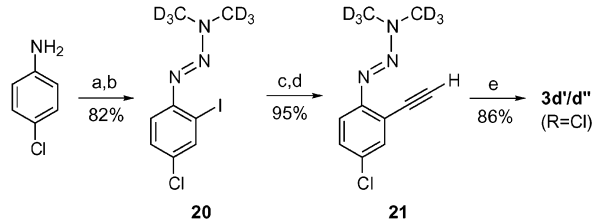
Of several possibilities, loss of the diethylamine moiety as either the nitrogen cation or as an imine generated by proton abstraction was the most reasonable. One solution to this question was to install methyl groups on the methylene carbons attached to the terminal nitrogen (N3) of the triazene. By doing so, cyclization to the cinnoline should be blocked if the mechanism occurs through an imine species, while the generation of a nitrenium ion should be enhanced by sterics and inductive stabilization. Toward this end, 4-chloroaniline was iodinated using BTEA·ICl_2, diazotized using HCl and $NaNO_2$, and reacted with 2,2,6,6-tetramethylpiperidine to give triazene **16a** (Scheme 10). Treatment of **16a** with trimethylsilylacetylene under Pd-mediated conditions, followed by desilylation with K_2CO_3 in MeOH/THF, provided ethynylphenyltriazene **17a** in 25% overall yield. Cyclization at 200 °C in ODCB provided only products resulting from isoindazole formation, isoindazole aldehyde **18** and dimer **19** in 98% combined yield. No cinnoline formation was observed. As a control, ethynylphenyltriazene

Scheme 10 [a]



[a] Reagents and conditions: (a) BTEA·ICl_2, $CaCO_3$, MeOH, $CHCl_3$; (b) (i) HCl, $NaNO_2$, MeCN, H_2O, −5 °C; (ii) piperidine or 2,2,6,6-tetramethylpiperidine, K_2CO_3; (c) $Me_3SiC{\equiv}CH$, $PdCl_2(PPh_3)_2$, CuI, Et_3N, 50 °C; (d) K_2CO_3, MeOH, THF; (e) ODCB, 200 °C.

Scheme 11 [a]



[a] Reagents and conditions: (a) BTEA·ICl_2, $CaCO_3$, MeOH, $CHCl_3$; (b) i. HCl, $NaNO_2$, MeCN, H_2O, −5 °C; ii. $(CD_3)_2NH$·HCl, K_2CO_3; (c) $Me_3SiC{\equiv}CH$, $PdCl_2(PPh_3)_2$, CuI, Et_3N, 50 °C; (d) K_2CO_3, MeOH, THF; (e) ODCB, 200 °C.

17b was synthesized for comparison with tetramethylated analogue **17a**. Compound **17b** was prepared similarly in 93% overall yield from 4-chloroaniline. Unlike **17a**, when **17b** was heated to 200 °C in ODCB, cinnoline **3d** (R = Cl) was observed in 96% yield. No isoindazole products were observed when the reaction was monitored by NMR.

These results encouraged us to confirm the generation of an imine species as the mechanism of diethylamine elimination. This could be done using a triazene with deuterated methylene groups on the 3-nitrogen. If a zwitterionic cinnolinium is generated through a pericyclic reaction, then this species could remove a proton from the triazene methylene carbon to generate the imine. Using a deuterated dimethyltriazene should then give a deuterated cinnoline as the product of thermal cyclization. Treating the diazonium salt of 4-chloro-2-iodoaniline with commercially available Me_2NH-d_6 gave the triazene **20** with >98% deuteration of the methyl groups (Scheme 11). Reaction of **20** with trimethylsilylacetylene in the usual manner, followed by desilylation, gave ethynylphenyltriazene **21** in 78% overall yield. When **21** was heated to 200 °C in ODCB, cinnoline **3d′** (R = Cl) was formed in 86% yield, with deuteration predominantly at the 4-position with some deuteration at the 3-position (Figure

(29) Zimmermann, G. *Eur. J. Org. Chem.* **2001**, 457−471.
(30) (a) Pan, W.; Shevlin, P. B. *J. Am. Chem. Soc.* **1997**, *119*, 5091−5094. (b) Emanuel, C. J.; Shevlin, P. B. *J. Am. Chem. Soc.* **1994**, *116*, 5991−5992.

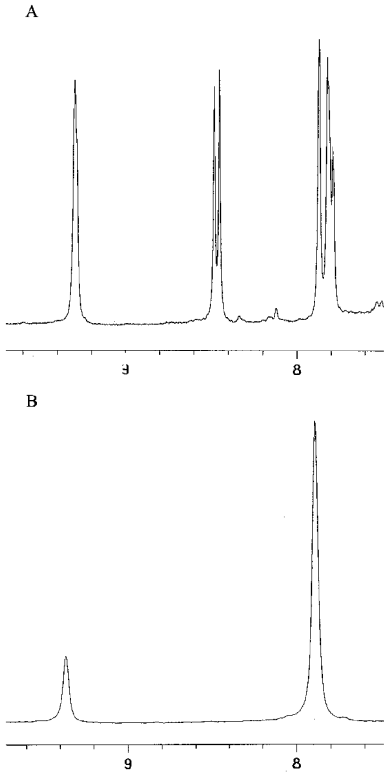


Figure 7. ^{1}H (a) and ^{2}H (b) NMR spectra of **3d′/3d″** showing deuterium incorporation predominantly at C4 with minor deuteration at C3.

7). ^{1}H NMR data indicated a ratio of deuteration of C4 versus C3 of ca. 9:1. The reaction produced only trace quantities (by NMR) of material where there was no deuterium incorporation.

Although this strongly suggested that loss of the diethylamino group occurred through an imine, deuterium incorporation at C3 was unexpected. Shevlin and Pan reported a similar rearrangement to give a more stable 1,2-zwitterionic pyridinium species prepared at low temperature.[30a] This might allow hydrogen or deuterium abstraction through an intramolecular, five-membered transition state. Cyclizations done under higher dilutions resulted in deuteration at C4 and C3 in ratios similar to those previously obtained (ca. 9:1). Although this might support an intramolecular pathway, proton abstraction from the carbon α to the nitrogen by the anion at C4 has a DFT calculated barrier of 52.5 kcal mol^{-1}. We therefore suggest that loss of the dialkylamino group as the imine and rearrangement to the 1,2-zwitterion (**22**) occur through intermolecular pathways, both of which originate from 1,3-zwitterion **23** (Scheme 12). In the latter case, rearrangement is less favored than imine loss.

Conclusions

Our results strongly support a carbene intermediate in the cyclization of ethynylphenyltriazenes to give isoindazoles through a pseudocoarctate rearrangement. Further trapping studies show that a pericyclic pathway is favored for the thermal cyclization of ethynylphenyltriazenes to cinnolines under neutral conditions. Proton abstraction by a partially charged zwitterionic cinnolinium species occurs through an intermolecular process that eliminates the dialkylamino moiety of the cinnolinium as an imine. Efforts are underway to determine the generality of this transformation with regard to other triazene and ethyne analogues as well as with heteroarene derivatives.

Computational Methods

All theoretical calculations have been performed using the Gaussian 98 suite of programs[31] at the B3LYP/6-31G* level[32] of DFT. All stationary points were confirmed by harmonic frequency analysis, and the energies of the stationary points were determined, including zero point energies at the same level of theory. Natural charges were calculated using Weinberger's NBO method[33] implemented in Gaussian. ACID scalar fields were computed using our own program.[25] In all ACID plots the standard isosurface value of 0.05 was used. Current density vectors were calculated using the CSGT method of Keith and Bader.[34] To save computational costs and to reduce the complexity of the energy hypersurface, in all calculations of the cyclization reactions the two ethyl groups at the terminal NEt_2 are replaced by hydrogen (NH_2). The stationary points of the intramolecular proton-transfer reactions (Scheme 12) were checked at the higher B3LYP/6-31+G**// B3LYP/6-31G* level of theory. The calculated activation barriers (53.6 and 25.5 kcal mol^{-1}) (52.5 and 23.1 kcal mol^{-1} at B3LYP/6-31G*) reveal a weak influence of diffuse and polarization functions, the anionic character of the species notwithstanding.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded using a Varian Inova 300 NMR (^{1}H: 299.94 MHz; ^{13}C: 75.43 MHz) spectrometer. Chemical shifts (δ) are expressed in ppm downfield from tetramethylsilane using the residual solvent as internal standard ($CDCl_3$ ^{1}H: 7.26 ppm; ^{13}C: 77.0 ppm). Coupling constants are expressed in hertz. IR spectra were recorded using a Nicolet Magna-FTIR 550 spectrometer. Melting points were determined on a Meltemp II apparatus and are uncorrected. Mass spectra were recorded using either an Agilent 1100 LC/MSD (ESI) or Kratos MS50 (HRMS) spectrometer. Et_3N and CH_2Cl_2 were distilled from CaH_2 under an N_2 atmosphere prior to use. THF was distilled from Na and benzophenone under an N_2 atmosphere prior to use. All other chemicals were of reagent quality and used as obtained from the manufacturers. Column chromatography was performed on Whatman reagent grade silica gel (230−400 mesh). Sorbent Technologies precoated silica gel plates were used for preparative (200 × 200 × 1 mm) thin-layer chromatography. Reactions were carried out in an inert atmosphere (dry nitrogen or argon) when necessary.

Trimer 6. To a solution of **1a**[6c] (R = CN, 350 mg, 1.5 mmol) in ODCB (20 mL) was added CuI (29 mg, 0.15 mmol). The mixture was brought to 110 °C and stirred for 16 h. After being cooled, the mixture was diluted with hexanes and vacuum filtered through silica, first washing with hexanes and then eluting with 1:1 CH_2Cl_2/EtOAc. Purification by column chromatography (3:1:1 hexanes/CH_2Cl_2/EtOAc) gave **2a**[6c] (R = CN, 215 mg, 62%) as the first component. Isolation of the second band furnished **6** (84 mg, 28%) as a bright red crystalline solid. Recrystallization from EtOH provided red needles suitable for X-ray diffraction. mp 270.6−271.9 °C. ^{1}H NMR ($CDCl_3$) δ 9.23−9.22 (m, 1H), 8.21 (d, J = 1.8 Hz, 1H), 7.95 (s, 1H), 7.93 (dd, J = 8.5, 1.8 Hz, 1H), 7.86 (d, J = 1.5 Hz, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.80 (d, J = 8.8 Hz, 1H), 7.54 (dd, J = 8.8, 1.5 Hz, 1H), 7.20 (d, J = 0.6 Hz, 1H), 7.17 (dd, J = 9.1, 1.8 Hz, 1H), 6.78 (d, J = 9.1 Hz, 1H),

(31) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.6; Gaussian, Inc.: Pittsburgh, PA, 1998.
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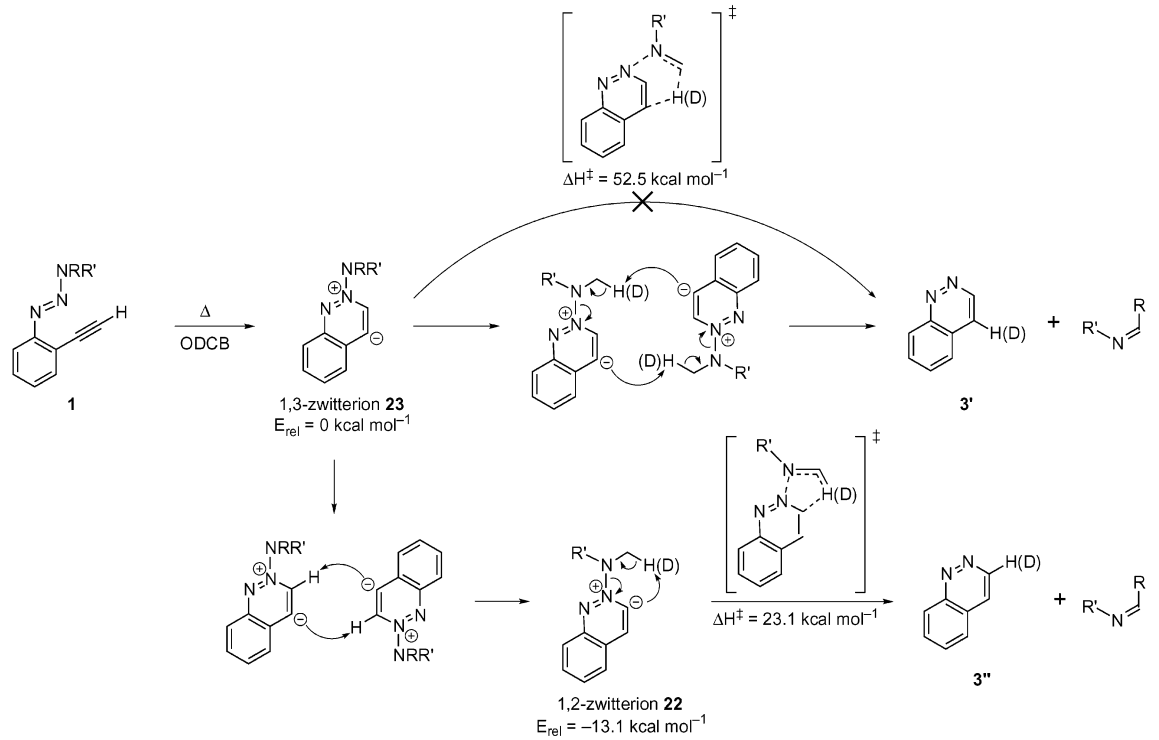
(33) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899−926.
(34) Keith, B. A.; Bader, R. F. W. *J. Chem. Phys.* **1993**, *99*, 3669−3682.

Scheme 12. Possible Mechanisms Leading to Cinnolines **3′** and **3″** [a]



[a] Relative energies E_{rel} and activation barriers $\Delta H^{\ddagger}$ are calculated at the B3LYP/6-31G* level of DFT theory where R = Me and R′ = H in **1**. The energies E_{rel} are relative to the 1,2-zwitterion, and the activation enthalpies $\Delta H^{\ddagger}$ are calculated with respect to the corresponding reactants (1,2- and 1,3-zwitterion).

3.58−3.48 (m, 4H), 3.34 (br s, 2H), 3.06−2.99 (m, 1H), 2.74−2.66 (m, 1H), 1.10 (t, J = 7.4 Hz, 3H), 0.89 (br s, 6H), 0.19 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 153.22, 147.72, 146.82, 145.66, 144.79, 135.59, 133.75, 133.59, 132.21, 130.26, 129.46, 128.75, 127.96, 126.44, 122.97, 120.38, 120.10, 119.80, 119.23, 118.83, 118.16, 115.54, 108.63, 107.52, 106.76, 106.36, 94.70, 53.00, 50.29, 42.56, 14.26, 12.23, 9.99. IR (KBr) 3153, 3116, 3064, 2978, 2223, 1593 cm^{-1}. HRMS: calcd for $C_{35}H_{31}N_{11}$, 605.2764; found, 605.2652. Anal. Calcd for $C_{35}H_{31}N_{11}$: C, 69.40; H, 5.16; N, 25.44. Found: C, 69.69; H, 5.19; N, 25.11.

Cyclopropane 7. A solution of **1b**[6c] (R = *t*-Bu, 54 mg, 0.21 mmol) and 2,3-dimethyl-2-butene (1.0 mL, 8.4 mmol) in dry CH_2Cl_2 (20 mL) was deoxygenated via bubbling with N_2 that had passed through Fieser's solution. After 30 min, CuCl (84 mg, 0.85 mmol) was added, and the mixture was stirred for 16 h. After vacuum filtration through silica and evaporation of solvent, purification by preparative TLC (9:1 hexanes/EtOAc) gave **7** (47 mg, 65%) as a yellow powder. mp 108.9−110.2 °C. ^{1}H NMR ($CDCl_3$) δ 7.58 (d, J = 9.0 Hz, 1H), 7.48 (d, J = 1.9 Hz, 1H), 7.37 (dd, J = 9.0, 1.9 Hz, 1H), 3.35 (br s, 2H), 3.18 (br s, 2H), 1.48 (s, 1H), 1.38 (s, 6H), 1.37 (s, 9H), 1.06 (s, 6H), 1.04 (t, J = 7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 144.75, 142.37, 133.58, 126.83, 125.24, 119.24, 116.73, 116.02, 51.51, 34.64, 31.27, 30.21, 24.28, 23.58, 19.88, 12.56. IR (KBr) 3085, 3040, 2964, 2867, 2735, 1464 cm^{-1}. MS (ESI) m/z (%): 342.3 (100, $M^+ + H$), 271.2 (10, $M^+ - C_4H_{10}N$). Anal. Calcd for $C_{22}H_{35}N_3$ (341.53): C, 77.37; H, 10.33; N, 12.30. Found: C, 77.19; H, 10.23; N, 11.99.

1-[2-([1,1′-Biphenyl]-2-ylethynyl)-4-methylphenyl]-3,3-diethyl-1-triazene (8). Triazene **1c** (R = Me, 1.41 g, 6.5 mmol), 2-iodobiphenyl[14] (1.81 g, 6.5 mmol), $PdCl_2(PPh_3)_2$ (182 mg, 0.26 mmol), and CuI (74 mg, 0.39 mmol) were combined in Et_3N (40 mL). The mixture was degassed by three successive freeze−pump−thaw cycles. The reaction was heated to 50 °C and stirred under N_2 overnight. After being cooled, the solvent was evaporated, and the crude product was redissolved (9:1 hexanes/CH_2Cl_2) and vacuum filtered through a pad of silica gel. Column chromatography (4:1 to 2:1 hexanes/CH_2Cl_2 gradient) gave **8** (1.81 g, 75%) as a tan oil. ^{1}H NMR ($CDCl_3$) δ 7.74−7.71 (m, 2H), 7.62 (dd, J = 7.5, 1.2 Hz, 1H), 7.47−7.41 (m, 3H), 7.40−7.27 (m, 4H), 7.06−7.02 (m, 2H), 3.75 (q, J = 7.4 Hz, 4H), 2.27 (s, 3H), 1.28 (t, J = 7.4 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 150.01, 143.37, 140.66, 134.13, 132.94, 129.74, 129.42, 129.39, 128.04, 127.83, 127.80, 127.24, 126.87, 122.31, 117.96, 116.72, 91.34, 48.5 (br), 41.7 (br), 20.67, 14.1 (br), 11.6 (br). IR (neat) 3060, 3022, 2973, 2872, 2207 cm^{-1}. MS (ESI) m/z (%): 368.2 (100, $M^+ + H$), 295.1 (60, $M^+ - C_4H_{10}N$), 267.1 (70, $M^+ - C_4H_{10}N_3$), 252.1 (100, $M^+ - C_5H_{13}N_3$).

Fluorene 9. A solution of **8** (51 mg, 0.14 mmol) in DCE (30 mL) was deoxygenated via bubbling with N_2. After 15 min, CuCl (100 mg, 1.0 mmol) was added, and the mixture was heated to 90 °C for 16 h. After being cooled, the mixture was vacuum filtered through silica using CH_2Cl_2 as eluent. The solvent was evaporated, and purification by preparative TLC (3:1 hexanes/EtOAc) provided **9** (28 mg, 55%) as a yellow solid. Recrystallization from EtOH gave crystals suitable for X-ray diffraction. mp 203.1−204.0 °C. ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 7.8 Hz, 2H), 7.50 (d, J = 8.7 Hz, 1H), 7.45−7.40 (m, 2H), 7.24−7.21 (m, 4H), 6.95 (d, J = 9.0 Hz, 1H), 6.12 (s, 1H), 5.93 (s, 1H), 3.58−3.42 (m, 4H), 2.01 (s, 3H), 1.23 (t, J = 7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 145.75, 145.04, 140.88, 133.20, 129.75, 129.06, 127.59, 127.50, 124.92, 120.06, 118.23, 116.92, 116.84, 52.39, 44.58, 21.55, 13.03. IR (KBr) 3062, 3015, 2975, 1447 cm^{-1}. MS (ESI) m/z (%): 368.2 (100, $M^+ + H$), 295.1 (10, $M^+ - C_4H_{10}N$), 165.1 (20, $C_{13}H_9^+$). Anal. Calcd for $C_{25}H_{25}N_3$ (367.49): C, 81.71; H, 6.86; N, 11.43. Found: C, 81.46; H, 6.69; N, 11.51.

Tosylhydrazone 10. Isoindazole **2d**[6c] (R = Cl, 192 mg, 0.81 mmol) was combined with *p*-toluenesulfonylhydrazide (166 mg, 0.89 mmol) and EtOH (4 mL) and refluxed for 16 h. The solvent was evaporated, after which column chromatography (3:1 EtOAc/hexanes) gave **10** (255 mg, 75%) as a clear oil. ^{1}H NMR ($CDCl_3$) δ 8.62 (br s, 1H), 8.30 (s, 1H), 7.97 (d, J = 8.4 Hz, 2H), 7.92 (d, J = 2.1 Hz, 1H), 7.57 (d, J =

9.1 Hz, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.27 (dd, J = 9.1, 2.1 Hz, 1H), 3.35 (br s, 2H), 3.10 (br s, 2H), 2.43 (s, 3H), 0.73 (t, J = 7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 144.78, 144.50, 138.17, 134.68, 129.87, 129.43, 128.24, 121.00, 119.05, 118.16, 52.37, 21.63, 11.87. IR (neat) 3197, 3069, 2925, 1167 cm^{-1}. MS (ESI) m/z (%): 420.1 (100, $M^+ + H$), 319.2 (30, $M^+ - C_4H_{10}N_3$). Anal. Calcd for $C_{19}H_{22}ClN_5O_2S$ (419.93): C, 54.34; H, 5.28; N, 16.68. Found: C, 54.62; H, 5.39; N, 16.57.

6-Chlorocinnoline (3d) from Tosylhydrazone 10. The following procedure for the formation of the sodium salt of **10** was modified from the literature.[15] To a mixture of NaH (4 mg, 0.17 mmol) in THF (3 mL) was added via syringe a solution of **10** (64 mg, 0.15 mmol) in THF (3 mL). After being stirred for 15 min, the solvent was evaporated. The solid obtained was suspended in ODCB (6 mL) and heated overnight at 200 °C. After being cooled, the solvent was removed, and the crude product was purified by preparative TLC (2:1:1 hexanes/CH_2Cl_2/EtOAc) to give **3d** (R = Cl, 13 mg, 51%) as a white solid. Spectral data were identical to those reported previously.[6c]

Triazene 13. 2-Iodoaniline (219 mg, 1.0 mmol) was dissolved in a minimal amount of MeCN (3 mL), after which concentrated HCl (0.67 mL, 8.0 mmol) and ice (~1 g) were added. The suspension was cooled to −5 °C, and a solution of $NaNO_2$ (173 mg, 2.5 mmol) in water (3 mL) and MeCN (1 mL) was added slowly such that the temperature remained between −5 and −2 °C. Once the addition was complete, the solution was stirred at −5 °C for 30 min, after which it was transferred slowly via cannula to a quench solution of amine **12**[28] (1.4 g, 10 mmol), K_2CO_3 (661 mg, 5 mmol), water (30 mL), and MeCN (10 mL) cooled to 0 °C. Once the transfer was complete, the mixture was allowed to gradually warm to room temperature overnight. The mixture was diluted with water and extracted with Et_2O. The combined organics were dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography (1:1 hexanes/CH_2Cl_2) provided **13** (343 mg, 91%) as a light yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.95 (dd, J = 7.8, 1.2 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 7.48−7.33 (m, 6H), 6.93 (td, J = 7.8, 1.5 Hz, 1H), 6.67 (d, J = 15.6 Hz, 1H), 6.40−6.26 (m, 1H), 4.59 (dd, J = 6.6, 1.5 Hz, 2H), 3.33 (br s, 3H). ^{13}C NMR ($CDCl_3$) δ 149.81, 138.98, 136.10, 133.58, 128.59, 128.51, 127.83, 126.84, 126.39, 124.25, 117.59, 96.67, 57.96, 34.97. IR (neat) 3058, 3026, 2919, 1449, 1345 cm^{-1}. HRMS calcd for $C_{16}H_{17}N_3I$: 378.0467. Found: 378.0460.

Alkyne 11. Triazene **13** (325 mg, 0.86 mmol) was reacted with trimethylsilylacetylene (TMSA, 0.18 mL, 1.3 mmol), $PdCl_2(PPh_3)_2$ (18 mg, 0.026 mmol), CuI (10 mg, 0.052 mmol), and Et_3N (20 mL) under conditions analogous to **8**. After concentration, the crude product was redissolved in MeOH (5 mL) and THF (25 mL), and K_2CO_3 (570 mg, 4.3 mmol) was added. After being stirred at room temperature for 24 h, the reaction was diluted with Et_2O and washed with concentrated NH_4Cl solution. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography (1:1 hexanes/CH_2Cl_2) gave **11** (233 mg, 96%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.53 (dd, J = 7.6, 1.5 Hz, 1H), 7.48 (d, J = 8.2 Hz, 1H), 7.42−7.24 (m, 6H), 7.11 (td, J = 7.3, 1.2 Hz, 1H), 6.63 (d, J = 15.8 Hz, 1H), 6.35−6.26 (m, 1H), 4.56 (dd, J = 6.7, 1.5 Hz, 2H), 3.29 (s, 4H). ^{13}C NMR ($CDCl_3$) δ 152.47, 136.34, 133.67, 129.38, 128.62, 127.91, 126.48, 125.03, 124.49, 117.22, 117.11, 81.88, 81.04, 58.1 (br), 34.1 (br). IR (neat) 3293, 3060, 3027, 2910, 2582, 2104 cm^{-1}. HRMS calcd for $C_{18}H_{18}N_3$: 276.1497. Found: 276.1497.

Thermal Cyclization of 11. Alkyne **11** (70 mg, 0.25 mmol) was dissolved in ODCB (7 mL) and heated to 200 °C for 24 h. The mixture was cooled, and the solvent was evaporated. Successive purification by column chromatography (40−60% CH_2Cl_2 in hexanes) and preparative TLC (4:1:1 hexanes/CH_2Cl_2/EtOAc) gave cinnoline **3** (20 mg, 62%) as a light oil along with several other byproducts. ^{1}H and ^{13}C NMR analyses and MS spectra of the separated byproducts gave no indication of structures corresponding to **14** or **15**.

Cyclization of 1e in the Presence of Benzhydrol-d_1/d_2. Alkyne **1e** (50 mg, 0.18 mmol) was combined with benzhydrol-d_1 or benzhydrol-d_2 (10 equiv) in ODCB (6 mL) and heated to 200 °C for 24 h. The mixture was cooled and diluted with hexanes. The mixture was vacuum filtered through silica, washing with 1:1 hexanes/CH_2Cl_2 to remove less polar compounds and then eluting the cinnoline products with 1:1 CH_2Cl_2/EtOAc. Purification by preparative TLC (3:1:1 hexanes/CH_2Cl_2/EtOAc) gave **3e/e′/e″** as given in Table 1. Ratios were determined by NMR spectroscopy.

6-Diethylaminocinnoline (3g). To a sealable glass pressure tube was added **1f** (R = F, 106 mg, 0.48 mmol) and ODCB (10 mL). The tube was sealed and heated to 170 °C with stirring overnight. After being cooled, the solvent was evaporated, and the crude product was purified by preparative TLC (2:1:1 hexanes/CH_2Cl_2/EtOAc) to provide 6-diethylaminocinnoline (**3g**) (32 mg, 33%) as a yellow oil, in addition to previously reported cinnoline **3f**[6c] (25 mg, 35%) and isoindazole **2f**[6c] (28 mg, 25%). **3g:** ^{1}H NMR ($CDCl_3$) δ 8.90 (d, J = 5.9 Hz, 1H), 8.24 (d, J = 9.7 Hz, 1H), 7.48 (d, J = 6.1 Hz, 1H), 7.37 (dd, J = 9.7, 2.9 Hz, 1H), 6.52 (d, J = 2.6 Hz, 1H), 3.51 (q, J = 7.1 Hz, 4H), 1.26 (t, J = 7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 148.57, 146.40, 144.81, 131.10, 129.07, 120.16, 119.76, 99.34, 44.74, 12.56. IR (neat) 3065, 2973, 2932, 2900, 2872, 1683, 1611 cm^{-1}. HRMS calcd for $C_{12}H_{16}N_3$: 202.1344. Found: 202.1342.

Triazene 16a. 4-Chloroaniline (750 mg, 5.9 mmol) was combined with BTEA·ICl_2 (2.5 g, 6.4 mmol) and $CaCO_3$ (650 mg, 6.5 mmol) in MeOH (5 mL) and $CHCl_3$ (40 mL) and stirred at room temperature for 24 h. The resulting mixture was filtered, and the solvent was evaporated. The crude product was redissolved in Et_2O and washed with 5% $NaHSO_3$ solution and then water. The combined organics were dried ($MgSO_4$), filtered, and concentrated. The resultant solid was used without additional purification.

The iodinated product (500 mg, 2.0 mmol) was dissolved in MeCN (5 mL) and reacted with concentrated HCl (1.3 mL, 15.8 mmol), $NaNO_2$ (301 mg, 4.4 mmol), 2,2,6,6-tetramethylpiperidine (3.3 mL, 19.8 mmol), and K_2CO_3 (1.32 g, 10 mmol) under conditions analogous to triazene **13**. Purification by column chromatography (50:1 hexanes/CH_2Cl_2) provided **16a** (260 mg, 32%) as a light yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.82 (d, J = 2.1 Hz, 1H), 7.24 (dd, J = 8.8, 2.1 Hz, 1H), 7.18 (d, J = 8.8 Hz, 1H), 1.75−1.70 (m, 6H), 1.56 (s, 12H). ^{13}C NMR ($CDCl_3$) δ 150.33, 138.11, 130.43, 128.60, 117.60, 96.14, 61.38, 41.53 (br), 28.88 (br), 16.54. IR (neat) 3067, 3015, 2933, 1423, 563 cm^{-1}. MS (ESI) m/z (%): 406.0 (100, $M^+ + H$), 368.2 (50, $M^+ - HCl$).

Alkyne 17a. Triazene **16a** (260 mg, 0.64 mmol) was reacted with TMSA (0.11 mL, 0.78 mmol), $PdCl_2(PPh_3)_2$ (21 mg, 0.03 mmol), CuI (11 mg, 0.06 mmol), and Et_3N (20 mL) under conditions analogous to **8**. The crude product was concentrated and treated with K_2CO_3 (790 mg, 6 mmol) under conditions analogous to **11**. Purification by column chromatography (9:1 hexanes/CH_2Cl_2) provided **17a** (150 mg, 77%) as a white semisolid. ^{1}H NMR ($CDCl_3$) δ 7.45 (d, J = 2.3 Hz, 1H), 7.29 (d, J = 8.5 Hz, 1H), 7.21 (dd, J = 8.5, 2.3 Hz, 1H), 3.26 (s, 1H), 1.71 (br s, 6H), 1.54 (s, 12H). ^{13}C NMR ($CDCl_3$) δ 152.56, 132.68, 129.43, 129.38, 118.79, 117.19, 81.63, 81.50, 61.15, 41.46 (br), 28.47 (br), 16.65. IR (neat) 3304, 3019, 2939, 2108 cm^{-1}. MS (ESI) m/z (%): 304.1 (100, $M^+ + H$), 142.1 (50, $C_9H_{19}N$).

Isoindazole Aldehyde 18 and Dimer 19. To a sealable glass pressure tube was added triazene **17a** (40 mg, 0.13 mmol) and ODCB (4 mL). The tube was sealed and heated overnight at 200 °C. After being cooled, the solvent was evaporated, and the crude product was purified by preparative TLC (6:1:1 hexanes/CH_2Cl_2/EtOAc) to provide **18** (10 mg, 23%) as a yellow oil and dimer **19** (30 mg, 75%) as a yellow powder. **18:** ^{1}H NMR ($CDCl_3$) δ 10.34 (s, 1H), 8.23 (d, J = 2.2 Hz, 1H), 7.77 (d, J = 9.1 Hz, 1H), 7.35 (dd, J = 9.1, 2.2 Hz, 1H), 1.76−1.72 (m, 6H), 1.59 (s, 6H), 0.74 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 182.54, 143.35, 132.72, 129.06, 128.64, 120.50, 120.30, 119.98, 60.17, 41.10, 31.30, 23.94, 17.71. IR (neat) 3074, 2930, 1728, 1664, 1453, 790 cm^{-1}. MS (ESI) m/z (%): 320.1 (100, $M^+ + H$), 282.3 (20, $M^+ - HCl$), 149.0 (100, $M^+ - C_9H_{18}N_3$), 142.0 (20, $C_9H_{18}N$). **19:** mp 323.5−325.0 °C. ^{1}H NMR ($CDCl_3$) δ 8.05 (d, J = 1.5 Hz, 2H), 7.80 (s, 2H),

7.72 (d, $J = 9.1$ Hz, 2H), 7.31 (dd, $J = 9.1$, 1.5 Hz, 2H), 1.90−1.74 (m, 6H), 1.62 (s, 6H), 0.76 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 143.63, 135.19, 128.24, 127.16, 120.27, 119.52, 118.28, 116.73, 60.00, 41.33, 30.70, 24.12, 17.77. IR (KBr) 3080, 3009, 2931, 1476, 805 cm^{-1}. MS (ESI) *m*/*z* (%): 607.3 (100, $M^+ + H$). Anal. Calcd for $C_{34}H_{44}Cl_2N_6$ (607.66): C, 67.20; H, 7.30; N, 13.86. Found: C, 66.95; H, 7.24; N, 13.81.

Triazene 16b. 4-Chloroaniline (750 mg, 5.9 mmol), BTEA·ICl_2 (2.5 g, 6.4 mmol), and $CaCO_3$ (650 mg, 6.5 mmol) were reacted under analogous conditions to **16a**. After workup, the iodinated product (438 mg, 1.7 mmol) was dissolved in MeCN (8 mL) and reacted with concentrated HCl (3.5 mL, 42 mmol), $NaNO_2$ (300 mg, 4.3 mmol), piperidine (4.5 mL, 45 mmol), and K_2CO_3 (1.32 g, 10 mmol) under conditions analogous to triazene **13**. Purification by column chromatography (20:1 hexanes/CH_2Cl_2) provided **16b** (583 mg, 96%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.82 (d, $J = 2.1$ Hz, 1H), 7.31 (d, $J = 8.6$ Hz, 1H), 7.24 (dd, $J = 8.6$, 2.1 Hz, 1H), 3.84 (br s, 4H), 1.72 (br s, 6H). ^{13}C NMR ($CDCl_3$) δ 148.73, 138.11, 130.94, 128.78, 117.73, 96.45, 52.9 (br), 44.4 (br), 26.5 (br), 24.3 (br), 24.24. IR (neat) 3078, 2939, 2855, 1552 cm^{-1}. MS (ESI) *m*/*z* (%): 350.0 (100, $M^+ + H$).

Alkyne 17b. Triazene **16b** (583 mg, 1.7 mmol) was reacted with TMSA (0.31 mL, 4.5 mmol), $PdCl_2(PPh_3)_2$ (47 mg, 0.07 mmol), CuI (22 mg, 0.11 mmol), and Et_3N (25 mL) under conditions analogous to **8**. The crude product was concentrated and treated with K_2CO_3 (1.32 g, 10 mmol) under conditions analogous to **11**. Purification by column chromatography (8:1 hexanes/CH_2Cl_2) provided **17b** (400 mg, 97%) as an orange oil. ^{1}H NMR ($CDCl_3$) δ 7.47 (d, $J = 2.4$ Hz, 1H), 7.41 (d, $J = 8.8$ Hz, 1H), 7.23 (dd, $J = 8.8$, 2.4 Hz, 1H), 3.84 (br s, 4H), 3.30 (s, 1H), 1.72 (br s, 6H). ^{13}C NMR ($CDCl_3$) δ 151.09, 132.93, 129.87, 129.58, 118.35, 118.00, 82.12, 80.53, 52.5 (br), 25.0 (br), 24.25. IR (neat) 3298, 3066, 2940, 2856, 2107 cm^{-1}. MS (ESI) *m*/*z* (%): 248.1 (100, $M^+ + H$).

6-Chlorocinnoline (3d) from Alkyne 17b. Compound **17b** (20 mg, 0.08 mmol) was dissolved in ODCB (2 mL) in a glass pressure tube and heated to 200 °C for 16 h. The mixture was cooled, diluted with hexanes, and vacuum filtered through silica. After evaporation, purification by preparative TLC (2:1:1 hexanes/CH_2Cl_2/EtOAc) gave **3d** (13 mg, 96%) as a white solid. Spectral data were identical to those reported previously.[6c]

1-(4-Chloro-2-iodophenyl)-3,3-dimethyl-d_6-triazene (20). 4-Chloroaniline (750 mg, 5.9 mmol), BTEA·ICl_2 (2.5 g, 6.4 mmol), and $CaCO_3$ (650 mg, 6.5 mmol) were reacted under conditions analogous to **16a**. After workup, the iodinated product (500 mg, 2.0 mmol) was dissolved in MeCN (8 mL) and reacted with concentrated HCl (1.3 mL, 16 mmol), $NaNO_2$ (300 mg, 4.3 mmol), $(CD_3)_2NH$·HCl (1.75 g, 20 mmol), and K_2CO_3 (3.9 g, 29 mmol) under conditions analogous to **13**. Purification by column chromatography (20:1 hexanes/CH_2Cl_2) provided **20** (520 mg, 82%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.82 (d, $J = 2.1$ Hz, 1H), 7.31 (d, $J = 8.8$ Hz, 1H), 7.24 (dd, $J = 8.8$, 2.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 148.77, 138.11, 130.77, 128.76, 117.80, 96.26. IR (neat) 3077, 2961, 2685, 2215, 2065, 1552, 1417 cm^{-1}. MS (ESI) *m*/*z* (%): 316.0 (100, $M^+ + H$).

1-(4-Chloro-2-ethynylphenyl)-3,3-dimethyl-d_6-triazene (21). Triazene **20** (520 mg, 1.7 mmol) was reacted with TMSA (0.33 mL, 4.8 mmol), $PdCl_2(PPh_3)_2$ (47 mg, 0.07 mmol), CuI (22 mg, 0.11 mmol), and Et_3N (25 mL) under conditions analogous to **8**. The solvent was evaporated, and the crude product was treated with K_2CO_3 (1.32 g, 10 mmol) under conditions analogous to **11**. Purification by column chromatography (8:1 hexanes/CH_2Cl_2) provided **21** (335 mg, 95%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.47 (d, $J = 2.3$ Hz, 1H), 7.38 (d, $J = 8.8$ Hz, 1H), 7.23 (dd, $J = 8.8$, 2.3 Hz, 1H), 3.30 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 151.15, 132.92, 132.88, 129.72, 129.55, 118.24, 82.02, 80.54. IR (neat) 3298, 3067, 2217, 2105, 2067 cm^{-1}. MS (ESI) *m*/*z* (%): 214.1 (100, $M^+ + H$).

6-Chlorocinnoline-d_1 (3d′) from Alkyne 21. Compound **21** (24 mg, 0.11 mmol) was dissolved in ODCB (2 mL) in a glass pressure tube and heated to 200 °C for 16 h. The mixture was cooled, diluted with hexanes, and vacuum filtered through silica. After evaporation, purification by preparative TLC (2:1:1 hexanes/CH_2Cl_2/EtOAc) gave 6-chlorocinnoline-d_1 (**3d′**) (16 mg, 86%) as a light yellow powder. Partial ^{1}H and ^{2}H NMR spectra are given in Figure 7.

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Supporting Information Available: Gaussian archive files for all structures in Figure 3 (cyclization of **1**); calculated energies of stationary points of the ethyne−vinylidene cyclization pathway (Supplemental Figure 1) and $-NEt_2$ elimination pathways (Supplemental Figures 2 and 3); X-ray structures of **6** and **9**, structure refinement details, tables of atomic coordinates, thermal parameters, bond lengths, bond angles, torsion angles, and mean planes. This material is available free of charge via the Internet at http://pubs.acs.org.

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