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Phenanthrene-Fused Azo-ene-ynes: Synthesis of Dibenzo[*f*,*h*]cinnoline and Dibenzo[*e*,*g*]isoindazole Derivatives

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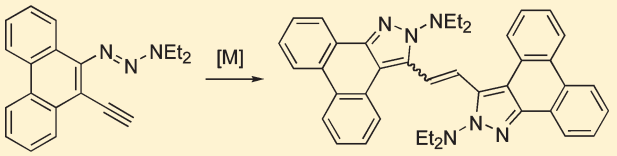
Supporting Information

ABSTRACT: The cyclization reactions of a phenanthreno-fused azo-ene-yne compound have been studied both experimentally and computationally. Experimental results show that this system is prone to dimerization, more so than previously studied naphthalene- and benzene-based analogues. Calculations reveal that pyrazoles and arene-fused pyrazoles strongly stabilize carbenes in the 5-position through "coarctate conjugation", suggesting a stationary concentration of the carbenes/carbenoids during cyclization that is high enough for dimerization.



During the past decade, there has been increased interest in the cyclization of "ene-ene-yne" compounds to produce aromatic heterocycles in high yields.[1] Specifically, we have been examining the dual reaction pathways of conjugated azo-ene-ynes (e.g., **1**, Scheme 1)[2−6] in which a cinnoline (**2**) is formed under thermal conditions via a pericyclic mechanism or an isoindazole (**3**) is formed in the presence of a carbene-stabilizing transition-metal salt via a coarctate mechanism.[7] While we have expended significant efforts exploring the scope and limitations of these reactions,[2−6,8−10] our synthetic and computational studies have focused predominantly on benzo-fused heterocycles (**a** in Scheme 1).

Motivated by potential optical and electronic applications of larger heteroaromatic compounds, we recently reported the dual cyclization of naphtho-fused azo-ene-ynes.[11] As anticipated, naphthalene-based systems **1b** and **1c** afforded the desired benzocinnolines **2b** and **2c** under thermal conditions (Scheme 1). Addition of carbene/carbenoid stabilizers furnished the desired isoindazolecarbaldehydes **3b**,**c**; however, the unanticipated dimers **4b**,**c** were also produced in low to moderate yield. Although we have previously observed dimers based on **4a**, they are typically not generated under the "optimized" coarctate reaction conditions.[2c] Formation of **4b**,**c** could be suppressed by saturating the reaction mixture with O_2 prior to the addition of the transition-metal salt.[11] To further explore the utility of our dual cyclization methodology, we report herein the synthesis and cyclization of phenanthrene-fused azo-ene-yne **5**. This study will illustrate a surprisingly high propensity for dimer formation via a more stable carbene/carbenoid intermediate, results that are corroborated computationally.

The synthesis of starting triazene **5** is shown in Scheme 2. Nitration of commercially available 9-bromophenanthrene afforded **6**, which was subsequently reduced with iron powder in the presence of acetic acid to give bromoaniline **7**.[12] Diazotization of **7** with $BF_3 \cdot Et_2O$ and *t*-BuONO followed by quenching with $HNEt_2$ furnished triazene **8**.[13] Sonogashira cross-coupling of **8** with TMSA afforded protected acetylene **9**, which was then desilated to give terminal acetylene **5** in 14% overall yield for the five steps.

Thermolysis of **5** at 200 °C in *o*-dichlorobenzene (ODCB) generated unknown dibenzo[*f*,*h*]cinnoline **10**[14] in 58% yield (Scheme 3). Treatment of **5** with excess CuCl in O_2-saturated 1,2-dichloroethane (DCE) gave dibenzo[*e*,*g*]isoindazolecarbaldehyde **11** at best in 17% yield along with a trans/cis mixture of dimer **12** as the major product in 38% isolated yield. Compound **12** was the sole product (49%) when catalytic $Rh_2(OAc)_4$ was used to effect the cyclization. A proton NMR spectrum of the crude material showed that the trans dimer (alkene proton singlet at 8.37 ppm) was the major isomer initially along with a small amount (~6:1 trans/cis) of the cis dimer (singlet at 7.37 ppm); however, attempted separation/purification resulted in partial isomerization, leading to an inseparable 2:1 trans/cis mixture of **12**.[15] Interestingly, using CuCl with diphenyl sulfoxide (DPSO) as the oxygen atom source[16] afforded only aldehyde **11** in 62% yield. Even when used in excess, CuCl represents a cheaper alternative to the $Ph_3PAuCl/AgSbF_6$ catalytic system recently reported by Toste et al. to mediate this transformation.[16]

The above experimental results suggest that upon expanding the aromatic system from benzo to naphtho to phenanthro fusion, there is an increasing propensity for the carbene/carbenoid to dimerize rather than to react with O_2 to form the aldehyde. Seeking answers to these observations, we examined the reaction computationally. The DFT-calculated energies (B3LYP/6-31G* + ZPE) for the cyclizations of **1a**−**c** and **5** are shown in Table 1, with a representative energy diagram given in Figure 1.[17] While the transition state energies are similar for the syn conformation of the coarctate reaction, both the anti conformer and the pericyclic TS energies become smaller with increasing size of the fused ring (ΔE ca. 3−4 kcal mol^{-1}). The differences are

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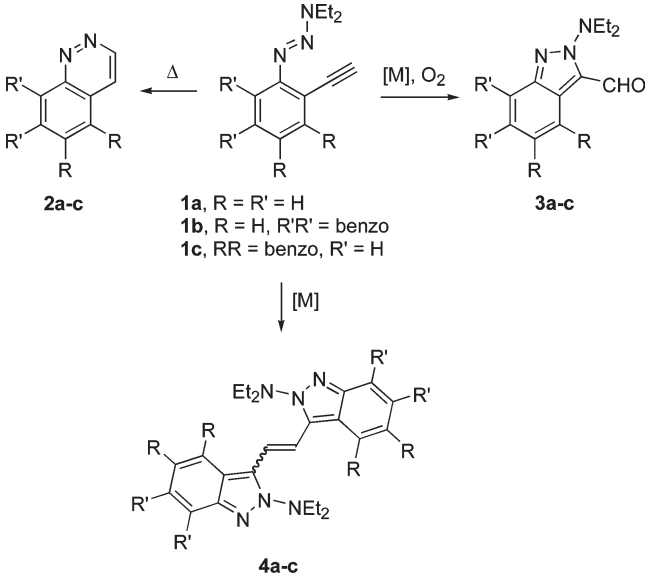
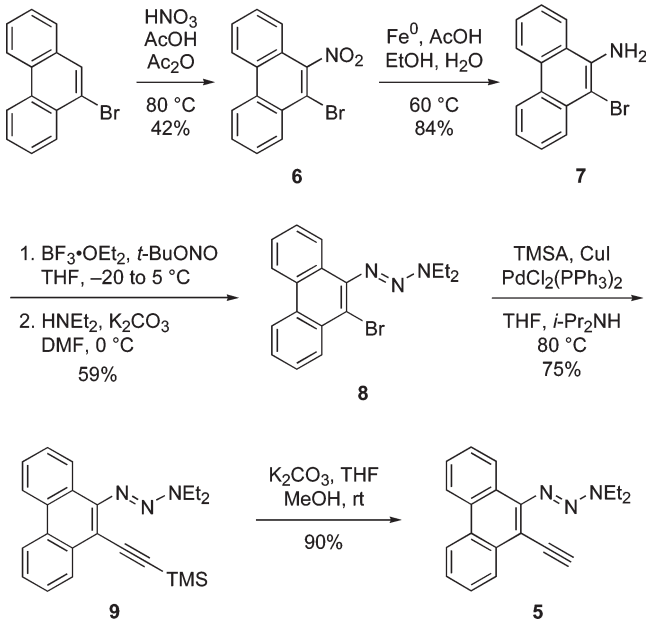
Scheme 1. Cyclization Reactions of Triazene-ene-ynes 1a−c



Scheme 2. Synthesis of Phenanthrene-Fused Azo-ene-yne 5



amplified in the intermediates, with the anti carbene and zwitterion intermediates 6.7 and 7.4 kcal mol^{-1}, respectively, lower in energy going from benzo to phenanthro fusion. A likely explanation for the lower energies and thus increased stability is the reduced aromaticity/delocalization of the fused bond. The 9,10-bond of phenanthrene is well-known to have appreciable double bond character and often reacts like a typical alkene.

The unexpected tendency of the intermediate carbenes to form dimers caused us to further investigate their electronic structure and thermodynamic energetic stability. One hypothesis was that the carbenes might be lower in energy, lasting longer in solution and thus giving them more time to find another carbene with which to dimerize. To probe this, a set of annelated and

Scheme 3. Cyclization of Phenanthrene-Fused Azo-ene-yne 5

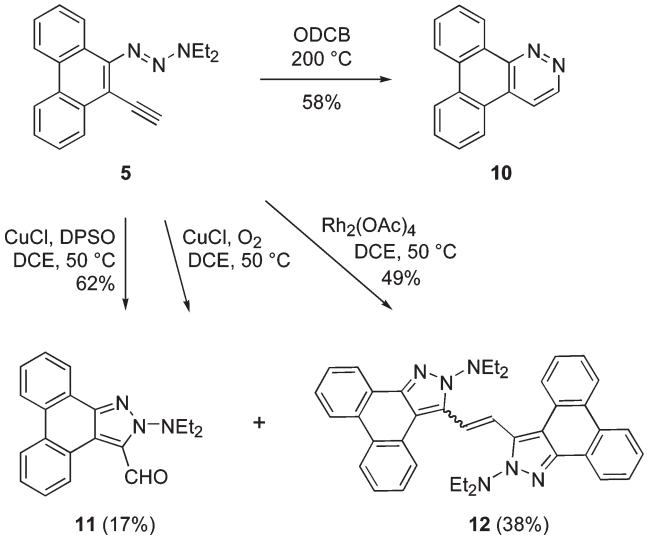


Table 1. DFT (B3LYP/6-31G* + ZPE)-Calculated Energies for the Cyclization Reactions of 1a−c and 5

mechanism/orientation	1a[a−c]	1b[a,b]	1c[a,b]	5[a,b]
pericyclic zwitterion	15.01	11.00	9.73	7.62
syn carbene	26.07	23.49	26.19	24.47
anti carbene	28.69	24.68	24.68	21.94
pericyclic TS	30.30	28.84	28.10	27.04
coarctate syn TS	30.60	29.28	30.70	29.47
coarctate anti TS	31.58	29.50	29.41	27.75

[a] kcal mol^{-1}. [b] NEt_2 replaced by NMe_2 in computations. [c] Values are 2.14 kcal mol^{-1} lower than in ref 6 as the reactive conformation is defined as 0 in Figure 1.

nonannelated reference model systems (Figure 2) was calculated using DFT (UB3LYP/6-31G*).

The hydrogenation energy of the carbenes to the corresponding methyl derivatives was calculated to ascertain if there is a significant thermodynamic stabilization associated with the coarctate position of the carbene (Table 2). To elucidate the nature of interaction with the neighboring π system, we compared the hydrogenation of our pyrazole substituted title carbenes (**Ia**−**IIIa**) with the corresponding open-chain compounds (**Ib**−**IIIb**) and with the corresponding phenyl-, naphthyl-, and phenanthryl-substituted systems (**Ic**−**IIIc**). Whereas the phenyl and open-chain derivatives are triplet ground states, the heterocyclic systems with the carbene center in the coarctate position are singlet carbenes. The hydrogenation energies indicate that the singlet state of the heterocyclic coarctate carbenes is strongly stabilized. For example, the isoindazole ring system in **IIa** is able to stabilize the singlet state of a neighboring carbene center roughly 16−17 kcal mol^{-1} more efficiently than a corresponding open-chain π system ((*E*)-4-iminobut-2-en-2-amine, **IIb**) and 9−10 kcal mol^{-1} more than a naphthyl group (**IIc**). Solvent effects (polarizable continuum model, dichloromethane ε = 10.125, Table 2) are small and do not change the relative stabilities.

We attribute the unusually large stabilization of our heterocyclic singlet carbenes to "coarctate conjugation". The carbene is

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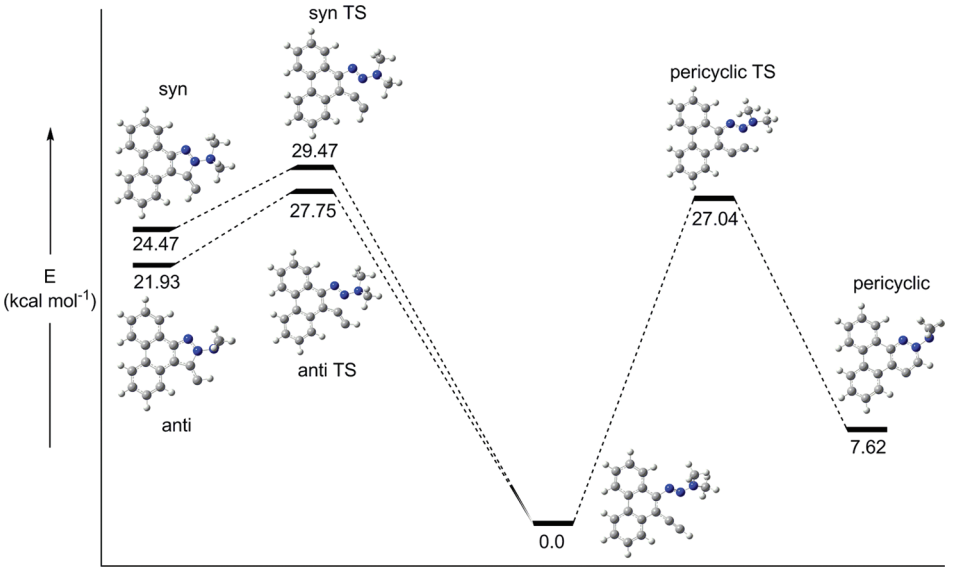

Figure 1. DFT (B3LYP/6-31G* + ZPE)-calculated energies for the dual cyclization pathways of **5**.

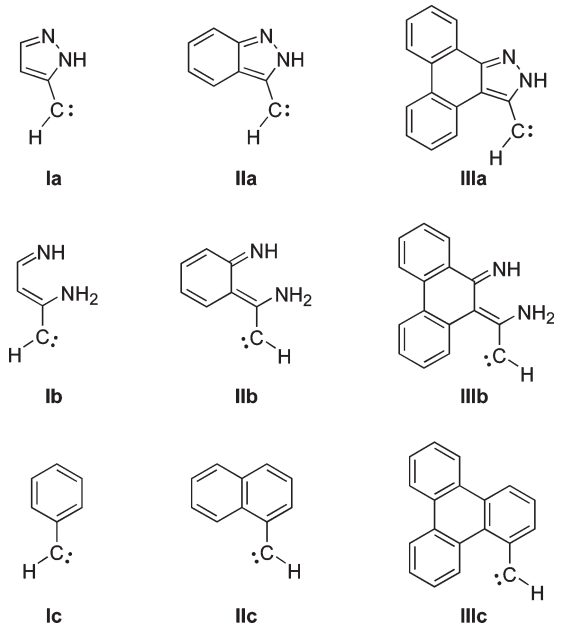

Figure 2. Model analogues of the intermediate carbenes generated by the coarctate cyclization of azo-ene-ynes.

generated by an endothermic, coarctate cyclization and therefore part of the electronic wave function of the reactant mixes into the carbene wave function, as depicted in terms of valence bond structures in Figure 3.[18] This leads to a significantly shorter bond length between the carbene center and the neighboring carbon atom in the coarctate carbenes compared to the corresponding phenyl and open-chain analogues ($C_{carbene}$−C bond in Table 2).

It is well-known that the singlet states of carbenes with π substituents are stabilized by an interaction of the carbene empty p orbital (LUMO) and the HOMO (and other occupied π MOs) of the π substituents, which also leads to shorter $C_{carbene}$−C bonds. The strength of interaction increases with increasing HOMO energy (decreasing LUMO−HOMO energy difference).

Table 2. DFT (B3LYP/6-31G*)-Calculated Singlet−Triplet Gap Energies (ΔE_{st}), Hydrogenation Energies (ΔE_{hyd}) of the Carbenes, and HOMO Energies of the Hydrogenated Model Compounds

carbene model systems[a]	$C_{carbene}$−C[b]	ΔE_{hyd}[c]	$\Delta E_{hyd,solv}$[c,d]	ΔE_{st}[e]	HOMO[f]
pyrazole carbenes					
Ia (anti)	1.403	−99.37	−99.46	1.89	−6.31
IIa (anti)	1.390	−93.57	−93.66	2.93	−5.36
IIIa (anti)	1.392	−94.81	−96.71	2.17	−5.58
open chain analogues					
Ib (syn)	1.438	−108.11	−108.31	−5.13	−5.15
IIb (syn)	1.446	−110.14	−110.47	−11.97	−4.63
IIIb (anti)	1.424	−105.81	−106.62	−9.47	−4.85
phenyl derivatives					
Ic (anti)	1.432	−105.69	−104.09	−4.10	−6.40
IIc (anti)	1.423	−103.60	−102.34	−4.37	−5.67
IIIc (anti)	1.405	−98.64	−98.74	−4.31	−5.75

[a] An extensive conformational search including syn and anti conformations of the carbenes was performed, and only the energetically most stable conformers are included in this table. [b] Bond length (Å) between the carbene center and the neighboring carbon atom. [c] The hydrogenation energies (ΔE_{hyd}, kcal mol^{-1}) were obtained computationally as the reaction energy of the singlet carbenes with molecular hydrogen. [d] Hydration enthalpies in solvent DCE calculated using a polarizable continuum model with ε = 10.125 as implemented in Gaussian09. [e] The singlet−triplet gap (ΔE_{st}, kcal mol^{-1}) is given as the relative energy of the T_0 electronic state with respect to the S_0 singlet state of the corresponding geometry-optimized carbene. [f] Energy (eV) of the highest occupied orbital in the hydrogenated carbene.

This mode of interaction, however, obviously does not account for the significant stabilization of our coarctate carbenes, since we make comparison with reference carbenes that are π substituted as well. Moreover, the HOMO energies in the open-chain analogues are significantly higher than those in the coarctate carbenes; nevertheless, the $C_{carbene}$−C bonds are longer, and the stabilization is lower.

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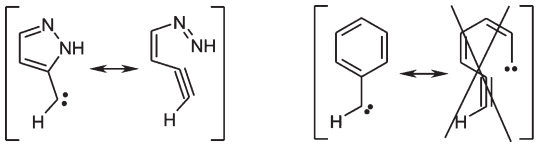

Figure 3. Mesomeric stabilization of a coarctate carbene, which is not operative for the analogous six-membered ring aromatic carbenes.

Whereas the coarctate stabilization explains the unusual mode of reaction (dimerization, reaction with oxygen) of our coarctate carbenes, our calculations do not reproduce the higher propensity for dimerization of the dibenzo[*e*,*g*]isoindazole system as compared to the benzoisoindazole- and isoindazole-substituted carbenes. Small differences in energies lead to relatively large shifts in equilibria. Coordination to the catalyst and different activation barriers for the carbene dimerization, which are not included in our calculations, are likely responsible for the different reactivity of the various arene-annelated isoindazole carbenes.

In conclusion, we have prepared the first examples of dibenzo[*f*,*h*]cinnoline and dibenzo[*e*,*g*]isoindazole derivatives and shown that the carbene intermediates for the latter systems have a strong propensity to dimerize. Calculations indicate that these pyrazole-based carbenes are stabilized through coarctate conjugation. Given that we are mainly interested in monomeric species, future efforts will focus on alternative pericyclic and coarctate azo-ene-yne cyclization routes to access heteroacene-like structures.

EXPERIMENTAL SECTION

General Methods. These have been described previously in ref 4.

Bromotriazene 8. To a flame-dried flask was added $BF_3 \cdot OEt_2$ (4.0 mL, 32.6 mmol) under an Ar atmosphere, and the flask was cooled to −20 °C. A solution of **7**[12] (2.22 g, 8.16 mmol) in dry THF (33 mL) was added slowly such that the internal temperature stayed below −10 °C. After complete addition, a solution of *t*-BuONO (3.4 mL, 28.6 mmol) in dry THF (27 mL) was added dropwise. The reaction was stirred for an additional 10 min at −20 °C and then warmed to 5 °C over a period of 20 min. Pentane was added, and the green precipitate that formed was isolated by suction filtration. The solid was then added in one portion to a stirred suspension of K_2CO_3 (5.64 g, 40.8 mmol) and $HNEt_2$ (8.4 mL, 81.6 mmol) in DMF (150 mL) at 0 °C and stirred for 2 h. The reaction was diluted with EtOAc and washed with aq NH_4Cl solution (2×) and brine (5×). The organic layer was dried ($MgSO_4$) and filtered and the solvent removed in vacuo. The crude material was purified by flash chromatography (1:19 EtOAc/hexanes) to yield bromotriazene **8** (1.71 g, 59%) as a red solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (t, J = 9.0 Hz, 2H), 8.51 (dd, J = 7.9, 1.3 Hz, 1H), 7.94 (dd, J = 8.2, 0.9 Hz, 1H), 7.73−7.53 (m, 4H), 3.93 (br s, 4H), 1.42 (br s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.7, 131.3, 130.4, 129.7, 129.3, 128.2, 127.6, 127.0, 126.9, 126.2, 124.9, 122.9, 122.6, 113.5, 49.2, 41.6, 15.1, 11.6; HRMS (EI+) for $C_{18}H_{18}BrN_3$ calcd 355.0684, found 355.0667.

Silyltriazene 9. A mixture of **8** (0.83 g, 2.3 mmol), CuI (0.018 g, 0.09 mmol), and $Pd(PPh_3)_2Cl_2$ (0.033 g, 0.045 mmol) was dissolved in THF (11 mL) and HN-*i*-Pr_2 (11 mL). The solution was purged with Ar for 45 min at rt after which TMSA (3.3 mL, 23.3 mmol) was added. The flask was stirred overnight at 80 °C. After being cooled to rt, the mixture was run through a short pad of silica and the solvent removed in vacuo. The crude material was purified by flash chromatography (1:9 EtOAc/hexanes) to yield the TMSethynyltriazene **9** (0.641 g, 75%) as an orange solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (dt, J = 6.0, 0.9 Hz, 2H), 8.48 (dd, J = 6.6, 1.5 Hz, 1H), 8.20 (dd, J = 8.1, 1.1 Hz, 1H), 7.71−7.53 (m, 4H), 3.93 (q, J = 7.0 Hz, 4H), 1.41 (t, J = 7.0 Hz, 6H), 0.31 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 132.1, 130.6, 128.4, 128.3, 127.4, 127.1, 127.0, 126.4, 125.6, 124.9, 122.5, 122.4, 107.3, 102.4, 101.0, 48.9, 41.2, 14.1, 11.0, 0.2; HRMS (EI+) for $C_{23}H_{27}N_3Si$ calcd 373.1974, found 373.1971.

Ethynyltriazene 5. A suspension of **9** (0.050 g, 0.134 mmol) and K_2CO_3 (0.185 g, 1.34 mmol) in THF (5 mL) and MeOH (1 mL) was stirred for 15 min. The solids were removed by filtration, and the solvent was removed under reduced pressure. The crude material was dissolved in EtOAc and washed with aq NH_4Cl solution (2×), H_2O (3×), and brine (3×). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to yield the free acetylene (0.036 g, 90%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (dd, J = 11.9, 4.6 Hz, 2H), 8.50 (dd, J = 7.9, 1.6 Hz, 1H), 8.23 (dd, J = 8.3, 1.2 Hz, 1H), 7.72−7.55 (m, 4H), 3.92 (q, J = 6.9 Hz, 4H), 3.43 (s, 1H), 1.41 (t, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 132.1, 130.7, 128.4, 128.3, 127.5, 127.1, 126.9, 126.5, 125.7, 124.9, 122.5, 122.4, 106.1, 83.6, 81.1, 48.9, 41.4, 14.1, 11.1; HRMS (EI+) for $C_{20}H_{19}N_3$ calcd 301.1579, found 301.1592.

Dibenzo[*f*,*h*]cinnoline 10. Triazene **5** (0.06 g, 0.2 mmol) was dissolved in ODCB (8 mL) in a screwtop pressure reaction vessel. The sealed vessel was placed in a preheated 200 °C sand bath. The reaction was stirred overnight and then cooled to rt. Removal of solvent in vacuo followed by preparative TLC (EtOAc) yielded cinnoline **10** (0.026 g, 58%) as a brown solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.56 (dd, J = 7.2, 2.1 Hz, 1H), 9.43 (d, J = 5.6 Hz, 1H), 8.62−8.47 (m, 3H), 8.38 (d, J = 5.6 Hz, 1H), 7.84−7.71 (m, 3H), 7.66 (dt, J = 6.9, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 148.2, 131.5, 131.2, 130.4, 130.2, 128.6, 128.3, 127.8, 126.1, 125.6, 125.2, 124.3, 123.6, 122.7, 118.4; UV−vis ($CHCl_3$) λ_{max} (ε) 258 (75,300), 280 (18,600) nm; HRMS (EI+) for $C_{16}H_{10}N_2$ calcd 230.0844, found 230.0845.

Dibenzo[*e*,*g*]isoindazolecarbaldehyde 11. A mixture of **5** (0.025 g, 0.01 mmol), diphenyl sulfoxide (0.201 g, 0.1 mmol), and CuCl (0.098 g, 0.1 mmol) in DCE (10 mL) was stirred at 50 °C for 2.5 h. After cooling, the mixture was filtered through a short pad of silica and the solvent removed under reduced pressure. Preparative TLC (CH_2Cl_2) yielded isoindazole **11** (0.016 g, 62%) as a tan solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.69 (s, 1H), 9.60−9.54 (m, 1H), 8.69−8.57 (m, 3H), 7.73−7.62 (m, 4H), 3.68−3.54 (m, 2H), 3.35−3.21 (m, 2H), 0.95 (t, J = 7.1 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 183.1, 130.7, 130.0, 128.4, 127.8, 127.51, 127.48, 127.3, 126.4, 124.9, 123.3, 123.3, 115.9, 52.6, 12.1; UV−vis ($CHCl_3$) λ_{max} (ε) 299 (1,840), 335 (1,270) nm; HRMS (EI+) for $C_{20}H_{19}N_3O$ calcd 317.1528, found 317.1523.

Dibenzo[*e*,*g*]isoindazole Dimer 12. A solution of **5** (0.030 g, 0.01 mmol) in DCE (10 mL) was purged with Ar for 45 min. Rh_2OAc_4 (0.0022 g, 0.005 mmol) was added and the mixture stirred at 50 °C for 90 min. After cooling, the mixture was filtered through a short pad of silica and the solvent removed under reduced pressure, affording crude dimer **12** as a 6:1 trans/cis mixture. Preparative TLC (1:9 EtOAc/hexanes) yielded pure dimer **12** (0.015 g, 49%) as a 2:1 trans/cis mixture. *trans*-**12**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (m, 2H), 8.61 (m, 6H), 8.39 (s, 2H), 7.65 (m, 4H), 7.55 (m, 4H), 3.60 (br s, 4H), 3.36 (br s, 4H), 1.05 (t, J = 7.2 Hz, 12H). *trans*-**12** isomerized to the 2:1 mixture upon purification, thus precluding definitive ^{13}C NMR data of this isomer: UV−vis ($CHCl_3$) λ_{max} (ε) 341 (22,500), 365 sh (19,700), 385 sh (15,500), 410 (7,260) nm; HRMS (EI+) for $C_{40}H_{38}N_6$ calcd 602.3158, found 602.3171.

ASSOCIATED CONTENT

Supporting Information. All computational details including Cartesian coordinates, total energies, and imaginary frequencies for all computed structures as well as transition state analysis; copies of ^{1}H and ^{13}C NMR spectra for **5** and **8**−**12**; X-ray data for *trans*-**12**(CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) An X-ray structure analysis confirmed that *trans*-**12** was indeed the major isomer and thus the source of the proton singlet at 8.37 ppm; see the Supporting Information for structural details.
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(17) In our model calculations, complexation with transition metals salts (e.g., Cu(I), Rh(II)) was not included, as the computed transition-state structures and the exact mechanism(s) under experimental conditions become much more complicated; see ref 5 as an example.
(18) Similar effects were theoretically predicted in enediynes reacting to 1,4-benzynes via Bergman cyclization; see: Galbraith, J. M.; Schreiner, P. R.; Harris, N.; Wei, W.; Wittkopp, A.; Shaik, S. *Chem.—Eur. J.* **2000**, *6*, 1446–1454.