2:1 Adducts Arising from Reactions between Benzynes and 1,3,4-Oxadiazoles

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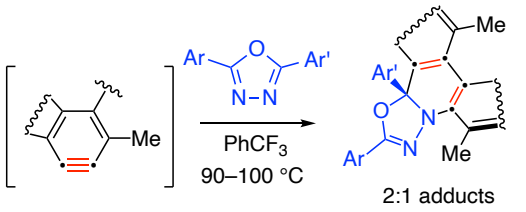
Supporting Information Placeholder

ABSTRACT: 2:1 Adducts arise from the reaction of 2,5-diaryl-1,3,4-oxadiazoles and benzynes generated from the hexadehydro-Diels-Alder (HDDA) reaction. DFT computations support a mechanistic manifold that includes a concerted S_NAr process. Additionally, the benzyne trapping reaction of 2,5-dimethyl-1,3,4-oxadiazole affords an unusual, acylimine-containing, 2:1 adduct, which is the first case in which a dearomatized product has arisen from an HDDA reaction.



The cycloaddition chemistry of 1,3,4-oxadiazoles is well precedented. [1] The 1,3,4-oxadiazoles that participate in such reactions typically contain electron-withdrawing substituents (EWGs) in order to efficiently engage in inverse electron-demand [4+2] cycloadditions. For a subset of these cycloadditions, alkynes are the cycloaddends. In 1988 Sauer and co-workers demonstrated a cascade reaction between cyclooctyne (**1**) and 1,3,4-oxadiazoles **2** (Figure 1a) to produce 2:1 adducts **3**.[2] This is explained by an initial [4+2] cycloaddition to generate an oxadiazabicyclo[2.2.1]hepta-2,5-diene intermediate (cf. **4**) that expels dinitrogen to set up a final [4+2] cycloaddition of the furan derivative **5** with a second molecule of **1** to afford the oxabicyclic product **3**. That same year, Seitz and Wassmuth disclosed an analogous reaction of 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole (**7**) with *o*-benzyne (**6**) to give **8** (Figure 1b).[3]

1,3,4-Oxadiazoles lacking EWGs have relatively higher LUMO orbitals and rarely participate in cycloaddition chemistry; other reaction pathways prevail. [4] For example, 2,5-dimethyl-1,3,4-oxadiazole (**9**) reacted with two equivalents of hexafluoro-2-butyne (**10**) to afford **11** (Figure 1c).[5] This reaction is believed to be initiated by nucleophilic attack of a nitrogen atom to the electrophilic alkyne carbon. Because benzynes are electrophilic alkynes, we were interested to examine more broadly the behavior of benzynes and various 1,3,4-oxadiazoles.

Our investigations began with heating the triyne hexadehydro-Diels-Alder (HDDA) substrate **12** [6] in the presence of one equivalent of 2,5-diphenyl-1,3,4-oxadiazole (**14**) at 90 °C in 1,2-dichloroethane (DCE) for 11 h (Figure 2). A similar triyne substrate is reported to undergo net [4+2]-cycloisomerization to its derived benzyne with a half-life of 5 h at 80 °C.[7] The intermediate HDDA-benzyne **13** engages the oxadiazole **14** to form predominantly **16** along with a small amount of the 1:1 adduct **15**. Product **15** appears to represent the first example of a reaction in which an oxadiazole has participated in a thermally driven, net [2+2] cycloaddition, although there is a report of a somewhat related photochemical transformation.[8]

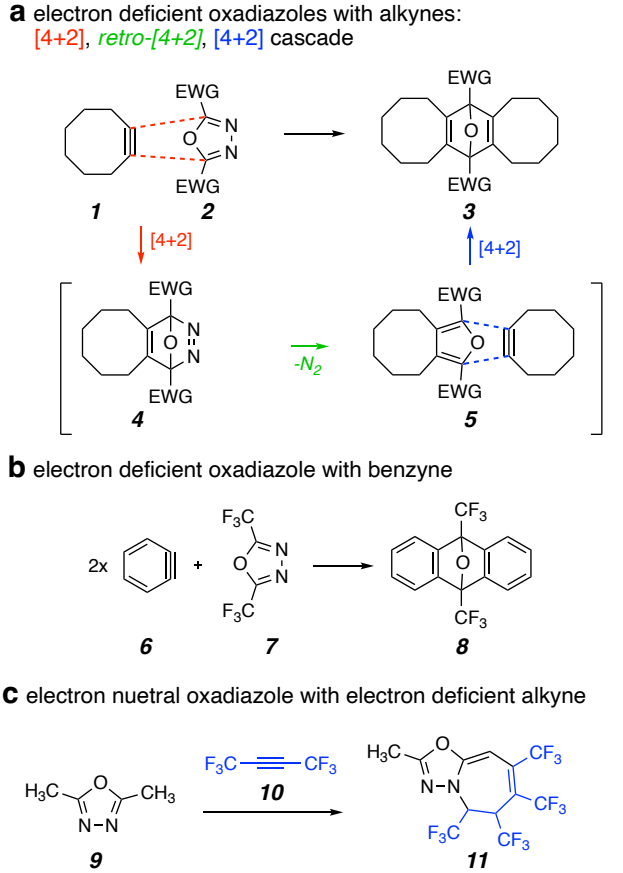


Figure 1. (a) Cascade reaction of cyclooctyne reacting with electron deficient 1,3,4-oxadiazoles to afford **3**. (b) *o*-Benzyne (**6**) reacting with 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole (**7**) in an analogous cascade reaction. (c) Reaction of 2,5-dimethyl-1,3,4-oxadiazole (**9**) with two equivalents of perfluorobut-2-yne (**10**) proceeding via a formal ene-reaction en route to **11**.

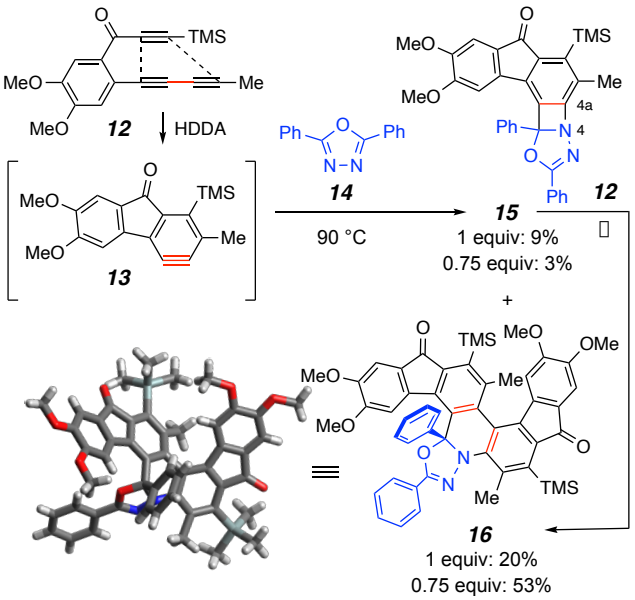


Figure 2. Reaction of benzyne **13**, derived from triyne **12**, with 2,5-diphenyl-1,3,4-oxadiazole (**14**) to afford 1:1 adduct **15** and **16**. When triyne **12** was heated in the presence of 1:1 adduct **15**, the 2:1 adduct **16** was generated.

The ratio of products **15** and **16** was somewhat dependent on the initial stoichiometric ratio of the reactants **12** and **14**, as indicated in Figure 2. A control experiment demonstrated that the 1:1 adduct **15** was transformed into **16** when heated in the presence of additional triyne **12** (and in the absence of the oxadiazole **14**). Thus, the 2:1 adduct arises from a formal insertion of a second benzyne molecule into the C(4a)–N(4) bond in **15**. We speculated that this might be initiated by nucleophilic attack of N-4 in **15** to the benzyne **13**.

We turned to DFT computations to gain more insight to guide a mechanistic hypothesis. We chose to evaluate the reaction between the simple *o*-benzyne (**6**) and diphenyl-1,3,4-oxadiazole (**14**) to give the 2:1 adduct **20** (Figure 3). Initially, the oxadiazole was seen to engage *o*-benzyne to form the zwitterionic intermediate **17** via **TS1**. This species proceeded to the benzazetidine derivative **18** by a 4-*endo-trig* cyclization via **TS2**. The azetidine nitrogen of **18** then adducted with a second equivalent of *o*-benzyne to form the zwitterionic intermediate **19** via **TS3**. The final product **20** arose from **19** by a concerted process in which aryl-aryl bond formation and nitrogen cleavage occur in unison. It is noteworthy that the activation energy for this transformation, a concerted S_NAr process,[9] is only 12.0 kcal mol^{-1} and that product formation is exceedingly exergonic (ca. 104 kcal mol^{-1}).

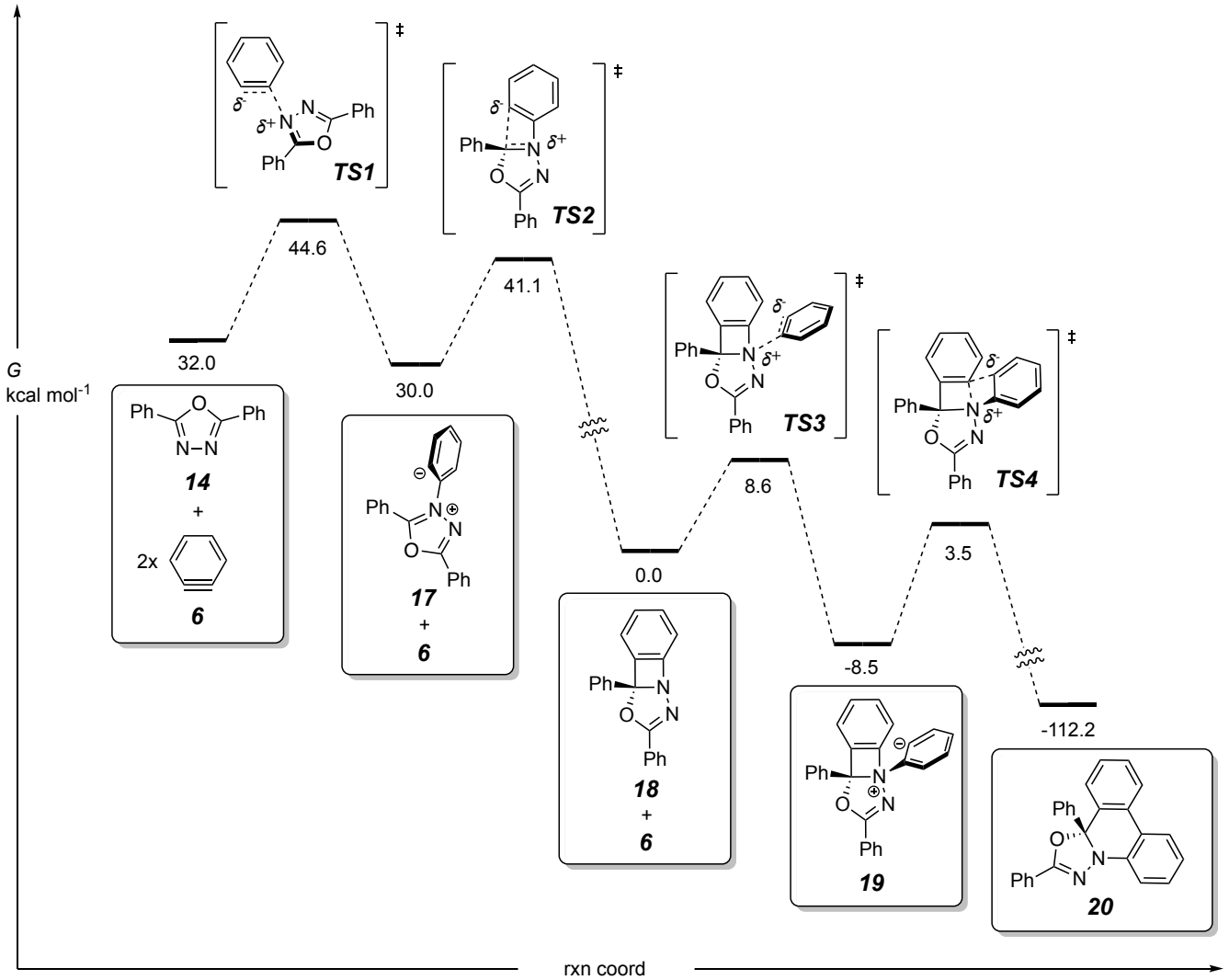
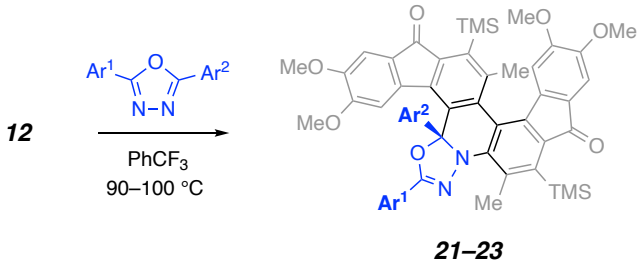


Figure 3. DFT[i] potential energy surface (PES) of *o*-benzyne (**6**) reacting with 2,5-diphenyl-1,3,4-oxadiazole (**14**) leading to **20**.
[i]IEFPCM(chloroform)/M06-2X/6-311+G(d,p).

We next explored the reactivity of other 2,5-diarylated 1,3,4-oxadiazoles (Figure 4). 2,5-Bis(4-methoxyphenyl)-1,3,4-oxadiazole furnished **21** in a 46% yield. Unsymmetric oxadiazoles led to the formation of two regioisomeric products in which the Ar^1 and Ar^2 substituents are swapped. For example, 2-(naphthalen-1-yl)-5-phenyl-1,3,4-oxadiazole leads to **22a/b** as a 5.7:1 mixture of co-eluting regioisomers in a 31% combined yield. The observed regioselectivity is presumably governed by the steric bulk of the naphthyl carbocycle, which diminishes the initial attack at the nitrogen atom adjacent to the larger of the two aryl substituents. Similarly, 2-phenyl-5-(thiophen-2-yl)-1,3,4-oxadiazole afforded **23a/b** as a nearly 1:1 mixture of co-eluting regioisomers in a 39% combined yield. The thiophene substituent, sterically comparable to that of a phenyl group, has essentially no influence in directing the regioselectivity of this reaction.



	Ar^1	Ar^2	isol. yield	*a* : *b* ratio
21	PMP	PMP	46%	na
22a	1-Naph	Ph	31%	5.7 : 1
22b	Ph	1-Naph		
23a	2-thiophenyl	Ph	39%	1 : 1
23b	Ph	2-thiophenyl		

Figure 4. 2:1 adducts arising from the reaction of HDDA-generated benzynes with other 2,5-diaryloxadiazoles.

In the examples above, the HDDA-derived benzyne does not engage in [4+2] cycloaddition chemistry, presumably due to the absence of electron-withdrawing groups on the oxadiazole. However, we wondered whether the steric bulk of the HDDA-benzyne was also playing a significant role in influencing the novel

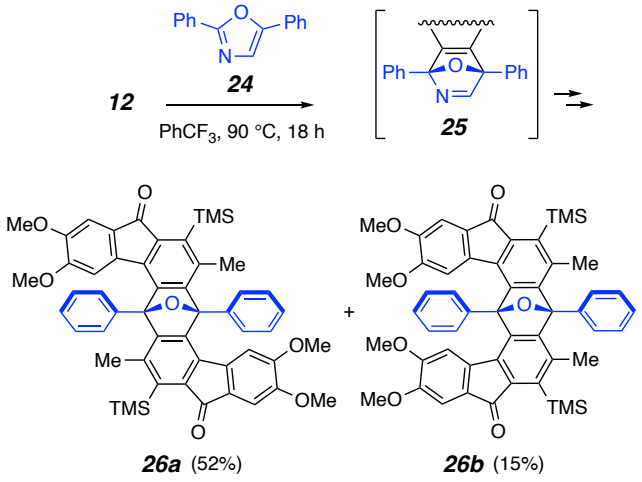


Figure 5. Reaction of triyne **12** with 2,5-diphenyloxazole (**24**) to produce two regioisomeric epoxyanthracene products: **26a** as the major "S" isomer and **26b** as the minor "U" isomer.

modality of the reaction. We therefore reacted triyne **12** with 2,5-diphenyl*oxazole* (**24**), a trapping agent that closely mimics the steric environment of 2,5-diphenyl-1,3,4-*oxadiazole* (**14**) (Figure 5) and that is known to trap both simple, unhindered benzynes[10] as well as HDDA-benzynes [11] via initial [4+2] cycloaddition. The two regioisomeric epoxyanthracene products **26a** and **26b** were isolated in a combined 67% yield. These arise from loss of HCN via a retro-Diels-Alder reaction of an initial adduct (cf. **25**) to produce an isobenzofuran species that is captured by a second molecule of the benzyne.[11]

To gain understanding for the stark difference between the different modes of reaction of **13** with the oxadiazole **14** vs. the oxazole **24** (i.e., no [4+2] product observed using **14**), we computed the transition structures for the possible concerted [4+2] cycloadditions of each pair (Figure 6 and larger PES in the SI). The E_{act} for the (unobserved) oxadiazole Diels-Alder reaction with **13*** (a slightly simplified version of the benzyne **13**; structure of **13*** is given in Figure 7) via **TS5** was 14.4 kcal mol^{-1} compared to the E_{act} of 10.5 or 9.9 kcal mol^{-1} for the oxazole via **TS6a** or **TS6b**, respectively. The lowest energy pair of HOMO/LUMO gap for $\mathbf{13^*}_{LUMO}/\mathbf{14}_{HOMO}$ vs. $\mathbf{13^*}_{LUMO}/\mathbf{24}_{HOMO}$ were larger for the former by 0.5 kcal mol^{-1} (see SI). This is reflected in the slightly shorter distances between the terminal pairs of diene/benzyne-dienophile carbon atoms in **TS5** compared to those for **TS6a** and **TS6b**. This results in higher steric repulsion in **TS5**, likely attributing to its higher energy.

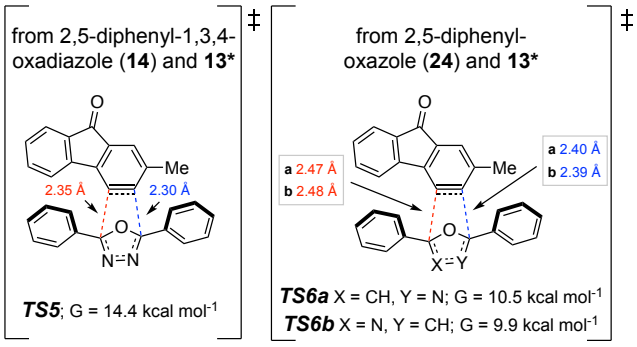


Figure 6. Computed[i] activation barriers for **14**+**13*** vs. **24**+**13***.

[i]IEFPCM(chloroform)/M06-2X/6-31+G(d,p).

Next, we explored the reactivity of 2,5-dimethyl-1,3,4-oxadiazole (**9**) (Figure 7). Koshelev and co-workers demonstrated that this di*alkyl*ated oxadiazole reacts with electron deficient alkynes in a formal ene-type reaction (cf. Figure 1c). When **9** was used to trap **13** (the benzyne derived from substrate **12**) a completely unexpected outcome was seen (Figure 7a). The major isolable product was the 2:1 adduct **27** (28%). The composition of this product was elucidated by X-ray diffraction analysis. Several things are surprising about this structure: i) the seven (blue) heavy atoms in the dimethyloxadiazole trapping agent are strewn across the two benzyne-derived skeletal fragments as three distinct subunits, no longer bonded to one another, ii) a relatively rare (and electrophilic) N-acylimine moiety is present, iii) the benzenoid ring from one of the two benzyne intermediates has been dearomatized, and iv) at a minimum: the three red bonds and one C–H bond are cleaved in **9** and five (green) bonds are formed in **27**! This transformation represents the first example of a HDDA reaction that results in a product having a dearomatized benzenoid ring.

A mechanistic proposal for how this unusual transformation may proceed is presented in Figure 7b. The atoms in **27** arising from the

dimethyl-1,3,4-oxadiazole (**9**) starting material are highlighted in blue. We hypothesize that the oxadiazole nitrogen adducts with the first equivalent of the HDDA-benzyne **13** to form zwitterion **28**, similar to the initial event seen with the diaryl substituted oxadiazoles. The aryl anion in **28** can abstract a proton from the adjacent methyl group to form **29**, the product of a formal ene-reaction between **13** and **9**. The nucleophilic enamine in **29** then engages a second equivalent of **13** in a formal [2+2] reaction via the intermediate zwitterion **30** to produce the spirocyclic intermediate **31**. The benzoxetene substructure within **31** can be expected to undergo a facile 4π-electrocyclic ring-opening to give the *o*-xylylene derivative **32**. A net proton transfer from the distal methyl group to the exocyclic methylene carbon in **32**, likely mediated by a proton shuttle such as a molecule of **9** (i.e., BH = an oxadiazolium ion) or a water molecule (i.e., BH = H–OH), would generate the delocalized zwitterion **33**. This could fragment the heterocycle so as to give the ketenimine (and penultimate) intermediate **34**. A final [3,3]-sigmatropic rearrangement with cleavage of the N–N σ- and cumulene π-bonds would provide the dearomatized product **27**.

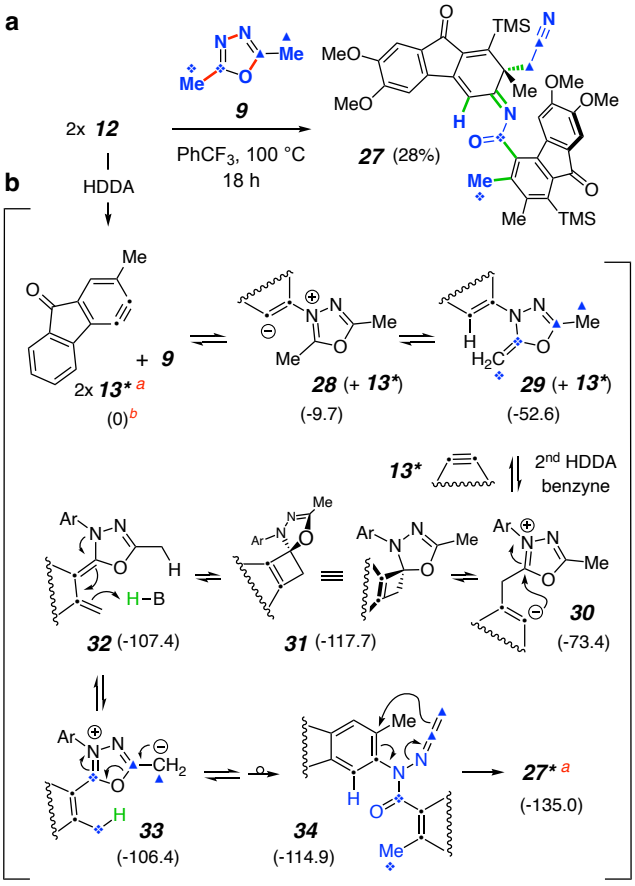


Figure 7. (a) The (remarkable) engagement of two HDDA-benzynes **13** (from **12**) with the dimethyloxadiazole **9** to give the dearomatized adduct **27**. (b) Proposed mechanism for the dismantlement and redistribution of the atoms in the heterocycle **9**.

[a] **13*** and **27*** are the analogs lacking the two methoxy and TMS groups present in structures **13** and **27**. [b] The numbers in parentheses are the DFT[i] free energies (kcal mol^{-1}) of each intermediate state. [i]IEFPCM(chloroform)/M06-2X/6-31G(d).

We mapped the minima on the PES for this multi-step mechanism using DFT. For computational simplification, all of the structures in Figure 7b are of the nor-dimethoxy/nor-TMS analogs of the species we propose to be involved in the actual conversion of **12** to **27**. The overall reaction energy is highly exergonic and no elementary step proceeds through a prohibitively high energy intermediate state. The most unusual interconversions occur in the final phase of the mechanism: namely, **32** ⇌ **33** ⇌ **34** ⇌ **27*** (see Figure S1 in the SI for a fuller representation of the computed PES). Unsurprisingly, given its geometry, we were unable to locate a transition structure (TS) for a unimolcular proton transfer to convert **32** to **33**; hence our suggestion (above) that this is mediated by an external proton transporter. The ring-opening of the zwitterion **33** to the ketenimine **34** was seen to proceed via a TS that was 9.9 kcal mol^{-1} higher than G° of **33**. The final, dearomative rearrangement to **27*** showed a barrier of 29.1 kcal mol^{-1} from **34**. The counterintuitive final cyclization onto the substituted (rather than unsubstituted) aromatic carbon in the last intermediate prior to **27** finds precedent in [3,3]-sigmatropic rearrangements of ortho-methylated phenylhydrazine derivatives.[12]

To further probe this process, we examined the reactivity of the 3H-indole derivative **35** containing a substructure related to one in 2,5-dimethyl-1,3,4-oxadiazole (**9**) to see if we could learn, by analogy, about the first steps of the dearomative mechanism leading to **27**. Reacting triyne **12** with **35** resulted in formation of i) a 1:1 adduct, the enamine **36**, in a 44% yield and ii) a benzocyclobutene spirocyclic compound **37** in a 30% yield (Figure 8). The enamine **36** was confirmed to be an intermediate along the reaction pathway to benzocyclobutene **37** by an experiment in which triyne **12** was cleanly converted to **37** when heated in the presence of excess enamine **36**.

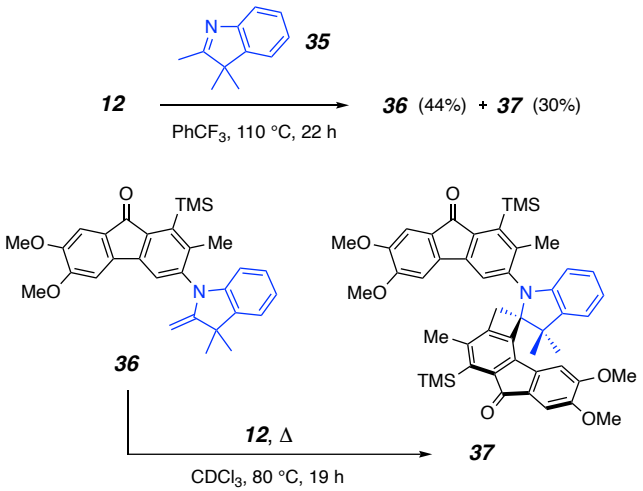


Figure 8. Reaction between triyne **12** with 2,3,3-trimethyl-3*H*-indole (**35**) to form enamine 1:1 adduct **36** and benzocyclobutene 2:1 adduct **37**. When isolated **36** was subsequently heated with triyne **12**, **37** was cleanly formed.

In conclusion, we have discovered novel oxadiazole and benzyne reactivity, leading to a series of structurally fascinating 2:1 adducts. 2,5-Diaryloxadiazoles adduct with HDDA-benzynes in formal [2+2] cycloadditions to afford benzazetidine-containing 1:1 adducts. We experimentally demonstrate that the benzazetidine 1:1 adducts may engage a second equivalent of benzye to afford the corresponding 2:1 adducts via a formal C-N insertion. DFT computations elucidated that a concerted S_NAr process is involved in the formal C-N insertion reaction. Evidence herein suggests that HDDA-benzyes do not participate in [4+2] cycloaddition chemistry with 2,5-diaryloxadiazoles due electronic rather than steric factors. We additionally disclose the first isolated example of a dearomatized HDDA product **27** arising from the trapping of 2,5-dimethyl-1,3,4-oxadiazole (**9**).

ASSOCIATED CONTENT

Data Availability Statement

"The data underlying this study are available in the published article and its Supporting Information."

Supporting Information Statement

"The Supporting Information is available free of charge on the ACS Publications website."

Experimental procedures describing the preparation and structural characterization data of all new compounds, copies of their NMR spectra, crystal data, and computational details for computed (DFT) stationary points (PDF).

FAIR data consisting of raw NMR FID files are given for compounds **15**, **16**, **21**, **22a–b**, **23a–b**, **26a-b**, **27**, **36**, and **37** (FID for Publication.zip).

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The manuscript was written collaboratively among all of its authors. All have approved the final version of the manuscript.

Notes

None of the authors has a competing interest.

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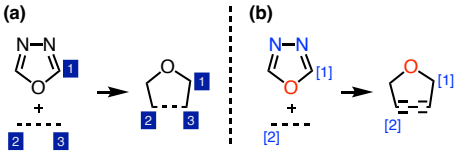

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[6] We have frequently used this substrate as a prototypical HDDA substrate because it is readily prepared by a scalable synthesis, it cycloisomerizes efficiently, its NMR properties are more readily tractable than those of the analogous bis-des-methoxy analog, the resulting benzyne often shows high regioselectivity in its engagement of various trapping agents (with the more electron rich site in the trapping reaction adding to the benzyne carbon that is distal rather than proximal to the ring fusion bond with the tether-derived five-membered ring), and the modes of trapping reaction are typical of those observed for the majority of the other >5 dozen HDDA-benzynes whose reactions have been reported to date. Fluegel, L.; Hoye, T. R. Hexadehydro-Diels–Alder reaction: Benzyne generation via cycloisomerization of tethered triynes. *Chem. Rev.* **2021**, *121*, 2413–2444.

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