OL | Organic Letters

pubs.acs.org/OrgLett Letter

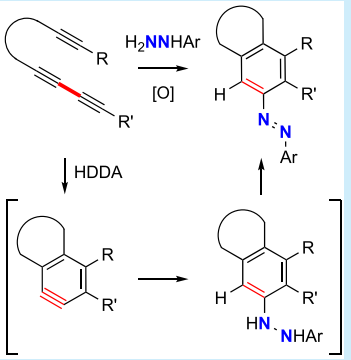
# Arylhydrazine Trapping of Benzynes: Mechanistic Insights and a Route to Azoarenes

Dorian S. Sneddon and Thomas R. Hoye*

Cite This: *Org. Lett.* 2021, 23, 3432−3436 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

**ABSTRACT:** Arylhydrazines ($ArN_\alpha HN_\beta H_2$) are ambident nucleophiles. We describe here their reactivity with benzynes generated in situ by thermal cyclization of several multiynes. Products arising from attack of both the alpha- and beta-nitrogen atoms are observed. These competitive modes of reaction were explored by DFT calculations. Substituent effects on the site-selectivity for several substituted phenylhydrazines were explored. Interestingly, the hydrazo products from beta-attack (ArNHNHAr′) can be oxidized, sometimes in situ by oxygen alone, to give structurally complex, unsymmetrical azoarenes (ArN═NAr′). Toluenesulfonohydrazide and benzohydrazide analogues were each demonstrated to undergo similar transformations, including oxidation to the corresponding benzyne-trapped azo compounds.






Azoarenes (ArN═NAr′) are notable for their light-driven *cis*/*trans* isomerization and, thereby, their potential to act as photoswitches. In this capacity, they have been employed in biological probes, molecular machines, drug delivery systems, optical devices, and data storage.[1] Currently (and classically), most azoarenes are constructed by way of the addition reaction of phenoxides to aryl diazonium ions (Figure 1a).[2] This reaction, however, has limitations in terms of its substrate scope and efficiency. Alternatively, the Mills reaction involves condensation of anilines with aryl nitroso compounds and allows for the synthesis of structurally more complex azoarenes (Figure 1b).[3−5] A limitation in that method is that the attacking aniline typically needs to be electron rich and efficiencies can suffer due to side reactions including overoxidation of the requisite nitroso compound.

To our knowledge, nucleophilic addition of an arylhydrazine to a benzyne species has never been reported. Herein, we demonstrate one-pot formation of azoarenes **4** via reaction of benzynes generated by the hexadehydro-Diels−Alder (HDDA) reaction (**1** to **1***) with arylhydrazines **2** to produce intermediate hydrazoarenes **3** (Figure 1c). These are readily and conveniently oxidized with $MnO_2$ (or, even, via autoxidation). Via this strategy, both electron-donating and, especially, electron-withdrawing substituents on the hydrazine are tolerated and significant structural complexity is introduced into the products in a single step via the trapping of **1***. The results described here constitute a complementary strategy for the construction of complex azoarenes.

Our initial experiment involved heating of the triyne HDDA substrate **5** in chloroform at 90 °C in the presence of 1 equiv of phenylhydrazine **2a** (Figure 2). The characterized products were the 1,2-diarylhydrazine (hydrazo compound) **6a**, the azoarene **7a**, the 1,1-diarylhydrazine **8a**, and, to a small extent, the aniline derivative **9a**.[6] The relative amounts of these products depended upon the amount of oxygen present in the reaction vessel. That is, under aerobic conditions, none of the hydrazo product **6a** was observed. Under an atmosphere of nitrogen, this compound was clearly evident in the NMR spectrum of the crude product mixture, and although it could be isolated, its further conversion to the oxidized azoarene **7a** occurred both upon routine handling as well as while kept in solution in an NMR sample tube over time. Notice that the ratio of the total amount of **6a** and **7a** to that of **8a** was ca. 1.5 in both experiments. This, in turn, implies that the nucleophilic addition of **2a** to the benzyne is competitive at the $\alpha$- vs $\beta$-nitrogen atoms.

The competition between the two nitrogen atoms is surprising given that the reaction of **2a** with dimethyl acetylenedicarboxylate (DMAD) is reported to occur exclusively at the $\beta$-nitrogen atom ($NH_2$).[7−9] This is in line with the notion that the phenyl substituent would reduce the nucleophilicity of the $\alpha$-nitrogen atom for both steric and electronic reasons. Therefore, we decided to explore whether DFT calculations would shed any light on this curious outcome of a preference for attack by $N_\alpha$. In particular, we

**Received:** March 15, 2021
**Published:** April 19, 2021

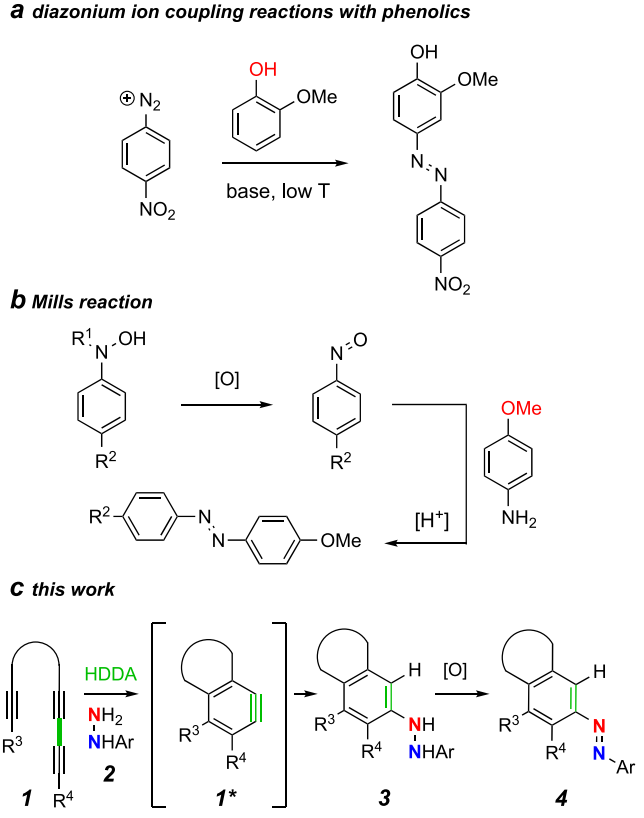


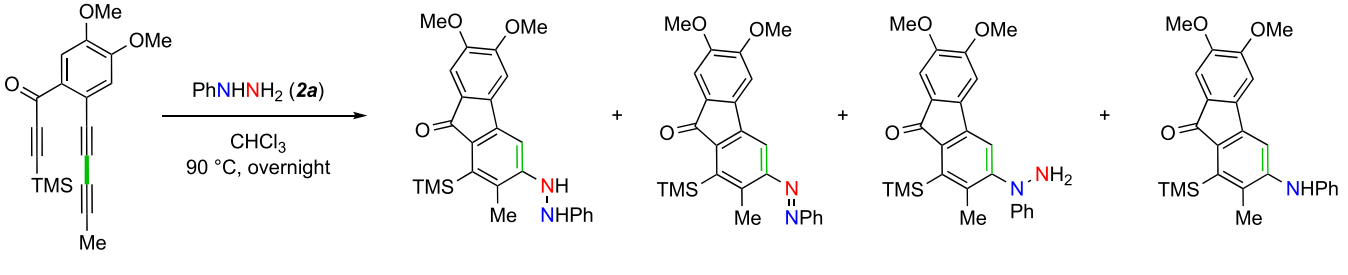

**Figure 1.** Complementarity of this de novo construction of one arene of an azoarene (panel c) with the most common, classical methods for their conjunctive synthesis (panels a and b).

computed the energetics for reaction of *o*-benzyne **I** with **2a** (Figure 3). The overall free energy of reaction leading to **IV**$\beta$ vs **IV**$\alpha$ (the analogues of **6a** and **8a**, respectively) is, as expected, largely exergonic, the former more so because of the greater resonance delocalization into each of the two phenyl rings.

The transition structures associated with attack by $N_\beta$ (**TS-I** → **II**$\beta$) vs $N_\alpha$ (**TS-I** → **II**$\alpha$), leading to the zwitterions **II**$\beta$ or **II**$\alpha$, respectively, are quite similar in energy, consistent with the experimental observation of comparable amounts of products arising from these two processes. The nearly barrierless exergonic events that convert **II**$\beta/\alpha$ to **III**$\beta/\alpha$ (simple proton transfers) indicate that the initial $\alpha$- vs $\beta$-attacks by **2a** onto **I** are both the rate- and product-determining steps for the two overall reactions. The final conversions of **III**$\beta/\alpha$ to products **IV**$\beta/\alpha$ would most likely be mediated by an external proton shuttle such as $PhNHNH_2$.

We also briefly explored by DFT the two modes of competitive reaction between $PhNHNH_2$ (**2a**) and DMAD (see the Supporting Information for details). While a full exploration of the potential surface for this process is complex, one potentially significant difference between the transition structures for the DMAD vs benzyne reactions is the distance between the attacking nitrogen atom and the electrophilic sp-hybridized carbon atom. In **TS-I** → **II**$\beta$ and **TS-I** → **II**$\alpha$, that distance is 3.0 and 3.7 Å, respectively. In contrast, for the analogous TSs for the addition to DMAD, the TSs have a much smaller separation of the reacting centers (2.0 Å for both $N_\beta$−C and $N_\alpha$−C). This reflects a reaction surface with a much later transition state, consistent with the considerably higher exergonicity for addition of **2a** to benzyne **I** vs DMAD ($\Delta\Delta G^\circ \sim 20$ kcal mol$^{-1}$) for the first elementary step of formation of the zwitterions **II**$\beta/\alpha$ vs that of the DMAD analogues. The much longer N−C distances in the reactions with benzyne via **TS-I** → **II**$\beta/\alpha$ significantly minimize the role of steric interaction in approach of the nucleophile to benzyne.

We next examined the effect of substituents on the arylhydrazine (Table 1). The presence of electron-withdrawing groups on the phenyl ring significantly enhanced the preference for attack by $N_\beta$; none of the products from reaction at $N_\alpha$ were seen (entries b−e). In the case of the *p*-nitrophenyl analogue, the diarylhydrazine precursor of **7b** was isolable, although it too was seen to air oxidize slowly, for example, in an NMR sample solution. $MnO_2$ was used to fully convert the crude product to the azo adduct. Likewise, the crude material from trapping with 2-hydrazinopyridine **2e** was also proactively oxidized with $MnO_2$ to ensure full conversion to **7e**. Entries f and g show results using phenylhydrazine derivatives similar in electronic character to that of **2a** itself. And, similarly, comparable amounts of products from both $N_\beta$ and $N_\alpha$ attack were isolated. Results using *p*-methoxyphenylhydrazine are conspicuously absent from Table 1. This substance is known to be very challenging to prepare and handle because of its sensitivity to autoxidation.[10] The *o*-methoxy analogue **2h** was free-based immediately prior to use; the azo derivative **7h** was isolated in low yield. Analysis of the NMR spectrum of the crude




| | | 5 | 6a | 7a | 8a | 9a |
|---|---|---|---|---|---|---|
| air | NMR ratio | | not observed | 1.0 (30%)[a] | 1.6 (43%)[a] | trace (ca. 3%)[a] |
| $N_2$ | NMR ratio | | 0.48 | 1.0 | 2.3 | trace |

**Figure 2.** Product distribution from reaction of the benzyne derived from heating triyne **5** in the presence of phenylhydrazine **2a**. [a]Isolated yield.



https://doi.org/10.1021/acs.orglett.1c00897
Org. Lett. 2021, 23, 3432−3436

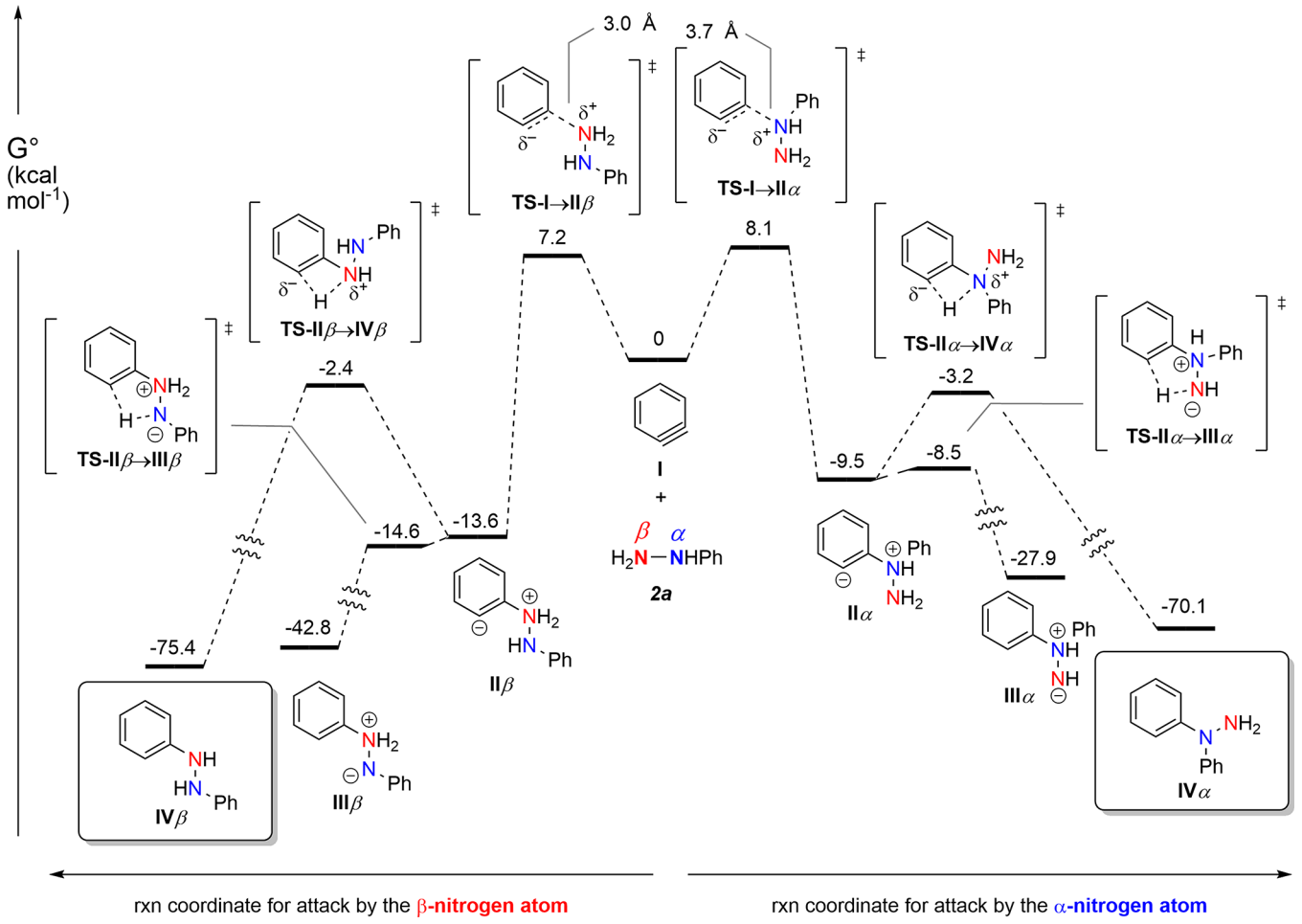



**Figure 3.** DFT calculations for reaction of *o*-benzyne **I** with phenylhydrazine **2a**. [SMD($CHCl_3$)/M11/6-31+G(d,p)].

reaction mixture suggested the presence of a significant amount of **8h**, but that material also degraded upon attempted purification.[11]

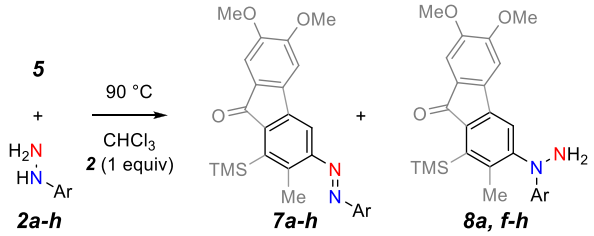
Several experiments were then performed to address several complementary aspects of this chemistry (Figure 4). Unsurprisingly, the iodophenyl derivative **7f** smoothly underwent cross-coupling to the biaryl derivative **10**. We then showed that the linker unique to triyne **5** was not a requirement for the reaction. That is, the tetraynes **11a** and **11b** were each trapped by the nitrophenylhydrazine **2b** to give, following oxidation, the azo compounds **12a** and **12b** (Figure 4b).[6] We also showed that hydrazides **13a** and **13b**, each perforce having a quite different level of nucleophilicity of its two nitrogen atoms, react smoothly with the benzyne produced by heating triyne **5**. Direct oxidation by addition of $MnO_2$ produced the azo derivatives **14a** and **14b**, respectively. It is notable that, while the former appeared to be quite stable, the arylazosulfone analogue was observed to photobleach rather easily upon handling under the ambient laboratory conditions. This presumably reflects the reported photoinitiated homolytic fragmentation of compounds containing an ArN=$NSO_2$R moiety.[12]

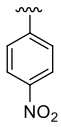
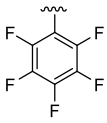
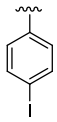
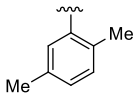
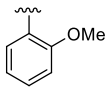
Finally, because we were unable to identify reports of any reactions of hydrazines with arynes generated by conventional methods (i.e., non-HDDA), we briefly explored the reaction of the Kobayashi benzyne from precursor **15**[13,14] with three phenylhydrazine derivatives (Figure 5). In each instance, by far, the major product, following isolation, was the 1,1-diarylhydrazine product **16**. Trace amounts of a compound deemed to be the corresponding azoarene were detected by GC-MS analysis of the crude product mixture. This high selectivity for attack by $N_\alpha$ in **2** suggests that hydrogen bonding by fluoride ion to the more acidic PhNH preferentially activates $N_\alpha$ for addition compared to the additive-free reaction conditions of the thermal HDDA variant.

We have described here the first examples of nucleophilic trapping of benzynes by arylhydrazines. Either of the nitrogen atoms is capable of adding to produce either 1,2- or 1,1-diarylhydrazine compounds via attack by either the $\beta$- vs $\alpha$-nitrogen atoms, respectively. The ratio of these competitive processes is influenced by the electronic character of the aryl substituent in the hydrazine. DFT calculations suggest that the greater proportion of addition through the $\alpha$-nitrogen compared to reactions with simple electron-deficient alkynes supports the idea that the addition to (the highly electrophilic) benzyne proceeds via a transition state lying much earlier on the reaction coordinate. In many instances, the 1,2-diarylhydrazines were observed to undergo air oxidation to the corresponding azo analogues. This process could be readily forced to completion by exposing the crude reaction products to $MnO_2$ prior to purification; the 1,1-isomer was not oxidized. The benzo- and sulfonohydrazide analogues **13a** and **13b** were shown to add to an HDDA-benzyne exclusively through the unsubstituted, more nucleophilic nitrogen atom. The initial adducts could again be oxidized to the


https://doi.org/10.1021/acs.orglett.1c00897
Org. Lett. 2021, 23, 3432−3436

**Table 1. Azoarenes 7 (and 1,1-Diarylhydrazines 8, Where Observed) Formed from Reactions of the HDDA-Benzyne from Triyne 5 in the Presence of Arylhydrazines 2, Followed by Oxidation (in Air or with $MnO_2$)**




| entry | Ar | $MnO_2$ | azoarene (yield) | 1,1-diaryl-hydrazine (yield) |
|---|---|---|---|---|
| a |  | No | **7a** (30%) | **8a** (43%) |
| b[a] |  | Yes | **7b** (65%) | not obs. |
| c |  | No | **7c** (62%) | not obs. |
| d |  | No | **7d** (61%) | not obs. |
| e |  | Yes | **7e** (50%) | not obs. |
| f |  | Yes | **7f** (49%) | **8f** (49%) |
| g |  | Yes | **7g** (33%) | **8g** (30%) |
| h |  | No | **7h** (10%) | (**8h**)[b] |

[a]This example was also performed on a 1 mmol scale, and **7b** was isolated in 74% yield. [b]Evidence for this compound was seen in the NMR spectrum of the crude product mixture, but it proved to be too labile for isolation.

corresponding azo compounds, now bearing an electron-withdrawing group. Several arylhydrazines were used to trap *o*-benzyne itself to produce the 1-phenyl-1-arylhydrazine isomer highly selectively. This method of construction of azoarenes complements known, classical approaches and is capable of providing structurally complex azo compounds.

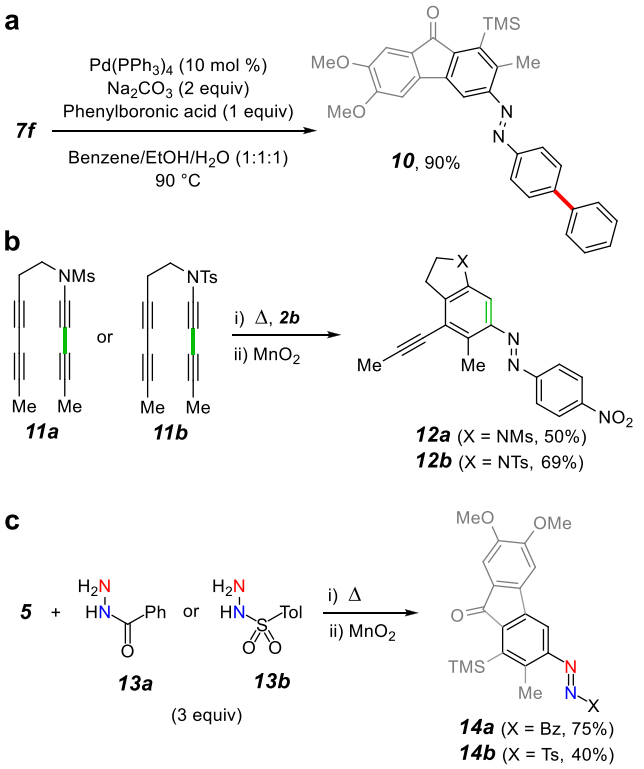



**Figure 4.** (a) The azo functionality is compatible with a $Pd^0$-catalyzed (Suzuki) cross-coupling reaction. (b) The nature of the HDDA-benzyne is not limited to that derived from **5**. (c) Benzo- and sulfonohydrazides undergo analogous transformations.

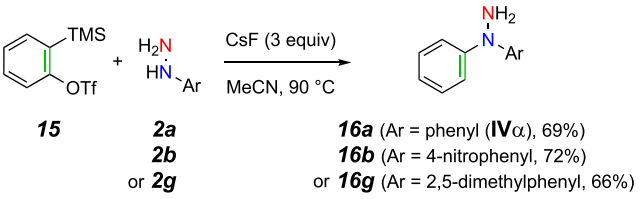



**Figure 5.** Reactions of *o*-benzyne with arylhydrazines **2a**,**b**,**g** gave 1-phenyl-1-arylhydrazines **16a**,**b**,**g**.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00897.

A .zip file containing the *XYZ* coordinates (.xyz files) of each computed structure (ZIP)

A PDF containing (i) preparative details for all new compounds, (ii) spectroscopic characterization data (including copies of both $^1H$ and $^{13}C$ NMR spectra) for all new compounds, and (iii) a description of DFT computational methods and the geometries and energies of each species shown in the manuscript (PDF)

FAIR data, including the primary NMR FID files, for compounds **2d**, **2g**, **6a**, **7a**, **7b**, **7c**, **7d**, **7e**, **7f**, **7g**, **7h**, **8a**, **8f**, **8g**, **9a**, **9h**, **10**, **12a**, **12b**, **14a**, **14b**, **16a**, **16b**, and **16g** (ZIP)



https://doi.org/10.1021/acs.orglett.1c00897
*Org. Lett.* 2021, 23, 3432−3436

## AUTHOR INFORMATION


### Corresponding Author

**Thomas R. Hoye** − *Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455, United States;* orcid.org/0000-0001-9318-1477; Email: hoye@umn.edu

### Author

**Dorian S. Sneddon** − *Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00897


### Author Contributions

D.S.S. performed all of the experimental work; both authors interpreted the data and co-wrote the manuscript.

### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

This research was supported through the National Institutes of General Medical Sciences of the U.S. Department of Health and Human Services (R35 GM127097). Support for some of the instrumentation came from an NIH Shared Instrumentation Grant (S10OD011952, NMR) and an NIH Cancer Center Support Grant (CA-77598, MS). DFT calculations were performed with resources provided by the Minnesota Supercomputing Institute.

## REFERENCES


(1) Merino, E.; Ribagorda, M. Control over molecular motion using the cis-trans photoisomerization of the azo group. *Beilstein J. Org. Chem.* **2012**, *8*, 1071−1090.

(2) Merino, E. Synthesis of azobenzenes: The coloured pieces of molecular materials. *Chem. Soc. Rev.* **2011**, *40*, 3835−3853.

(3) Baeyer, A. Nitrosobenzol und Nitrosonaphtalin. *Ber. Dtsch. Chem. Ges.* **1874**, *7*, 1638−1640.

(4) Mills, C. XCIII−Some new azo-compounds. *J. Chem. Soc., Trans.* **1895**, *67*, 925−933.

(5) Bamberger, E. Ueber die Einwirkung des Nitrosobenzols auf Amidoverbindungen. *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 102−104.

(6) The arynes from polyyne precursors like **5**,[a] **11a**,[b] and **11b**[b] are each known to react with high selectivity at C3 rather than C4 of the benzyne, consistent with the benzyne distortion model.[c−e] (a) Chen, J.; Palani, V.; Hoye, T. R. Reactions of HDDA-derived benzynes with sulfides: Mechanism, modes, and three-component reactions. *J. Am. Chem. Soc.* **2016**, *138*, 4318−4321. (b) Chen, M.; He, C. Q.; Houk, K. N. Mechanism and regioselectivity of an unsymmetrical hexadehydro-Diels−Alder (HDDA) reaction. *J. Org. Chem.* **2019**, *84*, 1959−1963. (c) Hamura, T.; Ibusuki, Y.; Sato, K.; Matsumoto, T.; Osamura, Y.; Suzuki, K. Strain-induced regioselectivities in reactions of benzyne possessing a fused four-membered ring. *Org. Lett.* **2003**, *5*, 3551−3554. (d) Garr, A. N.; Luo, D.; Brown, N.; Cramer, C. J.; Buszek, K. R.; VanderVelde, D. Experimental and theoretical investigations into the unusual regioselectivity of 4,5-, 5,6-, and 6,7-indole aryne cycloadditions. *Org. Lett.* **2010**, *12*, 96−99. (e) Cheong, P. H.-Y.; Paton, R. S.; Bronner, S. M.; Im, G.-Y. J.; Garg, N. K.; Houk, K. N. Indolyne and aryne distortions and nucleophilic regioselectivities. *J. Am. Chem. Soc.* **2010**, *132*, 1267−1269.

(7) Heindel, N. D.; Kennewell, P. D. Imine-enamine adducts from hydrazine addition to dimethyl acetylenedicarboxylate. *J. Chem. Soc. D* **1969**, *0*, 757−758.

(8) Heindel, N. D.; Kennewell, P. D. Imine-enamine tautomers from hydrazine and aryl hydrazine additions to acetylenedicarboxylate. *J. Org. Chem.* **1970**, *35*, 80−83.

(9) Sucrow, W. Reactions of acetylenes with hydrazines. *Org. Prep. Proced. Int.* **1982**, *14*, 91−155.

(10) Frahn, J. L.; Illman, R. J. The preparation of 4-methoxyphenylhyd-razine and some other arylhydrazines. *Aust. J. Chem.* **1974**, *27*, 1361−1365.

(11) Hong, S.-S.; Bavadekar, S. A.; Lee, S.-I.; Patil, P. N.; Lalchandani, S. G.; Feller, D. R.; Miller, D. D. Biosteric phentolamine analogs as potent α-adrenergic antagonists. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4691−4695.

(12) Dossena, A.; Sampaolesi, S.; Palmieri, A.; Protti, S.; Fagnoni, M. Visible light promoted metal- and photocatalyst-free synthesis of allylarenes. *J. Org. Chem.* **2017**, *82*, 10687−10692.

(13) Himeshima, Y.; Sonoda, T.; Kobayashi, H. Fluoride-induced 1,2-elimination of *o*-trimethylsilylphenyl triflate to benzyne under mild conditions. *Chem. Lett.* **1983**, *12*, 1211−1214.

(14) Shi, J.; Li, L.; Li, Y. o-Silylaryl triflates: A journey of Kobayashi aryne precursors. *Chem. Rev.* **2021**, *121* (7), 3892−4044.