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The Phenol–Ene Reaction: Biaryl Synthesis via Trapping Reactions between HDDA-Generated Benzynes and Phenolics

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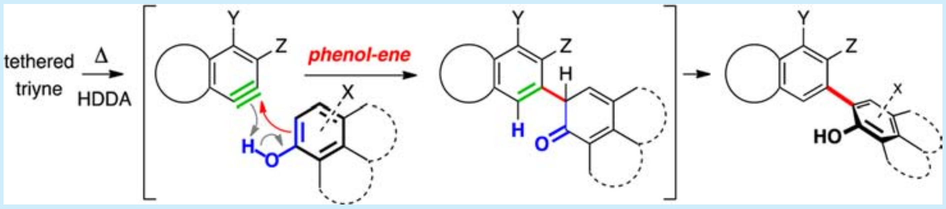
Ⓢ *Supporting Information*



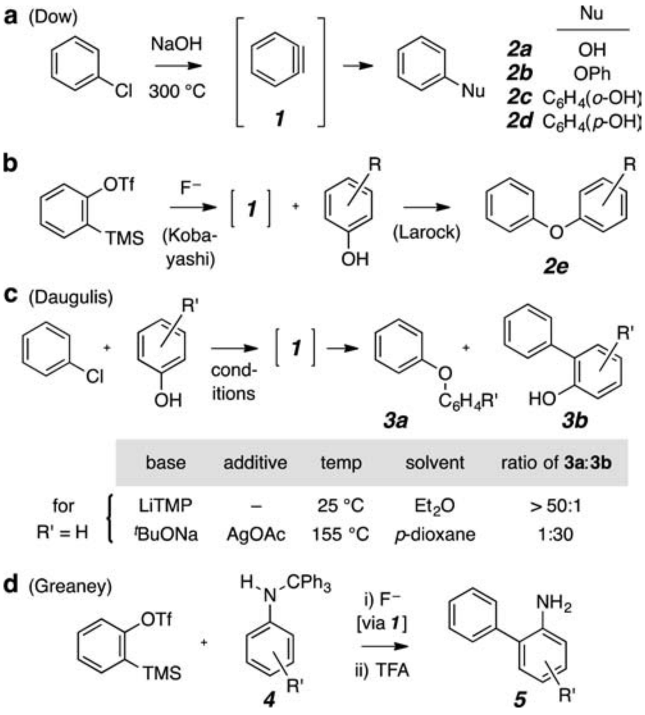
ABSTRACT: Benzynes produced thermally by the cycloisomerization of triyne-containing precursors [i.e., by the hexadehydro-Diels–Alder (HDDA) reaction] react with phenols at the carbon *ortho* to the hydroxyl in an enelike fashion. Following tautomerization of the intermediate cyclohexadienones, this produces biaryl derivatives. DFT calculations of model reactions support this mechanistic interpretation. Substituted, unsymmetrical phenols and bis-phenols react in a fashion that can be explained by engagement of the most readily available (non-hydrogen-bonded) hydroxyl in the phenol–ene process.

o-Benzyne (**1**) and related arynes compose a highly versatile class of reactive intermediate in organic chemistry.[1] They typically are generated by removal of two adjacent atoms or groups from a precursor arene. The reagents and/or byproducts that effect that net elimination most often are basic in character. Reactions of arynes generated in this fashion with phenolic compounds most typically result in diaryl ether formation, arising from nucleophilic attack of the phenoxide oxygen at the more electrophilic aryne carbon. The Dow process for conversion of chlorobenzene to phenol (**2a**)[2] via **1** (Scheme 1a) produces, as the major byproduct, diphenyl ether (**2b**) along with minor amounts of the hydroxylated biphenyls **2c** and **2d**. A more mildly basic variant for benzyne generation, introduced by Kobayashi[3a] (Scheme 1b), gives diaryl ethers **2e**, as generalized by Larock[3b] and subsequent investigators.

Daugulis and co-workers have shown that the nature of the phenoxide counterion or the reaction solvent can amplify reactivity at the position *ortho* to the phenolic oxygen, providing an attractive preparative route for accessing *o*-hydroxylated biaryls (Scheme 1c). Phenoxides react with *o*-benzyne (**1**) generated under strongly basic conditions to give, predominantly, either diaryl ethers **3a** or 2-hydroxybiaryls **3b**, depending upon the reaction conditions.[4a] Intramolecular constraints can further enforce reaction to occur at the (proximal) carbon rather than the (distal) oxygen atom of a tethered phenoxide.[4b]

We are unaware of any example of the reaction of a neutral phenolic species with an aryne prior to 2012.[5] However, Greaney and co-workers have reported highly selective *ortho*-arylation of aniline derivatives bearing a bulky trityl masking substituent on the nitrogen atom under conditions where the neutral aniline entity is likely the attacking nucleophile (Scheme 1d).[6]

Scheme 1. Reactions of Classically Generated Benzynes with Phenols and Phenoxides



	base	additive	temp	solvent	ratio of 3a:3b
for R' = H	LiTMP	–	25 °C	Et$_2$O	> 50:1
	^{t}BuONa	AgOAc	155 °C	*p*-dioxane	1:30

Benzynes generated thermally by the hexadehydro-Diels–Alder cycloisomerization (of a substrate comprising a 1,3-diyne and a remote, tethered, alkynyl diynophile) are produced (and trapped) in the absence of other extraneous reagents. This allows

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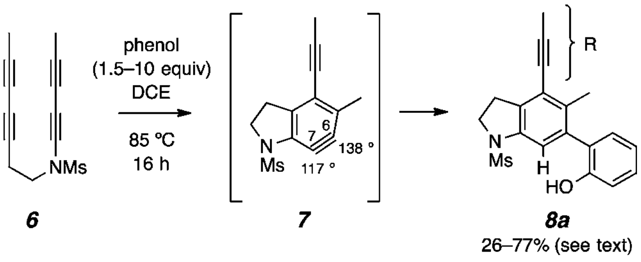
for exploration of trapping reactions wherein the capture reagent(s) is (are) neutral species. We report here reactions of HDDA benzynes with a variety of phenols to give biaryl products, a class valuable to many different subdisciplines of organic chemistry.[7]

As an initial example, consider the HDDA cascade (i.e, generation plus in situ trapping) between the tetrayne **6** and phenol itself (Scheme 2). When heated at 85 °C (1,2-dichloroethane) for ca. 16 h, the *o*-hydroxyphenyl-substituted arene **8a** was produced as the major product. This structure was assigned to have the new aryl substituent attached in the position shown on the basis of the chemical shift of the aryl methyl substituent at δ 2.18 ppm. This is significantly further upfield than is typically seen (ca. δ 2.4 ppm) for these protons in analogous compounds that lack an adjacent aryl substituent.[8] In addition, the chemical shift of the resonance from the analogous methyl group in **16c** (see Scheme 4) was at 2.25 ppm, whereas that resonance appeared at 2.45 for the regioisomeric biaryl **16c′** having a C4′ biaryl linkage (see the Supporting Information). This mode of attack by the nucleophilic phenol is consistent with the expected greater electrophilic character at C6 (greater internal bond angle of 138°) in the geometry of intermediate benzyne[8] **7**.[9] None of the product containing a 2-hydroxyphenyl substituent at C7 was observed. The half-life for disappearance of **6** via the initial, rate-limiting cyclization to the fused benzyne **7** is ca. 3 h.

Scheme 2. Phenol−Ene Reaction between the HDDA-Generated Benzyne 7 and Phenol Gives the Biaryl 8a



We also studied the dependence of this reaction on the number of equivalents of phenol that was used. Through direct analysis (^{1}H NMR; internal standard) of reaction solutions having 1.1, 3.3, and 10 equiv of phenol at the outset, we observed the "NMR yield" to increase from 35% to 62% to 78%, respectively. This compared well with the isolated yield following chromatographic purification (26% for 1.1 equiv and 77% for 10 equiv).

We envisioned this biaryl-forming trapping reaction to proceed by a mechanism involving concerted transfer of the hydroxyl proton and formation of the C−C bond to C2 of phenol.[10] This can be viewed as a phenol−ene process, reminiscent of the enol−ene (or Conia[11]) reaction.[12] HDDA-benzynes are known to engage in Alder−ene-type reactions both inter-[13a] and intramolecularly.[13b] The phenol−ene possibility was explored through DFT calculations for the reaction between *o*-benzyne (**4**) and phenol, which leads to the cyclohexadienone **10**, the precursor tautomer of **2** (Figure 1). We also explored a related process, the [4 + 2] Diels−Alder cycloaddition reaction between **4** and carbons C1−C4 of phenol, leading to the bicyclic diene **9**. This type of product was seen as a minor component in a few of the phenol−ene reactions we have studied (for example, see $\mathbf{14}_{[4+2]}$ in Scheme 3). Indeed, a transition-state geometry for each of these two pathways was identified. The energy of $\mathbf{TS}_{[4+2]}$ was considerably higher than that of $\mathbf{TS}_{\text{phenol−ene}}$. We conclude that a phenol−ene mechanism is the most likely pathway for formation of the biaryls whose formation we are reporting here (e.g., **7** to **8a**). This view is reinforced by some of the additional results we describe below.

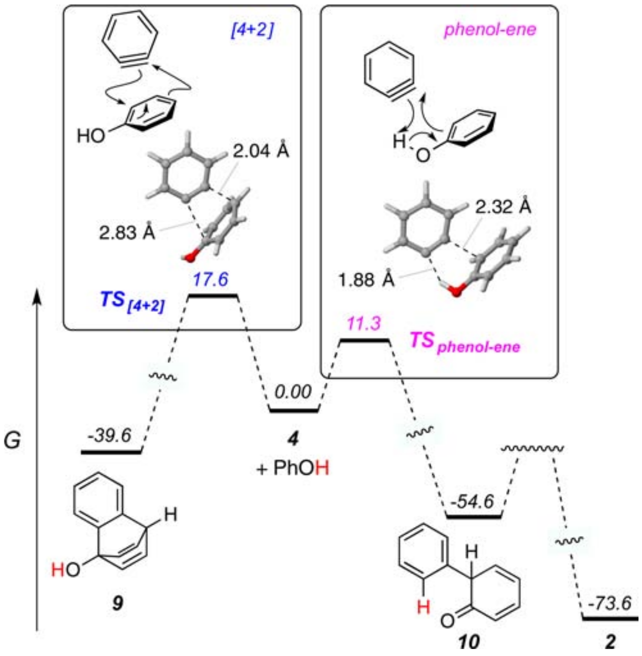


Figure 1. DFT calculations of the phenol−ene (right) and [4 + 2] Diels−Alder (left) reactions between the prototypical pair *o*-benzyne and phenol.

Shown in Figure 2 are the *o*-hydroxylated biaryl products from a host of other phenolics that we have used to trap benzyne **7**. The indicated yields are of material following chromatographic purification on silica gel. The yields generally reflect the overall cleanliness of the reaction (as judged by ^{1}H NMR analysis of the crude product mixture). For each entry, just 1.5 equiv of the trapping phenol was used in order to evaluate if the reaction could be useful even for precious phenols, where use of a larger excess would be less desirable.[14]

Products in panel a arose from trapping with a series of simple monosubstituted phenols. There is a clear trend that trapping agents with more electron-rich arenes capture the benzyne more efficiently. In fact, when *p*-nitrophenol was used, the biaryl product was not detected. Panel b shows the results of trapping with hydroquinone (to **8g**), resorcinol (to **8h** and **8i**), and catechol (to **8j**). As with *p*-methoxyphenol (to **8f**), each of these electron-rich benzenediols trapped efficiently.

4-Hydroxyindole and 5-hydroxyindole gave rise to **8k** and **8l**, respectively (panel c). The latter outcome is particularly interesting since there are two possible sites at which the phenol−ene reaction could take place, but only one isomer, **8l**, was observed. Naphthols proved to be particularly good traps (panel d). This likely reflects the reduced amount of aromatic resonance energy that needs to be sacrificed to arrive at the transition state for these phenol−ene reactions. By analogy with many other electrophilic substitution reactions of 2-naphthol, this benzyne trapping occurred exclusively at the 1-position, giving only **8m** via a TS that maximally retains the aromaticity of the bystander benzenoid ring. This thinking also accounts for the

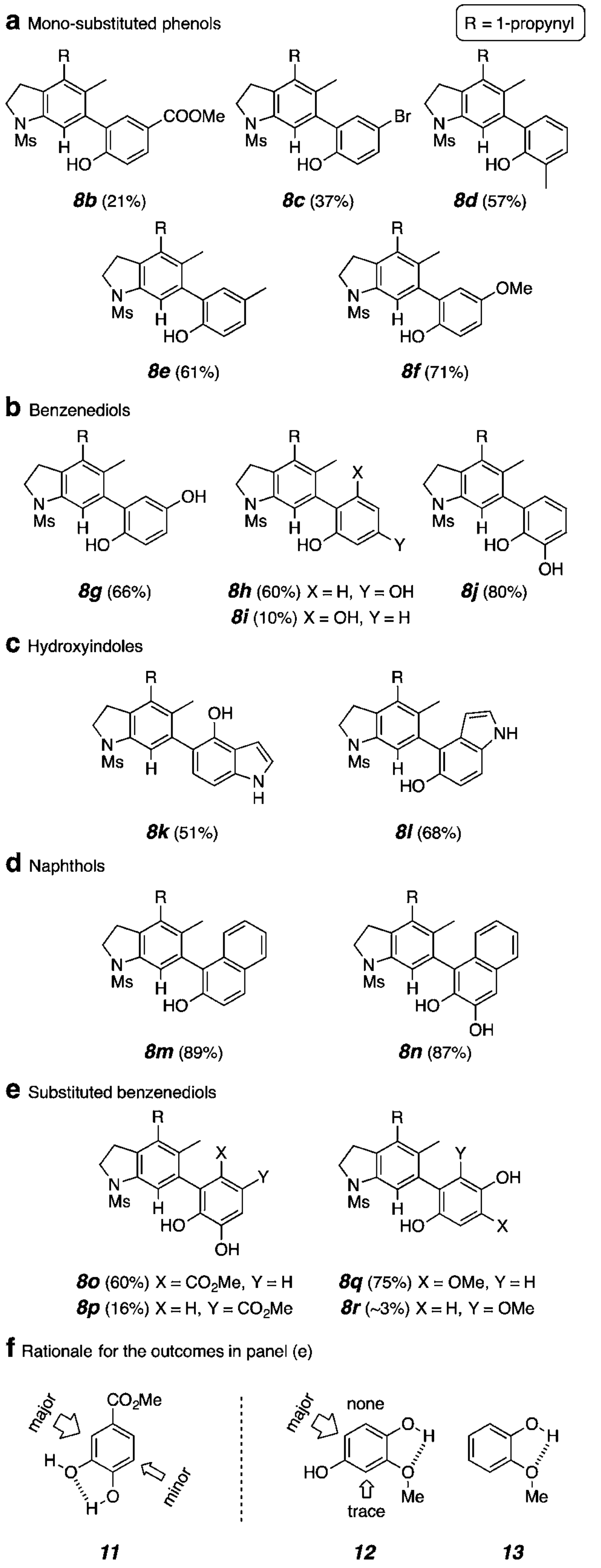


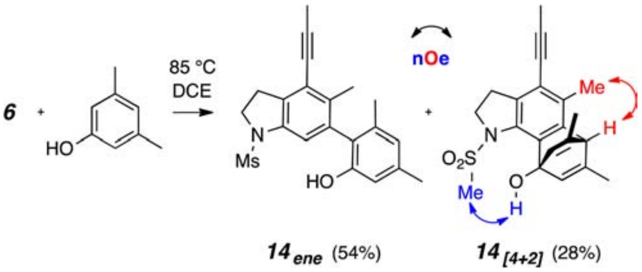
Figure 2. Biaryl products from trapping of benzyne **7** with (a) monosubstituted phenols; (b) catechol, resorcinol, and hydroquinone; (c) hydroxyindoles; (d) naphthols; and (e) catechol derivatives. (f) Rationale for the selectivities reported in panel (e).

regioselectivity observed for the formation of indole **8l**; here, it is pyrrole aromaticity that is fully retained.

The reactivity pattern of benzenediols containing a third substituent proved informative (panel e). Methyl 3,4-dihydroxybenzoate (**11**) gave rise to a preponderance of the (more hindered) adduct **8o** with an ca. 4:1 selectivity over the less hindered **8p**. 2-Methoxyhydroquinone (**12**) gave, predominantly, **8q**, along with a very small amount of the isomeric adduct **8r**. A rationale for these selectivities is offered by the graphics in panel f. In the case of the benzoate ester **11**, the *p*-hydroxyl proton is presumably the more acidic of the two OH groups and, therefore, the better internal hydrogen bond donor.[15] Thus, the arrangement shown in **11** should dominate for this unsymmetrical catechol derivative, leaving the proton of the *m*-hydroxyl group more available to participate in the phenol–ene reaction. An additional factor could be that the intermediate cyclohexadienone arising from the major ene reaction pathway enjoys a higher degree of conjugation (i.e., a 4-hydroxy dienoate) compared to that from the minor pathway.

In cases where the trapping phenol lacked a substituent in the *para* position, small amounts of [4 + 2] adducts (i.e., analogues of **9**, Figure 1) were formed. By far, the greatest proportion of this type of product was seen using 3,5-dimethylphenol, in which case the phenol–ene and DA adducts $\mathbf{14}_{\text{ene}}$ and $\mathbf{14}_{[4+2]}$, respectively, were produced in an approximately 2:1 ratio (Scheme 3). The *meta*-disposed methyl groups presumably provide a small steric barrier to the approach of **7** to an *ortho* carbon, en route to the TS leading to the dienone precursor of $\mathbf{14}_{\text{ene}}$.

Scheme 3. Competing Reactions with 3,5-Dimethylphenol

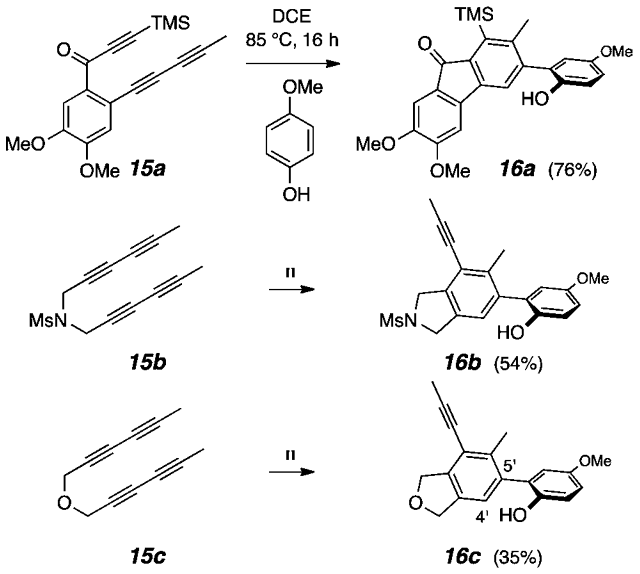


To establish that the phenol–ene reaction is not limited to benzyne **7**, we have trapped the HDDA benzynes derived from precursors **15a–c** with 4-methoxyphenol (Scheme 4). The electron-deficient benzyne from **15a** as well as those derived from the symmetrical tetraynes **15b** and **15c** give the biaryl products **16a–c** as the major product. A minor isomer of **16c**, having the new biaryl linkage to C4′ rather than C5′, was also formed (6:1 = **16c**/**16c′**, see the SI). The benzyne derived from **15c** has also been observed to react with reduced regioselectivity with other classes of nucleophiles.[8]

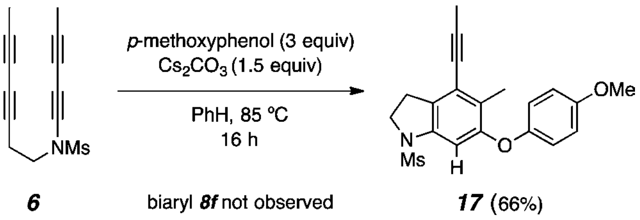
Finally, an experiment to probe the effect of the presence of a basic reagent was performed. Tetrayne **6** was heated with 4-methoxyphenol in the presence of a suspension of Cs_2CO_3 in benzene (Scheme 5). This substantially redirected the course of reaction; the diaryl ether **17** was formed in 66% yield, and none of the biaryl **8f** (Figure 2a) was observed. This result highlights the difference(s) that can arise in aryne trapping reactions under basic vs neutral reaction conditions, hallmarks of classical vs HDDA protocols for benzyne generation, respectively.

In summary, we have demonstrated that a variety of phenolic compounds react with thermally generated benzynes (and in the absence of any basic or metal-containing agents) at the carbon

Scheme 4. Other Types of Benzyne also Readily Trap



Scheme 5. Cs_2CO_3 Diverts the Reaction Course to Formation of Diaryl Ether 17



ortho to the phenolic hydroxyl group to produce 2-hydroxybiaryl derivatives. DFT computation suggests that this can occur through a concerted, six-atom transition structure that we have referred to here as a "phenol−ene" reaction. The selectivities observed with several more complex, substituted phenols can also be rationalized by this mechanistic view of the process.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02830.

> New compound preparation and characterization data, NMR spectra, and compilation of DFT computational results (PDF)

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Notes

The authors declare no competing financial interest.

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(10) A reviewer raised the possibility of the intermediacy of an initially formed biaryl ether since some are known to rearrange to *o*-hydroxybiaryls. This is essentially always effected under photochemical conditions or at high temperature in the presence of very strongly basic agents. Moreover, the ether **17** (see Scheme 5) was perfectly stable under the same temperature and time frame used to prepare all of the *o*-hydroxybiaryl products reported here.

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(14) In view of the improved yields of **8a** described in Scheme 2 upon use of increasing amounts of phenol, we speculated that this would also be the case for the substituted phenols in Figure 2. As a test case, we heated **6** in the presence of 10 equiv of *p*-bromophenol and, indeed, isolated the adduct **8c** in an increased yield of 74%.

(15) Using DFT [M06-2X/6-311+G(d,p)], we computed the energies of **11** and the alternative hydrogen bond isomer (*meta*-OH as the donor) and found **11** to be 1 and 0.7 kcal·mol^{-1} more stable in the gas phase and using 1,2-dichloroethane solvation (SMD), respectively.