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Ene Reaction of Arynes with Alkynes

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Arynes are one of the most important classes of organic species that have received great attention both for the structural aspects as well as for their use as organic reagents in synthetic organic chemistry.[1] A mild method for the in situ preparation of arynes at moderate temperatures from *ortho*-silyl aryltriflates[2] has rekindled the interest, especially in the past 5 years, in employing arynes as substrates in organic synthesis. As a result, the aryne chemistry has been extended to multicomponent assembling reactions,[3] element−element σ-bond additions,[4] and transition-metal-catalyzed multicomponent[5] and cyclotrimerization reactions.[6]

Apart from the transition-metal-catalyzed reactions, there are very few reports of reactions involving arynes and alkynes. Guitián's group has revealed a dehydro Diels−Alder reaction (DDAR) of 1,8-diethynylnaphthalene and benzyne.[7] In view of the low-lying LUMO of aryne, it is expected to be a powerful enophile in the ene reactions[8] with alkynes possessing a propargylic hydrogen to give phenylallenes. Considering the long history for arynes, we carefully checked the literature for any report about this reaction. In 1968, Wasserman et al. had proposed the formation of allenes from the reaction of benzyne and an alkyne.[9] Another report dealing with a reaction of benzyne with ethynylcyclopropane showed the formation of a trace amount of allene derivative.[10] Other than the above two reports, this fundamentally important ene reaction of aryne with alkyne is virtually unknown to us. The failure to isolate ene products is likely due to the nature of benzyne precursor and the reaction conditions used.[11] The feasibility of the ene reaction of benzyne and propyne was supported by a DFT calculation.[12] The results showed that the reaction proceeds via a concerted pathway with a barrier of 2.4 kcal/mol and is exothermic by 92.7 kcal/mol. The optimum transition-state geometry is a near planar cyclic-six-electron framework (four in-plane π electrons and two σ C−H bond electrons), as shown in Figure 1.

We next tested the above results experimentally employing *ortho*-silylaryl triflates as aryne precursors. When 2-(trimethylsilyl)phenyl triflate (**1a**) was treated with 1-hexyne (**2a**) (4 equiv) in the presence of KF (3 equiv) and 18-crown-6 (3.5 equiv) in THF at room temperature for 6 h, 1-propyl-3-phenylallene (**3a**) was formed in 69% yield. Product **3a** was thoroughly characterized by ^{1}H NMR, ^{13}C NMR, IR, and mass data. The use of CsF (4 equiv) as the fluoride source at 35 °C in acetonitrile also worked equally well. Product **3a** appears to further react with benzyne readily during the reaction, and it is essential to keep 1-hexyne in excess to inhibit this reaction. To the best of our knowledge, this is the first time that an alkyne was successfully used in the intermolecular ene reaction[13] and the first detailed account of the synthesis of phenylallene from a benzyne and an alkyne in good yields under mild conditions.

This ene reaction was smoothly extended to various alkylalkynes (Table 1). Thus, treatment of 4-methyl-1-pentyne (**2b**) and 3-cyclopentyl-1-propyne (**2c**) with **1a** gave the corresponding phenylallenes in 68 and 65% yields, respectively (entries 2 and 3). Similarly, when 3-phenyl-1-propyne (**2d**) was employed, 1,3-diphenylallene (**3d**) was obtained in 68% yield (entry 4). For the reaction of 1,6-heptadiyne (**2e**) with **1a**, ene reaction occurred at one of the alkyne groups to afford product **3e**; the other terminal alkyne group remained intact (entry 5). The reaction was also successfully applied to propargyl bromide (**2f**) and propargyl chloride (**2g**), yielding 1-bromo-3-phenylallene (**3f**) and 1-chloro-3-phenylallene (**3g**), respectively, in good yields (entries 6 and 7). The present reaction can be further extended to internal alkynes. When 3-hexyne (**2h**) was treated with **1b**, the corresponding trisubstituted phenylallene **3h** was formed in 57% yield (entry 8). However, the reaction of 2-hexyne (**2i**) with **1a** gave a mixture of two regioisomers in approximately a 1:1 ratio (entry 9).

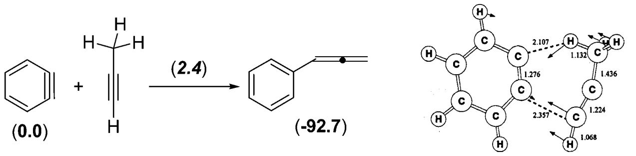

Figure 1. Free energies (kcal/mol) and optimized geometry of the transition state for the reaction of benzyne and propyne. Activation barrier is in italics, and bond lengths are in angstroms.

In addition to benzyne **1a**, substituted benzynes also underwent ene reaction with alkynes smoothly. Under the standard reaction conditions, an unsymmetrical 1,3-diarylallene **3k** was obtained from **1c**, a 1,3-benzodioxole derivative, and **2d** (entry 10). Similarly, benzyne precursor **1b** with two methyl groups on the phenyl ring furnished allene product **3l** in 70% yield, and indanyl derivative, **1d**, afforded **3m** in 68% yield (entries 11 and 12). The reaction of benzyne precursor **1c** with **2j** (entry 13) gave the corresponding allene, **3n**, in 62% yield. Further, the difluoro-substituted benzyne precursor **1e** gave allene **3o** in 66% yield (entry 14). In the case of benzyne precursor **1f**, the ene reaction gave a mixture of regioisomers (entry 15) as expected for a reaction using unsymmetrical 4-methylbenzyne as a substrate. When methoxy-substituted aryne precursor **1g** was used, the *meta*-isomer **3q** was the exclusive product (entry 16).

The experimental support for the mechanism was obtained from two labeling experiments. The use of 1-deuterium-1-hexyne (**2k**) as the ene reagent resulted in the deuterium incorporation on the allene double bond (entry 17). Conversely, the reaction of **1c** with α,α-dideuteriobenzylethyne (**2l**) possessing two propargylic deuteriums led to allene **3k-*d*$_2$**, in which a deuterium is on the allenyl moiety and the other is on the benzodioxole ring ortho to the allenyl moiety, as expected for an ene reaction (entry 18).

We also examined the reactivity of an alkyne without propargylic hydrogen toward benzyne. Thus, when *tert*-butylacetylene (**2m**) was treated with benzyne precursor **1a** under the standard conditions, we were surprised to see two products (Scheme 1). Product **4** was from the direct addition of the acetylenic C−H bond across benzyne, while phenanthrene derivative **5** in less than 5% yield is presumably from the dehydro Diels−Alder addition reaction (DDAR) of **4** and

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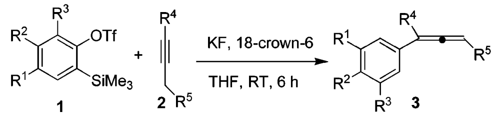
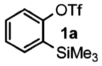
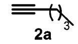
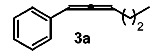
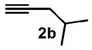
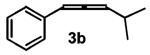
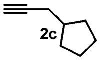
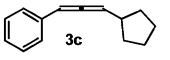
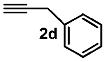
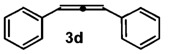
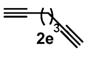
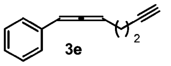
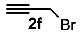
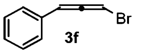
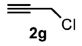
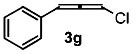
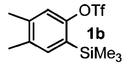
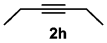
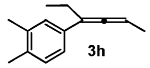
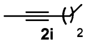
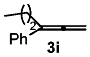
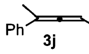
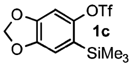
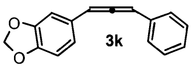
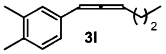
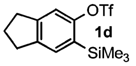
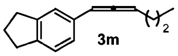
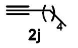
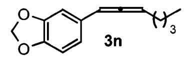
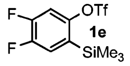
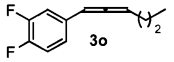
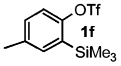
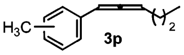
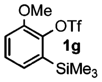
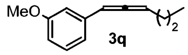
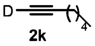
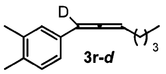
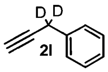
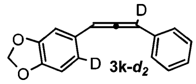
Table 1. Results of the Ene Reaction of Arynes **1** with Alkynes **2**[a]



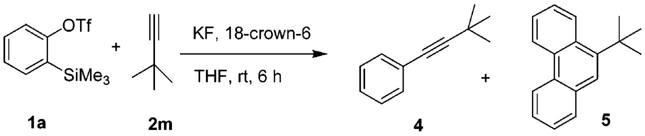
Entry	1	2	3	Yield (%)[b]
1	 **1a**	 **2a**	 **3a**	69
2	**1a**	 **2b**	 **3b**	68
3	**1a**	 **2c**	 **3c**	65
4	**1a**	 **2d**	 **3d**	68
5	**1a**	 **2e**	 **3e**	66
6	**1a**	 **2f**	 **3f**	55
7	**1a**	 **2g**	 **3g**	58
8	 **1b**	 **2h**	 **3h**	57
9	**1a**	 **2i**	 **3i**  **3j**	60 (1:1)
10	 **1c**	**2d**	 **3k**	55
11	**1b**	**2a**	 **3l**	70
12	 **1d**	**2a**	 **3m**	68
13	**1c**	 **2j**	 **3n**	62
14	 **1e**	**2a**	 **3o**	66
15	 **1f**	**2a**	 **3p**	71[c] (1:1)
16	 **1g**	**2a**	 **3q**	73
17	**1b**	 **2k**	 **3r-*d***	69
18	**1c**	 **2l**	 **3k-*d*$_2$**	52

[a] Reaction conditions: 0.50 mmol of aryne precursor **1**, 2.0 mmol of alkyne **2**, 1.50 mmol of KF, and 1.75 mmol of 18-crown-6 under nitrogen in 2.0 mL of THF at room temperature for 6 h. [b] Isolated yields. [c] Mixture of *meta*- and *para*-regioisomers (1:1).

1a. The same reaction with 2 equiv of benzyne relative to alkyne **2m** gave **5** in 92% yield. To the best of our knowledge, this is the first time that an acetylenic C−H addition across benzyne was observed.

At present, it appears that there are three basic reactions for the alkynes[14] with arynes: DDAR, ene, and acetylenic C−H addition reactions. These reactions provide simple and efficient routes for the synthesis of various phenanthrene, phenylallene, and phenylalkyne derivatives. A deeper understanding of these reactions and the application toward organic synthesis as well as a comprehensive theoretical study on the mechanistic details are of fundamental importance to the development of aryne chemistry. Further work toward this end is in progress in our laboratory.

Scheme 1



1a	2m	4	5
1 equiv	4 equiv	83 %	> 5%
2 equiv	1 equiv	trace	92 %

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Supporting Information Available: General experimental procedures, spectral data for all compounds, ^{1}H and ^{13}C NMR spectra for all compounds, and complete ref 12. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Reported intramolecular ene reaction of alkynes occurred only at very high temperatures. See: (a) Shea, K. J.; Burke, L. D.; England, W. P. *Tetrahedron Lett.* **1988**, *29*, 407. (b) Oppolzer, W.; Pfenninger, E.; Keller, K. *Helv. Chim. Acta* **1973**, *56*, 1807.
(14) (a) Alkynes having acetylenic carbon−hydrocarbon linkage. Alkynes having acetylenic carbon−heteroatom linkage might react in a different way. (b) For reaction of alkynylmetals with arynes, see: Du, C.-J. F.; Hart, H. *J. Org. Chem.* **1997**, *62*, 4896.

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