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Regioselective Asao–Yamamoto Benzannulations of Diaryl Acetylenes

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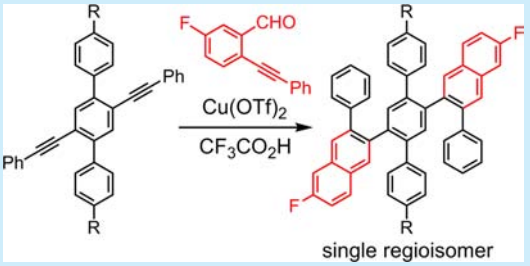
Supporting Information

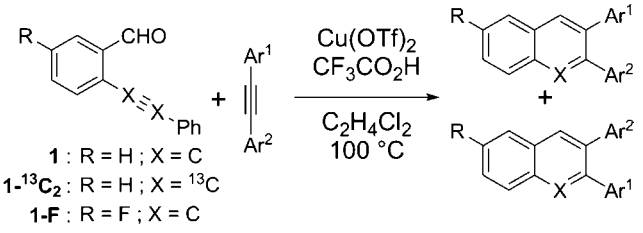
ABSTRACT: Asao–Yamamoto benzannulations transform diarylalkynes into 2,3-diarylnaphthalenes, and regioselective variants of this reaction are of interest for synthesizing substituted polycyclic aromatic systems. It is shown that regioselective cycloadditions occur when one alkyne carbon preferentially stabilizes developing positive charge. Simple calculations of the relative energies of carbocations localized at each alkyne carbon of a substrate predict the regioselectivity, which is not eroded by bulky substituents, including 2,6-disubstituted aryl groups.



Sterically congested aromatic systems such as hexaarylbenzenes,[1] *o*-arylene polymers and oligomers,[2] and polyphenylene dendrimers[3] exhibit desirable optoelectronic properties, often exhibit rigid structures or specific conformations, and are precursors of fused polycyclic aromatic hydrocarbons (PAHs)[4] and graphene nanoribbons (GNRs).[5] These motifs are most commonly accessed using transition metal-catalyzed cross-couplings,[5a,b] cycloadditions between tetraarylcyclopentadienones and alkynes,[1d,5c] or alkyne cyclotrimerizations.[1a−c] Although these approaches are useful and powerful, many structural motifs and substitution patterns remain outside their scope. Complementary methods for the preparation of highly substituted and congested aromatic systems are of great interest. For example, we recently demonstrated that a benzannulation reaction first reported by Asao and Yamamoto[6] converts the relatively unreactive alkynes along a poly(phenylene ethynylene) (PPE) backbone into 2,3-diaryl naphthalene moieties.[7] This process transforms easily prepared PPEs into otherwise inaccessible, densely substituted poly(arylene)s. The reaction also tolerates alkynes bearing both bulky *ortho*-substituents and triisopropylsilyl-protected alkynes, providing new contorted hexabenzocoronene derivatives[8] and branched oligo(*o*-naphthalenes).[9]

The remarkable efficiency of the benzannulation reaction warrants elaboration to functionalized benzaldehyde cycloaddition partners. These reactants will enable the synthesis of PAHs with otherwise unavailable substitution patterns, yet introduce the possibility of forming regioisomers. Excellent regioselectivity is paramount, and as the reaction's most desirable attribute, its ability to modify polyfunctional alkyne substrates would be rendered irrelevant if mixtures of regioisomers were produced. Previously, the regioselectivity of a related $AuCl_3$-catalyzed benzannulation, which provides naphthyl ketone products, was attributed to electronic effects.[10] This issue has not been addressed previously in the $Cu(OTf)_2$-catalyzed formation of naphthalenes, and substituted *o*-phenylethynylbenzaldehydes had not been employed prior to this study. Here we evaluate the regioselectivity of the benzannulation reaction (Scheme 1) using ^{13}C-labeled and F-substituted *o*-phenylethynylbenzaldehydes, **1**-$^{13}C_2$ and **1-F**. Single regioisomers are obtained for many diarylalkynes, including polyfunctional alkyne substrates that serve as desirable PAH precursors. The combinations of aryl substituents studied indicate that electronic effects determine the regioselectivity. Hindered alkynes, such as those bearing terphenyl or 2,6-dimethylphenyl groups, provide regiochemical outcomes consistent with their electronic properties, such that steric hindrance does not influence the product distribution. These findings provide a simple model to employ the benzannulation reaction to access specific substituted naphthalene derivatives and large functional π-electron systems.

Scheme 1. ^{13}C-Labeled and F-Substituted Derivatives of 1 Were Used to Probe the Regioselectivity of the Asao–Yamamoto Benzannulation of Diarylalkynes, Which Is Nontrivial When $Ar^1 \neq Ar^2$



The regioselectivity of the benzannulation reaction was first established for 1-methoxy-4-(phenylethynyl)benzene **2** to assess the role of the electron-donating methoxy group. We employed **1**-$^{13}C_2$ to probe the inherent regioselectivity of *o*-phenylethynylbenzaldehyde **1**, which is the prototypical cycloaddition partner for the benzannulation reaction. Compound **2** forms a single naphthalene product upon benzannulation with **1**-$^{13}C_2$

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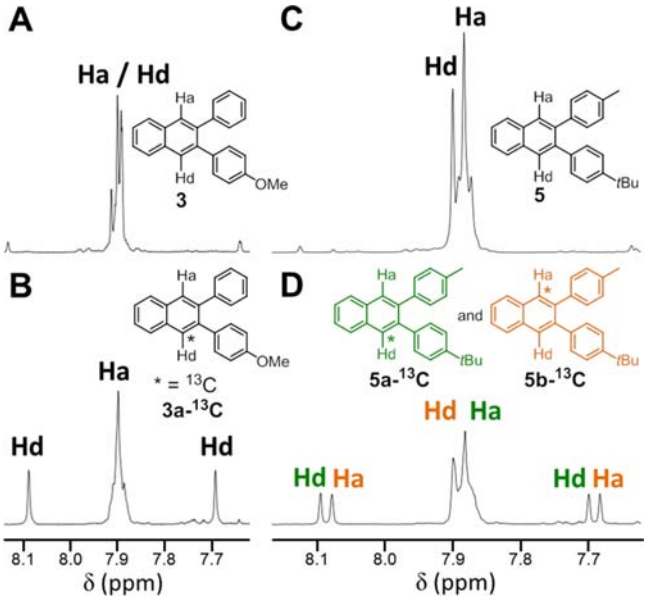
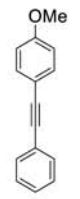
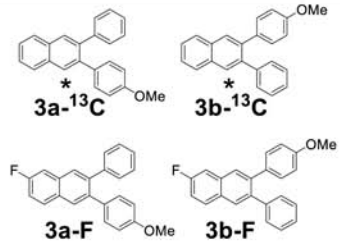
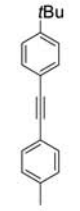
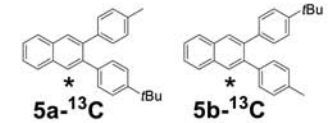
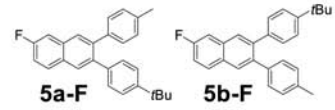
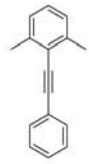
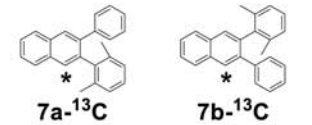
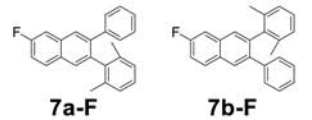
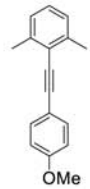
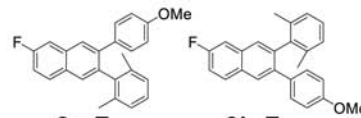
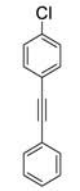
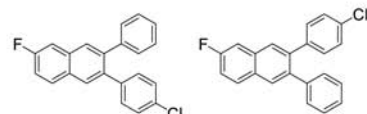


Figure 1. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$, 298 K) of (A) **3**, (B) its corresponding single isotopomer **3a-^{13}C** obtained from the regioselective benzannulation of **2** with **1-$^{13}C_2$**, (C) **5**, and (D) the 49:51 mixture of **5a-^{13}C** and **5b-^{13}C** obtained from the nonregioselective benzannulation of **4** with **1-$^{13}C_2$**.

(Figure 1). The complete regioselectivity of the reaction is readily diagnosed by comparing the ^{1}H NMR spectra of naphthalene **3** and its ^{13}C-enriched counterpart, **3a-^{13}C**. In the spectrum of **3** (Figure 1A), the hydrogens adjacent to each phenyl substituent, H_a and H_d, respectively, resonate with overlapping signals centered near 7.9 ppm. Only one of these resonances is split into a doublet in the spectrum of **3a-^{13}C** as a consequence of ^{1}H−^{13}C coupling, and the identity of this resonance was assigned unambiguously as H_d by analyzing its ^{1}H, ^{13}C, ROESY, and COSY NMR spectra (see Supporting Information). Likewise, the benzannulation of **2** with **1-F** produced a single fluoronaphthalene product **3a-F** (Table 1), which corresponds to the same regiochemical outcome as the isotopic labeling experiment. In contrast, a control experiment with compound **4**, which bears electronically similar 4-*t*-butyl and 4′-methyl substituents, provides a nearly equal mixture of regioisomers. A comparison of the ^{1}H NMR spectra of the 2,3-diarylnaphthalene **5** (Figure 1C) and mixture of **5a-^{13}C** and **5b-^{13}C** (Figure 1D) indicates that both H_a and H_d peaks are coupled to a ^{13}C nucleus. Benzannulation of **4** with **1-F** also provided nearly equal amounts of the fluoronaphthalenes **5a-F** and **5b-F**. These findings suggest that differences in electron donating ability of aryl substituents provide regioselective benzannulation reactions.

We selected additional substrates **6**, **8**, **10** (Table 1) and diyne **12** (Scheme 2) to evaluate these electronic effects more thoroughly and to determine if steric factors also influence the regioselectivity. Each substrate was benzannulated with **1** (see Supporting Information), as well as its isotopically labeled analogue **1-$^{13}C_2$** and/or fluorine-substituted **1-F**. The products were characterized using a full complement of 1D and 2D NMR experiments, in addition to high-resolution mass spectrometry and infrared spectroscopy, which allowed their structures to be determined unambiguously. Compound **6** provides insight into the effect of steric hindrance on the benzannulation's efficiency and regioselectivity. Our previous studies demonstrated the

Table 1. Regioselectivity and Isolated Yields Obtained for the Benzannulations of Various Diarylacetylenes

substrate	product(s)	ratio (isolated yield)
 **2**	 **3a-^{13}C** **3b-^{13}C**	>99:1 (78%)
	3a-F **3b-F**	>99:1 (63%)
 **4**	 **5a-^{13}C** **5b-^{13}C**	49:51 (95%)
	 **5a-F** **5b-F**	49:51 (82%)
 **6**	 **7a-^{13}C** **7b-^{13}C**	>99:1 (99%)
	 **7a-F** **7b-F**	>99:1 (97%)
 **8**	 **9a-F** **9b-F**	32:68 (99%)
 **10**	 **11a-F** **11b-F**	55:45 (60%)

remarkable tolerance of the benzannulation reaction to phenylacetylenes bearing an ortho substituent (such as **12**), but 2,6-disubstituted phenyl moieties were previously undemonstrated. Nevertheless, **6** was benzannulated efficiently with **1**, **1-$^{13}C_2$**, and **1-F** and provided single regioisomers for the latter two cycloaddition partners, **7a-^{13}C** and **7a-F**, respectively. These products correspond to the same regiochemical outcome as the methoxy-functionalized substrate **2**, which is consistent with the interpretation that the electron-donating property of the methyl groups, rather than their steric demands, direct the cycloaddition. The benzannulation of **10** provided poor regioselectivity and proceeded to only 60% conversion (remaining **10** was the only diarylalkyne substrate that was recoverable from the crude reaction mixture), which we attribute to the electron-with-

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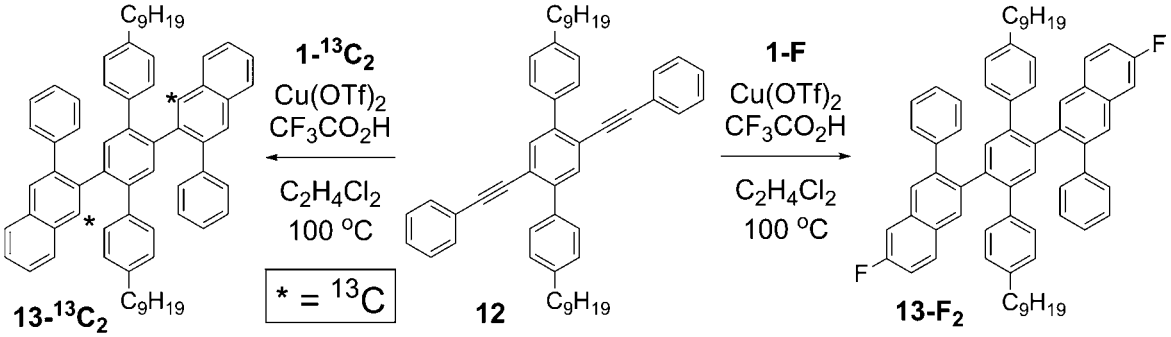
Scheme 2. Benzannulation of Diyne 12 by 1-$^{13}C_2$ and 1-F Provides Doubly Benzannulated Products as Single Products and Excellent Isolated Yields



drawing nature of its Cl substituent. The reaction efficiency decreases further when more powerful electron withdrawing substituents are present, such as a *p*-acetyl group (5% conversion). Dialkyne **12** preferentially forms a single regioisomer when reacted with both **1-**$^{13}C_2$ and **1-F** (Scheme 2). These observations indicate that the reactive intermediates derived from *o*-phenylethynylbenzaldehydes perfectly differentiate between the terphenyl- and phenyl-substituted alkyne carbons. We previously oxidized products similar to **13-F$_2$** to contorted hexabenzocoronene derivatives;[8] these results demonstrate that functionalized cycloaddition partners will provide access to these derivatives with controlled substitution of their peripheries. Overall, these observations of the regiochemical outcome and reaction efficiency form the basis of an intuitive model for predicting the products of benzannulation reactions and designing syntheses that are likely to provide naphthalene-containing systems as single regioisomers (see below).

The Cu(OTf)$_2$-catalyzed benzannulation is thought to proceed through a Cu-bound pyrylium ion intermediate (Figure 2A),[6] which undergoes a formal [4 + 2] cycloaddition with the diaryl alkyne that determines the regiochemical outcome. This study suggests that the cycloaddition proceeds either asynchronously or through a cationic intermediate, which involves positive charge developing on one of the alkyne carbons. Stepwise bond formation is also consistent with an established reactivity pattern of **1** with nucleophiles in the presence of transition metals or Lewis acids to provide substituted 1*H*-isochromenes.[11] The aryne substituent that stabilizes this positive charge more effectively reacts with the Cu-bound carbon atom, thus determining the naphthalene regioisomer that will be formed (Figure 2B). Complete regioselectivity is expected from diaryl alkyne substrates that preferentially stabilize positive charge on one alkyne carbon relative to the other.

DFT calculations (utilizing the B3LYP/6-31g(d) basis set, see Supporting Information) further support this interpretation. A comparison of the relative energies of the vinyl carbocations derived from both **2** and **6** indicate a strong preference (6.7−9.2 kcal/mol) for localizing positive charge at the alkyne carbon adjacent to the substituted aromatic ring, which is consistent with the formation of the observed regioisomers. In contrast, the two vinyl carbocations derived from diaryl acetylene **8**, which contains both 4-methoxyphenyl and 2,6-dimethylphenyl groups, are much closer in energy (1.3 kcal/mol in favor of the 4-MeOPh substituent). The benzannulation of **8** with **1-F** mirrors this trend: the regioisomers **9a-F** and **9b-F** are formed in a 32:68 ratio. These calculations also show that the regiochemical outcome may be predicted from the inherent electronic properties of the alkyne substrate without considering the energies of specific intermediates or transition states of the net [4 + 2] cycloaddition associated with the benzannulation mechanism, whose energies might be influenced by steric factors associated with each substrate.

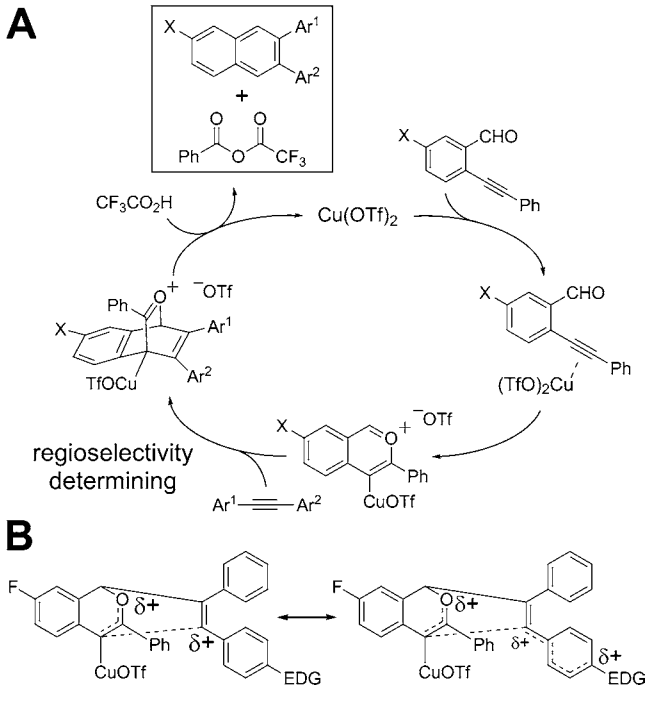


Figure 2. (A) Proposed mechanism of the Yamamoto benzannulation.[6] (B) Observed regioselectivity, shown here for reactions utilizing **1-F**, is consistent with asynchronous or sequential bond formation, during which positive charge develops on the distal alkyne carbon.

In conclusion, we have demonstrated that diaryl acetylenes that stabilize developing positive charge preferentially at one alkyne carbon undergo regioselective Asao−Yamamoto benzannulations. This reaction outcome may be predicted without considering steric factors, suggesting that they play a minor role in determining regioselectivity. These studies also confirm that the benzannulation reaction is remarkably tolerant of sterically demanding substituents, yet is inefficient for alkyne substrates

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bearing electron-poor aryl groups. Straightforward DFT calculations predict the nature and degree of the regioselectivity for diarylalkyne substrates. Regioselective cycloadditions provide rapid access to precursors of novel polycyclic aromatic hydrocarbons with predetermined substitution patterns and eliminate the need for symmetric substrates in planning complex syntheses. Overall, the remarkable efficiency, tolerance of bulky substituents, and regioselectivity of the benzannulation reaction make it a very attractive method for preparing elaborate aromatic architectures and carbon-based nanostructures.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, compound characterization data, and additional information regarding the DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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