

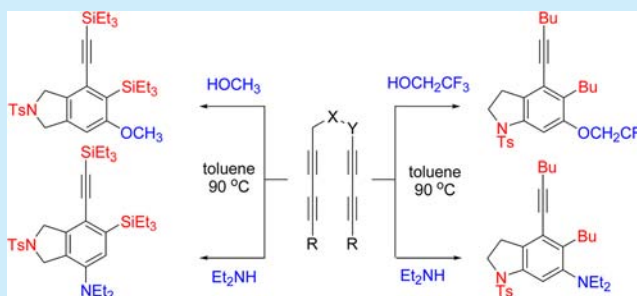
Regioselectivity in the Nucleophile Trapping of Arynes: The Electronic and Steric Effects of Nucleophiles and Substituents

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Supporting Information

ABSTRACT: The regioselectivity in nucleophile trapping is investigated with arynes generated directly from bis-1,3-diynes. The regioselectivity is profoundly influenced by not only the nature of nucleophiles but also the substituents on the arynes, which is the consequence of both the unfavorable steric interaction between the incoming nucleophile and the nearby substituent and the inherent electronic bias induced by different substituents on the arynes.

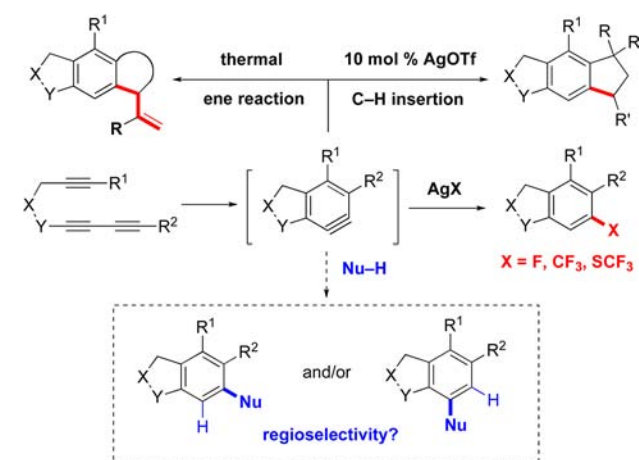


A variety of new addition reactions of arynes have been reported in the literature recently.¹ Although they show high reactivity toward nucleophiles due to their low-lying LUMO,² arynes have only been engaged in a relatively small number of useful reactions under traditional settings. This is mainly because of the limited availability of suitably functionalized precursors and a lack of efficiency in consumption of the resultant aryne intermediates. The development of protocols relying on the fluoride-induced 1,2-elimination of 1-trimethylsilyl-2-aryl triflate has significantly relieved these limitations.³ Alternatively, cycloaddition-based formation of arynes has emerged in the investigations by Ueda,⁴ and Johnson,⁵ which was further extended by Hoyer as the hexadehydro Diels–Alder reaction.⁶

Recently, we also took advantage of the hexadehydro Diels–Alder reaction of bis-1,3-diynes to generate arynes⁷ and used them for an intramolecular ene reaction^{7b,8} to generate various benzo-fused carbo- and heterocyclic products (Scheme 1). We also achieved alkane C–H functionalization by using these aryne species in the presence of silver salts (AgOTf or AgSbF₆) as catalysts.^{7a} Employing stoichiometric amounts of silver-bound nucleophiles, such as AgBF₄, AgCF₃, and AgSCF₃, we were able to promote the addition of nontraditional nucleophiles such as fluoride, the trifluoromethyl anion, and trifluoromethylthiolate with these arynes.^{7c,9} In addition to the intramolecular ene and C–H insertion reactions, excellent regioselectivity in fluorination was observed regardless of the substituent on the aryne intermediates; yet, trifluoromethylation and trifluoromethylthiolation showed strong substituent dependency.

To elucidate the factors dictating the observed regioselectivity, we further examined three classes of arynes (**1**, **3**, and **4**) containing different substituents using oxygen- and nitrogen-based nucleophiles.^{6a,10} Herein we report general regioselectivity trends of nucleophile additions that can be controlled not

Scheme 1. Reactions of an Aryne with and without Catalyst



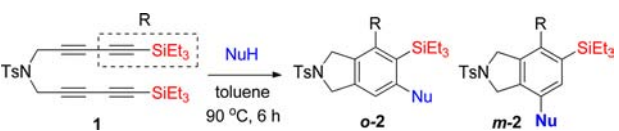
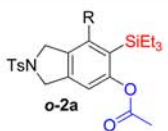


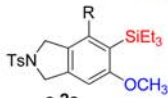

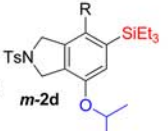





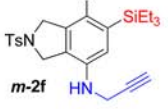

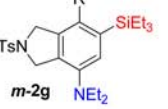


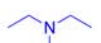

only by the steric and electronic factors on the arynes but also by the nature of the involved nucleophiles.

First, we examined a representative substrate **1** that contains a triethylsilyl group as the regiochemistry-controlling element (Table 1). Carboxylic acids such as acetic acid and propionic acid afforded **o-2a** and **o-2b** as single isomers devoid of **m-2a** and **m-2b** in 86 and 65% yield (entries 1 and 2). For the addition of alcohols, sterically undemanding methanol (MeOH) afforded **o-2c** in 84% yield (entries 3), while isopropanol provided a mixture of **o-2d** and **m-2d** in 59% yield with a 3.9:1 ratio (entry 4). The reduced selectivity with isopropanol may be the consequence of an increased steric interaction between the silyl group and the isopropyl group.¹¹

Received: August 1, 2013

Published: December 6, 2013

Table 1. Regioselectivity in Addition of Oxygen- and Nitrogen-Based Nucleophiles to Arynes Containing a Silyl Substituent

			
entry	NuH	products	yield (%) ^a
1	CH ₃ CO ₂ H		86
2			65
3	CH ₃ OH		84
4	(CH ₃) ₂ CHOH	 3.9:1 	59 ^{b,c}
5		 1:2.8 	88
6		 1:1.8 	70
7			90
8			71
9			80

^aIsolated yield after SiO₂ chromatography (same yield with silver catalyst). ^bThe low yield is caused by the formation of hydrogen adduct (ref 11). ^cNo addition product with *t*-BuOH.

While the reaction with primary amines provided mixtures of *o*-2e/*m*-2e (88%, 1:2.8, entry 5) and *o*-2f/*m*-2f (70%, 1:1.8, entry 6), those with secondary and tertiary amines afforded single isomers *m*-2g and *m*-2h in 90, 71, and 80% yield, respectively (entries 7–9). It is worthwhile to note that the addition of triethylamine afforded product *m*-2g (entry 9),

which is the same product of the diethylamine adduct (entry 7). The formation of *m*-2g from triethylamine and an aryne intermediate should involve the formation of a putative zwitterionic intermediate as shown followed by its disproportionation to the product and a molecule of ethylene. Because of the multistep nature of the process, the yield of this reaction is slightly lower (80 vs 90%) than that from the simple addition of diethylamine. In addition, the regioselectivity of the addition of amines to the silyl group containing aryne favorably generating *m*-2g and *m*-2h is in contrast with that of silylbenzynes reported by Akai and co-workers.¹²

Considering the strong directing effect of the triethylsilyl substituent demonstrated by bis-1,3-diyne 1 in Table 1, we examined the regioselectivity of the reactions with bis-1,3-diyne 3 and 4, where the silyl group of 1 is replaced with a butyl group, and the position of the NTs group is also reversed in 4 (Table 2). For the reactions of 3, with oxygen- and nitrogen-based nucleophiles, mixtures of products *o*-5a–d and *m*-5a–d were obtained with good to marginal selectivities in the range 10:1–1.4:1 (entries 1–4). The selectivity trend in these reactions is the consequence of the similar electronic and steric environment of both the carbon centers undergoing nucleophilic addition, where on one side there is a butyl group and on the other side there is a CH₂NTs moiety. The reversal of selectivity with triethylamine is noteworthy (entry 4).

In contrast, single isomers were obtained from all the reactions of an ynamide-containing bis-1,3-diyne 4 with every nucleophile examined (entries 5–9). The addition of trifluoroethanol and silver triflate (AgOTf) followed by subsequent protonation afforded the expected *o*-6a and *o*-6b in 91 and 82% yield, respectively (entries 5 and 6). However, the addition of silver trifluoroacetate (AgOCOCF₃) to the same aryne intermediate provided only water adduct *o*-6c (entry 7). Careful examination of the crude reaction mixture indicated that the trifluoroacetate adduct was indeed formed quantitatively, but it readily hydrolyzed during purification on silica gel. Because under the current reaction format the direct addition of water could not be achieved efficiently, the trifluoroacetate formation followed by its spontaneous deacylation constitutes an alternative approach for an effective water addition to arynes.

The uniform regioselectivity of the nucleophile addition with arynes derived from bis-1,3-diyne 4 containing an ynamide tether is the consequence of a strong electronic effect of the NTs moiety, directing the addition of nucleophiles exclusively at the *meta*-position (or the *ortho*-position of the butyl).¹³

While examining unsymmetrical bis-1,3-diyne 7a, containing two different substituents on the terminal position of bis-1,3-diyne, we noticed intriguing regioselectivity in the initial hexadehydro Diels–Alder reaction (Scheme 2). Because there is no sizable electronic bias in these bis-1,3-dienes, we expected that aryne intermediates 8 and 8' should be formed in roughly equal amounts, wherein only 8 would afford the intramolecular nucleophile trapped product 9 with a maximum 50% yield. To our surprise, however, 9 was produced in 87% yield, which clearly implies that the cycloaddition step to form aryne intermediate 8 should be much more favorable than that of 8'.

In conclusion, we investigated the regioselectivity of nucleophile trapping of the arynes formed from bis-1,3-dienes that contain different electronic and steric biasing elements. The reactions of these arynes with a series of oxygen- and nitrogen-based nucleophiles reveal that the selectivity is profoundly influenced not only by the nature of nucleophiles but also by the substituents on the arynes. This is the

Table 2. Regioselectivity in Addition of Oxygen- and Nitrogen-Based Nucleophiles to Arynes Containing Butyl Substituent

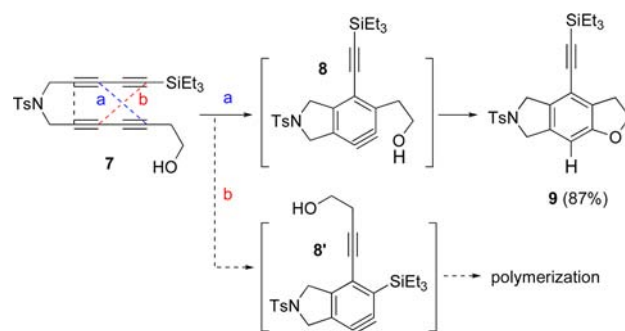
entry	diyne	NuH	products	yield (%) ^a
1	3	CH ₃ OH	 o-5a m-5a	89
		$\left[\begin{array}{c} \text{X-Y} = \\ \text{---N---C---} \\ \text{Ts H}_2 \end{array} \right]$	10:1	
2	3	CH ₃ CO ₂ H	 o-5b m-5b	88
			4.8:1	
3	3	BuNH ₂	 o-5c m-5c	95 ^b
			1.5:1	
4	3	Et ₂ NH (with NEt ₃)	 o-5d m-5d	99 (71)
			1.4:1 (1:10)	
5	4	CF ₃ CH ₂ OH	 o-6a	91
		$\left[\begin{array}{c} \text{X-Y} = \\ \text{---C---N---} \\ \text{H}_2 \text{ Ts} \end{array} \right]$		
6	4	AgOTf	 o-6b	82
7	4	AgOCOCF ₃	 o-6c	81
8	4		 o-6d	85 ^c
9	4	NEt ₃	 o-6e	84

^aIsolated yield after SiO₂ chromatography. ^bInseparable mixture of products. ^cA small amount of *meta*-adduct was observed in a 9:1 ratio.

consequence of both the unfavorable steric interaction between the incoming nucleophile and the nearby substituent as well as the inherently electronic bias induced by different substituents on the aryne core.

For silyl-substituted arynes, the addition of oxygen nucleophiles (alcohols and carboxylic acids) is predominantly dictated by the electronic effect of the silyl group which favors the *ortho*-addition (entries 1–4 in Table 1). Nitrogen nucleophiles (amines) are controlled by their steric effect, rendering the *meta*-addition as the major pathway for 1° amines

Scheme 2. Formation of Aryne Intermediates and Their Intramolecular Trapping of Nucleophiles



(entries 5 and 6 in Table 1) or an exclusive pathway for 2° and 3° amines (entries 7–9 in Table 1). For the NTs-substituted arynes, regardless of nucleophile, the addition is exclusively controlled by its electronic effect (entries 5–9 in Table 2). The regioselectivity of the nucleophile addition can be explained by the structural distortion of the aryne core caused by the respective substituents, as demonstrated by the DFT calculations of Houk and co-workers for simpler systems.¹⁴

■ ASSOCIATED CONTENT

§ Supporting Information

Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from UIC (LAS AFS) and the National Science Foundation (CHE 0955972) is greatly acknowledged. We are grateful to Mr. Furong Sun of the University of Illinois at Urbana–Champaign for high resolution mass spectrometry data.

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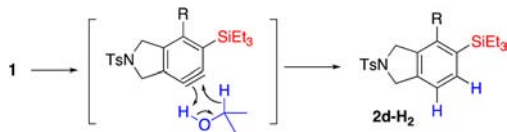
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