JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Steric Effects Compete with Aryne Distortion To Control Regioselectivities of Nucleophilic Additions to 3-Silylarynes

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Supporting Information

ABSTRACT: We report an experimental and computational study of 3-silylarynes. The addition of nucleophiles yield *ortho*-substituted products as a result of aryne distortion, but *meta*-substituted products form predominately when the nucleophile is large. Computations correctly predict the preferred site of attack observed in both nucleophilic addition and cycloaddition experiments. Nucleophilic additions to 3-*tert*-butylbenzyne, which is not significantly distorted, give *meta*-substituted products.

Despite once being a subject of controversy,[1] arynes are now a thriving area of chemical discovery.[2] Modern methods of aryne generation have led to greater control of reactivity, thus enabling the use of arynes in a host of synthetic applications.[3] Nonetheless, the control and understanding of regioselectivity in reactions of unsymmetrical arynes remains an important area of research.[2]

The aryne distortion model, reported by our laboratories in 2010,[4] shows that regioselectivity in nucleophilic additions and cycloadditions of arynes is governed by the inherent distortion present in unsymmetrical arynes and transition state distortion energies.[5] The model allows for reliable regioselectivity predictions to be made using simple computations, and has been validated for ring-fused arynes and arynes that possess neighboring inductively withdrawing substituents.[4,6] In the case of 3-methoxybenzyne,[7] the aryne is pre-distorted as suggested in Figure 1. Addition of the nucleophile occurs at the more electrophilic site, with flattening at the carbon undergoing attack, to give *meta*-substituted products.[8,9] As a means to further probe the aryne distortion model, we examined the influence of inductively donating silyl substituents on aryne regioselectivities.[10] Our experimental and computational study demonstrates that the sense of regioselectivity in silylaryne reactions is variable, but aryne distortion can play a significant role. Computations correctly predict the preferred site of attack observed in both nucleophilic addition and cycloaddition experiments.

Geometry optimization of 3-triethylsilylbenzyne was conducted using DFT methods (B3LYP/6-311+G(d,p)).[11] The silyl group severely distorts the aryne, such that the internal angles at C2 and C1 are 134° and 122°, respectively.[12] Following the aryne distortion model, nucleophilic addition at C2, the more electropositive terminus of the aryne, is favored electronically; however, *meta* substitution should be preferred based on steric factors. Only few examples of silylaryne reactions have been reported, but it should be noted that

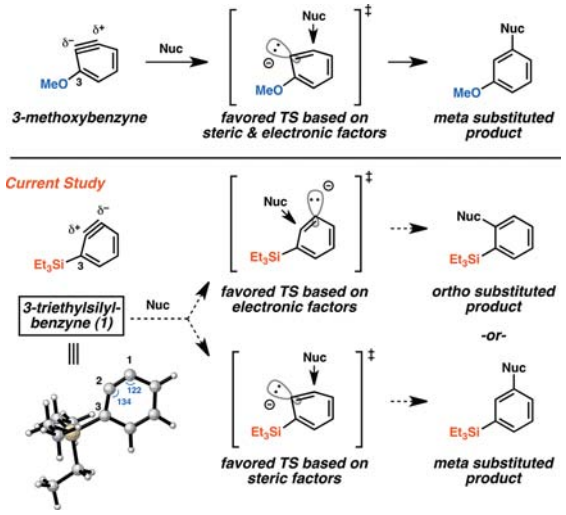
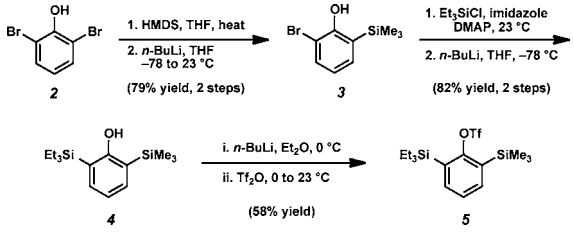


Figure 1. Influence of 3-methoxy and 3-silyl substituents on aryne regioselectivity.

additions of organolithium reagents to silylarynes occur with *meta*-selectivity,[10a−c] whereas additions of amines are primarily *ortho*-selective.[10g,13]

With the aim of studying regioselectivity patterns of silylarynes in a variety of nucleophilic addition and cycloaddition reactions, we prepared bis(silyl)triflate **5**, which was envisioned to be a suitable precursor to triethylsilylbenzyne **1** (Scheme 1).[14] Commercially available dibromophenol **2** was elaborated to known compound **3**[15] via a two-step procedure involving *O*-silylation followed by halogen−metal exchange-mediated *O*-to-*C* migration of the silyl substituent.[16] Next, an analogous sequence was employed to install the triethylsilyl

Scheme 1



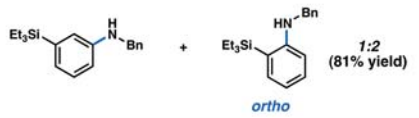
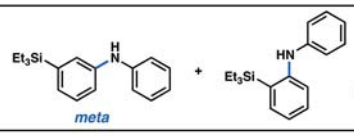
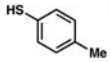
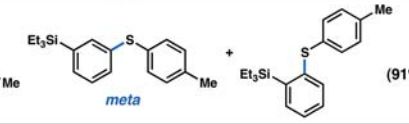
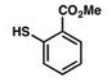
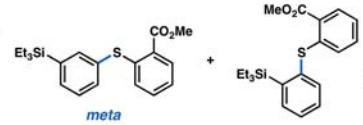
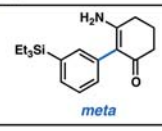
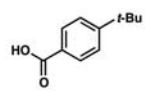
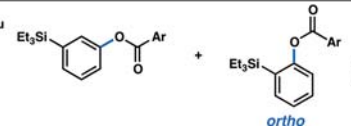
Received: July 10, 2012
Published: August 9, 2012

   dx.doi.org/10.1021/ja306723r | J. Am. Chem. Soc. 2012, 134, 13966−13969

group, thus providing **4**.[17] Triflation of **4** afforded the desired bis(silyl)triflate **5**.[18]

A comparative regioselectivity study was performed, where triethylsilylbenzyne **1** was generated in situ upon treatment of **5** with CsF in acetonitrile, in the presence of a variety of nucleophiles (Table 1).[19,20] Upon trapping of the aryne with

Table 1. Nucleophilic Additions to Triethylsilylbenzyne 1[a]

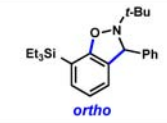
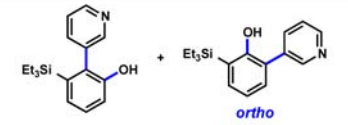
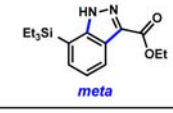
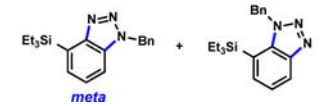
entry	trapping agent	product(s)	ratio (yield[b])
1	H_2N–Bn		1:2 (81% yield)
2			2:1 (99% yield)
3			4:1 (91% yield)
4			10:1 (77% yield)
5			(52% yield)
6			1:3 (53% yield)

[a]See Supporting Information for experimental details. [b]Yields determined by ^{1}H NMR analysis with external standard.

benzylamine, reaction occurred to give a 1:2 ratio of products favoring *ortho* substitution (entry 1). However, when aniline was employed, the regioselective preference switched to favor *meta* addition (entry 2), which is consistent with the observations reported by Akai.[10g] Other trapping agents that have not been used with silylbenzynes previously were also tested. Thiophenol based reagents also gave products of *meta* substitution predominantly (entries 3 and 4); in the later case, selectivity was 10:1. An enamine reagent, which functions as a carbon nucleophile, exclusively yielded the *meta*-substituted product (entry 5). Use of 4-*t*-Bu-benzoic acid, however, gave 1:3 selectivity, favoring *ortho* addition (entry 6).

Triethysilylaryne **1** was next evaluated in a series of cycloaddition reactions. As shown in Table 2, the selectivity patterns varied as a function of the trapping agent employed. A nitrone cycloaddition gave a 73% yield of a single regioisomer of product (entry 1), suggestive of *ortho* attack, as seen in previous nitrone cycloadditions of silylarynes.[10d] Trapping of the silylaryne with pyridine *N*-oxide[21] also proceeded with a significant preference for *ortho* addition (entry 2). Conversely, cycloaddition with a diazo ester[22] exclusively afforded the product resulting from initial *meta* attack (entry 3). Reaction with benzyl azide[23] gave a 6:1 ratio of products, favoring initial *meta* addition (entry 4). Despite variations in the initial site of

Table 2. Cycloaddition Reactions with Triethylsilylbenzyne 1[a]

entry	trapping agent	product(s)	ratio (yield[b])
1			(73% yield)
2			1:9 (60% yield)
3			(65% yield)
4	N_3–Bn		6:1 (85% yield)

[a]See Supporting Information for experimental details. [b]Yields determined by ^{1}H NMR analysis with external standard.

nucleophilic attack, the major regioisomer observed in each cycloaddition is presumably that which arises from the least sterically encumbered transition state.

These results demonstrate that nucleophilic additions and cycloadditions of 3-triethylsilylbenzyne do occur with significant regioselectivities, but the orientation of attack varies as a function of the trapping agent. DFT calculations were carried out to provide additional insights into the origins of these observations. All geometry optimizations were performed using Gaussian 09[24] using the B3LYP density functional and the 6-311+G(d,p) basis set. A frequency calculation was performed on all reactants and transition states to verify minima and first order saddle points, respectively, and an ultra fine grid was used for all numerical integration. Unscaled zero-point energies were used, and Truhlar's anharmonic correction was applied to frequencies that are less than 100 cm^{-1}.[25] Trimethylsilylbenzyne was used as a model for triethylsilylbenzyne.[26]

Figure 2 shows optimized transition states for the nucleophilic additions of benzylamine and aniline to 3-trimethylsilylbenzyne. The barrier for attack of benzylamine at C2 is predicted to be 0.7 kcal/mol lower than for attack at C1. Addition at C2 is favored because the aryne's pre-distorted bond angles favor nucleophilic attack at the flatter, more electrophilic carbon, which is C2 in this case. During the attack, the aryne has to undergo geometric changes, including an increase of the CCC angle at the site of attack and compression of the other terminus of the aryne. The terminus with the larger angle, like C2 in triethylsilylbenzyne, will be attacked preferentially. In contrast, for aniline, attack is predicted to be favored at C1 rather than C2 by 3.7 kcal/mol. Because aniline is a more bulky nucleophile, it suffers from more steric hindrance with the silyl group of the benzyne. As shown in Figure 2, the H–H distance of the two closest hydrogens in the C2 attack of aniline are very close at 2.13 Å. In the case of benzylamine the closest H–H distance is 2.52 Å. This steric interaction is overriding the aryne distortion preference for attack at C2. Although the magnitude of selectivity is exaggerated, computations correctly predict experimental regioselectivities.[27]

dx.doi.org/10.1021/ja306723r | J. Am. Chem. Soc. 2012, 134, 13966–13969

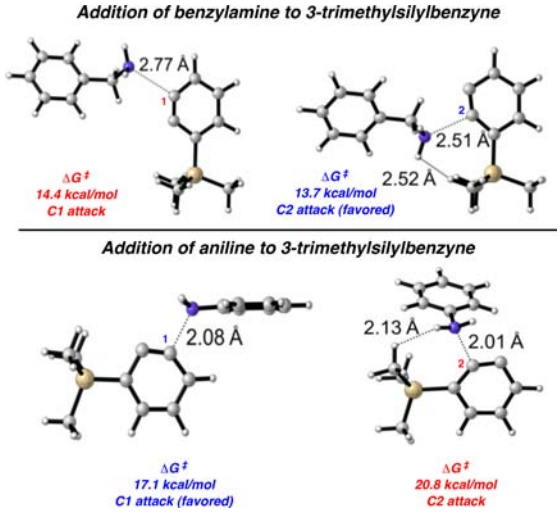


Figure 2. Transition states for nucleophilic additions of benzylamine and aniline to 3-trimethylsilylbenzyne.

The cycloaddition of methyl azide with 3-trimethylsilylbenzyne was also examined computationally, with methyl azide serving as a model for benzyl azide. Transition states are shown in Figure 3. C1 attack is favored, which is consistent with

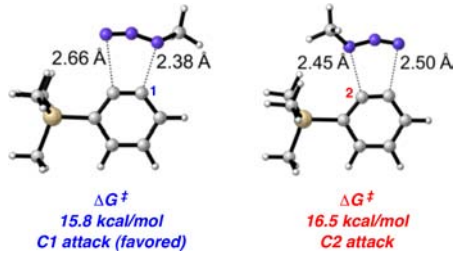


Figure 3. Cycloaddition of methyl azide with 3-trimethylsilylbenzyne.

experimental results, by 0.7 kcal/mol. Aryne distortion would favor attack of the nucleophilic substituted terminus at C2, but steric hindrance overrides this electronic preference leading to preferential attack at C1.

For comparison, we studied 3-*tert*-butylbenzyne (**6**),[28] which is sterically similar to 3-triethylsilylbenzyne (**1**), but varies electronically (Figure 4). The geometry-optimized structure of

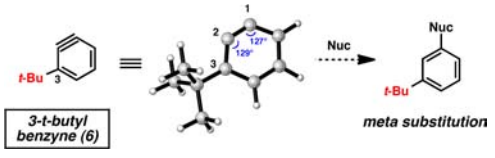


Figure 4. Geometry-optimized structure of 3-*tert*-butylbenzyne (**6**) and predicted regioselectivity.

6 (B3LYP/6-311+G(d,p)) revealed internal angles of 129° and 127° at C2 and C1, respectively. Given the minimal distortion present, **6** was predicted to undergo sterically guided attack at C1 to give *meta*-substituted products.

A silyl triflate precursor to aryne **6** was prepared from *o*-*t*-Bu-phenol and examined in nucleophilic addition reactions (Table 3).[29] When aniline was used as the trapping agent, formation of the *meta*-substituted product was preferred (entry 1), similar to the trend observed in the reaction of 3-triethylsilylbenzyne.

Table 3. Nucleophilic Additions to 3-*tert*-Butylbenzyne (6)[a]

entry	trapping agent	product[b]	ratio (yield[c])
1	H_2N	*meta*	(66% yield)
2	H_2N–Bn	*meta*	(61% yield)
3		*meta*	(50% yield)

[a]See Supporting Information for experimental details. [b]*Ortho*-substituted products were not observed. [c]Yields determined by ^{1}H NMR analysis with external standard.

Benzylamine and 4-*t*-Bu-benzoic acid were also tested with aryne **6**. In contrast to the outcome seen in reactions of **1**, only *meta* substitution was observed (entries 2 and 3). These results support the notion that aryne distortion plays a significant role in reactions of 3-silylaryne **1**. Quantum chemical calculations were performed for the reaction of **6** with aniline and benzylamine, and in both cases the attack at C1 was strongly favored.[29]

The effects of the inductively donating silyl group on arynes have been studied both experimentally and computationally. It has been shown that if the incoming nucleophile is not bulky, the aryne distortion model holds true and the flatter terminus of the aryne is the site of attack. If however, there is sufficient steric bulk on the nucleophile, then attack on the more accessible carbon of the aryne is favored. When the substituent adjacent to the aryne is an alkyl group, steric effects dominate, since there is no significant differential distortion of the aryne bond angles.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and compound characterization data. 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

The authors are grateful to the NIH-NIGMS (R01 GM090007), Boehringer Ingelheim, DuPont, Eli Lilly, Amgen, AstraZeneca, the Foote Fellowship (S.M.B.), the Stauffer Charitable Trust (S.M.B.), and the University of California, Los Angeles, for financial support. We thank Joshua Melamed (UCLA) for experimental assistance, and Dr. John Greaves (UC Irvine) for mass spectra. We are grateful to the National Science Foundation (CHE-0548209 to K.N.H.) for financial support. Computer time was provided in part by the UCLA Institute for Digital Research and Education (IDRE) and the XSEDE supercomputers Trestles and Gordon at San Diego Supercomputer Center. These studies were supported by shared instrumentation grants from the NSF (CHE-1048804)

and the National Center for Research Resources (S10RR025631).

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(11) The trimethylsilyl derivative was studied initially, but competitive product desilylation complicated regioselectivity analysis.
(12) For ring-fused arynes or those that possess inductively withdrawing groups, angle differences of >4° between the two aryne termini generally give synthetically useful regioselectivities, regardless of the trapping agent employed.
(13) The *ortho* selectivity for the addition of amines has previously been rationalized by the presumed formation of a pentavalent fluorosilicate, which in turn, perturbs the aryne electronically; see ref 10g.
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(27) This observation is consistent with previous studies of the aryne distortion model; see reference 4a for discussion.
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