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Regioselective Reactions of Highly Substituted Arynes

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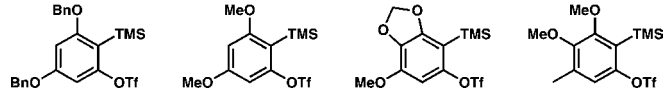
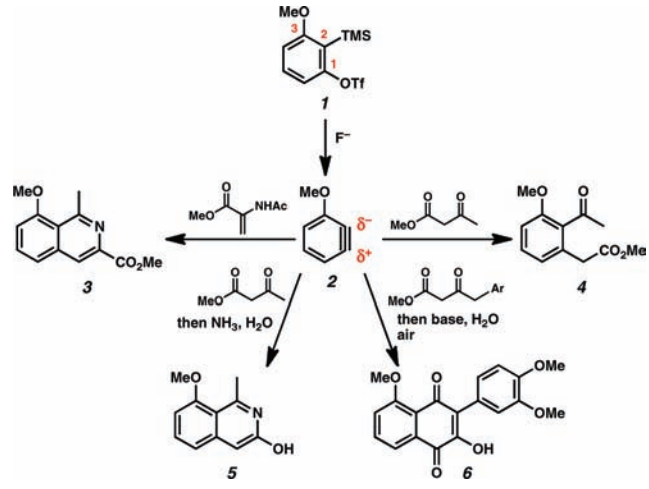
ABSTRACT



The fully regioselective reactivity of four new highly substituted silyl aryl triflate aryne precursors in aryne acyl-alkylation, acyl-alkylation/condensation, and heteroannulation reactions is reported. The application of these more complex arynes provides access to diverse natural product scaffolds and obviates late-stage functionalization of aromatic rings.

It has been well established that substituted arynes undergo nucleophilic attack with levels of regioselectivity dependent on the identity of substituents and their locations relative to the reactive aryne triple bond.[1] In our own investigations, we have observed fully regioselective acyl-alkylation[2] and aryne heteroannulation[3] reactions with the aryne (**2**) generated in situ from a 3-methoxy-substituted silyl aryl triflate (**1**) (Scheme 1). Each of these products (**3**−**6**) stems presumably from initial attack at C(1) of the aryne (**2**), which suggests that the *o*-methoxy substituent electronically polarizes the triple bond and sterically shields the adjacent atom to favor this reactivity. More recently, we have been able to exploit this selectivity in aryne acyl-alkylation/condensation sequences to produce either substituted hydroxynaphthoquinones (**6**) or hydroxyisoquinolines (**5**).[4] These observations led us to investigate whether more highly functionalized silyl aryl triflates would also exhibit the predictable regioselectivity seen for precursor **1**.

Scheme 1. Regioselective Reactions of 3-Methoxybenzyne



Specifically, we chose to examine whether unsymmetrically substituted polyalkyoxy silyl aryl triflates would react

(1) Bunnett, J. F.; Happer, D. A. R.; Patsch, M.; Pyun, C.; Takayama, H. *J. Am. Chem. Soc.* **1966**, *88*, 5250–5254. (b) Biehl, E. R.; Nieh, E.; Li, H.-M.; Hong, C.-I. *J. Org. Chem.* **1969**, *34*, 500–505. (c) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502–528. (d) Johnson, W. T. G.; Cramer, C. J. *J. Am. Chem. Soc.* **2001**, *123*, 923–928. (e) Biehl, E. R.; Nieh, E.; Hsu, K. C. *J. Org. Chem.* **1969**, *34*, 3595–3599. (f) Johnson, W. T. G.; Cramer, C. J. *J. Phys. Org. Chem.* **2001**, *14*, 597–603. (g) Cheong, P. H.-Y.; Paton, R. S.; Bronner, S. M.; Im, G.-Y. J.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 1267–1269.

(2) (a) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340–5341. (b) Ebner, D. C.; Tambar, U. K.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 161–171.

(3) Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558–1559.

(4) Allan, K. M.; Hong, B. D.; Stoltz, B. M. *Org. Biomol. Chem.* **2009**, *7*, 4960–4964.

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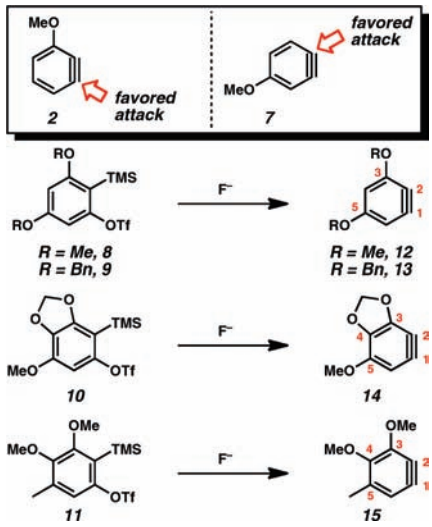
regioselectively. Similarly to the 3-methoxy aryne (**2**), 4-methoxy aryne **7** also reacts in a regioselective manner at C(1),[5] although more modestly than aryne **2** (Scheme 2). On the basis of these data, we chose to examine two silyl aryl triflates (**8** and **9**) bearing alkoxy groups at both C(3) and C(5), in which it is possible for the two alkoxy substitutents to favor opposing sites of nucleophilic attack upon the aryne triple bond (**12** and **13**). Investigation of the reactivity of precursors **8** and **9** would establish whether the influence exerted by the C(3) substituent can override that of the C(5) alkoxy group. Two additional silyl aryl triflates (**10** and **11**) we have targeted feature methoxy groups at C(3) and C(4) of the arynes (**14** and **15**), offering the potential for enhanced selectivity due to cooperative electronic polarization of the triple bond. Furthermore, precursors **10** and **11** incorporate additional substitution at C(5); to the best of our knowledge, arynes **14** and **15** are the first examples of trisubstituted arynes derived from silyl aryl triflate precursors.[6]

Scheme 2. Targeted Polyalkoxy Arynes



On the basis of the observation that aryne adducts derived from the 3-methoxy silyl aryl triflate (**1**) have been employed in the context of total synthesis (Figure 1, **16**),[7] we believe that these more highly substituted nonsymmetrical precursors (**8**−**11**) will provide valuable entry points into more complex natural products (e.g., **17**−**19**) if they too react in a regioselective manner. In general, the use of aryne-based methods enables the convergent construction of functionalized arenes, thereby circumventing the difficulties associated with traditional late-stage elaboration of embedded aromatic rings.

As a demonstration of the advantages of this strategy, we report the synthesis and regioselective reactions of four novel silyl aryl triflates (**8**−**11**) and the application of one of these precursors to the synthesis of a simple hydroxynaphthoquinone natural product. In fact, these particular aromatic substitution motifs (e.g., **12**−**15**) were targeted for their prevalence in classes of natural products that possess both diverse structures and significant biological activity (**17**−**19**).

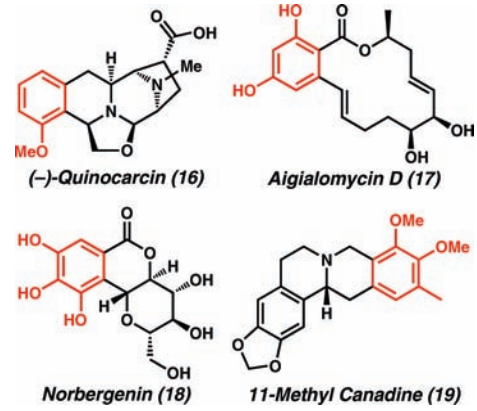
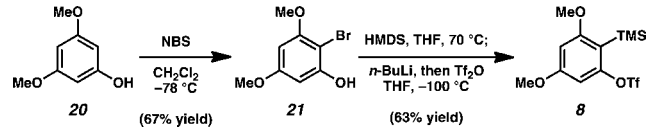


Figure 1. Natural products containing highly oxygenated arenes.

The first aryne precursor we targeted was a protected resorcinylic silyl aryl triflate (**8**) (Scheme 3). Preparation of dimethoxy silyl aryl triflate **8** began with bromination of commercially available 3,5-dimethoxyphenol (**20**) at low temperature to form bromophenol **21**. This compound was then converted to the silyl aryl triflate (**8**) by a known one-pot procedure involving silylation of the phenol, lithium−halogen exchange, silyl group migration, and triflation.[8]

Scheme 3. Preparation of Silyl Aryl Triflate **8**



Although dimethoxy silyl aryl triflate **8** contains functionality present in several natural products, removal of the methyl groups would be required to access a large number these targets.[9] To avoid the potentially harsh Lewis acidic conditions commonly used to cleave the methyl groups (e.g., BCl_3),[10] we designed a dibenzyl variant of precursor **8** (Scheme 4). Beginning with phloroglucinol (**22**), a sequence including monosilylation, dibenzylation, and desilylation generated phenol **23**, which was subsequently brominated

(5) For examples of regioselective reactions of aryne **7**, see: (a) Yoshida, H.; Morishita, T.; Ohshita, J. *Org. Lett.* **2008**, *10*, 3845–3847. (b) Ni, C.; Zhang, L.; Hu, J. *J. Org. Chem.* **2008**, *73*, 5699–5713. (c) Liu, Z.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 13112–13113.

(6) Trisubstituted arynes derived from precursors other than silyl aryl triflates are known.

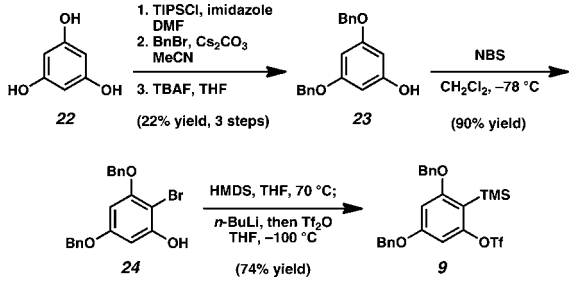
(7) Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 17270–17271.

(8) Peña, D.; Cobas, A.; Pérez, D.; Guitián, E. *Synthesis* **2002**, 1454–1458.

(9) *Macrolide Antibiotics: Chemistry, Biology, and Practice*, 2nd ed.; Omura, S., Ed.; Academic Press: San Diego, CA, 2002.

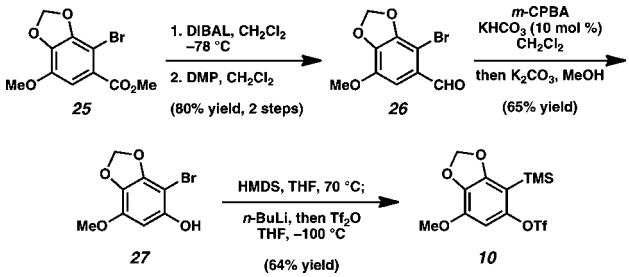
to produce bromophenol **24**. Bromophenol **24** was then converted to silyl aryl triflate **9** as before.

Scheme 4. Preparation of Silyl Aryl Triflate **9**



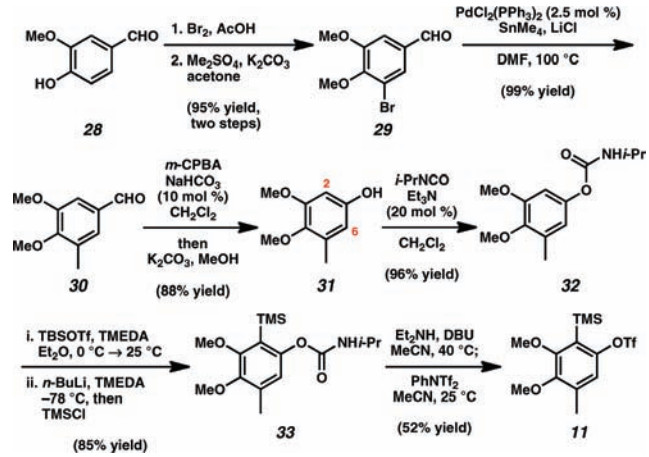
Following our preparation of silyl aryl triflates **8** and **9**, we progressed to more highly substituted variants. Specifically, we targeted a trioxygenated aryne derived from silyl aryl triflate **10** (Scheme 5). Beginning with brominated methyl gallate derivative **25**,[11] reduction with DIBAL followed by Dess−Martin oxidation provided aldehyde **26** in excellent yield. Baeyer−Villiger oxidation with *m*-CPBA and basic methanolysis of the resulting formate ester produced bromophenol **27**, which was readily converted to silyl aryl triflate **10**.

Scheme 5. Preparation of Silyl Aryl Triflate **10**



We next turned our attention to the preparation of silyl aryl triflate **11** because of the prevalence of its substitution motif in several bioactive natural products. We began with a regioselective bromination of vanillin (**28**) to provide exclusively the 5-bromo product, which was methylated to produce bromo dimethoxy benzaldehyde **29** (Scheme 6).[12] Next, Stille coupling of the bromoarene (**29**) with tetramethyltin enabled the introduction of the 5-methyl substituent to generate arene **30**.[13] Further elaboration of this intermediate via one-pot Baeyer−Villiger oxidation and cleavage of the resultant formate ester yielded intermediate phenol **31**. In order to selectively elaborate phenol **31**, we turned to a recently disclosed 3-step procedure for the general synthesis of *o*-silyl aryl triflates by Garg, et al.[14] Analysis of this approach indicated that conversion of the phenol to a carbamate might facilitate silylation at C(2) over C(6). Application of this sequence to our intermediate (**31**) allowed the direct *ortho*-silylation of carbamate **32** to produce the 2-silyl carbamate (**33**) exclusively. Subsequent cleavage of the carbamate and triflation of the resulting phenol furnished the desired aryne precursor (**11**) in 5 steps from known compounds.

Scheme 6. Preparation of Silyl Aryl Triflate **11** by Directed *ortho*-Lithiation of Phenol Derivative **32**

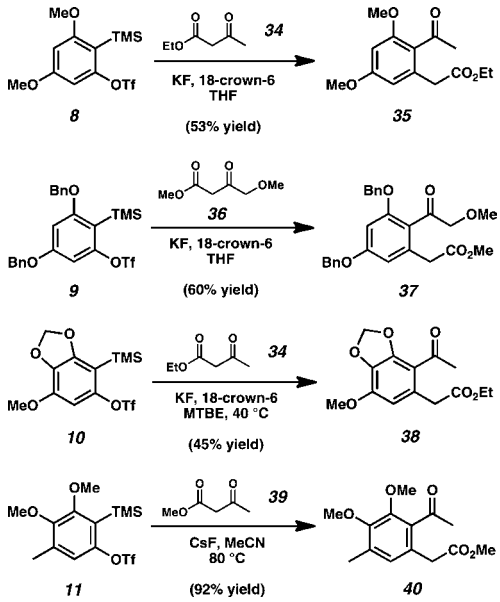


Following preparation of silyl aryl triflates **8**−**11**, we examined their reactivities in acyl-alkylation reactions with various β-ketoesters (**34**, **36**, and **39**) (Scheme 7).[15] To our delight, in each of these reactions only a single insertion product was observed. For silyl aryl triflates **8** and **9**, the closer *o*-alkoxy substituent completely overrides any influence of the distal alkoxy group. In the case of acyl-alkylation of precursors **10** and **11**, slightly modified reaction conditions varying solvent and fluoride sources were required to generate the desired products. The presence of methoxy groups at both the *ortho* and *meta* positions of the arynes derived from **10** and **11** potentially influences the regioselectivity of their reactions in a cooperative manner.[2]

Furthermore, we were able to verify the selectivity for arene **37** in the acyl-alkylation of silyl aryl triflate **9** with β-ketoester **36** by its conversion to a naturally occurring hydroxynaphthoquinone (**42**),[16] previously isolated from a species of *Cercospora* (Scheme 8). Cyclization and oxidation of ketoester **37** under basic conditions yielded quinone **41**.[4,17]

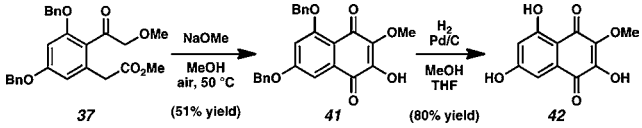
(10) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 4th ed.; Wiley-Interscience: New York, 2006.
(11) Alam, A.; Takaguchi, T.; Ito, H.; Yoshida, T.; Tsuboi, S. *Tetrahedron* **2005**, *61*, 1909–1918.
(12) Rao, D. V.; Stuber, F. A. *Synthesis* **1983**, 308.
(13) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202–9203.
(14) Bronner, S. M.; Garg, N. K. *J. Org. Chem.* **2009**, *74*, 8842–8843.
(15) No alternative substrate- or aryne-derived products were isolated or observed in each of the aryne reactions reported herein.
(16) Assante, G.; Locci, R.; Camarda, L.; Merlini, L.; Nasini, G. *Phytochemistry* **1977**, *16*, 243–247.
(17) Bentley, H. R.; Dawson, W.; Spring, F. S. *J. Chem. Soc.* **1952**, 1763–1768.

Scheme 7. Acyl-alkylation Reactions of Polyalkoxy Silyl Aryl Triflates **8**−**11**



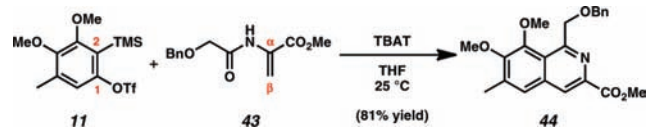
Subsequent debenzylation produced hydroxynaphthoquinone **42**, thus confirming the structure of arene **37**.

Scheme 8. Conversion of Ketoester **37** to *Cercospora* Isolate **42**



In addition to acyl-alkylation, exposure of silyl aryl triflate **11** to tetra-*n*-butylammonium difluorotriphenylsilicate (TBAT) in the presence of *N*-acyl enamide **43** produced a single isomer of the product isoquinoline (**44**) in good yield (Scheme 9).[3] Indeed, **44** corresponds to the isoquinoline produced from initial C(β) nucleophilic attack of enamide **43** at C(1) of the aryne derived from precursor **11**.

Scheme 9. Aryne Annulation of Enamide **43** with Silyl Aryl Triflate **11** To Yield Isoquinoline **44**



We have successfully completed concise syntheses of four unique, highly substituted aryne precursors and demonstrated their reactivity in a number of aryne methodologies. The regioselectivity displayed in these reactions underscores the importance of methods that facilitate the direct and predictable introduction of highly substituted arene components. In conjunction with their ability to form multiple C−C and C−N bonds in a single transformation, these arynes facilitate convergent approaches to several natural product classes.

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Supporting Information Available: Experimental details and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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