Regioselective Reactions of Highly Substituted Arynes

Pamela M. Tadross, Christopher D. Gilmore, Pradeep Bugga, Scott C. Virgil, and Brian M. Stoltz*

The Arnold and Mabel Beckman Laboratories of Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125
stoltz@caltech.edu

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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-alkylation2 and aryne heteroannulation3 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.

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

Scheme 1. Regioselective Reactions of 3-Methoxybenzyne

regioselectively. Similarly to the 3-methoxy aryne (2), 4-methoxy aryne 7 also reacts in a regioselective manner at C(1), 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 substituents 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.

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).

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), 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.

The first aryne precursor we targeted was a protected resorcylic 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. 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 of these targets. To avoid the potentially harsh Lewis acidic conditions commonly used to cleave the methyl groups (e.g., BCl₃), 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.

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


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

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.

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 produced bromophenol 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 car bamate might facilitate silylation at C(2) over C(6). Application of this sequence to our intermediate (31) allowed the direct ortho-silylation of car bamate 32 to produce the 2-silyl car bamate (33) exclusively. Subsequent cleavage of the car bamate and triflation of the resulting phenol furnished the desired aryne precursor (11) in 5 steps from known compounds.

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

(15) No alternative substrate- or aryne-derived products were isolated or observed in each of the aryne reactions reported herein.
Subsequent debenzylation produced hydroxynaphthoquinone 42, thus confirming the structure of arene 37.

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). 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.

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.