COMMUNICATION

A Simple Hückel Model-Driven Strategy to Overcome Electronic Barriers to Retro-Brook Silylation Relevant to Aryne and Bisaryne Precursor Synthesis

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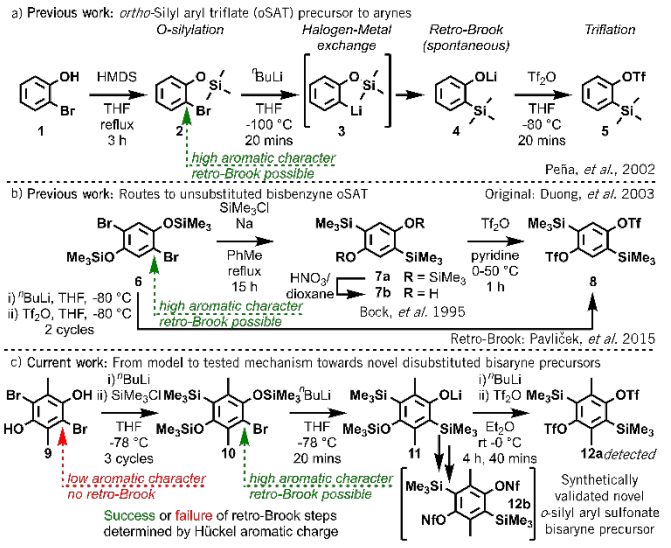
***Ortho*-silylaryl triflate precursors (oSATs) have been responsible for many recent advances in aryne chemistry and are most commonly accessed from the corresponding 2-bromophenol. A retro-Brook *O*- to *C*-silyl transfer is a key step in this synthesis but not all aromatic species are amenable to the transformation, with no functionalized bisbenzyne oSATs reported. Simple Hückel models are presented which show that the calculated aromaticity at the brominated position is an accurate predictor of successful retro-Brook reaction; validated synthetically by a new success and a predicted failure. From this, the synthesis of a novel difunctionalized bisaryne precursor has been tested, requiring different approaches to install the two *C*-silyl groups. The first successful use of a disubstituted *o*-silylaryl sulfonate bisbenzyne precursor in Diels-Alder reactions is then shown.**

Arynes are a class of highly reactive electron-deficient intermediates derived from an arene or heteroarene with two vacant positions, usually *ortho* to each other. The reactions of arynes generally involve the introduction or extension of a π-system and have been extensively reviewed.[1] These transformations are particularly useful in the pharmaceuticals industry and in the production of π-extended polyaromatic hydrocarbon (PAH) materials for fluorescent sensing, energy generation and other related applications.[1a,1c]

Classical methods of aryne generation typically required the use of strong bases, sodium metal, pyrophoric *tert*-butyllithium or potentially explosive *ortho*-diazocarboxylate precursors, as well as more extreme temperatures. In contrast, *ortho*-silylaryl triflate precursors (oSATs) operate under milder reaction conditions and possess a more attractive safety profile,[2a] which has led to their widespread uptake.[1,2b-d] Originally developed by Kobayashi in 1983,[3a] *o*-(trimethylsilyl)phenyl triflate **5** reliably affords benzyne upon treatment with either fluoride or carbonate base.[3b] In 2002 Peña *et al*. improved the synthesis of oSAT **5** through the initial silylation of 2-bromophenol **1** with hexamethyldisilazane (HMDS) (Scheme 1a).[4] Subsequent halogen-metal exchange then triggered instantaneous retro-Brook *O*- to *C*-silyl transfer (**3** to **4**) prior to triflation.

Whilst this synthetic strategy permits access to many aryne and heteroaryne precursors[6] with wide functional group tolerance, it is not universal. In some instances, longer routes are needed, such as Kobayashi's original approach[3a] via *C,O*-disilylation, *O*-desilylation, then triflation.[7] This method was used by Duong in 2003 to first produce 1,4-bisbenzyne oSAT precursor **8**[5b] before the successful retro-Brook optimization by Pavliček *et al.* in 2015 (Scheme 1b).[5c] 1,4-Bisbenzynes from **8** have appeared in around 15 papers,[5,8] as well as a recent trisaryne oSAT from its triphenylene trimer,[5d] yet no examples of oSAT bisbenzynes with additional arene substitution have been developed.



Scheme 1 – a) Synthesis of oSAT benzyne precursor **5** from 2-bromophenol **1** (Peña *et al.*)[4] b) Approaches to unsubstituted bisbenzyne oSAT precursor **8** from Bock *et al.*,[5a] Duong *et al.*[5b] and Pavliček *et al.*[5c] c) This work: novel route towards challenging disubstituted bisbenzyne precursors based on simple Hückel aromaticity models.

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The different methods of formation of bis/trisarynes have been reviewed by Shi, *et al.* and usually require more forceful conditions than oSATs, thus limiting functional group tolerance.[1d] This presents unrealized potential for the rapid generation of functionalized PAHs from bisbenzyne precursors. In this work, we demonstrate that an *electronic barrier* is responsible for the failure of the retro-Brook step during the formation of certain oSATs and that a fast and accessible Hückel calculation provides a reliable indication of success. We then validate this model by experimentally confirming three predicted outcomes: 1) a successful new approach to a known benzyne oSAT precursor; 2) the failure of the key step towards a 9,10-phenanthryne oSAT precursor;[9] and 3) the development of a synthetic route to a novel difunctionalized bisaryne precursor **12**, wherein only one of the two *C*-silyation steps proceeds via a retro-Brook rearrangement (Scheme 1c).

We hypothesized that *o*-bromophenyl silyl ethers, such as **2**, should undergo halogen-metal exchange then retro-Brook rearrangement if an aromatic charge is present at the brominated position. To this end, Hückel aromatic charges were calculated on MM2 energy-minimized models of a wide range of bromoaryl silyl ether intermediates (**2** and **13a-q**) towards reported or potential oSAT aryne precursors (Figure 1).[10]

As a benchmark, the intermediate (**2**) towards unsubstituted benzyne oSAT **5** has an aromatic charge of +0.056 (ESI S2).[3a] The sign of the charge was not important, as 1,3-benzodioxole derivative **13a**, reported to undergo successful retro-Brook reaction,[6a] was calculated at –0.029. A range of literature examples **13c-13m**[7,11a-i] were found to possess charges comparable to benchmark **2**, with just 4,5-difluoro **13e**[11a] showing a significantly lower value (+0.005). In light of this difference, it is noteworthy that several mechanisms for halogen-metal exchange have been proposed.[12] The model predicted that 3,6-dimethoxy **13n** (–0.011) should also undergo retro-Brook rearrangement to the known aryne precursor **13z**, originally accessed via *C*-deprotonation with ^{n}BuLi and direct *C*-silylation of the 2,5-dimethoxyphenol.[11k] Pleasingly, this novel retro-Brook application proved successful (70% yield; ESI S3).

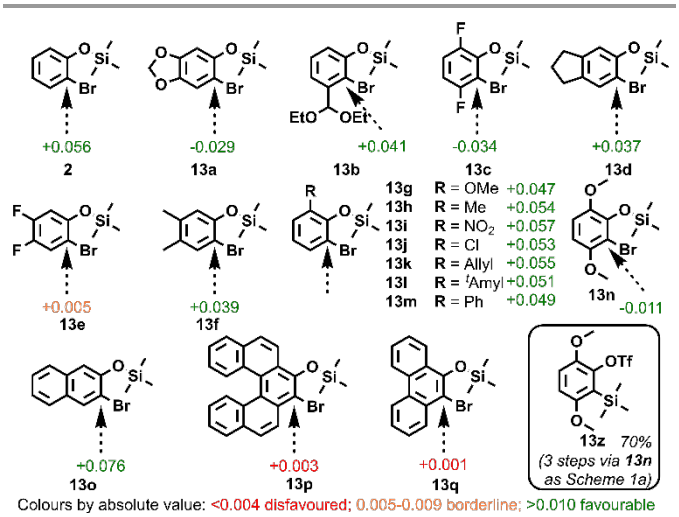


Figure 1 – Calculated Hückel aromatic charges at brominated positions in halogen-metal exchange intermediates for the synthesis of a range of aryne precursors (MM2 energy-minimized structures in PerkinElmer Chem3D).[10]

We next considered the extended aromatic precursors **13o-q**, with naphthalene derivative **13o**[11l] found to possess a high aromatic charge (+0.076). Interestingly, [5]helicene **13p**[11m] also successfully undergoes retro-Brook rearrangement but displays a significantly lower charge (+0.003). As Hückel approximations presume a planar aromatic system, twisted systems such as **13p** appear to represent a limitation of our model. By contrast, the planar 9,10-phenanthryne precursor intermediate **13q** has a near-zero aromatic charge (+0.001), which suggests the retro-Brook reaction to be disfavoured;[9] indeed, the synthesis of the corresponding phenanthryne oSAT precursor described by Peña *et al.* in 2000 did not involve this transformation.[13a] According to Clar's Rule,[14] the two peripheral rings in phenanthrene are more aromatic than the central ring, allowing the 9,10-bond to be functionalized in a manner similar to non-aromatic double bonds.[15] Even when conjugated alkenes have been exposed to conditions analogous to the retro-Brook reaction, halogen retention was preferred over halogen-metal exchange.[16]

With a view to accessing novel functionalized bisbenzyne oSATs we decided to apply our Hückel model to test the viability of a retro-Brook-based synthetic approach towards *para*-dimethylated bisxylyne oSAT **12**. As only small positive inductive effects are present, the steric encumbrance common to all pendant substituents can be tested for, while minimizing electronic effects specific to each. Investigations started by modelling the unfunctionalized bisbenzyne oSAT precursor **7** that was accessed via retro-Brook rearrangement by Pavliček *et al.*[5c] The MM2 energy-minimized models of post-*O*-silylation intermediates **13r** and **13s** confirmed that aromatic character was maintained in both brominated positions (Figure 2). Although calculations on the xylyne precursor **13t**[17] revealed suitable aromatic character (+0.026), significant deactivation was found for *O*-silylated bisxylyne prototype intermediates **13u** and **13v**. Intriguingly, if the first silyl transfer were to be forced, or silylation achieved via other means, then potential intermediates **13w** and **10** for the second stage both have a significant Hückel charge (+0.032). This would suggest that the second silyl transfer should be possible by retro-Brook. Elsewhere, sizeable aromatic charges were calculated for 1,3-diyne precursors **13x** (–0.019 and +0.015) and **13y** (–0.023), in agreement with the reported retro-Brook syntheses.[11n-o]

Encouraged by the ability of the Hückel model to predict successful retro-Brook syntheses, we experimentally investigated the two outliers: 9,10-phenanthryne and bisxylyne.

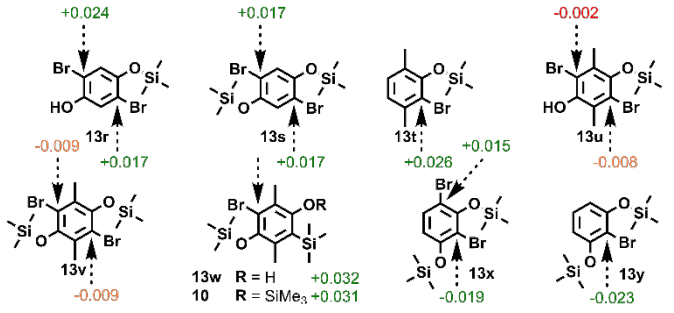
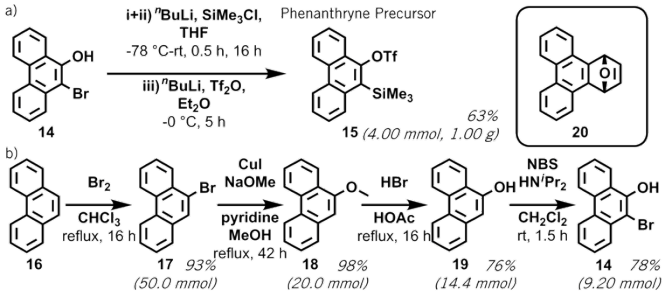


Figure 2 - Hückel aromatic charges on brominated positions in halogen-metal exchange intermediates for a range of literature bisbenzyne precursors and prototype models. (MM2 energy-minimized structures in PerkinElmer Chem3D)[10]



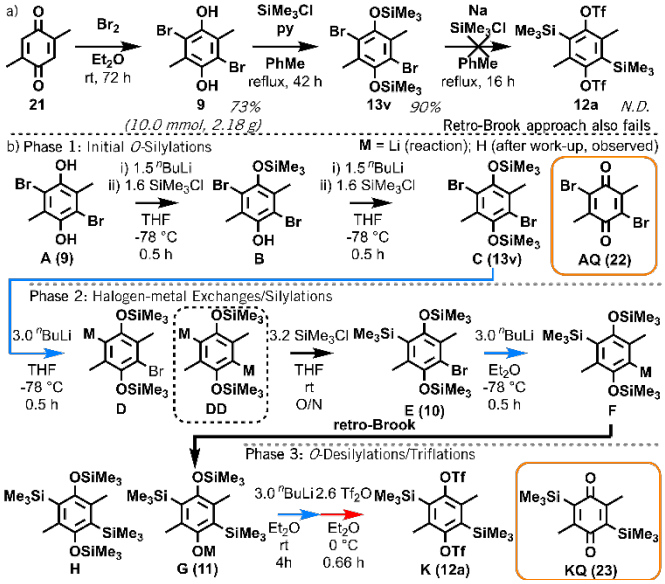
Scheme 2 - Synthesis of 9,10-Phenanthryne Precursor **15**: a) Our reported improvements in yield and scale for the final step; b) Our reported improvements in yield and scale for conversation of phenanthrene to precursor starting material 9-bromo-10-phenanthrol **14**. This does *not* involve a retro-Brook step.

The phenanthryne precursor **15** was first reported by Peña *et al.*, starting from 9-bromo-10-phenanthrol **14** and prepared using a *C,O*-disilylation method.[13a] We successfully repeated this on a gram scale, using an *in situ* solvent-exchange between steps to remove impurities and increase the yield by 8% (Scheme 2a).[13]

To test our aromaticity model, attempts were made to form oSAT **15** from **14** using HMDS and a retro-Brook reaction, which – although reported once[4] – failed in line with our predictions (ESI S5).[9] To provide sufficient material for these tests, an improved synthesis of **14** from phenanthrene **16** was developed (Scheme 2b). Interestingly, the bromination of **16** at C-9 and C-10 would not usually be possible at an aromatic carbon without Lewis acid catalyst.[15] Our updated synthesis of **15** has: a) full contemporary purification and characterization; b) replaces toxic CCl_4 with $CHCl_3$; c) a 76% yield of **19** from **18** (*cf.* 48%); and d) a 34% yield of **15** at gram scale over five steps from **16** (ESI S4).[13a,18] Finally, a quantitative Diels-Alder reaction between **15** and furan was successfully repeated to form adduct **20** (Scheme 2 inset)**,** validating its suitability as an aryne precursor (ESI S5).[19]

Attention now turned to the synthesis of 1,4-bisxylyne oSAT prototype **12a**. Our model suggests that the first prospective *O*- to *C*-silyl transfer in intermediate **13v** is disfavoured, whereas a second *C*-silyl group could be installed via a retro-Brook reaction using intermediate **13w** or **10**. To probe this prediction, 2,5-dimethylbenzoquinone **21** was reductively brominated to form 2,5-dibromo-3,6-dimethylhydroquinone **9** (Scheme 3a & ESI S6). Attempts to produce bisxylyne oSAT prototype **12a** directly from **9** and HMDS via a retro-Brook reaction afforded no product, producing a crude mixture highly prone to oxidation (ESI S7). Even when forcing conditions were used to access *O*-silyl intermediate **13v**, subsequent sodiation[5a] to initiate retro-Brook silyl transfer gave an insoluble mixture with no target.

Having verified the fates of intermediates **9** and **13v**, a synthetic route towards **12a** was developed based on our model. Initial *O,O'*-disilylation and *C*-silylation of **9**, as for phenanthryne precursor **15**, was proposed to access intermediate aryl silane **10**. Subsequent retro-Brook reaction and triflation would lead to oSAT **12a** (Scheme 3b, ESI S8-9). Reaction aliquots were analysed at each stage by NMR (ESI S14) and GC/MS (ESI S18). The *O*-silylations (Phase 1) proceeded well, although disilylated **13v** (**C**) was observed after the first step and *C*-lithiated **D** from halogen-metal exchange after the second, due to excess ^{n}BuLi.



Scheme 3 – a) Reductive bromination of 2,5-dimethyl-1,4-benzoquinone **21** with subsequent failed attempts to form a bisxylyne oSAT prototype **12a**; b) Abridged putative mechanism of the formation of **12a** (K) from **9** (A). Full Scheme in ESI S9.

Crucially, *no retro-Brook reactions were observed with **D*** despite the excess lithiation, as confirmed by a separate test on isolated **13v** (ESI S10). Following the first *C*-silylation step (Phase 2), *C,C'*-dilithiated **DD** was present despite overnight stirring at room temperature with chlorosilane. This suggests a significant barrier to intermolecular *C*-silylation *ortho* to *O*-silylated species precluding a first retro-Brook (Figure 3, top). Phenolic signals in the ^{1}H NMR spectrum confirm that the large triply-silylated species must be *C,C',O*-isomer **G** (**11**), rather than **F**. *Hence, a retro-Brook reaction on the second side is successful, in line with our mechanistic model.* After solvent exchange and further ^{n}BuLi, without further silylation, the next aliquot contains only **G** (**11**), **F** and tetrasilylated **H** (Figure 3, middle). Here, the 30-minute reaction time allows **E** (**10**) to undergo halogen-metal exchange to afford **F** but *retro*-Brook to **G** (**11**) cannot complete; **H** can only form from *O*-silyl exchanges. Unfortunately, after triflation and work-up (Phase 3), quinone **KQ** (**23**) predominated (Figure 3, bottom, 41% isolated yield); despite this, *C,C'-disilylated **K** (**12a**) is detected in situ* and the oxidation product successfully confirms our assignments. Intermediate **H** was later isolated in 74% yield but subsequent attempts to introduce the triflate only produced **KQ** (**23**), isolated in 56% yield. This

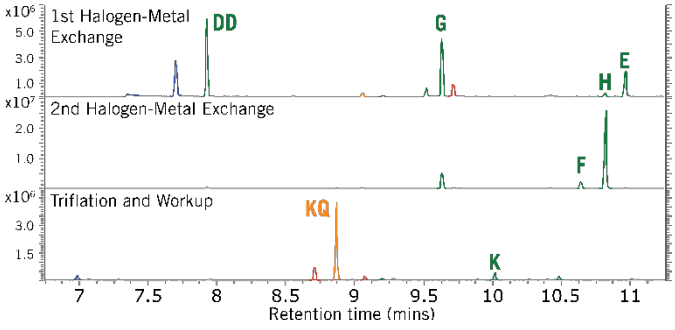
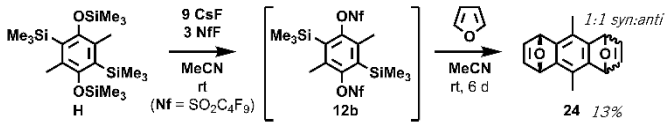


Figure 3 – Partial stack plot of GC/MS aliquots from the formation of bisxylyne oSAT prototype **12a** (**K**). Letters correspond to Scheme 3b.



Scheme 4 – Successful bisxylene formation from transient *ortho*-silylaryl nonaflate **12b** and *in situ* Diels-Alder reaction with furan to form adduct **24**. See ESI S12.

sensitivity of the triflates suggests that it might be an inherent limitation of functionalized bis-oSAT precursors. However, transient *o*-silylaryl nonaflates such as **12b** (putative structure, accessed from air-stable **H**) are also viable aryne precursors[9] and pleasingly the subsequent Diels-Alder reaction of furan with the bisaryne proceeded successfully in 13% yield (Scheme 4).

In summary, we have developed a quick and facile MM2/Hückel modelling strategy to test the success of retro-Brook *O*- to *C*-silyl transfer relevant to aryne precursor synthesis. A novel application (**13z**) and an expected failure (**15**) were validated experimentally. Next, a route towards 1,4-bisxylyne precursors **12a/b** was developed with a retro-Brook step for just one *C*-silylation. This is the first *C,C'*-disubstituted *o*-silylaryl sulfonate bisbenzyne precursor: with appropriate substituents, many previously elusive bisaryne precursors may now be accessible.

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Conflicts of interest

There are no conflicts to declare.

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