

3-Hydroxy-2-(trialkylsilyl)phenyl Triflate: A Benzyne Precursor Triggered via 1,3-C-sp²-to-O Silyl Migration

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(5) Supporting Information

ABSTRACT: 3-Hydroxy-2-(trialkylsilyl)phenyl triflates are presented as new versatile hydroxyaryne precursors. These are base-activated aryne precursors induced via a C-sp²-to-O 1,3-Brook rearrangement. The reaction of various arynophiles and 3-trialkylsiloxybenzyne generated from 3-hydroxy-2-(trialkylsilyl)phenyl triflate efficiently afforded highly regiose-



lective phenol derivatives. Furthermore, through crossover experiments, the intramolecular mechanism of silyl migration was demonstrated.

In the Brook rearrangement, initially introduced by Brook et al.,¹ a negative charge moves from an oxygen to carbon through the transfer of a silvl group. The mechanism of the Brook rearrangement has been extensively studied and is now known to be a reversible process proceeding intramolecularly via a hypervalent silicon intermediate (Scheme 1a).² This rearrange-

Scheme 1. Brook Rearrangement and Proposed Strategy for Benzyne Formation



ment has been well-established and applied to various synthetic transformations, including a multicomponent coupling.³ Specifically, Smith and co-workers have employed the Brook rearrangement for their multicomponent union tactic known as anion relay chemistry (ARC).⁴

The reverse process, namely the migration of silicon from oxygen to carbon, is known as the retro-Brook rearrangement and is also frequently employed in organic chemistry (Scheme 1b).⁵ For instance, the reactions of trialkyl(2-bromophenoxy)-silane with either lithium or sodium metal provide only *o*-

silvlphenol through a retro-Brook rearrangement process.⁶ This could be due to the relative stability of the resultant phenolate compared to that of the aryl carbanion derived from the starting aryl halide.⁸ Furthermore, treatment of the in situ generated phenolate with triflic anhydride can furnish o-silylaryl triflates, which are useful benzyne precursors developed by Kobayashi et al.^{6b} Currently, o-silylaryl triflates are the most widely employed benzyne precursors because of their efficiency and the mild conditions necessary to generate benzyne, which are triggered by a fluoride anion at room temperature or higher.⁷ For example, Li and co-workers reported a new domino aryne precursor that can be used for the preparation of 1,2,3-trisubstituted benzenes.^{7e} In 2016, Hosoya et al. demonstrated the synthesis of 3-aminoaryne precursors employing aryne relay chemistry and utilized them for the synthesis of various anilines.⁷ⁱ Considering the recent advances in benzyne chemistry, we hypothesized that hydroxysubstituted arynes could be used as potential intermediates in the synthesis of various phenol derivatives. In addition, as illustrated in Scheme 1c, we assumed that the treatment of 3-hydroxy-2-(trialkylsilyl)phenyl triflate with a base would result in the formation of the 3-(trialkylsiloxy)benzyne intermediate via a 1,3-Brook rearrangement, which could further be used in nucleophilic addition and cycloaddition. With these considerations in mind, we now report the first documented use of 3hydroxy-2-(trialkylsilyl)phenyl triflate as a hydroxyaryne precursor induced via intramolecular anionic 1,3-silyl migration in an aromatic system.

To demonstrate the proposed process for benzyne formation, the requisite benzyne precursors 4 and 7 were prepared from 2-bromoresorcinol 1 in three steps: *O*-silylation, lithium—halogen exchange/triflation, and selective desilylation (Scheme 2).

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Scheme 2. Preparation of Benzyne Precursors 4 and 7



The reaction conditions for nucleophilic addition to benzyne generated via 1,3-C-sp²-to-O silyl migration were initially optimized by employing 3-hydroxy-2-TBS phenyl triflate 4 and piperidine 8. As shown in Table 1, various bases, solvents, and

Table 1. Optimization Studies^a

OH	_TBS ₊ H `OTf		base, solvent	OTBS
4		8		9 🗸
entry	base	solvent	conditions	yield ^b (%)
1	n-BuLi	THF	−78 °C, 1 min, 0 °C, 12 h	67
2	NaHMDS	THF	-78 °C, 1 min, 0 °C, 2 h	75
3	NaH	THF	-78 °C, 1 min, 0 °C, 15 min	80
4	KHMDS	THF	-78 °C, 1 min, 0 °C, 3 h	62
5	KO ^t Bu	THF	-78 °C, 1 min, 0 °C, 30 min	83
6	MeMgCl	THF	–78 °C, 1 min, 0 °C, 12 h	0
7	K ₂ CO ₃	THF	60 °C, 6 h	82
8 ^c	KO ^t Bu	THF	-78 °C, 1 min, 0 °C, 30 min	78
9 ^d	KO ^t Bu	THF	–78 °C, 1 min, 0 °C, 1 h	69
10	KO ^t Bu	Et_2O	–78 °C, 1 min, 0 °C, 12 h	40
11	KO ^t Bu	DME	$-78~^\circ\text{C},$ 1 min, 0 $^\circ\text{C},$ 30 min	75
12	KO ^t Bu	THF	−40 °C, 12 h	15
13	KO ^t Bu	THF	−20 °C 12 h	57
14	KO ^t Bu	THF	rt, 5 min	87

^{*a*}Reaction conditions: 1 equiv of 3-hydroxy-2-TBS phenyl triflate, 3 equiv of piperidine, 1.1 equiv of base, solvent (0.1 M). ^{*b*}Isolated yield. ^{*c*}2 equiv of piperidine. ^{*d*}Piperidine was used as a limiting reagent.

temperatures were screened for the formation of the desired Narylated product 9. When 1.1 equiv of n-BuLi was used as a base at 0 °C, the coupled product 9 was isolated in 67% yield after 12 h (Table 1, entry 1). However, when the reactions were attempted at 0 °C in the presence of either a sodium or potassium base such as NaHMDS, NaH, KHMDS, or KO^tBu, the benzyne intermediate was generated within 3 h through a 1,3-Brook rearrangement process, providing product 9 in yields ranging from 62% to 83% (Table 1, entries 2-5). When MeMgCl was employed as the base, no conversion was observed (Table 1, entry 6). Interestingly, the use of K₂CO₃ as base in THF at 60 °C furnished the desired product 9 in 82% yield in 6 h (Table 1, entry 7). When the reaction was conducted with 2.0 equiv of 8, 9 was obtained in a slightly lower 78% yield in 30 min (Table 1, entry 8). Furthermore, when 8 was employed as a limiting reagent, 9 was obtained in 69% yield in 1 h (Table 1, entry 9). Next, we investigated the solvent effects for N-arylation of piperidine (Table 1, entries 10 and 11). As expected, when the reaction was carried out using KO^tBu in a nonpolar solvent such

as Et₂O, the desired product 9 was isolated in 40% yield after 12 h (Table 1, entry 10). However, the use of a polar aprotic solvent such as DME furnished 9 in 75% yield in 30 min (Table 1, entry 11). From these experiments, we conclude that the rate of silyl group migration for the generation of the benzyne intermediate depends on solvent polarity. As illustrated in entries 12 and 13, a reduced temperature of -40 °C afforded the product 9 in a lower yield of 15% after 12 h (Table 1, entry 12), while the yield showed significant improvement when the reaction was attempted at -20 °C (Table 1, entry 13). Finally, the use of 3 equiv of piperidine and 1.1 equiv of KO^tBu in THF at room temperature furnished 9 in 87% yield within 5 min (Table 1, entry 14).

With the optimized conditions (cf. Table 1, entry 14) in hand, we examined the scope of nucleophilic addition reactions employing 3-hydroxy-2-TBS-phenyl triflate 4 and the various nucleophiles (Scheme 3). Unfortunately, the use of our optimal

Scheme 3. Nucleophilic Addition Reactions Employing Hydroxybenzyne Precursor 4^a



"Reaction conditions: 1 equiv of 3-hydroxy-2-TBS phenyl triflate, 3 equiv of nucleophile, THF (0.1 M). ^bDesilylated product. ^c4 equiv of KO'Bu.

conditions proved not to be general for all substrates due to the desilylation of the TBS group. Thus, we employed two different sets of conditions to prevent the formation of the unwanted desilylated product. As illustrated in Scheme 3, most of the secondary amines (9a-c) and aromatic amines (9d-p) containing electron-neutral, -donating, and -withdrawing groups furnished the *meta*-selective *N*-arylated products in good to excellent yields within 30 min. In particular, when the reaction was conducted with 4-[(tert-butyldimethylsilyl)oxy]aniline, **9h** was obtained in 86% yield in 5 min. This result is especially meaningful since it indicates that a substrate involving trialkylsilyl

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protecting groups can serve as a nucleophile under the optimized conditions. When ethyl 2-aminobenzoate was reacted with 3hydroxy-2-TBS phenyl triflate 4, the desired product 9k was obtained in 80% yield along with a significant amount of 9kk. Recently, Singh and co-workers reported the synthesis of N-aryl sulfoximines using o-silylaryl triflates and sulfoximines in the presence of a fluoride anion at room temperature.^{7c} While they demonstrated the possibility for N-arylation of sulfoximines employing fluoride-activated aryne precursors, this reaction afforded the desired products in 5% to 77% yields in 2-4 h. In comparison, our method provided the product 90 in 82% yield in 15 min when methylphenylsulfoximine was employed. The reaction was also successful with a heteroaryl amine such as 2aminopyrimidine as coupling partner, furnishing **9p** in 74% yield in 5 min. In addition, other nucleophiles such as thiophenol and phenol proved to be effective coupling partners and afforded the desired products 9q and 9r in 85% and 65% yields in 10 min, respectively. Interestingly, the latter provided the undesired homocoupled product 9rr in 12% yield, presumably due to the competitive nucleophilic addition between the substrate and the unreacted benzyne precursor 4.

To further investigate the utility of a benzyne intermediate induced via a 1,3-Brook rearrangement, a series of 3-hydroxy-2-(trialkylsilyl)phenyl triflates **10** were employed as benzyne precursors under two different sets of reaction conditions (Scheme 4).⁸ Most of the reactions proceeded readily in 30 min





^{*a*}Reaction conditions: 1 equiv of hydroxybenzyne precursor, 3 equiv of aniline, THF (0.1 M). ^{*b*}Desilylated product.

to furnish the desired products in yields ranging from 68% to 91%. However, when 3-hydroxy-5-methoxy-2-TBS-phenyl triflate was used, the coupled product **10d** was obtained in 54% yield in 40 min along with a significant amount of the desilylated product **10dd** in 20% yield. Interestingly, when either 3-hydroxy-3-methyl-2-TBS-phenyl triflate or 3-hydroxy-6-methyl-2-TBSphenyl triflate was employed, the *meta*-selective products **10b** and **10c** were obtained in 91% and 77% yield in 10 min, presumably because of the steric and electronic effects resulting from the *tert*-butyldimethylsilyloxy group of the aryne. Encouraged by these results, we next turned our attention to the intermolecular [4 + 2], [3 + 2], and [2 + 2] cycloadditions using benzyne precursor 4 and the corresponding arynophiles (Scheme 5). Initially, when 3-hydroxy-2-TBS-phenyl triflate 4

Scheme 5. [4 + 2], [3 + 2], and [2 + 2] Benzyne Cycloadditions



and 2,5-dimethylfuran 12 were treated with KO^tBu at rt for 1 h in THF, cycloadduct 13 was obtained in 35% yield along with a significant amount of the homocoupled product **9rr** in 20% yield. However, when a weak base such as K_2CO_3 was employed at 60 °C in THF, the desired product was isolated in 72% yield in 8 h. In the case of intermolecular [3 + 2] benzyne cycloaddition, when either benzyl azide 14 or ethyl diazoacetate 16 was employed, single regioisomers 15 and 17 were obtained in 46% and 52% yield, respectively, in 12 h along with desilylated products 15a and 17a in 21% and 11% yield. Furthermore, when a mixture of 4 and 1,1-diethoxyethylene 18 was treated with K_2CO_3 at 60 °C, a single regioisomer 19 was isolated in 80% yield in 7 h.

From the outset of this work, it was hypothesized that the benzyne intermediate from 4 could be induced by a 1,3-C-sp²-to-O intramolecular silyl migration. With this in mind, we carried out a crossover experiment wherein an equimolar mixture of 7 and 20 in the presence of aniline 11 was treated with 2.2 equiv of KO^tBu in THF (Scheme 6). No crossover products were obtained in this reaction. This result indicates that silvl migration occurs intramolecularly, presumably via a 1,4-cyclic, hypervalent silicon intermediate and subsequent elimination of the triflate group, affording the benzyne intermediate. To the best of our knowledge, this is the first example of C-sp²-to-O 1,3-Brook rearrangement in an aromatic system. Next, to investigate the role of a fluoride anion in the presence of hydroxybenzyne precursors, we repeated the reactions using triflate 4 and 11 under Larock's conditions (Scheme 6b).^{7a} To our surprise, the desired product 9d was not isolated after 30 min, and desilylation occurred to afford 21 in 80% yield; nonetheless, we found that



the fluoride anion acts as a base and drives the Brook rearrangement to generate the benzyne intermediate. However, when 2-TBS-phenyl triflate **22** without a hydroxyl group was treated with CsF at rt in MeCN, the *N*-arylated product **23** was isolated in 16% yield, along with product **24** in 33% yield after 26 h with 68% conversion (Scheme 6c).

In summary, we have described a new hydroxybenzyne precursor induced by C-sp²-to-O 1,3-Brook rearrangement on the aryl group. The nucleophilic addition reactions employing base-activated benzyne precursors readily proceeded under two different sets of conditions with a broad substrate scope. Particularly, intermolecular [4 + 2], [3 + 2], and [2 + 2] benzyne cycloadditions employing K₂CO₃ provided highly regioselective cycloadducts in moderate to good yields. Furthermore, a fluoride anion in MeCN proved to drive the Brook rearrangement to generate benzyne intermediate from 3-hydroxy-2-TBS phenyl triflate. Finally, the mode of anionic 1,3-silyl migration in this system is intramolecular, which was demonstrated through a crossover experiment. Further investigation into the use of other benzyne precursors triggered via silyl migration is ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03160.

Detailed experimental procedures and characterization data (PDF) $% \left(PDF\right) =\left(PDF\right) \left(PDF\right) \left(PDF\right) \left(PDF\right) \right) \left(PDF\right) \left($

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The authors declare no competing financial interest.

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