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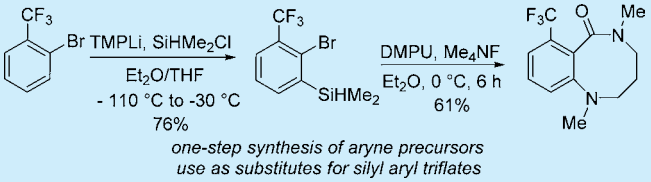
Silylaryl Halides Can Replace Triflates as Aryne Precursors

Milad Mesgar and Olafs Daugulis*

Department of Chemistry, University of Houston, Houston, Texas 77204-5003, United States

Supporting Information

ABSTRACT: Silylaryl bromides and iodides can be prepared in one step from commercially available starting materials. Arynes can be generated from these compounds under conditions nearly identical to those employed for silylaryl triflates. Three distinct transformations, ortho-arylation of *N*-tritylanilines, intermolecular addition of arynes to amides, and reaction of ureas with arynes, were shown to be successful for the new aryne precursors. The main advantage of silylaryl halides relative to silyl aryl triflates is their one-step preparation from commercially available starting materials.

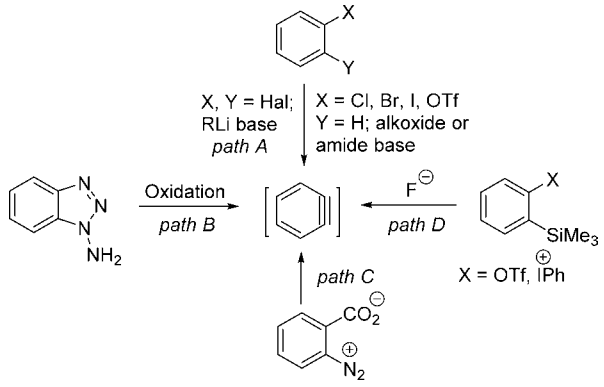


one-step synthesis of aryne precursors use as substitutes for silyl aryl triflates

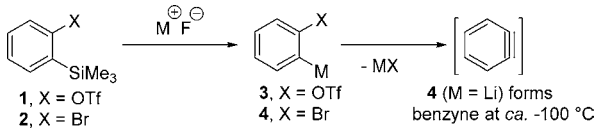
Arynes are important reactive intermediates in the synthesis of bioactive molecules,[1] organic materials,[2] and catalysts.[3] Early methods for aryne generation involve the reaction of aryl halides with strong bases (Scheme 1, A).[4] The harsh conditions used in these methods limit their use in synthesis. Subsequently, several other methods for aryne generation have been reported (Scheme 1, B–D). Oxidation of aminotriazoles or other N–N bond-containing substances generates arynes.[5] Benzenediazonium 2-carboxylate decomposes to benzyne under extremely mild conditions.[6] Recently, hexahydro Diels–Alder reactions were shown to generate arynes.[7]

Currently, the most widely used method for aryne generation involves the reaction of silylaryl triflates with fluoride reported by Kobayashi in 1983.[8a] An extension of this method was disclosed in 1995, when Kitamura showed that aryliodonium salts generate arynes in the presence of fluoride ion.[8b] The Kobayashi method has several advantages over other aryne generation procedures. Silylaryl triflates are bench stable and allow aryne generation under relatively mild and nonbasic conditions.[8] However, only a few silylaryl triflates are commercially available. Their preparation requires somewhat lengthy synthetic procedures starting from *o*-bromophenols,

Scheme 1. Generation of Aryne Intermediates



Scheme 2. Decomposition of Intermediates



which are of limited commercial availability as well.[9] In contrast, aryl halides are cheap, and a large number of them are commercially available. Their use in aryne generation, however, requires strong amide or alkoxide bases that are not compatible with many functional groups. An ideal aryne source would have availability close to that of an aryl halide and would form benzynes under mild conditions similar to those employed for silylaryl triflates. The ease of aryne formation from ortho-metalated species such as **3** and **4** should be related to the strength of the conjugate acid of the leaving group (Scheme 2). Examination of pK_a values of hydrogen halides and triflic acid in DMSO shows that the acidity of HI is close to that of CF_3SO_3H, while HCl is insufficiently acidic.[10a,b] Reaction of silylaryl triflate with a metal fluoride generates ortho-metalated aryl triflate that rapidly decomposes to form aryne. It is well-known that (2-bromophenyl)lithium eliminates LiBr at temperatures as low as −100 °C.[10c] The corresponding (2-iodophenyl)lithium should be even less stable. Consequently, ortho-silylated aryl bromides and iodides should be capable of generating arynes under mild conditions. We report here (1) a one-step synthesis of silylaryl bromides and iodide from commercially available starting materials and (2) use of these species in three types of reactions, where they show results comparable to those obtained with silylaryl triflates.

A few examples of silylaryl halide use in aryne generation have been reported.[11] In 1973, Cunico and Dexheimer reported that (2-halophenyl)- and [2-(tosyloxy)phenyl]trimethylsilanes are capable of generating arynes in the presence of KO-*t*-Bu or

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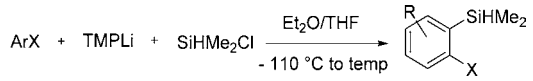

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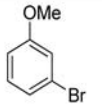
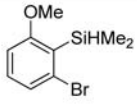
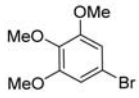
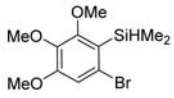
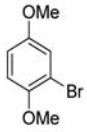
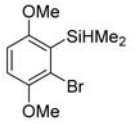
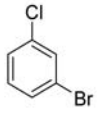
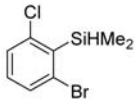
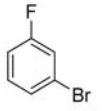
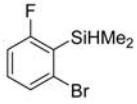
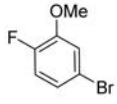
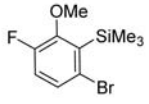
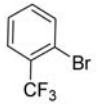
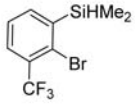
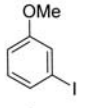
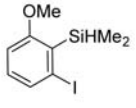
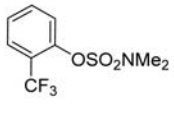
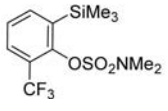
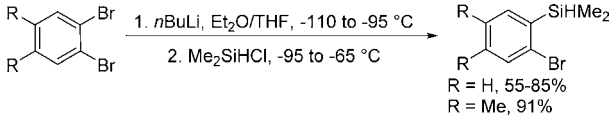
1			94
2			55
3			94
4			51
5			76
6[b]			35[c]
7			76
8			95
9[b]			81

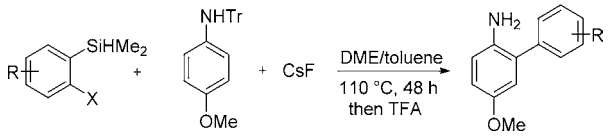
[a]ArX (10−20 mmol), $ClSiHMe_2$ (100−300 mmol), TMPLi (25−50 mmol), solvent (60−120 mL), −110 °C; warm to between −10 and −80 °C. Yields are isolated yields. See the Supporting Information for details. [b]Chlorotrimethylsilane used. [c]Disilylation product also isolated (47%).

Scheme 3. Synthesis by Lithium−Halogen Exchange



fluoride ion.[11a] However, yields of products derived from arynes were low. In 2010, Harrity and Browne first showed that arynes can be efficiently generated from silylaryl iodides.[11b] The silyl aryl iodides were prepared by cycloaddition of methyl coumalate with (trimethylsilyl)iodoacetylene as a 2:1 mixture of regioisomers. It would be more convenient if aryne precursors were synthesized in one step from commercial aryl halides that are available with a variety of functional groups. Lithium tetramethylpiperidide (TMPLi) has been used for in situ deprotonation/silylation of aromatic nitriles, esters, and

Table 2. Direct Arylation of Tritylanilines[a]



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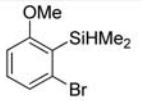
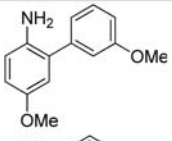
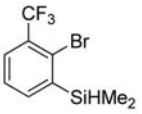
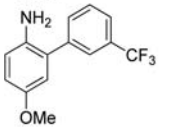
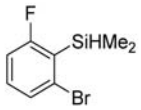
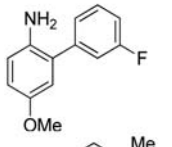
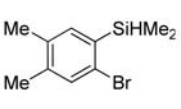
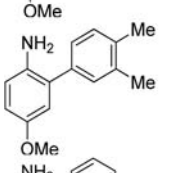
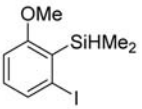
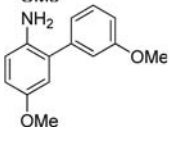
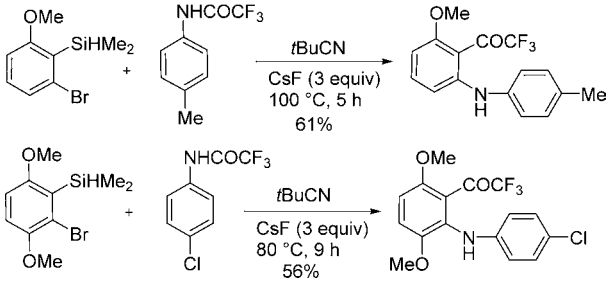
1			93
2			82
3			61
4			62
5			96

[a]4-Methoxy-*N*-tritylaniline (0.2 mmol), silyl aryl bromide or iodide (0.36 mmol), CsF (0.75 mmol), solvent (2.5 mL), 110 °C, 48 h; then TFA (1.5 mL). Yields are isolated yields. See the Supporting Information for details. TFA = CF_3CO_2H; DME = 1,2-dimethoxyethane.

Scheme 4. Addition of Amides to Arynes



pyridine derivatives.[12] Provided that the (2-haloaryl)lithium lifetime is sufficiently long, it should be possible to trap these intermediates to afford the desired silylaryl halides.[13] We initially attempted in situ trapping of (2-haloaryl)lithium reagents with chlorotrimethylsilane. Unfortunately, these reactions gave variable yields and were not successful with many substrates due to the competitive decomposition of (2-bromoaryl)lithium intermediate. Consistent results were obtained when sterically smaller and more electrophilic dimethylsilyl chloride (DMSCl) was used for in situ quenching. Best results were obtained by performing the reaction at −110 °C with subsequent warming. The scope of aryl halide silylation is presented in Table 1. All reactions were run on at least 10 mmol scale. The reaction works well with methoxy-substituted

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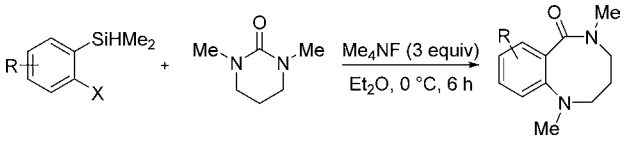
Table 3. Addition of Arynes to DMPU[a]



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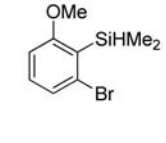
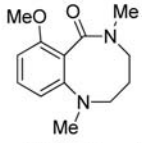
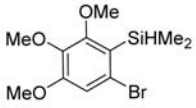
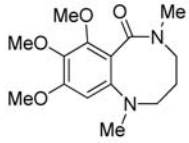
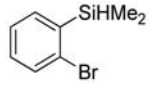
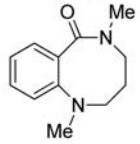
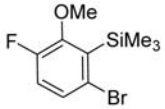
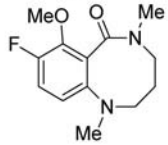
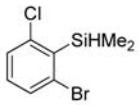
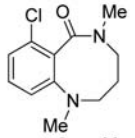
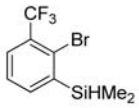
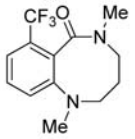
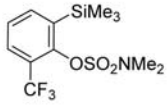
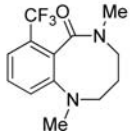
1			64
2			67
3			55
4			62
5			51
6			61
7			67

[a]Silyl aryl bromide or sulfamate (0.25 mmol), DMPU (0.75 mL), Me_4NF (0.75 mmol), diethyl ether (0.5 mL), 0 °C, 6 h. Yields are isolated yields. See the Supporting Information for details. DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone.

aryl bromides. Thus, 1-bromo-3-methoxybenzene gave silylation product in 94% yield (entry 1), while trimethoxybromobenzene afforded silylated species in 55% yield (entry 2). 2-Bromo-1,4-dimethoxybenzene reacted to give the dimethylsilyl derivative in 94% yield (entry 3). Products of entries 1 and 3 are alternative aryne precursors that can be used instead of 2-methoxy-6-(trimethylsilyl)phenyl triflate and 2,5-dimethoxy-6-(trimethylsilyl)phenyl triflate, which are among the most frequently used, functionalized aryne precursors.[14]

Other bromoarenes that possess groups assisting metalation can also be silylated successfully. Thus, 1-bromo-3-chlorobenzene is silylated in 51% yield (entry 4). Similarly, 1-bromo-3-fluorobenzene reacted to afford the product in 76% yield (entry 5). Silylation of 2-fluoro-5-bromoanisole gave a mixture mono- and disilylation products, from which monosilylation product was isolated in 35% yield (entry 6). The disilylated species was isolated in 47% yield. In this case, reaction with trimethylsilyl chloride gave better results. Silylation of 3-(trifluoromethyl)-bromobenzene was successful, affording the desired product in 76% yield (entry 7). Somewhat surprisingly, 3-iodoanisole was silylated in an excellent 95% yield (entry 8). The ester of *N,N*-dimethylsulfamoic acid was also successfully silylated by trimethylsilyl chloride (entry 9). Efforts to silylate bromobenzene did not give a reproducible yield of product. Tamborski reported the synthesis and reactivity of (*o*-bromophenyl) lithium in 1980.[10c] A modification of this method afforded 1-bromo-2-(dimethylsilyl)benzene and 1-bromo-3,4-dimethyl-6-(dimethylsilyl)benzene in 55−85% and 91% isolated yields (Scheme 3).

The feasibility of aryne formation was tested in three representative reactions. In each of the original publications, only five to six silyl aryl triflates were investigated, presumably due to their inaccessibility. The first reaction selected was the direct arylation of anilines reported by Greaney in 2012.[15] In the original paper, *N*-tritylanilines were reacted with an aryne precursor in the presence of CsF in toluene/acetonitrile 3:1 mixture at 110 °C for 48 h, followed by treatment with TFA to remove the trityl group. Nearly identical conditions allowed use of silyl aryl halides, underscoring the possibility of shortening the synthetic sequences (Table 2). The only difference in the reaction conditions was the use of dimethoxyethane/toluene instead of toluene/acetonitrile mixed solvent. 1-Bromo-3-methoxy-2-(dimethylsilyl)benzene reacts with 4-methoxy-*N*-tritylaniline to afford an excellent yield of the product (entry 1). Aryne precursors possessing electron-withdrawing trifluoromethyl and fluoro substituents gave 82% and 61% isolated yields (entries 2 and 3). We are aware of only two reports that disclose use of trifluoromethyl-substituted silyl aryl triflates in aryne generation.[16a,b] Attempts to employ 2-(trifluoromethyl)-6-(trimethylsilyl)phenyl triflate in arylation of tritylated 4-methoxyaniline gave 14−16% yields under conditions reported by Greaney and under the conditions of Table 2.[16c] These examples show that in some cases silyl aryl bromides may afford better results compared to silyl aryl triflates. An aryne precursor with two methyl substituents worked well, giving the product in 62% isolated yield (entry 4). Silyl aryl iodides are also competent aryne sources (entry 5). Thus, reaction of 1-iodo-3-methoxy-2-(dimethylsilyl)benzene with tritylated 4-methoxyaniline gave arylation product in 96% isolated yield (entry 5).

The second reaction investigated is the intermolecular addition of amides to arynes reported by Larock in 2005.[17] In the original communication, silyl aryl triflates were reacted with *N*-trifluoroacetylated anilines and CsF in acetonitrile solvent at ambient temperature. Some modifications of reaction conditions were required to obtain optimal results. Pivalonitrile solvent at elevated reaction temperature was used (Scheme 4). If acetonitrile solvent was employed, byproducts arising from protonation of 2-lithiobromoarenes were observed. 1-Bromo-3-methoxy-2-(dimethylsilyl)benzene reacts with trifluoro-*N*-(4-methylphenyl)acetamide in the presence of cesium fluoride to afford the product in 61% isolated yield. Similarly, 2-bromo-1,4-dimethoxy-3-(dimethylsilyl)benzene reacted with the trifluoroacetamide of 4-chloroaniline to give the C−N bond cleavage product in 56% yield.

The third reaction selected was addition of ureas to arynes reported by Shirakawa and Hiyama in 2002.[18] A reaction of silylaryl triflates with neat 1,3-dimethyl-2-imidazolidinone (DMI) or *N,N′*-dimethylpropyleneurea (DMPU) in the presence of CsF at 20 °C gave good yields of benzodiazepine

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and benzodiazocine derivatives. After some optimization of reaction conditions, we discovered that tetramethylammonium fluoride (TMAF) at 0 °C in diethyl ether solvent afforded the best results (Table 3).

1-Bromo-3-methoxy-2-(dimethylsilyl)benzene reacts with DMPU in the presence of TMAF to give the product as a single regioisomer in 64% isolated yield (entry 1). Similarly, 5-bromo-1,2,3-trimethoxy-4-(dimethylsilyl)benzene affords 67% isolated yield of the product (entry 2). 1-Bromo-2-(dimethylsilyl)benzene gives substituted benzodiazocine in 55% yield (entry 3). Entry 4 shows that fluorine is compatible with the reaction conditions. A chloro substituent is tolerated as well (entry 5). The trifluoromethyl-substituted derivative is reactive, and the product is isolated in 61% yield (entry 6). The *N,N*-dimethyl-2-(trimethylsilyl)-6-(trifluoromethyl)phenyl ester of sulfamic acid is a competent aryne source, and coupling with DMPU affords the product in 67% yield (entry 7). While a dimethylsulfamoyl group is a worse leaving group than triflate, it is a better directing group, and thus, direct deprotonative silylation of sulfamoic acid phenyl esters affords aryne precursors in one step as shown in Table 1, entry 9. Direct silylation of aryl triflates was not successful.

In conclusion, silyl aryl bromides and iodides can be conveniently prepared on large scale in one step from commercially available starting materials and can be used as aryne precursors under conditions similar to those employed for silyl aryl triflates. Use of silyl aryl halides was demonstrated in three transformations, ortho-arylation of *N*-tritylanilines, intermolecular addition of arynes to amides, and reaction of ureas with arynes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01952.

Detailed experimental procedures and characterization data for new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: olafs@uh.edu.

Notes

The authors declare no competing financial interest.

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