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Aryne Relay Chemistry en Route to Aminoarenes: Synthesis of 3-Aminoaryne Precursors via Regioselective Silylamination of 3-(Triflyloxy)arynes

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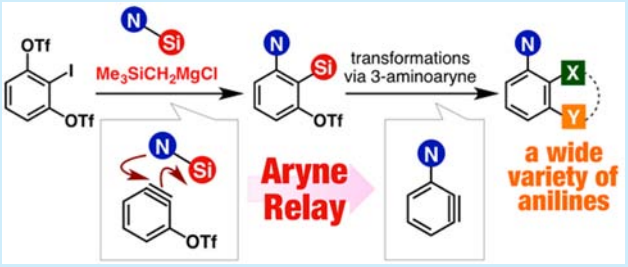
Supporting Information

ABSTRACT: A facile synthetic method for preparing 3-amino-2-silylaryl triflates via regioselective silylamination of 3-(triflyloxy)arynes with *N*-silylamines is described. Fluoride-mediated generation of 3-aminobenzyne from 3-amino-2-silylphenyl triflate, easily prepared by this method, in the presence of various arynophiles efficiently afforded diverse aniline derivatives, including a 5-aminocoumarin derivative, demonstrating the utility of aryne relay approach.



Aniline derivatives play an important role in several fields, including materials science and medicinal chemistry.[1,2] A number of synthetic methods, such as the reduction of aromatic nitro compounds, nucleophilic aromatic substitution of electron-deficient aryl halides, and Buchwald−Hartwig amination, have been developed for the preparation of aromatic amines.[1] Considering the recent advances in synthetic aryne chemistry,[3,4] amino group substituted arynes could serve as promising intermediates in the preparation of various aniline derivatives. Nevertheless, only a few studies on the transformation via aminoaryne species have been reported.[5] Herein, we report that 3-amino-2-silylaryl triflates, which have been anticipated to serve as 3-aminoaryne precursors, are easily prepared via regioselective silylamination of 3-(triflyloxy)arynes efficiently generated from *o*-iodoaryl triflate type aryne precursors. We also show that a 3-aminobenzyne is efficiently generated from a 3-amino-2-silylphenyl triflate synthesized by this method, which rendered a diverse range of aniline derivatives easily accessible, demonstrating the synthetic utility of aryne relay chemistry.

Since a wide range of aromatic compounds can be prepared via arynes that are generated from *o*-silylaryl triflates,[3,4] we initially aimed at preparing 3-amino-2-(trimethylsilyl)phenyl triflate **1**. We assumed that the treatment of **1** with a fluoride ion source in the presence of an arynophile would result in the generation of 3-aminobenzyne **I**, which could be used for the synthesis of a variety of aniline derivatives through various transformations such as cycloaddition, addition of a nucleophile, and direct difunctionalization (Figure 1A). However, our initial attempt to prepare 3-(dimethylamino)-2-(trimethylsilyl)-phenyl triflate **1** (R, R′ = Me) using the conventional method[6] was unsuccessful (Figure 1B); while carbamate **3** was obtained from 3-(dimethylamino)phenol (**2**) in a low yield, an attempt to deprotect **3** to obtain *o*-silylphenol **4** was unsuccessful, and instead, desilylprotonated phenol **2** was obtained.

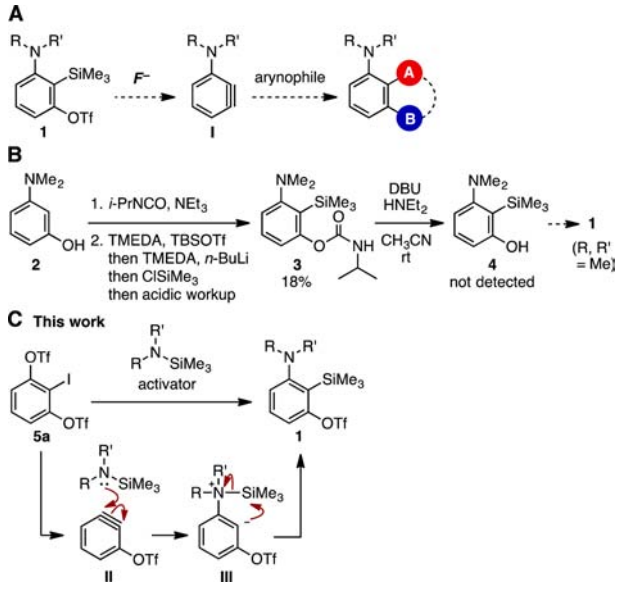


Figure 1. Proposed strategy. (A) Synthesis of aniline derivatives via 3-aminobenzyne **I** generated from 3-amino-2-silylphenyl triflate **1**. (B) Our initial attempt to prepare **1**. (C) This work: synthesis of 3-aminobenzyne precursor **1** via regioselective silylamination of 3-(triflyloxy)benzyne (**II**).

We then attempted to prepare 3-amino-2-silylphenyl triflate **1** via silylamination[7] of 3-(triflyloxy)benzyne (**II**) (Figure 1C).[8] This idea was based on our recent studies on the chemistry of

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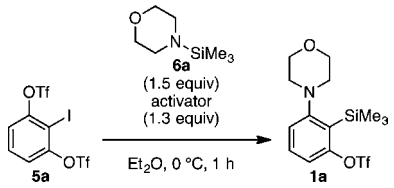
3-(triflyloxy)arynes; we have developed an efficient method for their generation from 1,3-bis(triflyloxy)-2-iodoarenes such as **5a** and examined their reaction with various arynophiles.[8a,f] On the basis of these studies, we assumed that the addition of the amino group of *N*-silylamine to **II** would take place regioselectively at the distal site owing to the presence of an electron-withdrawing triflyloxy group and subsequent migration of the silyl group would result in the formation of desired **1**.

Based on this scenario, we extensively screened the conditions for efficiently synthesizing 3-morpholino-2-(trimethylsilyl)phenyl triflate (**1a**) via the silylamination of 3-(triflyloxy)benzyne, generated from 1,3-bis(triflyloxy)-2-iodobenzene (**5a**), with *N*-(trimethylsilyl)morpholine (**6a**) (Table 1). Our initial attempts of treating a mixture of **5a** and **6a** in

Table 1. Optimization of the Reaction Conditions



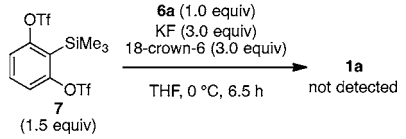
entry	activator	yield[a] (%)
1	*n*-BuLi	27
2	*i*-PrMgCl·LiCl	33
3	PhMgBr	28
4	Me_3SiCH_2MgCl	73
5[b]	Me_3SiCH_2MgCl	80
6[b,c]	Me_3SiCH_2MgCl	81[d]

[a]Yields based on ^1H NMR analysis, unless otherwise noted. [b]The reaction was performed at room temperature. [c]**5a** (10 mmol, 5.0 g) was used. [d]Isolated yield.

diethyl ether at 0 °C with an activator, such as *n*-butyllithium, isopropylmagnesium chloride–lithium chloride complex, or phenylmagnesium bromide, afforded the desired **1a** only in low yields (entries 1–3). The use of (trimethylsilyl)-methylmagnesium chloride as an activator[9] largely increased the yield of **1a** (entry 4), which was further improved by performing the reaction at room temperature (entry 5); these conditions allowed for a gram-scale synthesis of **1a** without decreasing the yield (entry 6). The formation of undesired byproducts, such as a regioisomer or a triflone derivative, which could be formed via the thia-Fries rearrangement of an aryl anion intermediate (**III**, Figure 1C),[8a,f] was not observed. On the other hand, an attempt to prepare **1a** from 1,3-bis(triflyloxy)-2-(trimethylsilyl)benzene (**7**),[8b,c] another 3-(triflyloxy)benzyne precursor, according to the conditions for silylamination of arynes reported by Yoshida, Kunai, and co-workers,[7] was unsuccessful; treating a mixture of **7** and **6a** with potassium fluoride and 18-crown-6-ether did not afford **1a**, probably due to the prior cleavage of the N–Si bond of **6a** (Scheme 1). These results indicated the advantage of using 1,3-bis(triflyloxy)-2-iodobenzene (**5a**) as a precursor of 3-(triflyloxy)benzyne and the silylmethyl Grignard reagent as its acivator for efficiently achieving the silylamination of 3-(triflyloxy)benzyne without cleaving the weak N–Si bond.[10]

The optimized conditions were successfully employed for the preparation of various 5-substituted 3-morpholino-2-(trimethylsilyl)aryl triflates (Figure 2). For example, methyl-, *p*-anisyl-, or *p*-fluorophenyl-substituted 3-(*N*-morpholino)aryne

Scheme 1. Attempt To Prepare 1a from an *o*-Silylphenyl Triflate Type Precursor



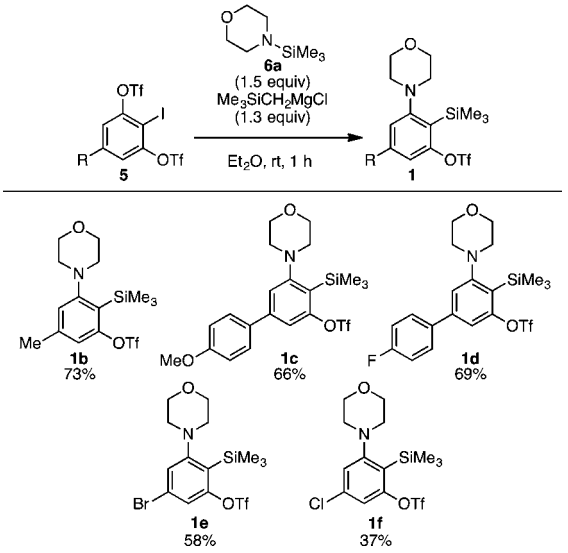


Figure 2. Synthesis of various 5-substituted 3-morpholino-2-silylaryl triflates.

precursors **1b–d** were obtained in good yields via silylamination of 3-(triflyloxy)arynes, generated from the corresponding 5-substituted 1,3-bis(triflyloxy)-2-iodobenzenes. Furthermore, the silylamination of 5-bromo- or 5-chloro-3-(triflyloxy)-benzyne afforded 3-morpholinoaryne precursors **1e** and **1f** bearing a transformable halogeno group in moderate yields without affecting the halogeno groups.

A wide range of *N*-(trimethylsilyl)amines were also applicable to the silylamination of 3-(triflyloxy)benzyne, which provided various 3-amino-2-silylaryl triflates **1g–m** (Figure 3). In addition to cyclic *N*-silylamines, acyclic substrates such as *N*,*N*-dimethyl- and *N*,*N*-diethyl-*N*-(trimethylsilyl)amine participated in the reaction to afford 3-(dialkylamino)-2-silylaryl triflates **1g** and **1h**, respectively, in good yields. *N*-Silylamines bearing an ethoxycarbonyl or *N*-(*tert*-butoxycarbonyl)amino group tolerated this transformation, as demonstrated in the synthesis of **1i** and **1j**. The reaction with *N*-aryl-*N*-methyl-*N*-(trimethylsilyl)amines, including those bearing an electron-donating or electron-withdrawing group on the aryl group, also took place to provide (*N*-methylanilino)aryne precursors **1k–m** in moderate yields.

3-Aminobenzyne reacted with a broad range of arynophiles with high regioselectivities in a fashion similar to that of 3-alkoxybenzyne (Table 2). For example, on treating 3-morpholinobenzyne precursor **1a** with potassium fluoride and 18-crown-6-ether in the presence of *N*-methylaniline (**8**), an unsymmetrical 1,3-diaminobenzene derivative **9** was obtained as a single regioisomer in high yield (entry 1). Similarly, regioselective nucleophilic addition of thiol **10** to 3-morpholinobenzyne took place efficiently to yield 3-morpholinophenyl sulfide **11** (entry 2). The cycloaddition of 3-morpholinobenzyne with nitrone **12** proceeded smoothly to

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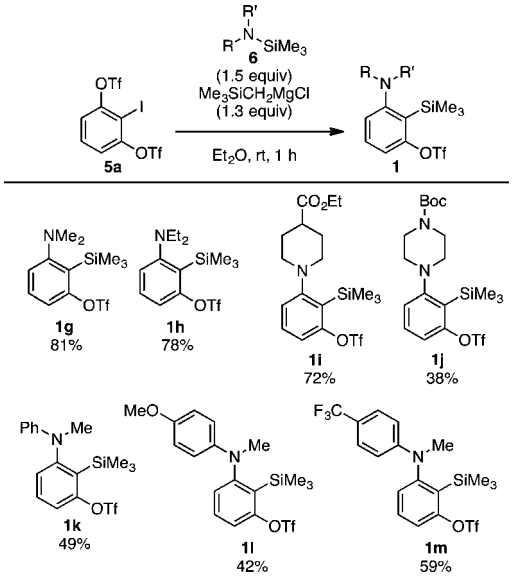
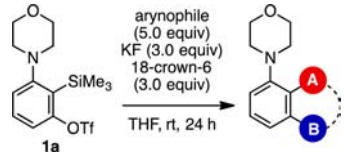
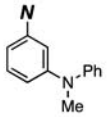
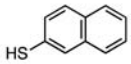
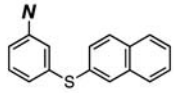
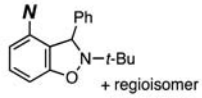
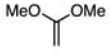
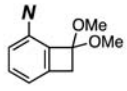
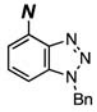
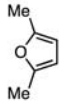
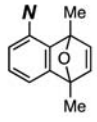
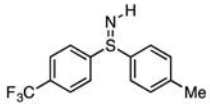
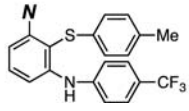


Figure 3. Synthesis of various 3-amino-2-silylphenyl triflates.

Table 2. Reactions of 3-Aminobenzyne with Various Arynophiles



entry	arynophile		product[a]		yield (%)
1		8		9	84
2		10		11	94
3		12		13	96 (95:5)[b]
4		14		15	68
5	N_3Bn	16		17	76
6		18		19	85
7[c]		20		21	66

[a]*N* = morpholino. [b]Ratio of regioisomers, determined on the basis of ^{1}H NMR analysis, shown in parentheses. [c]The reaction was performed using 2.0 equiv of **20** at 60 °C for 15 h.

afford the cycloadduct **13** with high selectivity (entry 3). When reactions were performed using ketene dimethyl acetal (**14**) or benzyl azide (**16**) as an arynophile, the corresponding cycloadducts **15** and **17** were exclusively obtained in good yields via [2 + 2] and [2 + 3] cycloadditions, respectively (entries 4 and 5). Diels–Alder reaction between 3-morpholinobenzyne and 2,5-dimethylfuran (**18**) also proceeded efficiently to give naphthalene derivative **19** (entry 6). Furthermore, similar to our recent report regarding the direct thioamination of 3-methoxybenzyne with sulfilimine **20**,[11] 3-morpholinobenzyne reacted regioselectively with **20** to afford 1,3-diaminophenyl sulfide **21** as a single product in good yield (entry 7).

3-Aminobenzyne was also useful for preparing a small red-shifted fluorescent molecule[12] (Scheme 2 and Table 3).

Scheme 2. Synthesis of 5-Morpholinocoumarin 23

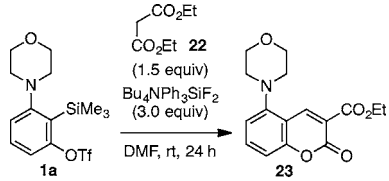
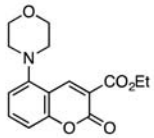
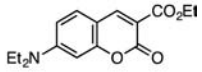


Table 3. Fluorescent Properties of Aminocoumarins

coumarin	 **23**		 **24**	
solvent	CH_2Cl_2	MeOH	CH_2Cl_2	MeOH
λ_{max} abs[a] (nm)	378	383	418	419
λ_{max} em[b] (nm)	540	573	452	465
Stokes shift (nm)	162	190	34	46
color	yellow	orange	blue	blue

[a]Wavelength of maximum absorption. [b]Wavelength of maximum fluorescent intensity.

Although various 7-aminocoumarins have been prepared and their fluorescent properties have been studied, the fluorescent properties of 5-aminocoumarins remain largely unexplored, which could probably be attributed to the lack of a general synthetic method. Applying the reported method for aryne-mediated synthesis of coumarins[13] to 3-aminobenzyne, we successfully prepared 5-morphorinocoumarin **23**; three-component coupling of 3-morphorinobenzyne precursor **1a**, diethyl malonate (**22**), and *N*,*N*-dimethylformamide resulted in the formation of **23** in good yield (Scheme 2). A solution of newly synthesized 5-morphorinocoumarin **23** in methanol or dichloromethane showed distinctive fluorescent properties as compared to that of 7-aminocoumarin such as **24**. Remarkable red-shifted emissions (from blue to yellow or orange) with dramatically expanded Stokes shifts (162 nm in dichloromethane and 190 nm in methanol) were observed. Although

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further studies are required, the unique fluorescent properties of 5-morphorinocoumarin **23** can be explained by a twisted-intramolecular charge transfer (TICT) process,[14] which is caused by the repulsion between the morpholino group and the peri hydrogen at the 3-position.

In summary, we have demonstrated the utility of an aryne relay chemistry for the synthesis of diverse aminoarenes. Various 3-amino-2-silylaryl triflates were easily prepared via silylamination of 3-(triflyloxy)arynes. The key to the success was generation of 3-(triflyloxy)arynes via an iodine−magnesium exchange reaction of readily available 1,3-bis(triflyloxy)-2-iodoarenes using a silylmethyl Grignard reagent, which allowed the regioselective reaction with *N*-silylamines without cleaving their weak N−Si bond. A wide variety of aromatic amines, which are difficult to synthesize using conventional methods, have been efficiently synthesized with high regioselectivities from a 3-aminobenzyne precursor prepared by our new method. Further studies expanding the scope of *N*-silylamines and the synthesis of other 5-aminocoumarin derivatives are now in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03304.

Experimental procedures, characterization for new compounds including NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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