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Silica gel-induced aryne generation from *o*-triazenylarylboronic acids as stable solid precursors†

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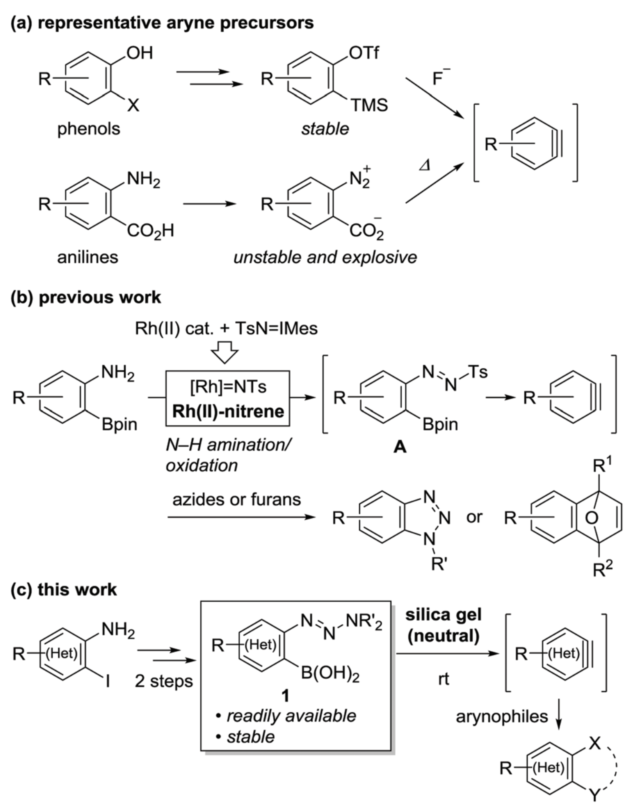
We report the development of *o*-triazenylarylboronic acids as new aniline-based aryne precursors. The readily available and shelf-stable solid precursors generate (hetero)arynes under remarkably mild conditions using silica gel as the sole reagent, which subsequently undergo reactions with a range of arynophiles. Furthermore, solid-state aryne reactions under solvent-free conditions were accomplished. Aryne generation proceeded *via* a dual activation mechanism, as rationalized using Jaffé's plot analysis based on Hammett constants.

Introduction

Arynes and heteroarynes are highly reactive synthetically useful reaction intermediates that enable the simultaneous creation of two bonds, including C–C, C–H, and C–X (X = heteroatom) bonds, on adjacent aromatic carbons *via* reactions with a range of arynophiles.[1–3] Because unstable arynes are typically generated *in situ*, a judicious choice of precursors that generate arynes under conditions compatible with the selected arynophiles is crucial for achieving the desired transformations. Over the last few decades, the use of 2-trimethylsilylphenyl triflates[4] in combination with fluoride ions has significantly contributed to the advancement of aryne chemistry, including the expansion of the arynophile scope, elegant reaction design, and syntheses of functional and biologically active compounds (Scheme 1a). These achievements are attributed to the stability and accessibility of the precursors, obtained from ubiquitous phenols, as well as the use of mild reaction conditions. In addition to phenol derivatives, aniline derivatives, represented by benzenediazonium 2-carboxylates, have been used as aryne precursors since the 1960s.[5] However, despite their latent synthetic utility associated with the ubiquity of anilines, being comparable to that of phenols, their use is presently limited owing to their explosive character.[6] In this context, we envisioned that the development of a methodology for aryne generation from readily available and stable aniline derivatives under mild conditions would contribute to further advancements of aryne chemistry, which would be distinct from that achieved hitherto with phenol-based precursors.[7]



Scheme 1 Aryne generation from phenol- and aniline-based precursors.

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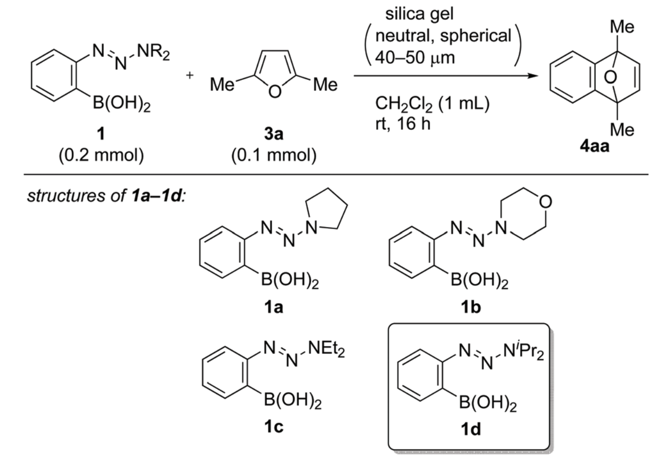
We recently reported the development of a new methodology for aryne generation from *o*-aminophenylboronates *via* the *in situ* preparation of a new aryne precursor, namely, *N*-tosyldiazene **A** (Scheme 1b).[8] However, under the conditions implemented for the *in situ* preparation of unstable **A**, including the generation of reactive Rh(II)-nitrene species from Rh(II) catalyst and iminoiodinane (TsN = IMes), the only applicable arynophiles were found to be azides and furans. These results prompted us to design a more stable precursor based on **A**, not requiring *in situ* preparation. After some consideration, we newly designed *o*-triazenylarylboronic acids **1** by replacing the diazene moiety of **A** with a triazenyl group, which is well-known as a masked diazonio group.[6c,9] Herein, we describe the unexpected discovery of (hetero)aryne generation from *o*-triazenylarylboronic acids **1** under remarkably mild reaction conditions using neutral silica gel as the sole reagent (Scheme 1c).

Table 1 Silica gel-induced reaction of *o*-triazenylphenylboronic acids **1** and 2,5-dimethylfuran (**3a**)[a]



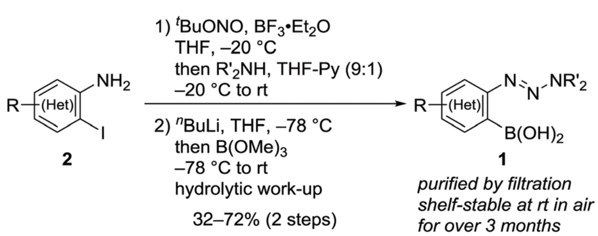
Entry	Triazene	Silica gel[b] (mg)	Variation from standard conditions	Yield[c] (%)
1	**1a**	0	None	ND (36)[d]
2	**1a**	40	None	33
3	**1a**	120	None	75
4	**1a**	200	None	88
5	**1b**	200	None	71
6	**1c**	200	None	93
7	**1d**	200	None	Quant. (92)[d,e]
8	**1d**	200	Silica gel (undried)	95
9	**1d**	200	**1d** : **3a** = 1.5 : 1	98
10	**1d**	200	**1d** : **3a** = 1 : 2	59
11	**1d**	200	MeCN instead of CH_2Cl_2	54
12	**1d**	200	THF[f] instead of CH_2Cl_2	NR
13	**1d**	200	Toluene instead of CH_2Cl_2	98
14	**1d**	200	Hexane instead of CH_2Cl_2	97

[a] Reaction conditions: **1** (0.200 mmol), **3a** (0.100 mmol), silica gel in CH_2Cl_2 (1.0 mL). [b] Silica gel was used after heating under vacuum to dryness. [c] Determined by ^1H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [d] Yields in parentheses refer to the yields of the isolated products. [e] In 5 mmol scale (**1d**: 10.0 mmol, **3a**: 5.00 mmol). [f] Stabilizer-free.

Results and discussion

Following a literature procedure,[10] *o*-triazenylarylboronic acids **1** were synthesized from *o*-iodoarylamines **2** in 32–72% yields over two steps, including triazene formation *via* diazotization followed by borylation *via* halogen–lithium exchange (Scheme 2). Notably, synthesized **1** were obtained as solids after purification by filtration and were shelf-stable at ambient temperature in air for over three months.

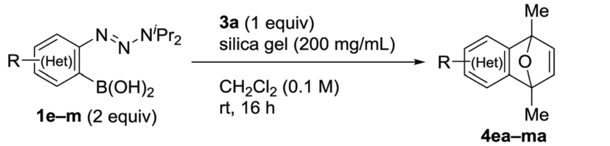
Initially, we examined the reaction of **1a** with 2,5-dimethylfuran (**3a**) in CH_2Cl_2 without the use of additives (Table 1, entry 1). Interestingly, TLC analysis indicated the formation of cycloadduct **4aa**, whereas the ^1H NMR spectrum of the crude product suggested that the reaction had not occured. Indeed, **4aa** was obtained in 36% isolated yield after column chromatography on silica gel (neutral, spherical, 40–50 μm). Inspired by these results, we examined the reaction of **1d** (0.2 mmol) in the presence of silica gel.[11] The yield of **4aa** increased with increasing amounts of silica gel, and a maximum yield of 88% was observed with 200 mg of silica gel (entries 2–4).[12] Regarding alkyl substituents on the triazenyl group, isopropyl groups were proven to be optimal, and quantitative ^1H NMR yield was obtained with the use of **1d** (entries 4–7). Notably, when **1d** was used on 5 mmol scale, **4aa** was isolated in 92% yield (entry 7). Silica gel displayed virtually no loss of activity when it was used without dryness (entry 8). Although the amount of **1d** could be reduced to 1.5 equiv. without significant loss of yield (entry 9), using **1d** as the limiting reagent (**1d** : **3a** = 1 : 2) decreased the yield to 59% (entry 10). Solvent screening revealed that polar solvents, such as MeCN and THF, were markedly less effective than CH_2Cl_2 (entries 11 and 12). In particular, virtually no conversion of **1d** was observed in THF. In contrast, the use of toluene provided a yield comparable to that obtained in CH_2Cl_2 (entry 13). Interestingly, a high product yield was also obtained using hexane, even though **1d** was hardly soluble (entry 14).

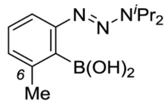
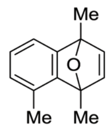
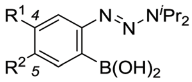
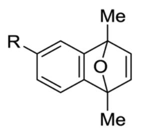
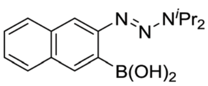
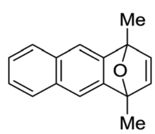
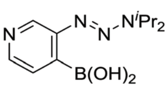
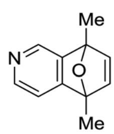
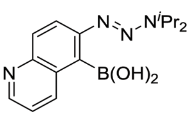
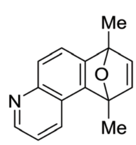
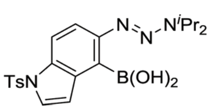
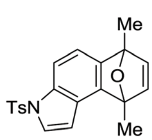


Scheme 2 Syntheses of *o*-triazenylarylboronic acids **1**.

With the optimized conditions in hand, we next examined the performance of functionalized aryne precursors **1e–j** and heteroaryne precursors **1k–m** (Table 2). Precursors **1e–i** bearing electron-donating or electron-withdrawing groups at the 4-, 5-, and 6-position provided **4ea–ia** in 68–98% yields (entries 1–7). The results obtained with chlorine-substituted (**1f**, **1f′**) and methoxy-substituted precursors (**1g**, **1g′**) demonstrated that the position of the substituent had little impact on

Table 2 Scope of aryne precursors **1**

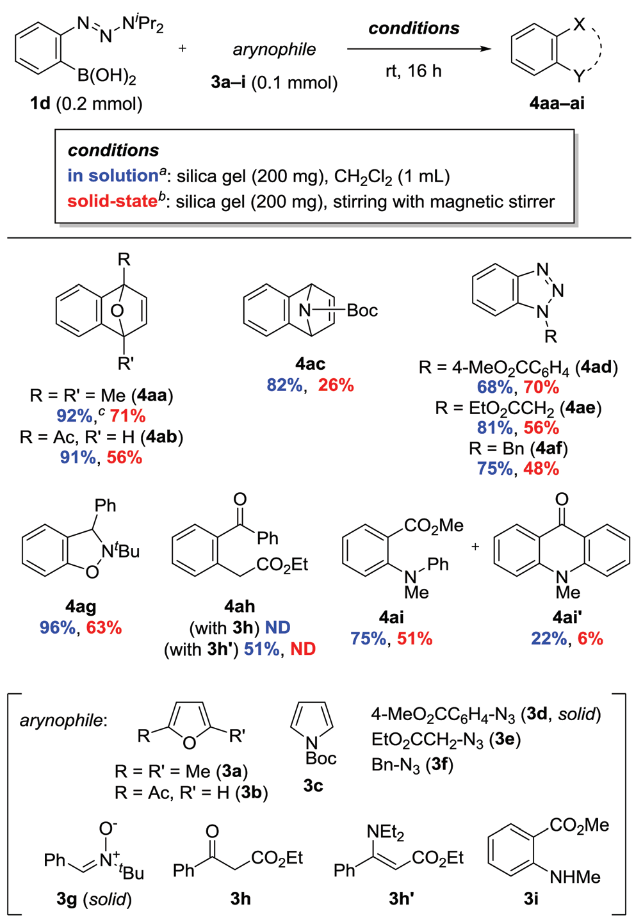


Entry	Triazene	Product; yield[a]
1	 **1e**	 **4ea**; 84%
	 **1f–i**	 (R = R^1 or R^2) **4fa–ia**
2	R^1 = H, R^2 = Cl (**1f**)	R = Cl (**4fa**); 98%
3	R^1 = Cl, R^2 = H (**1f′**)	R = Cl (**4fa**); 95%
4	R^1 = H, R^2 = OMe (**1g**)	R = OMe (**4ga**); 98%
5	R^1 = OMe, R^2 = H (**1g′**)	R = OMe (**4ga**); 86%
6	R^1 = H, R^2 = CF_3 (**1h**)	R = CF_3 (**4ha**); 68%
7	R^1 = H, R^2 = CN (**1i**)	R = CN (**4ia**); 96%
8	 **1j**	 **4ja**; 93%
9	 **1k**	 **4ka** 16% (**1k**:**3a** = 2:1) 13% (**1k**:**3a** = 1:2) 62% (**1k**:**3a** = 1:5)
10	 **1l**	 **4la** 28% (**1l**:**3a** = 2:1) 63% (**1l**:**3a** = 1:2)
11	 **1m**	 **4ma** 96% (**1m**:**3a** = 2:1) 83% (**1m**:**3a** = 1:2)

[a] Isolated yields.

the product yield (entries 2–5). In addition to benzynes, the present protocol was applicable to the reaction of 2,3-naphthalyne (entry 8) and heteroarynes (entries 9–11).[3] Under the standard conditions, 3,4-pyridyne precursor **1k** resulted in the formation of **4ka** in only 16% yield (entry 9). However, we found that the use of an excess amount of arynophile **3a** significantly improved the yield to 62%. Similar results were obtained with 5,6-quinolyne precursor **1l**, whereby only 2 equiv. of **3a** was sufficient to give **4la** in 63% yield (entry 10). In contrast to **1k** and **1l**, 4,5-indolyne precursor **1m** afforded **4ma** in excellent yields in both cases using **1m** and **3a** as the limiting reagent (entry 11).

Next, we investigated the reaction of **1d** with a range of arynophiles (Scheme 3). The precursor was applicable to [4 + 2] and [3 + 2] cycloadditions with various arynophiles, including furan **3b**, pyrrole **3c**, azides **3d–f**, and nitrone **3g**. Unfortunately, β-ketoester **3h** failed to produce the desired product **4ah**. Instead, using enamine **3h′** provided **4ah** in 51% yield.[13] The reaction with methyl *N*-methylanthranilate (**3i**) gave *N*-phenylated product **4ai** in 75% yield along with 22% of *N*-methylacridone (**4ai′**).[14] Surprisingly, the reactions also proceeded in the absence of solvent by mixing **1d**, **3**, and silica gel



Scheme 3 Reactions of **1d** with arynophiles **3a–i**. [a] Isolated yields. [b] ^{1}H NMR yields using 1,1,2,2-tetrachloroethane as an internal standard. [c] 5 mmol scale.

using a magnetic stirrer.[15] The formation of **4** under these solvent-free conditions indicated that the aryne had formed *via* the contact of **1d** and silica gel at the solid–solid interface. Furthermore, the generated aryne reacted effectively even with solid arynophiles **3d** and **3g**. Notably, compared with the outcome of reactions conducted in solution, no significant loss of yield was observed, except in the cases of **3c** and **3h′**, despite a lower diffusion rate in the solid-state than in solution. The results suggested that the lifetime of aryne was sufficiently long to encounter the arynophile through diffusion on the silica gel surface. Although a growing number of studies on solid-state reactions have emerged in recent years,[11b,d,16,17] our results represent a pioneering example of solid-state intermolecular reactions occuring *via* short-lived reactive species.[16d]

Along with the feasibility of solid-state operation, excellent functional group tolerance is a salient feature of the present method. In particular, the fluoride-free conditions allowed for the use of arynophiles bearing silyl functionalities (Scheme 4). The reaction of **1d** and *O*-*tert*-butyldimethylsilyl (TBS)-protected zidovudine **3j** provided **4aj** in a significantly higher yield than that obtained in a previous study, with the added advantage of inexpensive and environmentally benign conditions (Scheme 4a).[8] 2-Siloxy-1,3-diene **3k**, which is sensitive to various conditions, was also applicable as an arynophile to provide [2 + 2] cycloadduct **4ak** in 58% yield, while no evidence of [4 + 2] cycloaddition was observed.

To gain insight into the reaction mechanism, we performed a time-course study (Fig. 1). To a series of reaction vessels containing **3a** (0.1 mmol), silica gel, and CH_2Cl_2 was added **1d** (0.2 mmol), and each mixture was filtered after stirring for the indicated time to remove silica gel. ^{1}H NMR analysis of the crude mixture after stirring for 5 min indicated that only ∼0.05 mmol of **1d** (∼25% of initial amount) was contained in the mixture. The amount of **1d** slowly decreased over 4 h. Meanwhile, the formation of **4aa** proceeded in >90% yield within 4 h according to the rate of N_2 gas evolution.[18] This result indicated that **1d** was strongly adsorbed on the silica gel surface preceding aryne generation.

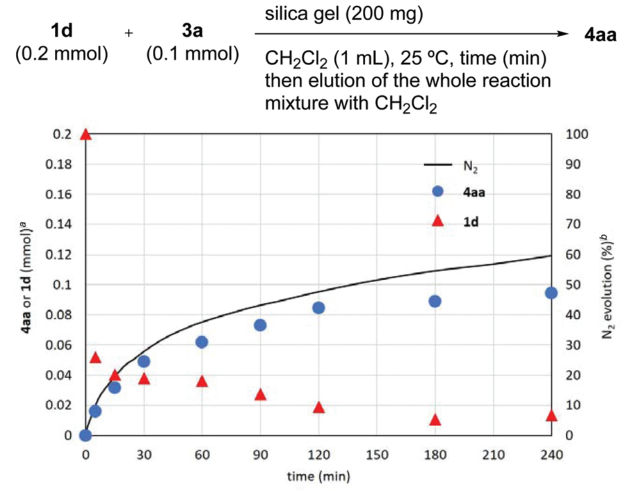
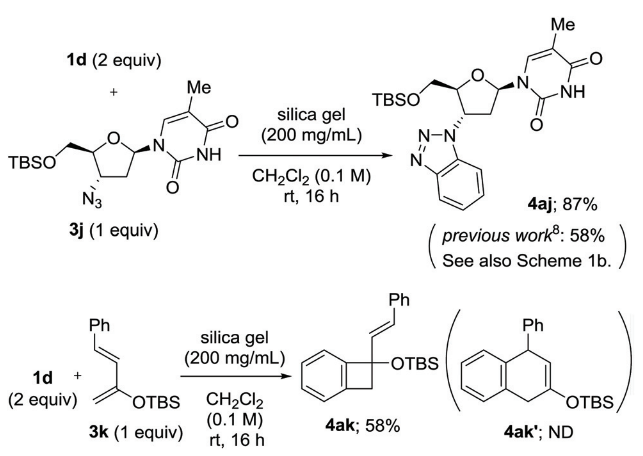


Fig. 1 Time course studies of the reaction of **1d** and **3a**. [a] Determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [b] Based on **1d** (0.8 mmol).



Scheme 4 Utilization of arynophiles bearing silyl functionalities.

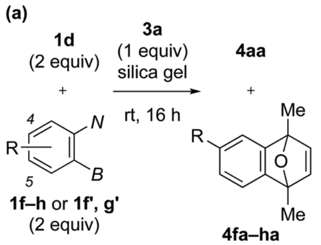
Next, we performed competition experiments between parent precursor **1d** and substituted precursors **1f–h** or **1f′**, **g′**, and analyzed the relative rate of the reaction (k_R/k_H) using Hammett constants based on the triazenyl group (σ_N) and those based on the borono group (σ_B) (Fig. 2a).[19] As a result, the plots according to Jaffé's eqn (2) and (3),[20] derived from the Hammett eqn (1), exhibited linearity with good R^2 values, as shown in Fig. 2b and c, respectively (see ESI for details†).

$$\log(k_R/k_H) = \rho_N\sigma_N + \rho_B\sigma_B \qquad (1)$$

$$\log(k_R/k_H)/\sigma_N = \rho_N + \rho_B(\sigma_B/\sigma_N) \qquad (2)$$

$$\log(k_R/k_H)/\sigma_B = \rho_N(\sigma_N/\sigma_B) + \rho_B \qquad (3)$$

The obtained negative ρ_N and positive ρ_B values suggest simultaneous build-up of positive and negative charges on the nitrogen atom and the boron atom, respectively, in the rate-determining step (see ESI for details†). Combining the results in Fig. 1 and 2, we propose a plausible reaction mechanism, as illustrated in Scheme 5. Precursor **1** is adsorbed onto the silica gel surface *via* the boronate moiety, followed by the formation of zwitterionic intermediate **B**.[21] In other words, triazenyl and borono groups were activated as diazonio and boronate groups, respectively. Upon this dual activation, highly stable precursor **1** is capable of generating an aryne under remarkably mild conditions without heating, photo-irradiation, or the use of acids or bases.[9] The role of silica gel remains unclear.[22] While the use of excess acetic acid instead of silica gel induced aryne generation from **1d**, the yield of **4aa** was only 47% (Scheme 6a). Thus, weak acidity of silica gel seems to be insufficient to activate **1**. On the other hand, (±)-camphorsulfonic acid [(±)-CSA] led to a formation of **4aa** in 97% yield (Scheme 6b). Thus, both heterogeneous conditions using silica



substituent	σ_N	σ_B	k_R/k_H[a]
5-Cl (**1f**)	0.23	0.37	1.30
4-Cl (**1f'**)	0.37	0.23	0.153
5-OMe (**1g**)	−0.27	0.12	12.7
4-OMe (**1g'**)	0.12	−0.27	0.170
5-CF$_3$ (**1h**)	0.53	0.49	0.180

[a] Determined by ^{1}H NMR.

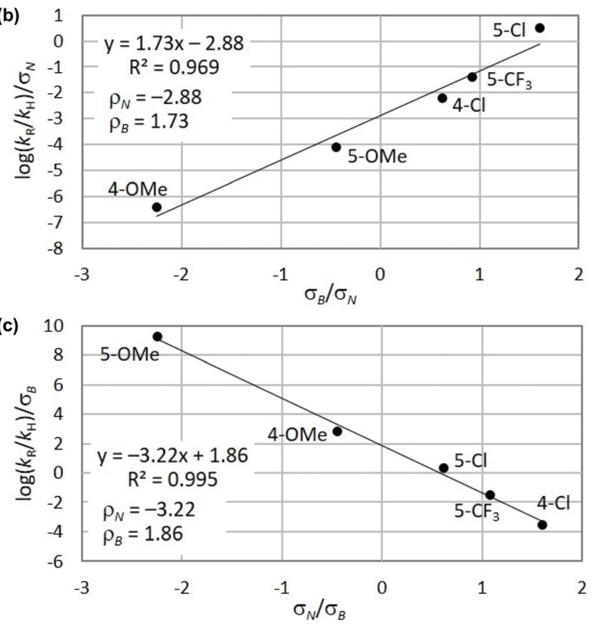
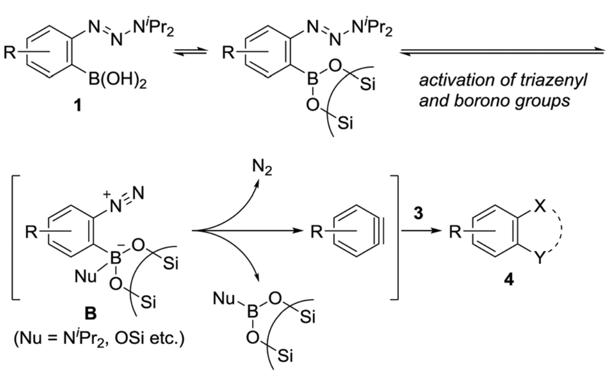
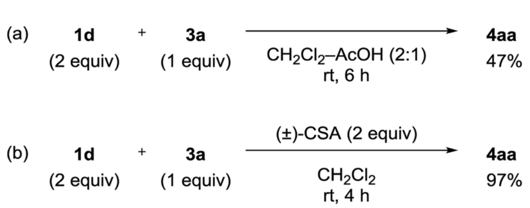


Fig. 2 (a) Competition experiments between **1d** and **1f–h**, or **1f'**, **g'**. (b) Jaffé's plot based on eqn (2). (c) Jaffé's plot based on eqn (3).



Scheme 5 Plausible dual activation mechanism for aryne generation from **1**.



Scheme 6 Reactions of **1d** with **3a** using Brønsted acid.

gel and homogeneous conditions using Brønsted acid were applicable to aryne generation from **1**.

Conclusions

We have developed new aniline-based aryne precursors **1**, which generate arynes under remarkably mild conditions through the use of silica gel as the activating agent. The protocol was applicable to a wide range of (hetero)arynes and various arynophiles reacting in solution and in the solid-state. The reaction proceeded *via* a dual activation mechanism to generate arynes, as rationalized through Jaffé's plot analysis based on Hammett constants. Investigation of further synthetic applications of the protocol as well as mechanistic studies on the role of silica gel are currently in progress.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank T. Koseki of the Analytical Center of Meiji Pharmaceutical University for conducting mass spectrometry measurements. The authors would like to thank Prof. Dr S. Akai for constructive comments on draft of the manuscript.

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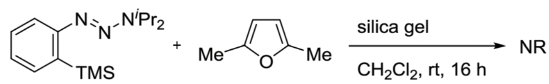

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22 No reaction was observed with the use of other adsorbents, such as alumina (neutral or basic) and MS 4A. Compared to that of spherical silica gel (40–50 μm, specific surface area: 630–730 m^2 g^{-1}), crushed-shape silica gel (40–63 μm, specific surface area: 480–540 m^2 g^{-1}) displayed lower activity. In addition, recycling of spherical silica gel slightly diminished the activity. Thus, the activity of silica gel depends on the properties of their surface. Additionaly, we consider that the silica gel did not play the role of a photocatalyst, because quantitative conversion of **1d** was observed in the dark. See ESI for details.†