Received: January 21, 2015 | Accepted: February 8, 2015 | Web Released: February 17, 2015 CL-150060

Generation of Arynes Using Trimethylsilylmethyl Grignard Reagent for Activation of *ortho*-Iodoaryl or *ortho*-Sulfinylaryl Triflates

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The trimethylsilylmethyl Grignard reagent triggered efficient generation of arynes from various *ortho*-iodoaryl or *ortho*-sulfinylaryl triflates. The moderate nucleophilicity and basicity of the reagent facilitated efficient reactions between the aryne precursors and arynophiles containing organometallic nucleophile-sensitive functionalities.

Arynes are highly reactive intermediates that enable facile synthesis of complex aromatic molecules, as clearly demonstrated in a number of total syntheses of complex natural products.[1,2] Diverse heterocyclic frameworks, which are difficult to construct by conventional methods, are straightforwardly formed through the reactions of arynes with various type of arynophiles.[3]

To effectively utilize aryne intermediates in diverse applications, numerous methods for the generation of arynes and their precursors have been developed;[4] e.g., fluoride-mediated activation of *ortho*-silylaryl triflates.[4a] Our group recently developed new methods for generating arynes from readily available precursors such as *ortho*-borylaryl triflates[4l] and *ortho*-sulfinylaryl triflates.[4m]

ortho-Iodoaryl sulfonates are also useful as aryne precursors. By treating them with an organometallic activator, arynes are generated via an iodine–metal exchange reaction and subsequent β-elimination of the sulfonyloxy group (Figure 1).[4b,5–7] Suzuki and co-workers have investigated a series of studies based on aryne generation from *ortho*-iodoaryl triflates using *n*-butyllithium as the activator.[4b,5] Knochel and co-workers successfully generated arynes from 2-magnesiated aryl sulfonates, which were prepared in situ by treating *ortho*-iodoaryl 4-chlorobenzenesulfonates with isopropylmagnesium chloride at −78 °C.[4e,6] This method enabled efficient generation and transformation of arynes bearing electrophilic moieties, such as the ester moiety in **1b**. We recently found that the trimethylsilylmethyl Grignard reagent serves as a better activator than those previously reported, for generating arynes bearing a base-sensitive terminal alkyne moiety[7a] or highly electrophilic 3-triflyloxybenzyne[7b] from the *ortho*-iodoaryl triflates **1c** or **1d**, respectively. Herein, we demonstrate the general scope of the trimethylsilylmethyl Grignard reagent for generating arynes from various *ortho*-iodoaryl triflates as well as the scope of applicable arynophiles.

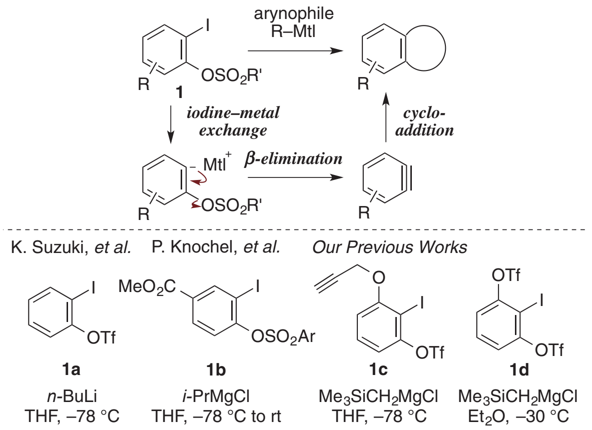
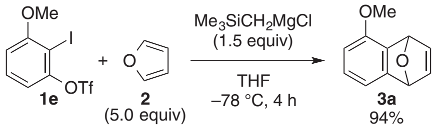
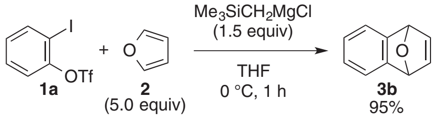


Figure 1. Generation of arynes from *ortho*-iodoaryl sulfonates. Tf = CF_3SO_2, Ar = 4-ClC_6H_4.

The optimal conditions for generating 3-(propargyloxy)benzyne from the precursor **1c** using the trimethylsilylmethyl Grignard reagent as the activator[7a] were also suitable for efficient generation of simple arynes such as 3-methoxybenzyne or unsubstituted benzyne. Treatment of a mixture of 2-iodo-3-methoxyphenyl triflate (**1e**) and furan (**2**) with (trimethylsilylmethyl)magnesium chloride at −78 °C afforded cycloadduct **3a** in high yield (eq 1). In the case of benzyne precursor **1a**, performing the reaction at a higher temperature (0 °C) gave a good result (eq 2). When the reaction was performed at −78 °C for 1 h, **3b** was obtained in only 28% yield with 66% recovery of **1a**, suggesting slower generation of benzyne from **1a** compared to that when methoxy congener **1e** was used.



(1)

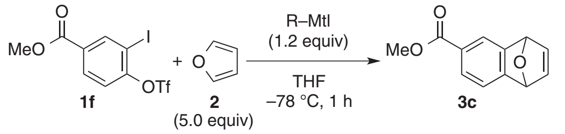


(2)

The trimethylsilylmethyl Grignard reagent served as an efficient activator for the generation of an aryne bearing an electrophilic functional group such as an ester moiety. Attempts to generate 4-(methoxycarbonyl)benzyne from 2-iodo-4-(methoxycarbonyl)phenyl triflate (**1f**) using various alkyl- or arylmetals in the presence of furan (**2**) at −78 °C showed that (trimethylsilylmethyl)magnesium chloride was the most effective activator (Table 1, Entries 1–6). The best result was obtained by performing the reaction at a higher temperature (−30 °C), affording cycloadduct **3c** in excellent yield (Entry 7).

The moderate nucleophilicity of the trimethylsilylmethyl Grignard reagent[8] allowed us to utilize an aryne intermediate bearing an organometallic nucleophile-susceptible ester group without special care. Indeed, treatment of a mixture of 4-(methoxycarbonyl)benzyne precursor **1f** and furan (**2**) with an excess of (trimethylsilylmethyl)magnesium chloride at room temperature afforded **3c** in high yield (Table 2, Entry 4). On the

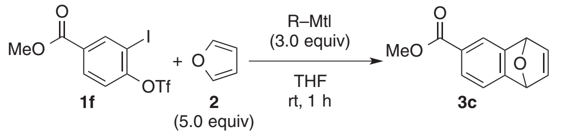
Table 1. Optimization of the reaction conditions



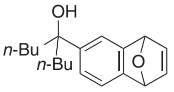
Entry	R–Mtl	**3c**/%[a]
1	*n*-BuLi	25
2	*i*-PrMgCl	64
3	*i*-PrMgCl•LiCl	67
4	EtMgBr	55
5	PhMgBr	11
6	Me_3SiCH_2MgCl	77
7[b]	Me_3SiCH_2MgCl	90[c]

[a]Yields based on ^1H NMR analyses, unless otherwise noted. [b]Reaction was performed at −30 °C. [c]Isolated yield.

Table 2. Reaction between **1f** and **2** using an excess amount of activators



Entry	R–Mtl	**3c**/%[a]
1	*n*-BuLi	8[b]
2	*i*-PrMgCl	11
3	*i*-PrMgCl·LiCl	11
4	Me_3SiCH_2MgCl	91



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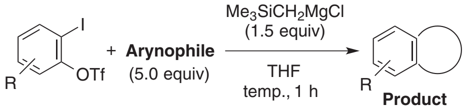
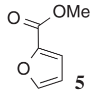
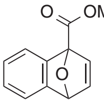
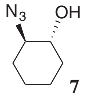
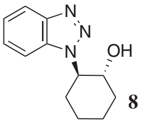
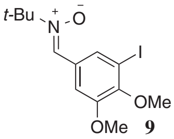
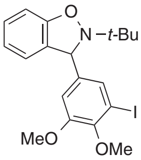
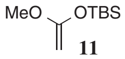
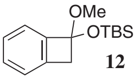
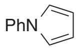
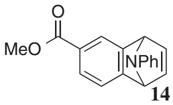
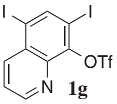
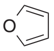
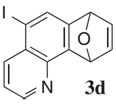
[a]Yields based on ^1H NMR analyses. [b]Alcohol **4** was obtained in 26% yield.

Table 3. Reactions between various aryne precursors and arynophiles



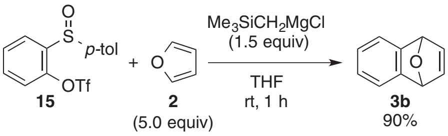
Entry	**1**	Arynophile	Temp./°C	Product	Yield/%[a]
1	**1a**	 **5**	0	 **6**	85
2[b]	**1a**	 **7**	0	 **8**	73
3	**1a**	 **9**	0	 **10**	87
4	**1a**	 **11**	0	 **12**	86
5[c]	**1f**	 **13**	−30	 **14**	86
6[c]	 **1g**	 **2**	−78	 **3d**	63

[a]Isolated yields. [b]8.0 equiv of Me_3SiCH_2MgCl was used. [c]1.2 equiv of Me_3SiCH_2MgCl was used.

other hand, **3c** was obtained in poor yield when more nucleophilic *n*-butyllithium, isopropylmagnesium chloride, or the turbo-Grignard reagent was used as an activator (Entries 1–3). From the reaction using *n*-butyllithium, a certain amount of alcohol **4** was obtained, indicating that the ester moiety of **3c** further reacted with the activator (Entry 1).

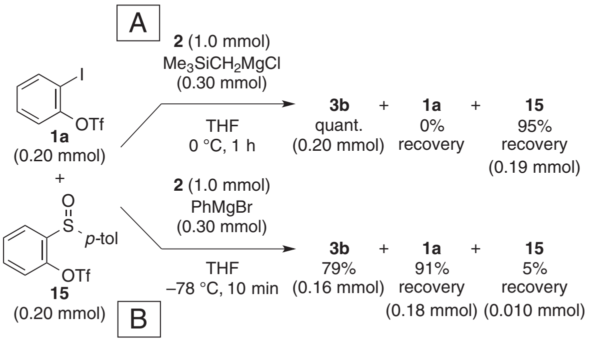
The optimized conditions were applicable to cycloadditions of arynes generated from *ortho*-iodoaryl triflates with an array of arynophiles. With slight modification depending on the substrates, these conditions were applicable even to those bearing organometallic nucleophile-susceptible functional groups (Table 3). Cycloaddition of benzyne with furoate **5** proceeded efficiently to afford cycloadduct **6** without damaging the ester moiety (Entry 1). Azide **7** with an unprotected hydroxy group was also utilizable as an arynophile, providing triazole **8** (Entry 2). In this case, the yield of **8** was improved by using a sufficient excess of the Grignard reagent to deprotonate the hydroxy proton of **7**, which facilitated complete consumption of the aryne precursor **1a**. Nitrone **9** containing an aromatic iodo group reacted with benzyne to afford cycloadduct **10** in high yield without losing the iodo group derived from the arynophile (Entry 3). The [2+2] cycloaddition of benzyne and ketene silyl acetal **11** proceeded efficiently to provide benzocyclobutene **12** (Entry 4). Cycloaddition of 4-(methoxycarbonyl)benzyne, generated from **1f**, with *N*-phenylpyrrole (**13**) afforded polyheterocycle **14** bearing an ester moiety (Entry 5). A quinolyne having an iodo group was also generated from diiodoquinolinyl triflate **1g**, which afforded cycloadduct **3d** in good yield when reacted with furan (**2**) (Entry 6).

An *ortho*-sulfinylphenyl triflate could also be activated with the trimethylsilylmethyl Grignard reagent to generate benzyne. This was accomplished through the treatment of a mixture of **15**[4m] and furan (**2**) in tetrahydrofuran with (trimethylsilylmethyl)magnesium chloride at room temperature, affording cycloadduct **3b** in high yield (eq 3). This result indicated that generation of benzyne via a sulfoxide–magnesium exchange reaction and subsequent β-elimination was efficiently prompted by the Grignard reagent.



(3)

Interestingly, the trimethylsilylmethyl Grignard reagent triggered benzyne generation via an iodine–magnesium exchange reaction prior to that via a sulfoxide–magnesium exchange reaction (Scheme 1). Treatment of an equimolar mixture of *ortho*-iodophenyl triflate (**1a**) and *ortho*-sulfinylphenyl triflate **15** with (trimethylsilylmethyl)magnesium chloride in the presence of an excess amount of furan (**2**) afforded



Scheme 1. Selective generation of benzyne from **1a** or **15** using a different Grignard reagent (yields are based on ^{1}H NMR analyses).

cycloadduct **3b** quantitatively, with almost complete recovery of **15** (Scheme 1A). This indicated that with the trimethylsilylmethyl Grignard reagent, the iodine–magnesium exchange reaction proceeded faster than the sulfoxide–magnesium exchange reaction.[9] In contrast, treatment of the mixture with a phenyl Grignard reagent afforded the product selectively from **15** (Scheme 1B), which was in good agreement with our previous report.[4m] The orthogonality in aryne generation based on the combination of aryne precursor and activator would enable a sequential transformation of a bisaryne equivalent molecule bearing both *ortho*-iodoaryl triflate and *ortho*-sulfinylaryl triflate moieties.

In summary, we demonstrated that the trimethylsilylmethyl Grignard reagent was capable of generating arynes from various *ortho*-iodoaryl and *ortho*-sulfinylaryl triflates. This provided easy access to numerous polycyclic aromatics equipped with various functional groups, which is advantageous in the construction of a chemical library that contains diversity-enriched molecules. Further studies are underway to expand the scope of this method.

The authors thank Central Glass Co., Ltd. for a generous gift of Tf_2O. This work was partially supported by Platform for Drug Discovery, Informatics, and Structural Life Science from MEXT, Japan; JSPS KAKENHI grant numbers 24310164 (T.H.) and 26350971 (S.Y.); a Grant-in-Aid for Scientific Research on Innovative Areas "Chemical Biology of Natural Products" from MEXT, Japan; the Nagase Science and Technology Foundation (T.H.); and Suntory Institute for Bioorganic Research (S.Y.).

Supporting Information for characterization of new compounds is available electronically on J-STAGE.

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9 Soft electrophilic nature of iodo group would be favored by the soft nucleophilic trimethylsilylmethyl Grignard reagent, although the reason for the selectivity is yet to be investigated.