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2-Bromo-6-(chlorodiisopropylsilyl)phenyl tosylate as an efficient platform for intramolecular benzyne–diene [4 + 2] cycloaddition†

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An intramolecular benzyne–diene [4 + 2] cycloaddition with broad substrate scope has been realized by using a cleavable silicon tether, allowing access to various polycyclic structures. 2-Bromo-6-(chlorodiisopropylsilyl)phenyl tosylate serves as an efficient platform for (1) rapid attachment of various arynophiles to the benzyne precursor *via* a Si–O bond and (2) facile generation of benzyne *via* halogen–metal exchange with Ph_3MgLi.

Introduction

Benzyne is a highly reactive species with a distorted formal triple bond.[1,2] The frontier orbital is the unusually low-lying LUMO, that is the origin of four representative reactivities, (1) [4 + 2] cycloaddition, (2) [2 + 2] cycloaddition, (3) ene reaction, and (4) addition of a nucleophile. Among these, the [4 + 2] cycloaddition is useful for constructing benzo-fused six-membered rings embedded in various natural/unnatural products.[2h–o] However, two major problems have stymied further advances in synthetic applications. (1) Periselectivity: the [4 + 2] reactions, in particular of carbocyclic dienes or acyclic dienes, are often accompanied by competing [2 + 2] and ene reactions (Fig. 1a).[3] (2) Regioselectivity: the formation and the ratio of two potential regioisomers depend on the steric and electronic effects of substituents A and B (Fig. 1b). Moreover, an effective frontier orbital interaction is essential for a successful [4 + 2] cycloaddition. Hence the diene component usually requires a high-lying HOMO and a constrained *s*-cis geometry, which are typically provided by a cyclic framework while limiting the scope of this reaction.

One of the solutions to overcome these issues is to exploit the intramolecular reaction by tethering the benzyne progenitors to the dienes (Fig. 1c and Scheme 1).[4] While furans are the most commonly used arynophiles for the intramolecular [4 + 2] cycloaddition as initially demonstrated by Wege,[4a] reactions with carbocyclic or acyclic dienes are rare. An early study by Buszek[4c,d] exemplifies the carbon tether for the benzyne–diene cycloaddition (Scheme 1a), which has later been investigated by Smith with the union of the anion relay chemistry (Scheme 1b).[4g] Danheiser reported an efficient intramolecular [4 + 2] cycloaddition of a benzyne with an acyclic diene by employing a nitrogen tether (Scheme 1c).[4f] Concerning a disposable linker,[5] Martin pioneered the application of the silicon tether, connecting the benzyne precursor with the arynophile *via* a Si–C bond.[4e] However, furans were the only arynophiles used in the study and the method was elegantly exploited in the syntheses of various aryl *C*-glycoside natural products (Scheme 1d).[6]

In this context, we have focused our efforts on developing a viable strategy to further expand the utility of the intramolecular benzyne–diene [4 + 2] cycloaddition. Herein, we report a practical, robust implementation of this reaction by exploiting arylsilyl chloride **I** as a novel benzyne platform (Scheme 1e). Arylsilyl chloride **I** having a silicon atom directly attached to the benzyne precursor allows a facile assembly with the diene partner **II** having a pendant hydroxy group *via* a Si–O linkage under mild conditions to give cycloaddition precursor **III**. This strategy provides the following advantages: (1) the vicinal halogen–sulfonate functionalities of compound **III** allow facile benzyne generation initiated by a halogen–metal exchange[4b,h,i,7] followed by the intramolecular cycloaddition. (2) The broad substrate scope resulting from various combinations of **I** and **II** gives useful cycloadduct **IV** that is amenable to numerous potential elaborations.

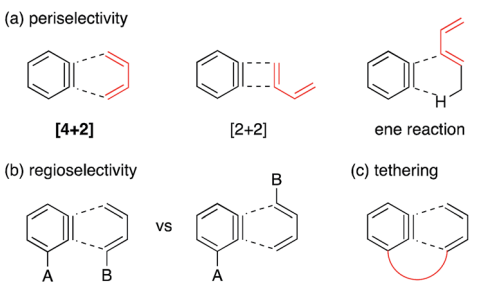

Fig. 1 Peri- and regioselectivity of the benzyne reaction with dienes.

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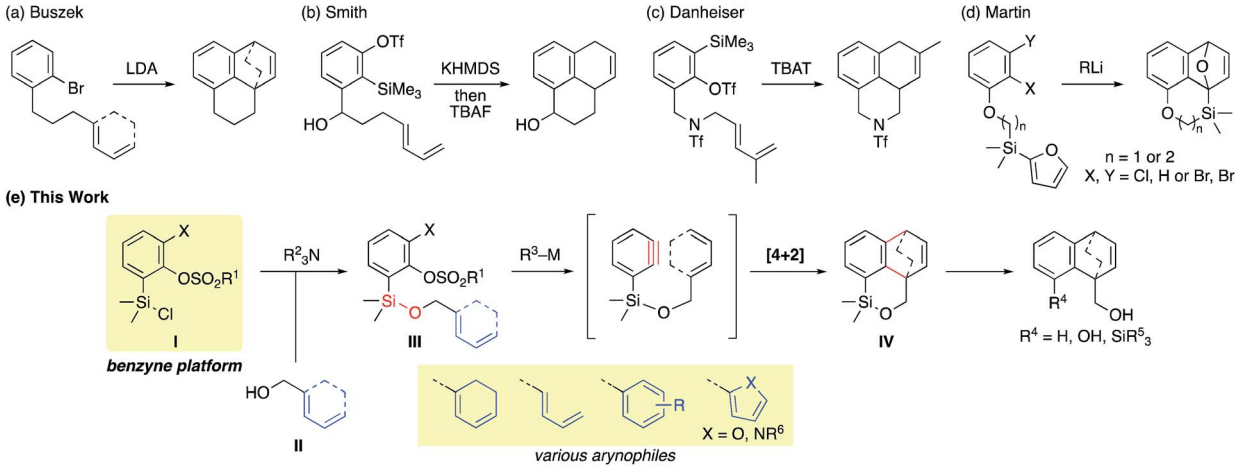


Scheme 1 Overview of the reported intramolecular [4 + 2] cycloaddition of benzyne with dienes (top) and our strategy (bottom).

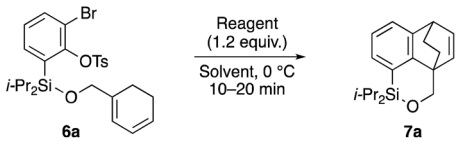
Results and discussion

Scheme 2 shows the preparation of the model substrate **6a**. 2,6-Dibromophenol (**1a**) was silylated with diisopropylsilyl chloride to give the corresponding silyl ether, which was treated with *n*-BuLi to induce a retro-Brook rearrangement[8] to give *o*-silyl phenol **2a** in 87% yield. Treatment of phenol **2a** with TsCl (K_2CO_3, acetone, 0 °C → RT, 1.5 h) gave tosylate **3a** in excellent yield,[9] which reacted with trichloroisocyanuric acid (TCCA), giving silyl chloride **4a** in quantitative yield.[10] It turned out that **4a**, once obtained as a white solid, was stable enough for storage over several months (at −15 °C).

Silyl chloride **4a**, thus obtained, served as a platform to combine various dienyl alcohols to give the cycloaddition precursors, as illustrated by the preparation of the model substrate **6a**. In the presence of imidazole, **4a** was combined with alcohol **5a** having a cyclohexadienyl moiety to give silyl ether **6a** in 80% yield.

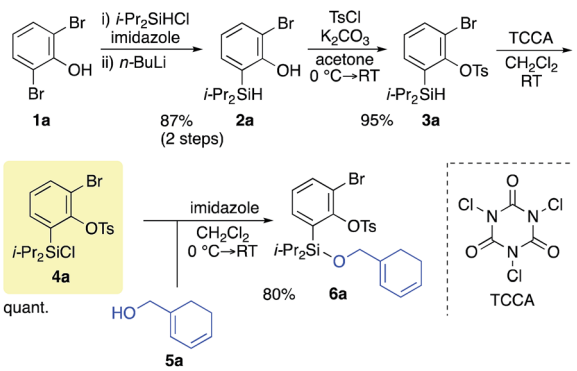
Having **6a** in hand, the intramolecular [4 + 2] cycloaddition was examined (Table 1). As the initial experiment, **6a** was treated with *n*-BuLi (THF, 0 °C, 20 min), where the desired cycloadduct **7a** was obtained in 53% yield (entry 1). The starting material **6a** was recovered in 5% yield, and a side product **8** was obtained in *ca.* 8% yield, arising from the addition of a butyl anion to the benzyne followed by the protonation or Br–Li exchange reaction of the resulting aryl anion. Notably, no other byproducts, derived from potential side reactions such as the [2 + 2] cycloaddition and ene reaction, were detected, which is in sharp contrast to the corresponding intermolecular version.[3,11] Concerning other organolithium reagents, *s*-BuLi gave lower yield of **7a** (entry 2), while PhLi gave comparable results (entry 3). We turned our attention to organomagnesium reagents. The initial attempt with *i*-PrMgCl[12] led to a slow reaction even at room temperature (entry 4). Pleasingly, Ph_3MgLi improved the yield of **7a** to 69% yield (entry 5).[13,14] Among other solvents tested (entries 6–9), Et_2O proved to be the solvent of choice, giving **7a** in 87% yield (entry 6).

Table 1 Optimization of the reaction conditions with tosylate **6a**

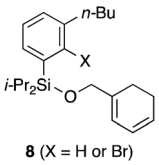


Entry	Reagent	Solvent	Yield[a] of **7a** (%)	Recovery[a] (%)
1	*n*-BuLi	THF	53	5
2	*s*-BuLi	THF	35	25
3	PhLi	THF	52	—
4[b]	*i*-PrMgCl	THF	37	41
5	Ph_3MgLi	THF	69	—
6	Ph_3MgLi	Et_2O	87	—
7	Ph_3MgLi	TBME	81	—
8	Ph_3MgLi	CPME	82	—
9	Ph_3MgLi	*n*-Bu_2O	83	—

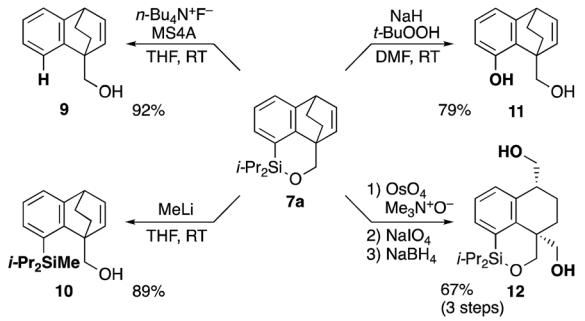
[a] Isolated yield. [b] Room temperature (23 h).



Scheme 2 Preparation of the benzyne platform **4a** and union with alcohol **5a**.



8 (X = H or Br)

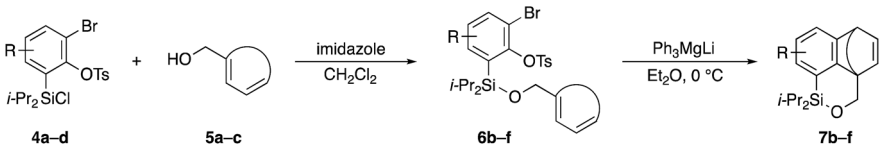


Scheme 3 Synthetic transformations.

The synthetic utility of cycloadduct **7a** was demonstrated by several orthogonal transformations (Scheme 3). The silyl group on **7a** provided an opportunity for further elaboration of the aromatic ring. Indeed, by treating with tetrabutylammonium fluoride in the presence of 4 A molecular sieves, both the silicon–oxygen and silicon–carbon bonds in **7a** were cleaved, giving alcohol **9** in 92% yield. By contrast, methyllithium cleaved only the silicon–oxygen bond to afford alcohol **10** in 89% yield. Tamao–Fleming oxidation[15] of **7a** by treatment with *t*-BuOOH and NaH gave phenol **11** in 79% yield. In addition, oxidative cleavage of the bridged double bond in **7a** followed by reduction gave diol **12**.

Table 2 shows the scope of this tethering strategy. The combination of **4a** with furfuryl alcohol (**5b**) and pyrrolylmethanol **5c** gave precursors **6b** and **6c** in high yields, which underwent the intramolecular [4 + 2] cycloaddition (Ph_3MgLi, Et_2O, 0 °C, 10 min) to give cycloadducts **7b** and **7c** in 90% and 84% yield, respectively (entries 1 and 2). Entries 3–5 show variation of the aryl moiety, using the precursors **6d–f** having a methoxy or a fluoro substituent(s), prepared from chlorosilanes **4b–d** and alcohol **5a**. The reactions of **6d** and **6e**, bearing a methoxy and a fluoro group at the *meta* position to the

Table 2 Substrate scope[a]



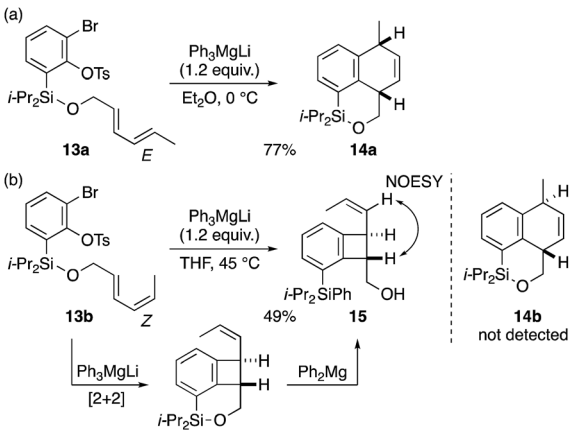
Entry	Silyl chloride **4**	Alcohol **5**	Precursor **6**	Yield[b] (%)	Cycloadduct **7**	Yield[c] (%)
1	**4a**	**5b**	**6b**	82	**7b**	90
2	**4a**	**5c**	**6c**	81	**7c**	84
3	**4b**	**5a**	**6d**	83	**7d**	78
4	**4c**	**5a**	**6e**	82[d]	**7e**	82
5	**4d**	**5a**	**6f**	59[d]	**7f**	86

[a] Conditions for the preparation of precursors **6b–f**: see the ESI. Conditions of cycloadditions: precursor **6** (1.0 equiv.) and Ph_3MgLi (1.2 equiv.) in Et_2O (0.05 M) at 0 °C for 10 min. [b] Isolated yield. [c] Isolated yield from **6**. [d] Overall yield for two steps from the corresponding arylhydrosilane: chlorination and *O*-silylation.

respective silyl substituents, proceeded smoothly to give cycloadducts **7d** and **7e** both in high yield (entries 3 and 4). The precursor **6f**, the *ortho*, *para*-dimethoxy derivative, also underwent a clean cycloaddition to give the desired product **7f** in excellent yield (entry 5).

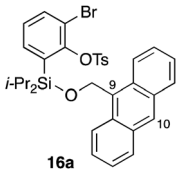
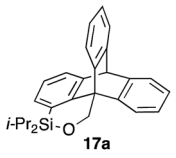
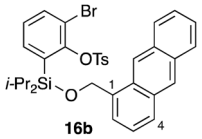
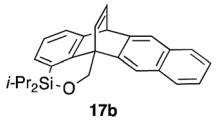
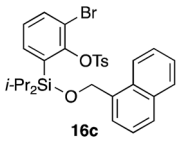
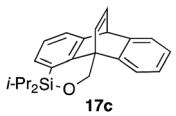
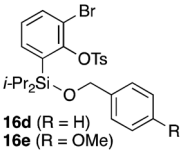
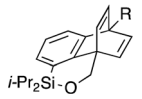
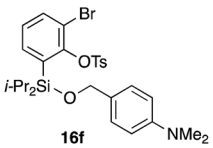
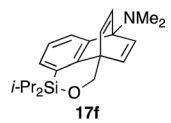
With excellent results obtained with cyclic dienyl arynophiles as discussed above, we further examined the applicability to the substrates with an acyclic diene, often less reactive than the cyclic counterpart,[3c,f,4c,f,g,16] which gave interesting results (Scheme 4). When the *E*,*E*-diene substrate **13a** was treated with Ph_3MgLi at 0 °C (Et_2O, 10 min), a clean [4 + 2] cycloaddition occurred to give dihydronaphthalene **14a** in 77% yield (Scheme 4a). By contrast, the reaction of the *E*,*Z*-congener **13b** (THF, 45 °C, 10 min) gave no [4 + 2] cycloadduct **14b**, but instead, the [2 + 2] cycloadduct **15**, albeit in 49% yield, which could be rationalized by a cycloaddition followed by Si–O bond scission by Ph_2Mg:[17] a remarkable finding given that, the regioselective [2 + 2] cycloaddition of an internal alkene in 1,3-dienes is less common (Scheme 4b).[3c–g] The relative *trans* configuration was verified by ^1H–^1H NOESY experiments.

Furthermore, we addressed the applicability to the synthesis of barrelenes, an attractive class of bicyclic compounds.[18] The question was whether or not the substrates having an internal arene moiety undergo the [4 + 2] cycloadditions with dearomatization, and the results are summarized in Table 3. Entries 1 and 2 show the cycloaddition reactions of bromoaryl tosylates **16a** and **16b**, whose anthracene moieties are tethered at the C9 and the C1 positions, respectively. Reaction of **16a** gave the corresponding triptycene **17a** in 64% yield (entry 1). By contrast, the precursor **16b** underwent clean cycloaddition at the 1,4-position of the anthracene ring to afford naphthobarrelene **17b** in 65% yield (entry 2). Note that here the C1 position of the anthracene served as the anchor for the tether, and therefore the benzyne reacted with the outer ring (1,4-position), despite the higher reactivity of the central ring (9,10-position).[19] The [4 + 2] cycloaddition of naphthalene as a diene is more challenging than that of anthracene due to higher aromaticity.[20] Nonetheless the reaction of precursor **16c** was realized at an elevated temperature (40 °C), giving dibenzobarrelene **17c** in 51% yield (entry 3).



Scheme 4 Reaction with acyclic dienes.

Table 3 Intramolecular cycloaddition with aromatic rings[a]

Entry	16	17	Yield[b] (%)
1[c]			64
2			65
3[d]			51
4			n.d. (**17d**)
5			n.d. (**17e**)
6			44

[a] Unless otherwise indicated, reactions were performed with precursor **16** (1.0 equiv.) and Ph_3MgLi (1.2 equiv.) in Et_2O (0.05 M) at room temperature for 10 min. [b] Isolated yield. [c] In THF at 0 °C. [d] At 40 °C.

To explore the limits of this dearomatization, simple benzenes were examined as aromatic diene components (entries 4–6).[21] The reaction of tosylate **16d** with a simple benzene ring resulted in failure, giving no cycloadduct **17d** (entry 4). With a hope of realizing the reaction by increasing the HOMO level of the benzene ring,[21d,22] we examined substrates **16e** and **16f**, having a methoxy group and a dimethylamino group, respectively. It turned out that **16e** gave no reaction (entry 5), whereas the dimethylamino group worked well for the cycloaddition to give benzobarrelene **17f** in 44% yield (entry 6).

Conclusions

In summary, we have described a silicon-tether strategy for the intramolecular [4 + 2] cycloaddition of benzynes with dienes. 2-Bromo-6-(chlorodiisopropylsilyl)phenyl tosylate, a versatile benzyne platform, plays a key role in the facile assembly of

various cycloaddition precursors by combining with dienes *via* a Si–O bond. This strategy would be applicable to various other potential arynophiles, and useful for complex polycyclic natural product syntheses. Further studies along these lines are in progress.

Experimental

A typical procedure for the internal cycloaddition is described for the reaction of **6a** with Ph_3MgLi in Et_2O (entry 6): To a solution of PhLi (0.67 M in cyclohexane and Et_2O, 1.1 mL, 0.74 mmol) in Et_2O (1.5 mL) was added PhMgBr (0.94 M in THF, 0.41 mL, 0.39 mmol) at 0 °C, and the mixture was stirred for 30 min. The resulting solution of Ph_3MgLi was used in the following experiment. To a solution of bromoaryl tosylate **6a** (165 mg, 0.300 mmol) in Et_2O (6.0 mL) was added dropwise Ph_3MgLi (*vide supra*) *via* cannula at 0 °C. After stirring for 10 min, the reaction was stopped by adding sat. NH_4Cl aq., and the mixture was extracted with EtOAc (x3). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (silica gel, hexane, EtOAc = 98/2, x2) to afford cycloadduct **7a** (77.8 mg, 87%) as a colorless oil.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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