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Intramolecular Benzyne–Phenolate [4+2] Cycloadditions

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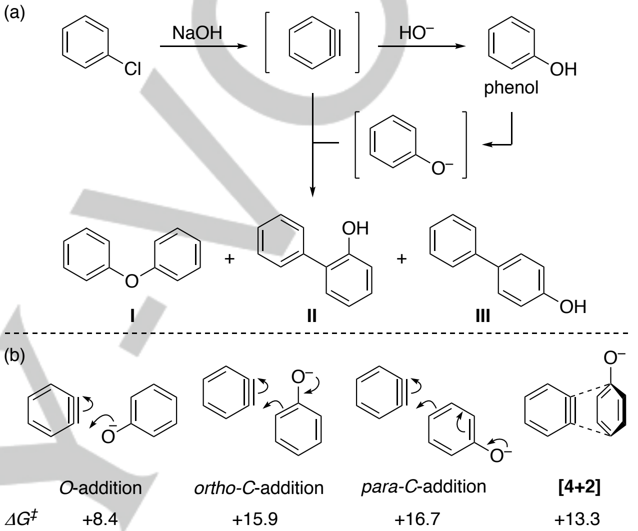
In memory of the late Professor Rolf Huisgen

Abstract: Intramolecular benzyne–phenolate [4+2] cycloaddition is reported, opening an effective route to various benzobarrelenes.

Benzyne, a versatile reactive species in organic chemistry,[1,2] was historically postulated about 70 years ago for explaining unusual observations in nucleophilic aromatic substitutions. The pioneering works of Wittig (1942)[3] and Huisgen (1954)[4] were for rationalizing the reaction of phenyllithium and fluorobenzene, generating biphenyllithium, while Roberts' ^{14}C-tracer experiment (1953)[5] addressed the rearrangements on the amination of aryl halides by metal amides. Another important reactivity of benzyne was discovered by Wittig (1955),[6] i.e., the [4+2] cycloaddition that has been extensively exploited in organic synthesis, including the reactions with arenes as arynophiles.[7,8] Some of the foregoing reactions of aromatic compounds must have unconsciously exploited benzyne species, as exemplified by the historical Dow phenol process (Scheme 1a),[9] in which the product distribution, phenol and side products **I**–**III**, is consistent with the intermediacy of a benzyne. Theoretical calculation supported three side reaction pathways,[10] but interestingly, suggested that the [4+2] cycloaddition may also be a competing pathway, albeit not reported (Scheme 1b). To our knowledge, there has been essentially no literature precedence on the [4+2] cycloadditions of benzyne to phenols or phenolates,[11] except for a single example described in Hoye's recent report: Upon thermal generation of a benzyne via cycloisomerization,[12] the reaction with one special phenol presents the single example where the [4+2] cycloadduct was formed as a minor byproduct, while the predominant path was the *ortho-C*-addition.[13]

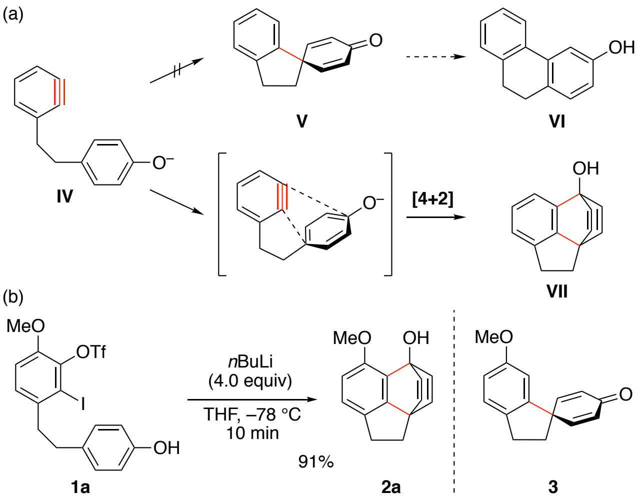
In our recent synthetic study on cavicularin, a natural product with an unusual polycyclophane structure, we incidentally discovered the benzyne–phenolate [4+2] cycloaddition (Scheme 2).[14] Our original aim was to construct dihydrophenanthrene **VI** via the *para-C*-addition of an internal phenolate to benzyne **IV**[11f] followed by dienone–phenol shift.[15] Surprisingly, a model reaction using iodoaryl triflate **1a**[16,17] did not give the expected product **3,** but instead cycloadduct **2a** in excellent yield.



Scheme 1. (a) Dow phenol process, (b) theoretical comparison of competing pathways (kcal/mol, B3LYP/6-31+G*, counter cation: Li⁺·2THF, gas phase).

This discovery clearly showed that, if the mutual spatial relationship was suitably set by tethering, a benzyne and a phenolate could indeed undergo selective [4+2] cycloadditions. Leaving the original aim aside, we further explored this finding.

In this communication, we now pleasingly report the broad scope of the intramolecular benzyne–phenolate [4+2] cycloadditions, allowing facile access to various benzobarrelene scaffolds often embedded in bioactive compounds[18] and useful materials.[19]



Scheme 2. (a) Reactions of benzyne with an internal phenolate, (b) Incidental discovery. THF = tetrahydrofuran, Tf = trifluoromethanesulfonyl.

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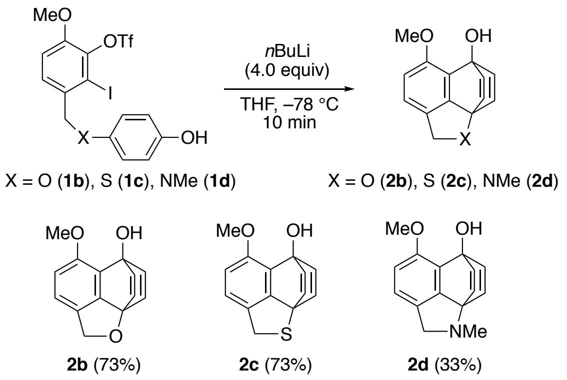
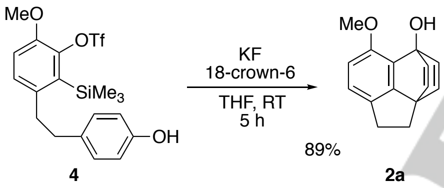
Scheme 3 shows the generality of the process by the successful reactions of iodoaryl triflates **1b**–**d**, which were prepared from known compounds in 4–5 steps.[20] By treatment with *n*BuLi (THF, –78 °C, 10 min), substrates with C–O and C–S tether, **1b** and **1c**, underwent smooth cycloadditions, giving the corresponding cycloadducts **2b**[21] and **2c** in high yields. By contrast, the reaction of **1d** having a C–N tether gave **2d** in low yield, which could be attributed to the competing attack of the nitrogen to benzyne.



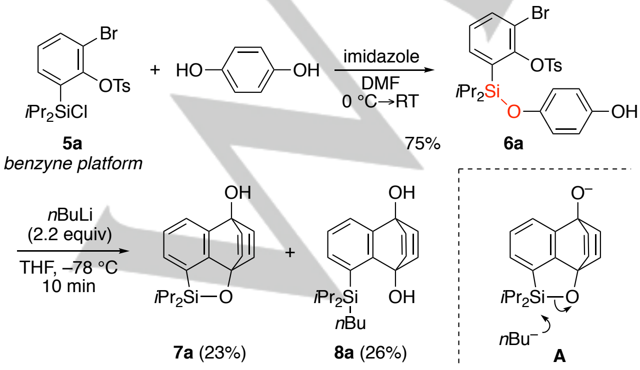
Scheme 3. Reactions with substrates having C–O, C–S, and C–N tethers.

Scheme 4 shows that silylaryl triflate **4** was also a viable precursor for this benzyne reaction.[22] Upon treatment of **4** with KF and 18-crown-6, the [4+2] cycloaddition proceeded slowly, but steadily to give cycloadduct **2a** in 89% yield.



Scheme 4. Reactions with silylaryl triflate **4**.

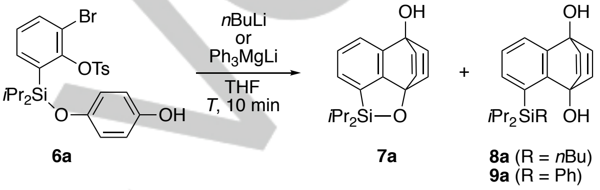
To further explore the scope, we tested a cleavable tether that we recently developed, *i.e.*, silyl chloride **5a**, which were prepared from 2,6-dibromophenol in four steps,[20] as a platform to link the benzyne precursor with various arynophiles (Scheme 5).[8] Bromoaryl tosylate **6a** was prepared in 75% yield by the reaction of **5a** and hydroquinone (imidazole, DMF, 0 °C→RT). Upon treatment of bromoaryl tosylate **6a** with *n*BuLi (THF, –78 °C), two products were isolated and identified as silyl ether **7a** (23% yield) and diol **8a** (26% yield), arising from Si–O bond scission of **7a** by *n*-butyl anion as in **A**.



Scheme 5. Preparation and reaction of bromoaryl tosylate **6a**. Ts = *p*-toluenesulfonyl, DMF = *N*,*N*-dimethylformamide.

An optimization study (Table 1) revealed a suitable set of conditions for smooth conversion to diol **8a**. The reaction of **6a** with *n*BuLi (2.2 equiv) at 0 °C did not give silyl ether **7a**, but diol **8a** in 55% yield (entry 2). However, the reaction was not complete (18% recovery of **6a**), suggesting the need of further loading of *n*BuLi. Indeed, when 3.5 equiv of *n*BuLi were used, the starting material **6a** was fully consumed to give **8a** in 90% yield (entry 3). When Ph_3MgLi was employed instead,[8,23] the yield was further improved even with less amount of reagent (2.2 equiv), giving diol **9a** (*n.b.*, R = Ph) in 95% yield (entry 4). We reasoned that Ph_2Mg, generated in situ, is nucleophilic enough for cleaving the distorted Si–O bond in **7a**.

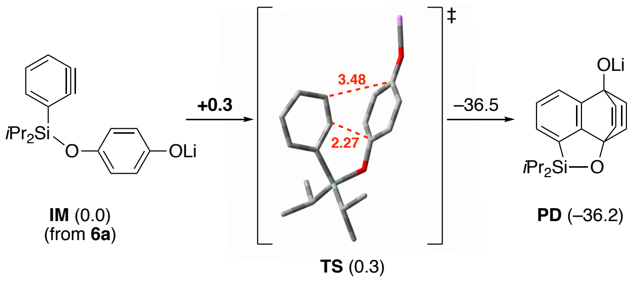
Table 1. Optimization.[a]



Entry	Reagent (equiv)	*T* [°C]	Yield of **7a** [%][c]	Yield of **8s** or **9a** [%][c]	Recovery of **6a** [%]
1[b]	*n*BuLi (2.2)	–78	23	26 (**8a**)	3
2	*n*BuLi (2.2)	0	–	55 (**8a**)	18
3	*n*BuLi (3.5)	0	–	90 (**8a**)	–
4	Ph_3MgLi (2.2)	0	–	95 (**9a**)	–

[a] 0.05 M. [b] See Scheme 5. [c] Isolated yield.

To gain mechanistic insights, we performed density functional theory (DFT) calculations using an aryne intermediate (**IM**), bearing a phenolate moiety, generated from bromoaryl tosylate **6a** (Scheme 6). The cycloaddition was computed to be a concerted process, albeit highly asynchronous in terms of the two C–C bond formations, giving the cycloadduct (**PD**). This is consistent with the fact that none of the corresponding *para*-C-adduct was observed, corresponding to an “interrupted” product during the cycloaddition. It turned out that the activation barrier (**IM**→**TS**) is remarkably low (+0.3 kcal/mol), probably due to the entropic benefit from the intramolecularity.



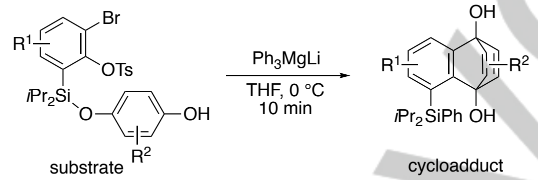
Scheme 6. DFT calculation results for the intramolecular benzyne–phenolate [4+2] cycloaddition using PCM(THF)/M06-2X/6-311++G**. Energy changes and bond lengths are shown in kcal·mol^{-1} and Å, respectively. Two THF coordinated to the Li cation and hydrogens are omitted for clarity.

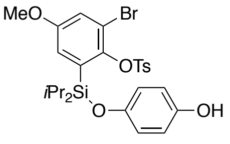
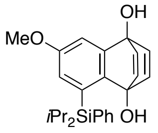
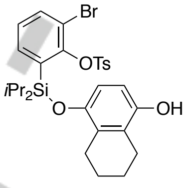
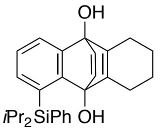
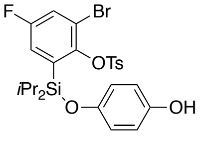
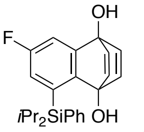
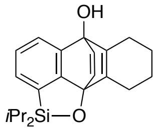
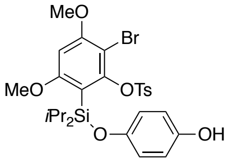
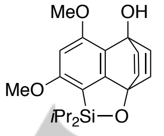
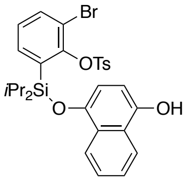
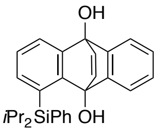
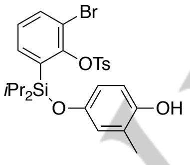
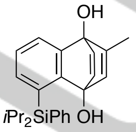
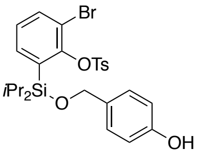
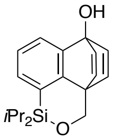
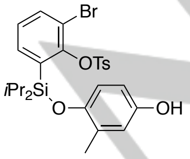
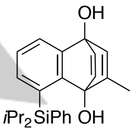
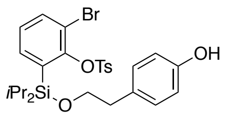
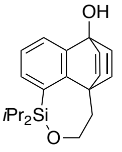
Table 2 shows the scope of the silicon-tether protocol. Entries 1–3 show variation in the aryl moiety. Upon treatment with Ph_3MgLi (2.2 equiv), substrates **6b** and **6c**, having a methoxy or a fluoro group located *meta* to the silyl groups, smoothly gave the cycloadducts **9b** and **9c** in high yields, respectively (entries 1 and 2). A dimethoxy-substituted precursor **6d** also underwent smooth cycloaddition (entry 3). However, the product was silyl ether **7b**, retaining the Si–O bond, which could be rationalized by the steric effect of the methoxy group *ortho* to the silyl group, retarding the nucleophilic attack of a phenyl anion.

Entries 4–9 show variation of the phenol moiety. A methyl substituent on the phenol at the *o*- or *m*-position of the hydroxy group does not interfere, and cycloadducts **9e** and **9f** were obtained in high yields (entries 4 and 5). In the case of phenol **6g** having a bicyclic phenol, cycloadduct **9g** was obtained in 75% yield, along with silyl ether **7c** in 13% yield (entry 6). The benzyne–naphtholate cycloaddition was also possible: the reaction of naphthol **6h** under the standard conditions gave dibenzobarrelene **9h** in 92% yield (entry 7).

Furthermore, we examined the length of the tether by the reactions of bromoaryl tosylates **6i** and **6j**, whose tethers are longer by one carbon or two carbons, respectively. While **6i** underwent a cycloaddition to give alcohol **10** in 57% yield (entry 8), the reaction of **6j** did not give cycloadduct **11** (entry 9).

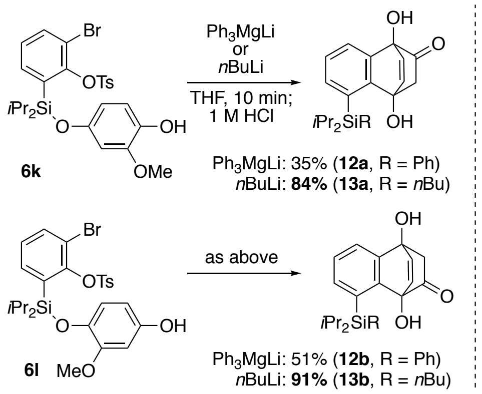
Table 2. Substrate scope.[a]



Entry	substrate	cycloadduct	Yield [%][b]	Entry	substrate	cycloadduct	Yield [%][b]
1	 **6b**	 **9b**	93	6	 **6g**	 **9g**	75
2	 **6c**	 **9c**	86			 **7c**	13
3	 **6d**	 **7b**	99	7	 **6h**	 **9h**	92
4	 **6e**	 **9e**	94	8	 **6i**	 **10**	57
5	 **6f**	 **9f**	87	9	 **6j**	 **11**	n.d.

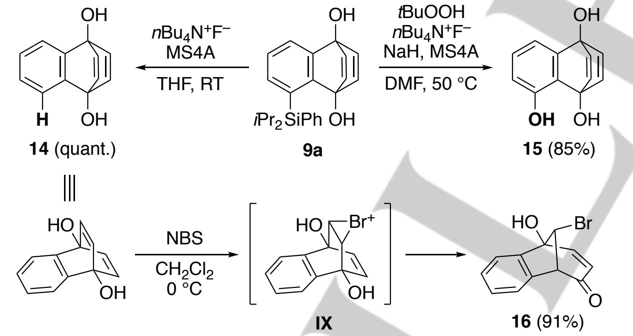
[a] Reactions were performed with phenol **6** (1.0 equiv) and Ph_3MgLi (2.2 equiv) in THF (0.05 M) at 0 °C for 10 min and quenched by sat. NH_4Cl. [b] Isolated yield.

Next, we examined the reactions of phenols **6k** and **6l** with a methoxy substituent on the phenol moiety, where interesting results were obtained (Scheme 6). Upon treatment of **6k** and **6l** with Ph_3MgLi, the cycloaddition proceeded to give the corresponding vinyl ethers **VIII** and **VIII'**, which turned out to be fairly unstable. Thus, we chose quenching with sat. NH_4Cl, where ketones **12a** and **12b** were obtained in modest yields, respectively. Upon further experimentation, we found that *n*BuLi was more effective for these instances: Upon the reaction of **6k** and **6l** with *n*BuLi (3.2 equiv, THF, 0 °C, 10 min) and quenching with 1 M HCl, ketones **13a** and **13b** were obtained in 84% and 91% yield, respectively.



Scheme 6. Reactions of phenols **6k** and **6l**

Scheme 7 demonstrates further elaborations of the cycloadducts, using **9** as a model substrate. Protodesilylation of **9a** by treatment with tetrabutylammonium fluoride in the presence of MS4A gave diol **14** in quantitative yield. The silyl group served also as an equivalent to a hydroxy group: upon treatment of **8b** with *t*BuOOH (DMF, 50 °C), Tamao–Fleming oxidation proceeded to give phenol **15** in 85% yield.[24] In addition, bromination of the bridged alkene in **14** triggered a skeletal rearrangement[25] via an aryl shift from bromonium intermediate **IX**, giving benzobicyclo[3.2.1]octadienone **16**[26] in 91% yield.[27]



Scheme 7. Synthetic transformations. MS = molecular sieves, NBS = *N*-bromosuccinimide

In summary, we have demonstrated the unprecedented intramolecular benzyne cycloaddition with phenolates. A variety of tethers proved applicable, among which the cleavable Si–O tether demonstrated a broad substrate scope, enabling access to various benzobarrelene derivatives. The synthetic utility of this methodology was further confirmed by transformations of the cycloadducts. Further investigation is in progress.

Acknowledgments

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Keywords: benzyne · phenol · intramolecular reaction · [4+2] cycloaddition · silicon tether

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[27] A minor amount (6%) of the isomeric product via the vinyl shift was obtained. For details, see the supporting information.

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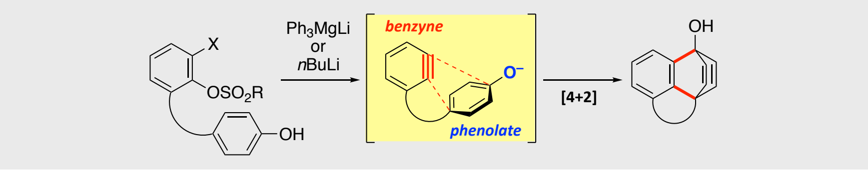

The Intramolecular benzyne–phenolate [4+2] cycloaddition has been developed. Benzyne precursors, having vicinal halogen–sulfonate functionalities, linked with a phenol(ate) by various tether groups undergo efficient intramolecular [4+2] cycloaddition by treatment of Ph_3MgLi or *n*BuLi for halogen–metal exchange to form various benzobarrelenes. The method is characterized by wide availability of reaction precursors and high yield for the products.

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