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Arynes

Catalytic Generation of Arynes and Trapping by Nucleophilic Addition and Iodination

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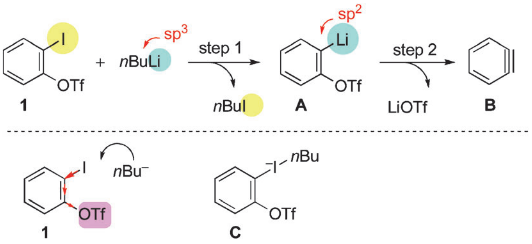
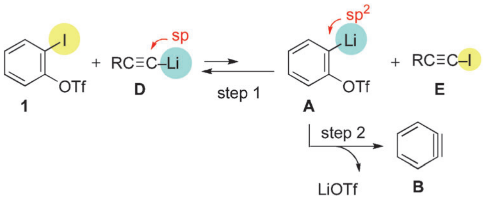
Benzyne is a highly reactive species with broad synthetic potential.[1] Among various methods for generating this species through elimination of 1,2-difunctionalized benzene precursors,[2] we have exploited 2-iodoaryl triflate (**1**) as an excellent benzyne precursor, which is immediately converted into benzyne even at −95 °C upon reaction with *n*BuLi (Scheme 1).[3] Two rapid consecutive processes are relevant: 1) The rapid and virtually irreversible halogen–lithium exchange by the formal anion transfer from *n*BuLi to the aryllithium (sp^3 carbanion→sp^2 carbanion),[4] and 2) the elimination of lithium triflate, which is also rapid because of the excellent leaving ability of triflate. An essential element in step 1 is the strong electron-withdrawing effect of the triflato ($CF_3SO_3^-$) group that reinforces the electrophilicity of the iodine atom in **1**, thus facilitating formation of the ate complex **C** and leading to the iodine–lithium exchange.



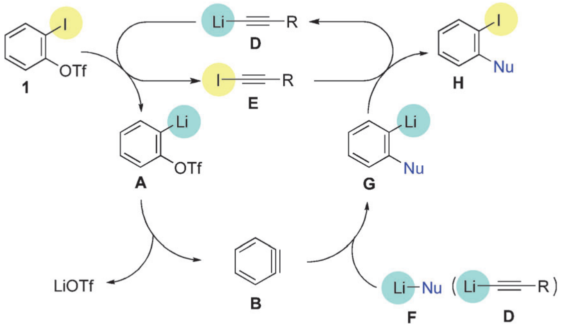
Scheme 1. Rapid benzyne generation. Tf = trifluoromethanesulfonyl.

Recently, we became interested in the slower generation of benzyne, hoping to form the basis of developing catalytic benzyne chemistry. Along these lines, we came up with an idea to use alkynyllithium **D**, instead of *n*BuLi, with the expected outcome depicted in Scheme 2. In spite of the poor ability of an alkynyl anion (sp carbanion) for the halogen–lithium exchange,[4] we expected that the slow release of benzyne (**B**) would be possible because of two prominent features of the iodo triflate **1**: 1) high susceptibility to the ate complex formation, and 2) excellent leaving ability of triflate. Even though the aryllithium **A** may be generated in a small amount from an unfavorable equilibrium, it would be converted into **B** at a certain rate. If **B** was suitably linked to a product-forming processes, we could exploit the catalytically generated benzyne species for organic reactions.



Scheme 2. Slow benzyne generation.

Scheme 3 shows the catalytic cycle we envisioned. The alkynyllithium **D** serves as an initiator for the benzyne generation by the iodine–lithium exchange (**1**→**A**→**B**). When lithio nucleophile **F** (Li-Nu) is present in a stoichiometric amount, **B** would be intercepted by **F** to generate aryllithium **G**, which may be "counter iodinated" by iodoalkyne **E** (that is, a favorable process by sp^2 carbanion→sp carbanion), thus giving the nucleo-iodination product **H**,[5] and regeneration of the alkynyllithium **D** completes a catalytic cycle. The alkynyllithium **D**, if employed in a stoichiometric amount, acts also as a nucleophile which attacks **B** (i.e., **D** = **F**). However, a stoichiometric amount of the nucleophile **F** could be different from alkynyllithium **D**, given that suitable reaction conditions are met.[6,7]



Scheme 3. Catalytic generation of benzyne and nucleo-iodinaton.

Herein, a positive answer to this scenario is described wherein the catalytic generation of benzyne species **B** from 2-iodoaryl triflate (**1**) is enabled, followed by interception with a stoichiometric amount of a nucleophile (halides or stabi-

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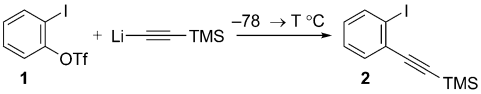
lized carbanions) and subsequent iodination. The overall process corresponds to the nucleophilic addition and iodination (nucleo-iodination) of the catalytically generated benzyne species, thus giving functionalized iodoarenes.

Table 1 summarizes the initial feasibility study, which gave promising results. Upon treatment of **1** with $LiC\equiv CSiMe_3$ (1.8 equiv) in Et_2O (−78→25 °C), alkynyl iodobenzene **2** was obtained, albeit in 10% yield (entry 1). The yield was improved by using DME as a solvent (entry 2), and additionally improved using THF at a lower temperature (−10 °C, entry 3).[8–10] In contrast, toluene gave poorer results (entry 4).

Table 1: Feasibility study.

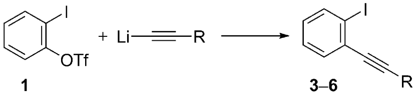


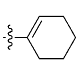
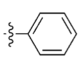
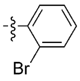
Entry[a]	Solvent	*T* [°C]	*t* [h]	Yield [%]
1	Et_2O	25	12	10
2	DME	0	3.5	67
3	THF	−10	2	82
4	toluene	25	12	11

[a] 1.8 equiv of alkynyllithium was used. DME = dimethyl ether, THF = tetrahydrofuran.

The reaction was applicable to various alkynyllithiums (Table 2). Upon treatment of **1** with 1-hexynyllithium in DME (−78→5 °C, 5 h), the iodoarene **3** was obtained in 81% yield. The substituent (R) on the alkynyllithium could be either cyclohexenyl or phenyl, thus giving good yields of the respective products **4** and **5**. The 2-bromophenyl group stayed intact in the reaction to give product **6** in 65% yield.

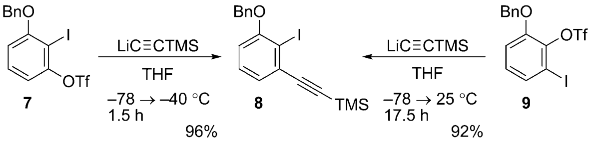
Table 2: Iodoalkynylation with various substrate combinations.



R	Bu			 Br
product	**3**	**4**	**5**	**6**
yield [%][c]	81[a]	74[a]	76[b]	65[b]

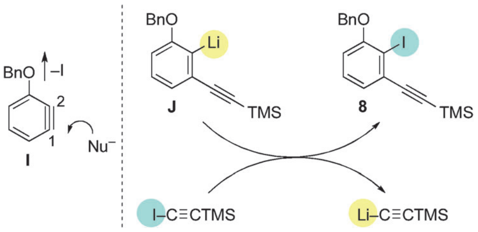
[a] In DME. [b] In THF. [c] For details, see the Supporting Information.

Intermediacy of the benzyne species was firmly supported by the following experiments [Eq. (1); TMS = trimethylsilyl]. Upon treatment of triflate **7** and $LiC\equiv CSiMe_3$, a single alkynylated product, **8**, was obtained in 96% yield.[11] Importantly, the same product **8** was also obtained in 92% yield from the isomeric substrate **9**, thus showing that the common α-alkoxybenzyne **I** was involved. Note that, in the latter case, the iodine atom formally migrated to the *ortho* position of the benzyloxy group.[12,13]



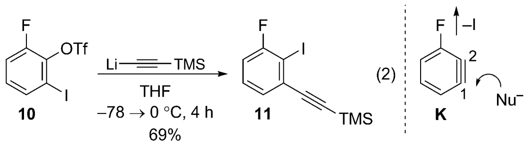
(1)

The regioselectivity[11] is rationalized by the nucleophilic attack at the more electrophilic C1 position of **I** by the inductive effect of an alkoxy group (Scheme 4).[14] The resulting aryl anion **J**[3c] is iodinated to give the product **8**. The iodoalkyne, generated by the initial iodine–lithium exchange with iodo triflate **7**, serves as an iodine source, and is a favorable process (sp^2 carbanion→sp carbanion).[15]



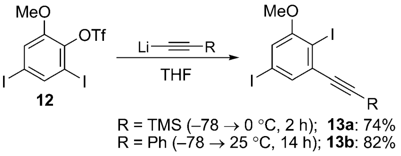
Scheme 4. Regioselectivity directed by an α-alkoxy group.

Such rigorous regioselectivity was seen also in the reaction of α-fluoro-substituted benzyne **K**, which was generated from **10**. Note that the iodine atom in the product **11** is formally migrating to the position nearer to the fluorine atom [Eq. (2)].



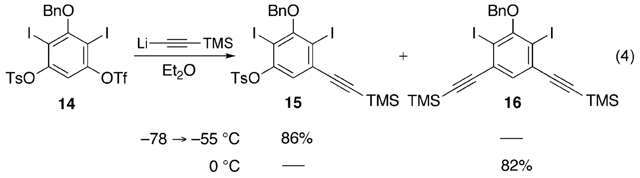
(2)

Worth noting are the dual roles of the triflato group in the substrate at the stage of benzyne generation. Before finally serving as an excellent leaving group, it initially acts as an activator of the neighboring iodine atom for the ate complex formation en route to the iodine–lithium exchange. A telling example is the reaction of bis(iodide) **12** [Eq. (3)]. Upon treatment with $LiC\equiv CSiMe_3$, **12** underwent the reaction to give product **13a** in 74% yield. Notably, the isolated iodine atom in **13a** was fully retained without undergoing the lithio exchange and protonation. Similarly, the reaction of **12** with $LiC\equiv CPh$ solely gave **13b** in 82% yield.



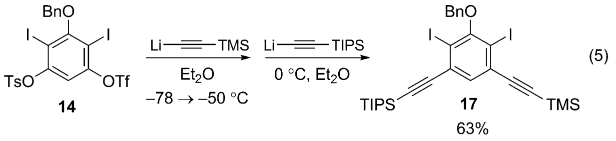
(3)

The reactivity of the iodine atom in the substrate is dependent on an even more subtle change of the neighboring groups. We previously reported that the benzyne generation of **14** by stoichiometric *n*BuLi occurs at low temperature (−95 °C) at the triflato side, while that of the tosylato side only proceeds at above −78 °C.[3c] Also under the present reaction conditions, the behavior of bis(iodide) **14** proved interesting [Eq. (4)].[16] Upon treatment of **14** with $LiC{\equiv}CSiMe_3$ (1.2 equiv, −78→−55 °C, Et_2O, 2 h), the selective reaction occurred to give product **15** as the sole product in 86 % yield. No indication of the products that resulted from the reaction at the iodo tosylate side of **14** was noted. However, by using $LiC{\equiv}CSiMe_3$ in excess (2.5 equiv) at 0 °C two alkynyl units were smoothly introduced (Et_2O, 0.1 h), thus converting bis(iodide) **14** into bis(alkyne) **16** in 82 % yield.



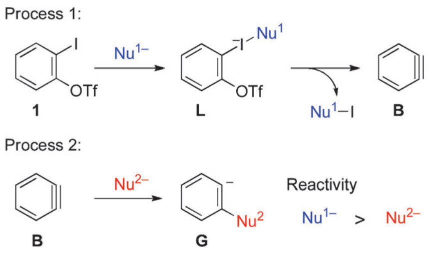
(4)

Furthermore, two different alkynyl units could be introduced in one pot. Upon treatment of bis(iodide) **14** with $LiC{\equiv}CSiMe_3$ (1.1 equiv) in Et_2O (−78→−50 °C), the starting material was gradually consumed, and formation of the monoadduct **15** was observed by TLC. As the second nucleophile, $LiC{\equiv}CSi(iPr)_3$ (2.0 equiv) was added to the mixture (0 °C, 0.1 h), thereby giving the asymmetrically bis(alkyn)ylated product **17** as a sole product in 63 % yield [Eq. (5); TIPS = triisopropylsilyl].



(5)

Our goal in this project was to explore the possibility of catalytic generation of benzyne, with an appropriate nucleophile serving as a stoichiometric reaction partner. Let us consider two roles played by the nucleophiles (Scheme 5; and see Scheme 3): process 1: Nu^{1-} attacks the iodine atom in **1** to form the ate complex **L**, thus leading to **B**; and process 2: Nu^{2-} attacks **B** to form aryl anion **G**. Note that the reactions described so far included a single nucleophile, $Nu^1 = Nu^2 = LiC{\equiv}CR$.

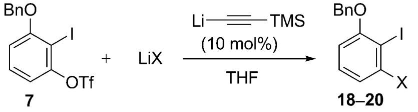


Scheme 5. Two roles played by nucleophilic species.

Could two nucleophilic species (Nu^{1-}, Nu^{2-}) be different? We assumed that process 2 should be more facile considering the extremely high reactivity of benzyne, and Nu^2 could be a stabilized anion. Knowing that $LiC{\equiv}CR$ could serve as the catalytic nucleophile for generating benzyne (Nu^{1-}), we could reasonably select stoichiometric nucleophile (Nu^{2-}) that is less reactive. A rough measure of the pK_a is 25 ($HC{\equiv}CH$), and we examined anionic nucleophiles derived from fairly acidic conjugate acids with pK_a values less than 25.[17]

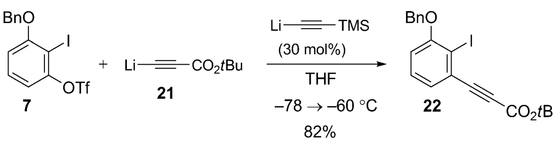
As a proof-of-concept experiment, we employed halides as weak nucleophiles (Nu^{2-}). Indeed, upon treatment of iodo triflate **7** with stoichiometric amounts of LiCl, LiBr, or LiI in the presence of $LiC{\equiv}CSiMe_3$ (10 mol %), smooth "haloiodination" of benzyne proceeded to give the corresponding chloro iodide **18**, bromo iodide **19**, and iodo iodide **20** in excellent yield (Table 3). The regiochemistries of **18** and **19** were assigned by NMR analysis (HMBC).[11] By contrast, in the absence of $LiC{\equiv}CSiMe_3$ none of the products **18**–**20** were obtained, even at higher reaction temperature (−78→25 °C); instead, only the starting material **7** was recovered.

Table 3: Alkynyllithium-catalyzed haloiodination of benzyne.



Entry	X	*T*	*t* [h]	Product	Yield [%]
1	Cl	−78→−20 °C	3	**18**	90
2	Br	−78→0 °C	3	**19**	97
3	I	−30→0 °C	1.5	**20**	91

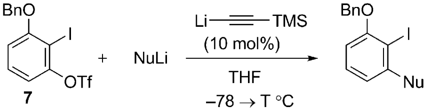
Pleasingly, it was found that lithio carbanions, if more stabilized than $LiC{\equiv}CR$, served as stoichiometric nucleophiles as well. A representative example is shown in Equation (6), wherein the alkynyllithium **21** with a *tert*-butyl ester moiety, thus more stabilized compared to the usual alkynyllithium, took part in the reaction. Upon treatment of **7** with **21** (3 equiv) in the presence of 30 mol % of $LiC{\equiv}CSiMe_3$ (−78→-60 °C), the carboiodination occurred smoothly to give the product **22** in 82 % yield [Eq. (6)]. No alkynylated product **8** was produced. It should be noted that the use of the stoichiometric **21** in the absence of $LiC{\equiv}CSiMe_3$ resulted in no reaction, thus confirming the inability of **21** to effect the benzyne generation.

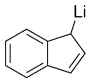
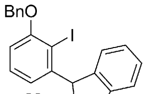
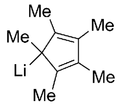
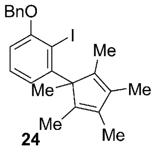
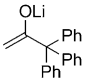
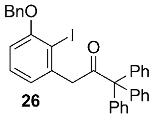
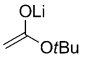
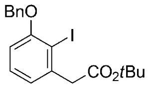


(6)

Various other carbon nucleophiles could be employed (Table 4). Indenyllithium and pentamethylcyclopentadienyl-

Table 4: Alkynyllithium-catalyzed carboiodination of benzyne.



Entry	NuLi	*T* [°C]	*t* [h]	Product	Yield [%]
1		−60	15	 **23**	77
2		25	19	 **24**	61
3	 **25**	5	5	 **26**	49
4	 **27**	−30	2	 **28**	72

lithium were found to serve as efficient carbon nucleophiles in the presence of 10 mol% of $LiC{\equiv}CSiMe_3$, selectively giving iodoarenes **23** and **24** in 77 and 61% yields, respectively (entries 1 and 2).[18] A precaution for the reaction of indenyllithium was to maintain the temperature (< −60 °C), otherwise a shift of the double bond occurred. The lithium enolate **25**[19] also worked nicely. Upon treatment of iodo triflate **7** in the presence of $LiC{\equiv}CSiMe_3$ (10 mol%, −78→5 °C), the reaction occurred to give ketone **26** in 49% yield (entry 3). Similarly, ester **28** was selectively obtained by using this method (entry 4).[20]

In summary, the catalytic generation of a benzyne species by alkynyllithium catalysis allowed efficient preparation of various iodoarenes through nucleo-iodination. Further studies on expansion of the scope of the catalytic process are being actively investigated.

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[12] For related “halogen migration” in benzyne chemistry, see Refs. [6g] and [6j].

[13] Superior reactivity of iodo triflate **7** relative to its regioisomer **9** is ascribed to the ease of iodine–lithium exchange in the presence of the neighboring benzyloxy group in **7**.

[14] For experimental and computational studies on the origin of the regioselectivities in the nucleophilic addition to substituted benzynes, see: a) P. H.-Y. Cheong, R. S. Paton, S. M. Bronner, G.-Y. Im, N. K. Garg, K. N. Houk, *J. Am. Chem. Soc.* **2010**, *132*, 1267 – 1269; b) G.-Y. Im, S. M. Bronner, A. E. Goetz, R. S. Paton, P. H.-Y. Cheong, K. N. Houk, N. K. Garg, *J. Am. Chem. Soc.* **2010**, *132*, 17933 – 17944.

[15] As another possibility, triflate **7** may also work as an iodinating agent. Further study is in progress.

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[17] An additional hope was that most of the Nu^{1-} used in a catalytic amount would be converted into the corresponding iodide (Nu^{1}-I), so that the crossover attack on the benzyne species would be minimized.

[18] The reaction of **7** with pentamethylcyclopentadienyllithium did not occur at all in the absence of $LiC{\equiv}CSiMe_3$. Details of the catalytic reactions using other lithio-nucleophiles will be described in a full paper.

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[20] Lithium enolate **27** was generated by reaction of the ketene silyl acetal, prepared from *tert*-butyl acetate, and MeLi. For related reactions, see: G. Stork, P. F. Hudrlik, *J. Am. Chem. Soc.* **1968**, *90*, 4464 – 4465.