Polycycles

DOI: 10.1002/ange.200602539

Two-Directional Annelation: Dual Benzyne Cycloadditions Starting from Bis(sulfonyloxy)diiodobenzene**

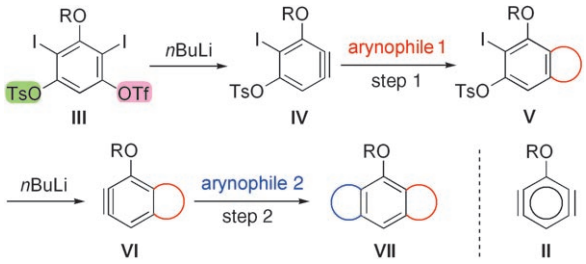
*Toshiyuki Hamura, Tetsu Arisawa, Takashi Matsumoto, and Keisuke Suzuki**

The construction of polycyclic structures with diverse functionalities is one of the subjects often encountered in the synthesis of natural and non-natural products. In this context, we became interested in two-directional annelations, that is, dual annelation of two rings onto a given core ring [Eq. (1)],

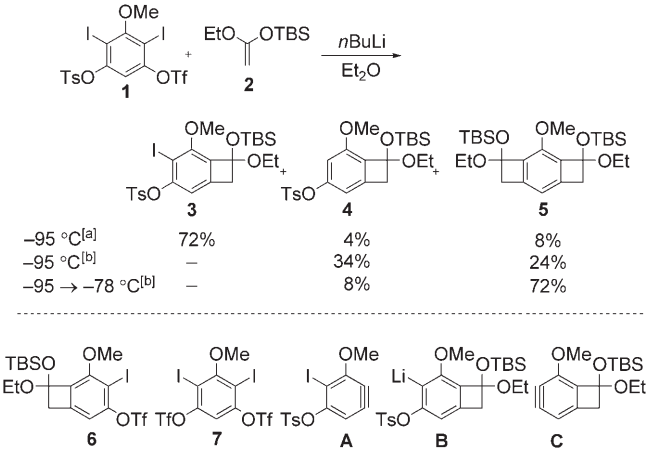
which would allow for the expeditious assembly of polycycles.[1] In particular, we were intrigued by the use of a formal equivalent to 1,4-benzdiyne (**I**), as it could serve as a reactive platform for linearly fused polycyclic compounds.[2,3]

We previously reported an efficient protocol for the generation of benzyne species from a 2-iodoaryl triflate by the rapid halogen–lithium exchange with *n*BuLi at low temperature,[4] and its regioselective trapping by furans,[4] nitrones,[5] and ketene silyl acetals (KSAs).[6] Herein, we disclose dual cycloadditions of benzynes successively generated in one pot from bis(sulfonyloxy)diiodobenzene (**III**), which can be viewed as a synthetic equivalent of 3-alkoxy-1,4-benzdiyne **II** (Scheme 1).[7] Importantly, selective halogen–lithium exchange of **III** enables the tandem generation of benzynes and dual cycloadditions with two identical or different arynophiles (steps 1 and 2). The presence of an alkoxy group on the central benzene ring is key to this strategy, as it directs the regioselectivity of both cycloaddition steps, thus allowing access to selectively functionalized polycyclic compounds.

Scheme 2 shows the model reactions for the stepwise generation of two benzyne species from bis-sulfonate **1**,[8] which was trapped by KSA **2** as an arynophile. Upon treatment of **1** with *n*BuLi (0.53 M in hexane; 1.05 equiv) in



Scheme 1. Stepwise generation of benzynes and iterative cycloadditions. Ts = *p*-toluenesulfonyl; Tf = trifluoromethanesulfonyl.



Scheme 2. Stepwise generation of benzynes from bis-sulfonate **1**. [a] 1.05 equiv *n*BuLi. [b] 2.3 equiv *n*BuLi. TBS = *tert*-butyldimethylsilyl.

the presence of KSA **2** (Et_2O, −95 °C, 5 min), the [2+2] cycloaddition proceeded cleanly to give mono-cycloadduct **3** in 72% yield. Small amounts of mono-cycloadduct **4** without an iodine atom (4%) and bis-adduct **5** (8%) were also obtained.[9–11]

Importantly, note that no trace was identified of the alternative cycloadduct **6**, which arises from the benzyne generation at the iodo-tosylate side of **1**. In sharp contrast, a similar reaction of bis-triflate **7** (Et_2O, −95 °C, 5 min) did not stop at the mono-cycloaddition stage, thus giving a low yield of mono-cycloadduct **6** (14%) and bis-cycloadduct **5** (13%).

Careful choice of the stoichiometry and the reaction temperature proved decisive for the controlled generation of the second benzyne species. When the reaction of bis-sulfonate **1** was performed with 2.3 equivalents of *n*BuLi at −95 °C, bis-cycloadduct **5** was obtained (24%) along with a considerable amount of mono-cycloadduct **4** which lacks the iodine atom (34%). This result implies that aryllithium species **B** generated by the I–Li exchange of the initial product **3** has a finite lifetime at −95 °C.

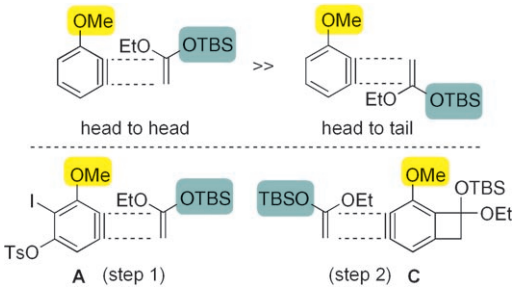
On the other hand, if the same reaction was performed initially at −95 °C followed by warming to −78 °C, bis-cycloadduct **5** was obtained as almost the exclusive product in high yield and as a single regioisomer. Lithiated species **B** undergoes 1,2-elimination of lithium *p*-toluenesulfonate (LiOTs) at −78 °C to generate the second benzyne species **C**. These behaviors provided us with the handle to control bis-annelations in one pot with different arynophiles (see below).

[*] Dr. T. Hamura, T. Arisawa, Dr. T. Matsumoto, Prof. Dr. K. Suzuki
Department of Chemistry
Tokyo Institute of Technology
and SORST Japan Science and Technology Agency (JST)
2-12-1 O-okayama, Meguro-ku, Tokyo 152-8551 (Japan)
Fax: (+81) 3-5734-2788
E-mail: ksuzuki@chem.titech.ac.jp

[**] Partial financial support provided by the 21st Century COE program is gratefully acknowledged.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

The selective formation of cycloadduct **5** is notable for two points: 1) this cycloadduct is a highly strained benzene unit that comprises two four-membered rings,[12] and 2) it is a sterically encumbered regioisomer, in which the two silyl acetals are located near the methoxy group. As reported previously, a methoxy group located *ortho* to the benzyne species exerts a significant directing effect to encourage head-to-head cycloaddition,[6] which in the present case worked twice in two successive cycloadditions of benzynes **A** and **C** (Scheme 3).

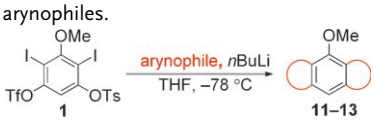


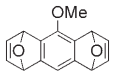
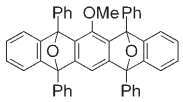
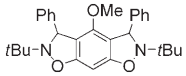
Scheme 3. Head-to-head mode in two iterative [2+2] cycloadditions.

Table 1 shows the results of this one-pot bis-cycloaddition with various arynophiles. A typical experimental procedure is represented by double furan cycloadditions (Table 1, entry 1): *n*BuLi (2.4 equiv in hexane) was slowly added at −78 °C to a mixture of bis-sulfonate **1** and furan (**8**, 3.0 equiv) in THF. The reaction was stopped after 5 minutes by adding water. Extractive workup followed by purification by column chromatography on silica gel gave bis-cycloadduct **11** in 81 % yield.[13] Similarly, isobenzofuran **9** proved to be applicable for dual [2+4] cycloadditions, thus affording heptacycle **12** in 69 % yield (Table 1, entry 2). The corresponding reaction with nitrone **10** (Table 1, entry 3) proceeded regioselectively to give the single regioisomeric bis-[2+3] cycloadduct **13**, in which the oxygen atom of the nitrone is located away from the methoxy group, in 41 % yield.

Moreover, two different rings could be fused to the central benzene unit in one pot by using two different arynophiles at different temperatures (Table 2). Upon treatment of bis-sulfonate **1** with *n*BuLi (1.1 equiv) in hexane in the presence of KSA **2** (1.2 equiv) in Et_2O at −95 °C, the starting material was quickly consumed and the formation of the mono-cycloadduct **3** was observed by TLC. The second arynophile, nitrone **10** (3.0 equiv), in THF[14] was added to the reaction mixture at −95 °C, and the temperature was raised to −78 °C. *n*BuLi (1.1 equiv) was slowly added to the reaction mixture to give the unsymmetrical bis-cycloadduct **14** in 68 % yield as a single regioisomer (Table 2, entry 1). In a similar manner, the successive [2+4] and [2+2] cycloadditions with furan (**8**) and KSA **2** gave the corresponding cycloadduct **15** in 68 % yield with perfect regioselectivity

Table 1: Symmetrical dual cycloaddition of the 1,4-benzdiyne equivalent **1** with various arynophiles.



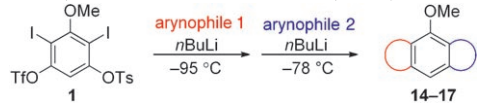
Entry	Arynophile		Bis-cycloadduct		Yield [%][a]
1		**8**		**11**	81
2		**9**		**12**	69
3		**10**		**13**	41

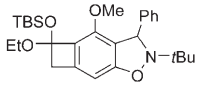
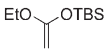
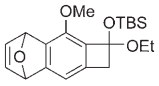
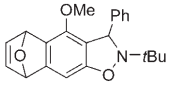
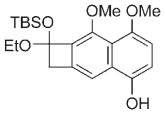
[a] *Syn*/*anti* mixture (see Ref. [8]).

(Table 2, entry 2). The dual reactions with **8** (arynophile 1) and nitrone **10** (arynophile 2) also gave cycloadduct **16** exclusively (Table 2, entry 3). In these reactions, each cycloaddition should be performed with consideration of the relative reactivity of the arynophiles, because the remaining highly reactive arynophile after the first cycloaddition can compete with the second arynophile with lower reactivity in the second cycloaddition to give a significant amount of the symmetrical bis-cycloadduct.[15] The successive processes also proved to be applicable to KSA **2** and 2-methoxyfuran (**18**), thus giving the highly oxygenated tricycle **17**, which could serve as a synthetic intermediate for further elaboration to polyaromatic systems (Table 2, entry 4).

In summary, dual cycloadditions of 1,4-benzdiyne equivalents with various arynophiles allowed the rapid construction of various highly functionalized bis-cycloadducts, which are amenable to selective transformation en route to polycyclic compounds. Synthetic applications are under active investigation.

Table 2: Unsymmetrical dual cycloaddition of the 1,4-benzdiyne equivalent with various arynophiles.



Entry	Arynophile 1		Arynophile 2		Bis-cycloadduct		Yield [%]
1[a]		**2**		**10**		**14**	68[b]
2[c]		**8**		**2**		**15**	68[b]
3[a]		**8**		**10**		**16**	61[b]
4[c]		**2**		**18**		**17**	58

[a] Et_2O was used as the solvent for the first cycloaddition; the second arynophile was added as a solution in THF. [b] *Syn*/*anti* mixture (see Ref. [8]). [c] In Et_2O.

Experimental Section

Synthesis of bis-adduct **14**: *n*BuLi (0.53 M in hexane, 0.50 mL, 0.27 mmol) was added to a mixture of bis-sulfonate **1** (170 mg, 0.25 mmol) and KSA **2** (58.4 mg, 0.29 mmol) in Et_2O (2.5 mL) at −95 °C. After 5 min, nitrone **10** (135 mg, 0.76 mmol) in THF (1.0 mL) was added to the reaction mixture at −95 °C, to which *n*BuLi (0.53 M in hexane, 0.50 mL, 0.27 mmol) was then slowly added at −78 °C. After 5 min, the reaction was quenched by adding water. The products were extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (98:2 hexane/EtOAc) to afford the less polar adduct **14** (39.9 mg, 32.9 %) and more polar adduct **14** (42.5 mg, 35.0 %).

Received: June 24, 2006
Revised: July 29, 2006
Published online: September 22, 2006

Keywords: arynes · chemoselectivity · cycloaddition · polycycles · regioselectivity

[1] K. P. C. Vollhardt, *Angew. Chem.* **1984**, *96*, 525 – 541; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 539 – 556.

[2] For reviews on arynes, see: a) R. W. Hoffmann, *Dehydrobenzene and Cycloalkynes*, Academic, New York, **1967**; b) S. V. Kessar in *Comprehensive Organic Synthesis*, *Vol. 4* (Ed.: B. M. Trost), Pergamon, Oxford, UK, **1991**, pp. 483 – 515; c) H. Pellissier, M. Santelli, *Tetrahedron* **2003**, *59*, 701 – 730; d) H. H. Wenk, M. Winkler, W. Sander, *Angew. Chem.* **2003**, *115*, 518 – 546; *Angew. Chem. Int. Ed.* **2003**, *42*, 502 – 528.

[3] Use of this reactive species, even as its synthetic equivalents, has been quite limited; for pioneering studies on the generation and trapping of 1,4-benzdiyne equivalents, see: a) H. Hart, D. Ok, *J. Org. Chem.* **1986**, *51*, 979 – 986; b) H. Hart, C.-Y. Lai, G. Nwokogu, S. Shamouilian, A. Teuerstein, C. Zlotogorski, *J. Am. Chem. Soc.* **1980**, *102*, 6649 – 6651; for other recent examples, see: c) Y.-L. Chen, J.-Q. Sun, X. Wei, W.-W. Wong, A. W. M. Lee, *J. Org. Chem.* **2004**, *69*, 7190 – 7197; d) G. E. Morton, A. G. M. Barrett, *J. Org. Chem.* **2005**, *70*, 3525 – 3529; e) I. I. Schuster, L. Cracium, D. M. Ho, R. A. Pascal, Jr., *Tetrahedron* **2002**, *58*, 8875 – 8882; f) H. M. Duong, M. Bendikov, D. Steiger, Q. Zhang, G. Sonmez, J. Yamada, F. Wudl, *Org. Lett.* **2003**, *5*, 4433 – 4436.

[4] a) T. Matsumoto, T. Hosoya, M. Katsuki, K. Suzuki, *Tetrahedron Lett.* **1991**, *32*, 6735 – 6736; b) T. Hosoya, E. Takashiro, T. Matsumoto, K. Suzuki, *J. Am. Chem. Soc.* **1994**, *116*, 1004 – 1015.

[5] T. Matsumoto, T. Sohma, S. Hatazaki, K. Suzuki, *Synlett* **1993**, 843 – 846.

[6] a) T. Hosoya, T. Hasegawa, Y. Kuriyama, T. Matsumoto, K. Suzuki, *Synlett* **1995**, 177 – 179; b) T. Hosoya, T. Hamura, Y. Kuriyama, K. Suzuki, *Synlett* **2000**, 520 – 522; c) T. Hamura, T. Hosoya, H. Yamaguchi, Y. Kuriyama, M. Tanabe, M. Miyamoto, Y. Yasui, T. Matsumoto, K. Suzuki, *Helv. Chim. Acta* **2002**, *85*, 3589 – 3604.

[7] We recently reported a viable route to functionalized tricyclobutabenzenes by exploiting benzyne–KSA [2+2] cycloaddition chemistry; see: a) T. Hamura, Y. Ibusuki, H. Uekusa, T. Matsumoto, K. Suzuki, *J. Am. Chem. Soc.* **2006**, *128*, 3534 – 3535; b) T. Hamura, Y. Ibusuki, H. Uekusa, T. Matsumoto, J. S. Siegel, K. K. Baldridge, K. Suzuki, *J. Am. Chem. Soc.* **2006**, *128*, 10032 – 10033.

[8] See the Supporting Information for details.

[9] Recently, the related chemoselective generation of polyfunctionalized arynes by I–Mg exchange of 2-iodophenyl sulfonates was developed; see: a) I. Sapountzis, W. Lin, M. Fisher, P. Knochel, *Angew. Chem.* **2004**, *116*, 4464 – 4466; *Angew. Chem. Int. Ed.* **2004**, *43*, 4364 – 4366; b) W. Lin, I. Sapountzis, P. Knochel, *Angew. Chem.* **2005**, *117*, 4330 – 4333; *Angew. Chem. Int. Ed.* **2005**, *44*, 4258 – 4261.

[10] For related regioselective halogen–lithium exchange of dihalobenzenes, see: M. Dabrowski, J. Kubicka, S. Lulinski, J. Serwatowski, *Tetrahedron* **2005**, *61*, 6590 – 6595.

[11] When the same reaction was performed in THF, mono-cycloadduct **3** and bis-cycloadduct **5** were obtained (52 and 10 %, respectively).

[12] R. Gray, L. G. Harruff, J. Krymowski, J. Peterson, V. Boekelheides, *J. Am. Chem. Soc.* **1978**, *100*, 2892 – 2893.

[13] The use of Et_2O as solvent led to a lower yield of **11** (71 %), presumably as a result of the low solubility of the initially formed mono-cycloadduct.

[14] The second arynophile, nitrone **10** was added in solution with THF because of its insolubility in Et_2O.

[15] The following order of reactivity was assessed by a competition experiment: nitrone **10** > KSA **2** > furan (**8**). The reaction of alkoxybenzyne with the same amount of **2**, **10**, and **8** gave the [2+3] cycloadduct (56 %), the [2+2] cycloadduct (30 %), and the [2+4] cycloadduct (13 %), respectively (see the Supporting Information).

