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Stereospecificity in [2 + 2] Cycloaddition of Benzyne and Ketene Silyl Acetal

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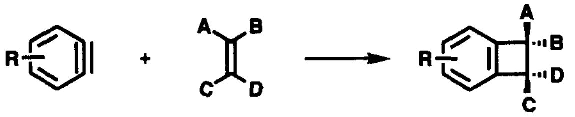
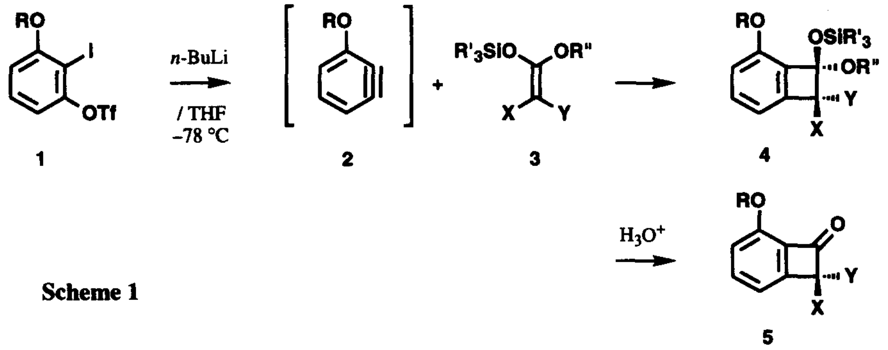
Abstract: The first observation of the stereospecificity in the benzyne–olefin [2 + 2] cycloaddition is described. The key points reside in (1) the efficient method for generating benzyne species by the halogen–lithium exchange reaction of *ortho*-halo aryl triflates, and (2) the choice of ketene silyl acetal as the partner olefin.

The formal triple bond of benzyne is unique with regard to its ability to undergo *thermal* [2 + 2] cycloaddition reaction with an olefinic double bond (eq 1).[1] Such an exception is accounted by invoking the pseudo-excitation effect due to the unusually low-lying LUMO of benzyne.[2] Given the concerted nature of the reaction, the frontier molecular orbital theory predicts that the cycloaddition may proceed in stereospecific manner. Such specificity, however, has never been realized experimentally, and all the reported examples involve partial stereo-randomization via, most probably, the intermediacy of biradical or zwitterionic species.[3]



(1)

We recently reported an efficient synthetic method of benzocyclobutenones via the [2 + 2] cycloaddition of benzynes and ketene silyl acetals (Scheme 1).[4a] Essential to the process are (1) the efficiency of the new generation method of benzyne (**1** → **2**),[4b–e] and (2) the use of a particularly efficient *arynophile*, ketene silyl acetal **3**. While the regiochemical sense of the cycloaddition, as represented by the example below, is significant from the synthetic standpoint,[4,5] the relative stereochemistry in **4** is of no consequence at the stage of benzocyclobutenone **5**.[6] We were nonetheless interested in the stereochemical course of this cycloaddition in relation to the question stated above, and we examined the reactions of geometrical isomers of ketene silyl acetal **3**. This communication will describe the first observation of the stereospecificity in the benzyne–olefin [2 + 2] cycloaddition.[7]



Scheme 1

As model substrates, geometrical isomers of ketene (*t*-butyldimethyl)silyl acetals **6** and **7** were prepared (Scheme 2).[8] According to the Yamamoto method,[8a] both isomers of β-siloxy ketene silyl acetal **6** were prepared with the geometrical purities shown below.[9] By the Ireland method,[8b] ethyl propionate was converted to the (*E*)- and (*Z*)-isomers of β-methyl ketene silyl acetal **7**. While (*Z*)-**7** was prepared in pure form,[9] (*E*)-**7** was only available contaminated by a small amount of (*Z*)-**7**.[9] With these stereoisomeric ketene silyl acetals in hand, we examined the reaction with a benzyne.

Scheme 2

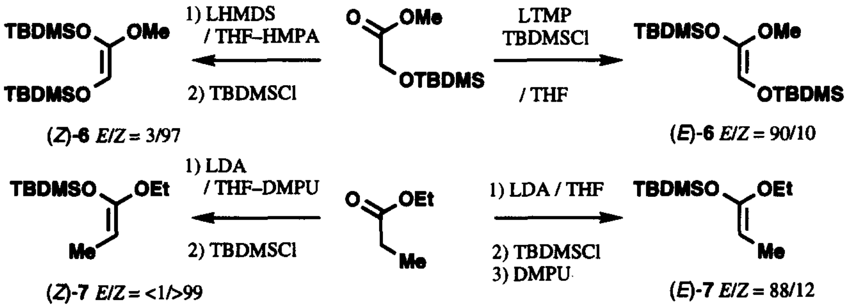
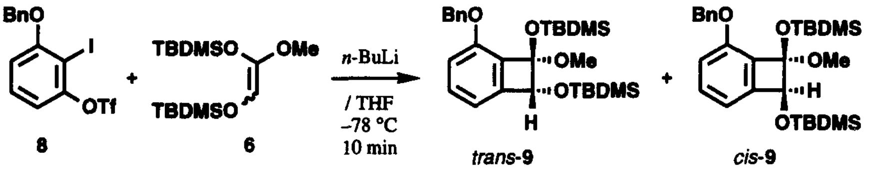
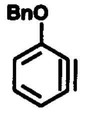


Table 1 shows the results of the reaction of ketene silyl acetal **6** with the benzyne **A**, generated from iodo triflate **8** under the conditions previously reported (*n*-BuLi / THF, –78 °C).[4] The cycloadditions proceeded regioselectively to give the cycloadduct **9** in high yields,[10,11] thereby showing that the *E*/*Z* ratios of **6** are perfectly reflected on the trans/cis ratios of the cycloadduct **9**.[11]

Table 1



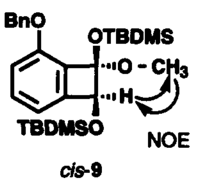


A

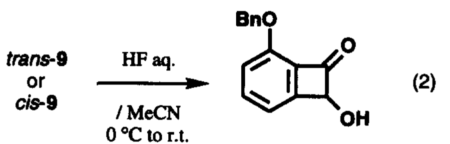
run	*E*/*Z* ratio of **6**[a]	yield/%[b]	trans/cis[c]
1	90/10	81	90/10
2	47/53	80	46/54
3	3/97	81	3/97

a) See ref. 9. b) Isolated yields. c) See ref. 11.

The relative configurations of isomeric cycloadducts of **9** were determined by the NOE experiments for the chromatographically separated isomers. While *cis*-**9** showed an NOE (see below), the trans isomer did not. Their diastereomeric relationship was confirmed by the acid hydrolysis, where the isomers converged to a common benzocyclobutenone **10** (eq 2).[10]



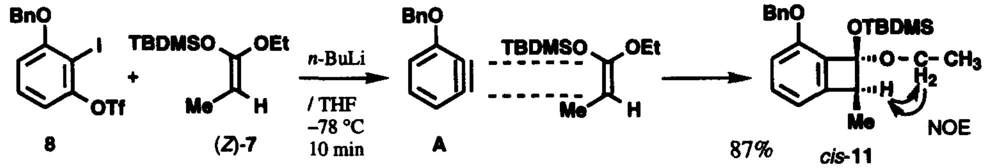
cis-**9**



(2)

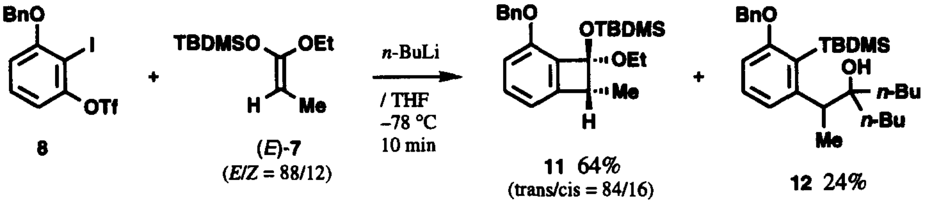
10 (99% from *trans*-**9**)
(99% from *cis*-**9**)

The reaction with ketene silyl acetal **7** also proceeded stereospecifically. Pure (*Z*)-**7** afforded the cycloadduct **11** in 87% yield,[10] which was solely composed of the cis isomer (eq 3).[12]

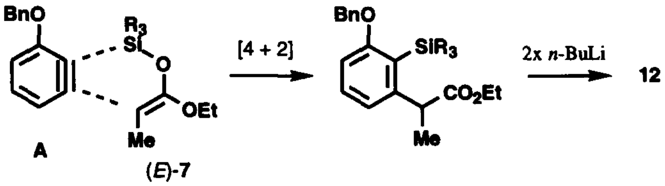


(3)

The (*E*)-isomer of **7** underwent also stereospecific cycloaddition, which, however, requires some comments. The reaction of (*E*)-**7** (*E*/*Z* = 88/12) gave only 64% yield of cycloadduct **11** with a slightly decreased ratio (trans/cis = 84/16; eq 4).[12] The lower yield is due to the formation of a byproduct, aryl silane **12** (24% yield),[4a,10] arising from the competing [4 + 2] reaction and exhaustive butylation (eq 5). Consideration of this side reaction explains the apparent loss of the stereospecificity. Note that (*E*)-**7** is the sole origin of **12** since the reaction of (*Z*)-**7** does not give this byproduct (vide supra). Thus, (*E*)-**7** diverges into *trans*-**11** and **12** in a ratio of 70/30, and the net trans/cis ratio of **11** is corrected as 88/12, thereby again proving the stereospecificity. To verify the validity of such a correction, we repeated several experiments by varying the *E*/*Z* ratios of **7**, which led to the same conclusion.



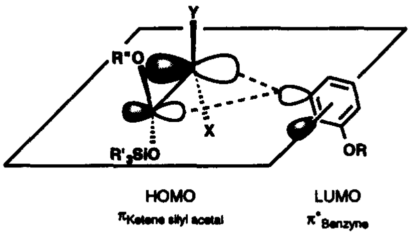
(4)



(5)

The Hoffmann[2a]–Fukui[2b] theory on the benzyne–olefin [2 + 2] cycloaddition comprises the initial three-centered structure (the HOMO–LUMO interaction, Fig 1) followed by its transition to the four-membered ring via the HOMO–HOMO and the LUMO–LUMO interactions at the pseudo-excited state. The present experiments score a first example of the stereo-retentive [2 + 2] cycloaddition of a benzyne and a strong donor olefin, ketene silyl acetal. The ***high HOMO level*** of this particular olefin facilitates the pseudo-excitation and is seemingly essential to the stereospecificity as well as the reactivity. Indeed, the attempted reactions of olefins with a lower HOMO, such as enol silyl ethers or allylsilane, resulted in low yields under the above stated conditions.

Figure 1



Further study on the theoretical aspects of this [2 + 2] cycloaddition is now in progress.

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References and Notes:

1) For reviews on arynes, see: a) Hoffmann, R. W. *Dehydrobenzene and Cycloalkenes*; Academic: New York, 1967. b) Kessar, S. V. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, U. K., 1991; Vol. 4, p 483.

2) a) Hayes, D. M.; Hoffmann, R. *J. Phys. Chem.* **1972**, *76*, 656. b) Inagaki, S.; Fukui, K. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2240. c) Epiotis, N. D. *Angew. Chem., Int. Ed. Eng.* **1974**, *13*, 751. d) Inagaki, S.; Fujimoto, H.; Fukui, K. *J. Am. Chem. Soc.* **1975**, *97*, 6108. e) Rondan, N. G.; Domelsmith, L. N.; Houk, K. N.; Bowne, A. T.; Levin, R. H. *Tetrahedron Lett.* **1979**, 3237.

3) a) Tabushi, I.; Oda, R.; Okazaki, K. *Tetrahedron Lett.* **1968**, 3743. b) Jones, M., Jr.; Levin, R. H. *Ibid.* **1968**, 5593. c) Wasserman, H. H.; Solodar, A. J.; Keller, L. S. *Ibid.* **1968**, 5597. d) Friedman, L.; Osiewicz, R. J.; Rabideau, P. W. *Ibid.* **1968**, 5735. e) Gassman, P. G.; Benecke, H. P. *Ibid.* **1969**, 1089. f) Jones, M., Jr.; Levin, R. H. *J. Am. Chem. Soc.* **1969**, *91*, 6411. g) Bowne, A. T.; Christopher, T. A.; Levin, R. H. *Tetrahedron Lett.* **1976**, 4111.

4) a) Hosoya, T.; Hasegawa, T.; Kuriyama, Y.; Matsumoto, T.; Suzuki, K. *Synlett in press.* b) Matsumoto, T.; Hosoya, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1991**, *32*, 6735. c) Matsumoto, T.; Hosoya, T.; Suzuki, K. *J. Am. Chem. Soc.* **1992**, *114*, 3568. d) Matsumoto, T.; Sohma, T.; Hatazaki, S.; Suzuki, K. *Synlett* **1993**, 843. e) Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1994**, *116*, 1004.

5) a) Stevens, R. V.; Bisacchi, G. S. *J. Org. Chem.* **1982**, *47*, 2393. b) Liebeskind, L. S.; Lescosky, L. J.; McSwain, C. M., Jr. *Ibid.* **1989**, *54*, 1435.

6) For reviews on the benzocyclobutenes, see: a) Durst, T.; Breau, L. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, U. K., 1991; Vol. 5, p 675. b) Oppolzer, W. *Ibid.*; Vol. 5, p 315.

7) Although Caubere *et al.* have studied [2 + 2] cycloaddition of benzyne with lithium enolates of medium- to large-ring cycloalkanones, little was described on the geometrical relationship between the enolates and the products. Gregoire, B.; Carre, M.-C.; Caubere, P. *J. Org. Chem.* **1986**, *51*, 1419.

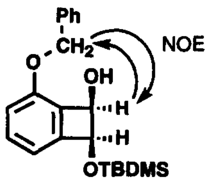
8) a) Hattori, K.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 3099. b) Ireland, R. E.; Wipf, P.; Armstrong, J. D. III *J. Org. Chem.* **1991**, *56*, 650.

9) The *E/Z* ratios were determined by integrating the vinyl proton and the methylene protons of the ethoxyl group for **6** and of the vinyl proton for **7** (400 MHz ^{1}H NMR in C_6D_6).

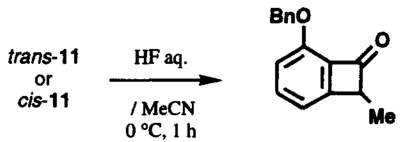
10) All new compounds were fully characterized by 400 MHz ^{1}H- and 100 MHz ^{13}C-NMR spectra, IR, and HRMS and/or combustion analysis.

11) The regiochemical assignment of **9** was confirmed by the NOE experiments for alcohol **13** (see below) derived from **10** in two steps: (a) TBDMSCl, imidazole / DMF, r.t., 15 min (97%); (b) L-Selectride / THF, –78 °C, 20 min (79%). The trans/cis ratios of **9** were determined by integrating the benzyl protons ($\text{-C}\underline{\text{H}}_2\text{Ph}$) (400 MHz ^{1}H NMR in C_6D_6).

12) The trans/cis ratios of **11** were determined by the integration of the methylene protons of the ethoxyl group (400 MHz ^{1}H NMR in C_6D_6). Again, the diastereomeric relationship was proved by obtaining the common hydrolysate **14** from both isomers of **11** (eq 6).



13



(6)

14 (99% from *trans*-**11**)
(99% from *cis*-**11**)

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