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Strain-Induced Regioselectivities in Reactions of Benzyne Possessing a Fused Four-Membered Ring

Toshiyuki Hamura, Yousuke Ibusuki, Kazuhiko Sato, Takashi Matsumoto, Yoshihiro Osamura,† and Keisuke Suzuki*

Department of Chemistry, Tokyo Institute of Technology, and CREST, Japan Science and Technology Corporation (JST), O-okayama, Meguro-ku, Tokyo 152-8551, Japan

ksuzuki@chem.titech.ac.jp

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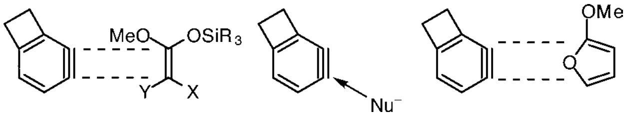
ABSTRACT



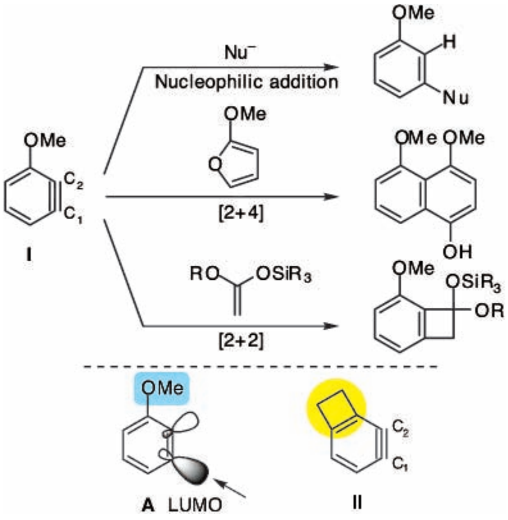
A fused four-membered ring has a powerful directing ability in effecting the regioselective reactions of benzyne with ketene silyl acetal, nucleophile, and α-alkoxyfuran.

Regioselective reactions of substituted benzynes are of theoretical and synthetic interest.[1] An α-alkoxy group within a benzyne species **I** exerts significant effects in determining the reaction course on processes such as nucleophilic addition,[2] [2 + 4] cycloaddition,[3] and [2 + 2] cycloaddition (Scheme 1).[4] A possible rationale to these aspects centers at the enhanced electrophilicity at C_1 relative to C_2 (see **A**) due to inductive electron withdrawal by the alkoxy group, rendering the C1 position the preferred site for initial interaction with nucleophilic reaction partners.[5]

We report here that fused four-membered rings, such as that in benzyne **II**, exert an apparently similar directing effect in these reactions. Judging from the absence of such an effect in the corresponding five- and six-membered rings (vide infra), it appears that the ring strain is the origin of such a directing effect.

Model substrate **5** was prepared by [2 + 2] cycloaddition of benzyne and ketene silyl acetal (KSA) **2a** as shown in

Scheme 1



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† Current address: Department of Chemistry, Rikkyo University, 3-34-1, Nishiikebukuro, Tokyo 171-8501, Japan.

(1) For reviews on arynes: (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, UK, 1991; Vol. 4, pp 483−515.

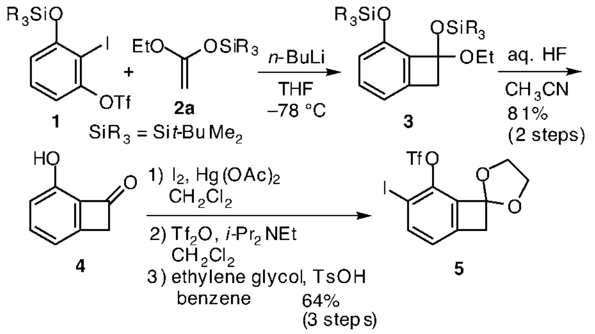
(2) For example: (a) Huisgen, R.; Rist, H. *Liebigs Ann. Chem.* **1955**, *594*, 137−158. (b) Benkeser, R. A.; DeBoer, C. E. *J. Org. Chem.* **1956**, *21*, 281−284. See also ref 1.

(3) Matsumoto, T.; Hosoya, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1991**, *32*, 6735−6736.

(4) (a) Hosoya, T.; Hasegawa, T.; Kuriyama, Y.; Matsumoto, T.; Suzuki, K. *Synlett* **1995**, 177−179. (b) Hosoya, T.; Hasegawa, T.; Kuriyama, Y.; Suzuki, K. *Tetrahedron Lett.* **1995**, *36*, 3377−3380. (c) Hosoya, T.; Hamura, T.; Kuriyama, Y.; Suzuki, K. *Synlett* **2000**, 520−522. (d) Hamura, T.; Hosoya, T.; Yamaguchi, H.; Kuriyama, Y.; Tanabe, M.; Miyamoto, M.; Yasui, Y.; Matsumoto, T.; Suzuki, K. *Helv. Chim. Acta* **2002**, *85*, 3589−3604.

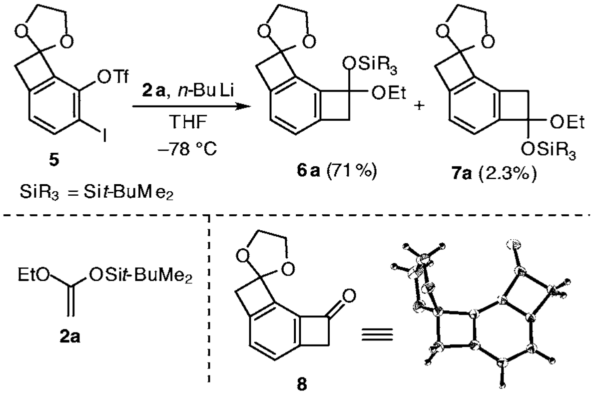
10.1021/ol034877p CCC: $25.00

Scheme 2



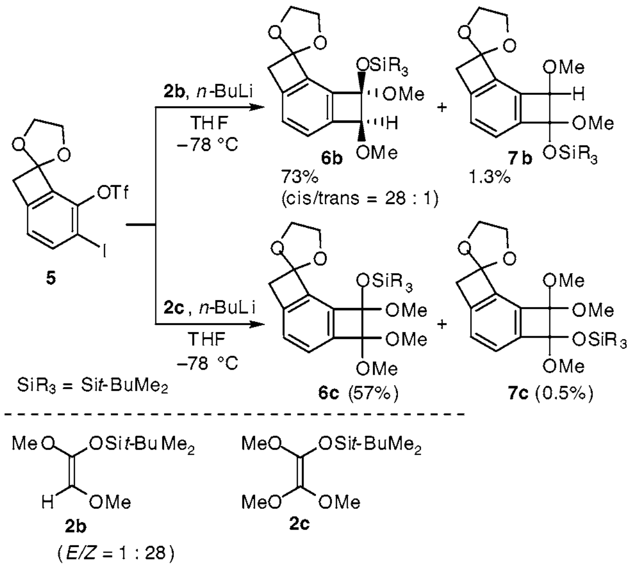
Scheme 2. Treatment of *o*-iodo triflate **1** with *n*-BuLi in the presence of KSA **2a** gave a single cycloadduct **3**, which was converted to ketone **4** by acid hydrolysis (81%, two steps). Regioselective iodination of phenol **4** followed by triflate formation and acetalization gave iodo triflate **5**, which was used for the subsequent model study.

Scheme 3



Scheme 3 shows the [2 + 2] cycloaddition of the benzyne generated from **5**.[6] Upon treatment of **5** with *n*-BuLi in the presence of KSA **2a** (THF, −78 °C, 5 min), the [2 + 2] cycloaddition proceeded cleanly and with high regioselectivity (31:1). The isomers were easily separable by silica gel preparative TLC to give mainly **6a** and a small amount of **7a**, respectively.[7] It is interesting that major cycloadduct **6a** is the one with greater steric congestion with respect to the acetal moieties (cf. **7a**).[8] Hydrolysis of **6a** (aqueous KF, n-Bu_4NCl, CH_3CN) gave mono-one **8** in 95% yield, whose structure was unambiguously assigned by X-ray analysis (see Scheme 3).[9]

Scheme 4



This regiochemical trend also applied to more oxygenated KSAs (Scheme 4). KSA **2b** with an additional methoxy group gave cycloadduct **6b** almost exclusively (**6b**/**7b** = 56:1).[10] The reaction was stereospecific, as the *E*/*Z* ratio of **2b** (*E*/*Z* = 1:28) was transferred to the relative stereochemistry of the four-membered ring in **6b** (cis/trans = 28:1).[4b,11] The fully oxygenated KSA **2c** showed even higher regioselectivity (**6c**/**7c** > 100:1), giving cycloadduct **6c** as essentially the only product.[12]

What is the origin of the regioselectivity? As a possible explanation, we initially envisaged that the steric effect posed by the ethylene acetal may play a key role, directing the initial interaction to occur at the distal site from the four-membered ring as in **B** (Scheme 5). The zwitterion **C** or its classical congeners **III** and/or **IV** are considered for the formation of regioisomeric products **D** and **E**. In either case, preference of **III** over **IV** (the case of less oxygenated KSAs, **2a** and **2b**) by considering the relative stability of the positive

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(5) While such initial HOMO−LUMO interaction directly correlates to the outcome for the nucleophile attack and the [2 + 4] cycloaddition, the [2 + 2] cycloaddition needs additional consideration in that the decisive step is the subsequent transformation of the zwitterion to the four-membered ring (Hoffmann−Fukui two-step mechanism); see: (a) Hayes, D. M.; Hoffmann, R. *J. Phys. Chem.* **1972**, *76*, 656−663. (b) Inagaki, S.; Fukui, K. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2240−2242.

(6) Pioneering study by vollhardt is noted for the generation and trapping of cyclobutabenzyne with furan; see: Hillard, R. L.; Vollhardt, K. P. C. *Angew, Chem., Int. Ed. Engl.* **1977**, *16*, 399−400.

(7) THF was the solvent of choice for good yield; cf. Et_2O (**6a**, 62%; **7a**, 2%), toluene (**6a**, 56%; **7a**, 2%) and DME (**6a**, 59%; **7a**, 2%).

(8) Recently, a related report has appeared using ketene dialkyl acetals, although the yields were extremely low (20−30%) and the precise ratio of the regioisomeric cycloadducts was not described; see: Maurin, P.; I-Ouali, M.; Santelli, M. *Tetrahedron Lett.* **2001**, *42*, 8147−8149.

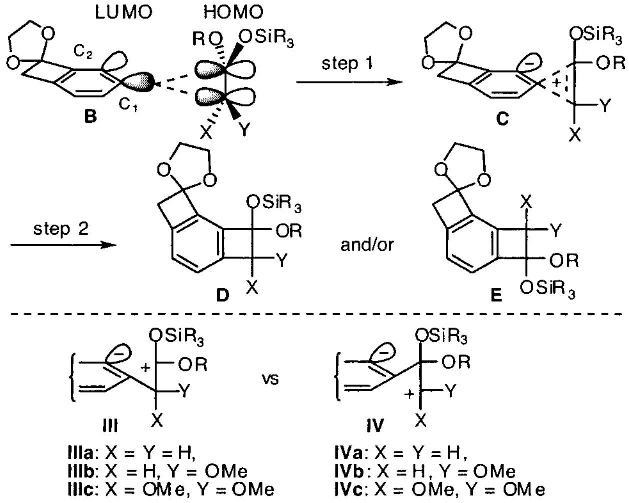
(9) We thank Ms. Sachiyo Kubo for X-ray analysis. Crystallographic data have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 218424.

(10) For preparation of KSA **2b**, see: Hattori, K.; Yamamoto, H. *Tetrahedron*, **1994**, *50*, 3099−3112. The ratio of cycloadducts **6b** and **7b** was determined by isolation by silica gel chromatography, and their structures were assigned by NMR study.

(11) Major regioisomer **6b** was composed of two stereoisomers with respect to the methoxy and siloxy groups; cis isomer *cis*-**6b** (71%) and trans isomer *trans*-**6b** (2.5%), whose stereochemistries were assigned by NOE study. The stereochemistry of minor regioisomer **7b** (1.3%) was not determined.

(12) Minor isomer **7c** could not be detected by high-field NMR analysis of the crude reaction mixtures. The ratio was determined after separating cycloadducts **6c** and **7c** by silica gel chromatography, and their structures were assigned by NMR study. See Supporting Information.

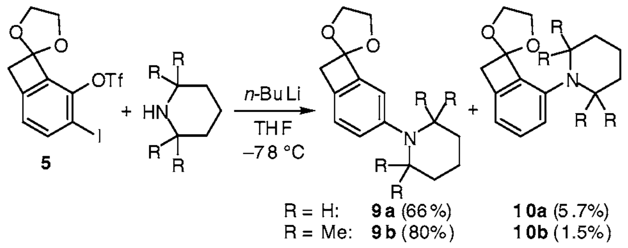
Scheme 5



charge explains the regiochemical outcome.[13] Furthermore, the case of KSA **2c** (X = Y = OMe) deserves particular attention. Relevant here is the extent of cation stabilization offered by two "oxy" substituents: the cation **IIIc** is preferable to **IVc** because of the more electropositive nature of silicon in comparison with carbon.[4c]

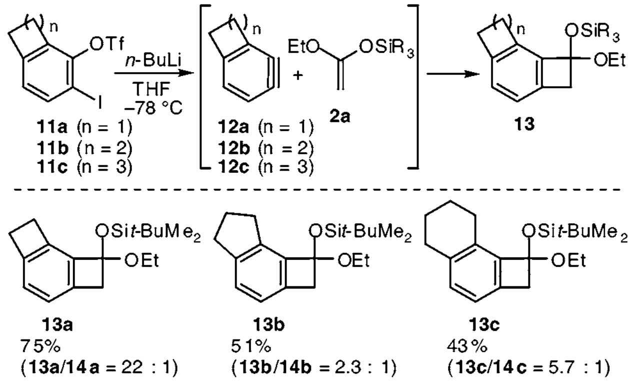
Indeed, the preferred site of initial interaction was proven by nucleophilic addition to **B** (Scheme 6). Upon treatment of **5** with *n*-BuLi in the presence of piperidine, the nitrogen attack occurred selectively at the expected site, giving **9a** as a major product (12:1).[14] We reasoned that the inferior selectivity in comparison with the [2 + 2] cycloadditions (vide supra) might be due to the reduced steric bulk of nucleophile. Indeed, 2,2,6,6-tetramethylpiperidine reacted with an even higher selectivity (53:1) to give **9b**.

Scheme 6



Such a rationale is basically fine with the acetal-containing benzyne. However, further experiments revealed that high, if not complete, regioselectivity was observed in the absence of the acetal, suggesting that *the crucial factor for determining the regioselectivity resides in the four-membered ring itself* rather than the steric bulkiness. Benzyne **12a**, lacking the ethylene acetal moiety, still showed an excellent regioselectivity (22:1), giving preferentially cycloadduct **13a** (Scheme 7).[15] Importantly, it was noted that the regioselectivity dramatically decreased for the corresponding benzyne **12b** with a five-membered ring, giving a regioisomeric mixture of **13b** and its isomer **14b** (not shown) in 2.3:1 ratio.[16,17] Benzyne **12c**, possessing a six-membered ring, reacted with moderate selectivity (5.7:1) to give **13c** as a major product.[18]

Scheme 7[a]



[a] Overall yields are given. Observed major products are shown.

Our attention was thus shifted to *the ring strain as the origin of the regioselectivity*. As described by Streitwieser and Finnegan,[19] the bridgehead carbon rehybridizes to use orbitals of higher p character in bonding to the strained ring, and hence, the remaining orbital has a higher s character. Thus, C_2 is bound to an orbital of higher electronegativity, rendering C_1 more electron deficient (see **12a** in Figure 1).[20] Indeed, calculations[21] showed that the C_1 carbon in **12a** distal from the four-membered ring is apparently more positive

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(13) Recently, a related reaction of cycloheptyne with 2,3-dihydropyran, which included a cyclopropylcarbene as an intermediate, was reported; see: Bachrach, S. M.; Gilbert, J. C.; Laird, D. W. *J. Am. Chem. Soc.* **2001**, *123*, 6706−6707. Also, in our case, computational studies showed that the structures of the initial adduct has considerable carbene-like character (unpublished results). For bookkeeping purposes, however, we described these regioselective features using the Hoffmann−Fukui zwitterionic mechanism.

(14) Presence of a proton source is indispensable for this reaction. If the reaction was performed under aprotic conditions [lithium piperidide (3.5 equiv), *n*-BuLi (1.5 equiv)], adduct **9** was not obtained. Instead, a complex mixture of products was observed.

(15) Although the regioisomers were not separable, the minor regioisomer **14a** (not shown) included in **13a** was identified by NMR.

(16) Regioisomers were not separable at the stage of cycloadduct **13b**. However, the corresponding isomeric ketones obtained by acid hydrolysis were separable, and the structures were determined by NMR study.

(17) Steric size has been suggested to be in the following order: cyclohexyl > cyclopentyl > cyclobutyl. See: N. L. Frank, J. S. Siegel, In *Advances in Theoretically Interesting Molecules*; Thummel, R. P., Ed.; JAI Press Inc.: Greenwich, CT, 1995; Vol. 3, pp 209−260.

(18) Et_2O was a better solvent for the reaction of benzyne **12c**. When THF was used, the yield was lower (24%), albeit the regioselectivity was almost the same (5.1:1).

(19) (a) Streitwieser, A. Jr.; Ziegler, G. R.; Mowery, P. C.; Lewis, A.; Lawler, R. G. *J. Am. Chem. Soc.* **1968**, *90*, 1357−1358. (b) Finnegan, R. A. *J. Org. Chem.* **1965**, *30*, 1333−1335.

(20) This kind of reactivity is inherent in strained four-membered rings; see: Bassindale, A. R.; Eaborn, C.; Walton, D. R. M. *J. Chem. Soc. B* **1969**, 12. See also refs 6 and 17.

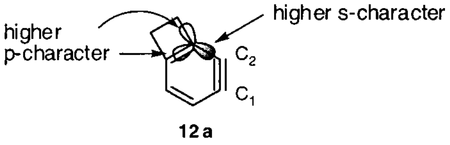


Figure 1.

than the C_2 center. By contrast, the differences in these values in **12b** were less pronounced and were opposite in **12c** (Figure 2).

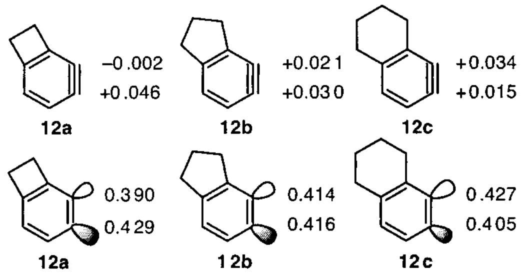
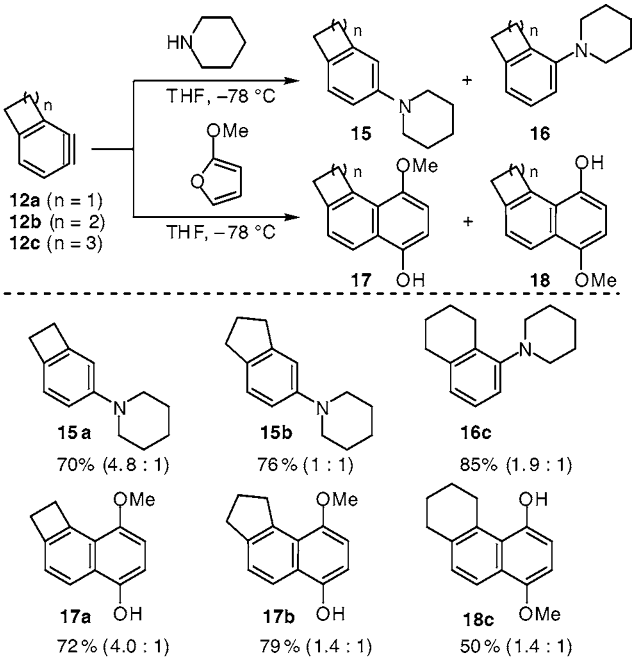


Figure 2. Natural atomic charges (above) and atomic populations of LUMO coefficients (below) at C_1 and C_2 calculated with the B3LYP/6-311G(d,p) method.

In line with this postulate, the regiochemical trend held in nucleophilic additions (Scheme 8). Reaction of benzyne **12a** with piperidine proceeded selectively (**15a**/**16a** = 4.8:1) to give **15a** as the major product. By contrast, no regioselectivity was observed in the reaction of benzyne **12b**, and the nucleophilc attack to **12c** occurred in the opposite manner compared with the reaction of **12a** to give mainly **16c** (**16c**/**15c** = 1.9:1) in 85% combined yield. Note that the nitrogen is located at the position nearer to the six-membered ring in the major product **16c**.

The same trend applied also to the corresponding [2 + 4] cycloaddition. Reaction of benzyne **12a** with 2-methoxyfuran proceeded regioselectively to give cycloadduct **17a** as a major product (4.0:1). In contrast, virtually no regioselectivity was observed in the reaction of benzyne **12b**, giving a regioisomeric mixture of **17b** and **18b** (1.4:1) in 79% combined yield. Interestingly, **12c** showed an opposite tendency, albeit with poor regioselectivity, to give cycloadduct **18c** as a major product (**18c**/**17c** = 1.4:1).

Scheme 8 [a]



[a] Overall yields are given. Observed major products are shown.

In summary, a four-membered ring fused to a benzyne has a sizable directing effect for the regioselective reactions with ketene silyl acetals, nucleophiles, and α-alkoxyfuran. Such findings open an opportunity for selective syntheses of various interesting aromatic compounds. Further studies are currently underway in our laboratories.

Acknowledgment. We thank Prof. Jay S. Siegel, UCSD, for helpful discussions. Thanks are also due to 21st Century COE program for partial financial support.

Supporting Information Available: General procedures and spectral data for compounds **4**−**10** and **13**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Atomic population of the lowest unoccupied molecular orbital (LUMO) on atom *A* can be defined as

$$C_A^{\text{LUMO}} = \sum_{B} \sum_{\mu \in A} \sum_{\nu \in A} C_\mu^{\text{LUMO}} C_\nu^{\text{LUMO}} S_{\mu\nu}$$

where C_μ^{LUMO} is the LUMO coefficient of the atomic orbital μ and $S_{\mu\nu}$ is the overlap integral between atomic orbitals μ and ν. Variables μ and ν run the atomic orbitals belonging to atoms *A* and *B* in the summation, respectively. Calculations were carried out by using Gaussian 98 package. (*Gaussian 98*, Revision A.11.2; Gaussian, Inc.: Pittsburgh, PA, 2001.)