Siloxy(trialkoxy)ethene undergoes regioselective [2 + 2] cycloaddition to ynones and ynoates *en route* to functionalized cyclobutenediones†

Shin Iwata, Toshiyuki Hamura‡ and Keisuke Suzuki*

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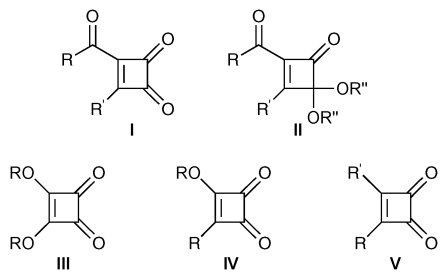
Regioselective [2 + 2] cycloaddition of ynones or ynoates to siloxy(trialkoxy)ethene (KSA) is described. A siloxy group on the KSA directs the perfect regioselectivity, allowing rapid construction of various functionalized cyclobutenedione derivatives.

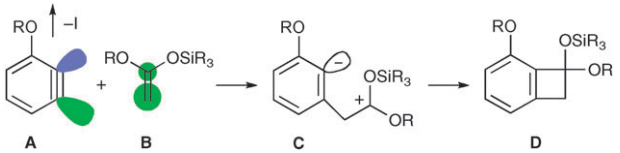
Highly oxidized four-membered carbocycles are useful in organic synthesis;[1] squarates **III** and the derivatives, **IV** and **V**, have been extensively used for the synthesis of complex molecules by exploiting molecular strain, and also as a scaffold for the hybrid assembly for biological studies.[2]



If flexible *de novo* access to such oxidized cyclobutanes became possible, new possibilities in organic synthesis would be opened. We report herein ready, selective access to a class of compounds related to **I** in its selectively protected form **II**, starting with several analogies as the background of the idea.

The [2 + 2] cycloaddition of two ethenes is a simple prototype to construct cyclobutenes. While the parent system needs photo-activation,[3] the corresponding donor/acceptor pair, **VI** and **VII**, reacts thermally through a polar two-step mechanism (Scheme 1).[4] The observed *head-to-head* regiochemistry could be expressed either by the incipient HOMO–LUMO interaction or the relative stability of the intermediary zwitterionic species **VIII** (*vs.* **VIII′**), and the two factors are usually closely related.

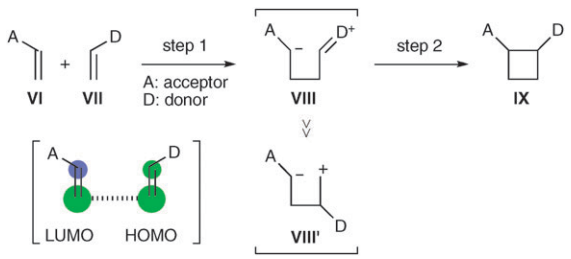
Analogy 1. We noted a close resemblance of such a stepwise [2 + 2] cycloaddition to the reaction of α-alkoxybenzyne **A** with ketene silyl acetal (KSA) **B** on two counts.[5,6] (1) The inductive electron-withdrawal of the α-alkoxy group in **A** makes the LUMO coefficient larger at the distal site to accept the incoming KSA **B**. We are even tempted to regard the reaction as a *σ-conjugate addition*. (2) At the following cyclization stage, the more stabilized, and thus more contributing zwitterion **C** is responsible, leading to the *head-to-head* cycloadduct **D**.



Analogy 2. Of further interest was the finding that, in spite of *pseudo*-symmetry, fully oxygenated KSA **E** reacts with **A** in a completely regioselective manner (Scheme 2).[7] Thus, a question arose whether or not such a selectivity also applies to the triple bond in electrophilic alkyne **G** that resembles **A** in polarity.

This paper describes an affirmative answer to this question: tetraoxyethene **E** indeed undergoes fully regioselective [2 + 2] cycloaddition to alkynone (or alkynoate) **G**, providing efficient access to highly functionalized cyclobutenedione derivatives **H** with considerable synthetic potentials.

Table 1 illustrates the initial model experiments. Upon heating ynone **1** and KSA **2** (1.3 equiv.) in toluene at 90 °C for 12 h, the [2 + 2] cycloaddition smoothly proceeded to give cycloadduct **3** in 54% yield (entry 1).[8] Importantly, the reaction was completely regioselective, giving **3** as a single regioisomer.[9] 1,3-Diene **4** was obtained in 26% yield as a side product, arising from the ring opening of the four-membered ring followed by silyl group migration.[11] As diene **4** was highly prone to hydrolysis by silica-gel chromatography, the yields of **3** and **4** were assessed by ^{1}H NMR analysis. Formation of diene **4** was almost completely suppressed by performing the reaction at lower temperature (entry 2).[12] Moreover, the reaction was even more efficient under solvent-free conditions, giving cycloadduct **3** in almost quantitative yield.



Scheme 1 Polar [2 + 2] cycloaddition.

Department of Chemistry, Tokyo Institute of Technology, and SORST, JST Agency, 2-12-1 O-okayama, Meguro-ku, Tokyo 152-8551, Japan. E-mail: ksuzuki@chem.titech.ac.jp; Fax: (+81)3-5734-2788

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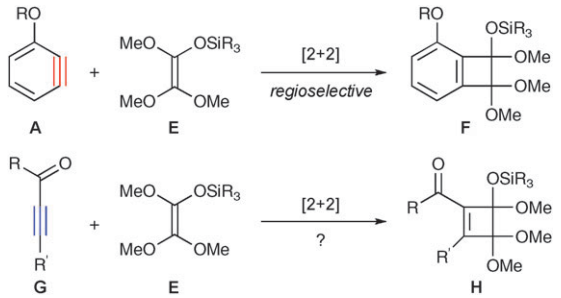
‡ Present address: Department of Chemistry, School of Science and Technology, Kwansei Gakuin University, and PRESTO, JST Agency, 2-1 Gakuen, Sanda, Hyogo 669-1337, Japan



Scheme 2 Possible access to functionalized cyclobutenediones.

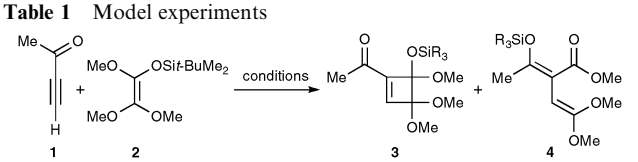
Isolation by silica-gel chromatography afforded 93% yield of **3** (entry 3).

As shown in Table 2, the regioselectivity persisted in the reactions of various other ynones (and a ynoate). Upon heating of ynone **5a** with KSA **2**, the [2 + 2] cycloaddition cleanly proceeded to give cycloadduct **6a** in excellent yield (entry 1).

Interestingly, ynones **5b** and **5c** with an additional alkene moiety, reacted smoothly at the triple bond, while the alkenyl groups remained intact, giving dialkenyl ketones **6b** and **6c**, respectively, in high yield (entries 2 and 3). Diynyl substrate **5d** also underwent rapid cycloaddition at room temperature to give mono-cycloadduct **6d** in 98% yield (entry 4). It should be noted that the reaction occurred selectively at the *terminal alkynyl group*: there was neither indication of the double cycloaddition nor a reaction at the phenylethynyl moiety. Moreover, phenyl propiolate (**5e**) was also a good substrate, affording **6e** in 94% yield (entry 5).[13]

Upon further attempts to examine the substrate scope, we found that β-substituted propiolate **7a** failed to react. Only the starting material was recovered, even when the reaction was performed at 110 °C for a prolonged reaction time (entry 1, Table 3). We were pleased to find, however, that the cycloaddition could be achieved under Lewis acid promoted conditions, and ynoate **7a** reacted with KSA **2** in the presence of Me_3Al (CH_2Cl_2, −78 → −20 °C) to give the desired [2 + 2] cycloadduct **8a** in 41% yield (entry 2).[14] In this case, however, the 1,2-addition competed, producing **9a** in 29% yield.[15] We found that this side reaction was suppressed by increasing the sterics of the ester moiety. The 1,2-addition was partially suppressed by replacing methyl by ethyl (entry 3) or isopropyl (entry 4), and completely suppressed by phenyl, giving the corresponding phenyl ester **8d** in good yield (entry 5).

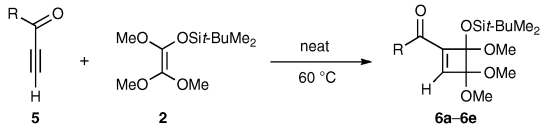
Table 1 Model experiments

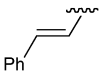
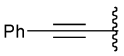


Entry[a]	Conditions	Yield of **3** (%)[b]	Yield of **4** (%)[b]
1	toluene, 90 °C, 12 h	54	26
2	toluene, 60 °C, 17 h	84	3
3	neat, 60 °C, 8 h	quant. (93)[c]	—

[a] The molar ratio of KSA **2** to alkyne **1** is 1.3. [b] NMR yield (internal standard: *p*-bromoanisole). [c] Isolated yield.

Table 2 Thermal [2 + 2] cycloaddition



Entry[a]	Alkyne	R	Time/h	Yield of **6** (%)
1	**5a**	Ph	2	93
2	**5b**		1	89
3	**5c**		8	75
4[b]	**5d**		0.2	98
5	**5e**	PhO	19	94

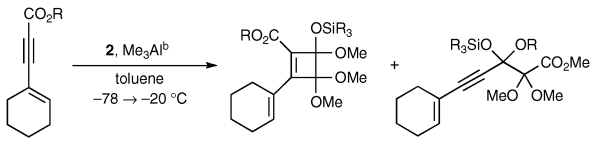
[a] The molar ratio of KSA **2** to alkyne **5** is 1.3–1.4. [b] Performed at room temperature.

Table 4 shows the Me_3Al-promoted [2 + 2] cycloaddition of **2** to various phenyl esters **10a–10e**, giving the corresponding cyclobutenes **11a–11e**, respectively, in high yields.[16–18]

Thus, the various cycloadducts are synthetically useful cyclobutenedione derivatives with two selectively protected carbonyl groups on the four-membered ring. Scheme 3 exemplifies some possibilities. Careful treatment of cycloadduct **11b** with $BF_3{\cdot}Et_2O$ and water in CH_2Cl_2 allowed selective hydrolysis of the silyl acetal, giving mono-ketone **12** in 85% yield.[19] Reduction of **11b** with $LiAlH_4$ afforded alcohol **13**. Bis-acetal **13** was selectively hydrolyzed with aq. KF and *n*-Bu_4NCl to give mono-one **14**, which was further converted to cyclobutenedione **15** by treatment with $BF_3{\cdot}Et_2O$ and water in CH_2Cl_2 (0 °C).

In summary, regioselective [2 + 2] cycloaddition of electrophilic alkynes and fully oxygenated ketene silyl acetals allows rapid access to synthetically attractive cyclobutenedione derivatives. Further studies on selective transformation *en route* to polycyclic compounds are underway in our laboratories.

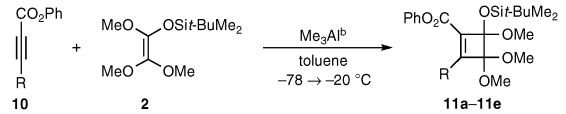
Table 3 Effect of the alkoxy moiety in the ester



Entry[a]	Alkyne	R	Time/h	Yield of **8** (%)	Yield of **9** (%)
1[c]	**7a**	Me	40	—	—
2	**7a**	Me	69	44	29
3	**7b**	Et	58	49	29
4	**7c**	*i*-Pr	11	59	10
5	**7d**	Ph	19	74	—

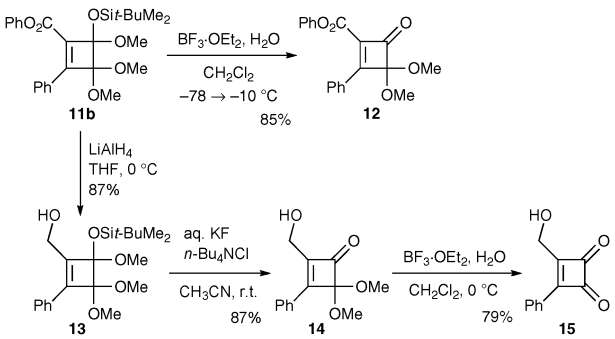
[a] The molar ratio of KSA **2** to alkyne **7** is 1.2–1.3. [b] 1.0 equiv. [c] The reaction was performed in toluene at 110 °C.

Table 4 Lewis acid mediated [2 + 2] cycloaddition



Entry[a]	Alkyne	R	Time/h	Yield of **11** (%)
1	**10a**	*n*-Bu	20	92
2	**10b**	Ph	68	81
3	**10c**	Br	23	85
4	**10d**[c]	PMBO	1	87
5	**10e**[c]	PMBO	1	92

[a] The molar ratio of KSA **2** to alkyne **10** is 1.2–1.3. [b] The molar ratio of Me_3Al to alkyne **10** is 1.0–1.1. [c] PMB: *p*-methoxybenzyl.



Scheme 3 Selective hydrolysis of cycloadduct **11b**.

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9 Cycloadduct **3** was reduced under Luche conditions[10] to give the alcohol as a 1 : 1 diastereomer mixture. One of the diastereomers gave single crystals suitable for X-ray analysis, thereby confirming the structure of compound **3**. For details, see ESI†.
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12 The reaction at higher temperatures (110 °C, 5 h) gave the ring-opened 1,3-diene **4** in quantitative yield. The stereochemistry of **4** was determined by an NOE study. See ESI†.
13 Choice of the substituent on the ester group was important: methyl ester reacted slowly (neat, 60 °C, 31 h, 67%).
14 $EtAlCl_2$ was much less effective and the yield was extremely low.
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18 Structure of **11a** was determined by NMR study (HMBC). See ESI†.
19 Ketone **12** gave single crystals suitable for X-ray analysis, thereby proving the structure of compound **11b**. For details, see ESI†.

