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COMMUNICATION

Facile *o*-Quinodimethane Formation from Benzocyclobutenes Triggered by Staudinger Reaction at Ambient Temperature

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Electron-donating iminophosphoranes were found to significantly enhance 4π-ring opening of benzocyclobutenes to generate *o*-quinodimethanes at 20–25 °C. These iminophosphorane benzocyclobutenes can be conveniently generated from azide benzocyclobutenes and phosphines via the Staudinger reaction. Thus, Staudinger reaction-triggered sequential molecular transformations of the azide benzocyclobutenes have been established via *o*-quinodimethanes at ambient temperature, which is expected to exhibit potential for a wide range of applications.

Thermal ring opening of benzocyclobutenes (BCB) via a 4π-electrocyclic process generates *o*-quinodimethanes (OQM), which have been utilized as highly reactive intermediates for the construction of various fused cyclic systems.[1] Despite such versatility in the synthetic field,[2] most BCBs require high temperatures of over 100 °C for the ring opening (Figure 1),[1c] which can limit their synthetic applications. On the other hand, BCBs possessing an electron-donating substituent such as a hydroxyl group on the sp^3 carbon have been reported to have lower energy barriers toward OQM formation and tend to undergo the ring fission at lower temperature.[1c] In fact, it has been reported that *trans*-bissiloxy derivatives can be cleaved at 40 °C,[3] and a naked oxy-anion enhances the ring fission further, even at –25 °C (Fig. 1).[4,5] Based on this oxy-anion effect, we have realized the extremely mild construction of a 2,3-benzodiazepine nucleus through successive electrocyclic reactions of benzocyclobutenones with diazomethylene anion.[6] In addition, we previously demonstrated that silylmethyl substituents significantly accelerate the ring cleavage under the influence of the σ-donating effect of the C–Si bond.[7,8] In this context, we envisioned a further application of the acceleration effects of electron donors toward OQM formation, in which iminophosphorane-BCBs would be novel precursors to generate OQMs under mild conditions due to the strong electron-donating nature of their anionic resonance structures. The iminophosphorane structure would be easily generated *in situ* through the Staudinger reaction of azide-BCBs with a tertiary phosphine reagent,[9] which would trigger the electrocyclic ring opening to form OQMs (Fig. 1). Herein, we report the first observation that azide-BCBs are promising substrates for facile OQM formation at ambient temperature via iminophosphorane-BCBs generated by the Staudinger reaction.

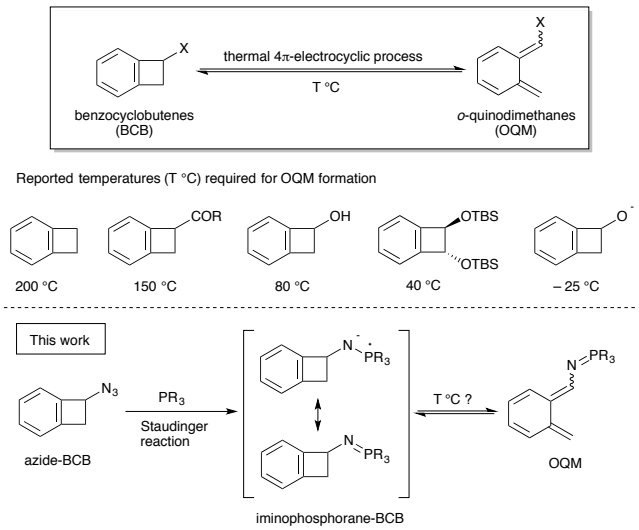

Fig. 1 Thermal 4π-ring opening of benzocyclobutenes

To verify our hypothesis regarding the sensitivity of the iminophosphorane-BCBs toward thermal ring cleavage, we designed azide-BCBs **1a** and **1b** as model substrates for the Staudinger reaction. The ring-opened ketone **2a** and aldehyde **2b** were the expected products of the ring fission (Table 1). The azide-BCBs **1a** and **1b** were prepared from the corresponding benzocyclobutenols and DPPA.[10] The methyl-

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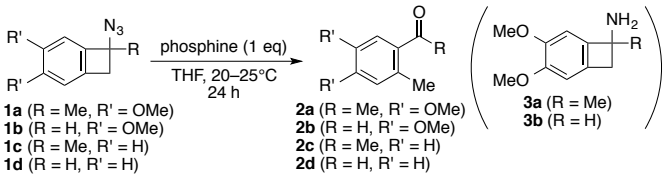
† Electronic Supplementary Information (ESI) available: Experimental procedures and characterization data, ^{1}H NMR, and ^{13}C NMR spectra of products. CCDC 1900168 for cis-5. CCDC 1900169 for trans-5. For ESI see DOI: 10.1039/x0xx00000x

substituted azide-BCB **1a** was completely recovered in the absence of phosphine at 20–25 °C, thus proving it to be stable at ambient temperature just like other conventional BCBs (entry 1). When reacted with PPh_3, which is used extensively for the Staudinger reaction,[9] only a small amount of the ketone **2a** (7%) was isolated, along with a considerable amount of the unreacted starting azide-BCB **1a** (entry 2). This indicated a slow Staudinger reaction probably due to steric bulkiness or poor nucleophilicity of the phosphine. However, the detection of the product **2a** suggested that the iminophosphorane formation might accelerate the ring fission. Encouraged by these results, less hindered and more reactive PMe_3 (1 eq.) was employed as a nucleophile. This reaction resulted in complete disappearance of the substrate **1a** and high yield of the ketone **2a** (71%) as expected (entry 3). While this observation strongly suggested that the ring cleavage was enhanced under the influence of the electron-donating effect of the iminophosphorane substituent, other possibilities could not be ruled out. For example, the amino-BCB **3a** generated by hydrolysis of the iminophosphorane through the conventional Staudinger reaction could be the true intermediate for accelerated ring opening.[11] In fact, addition of water to the reaction medium resulted in quantitative formation of the amino-BCB **3a**, without the ketone product **2a** (entry 4), suggesting that hydrolysis of the iminophosphorane was faster than ring fission, and more importantly that the amino-substituent thus formed did not induce the ring cleavage.

Table 1. Reaction of Azide-BCBs (**1a–d**) with Tertiary Phosphines at Ambient Temperature[a]



1a (R = Me, R' = OMe)
1b (R = H, R' = OMe)
1c (R = Me, R' = H)
1d (R = H, R' = H)

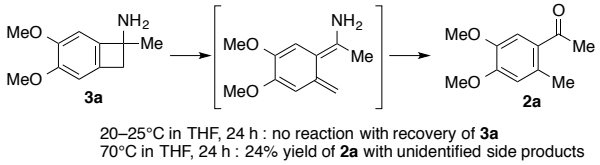
2a (R = Me, R' = OMe)
2b (R = H, R' = OMe)
2c (R = Me, R' = H)
2d (R = H, R' = H)

3a (R = Me)
3b (R = H)

entry	substrate	R	R'	phosphine	H_2O (%v/v)	yield (%)
1	**1a**	Me	OMe	–	–	0[b]
2	**1a**	Me	OMe	PPh_3	–	7 (**2a**)
3	**1a**	Me	OMe	PMe_3	–	71 (**2a**)
4	**1a**	Me	OMe	PMe_3	10	99 (**3a**)
5	**1b**	H	OMe	–	–	0[b]
6	**1b**	H	OMe	PPh_3	–	43 (**2b**)
7	**1b**	H	OMe	PMe_3	–	8 (**2b**)
8	**1b**	H	OMe	PPh_3	10	0[c]
9	**1c**	Me	H	PMe_3	–	48 (**2c**)[d]
10	**1d**	H	H	PPh_3	–	3 (**2d**)[d]

[a]After 24 h, the reaction mixture was treated with saturated aqueous NH_4Cl except for entries 4 and 8. [b]No reaction. [c]Complex mixture. [d]Voratility of the products **2c** and **2d** may lower the isolated yields.

For further verification of the stability of the amino-BCB **3a**, purely isolated **3a** was subjected to thermal conditions, which demonstrated that the amino-BCB **3a** itself was stable at 20–25 °C and the ring opening required heating to approximately 70 °C (Scheme 1). These facts unambiguously confirmed that the ring cleavage of the BCB was remarkably accelerated by the iminophosphorane substituent without the intermediacy of amino-BCB. To the best of our knowledge, this is the first observation of OQM formation from BCB at ambient temperature *triggered by Staudinger iminophosphorane formation*.

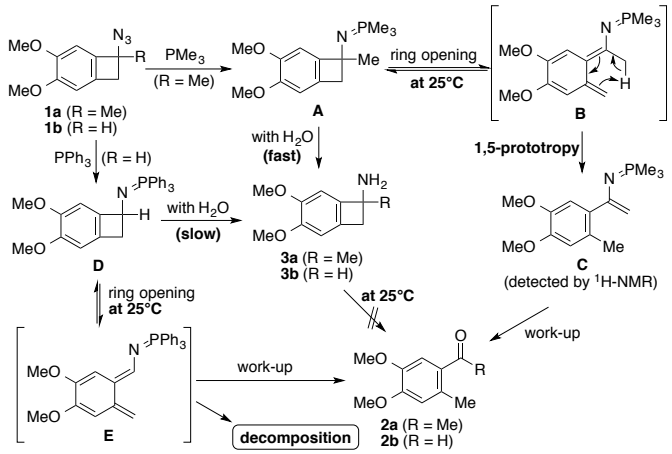


Scheme 1. Thermal Reaction of Amino-BCB (**3a**)

The azide-BCB **1b** lacking the methyl group was also subjected to the same manipulations to verify the Staudinger-triggered OQM formation (Table 1, entries 5–8). The azide-BCB **1b** was confirmed to be stable at 20–25 °C without phosphine (entry 5). Unlike the case of **1a**, however, it was found that **1b** could react with sterically congested PPh_3 (1 eq.) with complete consumption of the starting material to afford ring-opened aldehyde **2b** in moderate yield (entry 6). Although the diminished steric environment of **1b** would allow the approach of PPh_3 in the Staudinger reaction, the reaction was somewhat complicated compared with the case of **1a** (entry 3 vs. 6). Attempt to use more reactive PMe_3 resulted in further decrease of the yield of **2b** (entry 7). In addition, in the presence of water, neither amino-BCB **3b** nor ring-opened **2b** was detected, and the reaction gave a complex mixture (entry 8). These results suggested that the hydrolysis of iminophosphorane-BCB generated from **1b** and PPh_3 was much slower than that from **1a** and PMe_3 (entry 4 vs. 8), and that the OQM intermediate generated from **1b** was labile and susceptible to decomposition. One more set of the azide-BCBs **1c** and **1d**, lacking the methoxy group on the benzene ring, was also prepared and conducted to the optimal ring cleavage conditions, and the expected products **2c** and **2d** were observed in a similar manner, albeit rather lower yields (entries 9 and 10).

With these experimental data in hand, a rationale for the plausible reaction pathway is proposed as illustrated in Scheme 2. The azide-BCBs (**1a** and **1b**) are stable and invariable at ambient temperature, but exposure to the Staudinger reaction conditions with PMe_3 (for **1a**) or PPh_3 (for **1b**) generates the corresponding iminophosphorane-BCBs (**A** or **D**, respectively), which spontaneously undergo ring opening at 25 °C to form the OQM intermediates (**B** or **E**, respectively). This 4π-electrocyclic reaction is a reversible process, and the electron-donating imino-substituents should rotate outward with a high torquoselectivity.[12] Therefore, the methyl group in OQM **B** is inevitably forced to orient to an inner side, and 1,5-

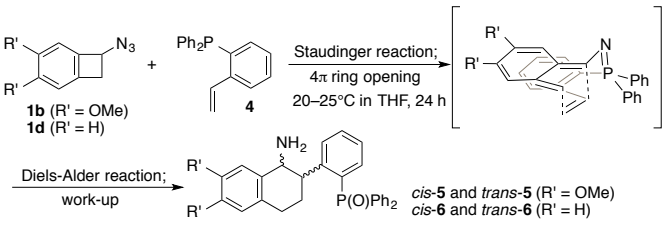
prototropy is facilitated to give relatively stable enamino-intermediate **C**,[13] which would effectively push the equilibrium toward the ring opening direction. The intermediate **C** was observed in ^{1}H-NMR analysis of the reaction medium (see ESI), and was transformed into the ketone product **2a** after an aqueous work-up process.[14] On the other hand, OQM **E** lacks such a stabilizing pathway, and consequently decomposes gradually or is converted to the aldehyde **2b** after work-up. This explains the complexity of the ring-opening reaction of **1b** (R = H) unlike in the case of **1a** (R = Me). Moreover, it is worthy of note that "trimethyl" iminophosphorane **A** was immediately hydrolyzed in the presence of H_2O to afford the thermally stable amino-BCB **3a** quantitatively, whereas "triphenyl" iminophosphorane **B** was sluggish to hydrolyze, based on the lack of detection of **3b** in the reaction medium. These amino-BCBs **3** were not precursors of ring-opened products **2**, at least under ambient temperature.



Scheme 2. Plausible Reaction Pathway

As mentioned above, the reaction system using **1b** was not productive because no pathway to trap the highly reactive OQM intermediate **E** existed. Thus, we intended to trap the OQM **E** by intramolecular Diels-Alder (IMDA) reaction employing styryl phosphine **4**[15] as the dienophile to elucidate the accelerated ring opening of the iminophosphorane-BCB **D** (Table 2). When the azide-BCB **1b** was reacted with the styryl phosphine **4** in dry THF at ambient temperature for 24 h, the desired sequential reaction, composed of Staudinger reaction/4π-ring opening/IMDA reaction, proceeded smoothly to afford cycloadduct **5** after work-up in 61% yield as a mixture of two diastereomers (entry 1). Additionally, even in the presence of water, the same sequential reaction gave the adduct **5**, albeit with a slightly decreased yield (entry 2). These results confirmed the acceleration effect of the iminophosphorane substituent toward the ring fission prior to hydrolysis, especially in the case of the azide-BCB **1b**. The relative stereochemistry of each diastereomer, *cis*-**5** and *trans*-**5**, was unambiguously determined by X-ray crystallographic analyses.[16] Moreover, it was found that the OQM generated from azide-BCB **1d** could be much more efficiently trapped by the IMDA reaction to give the adduct **6** in 92% (without H_2O) and 67% (with H_2O) yields (entries 3 and 4). This implies that the reactivity of the OQM intermediates toward IMDA can be controlled by suitable tuning of the substituents on the aromatic ring of the azide-BCBs.

Table 2. Intramolecular Diels-Alder Trap of the OQM Intermediate from **1b** and **1d**[a]



entry	sub-strate	R'	H_2O (%v/v)	yield (%)	ratio (*cis* : *trans*)
1	**1b**	MeO	–	61 (**5**)	1.5 : 1
2	**1b**	MeO	5	36 (**5**)	1.3 : 1
3	**1d**	H	–	92 (**6**)	1.8 : 1
4	**1d**	H	5	67 (**6**)	1.7 : 1

[a]After 24 h, the reaction mixture was treated with saturated aqueous NH_4Cl (entries 1 and 3).

In this study, we discovered that iminophosphorane-BCBs can readily cleave 4-membered rings via a 4π-electrocyclic process to generate OQMs at ambient temperature.[17] This unprecedented phenomenon is an exceptionally mild OQM formation compared to other BCBs without strong electron-donating substituents such as an oxide anion that only can exist in a strictly aprotic environment. It is noteworthy that the ring fission is triggered by the Staudinger reaction of thermally stable azide-BCBs and is thus activated only after the azide-BCBs encounter the phosphine reagent. We envisage that these findings have a potential application to a bioorthogonal chemical ligation reaction between the azide and the phosphine components,[18] which is an extension of Table 2 (Staudinger reaction/4π-ring opening/IMDA reaction sequence of **1b** or **1c**), and may take following advantages of this novel reaction system. The usability of mild PPh_3 instead of PMe_3, relatively slow hydrolysis of "triphenyl" iminophosphorane, applicability to an aqueous environment, and involvement of stable and irreversible C–C bond formation are features of this reaction system. Further efforts to improve and realize these applications are currently underway in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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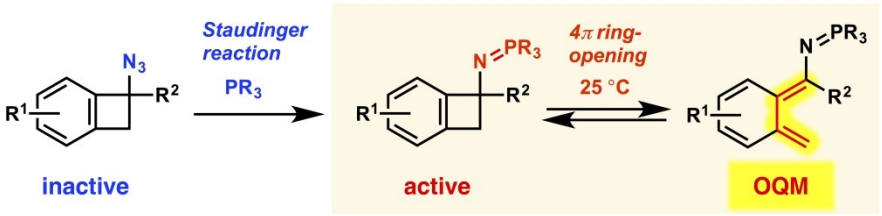

4π ring-opening at ambient temperature triggered by Staudinger reaction

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