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To be cited as: *Chem. Asian J.* 10.1002/asia.201700766

Link to VoR: http://dx.doi.org/10.1002/asia.201700766

A Journal of

ACES
Asian Chemical Editorial Society

A sister journal of **Angewandte Chemie** and **Chemistry – A European Journal**

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10.1002/asia.201700766

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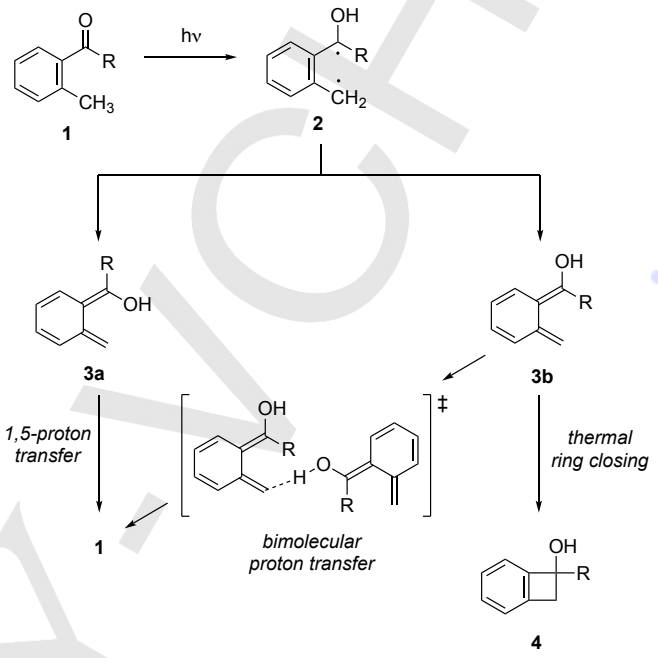
Photo-Induced Cyclization of (*o*-Alkylbenzoyl)phosphonates to Benzocyclobutenols

Naoki Ishida, Takaaki Yano, Tatsuya Yuhki, and Masahiro Murakami*[a]

Abstract: (*o*-Alkylbenzoyl)phosphonates readily cyclize to highly strained benzocyclobutenols simply upon irradiation with UV light. The remarkable efficiency is ascribed to the electron-accepting character of the phosphonate substituent, which facilitates thermal ring closing of the *o*-quinodimethane intermediate and suppresses reversion to the starting carbonyl compound.

A benzocyclobutene skeleton is a highly strained structural motif that has found a variety of applications in organic synthesis and material sciences.[1] Synthetic approaches to such a strained structure require highly energetic reactants like *n*-butyllithium and/or harsh reaction conditions in general.[1] A different approach is available with *o*-alkylphenyl ketones, which undergo photocyclization. This approach offers a straightforward and atom-economical access to benzocyclobutenols starting from readily available substrates in an endergonic manner.[2] However, successful and reproducible examples are considerably limited. Herein, we report that an extraordinarily efficient photocyclization reaction takes place with (*o*-alkylbenzoyl)phosphonates, which are easily prepared from acyl chlorides. Since the photoreaction is operationally simple and tolerant to various functional groups, the present approach would come into use for further derivatization of synthetic purposes.

The mechanism of the photocyclization of *o*-alkylphenyl ketones has been studied intensively (Scheme 1).[3] Upon excitation, intramolecular hydrogen transfer (C(sp^3)–H to O–H) occurs with **1** to generate biradical **2**. It isomerizes into *o*-quinodimethane **3**,[4,5] which has a closed shell configuration but lacks aromaticity. There are two stereoisomers **3a** and **3b** possibly generated from **2**. Two pathways are subsequently available for the dienes **3a** and **3b**. One is a proton transfer pathway reverting to **1**[6] and the other is a 4π-electrocyclic ring-closing pathway to benzocyclobutenol **4**. In the case of **3a**, an intramolecular 1,5-proton transfer reaction is so much faster than a ring-closing reaction that it readily reverts to the starting **1**. In the case of the other stereo-isomer **3b**, the hydrogen of the hydroxy group is located too remote to transfer intramolecularly onto the terminal carbon of the diene moiety. Although bimolecular proton transfer is an alternative pathway, it is much slower than the intramolecular 1,5-proton transfer occurring with **3a**. As a result, **3b** has a much longer lifetime so that a thermal 4π-electrocyclic ring-closing pathway becomes feasible. The ring-closing pathway leads to the formation of benzocyclobutenol **4**.



Scheme 1. Photocyclization of *o*-Alkylphenyl Ketones.

The substituent effect on thermal 4π-electrocyclic reactions has been a topic of interest from viewpoints of synthetic as well as theoretical chemistries.[7-11] A substituent of an electron-accepting nature at the 3-position of cyclobutene accelerates a ring opening reaction of cyclobutenes and prefers inward rotation.[7] When an electron-accepting substituent such as formyl and boryl groups rotates inward, its energetically low-lying unoccupied orbitals accept electron density from the HOMO of the cyclobutene backbone. This electron delocalization lowers the activation barrier. A related accelerating effect of electron-accepting substituents has been identified with a ring closing reaction of vinylallenes.[8] We recently found that a phosphonate substituent (-P(O)(OR')$_2$) also accelerates a thermal ring opening reaction of cyclobutenes and exhibits a preference for inward rotation over outward one.[11] This finding led us to examine a photocyclization reaction of phosphonate-substituted carbonyl compounds, *i.e.*, (*o*-alkylbenzoyl)phosphonates. A phosphonate substituent may facilitate a 4π-electrocyclic ring-closing process of a photochemically generated *o*-quinodimethane by way of a similar orbital interaction, and thus, the 4π-electrocyclic pathway may become dominant over the proton transfer pathway reverting to an acylphosphonate fruitlessly. Firstly, the model compound, *o*-toluoylphosphonate **5a** was prepared by the Michaelis-Arbuzov reaction[12] of *o*-toluoyl chloride with trimethyl phosphite, and the reactivities of **5a** and *o*-tolyl methyl ketone **8** were compared (Scheme 2). Their benzene solution (1.0 mmol, 0.05 M) in a Pyrex® tube was irradiated with UV light[13] under a nitrogen atmosphere for 12 h. The phosphonate **5a** readily underwent a photocyclization reaction to afford benzocyclobutenol **7a** almost quantitatively (93% isolated yield).

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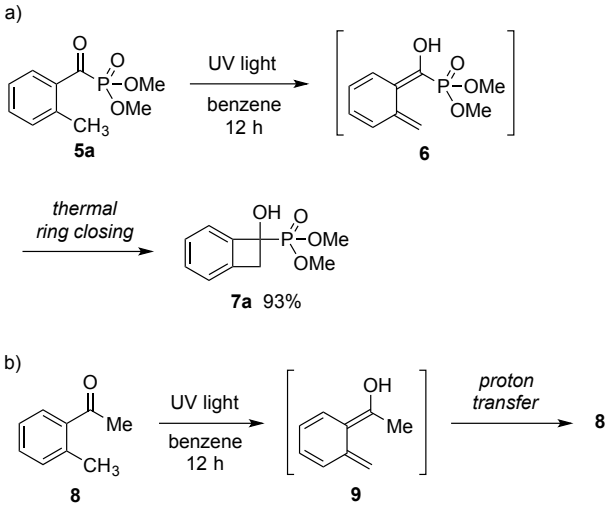


Scheme 2. Photocyclization of **5a.**

In sharp contrast, no reaction occurred with **8** (94% recovery), although the *o*-quinodimethane intermediate **9** was generated.[14] Thus, the phosphonate substituent brought in dramatic acceleration.

The photocyclization of **5a** would proceed through the mechanistic pathway shown in Scheme 1. The remarkable efficiency can be explained by assuming that the phosphonate substituent as R exerts the following two influences upon the *o*-quinodimethane intermediate; (i) at the transition state of the 4π-electrocyclic ring-closing process, the phosphonate substituent accepts electron density of the HOMO, thereby *accelerating* the ring closing, (ii) the electron-withdrawing nature of the phosphonate substituent makes the diene moiety less basic, thereby *suppressing* a proton transfer reaction reverting to **5a**.

In order to support this assumption, we carried out a theoretical study upon the *o*-quinodimethanes **9** and **6** using DFT calculation (Figure 1).[15] The activation energy for the bimolecular proton transfer pathway of **9** is 16.8 kcal/mol, lower than that for the 4π-electrocyclization (23.3 kcal/mol) by 6.5 kcal/mol. The energy profile of the reactions of **6** is reverse. The activation energy for the bimolecular proton transfer is as high as 24.1 kcal/mol, and that for the ring-closure is lower (18.3 kcal/mol). Thus, the phosphonate substituent favors ring closing and disfavors protonation. Natural bond orbital (NBO) analysis of the transition state for ring closing of **6** indicates that electrons of the developing σ-bond orbital which is still distorted (originally π-electrons of the diene moiety of **6**) delocalize into the low-lying σ*-orbitals of the P–O bonds, as is the case with the ring opening of 3-phosphorylcyclobutenes.[11] This electron delocalization stabilizes the transition state, lowering the activation energy.

When a benzoylphosphonate possesses an ethyl group instead of a methyl group as the *o*-substituent (**5b**, Scheme 3), two diastereomeric benzocyclobutenols would potentially arise. Nonetheless, only the *cis*-isomer **7b** was stereoselectively produced upon photoirradiation of **5b** and no *trans*-isomer was observed.[16] The stereoselective formation of the *cis*-isomer **7b**

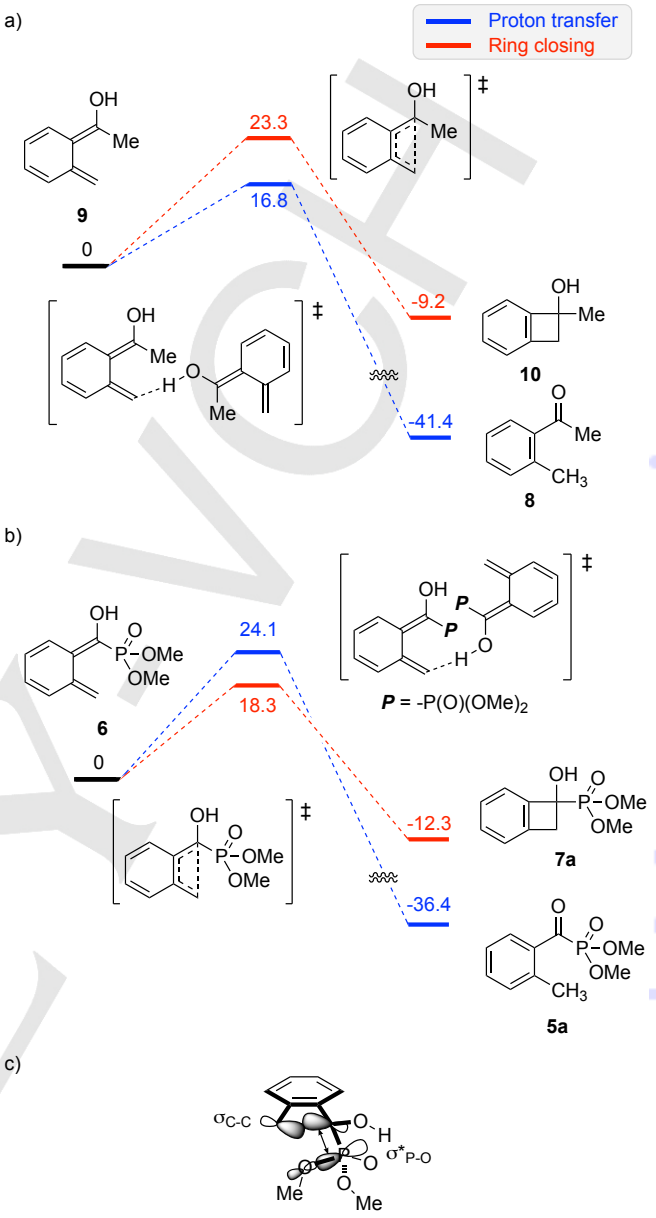
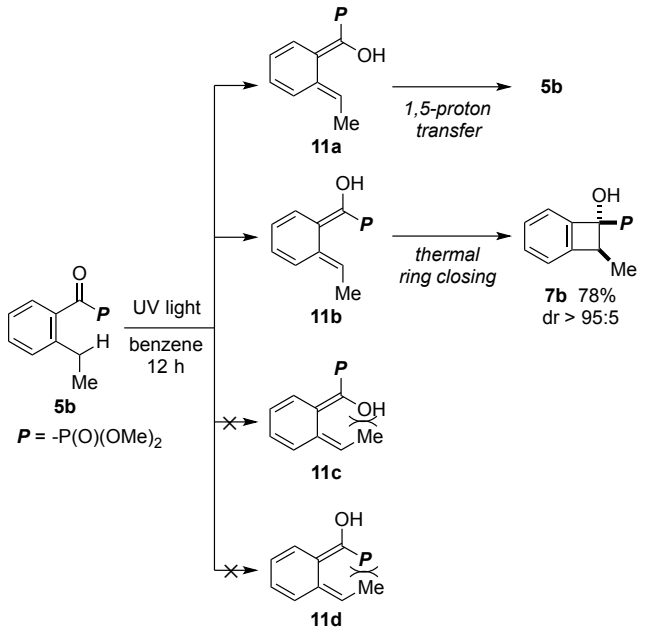


Figure 1. (a) Energy Profiles of Reactions of **9**, (b) Energy Profiles of Reactions of **6**, (c) Donor-Acceptor Interaction between Forming C–C σ-Orbital and P–O σ*-Orbital in TS for Ring Closure of **6**. All the calculations were carried out with the B3LYP/6-31+G(d) level of theory in benzene (PCM) at 25 °C. Shown are Gibbs' energies (kcal/mol).

can be reasonably explained. There are four possible stereoisomers for the *o*-quinodimethane intermediate **11**. Isomers **11c** and **11d** having an inward-oriented methyl group suffer from steric congestion, and the sterically less-congested isomers **11a** and **11b** having an outward-oriented methyl group would be preferentially formed. The isomer **11a** undergoes intramolecular 1,5-proton transfer to readily revert to the starting ketone. On the other hand, the isomer **11b** undergoes a thermal 4π-electron ring-closing reaction. The substituents at the diene terminals rotate in a conrotatory fashion in accordance with the Woodward-Hoffmann rule,[17] furnishing the *cis*-isomer **7b**

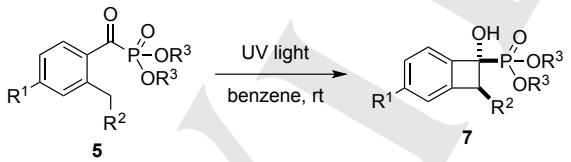


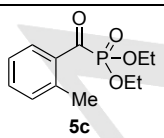
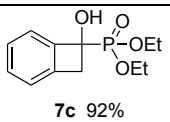
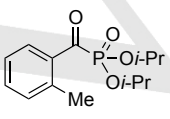
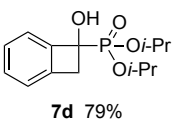
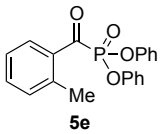
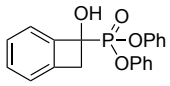
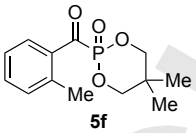
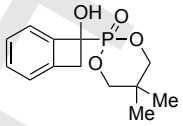
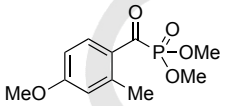
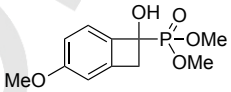
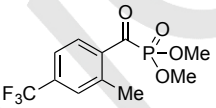
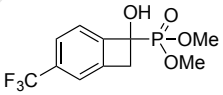
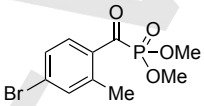
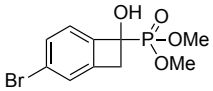
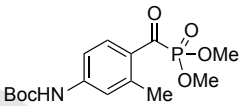
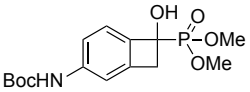
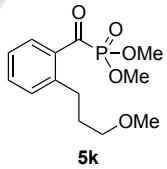
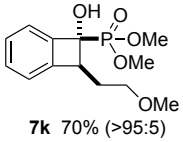
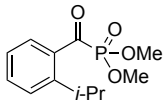
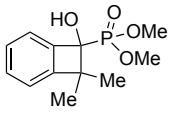
Scheme 3. Photocyclization of **5b**.

stereoselectively.

Experimentally examined next was the effect of various alkyl and aryl phosphonates (Table 1). Ethyl, *i*-propyl, and phenyl phosphonates efficiently underwent a photocyclization reaction to furnish the corresponding benzocyclobutenols in good yield (entries 1-3). Cyclic ester **5f** also afforded the benzocyclobutenol **7f** (87%, entry 4). Various functional groups like methoxy, trifluoromethyl, bromo, and carbamate groups were allowed on the aromatic ring to give the benzocyclobutenols **7g-j** in yields ranging from 74 to 89% (entries 5-8). A reaction of **5k** having a 3-methoxypropyl substituent at the *o*-position gave the *cis*-isomer **7k** exclusively (entry 9). The photoreaction of *o*-*i*-propyl substituted benzoylphosphonate **5l** necessitates addition of benzophenone (1.0 equiv) as the photosensitizer (entry 10). A sterically congested fully-substituted C–C linkage is created to afford α,α-dimethyl benzocyclobutenol **7l** in 88% yield.

Table 1. Scope.[a]



entry	5	7[b]
1[c]	 5c	 7c 92%
2	 5d	 7d 79%
3	 5e	 7e 97%
4	 5f	 7f 87%
5	 5g	 7g 89%
6	 5h	 7h 81%
7	 5i	 7i 77%
8	 5j	 7j 74%
9	 5k	 7k 70% (>95:5)
10[d]	 5l	 7l 88%

[a] Reaction conditions: aroylphosphonates **5** (1.0 mmol), benzene (20 mL), UV light, 12 h. [b] Isolated yield. [c] 24 h. [d] Benzophenone (1.0 equiv) was added.

In summary, we have found that an extraordinarily efficient photocyclization reaction takes place with (*o*-alkylbenzoyl)phosphonates to furnish benzocyclobutenols in an endergonic manner. Mechanistic studies suggest that the electron-accepting character of the phosphonate substituent leads to the remarkable efficiency in dual ways. Since highly energetic molecules with a variety of functionalities are synthesized from readily available substances through an operationally simple experimental procedure, the present photo-induced reaction would offer a convenient synthetic maneuver.

Experimental Section

Photo-induced cyclization of 5a: To a schlenk tube equipped with a magnetic stir bar was charged with (*o*-toluoyl)phosphonate **5a** (45.6 mg,

0.20 mmol) and benzene (4.0 mL). The mixture was irradiated with UV light for 12 h. The solvent was removed under reduced pressure, and the residue was purified by preparative thin layer chromatography to give **7a** (42.4 mg, 0.186 mmol, 93%).

Acknowledgements

This work was supported by JSPS KAKENHI Grant Numbers 15H05756, 15J07224, and JST ACT-C Grant Number JPMJCR12Z9, Japan. T. Yano acknowledged a JSPS fellowship for young scientists.

Keywords: cyclization • electrocyclic reactions • substituent effects • phosphorus

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[13] We employed the Rayonet photoreactor. See supporting information for the spectrum of the UV light employed.

[14] When a benzene solution containing **8** was irradiated with UV light in the presence of dimethyl acetylenedicarboxylate, Diels-Alder adduct was efficiently produced, proving the *o*-quinodimethane **9** was generated. For the Diels-Alder reaction of *o*-quinodimethanes, see refs. 4 and 5.

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[16] The stereochemistry of **7b** was unambiguously assigned by X-ray crystallography. CCDC 1535579 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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10.1002/asia.201700766

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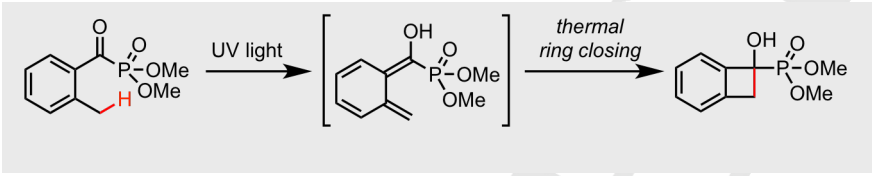

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Photo-Induced Cyclization of (*o*-Alkylbenzoyl)phosphonates to Benzocyclobutenols

(*o*-Alkylbenzoyl)phosphonates readily cyclize to highly strained benzocyclobutenols simply upon irradiation with UV light.