Title	Mechanism-Guided Development of Bifunctional Cyclooctenes as Active, Practical, and Light-Gated Bromination Catalysts
Author(s)	Nagano, Tagui; Shimazu, Takuto; Ono, Yusuke et al.
Citation	Chemistry-A European journal https://doi.org/10.1002/chem.202404011
Issue Date	2024-12-16
Doc URL	https://hdl.handle.net/2115/97364
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Type	journal article
File Information	CEJ-asano-HUSCAP.pdf

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RESEARCH ARTICLE

Mechanism-Guided Development of Bifunctional Cyclooctenes as Active, Practical, and Light-Gated Bromination Catalysts

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Abstract: Most molecular catalysts have been developed employing polar functional groups as catalytic sites. However, the use of non-polar functional groups for catalysis has received less attention due to their modest molecular interactions while the bioorthogonal reactivity of non-polar alkenes as substrates is frequently used in click chemistry. In this study, we conducted mechanistic studies on the catalysis of *trans*-cyclooctene (TCO) derivatives with the strained olefin as the catalytic site using kinetic and computational analyses to aid the design of more active olefin catalysts. The analysis reveals the significant role of the benzyl substituents in accelerating the generation of bromonium species through dispersion interaction in the rate-determining step. Guided by the mechanistic insights, we developed bifunctional TCO catalysts bearing a functionalized benzyl group, taking advantage of the remarkable substituent effects. Experimental studies confirmed the theoretical model and revealed that TCO with a *para*-hydroxybenzyl group provided excellent catalytic activity. Furthermore, inclusion of the functionalized benzyl groups allowed more readily available and robust *cis*-cyclooctenes to be used as active catalysts, expanding the practical utility of the olefin catalysts. By using a photochemically labile masking group on the *para*-hydroxybenzyl substituent, the first light-gated bromination catalyst was developed, enabling spatiotemporal control of the transformation.

Introduction

The design of catalytic sites is vital for the development of molecular catalysts, and the cooperative activation of substrates and/or reagents at multiple catalytic sites can accelerate their reactions while maintaining precise control of the selectivity.[1] During the past few decades, a variety of organocatalysts have been developed with a range of functional groups being employed as catalytic sites to attain different reactions.[2] Thus, the development of organocatalysts composed of previously unexploited functinoal groups will expand their use in many scientific fields. However, compared with the rich chemistry of polar functional groups containing heteroatoms as catalytic sites, the use of non-polar functional groups based on hydrocarbon structures has received less attention, probably due to their modest molecular interactions. On the other hand, cyclic alkenes and alkynes are frequently used as substrates in click chemistry for life science research due to the bioorthogonal nature of the reaction. Click reactions do not rely on the reactivity derived from the polarity of the carbon–carbon unsaturated bonds,[3,4] and thus the use of olefins as catalysts continues to find unexplored catalytic avenues toward bioorthogonal reactions.

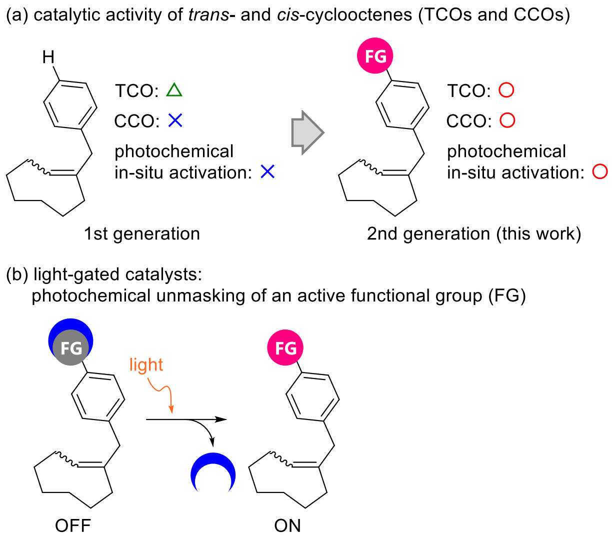


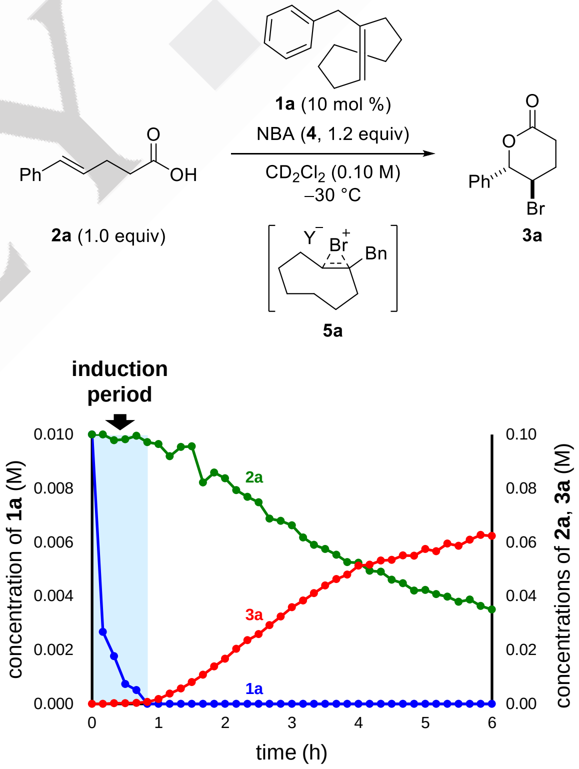
Figure 1. Bifunctional cyclooctene catalysts.

Meanwhile, we explored the use of olefins as catalytic sites by exploiting the catalytic performance of *trans*-cyclooctenes (TCOs), which offered a new functional-group-architecture for the design of novel molecular catalysis.[5] The strained olefin unit in TCOs featured a soft Lewis basicity that was used to facilitate organocatalytic halolactonization reactions.[5a,b] However, the catalytic activity was moderate. To address this issue, we examined the effect of the substituents on the olefin moieties and found that they are crucial in determining the catalytic activity; the benzyl group was the most efficient among the substituents that we initially investigated.[5a,b] Although the mechanistic details of the reaction were not clear, this result suggested that a more in-depth understanding of the substituent effects could enable the catalytic activity to be improved. In this study, we conducted kinetic analyses and DFT calculations on the catalysis of benzyl-substituted TCO to elucidate the mechanism and guide the design of more active olefin catalysts. We further tuned the electronic properties of the substituents computationally and experimentally to develop bifunctional catalysts composed of olefins and functionalized benzyl moieties that exhibit higher catalytic activity than those of the first-generation TCO catalyst[5a] (Figure 1a). Furthermore, the bifunctionality allowed the more easily accessible and more robust *cis*-cyclooctenes (CCOs) to be used as active catalysts in place of TCOs, expanding the practical utility of the olefin catalysts. Moreover, the remarkable substituent effects and the photochemical generation of an active functional group were leveraged to develop the first bromination catalyst that can be photochemically activated in situ (Figure 1b). This catalytic control combined with the biocompatibility of the cyclooctene derivatives should allow the system to be used in biological systems as an additional chemical biology tool.[4]

Results and Discussion

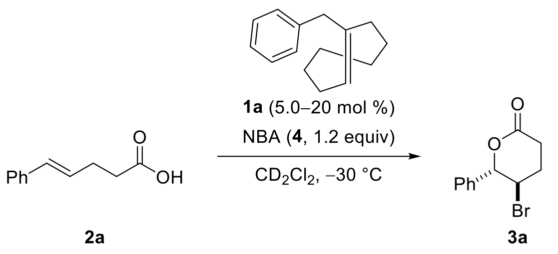
Kinetic Analyses

Initially, ^{1}H NMR analysis was used to monitor the concentrations of substrate **2a**, product **3a**, and catalyst **1a** during bromolactonization with *N*-bromoacetamide (NBA, **4**) (Scheme 1). It was observed that the peaks associated with **1a** disappeared during an induction period, after which the peaks associated with **3a** appeared. Higher catalyst loadings resulted in longer induction periods (Table 1).[6] Thus, the induction period was attributed to the time required to convert all of **1a** into the putative **1a**-derived bromiranium species **5a**; during this time **5a** preferentially reacts through olefin-to-olefin transfer of a bromonium ion with the remaining **1a** rather than **2a** because **1a** is more Lewis basic than the olefin of **2a** (Figure 2).[7] Moreover, variable time normalization analyses[8] of the reaction system revealed zero-order kinetics in substrate **2a** (see Scheme S1 in the Supporting Information for details). This suggested that the rate-determining step does not involve bromine transfer from catalytically generated brominating species **5a** to substrate **2a**, which is unique among Lewis base-catalyzed halocyclizations.[9]



Scheme 1. Reaction profiles using catalyst **1a**.

Table 1. Effects of catalyst loading on the induction periods.[a]



Entry	Loading of **1a** [mol %]	Induction period [min]
1	5.0	<10
2	10	50
3	20	80

[a] Reactions were run using **2a** (0.10 mmol), **4** (0.12 mmol), and **1a** (0.0050–0.020 mmol) in CD_2Cl_2 (1.0 mL).

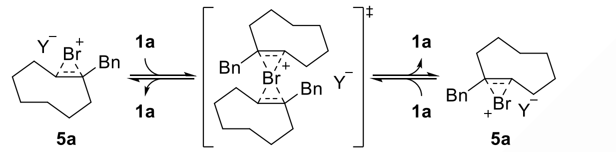


Figure 2. Olefin-to-olefin transfer of a bromonium ion between **5a** and **1a** during the induction period.

Computational Analyses

Based on the kinetic studies, DFT calculations were conducted at the B3LYP-D3 (PCM, solvent = CH_2Cl_2)/6-31+G* level to clarify the energetics of the **1a**-catalyzed bromolactonization of **2a** (Figure 3 and Figure S1 in the Supporting Information).[10a–c] A possible reaction pathway involves activation of **4** by **1a** (**TS1**) and subsequent bromine transfer/cyclization of **2a** (**TS2**) to afford the product (**PD**). The energetically highest transition state (**TS1**) indicates that generation of the brominating species is the rate-determining step rather than the bromine transfer step, which is consistent with the kinetics profiles discussed above.

Focusing on **TS1**, the benzyl group of **1a** coordinates with the bromonium center (Figure 4a). Non covalent interactions (NCI) analysis suggests the presence of dispersion interaction (shown in green) between the aromatic moiety and the bromonium center (Figure 4b).[10d] This indicates that the benzyl group plays an important role in stabilizing **TS1**. Thus, **1a** can be recognized as a bifunctional catalyst consisting of the olefin moiety and the benzyl group. Those computational insights on the generation of the brominating species motivated us to expand the approach to develop more efficient catalysts by functionalization of the benzyl group of **1a**.

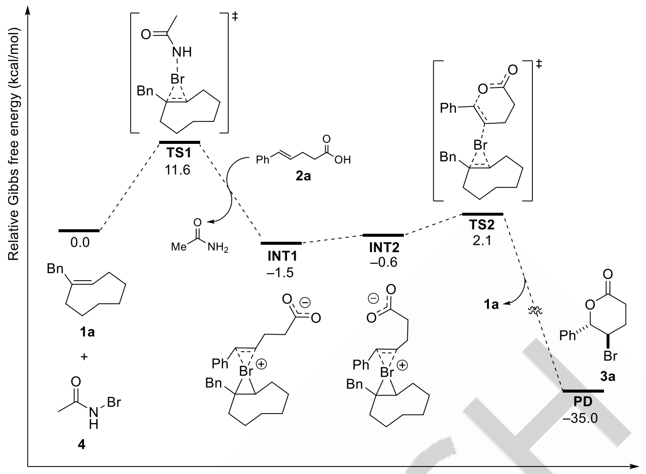


Figure 3. Energy profile of **1a**-catalyzed bromolactonization of **2a** [B3LYP-D3 (PCM, solvent = CH_2Cl_2)/6-31+G*].

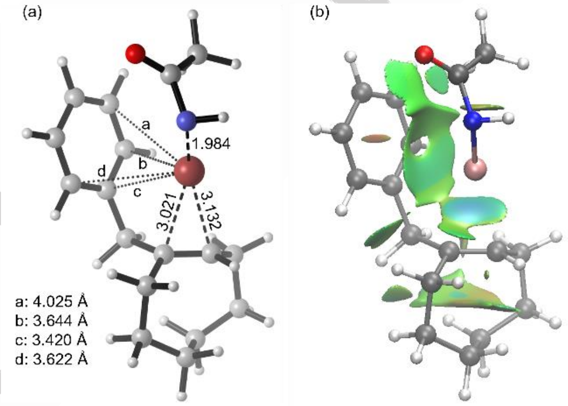


Figure 4. (a) 3D structure of **TS1**. (b) NCI plot of **TS1**. Gradient surfaces correspond to s = 0.25 au and a color scale of –0.05 < ρ < 0.05 au (blue, strongly attractive; green, weakly attractive; red, strongly repulsive).

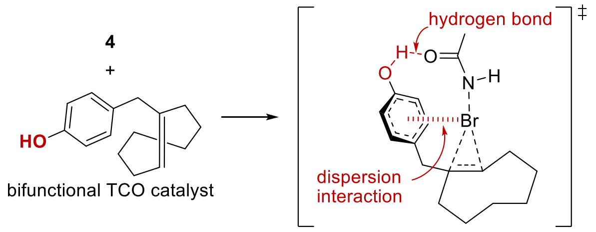


Figure 5. Computation-assisted design of a more active bifunctional TCO catalyst.

As a preliminary computational screening to optimize the functionalization of the benzyl group, the electronic properties of the substituent of the TCO catalyst were investigated by introducing electron-donating and -withdrawing groups at the *para*-position of the benzyl moiety in **TS1** (see Table S1 and Figure S2 in the Supporting Information for details). The in-silico screening suggested that the introduction of a *para*-OH group significantly enhances the dispersion interaction between the aromatic group and the bromonium center and enables the formation of a hydrogen bond between the OH group and the amido group of **4** (Figure 5).

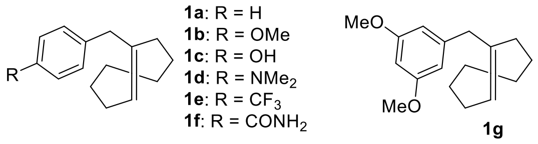
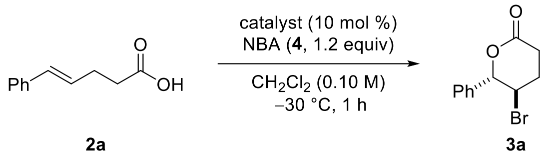


Figure 6. Bifunctional TCO catalysts with functionalized benzyl groups.

Table 2. Substituent effects of benzyl groups in the TCO catalysts.[a]

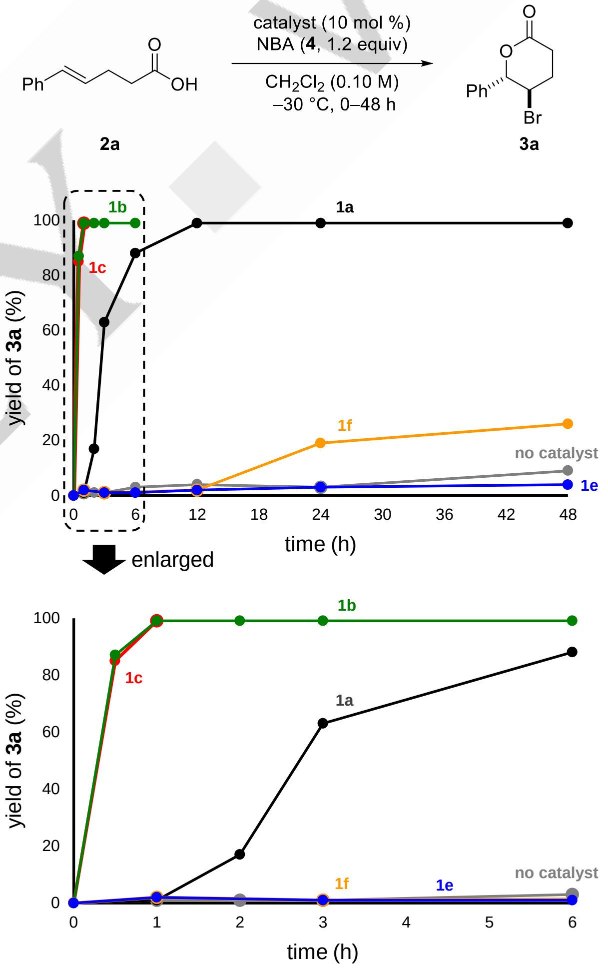


Entry	Catalyst	Concentration [M]	Yield [%]
1	none	0.10	1
2	**1a**	0.10	1
3	**1b**	0.10	99
4	**1c**	0.10	99
5	**1d**	0.10	71
6	**1e**	0.10	2
7	**1f**	0.10	2
8[b]	**1g**	0.10	2
9	**1b**	0.010	55
10	**1c**	0.010	99
11	**1d**	0.010	10

[a] Reactions were run using **2a** (0.10 mmol), **4** (0.12 mmol), and the catalyst (0.010 mmol) in CH_2Cl_2 (1.0 or 10 mL). [b] Reaction was run for 6 h.

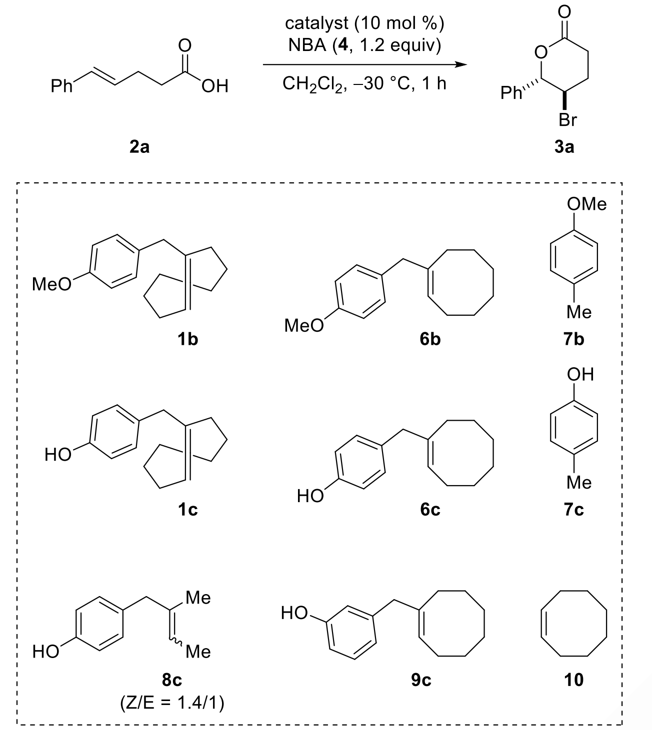
Substituent Effects of Benzyl Groups in the Cyclooctene Catalysts

Guided by the computational assessment, we synthesized a series of bifunctional TCO catalysts bearing electron-donating and -withdrawing groups (Figure 6). The catalytic activities were tested in the bromolactonization of **2a** for a short reaction time (1 h) (Table 2). Electron-donating groups at the *para*-position dramatically increased the catalytic activity when compared with **1a**, which was optimized in our previous study[5a] (Table 2, entries 1–5), whereas electron-withdrawing groups and *meta*-substitution of electron-donating groups were ineffective (Table 2, entries 6–8). Reaction profiles obtained with the TCO catalysts also revealed that **1b** and **1c** were more active than **1a**, whereas **1e** and **1f** were less active, thus indicating the importance of the electronic properties of the *para*-substituents (Scheme 2). Electron-rich catalysts **1b** and **1c** provided shorter induction periods, after which the reactions were also faster than that using **1a**. In addition, the activities of the electron-rich catalysts **1b**–**d** were tested at a lower concentration, and **1c** bearing the *para*-hydroxybenzyl group proved to be particularly catalytically active, which is consistent with the computational prediction illustrated in Figure 5 and Table S1 (Table 2, entries 9–11). Methoxy group-substituted **1b** was less active than **1c** but more active than dimethylamino group-substituted **1d**. Although the computational prediction presented in Table S1 suggests the activity of **1d** is comparable to that of **1b**, catalyst **1d** might operate through a different mechanism such as catalysis solely by the amino group without the involvement of the olefin moiety.[11]



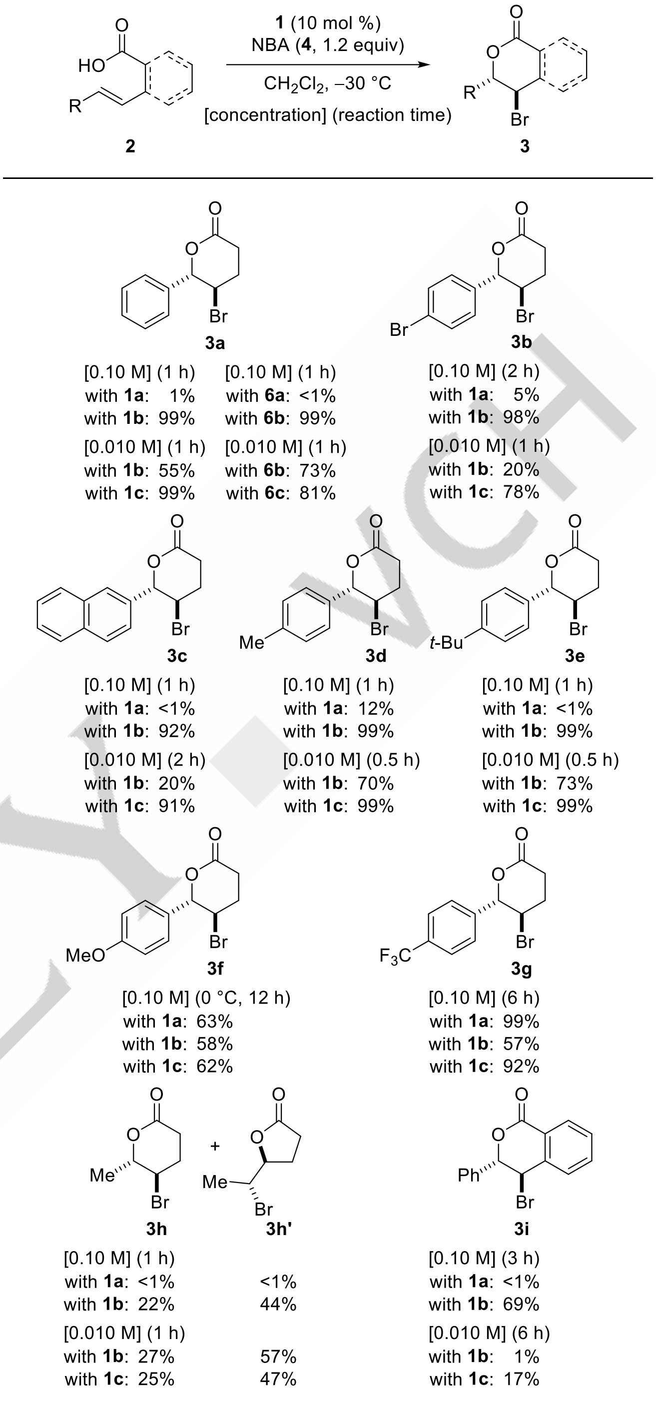
Scheme 2. Reaction profiles of TCOs in the bromolactonization of **2a**.

Table 3. Effects of olefins.[a]



Entry	Catalyst	Concentration [M]	Yield [%]
1	**1b**	0.10	99
2	**6b**	0.10	99
3	**7b**	0.10	2
4	**1c**	0.10	99
5	**6c**	0.10	97
6	**7c**	0.10	<1
7	**1b**	0.010	55
8	**6b**	0.010	73
9	**7b**	0.010	<1
10	**1c**	0.010	99
11	**6c**	0.010	81
12	**7c**	0.010	<1
13	**8c**	0.10	<1
14	**9c**	0.10	15
15	**9c**	0.010	<1
16	**10** + **7c**	0.10	<1

[a] Reactions were run using **2a** (0.10 mmol), **4** (0.12 mmol), and the catalyst (0.010 mmol) in CH_2Cl_2 (1.0 or 10 mL).



Scheme 3. Bromolactonization with **1a**, **1b**, and **1c**. Reactions were run using **2** (0.10 mmol), **4** (0.12 mmol), and **1** (0.010 mmol) in CH_2Cl_2 (1.0 or 10 mL). Yields were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as the internal standard.

The effects of the olefin moiety were then further investigated (Table 3). Notably, substituted benzyl CCO derivatives **6b** and **6c**, which are easier to synthesize and more robust than the corresponding TCOs, were also catalytically active (Table 3, entries 2, 5, 8, and 11). Control experiments using the corresponding olefin-free analogs **7b** and **7c** resulted in low yields

(Table 3, entries 3, 6, 9, and 12), indicating that the olefin moieties serve as the essential catalytic site. These results indicate that the activity of the bifunctional catalysts can be attributed to the olefin (Table 3, entries 4–6), the hydroxy group (Table 3, entries 7 and 10), and the electron-rich aromatic ring (Table 2, entries 2 and 3), suggesting multipoint activation of **4** at the catalytic sites in the transition state of the rate-determining step (Figure 5).[12] This conclusion is supported by the findings that acyclic olefin **8c**, *meta*-hydroxybenzyl group-substituted catalyst **9c**, and individual catalyst components **10** + **7c** (unsubstituted CCO and *p*-cresol) were less effective (Table 3, entries 13–16) than the cyclooctene frameworks bearing the *para*-hydroxybenzyl group.

Performances of Bifunctional TCO Catalysts

The higher catalytic activities of catalysts **1b** and **1c** than that of **1a** were demonstrated using a range of substrates (Scheme 3). In the reaction of **2a**, catalyst **1b** was much more active than **1a**. Furthermore, at a lower concentration, catalyst **1c** was more active than **1b** (Scheme 3, **3a**). Similar results were obtained using CCOs **6a**, which has a non-substituted benzyl group, **6b**, and **6c**, and the catalytic activity of CCOs were comparable to the corresponding TCOs. The same trends of the TCO catalysts were observed in the reactions of other substrates: in the cases of substrates bearing 4-bromophenyl, 2-naphthyl, 4-tolyl, and 4-(*tert*-butyl)phenyl groups, **1b** exhibited excellent catalytic activity, and **1c** exceeded the performance of **1b** (Scheme 3, **3b**, **3c**, **3d**, and **3e**); however, the activities of **1b** and **1c** were comparable to or less than that of **1a** for substrates bearing methoxy and trifluoromethyl groups (Scheme 3, **3f** and **3g**). For an aliphatic substrate, the activities of catalysts **1b** and **1c** were comparable, with both being more active than **1a**, providing a mixture of regioisomeric products (Scheme 3, **3h** and **3h'**). Higher catalytic activities of **1b** and **1c** were also observed in the reaction of (*E*)-2-styrylbenzoic acid (**2i**), albeit in a slower reaction (Scheme 3, **3i**). Substrates **1a**–**1g** and **1i** provided no regioisomer products **3'**.

Light-Gated Catalysts

The bifunctionality was used in the development of catalysts that can be photochemically activated in situ. Photochemical catalytic reactions enable spatiotemporal control of chemical transformations, which is useful for the development of techniques probing short-lived or transitional events.[13] To develop light-gated catalysts, a useful method is the photochemically triggered generation of catalytically active species.[14] In this context, protection and deprotection of the phenol moieties of **1c** and **6c** provide useful handles for controlling the catalytic activity; thus, we envisioned that light-gated catalysts might be accessed through photochemical deprotection (Figure 7). Phenol derivatives are suitable as masked molecules because many photoremovable protecting groups (PPGs) have been developed for the spatiotemporal release of phenol derivatives as pharmaceuticals and fluorescent probes, etc.[15] Given that the biocompatibility of cyclooctene derivatives and PPGs is well-recognized,[4,15] in a continuation of our interests in developing reaction tools for sensitive biomolecular mass-tag labeling through photocatalytic bromination,[16,17] the light-gated bifunctional cyclooctene catalysts would provide a useful chemical biology tool for bromination.

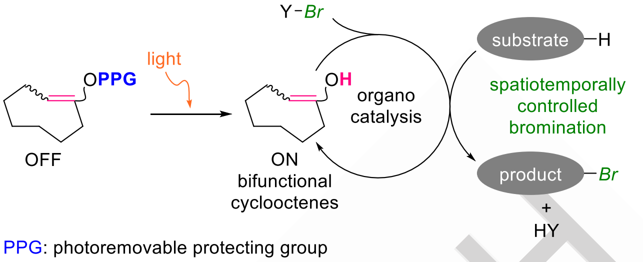
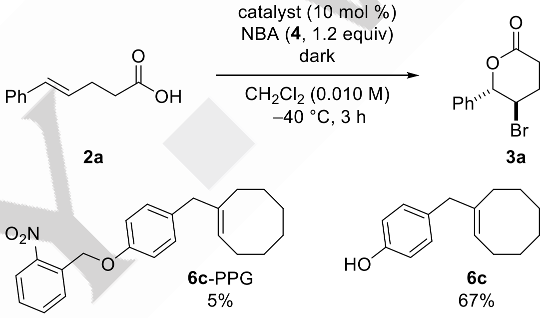
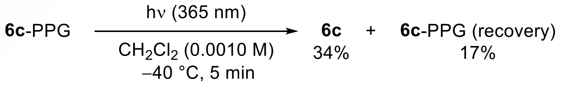


Figure 7. Design of light-gated bromination catalysis.

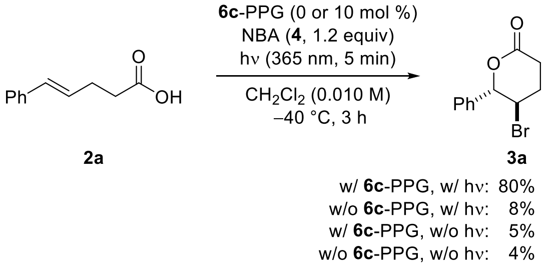
(a) effects of *ortho*-nitrobenzyl group on catalytic activity



(b) photochemical deprotection of **6c**-PPG

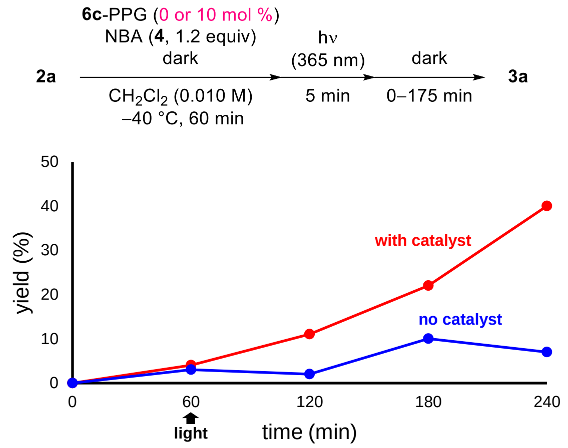


(c) light-gated catalysis of **6c**-PPG

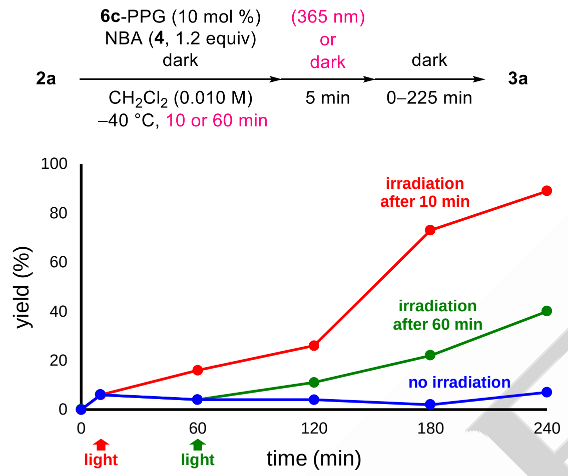


Scheme 4. Preliminary studies with **6c**-PPG.

(a) spatial control



(b) temporal control



Scheme 5. Spatial and temporal control of bromolactonization.

We used an *ortho*-nitrobenzyl group, which is a widely used PPG,[18] and the easily accessible CCO **6c** for preliminary studies. The protection with an *ortho*-nitrobenzyl group efficiently inhibited the catalytic activity of **6c**-PPG (Scheme 4a), with deprotection and release of the active catalyst **6c** upon light irradiation (365 nm UV-LEDs) (Scheme 4b).[19] **6c**-PPG was then used in photochemical catalytic bromolactonization experiments (Scheme 4c). As expected, the reaction was facilitated by light irradiation, and control experiments revealed that both **6c**-PPG and light are essential for the active reaction system. These results indicate that in the reaction shown in Scheme 4c, **6c**-PPG is activated in situ through photochemical deprotection.

Photochemical control was further demonstrated by initiating the reaction with light irradiation after stirring the mixture in the dark for 10 min and 60 min in the presence or absence of **6c**-PPG (Scheme 5). In the absence of **6c**-PPG, the reaction proceeded only slowly even under light irradiation (Scheme 5a, blue). In contrast, in the presence of **6c**-PPG, the reaction was accelerated upon light irradiation, whereas almost no reaction occurred before the irradiation (Scheme 5a, red). In addition, the initiation was temporally controlled by light irradiation; thus, after an initial slow reaction in the dark, the reactions were accelerated upon irradiation at 10 min or 60 min (Scheme 5b, red and green).[20] In the absence of irradiation, almost no reaction was observed even in the presence of **6c**-PPG (Scheme 5b, blue). These results indicate that both the catalyst and light irradiation are necessary for efficient reactions, making it possible to spatially and temporally control the bromination reactions. The system thus represents the first light-gated catalyst for bromination and serves as a proof-of-concept of our strategy of developing light-gated catalysts.

Conclusion

Guided by the mechanistic insights gained through kinetic and computational studies, which elucidated the significant role of the benzyl substituents in accelerating the generation of the brominating species through dispersion interaction in the rate-determining step, we developed bifunctional cyclooctene catalysts bearing functionalized benzyl groups. Particularly, cyclooctenes substituted with a *para*-hydroxybenzyl group exhibited excellent catalytic activity, which was attributed to the shorter induction period and faster reaction rate than those of the first-generation TCO catalyst. Substitution of the functionalized benzyl groups also allowed more practical CCOs to be used as active catalysts. The remarkable substituent effects were leveraged to develop the first light-gated bromination catalyst, which can be applied for spatiotemporal control of the reaction. The fundamental catalytic performance of the bifunctional cyclooctenes described in this study should stimulate further research leading to applications of the techniques for the spatiotemporal control of chemical processes. Our ongoing efforts to develop bromination probes using the bifunctional cyclooctene catalysts for labeling biomolecules will be reported in due course.

Supporting Information

Experimental procedures, results of additional investigations, characterization data and NMR spectra of synthesized compounds. The authors have cited additional references within the Supporting Information.[21,22]

Acknowledgements

We thank Technical Division of Institute for Catalysis, Hokkaido University, for technical support. We also thank the Open Facility, Global Facility Center, Creative Research Institution, Hokkaido University, for HRMS analyses. This work was supported financially by the Japanese Ministry of Education, Culture, Sports, Science and Technology (JP15H05845, JP18K14214, JP18H04258, JP20K05491, JP21H05076, JP23H01953, JP23K26646, and JP22K05101) and the JST FOREST Program (JPMJFR2323). K.A. also acknowledges Toyo Gosei Memorial Foundation, the Sumitomo Foundation, Fukuoka Naohiko

Memorial Foundation, Inoue Foundation for Science, Mizuho Foundation for the Promotion of Sciences, SPIRITS 2020 of Kyoto University, Japan Association for Chemical Innovation, Tobe Maki Scholarship Foundation, the NOVARTIS Foundation (Japan) for the Promotion of Science, the Kurata Grants by the Hitachi Global Foundation, the Inamori Foundation, the Society of Iodine Science, and the UBE Industries Foundation. T.N. also acknowledges the Japan Society for the Promotion of Science for Young Scientists for the fellowship support (JP21J14481).

Keywords: olefin • bifunctional organocatalyst • light-gated catalyst • bromination • biocompatibility

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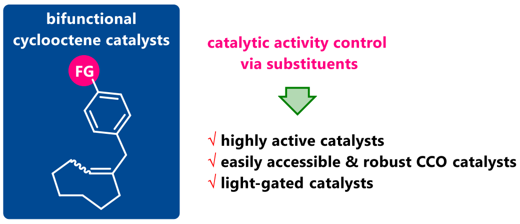

Mechanistic studies guided the development of bifunctional *trans*-cyclooctene (TCO) catalysts bearing a functionalized benzyl group. TCO with a *para*-hydroxybenzyl group is particularly active, and the functionalization allowed more practical *cis*-cyclooctenes (CCOs) to be used as active catalysts. By using a photochemically labile masking group on the *para*-hydroxybenzyl substituent, the first light-gated bromination catalyst was developed, enabling spatiotemporal control of the transformation.

Institute and/or researcher Twitter usernames: ((optional))