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Olefin-Catalyzed Aromatic Bromination toward Biocompatible Tyrosine Modification

Riku Sakaguchi,^[c] Takuto Shimazu,^[c] Rakuto Yoshida,^[a] Tagui Nagano,^[c] Seijiro Matsubara,^[c] Daisuke Uruguchi,^{*[a,b]} and Keisuke Asano^{*[a]}

[a] R. Yoshida, Prof. Dr. D. Uruguchi, Prof. Dr. K. Asano

Institute for Catalysis

Hokkaido University

Sapporo, Hokkaido 001-0021 (Japan)

E-mail: uruguchi@cat.hokudai.ac.jp; asano@cat.hokudai.ac.jp

[b] Prof. Dr. D. Uruguchi

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Hokkaido University

Sapporo, Hokkaido 001-0021 (Japan)

[c] R. Sakaguchi, T. Shimazu, T. Nagano, Prof. Dr. S. Matsubara

Department of Material Chemistry, Graduate School of Engineering

Kyoto University

Kyotodaigaku-Katsura, Nishikyo, Kyoto 615-8510 (Japan)

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Abstract: The chemical modification of biomolecules is an emerging technique for studying and manipulating biological mechanisms. Among these methods, catalysis offers advantages over stoichiometric strategies due to its ability to enhance selectivity, e.g., spatiotemporal control, via catalytic turnover, and the modification of tyrosine recently attracts considerable attention due to its significant biological functions. However, catalyst-controlled aromatic halogenation is challenging under near-physiological conditions due to the lack of biocompatible catalysts, despite the potential of tyrosine bromination as an attractive biomolecular labeling technique. In this study, inspired by the bioorthogonal reactivity of cyclic olefins, we developed catalytic aromatic bromination via the transfer of a bromonium ion from olefins to aromatic substrates based on the in-situ generation of bromiranium ions as active species. Bifunctional cyclooctenes bearing a hydroxybenzyl group efficiently catalyzed the bromination of phenol derivatives, which was applicable in tyrosine modification. The substituent effects of the catalysts primarily affected the rate of the generation of bromiranium ions, which provided the kinetics enabling light-gated catalysis that could be activated in situ via the photochemical deprotection of the hydroxybenzyl group. Such olefin catalysis was compatible with aqueous conditions, enabling the bromination of peptides, and the Lewis-base catalysis of the olefins proceeded even under acidic conditions.

Introduction

The chemical modification of peptides and proteins is an emerging technique for studying and manipulating biological mechanisms. Among such methods, biocompatible catalysis that can be used under physiologically favorable conditions broadens life science research via the in-situ activation of labeling reagents or substrates.^[1–5] A definitive advantage of catalysis over stoichiometric methods is its signal amplification (i.e., catalyst-controlled selectivity, such as spatiotemporal control) via catalytic turnover. Most traditional methods rely on the modification of lysine and cysteine, and the labeling of less reactive amino acids, including tyrosine, is still rare. Elucidating and controlling the biological functions of tyrosine based on side chains containing phenolic moieties that provide amphiphilicity, π - π and cation- π interactions, hydrogen bonding, etc., are critical.^[6–11] Increasing attention has been devoted to the halogenation of tyrosine to control pharmacokinetics^[12–14] and install cross-coupling tags for use in further derivatization.^[15–18] Moreover, bromination can be used to install mass tags, which are favorable in detection, even amidst numerous other signals, owing to diagnostic isotopic patterns of bromine, resulting from the natural abundance of its isotopes (⁷⁹Br: 50.69%, ⁸¹Br: 49.31%, Figure 1a).^[19–23] However, the catalytic aromatic halogenation of tyrosine side chains within peptides is limited to chlorination.^[24,25] In addition, catalyst-controlled halogenation is challenging under physiologically favorable conditions, such as ambient temperatures in aqueous media, due to the lack of biocompatible catalysts, although numerous catalysts have been developed to date for use in aromatic halogenation toward organic synthesis.^[26,27]

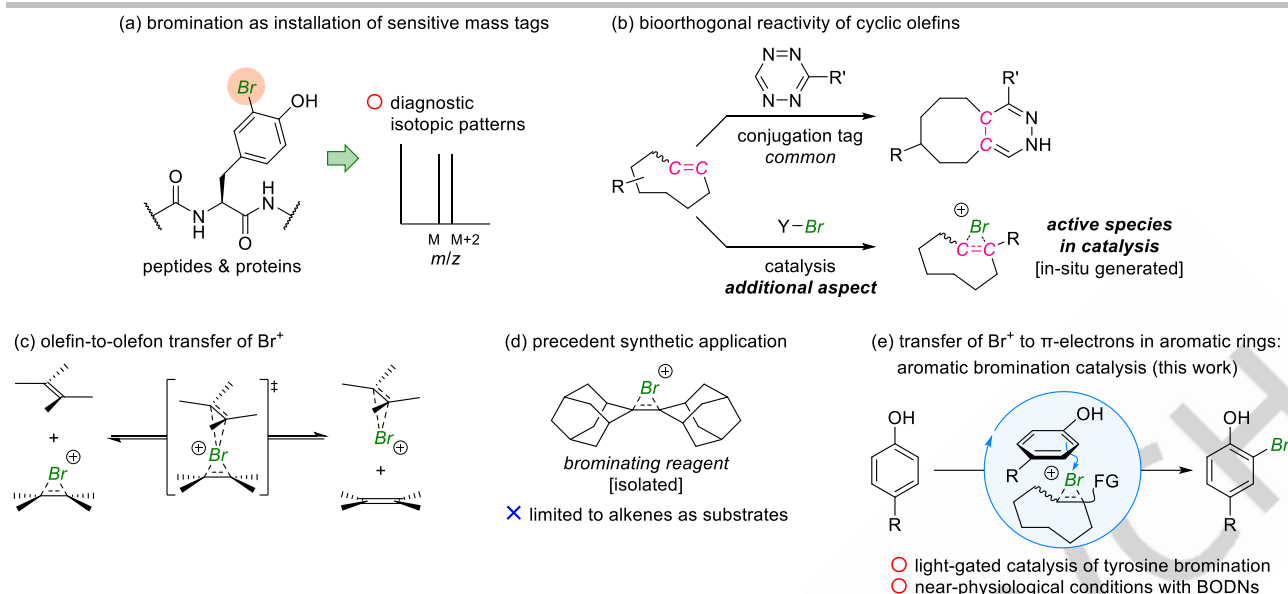


Figure 1. Transfer of Br^+ between π -electrons and its potential in catalysis toward tyrosine labeling.

To develop biocompatible catalysts for aromatic bromination, olefins would be used owing to the bioorthogonal reactivity as cyclic olefins have been frequently employed as bioconjugation tags (Figure 1b, top).^[28,29] The transfer of a bromenium ion (Br^+) between olefins was observed in 1991 during research regarding the electrophilic bromination of alkenes (Figure 1c).^[30,31] Although the olefin-to-olefin transfer of Br^+ is a detrimental process that racemizes bromiranium ions during asymmetric bromination,^[32] it also productively enables the use of isolable bromiranium ion salts derived from adamantylideneadamantane as brominating reagents in bromocyclization (Figure 1d).^[33–37] However, the substrates are limited to alkenes, and the synthetic utilities of bromiranium ions should be expanded to the bromination of less reactive substrates. To this end, the development of catalysis involving the in-situ generation of highly reactive bromiranium ions should be more effective in accelerating Br^+ transfer to substrates than the use of isolable but moderately reactive bromiranium ions as reagents. We explored organocatalysis using olefins as active sites, utilizing in-situ-generated bromiranium ions to transfer Br^+ to alkenes bearing a carboxylic acid in bromolactonization (Figure 1b, bottom).^[38–40] In developing the olefin catalysts, we used cyclooctene derivatives, where the olefins served as Lewis-basic catalytic sites.^[38,39] Furthermore, bifunctional cyclooctenes bearing a functionalized benzyl group were developed as considerably more active catalysts.^[40] In such olefin catalysis, the generation of the bromiranium ions from the cyclooctene and a brominating reagent is the rate-determining step (RDS). The functionalized benzyl groups of the catalysts accelerate this step by forming attractive non-covalent interactions to stabilize the transition state. We thus envisioned that such olefin catalysis is applicable in brominating aromatic compounds, which are less reactive than alkenes,^[41] via the in-situ generation of reactive bromiranium ions that are otherwise challenging to access. In this study, we developed a catalytic aromatic bromination method, in which Br^+ is transferred from the olefins of cyclooctene derivatives to aromatic substrates (Figure 1e). Bifunctional cyclooctenes efficiently catalyzed the bromination of phenol derivatives, and their *para*-hydroxybenzyl substituent, which provided particularly high catalytic activity, accelerated the generation of cyclooctene-derived bromiranium ions as active species. This mechanistic feature was used to realize light-gated catalysis that can be activated in situ via the photochemical deprotection of the *para*-hydroxybenzyl group, thus enabling spatiotemporal control over bromination.^[40,42–44] Furthermore, such catalysis was applicable in tyrosine modification under physiologically favorable conditions using biocompatible brominating reagents, 1-bromo-2-oxo-1,2-dihydronaphthalene-1-carboxylates (BODNs), that we recently developed.^[19] Thus, it should enable additional labeling techniques for use in probing transitional biomolecular events, thereby leading to cross-validation with our recently reported method of tyrosine bromination using BODNs and organic dyes as a photocatalyst.^[19]

Results and Discussion

Initially, we assessed the catalytic activity of *cis*- (CCOs) **1** and *trans*-cyclooctenes (TCOs) **2** bearing various substituents (Figure 2) in the bromination of *p*-cresol (**8**) as a model of the tyrosine side chain using *N*-bromoacetamide (NBA, **11**) in CH_2Cl_2 at -40°C (Table 1). While no reaction occurred in the absence of a catalyst (Table 1, entry 1), the use of CCOs **1a** and **1b** accelerated the reaction to provide **9** and **10** (Table 1, entries 2 and 3), indicating that cyclic olefins bearing a functionalized benzyl group can catalyze aromatic bromination. Among

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the CCOs, **1a** and **1b**, with electron-donating groups at their *para*-positions, provided high catalytic activity (Table 1, entries 2 and 3), whereas **1c–1e**, with electron-neutral and -withdrawing groups, provided low catalytic activity (Table 1, entries 4–6). Notably, protecting the hydroxybenzyl group had considerable effects, including deactivating the catalytic activity (Table 1, entries 2 and 5). The same trends were observed in the reactions using TCOs **2** (Table 1, entries 7–11), although TCOs were less active than CCOs as catalysts in aromatic bromination. This suggests that the extremely high Lewis basicity of TCOs compared to that of CCOs decreases the reactivity of in-situ-generated bromiranium ions, retarding Br⁺ transfer to **8**. *meta*-Hydroxybenzyl group-substituted CCO **3a** also provided high catalytic activity (Table 1, entry 12), whereas CCO **3b** with a *meta*-methoxybenzyl group was less active than **1b** (Table 1, entries 3 and 13). As a reaction without a catalyst did not proceed (Table 1, entry 1), **8** displays no catalytic activity, although its structure is analogous to those of the substituents of **1a**, **2a**, and **3a**. Thus, the olefin moieties of **1a**, **2a**, and **3a** served as essential catalytic sites. Furthermore, acyclic olefin **4** with a *para*-hydroxybenzyl group and unsubstituted CCO (**5**) were catalytically inactive (Table 1, entries 14 and 15). The ring size of the *cis*-cycloalkene also affected the catalytic activity, as cycloheptene **6** and cyclohexene **7**, with a *para*-hydroxybenzyl group, were less active (Table 1, entries 16 and 17). Therefore, the cyclooctene frameworks bearing a hydroxybenzyl group are effective.

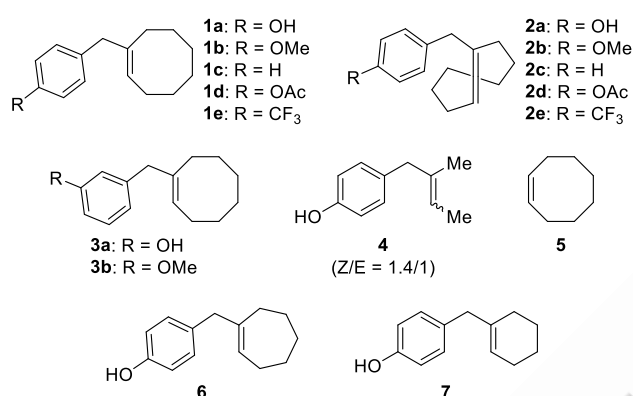
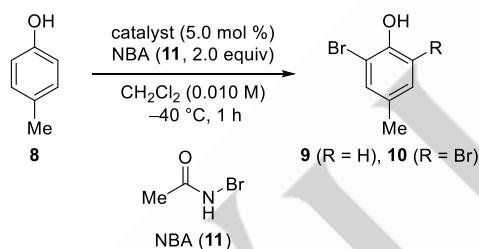


Figure 2. Olefin catalysts.

Table 1. Bromination of *p*-cresol using olefin catalysts.^[a]



Entry	Catalyst	Yield of 9 (%) ^[b]	Yield of 10 (%) ^[b]
1	none	<1	<1
2	1a	83	3
3	1b	46	54
4	1c	2	<1
5	1d	<1	<1

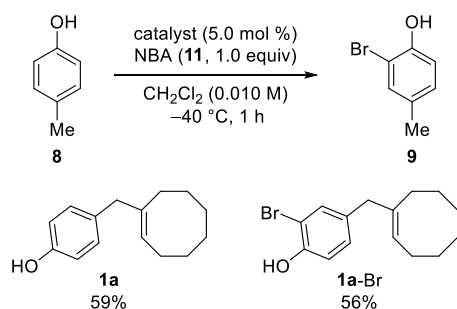
6	1e	3	<1
7	2a	63	<1
8	2b	58	<1
9	2c	8	<1
10	2d	7	<1
11	2e	5	<1
12	3a	82	11
13	3b	11	<1
14	4	<1	<1
15	5	<1	<1
16	6	47	<1
17	7	<1	<1

[a] Reactions were run using **8** (0.10 mmol), **11** (0.20 mmol), and the catalyst (0.0050 mmol) in CH₂Cl₂ (10 mL). [b] NMR yields. No side product other than **9** and **10** were yielded.

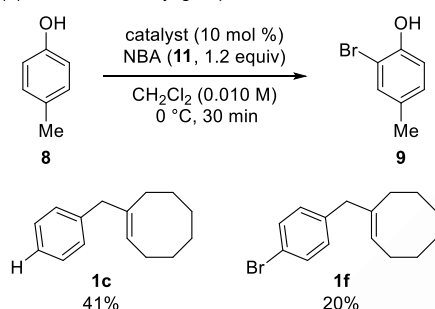
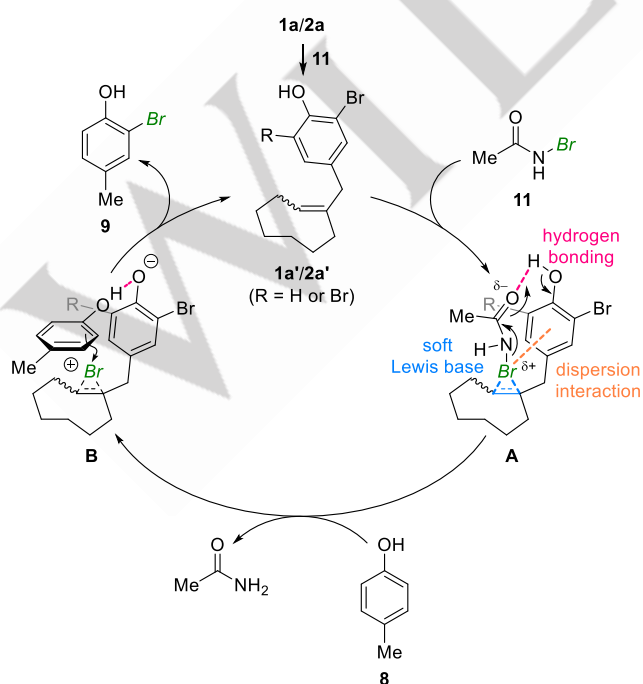
Mechanistic investigations were then conducted. As catalysts **1a** and **2a** contain phenol moieties, we analyzed whether the substituents of the catalysts were brominated in situ. Although the fate of each catalyst is difficult to analyze after the catalytic reaction due to the complexity of the resulting mixture, brominated catalysts were synthesized^[39] and assessed as catalysts in the bromination of **8** (Scheme 1).^[45] The catalytic activity of CCO **1a**-Br bearing a *meta*-bromo-*para*-hydroxybenzyl group was comparable to that of **1a** (Scheme 1a). Conversely, CCO **1f** bearing a *para*-bromobenzyl group was less catalytically active than **1c**, indicating that a bromo group displays a negative effect (Scheme 1b). Thus, in assessing the catalytic activity of **1a**, we likely observe the catalytic activity of in-situ-brominated **1a**, while less nucleophilic **1c** is not brominated in situ. Moreover, compared to the trends observed in Table 1, the bromination of anisole (**12**) exhibited different patterns with respect to the substituent effects of the catalysts (see Table S1 in the Supporting Information for details). The bromination of **12** was slower than that of **8**, and thus, the reactions were investigated at 25 °C. Regardless of the catalyst substituents, bromination proceeded with low-to-moderate yields, and protecting the *para*-hydroxybenzyl group was ineffective in deactivating the catalytic activity (Table S1, entries 2, 5, 7, and 10). The results shown in Tables 1 and S1 indicate the importance of the phenolic groups of the substrate and catalyst. Based on these results and the mechanistic insights observed in Scheme 1 and our recent study,^[40] we propose the reaction pathways of the **1a/2a**-catalyzed bromination of **8**, as shown in Figure 3. First, the phenol moieties of **1a** and **2a** are likely brominated, and a catalytic cycle is then initiated. Phenolic substrates can be activated via hydrogen bonding (**B**), which facilitates Br⁺ transfer from a catalyst-derived bromiranium species to the substrate. Thus, the reaction of **8** is faster compared to that of **12**. We conducted variable time normalization analyses^[46] of the bromination of 2,4-dimethylphenol (**8'**), which exhibits a single reaction site at the *ortho*-position, using **1a** and **1d** as catalysts (see Schemes S1 and S2 in the Supporting Information for details). The results indicate that the kinetics are first order in terms of **8'** in the **1a**-catalyzed reaction but zero order in terms of **8'** in the **1d**-catalyzed reaction. In our previous

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study, the kinetics were found to be zero order in terms of the substrate in **2c**-catalyzed bromolactonization using **11** as a brominating reagent, indicating that the RDS is the activation of **11**. Bifunctional catalysts **1a** and **2a** effectively facilitate the activation of **11** via hydrogen bonding and dispersion interactions, in addition to Lewis-basic activation by their olefin moieties (same as **A**).^[40] Here, in the **1a**-catalyzed aromatic bromination, the first-order kinetics in terms of the substrate were likely observed because the bifunctional catalyst **1a** effectively accelerates the activation of **11**, and Br⁺ transfer to the substrate (**B**) is the RDS. Conversely, the zero-order kinetics in terms of the substrate observed in the **1d**-catalyzed aromatic bromination indicate that the protection of the phenolic group of the catalyst retards the activation of **11**, making it the RDS. These results suggest that protecting the phenolic group of **1a/2a** suppresses the catalytic activity by altering the rate of the generation of bromiranium ions. This enables catalysis that can be activated in situ using a photochemically labile masking group on the *para*-hydroxybenzyl substituent (vide infra, Schemes 2 and 3).

(a) CCOs with *p*-hydroxybenzyl groups

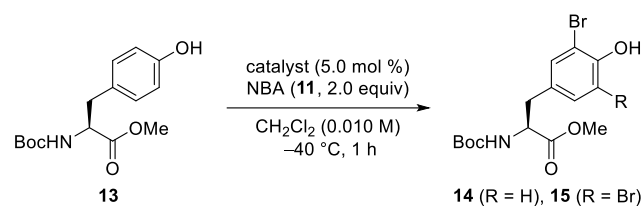
(b) CCOs with benzyl groups

**Scheme 1.** Substituent effects of the brominated benzyl groups of the CCO catalysts.

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Figure 3. Proposed pathways of the **1a/2a**-catalyzed bromination of *p*-cresol (**8**).

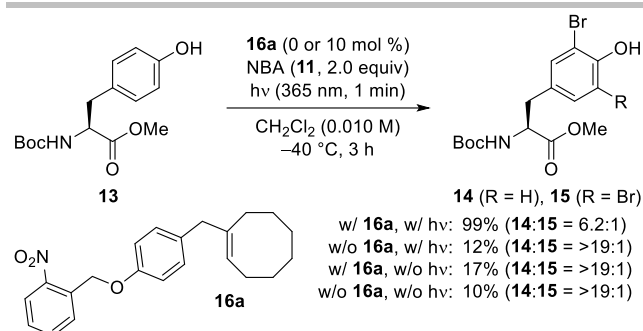
Cyclooctene **1a/2a**-catalyzed bromination was then applied to tyrosine derivative **13** (Table 2). The trends were similar to those shown in Table 1. **1a**, **1b**, **2a**, and **2b**, bearing a *para*-hydroxybenzyl or -methoxybenzyl group, were more catalytically active than the other cyclooctene derivatives (Table 2, entries 2, 3, 7, and 8). In addition, protecting **1a** and **2a** with an electron-withdrawing group effectively suppressed their catalytic activity (Table 2, entries 5 and 10). We thus conducted the bromination of **13** using light-gated catalyst **16a**^[40] (Scheme 2). The reaction efficiently proceeded in the presence of **16a** and light, whereas their absence resulted in slower reactions. To the best of our knowledge, this is the first light-gated catalysis of the bromination of an amino acid derivative.

Table 2. Bromination of the tyrosine derivative using cyclooctene catalysts.^[a]

Entry	Catalyst	Yield of 14 (%) ^[b]	Yield of 15 (%) ^[b]
1	none	<1	<1
2	1a	83	10
3	1b	83	<1
4	1c	<1	<1
5	1d	<1	<1
6	1e	<1	<1
7	2a	64	22
8	2b	87	3
9	2c	20	<1
10	2d	11	<1
11	2e	<1	<1

[a] Reactions were run using **13** (0.10 mmol), **11** (0.20 mmol), and the catalyst (0.0050 mmol) in CH₂Cl₂ (10 mL). [b] NMR yields.

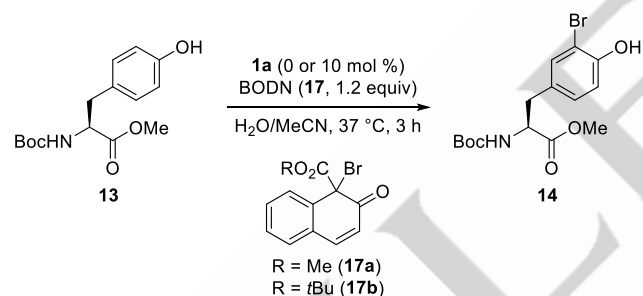
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Scheme 2. Light-gated catalysis of the bromination of the tyrosine derivative with NBA using **16a**.

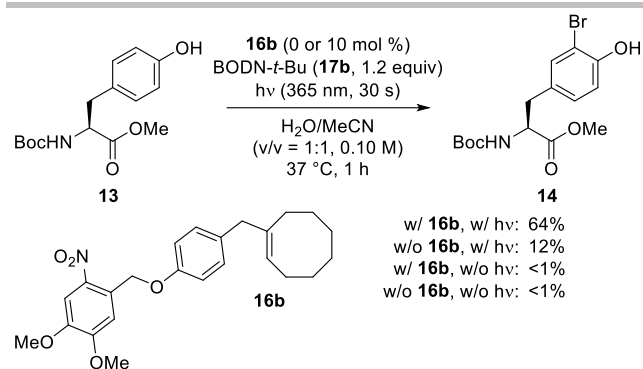
We then investigated the biocompatibility of this catalytic system. The high reactivity of conventional brominating reagents, such as **11**, causes non-catalyzed background reactions at physiologically benign temperatures. We recently revealed the biocompatible reactivity of BODNs (**17**) as brominating reagents, but they are inert in the absence of a catalyst even under near-physiological conditions.^[19] Here, we additionally identified the efficient reactivity of BODNs in the bifunctional cyclooctene-catalyzed bromination of the tyrosine derivative under biocompatible conditions (Table 3).^[47] BODNs **17** enabled catalytic reactions in aqueous media at 37 °C without causing non-catalyzed background reactions. To the best of our knowledge, this is the first Lewis base-catalyzed aromatic bromination in aqueous media.^[19,26,27] BODN-Me (**17a**) readily provided brominated tyrosine **14** in a high yield in the presence of **1a** (Table 3, entry 1), and the use of BODN-*t*-Bu (**17b**) also resulted in slower but practical **1a**-catalyzed reactivity under ambient aqueous conditions (Table 3, entries 2 and 3). Moreover, photochemically initiated bromination was realized under these biocompatible conditions by developing light-gated catalyst **16b** with a 4,5-dimethoxy-2-nitrobenzyl group^[48] as a photoremovable protecting group, which inhibited background reactions more effectively than **16a** (Scheme 3).^[47]

Table 3. Bromination of the tyrosine derivative Using BODNs.^[a]

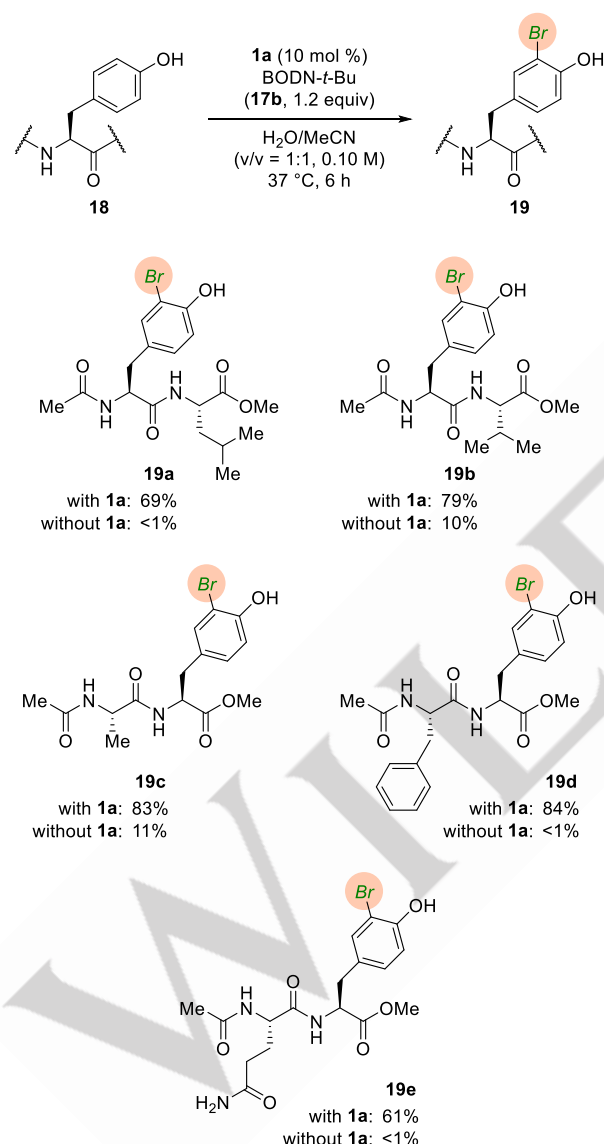


Entry	Reagent	Yield with 1a (%) ^[b]	Yield without 1a (%) ^[b]
1	17a	91	<1
2	17b	66	<1
3 ^[c]	17b	75	<1

[a] Reactions were run using **13** (0.10 mmol), **17** (0.12 mmol), and **1a** (0 or 0.010 mmol) in H₂O/MeCN (v/v = 1:1, 1.0 mL). [b] NMR yields. [c] Reaction was run for 6 h.



Scheme 3. Light-gated catalysis of the bromination of the tyrosine derivative with BODN-*t*-Bu using **16b**.

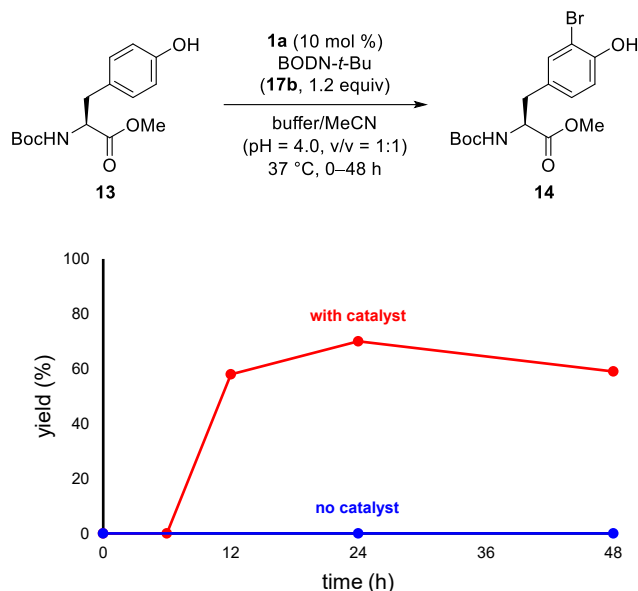


Scheme 4. Bromination of tyrosine-containing peptides.

The aqueous conditions expanded the scope of this method to the bromination of tyrosine-containing peptides (Scheme 4). Peptides bearing leucine (**19a**), valine (**19b**), alanine (**19c**), phenylalanine (**19d**), and glutamine (**19e**) were efficiently brominated in the presence of **1a**, providing only the desired product **19** without generating any side products. Furthermore, olefin-catalyzed aromatic bromination was tolerated under acidic conditions with pH values below 5, which occur under several physiological conditions, such as environments close to tumor cells and

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within endo- and lysosomes.^[49,50] The reaction of **13** was conducted using solvents comprising a buffer, with a pH of 4.0, and acetonitrile (Scheme 5). While no reaction occurred in the absence of a catalyst, **1a** catalyzed the reaction, albeit with an extended induction period,^[40] indicating a unique feature of the olefin catalyst, i.e., it serves as a Lewis base even under acidic conditions.



Scheme 5. Reactions under acidic conditions.

Conclusions

In summary, the cyclooctene-catalyzed bromination of phenol derivatives was developed, and it was applied to biocompatible tyrosine modification. The bifunctional cyclooctenes bearing a hydroxybenzyl group were particularly catalytically active. The substituent effects of the catalysts primarily affected the rate of the generation of bromiranium ions as active species, which provided the kinetics enabling light-gated catalysis. Such olefin catalysis was compatible with ambient aqueous conditions, enabling the bromination of tyrosine-containing peptides. The Lewis-base catalysis proceeded even under acidic conditions. Olefin-catalyzed tyrosine bromination offers biocompatible methods for use in selectively modifying peptides and proteins with bromo groups as attractive synthetic handles and mass tags. Studies regarding the application of olefin-catalyzed tyrosine bromination in labeling techniques as well as the development of more water-soluble reaction tools are currently underway and shall 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.^[51]

Acknowledgements

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Keywords: olefin • aromatic bromination • tyrosine modification • biocompatibility • light-gated catalyst

- [1] M. Mato, X. Fernández-González, C. D'Avino, M. Tomás-Gamasa, J. L. Mascareñas, "Bioorthogonal Synthetic Chemistry Enabled by Visible-Light Photocatalysis." *Angew. Chem. Int. Ed.* **2024**, 63, e202413506.
- [2] W. Qin, K. F. Cho, P. E. Cavanagh, A. Y. Ting, "Deciphering molecular interactions by proximity labeling." *Nat. Methods* **2021**, 18, 133.
- [3] C. P. Seath, A. D. Trowbridge, T. W. Muir, D. W. C. MacMillan, "Reactive intermediates for interactome mapping." *Chem. Soc. Rev.* **2021**, 50, 2911.
- [4] P. K. Sasmal, C. N. Streub, E. Meggers, "Metal complex catalysis in living biological systems." *Chem. Commun.* **2013**, 49, 1581.
- [5] S. A.-d. Castro, A. Terenzi, J. Gurruchaga-Pereda, L. Salassa, "Catalysis Concepts in Medicinal Inorganic Chemistry." *Chem. Eur. J.* **2019**, 25, 6651.
- [6] S. Sato, H. Nakamura, "Ligand-Directed Selective Protein Modification Based on Local Single-Electron-Transfer Catalysis." *Angew. Chem. Int. Ed.* **2013**, 52, 8681.
- [7] S. Sato, K. Hatano, M. Tsushima, H. Nakamura, "1-Methyl-4-aryl-urazole (MAUra) labels tyrosine in proximity to ruthenium photocatalysts." *Chem. Commun.* **2018**, 54, 5871.
- [8] R. C. Oslund, T. Reyes-Robles, C. H. White, J. H. Tomlinson, K. A. Crotty, E. P. Bowman, D. Chang, V. M. Peterson, L. Li, S. Frutos, M. Vila-Perelló, D. Vlerick, K. Cromie, D. H. Perlman, S. Ingale, S. D. O'Hara, L. R. Roberts, G. Piizzi, E. C. Hett, D. J. Hazuda, O. O. Fadeyi, "Detection of cell–cell interactions via photocatalytic cell tagging." *Nat. Chem. Biol.* **2022**, 18, 850.
- [9] P. A. Szijj, K. A. Kostadinova, R. J. Spears, V. Chudasama, "Tyrosine bioconjugation – an emergent alternative." *Org. Biomol. Chem.* **2020**, 18, 9018.
- [10] D. A. Dorta, D. Deniaud, M. Mével, S. G. Gouin, "Tyrosine Conjugation Methods for Protein Labelling." *Chem. Eur. J.* **2020**, 26, 14257.
- [11] F. A. Fellouse, C. Wiesmann, S. S. Sidhu, "Synthetic antibodies from a four-amino-acid code: A dominant role for tyrosine in antigen recognition." *Proc. Natl. Acad. Sci. U. S. A.* **2004**, 101, 12467.
- [12] P. Auffinger, F. A. Hays, E. Westhof, P. S. Ho, "Halogen Bonds in Biological Molecules." *Proc. Natl. Acad. Sci. U.S.A.* **2004**, 48, 16789.
- [13] M. Z. Hernandez, S. M. T. Cavalcanti, D. R. M. Moreira, W. F. de Azevedo Junior, A. C. L. Leite, "Halogen Atoms in The Modern Medicinal Chemistry: Hints for The Drug Design." *Curr. Drug Targets* **2010**, 11, 303.
- [14] H. Sun, C. E. Keefer, D. O. Scott, "Systematic and Pairwise Analysis of The Effects of Aromatic Halogenation and Trifluoromethyl Substitution on Human Liver Microsomal Clearance." *Drug Metab. Lett.* **2011**, 5, 232.
- [15] J. M. Chalker, C. S. C. Wood, B. G. Davis, "A Convenient Catalyst for Aqueous and Protein Suzuki–Miyaura Cross-Coupling." *J. Am. Chem. Soc.* **2009**, 131, 16346.
- [16] C. D. Spicer, T. Triemer, B. G. Davis, "Palladium-Mediated Cell-Surface Labeling." *J. Am. Chem. Soc.* **2012**, 134, 800.
- [17] N. Li, R. K. V. Lim, S. Edwardraja, Q. Lin, "Copper-Free Sonogashira Cross-Coupling for Functionalization of Alkyne-Encoded Proteins in Aqueous Medium and in Bacterial Cells." *J. Am. Chem. Soc.* **2011**, 133, 15316.
- [18] N. Saha, F. N. U. Vidya, R. Xie, V. Agarwal, "Halogenase-Assisted Alkyne/Aryl Bromide Sonogashira Coupling for Ribosomally Synthesized Peptides." *J. Am. Chem. Soc.* **2024**, 146, 30009.
- [19] BODNs can be activated as brominating reagents for tyrosine modification under visible light irradiation in the presence of a photocatalyst, but they are inert in darkness or the absence of a photocatalyst even under near-physiological conditions. See: R. Yoshida, Y. Hori, D. Uruguchi, K. Asano, "BODNs as biocompatible brominating reagents: visible-light photocatalytic tyrosine modification under physiologically favorable conditions." *Chem. Commun.* **2024**, 60, 12381.
- [20] H. Liu, C. F. Lichti, B. Mirfattah, J. Frahm, C. L. Nilsson, "A Modified Database Search Strategy Leads to Improved Identification of in Vitro Brominated Peptides Spiked into a Complex Proteomic Sample." *J. Proteome Res.* **2013**, 12, 4248.
- [21] S. S. Nair, C. L. Nilsson, M. R. Emmett, T. M. Schaub, K. H. Gowd, S. S. Thakur, K. S. Krishnan, P. Balaram, A. G. Marshall, "De Novo Sequencing and Disulfide Mapping of a Bromotryptophan-Containing Conotoxin by Fourier Transform Ion Cyclotron Resonance Mass Spectrometry." *Anal. Chem.* **2006**, 78, 8082.
- [22] M. G. Paulick, K. M. Hart, K. M. Brinner, M. Tjandra, D. H. Charych, R. N. Zuckermann, "Cleavable Hydrophilic Linker for One-Bead-One-Compound Sequencing of Oligomer Libraries by Tandem Mass Spectrometry." *J. Comb. Chem.* **2006**, 8, 417.
- [23] L. Yang, C. Chumsae, J. B. Kaplan, K. R. Moulton, D. Wang, D. H. Lee, Z. S. Zhou, "Detection of Alkynes via Click Chemistry with a Brominated Coumarin Azide by Simultaneous Fluorescence and Isotopic Signatures in Mass Spectrometry." *Bioconjugate Chem.* **2017**, 28, 2302.

COMMUNICATION

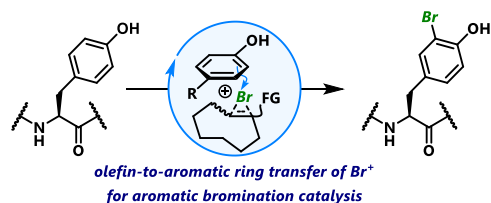
- [24] S. Song, X. Li, J. Wei, W. Wang, Y. Zhang, L. Ai, Y. Zhu, X. Shi, X. Zhang, N. Jiao, "DMSO-Catalysed Late-Stage Chlorination of (Hetero)arenes." *Nat. Catal.* **2020**, *3*, 107.
- [25] H. Mondal, S. Patra, S. Saha, T. Nayak, U. Sengupta, M. S. Maji, "Late-Stage Halogenation of Peptides, Drugs and (Hetero)aromatic Compounds with a Nucleophilic Hydrazide Catalyst." *Angew. Chem. Int. Ed.* **2023**, *62*, e202312597.
- [26] K. Tanemura, "Recent advances in the electrophilic halogenation of aromatic compounds using *N*-halosuccinimides (NXS)." *Tetrahedron Lett.* **2025**, *155*, 155419.
- [27] H. Mondal, "Halogen and Chalcogen Activation by Nucleophilic Catalysis." *Chem. Eur. J.* **2024**, *30*, e202402261.
- [28] M. L. Blackman, M. Royzen, J. M. Fox, "Tetrazine Ligation: Fast Bioconjugation Based on Inverse-Electron-Demand Diels–Alder Reactivity." *J. Am. Chem. Soc.* **2008**, *130*, 13518.
- [29] N. K. Devaraj, R. Weissleder, "Biomedical Applications of Tetrazine Cycloadditions." *Acc. Chem. Res.* **2011**, *44*, 816.
- [30] A. J. Bennet, R. S. Brown, R. E. D. McClung, M. Klobukowski, G. H. M. Aarts, B. D. Santarsiero, G. Bellucci, R. Bianchini, "An Unprecedented Rapid and Direct Br⁺ Transfer from the Bromonium Ion of Adamantylideneadamantane to Acceptor Olefins." *J. Am. Chem. Soc.* **1991**, *113*, 8532.
- [31] R. S. Brown, "Investigation of the Early Steps in Electrophilic Bromination through the Study of the Reaction with Sterically Encumbered Olefins." *Acc. Chem. Res.* **1997**, *30*, 131.
- [32] S. E. Denmark, M. T. Burk, A. J. Hoover, "On the Absolute Configurational Stability of Bromonium and Chloronium Ions." *J. Am. Chem. Soc.* **2010**, *132*, 1232.
- [33] A. A. Neverov, R. S. Brown, "Br⁺ Transfer to reactive alkenes from the bromonium ion of adamantylideneadamantane." *Can. J. Chem.* **1994**, *72*, 2540.
- [34] A. A. Neverov, R. S. Brown, "Br⁺ and I⁺ Transfer from the Halonium Ions of Adamantylideneadamantane to Acceptor Olefins. Halocyclization of 1,ω-Alkenols and Alkenoic Acids Proceeds via Reversibly Formed Intermediates." *J. Org. Chem.* **1996**, *61*, 962.
- [35] A. A. Neverov, T. L. Muise, R. S. Brown, "X⁺ transfer from the halonium ions of adamantylideneadamantane to acceptor olefins. The possibility of chiral induction in the transfer process." *Can. J. Chem.* **1997**, *75*, 1844.
- [36] C. Ascheberg, J. Bock, F. Buß, C. Mück-Lichtenfeld, C. G. Daniliuc, K. Bergander, F. Dielmann, U. Hennecke, "Stable Bromiranium Ions with Weakly-Coordinating Counterions as Efficient Electrophilic Brominating Agents." *Chem. Eur. J.* **2017**, *23*, 11578.
- [37] J. Bock, C. G. Daniliuc, U. Hennecke, "Stable Bromiranium Ion Salts as Reagents for Biomimetic Indole Terpenoid Cyclizations." *Org. Lett.* **2019**, *21*, 1704.
- [38] S. Einaru, K. Shitamichi, T. Nagano, A. Matsumoto, K. Asano, S. Matsubara, "*trans*-Cyclooctenes as Halolactonization Catalysts." *Angew. Chem. Int. Ed.* **2018**, *57*, 13863.
- [39] R. Murata, R. Yoshida, D. Uraguchi, K. Asano, "Synthesis of Substituted Cyclooctenes through Cross-Coupling Reactions." *Synlett* **2025**, *36*, 69.
- [40] T. Nagano, T. Shimazu, K. Kaneko, S. Matsubara, M. Yamanaka, D. Uraguchi, K. Asano, "Mechanism-Guided Development of Bifunctional Cyclooctenes as Active, Practical, and Light-Gated Bromination Catalysts." *Chem. Eur. J.* **2025**, *31*, e202404011.
- [41] H. Mayr, B. Kempf, A. R. Ofial, "π-Nucleophilicity in Carbon–Carbon Bond-Forming Reactions." *Acc. Chem. Res.* **2003**, *36*, 66.
- [42] N. Zivic, P. K. Kuroishi, F. Dumur, D. Gimes, A. P. Dove, H. Sardon, "Recent Advances and Challenges in the Design of Organic Photoacid and Photobase Generators for Polymerizations." *Angew. Chem. Int. Ed.* **2019**, *58*, 10410.
- [43] R. S. Stoll, S. Hecht, "Artificial Light-Gated Catalyst Systems." *Angew. Chem. Int. Ed.* **2010**, *49*, 5054.
- [44] S. Aubert, M. Bezagu, A. C. Spivey, S. Arseniyadis, "Spatial and temporal control of chemical processes." *Nat. Rev. Chem.* **2019**, *3*, 706.
- [45] Compound **10** was not generated via the reactions shown in Scheme 1.
- [46] J. Burés, "Variable Time Normalization Analysis: General Graphical Elucidation of Reaction Orders from Concentration Profiles." *Angew. Chem. Int. Ed.* **2016**, *55*, 16084.
- [47] Compound **15** was not generated via the reactions shown in Table 3 and Scheme 3.
- [48] A. Patchornik, B. Amit, R. B. Woodward, "Photosensitive Protecting Groups." *J. Am. Chem. Soc.* **1970**, *92*, 6333.
- [49] G. H. Diering, M. Numata, "Endosomal pH in neuronal signaling and synaptic transmission: role of Na⁺/H⁺ exchanger NHE5." *Front Physiol.* **2014**, *4*, 412.
- [50] B. A. Webb, M. Chimenti, M. P. Jacobson, D. L. Barber, "Dysregulated pH: a perfect storm for cancer progression." *Nat. Rev. Cancer* **2011**, *11*, 671.

COMMUNICATION

[51] D. K. Sinha, P. Neveu, N. Gagey, I. Aujard, C. Benbrahim-Bouzidi, T. Le Saux, C. Rampon, C. Gauron, B. Goetz, S. Dubruille, M. Baaden, M. Volovitch, D. Bensimon, S. Vriz, L. Jullien, *ChemBioChem* **2010**, *11*, 653.

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Biocompatible catalysis for aromatic bromination was attained via olefin-to-aromatic ring transfer of Br⁺. Bifunctional cyclooctenes catalyzed the bromination of phenol derivatives, which was applicable in tyrosine modification, and realized light-gated catalysis. Such olefin catalysis was compatible with aqueous conditions, enabling the bromination of peptides, and the Lewis-base catalysis of the olefins proceeded even under acidic conditions.