A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition

GDCh

Chemie

www.angewandte.org

Accepted Article

Title: trans-Cyclooctenes as Halolactonization Catalysts

Authors: Shunsuke Einaru, Kenta Shitamichi, Tagui Nagano, Akira Matsumoto, Keisuke Asano, and Seijiro Matsubara

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201808320
Angew. Chem. 10.1002/ange.201808320

Link to VoR: http://dx.doi.org/10.1002/anie.201808320
http://dx.doi.org/10.1002/ange.201808320

WILEY-VCH

10.1002/anie.201808320

WILEY-VCH

trans-Cyclooctenes as Halolactonization Catalysts

Shunsuke Einaru[+], Kenta Shitamichi[+], Tagui Nagano, Akira Matsumoto, Keisuke Asano,* and Seijiro Matsubara*

Abstract: The strained olefins in *trans*-cyclooctenes serve as efficient catalysts for halolactonizations, including bromolactonizations and iodolactonizations. The *trans*-cyclooctene framework is essential for excellent catalytic performance, and the substituents also play important roles in determining efficiency. These results represent the first demonstration of catalysis by a *trans*-cyclooctene; hence, these findings offer new functional-group-design entries for molecular catalysts.

trans-Cycloalkenes have garnered considerable attention since the discovery of their unique refractive indices and densities owing to their strained structures.[1] Their structural features have been extensively studied,[2] and their optically active forms, which are based on planar chirality, have been isolated[3] and used as chiral synthetic intermediates.[4] In addition, strained olefins exhibit high reactivities and chemoselectivities in organic reactions such as inverse-electron-demand Diels–Alder reactions, which are applicable to orthogonal bioconjugation reactions.[5] However, to the best of our knowledge, their catalytic behavior is unknown despite their potential as novel molecular-catalyst platforms that result from their unique reactivities, chemoselectivities, and fascinating chirality. In this context, we envisaged that the soft Lewis basicities of olefins would be useful for activating electrophilic halogenating reagents; the strained olefins of *trans*-cyclooctenes would be more Lewis basic than normal olefins (Figure 1). Herein, we describe the catalytic activities of *trans*-cyclooctenes in halolactonization reactions. This study offers new functional-group-design entries for catalysis, as olefins have hardly been used in this manner.[6]

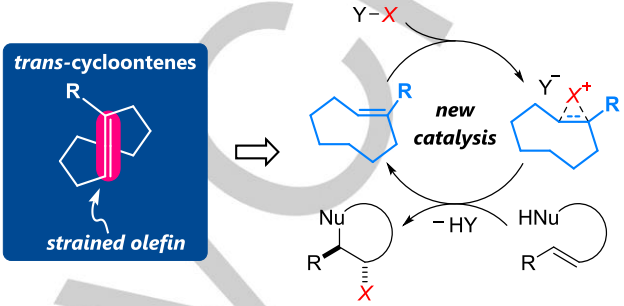
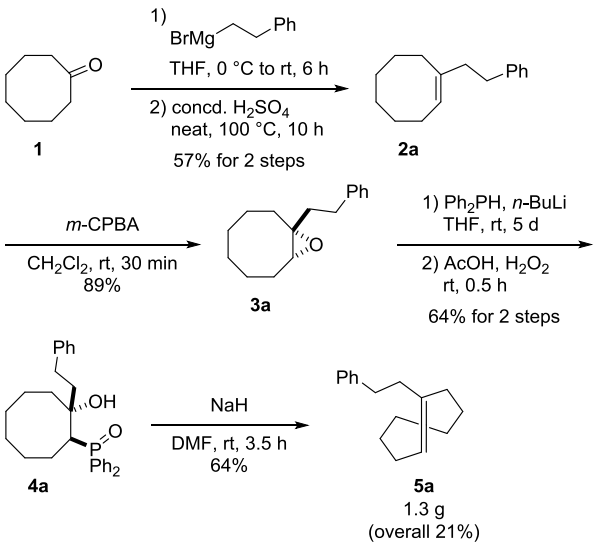


Figure 1. *trans*-Cyclooctenes as Lewis-base catalysts during electrophilic halogenation.

This study was initiated by the synthesis of *trans*-cyclooctenes bearing substituents[7] that are capable of tuning the steric and electronic properties of the *trans*-cyclooctene core (Scheme 1). Starting from cyclooctanone (**1**), alkylation with a Grignard reagent followed by dehydration yielded the alkylated *cis*-cyclooctene **2a**. Subsequent epoxidation and ring opening with lithium diphenylphosphide followed by oxidation gave the corresponding phosphine oxide **4a**. Finally, treatment with sodium hydride afforded *trans*-cyclooctene **5a**, on a gram-scale, in 21% overall yield. In order to confirm the olefin geometry, platinum complex **6a** was synthesized in order to prepare a single crystal for X-ray analysis (Figure 2).[8] The ORTEP drawing unambiguously identifies the alkene as the *trans*-isomer. Analogues **5b**–**5d** (Table 1) bearing other substituents were also synthesized via the same synthetic route (see Supporting Information for details).



Scheme 1. Synthesis of *trans*-cyclooctene **5a**.

[*] S. Einaru,[+] K. Shitamichi,[+] T. Nagano, A. Matsumoto, Prof. Dr. K Asano, Prof. Dr. Seijiro Matsubara
Department of Material Chemistry, Graduate School of Engineering
Kyoto University
Kyotodaigaku-katsura, Nishikyo, Kyoto 615-8510 (Japan)
E-mail: asano.keisuke.5w@kyoto-u.ac.jp
matsubara.seijiro.2e@kyoto-u.ac.jp

[+] These authors contributed equally to this work.

Supporting information for this article is given via a link at the end of the document.

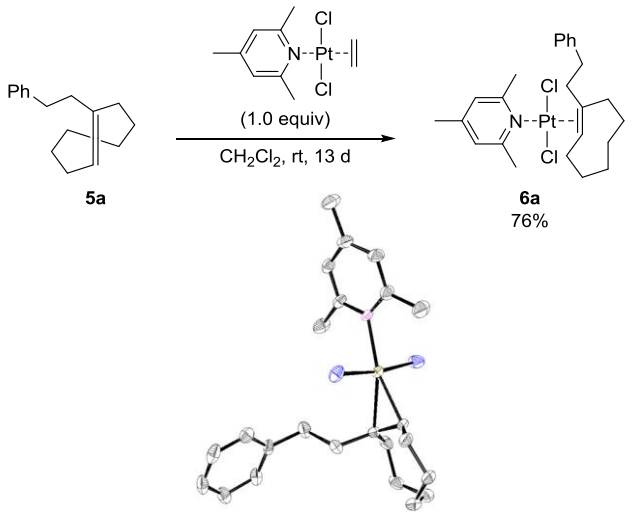
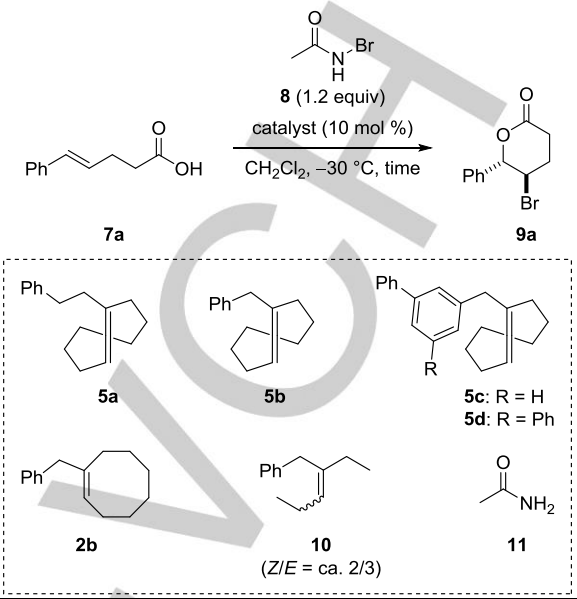


Figure 2. Synthesis and ORTEP drawing of platinum complex **6a**.

The catalytic performance of *trans*-cyclooctenes **5** was subsequently investigated during halolactonizations that are facilitated by catalytic amounts of Lewis bases.[9] Several alkenes (**5a**–**5d**, **2b**, and **10**) were examined as catalysts for (*E*)-5-phenylpent-4-enoic acid (**7a**) in the presence of *N*-bromoacetamide (NBA, **8**) in CH_2Cl_2 at –30 °C for 6–48 h (Table 1). While the reaction was slow in the absence of any catalytic alkene or in the presence of **5a** (Table 1, entries 1–4), the use of the benzyl-bearing **5b** promoted the reaction efficiently to provide product **9a** in 88% yield after 6 h (Table 1, entry 5). Reaction-time investigations revealed that the yield in the reaction of **5b** was quantitative after 12 h (Table 1, entry 6), while the reaction in the absence of the catalyst resulted in only 9% yield even after 48 h (Table 1, entry 2).[10] Moderate acceleration of the reaction was also observed using **5a**, which provided **9a** in 71% yield after 48 h (Table 1, entry 4); however, **5b** was much more efficient than **5a**. *trans*-Cyclooctenes **5c** and **5d** bearing additional phenyl groups on the benzyl group afforded lower yields than **5b** (Table 1, entries 7 and 8). These results suggest that *trans*-cyclooctenes have catalytic activities, and that their substituents play roles that determine catalytic performance, which is probably due to steric interactions. Moreover, *cis*-cyclooctene **2b** and acyclic trisubstituted alkene **10** were much less effective (Table 1, entries 9 and 10). These results clearly indicate that the *trans*-cyclooctene skeleton is responsible for catalytic efficiency during the bromolactonization of **7a**. In addition, the affect of acetamide (**11**), which is generated from **8** during the course of the reaction, was also investigated. The reaction was very slow in the presence of **11** instead of the olefin catalyst (Table 1, entry 11); the use of **11** in combination with **5a** also resulted in a low yield (Table 1, entry 12). Hence, **11** was revealed not to be involved as an active catalytic species.

Table 1. Catalytic performance of different alkenes in bromolactonization of **7a**.[a]

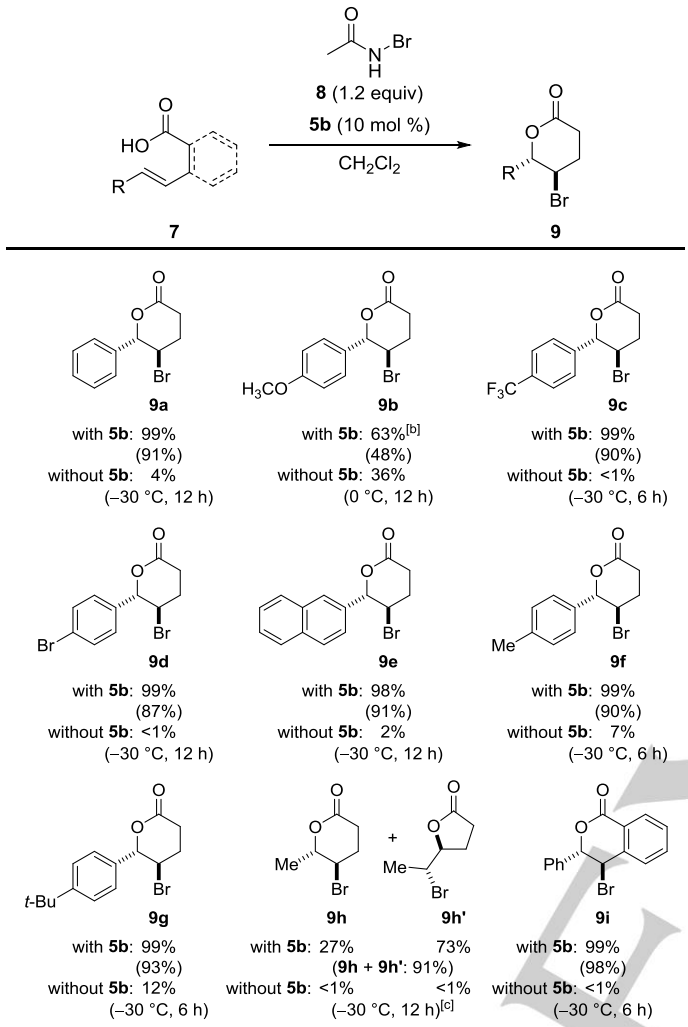


Entry	Catalyst	Time [h]	Yield [%][b]
1	None	6	3
2	None	48	9
3	**5a**	6	2
4	**5a**	48	71
5	**5b**	6	88
6	**5b**	12	99
7	**5c**	6	59
8	**5d**	6	4
9	**2b**	6	1
10	**10**	6	7
11	**11**	6	4
12[c]	**5a** + **11**	6	1

[a] Reactions were run using **7a** (0.10 mmol), **8** (0.12 mmol), and the catalyst (0.010 mmol) in CH_2Cl_2 (1.0 mL). [b] NMR yields. [c] Reaction was run using **5a** (0.010 mmol) and **11** (0.010 mmol).

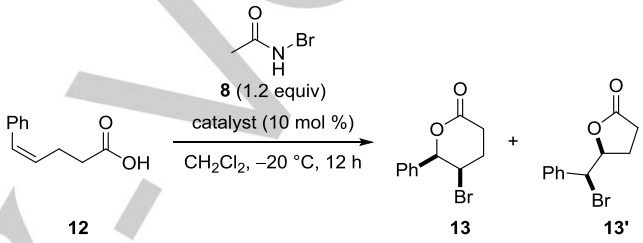
10.1002/anie.201808320

Table 2. Bromolactonizations of **7**.[a]



[a] Reactions were run using **7** (0.10 mmol), **8** (0.12 mmol), and **5b** (0.010 mmol) in CH_2Cl_2 (1.0 mL). [b] **7b** was recovered in 31% yield. [c] Reaction was run on a 0.50 mmol scale. Yields were determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as the internal standard. Yields in parentheses represent material isolated after silica-gel column chromatography.

High catalytic activity was also observed when other substrates **7** were investigated using **5b** as the catalyst (Table 2). While the reaction of electron-rich substrate **7b** was slow,[11] the reaction of electron-deficient substrate **7c** was efficiently accelerated. In addition, reactions of substrates **7d** and **7e** bearing 4-bromophenyl and 2-naphthyl groups, respectively, were also accelerated by **5b**. Similarly, substrates **7f** and **7g** bearing 4-tolyl and 4-(*tert*-butyl)phenyl groups, respectively, were efficiently transformed in the presence of **5b**. Substrate **7h** bearing an aliphatic group also exhibited similar reaction outcomes, although the product was obtained as a mixture of regioisomers **9h** and **9h'**. Furthermore, similar effects involving **5b** were also observed during the bromolactonization of (*E*)-2-styrylbenzoic acid (**7i**); the reaction proceeded quantitatively in the presence of catalyst **5b**, while it failed in the absence of the catalyst at –30 °C under the conditions examined. In all cases, only the *trans*-isomers of δ-valerolactones **9** were obtained. Moreover, the reaction of (*Z*)-5-phenylpent-4-enoic acid (**12**) catalyzed by **5b** afforded *cis*-δ-valerolactone **13** along with γ-butyrolactone **13'**, while *trans*-δ-valerolactone **9a** was not observed (Scheme 2). Hence, these reactions were revealed to proceed stereospecifically, which implies the intermediacy of putative cyclic bromiranium ions generated *in situ* from substrates **7** and **12** during catalysis.[12] Furthermore, the regioselectivity (**13**:**13'**) was affected by the Lewis-base catalysts; the regioselectivity of the reaction using **5b** was different from those without catalyst; it was also different from those using triethylamine and triphenylphosphine as Lewis-base catalysts. These results suggest that **5b** is also involved in the step of lactonization of the bromiranium ion intermediates generated from the substrates.[9a]



	13	13'	13:13'
with **5b**:	26%	71%	1:2.7
without catalyst:	<1%	2%	1:>99
with NEt_3:	<1%	99%	1:>99
with PPh_3:	15%	69%	1:4.6

Scheme 2. Bromolactonization of (*Z*)-5-phenylpent-4-enoic acid (**12**).

The effects of the amounts of **5a** and **5b** were next investigated (Figure 3). In the case of **5b**, the yield increased at catalyst loadings up to 20 mol %; however, the yield decreased in the presence of more than 20 mol % of **5b**. These results indicate that the olefin-to-olefin transfers of bromiranium ions take place between two molecules of **5b** at higher concentrations of **5b**, resulting in slower reactions. Furthermore, **5a** was less catalytically active than **5b** over the entire range of loadings, indicating that **5a** is more likely to inactivate the bromiranium ions by olefin-to-olefin transfer between *trans*-cyclooctenes. Hence, the dramatic substituent effect of **5b** observed in Table 1 is attributed to the well-balanced bulkiness of the benzyl group that inhibits unfavorable bimolecular association while maintaining the approach of the substrate.

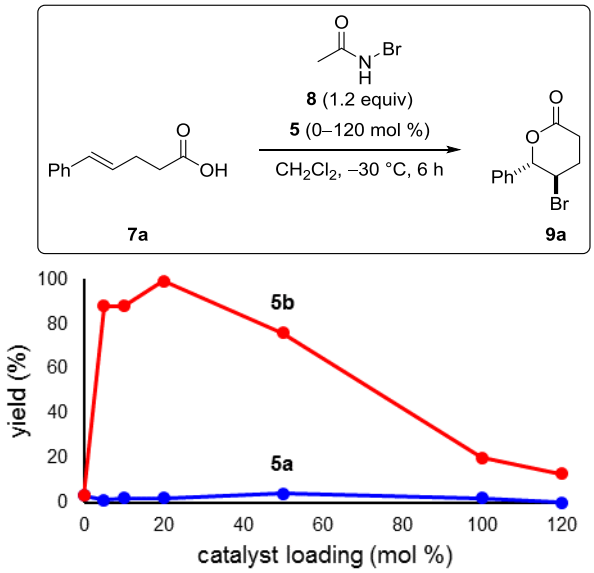
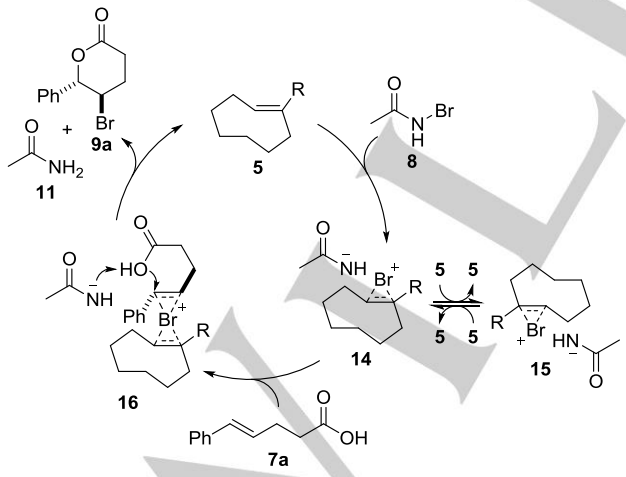


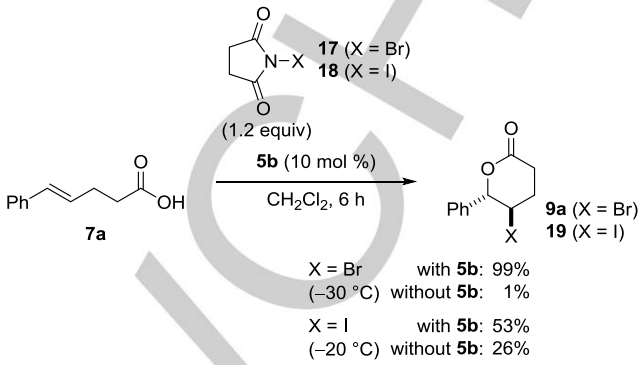
Figure 3. The effects of **5a** and **5b** loadings.

On the basis of the above-mentioned results, we propose a mechanism involving a catalytic cycle, as shown in Scheme 3. First, the bromiranium ion **14** is generated from **5** and **8**, after which association with another molecule of **5** makes the bromiranium ion shuttle between **14** and **15**. The olefin-to-olefin transfers of the bromiranium ion between two molecules of **5** retard the reaction; therefore, a key to increasing the catalytic efficiency is the inhibition of the unfavorable bimolecular association of **5**. Olefin-to-olefin transfer of the bromiranium ion with **7a** then takes place to stereospecifically form **16**; subsequent lactonization of **16**, in which **5** is still present, provides **9a** and regenerates **5**.[13]



Scheme 3. Proposed catalytic cycle.

Furthermore, **5b** also exerted a large influence on the halolactonizations of **7a** using other halogenating reagents (Scheme 4). A remarkable improvement in yield was observed with **5b** when *N*-bromosuccinimide (NBS, **17**) was used as the brominating reagent. Moreover, iodolactonization with *N*-iodosuccinimide (NIS, **18**) was also accelerated by **5b**, although the effect was moderate under the conditions examined.



Scheme 4. Halolactonizations of **7a** with *N*-halosuccinimides.

In summary, we demonstrated the catalytic behavior of *trans*-cyclooctenes in halolactonizations; these strained olefins efficiently facilitate the halolactonizations. The *trans*-cyclooctene framework is essential for good catalytic performance. In addition, substituents play important roles in determining efficiency, which reveals the potential of the substitutent to tune catalytic activity. The developed catalysts are useful in bromolactonization and iodolactonization reactions. These findings offer avenues for the design of novel molecular catalysts for synthetic transformations. Studies on the detailed reaction mechanism and applications in asymmetric catalysis[14] are currently underway in our laboratory.

Acknowledgements

We thank Professor Takuya Kurahashi (Kyoto University) for X-ray crystallographic analysis. This work was supported financially by the Japanese Ministry of Education, Culture, Sports, Science and Technology (15H05845, 16K13994, 17K19120, 18K14214, and 18H04258). K.A. also acknowledges the Asahi Glass Foundation, Toyota Physical and Chemical Research Institute, Tokyo Institute of Technology Foundation, the Naito Foundation, Research Institute for Production Development, the Tokyo Biochemical Research Foundation, the Uehara Memorial Foundation, the Kyoto University Foundation, the Institute for Synthetic Organic Chemistry, and Toyo Gosei Memorial Foundation. A.M. also acknowledges the Japan Society for the Promotion of Science for Young Scientists for the fellowship support.

Keywords: *trans*-cyclooctene • strained olefin • Lewis base • halolactonization • organocatalyst

[1] A. T. Blomquist, L. H. Liu, J. C. Bohrer, *J. Am. Chem. Soc.* **1952**, *74*, 3643.
[2] For reviews, see: a) J. A. Marshall, *Acc. Chem. Res.* **1980**, *13*, 213; b) M. Nakazaki, K. Yamamoto, K. Naemura, *Top. Curr. Chem.* **1984**, *125*, 1; c) K. Schlögl, *Top. Curr. Chem.* **1984**, *125*, 27; d) E. L. Eliel,

S. H. Wilen, L. N. Mander, in *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**, pp. 1172−1175.

[3] a) A. C. Cope, C. F. Howell, A. Knowles, *J. Am. Chem. Soc.* **1962**, *84*, 3190; b) A. C. Cope, C. R. Ganellin, H. W. Johnson, Jr. *J. Am. Chem. Soc.* **1962**, *84*, 3191; c) A. C. Cope, C. R. Ganellin, H. W. Johnson, Jr., T. V. Van Auken, H. J. S. Winkler, *J. Am. Chem. Soc.* **1963**, *85*, 3276; d) A. C. Cope, A. S. Mehta, *J. Am. Chem. Soc.* **1964**, *86*, 5626; e) A. C. Cope, K. Banholzer, H. Keller, B. A. Pawson, J. J. Whang, H. J. S. Winkler, *J. Am. Chem. Soc.* **1965**, *87*, 3644; f) A. C. Cope, B. A. Pawson, *J. Am. Chem. Soc.* **1965**, *87*, 3649. For selected examples of enantioselective syntheses, see: g) Y. Inoue, T. Yokoyama, N. Yamasaki, A. Tai, *Nature* **1989**, *341*, 225; h) K. Tomooka, K. Uehara, R. Nishikawa, M. Suzuki, K. Igawa, *J. Am. Chem. Soc.* **2010**, *132*, 9232; i) K. Igawa, N. Ichikawa, Y. Ano, K. Katanoda, M. Ito, T. Akiyama, K. Tomooka, *J. Am. Chem. Soc.* **2015**, *137*, 7294; j) T. Miura, T. Nakamuro, C.-J. Liang, M. Murakami, *J. Am. Chem. Soc.* **2014**, *136*, 15905; k) Y. Okayama, S. Tsuji, Y. Toyomori, A. Mori, S. Arae, W.-Y. Wu, T. Takahashi, M. Ogasawara, *Angew. Chem.* **2015**, *127*, 5009; *Angew. Chem. Int. Ed.* **2015**, *54*, 4927.

[4] For selected examples, see: a) K. Tomooka, N. Komine, D. Fujiki, T. Nakai, S. Yanagitsuru, *J. Am. Chem. Soc.* **2005**, *127*, 12182; b) K. Tomooka, M. Suzuki, K. Uehara, M. Shimada, T. Akiyama, *Synlett* **2008**, 2518; c) K. Tomooka, T. Akiyama, P. Man, M. Suzuki, *Tetrahedron Lett.* **2008**, *49*, 6327; d) K. Tomooka, C. Iso, K. Uehara, M. Suzuki, R. Nishikawa-Shimono, K. Igawa, *Angew. Chem.* **2012**, *124*, 10501; *Angew. Chem. Int. Ed.* **2012**, *51*, 10355; d) O. V. Larionov, E. J. Corey, *J. Am. Chem. Soc.* **2008**, *130*, 2954; e) M. Royzen, G. P. A. Yap, J. M. Fox, *J. Am. Chem. Soc.* **2008**, *130*, 3760; f) B. Hurlocker, C. Hu, K. A. Woerpel, *Angew. Chem.* **2015**, *127*, 4369; *Angew. Chem. Int. Ed.* **2015**, *54*, 4295.

[5] For selected examples, see: a) F. Thalhammer, U. Wallfahrer, J. Sauer, *Tetrahedron Lett.* **1990**, *31*, 6851; b) M. L. Blackman, M. Royzen, J. M. Fox, *J. Am. Chem. Soc.* **2008**, *130*, 13518; c) N. K. Devaraj, R. Weissleder, *Acc. Chem. Res.* **2011**, *44*, 816; d) F. Liu, Y. Liang, K. N. Houk, *J. Am. Chem. Soc.* **2014**, *136*, 11483; e) D. N. Kamber, Y. Liang, R. J. Blizzard, F. Liu, R. A. Mehl, K. N. Houk, J. A. Prescher, *J. Am. Chem. Soc.* **2015**, *137*, 8388.

[6] For selected reviews on olefins as ligands for metal catalysts, see: a) C. Defieber, H. Grützmacher, E. M. Carreira, *Angew. Chem.* **2008**, *120*, 4558; *Angew. Chem. Int. Ed.* **2008**, *47*, 4482; b) R. Shintani, T. Hayashi, *Aldrichimica Acta* **2009**, *42*, 31; c) X. Feng, H. Du, *Asian J. Org. Chem.* **2012**, *1*, 204; d) M. Nagamoto, T. Nishimura, *ACS Catal.* **2017**, *7*, 833.

[7] a) E. Vedejs, K. A. Snoble, P. L. Fuchs, *J. Org. Chem.* **1973**, *38*, 1178; b) K. J. Shea, J.-S. Kim, *J. Am. Chem. Soc.* **1992**, *114*, 3044.

[8] K. Tomooka, M. Shimada, K. Uehara, M. Ito, *Organometallics* **2010**, *29*, 6632.

[9] a) S. E. Denmark, M. T. Burk. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20655; b) S. E. Denmark, W. E. Kuester, M. T. Burk, *Angew. Chem.* **2012**, *124*, 11098; *Angew. Chem. Int. Ed.* **2012**, *51*, 10938; c) S. E. Denmark, G. L. Beutner, *Angew. Chem.* **2008**, *120*, 1584; *Angew. Chem. Int. Ed.* **2008**, *47*, 1560. For selected reviews on recent advance of halolactonization reactions, see: d) A. Sakakura, K. Ishihara, *Chem. Rec.* **2015**, *15*, 728; e) Y. A. Cheng, W. Z. Yu, Y.-Y. Yeung, *Org. Biomol. Chem.* **2014**, *12*, 2333; f) C. K. Tan, W. Z. Yu, Y.-Y. Yeung, *Chirality* **2014**, *26*, 328; g) S. Zheng, C. M. Schienebeck, W. Zhang, H.-Y. Wang, W. Tang, *Asian J. Org. Chem.* **2014**, *3*, 366; h) K. Murai, H. Fujioka, *Heterocycles* **2013**, *87*, 763; i) C. K. Tan, Y.-Y. Yeung, *Chem. Commun.* **2013**, *49*, 7985; j) S. R. Chemler, M. T. Bovino, *ACS Catal.* **2013**, *3*, 1076; k) U. Hennecke, *Chem. Asian J.* **2012**, *7*, 456; l) A. Castellanos, S. P. Fletcher, *Chem. Eur. J.* **2011**, *17*, 5766; m) C. K. Tan, L. Zhou, Y.-Y. Yeung, *Synlett* **2011**, 1335.

[10] Reaction profiles using **5a** and **5b**, as well in the absence of catalyst, were also monitored (see Scheme S1 in the Supporting Information for details).

[11] Side products, such as compounds brominated on the aromatic ring, were not isolated, although trace amounts were detected by HRMS.

[12] The olefin-to-olefin transfers of bromiranium and iodiranium ions are known, see: a) A. J. Bennet, R. S. Brown, R. E. D. McClung, M. Klobukowski, G. H. M. Aarts, B. D. Santarsiero, G. Bellucci, R. Bianchini, *J. Am. Chem. Soc.* **1991**, *113*, 8532; b) R. S. Brown, R. W. Nagorski, A. J. Bennet, R. E. D. McClung, G. H. M. Aarts, M. Klobukowski, R. McDonald, B. D. Santarsiero, *J. Am. Chem. Soc.* **1994**, *116*, 2448; c) A. A. Neverov, R. S. Brown, *J. Org. Chem.* **1996**, *61*, 962; d) R. S. Brown, *Acc. Chem. Res.* **1997**, *30*, 131; e) S. E. Denmark, M. T. Burk, A. J. Hoover, *J. Am. Chem. Soc.* **2010**, *132*, 1232.

[13] At this stage, all efforts to recover or detect catalysts **5** following their reactions have failed. However, we believe that *trans*-cyclooctenes **5** act as catalysts on the basis of the reasonable reaction profiles displayed in Scheme S1 and the results of control experiments summarized in Table 1 and Table S1 in the Supporting Information.

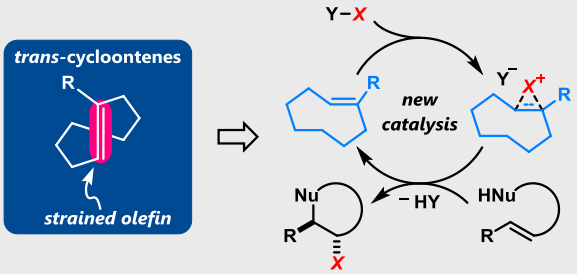
[14] At this stage, optically active forms of *trans*-cyclooctenes **5** failed to realize enantioselectivity in the halolactonization reactions presented herein (see Scheme S3 in the Supporting Information for details). We are currently optimizing catalyst structures for asymmetric catalysis in our laboratory.

10.1002/anie.201808320

WILEY-VCH

Entry for the Table of Contents

COMMUNICATION



Shunsuke Einaru, Kenta Shitamichi, Tagui Nagano, Akira Matsumoto, Keisuke Asano, and Seijiro Matsubara**

Page No. – Page No.

***trans*-Cyclooctenes as Halolactonization Catalysts**

The strained olefins in *trans*-cyclooctenes serve as efficient catalysts for halolactonizations, including bromolactonizations and iodolactonizations. The *trans*-cyclooctene framework is essential for excellent catalytic performance, and the substituents also play important roles in determining efficiency. These results represent the first demonstration of catalysis by a *trans*-cyclooctene; hence, these findings offer new functional-group-design entries for molecular catalysts.