RESEARCH ARTICLE

trans-Cyclooctenes as Scavengers of Bromine Involved in Catalytic Bromination

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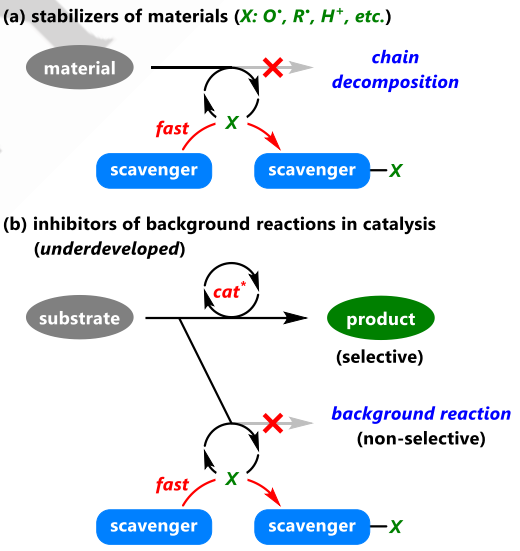
Abstract: Scavengers that capture reactive chemical substances are used to prevent the decomposition of materials. However, in the field of catalysis, the development of scavengers that inhibit background pathways has attracted little attention, although the concept will open up an otherwise inaccessible reaction space. In catalytic bromination, fast non-catalyzed background reactions disturb the catalytic control of the selectivity, even when using *N*-bromoamide reagents, which have a milder reactivity than bromine (Br_2). Here, we developed a *trans*-cyclooctene (TCO) bearing a 2-pyridylethyl group to efficiently retard background reactions by capturing Br_2 in bromocyclization using *N*-bromosuccinimide. The use of less than a stoichiometric amount of the TCO was sufficient to inhibit non-catalyzed reactions, and mechanistic studies using the TCO revealed that in situ-generated Br_2 provides non-catalyzed reaction pathways based on a chain mechanism. The TCO is useful as an additive for improving enantioselectivity and regioselectivity in catalytic reactions. Cooperative systems using the TCO with selective catalysts offer an alternative strategy for optimizing catalyst-controlled selectivity during bromination. Moreover, it also served as an indicator of Br_2 involved in catalytic reaction pathways; thus, the TCO was useful as a probe for mechanistic investigations into the involvement of Br_2 in bromination reactions of interest.



Scheme 1. Scavengers of reactive chemical substances.

Introduction

Scavengers that capture reactive chemical substances have been widely used to prevent the oxygen-, radical-, or proton-induced decomposition of materials, for example, as food additives,[1] polymerization inhibitors,[2] and organic solvent stabilizers,[3] among others (Scheme 1a). Agents such as 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) are useful probes for trapping key reactive species, providing fruitful insights into mechanistic studies on chemical reactions.[4] However, in the field of catalysis, developing scavengers for inhibiting background pathways has attracted little attention (Scheme 1b), although undesired non-catalytic reactions frequently occur concomitantly with desired catalytic reactions. To overcome the influences of background reactions on catalyst-controlled selectivity, several methods have been developed by making catalytic pathways much faster than non-catalytic background pathways (Figure

1a).[5,6] However, the scope of the strategy is limited, and other concepts that impede the background pathways using scavengers (Scheme 1b and Figure 1b)[7] will open up an otherwise inaccessible space for selective catalytic reactions.

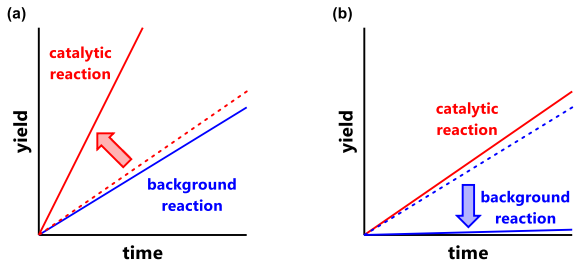


Figure 1. Concepts on alleviation of influences of concomitant non-catalyzed background pathways in catalytic reactions.

Bromination is an indispensable synthetic reaction because bromo-organic compounds are useful not only as functional molecules such as bioactive compounds,[8] electronic materials,[9] catalysts,[10] etc., but also as fundamental synthetic intermediates.[11] Classically, bromine (Br_2) was used as a brominating reagent;[12] subsequently, *N*-bromoamides such as *N*-bromosuccinimide (NBS) have been frequently used as Br_2 surrogates. They are safe, stable, and easy to handle under mild conditions,[13] but Br_2 is generated in situ from their thermal or photochemical degradation and is useful as a reactive species in various bromination reactions.[14] Meanwhile, the reactivity of *N*-bromoamides is also used for the catalytic control of selectivity because it is suppressed compared to that of Br_2. However, bromination often involves fast, non-catalyzed background reactions, even when using *N*-bromoamide reagents,[5] and it is possible that in situ-generated Br_2 is a reactive brominating species that causes non-catalyzed reactions (Figure 2). Reactions of Br_2 with substrates yield not only brominated products but also hydrogen bromide (HBr) as a byproduct, which then reacts with the remaining *N*-bromoamides, such as NBS, to generate another amount of Br_2, thereby leading to chain processes that cause quantitative background reactions. Thus, Lewis basic agents (LB) that rapidly capture Br_2 and diminish its reactivity might retard background reactions; however, such agents are unknown.

LB should be able to capture Br_2 faster than the substrates. Thus, we hypothesized that *trans*-cyclooctene (TCO) derivatives would be useful because their strained olefins have soft and high Lewis basicity and can rapidly capture soft cationic elements. Actually, the Lewis basicity of *trans*-cycloocten-5-ol was utilized to capture sulfenium ions as a chemical biology tool to probe the level of oxidative stress in live cells (Scheme 2a).[15] In this method, the hydroxy group at the 5-position is also important for irreversibly capturing thiiranium ion intermediates. However, based on the hypothesis shown in Figure 2, this type of molecular design is inadequate for retarding background bromination because the intramolecular attack by a pendant protic nucleophile yields HBr, which then generates another amount of Br_2 (Scheme 2b). To impede chain processes involving Br_2, both bromiranium and bromide ions should be captured. Therefore, we focused on a TCO bearing aprotic nucleophilic substituents (Scheme 2c). This molecule can capture both bromiranium and bromide ions as ion pairs. In this study, we developed a TCO bearing a 2-pyridylethyl group to efficiently inhibit background reactions during the bromocyclization of an allylic amide[5] by capturing Br_2. In addition, cooperative systems for selective catalysis were proposed using the TCO to retard non-selective background reactions and selective catalysts for enantioselectivity and regioselectivity. Furthermore, the TCO was used as an indicator of the involvement of Br_2 in a catalytic reaction pathway, which is useful as a probe for mechanistic studies.

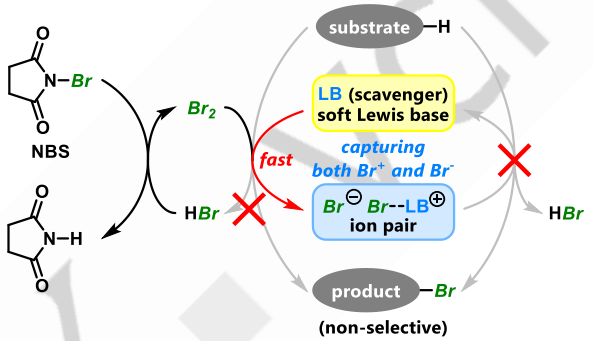
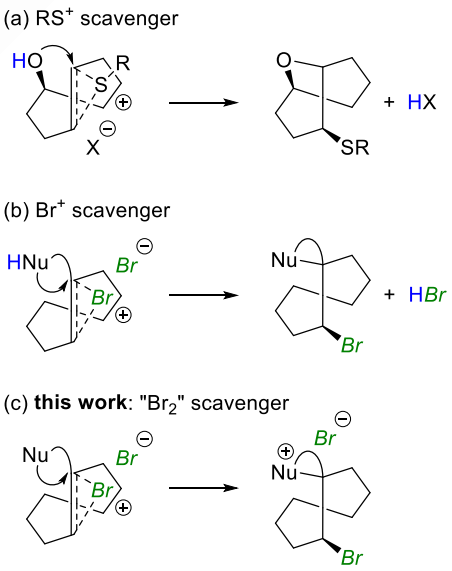


Figure 2. Working hypothesis for inhibition of background bromination pathways.



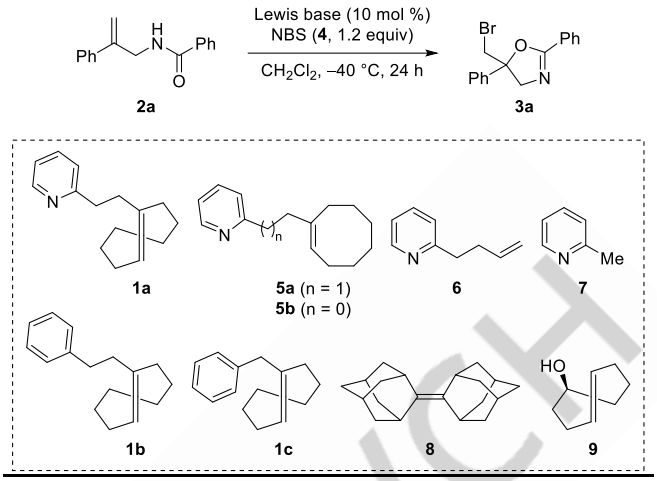
Scheme 2. Design of TCOs for capturing soft cationic elements.

Results and Discussion

Inhibition Effects of *trans*-Cyclooctenes.

Various TCO derivatives were investigated based on the design shown in Scheme 2c (Table 1). Optimization studies revealed that TCO **1a** bearing a 2-pyridylethyl group[16] exhibited excellent inhibitory effects on the bromocyclization of allylic amide **2a** using NBS (**4**) (Table 1, entries 1 and 2). Notably, 10 mol % of **1a** was sufficient to completely suppress the reaction, which proceeded quantitatively in the absence of **1a**. Other Lewis bases were also investigated. The corresponding *cis*-cyclooctene (CCO) **5a** and acyclic olefin **6** bearing 2-pyridylethyl groups were less effective than **1a**, whereas 2-picoline (**7**) did not work (Table 1, entries 1–3, 5, and 6), indicating the importance of the strained olefin moiety. CCO **5b**, bearing a 2-pyridylmethyl group, was much less efficient than **5a** (Table 1, entries 3 and 4); thus, the tether lengths in **1a** and **5a** were also important. TCOs without pendant pyridyl groups were then investigated and found to be less efficient than **1a** (Table 1, entries 2, 7, and 8). TCO **1b** bearing a phenethyl group was relatively effective, whereas TCO **1c** bearing a benzyl group was much less efficient. We have previously reported that **1b** and **1c** also serve as catalysts to activate *N*-bromoamide reagents, including **4**,[17] and **1c** is more active than **1b** as a catalyst, which is consistent with the current results showing that **1c** was less effective than **1b** as an inhibitor. These results indicated that **1a** preferentially captured Br_2 rather than the activation of **4**, thereby leading to a higher performance of **1a** than **1b** and **1c**. In addition, adamantylidene-adamantane (**8**) did not retard the reaction (Table 1, entry 9), which is consistent with the fact that the isolated bromiranium ion of **8** was used as a reactive brominating agents.[18] Moreover, as expected in Scheme 2b, *trans*-cycloocten-5-ol (**9**) did not possess inhibitory effects (Table 1, entry 10), indicating the negative influence of the generation of HBr. Indeed, the addition of pyridine hydrobromide significantly accelerated the reaction in the presence of **1a** (Table 1, entries 2 and 11). A variety of other Lewis bases possessing olefins, pyridines, etc. were also assayed,[19] but **1a** was still the most effective. These investigations revealed that the performance of **1a**, which consists of a TCO structure and a 2-pyridylethyl group, is remarkable.

Table 1. Inhibitory effects of different Lewis bases.[a]



Entry	Lewis base	Yield [%]
1	none	99
2	**1a**	<1
3	**5a**	8
4	**5b**	97
5	**6**	37
6	**7**	99
7	**1b**	3
8	**1c**	99
9	**8**	99
10	**9**	99
11	**1a** + py·HBr (10 mol %)	90

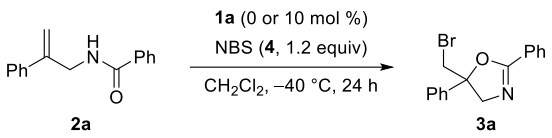
[a] Reactions were run using **2a** (0.10 mmol), **4** (0.12 mmol), and the Lewis base (0.010 mmol) in CH_2Cl_2 (2.0 mL).

Br_2 as the Reactive Species of Non-Catalyzed Pathways.

Hamashima et al. reported that an analogous reaction system contains a fast, non-catalyzed background pathway, although the mechanism of the background reaction is unclear.[5b] Thus, we investigated the mechanism of the non-catalyzed reaction based on the hypothesis shown in Figure 2 and the results in Table 1. To investigate the effects of Br_2 contained in **4**, recrystallized **4** was used for the reaction (Table 2). The recrystallization of **4** slowed the non-catalyzed reaction despite incomplete inhibition, indicating that Br_2 was the reactive species (Table 2, entries 1 and 2). In addition, in the presence of **1a**, the reactions were completely suppressed regardless of the recrystallization of **4**. These results demonstrate that it is difficult to completely remove Br_2 from **4** by recrystallization and that **1a** is more effective in inhibiting the background reaction involving Br_2.

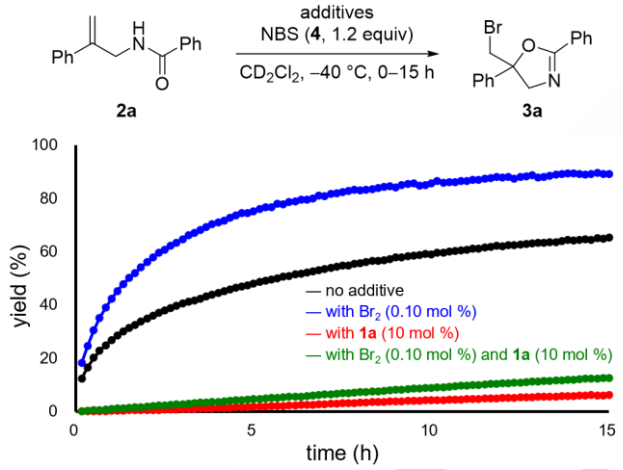
Next, the effects of Br_2 on the reaction profiles were investigated by ^1H NMR analysis of the reaction mixtures (Scheme 3). The addition of 0.10 mol % of Br_2 largely accelerated the reaction (Scheme 3, black and blue). In addition, these reactions diminished in the presence of **1a** even when Br_2 was also added (Scheme 3, red and green). These results indicate that a small amount of Br_2 causes a large acceleration of the reaction through the chain processes proposed in Figure 2; thus, less than the stoichiometric amount of **1a** was sufficient to stop the reaction (Table 1, entry 2). Furthermore, we conducted Raman analyses of the mixture of Br_2 and **1a** in acetonitrile at –40 °C (Figure 3).[20] A signal associated with Br_2 disappeared after adding the 1.0 equivalent of **1a**, indicating that Br_2 was consumed by **1a**.[21]

Table 2. Effects of recrystallization of **4** and **1a**.[a]



Entry	NBS (**4**)	**1a**	Yield [%]
1	not recrystallized	without	99
2	recrystallized	without	52
3	not recrystallized	with	<1
4	recrystallized	with	<1

[a] Reactions were run using **2a** (0.10 mmol), **4** (0.12 mmol), and **1a** (0 or 0.010 mmol) in CH_2Cl_2 (2.0 mL).



Scheme 3. Effects of Br_2 on reaction profiles.

Isolation of Salt 10.

Next, we focused on the structural analysis of the ion pair generated by the reactions of **1a** and Br_2. After stirring the mixture of **1a** and Br_2 at –40 °C for 5 min, workup followed by purification through gel permeation chromatography (GPC) enabled the isolation of a salt as a colorless oil compound in 25% yield (Scheme 4).[22,23] High-resolution mass spectrometry analysis (electronspray ionization in positive mode) of the isolated compound detected a cation of **10** (Scheme 4, found, *m/z* 294.0849, 296.0829; calcd for $[M–Br]^+$, 294.0852, 296.0831). The results of the 1D-NOESY and ^1H-^{13}C HMBC analyses were consistent with the structure of **10** (see Schemes S5 in the Supporting Information for details). The reactivity of **10** was investigated, and **10** did not brominate **2a** at –40 °C and 25 °C for 24 h, while Br_2 quantitatively reacted even at –40 °C for 10 min (Table 3). These results support our proposal shown in Figure 2; intramolecular attack by the pyridyl group of **1a**, which opens the three-membered bromiranium ion, is important for reducing reactivity. Actually, **8** did not work as an inhibitor (Table 1, entry 9) while it is known to form the corresponding three-membered bromiranium ion, which is stable enough to be isolated.[24]

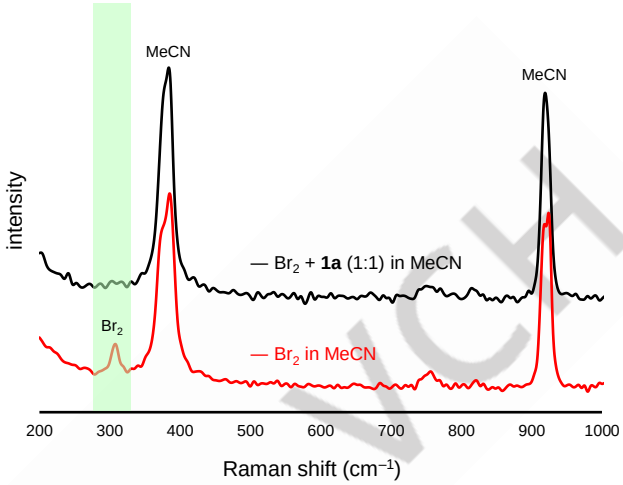
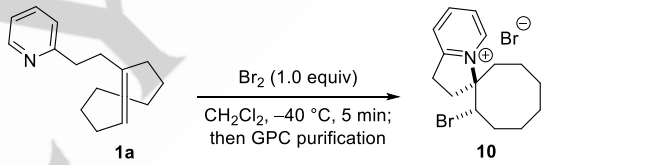
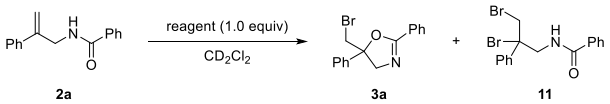


Figure 3. Raman analyses of the mixture of Br_2 and **1a**.



Scheme 4. Synthesis and isolation of **10**.

Table 3. Reactivity of **10** and Br_2.[a]

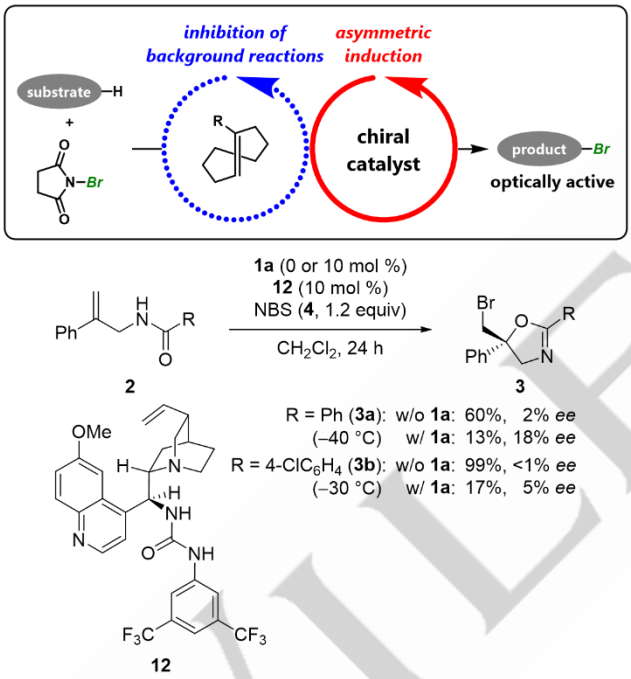


Entry	Reagent	Temp [°C]	Time	**3** + **11** [%]
1	Br_2	–40	10 min	99
2	**10**	–40	24 h	<1
3	**10**	25	24 h	<1

[a] Reactions were run using **2a** (0.036 mmol) and the reagent (0.036 mmol) in CH_2Cl_2 (0.78 mL).

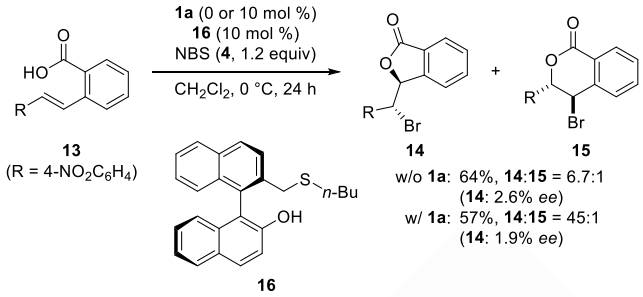
Cooperative Systems in Selective Catalysis.

Based on the ability of **1a** to inhibit non-catalyzed bromination by capturing Br_2, we designed a cooperative system for asymmetric catalysis using **1a** to retard non-selective background reactions and a chiral catalyst for enantioselectivity (Scheme 5). After preliminary optimization,[25] the chiral catalyst **12** provided a proof-of-concept. In the absence of **1a**, **3a** was obtained with a 60% yield and 2% *ee*. However, in the presence of **1a**, the enantioselectivity improved to 18%, while the reaction rate decreased and yielded **3a** in 13% yield. Substrate **2b** bearing a 4-chlorophenyl group also provided **3b** in 17% yield with 5% *ee* in the presence of **1a**, while racemic **3b** was obtained quantitatively in the absence of **1a**. These results indicate that **1a** deactivates Br_2 to inhibit the non-selective background pathway, whereas **12** activates **4** to accelerate the enantioselective pathway. This method provides an alternative strategy for optimizing catalytic asymmetric bromination when fast, non-catalyzed background reactions occur.



Scheme 5. Cooperative system in asymmetric catalysis.

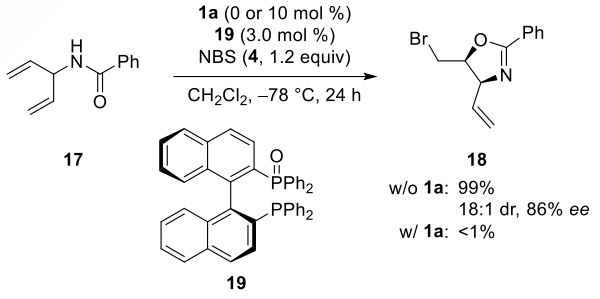
A cooperative system was further developed for regioselective catalysis (Scheme 6).[6c] Shirakawa et al. reported bifunctional sulfide-catalyzed bromolactonization using **4** as a reagent to selectively form 5-membered ring products, while a non-catalytic reaction using Br_2 as a reagent was revealed to yield a 6-membered ring product. We used **1a** as an additive in the bromolactonization of **13** with catalyst **16**, and the regioselectivity was improved. With **1a**, the products were obtained in 57% yield with 45:1 regioselectivity, although the reaction without **1a** resulted in a 64% yield with 6.7:1 regioselectivity. These results exhibit the generality of the cooperative systems, which can improve a range of catalyst-controlled selectivity.



Scheme 6. Cooperative system in regioselective catalysis.

A Probe of Br_2 for Mechanistic Studies.

Agents that make reactive species dormant are useful for mechanistic studies to identify the key reactive species in unknown organic reactions. For example, nitroxyl radicals such as TEMPO have been used as spin-trapping agents in radical reactions.[4a] Thus, we hypothesized that **1a** may be used as a probe in mechanistic studies of Br_2-involved bromination. Hamashima et al. recently reported an asymmetric reaction involving Br_2 in the catalytic pathway,[5d] and it was revealed that this reaction did not proceed in the absence of Br_2. Thus, we examined the addition of **1a** to Hamashima's reaction under conditions that generated Br_2 in situ (Scheme 7). As expected, 10 mol % of **1a** inhibited the reaction, whereas the reaction proceeded quantitatively in the absence of **1a**. These results demonstrate that **1a** is also useful as a probe for Br_2 in mechanistic investigations on the involvement of Br_2 in both the non-catalytic and catalytic bromination pathways.



Scheme 7. Probe of involvement of Br_2 in BINAP monoxide-catalyzed bromocyclization.

Conclusion

In summary, we developed the TCO bearing a 2-pyridylethyl group to efficiently retard the background reactions by capturing Br_2 in the bromocyclization of the allylic amide using **4**. Notably, the use of less than stoichiometric amounts of the TCO was sufficient to inhibit non-catalyzed reactions, and the mechanistic studies using the TCO revealed that in situ-generated Br_2 causes non-catalyzed reaction pathways based on the chain mechanism. In addition, the TCO, as an additive, improved the

enantioselectivity and regioselectivity of catalytic reactions. The cooperative systems using the TCO with selective catalysts offer alternative methods for optimizing catalyst-controlled selectivity in bromination reactions that suffer from non-selective background reactions. Moreover, it also served as an indicator of Br_2 involved in the catalytic reaction pathway. Thus, the TCO was demonstrated to be useful as a probe for mechanistic studies to determine whether Br_2 is involved in bromination reactions of interest. We believe that an unutilized reaction space will be opened by expanding the concept of impeding background reaction pathways using molecular scavengers in catalytic systems.

Experimental Section

Procedure for asymmetric bromocyclization of 2a: TCO **1a** (2.2 mg, 0.010 mmol) and substrate **2a** (24 mg, 0.10 mmol) were sequentially added to a 2-neck 20-mL flask. Chiral catalyst **12** (5.8 mg, 0.010 mmol) was additionally added. Under argon atmosphere, CH_2Cl_2 (1.6 mL) was added. The mixture was stirred at –40 °C for 15 min. NBS (**4**, 21 mg, 0.12 mmol) was added, and the flask wall was washed with cold CH_2Cl_2 (0.40 mL). The mixture was stirred at –40 °C for 24 h, and saturated aqueous $Na_2S_2O_3$ was added using a syringe pump (2.0 mL, 0.50 mL/min) at the same temperature. The resulting mixture was stirred at –40 °C for 1 h, and H_2O was added using a syringe pump (5.0 mL, 0.50 mL/min) at the same temperature. The resulting mixture was stirred at ambient temperature for 1 h, and CH_2Cl_2 (5.0 mL) and H_2O (5.0 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. $CDCl_3$ (1.0 mL) and 1,1,2,2-tetrachloroethane as an internal standard were added, and the yield was determined using ^{1}H NMR analyses. The enantiomeric excess was determined using chiral HPLC analyses after purification of the crude product by PTLC using hexane/EtOAc (v/v = 5:1) as an eluent.

Supporting Information

Experimental procedures, results of additional investigations, characterization data, NMR spectra, and HPLC chromatogram profiles of synthesized compounds. The authors have cited additional references within the Supporting Information.[26–33]

Acknowledgements

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Keywords: background reaction • bromine scavenger • probe • selective catalysis • *trans*-cyclooctene

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[21] The mixtures of **1a** and more than 1 equivanent of Br_2 exhibited the signal associated with Br_2. In addition, ^{1}H NMR analyses of the mixtures of Br_2 and **1a** provided consistent results. See Schemes S2 and S3 in the Supporting Information for details.

[22] The NMR analysis of the crude mixture of the reaction in Scheme 4 revealed **1a** was completely consumed, but there were side-products although they were unable to be isolated. Therefore, the isolated yield of the major product **10** was 25% after careful purification through GPC.

[23] A corresponding salt was generated as a single diastereomer through the reaction of *trans*-cyclooctene **1a** and I_2. In addition, the reaction of *cis*-cyclooctene **5a** and I_2 yielded the same diastereomer of the salt. These results suggest the reactions of **1a** with Br_2 and I_2 provide the corresponding salts through an S_N1 mechanism, while the reactions of **5a** provide them through an S_N2 mechanism. See Scheme S4 in the Supporting Information for details.

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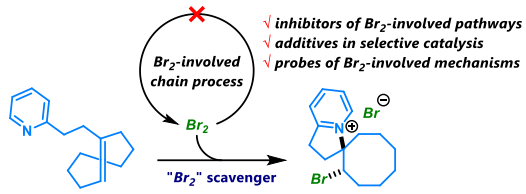
Entry for the Table of Contents



A *trans*-cyclooctene (TCO) bearing a 2-pyridylethyl group was developed to retard non-catalyzed reactions in bromination using *N*-bromosuccinimide by capturing in situ-generated bromine (Br_2), which was revealed to cause background reactions. The TCO is useful as an additive for improving catalyst-controlled selectivity and as a probe to investigate the involvement of Br_2 in catalytic bromination.

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