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Catalytic Desymmetrization of Cyclohexadienes by Asymmetric Bromolactonization

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ABSTRACT

Asymmetric bromolactonization of prochiral cyclohexadiene derivatives with *N*-bromosuccimide proceeded in the presence of $(DHQD)_2PHAL$ as a chiral catalyst to afford the corresponding bromolactones with up to 93% ee. This reaction was also applicable to the kinetic resolution of a racemic cyclic ene-carboxylic acid, where the starting material was recovered with high enantioselectivity.

Halolactonization of unsaturated carboxylic acids is a versatile transformation in organic synthesis, particularly for the preparation of natural products.[1] Therefore, considerable efforts have been made to develop efficient methods for catalytic asymmetric halolactonization.[2,3] In 2010, an important breakthrough yielded an organocatalytic system that is highly effective for halolactonization, with broad generality and excellent enantioselectivity (more than 90% ee).[4] Since then, several groups have reported elegant systems that use carefully designed organocatalysts.[5] However, the range of available substrates is still limited; only aryl-substituted penteno- or hexenoic acid derivatives were examined in most cases. During the course of our synthetic studies on natural products,[6] we became interested in the asymmetric desymmetrization of cyclohexadiene derivatives by bromolactonization (eq 1). This reaction can construct three contiguous stereogenic centers at once, including a chiral quaternary carbon center. Furthermore,

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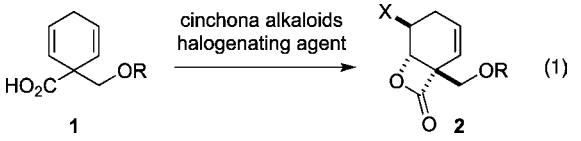
since the products are highly functionalized, they should be useful chiral building blocks in the synthesis of complex natural products. Notably, when we started our project, there had been no example of catalytic asymmetric halolactonization of prochiral cyclic dienes.[7] Quite recently, however, Martin and his co-workers documented the first example of such a reaction in their paper on asymmetric bromolactonization with their BINOL-derived bifunctional catalyst. But, they examined only one specific substrate, namely cyclohexa-2,5-dienecarboxylic acid, and the observed enantioselectivity was only modest.[8] Therefore, improvement in the reaction efficiency in terms of the substrate range and enantioselectivity remains important. In this communication, we report desymmetrization of prochiral cyclic dienes by catalytic bromolactonization with $(DHQD)_2PHAL$ to afford the corresponding lactones in up to 93% ee. Moreover, we found that our catalytic system was applicable to a racemic cyclic ene-carboxylic acid; this is the first example of kinetic resolution in halolactonization, to our knowledge.



With our synthetic targets in mind, we selected cyclic dienoic acid **1** having a quaternary carbon center as a model substrate, which was readily synthesized from benzoic acid via reductive alkylation under Birch conditions, followed by basic deprotection.[9,10] As the brominating agent, we chose relatively inexpensive *N*-bromosuccimide (NBS), since we intended to carry out future synthetic reactions on a large scale.

Based on previous reports,[4,5] we examined the reaction with various natural and unnatural chiral amines and less polar solvent systems. We soon found that the dimeric structure of cinchona alkaloid catalysts was essential to promote the reaction in an enantioselective manner (Figure 1). On the other hand, monomeric cinchona alkaloid catalysts gave negligible asymmetric induction.

As shown in Table 1, the reaction proceeded best in the presence of $(DHQD)_2PHAL$[11] (**3a**) (10 mol %) in a 1:1 mixture of chloroform and *n*-hexane. It is noteworthy that the protecting group of the primary alcohol of **1** had a significant impact on the stereoselectivity. Although the reaction of nonprotected **1a** proceeded smoothly at −40 °C, a racemic mixture of β-lactone **2a**[6] was formed (Table 1, entry 1). This was not associated with a background reaction, since no reaction proceeded at −40 °C in the absence

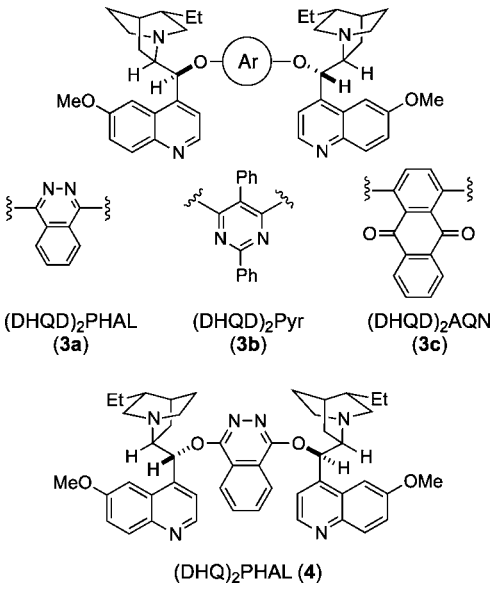


Figure 1. Selected examples of chiral catalysts examined.

of **3a**. Next, we examined the protecting group of the substrate. As shown in entries 2−4, the ee was greatly improved by an appropriate protecting group. It is likely that the bulkiness of the protecting group is important for discriminating the two prochiral olefins. Reactions of **1c** and **1d** reached completion within 1 h, and the desired bromolactones were isolated in good yield with excellent enantioselectivity (88 and 91% ee, respectively). Although the ee was slightly improved at −60 °C (entry 5), we selected −40 °C as the optimal reaction temperature because of the shorter reaction time. The absolute configuration of **2c** was determined to be (1*R*,5*S*,6*S*) by comparing the optical rotation with that of a reported compound after conversion, as described below.

We also examined reactions catalyzed by related cinchona alkaloids (entries 6, 7). Even though the same dihydroquinidine (DHQD) is incorporated, the reaction efficiency changes dramatically, depending on the linker moiety. We speculate that the nitrogen atom(s) of the phthalazine linker would play an important role in determining the stereoselectivity, but this issue requires further study. Importantly, we were able to obtain the corresponding enantiomer with a similar enantiomeric excess (86% ee) by changing the catalyst **3a** to pseudoenantiomeric **4** (entry 8).

Other brominating agents often examined in previous reports[4,5] were also tested with our substrate. Although the reactions were less enantioselective, the reactions with *N*-bromophthalimide (NBP), 2,4,4,6-tetrabromocyclohexadienone (TBCO), and *N,N*′-dibromodimethyl hydantoin (DBDMH) occurred to give the corresponding product (NBP: 61%, 66% ee; TBCO: 72%, 81% ee; DBDMH: 91%, 61% ee). In contrast, *N,N*′-dichlorodimethylhydantoin (DCDMH) did not react with **1d**. This is interesting because the combination of **3a** with DCDMH was reported to be effective for the chlorolactonization of

(7) For a stoichiometric reaction, see: Nishibayashi, Y.; Srivastava, S. K.; Takada, H.; Fukuzawa, S.; Uemura, S. *J. Chem. Soc., Chem. Commun.* **1995**, 2321.

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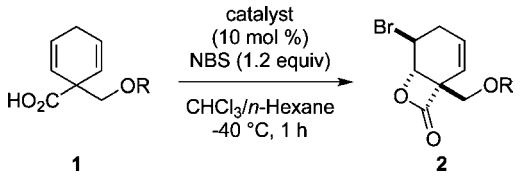
(10) See Supporting Information for the preparation of compounds **1**.

(11) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 448.

Table 1. Optimization of the Reaction Conditions



entry	R	catalyst	yield (%)	ee (%)
1	H (**1a**)	**3a**	70	0
2	Boc (**1b**)	**3a**	84	45
3	TIPS (**1c**)	**3a**	87	91
4	TBDPS (**1d**)	**3a**	93	88
5[a]	**1d**	**3a**	91	93
6	**1d**	**3b**	66	77
7	**1d**	**3c**	57	24
8[b]	**1d**	**4**	91	−86

[a] −60 °C, 24 h. [b] $(DHQ)_2PHAL$ (**4**) was used.

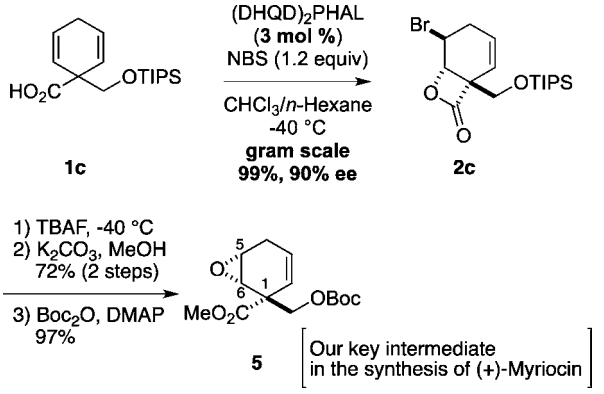
4-phenyl-4-pentenoic acid.[4a] Taken together, these findings indicate that the optimum reaction conditions vary depending on the nature of the substrate, and the development of a general catalytic system remains elusive.

As shown in Scheme 1, our reaction was easy to scale up. The reaction could be carried out without any precautions against air and moisture. It was also possible to reduce the catalyst amount to as little as 3 mol %, and the desired product was obtained without difficulty. It should be noted that simple acid−base liquid−liquid extraction was sufficient to obtain the product in almost pure form. The obtained **3c** was readily converted via a three-step sequence to epoxide **5**, which is a key intermediate in our total synthesis of (+)-myriocin.[6]

Under the optimized reaction conditions, we next examined the effect of substituents on the cyclohexadiene ring (Figure 2).[12] A substrate having a methyl group at the C4 position underwent the desired reaction to give **6** in good yield with high enantioselectivity. Although the bulkier MOM-oxy group retarded the reaction, reasonably high asymmetric induction was observed for compounds **7** and **8**. Reactions of less bulky substrates (**9** and **10**) were less enantioselective. We also tested the reaction of the 3,5-dimethylcyclohexadiene substrate. In this case, γ-lactone **11** was unexpectedly formed with only 37% ee, probably due to the formation of an electronically more stable tertiary carbocation intermediate.[13]

To further investigate the generality of the reaction, we examined the formation of brominated γ-lactones (Scheme 2). Thus, one-carbon-homologated cyclohexadiene derivatives **12** were prepared and subjected to asymmetric bromolactonization. Under the same conditions as described in Table 1, reactions of **12a** and **12b** proceeded regioselectively, affording the corresponding

Scheme 1. Gram Scale Preparation of **3c** and Further Transformation



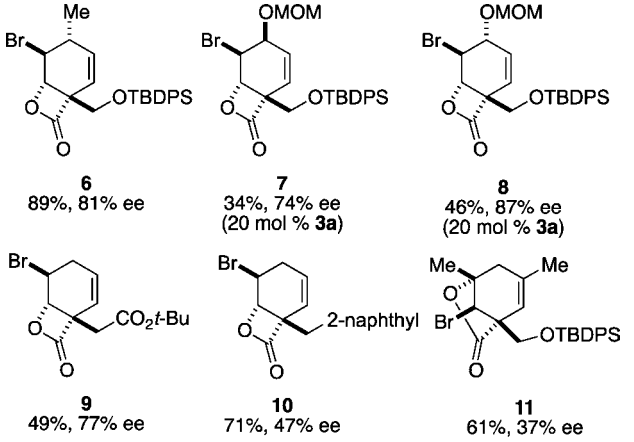


Figure 2. Desymmetrization of various cyclic dienes via asymmetric bromolactonization.

γ-lactones **13a** and **13b** with excellent enantioselectivity (92% ee, respectively).[14,15]

Finally, we demonstrated optical resolution[16] of racemic compounds by asymmetric bromolactonization, which has never before been reported, to our knowledge. As shown in Scheme 3, our catalytic system showed high enantiodifferentiation ability, allowing kinetic resolution of cyclic ene-carboxylic acid **14** derived from 1-naphthalenecarboxylic acid. In this reaction, $(DHQD)_2Pyr$ (**3b**)

(12) To avoid the difficulty in the isolation and detection by UV light, we chose a TBDPS group as a protecting group in Figure 2, even though the TIPS-protected substrate gave the best enantioselectivity in Table 1.

(13) Barnett, W. E.; Needham, L. L. *J. Org. Chem.* **1975**, *19*, 2843.

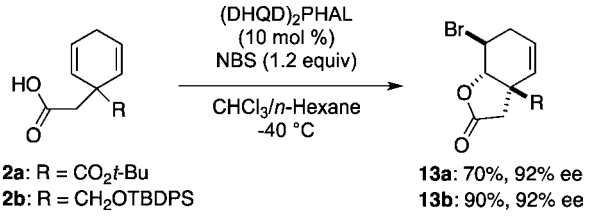
(14) While the reaction catalyzed by **3a** took place regioselectively, spontaneous reaction at room temperature gave an inseparable 2:1 mixture of γ-lactone and δ-lactone.

(15) In contrast to the formation of β-lactones, it is likely that the steric size of the substituent at the C1 position has minimal influence on the enantioselectivity, because both substrates were converted in a highly enantioselective manner. See also Figure 2.

(16) (a) Keith, M. J.; Larrow, F. J.; Jacobsen, N. E. *Adv. Synth. Catal.* **2001**, *343*, 5. (b) Robinson, D. E. J. E.; Bull, S. D. *Tetrahedron: Asymmetry* **2003**, *14*, 1407. (c) Rendler, S.; Oestreich, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 248. (d) Wills, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4264.

(17) Reaction in $CHCl_3$ gave unreacted **14** with 39% ee in the case of **3a**, while **3b** gave 78% ee at 50% conversion.

Scheme 2. Formation of Optically Active γ-Lactones[a]

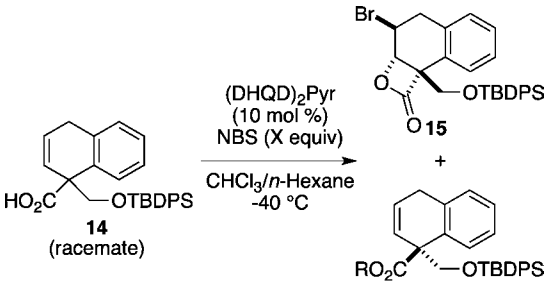


[a] The absolute stereochemistry was tentatively assigned by analogy to the reaction shown in Scheme 1.

was superior to $(DHQD)_2PHAL$ (**3a**).[17] The reaction with 0.5 equiv of NBS afforded β-lactone **15** with 86% ee, with the remaining starting material **14** being recovered as the corresponding methyl ester with similar enantioselectivity (84% ee). Thus, we next examined the amount of NBS. When 0.6 equiv of NBS was reacted with **14**, **15** was isolated in 55% yield with 78% ee. Gratifyingly, the starting carboxylic acid **14** was obtained in 39% yield with excellent enantioselectivity (92% ee). Since a variety of unsymmetrically substituted cyclohexadienes can be synthesized from commercially available benzoic acid derivatives, we expect that kinetic resolution by bromolactonization would be a potentially useful method to access novel chiral building blocks.

In summary, we have developed a catalytic desymmetrization of cyclohexadiene derivatives via asymmetric bromolactonization. Not only β-lactones but also γ-lactones were produced in a highly enantioselective manner. Additionally, the reaction was applicable to kinetic resolution of racemic cyclic ene-carboxylic acids. Since the products are densely functionalized, this reaction is expected to be valuable in synthetic studies of complex natural products. Recently, we have completed the total synthesis

Scheme 3. Kinetic Resolution by Asymmetric Bromolactonization.[a]



	15	(–)-16
X = 0.5, 10 h:	38%, 86% ee	48%, 84% ee
X = 0.6, 24 h:	55%, 78% ee	39%, **92% ee**

[a] The absolute stereochemistry was tentatively assigned by analogy to the reaction shown in Scheme 1.

of (−)-sphingofungin E from the epoxide **5**, the results of which to be reported in due course.

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Supporting Information Available. Experimental procedures and analytical data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.