Communication

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Enantioselective Halo-oxy- and Halo-azacyclizations Induced by Chiral Amidophosphate Catalysts and Halo-Lewis Acids

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Supporting Information Placeholder

ABSTRACT: Catalytic enantioselective halocyclization of 2-alkenylphenols and enamides have been achieved through the use of chiral amidophosphate catalysts and halo-Lewis acids. DFT calculations suggested that the Lewis basicity of the catalyst played an important role in the reactivity and enantioselectivity. The resulting chiral halogenated chromans can be transformed to α-tocopherol, α-tocotrienol, Daedalin A and Englitazone in short steps. Furthermore, a halogenated product with an unsaturated side chain may provide polycyclic adducts under radical cyclization conditions.

Biologically active compounds with a chiral chroman skeleton are abundant in nature and synthetic analogues (Figure 1a).[1] In addition to the well-known Vitamin E family (**1**[2], **2**[3]), small synthetic chiral chromans have also been shown to be effective against hyperpigmentation (**3**[4]), metabolic disorders (**4**[5], **5**[6]) and cancers (**6**[7]). Asymmetric catalysis has recently emerged as a powerful method for building the chiral chroman skeleton.[8] In constructing chiral chromans, it is important to control the stereoselectivity at position 2. We proposed that enantioselective halocyclizations of certain 2-alkenylphenols **7** could deliver chiral centers at position 2 (Figure 1b). Enantioselective alkene halogenation has been a subject of intense investigation over the past decade.[9–13] Although enantioselective halolactonizations have been well-documented, enantioselective cyclizations of **7** are still limited to some polyene systems.[10l,m] One major issue in the development of catalytic asymmetric alkene halogenations is the rapid racemization of chiral haliranium ions through olefin-to-olefin haliranium transfer.[14] Chiral nucleophilic base-catalyzed halofunctionalizations have been shown to be effective over the past decade because of the coordination effect.[15] However, there are important differences between iodonium and bromonium ions: 1) The ionic radius of iodonium ion is much longer than that of bromonium ion;[16] 2) Iodonium ion forms a stronger halogen bond with Lewis bases;[17] 3) While both iodonium and bromonium ions can form haliranium ions with alkenes, their stabilities and reactivities are quite different,[18] and thus the same nucleophilic catalysts do not work equally well in different halogenations.[9b,10j,n,11a,b] We have previously reported the cooperative activation system of I_2 using chiral phosphate catalysts and halo-Lewis acids for the enantioselective iodolactonization.[9f] However, the substrate scope is limited to 4-arylmethyl-4-pentenoic acids. Here, we describe an efficient, enantioselective, and site-selective (in the presence of multiple olefins) iodo- and bromocycloetherification of **7** to construct chiral chromans using chiral Lewis basic amidophosphate catalysts **9** (Lb*) and halo-Lewis acids (X–L). Moreover, the broad applicability of this catalytic system for not only halo-oxycyclization but also halo-azacyclization is demonstrated.

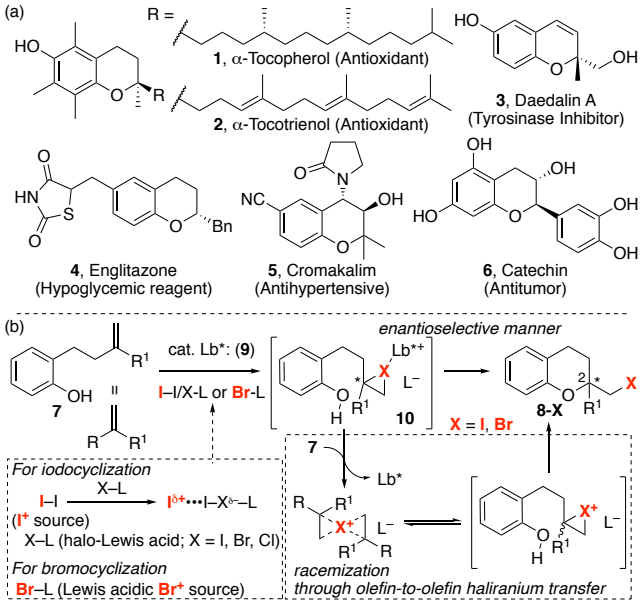
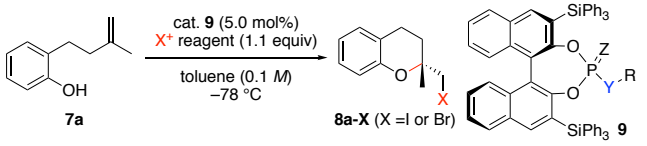


Figure 1. (a) Natural products or synthetic analogues containing chiral chromans. (b) Strategies for constructing chiral chromans through enantioselective halo-oxycyclization using chiral Lewis base catalysts and halo Lewis acids.

We initiated enantioselective halo-oxycyclization of 2-alkenylphenol **7a**. For the iodo-oxycyclization, I_2 was used as the iodine source in the presence of BINOL-derived phosphoric acid derivative **9** as a catalyst and Lewis acidic *N*-chlorosuccinimide (NCS).[19] For the bromo-oxycyclization, 1,3-dibromo-5,5-dimethylhydantoin (DBH) was used as the Lewis acidic bromine source in the absence of any other halo-Lewis acidic additives because of high reactivity of DBH (Table 1). The previous chiral phosphate triester catalyst **9a** promoted iodocyclization in 85% ee (entry 1).[9f] On the other hand, the electron-donating substituents of triesters **9b** and **9c** contributed to increase the ee values (entries 2 and 3). Interestingly, the amidophosphate **9d** catalyzed the iodocyclization more efficiently than triesters **9a–c** to provide chroman **8a-I** with 97% ee (entry 4). DFT calculations suggested that amidophosphates are more electron-rich than phosphate triesters, and electron-donating substituents increased the electron density. The stronger Lewis base catalyst **9** should form a more stable intermediate **10** that may help to suppress olefin-to-olefin racemization. Moreover, the N–H protons in amidophosphates were found to be relatively electron-poor.[20] Other approaches, including converting the amine moieties to more bulky (**9f**) or smaller (**9i**) substituents, as well as changing the P=O to P=S (**9g**, **9j**) or P=Se (**9h**) gave lower yields and ee values. As in iodocyclization, chiral amidophosphate catalyst was more efficient in enantioselective bromocyclizations. However, the best catalyst **9d** for iodocyclization did not provide the desired ee in bromocyclization. Surprisingly, the introduction of a bulky group at the *para*-position of the *N*-phenyl moiety in **9d**, dramatically increased the ee (entry 5).

Table 1. Halocycloetherification of 2-Alkenylphenol 7a Catalyzed by Nucleophilic Phosphoric Acid Derivatives[a]



entry	cat. **9** [P(=Z)YR]	yield (%),[d] ee (%)[e] of **8a-X** **8a-I**[b]	**8a-Br**[c]
1	**9a** [P(=O)OC$_6$H$_3$-2,6-Me$_2$]	85, 85	80, 71
2	**9b** [P(=O)OC$_6$H$_2$-2,4,6-Me$_3$]	85, 89	77, 81
3	**9c** [P(=O)OC$_6$H$_2$-4-MeO-2,6-Me$_2$]	95, 92	66, 82
4	**9d** [P(=O)NHC$_6$H$_3$-2,6-Me$_2$]	99, 97	90, 85
5	**9e** [P(=O)NHC$_6$H$_2$-4-*t*-Bu-2,6-Me$_2$]	98, 96	93, 94
6	**9f** [P(=O)NHC$_6$H$_3$-2,6-*i*-Pr$_2$]	84, 89	44, 58
7	**9g** [P(=S)NHC$_6$H$_3$-2,6-Me$_2$]	27, 13	15, 4
8	**9h** [P(=Se)NHC$_6$H$_3$-2,6-Me$_2$]	54, 33	26, 7
9	**9i** [P(=O)NHTf]	99, 9	90, 14
10	**9j** [P(=S)NHTf]	87, 17	10, 25

[a]Reactions were carried out with **7a** (0.10 mmol), **9** (0.0050 mmol), and X^+ reagent (0.11 mmol) in toluene (1 mL) at –78 °C. [b]A mixture of I_2 (0.11 mmol) and NCS (0.11 mmol) was used as I^+ reagent. [c]DBH (0.11 mmol) was used as Br^+ reagent. [d]Isolated yield. [e]Ee values were determined by HPLC analysis.

Based on the X-ray diffraction analysis of **9d** and the absolute configuration of **8-X**,[21] it was assumed that the addition of iodonium ion preferentially occurred on the *si*-face of **7a** to avoid steric repulsion between **7a** and **9d**, as shown in Figure 2. On the other hand, the addition of iodonium ion on the *re*-face of **7a** was sterically disfavored. Although the *para*-substituent effect of the *N*-phenyl moiety of **9e** for enantioselective bromocyclization is not clear, the bulkiness and electron-donating ability might stabilize the transition state close to that shown in Figure 2.

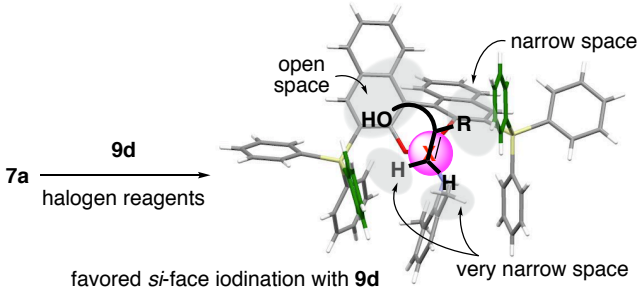


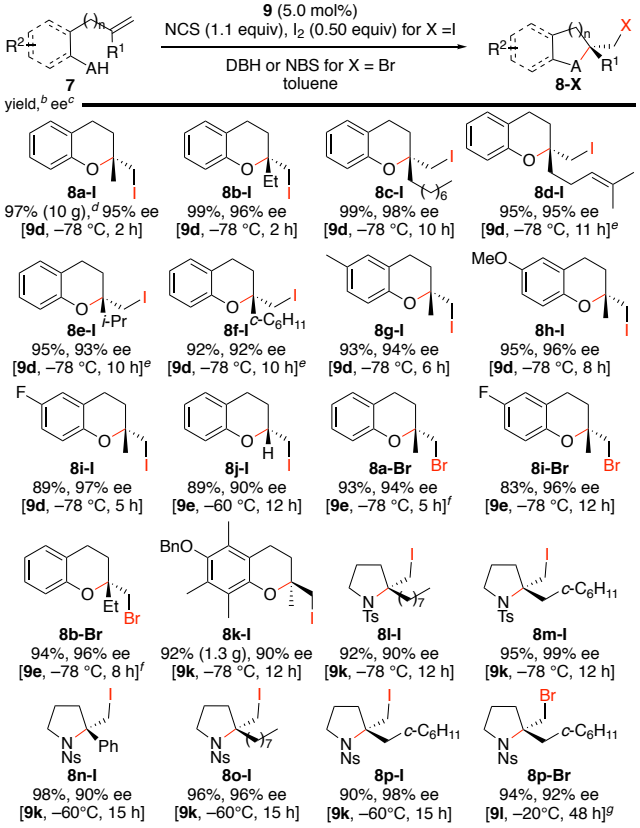
Figure 2. Proposed stereoselective process for halocyclizations using **9d** based on its crystal structure.

BINOL-derived amidophosphates are easily modifiable by replacing the 3,3'-substituents and amino moieties. Through the optimization of catalysts, we found that this system was suitable for both halo-*O*-cyclization and halo-*N*-cyclization. Representative examples are listed in Tables 2 and 3. Generally, excellent yields (89–99%) and enantioselectivities (91–98% ee) were observed for iodocycloetherification of 2-alkenylphenols with alkyl side chains that varied from methyl to cyclohexyl groups (Table 2, **7a–f**) in the presence of catalyst **9d**.[22] In particular, chiral chroman **8a-I** was obtained on a 10-gram scale in the presence of only 0.50 mol% of **9d**. Moreover, **8d-I** was obtained as a single product, and exhibited excellent chemoselectivity for terminal over internal olefins. The *para*-substituted phenols **7g**~**7i** were also suitable for use in this reaction. However, when **7j** (R^1 = H) was used as a substrate, the reactivity dropped (the reaction occurred only at temperatures higher than –60 °C), and catalyst **9e** was effective for achieving high enantioselectivity. As stated in Table 1, **9e** was effective for bromocyclization to give chiral chromans **8a-Br**, **8i-Br**, and **8b-Br** in high yields and ee values. On the other hand, for the enantioselective iodocyclization of sterically bulky 2-alkenylphenol **7k**, 3,3'-di(9-anthryl)BINOL-derived catalyst **9k** was effective. Interestingly, the inverted asymmetric induction was observed due to the steric bulkiness of **7k**.[21]

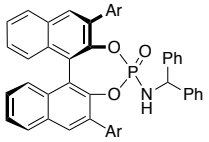
Furthermore, catalyst **9k** worked very well in the iodocyclization of unsaturated amides **7l**~**7p** to give enantioenriched pyrrolidines **8l-I**~**8p-I** in high yields and enantioselectivities.[22] Both alkyl and aryl side chains were acceptable.[9h,10b] Although both Ts and Ns protective groups were useful in the iodocyclization, the more electron-deficient Ns group was necessary for the high enan-

tioselectivity in bromocyclization to **8p-Br**.[10b] Moreover, catalyst **9k** was modified to **9l**, which possesses a 10-aryl-substituent on the 9-anthryl group for bromocyclization. We proposed that steric repulsion between the 10-aryl group and the amine moiety might change the angles of 3,3-substituents, which would increase the steric effect around the phosphine oxide.

Table 2. Asymmetric Halocyclization of 2-Alkenylphenols and Unsaturated Amides 7[a]



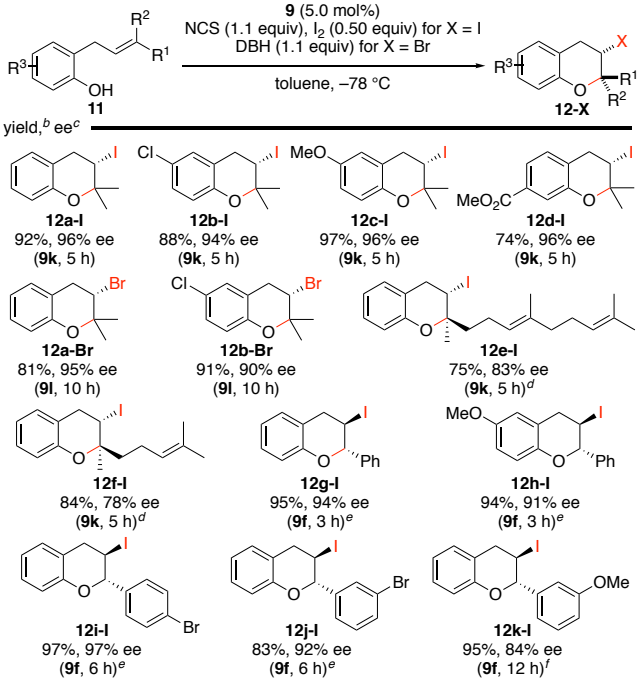
[a]Unless otherwise stated, reactions were carried out with substrate **7** (0.10 mmol) and **9** (0.0050 mmol) in toluene (1 mL). [b]Isolated yield. [c]Ee values were determined by HPLC analysis. [d]0.50 mol% of **9d** was used. [e]NIS was used in place of NCS. [f]DBH was used. [g]NBS was used.



9k: Ar = 9-anthryl
9l: Ar = 10-(4-*t*-Bu-C_6H_4)-9-anthryl

Table 3 presents the scope of internal olefins **11** that undergo *endo*-cyclization to give chiral halogenated chromans **12-X**. Catalysts **9k** and **9l** were effective for the iodo- and bromocyclization of 2-(3,3'-dialkylallyl)phenols **11**, respectively.[22] Neither electron-deficient nor electron-rich substituents at the *para*- or *meta*-positions on the hydroxyphenyl group of **11** influenced the high enantioselectivities (**12a-X**~**12d-X**).[21] In the case of polyenylphenols such as **11e** and **11f**, the carbon–carbon double bond closest to phenols selectively reacted to give chiral chromans with unsaturated side chains in good yields and enantioselectivities. However, iodocyclization did not proceed for 2-(3-arylallyl)phenols **11g**~**11k** under the same conditions as in Table 2. When a bromo-Lewis acid such as DBH or NBS was used in place of NCS, desired chiral chromans **12g-I**~**12k-I** were obtained in high yields with high enantio- and *anti*-selectivities. Interestingly, asymmetric induction in the cyclization of **11g**~**11k** was opposite to that of **11a**~**11f**.[21]

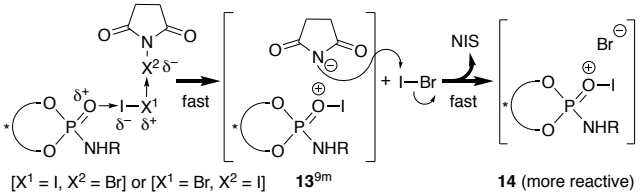
Table 3. Asymmetric Halocycloetherification of 11



[a]Unless otherwise stated, reactions were carried out with substrate **7** (0.10 mmol) and **9** (0.0050 mmol) in toluene (1 mL). [b]Isolated yield. [c]Ee values were determined by HPLC analysis. [d]NIS was used in place of NCS. [e]DBH was used in place of NCS. [f]NBS was used in place of NCS.

Based on the results of an NMR study, we confirmed that IBr and NIS were generated from the mixture of molecular iodine and NBS at ambient temperature.[23] Indeed, 0.2 equiv. of IBr and 1.1 equiv. of NIS with catalyst **9f** (5 mol%) efficiently promoted the iodocyclization of **11g** in high yield with high enantioselectivity.[24] These results suggest that a highly reactive species **14** was generated from **9f**, IBr and NIS (Scheme 1). First, the dual activation of I_2 with **9f** and NBS/DBH or the dual activation of *in situ*-generated IBr with **9f** and NIS provided iodonium species **13**,[23,24] which has been previously reported.[9f] However, **13** would be immediately transformed to species **14** because the succinimide anion preferred to react with IBr to give NIS. Thus, the enan-

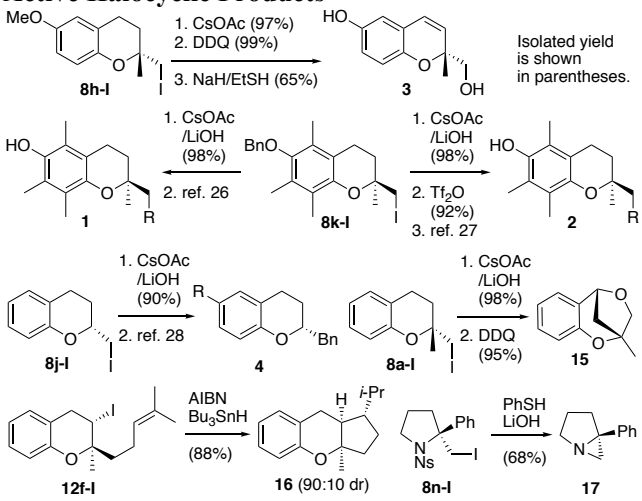
Scheme 1. Proposed New Active Species 14 from 13



tioselective iodocyclization of **11g** proceeded *via* species **14**, which was more electrophilic than **13**.[25]

Halogenated chiral chromans and halopyrrolidines are useful building blocks and synthetic intermediates (Scheme 2). Compound **8h-I** could be transformed to Daedalin A **3** through a 3-step process. Key intermediates in the synthesis of Vitamin E (**1**[26] and **2**[27]) and Englitazone **4**[28] could be obtained from **8k-I** and **8j-I**. In addition, a bicyclic adduct **15** was obtained from **8a-I** through DDQ oxidation. In particular, **12f-I** underwent radical cyclization to give a tricyclic adduct **16** with high diastereoselectivity. Although further improvement of the enantioselectivity is needed, we believe that this method is an efficient alternative approach for obtaining polycyclic compounds. Finally, halopyrrolidine **8n-I** could be transformed to chiral aziridine **17** through a known method.[10b]

Scheme 2. Synthetic Transformation of Optically Active Halocyclic Products



In conclusion, we have developed an efficient enantioselective iodo- and bromocyclization for the construction of chiral chromans and pyrrolidines using chiral amidophosphate catalysts based on the same strategy. Several natural products and key synthetic intermediates could be obtained through the easy transformation of halocyclic products. Experimental results and DFT calculations suggested that the nucleophilicity of the catalysts plays an important role in the enantioselectivity. Based on the results of NMR studies and control experiments, we proposed a new highly reactive species from catalyst, I_2 and NBS. Apparently, a deeper chiral cavity around the halonium ion is required to induce high enantioselectivity in bromocyclization compared to iodocyclization. Further studies will be needed to fully elucidate the reaction mechanism.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, spectroscopic data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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19. We previously reported that a halo-Lewis acid activated molecular iodine to promote iodocyclization. See reference 9f. The screening of halo-Lewis acids is described in SI (Section 1, Tables S1~4).
20. See details of DFT calculations in SI (Section 2, Table S5).
21. For the determination of the absolute configuration of **8h-I**, **8j-I**, **8k-I**, **8n-I**, **12b-I**, and **12g-I** and the proposed models for the asymmetric induction, SI (Section 4).
22. Iodocyclization of unsaturated aliphatic alcohol and aromatic amides gave the corresponding cyclic products with moderate ee values. Bromocyclization of **7a**, **7h**, and **11i** did not proceed successfully. For detail, see SI (Schemes S2 and S3).
23. IBr might be initially generated from I_2, **9f** and NBS/DBH at –78 °C under the optimized conditions of iodocyclization.
24. NIS does not directly react with **9f** to give **13** under the reaction conditions, because the **9f**-catalyzed cyclization of **7a** with NIS did not occur at all without I_2 in toluene at –78 °C. Thus, the possibility that **9f** attacks NIS directly to generate **13** is excluded.
25. See details in SI (Section 3, Table S6) for the screening of halo-Lewis acids and reactions using IBr. Although the iodocyclization of **11g** proceeded quite quickly with IBr even in the absence of catalyst, 0.20 equiv. of IBr was used for the enantioselective iodocyclization catalyzed by **9f**.
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