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# Catalytic Asymmetric Bromocyclization of Polyenes

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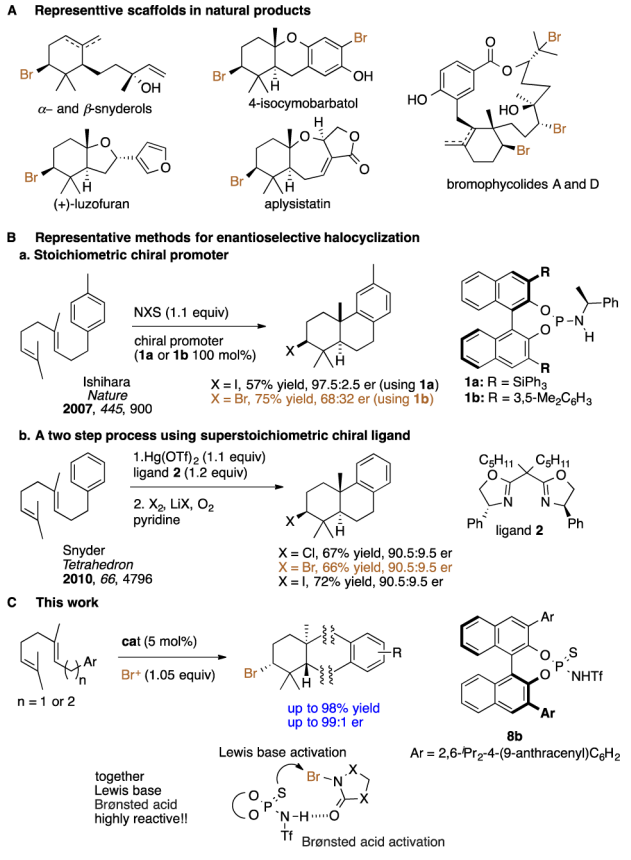
Supporting Information

**ABSTRACT:** The first catalytic asymmetric bromonium ion-induced polyene cyclization has been achieved by using a chiral BINOL-derived thiophosphoramide catalyst and 1,3-dibromo-5,5-dimethylhydantoin as an electrophilic bromine source. Bromocyclization products are obtained in high yields, with good enantiomeric ratios and high diastereoselectivity, and are abundantly found as scaffolds in natural products.

Thousands of polycyclic natural products containing halogen atoms have been isolated from marine sources with a particularly high abundance of bromine atoms.[1−4] Carbocycles containing a halogen atom with geminal disubstituents are ubiquitous in terpenoid natural products (Scheme 1A). Nature makes such molecules by a mechanism that is initiated by an electrophilic halogenation onto a double bond. Being enzymes, haloperoxidases produce electrophilic halogens, which trigger the formation of halogenated polycyclic terpenoids in an enantioselective manner.[5] Bromonium ion-induced cyclization of polyenes and cation−$\pi$ cyclization of preformed bromohydrine were developed in the 1970s to mimic the biosynthesis of halogenated terpenoids in racemic form, though in low yields.[6−9] Vanadium haloperoxidase has also been used for bromocyclization of geraniol and nerol.[10] Development of new reagents, such as $IPy_2BF_4$ by Barluenga et al.[11,12] and $Et_2SBr{\cdot}SbCl_5Br$ and its iodo and chloro variant by Snyder et al.,[13−15] has improved the yield of halocyclization reactions. While the racemic variant is well developed, asymmetric electrophilic halocyclization of polyenes to synthesize halogenated polycyclic terpenoids in optically active forms in the laboratory is highly demanding.

**Scheme 1. Asymmetric Bromocyclization**




The first asymmetric iodocyclization (Scheme 1B-a) was reported by Ishihara et al.[16] A stoichiometric amount of chiral phosphoramidite (**1a**, **1b**) was used as a chiral promoter, and the attempt at bromocyclization was unsuccessful (75% yield, 68:32 er).[17−20] Snyder et al. achieved the bromocyclization of polyenes by using a two-step method (Scheme 1B-b): enantioselective mercuration using 1.2 equiv of chiral ligand **2** and bromo-demercuration.[15] In contrast to these two stoichiometric methods, development of a catalytic method for asymmetric electrophilic halocyclization of polyenes has great potential.[20] Numerous catalysts have been developed for halofunctionalization of olefins with both internal and external nucleophiles. In all cases, they are heteroatoms (haloetherification, halolactonization, haloamination, etc.),[21−42] and the olefins are activated by nucleophiles, which has recently been studied by Borhan et al.[43] We have developed a catalytic asymmetric method for bromonium ion-induced polyene cyclization using a chiral thiophosphoramide catalyst.

The initial experiment was started with homogeranyltoluene **3a** as the standard substrate for polyene cyclization, using phosphoric acids or phosphoric acid derivatives as catalyst and *N*-bromosuccinimide (NBS) as an electrophilic bromine source, and the results are summarized in Scheme 2. Under the reaction conditions, the completely cyclized product **5a** was formed, together with partially cyclized products **4a** and **4b** (**4a**:**4b**:**5a** = 5.1:1.0:5.3). The crude reaction mixture was treated with chlorosulfonic acid ($ClSO_3H$) to promote the fully cyclized product **5a**. Chiral thiophosphoramides that have been developed and exploited as strong Brønsted acids in numerous reactions by our group[44,45] worked excellently in bromocyclization reactions. BINOL-derived chiral thiophosphoramide **8a**, with 2,4,6-triisopropylphenyl (TRIP) substituents at the

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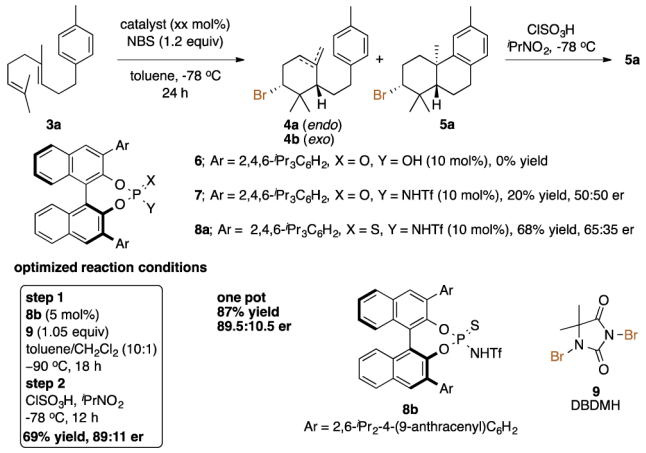
**Scheme 2. Optimization of Bromocyclization Reactions**



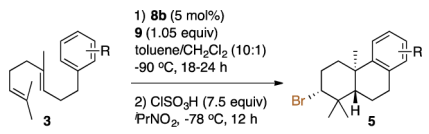

3,3′-position, delivered the desired product **5a** in a 68% yield with a low enantiomeric ratio (er) (65:35). In spite of having similar acidity, phosphoramide[46,47] **7** delivered the bromocyclization product **5a** in a low yield (20%) and with no selectivity (50:50 er). Therefore, we believe that the Lewis basicity of sulfur plays an important role, together with the Brønsted acidity of thiophosphoramide (Scheme 1C). Screening of various BINOL-derived chiral thiophosphoramide catalysts, solvents, reaction temperatures and electrophilic bromine sources was carried out extensively. Using catalyst **8b**, having 2,6-diisopropyl-4-(9-anthracenyl)phenyl substituents at the 3,3′-position, toluene/$CH_2Cl_2$ (10:1) as a solvent, and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH), **9**, as an electrophilic bromine source at −90 °C with an 18 h reaction time and an additional 12 h for treatment with $ClSO_3H$ in $^iPrNO_2$ delivered the product **5a** in a 69% yield with an 89:11 er. The yield was improved by performing two steps in one pot (87% yield and 89.5:10.5 er) (see Supporting Information for detailed optimization studies).

Using the optimized conditions, several homogeranylbenzene derivatives were examined. Compounds with both electron-withdrawing and -donating substituents on the aromatic ring (para-substituted) as well as unsubstituted benzene, **3a**−**3d**, were reacted to give the products **5a**−**5d** in good yields and with high er values (up to 91:9 er) (see Table 1). Substitution at the 3,5-positions of the arene ring with methyl groups, **3e**, had a negligible effect, while substitution with methoxy groups, **3f**, gave a bromocyclization product having additional bromination in the aromatic ring, **5f**, with slightly increased enantioselectivity (92.5:7.5 er). Introduction of one additional methoxy group, 3,4,5-trimethoxy-homogeranylbenzene, **3g**, gave the bromocyclization product **5g** in a high yield and with very high enantioselectivity (97:3 er).

Geranylphenol derivatives are another class of highly important but challenging substrates for bromonium ion-induced cyclization reactions resulting in low diastereo- and enantioselectivity.[20] 2-Geranylphenol, **10a**, was cyclized under optimized bromocyclization conditions to a single diastereomer, **11a**, in an 84% yield and with 90:10 er (Table 2); additional treatment by $ClSO_3H$ was not required.

Likewise, 4-substituted geranylphenols **10b**−**10d** delivered the bromocyclization products **11b**−**11d** as a single diastereomer with high yields and enantioselectivities (up to 93.5:6.5 er). 1-Geranyl-2-naphthol, **10e**, was cyclized to give **11e** as a

**Table 1. Scope of Bromocyclization for Different Homogeranylbenzenes**




| entry | substrate | product | yield | er |
|---|---|---|---|---|
| 1 | **3a**; R = Me | **5a**; R =Me | 69%<br>87%[a] | 89:11<br>89.5:10.5[a] |
| 2 | **3b**; R = H | **5b**; R = H | 70%<br>98%[a] | 90:10<br>89:11[a] |
| 3 | **3c**; R = F | **5c**; R = F | 69%<br>94%[a] | 91:9<br>89:11[a] |
| 4 | **3d**; R = OMe | **5d**; R = OMe | 44% | 87:13 |
| 5 | **3e** | **5e** | 64% | 89.5:10.5 |
| 6 | **3f** | **5f** | 76% | 92.5:7.5 |
| 7[b] | **3g** | **5g** | 81% | 97:3 |

All the reactions were performed on 0.1 mmol scale unless otherwise specified. Step 1: **3** (0.1 mmol), **8b** (0.005 mmol), **9** (0.105 mmol), toluene/$CH_2Cl_2$ (10:1, 4 mL) at −90 °C for 18 to 24 h. Step 2: $^iPrNO_2$ (2.0 mL), $ClSO_3H$ (0.75 mmol) at −78 °C for 12 h. Yields of the isolated products are given. Enantiomeric ratios (er) were determined by chiral HPLC. For compounds **5a**, **5b**, **5c**, and **5d**, the minor diastereomer was formed in >10:1 ratio, determined by $^1H$ NMR of the crude reaction mixture. [a]One-pot, two-step process; after the first step, $ClSO_3H$ (0.75 mmol) was added to the same reaction mixture, and stirring continued at −78 °C for 12 h. [b]Performed on 0.05 mmol scale. **5g** was isolated and characterized after the first step.

single diastereomer in a 58% yield and with 94:6 er. Surprisingly, 6-geranyl-2,4-dimethoxyphenol, **10f**, underwent cyclization via aromatic substitution to produce a [6,5,6]-fused ring product, **11f**, as a single diastereomer in 91% yield and with excellent enantioselectivity (99:1 er).

When this bromocyclization reaction was conducted on a 1 mmol scale, the products **5b** and **11d** were obtained with identical enantioselectivities but with slightly lower yields (Table 3). An increased yield and slightly lower enantioselectivity were obtained for product **5a**. Gratifyingly, the enantiomeric ratio of **5a** could be improved to 98.5:1.5 after single recrystallization.

Intriguingly, when geranylbenzene **12** was subjected to bromocyclization conditions, compound **13a** was formed in a 65% yield and with 93:7 er, together with the formation of compound **13b** in a 17% yield and with low enantioselectivity (63:37 er) (Scheme 3A). This clearly shows that a common bromonium ion intermediate cannot be involved, but much more likely the chiral thiophosphoramide remains bound to the bromonium ion, and the two diastereomeric complexes lead to different amounts of the product isomers.[48] These pathways,


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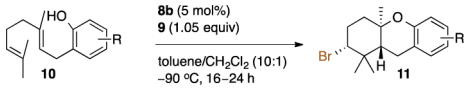
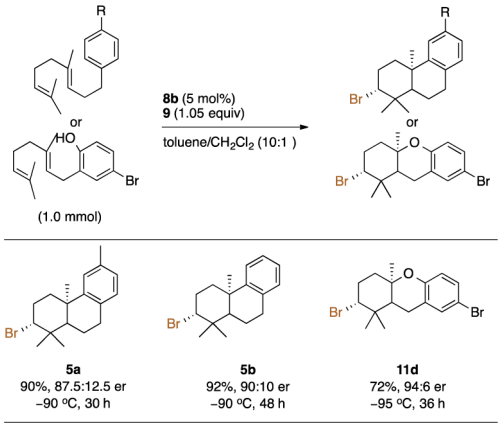
**Table 2. Bromocyclization of Geranylphenols**



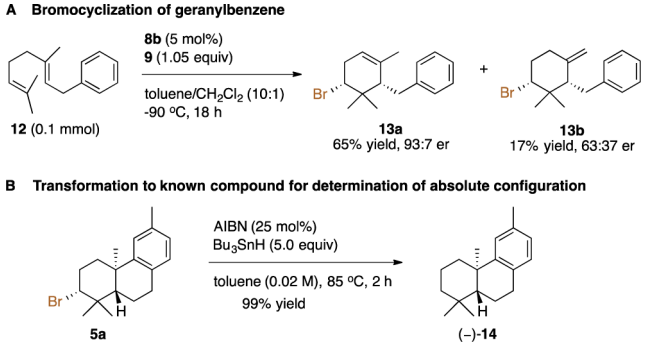

| entry | substrate | product | yield | er |
|---|---|---|---|---|
| 1 | **10a**; R = H | **11a**; R = H | 84% | 90:10 |
| 2 | **10b**; R = Me | **11b**; R = Me | 71% | 89.5:10.5 |
| 3 | **10c**; R = OMe | **11c**; R = OMe | 41% | 84.5:15.5 |
| 4 | **10d**; R = Br | **11d**; R = Br | 85% | 93.5:6.5 |
| 5 | **10e** | **11e** | 58% | 94:6 |
| 6 | **10f** | **11f** | 91% | 99:1 |

All the reactions were performed on 0.1 mmol scale: **10** (0.1 mmol), **8b** (0.005 mmol), **9** (0.105 mmol), toluene/$CH_2Cl_2$ (10:1/4 mL) at −90 °C for 16 to 24 h. Yields of the isolated products are given. Enantiomeric ratios (er) were determined by chiral HPLC.

**Table 3. Scale-Up Experiments**




**Scheme 3. Bromocyclization of Geranylbenzene and Determination of Absolute Configuration**




responsible for the formation of the partial cyclization products competing for the formation of the fully cyclized product, resulted in low enantioselectivity after treatment with $ClSO_3H$ to promote the completed cyclization product. For substrates having highly electron-rich arenes, the formation of partially cyclized products is minimized, which is consistent with the increased er obtained for highly activated arenes in the case of both homogeranyl benzene derivatives (97:3 er) and geranylphenols (99:1 er).

Compound **5a** was converted to a known compound, (−)-**14** (Scheme 3B), and from its specific rotation value, the absolute configuration of **5a** was determined.[49] The absolute configurations of **11a**−**11d** were determined by comparing the specific rotation value known in the literature.[20] Other compounds were assigned in analogy.

In conclusion, we have developed the first catalytic asymmetric halocyclization method for bromonium ion-induced polyene cyclization. A wide variety of homogeranyl benzene derivatives were cyclized with very high enantioselectivities (up to 97:3 er). Geranylphenols delivered the bromocyclization products as single diastereomers in good yields and with high enantioselectivities (up to 99:1 er). Detailed mechanistic studies and applications of this method to natural product synthesis are currently ongoing in our laboratory, and theoretical calculation is on our agenda.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b13193.

Experimental details and characterization data (PDF)

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### Notes

The authors declare no competing financial interest.

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