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Enantioselective bromocyclization of 2-geranylphenols induced by chiral phosphite–urea bifunctional catalysts

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Enantioselective bromocyclization of 2-geranylphenols induced by chiral phosphite–urea bifunctional catalysts†

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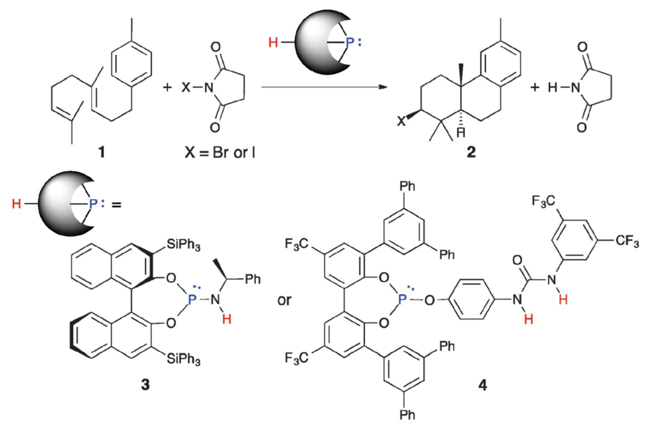
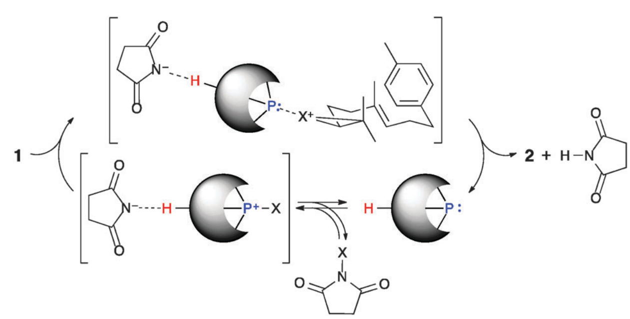
Chiral phosphite–urea bifunctional catalysts have been developed for the enantioselective bromocyclization of 2-geranylphenols with *N*-bromophthalimide (NBP) for the first time. The chiral triaryl phosphite moiety activates NBP to generate a bromophosphonium ion. On the other hand, the urea moiety interacts with a hydroxyl group of the substrate through hydrogen bonding interactions. Enantioselectivity is effectively induced through two-point attractive interactions between the catalyst and the substrate.

Optically active bromine-containing natural products isolated from marine organisms have been shown to possess several bioactivities such as anticancer and antiviral activities.[1] These natural products are biosynthesized by enantioselective bromocyclization induced by enzymes such as vanadium bromoperoxidase (V-BPO).[2] For example, in the biosynthesis of isoaplysin-20, the bromonium ion generated in the active site of V-BPO reacts with the terminal olefin of geranylgeraniol site- and enantioselectively. Subsequent diastereoselective π-cation cyclization gives isoaplysin-20.[3] While the diastereoselective bromocyclization of linear polyprenoids has been studied for about 50 years,[4,5] there have been few reports on the enantioselective bromocyclization of polyprenoids induced by chiral catalysts.[6] In 2010, Snyder and colleagues demonstrated enantioselective bromocyclization with stoichiometric amounts of a $Hg(OTf)_2$–chiral bis(oxazoline) complex.[6a] In 2013, Braddock and colleagues reported that enantiospecific polyene cyclization was initiated by the formation of an enantiopure bromiranium ion.[6b] However, these methods require stoichiometric amounts of promoters or multiple reaction steps.



Scheme 1 Halocyclization of **1** with nucleophilic phosphorous catalysts (our previous results).

Since 2007, we have also developed nucleophilic phosphorous(III) catalysts bearing protic functional groups, **3** and **4**, for the halocyclization of polyprenoids (Scheme 1).[7–14] Catalysts **3** and **4** activate *N*-halosuccinimides (X = I and Br) to generate active halophosphonium salt species *in situ* (Scheme 2). This activation step proceeds smoothly *via* a mechanism that involves catching a succinimide anion with protons of the catalysts under equilibrium.[15] A halophosphonium salt then reacts with polyprenoids at the



Scheme 2 Proposed mechanism (our previous results).

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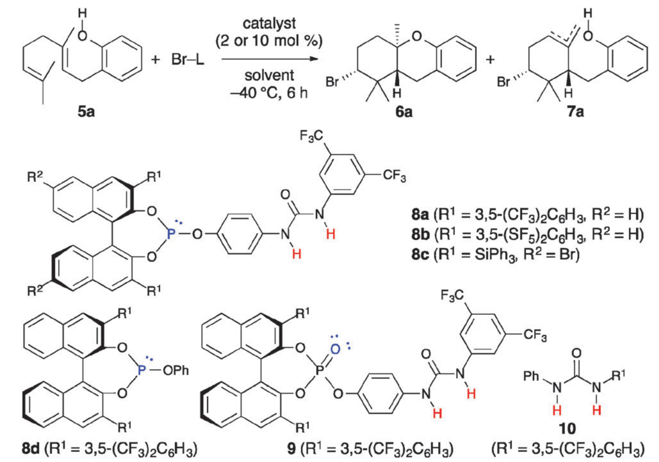
terminal olefin of **1** to mainly give a halogenated *trans*-fused AB-ring product **2**. Chiral phosphoramidite **3** gave an iodinated product **2** (X = I) with high enantioselectivity.[8a] However, a stoichiometric amount of **3** was required to give **2** (X = I) in sufficient yield due to strong acid–base affinity between **3** and succinimide. In contrast, low enantioselectivity was observed in the bromocyclization of **1** using **3** under the same conditions.[8a] More recently, we succeeded in the highly efficient site- and diastereoselective bromocyclization of **1** with the use of a catalytic amount of achiral triaryl phosphite–urea cooperative catalyst **4** to give a brominated product **2** (X = Br) in excellent yield.[8c,d] Nevertheless, we still have not achieved a catalytic enantioselective halocyclization of **1**.

One reason why enantioselective bromocyclization is difficult is that the three-membered cyclic bromiranium ion rapidly transfers to other olefins.[16] In the course of bromiranium ion-olefin transfer, the enantioenriched bromiranium ion is racemized. We envisioned that bromiranium ion-olefin transfer might be suppressed by second non-covalent bonding interaction between a substrate and a catalyst. Here we describe the rational design of chiral phosphite–urea bifunctional catalysts for the enantioselective bromocyclization of 2-geranylphenols.

We first examined the bromocyclization of 2-geranylphenol **5a** using chiral phosphite–urea bifunctional catalysts **8** (Table 1). The reaction was conducted with 1.1 equivalents of *N*-bromosuccinimide (NBS) as the brominating reagent in the presence of 10 mol% of **8a** in toluene at −40 °C for 6 h. As a result, a *trans*-fused brominated AB-ring product **6a** was obtained in 30% yield with 18% ee together with *endo*- and *exo*-isomeric A-ring products **7a** in 56% yield with 39% ee (entry 1).[17,18] A-ring products **7a** could be converted to a diastereomeric mixture of *trans*- and *cis*-fused AB-ring products **6a** (*trans* : *cis* = 3 : 1) by treatment with TfOH, and the enantioselectivity was determined at this stage.[19] Interestingly, products **7a** were obtained with higher enantioselectivity than **6a**. Next, we examined the use of other brominating reagents in place of NBS. Both the reactivity and enantioselectivity were decreased with *N*-bromoacetamide (NBA) (entry 2). In contrast, the use of 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCO) and *N*-bromophthalimide (NBP) slightly increased the enantioselectivity (entries 3 and 4). Thus, we chose NBP because it was less expensive than TBCO. Next, we examined the solvent effect. The enantioselectivity was decreased with chlorobenzene (entry 5) and the reactivity was decreased with mesitylene (entry 6). The use of **8b** gave especially high enantioselectivity for **7a**, while the enantioselectivity of **6a** was decreased (entry 7). Moreover, when the concentration was lowered to 0.02 M, the enantioselectivity was increased to 65% (entry 8). The enantioselectivity was rather decreased when the reaction was cooled to −60 °C (entry 9). This result suggests that catalysts may aggregate under these reaction conditions. The use of 2 mol% of **8b** was also effective, and both **6a** and **7a** were obtained without any loss of enantioselectivity (entry 10). Catalyst **8c** was examined because in our previous studies chiral 3,3′-bis(triphenylsilyl)-1,1′-binaphthol-derived catalysts were effective in inducing high enantioselectivity, such as in the iodo- and protocyclization of polyprenoids[8,9] and iodolactonization.[11c] However, **8c** did not induce high enantioselectivity (entry 11). The use of **8a** was much more effective than the use of **8d** or **8d–10** (entries 12 and 13). Some phosphites [P(III)] are readily oxidized to the corresponding phosphates [P(V)] in the presence of halogenating reagents and moisture or air. Although the reaction was examined using phosphate **9** as a catalyst or without catalysts just in case, **5a** was almost recovered (entries 14 and 15). The absolute configuration of **6a** and **7a** was determined to be (2*R*,4a*R*,9a*R*) by derivatization to a known optically active compound **11a** (Scheme 3).[19]

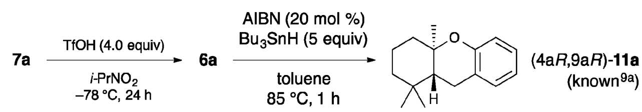
The substrate scope and limitations were investigated under the optimized conditions (Table 2). The results showed that

Table 1 Enantioselective bromocyclization of **5a** with **8a**[a]



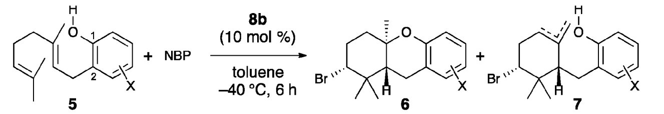
				6a		7a	
Entry	Cat.	Br–L	Solvent	Yield[b] (%)	ee (%)	Yield[b] (%)	ee[c] (%)
1	**8a**	NBS	PhMe	30	18	56	39
2	**8a**	NBA	PhMe	18	13	32	33
3	**8a**	TBCO	PhMe	31	21	55	44
4	**8a**	NBP	PhMe	29	21	57	43
5	**8a**	NBP	PhCl	35	4	40	19
6	**8a**	NBP	1,3,5-$Me_3C_6H_3$	22	24	47	36
7	**8b**	NBP	PhMe	25	16	54	51
8[d]	**8b**	NBP	PhMe	21	19	63	65
9[d,e]	**8b**	NBP	PhMe	21	13	66	61
10[d,f]	**8b**	NBP	PhMe	19	19	60	65
11	**8c**	NBP	PhMe	21	−16	34	−21
12	**8d**	NBP	PhMe	8	—	16	—
13[g]	**8d/10**	NBP	PhMe	29	—	26	—
14	**9**	NBP	PhMe	4	—	5	—
15	—	NBP	PnMe	0	—	0	—

[a] Unless otherwise noted, the reaction of **5a** (0.1 mmol) was conducted with Br–L (1.1 equiv.) in the presence of **8** (10 mol%) in toluene (1 mL) at −40 °C for 6 h. [b] Determined by ^{1}H NMR analysis using tetrachloroethane as an internal standard. [c] Determined after treatment with TfOH (4 equiv.) in i-$PrNO_2$ (0.6 mL) at −78 °C for 24 h. [d] The reaction was conducted in toluene (5 mL). [e] The reaction was conducted at −60 °C. [f] 2 mol% of **8b** was used for 12 h. [g] Each 10 mol% of **8d** and **10** was used.



Scheme 3 Determination of the absolute configuration of **6a** and **7a**.

Table 2 Enantioselective bromocyclization of **5** with NBP catalysed by **8b**[a]



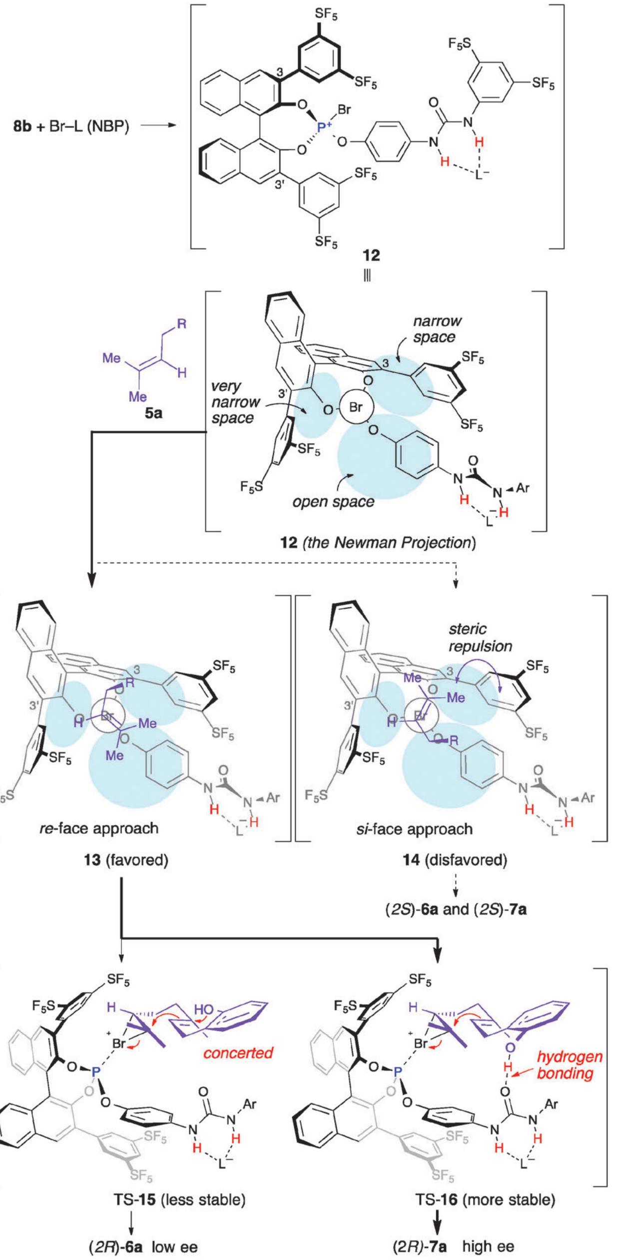
Entry	5 (X)	6	Yield[b] (%)	ee (%)	7	Yield[b] (%)	ee[c] (%)
1	**5b** (4-CF_3)	**6b**	23	29	**7b**	60	66
2	**5c** (4-Br)	**6c**	18	21	**7c**	61	71
3	**5d** (4-OMe)	**6d**	19	20	**7d**	68	67
4	**5e** (4-Me)	**6e**	16	19	**7e**	56	67
5	**5f** (5-Ph)	**6f**	28	13	**7f**	63	65

[a] The reaction of **5** (0.1 mmol) was conducted with NBP (1.1 equiv.) in the presence of **8b** (10 mol%) in toluene (5 mL) at −40 °C for 6 h. [b] Determined by ^{1}H NMR analysis using tetrachloroethane as an internal standard. [c] Determined after treatment with TfOH (4 equiv.) in i-$PrNO_2$ (0.6 mL) at −78 °C for 24 h.

4- or 5-substituted 2-geranylphenols were suitable as substrates. A-ring products **7** were obtained in good yields with good enantioselectivities (65–71% ee). In contrast, AB-ring products **6** were obtained in low yields with low enantioselectivities (13–29% ee).[17] Products **6** and **7** were easily separated by column chromatography on silica gel.

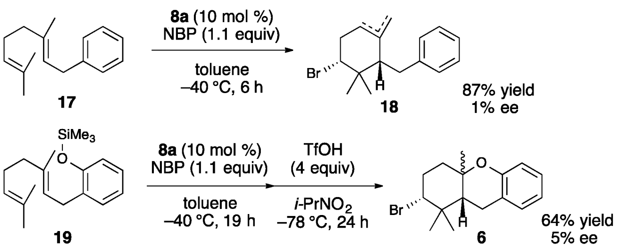
Our proposed mechanism is shown in Scheme 4. First, the bromophosphonium ion intermediate **12** should be generated from **8b** and NBP *in situ*. The geometry of **12** is also shown by the Newman projection viewed along the P–Br bond. The terminal alkenyl moiety of substrate **5a** reacted with the bromonium ion of **12**, which probably minimized steric hindrance for each other. The approach of the bromonium ion to the *Si*-face of **5a** might be disfavored because of steric repulsion between the 3-[3,5-bis(pentafluorosulfanyl)phenyl] group and the dimethylmethylene group of **5a**, as shown in **14**. Therefore, the *Re*-face approach *via* **13** might be favored to give (2*R*)-**6a** and (2*R*)-**7a** enantioselectively.

Next, we considered why A-ring products **7a** were obtained with higher enantioselectivity than AB-ring product **6a** (Table 1 and Scheme 4). The cyclization step to form the A-ring should be different in the reaction pathways to **6a** and **7a** because both enantioselectivities were not identical. The double-cyclization reaction should concertedly occur *via* a transition state (TS) **15**, since **6a** was obtained as only a *trans*-fused diastereomer. If **6a** is formed by a stepwise mechanism, *cis*-fused product **6a** should also be generated as a minor diastereomer. The ee value of **6a** was quite low, probably due to rapid racemization of a chiral cyclic bromiranium ion intermediate[16] or low enantioface discrimination of the terminal alkenyl moiety of **5a** with **8b**. In contrast, A-ring products **7a** were obtained as major products with good enantioselectivity. The deprotonation of a tertiary carbocation intermediate to give **7a** predominantly occurred in place of a second cyclization to give **6a**. Hydrogen bonding interactions between the 2-hydroxyl group of **5a** and the urea moiety of **8b** might dually suppress the second cyclization by decreasing the nucleophilicity of the 2-hydroxy group and controlling its conformation. Furthermore, these interactions might play a role in stabilizing TS-**16** to give **7a** with high enantioselectivity.[20]



Scheme 4 Proposed mechanism for the enantioselective bromocyclization of **5a** with NBP catalysed by **8b**.

To ascertain the significance of the hydrogen bonding in the present catalysis, we examined the bromocyclization of



Scheme 5 Bromocyclization of **17** and **19** with NBP catalysed by **8a**.

geranylbenzene **17** and *O*-protected substrate **19** under the same conditions (Scheme 5). In both cases, the corresponding brominated products were obtained in good yield with very low enantioselectivity. These results suggest that a hydroxyl group plays a crucial role in asymmetric control.

In conclusion, we designed chiral phosphite–urea bifunctional catalysts for the enantioselective bromocyclization of 2-geranylphenol **5**. Catalyst **8b** gave A-ring products **7** in good yield with good enantioselectivity. Subsequent treatment of **6** with TfOH gave the *trans*-fused AB-ring products **6** as major diastereomers. Hydrogen bonding interactions between the urea moiety of **8b** and the 2-hydroxyl group of the substrate strongly supported the enantioselective bromocyclization. Further studies on the catalyst to improve enantioselectivity and catalytic activity and investigation of the detailed reaction mechanism are underway.

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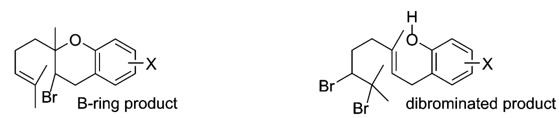
17 The B-ring product (*ca.* 5–10% yield) and the dibrominated product (*ca.* 0–5% yield) were obtained as byproducts in all cases.



18 The *para*-substituted *N*-[3,5-bis(trifluoromethyl)phenyl]urea moieties of **8a** as well as **4** were crucial (Scheme 2): the use of a *meta*-isomer of **8a** reduced not only catalytic activity but also enantioselectivity. See also ref. 8*c* and 8*d*.
19 The same optical purity was observed for *trans*- and *cis*-fused **11a**. See the ESI† (p. S16) for details.
20 We cannot exclude the possibility of an anion exchange reaction between the phthalimide anion (L^-) and **8b** or **5a**. In this case, good enantioselectivity might be induced through alternative hydrogen bonding interactions between the oxyanion of **5a** and the urea moiety of **8b**.