Design of Chiral Nucleophilic Phosphorous Catalysts for Enantioselective Halocyclizations

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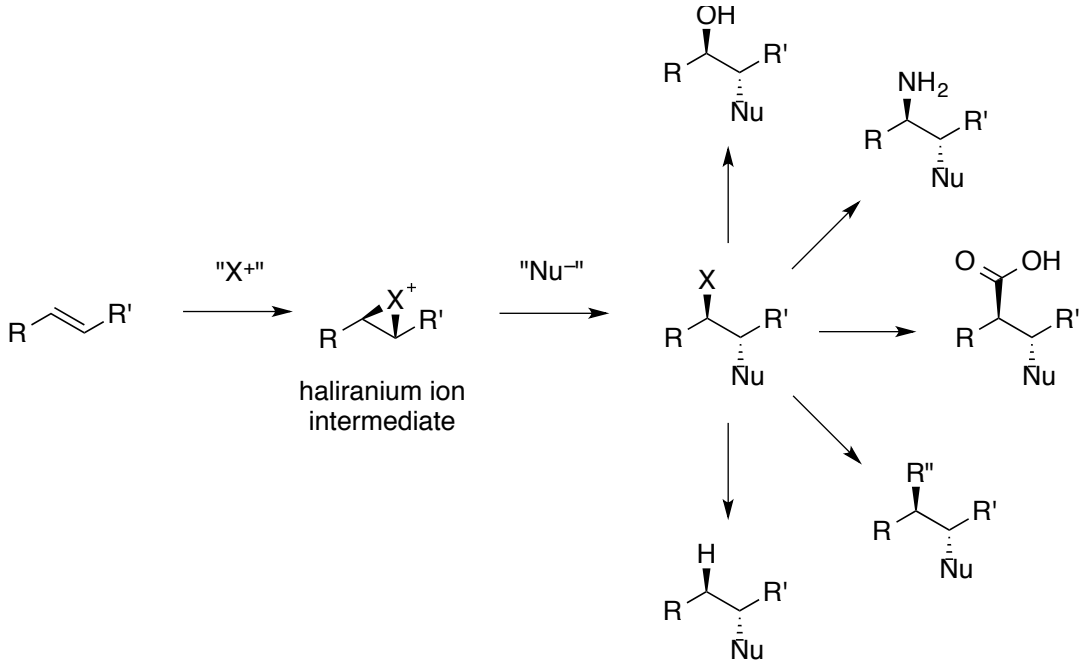
Chapter 1

Introduction and General Summary

1-1. Introduction

The electrophilic addition of a halogen to an olefin is one of the most powerful methods in organic synthesis.[1] The products of this reaction are synthetically valuable intermediates of drugs, bioactive compounds and other potentially useful compounds.[2] In some cases, they are bioactive compounds themselves.[3,4] The halogen–carbon bond can be readily modified to other useful functional groups such as amino, carboxyl, and hydroxyl groups. They can also be useful substrates for cross-coupling reactions (Scheme 1.1).

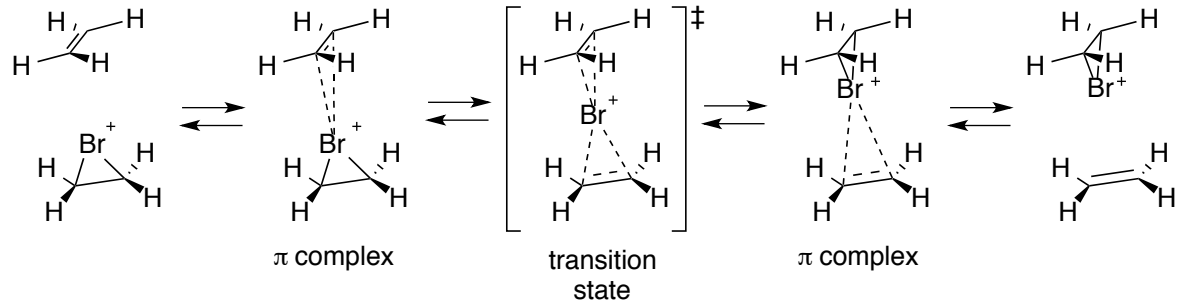
Scheme 1.1. Electrophilic Addition of Halogens to Olefins



Halocyclization proceeds *via* the electrophilic addition of a halogen to an olefin followed by the intramolecular attack of a nucleophile. Since several valuable halogen-containing cyclic compounds can be synthesized by using halocyclization, it has attracted the attention of many organic chemists. The first example of halocyclization was reported by Fittig and Stobbe in the late 19th century.[5] Since then, more efficient halocyclization methods have been developed. However, catalytic asymmetric halocyclization has not been reported until recently[6-11], although catalytic asymmetric electrophilic functionalizations, such as epoxidations, dihydroxylations and hydroaminations, have been well-developed.

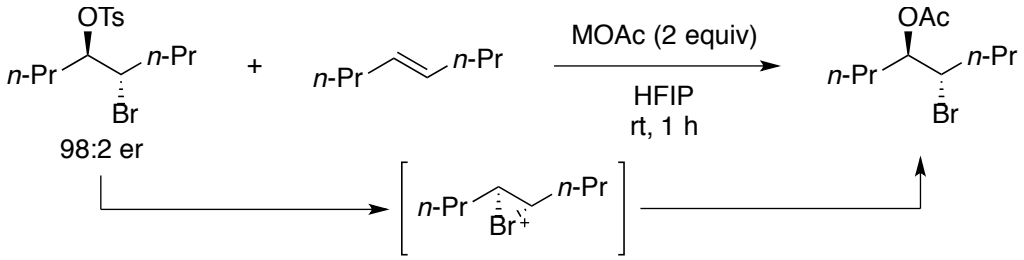
The electrophilic addition of a halogen to an olefin usually proceeds *via* cyclic halonium (haliranium) ion intermediates (Scheme 1.1).[12] Brown and co-workers investigated the reaction mechanism of halocyclization. They demonstrated that Br^+ and I^+ transfer rapidly from the haliranium ions of adamantylidene adamantine to other olefins.[13] Calculations of bromiranium ion transfer between two ethylenes revealed the reaction mechanism illustrated in Scheme 1.2.

Scheme 1.2. Mechanism of Bromiranium Ion Transfer between Two Ethylenes



In 2010, Denmark and co-worker demonstrated racemization of the enantiopure (4*R*,5*S*)-5-bromo-4-octyl tosylate *via* bromiranium ion-to-olefin transfer in acetolysis.[14] While no decrease in enantiospecificity was observed in the absence of the (*E*)-4-octene, in the presence of the (*E*)-4-octene, the enantiopure bromiranium ion generated from the (4*R*,5*S*)-5-bromo-4-octyl tosylate transferred to the (*E*)-4-octene, and enantiospecificity was lost at the same time (Scheme 1.3). Based on these reports, suppression of haliranium ion transfer from the *in situ*-generated enantiopure haliranium ion to an unreacted substrate is crucial for the successful catalytic asymmetric halocyclization.

Scheme 1.3. Decrease in Enantiospecificity in Acetolysis from Bromiranium Ion-to-Olefin Transfer



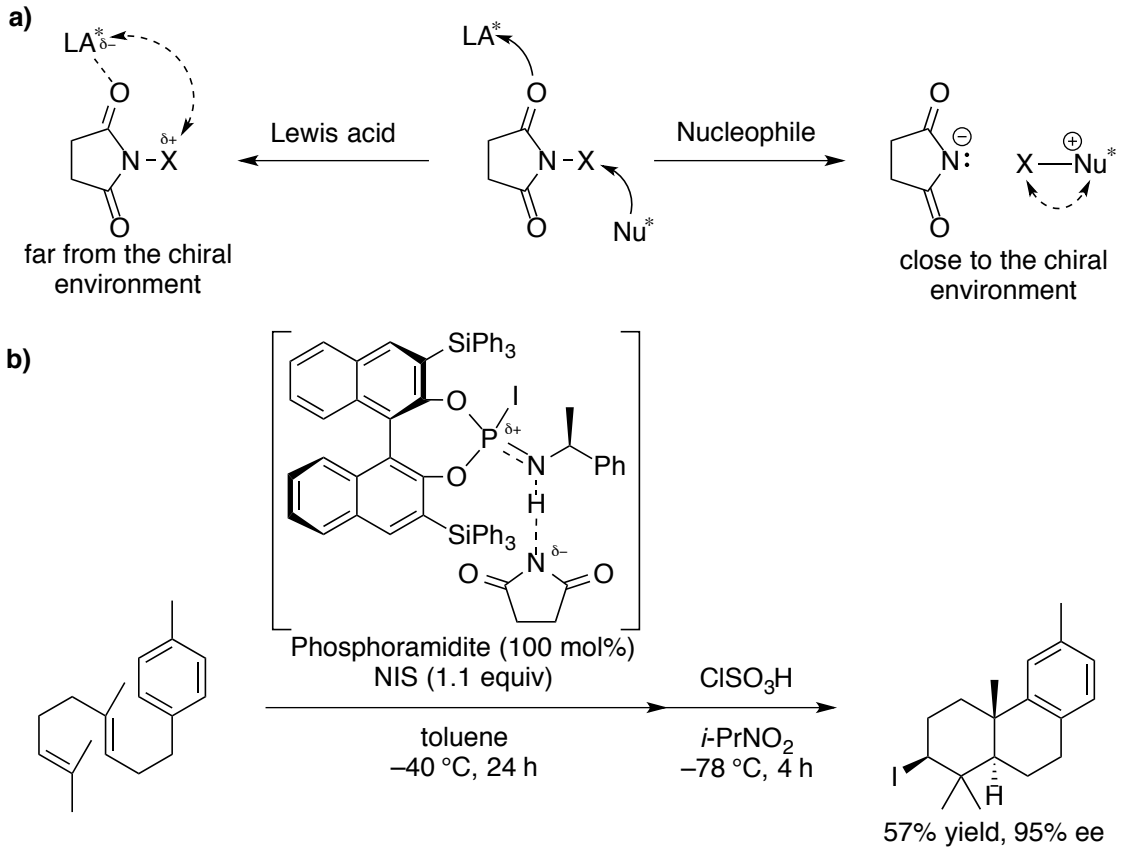
MOAc	(*E*)-4-Octene [equiv]	Yield [%]	Er
NaOAc	0	79	97 : 3
NaOAc	1.0	75	62 : 38
Bu_4NOAc	0	77	98 : 2
Bu_4NOAc	1.0	73	88 : 12

1-2. Design of Chiral Nucleophilic Phosphorous Catalysts

To further develop enantioselective halocyclization, we have continued to study a new catalytic system using a nucleophilic approach.[15] The concept of this nucleophilic approach is illustrated in Scheme 1.4a. A nucleophilic approach is considered to be suitable in the case of activation of the halogenating reagent, such as with *N*-halosuccinimides. While a Lewis acid (*LA**) can activate a halogenating reagent by coordinating to the carbonyl group, the activated halogen atom is placed far from the chiral environment of the Lewis acid. Thus, it is difficult to induce high enantioselectivities. In contrast, chiral nucleophilic promoters (*Nu**) can activate halogenating reagents by nucleophilic attack of the halogenating reagents, so the activated halogen atom is placed close to the chiral environment of the nucleophilic promoter in the active species.

In 2007, our group designed chiral phosphoramidite as a nucleophilic promoter for the enantioselective iodocyclization of polyprenoids (Scheme 1.4b).[15a] The chiral phosphoramidite activates the *N*-iodosuccinimide, and iodophosphonium salt can be generated as an active species. Site- and enantioselective iodination at the terminal olefin with iodophosphonium salt and subsequent diastereoselective cyclization then gives the iodinated cyclic products with high enantioselectivity.

Scheme 1.4. Enantioselective Iodocyclization of Polyprenoids Induced by a Chiral Nucleophilic Phosphoramidite



While this method gave iodinated products were with high enantioselectivity, stoichiometric amounts of the phosphoramidites were needed and the yields were only 52~64%. Since the P-N bond of the phosphoramidites might be weak, the phosphoramidites might have partially decomposed under these reaction conditions. Thus, it was difficult to use a catalytic amount of phosphoramidites. Therefore, we designed more robust and reactive nucleophilic phosphorous catalysts for asymmetric halocyclizations. Chapters 2~4 describe phosphite–urea cooperative catalysts for the site-, diastereo- and enantioselective bromocyclization of homogeranylarenes[15f] and 2-geranylphenols,[15g] and Chapter 5 presents phosphate catalysts for the enantioselective iodocyclization of 4-arylmethyl-4-pentenoic acids.[15h]

1-3. Catalytic Site- and Diastereoselective Bromocyclization of Polyprenoids

Many polycyclic natural compounds that contain bromine atoms have been isolated from several different marine organisms (Figure 1.1).[3,4] Most of them possess bioactivities of pharmacological interest, such as antibacterial, anticancer, antifungal, anti-inflammatory, and antiviral activities. Natural products that have an α-bromo-β,β-dimethylcyclohexane structure are also bioactive compounds. Their biosynthesis appears to be initiated by electrophilic bromination at the terminal olefin of polyprenoids in the chiral cavity of enzymes.[16,17] Subsequent diastereoselective cyclization gives bromine-containing natural products. Since several new quaternary and tertiary stereocenters and new rings are formed in one step, bromonium ion-induced polyene cyclization is one of the most remarkable reactions.

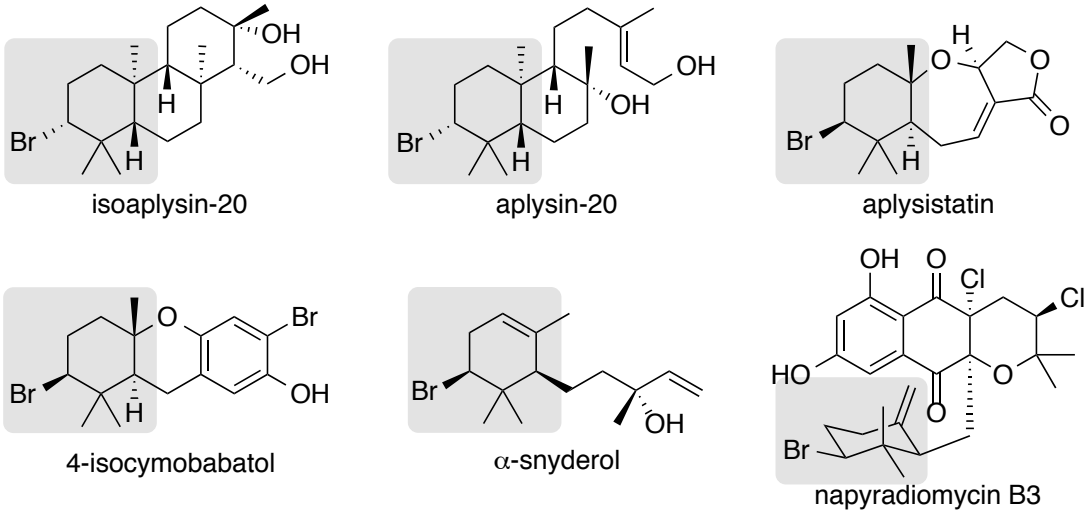
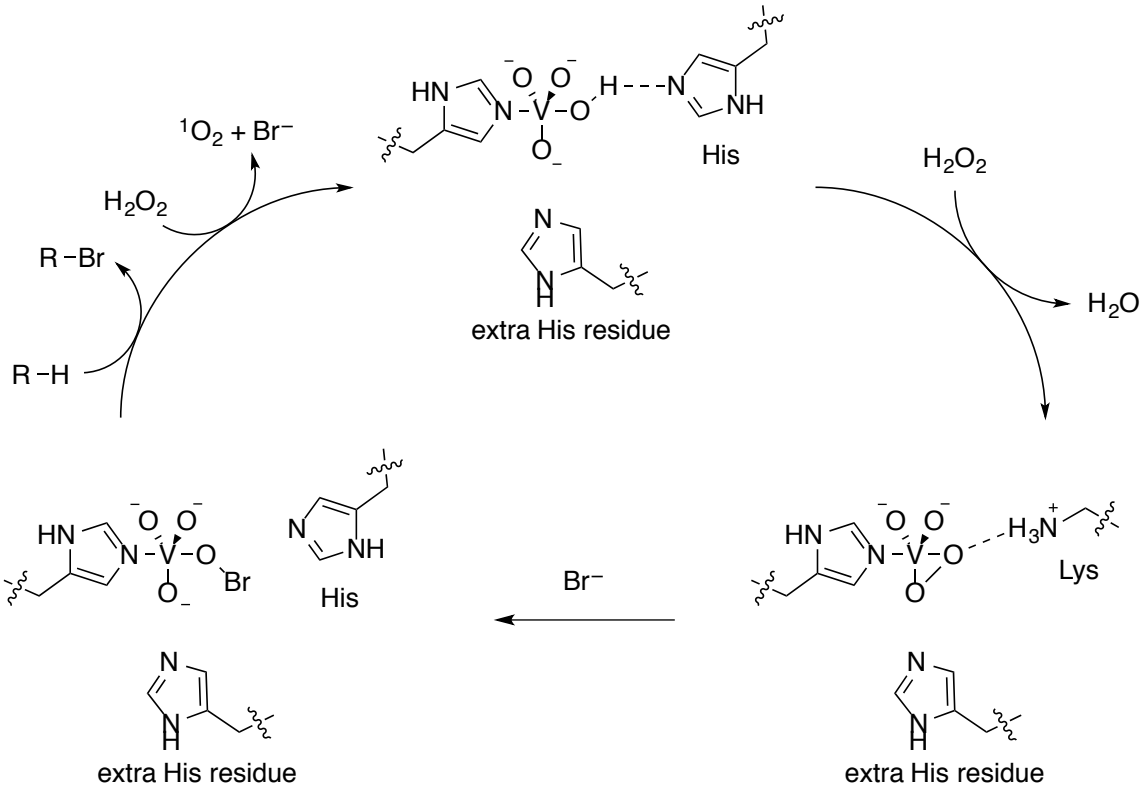


Figure 1.1. Bromine-Containing Natural Products

Vanadium haloperoxidases (V-HPO) promote the oxidation of halides (chloride, bromide, iodide) and the electrophilic halogenation of organic compounds. Vanadium bromoperoxidases (V-BPO) have been considered to be the predominant enzymes for the bromocyclization of polyprenoids. The vanadium active center of V-BPO acts as a Lewis acid and oxidizes a halide with H_2O_2. A proposed catalytic mechanism for V-BPO is shown in Scheme 1.5.[16,17b]

Scheme 1.5. Proposed Catalytic Mechanism for V-BPO

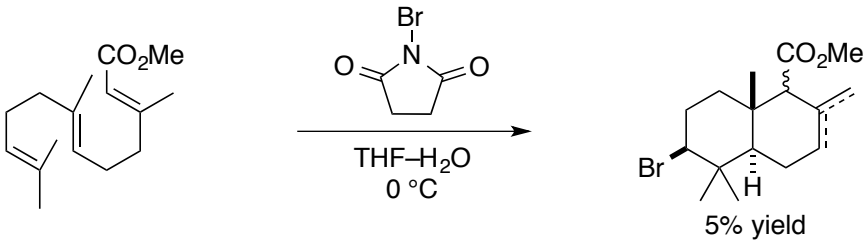


In the first stage, one equivalent of H_2O_2 coordinates to the resting vanadium(V) state, to form the oxoperoxovanadium(V) intermediate. The oxoperoxovanadium(V) intermediate is proposed to oxidize the bromide (Br^-) by two electrons and generate a bromonium ion (Br^+)-type intermediate. A Lys side chain is proposed to play a crucial role in the catalytic reaction because it would increase the potential of the oxoperoxovanadium(V) intermediate for the oxidation of bromides. The electrophilic halogenation of organic substrates with a bromonium ion-type intermediate affords the brominated compounds. In the absence of organic substrates, the electrophilic halogenation of a second equivalent of H_2O_2 gives the singlet oxygen and the bromide anion. While an extra His residue does not interact directly with the vanadium center, it has been proposed that the His side chain participates as a proton donor and acceptor during the catalytic cycle and could affect the overall oxidation potential of the oxoperoxovanadium(V) intermediate.

Chemical syntheses of brominated polycyclic compounds have been developed over the past 50 years.[1c] In 1966, the first bromonium ion-induced polyene cyclization was demonstrated by van Tamelen and co-workers.[18] The reaction of methyl farneate with

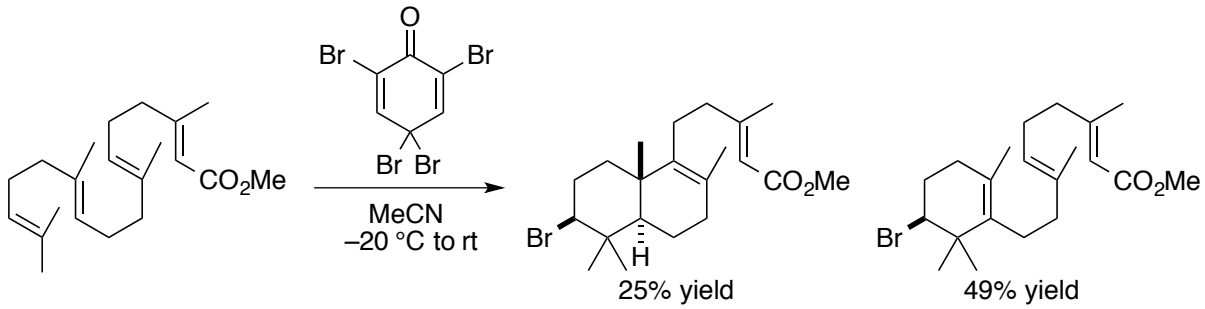
N-bromosuccinimide (NBS) in a mixture of THF and H_2O at 0 °C gave an isomeric mixture of brominated bicyclic esters, although the yield was very low. This may have been due to the low siteselectivity of the reaction of the brominating reagent with terminal or internal olefins (Scheme 1.6).

Scheme 1.6. First Electrophilic Bromocyclization of Polyprenoids



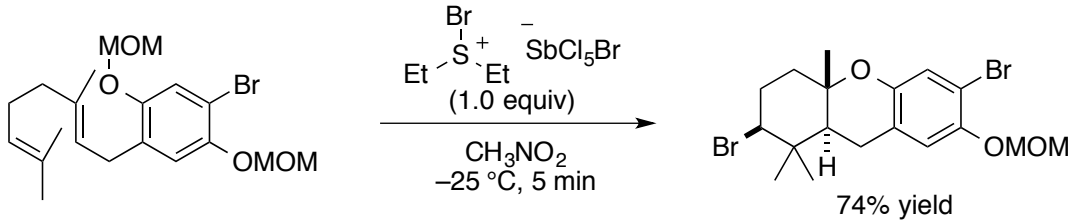
Kato and co-workers greatly advanced bromonium ion-induced polyene cyclization.[19] In 1986, they developed 2,4,4,6-tetrabromocyclohexa-2,5-diene (TBCO) as a brominating reagent, and reported that the bromocyclization of methyl geranyl geranate with TBCO afforded brominated bi- or mono-cyclic compounds (Scheme 1.7).[19f] While TBCO was used in several bromocyclizations, in many cases the yields were low to moderate.

Scheme 1.7. Bromocyclization of Methyl Geranyl Geranate with TBCO



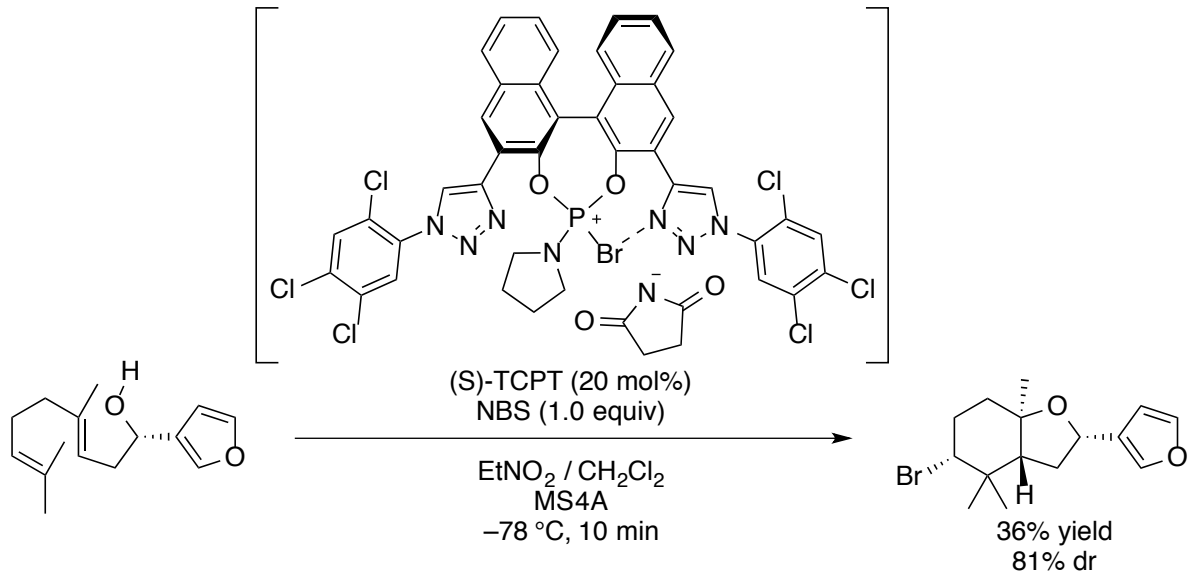
In 2009, Snyder and co-workers demonstrated that bromodiethylsulfonium bromopentachloroantimonate (BDSB) was an efficient brominating reagent.[20] Several brominated compounds were obtained in good yield with the use of BDSB (Scheme 1.8).

Scheme 1.8. BDSB-Promoted Bromonium Ion-Induced Polyene Cyclization



While several brominating reagents have been developed for the bromocyclization of polyprenoids, catalysts for this reaction have not been developed for many years. Recently, McErlean and co-workers reported bromocyclization for the synthesis of (+)-luzofuran.[21] 2,4,5-Trichlorophenyltriazole-flanked phosphoramidite (TCPT) was used as a catalyst. Triazole groups were introduced at the 3,3'-positions of BINOL, inspired by V-BPO which has several histidines at the active site. The reaction was promoted with 20 mol% of TCPT and 1.0 equivalent of NBS, although the yield and the diastereoselectivity were moderate (Scheme 1.9).

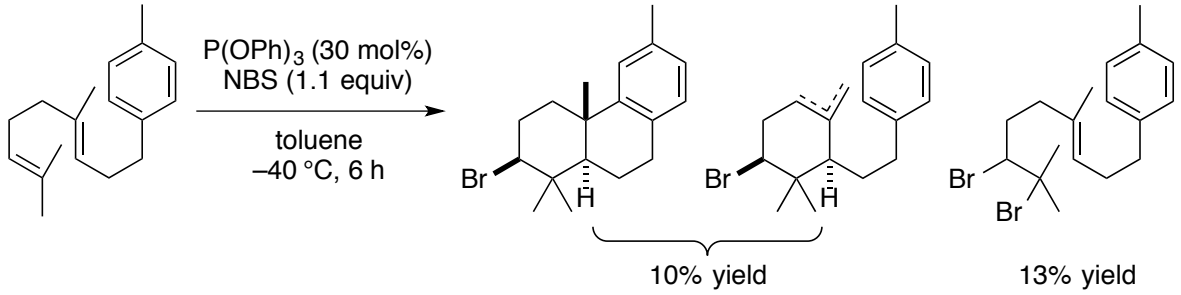
Scheme 1.9. Synthesis of (+)-luzofuran with (S)-TCPT



In our group, we have continued to develop new nucleophilic phosphorous catalysts. First, we examined the triphenyl phosphite $P(OPh)_3$-catalyzed bromocyclization of homogeranyltoluene (Scheme 1.10). Bromocyclization with 30 mol% of $P(OPh)_3$ and 1.1

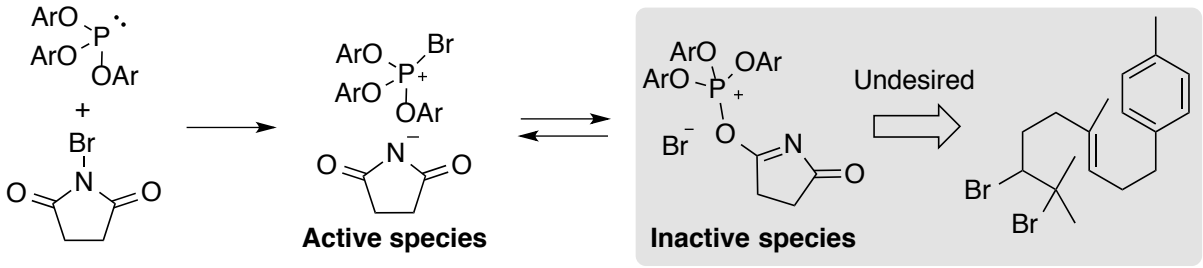
equivalents of NBS gave the desired cyclic products (10% yield) along with the undesired dibrominated byproduct (13% yield).

Scheme 1.10. $P(OPh)_3$-Catalyzed Bromocyclization of Homogeranyltoluene



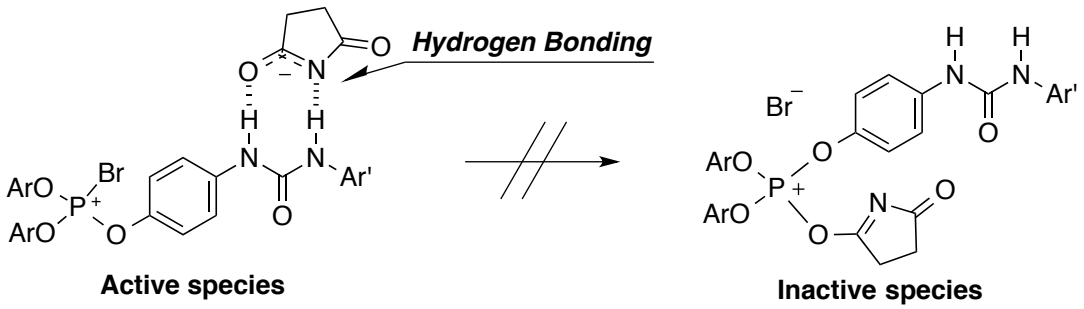
Through several experiments, we found that $P(OPh)_3$ was inactivated during generation of the dibrominated byproduct. In other words, $P(OPh)_3$ was inactivated by nucleophilic attack of the succinimide anion to the bromophosphonium salt, which is the active species.[22] The bromide anion was generated at the same time, which led to formation of the dibrominated byproduct (Scheme 1.11). Therefore, the nucleophilic attack of the succinimide anion to the bromophosphonium salt must be avoided if this reaction is to be successful.

Scheme 1.11. Proposed Mechanism for the Generation of Dibrominated Byproduct



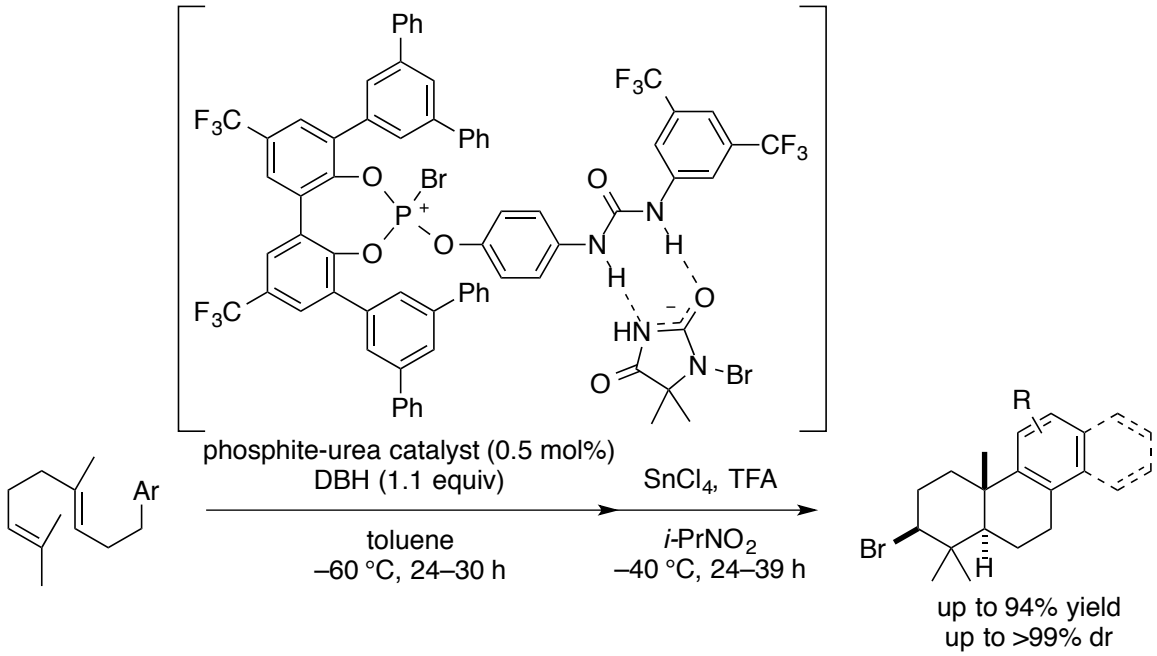
It was proposed that urea groups could capture the succinimide anion *via* hydrogen bonding, and inactivation of the catalyst could be suppressed (Scheme 1.12).

Scheme 1.12. Capture of Succinimide Anion *via* Hydrogen Bonding



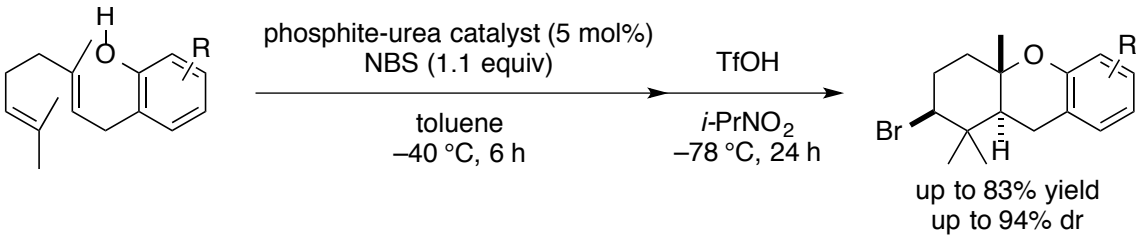
As a result, we found that phosphite–urea cooperative catalysts were efficient for the highly site- and diastereoselective bromocyclization of homogeranylarenes (Scheme 1.13).[15f] Moreover, we found that 1,3-dibromo-5,5-dimethylhydantoin (DBH) was a highly reactive brominating reagent. Only 0.5 mol% of the catalyst was sufficient to give the desired product in quantitative yield when the reaction of homogeranyltoluene was conducted with DBH. The *cis*-fused products were generated in the second acid-treatment step, while the first brominium-ion induced cyclization step gave only *trans*-diastereomers.

Scheme 1.13. Phosphite–Urea Cooperative Catalysis for the Site- and Diastereoselective Bromocyclization of Homogeranylarenes



The present method could also be applied to the bromocyclization of 2-geranylphenols (Scheme 1.14).[15g] NBS (1.1 equivalents) was used as the brominating reagent, since bromination at the *ortho*- and *pala*-positions of phenol occurred when DBH was used as a brominating reagent. The reactions were conducted using 5 mol% of the catalyst and the desired tricyclic compounds were obtained in good yields.

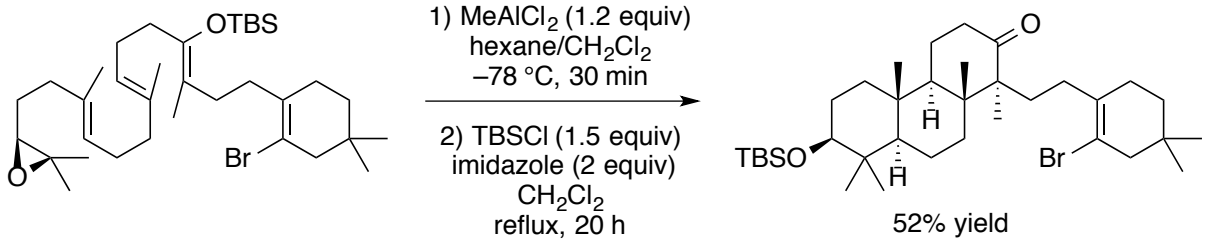
Scheme 1.14. Bromocyclization of 2-Geranylphenols



1-4. Catalytic Enantioselective Bromocyclization of Polyprenoids

According to the Stork–Eschenmoser hypothesis[23], many polycyclic terpenoids, such as hopene and lanosterol, are biosynthesized *via* the site- and enantioselective protonation or epoxidation of a terminal olefin followed by diastereoselective π-cation cyclization.[24] Corey and co-workers performed pioneering work on the cation-induced diastereoselective polyene cyclization of enantiopure epoxides (Scheme 1.15).[25,26]

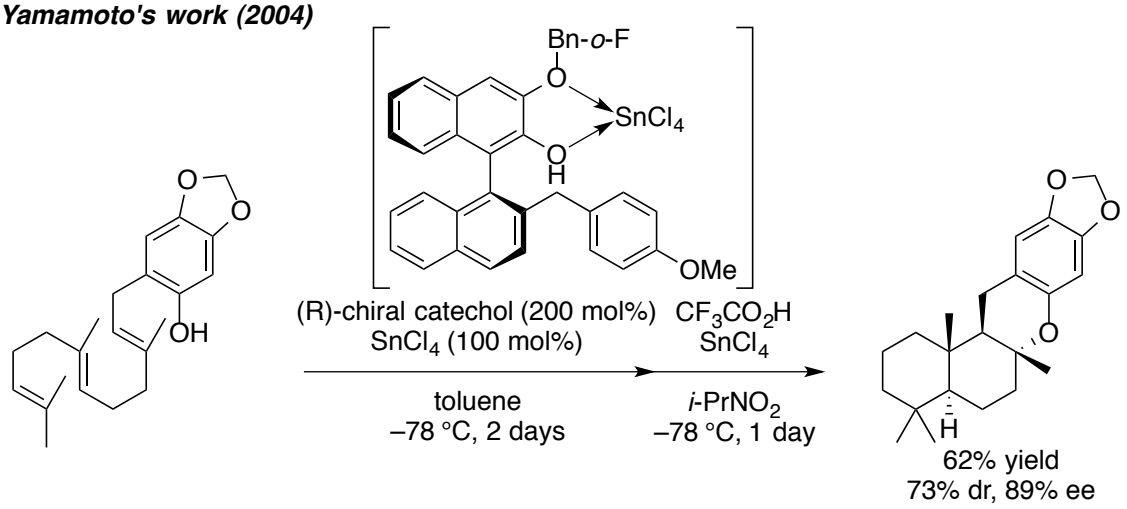
Scheme 1.15. Diastereoselective Polyene Cyclization of Enantiopure Epoxides



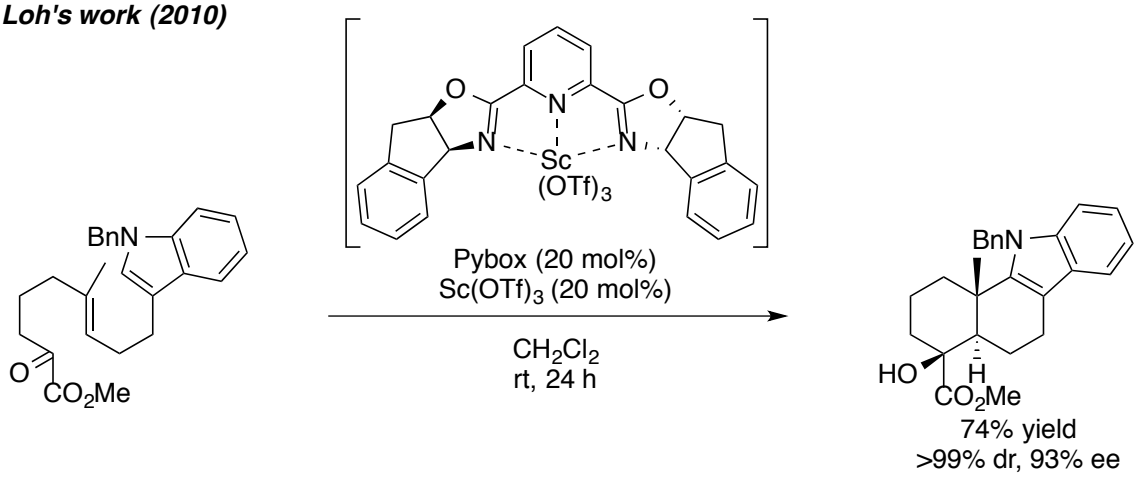
Over the past two decades, several cation-induced enantioselective polyene cyclizations have been reported by Yamamoto–Ishihara[27], Loh[28], Gagné[29] and others[30] (Scheme 1.16). The first enantioselective polyene cyclization was accomplished by Yamamoto, Ishihara and co-workers in 1999.[27a] Since then, they have developed Lewis acid-assisted chiral Brønsted acids (chiral LBA). In 2004, they demonstrated that the chiral catechol•$SnCl_4$ was effective for the enantioselective cyclization of 2-(polyprenyl)phenol derivatives (Scheme 1.16a).[27f] In 2010, Loh and co-workers reported a highly efficient catalytic enantioselective polyene cyclization.[28c] An α-ketoester was demonstrated to initiate enantioselective cationic polyene cyclization catalyzed by a $Sc(OTf)_3$–Pybox Lewis acid catalyst (Scheme 1.16b). In 2013, Gagné and co-workers demonstrated catalytic enantioselective polyene cyclization and C3-fluorination for fluorine-containing polycyclic products.[29c] The combination of (*S*)-(xylyl-PHANEPHOS)PtI_2, $AgBF_4$ and NCC_6F_5 generated the active [(*S*)-(xylyl-PHANEPHOS)$Pt(NCC_6F_5)_2$][$(BF_4)_2$] catalyst. This active catalyst induced enantioselective polyene cyclization, and the organoplatinum intermediates were formed. Subsequent reaction of the organoplatinum intermediates with XeF_2 generated the fluorine-containing polycyclic products (Scheme 1.16c).

Scheme 1.16. Examples of Enantioselective Polyene Cyclization

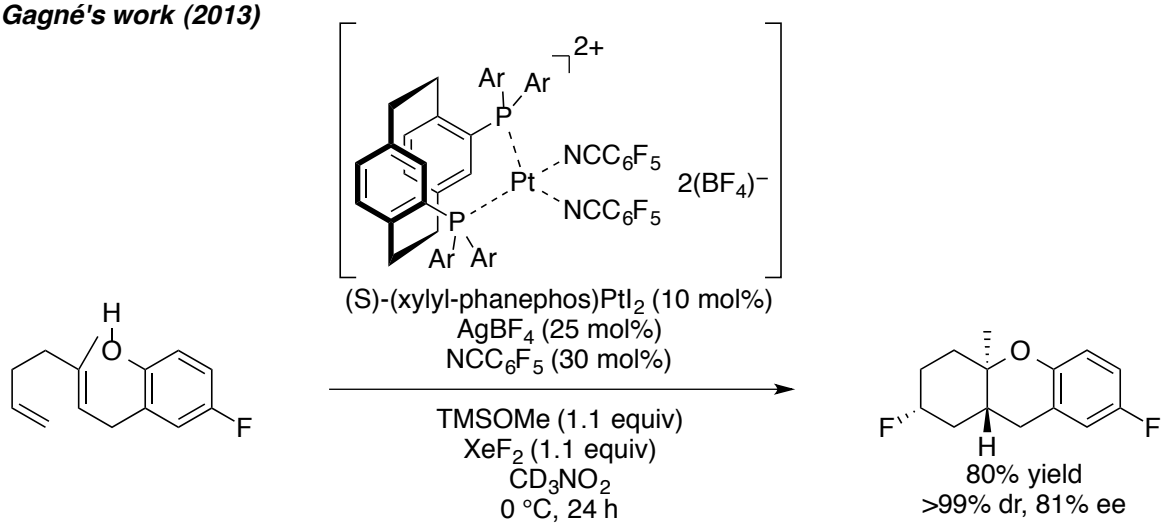
a) Yamamoto's work (2004)



b) Loh's work (2010)



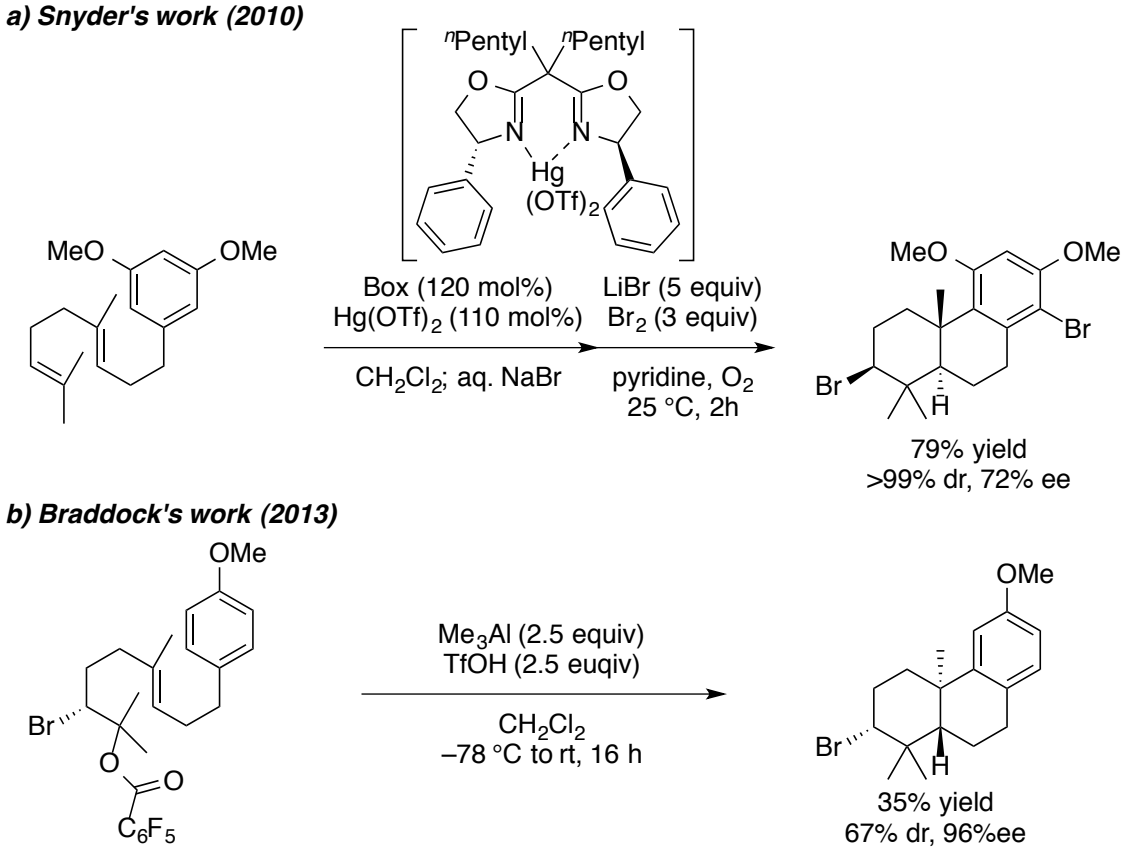
c) Gagné's work (2013)



Bromine-containing polycyclic terpenoids are also considered to be biosynthesized *via* the site- and enantioselective bromination of a carbon–carbon double bond followed by

diastereoselective π-cation cyclization. While several cation-induced enantioselective polyene cyclizations have been reported, the bromonium ion-induced polyene cyclization is very rare, since, in addition to the primary difficulty of polyene cyclization, which involves low reactivity and low stereoselectivity, the racemization of enantiopure bromiranium ion *via* inter- or intramolecular bromiranium ion-to-olefin transfer must be avoided. To overcome these problems, stepwise methods that require more than two steps have been reported by some groups (Scheme 1.17).[31] However, an efficient method for the direct enantioselective bromonium ion-induced polyene cyclization has not been reported.[32] Moreover, the further development of catalysts is needed to achieve catalytic enantioselective bromocyclization.

Scheme 1.17. Stepwise Enantioselective Bromocyclizations

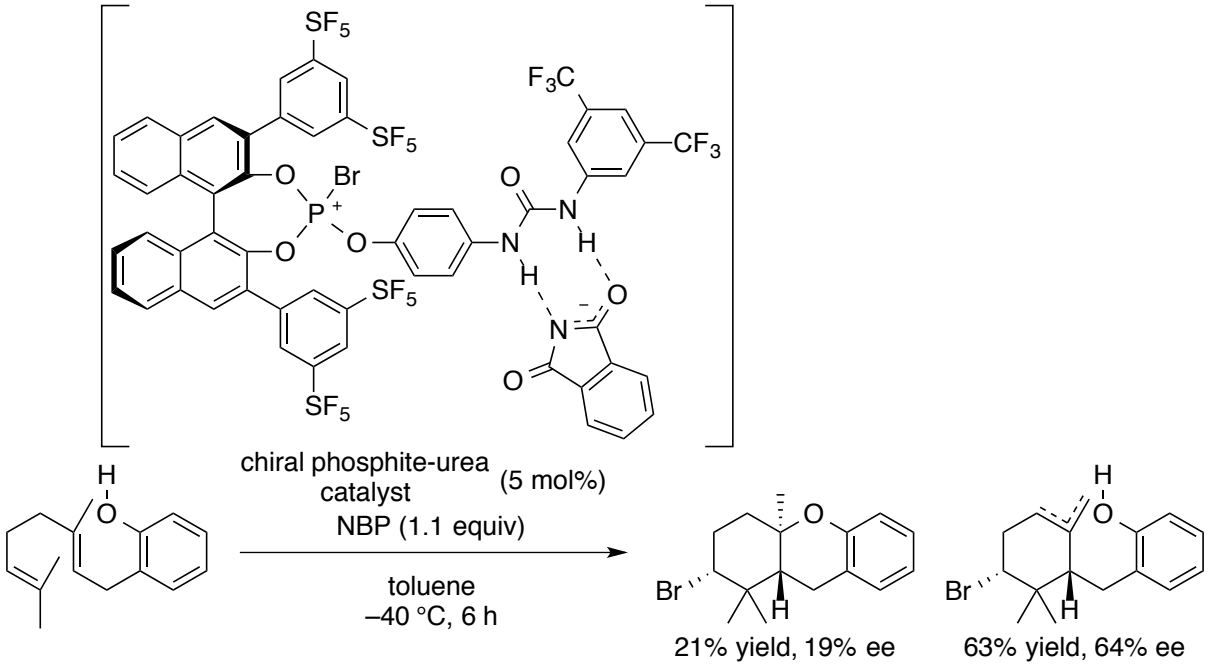


In 2010, Snyder and co-workers reported the Hg(II)-induced polyene cyclization and bromination of polyprenoids (Scheme 1.17a),[31a] which has a reaction mechanism similar to that in Gagné's polyene cyclization/fluorination reaction (Scheme 1.15c). The combination of 1.2 equivalents of chiral bis(oxazoline) ligand (Box) and 1.1 equivalents of $Hg(OTf)_2$

followed by treatment with aqueous sodium bromide generated the organomercury bromide. Subsequent treatment with Br_2 in oxygenated pyridine gave bromine-containing polycyclic products in high yield with high enantioselectivity. In 2013, Braddock and co-worker reported that enantiospecific polyene cyclization was initiated by the formation of an enantiopure bromiranium ion (Scheme 1.17b).[31b] Enantiopure bromohydrin esters were synthesized from the corresponding olefins in a three-step sequential reaction. The reaction gave the products without a loss of enantiomeric excess despite the low yield and diastereoselectivity.

We previously reported chiral phosphorous catalysts for the enantioselective iodonium ion- or proton-induced polyene cyclization of polyprenoids.[15] Encouraged by these results, we developed a new chiral phosphorous catalyst for the direct catalytic enantioselective bromonium ion-induced polyene cyclization. We demonstrated that the chiral phosphite-urea cooperative catalyst was efficient for the enantioselective bromocyclization of 2-geranylphenols (Scheme 1.18).

Scheme 1.18. Enantioselective Bromocyclization of 2-Geranylphenol



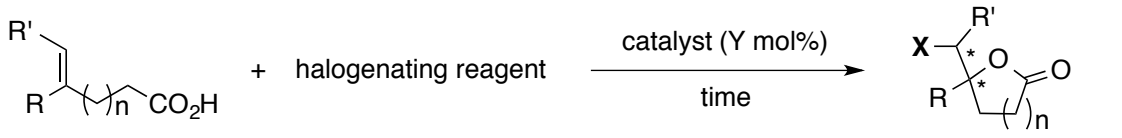
N-Bromophthalimide (NBP, 1.1 equivalents) was used as a brominating reagent and the reaction of 2-geranylphenol was conducted in the presence of 5 mol % of the chiral phosphite–urea cooperative catalyst in toluene at –40 °C for 6 h. Both of the tricyclic product and the monocyclic product were generated. Interestingly, the enantioselectivity of

the tricyclic product (19% ee) was different from that of the monocyclic product (64% ee). In the formation of the monocyclic product, there is coordination between the urea group of the catalyst and the hydroxyl group of the substrate. Thus, it is considered that the enantioselectivity of the monocyclic product was greater than that of the tricyclic product.

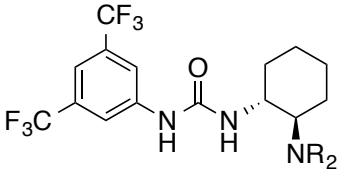
1-5. Enantioselective Iodolactonization Promoted by Chiral Phosphate Catalysts

Halolactonization is one of the most powerful reactions in total synthesis, and is well known as Corey's iodolactonization for the synthesis of prostaglandins.[33] The products of the reaction are important intermediates for the synthesis of bioactive natural products and other potentially useful compounds.[2] While diastereoselective halolactonization has been studied for more than 100 years, there has been little progress on an enantioselective version. Over the past few years, enantioselective halolactionizations[6-8], as well as haloetherifications[9], haloaminocyclizations[10] and other related reactions[11], have been reported by several groups. Examples of efficient catalysts for enantioselective halolactonization are shown in Scheme 1.19. Many of these catalysts are bifunctional catalysts. They have a functional group to activate the halogenating reagents and another functional group to coordinate with a substrate. Although these methods give the corresponding chiral products with high enantioselectivities, the reactivities are not so high and sometimes require long reaction times.

Scheme 1.19. Examples of Catalytic Enantioselective Halolactonization



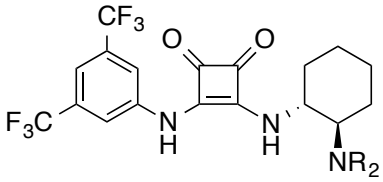
X = I



(15 mol%)
71-95% yield, 48-96% ee
5 days

Jacobsen, E. N. *et al.* (2010)

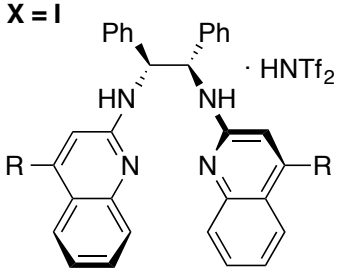
X = I



(15 mol%)
73-91% yield, 12-96% ee
24 h

Hansen, T. V. *et al.* (2012)

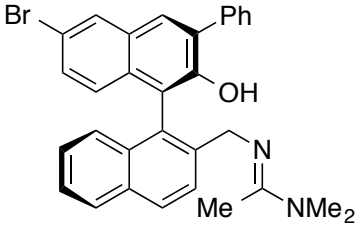
X = I



(5 mol%)
<10-99% yield, 33-98% ee
24 h

Johnston, J. N. *et al.* (2012)

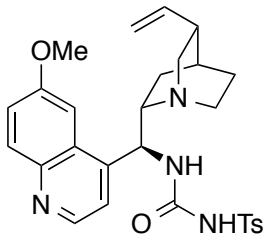
X = Br



(10 mol%)
87-99% yield, 42-96% ee
14 h

Martin, S. *et al.* (2012)

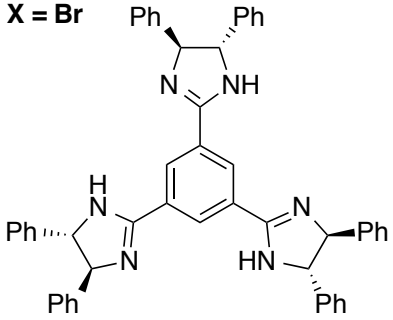
X = Br



(5 mol%)
70-88% yield, 80-99% ee
0.5–10 h

Tang, W. *et al.* (2010)

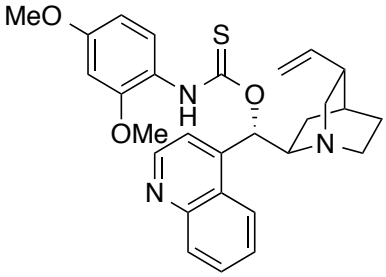
X = Br



(5 mol%)
74-99% yield, 71-91% ee
4–46 h

Fujioka, H. *et al.* (2010)

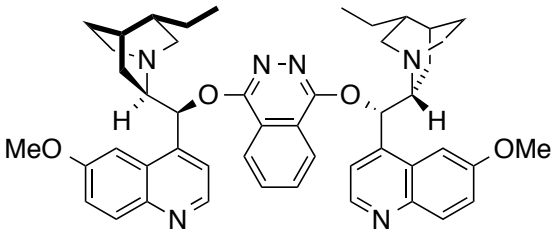
X = Br



(5 mol%)
67-99% yield, 28-93% ee
20–126 h

Yeung Y.-Y. *et al.* (2010)

X = Cl

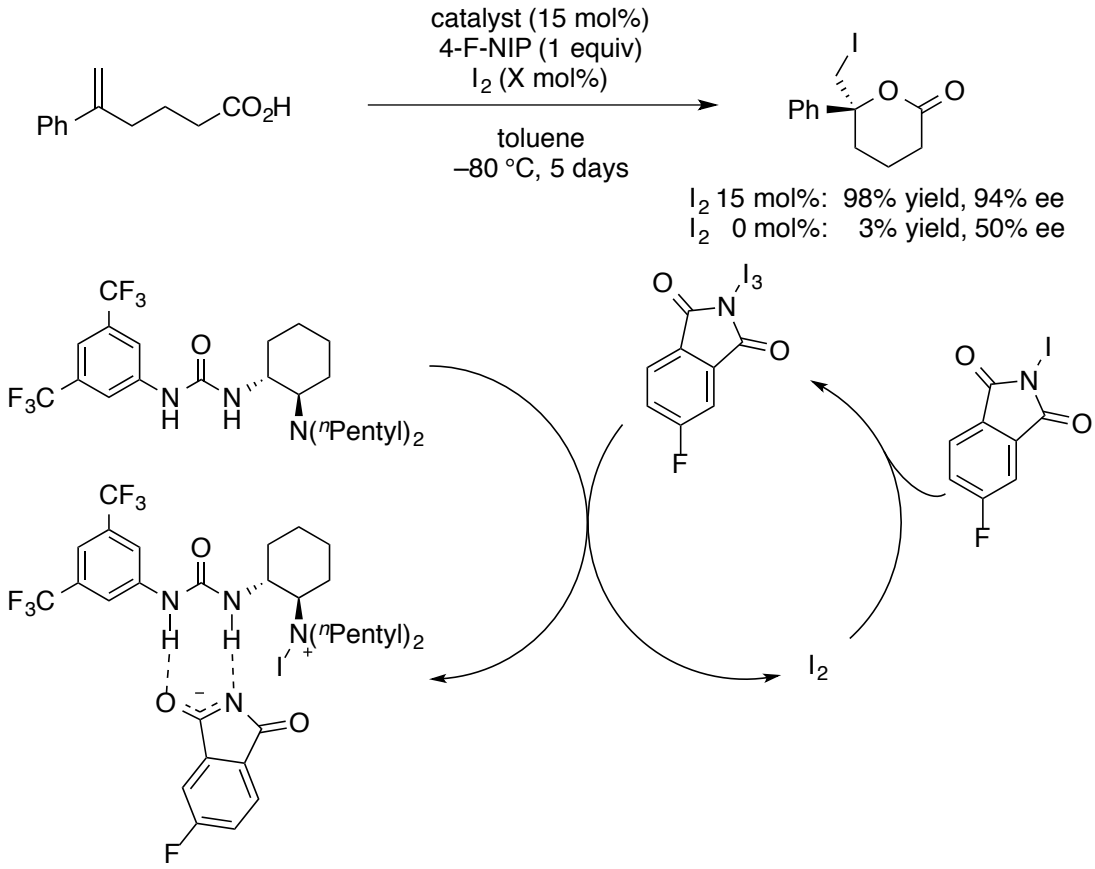


(10 mol%)
55-99% yield, <5-90% ee
0.5–3 h

Borhan, B. *et al.* (2010)

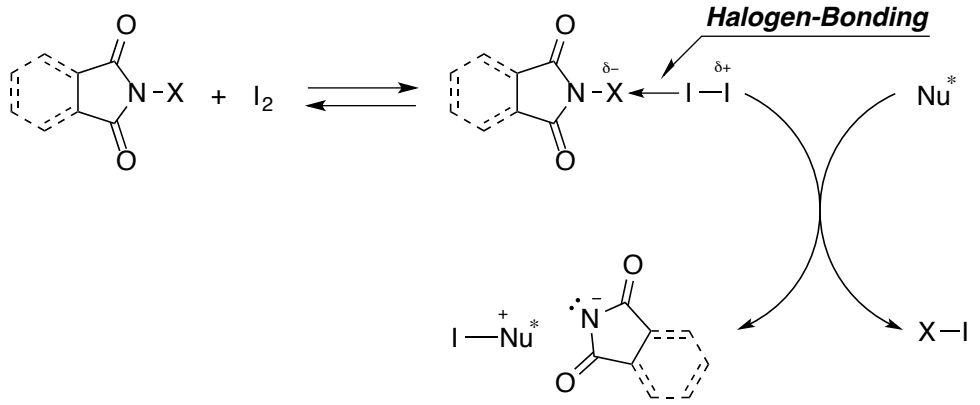
Jacobsen and co-workers reported that the addition of I_2 was effective in their enantioselective iodolactonization.[6a] They indicated that the formation of triiodide cation (I_3^+)[34] was crucial for high yields and enantioselectivities. With 15 mol% of I_2, an iodolactone was obtained in 98% yield with 94% ee. However, in the absence of I_2, an iodolactone was hardly obtained (Scheme 1.20).

Scheme 1.20. Additive Effect of I_2 in Enantioselective Iodolactonization



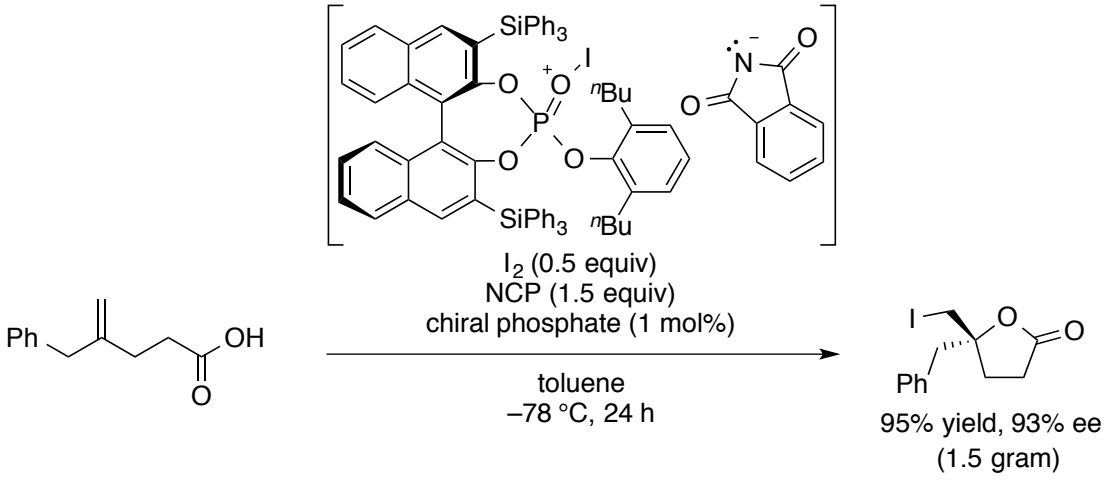
Based on this repot, we considered that halogen-bonding could activate the reactivity of I_2.[35] *N*-Haloimides act as Lewis acids and coordinate to I_2, and thus I_2 will be activated (Scheme 1.21). Phosphates are more stable, but less nucleophilic, than phosphites and phosphoramidites. We envisioned that, with the use of this halogen-bonding activation method, phosphates could be used as a catalyst instead of phosphites and phosphoramidites. Thus, we tried to develop a method of cooperative activation with chiral phosphates and *N*-haloimides for enantioselective iodolactonization.

Scheme 1.21. Activation of I_2 *via* Halogen Bonding



We demonstrated that the chiral phosphate and *N*-chlorophthalimide (NCP) cooperatively promoted the enantioselective iodolactonization of 4-arylmethyl-4-pentenoic acids (Scheme 1.22).[15h] Iodolactones were obtained with high yields and enantioselectivities. Interestingly, only 0.5 equivalents of I_2 was sufficient to promote conversion of the substrates. NCP was not only an effective activator of I_2, but also an oxidant of I^- which was generated in the process of the reaction.

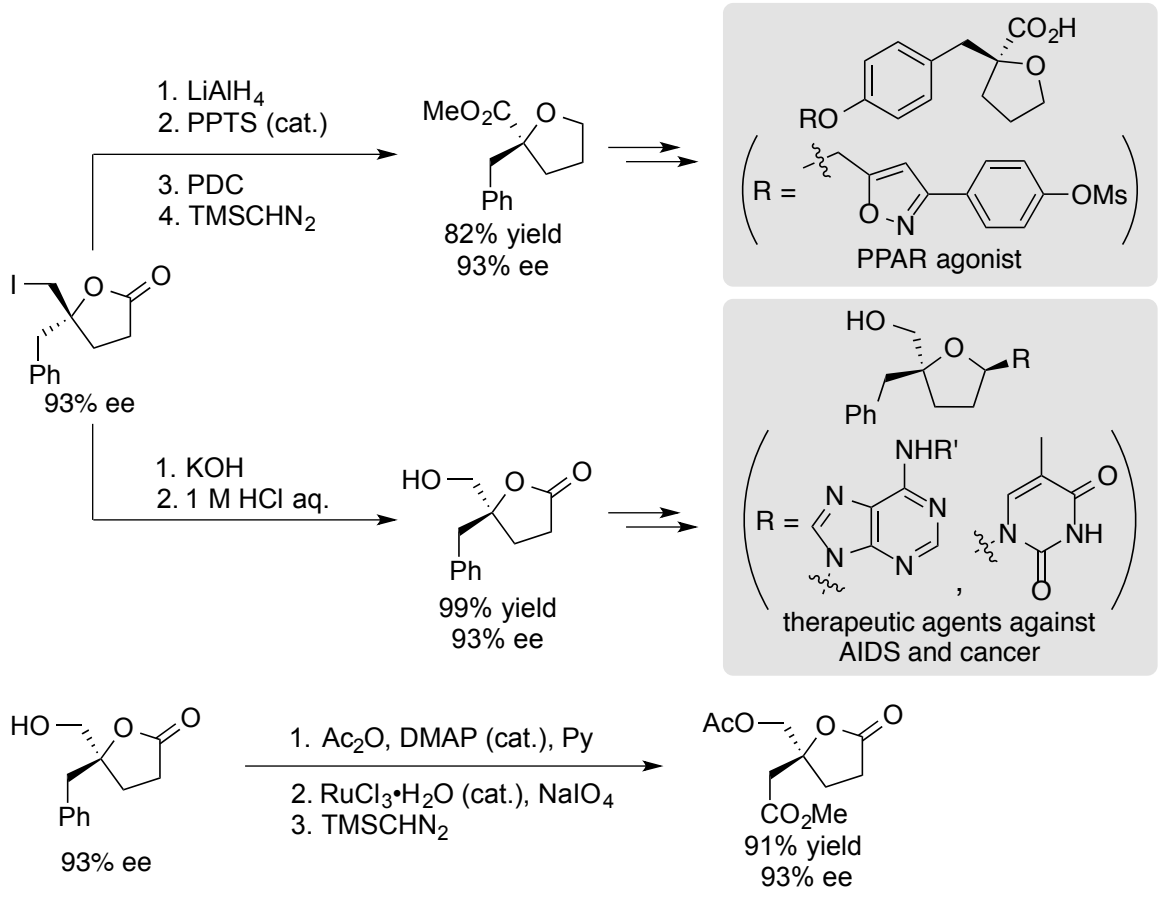
Scheme 1.22. Enantioselective Iodolactonization of 4-Benzyl-4-pentenoic Acid Promoted by a Chiral Phosphate.



The corresponding chiral iodolactone was converted to some key intermediates of bioactive compounds without a loss of enantiomeric excess (Scheme 1.23). The key intermediate of PPAR agonists[36] was formed by a four-step sequence of reduction,

acid-catalyzed etherification, oxidation and methylation. Hydrolysis followed by acid-promoted lactonization gave a corresponding hydroxylactone, which is a key intermediate of therapeutic agents used against AIDS and cancer[37]. The phenyl group could be converted to an ester group by a three-step reaction from the hydroxylactone.

Scheme 1.23. Transformations of the Chiral Iodolactone



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Chapter 2

Phosphite–Urea Cooperative Catalysts for the Site- and Diastereoselective Bromocyclization of Homogeranylarenes

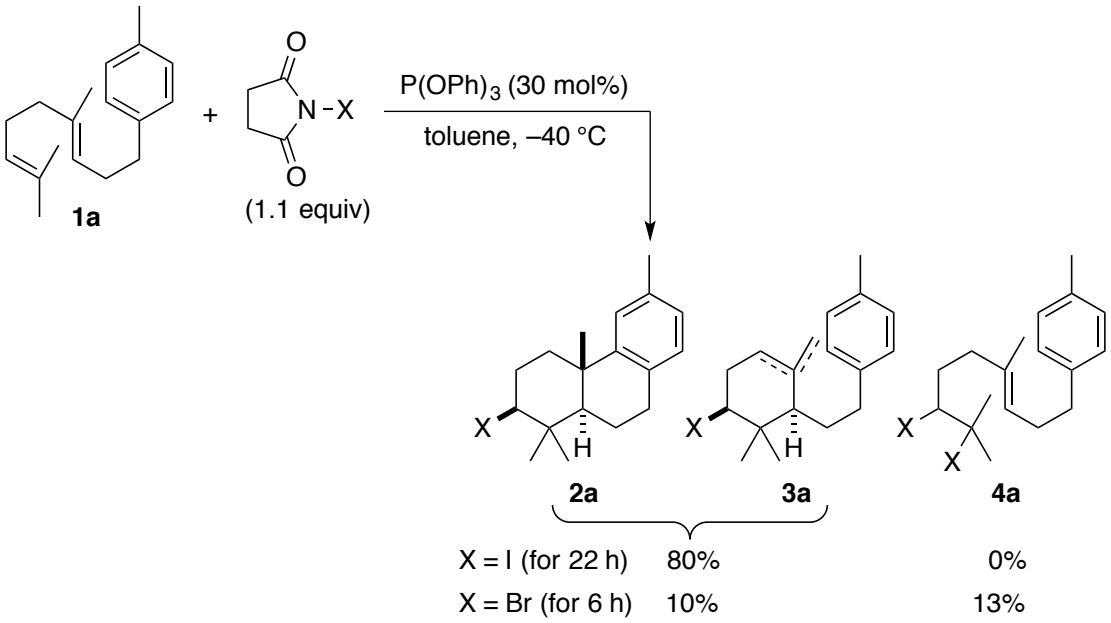
Abstract:

Nucleophilic phosphite(III)–urea cooperative high-turnover catalysts have been designed for the highly selective bromocyclization of homogeranylarenes. The introduction of a urea moiety and bulky aryl groups in the catalyst inhibits decomposition of the catalyst and the generation of byproducts. Only 0.5 mol% of the catalyst successfully promotes the bromocyclization of 4-homogeranyltoluene to give the desired product in 96% yield.

2-1. Introduction

Many polycyclic natural compounds that contain bromine atoms have been isolated from several different marine organisms.[1] In contrast, there are rare iodine-containing natural compounds. The biosynthesis of brominated polycyclic terpenoids appears to be initiated by an electrophilic bromination reaction at a carbon–carbon double bond[2] *via* a mechanism that is similar to proton-induced polyene cyclization.[3,4] The development of a site- and diastereoselective bromonium-induced polyene cyclization of polyprenoids is very important for the synthesis of bromine-containing polycyclic natural compounds. However, most of the conventional methods are not efficient and give poor to moderate yields of the bromocyclization products along with significant amounts of byproducts.[5,6] Recently, Snyder and colleagues reported $Et_2SBr•SbCl_5Br$ (BDSB) as a highly reactive electrophilic bromination reagent.[7] The use of BDSB successfully gives the bromocyclization products in good to high yields. In fact, the cyclization of 4-homogeranyltoluene (**1a**) with BDSB (1.0 equiv.) at –25 °C gave the corresponding bromocyclization product **2a** (X = Br) in 68% yield according to our preliminary experiments. We previously reported a chiral Lewis base-promoted enantioselective iodocyclization of isoprenoids.[8–11] The chiral nucleophilic phosphoramidite reacts with *N*-iodosuccinimide (NIS) to generate the corresponding phosphonium salt as an active species. Although this method gives polycyclic 3-iodoterpenoids with high enantioselectivity, the stoichiometric use of the phosphoramidite promoter is required for successful promotion of the reaction due to the deactivation of phosphoramidite with the generated acidic succinimide. In contrast, triphenyl phosphite [$P(OPh)_3$] catalytically promoted the iodocyclization of **1a** to give iodocyclization products (**2a** and **3a**, X = I) in 80% yield (Scheme 2.1). On the other hand, $P(OPh)_3$-catalyzed bromocyclization with *N*-bromosuccinimide (NBS) gave the desired **2a** and **3a** (X = Br, 10% yield) along with significant amounts of undesired dibromide **4a** (X = Br, 13% yield) and unknown byproducts (*ca.* 2% yield),[12,13] although the initial reaction rate of bromocyclization was faster than that of iodocyclization.[14]

Scheme 2.1. Catalytic Halocyclization of **1a**



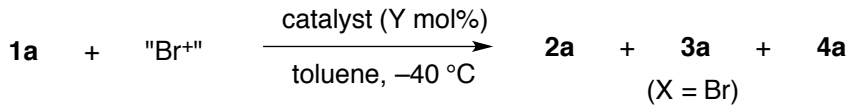
Hence, the development of a catalytic method for site- and diastereoselective bromocyclization is an important issue. We report here the first example of a highly selective bromocyclization reaction of homogeranylarenes **1** catalyzed by nucleophilic phosphite–urea cooperative catalysts with a high turnover number.

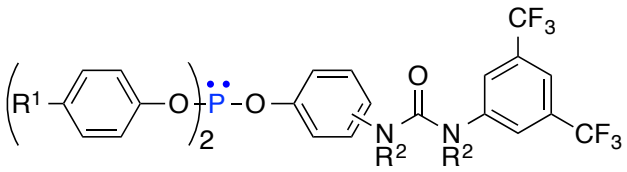
2-2. Results and Discussion

We first examined the activities of phosphorous(III) compounds[15] that catalyzed the bromocyclization of **1a**. 1.1 equiv. of NBS was used as a brominating reagent ("Br^+") and the reaction of **1a** was conducted in the presence of a phosphorous(III) compound (30 mol%) in toluene at –40 °C (Table 2.1). Although we previously reported that triphenylphosphine catalyzes the bromocyclization of **1a** in CH_2Cl_2,[8e] toluene was used as a solvent, since toluene is a more environmentally benign solvent than CH_2Cl_2. The reaction gave the desired *trans*-fused AB-ring product **2a** (X = Br) together with *endo*- and *exo*-isomeric A-ring products **3a** (X = Br) and undesired dibromide **4a** (X = Br). The ratio of **2a**, *endo*-**3a** and *exo*-**3a** in each reaction was *ca.* 1 : 1 : 1.[16] Since A-ring products **3a** could be quantitatively converted to AB-ring products **2a** by treatment with $SnCl_4$ and trifluoroacetic acid, the combined yield of **2a** and **3a** was evaluated by ^1H NMR analysis of the crude product. As a

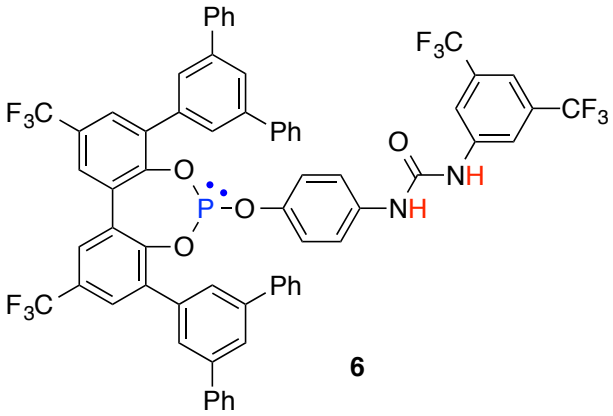
result, commercially available tributylphosphine (PBu_3), triphenylphosphine (PPh_3) and $P(OPh)_3$ gave poor results (1–10% yield), and undesired **4a** was obtained in 4–13% yield (entries 2–4). Very interestingly, triaryl phosphites bearing electron-withdrawing groups such as $P(OC_6H_4\text{-}4\text{-}F)_3$ and $P(OC_6H_4\text{-}4\text{-}CF_3)_3$ showed moderate catalytic activities and gave the bromocyclization products in respective yields of 24 and 39%, despite their low nucleophilicity. However, the use of these less nucleophilic phosphites also gave **4a** in yields of 19% and 22% (entries 5 and 6).

Table 2.1. Catalytic Activities of Phosphorous(III) Compounds for the Bromocyclization of **1a**





5a: *para*-substituted, R^1 = F, R^2 = H
5b: *para*-substituted, R^1 = CF_3, R^2 = H
5c: *meta*-substituted, R^1 = CF_3, R^2 = H
5d: *para*-substituted, R^1 = CF_3, R^2 = Me



6

Entry	Catalyst	Y [mol%]	"Br^+"	t [h]	Yield[a] [%]	
					2a + **3a**	**4a**
1	–	0	NBS	6	0	0
2	PBu_3	30	NBS	6	3	5
3	PPh_3	30	NBS	6	1	4
4	$P(OPh)_3$	30	NBS	6	10	13
5	$P(OC_6H_4\text{-}4F)_3$	30	NBS	6	24	19
6	$P(OC_6H_4\text{-}4CF_3)_3$	30	NBS	6	39	22
7[b]	$P(OC_6H_4\text{-}4CF_3)_3$	30	NBS	6	74	8
8[b]	–	0	NBS	6	0	0
9	**5a**	30	NBS	22	60	9
10	**5b**	30	NBS	6	96	0
11	**5c**	30	NBS	6	36	11
12	**5d**	30	NBS	6	84	6
13	**5b**	5	NBS	22	82	2
14[c,d]	**5b**	10	NBS	24	85	5
15[c]	**5b**	5	DBH	6	98	0
16[c]	**5b**	0.5	DBH	30	89	0
17	**6**	5	NBS	6	99	0
18[c]	**6**	0.5	DBH	30	96	0

[a] Yields were evaluated by ^1H NMR analysis. [b] The reaction was conducted in the presence of **10** (30 mol%). [c] The reaction was conducted at −60 °C. [d] The reaction was conducted in CH_2Cl_2.

Here we propose a mechanism of the triaryl phosphite-catalyzed bromocyclization of **1a** and the generation of undesired dibromide **4a** (Figure 2.1). Bromophosphonium ion **7** is presumably generated as an active species *via* the nucleophilic activation of NBS by the triaryl phosphite catalyst[8] (step 1). Siteselective bromination of the terminal double bond of **1a** with **7** (step 2) followed by cyclization gives the desired bromocyclization products **2a** and **3a**. Less nucleophilic phosphites [$P(OC_6H_4\text{-}4\text{-}F)_3$ and $P(OC_6H_4\text{-}4\text{-}CF_3)_3$] were more effective than nucleophilic phosphites and phosphines [PBu_3, PPh_3 and $P(OPh)_3$] as catalysts

(entries 2–6). Based on these results, it was proposed that electron-withdrawing groups on the phosphine atom increase the reactivity of **7**, and that step 2 is rate-determining.

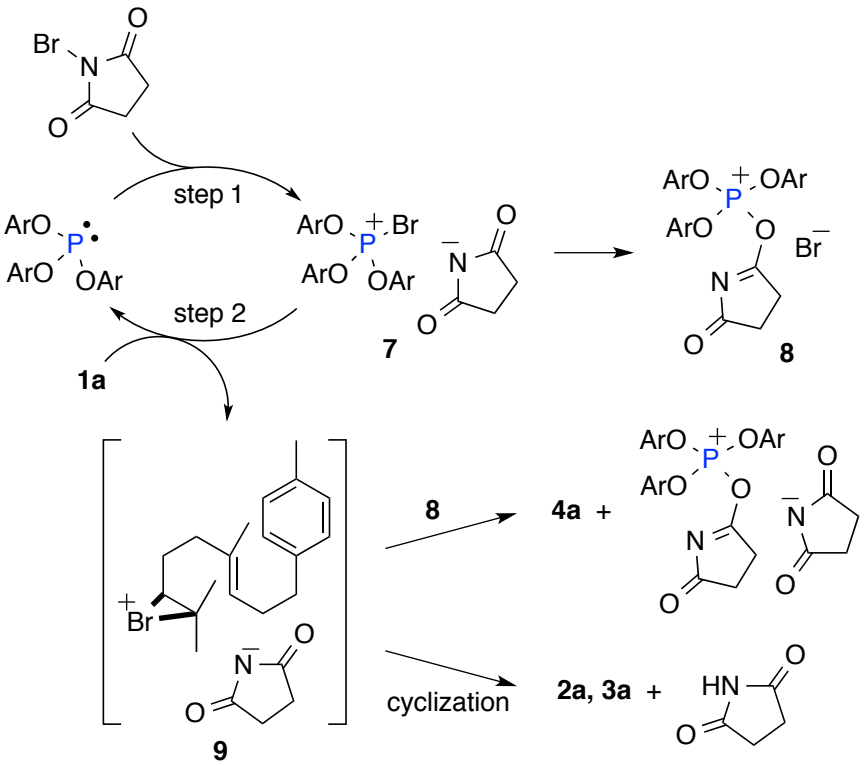


Figure 2.1. Proposed Mmechanism of the Phosphite-Catalyzed Bromocyclization of **1a** and Generation of Dibromide **4**

In another pathway, phosphonium bromide **8** might be generated[17] through the nucleophilic attack of the succinimide anion to the bromophosphonium ion **7**.[18] The reaction of **8** with bromonium ion **9** should give undesired dibromide **4a** and succinimide. As shown in Table 2.2, the yields of byproduct **4a** were almost the same as the amount of catalyst loading, and a lower catalyst loading resulted in lower conversion. These results might support the proposed mechanism shown in Figure 2.1.

Table 2.2. Correlation of Catalyst Loading and Generation of **4a**[a]

			Yield[b] [%]		
Entry	NBS [equiv.]	$P(OPh)_3$ [mol%]	**2a** + **3a**	**4a**	**1a**
1	1.1	10	17	9	74
2	1.1	30	17	24	55
3	1.1	50	15	49	30
4	2.0	50	23	48	22

[a] The reaction of **1a** was conducted with NBS (1.1–2.0 equiv.) in the presence of $P(OPh)_3$ (10–50 mol%) in CH_2Cl_2 at −40 °C for 22 h. [b] Yields were evaluated by ^{1}H NMR analysis.

For successful promotion of the bromocyclization of **1a**, it is critical to suppress the generation of phosphonium bromide **8**. Further investigation of the catalytic activities of various triaryl phosphites revealed that the introduction of urea at the *para*-position of the catalyst (**5a** and **5b** in Table 2.1)[19,20] successfully inhibited the generation of **4a** (yields of 9% and 0%) and other byproducts (*ca.* 0% yield) to improve the yields of **2a** and **3a** (60% and 96%, entries 9 and 10, Table 2.1). On the other hand, the *meta*-substituted derivative of **5b** (catalyst **5c**) and *N,N*'-dimethylated derivative of **5b** (catalyst **5d**)[21] were less effective than **5b** (entries 11 and 12, Table 2.1). *N*-[3,5-Bis(trifluoromethyl)-phenyl]-*N'*-phenylurea (**10**) was inert (entry 8), and the combined use of $P(OC_6H_4\text{-}4\text{-}CF_3)_3$ and **10** generated **4a** much more than the use of **5b** (entry 7, Table 2.1). These results indicated that the introduction of the urea group at the *para*-position was critical for the high catalytic activity. Catalyst **5b** was highly active and the use of 5 mol% of **5b** was sufficient to promote the reaction and give a mixture of **2a** and **3a** in 82% yield (entry 13, Table 2.1). Although the use of phosphite–urea combination catalyst **5** reduced the generation of **4a**, the reaction in CH_2Cl_2 gave **4a** much more than that in toluene (entry 14, Table 2.1).

A proposal for the active species generated from NBS and phosphite–urea combination catalyst **5** is shown in Figure 2.2. The activation of NBS with **5** presumably generates bromophosphonium ion **11**, in which the succinimide anion might interact with the urea group through hydrogen bonding.[22,23] ^{1}H NMR experiments suggested the hydrogen bonding between the succinimide anion and the urea group of the catalyst. In addition, a MS peak corresponding to a 1 : 1 complex of the catalyst and succinimide anion was observed in negative ESI-MS analysis.[24] This hydrogen bonding interaction in **11** might successfully

inhibit the nucleophilic attack of succinimide anion to the bromophosphonium ion and the formation of phosphonium bromide **12**. Therefore, the generation of dibromide **4a** might be suppressed. The hydrogen bonding complex **11** might be unstable in CH_2Cl_2, a more polar solvent than toluene, and easily decompose to **12**. This might be the reason why the **5b**-catalyzed reaction in CH_2Cl_2 gave **4a** much more than that in toluene.

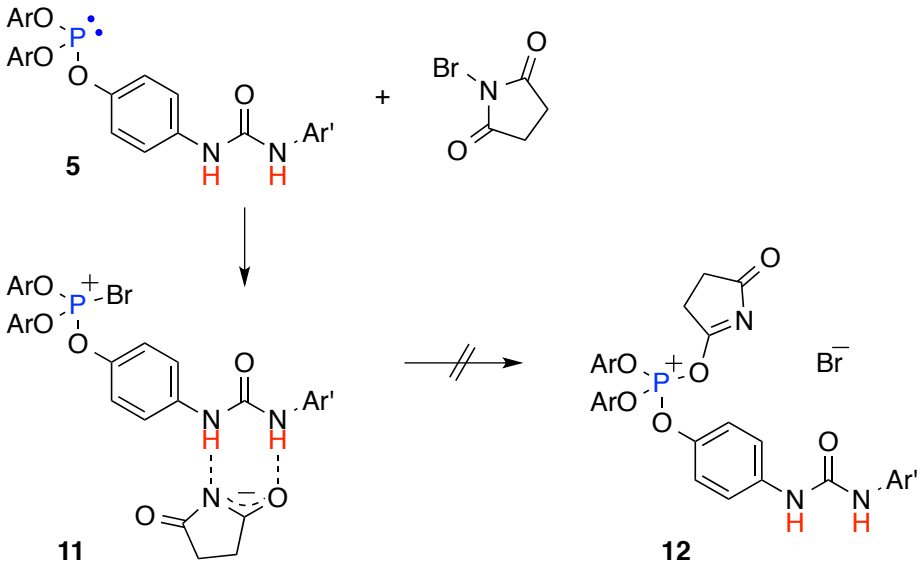


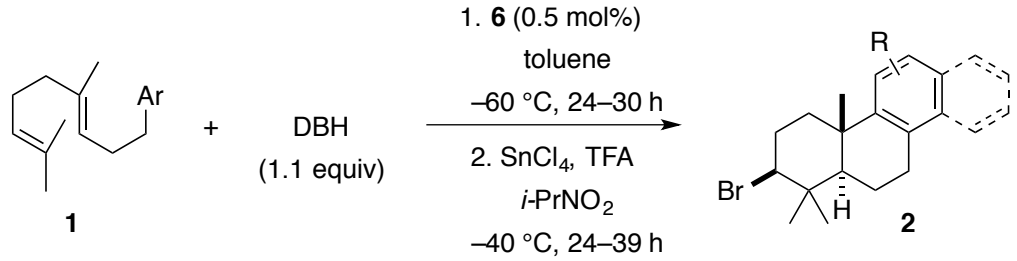
Figure 2.2. Proposed Active Species **11** Generated from Phosphite–Urea Cooperative Catalyst **5**.

Through optimization of the reaction conditions, we found that the use of 1,3-dibromo-5,5-dimethylhydantoin (DBH), a more reactive brominating reagent ("Br^+") than NBS, at −60 °C further improved the reactivity and decreased the reaction time (98% yield in 6 h, entry 15, Table 2.1).[25] The catalyst loading was successfully reduced to 0.5 mol% without any loss of yield of **2a** and **3a** (entry 16, Table 2.1). Biphenol-derived phosphite–urea cooperative catalyst **6** showed higher activity than **5b** and the bromocyclization products **2a** and **3a** were obtained in quantitative yield (entries 17 and 18, Table 2.1).[26] The steric effect of the 3,3'-terphenyl groups in the catalyst might further inhibit the decomposition of **6**, and the cavity effect of the catalyst might increase the siteselectivity in bromination.

With highly active phosphite–urea combination catalyst **6** in hand, we investigated the bromocyclization of various homogeranylarenes **1** (Table 2.3). The isolated yields of the corresponding AB-ring products **2** were evaluated after subsequent treatment with $SnCl_4$ and

TFA in *i*-$PrNO_2$ at –40 °C. As shown in Table 2.3, a variety of homogeranylarenes bearing an electron-donating or -withdrawing substituent on the aryl group were smoothly cyclized to give the desired *trans*-fused AB-ring products **2** in excellent yields along with small amounts of the corresponding *cis*-diastereomers. The *cis*-fused products were generated in the second acid-treatment step, while the first bromonium-induced cyclization step gave only *trans*-diastereomers.

Table 2.3. **6**-Catalyzed Bromocyclization of **1**

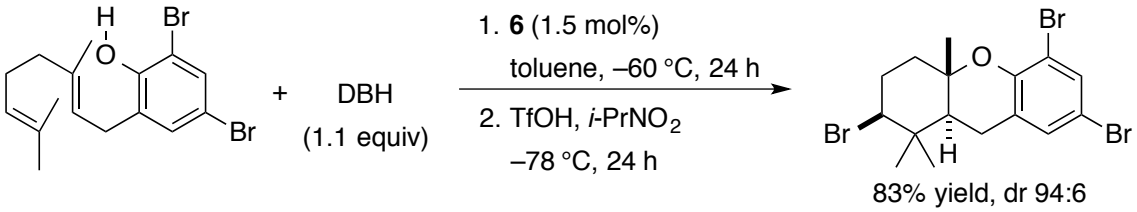


Entry	**1**	Ar	**2**	Yield (%)[a]	dr[b]
1	**1a**	4-MeC_6H_4	**2a**	94	95:5
2	**1b**	4-$MeOC_6H_4$	**2b**	90	96:4
3	**1c**	4-FC_6H_4	**2c**	91	>99:1
4	**1d**	4-ClC_6H_4	**2d**	90	>99:1
5	**1e**	3,5-$Me_2C_6H_3$	**2e**	84	>99:1
6	**1f**	4-MeO-3-*i*-PrC_6H_4	**2f**	91	95:5
7	**1g**	1-naphthyl	**2g**	91	92:8

[a] Isolated yield. [b] Ratio of *trans*- and *cis*-diastereomer.

The present method could also be applied to the bromocyclization of 2-geranylphenols. For example, the reaction of 2,4-dibromo-6-geranylphenol conducted in the presence of **6** (1.5 mol%) under the optimized conditions followed by the acid treatment gave the corresponding bromocyclization product in 83% yield (dr 94 : 6) (Scheme 2.2).

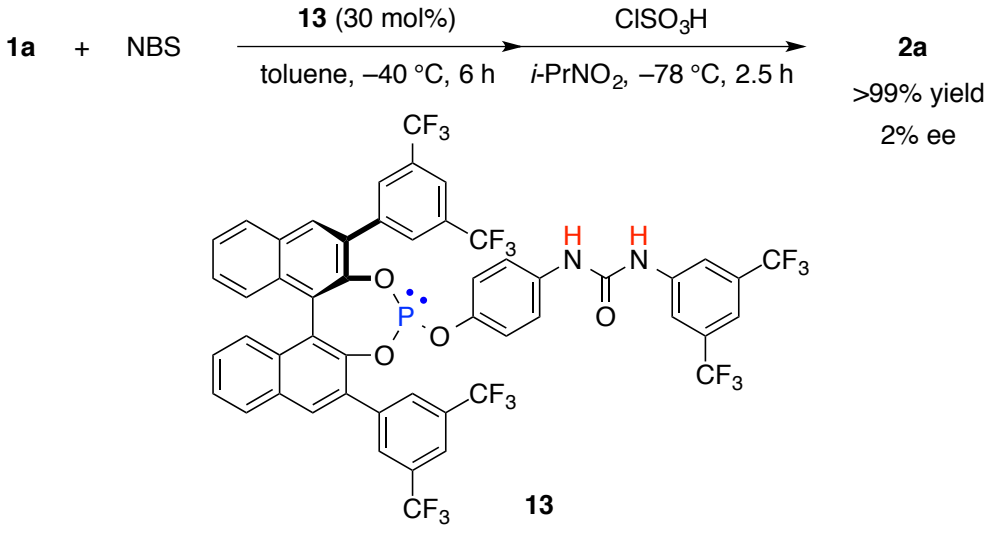
Scheme 2.2. Bromocyclization of 2,4-Dibromo-6-geranylphenol



2-3. Conclusions

In conclusion, we have designed phosphite–urea cooperative high-turnover catalyst **6** for the highly selective bromocyclization of homogeranylarenes **1**. The introduction of a urea and bulky aryl groups in the catalyst successfully inhibits decomposition of the catalyst and the generation of byproducts. The present method could also be applied to the bromocyclization of 2-geranylphenols. Development of an asymmetric version of the bromocyclization using a chiral catalyst is a next issue for this project. As a preliminary experiment, we conducted the bromocyclization of **1a** using chiral BINOL-derived phosphite–urea cooperative catalyst **13** (Scheme 2.3). But unfortunately, the reaction did not induce any enantioselectivity albeit the yield of **2a** was high.

Scheme 2.3. Attempt of Enantioselective Bromocyclization of **1a**



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L.; Peng, X.; Shi, Y. *Org. Lett.* **2011**, *13*, 6350. (c) Hennecke, U.; Müller, C. H.; Fröhlich, R. *Org. Lett.* **2011**, *13*, 860. (d) Kwon, H. Y.; Park, C. M.; Lee, S. B.; Youn, J.-H.; Kang, S. H. *Chem. Eur. J.* **2008**, *14*, 1023. (e) Kang, S. H.; Lee, S. B.; Park, C. M. *J. Am. Chem. Soc.* **2003**, *125*, 15748.

12. The unknown byproducts might include the bromination of the internal alkene.
13. The iodocyclization of **1a** proceeded cleanly, and gave only trace amounts (ca. 1%) of unknown compounds as byproducts.
14. The chlorocyclization of **1a** with *N*-chlorosuccinimide (NCS) did not proceed under the optimized conditions. See Experimental Section.
15. Nucleophilic amines were almost inert for the present bromocyclization. See ref. 8d.
16. The crude product did not include the tetrasubstituted A-ring product and the *cis*-fused AB-ring product.
17. (a) Leguern, D.; Morel, G.; Foucaud, A. *Tetrahedron Lett.* **1974**, *15*, 955. (b) Chasle, M.-F.; Marchand, E.; Foucaud, A. *Tetrahedron Lett.* **1971**, *12*, 963.
18. The fact that the iodocyclization of **1a** with NIS did not generate diiodide **4a** (X = I) (Scheme 2.1) suggested that the corresponding iodophosphonium ion was stable and did not decompose to phosphonium iodide.
19. For phosphine–urea or –thiourea combination catalysts, see: (a) Zhang, X.-N.; Shi, M. *ACS Catal.* **2013**, *3*, 507. (b) Deng, H.-P.; Wei, Y.; Shi, M. *Eur. J. Org. Chem.* **2012**, 183. (c) Hu, F.; Wei, Y.; Shi, M. *Tetrahedron* **2012**, *68*, 7911. (d) Zhong, F.; Han, X.; Wang, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 7837. (e) Gong, J.-J.; Li, T.-Z.; Pan, K.; Wu, X.-Y. *Chem. Commun.* **2011**, *47*, 1491. (f) Deng, H.-P.; Wei, Y.; Shi, M. *Eur. J. Org. Chem.* **2011**, 1956. (g) Yang, Y.-L.; Pei, C.-K.; Shi, M. *Org. Biomol. Chem.* **2011**, *9*, 3349. (h) Yuan, K.; Song, H.-L.; Hu, Y.; Fang, J.-F.; Wu, X.-Y. *Tetrahedron: Asymmetry* **2010**, *21*, 903. (i) Gong, J.-J.; Yuan, K.; Wu, X.-Y. *Tetrahedron: Asymmetry* **2009**, *20*, 2117. (j) Fang,Y.-Q.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 5660. (k) Yuan, K.; Zhang, L.; Song, H.-L.; Hu, Y.; Wu, X.-Y. *Tetrahedron Lett.* **2008**, *49*, 6262. (l) Shi, Y.-L.; Shi, M. *Adv. Synth. Catal.* **2007**, *349*, 2129.
20. Phosphate triesters of **5b**, which were prepared from **5b** by TBHP oxidation, did not show any catalytic activity for the bromocyclization of **1a**.
21. The conformational preference of *N,N'*-diaryl-*N,N'*-dimethylureas is proposed to be the "endo" or "stacked" conformer based on the conformational analysis of *N,N'*-diaryl-*N,*

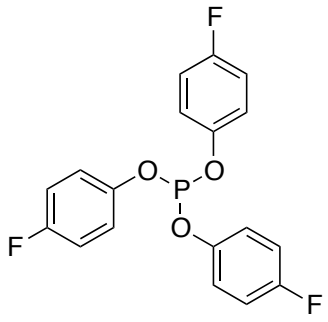
N'-dimethylureas by Clayden *et al.*: Clayden, J.; Henneche, U.; Vincent, M. A.; Hillier, I. H.; Helliwell, M. *Phys. Chem. Chem. Phys.* **2010**, *12*, 15056. The rather high activity of *N,N'*-dimethylated catalyst **5d** is probably due to steric hindrance of the folded urea moiety, which might inhibit the decomposition of active species **7** to **8**.

22. Veitch, G. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 7332.
23. For hydrogen bonding of (thio)urea group with carboxylates or hydrogen carbonate, see: (a) Boiocchi, M.; Boca, D. L.; Gómez, D. E.; Fabbrizzi, L.; Licchelli, M.; Monzani, E. *J. Am. Chem. Soc.* **2004**, *126*, 16507. (b) De, C. K.; Klauber, E. G.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 17060. (c) Kaluber, E. G.; Mittal, N.; Shah, T. K.; Seidel, D. *Org. Lett.* **2011**, *13*, 2464.
24. See Experimental Section for details.†
25. Low reaction temperature (−60 °C) might stabilize the hydrogen bonding interaction in **10** and inhibit the decomposition of the catalyst to reduce the generation of dibromide **4a**. The use of 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCO) as a brominating reagent gave slightly lower yield of **2a** than the use of NBS did. The steric bulkiness of the 2,4,6-tribromophenolate anion might be effective for the stabilization of active species **7**, albeit the phenolate is not an amide.
26. Strong Brønsted acids (0.5 mol%), such as TFA and TfOH, did not promote the bromocyclization of **1** with DBH under the same reaction conditions.

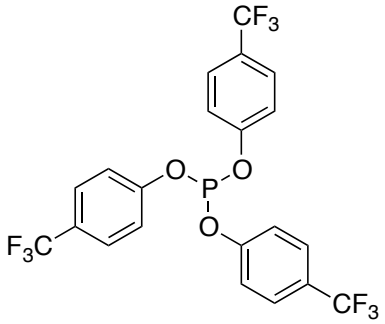
Experimental Section

General Methods. Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. ^{1}H NMR spectra were measured on a JEOL ECS-400 spectrometer (400 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet, sep = septet; m = multiplet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a JEOL ECS-400 spectrometer (100 MHz). Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.00 ppm). ^{19}F NMR spectra (376 MHz) and ^{31}P NMR spectra (162 MHz) were measured on a JEOL ECS-400 spectrometer. The reactions were carried out under an atmosphere of dry nitrogen. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254} 0.25 mm or silica gel NH_2 F_{254S} 0.25 mm) were used. The products were purified by column chromatography on silica gel (E. Merck Art. 9385). High resolution mass spectral analysis (HRMS) was performed at Chemical Instrumentation Facility, Nagoya University on JEOL JMS-700 spectrometer (for FAB) or JEOL JMS-T100GCV spectrometer (for EI) or Bruker Daltonics micrOTOF-QII (for ESI). HRMS analysis of an arylboronic acid was performed after conversion to its ester with 1,3-propanediol. Dry tetrahydrofuran, diethylether, toluene and dichloromethane were purchased from Kanto as the “anhydrous” and stored under nitrogen. Dry acetonitrile were purchased from Wako as the “anhydrous” and stored under nitrogen. Triethylamine were freshly distilled from calcium hydride. Other simple chemicals were analytical-grade and obtained commercially.

Preparation of Triaryl Phosphites.

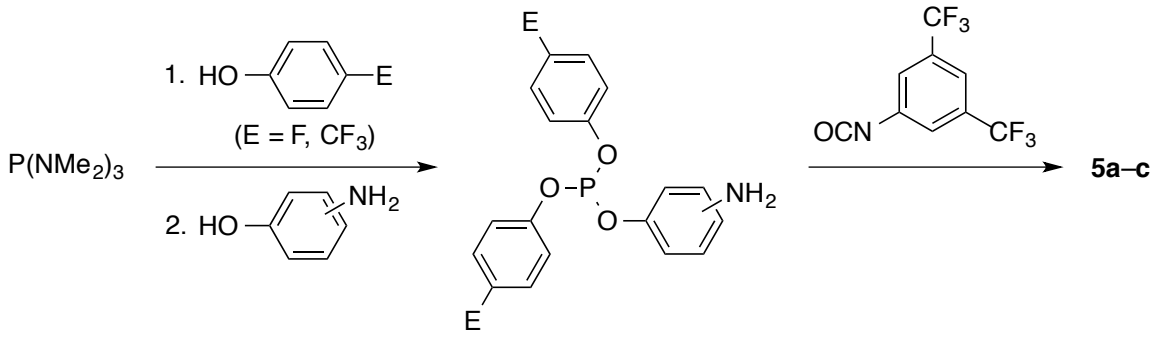


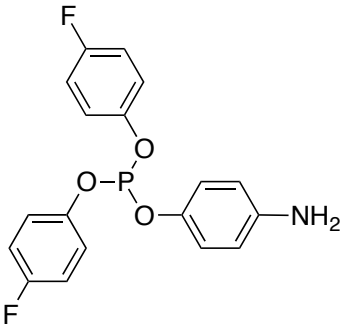
Tris(4-fluorophenyl) phosphite:[1] To a solution of 4-fluorophenol (2.43 g, 21.7 mmol) and Et_3N (3.22 mL, 23.1 mmol) in THF (140 mL) was added PCl_3 (610 μL, 7.0 mmol) dropwise at 0 °C. The mixture was warmed to ambient temperature and stirred for 20 h. The reaction mixture was filtered through a Celite pad and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane–toluene 5:1) to give tris(4-fluorophenyl) phosphite as a colorless oil (1.53 g, 60% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10–6.97 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4 (d, $J_{C\text{-}F}$ = 242 Hz, 3C), 147.1 (3C), 121.9 (d, $J_{C\text{-}F}$ = 7.7 Hz, $J_{C\text{-}P}$ = 7.7 Hz, 6C), 116.3 (d, $J_{C\text{-}F}$ = 24.0 Hz, 6C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –118.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ 128.0.



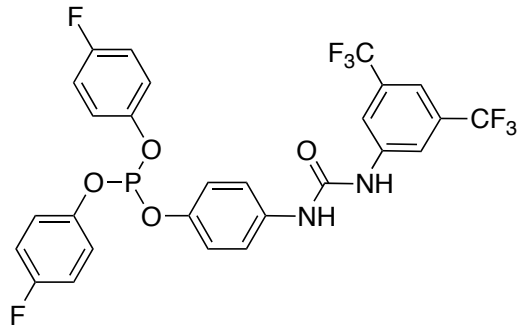
Tris(4-(trifluoromethyl)phenyl) phosphite:[1] Tris(4-(trifluoromethyl)phenyl) phosphite was prepared from PCl_3 and 4-hydroxybenzotrifluoride according to the same manner as tris(4-fluorophenyl) phosphite. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.7 Hz, 6H), 7.23 (d, J = 8.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8(3C), 127.3 (q, $J_{C\text{–}F}$ = 3.8 Hz, 6C), 127.0 (q, $J_{C\text{–}F}$ = 33.6 Hz, 3C), 123.9 (q, $J_{C\text{–}F}$ = 271 Hz, 3C), 120.7 (q, $J_{C\text{–}P}$ = 7.7 Hz, 6C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 126.2.

Preparation of Phosphite–Urea Cooperative Catalysts 5a–c.

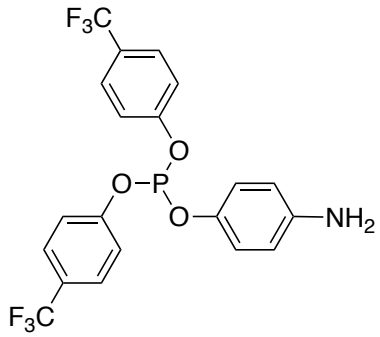




4-Aminophenyl bis(4-fluorophenyl) phosphite: To a solution of 4-fluorophenol (448 mg, 4.0 mmol) in DME (2.0 mL) was added *N*,*N*,*N*',*N*',*N*'',*N*''-hexamethylphosphinetriamine (363 μL, 2.0 mmol) at ambient temperature. The mixture was heated at reflux and stirred for 21 h, and then concentrated *in vacuo*. To a solution of the residue in acetonitrile (10.0 mL) was added 4-aminophenol (284 mg, 2.6 mmol) and *N*-phenylimidazolium trifluoromethanesulfonate salt (647 mg, 2.2 mmol) at ambient temperature. After stirring for 12 h at the same temperature, the reaction mixture was concentrated *in vacuo*. The residue was quickly purified by column chromatography on silica gel (hexane–toluene 1:1). Bulb to bulb distillation by elmination of *p*-fluorophenol (80 °C, 5 mmHg) afforded to 4-aminophenyl bis(4-fluorophenyl) phosphite (347 mg, 48% yield). IR (neat) 3458, 3379, 1871, 1623, 1498, 1186, 1091 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10–7.04 (m, 4H), 7.04–6.96 (m, 4H), 6.91 (d, J = 8.7 Hz, 2H), 6.63 (d, J = 8.7 Hz, 2H), 3.58 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 (d, $J_{C\text{-}F}$ = 241 Hz, 2C), 147.3 (2C), 143.3 (d, $J_{C\text{-}P}$ = 2.9 Hz), 143.1, 122.0 (dd, $J_{C\text{-}F}$ = 6.7 Hz, $J_{C\text{-}P}$ = 6.7 Hz, 4C), 121.5 (d, $J_{C\text{-}P}$ = 6.7 Hz, 2C), 116.2 (d, $J_{C\text{-}F}$ = 23.8 Hz, 4C), 116.0 (2C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –119.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 128.8; HRMS (FAB) calcd for $C_{18}H_{14}F_2NO_3P^+$ $[M]^+$ 361.0679, found 361.0667.

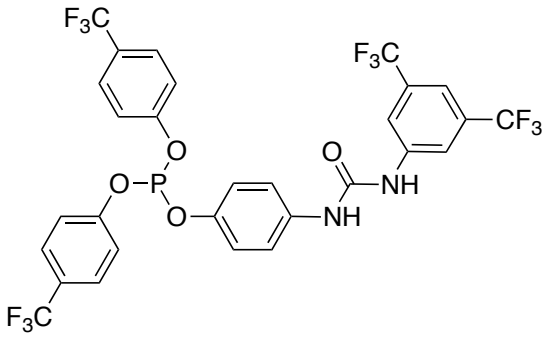


4-(3-(3,5-Bis(trifluoromethyl)phenyl)ureido)phenyl bis(4-fluorophenyl) phosphite (5a): To a solution of 4-aminophenyl bis(4-fluorophenyl) phosphite (347 mg, 0.96 mmol) in CH_2Cl_2 (3.0 mL) was added 3,5-bis(trifluoromethyl)phenyl isocyanate (200 μL, 1.15 mmol) at ambient temperature. After stirring for 3 h at the same temperature, the reaction mixture was diluted with hexane (10.0 ml) and insoluble urea starts to precipitate as a colorless solid. The solid was filtered off and washed with hexane to give **5a** (81% yield) as a product. IR (KBr) 3318, 1657, 1584, 1500, 1475, 1391, 1275, 1189, 1129 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 2H), 7.53 (s, 1H), 7.29 (d, J = 8.7 Hz, 2H), 7.12 (d, J = 8.7 Hz, 2H), 7.10–6.96 (m, 9H), 6.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4 (d, $J_{C\text{-}F}$ = 242 Hz, 2C), 154.2, 148.5, 147.0 (2C), 139.2, 132.9, 132.3 (q, $J_{C\text{-}F}$ = 33.4 Hz, 2C), 123.2 (2C), 123.0 (q, $J_{C\text{-}F}$ = 242 Hz, 2C), 121.8 (dd, $J_{C–F}$ = 7.6 Hz, $J_{C–P}$ = 7.6 Hz, 4C), 121.3 (d, $J_{C–P}$ = 6.7 Hz, 2C), 119.5 (2C), 116.9, 116.3 (d, $J_{C–F}$ = 22.9 Hz, 4C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –63.1, –118.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 128.0; HRMS (FAB) calcd for $C_{27}H_{18}F_8N_2O_4P^+$ $[M+H]^+$ 617.0871, found 617.0874.

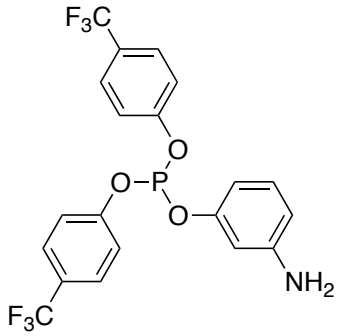


4-Aminophenyl bis(4-(trifluoromethyl)phenyl) phosphite: 4-Aminophenyl bis(4-(trifluoromethyl)phenyl) phosphite was prepared from *N*,*N*,*N*',*N*',*N*'',*N*''-hexamethylphosphinetriamine and 4-hydroxybenzotrifluoride according to the same manner as 4-aminophenyl bis(4-fluorophenyl) phosphite. IR (neat) 3383, 1612, 1507, 1416, 1324, 1207, 1169, 1123, 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J =

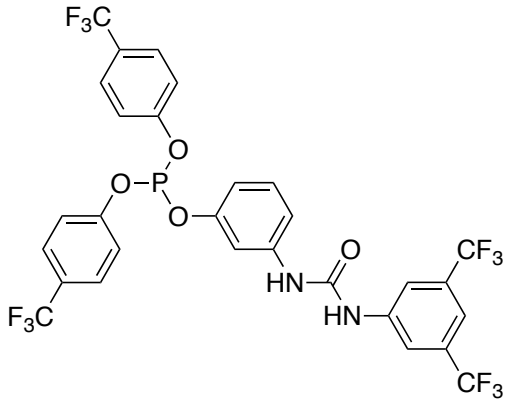
8.7 Hz, 4H), 7.22 (d, J = 8.7 Hz, 4H), 6.92 (d, J = 8.7 Hz, 2H), 6.63 (d, J = 8.7 Hz, 2H), 3.62 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2 (2C), 143.4, 142.9, 127.1 (q, $J_{C\text{-}F}$ = 3.8 Hz, 4C), 126.5 (q, $J_{C\text{-}F}$ = 33.4 Hz, 2C), 124.0 (q, $J_{C\text{-}F}$ = 271 Hz, 2C), 121.5 (d, $J_{C\text{-}P}$ = 5.7 Hz, 2C), 120.7 (d, $J_{C\text{-}P}$ = 6.7 Hz, 4C), 116.1 (2C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –61.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 127.5; HRMS (FAB) calcd for $C_{20}H_{14}F_6NO_3P^+$ $[M]^+$ 461.0615, found 461.0624.



4-(3-(3,5-Bis(trifluoromethyl)phenyl)ureido)-phenyl bis(4-(trifluoromethyl)phenyl) phosphite (5b): Compound **5b** was prepared from 4-aminophenyl bis(4-(trifluoromethyl)phenyl) phosphite and 3,5-bis(trifluoromethyl)phenyl isocyanate according to the same manner as **5a**. IR (KBr) 3344, 1657, 1612, 1571, 1508, 1474, 1388, 1326, 1280, 1168, 1139, 1067 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 2H), 7.62 (d, J = 8.7 Hz, 4H), 7.55 (s, 1H), 7.34 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 8.7 Hz, 4H), 7.14 (d, J =8.7 Hz, 2H), 6.78 (brs, 1H), 6.52 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8 (2C), 153.2, 148.2, 139.4, 133.4, 132.3 (q, $J_{C\text{–}F}$ = 33.4 Hz, 2C), 127.2 (q, $J_{C\text{–}F}$ = 3.8 Hz, 4C), 126.8 (q, $J_{C\text{–}F}$ = 33.4 Hz, 2C), 123.9 (q, $J_{C\text{–}F}$ = 271 Hz, 2C), 123.4 (2C), 122.9 (q, $J_{C\text{–}F}$ = 271 Hz, 2C), 121.5 (d, $J_{C\text{–}P}$ = 6.7 Hz, 2C), 120.6 (d, $J_{C\text{–}P}$ = 7.6 Hz, 4C), 119.3 (2C), 116.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.0, –63.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 126.7; HRMS (FAB) calcd for $C_{29}H_{17}F_{12}N_2O_4P^+$ $[M]^+$ 716.0734, found 716.0746.

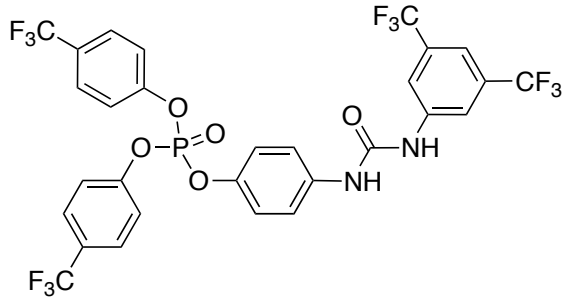


3-Aminophenyl bis(4-(trifluoromethyl)phenyl) phosphite: 3-Aminophenyl bis(4-(trifluoromethyl)phenyl) phosphite was prepared from *N*,*N*,*N*',*N*',*N*'',*N*''-hexamethylphosphinetriamine, 4-hydroxybenzotrifluoride and 3-aminophenol according to the same manner as 4-aminophenyl bis(4-fluorophenyl) phosphite. IR (KBr) 3482, 3392, 1909, 1611, 1510, 1493, 1417, 1321, 1208, 1067 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.7 Hz, 4H), 7.23(d, J = 8.7 Hz, 4H), 7.10 (dd, J = 7.8, 7.8 Hz, 1H), 6.51 (J = 7.8 Hz, 1H), 6.48 (J = 7.8 Hz, 1H), 6.42 (s, 1H), 3.74 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 152.1 (d, J_{C-P} = 5.7 Hz, 2C), 148.1, 130.5, 127.2 (q, J_{C-F} = 3.4 Hz, 4C), 126.6 (q, J_{C-F} = 32.4 Hz, 2C), 124.0 (q, J_{C-F} = 271 Hz, 2C), 120.8 (d, J_{C-P} = 7.8 Hz, 4C), 111.5, 110.0 (d, J_{C-P} = 7.6 Hz), 106.8 (d, J_{C-P} = 7.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –61.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 127.0; HRMS (FAB) calcd for $C_{20}H_{14}F_6NO_3P^+$ $[M]^+$ 461.0615, found 461.0614.



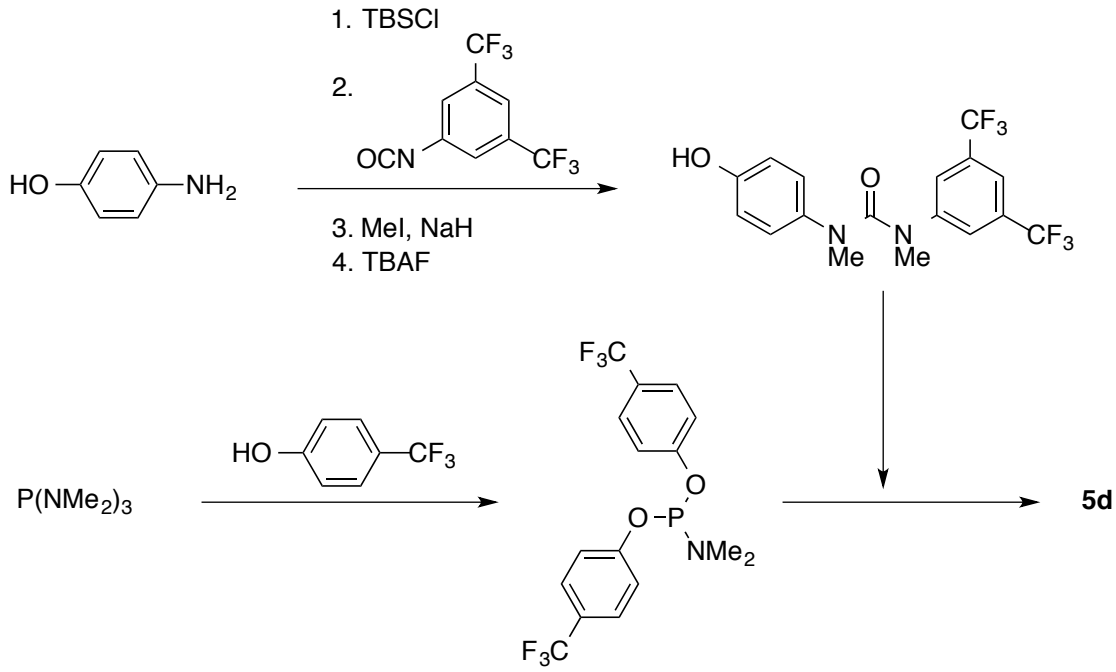
3-(3-(3,5-Bis(trifluoromethyl)phenyl)ureido)phenyl bis(4-(trifluoromethyl)phenyl) phosphite (5c): Compound **5c** was prepared from 3-aminophenyl bis(4-(trifluoromethyl)phenyl) phosphite and 3,5-bis(trifluoromethyl)phenyl isocyanate according to the same manner as **5a**. IR (KBr) 3339, 1657, 1611, 1573, 1389, 1327, 1277, 1170, 1127, 1068 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 2H), 7.55 (d, J = 8.7 Hz, 4H), 7.48 (s, 1H), 7.44 (s, 1H), 7.35 (s, 1H), 7.24 (s, 1H), 7.22 (dd, J = 7.8, 7.8 Hz, 1H), 7.17 (d, J

= 8.7 Hz, 4H), 6.93 (d, J = 7.8 Hz, 2H), 6.87 (d, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7 (2C), 153.3, 151.8, 139.1, 138.4, 132.3 (q, J_{C-F} = 33.4 Hz, 2C), 130.5, 127.1 (q, J_{C-F} = 3.8 Hz, 4C), 126.8 (q, J_{C-F} = 33.4 Hz, 2C), 123.8 (q, J_{C-F} = 270 Hz, 2C), 122.8 (q, J_{C-F} = 272 Hz, 2C), 120.6 (d, J_{C-P} = 6.7 Hz, 4C), 119.4 (2C), 117.1, 116.7, 116.5 (d, J_{C-P} = 7.6 Hz), 113.1 (d, J_{C-P} = 6.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.0, –63.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 126.7; HRMS (FAB) calcd for $C_{29}H_{17}F_{12}N_2O_4P^+$ $[M]^+$ 716.0734, found 716.0735



4-(3-(3,5-Bis(trifluoromethyl)phenyl)ureido)-phenyl bis(4-(trifluoromethyl)phenyl) phosphate: To a suspension of **5b** (143 mg, 0.2 mmol) in CH_2Cl_2 (5 mL) was added 5.5 M solution of TBHP in nonane (73 μL, 0.4 mmol) at 0 °C. After stirring for 3 h at ambient temperature, the reaction was quenched with saturated aqueous $Na_2S_2O_3$. The mixture was extracted with EtOAc, and the combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The residue was reprecipitated from CH_2Cl_2–heaxne to give 4-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)phenyl bis(4-(trifluoromethyl)phenyl) phosphate as a colorless solid (109 mg, 74% yield). IR (KBr) 3346, 1651, 1612, 1572, 1509, 1471, 1388, 1326, 1280, 1170, 1146, 1068 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (br s, 1H), 7.77 (s, 2H), 7.68 (d, J = 8.7 Hz, 4H), 7.48 (s, 1H), 7.38 (d, J = 8.7 Hz, 4H), 7.19 (brs, 1H), 7.09 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 152.0 (d, J_{C-P} = 7.6 Hz, 2C), 144.9 (q, J_{C-F} = 7.6 Hz), 140.3, 136.5, 132.1 (q, J_{C-F} = 33.4 Hz, 2C), 129.1 (q, J_{C-F} = 34.3 Hz, 2C), 127.8 (q, J_{C-F} = 3.8 Hz, 4C), 123.3 (q, J_{C-F} = 271 Hz, 2C), 123.1 (q, J_{C-F} = 271 Hz, 2C), 121.8 (2C), 120.3 (d, J_{C-P} = 4.8 Hz, 2C), 120.2 (d, J_{C-P} = 4.8 Hz, 4C), 118.0 (2C), 115.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.4, –63.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ –16.5; HRMS (FAB) calcd for $C_{29}H_{17}F_{12}N_2O_5P^+$ $[M]^+$ 732.0683, found 732.0697.

Preparation of 4-(3-(3,5-Bis(trifluoromethyl)phenyl)-1,3-dimethylureido)phenyl bis(4-(trifluoromethyl)phenyl) phosphite (5d).



To a solution of 4-aminophenol (1.09 g, 10.0 mmol) and imidazole (2.04 g, 30.0 mmol) in THF (20.0 mL) was added TBSCl (3.80 g, 15.0 mmol) at 0 °C. After stirring for 3 h at ambient temperature, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 50:1) to give 4-(*tert*-butyldimethylsilanyloxa)-phenyl aniline as pale yellow oil (2.17 g, 97% yield).

To a solution of 4-(*tert*-butyldimethylsilanyloxa)-phenyl aniline (2.17 g, 9.7 mmol) in CH_2Cl_2 (20 mL) was added 3,5-bis(trifluoromethyl)phenyl isocyanate (2.47 g, 9.7 mmol) at ambient temperature. After stirring for 1 h at the same temperature, the reaction mixture was diluted with hexane (10.0 mL) and insoluble urea starts to precipitate as a colorless solid. The solid was filtered off and washed with hexane to give 1-(3,5-bis(trifluoromethyl)phenyl)-3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)urea (8.54 g, 90% yield).

To a solution of 1-(3,5-bis(trifluoromethyl)phenyl)-3-(4-((*tert*-butyldimethylsilyl)oxy)-phenyl)urea (957 mg, 2 mmol) in THF (4.0 mmol) was added NaH (60% dispersion in oil; 160 mg, 4.0 mmol) at 0 °C. After stirring for 0.5 h, CH_3I (249 μL, 4.0 mmol) was added.

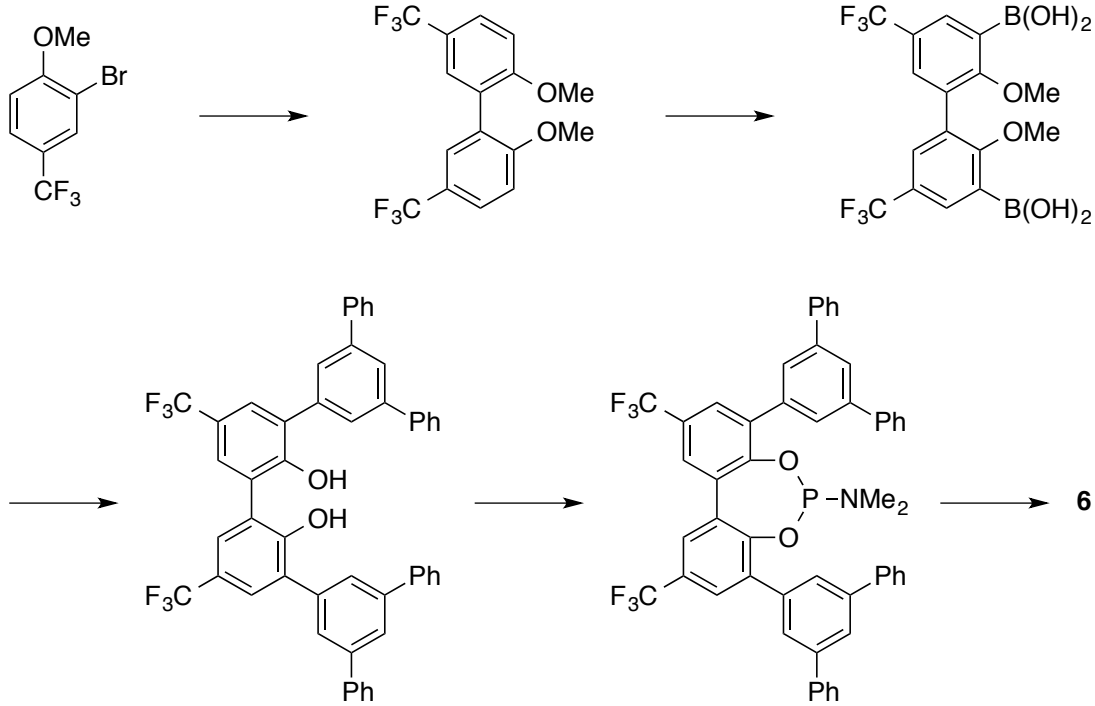
After stirring for 1 h at ambient temperature, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 50:1) to give 1-(3,5-bis(trifluoromethyl)phenyl)-3-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-1,3-dimet-hylurea as a pale yellow oil (729 mg, 72% yield).

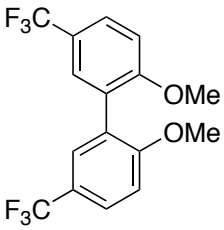
To a solution of 1-(3,5-bis(trifluoromethyl)phenyl)-3-(4-((*tert*-butyldimethylsilyl)oxy)p-henyl)-1,3-dimethylurea (729 mg, 1.44 mmol) in THF (7.0 mL) was added a THF solution of TBAF (1 M; 2.16 mL, 2.16 mmol) at ambient temperature. After stirring for 3 h at the same temperature, the reaction mixture was quenched with brine. The mixture was extracted with EtOAc, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 2:1) to give 1-(3,5-bis(trifluoromethyl)phenyl)-3-(4-hydroxyphenyl)-1,3-dimethylurea as a colorless solid (475 mg, 84% yield). ^{1}H NMR (400 MHz, acetone-d_6) δ 7.48 (s, 3H), 6.72 (d, J = 8.2 Hz, 2H), 6.55 (d, J = 8.2 Hz, 2H), 3.82 (s, 1H), 3.19 (s, 3H), 3.16 (s, 3H); 13C NMR (100 MHz, acetone-d_6) δ 160.3, 156.0, 148.2, 137.3, 132.1 (q, $J_{C–F}$ = 33.6 Hz, 2C), 127.8 (2C), 125.0 (2C), 124.0 (q, $J_{C–F}$ = 272 Hz, 2C), 117.3 (2C), 116.2 (2C), 39.8, 38.5.

To a solution of 4-hydroxybenzotrifluoride (324 mg, 2.0 mmol) in DME (1.0 mL) was added *N*,*N*,*N*',*N*',*N*'',*N*''-hexamethylphosphinetriamine (181 μL, 1.0 mmol) at ambient temperature. The mixture was heated at reflux and stirred for 21 h, and then concentrated *in vacuo*. To a solution of the residue in toluene (2 mL) was added 1-(3,5-bis(trifluoromethyl)phenyl)-3-(4-hydroxyphenyl)-1,3-dimethylurea (510 mg, 1.3 mmol) at reflux. After stirring for 2 h at the same temperature, the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane–EtOAc 5:1) to give **5d** as a colorless oil (156 mg, 21% yield). IR (neat) 1664, 1615, 1504, 1472, 1383, 1278, 1170 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.7 Hz, 4H), 7.39 (s, 1H), 7.19 (d, J = 8.7 Hz, 4H), 6.81 (d, J = 8.7 Hz, 2H), 6.73 (d, J =8.7 Hz, 2H), 3.26 (s, 3H), 3.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8 (2C), 153.8, 148.7 (d, $J_{C–P}$ = 3.8 Hz), 146.7, 141.2, 132.1 (q, $J_{C–F}$ = 33.4 Hz, 2C), 127.2 (q, $J_{C–F}$ = 3.8 Hz, 4C), 126.8 (q, $J_{C–F}$ = 32.6 Hz, 2C), 125.0, 123.9 (q, $J_{C–F}$ = 272 Hz, 2C), 122.7 (q, $J_{C–F}$ = 273 Hz, 2C), 120.8 (d, $J_{C–P}$ = 7.7 Hz, 2C), 120.6 (d, $J_{C–P}$ = 7.7 Hz, 4C), 117.8 (4C), 115.4, 39.6, 38.9; ^{31}P NMR (162

MHz, $CDCl_3$) δ 126.2; HRMS (FAB) calcd for $C_{31}H_{21}F_{12}N_2O_4P^+$ $[M]^+$ 744.1047, found 744.1071.

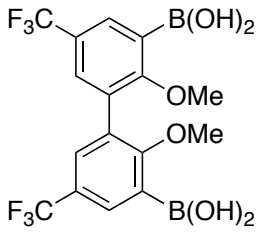
Preparation of Phosphite–Urea Cooperative Catalyst 6.



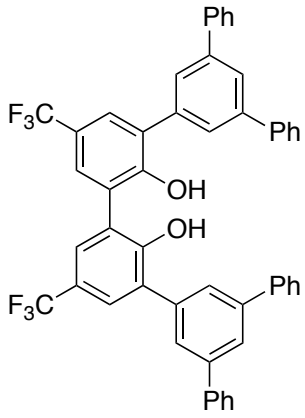


2,2'-Dimethoxy-5,5'-bis(trifluoromethyl)-1,1'-biphenyl: To a suspension of $NiBr_2$ (1.01 g, 4.63 mmol) in THF (25.0 mL) was added PPh_3 (2.43 g, 9.25 mmol) at ambient temperature. The mixture was heated at 80 °C for 0.5 h. After cooling to ambient temperature, Zn (909 mg, 13.9 mmol), Et_4NI (2.38 g, 9.25 mmol) and 2-bromo-1-methoxy-4-(trifluoromethyl)benzene (2.36 g, 9.25 mmol) in THF (5.0 mL) were added. The mixture was stirred at 50 °C for 58 h. After cooling to ambient temperature, the reaction mixture was filtered through a Celite pad and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane–EtOAc 10:1) to give 2,2'-dimethoxy-5,5'-bis(trifluoromethyl)-1,1'-biphenyl as a colorless solid (770 mg, 48% yield). IR (KBr) 1609, 1515, 1498, 1345, 1329, 1263, 1105 cm^{-1}; ^1H NMR (400

MHz, $CDCl_3$) δ 7.62 (dd, J = 8.7, 1.8 Hz, 2H), 7.49 (d. J = 1.8 Hz, 2H), 7.03 (d, J = 8.7 Hz, 2H), 3.82 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4 (2C), 128.4 (q, J_{C-F} = 3.8Hz, 2C), 126.8 (2C), 126.6 (q, J_{C-F} = 3.8 Hz, 2C), 124.4 (q, J_{C-F} = 271 Hz, 2C), 122.6 (q, J_{C-F} = 32.8 Hz, 2C), 110.8 (2C), 55.8 (2C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –61.3; HRMS (FAB) calcd for $C_{16}H_{12}F_6O_2^+$ $[M]^+$ 350.0741, found 350.0751.



(2,2'-Dimethoxy-5,5'-bis(trifluoromethyl)-[1,1'-biphenyl]-3,3'-diyl)diboronic acid: To a solution of 2,2'-dimethoxy-5,5'-bis(trifluoromethyl)-1,1'-biphenyl (1.05 g, 3.0 mmol) and TMEDA (1.35 mL, 9.0 mmol) in Et_2O (30.0 mL) was added 1.6 M solution of *n*-BuLi in hexane (5.6 mL, 9.0 mmol) at ambient temperature. After stirring for 3 h, the reaction mixture was cooled to –78 °C, and then added triethyl borate (3.55 mL, 21.0 mmol) dropwise. The mixture was warmed to ambient temperature and stirred for 11 h. To the mixture was added 1 M HCl (20.0 mL) solution and stirred at ambient temperature for 9 h. The aqueous layer was extracted with EtOAc, and the organic extract was washed with 1 M HCl solution and brine, dried over Na_2SO_4, filtered. The solvent was evaporated to leave a volume of 5 mL. To the residue was added hexane (50 mL), and the resulting solid was filtered and washed with hexane to give (2,2'-dimethoxy-5,5'-bis(trifluoromethyl)-[1,1'-biphenyl]-3,3'-diyl)diboronic acid as a pale yellow solid (990 mg, 75% yield). IR (KBr) 3410, 1606, 1590, 1469, 1431, 1302, 1158, 1123 cm^{-1}; ^{1}H NMR (400 MHz, THF–d_8) δ 7.96 (d, J = 2.3 Hz, 2H), 7.66 (d, J = 2.3Hz, 2H), 7.52 (s, 4H), 3.53 (s, 6H); ^{13}C NMR (100 MHz, THF–d_8) δ 166.0 (2C), 133.5 (2C), 131.3 (4C), 128.4 (2C), 125.9 (q, J_{C-F} = 32.4 Hz, 2C), 125.5 (q, J_{C-F} = 271 Hz, 2C), 61.7 (2C); ^{19}F NMR (376 MHz, THF–d_8) δ –62.5; HRMS (FAB, ester of (2,2'-dimethoxy-5,5'-bis(trifluoromethyl)-[1,1'-biphenyl]-3,3'-diyl)diboronic acid with 1,3-propanediol) calcd for $C_{22}H_{22}B_2F_6O_6^+$ $[M]^+$ 518.1507, found 518.1488.

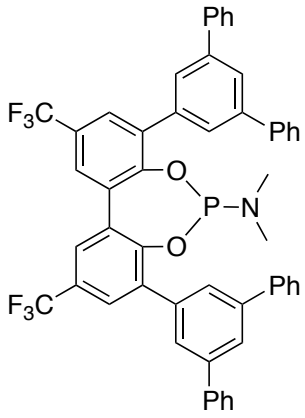


3,3'-Di([1,1':3',1''-terphenyl]-5'-yl)-5,5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2,2'-diol: To a solution of [1,1':3',1"-terphenyl]-5'-ol (4.93 g, 20.0 mmol) and pyridine (3.22 mL, 40.0 mmol) in CH_2Cl_2 (50.0 mL) was added trifluoromethanesulfonic anhydride (4.03 mL, 24.0 mmol) at 0 °C. The mixture was warmed to ambient temperature and stirred for 2 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with $CHCl_3$. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 5:1) to give [1,1':3',1"-terphenyl]-5'-yl trifluoromethanesulfonate as white solid (7.38 g, 98% yield).

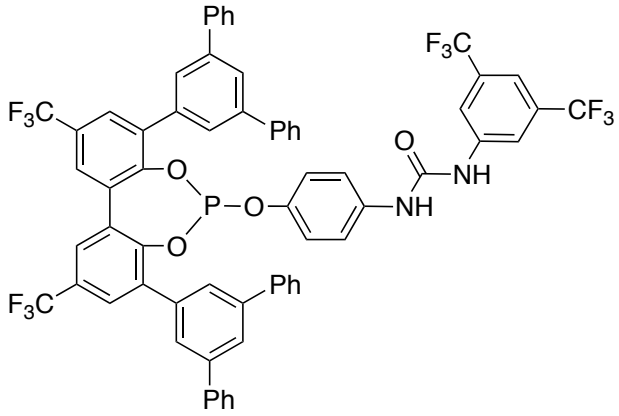
To a solution of (2,2'-dimethoxy-5,5'-bis(trifluoromethyl)-[1,1'-biphenyl]-3,3'-diyl) diboronic acid (427 mg, 1.0 mmol) in dioxane–water (16.0 mL, 3:1 v/v) were added [1,1':3',1"-terphenyl]-5'-yl trifluoromethanesulfonate (1.51 g, 4.0 mmol), $Ba(OH)_2 \cdot 8H_2O$ (946 mg, 3.0 mmol), and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) at ambient temperature. The mixture was stirred at reflux for 19 h. After cooling to ambient temperature, the reaction was quenched with 1 M HCl solution. To the mixture was added THF until a solid was dissolved, then extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to give crude coupling products.

To a solution of crude coupling products in CH_2Cl_2 (10.0 mL) was added a 1.0 M solution of BBr_3 in CH_2Cl_2 (4.0 mL, 4.0 mmol) at 0 °C. After stirring for 1 day at 0 °C, the reaction was quenched with water. The mixture was extracted with $CHCl_3$, and combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane–EtOAc 10:1) to give 3,3'-di([1,1':3',1"-terphenyl]-5'-yl)-5,5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2,2'-diol as a colorless solid (493 mg, 63% yield). IR (KBr) 3513, 1594, 1498, 1384, 1310, 1224, 1172, 1119 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (t, J = 1.4 Hz, 2H), 7.76–7.71 (m, 6H),

7.71–7.64 (m, 10H), 7.47 (t, J = 7.3 Hz, 8H), 7.40 (t, J = 7.3 Hz, 4H), 6.12 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5 (2C), 143.0 (4C), 140.3 (4C), 136.6 (4C), 126.9 (4C), 128.9 (8C), 128.4 (2C), 127.93 (2C), 127.87 (2C), 127.3 (8C), 126.8 (2C), 126.3 (2C), 124.7 (2C), 124.1 (q, J_{C-F} = 271 Hz, 2C), 123.9 (q, J_{C-F} = 32.4 Hz, 2C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –61.3; HRMS (FAB) calcd for $C_{50}H_{32}F_6O_2^+$ $[M]^+$ 778.2306, found 778.2291.



4,8-Di([1,1':3',1''-terphenyl]-5'-yl)-*N*,*N*-dimethyl-2,10-bis(trifluoromethyl)dibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-amine: To a solution of 3,3'-di([1,1':3',1''-terphenyl]-5'-yl)-5,5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2,2'-diol (493 mg, 0.63 mmol) and 1*H*-tetrazole (132 mg, 1.89 mmol) in THF (6.0 mL) was added *N*,*N*,*N*',*N*',*N*'',*N*''-hexamethylphosphinetriamine (228 μL, 1.26 mmol). The reaction mixture was heated at reflux for 4 h. After cooling to ambient temperature, the mixture was filtered through a Celite pad and a silica gel pad, washed with toluene, and the filtrate was concentrated to give 4,8-di([1,1':3',1''-terphenyl]-5'-yl)-*N*,*N*-dimethyl-2,10-bis-(trifluoromethyl)dibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-amine as a colorless solid (513 mg, 96% yield). IR (KBr) 1596, 1497, 1386, 1312, 1226, 1152, 1122 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88–7.80 (m, 10H), 7.68 (d, J =7.4 Hz, 8H), 7.47 (t, J = 7.4 Hz, 8H), 7.39 (t, J = 7.4 Hz, 4H), 2.16 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2 (2C), 141.9 (4C), 140.7 (4C), 137.4 (4C), 135.6 (4C), 132.1 (2C), 128.9 (8C), 127.9 (2C), 127.7 (2C), 127.24 (10C), 127.19 (q, J_{C-F} = 32.6 Hz, 2C), 126.4 (2C), 125.7 (2C), 123.9 (q, J_{C-F} = 272 Hz, 2C), 34.8, 34.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ –61.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ 151.3; HRMS (FAB) calcd for $C_{52}H_{37}F_6NO_2P^+$ $[M+H]^+$ 852.2461, found 852.2457.

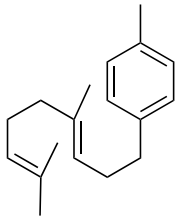


1-(3,5-Bis(trifluoromethyl)phenyl)-3-(4-((4,8-di([1,1':3',1''-terphenyl]-5'-yl)-2,10-bis(trifluoromethyl)dibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-yl)oxy)phenyl)urea (6): To a solution of 4,8-di([1,1':3',1''-terphenyl]-5'-yl)-*N*,*N*-dimethyl-2,10-bis(trifluoromethyl)dibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-amine (513 mg, 0.60 mmol) and *N*-phenylimidazolium trifluoromethanesulfonate salt (194 mg, 0.66 mmol) in CH_3CN/CH_2Cl_2 (6.0 mL, 1:1) was added 4-aminophenol (75 mg, 0.69 mmol). The mixture was stirred at 60 °C for 9 h, cooled to ambient temperature, and concentrated *in vacuo*. To the residue was added toluene, filtered through a Celite pad, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane–toluene 1:1) to give 4-((4,8-di([1,1':3',1''-terphenyl]-5'-yl)-2,10-bis(trifluoromethyl)dibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-yl)oxy)aniline (462 mg, 84% yield).

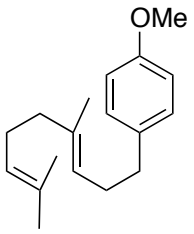
To a solution of this aniline (462 mg, 0.50 mmol) in CH_2Cl_2 (2.0 mL) was added 1-isocyanato-3,5-bis(trifluoromethyl)benzene (104 μL, 0.60 mmol) at ambient temperature. After stirring for 0.5 h, the mixture was added hexane, cooled to –78 °C, then an insoluble compound precipitated as a colorless solid. The solid was filtered off and washed with cooled hexane to give **6** as a colorless solid (503 mg, 86% yield). IR (KBr) 1507, 1386, 1313, 1280, 1185, 1160, 1129 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94–7.83 (m, 6H), 7.80–7.72 (m, 6H), 7.62 (d, J = 7.4 Hz, 8H), 7.52 (s, 1H), 7.43 (t, J = 7.4 Hz, 8H), 7.34 (t, J = 7.4 Hz, 4H), 6.70 (d, J = 8.7 Hz, 2H), 6.44 (s, 1H), 6.24 (d, J = 8.7 Hz, 2H), 6.07 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 148.5 (2C), 142.1 (4C), 140.4 (4C), 139.5, 137.0 (4C), 136.2 (4C), 132.7, 132.2 (q, $J_{C–F}$ = 33.4 Hz, 2C), 131.9, 128.9 (10C), 128.33 (q, $J_{C–F}$ = 32.4 Hz, 2C), 128.31 (2C), 127.8 (2C), 127.3 (2C), 127.2 (8C), 126.7 (2C), 125.8 (2C), 124.0 (2C), 123.7 (q, $J_{C–F}$ = 271 Hz, 2C), 123.0 (q, $J_{C–F}$ = 272 Hz, 2C), 120.5 (q, $J_{C–P}$ = 7.6 Hz, 2C), 119.1 (2C), 116.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ –61.8, –62.9; ^{31}P NMR (162 MHz, $CDCl_3$)

δ 144.7; HRMS (FAB) calcd for $C_{65}H_{40}F_{12}N_2O_4P^+$ $[M+H]^+$ 1171.2529, found 1171.2529.

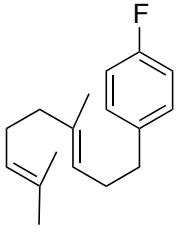
Preparation of Homogeranylarenes 1.



(*E*)-1-(4,8-Dimethylnona-3,7-dien-1-yl)-4-methylbenzene (1a):[2,3] Compound **1a** was prepared from 4-methylbenzyl magnesium chloride and (*E*)-geranyl diethyl phosphate according to the reported procedure.[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (s, 4H), 5.18 (t, *J* = 7.4 Hz, 1H), 5.09 (t, *J* = 6.9 Hz, 1H), 2.60 (t, *J* = 7.4 Hz, 2H), 2.32 (s, 3H), 2.28 (dt, *J* = 7.4, 7.4 Hz, 2H), 2.06 (dt, *J* = 6.9, 7.8 Hz, 2H), 1.97 (t, *J* = 7.8 Hz, 2H), 1.69 (s, 3H), 1.60 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 135.6, 135.0, 131.3, 128.9 (2C), 128.3 (2C), 124.3, 123.7, 39.7, 35.7, 30.1, 26.7, 25.7, 21.0, 17.7, 16.0.

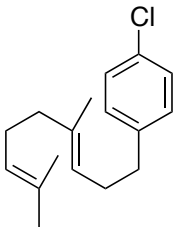


(*E*)-1-(4,8-Dimethylnona-3,7-dien-1-yl)-4-methoxybenzene (1b):[2c] Compound **1b** was prepared from (4-methoxybenzyl)magnesium chloride and (*E*)-geranyl diethyl phosphate according to the same manner as **1a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.17 (t, *J* = 7.3 Hz, 1H), 5.09 (t, *J* = 6.9 Hz, 1H), 3.79 (s, 3H), 2.58 (t, *J* = 7.8 Hz, 2H), 2.26 (dt, *J* = 7.3, 7.8 Hz, 2H), 2.06 (dt, *J* = 6.9, 7.3 Hz, 2H), 1.97 (t, *J* = 7.3 Hz, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 135.6, 134.5, 131.3, 129.3 (2C), 124.3, 123.6, 113.6 (2C), 55.2, 39.7, 35.2, 30.2, 26.7, 25.7, 17.7, 16.0.

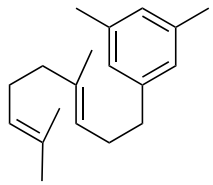


(*E*)-1-(4,8-Dimethylnona-3,7-dien-1-yl)-4-fluorobenzene (1c): Compound

1c was prepared from (4-fluorobenzyl)magnesium chloride and (*E*)-geranyl diethyl phosphate according to the same manner as **1a**. Colorless oil; IR (neat) 1602, 1509, 1448, 1376, 1223, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (dd, J_H = 8.7 Hz, J_{H-F} = 5.7 Hz, 2H), 6.95 (dd, J_H = 8.7 Hz, J_{H-F} = 8.7 Hz, 2H), 5.15 (t, *J* = 7.3 Hz, 1H), 5.08 (t, *J* = 6.9 Hz, 1H), 2.61 (t, *J* = 7.8 Hz, 2H), 2.27 (dt, *J* = 7.3, 7.8 Hz, 2H), 2.05 (dt, *J* = 6.9, 7.3 Hz, 2H), 1.97 (t, *J* = 7.3 Hz, 2H), 1.68 (s, 3H), 1.61 (s, 3H), 1.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2 (d, J_{C-F} = 242 Hz), 137.9 (d, J_{C-F} = 2.9 Hz), 135.9, 131.3, 129.7 (d, J_{C-F} = 7.6 Hz, 2C), 124.3, 123.3, 114.8 (d, J_{C-F} = 20.0 Hz, 2C), 39.7, 35.2, 30.0, 26.7, 25.6, 17.6, 15.9; HRMS (FAB) calcd for $C_{17}H_{23}F^+$ $[M]^+$ 246.1784, found 246.1805.

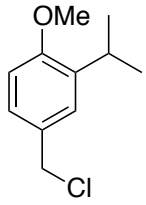


(*E*)-1-(4,8-Dimethylnona-3,7-dien-1-yl)-4-chlorobenzene (1d): Compound **1d** was prepared from (4-chlorobenzyl)magnesium chloride and (*E*)-geranyl diethyl phosphate according to the same manner as **1a**. Colorless oil; IR (neat) 1638, 1492, 1449, 1406, 1376, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.2 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 5.13 (t, *J* = 7.3 Hz, 1H), 5.06 (t, *J* = 7.3 Hz, 1H), 2.59 (t, *J* = 7.8 Hz, 2H), 2.26 (dt, *J* = 7.3, 7.8 Hz, 2H), 2.04 (dt, *J* = 7.3, 7.3 Hz, 2H), 1.96 (t, *J* = 7.3 Hz, 2H), 1.67 (s, 3H), 1.59 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 136.1, 131.35, 131.29, 129.8 (2C), 128.2 (2C), 124.2, 123.1, 39.6, 35.4, 29.7, 26.6, 25.7, 17.7, 15.9; HRMS (FAB) calcd for $C_{17}H_{23}Cl^+$ $[M]^+$ 262.1488, found 262.1464.

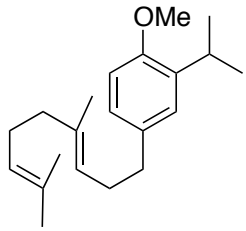


(*E*)-1-(4,8-Dimethylnona-3,7-dien-1-yl)-3,5-dimethylbenzene (1e): Compound **1e** was prepared from (3,5-dimethylbenzyl)magnesium chloride and (*E*)-geranyl diethyl phosphate according to the same manner as **1a**. Colorless oil; IR (neat) 1606, 1450, 1376 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.82 (s, 3H), 5.19 (t, *J* = 6.9 Hz, 1H), 5.10 (t, *J* = 6.9 Hz, 1H), 2.55 (t, *J* = 6.9 Hz, 2H), 2.31–2.23 (m, 2H), 2.29 (s, 6H), 2.11–2.02 (m, 2H),

2.02–1.94 (m, 2H), 1.69 (s, 3H), 1.61 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 137.6, 135.5, 131.3, 127.3 (2C), 126.3 (2C), 124.3, 123.8, 39.7, 36.0, 30.1, 26.8, 25.7, 21.3 (2C), 17.7, 16.0 ; HRMS (FAB) calcd for $C_{19}H_{29}^+$ $[M+H]^+$ 257.2264, found 257.2248.

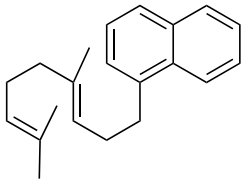


4-(Chloromethyl)-2-isopropyl-1-methoxybenzene: To a solution of PPh_3 (2.22 g, 8.5 mmol) in CCl_4 (6.0 mL) was added (3-isopropyl-4-methoxyphenyl)methanol (1.17 g, 6.5 mmol) at ambient temperature. The mixture was heated at 90 °C for 1 h. After cooling to ambient temperature, the mixture was added pentane, filtered through Celite, concentrated *in vacuo*. Bulb to bulb distillation by purification (120 °C, 80 Pa) afforded to 4-(chloromethyl)-2-isopropyl-1-methoxybenzene as a colorless oil (908 mg, 70% yield). IR (neat) 1608, 1500, 1464, 1250, 1172, 1116, 1091, 1033 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 1.8 Hz, 1H), 7.19 (dd, J = 8.2, 1.8 Hz, 1H), 6.81 (d, J = 1.8 Hz, 1H), 4.58 (s, 2H), 3.83 (s, 3H), 3.30 (sep, J = 6.9 Hz, 1H), 1.21 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 137.3, 129.4, 127.1, 126.7, 110.3, 55.4, 46.8, 26.7, 22.5 (2C); HRMS (FAB) calcd for $C_{11}H_{15}ClO^+$ $[M]^+$ 198.0811, found 198.0811.



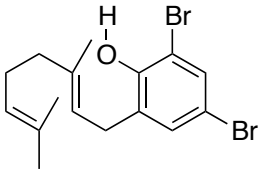
(*E*)-4-(4,8-Dimethylnona-3,7-dien-1-yl)-2-isopropyl-1-methoxybenzene (1f): Compound **1f** was prepared from (3-isopropyl-4-methoxybenzyl)magnesium chloride and (*E*)-geranyl diethyl phosphate according to the same manner as **1a**. Colorless oil; IR (neat) 1608, 1498, 1463, 1245, 1171, 1091, 1038 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, J = 2.3 Hz, 1H), 6.97 (dd, J = 2.3, 8.2 Hz, 1H), 6.76 (d, J = 8.2 Hz, 1H), 5.19 (t, J = 7.3 Hz, 1H), 5.10 (t, J = 7.3 Hz, 1H), 3.80 (s, 3H), 3.29 (sep, J = 6.9 Hz, 1H), 2.57 (t, J = 7.8 Hz, 2H), 2.27 (dt, J = 7.3, 7.8 Hz, 2H), 2.06 (dt, J = 7.3, 7.3 Hz, 2H), 1.97 (t, J = 7.3 Hz, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.56 (s, 3H), 1.20 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 136.6, 135.4,

134.3, 131.3, 126.2, 126.1, 124.4, 123.8, 110.2, 55.4, 39.7, 35.5, 30.3, 26.73, 26.65, 25.7, 22.7 (2C), 17.7, 16.0; HRMS (FAB) calcd for $C_{21}H_{32}O^+$ $[M]^+$ 300.2453, found 300.2465.



(*E*)-1-(4,8-Dimethylnona-3,7-dien-1-yl)naphthalene (1g):[4] Compound **1g** was prepared from (naphthalen-1-ylmethyl)magnesium bromide and (*E*)-geranyl acetate according to the reported procedure.[4,5] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 8.7 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.54–7.43 (m, 2H), 7.40 (dd, *J* = 7.4, 8.3 Hz, 1H), 7.32 (d, *J* = 7.4 Hz, 1H), 5.28 (t, *J* = 7.3 Hz, 1H), 5.11 (t, *J* = 6.9 Hz, 1H), 3.10 (t, *J* = 7.8 Hz, 2H), 2.44 (dt, *J* = 7.3, 7.8 Hz, 2H), 2.07 (dt, *J* = 6.9, 7.8 Hz, 2H), 1.99 (t, *J* = 7.8 Hz, 2H), 1.69 (s, 3H), 1.61 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 135.9, 133.8, 131.9, 131.4, 128.7, 126.5, 125.9, 125.6, 125.5, 125.3, 124.3, 123.8, 123.7, 39.7, 33.2, 29.2, 26.7, 25.7, 17.7, 16.0.

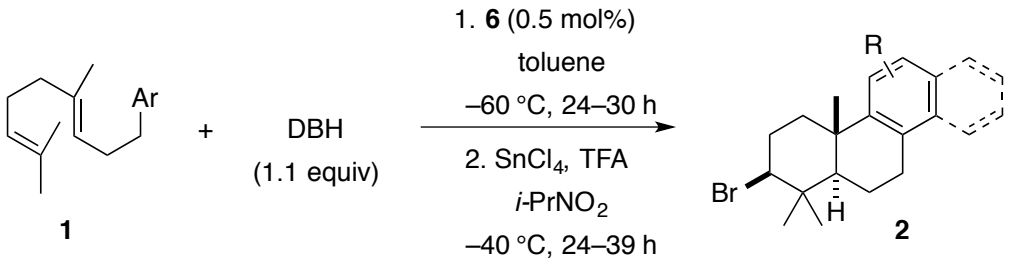
Preparation of 2,4-Dibromo-6-geranylphenol.



2,4-Dibromo-6-geranylphenol: To a solution of 2,4-dibromophenol (1.39 g, 5.5 mmol) in toluene was added sodium hydride (abt. 60% oil suspension) (220 mg, 5.5 mmol) at 0 °C. After stirring for 2 h, then geranyl chloride (927 μL, 5 mmol) was added. The mixture was warmed to ambient temperature and stirred for 11 h. The reaction was quenched with saturated aquerous $NaHCO_3$. The mixture was extracted with Et_2O, and combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane–EtOAc 98:2) to give 2,4-dibromo-6-geranylphenol as a yellow oil (775 mg, 40% yield). IR (neat) 3515, 1457, 1401, 1319, 1234, 1138cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 2.3 Hz, 1H), 7.18 (d, *J* = 2.3 Hz, 1H), 5.60 (s, 1H), 5.27 (t, *J* = 7.3 Hz, 1H), 5.09 (t, *J* = 6.9 Hz, 1H), 3.35 (t, *J* = 7.3 Hz, 2H), 2.16–2.03 (m, 4H), 1.70 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 138.2, 131.8, 131.7, 131.4, 130.9,

123.9, 120.4, 112.3, 110.6, 39.6, 29.0, 26.4, 25.7, 17.7, 16.1; HRMS (EI) calcd for $C_{16}H_{20}Br_2O^+$ $[M]^+$ 385.9881, found 385.9872.

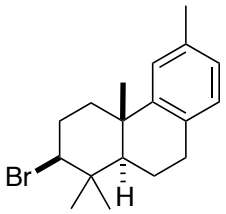
General Procedure for Selective Bromocyclization of Homogeranylarenes 1.



To a solution of **6** (1.8 mg, 0.0015 mmol) in toluene (1.5 mL) were added DBH (94.4 mg, 0.33 mmol) and **1** (0.30 mmol) successively at –78 °C, and the mixture was stirred at –78 °C for 0.5 h and then at –60 °C for 24–30 h. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (3.0 mL) and extracted with hexane (5.0 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The ratio of **2a**, *endo*-**3a**, *exo*-**3a** and **4a** was determined by ^{1}H NMR analysis: δ 4.04 (dd, J = 12.4, 4.1 Hz, 1H, **2a**), 4.17 (dd, J = 6.9, 9.6 Hz, 1H, *endo*-**3a**), 4.11 (dd, J = 4.6, 11.5 Hz, 1H, *exo*-**3a**), and 5.29 (t, J = 6.9 Hz, 1H, **4a**).

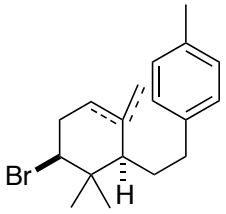
The crude product was purified by column chromatography on silica gel using hexane as an eluent. The resulting mixture of **2**, *endo*-**3** and *exo*-**3** was used for the next cyclization without further separation. To a solution of the resulting mixture of **2**, *endo*-**3** and *exo*-**3**, which were obtained in the above reaction, in *i*-$PrNO_2$ (4.5 mL) were added TFA (230 μL, 3.0 mmol), and 1 M $SnCl_4$ solution in hexane (600 μL, 0.60 mmol) at –78 °C. The mixture was stirred at –40 °C for 24–39 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, and extracted with Et_2O (5 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel using hexane as an eluent, to give **2**.

The corresponding physical and spectroscopic data for **2** are as follows.

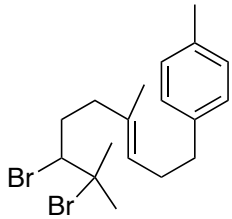


2-Bromo-1,1,4a,6-tetramethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (2a): Pale yellow solid; IR (KBr) 1611, 1500, 1438, 1377, 1261, 1096, 1066, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.00 (s, 1H), 6.98–6.88 (m, 2H), 4.04 (dd, *J* = 4.1, 12.4 Hz, 1H), 2.96–2.77 (m, 2H), 2.42–2.21 (m, 2H), 2.28 (s, 3H), 1.95 (ddt, *J* = 2.3, 6.9, 13.3 Hz, 1H), 1.85–1.71 (m, 1H), 1.58 (td, *J* = 3.2, 11.9 Hz, 1H), 1.45 (dd, *J* = 2.3, 11.9 Hz, 1H), 1.23 (s, 3H), 1.15 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 135.1, 131.5, 128.9, 126.5, 124.9, 68.9, 51.2, 39.9, 39.8, 37.8, 31.5, 30.5, 30.4, 24.8, 21.2, 20.6, 18.2; HRMS (FAB) calcd for $C_{18}H_{25}Br^+$ $[M]^+$ 320.1140, found 320.1138.

***Cis*-isomer of 2a:** ^1H NMR ($CDCl_3$, 400 MHz) δ 4.13 (dd, *J* = 5.0, 11.0 Hz, 1H), 1.21 (s, 3H), 1.09 (s, 3H), 0.44 (s, 3H), and other resonances could not be discerned.

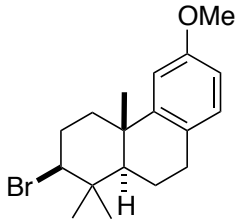


1-(2-(5-Bromo-2,6,6-trimethylcyclohex-2-en-1-yl)ethyl)-4-methylbenzene (*endo*-3a), 1-(2-(3-Bromo-2,2-dimethyl-6-methylenecyclohexyl)ethyl)-4-methylbenzene (*exo*-3a): Compounds ***endo*-3a**, and ***exo*-3a** could not be separated by column chromatography on silica gel. ***endo*-3a:** ^1H NMR (400 MHz, $CDCl_3$) δ 5.23 (brs, 1H), 4.17 (dd, *J* = 6.9, 9.6 Hz, 1H), 1.07 (s, 3H), 0.88 (s, 3H). Other resonances could not be discerned for this compound. ***exo*-10:** ^1H NMR (400 MHz, $CDCl_3$) δ 4.99 (s, 1H), 4.76 (s, 1H), 4.11 (dd, *J* = 4.6, 11.5 Hz, 1H), 1.12 (s, 3H), 0.82 (s, 3H). Other resonances could not be discerned for this compound.



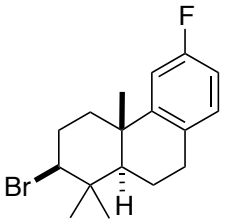
(*E*)-1-(7,8-Dibromo-4,8-dimethylnon-3-en-1-yl)-4-methylbenzene (4a): Colorless solid; IR (neat) 1516, 1456, 1370, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ

7.09 (s, 4H), 5.29 (t, J = 6.9 Hz, 1H), 4.09 (dd, J = 0.9, 11.0 Hz, 1H), 2.62 (t, J = 7.8 Hz, 2H), 2.46–2.56 (m, 1H), 2.32 (s, 3H), 2.39–2.27 (m, 3H), 2.21–2.12 (m, 1H), 1.96 (s, 3H), 1.89–1.78 (m, 1H), 1.81 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 139.1, 135.1, 133.5, 128.9 (2C), 128.3 (2C), 125.7, 68.8, 65.8, 37.7, 35.5, 35.3, 33.7, 30.0, 28.2, 21.0, 15.7; HRMS (FAB) calcd for $C_{18}H_{27}Br_2$ $[M+H]^+$ 401.0474, found 401.0470.



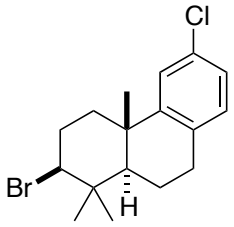
2-Bromo-6-methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (2b): Colorless solid; IR (KBr) 1612, 1574, 1501, 1264, 1044 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, J = 8.2 Hz, 1H), 6.74 (d, J = 2.8 Hz, 1H), 6.68 (dd, J = 2.8, 8.2 Hz, 1H), 4.04 (dd, J = 4.1, 12.4 Hz, 1H), 3.77 (s, 3H), 2.89 (dd, J = 6.9, 12.8 Hz, 1H), 2.80 (ddd, J = 7.3, 11.5, 16.9 Hz, 1H), 2.48–2.21 (m, 3H), 1.95 (dd, J = 6.9, 12.8 Hz, 1H), 1.78 (dddd, J = 6.8, 11.9, 11.9, 12.8 Hz, 1H), 1.60 (td, J = 4.1, 11.9 Hz, 1H), 1.45 (dd, J = 2.3, 11.9 Hz, 1H), 1.24 (s, 3H), 1.15 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 149.9, 129.8, 126.9, 111.1, 110.2, 68.8, 55.2, 51.2, 40.0, 39.8, 38.0, 31.5, 30.5, 29.9, 24.8, 20.7, 18.3; HRMS (FAB) calcd for $C_{18}H_{25}BrO^+$ $[M]^+$ 336.1089, found 336.1095.

***Cis*-isomer of 2b:** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.12 (dd, J = 4.1, 11.9 Hz, 1H), 3.79 (s, 3H) 1.12 (s, 3H), 1.09 (s, 3H), 0.45 (s, 3H), and other resonances could not be discerned.

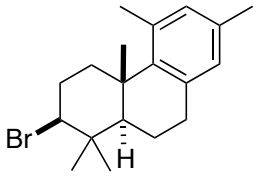


2-Bromo-6-fluoro-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (2c): Colorless solid; IR (KBr) 1610, 1585, 1497, 1473, 1379, 1259, 1176 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (dd, J_H = 8.2 Hz, J_{H-F} = 6.0 Hz, 1H), 6.87 (dd, J_H = 2.8 Hz, J_{H-F} = 11.0 Hz, 1H), 6.78 (ddd, J_H = 2.8, 8.2 Hz, J_{H-F} = 8.2 Hz), 4.03 (dd, J = 4.1, 12.4 Hz, 1H), 2.92 (dd, J = 6.4, 17.0 Hz, 1H), 2.81 (ddd, J = 7.3, 11.4, 17.0 Hz, 1H), 2.35 (qd, J = 3.2, 13.8 Hz, 1H), 2.31–2.18 (m, 2H), 1.97 (ddt, J = 1.8, 7.4, 13.3 Hz, 1H), 1.79 (dddd, J = 6.9, 11.9, 11.9, 13.3 Hz, 1H), 1.63–1.52 (m, 2H), 1.44 (dd, J = 2.3, 8.2 Hz,

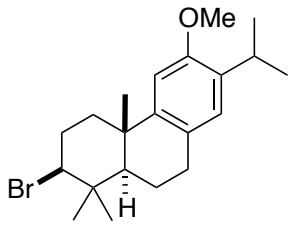
1H), 1.23 (s, 3H), 1.16 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3 (d, J_{C-F} = 240 Hz), 150.6 (d, J_{C-F} = 5.7 Hz), 130.2 (d, J_{C-F} = 7.6 Hz), 130.1 (d, J_{C-F} = 2.9 Hz), 112.6 (d, J_{C-F} = 21.0 Hz), 110.9 (d, J_{C-F} = 21.0 Hz), 68.3, 50.8, 39.84, 39.76, 38.0, 31.3, 30.5, 30.0, 24.7, 20.5, 18.2; HRMS (FAB) calcd for $C_{17}H_{22}BrF^+$ $[M]^+$ 324.0889, found 324.904.



2-Bromo-6-chloro-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (2d): Colorless solid; IR (KBr) 1594, 1488, 1394, 1379, 1215, 1108 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, J = 1.8 Hz, 1H), 7.05 (dd, J = 1.8, 8.2 Hz, 1H), 6.97 (d, J = 8.2 Hz, 1H), 4.03 (dd, J = 4.1, 12.8 Hz, 1H), 2.91 (dd, J = 5.5, 17.4 Hz, 1H), 2.81 (ddd, J = 7.3, 11.4, 17.4 Hz, 1H), 2.42–2.18 (m, 3H), 1.97 (dd, J = 7.3, 12.8 Hz, 1H), 1.79 (ddd, J = 6.9, 12.4, 12.4 Hz, 1H), 1.63–1.50 (m, 1H), 1.42 (dd, J = 1.8, 12.8 Hz, 1H), 1.23 (s, 3H), 1.16 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 133.1, 131.4, 130.4, 125.7, 124.6, 68.3, 50.8, 39.8, 38.0, 31.3, 30.5, 30.1, 24.8, 20.4, 18.2; HRMS (FAB) calcd for $C_{17}H_{22}ClBr^+$ $[M]^+$ 340.0593, found 340.0597.

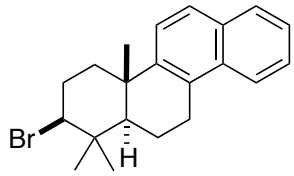


2-Bromo-1,1,4a,5,7-pentamethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (2e): Colorless solid; IR (KBr) 1610, 1475, 1443, 1392, 1375, 1169, 1157 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (s, 1H), 6.75 (s, 1H), 4.04 (dd, J = 4.1, 12.8 Hz, 1H), 2.88 (dd, J = 6.4, 13.7 Hz, 1H), 2.78 (dt, J = 3.7, 13.8 Hz, 1H), 2.44 (s, 3H), 2.32 (qd, J = 3.7, 13.8 Hz, 1H), 2.24–2.13 (m, 1H), 2.21 (s, 3H), 1.94–1.87 (m, 1H), 1.70 (dddd, J = 6.8, 11.4, 11.9, 13.3 Hz, 1H), 1.47 (td, J = 3.7, 13.8 Hz, 1H), 1.40 (dd, J = 0.9, 11.9 Hz, 1H), 1.36 (s, 3H), 1.16 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 136.3, 135.7, 134.8, 132.1, 128.5, 68.9, 54.3, 40.3, 40.1, 38.9, 33.1, 31.5, 30.8, 24.7, 20.5 (2C), 20.3, 18.7; HRMS (FAB) calcd for $C_{19}H_{27}Br^+$ $[M]^+$ 334.1296, found 334.1301.



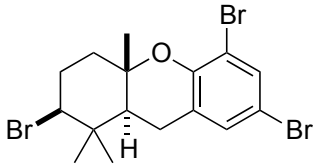
2-Bromo-7-isopropyl-6-methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (2f): Colorless oil; IR (neat) 1614, 1572, 1499, 1463, 1253, 1239, 1207, 1057, 1045 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.85 (s, 1H), 6.64 (s, 1H), 4.04 (dd, *J* = 4.1, 12.8 Hz, 1H), 3.78 (s, 3H), 3.21 (sep, *J* = 6.9 Hz, 1H), 2.87 (dd, *J* = 6.9, 17.0 Hz, 1H), 2.79 (ddd, *J* = 6.9, 11.4, 17.0 Hz, 1H), 2.42–2.21 (m, 3H), 1.95 (dd, *J* = 6.8, 12.8 Hz, 1H), 1.78 (dddd, *J* = 6.8, 11.9, 11.9, 12.8 Hz, 1H), 1.62 (ddd, *J* = 3.2, 11.9, 13.3 Hz, 1H), 1.46 (dd, *J* = 1.8, 11.9 Hz, 1H), 1.25 (s, 3H), 1.19 (d, *J* = 6.9 Hz, 3H), 1.17 (d, *J* = 6.9 Hz, 3H), 1.15 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 146.5, 134.7, 126.37, 126.34, 106.3, 69.0, 55.5, 51.4, 40.1, 39.8, 37.9, 31.5, 30.5, 30.2, 26.4, 24.8, 22.8, 22.6, 20.8, 18.2; HRMS (FAB) calcd for $C_{21}H_{31}BrO^+$ $[M]^+$ 378.1558, found 378.1553.

***Cis*-isomer of 2f:** ^1H NMR ($CDCl_3$, 400 MHz) δ 6.82 (s, 1H), 6.68 (s, 1H), 4.13 (dd, *J* = 4.1, 12.4 Hz, 1H), 1.09 (s, 3H), 0.45 (s, 3H), and other resonances could not be discerned.



2-Bromo-1,1,4a-trimethyl-1,2,3,4,4a,11,12,12a-octahydrochrysene (2g): Colorless solid; IR (neat) 1508, 1460, 1440, 1367, 1267, 1143, 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.2 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.66 (*J* = 8.7 Hz, 1H), 7.53–7.41 (m, 2H), 7.39 (d, *J* = 8.7 Hz, 1H), 4.07 (dd, *J* = 4.6, 12.8 Hz, 1H), 3.37 (dd, *J* = 6.4, 17.4 Hz, 1H), 3.20–3.08 (m, 1H), 2.49–2.35 (m, 2H), 2.34–2.26 (m, 1H), 2.18 (dd, *J* = 7.3, 12.8 Hz, 1H), 1.91 (dddd, *J* = 6.4, 12.4, 12.4, 12.8 Hz, 1H), 1.65–1.53 (m, 2H), 1.34 (s, 3H), 1.21 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 132.1, 131.5, 129.3, 128.1, 126.5, 126.0, 125.1, 123.2, 123.1, 68.7, 51.2, 40.1, 39.7, 38.2, 31.5, 30.5, 28.0, 24.3, 20.4, 18.2; HRMS (FAB) calcd for $C_{21}H_{25}Br^+$ $[M]^+$ 356.1140, found 356.1133.

***Cis*-isomer of 2g:** ^1H NMR ($CDCl_3$, 400 MHz) δ 4.19 (dd, *J* = 4.6, 11.4 Hz, 1H), 1.25 (s, 3H), 1.16 (s, 3H), 0.51 (s, 3H), and other resonances could not be discerned.

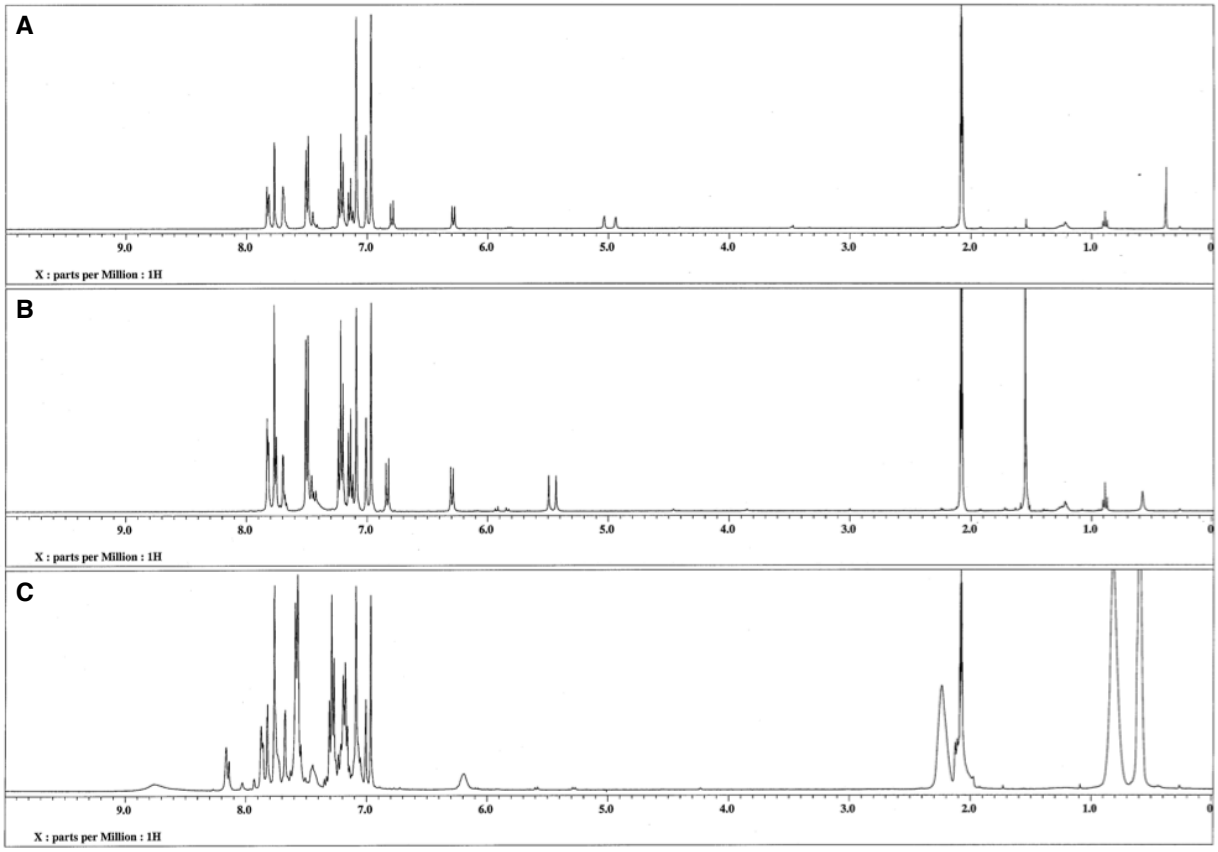


2,5,7-Tribromo-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene: To a solution of **6** (5.4 mg, 0.0045 mmol) in toluene (1.5 mL) were added DBH (94.4 mg, 0.33 mmol) and 2,4-dibromo-6-geranylphenol (116 mg, 0.30 mmol) successively at –78 °C, and the mixture was stirred at –78 °C for 0.5 h and then at –60 °C for 24 h. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (3.0 mL) and extracted with Et_2O (5.0 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel using (hexane–EtOAc 20:1) as an eluent. The resulting mixture was used for the next cyclization without further separation. To a solution of the resulting mixture, which were obtained in the above reaction, in *i*-$PrNO_2$ (3.0 mL) was added TfOH (106 μL, 1.2 mmol) at –78 °C. The mixture was stirred at –78 °C for 24 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, and extracted with Et_2O (5 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel using (hexane–EtOAc 40:1) as an eluent to give 2,5,7-tribromo-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene as colorless solid (58.1 mg, 83% yield, *trans/cis* = 94 : 6). IR (KBr) 1558, 1454, 1391, 1383, 1304, 1289, 1258, 1128, 1066 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 2.3 Hz, 1H), 7.15 (d, *J* = 2.3 Hz, 1H), 4.02 (dd, *J* =12.4, 4.1 Hz, 1H), 2.83–2.68 (m, 2H), 2.31 (dddd, *J* = 14.6, 4.1, 3.2, 3.2 Hz, 1H), 2.13 (ddd, *J* = 13.7, 13.2, 3.2 Hz, 1H), 2.09 (ddd, *J* = 13.2, 3.2, 3.2 Hz, 1H), 1.85 (ddd, *J* = 14.2, 13.7, 3.2 Hz, 1H), 1.79 (dd, *J* = 11.0, 6.9 Hz, 1H), 1.23 (s, 3H), 1.16 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 133.1, 131.2, 124.9, 112.1, 111.7, 77.5, 65.1, 47.5, 40.2, 39.1, 31.3, 29.5, 24.7, 19.9, 16.8; HRMS (EI) calcd for $C_{16}H_{19}Br_3O^+$ $[M]^+$ 463.8986, found 463.8999.

***Cis*-isomer:** ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 1.8 Hz, 1H), 7.15 (d, *J* = 1.8 Hz, 1H), 4.06 (dd, *J* = 3.7, 12.8 Hz, 1H), 3.12 (dd, *J* = 7.8, 18.3 Hz, 1H), 2.83 (d, *J* = 18.3 Hz, 1H), 2.49 (ddd, 3.7, 13.3, 14.2 Hz, 1H), 2.20 (ddd, *J* = 3.6, 4.1, 13.3 Hz, 1H), 2.09 (dddd, *J* = 3.6, 3.7, 3.7, 14.2 Hz, 1H), 1.70 (ddd, *J* = 4.1, 14.2, 14.2 Hz, 1H), 1.59 (d, *J* = 7.8 Hz, 1H), 1.18 (s, 3H), 1.13 (s, 3H), 0.75 (s, 3H).

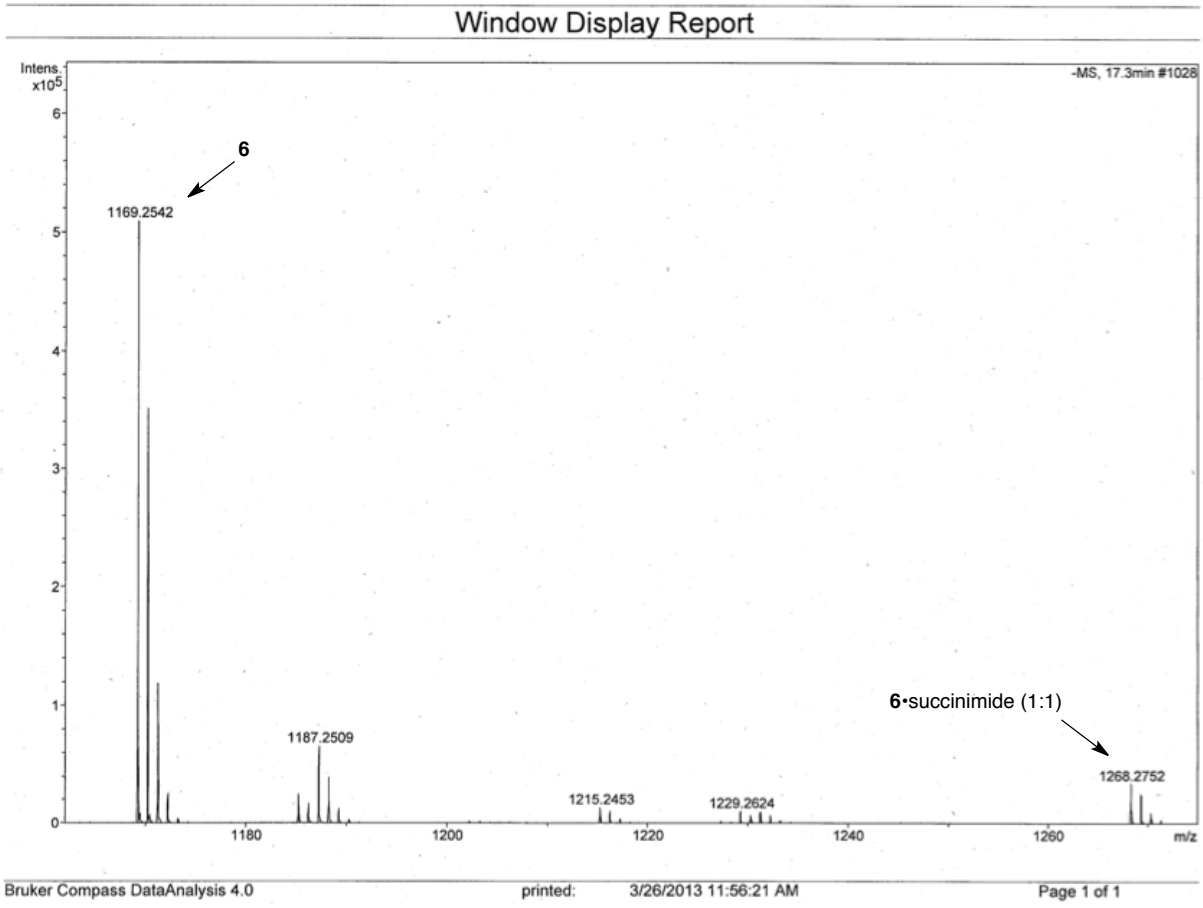
NMR Experiments of a Mixture of Catalyst 6 and Succinimide.

The ^{1}H NMR studies were carried out in toluene-d_8. When catalyst **6** was mixed with succinimide, two signals of urea (δ 5.03, 4.94 ppm, chart **A**) shifted downfield (δ 5.46, 5.40 ppm, chart **B**). Furthermore, signals of urea were observed at δ 8.77, 6.19 ppm when catalyst **6** was mixed with tertabutylammonium salt of succinimide (chart **C**). These results suggested that succinimide anion interacted with the urea group via hydrogen bonding.

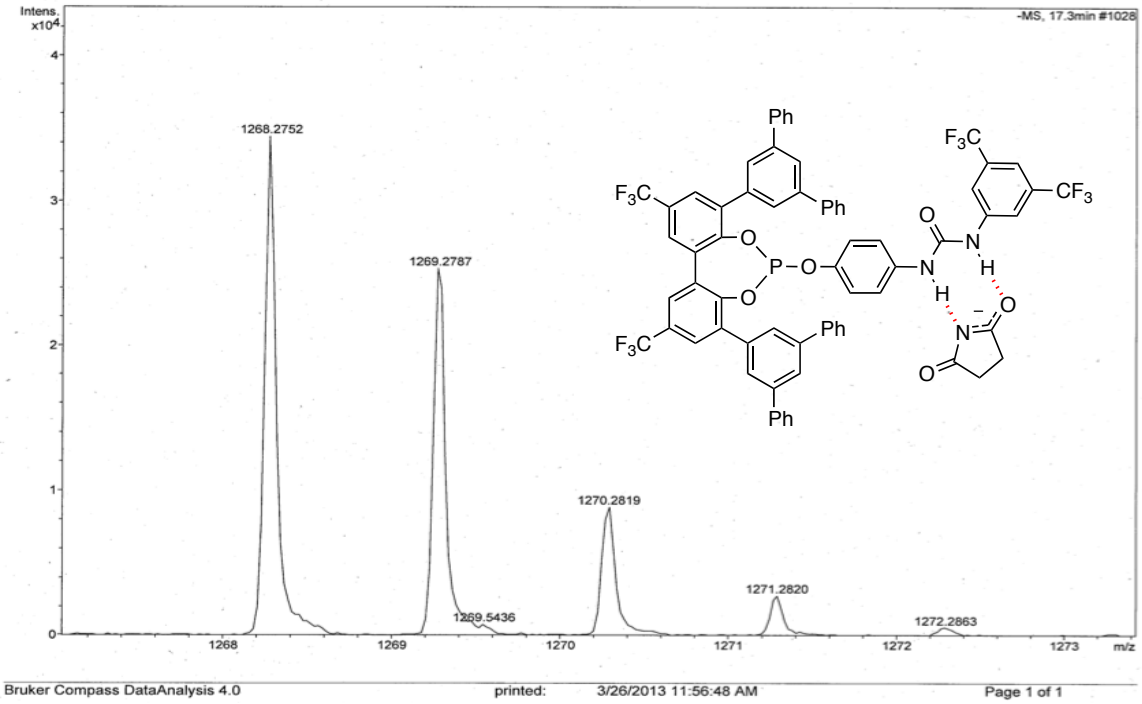


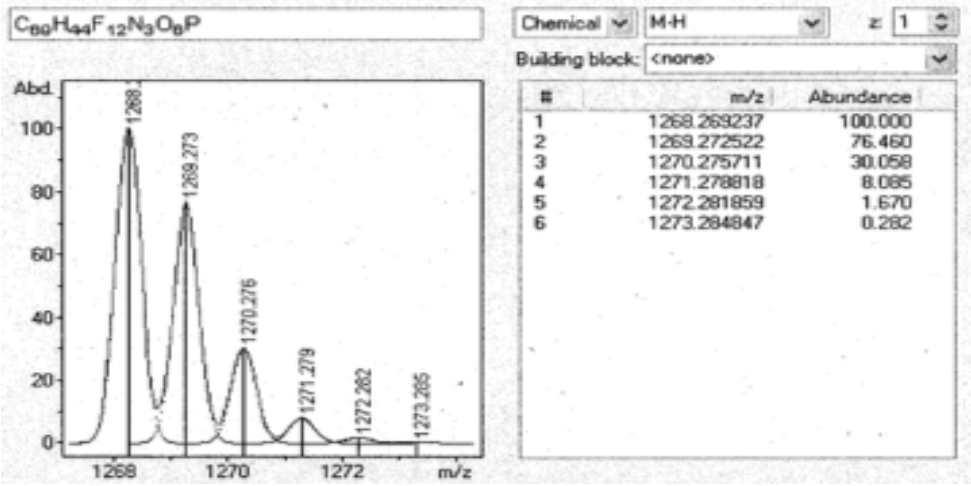
Negative ESI-MS Analysis of a Mixture of Catalyst 6 and Succinimide.

To a solution of catalyst **6** in CH_3CN (10 μM, 1.0 mL, 0.01 μmol) was added tetrabutylammonium succinimide (10 mM in CH_3CN, 1μL, 0.01 μmol). The resulting mixture was passed through a membrane filter (200 mm mesh) just before injection. A MS peak corresponding to a complex of catalyst **6** and succinimide (m/z 1268) was observed by ESI-MS analysis (negative mode).



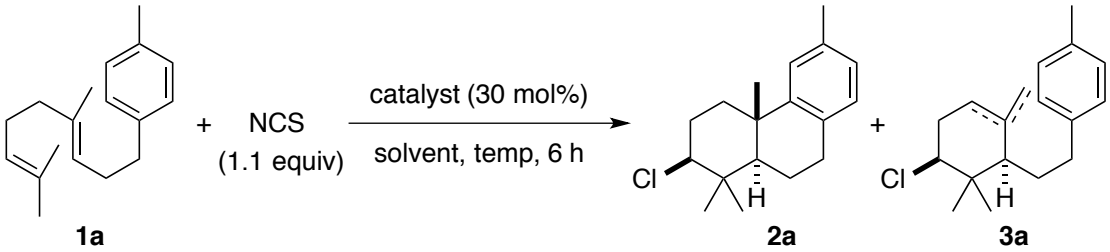
Correlation of theoretical and observed ion distirbution for the peak *m/z* = 1268 is shown below. For *m/z* = 1268, $C_{69}H_{44}F_{12}N_3O_6P$ is identified to [catalyst **6** + succinimide] as $[M–H]^-$.





HRMS (ESI$^-$) calcd for $C_{69}H_{43}F_{12}N_3O_6P$ $[M–H]^-$ 1268.2692, found 1268.1752

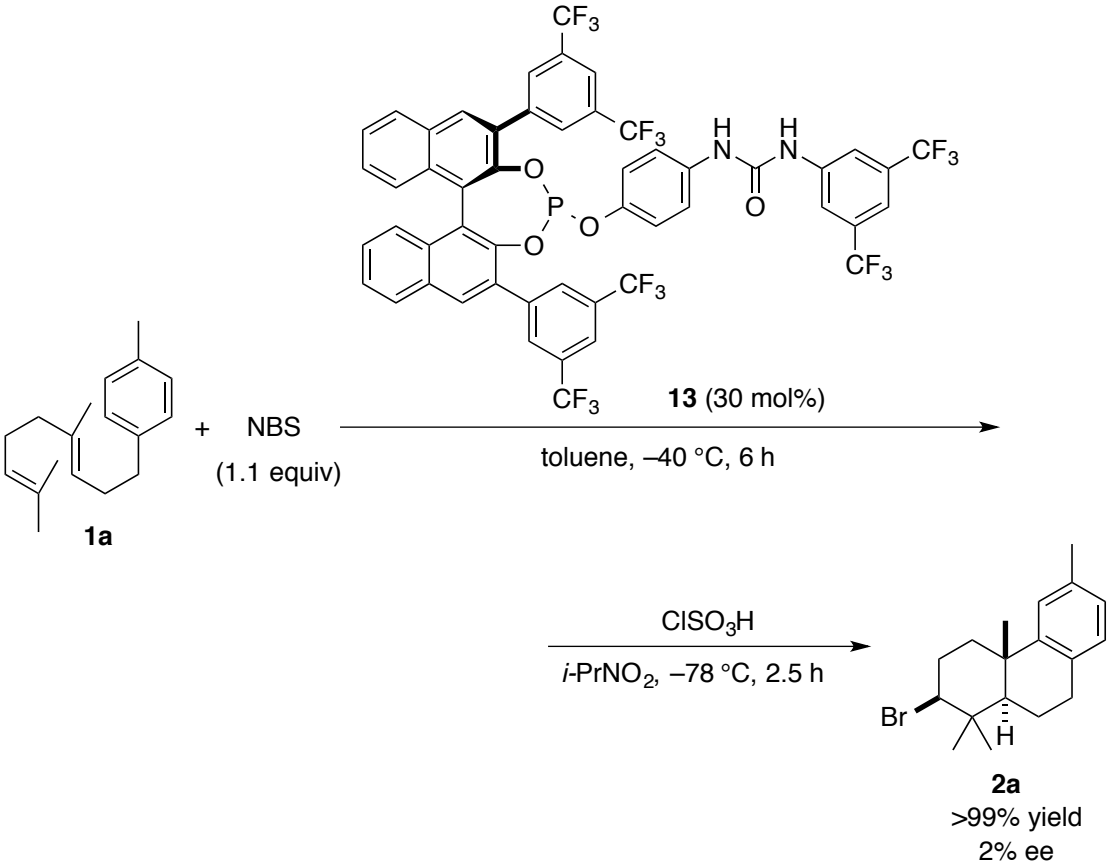
Chlorocyclization of 1a with NCS Using Nucleophilic Phosphite Catalysts.



1a **2a** **3a**

catalyst	solvent	temp	yield of **2a** + **3a**
$P(OPh)_3$	CH_2Cl_2	–78 °C	0%
$P(OPh)_3$	toluene	–40 °C	0%
$P(OC_6H_4\text{-}4\text{-}F)_3$	CH_2Cl_2	–78 °C	0%
$P(OC_6H_4\text{-}4\text{-}F)_3$	toluene	–40 °C	0%

Bromocyclization of 1a Using Chiral Phosphite–Urea Cooperative Catalyst 13.



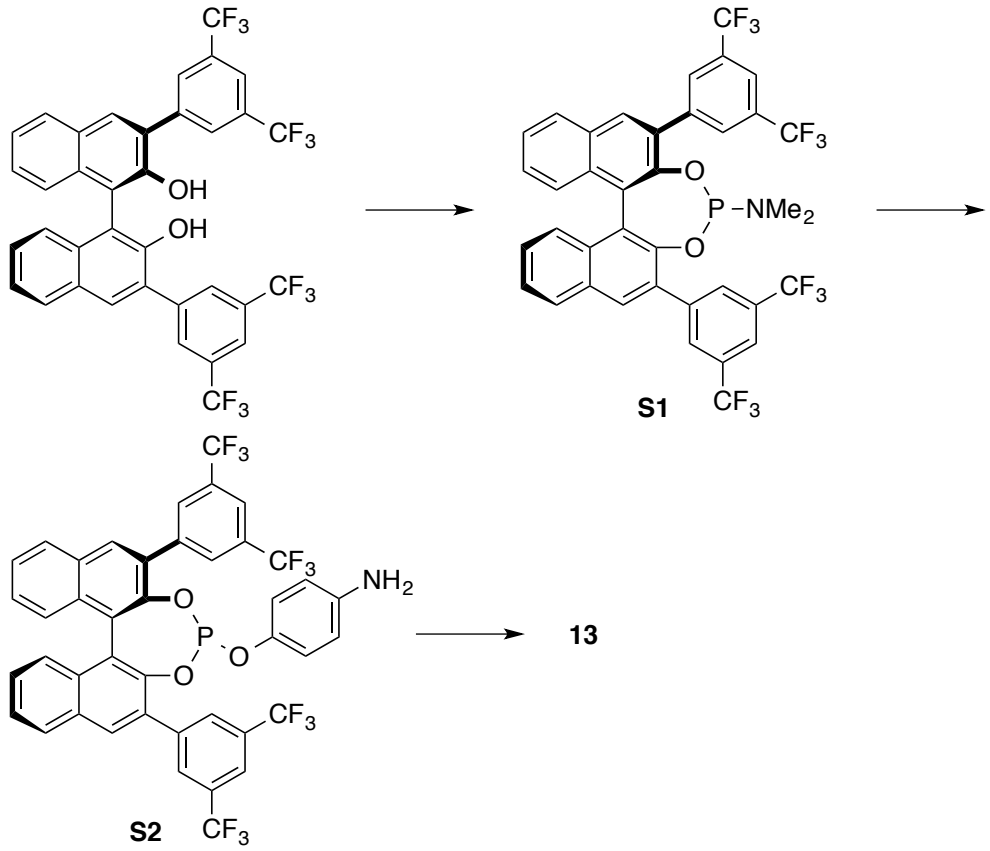
1a

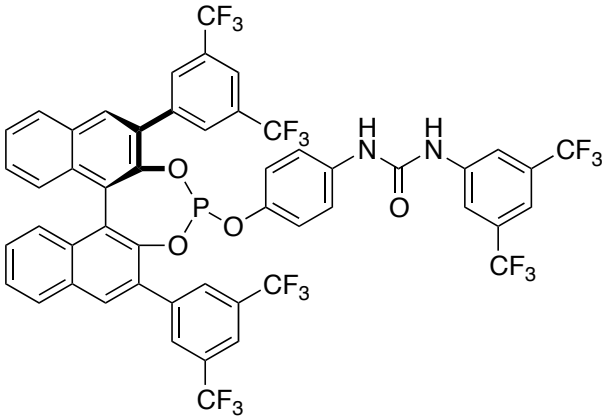
2a
>99% yield
2% ee

To a solution of **13** (33.1 mg, 0.03 mmol) in toluene (1.0 mL) were added NBS (0.11 mmol) and **1a** (0.10 mmol) successively at –78 °C, and the mixture was stirred at –78 °C for

0.5 h and then at –40 °C for 6 h. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (3.0 mL) and extracted with hexane (5.0 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel using hexane as an eluent to give mixture of **2**, *endo*-**3** and *exo*-**3**. To a solution of the mixture of **2a**, *endo*-**3a** and *exo*-**3a** in *i*-$PrNO_2$ (2.0 mL) was added $ClSO_3H$ (50 μL) at –78 °C. The mixture was stirred at –78 °C for 2.5 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, and extracted with Et_2O (5 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel using hexane as an eluent, to give **2a**. The enantiomeric excess of **2a** was determined to be 2% by HPLC analysis (Shimadzu LC-10 AD coupled diode array-detector SPD-MA-10A-VP, chiral column of Daicel CHIRALPACK AS-H (4.6 mm × 25 cm) and AS-3 (4.6 mm × 25 cm), hexane, flow rate = 1.0 mL/min, t_R= 48.0, 51.9 min.).

Preparation of Chiral Phosphite–Urea Cooperative Catalyst 13.





1-(4-(((11b*R*)-2,6-Bis(3,5-bis-(trifluoromethyl)phenyl)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yl)oxy)phenyl)-3-(3,5-bis(trifluoromethyl)phenyl)urea 13: To a suspension of (*R*)-3,3'-bis(3,5-bis(trifluoromethyl)phenyl)-2,2'-binaphthol (923 mg, 1.3 mmol) and tetrazole (273 mg, 3.9 mmol) in dry THF (15 mL) was added *N*,*N*,*N*',*N*',*N*'',*N*''-hexamethylphosphinetriamine (424 mg, 3.4 mmol). The reaction mixture was heated at reflux for 5 h, cooled to room temperature, and filtered through a Celite pad.

The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give **S1** (968 mg, 95% yield).

To a solution of **S1** (392 mg, 0.50 mmol) and *N*-phenylimidazolium trifluoromethanesulfonate salt (162 mg, 0.55 mmol) in dry CH_3CN (5.0 mL) was added 4-aminophenol (71 mg, 0.65 mmol). The reaction mixture was stirred at room temperature for 13 h, filtered through a Celite pad, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give **S2** (339 mg, 80% yield).

To a solution of **S2** (339 mg, 0.4 mmol) in CH_2Cl_2 (4.0 mL) was added 1-isocyanato-3,5-bis(trifluoromethyl)benzene (153 mg, 0.60 mmol). The reaction mixture was stirred at room temperature and insoluble urea starts to precipitate as a white solid. The reaction mixture was diluted with hexane, then the solid was filtered off and washed with hexane to give **13** (350 mg, 79% yield). Colorless solid; $[\alpha]^{25}_{D}$ –96.8 (*c* 1.00, THF); IR (KBr) 1643, 1577, 1508, 1473, 1381, 1326, 1279, 1176, 1136, 1083, 987 cm^{-1}; ^{1}H NMR (400 MHz, THF-d_8) δ 8.43 (s, 2H), 8.40–8.29 (m, 5H), 8.40–8.18 (m, 6H), 7.99 (s, 1H), 7.62–7.53 (m, 3H), 7.50–7.37 (m, 4H), 7.18 (d, J = 8.7 Hz, 2H), 6.20 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, THF-d_8) δ 152.8, 147.2, 147.1, 145.6 (d, $J_{C–P}$ = 2.9 Hz, 2C), 144.9 (d, $J_{C–P}$ = 2.9 Hz, 2C), 143.1, 141.5, 140.8, 136.9, 130.4, 133.7, 132.8, 132.66, 132.65 (q, $J_{C–F}$ = 33.4 Hz, 2C), 132.4, 132.34 (q, $J_{C–F}$ = 32.4 Hz, 2C), 132.30 (q, $J_{C–F}$ = 32.4 Hz, 2C), 132.0, 131.6 (2C), 131.4(2C), 129.9, 129.8, 128.3, 128.1, 127.6, 127.5, 127.1, 126.9, 126.5, 126.4, 125.2, 124.6 (q, $J_{C–F}$ = 272 Hz, 6C), 122.4, 122.1, 120.7 (2C), 199.9 (d, $J_{C–P}$ = 8.6 Hz, 2C), 118.8 (2C), 115.5; ^{19}F NMR (376 MHz, THF-d_8) δ –63.3, –63.7; ^{31}P NMR (162 MHz, $CDCl_3$) δ 145.7; HRMS (FAB) calcd for $C_{51}H_{25}F_{18}N_2O_4P^+$ $[M]^+$ 1102.1265, found 1102.1269.

References

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Chapter 3

Site- and Diastereoselective Bromocyclization of 2-Geranylphenols Promoted by Phosphite–Urea Cooperative Catalysts

Abstract:

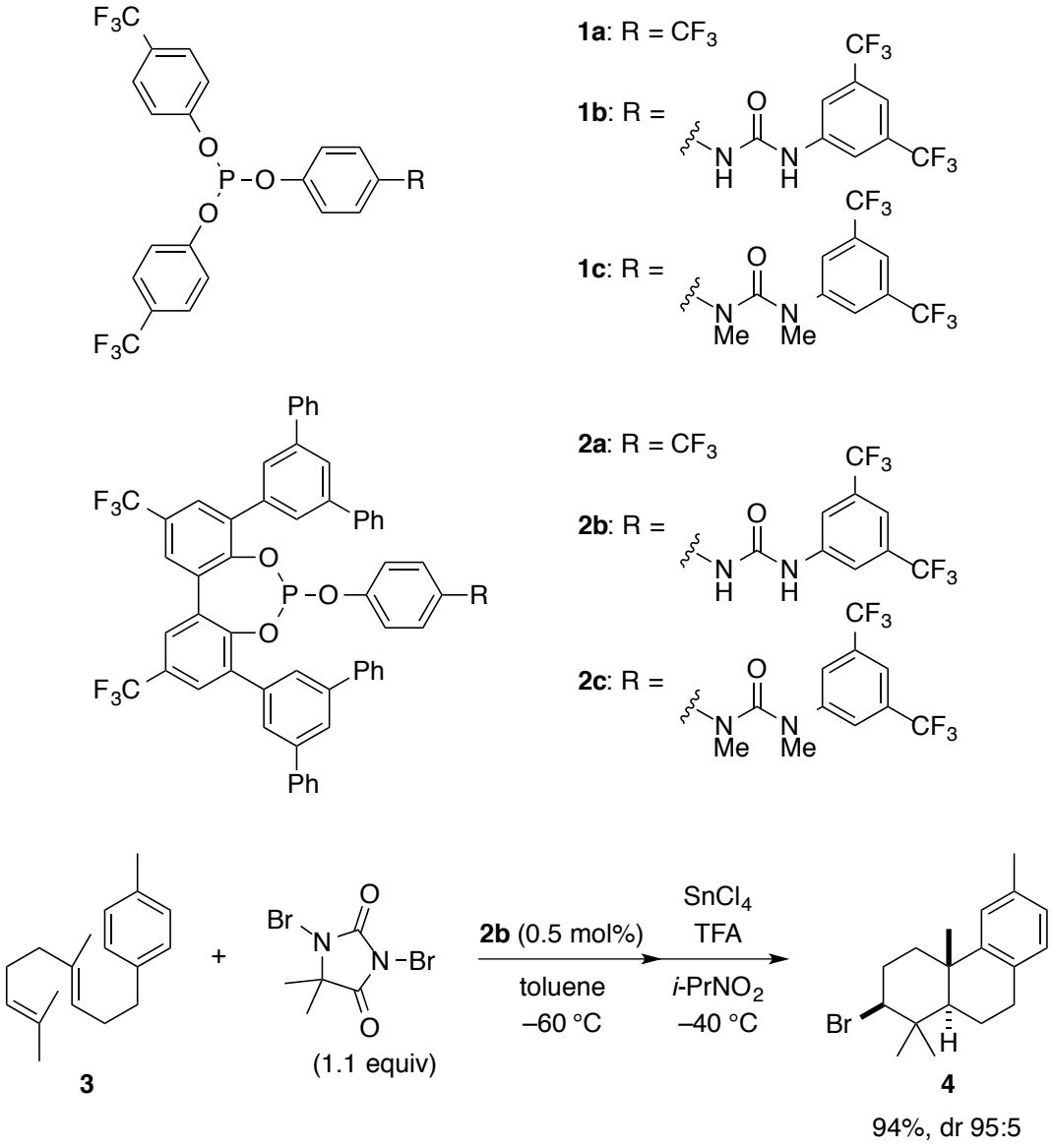
Nucleophilic phosphite–urea cooperative catalysts are highly efficient for the bromonium-induced cyclization of 2-geranylphenols. Phosphite–*N,N'*-dimethylurea catalysts also show moderate activity, probably due to the steric effect of their bent conformation.

3-1. Introduction

The biosynthesis of bromine-containing polycyclic terpenoids appears to include the site- and enantioselective bromination of a carbon–carbon double bond followed by diastereoselective π–cation cyclization.[1–3] Biomimetic bromonium-induced polyene cyclizations (π–cation cyclization) should be powerful tools for the construction of complex polycyclic structures of these bromine-containing natural products. Hence, much attention has been devoted to the development of biomimetic bromonium-induced polyene cyclizations. However, conventional methods that use a standard electrophilic brominating reagent such as Br_2, *N*-bromosuccinimide (NBS) or 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCO) are generally less reactive and generate significant amounts of byproducts.[4–15] Only a few efficient methods have been developed thus far for bromonium-induced polyene cyclizations.[16–20] In 2009, Snyder and colleagues reported that $Et_2SBr{\bullet}SbCl_5Br$ (BDSB) is a highly reactive electrophilic bromination reagent and gives the bromocyclization products in good to high yields.[21,22]

We recently reported nucleophilic phosphite–urea cooperative catalysts **1b** and **2b** (Scheme 3.1), which had high turnover rates for the highly selective bromocyclization of homogeranylarenes.[23–28] Only 0.5 mol% of **2b** successfully catalyzes the bromocyclization of 4-homogeranyltoluene (**3**) to give the corresponding bromocyclization product in 94% yield (Scheme 3.1). The nucleophilic phosphite group catalytically activates a brominating reagent such as NBS and 1,3-dibromo-5,5-dimethylhydantoin (DBH) to generate the corresponding bromophosphonium ion as an active species. The urea group probably interacts with the succinimide anion *via* hydrogen bonding to inhibit decomposition of the catalyst and the generation of byproducts. In the same report, we described that phosphite-*N,N'*-dimethylurea catalyst **1c** showed unexpectedly good activity for the bromocyclization of **3** (84% yield), although **1c** did not have any acidic protons to interact with the succinimide anion. Since we were interested in the ability of the *N,N'*-dimethylurea group to promote bromocyclization, we reinvestigated the catalytic activity of nucleophilic phosphite catalysts **1** and **2** for the bromocyclization of **3** in detail. We report here the results of our reinvestigation of the catalytic activity of phosphite–urea catalysts and an investigation of the bromocyclization of 2-geranylphenols.

Scheme 3.1. Nucleophilic Phosphite Catalysts **1** and **2**, and **2b**-Catalyzed Bromocyclization of 4-Homogeranyltoluene (**3**)

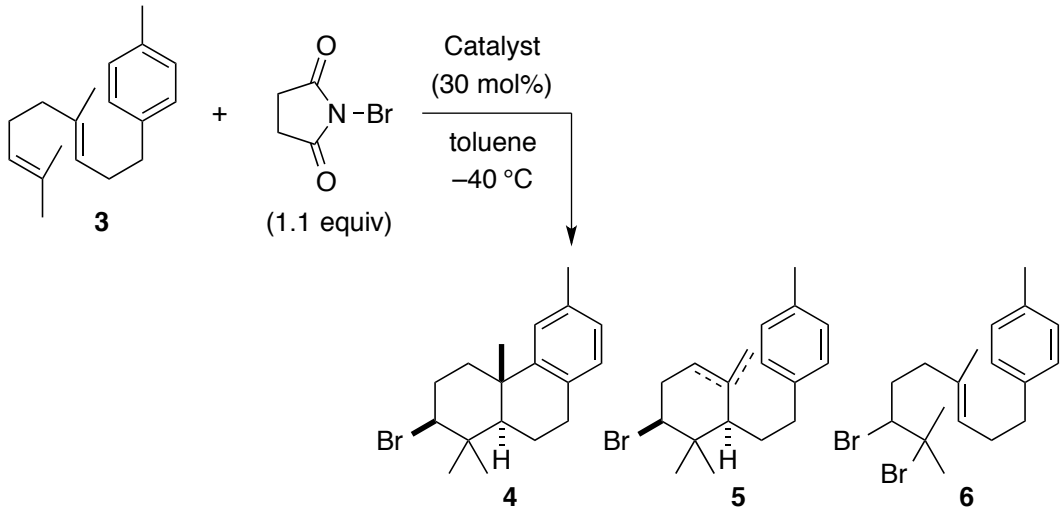


3-2. Results and Discussion

We first examined the catalytic activities of nucleophilic phosphites **1** and **2** for the bromocyclization of 4-homogeranyltoluene (**3**). The reaction of **3** was conducted with NBS (1.1 equiv) in the presence of **1** or **2** (30 mol%) in toluene at −40 °C for 6 h (Table 3.1). As we described in the previous report, the reaction diastereoselectively gave the desired *trans*-fused AB-ring product **4** together with *endo*- and *exo*-isomeric A-ring products **5** and undesired dibromide **6**. Dibromide **6** was generated *via* decomposition of the bromophosphonium active species.[23] The ratio of **4**, *endo*-**5** and *exo*-**5** in each reaction was ca. 1:1:1, and the crude products did not include the *cis*-fused isomer of **4** or the tetrasubstituted isomer of **5**. Since A-ring products **5** could be quantitatively converted to AB-ring product **4** by treatment with $SnCl_4$ and trifluoroacetic acid, the combined yield of **4** and **5** was evaluated by ^{1}H nuclear magnetic resonance (NMR) analysis of the crude products. As a result of the reexamination, phosphite–urea catalysts **1b** and **2b** gave the best results: the desired products **4** and **5** were obtained in almost quantitative yields and the generation of dibromide **6** was successfully suppressed (entries 3 and 4), as we noted in the previous report. On the other hand, the reaction did not proceed without a catalyst.

However, the use of phosphite–*N,N'*-dimethylurea catalyst **1c** gave **4** and **5** in only 43% yield (entry 5), although our previous report[23] stated that **1c** showed unexpectedly good activity (**4** + **5**: 84%yield). The rather high activity of **1c** in our previous report might have been due to some impurities (acidic materials such as 4-$CF_3C_6H_4OH$) in the sample of **1c**. The data in entry 4 were reproducible, and the purity of **1c** was >99% based by ^{1}H NMR analysis. Sterically bulky phosphite–*N,N'*-dimethylurea catalyst **2c** showed slightly higher activity than **1a** and **1c** (53% yield, entry 6). However, the activity of **2c** was almost the same as that of **2a** (52%, entry 2). These results suggested that the *N,N'*-dimethylurea group in **1c** and **2c** did not promote the bromocyclization of **3**, and steric hindrance around the phosphite moiety slightly improved the catalytic activity probably due to inhibition of the decomposition of the catalyst to the phosphonium salt.[23]

Table 3.1. Catalytic Activities of Phosphite–Urea Catalysts for the Bromocyclization of 4-Homogeranyltoluene (**3**)



		Yield [%][a]	
Entry	Catalyst	**4** + **5**	**6**
1	**1a**	39	22
2	**2a**	52	15
3	**1b**	96	0
4[b]	**2b**	99	0
5	**1c**	43	12
6	**2c**	53	14
7	no catalyst	0	0

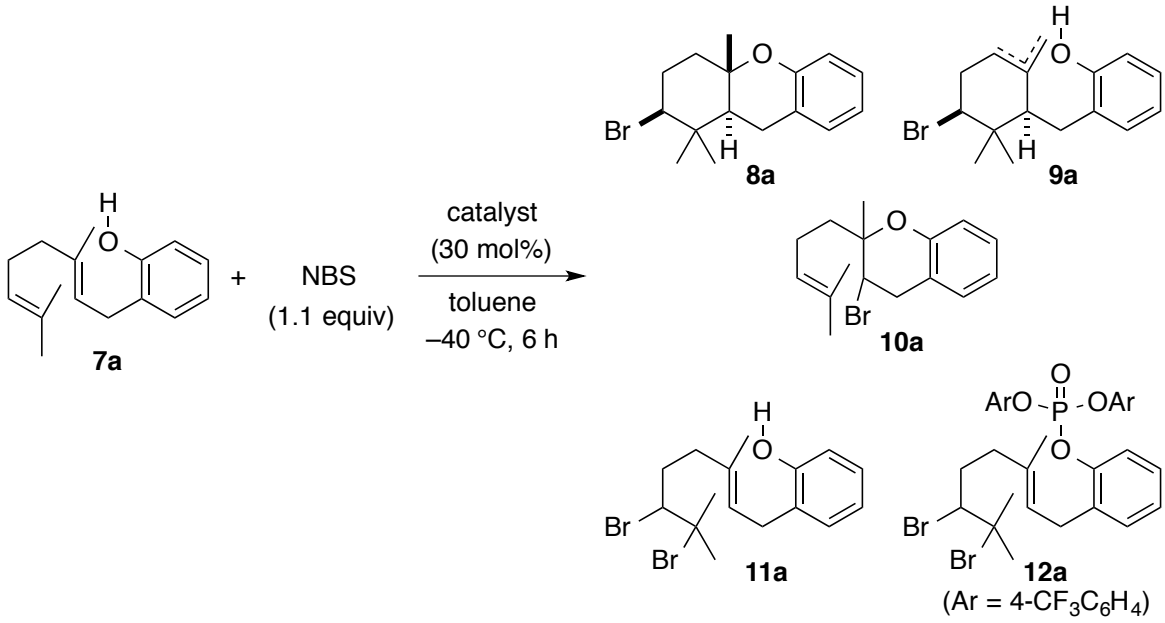
[a] Yields were evaluated by ^{1}H NMR analysis.

[b] The reaction was conducted with 5 mol% of **2b**.

We next examined the bromocyclization of 2-geranylphenol (**7a**) catalyzed by phosphite–urea catalysts **1** and **2** under the same conditions as the reaction of **3** (Table 3.2). The bromocyclization of **7a** generates a core structure of bromine-containing natural products such as 4-isocymobarbatol. The bromocyclization of **7a** gave the desired *trans*-fused AB-ring product **8a** together with *endo*- and *exo*-isomeric A-ring products **9a** (*endo* : *exo* = *ca.* 2 : 3) and undesired dibromide **11a**. As in the reaction of 4-homogeranyltoluene (**3**), phosphite–urea catalysts **1b** and **2b** showed high activities to give the desired products **8a** and **9a** in yields of 80–85% (entries 5 and 6). The use of **1b** or **2b** successfully suppressed the generation of dibromides **11a** and **12a**. However, the reaction also gave B-ring product **10a**.

Since the reaction of the internal carbon–carbon double bond was not observed at all in the bromocyclization of **3**, the reactivity of the internal carbon–carbon double bond of **7a** is thought to be much higher than that of **3**, probably due to the more nucleophilic hydroxy group.

Table 3.2. Catalytic Activities of Phosphite–Urea Catalysts for the Bromocyclization of 2-Geranylphenol (**7a**)

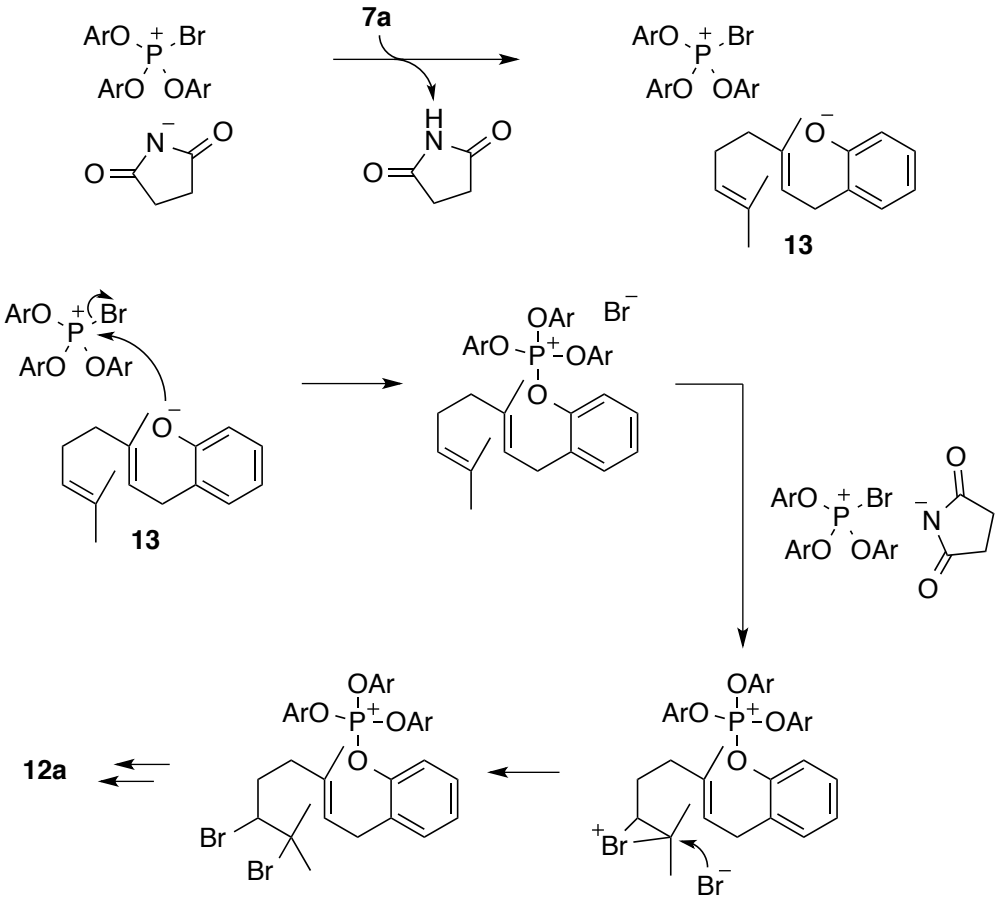


		Yield [%][a]		
Entry	Catalyst	**8a** + **9a**	**10a**	**11a** + **12a**
1	**1a**	9	7	24
2[b]	**1a**	35	20	25
3	**2a**	9	2	4
4[b]	**2a**	32	17	13
5	**1b**	80	12	2
6[c]	**2b**	85	10	0
7	**1c**	13	6	22
8	**2c**	43	9	12

[a] Yields were evaluated by ^{1}H NMR analysis. [b] The reaction was conducted in the presence of *N*-[3,5-bis(trifluoromethyl) phenyl]-*N'*-phenylurea (30 mol%). [c] The reaction was conducted with 5 mol% of **2b**.

The activity of less-hindered phosphite **1a** was very poor (9% yield, entry 1) since **1a** easily decomposed to form inert phosphonium salt under the reaction conditions.[23] The **1a**-catalyzed reaction of **7a** gave significant amounts of B-ring product **10a** (7%) and dibromides **11a** and **12a** (24%) as byproducts. The absence of a urea group would increase the reactivity of the internal carbon–carbon double bond of **7a** *via* the generation of phenoxide **13** (Scheme 3.2) to increase the yield of **10a**. The generation of phenoxide **13** may also have promoted phosphorylation of the phenolic hydroxyl group of **7a** by the bromophosphonium active species (Scheme 3.2). The phosphorylation generated bromide ion and gave dibromide **12a**.[23]

Scheme 3.2. Proposed Mechanism of the Generation of Phenoxide **13** and Dibromide **12a**



Sterically hindered phosphite **2a** showed almost the same activity as **1a** (9% yield, entry 3). The addition of *N*-[3,5-bis(trifluoromethyl)phenyl]-*N'*-phenylurea (30 mol%) to the **1a**- and **2a**-catalyzed reaction improved the reactivity and gave the desired products in respective

yields of 35 and 32% (entries 2 and 4). However, the yield of **10a** was also increased (20 and 17%). These results suggested that the introduction of the phosphite group and the urea group to the same molecule was critical for the selective promotion of bromocyclization.

Interestingly, phosphite–*N,N'*-dimethylurea catalysts **1c** and **2c** showed higher activities than the corresponding phosphites **1a** and **2a** (entries 7 and 8). These results suggested that the *N,N'*-dimethylurea group in **1c** and **2c** promoted the bromocyclization of **7a**. This positive effect might be ascribed to a steric effect of the *N,N'*-dimethylurea group. Density Functional Theory (DFT) calculations[29] of bromophosphonium salts **14**, which would be derived from phosphite–*N,N'*-dimethylurea catalyst **1c** and NBS, indicated that in the optimized conformation, the *N,N'*-dimethylurea group of **14** was folded (Figure 3.1).[30] The bromophosphonium moiety was surrounded by three electron-deficient aryl groups, and one of the fluorine atoms of the 3,5-bis (trifluoromethyl)phenyl groups seemed to interact with a proton of the 4-trifluoromethylphenyl group. The steric effect of these aryl groups might inhibit decomposition of the catalyst to improve the catalytic activity.

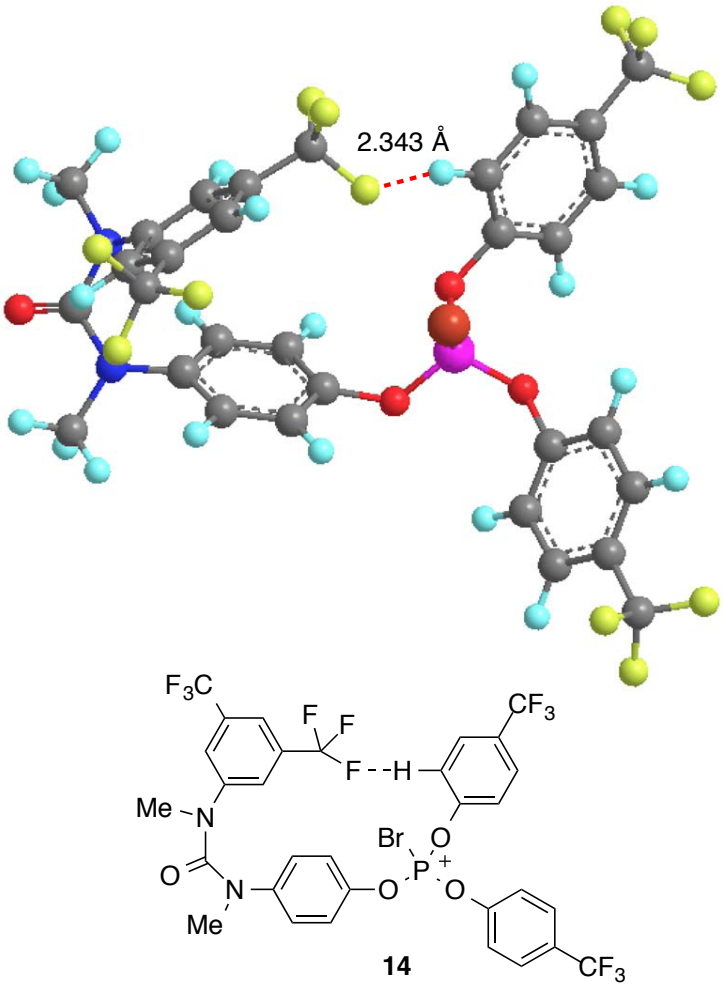
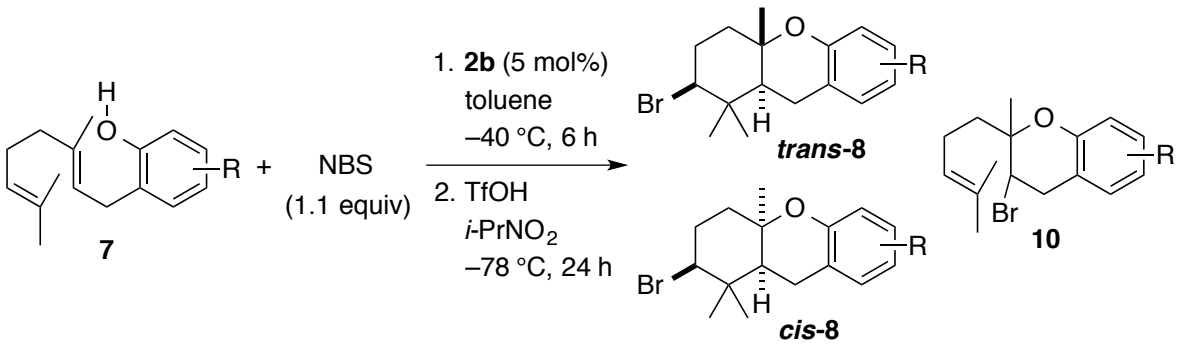


Figure 3.1. B3LYP/6-31G* Optimized Geometry of Bromophosphonium Ions **14**, which Would Be Derived from Phosphite–N,N'-Dimethylurea Catalysts **1c** and NBS

Since phosphite–urea catalyst **2b** showed high activity for the bromocyclization of **7a**, we investigated the bromocyclization of 2-geranylphenols **7** with various substituents on the phenol ring to explore the scope and limitation of the present bromocyclization. The reaction of **7** was conducted with NBS (1.1 equiv) in the presence of **2b** (5 mol%) in toluene at −40 °C for 6 h (Table 3.3). The isolated yields of the corresponding AB-ring products **8** were evaluated after subsequent treatment with TfOH in *i*-$PrNO_2$ at −78 °C.

Table 3.3. **2b**-Catalyzed Bromocyclization of 2-Geranylphenols **7**



	7		**8**		**10**
Entry		R	Yield[%][a]	*trans/cis*	Yield[%][b]
1	**7a**	H	67	88:12	10
2	**7b**	4-Br	71	89:11	5
3	**7c**	4-I	67	91:9	5
4	**7d**	4-OMe	68	79:21	<16
5	**7e**	4-Me	71	80:20	<20
6	**7f**	6-Br	74	97:3	13
7[c]	**7g**	4,6-Br_2	83	94:6	nd
8	**7h**	4,6-Me_2	67	79:21	17

[a] Isolated yields. [b] Yields were evaluated by ^{1}H NMR analysis. [c] The reaction was conducted with DBH (1.1 equiv) in the presence of **2b** (1.5 mol%).

As shown in Table 3.3, a variety of 2-geranylphenols **7** were smoothly cyclized to give the desired *trans*-fused AB-ring products **8** in good to high yields along with small amounts of *cis*-diastereomers and B-ring products **10**. Especially, 2-geranylphenols **7** bearing electron-withdrawing substituents were converted to the corresponding products **8** with high diastereoselectivities (entries 1–3, 6 and 7). On the other hand, the bromocyclization of 2-geranylphenols **7** bearing electron-donating substituents gave **8** with slightly low diastereoselectivities (entries 4, 5, and 8). Since the first bromination step did not give any *cis*-fused isomers of **8**, it was conceivable that the second acid-promoted B-ring cyclization step kinetically favored the *cis*-cyclization, and that the electron-rich hydroxyphenyl groups increased the ratio of *cis*-fused isomers of **8**. When the bromocyclization of 2-geranylphenols **7**, except for 4,6-dibromo derivative **7g**, was conducted with DBH (1.1

equiv), the yields of **8** were decreased due to the bromination of the phenol ring, although the use of DBH instead of NBS improved the yields for the bromocyclization of 4-homogeranylarenes. It is noteworthy that any protections of the phenolic hydroxyl group were not required for the successful promotion of the **2b**-catalyzed bromocyclization of **7**. On the other hand, for the bromocyclization with BDSB, an *O*-MOM-protected derivative was used as a substrate.[21,22]

3-3. Conclusions

In conclusion, we have demonstrated that the nucleophilic phosphite–urea catalysts **1b** and **2b** show high catalytic activities for the bromocyclization of 2-geranylphenols **7**. The reaction of **7** bearing electron-withdrawing substituents gives the desired products **8** with high diastereoselectivities in good isolated yields, while the reaction of **7** bearing an electron-rich phenol ring decreases the diastereoselectivity. In addition, the *N,N'*-dimethylurea moiety of **1c** and **2c** shows rather higher activity than the corresponding trifluoromethyl derivatives **1a** and **2a** to give **8a** in moderate yield. The DFT calculation suggests that the bent conformation of bromophosphonium ion **14**, in which the bromophosphonium moiety is surrounded by three aryl groups, may inhibit the decomposition of the catalyst.

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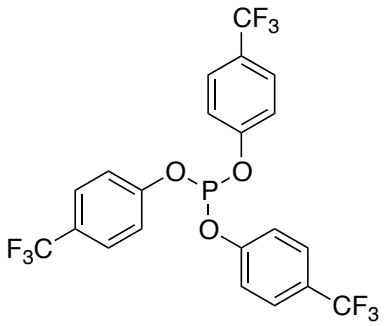
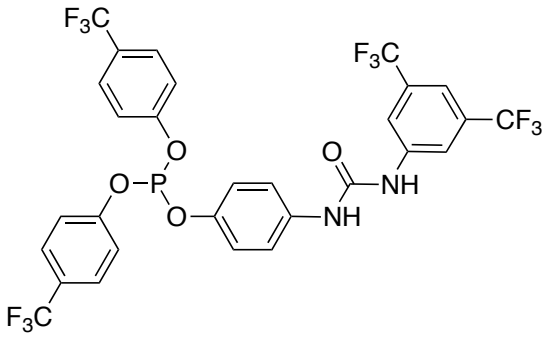
Experimental Section

General Methods. Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. ^{1}H NMR spectra were measured on a JEOL ECS-400 spectrometer (400 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet, sep = septet; m = multiplet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a JEOL ECS-400 spectrometer (100 MHz). Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.00 ppm). ^{19}F NMR spectra (376 MHz) and ^{31}P NMR spectra (162 MHz) were measured on a JEOL ECS-400 spectrometer. The reactions were carried out under an atmosphere of dry nitrogen. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254} 0.25 mm or silica gel NH_2 F_{254S} 0.25 mm) were used. For preparative TLC throughout this work, Merck precoated PLC plates (silica gel 60 GF_{254} 0.5 mm) were used. The products were purified by column chromatography on silica gel (E. Merck Art. 9385). High resolution mass spectral analysis (HRMS) was performed at Chemical Instrumentation Facility, Nagoya University on JEOL JMS-700 spectrometer (for FAB) or JEOL JMS-T100GCV spectrometer (for EI). Dry toluene was purchased from Kanto as the “anhydrous” and stored under nitrogen. Other simple chemicals were analytical-grade and obtained commercially.

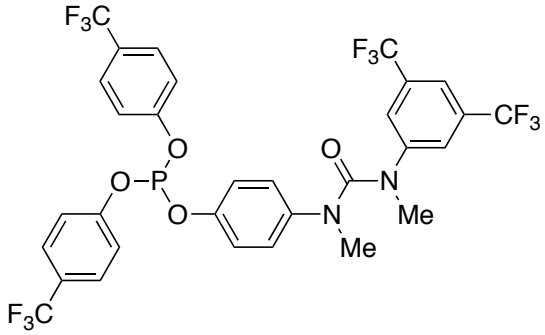
Preparation of Phosphite Catalysts 1a–c and 2a–c.



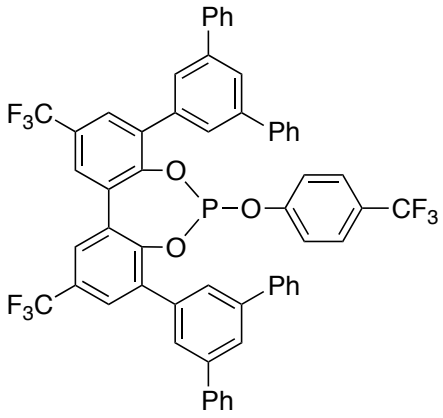
Tris(4-(trifluoromethyl)phenyl) phosphite (1a):[1] Compound **1a** was prepared from PCl_3 and 4-hydroxybenzotrifluoride according to the reported procedure.[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.7 Hz, 6H), 7.23 (d, J = 8.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8(3C), 127.3 (q, J_{C-F} = 3.8 Hz, 6C), 127.0 (q, J_{C-F} = 33.6 Hz, 3C), 123.9 (q, J_{C-F} = 271 Hz, 3C), 120.7 (q, J_{C-P} = 7.7 Hz, 6C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 126.2.



4-(3-(3,5-Bis(trifluoromethyl)phenyl)ureido)-phenyl bis(4-(trifluoromethyl)phenyl) phosphite (1b):[1] Compound **1b** was prepared according to the reported procedure.[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 2H), 7.62 (d, J = 8.7 Hz, 4H), 7.55 (s, 1H), 7.34 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 8.7 Hz, 4H), 7.14 (d, J =8.7 Hz, 2H), 6.78 (brs, 1H), 6.52 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8 (2C), 153.2, 148.2, 139.4, 133.4, 132.3 (q, J_{C-F} = 33.4 Hz, 2C), 127.2 (q, J_{C-F} = 3.8 Hz, 4C), 126.8(q, J_{C-F} = 33.4 Hz, 2C), 123.9 (q, J_{C-F} = 271 Hz, 2C), 123.4 (2C), 122.9 (q, J_{C-F} = 271 Hz, 2C), 121.5 (d, J_{C-P} = 6.7 Hz, 2C), 120.6 (d, J_{C-P} = 7.6 Hz, 4C), 119.3 (2C), 116.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.0, –63.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 126.7.

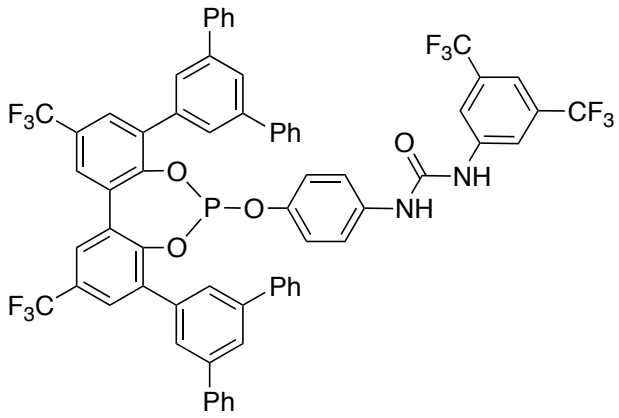


4-(3-(3,5-Bis(trifluoromethyl)phenyl)-1,3-dimethylureido)phenylbis(4-(trifluoromethyl)phenyl) phosphite (1c):[1] Compound **1c** was prepared according to the reported procedure.[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.7 Hz, 4H), 7.39 (s, 1H), 7.19 (d, J = 8.7 Hz, 4H), 6.81 (d, J = 8.7 Hz, 2H), 6.73 (d, J =8.7 Hz, 2H), 3.26 (s, 3H), 3.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8 (2C), 153.8, 148.7 (d, J_{C-P} = 3.8 Hz), 146.7, 141.2, 132.1 (q, J_{C-F} = 33.4 Hz, 2C), 127.2 (q, J_{C-F} = 3.8 Hz, 4C), 126.8 (q, J_{C-F} = 32.6 Hz, 2C), 125.0, 123.9 (q, J_{C-F} = 272 Hz, 2C), 122.7 (q, J_{C-F} = 273 Hz, 2C), 120.8 (d, J_{C-P} = 7.7 Hz, 2C), 120.6 (d, J_{C-P} = 7.7 Hz, 4C), 117.8 (4C), 115.4, 39.6, 38.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 126.2.

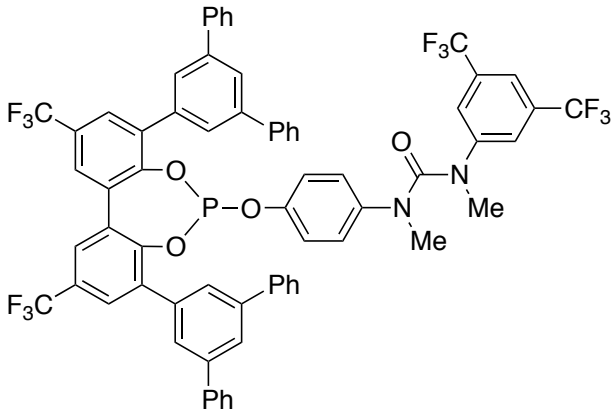


4,8-Di([1,1':3',1''-terphenyl]-5'-yl)-2,10-bis(trifluoromethyl)-6-(4-(trifluoromethyl)phenoxy)dibenzo[*d*,*f*][1,3,2]dioxaphosphepine (2a): To a solution of 4,8-di([1,1':3',1''-terphenyl]-5'-yl)-*N*,*N*-dimethyl-2,10-bis(trifluoromethyl)dibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-amine[1] (170 mg, 0.2 mmol) and 1*H*-tetrazole (70 mg, 1.0 mmol) in toluene (2.0 mL) was added 4-hydroxybenzotrifluoride (42 mg, 0.26 mmol). The reaction mixture was heated at reflux for 12 h. After cooling to ambient temperature, the mixture was filtered through a Celite pad and the filtrate was concentrated *in vacuo.* The residue was purified by column chromatography on silica gel (hexane–toluene 5:1) to give compound **2a** as a colorless solid (127 mg, 65% yield). IR

(KBr) 1595, 1386, 1324, 1259, 1201, 1162, 1128, 1067 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–7.88 (m, 4H), 7.85 (t, J = 1.8 Hz, 2H), 7.76 (d, J = 1.8 Hz, 4H), 7.61 (d, J = 7.3 Hz, 8H), 7.44 (t, J = 7.3 Hz, 8H), 7.37 (t, J = 7.3 Hz, 4H), 6.95 (d, J = 8.7 Hz, 2H), 6.31 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3 (d, J_{C-P} = 11.4 Hz), 148.4 (2C), 142.1 (4C), 140.3 (4C), 136.9 (4C), 136.2 (4C), 131.9 (2C), 128.9 (8C), 128.4 (q, J_{C-F} = 33.4 Hz, 2C), 128.3 (q, J_{C-F} = 3.8 Hz, 2C), 127.8 (2C), 127.22 (2C), 127.18 (8C), 126.79 (2C), 126.75 (2C), 126.4 (q, J_{C-F} = 33.4 Hz), 125.9 (2C), 123.7 (q, J_{C-F} = 271 Hz, 2C), 123.6 (q, J_{C-F} = 271 Hz), 119.4 (d, J_{C-P} = 8.6 Hz, 2C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –61.8, –62.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 144.2; HRMS (FAB) calcd for $C_{57}H_{35}F_9O_3P^+$ $[M+H]^+$ 969.2175, found 969.2188.

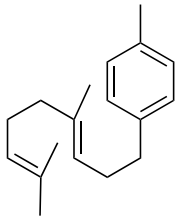


1-(3,5-Bis(trifluoromethyl)phenyl)-3-(4-((4,8-di([1,1':3',1''-terphenyl]-5'-yl)-2,10-bis(trifluoromethyl)dibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-yl)oxy)phenyl)urea (2b):[1] Compound **2b** was prepared according to the reported procedure.[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94–7.83 (m, 6H), 7.80–7.72 (m, 6H), 7.62 (d, J = 7.4 Hz, 8H), 7.52 (s, 1H), 7.43 (t, J = 7.4 Hz, 8H), 7.34 (t, J = 7.4 Hz, 4H), 6.70 (d, J = 8.7 Hz, 2H), 6.44 (s, 1H), 6.24 (d, J = 8.7 Hz, 2H), 6.07 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 148.5 (2C), 142.1 (4C), 140.4 (4C), 139.5, 137.0 (4C), 136.2 (4C), 132.7, 132.2 (q, J_{C-F} = 33.4 Hz, 2C), 131.9, 128.9 (10C), 128.33 (q, J_{C-F} = 32.4 Hz, 2C), 128.31 (2C), 127.8 (2C), 127.3 (2C), 127.2 (8C), 126.7 (2C), 125.8 (2C), 124.0 (2C), 123.7 (q, J_{C-F} = 271 Hz, 2C), 123.0 (q, J_{C-F} = 272 Hz, 2C), 120.5 (q, J_{C-P} = 7.6 Hz, 2C), 119.1 (2C), 116.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ –61.8, –62.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 144.7.



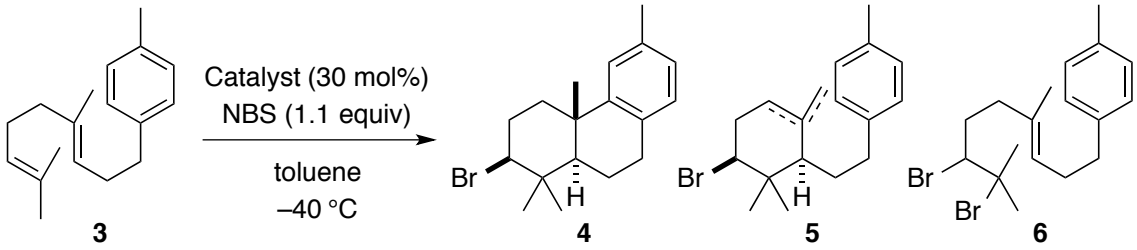
1-(3,5-Bis(trifluoromethyl)phenyl)-3-(4-((4,8-di([1,1':3',1''-terphenyl]-5'-yl)-2,10-bis(trifluoromethyl)dibenzo[*d*,*f*][1,3,2]dioxaphosphepin-6-yl)oxy)phenyl)-1,3-dimethylurea (2c): To a solution of 4,8-di([1,1':3',1''-terphenyl]-5'-yl)-*N*,*N*-dimethyl-2,10-bis(trifluoromethyl)dibenzo[*d*,*f*][1,3,2]-dioxaphosphepin-6-amine[1] (156 mg, 0.183 mmol) and 1*H*-tetrazole (64 mg, 0.915 mmol) in toluene (3.0 mL) was added 1-(3,5-bis(trifluoromethyl)phenyl)-3-(4-hydroxyphenyl)-1,3-dimethylurea[1] (144 mg, 0.356 mmol). The reaction mixture was heated at reflux for 11 h. After cooling to ambient temperature, the mixture was filtered through a Celite pad and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane–EtOAc 2:1) to give compound **2c** as a colorless solid (144 mg, 66% yield). IR (KBr) 1672, 1504, 1384, 1349, 1324, 1313, 1279, 1260, 1161, 1129 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91–7.83 (m, 6H), 7.75 (d, J = 1.4 Hz, 4H), 7.62 (d, J = 7.3 Hz, 8H), 7.44 (t, J = 7.3 Hz, 8H), 7.37 (t, J = 7.3 Hz, 4H), 7.09 (s, 1H), 6.93 (s, 2H), 6.07 (d, J = 8.7 Hz, 2H), 5.87 (d, J = 8.7 Hz, 2H), 2.98 (s, 3H), 2.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ159.8, 148.5 (2C), 146.5, 142.0 (4C), 140.8, 140.4 (4C), 137.0 (4C), 136.2 (4C), 131.90 (q, $J_{C–F}$ = 33.4 Hz, 2C), 131.88, 128.9 (10C), 128.3 (q, $J_{C–F}$ = 33.4 Hz, 2C), 128.2 (2C), 127.8 (2C), 127.2 (2C), 127.1 (8C), 126.7 (2C), 126.6 (2C), 125.7 (2C), 124.7 (2C), 123.7 (q, $J_{C–F}$ = 271 Hz, 2C), 122.5 (q, $J_{C–F}$ = 271 Hz, 2C), 119.7 (d, $J_{C–P}$ = 8.6 Hz, 2C), 117.7, 39.0, 38.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ –61.9, –63.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 144.74, 144.69; HRMS (FAB) calcd for $C_{67}H_{44}F_{12}N_2O_4P^+$ $[M+H]^+$ 1199.2842, found 1199.2835.

Preparation of Homogeranyltoluene 3.

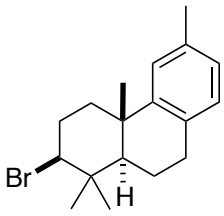


Homogeranyltoluene (3):[2,3] Compound **3** was prepared from 4-methylbenzyl magnesium chloride and (*E*)-geranyl diethyl phosphate according to the reported procedure.[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (s, 4H), 5.18 (t, *J* = 7.4 Hz, 1H), 5.09 (t, *J* = 6.9 Hz, 1H), 2.60 (t, *J* = 7.4 Hz, 2H), 2.32 (s, 3H), 2.28 (dt, *J* = 7.4, 7.4 Hz, 2H), 2.06 (dt, *J* = 7.8, 6.9 Hz, 2H), 1.97 (t, *J* = 7.8 Hz, 2H), 1.69 (s, 3H), 1.60 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 135.6, 135.0, 131.3, 128.9 (2C), 128.3 (2C), 124.3, 123.7, 39.7, 35.7, 30.1, 26.7, 25.7, 21.0, 17.7, 16.0.

Typical Procedure for Selective Bromocyclization of Homogeranyltoluene 3.

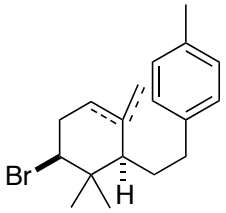


To a solution of **1a** (46.3 mg, 0.09 mmol) in toluene (1.5 mL) were added NBS (58.7 mg, 0.33 mmol) and **3** (0.30 mmol) successively at –78 °C, and the mixture was stirred at –78 °C for 0.5 h and then at –40 °C for 6 h. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (3.0 mL) and extracted with hexane (5.0 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The ratio of **4**, *endo*-**5**, *exo*-**5** and **6** was determined by ^{1}H NMR analysis: δ 4.04 (dd, *J* = 12.4, 4.1 Hz, 1H, **4**), 4.17 (dd, *J* = 9.6, 6.9 Hz, 1H, *endo*-**5**), 4.11 (dd, *J* = 11.5, 4.6 Hz, 1H, *exo*-**5**), and 5.29 (t, *J* = 6.9 Hz, 1H, **6**).

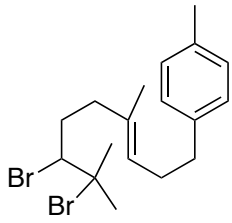


2-Bromo-1,1,4a,6-tetramethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (4): Pale yellow solid; IR (KBr) 1611, 1500, 1438, 1377, 1261,

1096, 1066, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.00 (s, 1H), 6.98–6.88 (m, 2H), 4.04 (dd, *J* = 12.4, 4.1 Hz, 1H), 2.96–2.77 (m, 2H), 2.42–2.21 (m, 2H), 2.28 (s, 3H), 1.95 (ddt, *J* = 13.3, 6.9, 2.3 Hz, 1H), 1.85–1.71 (m, 1H), 1.58 (td, *J* = 11.9, 3.2 Hz, 1H), 1.45 (dd, *J* = 11.9, 2.3 Hz, 1H), 1.23 (s, 3H), 1.15 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 135.1, 131.5, 128.9, 126.5, 124.9, 68.9, 51.2, 39.9, 39.8, 37.8, 31.5, 30.5, 30.4, 24.8, 21.2, 20.6, 18.2; HRMS (FAB) calcd for $C_{18}H_{25}Br^+$ $[M]^+$ 320.1140, found 320.1138.

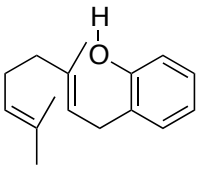


1-(2-(5-Bromo-2,6,6-trimethylcyclohex-2-en-1-yl)ethyl)-4-methylbenzene (*endo*-5), 1-(2-(3-Bromo-2,2-dimethyl-6-methylenecyclohexyl)ethyl)-4-methylbenzene (*exo*-5): Compounds ***endo*-5**, and ***exo*-5** could not be separated by column chromatography on silica gel. ***endo*-5:** ^1H NMR (400 MHz, $CDCl_3$) δ 5.23 (brs, 1H), 4.17 (dd, *J* = 9.6, 6.9 Hz, 1H), 1.07 (s, 3H), 0.88 (s, 3H). Other resonances could not be discerned for this compound. ***exo*-5:** ^1H NMR (400 MHz, $CDCl_3$) δ 4.99 (s, 1H), 4.76 (s, 1H), 4.11 (dd, *J* = 11.5, 4.6 Hz, 1H), 1.12 (s, 3H), 0.82 (s, 3H). Other resonances could not be discerned for this compound.

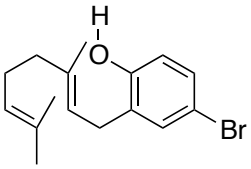


(*E*)-1-(7,8-Dibromo-4,8-dimethylnon-3-en-1-yl)-4-methylbenzene (6): Colorless solid; IR (neat) 1516, 1456, 1370, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.09 (s, 4H), 5.29 (t, *J* = 6.9 Hz, 1H), 4.09 (dd, *J* = 11.0, 0.9 Hz, 1H), 2.62 (t, *J* = 7.8 Hz, 2H), 2.56–2.46 (m, 1H), 2.32 (s, 3H), 2.39–2.27 (m, 3H), 2.21–2.12 (m, 1H), 1.96 (s, 3H), 1.89–1.78 (m, 1H), 1.81 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 139.1, 135.1, 133.5, 128.9 (2C), 128.3 (2C), 125.7, 68.8, 65.8, 37.7, 35.5, 35.3, 33.7, 30.0, 28.2, 21.0, 15.7; HRMS (FAB) calcd for $C_{18}H_{27}Br_2$ $[M+H]^+$ 401.0474, found 401.0470.

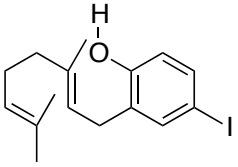
Preparation of 2-Geranylphenols 7a–h.



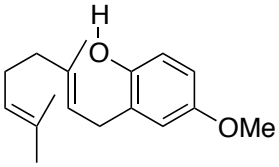
2-Geranylphenol (7a):[4,5] Compound **7a** was prepared from phenol and geranyl chloride according to the reported procedure.[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.08 (m, 2H), 6.86 (t, *J* = 7.3 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 5.33 (t, *J* = 7.1 Hz, 1H), 5.09 (s, 1H), 5.11–5.04 (m, 1H), 3.37 (d, *J* = 6.9 Hz, 2H), 2.16–2.05 (m, 4H), 1.77 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 138.4, 131.9, 129.9, 127.5, 126.8, 123.8, 121.6, 120.7, 115.7, 39.7, 29.7, 26.4, 25.7, 17.7, 16.1.



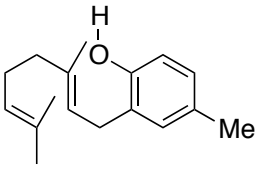
4-Bromo-2-geranylphenol (7b):[2b] Compound **7b** was prepared from 4-bromophenol and geranyl chloride according to the same manner as **7a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.18 (m, 2H), 6.69 (d, *J* = 8.7 Hz, 1H), 5.27 (t, *J* = 7.3 Hz, 1H), 5.12 (s, 1H), 5.06 (t, *J* = 6.9 Hz, 1H), 3.32 (d, *J* = 7.3 Hz, 2H), 2.17–2.04 (m, 4H), 1.75 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 139.2, 132.4, 132.1, 130.1, 129.2, 123.7, 120.7, 117.4, 112.6, 39.6, 29.4, 26.3, 25.7, 17.7, 16.2.



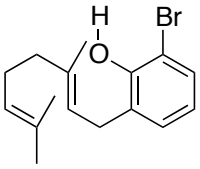
2-Geranyl-4-iodophenol (7c):[5] Compound **7c** was prepared from 4-iodophenol and geranyl chloride according to the same manner as **7a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.37 (m, 2H), 6.58 (d, *J* = 9.2 Hz, 1H), 5.27 (t, *J* = 7.3 Hz, 1H), 5.16 (s, 1H), 5.06 (t, *J* = 6.9 Hz, 1H), 3.30 (d, *J* = 7.3 Hz, 2H), 2.16–2.04 (m, 4H), 1.76 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 139.3, 138.4, 136.2, 132.1, 129.6, 123.6, 120.7, 118.1, 82.8, 39.6, 29.5, 26.3, 25.7, 17.7, 16.2.



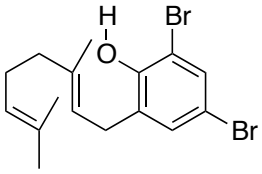
2-Geranyl-4-methoxyphenol (7d):[5] Compound **7d** was prepared from 4-methoxyphenol and geranyl chloride according to the same manner as **7a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (d, *J* = 8.7 Hz, 1H), 6.68 (d, *J* = 3.2 Hz, 1H), 6.66 (dd, *J* = 8.7, 3.2 Hz, 1H), 5.30 (t, *J* = 7.3 Hz, 1H), 5.07 (t, *J* = 6.8 Hz, 1H), 4.73 (s, 1H), 3.75 (s, 3H), 3.33 (d, *J* = 6.8 Hz, 2H), 2.16–2.04 (m, 4H), 1.77 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 148.3, 138.7, 132.0, 128.0, 123.8, 121.4, 116.4, 115.6, 112.0, 55.7, 39.7, 30.0, 26.4, 25.7, 17.7, 16.2.



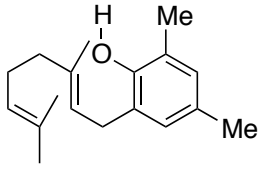
2-Geranyl-4-methylphenol (7e):[5] Compound **7e** was prepared from 4-methylphenol and geranyl chloride according to the same manner as **7a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94–6.86 (m, 2H), 6.70 (dd, *J* = 8.7, 5.0 Hz, 1H), 5.31 (t, *J* = 7.3 Hz, 1H), 5.07 (t, *J* = 6.9 Hz, 1H), 4.94 (s, 1H), 3.33 (d, *J* = 6.9 Hz, 2H), 2.25 (s, 3H), 2.15–2.04 (m, 4H), 1.77 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 138.3, 131.9, 130.5, 129.8, 127.9, 126.5, 123.8, 121.8, 115.6, 39.7, 29.9, 26.4, 25.7, 20.5, 17.7, 16.2.



2-Bromo-6-geranylphenol (7f): Compound **7f** was prepared from 2-bromophenol and geranyl chloride according to the same manner as **7a**. IR (neat) 1450, 1328, 1238 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.07 (dd, *J* = 7.8, 1.4 Hz, 1H), 6.73 (dd, *J* = 7.8, 7.8 Hz, 1H), 5.61 (s, 1H), 5.31 (t, *J* = 7.4 Hz, 1H), 5.09 (t, *J* = 6.9 Hz, 1H), 3.39 (d, *J* = 7.4 Hz, 2H), 2.16–2.03 (m, 4H), 1.71 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 137.4, 131.6, 129.5, 129.2, 129.0, 124.1, 121.34, 121.30, 110.3, 39.7, 29.1, 26.5, 25.7, 17.7, 16.1; HRMS (FAB) calcd for $C_{16}H_{22}BrO^{+}$ $[M+H]^{+}$ 309.0849, found 309.0836.

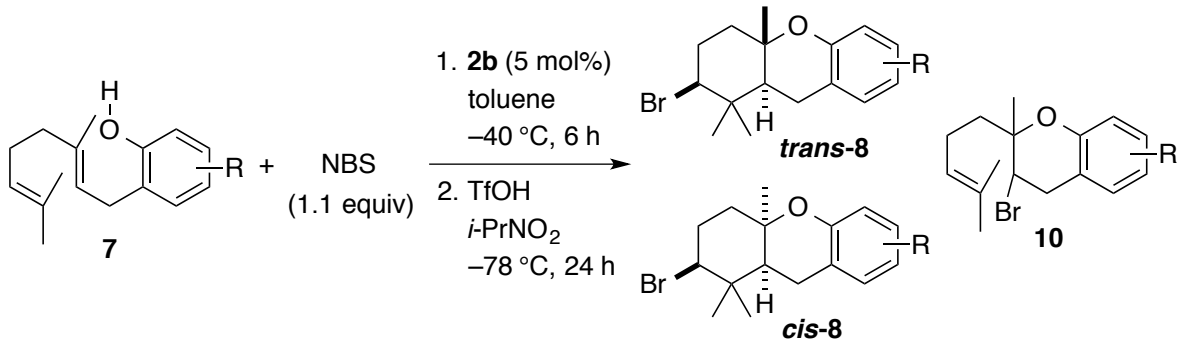


2,4-Dibromo-6-geranylphenol (7g):[1] Compound **7g** was prepared from 2,4-dibromophenol and geranyl chloride according to the same manner as **7a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 2.3 Hz, 1H), 7.18 (d, *J* = 2.3 Hz, 1H), 5.60 (s, 1H), 5.27 (t, *J* = 7.3 Hz, 1H), 5.09 (t, *J* = 6.9 Hz, 1H), 3.35 (d, *J* = 7.3 Hz, 2H), 2.16–2.03 (m, 4H), 1.70 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 138.2, 131.8, 131.7, 131.4, 130.9, 123.9, 120.4, 112.3, 110.6, 39.6, 29.0, 26.4, 25.7, 17.7, 16.1



2-Geranyl-4,6-dimethylphenol (7h):[6] Compound **7h** was prepared from 2,4-dimethylphenol and geranyl chloride according to the same manner as **7a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (s, 1H), 6.76 (s, 1H), 5.30 (t, *J* = 7.3 Hz, 1H), 5.06 (t, *J* = 6.4 Hz, 1H), 5.02 (s, 1H), 3.32 (d, *J* = 7.3 Hz, 2H), 2.22 (s, 3H), 2.19 (s, 3H), 2.16–2.03 (m, 4H), 1.78 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 138.3, 131.9, 129.5, 129.1, 128.0, 125.8, 124.2, 123.7, 122.1, 39.6, 30.3, 26.2, 25.6, 20.4, 17.6, 16.0, 15.7.

Typical Procedure for Selective Bromocyclization of 2-Geranylphenols 7.

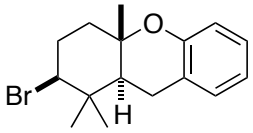


To a solution of **2b** (5.9 mg, 0.005 mmol) in toluene (1.0 mL) were added NBS (19.6 mg, 0.11 mmol) and 2-geranylphenol **7a** (23.0 mg, 0.10 mmol) successively at –78 °C, and the mixture was stirred at –78 °C for 0.5 h and then at –40 °C for 6 h. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (3.0 mL) and extracted with hexane (5.0 mL × 3).

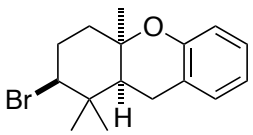
The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel using (hexane–EtOAc 20:1) as an eluent to give *trans*-**8a** (10.8 mg, 35% yield) and the mixture of *endo*-**9a** and *exo*-**9a**.

The resulting mixture of *endo*-**9a** and *exo*-**9a** was used for the next cyclization without further separation. To a solution of the resulting mixture (16.8 mg), which were obtained in the above reaction, in *i*-$PrNO_2$ (0.54 mL) was added TfOH (19.2 μL, 0.217 mmol) at –78 °C. The mixture was stirred at –78 °C for 24 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, and extracted with Et_2O (5 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative TLC using (hexane–EtOAc 20:1) as an eluent to give *trans*-**8a** and *cis*-**8a** as colorless solids (9.9 mg, 32% yield, *trans/cis* = 75 : 25).

The corresponding physical and spectroscopic data for **8** are as follows.

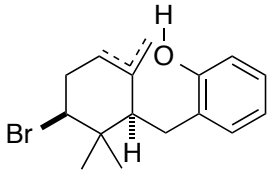


***Trans*-2-bromo-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (*trans*-8a):** Colorless solid; IR (KBr) 1488, 1454, 1242, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13–7.03 (m, 2H), 6.84 (t, *J* = 7.3 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 4.05 (dd, *J* = 12.4, 4.1 Hz, 1H), 2.83–2.69 (m, 2H), 2.28 (dddd, *J* = 13.7, 4.1, 3.6, 3.6 Hz, 1H), 2.13 (dddd, *J* = 13.7, 13.7, 12.4, 3.7 Hz, 1H), 2.01 (ddd, *J* = 12.8, 3.7, 3.6 Hz, 1H), 1.81 (dd, *J* = 11.9, 6.0 Hz, 1H), 1.78 (ddd, *J* = 13.7, 12.8, 3.6 Hz, 1H), 1.24 (s, 3H), 1.17 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 129.5, 127.3, 121.7, 120.0, 117.0, 75.7, 66.0, 48.0, 40.7, 39.2, 31.5, 29.6, 24.6, 19.8, 16.9; HRMS (FAB) calcd for $C_{16}H_{21}BrO^+$ $[M]^+$ 308.0776, found 308.0774.

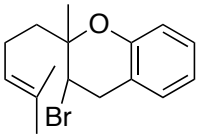


***Cis*-2-bromo-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (*cis*-8a):** Colorless solid; IR (neat) 1584, 1489, 1455, 1237 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.11–7.02 (m, 2H), 6.84 (t, *J* = 7.3 Hz, 1H), 6.74 (d, *J* = 8.3 Hz, 1H), 4.09 (dd, *J* = 12.8, 3.3 Hz, 1H), 3.12 (dd, *J* = 17.9, 7.8 Hz, 1H), 2.84 (d, *J* = 17.9 Hz, 1H), 2.48 (dddd, *J* = 13.7, 12.8, 12.8, 3.6 Hz,

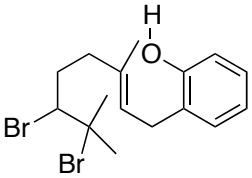
1H), 2.11–2.04 (m, 2H), 1.67 (ddd, J = 14.7, 13.7, 4.1 Hz, 1H) 1.57 (d, J = 7.8 Hz, 1H), 1.19 (s, 3H), 1.15 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 128.7, 127.0, 121.4, 120.3, 117.2, 74.4, 67.5, 45.1, 40.3, 40.2, 30.1, 29.9, 26.5, 27.8, 16.6; HRMS (FAB) calcd for $C_{16}H_{21}BrO^+$ $[M]^+$ 308.0776, found 308.0794.



2-((5-Bromo-2,6,6-trimethylcyclohex-2-en-1-yl)methyl)phenol (*endo*-9a), 2-((3-Bromo-2,2-dimethyl-6-methylenecyclohexyl)methyl)phenol (*exo*-9a): Compounds ***endo*-9a** and ***exo*-9a** could not be separated by column chromatography on silica gel. ***endo*-9a:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22 (brs, 1H), 4.27 (dd, J = 9.6, 6.4 Hz, 1H), 1.48 (s, 3H), 1.21 (s, 3H), 1.05 (s, 3H). Other resonances could not be discerned for this compound. ***exo*-9a:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 (s, 1H), 4.74 (s, 1H), 4.11 (dd, J = 11.0, 4.1 Hz, 1H), 1.12 (s, 3H), 1.01 (s, 3H). Other resonances could not be discerned for this compound.

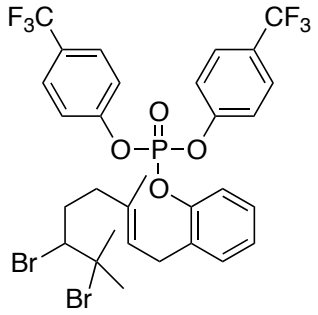


3-Bromo-2-methyl-2-(4-methylpent-3-en-1-yl)chroman (10a): Colorless oil; IR (neat) 1585, 1489, 1456, 1262, 1238 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (dd, J = 7.3, 7.3 Hz, 1H), 7.01 (d, J = 7.3 Hz, 1H), 6.86 (dd, J = 7.8, 7.3 Hz, 1H), 6.82 (d, J = 7.8 Hz, 1H), 5.13 (t, J = 7.4 Hz, 1H), 4.35 (dd, J = 9.6, 6.0 Hz, 1H), 3.36 (dd, J = 16.5, 6.0 Hz, 1H), 3.27 (dd, J = 16.5, 9.6 Hz, 1H), 2.24–2.05 (m, 2H), 1.91–1.75 (m, 2H), 1.69 (s, 3H), 1.63 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 132.2, 128.7, 128.0, 123.6, 120.5, 119.9, 117.4, 78.3, 50.6, 39.1, 34.0, 25.7, 21.4, 19.8, 17.6; HRMS (FAB) calcd for $C_{16}H_{21}BrO^+$ $[M]^+$ 308.0776, found 308.0769.

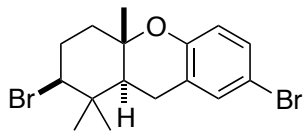


(*E*)-2-(6,7-Dibromo-3,7-dimethyloct-2-en-1-yl)phenol (11a): Colorless oil; IR (neat) 1591, 1489, 1454, 1370, 1221, 1097 cm^{-1}; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.14 (d, J = 7.4 Hz, 1H), 7.11 (dd, J = 7.8, 7.4 Hz, 1H), 6.87 (dd, J = 7.4, 7.4 Hz, 1H), 6.79 (d, J = 7.8 Hz, 1H), 5.45 (t, J = 7.4 Hz, 1H), 4.97 (s, 1H), 4.15 (dd, J = 11.0, 1.4 Hz, 1H), 3.39 (d, J = 7.4 Hz, 2H), 2.58 (dddd, J = 14.7, 7.8, 7.8, 1.4 Hz, 1H), 2.46–2.38 (m, 1H), 2.29–2.19 (m, 1H), 1.97 (s, 3H), 1.95–1.83 (m, 1H), 1.81 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 135.9, 129.9, 127.5, 126.8, 123.5, 120.8, 115.6, 68.8, 65.7, 37.8, 35.4, 33.7, 29.3, 28.1, 16.1; HRMS (FAB) calcd for $C_{16}H_{22}Br_2O^+$ $[M]^+$ 388.0037, found 388.0043.



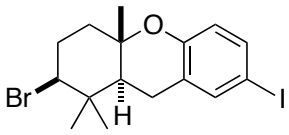
(*E*)-2-(6,7-Dibromo-3,7-dimethyloct-2-en-1-yl)phenyl bis(4-(trifluoromethyl)phenyl) phosphate (12a): Colorless oil; IR (neat) 1613, 1510, 1324, 1205, 1167, 1129, 1103, 1068 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.7 Hz, 4H), 7.36 (d, J = 8.7 Hz, 4H), 7.29–7.12 (m, 4H), 5.35 (t, J = 6.9 Hz, 1H), 4.12 (dd, J = 11.0, 0.9 Hz, 1H), 3.33 (d, J = 6.9 Hz, 2H), 2.55 (dddd, J = 14.2, 8.2, 8.2, 1.4 Hz, 1H), 2.42–2.32 (m, 1H), 2.18 (ddd, J = 14.2, 7.8, 7.8 Hz, 1H), 1.95 (s, 3H), 1.92–1.80 (m, 1H), 1.79 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6 (d, J_{C-P} = 6.7 Hz, 2C), 148.2 (d, J_{C-P} = 7.6 Hz), 135.4, 132.4 (d, J_{C-P} = 6.7 Hz), 130.6, 128.2 (q, J_{C-F} = 34.3 Hz, 2C), 127.4 (5C), 126.2 123.6 (q, J_{C-F} = 272 Hz, 2C), 122.8, 120.5 (d, J_{C-P} = 4.8 Hz, 4C), 119.7, 68.7, 65.7, 37.7, 35.4, 33.6, 28.2, 28.0, 15.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ –17.6; HRMS (FAB) calcd for $C_{30}H_{30}Br_2F_6O_4P^+$ $[M+H]^+$ 757.0147, found 757.0163.



***Trans*-2,7-dibromo-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (*trans*-8b):** Colorless solid; IR (KBr) 1480, 1258, 1240, 1147, 1130, 1070 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (s, 1H), 7.17 (dd, J = 8.7, 2.3 Hz, 1H), 6.63 (d, J = 8.7 Hz, 1H), 4.03 (dd, J = 12.4, 4.1 Hz, 1H), 2.80–2.66 (m, 2H), 2.28 (dddd, J = 13.8, 4.1, 4.1, 3.7 Hz, 1H), 2.12 (dddd,

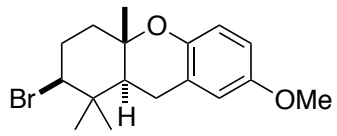
J = 13.8, 13.3, 12.4, 3.7 Hz, 1H), 1.99 (ddd, *J* = 13.3, 3.7, 3.7 Hz, 1H), 1.76 (dd, *J* = 12.4, 6.4 Hz, 1H), 1.75 (ddd, *J* = 13.3, 13.3, 4.1 Hz, 1H), 1.22 (s, 3H), 1.16 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 132.0, 130.3, 123.9, 118.8, 112.0, 76.1, 65.5, 47.7, 40.5, 39.2, 31.4, 29.6, 24.4, 19.8, 16.9; HRMS (FAB) calcd for $C_{16}H_{20}Br_2O^+$ $[M]^+$ 385.9881, found 385.9866.

***Cis*-isomer of 8b:** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.06 (dd, *J* = 12.4, 3.7 Hz, 1H), 3.09 (dd, *J* = 17.9, 7.8 Hz, 1H), 1.17 (s, 3H), 1.13 (s, 3H), 0.78 (s, 3H), and other resonances could not be discerned.



***Trans*-2-bromo-7-iodo-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (*trans*-8c):** Colorless solid; IR (KBr) 1476, 1260, 1248, 1150, 1131 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 6.51 (d, *J* = 8.2 Hz, 1H), 4.02 (dd, *J* = 12.4, 4.1 Hz, 1H), 2.79–2.64 (m, 2H), 2.28 (dddd, *J* = 13.8, 4.1, 4.1, 3.7 Hz, 1H), 2.11 (dddd, *J* = 13.8, 13.8, 12.4, 3.7 Hz, 1H), 1.99 (ddd, *J* = 12.8, 3.7, 3.7 Hz, 1H), 1.76 (dd, *J* = 11.9, 6.4 Hz, 1H), 1.76 (ddd, *J* = 13.3, 12.8, 4.1 Hz, 1H), 1.21 (s, 3H), 1.16 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 138.0, 136.2, 124.6, 119.4, 81.9, 76.2, 65.5, 47.7, 40.5, 39.2, 31.4, 29.6, 24.3, 19.8, 16.9; HRMS (FAB) calcd for $C_{16}H_{20}BrIO^+$ $[M]^+$ 433.9742, found 433.9727.

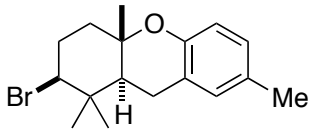
***Cis*-isomer of 8c:** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.07 (dd, *J* = 12.4, 3.2 Hz, 1H), 3.07 (dd, *J* = 18.3, 8.2 Hz, 1H), 1.16 (s, 3H), 1.13 (s, 3H), 0.78 (s, 3H), and other resonances could not be discerned.



***Trans*-2-bromo-7-methoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (*trans*-8d):** Pale yellow solid; IR (KBr) 1496, 1260, 1225, 1148, 1123, 1039 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69–6.66 (m, 2H), 6.63–6.60 (m, 1H), 4.05 (dd, *J* = 12.8, 4.1 Hz, 1H), 3.75 (s, 3H), 2.81–2.67 (m, 2H), 2.28 (dddd, *J* = 13.8, 4.1, 3.7, 3.7 Hz, 1H), 2.13 (dddd, *J* = 13.8, 13.8, 12.8, 3.7 Hz, 1H), 1.98 (ddd, *J* = 13.3, 3.7, 3.7 Hz, 1H), 1.80 (dd, *J* = 11.5, 6.4 Hz,

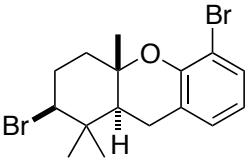
1H), 1.76 (ddd, *J* = 13.8, 13.3, 3.7 Hz, 1H), 1.21 (s, 3H), 1.17 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 146.6, 122.3, 117.5, 114.0, 113.4, 75.4, 66.1, 55.7, 48.1, 40.7, 39.2, 31.5, 29.6, 24.9, 19.7, 16.8; HRMS (FAB) calcd for $C_{17}H_{23}BrO_2^+$ $[M]^+$ 338.0881, found 338.0892.

***Cis*-isomer of 8d:** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.08 (dd, *J* = 10.1, 3.2 Hz, 1H), 3.08 (dd, *J* = 17.8, 7.8 Hz, 1H), 1.14 (s, 3H), 0.81 (s, 3H), and other resonances could not be discerned.



***Trans*-2-bromo-1,1,4a,7-tetramethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (*trans*-8e):** Pale yellow solid; IR (KBr) 1498, 1378, 1241, 1151 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (d, *J* = 7.8 Hz, 1H), 6.88 (s, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 4.05 (dd, *J* = 12.4, 3.7 Hz, 1H), 2.83–2.64 (m, 2H), 2.27 (dddd, *J* = 13.8, 4.1, 3.7, 3.7 Hz, 1H), 2.25 (s, 3H), 2.11 (dddd, *J* = 13.8, 13.8, 12.4, 3.7 Hz, 1H), 1.99 (ddd, *J* = 13.3, 3.7, 3.7 Hz, 1H), 1.79 (dd, *J* = 11.5, 6.0 Hz, 1H), 1.77 (ddd, *J* = 13.8, 13.3, 4.1 Hz, 1H), 1.22 (s, 3H), 1.16 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 129.9, 129.2, 128.0, 121.3, 116.7, 75.6, 66.1, 48.2, 40.7, 39.2, 31.5, 29.6, 24.5, 20.5, 19.7, 16.9; HRMS (FAB) calcd for $C_{17}H_{23}BrO^+$ $[M]^+$ 322.0932, found 322.0937.

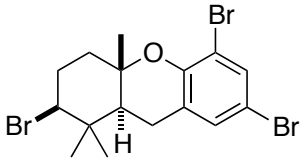
***Cis*-isomer of 8e:** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.08 (dd, *J* = 10.4, 3.6 Hz, 1H), 3.07 (dd, *J* = 17.8, 8.2 Hz, 1H), 1.17 (s, 3H), 1.14 (s, 3H), 0.80 (s, 3H), and other resonances could not be discerned.



***Trans*-2,5-dibromo-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (*trans*-8f):** Colorless solid; IR (KBr) 1450, 1382, 1251, 1148, 1129, 1066 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 7.3 Hz, 1H), 6.71 (dd, *J* = 7.8, 7.3 Hz, 1H), 4.05 (dd, *J* = 12.4, 4.1 Hz, 1H), 2.85–2.71 (m, 2H), 2.31 (dddd, *J* = 14.6, 4.1, 4.1, 3.2 Hz, 1H), 2.15 (dddd, *J* = 14.6, 13.7, 12.4, 3.2 Hz, 1H), 2.10 (ddd, *J* = 13.7, 3.2, 3.2 Hz, 1H), 1.87 (ddd,

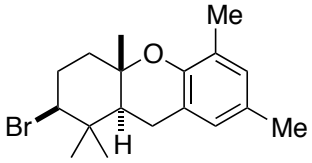
J = 13.7, 13.7, 4.1 Hz, 1H), 1.82 (dd, *J* = 11.4, 6.4 Hz, 1H), 1.25 (s, 3H), 1.17 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 131.0, 128.6, 123.4, 120.7, 111.4, 77.1, 65.6, 47.9, 40.4, 39.2, 31.4, 29.6, 24.8, 20.0, 16.8; HRMS (FAB) calcd for $C_{16}H_{20}Br_2O^+$ $[M]^+$ 385.9881, found 385.9884.

***Cis*-isomer of 8f:** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.08 (dd, *J* = 12.8, 3.2 Hz, 1H), 3.14 (dd, *J* = 17.9, 7.8 Hz, 1H), 1.20 (s, 3H), 1.14 (s, 3H), 0.75 (s, 3H), and other resonances could not be discerned.



***Trans*-2,5,7-tribromo-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (*trans*-8g):** Colorless solid; IR (KBr) 1558, 1454, 1391, 1383, 1304, 1289, 1258, 1128, 1066 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 2.3 Hz, 1H), 7.15 (d, *J* = 2.3 Hz, 1H), 4.02 (dd, *J* =12.4, 4.1 Hz, 1H), 2.83–2.68 (m, 2H), 2.31 (dddd, *J* = 14.6, 4.1, 3.2, 3.2 Hz, 1H), 2.13 (ddd, *J* = 13.7, 13.2, 3.2 Hz, 1H), 2.09 (ddd, *J* = 13.2, 3.2, 3.2 Hz, 1H), 1.85 (ddd, *J* = 14.2, 13.7, 3.2 Hz, 1H), 1.79 (dd, *J* = 11.0, 6.9 Hz, 1H), 1.23 (s, 3H), 1.16 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 133.1, 131.2, 124.9, 112.1, 111.7, 77.5, 65.1, 47.5, 40.2, 39.1, 31.3, 29.5, 24.7, 19.9, 16.8; HRMS (EI) calcd for $C_{16}H_{19}Br_3O^+$ $[M]^+$ 463.8986, found 463.8999.

***Cis*-isomer of 8g:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 1.8 Hz, 1H), 7.15 (d, *J* = 1.8 Hz, 1H), 4.06 (dd, *J* = 3.7, 12.8 Hz, 1H), 3.12 (dd, *J* = 7.8, 18.3 Hz, 1H), 2.83 (d, *J* = 18.3 Hz, 1H), 2.49 (ddd, 3.7, 13.3, 14.2 Hz, 1H), 2.20 (ddd, *J* = 3.6, 4.1, 13.3 Hz, 1H), 2.09 (dddd, *J* = 3.6, 3.7, 3.7, 14.2 Hz, 1H), 1.70 (ddd, *J* = 4.1, 14.2, 14.2 Hz, 1H), 1.59 (d, *J* = 7.8 Hz, 1H), 1.18 (s, 3H), 1.13 (s, 3H), 0.75 (s, 3H).



***Trans*-2-bromo-1,1,4a,5,7-pentamethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (*trans*-8h):** Colorless solid; IR (KBr) 1483, 1459, 1380, 1236, 1150 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ

6.77 (s, 1H), 6.71 (s, 1H), 4.06 (dd, J =12.4, 3.7 Hz, 1H), 2.78–2.63 (m, 2H), 2.27 (dddd, J = 13.8, 4.1, 3.7, 3.6 Hz, 1H), 2.22 (s, 3H), 2.14 (dddd, J = 13.8, 12.8, 12.4, 3.7 Hz, 1H), 2.10 (s, 3H), 2.00 (ddd, J = 13.3, 3.7, 3.6 Hz, 1H), 1.79 (ddd, J = 13.3, 12.8, 4.1 Hz, 1H), 1.77 (dd, J = 11.5, 6.4 Hz, 1H), 1.20 (s, 3H), 1.15 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 129.2, 128.4, 127.2, 125.8, 120.7, 75.2, 66.4, 48.2, 40.8, 39.2, 31.6, 29.6, 24.6, 20.4, 20.0, 16.8, 15.8; HRMS (FAB) calcd for $C_{18}H_{25}BrO^+$ $[M]^+$ 336.1089, found 336.1094.

***Cis*-isomer of 8h:** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.09 (dd, J = 12.8, 3.7 Hz, 1H), 3.07 (dd, J = 17.9, 8.2 Hz, 1H), 1.17 (s, 3H), 1.15 (s, 3H), 0.77 (s, 3H), and other resonances could not be discerned.

Computational Methods

Molecular geometry of the stable state of bromophosphonium ions **14** was optimized using Density Functional Theory with Becke's three-parameter hybrid functional[7] and Lee, Yang, and Parr's (LYP)[8] correlation functional. The 6-31G(d) basis set was used in this study. All geometry were optimized without any symmetry restrictions and characterized as minima (no imaginary frequencies) by calculations of harmonic vibrational frequencies. All calculations have been carried out using the Gaussian 03 program package.[9]

Bromophosphonium ion 14

Method: B3LYP/6-31G(d)
SCF Done: E(RB+HF-LYP) = -5715.35491521 A.U. after 9 cycles
Imaginary frequencies: 0
Zero-point correction= 0.488304 (Hartree/Particle)
Thermal correction to Energy= 0.535752
Thermal correction to Enthalpy= 0.536696
Thermal correction to Gibbs Free Energy= 0.392333
Sum of electronic and zero-point Energies= -5714.866611
Sum of electronic and thermal Energies= -5714.819163
Sum of electronic and thermal Enthalpies= -5714.818219
Sum of electronic and thermal Free Energies= -5714.962583

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.592768	-1.238181	-1.917519
2	6	0	-1.290776	-0.348555	-2.722113
3	6	0	-1.209587	-2.247471	-1.192119
4	8	0	0.844473	-1.171790	-1.894832
5	6	0	-2.674179	-0.489421	-2.810345
6	35	0	1.165103	-0.355560	1.062162
7	6	0	-3.343191	-1.492410	-2.087839
8	7	0	-4.745087	-1.677106	-2.203866
9	6	0	-2.595487	-2.361441	-1.275672
10	15	0	1.699435	-0.194169	-1.018763
11	8	0	1.473611	1.260046	-1.562469
12	8	0	3.212133	-0.550035	-1.241833
13	6	0	-5.633878	-0.598936	-2.369920
14	6	0	3.865278	-1.718829	-0.727850
15	6	0	-5.209200	-2.949864	-2.788166
16	7	0	-5.356952	0.547110	-1.617356
17	8	0	-6.591335	-0.667015	-3.121669
18	6	0	2.168193	2.427715	-1.088542
19	6	0	3.702033	-2.924752	-1.395687
20	6	0	4.681428	-1.560895	0.383414
21	6	0	1.561476	3.196868	-0.105828
22	6	0	3.377509	2.753138	-1.686888
23	6	0	-4.812338	0.477101	-0.301824
24	6	0	-5.230940	-0.498873	0.610050
25	6	0	-6.201608	1.715325	-1.927170
26	6	0	-3.863279	1.424088	0.101046
27	6	0	4.390418	-4.035654	-0.908498
28	6	0	-4.691212	-0.536744	1.896478
29	6	0	2.216823	4.359905	0.298862
30	6	0	-3.346349	1.389644	1.395463
31	6	0	-5.182438	-1.582204	2.869639
32	6	0	-3.752086	0.409193	2.302623
33	6	0	-2.267165	2.356450	1.794249
34	9	0	-6.339016	-1.212663	3.450478
35	9	0	-2.290954	3.489972	1.067177
36	9	0	-1.023353	1.804178	1.590319
37	9	0	-2.323343	2.686015	3.093010

38	9	0	-4.284693	-1.803089	3.852404
39	9	0	-5.404000	-2.759608	2.243735
40	6	0	4.015364	3.921067	-1.269948
41	6	0	5.362168	-2.682262	0.856124
42	6	0	5.212490	-3.914852	0.214875
43	6	0	3.436750	4.719484	-0.279983
44	6	0	5.906008	-5.138373	0.771846
45	9	0	5.126277	-5.751814	1.686220
46	9	0	7.062699	-4.812353	1.377949
47	6	0	4.104185	6.012989	0.131315
48	9	0	6.175376	-6.032340	-0.197821
49	9	0	3.632981	7.047842	-0.591432
50	9	0	5.437037	5.957821	-0.055036
51	9	0	3.874354	6.286552	1.430523
52	1	0	-0.768039	0.408216	-3.297171
53	1	0	-0.627699	-2.926631	-0.578289
54	1	0	-3.236689	0.173344	-3.458278
55	1	0	-3.104612	-3.126233	-0.698831
56	1	0	-6.264237	-3.085932	-2.552004
57	1	0	-4.633497	-3.772327	-2.361010
58	1	0	-5.094440	-2.953656	-3.877993
59	1	0	3.073530	-2.991881	-2.276883
60	1	0	4.794917	-0.590531	0.854287
61	1	0	0.609604	2.908850	0.324408
62	1	0	3.803031	2.122540	-2.459552
63	1	0	-5.972598	-1.232271	0.314808
64	1	0	-7.196506	1.618299	-1.477842
65	1	0	-6.317426	1.794664	-3.007815
66	1	0	-5.719821	2.616088	-1.542809
67	1	0	-3.529839	2.181541	-0.599535
68	1	0	4.296278	-4.991799	-1.411168
69	1	0	1.776877	4.984809	1.068304
70	1	0	-3.346728	0.383229	3.307182
71	1	0	4.962491	4.206923	-1.713605
72	1	0	6.016361	-2.593900	1.716380

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Chapter 4

Enantioselective Bromocyclization of 2-Geranylphenols Promoted by Chiral Phosphite–Urea Cooperative Catalysts

Abstract:

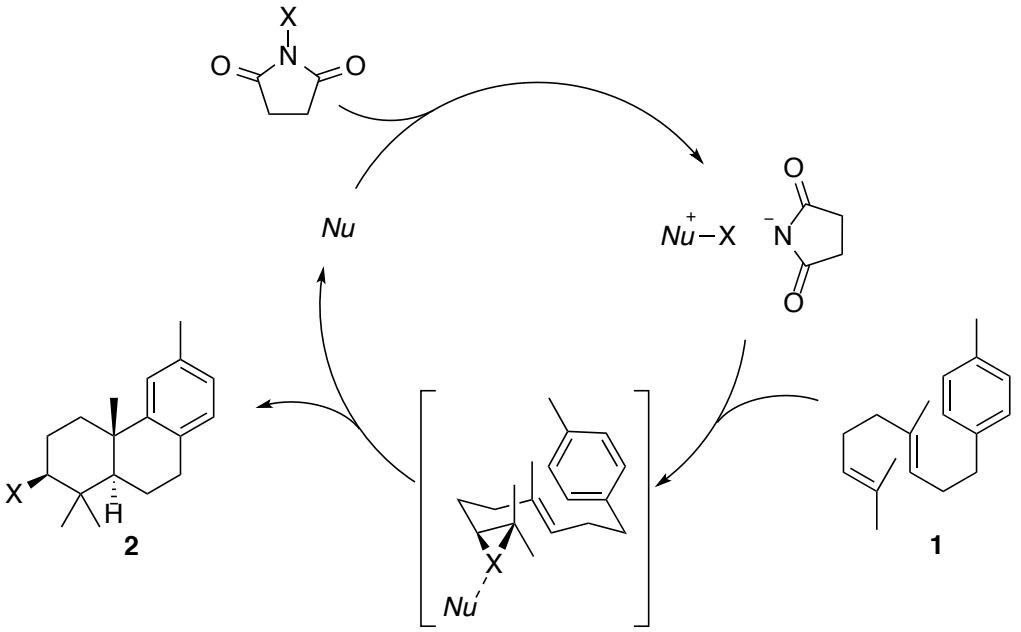
Chiral phosphite–urea cooperative catalysts were designed for the enantioselective bromocyclization of 2-geranylphenol. We demonstrate that the chiral triaryl phosphites derived from binaphthol bearing a 3,5-bis(pentafluorosulfanyl)phenyl group at the 3,3'-position are efficient catalysts. Hydrogen bonding between the urea group of the catalyst and the hydroxyl group of the substrate is thought to be crucial for high enantioselectivity.

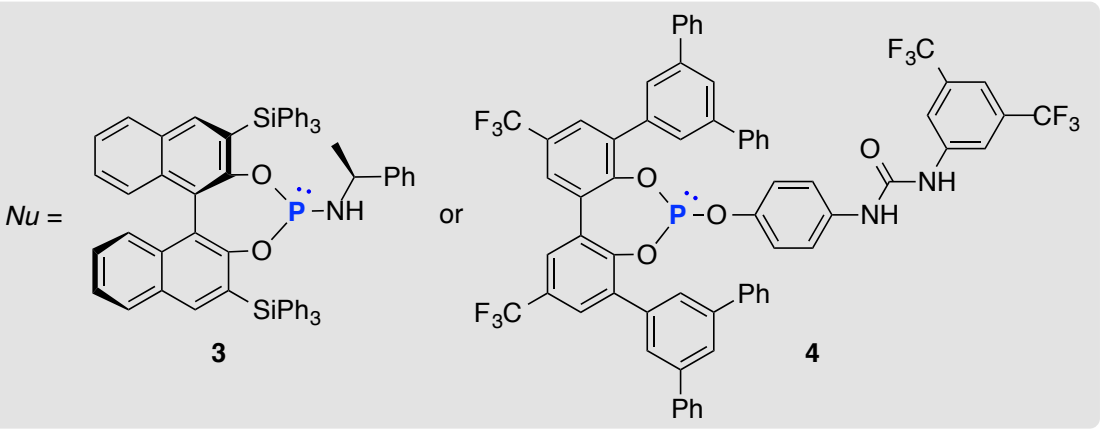
4-1. Introduction

Bromine-containing natural products isolated from marine organisms possess several bioactivities such as anticancer and antiviral activities.[1] These bromine-containing natural products are biosynthesized by bromocyclization in the cavity of 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 forms several carbon–carbon bonds and the structure of isoaplysin-20.[3] While the diastereoselective bromocyclization of polyene compounds has been developed for about 50 years,[4,5] there have been few reports on the enantioselective bromocyclization of polyene compounds.[6] Snyder and co-workers demonstrated enantioselective bromocyclization with a $Hg(OTf)_2$–chiral bis(oxazoline) complex. Braddock and co-worker reported that enantiospecific polyene cyclization was initiated by the formation of an enantiopure bromiranium ion. However, these methods required stoichiometric amounts of promoters and multiple reaction steps.

We previously developed nucleophilic phosphorous(III) catalysts for the halocyclization of polyprenoids (Scheme 4.1).[7-9] A nucleophilic phosphorous catalyst **3** or **4** activates a halogenating reagent such as *N*-iodo- or *N*-bromosuccinimide (X = I or Br), and a halophosphonium salt is generated as an active species. A halophosphonium salt then reacts with polyprenoids at the terminal olefin of **1** and halogenated polycyclic products are formed. Chiral phosphoramidite **3** gave *trans*-fused iodinated AB-ring product **2** (X = I) with high enantioselectivity. However, a stoichiometric amount of chiral phosphoramidite **3** was required to give the product in sufficient yield, and it was difficult to obtain brominated product **2** (X = Br) with high enantioselectivity. On the other hand, the bromocyclization of **1** is efficiently promoted with the use of a catalytic amount of triaryl phosphite–urea **4**, and *trans*-fused brominated AB-ring product **2** (X =Br) is obtained in excellent yield.

Scheme 4.1. Halocyclization of **1** with Nucleophilic Phosphorous Catalysts



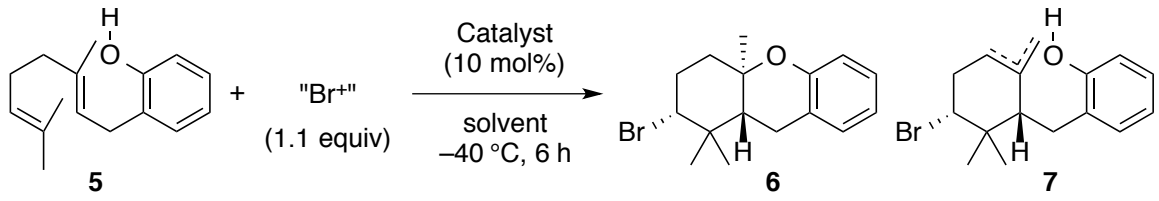


One reason why enantioselective bromocyclization is difficult is that the three-membered cyclic bromonium (bromiranium) ion rapidly transfers to other olefins.[10,11] In the course of bromiranium ion-olefin transfer, enantiopure bromiranium ion is racemized. We predicted that bromiranium ion-olefin transfer might be suppressed if the reaction could proceed in the cavity of a catalyst. Here we designed chiral phosphite–urea cooperative catalysts for the enantioselective bromocyclization of polyprenoids.

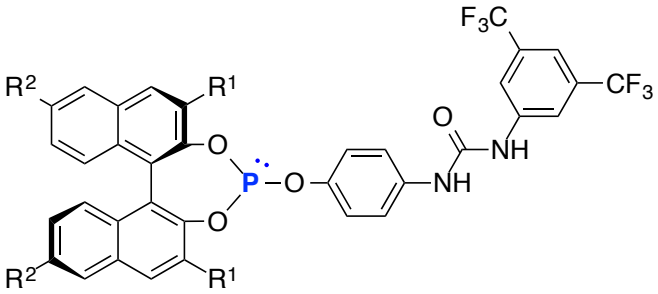
4-2. Results and Discussion

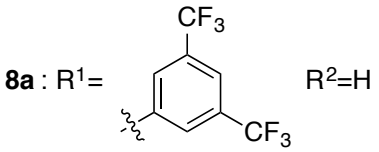
We first examined the bromocyclization of 2-geranylphenol **5** with chiral phosphate–urea cooperative catalyst **8** (Table 4.1). The reaction was conducted with 1.1 equivalents of *N*-bromosuccinimide (NBS) as the brominating reagent in the presence of 10 mol% of **8a** in toluene at –40 °C for 6 h. As a result, *trans*-fused brominated AB-ring product **6** was obtained in 30% yield with 18% ee together with *endo*- and *exo*-isomeric A-ring products **7** in 56% yield with 39% ee (entry 1).[12] A-ring products **7** could be converted to a diastereomeric mixture of *trans*- and *cis*-fused AB-ring products **6** (*trans* : *cis* = *ca.* 3 : 1) by treatment with TfOH, and the enantioselectivity was determined at this stage. Interestingly, A-ring products **7** showed greater enantioselectivity than AB-ring product **6**. Next, we examined the reactivity and enantioselectivity of the brominating reagents. Both the reactivity and enantioselectivity were decreased with *N*-bromoacetoamide (NBA) (entry 2). The use of 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCO) and *N*-bromophthalimide (NBP) were slightly increased enantioselectivity (entries 3,4). 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** (R^1 = 3,5-bis(pentafluorosulfanyl)phenyl, R^2 = H) gave especially high enantioselectivity for A-ring products **7**, while the enantioselectivity of AB-ring product **6** was decreased (entry 7). Moreover, when the concentration was lowered to 0.02 M, the enantioselectivity was increased to 65% (entry 8). Good results were not obtained when the reaction was cooled to –60 °C (entry 9). This result suggests that catalysts may aggregate under these reaction conditions. The use of 5 mol% of **8b** was also effective, and both **6** and **7** were obtained without any loss of enantioselectivity (entry 10). The triphenylsilyl catalyst **8c** was used because a triphenylsilyl group at the 3,3'-position gave high enantioselectivity in our previous studies, such as in the iodo- and protocyclization of polyprenoids[7,8] and iodolactonization.[9] However, it did not induce high enantioselectivity (entry 11). Since it could be considered that the phosphites [P(III)] were oxidized to phosphate [P(V)] *in situ*, we examined phosphate **8d** as a catalyst, but the reaction hardly proceeded at all (entry 12).

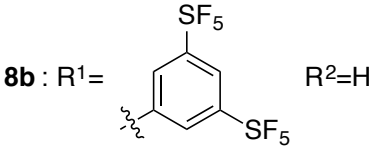
Table 4.1. Enatioselective Bromocyclization of **5** with **8**[a]



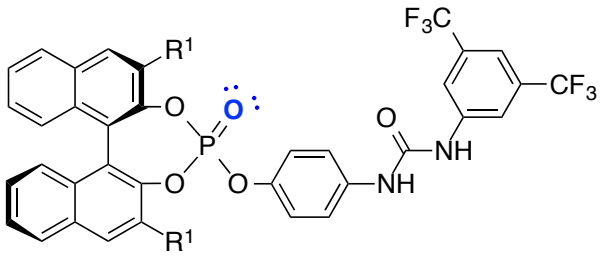
				6		**7**	
Entry	Catalyst	"Br^+"	Solvent	Yield[%][b]	Ee[%]	Yield[%][b]	Ee[%][c]
1	**8a**	NBS	toluene	30	18	56	39
2	**8a**	NBA	toluene	18	13	32	33
3	**8a**	TBCO	toluene	31	21	55	44
4	**8a**	NBP	toluene	29	21	57	43
5	**8a**	NBP	C_6H_5Cl	35	4	40	19
6	**8a**	NBP	mesitylene	22	24	47	36
7	**8b**	NBP	toluene	25	16	54	51
8[d]	**8b**	NBP	toluene	21	19	63	65
9[d,e]	**8b**	NBP	toluene	21	13	66	61
10[d,f]	**8b**	NBP	toluene	21	19	63	64
11	**8c**	NBP	toluene	21	–16	34	–21
12	**8d**	NBP	toluene	4	-	5	-

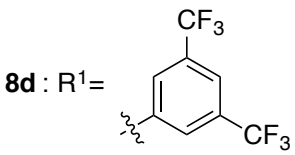






8c : R^1=$SiPh_3$, R^2=Br

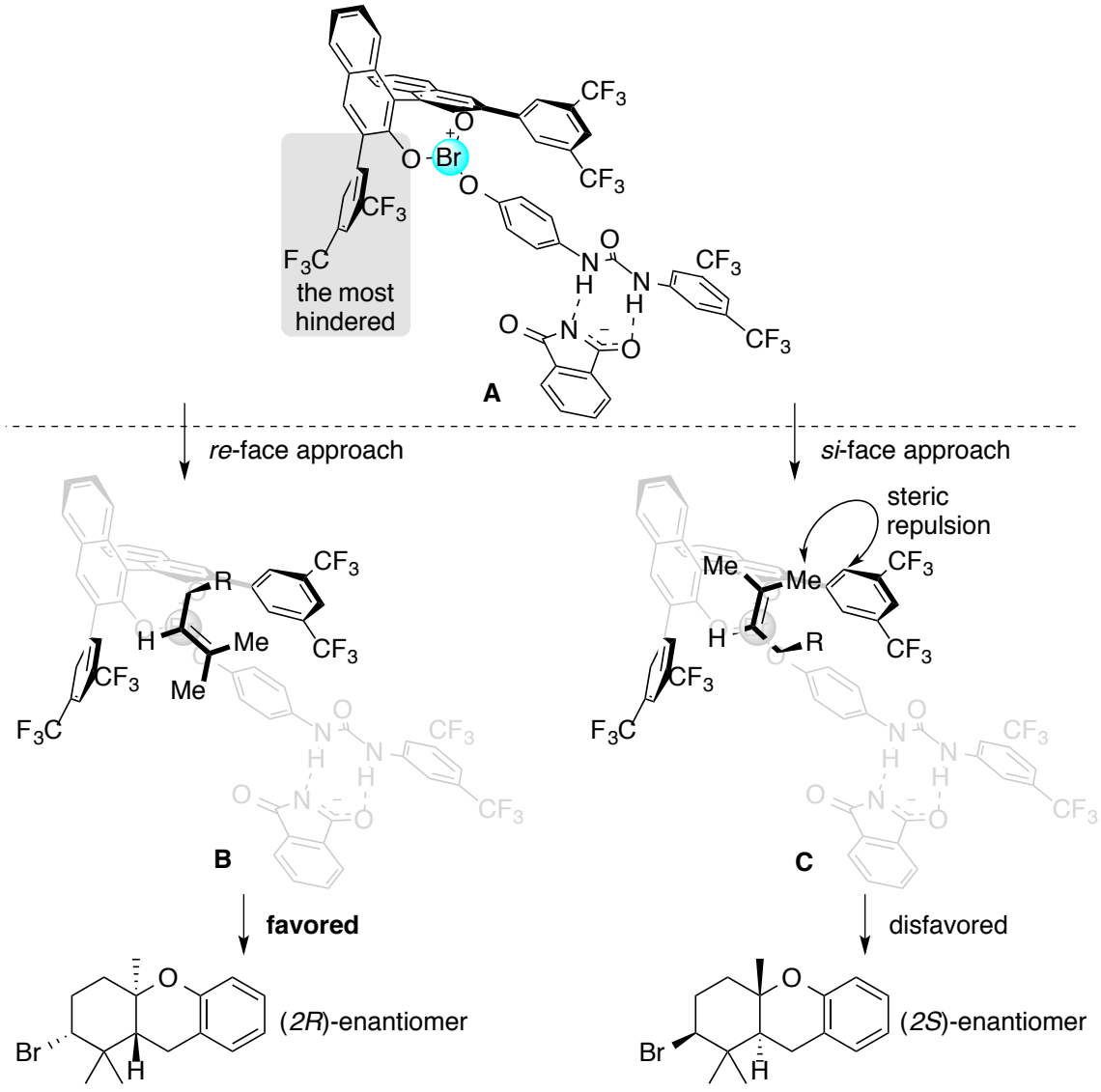




[a] The reaction of **5** (0.1 mmol) was conducted with "Br^+" (1.1 equiv) in the presence of **8** (10 mol%) in toluene (1 mL) at –40 °C for 6 h. [b] Determined by ^1H NMR analysis using tetrachloroethane as an internal standard. [c] Determined after treatment with TfOH (4 equiv) in *i*-$PrNO_2$ (0.6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

Our proposed mechanism is shown in Scheme 4.2. The absolute stereochemistry of the major enantiomers of **6** and **7** was determined to be (2*R*,4a*R*,9a*R*).

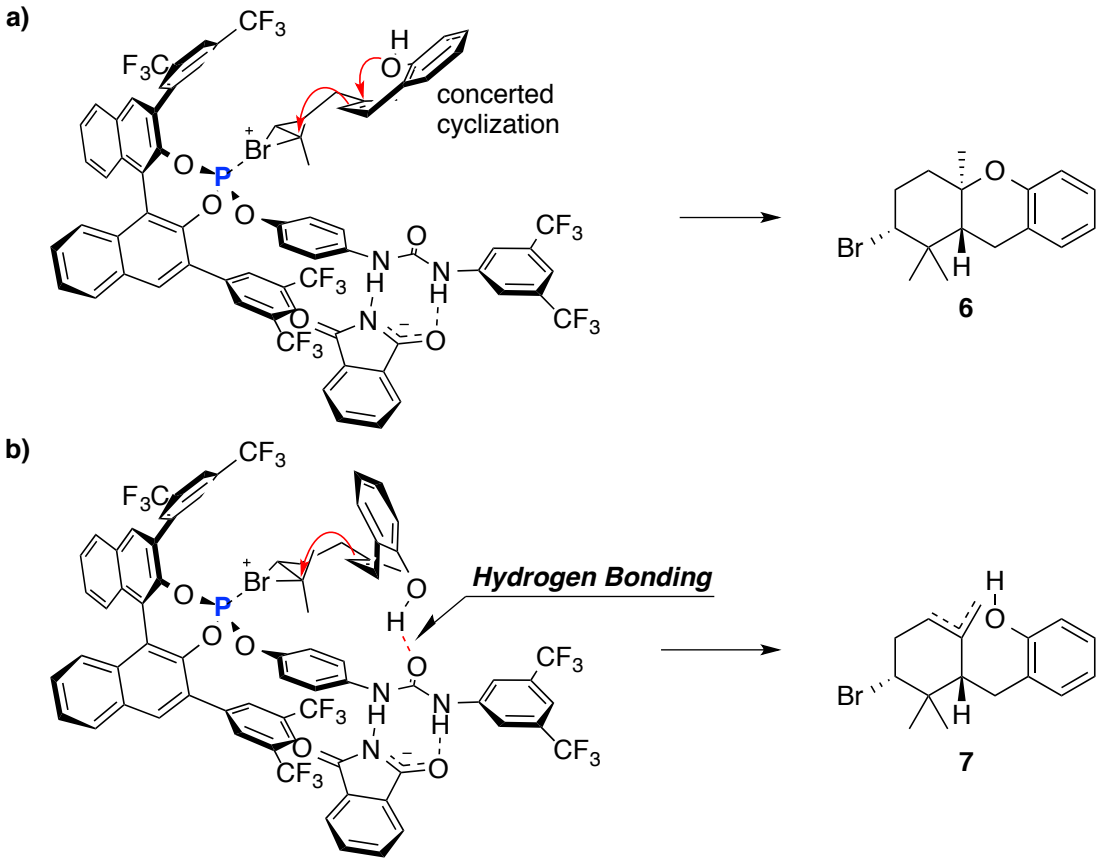
Scheme 4.2. Proposed Mechanism for the Absolute Stereopreference



Structure **A** is the Newman projection of the chiral bromophosphonium salt (**8a**•NBP) viewed along the P–Br bond. The substrate might approach the bromophosphonium salt, avoiding the most hindered 3,5-bis(trifluoromethyl)phenyl group. The *si*-face approach might be disfavored because of the steric repulsion between another 3,5-bis(trifluoromethyl)phenyl group and the dimethyl group of the substrate, as shown in structure **C**. Therefore, the *re*-face approach is favored and gives (*2R*)-enantiomers **6** and **7** selectively.

We next propose why the A-ring products **7** had higher enantioselectivity than AB-ring product **6**. It can be considered that the reaction mechanism and conformation of the substrate in each transition state are different between **6** and **7**. Since only *trans*-fused AB-ring product **6** was obtained, in formation of **6**, the cyclization reaction should proceed *via* a concerted pathway (Scheme 4.3a). If **6** is formed *via* a stepwise reaction (A-ring-forming cyclization followed by intramolecular nucleophilic attack of the 3° carbocation), *cis*-fused **6** should also be generated.

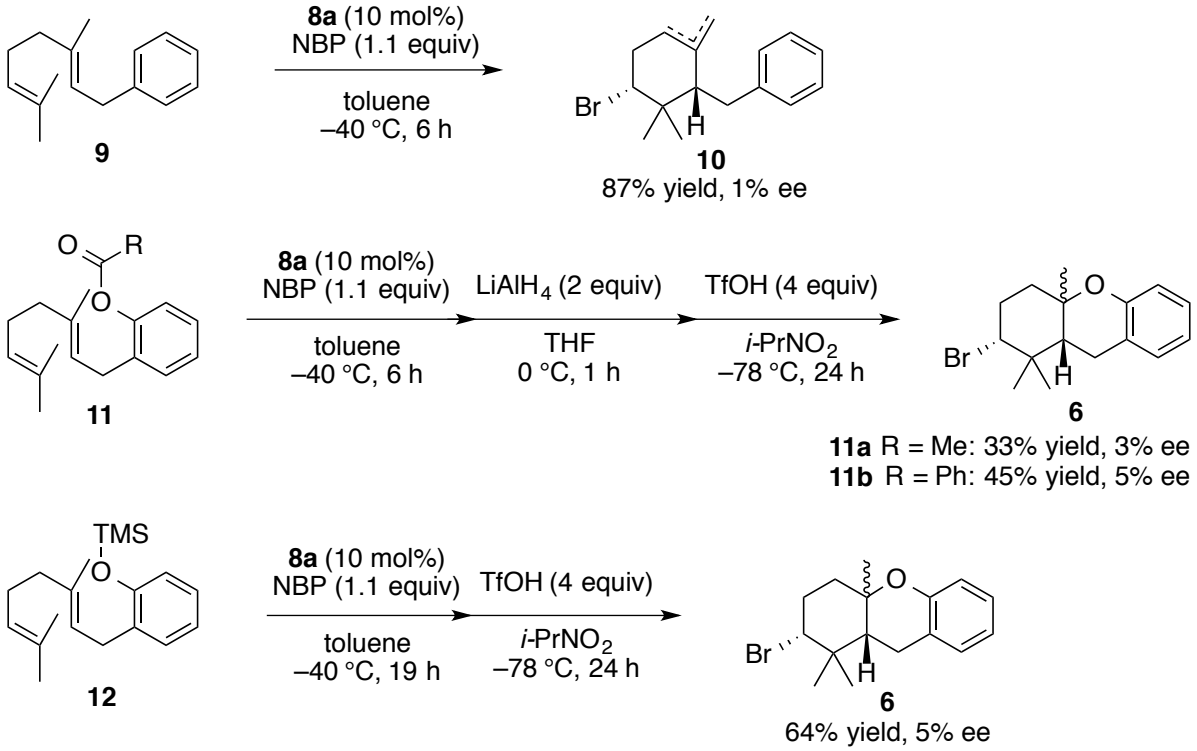
Scheme 4.3. Proposed Reaction Pathway for the Formation of **6** and **7**



In contrast, A-ring products **7** are generated from a 3° carbocation intermediate. Olefination could be faster than intramolecular nucleophilic attack. As shown in Scheme 4.3b, the conformation of substrate might be disfavored for the concerted cyclization and hydrogen bonding may occur between the carbonyl group of **8a** and a hydroxyl group of the substrate, which could support the *re*-face approach. Therefore, (*2R*)-enantiomers of **7** were obtained with higher enantioselectivity. However, the structure of the catalyst and its cavity are not fully designed, and the enantioselectivities of **6** and **7** are still not high enough.

We examined the bromocyclizaition of dehydroxylated substrate **9** and *O*-protected substrates **11** and **12** (Scheme 4.4). In all cases, the corresponding brominated products were obtained, but enantioselectivity was not observed. These results suggest that a hydroxyl group plays a crucial role in asymmetric control.

Scheme 4.4. Bromocyclization of Dehydroxylated Substrate **9** and *O*-Protected Substrates **11** and **12**



4-3. Conclusions

In conclusion, we designed chiral phosphite–urea cooperative catalysts for the enantioselective bromocyclization of 2-geranylphenol. Catalyst **8b** bearing a 3,5-bis(pentafluorosulfanyl)phenyl group at the 3,3'-position gives good enantioselectivity for **7**, although **6** showed low enantioselectivity. Hydrogen bonding between a carbonyl group of the catalyst and a hydroxyl group of the substrate could support the *re*-face approach. Further design of the catalyst to improve the enantioselectivity and investigation of the detailed reaction mechanism are underway.

References and Notes

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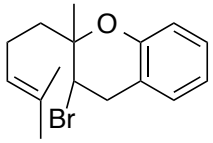
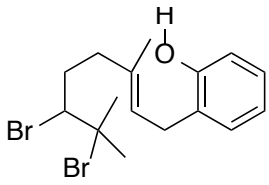
12. B-ring product (*ca*. 5~10% yield) and dibrominated product (*ca*. 0~5% yield) were obtained as byproducts in all cases.



B-ring product

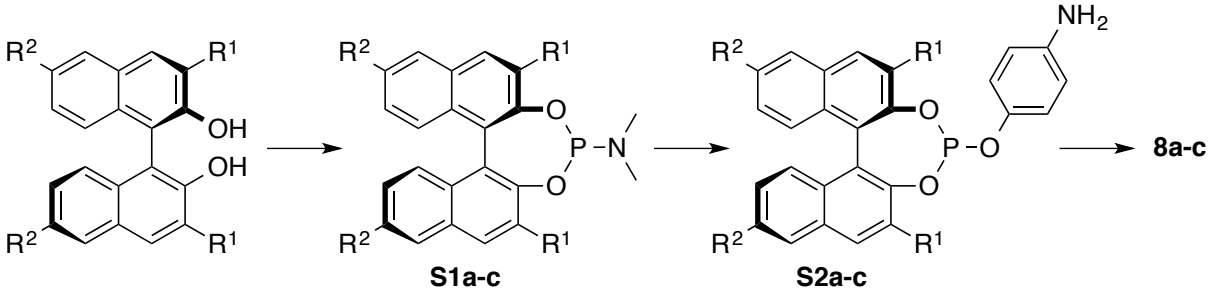


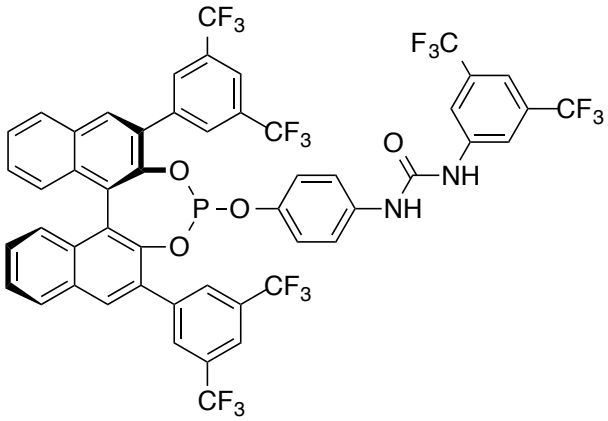
dibrominated product

Experimental Section

General Methods. Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. ^{1}H NMR spectra were measured on a JEOL ECS-400 spectrometer (400 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet, sep = septet; m = multiplet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a JEOL ECS-400 spectrometer (100 MHz). Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.00 ppm). ^{19}F NMR spectra (376 MHz) and ^{31}P NMR spectra (162 MHz) were measured on a JEOL ECS-400 spectrometer. Analytical HPLC was performed on a Shimadzu Model LC-10AD instrument coupled diode array-detector SPD-MA-10A-VP and a chiral column of Daicel CHIRALPACK AD-H (4.6 mm × 250 mm), IB-3 (4.6 mm × 250 mm). The reactions were carried out under an atmosphere of dry nitrogen. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254} 0.25 mm or silica gel NH_2 F_{254S} 0.25 mm) were used. The products were purified by column chromatography on silica gel (E. Merck Art. 9385). High resolution mass spectral analysis (HRMS) was performed at Chemical Instrumentation Facility, Nagoya University on JEOL JMS-700 spectrometer (for FAB) or Bruker Daltonics micrOTOF-QII (for ESI). Dry tetrahydrofuran, diethylether, toluene and dichloromethane were purchased from Kanto as the “anhydrous” and stored under nitrogen. Dry acetonitrile were purchased from Wako as the “anhydrous” and stored under nitrogen. Other simple chemicals were analytical-grade and obtained commercially.

Preparation of Chiral Phosphite-Urea Cooperative Catalysts 8a-c.



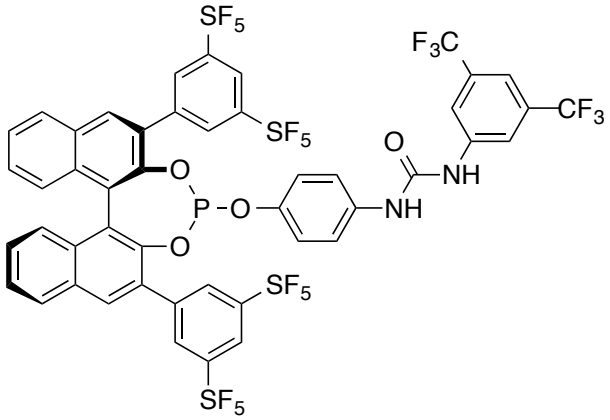


1-(4-(((11b*R*)-2,6-Bis(3,5-bis-(trifluoromethyl)phenyl)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yl)oxy)phenyl)-3-(3,5-bis(trifluoromethyl)phenyl)urea (8a): To a suspension of (*R*)-3,3'-bis(3,5-bis(trifluoromethyl)phenyl)-2,2'-binaphthol (923 mg, 1.3 mmol) and tetrazole (273 mg, 3.9 mmol) in dry THF (15 mL) was added *N*,*N*,*N*',*N*',*N*'',*N*''-hexamethylphosphinetriamine (424 mg, 3.4 mmol). The reaction mixture was heated at reflux for 5 h, cooled to room temperature, and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give **S1a** (968 mg, 95% yield).

To a solution of **S1a** (392 mg, 0.50 mmol) and *N*-phenylimidazolium trifluoromethanesulfonate salt (162 mg, 0.55 mmol) in dry CH_3CN (5 mL) was added 4-aminophenol (71 mg, 0.65 mmol). The reaction mixture was stirred at room temperature for 13 h, filtered through a Celite pad, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give **S2a** (339 mg, 80% yield).

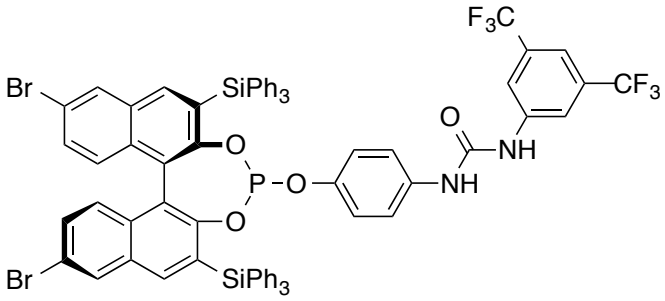
To a solution of **S2a** (339 mg, 0.4 mmol) in CH_2Cl_2 (4 mL) was added 1-isocyanato-3,5-bis(trifluoromethyl)benzene (153 mg, 0.60 mmol). The reaction mixture

was stirred at room temperature and insoluble urea starts to precipitate as a colorless solid. The reaction mixture was diluted with hexane, then the solid was filtered off and washed with hexane to give **8a** (350 mg, 79% yield). Colorless solid; $[\alpha]^{25}_{D}$ –96.8 (*c* 1.00, THF); IR (KBr) 1643, 1577, 1508, 1473, 1381, 1326, 1279, 1176, 1136, 1083, 987 cm^{-1}; ^{1}H NMR (400 MHz, THF-d_8) δ 8.43 (s, 2H), 8.40–8.29 (m, 5H), 8.40–8.18 (m, 6H), 7.99 (s, 1H), 7.62–7.53 (m, 3H), 7.50–7.37 (m, 4H), 7.18 (d, J = 8.7 Hz, 2H), 6.20 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, THF-d_8) δ 152.8, 147.2, 147.1, 145.6 (d, $J_{C–P}$ = 2.9 Hz, 2C), 144.9 (d, $J_{C–P}$ = 2.9 Hz, 2C), 143.1, 141.5, 140.8, 136.9, 130.4, 133.7, 132.8, 132.66, 132.65 (q, $J_{C–F}$ = 33.4 Hz, 2C), 132.4, 132.34 (q, $J_{C–F}$ = 32.4 Hz, 2C), 132.30 (q, $J_{C–F}$ = 32.4 Hz, 2C), 132.0, 131.6 (2C), 131.4(2C), 129.9, 129.8, 128.3, 128.1, 127.6, 127.5, 127.1, 126.9, 126.5, 126.4, 125.2, 124.6 (q, $J_{C–F}$ = 272 Hz, 6C), 122.4, 122.1, 120.7 (2C), 199.9 (d, $J_{C–P}$ = 8.6 Hz, 2C), 118.8 (2C), 115.5; ^{19}F NMR (376 MHz, THF-d_8) δ –63.3, –63.7; ^{31}P NMR (162 MHz, acetone-d_6) δ 145.7; HRMS (FAB) calcd for $C_{51}H_{25}F_{18}N_2O_4P^+$ $[M]^+$ 1102.1265, found 1102.1269.



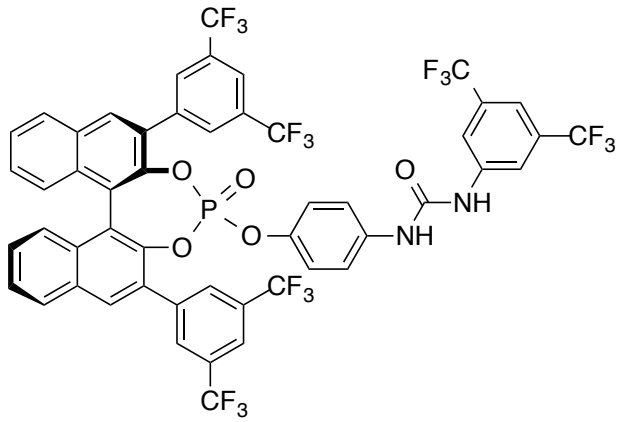
1-(4-(((11b*R*)-2,6-Bis(3,5-bis(pentafluoro-o-λ^6-sulfanyl)phenyl)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yl)oxy)phenyl)-3-(3,5-bis(trifluoromethyl)phenyl)urea (8b): Compound **8b** was prepared from (*R*)-3,3'-bis(3,5-bis(pentafluoro-λ^6-sulfanyl)phenyl)-[1,1'-binaphthalene]-2,2'-diol[1] according to the same manner as **8a**. Pale yellow solid; $[\alpha]^{22}_{D}$ –51.8 (*c* 1.00, THF); IR (KBr) 1508, 1388, 1281, 1187, 1139 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.72 (s, 1H), 8.64 (d, J = 1.8 Hz, 2H), 8.55 (s, 1H), 8.54 (d, J = 1.8 Hz, 2H), 8.50 (s, 1H), 8.42 (t, J = 1.8 Hz, 1H), 8.38 (s, 1H), 8.34 (t, J = 1.8 Hz, 1H), 8.26 (d, J = 8.2 Hz, 1H), 8.22 (d, J = 8.2 Hz, 1H), 8.18 (s, 2H), 7.70–7.62 (m, 2H), 7.61 (s, 1H), 7.56–7.39 (m, 4H), 7.29 (d, J = 8.7 Hz, 2H), 6.20 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, acetone-d_6) δ 153.9 (quintet, $J_{C–F}$ = 18.1 Hz), 153.0, 147.0, 146.9, 145.1 (d, $J_{C–P}$ = 3.8 Hz), 144.4, 142.9, 141.4, 140.8, 136.8, 133.9, 133.7, 133.1, 132.6,

132.5, 132.4 (q, J_{C-F} = 32.4 Hz), 132.2, 132.0, 131.6, 131.5, 130.2, 128.7, 128.6, 127.44, 127.37, 127.3, 127.2, 126.23, 126.17, 125.0, 124.5 (q, J_{C-F} = 271 Hz), 123.8, 123.7, 120.9, 119.4 (d, J_{C-P} = 9.5 Hz), 119.1, 115.6; ^{19}F NMR (376 MHz, acetone-d_6) δ 81.5 (quintet, J = 150 Hz), 63.1, 62.6, –63.5; ^{31}P NMR (162 MHz, acetone-d_6) δ 145.8; HRMS (ESI) calcd for $C_{47}H_{24}F_{26}N_2O_4PS_4^-$ $[M-H]^-$ 1332.9947, found 1332.9957.



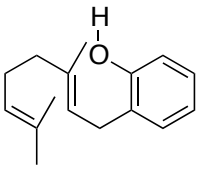
1-(3,5-Bis(trifluoromethyl)phenyl)-3-(4-(((11b*R*)-9,14-dibromo-2,6-bis(triphenylsilyl)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yl)oxy)phenyl)urea (8c): Compound **8c** was prepared from (*R*)-6,6'-dibromo-3,3'-bis(triphenylsilyl)-[1,1'-binaphthalene]-2,2'-diol[2] according to the same manner as **8a**. Colorless solid; $[\alpha]^{22}_D$ –168.9 (*c* 1.00, $CHCl_3$); IR (KBr) 1560, 1506, 1475, 1429, 1387, 1279, 1184, 1136, 1108 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 2H), 7.91 (d, J = 1.8 Hz, 1H), 7.82 (s, 2H), 7.81 (s, 1H), 7.59–7.48 (m, 13H), 7.38 (dd, J = 9.2, 1.9 Hz, 1H), 7.34 (t, J = 7.3 Hz, 6H), 7.29–7.19 (m, 13H), 7.13 (d, J = 9.2 Hz, 1H), 7.05 (d, J = 9.2 Hz, 1H), 6.83 (s, 1H), 6.79 (d, J = 8.7 Hz, 2H), 6.48 (s, 1H), 5.77 (d, J =8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 152.2, 152.1, 148.2, 140.2, 139.6, 139.7, 136.7, 136.4, 134.0, 133.1, 132.7, 132.3 (q, J_{C-F} = 33.4 Hz), 132.0, 131.9, 131.4, 130.71, 130.65, 130.5, 129.7, 129.5, 129.2, 128.5, 128.4, 128.3, 128.0, 127.7, 123.1, 123.0, 123.0 (q, J_{C-F} = 272 Hz), 122.9, 122.6, 121.6 (d, J_{C-P} = 6.7 Hz), 119.0, 118.8, 116.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 148.3; HRMS (ESI) calcd for $C_{71}H_{46}Br_2F_6N_2O_4PSi_2^-$ $[M-H]^-$ 1349.1010, found 1349.1021.

Preparation of Chiral Phosphate–Urea Cooperative Catalyst 8d.



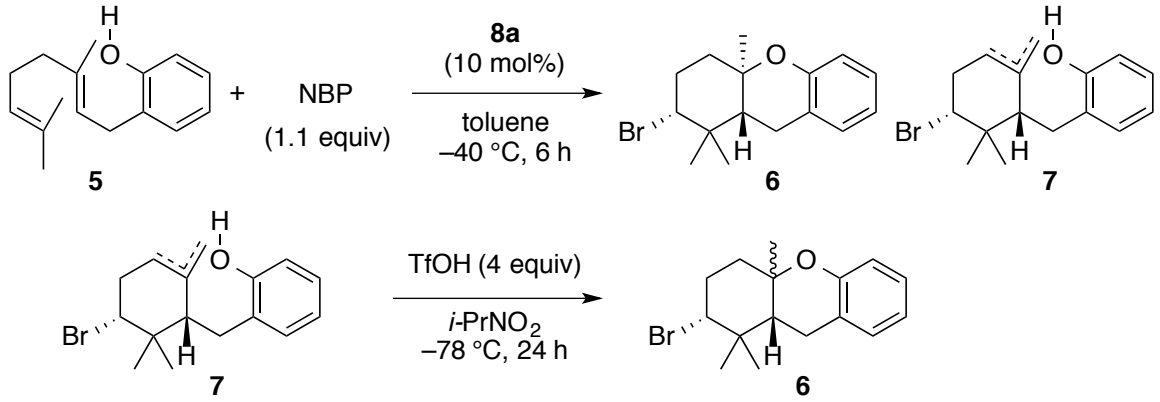
1-(4-(((11b*R*)-2,6-Bis(3,5-bis(trifluoro-methyl)phenyl)-4-oxidodinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yl)oxy)phenyl)-3-(3,5-bis(trifluoromethyl)phenyl)urea (8d): To a solution of **8a** (42 mg, 0.038 mmol) in CH_2Cl_2 (2 mL) was added 5.5 M solution of TBHP in nonane (13 μL, 0.072 mmol) at 0 °C. After stirring for 3 h at ambient temperature, the reaction was quenched with saturated aqueous $Na_2S_2O_3$. The mixture was extracted with EtOAc, and the combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The residue was reprecipitated from EtOAc–heaxne to give **8d** as a colorless solid (37 mg, 88% yield). $[\alpha]^{23}_D$ –105.8 (*c* 1.00, THF); IR (KBr) 1560, 1508, 1474, 1381, 1324, 1281, 1178, 1136 cm^{-1}; ^1H NMR (400 MHz, THF-d_8) δ 8.51 (s, 1H), 8.42 (s, 1H), 8.40 (s, 1H), 8.35 (s, 2H), 8.18 (t, *J* = 7.3 Hz, 2H), 8.08 (s, 4H), 8.05 (s, 1H). 7.67–7.58 (m, 2H), 7.57 (s, 1H), 7.48–7.36 (m, 4H), 7.21 (d, *J* = 8.7 Hz, 2H), 6.54 (d, *J* = 8.7 Hz, 2H); δ ^{13}C NMR (100 MHz, THF-d_8) δ 152.6, 145.8 (d, $J_{C–P}$ = 5.7 Hz, 2C), 145.2, 145.1, 143.9 (d, $J_{C–P}$ = 8.6 Hz, 2C), 142.9, 140.0, 139.8, 137.4, 133.6, 133.3, 133.2, 132.7, 132.4 (q, $J_{C–F}$ = 32.4 Hz, 2C), 132.2 (q, $J_{C–F}$ = 32.4 Hz, 2C), 132.1 (q, $J_{C–F}$ = 32.4 Hz, 2C), 131.8 (2C), 131.6, 131.3 (3C), 129.8, 129.7, 128.5, 127.6, 127.5 (3C), 124.41 (q, $J_{C–F}$ = 271 Hz, 2C), 124.39 (q, $J_{C–F}$ = 271 Hz, 2C), 124.3 (q, $J_{C–F}$ = 271 Hz, 2C), 123.4, 122.44, 122.36, 120.2 (2C), 119.3 (d, $J_{C–P}$ = 5.7 Hz, 2C), 118.6 (2C), 115.3; ^{19}F NMR (376 MHz, THF-d_8) δ –63.2, –63.7, –63.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ –4.6; HRMS (ESI) calcd for $C_{51}H_{25}F_{18}N_2NaO_5P^+$ $[M+Na]^+$ 1141.1106, found 1141.1107.

Preparation of 2-Geranylphenol.



2-Geranylphenol (5):[2,3] Compound **5** was prepared from phenol and geranyl chloride according to the reported procedure[4]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.08 (m, 2H), 6.86 (t, *J* = 7.3 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 5.33 (t, *J* = 7.1 Hz, 1H), 5.09 (s, 1H), 5.11–5.04 (m, 1H), 3.37 (d, *J* = 6.9 Hz, 2H), 2.16–2.05 (m, 4H), 1.77 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 138.4, 131.9, 129.9, 127.5, 126.8, 123.8, 121.6, 120.7, 115.7, 39.7, 29.7, 26.4, 25.7, 17.7, 16.1.

Typical Procedure for Enantioselective Bromocyclization of 2-Geranylphenol 5.

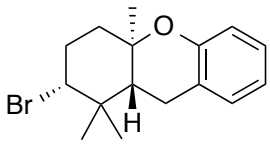


To a solution of **8a** (11 mg, 0.01 mmol) in toluene (1.0 mL) were added NBP (24.9 mg, 0.11 mmol) and **5** (23.0 mg, 0.10 mmol) successively at –78 °C, and the mixture was stirred at –78 °C for 0.5 h and then at –40 °C for 6 h. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (3.0 mL) and extracted with hexane (5.0 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The yield of *trans*-fused brominated AB-ring product **6** (30%) and *endo*- and *exo*-isomeric A-ring products **7** (56%) were determined by ^{1}H analysis of the crude mixture using tetrachloroethane as an internal standard. The crude product was purified by column chromatography on silica gel using (eluent: hexane–EtOAc 1000:1 to 20:1) to give AB-ring product **6** and the mixture of *endo*- and *exo*-isomeric A-ring products **7**.

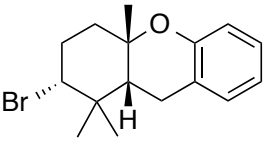
The resulting mixture of *endo*- and *exo*-isomeric A-ring products **7** was used for the next cyclization to determine the enantioselectivity. To a solution of the resulting mixture, which were obtained in the above reaction, in *i*-$PrNO_2$ (0.6 mL) was added TfOH (21 μL, 0.24

mmol) at –78 °C. After stirring at –78 °C for 24 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, and extracted with Et_2O (5 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The diastereomeric ratio (*trans/cis* = 75 : 25) was determined by ^1H analysis of the crude mixture. The residue was purified by preparative TLC using (hexane–EtOAc 20:1) as an eluent to give **6**.

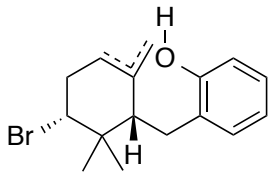
The corresponding physical and spectroscopic data for **6** and **7** are as follows.



(2*R*,4a*R*,9a*R*)-2-Bromo-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (*trans*-6): Colorless solid; $[\alpha]^{23}_D$ 28.0 (*c* 0.32, $CHCl_3$) for 65% ee (*trans/cis* 75:25); HPLC (Daicel CHIRALCEL AD-H column, hexane–*i*-PrOH = 1000:1, flow rate = 1.0 mL/min) t_R = 10.6 (minor enantiomer), 13.6 (major enantiomer) min; IR (KBr) 1488, 1454, 1242, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13–7.03 (m, 2H), 6.84 (t, *J* = 7.3 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 4.05 (dd, *J* = 12.4, 4.1 Hz, 1H), 2.83–2.69 (m, 2H), 2.28 (dddd, *J* = 13.7, 4.1, 3.6, 3.6 Hz, 1H), 2.13 (dddd, *J* = 13.7, 13.7, 12.4, 3.7 Hz, 1H), 2.01 (ddd, *J* = 12.8, 3.7, 3.6 Hz, 1H), 1.81 (dd, *J* = 11.9, 6.0 Hz, 1H), 1.78 (ddd, *J* = 13.7, 12.8, 3.6 Hz, 1H), 1.24 (s, 3H), 1.17 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 129.5, 127.3, 121.7, 120.0, 117.0, 75.7, 66.0, 48.0, 40.7, 39.2, 31.5, 29.6, 24.6, 19.8, 16.9; HRMS (FAB) calcd for $C_{16}H_{21}BrO^+$ $[M]^+$ 308.0776, found 308.0774.

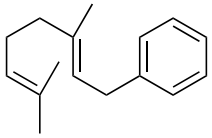


(2*R*,4a*S*,9a*R*)-2-Bromo-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (*cis*-6) : Colorless solid; IR (neat) 1584, 1489, 1455, 1237 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.11–7.02 (m, 2H), 6.84 (t, *J* = 7.3 Hz, 1H), 6.74 (d, *J* = 8.3 Hz, 1H), 4.09 (dd, *J* = 12.8, 3.3 Hz, 1H), 3.12 (dd, *J* = 17.9, 7.8 Hz, 1H), 2.84 (d, *J* = 17.9 Hz, 1H), 2.48 (dddd, *J* = 13.7, 12.8, 12.8, 3.6 Hz, 1H), 2.11–2.04 (m, 2H), 1.67 (ddd, *J* = 14.7, 13.7, 4.1 Hz, 1H) 1.57 (d, *J* = 7.8 Hz, 1H), 1.19 (s, 3H), 1.15 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 128.7, 127.0, 121.4, 120.3, 117.2, 74.4, 67.5, 45.1, 40.3, 40.2, 30.1, 29.9, 26.5, 27.8, 16.6; HRMS (FAB) calcd for $C_{16}H_{21}BrO^+$ $[M]^+$ 308.0776, found 308.0794.



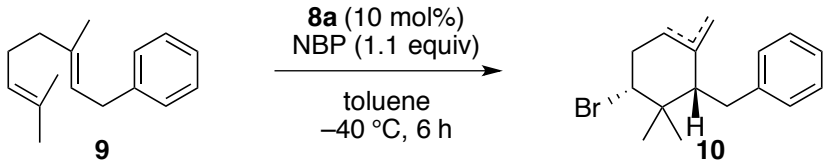
2-((5-Bromo-2,6,6-trimethylcyclohex-2-en-1-yl)methyl)phenol (*endo*-7), 2-((3-Bromo-2,2-dimethyl-6-methylenecyclohexyl)methyl)phenol (*exo*-7): Compounds ***endo*-7** and ***exo*-7** could not be separated by column chromatography on silica gel. ***endo*-7:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22 (brs, 1H), 4.27 (dd, J = 9.6, 6.4 Hz, 1H), 1.48 (s, 3H), 1.21 (s, 3H), 1.05 (s, 3H). Other resonances could not be discerned for this compound. ***exo*-7:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 (s, 1H), 4.74 (s, 1H), 4.11 (dd, J = 11.0, 4.1 Hz, 1H), 1.12 (s, 3H), 1.01 (s, 3H). Other resonances could not be discerned for this compound.

Preparation of Geranylbenzene 9.



Geranylbenzene (9):[5] Compound **9** was prepared from geraniol and bromobenzene according to the reported procedure.[5] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.24 (m, 2H), 7.21–7.15 (m, 3H), 5.34 (td, J = 7.3, 0.9 Hz, 1H), 5.10 (t, J = 6.8 Hz, 1H), 3.36 (d, J = 7.3 Hz, 2H), 2.16–2.02 (m, 4H), 1.71 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 136.2, 131.5, 128.3 (4C), 125.6, 124.2, 123.0, 39.7, 34.2, 26.6, 25.7, 17.7, 16.1

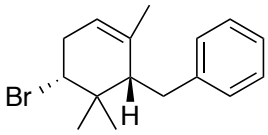
Procedure for Bromocyclization of 9.



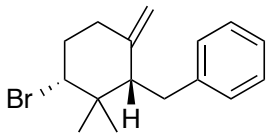
To a solution of **8a** (11 mg, 0.01 mmol) in toluene (1.0 mL) were added NBP (24.9 mg, 0.11 mmol) and **9** (21.4 mg, 0.10 mmol) successively at –78 °C, and the mixture was stirred at –78 °C for 0.5 h and then at –40 °C for 6 h. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (3.0 mL) and extracted with hexane (5.0 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel using (hexane–EtOAc 1000:1) as an eluent. The yield of *endo*-**10** and *exo*-**10** (87%) was determined by ^{1}H NMR analysis of the crude mixture using

tetrachloroethane as an internal standard: δ 4.27 (dd, J = 9.6, 6.4 Hz, 1H, *endo*-**10**), 4.11 (dd, J = 11.0, 4.1 Hz, 1H, *exo*-**10**).

The corresponding physical and spectroscopic data for *endo*-**10** and *exo*-**10** are as follows.

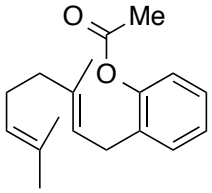


5-Bromo-2,6,6-trimethylcyclohex-2-en-1-yl)methyl)benzene (*endo*-10): IR (neat) 1649, 1604, 1496, 1453, 1389, 1369, 1225, 1206, 1146 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.13 (m, 5H), 5.20 (brs, 1H), 4.27 (dd, J = 9.6, 6.4 Hz, 1H), 3.09 (d, J = 14.7 Hz, 1H), 2.62–2.46 (m, 4H), 1.45 (s, 3H), 1.25 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 141.6, 128.5 (2C), 128.2 (2C), 125.6, 110.7, 67.1, 53.4, 42.0, 37.1, 35.8, 32.8, 28.7, 16.9; HRMS (FAB) calcd for $C_{16}H_{21}Br^+$ $[M]^+$ 292.0827, found 292.0826.



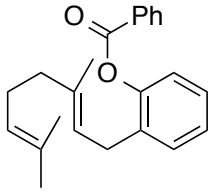
3-Bromo-2,2-dimethyl-6-methylenecyclohexyl)methyl)benzene (*exo*-10): IR (neat) 1603, 1496, 1453, 1388, 1368 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.22 (m, 2H), 7.19–7.12 (m, 3H), 4.87 (s, 1H) 4.67 (s, 1H), 4,22 (dd, J = 11.4, 4.6 Hz, 1H), 3.04 (dd, J = 15.2, 2.3 Hz, 1H), 2.85 (dd, J = 15.2, 10.6 Hz, 1H), 2.36–2.25 (m, 3H), 2.16–2.02 (m, 2H), 1.28 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 137.0, 128.4 (2C), 128.3 (2C), 125.7, 120.6, 64.9, 51.2, 38.9, 35.7, 35.3, 28.7, 23.2, 16.0; HRMS (FAB) calcd for $C_{16}H_{21}Br^+$ $[M]^+$ 292.0827, found 292.0842. The ee was determined by HPLC analysis (Daicel Chiralpack IB-3 column, hexane, flow rate = 1.0 mL/min) t_R= 7.1, 10.8 min.

Preparation of *O*-protected Geranylphenols 11 and 12.

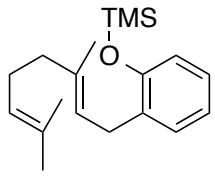


(*E*)-2-(3,7-Dimethylocta-2,6-dien-1-yl)phenyl acetate (11a): To a solution of 2-geranylphenol (115 mg, 0.5 mmol), triethylamine (139 μL, 1.0 mmol) and

N,*N*-dimethyl-4-aminopyridine (6.1 mg, 0.05 mmol) in CH_2Cl_2 (5 mL) was added acetyl chloride (53 μL, 0.75 mmol) at 0 °C. After stirring for 19 h at ambient temperature, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O, and the combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (hexane–EtOAc 10:1) to give **11a** as a pale yellow oil (111 mg, 84% yield). IR (neat) 1776, 1488, 1452, 1368, 1206, 1171, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.14 (m, 3H), 7.01 (dd, *J* = 7.8, 1.4 Hz, 1H), 5.24 (td, *J* = 7.3, 0.9 Hz, 1H), 5.10 (t, *J* = 6.9 Hz, 1H), 3.24 (d, *J* = 7.3 Hz, 2H) 2.31 (s, 3H), 2.14–2.01 (m, 4H), 1.68 (s, 6H), 1.60 (s, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 148.8, 136.8, 133.4, 131.5, 129.9, 126.9, 126.1, 124.1, 122.1, 121.4, 39.6, 28.5, 26.5, 25.7, 20.8, 17.6, 16.0 ; HRMS (FAB) calcd for $C_{18}H_{25}O_2^+$ $[M+H]^+$ 273.1849, found 273.1844.



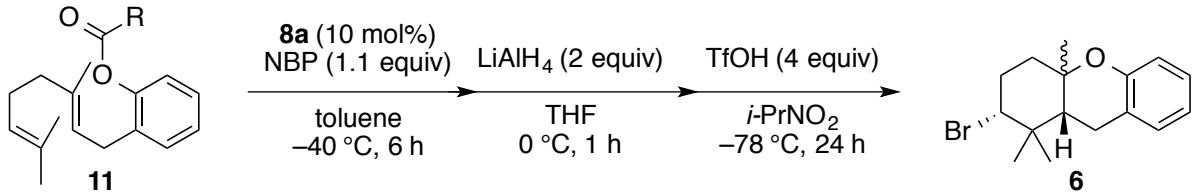
(*E*)-2-(3,7-Dimethylocta-2,6-dien-1-yl)phenyl benzoate (11b): Compound **11b** was prepared from 2-geranylphenol and benzoyl chloride according to the same manner as **11a**. Pale yellow oil; IR (neat) 1738, 1488, 1451, 1264, 1212, 1171, 1101, 1080, 1063 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, *J* = 7.3, 1.4 Hz, 2H), 7.64 (t, *J* = 7.3 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.31–7.19 (m, 3H), 7,14 (dd, *J* = 7.8, 1.4 Hz, 1H), 5.24 (td, *J* = 7.4, 1,4 Hz, 1H), 5.07 (t, *J* = 6.8 Hz, 1H), 3.31 (d, *J* = 6.8 Hz, 2H), 2.09–1.93 (m, 4H), 1.67 (s, 3H), 1.58 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 149.1, 136.8, 133.6, 133.5, 131.4, 130.1 (2C), 130.0, 129.5, 128.5 (2C), 127.0, 126.1, 124.2, 122.3, 121.4, 39.6, 28.7, 26.4, 25.7, 17.6, 16.1; HRMS (FAB) calcd for $C_{23}H_{27}O_2^+$ $[M+H]^+$ 335.2006, found 335.2001.



(*E*)-(2-(3,7-Dimethylocta-2,6-dien-1-yl)phenoxy)trimethylsilane (12): To a solution of 2-geranylphenol (115 mg, 0.5 mmol) and triethylamine (139 μL, 1.0 mmol)

in THF (5 mL) was added trimethylsilyl chloride (126 μL, 1.0 mmol) at 0 °C. After stirring for 2 h at ambient temperature, the mixture was filtered through a Celite pad, washed with Et_2O, and the filtrate was concentrated to give **12** as a pale yellow oil (79 mg, 85% yield). IR (neat) 1490, 1451, 1253 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, J = 7.3 Hz, 1H), 7.06 (t, J = 7.8 Hz, 1H), 6.89 (t, J = 7.3 Hz, 1H), 6.77 (d, J = 7.8 Hz, 1H), 5.29 (t, J = 7.3 Hz, 1H), 5.11 (t, J = 6.0 Hz, 1H), 3.29 (d, J = 7.3 Hz, 2H), 2.25–2.01 (m, 4H), 1.69 (s, 6H), 1.60 (s, 3H), 0.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 136.0, 132.3, 131.4, 129.4, 126.6, 124.3, 122.3, 121.3, 118.7, 39.7, 28.4, 26.6, 25.7, 17.7, 16.1 0.5 (3C); HRMS (FAB) calcd for $C_{19}H_{30}OSi^+$ $[M]^+$ 302.2066, found 302.2069.

Typical Procedure for Bromocyclization of 11.

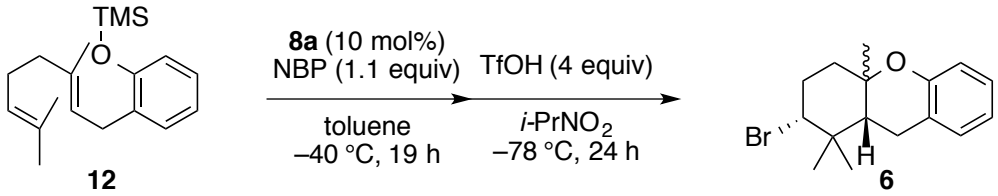


To a solution of **8a** (11 mg, 0.01 mmol) in toluene (1.0 mL) were added NBP (24.9 mg, 0.11 mmol) and **11a** (27.2 mg, 0.10 mmol) successively at –78 °C, and the mixture was stirred at –78 °C for 0.5 h and then at –40 °C for 6 h. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (3.0 mL) and extracted with EtOAc (5.0 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The yield (33%) was determined by ^1H analysis of the crude mixture using tetrachloroethane as an internal standard. The crude mixture was purified by column chromatography on silica gel using (hexane–EtOAc 20:1) as an eluent.

The resulting mixture of acetylated A-ring products was used for the next reactions to determine the enantioselectivity. To a solution of the resulting mixture (13.3 mg), which were obtained in the above reaction, in Et_2O (1.0 mL) was added $LiAlH_4$ (3.2 mg, 0.084 mmol) at 0 °C. After stirring for 1 h at 0 °C, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc, and the combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The resulting mixture of A-ring products **7** was used for the next reaction without further purification. To a solution of resulting mixture in *i*-$PrNO_2$ (0.5 mL) was added TfOH (15 μL, 0.164 mmol) at –78 °C. After stirring at –78 °C for 24 h, the reaction mixture was quenched with saturated

aqueous $NaHCO_3$, and extracted with Et_2O (5 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The diastereomeric ratio (*trans/cis* = 75 : 25) was determined by ^1H analysis of the crude mixture. The crude mixture was purified by preparative TLC using (hexane–EtOAc 20:1) as an eluent to give **6**.

Procedure for Bromocyclization of 12.



To a solution of **8a** (11 mg, 0.01 mmol) in toluene (1.0 mL) were added NBP (24.9 mg, 0.11 mmol) and **12** (30.3 mg, 0.10 mmol) successively at –78 °C, and the mixture was stirred at –78 °C for 0.5 h and then at –40 °C for 6 h. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (3.0 mL) and extracted with hexane (5.0 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The yield (64%) was determined by ^1H analysis of the crude mixture using tetrachloroethane as an internal standard. The crude product was purified by column chromatography on silica gel using (hexane–EtOAc 20:1) as an eluent to give the mixture of *endo*- and *exo*-isomeric A-ring products **7**.

The resulting mixture of *endo*- and *exo*-isomeric A-ring products **7** was used for the next cyclization to determine the enantioselectivity. To a solution of the resulting mixture, which were obtained in the above reaction, in *i*-$PrNO_2$ (0.6 mL) was added TfOH (21 μL, 0.24 mmol) at –78 °C. After stirring at –78 °C for 24 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, and extracted with Et_2O (5 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The diastereomeric ratio (*trans/cis* = 75 : 25) was determined by ^1H analysis of the crude mixture. The crude mixture was purified by preparative TLC using (hexane–EtOAc 20:1) as an eluent to give **6**.

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Chapter 5

Enantioselective Iodolactonization of 4-Arylmethyl-4-pentenoic Acids Promoted by Chiral Phosphate Catalysts

Abstract:

Chiral triaryl phosphates promote the enantioselective iodolactonization of 4-substituted 4-pentenoic acids to give the corresponding iodolactones in high yields with high enantioselectivity. *N*-Chlorophthalimide (NCP) is employed as a Lewis acidic activator and oxidant of I_2 for the present iodolactonization. In combination with 1.5 equivalents of NCP, only 0.5 equivalents of I_2 are sufficient to generate the iodinating reagent.

5-1. Introduction

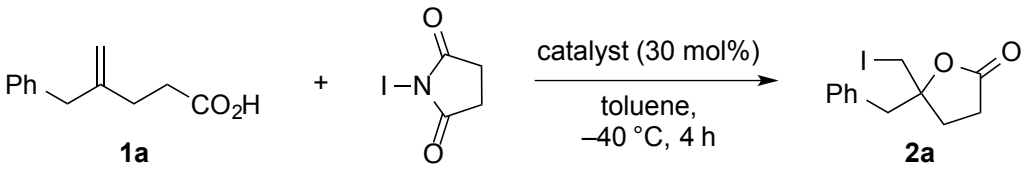
Electrophilic olefin halocyclizations are powerful tools for stereoselective functionalization of alkenes, the products of which are useful chiral building blocks for the synthesis of biologically relevant molecules.[1] Several recent studies have successfully provided catalytic enantioselective halolactonizations,[2–4] haloetherifications,[5] haloaminocyclizations,[6] and related reactions.[7] Although these methods give the corresponding chiral products with high enantioselectivities, reactivities are not so high and require long reaction times in some cases.

We previously reported a chiral Lewis base promoted enantioselective iodocyclization of isoprenoids.[8] The chiral nucleophilic phosphoramidite acts as a monofunctional Lewis base[8a–e,9] and reacts with *N*-iodosuccinimide (NIS) to generate the corresponding phosphonium salt as an active species. Although this method gives polycyclic 3-iodoterpenoids with high enantioselectivity, stoichiometric use of the phosphoramidite is required for successful promotion of the reaction and arises from the instability of the phosphoramidite under the reaction conditions and the deactivation of the phosphoramidite with the generated acidic succinimide. The development of a catalytic system for enantioselective iodocyclization based on acid-base chemistry[10] is an important issue. We report herein cooperative activation with chiral phosphate catalysts and *N*-haloimides for the enantioselective iodolactonization of 4-arylmethyl-4-pentenoic acids.

5-2. Results and Discussion

To obtain fundamental information of nucleophilic-base-catalyzed iodolactonization of unsaturated carboxylic acids, we began our study with examination of the catalytic activities of various achiral phosphorous bases, which might nucleophilically activate the iodinating reagent. The reaction of 4-benzylpent-4-enoic acid (**1a**) was conducted with NIS (1.1 equiv) in the presence of a base catalyst (30 mol %) in toluene at –40 °C for hours (Table 5.1).

Table 5.1. Catalytic Activities of Achiral Lewis Bases[a]



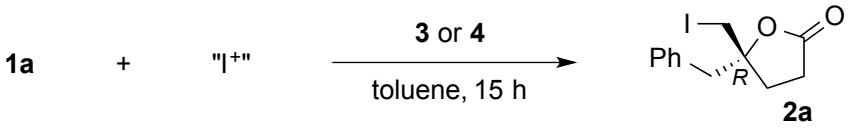
Entry	Catalyst	Yield [%][b]		
1	$P(OPh)_3$	60	(81)[c]	(0)[d]
2	$P(O^iPr)_3$	55	(85)[c]	
3	PPh_3	63	(80)[c]	
4	$O=P(OPh)_3$	0	(100)[c]	(18)[d]
5	$S=P(OPh)_3$	3	(100)[c]	
6	no catalyst	1	(37)[c]	(2)[d]

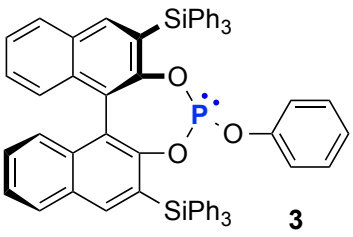
[a] The reaction of **1a** (0.1 mmol) was conducted with NIS (1.1 equiv) in the presence of a catalyst (30 mol%) in toluene (1 mL) at –40 °C for 4 h. [b] Determined by ^{1}H NMR analysis. [c] Yield when the reaction was conducted with I_2 (1.1 equiv) and NIS (1.1 equiv) for 1 h. [d] Yield when the reaction was conducted with I_2 (1.1 equiv) for 4 h.

As a result, phosphorus(III) compounds such as triphenyl phosphite, tri(isopropyl)phosphite, and triphenylphosphine showed good catalytic activities (entries 1–3).[11,12] In sharp contrast, pentavalent triphenyl phosphate and thiophosphate[13] were almost inert (entries 4 and 5). However, very surprisingly, when the triphenylphosphate- and triphenylthiophosphate-catalyzed reactions were conducted in the presence of I_2 and NIS (1.1 equiv each)[2a,d,f] as iodinating agents, the reactivities were remarkably increased to give **2a** in almost quantitative yield within 1 hour (entries 4 and 5). The combined use of I_2 and NIS was also somewhat effective for trivalent phosphine catalysts (entries 1–3). A highly active iodinating reagent might be generated from I_2 and NIS,[14] since the combined use of I_2 and NIS gave **2a** in 37% yield in the absence of any catalysts, and the reaction with NIS or I_2 was very low yielding (entry 6).

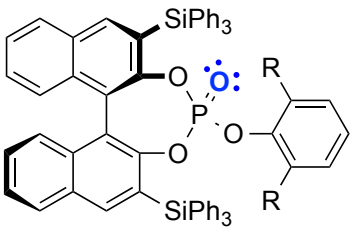
Based on these results, we next investigated enantioselective iodolactonization of **1a** using either the chiral phosphite **3** or phosphate **4a** (R = H) as the catalyst (Table 5.2).

Table 5.2. Enantioselective Iodolactonization of **1a** Using **3** or **4**[a]





3



4a: R = H
4b: R = Bu
4c: R = *i*-Bu

Entry	"I$^+$" (equiv)	**3** or **4** (mol%)	Temp [°C]	Yield [%][b]	ee [%]
1	NIS (1.1)	**3** (30)	–40	17	40
2	I_2 (1.1)	**3** (30)	–40	19	19
3[c]	I_2 (1.1), NIS (1.1)	**3** (30)	–78	55	50
4	NIS (1.1)	**4a** (30)	–40	18	38
5	I_2 (1.1)	**4a** (30)	–40	36	38
6[d]	I_2 (1.1), NIS (1.1)	**4a** (5)	–78	98	50
7[d]	I_2 (1.1), NIS (1.1)	**4b** (5)	–78	99	86
8[d]	I_2 (1.1), NIS (1.1)	**4c** (5)	–78	99	88
9[d]	I_2 (1.1), NCS (1.1)	**4c** (5)	–78	99	88
10[d]	I_2 (1.1), NCP (1.1)	**4c** (5)	–78	99	92
11[d]	I_2 (0.5), NCP (1.5)	**4c** (5)	–78	95	93
12[d,e]	I_2 (0.5), NCP (1.5)	**4c** (1)	–78	95[f]	93

[a] The reaction of **1a** (0.1 mmol) was conducted with "I$^+$" in the presence of either **3** or **4** in toluene (1 mL) for 15 h. [b] Determined by ^{1}H NMR analysis. [c] I_2, NIS, and **3** were stirred in toluene at –40 °C for 1 h prior to adding **1a** at –78 °C. [d] I_2 and NIS (or NCS, NCP) were stirred in toluene at –40 °C for 1 h prior to adding **4** and **1a** at –78 °C. [e] On 5 mmol scale for 24 h. [f] Yield of isolated product.

When the **3**- or **4a**-catalyzed reaction was conducted with either NIS or I_2 in toluene at –40 °C, moderate enantioselectivity was induced, and the yield of **2a** was low (entries 1, 2, 4, and 5). Since the combined use of I_2 and NIS (1.1 equiv each) significantly increases

reactivity, the reaction could be conducted at –78 °C to improve the enantioselectivity (entries 3 and 6). In particular, **4a** showed much higher catalytic activity than **3**, and only 5 mol % of **4a** was sufficient to promote the reaction, but the enantioselectivity induced by **4a** was almost same as that obtained with **3** (entry 6). The absolute stereochemistry of the major enantiomer of **2a** was determined to be *R*.[15]

When I_2 and NIS were stirred in toluene at –40 °C for 1 hour prior to adding **1a** and **4a** at –78 °C, the **4a**-catalyzed reaction showed higher reactivity than the reaction without the premixing protocol.[16] In contrast, for the **3**-catalyzed reaction, the pretreatment of I_2, NIS, and **3** in toluene at –40 °C for 1 hour was required for the successful promotion of the reaction at –78 °C.[14] These experimental results suggested that a complex of I_2 with NIS might be generated as the active iodinating species at –40 °C,[14] and that **3** might be oxidized to **4a** during the pretreatment.[17] The introduction of alkyl groups at the 2,6-position of the phenoxy group of **4** successfully increased the enantioselectivity. The use of **4b** (R = Bu) or **4c** (R = *i*Bu) gave especially high enantioselectivities (Table 5.2, entries 7 and 8).

Further investigation revealed that when either *N*-chlorosuccinimide (NCS)[18,19] or *N*-chlorophthalimide (NCP), which are more stable and inexpensive than NIS, was used instead of NIS, the reaction successfully proceeded to give **2a** in quantitative yields with excellent enantioselectivity (Table 2, entries 9 and 10).[20] Very interestingly, in the presence of 1.5 equivalents of NCP, the use of only 0.5 equivalents of I_2 successfully promoted the reaction to give **2a** in high yield with high enantioselectivity (entry11). These results indicated that NCP worked as not only the activator but also the oxidant of I_2 (0.5 equiv) to generate one equivalent of the iodonium ion (I^+). The fact that NCS and NCP were consumed during the reaction to generate succinimide or phthalimide also supported this consideration. Under the optimized reaction conditions, only 1 mol % of **4a** successfully promoted a 5 mmol scale reaction to give **2a** in 95% yield (1.5 gram) with 93% ee (entry 12). Since I_2 and NCP are much cheaper than other iodinating reagents such as NIS, the present asymmetric iodolactonization should be highly practical.

We propose here a mechanism for the present enantioselective iodolactonization of **1a**. Lewis-acidic NCP might activate I_2 through halogen-bonding interactions in toluene at –40 °C to form the active iodinating species **5** (X = I ; Figure 5.1a). The generation of **5** is supported by Raman spectra of a mixture of NCP and I_2 in toluene (observed at 114 cm^{-1}).[15] When the phosphite **3** is used as a precatalyst, **5** could oxidize **3** in situ to give the phosphate

4 as an active catalyst. The catalytic cycle would involve the reaction of **5** with **4** to give the chiral iodoxyphosphonium ion **6** as an active species (Figure 5.1b).[21] Since this step generates ICl (X = I), which could also act as an iodinating reagent through the activation by NCP,[22,23] the use of 0.5 equivalents of I_2 was sufficient to complete the iodolactonization. Electrophilic iodination of the double bond of **1a** followed by cyclization gives the desired (*R*)-**2a** and phthalimide.

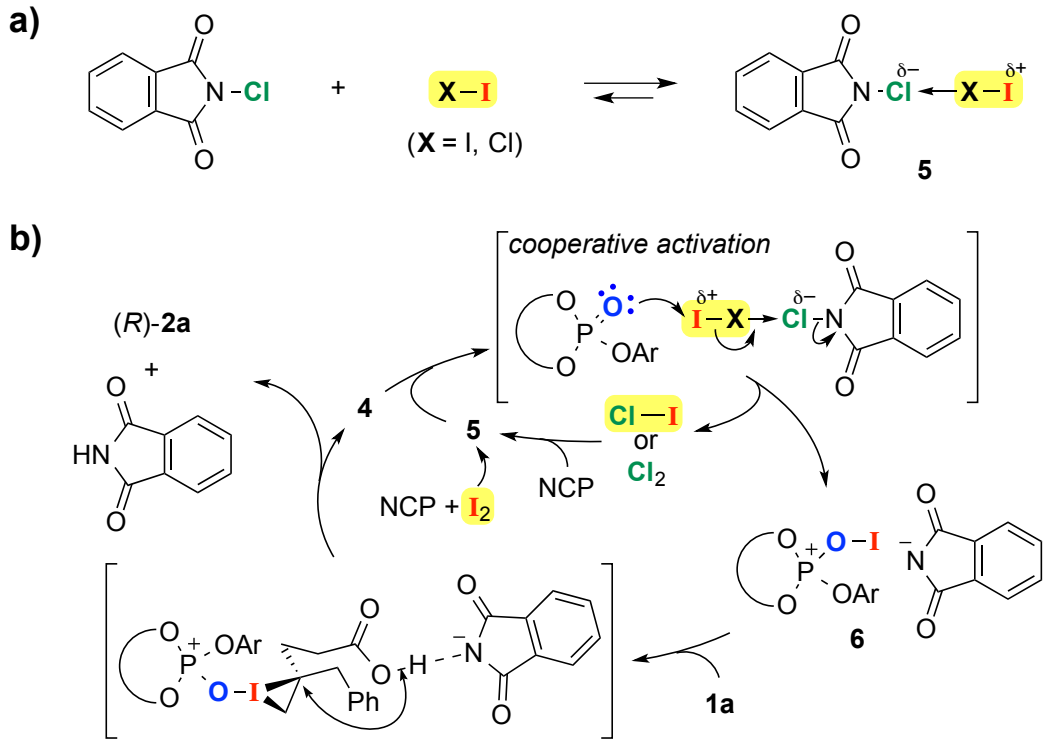
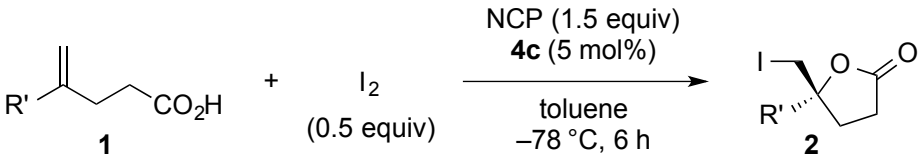


Figure 5.1. Proposed Mechanism

With the optimized catalyst and reaction conditions in hand, we next examined the enantioselective iodolactonization of 4-pentenoic acids (**1**) bearing various substituents at the 4-position. As shown in Table 5.3, the present method could be applied to a variety of 4-(arylmethyl)pent-4-enoic acids to give the corresponding iodolactones with high enantioselectivities within a short reaction time. For example, the **4c**-catalyzed reaction of 4-benzylpent-4-enoic acids bearing an electron-withdrawing fluoro and chloro substituent, and electron-donating methoxy and methyl substituents on the phenyl group gave the corresponding iodolactones **2b** and **2d–f** with respective enantiomeric excesses between 92 % and 94 % within 6 hours (entries 2, and 4–6). The high enantioselectivities were also

observed in the reaction of the 3-furylmethyl-substituted **1g** and 2-naphthylmethyl-substituted **1h** (entries 7 and 8). In addition to the 4-(arylmethyl)-substituted substrates, the 4-(cyclohexylmethyl)-substituted **1i**, and 4-isobutyl-substituted **1j** were successfully converted into **2i** and **2j**, respectively, with high enantioselectivities (entries 9 and 10). In contrast, the introduction of a fluoro substituent at the 2-position significantly decreased the enantioselectivity (entry 3). In addition, the reaction of phenyl- and *n*-octyl-substituted substrates showed poor enantioselectivity, albeit with good reactivity (entries 11 and 12).

Table 5.3. Enantioselective Iodolactonization of **1**[a]



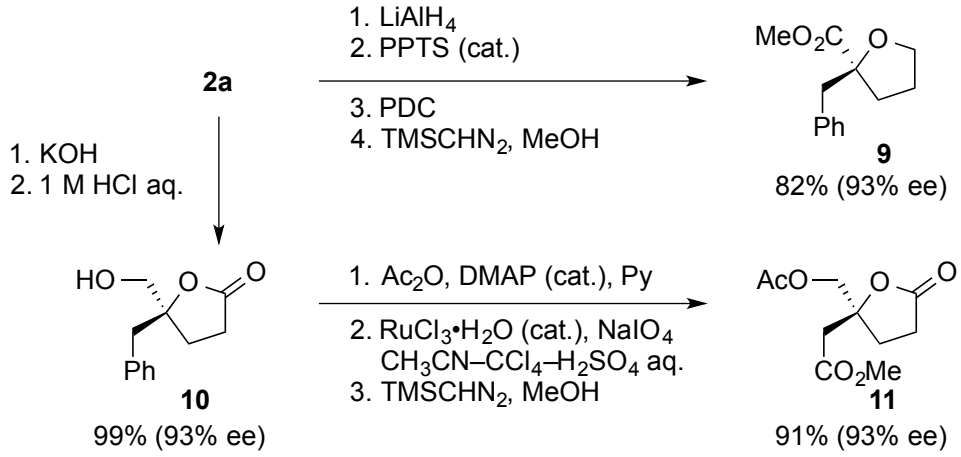
Entry	**1** (R')	Yield [%][b]	ee [%]
1	**1a** (C_6H_5)	95	93
2	**1b** (4-$FC_6H_4CH_2$)	95	93
3	**1c** (2-$FC_6H_4CH_2$)	99	2
4	**1d** (4-$ClC_6H_4CH_2$)	92	94
5	**1e** [4-$(MeO)C_6H_4CH_2$]	97	92
6	**1f** (4-$MeC_6H_4CH_2$)	90	92
7	**1g** (3-furylCH_2)	97	92
8	**1h** (2-naphthylCH_2)	99	90
9	**1i** (*c*-$C_6H_{12}CH_2$)	95	90
10	**1j** (*i*-Bu)	95	80
11	**1k** (Ph)	72	10
12	**1l** (*n*-C_8H_{15})	63	22

[a] The reaction of **1** (0.1 mmol) was conducted with I_2 (0.5 equiv) and NCP (1.5 equiv) in the presence of **3d** (5 mol%) in toluene (1 mL) at –78 °C. [b] Yield of isolated product.

The synthetic applications of **2a** were demonstrated by the several transformations shown in Scheme 5.1. A four-step sequence of reduction with $LiAlH_4$, acid treatment, oxidation with PDC, and methyl ester formation converted **2a** into the ester **9** in 82 % yield

without any loss of enantiomeric excess. The compound **9** has the same carbon skeleton as PPAR agonists.[24] Alkaline hydrolysis of **2a** and subsequent acid- catalyzed cyclization gave the hydroxylactone **10** in quantitative yield. The compound **10** is a key intermediate for the synthesis of nucleoside analogues, therapeutic agents against AIDS and cancer.[25] The three-step transformation of **10** gave the corresponding ester **11** in 91 % yield.

Scheme 5.1. Transformations of the Chiral Iodolactones **2**



DMAP = 4-(*N,N*-dimethylamino)pyridine, DIC = diisopropylcarbodiimide, PDC = pyridinium dichromate, PPTS = pyridinium p-toluenesulfonate, TMS = trimethylsilyl.

5-3. Conclusions

In conclusion, we have demonstrated that the chiral triaryl phosphate **4c** and NCP cooperatively promote the enantioselective iodolactonization of 4-substituted 4-pentenoic acids (**1**) to give the corresponding iodolactones **2** in high yields with high enantioselectivity within a short reaction time. The stable but less nucleophilic phosphate **4c** shows better catalytic activities than the phosphite **3** in the presence of NCP as a Lewis acid. NCP is an effective activator and oxidant of I_2 for the present enantioselective iodolactonization. Since I_2 and NCP are much less expensive than other iodinating reagents such as NIS, the present iodolactonization should be highly practical. The present method was successfully applied to 4-alkyl-substituted 4-pentenoic acids (**1**) with high enantioselectivities, while most previous methods are applicable to only 4-aryl-substituted substrates.

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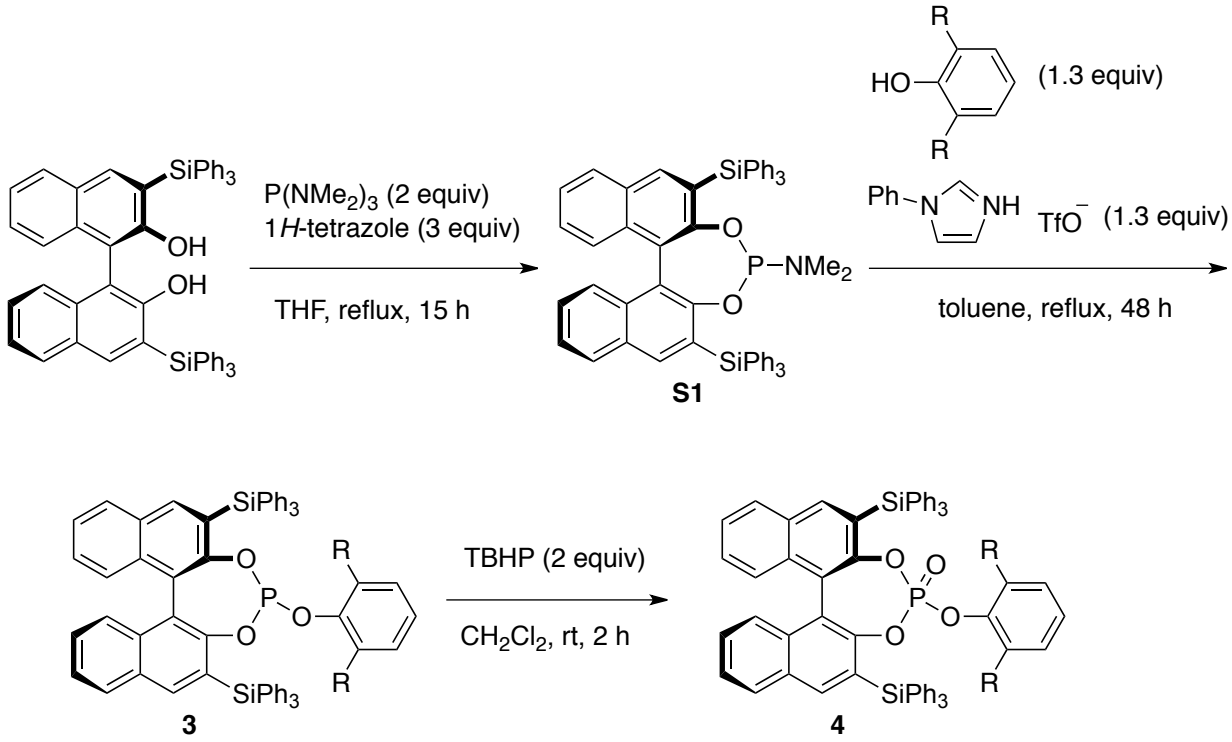
11. The catalytic activities of tertiary amines were low (15–36% yield). These Brønsted bases might activate the carboxyl group of **1a** through the formation of ammonium salts to promote the reaction. See Experimental Section for details.
12. The reaction did not give any other diastereomers.
13. Denmark, S. E.; Burk, M. T. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20655.
14. Chaikovskii, V. K.; Funk, A. A.; Filimonov, V. D.; Petrenko, T. V.; Kets, T. S. *Russ. J. Org. Chem.* **2008**, *44*, 935.
15. See Experimental Section for details.

16. The phosphite **3** was almost inert under the reaction conditions without the pretreatment with I_2 and NIS at –40 °C (7% yield, 7% ee). In contrast, the use of **4a** gave **2a** in 55% yield with 47% ee, even when the reaction was conducted without the pretreatment. These results are also comparable with entries 3 and 6, respectively, in Table 5.2.
17. The fact that the reaction of **1a** catalyzed by **3** gave **2a** with similar enantioselectivity to that catalyzed by **4a** might support this proposal. The oxidation of **3** was also strongly suggested by ^{31}P NMR study. See Experimental Section for details.
18. (a) Kang, S. H.; Lee, S. B.; Park, C. M. *J. Am. Chem. Soc.* **2003**, *125*, 15748. (b) Kang, S. H.; Park, C. M.; Lee, S. B.; Kim, M. *Synlett* **2004**, 1279. (c) Kwon, H. Y.; Park, C. M.; Lee, S. B.; Youn, J.-H.; Kang, S. H. *Chem. Eur. J.* **2008**, *14*, 1023.
19. In Ref. [18c], the authors proposed that NCS reacts with iodide anion to release ICl or that NCS oxidizes Cr^{III} to higher oxidation state(s) to enhance its Lewis acidity.
20. The corresponding chlorolactone was not obtained at all.
21. The generation of phthalimide was confirmed by ^{1}H NMR studies. ^{1}H NMR experiments also suggested that *N*-iodoimide was not generated under the reaction conditions. See Experimental Section for details.
22. In contrast to I_2, ICl might be activated by NCP at –78 °C to give the corresponding active iodinating species **6** (X = Cl) because ICl is more reactive than I_2. For reports of ICl as iodination reagent, see: (a) Haas, J.; Piguel, S.; Witrh, T. *Org. Lett.* **2002**, *4*, 297. (b) Haas, J.; Bissmire, S.; Wirth, T. *Chem. Eur. J.* **2005**, *11*, 5777.
23. The use of ICl as an iodinating agent decreased the yield and enantioselectivity of **2a** (30 %, 0 % ee) because of the generation of significant amounts of byproducts. The slow generation of ICl might be key to high yield and enantioselectivity..
24. Clark, R.; Matsuura, F.; Emori, E.; Shinoda, M.; Kasai, S.; Yoshitomi, H.; Yamazaki, K.; Inoue, T.; Miyashita, S.; Hihara, T. *Jpn. Kokai Tokkyo Koho* JP 2003016265 A1 20030227, **2003**.
25. (a) Paju, A.; Laos, M.; Jõgi, A.; Päri, M.; Jäälaid, R.; Pehk, T.; Kanger, T.; Lopp, M. *Tetrahedron Lett.* **2006**, *47*, 4491. (b) Jõgi, A.; Ilves, M.; Paju, A.; Pehk, T.; Kailas, T.; Müürisepp, A.; Lopp, M. *Tetrahedron: Asymmetry* **2008**, *19*, 628.

Experimental Section

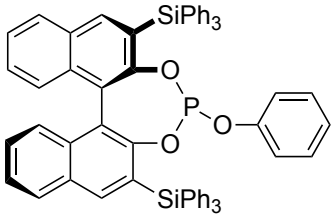
General Methods. Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. ^{1}H NMR spectra were measured on a JEOL ECS-400 spectrometer (400 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet, sep = septet; m = multiplet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a JEOL ECS-400 spectrometer (100 MHz). Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.00 ppm). ^{19}F NMR spectra (376 MHz) and ^{31}P NMR spectra (162 MHz) were measured on a JEOL ECS-400 spectrometer. Analytical HPLC was performed on a Shimadzu Model LC-10AD instrument coupled diode array-detector SPD-MA-10A-VP and a chiral column of Daicel CHIRALPACK AD-H (4.6 mm × 250 mm), AD-3 (4.6 mm × 250 mm). The reactions were carried out under an atmosphere of dry nitrogen. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254} 0.25 mm or silica gel NH_2 F_{254S} 0.25 mm) were used. The products were purified by column chromatography on silica gel (E. Merck Art. 9385). High resolution mass spectral analysis (HRMS) was performed at Chemical Instrumentation Facility, Nagoya University on JEOL JMS-700 spectrometer (for FAB) or JEOL JMS-T100GCV spectrometer (for EI). Raman spectra were measured on a Renishaw inVia Raman microscope. The wavelength of the incident laser was 532 nm. Dry tetrahydrofuran, diethylether, toluene and dichloromethane were purchased from Kanto as the "anhydrous" and stored under nitrogen. Dry acetonitrile and dry *N*,*N*-dimethylformamide were purchased from Wako as the "anhydrous" and stored under nitrogen. Triethylamine were freshly distilled from calcium hydride. Other simple chemicals were analytical-grade and obtained commercially.

Preparation of Chiral Triaryl Phosphites 3 and Triaryl Phosphates 4.

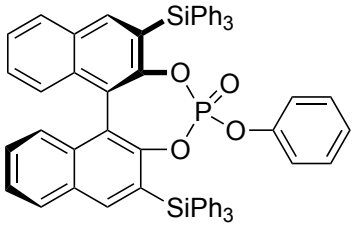


To a suspension of BINOL (1.04 g, 2.0 mmol) and 1*H*-tetrazole (462 mg, 6.0 mmol) in dry THF (15 mL) was added *N*,*N*,*N*',*N*',*N*'',*N*''-hexamethylphosphinetriamine (652 mg, 4.0 mmol). The mixture was heated at reflux for 15 h, and then cooled to ambient temperature, filtered through a Celite® pad, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane–toluene 2:1) to give **S1** (760 mg, 90% yield). To a suspension of **S1** (205 mg, 0.3 mmol) and *N*-phenylimidazolium triflate (105 mg, 0.36 mmol) in dry toluene (3 mL) was added a 2,6-dialkylphenol (0.39 mmol). The mixture was heated at reflux for 48 h, and then cooled to room temperature, filtered through a Celite® pad, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane–toluene 5:1) to give **3**.

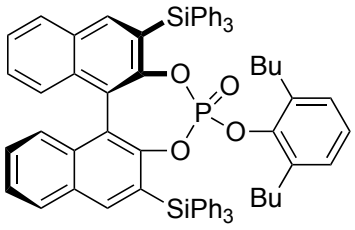
To a suspension of **3** (0.2 mmol) in dry toluene (1 mL) was added a 5.5 M solution of TBHP in nonane (72 μL, 0.4 mmol). After stirring for 2 h at ambient temperature, the reaction was quenched with H_2O. The mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–AcOEt 5:1) to give **4**.



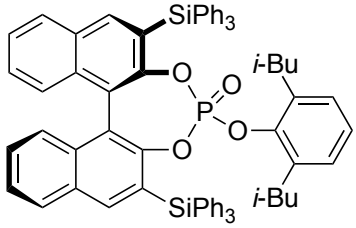
Phosphite 3:[1] $[\alpha]^{20}_{D}$ –284.24 (*c* 0.5, $CHCl_3$); IR (neat) 1591, 1491, 1428, 1387, 1200, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 8.06 (s, 1H), 7.92 (s, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.73 (d, *J* = 8.2 Hz, 1H), 7.58 (d, *J* = 6.9 Hz, 6H), 7.53 (d, *J* = 7.3 Hz, 6H), 7.43–7.11 (m, 24H), 6.80 (t, *J* = 7.3 Hz, 1H), 6.70 (dd, *J* = 7.3, 8.2 Hz, 2H), 5.77 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 152.9 (d, J_{C-P} = 5.7 Hz), 152.1 (d, J_{C-P} = 2.9 Hz), 150.8 (d, J_{C-P} = 6.7 Hz), 140.1 (2C), 136.9 (6C), 136.7 (6C), 134.9, 134.7 (3C), 134.6, 133.7 (3C), 130.9, 130.4, 129.6 (3C), 129.5 (3C), 129.2, 128.86, 128.82, 128.5 (2C), 128.4, 128.0 (6C), 127.8 (6C), 127.12, 127.08, 126.9, 125.4, 124.96, 124.91, 123.6, 123.3, 123.0, 120.79, 120.73; ^{31}P NMR (162 MHz, $CDCl_3$) 148.1; HRMS (FAB) calcd for $C_{62}H_{46}O_3PSi_2^+$ $[M+H]^+$ 925.2723, found 925.2739.



Phosphate 4a: $[\alpha]^{20}_{D}$ –136.0 (*c* 1.0, $CHCl_3$); IR (KBr) 1587, 1489, 1428, 1315, 1192, 1107 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 8.04 (s, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 7.78 (d, *J* = 8.7 Hz, 1H), 7.58 (dd, *J* = 1.8, 7.8 Hz, 6H), 7.49 (dd, *J* = 1.8, 7.8 Hz, 6H), 7.53–7.38 (m, 1H), 7.36–7.14 (m, 23H), 6.91 (t, *J* = 7.8 Hz, 1H), 6.80 (t, *J* = 7.8 Hz, 2H), 6.03 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8 (d, J_{C-P} = 10.5 Hz), 150.5 (d, J_{C-P} = 8.6 Hz), 149.5 (d, J_{C-P} = 7.7 Hz), 142.3, 142.2, 136.5 (6C), 136.4 (6C), 134.24, 134.19, 133.51 (3C), 133.46 (3C), 131.0, 130.7, 129.6 (3C), 129.4 (3C), 128.7, 128.6, 128.5 (2C), 127.8 (6C), 127.6 (6C), 126.9, 126.8, 126.3, 126.1, 125.7, 125.6, 124.3, 121.4, 121.0, 120.09, 120.05; ^{31}P NMR (162 MHz, $CDCl_3$) δ –8.1; HRMS (FAB) calcd for $C_{62}H_{45}O_4PSi_2^+$ $[M]^+$ 940.2594, found 940.2615.

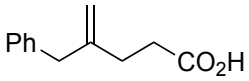


Phosphate 4b: $[\alpha]^{20}_{D}$ –127.2 (*c* 1.0, $CHCl_3$); IR (KBr) 1428, 1316, 1147, 1107 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 8.01 (s, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.60 (d, *J* = 8.2 Hz, 1H), 7.59 (dd, *J* = 1.8, 7.8 Hz, 6H), 7.49–7.37 (m, 2H), 7.40 (dd, *J* = 1.8, 7.8 Hz, 6H), 7.37–7.05 (m, 22H), 6.85 (t, *J* = 7.8 Hz, 1H), 6.69–6.58 (m, 2H), 1.88–1.66 (m, 2H), 1.66–1.39 (m, 2H), 1.39–1.15 (m, 5H), 1.05–0.77 (m, 6H), 0.67–0.41 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0 (d, $J_{C\text{-}P}$ = 11.5 Hz), 150.9 (d, $J_{C\text{-}P}$ = 8.6 Hz), 149.9 (d, $J_{C\text{-}P}$ = 10.5 Hz), 142.3, 142.1, 136.6 (6C), 136.3 (6C), 134.31, 134.28, 133.6 (3C), 133.4 (3C), 130.9, 130.8, 129.4 (3C), 129.2 (3C), 128.76, 128.69, 127.6 (6C), 127.5 (6C), 126.8, 126.6, 126.4, 126.2, 126.1 (2C), 125.6, 125.5, 124.6, 121.6, 121.3, 30.8 (2C), 28.3 (2C), 22.3 (2C), 14.0 (2C); ^{31}P NMR (162 MHz, $CDCl_3$) δ –9.5; HRMS (FAB) calcd for $C_{70}H_{62}O_3PSi_2^+$ $[M]^+$ 1052.3846, found 1052.3824.

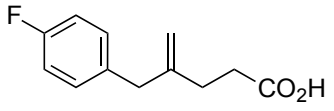


Phosphate 4c: $[\alpha]^{20}_{D}$ –138.6 (*c* 1.0, $CHCl_3$); IR (KBr) 1562, 1428, 1314, 1146, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.99 (s, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.59 (dd, *J* = 1.8, 7.8 Hz, 6H), 7.46–7.38 (m, 2H), 7.37 (dd, *J* = 1.8, 7.8 Hz, 6H), 7.46–7.10 (m, 22H), 6.81 (t, *J* = 7.8 Hz, 1H), 6.59 (brs, 2H), 1.38–1.16 (m, 4H), 1.03–0.83 (m, 2H), 0.76–-0.16 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9 (d, $J_{C\text{-}P}$ = 11.5 Hz), 150.8 (d, $J_{C\text{-}P}$ = 8.6 Hz), 146.8 (d, $J_{C\text{-}P}$ = 10.5 Hz), 143.4, 142.1, 136.6 (6C), 136.3 (6C), 134.4, 134.2, 133.7 (3C), 133.3 (3C), 130.9, 130.8, 129.6 (3C), 129.2 (3C), 128.8, 128.7, 127.7, 127.65 (6C), 127.57 (6C), 127.5, 127.4, 127.3, 126.8, 126.6, 126.3, 125.9, 125.6, 125.5, 124.2, 121.4, 121.2, 37.9 (2C), 26.2 (2C), 22.1 (4C); ^{31}P NMR (162 MHz, $CDCl_3$) δ –8.9; HRMS (FAB) calcd for $C_{70}H_{61}O_4PSi_2^+$ $[M]^+$ 1052.3846, found 1052.3850.

Preparation of 4-Pentenoic Acids 1.

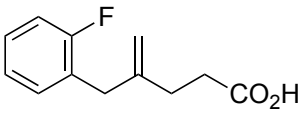


4-Benzylpent-4-enoic Acid (1a):[2] To a solution of CuI (5.71 g, 30 mmol) and Ethyl succinylchloride (5.36 g, 30 mmol) in THF (60 mL) was added a 1.0 M solution of BnMgCl in THF (60 mL, 60 mmol) at 0 °C. After stirring for 3 h at ambient temperature, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with AcOEt. The organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 10:1) to give ethyl 4-oxo-5-phenylpentanoate as pale yellow oil (3.93 g, 56% yield). To a solution of NaO*t*-Bu (2.41 g, 25 mmol) in THF (64 mL) was added $MePPh_3Br$ (10.15 g, 28.4 mmol) at 0 °C. After stirring for 30 min at the same temperature, a solution of ethyl 4-oxo-5-phenylpentanoate (3.93 g, 16.7 mmol) in THF (4 mL) was added. The mixture was warmed to ambient temperature, stirred for 15 h, and then quenched with saturated aqueous NH_4Cl. The organic layer was washed with brine, dried with Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give ethyl 4-benzylpent-4-enoate (460 mg, 29% yield). To a solution of ethyl 4-benzylpent-4-enoate (671 mg, 2.9 mmol) in MeOH (6 mL) was added a solution of KOH (811 mg, 14.5 mmol) in H_2O (1.2 mL) at 0 °C. After stirring for 2 h at ambient temperature, the reaction was quenched with concentrated aqueous HCl. The mixture was extracted with AcOEt. The organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 5:1) to give **1a** as pale yellow oil (577 mg, 99% yield). **1a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 7.3 Hz, 2H), 7.22 (d, J = 7.3 Hz, 1H), 7.18 (d, J = 7.3 Hz, 2H), 4.85 (s, 1H), 4.83 (s, 1H), 3.36 (s, 2H), 2.50 (t, J = 7.8 Hz, 2H), 2.30 (t, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.3, 146.8, 128.0 (2C), 128.4 (2C), 126.2, 111.7, 43.2, 32.2, 29.8.

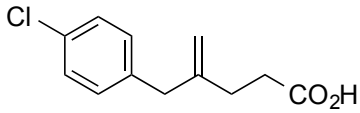


4-(4-Fluorobenzyl)pent-4-enoic Acid (1b): Compound **1b** was prepared from (4-fluorobenzyl)magnesium chloride according to the same manner as **1a**. IR (KBr) 1707, 1650, 1600, 1508, 1429, 1220 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (dd, J = 6.4, 8.2 Hz, 2H), 6.96 (t, J = 8.2 Hz, 2H), 4.84 (s, 1H), 4.79 (s, 1H), 3.31 (s, 2H), 2.48 (t, J

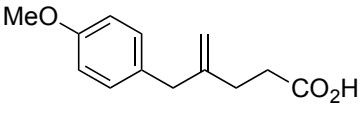
= 7.8 Hz, 2H), 2.27 (t, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 161.4 (d, $J_{C\text{-}F}$ = 243 Hz), 146.7, 134.7 (d, $J_{C\text{-}F}$ = 2.9 Hz), 130.2 (d, $J_{C\text{-}F}$ = 8.6 Hz, 2C), 115.1 (d, $J_{C\text{-}F}$ = 21.1 Hz, 2C), 111.7, 42.3, 32.2, 29.7; HRMS (FAB) calcd for $C_{12}H_{14}FO_2^+$ $[M+H]^+$ 209.0970, found 209.0971.



4-(2-Fluorobenzyl)pent-4-enoic Acid (1c): Compound **1c** was prepared from (4-fluorobenzyl)magnesium chloride according to the same manner as **1a**. IR (KBr) 1710, 1584, 1491, 1443, 1319, 1229 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.15 (m, 2H), 7.11–6.96 (m, 2H), 4.86 (s, 1H), 4.77 (s, 1H), 3.39 (s, 2H), 2.55 (t, J = 7.8 Hz, 2H), 2.35 (t, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.7, 161.1 (d, $J_{C\text{-}F}$ = 245 Hz), 145.6, 131.1 (d, $J_{C\text{-}F}$ = 4.8 Hz), 128.1 (d, $J_{C\text{-}F}$ = 7.7 Hz), 126.1 (d, $J_{C\text{-}F}$ = 16.3 Hz), 124.0 (d, $J_{C\text{-}F}$ = 3.8 Hz), 115.3 (d, $J_{C\text{-}F}$ = 22.0 Hz), 111.7, 35.5, 32.3, 30.1; HRMS (FAB) calcd for $C_{12}H_{14}FO_2^+$ $[M+H]^+$ 209.0970, found 209.0967.

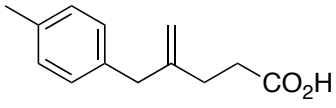


4-(4-Chlorobenzyl)pent-4-enoic Acid (1d): Compound **1d** was prepared from (4-chlorobenzyl)magnesium chloride according to the same manner as **1a**. IR (KBr) 1649, 1491, 1438, 1290, 1091 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.7 Hz, 2H), 7.11 (d, J = 8.7 Hz, 2H), 4.86 (s, 1H), 4.81 (s, 1H), 3.33 (s, 2H), 2.50 (t, J = 7.8 Hz, 2H), 2.28 (t, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.8, 146.3, 137.5, 132.0, 130.2 (2C), 128.4 (2C), 112.0, 42.5, 32.2, 29.7; HRMS (FAB) calcd for $C_{12}H_{14}ClO_2^+$ $[M+H]^+$ 225.0682, found 225.0679.

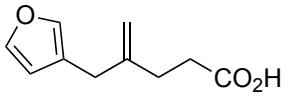


4-(4-Methoxybenzyl)pent-4-enoic Acid (1e): Compound **1e** was prepared from (4-methoxybenzyl)magnesium chloride according to the same manner as **1a**. IR (KBr) 1699, 1510, 1243, 1022 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 4.82 (s, 1H), 4.80 (s, 1H), 3.79 (s, 3H), 3.29 (s, 2H), 2.48 (t, J = 7.8 Hz, 2H), 2.28 (t, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.7, 158.0,

147.2, 131.2, 129.8 (2C), 113.7 (2C), 111.4, 55.2, 42.3, 32.3, 29.7; HRMS (FAB) calcd for $C_{13}H_{16}O_3^+$ $[M]^+$ 220.1099, found 220.1083.

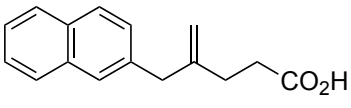


4-(4-Methylbenzyl)pent-4-enoic Acid (1f): Compound **1f** was prepared from (4-Methoxybenzyl)magnesium chloride according to the same manner as **1a**. IR (KBr) 1696, 1442, 1409, 1326, 1242 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.2 Hz, 2H), 7.06 (d, *J* = 8.2 Hz, 2H), 4.83 (s, 1H), 4.82 (s, 1H), 3.32 (s, 2H), 2.49 (t, *J* = 7.8 Hz, 2H), 2.32 (s, 3H), 2.29 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.7, 147.0, 139.0, 137.8, 127.9 (2C), 126.7 (2C), 111.5, 43.1, 32.3, 29.8, 21.2; HRMS (FAB) calcd for $C_{13}H_{17}O_3^+$ $[M]^+$ 205.1229, found 205.1229.

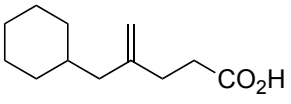


4-(Furan-3-ylmethyl)pent-4-enoic Acid (1g): To a solution of 3-bromofuran (5.00 g, 34 mmol) in THF (17 mL) was added a 1.6 M solution of *n*-BuLi in hexane (21 mL, 34 mmol) at –78 °C. After stirring for 30 min at the same temperature, the reaction mixture was warmed to 0 °C, and then CuI (3.23 g, 17 mmol) was added to the reaction mixture. After stirring for 1 h at the same temperature, a solution of ethyl 2-(bromomethyl)acrylate (3.28 g, 17 mmol) in THF (17 mL) was added. After stirring for 3 h at ambient temperature, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with AcOEt. The organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 40:1) to give ethyl 2-(furan-3-ylmethyl)acrylate as pale yellow oil (765 mg, 25% yield). To a solution of ethyl 2-(furan-3-ylmethyl)acrylate (517 mg, 2.86 mmol) in CH_2Cl_2 (7.2 mL) was added a 1.0 M solution of DIBAL-H in toluene (7.2 mL, 7.2 mmol) at –78 °C. After stirring for 2 h at ambient temperature, the reaction mixture was cooled to –78 °C, the reaction was quenched with MeOH and then H_2O was added. The mixture was extracted with AcOEt. The organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 5:1) to give ethyl 2-(furan-3-ylmethyl)prop-2-en-1-ol as colorless oil (325 mg, 82% yield). To a mixture of ethyl 2-(furan-3-ylmethyl)prop-2-en-1-ol (325 mg, 2.35 mmol) and

triethyl orthoacetate (3.81 g, 24 mmol) was added propionic acid (10 μL, 0.14 mmol) at ambient temperature. After stirring for 2 h at 140 °C, the reaction was quenched with H_2O. The mixture was extracted with AcOEt. The organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 40:1) to give 4-(furan-3-ylmethyl)pent-4-enoate as colorless oil (245 mg, 50% yield). To a solution of 4-(furan-3-ylmethyl)pent-4-enoate (245 mg, 1.2 mmol) in MeOH (2 mL) was added a KOH (330 mg, 5.9 mmol) in H_2O (0.5 mL) at 0 °C. After stirring for 2 h at ambient temperature, the reaction was quenched with concentrated aqueous HCl. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 5:1) to give **1g** as pale yellow oil (191 mg, 90% yield). IR (neat) 1710, 1651, 1436, 1290, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.25 (s, 1H), 6.25 (s, 1H), 4.87 (s, 1H), 4.83 (s, 1H), 3.17 (s, 2H), 2.52 (t, J = 7.8 Hz, 2H), 2.35 (t, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.4, 146.0, 142.9, 139.7, 122.3, 111.3, 111.2, 32.3, 32.2, 29.9; HRMS (FAB) calcd for $C_{10}H_{12}O_3^+$ $[M]^+$ 180.0786, found 180.0770.

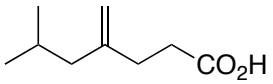


4-(Naphthalen-2-ylmethyl)pent-4-enoic Acid (1h): Compound **1h** was prepared from 2-(bromomethyl)naphthalene according to the same manner as **1g**. IR (KBr) 1699, 1640, 1430, 1407, 1328, 1241, 1214 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84–7.74 (m, 3H), 7.63 (s, 1H), 7.46 (dt, J = 1.8, 6.8 Hz, 1H), 7.43 (dt, J = 1.8, 6.8 Hz, 1H), 7.31 (dd, J = 1.4, 8.7 Hz, 1H), 4.90 (s, 1H), 4.89 (s, 1H), 3.53 (s, 3H), 2.52 (t, J = 7.8 Hz, 2H), 2.33 (t, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.7, 146.7, 136.6, 133.5, 132.2, 127.9, 127.6, 127.5, 127.4, 127.2, 125.9, 125.3, 112.0, 43.4, 32.3, 29.9; HRMS (FAB) calcd for $C_{16}H_{16}O_2^+$ $[M]^+$ 240.1150, found 240.1104.

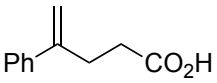


4-(Cyclohexylmethyl)pent-4-enoic Acid (1i): Compound **1i** was prepared from cyclohexylmethylmagnesium chloride according to the same manner as **1a**. IR (neat) 1712, 1646, 1448, 1292 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.75 (s, 1H), 4.73 (s, 1H), 2.51 (t, J = 7.8 Hz, 2H), 2.31 (t, J = 7.8 Hz, 2H), 1.92 (d, J = 7.3 Hz, 2H), 1.74–1.59 (m,

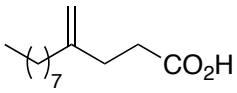
5H), 1.47–1.34 (m, 1H), 1.29–1.06 (m, 3H), 0.91–0.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3, 146.0, 110.6, 44.7, 35.4, 33.2 (2C), 32.4, 30.1, 26.5, 26.2 (2C); HRMS (FAB) calcd for $C_{12}H_{20}O_2^+$ $[M+H]^+$ 197.1536, found 197.1550.



6-Methyl-4-methyleneheptanoic Acid (1j): **1j** was prepared from Cyclohexylmethylmagnesium chloride according to the same manner as **1a**. IR (neat) 1710, 1439, 1293 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 (s, 2H), 2.51 (t, J = 7.8 Hz, 2H), 2.32 (t, J = 7.8 Hz, 2H), 1.91 (d, J = 6.9 Hz, 2H), 1.76 (sep, J = 6.9 Hz, 1H), 0.87 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 146.5, 110.6, 46.1, 32.5, 30.1, 26.0, 22.3 (2C); HRMS (FAB) calcd for $C_9H_{17}O_2^+$ $[M+H]^+$ 157.1229, found 157.1240.



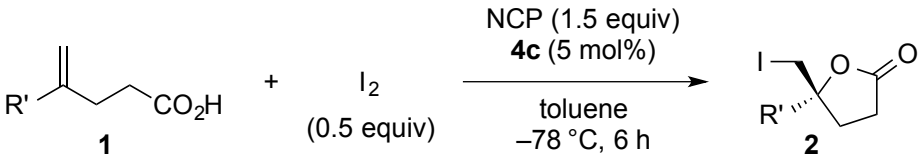
4-Phenylpent-4-enoic Acid (1k):[3] To a solution of NaO*t*-Bu (2.41 g, 25 mmol) in THF (64 mL) was added $MePPh_3Br$ (10.15 g, 28.4 mmol) at 0 °C. After stirring for 30 min at the same temperature, a solution of 3-benzoylpropionic acid (1.78 g, 10 mmol) in THF (4 mL) was added. The mixture was warmed to ambient temperature, stirred for 15 h, and then quenched with saturated aqueous NH_4Cl. The organic layer was washed with brine, dried with Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give ethyl 4-phenylpent-4-enoic acid (1.58 g, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.24 (m, 5H), 5.33 (s, 1H), 5.11 (s, 1H), 2.85 (t, J = 7.8 Hz, 2H), 2.54 (t, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.8, 146.4, 140.3, 128.4 (2C), 127.6, 126.0 (2C), 112.9, 32.9, 30.0.



4-Methylenedodecanoic Acid (1l): **1l** was prepared from octylmagnesium chloride according to the same manner as **1a**. IR (neat) 1713, 1647, 1440, 1294 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (s, 1H), 4.73 (s, 1H), 2.52 (t, J = 7.8 Hz, 2H), 2.34 (t, J = 7.8 Hz, 2H), 2.02 (t, J = 7.8 Hz, 2H), 1.51–1.38 (m, 2H), 1.36–1.18 (m, 12H), 0.88 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 147.9, 109.2, 36.3, 32.5, 31.9, 30.4, 29.5, 29.33, 29.28, 27.7, 22.7. 14.1; HRMS (FAB) calcd for $C_{13}H_{25}O_2^+$ $[M+H]^+$ 213.1855,

found 157.1859.

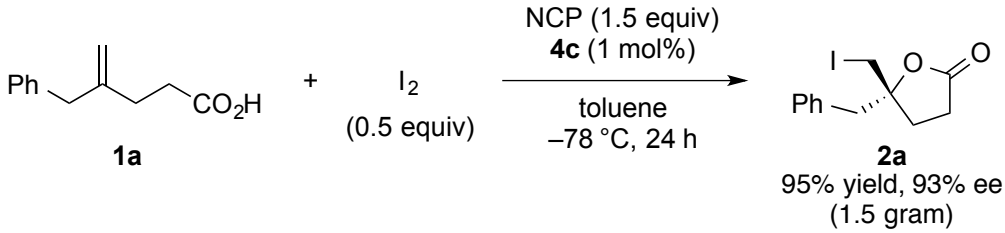
General Procedure for Enantioselective Iodolactonization of 4-Pentenoic Acids 1.



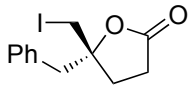
To a solution of **4d** (5.0 mg, 5.0 μmol) in toluene (1 mL) were added NCP (27 mg, 0.15 mmol) and I_2 (12 mg, 0.050 mmol) successively at –40 °C, and the mixture was stirred at –40 °C for 1 h. To the mixture was added 4-pentenoic acid **1** (0.10 mmol) dropwise at –78 °C, and the reaction mixture was stirred at –78 °C for 6 h. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (3.0 mL) and extracted with AcOEt (5.0 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–AcOEt 7:1) to give **2**.

The corresponding physical and spectroscopic data for **2** are as follows.

Gram Scale Experiment Procedure for Enantioselective Iodolactonization of 1a.

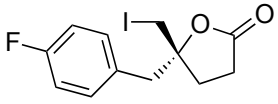


To a solution of **4d** (53 mg, 0.05 mmol) in toluene (75 mL) were added NCP (1.36 g, 7.5 mmol) and I_2 (635 mg, 2.5 mmol) successively at –40 °C, and the mixture was stirred at –40 °C for 1 h. To the mixture was added **1a** (951 mg, 5 mmol) in toluene (75 mL) dropwise at –78 °C, and the reaction mixture was stirred at –78 °C for 24 h. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (150 mL) and extracted with AcOEt (50 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–AcOEt 7:1) to give **2a** (1.50 g, 95% yield, 93% ee).

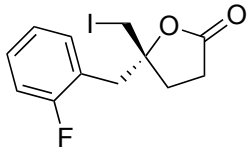


(*R*)-5-Benzyl-5-(iodomethyl)dihydrofuran-2(3*H*)-one (2a):[4]

Colorless oil; $[\alpha]^{25}_{D}$ 11.0 (*c* 1.0, $CHCl_3$) for 93% ee; IR (neat) 1774, 1735, 1456, 1244, 1173 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.25 (m, 5H), 3.44 (d, *J* = 10.1 Hz, 1H), 3.37 (d, *J* = 10.1 Hz, 1H), 3.20 (d, *J* = 14.2 Hz, 1H), 3.10 (d, *J* = 14.2 Hz, 1H), 2.48 (ddd, *J* = 6.8, 8.7, 18.3 Hz, 1H), 2.30–2.21 (m, 2H), 1.99 (ddd, *J* = 8.7, 10.1, 17.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 134.5, 130.2 (2C), 128.5 (2C), 127.3, 85.1, 43.9, 30.6, 29.2, 14.3; HRMS (EI) calcd for $C_{12}H_{13}IO_2^+$ $[M]^+$ 315.9960, found 315.9961. The ee was determined by HPLC analysis (Daicel Chiralpack AD-H column, hexane–EtOH = 9:1, flow rate = 1.0 mL/min) t_R= 21.1 (major enantiomer), 33.1 (minor) min.

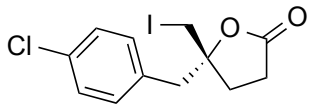


(*R*)-5-4-Fluorobenzyl)-5-(iodomethyl)dihydrofuran-2(3*H*)-one (2b): Colorless oil; $[\alpha]^{20}_{D}$ 15.9 (*c* 1.0, $CHCl_3$) for 93% ee; IR (neat) 1780, 1734, 1509, 1224, 1174 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (dd, *J* = 5.5, 8.7 Hz, 2H), 7.02 (t, *J* = 8.7 Hz, 2H), 3.39 (d, *J* = 10.5 Hz, 1H), 3.33 (d, *J* = 10.5 Hz, 1H), 3.18 (d, *J* = 14.2 Hz, 1H), 3.08 (d, *J* = 14.2 Hz, 1H), 2.52 (ddd, *J* = 5.5, 10.1, 17.9 Hz, 1H), 2.33–2.26 (m, 2H), 2.07 (ddd, *J* = 7.8, 10.1, 17.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 161.4 (d, $J_{C\text{-}F}$ = 243 Hz), 131.8 (d, $J_{C\text{-}F}$ = 8.6 Hz, 2C), 130.3 (d, $J_{C\text{-}F}$ = 2.9 Hz), 115.5 (d, $J_{C\text{-}F}$ = 21.0 Hz, 2C), 85.1, 43.1, 30.7, 29.2, 13.6; HRMS (EI) calcd for $C_{12}H_{12}FIO_2^+$ $[M]^+$ 333.9866, found 333.9857. The ee was determined by HPLC analysis (Daicel Chiralpack AD-H column, hexane–EtOH = 9:1, flow rate = 1.0 mL/min) t_R= 22.5 (major enantiomer), 30.0 (minor) min.

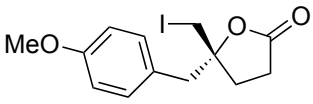


(*R*)-5-(2-Fluorobenzyl)-5-(iodomethyl)dihydrofuran-2(3*H*)-one (2c): Colorless oil; IR (neat) 1779, 1584, 1492, 1230, 1172 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.24 (m , 2H), 7.15–7.04 (m, 2H), 3.49 (d, *J* = 11.0 Hz, 1H), 3.44 (d, *J* = 11.0 Hz, 1H), 3.32 (d, *J* = 13.7 Hz, 1H), 3.13 (d, *J* = 13.7 Hz, 1H), 2.54 (ddd, *J* = 5.5, 9.6, 17.4 Hz, 1H), 2.33–2.20 (m, 2H), 2.13 (ddd, *J* = 6.9, 11.0, 17.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 161.1 (d, $J_{C\text{-}F}$ = 245 Hz), 132.7 (d, $J_{C\text{-}F}$ = 4.8 Hz), 129.5 (d, $J_{C\text{-}F}$ = 8.6 Hz), 124.4 (d,

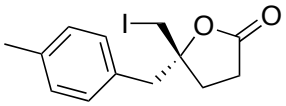
$J_{C\text{-}F}$ = 3.8 Hz), 121.7 (d, $J_{C\text{-}F}$ = 14.4 Hz), 115.6 (d, $J_{C\text{-}F}$ = 22.0 Hz), 85.2, 36.4, 30.7, 29.4, 14.1; HRMS (EI) calcd for $C_{12}H_{12}FIO_2^+$ $[M+H]^+$ 334.9944, found 334.9923. The ee was determined by HPLC analysis (Daicel Chiralpack AD-3 column, hexane–^{i}PrOH = 400:1, flow rate = 1.0 mL/min) t_R= 34.5, 35.5 min.



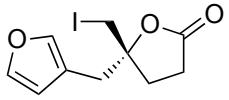
(*R*)-5-(4-Chlorobenzyl)-5-(iodomethyl)dihydrofuran-2(3*H*)-one (2d): Colorless oil; $[\alpha]^{20}_D$ 14.9 (*c* 2.0, $CHCl_3$) for 94% ee; IR (neat) 1789, 1492, 1411, 1245, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 3.38 (d, *J* = 10.5 Hz, 1H), 3.32 (d, *J* = 10.5 Hz, 1H), 3.19 (d, *J* = 14.2 Hz, 1H), 3.07 (d, *J* = 14.2 Hz, 1H), 2.53 (ddd, *J* = 5.5, 10.5, 16.5 Hz, 1H), 2.37–2.04 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 133.4, 133.0, 131.6 (2C), 128.7 (2C), 85.0, 55.2, 43.3, 30.8, 29.2, 14.4; HRMS (EI) calcd for $C_{12}H_{12}ClIO_2^+$ $[M]^+$ 349.9571, found 349.9578. The ee was determined by HPLC analysis (Daicel Chiralpack AD-H column, hexane–EtOH = 9:1, flow rate = 1.0 mL/min) t_R= 23.9 (major enantiomer), 25.1 (minor) min.



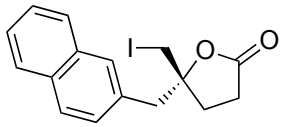
(*R*)-5-(Iodomethyl)-5-(4-methoxybenzyl)dihydrofuran-2(3*H*)-one (2e): Colorless oil; $[\alpha]^{20}_D$ 6.1 (*c* 1.0, $CHCl_3$) for 92% ee; IR (neat) 1772, 1508, 1216 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 3.80 (s, 3H), 3.43 (d, *J* = 10.5 Hz, 1H), 3.36 (d, *J* = 10.5 Hz, 1H), 3.13 (d, *J* = 14.2 Hz, 1H), 3.03 (d, *J* = 14.2 Hz, 1H), 2.52–2.41 (m, 1H), 2.28–2.18 (m, 2H), 2.06–1.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 158.9, 131.4 (2C), 126.5, 114.0 (2C), 85.5, 55.2, 43.2, 30.8, 29.4, 14.1; HRMS (EI) calcd for $C_{13}H_{15}IO_3^+$ $[M]^+$ 346.0066, found 346.0087. The ee was determined by HPLC analysis (Daicel Chiralpack AD-H column, hexane–EtOH = 9:1, flow rate = 1.0 mL/min) t_R= 34.3 (major enantiomer), 36.3 (minor) min.



(*R*)-5-(Iodomethyl)-5-(4-methylbenzyl)dihydrofuran-2(3*H*)-one (2f): Colorless oil; $[\alpha]^{20}_{D}$ 15.6 (*c* 0.2, $CHCl_3$) for 92% ee; IR (neat) 1774, 1514, 1456, 1415, 1173, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 7.8 Hz, 2H), 7.13 (d, *J* = 7.8 Hz, 2H), 3.43 (d, *J* = 10.5 Hz, 1H), 3.37 (d, *J* = 10.5 Hz, 1H), 3.15 (d, *J* = 13.7 Hz, 1H), 3.06 (d, *J* = 13.7 Hz, 1H), 2.46 (ddd, *J* = 6.9, 9.6, 17.4 Hz, 1H), 2.33 (s, 3H), 2.28–2.18 (m, 2H), 1.99 (ddd, *J* = 8.7, 11.0, 18.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 137.1, 131.5, 130.2 (2C), 129.3 (2C), 85.3, 43.6, 30.7, 29.4, 21.0, 14.2; HRMS (EI) calcd for $C_{13}H_{15}O_2I$ $[M]^+$ 330.0117, found 330.0120. The ee was determined by HPLC analysis (Daicel Chiralpack AD-H column, hexane–^{i}PrOH = 98:2, flow rate = 1.0 mL/min) t_R= 25.1 (minor enantiomer), 27.3 (major enantiomer) min.

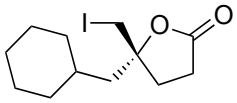


(*R*)-5-(Furan-3-ylmethyl)-5-(iodomethyl)dihydrofuran-2(3*H*)-one (2g): Colorless oil; $[\alpha]^{20}_{D}$ 8.0 (*c* 0.5, $CHCl_3$) for 92% ee; IR (neat) 1772, 1749, 1558, 1541, 1507, 1215 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.38 (s, 1H), 6.40 (s, 1H), 3.40 (d, *J* = 10.5 Hz, 1H), 3.35 (d, *J* = 10.5 Hz, 1H), 3.04 (d, *J* = 14.7 Hz, 1H), 2.95 (d, *J* = 14.7 Hz, 1H), 2.66–2.53 (m, 1H), 2.40–2.15 (m, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 143.5, 141.4, 112.0, 85.2, 34.2, 30.9, 29.6, 13.3; HRMS (EI) calcd for $C_{11}H_{11}IO_3^+$ $[M+H]^+$ 305.9753, found 305.9745. The ee was determined by HPLC analysis (Daicel Chiralpack AD-H column, hexane–EtOH = 9:1, flow rate = 1.0 mL/min) t_R= 25.1 (major enantiomer), 35.4 (minor) min.

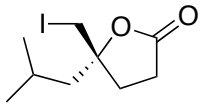


(*R*)-5-(Iodomethyl)-5-(naphthalen-2-ylmethyl)dihydrofuran-2(3*H*)- one (2h): Colorless oil; $[\alpha]^{20}_{D}$ 5.4 (*c* 0.5, $CHCl_3$) for 90% ee; IR (neat) 1772, 1558, 1541, 1507, 1216 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87–7.78 (m, 3H), 7.75 (s, 1H), 7.53–7.45 (m, 2H), 7.43 (dd, *J* = 1.8, 8.7 Hz, 1H), 3.46 (d, *J* = 10.5 Hz, 1H), 3.40 (d, *J* = 10.5 Hz, 1H), 3.37 (d, *J* = 13.7 Hz,

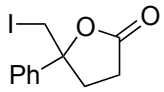
1H), 3.28 (d, J = 13.7 Hz, 1H), 2.49 (ddd, J = 6.0, 10.1, 18.3 Hz, 1H), 2.38–2.22 (m, 2H), 2.02 (ddd, J = 7.8, 10.6, 18.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 133.4, 132.6, 132.3, 129.4, 128.4, 128.3, 127.8, 127.8, 126.4, 126.2, 85.6, 44.3, 31.0, 29.5, 14.2; HRMS (EI) calcd for $C_{16}H_{15}IO_2^+$ $[M]^+$ 366.0116, found 366.0127. The ee was determined by HPLC analysis (Daicel Chiralpack AD-H column, hexane–EtOH = 9:1, flow rate = 1.0 mL/min) t_R= 29.0 (major enantiomer), 42.2 (minor) min.



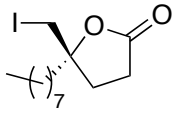
(*R*)-5-(Cyclohexylmethyl)-5-(iodomethyl)dihydrofuran-2(3*H*)-one (2i): Colorless oil; $[\alpha]^{20}_D$ 31.0 (c 0.5, $CHCl_3$) for 90% ee; IR (neat) 1776, 1447, 1236, 1174 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.42 (d, J = 10.8 Hz, 1H), 3.39 (d, J = 10.8 Hz, 1H), 2.75–2.52 (m, 2H), 2.30 (ddd, J = 6.3, 10.4, 13.4 Hz, 1H), 2.12 (ddd, J = 7.3, 10.4, 13.4 Hz, 1H), 1.90–1.79 (m, 2H), 1.77–1.56 (m, 5H), 1.50–1.37 (m, 1H), 1.33–0.94 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 86.2, 45.9, 34.6, 34.4, 33.8, 32.5, 29.1, 26.2, 26.1, 26.0, 13.4; HRMS (EI) calcd for $C_{12}H_{19}IO_2^+$ $[M]^+$ 322.0430, found 322.0412. The ee was determined by HPLC analysis (Daicel Chiralpack AD-H column, hexane–EtOH = 9:1, flow rate = 1.0 mL/min) t_R= 11.6 (major enantiomer), 16.5 (minor) min.



(*R*)-5-(Iodomethyl)-5-isobutyldihydrofuran-2(3*H*)-one (2j): Colorless oil; $[\alpha]^{20}_D$ 4.8 (c 0.5, $CHCl_3$) for 80% ee; IR (neat) 1773, 1465, 1232, 1158 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.42 (d, J = 15.1 Hz, 1H), 3.38 (d, J = 15.1 Hz, 1H), 2.69 (ddd, J = 6.9, 10.5, 18.3 Hz, 1H), 2.58 (ddd, J = 6.4, 10.5, 18.3 Hz, 1H), 2.31 (ddd, J = 6.9, 10.5, 13.7 Hz, 1H), 2.13 (ddd, J = 7.8, 10.5, 13.3 Hz, 1H), 1.89 (dd, J = 6.0, 14.2 Hz, 1H), 1.81 (sept, J = 6.4 Hz, 1H), 1.72 (dd, J = 6.4, 14.2 Hz, 1H), 1.01 (d, J = 6.4 Hz, 3H), 0.98 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 86.1, 47.1, 32.4, 29.1, 24.4, 24.2, 23.9, 13.1; HRMS (EI) calcd for $C_9H_{15}O_2I^+$ $[M]^+$ 282.0117, found 282.0114. The ee was determined by HPLC analysis (Daicel Chiralpack AD-H column, hexane–EtOH = 9:1, flow rate = 1.0 mL/min) t_R= 11.0 (major enantiomer), 11.7 (minor enantiomer) min.

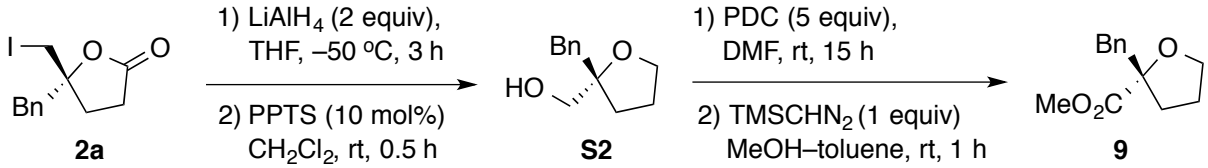


5-(Iodomethyl)-5-phenyldihydrofuran-2(3*H*)-one (2k):[5] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.31 (m, 5H), 3.65 (d, J = 10.9 Hz, 1H), 3.61 (d, J = 10.9 Hz, 1H), 2.84–2.44 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 140.7, 128.9 (2C), 128.7 (2C), 125.0, 86.1, 34.0, 29.3, 16.6. The ee was determined by HPLC analysis (Daicel Chiralpack AD-H column, hexane–*i*-PrOH = 98:2, flow rate = 1.0 mL/min) t_R= 22.9, 26.7 min.



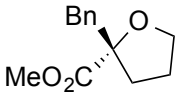
(*R*)-5-(Iodomethyl)-5-octyldihydrofuran-2(3*H*)-onee (2l): Colorless oil; IR (neat) 1773, 1465, 1415, 1330, 1249, 1158 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.40 (d, J = 11.0 Hz, 1H), 3.38 (d, J = 11.10 Hz, 1H), 2.76–2.54 (m, 2H) 2.26 (ddd, J = 6.4, 10.5, 13.7 Hz, 1H), 2.15 (ddd, J = 6.9, 11.0, 13.7 Hz, 1H), 1.94–1.75 (m, 12 H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 85.8, 38.8, 31.7, 31.2, 29.5, 29.32, 29.26, 29.1, 23.4, 22.6, 14.0, 13.3; HRMS (EI) calcd for $C_{13}H_{23}O_2I^+$ $[M]^+$ 338.0743, found 338.0750. The ee was determined by HPLC analysis (Daicel Chiralpack AD-H column, hexane–EtOH = 9:1, flow rate = 1.0 mL/min) t_R= 8.0 (minor enantiomer), 9.0 (major enantiomer) min.

Transformations of Chiral Iodolactones 2.

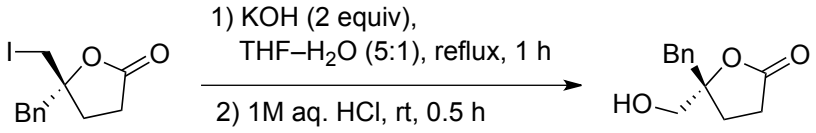


To a solution of **2a** (31 mg, 0.1 mmol, 93% ee) in THF (1 mL) was added $LiAlH_4$ (7 mg, 0.2 mmol) at –50 °C, and the reaction mixture was stirred at –50 °C for 3 h. The reaction mixture was quenched with saturated aqueous H_2O (3.0 mL) and extracted with AcOEt (5.0 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–AcOEt 1:1) to give the corresponding epoxy alcohol (19 mg). To a solution of the epoxy alcohol (19 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) was added PPTS (3 mg, 0.1 mmol) at ambient temperature. The mixture was stirred at ambient temperature for 0.5 h. The reaction mixture was quenched

with saturated aqueous H_2O (3.0 mL) and extracted with AcOEt (5.0 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–AcOEt 3:1) to give **S2** (20 mg). To a solution of **S2** (19 mg, 0.1 mmol) in DMF (1 mL) was added PDC (188 mg, 0.5 mmol) at ambient temperature. The mixture was stirred at ambient temperature for 15 h. The reaction mixture was quenched with saturated aqueous H_2O (3.0 mL) and extracted with AcOEt (5.0 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. To a solution of the residue in MeOH (1 mL) and toluene (1 mL) was added 2M solution of $TMSCHN_2$ in Et_2O (0.1 mL, 0.2 mmol) at ambient temperature. The mixture was stirred at ambient temperature for 1 h. The reaction mixture was quenched with saturated aqueous H_2O (3.0 mL) and extracted with AcOEt (5.0 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–AcOEt 2:1) to give **9** (17 mg, 82% yield, 93% ee).



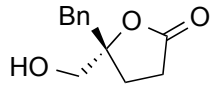
(*S*)-Methyl 2-Benzyltetrahydrofuran-2-carboxylate (9): Colorless oil; $[\alpha]^{20}_D$ 21.2 (*c* 0.5, $CHCl_3$) for 93% ee; IR (neat) 1733, 1216 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.18 (m, 5H), 3.96–3.85 (m, 2H), 3.68 (s, 3H), 3.20 (d, *J* = 13.7 Hz, 1H), 2.99 (d, *J* = 13.7 Hz, 1H), 2.27 (ddd, *J* = 5.3, 8.2, 12.8 Hz, 1H), 1.92 (ddd, *J* = 7.8, 8.7, 13.3 Hz, 1H), 1.88–1.75 (m, 1H), 1.73–1.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 136.4, 130.4 (2C), 128.2 (2C), 126.8, 86.9, 69.3, 52.3, 43.5, 34.7, 25.4; HRMS (EI) calcd for $C_{13}H_{16}O_3^+$ $[M]^+$ 220.1099, found 220.1098. The ee was determined by HPLC analysis (Daicel Chiralpack AD-H column, hexane–*i*-PrOH = 400:1, flow rate = 1.0 mL/min) t_R= 29.7 (minor enantiomer), 50.9 (major enantiomer) min.



2a **10**

To a solution of **2a** (31 mg, 0.1 mmol, 93% ee) in THF (1 mL) and H_2O (0.2 mL) was added KOH (28 mg, 0.5 mmol) at 0 °C. The mixture was heated to reflux for 1 h. To a reaction mixture was added 1 M HCl (1 mL) at ambient temperature and stirred at ambient

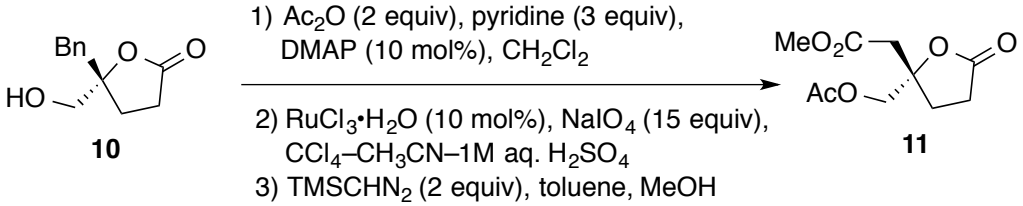
temperature for 0.5 h. The reaction mixture was quenched with saturated aqueous H_2O (3.0 mL) and extracted with AcOEt (5.0 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–AcOEt 2:1) to give **10** (21 mg, 99% yield, 93% ee).



(*S*)-5-Benzyl-5-(hydroxymethyl)dihydrofuran-2(3H)-one (10):[6]

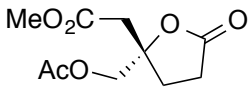
Colorless oil; $[\alpha]^{25}_D$ 60.0 (*c* 1.0, $CHCl_3$) for 93% ee [lit.[6] $[\alpha]^{23}_D$ 62.8 (c 3.0, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.19 (m, 5H), 3.76 (d, *J* = 12.4 Hz, 1H), 3.60 (d, *J* = 12.4 Hz, 1H), 3.05 (d, *J* = 13.7 Hz, 1H), 2.84 (d, *J* = 13.7 Hz, 1H), 2.46 (ddd, *J* = 5.0, 10.5, 16.9 Hz, 1H), 2.22 (ddd, *J* = 7.3, 10.1, 12.8 Hz, 1H), 2.13–2.01 (m 1H), 1.96 (ddd, *J* = 6.9, 10.5, 17.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 134.7, 130.4 (2C), 128.6 (2C), 127.1, 88.4, 67.5, 41.9, 29.3, 26.6. The ee was determined by HPLC analysis (Daicel Chiralpack AD-H column, hexane–EtOH = 9:1, flow rate = 1.0 mL/min) t_R= 20.7 (minor enantiomer), 27.9 (major enantiomer) min.

The absolute stereochemistry of the major enantiomer of **10** was determined to be *R* by the comparison of the optical rotation. Thus, the absolute stereochemistry of the major enantiomer of **10** was also determined to be *R*.



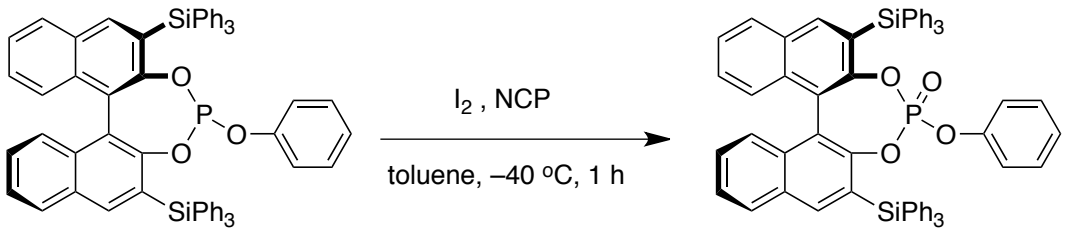
To a solution of **10** (50 mg, 0.24 mmol, 93% ee), pyridine (58 μL, 0.72 mmol) and DMAP (2 mg, 0.02 mmol) in CH_2Cl_2 (1 mL) was added Ac_2O (45 μL, 0.5 mmol) at 0 °C. After stirring for 2 h at ambient temperature, the reaction was quenched with concentrated aqueous HCl. The mixture was extracted with AcOEt. The organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 5:1) to give the corresponding acetate as pale yellow oil (59 mg, >99% yield). To a solution of $NaIO_4$ (321 mg, 1.5 mmol), in 1 M H_2SO_4 (0.3 mL) was added the acetate (25 mg, 0.1 mmol) in CCl_4 (0.3 mL) and CH_3CN (0.3 mL)

and $RuCl_3 \cdot H_2O$ (2 mg, 0.01 mmol) in H_2O (20 μL) at ambient temperature. After stirring for 36 h at ambient temperature, the reaction was quenched with concentrated aqueous HCl. The mixture was extracted with AcOEt. The organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. To a solution of the residue in MeOH (0.5 mL) and toluene (0.5 mL) was added 2 M solution of $TMSCHN_2$ in Et_2O (0.1 mL, 0.2 mmol) at ambient temperature. The mixture was stirred at ambient temperature for 1 h. The reaction mixture was quenched with saturated aqueous H_2O (3.0 mL) and extracted with AcOEt (5.0 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–AcOEt 3:1) to give **11** as colorless oil (21 mg, 91% yield).



(*S*)-Methyl 2-(2-(Acetoxymethyl)-5-oxotetrahydrofuran-2-yl)acetate (**11**) Colorless oil; $[\alpha]^{25}_D$ 16.5 (*c* 0.5, $CHCl_3$) for 93% ee; IR (neat) 1782, 1736, 1439, 1367, 1229 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.23 (d, *J* = 11.9 Hz, 1H), 4.19 (d, *J* = 11.9 Hz, 1H), 2.82 (s, 2H), 2.77–2.61 (m, *2*H), 2.39 (ddd, *J* = 7.8, 10.5, 13.3 Hz, 1H), 2.25 (ddd, *J* = 7.3, 10.7, 13.3 Hz, 1H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 170.2, 169.2, 82.8, 67.9, 52.1, 40.4, 28.7, 28.3, 20.7; HRMS (EI) calcd for $C_{10}H_{15}O_6^+$ $[M+H]^+$ 231.0869, found 231.0864. The ee was determined by HPLC analysis (Daicel Chiralpack AD-H column, hexane–EtOH = 9:1, flow rate = 1.0 mL/min) t_R= 26.1 (minor enantiomer), 39.6 (major enantiomer) min.

^{31}P NMR Study for Oxidation of Catalyst 3 with I_2 and NCP.

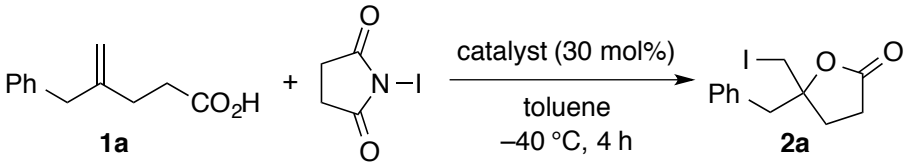


3
^{31}P NMR : 148.1 ppm

4a
^{31}P NMR : –7.6 ppm

To a solution of **3** (5 mg, 0.005 mmol) in toluene (1 mL) were added NCP (27 mg, 0.15 mmol) and I_2 (12 mg, 0.05 mmol) successively at –40 °C, and the mixture was stirred at –40 °C for 1 h. ^{31}P NMR analysis of the reaction mixture showed that the signal for **3** (148.1 ppm) completely disappeared and, instead, a new peak (–7.6 ppm, which was identical to **4a**) appeared.

Catalytic Activities of Tertiary Amines in the Iodolactonization.[a]

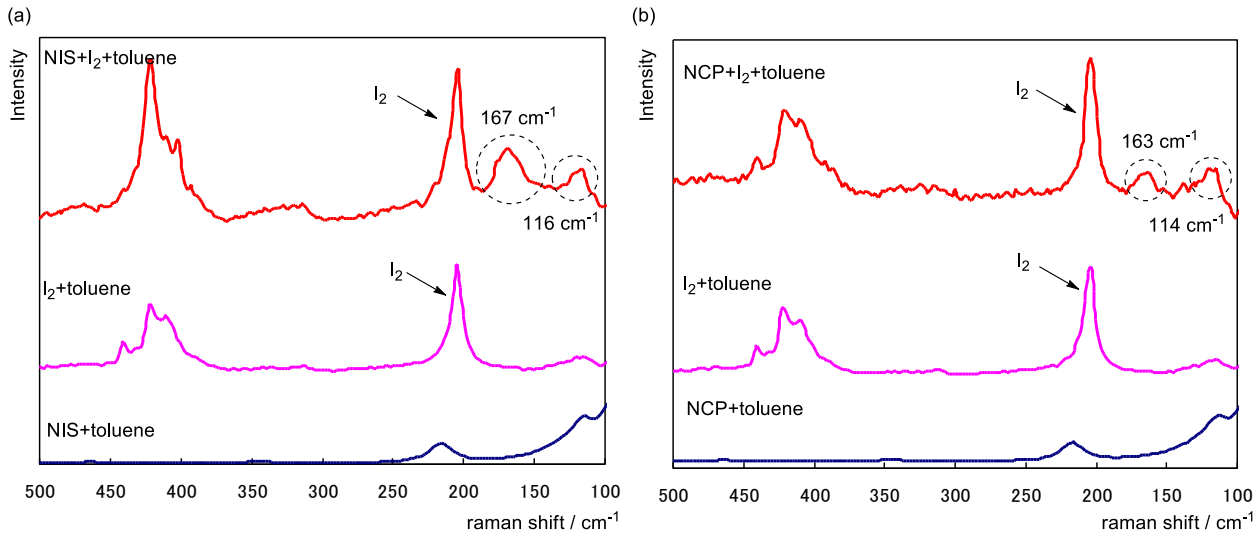


entry	catalyst	yield (%)
1	Et_3N	36
2	quinuclidine	22
3	DMAP	15
4	Bu_4NOH	35

[a] The reaction of **1a** (0.1 mmol) was conducted with NIS (1.1 equiv) in the presence of a catalyst (30 mol%) in toluene (1 mL) at –40 °C for 4 h.

Raman Spectra Experiment of a Mixture of Halogenateing Reagent (NIS or NCP) and I_2

To a solution of NIS or NCP (0.2 mmol) in toluene (2 mL) were added I_2 (48 mg, 0.2 mmol) successively at ambient temperature and stirred for 1 h. The mixture was measured by Raman spectra using a Renishaw inVia Raman microscope (Figure 1). The new bands were detected at 116, 167 cm^{-1} (in the case of NIS, I_2 and toluene) and 114, 163 cm^{-1} (in the case of NCP, I_2 and toluene). The bands at 116 and 114 cm^{-1} might be the I–I–I(Cl) bend according to previous reports[8]. These results suggest that NIS or NCP interacted with I_2 to form active species such as **5**.



(a) Spectra of a mixture of I_2 and NIS. (b) Spectra of a mixture of I_2 and NCP.

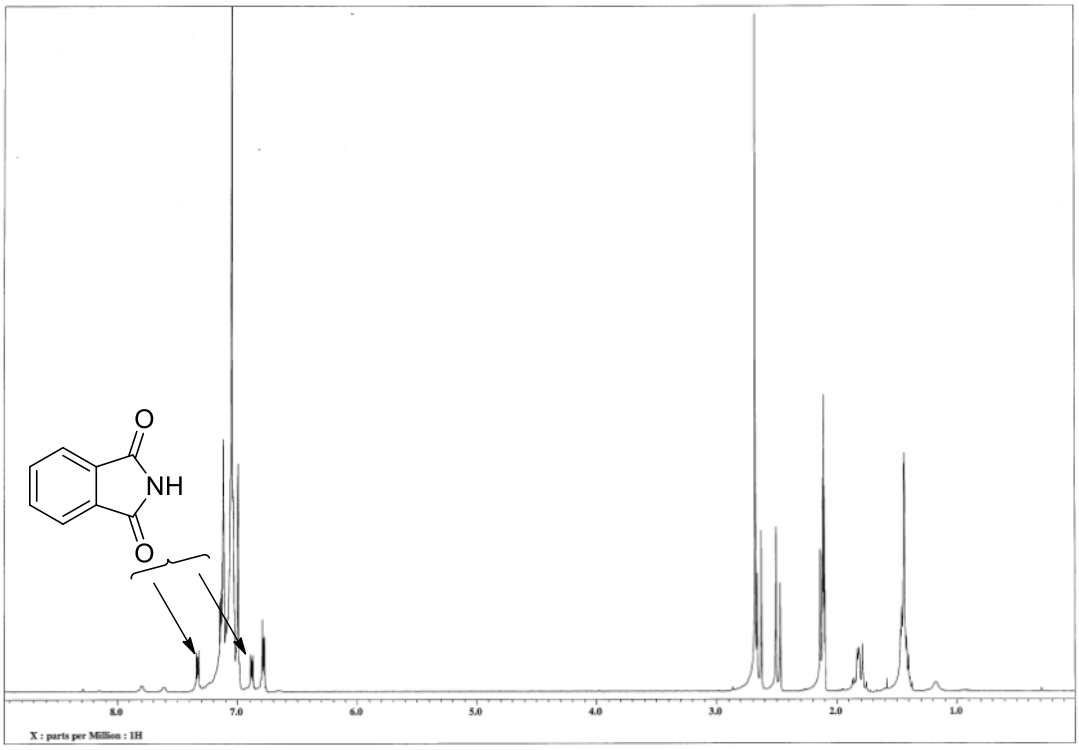
Reported Data of Raman Spectra of I_3^+ Cation[8]

$I_3^+AsF_6^-$	$I_3^+HSO_4^-$
211 cm^{-1} (asym str)	233 cm^{-1} (asym str)
205 cm^{-1} (sym str)	207 cm^{-1} (sym str)
110 cm^{-1} (bend)	114 cm^{-1} (bend)

^{1}H NMR Study for Generation of Phthalimide Under the Reaction Conditions

To a solution of **4c** (2.5 mg, 2.5 μmol) in toluene-d_8 (0.5 mL) were added NCP (13 mg, 0.075 mmol) and I_2 (6 mg, 0.025 mmol) successively at –40 °C, and the mixture was stirred at –40 °C for 1 h. To the mixture was added 4-pentenoic acid **1** (0.05 mmol) dropwise at –78 °C, and the reaction mixture was stirred at –78 °C for 6 h. The reaction mixture was measured by ^{1}H NMR at –80 °C. Signals of phthalimide [7.33 (dd, J = 3.2, 5.5 Hz, 2H), 6.88 (dd, J = 3.2, 5.5 Hz, 2H)] were detected.

^{1}H NMR Spectra of the Reaction Mixture in Toluene-d_8



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Research Achievement

Publications

1. Yasuhiro Sawamura, Hidefumi Nakatsuji, Akira Sakakura and Kazuaki Ishihara
   ""Phosphite-urea" cooperative high-turnover catalysts for the highly selective bromocyclization of homogeranylarenes"
   Chem. Sci. **2013**, *4*, 4181–4186.

2. Yasuhiro Sawamura, Hidefumi Nakatsuji, Matsujiro Akakura, Akira Sakakura and Kazuaki Ishihara
   "Selective Bromocyclization of 2-Geranylphenols Promoted by Phosphite–Urea Cooperative Catalysts"
   Chirality, **2014**, *26*, 356–360.

3. Hidefumi Nakatsuji, Yasuhiro Sawamura, Akira Sakakura and Kazuaki Ishihara
   "Cooperative Activation with Chiral Nucleophilic Catalysts and *N*-Haloimides on Enantioselective Iodolactoniaztion of 4-Arylmethyl-4-pentenoic Acids"
   Angew. Chem. Int. Ed. **2014,** *53*, 6974–6977.

International Conferences

Poster Presentations

1. ○Hidefumi Nakatsuji, Yasuhiro Sawamura, Akira Sakakura, Kazuaki Ishihara
   "Development of Chiral Nucleophilic Phosphite Catalysts for Enantioselective Iodolactonization"
   Nagoya Symposium 2013、P-28、名古屋、平成 25 年 5 月、査読有

2. ○Yasuhiro Sawamura, Hidefumi Nakatsuji, Akira Sakakura, Kazuaki Ishihara
   "Phosphite-Urea Cooperative Catalysts for Biomimetic Bromocyclization of Polyprenoids"
   IGER International Symposium on Chemical Science in Asia、P-5、名古屋、平成 26 年 5 月、査読有

Domestic Conferences

Oral Presentations

1. ○澤村　泰弘・仲辻　秀文・坂倉　彰・石原　一彰
   「ポリプレノイドのバイオミメティックハロ環化反応に有効な高活性求核触媒の設計」
   日本化学会第 91 春季年会、1C1-04、神奈川、平成 23 年 3 月、査読有

2. ○澤村　泰弘・仲辻　秀文・坂倉　彰・石原　一彰
「ポリプレノイドの不斉ブロモポリエン環化反応に有効なキラル求核性リン(III)触媒の設計」
日本化学会第 92 春季年会、1K7-02、神奈川、平成 24 年 3 月、査読有

3. ○仲辻　秀文・澤村　泰弘・坂倉　彰・石原　一彰
「エナンチオ選択的ヨードラクトン化反応に有効なキラル求核性リン(III)触媒システムの開発」
日本化学会第 92 春季年会、1K7-01、神奈川、平成 24 年 3 月、査読有

4. ○澤村　泰弘・仲辻　秀文・坂倉　彰・石原　一彰
「求核性亜リン酸エステル(III)触媒を用いるポリプレノイドの選択的ブロモポリエン環化反応」
日本化学会第 93 春季年会、2E5-05、滋賀、平成 25 年 3 月、査読有

5. ○仲辻　秀文・澤村　泰弘・坂倉　彰・石原　一彰
「エナンチオ選択的ヨードラクトン化反応に有効な求核性キラル亜リン酸エステル触媒の開発」
日本化学会第 93 春季年会、2E5-04、滋賀、平成 25 年 3 月、査読有

6. ○仲辻　秀文・澤村　泰弘・坂倉　彰・石原　一彰
「エナンチオ選択的ヨードラクトン化反応に有効な求核性キラル亜リン酸エステル触媒の開発」
第 103 回有機合成シンポジウム、2-11、東京、平成 25 年 6 月、査読有

7. ○澤村　泰弘・仲辻　秀文・坂倉　彰・石原　一彰
「求核性亜リン酸トリエステル(III)触媒を用いるポリプレノイドの選択的ブロモポリエン環化反応」
第 44 回中部化学関係学協会支部連合秋季大会、1A-03、静岡、平成 25 年 11 月、査読有

8. ○石原　一彰・澤村　泰弘・仲辻　秀文・坂倉　彰
「含フッ素亜リン酸エステル触媒を用いる位置及び立体選択的ブロモポリエン環化反応」
フルオラス科学研究会第 6 回シンポジウム、岡山、平成 25 年 11 月

9. ○澤村　泰弘・仲辻　秀文・坂倉　彰・石原　一彰
「亜リン酸トリエステル(III)–尿素協奏触媒を用いる 2-ゲラニルフェノールの選択的ブロモポリエン環化反応」
日本化学会第 94 春季年会、1B8-38、名古屋、平成 26 年 3 月、査読有

10. ○仲辻　秀文・澤村　泰弘・坂倉　彰・石原　一彰
「求核性キラルリン酸エステル触媒を用いるエナンチオ選択的ヨードラクトン化反応」
日本化学会第 94 春季年会、1B8-37、名古屋、平成 26 年 3 月、査読有

11. ○澤村　泰弘・仲辻　秀文・坂倉　彰・石原　一彰
「亜リン酸トリエステルー尿素協奏触媒を用いる 2-ゲラニルフェノールのエナンチオ選択的ブロモポリエン環化反応」
日本化学会第 95 春季年会、2E3-15、千葉、平成 27 年 3 月発表予定、査読有

Poster Presentations

1. ○仲辻　秀文・澤村　泰弘・坂倉　彰・石原　一彰
「エナンチオ選択的ヨードラクトン化反応に有効なキラル求核性リン(III)触媒システムの開発」
第 47 回天然物化学談話会、熊本、平成 24 年 7 月、査読無

2. ○澤村　泰弘・仲辻　秀文・坂倉　彰・石原　一彰
「ポリプレノイドの不斉ブロモポリエン環化反応に有効なキラル求核生リン(III)触媒の設計」
第 47 回有機反応若手の会、P-04、岡山、平成 24 年 8 月、査読無

3. ○澤村　泰弘・仲辻　秀文・坂倉　彰・石原　一彰
「求核性亜リン酸エステル(III)触媒を用いるポリプレノイドの選択的ブロモポリエン環化反応」
第 5 回臭素化学懇話会年会、P-46、岡山、平成 24 年 11 月、査読有

4. ○澤村　泰弘・仲辻　秀文・坂倉　彰・石原　一彰
“Design of Nucleophilic Phosphite(III) Catalysts for Selective Bromocyclization of Polyprenoids”
IGER annual meeting 2012、G-3、名古屋、平成 25 年 1 月、査読無

5. ○仲辻　秀文・澤村　泰弘・坂倉　彰・石原　一彰
「エナンチオ選択的ヨードラクトン化反応に有効なキラルリン求核触媒の開発」
第 30 回有機合成化学セミナー、岡山、平成 25 年 9 月、査読有

6. ○石原　一彰・澤村　泰弘・仲辻　秀文・坂倉　彰
「ブロモポリエン環化反応に有効な高活性酸塩基複合触媒の開発」
戦略的創造研究推進事業　戦略目的「プロセスインテグレーションによる次世代ナノシステムの創製」３領域合同公開シンポジウム、C-4、東京、平成 25 年 10 月

7. ○澤村　泰弘・仲辻　秀文・坂倉　彰・石原　一彰
“Phosphite(III)-Urea Cooperative Catalysis for Selective Bromocyclization of 2-Geranylphenols”
IGER annual meeting 2013、G-17、名古屋、平成 26 年 1 月、査読無

8. ○澤村　泰弘・仲辻　秀文・坂倉　彰・石原　一彰
「亜リン酸トリエステル(III)–尿素協奏触媒を用いるポリプレノイドの選択的ブロモポリエン環化反応」
創薬懇話会、P-27、岐阜、平成 26 年 7 月、査読有

9. ○澤村　泰弘・仲辻　秀文・坂倉　彰・石原　一彰
“Phosphite(III)–Urea Cooperative Catalysis for Selective Bromocyclization of 2-Geranylphenols”
IGER annual meeting 2014、G-46、名古屋、平成 26 年 12 月、査読無

Awards

1. 日本化学会東海支部長賞(日本化学会、平成 24 年 3 月)

2. ポスター賞（第 5 回臭素化学懇話会年会、平成 24 年 11 月）

3. VIP 賞（第 44 回中部化学関係学協会支部連合秋季大会、平成 25 年 11 月）

4. 優秀ポスター賞（創薬懇話会 2014 in 岐阜、平成 26 年 7 月）

5. ベストディスカッション賞（創薬懇話会 2014 in 岐阜、平成 26 年 7 月）

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