Design of Chiral Brønsted Acid Catalysts for Proton-Induced Enantioselective Reactions and Development of Catalytic Dehydrative Condensation of Phosphoric Acid with Alcohols

Masayuki Sakuma

Graduate School of Engineering, Nagoya University

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Chapter 1

Introduction and General Summary

1–1 Design of Chiral Lewis Base-Assisted Brønsted Acids (Chiral LBBAs)

Protons (H^+) are the simplest and most versatile catalysts for organic reactions, and mediate an extraordinary range of biological and synthetic transformations.[1] Although protons can not be rendered chiral, enantioselective Brønsted acid catalysis can be achieved through the influence of the conjugate base and through the application of a coordination complex. With respect to asymmetric catalysis, a variety of useful chiral Brønsted acids have been designed and developed; for example, chiral phosphoric acids,[2] *N*-triflyl phosphoramides,[3] aryl sulfonic acids,[4] bis(amidine)-based protic acid salts,[5] and Lewis acid-[6] or thiourea-assisted Brønsted acids[7] (Figure 1.1).

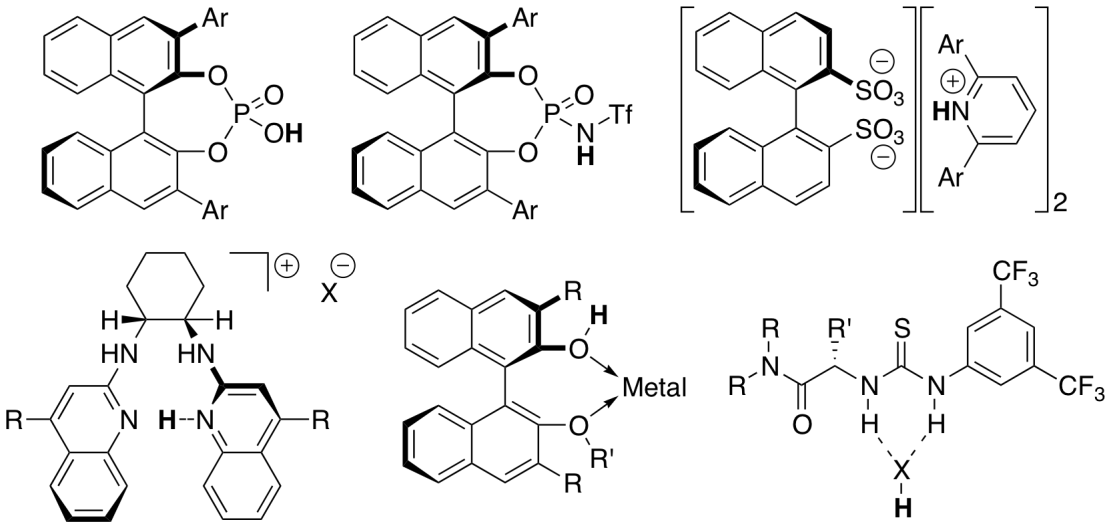
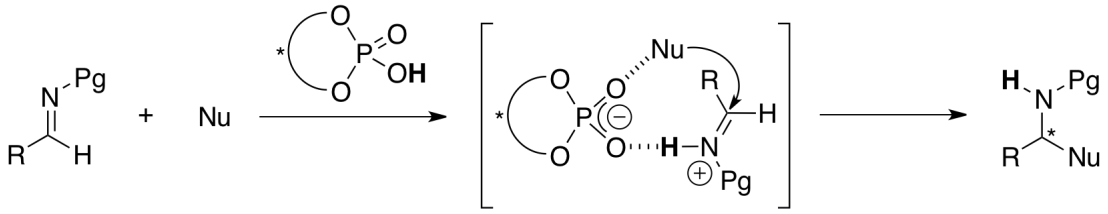


Figure 1.1. Examples of chiral Brønsted acids.

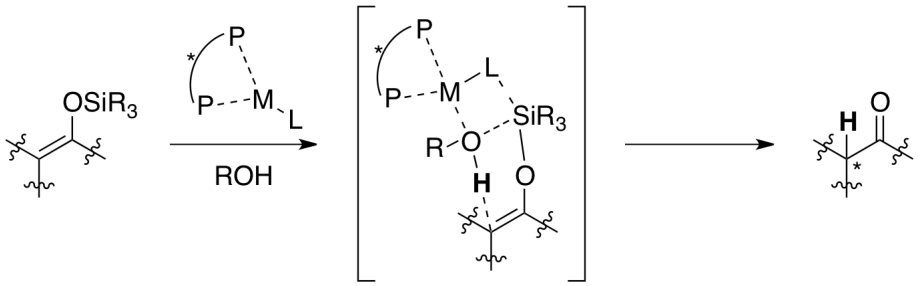
A representative approach, which involves the use of chiral Brønsted acids, generally employs hydrogen-bonding interaction between a protonated substrate and the chiral conjugate base of the chiral Brønsted acid (Scheme 1.1).[2d] This hydrogen bonding serves as a linker to keep the chiral information close to the reactive electrophile, and also contributes to a molecular organization that favors one particular diastereomeric transition state. Although several structurally diverse strong Brønsted acid catalysts have been developed, the highly enantioselective reactions that have been reported to date are restricted to the activation of electrophilic carbon–heteroatom or heteroatom–heteroatom multiple bonds, usually imines or carbonyls.

Scheme 1.1. Asymmetric Reaction Induced by the Conjugate Base of a Chiral Brønsted Acid



Another strategy usually involves the application of a coordination complex, which can provide chiral protons. For example, a chiral Brønsted acid can be generated by the complexation of an achiral protic solvent with a Lewis acid that includes a chiral ligand, which significantly enhances the acidity of the original proton source (Scheme 1.2).[8] This approach leads to the generation of chiral protons with a variety of structures and acidities through the combination of a protic reagent and an activating species for asymmetric reactions. Although several coordination complexes can give strong Brønsted acids, they require the use of expensive transition metals or strong Lewis acids, which limits the range of suitable substrates.

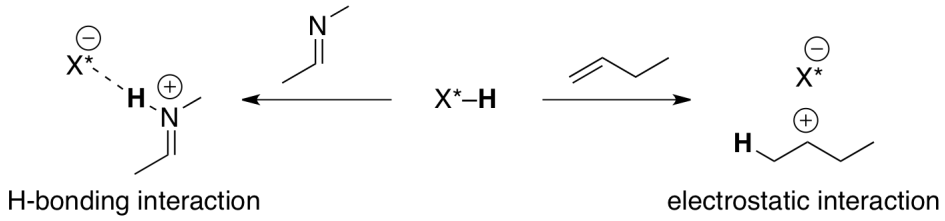
Scheme 1.2. Asymmetric Reaction through the Application of a Coordination Complex



Although the chiral Brønsted acid catalyses that have been developed thus far are remarkably effective for activating polarized functional groups, it is not clear whether Brønsted acids can catalyze the highly enantioselective transformation of nonpolarized carbon–carbon multiple bonds. The active intermediates generated in the protonation of nonpolarized multiple bonds are different from those generated in the protonation of polarized multiple bonds (Scheme 1.3). The protonation of an imine or carbonyl generates a species that can create a hydrogen-bonding interaction with the conjugate base of a chiral Brønsted

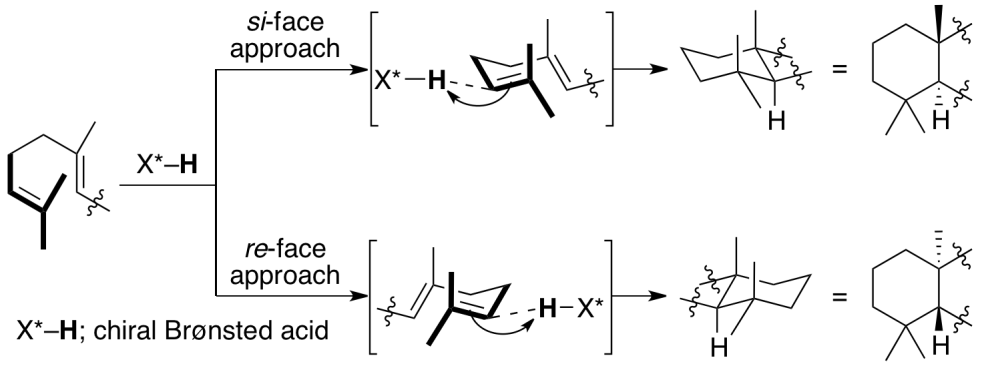
acid, as shown above. On the other hand, the protonation of a simple alkene leads to a carbocation. Although the conjugate base of the chiral acid can still be placed in proximity to the carbocation through electrostatic interactions, the lack of rigidity in this association presumably results in poor recognition between the enantiotopic faces of the carbocation. Therefore, it is difficult to achieve the desired enantioselective reaction of alkenes catalyzed by chiral Brønsted acids.

Scheme 1.3. Protonation of an Imine or an Alkene



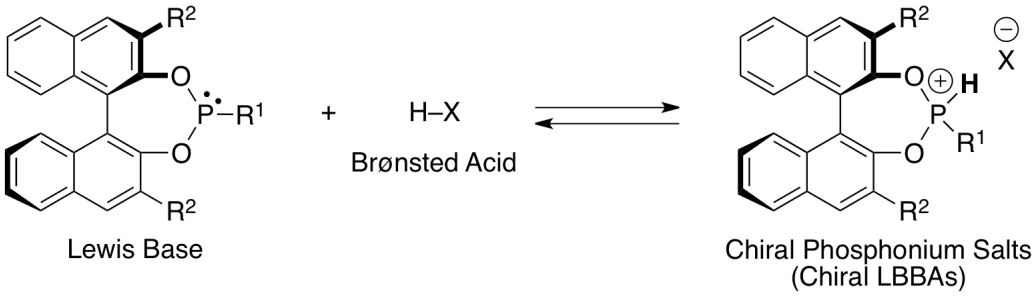
Many complicated natural products have been synthesized based on significant advances in organic chemistry.[9] However, it is not easy to synthesize optically active natural products, which are needed for both pharmacological and biological applications. Therefore, asymmetric synthesis is still one of the most important subjects in organic chemistry. Although several enzyme-induced enantioface-selective reactions of prochiral alkenyl compounds are known in biosynthetic chemistry,[10] a chiral Brønsted acid with suitable acidity, like an enzyme, is not easily available. In addition, stereoselective generation of the carbocation is highly important in asymmetric carbon–carbon bond formations, since the absolute and relative stereochemistries of the structure can be determined in that step with control over the conformation of the substrate.[11] Therefore, this thesis focuses on the development of a newly designed chiral Brønsted acid for the highly enantioselective transformations of unactivated carbon–carbon multiple bonds. In particular, asymmetric induction in the protonation of an isoprenyl group would provide optically active isoprenoid derivatives through biomimetic cyclization (Scheme 1.4).

Scheme 1.4. Recognition of an Enantioface of an Isoprenyl Group



In this thesis, the author designed Lewis base-assisted Brønsted acids (LBBAs), phosphonium salts,[12] which were prepared from a chiral phosphorus(III) compound with an achiral Brønsted acid (HX) (Scheme 1.5).[13] The chiral phosphorus(III) compound as a Lewis base could coordinate to the proton of the achiral Brønsted acid, to provide phosphonium salts. Since the active proton of that phosphonium salt is surrounded by the chiral environment of the chiral phosphorus(III) compound, the author envisioned that this catalytic system might facilitate a highly enantioselective transformation. Notably, the Brønsted acidity of chiral LBBAs should strongly depend on the structure of the chiral phosphorus(III) compound. Therefore, chiral LBBAs with suitable acidity should appropriately control asymmetric induction in the protonation of the isoprenyl group through the biomimetic cyclization of simple isoprenoids.

Scheme 1.5. Design of Chiral Lewis Base-Assisted Brønsted Acids (Chiral LBBAs)

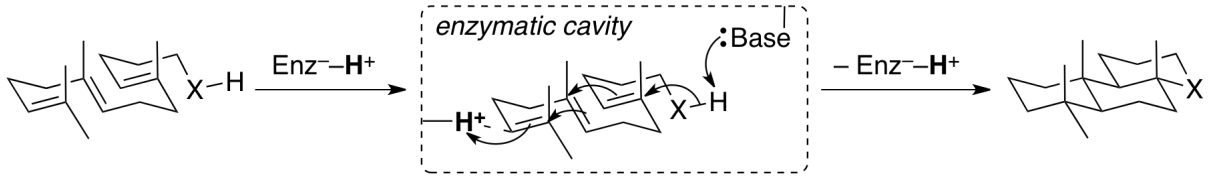


Chapters 2 and 3 describe chiral LBBA-catalyzed asymmetric protocyclization reactions accompanied by the recognition of an enantioface of a terminal isoprenyl group.

1–2 Chiral Lewis Base-Assisted Brønsted Acid (LBBA)-Catalyzed Enantioselective Cyclization of 2-Geranylphenols

Terpenoids are metabolite products that are commonly found in nature and have a variety of biological activities. According to the Stork-Eschenmoser hypothesis, many polycyclic isoprenoids are biosynthesized via cationic polyene cyclization, which is considered to one of the most complex carbon-carbon bond-forming reactions in nature.[14] The complicated polycyclic structures of isoprenoids, which have many chiral centers including quaternary carbons, are stereoselectively constructed by cyclase in a single step (Scheme 1.6).[10a,15]

Scheme 1.6. Enzymatic Polyene Cyclization



Optically active polycyclic compounds have a broad range of useful properties, which makes them valuable for industrial and pharmacological applications. For example, (–)-Ambrox® has a strong amber-like aroma. It is used in place of one of the constituents of ambergris, which is a metabolic product found in the gut of sperm whale.[16] Some marine natural secondary metabolites, such as (–)-chromazonarol,[17] 8-*epi*-(+)-puupehedione,[18] and their derivatives, are also known to show a wide range of potent biological activities, including cytotoxic, antiviral, antifungal, and immunomodulatory properties (Figure 1.2).[19]

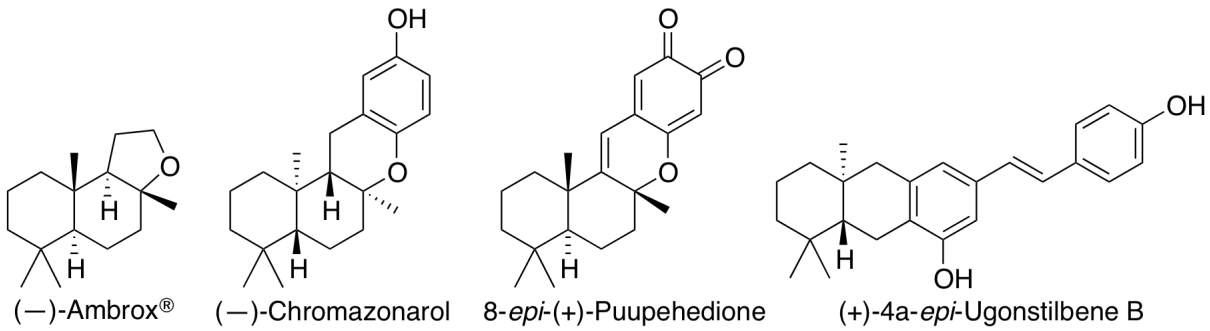
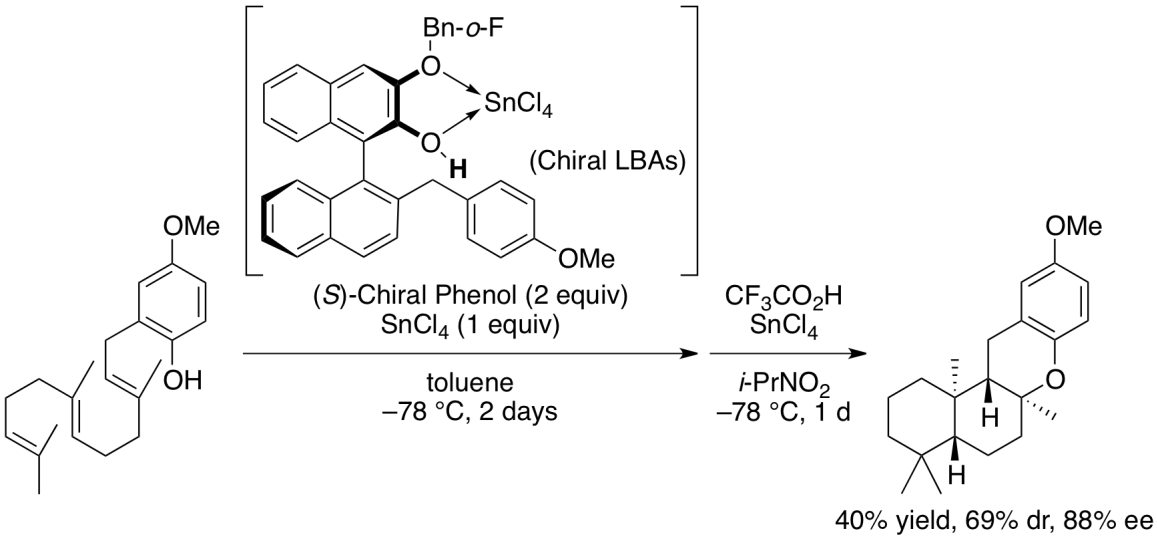


Figure 1.2. Optically active polycyclic compounds.

The stereoselective formation of polycyclic isoprenoids by the enzyme-catalyzed cyclization of polyprenoids is one of the most remarkable steps in biosynthesis because this reaction results in the formation of several new quaternary and tertiary stereocenters and new rings in a single step. The use of biomimetic cyclization with artificial cyclase is the most ideal chemical method for the synthesis of these polycyclic isoprenoids. Several studies on the synthesis of a multiply cyclized structure via non-enzymatic polyene cyclization have been reported.[20] However, these methods generally show low reactivity and low stereoselectivity since it is difficult to recognize the enantioface of a simple olefin and regioselectively generate a carbocation through the protonation of polyprenoids. In addition, despite extensive studies on asymmetric polyene cyclizations, catalytic promotion of the enantioselective processes remains challenging.

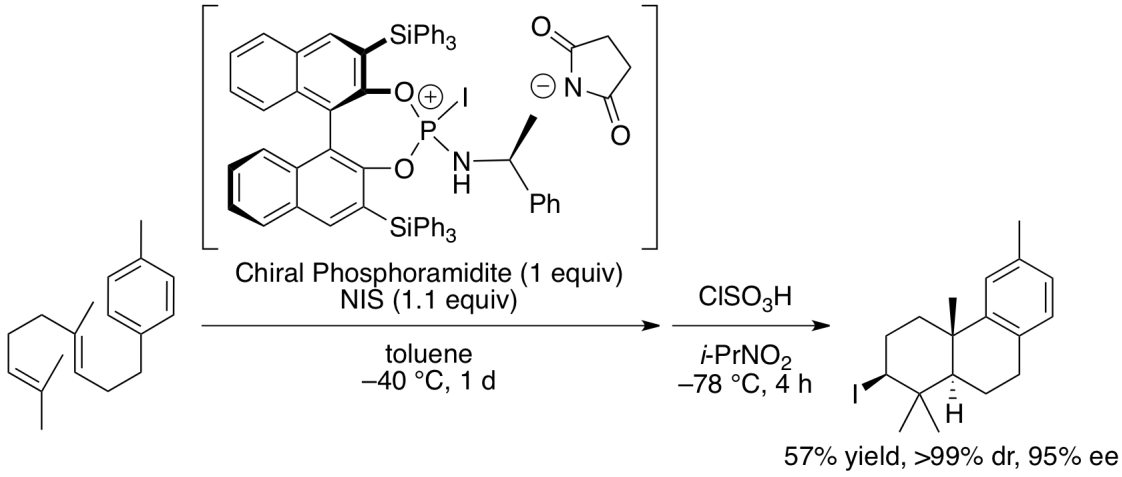
Our group previously overcame these difficulties with a Lewis acid-assisted chiral Brønsted acid (LBA) system.[5a] The coordination of a Lewis acid to a Brønsted acid restricts directional access of a substrate to the proton and increases the Brønsted acidity. When LBAs are prepared from chiral Brønsted acids, the active protons are placed in chiral environments. Therefore, chiral LBAs are highly effective chiral proton donors for enantioselective protonation[21] and enantioselective polyene cyclization (Scheme 1.7).[22] Although the enantioselective cyclization of polyprenoids induced by stoichiometric amounts of chiral LBAs has already been developed, its catalytic version is still challenging.[23]

Scheme 1.7. Enantioselective Polyene Cyclization Induced by Chiral LBAs



Our group has also developed a chiral Lewis base-promoted enantioselective iodocyclization of isoprenoids (Scheme 1.8).[24] The chiral nucleophilic phosphoramidite reacts with *N*-iodosuccinimide (NIS) to generate the corresponding phosphonium salt as an active species.

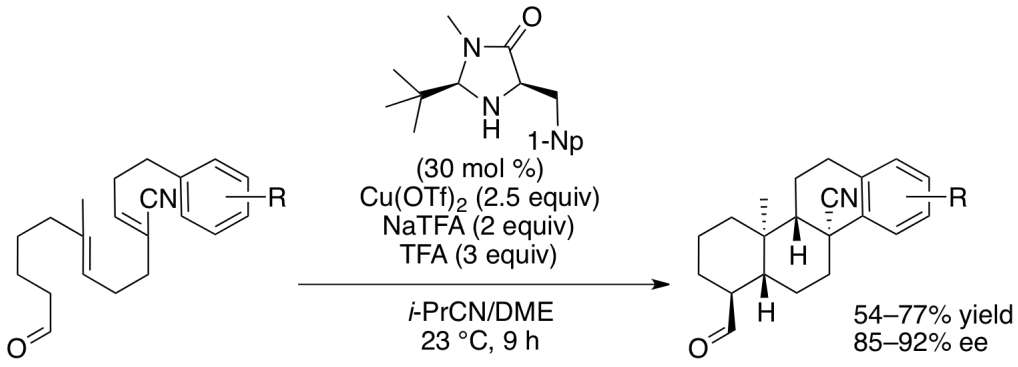
Scheme 1.8. Enantioselective Iodocyclization Induced by Chiral Phosphoramidite



Since the pioneering work on chiral LBAs, some elegant studies on enantioselective polyene cyclizations have been reported.[25] For example, MacMillan's group reported the first catalytic enantioselective cyclization strategy for accessing steroidal and terpenoidal frameworks using organocatalysis.[25d] This strategy represents an ambient-temperature

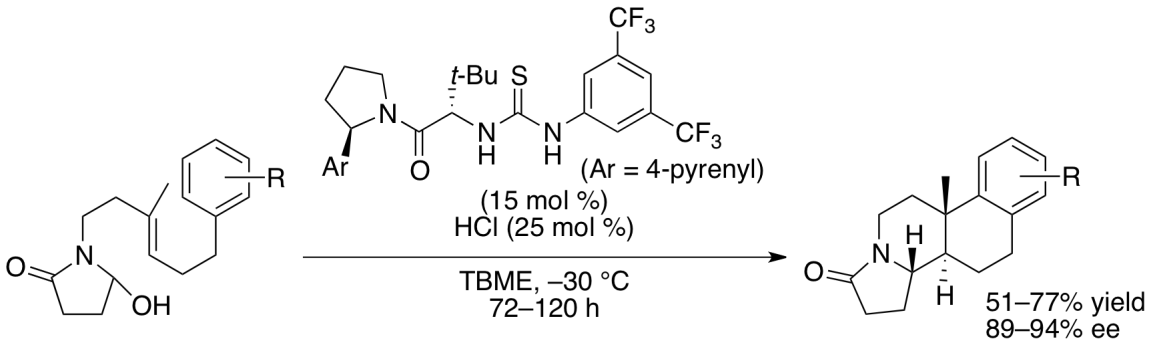
protocol, which is unprecedented in SOMO activation catalysis with respect to carbon-carbon bond formation (Scheme 1.9).

Scheme 1.9. Enantioselective Polyene Cyclization via Organo-SOMO Catalysis



Furthermore, Jacobsen's group reported the development of a new thiourea catalyst for the enantioselective bicyclization of hydroxylactams.[25c] The enantioselective cationic polycyclization reactions catalyzed by bifunctional thiourea derivatives appear to engage stabilizing cation-π interactions as a principal element of enantioselectivity (Scheme 1.10).

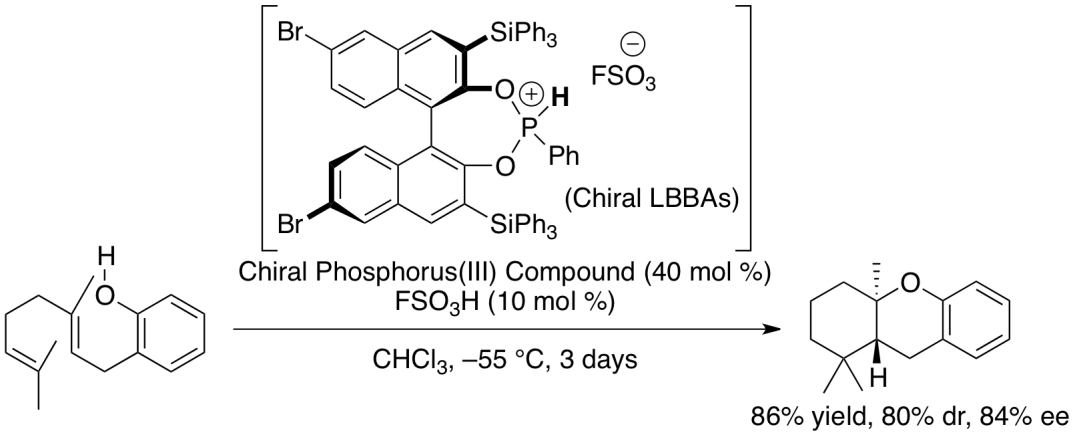
Scheme 1.10. Enantioselective Thiourea-Catalyzed Cationic Polycyclization



Although some catalytic enantioselective polyene cyclizations have been reported, they are accomplished through the use of substrates with the appropriate functional groups on the reactive sites, such as aldehydes and hydroxylactams. Therefore, these methods can not be applied to the enantioselective cyclization of simple isoprenoids with a terminal isoprenyl group.

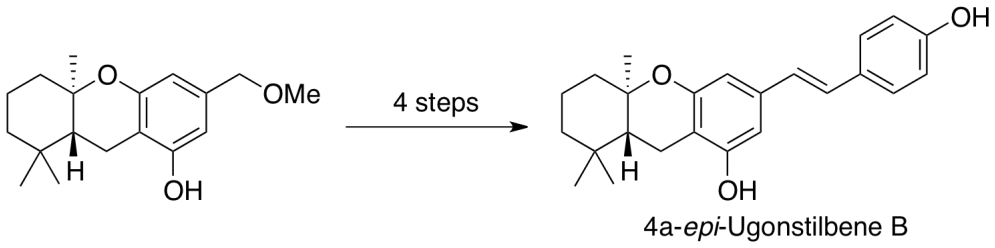
Based on these results, the author explored the enantioselective cyclization of simple isoprenoids catalyzed by chiral Brønsted acids, and sought to achieve a short-step synthesis of natural compounds using chiral cyclization products. First, the author designed chiral Lewis base-assisted Brønsted acids (LBBAs) as new chiral Brønsted acid catalysts for enantioselective cyclization. As a result of this investigation, the author found that chiral phosphonium salts prepared from a chiral phosphorus(III) compound and an achiral Brønsted acid catalyzed the enantioselective cyclization of 2-geranylphenols (Scheme 1.11).[13]

Scheme 1.11. Enantioselective Cyclization of 2-Geranylphenols Catalyzed by Chiral LBBAs



Next, the author conducted a short-step synthesis of natural compounds using this LBBA-catalyzed cyclization system. Cyclized products were useful chiral building blocks for the synthesis of various bioactive natural compounds.[26] The four-step conversion of chiral cyclized products gave 4a-*epi*-ugonstilbene B (Scheme 1.12).[27]

Scheme 1.12. Synthesis of 4a-*epi*-Ugonstilbene B



1–3 Kinetic Resolution of Racemic Carboxylic Acids Catalyzed by Chiral Lewis Base-Assisted Brønsted Acid (LBBA) through Asymmetric Protolactonization

The synthesis of optically active carboxylic acids and lactones is a very important subject in medicinal and pharmaceutical chemistry (Figure 1.3). Proteogenic and non-proteogenic α-amino acids constitute one of the five most important families of natural products and are essential molecules in many scientific areas.[28] Optically active carboxylic acids are found in a wide range of bioactive compounds. For example, DX-9065a[29] was developed as an inhibitor of factor Xa, which accelerates the conversion of prothrombin to thrombin, and JNJ-40418677[30] acts as a potent γ-secretase modulator, and thus represents a promising therapeutic approach for Alzheimer's disease. In addition, several bioactive natural products, such as (+)-discodermolide,[31] (–)-dysoxylumstatin A,[32] and their derivatives, which exhibit cytotoxic or antimicrobial activities, contain chiral lactone units. For the synthesis of these compounds, efficient methods for obtaining chiral building blocks that contain chiral carboxylic acids and lactones are needed.

The intramolecular cyclization of unsaturated carboxylic acids is one of the most straightforward routes to the synthesis of lactones, and leads directly to the desired products. In general, electrophilic reagents such as iodine, phenylselenium chloride, and mercuric or palladium salts promote this cyclization.[33] However, a second step is necessary to remove the reagent. Although the cyclization of unsaturated carboxylic acids promoted by a Brønsted acid is a well-known reaction, it occurs mostly with more than stoichiometric quantities of a Brønsted acid.[34] On the other hand, it was reported that a variety of substituted γ- and δ-lactones could be easily prepared from unsaturated carboxylic acids in excellent yields using trifluoromethanesulfonic acid (TfOH) as a catalyst (Scheme 1.13).[35] However, applications of this method, such as an asymmetric version, are limited because these reactions require harsh conditions. While there is a growing number of chiral Brønsted acid catalysts, the chiral proton-induced lactonization of unsaturated carboxylic acids is still rare.[21c] This is mainly due to the low nucleophilicity of the carboxyl group and the higher proton affinity of a carboxyl group compared to unactivated alkenes.

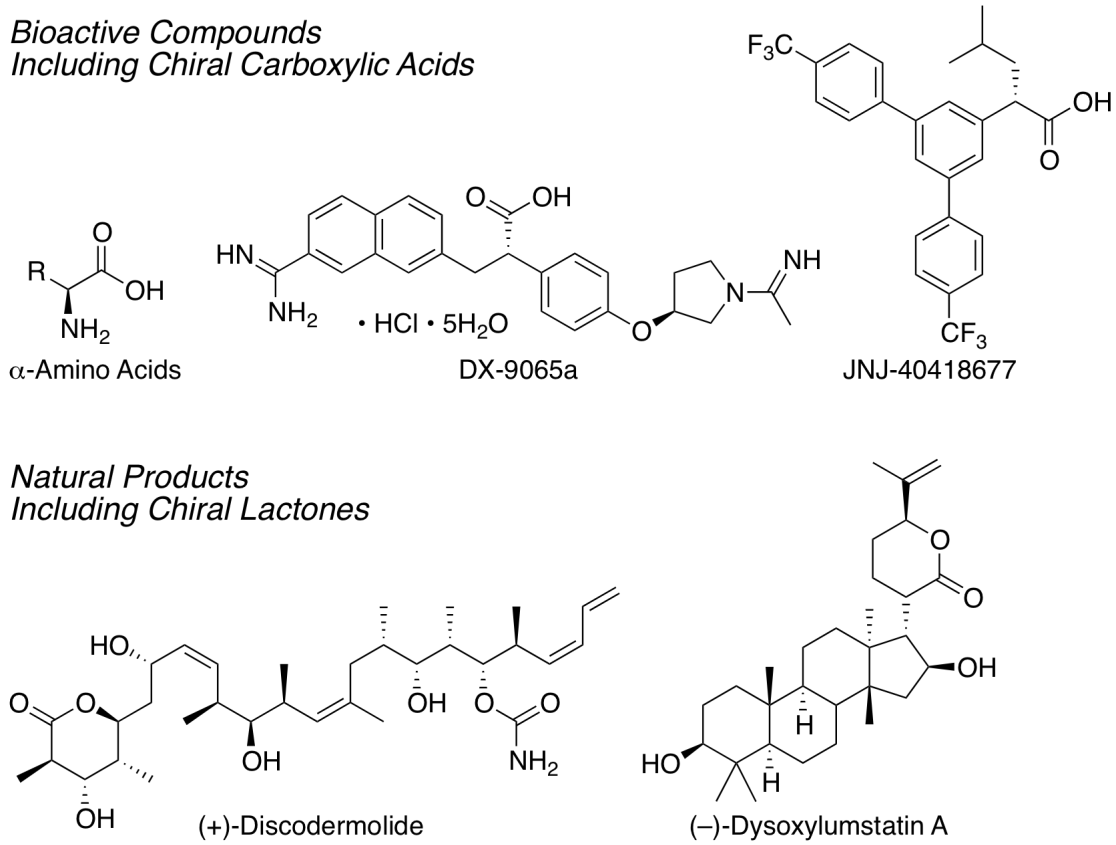
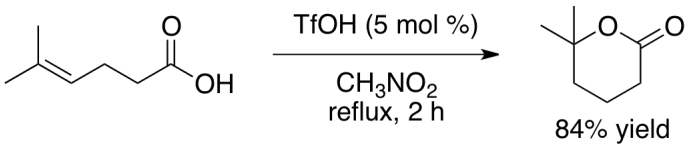


Figure 1.3. Optically active compounds containing carboxylic acids and lactones.

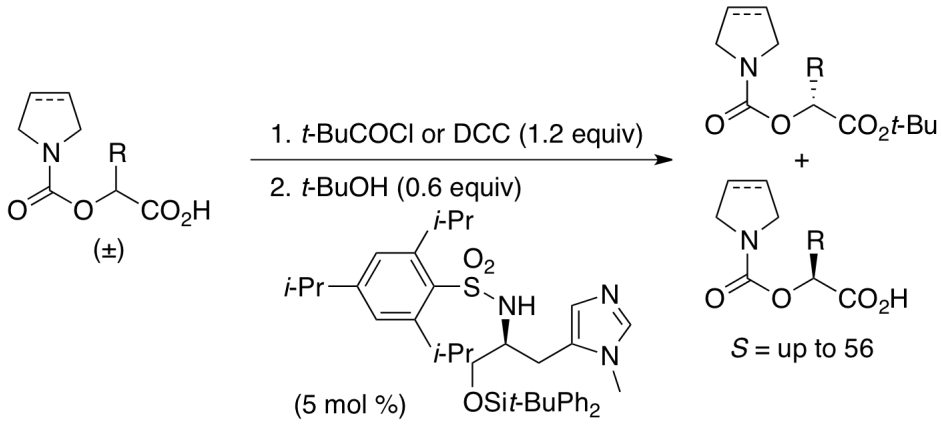
Scheme 1.13. Cyclization of Unsaturated Carboxylic Acids Catalyzed by TfOH



Some chiral resolving agents have been developed for the derivatization of racemic carboxylic acids to form pairs of diastereomers, which can be separated by conventional methods such as recrystallization. However, in some cases, this process requires several repetitions of salt formation between a carboxylic acid and an amine followed by recrystallization and subsequent separation of the chiral auxiliaries from the acid component to obtain a pure enantiomer. On the other hand, the conversion of a racemic substrate to enantioenriched products, commonly referred to as a kinetic resolution, is also an established method with broad applications.[36,37] Our group previously developed the kinetic resolution

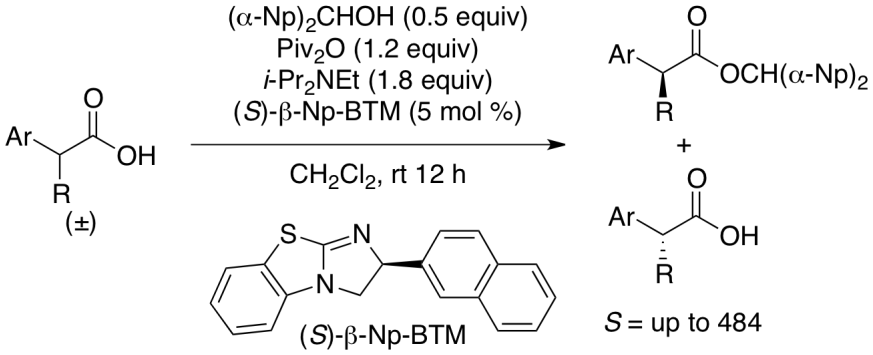
of racemic α-substituted carboxylic acids bearing a pyrrolidine- or pyrroline-1-carbonyl group via asymmetric acylation by L-histidine-derived organocatalysts (Scheme 1.14).[38] When a carboxylic acid is activated with DCC *in situ*, subsequent kinetic resolution of the carboxylic acid may occur at the generation of the acylammonium salt with or without an enantioselective hydrogen bonding interaction between the substrate and catalyst.

Scheme 1.14. Kinetic Resolution of Racemic Carboxylic Acids Using L-Histidine-Derived Organocatalysts



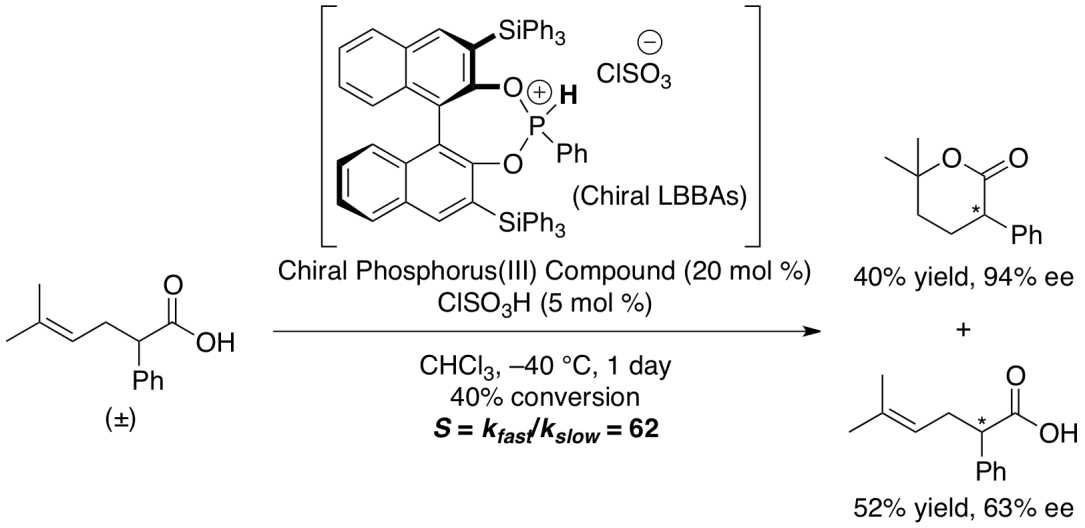
Other groups have also reported the kinetic resolution of racemic carboxylic acids using achiral alcohols with acid anhydrides and chiral acyl-transfer catalysts (Scheme 1.15).[39] For example, Shiina and colleagues developed a method for providing optically active 2-arylalkanoic acids and their esters by kinetic resolution with modified benzotetramisole-type catalysts.[39a] Although these methods can be used for kinetic resolution to give a variety of optically active carboxylic acids and esters, the reactions require generation of the mixed anhydrides followed by transacylation. Therefore, they are associated with the generation of byproducts derived from condensation reagents or acid anhydrides.

Scheme 1.15. Kinetic Resolution of Racemic Carboxylic Acids Using Benzotetramisole Derivative Catalysts



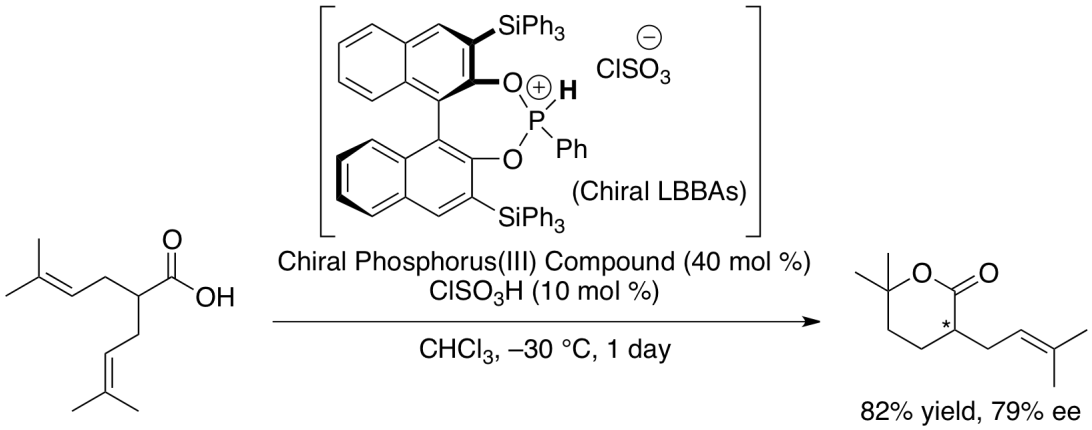
Based on the author's previous work (Scheme 1.11), the author explored the enantioselective reaction catalyzed by a chiral Lewis base-assisted Brønsted acid (chiral LBBA), which could recognize an enantioface of a terminal isoprenyl group. With regard to asymmetric protocyclization reactions, the author envisioned that the chiral LBBA-promoted method could be applied to the kinetic resolution of racemic unsaturated carboxylic acids via asymmetric protolactonization. Such a reaction system could lead to a novel and effective approach for providing optically active carboxylic acids and lactones without the generation of byproducts derived from activating reagents. As a result of this investigation, the author found that chiral LBBA promoted the kinetic resolution of racemic α-substituted carboxylic acids through asymmetric protolactonization (Scheme 1.16). This reaction gave cyclization products (lactones) and the recovered starting materials (carboxylic acids) with high selectivities and high *S* values.

Scheme 1.16. Kinetic Resolution of Racemic Carboxylic Acids Catalyzed by Chiral LBBAs



The next challenge is the application of the present method to the desymmetrization of *meso*-unsaturated carboxylic acids. The desymmetrization of *meso*-carboxylic acids catalyzed by chiral LBBAs through asymmetric protolactonization gave the desired lactones in good yield with good enantioselectivity (Scheme 1.17).

Scheme 1.17. Desymmetrization of *meso*-Carboxylic Acids Catalyzed by Chiral LBBAs



1–4 Selective Synthesis of Cyclic Phosphoric Acid Diesters through Oxorhenium(VII)-Catalyzed Dehydrative Condensation of Phosphoric Acid with Alcohols

Phosphoric acid esters are among the most important substances in materials and medicinal chemistry, as well as in many other fields (Figure 1.4). Many phosphoric acid esters are currently synthesized on an industrial scale and are widely used in everyday life.[40,41] As is well known, many bioactive substances contain phosphoric acid diesters.[42] For example, deoxyribonucleic acid (DNA) is the central storehouse of genetic information in each cell of most living organisms, and is composed of nucleotides bound together by phosphoric acid esters in a long chain. Phosphatidylcholine is usually the most abundant phospholipid in animal and plants, and is the key building block of membrane bilayers. Phosphoric acid diesters are also important substances as liquid ion exchangers for the recovery of valuable metals from waste liquors.[43] In addition, cyclic phosphoric acid diesters have recently been widely used in the fields of organic synthesis, materials chemistry, and so on. For example, cyclic phosphoric acid diesters of BINOL derivatives are useful chiral Brønsted acid catalysts for asymmetric synthesis.[2c] Amphiphilic cyclic phosphoric acid diesters are useful surfactants with biological activities.[44] From the perspective of green chemistry, the direct catalytic condensation of phosphoric acid with alcohols is attractive for the synthesis of phosphoric acid esters.[45]

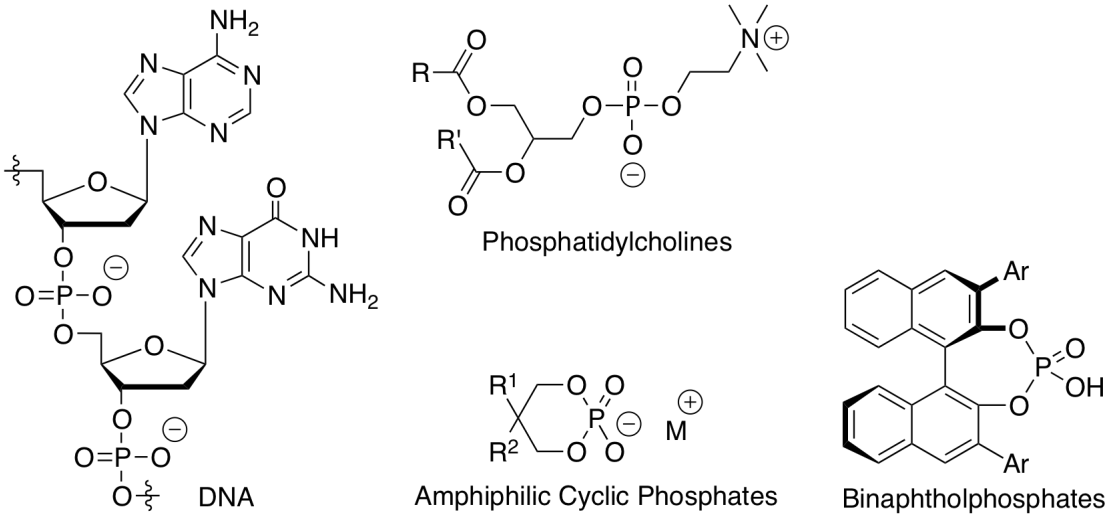
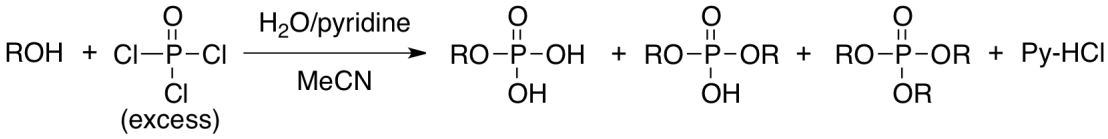


Figure 1.4. Several examples of phosphoric acid diesters.

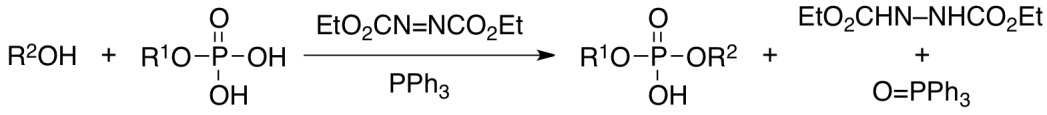
Many methods for preparing phosphoric acid esters have been reported.[41] However, from the perspective of green chemistry, there are some problems with the methods that are currently used. Phosphoryl chloride ($POCl_3$) and phosphorus pentoxide are some of the most widely used phosphorylating reagents for alcohols. However, the reaction of phosphoryl chloride with alcohols in the presence of water and pyridine provides phosphoric acid monoesters along with pyridine hydrochloride as a byproduct (Scheme 1.18). In this case, an excess amount of the reagent is required for the selective synthesis of phosphoric acid monoesters because these phosphorylating reagents are very reactive.

Scheme 1.18. Synthesis of Phosphoric Acid Monoesters Using Phosphoryl Chloride



Condensation reagents are also commonly used to prepare phosphoric acid esters. For example, the esterification of alkylphosphates is carried out with diethyl azodicarboxylate (DEAD) and triphenylphosphine (Scheme 1.19). This condensation is applicable to the phosphorylation of pyrimidine nucleosides. Although this condensation method can provide various types of phosphoric acid esters under mild conditions, it is associated with the generation of byproducts.

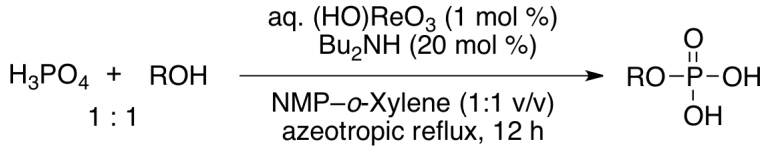
Scheme 1.19. Synthesis of Phosphoric Acid Diesters Using Condensation Reagents



Our group previously reported that a catalytic amount of perrhenic acid efficiently promoted the dehydrative condensation of phosphoric acid with equimolar amounts of alcohols in the presence of dibutylamine (Scheme 1.20).[46] This reaction is usually conducted under azeotropic reflux conditions, and selectively gives phosphoric acid monoesters in excellent yields. On the other hand, a catalytic method for the selective synthesis of phosphoric acid diesters has not yet been developed, except for the method that

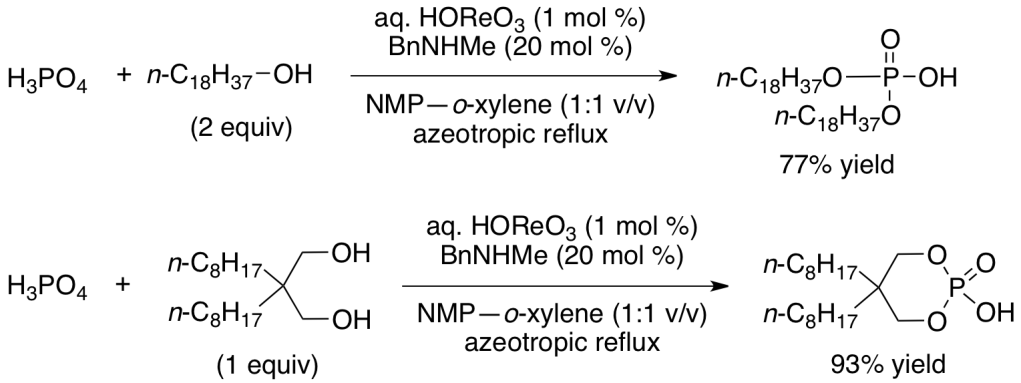
uses condensation reagents as shown above. Therefore, the author explored the catalytic dehydrative condensation of phosphoric acid to give phosphoric acid diesters.

Scheme 1.20. Catalytic Direct Condensation for Phosphoric Acid Monoesters



After intensive studies, the author found that phosphoric acid diesters were generated under catalytic dehydrative condensation for the synthesis of phosphoric acid monoesters, depending on the reaction conditions. Based on this result, the author envisioned that phosphoric acid diesters could be selectively obtained under the appropriate reaction conditions. First, the author examined the catalytic activities of various metal oxides and organic bases that were suitable for the selective synthesis of phosphoric acid diesters. As a result, the selective synthesis of phosphoric acid diesters was achieved through the oxorhenium(VII)-catalyzed dehydrative condensation of phosphoric acid with two equivalents of alcohols (Scheme 1.21). In particular, the present reaction was useful for the synthesis of cyclic phosphoric acid diesters. The combination of phosphoric acid with an equimolar amount of diols gave cyclic phosphoric acids in almost quantitative yields.[47]

Scheme 1.21. Catalytic Synthesis of Phosphoric Acid Diesters



References and Notes

1. Egen, M. *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 1.
2. (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566. (b) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804. (c) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (d) Terada, M. *Synthesis* **2010**, 1929.
3. Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626.
4. Hatano, M.; Maki, T.; Moriyama, K.; Arinobe, M.; Ishihara, K. *J. Am. Chem. Soc.* **2008**, *130*, 16858.
5. Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418.
6. (a) Ishihara, K.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 11179 (b) Yamamoto, H.; Futatsugi, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 1924.
7. (a) Weil, T.; Kotke, M.; Kleiner, C. M.; Schreiner, P. R. *Org. Lett.* **2008**, *10*, 1513. (b) Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2009**, *11*, 887.
8. For a selected example, see: Cheon, C. H.; Kanno, O.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 13248.
9. Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem. Int. Ed.* **2000**, *39*, 44.
10. (a) Poulter, C. D., *Comprehensive Natural Products Chemistry,* Vol. 5, ed. by Derek, D.; Nakanishi, K.; Methcohen, O., Pergamon, Oxford, **1999**. (b) Cane, D. E., *Comprehensive Natural Products Chemistry,* Vol. 2, ed. by Derek, D.; Nakanishi, K.; Methcohen, O., Pergamon, Oxford, **1999**.
11. (a) Harring, S. R.; Livinghouse, T. *Tetrahedron* **1994**, *50*, 9229. (b) Vlad, P. E. *Pure Appl. Chem.* **1993**, *65*, 1329. (c) Saito, A.; Matsushita, H.; Kaneko, H. *Chem. Lett.* **1984**, 591.
12. For the use of triphenylphosphonium triflate as a Brønsted acid catalyst, see: Iwahashi, H.; Oka, T.; Abiko, A. *Chem. Lett.* **2008**, *37*, 708.
13. Sakakura, A.; Sakuma, M.; Ishihara, K. *Org. Lett.* **2011**, *13*, 3130.
14. (a) Woodward, R. B.; Bloch, K. *J. Am. Chem. Soc.* **1953**, *75*, 2023. (b) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068. (c) Eshenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890. (d) van Tamelen, E. E. *Pure Appl. Chem.* **1981**, *53*, 1259. (e) Johnson, W. S. *Tetrahedron* **1991**, *47*, xi.

15. Abe, I.; Rohmer, M.; Prestwich, G. D. *Chem. Rev.* **1993**, *93*, 2189.
16. (a) Ohloff, G.; The Fragrance of Ambergris. In *Fragrance Chemistry*; Theimer, E. T., Ed.; Academic Press: New York, **1982**; pp 535–573. (b) Mookherjee, B. D.; Patel, R. R. In *Proceedings of the 7th International Congress on Essential Oils*; Kyoto, **1977**; p 479. (c) Stoll, M.; Hinder, M. *Helv. Chim. Acta* **1950**, *33*, 1251. (d) Hinder, M.; Stoll, M. *Helv. Chim. Acta* **1950**, *33*, 1308. (e) Decorzant R.; Vial, C.; Naf, F.; Whitesides, G. M. *Tetrahedron* **1987**, *43*, 1871. (f) Coste-Maniere, I. C.; Zahra, J. P.; Waegell, B. *Tetrahedron Lett*. **1988**, *29*, 1017. (g) Verstegen-Haaksma, A. A.; Swarts, H. J.; Jansen, B. J. M.; Groot, A. *Tetrahedron* **1994**, *50*, 10095. (h) Barrero, A. F.; Altarejos, J.; Alvarez-Manzaneda, E. J.; Ramos, J. M.; Salido, S. *J. Org. Chem*. **1996**, *61*, 2215. (i) Bolster, M. G.; Lagnel, B. M. F.; Jansen, B. J. M. *Tetrahedron* **2001**, *57*, 8369.
17. (a) Fenical, W.; McConnel, O. *Experientia* **1975**, *31*, 1004. (b) Cimino, G.; DeStefeano, S.; Minale, L. *Experientia* **1975**, *31*, 1117. (c) Djura, P.; Stiele, D. B.; Sullivan, B.; Faulkner, J.; Arnold, E.; Clardy, J. *J. Org. Chem*. **1980**, *45*, 1435. (d) Rodriguez, J.; Quinoa, E.; Riguera, R.; Peters, B. M.; Abrell, L. M.; Crewa, P. *Tetrahedron* **1992**, *48*, 6667.
18. Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Cortes, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181.
19. (a) Rodriguez, J.; Quinoa, E.; Riguera, R.; Peters, B. M.; Abrell, L. M.; Crewa, P. *Tetrahedron* **1992**, *48*, 6667. (b) Hamann, M. T.; Scheuer, P. J.; Kelly-Borges, M. J. *J. Org. Chem*. **1993**, *58*, 6565. (c) Navi, B. N.; Perzanowski, H. P.; Ross, R. A.; Erdman, T. R.; Scheuer, P. J.; Finer, J.; Clardy, J. *Pure Appl. Chem*. **1979**, *51*, 1893. (d) Nasu, S. S.; Yeung, B. K. S.; Hamann, M. T.; Scheuer, P. J.; Kelly-Borges, M. J. Goins, K. *J. Org. Chem*. **1995**, *60*, 7290.
20. (a) van Tamelen, E. E. *Acc. Chem. Res.* **1968**, *1*, 111. (b) Johnson, W. S. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 9. (c) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Org. Chem.* **1986**, *51*, 806. (d) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730.
21. For reports on asymmetric catalysis with chiral LBAs, see: (a) Cheon, C. H.; Imahori, T.; Yamamoto, H. *Chem. Commun*. **2010**, *46*, 6980. (b) Repka, L. M.; Ni, J.; Reisman, S. E. *J. Am. Chem. Soc*. **2010**, *132*, 14418. (c) Upar, K. B.; Mishra, S. J.; Nalawade, S. P.; Singh, S. A.; Khandare, R. P.; Bhat, S. V. *Tetrahedron: Asymmetry* **2009**, *20*, 1637. (d)

Rauniyar, V.; Zhai, H.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481. (e) Yanagisawa, A.; Touge, T.; Arai, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 1546. (f) Ishihara, K.; Nakashima, D.; Hiraiwa, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 24. (g) Nakamura, S.; Kaneeda, M.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8120. (h) Ishihara, K.; Nakamura, S.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 12854. (i) Ishihara, K.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 11179.

22. For asymmetric polyene cyclizations with LBA, see: (a) Uyanik, M.; Ishihara, K.; Yamamoto, H. *Bioorg. Med. Chem.* **2005**, *13*, 5055. (b) Uyanik, M.; Ishibashi, H.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 1601. (c) Ishibashi, H.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 11122. (d) Kumazawa, K.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2004**, *6*, 2551. (e) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2002**, *124*, 3647. (f) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2001**, *123*, 1505. (g) Nakamura, S.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8131. (h) Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 4906.
23. For catalytic enantioselective polycyclization with LBA prepared from $SbCl_5$, see: Surendra, K.; Corey, E. J. *J. Am. Chem. Soc*. **2012**, *134*, 11994.
24. (a) Sakakura, A.; Shomi, G.; Ukai, A.; Ishihara, K. *Heterocycles* **2011**, *82,* 249. (b) Sakakura, A.; Ishihara, K. *Chim. Oggi-Chem. Today* **2007**, *25*, 9. (c) Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900.
25. (a) Zhao, Y.-J.; Li, B.; Tan, L.-J. S.; Shen, Z.-L.; Loh, T.-P. *J. Am. Chem. Soc.* **2010**, *132*, 10242. (b) Sethofer, S. G.; Mayer, T.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 8276. (c) Knowles, R. R.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 5030. (d) Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027. (e) Mullen, C. A.; Campbell, A. N.; Gagn_e, M. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6011. (f) Yang, D.; Gu, S.; Yan, Y.-L.; Zhao, H.-W.; Zhu, N.-Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 3014.
26. For selected recent examples, see: (a) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *J. Am. Chem. Soc.* **2010**, *132*, 14303. (b) Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2009**, *131*, 13928.
27. Chen, C.-C.; Huang, Y.-L.; Yeh, P.-Y.; Ou, J.-C. *Planta Med.* **2003**, *69*, 964.
28. (a) Hughes, A. B. *Amino Acids, Peptides and Proteins in Organic Chemistry, Volume 1,*

Origins and Synthesis of Amino Acids, Wiley, Weinheim, **2009**. (b) For a selected review of the catalytic asymmetric synthesis of α-amino acids, see: Najera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584.

29. For selected examples, see: (a) Fujii, Y.; Kanamaru, T.; Kikuchi, H.; Yamashita, S.; Sakuma, S. *Eur. J. Pharm. Sci.* **2011**, *42*, 392. (b) Nagahara, T.; Yokoyama, Y.; Inamura, K.; Katakura, S.; Komoriya, S.; Yamaguchi, H.; Hara, T.; Iwamoto, M. *J. Med. Chem.* **1994**, *37*, 1200.
30. Broeck, B. V.; Chen, J.-M.; Tréton, G.; Desmidt, M.; Hopf, C.; Ramsden, N.; Karran, E.; Mercken, M.; Rowley, A. *Br. J. Pharmacol.* **2011**, *163*, 375.
31. Lemos, E. d.; Agouridas, E.; Sorin, G.; Guerreiro, A.; Commerçon, A.; Pancrazi, A.; Betzer, J.-F.; Lannou, M.-I.; Ardisson, J. *Chem. Eur. J.* **2011**, *17*, 10123.
32. Hu, J.; Wang, X.; Shi, X. *Eur. J. Org. Chem.* **2011**, 7215.
33. (a) Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1985**, *26*, 5307. (b) Larnck, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298. (c) Kang, S. H.; Lee, J. H.; Lee, S. B. *Tetrahedron Lett.* **1998**, *39*, 59. (d) Jonasson, C; Horvath, A.; Baeckvall, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 9600. (e) Chavan, S. P.; Shamia, A. K. *Tetrahedron Lett.* **2001**, *42*, 4923. (f) Tiecco, M.; Testaferri, L.; Temperini, A.; Bagnoli, L.; Marini, F.; Santi, C. *Synlett* **2001**, 1767. (g) GruUadauria, M.; Aprile, C; Noto, R. *Tetrahedron Lett.* **2002**, *43*, 1669. (h) Curini, M.; Epifano, F.; MarcoiuUio, M. C; Montanari, F. *Synlett* **2004**, *2*, 368.
34. (a) Anscll, M. F.; Palmer, M. H. *Q. Rev. (London)* **1964**, *18*, 211. (b) TIecco, M.; Testaferri, L.; Tingoli, M. *Tetrahedron* **1993**, *49*, 5351. (c) Mali, R. S.; Babu, K. N. *Helv. Chim. Acta* **2002**, *85*, 3525. (e) Miura, K.; Hayashida, J.; Takahashi, T.; Nishikori, H.; Hosomi, A. *J. Organomet. Chem.* **2003**, *686*, 242. (f) Zhou, Y.; Woo, L. K.; Angelici, R. J. *Appl. Catal., A: General* **2007**, *333*, 238.
35. Coulombel, L.; Duñach, E. *Synth. Commun.* **2005**, *35*, 153.
36. For selected examples, see: (a) Kagan, H. B.; Fiaud, J. C. *Topics in Stereochemistry*, Vol. 18, ed. by Eliel, E. L.; Wilen, S. H., Wiley, New York, **1988**, pp 249-330. (b) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N.; *Adv. Synth. Catal.* **2001**, *343*, 5. (c) Krasnov, V. P.; Gruzdev, D. A.; Levit, G. L. *Eur. J. Org. Chem.* **2012**, 1471. (d) Müller, C. E.; Schreiner, P. R. *Angew. Chem. Int. Ed.* **2011**, *50*, 6012. (e) Taylor, J. E.; Bull, S. D.; Williams, J. M. J. *Chem. Soc. Rev.* **2012**, *41*, 2109. (f) Vedejs, E.; Jure, M. *Angew.*

Chem. Int. Ed. **2005**, *44*, 3974.

37. For recent advances, see: (a) Peschiulli, A.; Procuranti, B.; O'Connor, C. J.; Connon, S. J. *Nat. Chem.* **2010**, *2*, 380. (b) Bumbu, V. D.; Birman, V. B. *J. Am. Chem. Soc.* **2011**, *133*, 13902. (c) Čorić, I.; List, B. *Nature* **2012**, *483*, 315. (d) Wang, Y.; Zheng, K.; Hong, R. *J. Am. Chem. Soc.* **2012**, *134*, 4096.
38. (a) Ishihara, K.; Kosugi, Y.; Umemura, S.; Sakakura, A. *Org. Lett.* **2008**, *10*, 3191. (b) Sakakura, A.; Umemura, S.; Ishihara, K. *Synlett* **2009**, 1647.
39. (a) Shiina, I.; Nakata, K.; Ono, K.; Onda, Y.; Itagaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 11629. (b) Shiina, I.; Nakata, K.; Onda, Y. *Eur. J. Org. Chem.* **2008**, 5887. (c) Yang, X.; Birman, V. B. *Adv. Synth. Catal.* **2009**, *351*, 2301. See also other non-enzymatic enantioselective acyl transfer reactions: (d) Narasaka, K.; Kanai, F.; Okudo, M.; Miyoshi, N. *Chem. Lett.* **1989**, 1187. (e) Notte, G. T.; Sammakia, T.; Steel, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 13502. (f) Notte, G. T.; Sammakia, T. *J. Am. Chem. Soc.* **2006**, *128*, 4230. (g) Yang, X.; Lu, G.; Birman, V. B. *Org. Lett.* **2010**, *12*, 892.
40. (a) Tadros, T. F. *Applied Surfactants: Principles and Applications,* Wiley, Weinheim, **2005.** (b) Toy, A. D. F.; Walsh, E. N. *Phosphorus Chemistry in Everyday Living*, American Chemical Society, Washington, DC, 2nd ed., **1987**.
41. For reviews of the synthesis of phosphoric acid esters, see: (a) Hayakawa, Y., *Comprehensive Organic Synthesis,* Vol. 6, ed. by Trost, B. M.; Fleming, I.; Winterfeldt, E., Pergamon, Oxford, **1991**, pp 601-630. (b) Reese, C. B. *Org. Biomol. Chem.* **2005**, *3*, 3851.
42. (a) Sankawa, U., *Comprehensive Natural Products Chemistry,* Vol. 1, ed. by Derek, D.; Nakanishi, K.; Methcohen, O., Pergamon, Oxford, **1999**, pp 285-302. (b) Kool, E. T., *Comprehensive Natural Products Chemistry,* Vol. 7, ed. by Derek, D.; Nakanishi, K.; Methcohen, O., Pergamon, Oxford, **1999**. (c) For a recent review of phosphatidylcholine, see: Cole, L. K.; Vance, J. E.; Vance, D. E. *Biochim. Biophys. Acta* **2012**, *1821*, 754.
43. Kurosaki, T.; Nishikawa, N., DE Patent, 3325337, **1984**.
44. (a) Buwalda, R. T.; Wagenaar, A.; Engberts, J. B. F. N. *Liebigs Ann./Recueil*, **1997**, 1745. (b) Shinitzky, M., WO Patent, 2003075902, **2003**.
45. Anastas, P. T.; Warner, J. C., *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, **1998**.

46. Sakakura, A.; Katsukawa, M.; Ishihara, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 1423.
47. Sakakura, A.; Sakuma, M.; Ishihara, K. *Heterocycles* **2008**, *76*, 657.

Chapter 2

Chiral Lewis Base-Assisted Brønsted Acid (LBBA)-Catalyzed Enantioselective Cyclization of 2-Geranylphenols

Abstract: Chiral Lewis base-assisted Brønsted acids (Chiral LBBAs) have been designed as new organocatalysts for biomimetic enantioselective cyclization. A salt of a chiral phosphonous acid diester with FSO_3H catalyzes the enantioselective cyclization of 2-geranylphenols to give the desired *trans*-fused cyclized products with high diastereo- and enantioselectivities (up to 98:2 dr and 93% ee).

2–1 Introduction

Biomimetic polyene cyclization of isoprenoids is a highly powerful method for constructing polycyclic structures of terpenoids. Considerable effort has been focused on the development of enantioselective polyene cyclizations using a chiral artificial cyclase. Since the pioneering work on Lewis acid-assisted Brønsted acid (LBA) catalysis by Yamamoto and Ishihara,[1–3] some elegant studies on enantioselective polyene cyclizations have been reported.[4]

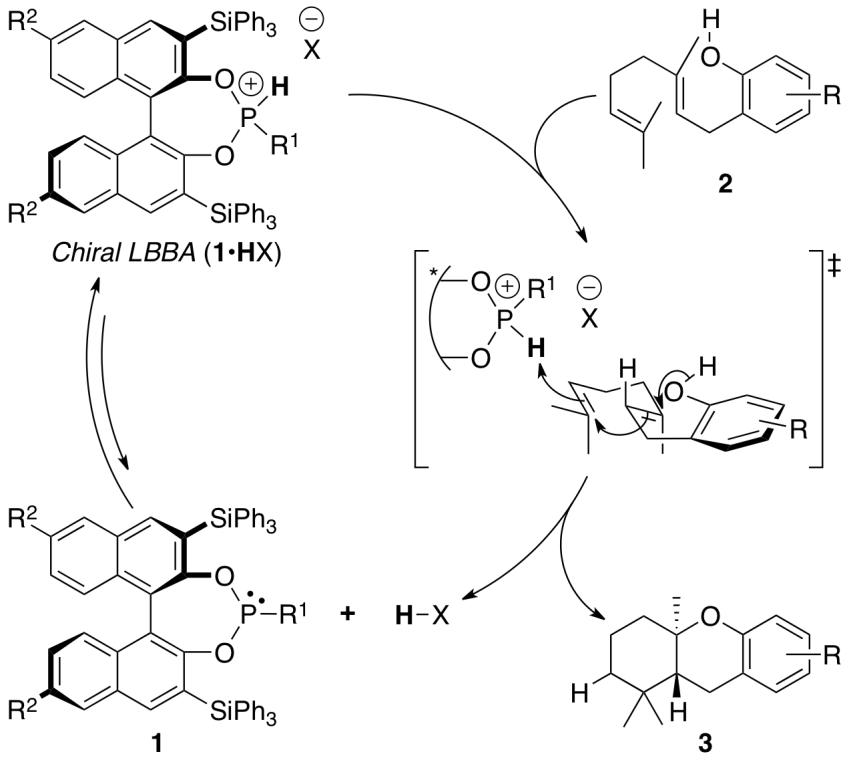


Figure 2.1. Chiral Lewis base-assisted Brønsted acids (Chiral LBBAs, **1**•HX) and proposed catalytic cycle for the LBBA-catalyzed cyclization of 2-geranylphenols **2**.

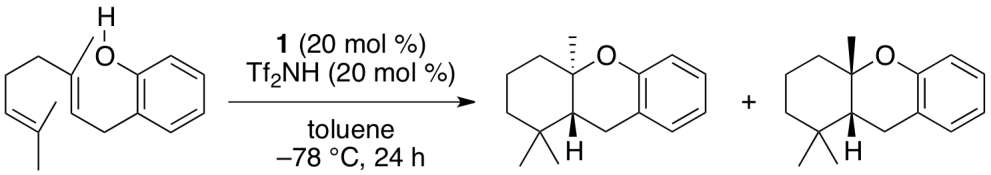
We recently developed a chiral Lewis base-promoted enantioselective iodocyclization of isoprenoids.[5,6] The chiral nucleophilic phosphoramidite, prepared from a binaphthol bearing triphenylsilyl groups at the 3,3'-positions, reacts with *N*-iodosuccinimide (NIS) to generate the corresponding phosphonium salt as an active species. This chiral Lewis base-promoted method can also be applied to the Brønsted acid-induced cyclization of isoprenoids. Thus, we pursued the design of new chiral Brønsted acids: Lewis base-assisted

Brønsted acids (LBBAs), phosphonium salts[7] prepared from a chiral phosphorus(III) compound **1** with an achiral Brønsted acid (HX) (Figure 2.1). We report here the chiral LBBA-catalyzed enantioselective cyclization of 2-geranylphenols.

2–2 Results and Discussion

The Brønsted acidity of the chiral LBBAs should strongly depend on the structure of **1**. For example, the Brønsted basicities of phosphorous acid triesters are higher than those of corresponding triaryl- and trialkylphosphines [pKa values of conjugate acids: $P(OPh)_3$ –2.0, $P(OMe)_3$ 2.6, PPh_3 2.7, and PMe_3 8.7].[8] We first examined the catalytic activities of chiral LBBAs prepared from **1** with Tf_2NH. The cyclization of 2-geranylphenol **2a** was carried out in the presence of 1 (20 mol %) and Tf_2NH (20 mol %) in toluene at –78 °C (Table 2.1). The reaction preferentially gave the corresponding *trans*-fused product **3a** (*trans*/*cis* = ca. 9:1). Based on the high trans selectivity, these reactions might proceed through concerted cyclization. Although chiral LBBAs prepared from phosphorous acid triesters **1a** (R^1 = OPh) and **1b** (R^1 = OCy) showed good catalytic activities (yields of 61 and 42%), the obtained *trans*-**3a** was racemic (entries 1 and 2). Due to the lower basicity of **1a**, the corresponding LBBA was thermodynamically unstable, and racemic product was obtained via a background reaction catalyzed by an achiral Brønsted acid (entry 1). LBBA **1b**•Tf_2NH, which was less acidic than **1a**•Tf_2NH, improved the diastereoselectivity, although it did not have enough stability to control the enantioselectivity (entry 2). On the other hand, the use of chiral phosphonous acid diesters **1c** (R^1 = Ph) and **1d** (R^1 = *i*-Pr), which are more basic than **1a** and **1b**, successfully induced enantioselectivity (22 and 14% ees), albeit the yields of **3a** were low (entries 3 and 5). The absolute stereochemistry of the obtained *trans*-**3a** was assigned to be (4a*R*).[1g] Further investigation revealed that when the reaction was conducted using **1c** (40 mol %) and Tf_2NH (10 mol %) a –40 °C, both the yield and enantioselectivity were improved (entry 4). The use of excess **1c** should promote rapid regeneration of the phosphonium salt in the catalytic cycle and prevent the background reaction. When the reaction was conducted in the absence of **1**, **3a** was obtained in 93% yield with moderate diastereoselectivity (79:21 dr, entry 6). This result suggested that use of Lewis base **1** controlled not only reactivity and enantioselectivity but also diastereoselectivity.

Table 2.1. Enantioselective Cyclization of 2-Geranylphenol (**2a**) Catalyzed by Chiral LBBAs **1**•Tf_2NH



2a *trans*-**3a** *cis*-**3a**

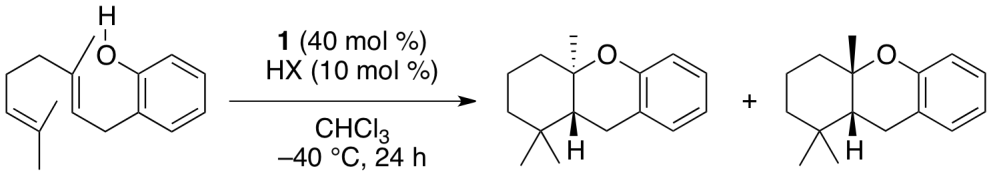
entry	**1** [R^1, R^2]	yield (%)	*trans* / *cis*	ee (%)[a]
1	**1a** [OPh, H]	61	85 : 15	0
2	**1b** [OCy, H]	42	95 : 5	0
3	**1c** [Ph, H]	28	93 : 7	22
4[b]	**1c** [Ph, H]	59	91 : 9	52
5	**1d** [*i*-Pr, H]	15	89 : 11	14
6[c]	–	93	79 : 21	–

[a] Ee of *trans*-**3a**. Determined by HPLC analysis. [b] Reaction was conducted in the presence of **1c** (40 mol %) and Tf_2NH (10 mol %) at –40 °C.
[c] Reaction was conducted in the absence of **1**.

Next, we investigated Brønsted acids (HX) in chiral LBBAs for the cyclization of **2a** (Table 2.2). The reaction was conducted in $CHCl_3$, since the use of $CHCl_3$ as a solvent generally gave **3a** in higher yield and enantioselectivity than with toluene when sulfonic acids were used as Brønsted acids.[9] As a result of our investigation of various Brønsted acids, we found that the enantioselectivity depended on the steric bulkiness as well as the acidity of Brønsted acids (entries 1–4). The low enantioselectivity of the **1c**•Tf_2NH-catalyzed reaction would be attributed to the background reaction caused by strongly acidic Tf_2NH (entry 1). The use of sterically less-hindered FSO_3H as a Brønsted acid gave the highest enantioselectivity (81% ee), albeit the yield of **3a** was moderate (42%, entry 4). The moderate yield of **3a** could mainly be attributed to the fact that **1c** gradually decomposed under the reaction conditions. Thus, the use of 100 mol % of **1c** improved the yield of **3a** (60%, entry 5). The use of 1e bearing two bromine atoms at the 6,6'-positions also increased the yield of **3a** without a significant loss of enantioselectivity (86%, 78% ee, entry 6). Importantly, the introduction of electron-withdrawing substituents at the 6,6'-positions reduced the decomposition of **1** under the acidic reaction conditions. When the **1e**•FSO_3H-catalyzed cyclization of **2a** was conducted at –55 °C for 3 days, the

enantioselectivity was increased to 84% ee without any decrease in the yield of **3a** (entry 7). On the other hand, the introduction of a trifluoromethyl group at the phenyl moiety decreased the yield and enantioselectivity of **3a** (entry 8). The electron-withdrawing substituent of **1f** did not decrease the decomposition of **1**, but increased the acidity of the corresponding LBBA.

Table 2.2. Optimization of the Reaction Conditions



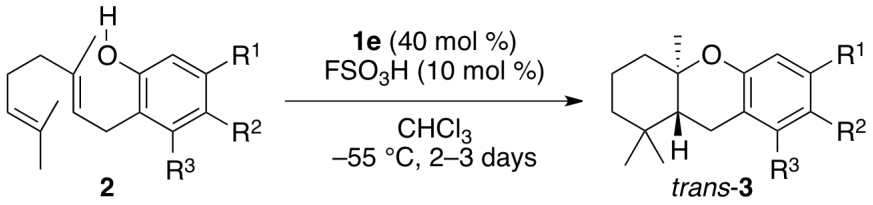
2a *trans*-**3a** *cis*-**3a**

entry	**1** [R^1, R^2]	HX	yield (%)	*trans* / *cis*	ee (%)[a]
1	**1c** [Ph, H]	Tf_2NH	30	97 : 3	19
2	**1c** [Ph, H]	TfOH	77	90 : 10	75
3	**1c** [Ph, H]	$ClSO_3H$	69	94 : 6	76
4	**1c** [Ph, H]	FSO_3H	42	98 : 2	81
5[b]	**1c** [Ph, H]	FSO_3H	60	97 : 3	81
6	**1e** [Ph, Br]	FSO_3H	86	85 : 15	78
7[c]	**1e** [Ph, Br]	FSO_3H	86	90 : 10	84
8	**1f** [4-$CF_3C_6H_4$, H]	FSO_3H	62	92 : 8	49

[a] Ee of *trans*-**3a**. Determined by HPLC analysis. [b] 100 mol % of **1c** was used.
[c] Reaction was conducted at –55 °C for 3 days.

With the optimized reaction conditions in hand, we next examined the enantioselective cyclization of 2-geranylphenol derivatives **2** using **1e**• FSO_3H as a catalyst (Table 2.3). The introduction of both electron-donating and electron-withdrawing groups at the 4- and 5-positions (R^1 and R^2) did not affect the enantioselectivity (87–93% ee), albeit the yields of **3** were decreased (entries 1–4). In contrast, the introduction of a substituent at the 3-position (R^3) slightly decreased the diastereo- and enantioselectivities (entries 5–7). Interestingly, substrate **2i** bearing a hydroxyl group at the 3-position showed high diastereoselectivity (93:7 dr, entry 8). The C_2 symmetry of **2i** might be suitable for the high-level induction of diastereoselectivity. The use of 100 mol % of **1e** and 20 mol % of FSO_3H increased the yield of **3i** without a loss of enantioselectivity (60% yield, entry 9).

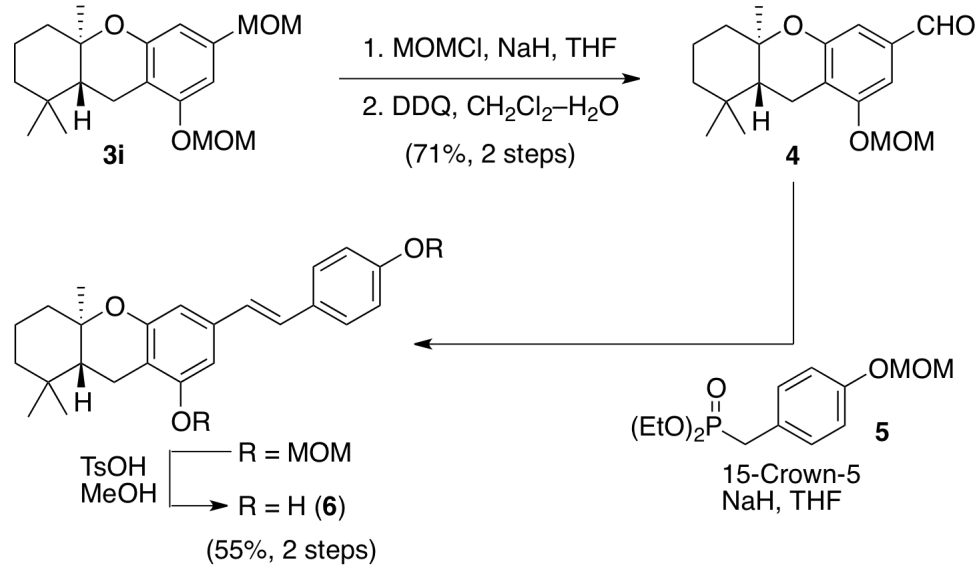
Table 2.3. Enantioselective Cyclization of 2-Geranylphenol Derivatives **2** Catalyzed by Chiral LBBA **1e**• FSO_3H



entry	**2** [R^1, R^2,R^3]	yield (%)	*trans* / *cis*	ee (%)[a]
1	**2b** [H, Me, H]	64	90 : 10	93
2	**2c** [H, OMe, H]	43	96 : 4	88
3	**2d** [H, I, H]	48	97 : 3	87
4	**2e** [OCH_2O, H]	44	91 : 9	88
5	**2f** [Me, H, Me]	80	88 : 12	72
6	**2g** [OMe, H, OMe]	65	65 : 35	79
7	**2h** [MOM, H, OMe]	57	80 : 20	74
8	**2i** [MOM, H, OH]	36	93 : 7	70
9[b]	**2i** [MOM, H, OH]	60	89 : 11	69

[a] Ee of *trans*-**3a**. Determined by HPLC analysis.
[b] 100 mol % of **1e** and 20 mol % of FSO_3H were used in $CHCl_3$ (0.02 M).

Scheme 2.1. Synthesis of 4a-*epi*-Ugonstilbene B (**6**)



Cyclized products **3** were useful chiral building blocks for the synthesis of various bioactive natural compounds.[10] Thus, after protection of the hydroxyl group of *trans*-**3i** with MOM, DDQ oxidation of the MOM group[11] at the 4-position gave aldehyde **4** in 71% yield (Scheme 2.1).[12] A subsequent Horner–Emmons–Wadsworth reaction of **4** with phosphonate **5**[13] followed by the removal of MOM groups gave 4a-*epi*-ugonstilbene B (**6**)[14] in 55% yield.

We propose the following mechanism to explain the absolute stereopreference we observed. Structure **A** in Figure 2.2 is the Newman projection of the chiral LBBA **1c**•FSO_3H viewed along the H–P bond. The substrate should approach the active proton of **A** with the terminal dimethyl group away from the triphenylsilyl groups, avoiding their steric hindrance. As shown in structure **C**, the reaction at the *si*-face would be disfavored because of steric repulsion with the triphenylsilyl group. Therefore, the *re*-face of the terminal isoprenyl group of the substrates would preferentially approach the active proton (**B**) to give (4a*R*)-**3** selectively.

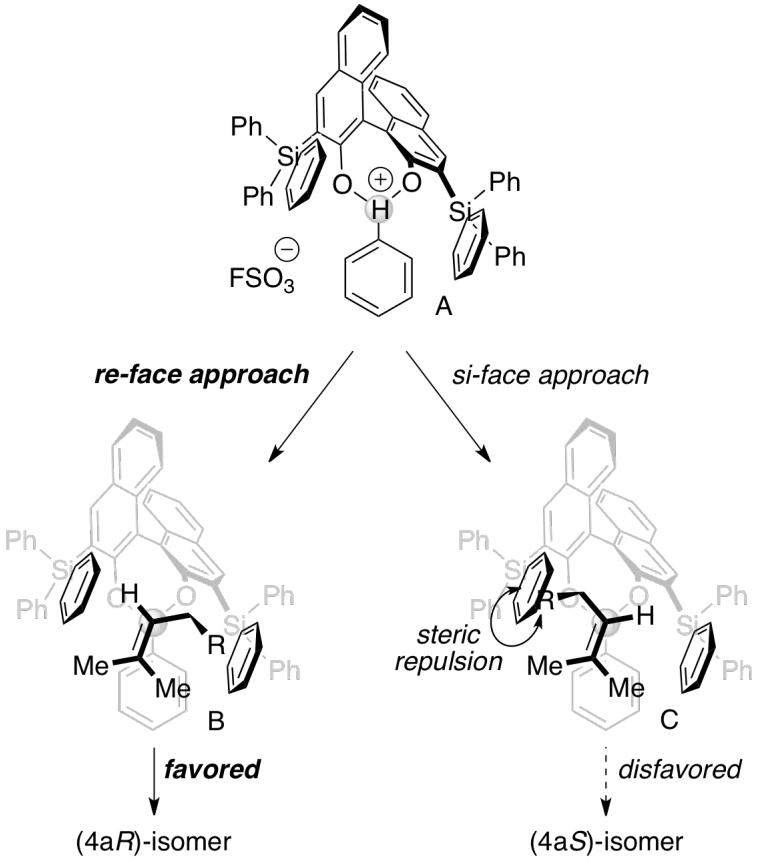


Figure 2.2. Proposed transition-state assembles.

2–3 Conclusion

We have developed chiral Lewis base- assisted Brønsted acids (LBBAs) as new chiral Brønsted acid catalysts for the enantioselective cyclization of 2-geranylphenols. Chiral phosphonium salt of **1e** with FSO_3H catalyzed the cyclization of 2-geranylphenols to give the corresponding *trans*-fused cyclized products with high diastereo- and enantioselectivities.

References and Notes

1. (a) Uyanik, M.; Ishihara, K.; Yamamoto, H. *Bioorg. Med. Chem.* **2005**, *13*, 5055. (b) Uyanik, M.; Ishibashi, H.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 1601. (c) Ishibashi, H.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 11122. (d) Kumazawa, K.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2004**, *6*, 2551. (e) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2002**, *124*, 3647. (f) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2001**, *123*, 1505. (g) Nakamura, S.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8131. (h) Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 4906.
2. For reports on asymmetric catalysis by chiral LBAs, see: (a) Cheon, C. H.; Imahori, T.; Yamamoto, H. *Chem. Commun.* **2010**, *46*, 6980. (b) Repka, L. M.; Ni, J.; Reisman, S. E. *J. Am. Chem. Chem.* **2010**, *132*, 14418. (c) Upar, K. B.; Mishra, S. J.; Nalawade, S. P.; Singh, S. A.; Khandare, R. P.; Bhat, S. V. *Tetrahedron: Asymmetry* **2009**, *20*, 1673. (d) Rauniyar, V.; Zhai, H.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481. (e) Yanagisawa, A.; Touge, T.; Arai, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 1546. (f) Ishihara, K.; Nakashima, D.; Hiraiwa, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 24. (g) Nakamura, S.; Kaneeda, M.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8120. (h) Ishihara, K.; Nakamura, S.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 12854. (i) Ishihara, K.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 11179.
3. For reviews of combined acids, see: (a) Yamamoto, H.; Futatsugi, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 1924. (b) Ishibashi, H.; Ishihara, K.; Yamamoto, H. *Chem. Rec.* **2002**, *2*, 177.
4. (a) Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027. (b) Knowles, R. R.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 5030. (c) Zhao, Y.-J.; Li, B.; Tan, L.-J. S.; Shen, Z.-L.; Loh, T.-P. *J. Am. Chem. Soc.* **2010**, *132*, 10242. (d) Mullen, C. A.; Campbell, M. A.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6011. (e) Yang, D.; Gu, S.; Yan, Y.-L.; Zhao, H.-W.; Zhu, N. Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 3014.
5. (a) Sakakura, A.; Shomi, G.; Ukai, A.; Ishihara, K. *Heterocycles* **2011**, *82*, 249. (b) Sakakura, A.; Ishihara, K. *Chimica Oggi-Chemistry Today* **2007**, *25*, 9. (c) Sakakura,

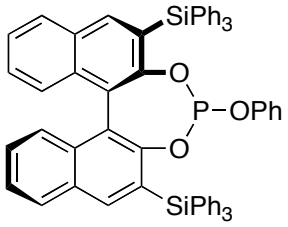
A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900.

6. For enantioselective halocyclizations, see: (a) Zhou, Li.; Chen, J.; Tan, C. K.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2011**, *133*, 9164. (b) Hennecke, U.; Müller, C. H.; Fröhlich, R. *Org. Lett.* **2011**, *13*, 860. (c) Jaganathan, A.; Garzan, A.; Whitehead, D. C.; Staples, R. J.; Borhan, B.; *Angew. Chem. Int. Ed.* **2011**, *50*, 2593. (d) Murai, K.; Matsushita, T.; Nakamura, A.; Fukushima, S.; Shimura, M.; Fujioka, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 9174. (e) Veitch, G. E.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2010**, *49*, 7332. (f) Denmark, S. E.; Burk, M. T. *Proc. Natl. Acad. Sci.* **2010**, *107*, 20655. (g) Snyder, S. A.; Treitler, D. S.; Schall, A. *Tetrahedon* **2010**, *66*, 4796. (h) Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B. *J. Am. Chem. Soc.* **2010**, *132*, 3298. (i) Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W. *J. Am. Chem. Soc.* **2010**, *132*, 3664. (j) Kwon, H. Y.; Park, C. M.; Lee, S. B.; Youn, J. H.; Kang, S. H. *Chem.–Eur. J.* **2008**, *14*, 1023. (k) Kang, S. H.; Lee, S. B.; Park, C. M. *J. Am. Chem. Soc.* **2003**, *125*, 15748.
7. For the use of triphenylphosphonium triflate as a Brønsted acid catalyst, see: Iwahashi, H.; Oka, T.; Abiko, A. *Chem. Lett.* **2008**, *37*, 708.
8. Rahman, Md. M.; Liu, H.-Y.; Eriks, K.; Prock, A.; Giering, W. P. *Organometallics* **1989**, *8*, 1.
9. The low yield and enantioselectivity in the reaction using Tf_2NH in $CHCl_3$ (entry 1) can be attributed to the rapid decomposition of **1c** due to the high acidity of Tf_2NH.
10. For selected recent examples, see: (a) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *J. Am. Chem. Soc.* **2010**, *132*, 14303. (b) Corey, E. J.; Surendra, K. *J. Am. Chem. Soc.* **2009**, *131*, 13928.
11. Lee-Ruff, E.; Ablenas, F. J. *Can. J. Chem.* **1989**, *67*, 699.
12. Topczewski, J. J.; Neighbors, J. D.; Wiemer, D. F. *J. Org. Chem.* **2009**, *74*, 6965.
13. Gester, S.; Pietzsch, J.; Wuest, F. R. *J. Label. Compd. Radiopharm.* **2007**, *50*, 105.
14. Chen, C.-C.; Huang, Y.-L.; Yeh, P.-Y.; Ou, J.-C. *Planta Med.* **2003**, *69*, 964.

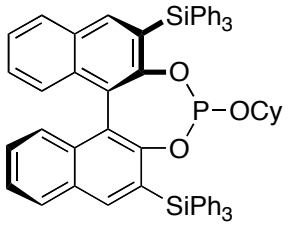
Experimental Section

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 d scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet, 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. High performance liquid chromatography (HPLC) analysis was conducted using Shimadzu LC-10 AD coupled diode array-detector SPD-MA-10A-VP and chiral column of Daicel CHIRALCEL OD-H (4.6 mm × 25 cm), Daicel CHIRALCEL OD-3 (4.6 mm × 25 cm) or Daicel CHIRALCEL OZ-H (4.6 mm × 25 cm) or Daicel CHIRALPAK IA (4.6 mm × 25 cm). Optical rotations were measured on a RUDOLPH AUTOPOL IV digital polarimeter. 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. Dry tetrahydrofuran, diethylether, toluene and dichloromethane were purchased from Kanto as the “anhydrous” and stored under nitrogen. Triethylamine were freshly distilled from calcium hydride. Chloroform were freshly distilled from diphosphorus pentoxide, and stored over MS 4Å under nitrogen in the dark. Other simple chemicals were analytical-grade and obtained commercially.

Preparation of Chiral Phosphorous Compounds 1.

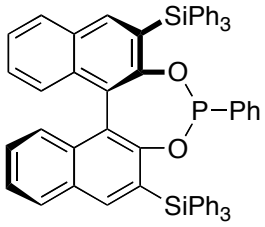


(11b*R*)-4-Phenoxy-2,6-bis(triphenylsilyl)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine (1a): To a solution of (*R*)-3,3'-bis(triphenylsilyl)-2,2'-binaphthol[1] (401 mg, 0.50 mmol) and Et_3N (0.35 mL, 2.5 mmol) in THF (4.0 mL) was added PCl_3 (52 mL, 0.60 mmol) dropwise at –78 °C. The mixture was stirred at –78 °C for ca. five minutes, and then at ambient temperature for 1 h. After the reaction mixture was cooled to –78 °C, a solution of phenol (52 mg, 0.55 mmol) in THF (1.0 mL) was added. The resultant mixture was stirred at –78 °C for a few minutes, and then at ambient temperature for 2 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 1:1) to give **1a** as a colorless solid (248 mg, 54% yield). IR (neat) 1591, 1491, 1428, 1387, 1200, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.77 (d, *J* = 8.2 Hz, 2H), 6.70 (dd, *J* = 7.3, 8.2 Hz, 2H), 6.80 (t, *J* = 7.3 Hz, 1H), 7.11–7.42 (m, 24H), 7.54 (d, *J* = 7.3 Hz, 6H), 7.59 (d, *J* = 6.9 Hz, 6H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.92 (s, 1H), 8.06 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.6, 122.8, 123.1, 123.4, 123.5, 124.76, 124.81, 125.3, 126.8, 126.88, 126.92, 127.0, 127.6, 127.8, 128.2, 128.4, 128.7, 129.0, 129.3, 129.4, 130.3, 130.7, 133.6, 134.5, 134.6, 134.7, 136.5, 136.7, 140.9, 150.6, 152.0, 152.8; ^{31}P NMR (162 MHz, $CDCl_3$) d 148.1; HRMS (FAB) calcd for $C_{62}H_{46}O_3PSi_2^+$ [M+H$^+$] 925.2723, found 925.2739.

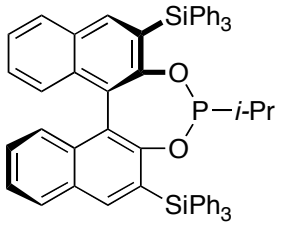


(11b*R*)-4-(Cyclohexyloxy)-2,6-bis(triphenylsilyl)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine (1b): Compound **1b** was prepared from (*R*)-3,3'-bis(triphenylsilyl)-2,2'-binaphthol[1] and cyclohexanol according to the same manner

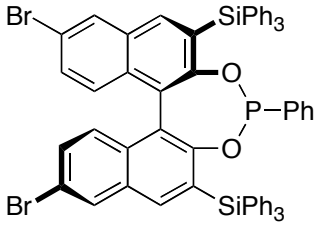
as **1a**. IR (neat) 1567, 1489, 1428, 1388, 1107 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.28–0.40 (m, 1H), 0.47–0.62 (m, 2H), 0.65–0.78 (m, 2H), 0.82–1.00 (m, 3H), 1.12–1.22 (m, 2H), 2.61–2.73 (m, 1H), 7.13–7.41 (m, 24H), 7.56 (d, *J* = 7.8 Hz, 6H), 7.60 (d, *J* = 7.8 Hz, 6H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.86 (s, 1H), 8.04 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 24.0, 24.8, 33.2, 33.7, 73.7, 122.8, 123.29, 123.34, 124.4, 124.5, 125.3, 126.7, 126.75, 126.82, 126.9, 127.0, 127.5, 127.8, 128.2, 128.6, 129.0, 129.3, 129.4, 130.0, 130.5, 134.1, 134.5, 134.7, 135.2, 136.6, 136.9, 140.4, 140.9, 152.6, 153.2; ^{31}P NMR (162 MHz, $CDCl_3$) d 153.7; HRMS (FAB) calcd for $C_{62}H_{52}O_3PSi_2^+$ [M+H^+] 931.3193, found 931.3198.



(11b*R*)-4-Phenyl-2,6-bis(triphenylsilyl)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine (1c): To a solution of (*R*)-3,3'-bis(triphenylsilyl)-2,2'-binaphthol[1] (240 mg, 0.30 mmol) and Et_3N (0.17 mL, 1.2 mmol) in THF (3.0 mL) was added $PhPCl_2$ (49 mL, 0.36 mmol) dropwise at –78 °C. The mixture was stirred at –78 °C for ca. five minutes, and then at ambient temperature for 3 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 1:1) to give **1c** as a colorless solid (250 mg, 83% yield). IR (neat) 1567, 1490, 1428, 1386, 1227, 1107 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.26 (dd, *J* = 7.3, 7.3 Hz, 2H), 6.86 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.08–7.43 (m, 31H), 7.54 (d, *J* = 6.9 Hz, 6H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.84 (s, 1H), 8.08 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.1, 123.8, 123.9, 124.5, 124.6, 125.3, 126.4, 126.7, 126.9, 127.0, 127.1, 127.4, 127.7, 128.2, 128.8, 129.0, 129.2, 129.3, 130.0, 130.7, 130.8, 130.9, 131.2, 134.0, 134.3, 134.4, 134.6, 136.7, 136.9, 138.5 (d, *J* = 41 Hz), 140.1, 140.8, 153.5, 154.3; ^{31}P NMR (162 MHz, $CDCl_3$) d 186.7; HRMS (FAB) calcd for $C_{62}H_{46}O_2PSi_2^+$ [M+H^+] 909.2774, found 909.2776.

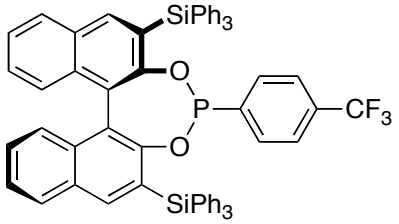


(11b*R*)-4-Isopropyl-2,6-bis(triphenylsilyl)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine (1d): Compound **1d** was prepared from (*R*)-3,3'-bis(triphenylsilyl)-2,2'-binaphthol[1] and *i*-$PrPCl_2$ according to the same manner as **1c**. IR (neat) 1568, 1488, 1428, 1387, 1217, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ –0.28– –0.42 (m, 1H), –0.18 (dd, *J* = 7.8, 19.7 Hz, 3H), 0.04 (dd, *J* = 6.0, 6.4 Hz, 3H), 7.07–7.44 (m, 24H), 7.59 (d, *J* = 6.8 Hz, 12H), 7.73 (d, *J* = 8.3, Hz, 1H), 7.77 (d, *J* = 8.2, Hz, 1H), 7.87 (s, 1H), 8.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 15.5 (d, *J* = 30 Hz), 32.7 (d, *J* = 37 Hz), 121.4, 123.38, 123.43, 124.3, 124.5, 125.3, 126.2, 126.5, 126.7, 126.9, 127.0, 127.66, 127.72, 128.1, 128.2 128.57, 128.65, 129.0, 129.2, 129.4, 129.5, 129.9, 130.6, 134.0, 134.2, 135.0, 135.1, 136.4, 136.5, 136.6, 136.8, 140.5, 141.2, 154.8, 155.4; ^{31}P NMR (162 MHz, $CDCl_3$) d 216.9; HRMS (FAB) calcd for $C_{59}H_{48}O_2PSi_2^+$ [M+H^+] 875.2931, found 875.2915.



(11b*R*)-9,14-Dibromo-4-phenyl-2,6-bis(triphenylsilyl)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine (1e): To a solution of (*R*)-3,3'-bis(triphenylsilyl)-2,2'-binaphthol[1] (1.6 g, 2.0 mmol) in CH_2Cl_2 (20 mL) was added a solution of Br_2 (0.26 mL, 5.0 mmol) in CH_2Cl_2 (10 mL) dropwise at –78°C. The mixture was stirred at –78 °C for ca. five minutes, and then at –10 °C for 3 h. To the reaction mixture was added aqueous $Na_2S_2O_3$ (20 wt%, 40 mL) at –10 °C, and the mixture was stirred at ambient temperature for 1 h. The resultant mixture was extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were washed with water and brine successively, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane–AcOEt 10:1) to give (*R*)-6,6'-dibromo-3,3'-bis(triphenylsilyl)-2,2'-binaphthol as a pale yellow solid (277 mg, 14% yield). IR (neat) 3519, 1576, 1484, 1428, 1349, 1109, 1045 cm^{-1}; ^1H NMR (400 MHz,

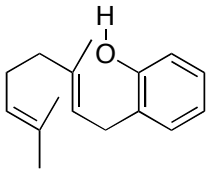
$CDCl_3$) δ 5.27 (s, 2H), 7.05 (d, J = 9.2 Hz, 2H), 7.32–7.47 (m, 20H), 7.59–7.65 (m, 12H), 7.81 (s, 2H), 7.87 (d, J = 1.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.6, 117.7, 125.5, 125.6, 127.9, 129.7, 130.2, 131.0, 131.4, 133.2, 133.7, 136.2, 141.1, 156.7; HRMS (FAB) calcd for $C_{56}H_{41}O_2Br_2Si_2$ [M+H$^+$] 959.1012, found 959.0983. To a solution of (*R*)-6,6'-dibromo-3,3'-bis(triphenylsilyl)-2,2'-binaphthol (277 mg, 0.289 mmol) and Et_3N (0.24 mL, 1.73 mmol) in THF (6.0 mL) was added $PhPCl_2$ (60 mL, 0.43 mmol) dropwise at –78 °C. The mixture was stirred at –78 °C for ca. five minutes, and then at ambient temperature for 3 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 1:1) to give **1e** as a colorless solid (262 mg, 85% yield). IR (neat) 1568, 1481, 1428, 1396, 1213, 1188, 1106, 1070 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (dd, J = 7.3, 7.3 Hz, 2H), 6.88 (dd, J = 7.3, 7.3 Hz, 2H), 7.02–7.43 (m, 29H), 7.51 (d, J = 7.3 Hz, 6H), 7.73 (s, 1H), 7.93 (s, 1H), 7.96 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.7, 122.8, 123.47, 123.53, 125.3, 127.1, 127.2, 127.5, 127.8, 128.2, 129.0, 129.4, 129.5, 130.38, 130.42, 130.8, 131.1, 131.9, 132.5, 132.9, 133.5, 133.9, 136.6, 136.8, 138.2 (d, J = 41 Hz), 139.2, 139.9, 153.8, 154.6; ^{31}P NMR (162 MHz, $CDCl_3$) d 188.4; HRMS (FAB) calcd for $C_{62}H_{44}Br_2O_2PSi_2^+$ [M+H$^+$] 1065.0984, found 1065.0979.



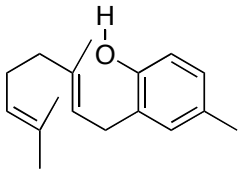
(11b*R*)-4-(4-(Trifluoromethyl)phenyl)-2,6-bis(triphenylsilyl)dinaphtho[2,1-*d*:1',2'-*f*][1,3, 2]dioxaphosphepine (1f): To a solution of 4-bromobenzotrifluoride (0.70 mL, 5 mmol) in Et_2O (10 mL) was added a 1.6 M solution of *n*-BuLi in hexane (3.4 mL, 5.5 mmol) dropwise at –78 °C. The reaction mixture was stirred at –78 °C for 1 h, and then at 0 °C for 1 h. To the mixture was added $ClP(NEt_2)_2$ (1.2 mL, 5.5 mmol) dropwise at 0 °C, and the reaction mixture was stirred at ambient temperature for 2 h. The solvent was evaporated under reduced pressure and the resultant residue was extracted with hexane (20 mL × 3). Insoluble inorganic salts were removed by filtration. The filtrate was concentrated under reduced pressure to give a crude *p*-$CF_3C_6H_4P(NEt_2)_2$ as a yellow oil. To a solution of (*R*)-

3,3'-bis(triphenylsilyl)-2,2'-binaphthol[1] (400 mg, 0.50 mmol) in toluene (5 mL) was added *p*-$CF_3C_6H_4P(NEt_2)_2$ (960 mg, 3.0 mmol) in three portions, and the mixture was refluxed for 3 days. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane–toluene 1:1) to give **1f** as a colorless solid (235 mg, 48% yield). IR (neat) 1564, 1487, 1428, 1387, 1323, 1170, 1130, 1106, 1060 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.32 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.11 (d, *J* = 7.3 Hz, 6H), 7.06–7.47 (m, 25H), 7.53 (d, *J* = 7.4 Hz, 6H), 7.60 (dd, *J* = 7.3, 7.3 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.84 (s, 1H), 8.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.1, 123.8, 124.8, 124.9, 126.4, 126.7, 127.0, 127.1, 127.2, 127.5, 127.8, 128.9, 129.38, 129.45, 130.1, 130.9, 131.1, 131.4, 132.1, 132.4, 133.9, 134.0, 134.2, 134.5, 136.6, 136.8, 140.4, 141.0, 142.6 (d, *J* = 45 Hz), 153.0, 153.9; ^{19}F NMR (376 MHz, $CDCl_3$) d –62.8; 31P NMR (162 MHz, $CDCl_3$) d 180.3; HRMS (FAB) calcd for $C_{63}H_{45}F_3O_2PSi_2^+$ [M+H^+] 977.2648, found 977.2629.

Preparation of 2-Geranylphenols 2.

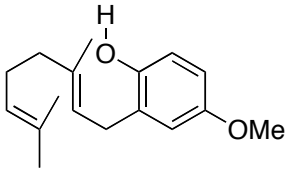


(*E*)-2-(3,7-dimethylocta-2,6-dienyl)phenol (2a):[2] Compound **2a** was prepared from (*E*)-geranylbromide and phenol according to the reported procedure.[2] ^1H NMR (400 MHz, $CDCl_3$) δ 1.60 (s, 3H), 1.69 (s, 3H), 1.77 (s, 3H), 2.05–2.16 (m, 4H), 3.37 (d, *J* = 6.9 Hz, 2H), 5.04–5.11 (m, 1H), 5.09 (s, 1H), 5.33 (t, *J* = 7.1 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 6.86 (t, *J* = 7.3 Hz, 1H), 7.08–7.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 17.7, 25.7, 26.4, 29.7, 39.7, 115.7, 120.7, 121.6, 123.8, 126.8, 127.5, 129.9, 131.9, 138.4, 154.4.

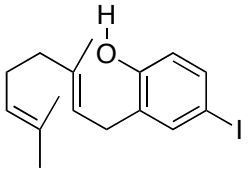


(*E*)-2-(3,7-Dimethylocta-2,6-dienyl)-4-methylphenol (2b): To a solution of 4-methylphenol (541 mg, 5.0 mmol) in toluene (20 mL) was added $Sc(OTf)_3$ (492

mg, 1.0 mmol) at ambient temperature, and then a solution of (*E*)-geraniol (1.3 mL, 7.5 mmol) in toluene (8 mL) was added dropwise over a period of 10 h at 0 °C. After stirring for 1 day at the same temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–ether 10:1) to give **2b** as pale yellow oil (363 mg, 30% yield). IR (neat) 3446, 1500, 1439, 1377, 1260, 1137, 1102 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.60 (s, 3H), 1.68 (s, 3H), 1.77 (s, 3H), 2.04–2.15 (m, 4H), 2.25 (s, 3H), 3.33 (d, *J* = 6.9 Hz, 2H), 4.94 (s, 1H), 5.07 (t, *J* = 6.9 Hz, 1H), 5.31 (t, *J* = 7.3 Hz, 1H), 6.70 (dd, *J* = 5.0, 8.7 Hz, 1H), 6.86–6.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2, 17.7, 20.5, 25.7, 26.4, 29.9, 39.7, 115.6, 121.8, 123.8, 126.5, 127.9, 129.8, 130.5, 131.9, 138.3, 152.2; HRMS (FAB) calcd for $C_{17}H_{24}O^+$ [M^+] 244.1827, found 244.1821.

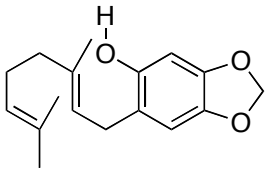


(*E*)-2-(3,7-Dimethylocta-2,6-dienyl)-4-methoxyphenol (2c): Compound **2c** was prepared from (*E*)-geraniol and 4-methoxyphenol according to the same manner as **2b**. IR (neat) 3407, 1504, 1433, 1200, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.60 (s, 3H), 1.68 (s, 3H), 1.77 (s, 3H), 2.04–2.16 (m, 4H), 3.33 (d, *J* = 6.8 Hz, 2H), 3.75 (s, 3H), 4.73 (s, 1H), 5.07 (t, *J* = 6.8 Hz, 1H), 5.30 (t, *J* = 7.3 Hz, 1H), 6.66 (dd, *J* = 3.2, 8.7 Hz, 1H), 6.68 (d, *J* = 3.2 Hz, 1H), 6.75 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2, 17.7, 25.7, 26.4, 30.0, 39.7, 55.7, 112.0, 115.6, 116.4, 121.4, 123.8, 128.0, 132.0, 138.7, 148.3, 153.6; HRMS (FAB) calcd for $C_{17}H_{24}O_2^+$ [M^+] 260.1776, found 260.1793.

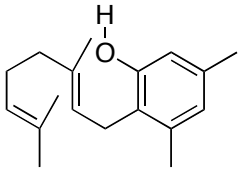


(*E*)-2-(3,7-Dimethylocta-2,6-dienyl)-4-iodophenol (2d): Compound **2d** was prepared from (*E*)-geraniol and 4-iodophenol according to the same manner as **2b**. IR (neat) 3441, 1480, 1443, 1405, 1261, 1162, 1102 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.60 (s, 3H), 1.69 (s, 3H), 1.76 (s, 3H), 2.04–2.16 (m, 4H), 3.30 (d, *J* = 7.3

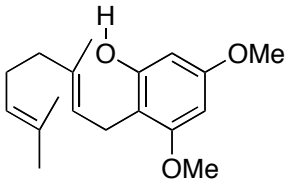
Hz, 2H), 5.02–5.09 (m, 1H), 5.16 (s, 1H), 5.27 (t, J = 7.3 Hz, 1H), 6.58 (d, J = 9.2 Hz, 1H), 7.37–7.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2, 17.7, 25.7, 26.3, 29.5, 39.6, 82.8, 118.1, 120.7, 123.6, 129.6, 132.1, 136.2, 138.4, 139.3, 154.3; HRMS (FAB) calcd for $C_{16}H_{21}IO^+$ [M^+] 356.0637, found 356.0647.



(*E*)-6-(3,7-Dimethylocta-2,6-dienyl)benzo[*d*][1,3]dioxol-5-ol (2e):[3] Compound **2e** was prepared from (*E*)-geraniol and benzo[*d*][1,3]dioxol-5-ol according to the reported procedure.[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (s, 3H), 1.69 (s, 3H), 1.74 (s, 3H), 2.03–2.16 (m, 4H), 3.25 (d, J = 7.3 Hz, 2H), 5.01–5.12 (m, 2H), 5.26 (t, J = 7.3 Hz, 1H), 5.86 (s, 2H), 6.41 (s, 1H), 6.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 17.7, 25.6, 26.3, 29.4, 39.6, 98.5, 100.8, 109.1, 118.6, 121.7, 123.8, 132.0, 138.4, 141.2, 146.3, 148.8.

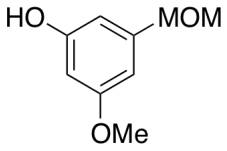


(*E*)-2-(3,7-Dimethylocta-2,6-dienyl)-3,5-dimethylphenol (2f): Compound **2f** was prepared from (*E*)-geraniol and 3,5-dimethylphenol according to the same manner as **2b**. IR (neat) 3455, 1619, 1584, 1488, 1375, 1295, 1045 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (s, 3H), 1.67 (s, 3H), 1.80 (s, 3H), 1.99–2.12 (m, 4H), 2.24 (s, 3H), 2.26 (s, 3H), 3.33 (d, J = 6.9 Hz, 2H), 4.96 (s, 1H), 5.05 (t, J = 6.9 Hz, 1H), 5.15 (t, J = 6.9 Hz, 1H), 6.51 (s, 1H), 6.59 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2, 17.7, 19.9, 20.9, 25.3, 25.7, 26.4, 39.6, 114.3, 121.9, 122.5, 123.5, 123.9, 131.8, 136.5, 137.2, 137.4, 154.2; HRMS (FAB) calcd for $C_{18}H_{26}O^+$ [M^+] 258.1984, found 258.1992.

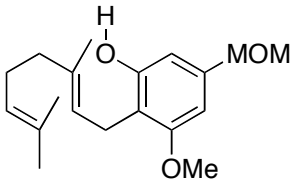


(*E*)-2-(3,7-Dimethylocta-2,6-dienyl)-3,5-dimethoxyphenol (2g): Compound **2g** was prepared from (*E*)-geraniol and 3,5-dimethoxyphenol according to the

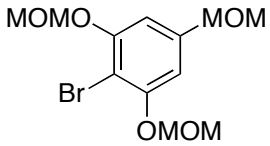
same manner as **2b**. IR (neat) 3420, 1620, 1594, 1509, 1455, 1202, 1146, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.59 (s, 3H), 1.68 (s, 3H), 1.80 (s, 3H), 2.01–2.14 (m, 4H), 3.35 (d, *J* = 6.9 Hz, 2H), 3.76 (s, 3H), 3.78 (s, 3H), 5.05 (t, J = 6.9 Hz, 1H), 5.22 (t, *J* = 6.9 Hz, 1H), 5.40 (s, 1H), 6.07 (d, *J* = 2.3 Hz, 1H), 6.09 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 17.7, 21.7, 25.7, 26.4, 39.7, 55.3, 55.7, 91.4, 93.7, 107.3, 122.3, 123.8, 131.9, 138.1, 156.2, 158.4, 159.3; HRMS (FAB) calcd for $C_{18}H_{26}O_3^+$ [M^+] 290.1882, found 290.1874.



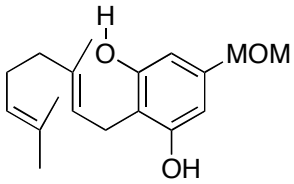
3-Methoxy-5-(methoxymethyl)phenol: To a solution of 3,5-dihydroxybenzylalcohol (14.0 g, 100 mmol) in 4 M aqueous NaOH (50 mL) was added isobutyric anhydride (25.0 mL, 150 mmol) at 0 °C. After stirring for 1 h at the same temperature, the reaction mixture was diluted with water and acidified with 1 M HCl before extracting with AcOEt. The combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–AcOEt 1:1) to give 3-hydroxy-5-(hydroxymethyl)phenyl isobutyrate as a colorless oil (3.9 g, 19% yield). To a solution of 3-hydroxy-5-(hydroxymethyl)phenyl isobutyrate (3.76 g, 17.9 mmol) in MeCN (180 mL) were added Ag_2O (41.5 g, 179 mmol) and MeI (22.3 mL, 358 mmol) at room temperature, followed by stirring at the same temperature for 1 day. The mixture was filtered through Celite and concentrated. To a solution of the residue in MeOH (300 mL) was added K_2CO_3 (12.4 g, 89.5 mmol), and the mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with water, acidified by 1 M HCl and extracted with ether. The combined extracts were dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–AcOEt 3:1) to give 3-methoxy-5-(methoxymethyl)phenol as a yellow oil (2.13 g, 71% yield). IR (neat) 3311, 1601, 1459, 1338, 1195, 1154, 1088, 1060 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.38 (s, 3H), 3.78 (s, 3H), 4.38 (s, 2H), 4.81 (br s, 1H), 6.33 (br t, *J* = 2.1 Hz, 1H), 6.42 (s, 1H), 6.48 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.2, 57.8, 74.4, 100.9, 105.4, 107.2, 140.1, 157.2, 160.8; HRMS (FAB) calcd for $C_9H_{13}O_3^+$ [$M+H^+$] 169.0865, found 169.0859.



(*E*)-2-(3,7-Dimethylocta-2,6-dienyl)-3-methoxy-5-(methoxymethyl)phenol (2h): Compound **2h** was prepared from (*E*)-geraniol and 3-methoxy-5-(methoxymethyl)phenol according to the same manner as **2b**. **2h:** IR (neat) 3336, 1596, 1513, 1452, 1425, 1380, 1166, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.59 (s, 3H), 1.67 (s, 3H), 1.80 (s, 3H), 2.00–2.14 (m, 4H), 3.38 (s, 3H), 3.40 (d, *J* = 7.3 Hz, 2H), 3.82 (s, 3H), 4.38 (s, 2H), 5.05 (br t, *J* = 6.4 Hz, 1H), 5.22 (br t, *J* = 6.4 Hz, 1H), 5.32–5.37 (m, 1H), 6.46 (s, 1H), 6.48 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 17.6, 22.1, 25.6, 26.4, 39.7, 55.7, 57.9, 74.6, 102.3, 108.2, 114.7, 121.9, 123.9, 131.7, 137.2, 137.4, 155.4, 158.0; HRMS (FAB) calcd for $C_{19}H_{28}O_3^+$ [M^+] 304.2038, found 304.2049.



2-Bromo-1,3-bis(methoxymethoxy)-5-(methoxymethyl)benzene: To a solution of (4-bromo-3,5-bis(methoxymethoxy)phenyl)methanol[4] (2.78 g, 9.08 mmol) in THF (50 mL) at 0 °C was added NaH (610 mg, 60% in oil, 15.2 mmol) followed by MeI (0.94 mL, 15.2 mmol). After stirring at ambient temperature for 5 h, the reaction was quenched by addition of water. The mixture was extracted with AcOEt, and the organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–AcOEt 3:1) to give 2-bromo-1,3-bis(methoxymethoxy)-5-(methoxymethyl)benzene as a white solid (2.1 g, 72% yield). IR (neat) 1589, 1432, 1395, 1153, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.40 (s, 3H), 3.52 (s, 6H), 4.39 (s, 2H), 5.26 (s, 4H), 6.82 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.4, 58.3, 74.1, 94.9, 102.4, 108.3, 139.1, 154.8; HRMS (FAB) calcd for $C_{12}H_{17}BrO_5^+$ [M^+] 320.0259, found 320.0265.



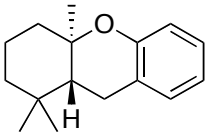
(*E*)-2-(3,7-Dimethylocta-2,6-dienyl)-5-(methoxymethyl)benzene-1,3-diol (2i): To a solution of 2-bromo-1,3-bis(methoxymethoxy)-5-(methoxymethyl)benzene (640 mg, 2.0 mmol) in THF (20 mL) at –78 °C was added a 1.6 M solution of *n*-BuLi in hexane (1.5 mL, 2.4 mmol), and the mixture was stirred at the same temperature for 2 h. CuBr•SMe_2 complex (452 mg, 2.2 mmol) was added in one portion. The resulting mixture was stirred for 30 min, and then geranyl bromide (0.60 mL, 3.0 mmol) was added dropwise. The mixture was stirred at –78 °C for a few minutes and allowed to stir at ambient temperature for 20 h. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with ether. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–AcOEt 5:1) to give MOM-protected **2i** as colorless oil (495 mg, 65% yield). To a solution of MOM-protected **2i** (479 mg, 1.27 mmol) in MeOH (26 mL) was added a solution of 12 M HCl (0.53 mL, 6.33mmol) in MeOH (6 mL) dropwise at 0 °C, and the mixture was stirred at room temperature for 1 day. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ solution, and methanol was removed under reduced pressure before extracting with AcOEt. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–AcOEt 3:1) to give **2i** (297 mg, 81% yield). IR (neat) 3348, 1598, 1432, 1382, 1165, 1078, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.59 (s, 3H), 1.67 (s, 3H), 1.81 (s, 3H), 1.99–2.15 (m, 4H), 3.37 (s, 3H), 3.41 (d, J = 6.8 Hz, 2H), 4.35 (s, 2H), 5.05 (t, J = 6.9 Hz, 1H), 5.26 (t, J = 6.9 Hz, 1H), 5.40–5.58 (m, 2H), 6.41 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 17.7, 22.3, 25.6, 26.3, 39.7, 57.7, 74.3, 107.6, 113.2, 121.5, 123.7, 132.0, 136.9, 138.8, 155.3; HRMS (FAB) calcd for $C_{18}H_{26}O_3^+$ [M^+] 290.1882, found 290.1911.

Typical Procedure for the Enantioselective Cyclization of 2-Geranylphenol 2a.

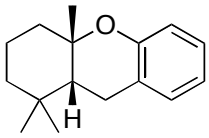
To a solution of **1e** (42.6 mg, 0.040 mmol) in $CHCl_3$ (1.8 mL) was added a 0.05 M solution of FSO_3H in $CHCl_3$ (0.20 mL, 0.010 mmol) at –55 °C, and the mixture was stirred

for ca. five minutes. To this solution, a solution of **2a** (23.0 mg, 0.10 mmol) in hexane (0.1 mL) was added dropwise at –40 °C, and the mixture was stirred for 2–3 days at –55 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ (3 mL) and the reaction mixture was extracted with ether. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (hexane–ether 20:1) to give **3a** (19.8 mg, *trans*/*cis* = 90:10, 86% yield) as a diastereomeric mixture.

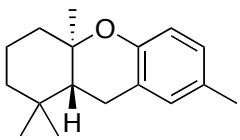
The corresponding physical and spectroscopic data for **3** are as follows.



(4a*R*,9a*R*)-1,1,4a-Trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (*trans*-3a):[5] $[a]^{23}_D$ +43.9 (*c* = 1.92, $CHCl_3$) for 84% ee; HPLC (Daicel Chiralcel OD-H × 2, hexane, flow rate 0.3 mL/min) t_R = 47.9 (major, (+)-enantiomer), 74.0 (minor, (–)-enantiomer) min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 3H), 1.01 (s, 3H), 1.23 (s, 3H), 1.25–1.76 (m, 6H), 1.93–2.01 (m, 1H), 2.61 (dd, *J* = 13.0, 16.1 Hz, 1H), 2.72 (dd, *J* = 5.6, 16.1 Hz, 1H), 6.75–6.86 (m, 2H), 7.07 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.78, 19.84, 20.68, 23.25, 32.10, 33.38, 40.00, 41.49, 48.06, 117.01, 119.60, 122.64, 127.10, 129.63, 153.25. Absolute configuration was assigned to be (4a*R*,9a*R*) by comparing the reported retention time as well as from the sign of measured optical rotation.[5]

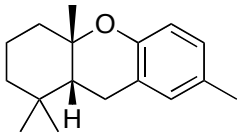


(4a*S*,9a*R*)-1,1,4a-Trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (*cis*-3a):[5] HPLC (Daicel Chiralcel OD-H × 2, hexane, flow rate 0.3 mL/min) t_R = 38.6 (major enantiomer), 30.5 (minor enantiomer) min.

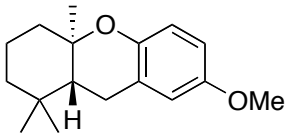


(4a*R*,9a*R*)-1,1,4a,7-Tetramethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (*trans*-3b):[5] $[a]^{23}_D$ +54.5 (*c* 1.51, $CHCl_3$) for 93% ee; HPLC (Daicel Chiralcel OD-H × 3, hexane, flow

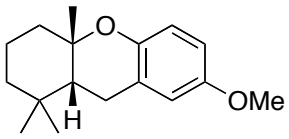
rate 0.3 mL/min) t_R = 83.7 (minor enantiomer), 90.7 (major enantiomer) min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 3H), 0.99 (s, 3H), 1.20 (s, 3H), 1.23–1.72 (m, 6H), 1.92–1.97 (m, 1H), 2.25 (s, 3H), 2.56 (dd, *J* = 12.8, 16.5 Hz, 1H), 2.66 (dd, *J* = 5.0, 16.5 Hz, 1H), 6.66 (d, *J* = 8.7 Hz, 1H), 6.84–6.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 19.8, 20.5, 20.7, 23.2, 32.1, 33.3, 40.0, 41.5, 48.1, 77.2, 116.7, 122.3, 127.7, 128.7, 130.0, 150.9.



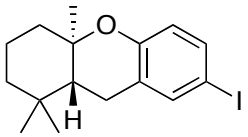
(4a*S*,9a*R*)-1,1,4a,7-Tetramethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (*cis*-3b): HPLC (Daicel Chiralcel OD-H × 3, hexane, flow rate 0.3 mL/min) t_R = 44.8 (minor enantiomer), 51.4 (major enantiomer) min.



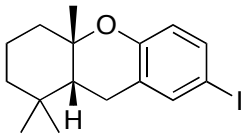
(4a*R*,9a*R*)-7-Methoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (*trans*-3c):[5] $[a]^{24}_D$ +51.9 (*c* 0.25, $CHCl_3$) for 88% ee; HPLC (Daicel Chiralcel OD-H × 2, hexane–*i*-PrOH 200:1, flow rate 0.5 mL/min) t_R = 30.3 (major enantiomer), 47.7 (minor enantiomer) min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 3H), 1.00 (s, 3H), 1.20 (s, 3H), 1.24–1.73 (m, 6H), 1.92–1.97 (m, 1H), 2.58 (dd, *J* = 13.3, 16.5 Hz, 1H), 2.69 (dd, *J* = 5.0, 16.5 Hz, 1H), 3.75 (s, 3H), 6.59–6.70 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 19.8, 20.6, 23.6, 32.1, 33.3, 41.5, 48.0, 55.7, 76.8, 113.1, 114.1, 117.5, 123.2, 147.2, 152.8.



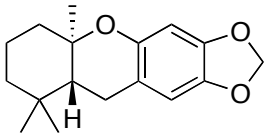
(4a*S*,9a*R*)-7-Methoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (*cis*-3c): HPLC (Daicel Chiralcel OD-H × 2, hexane–*i*-PrOH 200:1, flow rate 0.5 mL/min) t_R = 22.2 (minor enantiomer), 23.9 (major enantiomer) min.



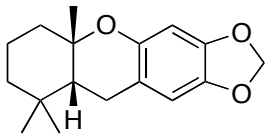
(4a*R*,9a*R*)-7-Iodo-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (*trans*-3d): $[a]^{24}_{D}$ +54.1 (*c* 1.62, $CHCl_3$) for 87% ee; HPLC (Daicel Chiralcel OD-H × 2, hexane, flow rate 0.3 mL/min) t_R = 55.8 (major enantiomer), 98.9 (minor enantiomer) min; IR (neat) 1569, 1477, 1378, 1248, 1154, 1099, 1041 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 3H), 0.99 (s, 3H), 1.19 (s, 3H), 1.22–1.69 (m, 6H), 1.92–1.98 (m, 1H), 2.56 (dd, *J* = 13.3, 16.5 Hz, 1H), 2.66 (dd, *J* = 5.0, 16.5 Hz, 1H), 6.52 (d, *J* = 8.2 Hz, 1H), 7.33 (dd, *J* = 2.0, 8.2 Hz, 1H), 7.37 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.69, 19.74, 20.6, 23.0, 32.0, 33.4, 39.8, 41.3, 47.7, 77.6, 81.5, 119.4, 125.5, 135.9, 138.1, 153.2; HRMS (FAB) calcd for $C_{16}H_{22}IO$ $[M+H^+]$ 357.0715, found 357.0725.



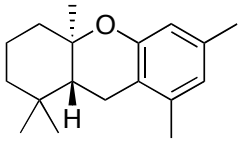
(4a*S*,9a*R*)-7-Iodo-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (*cis*-3d): HPLC (Daicel Chiralcel OD-H × 2, hexane, flow rate 0.3 mL/min) t_R = 36.4 (minor enantiomer), 41.8 (major enantiomer) min.



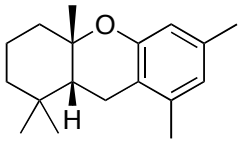
(5a*R*,9a*R*)-5a,9,9-Trimethyl-6,7,8,9,9a,10-hexahydro-5a*H*-[1,3]dioxolo[4,5-*b*]xanthene (*trans*-3e):[3] $[a]^{23}_{D}$ +51.7 (*c* 1.18, $CHCl_3$) for 84% ee; HPLC (Daicel Chiralcel OD-H, hexane–*i*-PrOH 200:1, flow rate 0.5 mL/min) t_R = 26.4 (minor enantiomer), 36.3 (major enantiomer) min; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (s, 3H), 0.98 (s, 3H), 1.18 (s, 3H), 1.20–1.68 (m, 6H), 1.87–1.95 (m, 1H), 2.49 (dd, *J* = 13.3, 16.0 Hz, 1H), 2.59 (dd, *J* = 5.0, 16.0 Hz, 1H), 5.84 (d, *J* = 1.4 Hz, 1H), 5.85 (d, *J* = 1.4 Hz, 1H), 6.31 (s, 1H), 6.51 (s,1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 19.7, 20.6, 23.4, 32.1, 33.3, 39.8, 41.5, 48.0, 77.2, 98.8, 100.6, 108.2, 113.9, 140.9, 146.2, 147.6.



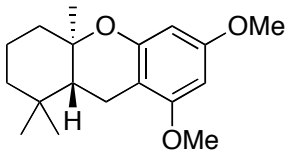
(5a*S*,9a*R*)-5a,9,9-Trimethyl-6,7,8,9,9a,10-hexahydro-5a*H*-[1,3]dioxolo[4,5-*b*]xanthene (*cis*-3e): HPLC (Daicel Chiralcel OD-H, hexane–*i*-PrOH 200:1, flow rate 0.5 mL/min) t_R = 14.8 (minor enantiomer), 18.8 (major enantiomer) min.



(4a*R*,9a*R*)-1,1,4a,6,8-Pentamethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (*trans*-3f):[5] $[a]^{22}_D$ +29.6 (*c* 1.70, $CHCl_3$) for 72% ee; HPLC (Daicel Chiralcel OD-H × 2, hexane, flow rate 0.3 mL/min) t_R = 47.4 (major enantiomer), 54.1 (minor enantiomer) min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 3H), 1.01 (s, 3H), 1.18 (s, 3H), 1.24–1.71 (m, 6H), 1.92–1.97 (m, 1H), 2.20 (s, 3H), 2.23 (s, 3H), 2.29 (dd, *J* = 13.3, 16.5 Hz, 1H), 2.57 (dd, *J* = 5.0, 16.5 Hz, 1H), 6.47 (s, 1H), 6.55 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 19.6, 19.8, 20.6, 20.8, 21.0, 32.1, 33.4, 39.9, 41.6, 48.1, 76.3, 115.2, 118.3, 122.2, 136.4, 137.1, 152.9.

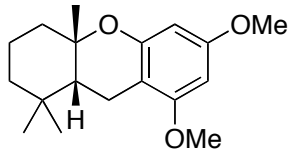


(4a*S*,9a*R*)-1,1,4a,6,8-Pentamethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (*cis*-3f): HPLC (Daicel Chiralcel OD-H × 2, hexane, flow rate 0.3 mL/min) t_R = 28.9 (minor enantiomer), 32.1 (major enantiomer) min.

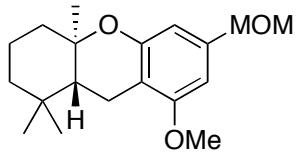


(4a*R*,9a*R*)-6,8-Dimethoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (*trans*-3g): $[a]^{24}_D$ +50.0 (*c* = 1.05, $CHCl_3$) for 79% ee; HPLC (Daicel Chiralcel OD-H and OD-3, hexane–*i*-PrOH 200:1, flow rate 0.2 mL/min) t_R = 80.6 (minor enantiomer), 101.9 (major enantiomer) min; IR (neat) 1619, 1591, 1496, 1454, 1202, 1146, 1111, 1053 cm^{-1}; ^{1}H

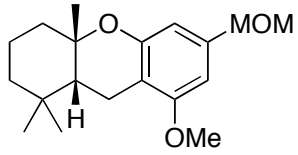
NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 3H), 1.01 (s, 3H), 1.21 (s, 3H), 1.24–1.67 (m, 6H), 1.92–1.97 (m, 1H), 2.20 (dd, *J* = 12.8, 16.5 Hz, 1H), 2.67 (dd, *J* = 5.0, 16.5 Hz, 1H), 3.74 (s, 3H), 3.80 (s, 3H), 6.00 (d, *J* = 2.3 Hz, 1H), 6.04 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 19.6, 19.8, 20.6, 32.1, 33.5, 39.9, 41.6, 47.8, 55.2, 55.3, 77.2, 90.7, 93.4, 103.8, 154.2, 158.4, 159.2; HRMS (FAB) calcd for $C_{18}H_{27}O_3^+$ [M+H$^+$] 291.1960, found 291.1956.



(4a*S*,9a*R*)-6,8-Dimethoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (*cis*-3g): HPLC (Daicel Chiralcel OD-H and OD-3, hexane–*i*-PrOH 200:1, flow rate 0.2 mL/min) t_R = 61.6 (minor enantiomer), 66.2 (major enantiomer) min.

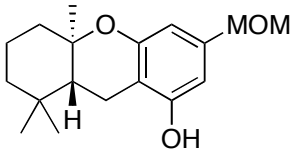


(4a*R*,9a*R*)-8-Methoxy-6-(methoxymethyl)-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene (*trans*-3h): $[a]^{22}_D$ +49.8 (*c* 1.25, $CHCl_3$) for 74% ee; HPLC (Daicel Chiralcel OD-H and OD-3, hexane–*i*-PrOH 200:1, flow rate 0.2 mL/min) t_R = 72.8 (major enantiomer), 88.7 (minor enantiomer) min; IR (neat) 1617, 1587, 1451, 1422, 1377, 1297, 1200, 1154, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 3H), 1.01 (s, 3H), 1.19 (s, 3H), 1.23–1.68 (m, 6H), 1.92–1.97 (m, 1H), 2.25 (dd, *J* = 13.3, 17.0 Hz, 1H), 2.73 (dd, *J* = 5.0, 17.0 Hz, 1H), 3.37 (s, 3H), 3.84 (s, 3H), 4.36 (s, 2H), 6.40 (s, 1H), 6.42 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 19.6, 19.8, 20.6, 32.1, 33.4, 39.9, 41.6, 47.6, 55.4, 58.0, 74.8, 77.2, 100.6, 109.3, 110.8, 137.2, 153.6, 157.9; HRMS (FAB) calcd for $C_{18}H_{29}O_3^+$ [M+H$^+$] 305.2117, found 305.2130.

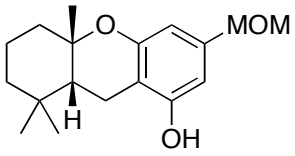


(4a*S*,9a*R*)-8-Methoxy-6-(methoxymethyl)-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-x

anthene (*cis*-3h): HPLC (Daicel Chiralcel OD-H and OD-3, hexane–*i*-PrOH 200:1, flow rate 0.2 mL/min) t_R = 51.8 (major enantiomer), 53.3 (minor enantiomer) min.

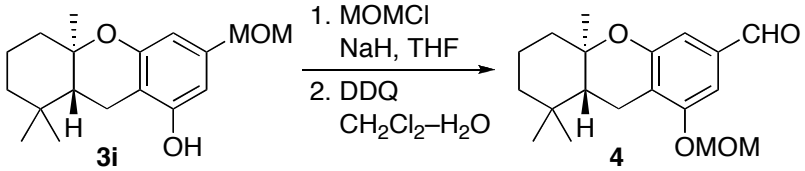


(4a*R*,9a*R*)-6-(Methoxymethyl)-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthen-8-ol (*trans*-3i): $[a]^{24}_D$ +35.2 (*c* 0.95, $CHCl_3$) for 70% ee; HPLC (Daicel Chiralcel OZ-H, hexane–*i*-PrOH 20:1, flow rate 0.3 mL/min) t_R = 27.3 (minor enantiomer), 40.5 (major enantiomer) min; IR (neat) 3339, 1625, 1589, 1429, 1378, 1136, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 3H), 1.02 (s, 3H), 1.21 (s, 3H), 1.23–1.70 (m, 6H), 1.93–1.98 (m, 1H), 2.31 (dd, *J* = 13.3, 16.5 Hz, 1H), 2.71 (dd, *J* = 5.0, 16.5 Hz, 1H), 3.36 (s, 3H), 4.32 (s, 2H), 4.79–4.86 (m, 1H), 6.355 (s, 1H), 6.364 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 19.6, 19.7, 20.6, 32.1, 33.4, 39.8, 41.5, 47.6, 57.6, 74.5, 77.1, 105.5, 109.0, 109.7, 136.9, 154.1, 154.4; HRMS (FAB) calcd for $C_{18}H_{27}O_3^+$ $[M+H^+]$ 291.1960, found 291.1969.



(4a*S*,9a*R*)-6-(Methoxymethyl)-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthen-8-ol (*cis*-3i): HPLC (Daicel Chiralcel OZ-H, hexane–*i*-PrOH 20:1, flow rate 0.3 mL/min) t_R = 17.5 (minor enantiomer), 19.7 (major enantiomer) min.

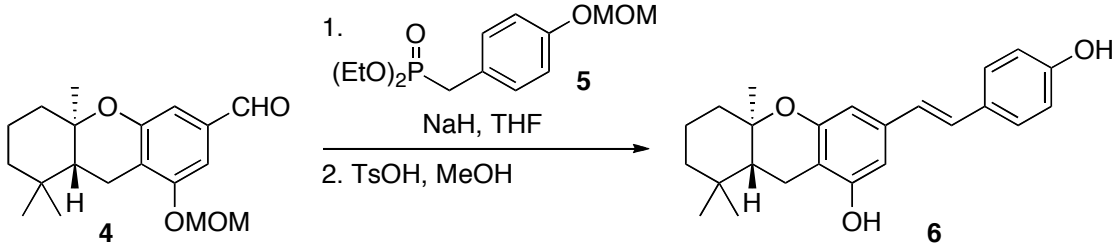
Synthesis of 4a-*epi*-Ugonstilbene B (8).



To a solution of **3i** (20.3 mg, 0.070 mmol) in THF (2 mL) was added NaH (28 mg, 60% in oil, 0.70 mmol) in one portion at ambient temperature. After stirring at the same temperature for 30 min, MOMCl (0.027 mL, 0.35 mmol) was added dropwise at 0 °C. The

reaction mixture was warmed up to ambient temperature and stirred for 3 h. After carefully quenching with water, the mixture was extracted with ether, and the organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–ether 10:1) to give MOM-protected **3i** (17.2 mg, 74% yield). To a solution of MOM-protected **3i** (13.6 mg, 0.0407 mmol) in CH_2Cl_2 (3 mL) and water (0.3 mL) at room temperature was added solid DDQ (56 mg, 0.25 mmol) in two portions. After stirring for 8 h, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ and extracted with ether. The organic extract was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–ether 5:1) to give **3i** (12.4 mg, 96% yield) as a diastereomeric mixture.

(4a*R*,9a*R*)-8-(Methoxymethoxy)-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-xanthene-6-carbaldehyde (4): IR (neat) 1698, 1582, 1437, 1381, 1344, 1298, 1154, 1105, 1060, 1012 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 3H), 1.04 (s, 3H), 1.16–1.76 (m, 6H), 1.21 (s, 3H), 1.96–2.02 (m, 1H), 2.36 (dd, *J* = 13.3, 17.9 Hz, 1H), 2.83 (dd, *J* = 4.8, 17.9 Hz, 1H), 3.52 (s, 3H), 5.27 (s, 2H), 6.97 (d, *J* = 1.4 Hz, 1H), 7.12 (d, *J* = 1.4 Hz, 1H), 9.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 19.6, 19.7, 20.5, 32.0, 33.4, 39.7, 33.4, 39.7, 41.4, 47.2, 56.3, 77.6, 94.4, 103.8, 113.9, 119.8, 135.8, 154.5, 156.0, 191.9; HRMS (FAB) calcd for $C_{19}H_{27}O_4$ $[M+H^+]$ 319.1909, found 319.1913.



To a solution of **4** (12.4 mg, 0.039 mmol) and phosphonate **5** (25 mg, 0.080 mmol) in THF (5 mL) at ambient temperature was added 15-crown-5 (8 mL, 0.040 mmol), followed by NaH (32 mg, 60% in oil, 0.80 mmol). After stirring at the same temperature for 1 day, the reaction mixture was quenched by addition of water, and then the mixture was extracted with AcOEt, and the organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–ether 10:1) to give MOM-protected **6** (12.4 mg, 70% yield). To a solution of

MOM-protected **6** (12.4 mg, 0.0274 mmol) in MeOH (2 mL) was added TsOH•H_2O (52 mg, 0.274 mmol) at ambient temperature, and the resulting mixture was stirred at the same temperature for 1 day. The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$, and methanol was removed under reduced pressure before extracting with AcOEt. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (hexane–AcOEt 3:1) to give **6** as a pale yellow solid (7.9 mg, 79% yield) as a diastereomeric mixture.

4a-*epi*-Ugonstilbene B (6): $[a]^{26}_D$ +49.4 (*c* 0.79, $CHCl_3$) for 69% ee; HPLC (Daicel Chiralpak IA, hexane–2-propanol 4:1, flow rate 0.5 mL/min) t_R = 16.5 (major enantiomer of *cis*-diastereomer), 18.6 (minor enantiomer of *cis*-diastereomer), t_R = 32.8 (major enantiomer of *trans*-diastereomer), 26.8 (minor enantiomer of *trans*-diastereomer) min; IR (neat) 3373, 1606, 1575, 1514, 1423, 1246, 1100, 1059, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 3H), 1.03 (s, 3H), 1.23 (s, 3H), 1.27–1.73 (m, 6H), 1.95–2.00 (m, 1H), 2.33 (dd, *J* = 13.3, 16.5 Hz, 1H), 2.72 (dd, *J* = 4.8, 16.5 Hz, 1H), 4.70 (s, 1H), 4.72 (s, 1H), 6.49 (d, *J* = 1.4 Hz, 1H), 6.57 (d, *J* = 1.4 Hz, 1H), 6.79 (d, *J* = 16.0 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 2H), 6.95 (d, *J* = 16.0 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 19.67, 19.74, 20.6, 32.1, 33.5, 39.8, 41.5, 47.6, 77.2, 104.2, 107.5, 109.4, 115.6, 126.2, 127.8, 127.9, 130.2, 136.9, 154.0, 154.3, 155.2; HRMS (FAB) calcd for $C_{24}H_{28}O_3$ $[M^+]$ 364.2038, found 364.2045.

References

1. (a) Maruoka, K.; Itoh, T.; Araki, Y.; Shirasaka, T.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2675. (b) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84.
2. (a) Tanaka, S.; Ono, F.; Katagiri, T.; Tanaka, J. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 750. (b) Bigi, F.; Casiragi, G.; Casnati, G.; Sartori, G. *Synthesis* **1981**, 310.
3. Kumazawa, K.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2004**, *6*, 2551.
4. Chakrapani, L.; Jung, E. M.; Lee, Y. R. *Helv. Chim. Acta* **2010**, *93*, 829.
5. (a) Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 4906. (b) Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8131.

Chapter 3

Kinetic Resolution of Racemic Carboxylic Acids Catalyzed by Chiral Lewis Base-Assisted Brønsted Acid (LBBA) through Asymmetric Protolactonization

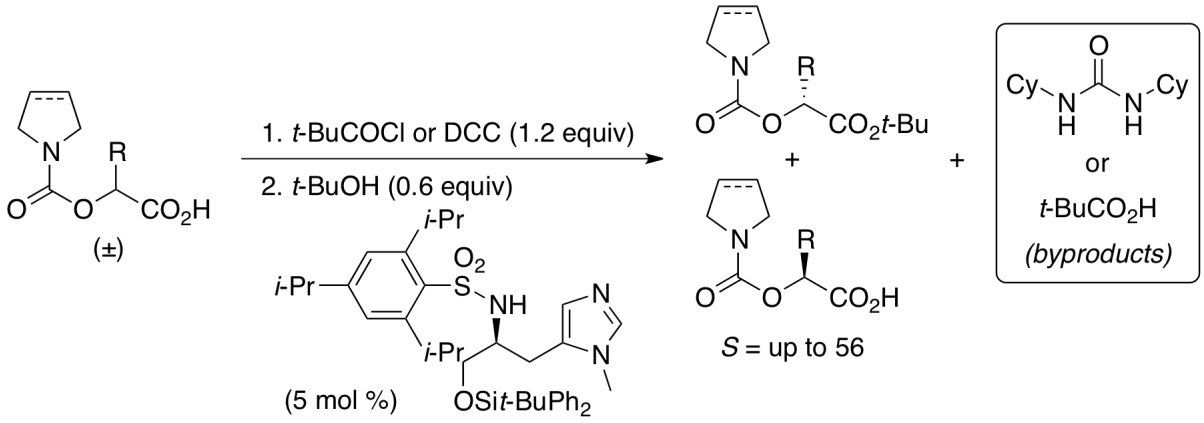
Abstract: Chiral Lewis base-assisted Brønsted acids (Chiral LBBAs) catalyze the kinetic resolution of racemic α-substituted carboxylic acids through asymmetric protolactonization. Both the lactones and the recovered carboxylic acids are obtained with high enantioselectivities and high *S* values. In addition, the desymmetrization of *meso*-carboxylic acids can also be accomplished via chiral LBBA-catalyzed asymmetric protolactonization.

3–1 Introduction

The synthesis of optically active carboxylic acids and lactones is a very important subject in medicinal and pharmaceutical chemistry. The intramolecular cyclization of unsaturated carboxylic acids is one of the most straightforward routes to the synthesis of lactones, and leads directly to the desired products. In general, electrophilic reagents such as iodine, phenylselenium chloride, and mercuric or palladium salts promote this cyclization.[1] However, these methods require an additional step to remove the reagent bound to the products. Although the cyclization of unsaturated acids promoted by a Brønsted acid is well-known, it most often occurs with more than a stoichiometric amount of a Brønsted acid.[2] On the other hand, it has been reported that a variety of α- or β-substituted γ- and δ-lactones can be easily prepared from unsaturated carboxylic acids in excellent yields using trifluoromethanesulfonic acid (TfOH) as a catalyst.[3] However, applications of this method such as an asymmetric version are limited because these reactions require harsh conditions. While there are a growing number of chiral Brønsted acid catalysts, the chiral proton-induced lactonization (protolactonization) of unsaturated carboxylic acids is still rare, mainly due to the difficulty of controlling the Brønsted acidities of the catalysts and the low nucleophilicity of a carboxyl group toward unactivated alkenes.[4]

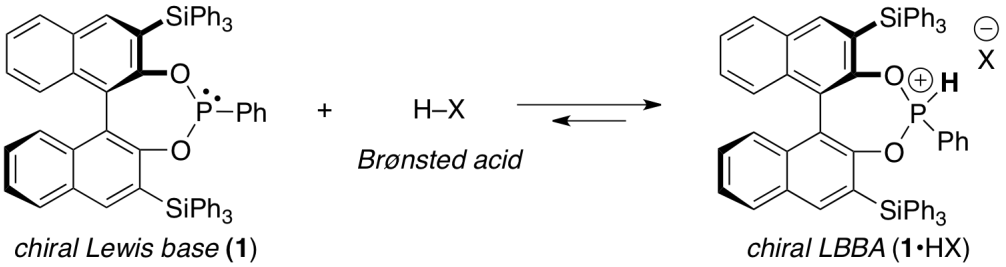
The kinetic resolution of racemic compounds through a catalytic asymmetric reaction is a useful method for obtaining optically active compounds.[5,6] Our group previously reported the kinetic resolution of racemic α-substituted carboxylic acids bearing a pyrrolidine- or pyrroline-1-carbonyl group through asymmetric acylation catalyzed by L-histidine-derived organocatalysts (Scheme 3.1).[7,8] Although these methods can be used for kinetic resolution to give a variety of optically active carboxylic acids and esters, the mixed anhydrides must first be generated, followed by transacylation to achieve the corresponding reactions. Therefore, they are associated with the generation of byproducts derived from acid chlorides or condensation reagents.

Scheme 3.1. Kinetic Resolution of Racemic Carboxylic Acid through Asymmetric Esterification

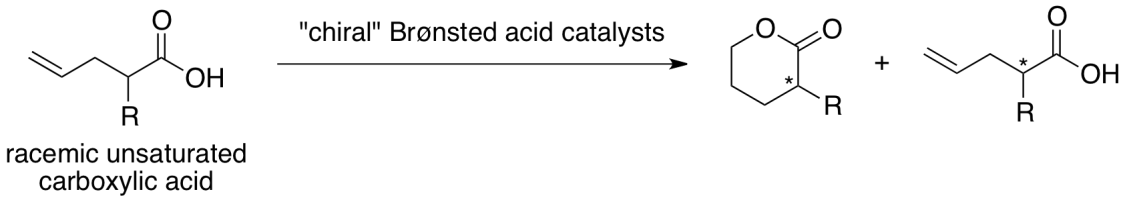


Recently, we developed chiral Lewis base-assisted Brønsted acids (LBBAs) as new chiral Brønsted acid catalysts for the enantioselective cyclization of 2-geranylphenols (Scheme 3.2).[9] With regard to the subject of asymmetric protocyclization reactions, we considered that the chiral LBBA-promoted method could be applied to the kinetic resolution of racemic unsaturated carboxylic acids through asymmetric protolactonization (Scheme 3.3). This reaction system could lead to a novel and straightforward approach for providing optically active carboxylic acids and lactones without the generation of byproducts derived from the activating reagents. Here, we describe the kinetic resolution of racemic α-substituted carboxylic acids catalyzed by chiral LBBAs through asymmetric protolactonization.

Scheme 3.2. Chiral Lewis Base-Assisted Brønsted Acids (Chiral LBBAs)



Scheme 3.3. Kinetic Resolution of Racemic Carboxylic Acid through Asymmetric Protolactonization

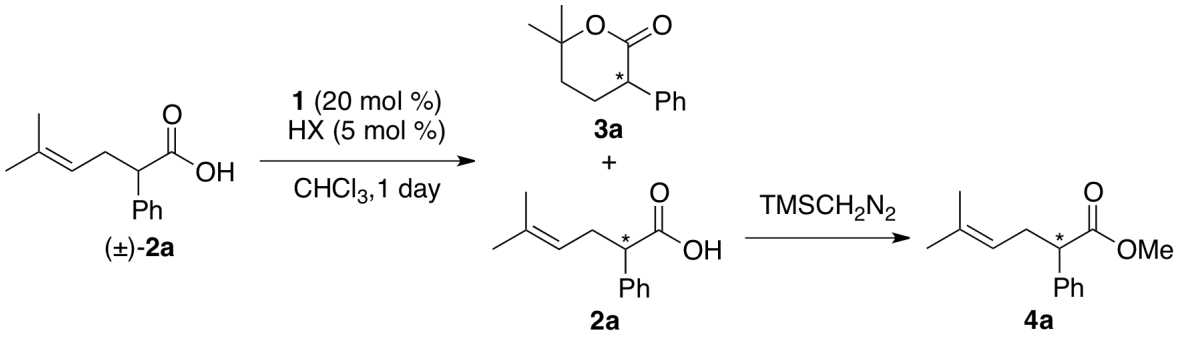


3–2 Results and Discussion

To begin our study, racemic carboxylic acid (±)-**2a** was chosen as a model substrate for the chiral LBBA-catalyzed kinetic resolution (Table 3.1). Based on our previous study, we envisioned that the use of chiral LBBA (**1**•HX) would be key for enantioface selection of the isoprenyl group of (±)-**2a**. First, the protolactonization of (±)-**2a** was conducted under the same conditions as LBBA-catalyzed polyene cyclization (in the presence of **1** (40 mol %) and TfOH (10 mol %) at –40 °C) (entry 1). As a result, the reaction gave the corresponding lactone **3a** with 95% ee (26% conv.). The unreacted carboxylic acid **2a** was recovered after transformation to the methyl ester **4a** (33% ee) using $TMSCH_2N_2$. Therefore, these results gave a selectivity factor ($S = k_{fast}/k_{slow}$) of 54 (entry 1). When the reaction was conducted at –30 °C, the recovered carboxylic acid was obtained with 98% ee (entry 2). The use of **1** (20 mol %) and TfOH (5 mol %) at –30 °C also gave **3a** with high enantioselectivity (95% ee) although the conversion was low (17%, entry 3). Next, achiral Brønsted acids (HX) were investigated under these conditions. The use of FSO_3H gave almost the same results as those obtained with TfOH, although FSO_3H was the optimal Brønsted acid in the cyclization of 2-geranylphenols (95% ee, 12% conv., entry 4). On the other hand, the use of $ClSO_3H$ improved the conversion of **3a** without a significant loss of enantioselectivity (92% ee, 41% conv., entry 5). To our delight, when **1**•$ClSO_3H$-catalyzed protolactonization was conducted at –40 °C, the enantioselectivity increased to 94% ee without any decrease in the conversion, which gave the highest selectivity factor (S = 62, entry 6). Additionally, when the reaction was conducted at –20 °C, the recovered carboxylic acid was obtained with 95% ee (entry 7). These results suggested that simple control of the reaction temperature could make it possible to easily access optically active carboxylic acids and lactones with high enantioselectivities.

Meanwhile, when the reaction was conducted in the absence of **1** at –20 °C, racemic lactone **3a** was obtained in 8% yield (entry 8). These results indicated that the use of Lewis base **1** controlled not only the stereoselectivity but also the reactivity.

Table 3.1. Kinetic Resolution of (±)-**2a** Catalyzed by Chiral LBBAs

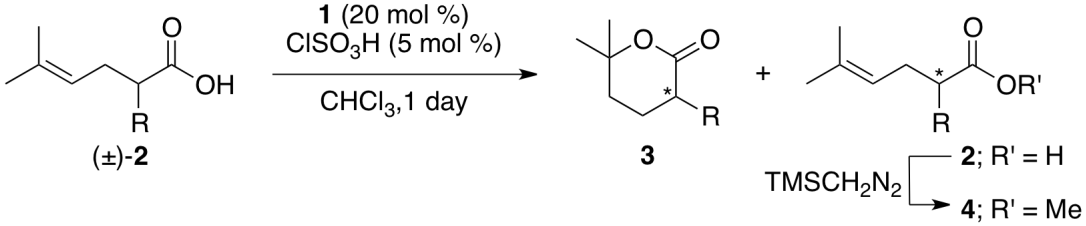


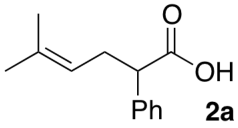
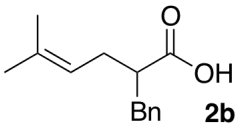
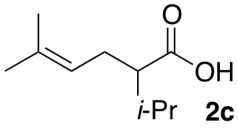
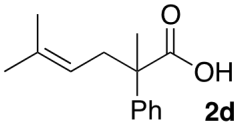
entry	HX	temp. (°C)	ee of **3a** (%)[a]	ee of **4a** (%)[a]	conv. (%)[b]	*S*[c]
1[d]	TfOH	–40	95	33	26	54
2[d]	TfOH	–30	76	98	56	29
3	TfOH	–30	95	20	17	47
4	FSO_3H	–30	95	13	12	44
5	$ClSO_3H$	–30	92	65	41	46
6	$ClSO_3H$	–40	94	63	40	62
7	$ClSO_3H$	–20	82	95	54	40
8[e]	$ClSO_3H$	–40	–	–	8[f]	–

[a] Determined by chiral HPLC. [b] The conversion was calculated as $C = ee_4/(ee_3 + ee_4)$.
[c] The selective factor was calculated as $S = \ln[1 - C\,(1 + ee_3)]/\ln[1 - C\,(1 - ee_3)]$.
[d] Reaction was conducted in the presence of **1** (40 mol %) and TfOH (10 mol %).
[e] Reaction was conducted in the absence of **1**. [f] Isolated yield of **3a**.

With the optimized reaction conditions in hand, we next examined the kinetic resolution of racemic carboxylic acids (±)-**2** bearing various α-substituents (Table 3.2). Although the introduction of aromatic rings at the α-position of carboxylic acids gave excellent selectivity (S = 62), this method was not effective for alkyl-substituted substrate **2b** such as a benzyl group due to the less steric nature of the primary alkyl substituent (entries 1 and 2). The absolute stereochemistry of the obtained lactone **3b** was assigned to be (*S*).[10] However, substrate **2c** bearing an *iso*-propyl group gave good selectivity (S = 37, entry 3). The kinetic resolution of racemic tertiary carboxylic acid **2d** did not give a satisfactory level of enantioselectivity (entry 4). These findings suggested that the steric size of the substituents on the chiral center significantly influenced the enantiocontrol.

Table 3.2. Substrate Scope for the Kinetic Resolution of (±)-α-Substituted Carboxylic Acids

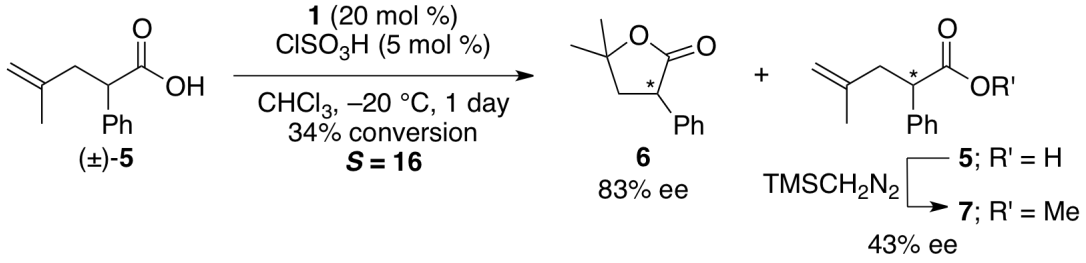


entry	(±)-**2**	temp. (°C)	ee of **3** (%)[a]	ee of **4** (%)[a]	conv. (%)[b]	S[c]
1	 **2a**	–40	94	63	40	62
2[d]	 **2b**	–30	49 (*S*)	42	46	4
3	 **2c**	–20	88[e]	78[e]	47	37
4	 **2d**	–20	62	33	35	6

[a] Determined by chiral HPLC. [b] The conversion was calculated as $C = ee_4/(ee_3 + ee_4)$.
[c] The selective factor was calculated as $S = \ln[1 - C\,(1 + ee_3)]/\ln[1 - C\,(1 - ee_3)]$.
[d] Reaction was conducted in the presence of **1** (40 mol %) and $ClSO_3H$ (10 mol %).
[e] Determined by chiral GC.

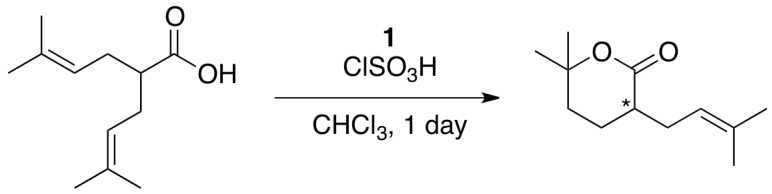
To explore the scope of the reaction with respect to the substrate, we examined the kinetic resolution of racemic carboxylic acids bearing structurally different alkenes. The asymmetric protolactonization of (±)-**5** in the presence of **1** (20 mol %) and $ClSO_3H$ (5 mol %) showed good selectivity (S = 16, Scheme 3.4). This reaction proceeded through *exo*-cyclization to give the corresponding 5-membered lactone **6** with 83% ee. This result indicated that this chiral LBBA-catalyzed method could also promote the kinetic resolution of racemic α-substituted carboxylic acids bearing 1,1-disubstituted alkenes.

Scheme 3.4. Kinetic Resolution of (±)-**5** Catalyzed by Chiral LBBAs



Based on the kinetic resolution of racemic α-substituted carboxylic acids, we envisioned that this chiral LBBA-catalyzed system could be used for the desymmetrization of *meso*-unsaturated carboxylic acids. It could also be used for the synthesis of optically active lactones. When the reaction of **8** was conducted in the presence of **1** (40 mol %) and $ClSO_3H$ (10 mol %) at –30 °C, the desired product **9** was obtained in 82% yield with 79% ee (Table 3.3, entry 1). The use of 100 mol % of **1** and 20 mol % of $ClSO_3H$ at –40 °C slightly increased the yield and the enantioselectivity of **9** (95% yield, 81% ee, entry 2). This reaction gave the corresponding lactone **9** with good enantioselectivity, while the selectivity of the kinetic resolution of a racemic carboxylic acid bearing a primary alkyl substituent at the α-position was low.

Table 3.3. Desymmetrization of *meso*-α-Substituted Carboxylic Acids



8 **9**

entry	**1** [mol %]	$ClSO_3H$ [mol %]	temp. (°C)	yield (%)[a]	ee (%)[b]
1	**1** [40]	$ClSO_3H$ [10]	–30	82	79
2[c]	**1** [100]	$ClSO_3H$ [20]	–40	95	81

[a] Isolated yield. [b] Determined by chiral GC.
[c] Reaction was conducted in $CHCl_3$ (0.02 M).

We propose the following mechanism to explain the absolute stereopreference we observed (Figure 3.1). Based on our previous study, chiral LBBA (**1**•HX) selectively reacts with the *re*-face of the terminal isoprenyl group, the dimethyl group of which is placed at the least-hindered side in the transition-state assembly (**A**).[9] At this point, (*S*)-carboxylic acid **2** immediately undergoes protolactonization through transition state **B** to give the corresponding (*S*)-lactone **3**. On the other hand, the reaction of (*R*)-carboxylic acid **2** through transition state **C** is slower than that through **B** because of steric repulsion associated with the substituent R with a triphenylsilyl group. Therefore, (*R*)-carboxylic acid **2** is recovered selectively after the reaction.

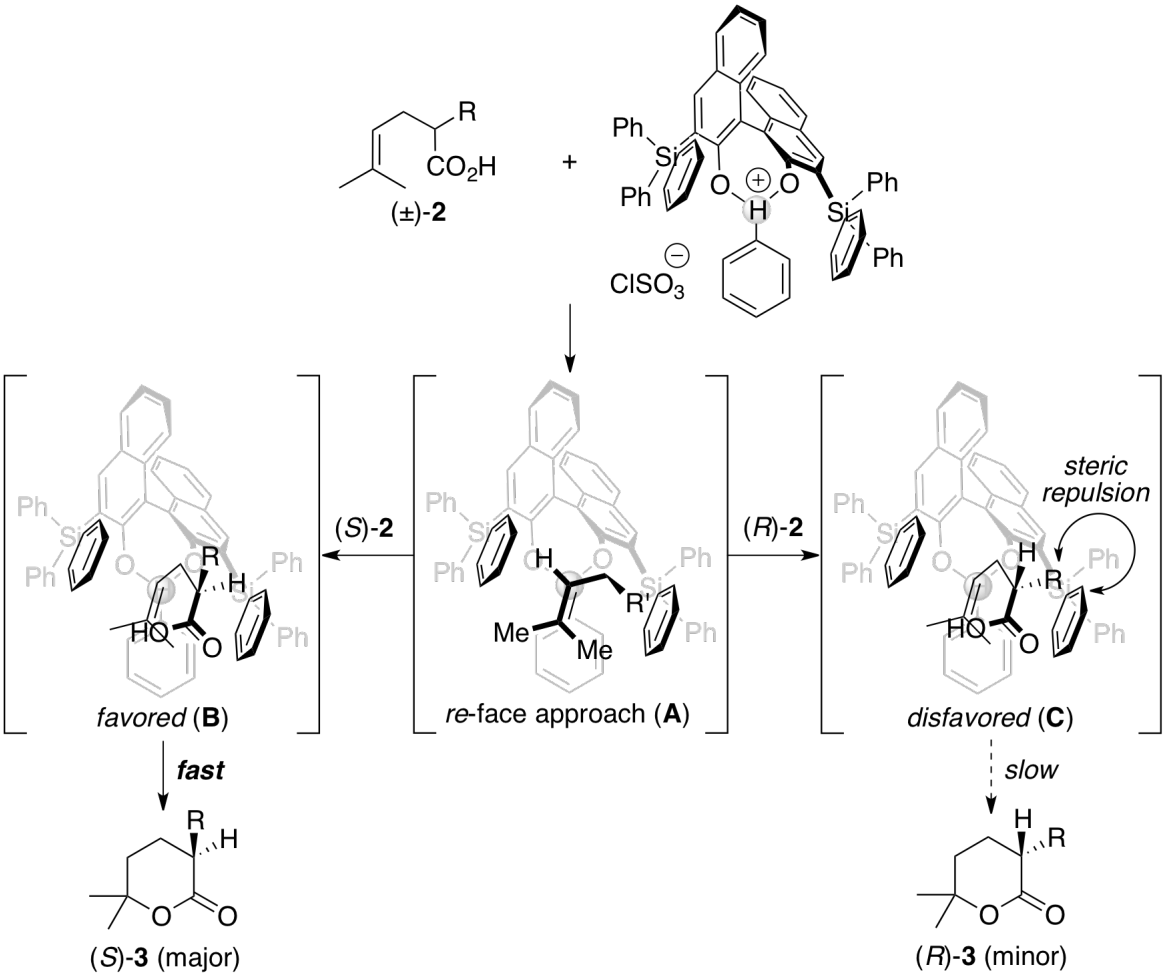


Figure 3.1. Proposed mechanism for kinetic resolution.

3–3 Conclusion

We have achieved the kinetic resolution of racemic α-substituted carboxylic acids **2** through asymmetric protolactonization catalyzed by chiral Lewis base-assisted Brønsted acids (Chiral LBBAs). This reaction system may represent a novel and straightforward approach for providing optically active carboxylic acids and lactones. In addition, the desymmetrization of *meso*-carboxylic acids **5** was also accomplished via chiral LBBA-catalyzed protolactonization. To the best of our knowledge, these are the first successful examples of reactions that give δ-lactones with high enantioselectivities through the chiral Brønsted acid-catalyzed asymmetric protolactonization of unsaturated carboxylic acids.

References and Notes

1. (a) Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1985**, *26*, 5307. (b) Larnck, R. C; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298. (c) Kang, S. H.; Lee, J. H.; Lee, S. B. *Tetrahedron Lett.* **1998**, *39*, 59. (d) Jonasson, C; Horvath, A.; Baeckvall, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 9600. (e) Chavan, S. P.; Shamia, A. K. *Tetrahedron Lett.* **2001**, *42*, 4923. (f) Tiecco, M.; Testaferri, L.; Temperini, A.; Bagnoli, L.; Marini, F.; Santi, C. *Synlett* **2001**, 1767. (g) GruUadauria, M.; Aprile, C; Noto, R. *Tetrahedron Lett.* **2002**, *43*, 1669. (h) Curini, M.; Epifano. F.; MarcoiuUio, M. C; Montanari, F. *Synlett* **2004**, *2*, 368.
2. (a) Anscll, M. F.; Palmer, M. H. *Quart. Rev. (London)* **1964**, *18*, 211. (b) TIecco, M.; Testaferri, L.; Tingoli, M. *Tetrahedron* **1993**, *49*, 5351. (c) Mali, R. S.; Babu, K. N. *Helv. Chim. Acta* **2002**, *85*, 3525. (e) Miura, K.; Hayashida, J.; Takahashi, T.; Nishikori, H.; Hosomi, A. *J. Organomet. Chem.* **2003**, *686*, 242. (f) Zhou, Y.; Woo, L. K.; Angelici, R. J. *Appl. Catal., A: General* **2007**, *333*, 238.
3. Coulombel, L.; Duñach, E. *Synth. Commun.* **2005**, *35*, 153.
4. For the report on the chiral LBA-induced polyene cyclization with a carboxylic group as a terminator, see: Upar, K. B.; Mishra, S. J.; Nalawade, S. P.; Singh, S. A.; Khandare, R. P.; Bhat, S. V. *Tetrahedron: Asymmetry* **2009**, *20*, 1637.
5. For selected reviews, see: (a) Kagan, H. B.; Fiaud, J. C. *Topics in Stereochemistry*, Vol. 18, ed. by Eliel, E. L.; Wilen, S. H., Wiley, New York, **1988**, pp 249-330. (b) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N.; *Adv. Synth. Catal.* **2001**, *343*, 5. (c) Vedejs, E.; Jure, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 3974. (d) Müller, C. E.; Schreiner, P. R. *Angew. Chem. Int. Ed.* **2011**, *50*, 6012. (e) Krasnov, V. P.; Gruzdev, D. A.; Levit, G. L. *Eur. J. Org. Chem.* **2012**, 1471. (f) Taylor, J. E.; Bull, S. D.; Williams, J. M. J. *Chem. Soc. Rev.* **2012**, *41*, 2109.
6. For recent examples, see: (a) Peschiulli, A.; Procuranti, B.; O'Connor, C. J.; Connon, S. J. *Nat. Chem.* **2010**, *2*, 380. (b) Bumbu, V. D.; Birman, V. B. *J. Am. Chem. Soc.* **2011**, *133*, 13902. (c) Čorić, I.; List, B. *Nature* **2012**, *483*, 315. (d) Wang, Y.; Zheng, K.; Hong, R. *J. Am. Chem. Soc.* **2012**, *134*, 4096. (e) Zhou, L.; Liu, X.; Ji, Jie; Zhang, Y.; Hu, X.; Lin, L.; Feng, X. *J. Am. Chem. Soc.* **2012**, *134*, 17024.
7. (a) Ishihara, K.; Kosugi, Y.; Umemura, S.; Sakakura, A. *Org. Lett.* **2008**, *10*, 3191. (b)

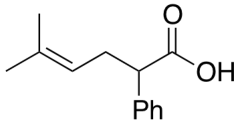
Sakakura, A.; Umemura, S.; Ishihara, K. *Synlett* **2009**, 1647.

8. For another example of the asymmetric esterification of racemic carboxylic acids, see: (a) Shiina, I.; Nakata, K.; Ono, K.; Onda, Y.; Itagaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 11629. (b) Shiina, I.; Nakata, K.; Onda, Y. *Eur. J. Org. Chem.* **2008**, 5887. (c) Yang, X.; Birman, V. B. *Adv. Synth. Catal.* **2009**, *351*, 2301. Also see also other non-enzymatic enantioselective acyl transfer reactions: (d) Narasaka, K.; Kanai, F.; Okudo, M.; Miyoshi, N. *Chem. Lett.* **1989**, 1187. (e) Notte, G. T.; Sammakia, T.; Steel, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 13502. (f) Notte, G. T.; Sammakia, T. *J. Am. Chem. Soc.* **2006**, *128*, 4230. (g) Yang, X.; Lu, G.; Birman, V. B. *Org. Lett.* **2010**, *12*, 892.
9. Sakakura, A.; Sakuma, M.; Ishihara, K. *Org. Lett.* **2011**, *13*, 3130.
10. The optical rotation of **3b** was measured to be $[\alpha]^{24}_{D}$ –17.8 (*c* 0.65, $CHCl_3$) for 49% ee, which can be compared with $[\alpha]^{23}_{D}$ +52.6 (*c* 1.06, $CHCl_3$) for 94% ee of (*R*)-**3h**, see: Matsuo, J.; Kobayashi, S.; Koga, K. *Tetrahedron Lett.* **1998**, *39*, 9723.

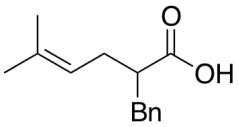
Experimental Section

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 d scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet, 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. High performance liquid chromatography (HPLC) analysis was conducted using Shimadzu LC-20 AD coupled diode array-detector SPD-M20A and chiral column of Daicel CHIRALCEL OD-H (0.46 cm × 25 cm), Daicel CHIRALPAK AS-H (0.46 cm × 25 cm), Daicel CHIRALPAK IB-3 (4.6 mm × 250 mm) or Daicel CHIRALPAK IC-3 (4.6 mm × 250 mm). Gas-liquid-phase chromatography (GC) was performed with Shimadzu GC-2010 Plus with a flame-ionization detector and a capillary column of CP-Cyclodextrin-β-2,3,6-M-19 (i.d. 0.25 mm×25 m; CHROMPACK; GL Science Inc.) or CHIRALDEX β-TA, γ-TA (i.d. 0.25 mm×20 m; Tokyo Kasei Kogyo Co., Ltd). Optical rotations were measured on a RUDOLPH AUTOPOL IV digital polarimeter. 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. Dry tetrahydrofuran was purchased from Kanto as the "anhydrous" and stored under nitrogen. Chloroform were freshly distilled from diphosphorus pentoxide, and stored over MS 4Å under nitrogen in the dark. Other simple chemicals were analytical-grade and obtained commercially. Chiral phosphorus(III) compound **1** was reported previously.[1]

Preparation of (±)-α-Substituted Carboxylic Acids 2 and 5.

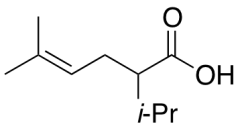


(±)-5-Methyl-2-phenyl-4-hexenoic acid (2a):[2] To a solution of *i*-Pr_2NH (1.7 mL, 12 mmol) in THF (40 mL) was added *n*-BuLi (1.6 M in hexane, 6.9 mL, 11 mmol) dropwise at –78 °C, and the reaction mixture was stirred for 30 minutes. A solution of ethyl 2-phenylacetate (1.6 mL, 10 mmol) in THF (5 mL) was added dropwise at –78 °C. After stirring at the same temperature for 1 h, 1-bromo-3-methyl-2-butene (1.4 mL, 12 mmol) was added at –78 °C. It was then warmed to room temperature and stirred for 5 h. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 10:1) to give ethyl ester of **2a** (1.97 g, 85% yield) as colorless oil. To a solution of ethyl ester of **2a** in EtOH (30 mL) was added a solution of 2M aq. NaOH (6.8 mL) and refluxed for 1 day. The reaction mixture was cooled, and then concentrated under reduced pressure to remove the solvent. The residue was taken with water and acidized with 1N HCl. The reaction mixture was extracted with EtOAc, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 2:1) to give of **2a** (1.72 g, 99% yield) as colorless oil. IR (neat) 3250–2750, 1706, 1495, 1415, 1288 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.57 (s, 3H), 1.64 (s, 3H), 2.45 (ddd, *J* = 7.3, 7.8, 14.2 Hz, 1H), 2.77 (ddd, *J* = 7.3, 7.8, 14.2 Hz, 1H), 3.56 (t, *J* = 7.8 Hz, 1H), 5.05 (t, *J* = 7.3 Hz, 1H), 7.26–7.34 (m, 5H), 9.68–11.17 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 25.7, 31.8, 51.7, 120.5, 127.4, 128.0, 128.6, 134.3, 138.3, 179.5; HRMS (FAB) calcd for $C_{13}H_{17}O_2^+$ [M+H$^+$] 205.1229, found 205.1228.

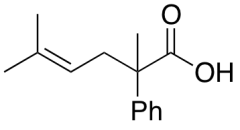


(±)-2-Benzyl-5-methyl-4-hexenoic acid (2b): Compound **2b** was prepared from ethyl 3-phenylpropionate and 1-bromo-3-methyl-2-butene according to the same manner as **2a**. IR (neat) 3250–2750, 1705, 1455, 1242 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.57 (s, 3H), 1.70 (s, 3H), 2.24 (dt, *J* = 7.3, 14.6 Hz, 1H), 2.34 (dt, *J* = 7.3, 14.6 Hz, 1H), 2.66–2.75 (m, 1H), 2.78 (dd, *J* = 6.6, 13.5 Hz, 1H), 2.96 (dd, *J* = 8.0, 13.5 Hz, 1H), 5.12

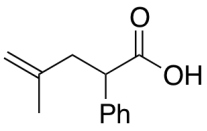
(t, J = 7.3 Hz, 1H), 7.16–7.23 (m, 3H), 7.26–7.30 (m, 2H), 9.86–11.22 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 25.8, 30.2, 37.3, 47.6, 120.4, 126.4, 128.4, 128.9, 134.4, 139.1, 181.7; HRMS (FAB) calcd for $C_{14}H_{19}O_2^+$ [M+H$^+$] 219.1385, found 219.1397.



(±)-2-Isopropyl-5-methyl-4-hexenoic acid (2c):[3] Compound **2c** was prepared from methyl isovalerate and 1-bromo-3-methyl-2-butene according to the same manner as **2a**. IR (neat) 3250–2750, 1706, 1440, 1223 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (d, J = 6.9 Hz, 3H), 0.99 (d, J = 6.9 Hz, 3H), 1.61 (s, 3H), 1.68 (s, 3H), 1.91 (dsept, J = 6.9, 6.9 Hz, 1H), 2.12–2.35 (m, 3H), 5.09 (t, J = 6.9 Hz, 1H), 10.82–11.52 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 20.1, 20.3, 25.8, 28.0, 30.0, 52.9, 121.2, 133.6, 182.4.



(±)-2,5-Diethyl-2-phenyl-4-hexenoic acid (2d): To a solution of i-Pr_2NH (1.8 mL, 13 mmol) in THF (10 mL) was added n-BuLi (1.6 M in hexane, 7.8 mL, 12.5 mmol) dropwise at –78 °C, and the reaction mixture was stirred for 30 minutes. A solution of 2-phenylpropionic acid (0.68 mL, 5 mmol) in THF (2.5 mL) was added dropwise at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. The mixture was then cooled to 0 °C, and 1-bromo-3-methyl-2-butene (1.4 mL, 12.5 mmol) was added. It was then warmed to room temperature and stirred for 20 h. The reaction was quenched with saturated aq. NH_4Cl, and extracted with 0.5 M KOH. Aqueous layer was washed with ether and acidized with 1N HCl. The product was extracted with ether, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 2:1) to give of **2d** (0.92 g, 84% yield) as colorless oil. IR (neat) 3250–2750, 1699, 1446, 1278 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (s, 3H), 1.58 (s, 3H), 1.67 (s, 3H), 2.61 (dd, J = 7.3, 14.2 Hz, 1H), 2.79 (dd, J = 7.3, 14.2 Hz, 1H), 5.00 (t, J = 7.3 Hz, 1H), 7.23–7.29 (m, 1H), 7.31–7.42 (m, 4H), 9.82–10.86 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 22.1, 26.0, 37.4, 50.2, 119.3, 126.3, 126.9, 128.4, 135.0, 142.8, 182.4; HRMS (FAB) calcd for $C_{14}H_{19}O_2^+$ [M+H$^+$] 219.1385, found 219.1399.

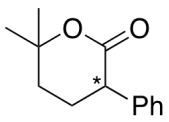


(±)-4-Methyl-2-phenyl-4-pentenoic acid (5):[4] Compound **5** was prepared from ethyl 2-phenylacetate and 3-bromo-2-methyl-1-propene according to the same manner as **2a**. IR (neat) 3250–2750, 1708, 1452, 1284, 895 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.72 (s, 3H), 2.45 (dd, *J* = 6.9, 14.6 Hz, 1H), 2.83 (dd, *J* = 8.7, 14.6 Hz, 1H), 3.81 (dd, *J* = 6.9, 8.7 Hz, 1H), 4.71 (s, 1H), 4.75 (s, 1H), 7.25–7.35 (m, 5H), 10.27–11.36 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 40.7, 49.9, 112.4, 127.5, 128.0, 128.6, 138.0, 142.1, 180.0; HRMS (FAB) calcd for $C_{12}H_{15}O_2^+$ [M+H$^+$] 191.1072, found 191.1050.

Typical Procedure for the Kinetic Resolution of (±)-2a.

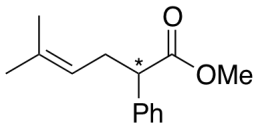
To a solution of **1** (18.2 mg, 0.020 mmol) in $CHCl_3$ (1.8 mL) was added a 0.05 M solution of $ClSO_3H$ in $CHCl_3$ (0.1 mL, 0.005 mmol) at –40 °C, and the mixture was stirred for ca. five minutes. To this solution, a solution of **2a** (21.8 mg, 0.10 mmol) in $CHCl_3$ (0.1 mL) was added dropwise at –40 °C, and the mixture was stirred at –40 °C for 1 day. The reaction was quenched with water (3 mL) and the reaction mixture was extracted with ether. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (hexane–$CHCl_3$–EtOAc 3:3:1) to give **3a** as a pale yellow solid (8.4 mg, 40% yield) and **2a** (10.6 mg, 52% yield). To a stirring solution of the recovered carboxylic acid **2a** in THF (1.0 mL) and MeOH (0.25 mL) was added dropwise (trimethylsilyl)diazomethane (2.0 M in diethyl ether, 0.10 mL) at 0 °C. The yellow solution was stirred at the same temperature for 10 minutes. The reaction was quenched with AcOH (ca. 0.10 mL) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane–EtOAc 10:1) to give **4a** as pale yellow oil (9.5 mg, 85% yield).

The corresponding physical and spectroscopic data for **3** and **4** are as follows.

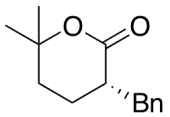


6,6-Dimethyl-3-phenyltetrahydro-2*H*-pyran-2-one (3a): $[a]^{23}_D$ +8.7 (*c* 0.42, $CHCl_3$) for 95% ee; HPLC (Daicel Chiralpak AS-H, hexane–*i*-PrOH 4:1, flow rate

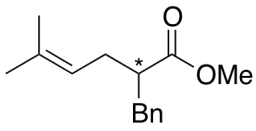
1.0 mL/min) t_R = 22.2 (minor enantiomer), 38.3 (major enantiomer) min; IR (neat) 1712, 1284, 1258, 1209, 1120 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.50 (s, 3H), 1.52 (s, 3H), 1.83–1.96 (m, 2H), 2.07–2.26 (m, 2H), 3.67 (dd, *J* = 6.9, 9.6 Hz, 1H), 7.19–7.30 (m, 3H), 7.32–7.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.7, 28.3, 29.9, 33.4, 47.2, 82.9, 127.1, 128.1, 128.8, 139.8, 172.2; HRMS (FAB) calcd for $C_{13}H_{17}O_2^+$ [M+H$^+$] 205.1229, found 205.1241.



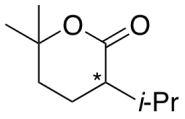
Methyl 5-methyl-2-phenyl-4-hexenoate (4a): $[a]^{25}_D$ –76.3 (*c* 0.49, $CHCl_3$) for 98% ee; HPLC (Daicel Chiralpak IB-3, hexane–*i*-PrOH 200:1, flow rate 0.3 mL/min) t_R = 17.8 (major enantiomer), 19.3 (minor enantiomer) min; IR (neat) 1738, 1435, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.57 (s, 3H), 1.65 (s, 3H), 2.44 (ddd, *J* = 7.1, 7.3, 14.2 Hz, 1H), 2.76 (ddd, *J* = 7.3, 8.5, 14.2 Hz, 1H), 3.55 (d, *J* = 7.1, 8.5 Hz, 1H), 3.65 (s, 3H), 5.03 (t, *J* = 7.3 Hz, 1H), 7.23–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 25.7, 32.2, 51.8, 51.9, 120.8, 127.2, 127.9, 128.5, 134.1, 139.0, 174.3; HRMS (FAB) calcd for $C_{14}H_{19}O_2^+$ [M+H$^+$] 219.1385, found 219.1413.



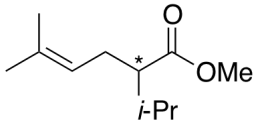
(*S*)-3-Benzyl-6,6-dimethyltetrahydro-2*H*-pyran-2-one (3b): $[a]^{24}_D$ –17.8 (*c* 0.65, $CHCl_3$) for 49% ee; HPLC (Daicel Chiralpak AS-H, hexane–*i*-PrOH 4:1, flow rate 1.0 mL/min) t_R = 15.6 (minor enantiomer), 19.0 (major enantiomer) min; IR (neat) 1709, 1454, 1369, 1113, 942 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 3H), 1.40 (s, 3H), 1.59–1.78 (m, 4H), 2.58–2.66 (m, 1H), 2.83 (dd, *J* = 9.2, 13.7 Hz, 1H), 3.35 (dd, *J* = 4.1, 13.7 Hz, 1H), 7.18–7.25 (m, 3H), 7.27–7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 27.8, 29.9, 33.7, 37.5, 41.5, 82.2, 126.5, 128.5, 129.3, 138.9, 173.4; HRMS (FAB) calcd for $C_{14}H_{19}O_2^+$ [M+H$^+$] 219.1385, found 219.1382. Absolute configuration was assigned to be (*S*) by comparing the sign of measured optical rotation.[5]



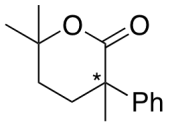
Methyl 2-benzyl-5-methyl-4-hexenoate (4b): $[a]^{27}_{D}$ –8.7 (*c* 0.39, $CHCl_3$) for 42% ee; HPLC (Daicel Chiralpak IB-3, hexane–*i*-PrOH 200:1, flow rate 0.5 mL/min) t_R = 15.1 (minor enantiomer), 16.4 (major enantiomer) min; IR (neat) 1738, 1436, 1207, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.57 (s, 3H), 1.69 (s, 3H), 2.21 (dt, *J* = 7.3, 14.6 Hz, 1H), 2.32 (dt, *J* = 7.3, 14.6 Hz, 1H), 2.64–2.72 (m, 1H), 2.77 (dd, *J* = 6.4, 13.3 Hz, 1H), 2.93 (dd, *J* = 8.5, 13.3 Hz, 1H), 3.59 (s, 3H), 5.08 (t, *J* = 7.3 Hz, 1H), 7.13–7.22 (m, 3H), 7.24–7.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 25.8, 30.5, 37.7, 47.8, 51.4, 120.7, 126.2, 128.3, 128.8, 134.1, 139.5, 175.7; HRMS (FAB) calcd for $C_{15}H_{21}O_2^+$ [M+H$^+$] 233.1542, found 233.1546.



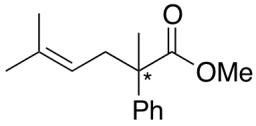
3-Isopropyl-6,6-dimethyltetrahydro-2*H*-pyran-2-one (3c): $[a]^{26}_{D}$ –36.3 (*c* 0.54, $CHCl_3$) for 88% ee; GC (β-TA, 100 kPa, column temperature 70 °C and then warm to 90 °C (+1 °C/min)) t_R = 35.9 (minor enantiomer), 37.6 (major enantiomer) min; IR (neat) 1719, 1461, 1375, 1284, 1114 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 1.36 (s, 3H), 1.41 (s, 3H), 1.71–1.87 (m, 4H), 2.29–2.36 (m, 1H), 2.55 (dsept, *J* = 3.4, 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9, 17.8, 20.0, 27.6, 28.5, 30.2, 34.1, 45.6, 81.4, 173.4; HRMS (FAB) calcd for $C_{10}H_{18}O_2Na^+$ [M+Na$^+$] 193.1204, found 193.1174.



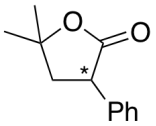
Methyl 2-isopropyl-5-methyl-4-hexenoate (4c):[6] $[a]^{27}_{D}$ –11.8 (*c* 0.20, $CHCl_3$) for 78% ee; GC (β-CP, 50 kPa, column temperature 70 °C and then warm to 75 °C (+0.25 °C/min)) t_R = 60.4 (major enantiomer), 61.4 (minor enantiomer) min; IR (neat) 1736, 1461 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 1.60 (s, 3H), 1.67 (s, 3H), 1.87 (dsept, *J* = 6.8, 6.8 Hz, 1H), 2.10–2.32 (m, 3H), 3.65 (s, 3H), 5.04 (t, *J* = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 20.3, 20.4, 25.8, 28.3, 30.3, 51.1, 53.0, 121.5, 133.3, 175.9.



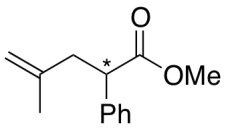
3,6,6-Trimethyltetrahydro-2*H*-pyran-2-one (3d): $[a]^{27}_{D}$ +10.1 (*c* 0.53, $CHCl_3$) for 62% ee; HPLC (Daicel Chiralpak IC-3, hexane–*i*-PrOH 9:1, flow rate 1.0 mL/min) t_R = 18.3 (minor enantiomer), 20.7 (major enantiomer) min; IR (neat) 1716, 1452, 1302, 1275, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.44 (s, 3H), 1.62 (s, 3H), 1.65 (dd, *J* = 5.0, 7.3 Hz, 2H), 2.09 (dt, *J* = 7.3, 14.2 Hz, 1H), 2.21 (dt, *J* = 5.0, 14.2 Hz, 1H), 7.23–7.30 (m, 3H), 7.32–7.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 28.5, 30.1, 31.4, 32.9, 47.2, 83.4, 125.9, 126.9, 128.7, 143.8, 175.2; HRMS (FAB) calcd for $C_{14}H_{19}O_2^+$ [M+H$^+$] 219.1385, found 219.1384.



Methyl 2,5-diethyl-2-phenyl-4-hexenoate (4d): $[a]^{27}_{D}$ –20.9 (*c* 0.61, $CHCl_3$) for 33% ee; HPLC (Daicel Chiralpak IC-3, hexane–*i*-PrOH 200:1, flow rate 1.0 mL/min) t_R = 8.0 (minor enantiomer), 9.7 (major enantiomer) min; IR (neat) 1732, 1446, 1236, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.51 (s, 3H), 1.58 (s, 3H), 1.67 (s, 3H), 2.59 (dd, *J* = 7.3, 14.2 Hz, 1H), 2.79 (dd, *J* = 7.3, 14.2 Hz, 1H), 3.65 (s, 3H), 4.97 (t, *J* = 7.3 Hz, 1H), 7.22–7.27 (m, 1H), 7.30–7.36 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 22.7, 26.0, 37.5, 50.6, 52.1, 119.5, 126.0, 126.6, 128.3, 134.7, 143.8, 176.6; HRMS (FAB) calcd for $C_{15}H_{21}O_2^+$ [M+H$^+$] 233.1542, found 233.1534.

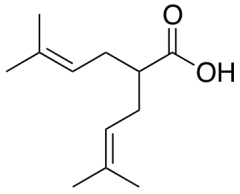


5,5-Dimethyl-3-phenyldihydrofuran-2(3*H*)-one (6):[7] $[a]^{27}_{D}$ +5.8 (*c* 0.62, $CHCl_3$) for 83% ee; HPLC (Daicel Chiralcel OD-H, hexane–*i*-PrOH 4:1, flow rate 1.0 mL/min) t_R = 8.4 (major enantiomer), 9.9 (minor enantiomer) min; IR (neat) 1766, 1456, 1376, 1259, 1139, 1113, 952 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.50 (s, 3H), 1.55 (s, 3H), 2.24 (dd, *J* = 11.9, 12.8 Hz, 1H), 2.58 (dd, *J* = 9.2, 12.8 Hz, 1H), 4.04 (dd, *J* = 9.2, 11.9 Hz, 1H), 7.27–7.32 (m, 3H), 7.34–7.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.9, 28.9, 44.2, 46.9, 82.1, 127.5, 128.0, 128.8, 136.9, 176.5; HRMS (FAB) calcd for $C_{12}H_{15}O_2^+$ [M+H$^+$] 191.1072, found 191.1061.



Methyl 4-Methyl-2-phenyl-4-pentenoate (7):[7] $[a]^{27}_{D}$ –40.6 (*c* 0.78, $CHCl_3$) for 43% ee; HPLC (Daicel Chiralpak IB-3, hexane–*i*-PrOH 200:1, flow rate 0.5 mL/min) t_R = 10.6 (major enantiomer), 11.3 (minor enantiomer) min; IR (neat) 1739, 1435, 1158, 894 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.72 (s, 3H), 2.43 (dd, *J* = 6.4, 14.6 Hz, 1H), 2.84 (dd, *J* = 9.2, 14.6 Hz, 1H), 3.65 (s, 3H), 3.81 (dd, *J* = 6.4, 9.2 Hz, 1H), 4.69 (s, 1H), 4.75 (s, 1H), 7.24–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 41.3, 49.9, 52.0, 112.1, 127.3, 127.8, 128.6, 138.7, 142.6, 174.1; HRMS (FAB) calcd for $C_{13}H_{17}O_2^+$ $[M+H^+]$ 205.1229, found 205.1208.

Preparation of *meso*-α-Substituted Carboxylic Acid 8

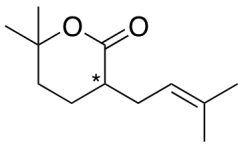


5-Methyl-2-(3-methylbut-2-en-1-yl)-4-hexenoic acid (8): To a suspension mixture of NaH (abt. 60% oil suspension, 1.2 g, 30 mmol) in THF (40 mL) was carefully added a solution of diethyl malonate (1.5 mL, 10 mmol) in THF (5 mL) at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 2 h. To this suspension, 1-bromo-3-methyl-2-butene (2.9 mL, 25 mmol) was added dropwise, and then the reaction mixture was refluxed for 1 day. After cooling to room temperature, the reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 10:1) to give the desired product of as pale yellow oil (2.52 g, 85 % yield). The synthesized disubstituted malonate was dissolved in DMSO (17 mL), followed by addition of H_2O (460 mL, 25.5 mmol) and LiCl (720 mg, 17 mmol). The reaction mixture was stirred at 180 °C for 1 day. After cooling to room temperature, the mixture was diluted with hexane/ether (1:1) and extracted with hexane/ether (1:1). The residue was purified by column chromatography on silica gel (hexane–EtOAc 10:1) to give ethyl ester of **8** of as pale yellow oil (1.49 g, 78 % yield). To a solution of ethyl ester of **8** in EtOH (30 mL) was added

a solution of 2M aq. NaOH (5 mL) and refluxed for 1 day. The reaction mixture was cooled, and then concentrated under reduced pressure to remove the solvent. The residue was taken with water and acidized with 1N HCl. The reaction mixture was extracted with EtOAc, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (hexane–EtOAc 2:1) to give of **8** (0.93 g, 72% yield) as colorless oil. IR (neat) 3250–2750, 1706, 1442, 1224 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.61 (s, 6H), 1.69 (s, 6H), 2.21 (dt, *J* = 7.3, 14.2 Hz, 2H), 2.32 (dt, *J* = 7.3, 14.2 Hz, 2H), 2.34–2.44 (m, 1H), 5.10 (t, *J* = 7.3 Hz, 2H), 9.52–11.12 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 25.8, 30.0, 46.1, 120.9, 134.0, 182.3; HRMS (FAB) calcd for $C_{12}H_{21}O_2^+$ $[M+H^+]$ 197.1542, found 197.1533.

Typical Procedure for the Desymmetrization of 8.

To a solution of **1** (36.4 mg, 0.040 mmol) in $CHCl_3$ (1.8 mL) was added a 0.10 M solution of $ClSO_3H$ in $CHCl_3$ (0.1 mL, 0.010 mmol) at –40 °C, and the mixture was stirred for ca. five minutes. To this solution, a solution of **8** (19.6 mg, 0.10 mmol) in $CHCl_3$ (0.1 mL) was added dropwise at –40 °C, and the mixture was stirred at –30 °C for 1 day. The reaction was quenched with water (3 mL) and the reaction mixture was extracted with ether. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (hexane–$CHCl_3$–EtOAc 3:3:1) to give **9** (16.0 mg, 82% yield).



6,6-dimethyl-3-(3-methylbut-2-en-1-yl)tetrahydro-2*H*-pyran-2-one (9): $[a]^{27}_D$ –34.1 (*c* 0.45, $CHCl_3$) for 79% ee; GC (γ-TA, 100 kPa, column temperature 90 °C and then warm to 110 °C (+1 °C/min)) t_R = 35.2 (minor enantiomer), 36.3 (major enantiomer) min; IR (neat) 1722, 1448, 1370, 1280, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.41 (s, 3H), 1.64 (s, 3H), 1.64–1.85 (m, 3H), 1.72 (s, 3H), 1.85–1.94 (m, 1H), 2.30–2.44 (m, 2H), 2.52–2.60 (m, 1H), 5.12 (t, *J* = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 21.9, 25.8, 27.9, 29.8, 30.0, 33.8, 40.0, 82.0, 120.8, 134.4, 173.8; HRMS (FAB) calcd for $C_{12}H_{21}O_2^+$

[$M+H^+$] 197.1542, found 197.1545.

References

1. Sakakura, A.; Sakuma, M.; Ishihara, K. *Org. Lett.* **2011**, *13*, 3130.
2. Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Tran, A. *J. Am. Chem. Soc.* **1993**, *115*, 8669.
3. Lee-Ruff, E.; Turro, N. J.; Amice, P.; Conia, J. M. *Can. J. Chem.* **1969**, *47*, 2797.
4. Stivala, C. E.; Zakarian, A. *J. Am. Chem. Soc.* **2011**, *133*, 11936.
5. Matsuo, J.; Kobayashi, S.; Koga, K. *Tetrahedron Lett.* **1998**, *39*, 9723.
6. Simon, H. L.; Kaufmann, A.; Schinz, H. *Helv. Chim. Acta* **1945**, *29*, 1133.
7. Lai, P.-S.; Dubland, J. A.; Sarwar, M. G.; Chudzinski, M. G.; Taylor, M. S. *Tetrahedron* **2011**, *67*, 7586.

Chapter 4

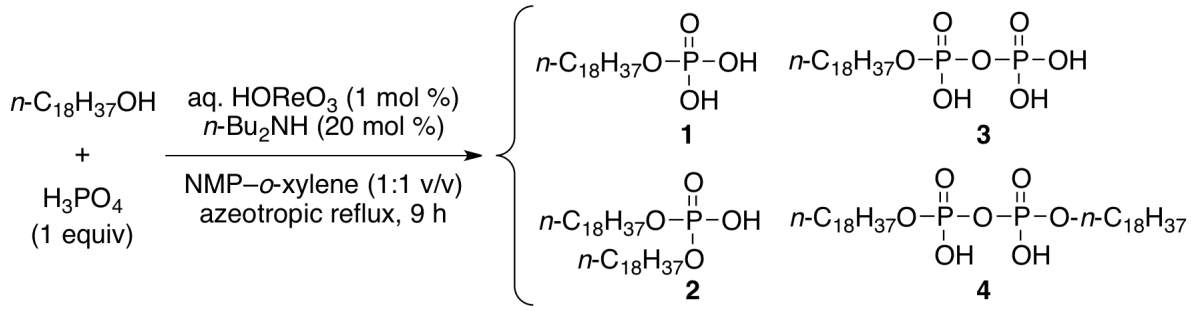
Selective Synthesis of Cyclic Phosphoric Acid Diesters through Oxorhenium(VII)-Catalyzed Dehydrative Condensation of Phosphoric Acid with Alcohols

Abstract: The selective synthesis of phosphoric acid diesters has been achieved through the direct catalytic dehydrative condensation of phosphoric acid with two equivalents of alcohols. The present method works especially well for the synthesis of cyclic phosphoric acid diesters. The combination of perrhenic acid and *N*-methylbenzylamine efficiently catalyzes the dehydrative condensation of phosphoric acid with equimolar amounts of diols to give cyclic phosphoric acid diesters in excellent yields.

4–1 Introduction

Many phosphoric acid esters are currently synthesized on an industrial scale and are widely used in everyday life.[1,2] Phosphoric acid diesters are important substances which have been used as liquid ion exchangers for the recovery of several valuable metals from waste liquors.[3] In particular, cyclic phosphoric acid diesters have recently been widely used in the fields of organic synthesis, materials chemistry, and so on. For example, cyclic phosphoric acid diesters of BINOL derivatives are useful chiral Brønsted acid catalysts for asymmetric synthesis.[4] Amphiphilic cyclic phosphoric acid diesters are useful surfactants with biological activities.[5,6] From the perspective of green chemistry, the direct catalytic condensation of phosphoric acid with alcohols is attractive for the synthesis of phosphoric acid esters.[7] Previously, we reported that a catalytic amount of perrhenic acid efficiently promoted the dehydrative condensation of phosphoric acid with equimolar amounts of alcohols in the presence of dibutylamine (20 mol %).[8] This reaction is usually conducted at 175–180 °C under azeotropic reflux conditions, and selectively gives phosphoric acid monoesters in excellent yields (Table 4.1).[9] After intensive studies, we found that yield of phosphoric acid diester **2** increased when the reaction of phosphoric acid with stearyl alcohol (1 equiv) was conducted at a higher reaction temperature (185–190 °C) (^{31}P NMR analysis).[10] These experimental results implied that phosphoric acid diesters may be selectively obtained when the oxorhenium(VII)-catalyzed condensation of phosphoric acid is conducted with 2 equivalents of alcohols under appropriate reaction conditions.

Table 4.1. Dehydrative Condensation of Phosphoric Acid with Equimolar Amounts of Stearyl Alcohol



temperature (°C)	conv. (%)[a]			
	1	**2**	**3**	**4**
175–180	71	4	10	5
185–190	60	13	12	8

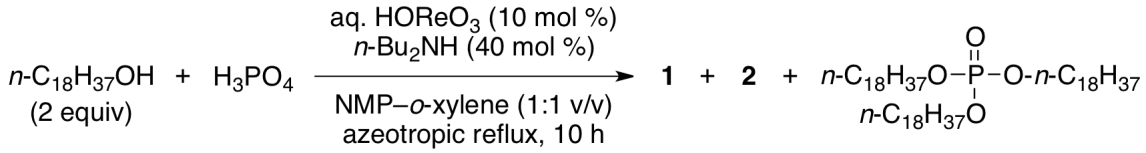
[a] Determined by ^{31}P NMR analysis.

4–2 Results and Discussion

In oxorhenium(VII)-catalyzed dehydrative condensation, 20 mol % of dibutylamine (Bu_2NH) was used to stabilize the oxorhenium(VII) catalyst under the reaction conditions.[11] Furthermore, we found that tetrakis-[tris(dimethylamino)phosphoranilidenamino]-phosphonium hydroxide, a strong organic base, also promoted the dehydrative condensation of phosphoric acid.[12] It is conceivable that the appropriate selection of organic bases is key for the selective synthesis of phosphoric acid diesters through the oxorhenium(VII)-catalyzed method. We first examined organic bases suitable for the selective synthesis of phosphoric acid diesters (Table 4.2). The condensation of phosphoric acid (0.5 mmol) with stearyl alcohol (2 equiv) was conducted in the presence of perrhenic acid (10 mol %) and an organic amine (40 mol %) in *N*-methyl-2-pyrrolidone (NMP)–*o*-xylene (1:1 v/v, 10 mL) at azeotropic reflux with the removal of water. The reaction gave phosphoric acid diester **2** along with monoester **1** and triester **5**. As a result, **2** was selectively produced when a sterically less hindered secondary amine was used. Inparticular, *N*-methylcyclohexanemethanamine (*c*-$C_6H_{11}CH_2NHMe$, 82%), *N*-methylbenzylamine (BnNHMe, 79%) and Bu_2NH (76%) gave excellent results (entries 1, 2 and 6). Among these, commercially available BnNHMe and

Bu_2NH were the most suitable. Sterically hindered secondary amines such as *N*-methyl-*tert*-butylamine (*t*-BuNHMe) and dibenzylamine (Bn_2NH) gave slightly lower yields of **2** (69 and 65%, entries 7 and 8). Tertiary amines such as tributylamine (Bu_3N) and *N,N*-dimethylbenzylamine ($BnNMe_2$) also gave **2** in lower yield (63 and 61%, entries 9 and 10). It is conceivable that the weaker interaction between these sterically hindered amines and perrhenic acid decreased the stability of the catalyst. When the reaction was conducted with primary amines such as octylamine (*n*-$C_8H_{17}NH_2$), the yield of **2** significantly decreased (21%, entry 11). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), a strong organic base, gave a very poor result (9%, entry 12). The strong coordination of DBU to perrhenic acid might significantly decrease the catalytic activity. Therefore, moderate interaction between perrhenic acid and an organic base is a key to stabilizing the catalyst and effectively promoting dehydrative condensation.

Table 4.2. Effect of Organic Amines for the Oxorhenium(VII)-Catalyzed Dehydrative Condensation of Phosphoric Acid with Stearyl Alcohol



entry	amine	conv. of **1**:**2**:**5** (%)[a]	entry	amine	conv. of **1**:**2**:**5** (%)[a]
1	*c*-$C_6H_{11}CH_2NHMe$	8:82:10	7	*t*-BuNHMe	28:69:0
2	BnNHMe	13:79:8	8	Bn_2NH	31:65:4
3[b]	BnNHMe	10:74:8	9	*n*-Bu_3N	22:63:5
4[c]	BnNHMe	17:77:6	10	$BnNMe_2$	22:61:17
5[d]	BnNHMe	38:55:3	11	*n*-$C_8H_{17}NH_2$	70:21:1
6	*n*-Bu_2NH	13:76:8	12	DBU	72:9:0

[a] Determined by ^{31}P NMR analysis.
[b] The reaction was conducted with aq. $HOReO_3$ (1 mol %) and BnNHMe (40 mol %) for 20 h.
[c] The reaction was conducted with aq. $HOReO_3$ (1 mol %) and BnNHMe (20 mol %) for 20 h.
[d] The reaction was conducted with aq. $HOReO_3$ (1 mol %) and BnNHMe (10 mol %) for 20 h.

The amount of the amine was also optimized under the reaction conditions in the presence of 1 mol % of perrhenic acid. The use of 20–40 mol % of BnNHMe gave similar results (entries 3 and 4). However, the yield of **2** significantly decreased when the reaction was conducted with 10 mol % of BnNHMe due to significant decomposition of the catalyst (entry 5). The use of 1 mol % of perrhenic acid and 20 mol % of BnNHMe was the most suitable for the synthesis of **2**.

Next, we optimized the concentration of phosphoric acid (Figure 4.1). The reaction of phosphoric acid (0.5 mmol) with stearyl alcohol (2 equiv) was conducted with perrhenic acid (1 mol %) and BnNHMe (20 mol %) in NMP–*o*-xylene (1:1 v/v) at azeotropic reflux with the removal of water. The yield of **2** *n*-$C_{18}H_{37}O$ increased as the concentration of phosphoric acid decreased in the range of 0.05–0.2 M. A lower concentration effectively may have increased the efficiency of dehydration under azeotropic reflux conditions. However, the reaction with 0.02 M of phosphoric acid gave a rather poor result (open circles). The best result was obtained with 0.05 M of phosphoric acid (closed circles).

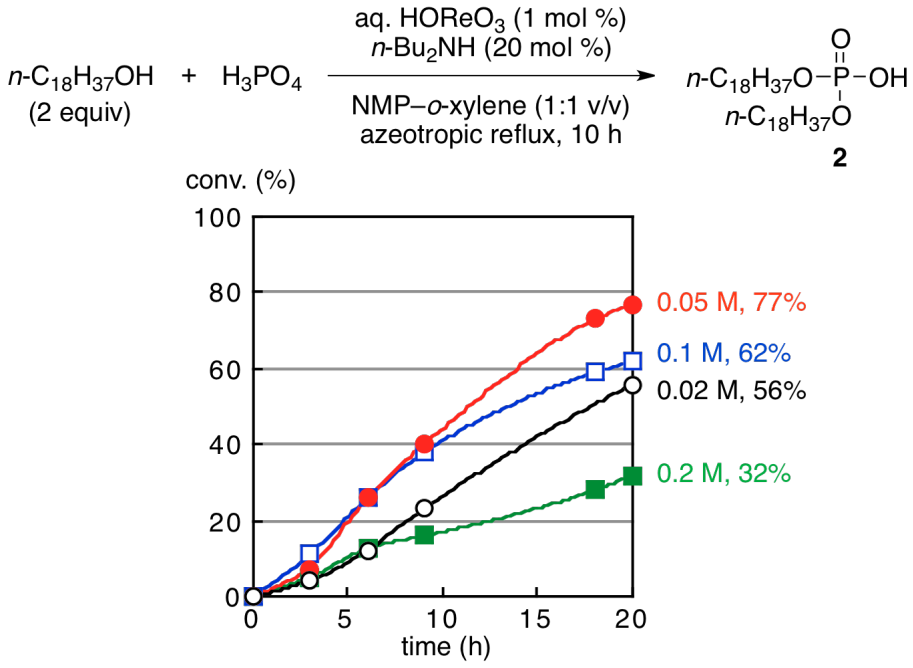


Figure 4.1. Plot of conversion versus time for the dehydrative condensation of phosphoric acid. Closed squares: 0.2 M of phosphoric acid; open squares: 0.1 M; closed circles: 0.05 M; open circles: 0.02 M.

Under the optimized conditions, the condensation reaction of phosphoric acid with stearyl alcohol (2 equiv) gave phosphoric acid diester **2** (77%) along with monoester **1** (17%) and triester **5** (6%). This selective production of **2** was attributed to the differences between the reactivities of phosphoric acid, **1**, and **2** with stearyl alcohol (1 equiv). These reactivities are compared in Figure 4.2. The reaction of phosphoric acid with stearyl alcohol proceeded the most rapidly to give **1** (circles). In contrast, the reactivity of phosphoric acid diester **2** was very low (triangles).

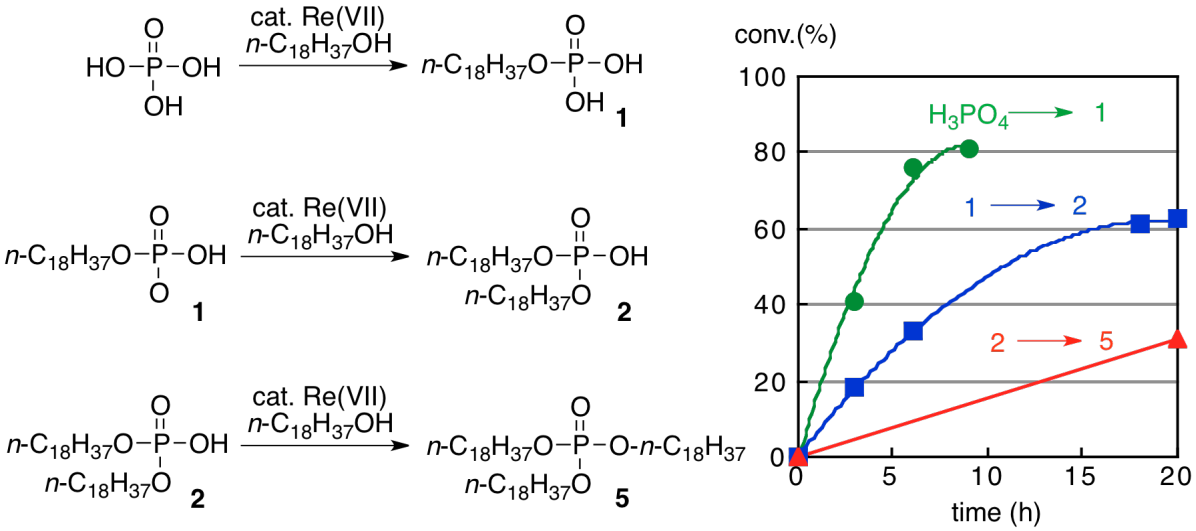
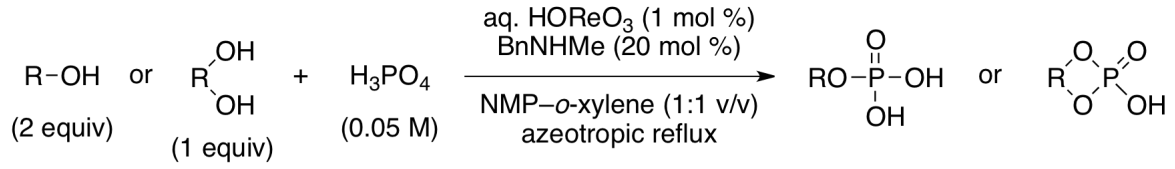
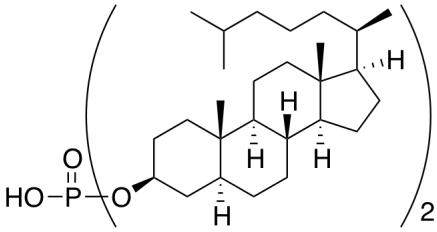
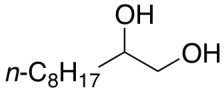
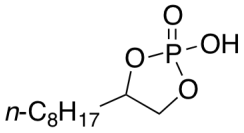
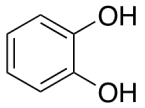
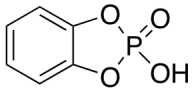
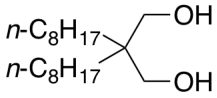
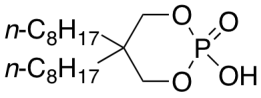
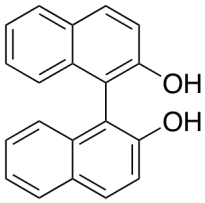
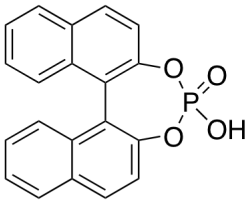


Figure 4.2. Comparison of the reactivities of phosphoric acids, **1** and **2**. The reaction was conducted with stearyl alcohol (1 equiv) in the presence of aq. $HOReO_3$ (1 mol %) and BnNHMe (20 mol %) in NMP–*o*-xylene (1:1 v/v) at azeotropic reflux with the removal of water.

With the optimized conditions in hand, we synthesized several phosphoric acid diesters (Table 4.3). The phosphoric acid diester of diethylene glycol dodecyl ether (**6**)[14] could be obtained in 72% yield, albeit with a prolonged reaction time (entry 1). A secondary alcohol, β-cholestanol, was also converted to the corresponding phosphoric acid diester **7** in 66% yield (entry 2). A prolonged reaction time caused decomposition of the product and the yield of **7** did not increase, although phosphoric acid monoester of β-cholestanol was obtained in an excellent yield without any decomposition.[8]

Table 4.3 Synthesis of Phosphoric Acid Diesters



entry	alcohol	product	time (h)	yield (%)[a]
1	*n*-$C_{12}H_{25}(OC_2H_4)_2OH$	*n*-$C_{12}H_{25}(OC_2H_4)_2O$–P(=O)–OH, *n*-$C_{12}H_{25}(OC_2H_4)_2O$	96	72[b]
2	b-cholestanol		30	66[b]
3			8	>99[c]
4			20	>99[c]
5			50	99 (100[b])
6			75	84 (97[b])
7			48	90[b]

[a] Isolated yield. [b] Conversion yield (determined by ^{31}P NMR analysis.
[c] Isolated as *N*-methylbenzylammonium salt.[13]
[d] The reaction was conducted with 40 mol % of BnNHMe.
[e] The reaction was conducted in the presence of 10 mol % of catecol.

The present reaction conditions worked very well for the synthesis of cyclic phosphoric acid diesters. The condensation of phosphoric acid with equimolar amounts of diols gave cyclic phosphoric acid diesters in almost quantitative yields. 1,2-Decandiol showed high reactivity to give the corresponding five-membered cyclic diester **8** in a short reaction time, which could

be isolated as *N*-methylbenzylammonium form[13] (entry 3). Catechol was also converted smoothly to the corresponding five-membered cyclic phosphoric acid diester **9**[15] (>99% yield, entry 4). However, compound **9** could not be isolated since it was very labile and decomposed during purifications even as its ammonium form. A 1,3-diol such as 9,9-bis(hydroxymethyl)heptadecane was also converted into the corresponding six-membered cyclic diester **10** in 93% isolated yield (entry 5). This double-tailed cyclic phosphate **10** is in a novel class of phosphate surfactants.[5] Since the reactivity of BINOL was slightly lower than those of aliphatic alcohols, the condensation of BINOL was conducted with 40 mol % of BnNHMe. After a 75-hour reaction, binaphthylphosphoric acid **11**[16] was obtained in 84% isolated yield (entry 6). Based on the good reactivity of catechol and the lability of **9**, we proposed that catechol might promote the dehydrative condensation of phosphoric acid with BINOL. In fact, when the reaction of phosphoric acid with BINOL was conducted in the presence of catechol (10 mol %) and BnNHMe (40 mol %), the reaction proceeded smoothly and gave **11** in 90% yield (48 h) (entry 7). Compound **9** might be generated *in situ* as an active intermediate.[17]

4–3 Conclusion

We have selectively synthesized phosphoric acid diesters through the oxorhenium(VII)-catalyzed dehydrative condensation of phosphoric acid with alcohols. The present reaction was especially useful for the synthesis of cyclic phosphoric acid diesters. The condensation of phosphoric acid with equimolar amounts of diols gave cyclic phosphoric acids in almost quantitative yields.

Reference and Notes

1. (a) Tadros, T. F. *Applied Surfactants: Principles and Applications*; Wiley: Weinheim **2005**. (b) Toy, A. D. F.; Walsh E. N. *Phosphorus Chemistry in Everyday Living: American Chemical Society*; Washington, DC, 2nd ed, **1987**.
2. For reviews of the synthesis of phosphoric acid esters, see: (a) Hayakawa, Y. in *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Winterfeldt, E., Pergamon: Oxford, **1991**, *6*, pp 601–630. (b) Reese, C. B. *Org. Biomol. Chem*. **2005**, *3*, 3851.
3. Kurosaki, T.; Nishikawa, N. *DE Patent Application* 3325337, **1984**. (*Chem. Abstr.* **1984**, *100*, 156819).
4. Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744.
5. Buwalda, R. T.; Wagenaar, A.; Engberts, J. B. F. N. *Liebigs Ann./Recueil* **1997**, 1745.
6. Shinitzky, M. *WO Patent Application* 2003075902, **2003** (*Chem. Abstr.* **2003**, *139*, 240393).
7. Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University: Oxford, **1998**.
8. Sakakura, A.; Katsukawa, M.; Ishihara, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 1423.
9. Since pyrophosphoric acid esters **3** and **4** were converted into **1** during workup and purification, **1** was obtained in 86% yield (determined by ^{31}P NMR analysis of the crude product).
10. In contrast, a phosphazenium cation-catalyzed method (ref. 11) gave only a trace amount of phosphoric acid diesters (ca. 5%) even when the reaction of phosphoric acid was conducted with 2 equivalents of an alcohol. This method could scarcely promote the condensation of phosphoric acid monoesters with alcohols.
11. Under the reaction conditions in the absence of dibutylamine, oxorhenium(VII) complexes gradually decomposed to dark insoluble, catalytically inactive species (ref. 8).
12. Sakakura, A.; Katsukawa, M.; Hayashi, T.; Ishihara, K. *Green Chem.* **2007**, *9*, 1166.
13. The phosphoric acid form of compound **8** gradually decomposed to give a mixture of phosphoric acid monoesters, while the ammonium form of **8** was stable.
14. (a) Nishimoto, T.; Takahashi, H.; Nasukawa, M. *JP Patent Application* 05179186, **1993** (*Chem. Abstr.* **1993**, *119*, 228219). (b) Matsufuji, Y. *JP Patent Application* 57033566, **1982** (*Chem. Abstr.* **1982**, *99*, 222497).

15. Groß, H.; Katzwinkel, S.; Gloede, J. *Chem. Ber.* **1966**, *99*, 2631.
16. (a) Jacques, J.; Fourquey, C. *Org. Synth.* **1989**, *67*, 1. (b) Yamakawa, M.; Ito, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 6756.
17. The reaction mixture contained a small amount of **9** (ca. 6%, determined by ^{31}P NMR analysis).

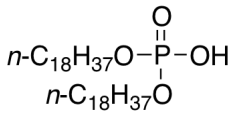
Experimental Section

General Methods. IR spectra were recorded on a JASCO FT/IR-460 plus spectrometer. ^{1}H NMR spectra were measured on a Varian Gemini-2000 spectrometer (300 MHz) or INOVA spectrometer (500 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethysilane on the d scale, multiplicity (s = singlet; d = doublet; t = triplet; m = multiplet), coupling constant (Hz), and integration. ^{13}C NMR spectra were measured on a Varian Gemini-2000 spectrometer (75 MHz) or INOVA spectrometer (125 MHz). Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm). ^{31}P NMR spectra were measured on a Varian Mercury-300 spectrometer (121 MHz). Chemical shifts were reported as d value in ppm downfield from 85% H_3PO_4. High resolution mass spectral analysis (HRMS) was performed at Chemical Instrument Room, Nagoya University. All experiments were carried out under an atmosphere of dry nitrogen. Chemical materials were obtained from commercial supplies and used without further purification. A 65–70 w% aqueous solution of perrhenic acid ($HOReO_3$ aq.) and a crystal form of phosphoric acid (99.999+%, Aldrich) were purchased from Aldrich.

Typical procedure for the dehydrative condensation of phosphoric acid with a diol (1 equiv): Synthesis of cyclic phosphoric acid diester 11.[16]

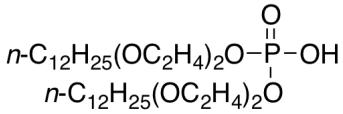
A 30-mL, single-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a 5-mL pressure-equalized addition funnel [containing a cotton plug and ca. 2 g of molecular sieves 4Å (pellets)] surmounted by a reflux condenser was charged with phosphoric acid (49 mg, 0.50 mmol), 1,1'-bi-2-naphthol (143 mg, 0.50 mmol), *N*-methylbenzylamine (26 μL, 0.10 mmol) and a 65–75 w% aqueous solution of perrhenic acid (0.9 μL, ca. 1 mol %) in NMP–*o*-xylene (1:1 v/v, 10 mL). The mixture was heated for 75 hours under azeotropic reflux conditions with the removal of water. After the reaction mixture was cooled to ambient temperature, solvents were removed *in vacuo*. A solution of the residue in Et_2O–$CHCl_3$ (4:1 v/v, 50 mL) was washed with 1 M aqueous HCl (40 mL). The aqueous layer was extracted with Et_2O–$CHCl_3$ (4:1 v/v, 50 mL x 2). The combined organic layers were concentrated under reduced pressure. The residue was purified by

column chromatography on silica gel (20 g) using hexane–EtOAc–MeOH (10:10:1 → 1:1:1) as eluents, and the fractions that contained phosphoric diester **11** were collected and concentrated. A solution of the obtained compound in Et_2O–$CHCl_3$ (4:1 v/v, 50 mL) was washed with 1 M aqueous HCl (40 mL). The combined organic layer was concentrated under reduced pressure to give **11** (147 mg, 84%).



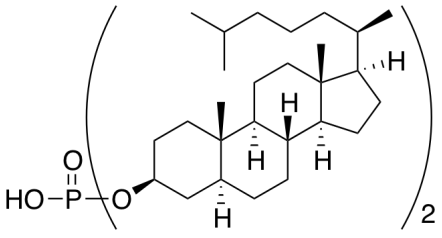
Distearyl phosphate (2).[3]

IR (KBr) 3423, 1655, 1637, 1469, 1263, 1209, 1092, 1067, 1035 cm^{-1}; ^1H NMR (300 MHz, CDCl3) δ 0.88 (t, *J* = 6.8 Hz, 6H), 1.16–1.49 (m, 60H), 1.67 (quint, *J* = 6.5 Hz, 4H), 4.01 (q, *J* = 6.5 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.7, 25.5, 29.2, 29.4, 29.6, 29.7, 29.7, 30.2, 31.9, 67.6; ^{31}P NMR (121 MHz, $CDCl_3$) δ 1.59; HRMS (FAB) calcd for $C_{56}H_{76}O_4P$ $[(M+H)^+]$ 603.5481, found 603.5494.



Bis[2-(2-dodecyloxy)ethoxy]ethyl phosphate (6).[12]

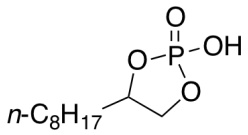
^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.6 Hz, 6H), 1.16–1.46 (m, 36H), 1.58 (tt, *J* = 6.0 Hz, 4H), 3.45 (t, *J* = 6.6 Hz, 4H), 3.53–3.79 (m, 12H), 4.10–4.26 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.6, 26.0, 29.3, 29.4, 29.5, 31.8, 66.3, 69.9, 70.4, 71.6; ^{31}P NMR (121 MHz, $CDCl_3$) δ 0.86.



Dicholestanyl phosphate (7).

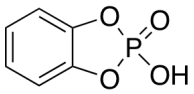
IR (KBr) 3416, 1637, 1467, 1383, 1264, 1208, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.64 (s, 6H), 0.81 (s, 6H), 0.858 (d, *J* = 6.6 Hz, 6H), 0.861 (d, *J* = 6.6 Hz, 6H), 0.89 (d, *J* = 6.6 Hz,

6H), 0.83–1.42 (m, 38H), 1.42–1.90 (m, 18H), 1.90–2.04 (m, 6H), 4.13–4.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0, 12.2, 18.6, 21.2, 22.5, 22.8, 23.9, 24.2, 28.0, 28.3, 28.6, 29.3, 32.0, 35.3, 35.4, 35.7, 35.8, 36.2, 36.8, 39.5, 39.9, 42.6, 44.7, 54.2, 56.3, 56.4, 78.1; ^{31}P NMR (121 MHz, $CDCl_3$) δ 0.57; HRMS (FAB) calcd for $C_{54}H_{95}NaO_4P$ [$(M+Na)^+$] 861.6866, found 861.6891.



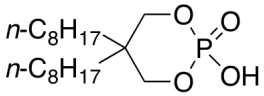
Cyclic phosphoric acid diester (8) (*N*-methybenzylammonium salt).

Compound **8** was isolated as follows: After the reaction mixture was cooled to ambient temperature, BnNHMe (64 μL, 0.50 mmol) was added, and solvents were removed *in vacuo*. The residue was purified by column chromatography on silica gel (10 g) using $CHCl_3$ with a trace amount of BnNHMe and then a mixture of $CHCl_3$–MeOH–BnNHMe (2:1:trace) as eluents to give *N*-methylbenzylammonium salt of **8** (191 mg, >99%); IR (KBr) 3416, 1639, 1575, 1469, 1430, 1396, 1208, 1127, 1089, 1025 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 2H), 1.18–1.41 (m, 11H), 1.41–1.62 (m, 2H), 1.62–1.79 (m, 1H), 2.42 (s, 3H), 3.79 (ddd, J = 4.8, 8.7, 8.7 Hz, 1H), 3.95 (s, 2H), 4.19 (ddd, J = 5.7, 8.7, 16.2 Hz, 1H), 4.31–4.43 (m, 1H), 7.31–7.43 (m, 3H), 7.51 (dd, J = 1.8, 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 25.2, 29.2, 29.4, 31.4, 31.8, 33.8, 52.0, 69.7, 128.9, 130.2, 131.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ 17.7; HRMS (FAB) calcd for $C_{10}H_{22}O_4P$ [$(M+H)^+$] 237.1256, found 237.1246.



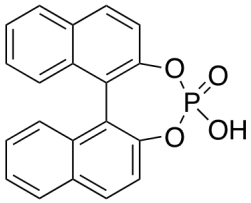
Cyclic phosphoric acid diester (9).[15]

^{31}P NMR (121 MHz, $CDCl_3$) δ 13.7.



Cyclic phosphoric acid diester (10).

IR (neat) 1654, 1468, 1266, 1200, 1104, 1071, 1037, 1008, 989 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.8 Hz, 6H), 1.14–1.48 (m, 28H), 4.09 (d, *J* = 12.6 Hz, 4H); ^{13}C NMR (75 MHz, CDCl3) δ 14.0, 22.6, 22.7, 29.2, 29.3, 30.1, 30.2, 31.8, 37.0, 37.0, 75.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ –3.30; HRMS (FAB) calcd for $C_{19}H_{40}O_4P$ $[(M+H)^+]$ 363.2664, found 363.2666.



Binaphthylphosphoric acid (11).[16]

^{1}H NMR (300 MHz, $CDCl_3$–CD_3OD 3:1) δ 7.26–7.34 (m, 2H), 7.38 (d, *J* = 8.7 Hz, 2H), 7.44–7.52 (m, 2H), 7.55 (d, *J* = 9.3 Hz, 2H), 7.95 (d, *J* = 8.1 Hz, 2H), 8.04 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$–CD_3OD 3:1) δ 120.3, 121.3, 125.4, 126.4, 126.7, 128.2, 130.8, 131.4, 132.0, 146.9, 147.0; ^{31}P NMR (121 MHz, $CDCl_3$–CD_3OD 3:1) δ 4.12.

Publication List

1. "Selective Synthesis of Cyclic Phosphoric Acid Diesters through Oxorhenium(VII)-Catalyzed Dehydrative Condensation of Phosphoric Acid with Alcohols"
   Akira Sakakura, Masayuki Sakuma, Mikimoto Katsukawa, Kazuaki Ishihara
   Heterocycles **2008**, *76*(1), 657–665.

2. "Chiral Lewis Base-Assisted Brønsted Acid (LBBA)-Catalyzed Enantioselective Cyclization of 2-Geranylphenols"
   Akira Sakakura, Masayuki Sakuma, Kazuaki Ishihara
   Org. Lett. **2011**, *13*(12), 3130–3133.
   Highlighted in *Synfacts* **2011**, *8*, 899.

3. "Kinetic Resolution of Racemic Carboxylic Acids Catalyzed by Chiral Lewis Base-Assisted Brønsted Acid (LBBA) through Asymmetric Protolactonization"
   Akira Sakakura, Masayuki Sakuma, Kazuaki Ishihara
   In preparation.

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