

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

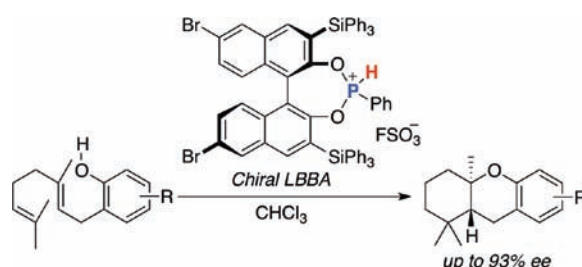
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ABSTRACT



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).

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

We recently developed a chiral Lewis base-promoted enantioselective iodocyclization of isoprenoids.^{5,6} The

(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. 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.

(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, A. N.; 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, L.; Chen, J.; Tan, C. K.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2011**, *1021*, ja201627h. (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. *Tetrahedron* **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.

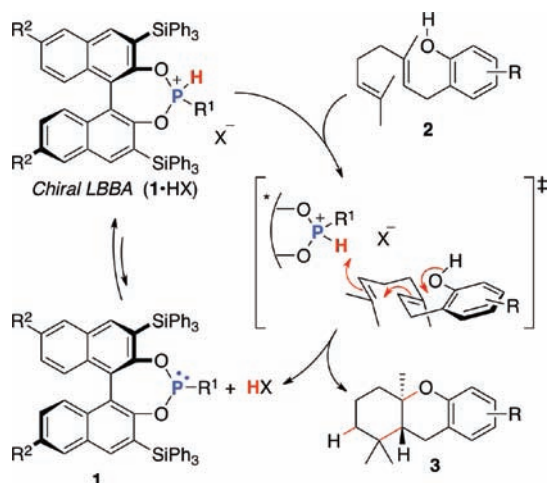


Figure 1. Chiral Lewis base-assisted Brønsted acids (Chiral LBBAs, **1**·HX) and proposed catalytic cycle for the LBBA-catalyzed cyclization of 2-geranylphenols **2**.

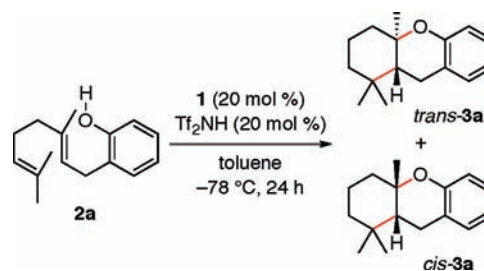
chiral nucleophilic phosphoramidite, prepared from a binaphthol bearing triphenylsilyl groups at the 3,3'-positions, reacts with *N*-iodosuccinimide (NIS) to generate the corresponding phosphonium salt as an active species. This chiral Lewis base-promoted method can also be applied to the Brønsted acid-induced cyclization of isoprenoids. Thus, we pursued the design of new chiral Brønsted acids: Lewis base-assisted Brønsted acids (LBBAs), phosphonium salts⁷ prepared from a chiral phosphorus(III) compound **1** with an achiral Brønsted acid (HX) (Figure 1). We report here the chiral LBBA-catalyzed enantioselective cyclization of 2-geranylphenols.

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 [pK_a values of conjugate acids: P(OPh)₃ -2.0, P(OMe)₃ 2.6, PPh₃ 2.7, and PMe₃ 8.7].⁸ We first examined the catalytic activities of chiral LBBAs prepared from **1** with Tf₂NH. The cyclization of 2-geranylphenol **2a** was carried out in the presence of **1** (20 mol %) and Tf₂NH (20 mol %) in toluene at -78 °C (Table 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** (R¹ = OPh) and **1b** (R¹ = 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

(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.

Table 1. Enantioselective Cyclization of 2-Geranylphenol (**2a**) Catalyzed by Chiral LBBAs **1**·Tf₂NH



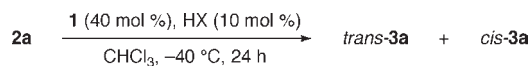
entry	1 [R ¹ , R ²]	yield (%)	<i>trans/cis</i>	ee (%) ^a
1	1a [OPh, H]	61	85:15	0
2	1b [OCy, H]	42	95:5	0
3	1c [Ph, H]	28	93:7	22
4 ^b	1c [Ph, H]	59	91:9	52
5	1d [<i>i</i> -Pr, H]	15	89:11	14
6 ^c		93	79:21	—

^a Ee of *trans*-**3a**. Determined by HPLC analysis. ^b Reaction was conducted in the presence of **1c** (40 mol %) and Tf₂NH (10 mol %) at -40 °C. ^c Reaction was conducted in the absence of **1**.

Brønsted acid (entry 1). LBBA **1b**·Tf₂NH, which was less acidic than **1a**·Tf₂NH, improved the diastereoselectivity, although it did not have enough stability to control the enantioselectivity (entry 2). On the other hand, the use of chiral phosphorous acid diesters **1c** (R¹ = Ph) and **1d** (R¹ = *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 (4*aR*).^{1g} Further investigation revealed that when the reaction was conducted using **1c** (40 mol %) and Tf₂NH (10 mol %) at -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.

Next, we investigated Brønsted acids (HX) in chiral LBBAs for the cyclization of **2a** (Table 2). The reaction was conducted in CHCl₃, since the use of CHCl₃ 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**·Tf₂NH-

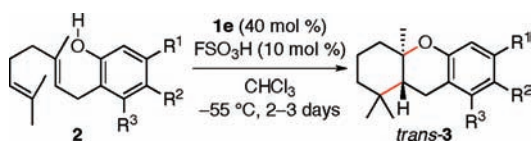
(9) The low yield and enantioselectivity in the reaction using Tf₂NH in CHCl₃ (entry 1) can be attributed to the rapid decomposition of **1c** due to the high acidity of Tf₂NH.

Table 2. Optimization of the Reaction Conditions

entry	1 [R ¹ , R ²]	HX	yield (%)	trans/cis	ee (%) ^a
1	1c [Ph, H]	Tf ₂ NH	30	97:3	19
2	1c [Ph, H]	TFOH	77	90:10	75
3	1c [Ph, H]	ClSO ₃ H	69	94:6	76
4	1c [Ph, H]	FSO ₃ H	42	98:2	81
5 ^b	1c [Ph, H]	FSO ₃ H	60	97:3	81
6	1e [Ph, Br]	FSO ₃ H	86	85:15	78
7 ^c	1e [Ph, Br]	FSO ₃ H	86	90:10	84
8	1f [4-CF ₃ C ₆ H ₄ , H]	FSO ₃ H	62	92:8	49

^aEe of *trans*-**3a**. Determined by HPLC analysis. ^bOne-hundred molar percent of **1c** was used. ^cReaction was conducted at -55 °C for 3 days.

catalyzed reaction would be attributed to the background reaction caused by strongly acidic Tf₂NH (entry 1). The use of sterically less-hindered FSO₃H 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**·FSO₃H-catalyzed cyclization of **2a** was conducted at -55 °C for 3 days, the enantioselectivity

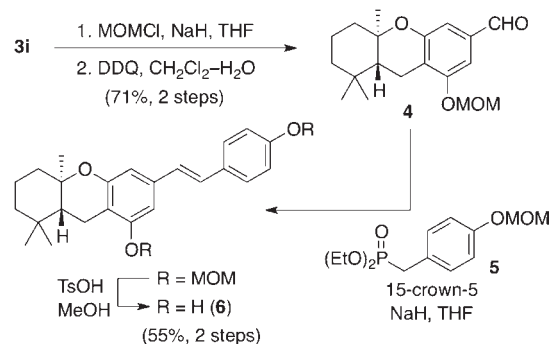
Table 3. Enantioselective Cyclization of 2-Geranylphenol Derivatives **2** Catalyzed by Chiral LBBA **1e**·FSO₃H

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 ₂ O, 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

^aEe of *trans*-**3**. Determined by HPLC analysis. ^bOne-hundred molar percent of **1e** and 20 mol % of FSO₃H were used in CHCl₃ (0.02 M).

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.

With the optimized reaction conditions in hand, we next examined the enantioselective cyclization of 2-geranylphenol derivatives **2** using **1e**·FSO₃H as a catalyst (Table 3). The introduction of both electron-donating and electron-withdrawing groups at the 4- and 5-positions (R¹ and R²) 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 (R³) 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 C₂ symmetry of **2i** might be suitable for the high-level induction of diastereoselectivity. The use of 100 mol % of **1e** and 20 mol % of FSO₃H increased the yield of **3i** without a loss of enantioselectivity (60% yield, entry 9).

Scheme 2. 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 group¹¹ at the 4-position gave aldehyde **4** in 71% yield (Scheme 2).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

(10) 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.

(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.

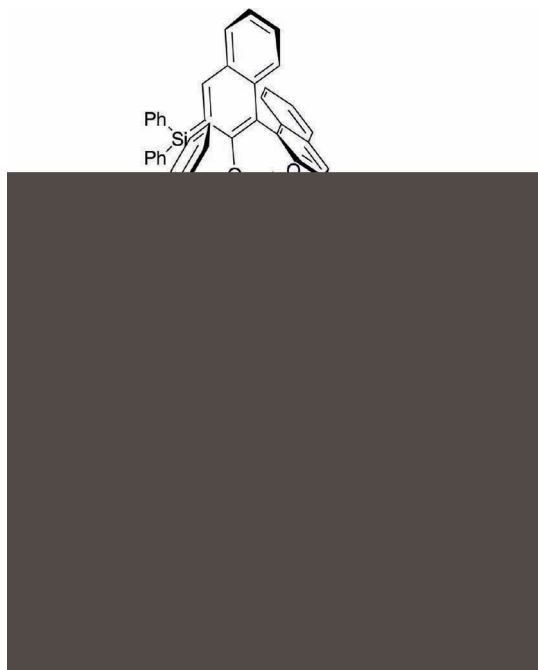


Figure 2. Proposed transition-state assemblies.

Figure 2 is the Newman projection of the chiral LBBA **1c**·FSO₃H 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.

In 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 FSO₃H catalyzed the cyclization of 2-geranylphenols to give the corresponding *trans*-fused cyclized products with high diastereo- and enantioselectivities.

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Supporting Information Available. Experimental procedures, spectroscopic data for all new compounds, NMR spectra, and HPLC charts. This material is available free of charge via the Internet at <http://pubs.acs.org>.