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

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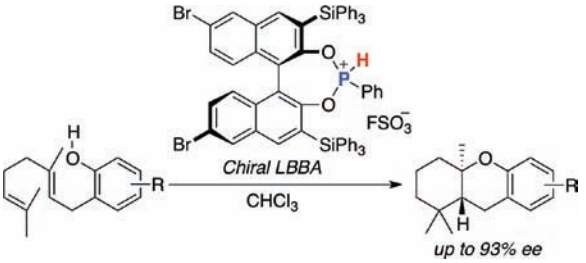
ABSTRACT



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. 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*, 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**10.1021/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. *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.

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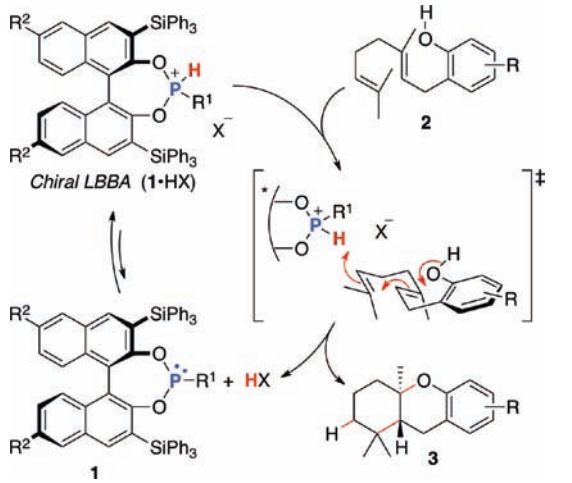
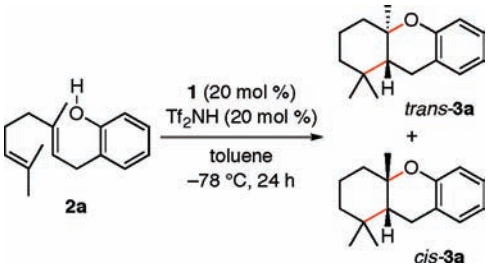


Figure 1. Chiral Lewis base-assisted Brønsted acids (Chiral LBBAs, **1**·HX) and proposed catalytic cycle for the LBBA-catalyzed cyclization of 2-geranylphenols **2**.

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 salts[7] 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, 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 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

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



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**.

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 %) 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.

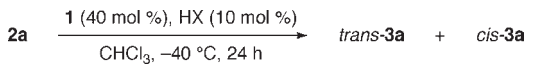
Next, we investigated Brønsted acids (HX) in chiral LBBAs for the cyclization of **2a** (Table 2). The reaction was conducted in $CHCl_3$, since the use of $CHCl_3$ as a solvent generally gave **3a** in higher yield and enantioselectivity than with toluene when sulfonic acids were used as Brønsted acids.[9] 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-

(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.

Table 2. Optimization of the Reaction Conditions



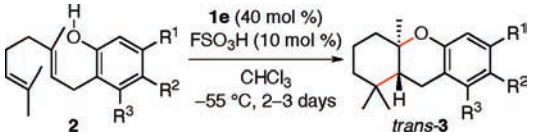
entry	**1** [R^1, R^2]	HX	yield (%)	*trans*/*cis*	ee (%)[a]
1	**1c** [Ph, H]	Tf_2NH	30	97:3	19
2	**1c** [Ph, H]	TfOH	77	90:10	75
3	**1c** [Ph, H]	$ClSO_3H$	69	94:6	76
4	**1c** [Ph, H]	FSO_3H	42	98:2	81
5[b]	**1c** [Ph, H]	FSO_3H	60	97:3	81
6	**1e** [Ph, Br]	FSO_3H	86	85:15	78
7[c]	**1e** [Ph, Br]	FSO_3H	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] One-hundred molar percent of **1c** was used. [c] Reaction was conducted at −55 °C for 3 days.

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.

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 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).

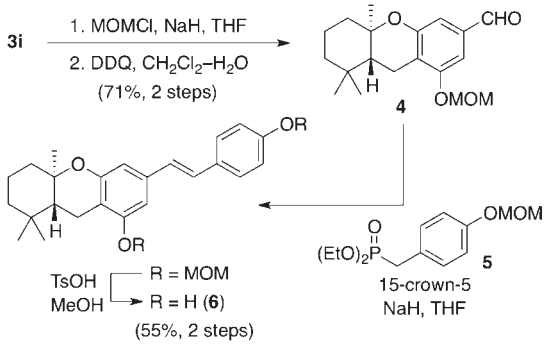
Table 3. Enantioselective Cyclization of 2-Geranylphenol Derivatives **2** Catalyzed by Chiral LBBA **1e**·FSO_3H



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*-**3**. Determined by HPLC analysis. [b] One-hundred molar percent of **1e** and 20 mol % of FSO_3H were used in $CHCl_3$ (0.02 M).

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 group[11] 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.

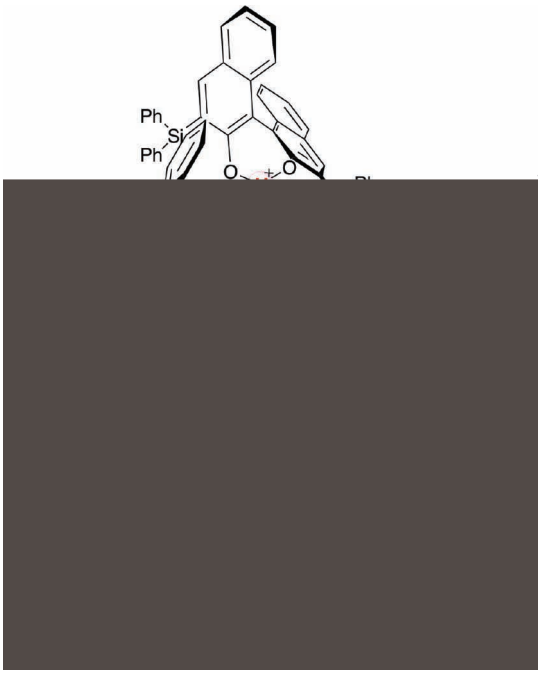


Figure 2. Proposed transition-state assemblies.

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

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 FSO_3H 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.