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Tin(IV) Chloride-Chiral Pyrogallol Derivatives as New Lewis Acid-Assisted Chiral Brønsted Acids for Enantioselective Polyene Cyclization

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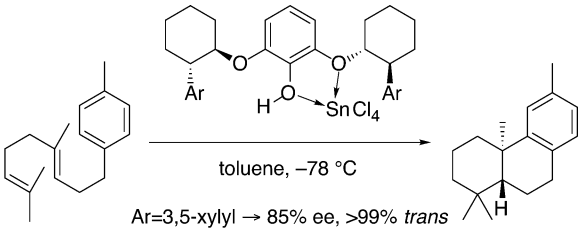
ABSTRACT



New Lewis acid-assisted Brønsted acids (LBAs), tin(IV) chloride-2,6-dialkoxyphenols, serve as artificial cyclases for biomimetic polyene cyclization. For example, the enantioselective cyclization of 4-(homogeranyl)toluene using tin(IV) chloride-2,6-di[(1′*R*,2′*R*)-trans-2′-(3″,5″-xylyl)cyclohexanoxy]-phenol gave a trans-fused tricyclic compound with 85% ee.

We recently reported the first example of the enantioselective cyclization of polyprenyl alcohols and homo(polyprenyl)arenes induced by Lewis acid-assisted chiral Brønsted acids (chiral LBAs).[1,2] Optically pure 2-alkoxy-2′-hydroxy-1,1′-binaphthyl **1** activated with $SnCl_4$ is effective for this enantioselective cyclization. The further refinement of LBAs was required to establish LBA-induced biomimetic polyene cyclization as a practical synthetic method. However, we could not design any chiral Brønsted acids that were superior to **1** by chemical modification of **1**. For example, the introduction of 3,3′-substituents on **1** unexpectedly decreased not only the activity of the LBA but also the enantioselectivity of the polyene cyclization. Thus, we pursued the design of new chiral Brønsted acids, that did not include a binaphthol skeleton, which were activated with $SnCl_4$. In this paper, we report a new design for Brønsted acids that include a pyrogallol skeleton, achiral 2,6-dialkoxyphenols **2**, and optically pure 2,6-di[*trans*-2′-(3″,5″-xylyl)-cyclohexanoxy]phenol (**3c**). $SnCl_4$ preferentially chelates pyrogallol derivatives compared with biphenol and binaphthol derivatives (Figure 1).

Our studies began with the diastereoselective cyclization of 4-(homogeranyl)toluene (**4**) induced by achiral LBA prepared in situ from a 1:1 molar mixture of a variety of phenol derivatives and $SnCl_4$. The reaction was conducted in the presence of 20 mol % ArOH·$SnCl_4$ in dichloromethane at −78 °C. The activity of the Brønsted acid was estimated by the GC ratio of the crude products. In most cases, the desired trans-fused AB-ring product **5** was obtained together

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(1) For a review, see: Ishibashi, H.; Ishihara, K.; Yamamoto, H. *Chem. Rec.* **2002**, *2*, 177.

(2) (a) Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 4906. (b) Nakamura, S.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8131. (c) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2001**, *123*, 1505. (d) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2002**, *124*, 3647.

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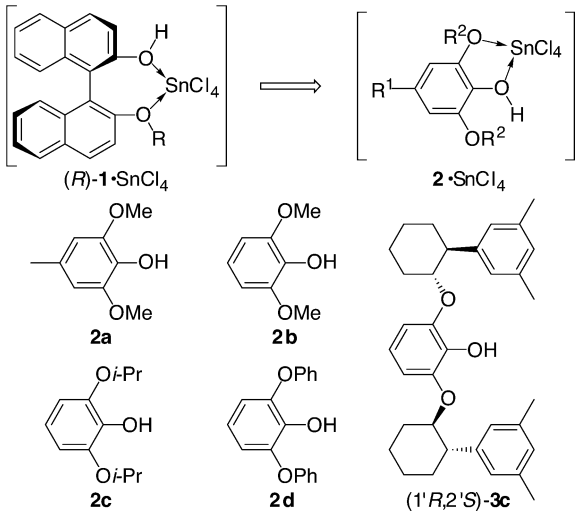
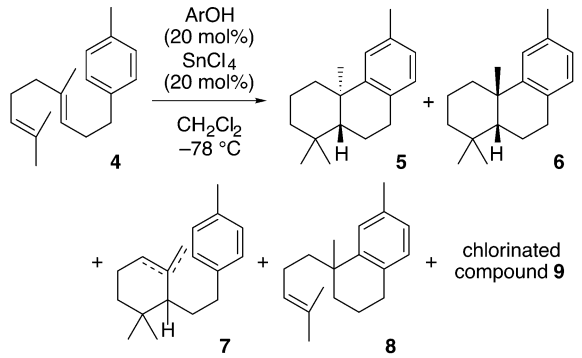
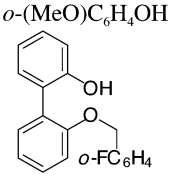


Figure 1. Chiral and achiral LBAs.

with its cis-fused isomer **6**, endo- and exo-isomeric A-ring products **7**, B-ring product **8**, chlorinated compound **9**,[3] and remaining **4** (Table 1). As a result, **2a**−**d** very effectively induced the cyclization of **4** to **5** in the presence of $SnCl_4$

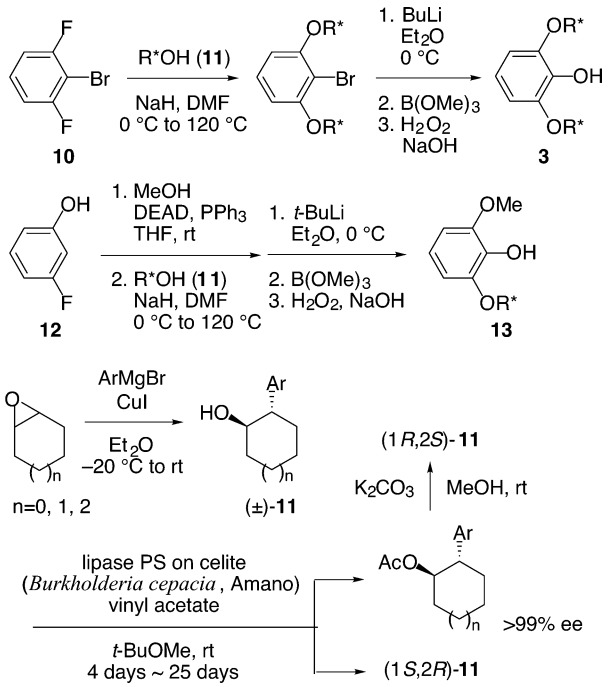
Table 1. Diastereoselective Cyclization of **4** Induced by Achiral LBA, ArOH·$SnCl_4$ [a]



entry	ArOH	time (h)	GC ratio **4** : **5** : **6** : **7** : **8** : **9**[b]
1	**2a**	3	4 : 95 : 1 : 0 : 0 : 10
2	**2b**	4	2 : 94 : 1 : 1 : 2 : 14
3	**2c**	3.5	0 : 92 : 0 : 7 : 1 : 10
4	**2d**	4	0 : 85 : 2 : 5 : 8 : 11
5	*o*-(MeO)C_6H_4OH	7	4 : 89 : 0 : 2 : 5 : 10
6		7	0 : 57 : 3 : 40 : 0 : 4
7	*o*-(*i*-PrO)C_6H_4OH	7	29 : 51 : 0 : 14 : 6 : 14

[a] All reactions were carried out using $SnCl_4$ (0.02 mmol), aryl alcohol (0.02 mmol), **4** (0.5 mmol), and dichloromethane (1 mL) at −78 °C under N_2 for the amount of time shown. [b] See ref 3.

Scheme 1. Preparation of Optically Active 2,6-Dialkoxyphenols **3** and **13**



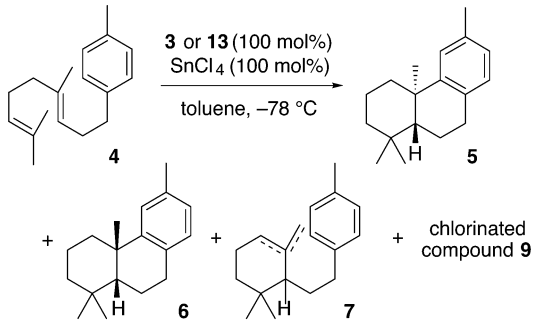
(entries 1−4). In particular, 2,6-dimethoxy-4-methylphenol (**2a**) gave the best results (entry 1). Not only sterically hindered 2,6-diisopropoxyphenol (**2c**) and 2,6-diphenoxyphenol (**2d**) but also 2-methoxyphenol were more effective than 2-(*o*-fluorobenzyloxy)-2′-hydoxybiphenyl (entries 3−5 versus entry 6). The activation effect of LBA was caused by the tight chelation of electron-rich 2-alkoxyphenol derivatives with $SnCl_4$. On the other hand, electron-deficient phenols were not effectively activated by $SnCl_4$ due to the relatively weak Lewis basicity of the phenolic oxygen atom. 2,6-Dimethylphenol and 3,5-dimethoxyphenol were almost inert due to the thermodynamic instability of $SnCl_4$-chelated complexes.

Next, we sought to design chiral 2,6-dialkoxyphenols that were chelated with $SnCl_4$ as a new chiral LBA for the enantioselective polyene cyclization (Scheme 1). C_2-symmetric chiral 2,6-dialkoxyphenol **3** was prepared from 1-bromo-2,6-difluorobenzene (**10**) in two steps: the nucleophilic substitution reaction of chiral alcohols **11** with **10** to give chiral 1-bromo-2,6-dialkoxybenzene and its subsequent oxidation to **3** via the corresponding 2,6-dialkoxybenzeneboronic acid. Asymmetric chiral 2-alkoxy-6-methoxyphenol **13** was prepared from 3-fluorophenol (**12**) in a similar manner.

Optically active *trans*-2-arylcycloalkanols **11** were suitable as chiral alkoxy groups in **3** and **13** because of their conformational rigidity. Both enantiomers of **11** were prepared in a facile three-step sequence starting from the substitution reaction of cycloalkene oxides with arylmagnesium bromide in ether in the presence of CuI, subsequent

(3) Although **9** was shown to contain a chlorine atom by LRMS analysis of the crude products, the chemical structure of **9** was not determined.

Table 2. Enantioselective Cyclization of **4** Using Chiral Pyrogallol Derivatives **3** or **13** and $SnCl_4$



entry	3 or 13, R*O	GC ratio[a] 4:5:6:7:9	ee (%) of 5[b,c]
1[d]	3a, Ph	0:60:3:32:5	24, (–)
2		15:12:0:73:0	54, (–)
3	3b, *o*-Tolyl	4:12:0:80:4	60, (–)
4	3c, *m*-Xylyl	22:3:0:75:0	77, (–)
5[e]		6:9:0:85:0	85, (–)
6	3d, *p*-Tolyl	30:4:0:66:0	46, (–)
7	3e, *m*-Xylyl	83:4:0:11:2	0
8	3f, *m*-Xylyl	8:9:0:73:0	67, (–)
9	13c, *m*-Xylyl	0:54:0:34:12	40, (+)

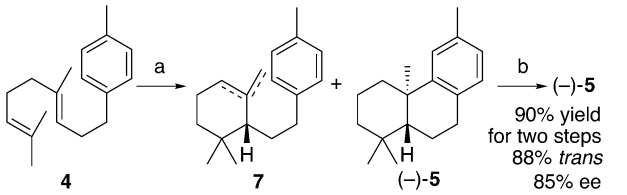
[a] B-ring product **8** was not obtained at all from the reaction in toluene. [b] Ee was determined by HPLC analysis (two linear Daicel OD-H columns). [c] Optical rotation of **5** is indicated in parentheses. [d] **3a**·$SnCl_4$ (20 mol %) was used in CH_2Cl_2. [e] **3c** (200 mol %) and $SnCl_4$ (100 mol %) were used.

kinetic resolution of (±)-**11** via acetylation induced by lipase PS-D "Amano" I (*Burkholderia cepacia*, Amano), and its hydrolysis (Scheme 1).[4]

Chiral pyrogallol derivatives **3** and **13** were examined in the enantioselective cyclization of **4** in the presence of $SnCl_4$ (Table 2). Although several optically active 2,6-di(acyclic alkoxy)phenols were examined as Brønsted acids, no asymmetric induction was induced. On the other hand, 2,6-di(2′-alkylcycloalkoxy)phenols led to some asymmetric induction. When 20 mol % (1′*R*,2′*S*)-2,6-di(2′-phenylcyclohexanoxy)-phenol (**3a**)·$SnCl_4$ was used in dichloromethane, (−)-**5** was obtained in 60% GC yield with 24% ee (entry 1). Fortunately, the optical yield of (−)-**5** could be improved to 54% ee with 100 mol % **3a**·$SnCl_4$ in toluene (entry 2). On the basis of

(4) (a) Takahashi, M.; Ogasawara, K. *Tetrahedron: Asymmetry* **1995**, *6*, 1617. (b) Carpenter, B. E.; Hunt, I. R.; Keay, B. A. *Tetrahedron: Asymmetry* **1996**, *7*, 3107.

Scheme 2. Enantioselective Synthesis of Diterpenoid (−)-**5** Using Chiral and Achiral LBAs[a]

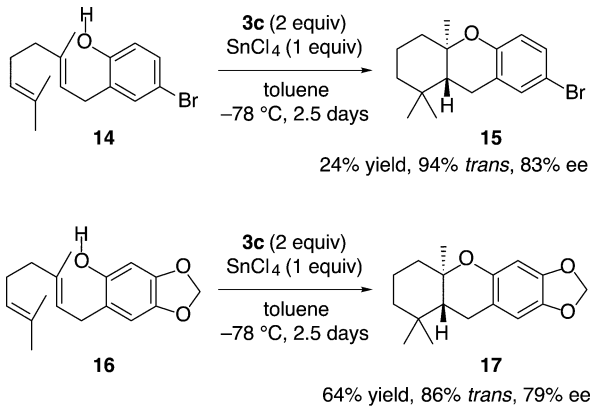


[a] Conditions: (a) **3c** (2 equiv), $SnCl_4$ (1 equiv), toluene, −78 °C, 1 day; (b) CF_3CO_2H (10 equiv), $SnCl_4$ (2 equiv), *i*-$PrNO_2$, −78 °C, 1 day.

this result, the substituent effect on the phenyl group in **3a** was investigated (entries 3−6). When (1′*R*,2′*S*)-**3c**·$SnCl_4$ was used, the optical yield of (−)-**5** was improved to 77% ee (entry 4). Furthermore, the enantioselectivity rose to 85% ee with the use of 2 equiv of **3c** and 1 equiv of $SnCl_4$ (entry 5). This result could be explained by the preferential formation of LBA in equilibrium between the association and dissociation of **3c** and $SnCl_4$. Although the size of cycloalkane of 2,6-di(2′-xylylcycloalkanoxy)phenol was also investigated (entries 7 and 8), the use of conformationally more stable **3c** gave the highest ee value. Interestingly, the use of asymmetric (1′*R*,2′*S*)-**13c** gave (+)-**5** with 40% ee (entry 9). The two contrasting results in entries 4 and 9 led us to anticipate that the two (1′*R*,2′*S*)-2′-xylylcyclohexanoxy groups in **3c** conformationally depend on each other.

Next, diastereoselective cyclization of **7** to **5** was explored with achiral LBAs to increase the chemical yield of **5** (Scheme 2). A 9:85 molar mixture of (−)-**5** and **7**, which were produced by the enantioselective cyclization of **4** under the conditions shown in entry 5 of Table 2, was treated with 10 equiv of trifluoroacetic acid and 1 equiv of $SnCl_4$ in 2-nitropropane at −78 °C. Thus, (−)-**5** was obtained from **4** in 90% yield and 88% trans selectivity without reducing its optical purity.

Scheme 3. Enantioselective Cyclization of 2-Geranylphenol Derivatives Using **3c**·$SnCl_4$



To explore the generality and scope of this new chiral LBA, **3c**·$SnCl_4$, the enantioselective cyclization of 2-gera-

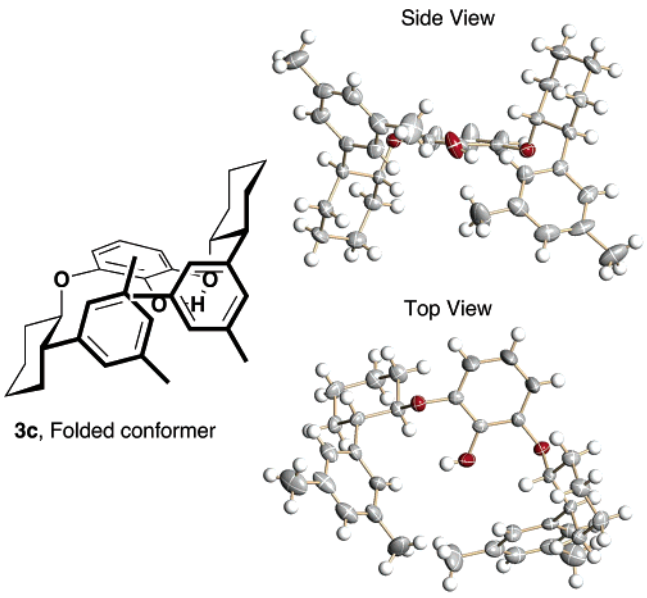


Figure 2. ORTEP plot of **3c**. Thermal ellipsoids are drawn at the 50% probability level.

nylphenol derivatives **14** and **16** was examined under the same conditions as in entry 5 of Table 2 (Scheme 3). As expected, trans-fused tricyclic compounds **15** and **17** were obtained with 83 and 79% ee, respectively. As in our previous reports,[2c,d] the chemical yield and diastereoselectivity of tricyclic compounds strongly depended on the nucleophilicity of the terminal group of geranyl derivatives.

To understand this absolute stereopreference in the enantioselective cyclization, the crystallization of **3c**·$SnCl_4$ was attempted. Although we did not succeed in crystallizing the LBA, a colorless crystal of **3c** was obtained. According to its single-crystal X-ray diffraction analysis, surprisingly, a phenolic proton was effectively enclosed with two alkoxy groups (Figure 2).

On the basis the X-ray structure of **3c**, the conformational structure of **3c**·$SnCl_4$ was considered as follows: **3c** might change from a folded conformer to an extended conformer by chelation of $SnCl_4$, as shown in Figure 3. The H−O bond in **3c**·$SnCl_4$ would be fixed in the phenoxy plane by chelation with $SnCl_4$ and hydrogen bonding with the neighboring ethereal oxygen atom. As in our previous report on the enantioselective protonation of silyl enol ethers with chiral LBA,[5] the stereochemical course in the enantioselective

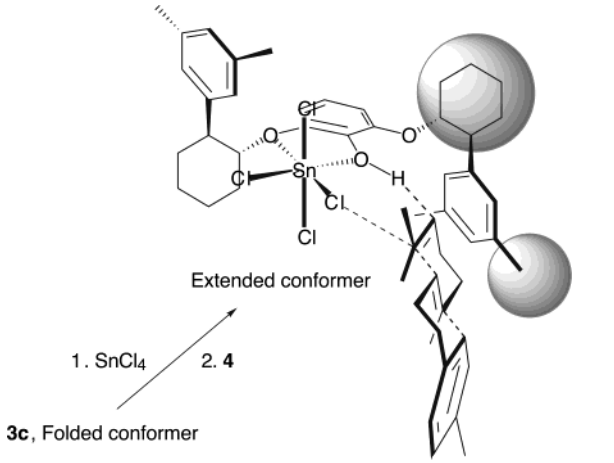


Figure 3. Possible explanation for the absolute stereochemistry.

cyclization would be controlled by a linear OH/π interaction with an initial protonation step. On the basis of the absolute stereochemistry of product (−)-**5**,[6] the *re*-face of the terminal isoprenyl group of **4** would preferentially approach the activated proton of LBA perpendicular to its H−O bond. The observed absolute stereopreference is reasonable considering the steric hindrance around the activated proton.

In summary, pyrogallol derivatives are more effective Brønsted acids than biphenol derivatives for preparing LBA with $SnCl_4$. Further investigation of chiral pyrogallol derivatives that are superior to **3c** is underway.

Acknowledgment. We thank H. Ishibashi (Nagoya University) for performing X-ray single-crystal analysis. Financial support for this project was provided by SORST, JST, the Kurata Memorial Hitachi Science and Technology Foundation, and the Tatematsu Foundation.

Supporting Information Available: Experimental procedures, full characterization of new compounds, and crystallographic data for **3c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) Ishihara, K.; Nakashima, D.; Hiraiwa, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 24.

(6) Absolute stereopreference of (1′*R*,2′*S*)-**3c**·$SnCl_4$ was opposite that of (*R*)-**1**·$SnCl_4$. Therefore, the absolute configurations of (−)-**5** were determined to be 4a*R* and 10a*R*.