The First Enantioselective Biomimetic Cyclization of Polyprenoids

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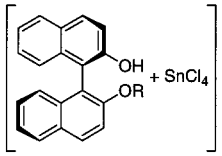
The stereospecific formation of polycyclic terpenoids by the enzyme-catalyzed cyclization of polyprenoids is one of the most remarkable steps in biosynthesis because this reaction results in the formation of several new quaternary and tertiary stereocenters and new rings in a single step.[1] Despite extensive studies on acid-catalyzed diastereoselective polyene cyclizations,[2,3] enantioselective processes using synthetic chiral catalysts have not yet been reported. Our primary objective is the design of artificial cyclases. The difficulty of asymmetric construction using structurally simple chiral Brønsted acids is mainly due to conformational flexibility between a proton and its conjugate base and to the small steric size of the proton. The stereochemical implications of polyene-cyclizations can be explained by the Stork−Eschenmoser hypothesis,[4,5] which postulates synchronous internal anti additions via chairlike conformations of nascent cyclohexane rings, initiated by protonation at the terminal C=C bond. However, the concertedness of the overall ring-forming process is a matter of debate.[6] The most important feature required for an artificial cyclase is asymmetric induction in the protonation of the terminal isoprenyl group of polyprenoids.

Our strategy for designing artificial cyclases is based on the combined system of a Lewis acid and a chiral Brønsted acid, which is called LBA.[7] The coordination of a Lewis acid to a Brønsted acid restricts directional access to the proton and increases its acidity. We describe herein that LBAs, **1**−**4** prepared



LBA **1** (R=H)
LBA **2** (R=Me)
LBA **3** (R=*i*-Pr)
LBA **4** (R=COPh)

from tin tetrachloride and optically active 2,2′-dihydroxy-1,1′-binaphthyl (BINOL) derivatives, are useful as artificial geranyl and farnesyl cyclases.

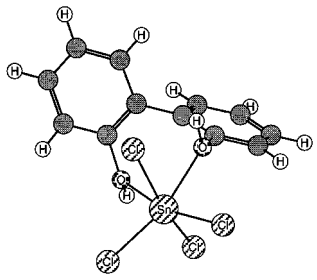
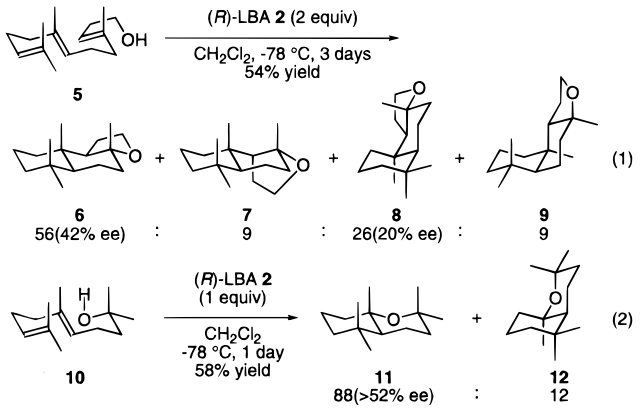


Figure 1. Optimized geometry of a biphenol−$SnCl_4$ complex.

(−)-Ambrox (**6**) is the most important commercial substitute for ambergris,[8] due to its unique olfactive and fixative properties. Its restricted amount has been a stimulus for chemical synthesis.[6,9] The first successful preparation of (−)-**6** was achieved by the enantioselective cyclization of homofarnesol (**5**) promoted with (*R*)-LBA **2**, although the enantioselectivity and diastereoselectivity were moderate (eq 1). Minor compounds **7**−**9** obtained were also identified by comparison with authentic samples.[9g,h] In a similar manner, cyclization of the aliphatic alcohol **10** derived from geranylacetone proceeded to give the *trans*-Decalin **11** with more than 52% ee (eq 2).



The catalytic activity of the LBAs is inhibited to some degree by a hydroxy group which serves as an internal nucleophilic terminator in polyolefinic alcohols. To investigate the present cyclization system in detail, we chose more reactive *o*-geranylphenol (**13**). The cyclization of **13** with (*R*)-LBA **1** in dichloromethane at −78 °C was completed within 1 day, and the trans-fused tricyclic compound *trans*-**14** was obtained as a major diastereomer (84% ds) in good yield (eq 3).[10] However, the optical yield of **14** was only 36% ee. The enantioselectivity was improved to 50% ee by using LBA **2**.[7c,d] Among various (*R*)-BINOL

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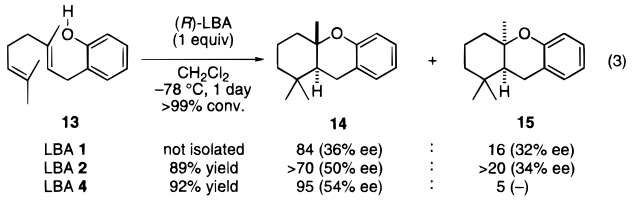
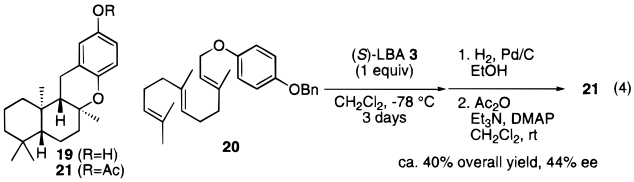


(3)

derivatives screened, we found that LBA **4** prepared from the monobenzoyl ester of (*R*)-BINOL and tin tetrachloride was the most effective for controlling the absolute and relative stereochemistries in this cyclization (54% ee, 95% ds). It seems that the stereoselectivity depends on the activity of LBA as a promoter; the activities decreased in the order **1**, **2**, and **4**. The cyclization was accelerated by the coordination of tin tetrachloride to several Brønsted acids although the reaction proceeded slowly even in the presence of tin tetrachloride alone.

We found that **14** was obtained with much better selectivity from the reaction of geranyl phenyl ether **16** (R^1═R^2═H) with LBA **4** (Table 1, entry 1). Surprisingly, the reaction proceeded smoothly even in the presence of 20 mol % of LBA **4** to give **14** with 77% ee and 98% ds (entry 2). Geranyl phenyl ether **16** is more reactive than **13** because of the lack of a hydroxy group in the latter. Although it is surmised that the reaction of geranyl aryl ether **16** takes place via [1,3]-rearrangement (abnormal Claisen rearrangement) and cyclization, it is not clear which of these two steps occurs first. Other examples are summarized in Table 1. The use of LBA **4** without exception resulted in the highest enantioselectivity and diastereoselectivity. However, the catalytic use of LBA **4** for relatively less reactive substrates **16** (R^1═OMe, R^2═H; R^1═H, R^2═Me) reduced the enantioselectivities. These results indicate the importance of performing the reaction under mild conditions suitable for each substrate to achieve maximal enantioselectivity and diastereoselectivity.

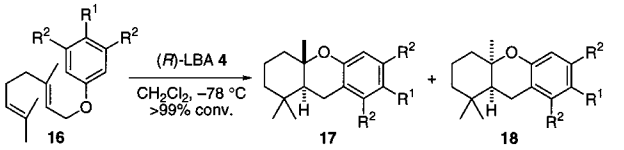
To demonstrate the effectiveness of LBA-promoted enantioselective cyclization, we synthesized (−)-chromazonarol (**19**), a minor constituent of the brown Pacific seaweed, *Dictyopteris undulata*,[11] biomimetically from the corresponding farnesyl derivatives. The cyclization of 4-benzyloxyphenyl farnesyl ether (**20**) with (*S*)-LBA **3**[7e] gave the desired tetracyclic compound **21** as a major diastereomer in 44% ee.



(4)

Finally, the optimized structure of a biphenol-tin tetrachloride complex was determined at the RHF/LANL2DZ[12] level to understand the absolute stereochemical outcome of the above reactions (Figure 1).[13] The calculations have predicted that the chelation of biphenol with tin tetrachloride occurs at an equatorial−equatorial site. It is noteworthy that two acidic protons are likely to be located at pseudoaxial sites parallel to an apical axis of the tin atom and electrostatic interaction between the acidic protons and the apical chlorides is expected. One interesting possibility emerges from the likelihood that an n−π* interaction between an oxygen lone pair (HOMO) of LBA and π* (LUMO) of the terminal C═C bond of the substrates stabilizes the transition state of the cyclization (or the initial protonation step). The transition-state assembly (Figure 2) proposed on the basis of the above assumption and the steric repulsion clearly would lead to the predominant approach of (*R*)-LBA to the *si* face of terminal isoprenyl group.

Table 1. Enantioselective Cyclization of Geranyl Aryl Ether **16**



	16		(*R*)-LBA **4**	time	**17**		ratio[c]
entry	R^1	R^2	(equiv)	(day)	yield (%)[a]	ee (%)[b]	**17**:**18**
1	H	H	1.1	1	98 (79)	69	98:2
2	H	H	0.2	4	98 (76)	77	98:2
3	Br	H	0.2	1	85 (71)	87	89:11
4	Me	H	0.2	4	94	67	97:3
5	OMe	H	1.1	1	84	70	95:5
6	H	Me	1.1	1	80	62	89:11

[a] Unless otherwise noted, GC yields are indicated. Isolated yields are indicated in parentheses. [b] Ee values were determined by GC or HPLC analysis of isolated pure product. [c] Ratios were determined by GC or HPLC analysis of crude products in which other minor products were included.

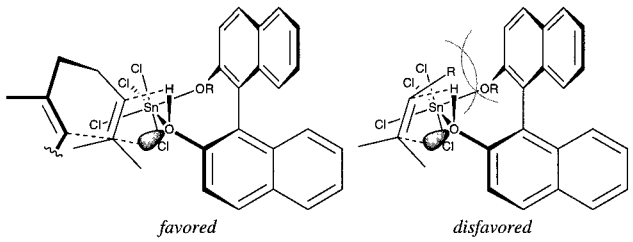


Figure 2. Proposed transition-state assemblies.

Nonenzymatic enantioselective polyene cyclizations are very attractive alternatives to the multistep synthesis from naturally occurring chiral synthons. Further studies on the rational design of "chiral proton catalysts" based on the concept of LBA are expected to provide practical artificial cyclases for the asymmetric synthesis of a wide range of polycyclic terpenoids.[14]

Supporting Information Available: Experimental details and optimized geometry in *Z*-matrix form (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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