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Useful Catalytic Enantioselective Cationic Double Annulation Reactions Initiated at an Internal π-Bond: Method and Applications

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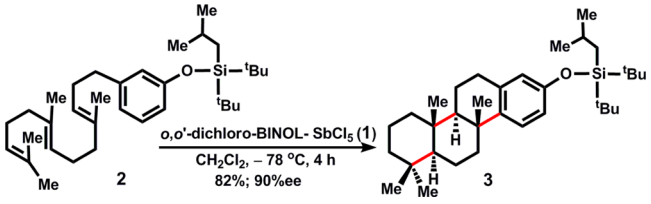
Supporting Information

ABSTRACT: The 1:1 complex of *o,o′*-dichloro-*R*-BINOL and $SbCl_5$ initiates the enantioselective cationic polycyclization of polyunsaturated substrates at a predictable π-bond which may be either terminal or, as shown herein, internal. The extension of this powerful construction to internal π-bonds expands the scope of this method and opens up very short pathways to numerous chiral polycyclic molecules, including natural products and their analogues. Especially simple synthetic routes are disclosed that provide access to dysideapalaunic acid, dehydroabietic acid, and epipodocarpic acid and illustrate the value of this enantioselective approach.

We recently reported that a 1:1 complex of *o,o′*-dichloro-*R*-BINOL and $SbCl_5$ (**1**) is an excellent catalyst for π-face-selective, enantioselective, cationic polycyclization reactions such as **2** → **3** (Scheme 1).[1] The cyclization occurs

Scheme 1. Enantioselective Cationic Polyclization Catalyzed by 1

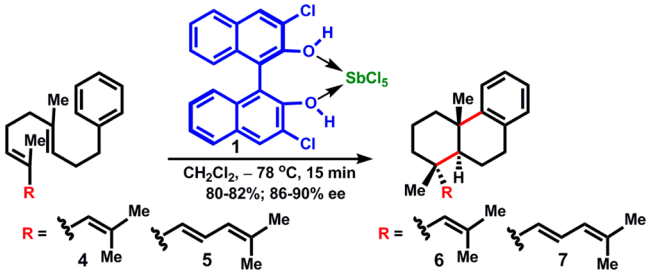


rapidly and efficiently at −78 °C, an indication of the very strong acidity of the complex and the selectivity for protonation of the terminal olefinic linkage. It is noteworthy that the *o,o′*-dichloro-*R*-BINOL ligand can be readily recovered for reuse. A pre-transition-state assembly has also been described which provides a rational basis for understanding the absolute stereochemical course of the cyclizations induced by the *o,o′*-dichloro-*R*-BINOL−$SbCl_5$ complex **1** (also, see Figure 1 below).

In this note we disclose three different ways in which the complex **1** can be used to initiate enantioselective, cationic polycyclizations at a *nonterminal* π-bond. These strategies, which enable the application of this methodology to a considerably broader range of polycyclic structures, depend on the modulation of the relative proton affinity of the π-bonds in the substrate to control the initiating site of cyclization.

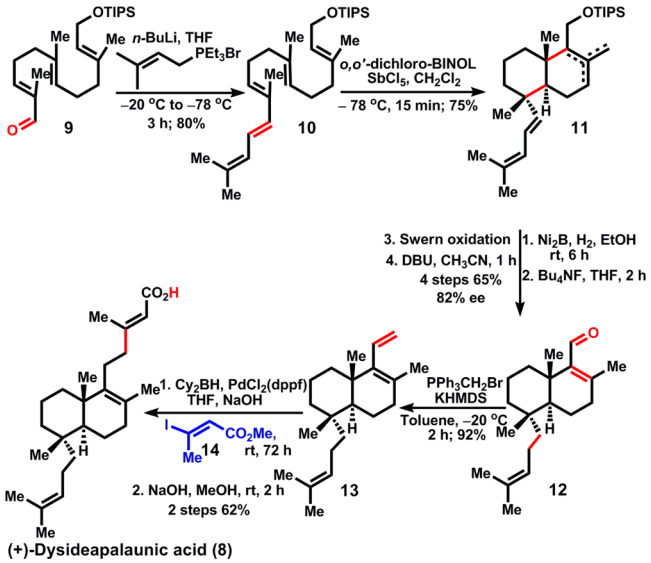
The first strategy involves activation of an internal double bond by an electron-supplying π-attachment. A simple example is the conversion of substrates **4** and **5** selectively to the tricycles **6** and **7**, under the influence of catalyst **1** at −78 °C for 15 min (Scheme 2). This type of process is quite useful, as is demonstrated by especially simple, enantioselective syntheses of three well-known natural products.

Scheme 2. Synthesis of Chiral Tricycle



First, the anti-diabetic aldose reductase inhibitor dysideapalaunic acid (**8**)[2] can be produced expeditiously and enantioselectively, as outlined in Scheme 3. In this process the substrate for cyclization (**10**), readily obtained starting from *E,E*-farnesol via the aldehyde triisopropylsilyl (TIPS) ether **9**,[3]

Scheme 3. Total Synthesis of (+)-Dysideapalaunic Acid



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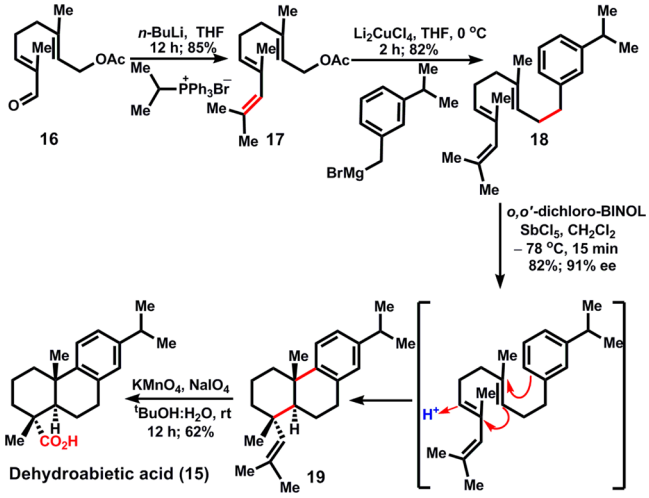
underwent smooth conversion to the required bicyclic product **11** (as a mixture of three C=C position isomers) under the influence of catalyst **1** (1.0 equiv) at −78 °C. The TIPS ether mixture **11** was then transformed into a single product, the conjugated aldehyde **12**, in good yield by a four-step sequence: (1) selective hydrogenation at the disubstituted olefenic linkage using Brown's P-2 nickel boride catalyst and H_2 at 1 atm; (2) desilyation; (3) Swern oxidation; and (4) base-catalyzed isomerization to a single product, the conjugated aldehyde **12**. Wittig methylenation of **12** afforded **13**, which by hydroboration and Suzuki coupling[4] with the iodo ester **14** and basic hydrolysis provided (+)-dysideapalaunic acid **8**.[5]

The enantioselectivity of the cyclization was determined to the 10:1 by HPLC analysis of the pure conjugated α,β-enal **12**.[3] The absolute stereochemical course of the cyclization **10** → **11** follows from the comparison of the synthetic product **8** with dysideapalaunic acid.[4] This pathway of synthesis is much simpler and shorter than the process that was employed in the original synthesis of **8** (17 steps from a chiral octalin dione).[2]

We have also applied this methodology to a very short synthesis of dehydroabietic acid (**15**)[6] as outlined in Scheme 4

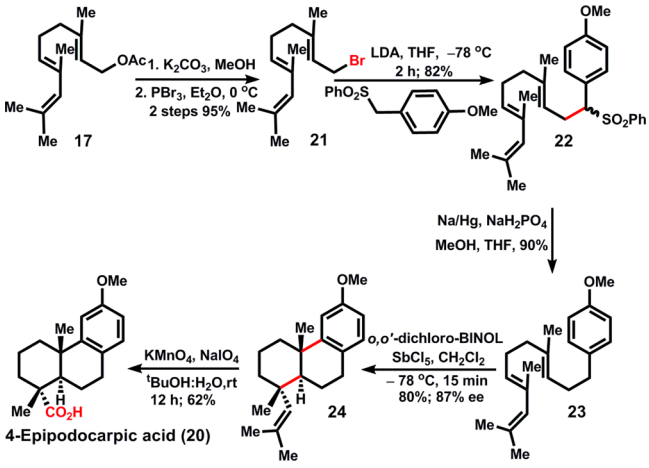
Scheme 4. Enantioselective Synthesis of Dehydroabietic Acid (15)



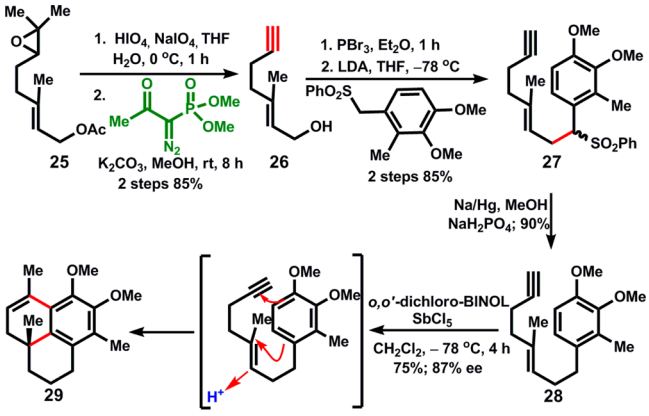
and of the C(4)-diasteroisomer of podocarpic acid (**16**)[7] as shown in Scheme 5. The brevity and enantioselectivity of these routes to **15** and **16** underscore the utility of the key enantioselective cationic polycyclization steps. The correspondence of optical rotation of synthetic **15** and dehydroabietic acid established the absolute stereochemical course of the cationic cyclization step, which clearly applies to the synthesis of **20** as well.

A second tactic for achieving enantioselective cationic cyclization originating in an internal π-bond is illustrated in Scheme 6, which shows a simple route to the acetylenic olefin **28** and its cyclization by the action of the chiral catalyst **1** in a single step to the tricyclic product **29** in 75% yield and 87% ee. This process is clearly initiated by protonation of the internal olefinic π-bond to from a bicyclic acetylene which then undergoes a second (and slower) cyclization to generate the tricycle **29**, which is of interest as a close analogue of the pseudopterosin core.[8,9] This second tactic succeeds because of the lower proton affinity of C≡C relative to C=C.

Scheme 5. Simple Route to 4-Epipodocarpic Acid (20)



Scheme 6. Enantioselective Route to Hydrophenylenes



This type of double annulation has considerable generality as is indicated by the five examples shown in Table 1. These tricyclic structures are versatile intermediates for the synthesis of many more complex structures by further elaboration. For example, the product of Table 1, entry 1, tricyclic olefin **30** has been transformed into a wide variety of tri- and tetracyclic products, as is illustrated by the transformations in Scheme 7.

Several of the transformations of **30** shown in Scheme 7 deserve comment. The addition of dichloroketene[10] to **30** is both regio- and diastereoselective to form **31**. The Bayer–Villiger oxidation of **31** gave **32** regioselectively, but the RuO_4 oxidation of **31** to give **33**[11] occurred with the opposite O-insertion regiochemistry. The allylic oxidation of **30** can be directed to either allylic terminus to form **34** or **35**,[12] depending on reagent. The hydroboration–Dess–Martin oxidation sequence **30** → **36** was diastereoselective.

A third way of utilizing the chiral catalyst **1** for the initiation of cationic cyclization at an internal π-bond is demonstrated by the process depicted in Scheme 8. In this approach bromine substituents at the terminal double bond are employed to enforce selective proton transfer from catalyst **1** to the internal double bond, as takes place in the enantioselective conversion of the dibromodiene **39** to the bicyclic product **40** (Scheme 8). The two bromine substituents on the terminal carbon of **38** decrease the proton affinity of the terminal π-bond sufficiently so that cyclization occurs solely by protonation of the internal double bond. The standby dibromovinyl group **40** also serves a useful purpose as a reactive center for further synthetic

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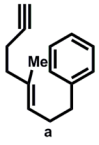
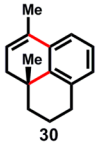
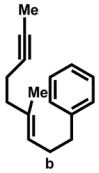
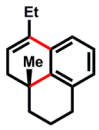
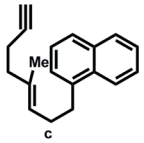
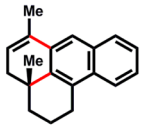
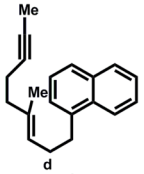
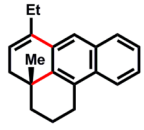
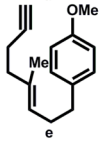
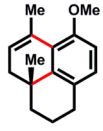
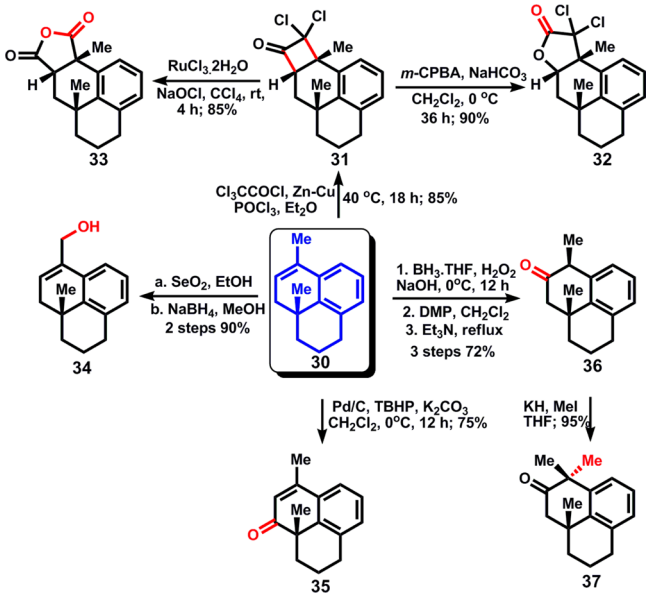
Table 1. Enantioselective Double Cyclization Reactions Catalyzed by 1 at −78 °C in CH_2Cl_2

Entry	Substrate	Product	Yield,[a,b] ee%[c]
1.	 a	 30	90, 92
2.	 b		87, 92
3.	 c		82, 85
4.	 d		85, 89
5.	 e		80, 84

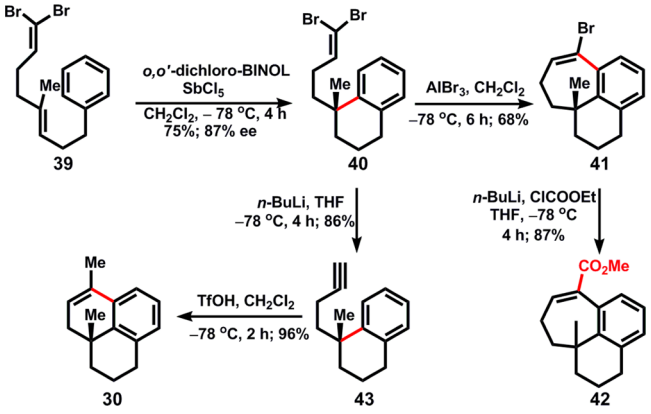
[a]Isolated yields of products fully characterized by NMR and MS. [b]One equiv of catalyst **1** was used. With 0.5 equiv **1** the yields were lower by 2−5%, but ee's were the same. [c]ee determined by HPLC analysis using a Chiralcel OD-H column.

Scheme 7. Synthetic Transformations of Tricycle 30



operations, including (1) transformation to the 6,6,7-tricycles **41** and **42** and (2) elimination to form the acetylene **43**, an intermediate for the formation of tricycle **30**.

Scheme 8. Enantioselective Synthesis of Chiral Tricycles from a Terminal 1,1-Dibromoolefin



The type of pre-transition-state assembly suggested earlier[1] for cyclization reactions initiated by **1** at a *terminal* π-bond can be extended to explain successfully the absolute sterochemical course of cyclizations initiated at an *internal* π-bond as shown in Figure 1, with concerted formation of C−H and C−C bonds (a and b).[13]

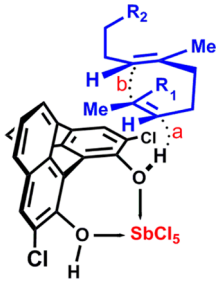


Figure 1. Pre-transition-state assembly for concerted cyclization initiated by proton transfer from catalyst **1**.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data for all reactions and products, including copies of ^1H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(2) See : Hagiwara, H.; Uda, H. *J. Chem. Soc., Perkin Trans 1* **1991**, 1803−1807 for background references.

(3) For experimental details see the Supporting Information. The 1 M solution of $SbCl_5$ in CH_2Cl_2 that was used in this work was obtained from Aldrich Co. and stored at −20 °C prior to use.
(4) The identity of synthetic with naturally derived dysideapalaunic acid was established by comparison of ^1H and ^{13}C NMR spectra and rotation.
(5) We found $PdCl_2(dppf)$ to be superior to $PdCl_2(Ph_3P)_2$ in the Suzuki coupling, and that aqueous NaOH gave better results than K_3PO_4 or KF/H_2O as base.
(6) For Stork's classical synthesis of dehydroabietic acid in 20 steps see: Stork, G.; Schulenberg, J. W. *J. Am. Chem. Soc.* **1962**, *84*, 284.
(7) (a) Welch, S. C.; Hagan, C. P.; Kim, J. H.; Chu, P. S. *J. Org. Chem.* **1977**, *42*, 2879. (b) Hao, X.-J.; Node, M.; Fuji, K. *J. Chem. Soc., Perkin Trans.* **1992**, *1*, 1505.
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