JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

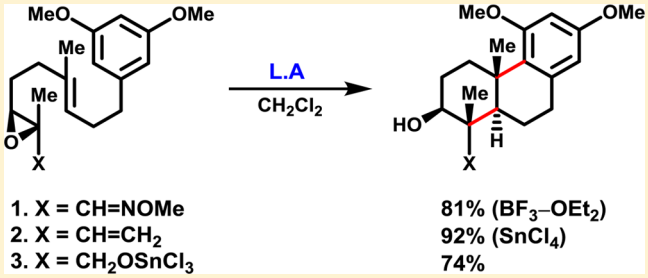
A Systematic Study of Functionalized Oxiranes as Initiating Groups for Cationic Polycyclization Reactions

Goreti Rajendar and E. J. Corey*

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138, United States

Supporting Information

ABSTRACT: Three different methods have been developed that effectively utilize chiral oxiranes derived from Katsuki–Sharpless epoxidation of allylic alcohols as initiating groups for cationic cyclization of unsaturated substrates to form chiral polycycles. This type of transformation has previously been problematic. These employ either epoxy-methoximes, vinyl-substituted oxiranes, or hydroxymethyl oxiranes. All three approaches are described in detail. In addition, this research has led to possible explanations for previously encountered difficulties in this area and provided two new insights into the Lewis acid activation of oxiranes. The methodology described herein constitutes a valuable link between two powerful synthetic constructions, enantioselective Katsuki–Sharpless epoxidation and cationic polycyclization reactions.

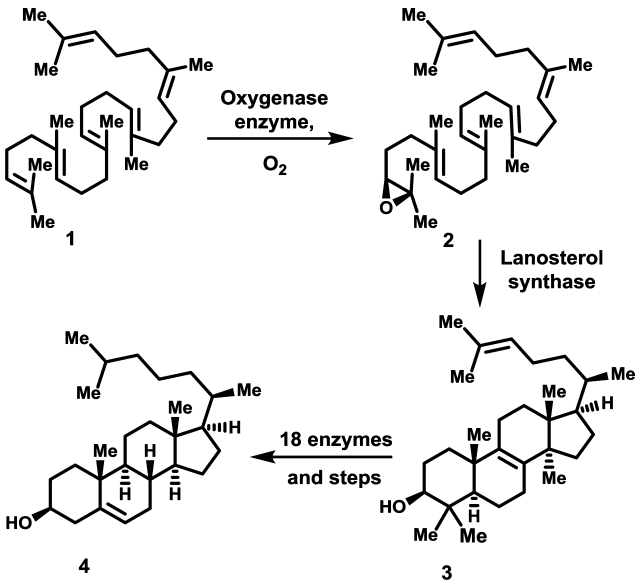


INTRODUCTION

This paper describes research on the fundamental understanding and application of epoxide-initiated cationic π-cyclization reactions, one of the most powerful constructions in both biosynthesis and chemical synthesis. It is the key step in the construction of squalene to lanosterol, as outlined in Scheme 1. Russey in our group[1] first showed that the initial step in the biosynthetic sequence is the oxidation of squalene (**1**) to (*S*)-2,3-oxidosqualene (**2**). The epoxide (**2**) is then transformed enzymatically and without O_2 in a single, but very complex step to lanosterol (**3**). From lanosterol, a total of 18 enzymes and 19 steps are required to generate cholesterol (**4**) (Scheme 1).[2] Previously, it had been known from the work of Bloch et al. that squalene is the precursor of lanosterol and cholesterol, but only in the presence of molecular O_2.[3] The biosynthetic power of the step **2** → **3** is so large that it has prevailed in nature even though many steps (ca. 19) are required to make cholesterol (**4**) from **3**. Since these early investigations on sterol and triterpene biosynthesis, there have been numerous studies on the synthetic application of epoxide-initiated cyclization reactions to the construction of polycyclic structures.[4] The power of such cationic polycyclizations has been repeatedly demonstrated by the realization of effective synthetic pathways to many natural products including pyripyropene E,[5] adociasulfate,[6] aphidicholin,[7] lanosterol,[8] many triterpenes in the β-amyrin family,[9,10] onocerin,[11] serratenediol,[12] germanicol,[13a] lupeol,[13b] hongoquercin B,[14] kaurene diterpenoids,[15] and limonoids.[16]

Despite these advances and the gradually increasing understanding of the biosynthetic process, there is still a large gap between the results in synthetic practice and the awesome efficiency, brevity, and stereocontrol shown in enzyme-catalyzed polycyclization reactions. The reason for this gap can be appreciated when the following properties of cyclase enzymes are considered: (1) the availability of an extensive binding pocket which imposes on the substrate a three-dimensional coiling in which the specific π-face of each participating C–C double bond is controlled and all intermediate carbocations are protected from nucleophilic attack by the protein itself or the aqueous environment; (2)

Scheme 1. Bioconversion of Squalene to Cholesterol



Received: April 2, 2015

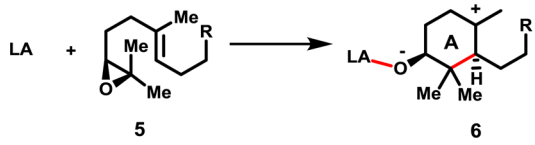
DOI: 10.1021/jacs.5b03229
J. Am. Chem. Soc. XXXX, XXX, XXX–XXX

proximity of an initiating proton donor (generally aspartic acid) in the enzyme to the oxirane function of the bound substrate; (3) ability of the enzyme to utilize the exothermicity of cyclization (ca. 20 kcal/mol for each ring formed) to access a higher energy conformation which continues to hold the reactive intermediates that are generated during cyclization and protect them from diversion to other pathways;[17] (4) a precisely positioned proton acceptor that controls the reaction product by accepting a proton from the last cationic intermediate, and only that proton, while also not attacking other cationic intermediates. In addition, because of conformational changes of cyclase enzymes during the course of a biosynthetic conversion, it is likely that dynamic protein−substrate interactions play an important role in guiding rearrangements of carbon and hydrogen toward the formation of a specific biochemical target molecule. At the same time, the enzyme group that accepts a proton in the final product determining step is held at bay until the crucial final intermediate is formed.

In contrast to such sophisticated enzyme control, current laboratory cyclizations are rudimentary and depend on the use of (1) Lewis acidic catalysis (or in some cases a protic acid) which selectively activate the oxirane function and (2) a non-nucleophilic and noncoordinating moderately polar medium (e.g., CH_2Cl_2) which can solvate, but not trap the various cationic intermediates. Given the enormous difference in sophistication of biochemical and chemical catalysis and the complexity of cationic polycyclization reactions, it is obvious that there is much room for improvement in the synthetic chemical methodology. This includes the initiating subunit in the substrate, the catalytic Lewis acid, the control of substrate conformation (e.g., restricting conformation so as to favor a particular product), deactivating potentially interfering groups, and controlling the termination process. We discuss herein specifically a systematic study of various kinds of oxirane-based initiating structures and the use of our findings both to assist in synthetic applications and to understand the electronic factors which influence the course of cyclization. This is just an early step in the important but lengthy journey that lies ahead, surely one of the great unmet challenges in synthetic chemistry.

RESULTS AND DISCUSSION

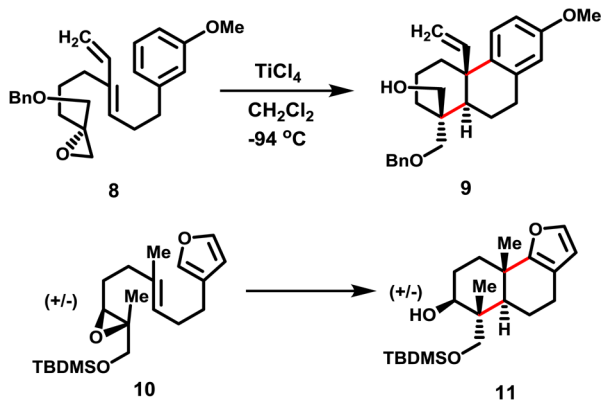
Most of the examples of epoxide-initiated cyclization in the successful multistep syntheses that are cited above[4b] are of the type **5** → **6** with respect to the initiating step (LA = Lewis acid). This closure of the initial ring can sometimes be concerted with C−O cleavage and thus efficient.[18] The epoxide initiated approach starting from **5** is convenient for syntheses of natural products having unfunctionalized A-ring methyl groups because of the synthetic accessibility of the required chiral oxirane **5** via enantioselective, position-selective dihydroxylation using a mechanistically designed chiral catalyst that binds OsO_4 and the polyunsaturated substrate.[19] In addition, the Katsuki−Sharpless catalytic epoxidation of allylic alcohols can be applied to the synthesis of substrates for epoxide-initiated cationic polycyclization processes. Indeed, extensive literature is available describing this approach,[5,6,20] which is especially appropriate when one of the gem-dimethyl groups of **6** is functionalized. In principle, the combination of the practicality of the Katsuki−Sharpless epoxidation with the power of epoxide-initiated cationic polycyclization, would seem to be an optimal strategy. In actual practice, this approach has been disappointing since the realized yields of cyclization product in most of the reported cases[5,6,20] with substrates of type **7** have fallen in the range of only 23−52%. These mediocre results also seem at odds with the expectation that epoxide activation might be facilitated by chelation of Lewis acid.



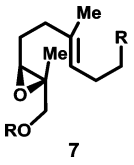
5 **6**

We are aware of two special cases in which of higher yields have been obtained. In the synthesis of neotripterifordin reported earlier from our laboratories,[21] the cyclization of **8** to **9** was accomplished in 86% yield (Scheme 2). In the other case,

Scheme 2. Best Previously Reported Cyclizations



the yield in the conversion of (±)-**10** to (±)-**11** could be improved from 23 to 35% (as originally reported[20a]) to 72% but only under special conditions and after extensive optimization.

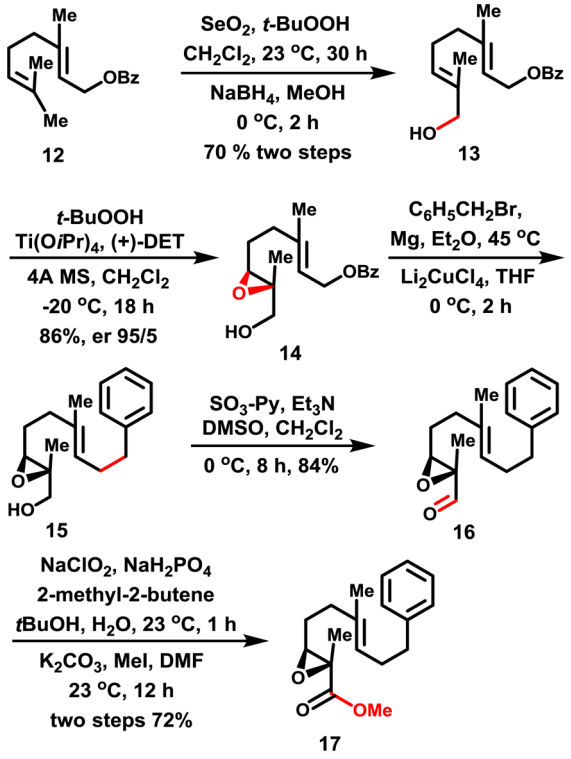


7

Our studies were motivated by the unexpected problems encountered previously with substrates derived from Katsuki−Sharpless epoxy alcohols and their derivatives. We chose specifically to study the bis-cyclization of the test series of compounds **15**−**17** which are readily synthesized by the route outlined in Scheme 3. The investigations of these three substrates turned out to be quite revealing and to provide valuable insights on the fine details of the epoxide-initiated cyclization, and some causes of the disappointing results of previous synthetic studies.[5,6,20] The epoxy ester **17** turned out to be surprisingly unreactive in Lewis acid induced cationic cyclization, despite the possibility that it can be a bidentate ligand for catalysts like $SnCl_4$ (generally an effective epoxide activating reagent). One possible stereorepresentation of such a complex is shown in expression **18**. Ester **17** was completely unchanged when exposed to 1.5 equiv of $SnCl_4$ in CH_2Cl_2 solution over the range −78 to −20 °C after 12 h. Even the potent Lewis acid $TiCl_4$ at −20 °C for 6 h left the epoxy ester largely unchanged (80% recovery with the remainder being a complex mixture that contained none of the desired tricyclic product). It should be noted that the unfunctionalized substrate

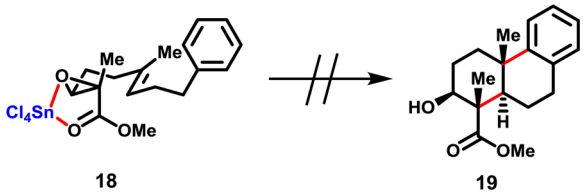
DOI: 10.1021/jacs.5b03229
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Scheme 3. Synthesis of Test Substrates



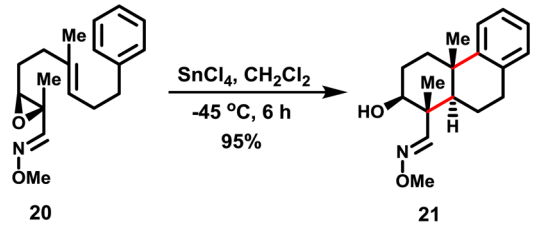
corresponding to **17** (CH_3 instead of $COOCH_3$) undergoes rapid conversion to tricyclic product (**19** with CH_3 instead of $COOCH_3$) under these conditions.

We have also performed similar experiments with $SnCl_4$ and the epoxy aldehyde **16** (Scheme 3). Again, there was no reaction at −78 °C in CH_2Cl_2, with no sign of tricyclic product (the aldehyde corresponding to the ester **19**). At −20 °C for 12 h in CH_2Cl_2, about 20% of unreacted aldehyde **16** was recovered along with a complex mixture of mainly uncyclized materials and none of the desired 6,6,6-tricycle. These results with the epoxy aldehyde **16** and the corresponding epoxy ester **17** indicate that chelate complexes such as **18** do not facilitate cyclization and, if anything, prevent it from occurring. Such a result would be understandable if coordination of Lewis acid to the carbonyl function makes it so electron deficient that heterolysis of the oxirane α-C−O bond is inhibited. Such an inhibiting effect seems to operate quite generally in series of the other results reported below. In addition, the reluctance of aldehyde **16** and ester **17** call in to question a chelation pathway even with $SnCl_4$ which readily chelates via six-membered cycle.



We attempted to counter the problems of Lewis acid activation of α-functionalized oxiranes by turning to the methoxime **20** corresponding to the test aldehyde **16**. This line of research was motivated by the idea that the electron donating methoxy group in **20** would significantly favor the heterolytic fission of the oxirane α-C-O bond and thus accelerate cationic cyclization. Indeed, that turned out to be the case. Thus, exposure of the methoxime **20** to $SnCl_4$ in CH_2Cl_2 at −45 °C led to clean formation of the desired tricyclic product **21** in 95% isolated yield (Scheme 4). Several other transformations of this type are summarized in Table 1.

Scheme 4. Cyclization of Epoxy Methoxime 20



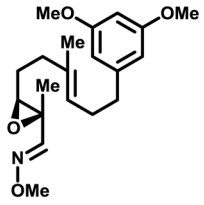
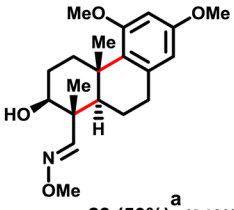
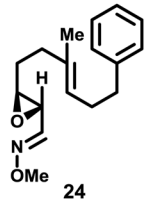
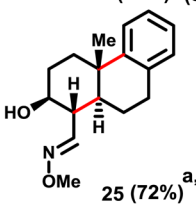
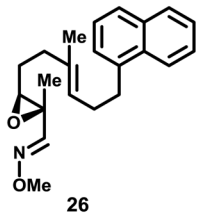
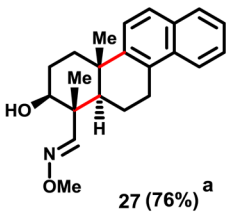
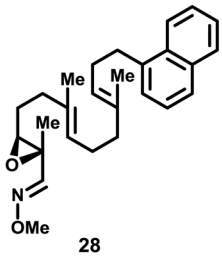
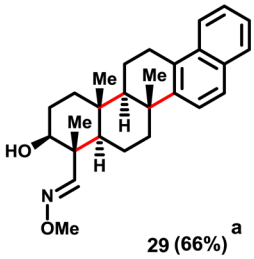
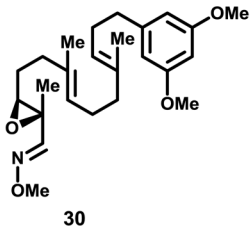
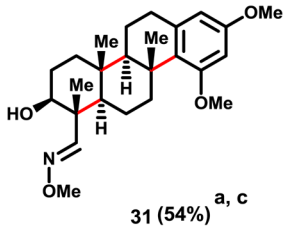
It is evident from the good results shown in Table 1 that α-methoxime oxirane substrates are satisfactory initiating subunits for cationic polycyclization reactions to form A-ring doubly functionalized products. The product β-hydroxy methoximes can be cleaved to the corresponding aldehydes under mild conditions (CH2O, aq. acetone, Amberlyst 15 sulfonic acid resin at room temperature) in high yield. There are, however, limitations in the structure of the α-methoxime oxirane substrate that arise when the Lewis acid can interact with groups elsewhere in the molecule. For example, in the case of substrate **22**, the yield of tricyclic product **23** is only 50% ($SnCl_4$, CH_2Cl_2 at −45 °C for 6 h) because of a side reaction which produces along with **23** a mixture of isomers chlorohydrins (40%) by simple oxirane cleavage *without* cyclization.

The simplest explanation of this observation may be the co-occurrence of Lewis acid coordination with the aromatic subunit which inhibits the cyclization. The same effect may operate in the last example **30** in Table 1 for which the yield is also lowered. If such competitive coordination (either to a methoxy group or the benzenoid π-electron system in **22**) does indeed compete with oxirane activation, it would cast some doubt on a bidentate interaction between $SnCl_4$, the oxirane oxygen, and the methoxime function. To follow up on this, we studied the cyclization of **22** using $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at −78 °C for 1 h. The cyclization is not only faster than that with $SnCl_4$ but also substantially more efficient, since it afforded **23** in 81% isolated yield (Scheme 5). Since BF_3 has only one vacant orbital for coordination and is unlikely to complex with **22** in a bidentate way, so this result provides compelling evidence that the transformation **22** → **23** is initiated by complexation of BF_3 at the oxiranyl oxygen and does not involve chelation of the methoxime.

The reluctance of the epoxy ester **17** and the epoxy aldehyde **16** to undergo cyclization with bis-coordinating Lewis acids such as $SnCl_4$ and the observation that the cyclization of methoxime **20** appears to occur by monodentate interaction of Lewis acid with the oxirane oxygen rather than by a bidentate pathway could be consequences of the electronic effects described above. For instance, bidentate complexation as shown above in **18** would impede α-C−O heterolysis of the oxirane by destabilizing the incipient carbocation because of electron transfer from carbonyl to $SnCl_4$. This same type of inductive effect can explain selectivity in many nucleophilic C−O cleavage reactions of epoxy carbinols by external nucleophiles using a coordinating metal, an example of which

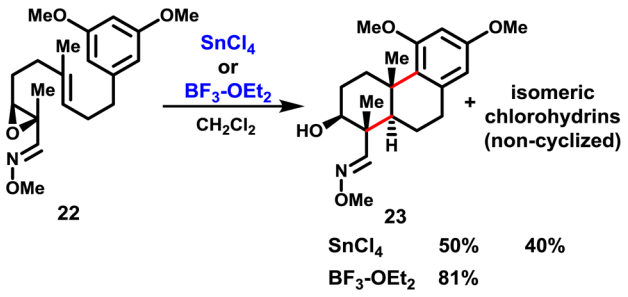
DOI: 10.1021/jacs.5b03229
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Table 1. Lewis Acid Catalyzed Cationic Cyclization of Epoxy Methoximes

Substrate	Product (yield(%))
 22	 23 (50%)[a] (81%)[b]
 24	 25 (72%)[a, c]
 26	 27 (76%)[a]
 28	 29 (66%)[a]
 30	 31 (54%)[a, c]

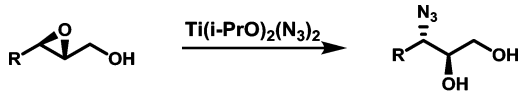
[a]Reaction carried out with $SnCl_4$ in CH_2Cl_2 at −45 °C. [b]Reaction carried out with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at −78 °C. [c]Yield is similar to that of both Lewis acids $SnCl_4$ and $BF_3{\cdot}OEt_2$.

Scheme 5. Cyclization of Epoxy Methoxime 22



is shown in Scheme 6.[22,23] In general, oxirane cleavage occurs selectively at C(β) in α,β-epoxy carbinol, α,β-epoxy acid, and α,β-epoxy ester systems.[22,23]

Scheme 6. Metal-Catalyzed Selective Oxirane Cleavage



R = *n*-Pr, 36 : 1 selectivity
R = C6H5 100 : 1selectivity

Density functional theory calculations indicate that BF_3 coordinates with ethylene oxide out of plane, as though the lone pairs on oxygen are in sp^3-hybridized orbitals.[24] With substrates such as **22**, there can be two diastereomeric complexes of this sp^3-hybridization type, as shown in Figure 1a. These are arbitrarily designated as α- and β- complexes. It is

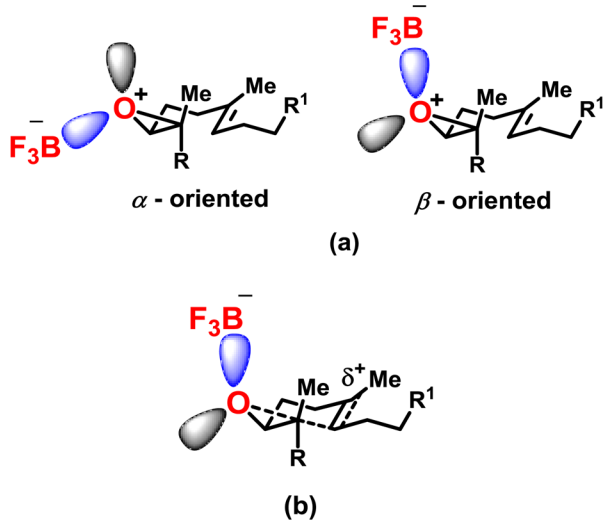


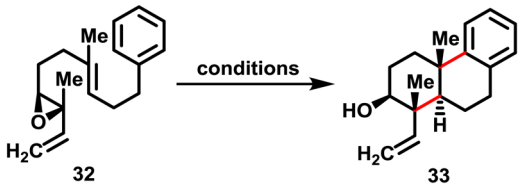
Figure 1. (a) α- and β-Oriented oxirane BF3 complexes; (b) partially cyclized β-complex.

not unreasonable to argue that the rates of concerted oxirane cleavage-cyclization would be different for these α- and β-complexes and, more specifically, that the β-complex might react faster because C−C bond formation involves less charge separation than for the α-diastereomer (Figure 1b). Thus, it possible that this is another factor that can favor the monodentate cyclization pathway over the bidentate mode with Lewis acids such as $SnCl_4$. This represents yet another kind of stereoelectronic/electrostatic effect.[25,26]

Another aspect of epoxide-initiated cyclization reactions that we have studied involved the use of vinyl oxiranes such as **32** which are readily accessed from the corresponding aldehydes, **16** in the case of **32**. It was expected from the above-described results that vinyl substitution would facilitate Lewis-acid activation of the epoxide function and beneficial in cyclization reactions relative to CH_3 or H in the corresponding position, that surmise was verified by the experimental finding that **32** was smoothly and rapidly converted to the 6,6,6-tricyclic product **33** at −78 °C in CH_2Cl_2 with $MeAlCl_2$, $SnCl_4$, $TiCl_4$, or *i*-$PrOTiCl_3$ (see Scheme 7). Even the quite mild Lewis acid $InBr_3$ transformed **32** efficiently and rapidly to **33** in CH_2Cl_2 at −10 °C. It is clear that π-electron donation from the vinyl substituent is significantly beneficial to both the rate and efficiency of epoxide-initiated cationic cyclization of substrates such as **32**. This conclusion is further supported by results with six other examples which are summarized in Table 2.

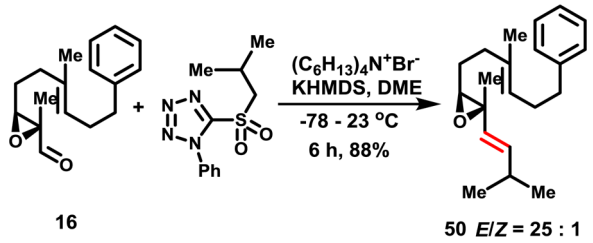
DOI: 10.1021/jacs.5b03229
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Scheme 7. Cyclization Results for Vinyl Epoxide 32



Reaction conditions:	Yield (%)
$MeAlCl_2$, CH_2Cl_2, −78 °C, 1 h	68
$SnCl_4$, CH_2Cl_2, −78 °C, 1 h	**84**
$TiCl_4$, CH_2Cl_2, −78 °C, 10 min	75
$TiCl_3(OiPr)$, CH_2Cl_2, −78 °C, 10 min	78
$InBr_3$, CH_2Cl_2, −10 °C, 20 min	70

The high efficiency of the cyclization **8** to **9**,[21] a key step in the total synthesis of neotripterifordin, can now be understood as due to π-electron donation from the vinyl group in **8** which assists in the closure of the first ring due to stabilization of the resulting carbocation.

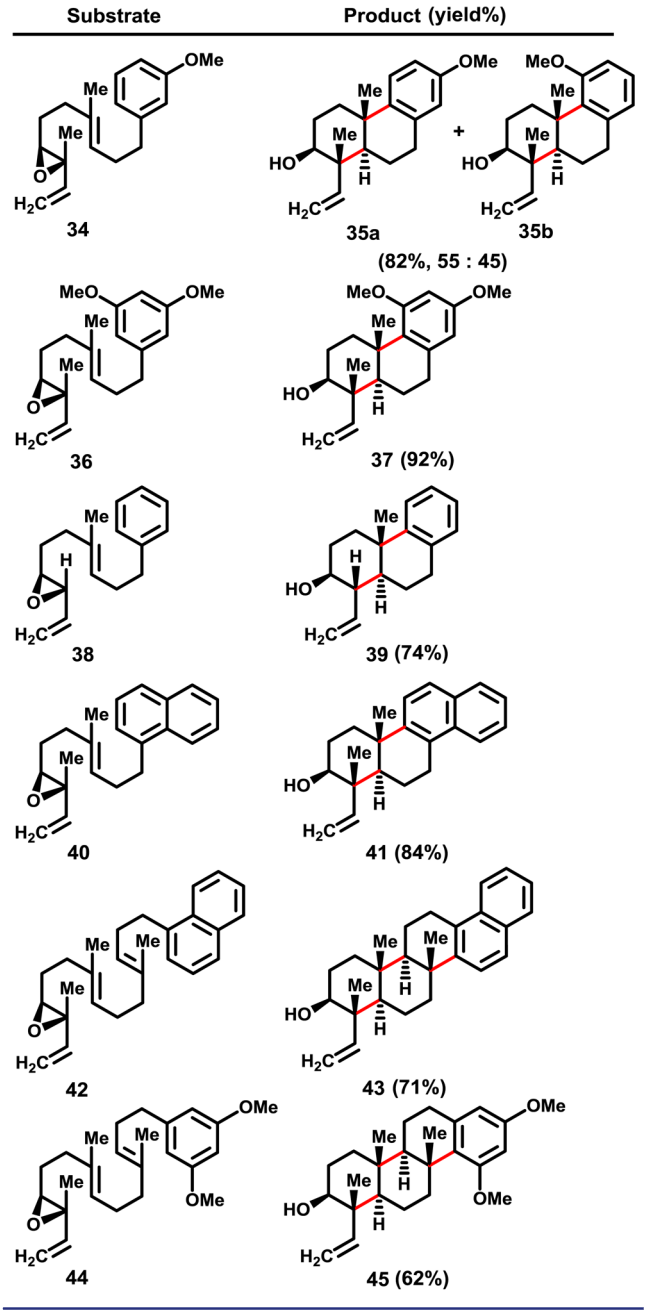


The cyclization of **38** to **39** is especially noteworthy since the corresponding reaction of the analogous substrate with CH3 replacing vinyl is both slow and low yielding. Evidence has been obtained from the study of alkyl-substituted vinyl groups that the vinyl group itself provides the optimum level of π-electron donation. The results with three substrates with terminal alkyl substituents attached to vinyl are shown in Table 3. The data on the cyclization **46** to **47** suggest that the degree of activation of the epoxide by the more strongly π-electron donating isobutenyl group may be beyond the optimum degree. In summary, the simple vinyl substituent leads to the most efficient cationic cyclization reactions. The vinyl substituent in the products is readily oxidized with C=C cleavage to form corresponding β-hydroxy aldehydes, useful intermediates for further functional group transformations.

The synthesis of *E*-substrate **50** was carried out by a simply but very beneficial modification of the Julia−Kocienski method which provides superior *E*/*Z* selectivity over published procedures, as shown. Our improved method utilizes the soluble quaternary ammonium salt *n*-hex4N$^+$Br$^-$ to improve *both yield* and *E*/*Z ratio* (72%, 5:1 without *n*-hex4N$^+$Br$^-$).[27] Because of the need for better *E*-selective olefin synthesis, we include here a representative procedure.[28]

The α-hydroxymethyl epoxide **15** was also studied as a reactant for cationic cyclization under a variety of conditions. One motivation for this part of our systematic investigation came from the possibility that the initiating Lewis acid might be covalently attached to the hydroxyl oxygen of **15** so as to internally direct activation to the oxirane C−O bond without

Table 2. Vinyl Substitution Alpha to Oxirane Facilitates Cyclization and Improves Generality (CH_2Cl_2, $SnCl_4$, −78 °C)

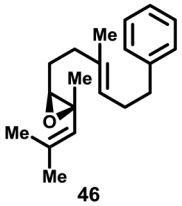
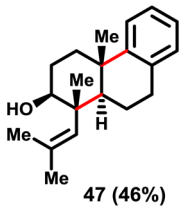
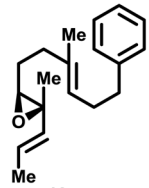
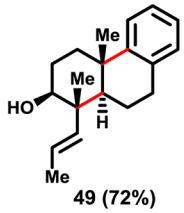
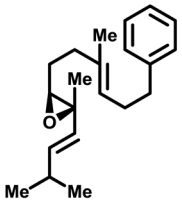
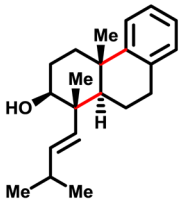


competing Lewis acid binding to other sites in the molecule. The early results were informative, but not especially useful. For example, reaction of **15** with 1 equiv of Me3Al, *i*-Bu_2AlH, or Et_2Zn in CH_2Cl_2 afforded the corresponding alkoxides of **15** ($ROAlMe_2$, ROAl*i*-Bu_2, and ROZnEt, respectively). However, these metallic derivatives *were incapable of activating the epoxide* for cyclization in CH_2Cl_2 even at 23 °C. Further activation of $ROAlMe_2$ by treatment with Br_2 (to form ROAlMeBr) also did not lead to cyclization. The failure of these internally bound Lewis acidic centers in proximity to the oxiranyl oxygen to initiate cyclization is consistent with the stereoelectronic effect posited above.

Fortunately, stronger activation by converting **15** to **53** did lead to cyclization, as shown in Scheme 8. The cyclization of **52**

DOI: 10.1021/jacs.5b03229
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Table 3. Cyclization Results with Substituted Vinyl Activating Groups (CH_2Cl_2, $SnCl_4$, −78 °C)

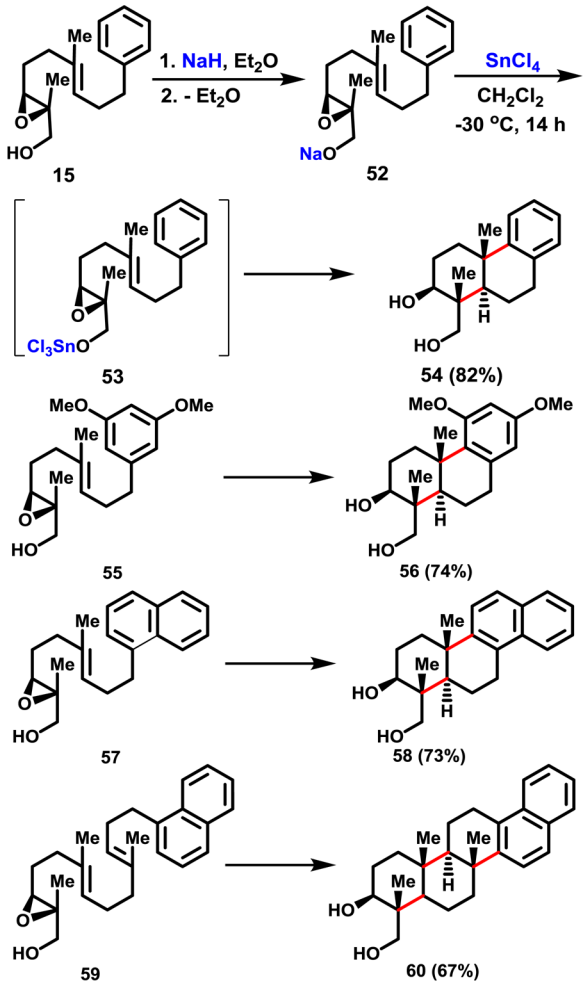
Substrate	Product (yield%)
 46	 47 (46%)
 48 (E/Z = 5 : 1)	 49 (72%) (E/Z = 5 : 1)
 50 (E/Z = 25 : 1)	 51 (76%) (E/Z = 25 : 1)

was *very slow at lower temperatures* and required 14 h *even at* −*30* °*C*. The structure of **54** was confirmed by single crystal X-ray diffraction analysis on the 4-bromobenzal acetal. The procedure with the alkoxy-$SnCl_3$ complex for the epoxide activation was equally effective for the three substrates shown in Scheme 8. The yields for formation of **54**, **56**, **58**, and **60** are lowered because in each case considerable starting material was recovered (possibly due to HCl formed in the cyclization). In these cases, it would seem that cyclization be induced by (the normally less activating) coordination between the $SnCl_3$ group and the oxygen lone pair in the α-oriented sp^3-orbital at the higher temperatures. A last example shown in Scheme 9 for the cyclization of **61** to **62**. This reaction was exceptionally rapid and efficient (94% yield after 1 h at −78 °C in CH2Cl2). The structure of the product was proven by single-crystal X-ray diffraction analysis of acetonide **63**. This last example also illustrates the ease of accessing A-ring trifunctionalyzed products. Further, it demonstrates that having simultaneously both a covalently attached Lewis acid and a vinyl activating group facilitates fission of the oxirane C−O bond. The results in Schemes 8 and 9 indicate that even though the geometry is not ideal for intramolecular metal-accelerated oxirane C−O cleavage, that factor is outweighed by the high Lewis acidity and proximity of the $ROSnCl_3$ group and also the presence of the activating vinyl group in the case of **61**. The use of $MeAlCl_2$, $TiCl_4$, or $SnBr_4$ in this type of process from the intermediate sodium alkoxide **52** did not lead to useful yields of the desired tricyclic product **54**.

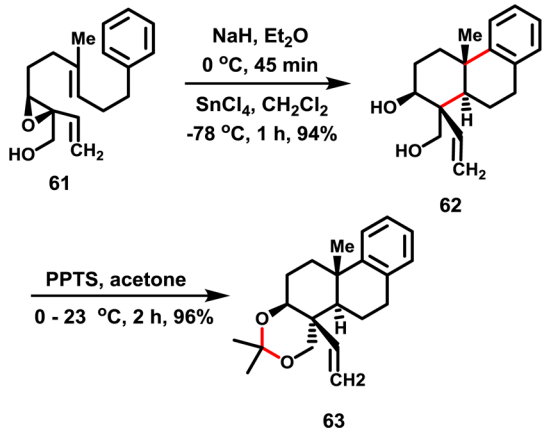
CONCLUSION

The full potential for application of Katsuki−Sharpless oxidation in combination with epoxide-initiated cationic cyclization process has hitherto been unrealized. What would seem to be an inherent advantage of this tactical combination of

Scheme 8. Cyclization of Epoxy Alcohols



Scheme 9. Cyclization of Epoxy Alcohol 61



powerful constructions, specifically the possibility of taking advantage of functionalized substrates for chelation between a catalytic Lewis acid, the epoxide oxygen and the functionalized substituent attached the oxirane ring could not be realized in practice.[5,6,20] Indeed our results with the test aldehyde **16** and ester **17** clearly shown that such chelation, if it occurs with these substrates, does not meaningfully accelerate cyclization. As pointed out above, one factor in the absence of chelate activation could be the inductive effect of a Lewis-acid-

DOI: 10.1021/jacs.5b03229
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

coordinated carbonyl (formyl in **16** and methoxy carbonyl in **17**) to destabilize heterolysis of an oxirane α-C−O bond.

The systematic studies that are described above have revealed three approaches which are highly effective for cationic cyclization process based on Katsuki−Sharpless-derived epoxides. First, the use of methoximes of aldehyde such as **16** leads to efficient cyclization reactions by way of a nonchelated complex of Lewis acid with the epoxide oxygen. These reactions (see Table 1) are clearly accelerated by the electron-donating properties of the methoxime group which favor Lewis-acid-induced oxiranyl C−O cleavage. A second, and related, method involves activation of the oxirane C−O group by attachment of vinyl substituent, such as in substrate **32**, or those listed in Table 2. Lastly, covalent attachment of a strong Lewis acid directly to oxygen of an α-hydroxymethyl oxirane can induce cyclization through an intramolecular mode of action. In this case, however, oxirane activation is unusually weak and only observed with quite strong Lewis acidic metals.

Our work has led to the identification of two factors which may play critical role in the Lewis-acid-induced cyclization of α-functionalized epoxides, one an inductive effect which results from chelation and the other a kind of stereoelectronic/electrostatic effect.

The knowledge gained from the work described herein can guide additional research on the application of epoxide induced cationic cyclization reactions to synthesis, which remains a major challenge.

■ ASSOCIATED CONTENT

Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Author

*corey@chemistry.harvard.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Dr. S.-L. Zeng of Harvard University for the X-ray crystallographic analysis. Financial support of Pfizer Inc., Bristol-Myers Squibb and Gilead Sciences is gratefully acknowledged.

■ REFERENCES

(1) (a) Corey, E. J.; Russey, W. E.; Ortiz de Montellano, P. R. *J. Am. Chem. Soc.* **1966**, *88*, 4750−4751. (b) Corey, E. J.; Russey, W. E. *J. Am. Chem. Soc.* **1966**, *88*, 4751−4752. (c) Russey, W. E. Ph.D. Thesis, Harvard University, 1966.

(2) For a broad review, see Schulz, G. E.; Corey, E. J.; Liu, D. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 2812−2833.

(3) See Maudgal, R. K.; Tchen, T. T.; Bloch, K. *J. Am. Chem. Soc.* **1958**, *80*, 2589−2590.

(4) For reviews, see (a) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730−4756. (b) Corey, E. J.; Kurti, L. *Enantioselective Chemical Synthesis*; Elsevier Publishers: Amsterdam, 2010; pp 281−307. (c) Pronin, S. V.; Shenvi, R. A. *Nat. Chem.* **2012**, *4*, 915−920. (d) Taylor, S. K. *Org. Prep. Proced. Int.* **1992**, *24*, 245−284.

(5) Aggarwal, V. K.; Bethel, P. A.; Giles, R. *Chem. Commun.* **1999**, 325−326.

(6) Bogenstatter, M.; Limberg, A.; Overmann, L. E.; Tomasi, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 12206−12207.

(7) Tanis, S. P.; Chaung, Y. H.; Head, D. B. *J. Org. Chem.* **1988**, *53*, 4929−4938.

(8) Corey, E. J.; Lee, J.; Liu, D. R. *Tetrahedron Lett.* **1994**, *35*, 9149−9152.

(9) Corey, E. J.; Lee, J. *J. Am. Chem. Soc.* **1993**, *115*, 8873−8874.

(10) Haung, A. X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 9999−10003.

(11) Mi, Y.; Schreiber, J. V.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 11290−11291.

(12) Zhang, J.; Corey, E. J. *Org. Lett.* **2001**, *3*, 3215−3216.

(13) (a) Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 8865−8869. (b) Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2009**, *131*, 13928−13929.

(14) Barrett, T. N.; Barrett, A. G. M. *J. Am. Chem. Soc.* **2014**, *136*, 17013−17015.

(15) Cherney, E. C.; Green, J. C.; Baran, P. S. *Angew. Chem., Int. Ed.* **2013**, *52*, 9019−9022.

(16) Behenna, D. C.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 6720−6721.

(17) Kurti, L.; Chein, R. J.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 9031−9036.

(18) Corey, E. J.; Staas, D. D. *J. Am. Chem. Soc.* **1998**, *120*, 3526−3527.

(19) (a) Corey, E. J.; Zhang, J. *Org. Lett.* **2011**, *3*, 3211−3214. (b) Corey, E. J.; Noe, M. C.; Lin, S. *Tetrahedron Lett.* **1995**, *36*, 8741−8744. (c) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 319−329.

(20) (a) Tanis, S. P.; Chuang, Y. H.; Head, D. B. *Tetrahedron Lett.* **1985**, *26*, 6147−6150. (b) Clark, J. S.; Myatt, J.; Wilson, C.; Roberts, L.; Walsh, N. *Chem. Comm* **2003**, 1546−1547. (c) Rosen, B. R.; Werner, E. W.; ÒBrien, A. G.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 5571−5574.

(21) Corey, E. J.; Liu, K. *J. Am. Chem. Soc.* **1997**, *119*, 9929−9930.

(22) (a) Caron, M.; Carlier, P. R.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 5185−5187. (b) Chong, J. M.; Sharpless, K. B. *Tetrahedron. Lett.* **1985**, *26*, 4683−4686. (c) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560−1563. (d) Saito, S.; Takahashi, N.; Ishikava, T.; Moriwake, T. *Tetrahedron. Lett.* **1991**, *32*, 667−670.

(23) (a) Roush, W. R.; Adam, M. A.; Peseckis, S. M. *Tetrahedron. Lett.* **1983**, *24*, 1377−1380. (b) Finan, J. M.; Kishi, Y. *Tetrahedron. Lett.* **1982**, *23*, 2719−2722.

(24) (a) Fraile, J. M.; Mayoral, J. A.; Salvatella, L. *J. Org. Chem.* **2014**, *79*, 5993−5999. (b) Seanz, P.; Cachau, R. E.; Seoane, G.; Kieninger, M.; Ventura, O. N. *J. Phys. Chem. A* **2006**, *110*, 11734−11751.

(25) (a) Corey, E. J. *Experientia* **1953**, *9*, 329−336. (b) Corey, E. J.; Sneen, R. A. *J. Am. Chem. Soc.* **1956**, *78*, 6269−6278.

(26) Kirby, A. J. *Stereoelectronic effect*; Oxford University Press: New York, 1996.

(27) (a) Blackemore, P. R.; Cole, W. J.; Kociensky, J. P.; Morley, A. *Synlett* **1998**, 26−28. (b) DiBlasi, C. M.; Macks, D. E.; Tan, D. S. *Org. Lett.* **2005**, *7*, 1777−1780.

(28) To a stirred solution of tetrazole sulfone (0.494 g, 1.86 mmol) and tetrahexylammonium bromide (0.905 g, 2.32 mmol) in dimethoxyethane (15 mL) was added a solution of aldehyde **16** (0.3 g, 1.16 mmol) in dimethoxyethane (5 mL). The reaction mixture was cooled to −78 °C, and treated with KHMDS (4.2 mL, 0.5 M) dropwise over 4 h using a syringe pump. After the addition was completed, the reaction mixture was stirred at −78 °C for 30 min and then warmed to 23 °C and stirred for 2 h. The reaction was followed by TLC analysis (triethylamine treated TLC plate). The resulting mixture was treated with water (5 mL) and then ether (10 mL). The organic layer was separated, and the aqueous layer was extracted with ether (2 × 10 mL). The combined organic extract was washed with water and brine, dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified by column chromatography (triethylamine treated silica gel, 0.5% ethyl acetate in hexane basified with a drop of triethylamine) to give the epoxy olefin **50** (0.304 g,

DOI: 10.1021/jacs.5b03229
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

88%) as a colorless liquid. E/Z = 25:1 (by NMR analysis); R_f = 0.85 (in 10% ethyl acetate in hexane); $[\alpha]_D^{23}$ +4.2 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (t, J = 5.0 Hz, 2H), 7.18 (d, J = 6.5 Hz, 3H), 5.71 (dd, J = 6.0, 16.0 Hz, 1H), 5.25−5.19 (m, 2H), 2.76 (t, J = 6.5 Hz, 1H), 2.64 (t, 6.0 Hz, 2H), 2.33−2.28 (m, 3H), 2.19−2.07 (m, 2H), 1.72−1.63 (m, 2H), 1.57 (s, 3H), 1.36 (s, 3H), 1.00 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 142.2, 139.4, 134.8, 129.8, 128.4, 128.2, 125.6, 124.3, 65.1, 59.4, 36.2, 36.0, 30.8, 29.9, 27.3, 22.2, 22.2, 15.9, 15.6; HRMS (ESI) calcd for $C_{21}H_{31}O$ $[M + H]^+$ 299.2375, found 299.2369.

DOI: 10.1021/jacs.5b03229
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX