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Regio- and Enantioselective Catalytic Monoepoxidation of Conjugated Dienes: Synthesis of Chiral Allylic *cis*-Epoxides

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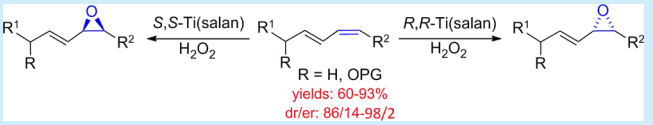
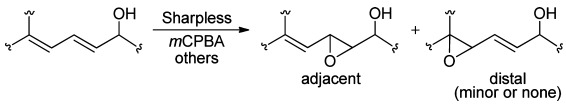
Supporting Information

ABSTRACT: Ti(IV)-salan **4** catalyzes the diastereo- and enantioselective monoepoxidation of conjugated dienes using 30% H_2O_2 at rt or below even in the presence of other olefins and adjacent stereocenters. Its enantiomer, *ent*-**4**, provides access to the opposite diastereomer or enantiomer. The resultant chiral allylic epoxides, and the triols derived from them, are versatile synthetic intermediates as well as substructures present in many bioactive natural products. The epoxidation is highly specific for *Z*-olefins. For 1-acyl(silyl)oxypenta-2,4-dienes, epoxidation of the distal olefin is generally favored in contrast to the adjacent regioselectivity characteristic of Sharpless, peracid, and other directed epoxidations of hydroxylated dienes.



Allylic epoxides display a facile and diverse reaction manifold that arises from the juxtaposition of the inherently strained three-membered epoxide with an olefinic π-system.[1] The rate of nucleophilic addition, for instance, can be up to 10^4 times faster than that for an isolated epoxide, proceeding via S_N2 or S_N2' pathways.[2] Due to their considerable synthetic appeal,[1,3] a variety of procedures have been introduced for the preparation of allylic epoxides.[1,4] One of the most popular and economic approaches is catalytic monoepoxidation of 1,3-conjugated dienes,[1a,5] including a smaller subset of asymmetric versions.[6] However, utilization of most extant protocols is constrained by one or more restrictions including modest yields,[5d,7] inadequate enantioselectivity,[8] polyoxidation,[5c] stereoisomerization,[5e] poor *cis*-/*trans*-discrimination,[5f,g] and/or decomposition of the product under the reaction conditions.[5a] A noteworthy exception is the Shi fructose-based dioxirane reagents,[6b,9] although the strict reaction regimen and catalyst availability are potential deterrences to its use.

The application of the catalytic monoepoxidation method to the special case of 2,4-pentadiene-1-ols has been an area of long-standing interest.[10] The resultant allylic epoxyols are versatile synthetic building blocks[1] as well as key subunits,[11] along with their chemically or enzymatically derived triols, in numerous bioactive natural products (Figure 1).[12] Functional group directed epoxidations, e.g., Sharpless,[13] peracid,[14] and others,[15] have played a prominent role in achieving an acceptable level of regio- and stereocontrol for substrates containing the 2,4-pentadien-1-ol moiety. In most instances, however, epoxidation occurs at the olefin adjacent to the hydroxyl and not the distal olefin (eq 1).[13−16] Our objective, consequently, was the



(1)

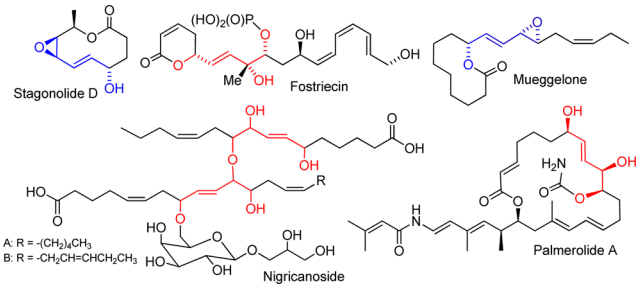


Figure 1. Representative allylic epoxyol and triol natural products.

development of an operationally simple, catalytic, distal-selective epoxidation of conjugated buta-1,3-dienes and penta-2,4-dien-1-ols and to validate the utility of this method as a key transformation in a biogenetically inspired[17] total synthesis[18] of the potent antimitotic marine natural products nigricanosides A/B[19] and clinically useful mimetics.

An assortment of catalysts and oxidants were examined for distal-selective epoxidation (Table 1). Diene **1** (R = H) was selected as the model substrate because (*i*) it is readily prepared in high stereochemical purity via multigram incubation[14,20] of linoleic acid with commercial soybean lipoxygenase, (*ii*) both diastereomeric distal epoxide diastereomers **2** and **3** are available,[21] and (*iii*) it offers a stereochemical point of reference and mechanistic probe of the reaction course.[22] Initially, epoxidations were conducted with the C(13)-hydroxyl unprotected; in many cases, however, complex product mixtures were obtained. Hence, most subsequent studies were conducted with the hydroxyl blocked as the acetate, i.e., **1** (R = Ac).

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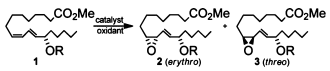
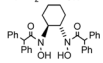
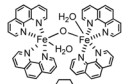
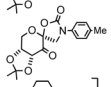
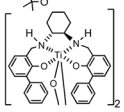
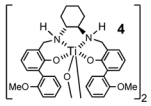
Table 1. Survey of Catalytic Systems for Asymmetric, Distal-Selective Epoxidation of 1



entry	catalyst[a]	additive	oxidant	solvent	R	yield (%)[b]	2:3[c]
a	$MnSO_4$	$NaHCO_3$	30% H_2O_2	*t*-BuOH	H Ac	<5 <5	na[d] na[d]
b	$Ti(O/Pr)_4$	na[d]	*t*-BuOOH	CH_2Cl_2	Ac	<5	na[d]
c	$Zr(OtBu)_4$		$PhCMe_2(OOH)$	PhCl	H Ac	<5[e] <5[e]	na[d] na[d]
d	$MoO_2(acac)_2$		*t*-BuOOH	$PhCH_3$	H Ac	<5[e] <5[e]	na[d] na[d]
e	$FeCl_3$		30% H_2O_2	*t*-BuOH	Ac	<5	na[d]
f	$MeReO_3$	pyridine	30% H_2O_2	CH_2Cl_2	Ac	80	3:2
g	$(nBu_4N)_4[SeO_4\{WO(O_2)_2\}_2]$	na[d]	30% H_2O_2	CH_3CN	Ac	40	1:1
h		na[d]	CH_3CO_3H	CH_3CN	Ac	75	1:1
i		na[d]	CH_3CO_3H	CH_3CN	Ac	69	3:2
j		na[d]	30% H_2O_2	CH_3CN	Ac	58	7:3
k		K_2CO_3	oxone	DME/DMM	TBDPS	35[f]	3:2
l		K_2CO_3	oxone	DME/DMM	Ac	60	4:1
m		na[d]	30% H_2O_2	CH_2Cl_2	Ac	80	95:5
n		na[d]	30% H_2O_2	CH_2Cl_2	Ac	92	99:1

[a]Epoxidation procedures: entry a (ref 23), entry b (ref 24), entry c (ref 25), entry d (ref 26), entry e (ref 27), entry f (ref 28), entry g (ref 29), entry h (ref 30), entry i (ref 32), entry j (ref 33), entry k (ref 6a), entry l (ref 9), entries m and n (ref 34). [b]Combined, isolated yield. [c]Determined by chiral HPLC. [d]na = not applicable or not available. [e]Mainly recovered diene. [f]Obtained as a 1:1 mixture with the 11,12-monoepoxide regioisomers.

Many well established transition metal epoxidation catalysts[23,24] provided little, if any, of the desired epoxide **2** or **3** (entries a and b). Despite their utility with styrenes, chiral complexes of Zr (entry c),[25] Mo (entry d),[26] and Fe (entry e)[27] proved ineffective with **1** as the substrate. Ruthenium (entry f),[28] tungsten (entry g),[29] and bis-iron (entry h)[30] salts displayed more encouraging distal regioselectivities and, in some cases, afforded good yields of distal epoxides. While a variety of reaction conditions were evaluated using these catalysts, mixtures of **2** and **3** were always obtained;[31] evidently, the chiral center had scant influence upon the diastereoselectivities. Manganese (entry (i)[32] and iron (entry j)[33] coordinated by chiral tetradentate N_2Py_2 platforms were likewise marginally diastereoselective, but did give acceptable yields. The Shi reagent (entry k)[6a] led to a complex product mixture consisting of **2** and **3** (3:2 ratio) and an equal amount of the 11,12-monoepoxides (3:2 ratio) when **1** was protected as the silyl ether. The second generation oxazolidinone reagent (entry l),[9] developed by Shi for diene applications, performed much better when applied to **1** (R = Ac) and afforded only **2** and **3** (4:1 ratio). This is likely due, in part, to the inductive deactivation of the adjacent olefin by the acetyloxy group; inductive deactivation with these reagents has been observed previously.[6,9] Titanium, sequestered within the salan-type ligands pioneered by Katsuki and colleagues,[34a] afforded both high yield and excellent control of diastereoselectivity (entry m). The yield and selectivity toward *erythro*-epoxide **2** was further boosted using (*R*,*R*)-Ti(salan) **4**, created by introduction of an *ortho*-methoxy onto the pendant phenyl (entry n).[34b]

When treating **1** (R = Ac) with **4** and 30% H_2O_2, yields of **2** were optimum in CH_2Cl_2 (92%) and trended progressively lower in THF (75%), $Cl(CH_2)_2Cl$ (70%), CH_3CN (65%), EtOAc (60%), toluene (60%), DME (55%), and CH_3NO_2 (<10%). Reaction rates were faster with 50% or 90% H_2O_2, but 30% H_2O_2 (1.5−2 equiv) was our preference for reasons of safety, cost, and availability. Attempts to accelerate the rate by using a large excess of 30% H_2O_2 (>6 equiv) were usually accompanied by minor, yet noticeable, amounts (5−10%) of triol from hydrolysis of **2**. For convenience, most reactions with **4** were conducted at or near room temperature.

To elucidate further the scope of monoepoxidation mediated by **4** (and its enantiomer, *ent*-**4**), a panel of representative 2,4-pentadien-1-ols and buta-1,3-dienes were oxidized under the standard reaction conditions (Table 2). As with many other reagents, epoxidation of **1** (R = H) with an unprotected hydroxyl eroded the yield and diastereoselectivity (entry 1); however, the regioselectivity was still entirely distal in sharp contrast to the adjacent selectivity characteristic of Sharpless-type processes. The corresponding benzyl ether **5**, benzoate **7**, pivaloate **9**, carbonate **11**, and silyl ether **13**, on the other hand, were all well behaved and afforded the anticipated distal, *erythro*-allylic epoxides in good yields and dr (entries 2, 3, 4, 5, and 6, respectively). The nature of the hydroxyl protecting group (i.e., ether, ester, silyl ether) made no difference in the stereochemical outcome (cf., Table 1, entries k and l). Despite having an additional *cis*-olefin, linolenate-derived trienes **15** and **17** preferentially furnished **16** (entry 7) and **18** (entry 8), respectively, and only minor amounts of additional epoxidation at the $\Delta^{15,16}$-olefin, i.e., *bis*-epoxide, were detected. Significantly, epoxidation of **17** mediated by *ent*-**4** gave rise to allylic epoxide **19** (entry 9), the *threo*-diastereomer of **18**, demonstrating that the existing chiral center adjacent to the diene does not influence epoxidation enantioselectivity. Triene **20** (entry 10), whose olefinic pattern differs from **17**, was also suitable as was the short chain diene **22** from which **23** (entry 11) was obtained in excellent yield and dr. An increase in the substitution level at the acyloxy carbon, e.g., **24** → **25** (entry 12), had no effect on the transformation, but it did for the distal olefin, e.g., **26** → **27** (entry 13), as revealed by a small decrease in the dr. For dienes **28**, **30**, and **32** without an existing stereocenter, it was reassuring to find epoxides **29** (entry 14), **31** (entry 15), and **33** (entry 16) were generated with a high level of enantioselectivity. Exposure of cholesta-4,6-diene **34** to *ent*-**4** and 30% H_2O_2 under the usual conditions culminated in α-epoxide **35** as the sole product (entry 17), yet **34** was completely immune to **4** even after prolonged reaction times and was recovered unchanged. The epoxidation of **36**, the methyl ester of natural conjugated linoleic acid (CLA), was instructive (entry 18). Even absent the inductive influence of an allylic oxygen substituent, epoxidation of the *cis*-olefin to give **37** predominated. While it might be tempting to attribute the distal regioselectivity in the preceding examples to an inductive deactivation of the adjacent olefin by the oxygen substituent, thus redirecting epoxidation to the distal olefin, this example cogently dispels this conjecture. This is an especially challenging example since there is no functional group located closely enough to guide

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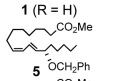
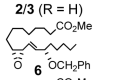
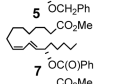
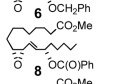
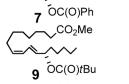
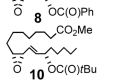
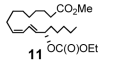
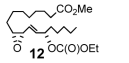
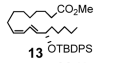
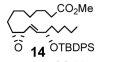
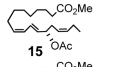
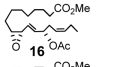
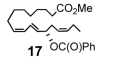
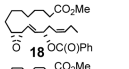
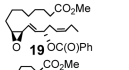
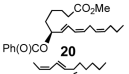
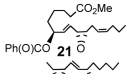
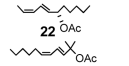
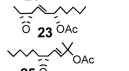
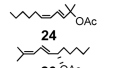
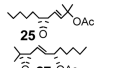
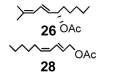
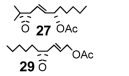
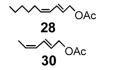
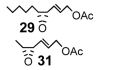
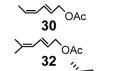
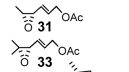
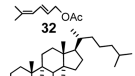
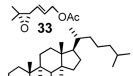
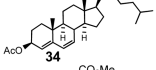
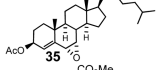
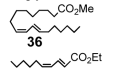
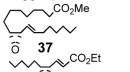
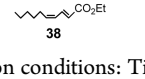
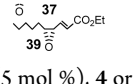
Table 2. Scope of Asymmetric, Monoepoxidation of Representative 1,3-Dienes by Ti(salan) 4 and *ent*-4a

entry	diene	salan	epoxide	time (h)	yield[b] (%)	dr/er[c]
1	**1** (R = H)	**4**	**2/3** (R = H)	6	60	86:14
2	 **5**	**4**	 **6**	12	88	98:2
3	 **7**	**4**	 **8**	12	91	98:2
4	 **9**	**4**	 **10**	20	82	98:2
5	 **11**	**4**	 **12**	12	87	98:2
6	 **13**	**4**	 **14**	16	86	98:2
7	 **15**	**4**	 **16**	12	83[d]	98:2
8	 **17**	**4**	 **18**	12	88[d]	98:2
9	**17**	*ent*-**4**	 **19**	12	87[d]	98:2
10	 **20**	*ent*-**4**	 **21**	12	76	98:2
11	 **22**	**4**	 **23**	10	93	98:2
12	 **24**	**4**	 **25**	12	77	99:1
13	 **26**	**4**	 **27**	12	73	94:6
14	 **28**	**4**	 **29**	10	88	99:1
15	 **30**	**4**	 **31**	8	93	98:2
16	 **32**	**4**	 **33**	12	81	98:2
17	 **34**	*ent*-**4**	 **35**	16	77	98:2
18	 **36**	**4**	 **37**	5	86[e]	99:1
19	 **38**	**4**	 **39**	16	70	98:2

[a]Reaction conditions: Ti(O*i*Pr)$_4$ (5 mol %), **4** or *ent*-**4** (6 mol %), 30% aq H_2O_2 (1.5−2 equiv), CH_2Cl_2, rt. [b]Isolated yield. [c]Determined by normal/chiral HPLC as appropriate. [d]5−10% bis-epoxide observed in crude NMR. [e]Conducted at 0 °C; ∼ 2−3% of the *trans*-epoxide was detected in the crude NMR, but was not isolated.

the epoxidation of the diene, yet excellent regio- and enantioselectivities were achieved. Our results compare quite well with earlier attempts at stereoselective epoxidation of **36** using other common reagents.[10i] Conversion of **38**, the most electron deficient in Table 2, exclusively to **39** (entry 19) is consistent with the preceding data. No *trans*-epoxide was found and there was no reaction in the absence of **4**, which together suggest a Michael addition is unlikely.

The mechanism of Ti(salan)-catalyzed epoxidations has been studied and is believed to proceed via a peroxo-Ti(salan) intermediate when using aqueous H_2O_2 as the oxidant.[34] Internal H-bonding between the salan amino proton and the O-atom of the peroxo species is vital for epoxidation. Based upon the available evidence and inspection of molecular models, we conclude facial selectivity is a consequence of steric interactions between the substrate and catalyst active site. The chiral hydroxyl centers in the examples herein are too distant from the site of epoxidation to exert any influence. This is not to say that stereocenters in other locations or conformational effects, especially in cyclic dienes, will be without effect; the epoxidation of steroid **34** by *ent*-**4**, but the total lack of reactivity with the enantiomeric catalyst **4**, is strong testament in favor of steric factors. In the case of **1** (R = H), H-bonding between the free alcohol and peroxo-Ti intermediate could explain the erosion of diastereoselectivity.

In summary, the Ti(IV)-salan catalyst **4** in combination with environmentally friendly 30% H_2O_2 is an efficient, room temperature catalytic system for the diastereo- and enantioselective monoepoxidation of conjugated dienes even in the presence of other olefins. Notably, the regioselectivity in some systems, e.g., 2,4-pentadien-1-ols, is complementary to that achievable using Sharpless and other directed epoxidations. There is a strong preference for *Z*- vs *E*-olefins. Progress in the development of a catalyst suitable for *E*,*E*-dienes will be reported elsewhere.

■ ASSOCIATED CONTENT

Supporting Information

The preparation and spectral characterization ($^1H/^{13}C$ NMR) of all new compounds and HPLC chromatograms. 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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