

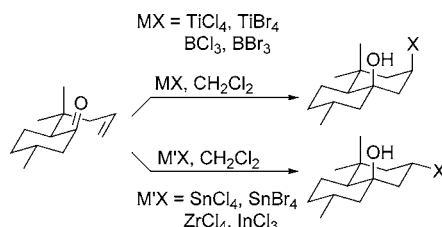
Syn- and Anti-Selective Prins Cyclizations of δ,ϵ -Unsaturated Ketones to 1,3-Halohydrins with Lewis Acids

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Received October 13, 2005

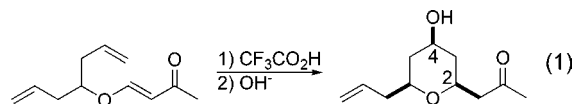


Ten acyclic and monocyclic δ,ϵ -unsaturated ketones, with and without methyl substituents on the double bond, underwent halide-terminated Prins (halo-Prins) cyclizations under anhydrous conditions in the presence of Lewis acids. $TiCl_4$, $TiBr_4$, BCl_3 , and BBr_3 promoted syn-selective cyclizations to sterically congested chloro- and bromohydrins, while $SnCl_4$, $SnBr_4$, $InCl_3$, $ZrCl_4$, and several other Lewis acids effected highly anti-selective reactions to furnish the corresponding trans halohydrins. The stronger Lewis acids (TiX_4 and BX_3) favor the syn process that involves axial delivery of a halide ligand. Competition experiments showed that substitution at the δ carbon (methallyl enones) led to increased rates (40–50-fold), while substitution at the ϵ position (cis and trans crotyl enones) retarded the rate and eroded the selectivity of the cyclizations. The trends in syn vs anti selectivity, reactivity, and effects of different Lewis acidic metal halides are rationalized by competitive reaction pathways proceeding through syn carbocation–halide ion pairs and a higher order transition state that leads to inversion of configuration and formation of trans halohydrins, along with cyclic olefins arising from proton elimination.

Introduction

The Prins reaction is the electrophilic hydroxyalkylation of $C=C$ double and $C\equiv C$ triple bonds by aldehydes, ketones, or their equivalents, with incorporation of a nucleophile from the protic or Lewis acid promoter, or from solvent capture, to form 1,3-difunctional adducts.¹ Intramolecular Prins reactions of unsaturated aldehydes, ketones, acetals, ketals, and enol ethers, as well as their acetylenic counterparts, have been widely employed in the synthesis of carbocyclic and heterocyclic compounds. These ring-forming reactions, as well as the closely related carbonyl ene reaction, Prins-initiated polyene cyclizations, and Prins-pinacol rearrangements, have found numerous synthetic applications.^{1–5} One example of current interest is the synthesis of oxygen heterocycles such as tetrahydropyrans

bearing the nucleophile in the 4 position and the related tetrahydropyranones and dihydropyrans (eq 1).^{3,6}



The stereochemistry of Prins cyclizations usually parallels that of electrophilic additions to $C=C$ double bonds, i.e.,

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(3) Tetrahydropyrans. (a) Kozmin, S. A. *Org. Lett.* **2001**, *3*, 755–758. (b) Cossey, K. N.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 12216–12217. (c) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 3407–3410. (d) Nussbaumer, C.; Fräter, G. *Helv. Chim. Acta* **1987**, *70*, 396–401.

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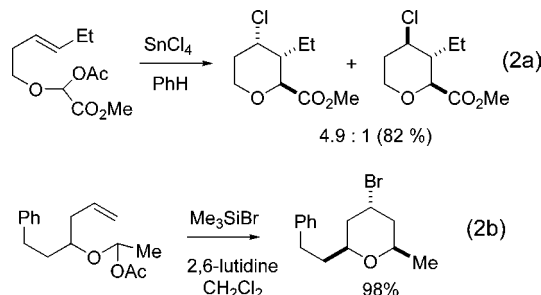
(5) (a) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143–7157. (b) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352–359.

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(1) (a) Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 2, pp 527–561. (b) Arundale, E.; Mikeska, L. A. *Chem. Rev.* **1952**, *51*, 505–555. (c) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661–672. (d) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2000; Vols. 1 and 2.

antiperiplanar orientation of the oxo-carbenium ion electrophile and the halide or oxygen nucleophile. Thus, cyclizations of homoallyl oxo-carbenium ions generated in various ways led to *cis*-2,4-disubstituted tetrahydropyrans (eq 1).^{3,6} Anti additions are apparent in the cyclizations of homoallylic acetals having *trans*- and *cis*-disubstituted double bonds to *trans,trans*- and *cis,cis*-2,3,4-trisubstituted tetrahydropyran adducts, respectively.⁷ However, the stereochemistry and regioselectivity may be eroded by fast oxonia-Cope rearrangements.^{6a,8} Prins cyclizations of 5-cyclodecenones proceed with strict anti stereochemistry.⁹

Despite the dominant trend of anti stereoselectivity, cases of *syn*-selective Prins cyclizations have been noted in the recent literature.^{6,8a,10,11} Protic- and Lewis acid-induced Prins cyclizations of (α -acetoxy)carboxymethyl homoallyl ethers in benzene gave predominantly *cis*-2,4-tetrahydropyran-2-carboxylates (axial Cl or O₂CH) (eq 2a).^{10a} Trimethylsilyl bromide- and acetyl bromide-initiated Prins cyclizations of α -acetoxyalkyl homoallyl acetals proceeded with high *syn* selectivity to give 4-bromo tetrahydropyrans with axial Br (e.g., eq 2b).^{6a,8a,10c} Trifluoroacetic acid-promoted Prins cyclizations of 1-phenyl-2-(silylmethyl)cyclopropylcarbinols with aldehydes in the presence of trifluoroacetic acid provided 2,4,6-substituted tetrahydropyran-4-ols with axial hydroxyl groups after hydrolysis.^{6b} The formation of a *cis* 1,3-chlorohydrin was observed in cyclizations of 3-(cyclohexen-1-yl)propyl trifluoromethyl ketone promoted by TiCl₄ and EtAlCl₂.^{10b} The anomalous stereochemistry in these formal *cis* additions has been rationalized by neighboring group participation (double inversion), least motion, and cyclic transition states.



Previous work in this laboratory has shown that δ,ϵ -unsaturated ketones cyclize to *cis* 1,3-chlorohydrins in the presence of TiCl₄, formal *syn* additions to the allyl double bonds (eq 3).^{11,12} In contrast, consistent anti selectivity was observed

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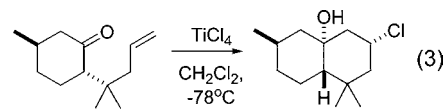
(11) Davis, C. E.; Coates, R. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 491–493.

TABLE 1. Cyclization of Acyclic δ,ϵ -Enones with TiCl₄^a

| entry | keto olefin | time (min) | yield ^b (%) | products | <i>cis/trans</i> ratio ^{b,c} |
|-------|-------------|------------|------------------------|----------|---------------------------------------|
| 1 | | 15 | 52 ^d | | 8.6:1 |
| 2 | | 5 | 57 | | 5.8:1 |
| 3 | | 0.5 | 93 | | 12:1 |
| 4 | | 240 | 47 ^e | | 1:4.2 |

^a In CH₂Cl₂ at –78 °C; quenched with Et₃N/MeOH in CH₂Cl₂ at –78 °C. ^b By integration of ¹H NMR spectra of the crude product mixture using DME as an internal standard. ^c *Cis* and *trans* refer to OH and Cl groups. Structures of minor chlorohydrin products denoted by substituents in parentheses. ^d Homoallylic alcohol and 1,3-diene also present (15%). ^e Olefin mixture also present (28%).

in the same Prins cyclizations effected by anhyd HCl. The purpose of the present research was to explore the scope and stereochemistry of the Prins cyclizations of δ,ϵ -enones. Here, we examine the effects of methyl substituents on the double bond, different Lewis acid co-reactants, and other variables, to elucidate the factors that influence the yields and the *syn* vs anti stereoselectivity. A clearer understanding of the tolerance of the reaction to these variables is necessary for further exploitation of this novel ring-forming reaction in the synthesis of functionalized carbocycles.



Preparation of δ,ϵ -Unsaturated Ketones. The scope and selectivity of the halo-Prins cyclizations were investigated through reactions of two types of δ,ϵ -enones differing in substitution pattern on the double bond (see Tables 1 and 2). Six of the 10 compounds were prepared by Sakurai reactions¹³ of methyl vinyl ketone, mesityl oxide, and (*R*)-pulegone with allyl- and methallyltrimethylsilanes (32–80%). The conjugate allylations of pulegone are given as examples in eq 4. The *cis* and *trans* allyl- and methallylpulegone isomers were readily separated by flash chromatography, and the stereochemistry was

(12) Isolated cases of similar TiCl₄-promoted Prins cyclizations have been reported. (a) Tokoroyama, T.; Pan, L.-R. *Tetrahedron Lett.* **1989**, *30*, 197–200. (b) Carbery, D. R.; Miller, N. D.; Harrity, J. P. A. *Chem. Commun.* **2002**, 1546–1547.

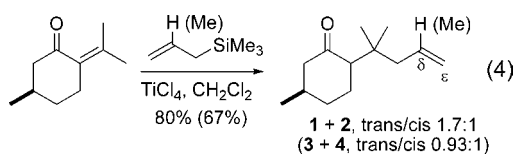
(13) (a) Sakurai, H.; Hosomi, A.; Hayashi, J. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, pp 443–446. (b) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673–1675.

TABLE 2. Cyclizations of Allyl Pulegones with TiCl_4^a

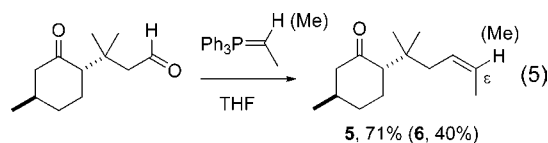
| entry | keto olefin | time (min) | yield ^b (%) | products ^c | cis/trans ratio ^{b,c} |
|-------|-------------|------------|------------------------|-----------------------|--------------------------------|
| 1 | | 1 | 70 | | 10 : 1 |
| 2 | | 1 | 55 ^d | | 13 : 1 |
| 3 | | 15 | 67 | | 1 : 6.7 |
| 4 | | 15 | 72 | | < 1 : 50 |
| 5 | | 30 | 55 ^e | | - |
| 6 | | 15 | 33 ^f | | 11 : 1 |

^a In CH_2Cl_2 at -78°C ; quenched with $\text{Et}_3\text{N}/\text{MeOH}$ in CH_2Cl_2 at -78°C . ^b By integration of ^1H NMR spectra of the crude product mixture using DME as an internal standard. ^c Cis and trans refer to OH and Cl groups. Structures of minor chlorohydrin products denoted by substituents in parentheses. ^d Mixture of endo and exocyclic olefin (12%) also obtained. ^e Olefin components (25%) also obtained. ^f Trans dichloride **32** (28%) also obtained.

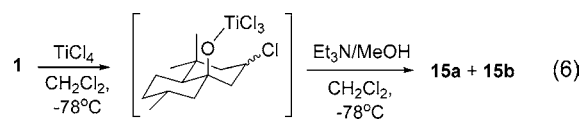
assigned by base-catalyzed equilibration to trans-enriched mixtures (KOH, MeOH; 4:1 trans/cis).



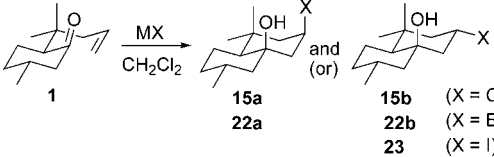
The other four enones bearing one or two methyl groups at the ϵ -position of the double bond (**5**, **6**, **13**, and **18**) were prepared by Wittig olefinations¹⁴ of keto aldehydes obtained by ozonolysis (CH_2Cl_2 , -78°C)¹⁵ of acyclic enone **9** and trans allylpulegone **1** (eq 5). Olefinations with $\text{MeCH}=\text{PPh}_3$ and $\text{Me}_2\text{C}=\text{PPh}_3$ in anhydrous THF at -78°C provided cis ϵ -methyl and ϵ,ϵ -dimethyl enones **5**, **6**, and **13**. The one trans enone (**18**) was isolated from a 2.8:1 mixture (66%) of trans and cis isomers resulting from a Schlosser–Wittig reaction¹⁶ with the keto aldehyde shown in eq 5: (a) $\text{MeCH}=\text{PPh}_3/\text{THF}$, -78°C ; 1 equiv of $\text{NaN}(\text{Me}_3)_2$; (c) MeOH. Addition of a second equivalent of the amide base had no effect on the Z/E ratio. The trans configuration of the E double bond in **18** was verified by the characteristic IR band at 971 cm^{-1} .



Chloro-Prins Cyclizations with TiCl_4 . The reactions of the 10 enones with TiCl_4 (and other Lewis acids) were carried out by adding a 1.0 M solution of the Lewis acid (1.0 equiv) in CH_2Cl_2 to the enone in CH_2Cl_2 at -78°C (or other temperature specified) under nitrogen. In the cases of TiBr_4 , TiI_4 , AlCl_3 , InCl_3 , ZrCl_4 , and GaCl_3 to be discussed below (Table 3), which were only partially soluble or insoluble in CH_2Cl_2 , a suspension of the Lewis acid was stirred vigorously as a solution of the enone in CH_2Cl_2 was slowly added. The reaction progress was followed by TLC analysis of reaction aliquots. Upon completion, an excess of $\text{Et}_3\text{N}/\text{MeOH}$ solution in CH_2Cl_2 was added at the reaction temperature, and the mixture was gradually warmed to room temperature to liberate the chlorohydrin (or halohydrin) from the trichlorotitanium alkoxide intermediate and to neutralize the HCl generated (eq 6). The product ratios and % yields were determined by quantitative integration of ^1H NMR spectra (DME as internal standard) of the crude product mixture prior to purification. Halohydrin products, and in some cases olefin byproducts, were separated by chromatography. Structure determinations are summarized in a later section.



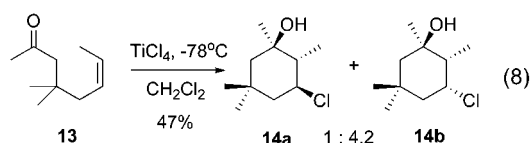
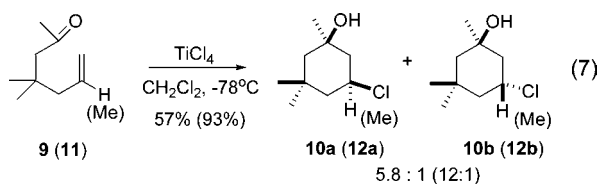
The predominant product in most cases with TiCl_4 was the cis chlorohydrin, with cis/trans ratios ranging from 13:1 to 6:1 (52–93% combined yields) (Tables 1 and 2). Two examples

TABLE 3. Cyclization of Allyl Pulegone with Various Lewis Acids^a


| entry | MX | T (°C) | time | yield ^b (%) | cis/trans ratio ^{b,c} |
|-------|-------------------|--------|--------|------------------------|--------------------------------|
| 1 | TiCl ₄ | -78 | 1 min | 70 | 10:1 |
| 2 | TiBr ₄ | -78 | 15 min | 76 | 15:1 |
| 3 | TiI ₄ | 0 | 30 min | 43 | <1:50 |
| 4 | BCl ₃ | 0 | 2 h | 75 | 25:1 |
| 5 | BBr ₃ | 0 | 2 h | 62 | 10:1 |
| 6 | SnCl ₄ | 0 | 3 h | 64 | 1:50 |
| 7 | SnBr ₄ | 25 | 2 d | 90 | <1:50 |
| 9 | AlCl ₃ | 25 | 3 d | 22 ^d | <1:50 |
| 10 | InCl ₃ | 25 | 3 h | 56 | <1:50 |
| 11 | ZrCl ₄ | 0 | 30 min | 63 | <1:50 |
| 12 | SiCl ₄ | 25 | 5 d | NR | |
| 13 | GaCl ₃ | 0 | 45 min | 66 | <1:50 |

^a In CH₂Cl₂ at the temperature specified; quenched with Et₃N/MeOH in CH₂Cl₂ at the temperature specified. ^b By integration of ¹H NMR spectra of the crude product mixture using DME as an internal standard. ^c Cis and trans refer to OH and Cl groups. ^d 60% conversion after 3 d. Homoallylic alcohol (60%) was obtained.

with the acyclic enones are presented in eq 7. However, quite different results were observed with the ϵ -methyl enones. All three enones bearing one ϵ -methyl group afforded mainly the corresponding trans chlorohydrins with cis/trans ratios of 1:4.2 to 1:6.7 (eq 8). Furthermore, the sole ϵ,ϵ -dimethyl enone **6** furnished the oxetane resulting from formal [2 + 2] cycloaddition of the C=O group across the C=C double bond (Table 2).¹⁷ The sterically crowded cis allylpulegone **2** provided the cis and trans chlorohydrins in a 8.5:1 ratio, and in addition, some trans dichloride was formed (Table 2, entry 6). The moderate yields of the chlorocyclohexanols in three of the four entries in Table 1 are a consequence of competing proton elimination to volatile homoallylic alcohols and conjugated dienes lost in the isolation procedures.



Most of the chloro-Prins reactions brought about by TiCl₄ were quite fast at -78 °C, with reaction times estimated from 0.5 to 15 min. Some of the very fast reactions were likely

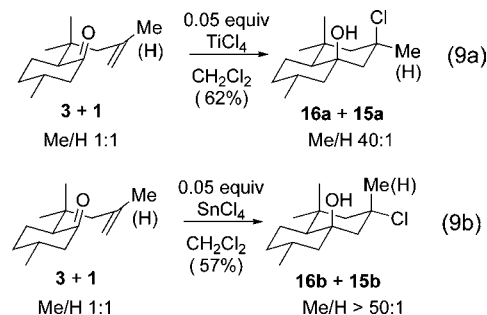
(14) Denmark, S. E.; Senanayake, C. B. W. *Tetrahedron* **1996**, *52*, 11579–11600.

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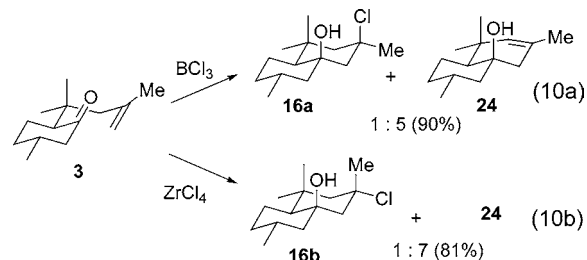
(17) Demole, E.; Enggist, P.; Borer, M. C. *Helv. Chim. Acta* **1971**, *54*, 1845–1864.

completed in shorter times. In general, the reaction times for the acyclic enones were considerably longer in comparison with those of the corresponding allylpulegones. However, the cyclizations of the ϵ -methyl enones in both series proceeded much more slowly than the allyl parents. For example, cis acyclic enone **13** required a 4 h reaction time at -78 °C compared to the 5 min period needed for enone **9** lacking the ϵ -methyl group (eq 8). A competition experiment was performed in order to determine the effect of the δ -methyl substitution more precisely. Reaction of a 1:1 mixture of allyl- and methallylpulegones with 0.05 equiv of TiCl₄ at -78 °C afforded a 40:1 mixture of cis chlorohydrins (eq 9a). A similar run with 0.05 equiv of SnCl₄ afforded exclusively the corresponding methyl-substituted trans chlorohydrin (Me/H \geq 50:1), as shown in eq 9b.



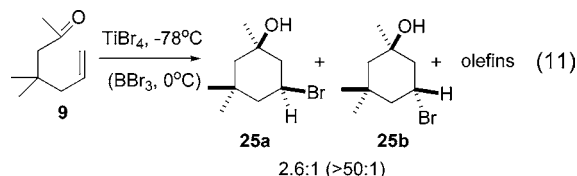
Survey of Other Lewis Acid Halides. The effects of several different Lewis acidic metal halides on the halo-Prins reactions were investigated with allylpulegone (Table 3) and to a more limited extent with methallylpulegone and 4,4-dimethylhept-6-en-2-one (eqs 10a, 10b, and 11). The cyclizations of allylpulegone with TiBr₄, BCl₃, and BBr₃, like those with TiCl₄, afforded the cis halohydrins with high selectivity and consistent yields (10–25:1, 62–76%). In striking contrast, TiI₄ provided trans iodohydrin, and the same high trans selectivity was observed with aluminum, gallium, indium, zirconium, and tin(IV) chlorides and tin(IV) bromide. The reactions with TiCl₄ and TiBr₄ took place rapidly at -78 °C, whereas all others required temperatures of 0 or 25 °C. The cyclizations with SnBr₄ and AlCl₃ proceeded very slowly at 25 °C (2 d, 90%; 3 d, 60% conversion), and no reaction was observed with SiCl₄.

A more limited survey of the reactions of other Lewis acids was conducted with methallylpulegone because of the lower halohydrin yields and higher proportions of olefin products formed. Nevertheless, as illustrated in eqs 10a and 10b, similar stereoselectivities were observed. Thus, reactions of **3** with BCl₃ and ZrCl₄ (CH₂Cl₂, 0 °C, 30 min) afforded cis and trans chlorohydrins **16a** (15%) and **16b** (10%), respectively. The stereoselectivities in the formation of the isomeric chlorohydrins were >50:1.



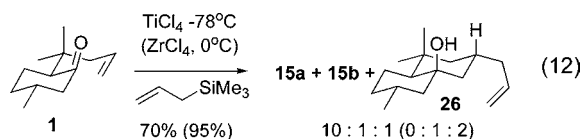
The few halo-Prins cyclizations of acyclic enone **9** investigated exhibited a similar trend. The reaction with TiBr₄ afforded

predominantly cis bromohydrin (44%) in 30 min at $-78\text{ }^\circ\text{C}$, albeit with lower stereoselectivity than TiCl_4 (cis/trans 2.6:1 vs 5.8:1) (eq 11). Similarly, reaction with BBr_3 gave exclusively cis bromohydrin (32%), together with olefins (34%).

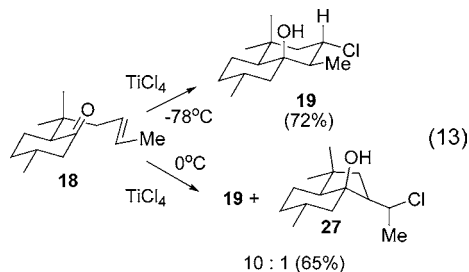


Variations in the Medium and Conditions. Several chloro-Prins reactions were conducted in pentane and toluene at $-78\text{ }^\circ\text{C}$ to evaluate the effect of these less polar solvents. Reaction times in toluene were approximately the same as those in $\text{CH}_2\text{-Cl}_2$, while those in pentane were longer. Interestingly, most of the cis/trans ratios in the hydrocarbon solvents were lower than those observed in CH_2Cl_2 . For example, with methallylpulegone the ratios were as follows: CH_2Cl_2 13:1 (55%), toluene 4:1 (65%), pentane 7:1 (41%).

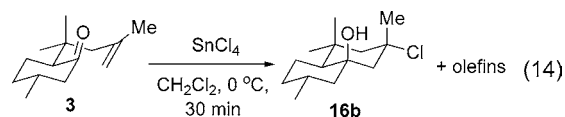
Cyclizations of allylpulegone with TiCl_4 and ZrCl_4 were also conducted in allyltrimethylsilane as solvent to determine whether an intermediate might be trapped¹⁸ and to test the potential of the reactions for C–C bond formation (eq 12). With TiCl_4 , the majority of the product consisted of the normal cis-rich chlorohydrin isomer mixture, accompanied by a small amount of the trans allylated adduct **26**. A higher proportion of the same allylated product was produced with ZrCl_4 as Lewis acid, and the remainder was the trans chlorohydrin. Thus, in both cases, the chlorohydrin products were formed with the same selectivity as they were in the absence of the allylsilane.



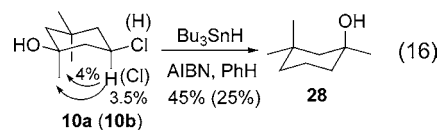
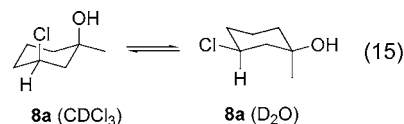
The Lewis acid concentration was varied to ascertain whether that variable might influence the cis/trans ratio. In fact, the ratio of cis and trans chlorohydrins from cyclization of allylpulegone increased from 10:1 to 30:1 when the concentration of TiCl_4 was reduced from 1 to 0.01 M. The effect of temperature on the TiCl_4 -mediated cyclization of trans ϵ -methylallylpulegone (**18**) was studied (eq 13). At $-78\text{ }^\circ\text{C}$, trans chlorohydrin **19** was formed as mentioned previously (Table 2). However, when the temperature was raised to $0\text{ }^\circ\text{C}$, a small amount of the exocyclic hydrindanyl chlorohydrin (**27**, 6%) was produced. It should be emphasized that equilibration would involve the chlorotitanium alkoxide intermediates prior to the buffered methanolysis workup procedure not shown.



The possibility that the trans selectivity of the allylpulegone cyclizations observed with most of the other Lewis acids (Table 3, entries 3, 6–11, and 13) might be thermodynamically controlled prompted some additional experiments with methallylpulegone. In this case, the trans chlorohydrin **16b** would be less stable owing to steric interactions of the axial methyl group. However, as shown in eq 14 below, the chloro-Prins reaction of **13** with SnCl_4 , like that with ZrCl_4 (eq 10b), afforded exclusively trans chlorohydrin **16b** (23%) bearing the axial methyl group, along with a sizable olefin fraction (77%). In contrast, the cyclization of methallylpulegone with BCl_3 gave the more stable cis chlorohydrin **16a** under comparable conditions (eq 10a). We conclude from the results illustrated in eqs 10 and 14 that most if not all of the halo-Prins cyclizations are in fact kinetically controlled.



Structures of 1,3-Halohydrins. The structures and stereochemistry of the halohydrin products were elucidated by analysis of NMR couplings, NOE measurements, X-ray crystallography,¹⁹ and chemical correlations through tin hydride reductions or dehydrohalogenation. The ^1H NMR spectrum of chlorohydrin **8a** proved to be solvent dependent. In CDCl_3 , the signal for CHCl appears as a quintet (δ 4.05 ppm, $J = 4.1$ Hz), whereas in D_2O the same proton is a triplet of triplets (δ 3.92 ppm, $J = 11.2, 4.1$ Hz), clearly indicating a change in conformation (eq 15). A 1, 3-diaxial relationship between CH_3 and CHCl was verified by a 4% NOE in D_2O . The ring inversion in D_2O is attributed to disruption of an intramolecular hydrogen bond between the 1,3 diaxial Cl and OH groups in CDCl_3 , the formation of intermolecular hydrogen bonds in D_2O , and minimization of the dipole moment. In contrast, the epimeric trans chlorohydrin **8b** has the conformation with equatorial Cl and axial OH regardless of solvent. The structures of chlorohydrins **10a** and **10b** were determined by NOE measurements and dechlorination with Bu_3SnH to the same tertiary alcohol (**28**) (eq 16).



Structure determination of chlorohydrins **12a** and **12b** was accomplished by X-ray crystallography and NOE measurements. An X-ray crystal structure was solved for cis chlorohydrin **12a**,

(18) (a) Chan, K.-P.; Loh, T.-P. *Tetrahedron Lett.* **2004**, *45*, 8387–8390. (b) Aubele, D. L.; Lee, C. A.; Floreancig, P. E. *Org. Lett.* **2003**, *5*, 4521–4523.

(19) CCDC 167997 (**12a**), 278151 (**14b**), 278592 (**15a**), 167996 (**16a**), 278153 (**17b**), 278059 (**21a**), 278060 (**21b**), 278152 (**22a**), 278061 (**22b**), 278058 (**23**), and 278150 (**25b**) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

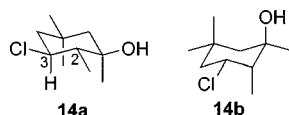
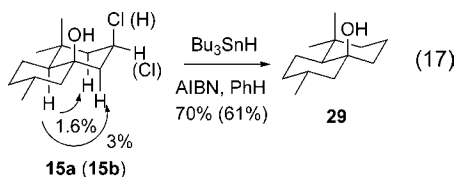


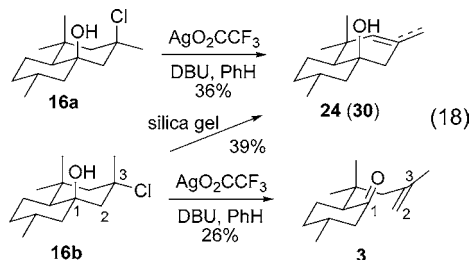
FIGURE 1. Conformations of chlorohydrins **14a** in CDCl_3 solution and **14b** in the solid state.

while a 2.3% NOE served to establish the 1,3-diaxial relationship between the C-3 and C-5 methyl groups of trans chlorohydrin **12b**. The stereochemistry of the minor chlorohydrin **14a** from the cyclization of cis enone **13** was deduced from coupling constants in the ^1H NMR spectrum. The triplet of doublets pattern observed for CHCl (δ 3.74, $J = 11.6, 4.0$ Hz) is only possible in the cis isomer conformation having H-3 axial and C-2 CH_3 equatorial. An X-ray structure was solved for the major chlorohydrin product **14b** (Figure 1).

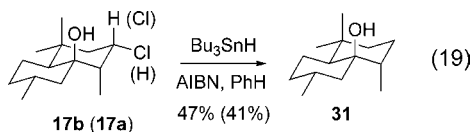
The structure of cis chlorohydrin **15a** was determined by ^1H NMR spin–spin coupling of CHCl (app quint, $J = 3.9$ Hz) and NOE analysis and confirmed by X-ray crystallography. Dechlorination of **15a** and **15b** gave the same tertiary alcohol (**29**), thus verifying the structure of the trans chlorohydrin (eq 17).



The structure of cis chlorohydrin **16a** was confirmed by single-crystal X-ray analysis and that of its trans epimer **16b** was elucidated by chemical correlation (eq 18). Dehydrochlorination of **16a** with silver trifluoroacetate and DBU gave an 18:1 mixture of endo- and exocyclic olefins **24** and **30**, while elimination of **16b** on silica gel furnished olefin **24**. Attempts to dehydrochlorinate chlorohydrin **16b** under the same conditions led to a Grob-type fragmentation, attributable to the antiperiplanar relationship between the C1–C2 and C3–Cl bonds.



An X-ray crystal structure was solved for chlorohydrin **17b**, and reductive dechlorination of **17a** and **17b** gave the same tertiary alcohol **31** (eq 19). The similarity of the ^1H and ^{13}C



NMR spectra of **19** in comparison with those of chlorohydrins **15b** and **17a**, as well as the multiplicity and coupling constants for CHCl (δ 4.08, td, $J = 11.7, 3.9$ Hz) and NOE measurements, served to establish the structure of trans chlorohydrin **19** (Figure

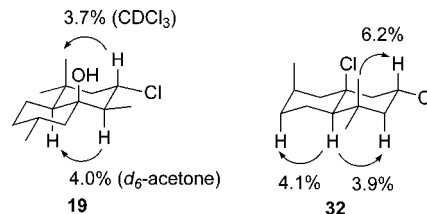


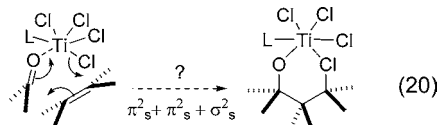
FIGURE 2. Structure determination of chlorohydrin **19** and dichloride **32** by NOE measurements.

2). The structures of cis and trans chlorohydrins **21a** and **21b**, cis and trans bromohydrins **22a** and **22b**, trans bromohydrin **25b**, and trans iodohydrin **23** were proven by single-crystal X-ray analyses. The structure of trans dichloride byproduct **32** was assigned based on NOE measurements and ^1H NMR spin–spin coupling of CHCl (δ 2.26, tt, $J = 11.0, 1.4$ Hz).

The very similar ^1H NMR spectra of cis bromohydrin **25a** and cis chlorohydrin **10a** was the basis for assignment of the same configuration. The ORTEPs of the eleven X-ray crystal structures all show the 6-membered rings in normal chair conformations (see the Supporting Information).

Discussion

The syn-selective halo-Prins cyclizations of δ,ϵ -unsaturated ketones effected by Ti(IV) and B(III) halides are remarkable reactions that have little precedent.^{6a,8a,b,10} This transformation may be considered as a concerted pericyclic process, or as a stepwise C=C addition reaction. Although a suprafacial, 6-electron [$\pi^2_s + \pi^2_s + \sigma^2_s$] cycloaddition (eq 20) is formally allowed, this mechanism for the syn-selective Prins reaction seems inadequate to explain the body of results presented above. The formation of allylated products in the presence of allyltrimethylsilane (eq 12) strongly suggests that an electrophilic intermediate has been trapped. The 40–50:1 initial rate ratios in the methallyl/allyl competition experiment (eqs 9a and 9b) clearly indicate considerable positive charge accumulation at the δ position of the C=C in the transition state. Without discounting the possibility that the pericyclic mechanism may compete with stepwise pathways in some cases, we prefer to rationalize the results in terms of competing syn and anti electrophilic additions.



The trends in syn/anti selectivity, reactivity, and medium effects, and the influence of different Lewis acids can be explained and correlated by the mechanistic scheme in Figure 3. Coordination of TiCl_4 with the carbonyl oxygen of the generic acyclic δ,ϵ -enone shown leads to activated intermediate **A**. This oxocarbenium–titanate complex is one potential branch point in the competing mechanisms on the way to the cis and trans chlorohydrins. Electrophilic attack of the electron-deficient carbonyl carbon on the C=C double bond effects cyclization and generates syn carbocation chloride (or chlorotitanate) ion pair **B**. Collapse of the ion pair onto the proximal carbocation face leads to covalent C–Cl bond formation and generation of the trichlorotitanium adduct **C**, precursor to the cis chlorohydrin

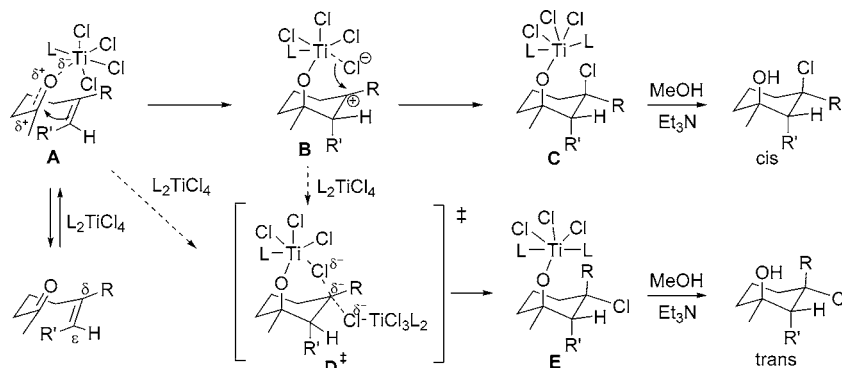


FIGURE 3. Proposed mechanisms for competing syn- and anti-selective chloro-Prins cyclizations of a generic acyclic δ,ϵ -enone with TiCl_4 .

product. Depending on the nature of the metal center, the halide nucleophile in ion pair **B** may interact strongly or weakly with the metal.²⁰

Since a lower concentration of TiCl_4 decreased the proportion of trans chlorohydrin product, we suppose that the anti addition mechanism probably has two molecules of TiCl_4 in the transition state as illustrated in **D[‡]**. Intermolecular nucleophilic attack of TiCl_4 on the opposite face of the syn carbocation–chloride ion pair **B** would proceed with “inversion of configuration” through transition state **D[‡]**. Transfer of a chloride ligand to carbon would produce chlorotitanium adduct **E**, thus completing an anti-addition to the $\text{C}=\text{C}$ double bond of the enone reactant. Alternatively, it seems plausible that the trans chlorohydrin might arise by a concerted antiperiplanar addition of the activated $\text{C}=\text{O}$ and chloride from the second molecule of TiCl_4 across the $\text{C}=\text{C}$, i.e., **A** \rightarrow **D[‡]** \rightarrow **E**. Another slight variation in the anti mechanism would involve a trans ion-pair intermediate similar to **D[‡]**, likely with a TiCl_5^- counterion on the opposite face of the carbocation.

The dispersal of positive charge in transition state **D[‡]** perhaps would decrease the sensitivity of the anti addition mechanism to solvent polarity,²¹ in comparison to that for the transition state leading to ion pair **B**, with its more localized charges. This difference affords a rationale for the decrease in the cis/trans ratios observed in pentane and toluene. The faster rate of methallylpulegone and the small increase in the syn-selectivity with this and related enones ($\text{R} = \text{Me}$) are consistent with more positive charge associated with the **[A \rightarrow B][‡]** transition state, presumably the rate-determining step on the pathway to the cis chlorohydrin.

Similar stereochemical and mechanistic issues arise in the electrophilic 1, 2-additions of hydrogen halides to olefins and epoxides. Syn additions to $\text{C}=\text{C}$ double bonds are frequently observed at low temperatures with tetrasubstituted olefins,^{22,23} and increased HX concentration favors the anti mode of addition. However, in contrast to the tendency toward enhanced anti stereoselectivity of the chloro-Prins cyclizations in the nonpolar hydrocarbon solvents noted above, less polar solvents favor syn addition to olefins.^{22b} The consistently high levels of anti

selectivity of the chloro-Prins reactions with anhydrous HCl (CH_2Cl_2 , -78°C)¹¹ contrast with the trend of syn-selective additions of HCl and HBr to olefins at low temperatures.²² Perhaps a linear alignment of $\text{O}\cdots\text{H}-\text{Cl}$ in a ketone $\cdot\cdot\cdot\text{HCl}$ complex would position the chloride nucleophile relatively far from the carbocation carbon in syn ion pair **B** and, therefore, favor the anti pathway. The observation of syn additions to epoxides bearing conjugating groups^{24,25} is usually explained in terms of syn facial ion pairs, similar to **B**.

The much slower chloro-Prins cyclizations of the cis and trans ϵ -methyl enones (e.g., $\text{R} = \text{H}$, $\text{R}' = \text{Me}$), compared to their unsubstituted counterparts ($\text{R} = \text{R}' = \text{H}$) (see Tables 1 and 2), is attributable to developing steric interactions of the incipient axial (or equatorial) methyl group with the α and α' carbons adjacent to the $\text{C}=\text{O}$ group. Evidently, these steric effects are more severe in the **[A \rightarrow B][‡]** transition state than they are in the **B \rightarrow D[‡] \rightarrow E** pathway, judging from the consistent increases in the proportion of trans chlorohydrin formed.

Lewis acidity, metal geometry, and $\text{M}-\text{X}$ and $\text{C}-\text{O}-\text{M}$ bond lengths and bond angles, as well as the corresponding bond energies, would be expected to influence the stereochemical course of the halo-Prins reactions. Table 4 shows the average bond lengths²⁶ and bond angles of several Lewis acids, taken in part by Schreiber and co-workers from the Cambridge Structural Database.²⁷ Generally, the stronger Lewis acids (TiX_4 and BX_3)²⁸ gave rise to syn addition while weaker Lewis acids lead to anti addition. The $\text{Ti}-\text{X}$ and $\text{Ti}-\text{O}$ bond lengths are similar to those of $\text{Sn}-\text{X}$, $\text{Zr}-\text{Cl}$, and $\text{Sn}-\text{O}$, and all adopt

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(24) See (a) Gorzynski Smith, J. *Synthesis* **1984**, 629–656. (b) Bartok, M.; Lang, K. L. In *The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups, and their Sulfur Analogues*; Patai, S., Ed.; Wiley: Chichester, 1980; Part 2, Suppl. E, pp 609–681. (c) Akhrem, A. A.; Moiseenkov, A. M.; Dobrynin, V. N. *Russ. Chem. Rev.* **1968**, *37*, 448–462 and references therein.

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(27) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 256–272.

(20) An ^1H NMR spectrum of the oxy- TiCl_3 intermediate (CD_2Cl_2 , -78°C) was similar to that of chlorohydrin **15a**, except that the signal for the CHOTiCl_3 proton appeared as a broad singlet instead of a quintet at the same position and a broad 1-H doublet at δ_{H} 2.55 was shifted out of the overlapping peaks at 1.9–2.2 for four ring protons.

(21) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row: New York, 1987; pp 361–367.

(22) (a) Fahey, R. C.; McPherson, C. A. *J. Am. Chem. Soc.* **1971**, *93*, 2445–2453. (b) Becker, K. B.; Grob, C. A. *Synthesis* **1973**, 789–790.

TABLE 4. Average Bond Lengths and Bond Angles for Lewis Acids and Their Complexes

| Lewis acid | M–X bond length ^a (Å) | O–M bond length ^b (Å) | C–O–M angle ^b (deg) |
|-------------------|----------------------------------|----------------------------------|--------------------------------|
| TiCl ₄ | 2.18 | 2.14 ± 0.07 | 125 ± 12 |
| TiBr ₄ | 2.31 | | |
| BCl ₃ | 1.75 | 1.58 ± 0.02 | 115 ± 3 |
| BBr ₃ | 1.87 | | |
| SnCl ₄ | 2.33 | 2.30 ± 0.1 | 127 ± 10 |
| SnBr ₄ | 2.46 | | |
| AlCl ₃ | 2.06 | 1.88 ± 0.09 | 136 ± 4 |
| ZrCl ₄ | 2.32 | | |
| InCl ₃ | 2.46 | | |

^a Reference 26. ^b Reference 27.

octahedral geometry when coordinated to a Lewis base. However, while the more Lewis acidic titanium reagents gave syn addition products, the weaker Lewis acids SnCl₄, SnBr₄, and ZrCl₄ resulted in anti addition. The relatively weaker Lewis acidities of the tin and zirconium halides^{28f} result in slower rates of cyclization and/or ion pair collapse, and thus, the higher order pathway leading to anti addition predominates.

Complexes of AlCl₃, BCl₃, and BBr₃ have pseudotetrahedral geometry and relatively short bond lengths, but they gave opposite stereochemistry in the halo Prins cyclizations. The stronger Lewis acidities of the boron halides compared to those of the corresponding aluminum halides are well documented,^{28f} which together with the smaller C–O–B bond angles of the boron complexes, accounts for this apparent inconsistency. The reaction temperature and reaction times with BCl₃, BBr₃, and SnCl₄ are similar (Table 3), implying comparable Lewis acidity toward the carbonyl substrate. Thus, it is somewhat surprising that boron halides are syn selective while SnCl₄ is anti selective. Presumably, the shorter bond lengths in the BX₃ complexes and ion pairs would place the halide ligands in closer proximity to the syn face of the δ carbon than the Cl ligand would be in the intermediates from SnCl₄. Most of the relative rates for the metal chlorides estimated from reaction times (Table 3) parallel the electropositive character of the metals: TiCl₄ > ZrCl₄ and BCl₃ > AlCl₃ > GaCl₃ > InCl₃.²⁸

Conclusions

The Lewis acid-mediated Prins cyclization of δ,ϵ -unsaturated ketones provides a promising method for stereocontrolled synthesis of cis and trans bromo- and chlorocyclohexanols, and hindered tertiary alcohols readily derived from them. The capability to tolerate steric hindrance is illustrated by the syn cyclization of enone **2** to chlorohydrin **21a** in which hydroxyl, chloro, and two methyl substituents occupy four of the five available axial positions on the trans decalin nucleus. Consistent syn selectivities were observed for cyclizations onto unsubstituted and δ -methyl substituted enones in the presence of TiCl₄, TiBr₄, BCl₃, and BBr₃, while a variety of other Lewis acids were trans selective. The slower cyclizations of enones bearing methyl groups on the terminal carbon gave trans chlorohydrins. The stereochemistry seems to correlate with the Lewis acidity

of the promoter. Syn addition is assumed to occur by formation and subsequent collapse of a metalloxy-halide ion pair. The anti addition process most likely proceeds by a higher order mechanism in which the oxocarbenium ion electrophile and halide nucleophile undergo antiperiplanar bonding on opposite faces of the double bond.

Experimental Section

Representative Halo-Prins Cyclization Procedure: Method A (15a and 15b). A solution of **1** (50 mg, 0.26 mmol) in CH₂Cl₂ (3 mL) was stirred and cooled at –78 °C as 1.0 M TiCl₄ (0.26 mL, 0.26 mmol) in CH₂Cl₂ was added over 30 s. The resulting yellow solution was stirred for 1 min at –78 °C after which a solution of Et₃N (175 μ L, 1.3 mmol) and MeOH (60 μ L, 1.3 mmol) in CH₂Cl₂ (2 mL) was slowly added. The suspension was stirred for 10 min, warmed to room temp, stirred for an additional 10 min, and diluted in Et₂O (25 mL). The organic phase was washed with 10% aq HCl (2 \times 5 mL), satd NaHCO₃ (5 mL), and satd NaCl (5 mL), dried (MgSO₄), and concentrated under reduced pressure to afford 57 mg of a yellow oil. GC and ¹H NMR analyses established the yield (70%) and cis/trans ratio of 10:1. **15a:** ¹H NMR (500 MHz, CDCl₃) δ 0.81 (t, 1H, *J* = 12.5 Hz), 0.85 (d, 3H, *J* = 6.4 Hz), 0.88 (m, 1H), 0.91 (s, 3H), 0.96 (dd, 1H, *J* = 10.1, 5.6 Hz), 1.19 (s, 3H), 1.57–1.62 (m, 2H), 1.66 (ddd, 1H, *J* = 13.1, 3.6, 2.4 Hz), 1.76 (dd, 1H, *J* = 15.0, 4.10 Hz), 1.78–1.87 (m, 2H), 1.87 (dd, 1H, *J* = 15.3, 4.8 Hz), 2.06 (ddd, 1H, *J* = 14.8, 3.6, 2.3 Hz), 2.15 (ddd, 1H, *J* = 15.2, 3.0, 2.4 Hz), 2.41 (br s, 1H, exch. D₂O), 4.53 (app. quint, 1H, *J* = 3.9 Hz); ¹³C NMR (126 MHz, CDCl₃) δ 22.0, 22.5, 24.4, 27.4, 32.9, 33.3, 36.0, 46.2, 47.4, 50.8, 50.9, 57.3, 72.0; IR (neat) ν_{\max} 3592, 3479, 2947, 2867, 1455, 1370, 1265, 1167, 1009 cm⁻¹; MS (EI, 70 eV) *m/z* (rel intensity %) 230 (13), 215 (88), 195 (30), 177 (25), 161 (27), 153 (100), 145 (20), 112 (62), 95 (21), 83 (45). Recrystallization from hexane gave an analytical sample: mp 63–65 °C; [α]_D²⁵ = +2.7 (*c* = 1.0, CHCl₃). **15b:** ¹H NMR (500 MHz, CDCl₃) δ 0.88 (d, 3H, *J* = 6.6), 0.91 (s, 3H), 0.95 (dd, 1H, *J* = 12.6, 3.2 Hz), 0.98 (s, 3H), 1.03 (t, 1H, *J* = 13.1 Hz), 1.12 (s, 1H, exch. D₂O), 1.31 (qd, 1H, *J* = 13.0, 3.5 Hz), 1.52 (ddd, 1H, *J* = 13.5, 3.9, 2.4 Hz), 1.52 (t, 1H, *J* = 12.4 Hz), 1.57 (t, 1H, *J* = 12.4 Hz), 1.62 (dq, 1H, *J* = 13.5, 3.4 Hz), 1.65–1.74 (m, 1H), 1.79 (app d quint, 1H, *J* = 12.9, 3.3 Hz), 1.99 (ddd, 1H, *J* = 12.8, 3.9, 2.5 Hz), 2.12 (ddd, 1H, *J* = 12.9, 4.0, 2.5 Hz), 4.38 (tt, 1H, *J* = 12.1, 4.0); ¹³C NMR (126 MHz, CDCl₃) δ 21.4, 22.0, 22.1, 27.6, 31.7, 35.3, 35.7, 50.0, 50.5, 51.0, 52.4, 54.6, 73.8; IR (neat) ν_{\max} 3567, 3483, 2948, 2869, 1456, 1368, 1240, 1028, 775; MS (EI, 70 eV) *m/z* (rel intensity) 230 (24), 215 (100), 195 (16), 177 (13), 161 (27), 153 (36), 137 (26), 112 (34), 81 (48). Recrystallization from hexane gave an analytical sample: mp 61–62 °C; [α]_D²⁵ = +5.2 (*c* = 1.0, CHCl₃).

Method B (22a and 22b). A slurry of finely crushed TiBr₄ (0.58 g, 1.54 mmol) in CH₂Cl₂ (20 mL) was vigorously stirred at –78 °C as a solution of **1** (0.30 g, 1.54 mmol) in CH₂Cl₂ (3 mL) was slowly added. After the solution was stirred at –78 °C for 15 min, buffered methanolysis at 0 °C with Et₃N (1.1 mL, 7.7 mmol) and MeOH (0.31 mL, 7.7 mmol) in CH₂Cl₂ (3 mL) and ether extraction as described above in method A afforded 0.41 g of a yellow oil. GC and ¹H NMR analyses on the crude product established the yield (76%) and cis/trans ratio of 15:1. Purification by flash chromatography on silica gel (98:2 hexane/Et₂O) of the yellow oil afforded 0.28 g (65%) of cis bromohydrin **22a** as a colorless oil that crystallized upon standing and 0.029 g (7%) of trans bromohydrin **22b** as a colorless oil that crystallized at 0 °C. **22a:** ¹H NMR (500 MHz, CDCl₃) δ 0.83 (app. q, 2H, *J* = 12.4 Hz), 0.85 (d, 3H, *J* = 6.4 Hz), 0.90 (s, 3H), 0.95 (app. q, 1H, *J* = 4.7 Hz), 1.19 (s, 3H), 1.56 (qd, 1H, *J* = 13.1, 3.2 Hz), 1.59 (dd, 1H, *J* = 6.4, 3.4 Hz), 1.65 (dt, 1H, *J* = 13.3, 2.4 Hz), 1.79 (dm, 2H, *J* = 11.0 Hz), 1.86 (dd, 1H, *J* = 15.0, 4.3 Hz), 2.01 (dd, 1H, *J* = 15.4, 5.2 Hz), 2.17 (ddd, 1H, *J* = 15.0, 4.7, 1.7 Hz), 2.21 (s, 1H), 2.25

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(ddd, 1H, $J = 15.4, 3.9, 1.7$ Hz), 4.57 (quint, 1H, $J = 4.5$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 21.9, 22.2, 24.3, 27.2, 32.7, 33.2, 33.6, 47.2, 47.7, 47.8, 49.8, 50.9, 72.2; IR (neat) ν_{max} 3573, 2948, 2867, 1618, 1455, 1368 cm^{-1} ; MS (EI, 70 eV) m/z (rel intensity) 276 (1), 274 (1), 196 (16), 195 (100), 95 (17), 83 (78), 81 (16), 69 (27), 55 (47); HRMS (EI, 70 eV) m/z calcd for $\text{C}_{13}\text{H}_{23}\text{BrO}$ M^+ 274.0932, found 274.0928; mp 54–57 °C; $[\alpha]_{\text{D}}^{24} = +10.3$ ($c = 4.8$, CHCl_3). **22b**: ^1H NMR (500 MHz, CDCl_3) δ 0.87 (d, 3H, $J = 6.4$ Hz), 0.90 (s, 3H), 0.96 (dd, 1H, $J = 8.5, 3.2$ Hz), 0.98 (s, 3H), 1.03 (t, 1H, $J = 13.1$), 1.30 (qd, 1H, $J = 13.1, 3.6$ Hz), 1.50 (dq, 1H, $J = 13.5, 1.9$ Hz), 1.60 (dq, 1H, $J = 13.5, 3.4$ Hz), 1.60 (s, 1H), 1.70 (m, 2H), 1.71 (t, 1H, $J = 12.6$ Hz), 1.75 (t, 1H, $J = 22.3, 12.6$ Hz), 1.79 (m, 1H), 2.11 (dq, 1H, $J = 13.1, 2.0$ Hz), 2.23 (dq, 1H, $J = 13.1, 2.0$ Hz), 4.51 (tt, 1H, $J = 12.4, 4.1$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 21.5, 21.8, 22.1, 27.7, 31.7, 35.3, 36.6, 47.1, 49.9, 50.4, 52.0, 53.4, 74.3; IR (neat) ν_{max} 3469, 2949, 2925, 2868, 1654, 1455 cm^{-1} ; MS (EI, 70 eV) m/z (rel intensity) 276 (3), 274 (3), 196 (16), 195 (100), 177 (53), 112 (31), 95 (18), 83 (82), 69 (27), 55 (49); mp 63–69 °C; $[\alpha]_{\text{D}}^{24} = +7.9$ ($c = 3.4$, CHCl_3).

Representative Dehalogenation Procedure (29). A solution of trans chlorohydrin **15b** (150 mg, 0.65 mmol), Bu_3SnH (350 μL , 1.3 mmol), and AIBN (21 mg, 0.13 mmol) in degassed PhH (4 mL) was heated at reflux under N_2 for 3 h, cooled to room temp, and diluted with Et_2O (10 mL) and satd KF (5 mL). The organic layer was washed with satd KF (2×5 mL), dried (MgSO_4), and

concentrated under reduced pressure to give 258 mg of white residue. Purification by flash chromatography on silica gel (2:98 Et_2O /hexane) gave 78 mg (61%) of **29** as a colorless oil: ^1H NMR (500 MHz, CDCl_3) δ 0.85 (s, 3H), 0.86 (d, 3H, $J = 6.6$ Hz), 0.86–0.96 (m, 3H), 0.94 (s, 3H), 1.08 (s, 1H, exch. D_2O), 1.19 (td, 1H, $J = 13.5, 3.6$ Hz), 1.25 (td, 1H, $J = 13.5, 4.0$ Hz), 1.34 (qd, 1H, $J = 13.1, 3.4$ Hz), 1.37–1.45 (m, 2H), 1.48 (ddd, 1H, $J = 13.5, 3.6, 2.4$ Hz), 1.54 (dq, 1H, $J = 13.5, 2.8$ Hz), 1.60 (dq, 1H, $J = 13.3, 3.3$ Hz), 1.68–1.84 (m, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 18.1, 21.5, 21.8, 22.3, 27.9, 32.1, 32.8, 35.7, 40.7, 42.2, 50.5, 51.5, 71.7; IR (neat) ν_{max} 3482, 2945, 2868, 2845, 1454, 1365, 1184, 945, 926 cm^{-1} ; MS (EI, 70 eV) m/z (rel intensity) 196 (25), 181 (100), 163 (12), 153 (35), 135 (4), 126 (8), 111 (20). Kugelrohr distillation at 70–75 °C (0.30 Torr) gave an analytical sample. Anal. Calcd for $\text{C}_{13}\text{H}_{24}\text{O}$ (196.32): C, 79.53; H, 12.32. Found: C, 79.57; H, 12.42.

Acknowledgment. We thank the Petroleum Research Fund (Am. Chem. 38885AC1) and the National Institutes of Health (GM 13952) for financial support.

Supporting Information Available: Complete experimental details, characterization of products, ^1H NMR spectra, and X-ray crystallographic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO052142N