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The reaction of β,γ−epoxy alcohols with titanium(III) reagents. A proposed role for intramolecular hydrogen bonding

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ABSTRACT

β,γ-Epoxy alcohols are unique substrates for ring-opening reactions with titanium(III) reagents. The site selectivity of the initial radical-forming step as well as the nature and selectivity of reactions of the resultant carbon-centered radicals are often reversed from those observed for non-hydroxyl-containing epoxides. In this Report we critically review previous mechanistic proposals regarding these effects and propose an alternative explanation, which implicates intramolecular hydrogen bonding as a key control element.

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Contents

1. Introduction 2
2. Reaction of non-hydroxyl-containing epoxides with Cp_2TiCl 2
3. Reaction of β,γ−epoxy alcohols with Cp_2TiCl 2
   3.1. Regioselectivity of epoxide ring-opening 2
   3.2. Deoxygenation versus dehydroxylation 3
   3.3. Stereoselectivity of C−C bond formation 4
4. Previous mechanistic proposals 6
   4.1. Titanium(III) alkoxide mechanism 6
   4.2. The 1,3-dioxatitanacycle mechanism 7
5. A possible role for hydrogen bonding 8
   5.1. Dehydroxylation as a group transfer reaction 9
   5.2. Additional applications to stereoselective reactions 10
6. Site selectivity in epoxide ring opening 12
   6.1. Site selectivity in electronically biased epoxides 12
   6.2. Electronically unbiased epoxides 13
   6.3. Reversibility of epoxide ring opening 14
   6.4. Regioselectivity in ring opening of β,γ-Epoxy alcohols 16
7. Conclusions 16
   Acknowledgement 17
   References 17

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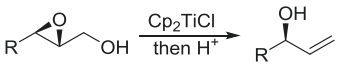
1. Introduction

Since its introduction in 1988 [1], the ring-opening reaction of epoxides with titanocene (III) monochloride (Cp_2TiCl) [2] has been widely embraced by synthetic organic chemists [3–5]. To date, this family of reactions has been utilized in more than 160 syntheses of natural products and advanced intermediates [6]. Contributing to this success have been a series of groundbreaking discoveries subsequent to the initial reports. These include development of catalytic [7,8] and asymmetric catalytic [9] versions of the original stoichiometric reaction, identification of β-scission of hydrogen as an important reaction path for tertiary radicals [10,11], and the remarkable activation of water as a hydrogen atom donor when bound to titanocene monochloride [12].

It was soon recognized that β,γ−epoxy alcohols are unique substrates for titanium (III) chemistry [13a,14]. Such reactions are not only mechanistically fascinating, but also synthetically invaluable. Optically enriched β,γ−epoxy alcohols are readily prepared using the Sharpless epoxidation, and the dehydroxylation of "Sharpless epoxides" with Cp_2TiCl has emerged as the most efficient route for the synthesis of enantiopure terminal allylic alcohols (Eq. (1)). This single application has been used in the synthesis of more than a dozen different natural products.



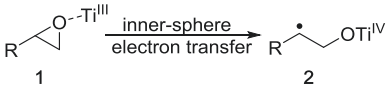
(1)

The optical purity of the allylic alcohol product in Eq. (1) is identical to that of the epoxy alcohol starting material, and e. e's in the range 98–99% have been reported [15,16]. Several applications of Eq. (1) in organic synthesis are summarized in Table 1.

This review has three principal goals. (1) to summarize the unusual/anomalous features of the reactions of Cp_2TiCl with epoxides bearing an adjacent hydroxyl group, (2) to evaluate mechanistic proposals that have been put forward to explain such results, and (3) to propose an alternative mechanism in which hydrogen bonding controls the outcome, and especially the stereoselectivity, of these reactions. To provide a context for this discussion, we will also review the reaction of Cp_2TiCl with typical (non-hydroxyl-containing) epoxides. Several reviews covering synthetic applications of this reaction have appeared [3–5]; however, a single review on the mechanism of these reactions focuses exclusively on the epoxide opening step [28a].

2. Reaction of non-hydroxyl-containing epoxides with Cp_2TiCl

When used in organic synthesis, Cp_2TiCl is usually generated in situ by reduction of Cp_2TiCl_2 with zinc or manganese metal powder [2]. A typical epoxide can bind to titanium as shown in structure **1** in Eq. (2). Homolysis of one epoxide C–O bond proceeds by inner-sphere electron transfer [28] and results in formation of a β-titanoxy radical, **2**. For a terminal epoxide exemplified by **1**, ring-opening at the secondary carbon atom C-2 is favored by both steric and electronic factors.

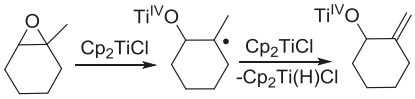


1 2

(2)

The resulting β-titanoxy radicals **2** can undergo a variety of subsequent reactions, depending on what additives are present, as shown in Scheme 1 [14]. In the presence of a hydrogen atom donor Q–H (for example, 1,4-cyclohexadiene or *tert*-butyl thiol) these radicals react by hydrogen atom transfer. The product, after hydrolysis of the resulting titanium alkoxide **3**, is the corresponding alcohol. β-Titanoxy radicals can also add to activated alkenes, exemplified by methyl acrylate in Scheme 1. In this case, the final product is hydroxy ester **4.** In the absence of additives, the β-titanoxy radical can be trapped by a second equivalent of Cp_2TiCl to afford an organotitanium intermediate **5a**, which rapidly undergoes deoxygenation to afford the alkene **5b**.

In the β-titanoxy radical **2** the radical center resides on a secondary carbon atom and therefore the titanium atom in organotitanium intermediate **5a** is bound to a 2° carbon atom. When C–O bond homolysis instead results in the formation of a tertiary radical (Eq. (3)), the radical center is too sterically encumbered to form an organometallic intermediate. Under such circumstances, β-scission of a hydrogen atom occurs. This process has been described as a "mixed disproportionation" between a carbon-centered radical such as **6** and the titanium-centered radical Cp_2TiCl [11,29].



6

(3)

Finally, epoxides containing a suitably positioned unsaturation can undergo intramolecular addition reactions as exemplified for the case of 6,7-epoxyhept-1-ene in Scheme 2. The β-titanoxy radical **7** undergoes rapid 5-hexenyl radical cyclization to afford the primary radical **8**, which is trapped by a second equivalent of Cp_2TiCl to afford the organotitanium complex **9**. Hydrolysis affords the alcohol **10** as a mixture of diastereomers. In the particular case of 6,7-epoxyhept-1-ene, the product **10** is formed as a 2:1 mixture of the *cis* and *trans* diastereomers (70% combined yield) [14].

3. Reaction of β,γ−epoxy alcohols with Cp_2TiCl

The reactions of β,γ−epoxy alcohols with Cp_2TiCl differ significantly from those with non-functionalized epoxides. Essentially every aspect of such reactions is impacted by the presence of the OH group: the regioselectivity of epoxide ring-opening, the nature of the deoxygenation pathway, as well as the stereoselectivity of subsequent inter- and intramolecular addition reactions. In this section we will examine each of these effects.

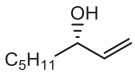
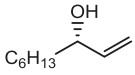
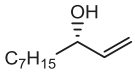
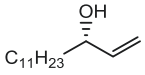
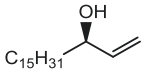
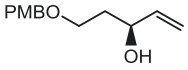
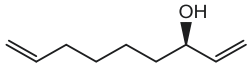
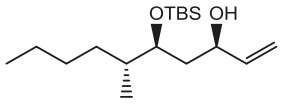
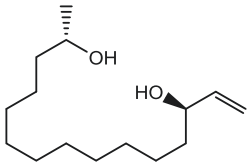
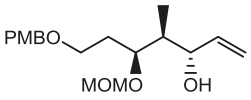
3.1. Regioselectivity of epoxide ring-opening

Treatment of trimethylsilyl-protected epoxy alcohol **11a** with Cp_2TiCl in the presence of *tert*-butyl thiol affords **12**, which results from predominant ring-opening at C-3 as shown in Scheme 3 (10:1 selectivity). After desilylation, the 1,2-diol is obtained in 61% yield. This regioselectivity is consistent with destabilization of the corresponding radical center at C-2 by the electron-withdrawing trimethylsiloxy group. C-3 cleavage was also observed when the protecting group is changed to acetate or toluenesulfonate [14].

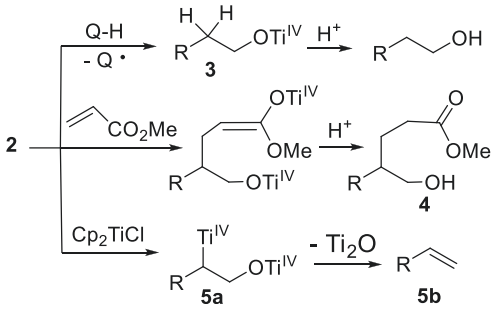
However, when the reaction is repeated with substrate **11b** containing an unprotected OH group, C–O bond cleavage occurs at C-2. Trapping with *tert*-butyl thiol now affords principally the 1,3-diol product **13** (17:1 selectivity) [14].

The preference for C–O bond cleavage at C-2 versus C-3 for terminal β,γ-epoxy alcohols is significant (C-2:C-3 > 10:1). However, other structural features in an epoxide substrate may override this site selectivity (Scheme 4). For example, cleavage of the C-3 bond in 3-phenylglycidol results in formation of a stabilized benzylic radical **14** and C-3 cleavage is favored [14]. Similarly, preferential cleavage of the C-3 C–O bond in *cis*-verbenol oxide affords the tertiary radical **15** which subsequently undergoes cyclobutene ring fragmentation to radical **16** [30].

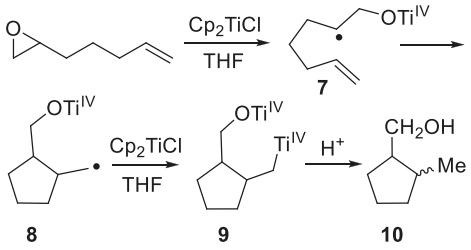
Table 1
Applications of the reaction in Eq. (1) in synthesis of natural products.

Synthetic Target	Allylic Alcohol	Yield (%)
trans-cognaclactone [17]		60[a]
8-aza-prostaglandin E1 [16]		84
(+)-*cis*-lauthisan [18]		64
(+)-awajanomycin [19]		85
Diacrisia obliqua pheromone [15]		90
α-galoctosylceramide *c*-glycoside [20]		76[b]
rhizoxin [21]		62 (*S*)
dendrodolide K [22]		84 (*S*)
amphidinol 3[23]		85 (*R*)
(+)-muconin [24]		88
caylobolide A [25]		80
(+)-aspicilin [26]		69
lyngbyaloside B [27]		85

[a] Combined yield for 2 steps, Sharpless epoxidation followed by dehydroxylation.
[b] Combined yield for two steps, dehydroxylation followed by benzoylation.



Scheme 1. Reaction pathways for radical **2** generated in Eq. (2).

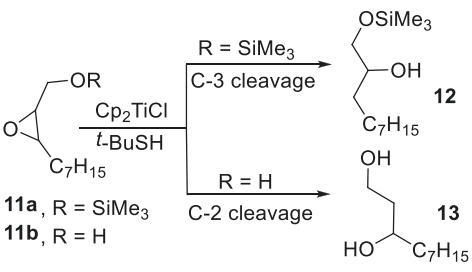


Scheme 2. Intramolecular addition of radical **7** generated from 6,7-epoxyhept-1-ene.

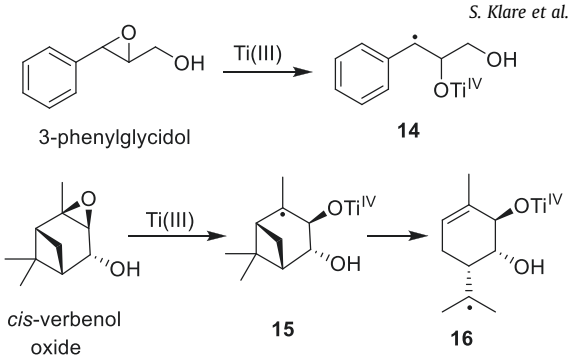
3.2. Deoxygenation versus dehydroxylation

When alcohol **17** is treated with Cp_2TiCl in THF the observed product is allylic alcohol **18** which results from loss of the hydroxyl group (Scheme 5) [31].

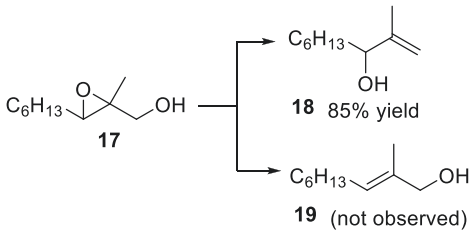
It is proposed that allylic alcohol **18** results from reaction of intermediate radical **20** with a second equivalent of titanium (III). In principle, radical **20** could react with Ti(III) with cleavage of the



Scheme 3. Effect of TMS protection on ring-opening of epoxide **11**.

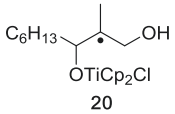


Scheme 4. C-3 opening of β,γ epoxy alcohols in response to other structural features.



Scheme 5. Exclusive dehydroxylation of epoxy alcohol **17**.

C—O bond at C-3 to afford deoxygenation product **19**. However, this product is not observed. (For convenience we will distinguish between the pathway leading to **18** and that leading to **19** with the terms "dehydroxylation" versus "deoxygenation", although both are formally deoxygenation reactions.)



Several additional dehydroxylation reactions are shown in Table 2. Methyl substituted epoxy alcohol **21** (which will give rise to a tertiary β-titanoxy intermediate) and the vinylogous epoxy alcohol **22** both undergo exclusive dehydroxylation upon treatment with Cp_2TiCl. Moreover, epoxy alcohol **23** wherein the hydroxyl group is bound to a secondary carbon atom likewise reacts with Cp_2TiCl via dehydroxylation rather than deoxygenation.

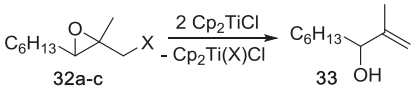
The substrates **21**, **22**, and **23** are all structurally biased in favor of dehydroxylation. The β-titanoxy radicals from **21** and **22** contain hydroxyl groups bound to a primary carbon atom; such a hydroxyl group would be sterically accessible to the second equivalent of Cp_2TiCl required for dehydroxylation. The β-titanoxy radical derived from **23** contains a hydroxyl group bound to a secondary carbon atom and would consequently be less sterically accessible. Balanced against this, the benzylic hydroxyl C—O bond will be weakened by the presence of the phenyl group. Cleavage of the C—O bond results in formation of a conjugated (styrenyl) double bond and the activation energy of the process should reflect this.

In contrast, substrate **24** lacks any such bias and other processes now become competitive with dehydroxylation. In this case, the dehydroxylation product **25** is isolated in only 34% yield. In addition, **27**, the product from β-scission of hydrogen is isolated in 23% yield while the nominal deoxygenation product **26** is obtained in 27% yield.

The hydroxyl group in the β-titanoxy radical derived from substrate **28** is bound to a tertiary carbon atom, further limiting access to the second equivalent of Cp_2TiCl. In this case, the isolated products are **29** derived from dehydroxylation (27%), as well as **31**, the product of β-hydrogen scission (4%), and the apparent deoxygenation product **30** (53%).

The observation that the amount of deoxygenation increases with steric bulk along the substrate series **21** < **24** < **28** is surprising. As noted in Scheme 1 deoxygenation requires formation of an organotitanium intermediate. Yet in unfunctionalized epoxides it is found that tertiary β-titanoxy radicals cannot undergo the necessary Ti—C bond forming step; instead, β-scission of hydrogen is observed as in Eq. (3). Why should the greater steric hindrance in substrate **28** actually promote deoxygenation?

The dehydroxylation in Scheme 5 can be regarded as the β-scission of a hydroxyl group from radical **20**. Other groups have been shown to undergo such β-scission reactions, notably the formyl and cyano groups [31,33]. For example, substrates **32a-c** all afford allylic alcohol **33** upon treatment with Cp_2TiCl followed by hydrolytic workup (Eq. (4)).



Substrate	Yield after H_3O^+
32a X = OH	85%
32b X = OCHO	83%
32c X = CN	65%

(4)

However, evidence has been reported that β-scission of a hydroxyl group is significantly more rapid than loss of either the formyl or cyano group [34]. The reactions in Scheme 6 utilize cyclobutane fragmentation as a "radical clock" reaction. When X = OH, the exclusive product is the exocyclic alcohol **35**, which is obtained in 90% yield. In contrast, when the leaving group is formate or cyanide, **35** is the minor product and the major product **36** arises from cyclobutane ring-opening and subsequent loss of a β-hydrogen atom [34].

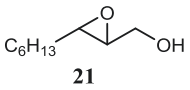
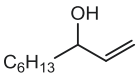
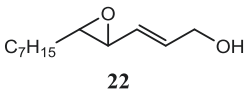
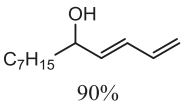
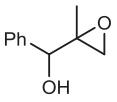
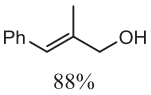
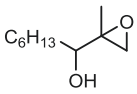
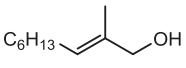
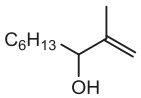
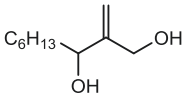
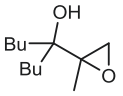
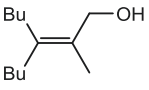
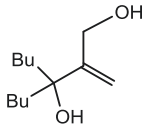
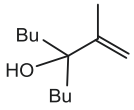
Initial C—O bond homolysis of **34** will give rise to a β-titanoxy radical **37** (Scheme 7). When X = OH, rapid abstraction of hydroxyl radical by a second equivalent of Cp_2TiCl results in formation of allylic alcohol **35**. However, abstraction of a cyanide or formyl radical appear to be considerably slower processes so that competitive cyclobutane ring fragmentation occurs resulting in formation of radical **38**. β-Hydrogen scission from radical **38** affords the isopropenyl product **36**.

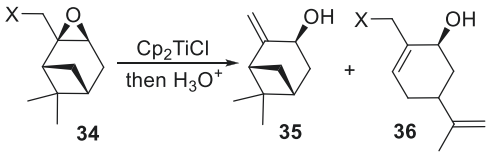
It is worthwhile noting that the bond dissociation enthalpy for the C—O bond of closed shell molecules such as alcohols is quite high (92—95 kcal/mol). However, as explained in the authoritative review of Blanksby and Ellison [35], the presence of a radical center β to a potential leaving group greatly diminishes its bond dissociation enthalpy. We have recently demonstrated that even loss of a hydrogen atom to Cp_2TiCl to form unstable $Cp_2Ti(H)Cl$ can occur when that hydrogen atom is β to a radical center [29].

3.3. Stereoselectivity of C—C bond formation

The presence of the hydroxyl group in β,γ—epoxy alcohols also impacts the stereoselectivity of radical addition reactions following Ti(III)-mediated epoxide ring opening. This type of effect has most frequently been observed for intramolecular addition reactions, as illustrated in Scheme 8. When a free hydroxyl group is present in substrate **39a**, the resulting configuration is mainly *cis* and the principal product after peracetylation is **40**. When the alcohol is protected as an acetate in substrate **39b**, the 1,2-stereoselectivity is reversed and the *trans* product **41** is formed predominantly [36].

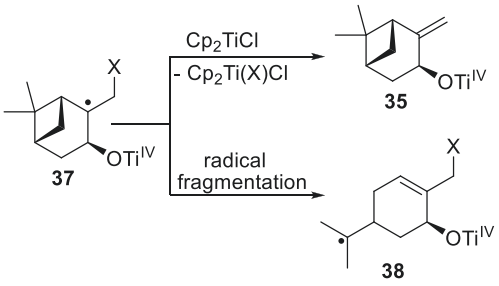
Table 2
Dehydroxylation of β,γ−epoxy alcohols.

Entry	Epoxy alcohol	Products
1[13]	 **21**	 82%
2[32]	 **22**	 90%
3[31]	 **23**	 88%
4[31]	 **24**	 **25** 34%  **26** 27%  **27** 23%
5[31]	 **28**	 **29** 27%  **30** 4%  **31** 53%



X	Yield **35** (%)	Yield **36** (%)
CN	20	47
OCHO	25	45
OH	90	0

Scheme 6. Effect of leaving group X on products from epoxide **34**.

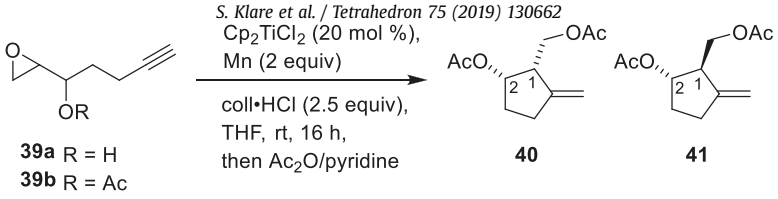


Scheme 7. Reaction pathways for β-titanoxy radical **37**.

Additional examples of stereochemical control in the cyclization of unsaturated β,γ−epoxy alcohols will be discussed later in this review.

Highly diastereoselective intermolecular addition has also been observed following the ring opening of a β,γ−epoxy alcohol with Cp_2TiCl. In Scheme 9, a chiral quaternary center is formed with complete stereochemical control [37]. (In this example, the product ester is reduced with LAH prior to analysis to circumvent complications due to lactone formation.) Higher diastereoselectivity is observed for this type of intermolecular addition when the substrate contains a trisubstituted rather than a disubstituted epoxide functionality [38]. Also, diastereoselectivity is higher for *syn* epoxy alcohols like **42** as compared with *anti* epoxy alcohols [37].

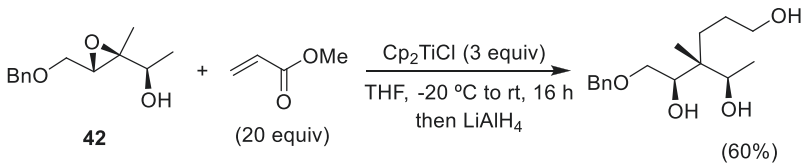
Highly stereoselective reduction of β,γ−epoxy alcohols has likewise been observed using 1,4-cyclohexadiene as a hydrogen atom transfer reagent. As shown in Scheme 10, *syn* epoxy alcohol **43** affords diol **44** upon treatment with Cp_2TiCl (5 equiv) in the presence of 1,4-CHD (5 equiv). Under the same conditions, the *anti* epoxy alcohol **45** gives exclusively diol **46** [39].



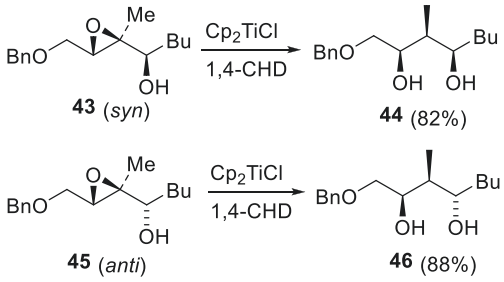
R	Yield **40+41** (%)	**40/41**
H	53	85:15
OAc	57	17:83

(ca. 35% deoxygenation product also formed in each case)

Scheme 8. Effect of protecting group on cyclization stereochemistry of epoxide **39**.



Scheme 9. Stereochemistry of intermolecular addition to epoxide **42**.



Scheme 10. Effect of *syn* vs *anti* configuration in reduction of epoxy alcohols **43** and **45**.

4. Previous mechanistic proposals

4.1. Titanium(III) alkoxide mechanism

The earliest attempt to provide a mechanistic rationale for the reaction Cp_2TiCl with β,γ-epoxy alcohols [13] was proposed by Yadav and coworkers in 1990 and is shown in Scheme 11. This work was published prior to the discovery of the stereoselective reactions in Schemes 8–10 and was intended to explain the observation of rapid dehydroxylation of β,γ−epoxy alcohols. This model hypothesizes that the first equivalent of Cp_2TiCl reacts with the hydroxyl functionality of the epoxy alcohol to produce a titanium (III) alkoxide and an equivalent of HCl. A second equivalent of Cp_2TiCl then induces the homolysis of the C–O bond at C-2. Finally, the carbon-centered radical undergoes β-elimination of $Cp_2Ti=O$ via a 4-membered ring ("Wittig-like") transition state **47**. A metallaoxetane intermediate had earlier been proposed for the deoxygenation of simple alkene oxides by low-valent titanium [40].

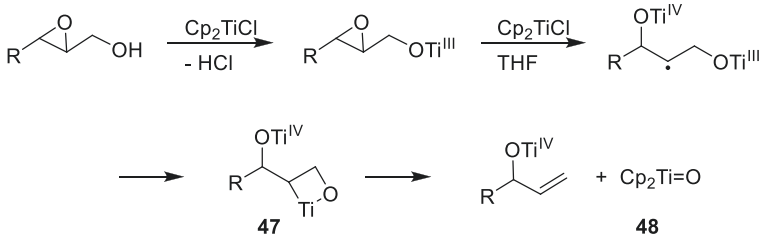
Mononuclear oxo complex **48** is not expected to be stable due to competition for d orbitals of appropriate symmetry to support the Ti=O multiple bond [41]. However, one can argue that it could exist as a short-lived intermediate that subsequently dimerizes. A greater concern is that Scheme 11 would require that the equilibrium in Eq. (5) lies far to the right, when ROH is a β,γ−epoxy alcohol. Spectroscopic studies of Cp_2TiCl in the presence of excess methanol do not support formation of a titanium (III) methoxide [42]. In fact, methanol has been used successfully as a co-solvent for the reaction of Cp_2TiCl with epoxides [43]. Titanocene (III) alkoxides including monomeric Cp_2TiO^tBu are known [44], but are expected to undergo protonolysis upon treatment with strong acids including HCl, as is observed with other early transition metal alkoxides [45].

$$Cp_2TiCl + ROH \rightleftharpoons Cp_2Ti(OR) + HCl \quad (5)$$

A case could be made that oxotitanium complex **48** (or its dimer) serves as an HCl scavenger in Scheme 11. Removal of HCl according to Eq. (6) would presumably shift the equilibrium in Eq. (5) to the right. A problem with this line of reasoning is that the formation of titanium (III) alkoxide must be fast relative to epoxide ring-opening (in order for all of the substrate to be present as titanium (III) alkoxide prior to attack by a second equivalent of Cp_2TiCl). Consequently, titanium (III) alkoxide must form before sufficient $Cp_2Ti=O$ is available to neutralize all of the HCl.

$$Cp_2Ti{=}O + HCl \rightleftharpoons Cp_2Ti(OH)Cl \quad (6)$$

It might also be argued that the equilibrium Eq. (5) could be



Scheme 11. Titanium(III) alkoxide mechanism for dehydroxylation of β,γ-epoxy alcohols.

shifted to the right when ROH is a β,γ−epoxy alcohol because of chelation with the epoxide oxygen atom. However, dehydroxylation occurs even in cases where chelation would be unlikely. For example, both the *cis* and *trans* isomers of epoxy alcohol **49** undergo facile dehydroxylation to afford **50** (along with smaller amounts of **51**) despite the fact that the epoxide oxygen atom in the *trans* isomer is remote from the hydroxyl group (Scheme 12) [46].

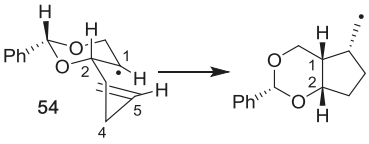
Moreover, the requirement that 1 M equivalent of Cp_2TiCl is consumed in formation of a titanium (III) alkoxide prior to epoxide ring-opening is inconsistent with the fact that these reactions can be run under catalytic conditions using a substoichiometric amount of titanium as exemplified by Scheme 8.

4.2. The 1,3-dioxatitanacycle mechanism

The titanium (III) alkoxide mechanism does not explain the diastereoselectivity observed in reactions such as Schemes 8–10. The alternative dioxatitanacycle mechanism was initially proposed by Chakraborty and Dutta to explain the high stereoselectivity observed in the reduction of β,γ−epoxy alcohols with Cp_2TiCl and 1,4-cyclohexadiene including those in Scheme 10 [39,47]. It was subsequently extended to both intramolecular [48] and intermolecular [49] C–C bond forming reactions as well as to dehydroxylation reactions [31].

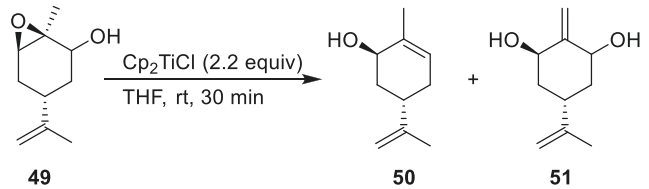
The high stereoselectivity in Schemes 8–10 suggests the intervention of a rigid intermediate involving some type of cyclic structure during radical addition. When a radical center residing on a ring participates in a 5-hexenyl cyclization, the result is high selectivity for *cis*-1,2 substitution. A compelling demonstration of this principle is seen in a non-titanium based cyclization where the radicals are generated via tributyltin hydride reduction (Scheme 13). For cyclization of radical **52**, which contains only benzyloxy substituents, mainly 1,2-*trans* stereoselectivity is observed. However, "tying back" two of the oxygen atoms as an acetal in **53** (so that the radical center resides on a six-membered ring) affords exclusive *cis*-1,2 stereoselectivity [50].

The tethers in both substrates **52** and **53** are highly functionalized; however, the same effect is observed when the tether is unsubstituted. In the generalized case, the stereochemical outcome may be attributed to rigidified structure **54**, where the radical center resides on a chair cyclohexane type structure (Eq. (7)) [50,51].



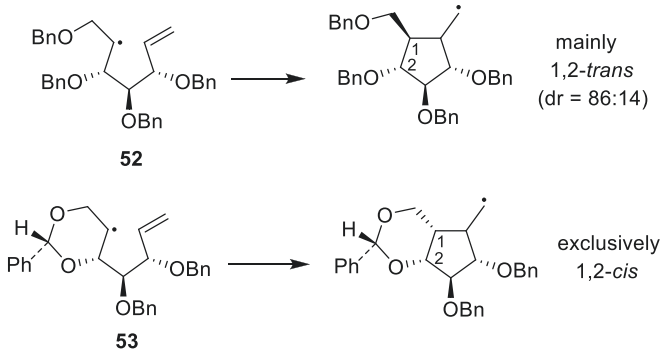
(7)

In a similar fashion, it has been suggested that formation of a 1,3-dioxatitanacycle ring provides a rigid intermediate which



OH Orientation	Yield **50+51** (%)	**50/51**
trans	91	88:12
cis	80	94:6

Scheme 12. Effect of hydroxyl group configuration on dehydroxylation of epoxide **49**.

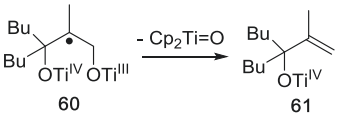


Scheme 13. Effect of "tying back" substituents on stereochemistry of radical cyclization.

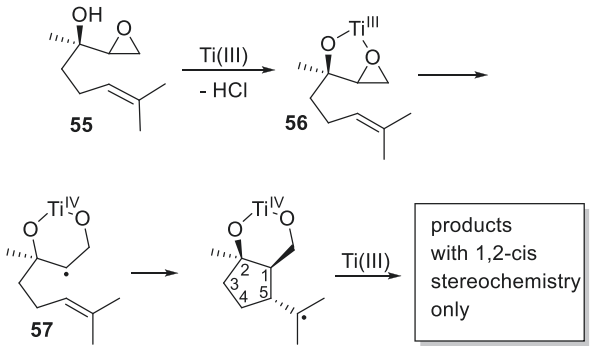
improves stereoselectivity of the reactions of β,γ−epoxy alcohols with Cp_2TiCl [39]. For example, this mechanism has been used to explain the stereochemical course of the cyclization of linalool-derived epoxide **55** (Scheme 14). As in Scheme 11, this proposal again requires the formation of a titanium (III) alkoxide (**56**); however, it differs from Scheme 11 in that the titanium (III) alkoxide itself (rather than a second equivalent of Cp_2TiCl) reacts with the epoxide. The resulting dioxatitanacyclic ring in **57** would confer 1,2-*cis* stereoselectivity in the subsequent cyclization [48].

The 1,3-dioxatitanocycle mechanism has been invoked to explain the unexpected observation of deoxygenation during the reaction of sterically encumbered β,γ−epoxy alcohols with Cp_2TiCl (last two entries of Table 2) [31]. It was suggested that the β-titanoxy radical **58** formed during initial epoxide ring-opening is too sterically congested to undergo trapping by a second equivalent of Cp_2TiCl (Scheme 15). In the absence of other available pathways, radical **58** is proposed to undergo epoxide ring-closure in the opposite sense to afford the primary titanium (III) alkoxide, **59**.

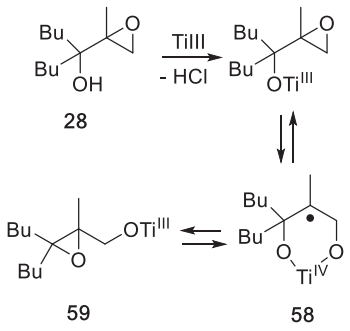
It was argued that reaction of epoxide **59** with a second equivalent of Cp_2TiCl would result in carbon-centered radical **60**. Cleavage of the C–OTi^{III} bond as shown in Eq. (8) would then afford titanium (IV) alkoxide **61** (which, after hydrolysis, gives allylic alcohol **31**). In these studies, rearranged epoxides were not observed [31]. However, evidence has been presented for reversible opening in other types of epoxides with Cp_2TiCl as discussed in Section 6.3 below [28,52,53].



(8)



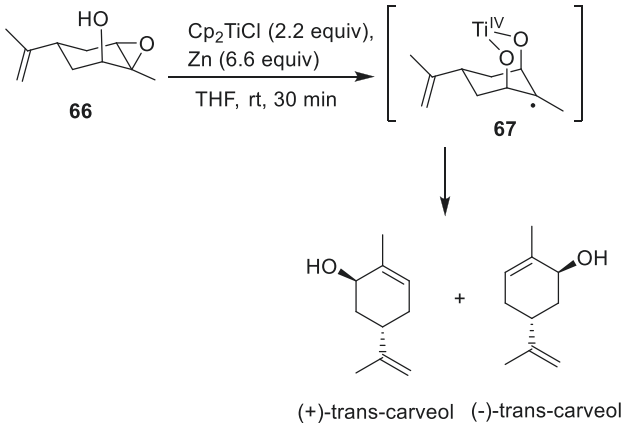
Scheme 14. Cyclization of epoxide **55** according to the 1,3-dioxatitanacycle mechanism.



Scheme 15. Proposed rearrangement of epoxide **28** via 1,3-dioxatitanacycle **58**.

Additional issues arise when the 1,3-dioxtitanacycle mechanism is applied the stereochemical course of reduction reactions such as those seen earlier in Scheme 10 [39]. Reaction of epoxy alcohol **43** would afford the cyclic radical **62** in which the benzyloxymethyl and butyl substituents are in similar chemical environments (Scheme 16). In order to account for the final diol configuration, hydrogen atom transfer to **62** must afford 1,3-dioxatitanacycle **63**. Similarly, epoxy alcohol **45** would afford cyclic radical **64** in which the butyl stereoselectivity is inverted relative to that in **62** and HAT results in formation of **65**. From this result it appears that the methyl group configuration is completely controlled by the configuration of the benzyloxymethyl group while the butyl group exerts no stereochemical control. Given the similar chemical environment of these two substituents in intermediates **62** and **64**, this seems unlikely. Nevertheless, it could be argued that these radicals are not completely stereochemically unbiased because the butyl and benzyloxymethyl substituents are not identical.

An example that is completely free of stereochemical bias was reported by Fernández -Mateos and coworkers (Scheme 17) [46]. When the carveol derivative **66** was treated with Cp_2TiCl, *trans*-carveol was obtained in 79% isolated yield after aqueous workup. *Trans*-carveol could in principle be obtained by either dehydroxylation or deoxygenation. However, the product isolated from this reaction was (+)-*trans*-carveol with an optical rotation $[\alpha]_D^{22} = +114.0$ ($CHCl_3$, *c* 0.4) which may be compared to the literature value [54] of $[\alpha]_D^{25} = 210.2$ ($CHCl_3$, *c* 2.00). This corresponds to an enantiomer ratio of 77:23. This result indicates that dehydroxylation is the predominant reaction pathway and further implies that the two oxygen atoms do not become equivalent after epoxide ring-opening. This outcome is not predicted by the 1,3-dioxatitanacyle mechanism since such a mechanism would result in formation of symmetrical intermediate **67**, which contains a mirror plane. Subsequent elimination of $Cp_2Ti=O$ from **67** would result in a racemic 1:1 mixture of (+)- and (−)-*trans*-carveol,



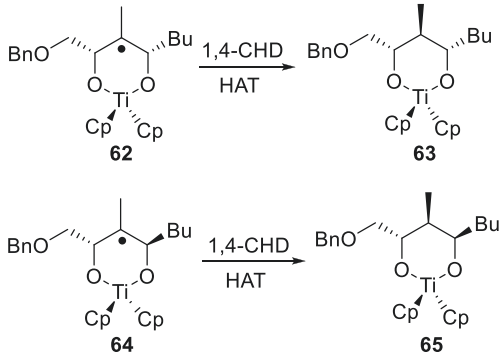
Scheme 17. Application of dioxatitanacycle mechanism to epoxide **66**.

contrary to observation [46]. This system will be discussed in more detail in Section 5.1 below.

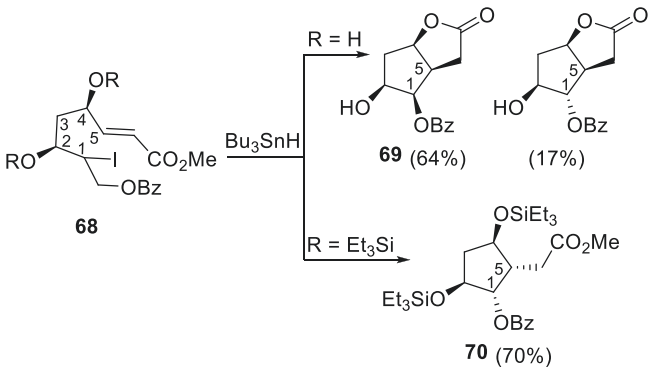
In summary, the strength of Yadav's titanium (III) alkoxide mechanism is that it successfully predicts that β,γ−epoxy alcohols will undergo dehydroxylation in preference to deoxygenation upon treatment with Cp_2TiCl. In doing so it asserts that the two oxygen atoms of the epoxy alcohol remain chemically inequivalent. It does not provide a rationalization for the high stereoselectivity observed in subsequent intra- and intermolecular addition reactions. The strength of Chakraborty's 1,3-dioxatitanacycle mechanism is in predicting high stereoselectivity in the reactions of β,γ−epoxy alcohols with Cp_2TiCl. It requires that the two oxygen atoms become chemically equivalent during the course of the reaction. Consequently, it offers no explanation for the observation that dehydroxylation occurs in preference to deoxygenation.

5. A possible role for hydrogen bonding

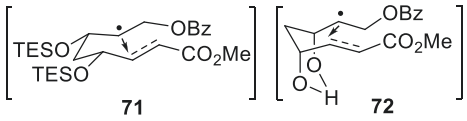
As noted previously, the high levels of stereoselectivity observed in the reactions of acyclic β,γ−epoxy alcohols with Cp_2TiCl strongly suggest the intermediacy of a rigidified, presumably cyclic radical. We propose that the cyclic structure may be the result of hydrogen bonding between the hydroxylic hydrogen atom and the electron-rich alkoxide oxygen atom. Although hydrogen bonding has not been previously proposed to play a role in titanium (III) chemistry, its role in enantioselective catalysis is well established [55,56]. Moreover, examples of stereochemical control of hexenyl radical cyclization through hydrogen bonding are known [57,58]. An example is shown in Scheme 18. Substrates **68** undergo radical



Scheme 16. Application of dioxatitanacycle mechanism to diastereomeric epoxides **43** and **45**.



Scheme 18. Stereochemical control of a 6-hexenyl radical cyclization by hydrogen bonding.



Scheme 19. Radical intermediates in the cyclization of epoxides **68**.

cyclization upon treatment with tri-*n*-butyltin hydride in xylene at room temperature. Both of the major products **69** and **70** contain a *cis*-1,5 ring junction as expected [59] if cyclization proceeds through a chair-like transition state.

According to Beckwith [60], the most favorable transition state for cyclization of substituted, acyclic hexenyl radicals will adopt a chair-like (or "folded envelope") conformation where all of the substituents are in a *pseudo*-equatorial orientation as a result of steric constraints. Thus, the 1,2-trans and 4,5-trans configuration of **70** are a natural consequence of transition state **71** (Scheme 19).

In contrast, the all-*syn* configuration of **69** requires a different explanation. In order for cyclization to proceed through chair-like transition state **72**, the two hydroxyl groups must occupy *pseudo*-axial positions. A 1,3-diaxial interaction is generally expected to be destabilizing; however, in this case the structure is favored by the existence of an intramolecular hydrogen bond. (For similar reasons, the most stable conformation of *cis*-1,3-cyclohexanediol in dilute solution contains two pseudo-axial hydroxyl groups.) [61–63].

As a simple illustration, we consider the epoxyacetylene cyclization seen previously in Scheme 8 [36]. In Scheme 20, when R = H in epoxyacetylene **39**, treatment with Cp_2TiCl results in radical **73**, wherein a hydrogen bond between the hydroxylic hydrogen and the alkoxide oxygen results a chair cyclohexane type structure. Titanium alkoxides are excellent acceptors for hydrogen bonds as has been shown both computationally and using x-ray crystallography [64,65]. Intramolecular addition of the radical center in **73** to the acetylenic triple bond (followed by hydrogen abstraction from solvent THF) results in a predominantly *cis* ring fusion in the product. When the hydroxyl is protected (R = Ac), no hydrogen bond is present and the stereoselectivity is reversed.

The structure of radical **73** has been investigated in a preliminary study using DFT calculations [36]. As shown in Fig. 1, the minimized structure indicates the presence of a hydrogen bond between the hydroxyl oxygen and the alkoxy oxygen atom. The calculated O–H distance for the alkoxide oxygen atom 1.937 Å, which is consistent with an interaction.

5.1. Dehydroxylation as a group transfer reaction

In both the titanium (III) alkoxide mechanism and the 1,3-dioxatitanacycle mechanism, the hydroxyl group of a β,γ-epoxy alcohol is converted into a titanium alkoxide prior to dehydroxylation. However, if we instead regard the unusual reactivity of these substrates as a consequence hydrogen bonding interactions, the hydroxyl group remains available for delivery to a second equivalent of the titanium (III) reagent. We propose that dehydroxylation represents a group transfer reaction in which a highly oxidizing hydroxyl radical is transferred to Cp_2TiCl with concomitant formation of a strong Ti–O bond. As noted in Section 3.2, the C–O bond dissociation enthalpy of the hydroxyl group is significantly diminished by the adjacent radical center [35]. As underscored by the results in Eq. (4), other leaving groups such as formate and cyanide are readily abstracted by Cp_2TiCl under these circumstances. Even the extreme example of epoxy alcohol **66** previously encountered in Scheme 17 can now be understood as shown in Scheme 21 as group transfer of the hydroxyl group in **74** to Cp_2TiCl.

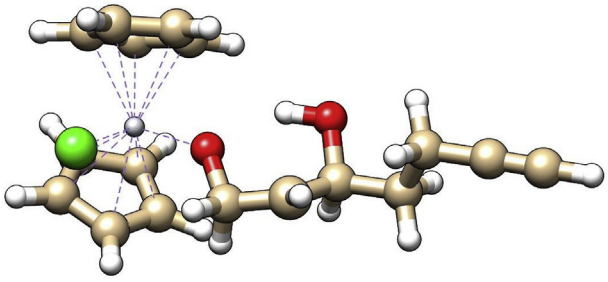
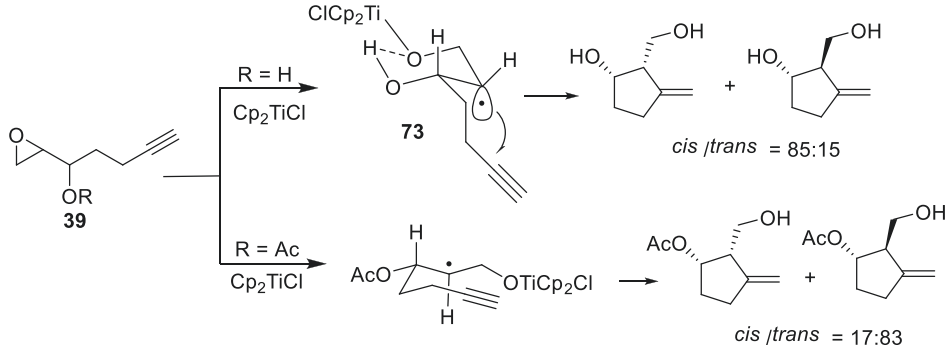


Fig. 1. Preliminary calculated structure of radical **73.**

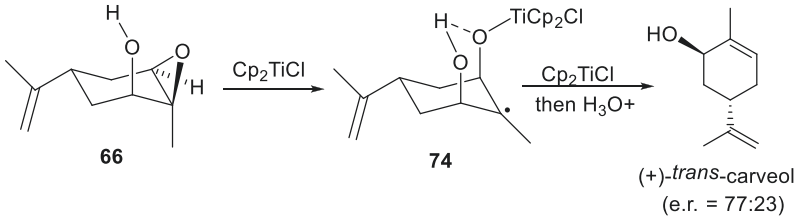
Structure **74** seems eminently reasonable. As noted previously, *cis*-1,3-cyclohexanediol adopts a diaxial conformation due to hydrogen bonding. The alkoxide oxygen atom in **74** is expected to be a suitable hydrogen bond acceptor. The preference for the relatively bulky isopropenyl group to adopt a pseudo-equatorial conformation will offset the energetic cost of strain introduced by the 1,3-diaxial interaction between the oxygen atoms.

It is noteworthy that selectivity for dehydroxylation versus deoxygenation in Scheme 21 is not 100%. Thus, the apparent enantiomer ratio for the product *trans*-carveol is only 77:23 (A note of caution regarding Scheme 21 is that the enantiomer ratio was determined by optical rotation. It would be desirable to repeat this experiment using chiral GLC to refine this result.). The incomplete selectivity for dehydroxylation raises the possibility that the hydroxylic and the alkoxide oxygen slowly interconvert via the hydrogen-bonded radical intermediate **74**. This would be consistent with the observation that titanium (IV) alkoxides are substitutionally labile in the presence of excess alcohols [45].

Regarding the proposed exchange of the titanoxy and hydroxyl



Scheme 20. Effect of hydrogen bonding on the cyclization of epoxides **39**.



Scheme 21. Effect of hydrogen bonding in the cyclization of epoxide **66**.

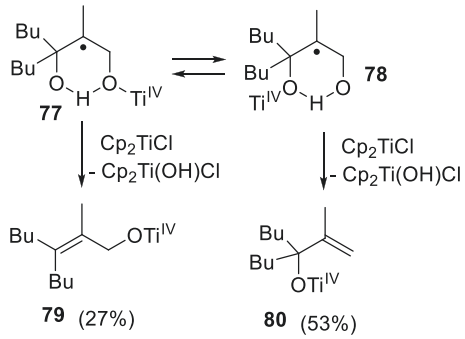
groups in **74**, it is instructive to consider the reaction of the epimeric alcohol **75** with Cp_2TiCl (Scheme 22) [46]. Again the product of dehydroxylation is (+)-*trans*-carveol but in this case deoxygenation would afford diastereomeric (−)-*cis*-carveol. No *cis*-carveol is observed, consistent with exclusive dehydroxylation. Moreover, the *trans* relationship between the two oxygen atoms in intermediate **76** will disfavor formation of a hydrogen bonded intermediate analogous to **74**. The optical rotation of (+)-*trans*-carveol obtained from **75** is $[\alpha]_D^{25} = +151.5$ (CHCl3, c 4 mg/mL), corresponding to an enantiomer ratio of 84:16, which is significantly higher than the 77:23 ratio observed from **66**.

Such a rearrangement could also provide an explanation for apparent formation of the deoxygenation product **31** from sterically encumbered epoxy alcohol **28** as noted earlier in Table 2. The initial homolysis of epoxy alcohol **28** would give rise to radical **77** as shown in Scheme 23. Equilibration of radicals **77** and **78** would interconvert the hydroxyl and alkoxide oxygen atoms. Alkoxide **79** would then arise by dehydroxylation of **77** while dehydroxylation of **78** would afford alkoxide **80**.

Depending on the relative rates of radical trapping by Cp_2TiCl and the interconversion of **77** and **78**, it is possible that the product distribution in this reaction would be sensitive to the concentration of Cp_2TiCl that is present. In order to probe this possibility, it would be interesting to examine the change in product distribution under conditions of "normal addition" (addition of Cp_2TiCl solution to epoxide) versus "inverse addition" for both Schemes 21 and 23.

5.2. Additional applications to stereoselective reactions

Hydrogen bonding can also be invoked to explain the extraordinary stereoselectivity observed for the cyclization of epoxy alcohol **55** that was noted earlier in Scheme 14 [48,66]. In this transformation, the 1,2-*cis* stereoselectivity is again a result of the hydrogen bonding interaction in structures **81** and **82** (Scheme 24) Moreover, the uncommon 1,5-*trans* stereoselectivity apparently reflects the steric bulk of the alkene acceptor. The 'boat-like'



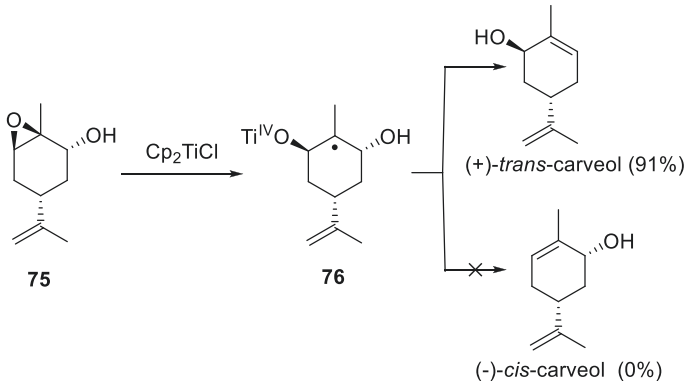
Scheme 23. Proposed slow interconversion of radicals **77** and **78**.

transition state **83** is presumably preferred to the 'chair-like' **81**, leading to the uncommon 1,5-*trans* selectivity in the formation of the products **83** and **84**.

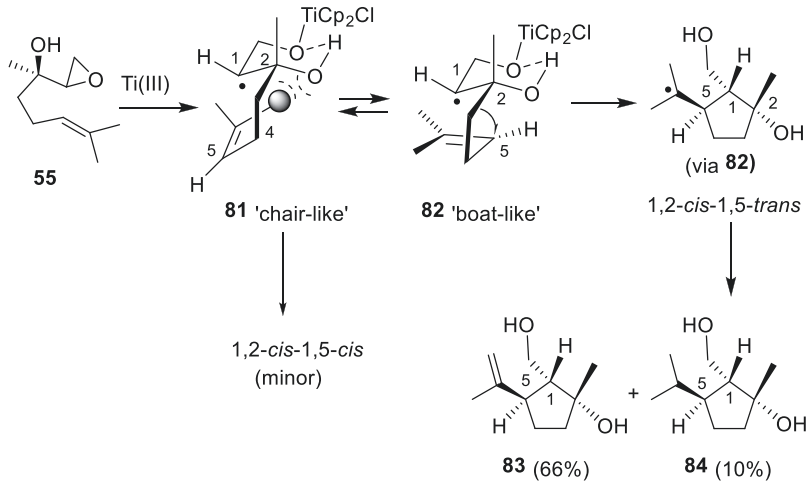
The examples shown in Schemes 20 and 24 involve an unactivated alkene or alkyne as an acceptor. In fact, a similar effect seems to occur when activated acrylate-type acceptors are employed (Scheme 25). Thus the epoxy acrylate **85** gives a high yield of cyclopentane **87** [37,67]. The stereochemical outcome of this reaction can be rationalized by invoking a transition state involving a H-bonded cyclic radical **86**.

Parallel arguments apply in the case of 6-*exo*-trig cyclizations (Scheme 26) [49]. In this example, cyclization of epoxy alkene **88** affords cyclohexane **89** in 50% isolated yield, along with minor amounts of "unidentified isomers". Examples of stereoselective syntheses of other structurally related carba-, oxa- [68] and aza- [69] cyclic compounds have been reported.

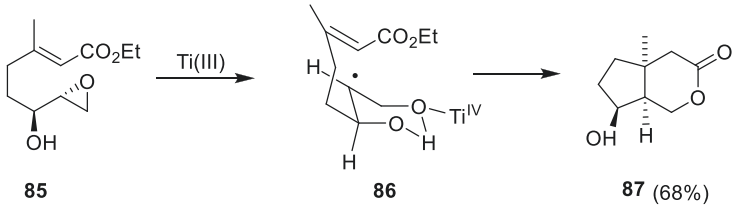
Because the hydroxyl group in β,γ-epoxy alcohols can direct the regioselectivity of epoxide ring opening, this provides a means to control the ring size in intramolecular additions. This is nicely illustrated by the formation of aza-cyclic compounds in Scheme 27 [69]. In these reactions, control of regioselectivity of the ring-



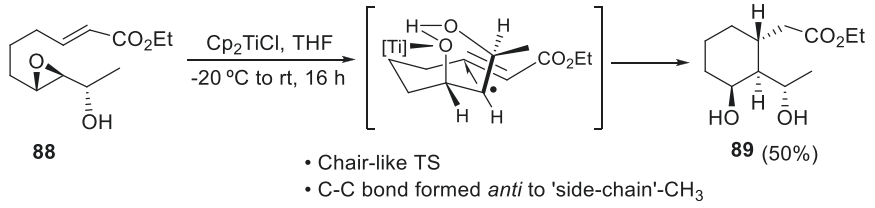
Scheme 22. Dehydroxylation of epoxide **75**.



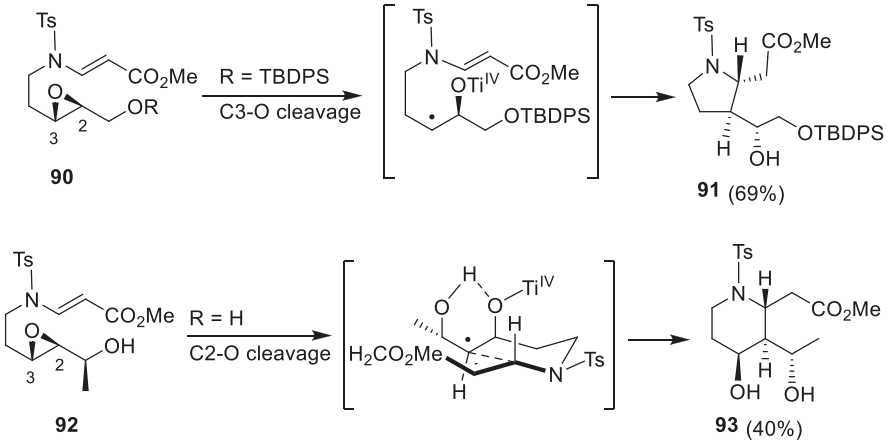
Scheme 24. Role of hydrogen bonding during cyclization of epoxide **55**.



Scheme 25. Role of hydrogen bonding in cyclization of epoxy acrylate **85**.

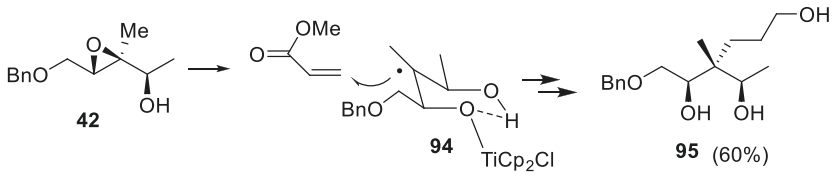


Scheme 26. Role of hydrogen bonding in a 6-*exo*-trig cyclization.



Scheme 27. Control of ring size and stereoselectivity through hydrogen bonding.

opening in the β,γ-epoxy alcohol depends on whether the alcohol is protected or not. Thus the protected derivative **90** undergoes C_3—O cleavage resulting in an *exo* hex-5-enyl radical cyclization to afford cyclopentane **91**. On the other hand, the unprotected derivative **92** undergoes C_2—O cleavage followed by an *exo* hept-6-enyl radical cyclization, giving **93** as the major product. Current models are



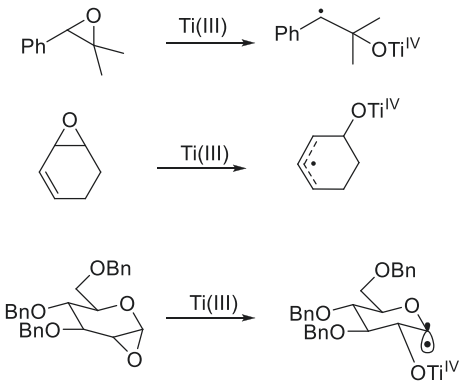
Scheme 28. Effect of hydrogen bonding on an intermolecular addition.

inadequate to explain the stereochemical outcome of these reactions. This is especially true in cyclizations involving acrylate-type acceptors giving stabilized terminal radicals, where the usual assumption of kinetic control may not prevail, with attendant stereochemical consequences [70].

In addition to these results pertaining to cyclizations, the stereochemical course of intermolecular addition reactions can likewise be understood in terms of the effects of hydrogen bonding. A case in point is the addition of epoxy alcohol **42** to methyl acrylate, which affords a single product diastereomer as shown earlier in Scheme 9. This outcome is the consequence of the rigidified structure **94** (Scheme 28). After LAH reduction the predicted product is triol **95**, consistent with the experimental result.

6. Site selectivity in epoxide ring opening

Mechanistic thinking regarding the site selectivity of Ti(III)-mediated epoxide opening has evolved considerably over the years, especially in the case of electronically unbiased epoxides.



Scheme 29. Effect of radical stability on the site selectivity of epoxide opening.

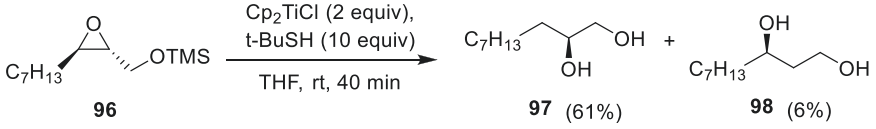
This subject has not been covered in review articles and it will be useful to address the topic here.

6.1. Site selectivity in electronically biased epoxides

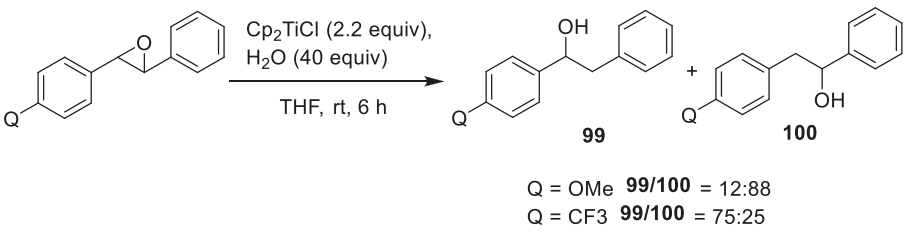
When a strongly radical-stabilizing group is attached to an epoxide, the corresponding C–O bond is usually broken upon treatment with Cp_2TiCl. Such radical-stabilizing substituents include the phenyl [71] and vinyl [72] groups. As shown in the final example in Scheme 29, anomeric radical stabilization in carbohydrate derivatives has likewise been used to control the selectivity of C–O bond cleavage [43,73].

In each of these examples, stabilization of the incipient radical weakens one C–O bond, facilitating epoxide ring-opening. In similar fashion, electronic effects can retard ring opening (Scheme 30). Reaction of epoxide **96** with Cp_2TiCl in the presence of *t*-BuSH as a hydrogen atom donor affords (after desilylation) 1,2-diol **97** rather than 1,3-diol **98** [14]. DFT calculations on a related system show that this type of selectivity reflects the electron-withdrawing effect of the silyloxy substituent, which destabilizes the developing radical center *en route* to **98** [74].

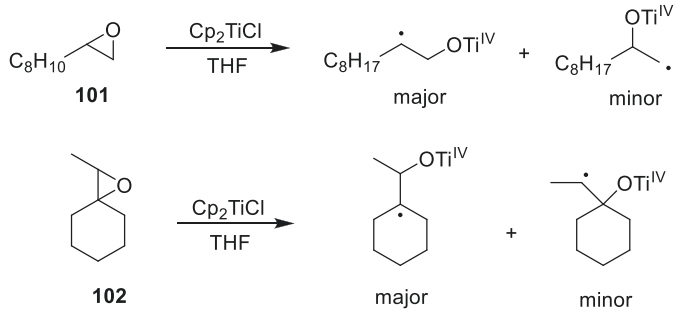
In some of the above cases, it is not possible to exclude any contribution of steric effects to site selectivity. However, a particularly clean example exists in the case of 1,2-diarylethylene oxides, wherein the aryl substituents on the epoxide are sterically similar (Scheme 31) [75]. Each epoxide is treated with Cp_2TiCl (2.2 equivalents) in the presence of water (40 equivalents) as a hydrogen atom transfer agent. In each case conversion is >99%. When substituent Q is an electron-donating methoxy substituent, alcohol **100** is formed preferentially, presumably because of stabilization of the radical adjacent to the methoxyphenyl ring. In contrast, an electron-withdrawing trifluoromethyl substituent destabilizes the adjacent radical center, resulting in preferential formation of alcohol **99**.



Scheme 30. Effect of radical destabilization on the site selectivity of epoxide opening.



Scheme 31. Site selectivity during ring-opening of substituted stilbene oxides.



Scheme 32. Site selectivity in the opening of electronically unbiased epoxides.

6.2. Electronically unbiased epoxides

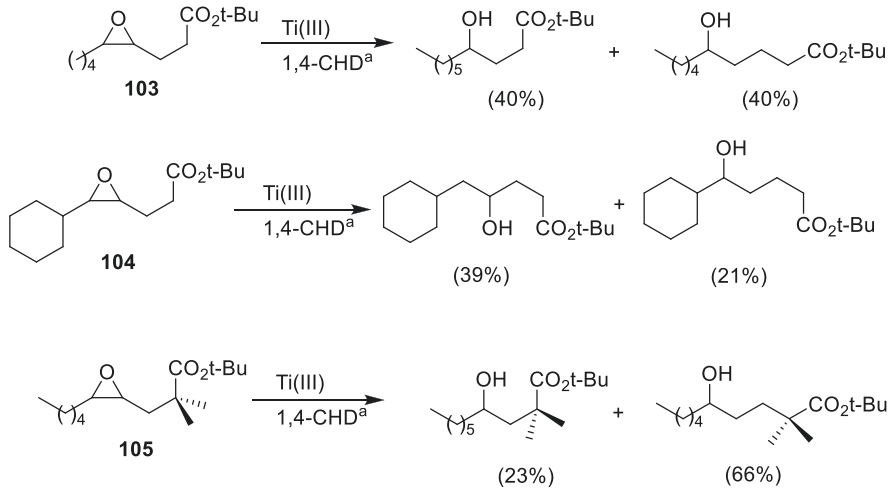
In the absence of a strongly directing functional group, C—O bond cleavage occurs preferentially at the more highly substituted carbon atom as exemplified by epoxides **101** and **102** in Scheme 32. For example, the bond to a 2° carbon atom in **101** is cleaved in preference to a terminal C—O bond, whereas the bond to a 3° carbon atom in **102** is cleaved more readily than the bond to a 2° carbon [14].

It was initially proposed [14] that the site selectivity in Scheme 32 reflects the order of radical stability (3° > 2° > 1°) of the resulting carbon-centered radicals formed by C—O bond cleavage. However, this view has changed as evidence for the importance of non-bonded interactions in controlling the regioselectivity of epoxide opening has emerged.

Consistent with proposed role of non-bonded interactions, sterically bulky groups influence site selectivity even when not directly bonded to an epoxide carbon atom (Scheme 33): Ti(III)-mediated epoxide opening is unselective in the case of **103** but proceeds with somewhat higher site selectivity for the cyclohexyl derivative **104** and for **105**. For both **104** and **105**, C—O bond cleavage occurs predominantly at the more congested end of the epoxide [76]. Another noteworthy conclusion from Scheme 33 is that any directing effect arising from chelation (for example the ester carbonyl in epoxide **103**) appears to be small compared to non-bonding interactions between the substrate and the cyclopentadienyl ligands [76]. (All of the substrates in Scheme 33 are *cis* epoxides.)

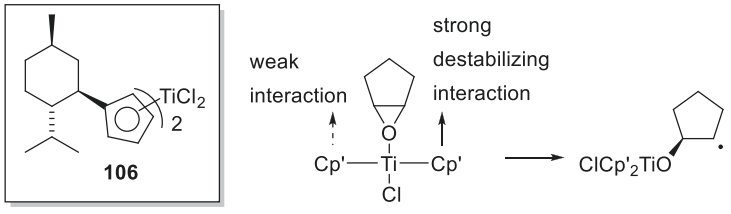
The development of asymmetric epoxide opening using chiral titanium catalysts provided incontrovertible evidence for the importance of non-bonded interactions in determining site selectivity. Catalytic formation of radicals from *meso* epoxides has been achieved by using chiral titanocene derivatives such as Kagan's complex, **106** [9]. Enantioselectivity in these reactions is attributed to steric interactions between the epoxide and the (menthyl) cyclopentadienyl ligands bound to titanium (Scheme 34).

A detailed study of the mechanism of the Ti (III)-induced C—O bond cleavage of epoxides has provided support for the importance of non-bonded interactions [28,77]. Computational studies show that such reactions have an early (reactant-like) transition state. Notably, in the transition structures the spin density on the evolving radical center is typically lower (approximately 0.3) than on titanium (approximately 0.7). Moreover, reaction energies do not correlate with bond dissociation energies. Thus, radical stability seems unlikely to be the only factor governing the regioselectivity

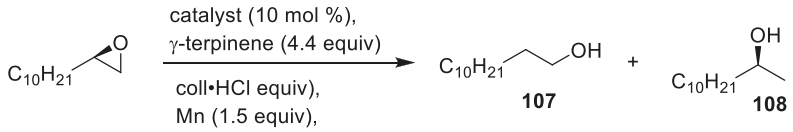


a) Conditions: Cp_2TiCl_2 (10 mol %), Mn dust (1.5 equiv), collidine hydrochloride (1.5 equiv), 1,4-cyclohexadiene (4.4 equiv), THF, rt, 16 h.

Scheme 33. Effect of bulky substituents not directly bonded to an epoxide carbon atom.

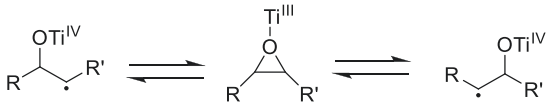


Scheme 34. Effect of destabilizing, non-bonded interactions on site selectivity.



Catalyst	Yield (%)	107/108
106	57	1:99
ent-**106**	29	53:47

Scheme 35. Ring-opening of 1,2-epoxydodecane with a "matched" vs "mismatched" catalyst.



Scheme 36. Reversibility of epoxide ring-opening with titanium(III) reagents.

of epoxide opening. The computational results, taken together with the ability of chiral cyclopentadienyl ligands to effect enantioselective opening of *meso* epoxides, make a strong case for the importance of steric interactions in controlling the site selectivity of the C—O bond breaking process [28].

A compelling demonstration of the critical influence of non-bonded interactions is the reversal in regioselectivity for opening (*R*)-1,2-epoxydodecane using "matched" catalyst **106** versus "mismatched" catalyst *ent*-**106** (Scheme 35) [28]. In this study, γ-terpinene is used to trap the radicals formed by C—O bond homolysis via hydrogen-atom transfer under catalytic conditions (Mn/coll•HCl). As a result of such evidence, the prevailing view is that "epoxide opening is directed by non-bonding interactions during electron transfer" [71].

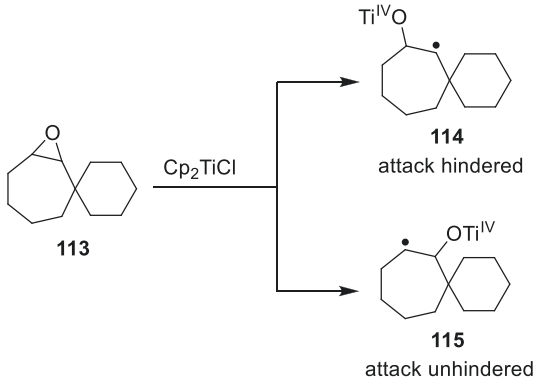
6.3. Reversibility of epoxide ring opening

One explanation for the effect of radical stability on site selectivity would result if C—O bond homolysis is reversible (Scheme 36). Preferential trapping of the more stable radical under a Curtin-Hammett scenario would account for the observed site selectivity. Again, the prevailing viewpoint on this issue has evolved considerably in recent years.

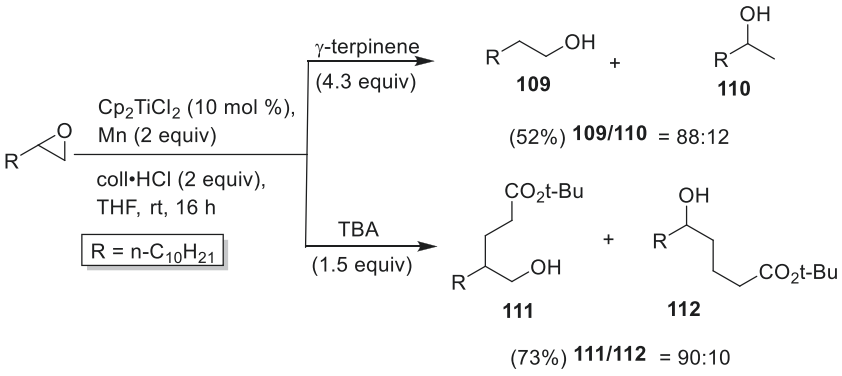
In early studies, the equilibrium in Scheme 36 was disfavored [78] based mainly on the observation that the same product ratios are observed when substantially different reagents are used to trap β-titanoxy radicals. To cite one example, the ring opening of 1,2-epoxydodecane produces a nearly identical distribution of 1- versus 2-substituted products, whether the trapping agent is γ-terpinene (hydrogen atom transfer) or *tert*-butyl acrylate (TBA, conjugate radical addition) (Scheme 37) [28].

More recently, several research groups have provided evidence for reversible epoxide cleavage by titanium (III). For example, Gansäuer and coworkers have explored the reduction of *cis*-1,2-disubstituted epoxide **113** where the two substituents have greatly different steric bulk [28]. Based on the foregoing discussion, ring-opening of **113** is expected to afford the more congested radical **114** in preference to the less congested **115** (Scheme 38). However, reaction of radical **114** with sterically demanding radical traps is expected to be particularly slow.

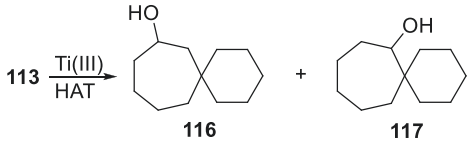
Treatment of epoxide epoxide **113** with Cp_2TiCl under catalytic conditions (10 mol % Cp_2TiCl_2, excess Zn, 1.5 equiv collidine hydrochloride) with 1,4-cyclohexadiene as hydrogen donor afforded alcohols **116** and **117** in a 4.7:1 ratio (Scheme 39). When 1,4-CHD was replaced with the sterically more demanding hydrogen atom donor γ-terpinene, the ratio of **116** to **117** was reduced to 1.6:1. This result is consistent with reversible opening of epoxide **113**, which allows interconversion of radicals **114** and **115**.



Scheme 38. Radical intermediates from ring-opening of epoxide **113**.

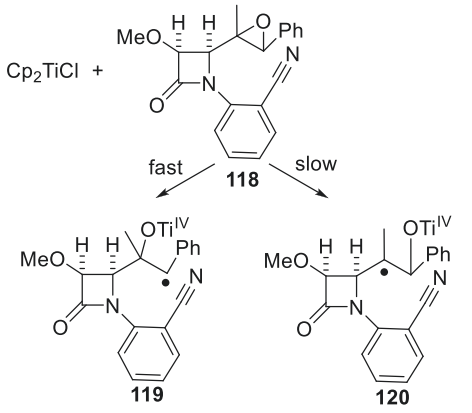


Scheme 37. Effect of different trapping agents on site selectivity of epoxide opening.

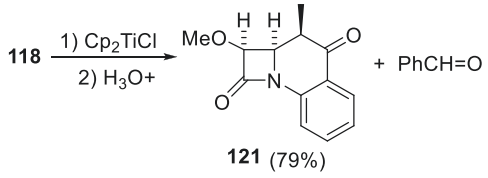


Hydrogen Donor	Yield **116** (%)	Yield **117** (%)
1,4-Cyclohexadiene	47	10
γ-Terpinene	37	23

Scheme 39. Effect of hydrogen atom donor on reduction of epoxide **113**.



Scheme 40. Radical intermediates from ring-opening of epoxide **118**.



Scheme 41. Cyclization of epoxide **118** via intramolecular addition to the nitrile group.

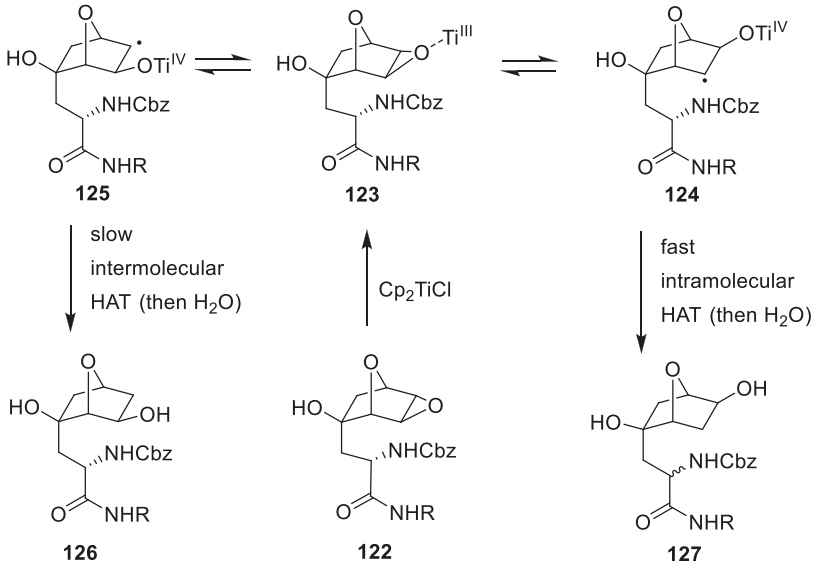
Grande and coworkers have examined the intramolecular addition of radicals generated from cyano epoxides such as **118** upon treatment with Cp_2TiCl (Scheme 40) [53]. They propose that C–O bond homolysis to afford the benzylic radical **119** should be significantly faster than that to produce the tertiary radical **120**. Preferential opening at the benzylic position has subsequently been confirmed in structurally similar epoxides [71].

However, the product of the reaction of the reaction is the 6-membered ring ketone **121**, which is obtained in 79% yield after hydrolytic workup (Scheme 41). Benzaldehyde is presumably lost via a retro-aldol reaction during hydrolysis. Cyclization of the benzylic radical **119** to produce a 7-membered ring ketone would be slow due to steric constraints. Consequently radical **119** has time to rearrange to **120** prior to ring-closure. This again provides evidence for the reversibility of epoxide ring opening by Cp_2TiCl.

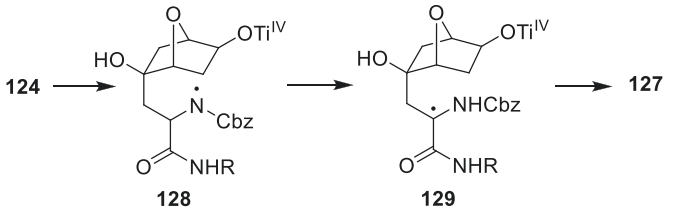
A final and especially compelling example is the observation of Carreira and coworkers [52] that the tricyclic epoxide **122**, upon reduction with titanium (III), affords alcohol **127** in preference to alcohol **126** in ca. 96:4 selectivity (Scheme 42). Labelling studies establish that hydrogen-atom transfer occurs from the carbamate N–H bond of **122**. The titanium (III) epoxide complex **123** is presumed to undergo reversible electron transfer to afford the interconverting radicals **124** and **125**.

In accordance with the Curtin-Hammett principle, radical **124** is rapidly trapped by intramolecular hydrogen-atom transfer from the carbamate N–H of the Cbz group, affording alcohol **127** after aqueous work-up. Although the N–H bond is normally too strong to allow transfer of hydrogen to a carbon-centered radical, the N–H bond strength in this case is attenuated by complexation of the carbonyl oxygen atom to titanium (III). There is strong evidence for such an effect in the case of amides [79,80]. Isotopic labelling studies indicate that the *N*-centered radical **128** that is formed by HAT can undergo a 1,2-[hydrogen] migration to a more stable C-centered radical **129** (Scheme 43). Consequently, the site adjacent to nitrogen undergoes epimerization unless an excess of a good hydrogen atom donor such as 1,4-CHD is added to the system to trap **128** prior to rearrangement. No corresponding pathway exists for radical **125**, which slowly undergoes intermolecular HAT (presumably from solvent THF) to afford the minor product **126** [52].

To our knowledge, reversible epoxide opening has not been proposed in the context of a β,γ-epoxy alcohol substrate. However,



Scheme 42. Reaction of epoxide **122** with Cp_2TiCl.



Scheme 43. Fate of radical **124** resulting from intramolecular N-H abstraction.

evidence has recently been presented for reversible ring opening in the case of a polycyclic δ,ε−epoxy alcohol in the elegant synthesis of rhodomolleins XX and XXII by Ding and coworkers [81].

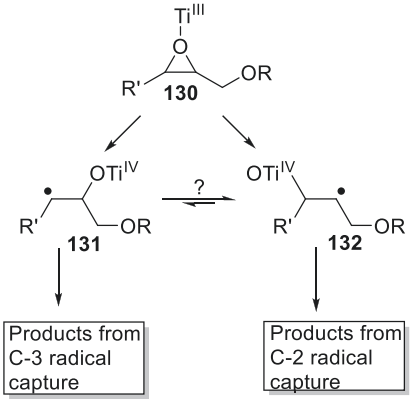
6.4. Regioselectivity in ring opening of β,γ-Epoxy alcohols

As seen earlier in Scheme 3, treatment of epoxy alcohol **11a** with Cp_2TiCl results in preferential opening at C-2, *despite* the inductive effect of the hydroxyl oxygen, which should destabilize a radical center at C-2. Indeed, the silylated analogue **11b** opens at C-3 as expected based on the inductive effect. This suggests that the presence of the hydroxylic hydrogen atom in some way influences site selectivity in the opening of **11a**. This could be rationalized as either a kinetic or a thermodynamic effect as shown in Scheme 44.

Ring opening proceeds through the inner-sphere complex **130** [28]. In the kinetic model, a hydrogen bonding effect in **130** when R = H lowers the transition state energy for formation of radical **132** which then affords the product of C-2 capture. In contrast, when R = trimethylsilyl or acetyl formation of radical **131** predominates, consistent with the inductive destabilization of **132**.

In the thermodynamic model, when R = H predominant ring opening at C-3 may still occur. However, interconversion of radicals **131** and **132** takes place prior to radical trapping. Since radical **132** is stabilized by intramolecular hydrogen bonding, it will be the predominant species and products from C-2 capture may be observed (subject to Curtin-Hammett considerations) [82].

The thermodynamic explanation is especially attractive because the same hydrogen bonding interaction that has already been invoked to explain the stereoselectivity of intra- and intermolecular additions for β,γ-epoxy alcohols would also explain the regioselectivity of these reactions. However, this model is not without concerns. The epoxides **113**, **118**, and **122**, which provide evidence for reversible epoxide opening, are all sterically congested. Steric congestion will slow the trapping of the radical intermediates and will allow time for their interconversion. In contrast, β,γ-epoxy alcohols such as **11a** are relatively unencumbered. Moreover, in Scheme 3, radical **11a** is trapped with *tert*-butyl thiol. Hydrogen atom transfer from *t*-BuSH is known to be extremely rapid; the rate constant for hydrogen transfer to alkyl radicals at 20 °C is $6 \times 10^6\ M^{-1}\ s^{-1}$ [83]. Thus, it is not clear that the rate of interconversion of radicals **131** and **132** in Scheme 44 would be sufficiently rapid compared with radical trapping in order for the thermodynamic model to be operational.



Scheme 44. Kinetic vs thermodynamic control of site-selectivity in epoxide ring-opening.

The kinetic model requires that a stabilizing hydrogen bonding interaction reduces the activation energy on the pathway leading to C-2 cleavage. This contrasts with the situation for non-hydroxyl-containing epoxides in Scheme 33 where selectivity is controlled by a *destabilizing* interaction between the titanium-bound epoxide and the cyclopentadienyl ligands. However, the nature of the hydrogen bond in this case is not clear. In principle, the hydroxylic hydrogen could hydrogen bond to either the epoxide oxygen atom or the titanium-bound chloride. There is experimental and computational evidence for a bonding interaction of the chloride ligand in Cp_2TiCl with water in solvent THF [84]. In fact, in one x-ray crystal structure an alcohol hydrogen bonds to a titanium-bound chloride ligand in preference to an alkoxide ligand [85].

The regioselectivity for epoxide ring-opening in the examples cited in this review can generally be rationalized in terms of a hydrogen-bonded transition state where either the epoxide or the chloride ion serves as the acceptor for the hydrogen bond. An exception is seen in Scheme 12 where *cis*-**49** and *trans*-**49** both lead to epoxide ring opening at C-2, despite the fact that a hydrogen bond involving the epoxide of the *trans* isomer is not possible [46]. However, ring opening at C-2 in this case may simply result from the competition between formation of secondary versus a tertiary radical. For example, it is known that reaction of 1,2-epoxy-1-methylcyclohexane with Cp_2TiCl affords exclusively the tertiary radical [29].

7. Conclusions

We have reviewed the reactions of Cp_2TiCl with β,γ−epoxy alcohols as well as with epoxides that lack a hydroxyl substituent. In particular, we have highlighted three stunning differences in the reactions of these two substrate classes: (1) The regioselectivity of epoxide ring-opening is opposite for β,γ-epoxy alcohols versus their O-protected analogues. (2) In the absence of radical trapping agents, β,γ-epoxy alcohols undergo dehydroxylation rather than the deoxygenation reaction observed with other epoxide substrates. (3) The reactions of the β-titanoxy radicals formed by ring-opening of β,γ-epoxy alcohols with radical trapping agents as well as their intramolecular addition reactions are frequently highly stereoselective and the stereoselectivity is often opposite that observed with substrates lacking a hydroxyl substituent.

We have critically reviewed the two mechanistic proposals that have been put forth to rationalize these reactions. The titanium (III) alkoxide mechanism explains the preference for dehydroxylation over deoxygenation observed for β,γ-epoxy alcohol substrates, but does not provide an explanation for the high stereoselectivity observed in these reactions. The dioxatitanacycle mechanism explains the stereoselectivity of the reactions but makes it difficult to understand the preference for dehydroxylation versus deoxygenation. Both mechanisms run contrary to the known chemistry of titanium alkoxides. Neither offers insight into the regioselectivity of epoxide opening.

For these reasons, we have proposed an alternative mechanism for the reaction of Cp_2TiCl with β,γ-epoxy alcohols in which hydrogen-bonding plays an important role. In this model, the hydroxyl group remains intact and sterically accessible. Therefore, dehydroxylation can be understood as group transfer of a highly

oxidizing hydroxyl radical to titanium (III) with formation of a strong Ti–O bond. The model also explains the stereoselectivity of these reactions. Stereoselectivity is a natural consequence of the fact that hydrogen bonding imparts a structurally rigid, cyclic structure to the β-titanoxy radical intermediates. Both of these assertions are supported by a variety of literature precedents. We have proposed that the regioselectivity of epoxide ring-opening by Cp_2TiCl is also the consequence of hydrogen bonding. In this case the detailed mechanism is less clear cut but should be clarified by future mechanistic studies.

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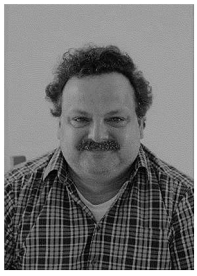

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