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Demystifying $Cp_2Ti(H)Cl$ and Its Enigmatic Role in the Reactions of Epoxides with Cp_2TiCl

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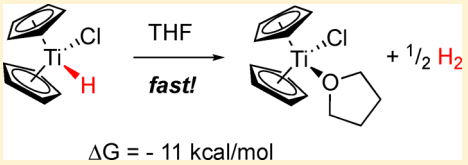
Supporting Information

ABSTRACT: The role of $Cp_2Ti(H)Cl$ in the reactions of Cp_2TiCl with trisubstituted epoxides has been investigated in a combined experimental and computational study. Although $Cp_2Ti(H)Cl$ has generally been regarded as a robust species, its decomposition to Cp_2TiCl and molecular hydrogen was found to be exothermic ($\Delta G = -11$ kcal/mol when the effects of THF solvation are considered). In laboratory studies, $Cp_2Ti(H)Cl$ was generated using the reaction of 1,2-epoxy-1-methylcyclohexane with Cp_2TiCl as a model. Rapid evolution of hydrogen gas was demonstrated, indicating that $Cp_2Ti(H)Cl$ is indeed a thermally unstable molecule, which undergoes intermolecular reductive elimination of hydrogen under the reaction conditions. The stoichiometry of the reaction (Cp_2TiCl:epoxide = 1:1) and the quantity of hydrogen produced (1 mol per 2 mol of epoxide) is consistent with this assertion. The diminished yield of allylic alcohol from these reactions under the conditions of protic versus aprotic catalysis can be understood in terms of the predominant titanium(III) present in solution. Under the conditions of protic catalysis, Cp_2TiCl complexes with collidine hydrochloride and the titanium(III) center is less available for "cross-disproportionation" with carbon-centered radicals; this leads to byproducts from radical capture by hydrogen atom transfer, resulting in a saturated alcohol.



INTRODUCTION

Titanocene hydride chloride (**1**) is an enigmatic molecule in organometallic chemistry: often invoked but never observed. On the one hand, **1** has been proposed as an intermediate in reactions as diverse as ethylene polymerization[1] and the aminolysis of *N*-acyl carbamates.[2] In particular, **1** is implicated as a product of the reaction between tertiary alkyl radicals and the titanium(III) reagent Cp_2TiCl.[3−5] Because of the expectation that **1** is a robust organometallic species, there has been concern that its formation might be an impediment in catalytic reactions using substoichiometric amounts of Cp_2TiCl. Specialized protocols have been developed to address this supposed issue.[3,4]

1

On the other hand, **1** has never been isolated or even observed in situ. Attempts to prepare **1** by treatment of Cp_2TiCl_2 with hydride reagents have instead consistently afforded the titanium(III) complex Cp_2TiCl.[6,7] In contrast, zirconocene hydride chloride, $Cp_2Zr(H)Cl$ (Schwartz's reagent) is a thermally stable organometallic compound with many useful applications in organic synthesis.[8,9] Interestingly, the permethylated analogue of **1**, bis(pentamethylcyclopentadienyl)titanium hydride chloride, has been synthesized and is stable in the solid state and in THF solution.[10,11]

Cp_2TiCl is a broadly useful reagent in organic synthesis.[12−14] Cp_2TiCl is usually generated in situ by reduction of Cp_2TiCl_2 with a metal powder, typically zinc or manganese as shown in eq 1. We are particularly interested in the role of **1** in the reactions of Cp_2TiCl with trisubstituted epoxides.

$$2\ Cp_2TiCl_2 + M \rightarrow 2\ Cp_2TiCl + MCl_2 \qquad M = Zn, Mn \qquad (1)$$

It is instructive to first consider the reaction of Cp_2TiCl with the simple monosubstituted epoxide **2** in the presence of a hydrogen atom donor Q−H. (Examples of such donors include 1,4-cyclohexadiene and *tert*-butanethiol.) When it is run under stoichiometric conditions,[15] the reaction proceeds as shown in Scheme 1. Initial homolysis of one epoxide C−O bond results in formation of the *β*-titanoxy radical **3**. The carbon-centered radical **3** abstracts hydrogen from Q−H to afford alkoxide **4**. Alkoxide **4** is then hydrolyzed in a separate step with dilute aqueous acid to afford the free alcohol.

In order to carry out such reactions in a catalytic manner, one must address the fact that titanium(IV) alkoxide **4** cannot be directly reduced to the +3 oxidation state. It is essential to first convert the alkoxide back to Cp_2TiCl_2 so that it may once

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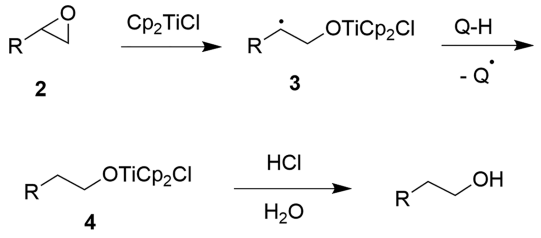
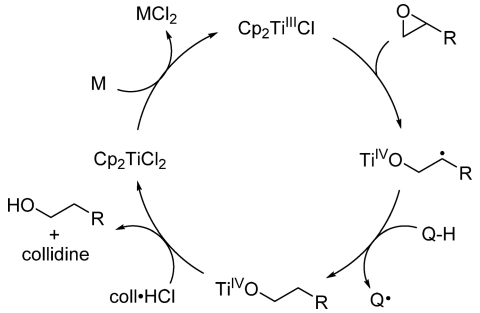
Scheme 1. Cp_2TiCl-Mediated Opening of an Epoxide in the Presence of Hydrogen Atom Donor Q–H

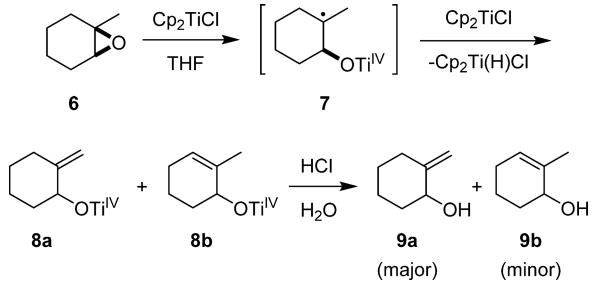


again be reduced according to eq 1. In one approach, this is accomplished by the use of a buffered Brønsted acid, most often 2,4,6-collidininium hydrochloride (coll·HCl).[16,17] When stoichiometric amounts of coll·HCl and metal reductant with a substoichiometric amount of Cp_2TiCl_2 as precatalyst are used, a catalytic cycle can be achieved as shown in Scheme 2.

Scheme 2. Protic Catalysis of Ti(III)-Mediated Epoxide Ring Opening (Ti^{IV} = Cp_2ClTi–)

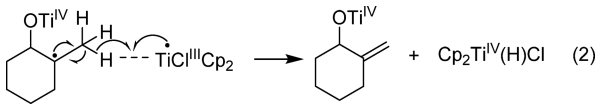


Scheme 3. Formation of Allylic Alcohols via Cp_2TiCl-Mediated Opening of Trisubstituted Epoxide



A different reaction path emerges when a trisubstituted epoxide such as **6** reacts with Cp_2TiCl. In Scheme 3, the initial C–O bond homolysis gives rise to the tertiary alkyl radical **7**. In the absence of a hydrogen atom donor, the observed product after hydrolysis is a mixture of allylic alcohols **9a** and **9b**. Examples of this type of reaction began to appear in the late 1990s,[18−20] and the transformation was subsequently explored in detail by Bermejo and Sandoval.[21]

In Scheme 3, the reaction between the radical **7** and Cp_2TiCl affords both **1** and either alkene **8a** or **8b**, depending on which β-hydrogen atom is transferred to Cp_2TiCl. This type of process is proposed to proceed via a "mixed disproportionation" between the carbon-centered radical **7** and the "titanium-centered radical" Cp_2TiCl, in which a β-hydrogen atom is abstracted by the Ti(III) reagent.[22] This is illustrated for the major pathway leading to **8a** in eq 2. (Alternatively, formation of $Cp_2Ti(H)Cl$ has been suggested to

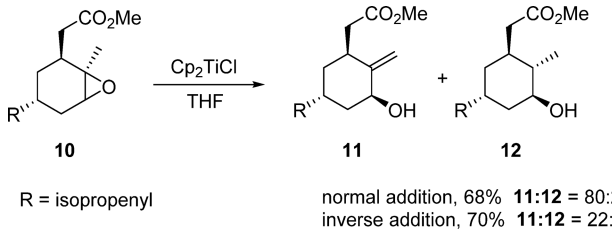


involve the combination of **7** with Cp_2TiCl to afford a 3° organotitanium complex, followed by β-hydride elimination.[21,23a] See the Supporting Information for a more detailed discussion; however, this distinction does not affect the conclusions of the current paper.)

Reactions of this type provide an efficient means for the isomerization of trisubstituted epoxides to allylic alcohols. Moreover, the loss of a β-hydrogen atom has also been observed as a radical termination step in other reactions of epoxides with Cp_2TiCl that give rise to a 3° alkyl radical. Examples include cyclization of epoxyolefins,[20,24] transannular cyclizations,[25,26] and the cascade cyclization of epoxypolyenes.[4,24]

β-Scission of hydrogen and reduction by hydrogen abstraction are sometimes observed as competitive processes, as is the case in Scheme 4. When Bermejo and Sandoval

Scheme 4. Effect of Mode of Addition on Reduction vs β-Hydrogen Scission



carried out the stoichiometric reaction of epoxide **10** with Cp_2TiCl (2.2 equiv), they discovered that different products were favored depending on the order of addition of the reactants (Scheme 4).[21] When a 0.5 M solution of **10** in THF was added dropwise to a 0.1 M solution of Cp_2TiCl in THF (normal addition), the predominant product was **11** derived from β-scission of hydrogen. When the order of addition was reversed (inverse addition) so that Cp_2TiCl was added to epoxide, the principal product was the saturated alcohol **12**. Inverse addition results in a very low instantaneous concentration of Ti(III), which disfavors mixed disproportionation. This suggests that the kinetic order in titanium(III) for the product-forming step is higher for the formation of **11** than for **12** and provides evidence for the requirement for a second equivalent of Ti(III) in the β-scission of hydrogen.

With few exceptions,[3] the Ti(III)-mediated rearrangement of trisubstituted epoxides to allylic alcohols has not been carried out under protic catalytic conditions. This is consistent with the prevailing view that $Cp_2Ti(H)Cl$ is a robust species that would not readily react with coll·HCl to regenerate Cp_2TiCl_2.[4,5] To address this issue, Takahashi and co-workers proposed the use of triethylborane as an additive to promote the reduction of $Cp_2Ti(H)Cl$.[3] In another approach, Barrero and co-workers introduced an alternative catalytic protocol, which proceeds under aprotic conditions.[26] The coll·HCl that is used in protic catalysis is replaced with a combination of chlorotrimethylsilane and 2,4,6-collidine. Under these conditions, the titanium alkoxide product will be converted to the corresponding trimethylsilyl ether, regenerating Cp_2TiCl_2, as illustrated for alkoxide **8a** in eq 3.

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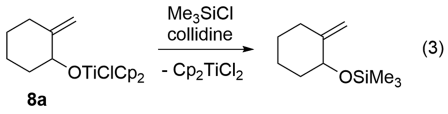
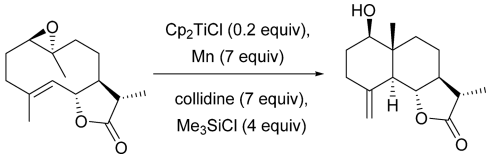


(3)

In addition, it has been proposed that chlorotrimethylsilane is able to regenerate Cp_2TiCl_2 from $Cp_2Ti(H)Cl$ according to eq 4.[4] This reaction is presumed to proceed by σ-bond metathesis and produces Me_3SiH as a coproduct (although no evidence for the formation of Me_3SiH has been reported).

$$Cp_2Ti(H)Cl + Me_3SiCl \rightarrow Cp_2TiCl_2 + Me_3SiH \quad (4)$$

Aprotic catalysis of titanium(III)-mediated epoxide opening has been successfully applied not only to simple reactions such as the rearrangement of trisubstituted epoxides but also to an array of cyclization and polycyclization reactions. A compelling example is the transannular cyclization of the simple germacrolide derivative in eq 5, which affords (after desilylative workup) a useful bicyclic product as a single stereoisomer in 68% isolated yield.[27]



(5)

RESULTS AND DISCUSSION

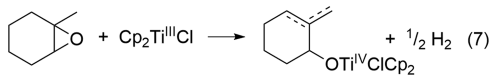
The fact that $Cp_2Ti(H)Cl$ has never been isolated caused us to wonder whether this complex is in actuality thermally stable. To address this question, we first examined the stability of **1** using DFT calculations. These studies revealed that the decomposition of $Cp_2Ti(H)Cl$ to Cp_2TiCl and molecular hydrogen in THF (eq 6) is in fact exothermic (ΔG = −9.4 kcal/mol at the PW6B95-D3 level of theory). The effects of explicit THF solvation were not included in this preliminary study.

$$Cp_2Ti(H)Cl \rightarrow Cp_2TiCl + 1/2H_2 \quad (6)$$

With this preliminary computational result in hand, we proceeded to the laboratory for a closer examination of Scheme 3. A 0.33 M solution of Cp_2TiCl was prepared by stirring a solution of Cp_2TiCl_2 (2.0 mmol) with excess zinc dust (6 mmol) in THF (6.0 mL). To this solution was added a solution of 1-methylcyclohexene oxide (2.0 mmol) in THF (2.0 mL) over the course of several minutes. During the addition, vigorous evolution of gas was observed. Rapid gas evolution ceased after 5 min. At this point the volume of gas produced could be determined by gas buret; after correction to standard temperature and pressure it corresponded to the release of 0.94 mmol of gas. The identity of the gas was confirmed to be hydrogen by gas chromatography.

GLC analysis after quenching with dilute acid indicated that the allylic alcohols **9a** and **9b** were formed in a 5:1 ratio (Scheme 3). Their identity was confirmed by GC-MS followed by isolation and spectroscopic analysis of the mixture. The combined yield of **9a** and **9b** was shown by GLC versus an internal standard to be 1.88 mmol (94%). These data show that the stoichiometry for the overall transformation is best described by eq 7.

On the basis of these experiments it appears that the Ti(IV)-intermediate $Cp_2Ti(H)Cl$ is in fact an unstable compound



(7)

which decomposes rapidly in THF solution at room temperature. A practical consequence of this fact is that it should not be necessary to employ 2 or 3 equiv of Cp_2TiCl in the conversion of trisubstituted epoxides to allylic alcohols as is the general practice.[21,22] The second equivalent of Cp_2TiCl is unnecessary, since half of the reagent would be converted to $Cp_2Ti(H)Cl$ which then decomposes, regenerating Cp_2TiCl. In fact, we have confirmed this experimentally (see Table 3, entry 1).

The observed instability of **1** stands in contrast to the known stability of its sterically encumbered pentamethylcyclopentadienyl (Cp*) analogue. Treatment of $(Cp^*)_2TiH$ with lead(II) chloride results in oxidation of titanium to the +4 oxidation state and affords $(Cp^*)_2Ti(H)Cl$.[10] The analogue $(PhC_5Me_4)_2Ti(H)Cl$ was similarly prepared.[11]

It is reasonable to assume that decomposition of $Cp_2Ti(H)Cl$ follows a bimolecular pathway because of the requirement that H_2 is generated in this process. A unimolecular pathway would require formation of atomic hydrogen, which is a high-energy intermediate.[28] Moreover, if formed, atomic hydrogen would be expected to rapidly abstract hydrogen from the solvent THF, which would not be consistent with the observed stoichiometry. A bimolecular pathway also helps to explain the kinetic stability of sterically hindered $(Cp^*)_2Ti(H)Cl$.

The calculations in Table 1 compare the energetics of the decomposition process in THF for three different complexes at two different levels of theory but ignore the specific effects of THF solvation. The ΔG_{solv} term in the last column employs the COSMO-RS solvation model to incorporate the overall effect of the solvent (dielectric constant, etc.) but does not include explicit THF coordination. Table 1 suggests that, independent of substitution on the cyclopentadienyl rings, the decomposition of the hydridochloride complexes is exothermic.

Table 1. Calculated Thermodynamic Parameters for $Cp_2Ti(H)Cl \rightarrow Cp_2TiCl + 1/2H_2$

complex	level[a]	ΔE (kcal/mol)	ΔG (kcal/mol)	ΔG_{solv} (kcal/mol)
Cp_2TiHCl	B3LYP-D3	−3.25	−8.95	−8.62
	PW6B95-D3	−4.00	−9.70	−9.37
$(ClC_5H_4)_2TiHCl$	B3LYP-D3	−4.25	−10.06	−11.06
	PW6B95-D3	−5.12	−10.93	−11.93
Cp^*_2TiHCl	B3LYP-D3	−2.68	−8.77	−7.96
	PW6B95-D3	−3.36	−9.45	−8.63

[a]B3LYP-D3-COSMO-RS/def2-QZVP//TPSS-D3/def2-TZVP in THF at 298.15 K or PW6B95-D3-COSMO-RS/def2-QZVP//TPSS-D3/def2-TZVP in THF at 298.15 K.

On comparison of the various complexes, differences in ΔG arise primarily from differences in the change in electronic energy ΔE. The other contributions to ΔG (entropy and zero-point energy) are essentially constant for all complexes. The order of stability of the three complexes is consistent with their expected redox potentials. The electron-withdrawing chlorine atoms in $(ClC_5H_4)_2Ti(H)Cl$ significantly destabilize that complex relative to the parent $Cp_2Ti(H)Cl$. The electron-donating methyl groups of $(Cp^*)_2Ti(H)Cl$ stabilize it relative to $Cp_2Ti(H)Cl$.

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However, the results in Table 1 are problematic in that the decomposition of $(Cp^*)_2Ti(H)Cl$ is predicted to be favorable. For this reason, we carried out additional calculations incorporating explicit THF solvation. It has been noted previously that explicit calculation of solvent molecules coordinating to a titanium(III) center can provide more reasonable energies.[33] (Cp_2TiCl exists in THF solution as a equilibrating mixture of monomeric $Cp_2TiCl(THF)$ and its dimer. For simplicity, we consider only the monomer and do not expect this simplification to significantly affect our conclusions.) These results are summarized in Table 2.

Table 2. Calculated Thermodynamics for Cp_2TiHCl + THF → $Cp_2Tl(THF)Cl$ + 1/2H_2

complex	level[a]	ΔE (kcal/mol)	ΔG (kcal/mol}	ΔG_{solv} (kcal/mol)
Cp_2TiHCl	B3LYP-D3	−15.25	−6.60	−10.50
	PW6B95-D3	−16.30	−7.65	−11.55
$(ClC_5H_4)_2TiHCl$	B3LYP-D3	−16.25	−7.52	−11.67
	PW6B95-D3	−17.03	−8.30	−12.45
Cp^*_2TiHCl	B3LYP-D3	−7.54	+2.19	−0.04
	PW6B95-D3	−8.64	+1.09	−1.15

[a]B3LYP-D3-COSMO-RS/def2-QZVP//TPSS-D3/def2-TZVP in THF at 298.15 K or PW6B95-D3-COSMO-RS/def2-QZVP//TPSS-D3/def2-TZVP in THF at 298.15 K.

The data in Table 2 indicate that decomposition of $Cp_2Ti(H)Cl$ and $(ClC_5H_4)_2Ti(H)Cl$ are further promoted by the effect of THF solvation. Explicit solvation of the titanium atom is possible and has the expected effect (quenching of Lewis acidity).

Interestingly, the data in Table 2 indicate that decomposition of $(Cp^*)_2Ti(H)Cl$ is approximately thermoneutral in THF solution. At first glance, it may seem strange that explicit solvation is actually unfavorable in the case of $(Cp^*)_2Ti(H)Cl$. However, in this case the THF is not strongly bonded in the $(Cp^*)_2TiCl$ product and in a sense Ti is actually not solvated. We suggest that decomposition of $(Cp^*)_2Ti(H)Cl$ is not observed in THF solution due to both kinetic and thermodynamic factors. The extreme steric bulk of the Cp* ligands precludes the necessary bimolecular pathway required for decomposition. In addition, there is little or no driving force for decomposition of $(Cp^*)_2Ti(H)Cl$ to $(Cp^*)_2TiCl$ and H_2.

Thus, the instability of $Cp_2Ti(H)Cl$ is confirmed both in the laboratory and by computations. It seems unlikely that the σ-bond metathesis in eq 4 plays a role in the mechanism of aprotic catalysis. In fact, our calculations suggest that eq 4 is approximately thermoneutral. The calculated ΔG value is −0.18 kcal/mol at the PW6B95-D3 level. Given that no experimental evidence for the formation of Me_3SiH has been reported,[4] σ-bond metathesis (eq 4) does not seem to be operating. Therefore, we limited our calculations to the thermodynamic features of both processes. Clearly, the H_2 formation is largely favored thermodynamically. The higher driving force seems to lead to a faster H_2 formation.

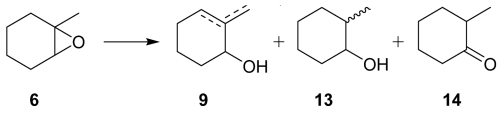
Aprotic catalysis has been successfully employed for the rearrangement of trisubstituted epoxides to allylic alcohols. In contrast, there is a single report where this transformation was attempted under the conditions of protic catalysis.[3] It is not clear whether this situation simply reflects the assumption that the formation of $Cp_2Ti(H)Cl$ would interrupt the catalytic cycle under protic conditions. To clarify this situation, we returned to the laboratory to examine the reaction of epoxide **6** under the conditions of protic catalysis.

In these experiments, zinc powder was employed as stoichiometric reductant and 2,4,6-collidine hydrochloride as buffered Brønsted acid. All of the reactions in Table 3 were carried out under similar conditions (THF, 20 h, room temperature, and 0.25 M except as otherwise indicated). When a substoichiometric amount of Cp_2TiCl_2 was utilized, in addition to the allylic alcohols **9**, the 2-methylcyclohexanols *cis*- and *trans*-**13** and 2-methylcyclohexanone **14** were also produced, as shown in eq 8.

Table 3. Product Distribution from Eq 8 under Stoichiometric Conditions versus Protic Catalysis[a,b]

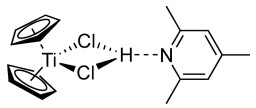
entry	Cp_2TiCl_2 (equiv)	coll·HCl (equiv)	solvent	**9** (%)	**13** (%)	**14** (%)
1[c]	1.00	0.00	THF	100	0	0
2	0.25	1.50	THF	44	53	3
3[d]	0.25	1.50	Et_2O	71	24	5
4	0.25	1.50	toluene	67	24	9

[a]Reaction conditions 0.25 M, room temperature, 3.0 equiv of Zn, 20 h unless otherwise indicated. [b]Product ratios determined by GC-MS and NMR. [c]Reaction complete in 15 min; gas evolution observed. [d]Reaction complete after 2.5 h.



6 9 13 14 (8)

When entries 1 and 2 in Table 3 are compared, it is evident that the diminished yield of allylic alcohols **9** under protic catalytic conditions is not due to a failure of catalytic turnover, since complete conversion of epoxide **6** is achieved in each case. Instead, a new pathway arises under protic catalytic conditions, in which a significant proportion of the starting epoxide is converted to the reduction product, alcohols **13**. This change in product distribution was also observed (although to a lesser extent) when the THF solvent was replaced with diethyl ether or toluene (entries 3 and 4). We suggest that this result is related to the fact that, in the presence of excess coll·HCl (especially in THF), titanium(III) is largely present as complex **15**. Recent studies have underscored the importance of complex **15** in stabilizing titanium(III) during protic catalytic reactions.[29]



15

The role of **15** in other reactions of epoxides with Ti(III) has been delineated using cyclic voltammetry, kinetics, and computational studies.[30] It was shown that reversible formation of **15** diminishes the concentration of active Cp_2TiCl reagent, suppressing radical trapping by Ti(III) and therefore increasing radical lifetime. In reactions such as reduction to the corresponding alcohol or inter- or intramolecular addition, trapping of intermediate radicals by Cp_2TiCl is an undesired intermolecular side reaction and consequently the formation of **15** has a beneficial effect.

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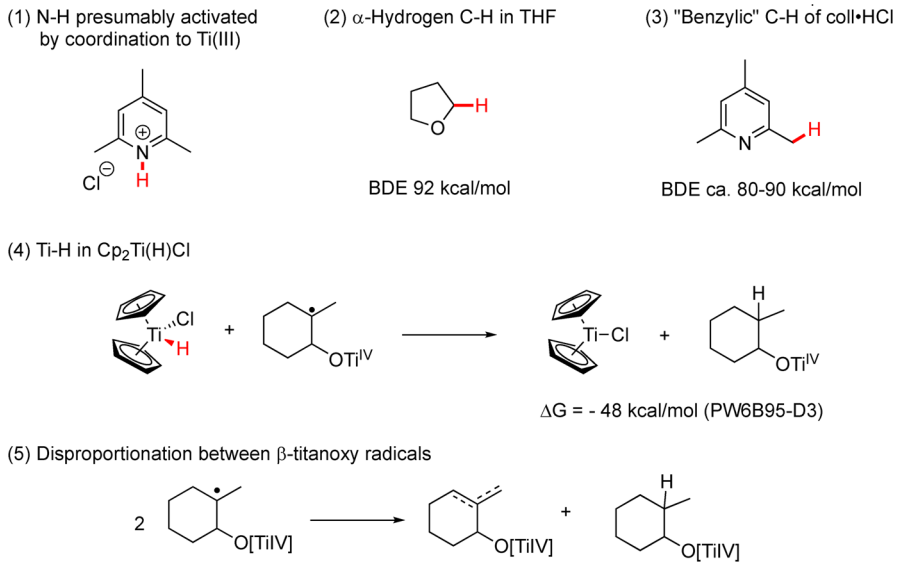
Scheme 5. Possible Sources of Hydrogen Atoms in Saturated Alcohols 13



However, mixed disproportionation (eq 2) requires interaction of the carbon-centered radical **7** with the active Cp_2TiCl species. The above results suggest that, in the presence of excess coll·HCl, reaction of radical **7** with Ti(III) is inhibited. Consequently, the extent of mixed disproportionation is diminished and reduction of **7** by hydrogen atom abstraction increases.

This raises the following question: what is the source of hydrogen in the formation of reduction product **13**? That is to say, what is serving as the hydrogen atom donor Q–H in Scheme 2? We considered five possible candidates: (1) the N–H hydrogen atom of **15**, (2) the α-hydrogen of solvent THF, (3) the methyl hydrogen of collidine, (4) the Ti–H hydrogen atom of $Cp_2Ti(H)Cl$, and (5) disproportionation between two β-titanoxy radicals to give one molecule each of **9** and **13**. These possibilities are illustrated in Scheme 5.[31]

The first possibility requires that the N–H bond of coll·HCl is activated (weakened) by coordination to titanium(III). This type of activation would be consistent with recent discoveries regarding the activation of heteroatom–hydrogen bonds by Ti(III). It has been shown that the O–H hydrogen of water,[25,32,33] the O–H hydrogen of methanol,[34] and the N–H hydrogen of amides[35−37] can all be activated as hydrogen atom donors when they are complexed to Cp_2TiCl.

The second possibility is that the α-hydrogen atoms in solvent THF are being abstracted by the intermediate β-titanoxy radicals. It can be noted that the BDE for the α-hydrogen of THF is 92 kcal/mol[38] and these hydrogens might arguably be further activated when THF is coordinated to Ti(III).

The third candidate would be the "benzylic" methyl groups on 2,4,6-collidine. The concentration of collidine is low in comparison to that of THF, but HAT from collidine benefits from a statistical factor of nine benzylic hydrogens per molecule. We are unaware of any reported BDE data for the C–H bonds of 2,4,6-collidine. However, the BDE for 2-picoline has been estimated to be 87.2 kcal/mol and that for 4-picoline as 86.5 kcal/mol.[39] It might be argued that electron release from multiple methyl groups in collidine would further lower this number. In the early stages of a protic catalytic reaction, collidine will be present as its hydrochloride salt, which we expect will be less reactive as a hydrogen atom donor. However, as the reaction proceeds, more and more of the hydrochloride is converted to the free base. It has been noted that when collidine is added to the *stoichiometric* reactions of trisubstituted epoxides with Cp_2TiCl, β-scission is greatly diminished and reduction via hydrogen abstraction is instead observed.[23b]

Fourth, it is conceivable that $Cp_2Ti(H)Cl$ is functioning as a hydrogen transfer agent. The instantaneous concentration of $Cp_2Ti(H)Cl$ will be low due to the fact that a substoichiometric amount of titanium is utilized and especially due to the rapid decomposition of $Cp_2Ti(H)Cl$ under the reaction conditions. Balanced against this, the reaction of a carbon-centered radical with $Cp_2Ti(H)Cl$ results in the replacement of a weak Ti–H bond with a far more stable C–H bond and the process should be highly exothermic. For example, we calculated ΔG for the reaction of radical **7** (see Scheme 3) with $Cp_2Ti(H)Cl$. At the PW6B95-D3 level of theory, after correction for the effect of bulk THF solvent, $\Delta G = -48$ kcal/mol for this process. (See the Supporting Information for details.)

Fifth, the final possibility would be disproportionation between two β-titanoxy groups. This process would necessarily produce equal amounts of unsaturated alcohols **9** and saturated alcohols **13**.

In an effort to determine the identity of the hydrogen atom donor, isotopic labeling studies were carried out using isotopically labeled THF-d_8, collidine deuteriochloride, or both. These studies might militate in favor of or against possibilities 1 and 2.

Table 4 summarizes GC-MS studies of the *cis*-**13** obtained when eq 8 was carried out. The observed (M + 1)/M ratios were adjusted for the 7.8% contribution to M + 1 from natural-abundance ^{13}C. Up to 26% deuterium incorporation was observed when the reaction was carried out in THF-d_8 using coll·DCl as the buffered acid.

The location of the isotopic label in *cis*-**13** produced in these experiments was confirmed to be the tertiary (methyl-bearing) carbon using 600 MHz ^1H NMR. The resonance for the tertiary hydrogen was located using a combination of COSY, HSQC, and 1D-decoupling and appears as a multiplet in the δ

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Table 4. GC-MS Results for Deuterium Labeling Studies

entry	sample	(M + 1)/M[a]	D incorporation (%)[b]
1	authentic *cis*-**10**	0.072	0
2	*cis*-**10** prepared using coll·HCl in THF-d_8	0.087	1
3	*cis*-**10** prepared using coll·DCl in protio THF	0.25	14
4	*cis*-**10** prepared using coll·DCl in THF-d_8	0.46	26

[a]Ratio of m/z 115 to m/z 114 before correction for 7.8% contribution from ^{13}C. [b]Calculated as % D = (ratio − 0.078)/(1.00 + ratio).

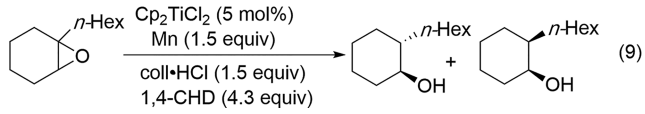
1.61−1.64 region. The tertiary hydrogen resonance itself is poorly resolved due to overlapping resonances, which interferes with integration. However, the associated methyl resonance proved more useful. In protio-*cis*-**13** the methyl group appears as a doublet (J = 6.8 Hz) at δ 0.94 ppm. For deuterium-labeled *cis*-**10** this resonance collapses to a singlet, which exhibits the expected[40] upfield isotopic shift to 0.93 ppm. Integration of these peaks was consistent with the results of GC-MS analysis.

Since the labeling studies in Table 4 account for only 26% of the saturated alcohol, the remaining hydrogen must originate from a source other than THF-d_8 or coll·DCl. The remaining candidates are the methyl hydrogen atoms of collidine, the hydride of $Cp_2Ti(H)Cl$, or direct disproportionation between β-titanoxy radicals. Distinguishing between these possibilities must await additional isotopic labeling studies: e.g., labeling of the epoxide (and indeed the final two possibilities would be difficult to distinguish on the basis of labeling studies).

We believe that our results are best understood in terms of the different titanium(III) species present in solution during protic catalysis versus stoichiometric conditions (or aprotic catalysis). Under stoichiometric conditions, Ti(III) is mainly present as $Cp_2TiCl(THF)$.[41,42] The weakly coordinated THF ligand is readily displaced so that titanium(III) is available for cross-disproportionation with a β-titanoxy radical such as **7**. However, in protic catalysis, Ti(III) is complexed with coll·HCl in the form of **15**.[30,43] The titanium(III) is not as readily available to trap the intermediate β-titanoxy radical. Therefore, carbon-centered radical **7** survives and is ultimately quenched by hydrogen abstraction.

Earlier we noted that the order of addition of epoxide and Ti(III) affected the products formed from epoxide **10**. We observed a similar, though considerably smaller, effect in the stoichiometric reaction of epoxide **6** with Cp_2TiCl. The ratio of the products of reduction (*cis*-**13** + *trans*-**13**) to the products of H atom loss (**9a** + **9b** + **14**) was different depending on the mode of addition. Normal addition under stoichiometric conditions gave less of the reduction product (ratio = 0.11) in comparison with reverse addition of Cp_2TiCl to the epoxide (ratio = 0.29). The corresponding ratio for the catalytic reactions was 0.39, although the reaction conditions are not strictly comparable, with excess coll·HCl also being present in the catalytic reactions. It is not clear why the magnitude of this effect is lower for epoxide **6** versus epoxide **10**, but presumably it reflects the greater steric encumbrance of **10**.

It is evident that aprotic catalysis will be superior to protic catalysis when the desired termination step from Ti(III)-catalyzed epoxide ring opening is β-scission of hydrogen. However, it is worth reiterating that the diminished reactivity of **15** as a hydrogen atom acceptor can be beneficial for types of reactions where β-scission is an undesired side reaction.[44] In particular, we note that the reduction of certain trisubstituted epoxides to the corresponding alcohol under protic catalysis is a clean and high-yielding transformation. For example, the reduction of epoxide **16** in eq 9 affords the secondary alcohol



(9)

17 in 86% yield as a 2:1 mixture of diastereomers using just 5% of Cp_2TiCl_2 as catalyst.[45] In this reaction, 1,4-cyclohexadiene functions as the hydrogen atom donor.

Finally, several attempts were made to observe $Cp_2Ti(H)Cl$, generated according to Scheme 3, using in situ infrared spectrometry. We hoped to observe the ν(Ti−H) band in the 1600 cm^{-1} region by analogy to the strong band observed at 1605 cm^{-1} for $Cp^*_2Ti(H)Cl$.[46] However, rapid gas evolution disrupted the operation of the IR detector of the spectrometer. It is noteworthy that gas evolution was rapid even when the reaction was carried out at −40 °C.

CONCLUSIONS

The combination of experimental work and computations used in this study has provided a series of surprises and has several practical consequences. The conventional wisdom that $Cp_2Ti(H)Cl$ is a robust species that resists reduction to the Ti(III) oxidation state is not correct. In contrast, $Cp_2Ti(H)Cl$ spontaneously decomposes to regenerate Cp_2TiCl and molecular hydrogen. The failure of protic catalytic conditions to cleanly promote the conversion of trisubstituted epoxides to allylic alcohols is the result of competing hydrogen atom transfer rather than an interruption in catalyst turnover. Aprotic catalysis does not require the putative σ-bond metathesis of $Cp_2Ti(H)Cl$ with Me_3SiCl. The stoichiometric reactions of trisubstituted epoxides with Cp_2TiCl have previously been carried out using 2 or 3 equiv of the titanium(III) reagent. Our results demonstrate that a single equivalent of Cp_2TiCl will suffice. (Nevertheless, it appears prudent to use a ca. 20% excess of Cp_2TiCl to avoid potential side reactions when the titanium(III) concentration becomes very low near the end of the reaction.) The previously undocumented, rapid evolution of hydrogen may represent a safety concern for emerging large-scale applications of this chemistry.[47]

The fundamental difference between protic and aprotic catalysis of the reaction of Cp_2TiCl with epoxides is the form of Ti(III) that is present. In aprotic catalysis, Ti(III) is present as $Cp_2TiCl(THF)$ where the titanium(III) center is available to participate in reactions with carbon-centered radicals. In protic catalysis, Cp_2TiCl and coll·HCl form the stable complex **15**, which less readily reacts with carbon-centered radicals. For these reasons, protic and aprotic catalysis of these reactions are in fact complementary protocols. Aprotic catalysis will generally prove superior when scission of β-hydrogen or deoxygenation is the desired termination step. Protic catalysis will be advantageous when reduction of the epoxide via hydrogen atom transfer is desired, especially with an added hydrogen atom donor such as 1,4-cyclohexadiene.

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EXPERIMENTAL SECTION

Reaction of Cp_2TiCl with 1,2-Epoxy-1-methylcyclohexane (6). Titanocene dichloride (0.498 g, 2.00 mmol) and zinc dust (0.393 g, 6.00 mmol) were placed in a Schlenk flask which was then flushed with argon. To the flask were added THF (6.0 mL) and *tert*-butyl methyl ether (238 mL, 0.177 g, 2.00 mmol) as an internal standard. The mixture was stirred for 30 min at which time the initial red color had discharged to lime green. The flask was closed to argon, and a thin tube was fed from the flask into an inverted buret filled with water (see photograph in the Supporting Information). A solution of epoxide (0.225 g, 2.00 mmol) in 1.5 mL of THF was added slowly, and as gas evolved, it bubbled into the buret to displace 22.4 mL of water. The reaction was quenched with 2.5 mL of saturated aqueous sodium hydrogen carbonate. Gas chromatographic analysis indicated the formation of allylic alcohols **9a** and **9b** (1.88 mmol) in a 5:1 ratio. The solution was filtered over Celite and rinsed with THF and was subjected to flash chromatography (4/1 pentane/diethyl ether). $CDCl_3$ was added to the residue and removed at reduced pressure to obtain an approximately 3/2 mixture of 2-methylenecyclohexan-1-ol (**9a**; major) and 2-methylcyclohex-2-en-1-ol (**9b**; minor) free of residual solvents. NMR analysis and comparison with literature data[48,49] allowed the assignment of the spectra as follows. For the major product **9a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (s, 1H), 4.77 (s, 1H), 4.09−4.13 (m, 1H), 2.41−2.45 (m, 1H), 1.94−1.53 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 105.0, 72.7, 36.7, 33.5, 27.7, 23.8; GC-MS m/z 112.10 ([M^+]), calcd for $C_7H_{12}O$ 112.09. For the minor product **9b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (br s, 1H), 4.00 (t, J = 4.4 Hz) (m, 1H), 1.94−1.53 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.3, 125.5, 68.5, 32.2, 25.4, 20.6, 18.1; GC-MS m/z 112.10 ([M^+]), calcd for $C_7H_{12}O$ 112.09.

Procedure for Catalytic Reactions in Table 3. In a Schlenk tube, 2,4,6-collidinium chloride (1.50 equiv) was sublimed in vacuo with careful heating. After they were cooled to room temperature, the solids were flushed with argon and transferred back to the bottom of the flask. Zn powder (3.00 equiv) and Cp_2TiCl_2 (0.05 to 1.00 equiv) were added, and the solids were evacuated and flushed with argon three times. Dry THF (substrate 0.25 M) was added via syringe, and the reaction mixture was stirred for 15 min at room temperature. The solution turned green within minutes. 1,2-Epoxy-1-methylcyclohexane (1.00 equiv) was added via syringe, and the reaction mixture was stirred under argon at room temperature for the indicated time. Saturated aqueous NH_4Cl solution was added (100% v/v THF), and the aqueous phase was extracted with ethyl acetate three times. The combined yellow organic phase was filtered through a short silica pad. The solvent was removed under reduced pressure (not below 150 mbar at 40 °C, due to volatility of the substrate and products) to yield the crude product, which was subjected to GC-MS analysis.

A sample of the product obtained under the conditions of Table 3, entry 2, was carefully chromatographed on silica using 10% ether in pentane to collect various fractions for identifications. The order of elution was as follows: *cis*-**13** Me at δ 0.939 (J = 6.6 Hz), α-H at δ 3.77; **9a**, α-H at δ 4.089; **9b** α-H at δ 3.987; *trans*-**13**, Me at δ 1.004 (J = 6.6 Hz), α-H at δ 3.10. The ketone **14** and the *cis*-**13** and *trans*-**13** alcohols were further confirmed by coinjection in the GC with authentic samples. Samples of the saturated alcohols were obtained by $NaBH_4$ reduction of the commercially available **14** (ratio of *cis*-**13** to *trans*-**13** 42:58). Pure samples of *cis*-**13** and *trans*-**13** were isolated by careful column chromatography on silica gel using 20/1 pentane/ether as eluent. Spectra for *cis*-**13** and *trans*-**13** match those in the literature.[50] The C_2-H in *cis*-**13** was identified by ^{1}H COSY and decoupling experiments. Irradiation of the CH_3 (δ 0.939) doublet shows simplification of the multiplet centered around δ 1.61−1.64. Conversely, decoupling of the broad peak at δ 1.63 causes the CH_3 signal to appear as a singlet. See Supporting Information for details.

Preparation of Collidine Deuteriochloride for Isotopic Labeling Studies. A Schlenk flask equipped with a stir bar was charged with 2,4,6-collidine (1 mL, 7.57 mmol, d = 0.917 g/mL, 1 equiv) in a N_2 filled glovebox before transferring to the Schlenk line. Diethyl ether (5 mL) was added followed by a commercial 1 M deuterium chloride (96% D) in ether solution (9.0 mL, 9.0 mmol, 1.2 equiv). A white solid precipitate formed immediately and was stirred for several minutes. The remaining Et_2O was decanted and removed with a syringe through the septum. The solid was washed with Et_2O (3 × 10 mL) and decanted using a syringe. The flask was then returned to the glovebox and the remaining Et_2O was removed under vacuum to yield coll·DCl (0.996 g, 83% yield). The deuterium content was established to be ca. 90% by integration of the residual NH resonance in the ^{1}H NMR at δ 17.3 ppm. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.52 (s, 6H), 2.90 (s, 3H), 7.20 (s, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 19.3, 22.1, 125.2, 153, 157.9.

Procedure for Isotopic Labeling Studies in Table 4. In a N_2-filled glovebox an oven-dried Schlenk flask (or a 20 mL screw-capped vial for small-scale reactions) equipped with a stir bar was charged with collidine·DCl (238 mg, 1.5 equiv) or collidine·HCl (235 mg, 1.5 equiv), activated Zn (199 mg, 3 equiv), and Cp_2TiCl_2 (62 mg, 0.25 equiv), after which was added distilled THF or THF-d_8 (4 mL, to make a 0.25 M solution in epoxide). The greenish turbid solution was stirred for 15 min before 1,2-epoxy-1-methylcyclohexane (124 μL, 1.00 mmol, 1 equiv, density = 0.905 g mL^{-1}) was added via a microsyringe. The solution showed a slight reddish color, and gas evolution was observed. After it was stirred for 1 h, the reaction mixture was quenched with saturated NH_4Cl (4 mL) and extracted with Et_2O. The yellow solution was filtered over a pad of silica and eluted with Et_2O (100 mL), and the solvent was evaporated under reduced pressure to obtain the crude product, which was analyzed by GC-MS (HP-5MS 5% phenyl methyl silicone (HP-5) capillary column, 30 m length, 250 μm diameter, 0.25 μm film thickness, 35 °C 5 min, 5°/min to 250 °C and hold 2 min). The relative intensities for the M and M + 1 peaks were determined by integrating the total ion current for the *cis*-**10** molecular ion (retention time 3.39 min) at m/z 114 and 115. For details of the determination of isotopic composition of products, see the Supporting Information.

Computational Details. DFT calculations were carried out with the TURBOMOLE 7.0 program package.[51] Geometries were first optimized at the TPSS[52]-D3[53,54]/def2-TZVP[55] level of theory. Final reaction free energy values were obtained through single-point calculations on the PW6B95[56]-D3 or B3LYP[57,58]-D3 level in the gas phase. Solvation contributions to ΔG were included using the COSMO-RS continuum solvation model.[59,60] For a full description of the computational methods and data, see the Supporting Information.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.8b00793.

General experimental details, preparation of **6** and authentic *cis*- and *trans*-**13**, ^{1}H and ^{13}C NMR data, GC-MS chromatograms, mechanistic discussion of β-hydrogen scission, and complete computational details (PDF)

Cartesian coordinates for optimized structures (XYZ)

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Notes

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(31) It cannot be completely ruled out that radical **7** could be trapped by Cp_2TiCl, affording a 3° alkyltitanium species which then undergoes protonolysis to afford saturated alcohols **13**. We believe this is unlikely for reasons discussed in detail in the pp S13−S14 in the Supporting Information. Moreover, the results in Table 4 would require that this be a minor pathway. Nevertheless, it can be noted that $Cp_2Ti(R)Cl$, R = 3° alkyl, can be prepared for bridgehead alkyl derivative where β-hydride elimination would result in formation of an anti-Bredt alkene: Dimitrov, V. Preparation and Properties of Cyclopentadienyltitanium(IV)-1-Norbornyl Compounds. *J. Organomet. Chem.* **1985**, *282*, 321−329.

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