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## Accepted Article

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## RESEARCH ARTICLE

# Direct and Unified Access to Carbon Radicals from Aliphatic Alcohols by Cost-Efficient Titanium-Mediated Homolytic C–OH Bond Cleavage

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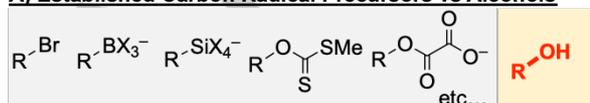
**Abstract:** Low-valent Ti-mediated homolytic C–O bond cleavage offers unified access to carbon radicals from ubiquitous non-activated tertiary, secondary, and even primary alcohols. In contrast to the representative Ti reagents, which were ineffective for this purpose, “TiCl<sub>2</sub>(cat)"/Zn (cat = catechol) was found to be specifically active. This method was applied to the addition reactions of radicals to alkenes and exhibited high generality and yields. More than 50 combinations were examined. The excellent cost-efficiency and accessibility of “TiCl<sub>2</sub>(cat)"/Zn further enhance its applicability. Control experiments proved the presence of a carbon radical intermediate and excluded the pathway via alkyl chlorides. Further mechanistic study indicated that the 1:2 complex of alkoxide (R–O<sup>−</sup>) and Ti(III) is an active species in the C–O cleavage.

## Introduction

Carbon radicals are still attracting the attention of many researchers despite being known for more than a century.<sup>1</sup> Their characteristic reactivity independent of the normal two-electron-transfer chemistry has promoted their synthetic applications. Accordingly, the applications of carbon radicals have been actively studied, specifically in the last decade.<sup>2</sup> With this progress, the demand for facile access to carbon radicals has considerably increased and prompted researchers to develop non-traditional strategies for this purpose (Scheme 1A).<sup>3</sup> However, advance preparation of appropriate carbon radical precursors is required to generate carbon radicals via these strategies. To overcome this drawback, numerous efforts have been made, for example, one-pot operation<sup>4</sup> and recovery methods for activating agents.<sup>5</sup>

Directly using ubiquitous organic species, such as alcohols, as carbon radical equivalents can solve this problem and can be an ideal method in terms of accessibility and cost-efficiency.<sup>6,7</sup> Our brief survey on the commercial availability of alcohols and halides clearly shows that the number of primary, secondary, and tertiary alcohols is more than that of primary, secondary, and tertiary halides, indicating the advantage of using alcohols in radical reactions (Scheme 1B). By comparing the prices of isopropyl derivatives, it is found that alcohols are excellent resources for general organic synthesis. Therefore, in 2018, our group developed a low-valent Ti-mediated homolytic C–OH bond cleavage method and applied it to radical alkene insertion reactions (Giese-type reaction)<sup>8</sup> utilizing benzyl alcohols as carbon radical precursors. TiCl<sub>4</sub>(collidine)/Mn system was a key

### A) Established Carbon Radical Precursors vs Alcohols



underdeveloped

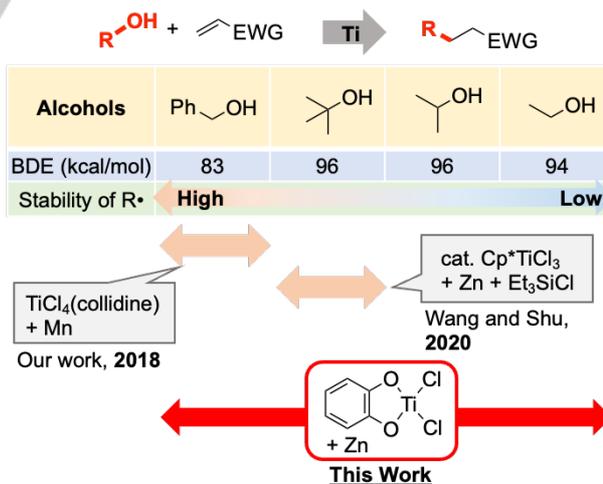
unmet benefits: cost-efficiency, high accessibility and skipping pre-transformations

### B) Examples of Accessibility to Alcohols

1. Number of commercially available compounds      2. Prices of isopropyl compounds (with highest grades)

	R-OH	R-Cl	R-Br	R-I	OH	Br	MgBr	B(OH) <sub>2</sub>
1°	958	453	461	52				
2°	923	76	106	8	1.1	7.8	440	3060
3°	346	18	28	3	USD/mol, from FUJIFILM Wako Pure Chemical Corporation			
total	2227	547	595	63	from Tokyo Chemical Industry, Co. Ltd.			

### C) Ti-Mediated C–OH Homolysis in Giese-Type Reaction



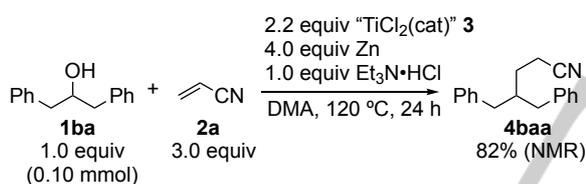
Scheme 1. Alcohols in Radical Chemistry.

to this discovery (Scheme 1C).<sup>9,10</sup> However, this study also demonstrated the stiffness of “non-activated” (without conjugation except for hyperconjugation) alcohols originating from the significant gap between the bond-dissociation energies (BDEs) of

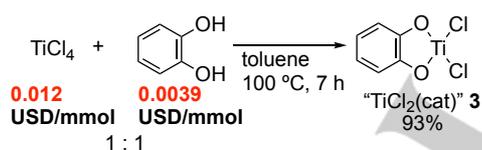
## RESEARCH ARTICLE

benzylic and non-activated C–OH bonds. For instance, the reported BDE of a benzylic C–OH bond is 83 kcal/mol, whereas those of tertiary, secondary, and primary C–OH bonds are 96, 96, and 94 kcal/mol, respectively.<sup>11</sup> Very recently, Wang and Shu's group partially overcame this obstacle by employing 10 mol% Cp\*TiCl<sub>3</sub><sup>12</sup> and sacrificial Zn/Et<sub>3</sub>SiCl.<sup>13</sup> Interestingly, this method can selectively activate tertiary hydroxy groups while keeping the primary, secondary, and even benzylic hydroxy groups intact, contrary to the expectation based on the stability order of carbon radicals. However, to date, other non-activated alcohols, which account for a large proportion of available aliphatic alcohols, have not been used for the radical alkene addition reactions. Activating these alcohols is more challenging because the corresponding radicals exhibit lower stability. For example, the relative thermodynamic stabilization energies of *tert*-butyl, isopropyl, and ethyl radicals toward methyl radical are estimated to be –6.7, –5.5, and –3.3 kcal/mol, respectively.<sup>14</sup> Nevertheless, because of the very high ubiquity of non-activated alcohols, their seamless application to radical reactions would offer a facile strategy to organic synthesis. In this study, a strategy to directly access all tertiary, secondary and primary carbon radicals from the corresponding alcohols using a highly cost-efficient Ti reagent is reported. Moreover, this method was successfully applied to various radical alkene insertion reactions.

## Results and Discussion



Scheme 2. C–OH Homolysis Under Optimized Conditions.



Scheme 3. Preparation of "TiCl<sub>2</sub>(cat)".

We screened various Ti reagents, reductants, and other conditions for the C–O cleavage of 1,3-diphenylpropan-2-ol (**1ba**) in the presence of acrylonitrile (**2a**) as a radical acceptor, and found that "TiCl<sub>2</sub>(cat)" **3** (cat = catecholate) exhibited an outstanding performance when it was used with Zn as a reductant in *N,N*-dimethylacetamide (DMA) (Scheme 2, see ESI for the optimization study). Note that "TiCl<sub>2</sub>(cat)" is correct only in composition, and the true structure has not been reported. Although **3** includes phenolic C–O bonds, these bonds should be tolerant to homolytic cleavage because of their high BDEs (112 kcal/mol for Ph–OH). Although **3** has been reported in the literature,<sup>15</sup> it has not been employed in organic synthesis except for the reductive cleavage of C–Br bonds.<sup>16</sup>

High accessibility to **3** is another advantage (Scheme 3). **3** can be readily prepared from TiCl<sub>4</sub> and catechol in a single step without a glovebox and can be stored in a refrigerator for at least half a year. Additionally, the cost-efficiency of **3** meets the requirement for stoichiometric use. The terminal prices of TiCl<sub>4</sub> and catechol (available in normal laboratories) are only 0.012 and 0.0039 USD/mmol,<sup>17</sup> respectively because of their mass production in the industry. TiCl<sub>4</sub> is produced as an intermediate for TiO<sub>2</sub> and Ti, and catechol is used as synthetic precursors for pesticides and medicines.

Table 1. Results with Deviated Reaction Conditions.<sup>[a]</sup>

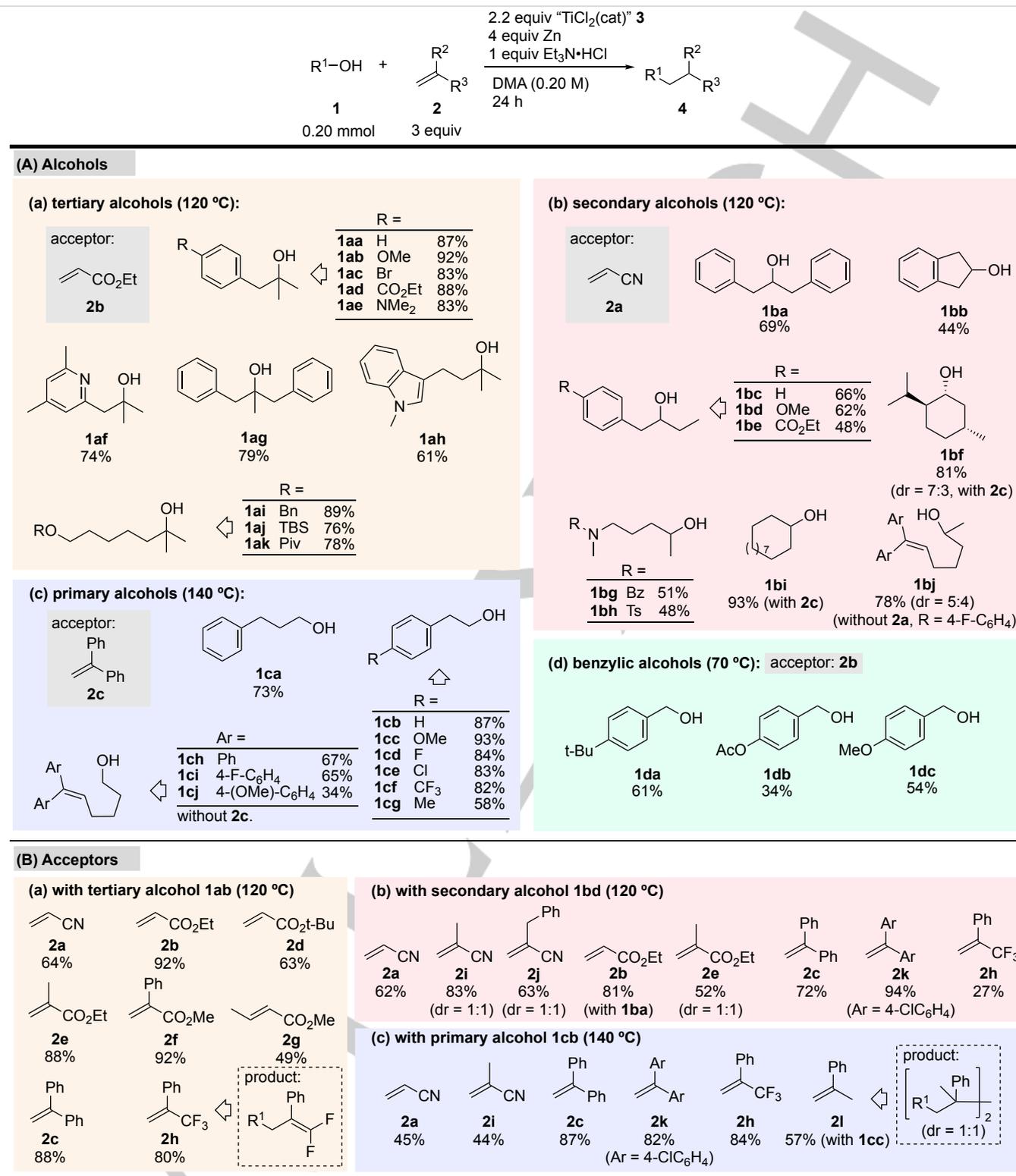
Entry	Deviation from Standard Conditions	Yield <sup>[b]</sup> /%
1	none	82
2	Cp <sub>2</sub> TiCl <sub>2</sub> instead of <b>3</b>	7
3	Cp*TiCl <sub>3</sub> instead of <b>3</b>	4
4	TiCl <sub>4</sub> (collidine) instead of <b>3</b>	8
5	TiCl <sub>4</sub> (tmeda) instead of <b>3</b>	9
6	Mn instead of Zn	32
7	without Et <sub>3</sub> N·HCl	59

[a] Standard conditions are provided in Scheme 2. [b] NMR yield.

To clearly demonstrate the effectiveness of **3**, some deviation experiments were performed using the following optimized conditions as a standard: **3**, Zn, Et<sub>3</sub>N·HCl, DMA, and 120 °C (Table 1). Representative cyclopentadienyl (Cp)-based Ti reagents Cp<sub>2</sub>TiCl<sub>2</sub> and Cp\*TiCl<sub>3</sub> demonstrated only slight reactivity to the C–O cleavage (entries 2 and 3). TiCl<sub>4</sub>(collidine)<sup>10</sup> and TiCl<sub>4</sub>(tmeda)<sup>18</sup>, which were previously reported by our group, were not very effective (entries 4 and 5). Mn powder as a reductant was less suitable than Zn (entry 6). The reaction proceeded without Et<sub>3</sub>N·HCl; however, the yield of **4baa** was considerably low (entry 7).

Selected tertiary, secondary and primary alcohols were subjected to the reaction (Table 2A). The reaction of tertiary alcohols with ethyl acrylate (**2b**) afforded the desired product in very high yields (Table 2Aa, typically 70–90% yields). The functional groups attached to the aromatic ring did not impede the reaction (**1aa–1ae**). The pyridine-derived alcohol **1af** also led to a good yield. When **1ah** was employed, a slight decrease in yield (61%) was observed owing to intramolecular hydrogen atom transfer (See Scheme 6 for the detail). The substrates bearing protected primary hydroxy groups reacted without the loss of the protective groups (**1ai–1ak**). The reactions of secondary alcohols with **2a** further confirmed the broad scope of this method (Table 2Ab, usually 50–60% yields). Benzamide **1bg** and *p*-toluenesulfonamide **1bh** were found to be suitable for this reaction. Primary radicals, one of the most challenging aliphatic carbon radicals to access, were acquired from the corresponding alcohols in very high yields (Table 2Ac, typically 60–90% yields). To date, only few studies have been reported on efficient intermolecular alkene insertion via homolytic cleavage of the non-activated primary C–O bond.<sup>19</sup> Because the intramolecular cyclization of **1ch** at 120 °C resulted in incomplete alcohol consumption (40% yield and 40% recovery), all the primary

## RESEARCH ARTICLE

Table 2. Scope of Substrates.<sup>[a]</sup>

[a] Isolated yield.

substrates were examined at a slightly higher temperature (140 °C). The reactions with benzyl alcohols completed at substantially lower temperature (Table 2Ad, 70 °C, 34–61% yields), although our previous conditions (TiCl<sub>4</sub>(collidine)/Mn

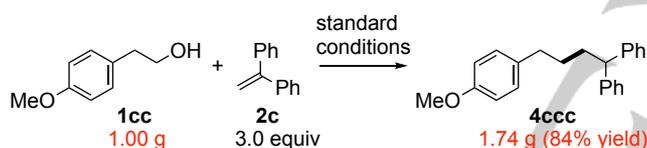
could provide a better outcome.<sup>10</sup> The reason for this relative unsuitability of conditions is the formation of deoxygenated products. For example, in the case of **1dc**, 4-methoxytoluene was produced in 42% yield. This indicated that **3/Zn** as a stronger

## RESEARCH ARTICLE

reductant further reduced the benzyl radicals.<sup>20</sup> The termination of the radical process will be discussed later.

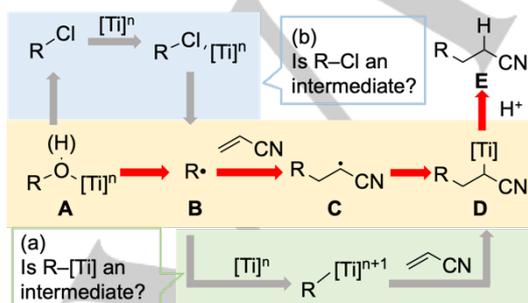
Although the primary alcohols were slightly less reactive, the “non-activated” alcohols completely reacted over a narrow temperature range (120–140 °C) regardless of the significant difference between their steric hindrances and reactivities to heterolytic C–O cleavage. In contrast, the “activated” benzylic alcohols entirely reacted at a considerably lower temperature (70 °C). These observations are in good agreement with the difference between the C–OH BDEs of these two distinct groups (94–96 vs. 83 kcal/mol) and the stability order of the corresponding free radicals.

Various radical acceptors were tested using representative tertiary, secondary, and primary alcohols (Table 2B). The reactions of tertiary alcohol **1ab** with **2a–h** afforded the corresponding adducts in high yields (Table 2Ba). Notably, the reaction of **1ab** with **2h** provided *gem*-difluoroalkene, which is gathering attention as a carbonyl isostere in medicinal chemistry.<sup>21</sup> Secondary alcohol **1bd** also successfully reacted with several acceptors (Table 2Bb). Although primary alcohol **1cb** was less suitable for radical conjugate addition to acrylonitrile derivatives, the yields acquired were still acceptable (Table 2Bc, **2a** and **2i** (45 and 44% yields), respectively). Moreover, styrene derivatives, such as **2h**, were found to be excellent acceptors even for primary radicals (84% yield).  $\alpha$ -Methyl styrene (**2l**), a presumably less reactive alkene, also reacted with **1cc** to furnish the adduct in a fair yield (57%). In this case, the product was a dimer of the benzyl radical.



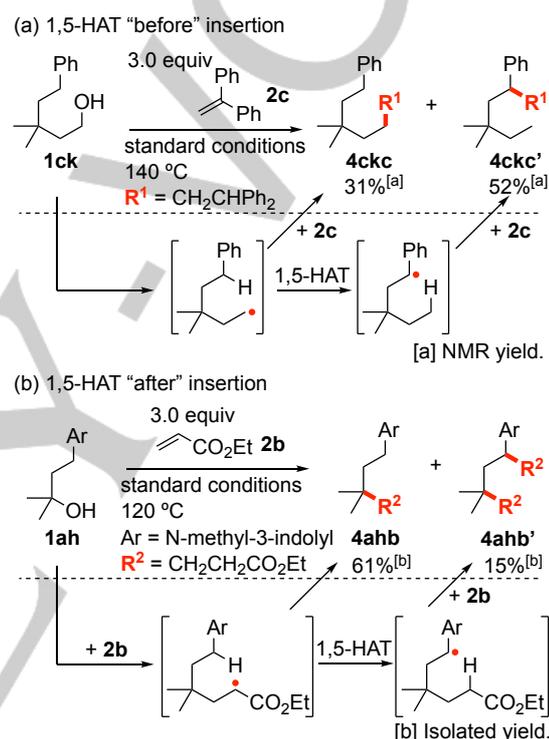
Scheme 4. Gram-Scale Synthesis Using Primary Alcohol.

Finally, we tried gram-scale synthesis to further ensure the utility of this reaction (Scheme 4). The reaction of primary alcohol **1cc** (1.00 g) and alkene **2c** successfully afforded the coupling product **4ccc** in 84% yield (1.74 g). All the reagents including **3** could be weighed under air, and a standard benchtop argon-filled balloon technique was sufficient for achieving the excellent yield. At least in this scale, the reaction could be conducted safely without the slow addition of the reagents and reactants.



Scheme 5. Proposed Mechanism and Other Scenarios.

Scheme 5 shows the proposed reaction mechanism (yellow). The reaction starts with the formation of an alcohol-Ti complex **A** followed by homolytic C–O bond cleavage, which generates a carbon radical **B**. The insertion of **B** into the alkene furnishes the adduct **C**, which is further reduced by another low-valent Ti species to furnish the enolate **D**. Finally, the protonation of **D** affords the product **E**. A couple of other possible scenarios originated from this mechanism: (a) A non-radical insertion mechanism is possible (green). Further reduction of **B** by the low-valent Ti can afford the alkyltitanium species R–[Ti], which can act as a nucleophile. (b) The corresponding alkyl chloride can be a true intermediate in the homolysis stage (blue). Indeed, Cp\*TiCl<sub>3</sub>/Zn is capable of C–Cl bond cleavage.<sup>12</sup>



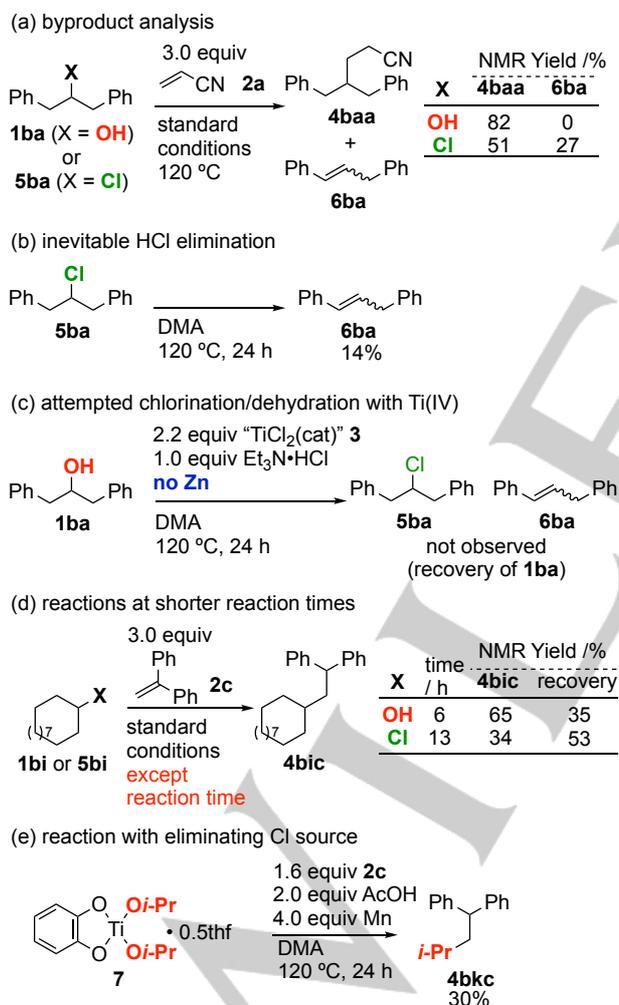
Scheme 6. 1,5-HAT Before/After Insertion.

Based on these scenarios, we conducted several mechanistic studies. To prove the participation of free radicals, we designed a couple of 1,5-hydrogen atom transfer (1,5-HAT)-based analyses,<sup>22</sup> and they proved the participation of free radicals both before and after the alkene insertion stage (Scheme 6). The reaction of **1ck** with the alkene **2c** afforded the 1,5-HAT product **4ckc'** (52% yield), supporting the presence of a primary carbon radical “before” the insertion stage (Scheme 6a). In contrast, the reaction of **1ah** with **2b** led to the double insertion product **4ahb'** (15% yield, Scheme 6b), implying that 1,5-HAT occurred “after” the insertion stage. The formation of a dimer in the reaction of **1cc** with **2l** (Table 2Bc) was similarly supportive for the free-radical insertion.

The experiments depicted in Scheme 7 excluded the intermediacy of alkyl chlorides. We found that our conditions also facilitated a reaction between the secondary alkyl chloride **5ba** and **2a**; however, this reaction was not as effective as that of **1ba** with **2a** (51% vs. 82% yield, respectively, Scheme 7a). This

## RESEARCH ARTICLE

relative ineffectiveness was mainly because of the substantial formation of alkene **6ba** (27% yield), which was not observed in the case of **1ba**. In addition, throughout our experiments demonstrated in Table 1 and Table 2, neither of alkenes nor chlorides were observed. The control experiment revealed that this alkene formation was inevitable even in the absence of additives probably owing to the high reactivity of benzylic hydrogen atoms (Scheme 7b). These analyses indicated that **1ba** was not converted to **5ba** during the reaction. Furthermore, **3** was incapable of converting **1ba** to **5ba** (Scheme 7c). The reactions with shorter reaction times also supported the direct alcohol activation mechanism (Scheme 7d). The reaction between **1bi** and **2c** provided radical adduct **4bic** in 65% yield after a reaction time of 6 h. In contrast, when chloride **5bi** was employed, only 34% yield was achieved despite the longer reaction time (13 h). In order to entirely exclude a chlorine source, we subjected "Ti(Oi-Pr)<sub>2</sub>(cat)·0.5thf" **7** to the reaction (Scheme 7e). As expected, isopropyl radical-derived product **4bkc** was obtained in 30% yield of theoretical maximum (0.5 equiv to **7**), proving that chlorine is not necessary for this reaction.



Scheme 7. Evidence for Direct C–O Cleavage.

Note that compounds with stronger C–OH bonds (BDE = ca. 95 kcal/mol) are more favorable for this reaction than those with

weaker C–Cl bonds (BDE = ca. 85 kcal/mol).<sup>11</sup> This twist can be attributed to the different kinetic features of these bonds (Figure 1). Quantitative analysis was difficult owing to the insolubility of Zn and the formation of byproducts in the reaction of chlorides. However, the observed trends were suitable for qualitative discussion. The reaction of **1bi** or **5bi** with **2c** at different concentrations proved that the consumption of **1bi** (Figure 1a) was completely independent of its concentration up to 6-fold dilution, whereas that of **5bi** (Figure 1b) apparently decreased at lower concentration. The proposed mechanisms shown in Figure 1c can reasonably explain these results. In the case of **1bi**, the **1bi**–[Ti] adduct is a major species, and its self-decomposition determines the reaction rate. In contrast, the formation of the **5bi**–[Ti] adduct would be reversible because of the low coordinating ability of Cl, and the equilibrium would mostly incline to the starting species. In brief, a larger quantity of the active precursor is the reason for the superior reactivity of **1bi**.

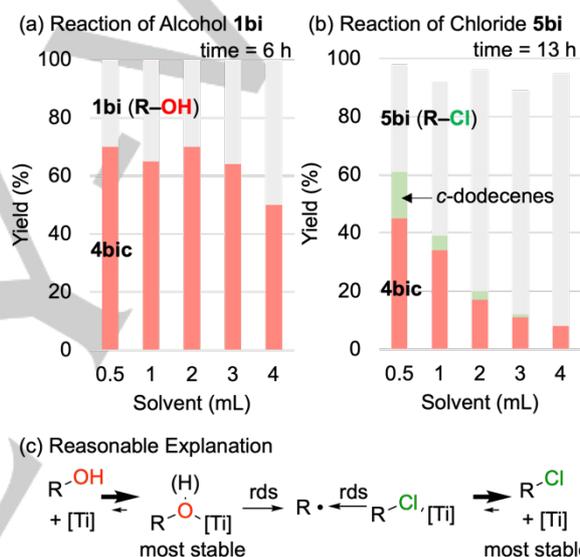
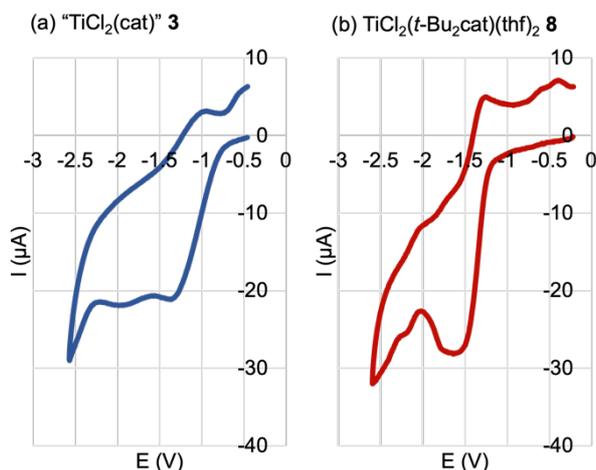


Figure 1. Concentration effects on yield. The reactions of 0.20 mmol **1bi** (R–OH) or **5bi** (R–Cl) with **2c** (3.0 equiv) were performed using different amounts of solvent (0.50, 1.0, 2.0, 3.0, and 4.0 mL). The reaction time was 6 h for **1bi** and 13 h for **5bi**. The yields were estimated by <sup>1</sup>H NMR spectroscopy without isolation. The gray areas indicate unreacted **1bi** or **5bi**, and the red areas represent **4bic**. Cyclododecenes were observed in the reactions of **5bi** (green area). The yield of **1bi** was quantitative under the optimized conditions (at 120 °C for 24 h, see ESI for details).

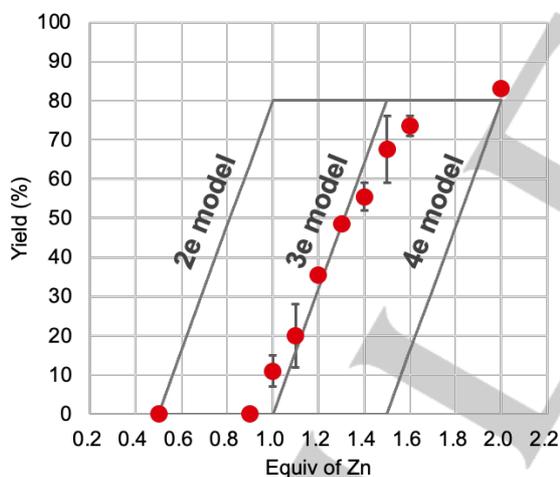
The mechanistic study described above revealed the behavior of alcohols and radicals in the reaction. However, the reason for the distinctive reactivity of "TiCl<sub>2</sub>(cat)" **3** remains unclear. To understand the basic features of this unfamiliar Ti reagent, we continued the mechanistic study. First, we conducted cyclic voltammetry (CV; Figure 2). The reduction potential is a good indicator of the reducing ability of the low-valent Ti reagent.<sup>23</sup> For example, the superior reactivity of Cp\*TiCl<sub>3</sub> to that of CpTiCl<sub>3</sub> in homolytic C–Cl bond cleavage has been explained by the significant difference in their reduction potential (Cp\*TiCl<sub>3</sub>: E<sub>1/2</sub> = –1.12 V and CpTiCl<sub>3</sub>: E<sub>1/2</sub> = –0.79 V vs Fc/Fc<sup>+</sup> in CH<sub>2</sub>Cl<sub>2</sub>).<sup>12</sup> "TiCl<sub>2</sub>(cat)" **3** exhibited an obscure response to electrolytic reduction, although the first reduction peak has E<sub>p/2</sub> = –1.31 V (Figure 2a). The <sup>1</sup>H NMR spectra of **3** indicated that the indiscrete nature of **3** was the reason for this observation (see

## RESEARCH ARTICLE

ESI). Indeed, we found that monomeric  $\text{TiCl}_2(\text{t-Bu}_2\text{cat})(\text{thf})_2$  **8** ( $\text{t-Bu}_2\text{cat} = 3,6\text{-di-tert-butylcatecholate}$ )<sup>24</sup> exhibited an obvious reduction peak ( $E_{p/2} = -1.55$  V, Figure 2b). The observed  $E_{p/2}$  values were comparable to those of known Cp-based complexes such as  $\text{Cp}^*\text{TiCl}_2$  ( $E_{p/2} = -1.55$  V),  $\text{Cp}_2\text{TiCl}_2$  ( $E_{1/2} = -1.19$  V) and  $\text{Cp}^*\text{TiCl}_3$ , and rationalize the high reducing ability of catecholate-based Ti complexes.



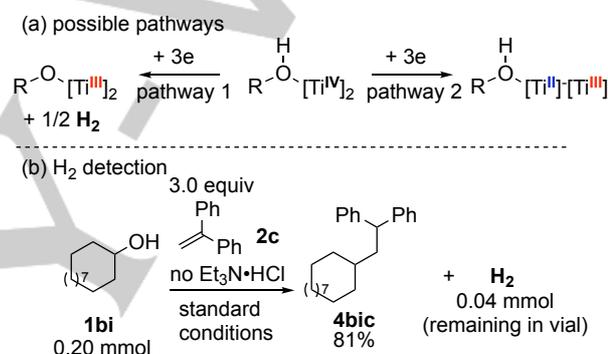
**Figure 2.** Cyclic voltammogram of (a)  $\text{TiCl}_2(\text{cat})$  **3** and (b)  $\text{TiCl}_2(\text{t-Bu}_2\text{cat})(\text{thf})_2$  **8**. Solution of **3** (3 mM) or **8** (2 mM) with 0.1 M  $\text{Bu}_4\text{NClO}_4$  in THF. Scan rate = 100 mV/sec. Potentials were described against  $\text{Fc}/\text{Fc}^+$  redox couple.



**Figure 3.** Stoichiometry of Zn.  $^1\text{H}$  NMR yields of **4bic** after the reactions of 0.20 mmol **1bi** with **2c** (3.0 equiv) using varied equivalent of Zn (120 °C, 24 h). The reactions were conducted by using 0.50, 0.90, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6 and 2.0 equiv Zn. The loading of  $\text{TiCl}_2(\text{cat})$  **3** was fixed to 2.0 equiv.  $\text{Et}_3\text{N}\cdot\text{HCl}$  was not added. The average yields of 2 runs were provided. The gray lines are ideal linear fits to the models in which the indicated equivalents of electrons (= a double of added Zn) serve for the reaction. 80% yield is assumed to be the maximum for these models.

The true oxidation states of low-valent Ti reagents in the reaction media are not necessarily obvious and depend on the reaction. In general, Ti(III) has been established in  $\text{Cp}_2\text{TiCl}_2$ -based reactions,<sup>25</sup> whereas Ti with lower oxidation states has been proposed in  $\text{TiCl}_4$ -based reactions.<sup>26</sup> With respect to the

alcohol C–O cleavage, an early study on the  $\text{TiCl}(\text{OBn})_2/\text{Na}$  naphthalenide system proved the participation of Ti(II).<sup>27</sup> To determine the oxidation state of low-valent Ti in this study, we investigated the stoichiometry of Zn (Figure 3).  $\text{Et}_3\text{N}\cdot\text{HCl}$  was not added in this experiment to rule out its reaction with Zn.<sup>28</sup> Ideally, 1 equiv Zn suffices for reducing all Ti(IV) to Ti(III) because 2 equiv **3** was employed. Similarly, 2 equiv of Zn is needed for Ti(II). No C–O cleavage was observed up to the Zn loading of 0.9 equiv, and it suddenly initiated at 1.0. The almost maximum yield was obtained at approximately 1.5–1.6. This stoichiometry fits well with a three-electron model, wherein all Ti(IV) species are reduced to Ti(III), while another 1 equiv of electrons is still necessary (middle line). The gradual and mild decay of consistency at the higher conversion indicate that Zn reduced the Ti species that were already used for the C–O cleavage. In the reactions without  $\text{Et}_3\text{N}\cdot\text{HCl}$ , the maximum yields were up to 80–85% regardless of the amount of Zn (e.g., 81% yield with 4.0 equiv Zn), while it was quantitative under identical conditions in the presence of  $\text{Et}_3\text{N}\cdot\text{HCl}$ . This is briefly discussed in the ESI.



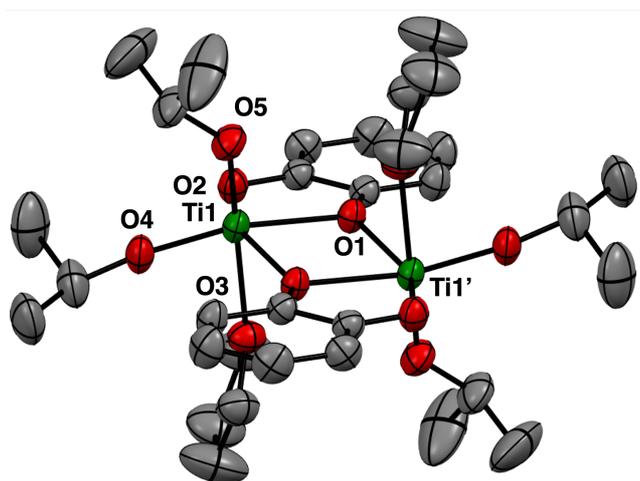
**Scheme 8.** Possible Mechanisms and H<sub>2</sub> Detection.

Two explanations are possible for this three-electron model: 1) one electron was consumed to reduce the alcohol (R–OH) to alkoxide (R–O<sup>−</sup>) and H<sub>2</sub>, and Ti(III)-alkoxide underwent C–O cleavage, and 2) Ti(II) was the active species of C–O cleavage (Scheme 8a). To further elucidate the mechanism, we checked the remaining amount of H<sub>2</sub> gas in the reaction vial after the reaction for 24 h, although the collection of entire generated H<sub>2</sub> was cumbersome owing to the technical problems (Scheme 8b).<sup>29</sup> Approximately 0.04 mmol H<sub>2</sub> was detected for 0.2 mmol **1bi** (40% yield), indicating that a Ti(III)-alkoxide complex was an active species of the C–O cleavage. This result is contradictory to the aforementioned study that established the intermediacy of Ti(II).<sup>27</sup> We propose that the catecholate ligand significantly enhanced the reducing ability of the low-valent Ti as found in the CV study, and it realized a new activation route from Ti(III).

As already demonstrated, the self-decomposition of Ti-alkoxide species determined the reaction rate (Figure 1), while the C–O cleavage occurred only when one alkoxide and two Ti(III) existed simultaneously (Figure 3). The most reasonable explanation for them is that a 1:2 complex of alkoxide and Ti(III) mainly exists in the reaction mixture and undergoes the subsequent rate-determining transformation, possibly the C–O cleavage.<sup>30</sup> In fact, Wilkinson's far-IR analysis supported that  $\text{TiCl}_2(\text{cat})$  **3** can be a dimer of which catechol oxygen atoms bridge two Ti centers.<sup>31</sup> Although direct observation of the active species was

## RESEARCH ARTICLE

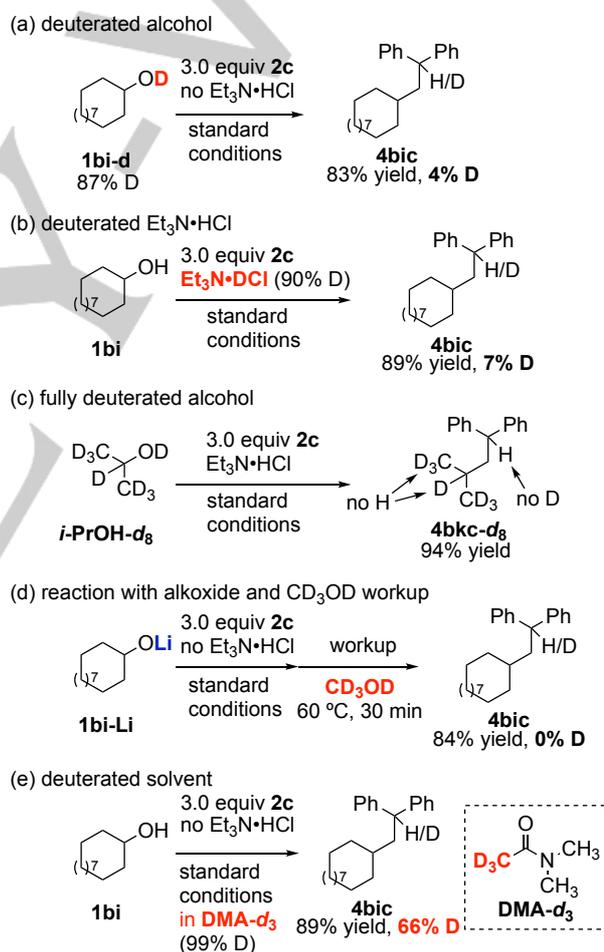
unsuccessful,<sup>32</sup> we expected that the X-ray crystal structure of such dimeric complex could illustrate the tentatively plausible substructure of the active species. We newly prepared  $[\text{Ti}(\text{O}i\text{-Pr})_2(\text{cat})(\text{thf})]_2$  **9** and acquired its crystal structure for this purpose (Figure 4).<sup>33</sup> This visualized Wilkinson's proposal with one oxygen atom at each of the catechol moieties bridging two Ti centers to construct a dimeric structure. The bridging oxygen atoms are more tightly coordinated to the other Ti center ( $\text{Ti1}'\text{-O1} = 2.016 \text{ \AA}$ ) than the chelation center ( $\text{Ti1-O1} = 2.114 \text{ \AA}$ ), suggesting that mono-catecholate ligands on Ti prefer to bridge two metallic centers. Interestingly, the oxygen atoms of isopropoxy moieties, presumably the most basic parts of **9**, do not bridge the Ti centers. At present, it is difficult to conclude that the cooperation of multiple Ti(III) components is decisive for the C–O cleavage. However, we consider such activation mode is quite reasonable because two Ti(III) can cooperate to facilitate the homolytic ring-opening of epoxides.<sup>34</sup> This is further supported by the fact that the reaction using "monomeric"  $\text{TiCl}_2(t\text{-Bu}_2\text{cat})(\text{thf})_2$  **8** did not afford the coupling product **4bic** at  $80^\circ\text{C}$ , while " $\text{TiCl}_2(\text{cat})$ " **3** reacted to afford 36% yield at the same temperature (20 h).



**Figure 4.** ORTEP diagram of  $[\text{Ti}(\text{O}i\text{-Pr})_2(\text{cat})(\text{thf})]_2$  ( $\text{C}_{32}\text{H}_{52}\text{O}_{10}\text{Ti}_2$ ) **9**. Thermal ellipsoids are shown with 50% probability level. Hydrogen atoms are omitted for clarity. Unit cell parameters:  $a = 8.7711(5)$ ,  $b = 13.1582(7)$ ,  $c = 15.6506(9)$ ,  $P2_1/n$ .  $R = 0.0494$ . Representative bond lengths ( $\text{\AA}$ ):  $\text{Ti1-O1} = 2.114(1)$ ,  $\text{Ti1}'\text{-O1} = 2.016(1)$ ,  $\text{Ti1-O2} = 1.920(2)$ ,  $\text{Ti1-O3} = 2.266(1)$ ,  $\text{Ti1-O4} = 1.790(2)$ ,  $\text{Ti1-O5} = 1.804(2)$ .

The loss of the hydroxy hydrogen atom implies that the extra hydrogen atom in the product was originated elsewhere. As expected, deuterium experiments demonstrated that the hydrogen atoms were primarily not derived from the protic hydrogen sources.<sup>35</sup> For instance, only 4% deuterium incorporation was observed at the benzylic position of product **4bic** when **1bi-d** (87% D) was employed (Scheme 9a), and  $\text{Et}_3\text{N}\cdot\text{DCI}$  (90% D) did not install deuterium into the product effectively (7% D, Scheme 9b). No H/D scrambling occurred with  $i\text{-PrOH-d}_8$  (Scheme 9c). Furthermore, lithium alkoxide **1bi-Li** reacted efficiently without an apparent protic hydrogen source (Scheme 9d). Traceless deuteration with a  $\text{CD}_3\text{OD}$  workup proved that the hydrogen source was already included in the reaction system. The deuterium experiment using  $\text{DMA-d}_3$  (99% D) revealed that the acetyl hydrogen atoms of DMA served as a

major hydrogen source (66% D, Scheme 9e). We believe that the hydrogenation occurred mainly by HAT in the case of alkene **2c** because only 7% of deuterium in  $\text{Et}_3\text{N}\cdot\text{DCI}$  was incorporated into the product despite its high acidity (Scheme 9b). This indicated that a series of the reaction processes occurred in the presence of  $\text{Et}_3\text{N}\cdot\text{DCI}$  without abstracting its protic hydrogen atom, and it was inconsistent with an ionic metalation-deprotonation mechanism. Alternatively, the consumption of  $\text{Et}_3\text{N}\cdot\text{DCI}$  by the reaction with Zn could explain the small deuterium incorporation. However, it was finally found to be of a secondary importance because this process was not significantly faster than the C–O cleavage. For example, 65% of  $\text{Et}_3\text{N}\cdot\text{HCl}$  was consumed by the reaction with excess Zn in DMA at  $120^\circ\text{C}$  for 6 h, whereas 65% conversion of **1bi** was observed under the C–O cleavage conditions after the identical reaction time (Scheme 7d). We consider that the coordination of DMA to low-valent Ti species facilitated the HAT process because direct HAT between 1,1-diphenylalkyl radical and acetamide would be thermodynamically unfavorable.<sup>36,37</sup>

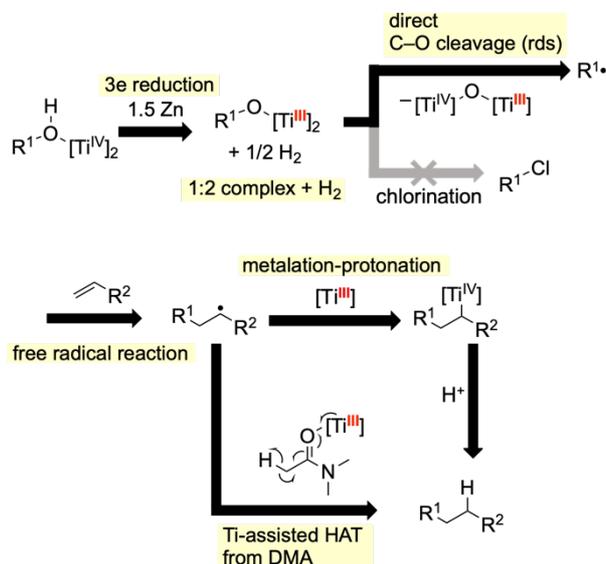


**Scheme 9.** Source of Extra Hydrogen Atom.

The suggested mechanism is illustrated in Scheme 10. The 1:2 complex of alcohol and Ti(IV) is reduced by three electrons to furnish the Ti(III)-alkoxide and  $\text{H}_2$ . In the subsequent rate-determining stage, the C–O bond is directly cleaved, and an alkyl radical is formed without the participation of the C–Cl species; subsequently, it reacts with alkenes. In addition to the

## RESEARCH ARTICLE

metallation-protonation pathway as reported in our previous study,<sup>18</sup> the low-valent Ti-promoted HAT from DMA was unexpectedly found to be another route for terminating the radical process, although its proportion would be largely dependent on the alkenes used.



Scheme 10. Summary of Mechanistic Study.

## Conclusion

In conclusion, we developed a straightforward access to carbon radicals from the corresponding aliphatic alcohols using the newly discovered “TiCl<sub>2</sub>(cat)” 3/Zn reagent. This method realized the efficient homolytic cleavage of all “non-activated” tertiary, secondary, and even primary C–OH bonds and was utilized for the addition reactions of radicals to various alkenes. Control experiments confirmed that free radicals were generated by direct C–O cleavage. The qualitative kinetic study explained the seemingly inverse reactivity order between C–OH and C–Cl. Further experiments focusing on the behavior of catecholate-based Ti reagents revealed the following: 1) they exhibit reasonably high reduction potentials to facilitate C–O bond cleavage of “non-activated” alcohols; 2) Ti(III) is an active oxidation state; 3) they are prone to form multimetallic complexes, and the multiple Ti components might cooperatively facilitate reactions; and 4) they are capable of activating DMA as an effective hydrogen source. We hope that this study will contribute to radical chemistry and these direct alcohol activation methods will become a standard choice for organic synthesis in the near future. In addition, we believe that our study evaluated the basic chemistry of catecholate-based Ti reagents, which are now ready to be utilized for undiscovered organic transformations.

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**Keywords:** Alcohols • Radicals • Reaction mechanisms • Synthetic methods • Titanium

- [1] a) P. Renaud, M. P. Sibi, *Radicals in Organic Synthesis*; Wiley-VCH: New York, **2001**; b) S. Crespi, M. Fagnoni, *Chem. Rev.* **2020**, *120*, 9790–9833.
- [2] a) M. Rueda-Becerril, C. C. Sazepin, J. C. T. Leung, T. Okbinoglu, P. Kennepohl, J.-F. Paquin, G. M. Sammis, *J. Am. Chem. Soc.* **2012**, *134*, 4026–4029; b) N. Noto, K. Miyazawa, T. Koike, M. Akita, *Org. Lett.* **2015**, *17*, 3710–3713; c) D. J. Weix, *Acc. Chem. Res.* **2015**, *48*, 1767–1775; d) C. K. Chu, Y. Liang, G. C. Fu, *J. Am. Chem. Soc.* **2016**, *138*, 6404–6407; e) A. Fawcett, J. Pradailles, Y. Wang, T. Mutsuga, E. L. Myers, V. K. Aggarwal, *Science* **2017**, *357*, 283–286.
- [3] a) G. Sorin, R. M. Mallorquin, Y. Contie, A. Baralle, M. Malacria, J.-P. Goddard, L. Fensterbank, *Angew. Chem., Int. Ed.* **2010**, *49*, 8721–8723; *Angew. Chem.* **2010**, *122*, 8903–8905; b) Y. Miyake, K. Nakajima, Y. Nishibayashi, *Chem. Commun.* **2013**, *49*, 7854–7856; c) V. Corcé, L.-M. Chamoreau, E. Derat, J.-P. Goddard, C. Ollivier, L. Fensterbank, *Angew. Chem., Int. Ed.* **2015**, *54*, 11414–11418; *Angew. Chem.* **2015**, *127*, 11576–11580; d) C. C. Nawrat, C. R. Jamison, Y. Slutskyy, D. W. C. MacMillan, L. E. Overman, *J. Am. Chem. Soc.* **2015**, *137*, 11270–11273.
- [4] L. K. G. Ackerman, L. L. Anka-Lufford, M. Naodovic, D. J. Weix, *Chem. Sci.* **2015**, *6*, 1115–1119.
- [5] a) Y. Sato, K. Nakamura, Y. Sumida, D. Hashizume, T. Hosoya, H. Ohmiya, *J. Am. Chem. Soc.* **2020**, *142*, 9938–9943; b) T. Morofuji, Y. Matsui, M. Ohno, G. Ikarashi, N. Kano, *Chem. – Eur. J.* **2021**, *27*, 6713–6718.
- [6] a) Y.-G. Xiang, X.-W. Wang, X. Zheng, Y.-P. Ruan, P.-Q. Huang, *Chem. Commun.* **2009**, 7045–7047; b) C. Bandari, K. M. Nicholas, *J. Org. Chem.* **2020**, *85*, 3320–3327; c) K. Sumiyama, N. Toriumi, N. Iwasawa, *Eur. J. Org. Chem.* **2021**, 2474–2478. The history of C–OH homolysis was reviewed recently: d) C. Bandari, K. M. Nicholas, *Synthesis* **2020**, *53*, 267–278; e) X. Pang, X.-Z. Shu, *Synlett* **2021**, *32*, 1269–1274.
- [7] Radical reactions including C–OH cleavage: a) X. Zheng, X.-J. Dai, H.-Q. Yuan, C.-X. Ye, J. Ma, P.-Q. Huang, *Angew. Chem., Int. Ed.* **2013**, *52*, 3494–3498; *Angew. Chem.* **2013**, *125*, 3578–3582; b) J. Jin, D. W. C. MacMillan, *Nature* **2015**, *525*, 87–90; c) K. Azizi, R. Madsen, *Chem. Sci.* **2020**, *11*, 7800–7806; d) Z. Li, W. Sun, X. Wang, L. Li, Y. Zhang, C. Li, *J. Am. Chem. Soc.* **2021**, *143*, 3536–3543. e) Z. Dong, D. W. C. MacMillan, *Nature* **2021**, *598*, 451–456.
- [8] B. Giese, *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753–764; *Angew. Chem.* **1983**, *95*, 771–782. For a representative low-valent Ti–H<sup>+</sup> system, see: b) A. Gansäuer, H. Bluhm, M. Pierobon, *J. Am. Chem. Soc.* **1998**, *120*, 12849–12859.
- [9] Recent reviews on low-valent titanium in organic synthesis: a) J. Streuff, A. Gansäuer, *Angew. Chem. Int. Ed.* **2015**, *54*, 14232–14242; *Angew. Chem.* **2015**, *127*, 14438–14448; b) T. McCallum, X. Wu, S. Lin, *J. Org. Chem.* **2019**, *84*, 14369–14380; c) A. Fermi, A. Gualandi, G. Bergamini, P. G. Cozzi, *Eur. J. Org. Chem.* **2020**, *2020*, 6955–6965; d) M. Manßen, L. L. Schafer, *Chem. Soc. Rev.* **2020**, *49*, 6947–6994; e) W. A. Nugent, T. V. RajanBabu, *Angew. Chem., Int. Ed.* **2021**, *60*, 2194–2201; *Angew. Chem.* **2021**, *133*, 2222–2229.
- [10] T. Suga, S. Shimazu, Y. Ukaji, *Org. Lett.* **2018**, *20*, 5389–5392.
- [11] S. J. Blanksby, G. B. Ellison, *Acc. Chem. Res.* **2003**, *36*, 255–263.
- [12] X. Wu, W. Hao, K.-Y. Ye, B. Jiang, G. Pombar, Z. Song, S. Lin, *J. Am. Chem. Soc.* **2018**, *140*, 14836–14843.
- [13] H. Xie, J. Guo, Y.-Q. Wang, K. Wang, P. Guo, P.-F. Su, X. Wang, X.-Z. Shu, *J. Am. Chem. Soc.* **2020**, *142*, 16787–16794.
- [14] H. Zipse, *Top. Curr. Chem.* **2006**, *263*, 163–189.

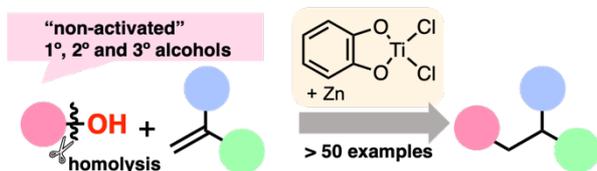
## RESEARCH ARTICLE

- [15] A. Gómez-Carrera, M. Mena, P. Royo, R. Serrano, *J. Organomet. Chem.* **1986**, *315*, 329–335.
- [16] U. M. Dzhemilev, R. L. Gaisin, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1988**, *37*, 2099–2102.
- [17] Reference prices were acquired from the websites of FUJIFILM Wako Pure Chemical Corporation and Oakwood Products, Inc., respectively.
- [18] T. Suga, M. Nakamura, R. Takada, Y. Ukaji, *Bull. Chem. Soc. Jpn.* **2021**, *94*, 1258–1260.
- [19] Net primary C–OTs homolysis via C–[Co] intermediate was reported very recently: a) K. Komeyama, T. Michiyuki, Y. Teshima, I. Osaka, *RSC Adv.* **2021**, *11*, 3539–3546. Each of the following works reported one example: b) S.-K. Kang, I.-H. Cho, *Tetrahedron Lett.* **1989**, *30*, 743–746; c) Y. Gao, Z. Wu, L. Yu, Y. Wang, Y. Pan, *Angew. Chem., Int. Ed.* **2020**, *59*, 10859–10863; *Angew. Chem.* **2020**, *132*, 10951–10955.
- [20] H. R. Diéguez, A. López, V. Domingo, J. F. Arteaga, J. A. Dobado, M. M. Herrador, J. F. Q. del Moral, A. F. Barrero, *J. Am. Chem. Soc.* **2010**, *132*, 254–259.
- [21] C. Leriche, X. He, C. T. Chang, H. Liu, *J. Am. Chem. Soc.* **2003**, *125*, 6348–6349.
- [22] S. Sarkar, K. P. S. Cheung, V. Gevorgyan, *Chem. Sci.* **2020**, *11*, 12974–12993.
- [23] A. Gansäuer, C. Kube, K. Daasbjerg, R. Sure, S. Grimme, G. D. Fianu, D. V. Sadasivam, R. A. Flowers II, *J. Am. Chem. Soc.* **2014**, *136*, 1663–1671.
- [24] I. N. Meshcheryakova, A. S. Shavyrin, A. V. Cherkasov, A. V. Piskunov, *Russ. Chem. Bull., Int. Ed.* **2019**, *68*, 1414–1423.
- [25] T. V. RajanBabu, W. A. Nugent, *J. Am. Chem. Soc.* **1994**, *116*, 986–997.
- [26] a) R. Dams, M. Malinowski, I. Westdorp, H. Geise, *J. Org. Chem.* **1982**, *47*, 248–259; b) J. E. McMurry, *Chem. Rev.* **1989**, *89*, 1513–1524.
- [27] E. E. van Tamelen, B. Åkermark, K. B. Sharpless, *J. Am. Chem. Soc.* **1969**, *91*, 1552–1554.
- [28] Et<sub>3</sub>N·HCl mildly lowered the conversion when non-excessive Zn was used because they reacted directly with Zn in part. See ESI.
- [29] The reaction vials were no longer pressurized after the reactions.
- [30] Otherwise, the Ti(III) could tautomerize to form Ti(II) and Ti(IV). However, we consider Ti(III) pathway is more plausible. See SI for the discussion.
- [31] A. Flamini, D. J. Cole-Hamilton, G. Wilkinson, *J. Chem. Soc., Dalton Trans.* **1978**, 454–459.
- [32] We attempted to analyze the reaction mixture by ESI-MS.
- [33] Deposited to CCDC 2096888.
- [34] a) K. Daasbjerg, H. Svith, S. Grimme, M. Gerenkamp, C. Mück-Lichtenfeld, A. Gansäuer, A. Barchuk, F. Keller, *Angew. Chem., Int. Ed.* **2006**, *45*, 2041–2044; *Angew. Chem.* **2006**, *118*, 2095–2098; b) A. Gansäuer, A. Barchuk, F. Keller, M. Schmitt, S. Grimme, M. Gerenkamp, C. Mück-Lichtenfeld, K. Daasbjerg, H. Svith, *J. Am. Chem. Soc.* **2007**, *129*, 1359–1371.
- [35] Recapturing H<sub>2</sub> would be unreasonable because it commonly requires an assistance of Rh co-catalyst in Ti-mediated reductive transformations. See: A. Gansäuer, C.-A. Fan, F. Piester, *J. Am. Chem. Soc.* **2008**, *130*, 6916–6917.
- [36] a) M. Paradas, A. G. Campaña, T. Jiménez, R. Robles, J. E. Oltra, E. Buñuel, J. Justicia, D. J. Cárdenas, J. M. Cuerva, *J. Am. Chem. Soc.* **2010**, *132*, 12748–12756; b) G. Povie, L. Ford, D. Pozzi, V. Soulard, G. Villa, P. Renaud, *Angew. Chem., Int. Ed.* **2016**, *55*, 11221–11225; *Angew. Chem.* **2016**, *128*, 11387–11391.
- [37]  $\alpha$ -Imino protons of amidines can participate in HAT. See: E. A. Mader, V. W. Manner, T. F. Markle, A. Wu, J. A. Franz, J. M. Mayer, *J. Am. Chem. Soc.* **2009**, *131*, 4335–4345.

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A combination of "TiCl<sub>2</sub>(cat)" and Zn (cat = catecholate) facilitates the homolytic cleavage of "non-activated" alcohol C–O bonds. All aliphatic primary, secondary and tertiary alcohols serve as good substrates. This method was applied to radical conjugate addition reactions successfully, and mechanistic studies indicate that alkyl chlorides are not intermediates. The active species is a 1:2 complex of alkoxide and Ti(III).

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