

Radical Dehydroxylative Alkylation of Tertiary Alcohols by Ti Catalysis

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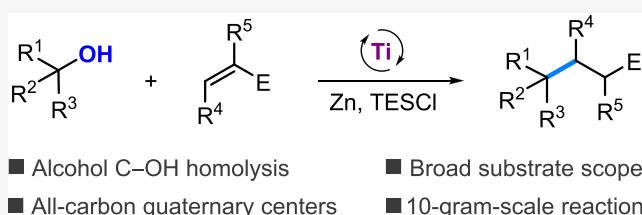


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ABSTRACT: Deoxygenative radical C–C bond-forming reactions of alcohols are a long-standing challenge in synthetic chemistry, and the current methods rely on multistep procedures. Herein, we report a direct dehydroxylative radical alkylation reaction of tertiary alcohols. This new protocol shows the feasibility of generating tertiary carbon radicals from alcohols and offers an approach for the facile and precise construction of all-carbon quaternary centers. The reaction proceeds with a broad substrate scope of alcohols and activated alkenes. It can tolerate a wide range of electrophilic coupling partners, including allylic carboxylates, aryl and vinyl electrophiles, and primary alkyl chlorides/bromides, making the method complementary to the cross-coupling procedures. The method is highly selective for the alkylation of tertiary alcohols, leaving secondary/primary alcohols (benzyl alcohols included) and phenols intact. The synthetic utility of the method is highlighted by its 10-g-scale reaction and the late-stage modification of complex molecules. A combination of experiments and density functional theory calculations establishes a plausible mechanism implicating a tertiary carbon radical generated via Ti-catalyzed homolysis of the C–OH bond.



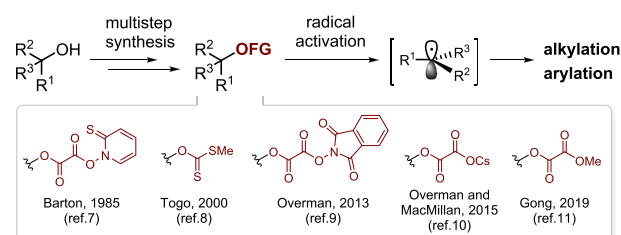
1. INTRODUCTION

All-carbon quaternary centers are a key structural element of a wide range of pharmaceuticals and natural products. However, the construction of such quaternary carbon centers remains a formidable challenge in synthetic chemistry because of the steric repulsion between the four carbon substituents.¹ Among the various approaches that can be used to achieve this construction, the bimolecular reaction of tertiary carbon radicals with carbon fragments is a straightforward method.² These alkyl radicals are usually generated from halide precursors.^{2,3} However, the synthesis of complex tertiary alkyl halides can be complicated by competing side reactions (e.g., elimination and rearrangement). Consequently, the development of alternative strategies for producing carbon radicals using stable, readily available, and especially naturally occurring functional groups could have a substantial impact on organic synthesis.^{4,5}

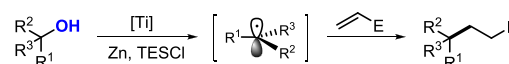
Alcohols are among the most accessible organic compounds, and they occur widely in medicines and natural products. The development of new radical C–C bond-forming reactions from tertiary alcohols has synthetic appeal, yet it remains a long-term challenge (Scheme 1a).⁶ The feasibility of this chemistry was first established in 1985 by Barton using *tert*-alkyl *N*-hydroxypyridine-2-thionyl oxalates to generate radicals from alcohols.⁷ Later on, the deoxygenative alkylation of hydroxyl groups via xanthates was reported by Togo et al.⁸ In 2013, Overman and co-workers introduced *N*-phthalimidoyl oxalate derivatives of tertiary alcohols for catalytic radical alkylation

Scheme 1. Deoxygenative Radical C–C Bond-Forming Reactions of Tertiary Alcohols

(a) Previous work: Reactions with preactivated alcohols



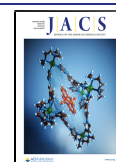
(b) This work: Catalytic dehydroxylative alkylation of tertiary alcohols



with activated alkenes.⁹ Inspired by these discoveries, the groups of Overman and MacMillan as well as Gong recently achieved the formation of tertiary carbon radicals from alkyl cesium oxalates¹⁰ and methyl oxalates,¹¹ respectively. These

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methods have also found promising applications in the total synthesis of natural products.¹² Despite the advances over the years, the existing methods for generating carbon radicals from alcohols typically require multistep synthetic procedures.

Herein, we report, for the first time to the best of our knowledge, a catalytic radical dehydroxylative C–C bond-forming reaction of tertiary alcohols and alkenes.¹³ This new method is simple and efficient in comparison to previous protocols. It demonstrates usefulness for the construction of all-carbon quaternary centers, with a broad substrate scope of alcohols and activated alkenes.

2. RESULTS AND DISCUSSION

2.1. Reaction Optimization. We recently achieved the reductive functionalization of several aliphatic C–O electrophiles, including benzyl oxalates,^{14a} primary and secondary alkyl sulfonates,^{14b} and allylic alcohols.^{14c} We then set out to explore whether it would be possible to use tertiary alcohols for reductive C–C bond formation. We focused on making use of titanium catalysis because titanium complexes are powerful reducing catalysts for a broad range of radical reactions of conventional C–O electrophiles (e.g., epoxides and ketones).¹⁵ There are also several reports on the Cp₂TiCl₂-catalyzed deoxygenation of alcohols¹⁶ and dehydroxylative alkylation of activated substrates such as hemiaminals and benzylic alcohols.^{13,17} Nevertheless, the dehydroxylative reaction of unactivated tertiary alcohols has not yet been achieved.

We began our investigation by studying the reaction of alcohol **1a** with ethyl acrylate **2a** (Table 1). After screening a range of reaction conditions, we determined that the combination of Cp^{*}TiCl₃ (10 mol %), TESCl (3.0 equiv), and Zn (3.0 equiv) in THF (0.4 M) afforded the best results (entry 1). A combination of electronic and steric factors

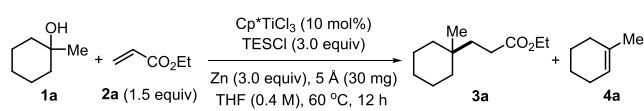
appeared to govern the efficiency of the titanium catalysts. The sterically hindered Cp^{*}₂TiCl₂ decreased the yield to 43%, whereas its less electron-rich counterpart Cp₂TiCl₂ lowered the yield further to 26% (entries 2 and 3). CpTiCl₃ [*E*_{1/2}(IV/III) = −0.82 V], which is less reducing than Cp^{*}TiCl₃ [*E*_{1/2}(IV/III) = −1.12 V],¹⁸ resulted in the lowest yield of **3a** and recovery of alcohol **1a** (entry 4). The trialkylsilyl halide additive plays an essential role in this catalytic process. The reaction afforded **3a** in 58% yield using TESBr (entry 5). When TBSCl was used, only 22% of **3a** was obtained, with most of alcohol **1a** recovered (entry 6). Density functional theory (DFT) calculations suggest that the large steric hindrance of TBSCl would hinder the regeneration of Cp^{*}TiCl₃ from Cp^{*}Ti(OH)Cl₂ (see Figure S1 in the Supporting Information for details), the rate-determining step of this reaction (see below). The use of TMSCl afforded **3a** in 41% yield, with a large quantity of dehydration byproduct generated (entry 7). We speculated that TMSCl could react with nucleophilic species to produce HCl, which promotes the dehydration of the tertiary alcohols. A combination of Cp^{*}TiCl₃ with Et₃N·HCl in toluene proved to be effective in the radical alkylation of tertiary chlorides.^{3h} However, in our reaction system, the use of Et₃N·HCl or Coll·HCl instead of TESCl led to the facile dehydration of the alcohol substrate (entries 8 and 9). Only the dehydration byproduct was obtained when toluene was used as a solvent (entry 10). The reaction in DME afforded **3a** in 58% yield (entry 11). The yield of **3a** decreased to 6% when the reaction was performed at 30 °C (entry 12). No desired product was obtained when Mn was used as a reductant (entry 13). The addition of 5 Å molecular sieves probably helped remove H₂O or HCl generated in situ, thus inhibiting the dehydration side reaction and improving the desired product yield (entry 14). The control experiments revealed that TESCl, the Ti catalyst, and Zn are all required for the dehydroxylative alkylation of tertiary alcohols (entries 15–17).

2.2. Substrate Scope of Tertiary Alcohols and Activated Alkenes. With the optimal conditions in hand, we studied the scope of the reaction for tertiary alcohols (Table 2). Cyclic alcohols, ranging from four- to eight-membered rings, were coupled with **2a** to afford the target products in moderate to good yields (**1b–1f**). A larger ring-sized alcohol, cyclododecanol, afforded an alkylated product in moderate yield (**1g**). A polycyclic alcohol, 2-methyl-2-adamantanol, afforded an alkylated product in 92% yield (**1h**). It is noteworthy that the reaction could be run on a 10-g scale to afford 13.6 g of the desired product (78% yield) (**1h**).

A wide range of acyclic tertiary alcohols underwent this coupling reaction with high efficiency (**1i–1v**). The reaction proved to be insensitive to the steric hindrance around the site of radical generation. Tertiary alcohols, ranging from the smallest tertiary butanol (**1i**) to sterically hindered substrates (**1j–1n**), all provided the respective products in good yields. The functionalities present in electron-rich arenes (**1o**, **1p**, **1ad**), terminal alkene (**1q**), esters (**1r**, **1v**), organosilane (**1t**), and aryl fluoride (**1u**) were all tolerated.

The reactions of secondary alcohols **1w** and **1x** did not give any desired product, but resulted in R–OTES in 17% and 23% yield, respectively. Benzyl alcohols could be reactive toward low-valent titanium reagents;¹³ however, under our reaction conditions, no coupling product was obtained from **1y** and R–OTES was produced in 36% yield. The unreacted alcohols **1w–1y** were mostly recovered. The reaction of secondary

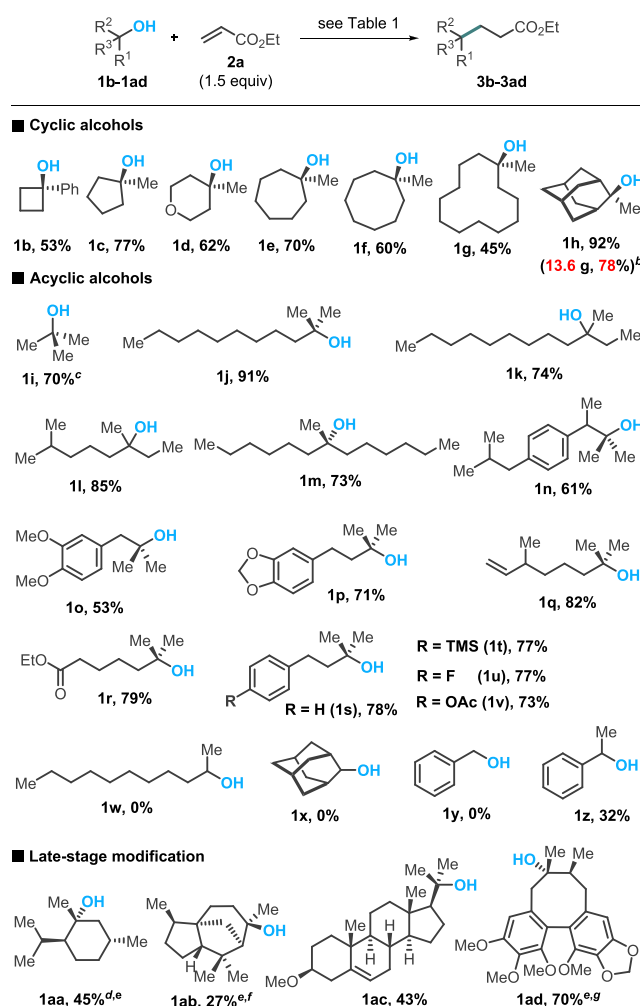
Table 1. Ti-Catalyzed Dehydroxylative Alkylation of **1a** and **2a**^a



entry	change of conditions	3a (%)	4a (%)	1a (%)
1	none	65 (62) ^b	24	6
2	Cp [*] ₂ TiCl ₂ instead of Cp [*] TiCl ₃	43	32	10
3	Cp ₂ TiCl ₂ instead of Cp [*] TiCl ₃	26	35	16
4	CpTiCl ₃ instead of Cp [*] TiCl ₃	24	12	61
5	TESBr instead of TESCl	58	23	trace
6	TBSCl instead of TESCl	22	16	50
7	TMSCl instead of TESCl	41	57	trace
8	Et ₃ N·HCl instead of TESCl	0	73	9
9	Coll·HCl instead of TESCl	0	85	13
10	toluene instead of THF	0	82	0
11	DME instead of THF	58	31	trace
12	30 °C instead of 60 °C	6	19	57
13	Mn instead of Zn	0	21	76
14	no 5 Å molecular sieves	51	43	0
15	no TESCl	trace	trace	91
16	no Ti catalyst	0	31	65
17	no Zn	0	24	73

^a**1a** (0.2 mmol) was used, reaction time was 12 h, and the yields were determined by GC analysis with hexadecane as the internal standard.

^bIsolated yield.

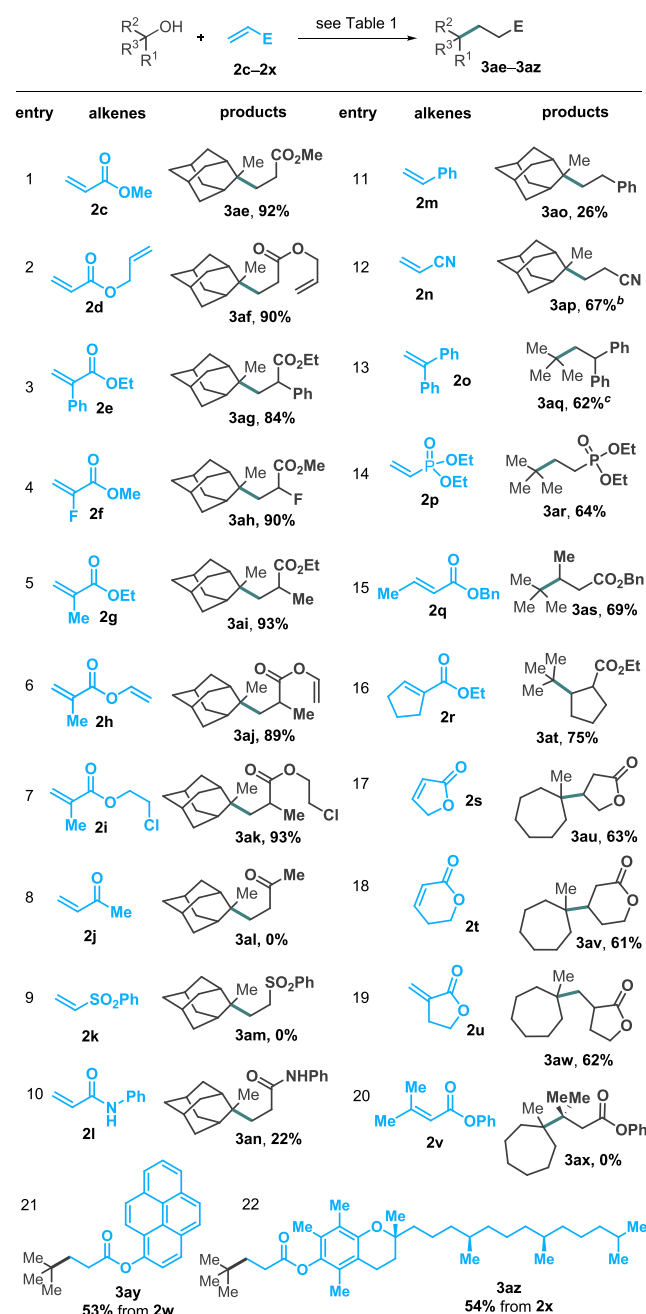
Table 2. Scope of Tertiary Alcohols^a

^aAlcohol **1** (0.2 mmol) was used, reaction time was 12 h, and the yields were isolated yields. ^bThe reaction was run on a 10-g scale, and Cp*TiCl₃ (8 mol %) and 5 Å (10.5 g) were used. ^c*tert*-Butanol (**1i**, 2.0 equiv) and benzyl acrylate (**2b**, 0.2 mmol) were used. ^d**3aa** (13:1 d.r.). ^eThe stereochemistry was not assigned. ^f**3ab** (>20:1 d.r.). ^gGomisin A (**1ad**, 6 mg) was used, **3ad** (1.8:1 d.r.).

benzyl alcohol **1z** afforded the coupling product in 32% yield, with the unreacted alcohol mostly recovered.

The tertiary alcohol functionality is a common structural motif found in various biologically active compounds. It can also be readily introduced during the total synthesis of natural products. This motivated us to apply our method to the late-stage construction of quaternary carbons in the tertiary alcohols **1aa–1ad**, which are natural products or their derivatives. The (–)-menthone and pregnenolone-derived alcohols **1aa** and **1ab** gave synthetically useful yields. (+)-Cedrol (**1ab**) and Gomisin A (**1ad**) were converted to quaternary products in a single step. It is worth noting that the sterically hindered **1aa** and **1ab** were alkylated with high diastereoselectivity.

The scope of activated alkenes is shown in Table 3. As expected, various acrylates were useful acceptors and afforded the desired coupling products in approximately 90% yields (entries 1 and 2). The allylic carboxylates are highly reactive toward low-valent transition-metal complexes and have been widely applied in the Tsuji–Trost reaction.¹⁹ This moiety was

Table 3. Scope of Activated Alkenes^a

^aConditions as shown in Table 1, isolated yields. ^bBuOH (**1i**, 2.0 equiv) was used for alkenes **2p–2r**, **2w**, and **2x**. Alcohol **1h** (0.2 mmol, 1.0 equiv) was used for reactions with volatile alkenes. Cyclic alcohol **1e** (0.2 mmol, 1.0 equiv) was used for the formation of bicyclic products. ^cAcrylonitrile (2.0 equiv) was used. ^d*tert*-Butanol (**1i**, 4.0 equiv) was used.

compatible with our Ti-catalyzed reaction (entry 2). The reactions of α -aryl, -fluoro, or -alkyl substituted acrylates afforded quaternary products in 84–93% yields (entries 3–7). The use of the fluoro-substrate **2f** provided a facile installation of the α -fluoro ester group at the quaternary carbon (entry 4).²⁰ The enol carboxylate and alkyl chloride moieties were tolerated (entries 6 and 7). Unsaturated ketone **2j** and vinyl sulfone **2k** did not give any desired product (entries 8 and 9). The reactions of unsaturated amide **2l** and styrene **2m** afforded the desired products in low yields (entries 10 and 11). Other

electron-deficient alkenes, such as acrylonitrile **2n**, 1,1-diphenylethylene **2o**, and vinyl phosphonates **2p**, all worked well (entries 12–14).

Although rarely reported in the literature, β -alkyl substituted acrylate **2q** could be used as a coupling partner in this reaction (entry 15). Cyclic acceptors could also be utilized (entries 16–19). The reactions of cyclic tertiary alcohol **1e** with furan-2(5H)-one **2s** and 5,6-dihydro-2H-pyran-2-one **2t** enabled Csp³–Csp³ bond formation between two rings, generating a new quaternary stereocenter, which otherwise would be hard to realize in organic synthesis (entries 17 and 18).^{2c} An attempt at forging a Csp³–Csp³ bond between the two quaternary carbons has not been successful as of yet (entry 20). Acrylates derived from 1-hydroxypyrene and (+)- α -tocopherol both worked well (entries 21 and 22).

2.3. Chemoselectivity. Transition-metal-catalyzed cross-coupling represents one of the most powerful tools for C–C bond formation.²¹ Our studies demonstrate that this Ti-catalyzed dehydroxylative alkylation of tertiary alcohol offers a selectivity that is complementary to other cross-coupling methods (Table 4). Aryl electrophiles, including chlorides,

Table 4. Chemoselectivity Complementary to the Transition-Metal-Catalyzed Cross-Couplings^a

entry	alcohols/alkenes	products	entry	alcohols/alkenes	products
1 ^b		3ba (78%)	7		3bg (70%)
2		3bb (82%)	8		3bh (65%)
3		3bc (86%)	9 ^c		3bi (51%)
4		3bd (75%)	10		3bj (84%)
5		3be (73%)	11		3bk (41%)
6		3bf (73%)	12		3bl (trace)

^aConditions as shown in Table 1, isolated yields. Ethyl acrylate **2a** was used for reactions with alcohols, and ^tBuOH **1i** (2.0 equiv) was used for reactions with alkenes. ^bMethyl acrylate **2c** was used. ^cAlcohol **1h** was used.

bromides, iodides, triflates, and pivalates, are frequently used in the cross-coupling reactions.^{3,21} These functionalities were all tolerated under our reaction conditions (entries 1–5). The same was also true of vinyl electrophiles, including a highly reactive triflate, and the tertiary alcohols were selectively alkylated (entries 6–8). Terminal alkynes, although known to

be reactive toward many transition-metal complexes,²² were compatible with our reaction (entry 9). The primary alkyl chloride **1ak** was tolerated well (entry 10). The alkyl bromide **1al** was partly activated to afford the bis-alkylated byproduct in 29% yield,²³ along with 41% of the desired product (entry 11). Secondary alkyl chlorides generally performed poorly, as shown by entry 12, giving only traces of the desired product alongside the bis-alkylated byproduct (52%).

Polyalcohols are a ubiquitous structural motif found in a wide range of natural products. This encouraged us to explore the possibility of selectively functionalizing a tertiary alcohol in the presence of other hydroxyl groups, such as primary/secondary alcohols and phenols (Table 5). The high selectivity

Table 5. Selective Alkylation of Diols^a

entry	alcohols/alkenes	products	entry	alcohols/alkenes	products
1		3bm (71%)	8		3bt (trace)
2		3bn (51%)	9		3bu (n/a)
3		3bo (48%)	10		3bv (n/a)
4		3bp (60%)	11		3bw (83%)
5		3bq (56%)	12 ^b		3bx (74%)
6		3br (51%)	13 ^b		3by (67%)
7		3bs (42%)			

^aConditions as shown in Table 1, TESCl (5.0 equiv) and THF (0.3 M) were used, isolated yields. ^bConditions as shown in Table 1, ^tBuOH **1i** (4.0 equiv) was used.

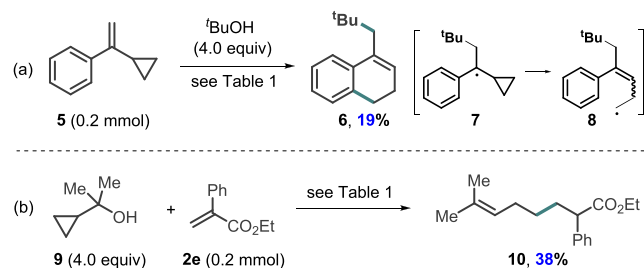
was observed when different diols were employed, where the primary and secondary alcohols remained intact (entries 1–7). In these cases, moderate yields of desired products were generally obtained, and dehydration of the tertiary alcohols was the major side reaction. It was possible that the less sterically hindered OH group reacted with TESCl to produce traces of HCl, which then promoted the dehydration of tertiary alcohols.

Indeed, a small amount of RO–SiEt₃ was detected, where the RO moiety derived from primary and secondary alcohols. Activated secondary alcohols such as benzylic/allylic/propargylic alcohols were not tolerated. The benzylic alcohol **1au** gave only a trace of the desired product and 43% of the bis-alkylated byproduct (entry 8), and the allylic and propargylic

alcohols **1av** and **1aw** were totally incompatible, resulting in unidentifiable mixtures (entries 9 and 10). The presence of phenol groups was tolerated by the reaction (entries 11 and 12). The incorporation of phenol and alcohol groups into alkene substrates was also tolerated (entries 12 and 13). The unique selectivity shown by this method makes up for the Ti-catalyzed alkylation of tertiary chlorides, where the presence of an alcohol or phenol group would impede the reaction.^{3h}

2.4. Mechanistic Studies. The radical clock experiments were performed to determine whether a radical process was involved in this dehydroxylative alkylation reaction. The reaction of ^tBuOH with the α -cyclopropylstyrene **5**, a well-known radical clock substrate probe,²⁴ gave ring-expanded product **6** under the standard conditions (Scheme 2a). In

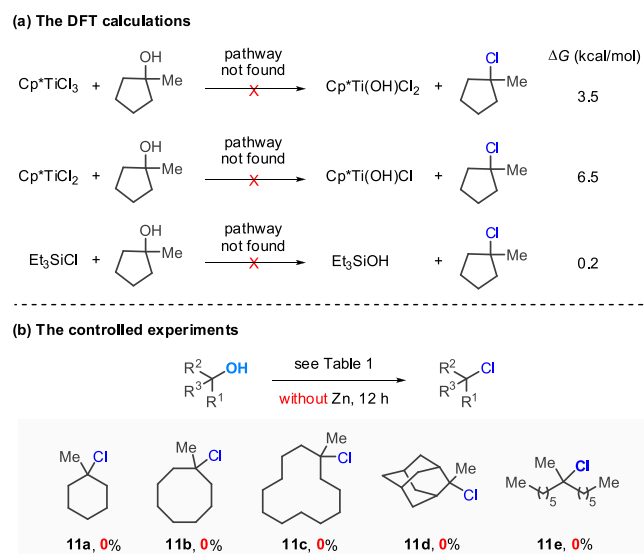
Scheme 2. Radical Clock Experiments



addition, the reaction of the cyclopropyl alcohol **9** with **2e** exclusively produced the ring-opening product **10** (Scheme 2b). These results suggest that the tertiary alcohols were activated by the Ti catalyst via a radical mechanism.

The substitution reaction of a tertiary alcohol with a chloride could yield the corresponding tertiary alkyl chloride that is prone to radical formation.^{3h} Thus, we considered the possible chlorination reaction of **1c** with each chloride species (i.e., Cp^{*}TiCl₃, Cp^{*}TiCl₂, and Et₃SiCl), which would produce 1-methylcyclopentyl chloride (Scheme 3a). Thermodynamically, these reactions would have no driving force, as shown by the computed free energy changes (>0), and kinetically no pathways could be found. Experimentally, no tertiary alkyl

Scheme 3. Chlorination Pathway Ruled Out by DFT Calculations and Controlled Experiments



chlorides could be observed by GC-MS analysis during the reactions. Furthermore, under the standard conditions without a reductant, the reactions of a range of alcohols did not yield any chlorination product, even after 12 h (Scheme 3b). Taken together, these results essentially rule out a mechanism involving the intermediacy of tertiary alkyl chlorides.

The DFT calculations support the mechanistic proposal that a carbon radical is generated from the alcohol substrate via a single-electron transfer (SET) reaction with a Ti(III) species (Figure 1). The precatalyst Cp^{*}TiCl₃ is reduced by zinc to Cp^{*}TiCl₂, which binds the alcohol substrate **1c** through the oxygen donor atom to form **IM1**. **IM1** undergoes a facile intramolecular titanium-to-hydroxy SET via **TS1** ($\Delta G^\ddagger = 11.3$ kcal/mol relative to **IM1**). The spin densities on the selected atoms in **TS1** indicate that it contains an emerging 1-methylcyclopentyl radical with a spin density of 0.39 on the tertiary carbon. With the release of the radical, **TS1** proceeds to the titanium(IV) complex Cp^{*}Ti(OH)Cl₂ (**IM2**), which is turned over to Cp^{*}TiCl₃ by metathesis with Et₃SiCl via the four-member transition state **TS2**. This is the rate-determining step with a free energy of activation of 28.1 kcal/mol. Reduction of Cp^{*}TiCl₃ by zinc regenerates the active catalyst Cp^{*}TiCl₂ for the next cycle of catalysis.

The DFT-calculated energy barrier for converting Cp^{*}Ti(OH)Cl₂ into Cp^{*}TiCl₃ for subsequent reduction to Cp^{*}TiCl₂ is 28.1 kcal/mol (**TS2** – **IM2**) and rate-limiting. This is considerably higher than the energy barrier of 11.3 kcal/mol required for the radical-forming C–OH homolysis (**TS1**–**IM1**). To check this calculation, we performed stoichiometric reactions of randomly selected alcohols with Cp^{*}TiCl₂ (Scheme 4). In contrast to the catalytic reactions that require an elevated temperature of 60 °C (Table 1, entries 1 vs 12), these stoichiometric reactions proceeded well at 30 °C. Furthermore, kinetic measurements showed that the reaction was significantly accelerated by increasing the amount of TESCl (Scheme S3), suggesting TESCl involvement in the rate-determining step. In summary, the DFT computational results generally agree with experiments, showing good experimental–theoretical synergy.

On the basis of the above findings and the literature reports, we propose a catalytic cycle as shown in Scheme 5. Coordination of an alcohol to Cp^{*}TiCl₂ gives the complex **A**, which undergoes an intramolecular single-electron transfer, affording a carbon radical and Cp^{*}Ti(OH)Cl₂.^{13,16} Reaction of the carbon radical with an activated alkene generates the radical **B**, which is subsequently reduced and protonated to deliver the desired product, probably assisted by Ti catalysis.^{3h} TESCl is used to regenerate Cp^{*}TiCl₃ from Cp^{*}Ti(OH)Cl₂.¹⁵ Reduction of Cp^{*}TiCl₃ by Zn generates the active Cp^{*}TiCl₂ species.

3. CONCLUSION

In conclusion, we have developed the first dehydroxylative radical C–C bond-forming reaction of unactivated tertiary alcohols and therefore established a new method for constructing all-carbon quaternary centers directly from an alcohol. The protocol is distinguished by its broad substrate scope, excellent chemoselectivity, high diastereoselectivity in the modification of sterically hindered complex molecules, and 10-g-scale reaction. The reaction is highly selective for the alkylation of tertiary alcohols, leaving secondary/primary alcohols and phenols intact. It therefore constitutes a new and complementary bond disconnection strategy that is likely

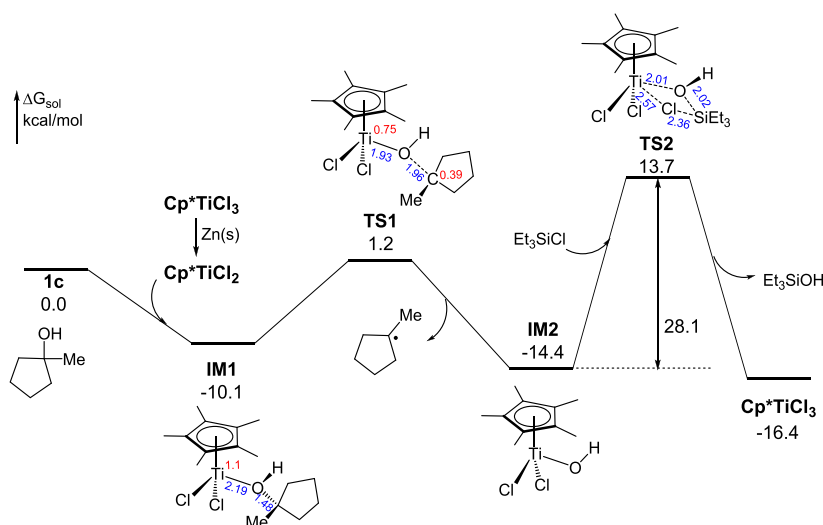
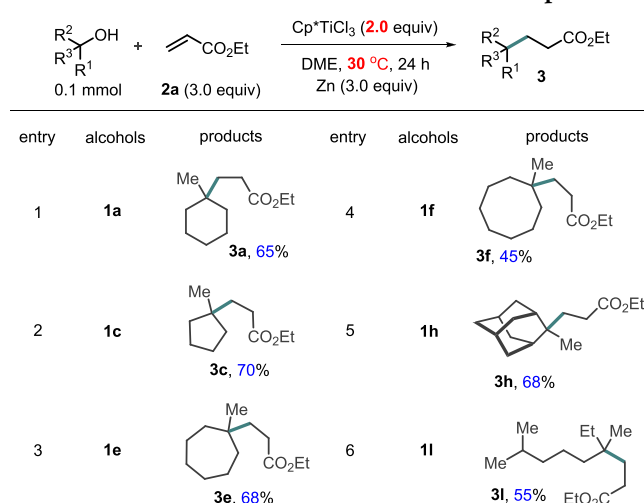


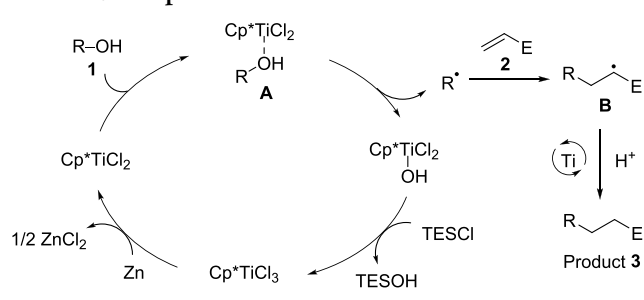
Figure 1. Free energy profile for the Ti(III)-catalyzed generation of 1-methylcyclopentyl radical from 1-methylcyclopentyl alcohol. Selected bond distances in blue font are given in Å. The numbers in red font on selected atoms in IM1 and TS1 denote spin densities.

Scheme 4. Stoichiometric Reaction at Room Temperature^a



^aIsolated yields.

Scheme 5. Proposed Mechanism



to find broad synthetic applications, particularly because of the easy availability of alcohols in both the natural world and the synthetic realm. The mechanistic probe reveals a plausible pathway involving a tertiary carbon radical generated via Ti-catalyzed homolysis of the C–OH bond. Work on the further expansion of the scope of coupling partners is in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.0c07492>.

Parts of the mechanistic studies, detailed experimental procedures, characterization data, copies of ¹H and ¹³C NMR spectra for new compounds, and computational methods and data (PDF)

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#H.X. and J.G. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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