Low-Valent Titanium-Mediated Radical Conjugate Addition Using Benzyl Alcohols as Benzyl Radical Sources
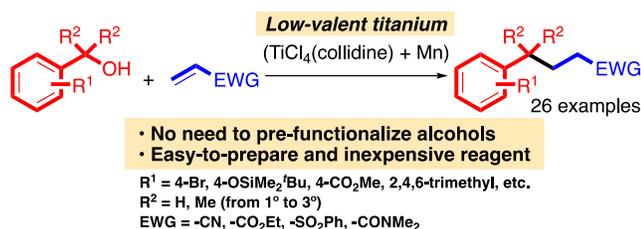
Low-Valent Titanium-Mediated Radical Conjugate Addition Using Benzyl Alcohols as Benzyl Radical Sources

Takuya Suga*, Shoma Shimazu and Yutaka Ukaji*

Division of Material Chemistry, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma, Kanazawa, Ishikawa 920-1192, Japan

Supporting Information Placeholder

ABSTRACT: A concise method to directly generate benzyl radicals from benzyl alcohol derivatives has been developed. The simple and inexpensive combination of $TiCl_4$(collidine) (collidine = 2,4,6-collidine) and manganese powder afforded a low-valent titanium reagent, which facilitated homolytic cleavage of benzylic C–OH bonds. The application to radical conjugate addition reactions demonstrated the broad scope of this method. The reaction of various benzyl alcohol derivatives with electron-deficient alkenes furnished the corresponding radical adducts.

Homolytic carbon–heteroatom bond cleavage is a promising strategy to introduce carbon radicals into organic synthesis. Generally, the hydroxy group has been regarded as a carbon radical synthon owing to its role as a synthetic precursor to halides and various esters that can undergo homolysis (e.g., xanthate,[1] oxalate[2], benzoate[3] and phosphate[4]). However, the necessity of additional synthetic steps for their preparation inevitably elongates synthetic schemes.[5] Despite its potential usefulness, the direct use of the hydroxy group in radical reactions remains underexplored.[6] In particular, its practical application to C–C bond formation is almost unknown. To realize the one-step radical C–C bond formation reaction via C–OH bond cleavage, we focused on low-valent titanium complexes that possess sufficient oxophilicity to extract oxygen atoms from organic compounds (Ti–O = ca. 660 kJ/mol, C–OH = ca. 400 kJ/mol[7]) and are capable of single-electron reduction.[8] The intriguing precedent for titanium-mediated homolytic C–O bond cleavage emerged more than 50 years ago (Scheme 1a). In 1965, van Tamelen and Schwartz reported that the thermal decomposition of low-valent benzyl titanate afforded a benzyl radical dimer.[9] Subsequently, a few improved procedures were reported in the 1960s and 1970s.[10] However, these reactions received little attention as possible foundations for C–C bond formation. Low-valent titanium reagents are also known deoxygenating agents (Scheme 1b).[11] Although more than one mechanism is possible, it is likely that deoxygenation proceeds through a carbon radical intermediate.[11c,12] Accessing carbon radicals for C–C bond formation via these methods for purposes other than dimerization has not yet been reported. For the most relevant example, Zheng recently reported the first one-step dehydroxylative radical conjugate addition

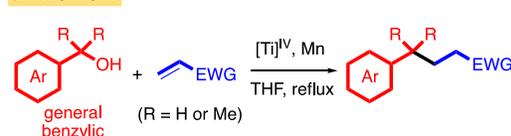## Scheme 1. Titanium-mediated C-OH bond cleavage
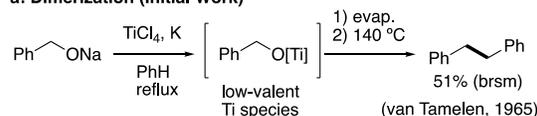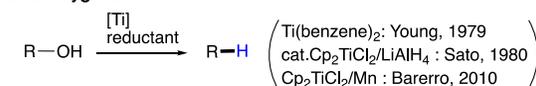
reactions of *N*-carbonyl hemiaminals by means of a Cp$_2$TiCl$_2$/Mg/TMSCl system (Scheme 1c).[13,14] Owing to the role of the alkyl chloride as an intermediate, this reaction should be distinguished mechanistically from van Tamelen and Schwartz's reaction.[13a] Presumably, the titanium-mediated homolytic C–O bond cleavage has not been applied actively to organic synthesis on account of the reported harsh reaction conditions[9,10] and the undesired deoxygenation pathway[11] as

depicted in Schemes 1a and 1b. Therefore, by addressing these problems, the titanium-mediated homolytic C–O bond cleavage would become a new promising tool for radical C–C bond formation reactions. We report here a general method for generating benzyl radicals from the corresponding benzyl alcohols by means of an inexpensive low-valent titanium reagent (Scheme 1d). This method works regardless of the electronic nature of the aromatic moiety and facilitates conjugate addition to a variety of electron-deficient alkenes.[15]

Table 1. Dimerization versus deoxygenation[a]
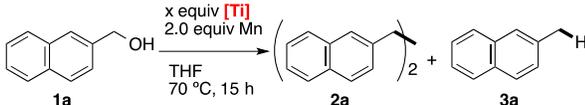
entry	[Ti]	x (equiv)	yield (%)[b] 2a	yield (%)[b] 3a
1	TiCl$_4$(collidine) (**4a**)	1.1	47	23
2[c]	Cp$_2$TiCl$_2$ (**4b**)	2.1	0	82
3[c]	Cp$_2$TiCl$_2$ (**4b**)	1.1	trace	41

[a] See SI for preparation of low-valent titanium reagents. [b] NMR yield. [c] Reproduction of experiment in ref 11c.

In the preliminary investigation, we found that harsh reductants (e.g., K, LiAlH$_4$) were unnecessary and that the simple and cheap TiCl$_4$/Mn system was sufficient to cleave the benzyl alcohol C–O bonds (Table 1). For instance, a combination of TiCl$_4$(collidine) (**4a**) (collidine = 2,4,6-collidine) and manganese powder effectively cleaved the C–O bond of 2-naphthalenemethanol (**1a**) to afford dimer **2a** and deoxygenated product **3a** in 47% and 23% yields, respectively (entry 1). The preferential formation of **2a** suggested that the benzyl radical was generated at a sufficiently high concentration to dimerize because the deoxygenation pathway was not operative. In contrast, the reaction with two equivalents of Cp$_2$TiCl$_2$ (**4b**) and manganese afforded only **3a** in 82% yield, as previously reported (entry 2).[11c] The use of one equivalent of **4b** halved the yield of **3a** (41% yield) and did not generate dimer **2a** (entry 3). Compound **4a** was prepared nearly quantitatively from inexpensive TiCl$_4$ and collidine.[16] This material had sufficient quality to use without purification. Compound **4a** is suitable for brief use under an air atmosphere and can be stored in a refrigerator for several months.

## Table 2. Application to radical conjugate addition[a]
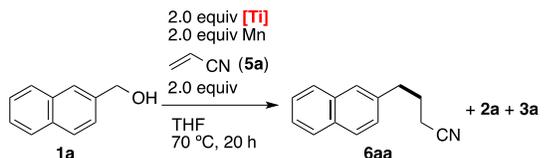
entry	[Ti]	yield (%)[b] 6aa	yield (%)[b] 2a	yield (%)[b] 3a
1	TiCl$_4$(collidine) (**4a**)	92	<5	<5
2	Cp$_2$TiCl$_2$ (**4b**)	13	0	58
3	TiCl$_4$(tmeda) (**4c**)	86	0	<5
4	TiCl$_4$(thf)$_2$ (**4d**)	64	<5	<5

[a] See SI for experimental detail. [b] NMR yield.

On the basis of these results, we applied the Ti/Mn system to Giese-type radical C–C bond formation reactions employing acrylonitrile (**5a**) as a radical acceptor (Table 2).[15] In this case, 2.0 equiv titanium reagent was necessary to obtain satisfactory yield (see SI). As expected, the radical conjugate addition product **6aa** was obtained in 92% yield when **4a** was used (entry 1). The substantially low yield of **6aa** (13% yield) and the predominant formation of **3a** (58% yield) with **4b** are consistent with the results reported in Table 1 (entry 2). Although **4a** was ultimately deemed the optimal reductant among the complexes that we examined, further screening of titanium complexes revealed that this reaction does not require the design of a specific titanium reagent under the tested conditions. For instance, the results obtained using TiCl$_4$(tmeda) (**4c**) (tmeda = *N,N,N',N'*-tetramethylethylenediamine) and TiCl$_4$(thf)$_2$ (**4d**) were comparable to those obtained with **4a** (entries 3 and 4, 86 and 64% yields).

Table 3. Scope of benzyl alcohols
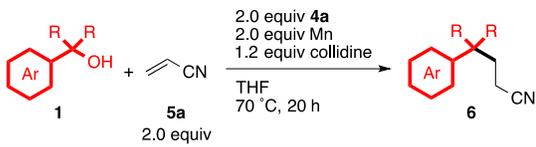
substrates[a]

a: alkylated and halogenated aromatics

1a, 88%   **1b**, 85%[b]   **1c**, 63%   **1d**, 74%

1e, 77%   **1f**, 63%   **1g**, 74%   **1h**, 74%

b: electron-deficient aromatics

1i, 63%   **1j**, 53%   **1k**, 71%

c: electron-rich aromatics

1l, 82%   **1m**, 85%   **1n**, 63%

d: substituents at *ortho*-positions

1o, 61%   **1p**, 72%   **1q**, 67%   **1r**, 92%

**e: methyl groups at *benzylic*-position**

1s, 88%   **1t**, 91%   **1u**, 92%   **1v**, 59%[b]

[a] Isolated yield of **6**. [b] 4 equiv alkene was used.

This method was applicable to various benzyl alcohol derivatives (Table 3). To improve the yields, 1.2 equiv 2,4,6-

collidine was added. Its effect was summarized in SI. Both 2-naphthalenemethanol (**1a**) and benzyl alcohol (**1b**) gave their corresponding products in very good isolated yields (88 and 85% yields, respectively). *Para*- and *meta*-alkyl substitutions did not significantly affect the yield (**1c-1e**, 63-77% yields), and the *para*-substituted halide series were also suitable substrates (**1f-1h**, 63-74% yields). Both electron-rich and electron-deficient benzyl alcohols underwent the desired reaction. For instance, 4-methoxycarbonyl-, cyano-, and trifluoromethyl-substituted benzyl alcohols afforded the products in good yields (**1i-1k**, 53-71% yields). The electron-rich 4-methoxy- and *tert*-butyldimethylsiloxy-benzyl alcohols were also good substrates (**1l** and **1m**, 82 and 85% yields).[17] The complete retention of the phenolic silyl ether moiety highlighted the mildness of the reaction conditions. Additionally, heteroaromatic 2-thiophenemethanol (**1n**) afforded the expected product in 63% yield. *Ortho*-substituted alcohols **1o-1q** reacted smoothly (61-72% yields), and the yield significantly increased when methyl groups occupied both the 2- and 6-positions (**1r**, 92% yield). The good yields obtained with secondary and tertiary benzyl alcohols promise a further expansion of the reaction scope (**1s-1v**, 59-92% yields).

Table 4. Scope of alkenes
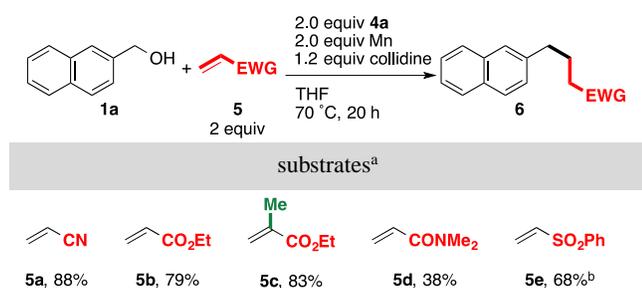
[a] Isolated yield of **6**. [b] 3 equiv alkene was used.

Several electron-deficient alkenes **5** were reacted with alcohol **1a** (Table 4). In addition to acrylonitrile (**5a**), ethyl acrylate (**5b**) underwent the conjugate addition to afford the expected product (79% yield). The successful utilization of methacrylate **5c** (83% yield) suggested that this reaction tolerates substitution at the internal position of the alkene moiety. *N,N*-dimethylacrylamide (**5d**) was a potentially suitable radical acceptor (38% yield). The considerable decreases in yields are likely due to the relatively low reactivity of the benzyl radical. Although phenyl vinyl sulfone (**5e**) was less reactive than **5a**, the radical adduct was obtained in reasonable yield (68% yield).

Scheme 2. Mechanistic study
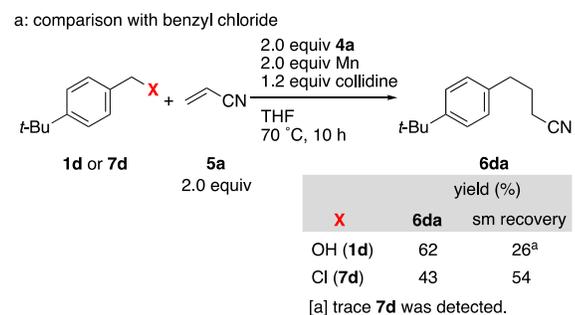
Finally, we conducted several mechanistic studies to exclude the possible intermediacy of benzyl chloride as observed in the previously described Zheng's reaction (Scheme 1c, Scheme 2).[13a] We found that the reaction with 4-*tert*-butylbenzyl chloride (**7d**) afforded the conjugate addition product **6da** under conditions identical to those used with benzyl alcohol **1d** (Scheme 2a);[18] however, its conversion after 10 h was noticeably lower than that observed for **1d**. In the reaction with **1d**, only a trace amount of **7d** (ca. 0.2% yield) was observed. Additionally, the treatment of **1a** with **4a** in the absence of manganese did not afford chloride **7a** at all, and the initial **1a** was recovered quantitatively (Scheme 2b). These experiments support the theory that the benzyl chloride pathway is not predominant at least in our reaction.

The proposed reaction mechanism is depicted in Scheme 3. Reaction between the benzyl alcohol and the low-valent titanium complex initiates the *in-situ* formation of titanate **A**. The thermal decomposition of **A** formally generates benzyl radical **B** and titanium oxide and is followed by radical conjugate addition. The generated radical **C** is trapped by another low-valent titanium species to give alkyltitanium **D**.[11c,12a] Protonation subsequently furnishes the conjugate addition product. Alternatively, **C** is directly converted to the final product through hydrogen atom transfer (HAT).[12b]

Scheme 3. Proposed mechanism
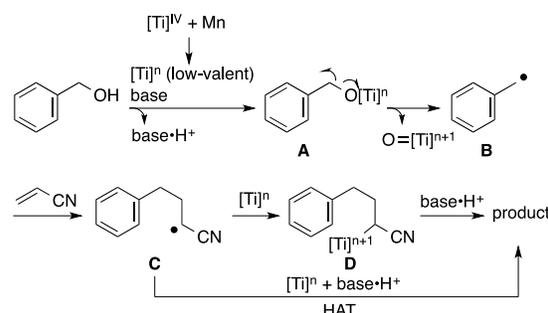
In summary, we have developed a concise method for generating benzyl radicals from benzyl alcohol derivatives and explored its synthetic application by exploiting the attractive nature of low-valent titanium species. This simplified access to carbon radicals will provide an opportunity to employ alcohols in a greater number of radical reactions.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, mechanistic studies, analytical data and copies of the ^{1}H, ^{13}C and ^{19}F NMR spectra for all new products **6** (PDF).

AUTHOR INFORMATION

Corresponding Author

*suga-t@se.kanazawa-u.ac.jp
*ukaji@staff.kanazawa-u.ac.jp

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