Chemistry Letters

p-Methylbenzyl 2,2,2-trichloroacetimidate: Simple Preparation and Application to Alcohol Protection

Kazutada Ikeuchi,* Kentaro Murasawa, Tomoki Arai, and Hidetsohi Yamada

Advance Publication on the web June 4, 2020
doi:10.1246/cl.200303

p-Methylbenzyl 2,2,2-trichloroacetimidate: Simple Preparation and Application to Alcohol Protection

Kazutada Ikeuchi,*[1,2] Kentaro Murasawa,[1] Tomoki Arai,[1] and Hidetsohi Yamada[1†]

[1]*School of Science and Technology, Kwansei Gakuin University, 2-1 Gakuen, Sanda 669-1337*
[2]*Department of Chemistry, Faculty of Science, Hokkaido University, Kita 10, Nishi 8, Kita-ku, Sapporo 060-0810*

E-mail: ikeuchi@sci.hokudai.ac.jp

A method for *p*-methylbenzyl (MBn) protection of alcohols by using MBn 2,2,2-trichloroacetimidate is described. The trichloroacetimidate can easily be prepared and isolated as a stable white powder without purification by silica gel chromatography. Catalytic use of zinc (II) triflate in diethyl ether activates the trichloroacetimidate to enable MBn protection of various alcohols.

Keywords: *p*-Methylbenzyl 2,2,2-trichloroacetimidate, Alcohol protection, Zinc (II) triflate

The benzyl (Bn) group and its analogues are widely used for alcohol protection in organic synthesis (Figure 1a).[1] Among these protecting groups, the Bn group is the most selected as a result of its stability under various conditions and specific cleavage under hydrogenolytic conditions.[2] The Bn group is typically installed on hydroxy groups via the Williamson ether synthesis (Figure 1b).[3] If the substrate is labile under basic conditions, acidic reaction conditions are employed by using benzyl 2,2,2-trichloroacetimidate (Bn-TCAI) and a Lewis acid/organic protonic acid (Figure 1b).[4] The *p*-methoxybenzyl (PMB) group is also frequently used for alcohol protection; the same protection method as that for the Bn group can be followed,[5] and the reactivity of the PMB group under oxidative conditions allows its selective removal in the presence of the Bn group.[6] Because of such advantages, further reaction methods for incorporating these two groups into alcohols have been reported.[7]

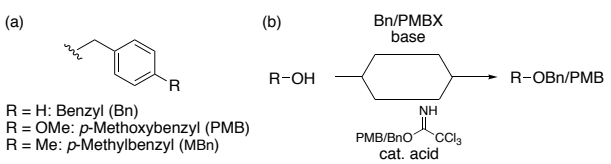
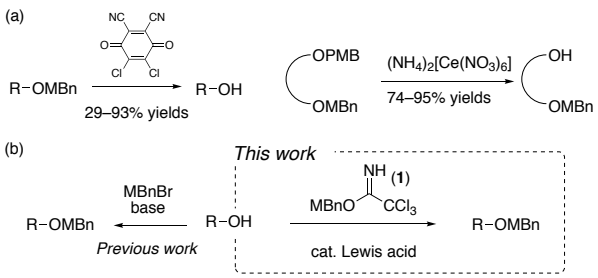


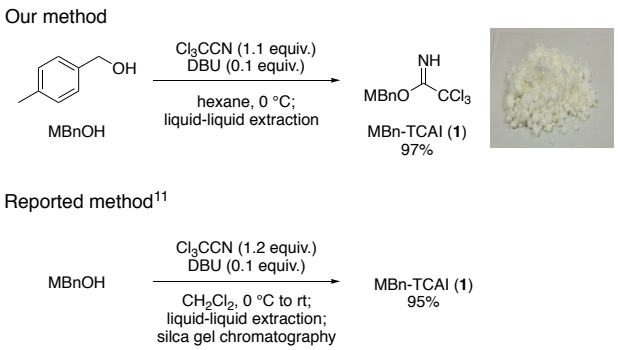
Figure 1. (a) Structures of the Bn group and its analogue. (b) General method for the Bn/PMB protection.

We have recently reported that, similar to PMB groups, *p*-methylbenzyl (MBn) groups installed on alcohols can be removed under oxidative conditions (Scheme 1a).[8] Furthermore, chemoselective removal of the PMB group in the presence of Bn and MBn groups was demonstrated. These results showed that the MBn group is a valuable protecting group for alcohols, in addition to the Bn and PMB groups. In the previous study, all the MBn groups in the substrates were incorporated via the Williamson ether synthesis because other introduction methods have not been explored in detail owing to the less general use of this group.[9] Herein, we describe a facile method for MBn protection by using MBn-TCAI (**1**) and a catalytic Lewis acid (Scheme 1b).



Scheme 1. (a) Our previous report about the MBn group. (b) Methods for protecting alcohols with the MBn groups.

MBn-TCAI (**1**) was prepared according to our previous simple method for synthesizing various TCAIs.[10] Thus, a suspension of *p*-methylbenzyl alcohol (MBnOH) in hexane was treated with trichloroacetonitrile and catalytic 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 0 °C. Similar to the appearance change that occurred in the established TCAI synthesis reactions, the suspected reaction mixture gradually changed to a colorless solution as the reaction proceeded. Subsequent work-up process with liquid-liquid extraction provided **1** in 97% yield as a white powder (Scheme 2). Although the synthesis of **1** has already been reported, that method requires purification by silica gel chromatography.[11] Our method provides **1** in high purity without such purification. Synthesized **1** can be kept at room temperature for a month without decomposition.

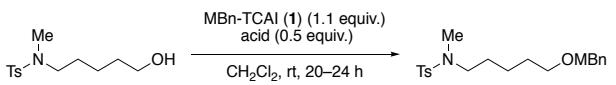


Scheme 2. Facile synthesis of MBn-TCAI (**1**).

With MBn-TCAI (**1**) in hands, we turned our attention to optimizing the reaction conditions for providing MBn-protected compounds by using **1**. Alcohol **2**[8] possessing a

sulfonyl amide moiety was used for the investigation, and the acid screening results are summarized in Table 1. The amounts of **1** and each acid were fixed at 1.1 and 0.5 equivalents, respectively. Dichloromethane was selected as the reaction solvent and the reaction was evaluated based on the NMR yield of crude products. Frequently used Lewis acids for activating Bn/PMB-TCAI, such as trimethylsilyl trifluoromethanesulfonate (TMSOTf),[12] $BF_3{\cdot}OEt_2$,[13] $Sc(OTf)_3$,[14] $La(OTf)_3$,[15] and $Cu(OTf)_2$,[16] induced the reaction; however, the NMR yields remained at 47%–60%, indicating that these Lewis acids have no catalytic activity in the reaction using **1** (entries 1–5). The use of the organic protonic acid, 10-camphorsulfonic acid (CSA),[17] resulted in almost no reaction (entry 6). Subsequently, we used an unreported catalyst for activating Bn/PMB-TCAIs. No reaction occurred with the use of $ZrCl_4$ (entry 7). Although the reaction with $In(OTf)_3$ gave the similar results to those in entries 4 and 5 (entry 8), the use of MeOTf and $Zn(OTf)_2$ improved the reaction conversion to give **3** in 78% and 71% NMR yields, respectively (entries 9 and 10). Both reactions also proceeded with similar yields when 0.1 equivalent of the catalyst was used. However, MeOTf occasionally produced a mixture of **4a** and **4b** as byproducts, in which a *p*-xylene unit is attached to the benzene ring of the MBn group of **3** (Scheme 3).[18] This side reaction involves the Friedel-Crafts alkylation of benzylic cation **5**, derived from **1** *in situ.* Addition of a scavenger such as anisole[19] and pentamethylbenzene[20] did not completely suppress the side reaction. Therefore, we further modified the $Zn(OTf)_2$-mediated reaction system and discovered that the reaction solvent was crucial for enhancing the reaction. Thus, the reaction in diethyl ether proceeded smoothly with a loading of 0.1 equivalent of $Zn(OTf)_2$ to give **3** in 98% NMR yield (entry 11). The use of TfOH[21] instead of $Zn(OTf)_2$ decreased NMR yield to 77% (entry 12), indicating that the zinc (II) cation is required for efficient conversion. The

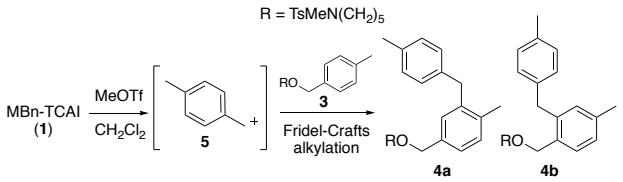
Table 1. Acid screening for reaction of alcohol **2** with MBn-TCAI (**1**).



2 **3**

entry	acid	yield (%)[a]	entry	acid	yield (%)[a]
1	$Sc(OTf)_3$	50	7	$ZrCl_4$	N.R.
2	$BF_3{\cdot}OEt_2$	47	8	$In(OTf)_3$	61
3	TMSOTf	54	9	MeOTf	78 (77[b])
4	$La(OTf)_3$	57	10	$Zn(OTf)_2$	71 (67[b])
5	$Cu(OTf)_2$	60	11[c]	$Zn(OTf)_2$	98 (94[d])
6	CSA	5	12[c]	TfOH	77

[a] NMR yield. [b] NMR yield with 0.1 equiv. of acid. [c] Reaction with 0.1 equiv. of acid and Et_2O as the reaction solvent. [d] Isolated yield. Ts = *p*-toluenesulfonyl.

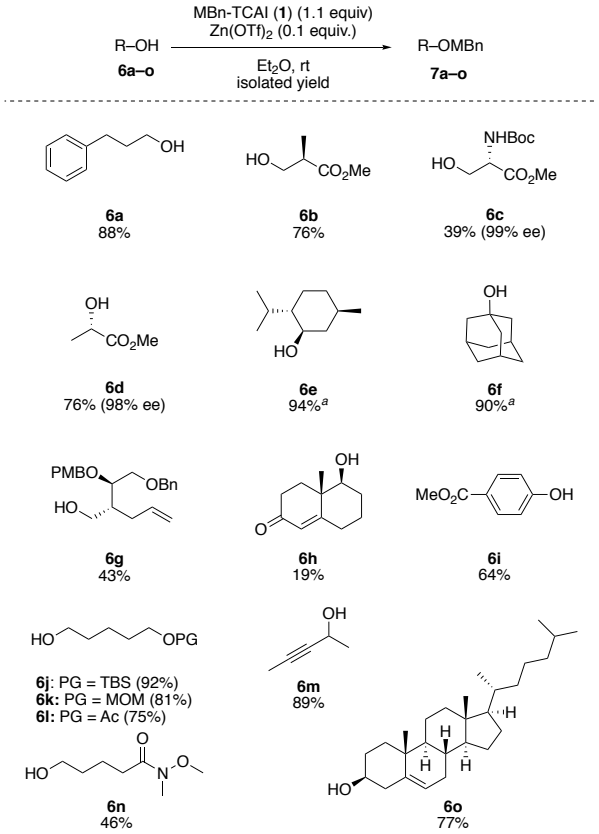


Scheme 3. Proposed mechanism for the formation of byproducts **4a** and **4b**.

isolated yield of **3** under the conditions given in entry 11 was 94%, and no byproducts, **4a** or **4b**, were formed.

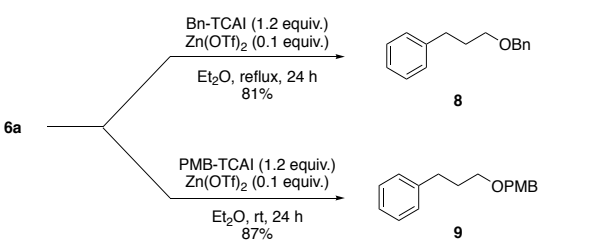
With the optimized reaction conditions established, the substrate scope was investigated (Scheme 4). 3-Phenyl-1-propanol (**6a**) and methyl (*R*)-3-hydroxyisobutyrate (**6b**) reacted easily with **1** to afford **7a** and **7b** in 88% and 76% yields, respectively. Protection of the primary alcohol in serine derivative **6c** resulted in a low yield (39%) because the Boc group was partially damaged under the reaction conditions. Secondary alcohols such as methyl lactate (**6d**) and L-menthol (**6e**) formed the corresponding MBn-protected compounds in 76% and 94% yields, respectively, the latter using 1.5 equiv. of **1**. Reaction of 1-adamantanol (**6f**), which is classified as a tertiary alcohol, proceeded smoothly with 1.5 equiv. of **1** to afford MBn ether **7f** in 90% yield. Using 1.1 equiv. of **1** in the reaction of **6e** and **6f** lingered in the MBn protection to decrease the yields of **7e** and **7f** to 73% and 66%, respectively. These results indicate that the presence of excess **1** accelerated the reaction. By contrast, a dramatical decrease in yield was observed when more hinder alcohols such as **6g** and **6h** were used. In particular, the secondary alcohol of **6h** hardly reacted with **1** and provided **7h** in only 19% yield. Although the reaction was also attempted in the presence of excess **1**, or under reflux conditions, the yield of **6h** was largely unchanged, indicating that steric hindrance around the alcohol group affects the reaction with **1**. Protection of the phenolic hydroxy group in methyl 4-hydroxybenzoate (**6i**) afforded **7i** with a minor *C*-alkylated compound with yield of 64%. Notably, the enantiomeric excess of both **7c** and **7d**, possessing a chiral center at the α-position to the carbonyl moiety, was ≥98% ee. These results indicate that no racemization of the chiral centers occurred under our reaction conditions.

The functional allowance of the MBn-protected reaction was further examined. Alcohol protection using TBS, Ac, and MOM groups in **6j–k** was not affected under the reaction conditions, thereby allowing the corresponding the MBn protections in satisfactory product yields. The alkyne moiety in **6m** also tolerated the reaction to protect the secondary alcohol, affording a yield of 89%. In contrast, Weinreb amide **6n** induced a side reaction triggered by amide activation via $Zn(OTf)_2$, decreasing the yield of **7n**, and providing inseparable byproducts. Finally, the reaction conditions were applied to the protection of cholesterol (**6o**) with a tri-substituted alkene in the tetra cyclic skeleton. The reaction proceeded uneventfully, affording the MBn-protected compound **7o** with a yield of 77% yield.



Scheme 4. Substrate scope. [a]1.5 equiv. MBn-TCAI (**1**) was used.

The $Zn(OTf)_2/Et_2O$ reaction system enabled the introduction of Bn and PMB protection (Scheme 5). Thus, treatment of **6a** with Bn-TCAI or PMB-TCAI and catalytic $Zn(OTf)_2$ in Et_2O provided the corresponding protected compounds **8** and **9** in 81% and 87% yields, respectively. Bn protection required reflux conditions for the reaction to proceed efficiency. This is the first report of these reaction conditions for Bn/PMB protection of alcohols. $Zn(OTf)_2$ is a stable and non-fuming solid; therefore, for Bn/PMB protection, the proposed method is safer and easier than reactions using TfOH, which is a fuming liquid acid.[7b, 7e–f, 21]



Scheme 5. Application of the $Zn(OTf)_2/Et_2O$ reaction system to Bn-TCAI and PMB-TCAI.

In summary, we established a simple preparation method for MBn-TCAI (**1**) and developed an MBn-protection method for various alcohols by using **1**. Treatment of MBnOH with trichloroacetonitrile and catalytic DBU in hexane produced **1** easily without purification by silica gel chromatography. Activation of **1** with catalytic $Zn(OTf)_2$ in Et_2O enabled the MBn protection of various types of alcohols in 19%–94% yields. These new results and our previous report will accelerate the use of MBn groups for the transformation of polyol compounds with orthogonal synthetic strategies.

This work was partly supported by JSPS KAKENHI (Grant numbers JP19K15549, JP18H04429, and JP19H02727). We thank Dr. Yasuko Okamoto at Tokushima Bunri University for measurements of the MS spectra of partial compounds.

[†]Deceased on November 23, 2019. This paper is dedicated to the memory of Prof. Dr. Hidetoshi Yamada.

Supporting Information is available on http://dx.doi.org/10.1246/cl.******.

References and Notes

1 P. G. M. Wuts, *Greene's Protective Groups in Organic Synthesis,* 5th ed., John Wiley & Sons, Hoboken, NJ, **2014**.
2 S. Czernecki, C. Georgoulis, C. Provelenghiou, G. Fusey, *Tetrahedron Lett.* **1976**, *17*, 3535.
3 Z. Wang, Ed., In *Comprehensive Organic Name Reactions and Reagents*, Wiley, New York, **2009**, Vol. 3, 3026.
4 a) P. Eckenberg, U. Groth, T. Huhn, N. Richter, C. Schmeck, *Tetrahedron* **1993**, *49*, 1619. b) A. N. Boa, P. R. Jenkins, In *Encyclopedia of Reagents for Organic Synthesis*, 2nd ed., ed. by L. A. Paquette, D. Crich, P. L. Fuchs, G. A. Molander, Wiley, New York, **2009**, Vol. 2, 680.
5 a) N. Nakajima, K. Horita, R. Abe, O. Yonemitsu, *Tetrahedron Lett.* **1988**, *29*, 4139. b) P. G. M. Wuts, In *Encyclopedia of Reagents for Organic Synthesis,* 2nd ed., ed. by L. A. Paquette, D. Crich, P. L. Fuchs, G. A. Molander, Wiley, New York, **2009**, Vol. 8, 6598.
6 a) Y. Oikawa, T. Yoshioka, O. Yonemitsu, *Tetrahedron Lett.* **1982**, *23*, 885. b) K. Horita, T. Yoshioka, T. Tanaka, Y. Oikawa, O. Yonemitsu, *Tetrahedron* **1986**, *42*, 3021.
7 a) H. Fujita, H. Terasaki, S. Kakuyama, K. Hioki, M. Kunishima, *Org. Lett.* **2019**, *21*, 3093. b) H. Fujita, S. Kakuyama, M. Kunishima, *Eur. J. Org. Chem.* **2017**, 833. c) K. Yamada, Y. Tsukada, Y. Karuo, M. Kitamura, M. Kunishima, *Chem. Eur. J.* **2014**, *20*, 12274. d) N. Barroca-Aubry, M. Benchekroun, F. Gomes, D. Bonnaffé, *Tetrahedron Lett.* **2013**, *54*, 5118. e) K. Yamada, H. Fujita, M. Kitamura, M. Kunishima, *Synthesis* **2013**, *45*, 2989. f) K. Yamada, H. Fujita, M. Kunishima, *Org. Lett.* **2012**, *14*, 5026. g) Y. Okada, M. Ohtsu, M. Bando, H. Yamada, *Chem. Lett.* **2007**, *36*, 992. h) K. W. C. Poon, G. B. Dudley, *J. Org. Chem.* **2006**, *71*, 3923. I) K. W. C. Poon, S. E. House, G. B. Dudley, *Synlett.* **2005**, 3142.
8 K. Ikeuchi, K. Murasawa, K. Ohara, H. Yamada, *Org. Lett.* **2019**, *21*, 6638.
9 There is one reaction example for alcohol protection by using MBn-TCAI (**1**); however, the detail reaction conditions and the result are not noted. See: J. W. Liebeschuetz, W. A. Wylie, B. Waszkowycz, C. W. Murray, A. D. Rimmer, P. M. Welsh, S. D. Jones, J. M. E. Roscoe, S. C. Young, P. J. Morgan, U.S. Pat. Appl. US 2002/0055522, **2002**.
10 K. Ikeuchi, K. Murasawa, H. Yamada, *Synlett* **2019**, *30*, 1308.
11 A. A. Adhikari, L. Radal, J. D. Chisholm, *Synlett* **2017**, *28*, 2335.
12 Selected papers for the use of TMSOTf: a) C. Dong, D. K. Reilly, C. Bergame, F. Dolke, J. Srinivasan, S. H. von Reuss, *J. Org. Chem.* **2018**, *83*, 7109. b) J. Zambrana, P. Romea, F. Urpí, *Org.*

Biomol. Chem. **2016**, *14*, 5219. c) A. A. S. Gietter-Burch, V. Devannah, D. A. Watson, *Org. Lett.* **2017**, *19*, 2957. d) L. Yu, H. Wang, N. G. Akhmedov, C. Sowa, K. Liu, H. Kim, L. Williams, *Org. Lett.* **2016**, *18*, 2868.

13 Selected papers for the use of $BF_3{\cdot}OEt_2$: a) Y.-X. Su, W.-M. Dai, *Tetrahedron* **2018**, *74*, 1546. b) R. S. Mancini, J. B. Lee, M. S. Taylor, *J. Org. Chem.* **2017**, *82*, 8777. c) M. Hutchby, A. C. Sedgwick, S. D. Bull, *Synthesis* **2016**, *48*, 2036. d) K. L. Jackson, J. A. Henderson, H. Motoyoshi, A. J. Phillips, *Angew. Chem. Int. Ed.* **2009**, *48*, 2346.

14 Selected papers for the use of $Sc(OTf)_3$: a) H. G. Gudmundsson, C. J. Kuper, D. Cornut, F. Urbitsch, B. L. Elbert, E. A. Anderson, *J. Org. Chem.* **2019**, *84*, 14868. b) H. Tsuchikawa, T. Hayashi, H. Shibata, M. Murata, Y. Nagumo, T. Usui, *Tetrahedron Lett.* **2016**, *57*, 2426. c) H. Fuwa, N. Yamagata, A. Saito, M. Sasaki, *Org. Lett.* **2013**, *15*, 1630. d) B. M. Trost, B. M. O'Boyle, D. Hund, *J. Am. Chem. Soc.* **2009**, *131*, 15061.

15 Selected papers for the use of $La(OTf)_3$: a) F. Della-Felice, A. M. Sarotti, M. J. Krische, R. A. Pilli, *J. Am. Chem. Soc.* **2019**, *141*, 13778. b) R. S. Mancini, J. B. Lee, M. S. Taylor *J. Org. Chem.* **2017**, *82*, 8777. c) Y. Hara, T. Honda, K. Arakawa, K. Ota, K. Kamaike, H. Miyaoka, *J. Org. Chem.* **2018**, *83*, 1976. d) V. K. Chatare, R. B. Andrade, *Angew. Chem. Int. Ed.* **2017**, *56*, 5909.

16 Selected papers for the use of $Cu(OTf)_2$: a) L. Brewitz, J. Llaveria, A. Yada, A. Fürstner, *Chem. Eur. J.* **2013**, *19*, 4532. b) B. M. Trost, D. J. Michaelis, S. Malhotra *Org. Lett.* **2013**, *15*, 5274. c) R. K. Malla, S. Bandyopadhyay, C. D. Spilling, S. Dutta, C. M. Dupureur, *Org. Lett.* **2011**, *13*, 3094. d) G. Sabitha, R. Srinivas, J. S. Yadav, *Synthesis* **2011**, 3343.

17 Selected papers for the use of CSA: a) D. P. de Sant'Ana, C. de Oliveira Rezende J., J.-M. Campagne, L. C. Dias, R. M. de Figueiredo, *J. Org. Chem.* **2019**, *84*, 12344. b) B. M. Trost, W.-J. Bai, C. E. Stivala, C. Hohn, C. Poock, M. Heinrich, S. Xu, J. Rey, *J. Am. Chem. Soc.* **2018**, *140*, 17316. c) A. Raju, G. Sabitha, *RSC Adv.*, **2015**, *5*, 34040. d) X. Gao, H. Han, M. J. Krische, *J. Am. Chem. Soc*. **2011**, *133*, 12795.

18 Excess use of MBn-TCAI (**1**) often caused the side reaction. Separation of **3** and by-products **4a**/**4b** was difficult. For the ^{1}H NMR spectrum of the mixture, see the supporting information.

19 Y. Masui, N. Chino, S. Sakakibara, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 464.

20 H. Yoshino, Y. Tsuchiya, I. Saito, M. Tsujii, *Chem. Pharm. Bull.* **1987**, *35*, 3438.

21 Selected papers for the use of TfOH: a) B. K. Ghotekar, A. R. Podilapu, S. S. Kulkarni, *Org. Lett.* **2020**, *22*, 537. b) A. Ghosh, A. C. Brueckner, P. H.-Y. Cheong, R. G. Carter, *J. Org. Chem.* **2019**, *84*, 9196. c) Y. Wakamiya, M. Ebine, M. Murayama, H. Omizu, N. Matsumori, M. Murata, T. Oishi, *Angew. Chem. Int. Ed.* **2018**, *57*, 6060. d) K. Ochiai, S. Kuppusamy, Y. Yasui, K. Harada, N. R. Gupta, Y. Takahashi, T. Kubota, J. Kobayashi, Y. Hayashi, *Chem. Eur. J.* **2016**, *22*, 3287.