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Efficient Method for the Deprotection of *tert*-Butyldimethylsilyl Ethers with $TiCl_4$−Lewis Base Complexes: Application to the Synthesis of 1β-Methylcarbapenems

Akira Iida, Hiroki Okazaki, Tomonori Misaki, Makoto Sunagawa,† Akira Sasaki,† and Yoo Tanabe*

Department of Chemistry, School of Science and Technology, Kwansei Gakuin University, 2-1 Gakuen, Sanda, Hyogo 669-1337, Japan, and Research Division, Sumitomo Pharmaceuticals Co., Ltd. 1-98, Kasugade Naka 3-Chome, Konohana-ku, Osaka 554-0022, Japan

tanabe@kwansei.ac.jp

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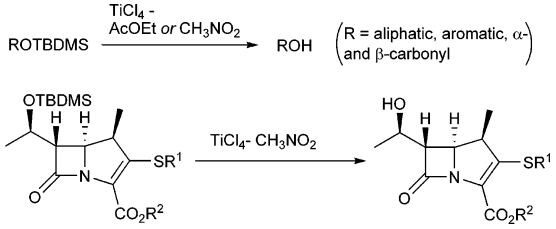
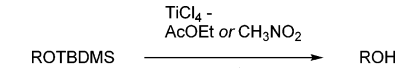


$TiCl_4$−Lewis base (AcOEt, CH_3NO_2) complexes smoothly deprotected *tert*-butyldimethylsilyl (TBDMS) ethers. The reaction velocity with these complexes, which seemed less reactive due to the influence of Lewis bases, was considerably greater than that with $TiCl_4$ alone. Selective desilylations between aliphatic and aromatic TBDMS ethers (**1** and **5**), between **1** and benzyl, allyl, tosyl, methoxyphenyl, and chloroacetyl ethers (**13**, **14**, **15**, **16**, and **17**), and between TBDMS and TBDPS ethers (**18** and **19**) were successfully performed. Desilylation of TBDMS-aldol, acyloin, and β-lactam analogues **9**−**12** proceeded smoothly due to anchimeric assistance by the neighboring carbonyl groups. The present method was successfully applied to the practical synthesis of 1β-methylcarbapenems **20a′**−**f′**.

The *tert*-butyldimethylsilyl (TBDMS) group is utilized in one of the most reliable protective methods for alcohols in organic synthesis,[1] due to its ready introduction and deprotection.[2] A number of methods for the deprotection have been exploited, involving representative fluoride anions, acidic and basic conditions, and oxidation, and reduction agents.[3] Lewis-acid promoted reactions are considered to be a complementary deprotection method; however, this method received relatively little attention. The use of BF_3·Et_2O,[4a] $Sc(OTf)_3$,[4b] TMSOTf,[4c] $Zn(BF_4)_2$,[4d] $InCl_3$,[4e] $ZnBr_2$,[4f] $ZrCl_4$,[4g] and $SbCl_5$[4h] has been reported.

SCHEME 1



In connection to our studies on the development of practical reactions[5a] such as esterifications,[5b−d] amide formations,[5c,d] sulfonylations,[6] and silylations,[7] we report here an efficient, practical, and chemoselective method for the deprotection of TBDMS ethers using economical and available $TiCl_4$−Lewis base (AcOEt or CH_3NO_2) complexes (Scheme 1).

The initial trial reaction of 2-(*tert*-butyldimethylsiloxy)nonane (**1**) with $TiCl_4$ resulted in considerable side formation of 2-chlorononane (∼30%), along with the desired 2-nonanol (Scheme 2, reaction A): S_Ni chlorination (C−O bond cleavage) of **1** and/or 2-nonanol proceeded due to the high inherent reactivity of $TiCl_4$. To circumvent the side chlorination, we examined less reactive $TiCl_4$−Lewis base complexes. Screening of nitrogen-type Lewis bases (alkylated amine, amide, aniline,

* Address correspondence to this author at Kwansei Gakuin University. Phone: +81-(0)795-565-8397. Fax: +81-(0)795-565-9077.

† Sumitomo Pharmaceuticals Co.

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SCHEME 2

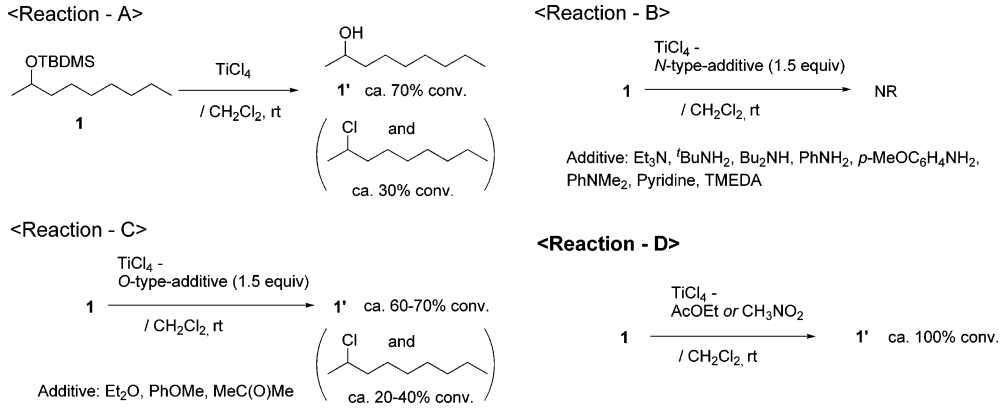
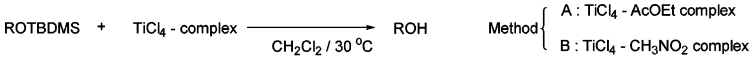
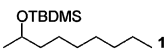
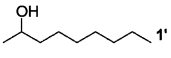
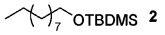
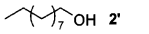
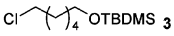
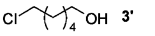
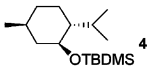
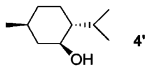
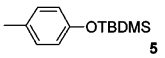
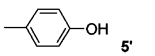
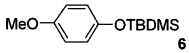
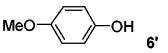
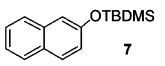
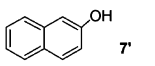
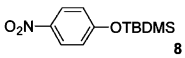
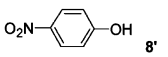
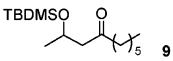
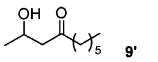
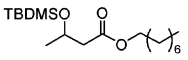
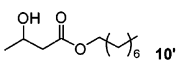
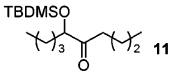
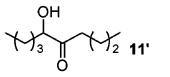
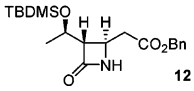
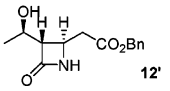


TABLE 1. Desilylation of Various TBDMS Ethers with $TiCl_4$–Lewis Base Complexes



Entry	Substrate	Product	Method	Equiv $TiCl_4$-complex	Time / min	Yield[a] / %
1			A	1.2	10	97
			B	1.2	10	94[b]
2			A	1.2	10	99
			B	1.2	10	96[b]
3			A	1.2	10	94
			B	1.2	10	91[b]
4			A	1.2	10	94
			B	1.2	10	85[b]
5			A	2.5	240	97
			B	2.5	10	99
6			A	2.5	60	95
			B	2.5	10	99
7			A	2.5	360	97
			B	2.5	15	99
8			B	3.6	500	97
9			A	2.4	30	94
			B	2.4	30	97[b]
10			A	2.4	30	98
			B	2.4	30	95[b]
11			A	2.4	10	97
			B	2.4	10	97[b]
12			A	2.4	240	97[b]
			B	2.4	120	95[c]

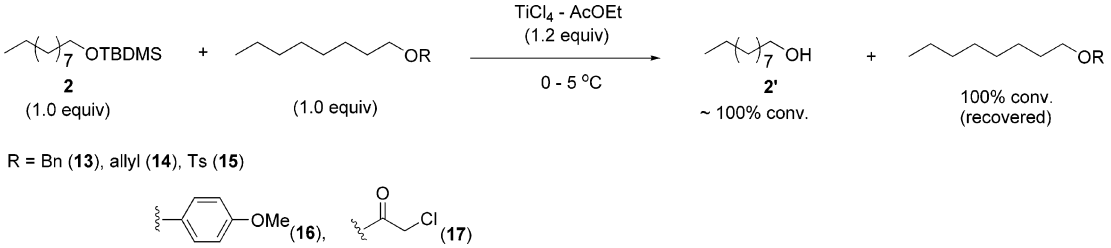
[a] Isolated. [b] Reaction temperature was 0−5 °C. [c] Reaction temperature was −45 to −50 °C.

pyridine) resulted in no reaction (reaction B), while oxygen-type bases did not decrease the side chlorination (reaction C). $TiCl_4$ has significant affinity for simple alkyl esters; for example, the crystal structure of a dimeric complex $(TiCl_4–AcOEt)_2$ was reported[8] and the ester carbonyl function exhibited higher reactivity than the ketone carbonyl function during the Ti-Claisen condensation.[9] As expected, use of the $TiCl_4$–AcOEt complex effected the smooth deprotection of **1** with sufficient suppression of the side formation of 2-chlorononane (reaction D). Surprisingly, the use of the $TiCl_4$–CH_3NO_2 complex was also successful, especially for aromatic and 1β-methylcarbapenem substrates (vide supra). Presumably, these Lewis bases not only maintained the reactivity of $TiCl_4$, but also facilitated the release of Cl^-, which selectively attacked the Si atom, but not the C atom.

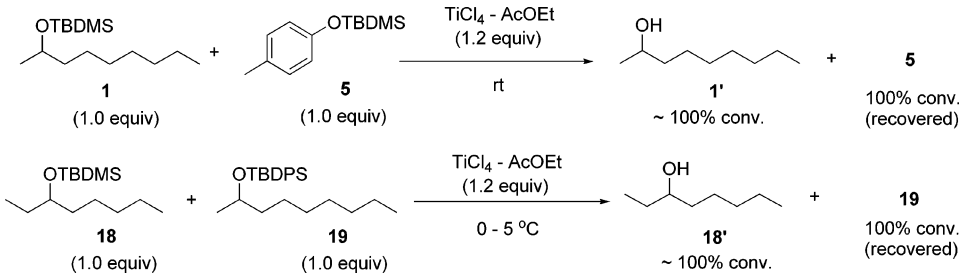
It should be noted that the reaction velocity with these complexes, which seemed less reactive due to the influence of Lewis bases, was considerably greater than that with $TiCl_4$ alone (Figure 1). This tendency was also observed and amplified in the deprotection of the TBDMS ether **5** of *p*-cresol (Figure 2).

Table 1 lists the successful results under optimized conditions

SCHEME 3



SCHEME 4



(method A with AcOEt and method B with CH_3NO_2). The present method produces smooth desilylation of aliphatic TBDMS ethers, wherein method A was slightly more advantageous than method B with regard to the yield (entries 1−4). In contrast, method B led to the desilylation with less reactive phenolic TBDMS ethers in a short period under mild conditions (entries 5−7). One desilylation-resistant 4-nitorophenyl analogue[3f,4f] was also possible (entry 8). Ketone, ester, and β-lactam functionalities tolerated the reaction conditions (entries 9−12). Tertiary and allylic TBDMS ethers, however, generally failed to undergo the desilylation due to undesirable formation of the corresponding chlorides.

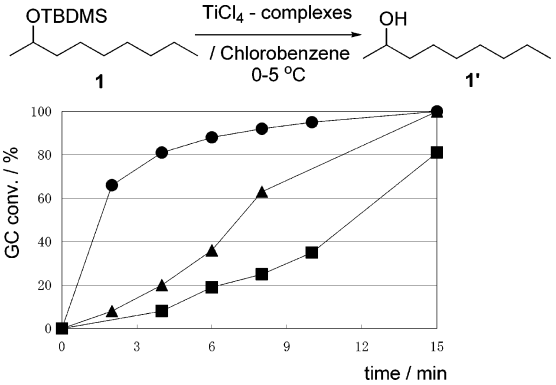


FIGURE 1. Comparable experiments of desilylation of **1** (GC conversion): ●, $TiCl_4$−AcOEt complex; ▲, $TiCl_4$−CH_3NO_2 complex; and ■, $TiCl_4$ alone.

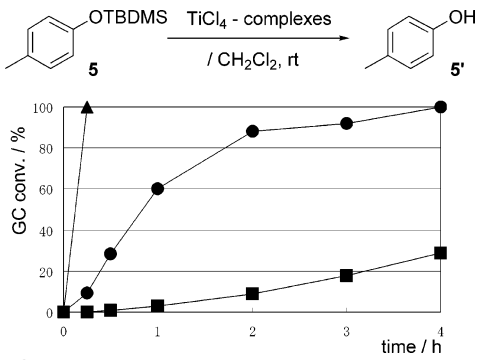


FIGURE 2. Comparable experiments of desilylation of **5** (GC conversion): ●, $TiCl_4$−AcOEt complex; ▲, $TiCl_4$−CH_3NO_2 complex; and ■, $TiCl_4$ alone.

To further investigate the chemoselectivity, compatibility of other conventional protecting groups was examined. As shown in Scheme 3, TBDMS ether **1** was successfully desilylated in the presence of benzyl, allyl, tosyl, methoxyphenyl, and chloroacetyl ethers (**13**, **14**, **15**, **16**, and **17**). Methoxybenzyl ether, unfortunately, did not tolerate identical conditions.

Note that selective desilylation of **1** in the presence of **5** was performed to give 2-nonanol, because aromatic substrates required considerably longer time to reach completion with method A (Scheme 4). In addition, chemoselective desilylation was successfully performed between TBDMS ether **18** and *tert*-butyldiphenylsilyl (TBDPS) ether **19**.

Neighboring group participation (anchimeric assistance) by the carbonyl groups may be expect to effect smooth desilylation

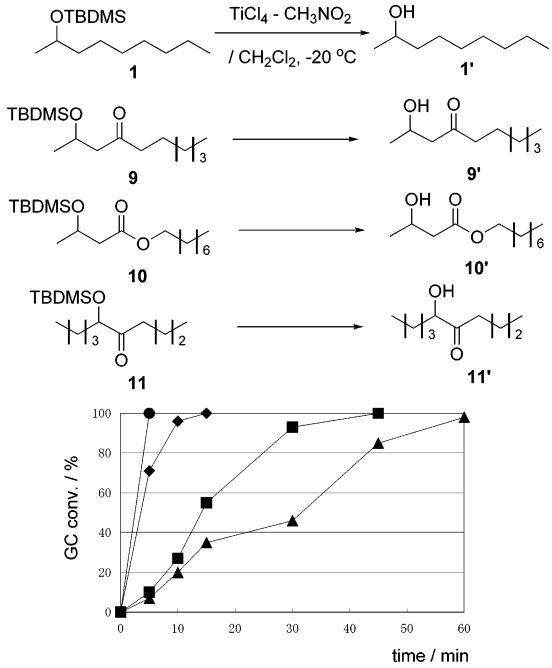
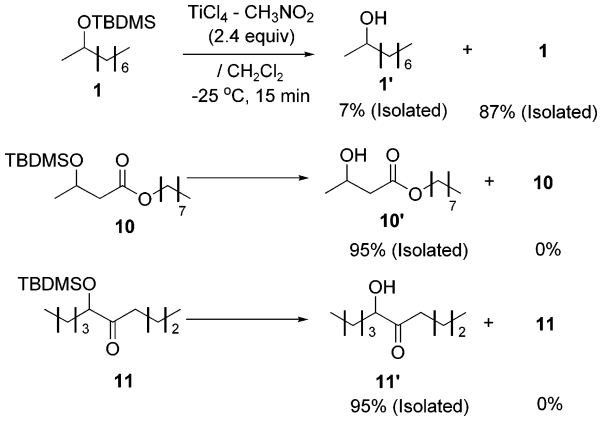


FIGURE 3. Comparable experiments of desilylation of TBDMS ethers **1**, **9**, **10**, and **11** (GC conversion): ▲, **1**; ■, **9**; ◆, **10**; and ●, **11**.

SCHEME 5



SCHEME 6

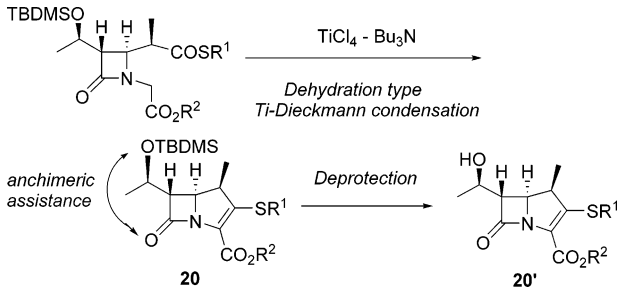
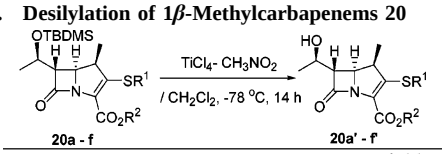
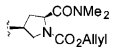


TABLE 2. Desilylation of 1β-Methylcarbapenems 20



Entry	R^1	R^2	Product	Yield / %[a]
1	*c*-hexyl	PNB	**20a'**	91 (trace)[b]
2	*n*-octyl		**20b'**	80
3	Ph		**20c'**	89
4	Bn		**20d'**	79[c]
5	*c*-hexyl	Allyl	**20e'**	82
6			**20f'**	60

[a] Isolated. [b] Use of $TiCl_4$−AcOEt complex. [c] Reaction time was 11 h.

due to the high chelation ability of the Ti(IV) species. Indeed, with method B, α- and β-TBDMS groups in **9**, **10**, and **11** adjacent to the corresponding carbonyl groups were more rapidly desilylated than comparable substrate **1** (Figure 3 and Scheme 5).

This notable finding of the anchimeric assistance prompted us to investigate the desilylation of potent and broad antibacterial active 1β-methylcarbapenems, because the practical synthesis of these pharmaceuticals is a major topic of interest.[10] One critical issue lies in the deprotection of the TBDMS of labile 1β-methylcarbapenems: (i) conventional TBAF and related mild TBAF−AcOH methods result in poor yield due to the undesirable β-lactam ring opening[11] and (ii) NH_4F·HF is an effective reagent, but requires 3 days for completion.[12] As part of our ongoing studies of the Ti-crossed Claisen condensation,[9] dehydration-type Ti-Dieckmann condensation was successfully applied to a short and practical synthesis ofTBDMS-protected 1β- methylcarbapenems.[13] These backgrounds lead us to apply the present desilylation method to the final stage of the synthesis (Scheme 6).

Although the reaction with the $TiCl_4$−EtOAc reagent (method A of Table 1) failed to proceed (decomposition), the use of the $TiCl_4$−CH_3NO_2 reagent (method B) was successful for several 1β-methylcarbapenems **20**. Table 2 lists these results (entries 1−5), including a precursor **20f′** of highly useful Meropenem[14] (entry 6). Anchimeric assistance by the carbonyl group of the β-lactam moiety is thought to effect this smooth desilylation.

In conclusion, we developed a novel mild, practical, chemoselective method for the desilylation of various TBDMS ethers using readily available $TiCl_4$−Lewis base (AcOEt, CH_3NO_2) complexes. The present method was successfully applied to the synthesis of 1β-methylcarbapenems and will be a new entry for desilylation of the TBDMS group.

Experimental Section

Desilylation of TBDMS Ethers (Table 1, Method A). General procedure: A solution of $TiCl_4$ (1.20−2.50 mmol) and AcOEt (1.20−2.50 mmol) in CH_2Cl_2 (1.50 mL) was added to a stirred solution of TBDMS ether (1.0 mmol) in CH_2Cl_2 (1.0 mL) at 30 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 10 min to 6 h. Water was added to the reaction mixture, which was extracted with Et_2O. The organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by silica gel column chromatography (hexane:ether = 6:1 to 1:1) to give the desired alcohol.

Desilylation of TBDMS Ethers (Table 1, Method B). General procedure: A solution of $TiCl_4$ (228 mg, 1.20 mmol) and CH_3NO_2 (1.20 mmol) in CH_2Cl_2 (1.50 mL) was added to a stirred solution of TBDMS ether (1.0 mmol) in CH_2Cl_2 (1.0 mL) at 30 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 10 min to 2 h. Water was added to the reaction mixture, which was extracted with diethyl ether. The organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by silica gel column chromatography (hexane:ether = 6:1 to 1:1) to give the desired alcohol.

Alcohols **1′**, **2′**, **3′**, **4′**, **5′**, **6′**, **7′**, **8′**, **11′**, and **18′** are commercially available. Alcohols **9′**,[15] **10′**,[16] and **12′**[17] are known compounds.

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Supporting Information Available: Experimental details, characterization date, ^1H NMR and ^{13}C NMR, and MS spectra for 1β-methylcarbapenems **20a′**−**f′**. This material is available free of charge via the Internet at http://pubs.acs.org.

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