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Low-valent titanium-catalyzed deprotection of allyl- and propargyl-carbamates to amines

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ABSTRACT

In the presence of Me_3SiCl, Ti(O-*i*-Pr)$_4$/Mg and $CpTiCl_3$/Mg reagents effectively catalyzed the deprotection of allyloxycarbonyl (alloc)- and propargyloxycarbonyl (poc)-protected amines in THF at around room temperature to produce parent amines in good yields. Alloc- and poc-protected secondary amines were smoothly deprotected to parent amines by a reaction catalyzed by a Ti(O-*i*-Pr)$_4$/Me_3SiCl/Mg reagent. The deprotection of alloc- and poc-protected primary amines was successfully catalyzed by a $CpTiCl_3$/Me_3SiCl/Mg reagent.

The protection/deprotection of organic functional groups is of great importance in organic synthesis.[1] Mild conditions that achieve high functional group compatibility and selectivity are desired for the introduction and removal of protective groups. Groups that protect amine functionalities are of significant interest for the synthesis of nitrogen-containing molecules. The allyloxycarbonyl (alloc) group has been a useful protecting group for amines, and allyl carbamates are readily formed by reacting with alloc chloride under mild conditions. The removal of an alloc moiety from allyl carbamates to give the parent amine has conventionally been accomplished under neutral, mild conditions through reactions catalyzed by transition metals such as Pd and Ni in the presence of a suitable nucleophile or hydride source, e.g., amines, thiols, HCO_2H, tin hydrides, and silyl hydrides.[1] However, there are drawbacks associated with heavy-metal-based deprotection reactions: the high cost of reagents, reagent toxicity, and/or the competitive formation of allylamine.[2,3]

The propargyloxycarbonyl (poc) group is stable at various acidic and basic conditions and is considered a protective group for alcohols and amines.[4] Deprotection of poc-protected alcohols and amines is conventionally conducted by reaction with a stoichiometric amount of benzyltriethylammonium tetrathiomolybdate $(BnNEt_3)_2MoS_4$.[4,5] The development of a milder, inexpensive deprotection method of poc-protected groups is desired.

We recently developed facile, selective C–O cleavage reactions of allyl and propargyl ethers that were catalyzed by a low-valent titanium Ti(O-*i*-Pr)$_4$ (**1a**)/Me_3SiCl/Mg reagent.[6,7] In addition, we found that a titanatrane complex **1b**[8] (Scheme 1) in the presence of Me_3SiCl and Mg powder selectively generated a Ti(III) species, which catalyzed the deallylation and depropargylation of allyl and propargyl ethers, respectively (Eq. 1 in Scheme 1).[7d] On the basis of these results, we conducted an extensive investigation of the deprotection of allyl and propargyl carbamates by low-valent titanium reagents. Consequently, we found that allyl carbamates **2** and propargyl carbamates **3** were efficiently deprotected to the parent amines **4** through a reaction catalyzed by low-valent titanium reagents generated from Ti(O-*i*-Pr)$_4$ (**1a**), the titanatrane complex **1b**, or $CpTiCl_3$ (**1c**)[9,10] in the presence of Me_3SiCl and Mg (Eqs. 2 and 3, respectively).

First, we investigated the reactions of the allyl carbamate **2a** and **2b** derived from dibenzylamine and 2-phenylethylamine, respectively, with Ti complex (**1**)/Me_3SiCl/Mg reagents (Equation in Table 1). Thus, to a mixture of allyl carbamate **2**, a Ti complex, and Mg powder in THF, Me_3SiCl was added at room temperature. The yields of **4** were determined by ^1H NMR analyses using an internal standard. The results are summarized in Table 1.

The allyl carbamate of secondary amine **2a** was successfully deprotected to its parent dibenzylamine by the reaction with Me_3SiCl/Mg in the presence of a catalytic amount of **1a**, **1b**, or **1c** in THF at room temperature (runs 1–6). Note that the presence of Me_3SiCl was essential for catalysis. However, deprotection of the alloc derivative of primary amine **2b** was problematic (runs 7–13).

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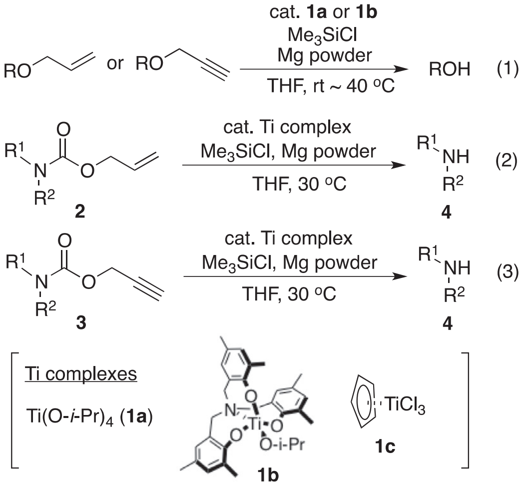
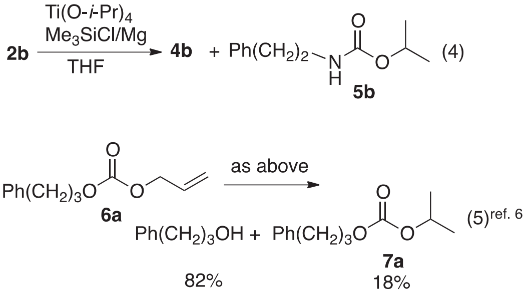


Scheme 1. Low-valent titanium-catalyzed deallylation and depropargylation.

The reaction in the presence of Ti(O-*i*-Pr)$_4$ (**1a**) produced $\mathrm{Ph(CH_2)_2NH_2}$ (**4b**), but the yield was moderate and the corresponding *i*-propyl carbamate **5b** was always coproduced in a yield of 30–40% (runs 7 and 8). Compound **5b** was formed by a titanium-catalyzed transesterification reaction (Eq. 4 in Scheme 2). A similar transesterification giving an alcohol and *i*-propyl carbonate **7a** has previously been observed in the deprotection reaction of allyl carbonate **6a** with a Ti(O-*i*-Pr)$_4$/$\mathrm{Me_3SiCl}$/Mg reagent (Eq. 5 in Scheme 2).[6] Although the titanatrane complex **1b** did not catalyze the deprotection of **2b** (run 9), the reaction in the presence of $\mathrm{CpTiCl_3}$ (**1c**) afforded **4b** without the formation of the *i*-propyl carbamate **5b**, albeit in a low yield (run 10). Because extending the reaction time did not improve the yield of **4b**, we investigated the effects of a Lewis base additive with the expectation of stabilizing the metastable titanium active species by coordination (runs 11–13). Although triphenylphosphine disrupted the reaction (run 11), to our satisfaction it was found that the addition of 20 mol % triethylamine assisted the catalysis to its completion (run 12). Moreover, the addition of triethylamine and increasing temperature to 45–50 °C could reduce the amount of $\mathrm{Me_3SiCl}$ that was needed to 15 mol % (run 13).

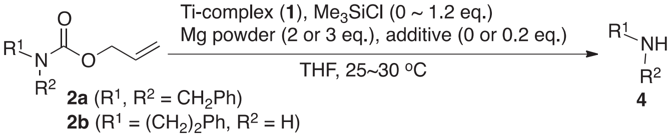


Scheme 2. Formation of *i*-propyl carbamate and carbonate in reactions with Ti(O-*i*-Pr)$_4$.

From these results, we decided to employ two procedures, Method A: Ti(O-*i*-Pr)$_4$ (20 mol %)/$\mathrm{Me_3SiCl}$ (15–120 mol %)/Mg (2 equiv) for alloc-protected secondary amines and Method B: **1c** (5 mol %)/$\mathrm{Me_3SiCl}$ (15–120 mol %)/$\mathrm{Et_3N}$ (20 mol %)/Mg (3 equiv) for alloc-protected primary amines, as optimal conditions and investigated the feasibility of the deprotection reaction of the various allyl carbamates illustrated in Scheme 3. The figure shows the structures of the substrate carbamates, the isolated yields of the parent amines, and the method employed (in parentheses).

In addition to the parent amines of **2a** and **2b**, acyclic and cyclic secondary amines **4c** and **4d** were quantitatively obtained from **2c** and **2d**, respectively, by the Ti(O-*i*-Pr)$_4$-catalyzed reaction (Method

Table 1
Optimization of titanium-catalyzed conversion of carbamates **2** to amines **4**[a]



Run	2	Ti (equiv)	Equiv of $\mathrm{Me_3SiCl}$	Additive[b]	Yield of 4[c] (time, h)
1	**2a**	**1a** (0.2)	1.2	–	>99% (12)
2	**2a**	**1a** (0.2)	0	–	NR[d] (24)
3	**2a**	**1a** (0.2)	0.15	–	94% (12)[e]
4	**2a**	**1b** (0.05)	1.2	–	>99% (12)
5	**2a**	**1c** (0.05)	1.2	–	>99% (12)
6	**2a**	**1c** (0.05)	0.15	–	>99% (12)
7	**2b**	**1a** (1.0)	1.2	–	68%[f] (12)
8	**2b**	**1a** (0.2)	1.2	–	60%[g] (12)
9	**2b**	**1b** (0.05)	1.2	–	NR[d] (36)
10	**2b**	**1c** (0.05)	1.2	–	8% (12)
11	**2b**	**1c** (0.05)	1.2	$\mathrm{Ph_3P}$	NR[d] (24)
12[h]	**2b**	**1c** (0.05)	1.2	$\mathrm{Et_3N}$	>99% (24)
13[h]	**2b**	**1c** (0.05)	0.15	$\mathrm{Et_3N}$	>99% (24)[e]

[a] Reagents: carbamate **2** (1.0 mmol), Ti-complex (**1**) (0.05–1.0 mmol), additive (0 or 0.2 mmol), $\mathrm{Me_3SiCl}$ (0–1.2 mmol), and Mg powder (2 mmol) in THF (5 mL). The reactions were performed at 25–30 °C.

[b] None or 0.2 equiv.

[c] ^{1}H NMR yield.

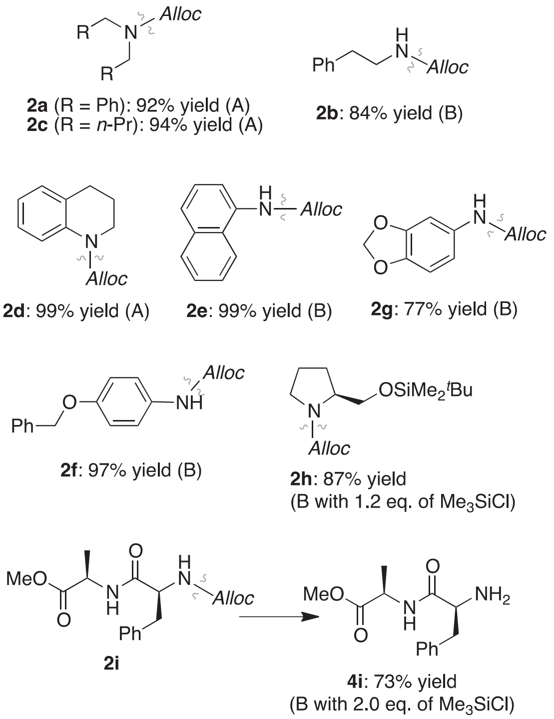
[d] No reaction.

[e] The reaction was carried out at 45–50 °C.

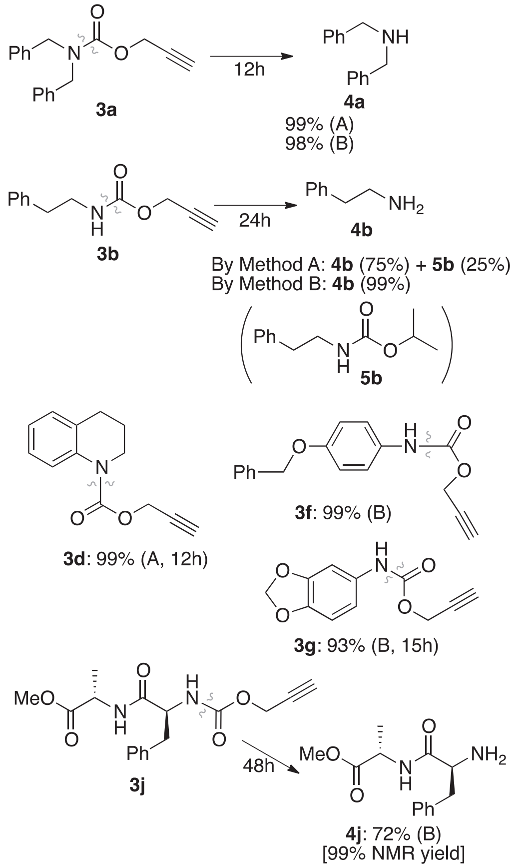
[f] A 32% yield of *i*-Pr carbamate **5b** was coproduced (see Scheme 2).

[g] A 40% yield of *i*-Pr carbamate **5b** was coproduced.

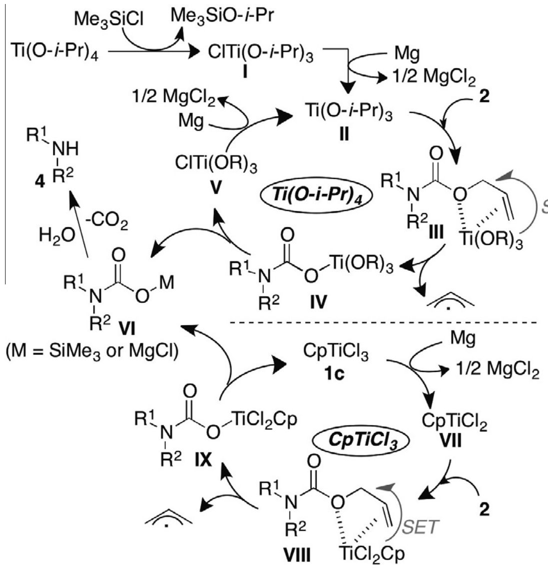
[h] Mg powder (3 equiv) was used.



Scheme 3. [11]Low-valent titanium-catalyzed deprotection of alloc-protected amines: isolated yields of the parent amines are indicated. Method utilized is indicated in parentheses. Method A: Ti(O-*i*-Pr)$_4$ (0.2)/$\mathrm{Me_3SiCl}$ (1.2)/Mg (**2**), THF, 50 °C, 24 h. Method B: **1c** (0.05)/$\mathrm{Me_3SiCl}$ (1.2)/$\mathrm{Et_3N}$ (0.2)/Mg (**2**), THF, 50 °C, 24 h.



Scheme 4. [11]Deprotection of propargyl carbamates: method utilized is indicated in parentheses. Method A: $Ti(O\text{-}i\text{-}Pr)_4$ (0.2)/Me_3SiCl (1.2)/Mg (**2**), THF, 50 °C, 24 h. Method B: **1c** (0.05)/Me_3SiCl (1.2)/Et_3N (0.2)/Mg (**2**), THF, 50 °C, 24 h.



Scheme 5. Proposed mechanism.

A). In the case of the alloc-protected form **2h** of *O*-silylated prolinol, the $Ti(O\text{-}i\text{-}Pr)_4$-catalyzed reaction resulted in failure, which was presumably due to coordination of an oxygen atom to Ti. Fortunately, however, the $CpTiCl_3$-catalyzed reaction of **2h** in the presence of a stoichiometric amount of Me_3SiCl produced the corresponding amine **4h** in good yield. The carbamates of aromatic and aliphatic primary amines **2e**, **2f**, **2g**, and **2i** were successfully deprotected by the $CpTiCl_3$-catalyzed reaction (Method B). Note that the present method is applicable to the deprotection of *N*-alloc peptide esters such as **2i**. As revealed from the results of the reactions of **2f**; **2g**; **2h**; and **2i**, benzyl ether; acetal; silyl ether; carboxylic amide; and ester functionalities were tolerated.

Based on the results of the deprotection of allyl carbamates mentioned above, the deprotection of propargyl carbamates **3** was extensively examined using the low-valent titanium system, and it was found that the methods successfully provided the parent amine **4** (Scheme 4). Similar to the alloc-protected forms, poc-protected secondary amines such as **3a** and **3d** were smoothly cleaved by the $Ti(O\text{-}i\text{-}Pr)_4$-catalyzed reaction without any formation of the transesterification product **5**. On the other hand, the $Ti(O\text{-}i\text{-}Pr)_4$-catalyzed reaction of the poc-protected primary amines caused the production of the corresponding *i*-propyl carbamates **5**. The use of a $CpTiCl_3$ catalyst instead of $Ti(O\text{-}i\text{-}Pr)_4$ was again effective for the quantitative formation of primary amines from their poc-protected forms such as **3b**, **3f**, **3g**, and **3j**. As can be seen from the results in Scheme 3, the methods provide reasonable functional group compatibility and are applicable to the deprotection of *N*-poc-protected peptide esters. Comparison of the NMR spectra of the product **4j** derived from **3j** with those of its diastereomer **4i** derived from **2i** showed no contamination of the diastereomer in either compound. Therefore, under the present conditions for deprotection, no epimerization occurred.

Scheme 5 illustrates the proposed mechanism for the de-alloc reaction: $Ti(O\text{-}i\text{-}Pr)_4$ reduced by Mg after converting to $ClTi(O\text{-}i\text{-}Pr)_3$ (**I**) by the ligand exchange reaction with Me_3SiCl. The resulting $Ti(O\text{-}i\text{-}Pr)_3$ (**II**) coordinates to an oxygen atom and alkene moiety of substrate **2** to give the structure **III**, which undergoes a single electron transfer (SET) to cleave **2** to a titanoxide **IX** and allyl radical. The complex **IX** reacts with Me_3SiCl and/or $MgCl_2$ to generate **VI** and chlorotitanium **V**. Hydrolysis of **VI** provides amine **4** through decarboxylation, and chlorotitanium alkoxide **V** can be reduced again to generate **II**. Similarly, a low-valent titanium **VII** generated by the reduction of $CpTiCl_3$ (**1c**) with Mg cleaves **2** through a SET process in the coordinated structure **VIII**. The resulting **IX** gives **VI** and **1c** by the ligand exchange and the following hydrolysis of **VI** gives amine **4**. Et_3N additive may effect on stabilizing **VII** by its coordination to prevent the disproportionation reaction and the following decomposition.

In summary, we have demonstrated that low-valent titanium reagents derived from $Ti(O\text{-}i\text{-}Pr)_4$ (**1a**) or $CpTiCl_3$ (**1c**) effectively catalyzed the C–O bond cleavage and deprotection of allyl and propargyl carbamates. The reactions provide reasonable compatibility with functional groups such as acetal, ketal, benzyl ether, silyl ether, carboxylic ester and amides. Note that the $CpTiCl_3$-catalyzed system can be applied to the deprotection of *N*-alloc and *N*-poc peptides.

Acknowledgment

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11. *General procedure for alloc- or poc-deprotection with Ti(O-i-Pr)$_4$*: To a mixture of the alloc- or poc-protected compound (1.0 mmol), Ti(O-*i*-Pr)$_4$ (0.20 mmol), and Mg powder (2.0 mmol) in THF (5 mL) was added dropwise Me_3SiCl (0.30 mmol) at room temperature and the resulting mixture was stirred at 30–50 °C. After confirming the completion of the reaction by thin-layer chromatography (TLC) analysis, saturated aqueous $NaHCO_3$ (0.15 mL) was added followed by NaF (1 g) and Celite (1 g). After being stirred for 0.5 h, the mixture was filtered through a pad of Celite with ether or AcOEt. The filtrate was concentrated under reduced pressure to give a crude mixture, which was purified by silica gel column chromatography. *General procedure for alloc- or poc-deprotection with CpTiCl$_3$*: To a mixture of the alloc- or poc-protected compound (1.0 mmol), Et_3N (0.20 mmol) and Mg powder (3.0 mmol) in THF (4 mL) were sequentially added Me_3SiCl (0.15 or 1.20 mmol) and a solution of $CpTiCl_3$ (0.05 mmol) in THF (1 mL) at room temperature and the resulting mixture was stirred at 30–50 °C. After confirming the completion of the reaction by TLC analysis, saturated aqueous $NaHCO_3$ (0.15 mL) was added followed by NaF (1 g) and Celite (1 g). After being stirred for 0.5 h, the mixture was filtered through a pad of Celite with ether or AcOEt. The filtrate was concentrated under reduced pressure to give a crude mixture, which was purified by silica gel column chromatography.