



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



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ABSTRACT

In the presence of Me_3SiCl , $\text{Ti}(\text{O}-i\text{-Pr})_4/\text{Mg}$ and $\text{CpTiCl}_3/\text{Mg}$ reagents effectively catalyzed the deprotection of allyloxy-carbonyl (alloc)- and propargyloxy-carbonyl (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 $\text{Ti}(\text{O}-i\text{-Pr})_4/\text{Me}_3\text{SiCl}/\text{Mg}$ reagent. The deprotection of alloc- and poc-protected primary amines was successfully catalyzed by a $\text{CpTiCl}_3/\text{Me}_3\text{SiCl}/\text{Mg}$ reagent.

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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 allyloxy-carbonyl (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 propargyloxy-carbonyl (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 ($\text{BnNEt}_3)_2\text{MoS}_4$.^{4,5} The development of a milder, inexpensive deprotection method of poc-protected groups is desired.

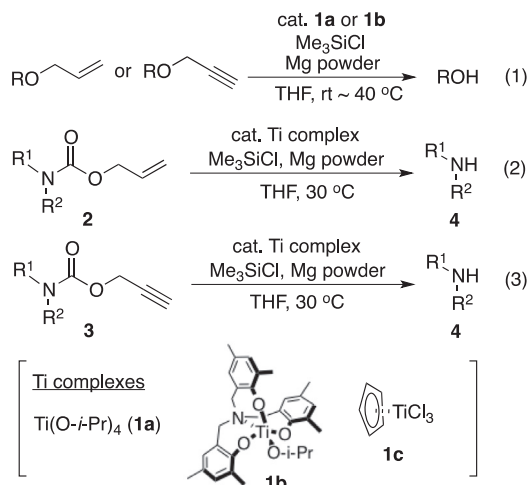
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We recently developed facile, selective C–O cleavage reactions of allyl and propargyl ethers that were catalyzed by a low-valent titanium $\text{Ti}(\text{O}-i\text{-Pr})_4$ (**1a**)/ $\text{Me}_3\text{SiCl}/\text{Mg}$ reagent.^{6,7} In addition, we 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 $\text{Ti}(\text{O}-i\text{-Pr})_4$ (**1a**), the titanatrane complex **1b**, or CpTiCl_3 (**1c**)^{9,10} in the presence of Me_3SiCl and Mg (Eqs. 2 and 3, respectively).

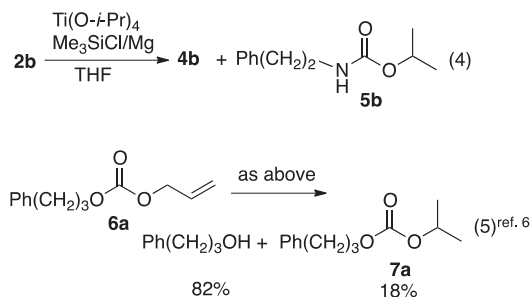
First, we investigated the reactions of the allyl carbamate **2a** and **2b** derived from dibenzylamine and 2-phenylethylamine, respectively, with Ti complex (**1**)/ $\text{Me}_3\text{SiCl}/\text{Mg}$ reagents (Equation in Table 1). Thus, to a mixture of allyl carbamate **2**, a Ti complex, and Mg 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 $\text{Me}_3\text{SiCl}/\text{Mg}$ 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).



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

The reaction in the presence of $\text{Ti}(\text{O}-i\text{-Pr})_4$ (**1a**) produced $\text{Ph}(\text{CH}_2)_2\text{NH}_2$ (**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 $\text{Ti}(\text{O}-i\text{-Pr})_4/\text{Me}_3\text{SiCl}/\text{Mg}$ 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 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



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

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 Me_3SiCl that was needed to 15 mol % (run 13).

From these results, we decided to employ two procedures, Method A: $\text{Ti}(\text{O}-i\text{-Pr})_4$ (20 mol %)/ Me_3SiCl (15–120 mol %)/Mg (2 equiv) for alloc-protected secondary amines and Method B: **1c** (5 mol %)/ Me_3SiCl (15–120 mol %)/ 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 $\text{Ti}(\text{O}-i\text{-Pr})_4$ -catalyzed reaction (Method

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

Run	2	Ti (equiv)	Equiv of 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	Ph_3P	NR ^d (24)
12 ^h	2b	1c (0.05)	1.2	Et_3N	>99% (24)
13 ^h	2b	1c (0.05)	0.15	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), 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 ¹H NMR yield.

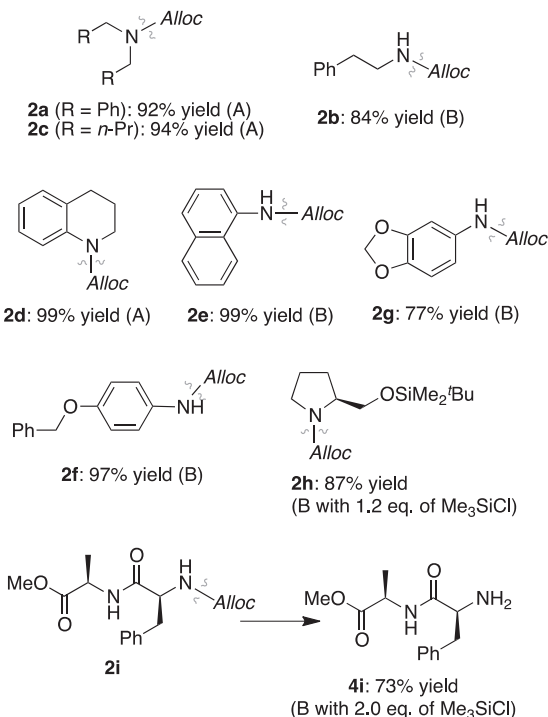
^d No reaction.

^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: $\text{Ti}(\text{O}-i\text{-Pr})_4$ (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.

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