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Selective Cleavage of Allyl and Propargyl Ethers to Alcohols Catalyzed by $Ti(O\text{-}i\text{-}Pr)_4/MX_n/Mg$

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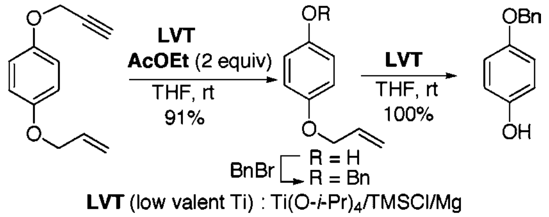
ABSTRACT



Allyl and propargyl ethers were effectively deallylated or depropargylated to the parent alcohols via a C–O bond cleavage catalyzed by a low-valent titanium reagent (LVT), $Ti(O\text{-}i\text{-}Pr)_4$/TMSCl/Mg or $Ti(O\text{-}i\text{-}Pr)_4/MgBr_2/Mg$, under mild reaction conditions. Differentiation between the allyl and propargyl ethers was achieved by the reaction in the presence of AcOEt as an additive. The reagent also catalyzed intra- and intermolecular cyclotrimerization reactions of alkynes to substituted benzenes.

Protection/deprotection of organic functional groups is of great importance in organic synthesis.[1] For removal of the protective groups, mild conditions attaining high functional group compatibility and selectivity are desired. Allyl and propargyl moieties have been used as a part of allyloxycarbonyl (alloc) and propargyloxycarbonyl (poc) protective groups. An alloc group is mildly deprotected by Pd(0) catalysis,[1] and an $MoS_5{}^{2}$-promoted reaction[2] has been reported for removal of a poc group. Allyl and propargyl ethers also are of importance as a stable protective group of alcohols, but their cleavage needs harsher conditions and the procedure has not necessarily been generalized for their deprotection. Thus, methods for deprotection of allyl ethers reported so far involve late transition-metal-catalyzed or -mediated (Co, Rh, Ir, Ru, Pd, Ni) reactions, low-valent zirconium- and titanium-mediated processes, *t*-BuLi-mediated reactions, and several oxidative procedures,[3] each of which entails an individual scope and limitation on functional group compatibility and selectivity. Meanwhile, deprotection of propargyl ethers has been less explored: oxidative cleavage of 1-naphthylpropargyl ether or allenyl ether generated by treatment with a base[4a,b] and $TiCl_3$/Mg-[4c] or $(BnNEt_3)_2MoS_4$-promoted[4d] reactions have been reported. Development of a deprotection method having a different scope and taking place under milder reaction conditions has

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(2) Depropargylation of poc compounds: (a) Sridhar, P. R.; Chandrasekaran, S. *Org. Lett.* **2002**, *4*, 4731. (b) Ramesh, R.; Bhat, R. G.; Chandrasekaran, S. *J. Org. Chem.* **2005**, *70*, 837.

(3) A leading reference for deallylation of allyl ethers: (a) Murakami, H.; Minami, T.; Ozawa, F. *J. Org. Chem.* **2004**, *69*, 4482. A low-valent titanium-mediated or -catalyzed deallylation: (b) Talukdar, S.; Nayak, S. K.; Banerji, A. *J. Org. Chem.* **1998**, *63*, 4925. (c) Kadam, S. M.; Nayak, S. K.; Banerji, A. *Tetrahedron Lett.* **1992**, *33*, 5129. (d) Lee, J.; Cha, J. K. *Tetrahedron Lett.* **1996**, *37*, 3663. (e) Kasatkin, A.; Nakagawa, T.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1995**, *117*, 3881. (f) Nakagawa, T.; Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, 36, 3207. A nickel-catalyzed electrochemical reaction of aryl ethers: (g) Yasuhara, A.; Kasano, A.; and Sakamoto, T. *J. Org. Chem.* **1999**, *64*, 4211. *t*-BuLi-mediated reaction: (h) Bailey, W. F.; England, M. D.; Mealy, M. J.; Thongsornkleeb, C.; Teng, L. *Org. Lett.* **2000**, *2*, 489. Cerium-mediated reaction: (i) Bartoli, G.; Cupone, G.; Dalpozzo, R.; De Nino, A.; Maiuolo, L.; Marcantoni, E.; Procopio, A. *Synlett* **2001**, 1897. SmI_2-promoted reaction: (j) Dahlén, A.; Sundgren, A.; Lahmann, M.; Oscarson, S.; Hilmersson, G. *Org. Lett.* **2003**, *5*, 4085.

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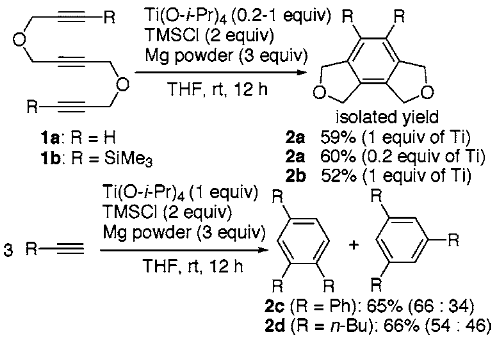
been desired. In addition, differentiation between allyl and propargyl ethers has been scarcely investigated.[5]

Herein, we wish to report facile deallylation and depropargylation reactions catalyzed by a low valent titanium generated from Ti(O-*i*-Pr)$_4$/Mg in the presence of a halogen source such as TMSCl (TMS═SiMe$_3$) and MgBr$_2$.

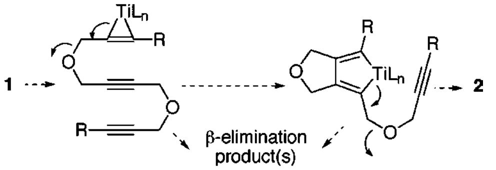
In the course of our study for developing a catalytic cyclotrimerization of alkynes to substituted benzenes[6] and also in low-valent titanium chemistry,[7] we found that Ti(O-*i*-Pr)$_4$ promoted cyclization of triynes **1a** and **1b** to the corresponding annulated benzene **2** in the presence of Mg powder and TMSCl in THF and the amount of the titanium could be reduced to be catalytic (Scheme 1).[8] Similarly, trisubstituted benzenes **2c** and **2d** were obtained as a regioisomeric mixture from the corresponding 1-alkynes by the reaction with a stoichiometric amount of the reagent.[8]

Scheme 1



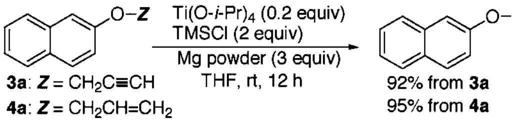
It was noteworthy that the yields of **2a** and **2b** were not necessarily high (40−60%), although the reaction consumed **1** completely and the concentrated crude residue had no other product than **2**. The loss of **1** may be explained by assuming that the β-elimination reactions from the possible intermediates, η^2-alkyne complex(es) and/or titanacyclopentadiene, occur as a side reaction[3d−f,9] as illustrated in Scheme 2.

Scheme 2



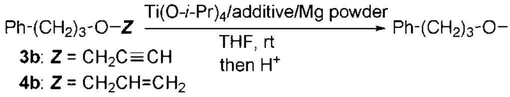
With these assumptions in mind, we carried out the reactions of 3-aryloxypropyne and -propene, 2-naphthyl propargyl ether (**3a**), and 2-naphthyl allyl ether (**4a**) with this Ti(O-*i*-Pr)$_4$/TMSCl/Mg reagent (Scheme 3). As expected, the ethers reacted within 12 h to provide 2-naphthol in nearly quantitative yield after aqueous acidic workup. Herein, we wish to focus on these deallylation and depropargylation reactions, expecting a new deprotective protocol, although the investigation on benzene formation shown in Scheme 1 is of interest and is underway in this laboratory.

Scheme 3



To clarify the requirement of reagents and conditions for these reactions, the reactions of allyl and propargyl ethers of 3-phenyl-1-propanol, **3b** and **4b**, were carried out, and the results are summarized in Table 1. Under reaction conditions identical to those for the reaction of aryl ethers **3a** and **4a** shown in Scheme 3, alkyl ether **3b** was effectively

Table 1. Reaction Conditions



		equiv				
entry	ether	Ti(O-*i*-Pr)$_4$	Mg[a]	additive (equiv)	h	yield,[b] %
1	**3b**	0.2	3			no reaction
2	**3b**	0.2		TMSCl (2)		no reaction
3	**3b**	0.2	2	TMSCl (1)	3	91
4	**3b**	0.05	2	TMSCl (0.15)	5	86
5	**3b**	0.05	2	MgBr$_2$ (0.15)	8	87[c] (85)[d]
6	**3b**	0.05	2	MgCl$_2$ (0.15)[e]	24	96
7	**4b**	0.05	2	TMSCl (0.15)	8	88
8	**4b**	0.05	2	MgBr$_2$ (0.15)[c]	11	100

[a] Other metal powders such as Zn, Mn, and Al were not effective. [b] Determined by ^{1}H NMR analysis using an internal standard. [c] A THF solution prepared by the reaction of 1,2-dibromoethane with Mg was used. [d] Commercial solid MgBr$_2$ was used. [e] Commercial solid MgCl$_2$ was used.

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(5) For selective cleavage of allyl propargyl ether, see ref 4c,d.

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(8) Low-valent titanium-promoted or -catalyzed benzene formation from alkynes: Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2001**, *123*, 7925. Tanaka, R.; Nakano, Y.; Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2002**, *124*, 9682. Eisch, J. J.; Gitua, J. N. *Organometallics* **2003**, *22*, 24. Xi, Z.; Sato, K.; Gao, Y.; Lu, J.; Takahashi, T. *J. Am. Chem. Soc.* **2003**, *125*, 9568. Morohashi, N.; Yokomakura, K.; Hattori, T.; Miyano, S. *Tetrahedron Lett.* **2006**, *47*, 1157 and references therein.

(9) Takayama, Y.; Gao, Y.; Sato, F. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 851. See also ref 7.

deprotected (entry 3). The reaction in the absence of TMSCl and/or Mg did not proceed at all (entries 1 and 2). THF was found to be suitable as a solvent: The reaction in CH_2Cl_2 or toluene did not proceed at all, and that in diethyl ether gave a trace amount (~10%) of the product alcohol. The reagents, Ti(O-*i*-Pr)$_4$, TMSCl, and Mg powder, were efficiently reduced to be 0.05, 0.15, and 2 equiv, respectively (entry 4). As an additive, $MgBr_2$ and $MgCl_2$ as well as TMSCl could be used, which may act as a halogen source (entries 5 and 6) (vide infra). Under the conditions, allyl ether **4b** was also converted to the product alcohol in good yields (entries 7 and 8).

These reaction conditions were subsequently utilized for the C−O bond cleavage of a series of representative allyl and propargyl ethers. Figure 1 shows the structure of the substrate and yield of the corresponding depropargylated or deallylated product. The results feature the following characteristics: Substituted propargyl and allyl ethers **3c**, **3d**, and **4e** as well as simple propargyl and allyl ethers were good substrates, although the reaction of **3c** having a bulky substituent was relatively slow. Cleavage of propargyl ethers **3j** and **3k** resulted in somewhat lower yields due to coproduction of benzene derivatives of the type **2**, but their silyl derivatives such as **3j-Si** were depropargylated smoothly to afford the parent alcohol quantitatively. The reactions using $MgBr_2$ instead of TMSCl proceeded smoothly as exemplified by the reactions of **4g**, **4h**, and **4k**. Functional groups such as benzyl ether (**3f** and **4f**),[10,4c] silyl ether (**4g**), acetal and ketal (**3k**, **4h**, and **4k**), and alkene (**3j**, **3j-Si**, and **4j**) tolerated the reaction conditions.[11] However, the reaction of allyl ether having an ester moiety (**4i**) was very slow and gave only 12% of the corresponding alcohol and 64% of the recovered ester after 72 h. This indicates that a pivaloyloxy group tolerated but retarded the reaction, probably due to deactivation of the low valent titanium reagent by coordination of the titanium atom to the ester carbonyl group. A similar result was obtained when the reaction of **4b** was performed in the presence of AcOEt (2 equiv) as an additive as illustrated in Scheme 4. Meanwhile, under the same reaction conditions, the corresponding propargyl ether **3b** reacted smoothly to provide the parent alcohol quantitatively. Using $Ph(CH_2)_2CO_2Et$ as an additive instead of AcOEt also enabled selective cleavage of propargyl ether **3a** in the presence of allyl ether **4a**, where the ester added was recovered quantitatively as a mixture of $Ph(CH_2)_2CO_2Et$ and its *i*-Pr ester derivative, the latter of which was generated by a titanium-catalyzed transesterification with the *i*-propoxy group derived from Ti(O-*i*-Pr)$_4$ (Scheme 4).

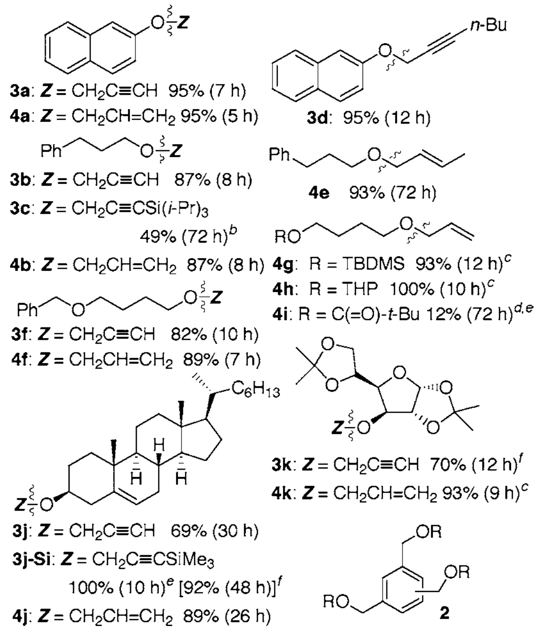
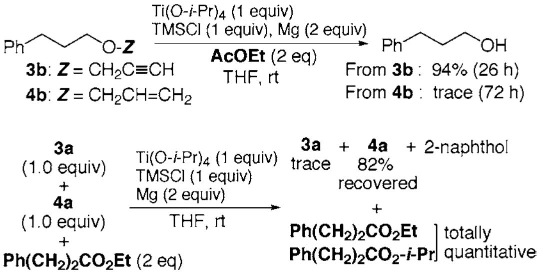


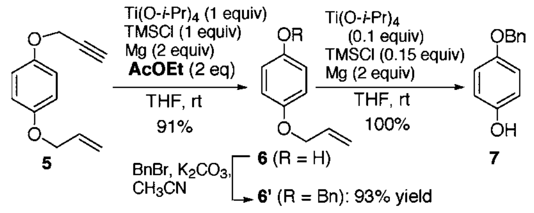
Figure 1. Low-valent titanium-catalyzed cleavage of allyl and propargyl ethers.[a] The structure of the substrate, isolated yield of the corresponding alcohol and the reaction time are indicated. (a) Unless otherwise indicated, the reaction was performed with 1.0 mmol of the substrate ether, Ti(O-*i*-Pr)$_4$ (0.05 mmol), TMSCl (0.15 mmol) and Mg powder (2 equiv) in THF (2 mL) at rt. (b) 50% of the substrate was recovered. (c) $MgBr_2$ (0.15 mmol) instead of TMSCl was used. (d) 64% of the substrate was recovered. (e) Ti(O-*i*-Pr)$_4$/$MgBr_2$/Mg (1.0/1.0/2.0 equiv). (f) Ti(O-*i*-Pr)$_4$/TMSCl/Mg (0.2/1.0/2.0 equiv).

Scheme 4



With these results, we set a diol derivative **5** as a substrate and demonstrated its selective transformation (Scheme 5). Thus, ether **5** was subjected to the reaction with the low-valent titanium reagent *in the presence of* AcOEt (2 equiv), and it provided selectively depropargylated product **6** in 91%

Scheme 5



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[10] It was noteworthy that benzyl ether tolerated the present reaction conditions. It has been reported that a low-valent titanium derived from $TiCl_3$−Li in THF could cleave benzyl ethers. See ref 3b,c.

[11] For workup procedures, see the Supporting Information.

yield. After its conversion to benzyl ether **6′**, treatment with the titanium reagent *in the absence of* AcOEt removed the allyl moiety to yield alcohol **7** quantitatively, whereas benzyl ether moiety did not react at all.

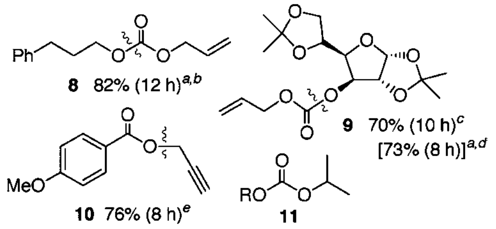
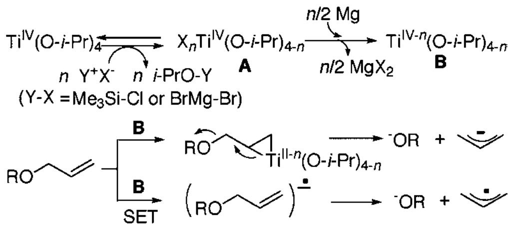


Figure 2. Low-Valent Titanium-Catalyzed Cleavage of Allyl and Propargyl Esters. The structure of the substrate, isolated yield of the corresponding alcohol and the reaction time are indicated. (a) Ti(O-*i*-Pr)$_4$ (1.0 mmol), MgBr$_2$ (1.0 mmol), and Mg powder (2.0 mmol) in THF (5 mL) at rt. (b) 14% of the corresponding *i*-Pr ester was obtained. (c) Ti(O-*i*-Pr)$_4$/TMSCl/Mg (0.2/1.0/2.0 equiv). (d) 20% of the corresponding *i*-Pr ester was obtained. (e) Ti(O-*i*-Pr)$_4$/TMSCl/Mg (0.05/0.15/2.0 equiv).

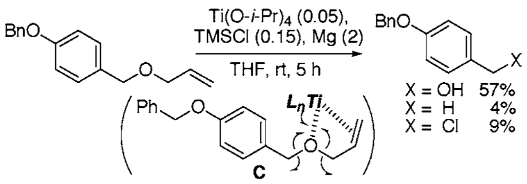
Figure 2 shows several results of depropargylation and deallylation of esters. Allyl carbonates **8** and **9** were deprotected and the parent alcohols were isolated in good yields, where use of a stoichiometric amount of the reagent gave somewhat better results. However, the crude mixture contained 10−20% of the corresponding isopropyl carbonates of the type **11**, which may be obtained by a titanium-catalyzed transesterification. The reaction of carboxylic acid esters such as **10** were also converted to the corresponding acids after acidic workup.

The fact that the reaction did not proceed in the absence of any halogen source or Mg may suggest that an *i*-propoxy group(s) of Ti(O-*i*-Pr)$_4$ might be exchanged with halogen X to give X$_n$Ti^{IV}(O-*i*-Pr)$_{4-n}$ (**A**), the generation of which might be essential to reduction of the titanium by the reaction with Mg powder to the corresponding low valent titanium species **B** (Scheme 6).[12] It may be assumed that the reaction of the substrate with **B** might afford the η^2-titanium complex[3d−f,7] and/or the anion radical via a single-electron transfer (SET).[3b,c,13] The results in Scheme 7 indicate that the reaction at least involves the SET process. Thus, deallylated benzylic alcohol was obtained in 57% yield but simultaneously a *p*-cresol derivative and a benzylic chloride compound were coproduced in 4% and 9% yields, respectively.[3j] These side products may be obtained through a competitive benzylic C−O bond cleavage shown as **C**.

Scheme 6



Scheme 7



In summary, we have developed a facile procedure for C−O bond cleavage at the allylic and propargylic positions, which might be expected as a deprotection method of allyl and propargyl ethers, esters, and carbonates. Selective cleaving of propargyl ether in the presence of allyl ether was attained by addition of AcOEt as an additive.

Acknowledgment. We thank the Ministry of Education, Culture, Sports, Science and Technology (Japan) for financial support.

Supporting Information Available: Experimental procedures and characterization for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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