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SELECTIVE CLEAVAGE OF ALLYL ETHERS

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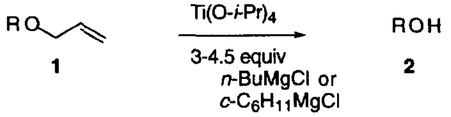
Abstract: A simple, one-step method for the selective cleavage of allyl ethers to alcohols has been developed by use of Ti(O-*i*-Pr)$_4$ and a commercially available Grignard reagent.

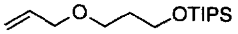
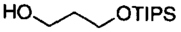
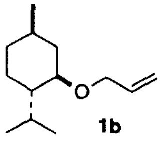
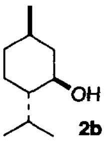
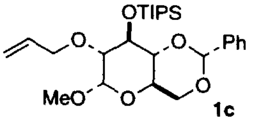
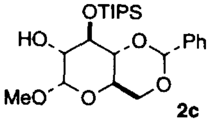
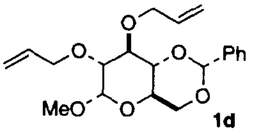
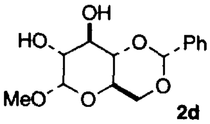
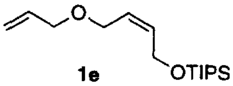
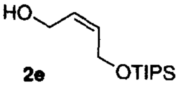
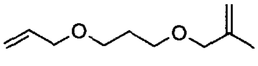
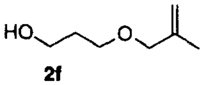
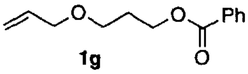
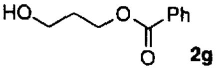
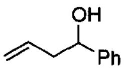
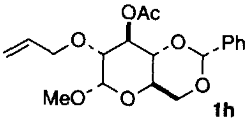
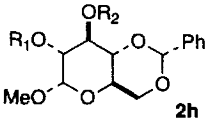
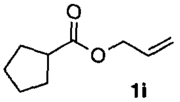
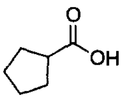
Protection of hydroxyl groups as allyl ethers is often employed in organic synthesis, largely due to their stability under basic and acidic conditions. Removal of the allyl protecting group is commonly effected by transition metal- or *t*-BuOK (DMSO, 100 °C)- catalyzed isomerization of the allyl ether to the corresponding enol ether and subsequent hydrolysis.[2] As part of our continuing interest in the Kulinkovich hydroxycyclopropanation,[3-5] herein we report a simple, one-step method for the cleavage of allyl ethers (**1**) to alcohols (**2**) by the action of Ti(O-*i*-Pr)$_4$ and a commercially available Grignard reagent. Particularly noteworthy is the ease of operation and the use of readily available, inexpensive reagents.



In 1989 Kulinkovich and coworkers developed a novel, stereoselective synthesis of *cis*-1,2-dialkylcyclopropanols, which involves treatment of a carboxylic ester with an excess (3 equiv) of a Grignard reagent at -78 to 0 °C in the presence of Ti(O-*i*-Pr)$_4$.[3] They also proposed the intermediacy of a titanacyclopropane. More recently, we and the Sato group independently reported the interception of the titanacyclopropane intermediate by ligand exchange with a monosubstituted olefin, which can be utilized both in intermolecular and intramolecular hydroxycyclopropanations.[5,6] Moreover, Sato and coworkers developed an elegant method for preparing functionalized allyltitanium compounds by applying the Kulinkovich protocol to allylic esters and related compounds.[6,7]

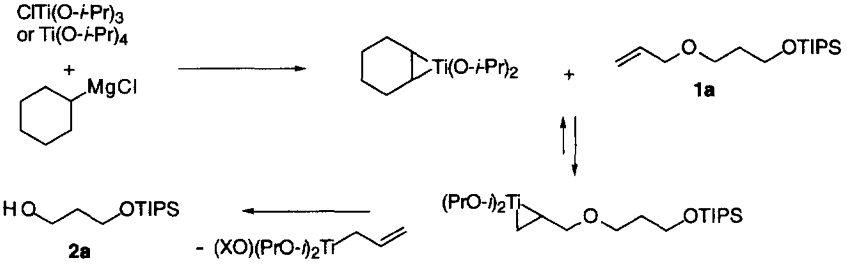
At the same time, we also recognized the synthetic utility of the Kulinkovich titanacyclopropane in the selective cleavage of allyl ethers (**1**) to alcohols (**2**) under relatively mild conditions. Indeed, treatment of **1a** with cyclohexylmagnesium chloride (4 equiv) in the presence of Ti(O-*i*-Pr)$_4$ or ClTi(O-*i*-Pr)$_3$ (1 equiv) at room temperature smoothly afforded alcohol **2a** in 92% yield. Additional results are summarized below. While most examples do not require special comment, the following aspects are particularly noteworthy. Cyclohexylmagnesium chloride and *n*-butylmagnesium chloride can be employed interchangeably. Bis(allylethers) **1d** also underwent

Table 1. Selective Cleavage of Allyl Ethers and Esters

entry	allyl ethers	Grignard reagent	products	yield
1	 **1a**	**A** or **B**	 **2a**	92%
2	 **1b**	**A**	 **2b**	94%
3	 **1c**	**B**	 **2c**	97%
4	 **1d**	**B**	 **2d**	97%
5	 **1e**	**A**	 **2e**	78%
6	 **1f**	**B**	 **2f**	92%
7	 **1g**	**B**	 **2g**  **3**  **4**	36% 28% 14%
8	 **1h**	**B**	 **2h** **2h(i)**: R_1 = H, R_2 = Ac (37%) **2h(ii)**: R_1 = Ac, R_2 = H (32%)	69%
9	 **1i**	**B**	 **2i**	77%

Reaction Conditions: 1 equiv Ti(O-*i*-Pr)$_4$ or ClTi(O-*i*-Pr)$_3$, an excess (3-4.5 equiv) of Grignard reagent (**A**: *n*-BuMgCl, or **B**: cyclohexylmagnesium chloride), THF, room temperature.

smooth deprotection to afford diol **2d** (entry **4**). As expected, the benzylidene acetal was not affected under the reaction conditions. More significant is the selective cleavage of allyl ethers in the presence of but-2-enyl (entry 5) and 2-methylallyl (entry 6) groups. This selectivity is in accord with our previous finding that di- or trisubstituted alkenes do not undergo ligand exchange, presumably due to their steric inaccessibility.[5b,c] Not unsurprisingly, this Ti(O-*i*-Pr)$_4$-Grignard reagent protocol is generally incompatible with ester groups. For example, when compound **1g** was subjected to the identical deprotection conditions, side-products **3** and **4** were obtained in addition to **2g**.[8] On the other hand, clean removal of the allyl group from acetate **1h** was achieved to afford a 1:1 mixture (69%) of monoalcohols **2h(i)**,**(ii)**, where transesterification took place during purification by column chromatography.



This deprotection protocol for allyl ethers appears to be equally effective for cleavage of allyl esters, as exemplified by the allyl ester **1i** (entry 9).

A typical experimental procedure is as follows: to a solution of *O*-allylmenthol (**1b**) (115 mg) in 6 mL of anhydrous THF was added ClTi(O-*i*-Pr)$_3$ (0.6 mL of 1.0 M solution in hexane; 1 equiv). *n*-Butylmagnesium chloride (1.3 mL of 2.0 M solution in diethyl ether; 4.5 equiv) was added at room temperature over a period of 1 h (via a syringe pump). The reaction mixture was stirred for one additional h and poured into water (10 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 x 10 mL). The combined extracts were washed with brine (10 mL), dried over MgSO$_4$ and filtered. Concentration under reduced pressure and purification by column chromatography on silica gel afforded 86 mg (94%) of menthol as a colorless solid.

In summary, the selective cleavage of allyl ethers and allyl carboxylates can be readily effected by employing the Kulinkovich titanacyclopropane intermediate, which is prepared in situ from Ti(O-*i*-Pr)$_4$ and a Grignard reagent (i.e., R'CH$_2$CH$_2$MgX).

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1. Recipient of an NIH Research Career Development Award, 1990-1995 (GM00575).

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