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Practical Zirconium-Mediated Deprotective Method of Allyl Groups

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The allyl protective group for hydroxyl function has been shown to be useful in organic synthesis, particularly in carbohydrate chemistry.[1] This is due to its ready availability and stability under acidic conditions. Various methods for deprotection of the allyl group have been developed in which cleavage involves mostly the isomerization of allyl ether to the enol ether system following acid hydrolysis.[2] Although recent progress has been made in the deprotection of the *O*-allyl group,[3] selective deprotection in the presence of other labile protective and/or functional groups is sometimes difficult owing to drastic reaction conditions.[1] Recently, we developed a new preparative method[4] for allylic zirconium reagents through β-elimination of the alkoxyl group of the intermediate, zirconacyclopropane, derived from allyl ether derivatives and in situ generated "Cp_2Zr"[5] (Scheme I). The generation of an allylic zirconium reagent from allyl ether derivatives is usually carried out under mild conditions (see the Experimental Section). Thus, our method for cleaving the allyl group of an allyl ether by Cp_2Zr should be applicable to the mild deprotection of allyl groups. We report herein that the zirconium-mediated deprotection of allyl group proceeds with remarkable regeneration of the parent molecule under mild conditions.

Scheme I

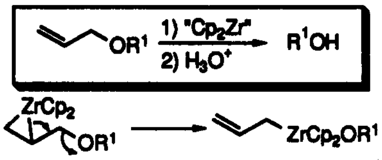
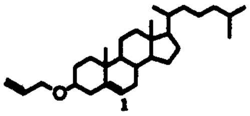
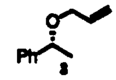
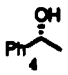
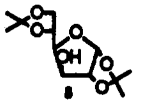
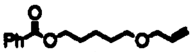
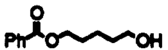
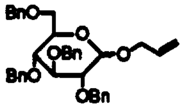
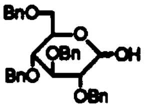
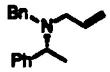


Table I. Zirconium-Mediated Deprotection of Allyl Ethers

entry	substrate	product[a]	yield (%)[b]
1	 1	Cholesterol (2)	97
2	 3	 4	97
3	 5	 6	97
4	 7	 8	98
5	 9	 10	50
6	 11	 12	91
7	 13	 14	68

[a] All products were identified by comparison with authentic sample (300-MHz ^{1}H NMR). [b] Isolated yield.

The results are summarized in Table I. In the reaction of allyl ether 1, containing an internal trisubstituted olefin, deallylation proceeded smoothly to give cholesterol (2) in excellent yield (entry 1). The 5,6-double bond of 1 should have little effect on this reaction since the reaction of Cp_2Zr with a highly substituted olefin proceeds sluggishly due to steric repulsion between bulky zirconocene and substituents on the double bond.[6] Allyl ether 3 was deallylated to give (*R*)-phenethyl alcohol (4) in excellent yield with complete retention of optical purity (entry 2). When deallylation of the compounds 5 and 7 possessing acid-labile protective groups (*O*-tetrahydropyranyl and *O*-isopropylidene) was conducted, deallylation occurred in excellent yield with no effect on the acid-labile group under buffered workup conditions (entries 3 and 4). Only moderate regeneration (50%) of the deallylated alcohol **10** was noted in the presence of ester carbonyl function (entry 5). This may possibly have been due to attack of the zirconocene equivalent Cp_2Zr on the ester carbonyl to cause a hydrolysis of the ester group.[7] The present procedure is also used to deprotect *O*-allyl ether at the anomeric carbon of a carbohydrate 11 in which the benzyl ether protective group is stable under cleavage conditions (entry 6). The *N*-allyl protecting group was also cleaved by the present method (entry 7). It should be noted that the selective deprotection of an *O*-allyl group is achieved in the presence of an *N*-allyl protective group. Thus, in the reaction of a mixture of 3 (1 mmol) and 13 (1 mmol) with Cp_2Zr (1.05 mmol) at room temperature for 1 h, the preferred deprotection of 3 to 4 and quantitative recovery of *N*-allyl compound 13 were observed[8] (Scheme II).

Our present procedure to deprotect the allyl protective group of an alcohol or secondary amine using the zirconocene equivalent Cp_2Zr is considered to enhance the value of allyl group as a protective group for alcohols and

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[1] Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley: New York, 1991. In carbohydrate chemistry: Manthorpe, P. A.; Gigg, R. *Methods Carbohydr. Chem.* 1980, *8*, 305–311.

[2] (a) Corey, E. J.; Suggs, W. J. *J. Org. Chem.* 1973, *38*, 3224. (b) Gigg, J.; Gigg, R. *J. Chem. Soc. C* 1966, 82–86.

[3] Recent reports on the deprotection of allyl groups: (a) Nakayama, K.; Uoto, K.; Higashi, K.; Soga, T.; Kusama, T. *Chem. Pharm. Bull.* 1992, *40*, 1718–1720. (b) Espanet, B.; Duñach, E.; Périchon, J. *Tetrahedron Lett.* 1992, *33*, 2485–2488. (c) Schmid, C. R. *Tetrahedron Lett.* 1992, *33*, 757–760. (d) Lamberth, C.; Bednarski, M. D. *Tetrahedron Lett.* 1991, *32*, 7369–7372. (e) Akiyama, T.; Hirofuji, H.; Ozaki, S. *Tetrahedron Lett.* 1991, *32*, 1321–1324.

[4] (a) Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* 1992, *33*, 1295–1298. (b) Ito, H.; Nakamura, T.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* 1992, *33*, 3769–3772. (c) Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.*, in press.

[5] The in situ generation of Cp_2Zr has been reported by Negishi et al.: Negishi, E.; Cederbaum, F. K.; Takahashi, T. *Tetrahedron Lett.* 1986, *27*, 2829–2832. See also Negishi's paper in ref 6.

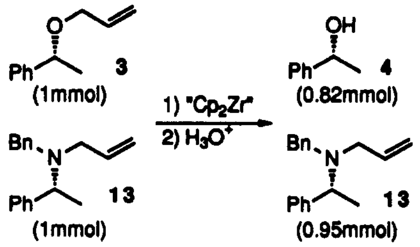
[6] See ref 4. See also: Swanson, D. R.; Negishi, E. *Organometallics* 1991, *10*, 825–826.

[7] In regard to the reaction of the ester group with Cp_2Zr, a complex reaction mixture including a small amount of 2-butenyl adduct of benzaldehyde was observed to be formed on treating ethyl benzoate with Cp_2Zr: Ito, H. Unpublished result.

[8] Differences in reactivities of *O*-allyl and *N*-allyl group toward Cp_2Zr have been reported by Negishi et al.: Rousset, C. J.; Swanson, D. R.; Lamaty, F.; Negishi, E. *Tetrahedron Lett.* 1989, *30*, 5105–5108.

0022-3263/93/1958-0774$04.00/0

Scheme II



amines in organic synthesis owing to milder conditions (ambient temperature and nearly neutral) than the previous method[1] and clear differentiation between *O*- and *N*-allyl protective groups.

Experimental Section

THF was distilled from sodium benzophenone ketyl before use. Zirconocene dichloride was purchased from Tokyo Kasei Kogyo and used without further purification. All starting allylic ethers and amines were prepared under the usual allylation conditions.[1] All reactions were conducted under an argon atmosphere by using standard Schlenk techniques. The structures of deallylated compounds were confirmed by comparison with authentic samples (300-MHz ^{1}H NMR and TLC analysis).

The following experimental procedures are representative:

Deallylation of Allyl Cholesteryl Ether (1) by Zirconocene Cp_2Zr. A solution of *n*-butyllithium (1.45 M in hexane, 1.26 mL, 1.82 mmol) was added dropwise to a solution of zirconocene dichloride (266 mg, 0.91 mmol) in THF (4 mL) at −78 °C with stirring. After stirring for 1 h at −78 °C, a solution of 1 (298 mg, 0.7 mmol) in THF (2 mL) was added, and the acetone–dry ice bath was removed. After the mixture was stirred for 1 h at ambient temperature, 1 N HCl was added at 0 °C, and the mixture was extracted with ether. The organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (hexane–ethyl acetate, 3:1) to give 263 mg of cholesterol (2) (97%).

Deallylation of 3-*O*-Allyl-1,2:5,6-di-*O*-isopropylidene-D-glucose (7) by Zirconocene Cp_2Zr (Containing an Acid-Labile Function). A solution of *n*-butyllithium (1.45 M in hexane, 1.79 mL, 2.6 mmol) was added dropwise to a solution of zirconocene dichloride (380 mg, 1.3 mmol) in THF (4 mL) at −78 °C with stirring. After the mixture was stirred for 1 h at −78 °C, a solution of 7 (300 mg, 1 mmol) in THF (2 mL) was added, and the acetone–dry ice bath was removed. After stirring for 1 h at ambient temperaure, saturated aqueous NH_4Cl was added at 0 °C, and the mixture was stirred for 1 h at ambient temperature. The mixture was extracted with dichloromethane, and the combined organic layers were washed with brine before drying ($MgSO_4$). Following filtration, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (hexane–ethyl acetate, 3:1) to give 256 mg of diacetone D-glucose (8) (98%).

Deallylation of (*R*)-*N*-Allyl-*N*-benzylphenethylamine (13) by Zirconocene Cp_2Zr. A solution of *n*-butyllithium (1.45 M in hexane, 1.79 mL, 2.6 mmol) was added dropwise to a solution of zirconocene dichloride (380 mg, 1.3 mmol) in THF (5 mL) at −78 °C with stirring. After stirring for 1 h at −78 °C, a solution of 13 (251 mg, 1 mmol) in THF (3 mL) was added, and the acetone–dry ice bath was removed. After the mixture was stirred for 4 h at ambient temperature, saturated aqueous NH_4Cl was added at 0 °C, and the mixture was stirred at ambient temperature for 1 h. The mixture was extracted with ether, and the combined organic layers were washed with brine before drying ($MgSO_4$). Following filtration, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (hexane–ethyl acetate, 4:1) to give 143 mg of 14 (68%).

Competitive Deallylation between (*R*)-Allyl Phenethyl Ether (3) and (*R*)-*N*-Allyl-*N*-benzylphenethylamine (13) by Zirconocene Cp_2Zr. A solution of *n*-butyllithium (1.45 M in hexane, 1.45 mL, 2.1 mmol) was added dropwise to a solution of zirconocene dichloride (307 mg, 1.05 mmol) in THF (4 mL) at −78 °C with stirring. After being stirred for 1 h at −78 °C, a mixture of 3 (162 mg, 1 mmol) and 13 (251 mg, 1 mmol) in THF (3 mL) was added, and the acetone–dry ice bath was removed. After the mixture was stirred for 4 h at ambient temperature, 1 N HCl was added at 0 °C, and the mixture was stirred at ambient temperature for 1 h. The mixture was extracted with ether, and the combined organic layers were washed with brine before drying ($MgSO_4$). Following filtration, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (pentane–ether, 2:1) to give 100 mg of 4 (82% yield). The aqueous phase was neutralized by the addition of saturated aqueous Na_2CO_3 and extracted with ether. The combined organic layers were washed with brine and dried over $MgSO_4$. The filtered solution was concentrated to dryness in vacuo to give crude residue which was subsequently passed through short silica gel column chromatography (hexane–ethyl acetate, 4:1) to give 238 mg of 13 (95% recovery).