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REDUCTIVE CLEAVAGES OF CHIRAL ACETALS USING LEWIS ACID-HYDRIDE SYSTEM

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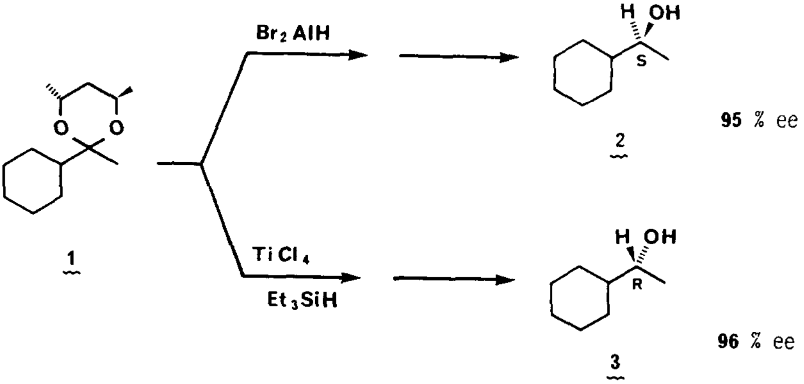
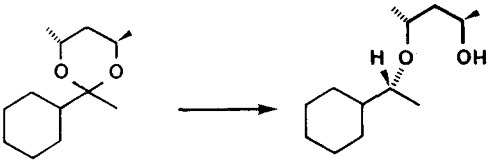
ABSTRACT The reaction of the acetal, derived from (2R,4R)-2,4-pentanediol and a ketone, with Lewis acid-hydride system produces the reductively cleaved product under the mild conditions with high stereoselectivity.

Recently we have reported the reductive cleavages of chiral acetals with organoaluminum reagent to give, after removal of chiral auxiliary, the corresponding (S)-carbinol with high stereoselectivities.[1] The reaction could be explained by the specific coordination of the aluminum hydride to one of the two oxygen atoms of the acetal followed by the reaction of the hydride from the Re-face of the carbonyl.[1b] In 1962 the reagent combination of triethylsilane-zinc chloride was reported to reduce noncyclic acetals and ketals to ethers.[2] It was found that acetals from 2,4-pentanediol on reaction with the similar system were converted into ethers.

Scheme 1



In dramatic contrast to the previous results, however, the stereochemical outcome of the reaction was the opposite to the previous results using aluminum hydrides, the reaction of the hydride from triethylsilane proceeds from the Si-face of the carbonyl (Scheme 1).[3] The study reported herein led to new level of selectivity in the asymmetric reduction of carbonyl compounds using homochiral protecting group,[1] and which is complementary to the previous procedure.[1a,1b]



1 4

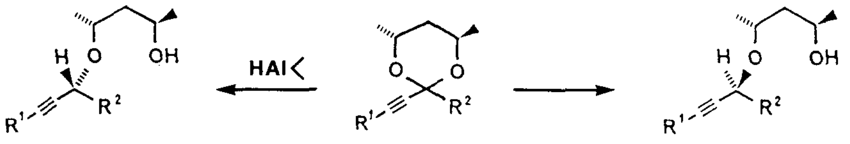
Table 1. Reductive cleavages of the acetal 1[a]

Lewis acid (equiv)		Hydride reagent (equiv)	conditions °C , h	4 yield (%)	4 ratio[b]
$TiCl_4$	(1.2)	Et_3SiH (1.2)	-78 , 0.5	85	98:2
$SnCl_4$	(1.0)	Et_3SiH (1.0)	-78 , 0.5 -20 , 2	93	65:35
$AlCl_3$	(1.2)	Et_3SiH (1.2)	-78 , 8	69	66:34
BF_3OEt_2	(1.0)	Et_3SiH (1.0)	-78 , 5 -20 , 15	93	93:7
$TiCl_4$	(1.2)	$^{t}BuMgCl$(5.0)[c]	-78 , 1	76	94:6

[a] The reaction was carried out as described in text. [b] The diastereomeric ratio was determined by gc on a 25 m PEG-HT capillary column. [c] A 0.82 M ether solution purchased from Tokyo Kasei Co. Ltd. Titrated prior to use.

Subsequent to the complexation of the acetal with 1.2 equiv of Lewis acid at low temperature 1.2 equiv of silane reagent was added slowly to give the reductively cleaved product 4, whose stereochemistry was found to be the opposite to that of the product obtained from the reaction with aluminum hydrides.[1a,1b] Some of our results were listed in Table 1. Among various Lewis acids examined, titanium (IV) chloride was highly effective both for selectivity and reactivity. Interestingly, t-butyl magnesiumchloride was also effective as a hydride source.[4]

The reaction of aromatic acetal afforded a complex mixture. Fortunately the use of tin (IV) chloride as a Lewis acid catalyst gave the desired product with the moderate selectivities.[5] The reaction of α,β-alkynyl acetal 5 produced the (S)-isomer 6 highly selectively, which also contrasts to the results using aluminum hydride in our foregoing paper.[6]



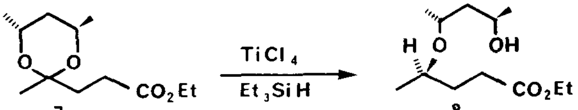
5 6

R^1 = Bu, R^2 = Me

$SnCl_4$; 67% Yield (95:5)

$TiCl_4$; 58% Yield (96:4)

It should be noted that the reaction of acetal with $TiCl_4$-Et_3SiH is highly chemoselective.[7,1b] Thus, the acetal of ethyl levulinate which has acetal and ester group in the same molecule, gave the corresponding ether 8 in good yield with high selectivity.



7 8

85% Yield (94:6)

The typical experimental procedure for the reaction of the acetal 1 is described below. To a solution of the acetal of methyl cyclohexylketone 1 (0.5 mmol) in dry dichloromethane (3 mL) was added $TiCl_4$ (0.6 mmol-0.6 mL of 1 M dichloromethane solution) at -78 °C and stirred there for 10 min. Triethylsilane (0.6 mmol) was added dropwise at -78°C. The reaction mixture was stirred for 30 min, and poured into 2 N hydrochloric acid. The product was extracted with ether twice. Removal of the dried solvent *in vacuo* afforded the crude product which was treated with potassium fluoride in methanol for 2 h to remove the silyl group of the product. After usual workup the crude one was purified by column chromatography on silica gel (hexane-ether, 5:1) to give the reduced product 4 in 85% yield. Gc analysis showed two peaks with the ratio of 98:2, and the minor peak was previously obtained (*R*)-isomer.[1a]

In summary, taken together with the previous procedure, the transformation detailed herein provides methodology for the syntheses of optically active alcohols.

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