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ASYMMETRIC REDUCTION OF KETONE
REDUCTIVE CLEAVAGE OF CHIRAL ACETALS USING ORGANOALUMINUM REAGENTS

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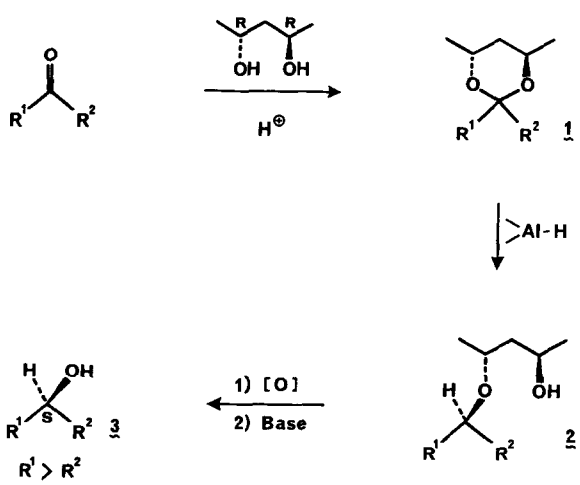
ABSTRACT: Some chiral acetals are cleaved by organoaluminum reagents. The products are formed diastereoselectively, and the removal of the chiral auxiliary affords optically active alcohols.

A recent communication by Bartlett, Johnson and Elliott[1] on the acetal derived from (-)-(2R,4R)-2,4-pentanediol has prompted us to report our own efforts in this area.

Although considerable success has been achieved in obtaining high asymmetric induction in the reduction of a prochiral ketone, one of the major drawbacks of the existing methods is that they are effective only for aromatic or α,β-unsaturated ketones.[2] For some time, we have been intrigued with the supposition that the optically active acetal may be cleaved regio- and stereoselectively by organoaluminum reagents under proper conditions.[3] Were this found to be the case, we felt that this might provide a practical solution to this problem. Scheme I illustrates the realization of such a process.

Scheme I



The following experiments provide details of the new process: A mixture of 1-cyclohexyl-1-ethanone (2.52 g, 20 mmol), (-)-(2R,4R)-2,4-pentanediol (2.08 g, 20 mmol),[4] and pyridinium p-toluenesulfonate[5] (20 mg) in benzene (20 mL) was heated at reflux for 10 h with continuous azeotropic removal of water. After cooling to room temperature, the mixture was poured into aq $NaHCO_3$, and the product was extracted with ether twice. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Chromatography on silica gel (30:1, hexane-EtOAc) afforded 3.28 g of the acetal 1 (77% yield).

$LiAlH_4$ (57 mg, 1.5 mmol) was added to a solution of $AlBr_3$ (1.20 g, 4.5 mmol) in dry ether (10 mL) at 0°C and the mixture was stirred at 0°C for 10 min. To the resulting suspension was added dropwise at -20°C the acetal 1 (212 mg, 1 mmol) in dry ether (1 mL), and the mixture was stirred at -20°C for 30 min. After the excess of Br_2AlH was destroyed with cold 2N HCl, the product was extracted with ether repeatedly. Removal of dried solvent left a crude oil which was purified by column chromatography on silica gel (5:1, hexane-EtOAc) to afford 212 mg of the alcohol 2 (99% yield).

To a solution of oxalyl chloride (0.20 mL, 2.2 mmol) in CH_2Cl_2 (2 mL) was added DMSO (0.34 mL, 4.8 mmol) in CH_2Cl_2 (0.5 mL) at -78°C.[6] The mixture was stirred for 2 min and the alcohol 2 (174 mg, 0.81 mmol) was added. Stirring was continued for an additional 15 min. Et_3N (0.48 mL, 5 mmol) was added and the reaction mixture was stirred at -78°C for 5 min and at room temperature for 30 min. Water (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 repeatedly. The dried organic layers were concentrated in vacuo. The crude ketone was dissolved in methanol (10 mL) and treated with K_2CO_3 (1.38 g, 10 mmol), and the suspension was stirred at room temperature for 12 h. The mixture was diluted with water and the product was extracted with ether three times. The ethereal layers were concentrated in vacuo and the product was purified by column chromatography on silica gel (5:1, hexane-EtOAc) to give 1-cyclohexyl-1-ethanol as a colorless liquid (84 mg, 81% yield).

Reagent, temperature, and solvent, the three variables in the reductive cleavage process, were explored in detail. Although almost every readily available aluminum hydride was tried, only i-Bu_2AlH, Cl_2AlH,[7] and Br_2AlH gave the satisfactory results. THF and other basic solvents were found to be unsatisfactory for the reaction. The lower reaction temperature gave us the better selectivities. Table I summarizes the results obtained with three different ketone systems under various conditions.

Further study is required before the stereochemical and mechanistic details of these reactions can be understood. In fact, observations of cleavage reaction of the cyclic acetals with organoaluminum reagents have previously been recorded, but detailed information, especially with regard to stereochemistry, is lacking. It should be pointed out, however, that the hydride approaches from the re-face of the carbonyl. On the other hand, allylsilane was shown to approach from the si-face of the carbonyl.[1] Thus, the behavior of the chiral acetal toward the aluminum reagent contrasts sharply with the titanium tetrachloride catalyzed coupling with allyltrimethylsilane.

Table I. Reduction of Chiral Acetals with Hydride Reagents[a]

1		hydride reagent (equiv)	conditions	2		% ee of 3[c,d] (confign)
R^1	R^2		solvent (°C, h)	yield (%)	ratio[b]	
c-hexyl	Me	DIBAH (5)	CH_2Cl_2 (0, 0.5)	88	13 : 1	88
		DIBAH (2)	CH_2Cl_2 (0, 1.5)	65	7 : 1	
		DIBAH (5)	Ether (0, 6)	76	8 : 1	76
		DIBAH (5)	Toluene (0, 0.5)	74	9 : 1	
		DIBAH (5)	Hexane (0, 1)	87	12 : 1	
		Et_2AlH (5)	Toluene (0, 0.5)	88	3 : 1	
		Et_2AlH (5)	Ether (0, 1.5)	81	8 : 1	
		Cl_2AlH (6)	Ether (0, 0.5)	98	19 : 1	92 (S)[h]
		Br_2AlH (6)	Ether (-20, 0.5)	99	23 : 1	95
Ph	Me[e]	DIBAH (5)	CH_2Cl_2 (0, 1.5)	88	28 : 1	93
		Br_2AlH (6)	Ether (-78, 1; 0, 0.5)	94	57 : 1	96 (S)[h]
n-hexyl	Me[f]	DIBAH (5)	CH_2Cl_2 (0, 2)	58	3.5 : 1	55[g]
		Cl_2AlH (6)	Ether (0, 1.5)	73	2 : 1	
		Br_2AlH (6)	Ether (0, 0.75)	69	4 : 1	
		Br_2AlH (20)	Ether (-40, 2)	87	4 : 1	58[g] (S)[h]
		Br_2AlH (20)	Ether (-78, 1)	64	8 : 1	78[g]

[a] Reduction of the chiral acetal was carried out as described in text. [b] The diastereomeric ratio was determined by GC on a 20-m PEG-HT capillary column. The reduction product 2 (R^1 = cyclohexyl, R^2 = Me) was also converted into the trimethylsilyl ether, which showed clean separation on GC. [c] Unless otherwise specified, the optical yield was determined by GC analysis of (S)-(-)-MTPA esters. See: Dale, J. A.; Dull, D. L.; Mosher, H. S. J. Org. Chem. 1969, 34, 2543. [d] The alcohols 3 were obtained by the two-step sequence from 2 in yields of 70~83% (See text). [e] Prepared from acetophenone dimethylacetal with (-)-(2R,4R)-2,4-pentanediol in the presence of catalytic p-TsOH (60~64% yield). [f] Prepared from 2-octanone exactly as described in text (83~86% yield). [g] Determined by NMR analysis of the MTPA derivative in the presence of tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium (III). [h] Optical rotation values of 3 were: $[\alpha]_D^{25}$ +4.58 (neat, d = 0.92) for R^1 = cyclohexyl, R^2 = Me; $[\alpha]_D^{25}$ -55.36 (c 0.98, cyclopentane) for R^1 = Ph, R^2 = Me; $[\alpha]_D^{25}$ +5.34 (neat, d = 0.82) for R^1 = n-hexyl, R^2 = Me.

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