Tetrahedron Letters,Vol.25,No.39,pp 4421-4424,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

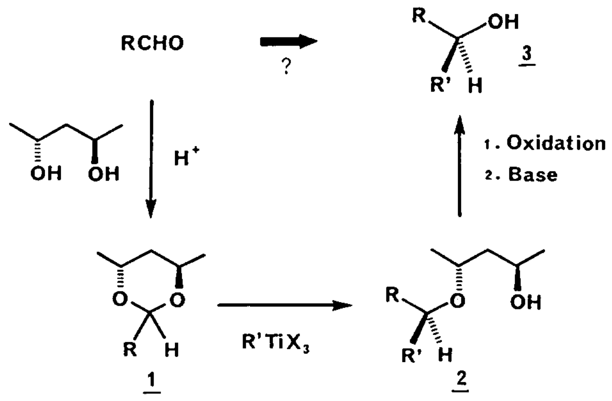
NUCLEOPHILIC CLEAVAGES OF ACETALS USING ORGANOTITANIUM REAGENTS. A NEW SYNTHESIS OF CHIRAL ALCOHOLS

Atsunori Mori, Keiji Maruoka, and Hisashi Yamamoto*
Department of Applied Chemistry, Nagoya University
Chikusa, Nagoya 464, Japan

ABSTRACT: A highly chemo- and stereoselective cleavage of acetals derived from (-)-(2R,4R)-2,4-pentanediol with organotitanium reagents has been demonstrated. The reaction proceeds under mild conditions in excellent yield and high chemoselectivity to give, after removal of auxiliary, the chiral alcohols of high enantiopurities. In addition, complexation of chiral acetals and $TiCl_4$ followed by treatment with n-butyllithium also results in formation of the corresponding n-butylated alcohols with high stereoselectivity.

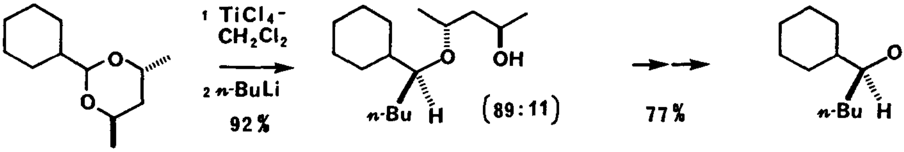
The central role of the carbonyl group in organic synthesis suggested the need for chiral synthetic equivalents. Indeed, the unusual versatility of the chiral acetals in synthetic chemistry has recently been demonstrated.[1,2] We wish to report herein that acetals, previously used as relatively inert protecting groups towards nucleophilic reagents ,[3] can be chemo- and stereoselectively activated by organotitanium reagents [4] to generate, after removal of auxiliary, the chiral alcohols of high purities. The new process is illustrated in Scheme 1.

Scheme 1

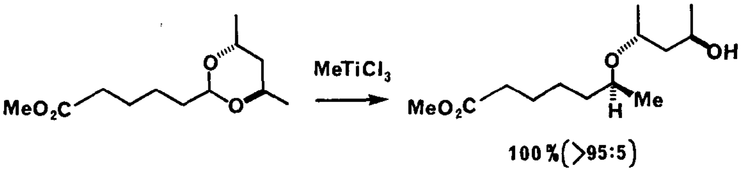


When the chiral acetal 1 was exposed with equimolar amounts of CH_3TiCl_3[5] at -78°C, the corresponding methylated product 2 was obtained quantitatively. The chiral auxiliary was readily removed in a manner previously detailed (oxidation-elimination sequence).[1] Several examples of this transformation are given in Table 1. A representative procedure for the new process is provided by the reaction of the acetal of cyclohexanecarbaldehyde and methyltitanium reagent (entry 1). To a solution of dimethylzinc (0.25 mmol)[6] in dry CH_2Cl_2 (5 mL) was added a solution of $TiCl_4$ (0.5 mL of 1 M CH_2Cl_2 solution, 0.50 mmol) at -78°C. The chiral acetal **1**, R = cyclohexyl, (0.50 mmol) was added at -78°C and stirred there for 30 min. Extractive isolation, evaporation of solvent, and chromatography on silica gel using 5:1 hexane-AcOEt for elution gave 2, R = cyclohexyl, R′ = methyl (107 mg, 100%) as a colorless oil. The stereochemistry of the products (96:4) was determined by GC comparison with the authentic samples prepared previously.[1,7]

Several examples are given in Table 1.[8] The chiral acetal **1** with CH_3TiX_3 in CH_2Cl_2 at -78° produced the methylated ether 2 with synthetically useful level of asymmetric induction. Most noteworthy are the extreme mildness of reaction conditions and the high yields which have been obtained. It should be noted that treatment of 1 with $TiCl_4$ followed by addition of n-butyllithium at -78°C also results in stereoselectivities of 89%.



It has also been possible to show that the reaction between acetal and titanium reagent is highly chemoselective[4] and that this is a factor of considerable importance in organic synthesis. Indeed, essentially complete chemoselectivity is observed in the following reactions.



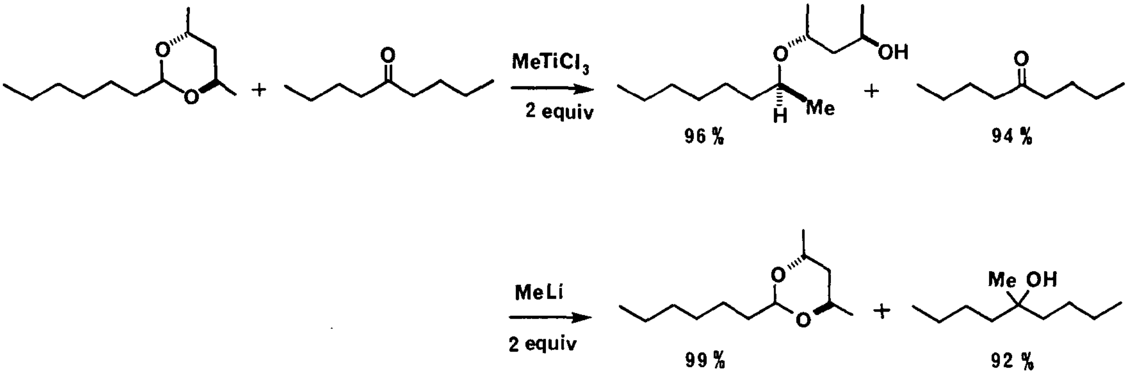


Table 1. Nucleophilic Cleavages of Acetals using Organotitanium Reagents[a,b]

Entry	Acetal R-	R'_nTiX_{4-n} R'-(Method)[c]	--Mono ether 2-- Yield (%)	 Ratio[d]	3 Configuration
1	*c*-Hexyl	Methyl (A)	100	96: 4	S[e]
2	*c*-Hexyl	Methyl (B)	100	96: 4	S[e]
3	*c*-Hexyl	Methyl (C)	91	97: 3	S[e]
4	*c*-Hexyl	*n*-Butyl (D)	92	89:11	S[f]
5	*n*-Hexyl	Methyl (A)	93	94: 6	S[e]
6	*n*-Hexyl	Methyl (C)	77	97: 3	S[e]
7	*n*-Hexyl	Ethyl (E)	100	81:19	S[g]
8	*n*-Hexyl	Ethyl (F)	100	81:19	S[g]
9	*n*-Hexyl	*n*-Butyl (D)	47	91: 9	-
10	*n*-Butyl	Methyl (A)	81	97: 3	-
11	*n*-Butyl	Ethyl (E)	86	78:22	-
12	Ethyl	*n*-Butyl (D)	45	87:13	-
13	Methyl	*n*-Butyl (D)	34	96: 4	-

---

[a] Unless otherwise specified, all reactions were carried out at -78°C for 30 min. [b] All products were identified by IR and PMR analysis. [c] Method of preparation; A: $MeTiCl_3$ (1 equiv); B: Me_2TiCl_2 (1 equiv); C: $MeTiBr_3$ (1-1.5 equiv); D: $TiCl_4$ (2 equiv) and then *n*-Butyllithium (2 equiv); E: $TiCl_4$ (1 equiv) and then Et_2Zn (1 equiv); F: $TiBr_4$ (1 equiv) and then Et_2Zn (1 equiv). [d] The diastereomeric ratio was determined by GC on a 25-m PEG-HT capillary column. [e] Determined by comparison with authentic samples, see ref. 1. [f] $[\alpha]_D = -8.85^\circ$ (c 1.10, benzene), see ref. 10. [g] $[\alpha]_D = +6.17^\circ$ (c 2.35, $CHCl_3$), see ref. 11.

In summary, the above described process opens up a practical and highly chemo- and stereoselective methodology to nucleophilic addition to carbonyl compounds.[9]

REFERENCES AND NOTES

(1) Reduction of chiral acetals: Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. Tetrahedron Lett. **1983**, 24, 4581. See also, Richter, W. J. J. Org. Chem. **1981**, 46, 5119.

(2) The $TiCl_4$ catalyzed coupling of chiral acetals with organo-silicon compounds: Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. J. Am. Chem. Soc. **1983**, 105, 2088; Johnson, W. S.; Elliott, R.; Elliott, J. D. J. Am. Chem. Soc. **1983**, 105, 2904; Elliott, J. D.; Choi, V. M. F.; Johnson, W. S. J. Org. Chem. **1983**, 48, 2294.; Choi, V. M. F.; Elliott, J. D.; Johnson, W. S., Tetrahedron Lett. **1984**, 25, 591.

(3) McOmie, J. F. W. "Protective Groups in Organic Chemistry"; Plenum Press: New York, 1973; Greene, T. W. "Protective Groups in Organic Synthesis"; Wiley; New York, 1981.

(4) Reviews of organotitanium reagents in organic synthesis: Reetz, M. T. Top. Curr. Chem. 1982, 106, 1; Weidmann, B.; Seebach, D. Angew. Chem., Int. Ed. Engl. **1983**, 22, 31.

(5) Reetz, M. T.; Westermann, J.; Steinbach, R. Angew. Chem., Int. Ed. Engl. **1980**, 19, 900.

(6) Generous samples of dimethyl and diethyl zinc were kindly donated by the Toyo Stauffer Chemical Co., Ltd.

(7) The diastereomeric ratio was determined by GC on a 25-m PEG-HT capillary column, which showed a base-line separation of the two peaks.

(8) Aromatic acetals are not employable: attempted alkylation of these acetal substrates gave rise to deteriorated reaction mixtures.

(9) Other approaches to this problem, see Mazaleyrat, J.-P.; Cram, D. J. J. Am. Chem. Soc. **1981**, 103, 4585 and references cited therein. See also ref. 10.

(10)(R)-(+)-1-Cyclohexyl-1-pentanol, 22.5% ee, was reported to give $[\ ]_D = +2.7^{\circ}$ (c 10.7, Benzene): Seebach, D.; Kalinowski, H. -O.; Bastani, B.; Crass, G.; Daum, H.; Dorr, H.; DuPreez, N. P.; Ehrig, V.; Langer, W.; Nussler, C.; Oei, H.-A.; Schmidt, M. Helv. Chim. Acta **1977**, 60, 301.

(11)Lit. $[\alpha]_D = +9.6^{\circ}$ (c 8.3, $CHCl_3$) for (S)-(+)-3-nonanol: Mukaiyama, T.; Hojo, K. Chem. Lett., 1976, 893.

(Received in Japan 4 June 1984)