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A FORMATION OF OPTICALLY ACTIVE OXETANES FROM SUGARS BY BORON TRIFLUORIDE CATALYZED [2+2]CYCLOADDITION REACTION

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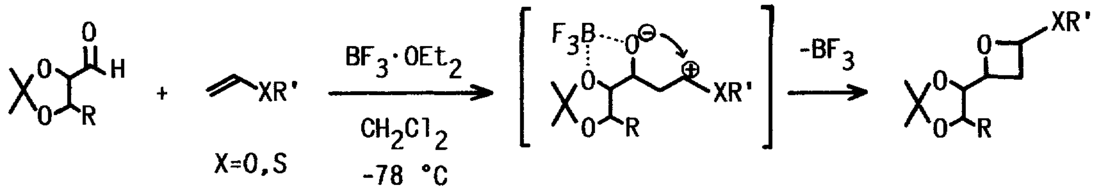
Summary: Boron trifluoride etherate catalyzed the formal [2+2]cycloaddition of 2,3-*O*-isopropylidene derivatives of *aldehyde*-*D*-aldose with enol ethers, vinyl sulfide, and disubstituted terminal olefins to afford chiral oxetanes.

Although synthesis of oxetanes by the photochemical [2+2]cycloaddition reaction has been extensively studied,1),2) difficulties have often arisen in the regio- and stereo-control of cycloadducts. Furthermore, Schreiber reported that the irradiation of a chiral aldehyde such as 2,3-*O*-isopropylidene-*D*-glyceraldehyde caused the racemization of the aldehyde to decrease the enantiometric purity of a cycloadduct.3) This fact seems to limit the synthetic potential of the method for an optically active oxetane formation.

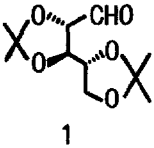
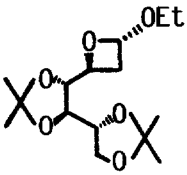
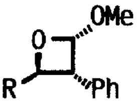
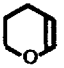
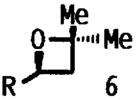
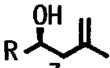
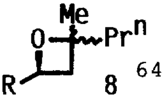
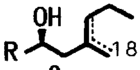
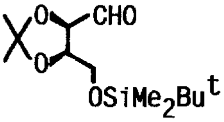
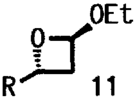
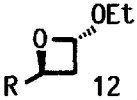
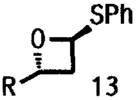
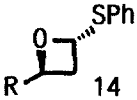
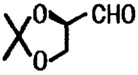
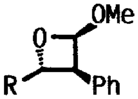
Recently, we found that when allylsilanes and 2,3-*O*-isopropylidene derivatives of *aldehyde*-aldose were treated with boron trifluoride etherate, a formal [2+2]cycloaddition proceeded *via* the cyclization of β-silyl cationic intermediate to give oxetane derivatives.4) This reaction process prompted us to explore the scope of a regiospecific cycloaddition using vinyl ether or sulfide, each of which has the capability of stabilizing the α-cation in the corresponding intermediate (Scheme 1). In this communication, we wish to describe a new and convenient method for the preparation of chiral oxetanes by the boron trifluoride etherate catalyzed [2+2]cycloaddition reaction.



Scheme 1

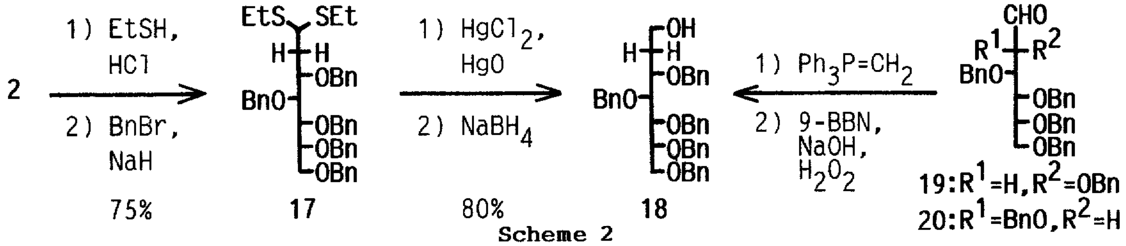
In the first examination we chose 2,3:4,5-di-*O*-isopropylidene-*aldehyde*-*D*-arabinose (**1**) as an enophile, because **1** could be expected to give highly diastereofacial selectivity on the basis of our previous work.4) Ethyl vinyl ether and phenyl vinyl sulfide were allowed to react with **1** in the presence of both catalytic and stoichiometric amounts of boron trifluoride etherate to provide *trans*-2-ethoxyoxetane 25) and 2-phenylthiooxetane **3** (Table 1).

Table 1. [2+2]Cycloaddition reaction catalyzed by $BF_3\cdot OEt_2$.[a]

Run	Enophile (RCHO)	Olefin	Equiv. of $BF_3\cdot OEt_2$	Time	Product(s)[b]	Yield(s)[c]
1	 1	$CH_2{=}CHOEt$	0.1	15 min	 2	94%
2			1.0	10 min		98%
3		$CH_2{=}CHSPh$	0.1	2 h	 3	69%
4			1.0	15 min		75%
5		PhCH=CHOMe (E/Z=0/100)	0.1	3 h	 4	80%
6		(E/Z=30/70)	0.1	2 h		75%
7		(E/Z=83/17)	0.1	2 h		79%
8			1.0	10 min	 5	39%
9[d]		$CH_2{=}CMe_2$	1.0	1 h	 6 71%  7 14%	
10		$CH_2{=}C(Me)$<u>n</u>-Pr	1.0	1 h	 8 64%[e]  9 18%[f]	
11	 10	$CH_2{=}CHOEt$	0.05	10 min	 11 64%  12 27%	
12		$CH_2{=}CHSPh$	1.0	30 min	 13 47%  14 25%	
13	 15	(Z)-PhCH=CHOMe	0.1	1 h	 16	21%

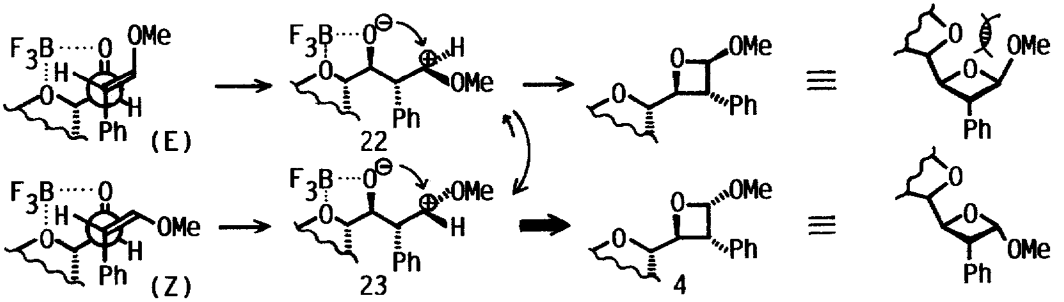
a) Unless otherwise noted, the reaction was carried out using 1.1-1.2 equiv. of olefin to aldehyde at -78 °C in CH_2Cl_2 under Ar. b) All the products gave satisfactory spectral data. c) Isolated yield by column or thin layer chromatography. d) An excess of olefin was used. e) Isomer ratio was 62:38 determined by the isolation of each isomer. f) Isomer ratio was 55:45 (methyl:methylene) determined by ^1H NMR spectrum.

The stereochemistry of the oxetane **2** was also studied. The relative configuration between 2-H and 4-H was shown by the J values of ^{1}H NMR spectra to be *trans* relationship6), but between 4-H and 5-H could not be assigned. In order to determine the absolute configuration of **2**, it was converted to an alcohol **18** and its authentic sample was synthesized from D-glucose and D-mannose derivatives **19** and **20**, respectively, as outlined in Scheme 2. ^{1}H and ^{13}C NMR spectra of **18** completely agreed with those of the authentic sample derived from D-glucose. Thus, the absolute configuration of **2** was proved as shown in Table 1. This result is consistent with Cram's cyclic model in which the nucleophile adds from the less hindered side of the chelate.



Scheme 2

Of special interest is the fact that despite the use of three different E/Z ratio mixtures of methyl styryl ether, the reactions proceeded stereoselectively to give 2,3-*cis*-3,4-*trans*-oxetane **4**7) (Runs 5—7). A mechanistic hypothesis for the stereoselective cycloaddition is indicated in Scheme 3. The cyclization of **23** may precede that of **22** owing to the steric and electronic repulsion between the methoxy group and the sugar side-chain.



Scheme 3

The lower yield of a cycloadduct in the reaction of dihydropyran is due to the production of many by-products (Run 8). 2-Methylpropene and 2-methyl-1-pentene, which form the tertiary carbonium ion intermediates, gave the cycloadducts **6** and **8** together with small amounts of ene reaction products **7** and **9**. It should be noted that the reactions of styrene and of 1-pentene with **1** were very sluggish under the same reaction conditions.

Next, other enophiles were examined. D-Erythrose derivative **10** was allowed to produce diastereomeric mixtures of *trans*-oxetanes (Runs 11 and 12). Unfortunately, in the case of D-glyceraldehyde derivative **15**, the yield of the desired cycloadduct was low.

At the present stage, a major limitation of the cycloaddition reaction is that yields or diastereofacial selectivities are dependent upon substrates. This methodology, however, surpasses the photochemical [2+2]cycloaddition with regard to the regiospecificity and stereoselectivity (the selective formation of trans-2-alkoxy- or 2-phenylthio-oxetanes) and the retention of chiralities (no racemization). These advantages will offer new possibilities in the synthetic applications of oxetanes and some of these are currently under study in our laboratory.

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References and Notes

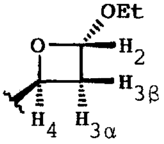
1) For reviews, see: a) D. R. Arnord, Advan. Photochem., **1968**, 6, 301. b) N. J. Turro, Pure Appl. Chem., **1971**, 27, 679.

2) For recent studies, see: a) A. Balsamo, G. Ceccarelli, P. Crotti, and F. Macchia, J. Org. Chem., **1975**, 40, 473. b) C. W. Funke and H. Cerfontain, J. Chem. Soc., Perkin Trans. II, **1976**, 1902. c) V. H. Gotthardt and W. Lenz, Angew. Chem., Int. Ed. Engl., **1979**, 18, 868. d) H. Ruotsalainen and T. Karki, Acta. Chem. Scand., **1983**, B37, 151. e) T. H. Morris, E. H. Smith, and R. Walsh, J. Chem. Soc., Chem. Commun., **1987**, 964.

3) S. L. Schreiber and K. Satake, Tetrahedron Lett., **1986**, 27, 2575.

4) H. Sugimura and M. Uematsu, Tetrahedron Lett., **1988**, 29, 4953.

5) A typical procedure for the stoichiometric condition: to a solution of **1** (450mg, 1.95mmol) and ethyl vinyl ether (224μl, 2.34mmol) in dry CH_2Cl_2 (20ml) under argon was added $BF_3\cdot OEt_2$ (305mg, 2.15mmol) in CH_2Cl_2(2ml) at -78 °C. After 10 min, Et_3N (1ml) was added at the same temperature. The reaction mixture was warmed to room temperature and a saturated aqueous solution of $NaHCO_3$ was added. The organic layer was separated and washed with water. After drying and evaporation of the solvent, flash column chromatography (silica gel, hexane:ethyl acetate=7:1) gave the oxetane **2** (577mg, 98%), crystallized on standing; mp 39.5-41.0 °C; $[\alpha]_D^{30}$ -85.1° (c 1.0, $CHCl_3$); IR (NaCl) 840,965,1030,1060,1145,1195,1243,1368,2900,2980 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ=1.21(t,J=7.1Hz,3H),1.36(s,6H),1.42(s,3H),1.43(s,3H),2.01(dt,J=4.6,14.2Hz,1H,3α-H),2.26(dd,J=5.7,14.2Hz,1H,3β-H),3.51(dd,J=7.1,10.0Hz,1H),3.81(dd,J=7.1,10.0Hz,1H),3.89(t,J=2.2Hz,1H),3.92(dd,J=2.2,7.3Hz,1H),3.96(dd,J=5.4,8.5Hz,1H),4.07(dd,J=6.1,8.5Hz,1H),4.33(ddd,J=5.4,6.1,7.3Hz,1H),4.41(dd,J=2.2,4.6Hz,1H,4-H),5.36(dd,J=4.6,5.7Hz,1H,2-H).



6) The vicinal cis coupling constants in oxetanes are larger than the corresponding trans ones.[2a,b] On the basis of this observation, the trans configuration of **2** was determined.

7) Compound **4**: mp 100-101.5 °C (hexane); $[\alpha]_D^{30}$ -107.7°(c, 1.0, $CHCl_3$); IR (NaCl) 840,955,1025,1065,1130,1200,1375,2880,2930,2990 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=1.39(s,3H),1.40(s,3H),1.41(s,3H),1.45(s,3H),3.35(s,3H),3.56(dd,J=1.7,5.9Hz,1H,3-H),3.92(dd,J=2.4,7.6Hz,1H),3.99(dd,J=5.1,8.6Hz,1H),4.11(dd,J=6.3,8.6Hz,1H),4.20(dd,J=2.4,2.9Hz,1H),4.41(dd,J=1.7,2.9Hz,1H,4-H);4.42(ddd,J=5.1,6.3,7.6Hz,1H),5.37(d,J=5.9Hz,1H,2-H),7.25-7.33(m,5H).

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