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Lactols in Stereoselection 2.
Stereoselective Synthesis of Disubstituted Cyclic Ethers.

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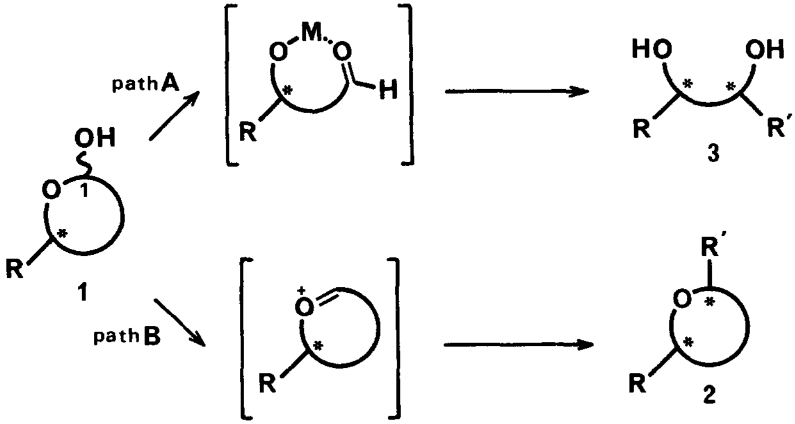
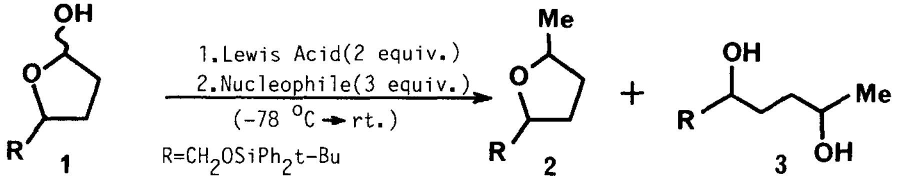
Summary: Direct reaction of lactols with organometals (Met. = Al, Ti, Zn, Sn) in the presence of Lewis acid provides disubstituted tetrahydrofurans and tetrahydropyrans with high diastereoselectivity.

Lactols exhibit two distinct types of reactivity in the reaction with nucleophiles. One is the behavior as the hydroxy aldehydes (path A), whose usefulness in the remote stereocontrol has been described.[1)] Another possible reactivity is the formal substitution of the hydroxyl group at C(1) to give the cyclic ethers (path B). Although a number of related reactions have been reported for the C(1)-activated derivatives (e.g. Cl, OAc, OMe, etc),[2)] little is known about the direct reaction of lactol itself.[3)] In the course of our research on the use of lactols in stereoselection, we became interested in the latter reaction with particular attention to the stereoselectivity as well as to the reaction conditions to discriminate the two paths (A or B). In this report, we wish to describe the diastereoselective direct introduction of various groups to γ- and δ-lactols leading to 2,5- and 2,6-disubstituted tetrahydrofurans and tetrahydropyrans 2.



The clue to modulate the reactivity to the path B lies in the employment of Lewis acid. Combined use of the Lewis acid ($BF_3 \cdot OEt_2$ or $TiCl_4$) with modestly nucleophilic reagents allows to direct the reaction to the path B. The results are summarized in Table 1. Me_2Zn was inert towards the lactol 1[1], but in combination with the Lewis acid it gave the desired product 2 in high yield (Run 1,2,3). When Me_3Al was used as a methylation reagent, coexsistence of Lewis acid dramatically altered the reaction path. Only diol 3 was obtained in the absence of the Lewis acid, while 2 was obtained as the sole product in the presence of $BF_3 \cdot OEt_2$ (Run 4,5). In the case of $MeTiCl_3$,[4] the reaction paths greatly varied with the solvents used (Run 6,7); the tendency can be ascribed to the change in the nucleophilic character by the Lewis basicity of the solvent. In contrast, highly nucleophilic reagents, such as MeMgBr or MeLi, are not suitable for the present reaction, since they only provided complicated reaction mixtures in the presence of $BF_3 \cdot OEt_2$.

Table 1. Nucleophilic Reaction to Lactol 1: Path A vs. Path B.[5]

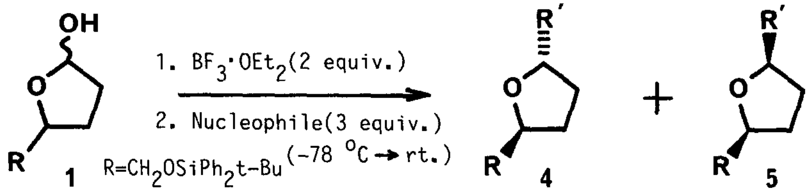


Run	Nucleophile[a]	Lewis acid[a]	Solvent	Yield (%)[b] 2	Yield (%)[b] 3
1	Me_2Zn	-----	CH_2Cl_2	0	0[c]
2	Me_2Zn	$BF_3 \cdot OEt_2$	CH_2Cl_2	82	0
3	Me_2Zn	$TiCl_4$	CH_2Cl_2	73	10
4	Me_3Al	-----	CH_2Cl_2	0	67
5	Me_3Al	$BF_3 \cdot OEt_2$	CH_2Cl_2	75	0
6	$MeTiCl_3$	-----	Et_2O	0	82
7	$MeTiCl_3$	-----	CH_2Cl_2	41	0
8	MeMgBr	-----	Et_2O	0	73
9	MeMgBr	$BF_3 \cdot OEt_2$	Et_2O	0	0[d]
10	MeLi	$BF_3 \cdot OEt_2$	Et_2O	0	0[d]

a) Lactol was treated with Lewis acid followed by nucleophile at -78 °C. Temperature was gradually raised to rt. b) Isolated yields. c) Lactol 1 was recovered quantitatively. d) Complicated reaction mixture. None of 1, 2, 3 were observed by TLC.

Further, several organometallic reagents were successfully employed as nucleophiles. Thus, organozinc,[6] organostannane[7] reagents gave good results, which are summarized in Table 2. Various groups were introduced to the C(1) position of lactol 1 to afford the corresponding disubstituted tetrahydrofurans in good yield.[8)]

Table 2. Synthesis of 2,5-Disubstituted Tetrahydrofurans.[5),9)]

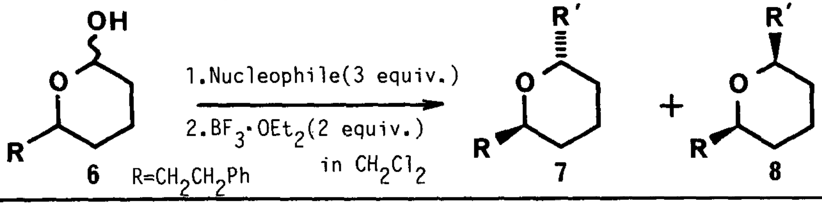


Run	4,5	R'	Nucleophile	Solvent	Yield (%)[a)]	4 / 5[b)]
1	a	Me	Me_2Zn	CH_2Cl_2	82	8.1 / 1
2	a	Me	Me_3Al	CH_2Cl_2	75	10 / 1
3	b	Et	Et_2Zn	CH_2Cl_2	80	8.6 / 1
4	b	Et	Et_3Al	CH_2Cl_2	61	13 / 1
5	c	$CH_2=CHCH_2-$	$(CH_2=CHCH_2-)_2SnBr_2$	CH_2Cl_2	72[c),d),10)]	12 / 1
6	d	$CH_2=CH-$	$(CH_2=CH-)_2SnBu_2$	CH_2Cl_2	66[d)]	47 / 1
7	e	Ph	Ph_2Zn	Et_2O	72[d)]	2 / 1

a) Isolated yields. b) Ratios were determined by HPLC[11)] except Run 7. c) The corresponding homoallylic alcohol was obtained (10 % yield) as the byproduct. d) 4, 5 were separable on SiO_2 TLC.

All reactions exhibited a high trans selectivity which is explained by considering the oxonium ion intermediate, where the attack of the nucleophile occurred from the opposite face to the substituent. Interestingly, efficient vinylation of 1 was found to be possible in excellent selectivity by employing $(CH_2=CH-)_2SnBu_2$.[7),12)] Furthermore, the reaction to δ-lactols 6 under similar conditions proceeded in good yield and with excellent trans selectivity (Table 3).[8)]

Table 3. Synthesis of 2,6-Disubstituted Tetrahydropyrans.[5),13)]



Run	7,8	R'	Nucleophile	Temperature[a)]	Yield (%)[b)]	7 / 8 [c)]
1	a	Me	Me_2Zn	0 °C → rt	78	50 / 1
2	b	Et	Et_2Zn	0 °C → rt	82	>100 / 1
3	c	$CH_2=CHCH_2-$	$(CH_2=CHCH_2-)_2SnBr_2$	-78 °C → rt	77	70 / 1

a) Temperature was raised to rt during 3 hr. b) Isolated yields. c) Ratios were determined by HPLC.[11)]

The salient feature of the present process lies in the chemoselectivity (path A vs. path B) and in the high diastereoselectivity. Further investigation on the synthetic application of the process is now under way.

References and Notes

1) K. Tomooka, T. Okinaga, K. Suzuki, and G. Tsuchihashi, the preceding paper in this issue.
2) For recent reports, see: G. H. Posner and S. R. Haines, Tetrahedron Lett., 26, 1823 (1985); P. DeShong, G. A. Slough, V. Elango, and G. L. Trainor, J. Am. Chem. Soc., 107, 7788 (1985), and references cited therein.
3) M. D. Lewis, J. K. Cha, and Y. Kishi, J. Am. Chem. Soc., 104, 4976 (1982); C. Brückner, H. Lorey, and H. -U. Reissig, Angew. Chem., Int. Ed. Engl., 25, 556 (1986), and references cited therein.
4) M. T. Reetz, J. Westermann, and R. Steinbach, Angew. Chem., Int. Ed. Engl., 19, 900 (1980).
5) All new compounds were fully characterized by ^{1}H NMR, IR, and high-resolution MS.
6) Ph_2Zn: D. Y. Curtin & J. L. Tveten, J. Org. Chem., 26, 1764 (1961).
7) $(CH_2{=}CH{-}CH_2{-})_2SnBr_2$: K. Sisido and Y. Takeda, J. Org. Chem., 26, 2301 (1961).
   $(CH_2{=}CH{-})_2SnBu_2$: D. Seyferth, Org. Synth. Coll. Vol., 4, 258 (1963).
8) A typical procedure for the ethylation of 1: To CH_2Cl_2 solution of 1 was added $BF_3{\cdot}OEt_2$ (2 equiv.) at -78 ^{o}C under an argon atmosphere followed by Et_2Zn (3 equiv. / hexane) and the temperature was gradually raised to rt during 4 hr. Usual extractive workup followed by purification on SiO_2 TLC afforded 4b and 5b in 80% yield. For the reactions of δ-lactols, better results were obtained by reversing the order of the addition (nucleophile followed by $BF_3{\cdot}OEt_2$).
9) Configuration of each isomer was assigned by the NOE analysis (400MHz NMR spectrum) for the ring protons. The detailed accounts will be described in our forthcoming paper.
10) In the absence of the Lewis acid, $(CH_2{=}CH{-}CH_2{-})_2SnBr_2$ provided only the corresponding diols as a 1 / 1 diastereomeric mixture in 85 % yield (via the path A).
11) Conditions of HPLC analysis: For 4,5 a: Develosil ODS-5 (4.6X250, Nomura. Chem. Co.), MeOH / H_2O. For 4,5 b,c,d, and 7,8 a,b,c: ZORBAX-SIL (4.6X250, DuPont), hexane / AcOEt.
12) It should be noted that the vinylation reaction should be carried out at - 78 ^{o}C for 10 minutes, whose conditions were necessary to suppress the side reactions. Further optimization of the process is currently under investigation.
13) Stereochemistry was determined by ^{13}C NMR. For the correlation of the stereochemistry with the chemical shifts of C(2), C(6) in 2,6-disubstituted tetrahydropyrans, see: E. L. Eliel, M. Manoharan, K. M. Pietrusiewicz, and K. D. Hargrave, Org. Magn. Reson., 21, 94 (1983). For ^{13}C NMR signals of C(2), C(6) see below.

δ	7	8	Solvent
a	69.58, 66.54	76.56, 73.69	C_6D_6
b	72.24, 70.26	79.29, 76.53	$CDCl_3$
c	70.43, 70.03	77.31, 76.51	C_6D_6

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