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NUCLEOPHILIC CLEAVAGE OF (2S,3S)-3-PHENYLGLYCIDOL

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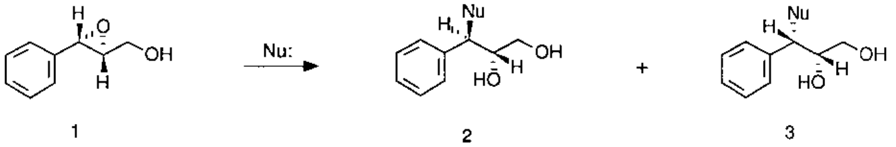
Abstract——Reaction of (2S,3S)-3-phenylglycidol with a variety of nucleophiles has been examined. The reaction occurred regioselectively at the benzylic center generally with an excellent diastereoselectivity. Although most of the nucleophiles yielded the products with inversion of the original chirality, trimethylaluminum furnished the retention product in a high diastereoselectivity.

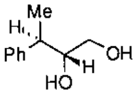
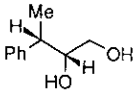
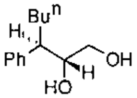
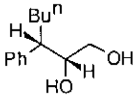
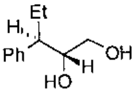
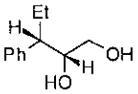
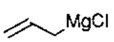
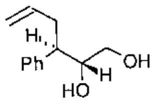
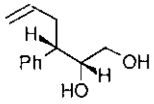
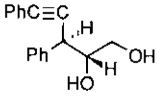
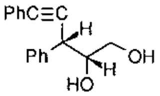
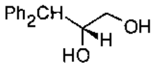
Since optically active 3-phenylglycidol (1) has now been accessible in a large quantity in high enantiomeric purity by the Sharpless chiral epoxidation method using a catalytic amount of chiral inducer,[1] it becomes an attractive building block for the construction of a variety of optically active compounds. In order to make this chiral epoxide utilizable as a versatile chiral building block,[2] we examined the reaction with a variety of nucleophiles using (2S,3S)-3-phenylglycidol[3] (1), obtained from trans-cinnamyl alcohol using diisopropyl (L)-tartrate as chiral catalyst.



Scheme 1

We chose a variety of nucleophilic reagents as shown in Table 1. All of the nucleophiles were introduced regioselectively at the benzylic carbon of the substrate to give the corresponding 1,2-diols. Although not all of the nucleophiles afforded single stereoisomers, the epimeric diols formed could be readily separated by using a silica gel column after converting them into the corresponding acetonides. Most of the cleavage reaction occurred predominantly with inversion of chirality. However, when trimethylaluminum was used as nucleophilic reagent, as has been pointed out the experiment using the racemic substrate,[4] the reaction occurred with high retention of the original chirality to give **3b** as major product (32:1) (Entry 2). This exceptional reaction may be particularly

Table 1. Reaction of (2S,3S)-3-Phenylglycidol (**1**) with Nucleophiles

Entry	Nucleophile	Product$^{a)}$		Ratio$^{b)}$	Yield$^{c)}$
		2 (inversion)	3 (retention)	(2:3)	(%)
1	Me$_2$Cu(CN)Li$_2$$^{d)}$	 **2a**	 **3b**	28:1	78
2	Me$_3$Al$^{e)}$	**2a**	**3b**	1:32	87
3	Bu$^n_2$Cu(CN)Li$_2$$^{d)}$	 **2b**	 **3b**	>99:1	47
4	Et$_3$Al$^{f)}$	 **2c**	 **3c**	1:1	73
5	 $^{g)}$	 **2d**	 **3d**	>99:1	96
6	PhC≡C·BF$_2$$^{h)}$	 **2e**	 **3e**	>99:1	90
7	PhC≡C·AlEt$_2$$^{i)}$	**2e**	**3e**	3.2:1	85
8	Ph$_2$Cu(CN)Li$_2$$^{c)}$		 **4**		88

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a) All products could be separated by column chromatography (SiO$_2$) after the conversion into the corresponding acetonides. All the inversion products were more polar than the retention products on silica gel plate and column.

b) Ratios were determined by ^{1}H-nmr spectra (500 MHz) of the products or their acetonides.

c) Combined (**2** and **3**) yield.

d) Treatment of **1** (1 eq.) with the cuprate, prepared in situ from RLi (6 eq.) and Cu(I)CN (3 eq.) in Et$_2$O at -68 °C (1 h), at -45 °C (10 min).

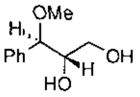
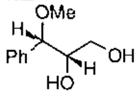
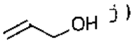
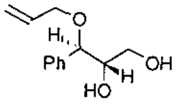
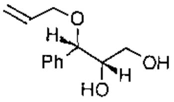
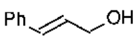
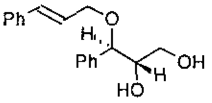
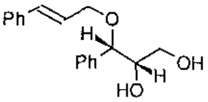
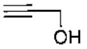
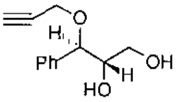
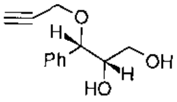
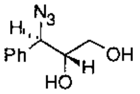
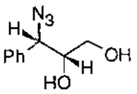
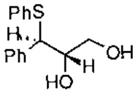
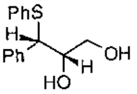
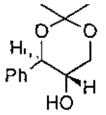
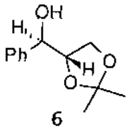
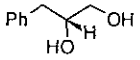
e) Treatment of 1 (1 eq.) with trimethylaluminum (1.5 eq.) in CH$_2$Cl$_2$ at -72 °C (25 h).

f) Treatment of 1 (1 eq.) with triethylaluminum (1.8 eq.) in CH$_2$Cl$_2$ at -40 - -30 °C (30 h).

g) Treatment of **1** (1 eq.) with allylmagnesium chloride (4 eq.) in THF at -20 °C (10 min).

h) Treatment of **1** (1 eq.) with the reagent, prepared in the same flask from phenylacetylene (3 eq.) with ^{n}BuLi (3 eq.) (10 min) followed by BF$_3$·OEt$_2$ (3 eq.) at -75 °C, at -75 °C (30 min).

Table 1. Reaction of (2S,3S)-3-Phenylglycidol (1) with Nucleophiles

Entry	Nucleophile	Product[a)] 2 (inversion)	3 (retention)	Ratio[b)] (2:3)	Yield[c)] (%)
9	MeOH[j)]	 **2f**	 **3f**	>99:1	99
10	 [j)]	 **2g**	 **3g**	>99:1	74
11	 [k)]	 **2h**	 **3h**	3:1	50
12	 [k)]	 **2i**	 **3i**	5.3:1	92
13	NaN_3[l)]	 **2j**	 **3j**	>99:1	95
14	PhSH[m)]	 **2k**	 **3k**	>99:1	81
15	MeCOMe[n)]	 **5**	 **6**	1:2.2[o)]	98
16	H_2[p)]		 **7**		87

i) Treatment of **1** (1 eq.) with the reagent, prepared in the same flask from phenylacetylene (2 eq.) with ^nBuLi (2.1 eq.) at 0 °C (30 min) followed by Et_2AlCl (2 eq.) at 0 °C (1.5 h), at 0 °C (30 min).

j) Treatment of 1 (1 eq.) in the alcohol with $BF_3{\cdot}OEt_2$ (0.03 eq.) at -30 °C (10 min).

k) Treatment of 1 (1 eq.) with the alcohol (5 eq.) in CH_2Cl_2 in the presence of $BF_3{\cdot}OEt_2$ (0.05 eq.) at -40 °C (2 h).

l) Treatment of 1 (1 eq.) with NaN_3 (2 eq.) in dioxane-H_2O (10:1 v/v) in the presence of NH_4Cl (0.5 eq.) at 80 °C (3 h).

m) Treatment of 1 (1 eq.) with PhSH (2 eq.) in dioxane-H_2O (10:1 v/v) containing NaOH (2 eq.) at room temperature (22 min).

n) Treatment of 1 (1 eq.) with $BF_3{\cdot}OEt_2$ (0.05 eq.) in acetone at -30 °C (1.5 min). Prolonged treatment (>24 h) furnished **6** as a sole product (∿100%).

o) Ratio of **5** and **6**

p) Hydrogenation (1 atm) of **1** in benzene in the presence of $Pd(OH)_2$ (5% mol) at room temperature (25 h).

useful to utilize a single chiral 3-phenylglycidol (**1**) as enantiodivergent synthon by combination with the inversion reaction promoted by the cuprate reagent[5] (Entry 1). In contrast, triethylaluminum as well as the aluminum complex of phenylacetylene[4,6] did not furnish the retention products selectively (Entries 4 and 7). The cuprate and Grignard reagents (Entries 3 and 5) and the borane-acetylene complex[7] (Entry 6) yielded the inversion products exclusively. All the hetero atom nucleophiles besides cinnamyl and propargyl alcohols (Entries 11 and 12) afforded the inversion products stereoselectively in good to excellent yields. Acetone reacted as an oxygen nucleophile[8] to give a mixture of the 1,3-dioxane (**5**) and the 1,3-dioxolane[9] (**6**) with complete inversion (Entry 15). The former isomer may be the kinetic product since only the latter was obtained as a sole product in an excellent yield under the same reaction conditions except prolonged reaction time (24 h).

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3. Optically pure material ($\sim$100% ee) could be obtained by recrystallization from a mixture of petroleum ether (bp 30-60 °C) and ether: needles, mp 50-51 °C, $[\alpha]_D^{26}$ $-50.4°$ (c 2.4, $CHCl_3$) [lit.[1] : mp 51.5-53 °C; $[\alpha]_D^{25}$ $-49.6°$ (c 2.4, $CHCl_3$)].
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8. B. N. Blackett, J. M. Coxon, M. P. Hartshorn, A. J. Lewis, G. R. Little, and G. J. Wright, Tetrahedron, **26**, 1311 (1976).
9. The structure was determined by comparison with an authentic sample prepared from (2S,3R)-3-phenyl-1,2,3-propanetriol.[2a]

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