ON THE PREPARATION OF OPTICALLY ACTIVE SECONDARY ALCOHOLS FROM A 1,3-DIOXAN-4-ONE: SUBSTITUTION WITH ORGANOCOPPER REAGENTS

Stuart L. Schreiber* and Jeff Reagan Sterling Chemistry Laboratory, Yale University New Haven, Connecticut 06511

Abstract Organocopper reagents react with a chiral nonracemic 1,3-dioxan-4-one to afford substitution products with high diastereoselectivity. After treatment of the adducts with potassium t-butoxide, optically active secondary alcohols are obtained.

Recently a new chiral, nonracemic acetal for use in the formation of optically active secondary alcohols was described by Seebach et al. (eq 1).¹ Several features of the 1,3-dioxan-4-one functional group were outlined that suggested these chiral auxiliaries may be preferred to related acetals that have seen wide-spread use in organic synthesis.²⁻⁴ The relevant properties included the lower cost of the β -hydroxy butyric acid chiral auxiliary, the ease of formation and purification of the chiral acetal, the excellent stereoselectivity observed in the substitution reactions with silyl nucleophiles, and the direct removal of the chiral auxiliary (upon treatment with base) without the need for an intermediate oxidation step. We have also investigated the use of the 1,3-dioxan-4-one functional group as a chiral nonracemic electrophile and wish to report the results of our studies. Two observations that extend the utility of this group include: (a) the cis disubstituted isomers can be formed at low temperature (-78°C) and with excellent stereocontrol by employment of Noyori's conditions for acetalization and (b) the acetals react with organocopper nucleophiles with diastereoselectivity that is comparable to that reported for silyl nucleophiles.



The acetalization of the bis-silyl derivative of (R)-3-hydroxybutyric $acid^5$ 1 with heptanal in methylene chloride at -78°C with 4% trimethylsilyltriflate⁶ and 2% 2,6-di-t-butylpyridine (eq. 2) afforded a 35:1 mixture of cis and trans isomers of the 1,3-dioxan-4-ones 2, respectively, in 77% yield (see Experimental Procedure). Subsequent reactions in these studies employed the 35:1 mixture of isomers; however pure cis-dioxanone can be obtained by low temperature crystallization as described by Seebach et al.¹

The reactions of several organometal reagents with the dioxanone 2 were investigated. Organolithium, organotitanium and Grignard species reacted predominantly at the lactonic carbonyl carbon to provide the (R)-3-hydroxy ketone and heptanal and/or the (racemic) product of addition to heptanal.⁷ On the other hand, organocopper reagents (prepared *in situ* from the organolithium according to the stoichiometry recorded in Table 1) reacted with high positional selectivity to afford the β -alkoxy acids 3. Entries 1-3 required the formation of higher order cuprates (R_3Cu_2Li) since diorganocuprates (R_2CuLi) tended to react at the carbonyl carbon. This competing addition reaction may be the result of free organolithium that is in equilibrium with the R_2CuLi species.⁸ Entries 2 and 3 illustrate it is possible to obtain a higher *de* in the products than

in the dioxanone substrate, a result that is in accord with the earlier report.¹ The addition of a vinyl group to the dioxanone (entry 4) proved to be troublesome. In this case, divinyl cuprate⁹ in combination with boron trifluoride etherate (1 equiv.) resulted in the desired addition product, but with diminished selectivity (4.8:1). However, the diastereomeric β -alkoxy acids could be separated by SiO₂ chromatography prior to removal of the chiral auxiliary.

The β -alkoxy acids 3 were converted to the secondary alcohols 4 by: (a) treatment with potassium t-butoxide in refluxing THF or (b) reaction with diazomethane and treatment of the resultant methyl esters with potassium t-butoxide in THF at room temperature. The results of these experiments are shown in Table 2. The absolute configuration of the 2-octanol product (entry 1) was shown to be S by comparison with an authentic sample.¹⁰ This corresponds to a displacement of the carboxylate with inversion of configuration at the acetal center and is analogous to the behavior of organosilicon reagents towards dioxanones¹ and dioxolanones.³g The stereochemistry of the remaining products (entries 2-4) was assigned in analogy to these precedents and entry 1.

3-Hydroxybutyric acid is readily available in either the R or S form.¹ The diastereoselective addition reactions of organosilicon and organocopper reagents to acetals derived from this chiral auxiliary suggest that a wide range of chiral nonracemic secondary alcohols may be prepared by this procedure.

EXPERIMENTAL PROCEDURE

 $\frac{(R)-2-(1-Hexyl)-(R)-6-methyl-1,3-dioxan-4-one.}{(1.86g, 7.5mmol), heptanal (0.813g, 7mmol), 2,6-di-t-butylpyridine (0.03ml), and methylene chloride (10ml) were added to a 25ml flask equipped with a stir bar. The flask was cooled to <math>-78^{\circ}C$ (dry ice, acetone) under nitrogen with stirring. After 5 minutes TMSOTF (.060ml, 0.31mmol) was added and the solution was stirred for 1 hour at $-78^{\circ}C$. The solution was quenched by adding 0.1ml of triethylamine followed by 0.1ml of methanol. The mixture was stirred at $-78^{\circ}C$ for 5 minutes and then allowed to warm to room temperature. The solvent was removed on a rotary evaporator and the residual oil was chromatographed on 40g of silica gel using 1:1 pentane/ether containing 1% triethylamine as eluant. A 35:1 mixture of cis and trans dioxanone isomers 2 (1.08g, 77% yield) was obtained.

<u>Methyl (R)-3-((S)-2-octyloxy)butyrate</u>. CuBr·Me₂S (1.005g, 4.89mmol) was added to a 50ml flask. To this was added 8ml of ether and 8ml of Me₂S. The homogeneous pale gold colored solution was cooled to -40° and 4.44ml of 1.65M MeLi (7.3mmol, 1.5eq) was added dropwise. The solution was warmed to 0° over a period of 10 minutes. The 35:1 (cis/trans) mixture of dioxanones 2 (180mg, 0.9mmol) in 1ml of ether was added to the yellow solution. The reaction was allowed to proceed at 0° for 1 hour at which time 3ml of 4N ammonium hydroxide was added. The mixture was warmed to room temperature and stirred for 15 minutes. 1N HCl was added until the aqueous layer was acidic. The mixture was extracted twice with 75ml of ether. The combined organic layers were washed with 1N HCl saturated with NaCl and dried over MgSO₄. The MgSO₄ was removed by filtration and the filtrate was concentrated by rotary evaporation. To remove the small amount of CuBr·Me₂S that remained in the residual oil, the oil was filtered through a l inch plug of silica gel using ether as eluant. The filtered material was treated with excess diazomethane for 5 minutes and the excess diazomethane was removed with a stream of nitrogen. After rotary evaporation of the solvent, the residual clear oil was analyzed by capillary GC and capillary GC/MS which indicated a 33:1 ratio of methyl esters



	Table 1	Formation of β -Alkoxy Acids 3					
Entry	R	RLi/CuBr∙Me ₂ S	Temp (°C)	Time (hr)	Yield	cis/trans ^c (de)	
1	Ме	1.5	0	1	58 ^b	33:1 (94)	
2	nBu	1.5	-25	1	68	70:1 (97)	
3	Ph	1.5	-30	1	90	66:1 (97) ^d	
4	Vinyl	2.0 ^a	-55	2	56	4.8:1 (66)	

^a1.0 eq of BF₃·OEt₂ was added. ^byield of methyl ester (CH₂N₂). ^cisomer ratios determined by capillary GC (50m carbowax WCOT) analysis of the methyl esters. ^destimated from ee (Tb 2).

Table 2		F	Formation of Secondary Alcohols 4					
Entry ^a	R	Method	Yield(%)	ee(%) ^b	corrected ee(%) ^c	Configuration		
1	Me	В	88	86	97	S		
2	nBu	А	72		d	S		
3	Ph	В	84	86	97	R		
4	Vinyl	В	75	55	62	R		

^aresults of experiments that employ the diastereomeric mixture of products 3. ^bee values were determined by the method of Feringa and Wynberg¹¹ with ³¹P NMR and/or Mosher¹² with ¹⁹F NMR and capillary GC. ^cbased on the value of 88% ee for the (R)-3-hydroxy butyric acid employed in these studies^b. ^dee could not be determined (calculated ee=97 based on de of entry 2 in Table 1).

 $(T=160^{\circ}, isothermal, RT major=8.9min, minor=9.29min)$ had been obtained. The oil was chromatographed on 50g of silica gel using 5:1 hexane/ether, then 2:1 hexane/ether, and then ether. Methyl (R)-3-((S)-2-octyloxy)butyrate was isolated as a 33:1 mixture of diastereomers (121mg) in 58% yield.

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