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Carbohydrates as Chiral Auxiliaries: The Asymmetric Epoxidation Reaction of Olefins

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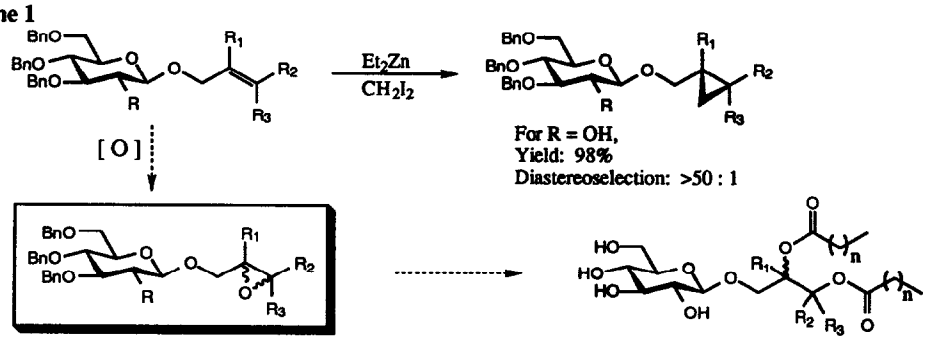
Abstract: Under optimized conditions, the epoxidation of 1-*O*-*trans*-2-butenyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranose gave a 9:1 mixture of diastereomers. The diastereoselectivities observed were shown to be highly dependent on the nature of the reagent used and of the protecting group at *C*-2 of the auxiliary.

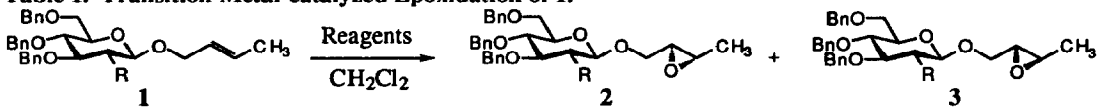
The epoxidation of allylic alcohols is of major importance in asymmetric synthesis.[2] The advent of the Katsuki-Sharpless reaction[3] has advantaged the oxirane function as an excellent precursor of optically pure derivatives. Being such a powerful catalytic process, the Sharpless epoxidation has completely overwhelmed other methodologies, thus, it is not surprising that there are no in depth investigations of the application chiral auxiliaries in this area.[4] We have recently shown that carbohydrates can be used as efficient chiral auxiliaries[5] in the stereoselective Simmons-Smith cyclopropanation of substituted allylic alcohols.[6] In the course of our research program which aims at developing new chiral auxiliaries for hydroxyl-directed reactions, we became interested in evaluating the potential of the glucose-derived template in the directed epoxidation reaction. This general methodology would be of interest not only to provide access to substituted epoxy alcohols, but also to provide an expedient entry to a variety of glycolipids[7] by oxirane opening (Scheme 1). In this communication, we report that 3,4,6-tri-*O*-benzyl-β-D-glucose can be used as an efficient chiral template for the epoxidation reaction of allylic ethers.

Scheme 1



Among the wide variety of epoxidizing reagents available, several have emerged as being particularly effective for the oxygen-directed epoxidation reaction.[8] The first class of reagents that was studied were those that involve formation of a covalent oxygen-metal bond.[9] It is well known, from literature data, that the metal-directed epoxidation requires an hydroxy group as an anchor for the reagent in order to achieve good diastereoselectivities.[10] Quite unexpectedly, the vanadium, molybdenum, or titanium-catalyzed epoxidation of *trans*-2'-butenyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranoside **1a** (R=OH) produced very low yields (0-40%) of the desired epoxides under a variety of reaction conditions (Table 1) . Most importantly, neither diastereomer was formed preferentially.

Table 1. Transition Metal-catalyzed Epoxidation of 1.



Entry	R	Reagents	Yield[c]	Ratio (2:3)[d]
1	OH (**1a**)	$VO(acac)_2$[a,b] *tert*-BuOOH	N.R.	----
2	OH (**1a**)	$Mo(CO)_6$[a] *tert*-BuOOH	N.R.	----
3	OH (**1a**)	MoOPH[b,e]	40%	1 : 1
4	OH (**1a**)	$Ti(O\text{-}i\text{-}Pr)_4$ [a,b] *tert*-BuOOH	10%	1 : 1

[a]Catalytic amount of metal was used. [b]Stoechiometric amount of metal was also ineffective in increasing the yields. [c]Determined by 200 MHz ^{1}H NMR. [d]Determined by 200 MHz ^{1}H NMR and HPLC of the crude product. [e]MoOPH: Oxodiperoxymolybdenum(pyridine)-hexamethylphosphoramide.

These results are rather surprising since the transition metal-catalyzed epoxidation of some trishomoallylic olefins are known to give relatively good diastereoselectivities.[11]

The failure of the transition metal-directed epoxidation led us to explore the second class of reagents which involves the use of peroxy acids as epoxidizing reagents. Since several functional groups are known to direct the epoxidation reaction via hydrogen bond formation, we initially focused on determining the best directing group at the *C*-2 position of the auxiliary. MCPBA was used for the initial study because of its ease in handling, availability, and intermediate reactivity. As shown in Table 2, the efficiency of the reaction is optimal in the case where a free hydroxy group is present at the 2-position (entry 1). This is presumably due to hydrogen bond formation between the reagent and the directing group on the auxiliary. Another important observation is that the relative rate of epoxidation appears to be highly dependent on the nature of the protecting group at *C*-2. The fastest epoxidation reaction occurred with a free hydroxy group at *C*-2 and it was also the most diastereoselective. This rate enhancement is consistent with the involvement of the hydroxy group at *C*-2 and with kinetic data for the directed epoxidation of simple allylic alcohols.[12] It is not surprising to see the efficiency of the hydroxy and carbamate groups knowing their high propensity to form hydrogen bonds.[13] Lower diastereoselectivities in the case of the carbamate are presumably the result of the longer distance between the hydrogen bonded reagent and the reactive site (entry 5). It is also interesting to observe that very low yields and diastereoselectivities were obtained with bulky protecting groups at *C*-2 (entry 4, 5).

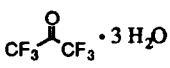
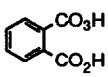
Table 2. Epoxidation of 1 with MCPBA (2 eq) in CH_2Cl_2 (0 °C).

Entry	R	Time	Yield[c]	Ratio (2:3)[d]
1	OH (**1a**)	4 hrs	>95%	4.1 : 1
2	OBn (**1b**)	12 hrs	40%	1 : 1
3	OTIPS (**1c**)[a]	12 hrs	30%	1 : 1
4	OPiv (**1d**)[b]	12 hrs	30%	1 : 1
5	OCONHPh (**1e**)	12 hrs	70%	2 : 1

[a]TIPS: Triisopropylsilyl. [b]Piv: Pivaloyl. [c]Determined by 200 MHz ^{1}H NMR. [d]Determined by 200 MHz ^{1}H NMR and HPLC of the crude product.

Having found the best directing group at the *C*-2 position of the glycoside, we then surveyed some other oxidizing reagents which are prone to react via a similar mechanism (Table 3). Unfortunately, most peroxides and peroxy acids that were studied produced lower yields and ratios (entry 1-4).

Table 3. Effect of the reagents on the diastereoselectivities in the epoxidation of 1a.

Entry	[O]	Solvent	Temp. (°C)	Time (h)	Yield (%)[a]	Ratio (2:3)[b]
1	CF_3CO_3H / Na_2HPO_4	CH_2Cl_2	-50	2	>90	2.1 : 1
2	 • 3 H_2O / H_2O_2	CH_2Cl_2	25	12	10	1.5 : 1
3		CH_2Cl_2	25	24	90	2.0 : 1
4		CH_2Cl_2	0	6	80	1 : 1
5	MCPBA	CH_2Cl_2	0	4	>95	4.1 : 1
6	MCPBA 3A mol. siev.	Toluene	-30	48	80	9 : 1

[a]Determined by 200 MHz ^{1}H NMR. [b]Determined by 200 MHz ^{1}H NMR and HPLC of the crude product.

The optimization of the reaction conditions, with MCPBA as the oxidant, have shown that the number of equivalents of peracid, the concentration of the substrate, the excess of *m*-chlorobenzoic acid and the presence of a buffer (Na_2HPO_4) had no effect on the selectivities of the epoxidation. Conversely, it is possible to favor one diastereomeric transition state by lowering the reaction temperature and to promote the hydrogen bond effect by using a less polar solvent. So when the reaction was performed in toluene at -30 °C a 9 : 1 mixture of diastereomers[14] was obtained in 80% yield along with 15% of recovered starting material (entry 6).[15] The level of stereochemical induction reported here is one of the highest known for the epoxidation reaction of trishomoallylic alcohols. Mechanistic studies are under investigation with different substrates in order to find out salient interactions which can account for the opposite face selectivity relative to the delivery of the carbenoid species in the cyclopropanation reaction. Conversion of epoxide 2 into glycolipids will also be reported in due course.

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14. The relative stereochemistry of the oxiranne was determined by comparison with authentic sample prepared from glycosylation of (2*S*-*trans*)-3-Methyloxiranemethanol (ref. 3b).
15. To a suspension of 100 mg (0.198 mmol) of trans-crotyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranose and 100 mg of powdered activated 3 A mol. siev. in 16 mL of toluene at -40 °C was added a 0.3M solution of MCPBA in toluene over 15 min. The mixture was stirred at -30 °C for 2 days and then quenched by successive addition of solid $NaHCO_3$, sat. aq. $NaHSO_3$ (1 mL). After a ususal extractive work-up, the residue was purified by flash chromatography on silica gel using Et_3N-EtOAc-$CHCl_3$ (1:5:94) as eluent to afford 82 mg (80%) of the desired epoxides (9:1 mixture of diastereomers) and 15.8 mg (15%) of unreacted starting material: ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.26 (m, 13 H, $H_{arom.}$), 7.19-7.16 (m, 2H, $H_{arom.}$), 4.95 (d, *J* = 11 Hz, 1 H, CH_2Ph), 4.84 (d, *J* = 11 Hz, 1 H, CH_2Ph), 4.84 (d, *J* = 11 Hz, 1 H, CH_2Ph), 4.61 (d, *J* = 12 Hz, 1 H, CH_2Ph), 4.54 (d, *J* = 11 Hz, 1 H, CH_2Ph), 4.54 (d, *J* = 12 Hz, 1 H, CH_2Ph), 4.29 (d, *J* = 7 Hz, 1 H, $CHOC_4H_7O$), 3.99 (dd, *J* = 12, 4 Hz, 1H, $CH_2C_3H_5O$), 3.80 (dd, *J* = 12, 3 Hz, 1 H, $CH_2C_3H_5O$), 3.74 (dd, *J* = 11, 2 Hz, 1H, CH_2OBn), 3.69 (dd, *J* = 11, 4 Hz, 1 H, CH_2OBn), 3.62-3.53 (m, 3 H, $CHOBn$, $CHOH$), 3.51-3.47 (m, 1 H, $CHCH_2OBn$), 3.04 (dq, *J* = 5, 2 Hz, 1 H, $CH_2CHOCHCH_3$), 2.95-2.92 (m ,1 H, $CH_2CHOCHCH_3$), 1.34 (d, *J* = 5 Hz, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 138.1, 128.4, 128.4, 128.4, 127.9, 127.8, 127.8, 127.7, 127.6, 103.3, 84.5, 77.4, 75.2, 75.1, 75.0, 74.8, 73.5, 68.9, 68.8, 57.5, 52.3, 71.2.