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First Sharpless Epoxidation of Electrophilic 2-Cyanoallylic Alcohols.

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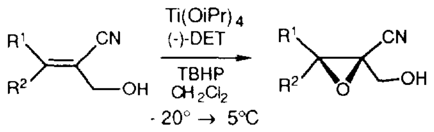
Abstract: For the first time we describe the synthesis of asymmetric cyano epoxy alcohols in good yield and high enantiomeric excess via a Sharpless epoxidation of electrophilic 2-cyanoallylic alcohols.

We have recently defined a new procedure for the preparation of 2-cyanoallylic alcohols which were very poorly represented until now.[1] We now describe the first results obtained running the Sharpless epoxidation on these olefins bearing a powerful withdrawing substituent.

At the moment the accepted mechanism for the Sharpless epoxidation[2] involves a nucleophilic attack by the π electrons of the olefin on the electrophilic oxidizing agent (i.e. the complexed TBHP). As a consequence, electrophilic 2-cyanoallylic alcohols seemed poor candidates for the Sharpless asymmetric epoxidation. However, Marko et al. successfully applied the Sharpless procedure to obtain a kinetic resolution of chiral allylic alcohols bearing in the 2 position an ester or a ketone residue ; however they observed that the reaction was ineffective when the allylic alcohols were substituted in the 2 position by a nitrile substituent.[3] At the same time we were investigating the Sharpless epoxidation on some of our achiral 2-cyanoallylic alcohols and we obtained the following results.

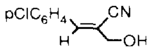
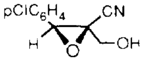
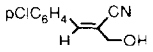
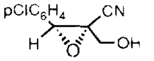
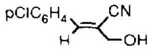
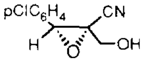
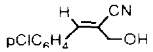
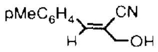
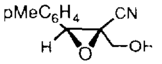
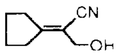
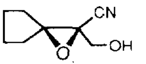
Under the standard Sharpless conditions (i.e. temperature about -20°C), we observed a very slow rate of epoxidation. However this first "encouraging" result lead us to carry on our study. We modified the procedure by running the reaction at room temperature (of course in all cases the reaction started at -20°C), in this case the epoxide was obtained in a few hours, but it was not stable enough in the reaction medium. Indeed, we isolated, besides the expected epoxide, a ring opened compound resulting from the nucleophilic attack of free isopropanol on the titanium complexed epoxide. Such a side reaction is a common problem in the Sharpless epoxidation that can be overcome by lowering the reaction temperature or by using $Ti(OtBu)_4$ instead of $Ti(OiPr)_4$.[4]



Scheme

We decided to adopt the following procedure : the reactants were mixed at -20°C, the reaction flask was placed into a fridge (temperature about 5°C). These new conditions allowed us to perform the epoxidation of the E isomers with reasonable yields and very good ees. The Z isomer is completely unreactive under these conditions probably due to the higher steric hindrance[5] combined with poor nucleophilicity of our substrates (entry 4). Our first results are summarized in table 1.

Table 1 : Stereoselective epoxidation of 2-cyano allylic alcohols

entry	allylic alcohols	epoxides	tartrate	time (h)	Yield (%)	$[\alpha]^{22}_{D}$	ee* (%, ± 2%)	configuration (C_2, C_3)
1			(-) DET	7	64	+ 99	98	(R, R)
2			(+) DET	7	61	- 99	98	(S, S)
3			(+) DiPT	9	53	- 98	98	(S, S)
4		No reaction	(-) DET	34	0	-	-	-
5			(-) DET	14	60	+96	96	(R, R)
6			(-) DET		49	+ 75	-	(R)

*Enantiomeric excess was measured by using $Eu(hfc)_3$ chiral shift reagent.

As expected the use of (+) or (-) DET led to inverse enantiomers ; the absolute configurations of each enantiomer was assigned following the enantiofacial selective rule of Sharpless.[6] At this time the ee for dialkyl derivatives is not known as we had difficulties in applying the shift reagent method to these substrates.

To the best of our knowledge, these preliminary results are the first examples of successful Sharpless epoxidation of achiral allylic alcohols bearing a nitrile function. The resulting functionalized epoxides are promising intermediates since they can be easily ring opened and decyanurated to lead to various α - α'-functionalized ketones.[7]

These results, in addition with those of Marko et al., show that the Sharpless procedure is not limited to strong nucleophilic allylic alcohols and extend the field of the reaction. We are now working to optimize our reaction conditions (in particular to obtain a total epoxidation of the olefin without subsequent ring opening) and to generalize the procedure to other new 2-cyanoallylic substrates we have prepared.

Experimental Section

Reagents and Methods. ^1H NMR spectra were recorded at 80 MHz on a Bruker WP 80 spectrometer and ^{13}C NMR spectra at 75 MHz on a Bruker AM 300 spectrometer using tetramethylsilane as internal reference. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. High resolution mass spectra were obtained with a Varian Mat 311 mass spectrometer. IR spectra were determined with a Perkin-Elmer 225 or 1420 spectrometer. M.p.s. were taken with a Kofler hot stage apparatus. Optical purities were measured by analyzing the ^1H NMR spectrum in the presence of Eu(hfc)$_3$.[8]

All reactions were maintained under dry nitrogen atmosphere. Anhydrous solvents were used ; CH_2Cl_2 freshly distilled from P_2O_5. Allylic alcohols were prepared according to published procedures.[1] *tert* - butyl hydroperoxide (TBHP) was obtained anhydrous in toluene according to the litterature procedure,[9] starting from commercially available 70% from Aldrich Chemical Co. Ti-(O-i-Pr)$_4$ was used as received from Acros Chimica.

General Procedure. Following the method of Sharpless, an oven-dried 100ml 1-necked round-bottomed flask equipped with a magnetic stirbar was charged with 3.0 g of 3A pellet, activated molecular sieves[10] and 20 mL of dry CH_2Cl_2. The flask was cooled to - 15°C, Ti(O-i-Pr)$_4$ (1.5 mL, 1.42g, 5.0 mmol, via syringe) and L-(+)- diethyl tartrate (1.1mL, 1.24g, 6.0 mmol) in 5mL of dry CH_2Cl_2 were added sequentially with stirring. The reaction mixture was stirred at -15°C for 45min. The 2-cyano allylic alcohols (0.5g, 5mmol,) dissolved in 5mL of CH_2Cl_2 and then TBHP (2.5mL, 10mmol, 4M in toluene) were succesively added by syringe. The mixture was stirred for an additional 2h , the reaction temperature rose to 5°C and the flask was placed for t h in a refrigerator. The reaction was cooled to - 20°C and a 10% aqueous tataric acid solution (15 mL) and 20% aqueous sodium sulfite solution was added while stirring. The stirring was maintained for 2h until the solidified aqueous layer became clear. The two phase mixture was then filtered on Celite pad. The organic layer was separated and the aqueous phase extracted with CH_2Cl_2. The organic extract was washed twice with water, dried over Na_2SO_4, filtered and concentrated, diluted with ether (30 mL), the resulting solution was cooled in ice bath, and 1N sodium hydroxide solution was added. This two phase mixture was stirred at 0°C for 45 min, separated and the organic phase was washed, dried over Na_2SO_4 and concentrated. Purification by column chromatography (silica gel, 3:7 ethyl acetate : hexane yielded the active epoxide which were characterized by comparison with the spectral data of racemic epoxide.[11] Enantiomeric excess was measured by using Eu(hfc)$_3$ chiral shift reagent.

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