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Kinetic Resolution Strategies I : Enhanced Product Enantiomeric Excesses and Yields in Sharpless Epoxidations.

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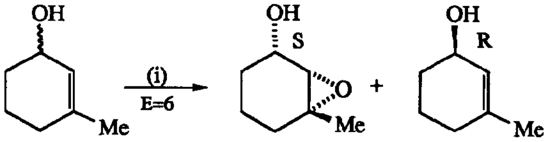
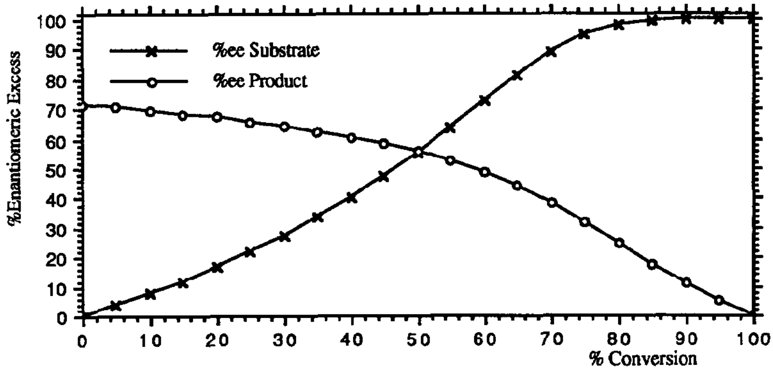
Abstract : The process of kinetic resolution has been considered with the aim of optimising yields and enantiomeric excesses of optically active products. Double kinetic resolution techniques can show significant advantages in these respects over single step processes.

Sharpless epoxidation[1] of the allylic alcohol shown in Figure 1 proceeds with a stereoselectivity factor[2], E of 6. If the product from the epoxidation is considered, the maximum enantiomeric excess obtainable is 71% at an infinitesimally small conversion. As the epoxidation proceeds the starting material becomes enriched in the slower reacting enantiomer and consequently mass action causes the enantiomeric excess of the product to decrease as shown graphically in Figure 1 (-o-o-)

Figure 1 : Sharpless Epoxidation.

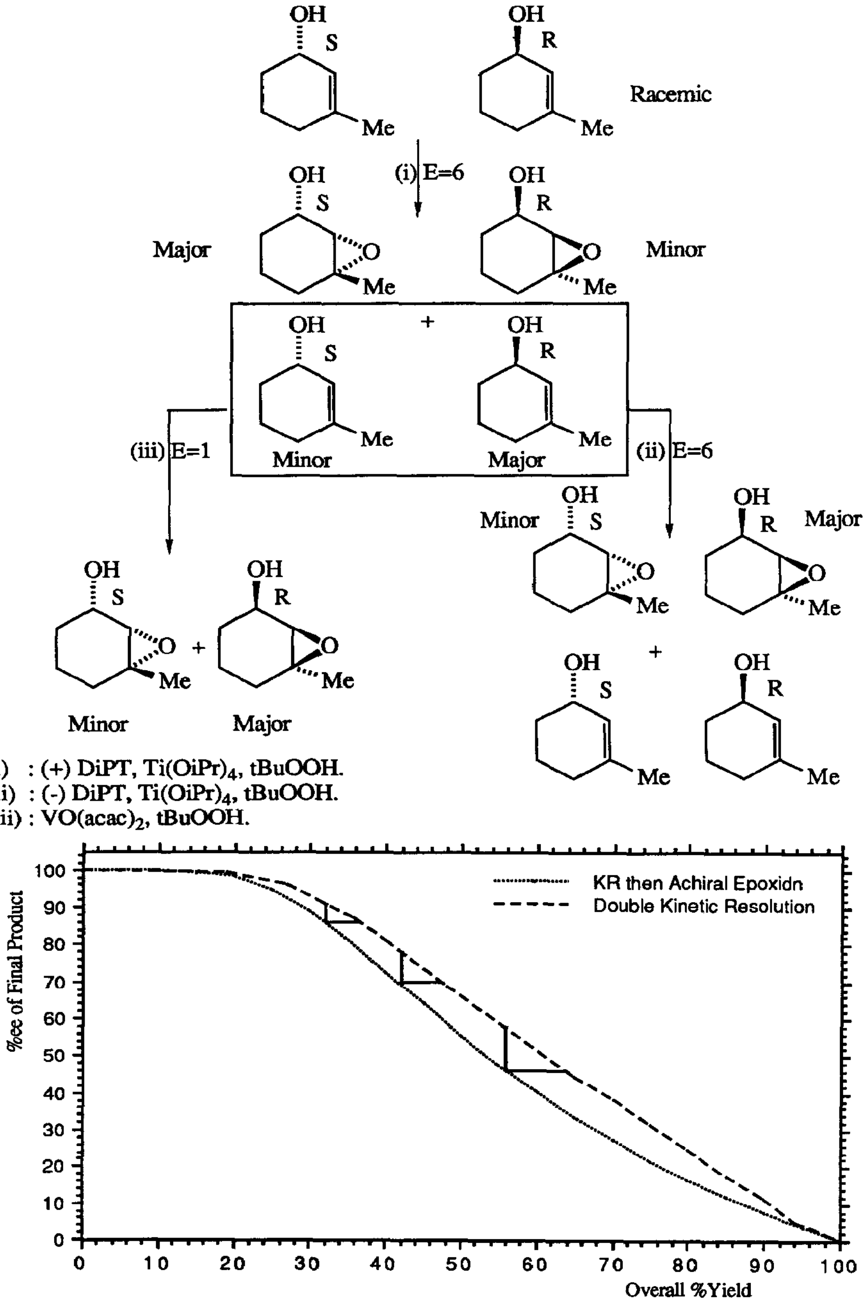


(i) : (+)DiPT, Ti(OiPr)$_4$, tBuOOH, CH$_2$Cl$_2$, sieves.



In contrast to the decreasing enantiomeric excess of the product, the enantiomeric excess of the starting material increases as the reaction progresses [Figure 1 (-x-x-)] reaching levels higher than the products maximum initial enantiomeric excess. Hence, higher product enantiomeric excesses can be obtained by simple non-selective epoxidation (E=1) of the partially resolved starting material, for example with vanadyl acetoacetate [VO(acac)$_2$] and t-butylhydroperoxide[3] as shown in Figure 2. Yield and enantiomeric excess of the product obtained correspond directly to the amount and enantiomeric excess of the recovered starting material.

Figure 2 : Methods of obtaining higher product enantiomeric excesses and yields.



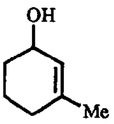
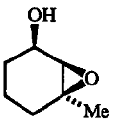
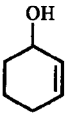
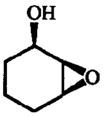
(i) : (+) DiPT, Ti(OiPr)$_4$, tBuOOH.
(ii) : (-) DiPT, Ti(OiPr)$_4$, tBuOOH.
(iii) : VO(acac)$_2$, tBuOOH.

The different concentrations of the two enantiomers of the starting material can however be used to advantage by performing a second kinetic resolution using the opposite enantiomer of the catalyst deployed in the first step. Under these circumstances the enantiomer in which the starting material is enriched is now the faster reacting enantiomer. In this way mass action works to enhance the enantiomeric excess of the product up to the point where the remaining starting material becomes once again racemic.

Obviously the enantiomeric excess of the final product from the double kinetic resolution procedure depends on the stereoselectivity factor and the extent of reaction for each step. A simple computer model was used to simulate a process where E=6; for a given enantiomeric excess the maximum calculated yield is as shown in Figure 2 (----); this line also corresponds to the maximum enantiomeric excess obtainable for a given yield. The difference between the two curves in Figure 2 represents the benefit achievable by using the double kinetic resolution procedure over the single kinetic resolution followed by achiral epoxidation. Taking any point on the single kinetic resolution followed by achiral epoxidation line (····), the vertical separation to the double kinetic resolution line (----) is the enhancement in enantiomeric excess obtainable without detriment to the yield, whilst the horizontal separation between the two lines is the enhancement of the yield obtainable without compromising the enantiomeric excess.

If, for example, product with an enantiomeric excess of 85% is required the yield obtainable by a single kinetic resolution followed by achiral epoxidation = 32%. Whereas for the double kinetic resolution the yield obtainable is 37%. Alternatively, for the same yield of 32% the enantiomeric excess can be increased to 91%. These calculations are valid only for substrates where both enantiomers have the same diastereoselectivites; for the two examples shown below this is known to be the case. However, if the diastereoselectivities are different for each substrate enantiomer the situation is more complicated and this will be dealt with in full elsewhere.

Table 1 : Enantiomeric Excess of Products obtained from Double Kinetic Resolutions.

Substrate	Conversion[c]		Reactant		Product		Selectivity Factor	Final product
			%ee[a]	%yield[f]	%ee[a]	%yield[f]		
	1st Step	58%	ca69(R)[d]	31	50(S)	41	6[b]	
	2nd Step	86%	ca38(S)[d]	10	**86(R)**	59	6[g]	
	1st Step	61%	44(R)	31	33(S)	38	3[b]	
	2nd Step	59%	5(R)	41[e]	**70(R)**	59[e]	3[g]	

(a) : Calculated by conversion to MTPA ester[5] followed by ^{19}F NMR, ^{1}H NMR, or HPLC. (unless otherwise indicated) (b) : Calculated with respect to the reactant from the standard formula[2]. (c) : Calculated by GC of the reaction mixture. (d) : Estimated from the specific rotation[6]. (e) : GC Yield. (f) : Isolated Yield. (unless otherwise indicated) (g) : Derived by fitting the experimental data with that obtained by simple iterative calculations.

All the above are theoretical considerations and do not take into account practical problems such as side reactions depleting yields, and isolation and recovery difficulties. However, it should be noted that the only difference between the single kinetic resolution followed by achiral epoxidation and the double kinetic resolution process is the catalyst used in the second step: in particular the same number of isolation and separation steps are involved. The theoretical benefits should therefore reflect realisable enhancements in practice.

Practical applications of the double kinetic resolution procedure were performed on two allylic alcohols both with rather modest stereoselectivity factors; the results are as in Table 1. In each case the allylic alcohol was first partially resolved using the (+)tartrate system and then the recovered substrate was epoxidised using the (-)tartrate system.

The computer model shows that, as the stereoselectivity factor increases for a kinetic resolution, the benefits of applying the double kinetic resolution technique diminish such that when E>50 there are no real improvements over conventional methods.

The main criterion that is required for the double kinetic resolution technique to be used is that both optical forms of the chiral reagent or chiral catalyst are available. Enhanced enantiomeric excesses and yields can be obtained using the Noyori RuBINAP hydrogenation of allylic alcohols[4] since both enantiomers of BINAP are readily available, alternatively a combination of the Sharpless and Noyori systems may be deployed. During our work we observed that a Sharpless epoxidation could be performed in the presence of the Noyori catalyst whereas the Noyori catalyst was unable to function in the presence of the Sharpless reagents.

Isolated examples of enantioselective reactions and kinetic resolutions performed on partially resolved substrates have been reported[4,7] but the potential of the concept, and benefits in enantiomeric excess and yield obtainable, have not been widely exploited.

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