A Simple Method for enriching the Enantiomeric Purity of a Functional Molecule already Rich in One Enantiomer

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1-Naphth-1-ylethanol **1** of 92% enantiomeric excess (e.e.) can be raised to 99.6% e.e. in an overall yield of 78% by attaching it to oxalyl chloride, separating the *lk* diester from the *ul* by crystallisation, and hydrolysing the diester; the method is potentially general for functional molecules that can easily be attached to and then taken off a bifunctional reagent.

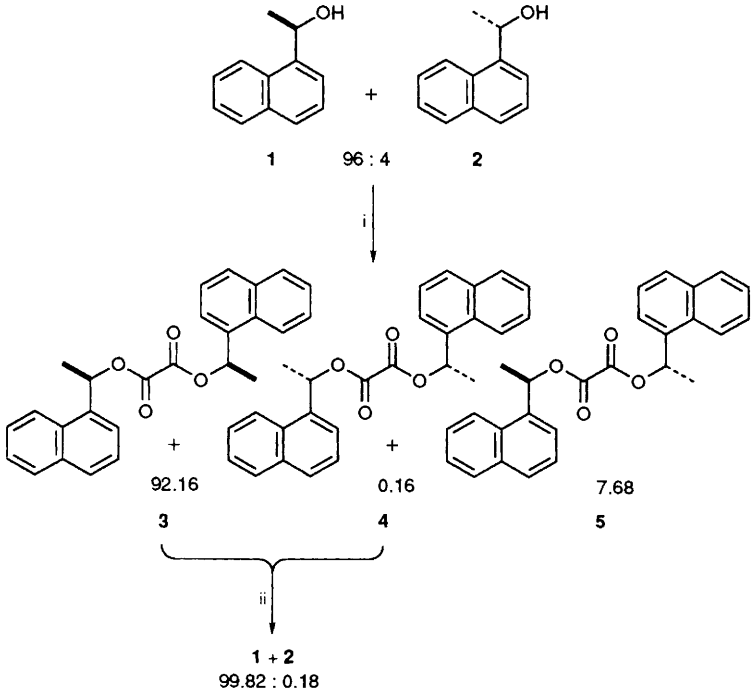
If an unequal mixture of the enantiomers of a functional molecule is attached to an achiral bifunctional molecule, there are three possible 2 : 1 products: the *RR* and its enantiomer the *SS*, and a diastereoisomer, the *RS*. If the mole fraction of the *R* isomer is x, then the ratios of the three products *RR* : *SS* : *RS*, assuming that there is no chiral recognition, is $x^2 : (1 - x)^2 : 2(1 - x)$. Thus the ratio of diastereoisomers can be used to measure the ratio of enantiomers without having to use a chiral auxiliary, a well-established technique.[1] The same fundamental idea has been expressed algebraically,[2,3] graphically[4] and preparatively[5] in showing how kinetic resolution coupled to asymmetric synthesis on bifunctional prochiral compounds can give non-linear improvements in stereoselectivity.

We now report that the same binomial algebra can be exploited to enrich the enantiomeric purity of an incompletely resolved functional compound. Provided that the diastereoisomeric intermediates can be separated, the ratio of enantiomers will be raised from $x : (1 - x)$ to $x^2 : (1 - x)^2$. To give a sense of what can be achieved, we record in Table 1 the minimum improvements that can be expected statistically, together with the maximum theoretical yield. The improvement in the enantiomeric excess (e.e.) is, of course, most conspicuous when the e.e. is already quite high. This device has been used by Brown to improve the enantiomeric purity of pinene and other alkenes, but the algebraic basis of the idea was not spelled out in his paper, which was in any case about an unusual situation in which the *R* and *S* isomeric boranes in question were in equilibrium.[6]

We illustrate such a sequence in practice using the (*R*)-naphthylethanol **1**, which we needed in a state of high enantiomeric purity. We repeated Theisen and Heathcock's procedure[7] for preparing it—enzymatic esterification using porcine pancreatic lipase and 2,2,2-trichloroethyl butyrate, followed by alkaline hydrolysis of the butyrate. They reported that they obtained the alcohol **1** optically pure. In our case, we obtained alcohol in 76% yield but of only 92% e.e., as measured on a β-cyclodextrin capillary GC column. This material was not good enough for our purpose.

We treated the 96 : 4 mixture of alcohols **1** and **2** with oxalyl chloride and obtained a mixture of the three possible diesters **3**, **4** and **5** in 100% yield (Scheme 1). Assuming that there is no chiral recognition, the statistical probability for the formation of these isomers is given by the numbers $(0.96)^2 : (0.04)^2 : (2 \times 0.96 \times 0.04)$, which means that we can expect 92.16% of **3**, 0.16% of **4** and 7.68% of **5**. The *R,R* and *S,S* diesters **3** and **4** could be separated easily from their diastereoisomer **5**, because they crystallised. The ester **5** remained as an oil, and we deliberately gave it no opportunity to crystallise. Recrystallisation gave the esters **3** and **4**, in 91% yield, free of the diastereoisomer **5**, as judged by the ^{1}H NMR spectrum. Two further recrystallisations gave material of mp 124–125 °C in an overall yield of 78%.

Alkaline hydrolysis of this mixture of esters **3** and **4**, an exceptionally easy process with oxalate esters, gave the mixture of alcohols **1** and **2** in 100% yield, and in a ratio of 99.8 : 0.2, identical within experimental error to the statistical ratio of 99.83 : 0.17 (Table 1, entry 7). Since the recrystallisa-



Scheme 1 *Reagents and conditions*: i, $(COCl)_2$, pyridine, DMAP, CH_2Cl_2, room temp., 3 h, 100%; ii, 1 mol dm^{-3} KOH, EtOH, H_2O, room temp., 2.5 h, 100%

Table 1 Improvements in e.e. theoretically possible using attachment to a bifunctional reagent, separation only of the diastereoisomers, and regeneration

Starting e.e. (%)	Finishing e.e. (%)	Yield (%)
20	38.5	52
40	69.0	58
60	88.2	68
70	94.0	75
80	97.6	82
90	99.4	91
92	99.7	92
96	99.9	96
98	99.98	98

tions may have been increasing the proportion of the enantiomer **3** relative to the enantiomer **4**, as well as removing the last traces of the diastereoisomer **5**, we could not at this stage say whether this is a coincidence or not. However, the separation of the diastereoisomer **5** had achieved our aim and enriched the enantiomeric purity of the alcohol **1** from 92% e.e. to 99.6% e.e. with an overall yield of 78%. The specific rotation of this material was $[\alpha]_D^{20}$ + 87.9 (*c*. 1.0, in Et_2O).

Like Theisen and Heathcock, we also recovered from the enzymatic reaction a mixture rich (88.1% e.e.) in the enantiomeric alcohol **2** in 74% yield. Mitsunobu reaction on this alcohol using *p*-nitrobenzoic acid,[8] and alkaline hydrolysis of the derived ester gave another mixture of the alcohols **1** and **2**, in 77% yield, rich in the enantiomer **1**, but now of only 80% e.e. We were able to repeat the same procedure using oxalyl chloride with this inferior material, and obtained, after *four* recrystallisations, followed by alkaline hydrolysis, another crop of alcohol **1** with the enantiomers in a ratio of 98.96 : 1.04 in an overall yield of 61%. In this case, starting from material with the enantiomers in a ratio of 90 : 10, the statistical ratio of **1** : **2**, if the recrystallisations were only removing the diastereoisomer **5**, would be 98.8 : 1.2 (Table 1, entry 5), so there must have been some concentration of the enantiomer **3** as well as removal of the diastereoisomer **5**. In agreement with this conclusion, the same procedure but using five, six and seven recrystallisations gave material of successively 99.3, 99.8 and 99.9% e.e. in overall yields of 57, 53 and 49%. We chose to use the material that had been recrystallised six times as the best compromise between yield and e.e. Thus by combining the two crops, we obtained overall, from the racemic mixture of alcohols **1** and **2**, the alcohol **1** of 99.7% e.e. in 44% conversion. Since we also recovered 23% of unchanged racemic alcohol, the overall yield is actually 57%.

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