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A tandem asymmetric synthesis approach for the efficient preparation of enantiomerically pure 9-(hydroxyethyl) anthracene

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ABSTRACT

A tandem approach for the preparation of gram quantities of enantiomerically pure 9-(hydroxyethyl)-anthracene is presented using an asymmetric reduction followed by kinetic resolution that has potential applicability to other chiral alcohols.

1. Introduction

Non-racemic chiral anthracenes, such as alcohol **1**, have numerous applications in synthetic chemistry including acting as chiral solvating agents;[1] perhaps the most well known of these is Pirkle's alcohol **2**, 9-(hydroxytrifluoroethyl)anthracene (Fig. 1). [2] In recent years, research from our group and others has championed the use of anthracene derivatives such as 9-(methoxyethyl)anthracene as chiral auxiliaries,[3] the role of the stereodirecting group being to both control the diastereoselectivity of an initial cycloaddition reaction, in addition to ensuring that high levels of regioselectivity are achieved in any subsequent asymmetric transformations.

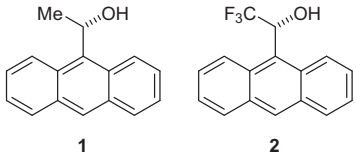
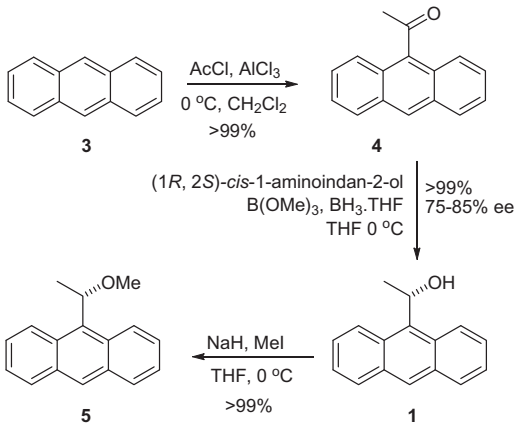


Figure 1. Chiral anthranyl carbinols.

A key feature of this methodology is being able to achieve the rapid and enantioselective preparation of the target auxiliary in high yield. This is generally conducted by Friedel–Crafts acylation of anthracene, followed by the asymmetric reduction of ketone **4** and O-methylation with sodium hydride and methyl iodide (Scheme 1).[3a]

Although the first and last steps are almost quantitative in yield, obtaining large quantities of alcohol by an asymmetric reduction process can be time consuming and challenging. Our established approach involves the reduction of ketone **3** using borane and an oxazaborolidine catalyst derived from *cis*-1-aminoindan-2-ol, which can provide the desired alcohol in almost quantitative yield and with an enantiomeric excess ranging from 75% to 85%. This mirrors a method originally reported by Reiners and Martens using a different oxazaborolidine, where good enantioselectivities are reported (90% ee) but no reference is given to the yield or to the conditions for the purification.[4] Other reported enantioselective routes to alcohol **1** include hydrosilylation (90% ee),[5] hydrogenation (80% ee),[6] hydroboration (87.5% ee)[7] and transfer hydrogenation (60% ee).[8] A single report details the preparation of alcohol **1** in excellent yield (92%) and >99.9% ee using 10 mol % of the traditional *B*-OMe CBS oxazaborolidine and borane *N*,*N*-diethylaniline complex as the reductant, employing only chromatography to purify the product.[9] We became interested in this latter route since it would considerably improve the efficiency of the synthesis of the key intermediate used to access our auxiliary.



Scheme 1. Standard synthesis of enantiopure ether **5**.

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2. Results and discussion

The preparation of alcohol **1** was undertaken by repeating the conditions used by Bichlmaier, with the use of 10 mol % of the *B*-OMe CBS oxazaborolidine and borane *N*,*N*-diethylaniline complex, with the slow addition of a solution of ketone to the activated catalyst. However, two separate experiments gave enantiomeric excesses of 90.6% (86% yield after column chromatography) and 86.8% (78% yield after column chromatography) using this procedure. Using the same *B*-OMe CBS catalyst but with borane-dimethylsulfide gave 84.3% ee, which is comparable to the results that we usually obtained using the oxazaborolidine derived from *cis*-1-aminoindan-2-ol and borane-dimethylsulfide.

Upgrading the ee of the material from any of these reactions to obtain a single enantiomer by recrystallisation is tedious and low yielding. Thus, in a typical experiment, alcohol **1** obtained in 80% ee from the asymmetric reduction requires three successive recrystallisations from petroleum ether/ethyl acetate to improve the ee to >99%. This leads to an overall yield from this reaction of only 44% and the whole process takes approximately 3 days to complete.

We wondered whether we could improve this process by upgrading the ee of the scalemic material obtained from the asymmetric reduction process through a kinetic resolution process. If a suitably efficient process could be identified, this would both save time and improve the yield of the reaction. Of the numerous options available to us for this type of process, the work described by Fu using planar chiral ferrocene complexes appeared to be the most attractive.[10] Initial experiments were aimed at determining which pair of enantiomers of catalyst and substrate would result in a matched pairing. Thus, (*S*)-alcohol **1** of 80% ee was treated with both enantiomers of catalyst **6** under the standard conditions described by Fu, using acetic anhydride (Scheme 2, Table 1, entries 1 and 2). As a result, (*S*)-**6** performed as required, providing high ee material (entry 1). However, it is important to note that even the mis-matched catalyst (*R*)-**6** provided some level of enhancement. The matched pair, however, performed exceptionally, with the alcohol of lower ee being upgraded just as effectively (entries 3 and 4). However, the alcohol and ester products from this reaction were inseparable by column chromatography and crystallisation, thus making the procedure impractical. An attempt to directly methylate a mixture of alcohol **1** and ester **7** using NaH and methyl iodide gave a mixture of alcohol **1**, ester **7** and ether **5**, which after separation gave ether **5** in 85% enantiomeric purity. This may be as a result of transesterification during the methylation step, ultimately leading to apparent partial epimerization .

In order to circumvent this issue, we examined other acylating agents. Use of, $(i\text{-PrCO})_2O$ did not give as high enantioselectivity as $(MeCO)_2O$ in line with the literature reports of this reagent (96% and 92% ee, entries 5 and 6),[11] however, alcohol **1** and ester **7** products were now separable. Furthermore, the enantiomeric excess of alcohol increased by 3% during the purification stage, leading to alcohol of 95% ee in 70% overall yield (entry 6). Such enhancements of enantiomeric excess are well documented and understood for crystallization processes,[12] but to our knowledge this appears to be the first documented report of this phenomenon.

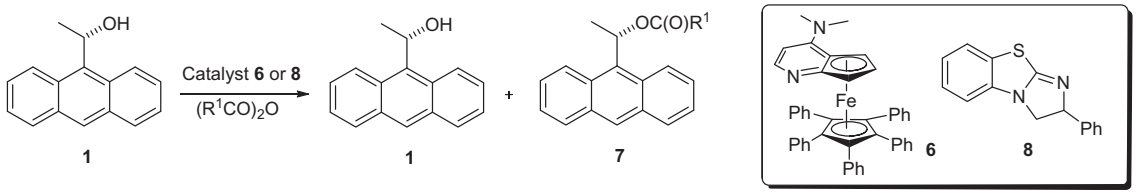
Armed with this knowledge, $(EtCO)_2O$ was employed as an acyl source, since this should lead to similar enantioselectivities to $(MeCO)_2O$, but may be more easily separable from the residual alcohol during purification. This was indeed the case (entries 7–8), yet again with a concomitant further upgrade of ee during purification. Essentially a single enantiomer of the product was obtained in approximately 70% yield over two steps from ketone **4**, with the whole process taking just under one day to complete.

Although this result was encouraging, the high cost of the Fu catalyst coupled with its relatively high molecular mass led us to consider an alternative. We were attracted by recent reports from Birman on the preparation and application of relatively simple, yet very efficient and selective acylation catalysts.[13] Furthermore, the selectivity profile of the anhydrides used in these systems mirrored that observed by Fu, which should facilitate the necessary upgrade in ee observed with the latter. Both enantiomers of the third generation catalyst **8** were prepared according to the literature procedure[13d] and evaluated in the kinetic resolution procedure

Table 1
Kinetic resolution of scalemic alcohol **1**[a]

Entry	Alcohol substrate **1** (configuration, ee)	Catalyst	Catalyst loading (mol %)	R^1	ee crude alcohol **1**[b] (%)	ee purified alcohol **1** (%)	Yield purified alcohol **1** (%)
1	(*S*) 80	(*S*)-**6**	1	Me	>99	—	—
2	(*S*) 80	(*R*)-**6**	1	Me	−91	—	—
3	(*R*) 75	(*R*)-**6**	1	Me	99	—	—
4	(*R*) 33	(*R*)-**6**	2	Me	>99	—	—
5	(*R*) 75	(*R*)-**6**	5	*i*-Pr	96	—	—
6	(*S*) 80	(*S*)-**6**	2	*i*-Pr	92	95	70
7	(*R*) 75	(*R*)-**6**	5	Et	97	99	68
8	(*S*) 75	(*S*)-**6**	5	Et	97	99	72
9	(*R*) 74	(*R*)-**8**	5	Et	33	—	—
10	(*S*) 76	(*R*)-**8**	5	Et	96	98	70
11	(*R*) 81	(*S*)-**8**	5	Et	98	99	67

[a] Reactions performed with catalyst **6** used anhydride (0.75 equiv), Et_3N (0.75 equiv) in *t*-amyl alcohol (5 cm^3/mmol alcohol) at 0 °C for 6 h. Reactions with catalyst **8** used anhydride (0.75 equiv), DIPEA (0.75 equiv) in dry $CHCl_3$ (3 cm^3/mmol alcohol) at 0 °C for 6 h.
[b] Enantiomeric excess determined by chiral phase HPLC using an Chiralcel OD column, 5% *i*-PrOH/hexane at 1 mL min^{-1}; details; R_t (*R*) 14.94 min, (*S*) 24.05 min.



Scheme 2. Kinetic resolution of alcohol **1**.

(entries 9–11). Selectivities and yields comparable to those obtained with the Fu system were obtained but with a significant reduction in the cost of the catalyst. The effectiveness of this two step procedure was demonstrated by transforming 1.00 g of ketone into 0.62 g of alcohol (70% yield) of 98% ee in a little over one day.[14] This is a significant improvement on the conventional sequential recrystallisation route, whereby only 0.40 g of alcohol of similar ee is obtained after 4 days.

3. Conclusion

In conclusion, we have developed a highly effective procedure for the rapid, cost effective synthesis of alcohol **1** in enantiomerically pure form. This procedure, therefore, offers significant savings in terms of cost and time and could be of general applicability for obtaining high yields of single enantiomers of chiral alcohols.

Acknowledgments

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14. Typical experimental procedure: *(S)-1-Anthracen-9-yl ethanol* **1**: At first, $B(OMe)_3$ (3.1 cm^3, 2.9 g, 28 mmol) was added to a solution of (1*R*,2*S*)-1-aminoindan-2-ol (0.4 g, 3 mmol, freshly crystallised with toluene) in dry THF (2 cm^3) and stirred at rt for 0.5 h. Next, BH_3.DMS complex (2.7 cm^3, 2.2 g, 28 mmol) in dry THF (2 cm^3) was added and the resulting solution cooled to 0 °C before the addition of 1-anthracen-9-yl ethanone **4** (5.0 g, 23 mmol) in dry THF (5 cm^3). The reaction mixture was stirred for 12 h at 0 °C, quenched by the slow addition of MeOH (20 cm^3) and allowed to warm to rt. Water was added (20 cm^3) and the product extracted with CH_2Cl_2 (3 × 20 cm^3), washed with 1 M HCl (10 cm^3) and water (10 cm^3) and the organic extracts dried over $MgSO_4$. Filtration and removal of the solvent gave the title compound (*S*)-**1** (5.1 g, 100%, 75% ee) as an orange solid. Repeated recrystallisation from CH_2Cl_2/petroleum ether 40–60 afforded a yellow-orange powder (2.0 g, >99.8% ee); $[\alpha]_D^{22} = -19$ (*c* 1, $CHCl_3$) [lit.[4] −18.8, (*c* 1.1, $CHCl_3$) ee >99% (*S*)-enantiomer]. *Kinetic resolution using (R)-***8** *with (S)-alcohol* **1**: To a solution of (*S*)-alcohol **1** (1.0 g, 4.5 mmol) in dry $CHCl_3$ (15 cm^3) at 0 °C, was added a solution of (*R*)-**8** (56.7 mg, 225 μmol) and DIPEA (0.6 cm^3, 3.4 mmol, freshly distilled from CaH_2) which was followed by the addition of $(EtCO)_2O$ (3.1 cm^3, 3.4 mmol). The reaction mixture was allowed to react at 0 °C for 6 h and then quenched with a saturated solution of NH_4Cl (5 cm^3). The resulting mixture was separated and extraction carried out with CH_2Cl_2 (3 × 20 cm^3), washed with brine (3 × 15 cm^3) and the organic extracts dried over $MgSO_4$. Filtration and removal of the solvent gave a mixture of alcohol **1** and ester **7**. The crude material was purified by column chromatography (90% petroleum ether 40–60/EtOAc) to give alcohol **1** as an orange powder (618 mg, 70%, 98% ee).