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Dynamic kinetic asymmetric synthesis of β-aminoalcohols from racemic epoxides in cyclodextrin complexes under solid state conditions†

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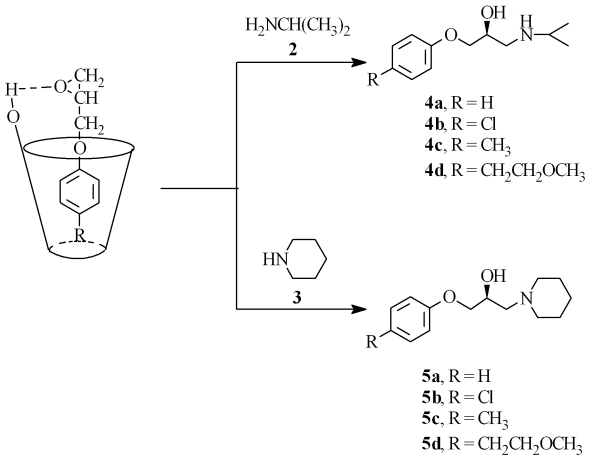
It has been shown for the first time that enantiopure β-aminoalcohols can be prepared from racemic epoxides by dynamic kinetic resolution involving enantio-differentiating racemisation in cyclodextrin complexes under solid state conditions.

The novel phenomenon of converting racemic substrates into a single enantiomer of the product by dynamic kinetic resolution *via* racemisation of the substrates has been a formidable challenge in asymmetric synthesis.[1] Recently, it has been receiving increasing attention and attempts are being made to achieve every useful asymmetric synthesis by dynamic kinetic resolution since it overcomes the severe limitation of the conventional kinetic resolution where the maximum yield of one stereoisomer of the starting material or product is only 50%. But, so far there is no report on the dynamic kinetic asymmetric synthesis of β-aminoalcohols of great significance from the easily accessible and inexpensive racemic epoxides. The β-aminoalcohol moiety is present in many natural products and drugs and acts as an intermediate in various asymmetric transformations.[2] The approaches hitherto reported from the racemic epoxides involve only kinetic resolution.[3] Further to our studies on cyclodextrins as chiral templates for the enantioselective synthesis of a variety of chiral building blocks,[4] we report herein the first biomimetic approach for the synthesis of a single enantiomer of β-aminoalcohols from the corresponding racemic epoxides by dynamic kinetic resolution involving enantio-differentiating racemisation in cyclodextrin complexes.[5]

The cyclodextrins are cyclic oligosaccharides possessing hydrophobic cavities and they mimic enzymes in their capability to bind substrates selectively and catalyse chemical reactions by supramolecular catalysis involving reversible formation of host–guest complexes with substrates through non-covalent bonding. Apart from this, with the cyclodextrin cavity being chiral it can induce asymmetric reactions.[6] It requires the following criteria to be fulfilled to ensure rigidity for chiral recognition by cyclodextrins: (i) a phenyl ring which can fit into the cyclodextrin cavity to form an inclusion complex, (ii) a functional group at the stereogenic center to form a strong interaction at the cyclodextrin cavity entrance. Since aryloxyepoxides **1** fulfil these criteria, they have been chosen as substrates.

The inclusion complexes of aryloxyepoxides **1** with β-cyclodextrin (β-CD) were prepared as described earlier.[4] The reaction of these cyclodextrin complexes of epoxides **1** with amines **2** or **3** (Scheme 1) when carried out in water as the reaction medium, yielded aminoalcohols that were nearly racemic (ee 2%). This may be due to free movement of the guest molecule in solution. Hence, it was planned to carry out these reactions in the solid state where the movement of the guest molecule would be restricted, resulting in better chiral recognition.

An intimate mixture of the epoxide **1**–β-cyclodextrin complex (1:1) and the amine **2** or **3** was mixed in equimolar amounts in an agate mortar using a pestle and the mixing continued until the starting epoxide disappeared on TLC (3–12 h). The time taken was always dependent on the frequency of mixing. However, in the case of amine **2**, it was added in excess due to its volatility and was added intermittently during the course of mixing. The resulting aminoalcohols **4** and **5** were extracted with ethyl acetate and purified through the formation followed by release of their hydrochlorides. The isolated yield of the product was always in the range 70–79% and the enantioselectivity was excellent in some of the compounds (Table 1). Compounds **4b** and **5b** have shown 100% ee followed by compound **4c** (ee 89%) and **4d** (ee 85%). The enantiomeric excesses (ee) of the products (**4** and **5**) were determined by chiral HPLC analysis. These aminoalcohols **4** and **5** have been shown to have *R* configuration by comparison of the sign of rotation with those of the known compounds.[7] However, these reactions when carried out using α-cyclodextrin inclusion complexes, gave enantioselectivities that were far lower than those obtained with β-cyclodextrin. This may be due to ineffective complexation.



Scheme 1

The formation of enantiopure β-aminoalcohols (**4** and **5**) from the racemic epoxides **1** may be postulated as follows:

Table 1 Solid state asymmetric synthesis of β-aminoalcohols

Entry	Product	ee (%)[a]	Yield (%)[b]
1	4a	73.8	79
2	4b	100	75
3	4c	89	72
4	4d	85	70
5	5a	1.4	74
6	5b	100	70
7	5c	0.8	76
8	5d	3.5	73

[a] Determined by HPLC analysis with the chiral column 'Diacel Chiralcel OD' (0.46 cm ϕ × 25 cm) using hexane: propan-2-ol: diethylamine (80:20:0.1) as eluent at a flow rate of 0.5 ml min^{-1} using UV detection (254 nm). [b] Isolated yields.

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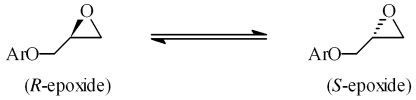
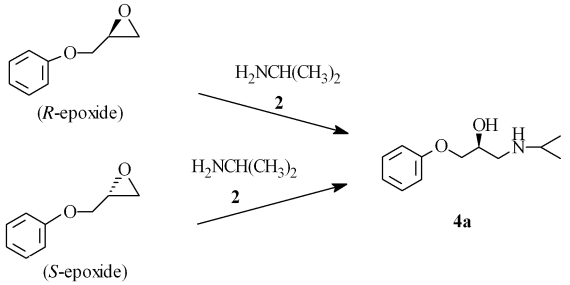


Scheme 2

The fact that the epoxide **1** isolated from the cyclodextrin complex is racemic and the yields of the aminoalcohols **4** and **5** were always more than 50%, suggests that kinetic resolution is not operating under these conditions as then only a maximum of 50% conversion can be expected. Hence, in the present investigation, to get a single enantiomer of the product (**4** or **5**) from the racemic starting epoxide **1**, it requires interconversion of one of the enantiomers of the epoxide **1** (Scheme 2). This is possible through racemisation which is controlled by entropy effects.[8] Racemisation can take place in the present case by the interconversion of the epoxide enantiomer facilitated under solid state conditions. Though racemisation is quite a slow process in the absence of suitable driving mechanism *i.e.* the external amine in the present case, the racemisation of the β-CD complexes of the individual *R* and *S* epoxides of **1a** (R = H) has been attempted by grinding them intimately for 5 h and analysing by chiral HPLC.[9] It is observed that racemisation does indeed take place only with *S*-enantiomer to an extent of ≅2% as seen by the change in %ee. This reaction also further substantiates the process of dynamic kinetic resolution *i.e.* as the *R*-enantiomer of the epoxide (**1**) in the CD complex reacts with the amine, the *S*-epoxide gets converted to the *R*-epoxide to take the reaction forward, leading to only the *R*-enantiomer of the product (**4**).

Thus, when one of the enantiomeric forms of the epoxide **1** in the β-cyclodextrin cavity, due to its favourable geometry, is captured selectively by the external amine (**2** or **3**), the phenomenon of dynamic kinetic resolution sets in under the reaction conditions. Hence, by dynamic kinetic resolution through racemisation of the starting epoxide, it is possible to get enantiomerically pure aminoalcohols (**4** and **5**). This has also been confirmed from the individual experiments utilizing either *R* or *S* epoxides (Scheme 3). Both *R* and *S* epoxides gave the aminoalcohol (**4a**) mainly as the *R* enantiomer (90% ee by HPLC). This gives further evidence to show that racemisation of the starting epoxide and dynamic kinetic resolution are operating under the reaction conditions to give a single enantiomer of the product.

Thus, in conclusion, it has been shown for the first time that enantiopure β-aminoalcohols of high potential can be made from the easily accessible and inexpensive racemic epoxides. This can be achieved by dynamic kinetic resolution involving



Scheme 3

enantio-differentiating racemisation in cyclodextrin complexes under solid state reaction conditions.

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