Towards a continuous dynamic kinetic resolution of 1-phenylethylamine using a membrane assisted, two vessel process

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A continuous process with two separated reaction vessels provides a solution to the problems surrounding the combination of two catalysts in dynamic kinetic resolution reactions by retaining the biocatalyst in a lower temperature vessel with a microfiltration membrane and allowing the racemisation to occur efficiently in a higher temperature vessel.

The search for more efficient chemical processes underlies many contemporary developments both in synthetic chemistry and in chemical engineering. The term "process intensification" is often used to describe the move to smaller, safer, continuous reactors in which high yields and purities are attained, thus adding value to products.[1] Synthetic chemists have taken up the challenge at the molecular level, by developing so-called "tandem reactions". A tandem reaction sequence is one in which more than one bond is formed sequentially, without the isolation of intermediates and without altering the reaction conditions.[2]

Dynamic kinetic resolution (DKR) is a tandem catalytic process of current interest for the syntheses of enantiomerically enriched products. DKR employs a combination of an enzyme catalysed kinetic resolution with a transition metal complex mediated *in situ* racemisation process.[3]

DKR of secondary alcohols is well established, and often uses chemocatalysts such as homogeneous ruthenium transition metals.[4] In contrast, the racemisation of unfunctionalised amines remains more difficult than that of secondary alcohols and therefore requires more harsh conditions.[5] As a result, reports on selective racemisation or DKR of amines are still limited.

Murahashi *et al.* first demonstrated that chiral primary amines such as 1-phenylethylamine can be racemised by the reaction of palladium black in the temperature range 50–100 °C.[6] Following this, Reetz *et al.* reported the first DKR of 1-phenylethylamine employing palladium on carbon in combination with *Candida antarctica* lipase B (CALB, or in immobilised form, Novozym 435).[7] However, the long reaction time (8 days) at 50–55 °C and a modest isolated yield (64%) are shortcomings of this process.

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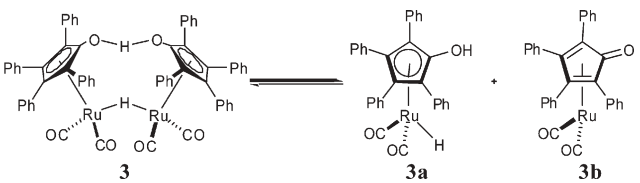
Pàmies *et al.* presented a two step DKR reaction where (*R*)-*N*-(1-phenylethyl)acetamide (*R*)-**1** was prepared by the enzymatic kinetic resolution of (*R*,*S*)-1-phenylethylamine **2** using Novozym 435 and ethyl acetate as the acyl donor. Acetamide (*R*)-**1** was then collected while the remaining amine (*S*)-**2** was extracted and racemised at 110 °C using Shvo complex **3** and 2,4-dimethyl-3-pentanol as a hydrogen donor.[8] Complex **3** is understood to dissociate under thermal conditions to a hydroxycyclopentadienyl hydride (18-electron species **3a**) and a dienone dicarbonyl complex (16-electron complex **3b**) as shown in Scheme 1.[8,9]

Work done by Pàmies and co-workers can be evolved into a continuous DKR reaction by applying the "membrane enhanced dynamic kinetic resolution" (MEDKR) concept. Instead of a two step DKR process, the racemisation can be performed in a high temperature vessel. Fluid can be withdrawn from the racemisation vessel and pumped through a cooling unit before entering a resolution vessel maintained at 30 °C, as shown in Fig. 1.

Increasing the racemisation temperature improves the efficiency of the reaction.[8] However, the enzyme activity is impeded by the rise in reaction temperature.[10] In this MEDKR process, a microfiltration membrane (Durapore®, 0.65 μm DVPP, Millipore, USA) in the resolution vessel retains the immobilised enzyme and prevents it from entering the high temperature racemisation vessel.

Ethyl acetate is the preferred acyl donor for the kinetic resolution as it reacts with amine **2** only when the enzyme is present.[8] However, butyl acetate and pentyl acetate were employed



Scheme 1

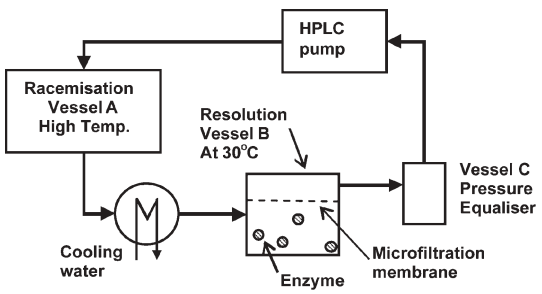
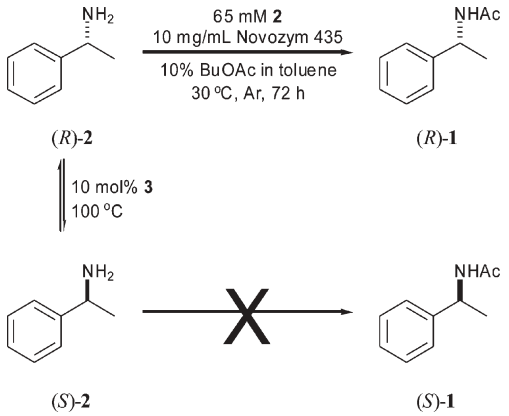


Fig. 1 Schematic of the proposed MEDKR process.



Scheme 2

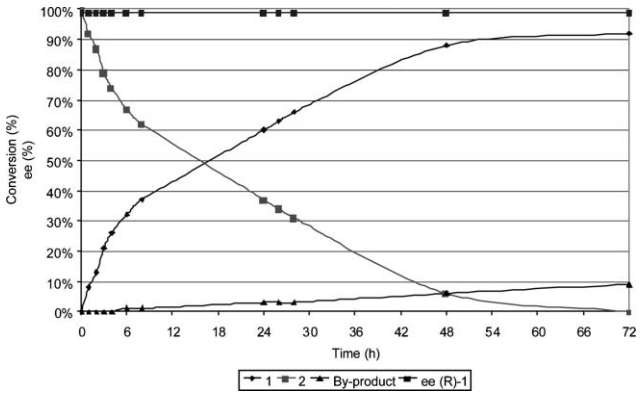


Fig. 2

as the acyl donor in this work as their boiling points are closer to that of toluene, the main organic solvent used. These esters limited the enzyme distortion by keeping the log P value of the combined reaction medium above 2.0, while maintaining the optimum water activity required for the reaction.[11,12]

Continuous DKR reactions were performed in the MEDKR apparatus (Fig. 1) which consists of three vessels: (A) a 60 mL closed stainless steel hydrogenation vessel for the racemisation; (B) an 83 mL closed stainless steel cross-flow cell for the kinetic resolution; (C) a 50 mL partially opened glass vessel connected to a gas bubbler used as a pressure equaliser. The HPLC pump was located between vessel C and A, the fluid circulation was from vessel A to B (passing through a cooling unit) and to vessel C before the cycle was repeated. The apparatus was degassed with argon during the initial 15–30 minutes before increasing the temperature of the racemisation reactor vessel A to 100 °C. The conditions for the MEDKR reaction are shown in Scheme 2.[13] The kinetic resolution of amine **2** without catalyst **3** advanced to 38% conversion at 99% ee after 48 hours.

The MEDKR reaction proceeded to 91% conversion at 99% ee after 72 hours in the membrane reactor, as illustrated in Fig. 2, with the remaining 9% of material corresponding to known amine and imine dimer by-products of the reaction.[7] Very similar results were obtained when the reaction was repeated on two further occasions. A conversion of over 50% proves that the racemisation was effective and the high ee shows that the kinetic resolution was effective in the 30 °C reactor chamber as planned. Therefore, we have proved the principle that a tandem catalytic process can be run in membrane separated chambers.

A considerable amount of work remains to render this a useful process. Isolated yields were poor and after 72 hours the mass balance was only 55%. Clearly, much of the material has been lost from solution. To probe the origins of this problem, on one occasion we held back addition of the catalyst **3** until the 72 hour mark, well after the kinetic resolution was complete. Under these conditions, while the quantity of amine (*S*)-**2** that remained after the kinetic resolution was racemised by catalyst **3**, very little new acetamide (*R*)-**1** was formed. This suggests that, after prolonged exposure to the conditions, either the kinetic resolution fails or the amine is subject to competing reactions.

Overall, this work has proved that a tandem catalytic reaction such as the DKR reaction can be operated as a continuous process using the MEDKR process. However, an improvement in the efficiency of the racemisation reaction is necessary in order to explore the full potential of the concept. Paetzold and Bäckvall reported a very high product yield (90% isolated yield) and purity (98% ee) of acetamide from the DKR of amine **2** with a tetramethoxy-analogue of the Shvo catalyst.[14] This remains the benchmark process for DKR of amines, but has the disadvantage that the racemisation catalyst is not, as yet, commercially available.

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12 The log P of a given solvent between octanol and water is commonly used to provide a measure of the compatibility of an organic solvent with enzyme activity.

13 Concentrations were determined using an Agilent 6850 Series gas chromatograph (GC) fitted with a flame ionisation detector (FID) and Agilent 7683 autoinjector. Separation was achieved on an HP-Chiral 20B capillary column (30 m × 250 μm × 0.25 μm nominal, J&W Scientific, USA).

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