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Chemoenzymatic dynamic kinetic resolution of secondary amines

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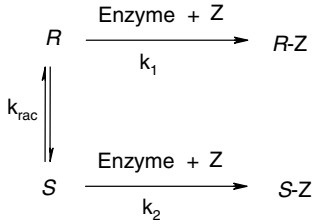
Abstract—The kinetic resolution of amines using a novel iridium based catalyst coupled with an enzyme catalysed step is achieved on a large scale with high yields and ee.

Enantiomerically pure chiral amines are particularly important to the pharmaceutical and agrochemical industries. The common procedures for their preparation include resolution from the racemate,[1] asymmetric reductive amination,[2] asymmetric hydrogenation[3] and alkylation of imines.[4] Due to its operational simplicity the majority of industrial scale syntheses employ a kinetic resolution via a diastereomeric recrystallisation or enzymatic acylation to separate the desired enantiomer from the racemic mixture. However, this methodology has the inherent disadvantage of limiting the yield to a maximum of 50% which has a considerable impact on the economic viability of the procedure. To overcome this drawback it is possible to combine the kinetic resolution with a simultaneous racemisation to give a theoretical yield of 100% in a procedure known as dynamic kinetic resolution (DKR) (Scheme 1). If the desired enantiomer is *R*, then this requires $k_{rac} > k_1 > k_2$.

This technique has been successfully utilised in the synthesis of amino acid derivatives[5] and alcohols.[6] The

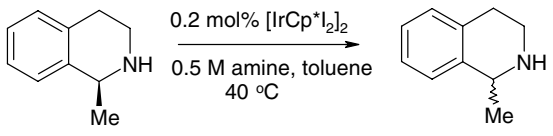


Scheme 1.

known methods for racemisation of amines[7] require harsh reaction conditions under which most enzymes would be denatured making them unsuitable for DKR. Recently, milder conditions for amine racemisation have been developed through the use of ruthenium[8] and palladium[9] based catalysts both of which have been employed in the successful DKR of chiral amines.[10] However, both systems have significant limitations that restrict their industrial applicability including high catalyst loading, limited substrate scope and high substrate dilution.

Herein, we report an efficient process for the DKR of a secondary amine using a novel iridium-based amine racemisation catalyst under significantly milder conditions than any previously reported. Pentamethylcyclopentadienyliridium(III) iodide dimer, $[IrCp^*I_2]_2$, successfully racemises 1-methyl-1,2,3,4-tetrahydroisoquinoline, **1**, with a low catalyst loading[11] (Scheme 2 and Fig. 1). Racemisation is observed under extremely mild conditions, $t_{1/2} = 215$ min at 40 °C using only 0.2 mol % $[IrCp^*I_2]_2$.

The drop in enantiomeric excess of **1** is accompanied by the formation of a small amount of the corresponding imine which increases with time indicating that



(*S*)-**1**

Scheme 2.

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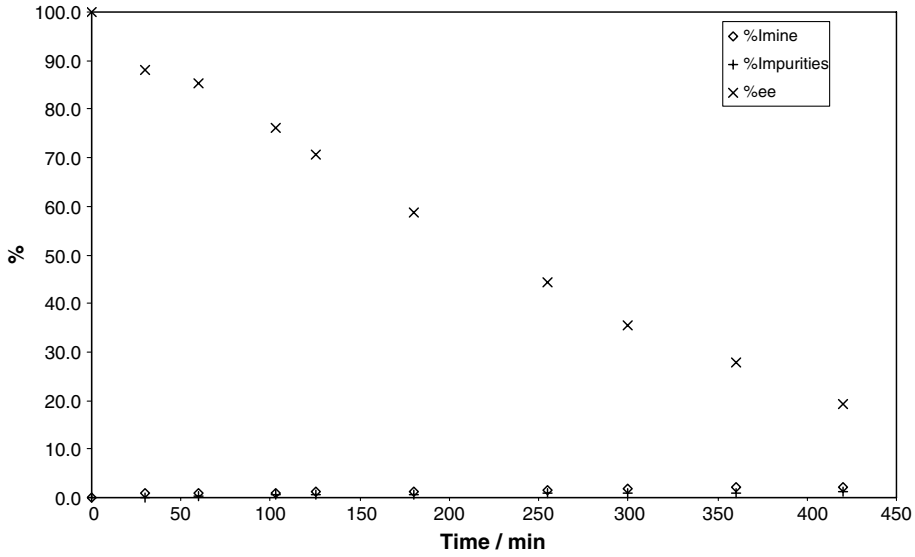
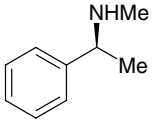


Figure 1. Racemisation of (*S*)-1-methyl-1,2,3,4-tetrahydroisoquinoline at 40 °C, showing % ee and % composition.

hydrogen is lost from the catalyst concurrently with imine hydrogenation. 1-Methylisoquinoline is also formed in low levels (<5%) presumably due to dehydrogenation of the intermediate imine by the racemisation catalyst. In general, it was found with other amines that a small amount of imine was formed during the racemisation which indicates that the catalyst can lose hydrogen during turnover. However, conducting the racemisation under an atmosphere of hydrogen considerably decreases the rate of racemisation. For example, the racemisation of (*S*)-*N*-methyl-α-methylbenzylamine **2** was complete in 5 h at 80 °C using 1 mol % $[IrCp^*I_2]_2$ under an air atmosphere, but still had 80% ee after the same time under a hydrogen atmosphere of 1 atm.



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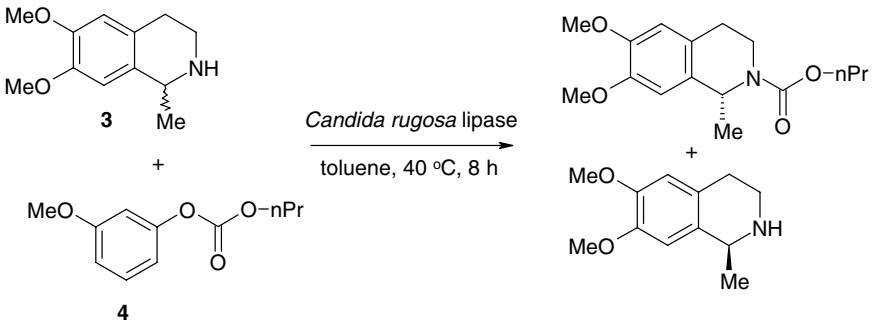
The next step, having found an efficient racemisation catalyst for amines, was to couple racemisation to an enzyme-catalysed resolution. The enzymatic resolution of racemic **3** using *Candida rugosa* lipase and 3-methoxyphenylpropyl carbonate **4** as an acyl donor (Scheme 3) was carried out at 40 °C (Fig. 2) to give 55% unreacted **3** in 70% ee (*S*) and 45% carbamoylated **3** in 91% ee (*R*) in just over 8 h, corresponding to an *E* value of 27. For the DKR to be successful both the racemisation and resolution need to work under the same conditions in the same reaction flask.

The racemisation process and the enzymatic resolution were then combined in the hope of achieving a dynamic kinetic resolution. Racemic amine **3** (0.48 M) was reacted with 3-methoxyphenylpropyl carbonate **4** (0.72 M) in toluene with 0.2 mol % $[IrCp^*I_2]_2$ and 50% w/w immobilised *C. rugosa* lipase (1100 units/mg), at 40 °C for 23 h (Fig. 3). This gave a 90% conversion to the product carbamate in a 96% ee. The reaction was performed at a 3 g scale and the product carbonate was isolated in a 82% yield with a 96% ee.

The DKR was also undertaken using other acyl donors and an interesting observation was made when using the conditions above with racemic 1-methyl-1,2,3,4-tetrahydroisoquinoline, **1**, and 3-methoxyphenyl allyl carbonate.[12] Although the corresponding allyl carbamate was successfully formed in a high enantiomeric excess (94%) in about 50% yield, the other major product



Scheme 3.

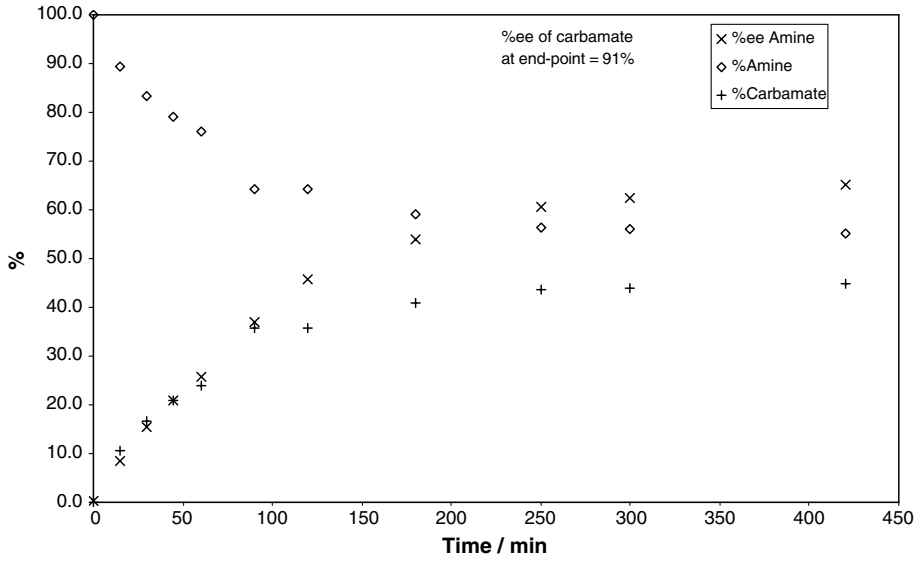


Figure 2. Enzymatic resolution of **3** using 3-methoxyphenylpropyl carbonate as the acyl donor, showing % ee and % composition.

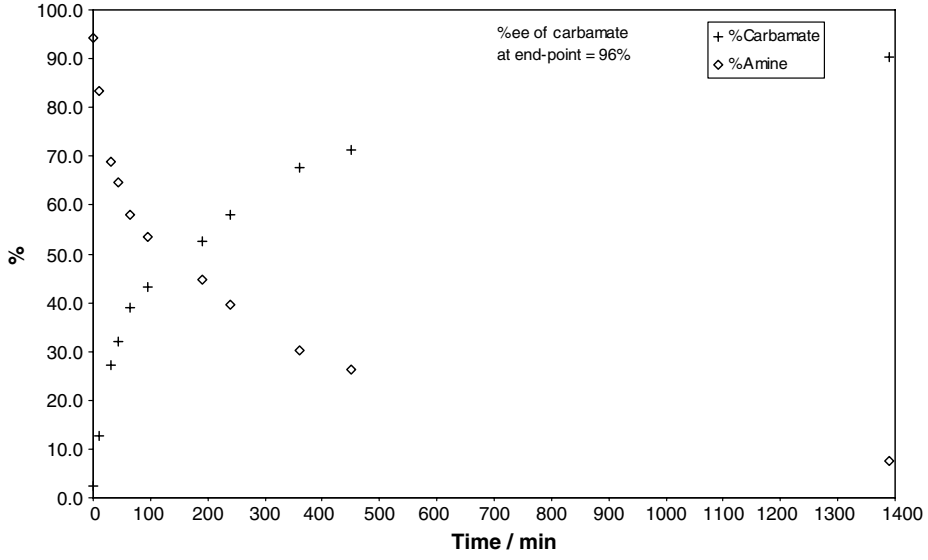


Figure 3. DKR of **3** using 3-methoxyphenylpropyl carbonate as the acyl donor, showing % ee and % composition.

was identified by NMR and GCMS analysis as *N*-allyl-1-methyl-1,2,3,4-tetrahydroisoquinoline. This product, after an initial lag period, is formed with zero-order kinetics, whereas carbamate formation shows a first-order profile. The concentration of the carbamate levels off at ~50% conversion, despite the amine still being present in 30% of its original concentration. The amine concentration continues to decrease with only the *N*-allyl amine being formed. Presumably amine **1** reacts with the carbamate product to form the *N*-allyl amine. This reaction must be catalysed by $[IrCp^*I_2]_2$ as the *N*-allyl amine is not formed in the enzymatic resolution of **1** under otherwise identical conditions in the absence of the metal catalyst. The carbamate concentration increases to the point at which the rate of its formation equals the rate of the *N*-allyl amine formation and as a consequence its measured concentration remains constant.

This unwanted reaction did not occur with alkyl aryl carbonates. In conclusion, we have developed a highly efficient, extremely mild process for the dynamic kinetic resolution of isoquinoline-based chiral secondary amines in a good yield and a high enantiopurity using a simple, air-stable iridium-based amine racemisation catalyst. This result constitutes the first example of a chemoenzymatic dynamic kinetic resolution on a secondary amine. Work is ongoing to extend the scope of the procedure towards the dynamic kinetic resolution of primary amines.

Synthesis of the catalyst: Pentamethylcyclopentadienyliridium(III) chloride dimer (4.38 g, 5.51 mmol) and sodium iodide (8.46 g, 56.7 mmol) were added to a single neck 1000 ml round-bottomed flask. A water condenser was fitted to the flask, the remaining necks were stop-

pered and argon was purged through the vessel at 500 ml/min for 30 min. The purge of argon was then reduced to 20 ml/min and acetone (525 ml < 100 ppm H_2O) was added, the flask was then placed in an oil bath at 60 °C and the reaction stirred using a magnetic stirrer resulting in a dark orange solution containing some insoluble iridium dimer. The reaction was allowed to reflux under argon for 3 h before being cooled to room temperature. The reaction was concentrated to dryness under vacuum to yield a brown/red solid that was dissolved in dichloromethane (500 ml) and washed with water (3×250 ml), the organic layer was separated, dried using sodium sulfate, filtered and concentrated to dryness under vacuum to yield a brown solid. The solid was crystallised from chloroform/methanol to yield brown needle-like crystals, the filtrates were concentrated to dryness and the resulting residue was recrystallised form chloroform/methanol, this was repeated a third time and the three crops of catalyst combined to yield 5.10 g (78% isolated yield). The crystals were analysed by carbon and proton NMR: δH ($CDCl_3$) 1.83 (s, Cp^*-CH_3), δC (300 MHz, solvent $CDCl_3$, reference $SiMe_4$) 11.13 (Cp^*-CH_3), 89.3 (Cp^*). Elemental Anal. Calcd for $Ir_2I_4C_{20}H_{30}$: C, 20.7; H, 2.6. Found: C, 20.6; H, 2.5.

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