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Technical Notes

Catalytic Racemisation of Chiral Amines and Application in Dynamic Kinetic Resolution

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Abstract:

A mild and efficient procedure for the racemisation of optically active amines has been developed and applied to the dynamic kinetic resolution (DKR) of a racemic amine. Pentamethylcyclopentadienyliridium (III) iodide dimer dissolved in a convenient solvent is the precatalyst that reacts in situ with primary, secondary, or tertiary amines to form what we have named a SCRAM catalyst. This is able to dehydrogenate a substrate amine to form an imine, which, depending upon the reaction conditions, is then reduced back to the amine. When an optically active amine is mixed with the iridium precatalyst, racemisation is observed. The SCRAM catalyst is used under mild conditions compatible with suitable enzymes and acyl donors, and thus the DKR of an amine has been effected, giving significantly higher yield than if the enzyme alone was used. A mixed carbonate was identified as the optimal acyl donor, giving a carbamate product that is readily removed by acidic hydrolysis.

Introduction

It is estimated that about 20% of drugs contain at least one amine chiral centre, so there is an enormous demand for a variety of methods for the synthesis of optically active amines. These include manipulation of optically active alcohols, amino acids, and amines from the chiral pool,[1] use of chiral auxiliaries to induce asymmetry,[2] and catalytic asymmetric synthesis using bio- or chemocatalysts.[3] With some notable exceptions, the catalytic asymmetric synthesis of amines in high optical purity has rarely been achieved on a commercial production scale.[4] Reasons for this include the following: insufficiently advanced technology and the length of time and level of resource required to develop this type of process; the difficulty in achieving a consistent and economic process that gives a product with very low catalyst contamination; less than desired optical purity of the products which often then require a "polishing" crystallization with attendant loss of yield. The most common method for manufacturing optically active amines is still by diastereomeric crystallization.[5,6] This provides a simple, robust process that gives a product of consistently high quality. The main disadvantage is the low (less than 50%) yield, which is particularly problematic if the optical resolution is carried out on expensive or high-volume products. Whilst resolutions are simple, it is less widely recognized that they are often poorly productive and operationally expensive, a result of the number and length of processing steps and isolations. Recycling of the undesired enantiomer may be possible in some cases if the pK_a of the proton at the chiral centre is low or can be lowered for example by formation of a Schiff base. Most optically active amines are not amenable to this type of racemisation; consequently, many drugs are manufactured, often accompanied with large waste streams of the unwanted isomer(s).

Whilst the efficient racemisation of optically active alcohols has now been reported with a variety of different catalysts,[7−10] there is little precedent for the racemisation of homochiral amines. Bäckvall et al.[11−13] have reported the catalytic racemisation of amines using the Shvö and related catalysts. Unfortunately, from an industrial perspective the catalyst turnover is low, making the process not economical; moreover, the high temperatures required for racemisation

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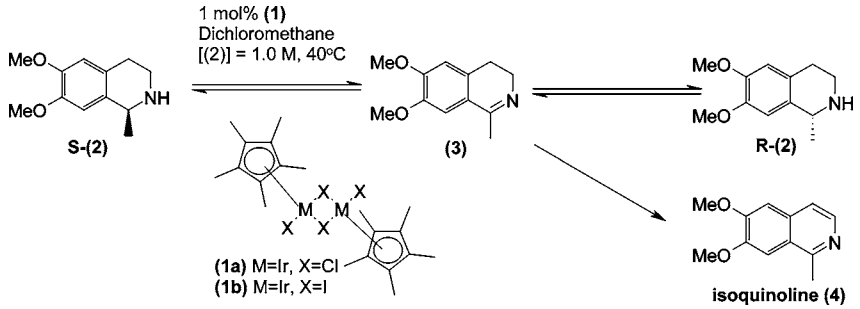
Scheme 1. **Dehydrogenation and racemisation of (1*S*)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline using $[IrCl_2Cp^*]_2$ catalyst 1a**



are not compatible with some other reagents and catalysts (for example, acyl donors and enzymes). Murahashi et al.[14] reported the racemisation of optically active 2-methylbenzylamine using palladium black although high levels of dimeric impurities were formed. More recently, Jacobs et al.[15] have used Pearlman's catalyst, palladium on barium sulfate under hydrogen gas; however, the reaction is limited to benzylic amines having substituents not susceptible to reduction.

Dynamic kinetic resolution is a method that has the advantage of combining a resolution with a racemisation. In this way the stereoisomers within a racemate are subjected to a fast dynamic equilibrium, and one enantiomer is selectively removed, for example by chemical modification using an enzyme, by physical removal, through crystallization, or by chiral chromatography. Chemists at BASF have developed a process for the resolution of primary and secondary amines by enzyme-catalysed acylation using activated acyl donors.[16] Although there are few details, they have alluded to an amine racemisation and recyle process.[17] Reetz et al.[18] reported the first example of an amine dynamic kinetic resolution (DKR) in 1996. They exploited the ability of palladium supported on carbon in a hydrogen atmosphere to racemise (*S*)-1-methylbenzylamine which, when used in conjunction with *Candida antarctica* lipase and ethyl acetate in triethylamine at 50−55 °C the (*R*)-amide was isolated in 64% yield and 99% ee after 8 days. Jacobs et al.[15] recently extended this work to some other benzylic amines. Bäckvall has described the use of Shvö's catalyst in the DKR of primary amines.[19] Use of 4 mol % of the catalyst along with sodium carbonate, isopropyl acetate, and *Candida antarctica* lipase at 90 °C for 3 days resulted in the acylation of (*R*)-1-methylbenzylamine in 90% yield and 98% ee. The method was successfully used with a number of benzylic and aliphatic primary amines. The product of these DKR reactions is an amide, which requires harsh conditions to effect its removal, thereby limiting the utility of the process when sensitive groups are present in the amine. Turner et al.[20−23] have developed an interesting process for the deracemisation of amines in water using a genetically modified amine oxidase to selectively dehydrogenate the (*S*)-amine to an imine that is reduced in situ with a nonselective metal hydride reagent to give the racemic amine. Although elegant, the method is currently limited by the enantioselectivity of the enzyme to the (*S*)-enantiomer. Some years ago an elegant industrial process was developed by Celgene, in which one enantiomer of a racemic amine is selectively dehydrogenated and hydrolyzed to a ketone using a transaminase enzyme and amine acceptor such as an α-keto acid; in the reverse reaction the ketone is then reductively aminated by an amine donor, such as an amino acid, to the opposite enantiomer, resulting overall in a deracemisation process.[24]

Catalyst Identification

Whilst carrying out some work on the asymmetric transfer hydrogenation of some 1-methyl-3,4- dihydroisoquinolines using iridium pentamethylcyclopentadienyl complexes, CATHy catalysts,[25] we noticed a reproducible and in some cases significant fall in the enantiomeric excess of the product amine, despite the fact that we were using a formate salt hydrogen donor that was expected to give an irreversible reaction. Investigation of these results led us to the finding that this type catalyst is able to dehydrogenate amines, i.e. that amines can serve as hydrogen donors.

Initial studies demonstrated that the precursor to the CATHy catalysts pentamethylcyclopentadienyl-rhodium and -iridium (III) chloride dimers will slowly racemise (*R*)- or (*S*)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline. It was found that the TsDPEN ligand inhibits the racemisation. As shown in Scheme 1, the precatalyst pentamethylcyclopentadienyliridium chloride dimer (**1a**) effects

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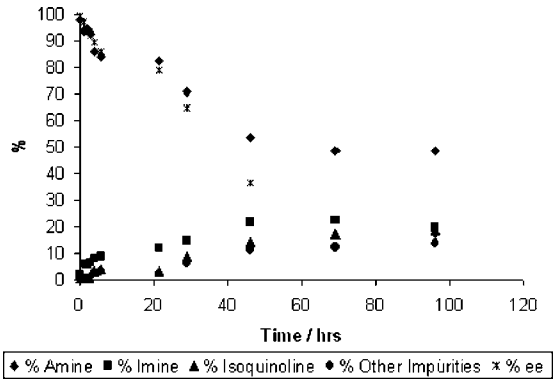

Figure 1. **Reaction profile of (1*S*)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline with $[IrCl_2Cp^*]_2$ catalyst 1a according to Scheme 1.**

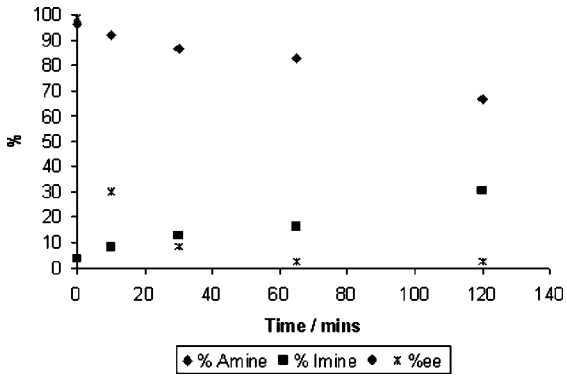

Figure 2. **Reaction profile of (1*S*)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (2) with $[IrI_2Cp^*]_2$ catalyst 1b according to Scheme 1.**

the dehydrogenation of the substrate amine to generate an observable imine that can be reduced to either amine enantiomer, thus racemising the optically active starting material. The reaction profile is shown in Figure 1, and noticeable is the accumulation of imine, isoquinoline, and other unidentified impurities (likely to be dimers), as well as hydrogen gas as the other reaction by-product.

Although a high level of impurities was formed and the rate of racemisation low, this reaction demonstrates the ability of the iridium dimer **1a** to racemise amines under particularly mild reaction conditions.

The rate of racemisation catalysed by the iridium complex **1a** is presumably dependent on the effective positive charge on the metal, its ability to act as a Lewis acid and to donate/accept a hydride ion. The simplest way to modify this effective charge and hence change catalytic activity is to change or substitute the ligands attached to the metal. The most convenient modification is to substitute the halide ion, and it is known that the addition of metal halide salts to organometallic complexes can lead to halogen exchange.[26] The pentamethylcyclopentadienyliridium (III) iodide dimer **(1b)** has been reported in the literature,[27,28] and it was expected that the addition of potassium iodide to the iridium catalyst **1a** would form **1b** by an in situ salt-exchange mechanism. Indeed the precatalyst was isolated, characterized by ^{1}H, ^{13}C NMR, and elemental analysis, and single-crystal X-ray diffraction confirmed the structure of the tetra-iodo complex. The racemisation of **2** was repeated with the addition of an equivalent of potassium iodide, but chloroform was used instead of dichloromethane due to its higher boiling point; tetrahydrofuran was added as a cosolvent to aid the dissolution of potassium iodide (although the vast majority remained insoluble).

The results in Figure 2 show that changing the anionic ligand from chloride to iodide has a large effect on the catalytic activity, the rate of racemisation increasing by about 120-fold. The magnitude of this was surprising as Bäckvall et al. observed no significant difference between chloride, bromide, and iodide as anionic ligands in their cyclopentadienylruthenium catalysts for alcohol racemisation.[5b] This probably indicates that either the mechanisms or the rate-limiting steps of the two racemisation systems are substantially different. The amount of imine **3**, formed is similar to that observed with catalyst **1a**. If desired, the imine can be easily reduced back to the racemic amine, thus increasing the overall recovery to 99%. Interestingly, the amount of isoquinoline **4**, formed was significantly less with the iodocatalyst **1b**. Use of the isolated tetra-iodo complex rather than its preparation in situ led to very similar results. Use of the catalyst in this way is preferred as the reaction mass is then monophasic.

The reaction is conveniently carried out by dissolving the precatalyst in a suitable solvent and mixing with the amine as a homogeneous solution. Suitable solvents are aromatics, ethers, esters, and even biphasic systems. Only dipolar aprotic solvents such as dimethylformamide have led to poor results. The reactions are almost thermoneutral, making them safe but unsuitable for calorimetric monitoring. The use of a nitrogen blanket or purge is desirable as hydrogen is slowly evolved, although the use of a gas purge had very little effect on the reaction profile which remained first order.

The combination of iridium and iodide ligands gives the most active catalyst, and the addition of a bidentate ligand destroys activity, which provides a pointer to the mechanism of the dehydrogenation. The rhodium analogue was also prepared but showed lower activity than iridium. The chloro analogues were less active. Interestingly, the use of the trifluoromethyltetramethylcyclopentadiene ligand improved the rate of racemisation by the iodorhodium complex by a factor of about 3, but the analogous iridium complex showed the same racemisation rate with either the pentamethyl- or trifluoromethyltetramethylcyclopentadiene ligand.

Reaction Scope

The scope of the reaction has been evaluated using a range of optically active amines shown in Scheme 2 and the half-life ($t_{1/2}$) racemisations are shown in Table 1.

Secondary amines are racemised with $t_{1/2}$ 22 min to 24 h (entries 1−3, 5, 6, 8−10). Entry 10, that of the anti-depressant drug Sertraline, is an interesting case where epimerisation of the secondary amine is at least partially under thermodynamic control of the remote tertiary carbon

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Scheme 2. **Amine substrates tested in the SCRAM-catalysed racemisation**

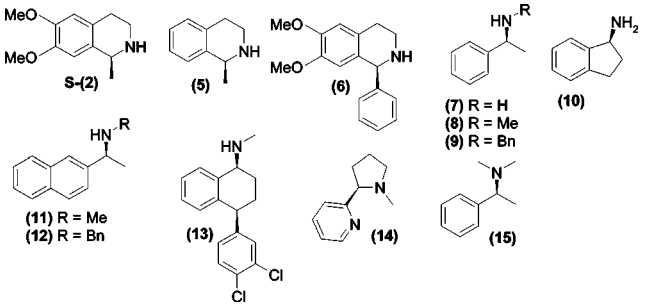


Table 1. **Half-life ($t_{1/2}$) racemisation rates of different optically active amines with catalyst 1b**

entry	substrate	temp (°C)	catalyst loading (mol %)	racemisation $t_{1/2}$ (min^{-1})
1	2	40	0.2	45
2	5	40	0.2	220
3	6	80	0.5	180
4	7	80	1.0	dimeric impurities[a]
5	8	80	1.0	45
6	9	80	1.0	250
7	10	80	1.0	dimeric impurities[a]
8	11	80	1.0	900
9	12	80	1.0	1400
10	13	80	0.1	22
11	14	80	1.0	>7200
12	15	90	1.0	1250

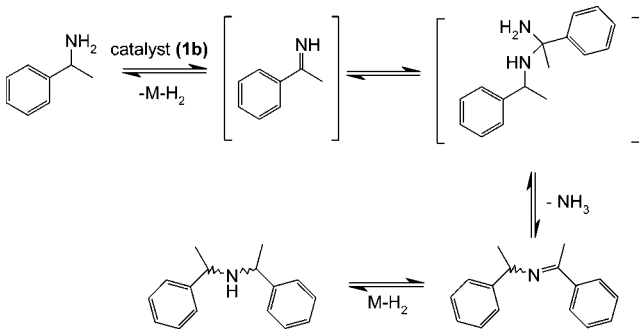
[a] 30% of the product is the racemised amine, the remainder is a mixture of dimers.

chiral centre. Depending upon the solvent and temperature, the *cis*-isomer can be epimerised to give 90% of the *trans*-isomer. The tertiary carbon chiral centre can be racemised with base, and thus a process has been devised in which the three waste isomers from Sertraline manufacture can be racemised, recycled, and turned into useable drug substance. The substrates with a *N*-methyl are racemised more rapidly than with a *N*-benzyl substituent. Possible explanations may be the greater steric encumbrance of the latter, the greater difficulty in reducing benzylimine, or because the imine may be either *cis* or *trans*, the rate of reduction of these geometrical isomers may be different, giving a lower rate of reaction. The cyclic amines (entries 1−3) do not give this problem as there can only be one geometrical isomer, and generally they tend to racemise more quickly. Some preliminary work has been done on electron-donating and -withdrawing substituents, and generally it seems that the former racemise more quickly. From observation of the imine concentration in solution it seems that the slow step in the catalytic cycle is the dehydrogenation.

From the data it is evident that primary amines are rapidly dehydrogenated. However, as previously observed, the reactivity of primary imines results in their rapid reaction with substrate amine, elimination of ammonia, and the formation of dimeric alkylated imines.[6a] These products can subsequently be reduced to an isomeric mixture of dimeric amines (Scheme 3).

Interestingly one tertiary amine has been efficiently racemised (entry 12), indicating that a quaternary iminium

Scheme 3. **Formation of dimeric products following the dehydrogenation of primary amines**



species is generated as an intermediate and supporting other evidence that iminium salts are good substrates in transfer hydrogenation.[29] The catalyst **1b** failed to racemise the bidentate tertiary amine (*S*)-nicotine (entry 11), and further studies showed that this was due to its ligation with the iridium to give an inactive catalyst.

Whilst a variety of optically active amine substrates have been racemised, work is still ongoing for example with amino acids and *N*-heteroatom-substituted amines (e.g., oximes, hydrazines, sulfonylamines, phosphinylamines) to test the scope of the reaction. The mechanism of the reaction is currently being studied, and the identity of the active catalyst is being determined.

This mild procedure for the racemisation of optically active amines lends itself to application in recycling the waste enantiomer produced in a resolution process, an "end-of-pipe" solution, and a range of applications are being evaluated. A further refinement of the technology is to integrate it with a resolving technique to provide a dynamic kinetic resolution process (DKR).

Dynamic Kinetic Resolution

For the DKR to be successful, both the racemisation and resolution need to work under the same conditions in the same reaction vessel, the former needs to be rapid, and the resolution needs to be highly selective, and enzymes are well suited to this task. Since our SCRAM catalysts are efficient in the racemisation of secondary amines, we chose to use these; however, there are few reports of enzymatic resolution of secondary amines.[16,30] Perhaps the best example is from Breen who has devised a procedure for the resolution of 1-methyl-1,2,3,4-tetrahydroisoquinoline **(5)** using *Candida rugosa* lipase and a novel allyl carbonate acyl donor.[31] The maximum yield achieved in this process is 46% and 99% ee. Our target for the DKR process was to maintain the high optical purity but to increase the yield.

The enzymatic resolution of racemic **2** was carried out using Breen's process but at the slightly higher temperature of 40 °C where only minor denaturation of the enzyme and very little uncatalyzed acylation were observed. In the next experiment catalyst **1b** was added to perform the DKR, but

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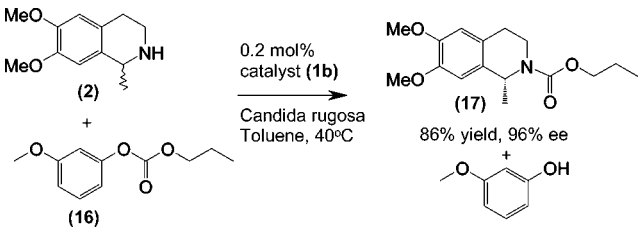
Scheme 4. **Dynamic kinetic resolution process for racemic secondary amine 2**



although the product carbonate was formed in high ee, a large amount of impurity was formed that was identified by NMR and GC/MS analysis as *N*-allyl-1-methyl-1,2,3,4-tetrahydroisoquinoline. This side reaction must be catalysed by **1b** as the impurity was not observed in the absence of the catalyst. The evidence points to catalysed allylation of the amine by the allylcarbamate rather than reaction with 3-methoxyphenyl allyl carbonate. A simple modification of this reagent to 3-methoxyphenyl propyl carbonate was made, and then this reagent was tested in the DKR process as shown in Scheme 4 and Figure 3.

A successful DKR was observed with 90% conversion to the product carbonate in 96% ee using 0.2 mol % catalyst. The reaction was performed at 10-g scale. and the product carbamate was isolated in 82% yield with 96% ee.[32] The formation of a carbamate product is a useful feature of the process since this protecting group is readily removed by acidic hydrolysis. This can be compared to most enzyme-catalysed amine resolutions and DKRs that involve the formation of an amide, which is harder to remove.

Conclusion

We have developed a simple, efficient, iridium-based catalyst system for the dehydrogenation and racemisation of a variety of amines. The catalyst is air- and water stable and can be used in mild conditions compatible with enzymes. A process for the DKR of a secondary amine has been developed, giving a product in high yield and enantiopurity.

Experimental Methods

Elemental Analyses. These were carried out by the University of Huddersfield using standard techniques. Chromatography: GC data were obtained using a HP6890 series GC; GC/MS data were obtained using a HP6890 series GC with a HP5973 MSD detector; LC data were obtained using either a HP1050 series or HP1100 series HPLC. Nuclear magnetic resonance spectroscopy: NMR spectra were recorded using a Bruker Advance 400 MHz spectrometer. Deuterated NMR solvents were purchased from Aldrich and used without further purification. Catalyst **(1a)** was purchased from Aldrich, Johnson-Matthey, and Heraeus. Optically active amine substrates **(2−15)** were synthesized by known literature methods.

Synthesis of Pentamethylcyclopentadienyliridium (III) Iodide Dimer (1a). Pentamethylcyclopentadienyliridium (III) chloride dimer **(1a)** (4.57 g of 96% ≡ 4.38 g ≡ 5.50 mmol)

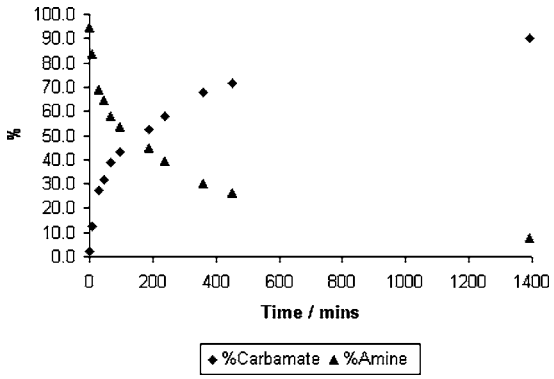


Figure 3. **DKR of racemic 2 using 3-methoxyphenylpropyl carbonate as the acyl donor.**

and sodium iodide (8.55 g of 99% ≡ 8.46 g ≡ 56.70 mmol) were added to a side-armed, 1000 mL, round-bottom flask. A water condenser was fitted to the flask, and argon was sparged through a pipet in the sidearm 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 reaction flask was then placed in an oil bath at 60 °C and 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 ultrapure water (250 mL, 3×), the organic layer was separated, dried using sodium sulfate, filtered, and concentrated to dryness under vacuum to yield a brown solid. The solid was recrystallized from chloroform/methanol to yield brown needlelike crystals; the filtrates were concentrated to dryness, and the resulting residue was recrystallized from chloroform/methanol; this was repeated a third time, and the three crops of catalyst combined to yield 5.102 g (78.2% isolated yield, assuming 98% pure). The crystals were analyzed by carbon and proton NMR, elemental analysis, and X-ray crystallography. δH (300 MHz, solvent $CDCl_3$, reference $SiMe_4$) 1.83 (s, Cp*-CH_3). δC (300 MHz, solvent $CDCl_3$, reference $SiMe_4$) 11.13 (Cp*-CH_3), 89.3 (Cp*). Elemental analysis: Calcd C = 20.7, H = 2.6. Found: C = 20.6, H = 2.5. X-ray analysis: see Supporting Information.

General Procedure for Racemisation of Amines, Using Pentamethylcyclopentadienyliridium (III) Chloride Dimer (1a) and Potassium Iodide. The chosen solvent (10 vol equiv) was charged to a nitrogen-blanketed, over-head stirred, round-bottomed flask and warmed to between 40 °C and 110 °C. The optically active amine (1 mol equiv) was charged in one portion and allowed to dissolve; then the potassium iodide (1 mol equiv) and catalyst, pentamethylcyclopentadienyliridium (III) chloride dimer (0.01 mol equiv), were charged to give a transparent orange solution. The reactions were sampled by quenching ∼100 μL into dichloromethane (2 mL) and water (2 mL); the organic layer was dried using sodium sulfate and concentrated to dryness under vacuum. The resulting residue was redissolved in an appropriate solvent to a concentration of ∼1 mg/mL and then was analyzed by HPLC and/or GC for enantiomeric excess

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and impurities. When analysis was complete, the reaction mass was quenched with acid to extract the amine and separate it from the catalyst. The phases were separated, and the amine was back extracted into an organic solvent by neutralization and then concentrated to dryness to give a yield of the crude mass.

Racemisation of (*S*)-6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (2). Into a 5-mL round-bottom flask was added pentamethylcyclopentadienyliridium (III) chloride dimer **(1a)** (8.30 mg of 96% ≡ 7.97 mg ≡ 0.01mmol). Chloroform (250 μL) was added, and the catalyst solution was stirred using a magnetic stirrer until all the catalyst had dissolved, resulting in an orange solution. (*S*)-(**2**) (218.2 mg of 95% ≡ 207.25 mg ≡ 1.00 mmol) and potassium iodide (167.7 mg of 99% ≡ 166.01 mg ≡ 1.00 mmol) were added and washed in using tetrahydrofuran (750 μL). The flask was fitted with a water condenser and was placed into an oil bath at 40 °C, and a timer was started. The potassium iodide remained predominantly out of solution, and after about 5 min at 40 °C the reaction solution had become brown and remained this color throughout. Samples were taken at regular intervals by adding 40 μL of the reaction solution to dichloromethane (2 mL) and 2.5 M sodium hydroxide solution (2 mL). The organic layer was separated and dried using sodium sulfate. The resulting solution was analyzed by chiral and achiral GC. Analysis: gas chromatography (for conversion). Column = HP Crosslinked 5% Ph Me siloxane (25 m × 0.32 mm × 0.52 μm). Oven temperature = 150 °C for 7 min then ramp at 10 °C/min to 300 °C and hold for 5 min. Inlet pressure = 12.0 psi. 6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline **(2)** retention time = 12.4 min. 6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline **(3)** retention time = 12.7 min. 6,7-Dimethoxy-1-methylisoquinoline **(4)** retention time = 13.9 min. Unknown impurity retention time = 12.45 min. Analysis: gas chromatography (for ee). Column = Varian Chirasil-Dex-CB column (25 m × 250 μm × 0.25 μm). Oven temperature = 165 °C isothermal for 60 min. Inlet pressure = 10.0 psi. N.B. Samples were derivatised using trifluoroacetic anhydride prior to injection. (*R*)-**(2)** retention time = 41.6 min. (*S*)-**(2)** retention time = 42.5 min.

Racemisation of (*S*)-*N*-Methyl-1-methylbenzylamine (8). Pentamethylcyclopentadienyliridium (III) chloride dimer **(1a)** (16.6 mg of 96% ≡ 15.9 mg ≡ 0.02 mmol), (*R*)-*N*-methyl-α-methylbenzylamine (*R*)-**(8)** (275.9 mg of 98% ≡ 270.4 mg ≡ 2.00 mmol), potassium iodide (335.4 mg of 99% ≡ 332.0 mg ≡ 2.00 mmol), and internal standard biphenyl (155.0 mg of 99.5% ≡ 154.2 mg ≡ 1.00 mmol) were charged to a 5-mL round-bottom flask. Toluene (4 mL) was added, a water condenser was attached to the flask which was then placed in a oil bath at 80 °C, and a timer was started. The reaction solution immediately turned to a dark red/brown that faded over 60 min to a dark orange solution. The colour of the solution gradually faded and was a clear orange solution after stirring overnight. Samples were taken at regular intervals by removing 100−200 μL and quenching into dichloromethane (2 mL) and 2.5 M sodium hydroxide (2 mL); the organic layer was separated and dried using sodium sulfate. The resulting organic layer was analyzed by chiral and achiral GC. Analysis: gas chromatography (for conversion). Column = HP-5 5% Ph Me siloxane capillary column (30 m × 320 μm × 0.25 μm). Oven temperature = 70 °C isothermal for 30 min. Inlet pressure = 15.0 psi. *N*-Methyl-1-methylbenzylamine **(8)** retention time = 6.8 min. Gas chromatography (for ee): column = Varian Chirasil-Dex-CB column (25 m × 250 μm × 0.25 μm). Oven temperature = 100 °C isothermal for 60 min. Inlet pressure = 10.0 psi. N.B. The samples were derivatised using trifluoroacetic anhydride prior to injection. (*R*)-*N*-Methyl-1-methylbenzylamine (*R*)-(**8**) retention time = 58.4 min, (*S*)-*N*-methyl-1-methylbenzylamine (*S*)-**(8)** retention time = 54.8 min.

Racemisation of (*S*)-*N*-Methyl-1-methylbenzylamine (8) Using Pentamethylcyclopentadienyliridium (III) Iodide Dimer (1b). 1b (24.2 mg of 96% ≡ 23.25 mg ≡ 0.02 mmol), (*S*)-**(8)** (275.9 mg of 98% ≡ 270.4 mg ≡ 2.00 mmol), and internal standard tridecane (186.2 mg of 99% ≡ 184.4 mg ≡ 1.00 mmol) were charged to a 5-mL round-bottom flask. Toluene (4 mL) was added, a water condenser was attached to the flask that was then placed in an oil bath at 80 °C, and a timer was started. The reaction solution immediately turned to a dark red/brown that faded over 60 min to a dark orange solution. The color of the solution gradually faded and was a clear orange solution after stirring overnight. Samples were taken at regular intervals by removing 100−200 μL and quenching into dichloromethane (2 mL) and 2.5 M sodium hydroxide (2 mL); the organic layer was separated and dried using sodium sulfate. The resulting organic layer was analysed by chiral and achiral GC using the conditions described in the previous experiment.

3-Methoxyphenylpropyl Carbonate (16). To a three-neck, 100-mL round-bottom flask was added 3-methoxyphenol (6.47 g of 96% ≡ 6.21 g ≡ 50.00 mmol), tetrabutylammonium iodide (131.9 mg of 98% ≡ 129.3 mg ≡ 0.35 mmol), and dichloromethane (40 mL), resulting in a red/orange solution. A thermometer was attached and magnetic agitation started. Sodium hydroxide solution (20 mL of 4.0 M) was added which caused the reaction mixture to turn a brown colour. The reaction flask was then placed in an ice/salt bath and cooled to 0−5 °C. Propyl chloroformate (7.06 g of 98% ≡ 6.92 g ≡ 56.50 mmol) was added over an hour using a syringe pump, and the reaction solution was kept between 0 and 5 °C during the addition. A yellow precipitate formed during the addition. The reaction was stirred for a further hour at 0−5 °C and then separated. The aqueous layer was a dark-brown colour, and the organic layer was yellow. The organic layer was washed with sodium hydroxide solution (10 mL of 2.0 M), separated, dried using magnesium sulfate, and filtered. The filtrates were concentrated to dryness under vacuum to leave a yellow oil (10.67 g, 100% = 10.51 g). The crude product was purified using flash column chromatography with a 70/30 hexane/ethyl acetate mobile phase, producing after vacuum distillation a yellow oil (10.17 g = 93% isolated yield). The oil was analysed by GC, GC/MS, and NMR.

Analysis: gas chromatography (for conversion). Column = Chirasil-Dex-CB column (25.0 m × 250 μm × 0.25 μm). Oven temperature = 140 °C for 20 min then ramp at 10 °C/min to 190 °C and hold for 20 min. Inlet pressure = 10.0 psi. 3-Methoxyphenylpropylcarbonate (**16**) retention time = 22.8 min.

Dynamic Kinetic Resolution of Racemic 6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (2). Prior to the reaction a stock solution of toluene saturated with water was prepared by vigorously stirring a toluene/water mixture for 1 h and then allowing the two layers to separate; the toluene layer was used for the reaction solvent. To a two-neck, 50-mL round-bottom flask was added 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline **(2)** (3.093 g of 97% ≡ 3.00 g ≡ 14.47 mmol), *Candida rugosa* lipase (1.5 g, 1410 units/mg), pentamethylcyclopentadienyliridium (III) iodide (**1b**) (34.3 mg of 98% ≡ 33.6 mg ≡ 0.03 mmol), and toluene saturated with water (25 mL), resulting in an orange solution containing some insoluble amine. The reaction vessel was placed in an oil bath at 40 °C and connected to a second flask containing saturated brine at 50 °C. 3-Methoxyphenylpropyl carbonate **(16)** (4.657 g of 98% ≡ 4.564 g ≡ 21.71 mmol) was added and washed in using toluene saturated with water (5 mL), resulting in an orange/brown solution containing brown insoluble material (enzyme). The reaction flask was sealed so that the system was closed and was stirred overnight. After 24 h additional aliquots of **16** (1.55 g 98% ≡ 1.52 g ≡ 7.23 mmol) and *Candida rugosa* lipase (600 mg of 1410 units/mg) were added. After a total reaction time of 48 h the reaction solution was filtered through Celite to remove any enzyme. The filtrates were added to dichloromethane (100 mL) and washed with hydrochloric acid (2 × 50 mL of 1.0 M) and sodium hydroxide solution (2 × 50 mL of 1.0 M). The organic layer was removed, dried using sodium sulfate, filtered, and concentrated to dryness under vacuum to yield a brown oil (6.10 g) which was purified through a silica column using a hexane/ethyl acetate gradient elution system. The fractions containing only the product were combined and concentrated to dryness under vacuum to yield a yellow oil (3.53 g, 100% yield = 4.24 g; therefore, isolated yield = 81.6%, assuming the product is 98% pure). The product was analyzed by GC, dissolved in hexane/propan-2-ol (70/30), and analyzed by chiral HPLC and dissolved in $CDCl_3$ for NMR analysis (H^1, C^{13}, and HMQC) (see Supporting Information).

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Supporting Information Available

X-ray analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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