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A Low-Waste Process To Sertraline By Diastereomeric Crystal Resolution and Waste Isomer Racemisation

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Abstract:

A semi-continuous method for recovering waste sertraline isomers from a diastereomeric crystallisation process is described in which the mother liquors from a highly selective mandelic acid resolution for the (1*S*,4*S*) isomer are treated sequentially with SCRAM, an iridium-based chiral amine racemisation catalyst, and then catalytic potassium tertiary butoxide to epimerise the methine chiral centre. The green, low-waste process also deals with recovery and recycle of the precious-metal catalyst, providing both good economics and high-quality product.

1. Introduction

There are a variety of resolution strategies for chiral amines, and we report a new paradigm integrating diastereomeric crystal resolution and catalysed amine racemisation to achieve theoretically quantitative yields and consistently low waste.

Enzyme-based processes for the resolution of chiral amines have been widely reported,[1] and product yields have been greatly improved by integrating with amine racemisation procedures.[2] We recently reported the use of $[Cp^*IrI_2]_2$, (SCRAM, **1**) catalyst, for the efficient racemisation of primary, secondary, and tertiary amines and their use in dynamic kinetic resolution (DKR) of secondary amines.[3] Bäckvall has reported dynamic kinetic resolution (DKR) of primary amines using the ruthenium-based Shvö racemisation catalyst and *Candida antarctica* lipase that perform across a wide range of substrates with high yield and excellent enantioselectivities, but with high catalyst loadings and long reaction times.[4] Similarly Jacobs has used Adam's catalyst with a lipase enzyme to effect the DKR of a variety of amines in high yield and optical purity.[5] There are a number of industrial limitations of enzymatic amine DKR processes: only primary and secondary amines, not tertiary or quaternary amines can be resolved; most primary amines are resolved by (*R*)-selective enzymes,[1] and there are few examples of secondary amine resolution;[6] the reaction requires the rate of racemisation to exceed that of the acylation, but to achieve this both catalysts are operated under suboptimal conditions; the activity of enzymes in organic solvents is generally low, resulting in high loadings, high temperatures, and long reaction times; acyl donors must be selected for catalysed rather than uncatalysed reaction; and the reaction requires an additional step to remove the acyl group. These factors make the enzyme DKR process of limited utility and led us to consider the asymmetric transformations: crystallisation-induced diastereomeric transformation (CIDT), and (semi)continuous resolution−recycle processes.

Diastereomeric crystallisations have the advantage of being robust and simple to operate, however the low yields (max. 50%) implicit in these strategies give poor performance, due to low productivity, long cycle times, poor asset usage and large waste streams, especially if multiple recrystallisations, and/or chiral acid recovery is required. Nevertheless the use of this technique in pharmaceutical and fine chemical manufacture is widespread.[7] Racemisation of the soluble waste amine isomer present in the mother liquors would enable its conversion to product, improving the yield and productivity in these processes. A CIDT process uses a selected homochiral acid to form a salt selectively with one enantiomer; the diastereomer thus formed has, for example, a lower solubility than the other diastereomeric salt and crystallises from the solution. Concurrently, the soluble isomer is racemised, making more of the less soluble diastereomer available for crystallisation. In principle the isomeric mixture is turned into a single isomer product, doubling the theoretical yield. A number of dynamic crystallisation processes are described, including those from conglomerate and diastereomeric crystals.[8] The majority of amine racemisations rely on chiral centres that have α-protons with a low pK_a, for example Schiff bases of some amino acids can allow racemisation of an

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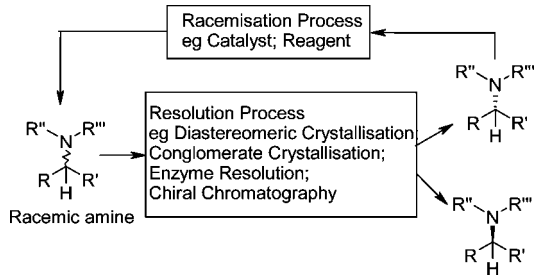

Figure 1. **Conceptual asymmetric transformation process involving separate, but linked resolution and racemisation stages.**

unwanted isomer. There are several industrial examples of this type of deracemisation process such as Merck's asymmetric transformation of an aminodiazepam with (*S*)-camphorsulfonic acid and benzaldehyde, Tanabe's (*S*)-phenylglycine with (*S*)-camphorsulphonic acid catalysed with salicylaldehyde, and GSK's D-*p*-hydroxyphenylglycinamide with (*S*)-mandelic acid and benzaldehyde.[9]

We report here the development of a crystal resolution process potentially applicable to a broad range of chiral amines by virtue of the fact that the racemisation does not rely on a low pK_a proton at the chiral centre. The process retains the simplicity and robustness of diastereomeric crystallisation, enables low-yielding crystallisation processes to be considered, and might be preferred over asymmetric processes to make homochiral amines. The practical difficulty with carrying out a CIDT process is the need to operate under conditions that allow selective crystallisation of the least soluble diastereomer whilst permitting the racemisation to take place. Amine racemisation catalysts such as SCRAM, Shvö, Pd/C, and Adam's are more active at higher temperatures which runs counter to the conditions required for crystallisation. A solution to this problem is to separate the diastereomeric resolution and racemisation steps but couple them with a flow engineering design. In this way each reaction can be operated under optimal conditions, for example, temperature, concentration, and solvent via an intermediary solvent exchange unit. Since the racemisation catalyst itself may affect the crystallisation or *vice versa*, it is preferred to keep them separate. This can be achieved by having the catalyst or product either permanently or temporarily in a different phase through immobilisation, extraction, precipitation, distillation, or the like, Figure 1. This semi-continuous process ought to be more versatile than a one-pot procedure, and to test this concept we selected the chiral amine pharmaceutical sertraline.

2. Sertraline Case Study

Sertraline (**2**) is the active pharmaceutical ingredient (API) in Pfizer's antidepressant Zoloft.[10] The developed commercial process employs an SMB chromatographic resolution of the racemic tetralone, followed by diastereoselective reductive amination to give at least 95% *cis*- and 5% *trans*-sertraline; the 4(*R*)-tetralone can be racemised with an alkoxide base.[11] Asymmetric processes to sertraline have been described.[12] Our studies employed a 4:1 racemic mixture of *cis*- and *trans*-isomers produced using the unoptimised original process.[13] The (1*S*,4*S*)-enantiomer can be produced by selective crystallisation of the major diastereomer followed by diastereomeric crystallisation of the racemate using (*R*)-mandelic acid in ethanol in an overall 26% yield, and by difference, 74% isomeric waste. The sertraline API is produced following a salt exchange to the hydrochloride. Whilst the process is robust, it is low yielding, providing us the incentive to improve it. The case study was made particularly challenging by the need to use the technology at the API stage, introducing product quality issues relating to the precious metal, potential new impurities and their effect on the crystallisation. The price of sertraline sold on the open market is very low, making our target especially demanding.

The patent literature describes processes for the epimerisation of the methine chiral centre using an alkoxide base, and for reagent-based epimerisation of the amine.[11,14,15] These processes are considered unlikely to meet the product challenges described above. We envisaged epimerisation of the chiral amine centre using the SCRAM catalyst and the methine chiral centre using an alkoxide base. Early on it was shown that integrating both epimerisations was not feasible, due to the incompatibility of base and catalyst. Similarly a CIDT process failed due to reduced catalyst activity and loss of hydrogen, resulting in imine accumulation.[3] The strategy we adopted was to carry out each of the epimerisation steps and the resolution separately, in effect providing a recycle process. An important element of this would be the use of a single, water-immiscible solvent. Other important considerations were the removal and possible recycle of the SCRAM catalyst and the order of the two epimerisation steps.

Each stage was evaluated separately and then integrated into a semi-continuous process, Figure 2. It was recognised from the outset that a single solvent would facilitate the continuous process, and consideration of each of the stages led us to evaluate toluene and *tert*-butyl methyl ether (tBME) as candidates.

2.1. Resolution of Racemic Sertraline. The selective crystallisation of the (1*S*,4*S*)-isomer from the mixture of all four diastereomers was achieved using (*R*)-mandelic acid in toluene or tBME in >99% ee and 90−98% de. Whilst the isolated yield of 35% is quite reasonable, it is a feature of the technology that the resolution yield is not critical, since the waste isomers are being recycled and, in theory, can all be transformed into the product, albeit with lower efficiency and higher operational cost. Using 100 g (0.327 mol) of a racemic 90:10 *cis/trans* mixture in 500 mL of toluene with 0.35 mol equiv of (*R*)-mandelic acid, the mixture was stirred at 85 °C with a

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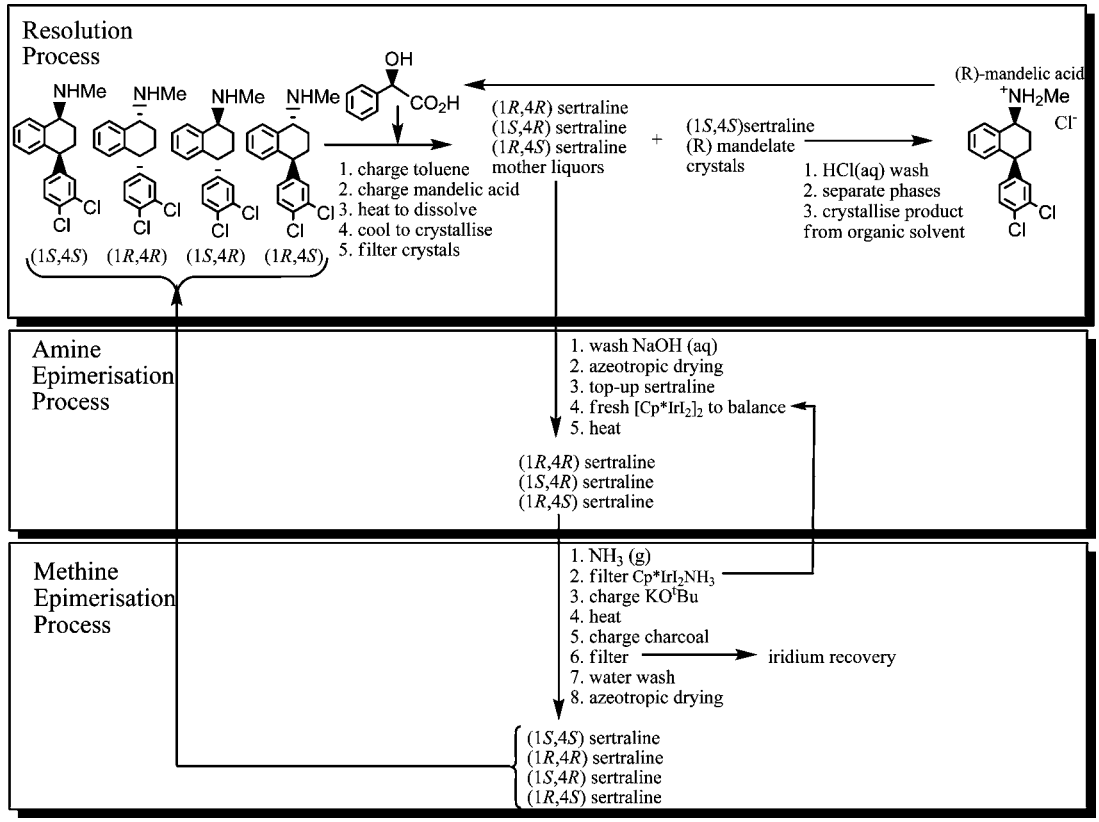


Figure 2. **Semi-continuous resolution−racemisation process for sertraline.**

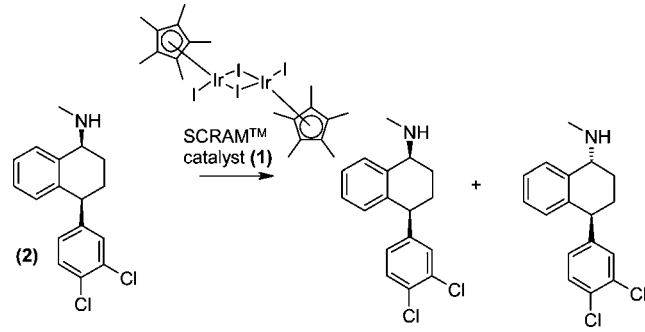
cooling/hold reaction profile and seeding with the (1*S*,4*S*)-sertraline (*R*)-mandelate salt. We isolated 52.1 g (0.114 mol) of the desired (1*S*,4*S*)-sertraline (*R*)-mandelate salt by filtration, which is quantitative with respect to the mandelic acid. The product was analysed by chiral HPLC and found to be 99% ee and 95% de. By using tBME solvent, the results were similar.

2.2. Mandelic Acid Recycle. Taking the product (1*S*,4*S*)-sertraline (*R*)-mandelate in ethyl acetate we charged an equal volume of 1 M sodium hydroxide base and extracted the sodium mandelate, which could be recycled and used in the next resolution. The mixture of waste sertraline isomers in toluene was washed with water and topped up with a fresh 35 g of the racemic 90:10 sertraline mixture.

2.3. Catalytic Epimerisation of the 1-(*N*-Methyl)amino Chiral Centre. It was found by screening racemisation catalysts that SCRAM catalyst (**1**) had the highest turnover frequency. Indeed using 0.1 mol % catalyst in toluene at 80 °C the (1*S*) chiral centre was racemised with a $t_{1/2}$ of 15 min, Scheme 1 and Figure 3.

The chloro-, bromo-, and rhodium analogues of Cp*MX_2 were poorly active, as were the Shvö catalyst and various Ir(I) species. When the reaction was left for an extended period, we noticed a slow accumulation of sertraline imine, which forms as molecular hydrogen is lost from the system. If reactions were carried out under a hydrogen atmosphere, the epimerisation rate was slowed, demonstrating that the reaction is an equilibrium. Sparging nitrogen or air mixtures through the reaction had little effect on the rate of epimerisation and, in fact, increased the formation of imine. A possible mechanism is shown in Scheme 2.

Scheme 1. **Epimerisation of (1*S*,4*S*)-sertraline with SCRAM catalyst (1)**



Epimerisation studies were all carried out on homogeneous solutions of pure (1*S*,4*S*)-sertraline in a range of solvents, and the results are shown in Table 1.

It can be seen that the solvents give different epimerisation end points. The diastereomeric excess does not reach zero, as the benzylic chiral centre induces diastereoselective imine reduction depending upon the system thermodynamics, i.e. solvent and temperature. The aromatic, ether, and ester solvents, entries 1−3, 8−10, and 11, gave consistent rates and thermodynamic end points of 14−20% de. This might be a result of thermodynamic equilibrium or catalyst decomposition, so to confirm this we carried out the same experiment as entry 1 starting with a racemic mixture of −50% de sertraline (excess of *trans*). The kinetics followed a similar profile with an end point at +13% de, confirming that under these conditions this was indeed the thermodynamic end point resulting from the (4*S*) stereocontrol. With anisole, entry 5, the de fell to 43%, this solvent apparently affecting the thermodynamic equilibrium.

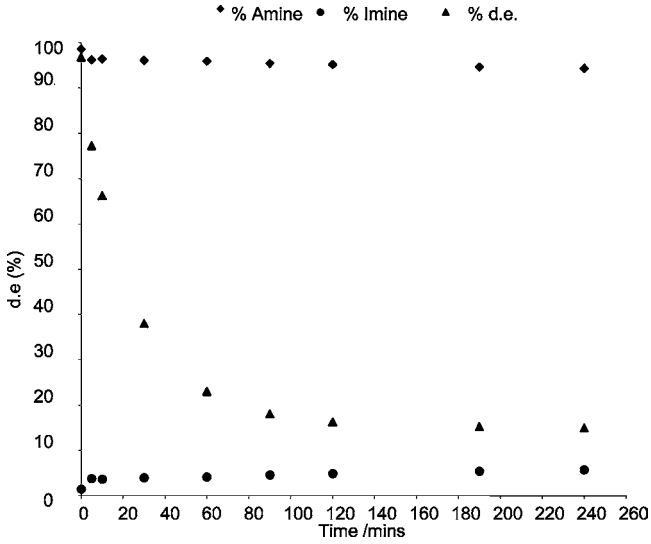


Figure 3. **Epimerisation profile of (1*S*,4*S*) sertraline to (1*R*,*S*,4*S*)-sertraline with SCRAM catalyst (1).**

With nitrobenzene and 1,1,2,2-tetrachloroethane, entries 6 and 7, only minor falls in the de were observed, and it is possible that the catalyst is inactive in these solvents. Cyclohexene, entry 4, was used as a potential hydrogen donor/acceptor and, interestingly, seems to slow the rate of racemisation, giving 65% de at 4 h and 58% de at 10 h. A surprising observation is seen when an equal volume of water is added to toluene: the racemisation end point is then 40% de rather than 15% de with toluene alone, entry 12. The other factor affecting the epimerisation is temperature, entry 13; it was found that the reduced catalyst lifetime outweighs the benefit in faster reaction and lower de. Other additives such as base, acid, ligands, or salts had little effect on reaction rate or epimerisation end point. Toluene was the solvent selected for further studies as it is a good general process solvent and could be integrated with the other parts of the process. Since the process is zero order with respect to the mixture of isomers, the process is unaffected by concentration and was conveniently run at the same high concentration as the mother liquors from the resolution process.

A critical part of the process was separation of the catalyst from product, and its removal after the amine epimerisation was preferred as this provided the greatest potential for its recycle. The options considered were adsorption or extraction of the soluble catalyst and use of an immobilised form of the catalyst. The catalyst was found to bind poorly to adsorption media such as charcoal, silica, ion-exchange resins, and the like. Extraction into water using reagents such as cysteine, thiourea, and methylamine were partially effective. The idea of these was to displace sertraline ligand from the catalyst; however, further investigation showed the techniques gave only about 50% iridium removal. Model studies with (*R*)-*N*-methyl-2-methylbenzylamine indicate that part of the catalyst may be transformed into a C-metalated species which is resistant to displacement by the aqueous extractants, Scheme 3. The structure (**5**) was characterised by mass spectrometry and ^{1}H and ^{13}C NMR. If this reaction is analogous to that occurring with sertraline, this represents a catalyst decomposition pathway, probably exacerbated by operating at high temperature.

An alternative process for removal of the catalyst was found in which a previously unknown, insoluble ammonio complex was formed by bubbling gaseous ammonia through the racemised reaction solution. The identity of this solid was confirmed by X-ray crystallography and ^{1}H and ^{13}C NMR as $Cp^{*}IrI_2(NH_3)$ (**4**), Figure 4.[16] The recovery of Ir was >50%. An advantage of this method over extraction is that heating the ammonio complex (**4**) reformed an active catalyst for use in the next reaction. Conveniently the ammonio complex was introduced directly into the amine racemisation stage, the catalyst re-entering the catalytic cycle upon heating. The remainder of the iridium appeared to be tied up as a C-metalated complex. Fortunately, this could be removed at the next stage of the process.

A further method for removal of the catalyst using immobilisation was devised in collaboration with Reaxa Ltd. In one system a 1-hydroxypentyl-2,3,4,5-tetramethylcyclopentadiene ligand was prepared. Immobilisation via the cyclopentadienyl has the advantage of being a very stable *eta*-5 coordinated ligand which prevents leaching of the metal often seen with tethering via more labile bidentate ligands. The $CpMe_4(CH_2)_5OH$ was metalated using iridium trichloride, then tethered to a variety of polyethyleneglycols of different masses. The iridium chloro complex was converted to the iodo complex by potassium iodide salt exchange. Scheme 4 shows the synthesis and PEGylation procedure using polydisperse PEG2000, and Figure 4 shows the X-ray crystal structure of the 1-hydroxypentamethylene SCRAM catalyst.[16b]

The PEGylated catalyst was used in a nanomembrane reactor,[17] the idea being to retain the high-molecular weight catalyst whilst enabling the low-molecular weight sertraline to pass through the membrane in a semi-continuous process. We found no leaching of iridium across the membrane, whilst the sertraline could pass through in high yield. The catalyst activity fell to about half after each of three recycles and is perhaps related to the deactivation mechanism described above, as the loss was greater at higher temperatures and addition of neither iodide, iodine, formic acid or hydrogen restored activity.

2.4. Catalytic Epimerisation of the Methine Chiral Centre. The epimerisation of the methine chiral centre of sertraline, is known using *tert*-butoxide as base.[14] We evaluated a series of bases at different stoichiometries and temperatures in toluene shown in Table 2.

The use of concentrated NaOH with Bu_4NOH phase transfer catalyst (PTC) was successful, although its use was stopped when we observed decomposition and carry-over of the PTC into the product. We were pleased to find that catalytic sodium or potassium tertiary butoxide were effective at epimerising the benzylic centre to 16% de in 1 h at 80 °C. During the reaction the solution turned black. When the stirring was stopped, a fine precipitate of black solid separated. ICP analysis of this showed it was the residual iridium, although the identity of the solid has not been determined. The partially epimerised toluene

(16) Structure determinations: compound **4** by Duckett, S.; Taylor, D.; Perutz, R.; Whitwood, A. University of York, CCDC 725450 and compound **6** by Kilner, C. University of Leeds, CCDC 724479.

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Scheme 2. **Possible mechanism for sertraline epimerisation and sertraline imine formation**

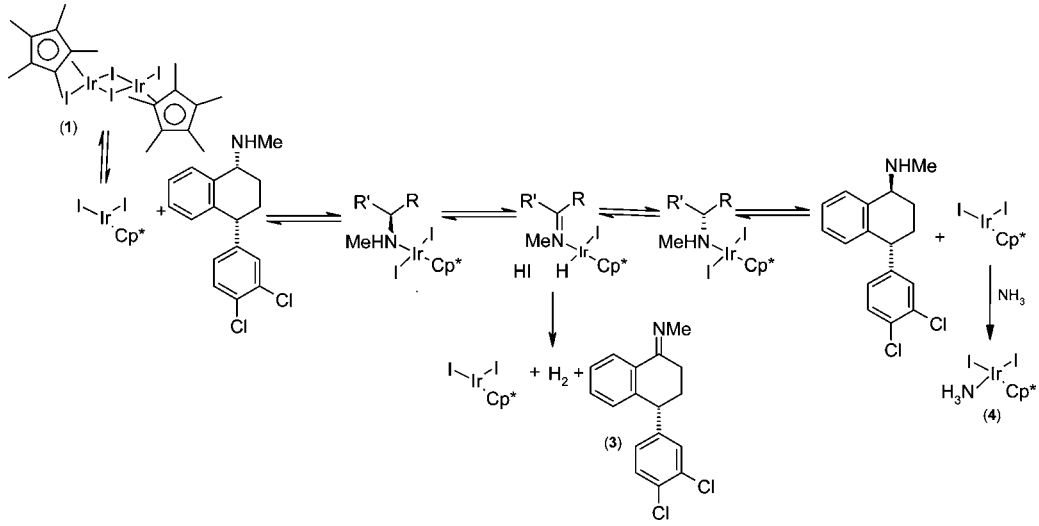


Table 1. **Epimerisation of (1*S*,4*S*)-sertraline with 0.1 mol % catalyst (1)[a]**

entry	solvent	de (%)[b]
1	toluene	15
2	mesitylene	14
3	cumene	16
4	cyclohexene	65
5	anisole	43
6	nitrobenzene	97
7	tetrachloroethane	95
8	1,4-dioxane	20
9	cyclopentyl methyl ether	18
10	*tert*-butyl methyl ether	15
11	*tert*-butyl acetate	19
12	toluene−water	40
13	toluene	13[c]

[a] Reactions 0.5 M at 80 °C. [b] Diastereomeric excess at 240 min. [c] Reaction conducted at 110 °C for 60 min.

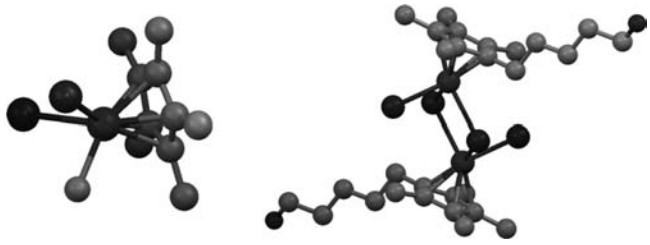
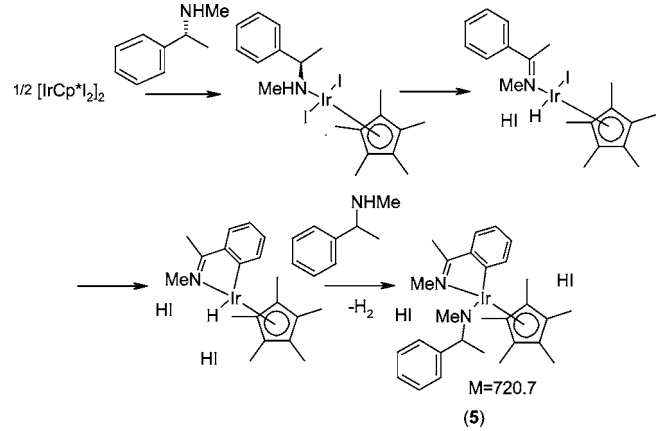


Figure 4. **X-ray crystal structures of ammonio−SCRAM complex (4) and tethered SCRAM catalyst (6).**

solution of sertraline with iridium is cooled, treated with charcoal, and then screened through a plug of Celite. The filtrates were washed with water to remove the base and *tert*-butanol and then azeotropically dried before the next resolution. Unfortunately the level of iridium in these solutions was not measured, although it was measured with other workup regimes and showed a small accumulation.

2.5. Semi-continuous Resolution−Racemisation Process for Sertraline. The process is designed with a single solvent which facilitates a semi-continuous process, Figure 2. Starting with the resolution process, the resolving reagent is charged to a warmed toluene solution of the sertraline diastereomers; upon cooling, the desired sertraline enantiomer crystallises, is separated, and can be further treated to form sertraline hydrochloride. In the pre-SCRAM preparation stage, the waste isomers contained in the mother liquors are washed to removal residual acid. Following the first cycle, an amount of fresh racemic sertraline is charged to replace that taken out at the resolution stage. A mixture of fresh SCRAM catalyst and recycled ammonio−SCRAM complex is then charged to give a total of

Scheme 3. **Possible catalyst decomposition pathway based on model study with (*R*)-*N*-methyl-2-benzylamine**



Scheme 4. **Synthetic route to PEG-tethered SCRAM catalyst**

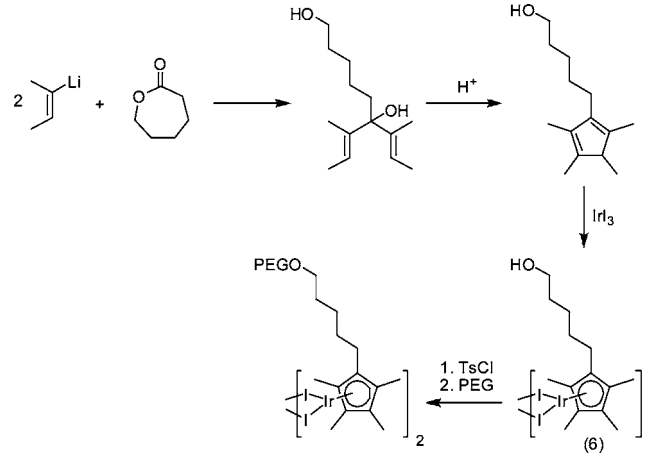


Table 2. **Catalytic epimerisation of the methine chiral centre using different bases and conditions**

entry	base	mol equiv	solvent	temp (°C)	time (h)	de (%)
1	NaOH (47%)[a]		toluene−water	110	3.5	38
2	$NaNH_2$	0.6	toluene	120	4	100
3	KOMe	0.1	toluene	120	3	100
4	KOE^t	0.1	toluene	120	3	100
5	NaO^{t}Bu	0.1	toluene	120	3	100
6	KO^{t}Bu	0.1	toluene	120	3	16
7	KO^{t}Bu	0.5	toluene	120	3	16
8	KO^{t}Bu[b]	0.1	toluene	125	4	40
9	KO^{t}Bu	0.1	THF	70	7	84
10	KO^{t}Bu	0.5	THF	70	1	20

[a] 0.1 mol equiv Bu_4NOH was added as a phase transfer catalyst. [b] 0.1 mol % iridium complex present from the previous stage.

0.1 mol % iridium and the mixture heated as before to epimerise the 1-position. The ammonio−catalyst complex is presumably decomposed to release ammonia and active catalyst. The partially epimerised sertraline solution is cooled. At the catalyst separation stage, ammonia is passed through the solution to precipitate part or all of the catalyst which is then screened and may be recycled. A catalytic quantity (10 mol %) of potassium *tert*-butoxide base is charged to the toluene solution and the mixture heated to racemise the 4-position and then cooled. Washing with water removes the base, water-soluble materials and residual catalyst. The nonpolar organic solution of racemised sertraline isomers is then ready for the next resolution stage.

A problem with any recycling process is the buildup of impurities. The main side product we observed was sertraline imine and the tetralone formed by its hydrolysis. Buildup of these could be prevented by applying a hydrogen atmosphere at the end of the SCRAM catalyst epimerisation stage to hydrogenate the imine back to sertraline. The process was operated in the laboratory for five recycles, and the results are shown in Tables3 and4.

3. Conclusions

A semi-continuous process for the asymmetric transformation of racemic into optically active sertraline using a single solvent has been developed. The process relies on a highly selective, but not necessarily high-yielding, diastereomeric resolution carried out in toluene. The waste mother liquors are then recycled using sequential epimerisation of first the amino-chiral centre, using 0.1 mol % or less of the highly active iridium-based SCRAM catalyst, and then the methine chiral centre using catalytic amounts of potassium *tert*-butoxide. The SCRAM catalyst is partially recovered as a solid made by precipitating with gaseous ammonia a toluene-insoluble, but reversibly formed, ammonio complex, in this case used in preference to an immobilised catalyst. After the addition of charcoal the remaining catalyst is then separated from the racemised sertraline prior to resolution, which both prevents precious metal carry-over into the product and enables recovery of its value. The process might be further considered sustainable through the recycle of the resolving reagent (*R*)-mandelic acid, making the net waste-excluding solvent less than 1 kg/kg product.

This type of process is also applicable to manufacture of other chiral amines and has been demonstrated with (*R*)-2-amino-7-methoxytetralin and (*R*)-3-aminopyrrolidine, details of which will be reported elsewhere. One particularly important feature of the asymmetric transformation process demonstrated above is that the problem of a wasteful, low yield inherent in a diastereomeric resolution can be overcome, providing a robust and potentially widely applicable methodology that might rival asymmetric synthesis.

4. Experimental Section

4.1. General. A Hewlett-Packard HP6890 gas chromatograph was used to analyse the ratio of sertraline isomers, and these were assigned using known standards. For the *cis*- and *trans*-diastereomers a 30 m × 320 mm, 0.25 μm, HP-5 5% phenyl methyl siloxane column, with inlet pressure of 12 psi, was held isothermally at 220 °C for 30 min, then ramped to 290 °C, resulting in elution times for the isomers of (1*S*,4*S*) and (1*R*,4*R*) 10.5 min; (1*R*,4*S*) and (1*S*,4*R*) 11.1 min; imine 13.6 min. For the enantiomers a Chirasil-DEX CB chiral column was held isothermally at 180 °C with elution times of the enantiomers (1*R*,4*R*) 55.8 min, (1*S*,4*S*) 57.0 min, (1*S*,4*R*) 63.9 min, (1*R*,4*S*) 68.3 min, ketone isomers 76.2 and 79.1 min, imine isomers 83.6 and 86.6 min. Alternatively, the isomers were resolved using a Hewlett-Packard HP1100 Chiracel OD-H 4.6 cm × 25 cm column from Chiral Technology using the method described by Singh et al. in *Org. Process Res. Dev.* **2007**, *11*, 726.

4.2. Resolution. Sertraline [260 g (0.85 mol)] with isomer composition (1*S*,4*S*) 47.9%, (1*R*,4*R*) 47.8%, (1*R*,4*S*) 0.6%, (1*S*,4*R*) 0.0%, and imine 3.7% was dissolved in 500 mL of toluene, and 53 g (0.35 mol) of (*R*)-mandelic acid was charged. The mixture was warmed and stirred until homogeneous and then cooled slowly whilst seeding with 1% (w/w) crystals of the (1*S*,4*S*)-sertraline (*R*)-mandelate salt and held for 3 h. The reaction mass was filtered, and the cake was washed with toluene and dried, yielding 160 g (0.35 mol). The product was analysed and found to be (1*S*,4*S*)-sertraline (*R*)-mandelate of 99% ee and 99% de. The filtrates from the resolution stage were first washed with an equal volume of 1 M sodium hydroxide and further washed with water, then azeotropically dried. The composition of isomers was found to be (1*S*,4*S*) 20.0%, (1*R*,4*R*) 73.5%, (1*R*,4*S*) 0% (1*S*,4*R*) 0.9%, ketone 5.6%, imine 0%.

4.2.1. Chiral Amine Epimerisation. Racemic sertraline (88 g) with the composition described above and *bis*-diiodoiridiumpentamethylcyclopentadiene (SCRAM catalyst **1**) [0.25 g (85 μmol)] were charged to the mother liquors from the previous stage. The mixture was heated at 80 °C for 8 h and then cooled to ambient. Gaseous ammonia was bubbled through the solution for 6 h during which a fine precipitate formed. The solid recovered was screened and reused in the next cycle whilst the reaction mass was used directly in the next stage.

4.2.2. Chiral Methine Epimerisation. Potassium *tert*-butoxide [9.5 g (0.085 mol)] was charged to the toluene solution and heated to reflux for 1 h. The solution turned dark and was cooled to ambient. Norit ROX 0.8 charcoal was added and the solution screened before adding an equal volume of water, stirring, settling, and separating. After a further aqueous wash the solution was dried azeotropically. HPLC analysis of the isomer

Table 3. **Enantiomer composition at different stages of the process**

process stage	cycle no.	(1*S*,4*S*)	(1*R*,4*R*)	(1*R*,4*S*)	(1*S*,4*R*)	tetralone	imine (**3**)
starting material	0	44.2	51.5	0.6	0	0	3.7
post resolution (mother liquors)	1	20.0	73.5	0	0.9	5.6	0
post resolution (mother liquors)	2	8.2	50.3	18.4	17.0	5.3	0.9
post amine epimerisation	2	14.3	39.6	12.1	24.6	0.7	–
post base epimerisation	2	23.2	33.0	19.6	16.7	0.0	7.4
post resolution (mother liquors)	3	5.7	55.1	17.2	13.5	7.4	0.7
post amine epimerisation	3	13.2	38.5	10.3	25.4	6.3	6.1
post base epimerisation	3	22.8	32.5	18.2	18.1	1.4	7.0
post resolution (mother liquors)	4	8.2	59.2	12.9	11.4	7.5	0.7
post amine epimerisation	4	11.7	41.2	8.5	24.7	7.9	5.9
post base epimerisation	4	21.2	34.1	18.4	18.5	1.4	6.4

Table 4. **(1*S*,4*S*)-Sertraline mandelate yields and purities**

cycle no.	*rac*-sertraline added (g)	yield (%)[a]	chiral purity % de (% ee)[b]	Ir content (ppm)[c]
0	50		99 (0)	0
1	15	98	92 (99)	<10
2	15	85	95 (99)	<10
3	22	97	95 (99)	<10
4	15	82	94 (99)	<10

[a] Based on theoretical vs mole equiv of resolving reagent. [b] Determined by HPLC. [c] Determined by ICPMS.

composition showed (1*S*,4*S*) 26.4%, (1*R*,4*R*) 34.3%, (1*R*,4*S*) 16.9%, (1*S*,4*R*) 16.6%, imine 5.7%.

4.3. Cycle 2. (*R*)-Mandelic acid [53 g (0.35 mol)] was charged to the warmed reaction mass above. The mixturewas stirred until homogeneous then cooled slowly whilst seeding with 1% (w/w) crystals of the (1*S*,4*S*) sertraline (*R*)-mandelate salt and held for 3 h. The reaction mass was filtered, the cake washed with toluene and dried, yielding 135 g (0.3 mol). The product was analysed and found to be (1*S*,4*R*)-sertraline (*R*)-mandelate of 99% ee and 95% de. The filtrates from the resolution stage were first washed with an equal volume of 1 M sodium hydroxide and further washed with water, then azeotropically dried. The composition of isomers was found to be (1*S*,4*S*) 8.2%, (1*R*,4*R*) 50.3%, (1*R*,4*S*) 18.4%, (1*S*,4*R*) 17.0%, ketone 5.3%, imine 0.9%.

4.3.1. Chiral Amine Epimerisation. Racemic sertraline (88 g) with the composition described above and 0.25 g (85 μmol) *bis*-diiodoiridiumpentamethylcyclopentadiene (SCRAM catalyst **1)** were charged to the mother liquors from the previous stage. The mixture was heated at 80 °C for 8 h then cooled to ambient. In-situ HPLC monitoring showed a composition of (1*S*,4*S*) 14.3%, (1*R*,4*R*) 39.6%, (1*R*,4*S*) 12.1%, (1*S*,4*R*) 24.6%, ketone 0.7%. Gaseous ammonia was bubbled through the solution for 6 h during which a fine precipitate formed. The solid recovered was screened and reused in the next cycle whilst the reaction mass was used directly in the next stage.

4.3.2. Benzylic Epimerisation. Potassium *tert*-butoxide [9.5 g (0.085 mol)] was charged to the toluene solution and heated to reflux for 1 h. The solution turned dark and was cooled to ambient. Norit ROX 0.8 charcoal was added and the solution screened before adding an equal volume of water, stirring, settling and separating. After a further aqueous wash the solution was dried azeotropically. HPLC analysis of the isomer composition showed (1*S*,4*S*) 23.2%, (1*R*,4*R*) 33.0%, (1*R*,4*S*) 19.6%, (1*S*,4*R*) 16.7%, ketone 0%, imine 7.4%.

4.4. Cycle 3. (*R*)-Mandelic acid [53 g (0.35 mol)] was charged to the warmed reaction mass above. The mixture stirred until homogeneous then cooled slowly whilst seeding with 1% (w/w) crystals of the (1*S*,4*S*) sertraline (*R*)-mandelate salt and held for 3 h. The reaction mass was filtered, the cake washed with toluene and dried yielding 155 g (0.34 mol). The product was analysed and found to be (1*S*,4*R*) sertraline (*R*)-mandelate of 99% ee and 95% de. The filtrates from the resolution stage were first washed with an equal volume of 1 M sodium hydroxide and further washed with water then azeotropically dried. The composition of isomers was found to be (1*S*,4*S*) 5.7%, (1*R*,4*R*) 55.1%, (1*R*,4*S*) 17.2%, (1*S*,4*R*) 13.5%, ketone 7.4%, imine 0.7%.

4.4.1. Chiral Amine Epimerisation. Racemic sertraline (88 g) with the composition described above and 0.25 g (85 μmol) *bis*-diiodoiridiumpentamethylcyclopentadiene (SCRAM catalyst **1)** were charged to the mother liquors from the previous stage. The mixture was heated at 80 °C for 8 h then cooled to ambient. In situ HPLC monitoring showed a composition of (1*S*,4*S*) 13.2%, (1*R*,4*R*) 38.5%, (1*R*,4*S*) 10.3%, (1*S*,4*R*) 25.4%, ketone 6.3%, imine 6.1%. Gaseous ammonia was bubbled through the solution for 6 h during which a fine precipitate formed. The solid recovered was screened and reused in the next cycle whilst the reaction mass was used directly in the next stage.

4.4.2. Benzylic Epimerisation. Potassium *tert*-butoxide [9.5 g (0.085 mol)] was charged to the toluene solution and heated to reflux for 1 h. The solution turned dark and was cooled to ambient. Norit ROX 0.8 charcoal was added and the solution screened before adding an equal volume of water, stirring, settling and separating. After a further aqueous wash the solution was dried azeotropically. HPLC analysis of the isomer composition showed (1*S*,4*S*) 22.8%, (1*R*,4*R*) 32.5%, (1*R*,4*S*) 18.2%, (1*S*,4*R*) 18.1%, ketone 1.4%, imine 7.0%.

4.5. Cycle 4. 53 g (0.35 mol) of (*R*)-mandelic acid was charged to the warmed reaction mass above. The mixture stirred until homogeneous then cooled slowly whilst seeding with 1% (w/w) crystals of the (1*S*,4*S*) sertraline (*R*)-mandelate salt and held for 3 h. The reaction mass was filtered, the cake washed with toluene and dried yielding 131 g (0.29 mol). The product was analysed and found to be (1*S*,4*R*) sertraline (*R*)-mandelate of 99% ee and 94% de. The filtrates from the resolution stage were first washed with an equal volume of 1 M sodium hydroxide and further washed with water then azeotropically dried. The composition of isomers was found to be (1*S*,4*S*) 8.2%, (1*R*,4*R*) 59.2%, (1*R*,4*S*) 12.9%, (1*S*,4*R*) 11.4%, ketone 7.5%, imine 0.7%.

4.5.1. Chiral Amine Epimerisation. Racemic sertraline (88 g) with the composition described above and 0.25 g (85 μmol) *bis*-diiodoiridiumpentamethylcyclopentadiene (SCRAM catalyst **1)** were charged to the mother liquors from the previous stage. The mixture was heated at 80 °C for 8 h then cooled to ambient. In-situ HPLC monitoring showed a composition of (1*S*,4*S*) 11.7%, (1*R*,4*R*) 41.2%, (1*R*,4*S*) 8.5%, (1*S*,4*R*) 24.7%, ketone 7.9%, imine 5.9%. Gaseous ammonia was bubbled through the solution for 6 h during which a fine precipitate formed. The solid recovered was screened and reused in the next cycle whilst the reaction mass was used directly in the next stage.

4.5.2. Benzylic Epimerisation. Potassium *tert*-butoxide [9.5 g (0.085 mol)] was charged to the toluene solution and heated to reflux for 1 h. The solution turned dark and was cooled to ambient. Norit ROX 0.8 charcoal was added and the solution screened before adding an equal volume of water, stirring, settling and separating. After a further aqueous wash the solution was dried azeotropically. HPLC analysis of the isomer composition showed (1*S*,4*S*) 21.2%, (1*R*,4*R*) 34.1%, (1*R*,4*S*) 18.4%, (1*S*,4*R*) 18.5%, ketone 1.4%, imine 6.4%.

4.6. Recovered Catalyst. The solid recovered after ammonia precipitation was washed with toluene and dried. The product was characterised: ^{1}HNMR (CD_2Cl_2) $CpMe_5$ 1.84 (s, 15H); NH_3 3.27 (b, 3H); ^{13}CNMR (CD_2Cl_2) $CpMe_5$ 10.7, 86.9; MS 605, 472; Microanalysis % theory (% actual): C 20.08 (20.17); H 3.03 (2.97); N 2.34 (2.23); other 74.55 (74.63); UV−vis ($CHCl_3$) (nm, M^{-1} cm^{-1}) 232 (1.6×10^4), 336 (4.3×10^3), 384 (4.2×10^3); IR (cm^{-1}): 2923 (m), 2959 (m), 2904 (m),1459 (l), 1412 (m), 1380 (l),1356 (m), 1155 (m), 1076 (m), 1022 (l), 951 (m), 609 (m), 533 (m), 422 (m). Single crystal X-ray diffraction: Ir−I1 2.7166(4) Å, Ir−I2 2.7140(4) Å, Ir−N 2.133(4) Å, Cp(cent)−Ir 1.783(3) Å; I1−Ir−I2 91.46°(1), N−Ir−I1 85.37°(14), N−Ir−I2 83.51°(14).

4.7. Tethered Iridium Catalyst. An oven-dried three-necked 1 L round-bottom flask with reflux condenser and dropping funnel attached was placed under a nitrogen atmosphere and then charged with anhydrous diethyl ether (130 mL). Lithium wire (7.92 g, 1.14 mmol, 3.2 mm diameter, 0.5−1% sodium) was washed with hexane, cut into small pieces, and added to the reaction flask. 2-Bromo-2-butene (80.0 g, 0.59 mmol, mixture of *cis* and *trans* isomers) was placed in the dropping funnel and a small portion added to the vigorously stirred lithium suspension. Once reaction had initiated, evidenced by refluxing of the solvent, the remaining 2-bromo-2-butene was diluted with diethyl ether (70 mL), the reaction mixture diluted with ether (80 mL), and addition continued at a rate to maintain a gentle reflux. After complete addition, the reaction mixture was stirred for 2 h at rt. Caprolactone (29.0 mL, 0.27 mmol) in diethyl ether (50 mL) was then added dropwise. After stirring for a further 1 h, the reaction mixture was poured into sat. NH_4Cl aq (600 mL), the ether layer separated, and the aqueous layer extracted with *tert*-butyl methyl ether (3×100 mL). The combined ether layers were washed with brine, dried over $MgSO_4$, and concentrated to approximately 100 mL. Aqueous hydrochloric acid (10%, 300 mL) was added to the concentrate, and the two-phase mixture stirred for 3 h at rt. The organic layer was separated and the aqueous layer extracted with *tert*-butyl methyl ether (3×50 mL). The combined ether layers were washed with water (2×100 mL) and dried over Na_2SO_4, and solvent was removed to give an orange/brown oil. Purification by eluting through a large plug of silica (heptane/EtOAc 10:1 as eluent) gave the product as a pale-yellow oil (25.8 g, 45%). HPLC Retention time 8.0 min; ^{1}H NMR (300 MHz, $CDCl_3$) 3.63 (t, $J = 6.6$ Hz, 2 H, C*H*$_2$OH), 2.21 (m, 2 H, CH_2), 1.81 (s, 6 H, $2 \times CH_3$), 1.78 (s, 3 H, CH_3), 1.59 (m, 2 H, CH_2), 1.38 (m, 5 H, $2 \times CH_2$ and allyl CH), 1.01 (dd, $J = 7.2$, 3.3, 3 H, CH_3); GC/MS (Trimethylsilyl chloride added) 280.0 (M^+ + TMS) 7.49 min, 83%.

Iridium trichloride hydrate (1.50 g, 4.25 mmol) and sodium bicarbonate (0.39 g, 4.68 mmol) were added to degassed methanol (10 mL) in a 20 mL capacity microwave tube, and the suspension was purged with nitrogen for 10 min. 1-(5-Hydroxypentyl)-2,3,4,5-tetramethylcyclopentadiene (1.77 g, 8.5 mmol) was added, and the purge continued for 5 min. The tube was sealed, and microwave heating was applied with a set temperature of 150 °C for 10 min. After cooling, a nitrogen balloon was attached via a needle through the reaction tube lid septum which resulted in effervescence from the solution. Once this had subsided, the tube was opened, and the reaction mixture was diluted with DCM (20 mL), then washed with water (15 mL), extracting the aqueous layer with DCM (2×10 mL). The combined DCM layers were washed with brine and dried over Na_2SO_4, and solvent was removed. The oily red residue was taken up in DCM (3−5 mL) and product precipitated with heptane. An orange powdery solid was obtained (1.87 g, 93%). HPLC retention time 5.0 min; ^{1}H NMR (300 MHz, $CDCl_3$) 3.65 (t, 2 H, C*H*$_2$OH), 2.16 (m, 2 H, CH_2), 1.86 (m, 2 H, CH_2), 1.62 (s, 6 H, $2 \times CH_3$), 1.58 (s, 6 H, $2 \times CH_3$), 1.45 (m, 4 H, $2 \times CH_2$).

Iridium chloro complex (1.00 g, 1.0 mmol) and sodium iodide (1.59 g, 10.6 mmol) were heated at reflux in degassed acetone (40 mL) under a nitrogen atmosphere. After 18 h, the solution was cooled, concentrated to approximately 10 mL on a rotary evaporater, and diluted with chloroform (40 mL). This solution was washed with water (2×40 mL) and then brine. The organic layer was dried over $MgSO_4$, and the solvent was removed. Product was precipitated with heptane after dissolution in a minimum volume of DCM to give a brick-red solid, 1.19 g (87%). ^{1}H NMR (300 MHz, $CDCl_3$) 3.65 (t, 2 H, C*H*$_2$OH), 2.26 (m, 2 H, CH_2), 1.85 (s, 6 H, $2 \times CH_3$), 1.80 (s, 6 H, $2 \times CH_3$), 1.58 (m, 4 H, $2 \times CH_2$), 1.42 (m, 4 H, $2 \times CH_2$). Single crystal X-ray diffraction confirmed the identity of this structure: Ir−I1 2.740 Å, Ir−I2 2.714 Å, Cp(cent)−Ir 1.841 Å, I1−Ir−I2 90.1°.

1-(5-Hydroxypentyl)-2,3,4,5-tetramethylcyclopentadiene (2.0 g, 9.6 mmol) was dissolved in anhydrous DCM (25 mL) and triethylamine (3.2 mL, 23.0 mmol), and DMAP (12 mg, 0.1 mmol) was added to the stirred solution which was cooled to 0 °C. Tosyl chloride (2.4 g, 12.6 mol) in DCM (20 mL) was added dropwise and then the reaction mixture stirred at rt for 20 h until TLC showed completion. The reaction mixture was washed with sat. $NaHCO_3$ aq (2×50 mL), then water (2×50 mL), and finally brine (50 mL). The organic phase was dried over $MgSO_4$, and solvent was evaporated to give a dark-yellow oil (3.3 g, 95%).

mPEG 2000 (poly(ethylene)glycol monomethyl ether, average molecular weight 2000, 18.0 g, 9.0 mmol) was dissolved in dry THF (100 mL) under a nitrogen atmosphere. Sodium hydride (0.40 g, 9.9 mmol) was added in portions over 10 min. After stirring at rt for 30 min, tosylate Cp*C_5OTs (3.3 g, 9.0 mmol) in THF (25 mL) was added dropwise, then the reaction mixture was heated at 60 °C overnight. After cooling, the reaction mixture was diluted with EtOAc (100 mL) and passed through a Celite pad to remove salt, eluting with EtOAc (20 mL). Evaporation of solvents gave a yellow oil which solidified on cooling, 16.5 g, 84%. *m*/*z* (ES +ive ion) *m*/*z* 760, 804, 848, 892, ..., to 1222 and *m*/*z* 483, 498, 513, 527, ..., to 835 consistent with $[M + 2NH_4]^{2+}$ and $[M + 3NH_4]^{3+}$ from product containing mPEG with 31 to 55 repeat units.

mPEG2000Cp* (10.0 g, 4.6 mmol) was dissolved in MeOH (7 mL) and degassed with a nitrogen purge. The resulting solution was added to iridium trichloride hydrate (0.92 mg, 2.6 mmol) and sodium bicarbonate (0.21 g, 2.6 mmol) in a 20 mL capacity microwave tube and the suspension purged with nitrogen for 10 min. The tube was sealed, and microwave heating was applied with a set temperature of 150 °C for 10 min. After cooling, a nitrogen balloon was attached via a needle through the reaction tube lid septum which resulted in effervescence from the solution. Once this had subsided, the tube was opened, and the reaction mixture was evaporated to dryness on the rotary evaporator. The residue was diluted, dissolved in DCM (5 mL), and then heptane (75 mL) was layered on top to precipitate the product. The heptane was decanted, the residue was dried under reduced pressure, and then redissolved in DCM (5 mL). To this vigorously stirred concentrated solution was added MTBE (40 mL) which precipitated a beige solid over the course of 1 h. The solid was collected by filtration to give a fine, beige powder (8.13 g).

$[Ir(mPEG2000Cp^*)Cl_2]_2$ (8.24 g) and sodium iodide 1.96 g, 13.5 mmol) were heated at reflux in degassed acetone (80 mL) under a nitrogen atmosphere. After 18 h, the solution was cooled, and the solvent was removed on the rotary evaporator. The residue was taken up in chloroform (150 mL) and washed with water (3 × 100 mL) and then brine (100 mL). The organic layer was dried over $MgSO_4$ and the solvent removed. The residue was dissolved in DCM (5 mL). To this vigorously stirred concentrated solution was added MTBE (60 mL) which precipitated a beige solid over the course of 1 h. The solid was collected by filtration to give a fine, beige powder (7.15 g).

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