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## Graphical Abstract

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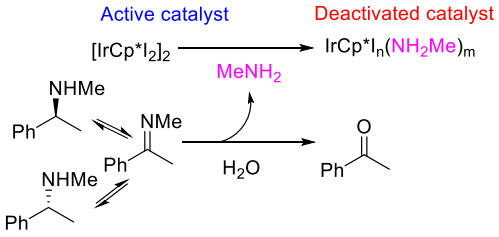

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# Deactivation Mechanisms of Iodo-Iridium Catalysts in Chiral Amine Racemization

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ABSTRACT

The homogenous, $[IrCp^*I_2]_2$, SCRAM catalyst (1) is active in the racemization of chiral amines. NMR, kinetic and structural mechanistic studies have determined the cause of catalyst deactivation to occur when ammonia or methylamine are liberated by hydrolysis or aminolysis of the intermediate imine, which tightly coordinate to the iridium centre to block turnover. Control of moisture and substrate concentration can suppress deactivation, whilst partial reactivation of spent catalyst was identified using hydroiodic acid.



Dedicated to the memory of our colleague, collaborator and friend Professor Jonathan Williams

## 1. Introduction

In the pharma industry racemic amines are commonly resolved by diastereomeric crystallization as the process is generally simple, economic and provides a consistent, high quality product.[1] Examples include dextromethorphan,[2] cetirizine,[3] cinacalcet[4] and vestipitant.[5] A disadvantage is the large amount of enantiomeric waste produced that exceeds half the input. In this regard racemization is being studied as a means of recycling the unwanted material.[6-9] Amines that possess an acidic chiral proton, produced for example by Schiff bases or alpha-carbonyl groups, can be racemized by mild bases, and there are many examples where this is combined with *in-situ* resolution for dynamic resolution processes.[10-12] Unfortunately, many chiral amines lack labile protons, with examples that include *N*-heterocycles and *N*-(di)alkylamines. Pd,[13-14] Ru,[15-16] and Ir,[17-18] based catalysts have been shown to reversibly dehydrogenate these types of amines. The $[IrCp^*I_2]_2$ catalyst is active in the racemization of *N*-substituted amines and has been used in both enzyme dynamic kinetic resolution,[19-20] and dynamic thermodynamic resolution processes, which is a crystallization induced deracemization.[21] The latter study reports an immobilized $[IrCp^*I_2]_2$ catalyst used in a combined continuous flow racemization and diastereomeric crystallization of amine salts. The immobilized catalyst lifetime was up to 242 hours, but with *N*-methylated amines, a linear deactivation of 2.8% ee.$h^{-1}$ was seen. This paper reports a detailed investigation of the cause of the catalyst deactivation, Figure 1.

Previous work on the $[IrCp^*I_2]_2$ catalyst, reports the kinetics and mechanism of chiral amine racemization and shows amine coordination to the iridium followed by hydride transfer.[22] With *N*-substituted amines it was shown that the racemization occurs by release of the imine/iminium into the bulk solvent prior to non-selective reduction by a hydridoiridium species. A similar system has been reported by Yamaguchi *et al*, in which $IrCp^*(NH_3)_3I_2$ catalyst carries out alkylation of aqueous ammonia with a range of alcohols.[24, 25]

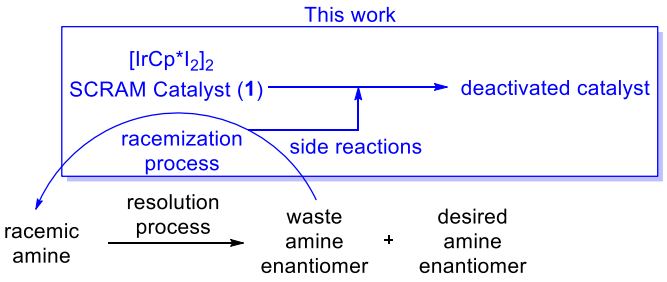



**Figure 1.** Integrated amine resolution-racemization process and study of catalyst deactivation reported in this paper.

## 2. Results/discussion

The racemization of different concentrations of (*S*)-*N*-methyl-2-phenethylamine (*S*)-(**2**) by catalyst (**1**) in toluene at 105ºC

shows unusual differences in both the initial rates and racemization endpoint, Figure 2.

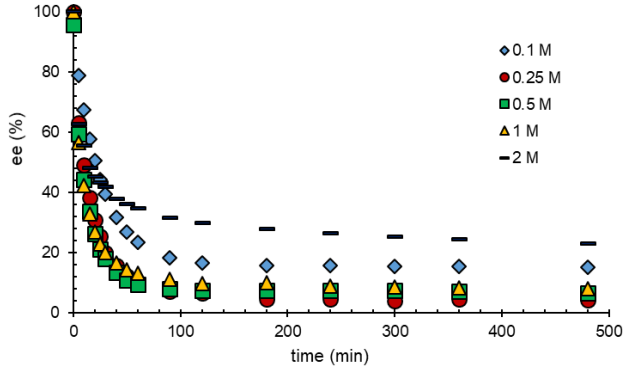



**Figure 2.** Racemization of different concentrations of amine (*S*)-(**2**) by catalyst (**1**) 0.2 mol% starting from ~100% e.e.

The fastest initial rates were observed at 0.25, 0.5 and 1.0 M concentrations, whereas at 0.1 and 2.0 M the rates were significantly lower. Furthermore, none of the experiments gave a racemate, depending upon concentration stopping between 23% and 4% e.e after 480 minutes. First order plots were fitted to the initial rates according to Equation 1, where $[S]_0$ is the initial concentration of enantiomer (*S*)-(**2**) and $[R]_t$ is the concentration of enantiomer (*R*)-(**2**) at time t.

$$\ln\left(\frac{[S]_0}{[S]_0 - 2[R]_t}\right) = k_{obs}t \qquad \text{Equation 1}$$

Linear fits for 0.1 and 2.0 M concentrations were poor, with $R^2$ values of 0.88 and 0.64, however, good fits were obtained with 0.25, 0.5 and 1 M concentrations and $k_{obs}$ of 0.092, 0.102 and 0.114 $min^{-1}$ respectively.

To understand the reason for these observations, a spiking experiment was carried out in which an additional 0.5 equiv. of (*S*)-(**2**) was added at 24 h making the solution 55% e.e. The graph shows the catalyst is inactive before 24 h since no racemization of the extra amine occurs, Figure 3(a).

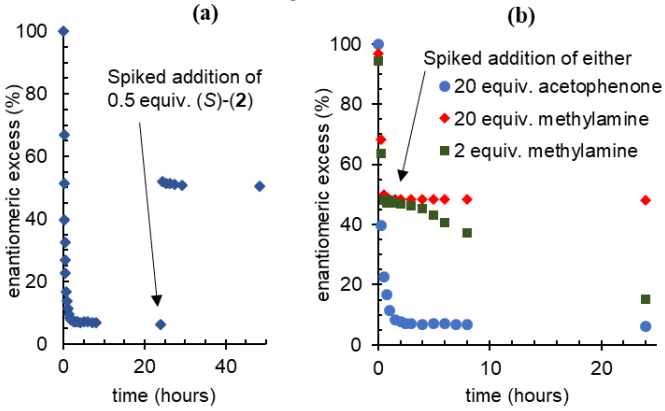



**Figure 3.** Racemization of (*S*)-(**2**) 0.5 M by (**1**) 0.2 mol% in toluene at 105°C (a) Spiked addition of 0.5 equiv. (*S*)-(**2**) at 24 h resulting in an increase in e.e. but little racemization (b) spiking of 20 equiv. acetophenone or 20 or 2 equiv. methylamine (with respect to (**1**)) at 30 minutes.

Interference of oxygen was eliminated as a cause of catalyst deactivation, but a reaction mass balance indicated that around 5% of the amine was converted to acetophenone. This allowed us to postulate hydrolysis of the imine intermediate as the cause of the loss of catalyst activity. Adding acetophenone midway through, had no effect on the racemization of (*S*)-(**2**), whilst, adding 20 equiv. methylamine (with respect to iridium), 30 minutes after the start of reaction, stopped the racemization completely, Figure 3(b). The addition of 2 equiv. of methylamine initially retarded the catalyst, but at 105°C it may be lost from the system as a vapor, and the catalyst regained a little activity.

A $^1$HNMR experiment was done to investigate methylamine complexation to the catalyst. Figure 4 shows the change in the integrals of selected protons (chemical shifts A-F) in a $d^6$-DMSO solution of catalyst (**1**) upon titration of methylamine/THF solution.

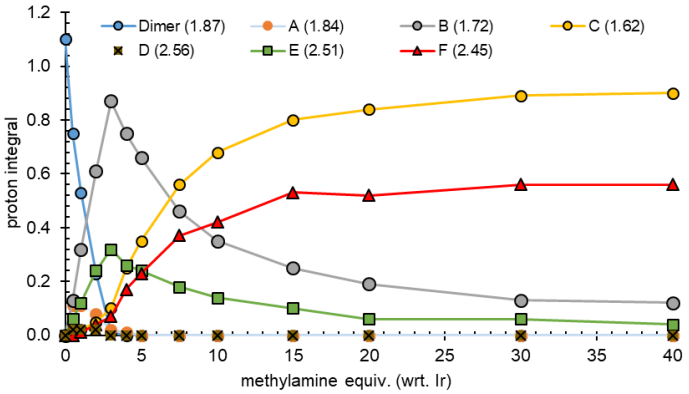
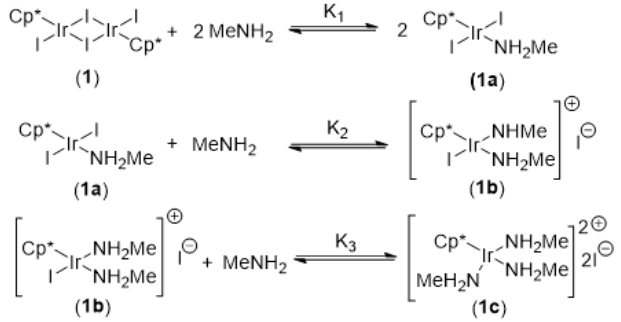



**Figure 4.** Changes in $^1$HNMR ($d^6$-DMSO) chemical shift of the $(CH_3)_5Cp$ and $CH_3NH_2$ protons when methylamine/THF solution is titrated into the catalyst dimer (**1**).

Four different catalyst species were identified, based on the Cp* methyl and methylamine protons and were assigned as the iridium dimer (**1**), mono- (**1a**), di-(**1b**) and tri-(**1c**) aminomethyl iridium species, Scheme 1, (ESI 5).




**Scheme 1.** Putative complexes formed by addition of methylamine to (**1**)

$^1$HNMR ($CDCl_3$) signals for the $IrCp^*Cl_2(H_2NMe)$ complex, analogous to (**1a**), have been reported at δ=1.70 (s, 15H, Me, Cp*), 2.77 (t, 3H, Me, $^3$JHH 6.7 Hz) and for $[IrCp^*Cl(H_2NMe)_2]Cl$ ($d^6$-DMSO): 1.62 (s, 15H, Me, Cp*), 2.46 (t, 6H, Me, $^3$JHH 6.0 Hz).[26] The relative concentration of each species was determined as a function of the methylamine added, with dimer (**1**) transformed into IrCp* species (**1a-c**). It appears that these species are in dynamic equilibrium and the data was fitted to the Scheme 1 model. The observed equilibrium constants, Equations 2-4, were calculated at 3 equivalents of me

$$K_1 = \frac{[\mathbf{1a}]^2}{[\mathbf{1}] \times [MeNH_2]^2} = 0.16\ mM^{-1} \qquad \text{Equation 2}$$

$$K_2 = \frac{[\mathbf{1b}]}{[\mathbf{1a}] \times [MeNH_2]} = 17.31\ mM^{-1} \qquad \text{Equation 3}$$

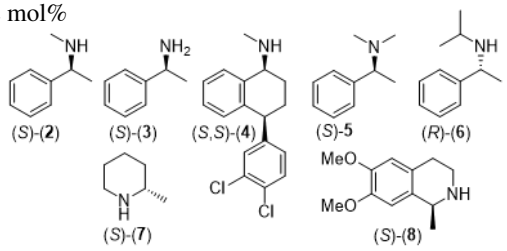
$$K_3 = \frac{[\mathbf{1c}]}{[\mathbf{1b}] \times [MeNH_2]} = 0.046\ mM^{-1} \qquad \text{Equation 4}$$

Their integrations were converted to concentrations based on the internal standard, benzene, see ESI5.

Under this set of conditions, the equilibrium constants lie mainly towards the disubstituted methylamine-iridium complex (**1b**); while the formation of tri-substituted methylamine-iridium complex (**1c**) is less favored due to steric hindrance. Although (**1a**) is the least sterically demanded, the dissociation of methylamine is unfavorable resulting in a relatively small equilibrium constant. Unfortunately, further characterization of species (**1a-c**) was unsuccessful, either by isolation of complexes from the mixture, or mass spectrometric data. Attempts to prepare (**1c**) directly using an excess of methylamine under pressure, were similarly unsuccessful. It is unclear which of the aminomethyl species are catalytically inactive but based on the level of methylamine in the racemizing solution and the estimated equilibrium constants, species (**1b**) and (**1c**) may be inactive whilst (**1a**) may retain some activity. Heating (**1a-c**) to displace methylamine resulted in only minor reactivation of the catalyst, which was also observed in Figure 3(b). Competition experiments, done by adding *iso*-propylamine, di-*iso*-propylamine or *tert*-butylamine into a racemization of (*S*)-(**2**) by catalyst (**1**), failed to prevent catalyst deactivation, as evidenced by the reaction stopping at ~6% e.e., further indicating the strength of the methylamine complexes (**1a-c**), ESI 6. The evidence indicates that bulky amines and secondary imines bind reversibly but methylamine and ammonia bind strongly and can multiply coordinate to deactivate the catalyst. The reason these may be potent inhibitors is because the catalyst is unable to dehydrogenate them. Methanol is similarly a poor hydrogen transfer donor with this catalyst, with formaldehyde never observed.

The analogous $IrCp^*I_2NH_3$ (**1d**), and $IrCp^*(NH_3)_3I_2$ complexes have been isolated and the crystal structures reported.[17, 24] The low TOF and incomplete racemization with primary amine (*S*)-2-phenethylamine (*S*)-(**3**), indicates a similar deactivation process with ammonia, generated as a result of substrate dimerization. A solid isolated from the reaction was identified by single crystal x-ray crystallography as (**1d**) and heating this failed to rejuvenate its racemization activity.

**Table 1.** Racemization of amines with homogeneous catalyst (**1**) 0.2 mol%

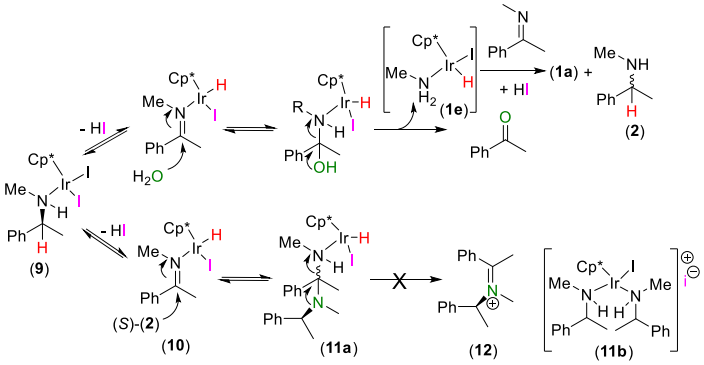



| Entry | amine[a] | $k_{obs}$ ($min^{-1}$) | ketone[b] (mol%) | limit e.e. (%) |
|---|---|---|---|---|
| 1 | (*S*)-(**2**) | 0.047 | 0.72 | 15 |
| 2[c] | (*S*)-(**3**) | 0.003 | N/D | 10[d] |
| 3[e] | (*S,S*)-(**4**) | 0.044 | 1.77 | 18 |
| 4 | (*S*)-(**5**) | 0.005 | 1.05 | 16 |
| 5 | (*R*)-(**6**) | 0.022 | 1.26 | 0 |
| 6 | (*S*)-(**7**) | 0.18 | N/D | 0 |
| 7[f][g] | (*S*)-(**8**) | 0.093 | N/D | 0 |

[a] 0.1 M; [b] at end of experiment 6-24h, N/D = not detected [c] in solvent 2,4-dimethyl-3-pentanol/toluene 1:1(v/v) [d] however, this represents only 5% yield, the main products are dimers [e] compares with 0,042 $min^{-1}$ in reference 22; [f] in solvent EtOAc/ iPrOH 7:1 (v/v) [g] carried out at 60°C

A scoping study was done to determine whether catalyst inactivation occurred with other *N*-alkylated substrates, Table 1. Notable, is the wide variation in racemization rate between the acyclic amines (**2**)-(**6**), entries 1-5 and cyclic amines (**7**) and (**8**), entries 6&7. The *N*-methylamino chiral center in sertraline (*S,S*)-(**4**), entry 3, was epimerized rapidly from cis to trans but stopped at around 18% d.e. This observation was previously assumed to be the thermodynamic equilibrium between the diastereomers.[17] However, a substrate spiking experiment, Figure S7 shows a largely inactive catalyst with adventitious hydrolysis of the imine producing an amount methylamine that equates to 8.8 equiv. vs (**1**), entry 3. The *N,N*-dimethyl analogue (*S*)-(**5**), also failed to racemize completely, stopping at 16% e.e., entry 4, with 1 mol% acetophenone (5 equiv. vs (**1**)) observed in the final samples. This indicates *N,N*-dimethylamine can also coordinate and inactivate (**1**). Contrary to this, the *N-iso*-propylamine (*R*)-(**6**) was completely racemized under these conditions, albeit more slowly than (*S*)-(**2**), entry 5. Furthermore, acetophenone was seen (1.26 mol%, 6.3 equiv. vs (**1**)), indicating that *iso*-propylamine is ineffective at inhibiting the catalyst. Racemization of the heterocyclic amines (*S*)-(**7**) and (*S*)-(**8**) is fast. Indeed, the latter was too rapid to determine accurately, even at 60°C rather than 105°C. In these cases, hydrolysis of the intermediate imine is unfavorable and reduction to produce the racemic amine is more likely. Their steric size may prevent multiple coordination and, as previously reported, the secondary imine dissociates readily enabling high catalyst turnover.[22]

Having determined the cause of catalyst deactivation as hydrolysis of the intermediate imine, the obvious remedy is to exclude water. A control reaction, with *N*-methyl-2-phenethylimine in wet toluene but without catalyst, showed little hydrolysis, however the addition of catalyst (**1**) resulted in rapid formation of acetophenone. Similarly, water added to an actively racemizing solution of (*S*)-(**2**) was shown to affect the rate and end point. These results indicate the imine is coordinated to the iridium sufficiently long to allow reactions with nucleophiles. Real time analysis of the catalytic racemization of (*S*)-(**2**) by (**1**) using high field continuous flow $^1$HNMR and +ESI-MS were inconclusive but showed accumulation of complex (**9**), $M^+$ = 717, and a smaller, steady-state, concentration of (**10**), $M^+$ = 589. Using a selective excitation pulse sequences technique,[23] hydrido signals at -13.1 and -15.2 ppm with $M^+$ of 783 and 908 and isotope patterns that indicate bridging species $(Cp^*Ir)_2IH_2$ and $(Cp^*Ir)_2I_2H$ that may be off cycle. Complex (**1e**) was not seen but may rapidly reduce the imine to generate racemic (**2**) and, with re-addition of HI, catalyst species (**1a**). Unlike the racemization of (*S*)-(**3**), dimer (**12**) and reduced diastereomers are never seen with (*S*)-(**2**). A species with $MH^+$ of 725.18 (**11a**) is observed and this invokes the precursor (**10**), although (**11b**) has the same mass and isotope pattern and cannot be excluded. A plausible mechanism for the hydrolysis is shown in Scheme 2.



**Scheme 2.** Proposed mechanism of formation of complex (**1a**) showing the failed nucleophilic attack of (*S*)-(**2**) on the coordinated imine (**10**) and no observed dimer, but its reaction with water to give acetophenone, complex (**1a**) and the racemized amine (**2**).

Reactivation of the catalyst was tried by adding sodium iodide $d^6$-DMSO solution into a reaction mixture containing (**1a-c**) in an NMR tube. The spectra showed an increase in the concentration of (**1**) and (**1a**), but also what might be the anionic triiodoiridium species $IrCp^*I_3Na$ (**1f**). Unfortunately, including NaI in the racemization of (*S*)-(**2**) made no difference to the rate or end point. Hydroiodic acid was also tested but resulted in loss of the amine to side reactions.

Another way to overcome the problem of catalyst inhibition is to encourage reduction of the imine by adding hydrogen donor solvents into the reaction. Figure 5 shows the effect of adding 20%(v/v) alcohols to the racemization of (*S*)-(**2**) in ethyl acetate.

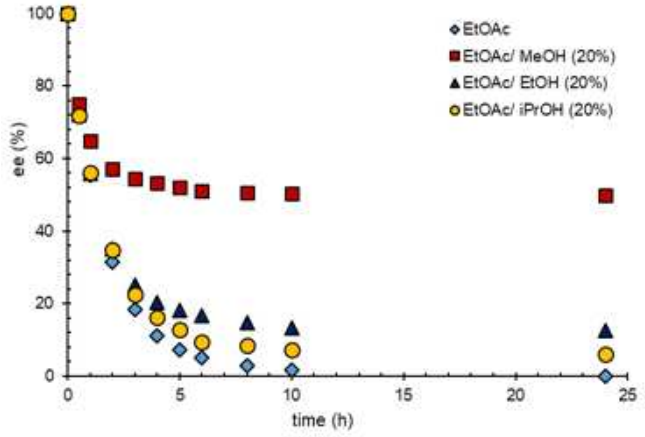
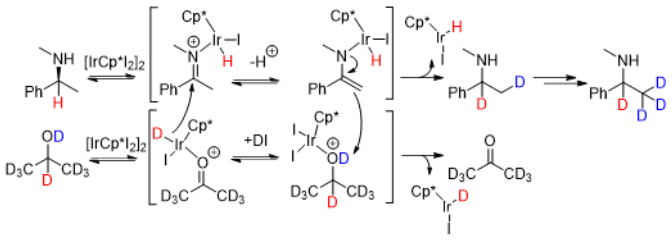



**Figure 5.** The effect of alcohol donor solvents on racemization rates of (*S*)-(**2**) with 1 mol% catalyst (**1**) at 60°C.

The racemization half-life ($t_{1/2}$) with ethyl acetate is 66 minutes corresponding to second order rate constant of $k_{cat}$ of $1.77x10^{-2}$ $M^{-1}.s^{-1}$ (compared to $2.16x10^{-2}$ $M^{-1}.s^{-1}$ in toluene at the same temperature)[22] and complete racemization is observed. Whereas, the addition of *iso*-propanol and ethanol slightly increase the $k_{cat}$ to $1.83x10^{-2}$ $M^{-1}.s^{-1}$, with end points of 6% and 13% e.e. respectively. The effect of methanol is more marked, with a reduced $k_{cat}$ of $1.49x10^{-2}$ $M^{-1}.s^{-1}$ and end point of 50% e.e. Methanol may coordinate to the iridium in the same way as methylamine, Scheme 1, or act as a nucleophile, as in Scheme 2, though the mechanism has not yet been investigated. The small rate increase seen with ethanol and *iso*-propanol can be attributed to their hydrogen donor properties. Time resolved $^1$HNMR and +ESI-MS deuterium labelling studies using $d^8$-*iso*-propanol, indicate a bimolecular catalytic mechanism in which the deuterido-iridium complex formed from the alcohol, reduces the coordinated imine, Scheme 3 and ESI 8.




**Scheme 3.** Proposed mechanism for the observed incorporation of deuterium into (*S*)-(**2**) which requires the interaction of two different catalyst species transferring either a deuteride or deuteron to the coordinated imine/enamine to explain the labelling pattern.

For deuterium to appear at the chiral center of (**2**), the deuteride must come from a catalyst that has dehydrogenated $d^8$-*iso*-propanol. Deuterium incorporation is also seen beta- to the chiral center, confirming the reaction of an iridium-bound enamine with deuteron. Indeed, multiple deuteron incorporation is seen at the $C_1$ methyl but not $C_3$, the *N*-methyl group in (**2**), ESI 9.

## 3. Conclusions

The studies reported here explain the observed differences in iodo-iridium mediated racemization rates of acyclic *N*-alkyl and heterocyclic amines. Catalyst deactivation was suspected when *N*-methylamines failed to completely racemize. Deactivation was found to occur by strong coordination of ammonia from primary amines, and methylamine from *N*-methyl amines. This occurs through hydrolysis or aminolysis of the catalyst-activated imine. Several *N*-methyl coordinated iridium species have been observed by $^1$NMR and are in dynamic equilibrium. Although the racemization activity of each is still unknown, the calculated equilibria show the disubstituted methylamine-iridium complex (**1b**) predominates, and this may be the inactive catalyst species. This would explain why racemization of *N*-*iso*-propyl or heterocyclic amines do not deactivate the catalyst, as their larger size may preclude disubstitution. For *N*-methyl amines, poisoning of the catalyst was prevented by ensuring anhydrous conditions, whilst adding hydrogen donor alcohols helped shift the equilibrium away from the imine and slightly improved the racemization rates. The addition of methanol was detrimental to the reaction as it seems to behave like water in alcoholising the catalyst-activated imine. The addition of sodium iodide was also successful in moving the equilibrium away from the amine coordinated species, though its use within the reaction was unsuccessful. Some insights into the catalytic mechanism were gained with continuous flow NMR with observation of hydridoiridium species and by +ESI-MS amine coordinated complexes, though more work is required to more fully characterize catalytic intermediates. The use of $d^8$-*iso*-propanol solvent showed deuterium incorporation at positions alpha- and beta- to the chiral center through deuteride and deuteron addition. This indicates both imine/iminium and enamine coordinated species are present in the manifold, and that separate catalytic species are interacting to produce the observed products. Further studies on the use of the SCRAM catalyst to introduce deuterium into amines will be reported elsewhere.

## 4. Experimental

Materials and equipment. Unless otherwise stated, all chemicals were obtained from Sigma-Aldrich, Fisher Scientific, Alfa Aesar or Fluorochem and were used without further purification. Catalyst (1) was prepared as described previously.20 All solvents used were HPLC grade.

General procedures for racemization in batch. The racemization of (*S*)-(**2**) (0.5 M) in toluene by $[IrCp^*I_2]_2$ (**1**) is described as an example. Catalyst (**1**) (5.1 mg, 4.4 µmol) and a stirrer bar were added to a three-neck round bottom flask and flushed with nitrogen for 10 minutes. (*S*)-(**2**) (0.3 g, 2.2 mmol, 323 µL) and n-decane (31.2 mg, 0.22 mmol, 43 µL) were dissolved into toluene (4 mL, dried over molecular sieves). The solution was added to the catalyst. The reaction was stirred and heated to 105°C for 24 hours. The reaction was sampled (20 µL) before heating and during the reaction by diluting the sample into ethyl acetate (980 µL). The samples were analyzed by GC for

conversion and chiral GC for the determination of e.e., after derivatization with trifluoroacetic anhydride (30 µL).

A similar procedure was employed for the racemization of other substrates under designated conditions (Table S1). The e.e. of the samples were determined by either chiral GC, HPLC or $^1$HNMR (Table S2).

Racemization of (*S*)-(**2**) (0.5 M) in batch with spiking of (*S*)-(**2**). After 25 hours, where the racemization stopped or reached 0% e.e., (*S*)-(**2**) (0.5 equiv. with respect to the original amount of (*S*)-(**2**) in the reaction) and n-decane (0.25 equiv.) were dissolved into toluene and charged to the reaction mixture at 105°C. The reaction was sampled immediately after the addition and at specific times.

Racemization of (*S*)-(**2**) (0.5 M) in batch with spiking of methylamine (2 or 20 equiv. with respect to iridium). A similar procedure to above was employed. Catalyst (**1**) (25.8 mg, 22.2 µmol) and tetrahydrofuran (4 mL) were used and the reaction was heated to 60°C. After 30 minutes, where the e.e. of (**2**) reached approximately 50%, methylamine/ tetrahydrofuran solution (1.7 M, 52.2 µL, 88.7 µmol) was added. The reaction was sampled 15 minutes after the addition and at specific times for 24 hours. The same procedures were repeated for spiking 20 equiv. of methylamine (520 µL, 0.88 mmol) after 30 minutes from the start of the reaction.

NMR titration of catalyst (**1**) with methylamine. Catalyst (**1**) (3.1 mg, 2.7 µmol, 5.3 µmol iridium) and benzene (9.1 mg, 10 µL, 0.117 mmol) were dissolved into d$^6$-DMSO (0.6 mL). The sample was analyzed by $^1$HNMR (500 MHz). Methylamine/ methanol solution (2 M) was added as shown in Table S4. After each addition, the sample was shaken for 60 seconds and the $^1$HNMR was recorded.

General procedure for deuterium/ proton exchange of chiral amines by d$^8$-*iso*-propyl alcohol. Catalyst (**1**) (29.1 mg, 25.0 µmol) was added to a microwave tube with a magnetic stirrer. The chiral amine (1 mmol) was dissolved into d$^8$-*iso*-propyl alcohol (766 µL) and d$^8$-toluene (306 µL), analyzed by $^1$HNMR (300 MHz) then added to the catalyst and heated to 110°C by microwave. After each hour of heating, the reaction mixture was cooled down to room temperature and sampled for $^1$HNMR analysis, then returned to the microwave vial and reheated to 110°C by microwave. The heating, cooling and sampling process was repeated for 4 to 6 hours. For amines (**2**) and (**6**), a d$^6$-DMSO insert (which was prepared by filling a melting point capillary tube with d$^6$-DMSO and sealed at both ends) was placed into the NMR sample for analysis.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

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## Notes and references

1. J. Wouters and L. Quéré, Pharmaceutical Salts and Co-crystals. RSC Publishing, 2011.

2. H. Morris and J. Wallach, From PCP to MXE: a comprehensive review of the non-medical use of dissociative drugs. Drug Testing and Analysis 2014, 6 (7-8), 614-632.

3. D. A. Pflum, H. S. Wilkinson, G. J. Tanoury D. W. Kessler, H. B. Kraus, C. H. Senanayake. and S. A. Wald, Org. Proc. Res. Dev., 2001, 5 (2), 110-115.

4. V. T. Mathad, G. B. Shinde, S. S. Ippar, N. C. Niphade, R. K. Panchangam and P. J. Vankawala, Syn. Commun. 2011, 41 (3), 341-346.

5. C. M. Brandel, J. W. B. Cooke, R. A. J. Horan, F. P. Mallet and D. R. Stevens, Org. Proc. Res. Dev. 2015, 19 (12), 1954-1965.

6. E. J. Ebbers, G. J. A. Ariaans, J. P. M. Houbiers, A. Bruggink, A. and B. Zwanenburg, Tetrahedron 1997, 53 (28), 9417-9476.

7. J. H. Lee, K. Han, M.-J. Kim and J. Park, Eur. J. Org. Chem. 2010, (6), 999-1015.

8. N. J. Turner, Curr. Opin. Chem. Biol. 2010, 14 (2), 115-121.

9. C.-J. Jiang and G.-L. Cheng, Curr. Org. Chem. 2013, 17 (11), 1225-1234.

10. K. M. J Brands and A. J. Davies, Chem. Rev. 2006, 106 (7), 2711-2733.

11. W. L Noorduin, T. Izumi, A Millemaggi, M. Leeman, H. Meekes, W. J. P Van Enckevort, R. M Kellogg, B. Kaptein, E.Vlieg and D. G. Blackmond, J. Am. Chem. Soc., 2008, 130 (4), 1158-1159.

12. O. Verho and J.-E. Backvall, J. Am. Chem. Soc. 2015, 137 (12), 3996-4009.

13. M. T. Reetz and K. Schimossek, Chimia International Journal for Chemistry 1996, 50 (12), 668-669.

14. A. N. Parvulescu, P. A Jacobs and D. E. De Vos, Chemistry – A European Journal 2007, 13 (7), 2034-2043.

15. O. Pamies, A. H. Ell, J. S. M. Samec, N. Hermanns and J.-E. Backvall, Tetrahedron Letts. 2002, 43 (26), 4699-4702.

16. J. Paetzold and J. E. Backvall, J. Am. Chem. Soc., 2005, 127 (50), 17620-1.

17. A. J. Blacker, S. Brown, B. Clique, B. Gourlay, C. E. Headley, S. Ingham, D. Ritson, T. Screen, M. J. Stirling and D. Taylor, Org. Proc. Res. Dev., 2009, 13 (6), 1370-1378.

18. A. J Blacker and C. E. Headley in Green Chemistry in the Pharmaceutical Industry (Eds. P. J. Dunn, A. S. Wells, M. T. Williams) 2010, 269-288 Wiley-VCH Verlag GmbH & Co. KGaA.

19. A. J. Blacker, M. J. Stirling and M. I. Page, Org. Proc. Res. Dev. 2007, 11 (3), 642-648.

20. M. J. Stirling, A. J. Blacker and M. I. Page, Tetrahedron Letts. 2007, 48, 1247-1250.

21. Manuscript submitted for publication

22. M. J. Stirling, J. M. Mwansa, G. Sweeney, A. J. Blacker and M. I. Page, Org. Biomol. Chem. 2016, 14 (29), 7092-7098.

23. A. M. R. Hall, P. Dong, A. Codina, J. P. Lowe and U. Hintermair, ACS Catalysis 2019 9 (3), 2079-2090

24. R. Kawahara, F.-i. Fujita and R. Yamaguchi, J. Am. Chem. Soc., 2010, 132 (43), 15108-15111.

25. R. Kawahara, K.-i. Fujita and R. Yamaguchi, Adv. Syn. Cat., 2011, 353 (7), 1161-1168.

26. J. Vicente, M. T. Chicote, I. Vicente-Hernández and D. Bautista, Inorg. Chem., 2008, 47 (20), 9592-9605.