Conference paper

Joseph M. Mwansa, Matthew J. Stirling and Michael I. Page*

Changing the kinetic order of enantiomer formation and distinguishing between iminium ion and imine as the reactive species in the asymmetric transfer hydrogenation of substituted imines using a cyclopentadienyl iridium (III) complex

https://doi.org/10.1515/pac-2019-0222

Abstract: The iridium (III) complex of pentamethylcyclopentadiene and (*S*,*S*) or (*R*,*R*)-1,2-diphenyl-*N*′-tosylethane-1,2-diamine is an effective catalyst for the asymmetric transfer hydrogenation of imines under acidic conditions. However, the enantiomeric excess (*ee*) of the product amines from the reduction of 1-methyl-3,4-dihydroisoquinolines in either acetonitrile or dichloromethane, decreases exponentially. The dominant cause of the enantioselectivity is the difference in kinetic order of the formation of the two enantiomers with the *S*-enantiomer being formed in a first-order process whereas that for the *R*-enantiomer follows zero-order kinetics when (*R*,*R*)-TsDPEN is employed, due to different rate-limiting steps for the two processes. A series of 1-fluorinated methyl-3,4-dihydroisoquinolines were synthesised to change the rate-limiting dissociation of the (*R*) amine product from Ir (III) so that both enantiomers are formed with the same kinetic order. This results in almost complete removal of the enantioselectivity of the reduction. It has been suggested that reduction of imines using transition metal complexes occurs through the neutral imine rather than the more reactive iminium-ion. α-Substituted imines with electron-withdrawing groups make protonation more difficult but enhance the electrophilicity of the imine carbon facilitating nucleophilic attack. The pK_a of the iminium ions of 1-fluorinated methyl-3,4-dihydroisoquinolines were determined. Using the relative rates of the cyclopentadienyl iridium (III) complex catalysed reduction of these 1-fluorinated methyl-3,4-dihydroisoquinoline in acetonitrile and, under the acidic conditions of a 5:2 ratio of formic acid:triethylamine, showed that the iminium ion is the reactive species.

Keywords: asymmetric catalysis; asymmetric hydrogenation; ICPOC-24; iridium catalysis; kinetics; mechanism.

Introduction

The iridium (III) complex of pentamethylcyclopentadiene and (*R*,*R*)-1,2-diphenyl-*N*′-tosylethane-1,2-diamine (**1**) catalyses the asymmetric reduction of imines to amines under acidic conditions using a 5:2 mixture of excess formic acid and triethylamine in either acetonitrile or dichloromethane [1]. Formic acid provides the source of reducing hydride ion and also protonation of the imine to increase its reactivity. However, this Ir complex (**1**) catalysed reduction of imines shows unusual enantiomeric excess (*ee*) profiles for the product amines [1]. The initial product amines are predominantly the (*S*)-enantiomers with >90 % *ee* but

Article note: A collection of invited papers based on presentations at the 24th IUPAC International Conference on Physical Organic Chemistry (ICPOC 24) held in Faro, Portugal, 1–6 July 2018.

***Corresponding author: Michael I. Page,** School of Chemistry, University of Edinburgh, Joseph Black Building, David Brewster Road, Edinburgh EH9 3FJ, UK, e-mail: mike.page@ed.ac.uk
Joseph M. Mwansa: School of Chemistry, University of Edinburgh, Joseph Black Building, David Brewster Road, Edinburgh EH9 3FJ, UK
Matthew J. Stirling: iAnalytical, Shaw Park, Huddersfield HD5 9AG, UK

this then decreases exponentially and significantly during the reaction. The decrease in *ee* is due to the rate of formation of the (*S*)-enantiomer following first-order kinetics whereas that for the (*R*)-enantiomer is zero-order as shown for the reduction of 1-methyl-3,4-dihydroisoquinoline in dichloromethane (Fig. 1). As the reaction proceeds the *rate* of formation of the (*S*)-enantiomer decreases exponentially with time while that for the (*R*)-enantiomer remains constant leading to a change in selectivity with time. After 2 mins the rate of the pseudo first-order formation of the (*S*)-enantiomer is 4-fold faster than that of the (*R*)-enantiomer in dichloromethane corresponding to a 60 % *ee*. After 20 mins the rate difference is reversed with that for the (*R*)-enantiomer now being 4-fold greater than that for the (*S*)-amine. The higher the initial concentration of imine the greater is the difference in the rates of formation of the two enantiomers and the greater the % *ee* as the initial rate of formation of the (*S*)-enantiomer increases with concentration of imine whereas that for the (*R*)-enantiomer is independent of the imine concentration. That the catalyst remains active and stable during the reaction time period is demonstrated by adding a second aliquot of imine after reduction was complete which generates the same reaction profile (Fig. 1). It was proposed that the first-order rate of formation of the (*S*)-amine requires rate-limiting hydride transfer from the iridium hydride to the iminium ion but rate-limiting dissociation of the product for the zero-order rate of formation of the (*R*)-enantiomer as $k_{-2} > k_3$ (Scheme 1) [1]. This difference in rate-limiting steps is presumably due to the subtle changes in intermolecular interactions between the diastereomeric complexes of product amine and the iridium catalyst. Using the (*S*,*S*)-, rather than the (*R*,*R*)-, ligand TsDPEN to generate the iridium catalyst inverts the kinetic profiles so that the reduction of the 1-methyl-3,4-dihydroisoquinoline in dichloromethane produces the (*S*)-amine by zero-order kinetics and the (*R*)-enantiomer by a first-order process.

Substituents in the imine may be capable of changing the rate-limiting step of the reaction by, for example, the introduction of electron-withdrawing substituents to reduce the basicity of the amine product which may increase the rate of dissociation such that $k_3 > k_{-2}$ changing the rate limiting step to k_2.

The asymmetric transfer hydrogenation of imines with formic acid-triethylamine mixtures has been suggested [2] to occur with the neutral imine being the reactive species, conversely imine protonation prior to hydride transfer has been proposed based on the observation that an isolated ruthenium hydride reacts faster with an imine substrate than a corresponding ketone [3–5]. The opposite order of reactivities would have been anticipated if the neutral imine was the main reactive component. It would be expected that the iminium would be the reactive species based on the reactivities of the nucleophilic addition to imines in aqueous solution which also avoids the formation of an unstable amine anion [6]. A potential way of ensuring a constant *ee* throughout the reaction profile would be to adjust the substrate structures so that they have the same kinetic order. For example, decreasing the basicity of the amine product or decreasing the charge density on the metal-ion so that the rate of dissociation (**2**) becomes faster could possibly lead to a change in

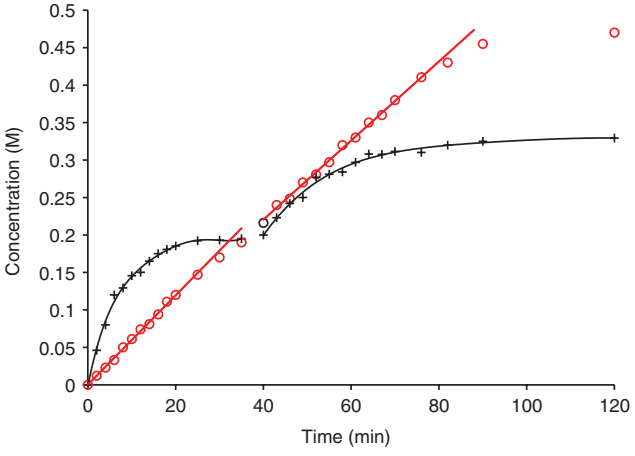
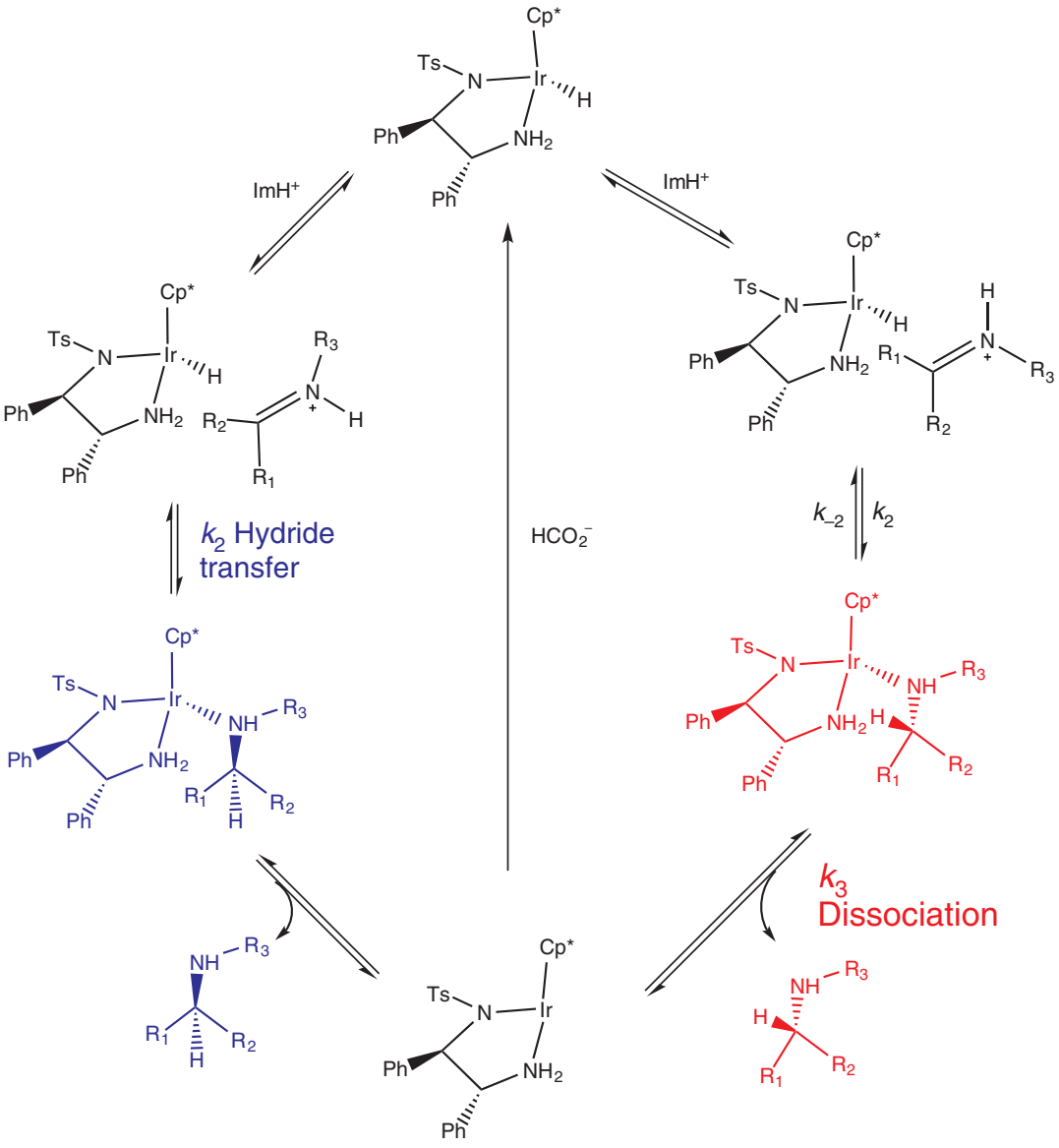
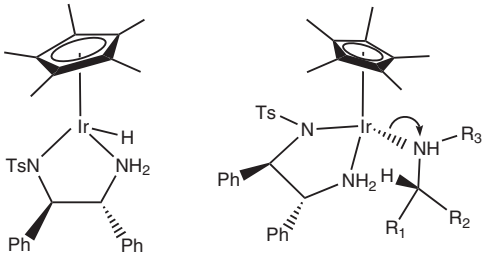


Fig. 1: Rate profiles for the formation of the (*R*) (o) and (*S*) (+) – enantiomers of amine for the transfer hydrogenation of 0.40 M imine using 1.0×10^{-3} M of the (*R*,*R*)-TsDPEN ligand iridium catalyst in dichloromethane at 20 °C. After 40 min an addition of a further aliquot of 0.4 M imine and 2 eq. formic acid is made.



Scheme 1: Mechanism pathway for the iridium (III) complex (1) catalysed reduction of imines showing the different rate-limiting steps for the formation of the two enantiomeric amine products.

rate-limiting step and kinetic order. Similarly, these substitutions could be used to differentiate between the neutral imine or the iminium ion as being the reactive species. The effect of α-fluorinated imines are used here to examine their influence on the kinetic order of the reduction and on relative reactivities.



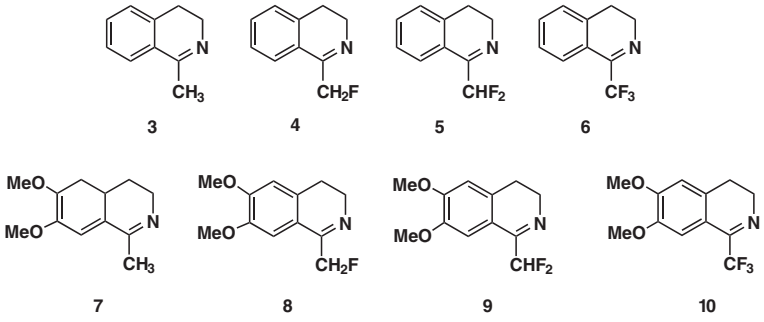
1 2

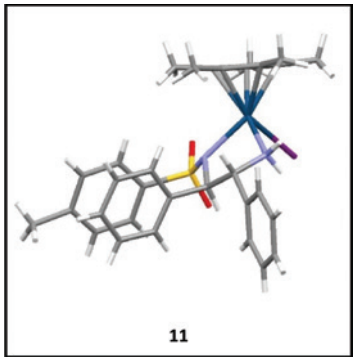
Results and discussion

Synthesis

The iridium (III) complex (**1**) was synthesised as previously described [1]. The crystal structure (**11**) of the iodo precursor of the active hydride (**1**) shows the expected parameters – selected bond lengths (Å): Ir-Cp* – 2.162, Ir-I – 2.746, Ir-NH_2 – 2.121, Ir-NTs – 2.140, N-Ts – 1.620.

A series of 1-fluorinated methyl substituted 3,4-dihydroisoquinolines and analogous 6,7 dimethoxy derivatives (**3–6** and **7–10**) were synthesised by cyclisation of the corresponding amides. Traditionally, accessing dihydroisoquinolines has been through Bischler-Napieralski conditions whereby intramolecular electrophilic aromatic substitution allows for the cyclization of β-arylethylamides activated by dehydrating agents to react with electron rich arenes to give the required product [7]. However, Movassaghi and Hill [8] reported an efficient process through electrophilic amide activation with trifluoromethanesulfonic anhydride (Tf_2O) in the presence of 2-chloropyridine followed by cyclization and subsequent deprotonation. Application of this process enabled access to six novel fluorinated imines in good yields (>70 %). It is worth noting that use of $POCl_3$ as in the classic Bischler-Napieralski conditions did not afford any of the fluorinated imines; the use of $FeCl_3$ was also unsuccessful.





pK_a determinations

The pK_a in water of the reactant substituted dihydroisoquinolines and their corresponding product amines were determined by titration and/or measuring the changes in UV spectra as a function of pH (Table 1). A Hammett plot of these values against σ_I [9] for CH_3 and the fluorinated groups CH_2F, CHF_2 and CF_3 yields a $\rho_i = -19.0$ for the 6,7-dimethoxy substituted iminium ions (**7–10**) (Fig. 2) and –18.0 for the unsubstituted series (**3–6**). A similar plot for fluorinated ethylaminium ions yields a lower $\rho_i = -13.5$, presumably due to the differences caused by the change from unsaturated (C=N) to saturated (C–N) systems. Prior protonation of imine substrates is thought to be necessary for ATH to occur, thus the imine substrates were considered in terms of the amount of protonation under the experimental conditions. This involved adding to a solution of the imine (0.1 M) in d_3MeCN 1 equivalent (eq.) aliquots of formic acid. In the usual synthetic protocol [1]. 0.6 M HCO_2H and 0.24 M Et_3N leaves 0.36 M formic acid for protonation of the imine (3.6 eq.) and, although 1 eq. is consumed in the reaction, there is still an excess at the end of the reaction.

There is a linear relationship between the pK_a of nitrogen bases in acetonitrile and in water and for amines there is an almost constant increase in pK_a of about 7.7 units on transfer from water to acetonitrile [10]. The pK_a of formic acid in acetonitrile is estimated to be 20.9 and even with typical ion-pairing formation constants being of the order 10^2–10^3 M^{-1} [11], it was anticipated that the fluorinated imines would not be completely protonated under the reaction conditions. Therefore, the imines were titrated against formic acid in acetonitrile determined by ^{1}H NMR and the % of protonated species by 3.6 eq. is shown in Table 1.

Table 1: The pK_a of the reactant 1-substituted 3,4-dihydroisoquinolines in water at 25 °C and the % protonated with 3.6 eq. formic acid in acetonitrile.

1-substⁿᵗ	pK_a iminium ion (3–6) (H_2O)	% Protonated in ACN with 3.6 eq. HCO_2H	pK_a iminium ion (7–10) (H_2O)	% Protonated in ACN with 3.6 eq. HCO_2H
CH_3	8.33	96.5	9.01	97
CH_2F	6.19	47.5	6.68	55
CHF_2	3.03	2.9	3.95	6.5
CF_3	1.90	<1	1.95	<1

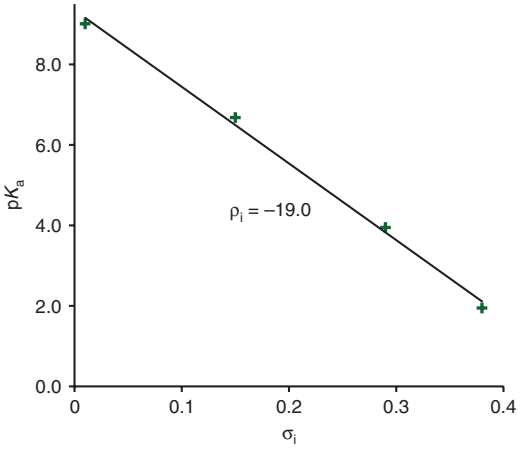


Fig. 2: pK_a of the 6,7-dimethoxy-substituted fluorinated dihydroisoquinolines (**7**–**10**) as a function of σ_i values.

Reduction of fluorinated imines with IrCp*(*R*,*R*) TsDPEN

The kinetic profiles of the reduction of the eight imines (**3–10**) (0.1 M) with the organo-iridium (**1**) [IrCp*I-(*R*,*R*) TsDPEN] catalyst (5×10^{-4} to 1×10^{-3} M) were obtained in acetonitrile at 28 °C with a 5:2 ratio of formic acid (0.6 M) and triethylamine (0.24 M). The 1-methyl substituted compounds (**3**, **7**) have been previously studied [1] and this study confirmed the different kinetic orders of formation of the respective enantiomers – with the rate of formation of the (*S*)-enantiomer following first order kinetics whereas that for the (*R*)-enantiomer is zero order when IrCp*I-(*R*,*R*) TsDPEN is employed as the catalyst [1]. The rate of reduction the 1-monofluoromethyl imine (**8**) is faster than that of the 1-methyl compound (**7**) (Fig. 3), achieving a faster conversion (~15 min) with half the catalyst loading. Despite the smaller ratio of protonated imine (~0.5 %, Table 1) the fluorine shows a dominating effect on the electrophilicity of the imine carbon facilitating faster hydride transfer.

Analysis of the formation of the individual enantiomers confirms that the catalyst is still selective for the (*S*)-enantiomer, however, interestingly, the formation of *both* enantiomeric amine products follow first order kinetics (Fig. 4) indicating a change in the rate limiting step (RLS) for the (*R*)-enantiomer in the proposed mechanism (Scheme 1). Presumably, this is due to the increased rate of dissociation of the product amine (2) due to its decreased basicity such that $k_3 > k_{-2}$ thus changing the rate limiting step to k_2. The introduction of the fluorine makes it harder to protonate the imine nitrogen but increases the electrophilicity of the imine carbon leading to increased reactivity compared with the 1-methyl derivative as the result of a more active monofluoro iminium ion. The more electrophilic carbon promotes hydride transfer to the sp^2 centre, even though the amount of protonation is only 55 % compared with the 97 % of iminium of the 1-methyl compound (Table 1).

The introduction of a second fluorine in di-fluoromethyl (CHF_2) at the imine α-position significantly decreases the pK_a from CH_3 (**7**) (9.01), CH_2F (**8**) (6.68) to CHF_2 (**9**) (3.95), thus decreasing the amount of protonated

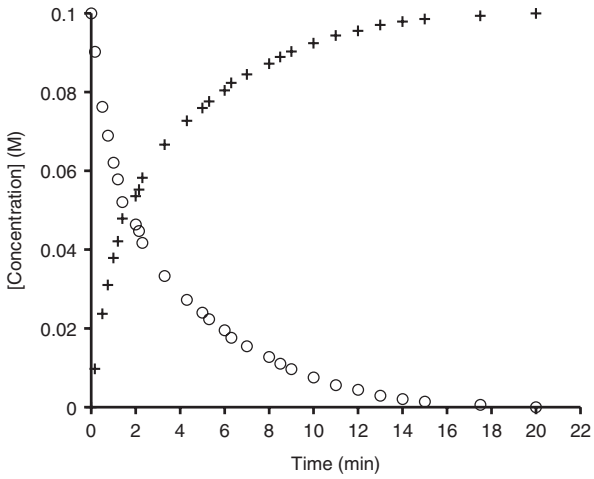


Fig. 3: Rate of reduction of 1-fluoromethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**8**) (0.1 M) (o) to the corresponding amine (+) with IrCp*I-(*R*,*R*) TsDPEN (5×10^{-4} M) in ACN at 28 °C with HCO_2H (0.6 M) and TEA (0.24 M).

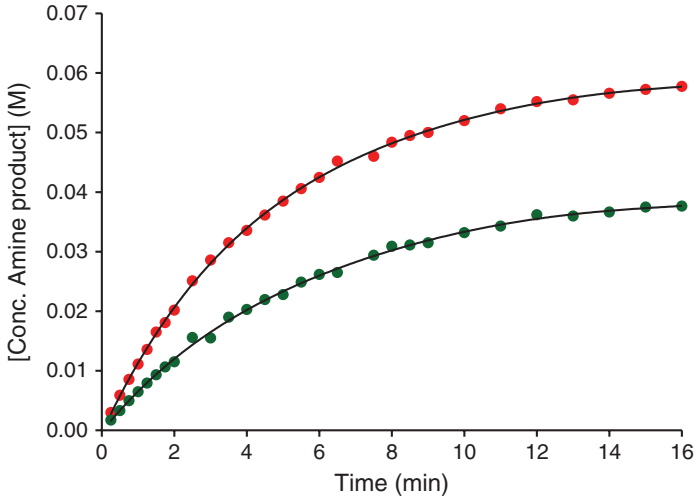


Fig. 4: Rate of formation of *S* (●) and *R* (●) 1-fluoromethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline with IrCp*I-(*R*,*R*) TsDPEN (5×10^{-4} M) in ACN at 28 °C with HCO_2H (0.6 M) and TEA (0.24 M].

species under the reaction conditions (Table 1). The observed reactivity however does not increase under the same reaction conditions, being 10-fold slower than the mono-fluoro derivative (Fig. 5). This confirms that the iminium is the active species as the introduction of two fluorines results in a considerable reduction in basicity and less protonated species under the reaction conditions. Even though the di-fluoromethyl iminium ion is presumably more reactive there is a reduced amount of it (6.5 % with 3.6 eq. formic). Interestingly, the difluoromethyl derivative also demonstrates first order kinetics in the formation of both enantiomeric amine products. However, whereas selectivity was observed in the formation of (*S*)-enantiomer in the mono-fluoromethyl derivative, a much closer formation of the 2 enantiomeric products is observed (Fig. 6).

The 1-trifluoromethyl 3,4-dihydroisoquinolines were inactive towards reduction by the Ir complex even with a higher catalyst loading (5 mol%) and 7 days of profiling. This provides further evidence for the need of protonation of the imine substrate prior to reduction (Table 1) even though the electrophilicity of the carbon has been increased considerably by the CF_3 substituent [12]. The aqueous pK_a of the trifluoromethyl quinoline (1.95) is lower than that of formic acid (3.77), a difference which would be accentuated in acetonitrile or

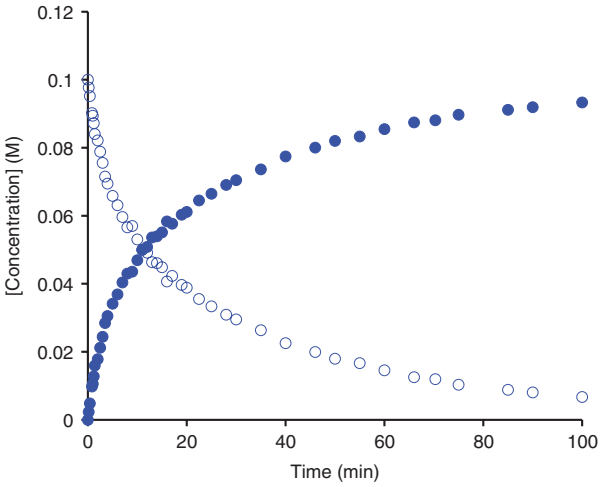


Fig. 5: Rate of reduction of 1-(difluoromethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (**9**) (o) (0.1 M) to the corresponding amine (●) with IrCp*I-(*R*,*R*) TsDPEN (5×10^{-4} M) in ACN at 28 °C with HCO_2H (0.6 M) and TEA (0.24 M).

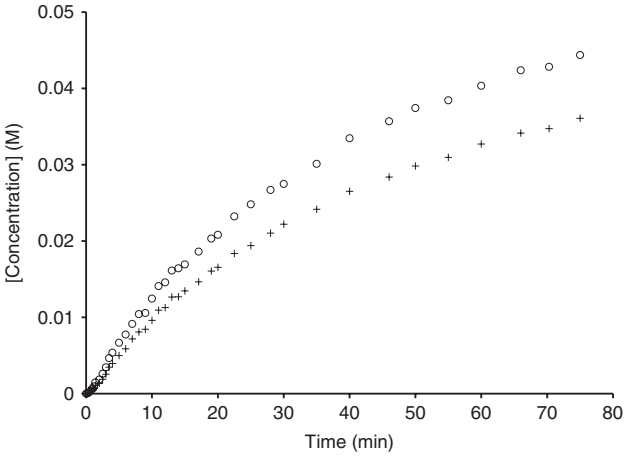


Fig. 6: Rate of formation for (*S*)-(o) and (*R*) (+)-1-(difluoromethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline enantiomers.

dichloromethane [10], so the dominant species present will be the neutral imine and undissociated formic acid. Given that no protonation of the trifluoromethyl analogue was observed with formic acid by ^{1}H NMR, the stronger acid trifluoroacetic acid TFA was used. TFA was introduced to the stirring solution of the imine (0.1 M) in acetonitrile at 28 °C, followed by the introduction of the dimer $[IrCp^*I_2]_2$ and *R*,*R*-TsDPEN ligand. The reagents were allowed to stir for 5 min before the introduction of the azeotropic mixture (HCO_2H/Et_3N 5:2). The reaction was monitored for 60 h but no reduction was observed. This is perhaps not surprising given that NMR studies showed ion-pair formation between TFA and Et_3N and protonation of the formate ion, rendering it incapable of transferring hydride ion to the pre-catalyst. The aqueous pK_a of 0.23 for TFA is expected to protonate formate (pK_a 3.77) more than the trifluoromethyl imine substrate (pK_a 1.95) (Table 1). Indeed, the trifluoromethyl iminium ion is also capable of protonating the formate ion, further depleting the amount of protonated imine in the system.

All of the observed rate constants, k_{obs}, are first-order in catalyst concentration and the corresponding catalytic coefficients $k_{cat} = k_{obs}/[\text{catalyst}]$ together with the normalised values allowing for the different degrees of protonation (*corr* k_{cat}) are summarised for both the 3,4-dihydroisoquinolines (Table 2) and the 6,7-dimethoxy-3,4-dihydroisoquinoline (Table 3).

Table 2: Summary of the observed rate constants, k_{obs}, the catalytic coefficients, k_{cat}, and their normalised values allowing for the different degrees of protonation, corr. k_{cat}, for the reduction of 1-substituted 3,4-dihydroisoquinolines in ACN at 28 °C by IrCp*I-(*R*,*R*) TsDPEN.

1-Substⁿᵗ	(*S*) k_{obs} (s^{-1})	(*S*) k_{cat} (M^{-1} s^{-1})	(*S*) corr. k_{cat} (M^{-1} s^{-1})	(*R*) k_{obs} (s^{-1})	(*R*) k_{cat} (M^{-1} s^{-1})	(*R*) corr. k_{cat} (M^{-1} s^{-1})
CH_3	1.23×10^{-3}	1.23	1.27	2.50×10^{-5} M^{-1}	2.50×10^{-2}	2.59×10^{-2}
CH_2F	6.35×10^{-3}	12.7	26.7	6.38×10^{-3}	12.6	26.8
CHF_2	1.35×10^{-3}	0.45	15.7	6.66×10^{-4}	0.22	7.74

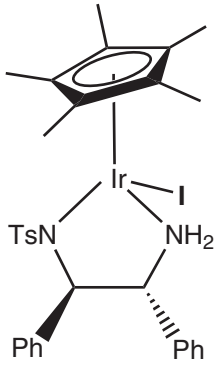
Table 3: Summary of the observed rate constants, k_{obs}, the catalytic coefficients, k_{cat}, and their normalised values allowing for the different degrees of protonation, corr. k_{cat}, for the reduction of 1-substituted 6,7-dimethoxy 3,4-dihydroisoquinolines in ACN at 28 °C by IrCp*I-(*R*,*R*) TsDPEN.

1-Substⁿᵗ	(*S*) k_{obs} (s^{-1})	(*S*) k_{cat} (M^{-1} s^{-1})	(*S*) corr. k_{cat} (M^{-1} s^{-1})	(*R*) k_{obs} (s^{-1})	(*R*) k_{cat} (M^{-1} s^{-1})	(*R*) corr. k_{cat} (M^{-1} s^{-1})
CH_3	1.07×10^{-3}	1.07	1.1	1.87×10^{-5} M^{-1}	1.87×10^{-5}	1.93×10^{-2}
CH_2F	3.41×10^{-3}	6.83	12.4	2.94×10^{-3}	5.89	10.7
CHF_2	4.05×10^{-4}	0.81	12.5	3.90×10^{-4}	0.78	12.2

Conclusions

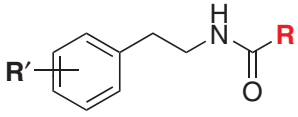
The enantioselectivity of the iridium (III) complex of pentamethylcyclopentadiene and (*R*,*R*)-1,2-diphenyl-*N*′-tosylethane-1,2-diamine catalysed reduction of imines under acidic conditions decreases exponentially. The dominant cause of the initial enantioselectivity is the difference in kinetic order of the formation of the two enantiomers with the *S*-enantiomer being formed in a first-order process whereas that for the *R*-enantiomer follows zero-order kinetics due to different rate-limiting steps for the two processes. With 1-fluorinated methyl-3,4-dihydroisoquinolines as substrates the electron-withdrawing substituents change the rate-limiting dissociation of the (*R*)-amine product from Ir (III) so that both enantiomers are formed with the same kinetic order. This results in almost complete removal of the enantioselectivity of the reduction. These α-substituted fluoro-imines make protonation more difficult but enhance the electrophilicity of the imine carbon facilitating nucleophilic attack. The relative rates of the cyclopentadienyl iridium (III) complex catalysed reduction of these 1-fluorinated methyl-3,4-dihydroisoquinolines in acetonitrile and, under the acidic conditions of a 5:2 ratio of formic acid: triethylamine, demonstrate that the iminium ion is the reactive species.

Experimental

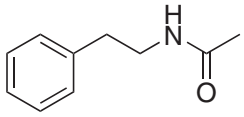


^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.43 (d, J = 8.1 Hz, 2H), 7.17–7.10 (m, 3H), 6.93–6.81 (m, 7H), 6.66 (d, J = 7.2 Hz, 2H), 4.49 (t, J = 12.0 Hz, 1H), 4.29 (d, J = 10.5 Hz, 1H), 4.04 (d, J = 8.4 Hz, 1H), 3.72–3.63 (m, 1H), 2.23 (s, 3H), 1.84 (s, 15H); **^{13}C NMR (75 MHz, $CDCl_3$,** 25 °C, TMS): δ = 140.6, 139.5, 139.0, 138.7, 128.8, 128.7, 128.6, 128.5, 127.9, 127.2, 127.0, 126.6, 85.7, 74.0, 69.6, 21.3, 9.7.

General procedure for acylation of phenylethylamine

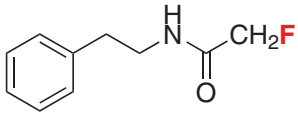


To a stirring solution of phenylethylamine (1 eq.) and triethylamine (1.2 eq.) in DCM (3 M based on amine) at 0 °C was added the anhydride (1.2 eq.) solution in DCM (3.96 M based on anhydride) over an hour using a syringe pump. After completion of the addition, the reaction was then allowed to stir at r.t. for 20 h. The resulting reaction mixture was poured into a separating funnel and washed with 1 M NaOH (2×20 mL) and with 1 M HCl (2×10 mL), dried with Na_2SO_4, filtered and dried in vacuo to afford the respective amide.



N-phenethylacetamide

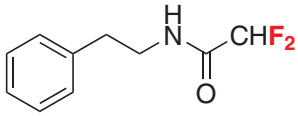
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.52 (d, 1H, J = 6.72), 7.4–7.36 (t, 1H, J = 6.03), 7.34–7.3 (t, 1H, J = 7.06, 7.25–7.22 (d, 1H, J = 6.85), 3.53–3.5 (t, 2H, J = 7.56), 3.38 (brs), 2.64–2.6 (t, 2H, J = 7.67), 2.3 (s, 3H). **^{13}C NMR (400 MHz, $CDCl_3$) δ** 163.3 (C=O), 137.4 (qC), 131 (Ar), 129.5 (Ar), 129.0 (Ar), 128.7 (Ar), 127.4 (Ar), 125.9 (Ar), 46.6 (CH_2–N), 25.9 (CH_2–Ar), 23 (CH_3). **HRMS** (m/z) calculated for $C_{10}H_{13}NO^+$ $[M+H]^+$: 163.1, found: 164.1086. **Mp**: 54.1 °C.



2-fluoro-*N*-phenethylacetamide

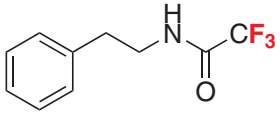
***NOTE**: *The monofluoro amide derivative was prepared by an alternative route that employs sodium methoxide as a catalyst.*

A mixture of sodium methoxide (5 mol% based on ester), ethyl fluoroacetate (1 g, 9.2 mmol, 1 eq.), phenylethylamine (1.5 g, 12.25 mmol, 1.3 eq.), and toluene (3 mL) was heated at 50 °C for 20 h under argon. The resulting mixture was quenched with aqueous saturated NH_4Cl, dried with Na_2SO_4, filtered and dried in vacuo to afford 2-fluoro-*N*-phenethylacetamide as a white solid. **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.35–7.31 (t, 2H, J = 7.02), 7.26–7.24 (d, 1H, J = 4.94), 7.21–7.20 (d, 2H, J = 6.89), 6.32 (brs, 2H), 4.83 (s, 1H), 4.71 (s, 1H), 3.63–3.58 (q, 2H, CH_2–N, J = 6.92), 2.88–2.84 (t, 2H, CH_2–Ar, J = 7.11). **^{13}C NMR (400 MHz, $CDCl_3$) δ** 167.6 (C=O), 138.32 (qC), 128.75 (Ar), 128.71 (Ar), 126.7 (Ar), 125.9 (Ar), 81.2 (CFH_2), 40 (CH_2–N), 35.6 (CH_2–Ar), **^{19}F NMR (400 MHz, $CDCl_3$): δ** –224.63 (–) –224.8 (t, CF, J = 3.17). **HRMS** (m/z) calculated for $C_{10}H_{12}FNO^+$ $[M+H]^+$: 181.09, found: 182.0987. **Mp:** 63.4 °C.



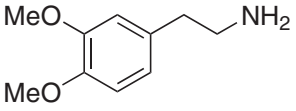
2,2-difluoro-*N*-phenethylacetamide

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.31 (t, 2H, J = 7.58), 7.26–7.23 (d, 1H, J = 6.26), 7.2–7.18 (d, 2H, J = 7.58), 6.4 (brs), 5.99–5.71 (t, 1H, J = 54.73), 3.62–3.57 (q, 2H, J = 7), 2.88–2.85 (t, 2H, J = 7.08). **^{13}C NMR (400 MHz, $CDCl_3$) δ** 162.8 (C=O), 139.34 (qC), 129.0 (Ar), 128.8 (Ar), 126.6 (Ar), 111.4 (Ar), 108 (Ar), 106 (Ar), 40.3 (Ar), 35.1 (Ar). **^{19}F NMR (400 MHz, $CDCl_3$): δ** –125.7 (–) 125.9 (d, 2F, CF_2H, J = 53.76). **HRMS** (m/z) calculated for $C_{10}H_{11}F_2NO^+$ $[M+H]^+$: 199.08, found: 200.0890.



2,2,2-trifluoro-*N*-phenethylacetamide

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.32 (t, 2H, J = 7.28), 7.26–7.25 (d, 1H, J = 4.37), 7.2–7.18 (d, 2H, J = 7.28), 6.33 (brs), 3.65–3.6 (q, 2H, J = 6.8), 2.9–2.87 (t, 2H, J = 7.07). **^{13}C NMR (400 MHz, $CDCl_3$) δ** 156.7 (C=O), 156.4 (CF_3), 139.0 (qC), 129.1 (Ar), 128.8 (Ar), 126.7 (Ar), 55.36 (CH_2–N), 51.0 (CH_2–Ar). **^{19}F NMR (400 MHz, $CDCl_3$): δ** –74.5 (s, CF_3). **I.R.** 3290.7, 3031.4, 2952.3, 2173.2, 1698.1, 1148.7, 748.6 **HRMS** (m/z) calculated for $C_{10}H_{10}F_3NO^+$ $[M+H]^+$: 217.07, found: 218.0798. **Mp:** 58.0 °C.

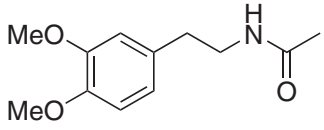


2-(3,4-dimethoxyphenyl)ethan-1-amine

***Note:** *Product cannot be purchased from vendors without a license due to its potential use as a precursor to amphetamine based psychoactive substances*.

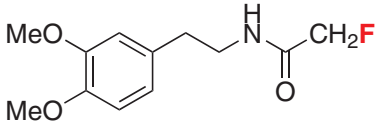
To a stirring solution of 2-(3,4-dimethoxyphenyl) acetonitrile (4.5 g, 25.3 mmol) in dry THF (50 mL) at r.t was added borane in THF (50 mL, 1 M sol., 50 mmol) and this was stirred at 55 °C for 16 h. The mixture was then cooled to 0 °C and quenched by the slow addition of water (5 mL), followed by the addition of conc. HCl (25 mL). After stirring at r.t for an hour, the mixture was diluted with water (125 mL) and made alkaline (pH 9) by addition of NaOH (12.5 g). The mixture was extracted with DCM (3×) and the organic layers were washed with water (50 mL), brine (50 mL), dried (Na_2SO_4), filtered and dried in vacuo. The crude oil was purified by flash chromatography (DCM/MeOH/conc. NH_4OH-90/9/1) to afford 3,4-dimethoxyphenethylamine as a colourless oil, 4.3 g, 93 %.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82–6.8 (d, 1H, J = 8.02), 6.75–6.72 (d, 2H, J = 9.05), 3.88–3.86, (d, 6H, J = 6.2), 2.96–2.92 (t, 2H J = 6.7), 2.71–2.68 (t, 2H, J = 6.83), 1.4 (brs).



N-(3,4-dimethoxyphenethyl)acetamide

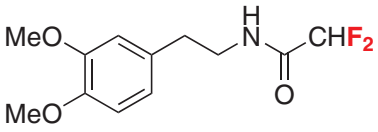
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86–6.84 (d, 1H, J = 8.23), 6.79–6.78 (d, 1H, J = 1.91), 6.71 (d, 1H, J = 8.23), 3.73–3.7 (d, 6H, 2× OMe, J = 10.52), 3.36 (brs), 3.24–3.2 (q, 2H, J = 7.07), 2.64–2.6 (t, 2H, J = 7.8), 1.78 (s, 3H). **^{13}C NMR (400 MHz, $CDCl_3$) δ** 169.5 (C=O), 149 (qC), 147.6 (qC), 132.4 (qC), 120 (qC), 112.9 (Ar), 112.3 (Ar), 55.9 (OCH_3), 55.8 (OCH_3), 26.2 (CH_2–N), 23 (CH_2–Ar). **HRMS** (m/z) calculated for $C_{12}H_{17}NO_3^+$ $[M+H]^+$: 223.12, found: 224.1291. **Mp:** 101.9 °C.



N-(3,4-dimethoxyphenethyl)-2-fluoroacetamide

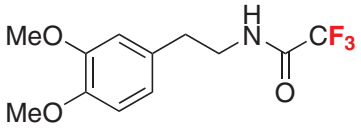
Sodium methoxide (5 mol%) was added to a stirring solution of ethyl fluoroacetate (1 g, 9.2 mmol, 1 eq.) and phenylethylamine (2.2 g, 12.25 mmol, 1.3 eq.) in toluene (3 mL) and this heated at 50 °C for 20 h under Argon. The resulting mixture was quenched with aqueous saturated NH_4Cl, dried (Na_2SO_4), filtered and dried in vacuo to afford 2-fluoro-*N*-phenethylacetamide as a white solid, 2.5 g, 84.7 %.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83–6.81 (d, 1H, J = 8.12), 6.76–6.72 (m, 2H), 6.34 (brs NH), 4.84 (s, CFH), 4.72 (s, CFH), 3.88–3.87 (d, OMe × 2 J = 2.85), 3.61–3.56 (q, CH_2N J = 6.9), 2.82–2.79 (t, Benzylic CH_2, J = 7.14). **^{13}C NMR (400 MHz, $CDCl_3$) δ** 167.41 (C=O), 149.08 (Ar–O), 147.82 (Ar–O), 130.78 (qC), 120.62 (Ar), 111.76 (Ar), 111.38 (Ar), 81.2 (CH_3O), 79.35 (CH_3O), 55.92 (CH_2N), 40.07 (Ar–CH_2), 35.2 (CH_2F). **^{19}F NMR (400 MHz, $CDCl_3$): δ** –224.56 (–) –224.7 (ddd, CH_2F, J = 3.29). **I.R. 3321.1**, 2939.1, 2841.4, 1651.8, 761.9. **Mp:** 89.9 °C.



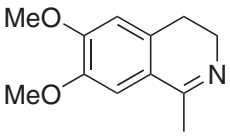
N-(3,4-dimethoxyphenethyl)-2,2-difluoroacetamide

Yield 90 %. **^{1}H NMR (400 MHz, $CDCl_3$) δ** 6.84–6.82 (d, 1H, J = 8.16), 6.74–6.7 (m, 2H), 6.35 (brs) 6-0-5.7 (t, CF_2H, J = 54.4), 3.87 (s, CH_3O × 2, 6H), 3.6–3.55 (q, CH_2–NH J = 6.7), 2.83–2.8 (t, CH_2–Ar J = 6.92). **^{13}C NMR (400 MHz, $CDCl_3$) δ** 162.5 (C=O), 149.16 (Ar–O), 147.94 (Ar–O), 130.36 (CF_2H), 120.63 (Ar), 111.79 (Ar), 111.46 (Ar), 55.9 (CH_3O), 55.84 (CH_3O), 40.56 (CH_2N), 34.8 (CH_2-Ar). **^{19}F NMR (400 MHz, $CDCl_3$): δ** –126.13 (–) –126.3 (CF_2H, J = 55.02). **HRMS** (m/z) calculated for $C_{12}H_{15}F_2NO_3^+$ $[M+H]^+$: 259.10, found: 260.1098. **Mp:** 63.4 °C.



N-(3,4-dimethoxyphenethyl)-2,2,2-trifluoroacetamide

Yield 92 %. **^{1}H NMR (400 MHz, $CDCl_3$) δ** 6.84–6.82 (d, 1H, J = 8.01), 6.74–6.69 (m, 2H), 6.5 (brs, 2H), 3.87 (s, 2 × OMe, 6H), 3.61–3.56 (q, CH_2–N, J = 6.57), 2.85–2.81 (t, CH_2–Ar, 2H J = 7). **^{13}C NMR (400 MHz, $CDCl_3$) δ** 157.3 (C=O), 149.2 (qC), 148 (qC), 130 (Ar), 120 (Ar), 117.2 (CF_3), 111.7 (Ar), 111.5 (Ar), 55.9 (OCH_3), 55.8 (OCH_3), 41.15 (CH_2–N), 34.5 (CH_2–Ar). **^{19}F NMR (400 MHz, $CDCl_3$): δ** –76 (s, CF_3). **I.R.** 3317.9, 2998.8, 2945.1, 2839.8, 1697.6, 761.9, 695.1. **HRMS** (m/z) calculated for $C_{12}H_{14}F_3NO_3^+$ $[M+H]^+$: 277.09, found: 278.1016. **Mp:** 84.5 °C.



6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline

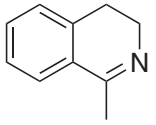
N-(3,4-Dimethoxyphenethyl) acetamide (20.0 g, 95.6 mmol), was suspended in *o*-xylene (200 mL), in a 500 mL flask equipped with a reflux condenser and a dropping funnel and this was cooled in an ice bath. To the stirring solution $POCl_3$ (41.8 mL, 73.3 mol) was added dropwise, with the reaction cooling in ice. The $POCl_3$ had only partially dissolved by the time the addition was complete. The reaction was then heated to reflux. On heating the $POCl_3$ dissolved to give a yellow brown solution, which darkened in colour over time and after 3 h the reaction was a deep orange oil. The reaction was then allowed to cool overnight. The cooled reaction mixture was poured into ice-water and extracted with EtOAc (2×200 mL). The aqueous layer was basified with solid NaOH pellets to pH 11 and this was extracted with EtOAc (2×100 mL), dried with Na_2SO_4 and dried in vacuo to afford 1-methyl-3,4-dihydroisoquinoline as a white solid, 12.5 g, 90 %.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.69 (s, 1H), 3.92–3.91 (d, 6H 2 × CH_3O, J = 3.23), 3.65–3.61 (t, 2H, J = 7.64), 2.65–2.62 (t, 2H, J = 7.66), 2.36 (s, 3H). **^{13}C NMR (400 MHz, $CDCl_3$) δ** 163.7 (C=N), 150.8 (qC), 147.4 (qC),

131 (qC), 122.5 (qC), 110 (Ar), 109 (Ar), 56.2 (CH_3O), 55.9 (CH_3O), 47.0 (CH_2-N), 25.7 (CH_2-Ar). **I.R.** 2941.7, 2923.5, 2836.4, 2158.5, 2015.8, 1625.2, 854.9.

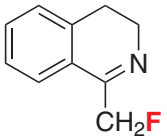
General procedure for cyclisation of fluorinated amides

Under a N_2 atmosphere the amide (1 eq.), 2-chloropyridine (1.2 eq.) and *anhydrous* DCM (0.03 M based on the respective amide) were mixed in a two-necked round bottom flask equipped with a condenser and a stirring bar. The solution was cooled to –78 °C (dry ice/acetone bath) and then trifluoromethanesulfonic anhydride (1.1 eq.) was added dropwise over 10 min. After completion of the addition the mixture was allowed to warm to 0 °C in an ice-water bath. After stirring at 0 °C for 1 h the mixture was warmed to 45 °C and stirring was continued for 48 h. The reaction mixture was cooled to room temperature before triethylamine (3 eq.) was introduced carefully. The dark red solution was washed with brine, dried over Na_2SO_4 and concentrated in vacuo to obtain the crude product, which was purified by flask chromatography to give the corresponding imine.



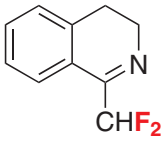
1-methyl-3,4-dihydroisoquinoline

72 %, yellow oil. **^{1}H NMR (CDCl3, 400 MHz): δ** 7.48 (d, 1H, J = 7.2 Hz), 7.29–7.38 (m, 2H), 7.18 (d, 1H, J = 7.6 Hz), 3.67 (td, 2H, J1 = 7.6 Hz, J2 = 1.2 Hz), 2.71 (d, 2H, J = 7.4 Hz), 2.40 (s, 3H); **^{13}C NMR ($CDCl_3$, 400 MHz)**: **δ** 164.5, 137.4, 130.7, 129.5, 127.4, 126.9, 125.4, 46.8, 26.0, 23.2.



1-(fluoromethyl)-3,4-dihydroisoquinoline

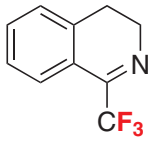
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.5 (d, 1H, J = 7.71), 7.41–7.36 (t, 1H, J = 8.04), 7.33–7.29 (t, 1H, J = 7.71), 7.22–7.2 (d, 1H, J = 7.04), 5.41 (s, 1H, CFH_2), 5.29 (s, 1H, CFH_2), 3.8–3.75 (m, 2H), 2.77–2.73 (t, 2H, J = 7.91). **^{13}C NMR (400 MHz, $CDCl_3$) δ** 164.6 (C=N), 137.8 (qC), 134.4 (qC), 130.9 (Ar–C), 127.8 (Ar–C), 127.8 (Ar–C), 124.4 (Ar), 89.3 (CFH_2), 46.4 (CH_2–N), 25.8 (CH_2–Ar). **^{19}F NMR (400 MHz, $CDCl_3$): δ** –220.9 (–) –221.24 (3× q, CFH_2, J = 3.46).



1-(difluoromethyl)-3,4-dihydroisoquinoline

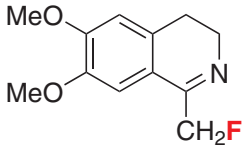
The resulting brown oil was purified by flash chromatography (50:1 Hex/EtOAc) to afford 1-(difluoromethyl)-3,4-dihydroisoquinoline as a colourless oil, 1.2 g, 63.2 %.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.76 (d, 1H, J = 7.85), 7.43–7.40 (t, 1H, J = 7.47) 7.34–7.30 (t, 1H, J = 7.66), 7.22–7.2 (d, 1H, J = 7.48), 6.41–6.14 (t, 1H, CF_2H, J = 54.47), 3.83–3.79 (m, 2H, CH_2–N), 2.77–2.73 (t, 2H, CH_2–Ar, J = 7.8). **^{13}C NMR (400 MHz, $CDCl_3$) δ** 160.3 (C=N), 138.7 (qC), 137.7 (qC), 131 (Ar-C), 127.8 (Ar-C), 127.12 (Ar-C), 124.5 (CF_2H), 124.2 (Ar-C), 47.1 (CH_2–N), 25.4 (CH_2–Ar). **^{19}F NMR (400 MHz, $CDCl_3$): δ** –116.5 (–) –116.7 (2× q, CF_2H, J = 3.05). **I.R.** 2951.9, 2849.4, 1636.8, 1602.2, 780.0, 706.1.



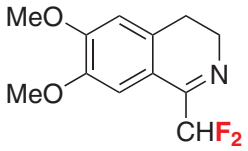
1-(trifluoromethyl)-3,4-dihydroisoquinoline

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.6 (d, 1H, J = 8.2), 7.47–7.43 (t, 1H, J = 7.5), 7.4–7.33 (t, 1H, J = 7.92), 7.26–7.23 (d, 1H, J = 7.34), 3.93–3.9 (m, 2H, CH_2–N), 2.82–2.78 (t, 2H, CH2–Ar, J = 8.18). **^{13}C NMR (400 MHz, $CDCl_3$) δ** 155.85 (C=N), 149.8 (qC), 138.7 (qC), 137.7 (Ar), 132.1 (Ar), 127.9 (Ar), 127.3 (Ar), 118.8 (CF_3), 47.12 (CH_2N), 25.3 (CH_2–Ar). **^{19}F NMR (400 MHz, $CDCl_3$): δ** −67 (–) −68 (q, CF_3, J = 1.72). **I.R.** 2955.9, 1638.9, 1574.4, 1117.1, 779.3.



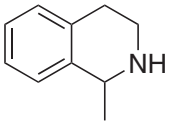
1-(fluoromethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline

Orange solid, Yield 67 %. **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.07 (s, 1H), 6.72 (s, 1H), 5.38 (s, CH_2F, 1H), 5.26 (s, CH_2F, 1H), 3.93–3.91 (d, 2× OMe, 6H J = 7.78), 3.76–3.72 (m, CH_2–N), 2.7–2.66 (t, CH_2–Ar, 2H, J = 7.95). **^{13}C NMR (400 MHz, $CDCl_3$) δ** 161.94 (C=N), 151.34 (qC), 147.6 (qC), 131.5 (qC), 119.76 (qC), 110 (Ar), 108 (Ar), 85.8 (CF), 56.2 (OMe), 56 (OMe), 47.2 (N–CH_2), 25.3 (Ar–CH_2). **^{19}F NMR (400 MHz, $CDCl_3$): δ** –219.5–219.82 (3× sextet, CFH_2, J = 3.85). **I.R.** 2966.3, 2943.2, 2837.6, 1603.3, 1146.9, 731.0.



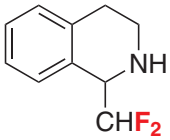
1-(difluoromethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline

White solid, Yield 75 %. **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.27 (s, 1H), 6.72 (s, 1H), 6.37–6.1 (t, CF_2H, J = 54.53), 3.93–3.91 (d, 2× OMe, 6H, J = 8.34), 3.8–3.74 (m-CH_2–N, 2H), 2.72–2.68 (t, CH_2–Ar, 2H, J = 7.97). **^{13}C NMR (400 MHz, $CDCl_3$) δ** 159.7 (C=N), 151.7 (qC), 147.51 (qC), 131.8 (qC), 119.5 (qC), 117 (CF_2H), 114 (Ar), 110.36 (Ar), 56.1 (OMe), 55.97 (OMe), 47.17 (N–CH2), 25.2 (Ar–CH_2). **^{19}F NMR (400 MHz, $CDCl_3$): δ** –116–116.16 (d, CF_2H, J = 53.7). **I.R.** 2981.0, 2939.4, 2363.2, 1995.2, 1604.1, 750.5.



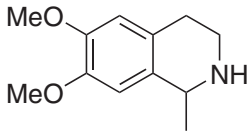
1-methyl-1,2,3,4-tetrahydroisoquinoline

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.08–7.15 (m, 4H), 4.09–4.14 (q, J = 6.8 Hz, 1H), 3.26–3.30 (m, 1H), 3.03–3.05 (m, 1H), 2.81–2.91 (m, 1H), 2.72–2.76 (m, 1H), 1.94 (br, 1H), 1.46 (d, J = 6.8 Hz, 3H). **^{13}C NMR ($CDCl_3$, 400 MHz) δ (ppm):** 140.45, 134.73, 129.17, 125.90, 125.85 (2C), 51.52, 41.73, 29.97, 22.65.



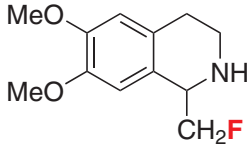
1-(difluoromethyl)-1,2,3,4-tetrahydroisoquinoline

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.19–7.1 (m, 4H), 4.74–4.51 (m, 2H), 4.39–4.32 (m, 1H), 3.28–3.22 (m, 1H), 3.09–3.04 (m, 1H), 2.85–2.83 (m, 2H). **^{13}C NMR ($CDCl_3$, 400 MHz) δ (ppm):** 136.02 (qC), 132.63 (qC), 129.64 (CH_2F), 126.98 (ar CH), 126.64 (ar CH), 126.44 (ar CH), 125.96 (ar CH), 55.5 (**C**–CHF_2), 39.68 (CH_2–N), 30.97 (CH_2–Ar).



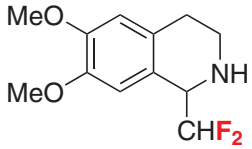
6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (s, 1H), 6.56 (s, 1H), 4.07–4.03 (q, *J* = 6.75, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.28–3.22 (m, 1H), 3.03–2.96 (m, 1H), 2.83–2.75 (m, 1H), 2.68–2.62 (m, 1H), 2.02 (brs, 1H), 1.45–1.43 (d, *J* = 6.67Hz, 3H). **^{13}C NMR (400 MHz, $CDCl_3$) δ** 147.31 (*q*C), 147.23 (*q*C), 132.30 (*q*C), 126.74 (*q*C), 111.72 (ar. C–H), 108.99 (ar. C–H), 55.993 (OCH_3), 55.86 (OCH_3), 41.77 (CH_2–N), 30.96 (Ar–CH_2), 29.47 (CH_3).



1-(fluoromethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (s, 1H), 6.59 (s, 1H), 4.69–4.61 (sextet, *J* = 13.81, 1H, CH_2F), 4.69–4.61 (sextet, *J* = 13.81, 1H, CH_2F), 4.57–4.49 (sextet, J = 13.77, 1H, CH_2F), 4.29–4.22 (m, 1H), 3.85 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.24–3.18 (m, 1H), 3.06–3.01 (m, 1H), 2.76–2.69 (m, 2H). **^{13}C NMR (400 MHz, $CDCl_3$) δ** 148.02 (*q*C), 147.02 (*q*C), 128.29 (*q*C), 124.61 (CH_2F), 124.54 (*q*C), 112.02 (ar C–H), 109.37 (ar C–H), 86.02 (**C**–CH_2F), 56.03 (OCH_3), 55.84 (OCH_3), 39.67 (CH_2–N), 30.96 (Ar–CH_2).



1-(difluoromethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (s, 1H), 6.62 (s, 1H), 5.97–5.67 (m, 1H), 4.17–4.10 (sextet, *J* = 11.64, 1H), 3.23–3.17 (m, 1H), 3.07–3.01 (m, 1H), 2.76–2.73 (t, *J* = 5.85, 2H), 1.81 (brs, 1H, NH). **^{13}C NMR (400 MHz, $CDCl_3$) δ** 148.40 (*q*C), 147.22 (*q*C), 128 (*q*C), 121.93 (CHF_2), 119.66 (ar CH), 117.22 (ar CH), 56.88 (**C**–CHF_2), 56.67 (OCH_3), 56.46 (OCH_3), 40.43 (CH_2–N), 30.97 (Ar–CH_2).

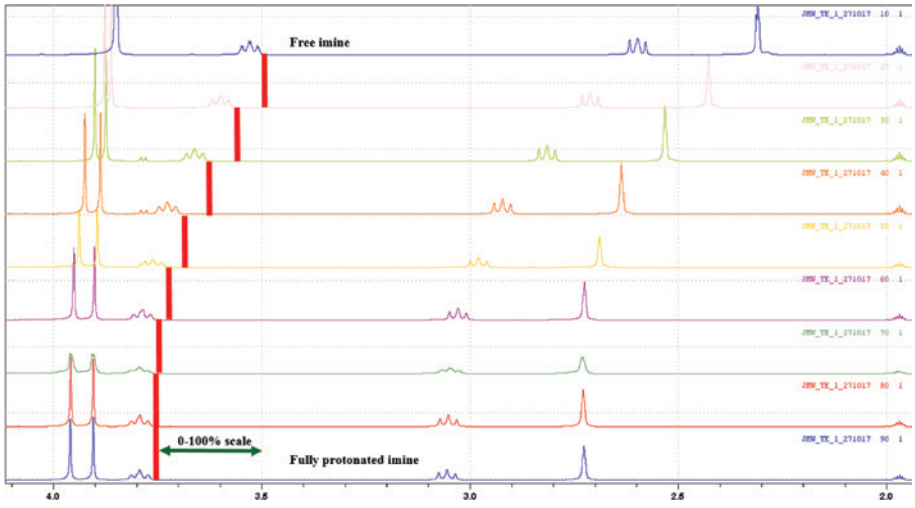
General procedure for ATH of imines

The dimer ($[IrCp^*Cl_2]_2$ or $[IrCp^*CONMe_2Cl_2]_2$) was added to a 10 mL vial and washed in with acetonitrile (1 mL), this was then sonicated for 1 min before the addition of *R*,*R*-TsDPEN and this was washed in with (1 mL) acetonitrile. The imine was introduced in one portion to the preformed catalyst as a 2 mL solution. This was allowed to stir for 5 min before the introduction of the azeotropic mixture (HCO_2H/Et_3N) in (1.78 mL) acetonitrile. The reaction was sampled at different time points by extraction of a 50 µL into a biphasic 2 M NaOH/DCM (1:1) solution to quench the reaction. The aqueous layer was removed, and the organic was dried with Na_2SO_4 and added to a GC vial.

*All ATH data reported was obtained from GC-FID analysis. The peak areas for the imine and the amine product were used to determine the percentage conversion.

General procedure for ^{1}H protonation experiments

The imine (0.1 M) in acetonitrile-D_3 was subjected to 0.05 eq. additions of formic and trifluoroacetic acid, respectively. The methylene signals' (C=N–**CH_2**) chemical shift was used to determine the amount of protonation due to the close proximity to the C=N bond. As shown in the example below the free imine (6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline) is in neat acetonitrile-D_3 and as consecutive additions of acid are made the signals shift until a point of no more shift which indicates full protonation. This was converted to a percentage, enabling determination of the extent of protonation in our reported conditions.



References

[1] M. J. Stirling, G. Sweeney, K. MacRory, A. J. Blacker, M. I. Page. *Org. Biomol. Chem*. **14**, 3614 (2016).
[2] M. Stefinovic, M. Ropic, D. Blackmond, *Org. Proc. Res. Dev*. **10**, 457 (2006).
[3] C. P. Casey, S. W. Singer, D. R. Powell, R. K. Hayashi, M. Kavana. *J. Am. Chem. Soc*. **123**, 1090 (2001).
[4] J. B. Aberg, J. S. M. Samec, J.-E. Backvall. *Chem. Commun*. 2771 (2006).
[5] J. E. D. Martins, G. J. Clarkson, M. Wills. *Org. Lett*. **11**, 847 (2009).
[6] E. H. Cordes, W. P. Jencks. *J. Am. Chem. Soc*. **85**, 2843 (1963).
[7] G. Fodor, S. Nagubandi. *Tetrahedron* **36**, 1279 (1980).
[8] M. Movassaghi, M. D. Hill. *Org. Lett*. **10**, 3485 (2008).
[9] P. J. Taylor. *J. Chem. Soc. Perkin. Trans*. **2**, 1423 (1993); C. Hansch, A. Leo, R. W. Taft. *Chem. Rev*. **91**,165 (1991).
[10] B. Cox. *Acids and Bases, Solvent Effects on Acid-Base Strength*, Oxford UP, UK (2013).
[11] W. N. Olmstead, F. G. Bordwell. *J. Org. Chem*. **45**, 3299 (1980).
[12] V. P. Reddy, G. K. SuryaPrakash, G. Rasul. *J. Fluor. Chem*. **210**, 83 (2018).