ELECTRONIC SUPPLEMENTARY INFORMATION

The Kinetics and Mechanism of the Organo-Iridium Enantioselective Reduction of Imines

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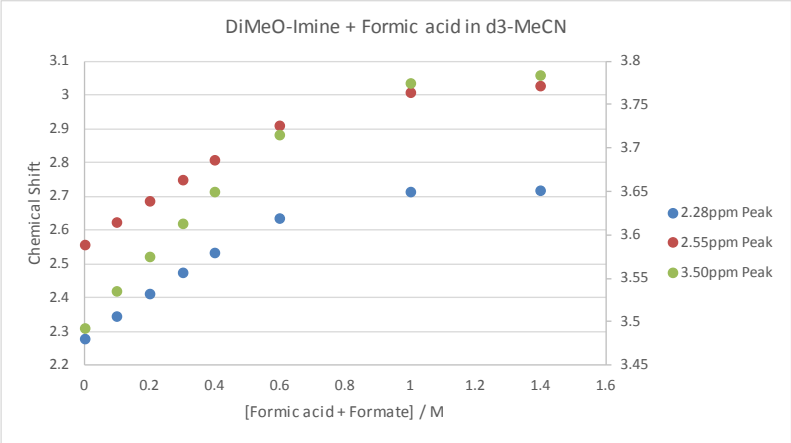
1. Solutions of the imines, corresponding amine products and triethylamine were titrated against varying concentrations of added formic acid in d_3-acetonitrile and d_2-dichloromethane and their NMR chemical shift values used to show the fraction of base protonated as shown in the following tables and graphs.

2. Further details related to the asymmetric transfer hydrogenation experiments are reported.

1H NMR Titrations formic acid with amines in Acetonitrile and dichloromethane

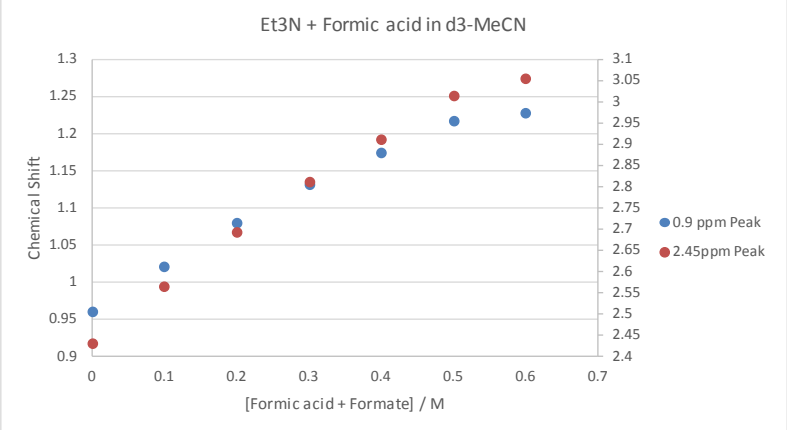
1. 0.4M 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline titrated against formic acid in d3-acetonitrile

		1H chemical shift ppm			[Iminium] / M based on 2.28ppm	[Iminium] / M based on 2.55ppm	[Iminium] / M based on 3.50ppm
Eq. Formic Acid	[Formic+Formate] / M	2.28ppm Peak	2.55ppm Peak	3.50ppm Peak			
0	0	2.2793	2.5578	3.4931	0	0	0
0.25	0.1	2.347	2.623	3.5353	0.060	0.054	0.057
0.5	0.2	2.4126	2.6871	3.5754	0.118	0.107	0.111
0.75	0.3	2.4751	2.749	3.6131	0.174	0.159	0.162
1	0.4	2.5334	2.8073	3.6505	0.226	0.207	0.212
1.5	0.6	2.6354	2.9121	3.7155	0.316	0.294	0.300
2.5	1	2.7155	3.0105	3.7753	0.387	0.376	0.380
3.5	1.4	2.7192	3.0302	3.7841	0.390	0.392	0.392
	End point	2.73	3.04	3.79			



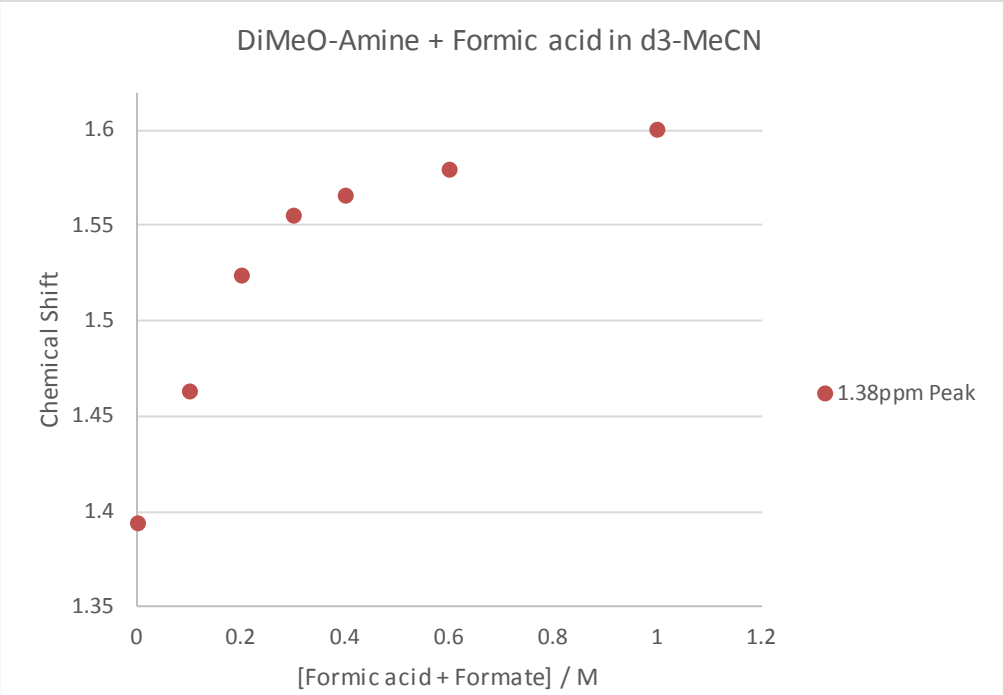
2. 0.4M triethylamine titrated against formic acid in d3-acetonitrile

		1H chemical shift ppm		[Et3NH+] / M based on 0.9ppm	[Et3NH+] / M based on 2.45ppm
Eq. Formic Acid	[Formic+Formate] / M	0.9 ppm Peak	2.45ppm Peak		
0	0	0.961	2.4322	0.000	0.000
0.25	0.1	1.022	2.5668	0.087	0.084
0.5	0.2	1.0799	2.6951	0.170	0.164
0.75	0.3	1.1329	2.8136	0.246	0.237
1	0.4	1.1755	2.911	0.308	0.298
1.25	0.5	1.2172	3.0146	0.367	0.362
1.5	0.6	1.229	3.0544	0.384	0.387
	End point	1.24	3.075		



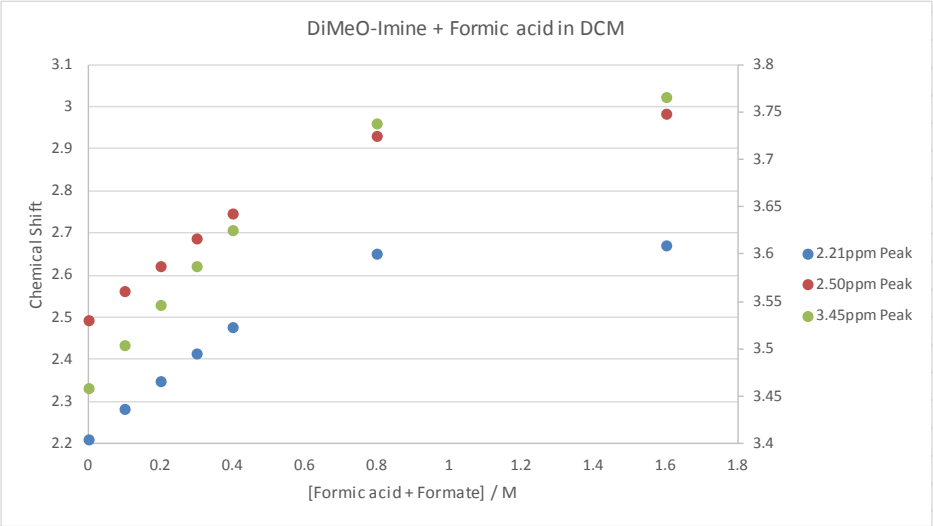
3. 0.4M 6,7-dimethoxy-1-methyl-tetrahydroisoquinoline titrated against formic acid in d3-acetonitrile

		1H chemical shift ppm	
Eq. Formic Acid	[Formic+Formate] / M	1.38ppm Peak	[Aminium ion] / M
0	0	1.3947	0.000
0.25	0.1	1.4634	0.128
0.5	0.2	1.5245	0.241
0.75	0.3	1.5555	0.299
1	0.4	1.5662	0.319
1.5	0.6	1.5795	0.343
2.5	1	1.6013	0.384
	End point	1.61	



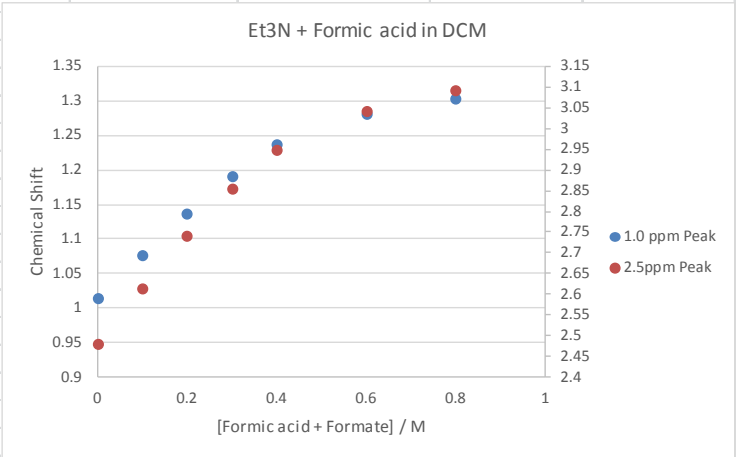
4. 0.4M 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline titrated against formic acid in dichloromethane

		1H chemical shift ppm			[Iminium] / M based on 2.21ppm	[Iminium] / M based on 2.50ppm	[Iminium] / M based on 3.45ppm
Eq. Formic Acid	[Formic+Formate] / M	2.21ppm Peak	2.50ppm Peak	3.45ppm Peak			
0	0	2.2121	2.4951	3.4593	0.000	0.000	0.000
0.25	0.1	2.2839	2.5613	3.5049	0.062	0.054	0.059
0.5	0.2	2.3496	2.6232	3.5462	0.120	0.104	0.112
0.75	0.3	2.416	2.6868	3.5875	0.177	0.155	0.165
1	0.4	2.4763	2.7457	3.6249	0.230	0.203	0.213
2	0.8	2.6515	2.9297	3.7376	0.382	0.351	0.358
4	1.6	2.6717	2.985	3.7663	0.400	0.396	0.395
	End point	2.672	2.99	3.77			



5. 0.4M triethylamine titrated against formic acid in dichloromethane

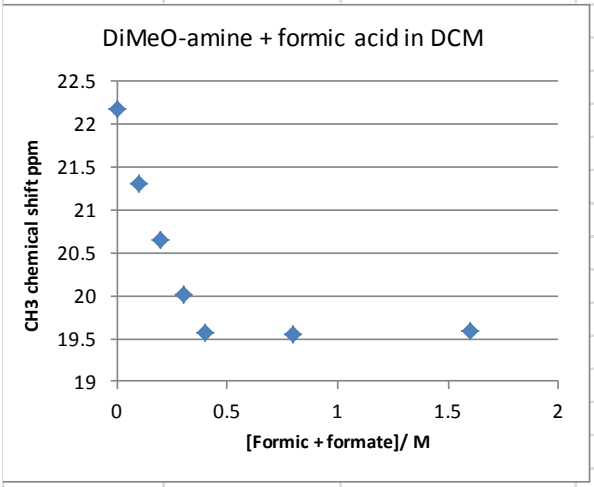
		1H chemical shift ppm		[Et3NH+] / M based on 1.0ppm	[Et3NH+] / M based on 2.5ppm
Eq. Formic Acid	[Formic+Formate] / M	1.0 ppm Peak	2.5ppm Peak		
0	0	1.0141	2.4825	0.000	0.000
0.25	0.1	1.0771	2.615	0.082	0.082
0.5	0.2	1.1366	2.7401	0.160	0.159
0.75	0.3	1.1915	2.8553	0.232	0.230
1	0.4	1.2368	2.9492	0.291	0.288
1.5	0.6	1.2818	3.0421	0.350	0.346
2	0.8	1.3034	3.0929	0.378	0.377
	End point	1.32	3.13		

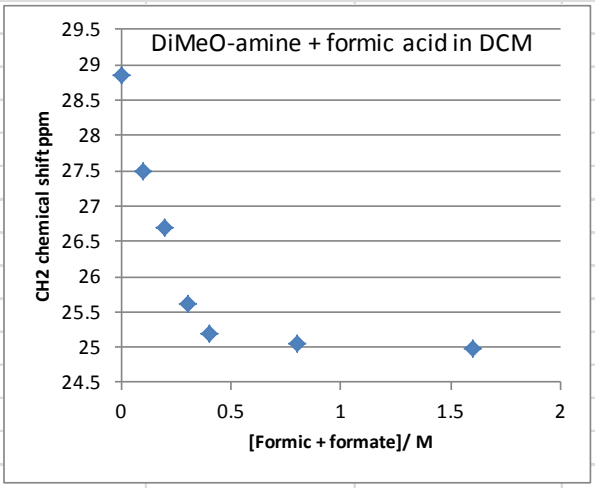


6. 13C NMR 1-methyl-6, 7-dimethoxy-tetrahydroisoquinoline [0.4]M titrated against formic acid in dichloromethane

referenced against CD2Cl2 at 53.5ppm

		13C Chemical shift		[Aminium ion]/ M	
[Formic + formate]/M	Equivalents of formic acid	Methyl group ppm	CH2 ppm	based on CH3	based on CH2
0	0	22.17	28.84	0.000	0.000
0.1	0.25	21.3	27.5	0.133	0.139
0.2	0.5	20.65	26.69	0.233	0.223
0.3	0.75	20.02	25.61	0.330	0.335
0.4	1	19.56	25.19	0.400	0.378
0.8	2	19.55	25.05	0.402	0.393
1.6	4	19.58	24.98	0.397	0.400





Attempted racemisation of (R)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline, ***12***

Pentamethylcyclopentadienyliridium (III) chloride dimer, **10**, (1.9 mg, 2.385 x 10^{-3} mmol) and (R)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline, **14**, (100 mg, 0.4873 mmol) were dissolved in dichloromethane (1.95ml) to give an orange solution that was agitated using a magnetic stirrer. Samples were taken after 2 and 12 hrs and analysed by GC by adding one drop to a GC vial containing dichloromethane by chiral capillary electrophoresis by adding 200 µl of the reaction solution to 10 ml ultra-pure water.

A similar experiment was conducted in the presence of a solution of TEAF - pentamethylcyclopentadienyliridium (III) chloride dimer, **10**, (1.9 mg, 2.385 x 10^{-3} mmol), (S,S)-TsDPhEN (1.8 mg, 4.9 x 10^{-3} mmol), (R)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline, **14**, (100 mg, 0.4873 mmol) and a pre-prepared TEAF solution in dichloromethane(1.95ml, 1.225 x 10^{-2} mmol HCO_2H) resulting in an orange solution that was agitated using a magnetic stirrer. Samples were taken after 2 and 12 hrs and analysed as above. Finally, the experiments were repeated using (R)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline, **14**, Iridium CATHy catalyst, **3** and 6 mol. eq. formic acid.

Transfer hydrogenation of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline, ***7****, using 0.25 mol% of the iridium catalyst,* ***2****, and 6 mol. eq. formic acid added as TEAF in dichloromethane at 20°C.*

Pentamethylcyclopentadienyliridium(III)chloride dimer, **3**, (6.1 mg 96% ≡ 5.8 mg ≡ 7.341 x 10^{-3} mmol), (S,S)-TsDPhEN, **5**, (5.4 mg 99% ≡ 5.38 mg ≡ 0.0147 mmol) were weighed into a three-neck 25 ml round bottom flask and dissolved in dichloromethane (5.0 ml) at room temperature (~20 °C). The reaction solution was agitated using a magnetic stirrer and sparged at 50 ml/min with nitrogen via a needle placed into the solution for 30 mins resulting in a yellow solution. The nitrogen sparge was passed through a 500 ml round bottom flask containing dichloromethane prior to entering the reaction flask to minimise the amount of dichloromethane lost during the reaction due to evaporation and was maintained, with agitation, throughout the reaction. 6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline, **7**, (1.21 g 99% ≡ 1.204 g ≡ 5.873 mmol) and biphenyl (455.0 mg 99.5% ≡ 452.8 mg ≡ 2.937 mmol) were added and washed in using dichloromethane (6.7 ml) when all the solid had dissolved TEAF (3.11 g 98%, 3.048g, 35.24 mmol formic acid) was added in one aliquot causing the reaction solution to fade to a pale yellow. The reaction was sampled at regular intervals for GC analysis by quenching ~100 µl into 2.5M sodium hydroxide (2.0 ml) / dichloromethane (2.0 ml) and isolating and drying the organic layer using sodium sulfate.

Transfer hydrogenation of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline, ***7****, using 0.125 mol% of the iridium catalyst,* ***2****, and 6 mol. eq. formic acid added as TEAF in dichloromethane at 20°C.*

Pentamethylcyclopentadienyliridium(III)chloride dimer, **3**, (3.0 mg 97% ≡ 2.9 mg ≡ 3.67 x 10^{-3} mmol), (S,S)-TsDPhEN, **5**, (2.7 mg 99% ≡ 2.7 mg ≡ 0.00734 mmol) were weighed into a three-neck 25 ml round bottom flask and dissolved in dichloromethane (5.0 ml) at room temperature (~20 °C). The reaction solution was agitated using a magnetic stirrer and sparged at 50 ml/min with nitrogen via a needle placed into the solution for 30 mins resulting in a yellow solution. The nitrogen sparge was passed through a 500 ml round bottom flask containing dichloromethane prior to entering the reaction flask to minimise the amount of dichloromethane lost during the reaction due to evaporation and was maintained, with agitation, throughout the reaction. 6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline, **7**, (1.21 g 99% ≡ 1.204 g ≡ 5.873 mmol) and biphenyl (455.0 mg 99.5% ≡ 452.8 mg ≡ 2.937 mmol) were added and washed in using dichloromethane (6.7 ml) when all the solid had dissolved TEAF (3.11 g 98% ≡ 3.048g ≡ 35.24 mmol formic acid) was added in one aliquot causing the reaction solution to fade to a pale yellow. The reaction was sampled at regular intervals for GC analysis by quenching ~100 µl into 2.5M sodium hydroxide (2.0 ml) / dichloromethane (2.0 ml) and isolating and drying the organic layer using sodium sulfate.

Transfer hydrogenation of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline, ***7****, using 0.0625 mol% of the iridium catalyst,* ***2****, and 6 mol. eq. formic acid added as TEAF in dichloromethane at 20°C.*

A standard solution of pentamethylcyclopentadienyliridium (III) chloride dimer, **3**, was prepared by dissolving the dimer (38.1 mg 96% ≡ 36.6 mg ≡ 0.04588 mmol) in dichloromethane (50 ml) in a volumetric flask. Standard solution A.

A standard solution of (S,S)-TsDPhEN, **5**, was prepared by dissolving the ligand (34.0 mg 99% ≡ 33.6 mg ≡ 0.09177 mmol) in dichloromethane (50 ml) in a volumetric flask. Standard solution B.

To a 2-neck 25 ml round-bottom flask was added standard solution A (2 ml) and standard solution B (2 ml) resulting in a yellow solution. A nitrogen sparge was then applied (50 ml/min) via a needle placed as low in the flask as possible (the nitrogen was first past through a flask containing dichloromethane to saturate it thereby minimising the reaction solvent lost through evaporation). 6,7-Dimethoxy-1-methyl-3,4,dihydroisoquinoline, **7**, (1.21 g 99% ≡ 1.20 g ≡ 5.873 mmol) and biphenyl (455.1 mg 99.5% ≡ 452.8 mg ≡ 2.937 mmol) were then added and washed in using dichloromethane (7.7 ml).

When all the substrate had dissolved TEAF (3.11 g 98% ≡ 3.05 g ≡ 35.238 mmol formic acid) was added in one aliquot causing the reaction solution to fade to a pale yellow.

Samples were taken at regular intervals and quenched in a vial containing dichloromethane (2 ml) and sodium hydroxide solution (2 ml of 1.0 M), the dichloromethane layer was removed, dried using sodium sulfate, filtered and analysed by achiral g.c., a portion of the dried dichloromethane was added to a separate vial containing trifluoroacetic anhydride (~200 μl) and left for a minimum of 30 mins before being concentrated to dryness under vacuum, redissolved in dichloromethane and analysed by chiral GC.

*Transfer hydrogenation of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline, **7**, using 0.5 mol% of the iridium catalyst, **2**, and 6 mol. eq. formic acid added as TEAF in dichloromethane at 20°C with the addition of 1 mol. eq. **7** and 2 mol. eq. formic acid after 35 minutes.*

To a 2-neck 25 ml round-bottom flask was added pentamethylcyclopentadienyliridium (III) dichloride dimer, **3**, (12.1 mg 97% ≡ 11.7 mg ≡ 0.0147 mmol) and (S,S)-TsDPhEN, **5**, (10.9 mg 99% ≡ 10.8 mg ≡ 0.0294 mmol) and dichloromethane (5 ml) resulting in a yellow solution. A nitrogen sparge was then applied (50 ml/min) via a needle placed as low in the flask as possible (the nitrogen was first past through a flask containing dichloromethane to saturate it thereby minimising the reaction solvent lost through evaporation). 6,7-Dimethoxy-1-methyl-3,4,dihydroisoquinoline, **7**, (1.21 g 99% ≡ 1.20 g ≡ 5.873 mmol) and biphenyl (455.1 mg 99.5% ≡ 452.8 mg ≡ 2.937 mmol) were then added and washed in using dichloromethane (6.7 ml).

When all the substrate had dissolved TEAF (3.11 g 98% ≡ 3.05 g ≡ 35.238 mmol formic acid) was added in one aliquot causing the reaction solution to fade to a pale yellow.

After 35 mins 6,7-dimethoxy-1-methyl-3,4,dihydroisoquinoline, **7**, (1.21 g 99% ≡ 1.20 g ≡ 5.873 mmol) was added and washed in using dichloromethane (1 ml) immediately followed by the addition of formic acid (546.1 mg 99% ≡ 540.7 mg ≡ 11.746 mmol). The reaction solution slowly darkened to a brown colour over three hours.

Samples were taken at regular intervals and quenched in a vial containing dichloromethane (2 ml) and sodium hydroxide solution (2 ml of 1.0 M), the dichloromethane layer was removed, dried using sodium sulfate, filtered and analysed by achiral GC, a portion of the dried dichloromethane was added to a separate vial containing trifluoroacetic anhydride (~200 μl) and left for a minimum of 30 mins before being concentrated to dryness under vacuum, redissolved in dichloromethane and analysed by chiral GC

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*Transfer hydrogenation of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline, **7**, using 0.125 mol% of the iridium catalyst, **2**, and 6 mol. eq. formic acid added as TEAF in dichloromethane at 20°C with the addition of 0.5 mol. eq. (S)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline, **8**, at t = 0 minutes.*

To a 2-neck 25 ml round-bottom flask was added pentamethylcyclopentadienyliridium (III) dichloride dimer, **3**, (3.0 mg 97% ≡ 2.9 mg ≡ 0.00367 mmol) and (S,S)-TsDPhEN, **5**, (2.7 mg 99% ≡ 2.7 mg ≡ 0.00734 mmol) and dichloromethane (5 ml) resulting in a yellow

solution. A nitrogen sparge was then applied (50 ml/min) via a needle placed as low in the flask as possible (the nitrogen was first past through a flask containing dichloromethane to saturate it thereby minimising the reaction solvent lost through evaporation). 6,7-Dimethoxy-1-methyl-3,4,dihydroisoquinoline, **7**, (1.21 g 99% ≡ 1.20 g ≡ 5.873 mmol) and biphenyl (int. std. 455.1 mg 99.5% ≡ 452.8 mg ≡ 2.937 mmol) were then added and washed in using dichloromethane (3.0 ml).

(S)-6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline, **8**, (627.4 mg 97% ≡ 605.6 mg ≡ 2.937 mmol) was dissolved in dichloromethane (3.7 ml) and added to the reaction vessel immediately followed by TEAF (3.11 g 98% ≡ 3.05 g ≡ 35.238 mmol formic acid) added in one aliquot causing the reaction solution to fade to a pale yellow.

Samples were taken at regular intervals and quenched in a vial containing dichloromethane (2 ml) and sodium hydroxide solution (2 ml of 1.0 M), the dichloromethane layer was removed, dried using sodium sulfate, filtered and analysed by achiral GC, a portion of the dried dichloromethane was added to a separate vial containing trifluoroacetic anhydride (~200 μl) and left for a minimum of 30 mins before being concentrated to dryness under vacuum, redissolved in dichloromethane and analysed by chiral GC.

*Transfer hydrogenation of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline, 7, using 0.125 mol% of the iridium catalyst, **2**, and 6 mol. eq. formic acid added as TEAF in dichloromethane at 20°C with the addition of 0.5 mol. eq. triethylamine at t = 0 minutes.*

To a 2-neck 25 ml round-bottom flask was added pentamethylcyclopentadienyliridium (III) dichloride dimer, **3**, (3.0 mg 97% ≡ 2.9 mg ≡ 0.00367 mmol) and (S,S)-TsDPhEN, **5**, (2.7 mg 99% ≡ 2.7 mg ≡ 0.00734 mmol) and dichloromethane (5 ml) resulting in a yellow solution. A nitrogen sparge was then applied (50 ml/min) via a needle placed as low in the flask as possible (the nitrogen was first past through a flask containing dichloromethane to saturate it thereby minimising the reaction solvent lost through evaporation). 6,7-Dimethoxy-1-methyl-3,4,dihydroisoquinoline, **7**, (1.21 g 99% ≡ 1.20 g ≡ 5.873 mmol) and biphenyl (455.1 mg 99.5% ≡ 452.8 mg ≡ 2.937 mmol) was then added and washed in using dichloromethane (6.7 ml).

When all the substrate had dissolved triethylamine (298.7 mg 99.5% ≡ 297.2 mg ≡ 2.937 mmol) was added causing the reaction solution to darken slightly to an orange colour, TEAF (3.11 g 98% ≡ 3.05 g ≡ 35.238 mmol formic acid) was then added in one aliquot causing the reaction solution to fade to a pale yellow.

Samples were taken at regular intervals and quenched in a vial containing dichloromethane (2 ml) and sodium hydroxide solution (2 ml of 1.0 M), the dichloromethane layer was removed, dried using sodium sulfate, filtered and analysed by achiral GC, a portion of the dried dichloromethane was added to a separate vial containing trifluoroacetic anhydride (~200 μl) and left for a minimum of 30 mins before being concentrated to dryness under vacuum, redissolved in dichloromethane and analysed by chiral GC.

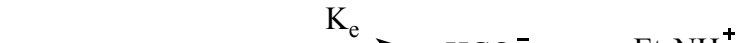
*Transfer hydrogenation of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline, 7, using 0.25 mol% of the iridium catalyst, **2**, and 6 mol. eq. formic acid added as TEAF in dichloromethane at 20°C with the addition of 1.0 mol. eq. (S,S)-TsDPhEN at t = 0 minutes.*

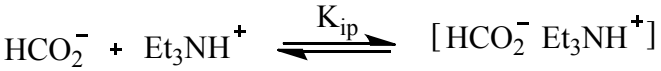
To a 2-neck 25 ml round-bottom flask was added pentamethylcyclopentadienyliridium (III) dichloride dimer, **3**, (6.1 mg 96% ≡ 5.8 mg ≡ 0.00734 mmol) and (S,S)-TsDPhEN, **5**, (2.174 g 99% ≡ 2.152 g ≡ 5.873 mmol) and dichloromethane (5 ml) resulting in a yellow solution. A nitrogen sparge was then applied (50 ml/min) via a needle placed as low in the flask as possible (the nitrogen was first past through a flask containing dichloromethane to saturate it thereby minimising the reaction solvent lost through evaporation). 6,7-Dimethoxy-1-methyl-3,4,dihydroisoquinoline, **7**, (1.21 g 99% ≡ 1.20 g ≡ 5.873 mmol) and biphenyl (455.1 mg 99.5% ≡ 452.8 mg ≡ 2.937 mmol) were then added and washed in using dichloromethane (6.7 ml).

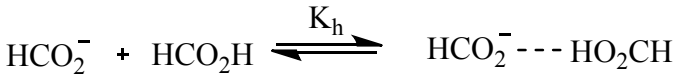
When all the substrate had dissolved TEAF (3.11 g 98% ≡ 3.05 g ≡ 35.238 mmol formic acid) was added in one aliquot causing the reaction solution to fade to a pale yellow.

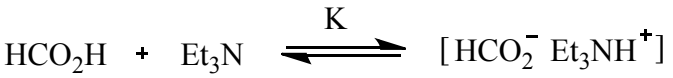
Samples were taken at regular intervals and quenched in a vial containing dichloromethane (2 ml) and sodium hydroxide solution (2 ml of 1.0 M), the dichloromethane layer was removed, dried using sodium sulfate, filtered and analysed by achiral GC, a

portion of the dried dichloromethane was added to a separate vial containing trifluoroacetic anhydride (~200 µl) and left for a minimum of 30 mins before being concentrated to dryness under vacuum, redissolved in dichloromethane and analysed by chiral GC.









$$K = \frac{K_e \cdot K_{ip}}{K_h}$$