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Continuous Flow Asymmetric Transfer Hydrogenation with Long Catalyst Lifetime and Low Metal Leaching

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Dedicated to the memory of Prof. Jonathan M. J. Williams

Abstract: Homogenous iridium complexes with asymmetric ligands and different tether lengths have been solid-supported and prepared in multi-gram quantities. Packed in a fixed-bed, they have been used in continuous flow for up to 120 hours in the asymmetric transfer hydrogenation of APs in isopropanol to make 1-phenethyl alcohols in >95% conversion and ee. The CsDPEN ligand and C_5 tether showed higher performance than TsDPEN and the C_{14} tether, whilst the ketone feed concentration and reaction temperature were optimized to enable the catalyst to be used at 5 mol% loading with a residence time of 39 minutes. The total amount iridium leaching of from the support during sustained operation was 58-147 ppm. The flow system gives higher catalyst turnover numbers than the related batch reactions, but the nature and concentration of the base were found to influence strongly the catalyst's performance, with the finding that triethylamine maintains high enantioselectivity but slowly deactivates the catalyst, whilst potassium *tert*-butoxide does the opposite. The utility of the system is shown in the high ee's and good conversions achieved for a range of aryl alcohols.

Introduction

Since the discovery of the Noyori Ru(arene) catalysts in 1995,[1] and the isoelectronic Ir/Rh Cp* catalysts in 1997,[2] catalytic asymmetric transfer hydrogenation (CATHy) has been used widely to make chiral alcohol and amine building blocks, with numerous scaled-up industry examples.[3] Despite this, the turnover number (TON) and frequencies (TOF) are not as high as those of asymmetric hydrogenation catalysts.[4] To overcome this, loadings of 0.1-1 mol% are used, that both increase the cost and complicate separation of the catalyst from the product. Immobilization is a strategy that has been greatly researched, and is used widely with enzymes, but is unsuccessful for homogeneous catalysts[5] Most reports use functionalized bidentate ligands with catalysts used in batch, separated and re-used, Figure 1,[6] Whilst the total turnover numbers (TTN) are satisfactory, problems include: the fall in activity after a few recycles due to metal leaching or catalyst poisoning; the solid support itself causing lower activity because of reduced mass transfer; the increased cost of complex ligands versus the benefit in TTN. Surprisingly, there are few reports of transfer hydrogenation in continuous flow, where a benefit of operating in steady-state is information about catalyst deactivation and leaching rates. Liese *et al* attached a functionalized tetradentate ruthenium catalyst to a soluble polysiloxane polymer and used this in a continuous flow membrane reactor with isopropanol/dichloromethane.[7] This was operated over 175 reaction volumes, but, due to deactivation, required a top-up of 0.5% fresh catalyst per reaction volume. In this way, they achieved a steady-state conversion of 79% AP giving the alcohol in 91% ee, with a productivity of 578 g/L/day, giving a catalyst TTN of 2630. Van Leeuwen *et al* tethered a ruthenium norephedrine catalyst to silica.[8] They used this in a fixed-bed continuous flow mode over 1 week, to reduce AP with isopropanol at 95% steady-state conversion to 1-phenylethanol with 90% ee. The leaching of ruthenium was less than 1% during 3-11 h of catalysis and a fall in performance was only seen after 170 h of operation.

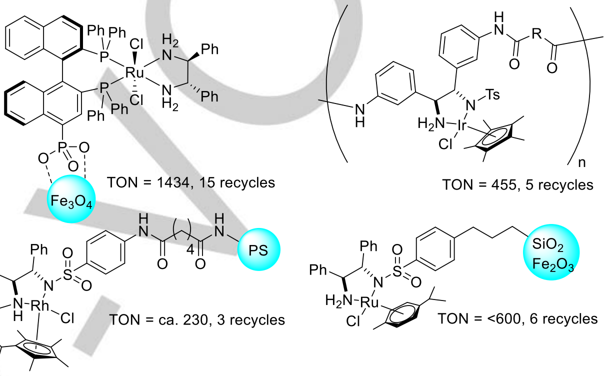

Figure 1. Structures, turnover and recycle numbers of some immobilized asymmetric transfer hydrogenation catalysts.[6a-d]

This study reports a new application of our published alkyl tethered tetramethylcyclopentadienyl (Cp**) metal complex immobilized on Wang-resin.[9][10] Here, the modular design anchors iridium through an anionic η5 complex, and retains three free coordination sites.

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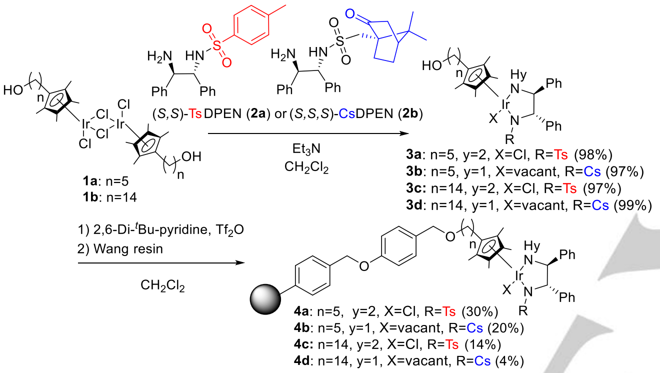
Results and Discussion

The (*S*,*S*)-*N*-tosyl-1,2-diphenylethylene diamine (TsDPEN, **2a**), and (*S*,*S*,*S*)-*N*-camphorsulfonyl-1,2-diphenylethylene diamine (CsDPEN, **2b**), ligands were selected for this work, as these have previously given good results in homogeneous asymmetric transfer hydrogenation reactions.[11] The catalyst's performance with C_5 and C_{14} linkers (expressed as the number of carbon atoms in the chain) were compared, as this gives an indication of mass transfer effects in the boundary layer around the solid support. The sequence in which the metalation, ligation and addition to the support were carried out, was found to be important. Attempts to coordinate the diamine ligand directly to the tethered dichloroiridium Cp** complex immobilized on Wang resin were unsuccessful, whilst ligation of the soluble complex, followed by activation of the terminal hydroxyl group as a triflate, then reaction with the Wang resin solid support, gave the desired immobilized catalysts in reasonable yields, Scheme 1.



Scheme 1. Reaction sequence and results for making the C_5 and C_{14} tethered TsDPEN and CsDPEN Cp** iridium complexes.

This highlights the difficulties in doing reactions on solid supported materials. Both the C_5 and C_{14} tethered chloro Cp* iridium complexes, **1a** and **1b**, were prepared in multi-gram quantities by previously described methods.[9] The ligands TsDPEN, **2a**, and CsDPEN, **2b**, were reacted with **1a** or **1b** in dichloromethane with triethylamine to give the soluble complexes, **3a-d** in near quantitative yield. Interestingly, **3a** and **3c** were obtained with the chloride ligand, however **3b** and **3d** were isolated as the 16-electron species lacking HCl, as confirmed by ^{1}HNMR and HRMS, despite using the same conditions (ESI 2.0). The primary alcohol tethers were then activated with triflic anhydride and reacted with Wang resin (1% degree of crosslinking, 100-200 mesh) to give the solid-supported catalysts, **4a-d**. After extensive washing, first with dichloromethane, then water, 1M HCl (aq), water, methanol and isopropanol, the solid was vacuum dried. ICP analysis of the iridium showed immobilization reaction yields of 30% for **4a**, 20% for **4b**, 14% for **4c**, and only 4% for **4d**. As previously observed, the longer tether seems to cause problems with attachment. The solid supported catalysts were analyzed by EDX TEM (ESI 10.0), showing spherical particles of average 120 μm diameter with an even surface distribution of the catalyst's constituent elements.

Table 1. Activity and selectivity of soluble and immobilized catalysts used in batch with AP, isopropanol, KO^{t}Bu.

#[a]	Catalyst	Mode	Ee[b] (%)	Conv. [b] (%)	TON	Time (h)	TOF (h^{-1})
1	IrClCp*TsDPEN	Batch	79	59	15	5	3.0
2	IrCp*CsDPEN	Batch	95	90	23	5	4.6
3	**3a**	Batch	82	60	15	5	3.0
4	**3b**	Batch	95	96	24	5	4.8
5	**3c**	Batch	85	67	17	5	3.4
6	**3d**	Batch	96	97	24	5	4.8
7	**4a**	Batch	24	62	16	24	1.5
8	**4b**	Batch	82	95	24	24	1.0
9	**4c**	Batch	46	86	22	24	1.1
10	**4d**	Batch	67	96	24	24	1.0
11	IrCp*CsDPEN (no base)	Batch	95	93	23	5	4.6
12	**3b** (no base)	Batch	91	86	22	5	4.4
13	**4b** (no base)	Batch	3	33	8	24	0.3

[a] Substrate/Catalyst/Base (mole ratio) = 100/4/10 (entries 1-6), 100/4/100 (entries 7-10), 100/4/0 (entries 11-13). [b] Measured by GC (ESI 11.1)

The specific surface area was measured by BET analysis at 11.2 m^2/g.[12] It is calculated for **4a** that each tethered catalyst molecule at the polymer surface is 1.9Å apart, **4b** 2.5Å, **4c** 3Å and **4d** 4.5Å. The extended length of the tether & iridium catalyst from the surface are about 28Å **4a** and 40Å **4d**. From these estimates, it is clear that each site is not isolated and tethered catalyst molecules can interact, and might entangle.

Table 1 shows the results a comparison of the homogenous and solid-supported catalysts in the asymmetric transfer hydrogenation of acetophenone (AP) to 1-phenylethanol by isopropanol (IPA). Potassium *tert*-butoxide (KO^{t}Bu) is used commonly in this system to activate the catalyst from the 18-electron chloroiridium precatalyst, to the 16-electron species.[1] However, it was found that when the base and ketone were combined into a single isopropanol solution, the mixture darkened in a few hours, due to the formation of Claisen condensation products, which over extended run times was problematic. Accordingly, separate solutions of each were pumped and mixed together with the catalyst (ESI 4.0). The conventional IrCp* homogenous catalysts used in batch mode, entries 1-2, showed similar performance to the soluble C_5 and C_{14} Cp** analogues, **3a-d**, entries 3-6, indicating that the tether does not interfere in the reaction. Also, the CsDPEN ligand gave significantly higher ee and conversion than TsDPEN ligand. Comparing the solid-supported catalysts, entries 7-10, with the homogenous, in which 1 equiv. of base was used, the conversions and TONs were similar, but the enantioselectivities and TOFs were considerably lower. The base was suspected to be the problem, so the catalysts were retested without it. Surprisingly, the homogenous catalysts IrCp*CsDPEN and **3b** showed little change in performance, entries 11-12, and investigation by ^{1}HNMR, showed the isolated pre-catalysts were present as the 16-electron species, as opposed to the IrCp*TsDPEN and **3a** that were observed as the 18-electron chloroiridium species (ESI 2.0). As is frequently observed with immobilized catalysts, **4a-d** were also less active than the homogenous ones. For example the turnover frequency (TOF) of **3b** is 4.8 h^{-1} compared with 1.0 h^{-1} with **4b**, entries 4 and

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8. This time however, when the base was omitted from the reaction using catalyst **4b** it showed poor activity, TOF=0.3, and very low ee, entry 13.

From these initial studies, it was clear that the base is important in delivering both high conversion and ee over a sustained time, however no studies were found to help us develop the IPA CATHy system. Accordingly, we evaluated different bases in batch mode using catalyst **4b**, with the results shown in Figure 2.

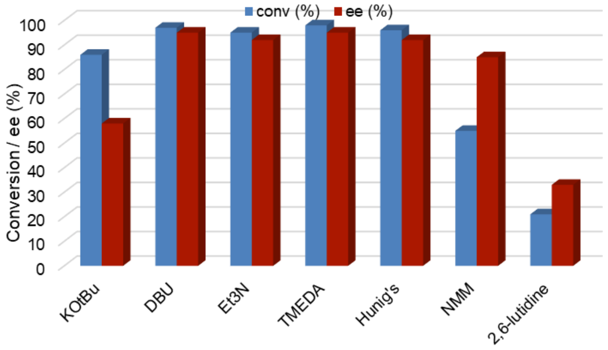

Figure 2. The effect of 100 mol% of different bases on the conversion and enantioselectivity in the IPA reduction of AP with 3.7 mol% solid-supported catalyst **4b** used in batch-mode.

It was found that the conversions and ee's correlate with the base pKa. The traditional base used is KO^{t}Bu (pKa = 16-19),[13a], whilst 2,6-lutidine (6.75),[13b] and *N*-methylmorpholine (NMM) (7.4),[13c] were found to be too weak to fully activate the catalyst by dehydrochlorination to generate the 16-electron species. On the other hand, amine bases with a moderate pKa performed well, giving both high ee and conversion: DBU (11.9),[13d] Et$_3$N (10.7),[13a] Hünig's base (10.7),[13e] and TMEDA (10.4).[13f] Triethylamine is the cheapest amine base, so its reaction stoichiometry was investigated further, Table 2.

Table 2. The influence of Et$_3$N equivalents on AP reduction in batch using catalyst **4b**.

#	Equivalents of Et$_3$N[a]	Conv.(%)(Ee %) 5 h	24 h
1[b]	0	9 (2)	33 (3)
2[b]	0.1	31 (93)	94 (96)
3[c]	1.0	85 (95)	95 (92)
4[d]	3.0	87 (95)	93 (94)
5[c]	10.0	94 (95)	98 (94)

[a] Mole ratio based on AP with catalyst **4b** in IPA. [b] 3.7 mol% catalyst at 60°C. [c] 2.3 mol% catalyst at 30°C. [d] 2.3 mol% catalyst at 60°C.

Without base the catalyst performed poorly, entry 1. Using 10 mol% with respect to AP, a slow reaction occurred with 31% conversion after 5h, entry 2. One equivalent gave a faster rate, whilst 10 equivalents gave near full conversion in 5 h with a high ee, entry 4. Based on this, triethylamine works well at ≥1 equiv. to substrate, whilst previous results show that KO^{t}Bu works best sub-stoichiometrically.

To understand further the effects of base, experiments were carried out in continuous flow. 0.5 g of each solid-supported catalyst, were blended together with 2.5 g washed sand and packed into 170 mm length, 4.5 mm diameter, empty HPLC columns, and placed into a temperature controlled electrical heating block. The column void space was determined to be 1.4 mL (ESI 8.0), and a combined flow rate of 0.036 mL/min substrate and base in IPA, gave a residence time (T_{res}) of 39 minutes. After reaching steady state, each sample was collected over 2 minutes and analysed for conversion of AP to 1-phenylethanol, along with its ee. Figure 3 shows the effect of KO^{t}Bu on catalyst performance over 48 hours.

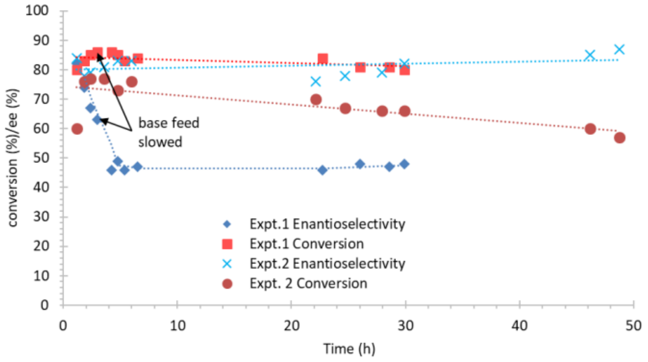

Figure 3. Experiments comparing the effect of base feed regime on conversion and ee. Expt.1 started at 5 mol% KO^{t}Bu and reduced after 3 h to 0.5 mol%. Expt.2 started at 5 mol% KO^{t}Bu and reduced at 0.9 h to 0.5 mol%. Dotted lines show the overall trend.

In experiment 1, it was found that a base feed concentration of 50 mM was too high (5 mol% of substrate, 100 mol% of catalyst), and the product ee fell rapidly from 82 to 47% (0.2%ee.min^{-1}) whilst the conversion remained constant at ~83%. When the base concentration was reduced at 3 h to 5 mM, the ee remained steady for a further 26 hours (40 reactor volumes (RV)). The fall in ee might be loss of ligand or its racemization, both of which have been observed in related studies.[14] In experiment 2, the base was used at 50mM for 0.9 h, then at a tenth of this thereafter. In this way, the selectivity was more consistent at ~85% ee for 48 hours however the conversion fell slowly from 77 to 60%. Purification of the feed materials had no effect on the loss of conversion, showing that residual impurities were unlikely to be the problem. The total amount of iridium collected in the eluent over 48 h continuous flow was measured by ICP-MS at 147 ppm (ESI 1), indicating that loss of activity is not caused by metal leaching.[9] Similarly, the leaching of ligand was investigated, however non was found in the eluent and including 0.5 mol% of CsDPEN into the feed only slightly improved the TTN.

The continuous flow reaction conditions were optimized using catalyst **4a**. It was found that both the reaction temperature and substrate concentration influenced the conversion and enantioselectivity, Figures 4a and 4b.

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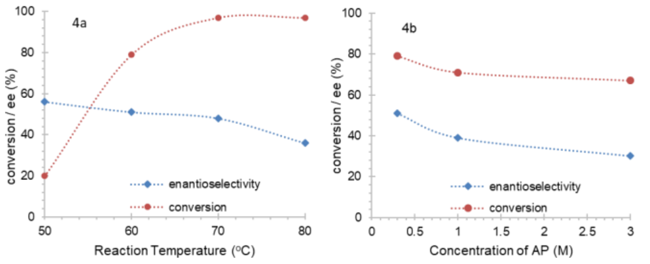


Figure 4. AP conversion and 1-phenethyl alcohol ee at steady-state continuous flow. a) The effect of temperature at 0.3 M AP, b) The effect of AP concentration at 60ºC.

A temperature of up to 80 ºC enhanced the reaction rate, giving up to 100% conversion during the 39 minutes residence time, however this was at the expense of enantioselectivity falling from 58% ee to 36% ee, Figure 4a. The intermediate temperature of 60 ºC was selected for future studies. To improve productivity, the effect of increasing the AP feed concentration was evaluated: 0.3 M AP gave 79% conv. and 51% ee, whilst 3 M AP gave 67% and 30% respectively, Figure 4b. By calculation, at a residence time of one hour the 3 M concentration would give 100% conv. giving a productivity of 1.65 moles/L/h, however, the lower ee favored the use of 0.3 M AP. The lower ee at higher concentrations, is due to the acetone by-product that accelerates the reverse dehydrogenation reaction (ESI Figure S3).

Using the optimized conditions, experiments were performed over 120 hours (185 RV) continuous flow using the C_5 tethered catalyst **4b** and either 5 mol% KO^{t}Bu, Figure 5a, or 300 mol% Et_3N, Figure 5b.

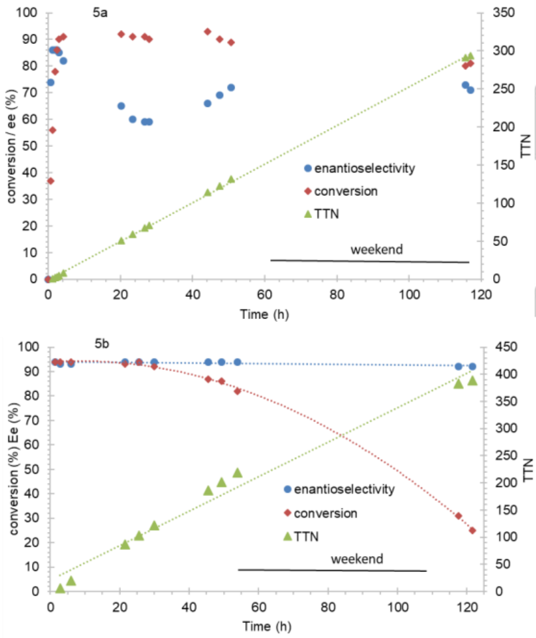


Figure 5. The conversion, ee and total turnover number (TTN) in continuous flow asymmetric reduction of AP (0.3 M) at 60ºC with catalyst **4b**. a) 5mM KO^{t}Bu. b) 300 mol% Et_3N. The dotted lines show the overall trends.

In the former, the ee varied between 82 and 59%, but the conversion fell only slightly from 92 to 80 over the 5 days operation. Using triethylamine, the ee remained consistently around 92% over the entire experiment, however the conversion fell increasingly from 95 to 25%. ICP-MS showed only 58 ppm iridium in the eluent. The TTN is 294 in the KO^{t}Bu system and 388 in the triethylamine system, both of which exceed the TON of 24 achieved with the homogenous catalyst in batch. The results also indicate that that the system could be operated for longer to give increased catalyst use, though there is clearly some fall-off in performance discussed below.

The length of the tether was shown to affect the catalyst lifetime and TOF. Figure 6 shows a comparison between the C_5 and C_{14} tethered catalysts.

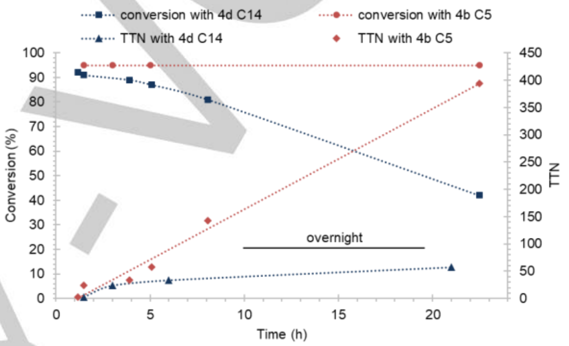
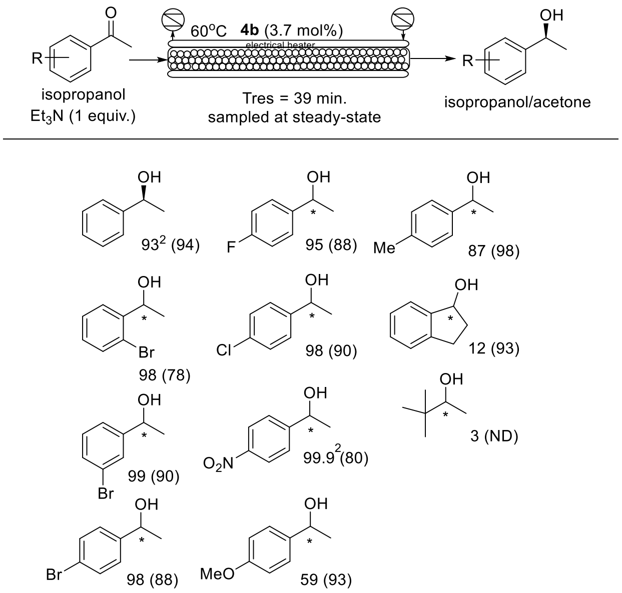


Figure 6. Comparison of catalysts **4b** (C_5) and **4d** (C_{14}) with different tether length. S/C(4b)/B(Et_3N)=100/33/300, S/C(4d)/B(Et_3N) = 100/13/300. The dotted lines show the overall trends.

At normalized iridium concentrations, the C_{14} catalyst **4d** lost activity more quickly in 24 hours than the C_5 catalyst **4b**. However the maximum TOF of **4d** was 8.9 h^{-1}, twice that of the homogenous catalysts or **4b** (4.4 h^{-1}), which implies a higher concentration in the catalytic cycle, but a higher deactivation rate. To investigate the scope of the continuous flow asymmetric transfer hydrogenation, a series of different substrates were tested, Figure 7. After reaching steady state, each sample was analysed by GC for conversion and ee. AP analogues with *ortho*-, *meta*- and *para*- electron-withdrawing substituents (-Br, -Cl, -F, -NO_2) gave good conversion (94-100%) and enantioselectivity (78-94% ee). Electron donating groups, -*p*OMe, -*p*Me, gave 59% and 87% conversion and 93 and 98% ee, respectively. Surprisingly, both 1-indanol and pinacol were obtained in only 12% (93% ee) and 3% conversion respectively, which is surprising given previous good results with these substrates with related homogenous catalysts.[15]

Conclusions

This study has shown that a continuous flow asymmetric transfer hydrogenation process, using IPA as the hydrogen donor and solvent, can been catalyzed efficiently by an immobilized chiral iridium Cp** complex of modular design. The process has



[1] Measured by GC against authentic standards (see ESI). [2] isolated yield after column purification. A mass balance of 7% acetophenone was also collected. [3] 0.05 mol/L solution was used because of low solubility in IPA.

Figure 7. Other ketones reduced by CATHy in continuous flow, to give chiral alcohols, showing steady-state conversions (%) (ee(%)).

been operated over 5 days with low levels of iridium (58-147 ppm) leaching over this period. Two asymmetric ligands and two tether lengths have been evaluated, with CsDPEN and the C_5 tether giving an average 94% ee and TTN of 388 over 120 hours, which is significantly better than the homogeneous catalyst TON of 24 used in batch. The type and concentration of base used in the reaction has been identified as an important condition. The correlation of activity with base pKa and strength is likely related to the concentration of the catalytically active 16-electron species. An initial stoichiometric quantity of KO^{t}Bu is sufficient to activate the catalyst, and a sub-stoichiometric feed neutralizes any residual acidity that would allow it to revert to the inactive 18-electron species, in this way high activities and ee's are maintained over days. On the other hand, an excess KO^{t}Bu is able to remove the ligand but retain a catalytically active species, causing the ee to fall not the conversion. The same solid-supported catalyst, lacking an asymmetric ligand was observed by x-ray synchrotron techniques to react with tert-butoxide.[14a] Triethylamine is unable to displace the ligand so the optical purities remain consistently high over a long time, however the conversion falls increasingly. This unusual behavior may be explained by physical effects such as entanglement of the tethers. Based on the loadings used, an estimate of site-isolation showed the catalysts are close enough to entangle, and it might be anticipated that the longer the tether the more readily this might happen. Indeed, the C_{14} is initially more active than the C_5 but loses activity more rapidly. Clearly more research is required to understand the cause of these observations, so it would be interesting to prepare supported catalysts with lower loadings to increase site-isolation and to compare their turnover. The use of formate hydrogen donor is being tested in continuous flow systems, with the additional problem of CO_2 (g) evolution.[15] The immobilized catalysts are also being used in amine racemization and alkylation reactions which will be reported elsewhere.

Experimental Section

Typical procedure of ATH in batch mode:

Homogenous catalyst. Under a nitrogen atmosphere, the Ir(Cp*C_5H_{10}OH){(*S,S*)-TsDPEN}Cl **3a** (16.0 mg, 0.02 mmol, 0.04 equiv.) and KO^{t}Bu (5.6 mg, 0.05 mmol, 0.10 equiv.) were added to 2-propanol (2.0 ml). AP (58 μl, 0.50 mmol, 1.0 equiv.) was added, followed by 2-propanol (0.50 ml). After stirring for 5 hours at 60ºC, the reaction mixture was sampled and analysed by GC for conversion and enantioselectivity.

Immobilized catalyst. Under a nitrogen atmosphere, the immobilized C_5 tethered/CsDPEN catalyst **4b** (41.7 mg, 9.2 μmol, 0.22 mmol/g, 0.037 equiv.) and Et_3N (35 μl, 0.25 mmol, 1.0 equiv.) were added to 2-propanol (1.0 ml). AP (29 μl, 0.25 mmol, 1.0 equiv.) was added, followed by 2-propanol (0.25 ml). After stirring for 24 hours at 60ºC, the reaction mixture was sampled and analysed by GC for conversion and enantioselectivity.

Typical procedure of ATH in flow mode:

Two pump system. The immobilized C_5 tethered/TsDPEN catalyst **4a** (500 mg, 0.35 mmol/g, 0.18 mmol) and sand (low iron, 2.50 g) were mixed by shaking and placed in the steel column (length: 170 mm, inner diameter: 4.5 mm, volume: 2.7 ml) with filter. Two HPLC pumps (JASCO, PU-980) were connected to the T-shape mixer and packed column with heating block. After being filled with isopropanol (each flow rate: 0.2 ml/min, 30 min), the heating block was maintained at 50 ºC. Feed A: AP (3.60 g, 30 mmol) was dissolved and make up to 100 ml by isopropanol at room temperature. Feed B: KO^{t}Bu (168 mg, 1.5 mmol) was dissolved and make up to 100 ml by isopropanol at room temperature. Each solution was fed into the packed column at each flow rate of 18 μl/min whilst maintaining the reaction temperature at 50ºC. For reaction monitoring, the reactor eluent was collected for 6 minutes each time and analysed by GC.

Single pump system. The immobilized C5 tethered/CsDPEN catalyst 4b (500 mg, 0.14 mmol/g, 0.07 mmol) and Sand (low iron, 2.50 g) were mixed by shaking and placed in the steel column (Length: 170 mm, Inner diameter: 4.5 mm, Volume: 2.7 ml) with filter. The HPLC pump (JASCO, PU-980) was connected to the packed column with heating block. After being filled with isopropanol (0.3 ml/min, 30 min), the heating block was maintained at 60ºC. AP (3.60 g, 30 mmol), Et_3N (9.11 g, 90 mmol) and (*S,S,S*)-CsDPEN (621 mg, 0.15 mmol) were dissolved at 30-40ºC in isopropanol and make up to 200 ml by isopropanol at room temperature. The prepared mixture was fed into the packed column at the flow rate of 36 μl/min whilst maintaining the reaction temperature at 60ºC. The reactor eluent was continuously collected in the flask at room temperature. Once the feed solution was nearly empty, the feed solution was prepared anew and was replaced with previous one. The reactor eluent was collected for 3 minutes each time and analysed by GC.

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Keywords: homogenous supported catalyst • immobilized iridium catalyst • continuous flow • asymmetric transfer hydrogenation • phenylethanol

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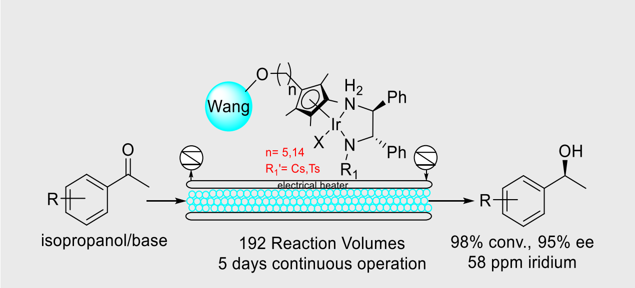

Continuous flow catalytic asymmetric transfer hydrogenation of ketones is reported using iridium complexes attached to Wang resin. The system gives higher TONs than homogenous batch, but lower TOFs. The base was found to affect the conversion and ee, and only low levels of iridium were found to leach. A range of aryl ketones were reduced in good ee and conversion.

Continuous Flow Asymmetric Transfer Hydrogenation

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