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Straightforward Preparation of Highly Enantioselective Anchored Chiral Homogeneous Catalysts

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Abstract:

A new method of anchoring homogeneous catalysts onto basic carbons is presented. The ease of the preparation is particularly remarkable, and the method proved to be suitable for scale-up. In the case of asymmetric heterogeneous catalysts for hydrogenation reactions, enantioselective improvement was observed in all cases where a comparison was made with the homogeneous species. Cationic rhodium catalysts are more suitable for this technology, but loading of other types of catalysts based on a variety of metals is also possible.

Introduction

There is a worldwide interest in developing new anchored homogeneous catalysts, and extensive efforts have been made to find original methods of preparation for such catalysts.[1] Anchored catalysts have advantages in that they avoid the need for costly separations required for homogeneous catalysts. In most supported catalysts reported so far, the catalyst has been grafted to the support via a tether.[2] Such methods present a synthetic challenge when tethering the ligand. In addition, for chiral catalysts enantioselectivity can be reduced/lost when tethered. Noncovalently bonded catalysts have been reported as well;[3−5] for example, homogeneous catalysts can be anchored using a polar counterion, which through strong H-bonding binds to mesoporous silica.[6,7] These forms of attachment of the catalyst are not robust, and the catalyst can be removed by an exchange reaction occurring under the catalytic reaction conditions. Another method of anchoring an asymmetric organometallic catalyst emerged with the commercialised CATAXA technology.[8] Here, chiral Rh(diphosphine) catalysts are attached to a heteropolyacid (HPA) modified support directly through the metal itself.[9,10] This method of attachment reduces the likelihood of metal leaching and avoids any chiral ligand modification at the same time.[11]

We describe here a straightforward procedure by which preformed homogeneous complexes are grafted onto carbon supports to give heterogeneous catalysts. We point out the simplicity of the method, since no modification of the support is required to anchor the organometallic complex. Indeed, the process corresponds to a simple sorption of the homogeneous catalysts from a slurry onto the carbon surface. The resulting catalysts show high activity in hydrogenation reactions with higher enantioselectivity than the equivalent homogeneous species in the reactions tested. No leaching is observed during catalytic testing.

Results and Discussion

Experimentation with Rh(diphosphine)-like species was chosen because they are known to be powerful catalysts for chiral hydrogenation reactions.[12] Typically, a preformed catalyst was prepared by reaction of 1 mol equiv of each of $[Rh(nbd)_2]^+BF_4^-$ and a bidentate chiral diphosphine in ethanol to give the complex $[Rh(nbd)(diphosphine)]^+BF_4^-$. Carbon was then added directly to the complex without previous purification. The mixture was allowed to stir overnight at room temperature, and the heterogeneous catalyst was filtered and thoroughly washed with alcohol to remove any excess or unattached homogeneous complex. This material was further dried in vacuo to give the desired heterogeneous catalyst.

Optimisation of the loading capacity was carried out by running a preparation with excess of the homogeneous complex $[Rh(nbd)(Skewphos)]^+BF_4^-$ with Acticarbone 2S. Excess catalyst was carefully removed, and the material metal content was analysed by ICP-MS analysis. Results showed a loading of 0.52% (w/w) Rh metal on the support, which correspond to 50 μmol of anchored homogeneous catalyst per gram of material. These data allowed us to optimise the preparation method to avoid extensive washing to remove excess homogeneous complex.

The binding efficiency can obviously change from one carbon support to another. Different types of carbon were thus tested, and the metal loadings obtained are shown in Table 1. The best results, with the same preparation method being used each time, were obtained with basic carbons,

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Table 1. **Rhodium contents of different types of carbon**

carbon	nature	rh content (%w/w)
ActicarboneL2S	acid	0.15
Acticarbone 2S	basic	0.52
CECA 2S	basic	0.36

Acticarbone 2S and CECA 2S. These results are understandable, as a basic carbon will have negatively charged donors on its surface to interact with the cationic species.

The method by which the metal is anchored to the support is still not fully understood; however, we can make comparisons with the CATAXA systems, in which the same cationic species are attached via a covalent Rh−O bond to HPA.[13−16] There have also been studies by Freire et al., who demonstrate similar M−O linking of Jacobsen catalyst on a carbon surface.[17] By comparison with this literature we can speculate that the Rh(diphosphine) complexes in our case are also attached via a Rh−O bond.

To investigate the asymmetric catalytic performance of the heterogenised catalysts, their efficiency in the hydrogenation of a prochiral C═C bond was studied with dimethyl itaconate (DMIT) substrate (Table 2).

The results show a marked increase in the enantiomeric excess once the catalyst is anchored onto the carbon support. The change in stereoselectivity emphasises the role played by supports in these systems during the chiral selection process.[18] Activity was in each case remarkable, being little different from the homogeneous reaction. The catalysts retained activity going from 500 TON to 1000 TON since total conversion was always reached within minutes. The reuse test of [Rh(nbd)(Skewphos)]/carbon showed the catalyst conserves its enantioselectivity and activity. This result demonstrates the stability toward reuse of the catalyst under these conditions. However, as is the case with most Rh-(diphosphine)-like catalysts, the supported complexes are sensitive to oxidation. Indeed, exposure of the heterogenised catalysts to air overnight led to fairly inactive species. The metal leaching study raises another important matter of heterogeneous catalysts. In our case, no leaching was discernible by ICP analysis, showing the homogeneous catalysts were strongly anchored to the support with this simple technology. Other prochiral substrates, like methyl acetamidoacrylate, were also tested in hydrogenation reactions. In this case [Rh(nbd)(Phanephos)]/Acticarbone 2S and [Rh(nbd)(Xylyl-phanephos)]/Acticarbone 2S were the best catalysts obtained, giving total conversion with 98% and 97% enantioselective excess, respectively, and no metal leaching (see Table 3).

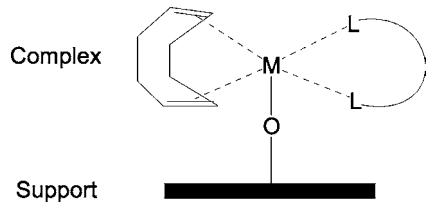

Figure 1. **Proposed structure of the homogeneous catalyst anchored onto carbon support.**

Attempts to scale-up this procedure to 5 g were studied with the Rh(Skewphos) catalysts and both Acticarbone 2S and CECA 2S. The method used for small batches was carefully followed for this scale-up, and particular care was taken in the washing of the material. Rhodium content of the final material was 0.38% (w/w) of Rh for both carbons. These results are comparable to the results obtained with small-scale materials (Table 2). Use of these catalysts in DMIT hydrogenation showed that activity and enantioselectivity were at least as good as those on the smaller scale. No metal leaching was observed showing the catalyst is still attached to the support during and after use.

To extend the potential of this technology to other catalytic reactions, complexes based on other metals have also been tested. Palladium complexes are of great commercial interest, since they are the catalysts of choice for C−C coupling reactions. Thus, $PdCl_2(PPh_3)_2$ was a suitable complex with which to start. Rather low loading was achieved in toluene at room temperature (0.12 wt % Pd on the solid). When tested in a Suzuki reaction using bromoanisole and benzeneboronic acid, the catalyst proved to be active (65% conversion in 2 h reaction time) accompanied with very encouraging low Pd leaching (2 ppm Pd). This means that homogeneous catalysts other than cationic species can be used in this technology, but cationic species are probably more suitable. The catalyst was also tested in a Heck reaction involving the commonly used substrates, 4-bromoacetophenone and butyl acrylate. Despite good activity with a nearly total conversion in a 2 h reaction time, strong Pd leaching was observed (leaching: 13 ppm Pd). This was probably due to the reaction conditions, in particular the solvent dimethylacetamide and base NaOAc.

Wilkinson's catalyst, which is also not a cationic complex, was also successfully anchored onto Acticarbone 2S. The loading (0.33% of Rh per gram of material) was achieved in toluene while stirring overnight at 55 °C in the presence of triphenylphosphine (added to stabilize $RhCl(PPh_3)_3$ during the adsorption process). The washed final catalyst was tested in 1-hexene hydrogenation and showed good activity (in comparison with homogeneous catalyst) with 72% of hexane produced in a 2 h reaction time and 28% of 2-hexene due to isomerisation side reaction. Encouragingly, no leaching was observed (less than 0.5 ppm of Rh leaching was detected).

Experimental

S-Bophoz ligand was generously supplied by Eastman. (*S*)-(+)-4,12-Bis(diphenylphosphino)[2.2]paracylophane (S-Phanephos) was purchased from Strem, and Xylyl-Phanephos

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Table 2. **DMIT hydrogenation results with [Rh(nbd)(diphosphine)]/carbon catalysts**

catalyst	turnover number	conversion (%)	ee (%) (homogeneous)	Rh leaching (ppm)
[Rh(nbd)(dppb)]/Acticarbone-2S	500	100	not applicable	<0.5
[Rh(nbd)(dppb)]/Acticarbone 2S	1000	100	not applicable	<0.5
[Rh(nbd)(S−Bophoz)]/Acticarbone 2S	500	100	89 (82)	<1
[Rh(nbd)(S−Bophoz)]/Acticarbone 2S	1000	100	91 (82)	<1
[Rh(nbd)(Skewphos)]/Acticarbone 2S	500	100	78 (70)	<0.5
[Rh(nbd)(Skewphos)]/Acticarbone 2S	1000	100	78 (70)	<0.5
[Rh(nbd)(Skewphos)]/Acticarbon 2S recycled twice	1500	98	77	<0.5
[Rh(nbd)(Skewphos)]/Acticarbone 2S (5 g batch)	500	100	78	<0.5
[Rh(nbd)(Skewphos)]/CECA 2S (5 g batch)	500	100	79	<0.5

Table 3. **Methyl acetamidoacrylate hydrogenation results with [Rh(nbd)(diphosphine)]/carbon catalysts**

catalyst	conversion (%)	ee (%)	Rh leaching (ppm)
[Rh(nbd)(Phanephos)]/Acticarbone 2S	100	98	<0.5
[Rh(nbd)(Xylyl-Phanephos)]/Acticarbone 2S	100	97	<0.5
[Rh(nbd)(Xylyl-Phanephos)]/Acticarbone 2S	100	97	<0.5

was supplied by Johnson Matthey (Chiral Technologies, Cambridge). (2*S*,4*S*)-(−)-2,4-Bis(diphenylphosphino)pentane (S,S-Skewphos) was purchased from Strem. All ligands were used without further purification. $[RhCl(PPh_3)_3]$, $[Rh(nbd)_2]^+BF_4^-$, and $PdCl_2(PPh_3)_2$ were purchased from Johnson Matthey and used as received. Solvents were anhydrous grade in Sure Seal bottles and were purchased from Aldrich. They were used without further purification, apart from dimethylacetamide 99.5% that was purchased from VWR and was degassed with argon before use. Acticarbone 2S and L2S were supplied by Atofina, and carbon CECA 2S was supplied by Elf-Atochem. *N*-butylacrylate, bromoacetophenone, bromoanisole, benzene boronic acid, methyl-2-acetamidoacrylate, and 1-hexene were purchased from Aldrich. They were all used as received apart from 1-hexene, which was distilled under argon. Dimethyl itaconate (DMIT) was purchased from Fluka and was distilled before use. K_2CO_3 anhydrous and NaOAc anhydrous were purchased from VWR. Hydrogen Premier grade was purchased from Air Product. Gas chromatography was performed with an AutoSystem XL Arnel apparatus from Perkin-Elmer. HPLC was performed with an Agilent 1100 Series chromatograph. Metal contents of heterogeneous catalysts were analysed by ICP-ES spectroscopy with an Optima 3300RL apparatus from Perkin-Elmer. Metal contents of organic liquids were studied with Poliscan 61E from Thermo Jarrell Ash.

All experiments were run under inert atmosphere using Schlenk techniques or a glovebox.

General Procedure for the Preparation of the [Rh(nbd)(diphosphine)]/Carbon. A solution of $[Rh(nbd)_2]^+BF_4^-$ (8.8 mg, 2.35×10^{-5} mol) and diphosphine ligand (2.35×10^{-5} mol) in methanol was stirred for 2 h under inert atmosphere. After this time, carbon (0.5 g) was added and the mixture was stirred overnight under inert atmosphere. The solid was filtered and washed with methanol (3×10 mL). It was dried for 5 min on the filter and 30 min in vacuo.

Preparation Method for the Anchored $PdCl_2(PPh_3)_2$ on Acticarbone 2S. A mixture of $PdCl_2(PPh_3)_2$ (16.5 mg, 2.35×10^{-5} mol) and Acticarbone 2S (0.5 g) in toluene (15 mL) was allowed to stir for 2 h under inert atmosphere. The mixture was filtered, and the solid was washed with toluene (4×10 mL). It was then dried for 5 min on the filter and 30 min in vacuo.

Preparation Method for the Anchored $RhCl(PPh_3)_3$ on Acticarbone 2S. A solution of Wilkinson's catalyst (21.8 mg, 2.35×10^{-5} mol) and triphenylphosphine (2.1 mg, 7.86×10^{-6} mol) in toluene (10 mL) was allowed to stir for 30 min under inert atmosphere. The solution was added dropwise to a slurry of Acticarbone 2S (0.5 g) in toluene. The mixture was allowed to stir overnight at 55 °C under inert atmosphere. It was filtered, and the solid was washed with toluene (2×10 mL). It was then dried on the filter and for 30 min in vacuo.

Procedure for the Hydrogenation of DMIT. [Rh(nbd)(diphosphine)]/carbon (weight corresponding to 7.08×10^{-6} mol of Rh) and DMIT (0.559 g, 3.54×10^{-3} mol for 500 TON or 1.118 g, 7.08×10^{-3} mol for 1000 TON) were suspended in methanol (15 mL) under inert atmosphere in a glass reactor equipped with an overhead magnetic stirring bar. The reactor was connected to the hydrogenation apparatus, and the system was evacuated and refilled with argon and then hydrogen several times. The reaction pressure was reset to 3.5 bar, and stirring (600 rpm) begun along with the collection of reaction data. Hydrogen uptake was monitored by computer until no more reaction was observed. On completion, the stirring was stopped and the reactor was depressurised. The mixture was filtered, and the filtrate was collected for HPLC analysis in order to determine conversion and enantiomeric excess. For reuse tests, further DMIT (0.559 g, 3.54×10^{-3} mol) in methanol (5 mL) was added to the reactor by syringe through a septum after the reaction was finished. The mixture was purged with hydrogen before the reactor being charged at 3.5 bar and the reaction run again.

HPLC Conditions Used for Analysis of the Products: Samples were prepared by dilution of 100 μL with 900 μL

of a mixture hexane/2-propanol 92/8. CHIRACEL-OD-H 0.46 cm × 25 cm column (Daicel Chemical Industries Ltd), 5.0 μL sample injection, hexane/2-propanol 92/8 eluent, 1 mL/min flow, 15 min stop time, 25 °C temperature set, UV−vis detection at 220 nm.

Procedure for the Hydrogenation of Methyl-2-acetamidoacrylate. [Rh(nbd)(diphosphine)]/carbon (weight corresponding to 7.08×10^{-6} mol of Rh) and methyl-2-acetamidoacrylate (0.101 g, 7.08×10^{-4} mol) were suspended in methanol (15 mL) under inert atmosphere in a glass reactor equipped with an overhead stirring bar. The reactor was connected to the hydrogenation apparatus, and the system was evacuated and refilled with argon and then hydrogen several times. The reaction pressure was reset to 4 bar, and stirring (600 rpm) begun along with the collection of reaction data. Hydrogen uptake was monitored by computer until no more reaction was observed. On completion, the stirring was stopped, and the reactor was depressurised. The mixture was filtered, and the filtrate was collected for GC analysis in order to determine conversion and enantiomeric excess.

GC Conditions Used for Analysis of the Products: 1.0 μL sample injection, 25 m × 0.25 mm Chirasil Dex CB (Chrompack), injection port 200 °C, initial temperature 130 °C, hold 6 min, ramp at 15 °C/min to 190 °C, hold 0 min, detector 200 °C, head pressure 20 psig, split ratio 34/1.

Procedure for the Hydrogenation of 1-Hexene. $RhCl(PPh_3)_3$/carbon (weight corresponding to 7.08×10^{-6} mol of Rh) was suspended in a mixture of toluene/ethanol 5/95 (10 mL total volume) under inert atmosphere in a glass reactor equipped with a overhead stirring bar. The reactor was connected to the hydrogenation apparatus. The system was purged with argon and with hydrogen several times before being charged with hydrogen (3.5 bar) for a 2 h prehydrogenation at a 600 rpm stirring speed. Then, 1-hexene (0.290 g, 3.54×10^{-3} mol) in a mixture of toluene/ethanol 5/95 (10 mL total volume) was injected. The mixture was purged with hydrogen before being charged with hydrogen to 3.5 bar. It was allowed to stir at 600 rpm at 40 °C, and the hydrogen consumption was monitored. After completion of the reaction, it was stopped, the mixture was filtered, and the filtrate was analysed by GC to determine conversion.

GC Conditions Used for Analysis of the Products: 1.0 μL sample injection, 30 m × 0.32 mm RTX5 and DF 1.0 μm (Restek Corporation), injection port 200 °C, isothermal 40 °C, hold 10 min, detector 270 °C, head pressure 9 psig, split ratio 20/1.

Procedure for the Suzuki Reaction. To $PdCl_2(PPh_3)_2$/Acticarbone 2S (weight corresponding to 1.19×10^{-6} mol of Pd) in toluene (10 mL) were added bromoanisole (0.125 mL, 1×10^{-3} mol), $PhB(OH)_2$ (0.146 g, 1.2×10^{-3} mol), K_2CO_3 (0.276 g, 2×10^{-3} mol), and mesitylene (0.139 mL, 1×10^{-3} mol), as a reference, under inert atmosphere. The mixture was allowed to stir at 100 °C for 2 h. The mixture was filtered, and the filtrate was analysed by GC to determine conversion.

GC Conditions Used for Analysis of the Products: 1.0 μL sample injection, 10 m × 0.53 mm and DF 5.0 μm CP-SIL5 (Chrompack), injection port 320 °C, initial temperature 130 °C, hold 2 min, ramp at 30 °C/min to 300 °C, hold 20 min, detector 320 °C, head pressure 2.0 psig, split ratio 25/1.

Procedure for the Heck Reaction. To $PdCl_2(PPh_3)_2$/Acticarbone 2S (weight corresponding to 1.19×10^{-6} mol of Pd) in dimethylacetamide (10 mL) were added bromoacetophenone (0.199 mL, 1×10^{-3} mol), *n*-butylacrylate (0.200 mL, 1.4×10^{-3} mol), sodium acetate (0.115 g, 1.4×10^{-3} mol), and mesitylene (0.139 mL, 1×10^{-3} mol), as a reference, under inert atmosphere. The mixture was allowed to stir at 100 °C for 2 h. The mixture was filtered, and the filtrate was analysed by GC to determine conversion.

GC Conditions Used for Analysis of the Products: 1.0 μL sample injection, 10 m × 0.53 mm and DF 5.0 μm CP-SIL5 (Chrompack), injection port 320 °C, initial temperature 130 °C, hold 2 min, ramp at 30 °C/min to 300 °C, hold 20 min, detector 320 °C, head pressure 2.0 psig, split ratio 25/1.

Conclusion

We have developed a technique for anchoring homogeneous catalysts onto carbons. This technology is remarkable for the ease of the preparation method and for the high activity and enantioselectivity of the heterogeneous catalysts obtained. Indeed, improved enantioselectivity was observed in all cases where a comparison was made with the homogeneous counterpart. Further work will involve catalytic experiments at higher turnover numbers and the application of this technology to complexes other than those of Rh and Pd.

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