ChemComm

A one-step, enantioselective reduction of ethyl nicotinate to ethyl nipecotinate using a constrained, chiral, heterogeneous catalyst†

Stuart A. Raynor,[ab] John Meurig Thomas,*[a] Robert Raja,[ab] Brian F. G. Johnson,*[b] Robert G. Bell[b] and Mike D. Mantle[c]

[a] *Davy-Faraday Research Laboratory, The Royal Institution of Great Britain, 21 Albemarle Street, London, UK W1X 4BS. E-mail: jmt@ri.ac.uk*
[b] *University of Cambridge, Department of Chemistry, Lensfield Road, Cambridge, UK CB2 1EW*
[c] *Department of Chemical Engineering, The University of Cambridge, New Museum Site, Cambridge, UK CB2 3QZ*

Received (in Liverpool, UK) 12th July 2000, Accepted 29th August 2000
First published as an Advance Article on the web

A chiral catalyst derived from 1,1′-bis(diphenylphosphino)-ferrocene and anchored within MCM-41 displays remarkable increases in both enantioselectivity and activity, in the hydrogenation of ethyl nicotinate to ethyl nipecotinate, when compared to an analogous homogeneous model compound.

It is acknowledged that, in view of their biological activity, the enantioselective synthesis of chiral saturated ring systems involving piperidine or cyclohexane is of considerable practical interest. Previously, efforts to hydrogenate enantioselectively an aromatic ring such as that in ethyl nicotinate (Scheme 1) have resulted in values of enantiomeric excess (ee) that are less than 6%.[1] However, very recently, a two-step process, involving initial hydrogenation in high yield to the comparatively stable 1,4,5,6-tetrahydronicotinate, followed by subsequent hydrogenation in the presence of a dihydrocinchonidine modified noble metal catalyst, yielded a quite high ee of the nipecotinate. The best activity reported by Blazer *et al.* [using a Pd on carbon (plus cinchonidine) catalyst for step (ii)] was 19% ee at 12% conversion.[2] Using the principle, first conceived five years ago,[3] of chirally constraining a designed active centre attached to a chiral ligand and tethered to the inner walls of mesoporous silica, as schematized in Fig. 1, we have produced an effective enantioselective catalyst for the direct hydrogenation of ethyl nicotinate to ethyl nipecotinate, with an ee of 17% and conversions in excess of 50%.

We have previously demonstrated that in the allylic amination of cinnamyl acetate, the enantiomeric excess achieved by the spatially confined (tethered) catalyst, which is derived from 1,1′-bis(diphenylphosphino)ferrocene (dppf), far exceeds that attained with the same active site when it is unconfined.[4] Mesoporous silica of the M41S type (used earlier as the support for several high performance catalysts[5]) was used to confine the designed catalyst, thereby creating the chiral space. The confinement is a crucial feature of the enantioselectivity of our catalyst. When an alkyl silsesquioxane with the same tethered, designed catalyst is subjected to identical conditions, degrees of conversion are appreciably lower and the catalyst exhibits no enantiodiscrimination.

Our approach in the synthesis of the heterogeneous catalyst was to design a homogeneous, metal-containing ferrocenyl precursor which possessed a functionality capable of reacting directly with a silica surface. This precursor could be characterized in detail using solution spectroscopic techniques, and then anchored to the surface of the mesoporous silica support in a one-step reaction. The synthetic strategy involved the reaction between (*S*)-1-[(*R*)-1,2′-bis(diphenylphosphino)ferrocenyl]-ethyl acetate[6,7] and 3-(methylamino)propyltrimethoxysilane to form a silane functionalised ferrocenyl ligand (**1**), the incorporation of palladium dichloride to which forms the target ferrocenyl precursor (**2**) (Scheme 2). The ferrocenyl precursor **2** was then reacted with the mesoporous silane MCM-41, the outer walls of which were previously deactivated *via* treatment with [Ph_2SiCl_2], a method which we have already shown to be applicable in this situation.[8]

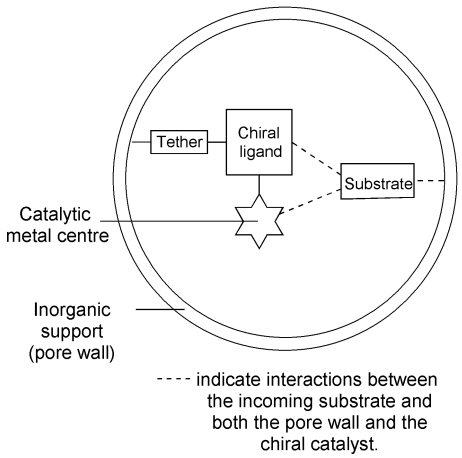
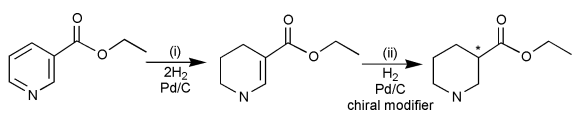
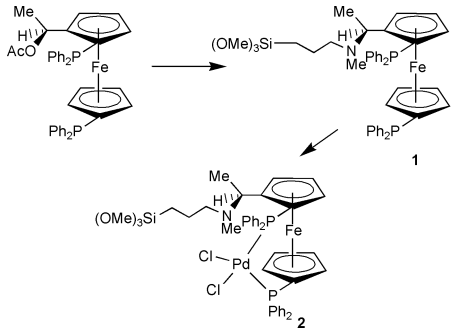


Fig. 1 Schematic diagram of the chiral catalyst constrained within a mesopore.

The anchored catalyst was characterised using ^{13}C and ^{31}P MAS NMR spectroscopy (ESI†). The ^{13}C spectrum was fully assignable when compared to that of (*S*)-1-[(*R*)-1,2′-bis(diphenylphosphino)ferrocenyl]ethylallylamine palladium dichlor-



Scheme 1 The two-step hydrogenation of ethyl nicotinate to ethyl nipecotinate *via* 1,4,5,6-tetrahydronicotinate.



Scheme 2 The synthesis of the ferrocenyl precursor **2** from a chiral ferrocenyl acetate, *via* the silane functionalised ferrocenyl ligand **1**.

† Electronic supplementary information (ESI) available: ^{1}H, ^{13}C and ^{31}P NMR spectroscopic data for the ferrocenyl precursor **2**, the anchored heterogeneous catalyst and the silsesquioxane-bound homogeneous catalyst. See http://www.rsc.org/suppdata/cc/b0/b005689h/

This journal is © The Royal Society of Chemistry 2000

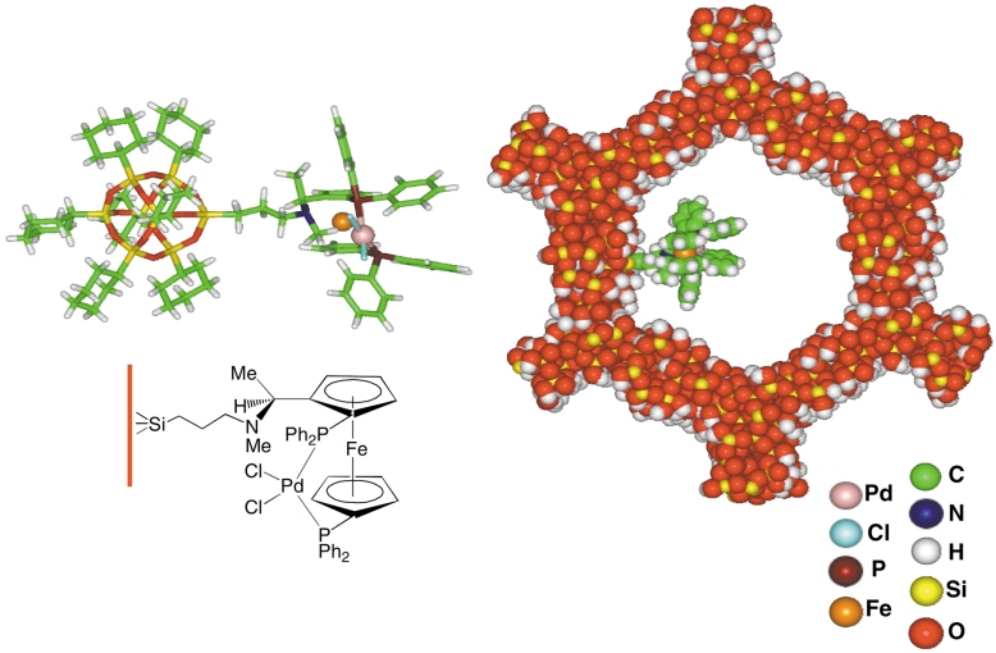


Fig. 2 Depiction of the catalytically active centre attached to a soluble silsesquioxane moiety and bound in a constrained manner inside mesoporous silica.

ide.[9] The spectrum showed two broad peaks centred at δ 135 and 75 which may be attributed to the phenyl and cyclopentadienyl rings, respectively. There is a peak at δ 12 which may be assigned to the methyl group bound to the chiral carbon and the carbon bound to the silicon. The central carbon in the propyl tether may be assigned to the peak at δ 22, whilst the final carbon of the tether, that bound to the nitrogen, can be attributed to the peak at δ 52. The final peaks in the spectrum are at δ 41 and 58 and may be assigned to the methyl group of the amine and the chiral carbon, respectively. The ^{31}P MAS NMR spectrum revealed a broad, split signal centred around δ 30, which is comparable to that observed with the ferrocenyl precursor **2**.

The ferrocenyl precursor **2** was also reacted with an incompletely condensed silsesquioxane cube,[10] to form a homogeneous model of the anchored heterogeneous catalyst. Solution ^{1}H NMR spectroscopy in C_4D_8O was used to characterise the model compound (ESI†), and the absence of the peaks for the hydroxy protons of the box at δ 6.97 and the methoxy protons of **2** at δ 3.47, are diagnostic in this regard. The MCM-41 bound catalyst and the silsesquioxane catalyst are illustrated in Fig 2.

The two catalysts were tested in the one-step hydrogenation of ethyl nicotinate to ethyl nipecotinate.‡ The catalysis was performed under mild conditions (20 bar H_2, 40 °C) and in both cases proceeded with the formation of the desired nipecotinate. However, analysis of the products revealed that the MCM-41 anchored species catalysed the reaction with a 17% ee whilst the use of the homogeneous silsesquioxane complex resulted in a racemic product. This remarkable change in stereoselectivity demonstrates the profound importance of confinement in the catalysis. The free catalyst shows no enantioselectivity whilst chiral confinement results in a catalyst that shows greater selectivity by almost a *threefold* margin than any other reported.[1] The confined catalyst also displayed a higher degree of activity (TON = 291) compared to the homogeneous form (TON = 98), after a reaction time of 72 h, and is remarkably stable. The reaction mixture of the anchored catalyst contained less than 3 ppb of metal (by ICP analysis), thereby ruling out the possibility of any leaching.

These results show the considerable potential that this type of catalyst offers, and how, by careful design of an active centre, a heterogeneous catalyst may be engineered, the performance of which is far superior than its free, homogeneous analogue.

We thank EPSRC for a rolling grant to J. M. T. and an award to B. F. G. J. We also wish to thank ICI for a case studentship to S. A. R. M.S.I. Inc. is gratefully acknowledged for the molecular modelling software. We are also grateful for assistance from Professor L. F. Gladden.

Notes and references

‡ The catalytic testing was performed in a high-pressure stainless steel reactor (Cambridge Reactor Design) lined with PEEK (polyether ether ketone). The catalyst (250 mg MCM-anchored, 100 mg box) was added to 5 g of ethyl nicotinate in 100 ml solvent (90 ml THF, 10 ml methanol). The vessel was pressurised to 20 bar with hydrogen and heated to 40 °C, whilst stirring was maintained at 400 rpm. During the reaction small aliquots were removed, using a mini-robot autosampler, to enable the kinetics to be studied. The products of the reaction were analysed by gas chromatograpy (GC, Varian, Model 3400 CX) employing a BPX5 capillary column (25 m × 0.32 mm) and flame ionisation detector. The ee was determined on the same machine *via* the conversion of the nipecotinate to a diastereomeric amide using (*R*)-(−)-Mosher's acid chloride.[2]

1 (*a*) R. M. Laine, G. Hum, B. J. Wood and M. Dawson, *Stud. Surf. Sci. Catal.*, 1981, **7**, 1478; (*b*) K. Nasar, F. Fache, M. Lemaire, J.-C. Beziat, M. Besson and P. Gallezot, *J. Mol. Catal.*, 1994, **87**, 107; (*c*) C. Exl, E. Ferstl, H. Honig and R. Rogi-Kohlenprath, *Chirality*, 1995, **7**, 211.
2 H.-U. Blazer, H. Honig, M. Studer and C. Wedemeyer-Exl, *J. Mol. Catal. A: Chem.*, 1999, **139**, 253.
3 (*a*) T. Maschmeyer, Unpublished Presentation at the Annual Progress Meeting of the Davy-Faraday Research Laboratories, 17 March 1995; (*b*) J. M. Thomas, *Philos. Trans. R. Soc. London, Ser. A*, 1990, **333**, 173; (*c*) J. M. Thomas, T. Maschmeyer, B. F. G. Johnson and D. S. Shephard, *J. Mol. Catal.*, 1999, **141**, 139.
4 B. F. G. Johnson, S. A. Raynor, D. S. Shephard, T. Mashmeyer, J. M. Thomas, G. Sankar, S. Bromley, R. Oldroyd, L. Gladden and M. D. Mantle, *Chem. Commun.*, 1999, 1167.
5 (*a*) T. Maschmeyer, F. Rey, G. Sankar and J. M. Thomas, *Nature*, 1995, **378**, 159; (*b*) R. D. Oldroyd, J. M. Thomas and G. Sankar, *Chem. Commun.*, 1997, 2025.
6 G. W. Gokel and I. K. Ugi, *J. Chem. Educ.*, 1972, **49**, 294.
7 T. Hayashi, T. Mise, M. Fukushima, M. Kagotani, N. Nagashima, Y. Hamada, A. Matsumoto, S. Kawakami, M. Konishi, K. Yamamoto and M. Kumada, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 1138.
8 D. S. Shephard, W. Z. Zhou, T. Mashmeyer, J. M. Matters, C. L. Roper, S. Parsons, B. F. G. Johnson and M. Duer, *Angew. Chem., Int. Ed.*, 1998, **37**, 2719.
9 S. A. Raynor, R. Raja, J. M. Thomas, B. F. G. Johnson and M. D. Mantle, manuscript in preparation.
10 F. J. Feher, D. A. Newman and J. F. Walzer, *J. Am. Chem. Soc.*, 1989, **111**, 1741.