

Hydrogenation of α -acetamidocinnamic acid with polystyrene-supported rhodium catalysts

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Abstract

Divinylbenzene cross-linked chloromethylated polystyrene has been functionalised with cinchonine, ephedrine, 3*S*,4*S*-*N*-benzylpyrrolidinediol and four achiral amines. The resins have been used as supports for anchoring $[\text{Rh}(\text{CO})_2\text{Cl}_2]^-$. The polymer-supported complex has been tested as a catalyst precursor for the hydrogenation of α -acetamidocinnamic acid. Highest rate and modest enantioselectivity are obtained with cinchonine functionalized polymer-supported complex. This complex also undergoes reversible decarbonylation.

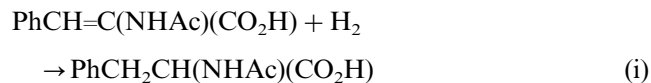
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1. Introduction

Asymmetric hydrogenation reactions with homogeneous catalysts play increasingly important roles in chemical and pharmaceutical industries [1–3]. The development of heterogeneous catalysts for such reactions is of importance since this would allow easy separation and recycling of the catalyst [4]. Several years ago we had shown that anionic metal carbonyl clusters anchored onto commercial anion exchangers can be decarbonylated to give novel hydrogenation catalysts [5]. Subsequently, we extended this approach towards a general synthetic method for asymmetric heterogeneous hydrogenation catalysts. The method consists of ion pairing chiral quaternary ammonium groups with anionic metal complexes on cross-linked polystyrene [6]. Recently, we have reported the mechanism of enantioselective hydrogenation of methylpyruvate to methyl lactate by a chiral catalyst designed this way [7].

Development of enantioselective heterogeneous hydrogenation catalysts for the enantioselective syntheses of amino acids is an important research target [8]. While for reaction (i) remarkable success has been

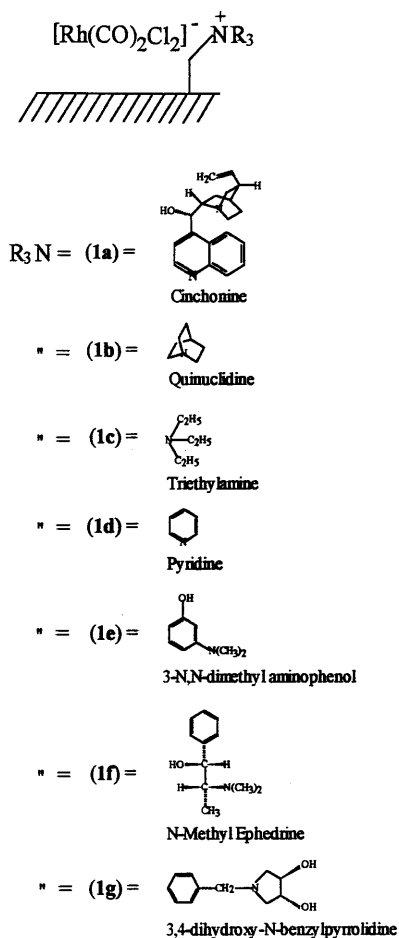
achieved with a variety of homogeneous catalysts, the number of effective *heterogeneous catalysts with easily synthesized chiral environment* remains scarce [8,9]. The work reported here had two objectives. First, to screen a number of anionic carbonyl complexes ion paired with cinchonium cation as potential pre-catalysts for reaction (i). The successful use of cinchona alkaloids as chiral auxiliaries in the asymmetric homogeneous dehydroxylation and the heterogeneous Orito reaction is well documented [1,7,10]. Second, to see if the ligand environment has an observable effect on the rates of the reaction and highest rate is also associated with the ligand that gives best enantioselectivity. This is important since such a phenomenon has been observed for the cinchona modified platinum catalyst in the Orito reaction [7,10].



2. Results and discussion

A large number of metal carbonyl anions, have been anchored onto cinchonine functionalized 20% divinylbenzene (DVB) cross-linked polystyrene. After thermal

decarbonylation the polymer-supported complexes have been tested as potential catalysts for reaction (i). The precursor complexes found to be unsatisfactory in terms of catalytic activity (turnover ≤ 10) and not investigated any further are $[\text{Co}(\text{CO})_4]^-$, $[\text{RhCl}_6]^{3-}$, $[\text{HFe}_3(\text{CO})_{11}]^-$, $[\text{HRu}_3(\text{CO})_{11}]^-$, $[\text{H}_3\text{Ru}_4(\text{CO})_{12}]^-$ and $[\text{Ru}_6(\text{CO})_{18}]^{2-}$ and $[\text{Pt}_{15}(\text{CO})_{30}]^{2-}$. In contrast the catalyst derived from two rhodium complexes, $[\text{Rh}(\text{CO})_2\text{Cl}_2]^-$ (**1**) and $[\text{Rh}_{12}(\text{CO})_{30}]^{2-}$ (**2**) show reasonable activity and enantioselectivity (~ 80 turnovers in 24 h and 20% ee). This unique activity of rhodium is not surprising in view of the fact that for the enantioselective hydrogenation of dehydroamino acids, most of the active homogeneous catalysts are rhodium phosphine complexes. With catalysts derived from **1** and **2** quantitative rhodium analysis before and after a catalytic run did not show any observable rhodium loss. In other words rhodium leaching into the solution during a catalytic run does not take place.



(1) = Free $[\text{Rh}(\text{CO})_2\text{Cl}_2]^- \text{H}^+$, (2a) = $[\text{Rh}_{12}(\text{CO})_{30}]^{2-}$ with cinchonine on polymer

////// Represents 20% divinyl benzene cross-linked polystyrene

Scheme 1.

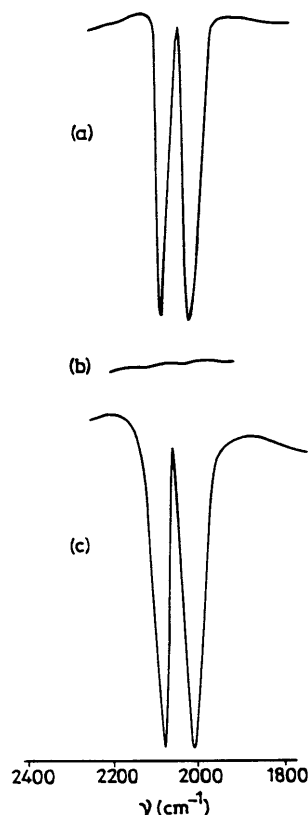


Fig. 1. IR spectra (KBr disc): (a) freshly prepared, (b) after a catalytic run and (c) after recarbonylation (500 psi of CO) of the used catalyst for the catalyst **1a**.

Although both **1** and **2** can be supported on the polymer, the material derived from the cluster has an IR spectrum different from that of the free cluster. In other words on polymer anchoring the cluster undergoes a change in its molecular structure. Similar observation on the interaction of **2** with a commercial anion exchanger (IRA 401) was reported by one of us [5]. Consequently, apart from initial screening of its catalytic activity, the cluster-supported material has not been studied any further.

Precatalyst **1a** is made by exchanging Cl^- ions of the cinchonine functionalized chloromethylated polystyrene with the H^+ salt of **1** in methanol (see Scheme 1 and Section 4). As shown in Fig. 1, in the inorganic carbonyl region the IR spectra of the polymer-supported material, and free **1** isolated as the CH^+ (C = cinchonine) salt are identical. The solution $^1\text{H-NMR}$ spectra of the CH^+ salt of **1** and CH^+Cl^- are also identical. None of the NMR signals show any significant shift indicating the absence of interaction between rhodium and the nitrogen of the aromatic ring. The comparative IR data of **1a** and the CH^+ salt of **1**, as well as the solution NMR data of the latter suggest the formulation of **1a** as shown in Scheme 1.

The effect of the ligand environment on catalytic activity has been studied to optimize conversion and

selectivity. This was done also to find out if there was any evidence of rate acceleration for a particular ligand environment. Variation in the ligand environment was achieved by anchoring the carbonyl anion **1** on anion exchangers with different quaternary ammonium groups. The designations of various catalysts are given in Scheme 1. In homogeneous catalysis, rate acceleration due to a specific ligand and/or a specific metal to ligand stoichiometry, is called *ligand accelerated catalysis* (LAC). In fact, LAC is the basis of most of the

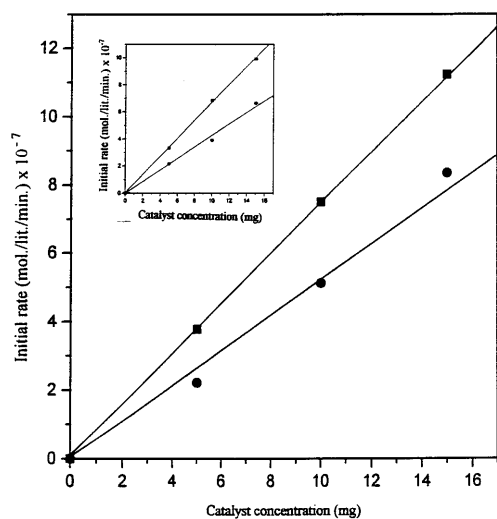


Fig. 2. Rate plot (% conversion after 360 min) for the hydrogenation of α -acetamidocinnamic acid with thermally activated catalyst **1a** (■) and **1c** (●) against catalyst concentration (mg). Inset: shows the same rate plot at 720 min.

Table 1
Observed rate constants (k_{obs}) and enantioselectivity for compounds **1**, **1a-g** and **2a**^a

Catalysts	$k'_{\text{obs}} (\times 10^{-3})$	$k''_{\text{obs}} (\times 10^{-3})$	Enantioselectivity (% ee)
1a	77 ^{b,c}	75	20
1b	59	52	0
1c	53	46	0
1d	62	62	0
1e	60	45	0
1f	62	59	5
1g	65	61	14
1 ^d	0	0	0
2a	75	73	18

^a All catalysts have divinylbenzene cross-linked (20%) polystyrene as the support. Metal content is $\leq 10\%$, 500 psi H_2 , amount of catalyst 15 mg (≤ 1.5 mg metal).

^b The first number is k_{obs} (min^{-1}) and the second number is the ee (%), estimated on the basis of optical rotation measurements. Barring cinchonine all the other amines had optical rotation values of approximately zero.

^c Reactions carried out at 60°C, 410 mg α -acetamidocinnamic acid. Initial rate measured on the basis of conversion after 360 min.

^d Reactions carried out with **1** as a homogeneous catalyst in the absence of any polymeric support. No activity is observed.

successful asymmetric homogeneous catalytic system [11]. A recent review highlights the importance of rate acceleration in some heterogeneous catalytic reactions as well [12]. In conventional heterogeneous catalysts for any kinetic analyses a distinction has to be made between active sites, and other surface assemblies which may not be active or less active. In contrast, our molecular approach ensures that at a first approximation all the metal centers are in a uniform ligand environment. Thus it allows a systematic variation of the ligand environment and the study of the effect of such a variation on the rate and selectivity.

The initial rates of reaction (i) with the catalysts **1a-g** have been measured under pseudo first order conditions with respect to the concentrations of the substrates and dihydrogen. A recent literature report shows that in the hydrogenation of pyruvate esters catalyzed by cinchona modified conventional platinum catalyst, initial rate measurement carried out at two different time intervals adds to the accuracy of the results [13]. Accordingly initial rates have been measured with three different catalyst concentrations and at more than two time intervals. As shown in Fig. 2, good linearity is obtained in the plots of initial rates against catalyst concentrations. Slopes of these straight lines, i.e. the observed rate constants (k_{obs}), are given in Table 1. The observed rate constants cover a relatively narrow range. In homogeneous systems examples of LAC, resulting in large (ratios of rate constants > 100) as well as small (ratios of rate constants ~ 1.5) effects on rate constants are known [14,15]. The catalyst system described in this work shows a small effect of the ligand environment on the rate. However, it is interesting to note that maximum k_{obs} is associated with cinchonine where modest enantioselectivity is also obtained. For the other chiral ligand *N*-methylephedrine and pyrrolidine diol lower rate and poor enantioselectivities are observed.

For optimum catalytic activities, the polymer anchored complexes must be carefully activated by thermal decarbonylation (see Section 4). The structural details of the decarbonylated species, i.e. the active catalyst, is not known, and at best may be speculated upon as coordinatively unsaturated rhodium centers. However, after use in the catalytic runs, when left under CO pressures of 500 psi for 24 h, the catalyst sample derived from **1a** undergo recarbonylation to give IR spectra identical to that of freshly prepared **1a** (see Fig. 1). There are many reports in the literature where reversible decarbonylation has been used as an indication of the retention of molecular identity of the organometallic species on an inorganic or organic support [16,17]. To the extent reversible decarbonylation is a reliable criterion, catalysts **1a** does not seem to undergo an irreversible structural change during catalysis.

3. Conclusion

The work described here shows that ion-pairing a chiral quaternary amine with an anionic rhodium carbonyl may be a viable method for designing asymmetric heterogeneous catalysts for the hydrogenation of dehydroamino acids. Among the amines and complexes studied so far, cinchonine plus $[\text{Rh}(\text{CO})_2\text{Cl}_2]^-$ couple gives the best result. We also find that this particular combination results in maximum rate (and enantioselectivity) as is normally observed in LAC.

4. Experimental

$\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ was purchased from Johnson Mathey, London. All the amines and chloromethylated divinyl benzene cross-linked (20%) polystyrene were purchased from Fluka, USA. Infrared spectra were recorded on a Nicolet FT spectrophotometer. Atomic absorption measurements were carried out on an IL 751 spectrophotometer. Microanalyses were carried out with a Carlo-Erba 1106 model C, H, N analyzer. Complexes **1** and **2** were synthesized according to literature reported procedures as the H^+ and Na^+ salts, respectively [18,19]. NMR spectra were recorded on a Bruker 300 MHz instrument. Hydrogenation experiments were carried out in a Parr autoclave (Parr, USA). Conversion of α -acetamidocinnamic acid to *N*-acetylphenylalanine was monitored by gas chromatography (GC) using an SC-30 (mesh, 1000–2000) GC column with FID detection.

Optical rotations were measured using a JASCO model CT-10 polarimeter (JASCO, Japan). Optical rotation measurements were carried out on purified products. The product was passed through a short silica gel column. The NMR spectrum of the purified material showed it to be *N*-acetylphenylalanine not contaminated with any other organic compounds. The observed optical rotation values could thus be ascribed solely to optical enrichment of *N*-acetylphenylalanine. All the solvents and organic compounds were thoroughly dried and distilled under nitrogen before use.

4.1. Functionalization of the polymer

A mixture of chloromethylated 20% DVB cross-linked polystyrene beads (1.0 g) and cinchonine (1.0 g) were stirred in a mixture of toluene (40 ml) and ethanol (40 ml) for 24 h at 100°C. The polymer beads were filtered, washed successively with ethanol, chloroform, dichloromethane and ether and then dried under vacuum. Resins functionalized with other amines were prepared in a similar fashion. Repeated nitrogen analyses indicate the presence of one cinchonine group approximately per 75 monomeric unit of the polymer.

4.2. Synthesis of **1a**

To a pale yellow solution of $[\text{Rh}(\text{CO})_2\text{Cl}_2]^-$ (0.2 g) in methanol (10 ml) chloromethylated 20% DVB cross-linked polystyrene beads quaternized with cinchonine was added and the mixture was stirred for 24 h at 25°C under nitrogen. Complete anion exchange took place to give pale brown beads of **1a**, which were filtered, washed thoroughly with methanol and vacuum dried. Catalysts **1b–f** were prepared by this general procedure using resins quaternized with different amines. Catalyst **2a** was synthesized by this general procedure starting from **2** and cinchona-functionalized resin.

The salt CH^+ [**1**] (C = cinchonine) was made and crystallized by adding excess (1.0 g) CH^+Cl^- to a solution of $[\text{Rh}(\text{CO})_2\text{Cl}_2]^-$ (0.2 g) in methanol (2 ml) and cooling the resultant solution overnight at 0°C.

4.3. Use of decarbonylated **1a** as a catalyst and recarbonylation of the used catalyst

For a typical catalytic experiment **1a** (0.1 g) was heated for 6 h at 60°C under vacuum. The IR spectrum of a portion of the solid showed the total disappearance of the inorganic carbonyl bands. A methanol (5 ml) solution of α -acetamidocinnamic acid (410 mg, 2 mmol) in a glass vessel was placed in the Parr pressure reactor of 100 ml capacity. Thermally activated **1a** (0.15 g) was added to this solution and stirred magnetically under a pressure of 500 psi of hydrogen for 24 h at 60°C. Samples were taken out at regular time intervals and analyzed by GC. At the end of the catalytic run the used catalyst in methanol was subjected to a CO pressure of 500 psi for 24 h. The solid was then filtered and the IR spectrum recorded again.

Acknowledgements

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