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Proline-induced enantioselective heterogeneous catalytic hydrogenation of isophorone on basic polymer-supported Pd catalysts

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The mode of enantioselection in the proline-modified asymmetric hydrogenation of isophorone (3,5,5-trimethyl-2-cyclohexenone) on polymer-supported Pd catalysts has been studied. Based on earlier results, polymers of basic nature, such as poly(vinyl-pyridine) (PVP), aminomethylated polystyrene (AMPS) and Amberlyst-OH (AOH), have been applied. The study has been focused on the early events in the reaction. The effect of different parameters such as hydrogen pressure and proline configuration and concentration has been studied. The pristine and proline pretreated catalysts have also been investigated with FT-IR spectroscopy. In the case of the AMPS-supported catalyst, the spectra indicated the formation of an amido group-anchored proline, which was potentially formed by the reaction of the surface amino groups with the carboxylic acid unit of proline. Our results provide convincing support for the existence of heterogeneous enantioselection in this system. These studies indicate that the basic nature of the support is clearly able to contribute to the observed enantioselectivities through the strong, potentially covalent, adsorption of the modifier.

Introduction

The high demand for chiral compounds and the ever stringent environmental policies provide a synergistic inspiration for the development of new asymmetric heterogeneous catalytic processes. Metal-catalyzed chiral hydrogenation clearly dominates this area.[1] Several successful modifier–catalyst hydrogenation systems had been described to achieve excellent enantioselectivities, including the Pt/cinchona alkaloids (for activated α-carbonyl group),[2] Pd/cinchona alkaloids (for activated C=C bond),[3] RANEY® Ni–tartaric acid (for activated β-carbonyl group),[4] and the Pd/proline (for C=C bond of cyclic α,β-unsaturated compounds).[5] The success of the first three systems had been attributed to direct enantioselective hydrogenation of the substrates.[2–4] In contrast, the Pd/proline system appeared to achieve high enantioselectivities *via* a secondary kinetic resolution of the product with the modifier. The system, that was first developed by Tungler *et al.*,[5,6] has been a target for extended investigations over the past decade, and several updated mechanistic proposals were published.[7] Findings from independent groups confirmed[7] our original suggestion of the significant role of the secondary kinetic resolution.[8] Earlier, we have also pointed out that the basic support of the Pd catalysts aided the enantioselection during the kinetic resolution.[9] Among many variables, the role of proline-based modifiers were also investigated, which proved the unique character of the proline skeleton in generating enantioselectivity.[10]

Our recent studies in organic polymer-supported catalysts[11] indicate that the changing chemical nature of the catalyst support contributes to the events in the reaction and may provide additional insight into the mechanism of the reaction. Bhaduri *et al.*[12] pioneered the application of polymers as stabilizing entities for heterogeneous catalysis. This approach that was later followed by others[13] describes the use of soluble organic polymers to stabilize Pt nanoparticles. The stabilized nanoparticles mimic homogeneous conditions and resulted in good to excellent enantioselectivities. More recently, Bykov *et al.* have reported the use of Pt supported in the pores of hyper-cross-linked polystyrene as a catalyst for the hydrogenation of ethyl pyruvate. In addition, Ding *et al.* described the application of homochiral coordination polymers for heterogeneous enantioselective hydrogenation.[14]

Due to our interest in enantioselective hydrogenation, particularly our recent contribution to the description of the Pd/proline system in the hydrogenation of isophorone, we have extended our previous studies. Based on our earlier work on polystyrene-supported catalysts,[11] several new polymer-based Pd catalysts were prepared. We intended to study the

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isophorone hydrogenation over these catalysts in order to gain additional information that would further clarify the mechanism of the reaction and/or would provide an opportunity to improve the chemical yields and selectivity of the product.

Experimental

Materials

Isophorone (>99%) was purchased from Aldrich, while solvents (99.5% minimum purity) were Fisher products. (*S*)- and (*R*)-Prolines (minimum purity >99.5%) were purchased from Sigma-Aldrich. Pd catalysts used for comparison in this study (5% Pd/$BaCO_3$ (Alfa Aesar), 5% Pd/Al_2O_3 (Engelhard), 5% Pd/C (Aldrich)) were commercially available. Materials used for the preparation of catalysts, including $NaBH_4$, $PdCl_2$ and polymers poly(4-vinyl-pyridine) (2% cross-linked) (denoted as PVP), amino-polystyrene (poly(styrene-(*o*-divinylbenzene)-amino functionalized, 2% cross-linked, 4 mmol g^{-1} loading)) (denoted as AMPS), and Amberlyst A26 hydroxide form (denoted as AOH), were all Aldrich products.

Preparation of polymer-supported Pd catalysts

The polymer-supported palladium catalysts were prepared using a direct precipitation method.[15] $PdCl_2$ (83.4 mg, 0.47 mmol) was dissolved in 5 ml of ethanol and 950 mg of polymer was added to the solution and stirred for 30 min. 30 mg (0.79 mmol) of $NaBH_4$ was carefully added (in 30 min) to this suspension under continuous stirring. After the $NaBH_4$ addition was complete, the mixture was stirred continuously for an additional 4 h. Finally, the black solid was filtered and air dried. The Pd loading of the catalysts was 5%. Mean metal particle sizes of the catalysts were determined by high-resolution transmission electron microscopy (JEOL 4000FX electron microscope) as described previously.[9] The obtained mean particle sizes were given as follows: 5% Pd/PVP – 2.3 nm; 5% Pd/AMPS – 3.4 nm; 5% Pd/AOH – 2.7 nm.

General procedure for asymmetric hydrogenation of isophorone on proline-modified Pd catalysts

Hydrogenation was carried out in a Berghof HR-100 vessel equipped with a Teflon liner at room temperature (25 °C). The initial reaction mixture (25 mg of supported Pd catalyst, 57 mg (0.5 mmol) of (*S*)-proline and 5 ml of EtOH) was premixed and prehydrogenated (30 bar hydrogen pressure, 30 min stirring). Then, 0.5 mmol of isophorone (75 μl) was introduced, and the autoclave was flushed with hydrogen several times and filled to the desired pressure and stirred (1000 rpm) for the required reaction time. After certain time points, samples were removed and subjected to GC-MS, HPLC-MS and chiral GC analysis in order to determine chemical yield, selectivity and optical yield.

Analysis

The identification of products and the determination of their yields were carried out by GC-MS using an Agilent 6850 GC-5973N MS (EI ionization) system and an Agilent 1200 Series HPLC-MS (APCI ionization) system. A ZB-5MSi (Zebron) column was used for the GC separation, while an Agilent Symmetry C_{18} 5 μM column was applied in the HPLC separation with MeOH/H_2O eluent (25% MeOH/75% water to 100% MeOH over 4 min, maintains 100% MeOH for 2 min and then to the initial mixture over 1 min). Enantiomeric excess of products (ee (%) = $|[R] - [S]| \times 100/([R] + [S])$) was determined by gas chromatography (Agilent 6850 GC-FID) using a 30 m long Betadex (Supelco) chiral capillary column. The absolute configuration of products was determined by comparison to an authentic sample.[6] The ee values were reproducible within 1%. FT-IR spectra were taken using neat, dry samples by using a Thermo Fisher Nicolet 380 FT-IR equipped with a Smart Orbit.

Determination of the yield of the products

In analyzing the outcome of the reactions, it was decided that the actual amount of all three major species, isophorone (IP), dihydroisophorone (DHIP) and the hydrogenated dihydroisophorone-proline adduct (DHIP-Pro), will be determined by an internal standard method. Decane was used as an internal standard for the determination of the amount of remaining IP and formed DHIP, while caffeic acid fulfilled the same role for DHIP-Pro. While it is an unusual internal standard, the size and polarity of caffeic acid made its chromatographic characteristics similar to that of DHIP-Pro and was a good fit for the HPLC analysis.

In each case, about 0.5 mL of sample was removed from the reaction vessel. The catalyst was removed by centrifugation, and the supernatant was transferred into another vessel. For the determination of IP and DHIP amounts, 20 μL of the sample was mixed with 20 μL of 0.05 M decane solution (9.5 μl of decane in 1 ml of iPrOH) and diluted with iPrOH to 500 μL. The obtained mixture was thoroughly mixed and injected into an Agilent GC-MS system. The decane/IP and decane/DHIP ratios were determined, and a comparison to the calibration curves yielded the actual amounts.

Since DHIP-Pro is a relatively large compound, the analysis was carried out by HPLC-MS. For the determination of the amount of DHIP-Pro, 20 μL of the sample was mixed with 40 μL of 0.3 M caffeic acid solution (54 mg of caffeic acid in 1 ml of MeOH) and diluted with methanol to 500 μL.

In order to determine the actual amount of the components in the mixture, calibration curves were determined for each compound. The DHIP (racemic) and DHIP-Pro adduct were synthesized and isolated separately. The purified products were then used to prepare the calibration solutions. First, a 0.3 M solution of the compounds was made (41 mg of IP in 1 ml of MeOH; 42 mg of DHIP in 1 ml of MeOH and 72 mg of DHIP-Pro in 1 ml of MeOH) and further diluted. The following concentrations were used for the calibration: 0.3 M, 0.15 M, 0.075 M, 0.0375 M, 0.01875 M and 0.009375 M. The calibration curves showed a good fit with r^2 values of 0.9904 (IP), 0.9992 (DHIP) and 0.9932 (DHIP-Pro).

Pretreatment of catalyst samples for IR analysis

The catalyst (12 mg) was suspended in 2.5 mL of EtOH and 29 mg of (*S*)-proline was added. The mixture was stirred under 30 bar H_2 pressure for 30 min, and then the catalyst was filtered, washed with 0.5 mL of water and dried under vacuum for 16 h. The data obtained with a Pd/PS catalyst, which cannot adsorb proline due to the lack of acid–base interactions, showed no significant difference between the neat and pretreated samples indicating that all non-adsorbed proline was removed by the aqueous washing.

Results and discussion

Among different types of chiral auxiliaries, proline, an abundant, inexpensive amino acid available in both enantiomeric forms, has re-emerged as a practical and versatile modifier, especially in organocatalysis.[16] It has also been applied as a modifier in heterogeneous enantioselective hydrogenation.[6–8] Earlier, we have shown that proline-modified Pd catalysts are able to induce very high enantioselectivities through selective adsorption,[8] which was confirmed by independent groups.[7] Without detailing the elementary steps, the formation of the major products are illustrated in a general reaction scheme (Fig. 1).

Without discussing the mechanism in detail, the current broadly accepted pathway includes the fast racemic hydrogenation of IP. The (*R*)-DHIP then rapidly forms an iminium complex with proline and undergoes a C=N double bond hydrogenation to yield (*R*)-DHIP-Pro, leaving the (*S*)-DHIP behind. Therefore, the enantioselection in the reaction is purely the result of the secondary kinetic resolution and the first actual C=C hydrogenation occurs in a racemic fashion. The latter part of the statement was challenged by the work by Lambert *et al.* The authors described the application of proline-derived sulfide ligands as chiral modifiers and observed some enantioselection that occurred during the first step of the reaction, thus pointing out that the IP hydrogenation can indeed be an enantioselective process.[17]

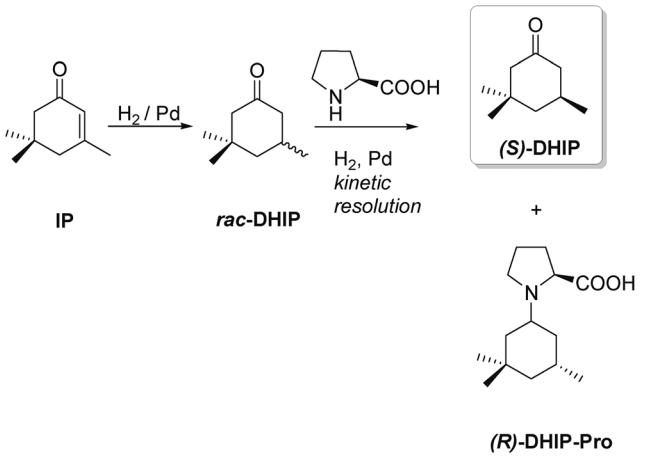

Fig. 1 The general scheme and major products of proline-modified Pd-catalyzed hydrogenation of isophorone.

These findings initiated us to investigate the early phase of the reaction.

Based on our earlier positive results on alkaline earth carbonate-supported Pd catalysts[8] as well as polystyrene-supported Pt catalysts,[9] three basic polymers were selected for the preparation of new polymer-supported Pd catalysts. Our intention was to maintain the basicity of the support, hence the stronger adsorption of proline, while providing a less polar environment on the catalyst surface that could improve the reversible IP-proline complex formation. The general formulae of the supports are illustrated in Fig. 2.

The catalysts showed much more sluggish behaviour than those of the alkaline earth carbonates used in our previous study;[8] however, given enough time (over 24 h) they were able to produce the near 100% ee product with the expected less than 50% chemoselectivity. Due to the low activity, however, the new catalysts were found to be well suited for studying the early events of the reaction. First, the performance of the polymer-supported Pd catalysts was compared using the standard conditions (30 bar hydrogen pressure with 1 eq. of (*S*)-proline) that were found optimal in our previous studies with basic catalyst supports. The data are shown in Fig. 3.

The data clearly indicate that the activity of the tailored polymer-supported catalysts is lower than that of the earlier applied commercial inorganic carbonate-supported samples. The three catalysts, though all prepared with a basic polymer support, showed significant differences in activity. As shown in Fig. 3(A), the PVP-supported sample was found to be the most active, whereas Pd/AMPS was the least active. Due to the different activities, the product accumulation curves are also significantly different. Since our goal was to focus on the early events in the hydrogenation process, the reactions were stopped after 8 h. Accordingly, with the most active Pd/PVP the dihydroisophorone (DHIP) concentration passes through a maximum, while with the least active Pd/AMPS it shows a constantly increasing accumulation of DHIP. As a consequence of the different DHIP accumulation curves, the formation of the ultimate product of the reaction, the hydrogenated product of the DHIP and proline condensation (Fig. 1) (DHIP-Pro), also shows significant differences. While Pd/PVP and Pd/AOH both allow the approximately linearly increasing concentration of DHIP-Pro, in the presence of Pd/AMPS, this product did not appear in the first 4 hours of the reaction. Studying the enantiomeric excess of the DHIP product, the findings

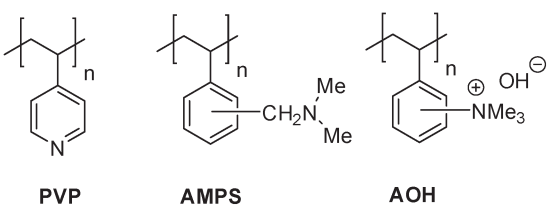

Fig. 2 General formulae of the polymers applied as catalyst supports (PVP – poly(4-vinyl-pyridine), 2% cross-linked; AMPS – aminomethylated polystyrene, 2% cross-linked with 4 mmol loading; AOH – Amberlyst 26 hydroxide form).

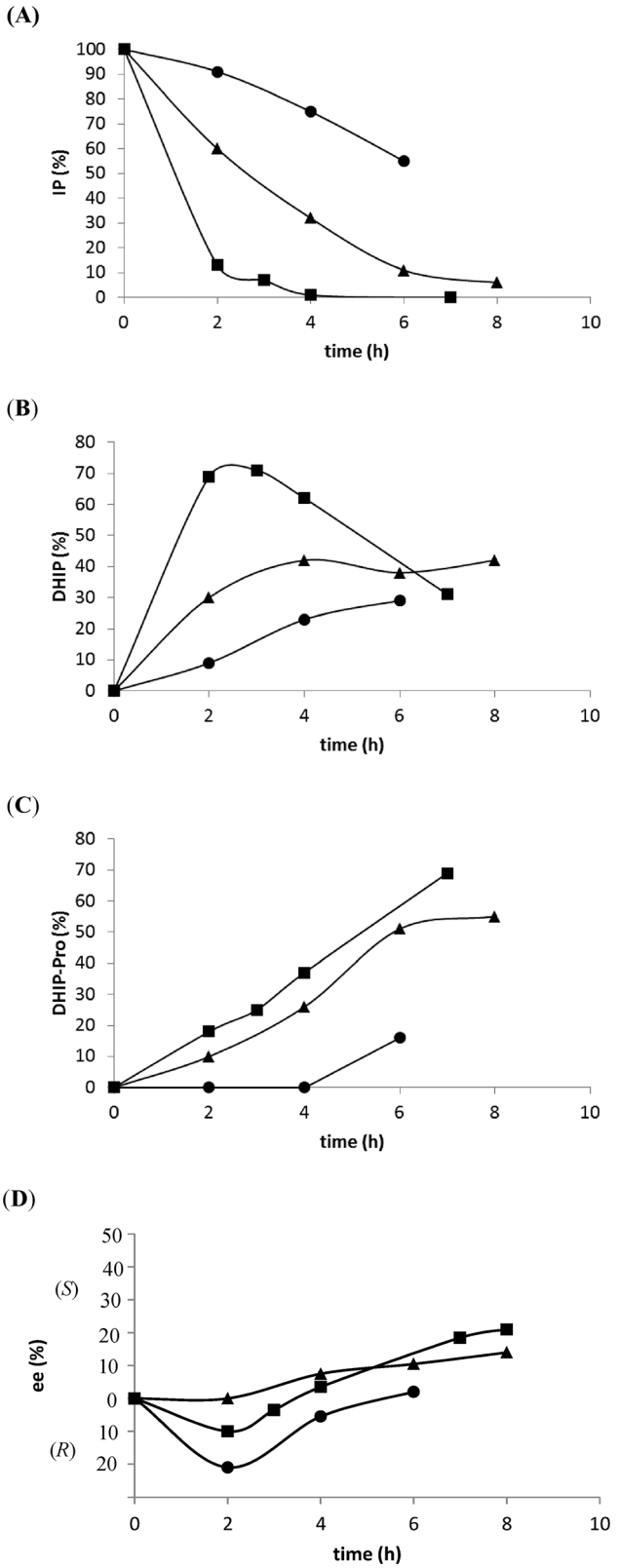

Fig. 3 Effect of catalyst support on the enantiomeric excess of DHIP and the amount of the major species as a function of time in the hydrogenation of isophorone over 5% Pd/AMPS (●), 5% Pd/PVP (■) and 5% Pd/AOH (▲) catalysts in ethanol with 1 eq. proline at 30 bar hydrogen pressure. (A) Isophorone (IP); (B) dihydroisophorone (DHIP); (C) hydrogenated dihydroisophorone-proline adduct (DHIP-Pro); (D) enantiomeric excess of (*S*)-DHIP.

are even more surprising. Earlier findings from independent groups, including our own, are in a clear agreement that the use of (*S*)-proline would yield an (*S*)-DHIP product.[6–8] In light of this, it is surprising that both the PVP and the AMPS-supported catalysts yield (*R*)-DHIP in excess, as observed *via* the opposite ee values at the early part of the reaction. As the reaction progresses, (*R*)-DHIP still remains a dominant species, and the ee stays negative until about 6 h for both reactions to varied extent. It then turns positive and progresses as expected based on the preliminaries. The comparative analysis of the DHIP-Pro concentration (Fig. 3C) and the ee *vs.* time (Fig. 3D) curves especially over the Pd/AMPS catalyst indicate a controversy. While the DHIP-Pro is not present in the system, the trend of the ee changes directions symmetrically. This cannot be explained by the simple contribution of the racemic hydrogenation. Since the conversion values are still relatively low in the system and proline is present in a 1 : 1 molar ratio, it is suggested that the surface-bound proline forms an iminium ion-type adduct with the (at that point) excess (*R*)-DHIP, similar to the typical kinetic resolution. This surface-bound intermediate will undergo subsequent hydrogenation and the product will be released later to the reaction mixture. The anchoring of the (*R*)-DHIP will result in its partial removal from the solvent and the reversal of ee, while the DHIP-Pro adduct is not released yet. After the lag phase (4 h), the released adduct appears in the mixture and its concentration steadily increases. It is worth noting that the reaction yields 100% ee (and 19% selectivity) for (*S*)-DHIP on the Pd/AOH catalyst. After a similar time, Pd/AMPS provides only 26% ee. These observations initiated further investigations on the PVP and AMPS-supported catalysts and the hydrogen pressure dependence of the reactions has been determined. The data are summarized in Fig. 4.

The hydrogen pressure dependency data confirm the above observation regarding the selective formation of (*R*)-DHIP at the early stages of the reaction. The multiple measurements of negative ee values unambiguously show that the reaction is producing (*R*)-product without a detectable concentration of the DHIP-Pro adduct. The two catalysts show varying data that are expected in light of the reasonable difference in activity. The AMPS-supported catalyst with lower activity produces a negligible amount of DHIP-Pro adduct (<1%) until 4 h. Even after 4 h, the DHIP-Pro amount increases slowly. While the data show a more pronounced formation of DHIP-Pro at 30 bar pressure, the difference from the data obtained at other hydrogen pressures appear minor (within a few %). Interestingly, this is the point when the ee turns first to 0% and then gradually increases eventually producing (*S*)-DHIP in excess. After the initial period, the ee remains on an upward trajectory. The hydrogen pressure appears to affect the studied data to a relatively insignificant extent.

While the differences as a function of hydrogen pressure are more visible on the PVP-supported catalyst, the observations are generally similar. The Pd/PVP also yields (*R*)-product in excess in the first few hours of the reaction. However,

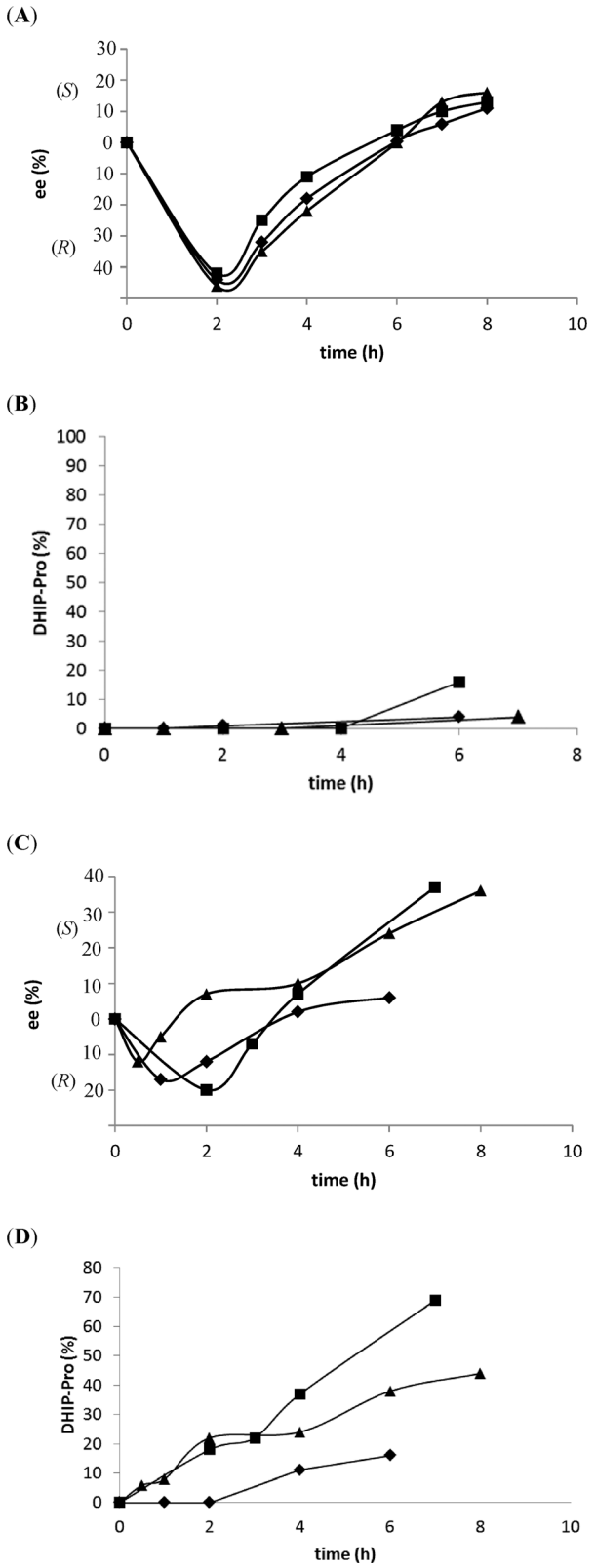

Fig. 4 Effect of hydrogen pressure on the accumulation of DHIP-Pro and the ee of (*S*)-DHIP as a function of time in the hydrogenation of isophorone. The experiments were carried out over a 5% Pd/AMPS and 5% Pd/PVP catalysts with 1 eq. of (*S*)-proline in ethanol. (A) ee of (*S*)-DHIP on Pd/AMPS; (B) DHIP-Pro concentration on Pd/AMPS; (C) ee of (*S*)-DHIP on Pd/PVP; (D) DHIP-Pro concentration on Pd/PVP. ♦ – 15 bar H_2; ■ – 30 bar H_2; ▲ – 60 bar H_2.

it seems that the system generally reaches the racemic mixture (0%) and continues to grow to a reasonable value (~35% for (*S*)-DHIP), even within the relatively short time window. This is also reflected in the steady increase of the DHIP-Pro product, although it is relatively slow under 15 bar hydrogen pressure.

Based on the above experiments, it is clear that these catalysts produced the (*R*)-DHIP in excess at the early phase of the reaction; hence, proline was able to generate reasonable enantioselectivity even without the contribution of the later kinetic resolution. This fact raised the question of whether the change in proline concentration would have an effect on these early events in the reaction. Thus, reactions with decreasing (*S*)-proline concentrations and with (*R*)-proline were carried out to confirm that the configuration change of the chiral auxiliary would result in a configuration change in the product as well, as often observed in enantioselective reactions.[2–4] Since the ee for (*R*)-DHIP is the highest on Pd/AMPS catalyst, this sample was selected for the proline concentration dependence studies. The data are summarized in Fig. 5.

The data show that the change in proline concentration, indeed, has a profound effect on the early phase of the reaction. All reactions with (*S*)-proline as a chiral auxiliary yielded (*R*)-DHIP in excess. In contrast, the use of (*R*)-proline reversed the chirality of the product and provided (*S*)-DHIP within the first 4 hours of the reaction. The extent of the enantiomeric excess also varied significantly. The ee for (*R*)-DHIP passes through a maximum at 0.5 eq. of proline (51% ee), while further decreasing the proline concentration diminishes the ee. In parallel, the formation of the DHIP-Pro product, that is responsible for reversing the enantiomeric excess, does not occur in a reasonable amount (all data are less than 5%) in this period. After 4 hours, a steady increase in the formation of the end product (Fig. 5C) is observed, and accordingly, the ee decreases toward the racemic product and then surpasses the borderline and (*S*)-DHIP will remain in excess. It is worth mentioning that the ee values obtained with an identical amount of (*S*)- or (*R*)-proline show a notable difference. Since it was not the case with other catalysts,[8,9] it appears reasonable to suggest that the different surface characteristics of the polymer-supported catalysts are partially responsible for this phenomenon. In addition, while such phenomenon, namely that the two enantiomers of a chiral catalyst give different ee values in the same reaction, is known in asymmetric catalysis,[18] the reasons for such behaviour are not well established, even in homogeneous systems, despite that the lack of a solid/liquid interface simplifies the problem.

After studying the reaction itself under various conditions, we decided to investigate the potential interactions between the chiral auxiliary and the three catalysts. These studies also included a simple unmodified poly(styrene)-supported catalyst (Pd/PS). It was expected that the completely nonpolar support would affect the proline adsorption as compared to the other basic polymer supports. The catalysts were pretreated with proline for 30 min, filtered and dried. Then, the FT-IR

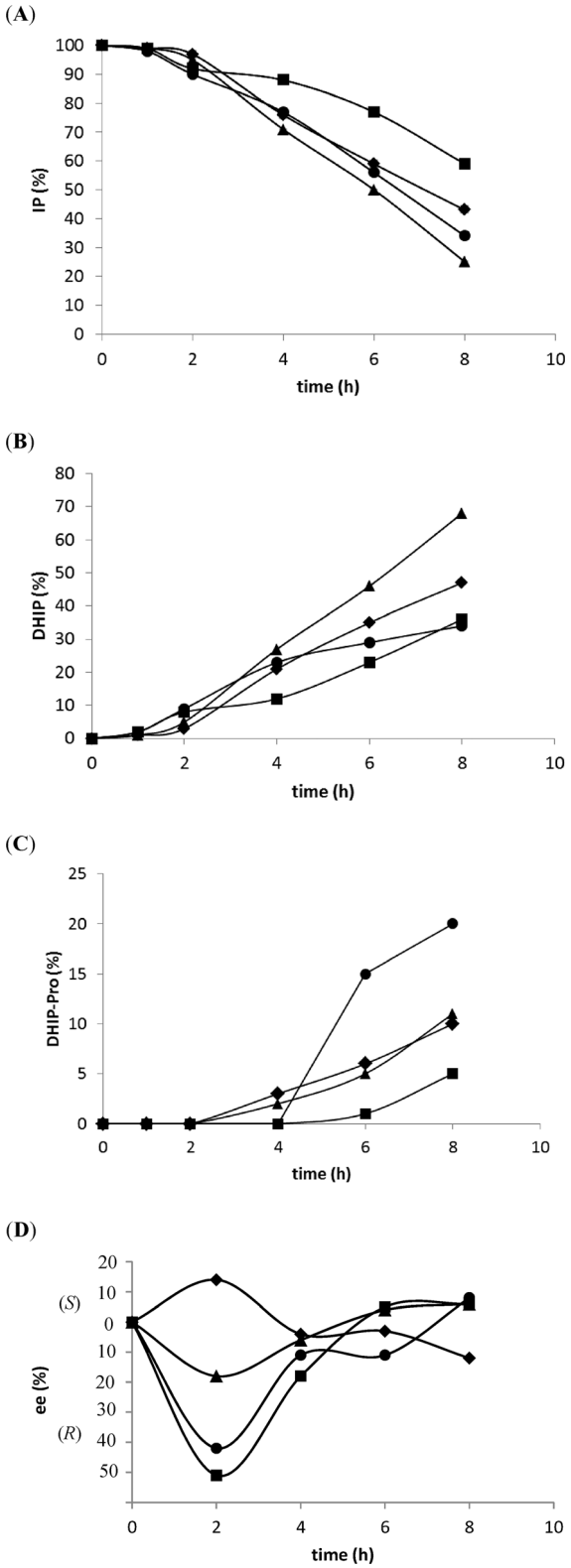

Fig. 5 Effect of proline configuration and concentration on the amount of the major species as a function of time in the hydrogenation of isophorone, as well as the ee of the (*S*)-DHIP product. The experiments were carried out over a 5% Pd/AMPS catalyst in ethanol under 30 bar hydrogen pressure. (A) Isophorone (IP); (B) dihydroisophorone (DHIP); (C) hydrogenated dihydroisophorone-proline adduct (DHIP-Pro); (D) enantiomeric excess with 1 eq. (*S*)-proline – ●; with 0.5 eq. (*S*)-proline – ■; with 0.25 eq. (*S*)-proline – ▲; with 0.5 eq. (*R*)-proline – ♦.

spectra of the pristine and pretreated catalysts were recorded and plotted in Fig. 6.

As indicated by the spectra, the poly(styrene)-supported sample (Fig. 6A) did not show significant changes upon proline treatment. Other than change in the intensity of certain bands, the PVP and AOH supports also do not show striking differences. These catalysts might develop meaningful acid–base interactions with proline in solution; however, removing the proline solution appears to remove proline from these catalysts almost completely. The most important observation can be seen on the spectra of the Pd/AMPS catalyst. The original catalyst show a well-developed broad band

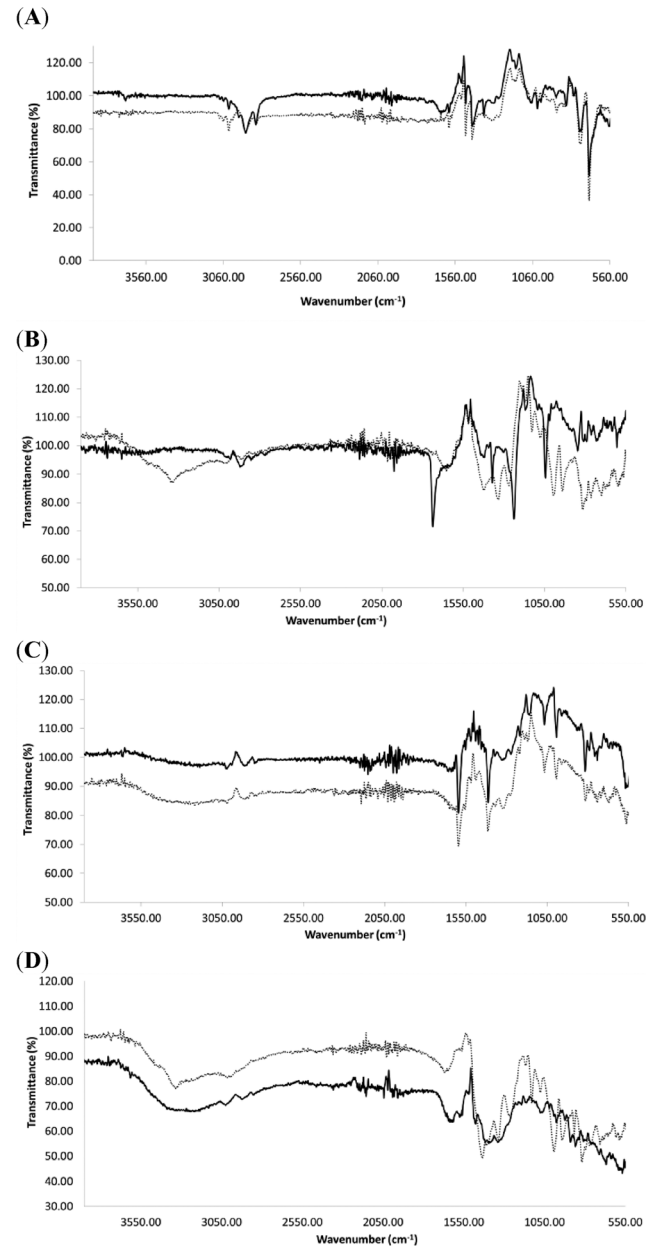

Fig. 6 Infrared spectra of the polymer-supported Pd catalyst. (A) Pd/PS; (B) Pd/AMPS; (C) Pd/PVP; (D) Pd/AOH. Grey line – pristine catalyst; dark/black line – (*S*)-proline pretreated catalyst.

around 3400 cm^{-1}, probably indicating the presence of the hydrated dimethylamino groups (Fig. 2, AMPS). The complete lack of bands around 1700 cm^{-1} is also noteworthy. After treatment with proline, the spectrum changes significantly. The original broad signal almost completely disappears and an intense, sharp signal develops at 1733 cm^{-1}. It is worth noting that this bond is missing from the spectrum of the neat (*S*)-proline as well (data not shown). This indicates that the appearance of this band is not due to a weak surface interaction of proline with the AMPS support. The other samples clearly show that the simple physical adsorption of proline on the catalysts was not a strong interaction and proline was removed with the solvent *via* filtration. This was not the case with the AMPS support. The spectra indicate a strong interaction between the support and the modifier. The disappearance of the broad OH signal with the parallel appearance of the C=X (X = O, N) signal indicate a strong interaction of the amino acid with the surface amino groups possibly *via* an ionic bond (Fig. 7).

The suggested arrangement of the chemically adsorbed proline raises an interesting question that requires further investigations. As shown, proline is anchored *via* an ionic bond. Adsorption of the DHIP-Pro adduct can also occur in a similar manner. As this adduct is chiral, containing mostly (*R*)-DHIP-(*S*)-Pro and a smaller amount of (*S*)-DHIP-(*S*)-Pro, it can be considered as a potential chiral catalyst for the hydrogenation, thus further complicating this system. The synthesis and assessment of the effect of the individual DHIP-Pro adducts will clarify the potential role of this compound in the reaction.[19]

The analysis of the above data reveal additional information regarding the mechanism of the reaction on base-supported catalysts. Two catalysts (Pd/AMPS and Pd/PVP) appeared to consistently produce (*R*)-DHIP with significant enantiomeric excess (up to 51% ee) under varied experimental conditions. While it is not common, such behaviour has been observed and described in the literature. For instance, Shen *et al.* observed the initial formation of (*R*)-DHIP on Pd catalysts with varying metal particle size.[20] As those catalysts had different supports, it appears that the (*R*)-DHIP formation early in the reaction is not exclusive for the AMPS and PVP-supported catalysts. While unexpected, as the earlier reactions[6–8] always produced (*S*)-DHIP, this unambiguously indicates that it is a real phenomenon. In fact, efforts have been made to observe whether the earlier applied alkaline metal earth carbonate-supported catalysts would provide any reversed selectivity. It was observed that the least reactive 5% $Pd/CaCO_3$ catalyst gave 6% ee for the (*R*)-DHIP after 5 min of reaction (7% conversion, 0% DHIP-Pro), confirming that the early events on this catalyst also involve direct enantioselective hydrogenation of IP. Using $Pd/BaCO_3$, the formation of (*R*)-DHIP was also observed within the first 10 min of the reaction. Based on the abovementioned results of the Shen group,[20] there is also a possibility that the special behaviour of the catalysts can be attributed to their small Pd particle size or the potential formation of PdB alloy upon the $NaBH_4$ reduction of the Pd^{2+} ions.

Upon further progress, the ee for (*R*)-DHIP gradually decreased to racemic and the formation of the (*S*)-DHIP kept dominating the system eventually reaching the nearly 100% ee as described by multiple sources.[7,8] It was also observed that the change in ee is closely related to the lack or formation of the DHIP-Pro final product. During the early events of the reaction, this product does not form, allowing the formation of the (*R*)-DHIP. After the initial induction period when the DHIP-Pro formation occurs in a reasonable extent, it's selective reaction with (*R*)-DHIP changes the ratio of the two enantiomers and eventually consumes all (*R*)-DHIP resulting in 100% ee for (*S*)-DHIP. This, however, means that the reaction is not simply going through *rac*-DHIP formation and kinetic resolution, which would yield 50% (*S*)-DHIP. The observed chemical yields for reactions that reach the 100% ee for (*S*)-DHIP, in our hands, were always significantly lower than 50%, more commonly in 20–30% only. This can be explained by the parallel formation of the (*R*)-DHIP, which forms in a higher amount than 50% (expected from the racemic product) and thus further decreases the actual yield of (*S*)-DHIP at the completion of the reaction. This is supported by the results of the proline concentration dependency experiments. It was observed that while the formation of (*R*)-DHIP occurs at any proline concentration reported, in fact the maximum ee (51% (*R*)-DHIP) was observed with 0.5 eq. proline, the subsequent domination of the (*S*)-DHIP becomes much slower in the presence of decreased proline content. This is most likely due to the diminished overall rate of DHIP-Pro formation as a result of the lower proline concentration.

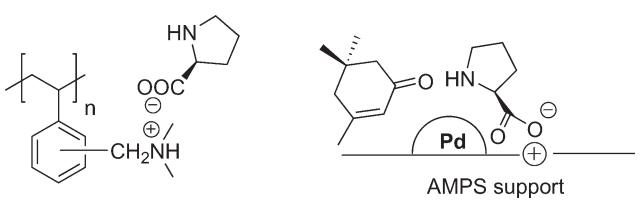

Fig. 7 The proposed interaction of proline with the amino group of the AMPS support and the illustration of a potential mode of action of this surface intermediate in yielding a chiral DHIP product.

Conclusions

Investigations of the early events in the proline-modified asymmetric hydrogenation of isophorone over basic polymer-supported Pd catalysts have resulted in the consistent observation of the selective formation of (*R*)-DHIP without the contribution of a secondary kinetic resolution. This has led to the conclusion that in the presence of these catalysts a direct enantioselective proline-modified hydrogenation of isophorone occurs. It was also observed that after the initial period of the reaction, particularly when the kinetic resolution began to occur, (*S*)-DHIP became the dominant chiral product, in agreement with earlier reports. It appears that the formation of the excess (*R*)-DHIP is a separate process that

occurs parallel with the racemic hydrogenation and subsequent kinetic resolution to (*S*)-DHIP, the major chiral product at 100% conversion. This leads to the overall conclusion that higher than 50% yields for the (*S*)-DHIP in this catalyst–modifier system is likely not possible; however, immobilized proline containing Pd catalysts appear promising in yielding enantiomeric product in a true chiral catalytic fashion.

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