Catal Lett (2008) 123:156–163
DOI 10.1007/s10562-008-9411-y

Nature of Proline-induced Enantiodifferentiation in Asymmetric Pd Catalyzed Hydrogenations: Is the Catalyst Really Indifferent?

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Received: 12 December 2007 / Accepted: 19 January 2008 / Published online: 8 February 2008

Abstract The mode of enantioselection in the proline modified asymmetric hydrogenation of isophorone (3,5,5-trimethyl-2-cyclohexenone) on supported Pd catalysts has been studied. It is shown that several experimental factors, such as modifier structure and chemical nature of the catalyst support, strongly affect the outcome of the hydrogenations. Secondary kinetic resolution was found to be the major reason for obtaining high enantioselectivities on most catalysts. Extensive studies have been carried out to clarify the importance of the interaction of the proline–dihydroisophorone complex with the catalyst. The secondary kinetic resolution of dihydroisophorone was investigated under different conditions. First, racemic-dihydroisophorone was studied using several (*S*)-proline modified supported Pd catalysts, then the individual enantiomers were subjected to a similar reaction on Pd/$BaCO_3$ catalyst in the presence of (*S*)-proline. Our results provide convincing support for the heterogeneous enantioselection model under the current experimental conditions.

Keywords Hydrogenation · Enantiodifferentiation · Pd catalysts · Proline · Isophorone · Kinetic resolution

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1 Introduction

The high demand for chiral pharmaceuticals, agrochemicals, flavors and fragrances provides extraordinary inspiration to develop new synthetic methods to prepare enantiomerically pure compounds [1]. Asymmetric saturation of alkenes, ketones and imines provides ideal access to chiral alkanes, alcohols and amines. Thus asymmetric hydrogenation has become increasingly important in organic syntheses. Heterogeneous methods possess many potential advantages over homogeneous approaches, such as the ease of storage, use, separation and recycling [2]. Heterogeneous chiral hydrogenation is clearly dominating the asymmetric catalysis on surfaces. The most prominent systems are the cinchona modified Pt [3], and the tartaric acid modified Raney Nickel [4]. The number of practical applications increases continuously and heterogeneous catalytic asymmetric hydrogenations are in the forefront of contemporary catalysis research [5, 6]. Following the extensive number of applications with carbonyl compounds, C=C double bond hydrogenation has also attracted significant attention [7]. After many years of struggling, the hydrogenation of 4-methoxypyrone and 4-hydroxypyrone on cinchona-modified Pd/TiO_2 catalyst (up to 94% ee) opened up the possibility of developing practical solid hydrogenation catalysts for enantioselective C=C hydrogenation [8]. Two very recent reviews summarize the latest developments in the area of enantioselective catalysis on modified metals [9].

The significant renewed interest in application of proline and proline-like chiral organocatalysts in asymmetric synthesis [10] reignited the activity in the field of proline-induced asymmetric hydrogenations of C=C bond in unsaturated ketones. A recent extensive review summarized the progress made in this area [11]. Current efforts

concentrate on: (i) improving the optical yields, (ii) widening the scope of the reaction, and (iii) refining the mechanistic model. Our studies on the subject indicated the strong connection between (i) and (iii). The original mechanistic model by Tungler et al. strongly emphasized the importance of unsaturated ketone–proline complex formation prior to hydrogenation [11, 12]. We have refined this model and have pointed that strong proline adsorption is necessary to obtain high enantioselectivities [13]. Using this observation as a hypothesis led us to first observe that ultimately a secondary kinetic resolution is responsible for the excellent enantioselectivities [14]. A few months later (see publication dates in [15]) in a mechanistic study Lambert et al. came to the same conclusion concerning the importance of the kinetic resolution [16]. However, they emphasized the importance of phenomena occurring in the solution (complex formation prior to hydrogenation, kinetic resolution etc.) concluding that the nature of enantiodifferentiation is homogeneous [16]. Unfortunately, given the difference in the two catalytic systems (atmospheric vs. high pressure) a direct comparison might result false conclusions. Even if one acknowledges the principal importance of the homogeneous complex formation it cannot be overlooked that the purely homogeneous model is not able to interpret the role of the catalyst, although it is usually one of the most important factors. In very recent papers, Shen et al. disclosed investigations of the same reaction in the presence of several base-supported Pd catalysts, and found that the enantioselectivity was strongly dependent on the catalyst support, providing further support for the heterogenous enantioselection model [17].

It seems safe to conclude that more data are necessary to build a comprehensive mechanistic proposal. It prompted us to investigate this catalytic system further. The current work provides additional experimental evidence to promote mechanistic considerations that involve the catalyst as a major factor in the enantiodifferentiation model. In addition, in the light of these new data and considering earlier mechanistic descriptions, here we propose a unified mechanistic pathway that is able to interpret the phenomena.

2 Experimental

2.1 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 Fluka. Pd catalysts used in this study (5% $Pd/BaCO_3$—Alfa Aesar, 5% Pd/Al_2O_3, 5% Pd/C—both Engelhard) were commercially available.

Mean metal particle sizes of the catalysts have been determined [13, 14] by high resolution transmission electron microscopy (JEOL 4000FX electron microscope) as described earlier [18]. The mean metal particle sizes and dispersion values are as follows: 5% $Pd/BaCO_3$—4.3 nm ($D = 0.20\%$), 5% Pd/Al_2O_3—4.1 nm ($D = 0.21$), 5% Pd/C—4.2 nm ($D = 0.20$).

2.2 General Procedure for Hydrogenation of Isophorone on Pd Catalysts in the Presence of Proline

The hydrogenations were performed in a Berghof HR-100 vessel using a Teflon liner at room temperature. 50 mg of Pd catalyst, was prehydrogenated in 5 mL of EtOH in the presence of 114 mg (1.0 mmol) of (*S*)-proline and (30 bar, p_{H2} 30 min, RT). Then, 1 mmol of isophorone (150 µl) was added, and the mixture was stirred (1000 rpm) at the desired pressure for the required time.

2.3 General Procedure for Kinetic Resolution of *rac.*-dihydroisophorone on Pd Catalysts in the Presence of Proline

Racemic dihydroisophorone has been synthesized at room temperature by the hydrogenation of isophorone (20 mmol) on 100 mg Pd/Al_2O_3 in 15 mL of ethanol, at 30 bar hydrogen pressure in a Berghof HR-100 autoclave. The catalyst has been removed by membrane filtration, and the solvent has been evaporated in vacuo. The product *rac*-dihydroisophorone was of 99.5% purity (GC).

The supported (5%) Pd catalyst (50 mg) was prehydrogenated with 1.0 mmol of (*S*)-proline in 5 mL of EtOH (see above). Then 1 mmol of *rac.*-dihydroisophorone was added and the mixture was hydrogenated at room temperature at 30 bar hydrogen pressure in a Berghof HR-100 autoclave (see above) until the required time.

2.4 Synthesis and Isolation of Enantiopure (*S*)- and (*R*)-Dihydroisophorones by Kinetic Resolution of *Racemic* Dihydroisophorone on Pd Catalysts in the Presence of Proline

Dihydroisophorone enantiomers have been synthesized by kinetic resolution of *rac*-dihydroisophorone as described above. In the presence of (*S*)-proline (*S*)-, while in the presence of (*R*)-proline (*R*)-dihydroisophorone formed. After reaching 99.9% ee the reaction was stopped. The catalyst was removed by filtration and majority of the solvent was evaporated. Water was added to the mixture

and while proline-containing adducts of zwitterionic character remained dissolved in the aqueous solution, dihydroisophorone was extracted with *n*-hexane. The collected organic layers were dried over Na_2SO_4. After filtration of the drying agent and removal of the solvent the product was obtained. Both (*S*)- and (*R*)-dihydroisophorone have been isolated with >99% ee and 99.5% purity.

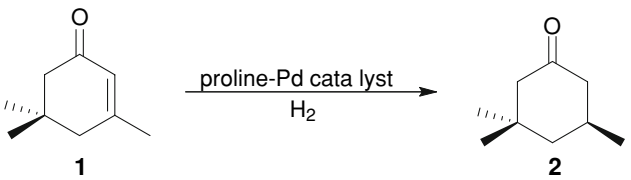
2.5 Analysis

Product identification was monitored by GC–MS using Shimadzu QP 5050 and Agilent 6850 GC-5973N MS Systems. All calculations regarding to the selectivity of product formation were based on the use of the internal standard method. To ensure the reliability of the determination of the dihydroisophorone amount *n*-decane was used as an internal standard. Enantiomeric excesses of products ($ee\% = |[R] - [S]| \times 100/([R] + [S])$) were determined by gas chromatography (HP 5890 GC-FID, and 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 [12]. The ee values were reproducible within 1%.

3 Results and Discussion

3.1 Effect of Modifier Structure on Adsorption and Enantioselectivity

Analyzing the structural necessities of an active modifier can provide better insight into the mechanism of a reaction. Therefore, we have tested several modifiers in the hydrogenation of isophorone (**1**).



These modifiers were proline derivatives and structurally related compounds. Theoretically, all of them were capable of participating in a chiral induction through a conventional enamine-type mechanism [10–12]. 5% $Pd/BaCO_3$ was selected as this catalyst was able to provide up to 99% ee values in earlier studies [14]. The results are tabulated in Table 1.

As shown, proline enantiomers appeared to provide the best performance in agreement with earlier data [11–14, 16, 17]. As pointed out earlier [13, 14] the acidic, electron rich carboxylic acid group is mainly responsible for adsorption, and it is able to anchor proline to both the metal and a suitable support [13, 14]. Introduction of a second substituent (OH) or change in ring structure decreases the ee values. The additional element distorts the near-flat nature of the C5 ring (in case of six-membered rings) or induces steric constraints between the ring and the surface of the catalyst (in the case of a substituent). The same effect was observed when the electron rich carboxylic acid function was reduced to CH_2OH. The generally very effective MacMillan's catalyst [10] completely failed in this hydrogenation, both in its salt and its free base forms, most likely due to its very weak adsorption capability.

The above observations are in line with our earlier experimental data [13, 14], namely, that efficient adsorption capability is necessary to achieve high enantioselectivities. Changes made to the original proline structure usually resulted in a decrease in the ee values. When the chiral auxiliary is not able to strongly adsorb on the catalyst the ee values are poor. This is shown using prolinols or the MacMillan's catalyst [10] that lacks the electron rich carboxylic acid group. Effective surface adsorption appears to guarantee significantly higher ee values, signaling a relationship between effective enantioselection and adsorption on the catalyst.

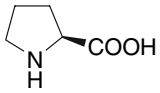
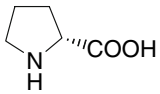
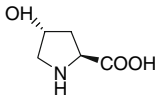
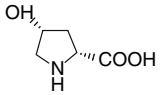
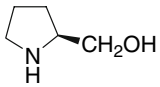
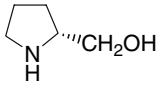
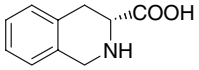
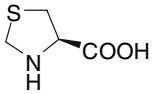
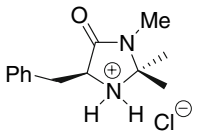
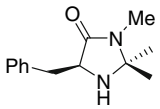
3.2 Role of Catalyst in Secondary Kinetic Resolution

It is apparent from recent findings by independent groups [13–14, 16, 17] that a secondary kinetic resolution is responsible for effective enantiodifferentiation. The secondary reaction of the product dihydroisophorone (**2**) with proline and the subsequent hydrogenation of the adduct results in a significant increase in ee with a parallel drop in chemoselectivity as the reaction consumes one enantiomer of the product (Scheme 1).

The question, however, still remains: Where does the enantioselection occur during kinetic resolution, in the homogeneous phase or on the surface of the catalyst? To learn more about the mode of enantiodifferentiation, we have studied the secondary kinetic resolution of *rac*-dihydroisophorone Pd catalysts with different supports in the presence of proline. We also determined the initial rate of isophorone hydrogenation on these catalysts in order to be able to compare the rates of these two successive reactions. The results are summarized in Fig. 1 and Table 2.

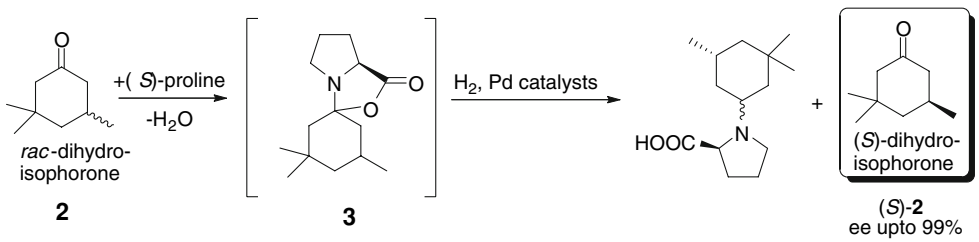
The results show that the kinetic resolution is highly dependent on the catalyst used. It is important noting that $Pd/BaCO_3$ catalyst shows the slowest rates of all three catalysts. The rate of hydrogenation of the proline–dihydroisophorone complex (**3**) appears to be in no direct relationship with the produced enantioselectivity (Fig. 1). Pd/C catalyst was very active (Table 2) in both hydrogenation of the C=C bond of

Table 1 Effect of modifier structure on the asymmetric hydrogenation of isophorone in methanol at room temperature and 10 bar hydrogen pressure (50 mg 5% $Pd/BaCO_3$, 1.0 mmol of modifier, 150 μL (1.0 mmol) isophorone and 5 mL of solvent)

Modifier	Name	Time (h)	Conversion (%)	Product configuration	Ee (%)
	(*S*)-Proline (L)	1.5	92	(*S*)	64
	(*R*)-Proline (D)	1.5	92	(*R*)	62
	*trans*-4-Hydroxy-L-proline	1	100	(*S*)	5
	*Cis*-4-hydroxy-D-proline	1	100	(*R*)	7
	L-Prolinol	1	75	(*S*)	17
	D-Prolinol	1	71	(*R*)	16
	(*S*)-1,2,3,4-Tetrahydro-3-isoquinoline	1	93	(*S*)	10
	L-Thiaproline	1	2	(*S*)	77
	MacMillan's catalyst	1	100	–	0
	MacMillan's catalyst (free base)	1	100	(*S*)	2

The ee values were determined at conversions noted

Scheme 1 Schematic representation of secondary kinetic resolution of *rac*-dihydroisophorone in the presence of proline and Pd catalyst



isophorone and in secondary hydrogenation of dihydroisophorone (Fig. 1(b)). It performed, however, poorly in terms of enantioselectivity. In contrast, $Pd/BaCO_3$ resulted in the best enantioselectivity in both reactions, despite its lower activity. These results provide substantial experimental evidence for the principal role of the catalyst in the enantiodifferentiation process regardless the contribution from the prior proline–substrate complex formation. Such support–metal interaction is known to improve selectivity in other hydrogenations as well [19].

To provide further support we have decided to determine the reaction rates for the hydrogenation of individual

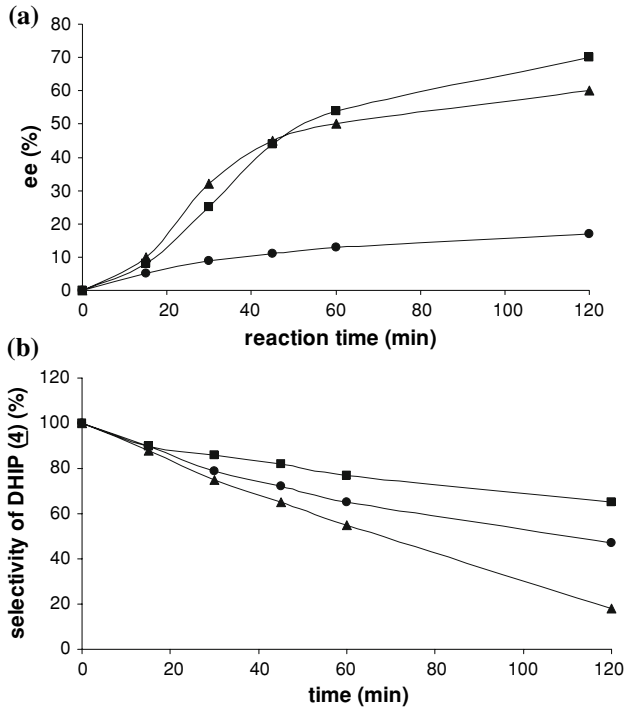


Fig. 1 Effect of reaction time on enantiomeric excess (**a**) and DHIP selectivity (**b**) in the kinetic resolution of *rac*-dihydroisophorone at room temperature in ethanol at 30 bar hydrogen pressure on different Pd catalysts (50 mg catalyst, 114 mg (1.0 mmol) of (*S*)-proline, 150 µL (1.0 mmol) dihydroisophorone, 5 mL of solvent; (*S*)-dihydroisophorone formed in excess in each case: (■—$Pd/BaCO_3$, ▲—Pd/Al_2O_3, ●—Pd/C. (*S*)-dihydroisophorone formed in excess in each case

Table 2 Initial reaction rates of isophorone hydrogenation and kinetic resolution of *rac*-dihydroisophorone on supported Pd catalysts in the presence of proline (50 mg catalyst, 114 mg (1.0 mmol) of (*S*)-proline, 1.0 mmol of isophorone (IP) or dihydroisophorone (DHIP), RT, 30 bar hydrogen pressure, 5 mL EtOH; (*S*)-dihydroisophorone formed in excess in each case

Catalyst	Reaction rate of the 2,3 C=C group hydrogenation in IP (**1**) (TOF in h^{-1})	Reaction rate of *rac*-DHIP kinetic resolution (hydrogenation of **3**) (TOF in h^{-1})
$Pd/BaCO_3$	242.6	54.8
Pd/Al_2O_3	345.2	77.1
Pd/C	363.4	62.3

dihydroisophorone enantiomers on $Pd/BaCO_3$ catalyst in the presence of proline. For this purpose we have synthesized and isolated both enantiomers. Then, the condensation and subsequent hydrogenation of the enantiomers have been studied in the presence of (*S*)-proline. The results are shown in Scheme 2.

The above data show that in the presence of (*S*)-proline, (*R*)-dihydroisophorone undergoes hydrogenation with about four times higher reaction rate than that of the (*S*)-enantiomer under the same experimental conditions. This observation explains what we have observed in the current and earlier hydrogenations. In the presence of (*S*)-proline the catalyst consumes the (*R*)-enantiomer significantly faster than the (*S*)-enantiomer leading to the excellent enantioselectivities observed. Data show that in the homogeneous phase the formation of the (*R*)–(*S*) and (*S*)–(*S*) complexes produces only 7.7% ee for dihydroisophorone in equilibrium [16], therefore the enantiodifferentiation must take place on the catalyst's surface. These results provide a strong experimental proof for the heterogeneous enantiodifferentiation model.

The above detailed results allow us to make some important statements regarding the reaction mechanism. We have provided multiple experimental evidence to support the importance of the heterogeneous enantiodifferentiation model in the proline-induced Pd catalyzed C=C bond hydrogenation reactions.

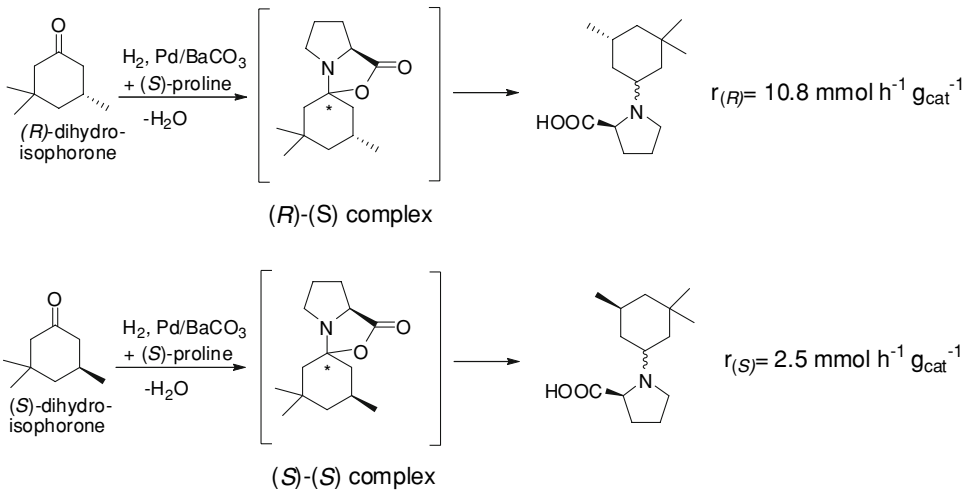
(1). The first important fact (Tables 1, 2) is that the time frame of the catalytic hydrogenation is significantly shorter than that observed in proline–isophorone complex formation in the homogeneous medium [16]. The reaction rate for the complete hydrogenation process (a three step reaction including complex formation between isophorone and proline, hydrogenation and decomposition of the hydrogenated complex) is significantly faster on the surface of catalysts than the complex formation itself under exclusively homogeneous conditions. In one of their early papers on this topic Tungler et al. already pointed out that the complete homogeneous complex formation would require longer times and reflux conditions [12]. This clearly shows that the homogeneous formation of intermediate complex **3** itself is negligible regarding the observed enantioselectivity.

(2). The reaction shows a very significant support effect. Basic supports remarkably enhance the enantioselectivity of the reaction (Table 2, Fig. 1). These catalysts improve proline adsorption on the catalyst's surface and decrease proline concentration in the solution [13, 14, 17]. The lower concentration of proline negatively affects the complex formation in the solution. Despite, the enantioselectivity increases.

(3). The results indicate that the very high enantioselectivities are the result of a secondary kinetic resolution on most catalysts. The reaction rates suggest that the rate-limiting step of the secondary kinetic resolution occurs on the surface of the catalyst and not in the solution.

(4). The reaction rates of the hydrogenation of individual dihydroisophorone enantiomers in the presence of proline are significantly different on $Pd/BaCO_3$ catalysts. It suggests that the reaction leading to enantiodifferentiation occurs on the catalyst's surface.

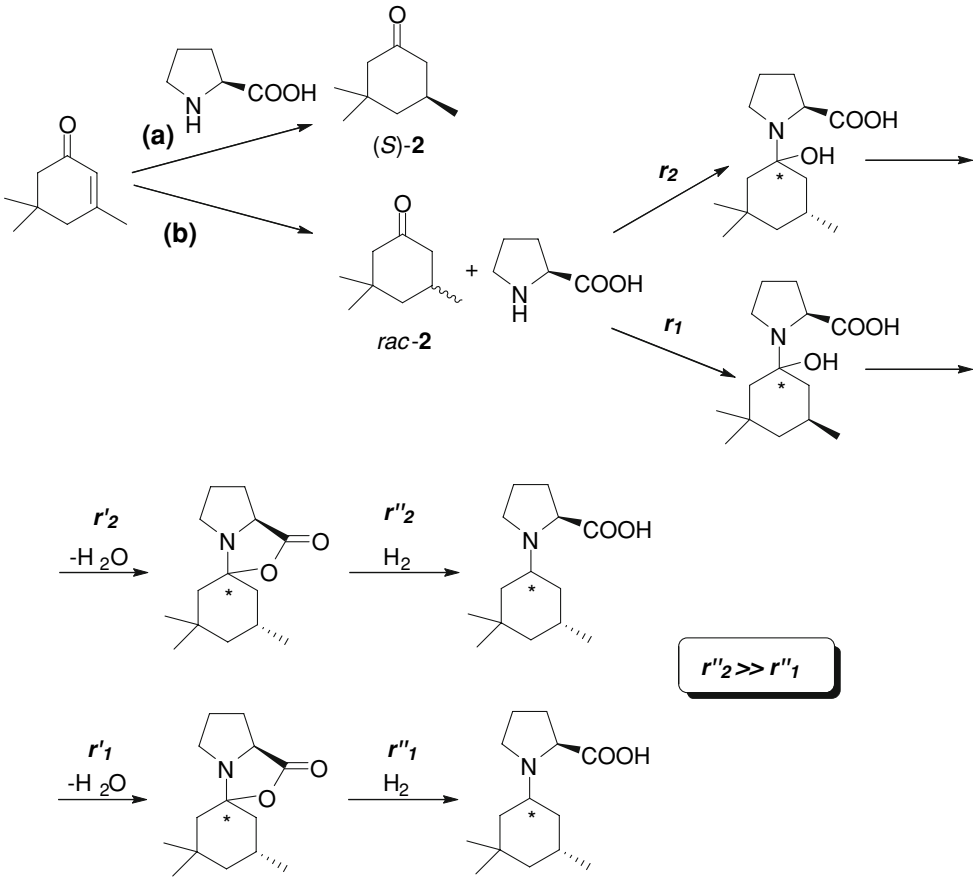
Scheme 2 Effect of substrate stereochemistry on the rate of condensation and subsequent hydrogenation of dihydroisophorone enantiomers on $Pd/BaCO_3$ catalyst in the presence of (*S*)-proline



The above new findings provide significant new information regarding the enantioselection in this reaction. Considering earlier mechanistic explanations [11–14, 16, 17] and incorporating the new information we propose a new cohesive pathway for the reaction that takes into account possibly all available data. A summarized scheme of the unified model is presented in Scheme 3.

The reaction sequence begins with two possibilities. One possibility, the direct asymmetric hydrogenation of isophorone to optically active dihydroisophorone (pathway a) that was proposed more than a decade ago is questionable now. Most recent publications agree on that the first step is the very rapid hydrogenation of isophorone to *rac*.-dihydroisophorone (pathway b), that is followed by a slower, nonetheless, very effective secondary kinetic resolution [14, 16, 17]. The kinetic resolution partially occurs in the solution [16]. It was pointed out that the reaction of *rac*-DHIP with (*S*)-proline at ambient temperature resulted in only 7% ee, hence indicating that r_2 and r_1 are comparable [16]. Experimental evidence [11, 20] and theoretical

Scheme 3 Unified model of the proline-induced asymmetric hydrogenation of isophorone on supported Pd catalyst



calculations [11] suggest that the intermediate is an oxazolidinone as Tungler et al. earlier suggested not an iminium ion or enamine. The formation of these intermediates is unlikely as it would necessitate a 1,3-H shift that usually requires higher temperatures. In the final step the oxazolidinone isomers undergo hydrogenation on the catalyst's surface. The experimental results from the present work indicate that the overall rate of the $(r_1 + r_1^{'} + r_1^{''})$ vs. $(r_2 + r_2^{'} + r_2^{''})$ pathways are significantly different; in fact, the first route takes place with $\sim$ 4 times higher rate. Since $r_1 \approx r_2$ and $r_1^{'} \approx r_2^{'}$ we propose that the overall difference is based on the significantly different rates of hydrogenation. Therefore mainly the surface reaction is responsible for the enantiodifferentiation. Consequently this reaction will consume the (*R*)-**2** enantiomer from the racemic mixture significantly faster, and will ensure the high ee for (*S*)-**2** in the reaction mixture.

4 Conclusions

In the present study we have provided further experimental evidence to support the heterogeneous enantiodifferentiation model in the proline modified Pd catalyzed C=C double bond hydrogenation of α, β-unsaturated ketones. Using the enantioselective hydrogenation of isophorone as a test reaction we have shown that several experimental factors, such as modifier structure, and chemical nature of the catalyst support affect the outcome of the hydrogenations. Our results point out that the secondary kinetic resolution is a major reason for obtaining high enantioselectivities on most catalysts. The data also indicate that in the case of effective modifier–catalyst interaction the heterogeneous enantiodifferentiation model is primarily responsible for the high enantioselectivities. We have proposed a new unified enantioselection model by integrating our results into the currently existing incoherent mechanistic schemes.

Acknowledgments Financial support provided by the ACS-Petroleum Research Fund, University of Massachusetts Boston and Michigan Technological University is highly appreciated.

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15. One of the reviewers raised concerns regarding our statement that our group suggested (published) first the paramount importance of kinetic resolution in this reaction. To support our statement, here, we list the relevant publication data: Mhadgut et al. (2006) J Catal (see [14] above): submitted: October 25, 2005; accepted: January 05, 2006; published: February 07, 2006 (online) March 10, 2006 (hardcopy). McIntosh et al. (2006) J Am Chem Soc (see

[16] below): submitted February 15, 2006; accepted: date is not available; published: May 12, 2006 (online) June 07, 2006 (hardcopy)
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