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Asymmetric hydrogenation of isophorone in the presence of (*S*)-proline: Revival of a 20 years old reaction

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This paper be dedicated to the memory of a colleague, Tibor Tarnai (41), who died in summer 2007 in a car accident leaving behind a family with two children.

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ABSTRACT

The asymmetric hydrogenation of isophorone in the presence of (*S*)-proline was reinvestigated in the light of recent papers of Torok et al. and Lambert et al. Beside kinetic resolution of trimethyl cyclohexanone with (*S*)-proline, the chemo- and diastereoselective hydrogenation of isophorone is the source of optically active trimethyl cyclohexanone, which was proved by reaction rate, GC, GC–MS measurements and preparative experiments.

1. Introduction

The first report on the asymmetric hydrogenation of isophorone was published in this journal 18 years ago after presenting it at two catalysis conferences [1–3]. The Pd/C catalyzed hydrogenation of different α,β-unsaturated ketones, in the presence of (*S*)-proline, in methanolic solution was tested, among others that of isophorone (Scheme 1).

Isophorone (3,5,5-trimethyl cyclohex-2-enone) was the only substrate which afforded significant *ee* (60% at 55% chemical yield of trimethyl cyclohexanone) in this reaction [4].

Continuation of this work was the asymmetric hydrogenation of acetophenone [5,6], diastereoselective reductive alkylation of (*S*)-proline with ethyl pyruvate [7,8], asymmetric hydrogenation of benzylidene benzosuberone [9], synthesis of chiral modifiers based on (*S*)-proline and their use in the enantioselective hydrogenation of isophorone [10–14].

In the hydrogenation of acetophenone with Pd, stoichiometric (*S*)-proline and methanol as solvent, the enantiomeric excess of 1-phenyl ethanol was around 20% [5,6]. The reaction with ethyl pyruvate afforded only alkylated proline with high diastereoselectivity [7,8].

Detailed circular dichroism, NMR and IR spectroscopy measurements, preparative experiments resulted in the conclusion that the asymmetric hydrogenation of isophorone can proceed according to Scheme 2.

The probability of the oxazolidinone type intermediate was verified on the basis of the work of Joucla and Mortier [15].

The optical purity of trimethyl cyclohexanone (TMCH) depended on the catalytic metal, Pd and Rh gave higher *ee*, but with Pt only alkylated proline was formed. The rate of reductive alkylation vs. C═C saturation determines not only chemoselectivity but the optical purity of the product as well.

According to molecular modelling calculations the lower energy conformer of the oxazolidinone can turn with its pro*S* side towards the catalyst surface, which agreed with the absolute configuration (*S*) of the product TMCH.

The special stereoguiding power of the proline molecule initiated further work, the synthesis of different proline esters and amides and their use in enantioselective hydrogenations as chiral modifiers (Scheme 3) [11].

The *ee* values in the hydrogenation of isophorone were moderate with these compounds (5–25%). In an other attempt arylated derivatives of proline were synthesized and applied in

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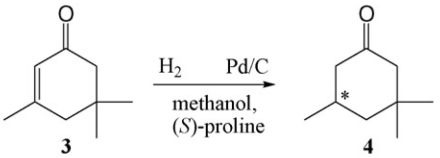


Scheme 1. Asymmetric hydrogenation of isophorone in the presence of (*S*)-proline.

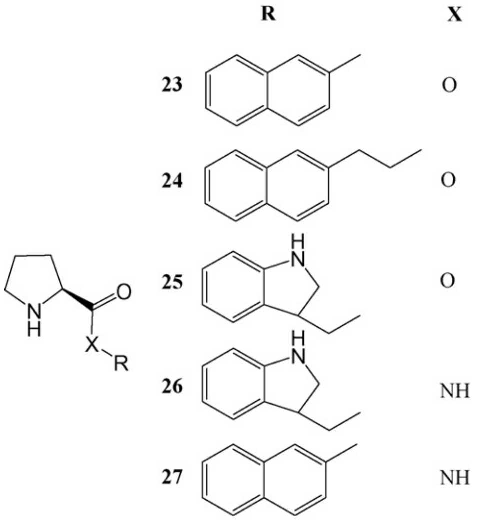
hydrogenations (Scheme 4) [10–14,16], the highest *ee* was 41,5% in isophorone hydrogenation with Pd black in methanol–water mixture with DPPM.

Recently an optically pure alkylated proline derivative has been prepared. The hypothesis was the utilization of the so-called ''own-derivative'' effect, known from optical resolution, in catalytic hydrogenation of isophorone, where the proline derivative, the naphtylethylester of *N*-trimethylcyclohexyl proline may act as chiral modifier (Scheme 5). The preparation of the enantiopure trimethylcyclohexyl proline was the most difficult task.

Four years ago Török and his coworkers [17] ''took out of the cupboard'' the Pd mediated asymmetric hydrogenation of isophorone with (*S*)-proline chiral auxiliary. They interpreted the role of proline as it would be a chiral modifier, not a reactant. An added compound, like proline is called chiral auxiliary, if it is used in stoichiometric ratio with respect to the hydrogenated substrate, isophorone. This is not only the matter of definition, but the mode of action. A modifier changes the catalyst surface even in small concentration, an auxiliary is applied in stoichiometric ratio and usually takes part in the reaction, acts in solution also with changing the intermediates, the reaction route. In this paper the thorough analysis of the reaction mixture missed, the formation of the byproduct that of the trimethylcyclohexyl proline was neglected.

Two years later, practically simultaneously (in the moment of the publication of the paper of Török and his coworkers [18] the manuscript of Lambert et al. [19] was already at the editor of JACS) the two research groups described the kinetic resolution of TMCH, as the main source of optically active TMCH in the hydrogenation of isophorone.

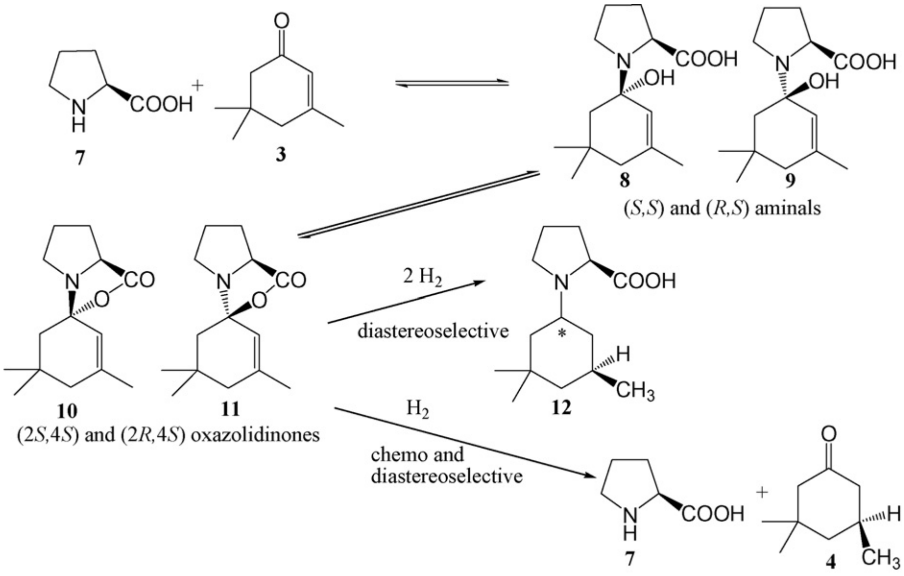
In their paper Török and his coworkers [18] introduced another mechanism for isophorone/proline hydrogenation on different Pd catalysts. The participation of kinetic resolution in the formation of optically active TMCH was stressed, but their catalyst was on a basic support, adsorbing proline more strongly, which influenced the optical and chemical yields. They emphasized the role of the catalyst surface in kinetic resolution, contradicting Lambert, who said that enantiodifferentiation takes place only in solution. Török et al. described that the diastereomeric condensates of proline and TMCH were hydrogenated with different rates affording the remaining optically active TMCH.



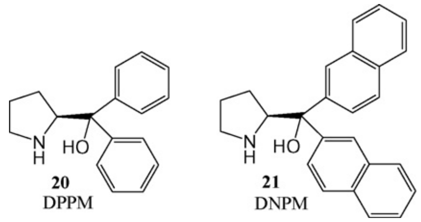
Scheme 3. (*S*)-Proline-based chiral modifiers.

Lambert and coworkers tested the isophorone hydrogenation extensively [19], they tried to verify by spectroscopic and kinetic measurements that optically active TMCH was formed solely in the kinetic resolution of this compound, namely with reductive alkylation of (*S*)-proline.

In spite that their basic conclusion about the existence of kinetic resolution is right, some other conclusions are not completely supported by experimental data and they leave also some important facts out of consideration:



Scheme 2. Intermediates of the asymmetric hydrogenation of isophorone.



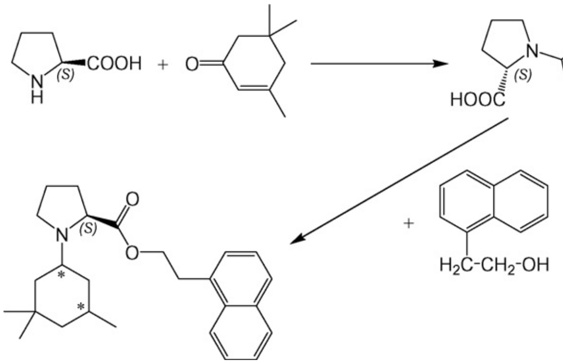
Scheme 4. Arylated proline derivatives as chiral modifiers for enantioselective hydrogenations.

(1) They prefer the formation of enamines instead of oxazolidinone, the enamine formation involves the H shift, which requires usually higher reaction temperature.
(2) They claim that the source of the optically active TMCH is exclusively the homogeneous reaction between proline and TMCH. However the optical and chemical yield of the remaining TMCH depends on different hydrogenation rates of two diastereomeric condensates.
(3) During standing of reaction mixture the amount of isophorone decreases in the solution, not only in consequence of the condensation reaction with proline, but due to the formation of polymeric products as well. This is accompanied by developing of dark reddish colour of the solution within 12–24 h.

In the following paper [20], Lambert and coworkers tried to follow the adsorption of isophorone, (*S*)-proline and TMCH on metal surfaces in order to prove their view about the formation of optically active TMCH and negate the theory of Török et al., about the role of proline as chiral modifier. As they applied electrochemical detection of surface coverage, the tested metal had to be Pt. The acquired results were extrapolated to Pd which was impermissible as these two metals behave in this hydrogenation completely different. Hydrogenating isophorone–proline mixture on Pt, alkylated proline was the major product even at small conversions.

Li and coworkers [21] agreed on that only kinetic resolution gave optically active TMCH, but they did it on the basis of relatively few experiments, which were not carried out among optimized conditions, for example with less than one mole proline with respect to isophorone. Moreover the authors used Pd catalysts on supports with basic additives, which underwent leaching, their Pd content decreased after repeated use.

All these papers inspired us to reinvestigate the hydrogenation of isophorone and that of TMCH also, in the presence of (*S*)-proline, to find out in what we were wrong and in what in right 20 years ago.



Scheme 5. Synthesis of *N*-trimethylcyclohexyl proline naphtylethylester.

2. Experimental

2.1. Materials

A Pd/C catalyst was Selcat Q, 10% metal content, purchased from Fine Chemical Comp. (*S*)-Proline and isophorone were supplied by Sigma–Aldrich. The latter was distilled in vacuum before use. TMCH was prepared in our laboratory, hydrogenating isophorone without solvent, with Pd/C catalyst at ambient temperature and 10 bar hydrogen pressure.

2.2. Hydrogenation

The hydrogenations were carried out at 25 °C and under 5–15 bar hydrogen pressure in a stainless steel autoclave (Technoclave). Before hydrogenation reaction mixtures were stirred under nitrogen for 10 min in the reaction vessel.

2.3. Analysis

Reaction mixtures were analysed with a gas chromatograph equipped with a cyclodextrine capillary column (analysis temperature: dihydroisophorone at 110 °C) and FID. Chromatograms were recorded and peak area was calculated with Chromatography Station for Windows V1.6 (DataApex Ltd., Prague). Enantiomeric excess was defined as

$$ee(\%) = \frac{[R]-[S]}{[R]+[S]} \times 100$$

GC–MS measurements were made on a Finnigan MAT GCQ equipment attached to a Finnigan MAT Automass detector. Acquisition and evaluation of data was done with Lucy v3.10 software.

3. Results and discussion

Rate change of the hydrogenations at 1 mol equivalent hydrogen consumption without premixing and at 0.3–0.5 mol with increasing premixing time is an important argument of Lambert et al. in favour of the kinetic resolution as the sole source of optically active TMCH. According to their view stereodifferentiation occurs only in homogeneous, liquid-phase reactions, catalyst surface is not involved. Neither in the hydrogenation of isophorone, nor that of TMCH with (*S*)-proline there was no breakpoint on the hydrogen consumption curves in our experiments (Fig. 1), they are zero order reactions with respect to the substrate.

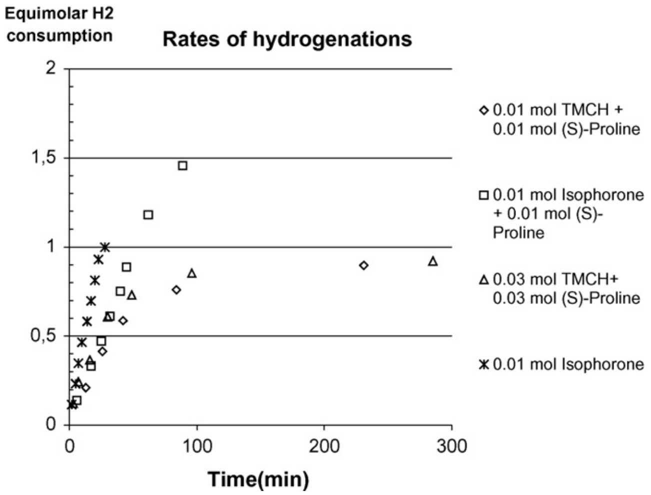


Fig. 1. Hydrogenation curves of isophorone and TMCH in the presence of (*S*)-proline.

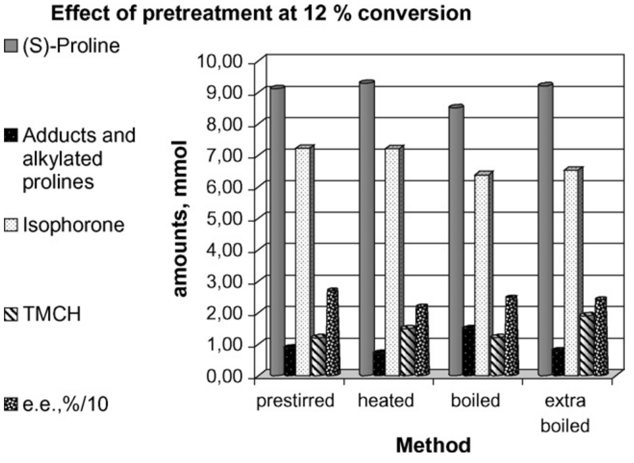


Fig. 2. Composition of the reaction mixtures and the *ee* after 12% conversion, applying different pretreatment methods in isophorone hydrogenation.

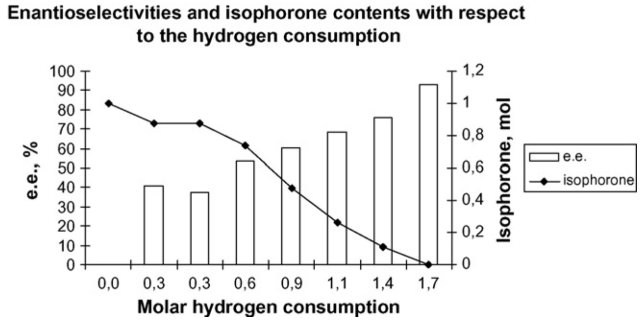


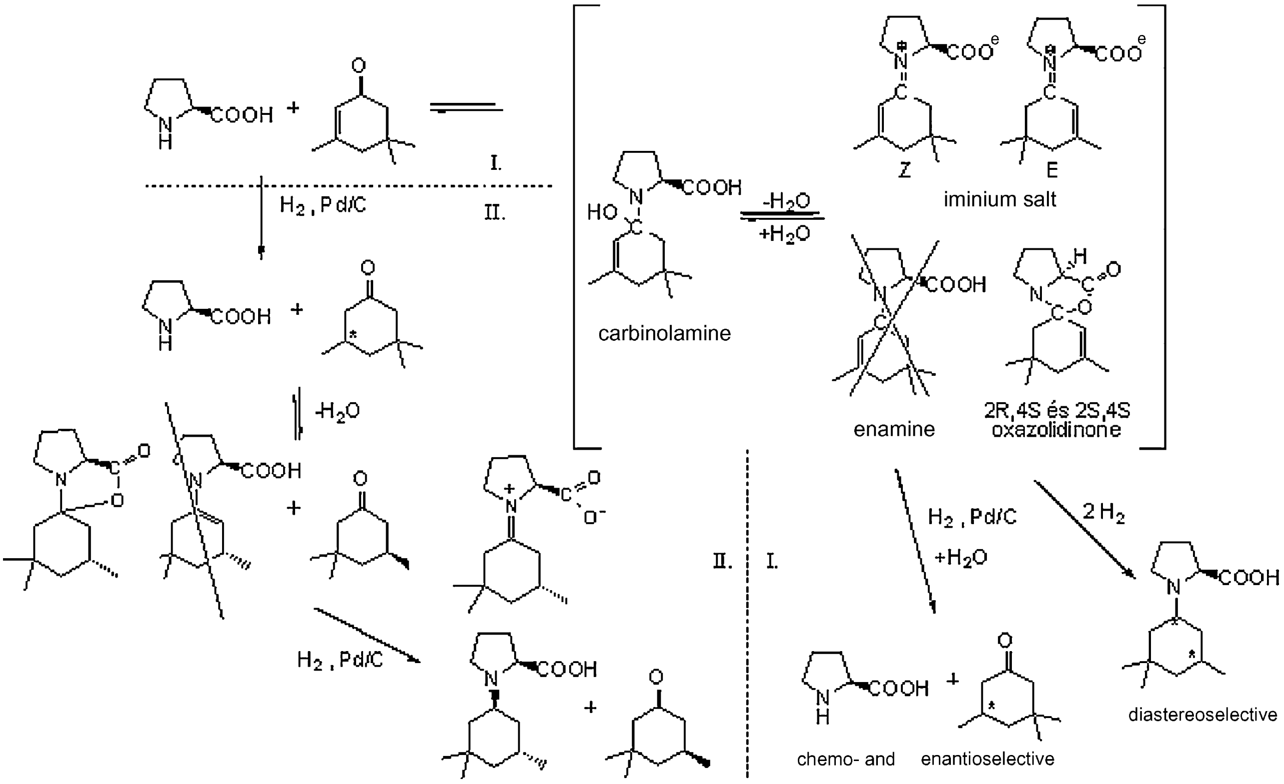
Fig. 3. Hydrogenation of isophorone-proline mixture, *ee* and isophorone amount with increasing hydrogen consumption.

The fast racemic hydrogenation of isophorone to TMCH could be observed only in the absence of proline.

The reason of the rate change experienced by Lambert et al. can be the “aging” of the isophorone–proline solution. Mixing isophorone with equimolar proline in methanolic solution for longer time, 24–48 h, the solution becomes dark purple colour, the isophorone content, detectable with GC, decreases, polymeric products form. So it is understandable that the *ee* and the rate in the hydrogenation of such mixtures are less and less with longer premixing time. The other hand the long premixing is beneficial for TMCH-proline hydrogenation, it is necessary for the formation of the condensated product.

Different pretreatment methods were tested in order to evaluate their effect (prestirred: 5 min stirring on room temperature, heated: 5 min stirring at 50 °C, boiled: 5 min boiling at 65 °C, extra boiling: 30 min boiling at 65 °C). The results are in Fig. 2; the differences are not significant. It seems that the equilibrium is attainable rather fast, which is in accordance with our original experiences obtained by CD spectroscopy [2,3].

Besides admitting the existence of kinetic resolution of TMCH, however insisting on the “old” mechanism as well, namely on the formation of optically active TMCH directly from isophorone, our main goal was to find supporting facts and arguments. Repeating the hydrogenation of equilibrated isophorone–proline 1:1 mixture several times, taking samples at different hydrogen consumptions, the results are unambiguous. (Fig. 3). (Reaction conditions: 10 ml methanol, 50 mg 10% Pd/C catalyst, 0.01 mol isophorone, 0.01 mol (*S*)-proline.) The most important experience is, what contradicts to conclusions of Lambert et al.: at small conversions, before the consumption of 1 mol hydrogen, optically active TMCH is formed with significant *ee*. The hydrogenation is not racemic up to one mol hydrogen consumption, the isophorone–proline condensate is not a “spectator molecule”, but takes part in the hydrogenation giving



Scheme 6. Reaction scheme of the hydrogenation of isophorone and (*S*)-proline.

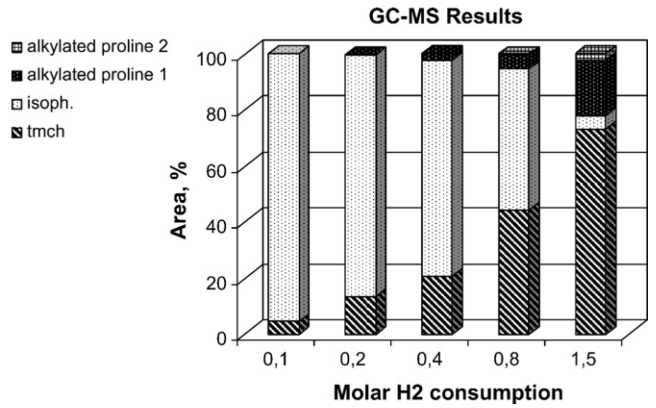


Fig. 4. Composition of the reaction mixture vs. hydrogen consumption.

optically active TMCH. At the same time the *ee* of TMCH increases, which refers to the kinetic resolution of the saturated ketone.

These findings together with the observation of Torok and Lambert about kinetic resolution of TMCH permitted that the reaction scheme of the asymmetric hydrogenation of isophorone in the presence of (*S*)-proline has been completed (Scheme 6). The optically active TMCH can be formed on two routes, by the chemo- and enantioselective hydrogenation of the oxazolidinone intermediate of isophorone and by the kinetic resolution of the racemic TMCH.

There is another debated point about the enantiodifferentiating step, whether it takes place on catalyst surface (Torok, Tungler) or in solution as a homogeneous reaction (Lambert). Lambert and coworkers [19] claim that (*S*)-proline reacts exclusively with (*R*)-TMCH. According to GC–MS results (Fig. 4) both diastereomeric alkylated proline were detected after 1 mol hydrogen consumption. This means that both diastereomeric condensation product of TMCH and (*S*)-proline are present in the reaction mixture, obviously in different concentrations. Beside the discriminating role of the proline in the condensated product formation, the rates of reductive alkylation of the two diastereomers differ also (Fig. 6) the catalyst has a discriminating role. Proved conclusion is that kinetic resolution of TMCH occurs. This process enhances the optical purity of TMCH but decreases its chemical yield.

The following question arises obviously: why did we pass by this phenomenon 20 years ago? Looking through our old protocols, there were experiments, where the reductive alkylation of (*S*)-proline with TMCH was investigated, but no hydrogen consumption was observed. Two reasons could be recognized retroactively: the reactions were carried out on atmospheric pressure, the hydrogenation was too slow, the other: no long premixing of the ketone-proline mixture was used, the condensate formation was negligible.

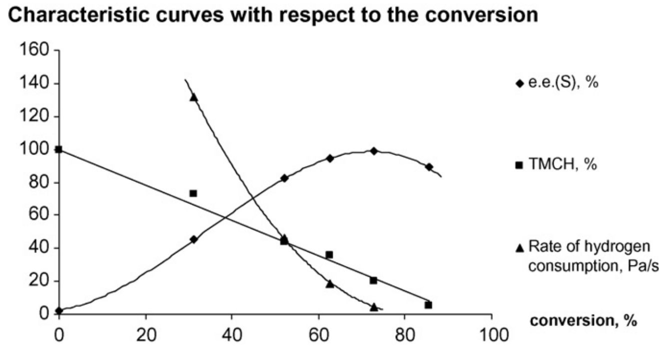


Fig. 5. Rate, *ee* and TMCH concentration with conversion in TMCH–proline hydrogenation.

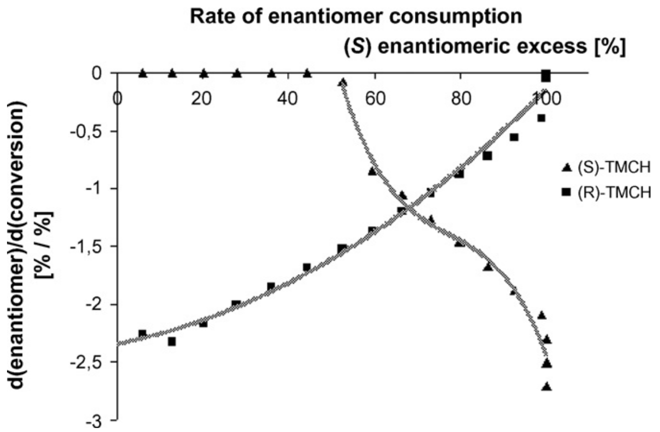


Fig. 6. Conversion rates of the two diastereomeric condensates of TMCH and (*S*)-proline.

In order to revise our old mistake, the reductive alkylation of (*S*)-proline with TMCH was tested also. Reaction rate and *ee* was detected with conversion (Fig. 5).

Reaction conditions were: 0.03 mol TMCH, 0.03 mol (*S*)-proline, 0.1 g 10% Pd/C, 50 ml MeOH, 9 bar, 25 °C, premixing: 45 h. Calculating the individual hydrogenation rate of the two diastereomeric condensate, data in the function of *ee* of remaining TMCH are presented in Fig. 6.

Up to ~50% *ee* only the (*R*)-TMCH, but after that the other enantiomer is consumed also. These data prove that the (*S*)-TMCH containing condensate is hydrogenated with measurable rate also. The catalyst discriminates between the two compounds both being present in the reaction mixture.

Finally the resolution of TMCH with (*S*)-proline in solution was tested, TMCH and (*S*)-proline were measured together in different molar ratio and dissolved in methanol, stirred at least for 24 h, finally analyzed with chiral GC, where the condensated compounds could not be detected, only TMCH enantiomers. The *ee* according to this method was between 7–10%. Calculating an approximate material balance for all reactants, both enantiomers of TMCH form condensate with (*S*)-proline, but in different ratio. The *ee* of hydrogenation (40–100%) is much higher than the *ee* of resolution. This means that catalyst surface has to be instrumental in stereodifferentiation.

4. Conclusion

In Pd/C mediated hydrogenation of isophorone in presence of stoichiometric amount of (*S*)-proline even at small conversions (0.12–0.2 mol hydrogen consumption), optically active TMCH is formed in significant amount, this is due to the asymmetric hydrogenation of isophorone, not to kinetic resolution of the saturated ketone only.

With increasing hydrogen consumption increases the amount of condensated product and optical purity of (*S*)-TMCH. This is the consequence of kinetic resolution.

At high conversions a mixture of the two alkylated proline products could be obtained which shows that (*S*)-proline reacts with (*S*)-TMCH also.

Resolution of TMCH by (*S*)-proline takes place, but this is not the only process resulting in optically active TMCH. There is a significant difference in the excess of (*S*)-TMCH if we start the reaction with isophorone comparing to that with racemic TMCH. Catalyst surface is involved in asymmetric induction as well.

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