Reductive transamination of methoxyacetone with benzylamine over Pd/SiO$_2$ catalyst modified with anchored chiral compounds

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Methoxyacetone was transaminated with benzylamine to methoxyisopropylamine over a Pd/SiO$_2$ catalyst modified with L-alaninol or L-phenylalaninol covalently anchored to the surface of the support via an organo-silicon spacer group. In the first step of transamination a Schiff base was formed from the ketone and benzylamine, and then it was hydrogenated in the second step on the chirally modified Pd/SiO$_2$ catalysts to an asymmetric secondary amine (N-benzyl-methoxyisopropylamine). In the third step the hydrogenolysis of the asymmetric secondary amine resulting in methoxyisopropylamine and toluene was carried out over a 10 wt% Pd/C catalyst. The highest enantiomeric excess of (S)-methoxyisopropylamine was observed in cyclohexane (ee $= -20$–21%) using anchored L-alaninol as a chiral modifier.

Keywords: enantioselective amination, reductive transamination, enantioselective hydrogenation, Schiff base, methoxyisopropylamine, chiral modifiers, methoxyacetone, palladium catalysts

1. Introduction

Optically active primary amines including alkoxyalkylamines have gained great importance in agrochemical and pharmaceutical industries. Asymmetric primary amines are either prepared by resolution of racemic amines or synthesized by using chiral auxiliary groups, chiral reagents, chiral homogeneous catalysts [1]. However, little is known about the preparation of asymmetric amines from prochiral substrates over heterogeneous catalysts [2].

Based on literature survey and theoretical considerations ketones appeared to be promising precursors for the heterogeneous catalytic enantioselective synthesis of primary amines via their reductive transamination with an aralkylamine. In this reductive transamination the key reaction step is the enantioselective hydrogenation of the C=N double bond of the imine formed by the condensation reaction of the ketone with a transaminating agent.

In this study, methoxyacetone (MEOAC) was transaminated with benzylamine (BzNH$_2$) over silica-supported palladium catalysts modified with L-alaninol (ALOL) (2-amino-1-propanol), or L-phenylalaninol (PhALOL) (3-phenyl-2-amino-1-propanol) *anchored* onto the silica surface via an organo-silicon spacer group. As seen in scheme 1, in the first step (1) of transamination, Schiff base (secondary imine = N-(methoxy-2-propylidene)benzylamine) was formed form the ketone and benzylamine, and then it was hydrogenated in the second step (2) to N-benzyl-methoxyisopropylamine (BMEOIPA) secondary amine on the chirally modified Pd/SiO$_2$ catalyst. In the third step (3) of the transamination, the hydrogenolysis of the secondary amine resulting in methoxyisopropylamine (MEOIPA) and toluene was carried out over a 10 wt% Pd/C catalyst. In this work, the influence of two chiral modifiers and different solvents, i.e., cyclohexane (CH), tetrahydrofuran (THF), and dioxane (DIOX) on the enantioselectivity of methoxyisopropylamine was studied. According to our preliminary experiments the Pd/SiO$_2$ catalyst modified with *adsorbed* chiral compounds was not effective in the enantioselective transamination of MEOAC. Thus, for comparison results obtained on a 5 wt% Pd/C catalyst modified with adsorbed L-alaninol are also included.

2. Experimental

2.1. Catalysts

Carbon-supported palladium catalysts with 5 and 10 wt% metal contents, Selcat SQ3 and Selcat SQ6, respectively, both powdered and prereduced were obtained from Chinoin. The unit surface area of the carbon support of Selcat catalysts was $S_{\mathrm{BET}} = 1000$ m^2/g, and the dispersion of palladium measured by CO chemisorption was around 50% [3]. Prior to the activity test, 0.4 g of Pd/C catalyst was pretreated in nitrogen at 150 °C for 1 h followed by treatment in a hydrogen atmosphere at 200 °C for 2 h. The catalyst was then cooled to room temperature under hydrogen flow.

The silica-supported palladium catalyst with 1.7 wt% metal content was prepared by ion exchange using [Pd(NH$_3$)$_4$]Cl$_2$ as a precursor compound and a commercial silica support (Ventron, unit surface area $S_{\mathrm{BET}} = 285$ m^2/g, pore volume $V_{\mathrm{P}} = 1.06$ cm^3/g, pore diameter $d_{\mathrm{P}} > 10$ nm).

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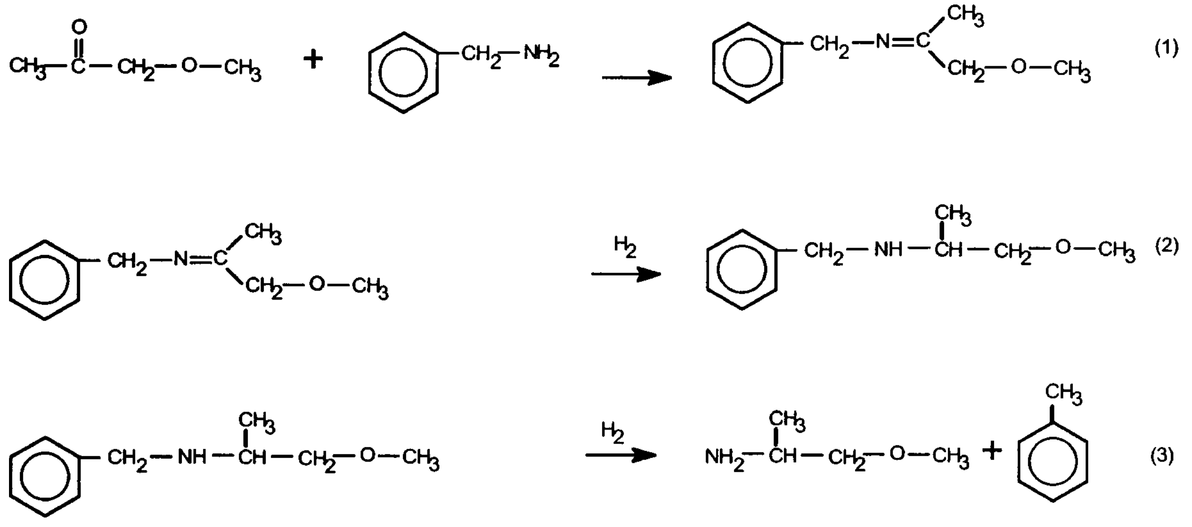
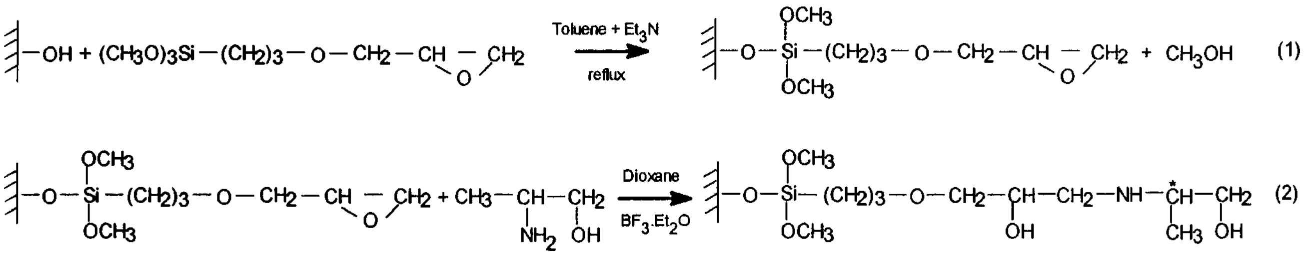


Scheme 1. Reductive transamination of methoxyacetone with benzylamine to methoxyisopropylamine.



Scheme 2.

The silica support dried in air at 150 °C for 24 h was ion exchanged with a solution of the palladium compound (2.5 g Pd/l solution, 30 ml solution/g catalyst). After 24 h of ion exchange, the catalyst was washed with diluted NH_4OH, filtered and dried at 105 °C for 24 h. The dried catalyst was reduced in flowing hydrogen at 100 and 200 °C for 1 and 2 h, respectively. The dispersion of palladium on the silica support measured by CO chemisorption was 23% [3]. The above Pd content and dispersion value accounts for 5.2×10^{13} metal particle/m^2 silica support.

The 5 wt% Pd/C catalyst (0.5 g) was modified by incipient wetness impregnation (IWI) with 6.4 mmol L-alaninol or 1.1 mmol L-phenylalaninol dissolved in the solvent used [4]. However, this modification technique was not successful in the case of Pd/SiO_2, due probably to the relatively low adsorption capacity of the silica support.

2.2. Chiral modification of silica-supported palladium catalyst

The surface chemistry involved in the catalyst modification is shown in scheme 2. Prior to modification, 5 g of the prereduced Pd/SiO_2 catalyst was treated in H_2 at 200 °C for 2 h and cooled in hydrogen flow to RT and then purged with argon for 30 min. The support of the Pd/SiO_2 catalyst was functionalized with epoxy groups using the reactivity of surface hydroxyls towards (3-glycidyloxypropyl)-trimethoxysilane [5]. Prior to the functionalization the surface of Pd was covered by CO in order to avoid the adsorption of the (3-glycidyloxypropyl)-trimethoxysilane onto the palladium surface. A similar approach, i.e., the protection of the Group VIII metal from the adsorption of organo-silicon compound by CO preadsorption has been applied earlier [6].

The anchoring reaction was carried out in dry toluene at reflux temperature for 3 h. Then the epoxy–Pd/SiO_2 was reacted with L-alaninol or L-phenylalaninol in dioxane in the presence of boron trifluoride etherate at reflux temperature for 5 h [5]. After washing with dioxane the modified catalyst was dried by evacuation at 50 °C. Prior to activity test the chirally modified Pd/SiO_2 catalysts were pretreated in hydrogen at 180 °C for 2 h.

The amount of modifier anchored to the support was determined from the nitrogen content of the catalysts. The amount of chiral entities in the modified catalysts was 0.6 mmol/g catalyst, which corresponded to 0.21 entity/nm^2. Despite what is considered a relatively low surface coverage, a ratio of 2.7 chiral moieties to surface palladium is achieved. Taking into account the average size of Pd crystallites (ca. 5 nm), the ratio of anchored chiral entities to the number of palladium particles is about 4000. The anchored surface species, i.e., the Si–C bond of the organo-silicon moiety, appeared to be thermally stable. In hydrogen atmosphere the threshold temperature of its decomposition was 190 °C [7].

2.3. Catalytic reaction

Methoxyacetone was prepared from methoxyisopropanol and Na_2CrO_4 using the method developed by Mariella and Leech [8]. Catalytic activity tests were carried out in a stainless-steel stirred autoclave ($V = 300$ ml) under the conditions: $V_{\text{liquid}} = 100$ ml, $V_{\text{solvent}} = 80$ ml, $P_{\text{hydrogen}} = 60$ bar, amount of MEOAC and benzylamine $=$ 0.1–0.1 mol, molar ratio of ketone/Pd $= 500$.

The chemical analysis of the reaction products was carried out by GC using a glass column filled with 5 wt% KOH + 18 wt% Carbowax 2000 on 60/80 mesh Chromosorb PNAW. The two enantiomers of MEOIPA were separated after derivatization with trifluoroacetic anhydride by GC using a capillary column coated with Chirasil Dex CB and purchased from Chrompack. In preliminary experiments, the enantioselectivity of the formed secondary amine (BMEOIPA) was also determined using the above described derivatization technique. It has been found that within the experimental error the ee value of secondary amine has been maintained in the hydrogenolysis step. For this reason in this work we report only the ee values of MEOIPA.

2.4. Computer modelling

Molecular modelling and different approaches of computational chemistry were used to calculate the conformation of the substrate and modifier molecules and their interaction. The Molecular Simulation Discover program was used for the geometry optimization of the substrate–modifier interaction and the Solid State Catalysis program was applied to model the interaction of the substrate–anchored modifier complex with the palladium(111) surface.

Abbreviations	
EA and EPhA	L-alaninol and L-phenylalaninol anchored to silica via epoxy spacer group, respectively
ALOL	L-alaninol introduced by IWI technique onto the surface of 5 wt% Pd/C catalyst
PhALOL	L-phenylalaninol introduced by IWI technique onto the surface of 5 wt% Pd/C catalyst
t_{21} and t_{22}	reaction time of hydrogenation of imine (Schiff base) at 25 and 120 °C, respectively
t_3	reaction time of the hydrogenolysis of BMEOIPA to MEOIPA
T_{21} and T_{22}	temperature of the hydrogenation of imine at 25 and 120 °C, respectively
T_3	temperature of the hydrogenolysis of BMEOIPA to MEOIPA
C_{21} and C_{22}	conversion of MEOAC in the hydrogenation step at 25 and 120 °C, respectively
C_3	conversion of BMEOIPA to MEOIPA in the hydrogenolysis step
Y_{21} and Y_{22}	yield of BMEOIPA in the hydrogenation of imine at 25 and 120 °C, respectively
Y_3	yield of MEOIPA in the hydrogenolysis step
ee	enantiomeric excess, ee (%) $= [(\text{R})-(\text{S})]/[(\text{R})+(\text{S})] \times 100$

3. Results and discussion

3.1. Transamination of methoxyacetone on modified Pd/SiO$_2$ catalyst

Preliminary results, i.e., the effect of the modifier and the solvent on the transamination of MEOAC with $BzNH_2$ on the Pd/SiO_2 catalyst modified by the anchoring technique and details on the reaction conditions are given in table 1. For comparison results obtained on the 5 wt% Pd/C catalyst (SQ3) in cyclohexane, THF and dioxane are also included in table 1 [4].

It is generally known that the temperature of the enantioselective hydrogenation can strongly influence the enantioselectivity, i.e., the lower the reaction temperature, the higher the enantioselectivity. For this reason the hydrogenation of imine (Schiff base) on the chirally modified silica-supported palladium was carried out either in one step at 25 °C for 20–33 h or in two steps at 25 and 120 °C for 18–33 and 4 h, respectively. In the hydrogenation step of the transamination the reaction product is the secondary amine (BMEOIPA), however, both unconverted Schiff base and methoxyacetone can also be detected in the reaction mixture. The literature states [9] only carbon-supported catalysts are active in the hydrogenolysis of the C–N bond of secondary alkyl benzylamines. This is held for the modified Pd/SiO_2 except in the case noted in table 1, footnote c. Therefore, the third step of the transamination, i.e., the hydrogenolytic cleavage of the C–N group of the secondary amine (see scheme 1) was performed on a 10 wt% Pd/C catalyst (SQ6) at 180 °C for 3 h. In this step methoxyisopropylamine and toluene are the reaction products.

The Pd/SiO_2 catalysts modified with a chiral modifier anchored to the silica support via an organo-silicon spacer group showed lower activity in the hydrogenation of imine than the carbon-supported ones modified with adsorbed chiral modifiers [4]. The extremely low activity at 25 °C can probably be attributed to both the relatively low dispersion of palladium (23%) and the presence of chemisorbed CO. The final pretreatment of the catalyst prior to the catalytic reaction was done at 180 °C in order to prevent the thermal decomposition of the anchored surface species. It is known that the full desorption of chemisorbed CO from supported palladium requires temperatures higher than 200 °C. Because of the partial poisoning of the palladium by CO, an increase of the reaction temperature to 100–120 °C was required to achieve sufficient hydrogenation activity. The moderate activity observed at 120 °C can also be related to the partial poisoning of the metal by the chiral modifier. Despite the moderate activity, both catalysts modified with anchored chiral modifier showed significant enantiodifferentiation ability.

As emerges from data given in table 1, L-alaninol covalently bound via an organo-silicon spacer group onto the

Table 1
Transamination of methoxyacetone with benzylamine on Pd/SiO_2 catalyst modified with anchored chiral compounds. Two-step hydrogenation (21 and 22) of the imine to secondary amine at 25 and 120 °C.[a]

Solvent	Modifier	t_{21} (h)	Conversion of MEOAC (%) C_{21}	Conversion of MEOAC (%) C_{22}	Yield of BMEOIPA (%) Y_{21}	Yield of BMEOIPA (%) Y_{22}	ee (%)
CH	EPhA	23	96	96	13	88	−13.8
CH[b]	EPhA	24	97	98	38	98	−15.0
CH	EA	33	96	–	64	–	−20.4
CH[c]	EA	33	96	–	64	–	−20.1
THF	EA	33	90	100	29	100	−14.7
THF	EA	20	81	–	8	–	−17.8
THF[b]	EA	20	95	100	13	100	−16.3
DIOX	EA	18	91	99	20	98	−12.1
CH[d]	ALOL	24	98	–	93	–	−17.4
THF[d]	ALOL	24	100	–	98	–	−13.0
DIOX[d]	ALOL	24	100	–	100	–	−17.8
CH[d]	PhALOL	24	77	–	33	–	−12.7

[a] $T_{21} = 25\,°C$, $T_{22} = 120\,°C$, $t_{22} = 4$ h, $T_3 = 180\,°C$, $t_3 = 3$ h, $C_3 = 100\%$, $Y_3 = 100\%$.

[b] Prior to the first hydrogenation step, methoxyacetone was reacted with benzylamine at 25 °C to form Schiff base with 65% conversion ($BzNH_2$/MEOAC molar ratio = 1).

[c] Hydrogenolysis of the secondary amine was exceptionally performed over the modified Pd/SiO_2 catalyst with $C_3 = 18\%$ conversion.

[d] Both the hydrogenation of the Schiff base and the hydrogenolysis of the secondary amine formed was carried out on 5 wt% Pd/C catalyst; $t_3 = 6$ h.

surface of silica exerted a significant chiral induction effect in the transamination of methoxyacetone. Thus, the anchored surface species such as [–Si–O–Si–$(CH_2)_3$–O–CH_2–CH(OH)–CH_2–NH–$C^*H(CH_3)$–CH_2OH] can induce significant enantio-differentiation in the hydrogenation of the C=N double bond. The enantiomeric excess was strongly influenced by the solvent used. The highest ee value (−20.4%) was obtained in cyclohexane, whereas in solvents with increased coordination ability, i.e., in THF and dioxane, the enantiomeric excess decreased to −16.3 and −12.1%, respectively.

In cyclohexane the anchored L-phenylalaninol gave an ee value of −15% while the anchored L-alaninol gave −20.4%. The elucidation of this difference needs further investigation.

Under the same reaction conditions on the 5 wt% Pd/C catalyst modified with adsorbed L-alaninol introduced by incipient wetness impregnation, the ee values for CH, THF and DIOX were −17.4, −13.0 and −17.8%, respectively. Thus, the enantio-differentiation ability of catalysts containing anchored modifier is in the same range as that of the catalysts modified either by incipient wetness impregnation or equilibrium adsorption [4]. Upon using the 5 wt% Pd/C catalyst modified with adsorbed PhALOL the conversion of MEOAC and the yield of BMEOIPA were 77 and 33%, respectively. However, the ee value of the product MEOIPA was sligthly higher in the case of the catalyst containing anchored modifier than on the chirally modified Pd/C catalyst (compare data given in the first and last row of table 1). It is also remarkable that in CH and THF solvent upon using Pt/SiO_2 catalysts modified with anchored chiral entities the ee values were slightly higher than on 5 wt% Pd/C catalysts modified by incipient wetness impregnation of the chiral modifier.

It is important to mention that when the L-alaninol chiral modifier was introduced in a conventional way into the Pd/C catalyst, i.e., using the method of incipient wetness impregnation, the total amount of modifier was about ten times higher (6.4 mmol per 100 ml reaction volume) than the amount of covalently bound chiral modifier on the surface of the Pd/SiO_2 catalyst. However, under reaction condition a certain part of the chiral modifier introduced onto the surface of the Pd/C catalyst by incipient wetness impregnation was partially desorbed into the reaction mixture. Thus, the chiral modifier in its covalently bound form seems to be more effective than in its preadsorbed form.

3.2. Action of the modifier

With respect to the action of the modifier we suggest that in this reaction the modifier anchored to the support in the vicinity of metallic palladium particles is involved in the chiral induction. Computer modelling of the modified Pd/SiO_2 catalyst containing anchored L-alaninol chiral moiety is shown in figure 1.

In this modelling a relatively large palladium cluster (d = 5 nm) corresponding to 23% metal dispersion was considered. The palladium cluster consisted of 5 layers of Pd atoms built up on a hexagonal-shape plane. As shown in figure 1, the anchored chiral moiety can only interact with (or adsorb onto) the auxiliary (111) surface of the supported palladium cluster. In this interaction, probably the –NH– group of the anchored L-alaninol might be involved. This interaction leads to the formation of "modified Pd sites". In the form shown in figure 1 both the chiral pocket (secondary alcohol) and the –CH_2OH is intact, i.e., these functional groups are available to interact with the Schiff base. Taking into account the number of palladium

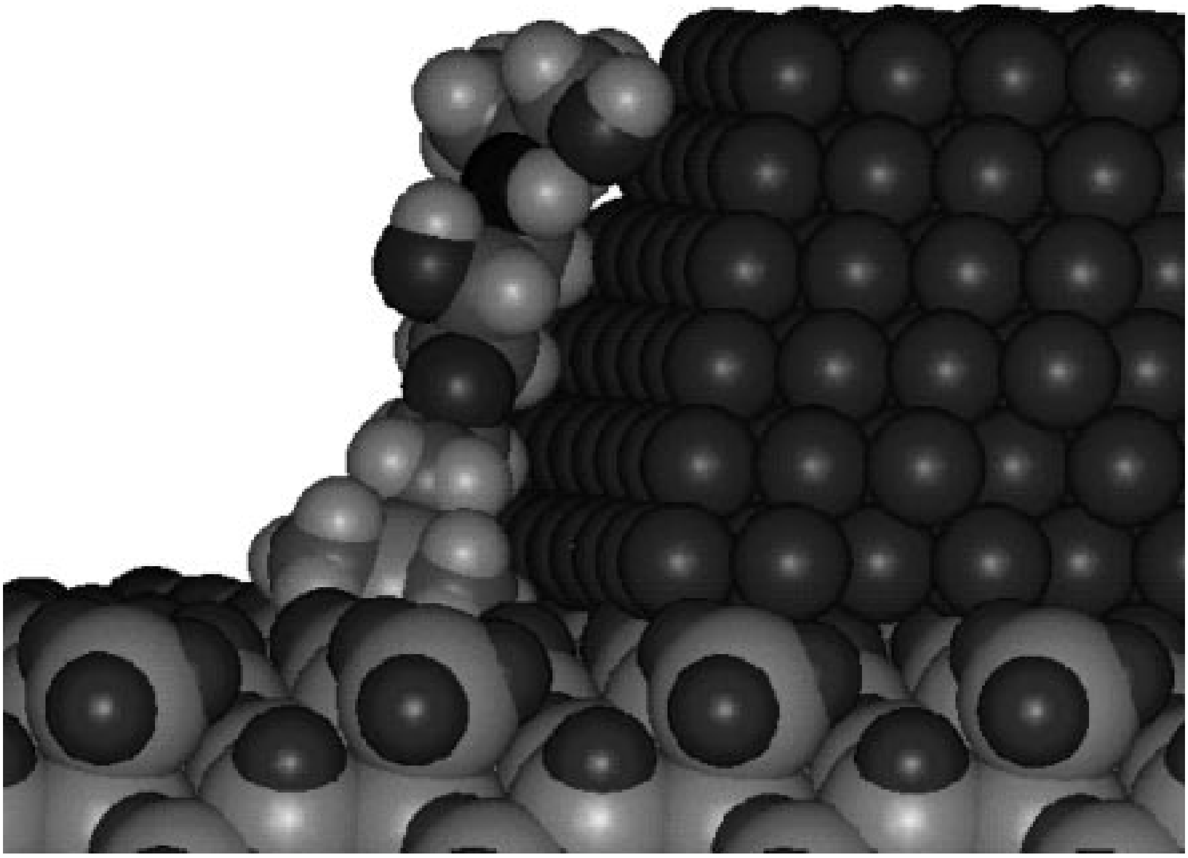


Figure 1. Anchored chiral modifier on the surface of Pd/SiO_2 catalyst.

crystallites and the number of anchored chiral moieties randomly distributed on the surface of the silica support, 5 or 6 anchored chiral modifier can be expected near to each palladium crystallite. The maximum length of the anchored moiety is 1.5 nm (the distance between the O atom of the anchoring site (see the Si–O–Si bond) and the oxygen atom of the OH group at the end of the chain (see scheme 3(a)). Molecular mechanics calculations indicate that the above length can be shortened if the conformation of the spacer groups is changed [6]. The above calculation also indicated that the *2-propyl-1-OH* group can freely rotate around the C–N axis. Thus, the anchored L-alaninol chiral moiety can exist in different conformations, however, we suggest that in the asymmetric induction only those conformers can be involved in which the two OH groups are positioned at the same site of the molecule.

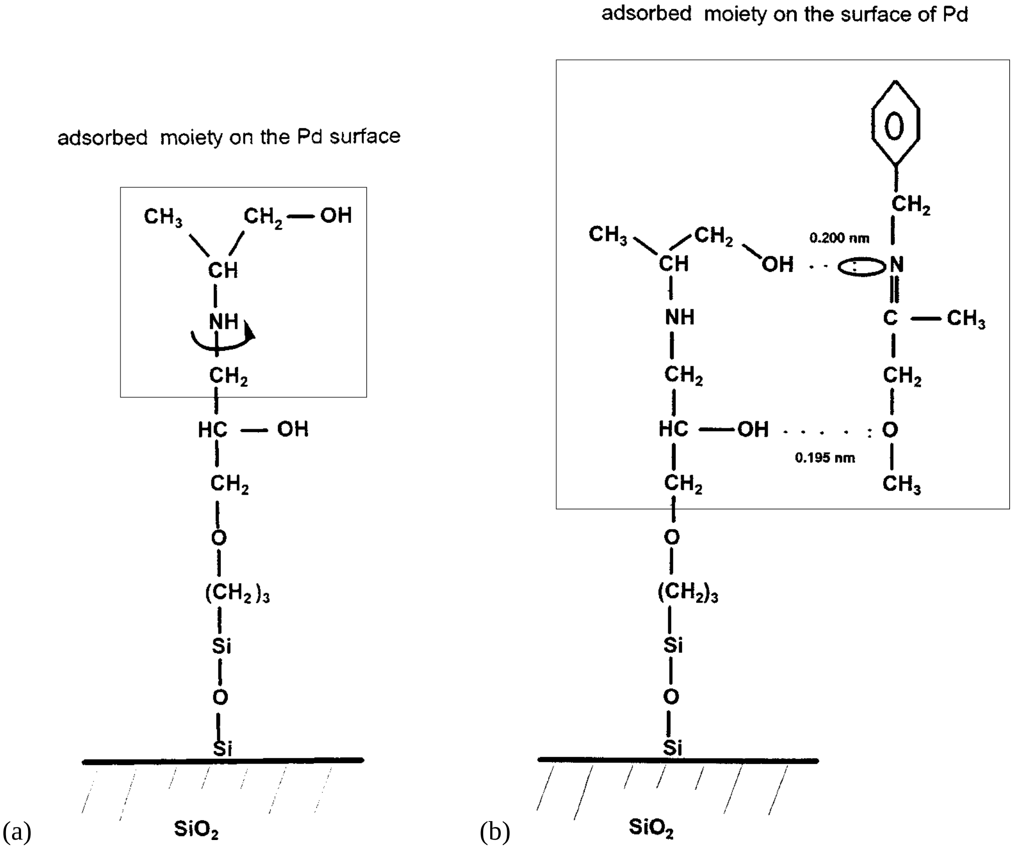
According to our earlier suggestion in heterogeneous catalytic enantioselective hydrogenation the key issue is the formation of a complex between the chiral modifier and the substrate [10]. This interaction can take place either on the metal surface or in the bulk liquid phase. The role of the chiral modifier is to stabilize the substrate molecule in an appropriate conformation which can result in asymmetric induction. In this stabilization the modifier should have a “bidentate” character. *In anchored L-alaninol the two OH groups provide the required “bidentate” character and these groups can be involved in the formation of a substrate–modifier complex via hydrogen bonding.*

There are two functional groups in the substrate (Schiff base) which are electron donors, i.e., the imine and the ether groups via their lone pairs of electrons. Thus, the stabilization of the substrate molecule via two hydrogen bonds is possible. This possibility is shown in scheme 3(b).

As seen in scheme 3(b), the anchored L-alaninol chiral moiety interacts with the substrate molecule via two hydrogen bonding. As emerges from the molecular mechanics calculation, the distance between the OH group of L-alaninol at the end of the anchored chain and the nitrogen atom of the Schiff-base molecule is 0.200 nm, whereas the distance between the secondary OH group in the middle of the anchored chain and the oxygen atom of the methoxy group of the substrate is 0.195 nm. However, it should be emphasized that this interaction can take place only on the auxiliary surface of supported palladium particles.

Figure 2 shows computer modelling of the interaction between the substrate and the chiral modifier at the auxiliary surface of Pd(111). The surface intermediate shown leads to the formation of S-enantiomer.

The substrate–modifier complex described above (see scheme 3(b) and figure 2) strongly resembles that suggested in the enantioselective hydrogenation of β-keto esters in the presence of (+)-tartaric acid and different nickel catalysts [11]. There is a general opinion that in the hydrogenation of β-keto esters the two OH groups of the (+)-tartaric acid are involved in the hydrogen bonding with the carbonyl groups (electron donors) of the β-keto ester [11].



Scheme 3. (a) Anchored modifier on the support surface of Pd/SiO_2 catalyst; (b) modifier–substrate interaction on the surface of Pd/SiO_2 catalyst.

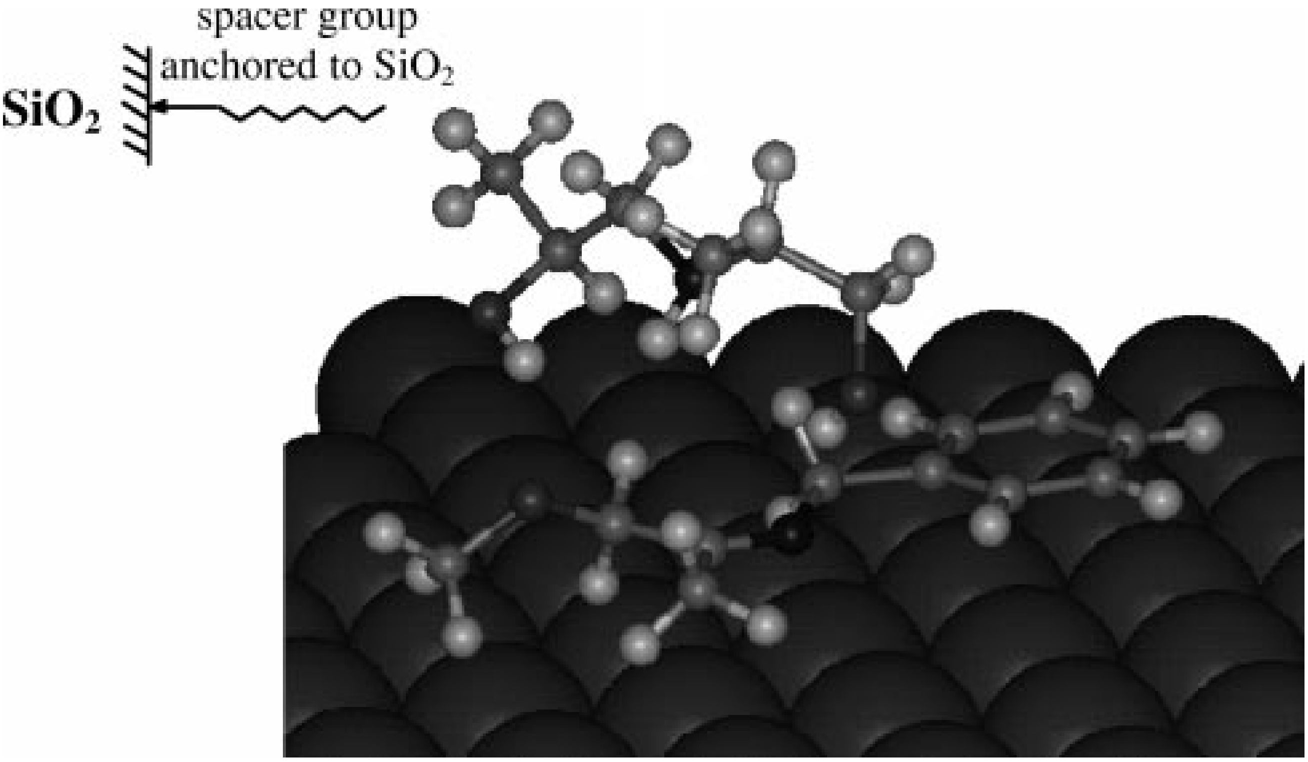


Figure 2. Interaction of substrate–chiral modifier complex with the auxiliary Pd(111) surface. Surface intermediate resulting in the formation of S-enantiomer.

The moderate enantioselectivity (ee $= -20$–21%) can be attributed to the following circumstances: (i) racemic hydrogenation on “unmodified Pd sites”, (ii) the existence of the substrate (Schiff base) both in (Z) and (E) conformers, (iii) conformational changes of the L-alaninol chiral moiety (free rotation of the *2-propyl-1-OH* group around the C–N axis. However, the enantioselectivity was even lower when Pd/C catalyst modified with adsorbed L-alaninol was used. This fact suggest that probably the moderate enantioselectivity is attributed to conformational changes both in the substrate and the modifier. Further studies are needed to elucidate the role of conformational changes in the asymmetric induction.

Based on computer modelling it is also quite understandable why anchored L-phenylalaninol is a less effective modifier than the anchored L-alaninol. In L-phenylalaninol the chiral moiety contains a phenyl group, instead of the methyl one. The phenyl group can be involved in the adsorption on the Pd sites decreasing in this way the probability of the interaction of the –CH_2OH group with the lone electron pair of the imine.

4. Conclusions

In the transamination of methoxyacetone with benzylamine the hydrogenation of the C=N double bond of the imine (Schiff base) intermediate can only be performed at 100–120 °C on a Pd/SiO_2 catalyst containing a chiral modifier covalently bound to the support. The hydrogenolysis of the chiral secondary amine formed from the Schiff base can be carried out at 160–180 °C on the 10 wt% Pd/C catalysts.

The introduction of a chiral modifier covalently anchored to the support decreases the activity of the palladium catalysts. Anchored chiral modifiers on the Pd/SiO_2 catalyst revealed, however, notable chiral induction in the transamination of MEOAC, and the highest enantiomeric excess (ee $= -20$–21%) was obtained in cyclohexane using L-alaninol as a modifier.

Upon using cyclohexane solvent the chiral modifier (L-alaninol, L-phenylalaninol) covalently anchored via an epoxy spacer group onto the surface of the Pd/silica catalyst induces slightly higher enantioselectivity in the transamination of MEOAC than the same modifier adsorbed onto the surface of 5 wt% Pd/C catalysts.

Computer modelling and molecular mechanics calculations have shown that the chiral moiety in the anchored modifier can reach the palladium surface and thus interact via hydrogen bonding with the adsorbed prochiral substrate molecule. The action of the anchored chiral modifier as well as the difference between L-phenylalaninol and L-alaninol modifiers have been rationalized.

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