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Asymmetric synthesis of (*S*)-alkylamines via reductive transamination of ketones over carbon-supported palladium catalysts

S. Göbölös [a,*], E. Tfirst [a], J.L. Margitfalvi [a], K.S. Hayes [b]

[a] *Chemical Research Center, Institute of Chemistry, Hungarian Academy of Sciences, 1025 Budapest, Pusztaszeri út 59-67, Hungary*
[b] *Air Products and Chemicals, 7201 Hamilton Blvd., Allentown, PA 18195, USA*

Abstract

Methylethylketone (MEK) and methoxyacetone (MEOAC) were transaminated with benzylamine ($BzNH_2$) or L-(−)-α-methylbenzylamine [L-(−)-α-$MeBzNH_2$] over Pd/C catalysts in the presence of chiral modifiers (L-alanine, L-alaninol, L-phenylalaninol, L-lysine and methyl-, *t*-butyl- and benzyl-esters of L-alanine) introduced either by incipient wetness impregnation or by equilibrated impregnation onto the catalyst surface. In the first step of the transamination the Schiff base was formed from the ketone and aralkylamine which was then hydrogenated to secondary amine in the second step. In the third step of the transamination the hydrogenolysis of the secondary amine resulting in primary alkylamine and a hydrocarbon was carried out. In the transamination of both MEK and MEOAC on Pd/C catalysts the highest enantiomeric excess was observed in cyclohexane (ee = −20%–21%) using L-alanine alkyl esters or L-alaninol as modifier. In different solvents the ee of the corresponding primary amine increased in the order: MeOH < Dioxan < H_2O < CH. Upon using (L)-(−)-α-$MeBzNH_2$, as a chiral transaminating agent, (*S*)-methoxyisopropylamine was obtained, with ee value around 70%. The conformational analysis of *N*-(methoxy-2-propylidene)-methylbenzylamine strongly supports the validity of Prelog's rule in the enantio- or diastereoselective hydrogenation of Schiff base over heterogeneous catalysts.

Keywords: Enantioselective amination; Reductive transamination; Enantioselective hydrogenation; Schiff base; 2-Butanamine; Methoxyisopropylamine; Chiral modifiers; Methylethylketone; Methoxyacetone; Palladium catalyst; Conformational analysis

1. Introduction

Optically active primary amines including alkoxyalkylamines has 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 heterogeneous catalytic preparation of asymmetric amines from prochiral substrates [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.

* Corresponding author. Fax: +36-12-25020; E-mail: gobolos@cric.chemres.hu

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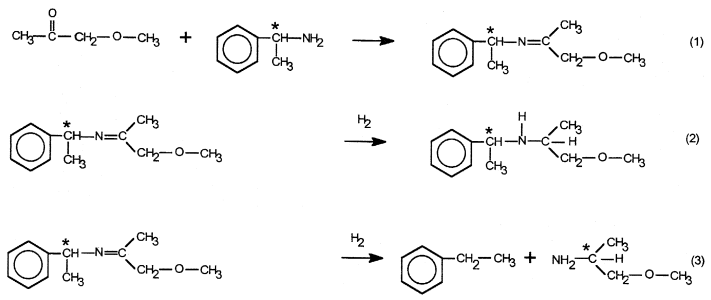


Scheme 1. Transformation of MEOAC into (*S*)-methoxyisopropylamine in the presence of a chiral template, L-(−)-α-methylbenzylamine.

In this case the enantioselective hydrogenation of the C=N double bond of the ketimine type intermediate formed in the equilibrium condensation reaction of ketone with a transaminating agent is the task to be solved.

In this study methylethylketone (MEK) and methoxyacetone (MEOAC) were transaminated with benzylamine ($BzNH_2$) or L-(−)-α-methylethylbenzylamine [L-(−)-α-$MeBzNH_2$] over carbon supported palladium catalysts in the presence of chiral modifiers, i.e. L-alanine (AL), L-alaninol (ALOL), L-phenylalaninol (PhALOL) and methyl-(ALMe), *t*-butyl-(ALtBu) and benzyl-esters (ALBz) of L-alanine, tri-L-alanine (AL3) and L-lysine (LYS). The general formula of the acid and ester modifiers is the following: $R^1(CH_2)_nCH(NH_2)COOR^2$, where R^1,$R^2 = H$, $n = 1$ for L-alanine, $R^1 = H$, $R^2 = Me$, *t*-Bu or Bz, $n = 1$ for the L-alanine esters, $R^1 = NH_2$, $R^2 = H$ and $n = 4$ for L-lysine. The formula of aminoalcohols and tri-L-alanine is $RCH_2CH(NH_2)CH_2OH$ (R = H or Ph), and $CH_3CH(NH_2)[CONHCH(CH_3)]_2COOH$, respectively. In the first step of transamination Schiff base (secondary imine) formed from the aliphatic ketone and aralkylamine which was then hydrogenated to secondary amine in the second step. In the third step of the transamination the hydrogenolysis of the secondary amine resulting in primary alkylamine and a hydrocarbon (toluene or ethylbenzene) was carried out over the palladium catalysts. The reactions involved in the transformation of MEOAC into (*S*)-methoxyisopropylamine in the presence of L-(−)-α-$MeBzNH_2$ are given in Scheme 1.

In this contribution the influence of different chiral modifiers and solvents (cyclohexane (CH), methanol (MeOH), tetrahydrofuran (THF), dioxan (DIOX), CH_2Cl_2, water) on the enantioselectivity of the primary amines was studied. Conformational analysis of *N*-(methoxy-2-propylidene)-methylbenzylamine, i.e., the Schiff-base intermediate of the methoxyisopropylamine (MEOIPA), was also performed.

2. Experimental

2.1. Catalysts

Carbon supported palladium catalysts with 5 wt.% metal content Escat 10 and 11, referred to as E10 and E11, and 5 wt.% Pd/C (Selcat SQ3) all powdered and prereduced were obtained from Engelhard and Chinoin, respectively. The surface area of the carbon support was 1000 and 800 m^2/g for the SQ and E type of catalysts, respectively. The dispersion of palladium was around 50%. Prior to activity test and/or modification 0.5 g of Pd/C catalyst was pretreated in nitrogen at 150°C for 1 h followed by the treatment in hydrogen at 200°C for 2 h. The catalysts were then cooled to room temperature under hydrogen flow and were introduced into the reactor used either for modification or catalytic test without any contact with air.

2.2. Modification of carbon supported palladium catalysts

Stepwise incipient wetness impregnation (IW) of the catalysts (0.5 g) with aqueous solution of L-alanine, L-lysine and tri-L-alanine was carried out at room temperature. L-alaninol dissolved in the solvent used (CH, MeOH, THF or DIOX), PhALOL, ALBz, ALMe and ALtBu dissolved in ethanol were used to impregnate the Pd/C catalysts. Prior to activity test modified catalysts were dried at room temperature (except the catalyst modified by L-alaninol) and pretreated in nitrogen and hydrogen at 100°C and 150°C, respectively. Other portions of hydrogen pretreated palladium catalysts were modified with L-alanine, L-lysine, L-alaninol or ALtBu dissolved in 10 ml solvent via equilibrated impregnation (EI) at room temperature for 15 min. In this case the modifier was partly adsorbed on the catalyst and partly dissolved in the reaction mixture.

2.3. Reaction conditions

MEOAC was prepared from methoxyisopropanol and Na_2CrO_4 using the method developed by Mariella and Leech [3].

Catalytic activity tests were carried out in a stainless steel stirred autoclave ($V = 300$ ml) under the conditions: V_{liquid}: 100 ml, $V_{solvent}$: 80 ml, $P_{hydrogen}$: 60 bar, amount of ketone and aralkylamine: 0.1, 0.1 mol, molar ratio of ketone/Pd: 400.

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 separation of trifluoro acetic anhydride derivatized amine enantiomers was performed by GC using a capillary column coated with Chirasil Dex CB (β-cyclodextrin based) (CHROMPACK Cat. No. 7503).

The conformational analysis including the calculation of the energy barriers for the conformational transformations of Schiff base reaction intermediates was performed by using Hyperchem 5.0 version.

2.4. Abbreviations

IW, EI	modifier introduced by incipient wetness impregnation and equilibrated impregnation, respectively
M	modifier added to the reaction mixture (mixing)
t_2, t_3	reaction time of hydrogenation of imine and hydrogenolysis of secondary amine, respectively
T_2, T_3	temperature of the hydrogenation and the hydrogenolysis steps, respectively
C_2, C_3	conversion of ketone in the hydrogenation and hydrogenolysis steps, respectively
Y_2, Y_3	yield of secondary amine in the hydrogenation step and that of 2-butanamine or methoxy-isopropylamine in the hydrogenolysis step, respectively
ee	enantiomeric excess, $ee = [(R) - (S)]/[(R) + (S)] \times 100\%$

3. Results and discussion

3.1. Catalytic activities

3.1.1. Transamination of methylethyl ketone

Catalytic activity and selectivity results obtained in the reductive transamination of MEK with $BzNH_2$ are shown in Tables 1–4. Details on reaction conditions are also given in the tables. It is noteworthy, that in the hydrogenation (second) step of transamination the secondary amine was the reaction product, and unconverted Schiff base and ketone could also be detected in the reaction mixture. In the third step of the transamination, i.e., in the hy-

Table 1
Transamination of MEK with $BzNH_2$ in cyclohexane over L-alanine modified 5 wt.% Pd/C catalyst (E10) (the influence of the amount of L-alanine introduced by incipient wetness impregnation)

Amount of L-alanine (mmol)	Conversion of ketone, C_2 (%)	Yield of secondary amine, Y_2 (%)	Yield of primary amine, Y_3 (%)	ee (%)
0.00	98	97	96	0.0
0.14	98	97	85	−12.6
0.22	97	96	79	−13.7
0.56	97	96	77	−16.9
1.12	87	77	83	−18.4

$T_2 = 25°C$, $t_2 = 24$ h, $T_3 = 100°C$, $t_3 = 4$ h, $C_3 = 100\%$.

drogenolysis step the conversion of ketone and Schiff base was complete. In this step the primary amine and a hydrocarbon and unconverted secondary amine are the reaction products.

Catalytic activities and selectivities obtained in the reductive transamination of MEK with $BzNH_2$ on 5 wt.% Pd/C (E 10) catalyst modified by incipient wetness impregnation with different amounts of L-alanine are given in Table 1. These data indicate that upon increasing the amount of L-alanine the yield of secondary amine in the second step (Y_2), i.e., the hydrogenation activity of the catalyst slightly decreases, whereas the hydrogenolysis activity of the catalyst and thus the yield of primary amine (Y_3) significantly decreases. The increase of the amount of modifier resulted in monotonous increase of the selectivity of (*S*)-*s*-butylamine [(*S*)-*s*-$BuNH_2$] up to 18.4%.

The effect of the modification method and the solvent on the transamination of MEK with $BzNH_2$ on 5 wt.% Pd/C (E10) catalyst modified with different amounts of L-alanine can be seen in Table 2. The results listed in Table 2 indicate that compared to modification method EI and M the incipient wetness impregnation of the catalyst with the modifier decreases the conversion of MEK (C_2) and the hydrogenation activity (Y_2) of the catalyst.

As shown in Table 2, the hydrogenolysis of secondary amine, i.e., the formation of primary amine (Y_3) was significantly faster in methanol than in cyclohexane. However, the ee value of (*S*)-*s*-$BuNH_2$ is significantly lower in methanol (ca. 10%–11%) than in cyclohexane (18.4%) and in water (17.9%). This can be explained by partial desorption of the modifier from the catalyst surface in MeOH. With respect to the solvents the ee value decreases in the order: CH > H_2O > MeOH.

The transamination of MEK with $BzNH_2$ in the presence of L-alaninol modifier was per-

Table 2
Transamination of MEK with $BzNH_2$ in different solvents over 5 wt.% Pd/C catalyst (E10) modified with L-alanine (effect of modification method EI, IW or M and solvent)

Modification method, solvent, amount of modifier added (mmol)	Conversion of ketone, C_2 (%)	Yield of secondary amine, Y_2 (%)	Yield primary amine, Y_2 (%)	ee (%)
EI, MeOH, 1.12	100	99	100	−11.0
M, MeOH, 1.35	100	99	100	−11.0
IW, MeOH, 1.12	83	82	99	−9.8
IW, CH, 1.12	87	77	83	−18.4
M, H_2O, 5.6	89	87	99	−17.9

$T_2 = 25°C$, $t_2 = 24$ h, $T_3 = 100°C$, $t_3 = 4$ h, $C_3 = 100\%$.

Table 3
Transamination of MEK with $BzNH_2$ in different solvents over 5 wt.% Pd/C catalysts modified with L-alaninol (effect of catalyst, modification method and solvents)

Catalyst, modification method, solvent	Conversion of ketone, C_2 (%)	Yield of secondary amine, Y_2 (%)	Yield of primary amine, Y_3 (%)	ee (%)
E10, EI, MeOH	99	99	98	−11.5
E10, EI, CH	91	90	98	−16.8
SQ3, EI, CH	92	77	98	−20.5
SQ3, IW, CH	85	72	55	−20.8

$T_2 = 25°C$, $t_2 = 20$ h, $T_3 = 120°C$, $t_3 = 4$ h, $C_3 = 100\%$, amount of modifier added = 6.4 mmol.

formed on different carbon supported palladium catalysts (E10, SQ3) (see Table 3). Conversion, yield and enantiomeric excess data indicate that the highest MEK conversion can be obtained on E10 catalyst in methanol. In cyclohexane the hydrogenation activity (Y_2) of E10 catalyst is slightly higher than that of SQ3 catalyst modified by EI method; however, not much difference can be found in the hydrogenolysis activity (Y_3) of the catalysts. The introduction of L-alaninol via equilibrated impregnation resulted in more active catalyst than the incipient wetness impregnation of the SQ3 catalyst with 6.4 mmol of modifier. This can be explained by the fact that the incipient wetness impregnation of the catalyst with the modifier results in higher modifier surface concentration, and thus certain extent of catalyst poisoning, than the modification by the EI method. Due probably to the slightly higher surface area of the carbon support and thus the higher surface concentration of the chiral modifier, the ee value of (*S*)-*s*-$BuNH_2$ in cyclohexane for both types of modification method (IW or EI) was higher (20%–21%) on SQ3 catalyst than on E10 catalyst.

The results of the transamination of MEK with $BzNH_2$ in cyclohexane over SQ3 catalyst modified with different L-alanine based chiral modifiers are summarized in Table 4. Upon changing the chemical nature of the chiral modifiers introduced onto the catalyst surface by incipient wetness impregnation significant differences were observed in the conversion of ketone (C_2), hydrogenation of Schiff base (Y_2) and hydrogenolysis of secondary amine (Y_3) as well as in the ee value. The highest ee value (ee = −20%–21%) was obtained using L-alanine methyl and *t*-butyl ester as modifiers, whereas the lowest ee value was obtained with tri-L-alanine. The introduction of L-alanine methyl or benzyl esters and phenyl-L-alaninol into the catalysts resulted in significant decrease in MEK conversion and the hydrogenation activity (for PhALOL and ALBz) and in the hy-

Table 4
Transamination of MEK with $BzNH_2$ in cyclohexane over 5 wt.% Pd/C catalyst (SQ3) modified with different chiral compounds by incipient wetness impregnation (the influence of the type of modifier)

Modifier and its amount (mmol)	Conversion of ketone, C_2 (%)	Yield of secondary amine, Y_2 (%)	Yield of primary amine, Y_3 (%)	ee (%)
AL3, 0.22	95	89	98	−11.4
PhALOL, 1.12	77	33	16	−12.7
ALBz, 0.93	71	23	46	−14.2
ALMe, 1.43	73	71	25	−21.2
ALtBu, 1.10	94	85	94	−20.2

$T_2 = 25°C$, $t_2 = 24$ h, $T_3 = 120°C$, $t_3 = 6$ h, $C_3 = 100\%$.

drogenolysis activity. This can be attributed to the strong adsorption of the aromatic ring of the modifier on palladium. Upon using ALBz and PhALOL modifiers ee value of 13–14% was obtained. The low hydrogenolysis activity of the catalyst modified with ALMe requires further elucidation.

3.1.2. Transamination of MEOAC

The results of the transamination of MEOAC with $BzNH_2$ in cyclohexane on SQ3 catalyst modified with L-alaninol by EI method are summarized in Table 5. The best ee values (17–18%) were obtained in dioxan and cyclohexane. In CH_2Cl_2 both the conversion of MEOAC and the ee value of (*S*)-methoxyisopropyamine (MEOIPA) was lower than in other solvents. This can probably be attributed to the poisoning effect of HCl formed from CH_2Cl_2 in the presence of palladium catalyst and amine reactant at 180°C. Indeed, amine-assisted dehalogenation of chlorinated methanes was observed on heating under homogeneous conditions [4]. In addition, halogen–chlorine exchange occured in the presence of supported NiOs bimetallic catalyst at 230°C. Methane was obtained from dichloromethane with 30% yield [5].

Catalytic activity results obtained in the reductive transamination of MEOAC with $BzNH_2$ on 5 wt.% Pd/C SQ3 catalyst in the presence of different modifiers (L-lysine, L-alaninol and *t*-butyl ester of L-alanine) and different solvents are given in Table 6. Conversion and yield data indicated that the modification of the catalyst by incipient wetness impregnation instead of EI method resulted in significant decrease of the hydrogenolysis activity (Y_3) and a decrease of the hydrogenation activity only for the ALtBu modified catalyst. Upon modifying the catalyst with L-lysine ca. 12% ee value can be obtained. Slightly higher ee values were obtained with L-alaninol and the highest ee value (−20%) was obtained on catalyst modified with ALtBu by incipient wetness impregnation.

All differences observed between the modification methods (EI or IW) used can be interpreted in terms of changes in the surface concentration of the chiral modifier on the catalyst. The same amount of chiral modifier added to the catalyst results in higher surface concentration in the case of IW impregnation than in the case of EI method. Depending on the surface area and properties of carbon support, the method of introduction of the chiral modifier and the solvent used in the activity test the amount of modifier desorbed from the surface can be different (10–90%). Therefore, an equilibrium exists between the amounts of chiral modifier in the liquid phase and on the catalyst surface. It is suggested in these type of heterogeneous hydrogenation reactions the chiral modifier on the catalyst surface can only be efficient if it is adsorbed in the vicinity of the supported metallic palladium crystallites.

3.1.3. Transamination of ketones with L-(−)-α-$MeBzNH_2$

The results of the transamination of MEK and MEOAC with L-(−)-α-$MeBzNH_2$ on carbon supported palladium catalysts are given in

Table 5
Transamination of MEOAC with $BzNH_2$ in different solvents over 5 wt.% Pd/C catalyst (SQ3) modified with L-alaninol by EI method

Solvent	Conversion of ketone, C_2 (%)	Yield of secondary amine, Y_2 (%)	Yield of primary amine, Y_3 (%)	ee (%)
Cyclohexane	97	95	100	−17.4
THF	100	98	100	−13.0
Dioxan	100	100	100	−17.8
CH_2Cl_2	84	83	100	−10.0

$T_2 = 25$°C, $t_2 = 24$ h, $T_3 = 180$°C, $t_3 = 6$ h, $C_3 = 100$%, amount of modifier = 6.4 mmol.

Table 6
Transamination of MEOAC with $BzNH_2$ in cyclohexane over 5 wt.% Pd/C catalyst (SQ3) modified with different chiral compounds (effect of modifier and modification method)

Modification method, amount of modifier (mmol)	Conversion of ketone, C_2 (%)	Yield of secondary amine, Y_2 (%)	Yield of primary amine, Y_3 (%)	ee (%)
ALOL, IW, 6.4	98	93	15	−12.5
ALOL, EI, 6.4	97	95	100	−17.4
LYS, IW, 6.8	98	90	75	−11.8
LYS, EI, 6.8	99	94	99	−12.2
ALtBu, IW, 1.1	95	40	51	−20.0
ALtBu, EI, 1.1	99	94	88	−12.0

$T_2 = 25°C$, $t_2 = 24$ h, $T_3 = 180°C$, $t_3 = 6$ h, $C_3 = 100\%$.

Table 7. Reaction time (t_2) data given in Table 7 indicate that in the second reaction step the hydrogenation of the secondary imine is significantly faster in methanol than in cyclohexane. The same ketone conversion (C_2) and secondary amine yield (Y_2) can be achieved faster in the case of MEOAC than with MEK. The hydrogenolysis of the secondary amine formed from MEK could be carried out at 70–100°C and the ee value of (*S*)-*s*-$BuNH_2$ was about 40%. The secondary amine formed from MEOAC and L-(−)-α-$MeBzNH_2$ could not be hydrogenolysed to (*S*)-MEOIPA and ethylbenzene at 100°C for 9 h ($Y_3 = 4\%$). The secondary amine could only be hydrogenolysed at 180°C for 3 h ($Y_3 = 100\%$). In both cases the ee value of (*S*)-MEOIPA was ca. −70%. The difference between the ee values of (*S*)-*s*-$BuNH_2$ (*S*)-MEOIPA can be attributed either to a stronger or a more specific substrate–modifier interaction in the case of MEOAC than in the case of MEK. We consider that the presence of the ether oxygen in MEOAC provides an additional coordination site for the substrate molecule in the substrate–modifier complex. This additional coordination is reflected in the substantial increase of the ee values.

3.2. Conformational analysis

The above catalytic results indicate that in the transaminantion of MEOAC the selectivity control can be achieved by using a chiral template molecule, i.e., L-(−)-α-$MeBzNH_2$. In order to understand the driving force for the high enantioselectivity of primary amine formed by the hydrogenolysis of secondary amine, detailed conformational analysis was performed on its precursor compound, i.e., on the corresponding imine formed from the chiral template ($MeBzNH_2$) and MEOAC. In this calculation we supposed that the chirality of the template molecule is maintained in the secondary imine formed.

As emerges from simple geometric analysis the imine molecule has at least two different forms. In the open (O) *E*-forms the phenyl

Table 7
Transamination of MEK and MEOAC with L-(−)-α-$MeBzNH_2$ on 5 wt.% Pd/C catalyst (E10 for MeOH and E11 for cyclohexane)

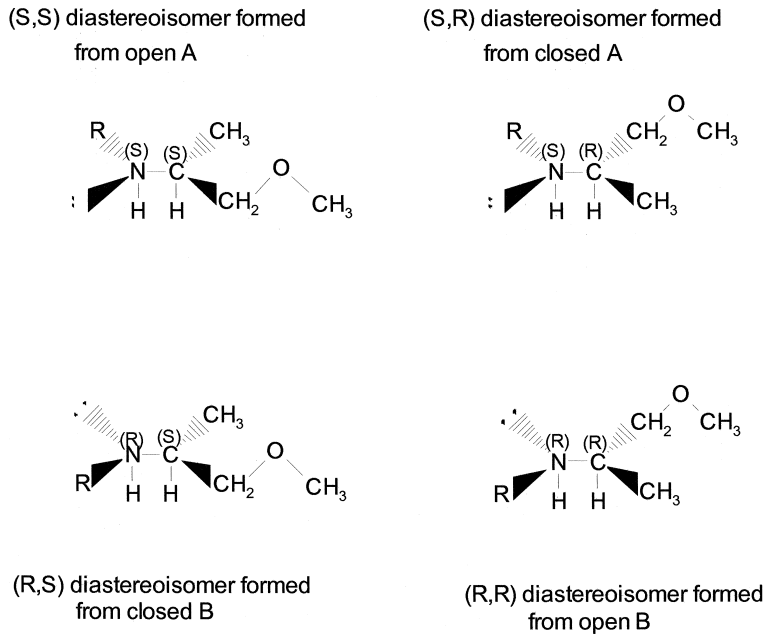
Substrate, solvent	Time of reduction of imine, t_2 (h)	Temperature of the hydrogenolysis step, T_3 (°C)	Time of hydrogenolysis of secondary amine, t_3 (h)	Yield of primary amine, Y_3 (%)	ee (%)
MEK, CH	71	100	1	93	−40.4
MEK, MeOH	48	70	6	100	−39.0
MEOAC, MeOH	24	180	3	100	−68.0
MEOAC, CH	76	100	9	4	−69.4

$T_2 = 25°C$, $C_2 = 95$–100%, $Y_2 = 92$–100%, $C_3 = 100\%$.

group of the template molecule and the methyl group of the substrate molecule are in *cisoid* position to each other. In the closed (C) *Z*-form the phenyl group and the CH_3–O–CH_2– moiety are in *cisoid* position. These two forms of the imine will result in four different possible modes of adsorption (O_a, O_b, C_a, C_b) supposing that the C=N double bond is the adsorption site in the imine molecule. If the hydrogenation of the imine takes place from the bottom site, four different adsorbed forms of the secondary amine can form (see Scheme 2). The O_a and O_b forms can lead to (*S,S*) and (*R,R*) diastereoisomers, respectively. The hydrogenation of the C_a and C_b results in the formation of (*S,R*) and (*R,S*) diastereoisomers. The formation of (*S*)-MEOIPA can take place only from the (*S,S*) and (*R,S*) diastereoisomer after subsequent hydrogenolysis.

Conformational analysis was carried out to investigate the geometrical and energetical properties of both the open (*E*) and the closed forms (*Z*) of the imine. The analysis was done using the MM + forcefield, which was built in the Hypercube: HyperChem program. The two dimensional energy maps (not shown) were calculated by changing the torsional angles around the single bonds next to the C=N double bond. Otherwise the imine was considered as a rigid molecule. For the open and the closed conformations the torsion angle around the C=N bond was set to 180° and 0°, respectively. The interval of the angles between the calculated structures was 5°. After calculating the energy maps, all structures corresponding to local minima were fully optimized using the MM + forcefield.

Six energy minima corresponding to $O1_a$, $O2_a$, $O3_a$, $O1_b$, $O2_b$, $O3_b$ conformers with MME (kcal/mol) 1.82, 2.52, 1.87, 2.75, 3.39, 2.73, respectively were found for the open forms (Fig. 1). Four minima $C1_a$, $C2_a$, $C1_b$, $C2_b$ with MME of 1.05, 1.84, 2.81, 2.69, respectively were detected for the closed forms (Fig. 2). The most stable conformer is $C1_a$, in this conformer the imine has a closed *Z*-form, in which the



Scheme 2. Diastereoisomers of *N*-(methoxy-2-propyl)methylbenzylamine.

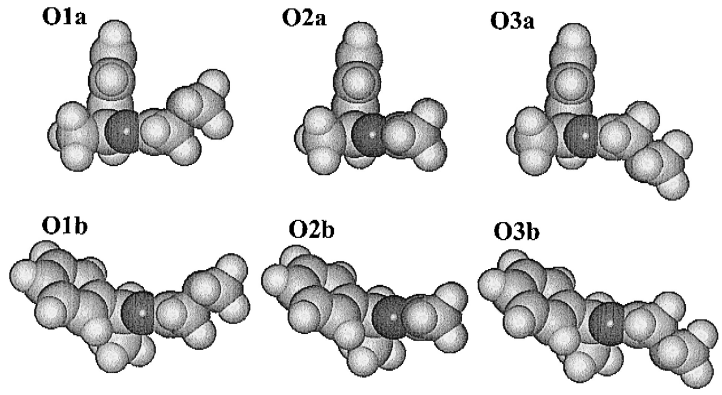


Fig. 1. Open (*E*) conformers of *N*-(methoxy-2-propylidene)-methylbenzylamine.

phenyl group and the ether oxygen interacts with each other.

We suggest that the adsorption of imine takes place via its double bond. In this case some of its conformers can adsorb only in one mode, i.e., the mirror image of the adsorbed form can not exist due to steric hinderance. For instance, the conformers $O1_a$, $O1_b$, $O2_a$, $O3_a$, $C1_a$, $C1_b$, $C2_a$ and $C2_b$ can have only one form of adsorption, only two conformers $O2_b$ and $O3_b$ can have two forms of adsorption. All of the calculated closed *Z*-forms can give only the (*S*,*R*) and (*R*,*S*) diastereoisomers after adsorption and subsequent bottom site hydrogenation. However, it should be mentioned that according to Prelog's rule [6] the formation of the closed conformers should be sterically hindered.

Therefore, the (*S*,*S*) diastereoisomer of secondary amine, precursor of *S*-MEOIPA, can form from $O1_a$, $O2_a$, and $O3_a$ conformers, which are energetically favored compared to O_b forms. As emerges from the Boltzmann equation the thermodynamic probability of the existence of the various conformers is proportional to the reciprocal energy differences calculated by using MM + forcefield. Based on the six energy

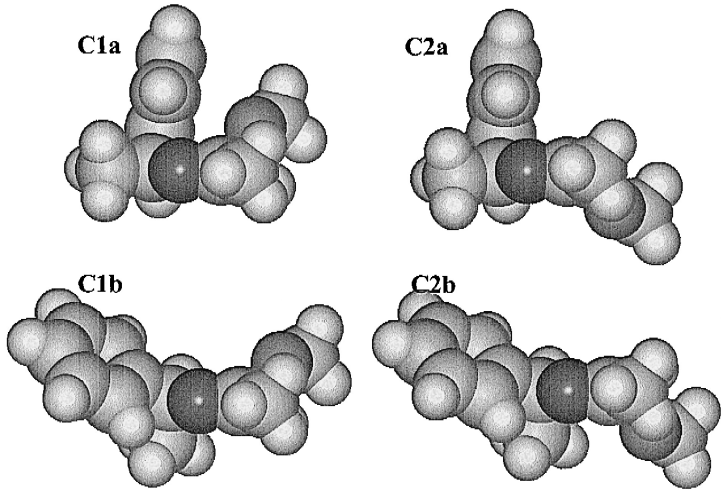


Fig. 2. Closed (*Z*) conformers of *N*-(methoxy-2-propylidene)-methylbenzylamine.

minima of O_a and O_b conformers, the probability of O_a conformers resulting in (*S*,*S*) diastereoisomers is ca. 59%, which is close to the experimentally obtained ee value of −68% for *S*-MEOIPA. Therefore, it is very likely that the control of the diastereoselectivity, and thus the enantioselectivity of *S*-MEOIPA, is probably attributed to steric factors predicted by Prelog's rule [6] and to the conformational changes of the formed imine. NMR investigations will be needed to confirm this suggestion.

4. Conclusions

In the transamination of MEK and MEOAC with $BzNH_2$ the hydrogenation of C=N double bond of the imine intermediate can be performed at room temperature over carbon supported palladium catalysts. On the Pd/C catalyst the hydrogenolysis of the secondary amine formed can be carried out at 80–100°C and 160–180°C for MEK and MEOAC, respectively.

The introduction of L-alanine, tri-L-alanine, L-alaninol and L-alanine methyl and *t*-butyl ester only slightly decreases the activity of the Pd/C catalysts, whereas the addition of L-alanine benzyl ester and phenyl-L-alanine significantly decreases the activity of the catalysts especially in the hydrogenolysis step.

In the tansamination of both MEK and MEOAC on Pd/C catalysts the highest enantiomeric excess values (ee = −20–21%) were obtained upon using L-alanine alkyl esters and L-alaninol as modifiers. Upon using L-alanine, tri-L-alanine, L-alanine benzyl ester and phenyl-l-alaninol chiral modifiers the ee value of the desired primary amine was only −11–17%.

Upon changing the nature of solvent the rate of Schiff-base hydrogenation was less affected than that of the hydrogenolysis step. The rate of hydrogenolysis of secondary amine decreased in the order: MeOH > CH > H_2O. The ee value of the product primary amine increased in the order: MeOH < H_2O < CH.

S-MEOIPA can be formed from MEOAC and L-(−)-α-$MeBzNH_2$ in cyclohexane with an ee value of 68%.

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