In situ CHIRAL MODIFICATION OF NICKEL CATALYSTS FOR ENANTIOSELECTIVE HYDROGENATION OF METHYL ACETOACETATE

Lukáš BARTEK[1], Petr KLUSOŇ[2] and Libor ČERVENÝ[3],*

Department of Organic Technology, Institute of Chemical Technology, Prague, Technická 5, 166 28 Prague 6, Czech Republic; e-mail: [1] lukas.bartek@vscht.cz, [2] p.kluson@seznam.cz, [3] libor.cerveny@vscht.cz

Chiral modifications of SiO_2-supported and Raney nickel catalysts were studied. The catalysts were employed in asymmetric hydrogenation of methyl acetoacetate (MAA) to (*R*)- and (*S*)-enantiomers of methyl 3-hydroxybutanoate. The effects of modification parameters such as type and concentration of modifier; presence of a co-modifier and other additives, pH of modification solution on the enantioselectivity of MAA hydrogenation were discussed. Characteristic features of the *in situ* modification of Ni/SiO_2 were also evaluated and the results obtained were compared with the conventional (premodification) approach. Parameters for the conventional and *in situ* methods were optimised in a series of experiments for both types of catalysts. The *in situ* modified Ni/SiO_2 was found specifically suitable for repeated use due to virtually no decrease in selectivity and activity.

Keywords: Enantioselective catalytic hydrogenation; *In situ* modification; Tartaric acid modified Raney nickel catalyst; Sol-gel; Asymmetric reductions; Heterogeneous catalysis.

Enantioselective reactions have become an essential part of many manufacturing processes for fine chemicals, pharmaceuticals, agrochemicals, flavours and fragrances. Heterogeneous asymmetric catalysis as a promising tool for such purposes has been growing rapidly in recent years[1]. Among established strategies for optically pure compounds, enantiodifferentiation on heterogeneous catalysts represents one of the most promising options. Attention has been paid to noble metals (typically Pt or Pd) chirally modified with cinchona alkaloids[2–5] or to transition metals (typically Ni [6–9]) modified with tartaric acid. The latter catalytic system has been extensively tested in model hydrogenations of β-ketoesters[10–14] and β-diketones[15,16] affording high optical yields (up to 98%). One of these reactions was asymmetric hydrogenation of methyl acetoacetate[17–21] (MAA) as a model β-ketoester to (*R*)- and (*S*)-enantiomers of methyl 3-hydroxybutanoate (Fig. 1). Nickel catalysts modified with tartaric acid usually required partici-

pation of other selectivity- or activity-enhancing factors. Those included e.g. specific forms of the active phase (Raney nickel[22], supported nickel catalysts[23], nickel black[24–26], bimetallic catalyst[27,28]), presence of modifier and co-modifier. Besides tartaric acid (TA), other modifiers such as α-hydroxy acids[29] or α-amino acids[30,31] were also tested. The presence of NaBr in the modification solution involving TA enhanced the achieved enantioselectivity by 10–30% in comparison with experiments performed without this co-modifier. Addition of pivalic acid[32], acetic acid[33] or sodium 2-ethylhexanoate[34] in small quantities further increased optical yields. Another possibility comprised utilisation of sodium tartrates instead of TA. The role of sodium ions as a part of the active species adsorbed[35] on the nickel surface has not been fully elucidated[36] yet. The effects of factors such as temperature, pH, impregnation period, concentration and volume of a modifier (co-modifier) solution were identified[37–41] as essential. The modification step (introduction of modifiers or co-modifiers) for obtaining a catalytic system with enhanced enantioselectivity could be arranged either as premodification (nickel catalyst, both Raney and sol-gel, is immersed and modified in an aqueous solution containing TA and NaBr before hydrogenation) or as *in situ*[42,43] modification. Although the premodification approach is simple and leads to high enantioselectivities of many types of nickel catalysts, it has not been scaled up for industrial use. One of the main reasons is the generation of a large amount of waste solution involving nickel ions during the premodification procedure. The latter approach comprised direct addition of modifiers (and co-modifiers) to the reaction mixture already including MAA or other model reactants. Surprisingly enough, the *in situ* modification provided a chirally active catalytic system with at least comparable optical yields to those achieved with standard impregnation. The *in situ* modification also represents an environmentally friendly process that generates no waste solutions containing nickel ions.

The type[44] of the nickel catalyst plays a key role. Raney nickel is one of the most convenient materials for preparation of modified Ni catalysts. Raney nickel modified by ultrasonic irradiation[45] embodied the highest optical yield ever attained (ee 98%). Modified supported Ni catalysts were also
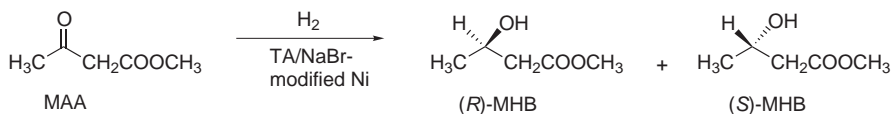

FIG. 1
Reaction scheme of MAA hydrogenation over TA/NaBr-modified Ni catalysts

intensively studied[46–48]. It should be noted that the preparation of a modified supported catalyst comprises more parameters affecting the optical yield than that of a modified RaNi. Besides the standard preparation procedure (impregnation of a support with an active species precursor) the sol-gel method should also be considered.

In this paper we report on comparison of supported nickel catalysts prepared by the sol-gel method with Raney nickel catalysts in terms of their performance in asymmetric hydrogenation of MAA. Characteristic features of the catalytic systems produced by impregnation with tartaric acid (and its sodium salts – NaHTA, Na$_2$TA) and by the *in situ* modification are discussed.

EXPERIMENTAL

Catalysts

Raney nickel was Actimet supplied by Engelhard (S_{BET} = 92 m^2 g^{-1}, particle size 5–100 nm). Precursors of Ni/SiO$_2$ (50 wt.% Ni) – tetraethoxysilane (0.3 mol, Aldrich) and Ni(NO$_3$)$_2$·6H$_2$O (0.3 mol, Aldrich), were mixed with 3 mol of ethanol and boiled for 1 h. To this mixture water was slowly added (160 ml) and the formed gel was allowed to stand for 14 h. Finally the mixture was dried in vacuum and decomposed in a furnace at 573 K for 3 h. The material was reduced with H$_2$ (120 ml min^{-1}) at 773 K for 4 h. The S_{BET} of the catalyst was 450 m^2 g^{-1} and the evaluated mean particle size of Ni was 100 nm.

Chemicals

Methanol, ethanol, and tetrahydrofuran were supplied by Fluka (HPLC grade); methyl acetoacetate (MAA), HPLC grade water, NaBr, NaOH, (+)-(2R,3R)-tartaric acid (TA), sodium hydrogen-L-(+)-tartrate (NaHTA) and sodium L-(+)-tartrate dihydrate (Na$_2$TA) were all of Aldrich.

Premodification Procedure

Raney nickel (10 g) stored in alkaline water solution was washed three times with 50 ml of distilled water and then introduced to the modification solution of TA, NaHTA or NaBr (co-modifier, Aldrich). pH was adjusted by 20% NaOH using potentiometric indication. The suspension of the catalyst and modification solution was stirred in a flask with a condenser at 373 K (90 min). The modification solution was decanted and the catalyst washed with methanol and tetrahydrofuran. The sol-gel catalyst (3 g) was introduced to the modification solution (100 ml) containing TA or NaHTA or Na$_2$TA and NaBr (co-modifier). Optimum pH was found in a series of screening experiments. The suspension was stirred for 1 h, then the solution was removed and the catalyst washed successively with 50 ml of water, methanol and tetrahydrofuran.

In situ Modification

The *in situ* modification required direct introduction of the modifier, co-modifier and additives mixture (TA, NaBr, acetic acid) into the reaction vessel (already containing MAA and the catalyst) in solid form[26] (the method noted here as "*in situ* A") or dissolved in a small quantity of water[30] (the method noted here as "*in situ* B").

Typical Experiment

Reactions were carried out in liquid phase in a stainless steel autoclave (300 ml) with MAA (20 ml) in tetrahydrofuran (70 ml) at 373 K, 10 MPa and with 2–3 g of a catalyst. Samples of a reaction mixture were analysed by GC on an HP5890 with a chiral cyclodextrin column BETA-DEX 325 (0.5 μm × 0.5 mm × 50 m, Supelco) and on an MS/GC – Varian Saturn (the GC part was equipped with the same GC column). Optical yields (ee) were calculated using the following equation:

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

RESULTS AND DISCUSSION

Raney Nickel – Premodification

Initial screening experiments with Raney nickel were designed to elucidate the role of the modifier/co-modifier ratio on the enantioselectivity (ee) of MAA hydrogenation. Enantioselective properties of the catalyst modified with NaHTA and NaBr were studied first. The maximum value of ee (71%) was attained at the NaHTA/NaBr weight ratio 1:2. This value was kept constant throughout the experiments (Fig. 2). Figure 3 shows the effect of variable NaHTA concentration. The highest ee (78%) was achieved at $c_{\text{NaHTA}} = 0.19$ mol l^{-1}. The concentration was in the "compositional area" (0.15 to 0.22 mol l^{-1}), in which the catalytic surface was loaded with an optimum amount of the modifier (with respect to ee) and no leaching of nickel was observed. Then the TA/NaBr modification system was tested including assessment of the effect of various modifier/co-modifier ratios. The optimal TA/NaBr weight ratio was found again at 1:2. The influence of pH of the modification solution is shown in Fig. 4. The optimum pH was ~3 (ee 64%); above this value optical yields decreased rapidly, below pH 3 the region of Ni surface corrosion (high leaching of Ni) was located. Premodification using Na$_2$TA revealed generally poor enantioselectivity (~ee 5%).
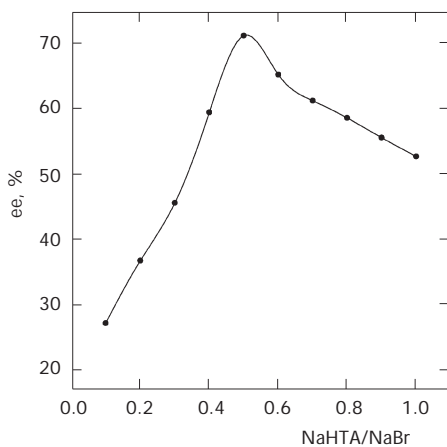
The effect of the NaHTA/NaBr weight ratio on the enantioselectivity of MAA hydrogenation (volume of modification solution 150 ml, c_{NaHTA} = 0.16 mol l^{-1}; T = 293 K; t = 60 min; m_{cat} = 10 g of RaNi suspension)
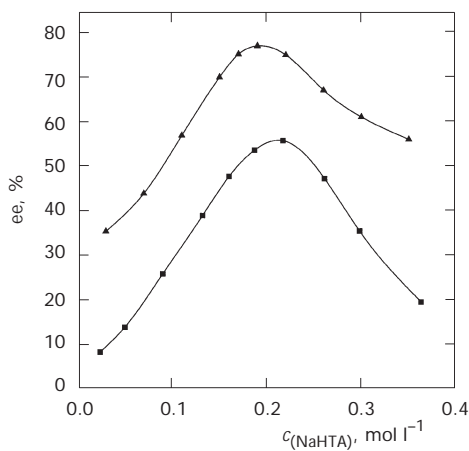
The effect of the modifier NaHTA concentration on the enantioselectivity of the RaNi (▲) and Ni/SiO$_2$ (■) catalysts (volume of modification solution 150 ml (RaNi), 100 ml (Ni/SiO$_2$), NaHTA/NaBr = 0.5; T = 293 K; t = 60 min; m_{cat} = 10 g of RaNi suspension, 3 g of Ni/SiO$_2$)

Raney Nickel – in situ A

Catalytic performance of *in situ* modified Raney nickel was studied in parallel. This modification approach has not been previously applied to Raney nickel. The results obtained with direct addition of the modifier, co-modifier and additive (TA, NaBr and CH_3COOH) in their crystalline forms (TA, NaBr) to the reaction mixture were not satisfactory. Addition of TA to the reaction media retarded the hydrogenation rate and provided very low optical yields (~ee 2%).

Raney Nickel – in situ B

The modification procedure with dissolved modifier (TA), co-modifier (NaBr) and additive (acetic acid) did not show more promising results than via previous method (*in situ* A). The optical yields obtained were slightly better (ee 8%) but low ee values were observed in a wide range of modifier (co-modifier) concentrations. The reasons for low enantiodifferentiation ability of *in situ* modified RaNi have not been clarified.
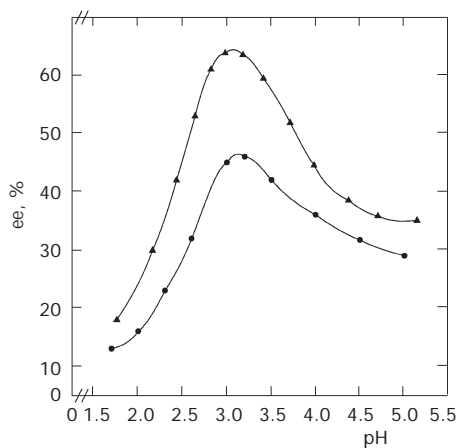
FIG. 4

The effect of pH of the modification solution on the enantioselectivity of the RaNi (▲) and Ni/SiO$_2$ (●) catalysts (volume of modification solution 150 ml (RaNi), 100 ml (Ni/SiO$_2$), c_{TA} = 0.2 mol l^{-1}; T = 293 K; t = 60 min; m_{cat} = 10 g of RaNi suspension, 3 g of Ni/SiO$_2$, pH adjusted with 0.1 M NaOH)

Catalysts Prepared by Sol-Gel Method – Premodification

The premodification strategy for sol-gel catalysts was similar to that for Raney nickel. Effect of the TA amount on ee was tested first. Its optimal concentration was c_{TA} = 0.056 mol l^{-1} and optimal TA/NaBr weight ratio 1:2. The effect of pH of the modification solution is shown in Fig. 4. pH 3.2 represented the region with the best enantiodifferentiation similarly as for Raney nickel (ee 46%). The optimal NaHTA/NaBr weight ratio was found at 0.5; the best enantioselectivity (ee 55%) was achieved for c_{NaHTA} = 0.21 mol l^{-1} (Fig. 3). In analogous experiments with Na$_2$TA, poor enantio-selectivity was revealed as observed also for Raney Ni (ee ~5%). Experiments involving TA at pH adjusted with NaOH and with NaHTA proved an essential role of sodium ions in stabilisation of a surface complex. Similarly positive effect of the disodium salt as suggested elsewhere[49] was not confirmed.

Catalysts Prepared Sol-Gel Method – in situ A

In situ modification involved direct additions of the modifier, co-modifier and additive (TA, NaBr and CH$_3$COOH) in their solid crystalline forms (TA, NaBr) to the reaction system (methyl acetoacetate in tetrahydrofuran). The effect of TA loading on ee is shown in Fig. 5. This dependence revealed a clear maximum at 0.15 g of TA with the weight ratios TA/NaBr = 50 and TA/CH$_3$COOH = 1. It must be noted that only low enantioselectivites were achieved (~21%) likely due to the limited solubility of TA and NaBr in low-polar tetrahydrofuran.

Catalysts Prepared by Sol-Gel Method – in situ B

This approach was analogous to *in situ* A regarding the components (TA, NaBr, CH$_3$COOH); however, TA and NaBr were dissolved in water first and then together with acetic acid introduced to the reactor with MAA. The weight ratios were constant in all the experiments (TA/NaBr = 6.25, TA/CH$_3$COOH = 0.05, TA/H$_2$O = 0.1). The catalysts modified by the *in situ* method B were generally highly active and selective. Figure 5 clearly documents the dependence of ee on the amount of TA. The optimum was at 10.5 mg of the modifier. In this case the components were well available on the catalytic surface unlike in the *in situ* method A. The catalyst modified as described was used repeatedly in MAA hydrogenation without any signifi-cant decrease in its activity and enantioselectivity (Fig. 6). In a single run
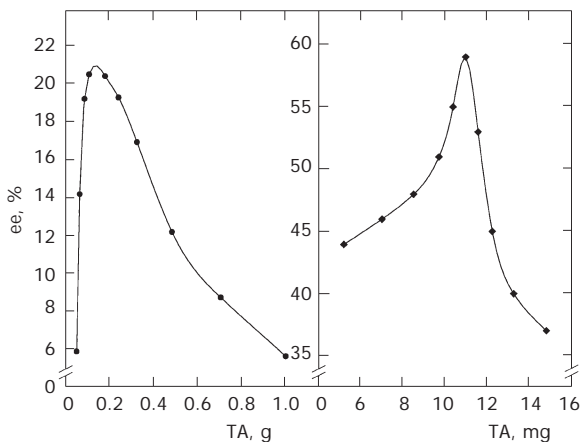
FIG. 5

The effect of TA amount in reaction media on the enantioselectivity for the *in situ* modified Ni/SiO$_2$ catalyst (m_{cat} = 3 g of Ni/SiO$_2$, *in situ* A (●): TA/NaBr = 50, TA/CH$_3$COOH = 1; *in situ* B (◆): TA/NaBr = 6.25, TA/CH$_3$COOH = 0.05, 100 μl of water)
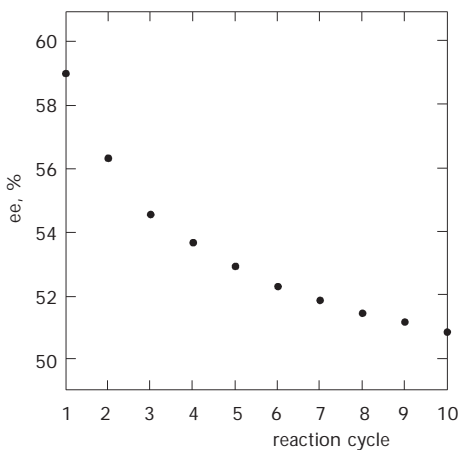

FIG. 6

The dependence of ee on the number of consecutive reaction cycles for the *in situ* B modified Ni/SiO$_2$ in a number of consequent reaction cycles (m_{cat} = 3 g of Ni/SiO$_2$, TA/NaBr = 6.25, TA/CH$_3$COOH = 0.05, 100 μl of water; catalyst washed with 50 ml of THF after each run)

the ee as high as 59% was achieved. After every cycle the catalyst was kept in the reactor and only washed with tetrahydrofuran.

Experimental kinetic data for all catalytic systems are summarised in Table I. It is evident that of all the catalysts Raney nickel conventionally modified with NaHTA could be considered as the most suitable due to the highest enantioselectivity. Conventionally modified sol-gel catalysts with NaHTA were also markedly good. The same applied to the *in situ* method B with dissolved TA and NaBr. In this specific case high resistance to deactivation must not be omitted.

TABLE I
The effect of the catalyst type and modification method on the enantioselectivity and reaction rate

Catalyst	Modification method	Modifier[a]	Additive	Water solution	ee %	r mmol g_{cat}^{-1} min^{-1}
RaNi	premodification	TA	–	Yes	64	0.31
		NaHTA	–	Yes	78	0.42
		Na$_2$TA	–	Yes	5	0.21
	in situ A	TA	acetic acid	No	2	0.05
	in situ B	TA	acetic acid	Yes	8	0.08
Ni/SiO$_2$	premodification	TA	–	Yes	46	0.47
		NaHTA	–	Yes	55	0.55
		Na$_2$TA	–	Yes	5	0.09
	in situ A	TA	acetic acid	No	12	0.43
	in situ B	TA	acetic acid	Yes	59	0.58

[a] NaBr as co-modifier.

REFERENCES

1. Bartek L., Klusoň P., Červený L.: *Chem. Listy* **2005**, *99*, 157.
2. Baiker A.: *J. Mol. Catal. A* **2000**, *163*, 205.
3. Blaser H. U., Jalett H. P., Lottenbach W., Studer M.: *J. Am. Chem. Soc.* **2000**, *122*, 12675.
4. Baiker A.: *J. Mol. Catal. A* **1997**, *115*, 473.
5. Wells P. B., Wilkinson A. G.: *Top. Catal.* **1998**, *5, 39*.

6. Nitta Y., Yamanishi O., Sekine F., Imanaka T., Teranishi S.: *J. Catal.* **1983**, *79*, 475.
7. Osawa T., Harada T., Takayasu O.: *Top. Catal.* **2000**, *13*, 155.
8. Tai A.: *Chem. Ind. (Dekker)* **2003**, *89*, 191.
9. Tai A., Sugimura T. in: *Chiral Catalyst Immobilization and Recycling* (D. E. De Vos, I. F. J. Vankelecom and P. A. Jacobs, Eds), p. 173. Wiley-VCH, Weinheim 2000.
10. Nakagawa S., Tai A., Okuyama T., Sugimura T.: *Top. Catal.* **2000**, *13*, 187.
11. Agbossou F., Carpentier J.-F., Hapiot F., Suisse I., Mortreux A.: *Coord. Chem. Rev.* **1998**, *178–180*, 1615.
12. Wittmann G., Gondos G., Bartok M.: *Helv. Chim. Acta* **1990**, *73*, 635.
13. Bennett A., Christie S., Keane M. A., Peacock R. D., Webb G.: *Catal. Today* **1991**, *10*, 363.
14. Osawa T., Mita S., Iwai A., Takayasu O., Hashiba H., Hashimoto S., Harada T., Matsuura I.: *J. Mol. Catal. A* **2000**, *157*, 207.
15. Slipszenko J. A., Griffiths S. P., Johnston P., Simons K. E., Vermeer W. A. H., Wells P. B.: *J. Catal.* **1998**, *179*, 267.
16. Tai A., Kikukawa T., Sugimura T., Inoue Y., Osawa T., Fujii S.: *J. Chem. Soc., Chem. Commun.* **1991**, 1324.
17. Kukula P., Červený L.: *Res. Chem. Intermed.* **2003**, *29*, 91.
18. Nitta Y., Sekine F., Imanaka T., Teranishi S.: *J. Catal.* **1982**, *74*, 382.
19. Osawa T., Mita S., Iwai A., Miyazaki T., Takayasu O., Harada T., Matsuura I.: *Chem. Lett.* **1997**, 1131.
20. Wittmann G., Bartok G. B., Bartok M., Smith G. V.: *J. Mol. Catal.* **1990**, *60*, 1.
21. Bartek L., Drobek M., Kuzma M., Kluson P., Cerveny L.: *Catal. Commun.* **2005**, *6*, 61.
22. Osawa T.: *Chem. Lett.* **1985**, 1609.
23. Keane M. A.: *Can. J. Chem.* **1994**, *72*, 372.
24. Brunner H., Muschiol M., Wischert T., Wiehl J.: *Tetrahedron: Asymmetry* **1990**, *1*, 159.
25. Osawa T., Harada T., Tai A., Takayasu O., Matsuura I.: *Stud. Surf. Sci. Catal.* **1997**, *108*, 199.
26. Osawa T., Ozawa A., Harada T., Takayasu O.: *J. Mol. Catal. A* **2000**, *154*, 271.
27. Kuznetsova T. I., Murina I. P., Vedenyapin A. A., Akimov V. M., Klabunovskii E. I.: *React. Kinet. Catal. Lett.* **1988**, *37*, 363.
28. Brunner H., Amberger K., Wiehl J.: *Bull. Soc. Chim. Belg.* **1991**, *100*, 571.
29. Yasumori I., Yokozeki M., Inoue Y.: *Faraday Discuss. Chem. Soc.* **1981**, *72*, 385.
30. Keane M. A.: *Langmuir* **1994**, *10*, 4560.
31. Keane M. A., Webb G.: *J. Mol. Catal.* **1992**, *73*, 91.
32. Harada T., Kawamura T., Haikawa S., Osawa T.: *J. Mol. Catal.* **1994**, *93*, 211.
33. Osawa T., Mieno E., Harada T., Takayasu O.: *J. Mol. Catal. A* **2003**, *200*, 315.
34. Osawa T., Harada T.: *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3191.
35. Jones T. E., Baddeley C. J.: *Surf. Sci.* **2002**, *519*, 237.
36. Osawa T., Sawada K., Harada T., Takayasu O.: *Appl. Catal. A* **2004**, *264*, 33.
37. Keane M. A.: *Catal. Lett.* **1993**, *19*, 197.
38. Kukula P., Červený L.: *J. Mol. Catal. A* **2002**, *185*, 195.
39. Keane M. A.: *Langmuir* **1997**, *13*, 41.
40. Keane M. A., Webb G.: *J. Catal.* **1992**, *136*, 1.
41. Kukula P., Červený L.: *Appl. Catal. A* **2001**, *210*, 237.
42. Osawa T., Hayashi Y., Ozawa A., Harada T., Takayasu O.: *J. Mol. Catal. A* **2001**, *169*, 289.
43. Osawa T., Sakai S., Deguchi K., Harada T., Takayasu O.: *J. Mol. Catal. A* **2002**, *185*, 65.
44. Osawa T., Amaya Y., Harada T., Takayasu O.: *J. Mol. Catal. A* **2004**, *211*, 93.

45. Tai A., Kikukawa T., Sugimura T., Inoue Y., Abe S., Osawa T., Harada T.: *Stud. Surf. Sci. Catal.* **1993**, *75*, 2443.
46. Bostelaar L. J., Sachtler W. M. H.: *J. Mol. Catal.* **1984**, *27*, 387.
47. Bostelaar L. J., Sachtler W. M. H.: *J. Mol. Catal.* **1984**, *27*, 377.
48. Fu L., Kung H. H., Sachtler W. M. H.: *J. Mol. Catal.* **1987**, *42*, 29.
49. Sugimura T., Osawa T., Nakagawa S., Harada T., Tai A.: *Stud. Surf. Sci. Catal.* **1996**, *101*, 231.