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The durability of the enantio-differentiating ability of a tartaric acid–NaBr-modified reduced nickel catalyst pre-modified in tetrahydrofuran

Tsutomu Osawa[a,]*, Miho Maegawa[a], Masako Yoshihisa[a], Mika Kobayashi[a], Tadao Harada[b], and Osamu Takayasu[a]

[a]*Faculty of Science, University of Toyama, Toyama 930-8555, Japan*
[b]*Faculty of Science and Technology, Ryukoku University, Otsu 520-2194, Japan*

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The enantio-differentiating hydrogenation of methyl acetoacetate was carried out over a (*R*,*R*)-tartaric acid–NaBr-modified reduced Ni catalyst. The reduced Ni was pre-modified in a tetrahydrofuran solution of tartaric acid and NaBr at atmospheric pressure or at a high hydrogen pressure. The enantio-differentiating ability of 70–90% was maintained during 40 runs over the reduced nickel catalyst pre-modified at 9 MPa hydrogen and 373 K. The results indicated that the durability of a high enantio-differentiating ability of an *in-situ*-modified catalyst would be attributed to the modification conditions at the high hydrogen pressure of 9 MPa and the high temperature of 373 K in the autoclave.

KEY WORDS: pre-modified nickel catalyst; THF; tartaric acid; enantio-differentiating; hydrogenation.

1. Introduction

The synthesis of the desired optically pure enantiomer is an important issue for the production of pharmaceuticals and agrochemicals whose physiological activities depend on the antipode. For this purpose, homogeneous catalysts and heterogenized catalysts have been intensively studied and have been used for the various kinds of enantio-differentiating reactions [1–3]. For the enantio-differentiating solid catalysts, only the enantio-differentiating hydrogenation over a tartaric acid-modified nickel catalyst [4–6] and cinchona modified platinum group metal catalysts [7–9] have attained high enantioselectivities. In spite of the greater difficulty of the stereo-differentiation on the solid surface than that with a molecular catalyst (homogeneous catalyst) or with a molecule anchored on the solid surface (heterogenized catalyst), the enantio-differentiating solid catalysts, which are prepared by the chiral modification of a solid surface with an intrinsic catalytic activity, are expected to be developed for industrial use, because the enantio-differentiating solid catalyst has the advantages of easy preparation, easy separation, easy recovery and reuse, and easy scale up.

A tartaric acid–NaBr-modified nickel catalyst has been conventionally prepared by immersing a nickel catalyst in an aqueous solution of tartaric acid and NaBr (the pre-modification method) [10]. In 2001, it was reported that an *in-situ*-modification (tartaric acid and NaBr were added to the reaction media and the modification was carried out in the same vessel for the hydrogenation reaction) was applied for the preparation of the modified nickel catalyst and that a high enantioselectivity of 80–90% was attained, when reduced nickel or fine nickel powder was used as the base nickel catalyst [11]. A high enantioselectivity of the *in-situ*-modified fine nickel powder catalyst was maintained during 30 runs for the repeated use of the recovered catalyst, while the enantioselectivity of the pre-modified Raney nickel catalyst was almost lost in the 3rd run [12].

The *in-situ*-modification is carried out in an organic solvent. Several groups have reported the pre-modification of nickel in an organic solvent. Bostellaar *et al.* reported that pre-modified Ni/SiO_2 in a methanol solution of tartaric acid showed an e.d.a. of 14–17% for the hydrogenation of methyl acetoacetate [13]. Keane reported that the enantio-differentiating hydrogenation of methyl acetoacetate over a tartaric acid-pre-modified Ni/SiO_2, modified in a solution of methanol, ethanol, or 1-butanol, attained an e.d.a. of 26–36% [14]. They demonstrated that the enantioselectivity of the catalyst modified in alcohol was higher than that modified in an aqueous solution. We reported that the amount of water and Na^+ in the pre-modification solvent, methanol, significantly affected the enantio-differentiating ability (e.d.a.) and e.d.a. durability [15]. The present paper describes a study of the pre-modification of the reduced nickel in THF under atmospheric pressure or under a high hydrogen pressure, because THF was usually used as the reaction solvent for the hydrogenation over the *in-situ*-modified catalyst. The study was undertaken as

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*To whom correspondence should be addressed.
E-mail: osawa@sci.toyama-u.ac.jp

part of an ongoing study for investigating the features of the pre-modification and the *in-situ*-modification.

2. Experimental

Tetrahydrofuran (THF) (Wako Pure Chemical Ind., Ltd., > 99.5% with no stabilizer) was used as received or was used after drying with NaH and distilled. THF treated with molecular sieves 3A 1/16 (Wako Pure Chemical Ind., Ltd., pre-heated at 473 K for 5 h) was also used as the modification solvent. The GLC measurements for determining the conversion and the enantiomer excess (e.e.) were carried out using a Hitachi 263-30 gas chromatograph and a Shimadzu GC-18A gas chromatograph, respectively. The measurement of the optical rotations was carried out using a JASCO DIP-1000 polarimeter.

Reduced nickel catalyst: Nickel oxide (1.5 g) (Wako Pure Chemical Ind., Ltd., lot LDQ3413) was reduced at 623 K in a hydrogen stream (40 cm^3 min^{-1}) for 1 h.

2.1. Modification of the reduced nickel

The reduced nickel was modified by a pre-modification method.

(i) Modification under atmospheric pressure (0.1 MPa): The reduced nickel was immersed in a THF solution (118 cm^3) containing (*R*,*R*)-tartaric acid and NaBr (the amounts were stated in the text) at 273 or 339 K (boiling point of THF) for 1 h. After the modification, the catalyst was washed with THF (two 25 cm^3 portions).

(ii) Modification under a high hydrogen pressure: The reduced nickel and a THF solution (30 cm^3) containing (*R*, *R*)-tartaric acid and NaBr (the amounts were stated in the text) were placed in an autoclave. The modification solution was stirred at 1200 r.p.m. and at 285 or 373 K for 1 h. The modification was carried out under the hydrogen pressure of 9 MPa. After the modification, the catalyst was washed with THF (three 7.5 cm^3 portions).

Enantio-differentiating hydrogenation of methyl acetoacetate: The reaction mixture of methyl acetoacetate (5.0 g), THF as received (10 cm^3) and acetic acid (0.1 g) was subjected to hydrogenation over the modified reduced nickel catalyst. The hydrogenation was carried out in a reciprocal shaking autoclave at 373 K and the initial hydrogen pressure was 9 MPa. The conversion was determined by GLC analyses (5% Thermon 1000 on Chromosorb W at 383 K). For the repeated use of the catalyst, the recovered catalyst was washed with THF (three 10 cm^3 portions) and the freshly prepared reaction mixture was subjected to hydrogenation over the catalyst.

Determination of e.d.a.: The e.d.a. of the modified catalyst was evaluated using the optical purity of the hydrogenated product determined by polarimetry.

e.d.a.(%) = ($[\alpha]_D^{20}$ of methyl 3-hydroxybutyrate $[\alpha]_D^{20}$ of pure enantiomer)$\times$100

The $[\alpha]_D^{20}$ of methyl 3-hydroxybutyrate was calculated using its specific gravity; $d_{20} = 1.058$. The specific optical rotation $[\alpha]_D^{20}$ of the optically pure (R)-methyl 3-hydroxybutyrate is $[\alpha]_D^{20} = -22.95°$ (neat) [10]. When the purity of the methyl 3-hydroxybutyrate after distillation was less than 100% (in the case of the low conversion), the e.d.a. was evaluated by the e.e. determined by GLC. Acetylation of the sample was carried out using acetyl chloride and pyridine. A portion of the acetylated sample was subjected to the analysis using a chiral capillary gas chromatograph equipped with a CP Chirasil DEX-CB (0.25 mm $\times$ 25 m). The e.e. was calculated from the peak integration of the corresponding enantiomers.

3. Results and discussion

3.1. Effect of the Na^+ and water in the modification solution on e.d.a. and on the e.d.a. durability

It was reported that for a pre-modification in methanol, the presence of an appropriate amount of Na^+ and a lower content of water in the modification solution were required to attain a high e.d.a. and good durability, and that the pre-treatment of methanol by molecular sieves was preferable for drying the solvent and supplying Na^+ in addition to Na^+ from NaBr added as an auxiliary modifier [15]. While the *in-situ*-modification attained a high e.d.a. in the presence of Na^+ supplied by only NaBr, pre-modification in methanol required more Na^+ than the *in-situ*-modification.

The effects of the Na^+ and water in the THF pre-modification solution on the e.d.a. and the e.d.a. durability were investigated for the enantio-differentiating hydrogenation of methyl acetoacetate using the reduced nickel catalyst modified at atmospheric pressure and 273 K. Figure 1 shows the effect of the drying of THF on the conversion and e.d.a. The uses of the as received THF and those of dried THF with NaH resulted in the low e.d.a. and conversion during the initial several runs. After the jumps of e.d.a. and the conversion, about 80–90% e.d.a. and 100% conversion were attained during 10 runs for both cases. The results that the e.d.a. values and the e.d.a. durability were almost the same with or without drying the THF indicated that the presence of water in a commercial THF would not affect the e.d.a. and the e.d.a. durability, while the content of water significantly affected the e.d.a. and the e.d.a. durability for the modification in methanol [15]. This would be attributed to the lower content of water in the commercial THF compared with that of methanol. Although the e.d.a. durabilities after the jump in figure 1 were higher than those attained with the tartaric acid–NaBr-modified reduced nickel catalyst pre-modified in

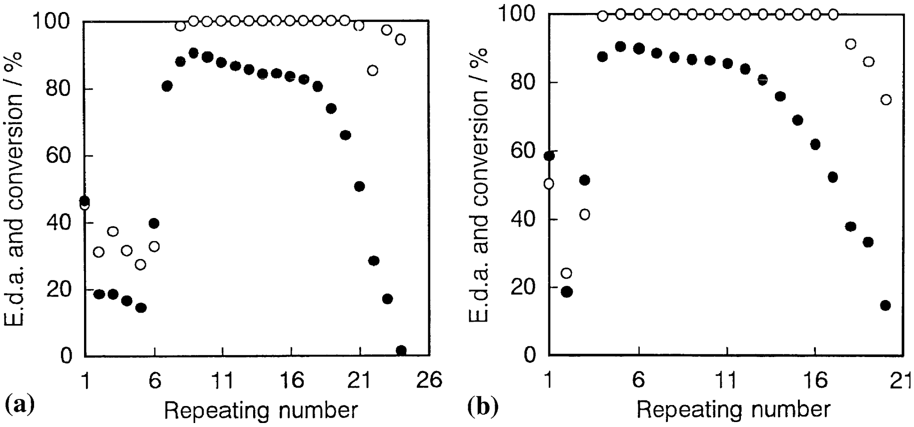

Figure 1. Enantio-differentiating hydrogenation of methyl acetoacetate over nickel catalyst modified in THF as received (a) or THF dried with NaH (b). Modification solution: tartaric acid (1.18 g) and NaBr (18 mg) in 118 cm^3 of THF. Modification condition: 0.1 MPa (atmospheric pressure), 273 K, 1 h. ●, e.d.a.; ○, conversion.

water (e.d.a. lowered to 43% in the 12th run) [16], they are lower than the results attained with the *in-situ*-modified reduced nickel catalyst (e.d.a. of 78% was maintained in the 19th run) [16]. The low e.d.a. and the low conversion observed in the initial runs in figure 1(a) and (b) would be caused by the presence of NaBr crystals in the reaction media in the autoclave. The solubility of NaBr in THF is very low and the modification was carried out in the presence of the undissolved fine NaBr crystals. These undissolved NaBr crystals were difficult to remove from the pre-modification solution by the conventional catalyst washing procedure with THF after the modification. A part of the undissolved NaBr crystals would moved from the pre-modification solution to the reaction media and inhibited the hydrogenation reaction. It is presumed that once the undissolved NaBr was removed from the reaction media by washing after each reaction, the conversion reached 100% and the e.d.a. jumped to over 80%.

In order to confirm the assumption, undissolved NaBr in the pre-modification solution was manually removed as much as possible by sucking with a pipette after the pre-modification and the effect of the removal of undissolved NaBr from the modification solution on the e.d.a. and conversion were investigated. These results are shown in figure 2. When the undissolved NaBr crystals were removed, the low e.d.a. and the low conversion during the initial runs were not observed.

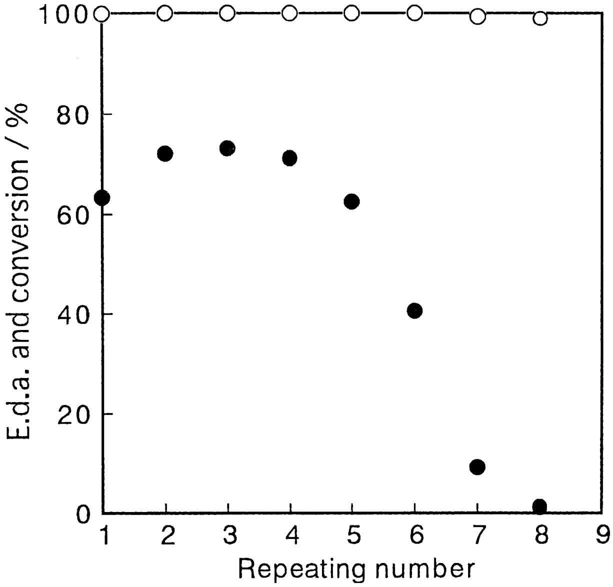

Figure 2. Effect of the remaining NaBr in the modification solution (reaction mixture) on e.d.a. and conversion. Modification solution: tartaric acid (1.18 g) and NaBr (2 mg) in 118 cm^3 of THF. Modification condition: 0.1 MPa (atmospheric pressure), 273 K, 1 h. Remaining NaBr in the modification solution was removed by a pipette after the modification. ●, e.d.a.; ○, conversion.

However, the e.d.a. value and the e.d.a. durability were lower compared with those shown in figure 1 after the jump. These results can be rationalized by the following interpretation. The pre-modification by tartaric acid and NaBr in THF in the presence of the undissolved NaBr crystals (figure 1) was followed by the *in-situ*-modification of NaBr in the reaction media. The *in-situ*-modification of NaBr was one of the important factors for realizing the high e.d.a. and the e.d.a. durability.

Concerning the effect of the Na^+ in the THF modification solution, a high e.d.a. and e.d.a. durability were attained even by using the THF pre-modification solution which was not treated with molecular sieves (figure 1(a)). The result indicated that the amount of Na^+ supplied to the THF solution was adequate due to the addition of NaBr and that the addition other than NaBr was not required. In order to investigate in more detail the effect of the presence of Na^+ in the modification solution, the treatment of THF by molecular sieves without the addition of NaBr was examined. These results are shown in figure 3. Using THF as received in the absence of NaBr (there was no Na^+ in modification solution and in the reaction media), a low e.d.a. was attained. However, when THF was treated with molecular sieves (Na^+ would be leached to THF from molecular sieves [15]), the e.d.a. and the e.d.a. durability were significantly increased. These results indicated that Na^+ in the THF modification solution would be significant in order to have the ability of enantio-differentiation as well as modification in methanol [15] or in water [10]. However, as indicated by the results of figure 1, being different from the pre-modification in methanol, Na^+ was sufficiently supplied by the addition of NaBr to the THF pre-modification solution.

3.2. *Effect of modification temperature and pressure on e.d.a. and on the e.d.a. durability*

Figure 1 shows that the e.d.a. increased after the initial several runs. The increase was attributed to the removal of NaBr crystals by the catalyst washing process after each run. It can be recognized that NaBr existing in the reaction media worked as a modifier under the *in-situ*-condition. That is, figure 1 indicates that the combination of the pre-modification of tartaric acid/NaBr and the *in-situ*-modification of NaBr attained over an 80% e.d.a. during 10 runs. The maximum e.d.a. value was almost the same as that attained over the reduced nickel catalyst prepared by the *in-situ*-modification of tartaric acid and NaBr, however, the e.d.a. durability was lower than the result of the *in-situ*-modification [16]. In order to reveal the factors, which are necessary for attaining a high e.d.a. durability for the hydrogenation over the *in-situ*-modified nickel catalyst, the effects of the modification temperature and pressure were investigated. Figure 4 shows the results of the hydrogenation of methyl acetoacetate over a reduced nickel catalyst modified in THF at 0.1 MPa and at the boiling point temperature of THF (339 K). NaBr crystals remaining in the modification solution was carefully removed after the modification. The e.d.a. and the e.d.a. durability were significantly improved compared to the results of figure 2 (modification was carried out at 0.1 MPa and 273 K). However, the values are much lower than the results attained by the *in-situ*-modifica-

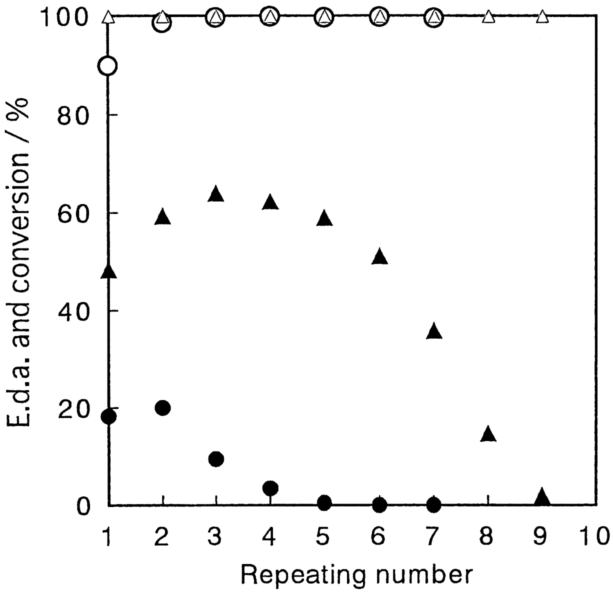

Figure 3. Effect of the Na^+ in the modification solution on e.d.a. and conversion. Modification solution: tartaric acid (1.18 g) in 118 cm^3 of THF. Modification condition: 0.1 MPa (atmospheric pressure), 273 K, 1 h. ●, e.d.a.; ○, conversion (THF was used as received); ▲, e.d.a.; △, conversion (THF was treated with molecular sieves 3A).

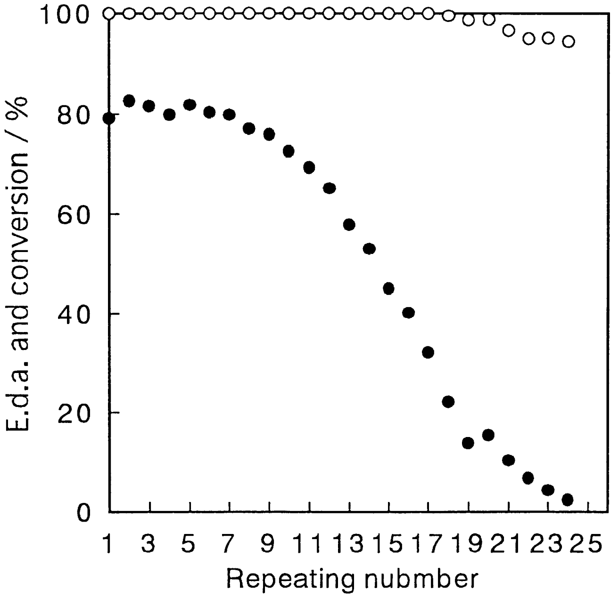

Figure 4. Enantio-differentiating hydrogenation of methyl acetoacetate over a reduced nickel catalyst pre-modified in THE at atmospheric pressure. Modification solution: tartaric acid (1.18 g) and NaBr (1.8 mg) in 118 cm^3 of THF. Modification condition: 0.1 MPa (atmospheric pressure), 339 K, 1 h. Remaining NaBr in the modification solution was removed after the modification. ●, e.d.a.; ○, conversion.

tion. Figure 5(a) shows the results of the hydrogenation of methyl acetoacetate over the modified catalyst prepared at a high hydrogen pressure. The catalyst was pre-modified under conditions similar to those of the *in-situ*-modification (at 9 MPa and at 373 K). The e.d.a. and e.d.a. durability of the obtained catalyst were high and almost the same as those attained by the *in-situ*-modified reduced nickel catalyst. Even in run 40, a 67% e.d.a. was maintained. Figure 5(b) shows the results of the hydrogenation over the catalyst pre-modified at 9 MPa and 285 K. The values of the e.d.a. and the e.d.a. durability up to run 15 were almost the same as the results obtained by the catalyst pre-modified at 9 MPa and 373 K. However, after run 15, the e.d.a. gradually decreased and was almost zero at run 32. Although, after the modifications under a high hydrogen pressure, the crystals of NaBr were not visually observed in the modification solution, the catalyst exhibited a low e.d.a. and conversion during the initial several runs. The initial low e.d.a. and conversions in figure 5(a) and (b) could be attributed to the very fine crystals of NaBr in the reaction mixture or excess amount of NaBr adsorbed on the nickel surface. Table 1 shows a summary of the effects of the modification temperature and pressure on the maximum attained e.d.a. and the number of runs over 70% e.d.a. during the repeated runs. The high e.d.a. value and the high e.d.a. durability were attained by the modification at 9 MPa and at a high temperature

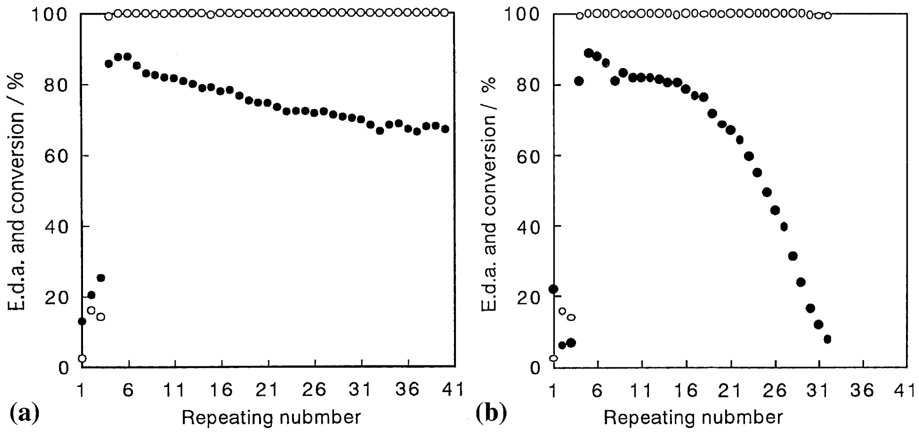

Figure 5. Enantio-differentiating hydrogenation of methyl acetoacetate over reduced nickel catalyst pre-modified in THF at a high hydrogen pressure. Modification solution: tartaric acid (0.3 g) and NaBr (4.5 mg) in 30 cm^3 of THF. Modification condition: 9 MPa (hydrogen pressure), 373 K (a), 285 K (b), 1 h. ●, e.d.a.; ○, conversion.

Table 1
Summary of the effect of the modification temperature and pressure on the maximum e.d.a. and the number of runs over 70% e.d.a.

Modification pressure	Modification temperature	
	Low (273 or 285 K)	High (339 or 373 K)
0.1 MPa	73% 4 runs (figure 2)	83% 10 runs (figure 4)
9 MPa	89% 17 runs (figure 5(b))	88% 28 runs (figure 5(a))

in THF. These results attained by the pre-modification at 9 MPa and at high temperature in THF indicated that the high e.d.a. and the high e.d.a. durability of the *in-situ*-modified catalyst would also be attributed to the modification of tartaric acid and NaBr under the high hydrogen pressure of 9 MPa and the high temperature of 373 K in the autoclave.

4. Conclusion

The enantio-differentiating hydrogenation of methyl acetoacetate was carried out over a tartaric acid–NaBr-pre-modified reduced nickel catalyst. The nickel catalyst was modified in a THF solution of the modifiers. The e.d.a.s of 70–90% were maintained during 40 runs over the reduced nickel catalyst pre-modified at 9 MPa and 373 K. As these conditions of the pre-modification in THF are similar to those of the *in-situ*-modification, it can be presumed that the high e.d.a. and the e.d.a. durability of the *in-situ*-modified catalyst are attributed to the modification under the high hydrogen pressure of 9 MPa and the high temperature of 373 K in the autoclave. For the pre-modification at atmospheric pressure, the drying of THF did not affect the e.d.a. and the e.d.a. durability. The presence of Na^+ in the modification solution was required for attaining a high e.d.a. and the e.d.a. durability, and sufficient by the supply from NaBr. These features of the modification in THF were different from those previously reported in methanol (drying of methanol and the additional supply of Na^+ were required for attaining a high e.d.a. and an e.d.a. durability).

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