

Catalytic Hydrogenation of Chiral α -Amino and α -Hydroxy Esters at Room Temperature with Nishimura Catalyst without Racemization

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Abstract: The hydrogenation of carboxylic acid derivatives at room temperature was investigated. With a mixed Rh/Pt oxide (Nishimura catalyst), low to medium activity was observed for various α -amino and α -hydroxy esters. At 100 bar hydrogen pressure and 10% catalysts loading, high yields of the desired amino alcohols and diols were obtained without racemization. The most suitable α -substituents were NH_2 , NHR , and OH , whereas $\beta\text{-NH}_2$ were less effective. Usually, aromatic rings were also hy-

drogenated, but with the free bases of amino acids as substrates, some selectivity was observed. No reaction was found for $\alpha\text{-NR}_2$, $\alpha\text{-OR}$, and unfunctionalized esters; acids and amides were also not reduced under these conditions. A working hypothesis for the mode of action of the catalyst is presented.

Keywords: 1,2-amino alcohol; α -amino ester and α -hydroxy ester; 1,2-diol; catalytic hydrogenation

Introduction

Chiral 1,2-diols and 1-hydroxy-2-amino compounds are versatile building blocks for a variety of biologically active ingredients.^[1] These products can be prepared catalytically via aminohydroxylation and dihydroxylation of terminal $\text{C}=\text{C}$ bonds^[1,2], and via hydrolytic kinetic resolution of terminal epoxides using Jacobsen's methodology.^[3] Another attractive approach is obviously the reduction of α -hydroxy- and α -amino acids or esters from the chiral pool. In most cases, this is carried out using metal hydrides which are reactive at low temperatures thereby guaranteeing the integrity of the stereogenic center.^[4] Even though such reactions can be carried out at room temperature on a 100–150 g scale,^[5] the costs and the large amount of waste render this methodology less attractive for technical applications. From this point of view, catalytic hydrogenation would, in principle, be a perfect alternative. However, carboxylic acids and esters are the least reactive functional groups for the classical hydrogenation catalysts and usually temperatures $>200^\circ\text{C}$ are needed for efficient transformations. It is thus not surprising that under such drastic conditions the reduction of the ester is often paralleled by racemization.

There are a few exceptions: for Ru oxide modified with a second metal like Re reasonable activity even at 60°C and 200 bar was claimed for the hydrogenation

of malic acid to the corresponding triol,^[6,7] with little or no racemization. However, the catalyst loading was very high and the catalysts are not commercially available. Ru oxide was able to hydrogenate alanine at 100°C and 200 bar with moderate to good yields but long reaction times and some racemization (93–98.5% ee) were observed.^[8] He et al.^[9] modified supported Rh, Pt, Pd, and Ru catalysts or the corresponding metal salts with Mo, Re, or W carbonyls and the resulting bimetallic catalysts were able to reduce carboxylic acids at $145^\circ\text{C}/100$ bar. Other catalyst systems able to reduce carboxylic acids below 200°C were Re oxides ($150\text{--}250^\circ\text{C}$, 150–300 bar),^[10,11] homogeneous Ziegler-type Ni catalysts and Ru chloride complexes,^[12] and Ru-CO-clusters bearing $\text{P}(\text{CH}_2\text{OH})_3$ ligands ($100\text{--}130^\circ\text{C}$ and 130 bar).^[13] The application of these catalysts to the hydrogenation of chiral acids was not investigated but we suspect that racemization would occur above 100°C .

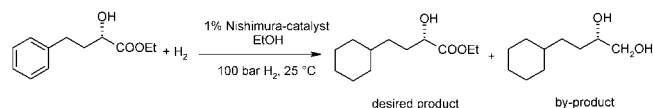
Esters are somewhat easier to hydrogenate than the corresponding acids. With high loading (weight catalyst $>$ weight substrate!), activated Raney nickel but also Cu chromites were claimed to be active even at room temperature.^[14] However, no follow-up results were reported by other investigators and reproduction might be difficult. Other systems like Cu–Al oxides for the hydrogenation of malic acid diisopropyl ester^[15] and homogeneous Ru complexes for the hy-

drogenation of electron-deficient esters^[16,17] also needed $T > 100^\circ\text{C}$ and high pressure, or were only active for a very limited range of substrates.

To summarize: all catalytic systems described above have drawbacks. Most of the catalysts are not commercially available, catalysts loading is usually high, racemization can be a problem above 100°C and it is not always clear whether the results are really reproducible. Undoubtedly there is room for improvement and in this contribution we describe a very mild method for the hydrogenation of a variety of chiral α -amino and α -hydroxy acid esters to the corresponding chiral diols and amino alcohols in good chemical yields and with high ee.

Results and Discussion

We started our investigation after a serendipitous observation. When attempting to hydrogenate the aromatic ring of ethyl 2-hydroxy-4-phenyl butyrate using Nishimura's catalysts (mixed Pt/Rh oxide with the composition 45.9% Rh, 19.9% Pt) we obtained a by-product, identified as the corresponding diol (Scheme 1). This finding led us to hypothesize that Nishimura's catalyst, which is often used for ring hydrogenation, might also be active for ester reductions.



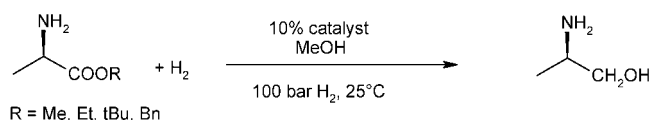
Scheme 1. Ring hydrogenation and by-product formation with Nishimura catalysts.

In a first phase we tried to confirm this hypothesis and tested a series of different catalysts and substrates and carried out a systematic screening with alanine esters (Scheme 2, Table 1). We quickly found that it is indeed possible to reduce certain esters with good yield but that the scope of the new reaction is rather narrow:

- ♦ **Catalyst type:** Only the Nishimura catalyst is really suitable; while Ru and Pt oxide showed weak activity, Rh, Pd, Ir, and Re oxide as well as various supported catalysts, including a 2% Pt, 4% Rh/C were completely inactive (results not shown). Pre-reduction of the oxide catalysts gave an almost inactive system.
- ♦ **Catalyst loading:** A relatively high catalyst loading of 10% (w/w) Nishimura catalyst was necessary. With 1% catalyst loading, conversion was still high but a variety of by-products (mostly dimers and oligomers) was formed.
- ♦ **Substrate:** Only the esters of α -hydroxy and α -amino acids were converted. Under the same condi-

tions, non-functionalized esters, acids, or amides did not react (results not shown). As expected, aromatic rings were usually completely hydrogenated.

- ♦ **Solvent and additives:** The solvents giving the highest activities and yields were methanol or ethanol but other polar solvents like THF, dioxane, DMF, AcOH, or water are also suitable ($>50\%$ yield of the desired amino alcohol). In DMA, diglyme, triglyme, or pyrrolidone conversions of $>50\%$ but many unidentified di- and polymers were obtained. High conversion to polymers but no amino alcohol was observed in hexane. The addition of bases such as Et_3N , imidazole, or *p*-dimethylaminopyridine gave no improvement or lower activities; the addition of strong acids such as HCOOH or CF_3COOH blocked the reaction.



Scheme 2. Hydrogenation of alanine esters.

In the light of these screening results, we concentrated our study on the investigation of selected α -amino and α -hydroxy esters in order to show the scope and limitation of the Nishimura catalyst. Results are listed in Tables 2 and 3.

High yields of the amino alcohols or lactams were obtained for all α -amino acid esters investigated (alanine, glutamic acid, leucine, phenylalanine, serine, and homophenylalanine), irrespective of the nature and functionalization of at the α -carbon. An additional alkyl substituent on the α -carbon (entry 2.3) and monomethylation of the amino group (entry 2.2) were tolerated without significant loss in activity. However, the corresponding alanine derivatives with an $\text{N}(n\text{-Pr})_2$ or an NH-BOC group did not react at all (results not shown).

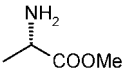
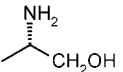
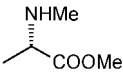
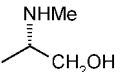
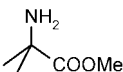
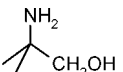
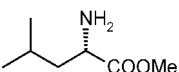
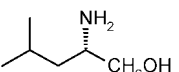
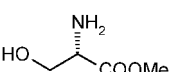
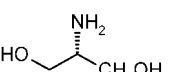
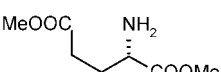
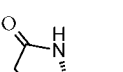
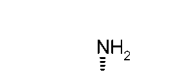
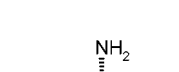
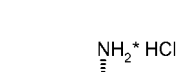
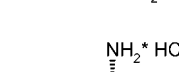
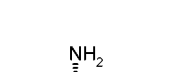
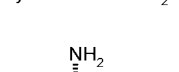
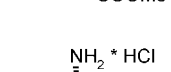
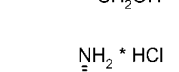
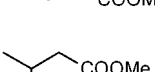
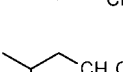
For aliphatic amino acid esters, higher conversion and yield were obtained with the free base than with

Table 1. Screening studies: Effect of catalyst type and loading, and ester group. Conditions: 1 – 10 mg catalyst, 100 mg alanine ester, MeOH, 100 bar hydrogen pressure, 16 h, 25°C .

Catalyst	Catalyst loading (%)	R	Conversion (%) ^[a]	Alaninol (%) ^[a]	By-products (%)
Nishimura	10	Me	>90	>90	<10
RuO_2	10	Me	≥ 35	35	<10
PtO_2	10	Me	30	20	10
Nishimura	1	Me	≥ 70	50	20
Nishimura	5	Me	>90	90	10
Nishimura	10	Me	>90	>90	<10
Nishimura	10	Et	>90	>90	<10
Nishimura	10	<i>t</i> -Bu	60	40	<10
Nishimura	10	Bn	>90	90	10

^[a] NMR results.

Table 2. Scope of Nishimura catalyst: Effect of amino acid structure. 10 mg catalyst, 100 mg substrate, MeOH, 100 bar hydrogen pressure, 25 °C, 16 – 20 h.

Substrate	Main product	Conversion ^[a] (%)	Yield ^[a] (%)	Comments	Entry
		> 90	> 90	the HCl salt gave 40% conv. to the desired amino alcohol	2.1
		75	75		2.2
		> 90	> 90		2.3
		> 90	> 90	the HCl salt gave only 10% conv.	2.4
		> 90	90	10 mg serine, 10% byproduct; the HCl salt gave 60% conv.	2.5
		> 90	90		2.6
		> 90	40	40% ring hydrogenated amino alcohol, 20% byproducts	2.7
		> 90	> 90		2.8
		> 90	40	40% ring hydrogenated amino alcohol, 20% byproducts	2.9
		20	20	80% ring hydrogenated amino ester	2.10
		15	15	–	2.11

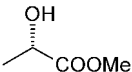
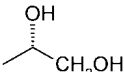
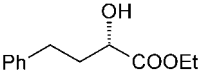
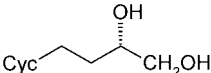
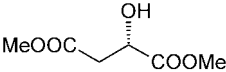
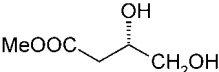
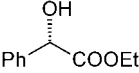
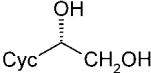
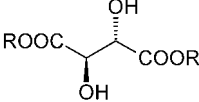
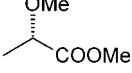
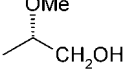
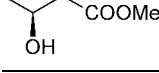
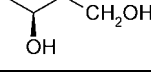
^[a] NMR results.

the HCl salt (see comments in entries 2.1, 2.4, 2.5). With aromatic derivatives, the reactions of the free bases showed an approximately 1:1 mixture of ring hydrogenated and aromatic amino alcohols (entries 2.7 and 2.9). In contrast, the HCl salts always gave 100% ring hydrogenation, and in the case of phenylalanine, the ester hydrogenation of the HCl salt was again much slower than for the free base. These examples show that the presence of a free amino group slows down the rate of ring hydrogenation. The reduction of the ester of glutamic acid (entry 2.6)

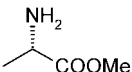
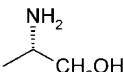
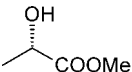
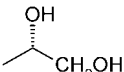
clearly shows that α -functionalized carboxylic acid derivatives can be selectively hydrogenated in the presence of another ester group: The non-activated ester function is not reduced but forms a lactam under our reaction conditions. The β -amino acid ester tested showed some conversion to the desired β -amino alcohol, but the reaction was much slower than with the α -amino acids (entry 2.11).

The scope of the catalyst system was also tested for α -hydroxy esters (Table 3). For a variety of derivatives, high conversions and yields were obtained, but

Table 3. Variation of α -hydroxy esters. 10 mg Nishimura catalyst, 100 mg substrate, MeOH, 100 bar hydrogen pressure, 25 °C.

Substrate	Main product	Conversion ^[a] (%)	Yield ^[a] (%)	Remarks	Entry
		77	77	–	3.1
		> 90	> 90	–	3.2
		60 (> 90) ^[b]	45 (71) ^[b]	15 (29) ^[b] % lactone	3.3
		69 (> 90) ^[c]	51 (> 90) ^[c]	20 mg catalysts	3.4
	–	< 10	< 10	R = Me, Et, <i>i</i> -Pr	3.5
		< 10	< 10		3.6
		< 10	< 10		3.7

^[a] NMR results.^[b] With 30 mg catalyst.^[c] With 60 mg catalyst**Table 4.** Preparative-scale experiments. 10% Nishimura catalysts (w/w), 30% substrate loading (w/v), 100 bar hydrogen pressure, 25 °C.

Substrate	Main product	Conversion ^[a] (%)	Yield ^[a] (%)	Comments	Entry
		> 95	> 80	2 g substrate, 100% isolated yield, 15% di- and oligomers	4.1
		> 90	> 90	6 g substrate, 91% isolated yield	4.2

^[a] NMR results.

sometimes higher catalyst loadings were necessary than for the corresponding amino esters. As expected, phenyl groups were completely converted to cyclohexyl groups (entries 3.2 and 3.4). Selective hydrogenation of an α -substituted ester was possible without reducing other ester functions but also here the cyclization product was formed (entry 3.3). No reaction was observed with esters of tartaric acid (entry 3.5), α -methoxy (entry 3.7), and β -hydroxy esters (entry 3.7).

In order to improve the performance of the Nishimura catalyst, the influence of pressure, temperature and starting material concentration were investigated in more detail using the reduction of methyl lactate as a model reaction. Lowering the hydrogen pressure to 10 bar resulted in very low conversions, while there was no significant difference between 100 and 140 bar. Figure 1 shows the effect of the starting material concentration on the yield of propane-

diol at different temperatures. Usually, the highest yields and conversions were obtained at a starting material concentration of 30% with the highest yields at the lowest temperature. Similar results were also observed for alanine methyl ester (results not shown). In both cases, the catalyst had a different aspect in the low temperature experiments (finely divided powder instead of aggregates observed at higher temperatures); re-use was not possible in any case.

Two preparative-scale experiments were carried out with alanine methyl ester and methyl lactate under optimized conditions (Table 4). In both cases, >90% conversion and >80% chemical purity of the desired alcohols were obtained without any racemization. In these experiments, a distinct induction period of about 4 minutes was observed after hydrogen saturation (see Figure 2).

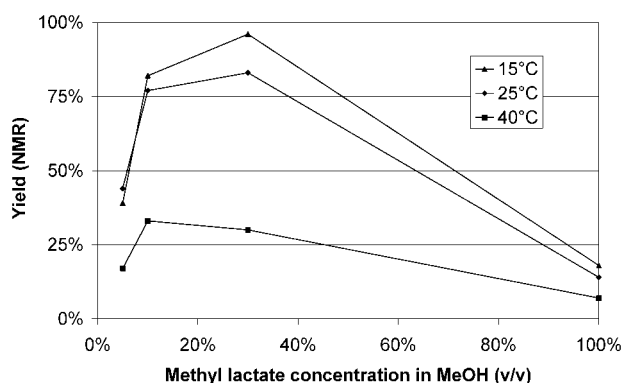


Figure 1. Effect of substrate concentration on diol yield. Catalyst loading 10% (w/w), for 5%, 10% and 30% substrate concentration, 3% for 100% substrate concentration, MeOH, 16 h, 100 bar hydrogen pressure, 25 °C. NMR results.

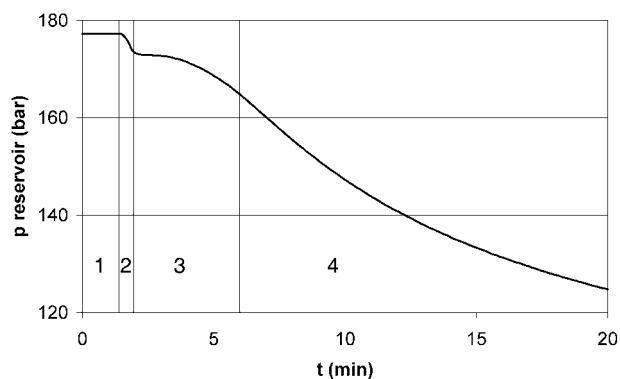


Figure 2. Pressure drop in the reservoir with reaction time (entry 1, Table 4). Conditions see experimental. Phase 1: no stirring, check for leaks; phase 2: hydrogen saturation of solution; phase 3: induction period/hydrogenation; phase 4: hydrogenation.

For the discussion of a possible mode of action, we think that the following results are pertinent:

i) The ease of ester reduction decreases in the sequence: α -NH₂ > α -OH, NH-alkyl > β -NH₂. Acids, unsubstituted esters or esters with an α -N(alkyl)₂, α -O-alkyl, α -NH-BOC, or β -OH group are not reactive.

ii) Only the oxidic, bimetallic Nishimura catalyst is active under these mild reaction conditions

iii) The addition of acid leads to a significantly lower hydrogenation rate.

iv) Pre-hydrogenation of the catalyst in absence of substrate leads to catalysts with low activity.

v) A distinct induction period and a significant deactivation of the catalyst especially at higher temperatures are observed.

Based on these observations, we propose as a working hypothesis the formation of a multi-functional active center consisting of a basic and multi-metallic sites. On this ensemble, the substrate is adsorbed, transformed in several steps and the desired product is desorbed as depicted in Figure 3. We think that the α -NH₂, α -NHR, or α -OH groups act as efficient anchoring groups by interaction with a basic (oxidic) site situated very close to the metallic centers leading to the strongly adsorbed and activated ester. Such an interaction would not be possible with OR or NR₂ groups and less favored with β -functions. Our model also explains why we need an oxidic catalyst which has to be reduced *in situ* and can not be re-used. From the induction period it is obvious that the original Pt-Rh oxide is not the active catalyst. The observed induction period indicates that the active site is a reduced (bimetallic?) species formed in presence of hydrogen and stabilized by a suitable substrate. It seems to be generated only under certain well-defined conditions, which we do not completely understand. This active form is thermally (and probably chemically) rather unstable but is able to perform the necessary transformations. Longer exposures to hydrogen (pre-hydrogenation or at the end of the reaction) will probably result in larger metallic particles where the basic sites are no longer close to the metallic sites. After adsorption, we propose that the C-OR bond of the activated intermediate is cleaved by reaction with an M-H species giving an adsorbed aldehyde and an M-OR species. Similar reactions have been proposed for instance by Turek et al.^[12] The aldehyde can either desorb or be hydrogenated to the desired alcohol. As a last step in the cycle, the active metallic center will be restored by reaction of the M-OR species with hydrogen (in a sort of Mars-Van Krevelen mechanism). If the hydrogenolysis step or the reduction of the aldehyde is too slow, the adsorbed species and/or the free aldehyde can react with starting material or products to a variety of byproducts (dimers, oligomers). This could explain, why two metals are necessary for good activity and selectivity, one for the C-OR cleavage (probably Rh) and for fast hydrogenation of the aldehyde (most likely Pt).

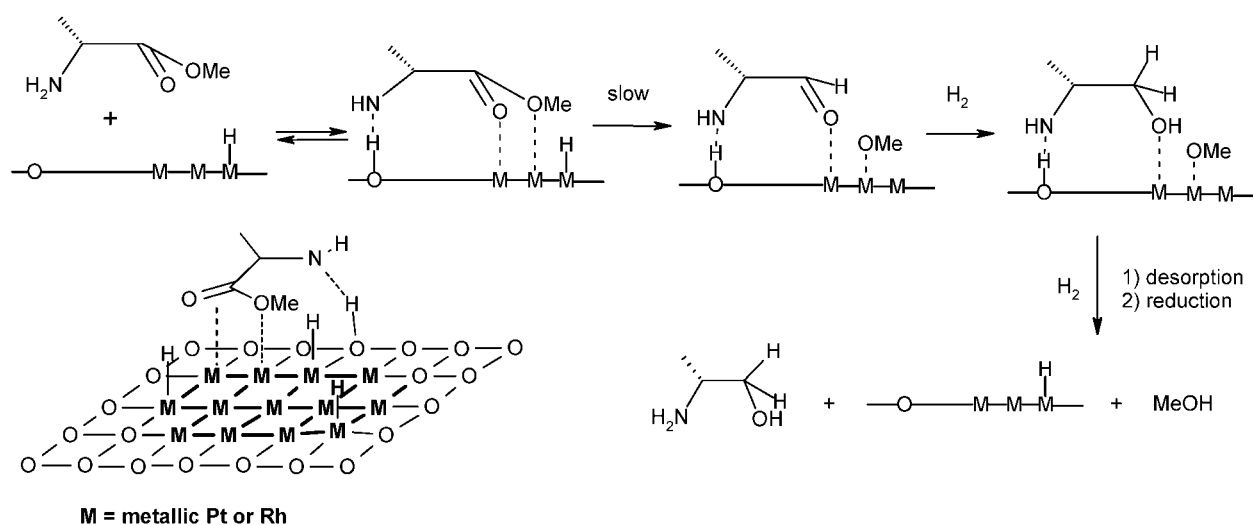


Figure 3. Artists view of the active site and of important stages of the reaction.

While this working hypothesis can rationalize many of our observations, we still do not really understand why only the Nishimura catalyst and no other oxidic or supported bimetallic catalysts are active.

Conclusion

We have shown that the Nishimura catalyst can be used for the hydrogenation of chiral α -amino and α -hydroxy esters to the corresponding chiral alcohols under very mild conditions with reasonable yields. Usually, α -amino acid esters show a higher reactivity than the related hydroxy acid esters. No racemization occurs, and the system does not hydrogenate unfunctionalized esters. Under basic conditions, some selectivity for the ester vs. aromatic ring hydrogenation is observed. Since the Nishimura catalysts are very expensive and high loadings are necessary, this system is only feasible for preparative but not yet for technical applications. Further investigation regarding the nature of the active catalytic species and improvement of the chemoselectivity are in progress and will be reported in due course.

Experimental Section

General Remarks

The Nishimura (mixed Rh/Pt oxide, composition 45.9% Rh, 19.9% Pt), the PtO₂ (80.8% Pt), and the 2% Pt/4% Rh/C catalyst (FG 209/RD) were supplied by Degussa, the Rh₂O₃ by Engelhard (E 3867). The substrates and solvents were used as received or prepared according to literature procedures. Most of the analysis was done on a Bruker 300 MHz machine equipped with an auto sampler with CDCl₃ or CD₃OD as solvents. Usually, a few microliters of the product solutions

were diluted with 0.8 mL of CD₃OD and analyzed directly, to avoid problems related to the work-up. The ee of 1,2-propanediol and of alaninol (derivatization with Ac₂O) were determined on a chiral GLC column (Beta-dex 110, Supelco hydrogen carrier). All screening experiments were carried out in a 50-mL autoclave, where four parallel experiments were run at the same pressure and reaction temperature.

Typical Screening Experiment

10 mg Nishimura catalysts were placed in a 2.5 mL glass vial equipped with a small stirrer bar. 1 mL of solvent and 100 mg alanine methyl ester (liberated from the hydrochloride by extraction from a NaHCO₃ solution with CH₂Cl₂) were added. A total of 4 vials were placed in the autoclave. After sealing, it was purged with argon (3 times 10 bar) and with hydrogen (3 times 10 bar) and the pressurized to 100 bar.

Preparative-Scale Experiments for (*R*)-Methyl Lactate

600 mg Nishimura catalyst were wetted with a small amount of MeOH under inert atmosphere and placed in a 50-mL autoclave equipped with a magnetic stirrer bar and baffles. 6 g substrate dissolved in MeOH (total volume 20 mL) were added, and the autoclave was sealed and purged with argon (3 times 10 bar) and hydrogen (3 times 10 bar). After pressurizing to 100 bar, the reaction was started by turning the stirrer on. After 16 h, the pressure was released, and the autoclave was purged with argon. After filtration, the solution was evaporated to dryness and analyzed by NMR and GLC (ee determination). Yield: 4.39 g (91%, purity > 90%). The ee values of the product was >99%.

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