Mechanism of Homogeneously and Heterogeneously Catalysed Meerwein–Ponndorf–Verley–Oppenauer Reactions for the Racemisation of Secondary Alcohols

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Abstract: The mechanism of hydrogen transfer from alcohols to ketones, catalysed by lanthanide(III) isopropoxides or zeolite Beta has been studied. For the lanthanide catalysed reactions, (*S*)-1-phenyl-(1-$^2H_1$)ethanol and acetophenone were used as case studies to determine the reaction pathway for the hydrogen transfer. Upon complete racemisation all deuterium was present at the 1-position, indicating that the reaction exclusively takes place via a carbon-to-carbon hydrogen transfer. Zeolite Beta with different Si/Al ratios was applied in the racemisation of (*S*)-1-phenylethanol. In this case the racemisation does not proceed via an oxidation/reduction pathway but via elimination of the hydroxy group and its re-addition. This mechanism, however, is not characteristic for all racemisation reactions with zeolite Beta. When 4-*tert*-butyl cyclohexanone is reduced with this catalyst, a classical MPV reaction takes place exclusively. This demonstrates that zeolite Beta has a substrate dependent reaction pathway.

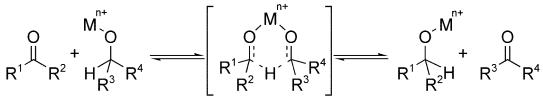
Keywords: hydrogen transfer · lanthanides · Meerwein–Ponndorf–Verley reduction · Oppenauer oxidation · zeolites

Introduction

The oxidation of alcohols and the reduction of ketones has always been a mainstay of organic chemistry. Recently, the racemisation of alcohols via the corresponding ketone has attracted considerable attention. This racemisation in combination with an enzyme catalysed resolution is the backbone of many dynamic kinetic resolutions.[1]

In 1925, Meerwein and Schmidt reported a mild method for the reduction of ketones and aldehydes by alcohols with metal alkoxides as the catalysts.[2] Verley,[3] Ponndorf[4] and Lund[5] independently investigated the scope of this reaction. Twelve years later, Oppenauer recognised the possibility to reverse the reaction and utilised it as an oxidation.[6] Ever since, the Meerwein–Ponndorf–Verley (MPV) reduction and the Oppenauer oxidation have been textbook examples of highly selective and efficient reactions under mild conditions. Usually, readily available reductants such as ethanol or 2-propanol are used as hydrogen donor in the MPV reduction, whereas oxidants such as acetone or cyclohexanone are used as hydrogen acceptor in the Oppenauer oxidation. Several reviews on the Meerwein–Ponndorf–Verley and Oppenauer (MPVO) reactions have been published.[7–10]

The mechanism of the MPV reaction is generally believed to involve a six-membered cyclic transition state in which both the substrate and the reductant/oxidant are coordinated to the metal ion (Scheme 1). A similar bimolecular reaction between a coordinated alcohol and a coordinated ketone has been proposed as well.[11] As an exception, a single electron transfer pathway was observed for alkali metal ions catalysed MPV reductions.[12] Metal hydrides are only formed during hydrogenations catalysed by transition metals such as ruthenium.[13] In addition, a few examples are known of MPV alkynylations and cyanations.[14,15] In these cases, the transfer mechanism is reported to be similar to the mechanism of the hydride transfer as depicted in Scheme 1.



Scheme 1. Generally accepted mechanism of the MPV reduction and Oppenauer oxidation.

In the MPV reduction, the ketone or the aldehyde coordinates to the metal centre of the catalyst, which causes the activation of the double bond (Scheme 1). A hydride shift takes place and the alkoxide is released as ketone or alde-

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DOI: 10.1002/chem.200305460

hyde. Alkoxides can exchange with alcohols present in solution, so an equilibrium of various metal alkoxides may exist during the reaction.

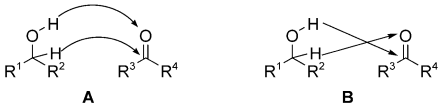
In 1953, deuterium tracer studies of aluminium(III) isopropoxide catalysed reactions were reported that supported the mechanism proposed.[16] However, the experimental methodology available at that time was rather inaccurate. The authors estimated the error margin in their procedure for the deuterium determination (falling-drop method[17]) to be 10%.

Traditionally, MPVO reactions are performed with stoichiometric amounts of Al^{III} alkoxides. The reactions were improved considerably by the introduction of Ln^{III} alkoxides as the catalyst.[18] With these catalysts, only catalytic amounts of this metal ion are required. Recently, much higher reactivities for aluminium catalysed MPVO reactions have been achieved with dinuclear Al^{III} complexes[19] and with Al^{III} alkoxides generated in situ.[20] Most likely, the relatively high activity of the Ln^{III} ions can be ascribed to the high ligand exchange rates with these ions.

Recently, doubts were raised whether the mechanism proceeds exclusively via a carbon-to-carbon hydrogen transfer (Scheme 2, mechanism A).[21] During racemisation of (*S*)-1-phenyl-(1-$^2H_1$)ethanol with samarium(III) or aluminium(III) isopropoxide in the presence of acetophenone, part of the deuterium atoms disappeared from the 1-position. This was suggested to be due to the occurrence of a second pathway involving an oxygen-to-carbon hydrogen transfer (Scheme 2, mechanism B).

A different class of catalysts for the MPVO reaction consists of zeolite Beta and its derivatives containing other metals. Several examples are known and the reduction or oxidation can be performed either in the gas phase[22–24] or in solution.[25–29] In the latter case stereoselectivity has also been reported. It was proposed that the reaction proceeds within the pores of the zeolite via the same mechanism as in the homogeneous case (Scheme 1). However, no conclusive experimental evidence was given. The heterogeneous catalysts have the advantage that the work-up of the reaction mixture is easier. Furthermore, they are less water sensitive than the homogeneous MPVO catalysts. The MPVO reactions can be exploited for the racemisation of alcohols via Oppenauer oxidation of the alcohol followed by non-selective reduction of the resulting ketone by the Meerwein–Ponndorf–Verley reaction.[30] Obviously, racemisation reactions can be performed using relatively small amounts of a ketone. Zeolite Beta has also been used for the racemisation of secondary phenylic alcohols in a dynamic kinetic resolution, however, in this case water elimination/addition via a carbenium ion is involved rather than a redox mechanism.[31]

Here, we report on a study of the racemisation of alcohols using both homogeneously and heterogeneously catalysed MPVO reactions. The reaction mechanisms of these reactions were established using deuterium and ^{17}O labelling techniques.



Scheme 2. Two possible pathways for the hydrogen transfer.

Abstract in Dutch: *Het mechanisme van de waterstofoverdracht van alcoholen naar ketonen, gekatalyseerd door lanthanide(III) isopropoxides of zeoliet Beta, werd onderzocht. Voor de lanthanide gekatalyseerde reacties is gebruik gemaakt van (S)-1-fenyl-(1-$^2H_1$)ethanol en acetofenon om het reactiepad van deze overdracht vast te stellen. Na volledige racemisatie bevond alle deuterium zich op de 1-positie. Dit toont aan dat de overdracht van waterstof alleen van koolstof naar koolstof plaatsvindt. In de zeoliet Beta gekatalyseerde racemisaties van (S)-1-fenylethanol is gewerkt met verschillende Si/Al verhoudingen in de zeoliet. Het bleek dat de reactie niet verloopt volgens een oxidatie/reductie mechanisme, maar dat er een eliminatie en readditie van de hydroxygroep plaatsvindt. Dit mechanisme is echter niet kenmerkend voor alle racemisaties met zeoliet Beta. Gedurende de reductie van 4-tert-butylcyclohexanon, een stof die minder makkelijk deprotoneert, vindt een klassieke MPV reactie plaats. Het reactiepad dat wordt gevolgd tijdens de reductie door zeoliet Beta is dus substraatafhankelijk.*

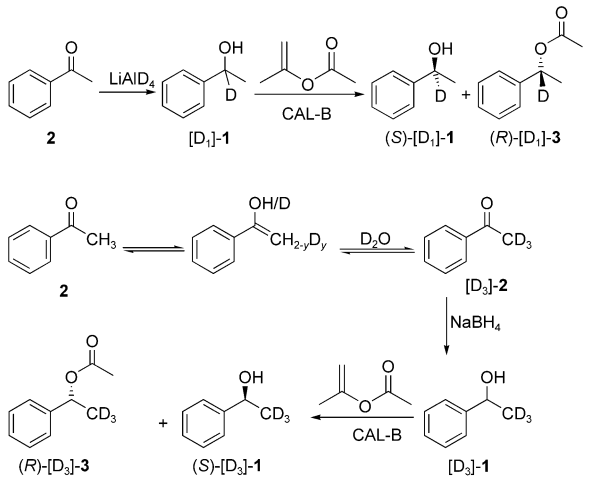
Results and Discussion

The mechanism of the MPVO reactions was studied by monitoring the racemisation of (*S*)-1-phenylethanol [(*S*)-**1**] in the presence of the hydrogen acceptor acetophenone (**2**) or acetone either catalysed by a lanthanide(III) isopropoxide or zeolite Beta. The fate of the various hydrogen atoms during these reactions was traced by means of ^2H-substitution on the tertiary carbons of **1** and of the isopropoxide ligand of the complex. Furthermore, some reactions were performed with **1**, in which the methyl group was labeled with ^2H.

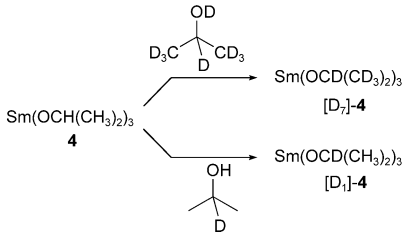
Synthesis of isotopically substituted compounds: (*S*)-1-phenyl-(1-$^2H_1$)ethanol ((*S*)-[D_1]-**1**) was prepared by reduction of acetophenone (**2**) with $LiAlD_4$ followed by a kinetic resolution of the product alcohol **1** utilising *Candida antarctica* lipase B (CAL-B) and isopropenyl acetate. The enantiopure alcohol (*S*)-[D_1]-**1** and acetate (*R*)-[D_1]-**3** were obtained in good yields (both 39% in two steps) and excellent optical purity (both *ee* > 99%) (Scheme 3).

1-Phenyl-(2-$^2H_3$)ethanol ([D_3]-**1**) was synthesised via a straightforward base catalysed H/D exchange reaction of acetophenone (**2**) in D_2O. Subsequent $NaBH_4$ reduction gave the desired racemic compound [D_3]-**1**, which was submitted to a CAL-B catalysed kinetic resolution (Scheme 3). The alcohol (*S*)-[D_3]-**1** and acetate (*R*)-[D_3]-**3** were obtained in three steps in 38 and 39% yield, respectively, and excellent optical purity (both *ee* > 99%).

Deuterated catalysts were obtained by ligand exchange reactions of samarium(III) isopropoxide (**4**) with the isopropanol labeled with ^2H at the appropriate position(s) (Scheme 4).



Scheme 3. Synthesis of enantiopure deuterium substituted alcohols.



Scheme 4. Synthesis of the deuterated samarium(III) catalysts through ligand exchange.

Catalytic reactions with samarium(III) isopropoxide: The racemisations of (*S*)-[D_1]-**1** and (*S*)-**1** were performed with an equimolar amount of acetophenone (**2**) and 10 mol% of [D_7]-**4** or [D_1]-**4** as the catalyst. THF was used as a solvent to enable the direct comparison with the results published by Pàmies and Bäckvall.[21] In addition, some experiments were performed with heptane as the solvent, which has the advantage that it does not coordinate to the Ln^{III} ion. The reactions were run for 18 h (Table 1).

Table 1. Deuterium contents after complete racemisation of (*S*)-**1** and (*S*)-[D_1]-**1**.[a]

Entry	Alcohol	Catalyst	Solvent	% ^{2}H at 1-position[b]	% ^{2}H at Me[b]
1	(*S*)-[D_1]-**1**	[D_7]-**4**	THF	>99	15
2	(*S*)-**1**	[D_7]-**4**	THF	11	16
3	(*S*)-[D_1]-**1**	[D_7]-**4**	heptane	>99	17
4	(*S*)-**1**	[D_7]-**4**	heptane	15	20

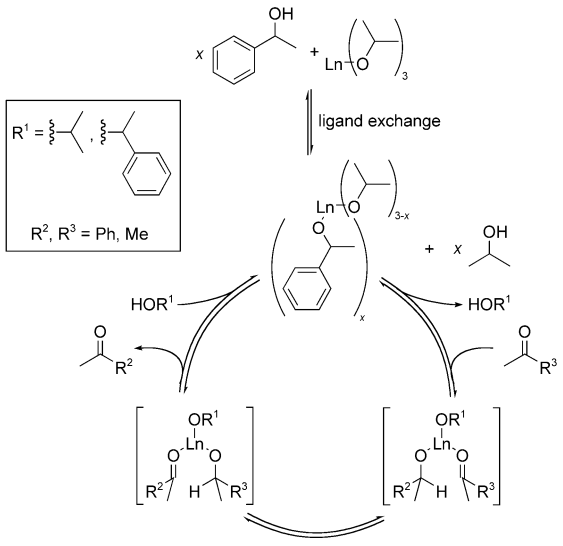
[a] Alcohol (0.5 mmol), **2** (0.5 mmol), catalyst (0.05 mmol), solvent (0.75 mL), $T = 70\,^{\circ}C$, 18 h. [b] Calculated from NMR and MS.

Entries 1 and 3 show complete retention of deuterium at the α-position with respect to the hydroxyl group. This strongly supports a direct transfer of deuterium from carbon to carbon (Scheme 2, mechanism A) and excludes the occurrence of a reduction via transfer of H/D from the alcohol function to the carbonyl carbon atom (Scheme 2, mechanism B). Similar experiments with unlabeled starting compound (entries 2 and 4) show that during the racemisation of **1**, deuterium present on the 2-position of the isopropoxide groups is transferred to the 1-position of the alcohol. Complete scrambling of the deuterium atoms over the tertiary carbons of the isopropoxy groups of the catalyst and the 1-position of phenylethanol would have resulted in 23% of ^{2}H on the latter position. This confirms that the racemisation takes place exclusively via the mechanism depicted in Scheme 1. Remarkably, a substantial amount of deuterium was found in the methyl group of phenylethanol in each of the experiments. This can be ascribed to H/D exchange between the methyl groups of acetophenone (formed by Oppenauer oxidation of **1**) and those of acetone (formed by oxidation of the isopropoxy groups of the catalyst) via keto–enol equilibria, under influence of the alkaline conditions in the reaction mixture.

Analoguous experiments were performed using [D_1]-**4**. The ^{2}H distribution at the 1-position in the products was similar to that with the completely deuterated catalyst [D_7]-**4**. The methyl group, however, did not show any incorporation of deuterium, supporting the keto–enol equilibria proposed above for the H/D exchange between acetone and acetophenone. This also rules out that any D from CD_3 is transferred to the 1-position of the alcohol.

A reaction performed without hydrogen acceptor (acetone or acetophenone) did not show any activity. This indicates that the reaction has to proceed via the reduction of a ketone or aldehyde.

All results described above strongly support that the MPVO reaction exclusively proceeds via mechanism A (Scheme 2). This is also in agreement with results reported by Pàmies and Bäckvall,[21] who observed 24% loss of deuterium upon racemisation of (*S*)-1-phenyl-(1-$^2H_1$)ethanol using 10 mol% of a Sm-isopropoxide catalyst without deuterium. This is very close to the theoretical loss of 23% of deuterium in phenylethanol upon complete scrambling as mentioned above. The reason for the deuterium loss in the product, is the ligand exchange that takes place in the reaction mixture, during which the isopropoxy groups of the catalyst will exchange against the reactant alcohol (Scheme 5).



Scheme 5. Ligand exchange and subsequent reactions in the MPVO cycle.

Catalytic reactions with zeolite H-Beta: Zeolite Beta is also known to oxidise alcohols and to reduce ketones in a similar fashion as the homogeneous Ln^{III} catalysts.[25–29] Herein, some mechanistic studies are reported.

Zeolite H-Beta, activated at 400 °C, was used as catalyst and acetone was applied as hydrogen acceptor. The experiments were carried out at 50 °C, in order to minimise the loss of acetone from the reaction mixture. The reactions were terminated after one hour, after which the enantiomeric excess and the mass balance were determined (Figure 1).

Zeolite Beta catalysed the racemisation, even in the absence of an oxidant. This is in contrast to the findings with samarium(III) isopropoxide. In most cases, this racemisation reaction was even faster than in the presence of acetone. Furthermore, when the reaction was performed in the presence of acetone no acetophenone could be detected in the reaction mixture. Acetophenone would be the reaction intermediate when the racemisation proceeds via an oxidation/reduction of the alcohol and, therefore, it can be concluded that the reaction proceeds via a different pathway. The incomplete mass balance as determined by GC analysis also supports the presence of another pathway differing from the redox reactions. The phenomena observed can be rationalised by the occurrence of an elimination/addition mechanism in which the hydroxy group is eliminated from the alcohol, forming a carbocation intermediate. This intermediate gives upon rehydration phenylethanol. However, instead of an S_N1 reaction an E1 elimination takes place and styrene is formed. Indeed, when a small quantity of $H_2{}^{17}O$ was added to the reaction mixture, ^{17}O was found to be incorporated into the produced racemic alcohol. The occurrence of the carbocation and subsequent formation of styrene also explains the incomplete mass balance, since styrene can polymerise and the polymer escapes detection by GC.

The occurrence of a carbocation intermediate was confirmed by reactions of styrene and (*S*)-1-phenylethanol (**1**) with one equivalent of water in the presence of zeolite Beta (Si/Al = 16). Styrene showed a very slow reaction to 1-phenylethanol, only 6 % of it was formed after 20 h. During the same reaction time, however, (*S*)-1-phenylethanol was completely racemised; in this case styrene could be detected by GC and as expected the mass balance was incomplete.

As can be seen in Figure 1 the acidity of the zeolite, which depends on the Si/Al ratio, determines the racemisation rate. The highest rate was obtained with a zeolite with Si/Al = 16.

Since phenylethanol is very susceptible to dehydration, zeolite Beta catalysed reactions were also performed with 4-*tert*-butylcyclohexanone (**6**).

From previous work it is known that zeolite Beta preferably catalyses the reduction towards the *cis*-4-*tert*-butyl cyclohexanol (**7**).[25–28] In oxidations *cis*-isomer **7** is converted into ketone **6**, whereas the other isomer of the alcohol is rather unreactive. Therefore, we monitored the reduction of the ketone rather than the epimerisation of the two alcohols (Scheme 6). Zeolite Beta, activated at different temperatures, was applied since it has been shown that the activation temperature plays a crucial role in the catalytic activity.[24,25]

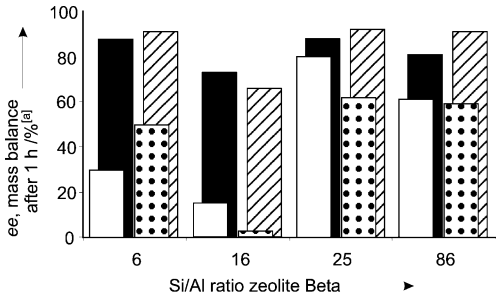
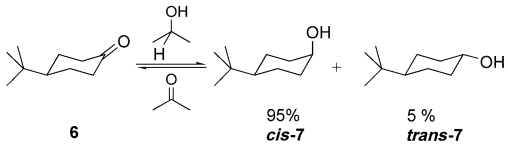


Figure 1. Zeolite Beta catalysed racemisations of (*S*)-1-phenylethanol in the presence and in the absence of acetone. □ *ee*, with 1 equiv acetone; ● *ee*, without acetone; ■ mass balance, with 1 equiv acetone; // mass balance, without acetone. [a] Determined by chiral GC.



Scheme 6. The reduction of 4-*tert*-butylcyclohexanone and the oxidation of 4-*tert*-butylcyclohexanol.

For both catalysts complete conversion of **6** was observed after 18 h. From Table 2 it is evident that the deuterium that was present at the 2-position of isopropanol is fully transferred to the 2-position of the product alcohol; this indicates a hydrogen transfer according to Scheme 2, mechanism A, independent of the activation temperature. Furthermore, no loss in the mass balance was observed and no deuterium was detected at other positions of the product, proving that here exclusively a direct carbon-to-carbon hydrogen transfer takes place (see Scheme 2, mechanism A).

Table 2. Deuterium contents of **7** after reduction of **6**.[a]

Entry	Ketone	Catalyst[b]	Solvent	% ^2H at 1-position[c]
1	**6**	Beta 16 (400)	2-(2-$^2H_1$)propanol	>99
2	**6**	Beta 16 (600)	2-(2-$^2H_1$)propanol	>99

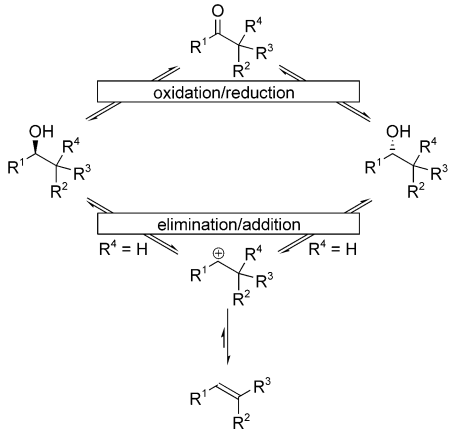
[a] Ketone (2.0 mmol), catalyst (30 mg), solvent 3 mL, $T = 50$ °C, 18 h. [b] The first number is the Si/Al ratio, the number in parentheses is the activation temperature in °C, activation overnight. Prepared according to van Bekkum et al.[35] [c] Calculated from NMR and MS, 3–5 % of the *trans* isomer was found, also with >99 % ^2H at the 1-position.

It is remarkable that the Beta zeolite catalyses both the elimination/addition and the MPVO reaction. In both cases the zeolite is activated at 400 °C in order to expel water and to increase the number of Lewis acid sites. Apparently, with exactly the same catalyst it is possible to follow two different pathways. The elimination is most likely catalysed by the Brønsted acid sites whereas the MPV reduction is carried out at the Lewis acid sites. Corma et al. showed that with Beta resembling zeolites, like Sn-Beta, where only Lewis acid sites are available in the catalyst, it is possible to reduce **2** without any elimination.[29]

Conclusion

The MPVO reaction catalysed by lanthanide(III) isopropoxides proceeds exclusively via a hydride transfer from the carbon at the α-position with respect to the alcohol function to the carbonyl carbon of the ketone or the aldehyde. Here, for the first time the mechanism was proven in a reliable and undisputable way using deuterium substituted alcohols and catalysts. Furthermore, it was observed that a keto–enol tautomerisation takes place during the reaction through which hydrogen atoms other than in the 1-position can be exchanged.

The racemisation of (*S*)-**1** catalysed by zeolite Beta proceeds, (predominantly) via an elimination/addition mechanism. ^{17}O studies support this observation. Furthermore, the rate of racemisation and the extent of oligomerisation in the reaction is determined by the acidity of the zeolite and the number of active sites. On the other hand, zeolite Beta possesses the capacity to reduce ketones also via a regular reduction pathway as is shown by the reduction of **7**. This is summarised in Scheme 7. The preference for either of the pathways in racemisations depends on the substrate used and is not influenced by the activation temperature and therefore the number of Lewis acid sites of zeolite Beta.



Scheme 7. The two possible reaction pathways for zeolite Beta.

Experimental Section

All experiments were performed in dried glassware under a nitrogen atmosphere unless stated otherwise. All chemicals were purchased from Aldrich. Anhydrous solvents and solids were used as received, the other liquids were dried and distilled prior to use. The zeolites with a Si/Al ratio of 16 and 86 were commercially available from CU Chemie, Uetikon. The *ee* values were determined and reactions were followed by gas chromatography by using a Hewlett–Packard 5890 Series II gas chromatograph, equipped with a 40 m × 0.25 mm chiral column Chiraldex B-PH (β-cyclodextrins permethylated hydroxypropyl), split injector (1:100) at 220 °C, a Flame Ionisation Detector at 250 °C and using He as carrier gas. In the catalytic reactions 1,3,5-triisopropylbenzene was used as internal standard. Retention times (min) at 120 °C isotherm: 1,3,5-triisopropylbenzene (11.0), acetophenone (11.5), (*S*)-1-methylbenzyl acetate (14.5), (*R*)-1-methylbenzyl acetate (15.0), (*R*)-1-phenylethanol (23.0), (*S*)-1-phenylethanol (23.5). Non-enantiomeric compounds were analysed by a Varian Star 3400 CX, equipped with a 50 m × 0.53 mm column CP wax 52 CB, on column injector at 60 °C, a Flame Ionisation Detector at 250 °C and nitrogen as carrier gas. Retention times (min) (0–2 min: 100 °C; 2–18 min: 5 °C min^{-1}; 18–20 min: 180 °C): 1,3,5-triisopropylbenzene (10.7), 4-*tert*-butylcyclohexanone (15.5), *cis*-4-*tert*-butylcyclohexanol (16.4), *trans*-4-*tert*-butylcyclohexanol (17.5). NMR spectra were recorded on a Varian VXR-400S or a Varian Unity Inova-300 spectrometer at 25 °C. Chemical shifts are reported in ppm with TMS as an internal standard ($\delta = 0$ ppm). The deuterium content of the isotopically substituted compounds was calculated from the ^1H- and ^2H NMR spectra. Mass spectra were recorded with a VG SE spectrometer at 70 eV. Elemental analysis ICP-OES was performed with Perkin–Elmer Optima 4300DV. Immobilised *Candida antarctica* Lipase B (CAL-B) as Chirazyme L2, c-f. C2, lyo was a gift from Roche Diagnostics. The enzyme activity was determined following a standard procedure.[32] Prior to use, the enzyme was dried overnight under vacuum over silica in a desiccator. For column chromatography Fluka silica gel 60 was used and Merck aluminium sheets with silica gel 60 F_{254} were used for TLC. Elution was carried out with mixtures of petroleum ether 40–65 °C (PE) and diethyl ether (Et_2O).

1-Phenyl-(1-$^2H_1$)ethanol ([D_1]-1): At −20 °C, lithium aluminium deuteride (5 g, 119 mmol) was dissolved in diethyl ether (80 mL). Freshly distilled acetophenone (**2**) (22.6 mL, 192 mmol) was added dropwise to the stirred mixture. The reaction mixture was allowed to warm to room temperature after which the stirring was continued for 2 h. The temperature was lowered again to −20 °C. Subsequently, water (5 mL), 15 % aqueous NaOH solution (5 mL) and water (15 mL) were carefully added.[33] The solids were filtered off and washed thoroughly with diethyl ether. Distillation under reduced pressure yielded [D_1]-**1** as a colourless oil (20.8 g, 169 mmol, >99 % deuterated, 88 %). B.p. 98 °C at 30 mbar; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.49$ (t, $J = 0.90$ Hz, 3H, C*H*$_3$), 1.84 (s, 1H, O*H*), 7.24–7.39 (m, 5H, ar-*H*).

(*S*)-1-Phenyl-(1-$^2H_1$)ethanol ((*S*)-[D_1]-1) and (*R*)-(1-$^2H_1$)-1-methylbenzyl acetate ((*R*)-[D_1]-3): [D_1]-**1** (2.0 g, 16.3 mmol) and isopropenyl acetate (1.9 mL, 16.3 mmol) were dissolved in toluene (20 mL). The temperature was raised to 60 °C and CAL-B (0.4 g, 1.5 kU) was added to the mixture. The reaction was monitored by chiral GC. After 2 h the enzyme was removed by filtration and the solution was concentrated in vacuo. The two products were separated by column chromatography (PE/Et_2O 4:1, after the acetate was eluted: PE/Et_2O 1:1). After removal of the solvents alcohol (*S*)-[D_1]-**1** (0.84 g, 6.8 mmol, *ee* > 99 %, >99 % deuterated, 42 %) and acetate (*R*)-[D_3]-**3** (1.18 g, 7.1 mmol, *ee* > 99 %, >99 % deuterated, 44 %) were obtained. The ^1H NMR spectrum of the alcohol was identical to that of [D_1]-**1**. (*R*)-[D_3]-**3**: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.53$ (t, $J =$ 0.82, 3H, CD-C*H*$_3$), 2.06 (s, 3H, C(O)C*H*$_3$), 7.23–7.39 (m, 5H, ar-*H*).

(*S*)-1-Phenyl-(2-$^2H_3$)ethanol ((*S*)-[D_3]-1) and **(*R*)-1-($^2H_3$)methylbenzyl acetate ((*R*)-[D_3]-3)**: Acetophenone (**2**) (2.0 mL, 17.1 mmol), D_2O (20 mL, 1.0 mol) and a catalytic amount of potassium carbonate were stirred vigorously overnight at 100 °C. The mixture was cooled to room temperature and $NaBH_4$ (324 mg, 8.6 mmol) was added. After 3 h, the reaction mixture was extracted with diethyl ether (3 × 20 mL), the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was dissolved in toluene (20 mL). CAL-B (206 mg, 0.7 kU) and isopropenyl acetate (2.0 mL, 18.2 mmol) were added and the temperature was raised to 50 °C. The reaction was followed by chiral GC. After 3 h the enzyme was filtered off and the solution was concentrated in vacuo. The products were purified as described above yielding, after evaporation of the solvents, the desired alcohol (*S*)-[D_3]-**1** (811 mg, 6.49 mmol, *ee* 99 %, 97 % deuterated, 38 % (over three steps)) and acetate (*R*)-[D_3]-**3** (1.11 g, 6.65 mmol, *ee* 99 %, 96 % deuterated, 39 % (over three steps)). (*S*)-1-phenyl-(2-$^2H_3$)ethanol: ^1H NMR (300 MHz, [D_8]dioxane): $\delta = 3.80$ (s, 1H, C*H*), 4.77 (d, $J = 2.7$ Hz, 1H, O*H*), 7.19–7.40 (m, 5H, Ar-*H*); ^2H NMR (46 MHz, dioxane): $\delta = 1.29$ (C*D*$_3$); (*R*)-1-($^2H_3$)methylbenzyl acetate: ^1H NMR (300 MHz, [D_8]dioxane): $\delta = 2.03$ (s, 3H, C(O)-C*H*$_3$), 5.86 (s, 1H, C*H*), 7.23–7.40 (m, 5H, Ar-*H*); ^2H NMR (46 MHz, dioxane) $\delta = 1.41$ (C*D*$_3$).

2-(2-$^2H_1$)Propanol: This alcohol was synthesised in an analogous way as [D_1]-**1**, using acetone (17.6 mL, 238 mmol), $LiAlD_4$ (5 g, 119 mmol) in diethyl ether (50 mL).[33,34] Distillation (82 °C/atmospheric pressure) yielded the desired alcohol (12.2 g, 101 mmol, >99 % deuterated, 85 %). ^1H NMR (300 MHz, [D_8]dioxane): $\delta = 1.20$ (t, $J = 0.9$ Hz, 6H, 2 × C*H*$_3$), 2.08 (s, 1H, O*H*).

Samarium(III) ($^2H_7$)isopropoxide ([D_7]-4): Samarium(III) isopropoxide (1 g, 30.5 mmol) in 2-($^2H_8$)propanol (10 mL, 131 mmol) was stirred overnight. After settling of the solids, the solution was transferred into another flask. This solution was concentrated under vacuum. For ^{1}H NMR, the catalyst was dissolved in [D]trifluoroacetic acid to which a drop of D_2O was added to increase solubility. Dioxane was added as internal standard. ^{1}H NMR (300 MHz, [D_1]TFA): $\delta = 0.80$–1.00 (m, CH_3). Integration of the ^{1}H NMR spectrum showed the deuterium content to be 87%.

Samarium(III) (2-$^2H_1$)isopropoxide ([D_1]-4): This catalyst was prepared in a similar manner as above, with 2-(2-$^2H_1$)propanol (10 mL, 128 mmol). From NMR the deuterium contents was determined to be 85%.

General procedure for the synthesis of zeolite Beta:[35] Several zeolites have been prepared with different Si/Al ratios. The amounts used are given after the general procedure.

$NaAlO_2$ and a 35% TEAOH solution in water were mixed and stirred for 15 min in a Teflon insert for an autoclave. To this, LUDOX HS-40 was added. A thick gel formed which was homogenised manually. The insert was put into the autoclave and then the mixture was heated at 170°C for four days. The autoclave was quickly cooled with water and the white powder obtained was centrifuged, washed with water three times and then dried in air overnight.

The zeolite was placed in an oven and heated to 550°C at a rate of 1°C min^{-1}. It was kept at that temperature for 15 h. After cooling, Na^+ was exchanged by H^+ by stirring the zeolite three times for 48 h with a 0.1 M NH_4NO_3 solution (250 mL). The zeolite obtained was calcined at 450°C for 15 h to yield a white powder. The Si/Al ratio was determined by elemental analysis and calculated from the ^{29}Si NMR spectrum.[36]

Zeolite Beta (Si/Al = 6): $NaAlO_2$ (2.12 g, 25.9 mmol), 35% TEAOH in water (8 mL, 19.5 mmol) and LUDOX HS-40 (15 mL). Zeolite Beta (Si/Al = 25) $NaAlO_2$ (0.53 g, 6.5 mmol), 35% TEAOH in water (8 mL, 19.5 mmol) and LUDOX HS-40 (15 mL).

General procedure for the samarium(III) catalysed MPVO racemisation: Samarium(III) isopropoxide (0.050 mmol) was dissolved in the solvent of choice (Table 1) (0.75 mL), acetophenone (**2**) (58.3 μL, 0.50 mmol) and (*S*)-1-phenylethanol ((*S*)-**1**) (60.7 μL, 0.50 mmol) were added and the temperature was raised to 70°C, after which the solution was stirred overnight for 18 h towards complete racemisation. At regular time intervals, samples of 20 μL were taken, which were analysed by chiral GC.

General procedure for the zeolite Beta catalysed racemisation of (*S*)-1: Zeolite Beta was activated at 400°C overnight. This zeolite (20 mg) was introduced into a Schlenk flask. Toluene (4 mL) was added followed by (*S*)-1-phenylethanol ((*S*)-**1**) (0.24 mL, 2 mmol). If required, acetone (0.15 mL, 2 mmol) was added (Figure 1). The mixture was heated to 50°C. The reaction was followed by taking 20 μL samples at regular intervals and analysing them with chiral GC.

Zeolite Beta catalysed reaction with styrene: Zeolite Beta (Si/Al = 16) was activated at 400°C overnight. This zeolite (20 mg) was introduced into a Schlenk flask. Toluene (4 mL) was added followed by styrene (0.23 mL, 2 mmol), acetone (0.15 mL, 2 mmol) and water (36 μL, 2 mmol). The mixture was heated to 50°C. The reaction was followed by taking 20 μL samples at regular intervals and analysing them with chiral GC. 6% **1** was observed after 20 h.

As a control experiment, the reaction was also performed using (*S*)-**1** (0.24 mL, 2 mmol) instead of styrene. After 20 h complete racemisation and formation of styrene was observed.

Zeolite Beta catalysed racemisation of (*S*)-1 in the presence of $H_2{}^{17}O$: Zeolite Beta (Si/Al = 13.5) was activated at 400°C overnight. This zeolite (20 mg) was introduced into a Schlenk flask. Toluene (4 mL) was added followed by (*S*)-1-phenylethanol ((*S*)-**1**) (0.24 mL, 2 mmol) and $H_2{}^{17}O$ (5 μL, 0.26 mmol, degree of ^{17}O labelling: 25.7%). The mixture was heated to 50°C and was analysed by MS after 2 h. It was calculated from the mass spectrum that the product was 1.0% ^{17}O enriched.

General procedure for the zeolite Beta catalysed reduction of 7: Zeolite Beta was activated at the appropriate temperature overnight (Table 2). This zeolite (20 mg) was introduced into a Schlenk flask. 2-(2-$^2H_1$)Propanol (3 mL) was added followed by 4-*tert*-butyl cyclohexanone **7** (0.31 g, 2 mmol). The mixture was heated to 50°C. The reaction was followed by taking 20 μL samples at regular intervals and analysing them with achiral GC.

Acknowledgement

U.H. thanks the Royal Netherlands Academy of Arts and Sciences (KNAW) for a fellowship. The authors gratefully acknowledge Roche Diagnostics Penzberg (Dr. W. Tischer) for the generous gift of the enzyme (CAL-B, Chirazyme L-2, c.f., C2, Lyo). We thank Kristina Djanashvili and Anton van Estrik for measuring the NMR-spectra, Adrie Knol-Kalkman for the mass-spectra and Dr. Göran Verspui (Avantium Technologies) for stimulating discussions.

[1] H. Pellissier, *Tetrahedron* **2003**, *59*, 8291–8327.
[2] H. Meerwein, R. Schmidt, *Justus Liebigs Ann. Chem.* **1925**, *444*, 221–238.
[3] A. Verley, *Bull. Soc. Chim. Fr.* **1925**, *37*, 537–542.
[4] W. Ponndorf, *Angew. Chem.* **1926**, *38*, 138–143.
[5] H. Lund, *Ber. Dtsch. Chem. Ges.* **1937**, *70*, 1520–1525.
[6] R. V. Oppenauer, *Recl. Trav. Chim. Pays-Bas* **1937**, *56*, 137–144.
[7] A. L. Wilds, *Org. React.* **1944**, *2*, 178.
[8] C. Djerassi, *Org. React.* **1953**, *6*, 207.
[9] J. F. de Graauw, J. A. Peters, H. van Bekkum, J. Huskens, *Synthesis* **1994**, 1007–1018.
[10] K. Nishide, M. Node, *Chirality* **2002**, *14*, 759–767.
[11] W. N. Moulton, R. E. van Atta, R. R. Ruch, *J. Org. Chem.* **1961**, *26*, 290–292.
[12] E. C. Ashby, J. N. Argyropoulos, *J. Org. Chem.* **1986**, *51*, 3593–3597.
[13] S. Muthukumaru Pillai, S. Vancheesan, J. Rajaram, J. C. Kuriacose, *J. Mol. Catal.* **1983**, *20*, 169–173.
[14] T. Ooi, T. Miura, K. Maruoka, *J. Am. Chem. Soc.* **1998**, *120*, 10790–10791.
[15] T. Ooi, T. Miura, K. Takaya, H. Ichikawa, K. Maruoka, *Tetrahedron* **2001**, *57*, 867–873.
[16] E. D. Williams, K. A. Krieger, A. R. Day, *J. Am. Chem. Soc.* **1953**, *75*, 2404–2407.
[17] M. Cohn, *Preparation and measurement of isotopic tracers* (Ed.: J. Edwards), Ann Arbor, Michigan, **1947**, p. 51.
[18] J. L. Namy, J. Souppe, J. Collin, H. B. Kagan, *J. Org. Chem.* **1984**, *49*, 2045–2049.
[19] T. Ooi, T. Miura, Y. Itagaki, H. Ichikawa, K. Maruoka, *Synthesis* **2002**, 279–291.
[20] E. J. Campbell, H. Zhou, S. T. Nguyen, *Org. Lett.* **2001**, *3*, 2391–2393.
[21] O. Pàmies, J.-E. Bäckvall, *Chem. Eur. J.* **2001**, *7*, 5052–5058.
[22] J. Shabtai, R. Lazar, E. Biron, *J. Mol. Catal.* **1984**, *27*, 35–43.
[23] M. Berkani, J. L. Lemberton, M. Marczewski, G. Perot, *Catal. Lett.* **1995**, *31*, 405–410.
[24] M. Huang, P. A. Zielinsky, J. Moulod, S. Kaliaguine, *Appl. Catal. A* **1994**, *118*, 33–49.
[25] J. C. van der Waal, E. J. Creyghton, P. J. Kunkeler, H. van Bekkum, *Top. Catal.* **1997**, *4*, 261–268.
[26] E. J. Creyghton, S. D. Ganeshie, R. S. Downing, H. van Bekkum, *J. Mol. Catal.* **1997**, *115*, 457–472.
[27] A. Corma, M. E. Domine, L. Nemeth, S. Valencia, *J. Am. Chem. Soc.* **2002**, *124*, 3194–3195.
[28] M. A. Aramendía, V. Borau, C. Jiménez, J. M. Marinas, J. R. Ruiz, F. J. Urbano, *J. Chem. Soc. Perkin Trans. 2* **2002**, 1122–1125.
[29] A. Corma, M. E. Domine, S. Valencia, *J. Catal.* **2003**, *215*, 294–304.
[30] P. M. Dinh, J. A. Howarth, A. R. Hudnott, J. M. J. Williams, W. Harris, *Tetrahedron Lett.* **1996**, *37*, 7623–7626.
[31] S. Wuyts, K. de Temmerman, D. de Vos, P. Jacobs, *Chem. Commun.* **2003**, 1928–1929.
[32] L. Veum, M. Kuster, S. Telalovic, U. Hanefeld. T. Maschmeyer, *Eur. J. Org. Chem.* **2002**, 1516–1522.
[33] V. M. Mićović, M. L. Mihailović, *J. Org. Chem.* **1953**, *18*, 1190–1200.
[34] L. Friedman, A. T. Jurewicz, *J. Org. Chem.* **1968**, *33*, 1254–1255.
[35] P. J. Kunkeler, B. J. Zuurdeeg, J. C. van der Waal, J. A. Bokhoven, D. C. Koningsberger, H. van Bekkum, *J. Catal.* **1998**, *180*, 234–244.
[36] G. Engelhardt, D. Michel, *High-Resolution Solid-State NMR of silicates and Zeolites*, Wiley, Chichester, **1987**, pp. 145–154.

Received: August 18, 2003
Revised: November 28, 2003 [F5460]

