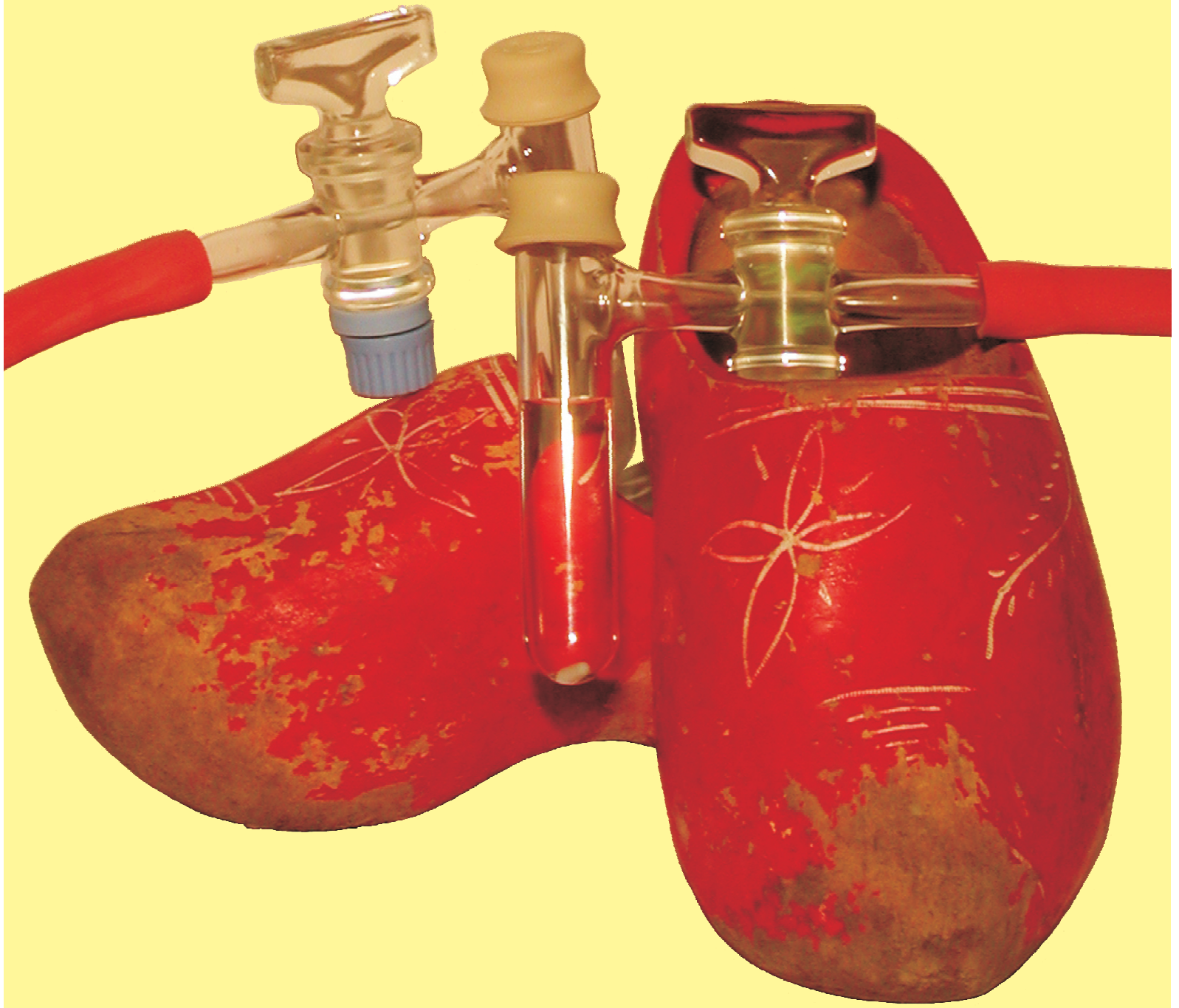
transfer hydrogenations and kinetic resolutions



Dirk Klomp

transfer hydrogenations and kinetic resolutions

Dirk Klomp

Uitnodiging

voor het bijwonen van de
openbare verdediging van
het proefschrift en
de stellingen op

maandag
13 maart 2006
13.00 uur

en de daaraan
voorafgaande toelichting
voor niet-chemici om

12.30 uur

in de Senaatszaal van de
Technische Universiteit Delft
Mekelweg 5 te Delft

Na afloop van de
plechtigheid bent u ook van
harte welkom op de receptie
in hetzelfde gebouw.

Dirk Klomp
Esdoornlaan 32
1521 EB Wormerveer
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dirkklomp@gmail.com

Stellingen

behorende bij het proefschrift

transfer hydrogenations and kinetic resolutions

van Dirk Klomp

1- De door Kao et al. gebruikte structuurbepalende verbinding fructose voor de synthese van de mesoporeuze silica SBA-1 bepaalt niet de structuur van het materiaal.
H.-M. Kao, C.-C. Ting, A. S. T. Chiang, C.-C. Teng, C.-H. Chen, *Chem. Commun.* **2005**,1058-1060.

2- Het door Kim et al. gesuggereerde mechanisme voor de deactivering van het enzym α-CT in de hydrolyse van β-lactonen, waarbij het lacton opent op de 4-positie, is zeer onwaarschijnlijk.
D. H. Kim, J. Park, S. J. Chung, J. D. Park, N.-K. Park, J. H. Han, *Bioorg. Med. Chem.* **2002**, *10*, 2553-2560.

3- Psychologisch gezien betekent de omschakeling door wetenschappelijke tijdschriften van papieren versies naar elektronische, een verlies aan kennis voor de wetenschapper.

4- Omdat de aarde langzamer gaat draaien is soms de toevoeging van schrikkelsecondes noodzakelijk. Wetenschappers die deze secondes pas willen toevoegen op het moment dat ze zijn opgespaard tot een schrikkeluur, omdat de toevoegingen storingen kunnen veroorzaken in elektronische apparatuur, hebben de menselijke factor uit het oog verloren.

5- In de weekeindes waarin een nieuw boek over Harry Potter uitkomt, is het aantal kinderen dat op de eerstehulpafdeling van het ziekenhuis belandt bijna half zo groot als in andere weekeindes. Gwilym et al. hebben de afname over de lange termijn waarschijnlijk onderschat.
S. Gwilym, D. P. J. Howard, N. Davies, K. Willet, *Br. Med. J.* **2005**, *331*, 1505-1506.

6- Het testen van racemisaties van alcoholen onder invloed van zeoliet H-Beta in water met substraten die geen carbeniumion intermediair kunnen vormen levert geen extra informatie op. Het zou interessanter zijn geweest om een benzylisch substraat met een alcoholgroep op de β-positie te testen.
S. Wuyts, K. de Temmerman, D. E. de Vos, P. A. Jacobs, *Chem. Eur. J.* **2005**, *11*, 386-397.

7- Bij natuurkundige proeven zoals het pekdruppelexperiment worden geleidelijke scheikundige veranderingen over het hoofd gezien.
R. Edgeworth, B. J. Dalton, T. Parnell, *Eur. J. Phys.* **1984**, 198-200.

8- Het nut van een katalysator voor de MPVO reactie die in een organisch oplosmiddel met 10% water nog steeds werkt, is dubieus.
A. Corma, M. E. Domine, S. Valencia, *J. Catal.* **2003**, *215*, 294-304.

9- De vervanging van het springpaard door Pegases heeft het turnen mythologische proporties gegeven.

Deze stellingen worden verdedigbaar geacht en zijn als zodanig goedgekeurd
door de promotor.

Propositions

belonging to the thesis

transfer hydrogenations and kinetic resolutions

by Dirk Klomp

1- The template fructose used by Kao *et al.* for the synthesis of the mesoporous silica SBA-1 does not determine the structure of the material.
H.-M. Kao, C.-C. Ting, A. S. T. Chiang, C.-C. Teng, C.-H. Chen, *Chem. Commun.* **2005**,1058-1060.

2- The mechanism postulated by Kim *et al.* for the deactivation of the enzyme α-CT in the hydrolysis of β-lactones, in which the lactone opens at the 4-position, is highly unlikely.
D. H. Kim, J. Park, S. J. Chung, J. D. Park, N.-K. Park, J. H. Han, *Bioorg. Med. Chem.* **2002**, *10*, 2553-2560.

3- From a psychological point of view, the replacement of printed versions of scientific journals by electronic ones results in a loss of knowledge for the scientist.

4- The slowing down of the rotation of the earth requires the occasional introduction of a leap second. Scientists wanting to introduce these seconds after saving them up to a leap hour to avoid disturbances in electronic equipment neglect the human factor.

5- In the weekends in which a new book about Harry Potter is released, the number of children ending up at the first aid department of the hospital is almost halved with respect to other weekends. Gwilym *et al.*, however, have probably underestimated the extent of the decrease in the long term.
S. Gwilym, D. P. J. Howard, N. Davies, K. Willet, *Br. Med. J.* **2005**, *331*, 1505-1506.

6- Testing of racemisations of alcohols by zeolite H-Beta in water with substrates that cannot form carbenium ion intermediates does not yield additional information. It would have been more interesting if a benzylic substrate were tested with an alcohol group on the β-position.
S. Wuyts, K. de Temmerman, D. E. de Vos, P. A. Jacobs, *Chem. Eur. J.* **2005**, *11*, 386-397.

7- In physical experiments like the pitch drop experiment gradual chemical changes are overlooked.
R. Edgeworth, B. J. Dalton, T. Parnell, *Eur. J. Phys.* **1984**, 198-200.

8- The benefits of a catalyst for the MPVO reaction that still works in an organic solvent containing 10% of water, are doubtful.
A. Corma, M. E. Domine, S. Valencia, *J. Catal.* **2003**, *215*, 294-304.

9- Replacing the vaulting horse by Pegases gave gymnastics mythological proportions.

These propositions are regarded as defendable, and have been approved as such by the supervisor.

transfer hydrogenations and kinetic resolutions

Dirk Klomp

Cover:
My first clogs and the Schlenk flasks I used most often for my experiments.

transfer hydrogenations
and
kinetic resolutions

Proefschrift

ter verkrijging van de graad van doctor
aan de Technische Universiteit Delft,
op gezag van de Rector Magnificus prof. dr. ir. J. T. Fokkema,
voorzitter van het College voor Promoties,

in het openbaar te verdedigen op maandag 13 maart 2006 om 13.00 uur

door

Dirk KLOMP
doctorandus in de scheikunde
geboren te Zaandam

Dit proefschrift is goedgekeurd door de promotor:

Prof. dr. R. A. Sheldon

Toegevoegd promotor:

Dr. ir. J. A. Peters

Samenstelling promotiecommissie:

Rector Magnificus	voorzitter
Prof. dr. R. A. Sheldon	Technische Universiteit Delft, promotor
Dr. ir. J. A. Peters	Technische Universiteit Delft, toegevoegd promotor
Prof. dr. ir. H. van Bekkum	Technische Universiteit Delft
Prof. dr. ir. J. Huskens	Universiteit Twente
Prof. dr. J. G. de Vries	Rijksuniversiteit Groningen
Dr. U. Hanefeld	Technische Universiteit Delft
Dr. G. Verspui	MercaChem Process Research B.V.

Reservelid

Prof. dr. F. Kapteijn	Technische Universiteit Delft

Dr. U. Hanefeld heeft als begeleider in belangrijke mate aan de totstandkoming van het proefschrift bijgedragen.

ISBN 90-6464-591-4

Voor mijn ouders

Table of contents

1 Homogeneous transfer hydrogenations

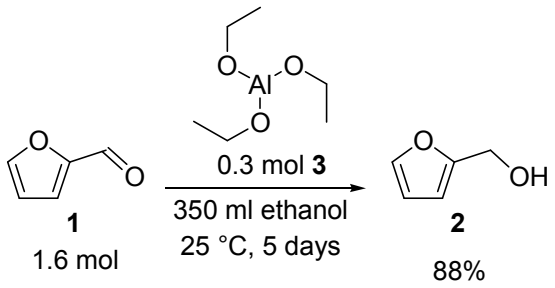
This chapter will be published in the Handbook of Homogeneous Hydrogenations
editors J. G. de Vries and C. J. Elsevier, Wiley

1.1 Introduction

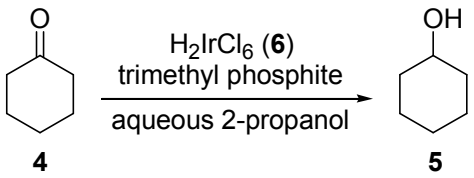
The first homogeneous transfer hydrogenation was reported in 1925 when Meerwein and Schmidt described the reduction of ketones and aldehydes using alcohols as reductants and aluminium alkoxides as the catalysts (Scheme 1).[1] The major difference with previous work was the hydrogen source. Instead of molecular hydrogen, a small organic molecule was utilised to provide the hydrogen necessary to reduce the carbonyl compound. The scope of the reaction was independently investigated by Verley,[2] Ponndorf,[3] and Lund.[4] Twelve years later, Oppenauer recognised the possibility to reverse the reaction into an oxidation procedure.[5] 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.

More recently, Ln^{III} alkoxides were shown to have much higher catalytic activity in this reaction, which allowed the use of only catalytic amounts of them.[6,7] Lately, also much higher reactivities for Al^{III} catalysed MPVO reactions have been achieved with dinuclear Al^{III} complexes[8,9] and with Al^{III} alkoxides generated *in situ*.[10] Several reviews on the Meerwein-Ponndorf-Verley and Oppenauer (MPVO) reactions have been published.[11-14]

Pioneering work on a different class of transfer hydrogenation catalysts



Scheme 1. The first homogeneous transfer hydrogenation reduction of furfural (**1**) to furfuryl alcohol (**2**) described by Meerwein and Schmidt using 0.18 equivalents of aluminium ethoxide (**3**).[1]



Scheme 2. A new approach towards the transfer hydrogenation of ketones in 1964.

was performed by Henbest *et al.* in 1964.[15] These authors reported the reduction of cyclohexanone (**4**) to cyclohexanol (**5**) in aqueous 2-propanol using chloroiridic acid (H_2IrCl_6) (**6**) as catalyst (Scheme 2). In the initial experiments turn over frequencies (TOF) of 200/h were reported.

A major step forward was the introduction of the Wilkinson catalyst ($RhCl(PPh_3)_3$) (**7**), for hydrogen transfer reactions.[16] Although actually designed for the hydrogenation with molecular hydrogen, this catalyst has been intensively used in transfer hydrogenation catalysis. Ever since, iridium, rhodium and also ruthenium complexes have been widely used in reductive transfer hydrogenations. The main advantage of these catalysts over the MPVO catalysts known until then was their comparatively higher catalytic activity. The turnover frequencies of the transition metal catalysts could be improved even further by the use of a base as additive, which deprotonates the substrate, facilitating the complexation of the substrate to the metal ion in the intermediate complex.[17-21] Numerous reviews have been published on the topic of transition metal catalysed transfer hydrogenations.[22-28]

The scope of hydrogen transfer reactions is not limited to ketones. Imines, carbon-carbon double and triple bonds have been reduced in this way too, although homogeneous and heterogeneous catalysed reductions using molecular hydrogen are generally preferred for the latter compounds.

The advantages of hydrogen transfer over other methods of hydrogenation comprise the use of readily available hydrogen donors such as 2-propanol, the very mild reaction conditions and the high selectivity. High concentrations of the reductant can be applied and the hydrogen donor is often used as the solvent, which means mass transfer limitations can not occur in these reactions. The uncatalysed reduction of ketones requires

temperatures of 300 °C.[29]

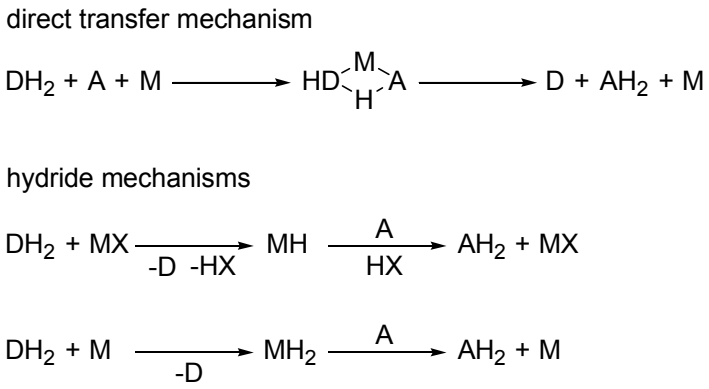
Hydrogen transfer reactions are reversible. Recently, this has been exploited extensively in racemisation reactions in combination with a kinetic resolution of racemic alcohols: this resulted in dynamic kinetic resolutions, kinetic resolutions with 100% yield of the desired enantiopure compound.[30] The kinetic resolution is typically performed with an enzyme that converts one of the enantiomers of the racemic substrate and a hydrogen transfer catalyst that racemises the remaining substrate (Scheme 31).

Eighty years after the first reports on transfer hydrogenations, they are well established in synthesis and are employed in ever new fields of chemistry.

1.2 Reaction mechanisms

Since the first use of catalysed hydrogen transfer, speculations about and studies on their mechanism have been published. Especially in recent years several investigations elucidating the reaction pathways were performed. With better analytical methods and computational chemistry, the catalytic cycles of many systems have been clarified. The mechanism of transfer hydrogenations depends on the metal used and on the substrate. Here, we focus our attention on mechanisms of hydrogen transfer reactions with the most frequently used catalysts. Two main mechanisms can be distinguished: a direct transfer mechanism by which a hydride is directly transferred from the donor to the acceptor molecule and an indirect mechanism by which the hydride is transferred from the donor to the acceptor molecule via a metal hydride intermediate. (Scheme 3).

In the direct transfer mechanism, the metal ion coordinates both reactants enabling an intramolecular reaction and activates them via polarisation. Consequently, strong Lewis acids including Al^{III} and the Ln^{III} ions are the most suitable catalysts in this type of reactions. In the hydride mechanism, a hydride is transferred from a donor molecule to the metal of



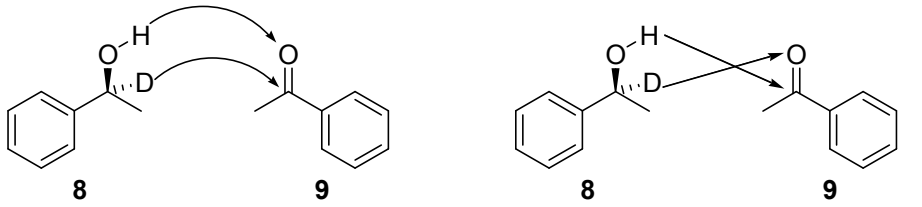
Scheme 3. Schematic representation of the two different hydrogen transfer mechanisms (D = donor molecule, A = acceptor molecule, M = metal).

the catalyst, hence forming a metal hydride. Subsequently, the hydride is transferred from the metal to the acceptor molecule. Metals that have a high affinity for hydrides, such as Ru, Rh and Ir are therefore the catalysts of choice. The Lewis acidity of these metals is too weak to catalyse a direct hydride transfer and *vice versa* the affinity of Al^{III} and Ln^{III} to hydride-ions is too low to catalyse the indirect hydrogen transfer. Two distinct pathways are possible for the hydride mechanism: one in which the catalyst takes up two hydrides from the donor molecule and the other in which the catalyst facilitates the transfer of a single hydride.

All hydrogen transfer reactions are equilibrium reactions. Consequently, both a reduction and an oxidation can be catalysed under similar conditions. The balance of the reaction is determined by the thermodynamic stabilities of the species in the redox equilibrium involved and by the concentrations of the hydride donors and acceptors.

1.2.1 Hydrogen transfer reduction of carbonyl compounds

Transfer hydrogenations of carbonyl compounds are often conducted using 2-propanol as the hydrogen donor. An advantage of this compound is that it can be used as solvent at the same time. A large excess of the hydrogen



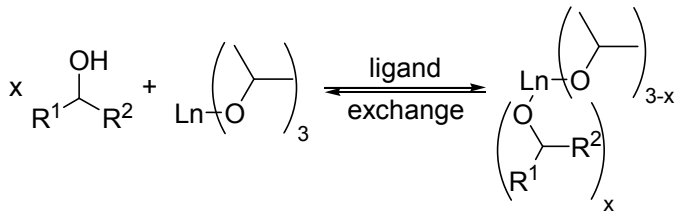
Scheme 4. Possible pathways of hydrogen transfer during the racemisations of alcohols using the corresponding carbonyl compound and a hydrogen transfer catalyst.

donor shifts the redox equilibrium towards the desired product (see also paragraph 1.3.1).

Studies aimed at the elucidation of reaction mechanisms have been performed by many groups, notably by Bäckvall's.[28] In test reactions typically enantiopure 1-phenylethanol labelled with deuterium at the 1-position (**8**) is used. The compound is racemised with acetophenone (**9**) under the influence of the catalyst and after complete racemisation of the alcohol, the deuterium content of the racemic alcohol is determined. If the deuterium transfer proceeds from the α-carbon atom of the donor to the carbonyl carbon atom of the acceptor the deuterium is retained, if it is transferred to the oxygen atom of the acceptor it is lost due to subsequent exchange with alcohols in the reaction mixture (Scheme 4).

1.2.1.1 Meerwein-Ponndorf-Verley reduction and Oppenauer oxidation

The most common catalysts for the Meerwein-Ponndorf-Verley reduction and Oppenauer oxidation are Al^{III} and Ln^{III} isopropoxides, often in combination with isopropanol as hydride donor and solvent. These alkoxide ligands are readily exchanged under formation of isopropanol and the metal complexes of the substrate (Scheme 5). Therefore, the catalytic species actually is a

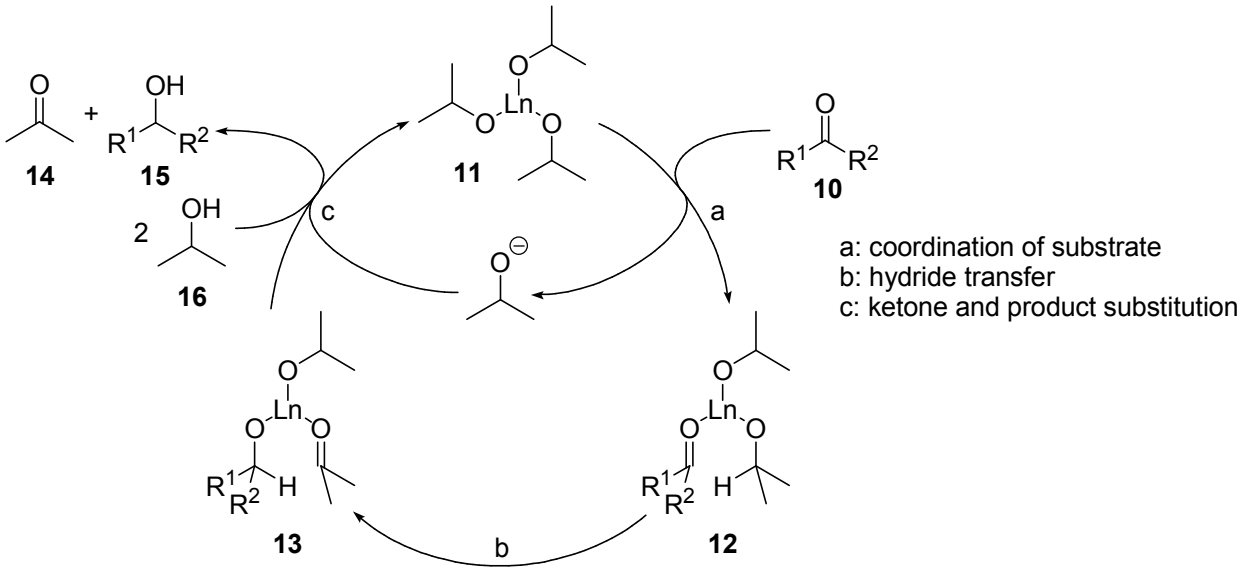


Scheme 5. Ligand exchange in MPVO reactions.

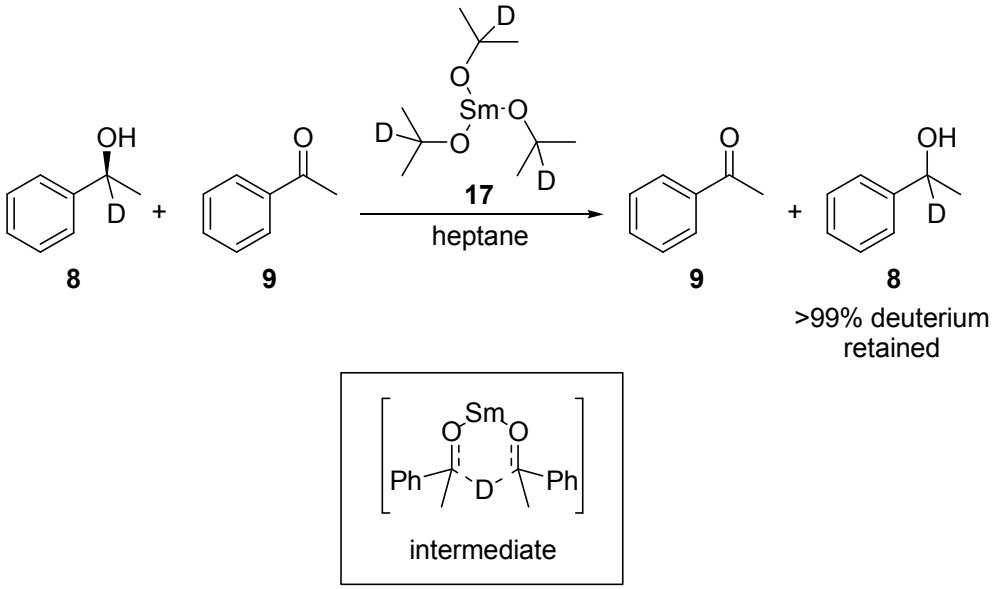
mixture of metal alkoxides.

The catalytic cycle of the reaction is depicted in Scheme 6.[31] After the initial ligand exchange, the ketone (**10**) is coordinated to the metal ion of **11** (a), yielding complex **12**. A direct hydride transfer from the alkoxide to the ketone takes place via a six-membered transition state (b) in which one alkoxy group is oxidised (**13**). Acetone (**14**) and the newly formed alcohol (**15**) are released from the metal centre by substitution for new donor molecules (**16**) (c) completing the cycle.

The mechanism of the MPVO reaction has been investigated and questioned several times and over the years various direct H-transfer pathways have been suggested (Scheme 4).[31-35] Recently, racemisation of D-labelled 1-phenylethanol with deuterated samarium(III) isopropoxide (**17**)



Scheme 6. Mechanism of the Meerwein-Ponndorf-Verley-Oppenauer reaction.



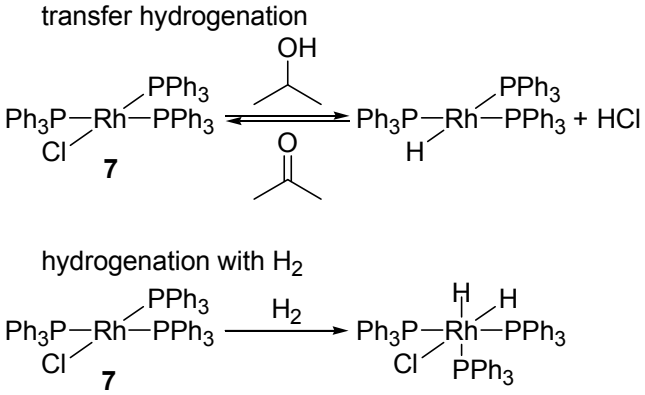
Scheme 7. Racemisation of (*S*)-1-deutero-1-phenylethanol (**8**) with deuterated samarium(III) isopropoxide (**17**).

proved that the MPVO reaction occurs via a direct hydrogen transfer from the α-position of the isopropoxide to the carbonyl carbon of the substrate. (Scheme 7).[31]

The selectivity of the hydrogen transfer is excellent. When employing a catalyst with deuterium at the α-positions of the isopropoxide ligands (**17**), complete retention of the deuterium was observed. A computational study using the density functional theory comparing the six-membered transition state (as in Scheme 3, the direct transfer mechanism) with the hydride mechanism (Scheme 3, the hydride mechanism) supported the experimental results.[36] A similar mechanism has been proposed for the MPV alkynylations[37] and cyanations.[38]

1.2.1.2 Transition metal catalysed reductions

The Wilkinson catalyst, ($RhCl(PPh_3)_3$) (**7**), is not only an excellent hydrogenation catalyst when using molecular hydrogen as hydrogen donor,



Scheme 8. Different behaviour of the Wilkinson catalyst (**7**) for transfer hydrogenation and hydrogenation using molecular hydrogen.

it can also be employed as hydrogen transfer catalyst. It is a square planar, 16-electron complex, which catalyses these reactions via different pathways depending on the hydrogen donor. The intermediate rhodium complexes tend to retain a 4-coordinated square planar configuration, whereas the molecular hydrogen pathway proceeds through an octahedral state[35,39-42] (Scheme 8).

In transfer hydrogenations with 2-propanol, the chloride ion in a Wilkinson type of catalyst (**18**) is rapidly replaced by an alkoxide (Scheme 9). β-Elimination then yields the reactive 16-electron metal monohydride species (**20**). The ketone substrate (**10**) then substitutes one of the ligands and coordinates to the catalytic centre to give complex **21** upon which an insertion into the metal hydride bond takes place. The formed metal alkoxide (**22**) can undergo a ligand exchange with the hydride donor present in the reaction mixture, liberating the product (**15**). After a β-elimination acetone is released and the metal monohydride (**20**) is obtained again from **23**, closing the catalytic cycle.

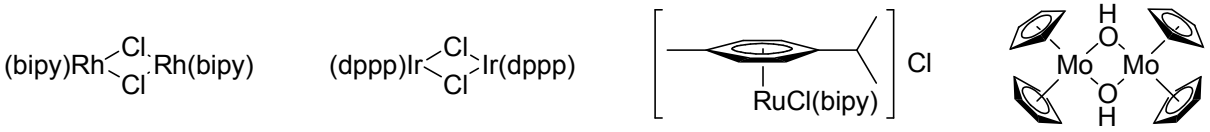
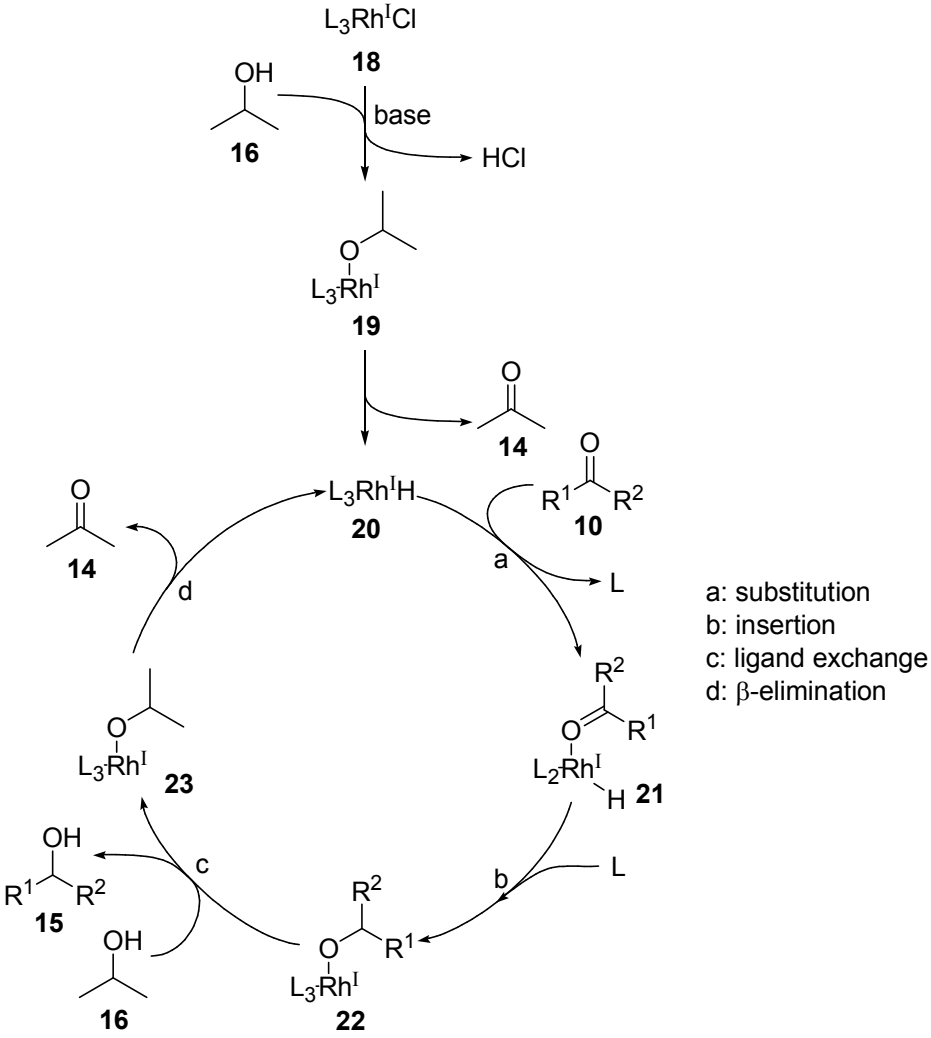
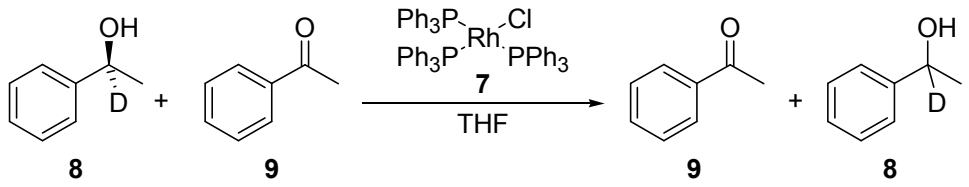


Figure 1. Examples of catalysts operating via the same mechanism as the Wilkinson catalyst (bipy = 2,2'-bipyridine, dppp = 1,3-bis(diphenylphosphinopropane).[35,44,45]



Scheme 9. Transition metal alkoxide mechanism.

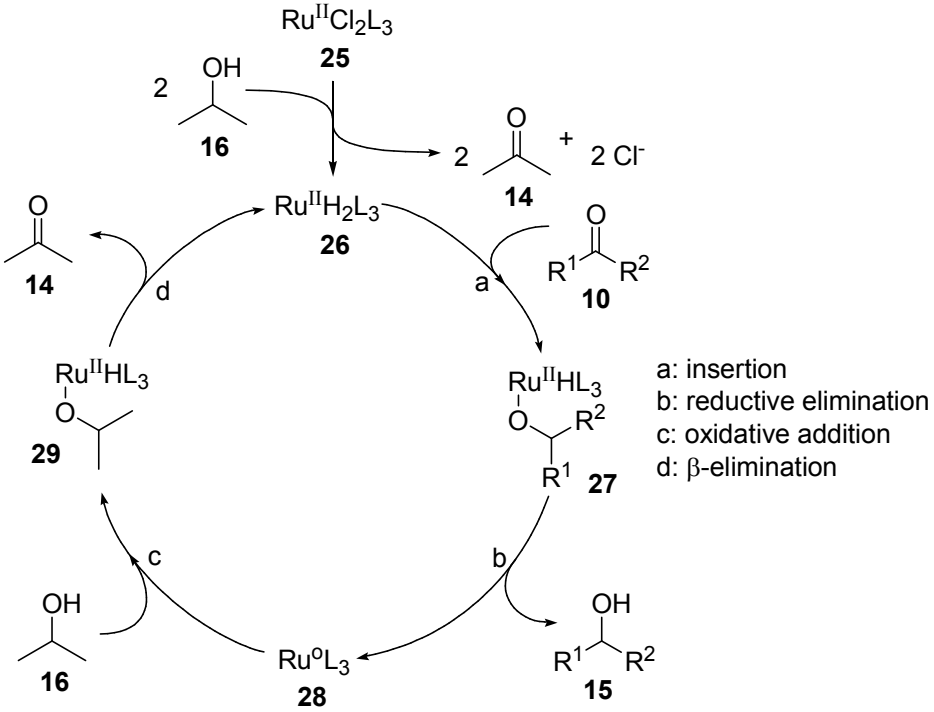
Mechanistic studies show that the extent of deuterium-labeling at the α-position of (*S*)-1-deutero-1-phenylethanol (**8**) remains almost unchanged during a racemisation reaction with this system (Scheme 10).[35] This indicates that a single hydride is transferred from the α-position of the donor to the α-position of the acceptor. Only a slight decrease of deuterium content occurs (5%), which may be attributed to exchange with traces of water. In catalysts bearing phenylphosphine ligands, loss of deuterium can also be explained by orthometalation[43] leading to H/D exchange. Several other catalysts have been shown to operate *via* the same mechanism as the



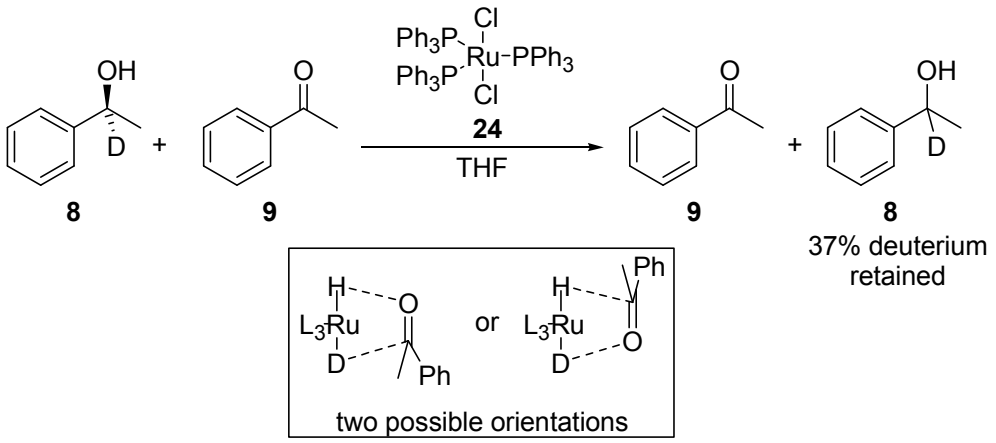
Scheme 10. Racemisation of (*S*)-1-deutero-1-phenylethanol (**8**) with the Wilkinson catalyst (**7**).

Wilkinson catalyst (for examples see Figure 1).

A different mechanism is operative with the 16-electron complex $RuCl_2(PPh_3)_3$ (**24**) (Scheme 11). Here, the dichloride complex (**25**) is rapidly converted into a dihydride species (**26**) by substitution of both chloride ligands with alkoxides and subsequent eliminations similar to the conversion of **18** to **20** described above.[46,47] Subsequently, the ruthenium dihydride species **26** reacts (a) with a substrate molecule (**10**) to give the monohydride alkoxide complex (**27**). Reductive elimination (b) liberates the product (**15**) and a Ru^0 species (**28**). Oxidative addition (c) of an alcohol (**16**) yields a new monohydride alkoxide complex (**29**). After a β-elimination step (d)



Scheme 11. Transition metal dihydride mechanism.

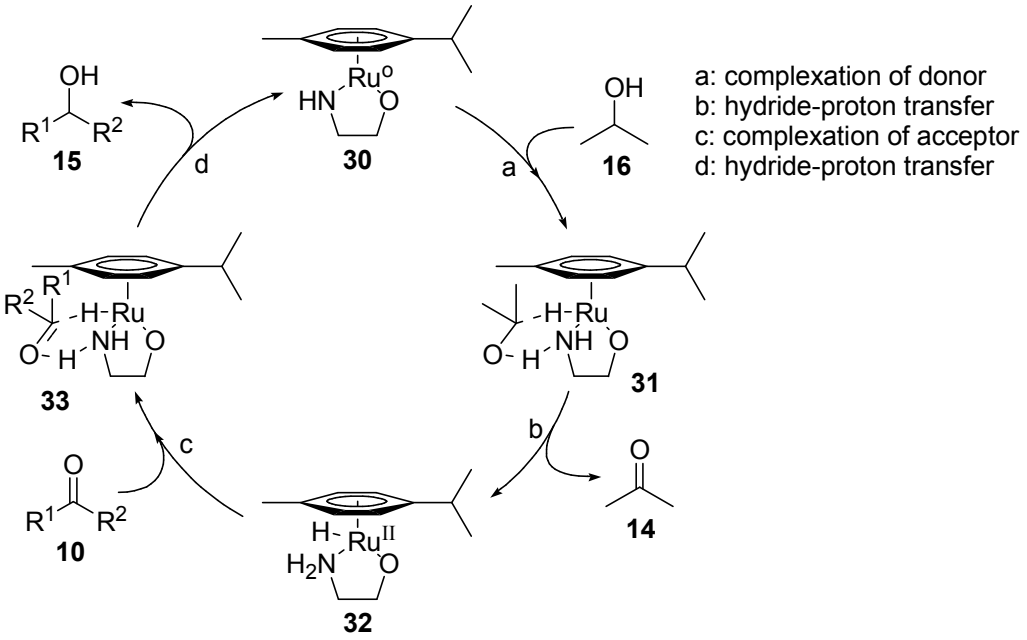


Scheme 12. Racemisation of (*S*)-1-deutero-1-phenylethanol (**8**) with $RuCl_2(PPh_3)_3$ (**24**).

Ru^{II} dihydride (**26**) is formed again. This mechanism is supported by the fact that racemisation of (*S*)-1-deutero-1-phenylethanol (**8**) catalysed by this and similar catalysts decreased the deuterium content to about 40%.[35] Theoretically, the mechanism depicted in Scheme 11 leads to an equal distribution of the deuterium-label over the α-position of the alcohol and its hydroxyl function (Scheme 12). The deuterium content of the product is probably somewhat lower due to H-D exchange between the alcohol function and traces of water and other alcohols in the reaction mixture.

In the transition metal catalysed reactions described above, addition of a small amount of base dramatically increases the reaction rate.[17-21] A more elegant approach is to include a basic site into the catalysts as is depicted in Scheme 13. Noyori and others proposed a mechanism for reactions catalysed with these 16-electron ruthenium complexes (**30**) that involves a six-membered transition state (**31**).[48-50] The basic nitrogen atom of the ligand abstracts the hydroxyl proton from the hydrogen donor (**16**) and in a concerted manner a hydride shift takes place from the α-position of the alcohol to ruthenium (a), releasing a ketone (**14**) (b). The Ru^{II} monohydride (**32**) formed is now able to bind to the substrate ketone (**10**) (c) and in another concerted reaction, the alcohol (**15**) is formed together with the 16-electron ruthenium complex (**30**) (d).

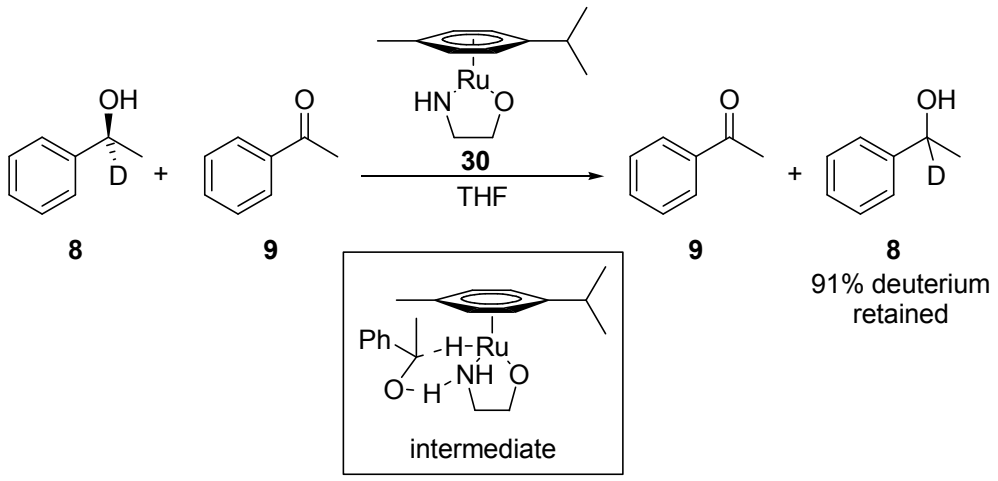
The formation of the Ru^{II} hydride species is supported by deuterium



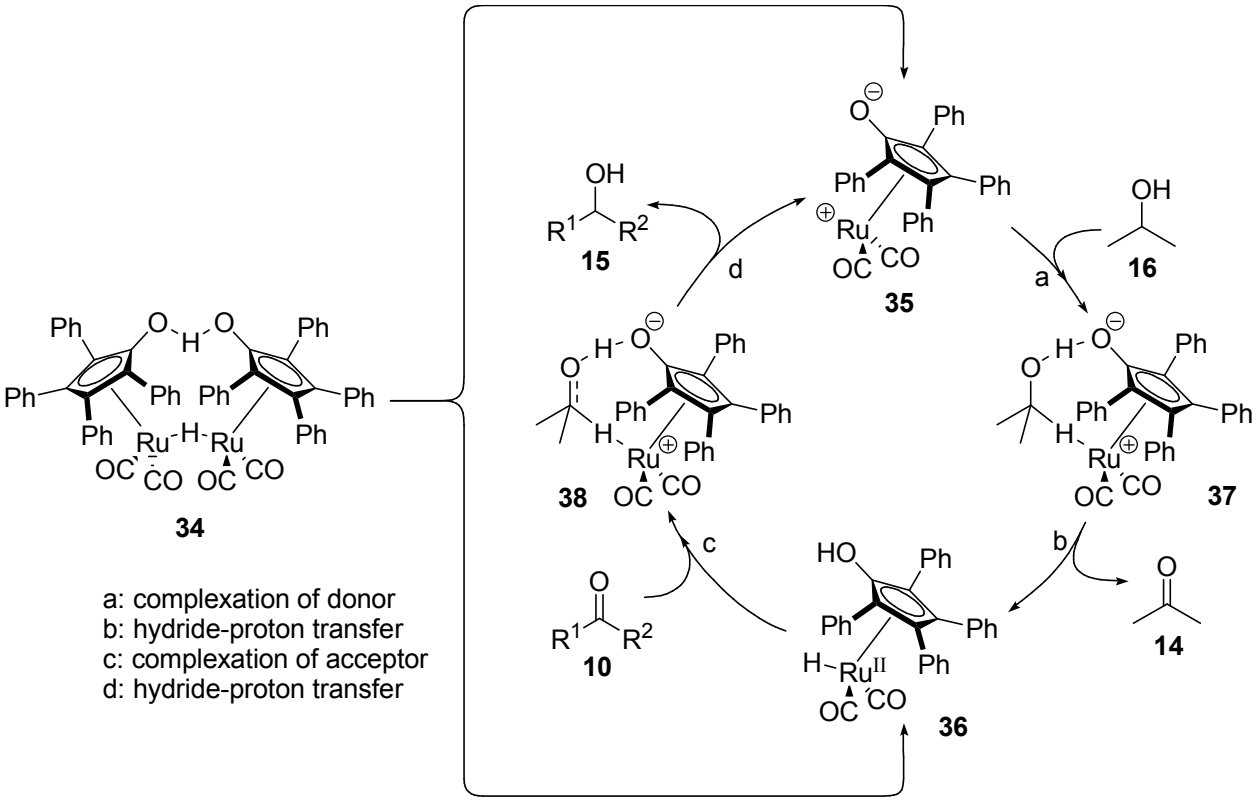
Scheme 13. Concerted hydride-proton transfer mechanism.

labelling studies (Scheme 14).[35] The deuterium label remains at the α-position of the alcohol during racemisations. This is due to the orientation of the alcohol when it coordinates to the Ru-complex. Once again, some deuterium is probably lost due to H/D exchange with traces of water or alcohol in the reaction mixture.

The most reactive transition metal transfer hydrogenation catalysts to



Scheme 14. Racemisation of (*S*)-1-deutero-1-phenylethanol (**8**) with $Ru(OC_2H_4NH)$(*p*-cymene) (**30**).



Scheme 15. The catalytic cycle of the Shvo catalyst (**34**).

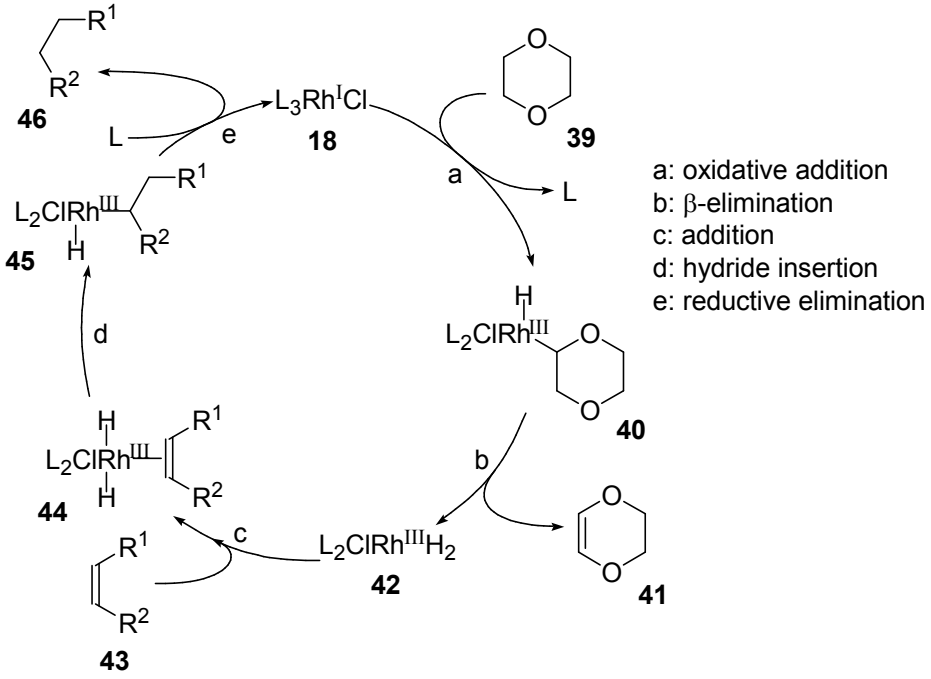
date have bidentate ligands. Studies towards active catalysts are mainly directed towards the size and nature of the bridge in the ligand[51] and towards the nature of atoms coordinating to the metal.[52-54] It seems that ligands containing both a phosphorous and a nitrogen atom possess the best properties for this kind of reactions (see also 1.3.3).

Particularly interesting is the dinuclear Ru complex **34**, the so-called Shvo catalyst.[55,56] It has been established that under the reaction conditions this complex is in equilibrium with two monometal complexes (**35** and **36**).[57-59] Both of them resemble catalytic intermediates in the concerted proton-hydride transfer pathway (Scheme 13) and will react in a similar way (Scheme 15) involving the six-membered transition state **37** and the reduction of the substrate via **38**.

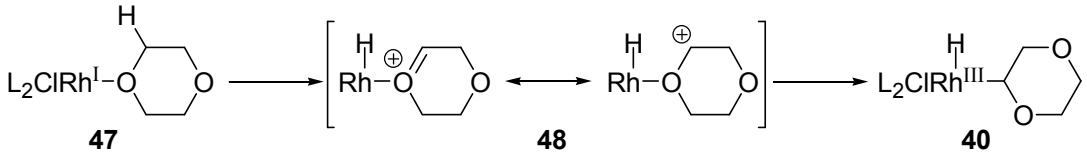
1.2.2 Transfer hydrogenation catalysts for reduction of C-C double and triple bonds

The reduction of C-C double and triple bonds using molecular hydrogen is generally preferred over transfer hydrogenation. However, some interesting examples of transfer hydrogenations of alkenes and alkynes are known. As an illustration of the mechanism of a typical transfer hydrogenation, the reduction of an alkene with dioxane as the hydride donor and the Wilkinson catalyst (**7**) is discussed. The reduction does not necessarily have to be performed with dioxane, but this hydride donor is rather common in these reductions. The use of hydrogen donors and their distinct advantages and disadvantages are discussed in chapter 1.3.1.

The first step consists of the substitution of one of the ligands (L) of **18** by dioxane (**39**) in an oxidative addition (a) (Scheme 16). β-Elimination of **40** releases 2,3-dihydro-dioxine **41** and the 16-electron dihydrogen rhodium complex (**42**) (b). Alkene **43** coordinates to the vacant site of **42** (c) to give



Scheme 16. Alkene reduction with dioxane (**39**) as hydride donor and a Wilkinson type catalyst (**18**).



Scheme 17. Step a of Scheme 16: the coordination and oxidative addition of dioxane.

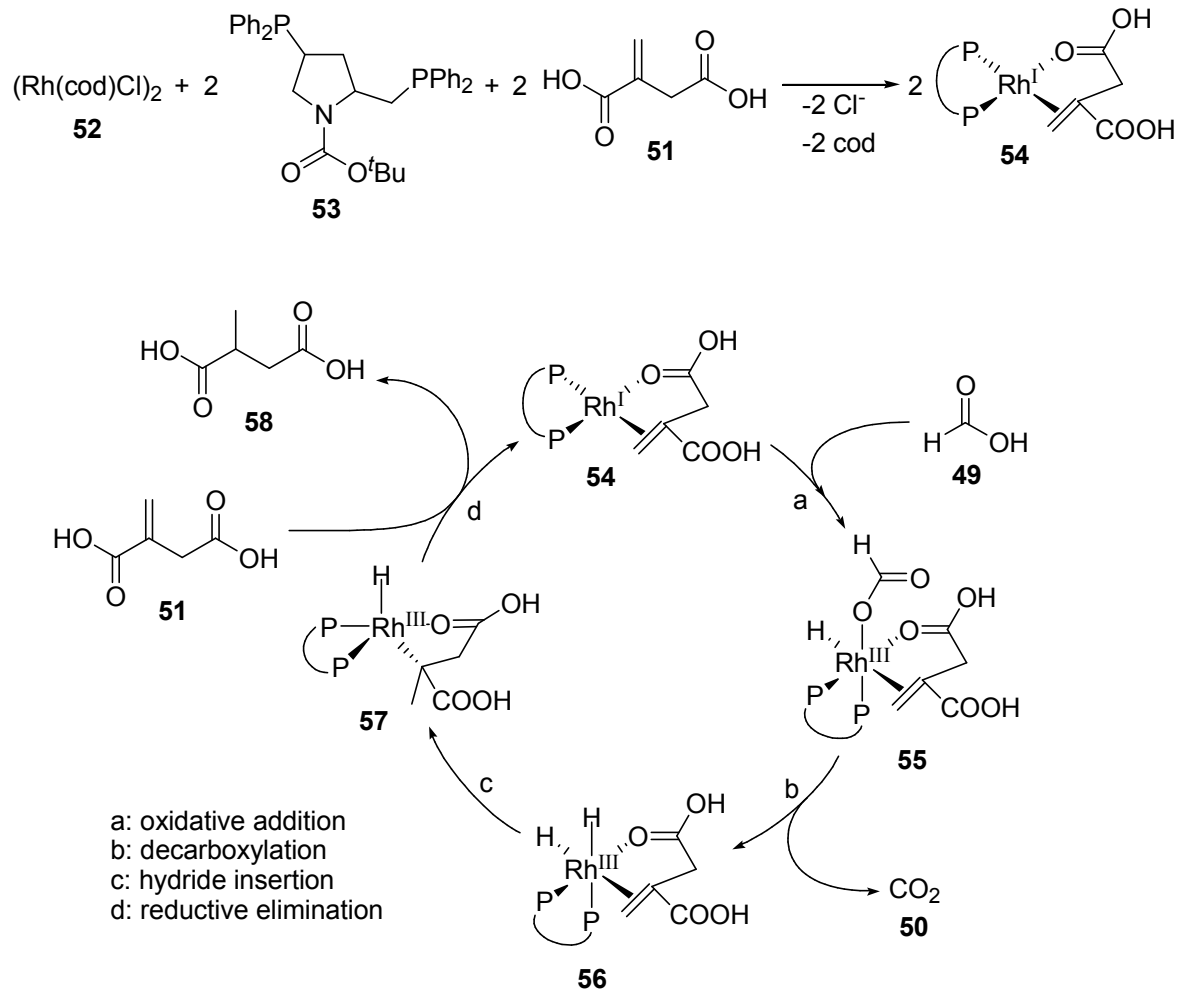
complex **44**. Then, a hydride insertion takes place (d) affording complex **45**. After a reductive elimination (e) of the product **46**, the coordination of a ligand reconstitutes the Wilkinson type catalyst (**18**).

The coordination of dioxane and subsequent oxidative addition to the catalytic species (step a in Scheme 16) probably proceeds after the oxygen atom coordinates to the rhodium (**47**), followed by abstraction of a hydride ion. The cationic species (**48**) rearranges then to a complex in which the dioxane is bound to the rhodium via the carbon atom (**40**) (Scheme 17).[60]

Transfer hydrogenations are typically equilibrium reactions, however, when formic acid (**49**) is utilised as hydrogen donor, carbon dioxide (**50**) is formed which escapes from the reaction mixture.[61-64]

Here, an example is given for the reduction of itaconic acid (**51**) with a rhodium catalyst precursor (**52**) and a phosphine ligand (**53**) (Scheme 18). The itaconic acid (**51**) is a good chelating ligand for the catalyst and when the 16 electron Rh^{I} active species **54** is formed, an oxidative addition of formic acid (**49**) takes place (a). Decarboxylation (b) of **55** liberates CO_2 (**50**) while forming a Rh^{III}-dihydride (**56**). A hydride insertion (c) leading to a pentacoordinated metal (**57**) and subsequent reductive elimination (d), in which the product (**58**) is liberated and a new substrate (**51**) is coordinated, closes the cycle.

This system is very selective towards the reduction of C-C double bonds and the oxygen of the acid group that coordinates to the metal is important for good catalytic properties. In the reaction mixture, triethylamine is added in a molar ratio of formic acid : triethylamine 5:2, which is the commercially available azeotropic mixture of these compounds.



Scheme 18. Reduction of the C-C double bond of itaconic acid (**51**) utilising a rhodium catalyst (**54**) and formic acid (**49**) as hydrogen donor.

1.3 Reaction conditions

1.3.1 Hydrogen donors

By definition, hydrogen transfer is a reaction during which hydrogen is transferred from a source other than molecular hydrogen. In theory the donor can be any compound that has an oxidation potential that is low enough to allow hydrogen abstraction under the influence of a catalyst under mild

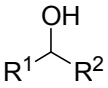
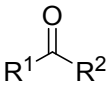
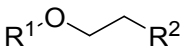
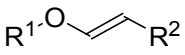
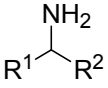
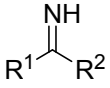
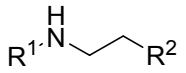
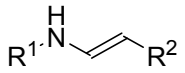
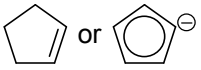
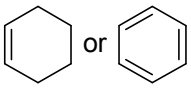
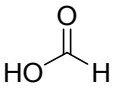
reaction conditions. Another requirement is that the donor is able to coordinate to the catalytic centre and does not bind tightly after donation of the hydrogen.

The hydrogen donors vary widely from heteroatom containing compounds like alcohols, amines, acids and cyclic ethers to hydrocarbons like alkanes (Table 1). The choice of donor is largely dependent on several issues:

- the **type** of reaction: MPVO or transition metal catalysed,
- the **affinity** of the substrate to the metal concerned,
- the **exchange rates** of the substrate between the metal bound and the free form,
- its **solubility** in the reaction medium or its ability to **dissolve** all other reaction ingredients,
- its influence on the **equilibrium** of the reaction,
- the **temperature** at which the reaction is taking place,
- its ability to avoid harmful **side-products,**
- the **nature** of the functional group to be reduced.

Alcohols have always been the major group of hydrogen donors. Indeed, they are the only hydrogen donors that can be used in MPV reductions. 2-Propanol (**16**) is most commonly used both in MPV reductions and in transition metal catalysed transfer hydrogenations. It is generally available and cheap and its oxidation product, acetone (**14**), is non-toxic and can usually be removed readily from the reaction mixture by distillation, which may have the additional advantage that the redox equilibrium is shifted even more into the direction of the alcohol. As a result of sigma inductive electronic effects, secondary alcohols are generally better hydrogen donors than primary ones. However, many examples of the use of primary alcohols have been reported. Ethanol, as already pointed out by Meerwein and Schmidt,[1] yields acetaldehyde, which even at room temperature leaves the reaction mixture resulting in irreversible reductions. Unfortunately, the aldehydes resulting from primary alcohols as donors are known to act as catalyst poisons. Furthermore, they may decarbonylate,

Table 1. Hydrogen donors and their oxidation products.

entry	donor	acceptor
1[a]		
2[b]		
3		
4		
5[c]		
6[d]		
7		CO_2

[a] Both primary and secondary alcohols.

[b] Typically from cyclic ethers as dioxane and THF, only one pair of hydrogens is abstracted.

[c] The cyclopentadienyl ring coordinates to the catalyst.

[d] The reaction preferably stops at cyclohexene.

forming CO, which may modify the catalysts and consequently change their activity.[65,66]

Other alcohols, such as diols,[67-69] polyols like furanose and pyranose sugars[70,71] and poly-vinyl alcohol[72] have been reported to enable the reduction of ketones to alcohols.

Heterocyclic compounds are frequently used as hydrogen donors in the reduction of C-C double and triple bonds catalysed by complexes of transition metals. Cyclic ethers such as 1,4-dioxane (**39**) and 2,3-dihydrofuran are known to donate a pair of hydrogen atoms to this kind of compounds. 2,3-Dihydro-1,4-dioxine (**41**), the product of dioxane (**39**) is not able to donate another pair of hydrogen atoms.[46,60,73,74] These heterocyclic

compounds are in general also very good solvents for both the catalyst and the substrate.

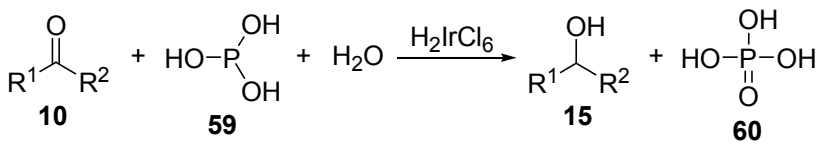
Nitrogen containing heterocyclic compounds, including 1,2,3,4-tetrahydroquinoline, piperidine, pyrrolidine and indoline are also popular hydrogen donors for the reduction of aldehydes, alkenes, and alkynes.[75,76] With piperidine as hydrogen donor the highly reactive 1-piperidene intermediate undergoes trimerisation or in the presence of amines, an addition reaction.[77] Pyridine was not observed as a reaction product.

Hydrocarbons are also able to donate hydrogen atoms. Especially indan and tetralin, which are able to form conjugated double bonds or a fully aromatic system, are commonly used.[74]

Once again, use of these donors as solvent may shift the reaction equilibrium towards the desired product. Since the reactivity of olefins is lower than that of carbonyl compounds, usually higher reaction temperatures are required to achieve acceptable TOF's and then the relatively higher boiling hydrogen donor solvents mentioned above may be the best choice.

Henbest and Mitchell[78] have shown that water can be used as hydrogen source with chloroiridic acid (**6**) as the catalyst through oxidation of phosphorous acid (**59**) to phosphoric acid (**60**) in aqueous 2-propanol (Scheme 19). Under these conditions, no hydrogen transfer occurs from 2-propanol. However, iridium complexes with sulfoxide or phosphine ligands show the usual transfer from 2-propanol.[79-81]

Hydrogen transfer reactions are highly selective, usually no side products are formed, but a major problem is that these reactions are redox equilibria and high TOF's can often only be reached when the equilibria involved are shifted towards the product side. As stated above, this can be achieved by adding an excess of the hydrogen donor. (For a comparison,



Scheme 19. Transfer hydrogenation with the Henbest system.

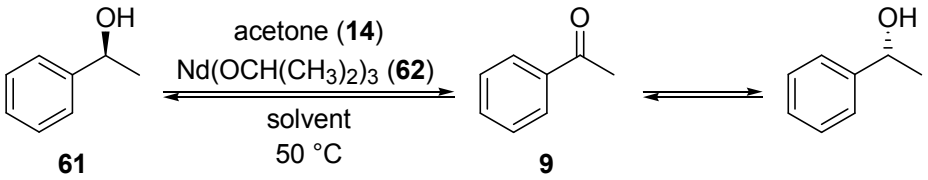
see Table 2, entry 8 and Table 7, entry 3 in which a tenfold increase in TOF (from 6 to 60) can be observed for the reaction catalyzed by neodymium isopropoxide upon changing the amount of hydrogen donor from an equimolar amount to a solvent.) Also, removing the oxidation product by distillation increases the reaction rate. When formic acid (**49**) is employed, the reduction is a truly irreversible reaction.[82] This acid is mainly used for the reduction of C-C double bonds. As the proton and the hydride are removed from the acid, carbon dioxide is formed, which leaves the reaction mixture. Typically, the reaction is performed in an azeotropic mixture of formic acid and triethylamine in the molar ratio 5:2.[83]

In summary, the most popular hydrogen donors for the reduction of ketones, aldehydes and imines are alcohols and amines, while cyclic ethers or hydroaromatic compounds are the best choice for the reduction of alkenes and alkynes.

1.3.2 Solvents

As mentioned above, the hydrogen donor is the solvent of choice in hydrogen transfer reactions. If for any reason another solvent is needed, it is important to select one that does not compete with the substrate or the ligands of the catalyst. By replacing ligands of the catalyst, the electron density of the metal changes, which may have a detrimental effect on the activity of the catalyst.

As an example, Table 2 gives the rate of the racemisation of **61** via an MPVO procedure utilising the catalyst neodymium(III) isopropoxide (**62**) as a function of the solvent. In this case an equimolar amount of acetone was applied as the oxidant. The best results were obtained with hydrocarbons like hexane (entry 7) and heptane (entry 8) as solvents, while the reaction rates in dioxane (entry 2) and acetonitrile (entry 1) were much lower due to inactivation of the catalyst by coordination of the solvent to the metallic centre (Table 2).[84]



Scheme 20. Racemisation of **61** with 19% neodymium(III) isopropoxide (**62**) and 1 equivalent of acetone (**14**).

Table 2. Racemisation of (*S*)-1-phenylethanol (**61**) in different solvents (Scheme 20)[a]

entry	solvent	time (h)	*ee*[b] (%)	TOF (h^{-1})[c]
1	acetonitrile	>48	>99	0
2	dioxane	5	28	2
3	THF	3.5	0	4
4	diisopropyl ether	3.5	0	4
5	MTBE	3.5	0	4
6	toluene	3	0	5
7	hexane	2	0	6
8	heptane	2	0	6

[a] Solvent (12 mL), zeolite NaA (30 mg, dried at 400 °C), (*S*)-1-phenylethanol (**61**) (0.24 mL, 2 mmol), acetone (**14**) (0.15 mL, 2 mmol, 1 equiv.), 1,3,5-triisopropylbenzene (int. std.) (0.2 mL) and neodymium(III) isopropoxide (120 mg, 0.37 mmol, 0.185 equiv.) were stirred at 50 °C.

[b] *ee* (starting material) >99%.

[c] As determined in the first 15 minutes of the reaction. In this period predominantly oxidation takes place.

1.3.3 Catalysts and substrates

Meerwein-Ponndorf-Verley-Oppenauer catalysts typically are aluminium alkoxides or lanthanide alkoxides (see above). The application of catalysts based on metals such as ytterbium (Table 7, entries 6+20) and zirconium[85,86] has been reported.

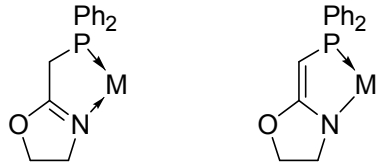
Lanthanide(III) isopropoxides show higher activities in MPV reductions than $Al(OiPr)_3$, enabling their use in truly catalytic quantities (Table 7,

compare entry 2 with entries 3-6). Aluminium catalysed MPVO reactions can be accelerated by the use of triflioroacetic acid (TFA) as additive (Table 7, entry 11)[87,88], by utilising bidentate ligands (Table 7, entries 14)[89] or by using binuclear catalysts (Table 7, entries 15, 16).[8,9] With bidentate ligands, the aluminium catalyst does not form large clusters as it does in aluminium(III) isopropoxide. This increase in availability per aluminium ion increases the catalytic activity. Lanthanide catalysed reactions have been improved by the *in situ* preparation of the catalyst; the metal is treated with iodide in 2-propanol as the solvent (Table 7, entries 17-20).[90] Lanthanide triflates have also been reported to possess excellent catalytic properties.[91]

A drawback of all these catalysts is their extreme water sensitivity. To avoid this problem, reactions should be carried out under inert atmosphere and, if possible, in the presence of type A molecular sieves.[92] The molecular sieves also suppress aldol reactions as will be discussed in chapter 1.4.

For reductions of carbonyl groups or the oxidation of alcohols in the presence of C-C double and triple bonds, MPVO catalysts seem to be the best choice with respect to selectivity for the carbonyl group, the reductions with complexes of transition metals are less selective (see 1.3.4). In the vast majority of syntheses, aluminium(III) isopropoxide is used as the catalyst. From a catalytic point of view, this is not the best choice, since it typically has to be added in equimolar amounts. Probably due to its availability in the laboratory and ease of handling, it is the most frequently used MPVO-catalyst, despite of the development of the more convenient lanthanide(III)isopropropoxides. An advantage of the aluminium catalyst in industrial processes is the possibility to distil the products off while the catalyst remains as active catalyst in the production vessel.

In recent years many active transition metal catalysts have been developed (Table 7, entries 21-53). A careful design of the ligands of the transition metal complexes has led to catalysts with high activities. Mixed chelate ligands containing both a phosphorus and a nitrogen binding site, were employed to prepare catalysts with unusual electronic properties (entries 24-29, 40-42, 44). Especially, the catalyst in entry 44 shows a very



63 **64**

Figure 2. The neutral PCH_2-oxazoline ligand (**63**) and the anionic PCH-oxazoline ligand (**64**).

high TOF for the reduction of acetophenone (10^6 h^{-1}). Other very good catalysts have bidentate phosphine ligands and TOF's of up to 2300 h^{-1} (entries 34-35), contain both nitrogen and phosphorous ligands and TOF's of up to 900 h^{-1} (45-47) or have different bidentate moieties (48, 50-52) and TOF's of up to 14700 h^{-1}.

Neutral mixed chelate ligands containing both a phosphorus and a nitrogen binding site often show a hemilabile character (they are able to bind via one or two atoms to the metal), which allows for the temporary protection and easy generation of reactive sites in the complexes.

Furthermore, the acidity of PCH_2 protons in oxazoline ligands (**63**) enables easy deprotonation of the chelate, giving rise to a static (non-dissociating) anionic 4-electron donating ligand (**64**). These properties give rise to a high activity (Figure 2).[52]

Transition metal catalysts are in general more active than the MPVO catalysts in the reduction of ketones via hydrogen transfer. Especially, upon the introduction of a small amount of base into the reaction mixture, TOF's of transition metal catalysts are typically 5 to 10 times higher than those of MPVO catalysts (Table 7, MPVO catalysts: entries 1-20, transition metal catalysts: entries 21-53). The transition metal catalysts are less sensitive to moisture than MPVO catalysts. Transition metal catalysed reactions are frequently carried out in 2-propanol/water mixtures. Successful transition metal catalysts for transfer hydrogenations are not only based on iridium, rhodium or ruthenium ions but also on nickel[93], rhenium[94] and osmium[95]. It has been reported that MPVO reductions with aluminium(III) isopropoxide as the catalyst can be hugely enhanced by microwave irradiation.[96]

In summary, reduction of ketones and aldehydes can both be performed with MPVO and transition metal complexes as catalysts. Reductions of alkenes, alkynes, and imines require transition metal catalysts; MPV reductions with these substrates are not possible.

Hydrogen transfer towards imines is in general slower than towards the corresponding carbonyl compounds. Nonetheless, the reduction can be performed using the same catalysts, although harsher reaction conditions may have to be applied.[97] This is probably a result of the relative stability of imines with respect to carbonyls. The hydrogen transfer of imines proceeds in general faster with aldimines than with ketimines. The Shvo catalyst (**34**), however, is slightly more reactive towards the latter.[56]

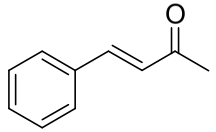
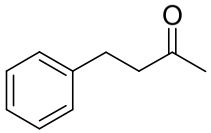
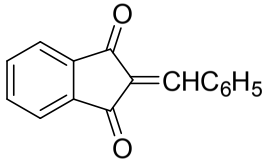
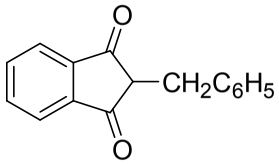
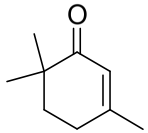
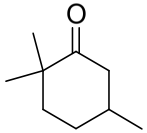
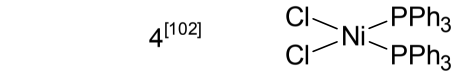
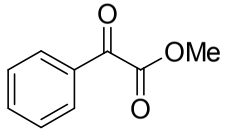
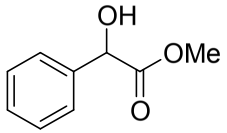
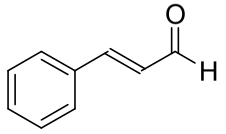
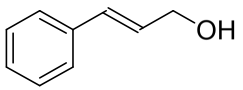
In general, the activity of transition metal catalysts is higher in hydrogenation reactions than in hydrogen transfer reactions. In the few cases where both hydrogenation methods were performed with the same catalyst, it has been shown that reaction rates are lower for transfer hydrogenations. Some examples are known in which transfer hydrogenation is faster than hydrogenation with H_2.[98-100] The simplicity of the transfer hydrogenation protocol and the abundance of selective and active catalysts make this method very competitive with hydrogenations utilising H_2 and it is often the preferred reaction.

1.3.4 Selectivity

As mentioned above, MPVO catalysts are very selective towards carbonyl compounds. Alkenes, alkynes or other heteroatom containing double bonds are not affected by these catalysts, while they can be reduced by transition metal catalysts. Examples of reduction of α,β-unsaturated ketones and other multi-functional group compounds are compiled in Table 3.

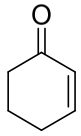
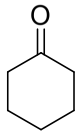
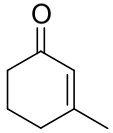
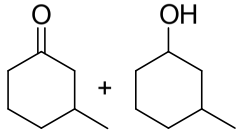
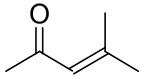
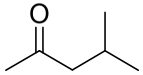
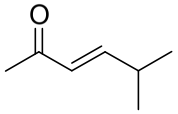
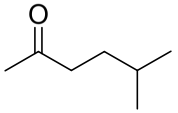
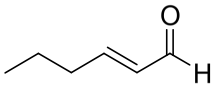
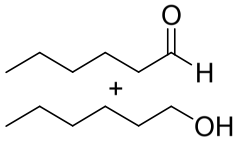
Transition metals can display selectivities for either carbonyls or olefins (Table 3). $RuCl_2(PPh_3)_3$ (**24**) catalyses the reduction of the C-C double bond function in the presence of a ketone function (entries 1-3). With this catalyst,

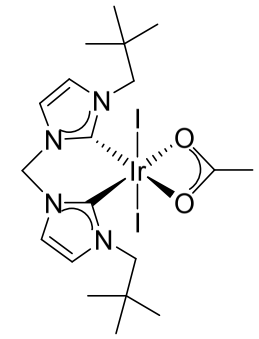
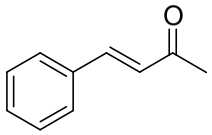
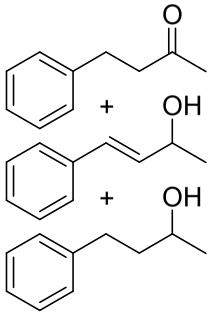
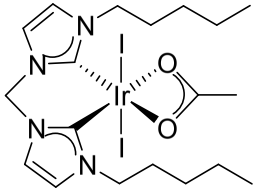
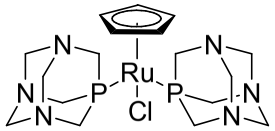
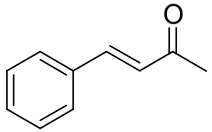
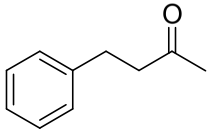
Table 3. Selectivity towards functional groups.

entry	catalyst	substrate ([S]/[C])[a]	product	reductant	T(t) (°C, h)[b]	conversion (ratio) (%)	TOF (h^{-1})
1[101]	$RuCl_2(PPh_3)_3$	 (400)		1-phenylethanol	180 (1)	95	380
2[101]	”	 (400)		”	180 (1)	45	180
3[101]	”	 (400)		”	180 (1)	54	216
4[102]		 (7)		2-propanol	82 (36)	65	0.12
5[102]	”	 (7)		”	82 (30)	51	0.11

The table continues on the next page.

Table 3 (continued).

entry	catalyst	substrate ([S]/[C])[a]	product	reductant	T(t) (°C, h)[b]	conversion (ratio) (%)	TOF (h^{-1})
6[103]	$[Ir(cod)Cl]_2$	 (500)		”	80 (4)	99	12.0
7[103]	”	 (500)		”	80 (4)	91 (3:1)	23.0
8[103]	”	 (500)		”	80 (4)	99	12.0
9[103]	”	 (500)		”	80 (4)	90	6.0
10[103]	”	 (500)		”	80 (4)	75 (10:1)	9.0

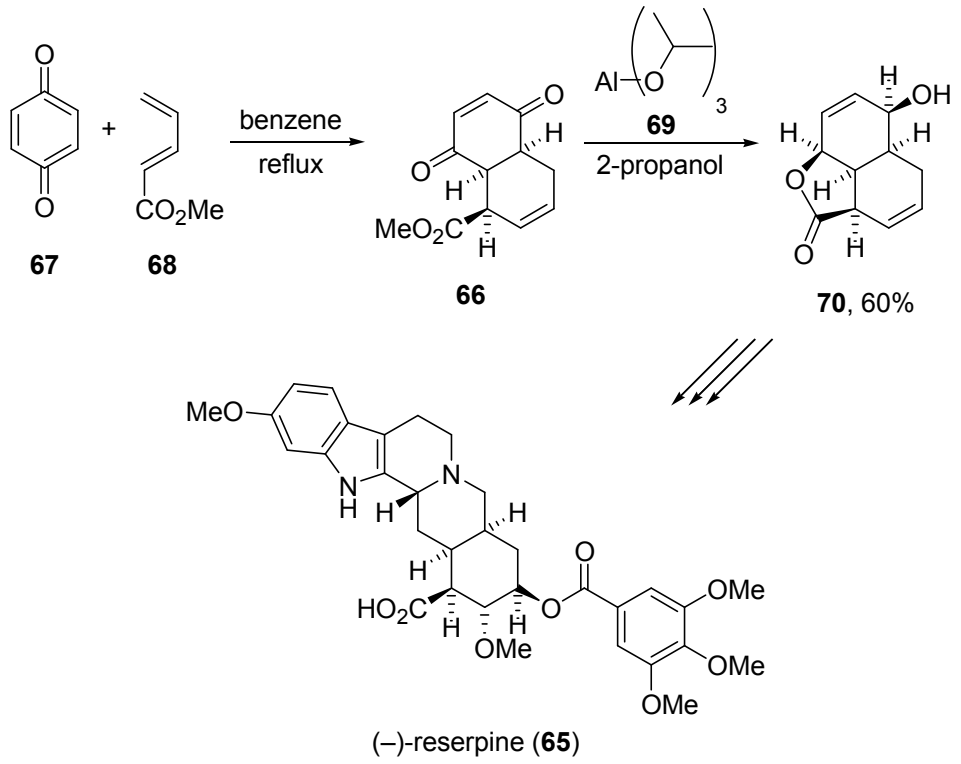
11[104]		 (1000)		”	82 (20)	92 (9:3:2)	1.0
12[104]	”	” (200)	”	”	82 (4)	>98 (0:0:1)	1.0
13[104]		” (1000)	”	”	82 (20)	66 (7:1:0)	0.7
14[104]	”	” (200)	”	”	82 (7)	100 (1:0:5)	0.6
15[105]		 (100)		HCO_2Na/ $MeOH/H_2O$	90 (6)	97	16.0

[a] The [substrate]/[catalyst] molar ratio is given between brackets.

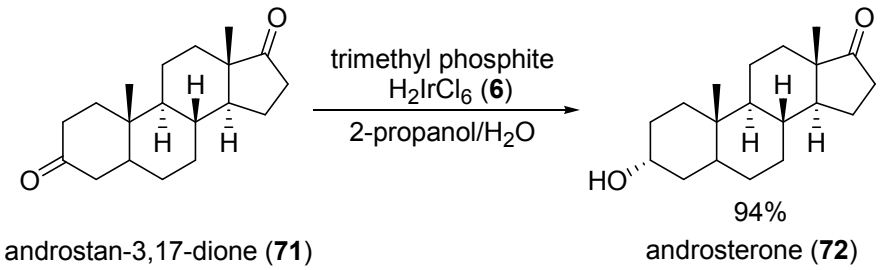
[b] Reaction temperature with the reaction time in brackets.

reaction rates of the reduction of alkenes are usually higher than for ketones. This is also the case with various iridium catalysts (entries 6-14) and a ruthenium catalyst (entry 15). One of the few transition metal catalysts that shows good selectivity towards the ketone or aldehyde function is the nickel catalyst (entries 4 + 5). Many other catalysts have never been tested for their selectivity for one particular functional group.

In total syntheses where a homogeneously catalysed transfer hydrogenation is applied, almost exclusively aluminium(III) isopropoxide is utilised as the catalyst. At an early stage in the total synthesis of (–)-reserpine (**65**) by Woodward *et al.*,[106] an intermediate with two ketone groups and two C-C double bonds is formed (**66**) by a Diels-Alder reaction of *para*-benzoquinone (**67**) and vinyl acrylate (**68**). The two ketone groups were reduced with aluminium(III) isopropoxide (**69**) while leaving the remainder of the molecule unaltered. The resulting dialcohol is immediately lactonised to the tricyclic compound **70** (Scheme 21).



Scheme 21. Woodward's total synthesis of (–)-reserpine (**65**).



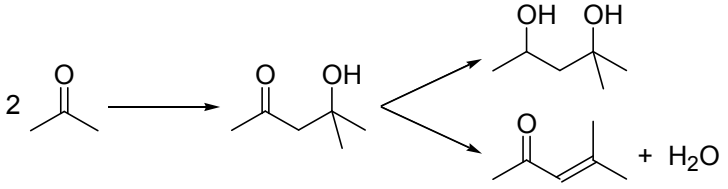
Scheme 22. The reduction of androstan-3,17-dione (**71**) using an iridium catalyst.

One of the very few examples of a practical application of a transition metal catalyst in total synthesis is shown in Scheme 22.[107] The chloroiridic acid catalyst (H_2IrCl_6) (**6**) reduces **71** to androsterone (**72**) by selective attack of the sterically less hindered ketone in the 3-position of **71**.

1.4 Related reactions and side-reactions

1.4.1 Aldol reaction

In the MPVO reaction, several side-reactions can occur. For example an aldol reaction between two molecules of acetone is possible, which then leads to the formation of diacetone alcohol (Scheme 23). The latter acts as a very good ligand for the metal of the MPVO catalyst, rendering it inactive. Moreover, the aldol product may subsequently eliminate water, which hydrolyses the catalyst. The aldol reaction can be suppressed by adding zeolite NaA.[84,92]

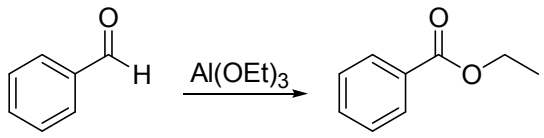


Scheme 23. The aldol reaction and consecutive reactions.

1.4.2 Tishchenko reaction

When aldehydes are reduced, the Tishchenko reaction may be a side-reaction. It is the result of an attack of the oxygen atom of the alkoxide on the carbonyl function of the aldehyde. Especially aldehydes lacking an α-hydrogen atom such as benzaldehyde are prone to form esters in this manner (Scheme 24)[108]

It has been reported that many aldehydes can be converted into Tishchenko esters at room temperature almost quantitatively with high turnovers using SmI_2 catalysts[109] or a bi-aluminium catalyst.[8]

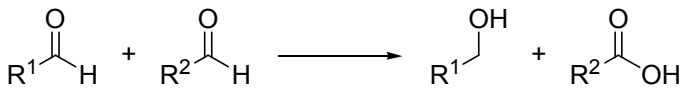


Scheme 24. The original Tishchenko reaction.

1.4.3 Cannizzaro reaction

In the Cannizzaro reaction[110,111] two aldehyde functionalities disproportionate into the corresponding hydroxyl and carboxyl functions, either as separate compounds or as an ester (Scheme 25).

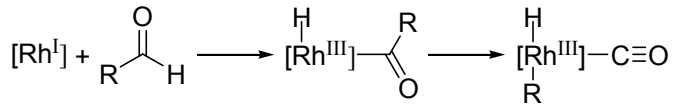
Reaction conditions needed for this reaction are rather harsh, except when R^1 or R^2 is a phenyl group. Typically, an excess of sodium or potassium hydroxide is needed. Therefore, in general, during Meerwein-Ponndorf-Verley-Oppenauer reactions only traces of Cannizzaro products are formed.



Scheme 25. The Cannizzaro reaction.

1.4.4 Decarbonylation

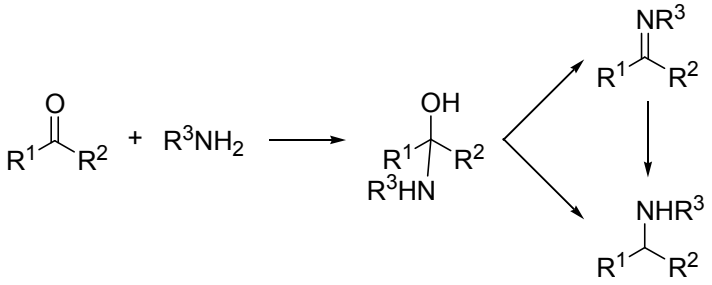
Aldehydes may sometimes pose a problem in transfer hydrogenations catalysed by transition metals. They can poison the catalyst or decarbonylate, forming CO, which may coordinate to the metal complex resulting in change in activity (Scheme 26).[65,66]



Scheme 26. Decarbonylation of an aldehyde under influence of a transition metal catalyst.

1.4.5 Leuckart-Wallach and Eschweiler-Clarke reactions

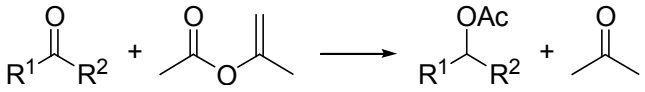
The reductive alkylation of amines is called the Leuckart-Wallach reaction.[112-115] The primary or secondary amine reacts with the ketone or aldehyde. The formed imine is then reduced with formic acid as hydrogen donor (Scheme 27). When amines are reductively methylated with formaldehyde and formic acid, the process is called the Eschweiler-Clarke procedure.[116,117]



Scheme 27. The Leuckart-Wallach reaction.

1.4.6 Reductive acetylation of ketones

In the presence of an active acyl donor such as isopropenyl acetate, a reductive acetylation of a ketone can be performed in the presence of MPVO catalysts (Scheme 28).[84,118] The first step in this procedure is the reduction of the ketone followed by the acetylation of the formed alkoxide. It may be noted that aluminium(III) isopropoxide and zirconium(IV) isopropoxide do not catalyse the acetylation. With these catalysts, the alcohol is obtained.

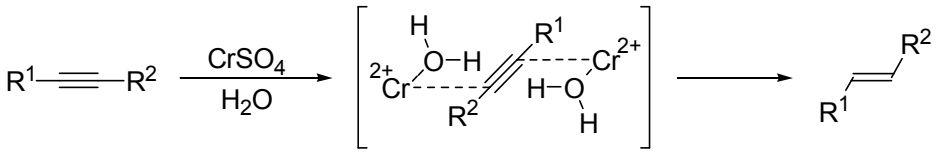


Scheme 28. Reductive acetylation of ketones.

1.4.7 Other hydrogen transfer reactions

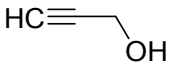
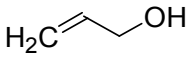
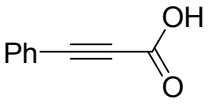
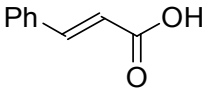
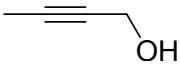
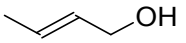
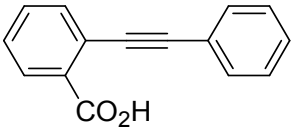
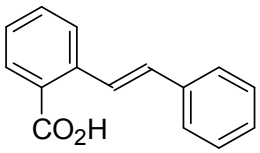
A few remarkable but rather uncommon transfer hydrogenations also deserve to be mentioned in the context of this review: the reduction of alkynes to alkenes using a chromium catalyst and the reduction of double bonds using diimines

In the reduction of C-C triple bonds with chromous sulfate in water, the key intermediate consists of a dichromium complex with the alkyne (Scheme 29)[119] This configuration assures the selective formation of *trans* double bonds. Various substrates have been reduced in excellent yields without the occurrence of isomerisations or by-products (Table 4).

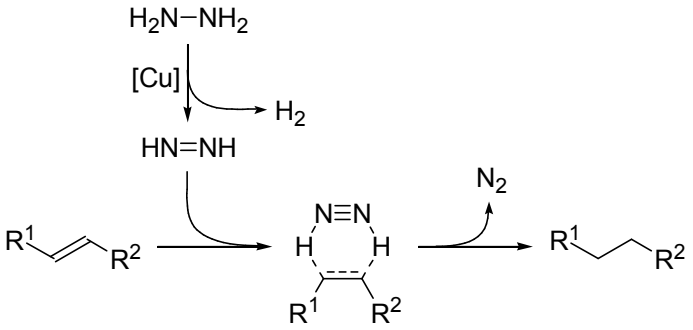


Scheme 29. Reduction of alkynes to trans-alkenes by chromous sulfate.

Table 4. Reduction of alkynes to trans-alkenes by chromous sulfate.

entry	substrate	product	reaction time (h)	yield (%)	TOF (h^{-1})
1			0.08	89	5.0
2			0.25	91	2.5
3			2	84	0.4
4			24	85	0.02

A very fast and reliable method for the reduction of double bonds is transfer hydrogenation with diimine (Scheme 30). Under influence of traces of copper ions and oxygen from air, hydrazine is rapidly transformed into diimine. This compound is able to hydrogenate double bonds with great ease under the formation of nitrogen.[120]



Scheme 30. Reduction of alkenes with hydrazine.

1.5 Racemisations

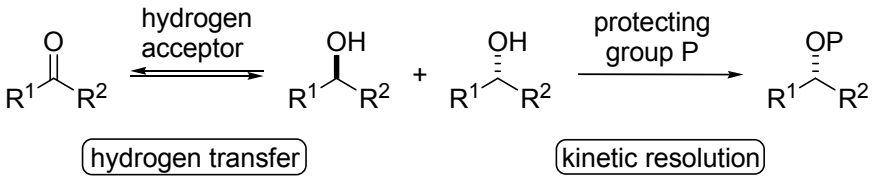
Since transfer hydrogenation reactions of carbonyls are always equilibrium reactions, it is possible to perform both a reduction and an oxidation of a substrate at the same time. In this way, these reactions can be utilised for racemisations and epimerisations.

In contemporary production of enantiopure compounds this feature is highly appreciated. Currently, the kinetic resolution of racemates is the most important method for the industrial production of enantiomerically pure compounds. This procedure is based on chiral catalysts or enzymes, which catalyse the conversion of the enantiomers with different rates. The theoretical yield of this kind of reactions is only 50%, because the unwanted enantiomer is discarded. This generates a huge waste stream, an undesirable situation both from an environmental and an economical point of view. Efficient racemisation catalysts that enable recycling of the undesired enantiomer are therefore of great importance.

In order to accomplish a racemisation rather than an oxidation of an alcohol, the hydrogen acceptor should be added in an equimolar or lower concentration. This is illustrated by Table 5.[84] In order to have acceptable reaction times and yields, the amount of hydrogen donor has to be adjusted to meet every single reactant.

Racemisations are not limited to alcohols; some racemisations of amines have also been reported.[121]

The next step in the use of transfer hydrogenation catalysts for the recycling of the unwanted enantiomer is the dynamic kinetic resolution. This is the combination of two reaction systems: the continuous racemisation of



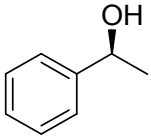
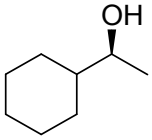
Scheme 31. The dynamic kinetic resolution of a racemic alcohol.

the alcohol via hydrogen transfer and the enantioselective protection of the alcohol using a stereoselective catalyst, typically an enzyme.[122-127] As was first demonstrated by Williams *et al.*,[30] a dynamic kinetic resolution of racemic alcohols by the combination of two catalysts, is a mild and effective way to obtain enantiomerically pure alcohols in high yields and selectivities (Scheme 31).

It is important that the catalysts are stable in each other's presence. Typically, the kinetic resolution of the reaction is performed with an enzyme, which always will contain traces of water. Hence, MPVO catalysts and water sensitive transition metal catalysts cannot be used in these systems. The influence of the amount of the hydrogen acceptor in the reaction mixture during a dynamic kinetic resolution is smaller than in a racemisation, since the equilibrium of the reaction is shifted towards the alcohol side of the reaction.

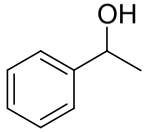
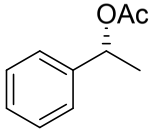
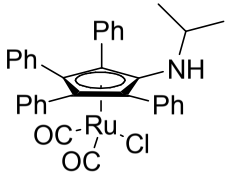
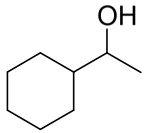
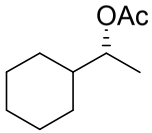
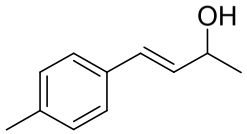
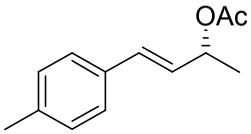
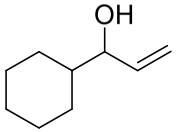
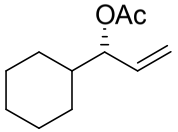
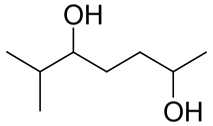
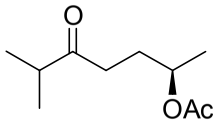
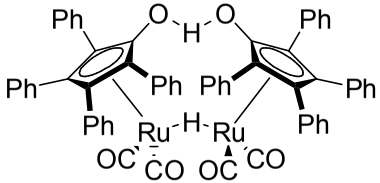
Since the introduction of the dynamic kinetic resolution, several groups have been active in the field of dynamic kinetic resolutions. They have been able to obtain products at almost quantitative yields and with excellent enantiomeric excesses (Table 6).[128-130]

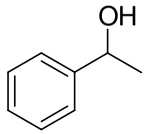
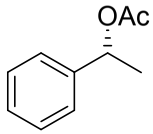
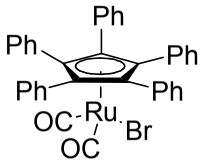
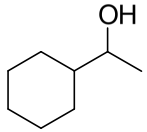
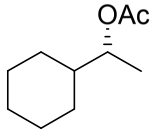
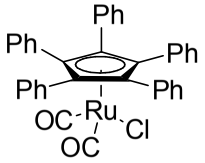
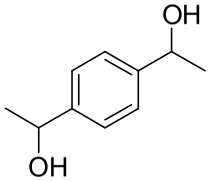
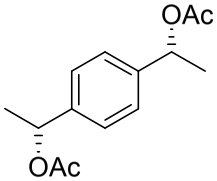
Table 5. Racemisation involving a conjugated and a non-conjugated ketone.

entry	substrate	acetone (equiv.)	time (h)[a]	ketone formed (%)
1		1	1.5	50
2	”	0.1	3	10
3		1	2.5	25
4	”	0.1	>7	9

[a] Time needed for complete racemisation.

Table 6. Recent examples of successful dynamic kinetic resolutions.

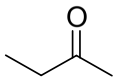
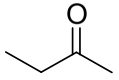
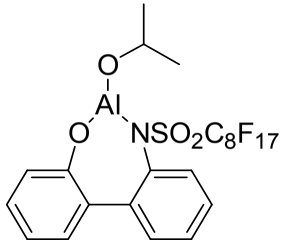
entry	substrate	product	racemisation catalyst[a]	subs./cat. ratio [b]	time (h)	T (°C)	yield (%)	*ee* (%)
1[128]				25	31	25	95	>99
2[128]			”	25	48	25	86	>99
3[128]			”	25	96	25	92	>99
4[128]			”	25	96	25	90	>99
5[129]				20	18	70	77	89

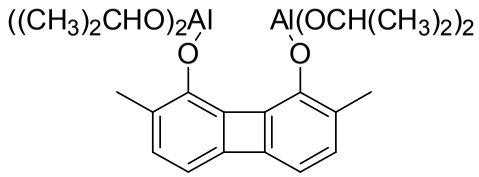
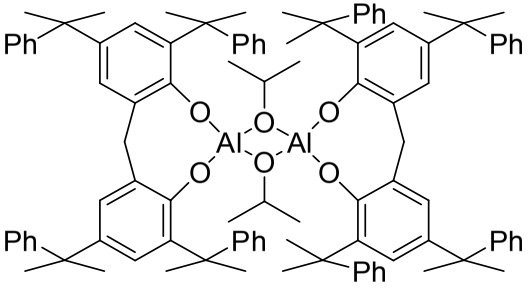
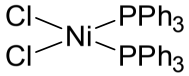
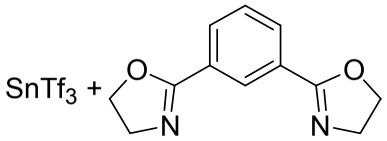
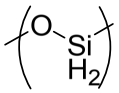
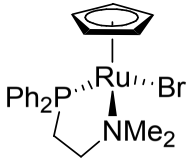
6[130]				25	3	25	98	>99
7[130]				20	17	25	98	>99
8[130]			”	20	10	25	94	>99 (99:1 d.r.)

[a] The catalyst for the kinetic resolution is in all cases *Candida antarctica* Lipase B.

[b] Substrate/catalyst ratio is the ratio between the racemic alcohol and the hydrogen transfer catalyst.

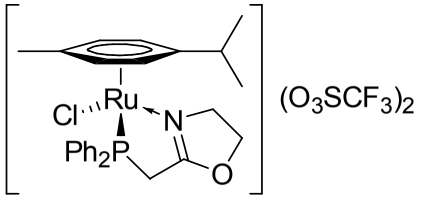
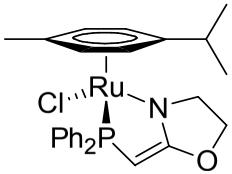
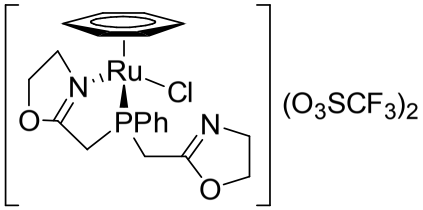
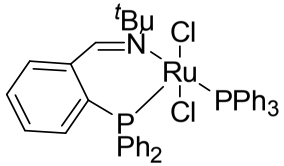
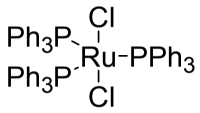
Table 7. Short overview of the reduction of acetophenone with MPVO catalysts and transition metal catalysts developed during the last five years.

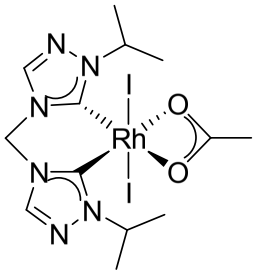
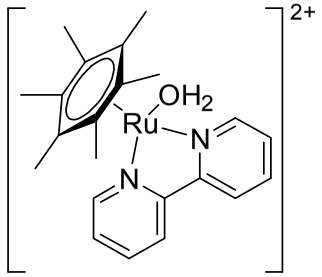
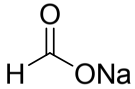
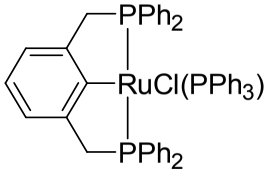
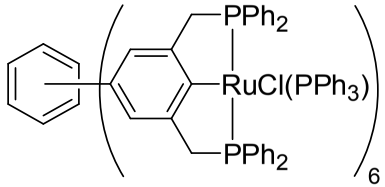
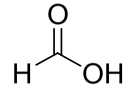
entry	catalyst	reducing agent[a]	additive/ solvent[b]	T (°C)	substrate/ catalyst ratio	conversion (%)	reaction time (h)	TOF (h^{-1})[c]
1[131]	$^{t}BuOSmI_2$	 [d]	THF	65	10	98	24	0.4
2[7]	$Al(OCH(CH_3)_2)_3$			50	10	1	1	0.1
3[7]	$Nd(OCH(CH_3)_2)_3$	”		50	100	57	1	60
4[7]	$Gd(OCH(CH_3)_2)_3$	”		50	100	58	1	60
5[7]	$Er(OCH(CH_3)_2)_3$	”		50	100	22	1	20
6[7]	$Yb(OCH(CH_3)_2)_3$	”		50	100	5	1	5
7[132]	$La(OCH(CH_3)_2)_3$	 [d]		80	20	75	60	0.3
8[132]	$Ce(OCH(CH_3)_2)_3$	”		80	20	15	48	0.1
9[132]	$Sm(OCH(CH_3)_2)_3$	”		80	20	70	24	0.6
10[132]	$Yb(OCH(CH_3)_2)_3$	”		80	20	98	24	0.8
11[88]	$Al(OCH(CH_3)_2)_3$		TFA (1)	25	12	44	22	0.3
12[133]	$Pu(N(Si(CH_3)_3)_2)_3$	”		25	20	91	24	0.8
13[10]	$Al(CH_3)_3$	”		65	10	80	12	0.7
14[89]		 (10)	CH_2Cl_2	25	10	85	5	1.5

15[8]		 (3)	”	25	20	96	1	20
16[9]		 (100)	toluene	111	40	93	1	40
17[90]	La + 5% I_2			25	1	48	20	0.048
18[90]	Ce + 5% I_2	”		25	1	34	20	0.039
19[90]	Sm + 5% I_2	”		25	1	96	20	0.05
20[90]	Yb + 5% I_2	”		25	1	24	20	0.036
21[102]		”	NaOH (0.33)	82	7	82	30	0.2
22[134]	$NiBr_2$	”	NaOH (85)	95	250	60	4	10
23[135]			MeOH	25	10	98	12	0.8
24[136]			 (0.02)	82	200	>99	48	5

The table continues on the next page.

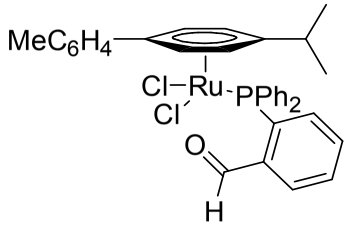
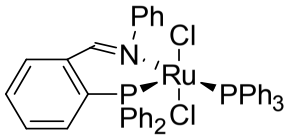
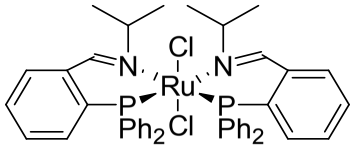
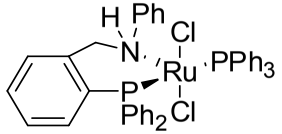
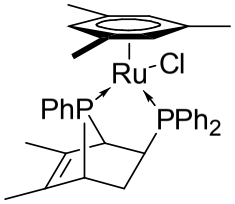
Table 7 (continued).

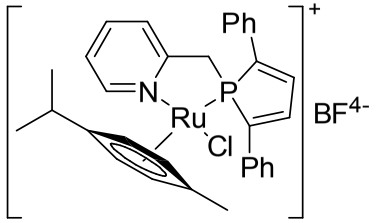
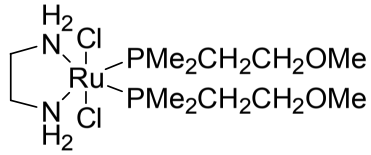
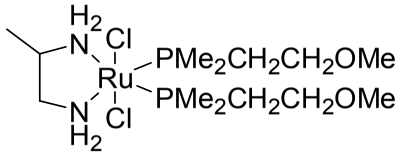
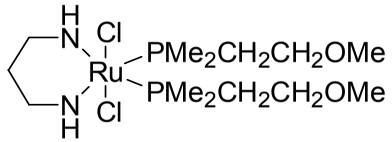
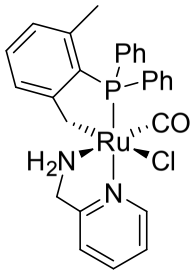
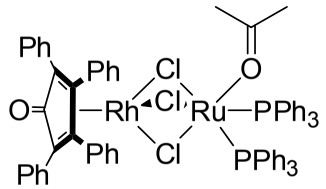
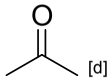
entry	catalyst	reducing agent[a]	additive/ solvent	T (°C)	substrate/ catalyst ratio	conversion (%)	reaction time (h)	TOF (h^{-1})[b]
25[52]		”	 (0.025)	82	200	61	1	120
26[52]		”	 (0.025)	82	200	25	0.25	200
27[52]	”	”	 (0.025)	82	200	94	6	30
28[52]		”	 (0.12)	82	200	54	1	110
29[137]		”	NaOH (0.5)	90	5	91	0.5	910
30[138]		”	NaOH (0.024)	82	500	50	2	2.0

31[138]	”	”	NaOH (0.024) $Yb(OTf)_3$ (0.004)	82	500	86	2	3.5
32[139]		”	KOH (0.5)	82	1000	>98	10	100
33[140]		 (30)	H_2O	70	200	98	4	50
34[141]				82	1000	50	0.22	2300
35[141]		”		82	1000	50	0.23	2200
36[142]	$[Cp^*Ir^{III}(bpy)(H_2O)]^{2+}$	 (5)	H_2O	70	200	97	1	194

The table continues on the next page.

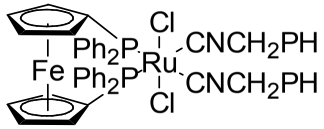
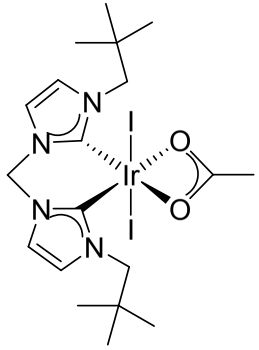
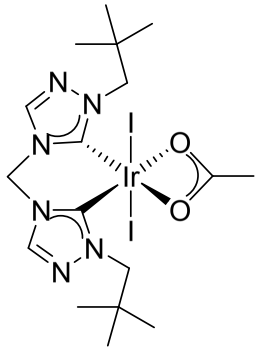
Table 7 (continued).

entry	catalyst	reducing agent[a]	additive/ solvent	T (°C)	substrate/ catalyst ratio	conversion (%)	reaction time (h)	TOF (h^{-1})[b]
37[143]			NaOH (0.048)	82	500	98	10	50
38[143]	”	”	NaOH (0.048)	82	500	97	9	55
39[143]	”	”	NaOH (0.048)	82	500	96	6	80
40[144]		”	NaOH (0.048)	82	500	98	1	485
41[144]		”	NaOH (0.048)	82	500	97	1	240
42[144]		”	NaOH (0.048)	82	500	96	2	240
43[145]		”	KOH (0.025)	82	200	>99	0.5	400

44[53]		”	KOH (0.5)	90	$60 \cdot 10^6$	>99	60	$1 \cdot 10^6$
45[146]		”	KOH (0.1)	82	500	93	0.5	935
46[146]		”	KOH (0.1)	82	500	82	0.5	815
47[146]		”	KOH (0.1)	82	500	90	0.5	900
48[54]		”	NaOH (0.02)	82	400	98	0.08	4700
49[147]		 [d]	K_2CO_3 (1)	RT	1000	70	6	60

The table continues on the next page.

Table 7 (continued).

entry	catalyst	reducing agent[a]	additive/ solvent	T (°C)	substrate/ catalyst ratio	conversion (%)	reaction time (h)	TOF (h^{-1})[b]
50[148]			NaOH (0.096)	250	250	84	0.17	1260
51[51]		”	KOH (0.005)	82	1000	98	0.07	14700
52[51]	”	”	K_2CO_3 (0.5)	82	1000	97	0.67	1455
53[51]		”	KOH (0.005)	82	1000	80	2	400

[a] The number between brackets denotes the number of equivalents used. If no number is given, the donor is used as solvent.

[b] The number between brackets denotes the number of equivalents used. If no number is given, the additive is used as solvent.

[c] TOF = [substrate]/[catalyst]/h, calculated from the yield and stated reaction time.

[d] Oxidation of 1-phenylethanol.

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2

Mechanism of homogeneously and heterogeneously catalysed Meerwein-Ponndorf-Verley-Oppenauer reactions for the racemisation of secondary alcohols

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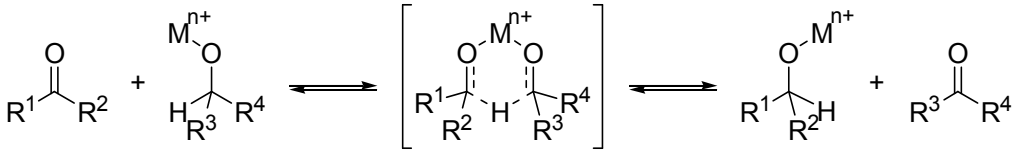
2.1 Introduction

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 like ethanol or 2-propanol are used as hydrogen donor in the MPV-reduction, whereas oxidants like 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



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

catalysed by transition metals like 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.

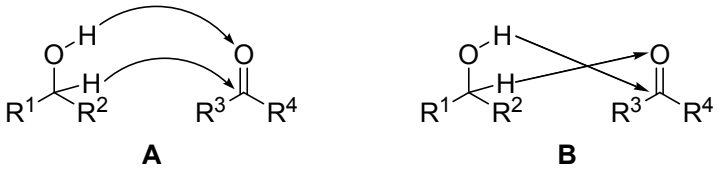
In the MPV reduction, the ketone or the aldehyde coordinates to the metal centre of the catalyst, which causes the activation of the double bond (Scheme 1). A hydride shift takes place and the alkoxide is released as ketone or aldehyde. Alkoxides can exchange with alcohols present in solution, so an 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



Scheme 2. Two possible pathways for the hydrogen transfer.

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 benzylic 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.

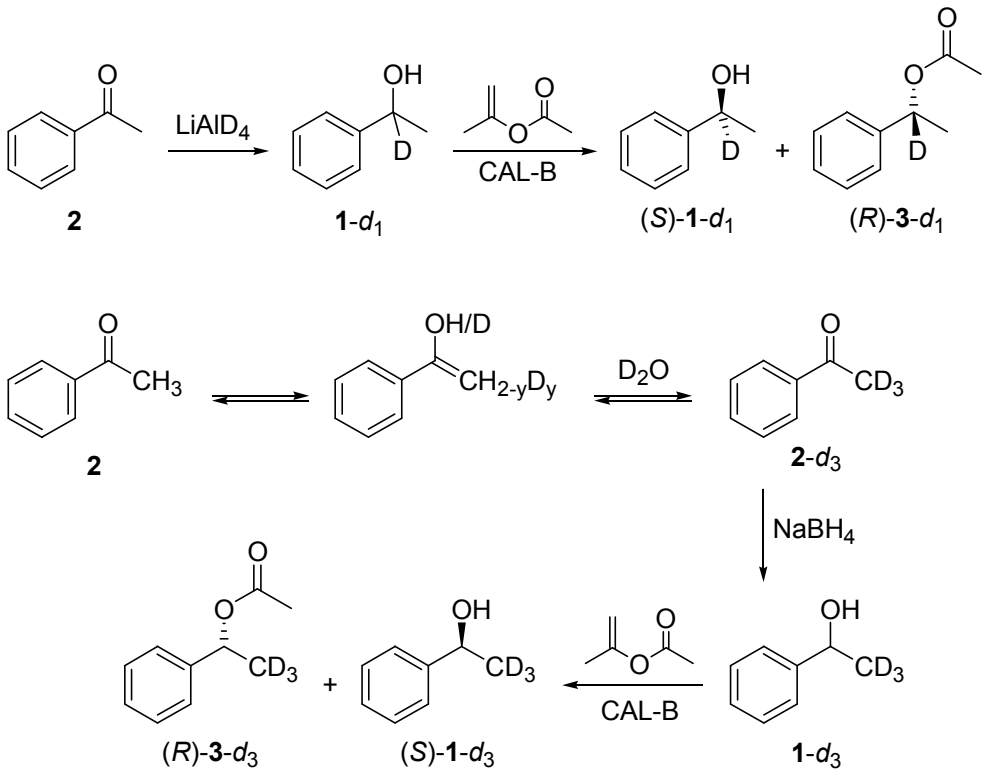
2.2 Results and discussion

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 ^{2}H-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 ^{2}H.

2.2.1 Synthesis of isotopically substituted compounds

(*S*)-1-phenyl-(1-^{2}H$_1$)ethanol ((*S*)-**1**-d_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

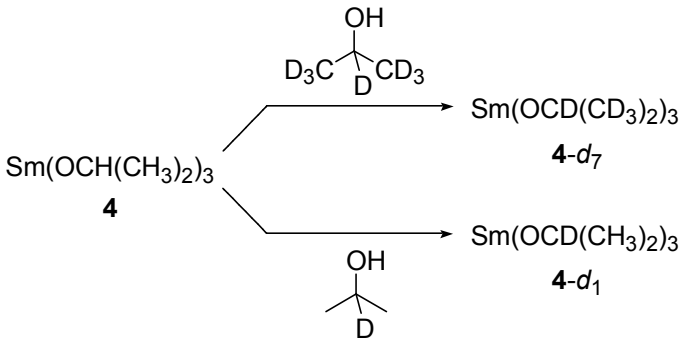


Scheme 3. Synthesis of enantiopure deuterium substituted alcohols.

acetate. The enantiopure alcohol (*S*)-**1**-d_1 and acetate (*R*)-**3**-d_1 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 (**1**-d_3) 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 **1**-d_3, which was submitted to a CAL-B catalysed kinetic resolution (Scheme 3). The alcohol (*S*)-**1**-d_3 and acetate (*R*)-**3**-d_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 4. Synthesis of the deuterated samarium(III) catalysts through ligand exchange.

2.2.2 Catalytic reactions with samarium(III) isopropoxide

The racemisations of (*S*)-**1**-d_1 and (*S*)-**1** were performed with an equimolar amount of acetophenone (**2**) and 10 mol% of **4**-d_7 or **4**-d_1 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).

Entries 1 and 3 show complete retention of deuterium at the α-position

Table 1. Deuterium contents after complete racemisation of (*S*)-**1** and (*S*)-**1**-d_1.[a]

entry	alcohol	catalyst	solvent	% ^{2}H at 1-position[b]	% ^{2}H at Me[b]
1	(*S*)-**1**-d_1	**4**-d_7	THF	>99	15
2	(*S*)-**1**	**4**-d_7	THF	11	16
3	(*S*)-**1**-d_1	**4**-d_7	heptane	>99	17
4	(*S*)-**1**	**4**-d_7	heptane	15	20

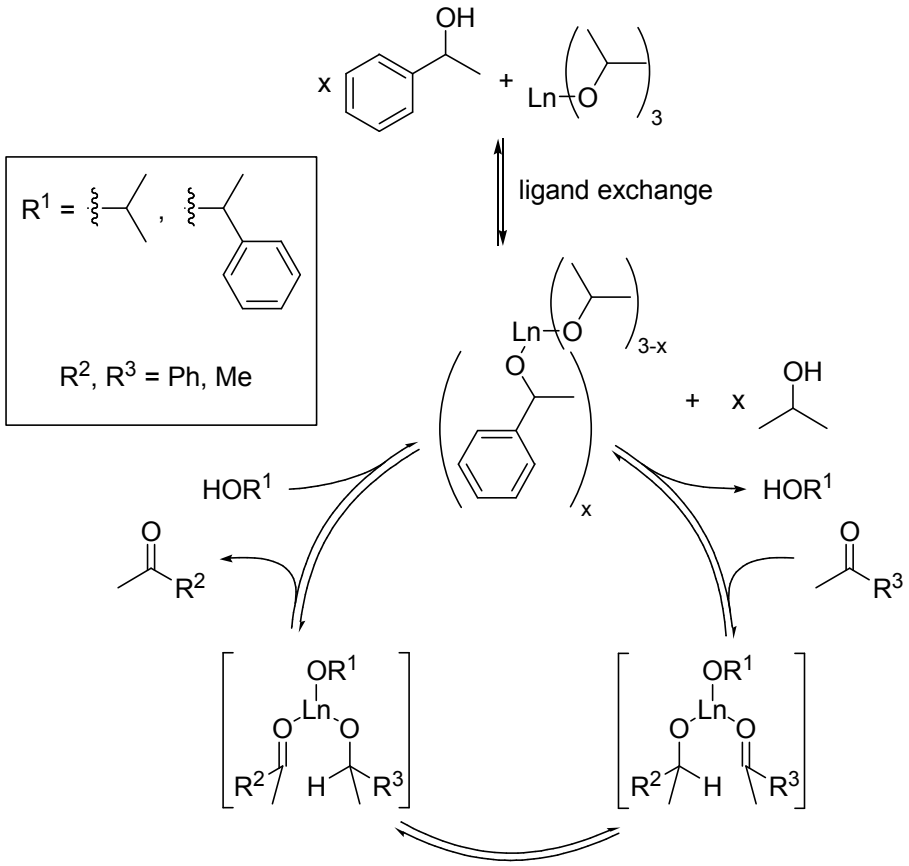
[a] alcohol (0.5 mmol), **2** (0.5 mmol), catalyst (0.05 mmol), solvent (0.75 mL), T=70 °C, 18 h.
[b] calculated from NMR and MS.

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 1-phenylethanol would have resulted in 23% of ^{2}H on the latter position. This confirms that the racemisation takes place exclusively via the mechanisms depicted in Scheme 1. Remarkably, a substantial amount of deuterium was found in the methyl group of 1-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.

Analogous experiments were performed using **4**-d_1. The ^{2}H distribution at the 1-position in the products was similar to that with the completely deuterated catalyst **4**-d_7. 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 transfered 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 1-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).



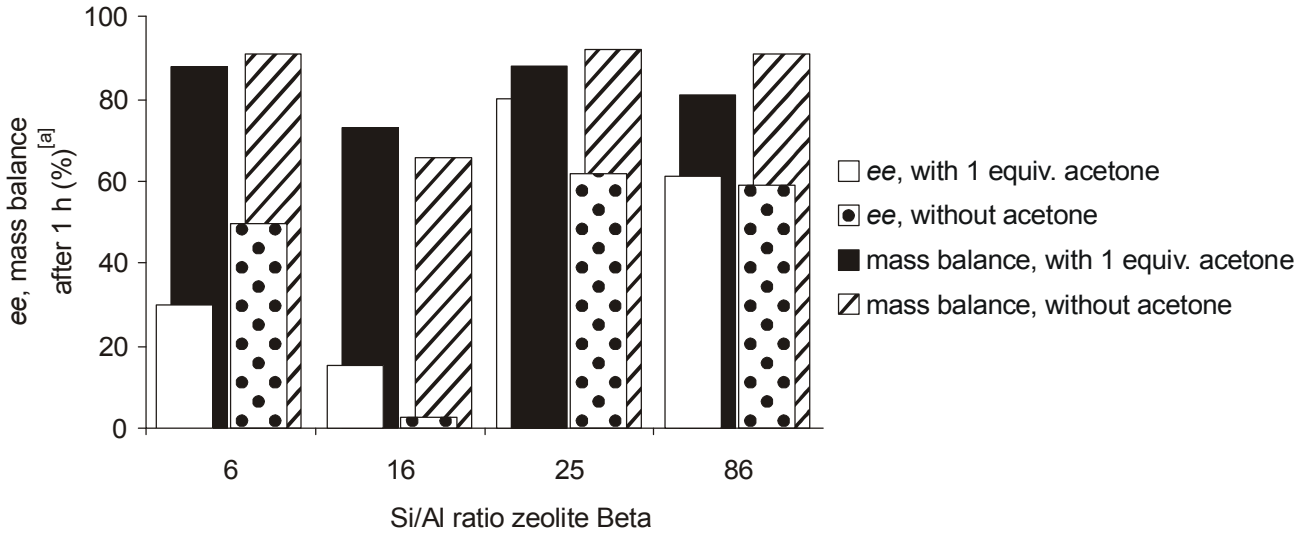
Scheme 5. Ligand exchange and subsequent reactions in the MPVO cycle.

2.2.3 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] Here, 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 as was shown by Wuyts *et al.*.[31] 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



[a] determined by chiral GC.

Figure 1. Zeolite Beta catalysed racemisations of (*S*)-1-phenylethanol in the presence and in the absence of acetone.

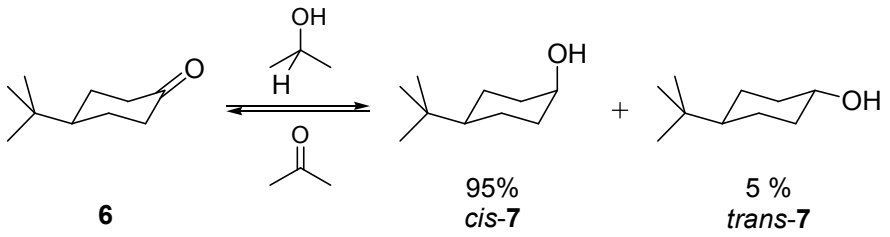
via a different pathway. The incomplete mass balance as determined by GC analysis also supports the presence of another pathway differing from the redox reactions. The phenomena observed can be rationalised by the occurrence of an elimination/addition mechanism in which the hydroxygroup is eliminated from the alcohol, forming a carbocation intermediate. This intermediate gives upon rehydration 1-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 1-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*-butylcyclohexanol (**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]



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, indicating 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).

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-

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

entry	ketone	catalyst[b]	solvent	% ^{2}H 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]

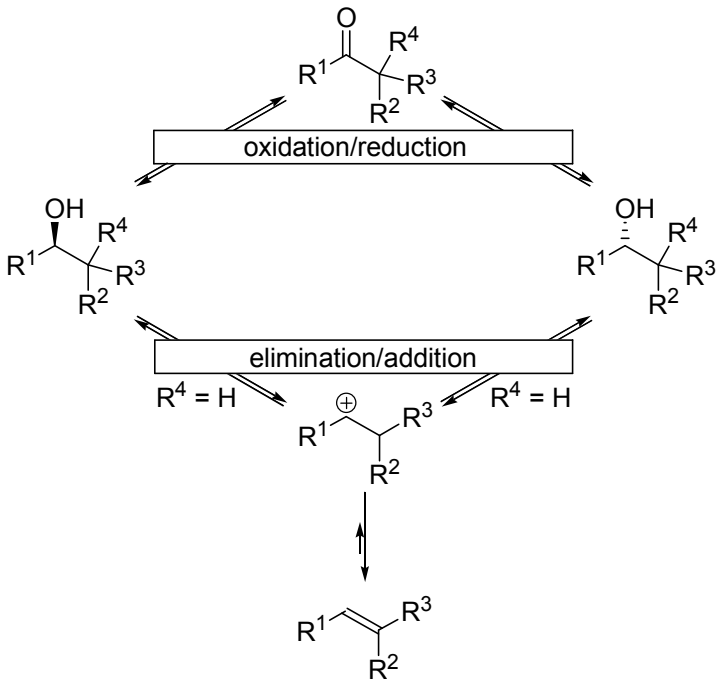
[c] calculated from NMR and MS, 3-5% of the *trans* isomer was found, also with > 99% ^{2}H at the 4-position.

Beta, where only Lewis acid sites are available in the catalyst, it is possible to reduce **2** without any elimination.[29]

2.3 Conclusions

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



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

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.

2.4 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 13.5 and 150 were commercially available from CU Chemie, Uetikon. Enantiomeric excesses 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 (Beta-cyclodextrin 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.; 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 (δ = 0 ppm). The deuterium content of the isotopically substituted compounds was calculated from the ^{1}H- and ^{2}H-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 ° (PE) and diethyl ether (Et_2O).

1-Phenyl-(1-^{2}H$_1$)ethanol (1-*d*$_1$)

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 20.8 g (169 mmol, >99% deuterated, 88%) of **1**-*d*$_1$ as a colourless oil. B.p. 98 °C/30 mbar. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 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-^{2}H$_1$)ethanol ((*S*)-1-*d*$_1$) and **(*R*)-(1-^{2}H$_1$)-1-methylbenzyl acetate ((*R*)-3-*d*$_1$)**

1-*d*$_1$ (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 0.84 g (6.8 mmol, *ee*>99%, >99% deuterated, 42%) of alcohol (*S*)-**1**-d_1 and 1.18 g (7.1 mmol, *ee*>99%, >99% deuterated, 44%) of acetate (*R*)-**3**-d_3 were obtained. The ^{1}H-NMR spectrum of the alcohol was identical to that of **1**-d_1. (*R*)-**3**-d_3: ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 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*)-1-d_3) and **(*R*)-1-($^2H_3$)methylbenzyl acetate ((*R*)-3-d_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 3h, 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 3h 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, 811 mg of the desired alcohol (*S*)-**1**-d_3 (6.49 mmol, *ee*=99%, 97% deuterated, 38% (3 steps)) and 1.11 g of the acetate (*R*)-**3**-d_3 (6.65 mmol, *ee*=99%, 96% deuterated, 39% (3 steps)). (*S*)-1-phenyl-(2-$^2H_3$)ethanol: ^{1}H-NMR (300 MHz, dioxane-d_8) δ = 3.80 (s, 1H, C*H*), 4.77 (d, *J*=2.7 Hz, 1H, O*H*), 7.19-7.40 (m, 5H, Ar-*H*); ^{2}H-NMR (46 MHz, dioxane) δ = 1.29 (C*D*$_3$); (*R*)-1-($^2H_3$)methylbenzyl acetate: ^{1}H-NMR (300 MHz, dioxane-d_8,) δ = 2.03 (s, 3H, C(O)-C*H*$_3$), 5.86 (s, 1H, C*H*), 7.23-7.40 (m, 5H, Ar-*H*); ^{2}H-NMR (46 MHz, dioxane) δ = 1.41 (C*D*$_3$).

2-(2-$^2H_1$)Propanol

This alcohol was synthesised in an analogous way as **1**-d_1, using acetone

(17.6 mL, 238 mmol), $LiAlD_4$ (5 g, 119 mmol) in diethyl ether (50 mL).[34, 33] Distillation (82 °C/atmospheric pressure) yielded 12.2 g (101 mmol, >99% deuterated, 85%) of the desired alcohol. ^{1}H-NMR (300 MHz, dioxane-d_8) δ = 1.20 (t, *J*=0.9 Hz, 6H, 2´CH_3), 2.08 (s, 1H, O*H*).

Samarium(III) ($^2H_7$)isopropoxide (4-d_7))

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 trifluoroacetic acid-*d* to which a drop of D_2O was added to increase solubility. Dioxane was added as internal standard. ^{1}H-NMR (300 MHz, TFA-d_1) δ = 0.80-1.00 (m, CH_3). Integration of the ^{1}H NMR spectrum showed the deuterium content to be 87%.

Samarium(III) ($^2H_7$)isopropoxide (4-d_1)

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 minutes 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. It was kept at that temperature for 15 h. After cooling, Na^+ was exchanged

by H^+ by stirring the zeolite 3 times for 48 hours 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]
Synthesis of zeolite Beta (Si/Al=5): $NaAlO_2$ (2.12 g, 25.9 mmol), 35% TEAOH in water (8 mL, 19.5 mmol) and LUDOX® HS-40 (15 mL). Synthesis of zeolite Beta (Si/Al=20) $NaAlO_2$ (0.53g, 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.

2.5 Acknowledgements

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3 Combined epimerisation and acylation: Meerwein-Ponndorf-Verley-Oppenauer catalysts in action

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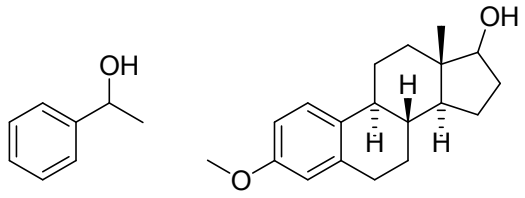
Organic and Biomolecular Chemistry **2005**, *3*, 483-489.

3.1 Introduction

The synthesis of complex chiral compounds is becoming increasingly important. However, not all conversions can be performed enantiospecifically. In these cases, the unwanted stereoisomer is separated from the desired compound and is often discarded, even at a relatively late stage of an elaborate reaction sequence. It is, therefore, desirable to have available gentle and selective racemisation and epimerisation reactions, which allow recycling of the undesired isomer, thus reducing the loss of valuable material.

In this chapter, a mild procedure for the epimerisation of secondary alcohols is presented. It exploits the reversible Meerwein-Ponndorf-Verley-Oppenauer (MPVO) reduction-oxidation reactions.[1-5] The MPV-reduction of ketones and the Oppenauer-oxidation of alcohols have been widely studied and typically both reactions can be performed under very mild reaction conditions.[6-9] Their mechanisms have recently been shown to proceed exclusively via a carbon-to-carbon hydride transfer.[10] Combination of the two reactions results in a convenient racemisation procedure. Originally, aluminium(III) isopropoxide was used as the catalyst for the MPV reduction and Oppenauer oxidation. Through the years, several improved catalysts have been developed.[11-13] In the present study several catalytic systems were tested for their activity in racemisations of secondary alcohols.

Most reactions have been performed with 1-phenylethanol (**1**) as a model compound. The best catalyst was then tested in the epimerisation of



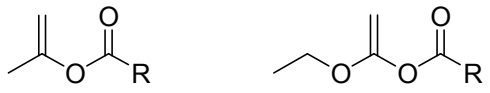
1 **2**

Figure 1. The model compound 1-phenylethanol (**1**) and the steroid estradiol 3-methyl ether (**2**).

the estradiol derivative **2** (Figure 1). Estradiol is a steroid hormone from the family of estrogens, which can be prepared by reduction of the corresponding ketone. Achiral reducing reagents, such as $NaBH_4$ or $LiAlH_4$, give the epimers α-estradiol and β-estradiol in a ratio of typically 1:4.[14] Since it is difficult to obtain the desired β-estradiol in high yields, the epimerisation of estradiol is an interesting test case for the scope of the newly developed methodology.

Additionally, recycling of unwanted isomers of alcohols produced during enzymatic kinetic resolutions of esters is a further example of a process where racemisations are important. It may be particularly useful to convert the racemised alcohols directly into the appropriate esters so as to be able to use them again in a subsequent kinetic resolution.

The catalytic systems that are proposed for the racemisation and epimerisation are also known to be active for the acylation of alcohols.[15] Therefore, we studied a one-pot reaction for the combined racemisation and acylation of secondary alcohols. For the acylation, isopropenyl and ethoxyvinyl esters (**3** and **4**) were applied as activated acyl donors (Figure 2).[16-18]



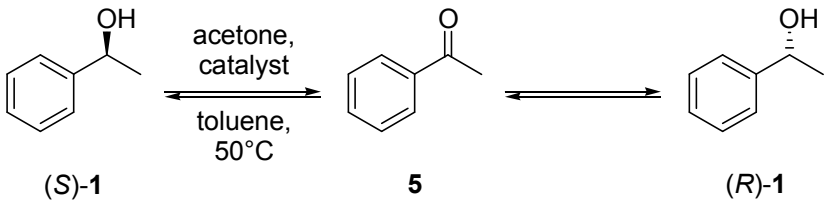
3 **4**

Figure 2. Isopropenyl ester (**3**) and ethoxyvinyl ester (**4**).

3.2 Results and discussion

3.2.1 Selection of the catalyst

Several racemisation reactions of (*S*)-1-phenylethanol ((*S*)-**1**) were performed using 2 mol% of a metal isopropoxide as the catalyst and acetone



Scheme 1. Racemisation of (*S*)-1-phenylethanol ((*S*)-**1**).

as the initial oxidant (Scheme 1, Table 1).

Aluminium(III) isopropoxide is the traditional catalyst for MPV reductions and Oppenauer oxidations. When catalytic amounts are used the racemisation reactions are very slow (entry 7); thus, it is commonly used in stoichiometric amounts. Catalysts based on lanthanide ions (entries 9-18), however, are generally more active, most likely because the ligand-exchange rates for lanthanide complexes are higher than those for aluminium complexes. Figure 3 shows a typical plot of the conversion as a function of time. The reaction slows down within a short period of time and does not follow straightforward kinetics. Small amounts of diacetone alcohol were detected in the reaction mixture. This compound can be formed by an aldol reaction from acetone. Diacetone alcohol may bind the metal ion in a bidentate fashion and, therefore, inhibit the catalyst. Furthermore, the aldol

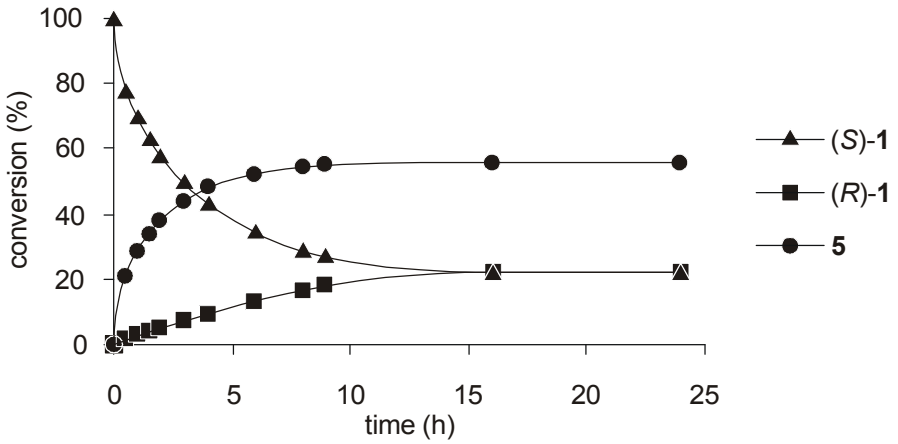


Figure 3. Conversion *versus* time in the racemisation of (*S*)-**1** into (*R*)-**1** and **5** with $Gd(OCH(CH_3)_2)_3$ under the conditions described in Table 1, entry 17.

Table 1. Racemisation of (*S*)-1-phenylethanol ((*S*)-**1**) with different MPVO catalysts[a]

entry	catalyst	additive[b]	time (h)	*ee* (*S*)-**1** (%)[c]	reaction rate (h^{-1})[d]
1	–	–	24	>99	0.0
2	–	NaA	24	>99	0.0
3	–	NdA(180)	24	>99	0.0
4	–	NdA(400)	24	>99	0.0
5	$Na(OCH(CH_3)_2)$	–	24	99	0.0
6	$Na(OCH(CH_3)_2)$	NaA	24	99	0.0
7	$Al(OCH(CH_3)_2)_3$	NaA	24	92	1.3
8	$Zr(OCH(CH_3)_2)_4$	NaA	24	92	3.5
9	$La(OCH(CH_3)_2)_3$	NaA	24	93	0.9
10	$Nd(OCH(CH_3)_2)_3$	–	6[e]	87	14.9
11	$Nd(OCH(CH_3)_2)_3$	NaA	24	0	17.1
12	$Nd(OCH(CH_3)_2)_3$	NdA(180)	24	13	17.3
13	$Nd(OCH(CH_3)_2)_3$	NdA(400)	24	13	17.4
14	$Sm(OCH(CH_3)_2)_3$	NaA	24	0	15.4
15	$Gd(OCH(CH_3)_2)_3$	–	6[e]	84	18.6
16	$Gd(OCH(CH_3)_2)_3$	NaA	24	45	20.9
17	$Gd(OCH(CH_3)_2)_3$	NaA	24	0	20.9
18	$Yb(OCH(CH_3)_2)_3$	NaA	24	50	18.5
19	$Nd(OCH(CH_3)_2)_3$	–[f]	24	>99	0.0
20	$Nd(OCH(CH_3)_2)_3$	NaA[f]	24	99	0.0

[a] Toluene (4 mL), (*S*)-1-phenylethanol (0.24 mL, 2 mmol), acetone (0.15 mL, 2 mmol, 1 equiv.), 1,3,5-triisopropylbenzene (int. std.) (0.1 mL) and the catalyst (0.04 mmol, 0.02 equiv.) were stirred at 50 °C.

[b] Zeolite NaA (30 mg, dried at 400 °C) or NdA(T) (30 mg, where T is the activation temperature in °C) were added.

[c] *ee* (starting material) >99%.

[d] Reaction rate during first 30 min in [mol substrate]/[mol catalyst]/hour.

[e] Reaction stopped due to deactivation of the catalyst.

[f] In the presence of diacetone alcohol (0.22 mL, 2 mmol).

condensation produces water, which destroys the Ln-isopropoxide catalyst. To verify this, the reactions were also performed in the presence of one equivalent of diacetone alcohol (entries 19 + 20). Indeed, the reaction was suppressed almost completely. This inhibition is prevented by the addition of zeolite NaA (4Å molecular sieves), which was activated overnight at 400 °C (compare entries 10 + 15 with 11 + 16). In its presence, the conversions were much faster. Complete racemisation was achieved with Gd-isopropoxide in the presence of zeolite NaA within 16 h (entry 17).

It is known that in aqueous suspensions, the Na^+ counterions in zeolite NaA readily exchange for lanthanide ions. Such a transmetallation reaction between Ln-isopropoxide and zeolite NaA may also occur in the present system. In order to rule out that catalysis is taking place by exchanged sodium from the zeolite, experiments were performed with zeolite NaA, neodymium exchanged zeolite A, sodium isopropoxide and combinations thereof (entries 2-6). None of these appeared to be active as a catalyst in the racemisation reaction. Furthermore, when using neodymium exchanged zeolites[19] (entries 12 + 13) instead of zeolite NaA as the additive to the reaction, only a slight increase of initial reaction rate was observed: in the absence of an isopropoxide neither NdA(180) nor NdA(400) showed any catalytic activity (entries 3 + 4, the number in brackets is the activation temperature in °C). Obviously, the role of zeolite NaA in these reactions is important. It suppresses the negative effects of diacetone alcohol, possibly by absorbing it; additionally it removes any water formed by aldol condensations of acetone. Due to the larger counterion, NdA is less efficient in absorbing water and the aldol product.

3.2.2 Solvent effects

The results of experiments with various solvents (Table 2) show a general trend towards lower reactivities upon the increase of Lewis basicity of the solvent. The higher the Lewis basicity, the better the solvent can coordinate

Table 2. Racemisation of (*S*)-1-phenylethanol ((*S*)-**1**) in different solvents[a]

entry	solvent	time (h)	*ee*[b] (%)
1	acetonitrile	>48	>99
2	dioxane	5	28
3	THF	3.5	0
4	diisopropyl ether	3.5	0
5	MTBE	3.5	0
6	toluene	3	0
7	hexane	2	0
8	heptane	2	0

[a] Solvent (12 mL), zeolite NaA (30 mg, dried at 400 °C), (*S*)-1-phenylethanol (0.24 mL, 2 mmol), acetone (0.15 mL, 2 mmol, 1 equiv.), 1,3,5-triisopropylbenzene (int. std.) (0.2 mL) and neodymium(III) isopropoxide (120 mg, 0.37 mmol, 0.185 equiv.) were stirred at 50 °C.

[b] *ee* (starting material) >99%.

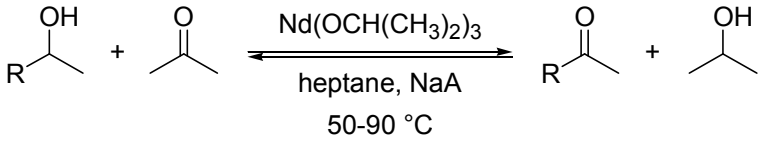
to the catalytic metal ion. This is supported by the observation that a change of colour occurs from blue (typically, the colour of a $Nd(OCH(CH_3)_2)_3$ solution) to green/yellow of an ethereal solution of the Nd-triisopropoxide catalyst upon standing. This yellow solution does not show any catalytic activity in the racemisation reaction. In view of these findings, further experiments were carried out with heptane or toluene as the solvent.

3.2.3 Oxidant-substrate ratio

The rate of racemisation and the yield of racemised alcohol depend not only on the catalyst and solvent, but also on the amount of the oxidant (acetone) used. The optimal conditions will also depend on the nature of the alcohol, since that determines the thermodynamics of the overall MPVO equilibrium (Scheme 2 and Table 3).[8]

The shortest reaction time for the racemisation of (*S*)-**1** was achieved with 1 equivalent of acetone (entry 1). However, in this case the amount of

acetophenone (**5**) formed is 50%. A good compromise was achieved with a 0.1 equivalent of acetone; although longer reaction times were required, a considerably higher yield of the racemic alcohol was obtained (entry 3). Under comparable conditions, the racemisation of **6** was much slower and produced smaller amounts of ketone **7**. The difference in behaviour of **1** and **6** in the racemisation reaction can be explained by the difference in the



1: R = phenyl
6: R = cyclohexyl

5: R = phenyl
7: R = cyclohexyl

Scheme 2. Racemisation of **1** and **6**.

Table 3. Racemisation of (*S*)-1-phenylethanol (**1**) and (*S*)-1-cyclohexylethanol (**6**) with varying amounts of acetone[a]

entry	substrate	catalyst	acetone (equiv.)[b]	time (h)[c]	ketone (**5**/**7**) formed (%)[d]
1	(*S*)-**1**	$Nd(OCH(CH_3)_2)_3$	1	1.5	50 (**5**)
2	”	”	0.2	2.5	12 (**5**)
3	”	”	0.1	3	10 (**5**)
4	”	”	0.05	>6	6 (**5**)
5	”	”	0.025	>6	3 (**5**)
6	(*S*)-**6**	”	1	2.5	25 (**7**)
7	”	”	0.5	4	10 (**7**)
8	”	”	0.1	>7	9 (**7**)

[a] Heptane (12 mL), zeolite NaA (30 mg, dried at 400 °C), (*S*)-**1** or (*S*)-**6** (0.24 mL, 2 mmol, *ee*>99%), acetone as in the table, 1,3,5-triisopropylbenzene (int. std.) (0.2 mL) and the catalyst (0.37 mmol, 0.185 equiv.) were stirred at 50 °C. After 30 min. the temperature was increased to 90 °C.

[b] Equivalents of acetone with respect to the substrate.

[c] Time needed for complete racemisation.

[d] After complete racemisation (ketone formed in brackets).

equilibrium constants for the two reactions. Since acetophenone (**5**) is stabilised by conjugation, the equilibrium between alcohol **1** and ketone **5** lies further on the ketone side than the corresponding equilibria for **6** and **7**.

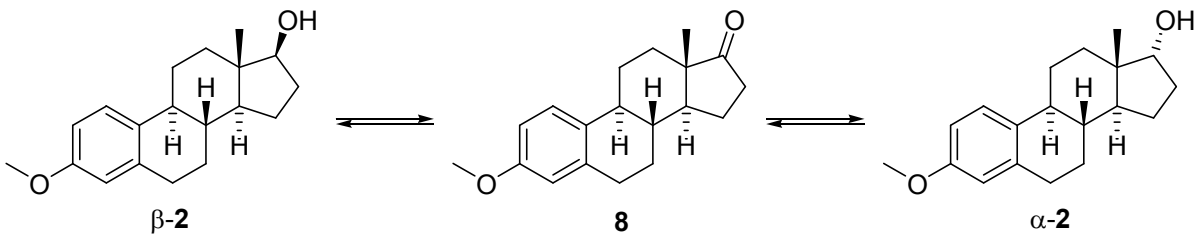
In conclusion, secondary alcohols can be racemised smoothly with Ln(III) isopropoxides (Ln = Nd → Yb) in the presence of 4Å molecular sieves (zeolite NaA) with heptane as the solvent and an appropriate amount of acetone as the oxidant.

3.2.4 Epimerisation

As mentioned in the introduction, the reduction of **8** with $NaBH_4$ or $LiAlH_4$ gives mixtures of α-**2** and β-**2** in a molar ratio of about 1:4. A similar ratio was obtained with a MPV reduction using neodymium triisopropoxide as the catalyst in isopropanol. We assume that these products are determined by kinetic control. The epimerisation of estradiol 3-methyl ether (**2**) via estrone methyl ether (**8**) is therefore an interesting test case for our racemisation/ epimerisation methodology (Scheme 3).

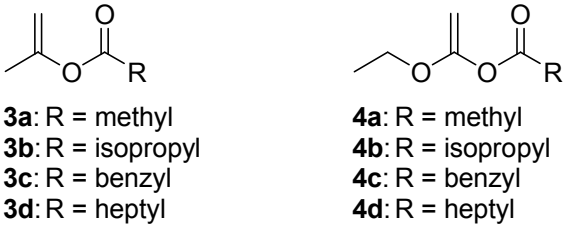
The reaction was carried out as described for the racemisation above, however, toluene was used as solvent. To improve the solubility of estradiol its methyl ether **2** was used for the epimerisation.

With 0.5 equivalents of acetone in toluene, the epimerisation successfully proceeded in 16 h, giving a 3:2 ratio of the epimerised product and the ketone. None of the other stereocentres was affected, demonstrating



β-**2** **8** α-**2**

Scheme 3. Epimerisation of β- and α-estradiol 3-methyl ether **2**.



3a: R = methyl
3b: R = isopropyl
3c: R = benzyl
3d: R = heptyl

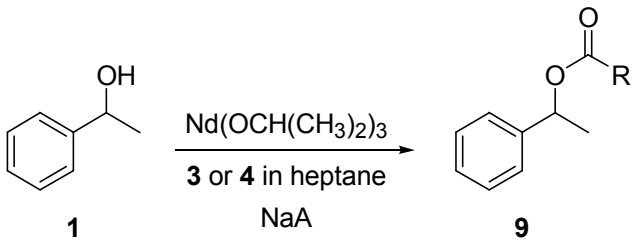
4a: R = methyl
4b: R = isopropyl
4c: R = benzyl
4d: R = heptyl

Figure 4. The synthesised acyldonors **3** and **4**.

the selectivity of the epimerisation. All products could readily be separated by column chromatography and recycled. As expected, the equilibrium shifted towards the alcohol upon use of less acetone (6:1 ratio with 0.1 equivalent instead of a 3:2 ratio with 0.5 equivalent). This occurs, however, at the expense of a longer reaction time. The α-**2**:β-**2** ratio after epimerisation was 2:3 and is independent of the amount of acetone used. This ratio is much more favourable for recycling procedures than the 1:4 α-**2**:β-**2** ratio obtained after the reduction of **8** with neodymium(III) isopropoxide in isopropanol.

3.2.5 Racemisations and acylations

Since the lanthanide isopropoxides are not only versatile redox catalysts, but also catalyse acylations,[15] their potential for a one-pot racemisation and acylation was investigated. Acylation studies were carried out with the same alcohol to catalyst ratio as in the racemisation. To the mixture of a racemic alcohol, 1.1 equivalent of an acyl donor, isopropenyl ester (**3**) or ethoxyvinyl



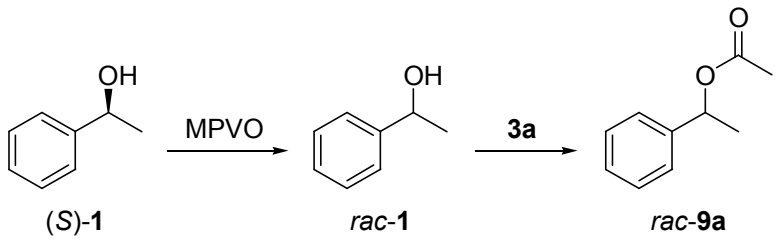
1 **9**

Scheme 4. $Nd(OCH(CH_3)_2)_3$ catalysed acylation with **3** and **4**.

ester (**4**), was added (Figure 4). These acyl donors release acetone or ethyl acetate as leaving groups. Both by-products are inactive in the acylation reaction and can readily be removed. The acyl donors used were synthesised via well-established procedures.[20-22] Typically, the acylations of **1** proceeded within 15 minutes without any trace of side-products (Scheme 4). The reaction times were independent of the type of acyl donor and the reaction is much faster than the racemisation. After purification, the racemic esters were obtained in good yields (71-88%), again the type of acyl donor showed little influence. It should be noted that in the absence of the catalyst, no reaction was observed.

With the two above-described reactions, the racemisation and the acylation, it is possible to recycle the "wrong" enantiomer that is obtained as undesired side-product after an enzymatic kinetic resolution. For this purpose, it is of particular interest to perform these reactions in a one-pot two-step sequence by adding the acyl donor once the racemisation is complete. Since the acylation (15 min for **1**) is significantly faster than the racemisation (16 h), the influence of by-products released by the acylation (acetone or ethyl acetate) is negligible. When (*S*)-**1** was racemised under standard conditions and **3a** was added, racemic **9a** was obtained in good yield (88%; Scheme 5). The ester is not susceptible to reactions catalysed by neodymium(III) isopropoxide, as was shown by an attempt to racemise (*R*)-**9a** with this catalyst.

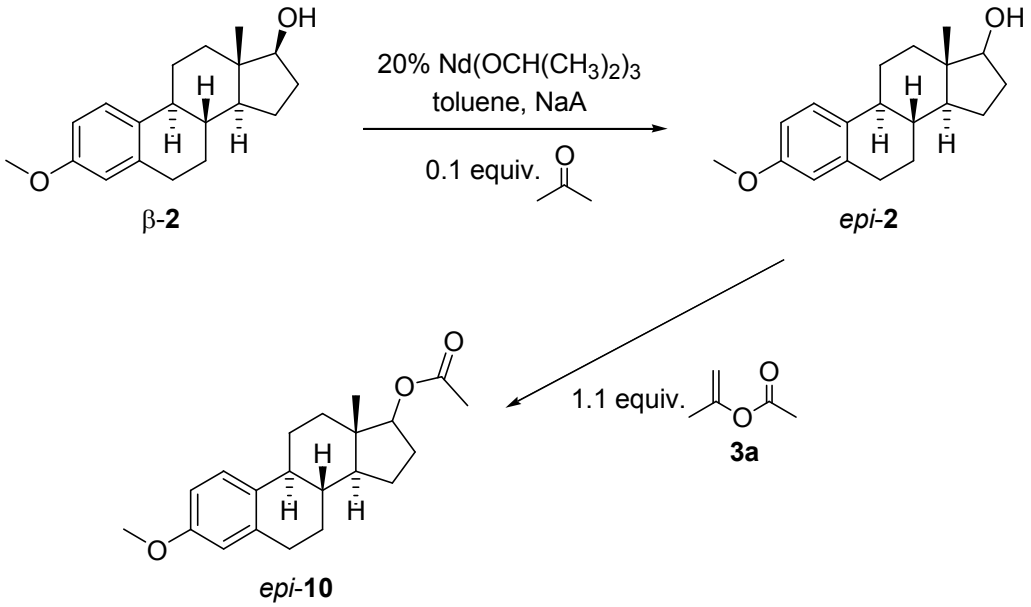
To investigate whether catalytic activity in the acylation was similar to that in the racemisation, two promising catalysts, samarium(III) isopropoxide and gadolinium(III) isopropoxide, were tested as well in this reaction.



Scheme 5. Recycling of unwanted chiral alcohol to racemic acetate.

Although the racemisation catalysed by Gd^{III} is faster than the racemisation catalysed by other catalysts (see also Table 1), no significant rate difference is observed in the acylation. The same was observed when **6** was acylated either by the Nd^{III}, Sm^{III} or Gd^{III} catalysts: the acylation is fast and proceeds within 20 minutes.

Ultimatly, this one-pot two reaction sequence was applied to β-**2**. Subsequent to the epimerisation **3a** was added. Complete acylation proceeded within 1 hour yielding epimeric **10**. No other diastereoisomers of **10** were detected in the reaction mixture, proving the high selectivity of the developed methodology (Scheme 6). After column chromatography 40% of β-**10** and 33% of α-**10** were obtained.



Scheme 6. Epimerisation and acylation of β-**2**.

3.3 Conclusions

Neodymium triisopropoxide is a powerful and selective catalyst for the racemisation of secondary alcohols. Product inhibition due to aldol reactions can be suppressed by the use of zeolite NaA. The same catalytic system is

very effective in the acylation of alcohols with the use of activated acyldonors including isopropenyl and ethoxyvinyl esters. Combination of the racemisation and acylation in a one-pot two-step sequence allows a mild and rapid recycling of undesired products from kinetic resolutions. The procedure proves to be selective for alcohol functions as was proven by the epimerisation of estradiol 3-methyl ether **2**.

3.4 Experimental

All experiments were performed in dried glassware under a nitrogen atmosphere unless stated otherwise. All chemicals were purchased from Aldrich or Acros. Anhydrous solvents and solids were used as received, liquids were dried and distilled prior to use. Enantiopure alcohols (*S*)-**1** and (*S*)-**6** were prepared as described earlier.[10] Zeolite NaA (4Å molecular sieves) was dried overnight at 400 °C unless stated otherwise. Zeolite NdA was prepared according to a literature procedure.[19] Enantiomeric excesses 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 (Beta-cyclodextrin 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) or a Shimadzu GC-17A gas chromatograph, equipped with a 25 m × 0.32 mm chiral column Chrompack™ Chirasil-Dex CB, split injector (1/97) at 220 °C, a Flame Ionisation Detector at 220 °C and He as carrier gas. Retention times (min) at 120 °C isotherm: 1,3,5-triisopropylbenzene (4.0), (*S*)-1-phenylethanol (4.3), (*R*)-1-phenylethanol (4.5). NMR spectra were recorded on a Varian VXR-400S or a Varian Unity Inova-300 spectrometer at 25 °C. Some coupling

constants were determined by spin iteration with the SpinWorks 1.2 program, using the NUMARIT[23] or NUMMRIT[24] algorithm. Mass spectra were recorded with a VG SE spectrometer at 70 eV. 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 ° (PE), diethyl ether (Et_2O) and methyl *tert*-butyl ether (MTBE).

General procedure for the racemisation of (*S*)-1 with various catalysts

The catalyst (0.04 mmol) was dissolved in toluene (4 mL). In some experiments, zeolite (30 mg) was added. Then, 1,3,5-triisopropylbenzene (0.1 mL) and acetone (0.15 mL, 2.0 mmol) were added to this solution and the temperature was raised to 50 °C. Subsequently, (*S*)-**1** (0.24 mL, 2.0 mmol) was added and samples of 20 µL, which were analysed by chiral GC, were taken at regular time intervals. When diacetone alcohol (0.22 ml, 2 mmol) was added to the reaction mixture, it was added before raising the temperature. For results, see Table 1.

General procedure for the racemisation of (*S*)-1 in various solvents

Zeolite NaA (30 mg) was suspended in a solution of neodymium(III) isopropoxide (120 mg, 0.37 mmol) in the appropriate solvent (12 mL). 1,3,5-Triisopropylbenzene (0.2 mL) and acetone (0.15 mL, 2.0 mmol) were added and the temperature was raised to 50 °C. Subsequently, (*S*)-**1** (0.24 mL, 2.0 mmol) was added and samples of 20 µL, which were analysed by chiral GC, were taken at regular time intervals. For results, see Table 2.

General procedure for the racemisation of (*S*)-1 and (*S*)-6 with varying amounts of acetone

Zeolite NaA (30 mg) was added to a solution of neodymium(III) isopropoxide (120 mg, 0.37 mmol) in heptane (12 mL). 1,3,5-Triisopropylbenzene (0.2 mL) and the appropriate amount of acetone were added and the temperature was raised to 50 °C. Subsequently, (*S*)-**1** or (*S*)-**6** (0.24 mL, 2.0 mmol) was added and after 30 minutes the temperature was increased to 90 °C.

Samples of 20 µL were taken at regular time intervals and analysed by chiral GC. For results, see Table 3.

Estrone methyl ether (8)

Method 1: An aqueous solution of sodium hydroxide (12.5 mM, 0.25 mL, 3.13 mmol) was added to a mixture of estrone (0.50 g, 1.85 mmol), phenyltrimethylammonium chloride (0.43 g, 2.52 mmol) and toluene (4.9 mL).[25-26] The mixture was refluxed for 2 h and then cooled to 50 °C. Water (4.9 mL) and acetic acid (93 µL, 1.61 mmol) were added and after 15 min the volatiles were evaporated. The solids were washed with water and diethyl ether, giving 0.45 g (1.57 mmol, 85%) of the methylated estrone **8**.[27] Method 2: To a solution of estrone (500 mg, 1.85 mmol) in a mixture of dry acetone (15 mL) and dry 1,4-dioxane (10 mL), water free potassium carbonate (256 mg, 1.85 mmol) and dimethyl sulfate (0.18 mL, 1.85 mmol) were added. After refluxing the mixture overnight the reaction was quenched with an aqueous 1 M NaOH solution (15 mL). After evaporation of the solvents and redissolving with dioxane, the product was purified by column filtration (MTBE:PE = 1:1) giving 0.42 g (1.48 mmol, 80%) of the product **8**. ^{1}H-NMR (400 MHz, dioxane-d_8) δ = 0.86 (s, 3H, C-CH_3), 1.25-1.68 (m, 7H, C(14)*H*, C(6)H_2, C(12)*H*H, C(7)*H*H, C(11)*H*H, C(15)*H*H), 1.78-1.88 (m, 1H, C(12)H*H*), 1.88-2.10 (m, 3H, C(15)H*H*, C(7)H*H*, C(16)*H*H), 2.10-2.30 (m, 1H, C(9)*H*), 2.30-2.46 (m, 2H, C(11)H*H*, C(16)H*H*), 2.85-2.90 (m, 1H, C(8) *H*), 3.70 (s, 3H, OCH_3), 6.58 (d, *J*=2.80 Hz, 1H, C(4)*H*), 6.65 (dd, *J*=8.40, 2.80 Hz, 1H, C(2)*H*), 7.17 (d, *J*=8.40, 1H, C(1)*H*); ^{13}C-NMR (100 MHz, dioxane-d_8) δ = 13.76 (C-CH$_3$), 22.00 (*C*(15)), 26.50 (*C*(11)), 27.25 (*C*(7)), 30.20 (*C*(8)), 32.35 (*C*(12)), 35.58 (*C*(16)), 39.17 (*C*(6)), 44.81 (*C*(9)), 48.18 (*C*(13)), 50.89 (*C*(14)), 55.05 (O-CH$_3$), 112.05 (*C*(2)), 114.28 (*C*(4)), 126.84 (*C*(1)), 132.75 (*C*(10)), 138.06 (*C*(5)), 158.47 (*C*(3)), 218.82 (*C*(17)).

Estradiol 3-methyl ether (2)

To a solution of estrone methyl ether (**8**) (400 mg, 1.41 mmol) in 2-propanol (20 mL), neodymium(III) isopropoxide (46 mg, 0.14 mmol) was added. The

mixture was refluxed overnight. Toluene was added (20 mL), the organic layer was washed with 1 M HCl in water (20 mL), dried over $MgSO_4$ and the solvent was evaporated under vacuum. With ^{1}H-NMR (methyl signals at 0.76 and 0.69 ppm) the ratio β-**2**: α-**2** was determined to be 78:22. The two epimers were separated by column chromatography (MTBE:PE 1:3) giving the major epimer (β-**2**) in 0.18 g (0.63 mmol, 45%), the minor epimer (α-**2**) in 0.05 g (0.17 mmol, 12%) and 0.16 g of a mixture of the epimers (0.55 mmol, 39%).[27] β-**2**: ^{1}H-NMR (400 MHz, dioxane-d_8) δ = 0.73 (s, 3H, C-CH_3), 1.10-1.50 (m, 6H, C(14)*H*, C(6)H_2, C(12)*H*H, C(7)*H*H, C(11)*H*H,), 1.58-1.70 (m, 1H, C(15)*H*H), 1.80-2.00 (m, 3H, C(12)H*H*, C(15)H*H*, O*H*), 2.10-2.18 (m, 1H, C(7)H*H*), 2.25-2.35 (m, 1H, C(16)*H*H), 2.50-2.60 (m, 2H, C(9)*H*, C(11)H*H*), 2.70-2.88 (m, 2H, C(16)H*H*, C(8)*H*), 3.24 (d, *J*=4.76 Hz 1H, C(17)*H*), 3.69 (s, 3H, OCH_3), 6.56 (d, *J*=2.80 Hz, 1H, C(4)*H*), 6.63 (dd, *J*=2.80, 8.40 Hz, 1H, C(2)*H*), 7.14 (d, *J*=8.40 Hz, 1H, C(1)*H*); ^{13}C-NMR (100 MHz, dioxane-d_8) δ = 11.36 (C(13)*C*H$_3$), 23.62 (*C*(15)), 26.98 (*C*(7)), 27.99 (*C*(11)), 30.29 (*C*(8)), 30.96 (*C*(16)), 37.60 (*C*(12)), 39.70 (*C*(6)), 43.85 (*C*(13)), 44.79 (*C*(9)), 50.78 (*C*(14)), 55.01 (O*C*H$_3$), 81.65 (*C*(17)), 111.97 (*C*(2)), 114.21 (*C*(4)), 126.71 (*C*(1)), 133.13 (*C*(10)), 138.22 (*C*(5)), 158.30 (*C*(3)); α-**2**: ^{1}H-NMR (400 MHz, dioxane-d_8) δ = 0.67 (s, 3H, C-CH_3), 1.16-1.68 (m, 7H, C(14)*H*, C(6)H_2, C(12)*H*H, C(7)*H*H, C(11)*H*H, C(15)*H*H), 1.74-2.40 (m, 7H, C(12)H*H*, C(15)H*H*, C(7)H*H*, C(16)*H*H, O*H*, C(9)*H*, C(11)H*H*), 2.72-2.85 (m, 2H, C(16)H*H*, C(8)*H*), 3.21 (dd, *J*=5.60, 11.20 Hz, 1H, C(17)*H*), 3.69 (s, 3H, OCH_3), 6.57 (d, *J*=2.80 Hz, 1H, C(4)*H*), 6.64 (dd, *J*=2.80, 8.40 Hz, 1H, C(2)*H*), 7.17 (d, *J*=8.80 Hz, 1H, C(1)*H*); ^{1}H-NMR (400 MHz, dioxane-d_8) δ = 17.36 (C(13)*C*H$_3$), 24.78 (*C*(15)), 26.93 (*C*(7)), 28.84 (*C*(11)), 30.42 (*C*(8)), 32.28 (*C*(16)), 33.00 (*C*(12)), 39.99 (*C*(6)), 44.47 (*C*(13)), 46.11 (*C*(9)), 48.23 (*C*(14)), 55.03 (O*C*H$_3$), 79.70 (*C*(17)), 111.97 (*C*(2)), 114.17 (*C*(4)), 126.77 (*C*(1)), 133.30 (*C*(10)), 138.29 (*C*(5)), 158.27 (*C*(3)).

Epimerisation of β-estradiol 3-methyl ether (β-2)

Zeolite NaA (10 mg) was added to a solution of neodymium(III) isopropoxide (8.4 mg, 0.064 mmol per 0.77) in toluene (2.2 mL). Acetone (2.6 µL, 0.04 mmol) was added and the temperature was raised to 50 °C. Subsequently, β-**2** (100

mg, 0.35 mmol) was added and after 30 min the temperature was increased to 90 °C. After 24 h, the mixture was cooled to room temperature and washed with aqueous 1 M HCl (5 mL), dried and concentrated. The product was purified by column chromatography (MTBE:PE=1:1) yielding 69.3 mg of the epimeric mixture of alcohols **2** (0.24 mmol, 69%) and 13.4 mg of ketone **8** (0.046 mmol, 13%). With ^{1}H-NMR the ratio β-**2**: α-**2** was determined to be 58:42.

General procedure for the synthesis of isopropenylesters (3)[20]

A 30 wt.% potassium hydride (KH) dispersion in mineral oil was washed with pentane. The pure KH was suspended in DME. The mixture was cooled down to 0 °C, after which acetone was added carefully. After 30 min the mixture was added to an ice cooled solution of the acid chloride in DME. The mixture was allowed to warm up to room temperature and was stirred overnight. Then, diethyl ether and water were added and the layers were separated. The organic fraction was dried over magnesium sulfate and concentrated. After distillation the desired compound was obtained.

Isopropenyl isobutyrate (3b)

Compound **3b** was synthesised according to the general procedure using KH (8.43 g, 0.21 mol) in DME (160 mL), acetone (11.6 g, 0.19 mol) and freshly distilled isobutyryl chloride (20.2 g, 0.19 mol) in DME (180 mL). After distillation (115-124 °C, 1.2 mbar) 7.4 g (55 mmol, 29%) of the product was obtained.[28] ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.21 (d, *J*=6.96 Hz, 6H, C(C*H*$_3$)$_2$), 1.92 (dd, *J*=1.19, 0.58 Hz, 3H, =CC*H*$_3$), 2.62 (sept, *J*=6.96 Hz, 1H, C*H*), 4.66 (dq, *J*=1.21, 0.58 Hz, 1H, =C(H)*H*) 4.70 (dq, *J*=1.21, 1.19 Hz, 1H, =C(*H*)H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 18.86 (2 × *C*H$_3$), 19.46 (*C*H), 34.08 (=C-*C*H$_3$), 101.76 (*C*H$_2$=), 153.13 (*C*=), 175.26 (*C*=O).

Isopropenyl phenylacetate (3c)

Compound **3c** was synthesised according to the general procedure using KH (4.82 g, 0.12 mol) in DME (145 mL), acetone (7.3 g, 0.12 mol) and freshly

distilled phenylacetyl chloride (17.0 g, 0.11 mol) in DME (165 mL). After distillation (85 °C, 1.1 mbar) 10.3 g (57 mmol, 52%) of the product was obtained as an oil that solidified upon standing at 4 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.89 (dd, *J*=1.10, 0.54 Hz, 3H, C*H*$_3$), 3.68 (s, 2H, C*H*$_2$), 4.69 (dq, *J*=1.27, 0.54 Hz, 1H, =C(H)*H*), 4.68 (dq, *J*=1.27, 1.10 Hz, 1H, =C(*H*)H), 7.20-7.33 (m, 5H, ar*H*); ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 19.41 (*C*H$_3$), 40.94 (*C*H$_2$), 102.08 (H$_2$*C*=C), 127.22 (ar*C-4*), 128.65 (ar*C-3,5*), 129.22 (ar*C-2,6*), 133.61 (ar*C-1*), 153.04 (*C*=), 176.80 (*C*=O).

Isopropenyl octanoate (3d)

Compound **3d** was synthesised according to the general procedure using KH (2.4 g, 61 mmol) in DME (52 mL), acetone (3.5 g, 61 mmol) and octanoyl chloride (9.3 g, 57 mol) in DME (55 mL). After distillation (85 °C, 1.4 mbar) 3.1 g (17 mmol, 29%) of the product was obtained as an oil.[29] ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 0.89 (t, *J*=6.82 Hz, 3H, C*H*$_3$) 1.20-1.40 (m, 8H, C*H*$_2$), 1.58-1.72 (m, 2H, C*H*$_2$), 1.92 (dd, *J*=0.60, 1.22 Hz, 3H, =C-C*H*$_3$), 2.38 (t, *J*=7.50 Hz, 2H, C*H*$_2$C=O), 4.67 (dq, *J*=1.21, 0.59 Hz, 1H, =C(H)*H*), 4.69 (dq, *J*=1.22, 1.21 Hz, 1H, =C(*H*)H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 14.06 (CH_3), 19.58 (*C*H$_2$), 22.60 (*C*H$_2$), 24.93 (*C*H$_2$), 28.91 (*C*H$_2$), 29.04 (=C-*C*H$_3$), 31.67 (*C*H$_2$), 34.39 (*C*H$_2$), 101.91 (*C*H$_2$=), 153.06 (*C*=), 171.97 (*C*=O).

Ethoxyacetylene[30]

At –70 °C $Fe(NO_3)_3 \times 9H_2O$ (0.5 g, 2.1 mmol) was dissolved in liquid ammonia (500 mL). Freshly cut sodium (38 g, 1.7 mol) was added and allowed to react completely. Within 20 min, chloroacetaldehyde diethyl acetal (76.5 g, 0.5 mol) was added to the reaction mixture. After the addition was complete, the flask was allowed to warm up to room temperature to evaporate the ammonia. The flask and its solid contents were cooled again to –70 °C and brine (325 mL) at –20 °C was added rapidly. The set-up was then equipped with a distillation bridge and the flask was carefully heated to distil of the product. The organic fraction was neutralised with a saturated aqueous solution of NaH_2PO_4. After freezing the water layer the organic fraction was

decanted, dried over $CaCl_2$ (4 g) and distilled (48-50 °C). The product was obtained as a colourless oil in a yield of 26.4 g (0.38 mol, 75%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.39 (t, *J*= 7.20 Hz, 3H, C*H*$_3$), 1.54 (s, 1H, ≡C*H*), 4.13 (q, *J*=7,20 Hz, 2H, C*H*$_2$); ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 14.22 (*C*H$_3$), 26.44 (O-*C*≡), 74.61 (*C*H$_2$), 90.85 (≡*C*H).

General procedure for the synthesis of 1-ethoxyvinylesters (4)[21-22]

Ethoxyacetylene (3.43 g, 49 mmol) and Bennet's ruthenium complex ([$RuCl_2$(*p*-cymene)]$_2$) (0.16 mmol, 100 mg) were dissolved in diisopropyl ether (200 mL). The mixture was cooled to 0 °C and a solution of freshly distilled acid in diisopropyl ether (150 mL) was added dropwise. The reaction was allowed to warm up to room temperature and was stirred overnight. After concentration the product was distilled from the residue.

1-Ethoxyvinyl acetate (4a)

Compound **4a** was synthesised following the general procedure using acetic acid (1.80 g, 30 mmol). After distillation (80 °C, 0.4 mbar) the desired product was obtained as a colourless oil in a yield of 2.67 g (20 mmol, 67%).[21] ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.33 (t, *J*=7.02 Hz, 3H, C*H*$_3$-CH_2), 2.16 (s, 3H C*H*$_3$-CO_2), 3.76 (d, *J*=3.7 Hz, 1H, HC*H*=CO_2), 3.82 (d, *J*=3.7 Hz, 1H, *H*CH=CO_2), 3.86 (q, *J*=7.02 Hz, 2H, C*H*$_2$); ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 14.12 (*C*H$_3$-CH_2), 20.64 (*C*H$_3$C=O), 64.85 (*C*H$_2$), 71.75 (*C*H$_2$=), 157.22 (*C*=), 168.13 (*C*=O).

1-Ethoxyvinyl isobutyrate (4b)

Compound **4b** was synthesised following the general procedure using isobutyric acid (2.64 g, 30 mmol). After distillation (70-72 °C, 0.4 mbar) the desired product was obtained as a colourless oil in a yield of 3.06 g (20 mmol, 67%).[31] ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.23 (d, *J*=6.90 Hz, 6H, CH_3), 1.33 (t, *J*=6.78 Hz, 3H, C*H*$_3$-CH_2), 2.65 (sept, *J*=6.90 Hz, 1H, C*H*), 3.75 (d, *J*=3.58 Hz, 1H, =C*H*H), 3.80 (d, *J*=3.58 Hz, 1H, =CH*H*), 3.87 (q, *J*=6.78 Hz, 2H, C*H*$_2$); ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 14.12 (CH_2*C*H$_3$), 18.69 (2×*C*H$_3$), 33.83

(*C*H), 64.81 (*C*H_2), 71.53 (*C*=), 157.46 (*C*H_2=), 174.34 (*C*=O).

1-Ethoxyvinyl phenylacetate (4c)

Compound **4c** was synthesised following the general procedure using phenylacetic acid (4.08 g, 30 mmol). After distillation (210 °C, 0.4 mbar) the desired product was obtained as a colourless oil in a yield of 2.67 g (15 mmol, 50%).[32] ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.25 (t, *J*=7.12 Hz, 3H, C*H*$_3$CH$_2$), 2.03 (s, 2H, C_6H_5C*H*$_2$), 3.75 (d, *J*=3.60 Hz, 1H, HC*H*=), 3.80 (d, *J*=3.60 Hz, 1H, *H*CH=), 3.84 (q, *J*=7.12 Hz, 2H, C*H*$_2$), 7.12-7.38 (m, 5H, arH); ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 14.20 (*C*H$_3$), 42.06 (Ph*C*H$_2$), 64.90 (*C*H$_2$CH$_3$), 71.86 (*C*=), 157.00 (*C*H$_2$=), 128.56 (ar*C*), 128.65 (ar*C*), 129.40 (2×ar*C*), 129.55 (2×ar*C*), 171.15 (*C*=O).

1-Ethoxyvinyl octanoate (4d)

Compound **4d** was synthesised following the general procedure using octanoic acid (4.33 g, 30 mmol). After distillation (190 °C, 0.4 mbar) the desired product was obtained as a colourless oil in a yield of 5.43 g (27 mmol, 89%).[18] ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 0.88 (t, *J*=6.78 Hz, 3H, C*H*$_3$CH$_2$), 1.20-1.40 (m, 11H, 4×CH$_2$+CH$_3$), 1.55-1.75 (m, 2H, CH$_2$), 2.41 (t, *J*=7.51 Hz, 2H, C*H*$_2$C=O), 3.75 (d, *J*=3.57 Hz, 1H, HC*H*=), 3.80 (d, *J*=3.57 Hz, 1H, *H*CH=), 3.86 (q, *J*=7.08 Hz, 2H, C*H*$_2$); ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 14.06 (*C*H$_3$), 14.12 (OCH$_2$*C*H$_3$), 22.59 (*C*H$_2$), 24.63 (*C*H$_2$), 28.88 (*C*H$_2$), 28.94 (*C*H$_2$), 31.63 (*C*H$_2$), 33.93 (*C*H$_2$), 64.79 (O*C*H$_2$), 71.65 (*C*H$_2$=), 157.28 (*C*=), 171.07 (*C*=O).

Procedure for the acylation of *rac*-1

Neodymium(III) isopropoxide (120 mg, 0.37 mmol) and zeolite NaA (30 mg, dried at 400 °C) were dissolved and suspended in heptane (12 mL). 1,3,5-Triisopropylbenzene (0.2 mL) and **1** (0.24 mL, 2.0 mmol) were added and the temperature was raised to 50 °C. Subsequently, an acyl donor (**3** or **4**) (2.2 mmol) was added. After 15 min, 1 M aqueous HCl (6 mL) was added and the two layers were separated. The aqueous layer was washed with heptane (10 mL) and the combined organic layers were dried over $MgSO_4$ and

concentrated under vacuum. After column filtration with PE:Et_2O 4:1 mixture over silica gel, the acylated product could be recovered in almost quantitative yield.

Acetic acid 1-phenyl-ethyl ester (9a)

This compound was prepared as described above with **3a** (0.24 ml, 2.2 mmol) as acyl donor yielding 317 mg (1.76 mmol, 88%) or **4a** (286 mg, 2.2 mmol) yielding 257 mg (1.42 mmol, 71%) of the product as a colourless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.53 (d, *J*=6.61 Hz, 3H, CHC*H*$_3$), 2.06 (s, 3H, C(O)C*H*$_3$), 5.88 (q, *J*=6.61 Hz, 1H, C*H*), 7.22-7.38 (m, 5H, ar*H*).

Isobutyric acid 1-phenyl-ethyl ester (9b)

This compound was prepared as described above with **3b** (282 mg, 2.2 mmol) as acyl donor yielding 363 mg (1.78 mmol, 89%) of the product as a colourless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.16 (dd, *J*=7.80, 6.90 Hz, 6H, 2×C*H*$_3$), 1.52 (d, *J*=6.60, 3H, CH_3-C*H*), 2.56 (sept, *J*=6.90 Hz, 1H, C*H*-C=O), 5.87 (q, *J*=6.60, 1H, C*H*-O,), 7.22-7.36 (m, 5H, Ar*H*).

Octanoic acid 1-phenyl-ethyl ester (9c)

This compound was prepared as described above with **3c** (405 mg, 2.2 mmol) as acyl donor yielding 398 mg (1.50 mmol, 75%) or **4c** (471 mg, 2.2 mmol) yielding 439 mg (1.66 mmol, 83%) of the product as a colourless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 0.88 (t, *J*=3.60 Hz, 3H, C*H*$_3$), 1.20-1.40 (m, 8H, 4×C*H*$_2$), 1.53 (d, *J*=6.45, 3H, C*H*$_3$-CH), 2.32 (dt, *J*=7.50, 0.90 Hz, 2H, C(O)C*H*$_2$), 5.89 (q, *J*=6.45, 1H, C*H*-O), 7.23-7.38 (m, 5H, Ar*H*).

Phenyl-acetic acid 1-phenyl-ethyl ester (9d)

This compound was prepared as described above with **3d** (388 mg, 2.2 mmol) as acyl donor yielding 489 mg (1.60 mmol, 80%) of the product as a colourless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.50 (d, *J*=6.61, 3H, C*H*$_3$-CH), 3.62 (s, 2H, C*H*$_2$), 5.89 (q, *J*=6.61, 1H, C*H*), 7.19-7.35 (m, 10H, Ar*H*).

Procedure for the one-pot racemisation and acylation of (*S*)-1 or (*S*)-6

Neodymium(III), samarium(III) or gadolinium(III) isopropoxide (0.37 mmol) and zeolite NaA (30 mg, dried at 400 °C) were dissolved and suspended in heptane (12 mL). 1,3,5-Triisopropylbenzene (0.2 mL) and acetone (15 µL, 0.20 mmol) were added and the temperature was raised to 50 °C. (*S*)-**1** or (*S*)-**6** (0.24 mL, 2.0 mmol) was added. The reaction was followed by GC. After complete racemisation (less than 18 h) isopropenyl acetate (**3a**) (0.24 mL, 2.2 mmol) was added. Alcohol **1** was converted into the racemic acetate *rac*-**9a** in 15 minutes. Alcohol **6** was converted into its racemic acetate in 20 minutes. The reaction mixture was concentrated in vacuo and the product was purified by column chromatography (PE:Et_2O 4:1).

Nd^{III} + (*S*)-**1** yielded 288 mg (1.76 mmol, 88%) of the racemic acetate, Sm^{III} + (*S*)-**1** yielded 284 mg (1.74 mmol, 87%), Gd^{III} + (*S*)-**1** yielded 295 mg (1.80 mmol, 90%), Nd^{III} + (*S*)-**6** yielded 296 mg (1.74 mmol, 87%), Sm^{III} + (*S*)-**6** yielded 289 mg (1.70 mmol, 85%), Gd^{III} + (*S*)-**6** yielded 306 mg (1.80 mmol, 90%).

Procedure for the one-pot epimerisation and acylation of β-2

Neodymium(III) isopropoxide (8.4 mg, 0.064 mmol) and zeolite NaA (10 mg, dried at 400 °C) were added to toluene (2.2 mL). Acetone (2.6 µL, 0.04 mmol) was added and the temperature was raised to 50 °C. β-**2** (90 mg, 0.32 mmol) was dissolved in the reaction mixture. After 1 h the temperature was raised to 90 °C and after 24 h isopropenyl acetate (**3a**) (38 µL, 0.35 mmol) was added. The reaction was monitored by TLC. Complete acylation was achieved after 1 h. The mixture was cooled, washed with an aqueous 1 M HCl solution (5 mL), dried over $MgSO_4$ and concentrated. Column chromatography (PE:MTBE 3:1) yielded 41 mg of β-**10** (0.12 mmol, 40%) and 34 mg of α-**10** (0.10, 33%), both as white solids.[33] β-**10**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 0.81 (s, 3H, C-C*H*$_3$), 1.10-1.60 (m, 7H, C(14)*H*, C(6)*H*$_2$, C(12)*H*H, C(7)*H*H, C(11)*H*H, C(15)*H*H), 1.60-1.80 (m, 1H, C(12)H*H*), 1.80-2.00 (m, 2H, C(15)H*H*, C(7)H*H*), 1.93 (s, 3H, C*H*$_3$-CO), 2.05-2.22 (m, 2H, C(16)*H*H, C(9)*H*), 2.22-2.40 (m, 1H, C(11)H*H*), 2.70-2.90 (m, 2H, C(16)H*H*, C(8)*H*), 3.68 (s, 3H, O-

C*H*$_3$), 4.66 (dd, *J*=7.61, 8.91 Hz, 1H, C(17)*H*), 6.56 (d, *J*=2.70 Hz, 1H, C(4)*H*), 6.64 (dd, 1H, *J*=2.70, 8.40 Hz C(2)*H*), 7.14 (d, *J*=8.40 Hz, 1H, C(1)*H*); ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 12.36 (C(13)*C*H$_3$), 20.65 (*C*H$_3$-CO), 23.61 (*C*(15)), 26.96 (*C*(7)), 27.97 (*C*(11)), 30.27 (*C*(8)), 30.93 (*C*(16)), 37.57 (*C*(12)), 39.68 (*C*(6)), 43.83 (*C*(13)), 44.76 (*C*(9)), 50.23 (*C*(14)), 55.01 (O*C*H$_3$), 81.64 (*C*(17)), 111.96 (*C*(2)), 114.20 (*C*(4)), 126.69 (*C*(1)), 133.12 (*C*(10)), 138.20 (*C*(5)), 158.27 (*C*(3)), 170.76 (*C*=O); α-**10**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 0.67 (s, 3H, C-C*H*$_3$), 1.10-1.70 (m, 7H, C(14)*H*, C(6)*H*$_2$, C(12)*H*H, C(7)*H*H, C(11)*H*H, C(15)*H*H), 1.70-1.95 (m, 3H, C(12)H*H*, C(15)H*H*, C(7)H*H*), 1.99 (s, 3H, C*H*$_3$-CO), 2.00-2.40 (m, 3H, C(16)*H*H, C(9)*H*, C(11)H*H*), 2.75-2.85 (m, 2H, C(16)H*H*, C(8)*H*), 4.10-4.20 (m, 1H, C(17)*H*), 6.56 (d, *J*=2.75 Hz, 1H, C(4)*H*), 6.63 (dd, *J*=2.75, 8.42 Hz, 1H, C(2)*H*), 7.16 (d, *J*=8.42 Hz, 1H, C(1)*H*); ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 17.38 (C(13)*C*H$_3$), 20.44 (*C*H$_3$-CO), 24.80 (*C*(15)), 26.95 (*C*(7)), 28.86 (*C*(11)), 30.45 (*C*(8)), 32.31 (*C*(16)), 33.08 (*C*(12)), 40.01 (*C*(6)), 44.49 (*C*(13)), 46.13 (*C*(9)), 48.24 (*C*(14)), 55.02 (O*C*H$_3$), 79.67 (*C*(17)), 111.98 (*C*(2)), 114.18 (*C*(4)), 126.77 (*C*(1)), 133.31(*C*(10)), 138.29 (*C*(5)), 158.30 (*C*(3)), 170.79 (*C*=O).

3.5 Acknowledgments

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4 Zr-TUD-1: a novel heterogeneous catalyst for the Meerwein-Ponndorf-Verley reaction

This chapter was submitted for publication.

4.1 Introduction

The Meerwein-Ponndorf-Verley reduction and its counterpart, the Oppenauer oxidation are well-established, mild redox reactions.[1,2] Its high selectivity has made it particularly popular in steroid chemistry, allowing efficient reductions even on an industrial scale. They are commonly catalysed by equimolar amounts of aluminium(III) isopropoxide, however more recently the catalytic application of bis (dialkoxyaluminium) complexes[3,4] or aluminium(III) isopropoxide,[5] zirconium(IV) isopropoxide[6,7] and lanthanide isopropoxides[8-10] have been described. A significant step forward was the introduction of the heterogeneous zeolite H-Beta as a catalyst for this reaction,[11,12] recently followed by the very active Al-free Sn-Beta[13] and Al-free Zr-Beta.[14,15] The mechanisms of the homogeneous and heterogeneous reaction have been elucidated. The reactions were proven to proceed via a carbon to carbon hydride transfer reaction, while the Lewis acid catalyses and coordinates this process.[16,17]

Drawbacks of the Al-free Sn and Zr substituted Beta zeolites are their limited pore size and their complex synthesis. Similarly, the grafting of zirconium(IV) propoxide onto MCM-41, MCM-48 and SBA-15 is labour intensive.[18] In contrast, it was recently demonstrated that the three-dimensional, mesoporous silicate TUD-1[19] can readily be prepared with framework incorporated, isolated metals such as Al, Co, Cu, Fe and Ti.[20-25] Utilising zirconium(IV) propoxide as metal source with triethanolamine as template in a one-pot surfactant free procedure based on the sol-gel technique, Zr-TUD-1 with a Si/Zr ratio of 25 was readily prepared. Zirconium was the metal of choice, since it is tetrahedrally coordinated and was shown to be particularly active in the Meerwein-Ponndorf-Verley reaction when incorporated into Al-free zeolite Beta.[13-15] In addition the pores of TUD-1 are large enough to accommodate steroids such as cholesterol, that cannot enter the pores of zeolite H-Beta. (According to a HyperChem calculation the smallest cubic box into which cholesterol fits is:

7.5 × 3.9 × 15.6 Å. The pore diameter of zeolite Beta is <7.5 Å.)

In this chapter, the direct hydrothermal, cost-effective synthesis of zirconium containing 3D-mesoporous silica Zr-TUD-1 with a Si/Zr ratio of 25 and its application as catalyst in the Meerwein-Ponndorf-Verley reaction is reported.

4.2 Results and discussion

Zr-TUD-1 with a Si/Zr ratio of 25 was prepared from tetraethyl orthosilicate and zirconium(IV) propoxide using triethanolamine as template. After aging at room temperature for 24 h and drying at 98 °C for another 24 h, the gel was hydrothermally treated for an additional 24 h in an autoclave at 180 °C. To finally yield the desired, active Zr-TUD-1, it was carefully calcined at temperatures of up to 600 °C. The material was analysed with various methods and tested as catalyst.

4.2.1 Analysis of Zr-TUD-1

A broad peak at the low angle was observed in the X-ray powder diffraction pattern for calcined Zr-TUD-1 (Figure 1), indicating a mesoporous character of the material. No evidence of crystalline ZrO_2 was observed in the X-ray diffractograms, indicating that Zr is incorporated into the framework of TUD-1. The mesoporosity was also confirmed by transmission electron micrographs (Figure 2). As expected no crystalline zirconia particles were observed. Zr-TUD-1 showed a type IV isotherm, pointed out by the large uptake of nitrogen at relative pressures between 0.5 and 0.9 p/p_0, due to capillary condensation in the mesopores (Figure 3). It appears from the desorption data of Zr-TUD-1, as if the distribution is narrow but the adsorption data show a much broader distribution. This

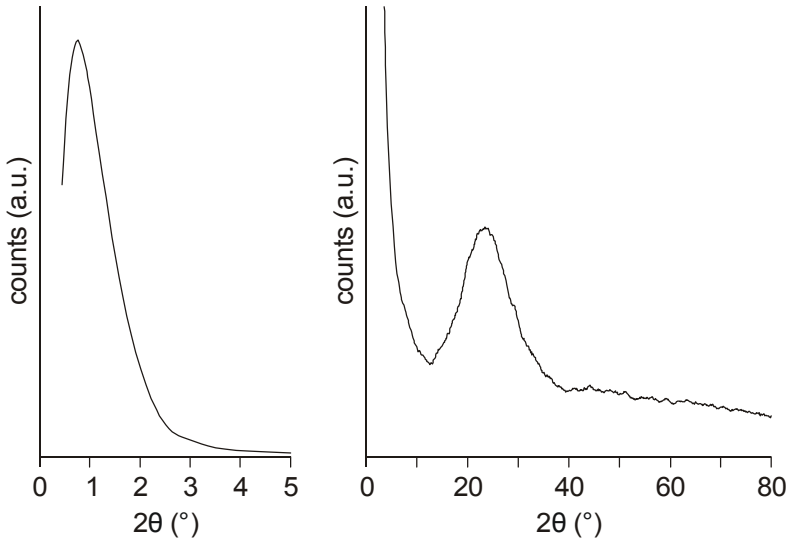


Figure 1. XRD powder pattern of calcined Zr-TUD-1.

discrepancy is caused by networking effects, from which it can be concluded that the outside of the material is homogeneous, while larger pores or cavities exist inside the material. Physico-chemical properties of Zr-TUD-1 are listed in Table 1. The excellent correlation of the Si/Zr ratio in the synthesis gel with that in the product demonstrates the high predictability of the synthesis, as was also observed with other M-TUD-1 materials.[22-24]

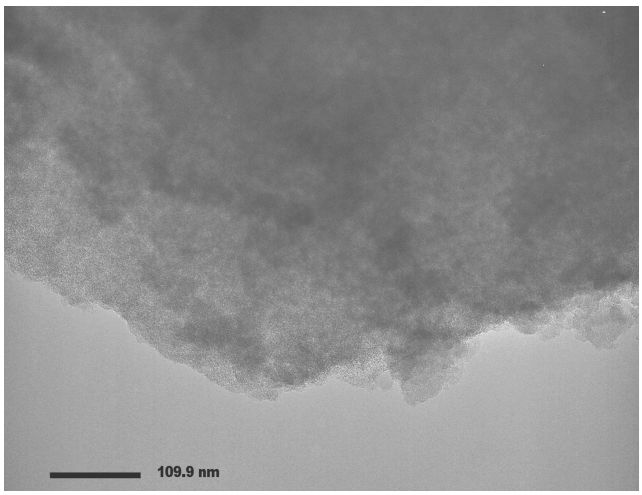


Figure 2. Transmission electron micrograph of calcined Zr-TUD-1.

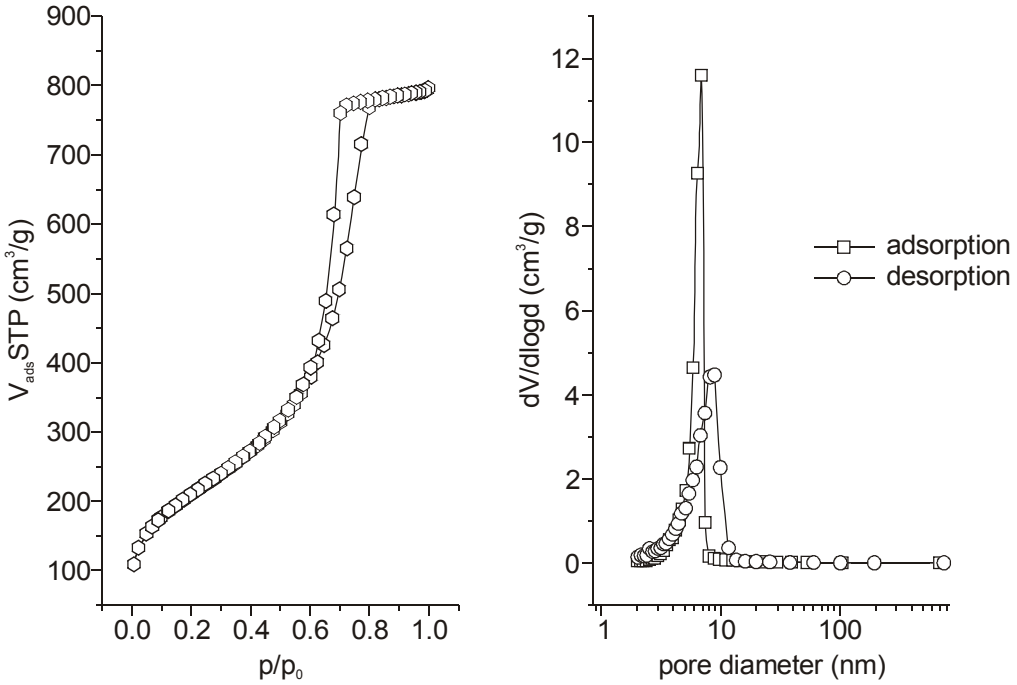


Figure 3. N_2 adsorption and desorption isotherms at 77 K and the corresponding pore size distribution of Zr-TUD-1.

The observed binding energy of Zr $3d_{5/2}$ (183.2 eV), as determined by XPS measurements, is significantly higher than that of ZrO_2 (182.2 eV) and close to that of Zr in $ZrSiO_4$ (183.3 eV).[26] Also the binding energies of O 1s were observed at 532.4 eV and they are significantly higher than that of ZrO_2 (530.2 eV).[26] The binding energy values for Zr $3d_{5/2}$ and O 1s are similar to those observed for Zr in the MFI structure,[27] zeolite Beta[14,15] and mesoporous silicas.[28] These two observations are strong evidence for the

Table 1. Physico-chemical characteristics of Zr-TUD-1.

sample	Zr-TUD-1
Si/Zr ratio in synthesis gel	25
Si/Zr ratio in the product[a]	25
BET surface area (m^2/g)	764
pore volume (cm^3/g)	1.23
pore diameter (nm)	6.9

[a] determined by ICP.

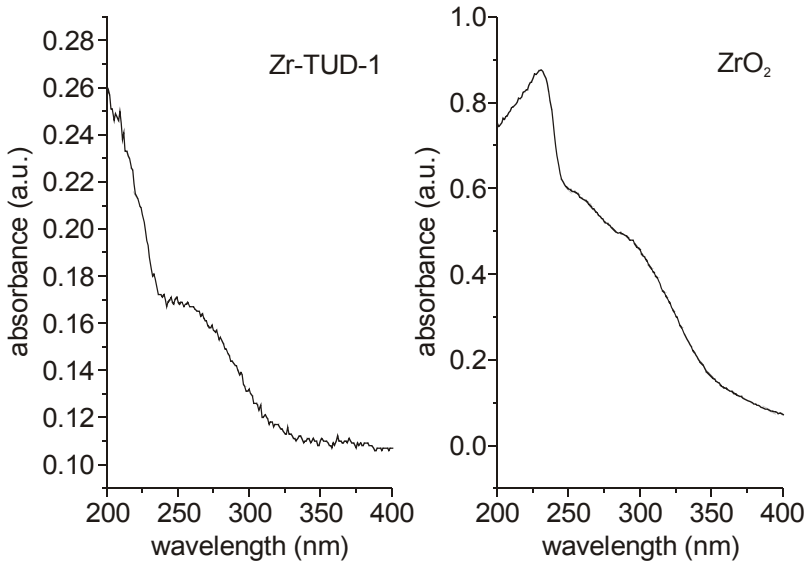


Figure 4. Diffuse reflectance UV-VIS spectra of Zr-TUD-1 compared with commercial ZrO_2.

presence of zirconium in the framework of TUD-1 matrix.

Diffuse reflectance UV-VIS spectra of Zr-TUD-1 (Figure 4) showed a weak and broad peak between 240 and 280 nm which are assigned to $O^{2-} \rightarrow Zr^{4+}$ charge transfer interactions with Zr in low coordination states either isolated or present in small Zr_xO_y clusters in the silica network of TUD-1.[28] This is further supported by the fact that this spectrum is entirely different from the spectrum of commercial ZrO_2.

In the skeletal region of the IR spectra of a KBr-pressed disc of Si-TUD-1 and of Zr-TUD-1 (Figure 5) typical bands at 1093 cm^{-1} and a shoulder at 1220 cm^{-1} due to asymmetric stretching vibrations of Si-O-Si bridges and at 798 cm^{-1} due to symmetric stretching vibration of Si-O-Si are visible. The peak at 972 cm^{-1} (Si-TUD-1) is assigned to stretching vibrations of terminal silanol groups (Si-OH) present at defect sites.[29] Additionally this peak is also assigned to Si-O-M stretching vibrations.[30] The presence of both of these vibrations leads to a less resolved peak at 975 cm^{-1} in the case of Zr-TUD-1.

FTIR spectra of both Si-TUD-1 and Zr-TUD-1 in the hydroxyl region (Figure 6a) showed a band centered at 3745 cm^{-1} that is attributed to free

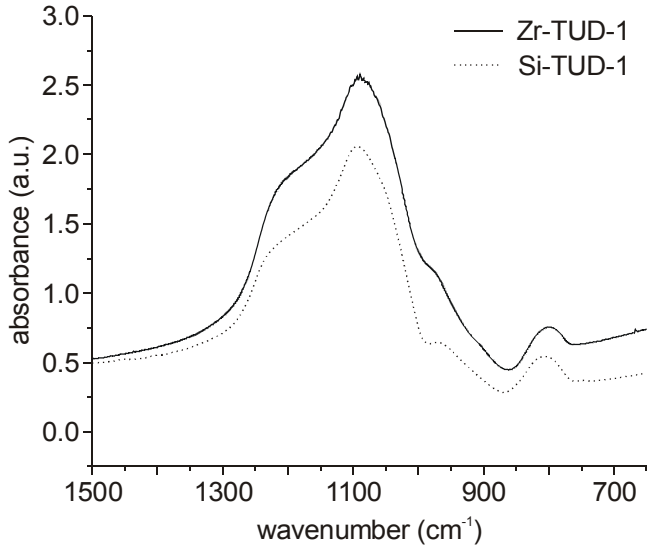


Figure 5. FTIR skeletal spectra of Zr-TUD-1 in comparison with all silica TUD-1 in KBr.

silanol groups. However, no band corresponding to terminal Zr-OH groups, as described by Jiménez-López et al. was detected,[26] which is additional evidence that the zirconium is framework incorporated.

FTIR spectra of adsorbed pyridine (Figure 6b) indicate the presence of Brønsted and Lewis acid sites. However, the Lewis acid sites necessary for the Meerwein-Ponndorf-Verley reaction are the dominant species. Thus Zr-TUD-1 combines all the characteristics for an ideal Meerwein-Ponndorf-Verley catalyst: high Lewis acidity, isolated Zr atoms, large surface area and a predictable and straightforward preparation.

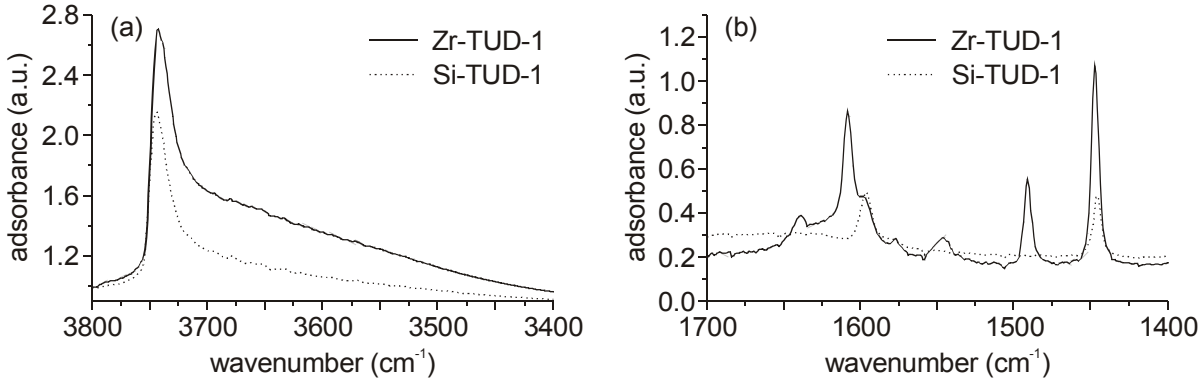


Figure 6. FTIR spectra of self supported wafer disc samples of Zr-TUD-1 (solid line) and Si-TUD-1 (dotted line) in (a) hydroxyl region (b) adsorbed pyridine at 200 °C.

4.2.2 Zr-TUD-1 as promising Meerwein-Ponndorf-Verley catalyst

The catalytic activity of Zr-TUD-1 was compared with Al-TUD-1 and zeolite H-Beta, all with a Si/M ratio of 25 (Table 2). As expected Zr-TUD-1 shows higher activity than Al-TUD-1 in the reduction of 4-*tert*-butyl cyclohexanone (**1**), while zeolite H-Beta showed the highest *cis*:*trans* selectivity for this substrate (entries 1, 12 and 14). This is due to the narrow pore size of the zeolite in comparison to M-TUD-1. Surprisingly it is also more active than Zr-TUD-1 or Al-TUD-1. This is unexpected since both Al-free Zr-Beta[14,15] and Zr-SBA-15[18] perform better in this reaction than H-Beta. Figure 7 shows a plot of the conversion of **1** as a function of time. The reaction proceeds slowly according to a first order reaction rate of the substrate.

Zr-TUD-1 catalyses the reduction of acetophenone (**4**) while both Al-TUD-1 and H-Beta are inactive (entries 2, 13 and 15). This is good evidence for the influence of the metal on the activity of the catalytic material. The importance of the appropriate choice of metal is also supported by the fact that Al-free Sn- and Zr-Beta catalyse this reaction, too.[13-15] Similar to these catalysts Zr-TUD-1 also catalyses the reduction of

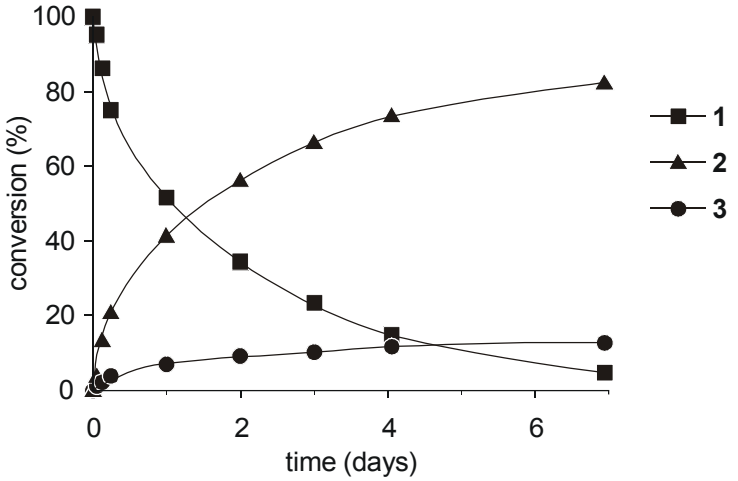
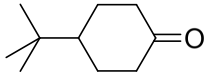
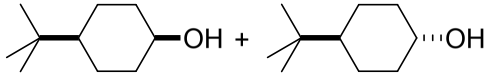
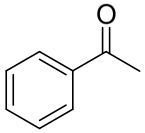
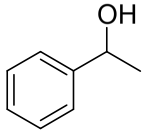
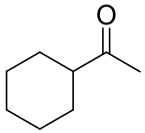
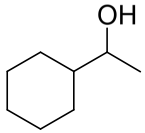
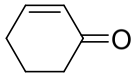
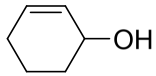
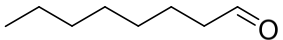
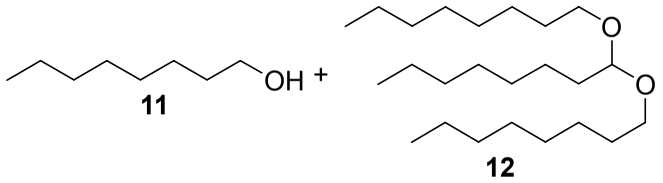
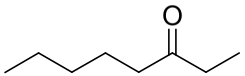
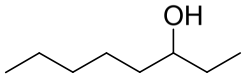
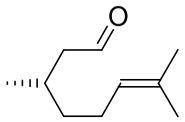
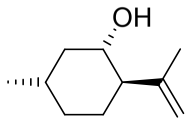
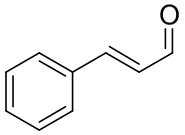
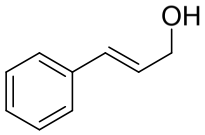
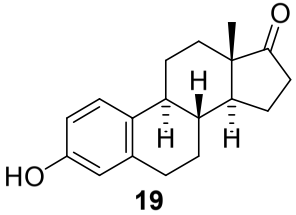
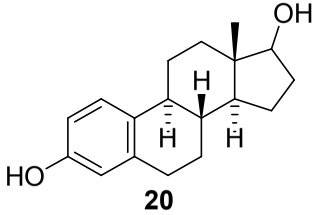
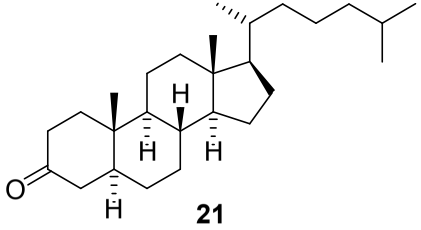
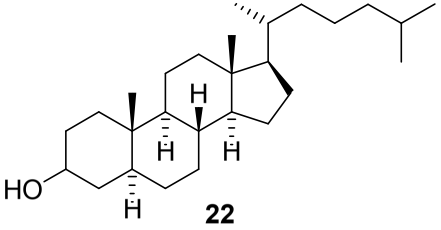


Figure 7. Conversion *versus* time in the reduction of 4-*tert*-butylcyclohexanone (**1**) into the alcohols **2** and **3** with Zr-TUD-1.

Table 2. Meerwein-Ponndorf-Verley-reductions catalysed by Zr-TUD-1, Al-TUD-1 and zeolite H-Beta.[a]

entry	catalyst	substrate	products	conversion[b]	reaction time
1	Zr-TUD-1	 **1**	 **2** + **3**	95 (**2**:**3** = 13:2)	7 d
2	Zr-TUD-1	 **4**	 **5**	20	7 d
3	Zr-TUD-1	 **6**	 **7**	22	7 d
4	Zr-TUD-1	 **8**	 **9**	8	7 d
5	Zr-TUD-1	 **10**	 **11** + **12**	60 (**11**:**12** = 8:1)	4 h
6	Zr-TUD-1	**10**	**11** + **12**	85 (**11**:**12** = 1:4)	7 d
7	Zr-TUD-1	 **13**	 **14**	6	7 d

8	Zr-TUD-1	 **15**	 (+)-**16**	95 ((+)-**16**:isomers = 3:1)	5 d
9	Zr-TUD-1	 **17**	 **18**	80	5 d
10	Zr-TUD-1	 **19**	 **20**	0	7 d
11	Zr-TUD-1	 **21**	 **22**	>95 (α-**22**:β-**22** = 1:6)	7 d
12	Al-TUD-1	**1**	**2** + **3**	10 (**2**:**3** = 15:2)	7 d
13	Al-TUD-1	**4**	**5**	0	7 d
14	H-Beta	**1**	**2** + **3**	99 (**2**:**3** = 19:1)	18 h
15	H-Beta	**4**	**5**	0	7 d

[a] Reactions performed with Zr-TUD-1, Al-TUD-1 or H-Beta (all with Si/M=25) (50 mg) and substrate (2 mmol) in 2-propanol (4 mL) at 80 °C.

[b] Ratio of products in brackets.

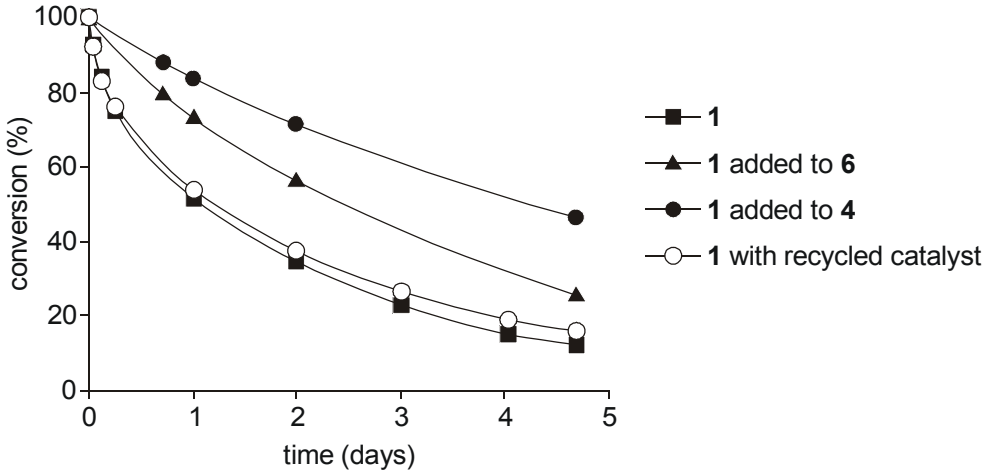


Figure 8. Zr-TUD-1 catalysed reduction of 4-*tert*-butylcyclohexanone (**1**).

8 (entry 4) and the reduction of cinnamaldehyde (**17**). However, for the aldehydes **10** and **15** (entries 5, 6 and 8) other reactions are observed. Octanal (**10**) is not only reduced but the resulting alcohol **11** subsequently reacts with the starting material with a lower reaction rate to the symmetric acetal (**12**). When (*S*)-citronellal (**15**) was treated with Zr-TUD-1 no reduction occurred but a Prins reaction yielded (+)-isopulegol ((+)-**16**) with good selectivity. It is well known that Lewis acids catalyse this reaction, indeed it is part of the Takasago process leading to (–)-menthol.[31] Only recently it was demonstrated that other Meerwein-Ponndorf-Verley catalysts such as H-Beta, Al-free Sn-Beta and in particular Al-free Zr-Beta catalyse this reaction, too.[32]

A remarkable selectivity towards the steroids estrone (**19**) and 5α-cholestan-3-one (**21**, entries 10 and 11) was observed. The keto group on ring A of **21** was reduced almost quantitatively to yield 5α-cholestan-3-ol (**22**) with an α:β ratio of 1:6. Unlike the reduction of **1** a clear preference for the *trans*-product is observed. This is most likely due to the steric hindrance induced by the C-19 methyl group on C-10. The keto group on ring D of estrone (**19**), however, was no substrate for Zr-TUD-1, most likely due to steric hindrance induced by the substituents in the α-position.

To gain further insight into the different reactivities of Zr-TUD-1

towards the sterically not so demanding ketones **1**, **4** and **6** (entries 1, 2 and 3), the reduction of **1** was performed in the presence of equimolar amounts of **4** or **6**. Both slowed down the reduction of **1** significantly (Figure 8), indicating that they, too, are attached to the catalyst, making it less accessible for **1**. The lower reactivity of **4** is due to conjugation, that of **6** to the sterically demanding substituent in the α-position. This is reflected by the fact that **6** has less influence on the reduction of **1** than **4**.

The addition of **4** and **6** did however, not influence the *cis*:*trans* ratio of the reduction of **1**. The Zr-TUD-1 was reactivated and recycled after the competition experiment with **1** and **4**. It regained virtually all of its activity upon calcination (Figure 8).

4.3 Conclusions

The synthesis of zirconium incorporated into the three-dimensional mesoporous silicate TUD-1, was achieved by a direct hydrothermal method using triethanolamine as template. This Zr-TUD-1 material was shown to possess a high surface area and acidity arising mainly from Lewis acid sites. No detectable zirconia phases were observed both in XRD and TEM. This is further supported by UV-VIS and XPS studies. Zr-TUD-1 is an active, mild and recyclable catalyst in the Meerwein-Ponndorf-Verley reduction, displaying high selectivity, in particular towards the bulky and sterically demanding steroids. Thus it widens the range of substrates that can be reduced with heterogeneous Meerwein-Ponndorf-Verley catalysts significantly.

4.4 Experimental section

All chemicals were purchased from Acros, Aldrich or Janssen. In the synthesis of Zr-TUD-1 the chemicals were used as received. For the

catalysis experiments, the anhydrous solvents and solids were used as received, liquids were dried and distilled prior to use and Zr-TUD-1 was activated according to the calcination procedure described in the synthesis of Zr-TUD-1. These experiments were performed in dried glassware under a nitrogen atmosphere.

For the elemental analysis of Si and Zr, the samples were dissolved in an aqueous solution of 1% HF and 1.3% H_2SO_4. The resulting solution was measured with Inductively Coupled Plasma - Optical Emission Spectroscopy (ICP-OES) on a Perkin Elmer Optima 3000DV instrument. Powder XRD patterns were obtained on a Philips PW 1840 diffractometer equipped with a graphite monochromator using CuKα radiation. The textural parameters were evaluated from volumetric nitrogen physisorption at 77 K on a Quantachrome Autosorb-6B instrument. Transmission electron microscopy (TEM) was performed using a Philips CM30T electron microscope with a LaB6 filament as the source of electrons operated at 300 kV. UV-VIS spectra were collected at room temperature on a Shimadzu UV-2450 spectrophotometer using $BaSO_4$ as reference. FTIR spectra of self-supported wafers and KBr diluted wafers of Zr-TUD-1 samples were recorded using a Nicolet AVATAR 360 FT-IR instrument. The acid strength distribution was evaluated by contacting pyridine vapour (20 Torr) for 30 min at 100 °C on self-supported wafers of Zr-TUD-1 (15-25 mg/cm^2) after evacuation (500 °C, 2 h, 10 Pa) in a custom made vacuum cell with CaF_2 windows. The physisorbed pyridine was subsequently removed by evacuation at 150 °C for 30 min. The spectra were recorded at room temperature with a resolution of 2 cm^{-1} averaging over 500 scans after desorbing pyridine at 200 °C. The XPS measurements were performed with a PHI 5400 ESCA provided with a dual Mg/Al anode X-ray source, a hemispherical capacitor analyser and a 5 keV ion-gun. All spectra were recorded with unmonochromated magnesium radiation. The X-ray source was operated at an acceleration voltage of 15 kV and power of 400 W. The spectra of the separate photoelectron and Si-Auger electron lines were recorded with a pass energy of 35.75 eV and a step size of 0.2

eV. The Zr-Auger electron line was recorded with a pass energy of 89.45 eV and a step size of 0.5 eV. The spectra were evaluated with Multipak 6.1A software (Physical Electronics).

NMR spectra were recorded on a Varian Unity Inova-300 spectrometer at 25 °C. Mass spectra were recorded with a VG SE spectrometer at 70 eV. Reactions were followed by gas chromatography by using a Shimadzu GC-17A gas chromatograph, equipped with a 25 m × 0.32 mm chiral column Chrompack™ Chirasil-Dex CB, split injector (1/97) at 220 °C, a Flame Ionisation Detector at 220 °C and He as carrier gas. Retention times (min) at 120 °C isotherm: 1,3,5-triisopropylbenzene (internal standard) (4.0), 4-*tert*-butylcyclohexanone (**1**) (4.7), *trans*-4-*tert*-butylcyclohexanol (**3**) (5.6), *cis*-4-*tert*-butylcyclohexanol (**2**) (5.9), acetophenone (**4**) (1.7), (*S*)-1-phenylethanol ((*S*)-**5**) (3.4), (*R*)-1-phenylethanol ((*R*)-**5**) (3.7), cyclohexyl methyl ketone (**6**) (1.6), (*S*)-1-cyclohexylethanol ((*S*)-**7**) (2.70), (*R*)-1-cyclohexylethanol ((*R*)-**7**) (2.75), cyclohex-2-enone (**8**) (1.2), (*S*)-cyclohex-2-enol ((*S*)-**9**) (1.52), (*R*)-cyclohex-2-enol ((*R*)-**9**) (1.56), octanal (**10**) (0.9), 1-octanol (**11**) (1.0), 1,1-bis (octyloxy)octane (**12**) (1.4), 3-octanone (**13**) (0.8), 3-octanol (**14**) (1.1), (*S*)-citronellal (**15**) (2.0), (*S*)-citronellol (4.1), (+)-isopulegol ((+)-**16**) (2.9), isomer(s) of (**16**) (3.6), cinnamaldehyde (**17**) (5.3), cinnamyl alcohol (**18**) (10.3). The structure of (+)-isopulegol ((+)-**16**) was confirmed by NMR spectroscopy. Direct comparison with a commercial sample of (–)-**16** by ^{1}H and ^{13}C NMR spectroscopy with a Varian Unity Inova-300 spectrometer at 25 °C revealed identical spectra. Conversions of the steroids estrone (**19**) and 5α-cholestan-3-one (**21**) and α:β ratios of **20** and **22** were determined by integration after quantitative ^{13}C NMR spectroscopy with a Varian Unity Inova-300 spectrometer at 25 °C. In the case of **19** the signal for the carbonyl group (C-17 = 219.4 ppm) remained unchanged while no signals for the α- or β-alcohol **20** (α-C-17 = 77.91 ppm; β-C-17 = 79.96 ppm) were detected. The ^{13}C NMR spectrum of the reaction product **22** (reduction of **21**) showed no carbonyl resonance (C-3 of **21** = 212.1 ppm). Two sets of signals were observed, which could be assigned to α- and β-**22**. The molar

ratio of these isomers was determined by integration of the resonances at 71.0 ppm (β-C-3 of **22**) and 66.2 ppm (α-C-3 of **22**) in a quantitative ^{13}C NMR spectrum.[33]

Synthesis of Zr-TUD-1 (Si/Zr=25)

Tetraethyl orthosilicate (98%, 33.8 g) was added to a mixture of zirconium (IV) propoxide (70 wt.% in 1-propanol, 2.98 g) and 2-propanol (25 mL). After stirring for a few minutes, a mixture of triethanolamine (97%, 24.5 g) and water (18.5 mL) was added followed by addition of a tetraethylammonium hydroxide solution (35 wt%, 20.1 g) under vigorous stirring. The clear gel obtained after these steps was then aged at room temperature for 12-24 h, dried at 98 °C for 12-24 h, followed by hydrothermal treatment in a Teflon lined autoclave at 180 °C for 4-24 h and finally calcined in the presence of air at up to 600 °C at a temperature ramp of 1 °C/min and subsequent heating at 600 °C for 10 h. The Zr-TUD-1 was obtained in almost quantitative yield and could be used for catalysis immediately or was, upon standing for a prolonged period of time, reactivated by repeating the calcination procedure.

General procedure for the Meerwein-Ponndorf-Verley reductions

All catalysis experiments were performed in dried glassware under a nitrogen atmosphere. Zr-TUD-1 (50 mg) was introduced into a Schlenk flask. Isopropanol (4 mL) was added followed by 1,3,5-triisopropylbenzene (0.1 mL) and the ketone or aldehyde (2 mmol). The mixture was heated to 80 °C and during the reaction small samples were taken, which were analysed by chiral GC. After the reactions were finished, some of the reaction mixtures were analysed by NMR and MS as well to establish the correct composition.

The experiments with Al-TUD-1 (Si/Al = 25) and H-Beta (Si/Al = 25) were performed analogously, also using 50 mg of the solid catalyst.

4.5 Acknowledgements

This chapter was written in close cooperation with Anand Ramanathan who performed the synthesis and characterisation of Zr-TUD-1. Without him, this chapter would never have been written and his contributions are very much appreciated. C. Kwakernaak and W. Sloof are acknowledged for performing the XPS studies.

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5

Enzymatic kinetic resolution of tropic acid

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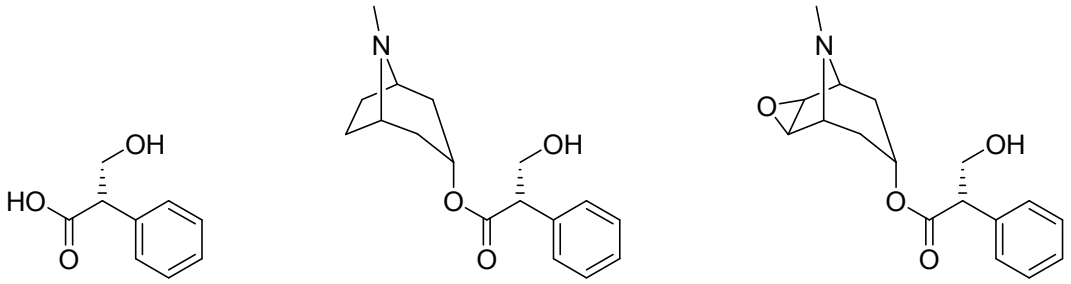
5.1 Introduction

(*S*)-Tropic acid ((*S*)-**1**) is an important building block for biologically active alkaloids like hyoscyamine (**2**) and hyoscine (**3**) (Figure 1), which are well established pharmaceuticals. The synthesis of the enantiomers of tropic acid (**1**) is a big challenge, since this compound racemises under alkaline conditions. Analogously, hyoscyamine and hyoscine racemise easily into their racemates atropine and scopolamine. The enantiomers of tropic acid are not only applied in alkaloid synthesis but are also building blocks in polyester synthesis. Poly-3-hydroxyacids are of great interest for bioerodable and biodegradable polymers[1] and the enantiomeric ratio of the monomers has a dramatic effect on the crystallinity and the solubility of the resulting polymer.[2,3]

The enzymatic kinetic resolution of 2-arylpropionic acids, mainly ibuprofen,[4-12] and related structures[13-19] has been studied intensively, but the literature on enzymatic kinetic resolutions of 2-aryl-3-hydroxycompounds such as tropic acid is scarce. Only recently, an enzymatic kinetic resolution of this hydroxy acid utilising lipase PS (*Pseudomonas cepacia* lipase) to target the primary alcohol was reported.[20] The ethyl ester of tropic acid was resolved, giving (*S*)-acetoxy tropic acid ethyl ester in 39% yield and 87% *ee* and (*R*)-tropic acid ethyl ester in 46% yield and 94% *ee*. Until now, only few reports on



(*S*)-tropic acid (**1**) hyoscyamine (**2**) hyoscine (**3**)

Figure 1. Tropic acid and some tropic acid containing alkaloids.

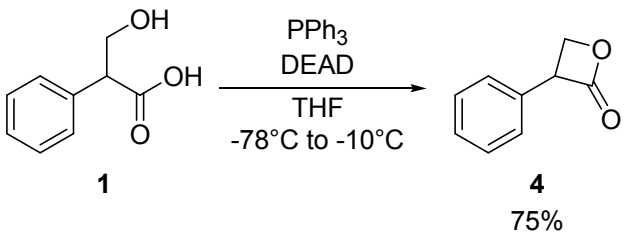
the resolution or enantioselective synthesis of tropic acid have been published. So far, the most convenient method for the preparation of enantiopure (*S*)-tropic acid is the hydrolysis of hyoscyamine and similar compounds isolated from plants. Racemic tropic acid can be resolved in various ways, for example by employing quinine[21] or other co-crystallisation agents,[22] preparative LC[23] or electrophoreses.[24] A report on an elaborate synthesis of (*R*)-tropic acid appeared a few years ago.[25]

Here, we describe a successful strategy for the enzymatic kinetic resolution of tropic acid. In contrast to the enzymatic resolution described in the literature, this will be achieved through functionalisation of the carboxylate rather than of the primary alcohol group.

5.2 Results and discussion

5.2.1 Screening of enzymes for the hydrolysis of esters of tropic acid

A hydrolysis reaction was chosen as enzyme screening experiment, since in this way the reaction could be followed in real time by monitoring the hydroxide consumption. Initially, tropic acid lactone (**4**) was studied as a test substrate. This β-lactone was synthesised *via* a Mitsunobu reaction in 75% yield (Scheme 1).[26] The major advantages of this compound are that both the hydroxyl and the carboxylic acid groups are protected and that the ester



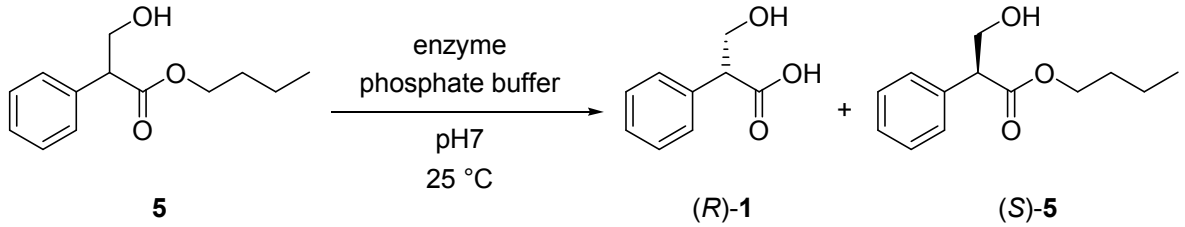
1 **4**
75%

Scheme 1. Synthesis of tropic acid lactone **4**.

is activated as a result of the ring-tension in the four membered lactone. The dual protection blocks polyester formation. The hydrolysis reactions were carried out at 25 °C in a 10 mM phosphate buffer at pH 7.

The blank reaction, however, showed that **4** is too reactive in the buffer. The starting material is converted to racemic **1** within 24 h and therefore tropic acid butyl ester (**5**) was chosen as an alternative test substrate. Now, the blank reaction showed <2% conversion in 24 h. The hydrolysis (Scheme 2) was performed with the commercially readily available enzymes that have earlier been used with success in the kinetic resolution of phenylpropionic acids (Table 1).

From the enzymes tested, CAL-B showed the most promising results. After 18 h, (*R*)-tropic acid ((*R*)-**1**) and (*S*)-tropic acid butyl ester ((*S*)-**5**) were obtained in 90% and >99% *ee* respectively. CAL-B is not generally known to



5 (*R*)-**1** (*S*)-**5**

Scheme 2. Hydrolysis of tropic acid butyl ester (**5**).

Table 1. Screened enzymes for the hydrolysis of **5** and their activity.

enzyme	reaction time (h)[a]	initial reaction rate (mmol/h)[b]
acylase	–	–
α-chymotrypsin	–	–
Achromobacter sp. lipase	–	–
Candida rugosa Lipase	–	–
Candida antarctica lipase B	18	0.071
Humicola lanuginosa lipase	–	–
pig liver esterase	–	–
Rhizomucor miehei lipase	–	–
subtilisin	96	0.018

[a] Time needed for separation of the enantiomers; – indicates no activity.

[b] Initial reaction rate for 200 U enzyme.

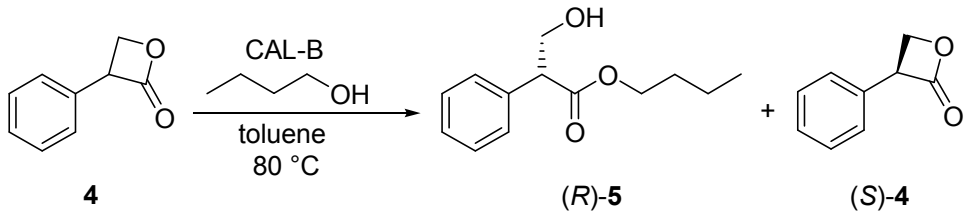
resolve racemic acids, although a few examples are known in which a transesterification with amines[27,28] or alcohols[29,30] takes place. A successful application for the resolution of α-methylene β-lactones of this enzyme has also been reported.[31] Some of the other enzymes tested showed unexpectedly low activity towards this substrate. CRL was reported to be successful in the resolution of 2-arylpropionic acids,[9] but apparently the additional hydroxyl group of tropic acid renders this enzyme inactive towards ester **5**. The enzyme α-CT, which promoted the hydrolysis of 2-benzyl-3-hydroxypropionic acid methyl ester, although not enantioselectively,[32] does not show any reactivity with tropic acid as the substrate. The lactone (3*R*)-(4*S*)-3-benzyl-4-(bromoethyl)oxetan-2-one, a similar compound to **4**, was reported to bind to and act as inhibitor for this enzyme.[33] Inhibition of the enzyme with **4** or **5** in an analogous pathway (an S_N2 reaction forming an ether) is unlikely to take place, however, still no reaction was observed. Subtilisin showed some activity towards the hydrolysis of the tropic acid butyl ester, but the reaction took over 4 days to complete.

Attempts on the hydrolysis of tropine acetate with CAL-B or subtilisin were unsuccessful, hence a coupling with tropic acid to synthesise hyoscyamine by these enzymes seems not to be feasible. The two parts are probably too bulky to be able to fit into the active site, preventing an enzymatic coupling. Based on the results described, CAL-B was selected as the enzyme for the enzymatic kinetic resolution of tropic acid.

5.2.2 Enzymatic kinetic resolution in toluene

With an enzyme in hand that has proven to be very stable and selective in organic solvents, our attention next focussed on esterification reactions in toluene. Therefore, the β-lactone **4**, which is activated due to the ring strain, was selected as the starting compound.

The enzymatic resolution of **4** with 1-butanol, employing CAL-B as the



Scheme 3. Enzymatic resolution of tropic acid lactone (**4**).

catalyst in toluene, gave a very fast and clean reaction towards butyl ester (*R*)-**5** (Scheme 3).

The resolution of lactone **4** towards (*R*)-**5** and (*S*)-**4** proceeds in 70 minutes with an initial reaction rate of 2.6 mmol/h/200 U (Scheme 3, Figure 2). Both compounds were obtained in an enantiomeric excess of >98% in almost quantitative yields. With longer primary alcohols such as 1-octanol, the results and reaction times are similar. The inversion of the stereoselectivity of the enzyme by the long chain alcohols which was shown for CRL in the esterification of 3-hydroxybutyric acid,[34] was not observed for CAL-B. Remarkably, CAL-B does not attack the primary alcohol that is released upon ring opening of the lactone, no dimers or oligomers were formed during the experiment. It is also striking that in the resolution of the similar 2-phenylbutyric acid vinyl ester with butanol, the product is also the (*R*)-butyl ester.[29] This means that the relative stereochemistry is opposite from that

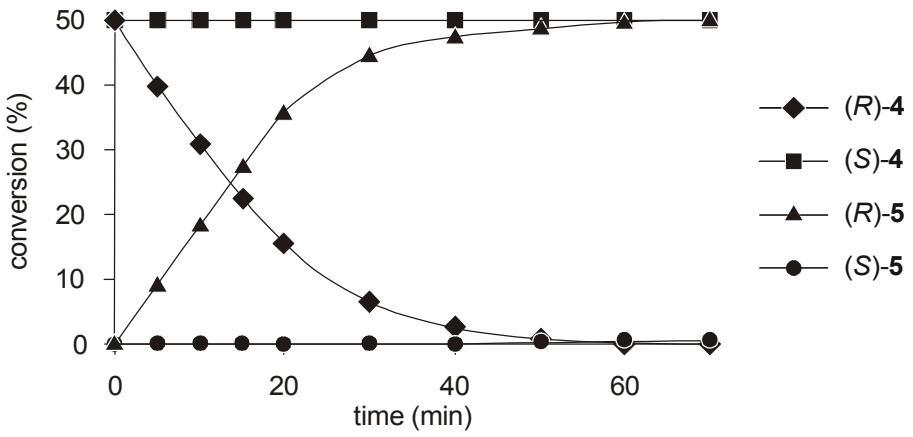


Figure 2. Reaction progress of the resolution of tropic acid lactone (**4**).

observed with lactone **4**. Apparently, substitution of the hydroxyl group in tropic acid by a methyl group causes the enzyme to change its preference for the different groups in the molecule.

Since an enzymatic coupling of tropic acid and tropine was not possible, a chemical coupling of (*S*)-**4** and *endo*-tropine was attempted. Due to the alkaline properties of the tertiary amine in tropine, the lactone is easily opened in this way. However, the chiral centre in tropic acid is also readily racemised under these conditions. The classical syntheses of atropine by refluxing the two components in hydrochloric acid[35,36] or by treating tropic acid subsequently with acetyl chloride, thionyl chloride and tropine hydrochloride[21] do however offer an alternative route, starting from enantiopure (*S*)-tropic acid and will give enantiopure hyoscyamine.

5.3 Conclusion

The enzymatic resolution of tropic acid with CAL-B is very successful with the strategies described. Both (*R*)- and (*S*)-tropic acid butyl ester can be obtained in >98% *ee* and high yields. The complementary (*S*)-tropic acid and (*R*)-tropic acid lactone were also obtained in high yields in 90% and >98% *ee* respectively. As described earlier, the primary alcohol group of tropic acid is no substrate for CAL-B[20] and therefore, no polyesters are formed.

CAL-B is an outstanding enzyme for the resolution of this β-hydroxy acid and it may be expected that it is also a good enzyme for the resolution of 3-hydroxy-2-aryl-propionic acids in general.

5.4 Experimental section

All experiments were performed in dried glassware under a nitrogen atmosphere unless stated otherwise. All chemicals were purchased from

Aldrich or Acros. Anhydrous solvents and solids were used as received. Enzymes were purchased from Sigma, immobilised *Candida antarctica* Lipase B (CAL-B) as Chirazyme L2,c-f.C2, lyo was a gift from Roche Diagnostics. Enantiomeric excesses were determined and reactions were followed by gas chromatography using a Shimadzu GC-17A gas chromatograph, equipped with a 25 m × 0.32 mm chiral column Chrompack™ Chirasil-Dex CB, split injector (1/97) at 220 °C, a Flame Ionisation Detector at 220 °C and He as carrier gas. Retention times (min) at 120 °C isotherm: (*R*)-3-phenyl-oxetan-2-one ((*R*)-**4**) (9.9), (*S*)-3-phenyl-oxetan-2-one ((*S*)-**4**) (10.7), (*S*)-3-hydroxy-2-phenyl-propionic acid butyl ester ((*S*)-**5**) (56.3), (*R*)-3-hydroxy-2-phenyl-propionic acid butyl ester ((*R*)-**5**) (58.4), (*S*)-3-hydroxy-2-phenyl-propionic acid methyl ester (63.9), (*R*)-3-hydroxy-2-phenyl-propionic acid methyl ester (70.0). NMR spectra were recorded on a Varian Unity Inova-300 spectrometer at 25 °C. 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° (PE) and ethyl acetate (EtOAc).

3-Hydroxy-2-phenyl-propionic acid butyl ester (5)

Tropic acid (3.3 g, 20 mmol) and 1-butanol (1.8 mL, 20 mmol) were dissolved in toluene (50 mL). The mixture was refluxed in a Dean-Stark setup for 6 h and the volatiles were evaporated. After column chromatography (PE:EtOAc = 17:3) 3.8 g (17 mmol, 85%) of the ester **5** was obtained as a liquid. ^{1}H-NMR (300 MHz, $CDCl_3$) d 0.87 (t, 3H, *J*=7.20 Hz, C*H*$_3$), 1.25 (sextet, 2H, C*H*$_2$-CH_3), 1.56 (quintet, 2H, *J*=7.20 Hz, C*H*$_2$-CH_2-CH_3), 2.38 (bs, 1H, O*H*) 3.83 (t, 2H, *J*=5.70 Hz, C*H*$_2$-CH_2-CH_2-CH_3), 4.04-4.18 (m, 3H, C*H*-C*H*$_2$-OH), 7.22-7.40 (m, 5H, Ar*H*).

3-Phenyl-oxetan-2-one (4)

DEAD (diethyl azodicarboxylate) (1.89 mL, 12 mmol) was added dropwise to a stirred solution of triphenylphosphine (3.18 g, 12 mmol) in THF (40 mL) at –78 °C. After about 30 min, the suspension became white and then a solution

of tropic acid (2.00 g, 12 mmol) in THF (40 mL) was added dropwise. The resulting mixture was stirred and warmed in about 2 h to –10 °C at which temperature the solution was homogeneous. After concentration at room temperature and purification by column chromatography (PE:EtOAc = 17:3), the product was isolated as a clear liquid in 1.30 g yield (9.00 mmol, 75%). ^{1}H-NMR (300 MHz, $CDCl_3$) d = 4.34 (dd, 1H, *J*=4.76, 5.12 Hz, C*H*$_2$), 4.64 (dd, 1H, *J*=5.12, 6.78 Hz, C*H*$_2$), 4.92 (dd, 1H, *J*=4.76, 6.78 Hz, CH), 7.26-7.42 (m, 5H, Ar-H), ^{13}C-NMR (75 MHz, $CDCl_3$) d = 56.91 (*C*H), 66.38 (*C*H$_2$), 127.15 (2´Ar-*C*), 128.31 (Ar-*C*), 129.19 (2´Ar-*C*), 132.63 (Ar-*C*), 169.54 (*C*O).

Enzyme activity test, general procedure[37]

In the enzymatic resolution experiments, 200 U of enzyme was added to the reaction mixture. The activity of the enzymes was determined in an experiment using an automatic burette. Tributyrin (1.47 mL, 5.0 mmol) was added to a 10 mM potassium phosphate buffer of pH 7 (48.5 mL). The mixture was stirred at 25 °C and the enzyme was added. The pH was kept constant by the addition of a 0.1 M NaOH solution. The activity was determined by the addition of NaOH per minute when the reaction rate was constant. 1 unit (1 U) corresponds to 1 mmol of NaOH solution added per minute.

General procedure for the hydrolysis of 3-Hydroxy-2-phenyl-propionic acid butyl ester (5)

3-Hydroxy-2-phenyl-propionic acid butyl ester (222 mg, 1 mmol) was added to a 10 mM phosphate buffer at pH 7 (10 mL) at 25 °C. The enzyme (200 U) was added and the pH was kept constant by the addition of a 0.1 M NaOH solution with an automatic burette. Then, using CAL-B (60 mg) as the enzyme, the reaction was stopped after 18 h. At neutral pH, the ester ((*S*)-**5**) was extracted with ether and after decreasing the pH to about 2 with a few drops of concentrated hydrochloric acid, the acid ((*R*)-**1**) was extracted with toluene yielding (*S*)-tropic acid butyl ester ((*S*)-**5**) (95 mg, 0.43 mmol, 43%, *ee* >99%) and (*R*)-tropic acid ((*R*)-**1**) (105 mg, 0.47 mmol, 47%, *ee* 90%). The *ee*

of (*R*)-**1** was determined by GC analysis after converting it with diazomethane into its methylester.

(*R*)-3-Hydroxy-2-phenyl-propionic acid butyl ester ((*R*)-5) and (*S*)-3-phenyl-oxetan-2-one ((*S*)-4)

3-Phenyloxetan-2-one (**4**) (296 mg, 2 mmol) and 1-butanol (0.18 mL, 2 mmol) were dissolved in dry toluene (4 mL). The temperature was raised to 80 °C and CAL-B (50,0 mg, 160 U) was added. After 70 min the reaction was stopped by filtering off the enzyme. The filtrate was concentrated. The products were separated by column chromatography (PE:EtOAc = 17:3) giving 204 mg (0.94 mmol, 47%, *ee* >98%, $[\alpha]_D^{25}$ = +40.0° (*c* 3.4, $CHCl_3$)) of (*R*)-3-hydroxy-2-phenyl-propionic acid butyl ester ((*R*)-**5**) as a colourless liquid and 139 mg (0.92 mmol, 46%, *ee* >98%, $[\alpha]_D^{25}$ = +24.0° (*c* 4.0, $CHCl_3$), mp.: 45.6 °C) of (*S*)-3-phenyl-oxetan-2-one ((*S*)-**4**) as a white crystalline solid. Hydrolysis of (*S*)-**4** yielded (*S*)-**1** with $[\alpha]_D^{25}$ = –63.3° (c 0.3, acetone); (literature: $[\alpha]_D^{15}$ = –65.1° (c 0.22, acetone).[38]

5.5 Acknowledgments

Roche Diagnostics Penzberg (Dr. W. Tischer) is gratefully acknowledged for the generous gift of the enzyme (CAL-B, Chirazyme® L-2, c.-f., C2, Lyo).

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Summary

Chapter 1 is an extensive review on homogeneous transfer hydrogenations. It shows the different reaction mechanisms involved for different types of catalysts. Although these transfer hydrogenation catalysts are mainly used for the reduction of ketones they can be employed for reducing a wide variety of substrates like imines and C-C double and triple bonds. Additionally, the importance of the right choice of hydrogen donors and solvents is discussed. The substrates that can be reduced in this way consist of a wide range of compounds. Typically, the selectivity of hydrogen transfer catalysts is very high, however, unwanted reactions can occur and the main side-reactions are briefly discussed. Finally, the most recent developments in racemisation reactions and dynamic kinetic resolutions are mentioned.

Chapter 2 deals with the various mechanisms involved both in the homogeneous and heterogeneous Meerwein-Ponndorf-Verley-Oppenauer reactions. 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-$^{2}H_{1}$)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 hydroxygroup and its readdition. This mechanism, however, is not characteristic for all racemisations with zeolite Beta. When 4-*tert*-butylcyclohexanone is reduced with this catalyst, a classical MPV-reaction takes place exclusively. This demonstrates the reaction pathway

followed by zeolite Beta catalysed reactions is substrate dependent.

Chapter 3 shows the application of the homogeneous catalysts described in the previous chapter. A practical racemisation/epimerisation method for chiral secondary alcohols has been developed. Meerwein-Ponndorf-Verley-Oppenauer catalysts such as neodymium(III) isopropoxide are able to racemise these alcohols with retention of other stereocentres in the molecule. This is particularly useful for the recycling of the undesired products of kinetic resolutions of alcohols. By combination of such a racemisation with an acylation using isopropenyl or ethoxyvinyl esters as acyl donors, a fast straightforward recycling of starting materials may be achieved. The combined epimerisation and acylation process is demonstrated for the steroid estradiol 3-methyl ether.

Chapter 4 presents the results of the Meerwein-Ponndorf-Verley reduction catalysed by Zr-TUD-1, a newly developed heterogeneous catalyst. This new, three-dimensional, amorphous mesoporous silicate containing zirconium was synthesised *via* a direct hydrothermal treatment method using triethanolamine as the template. The mesoporosity of Zr-TUD-1 was confirmed by XRD, N_2 sorption and HR-TEM studies. The acid sites present in Zr-TUD-1 were evaluated by FTIR studies of pyridine adsorption and shown to be predominantly Lewis acidic. The nature of zirconium in Zr-TUD-1 was established by FTIR, XPS and UV-VIS studies. Zr-TUD-1 was tested in the Meerwein-Ponndorf-Verley reduction. The activity is strongly dependent on steric factors which can be exploited in the selective reduction of multifunctional steroids.

Finally, chapter 5 introduces a new strategy that was developed for the CAL-B catalysed kinetic resolution of tropic acid by which both enantiomers of tropic acid can be obtained in good optical purity. (*R*)-tropic acid was synthesised with 90% *ee* and (*S*)-tropic acid butyl ester in 99% *ee* in the hydrolysis of tropic acid butyl ester. The other enantiomers are available through the enzymatically catalysed reaction of tropic acid lactone with 1-butanol to give (*S*)-tropic acid lactone and (*R*)-tropic acid ester in more than >98% *ee*.

Samenvatting

Hoofdstuk 1 is een uitgebreid literatuuroverzicht van homogene waterstofoverdrachtskatalysatoren. De verschillende reactiemechanismen van diverse katalysatoren worden behandeld. Hoewel deze katalysatoren voornamelijk gebruikt worden voor de reductie van ketonen, kunnen ze ook ingezet worden voor het reduceren van een grote verscheidenheid aan substraten, zoals imines en C-C dubbele en drievoudige bindingen. Ook wordt het belang van de verschillende waterstofdonoren en oplosmiddelen besproken. Gewoonlijk hebben waterstofoverdrachtskatalysatoren een erg hoge selectiviteit. Er kunnen zich echter nevenreacties voordoen die ook kort worden besproken. Tenslotte worden de meest recente ontwikkelingen op het gebied van racemisaties en dynamisch kinetische resoluties bekeken.

Hoofdstuk 2 gaat over de verschillende reactiemechanismen die van toepassing zijn op de homogene en heterogene Meerwein-Ponndorf-Verley-Oppenauer reacties. 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-$^{2}H_{1}$)ethanol en acetofenon om het reactiepad van deze overdracht te bepalen. 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 waarvan de afgeleide

alcoholen minder makkelijk water elimineren, vindt een klassieke MPV-reactie plaats. Het reactiepad dat door zeoliet Beta gekatalyseerde reacties wordt gevolgd tijdens de reductie is dus substraatafhankelijk.

Hoofdstuk 3 toont de toepassing van de homogene katalysatoren die beschreven zijn in het voorgaande hoofdstuk. Een eenvoudige methode is ontwikkeld voor de racemisatie/epimerisatie van secundaire alcoholen. Deze alcoholen kunnen met behoud van andere stereocentra in het molecuul geracemiseerd worden met Meerwein-Ponndorf-Verley-Oppenauer katalysatoren zoals neodymium(III)isopropoxide. Dit is vooral nuttig voor het hergebruik van ongewenste enantiomeren die gevormd worden tijdens de kinetische resolutie van alcoholen. Een snelle en eenvoudige manier om de uitgangsstoffen her te gebruiken kan worden bereikt door zo'n racemisatie te combineren met een acylering door isopropenyl- of ethoxyvinylesters als acyldonoren. Het samenspel tussen de epimerisatie en de acylering wordt gedemonstreerd aan de hand van estradiol 3-methylether, een steroïde .

Hoofdstuk 4 betreft de resultaten die zijn geboekt met Meerwein-Ponndorf-Verley reducties gekatalyseerd door Zr-TUD-1, een nieuw ontwikkelde heterogene katalysator. Dit nieuwe zirconium houdende, driedimensionale, amorfe, mesoporeuze silicaat werd gesynthetiseerd met een directe hydrothermische behandeling en triethanolamine als structuurbepalende verbinding. De mesoporeuze structuur van Zr-TUD-1 werden aangetoond met behulp van XRD (röntgendiffractie), stikstofsorptie en HR-TEM (hoge resolutie transmissie elektron microscopie) metingen. De zure posities in Zr-TUD-1 werden beoordeeld met FTIR (Fouriertransformatie infrarood spectroscopie) metingen na pyridineadsorptie en hieruit bleek dat deze posities voornamelijk Lewiszuur zijn. De eigenschappen van het zirconium in Zr-TUD-1 werden vastgesteld met behulp van FTIR, XPS (röntgen foto-emissie spectroscopie) en UV-VIS (ultraviolet-zichtbaar licht) metingen. Het gesynthetiseerde en gekarakteriseerde Zr-TUD-1 werd vervolgens met goede resultaten getest in de Meerwein-Ponndorf-Verley reductie. De activiteit is sterk afhankelijk van sterische factoren. Hiervan kan gebruik worden gemaakt in de selectieve reductie van multifunctionele steroïden.

Tenslotte wordt in hoofdstuk 5 een nieuwe resolutie van tropazuur met CAL-B (*Candida antarctica* lipase B) beschreven, waarmee beide enantiomeren van tropazuur in een goede optische zuiverheid kunnen worden verkregen. Via een CAL-B gekatalyseerde hydrolyse van tropazuurbutylester werd (*R*)-tropazuur gesynthetiseerd met een enantiomere overmaat van 90% en (*S*)-tropazuurbutylester met 99%. Een enzymatisch gekatalyseerde reactie van tropazuurlacton met 1-butanol geeft de andere enantiomeren (*S*)-tropazuurlacton en (*R*)-tropazuurbutylester in een enantiomere overmaat van >98%.

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Curriculum Vitae

Dirk Klomp werd geboren op 31 oktober 1976 in Zaandam. Na het begin van zijn schoolloopbaan aan kleuterschool "De kabouters" in Wormerveer ging hij in 1983 naar de lagere school "Jan Ligthart school" (later o.b.s. "De Pionier") in dezelfde plaats. Vervolgens ging hij in 1989 naar het VWO van "Bertrand Russell" (later "Bertrand Russell college") in Krommenie waar hij in 1995 zijn diploma behaalde.

Ondertussen was hij in 1994 aan een opleiding verenigingsleider gymnastiek begonnen die hij in 1996 succesvol afrondde. Sindsdien was en is hij als turntrainer actief bij gymnastiekverenigingen "Saenden" (later "Wormerveer 2000") in Wormerveer en "Lycurgus-Hygiëa" in Krommenie.

In 1995 is hij scheikunde gaan studeren aan de "Universiteit van Amsterdam". Van oktober 1999 tot april 2000 liep hij stage bij DSM-resins in Zwolle en in 2000 is hij afgestudeerd in de groep van synthetisch organische chemie op het afstudeerproject "palladium gekatalyseerde cyclisaties van allenyllactamen". Datzelfde jaar begon hij aan zijn promotieonderzoek in de groep toegepaste organische chemie en katalyse van de "Technische Universiteit Delft" waarvan dit proefschrift de afronding is.