Carrier enabled catalytic reaction cascades

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Catalytic cascade reactions increase atom efficiency and help to reduce waste. Therefore they have recently attracted considerable attention. When performing them we have experienced that the immobilisation of the catalyst and the nature of the support are crucial factors. The carriers can play various roles from facilitating filtration and compartmentalisation to specifically binding unwanted compounds in the reaction media. In this Feature Article we give an overview of our work on such carrier dependent cascade reactions.

1 Introduction

When organic chemists set out to develop their first syntheses their curiosity drove them to try many daring combinations of chemicals. This led to the successful synthesis of numerous heterocyclic, aromatic ring systems.[1] The growing understanding of the underlying reaction mechanisms enabled Robinson already in 1917 to perform a cascade of reactions to obtain tropinone starting from succindialdehyde, methylamine and the calcium salt of acetone dicarboxylic acid.[2] However, after this milestone in the development of chemistry, most reactions were performed in a step-by-step approach for a long time. Efficient cascades of reactions,[3–5] multi-component reactions[1] and domino reactions[5–7] only became fashionable again during the last decade or two. Similarly catalysis and more specifically biocatalysis were introduced into organic chemistry already in the nineteenth century,[8] but their application in total synthesis is still not such, that their full potential has been realised.[9]

The combination of different types of catalysis, chemocatalysis and biocatalysis, opens the way to many attractive reaction cascades.[3–5] The two types of catalysts complement each other: transition metals are particularly versatile for (enantioselective) oxidations and reductions, tasks often difficult to perform with enzymes, due to problems with co-factor regeneration. On the other hand hydrolytic reactions and their reversal are readily performed with the aid of enzymes, while chemically they often require drastic reaction conditions and generate large amounts of salts as waste. Another interesting opportunity arises in the area of the enantioselective synthesis of C–C bonds.[9] A common point of criticism is that there are not enough enzymes for this purpose. Dynamic kinetic resolutions offer versatile solutions for this shortcoming. By combining a chemical catalyst that forms a C–C bond racemically with a hydrolytic enzyme that catalyses the enantioselective formation of an ester, hydrolases can be utilised in a chemoenzymatic cascade of reactions to synthesise new C–C bonds.[10]

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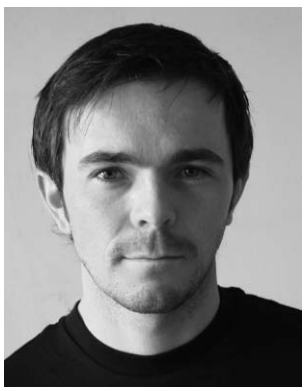

Lars Veum

Lars Veum was born in 1975 in Voss, Norway. He obtained his master level degree at the Norwegian University of Science and Technology (Trondheim) in 2001 after performing his graduation project at Ecole Nationale Superieure de Chimie de Paris under the supervision of Dr Marc Larchevêque. Currently he is a PhD student in the group of Dr Ulf Hanefeld working on the enzyme-catalysed synthesis and the use of optically pure cyanohydrins. During his PhD study he spent one year at the Institut de Recherches sur la Catalyse, Lyon, France working on the encapsulation of HbHNL in a sol–gel matrix under the supervision of Professor Alain Pierre.

Ulf Hanefeld was born in 1966 in Köln, Germany, and grew up in then West-Berlin and London. In 1993 he received his PhD from the Georg-August-Universität zu Göttingen, Germany, having performed the research both in Göttingen (Professor H. Laatsch) and Seattle, WA, USA (Professor H. G. Floss). After many post-doctoral years with Professor C. W. Rees at Imperial College London, UK, Professor J. Staunton in Cambridge, UK and Professor J. J. Heijnen and Dr A. J. J. Straathof in Delft, the Netherlands, he received a research fellowship for five years from the Royal Netherlands Academy of Arts and Sciences (KNAW). He is an academic staff member of the Technische Universiteit Delft in the Netherlands. His research focuses on enzymes in organic synthesis and transition metal catalysis.

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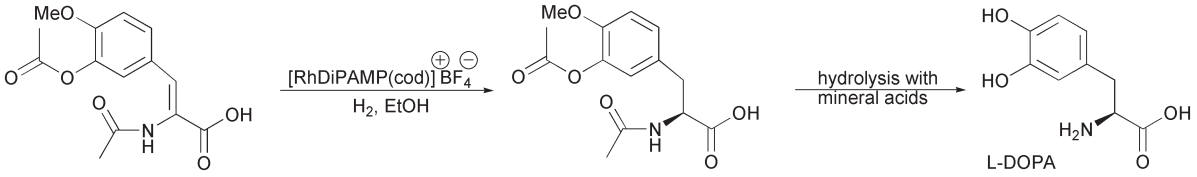


Scheme 1 The Monsanto L-DOPA process.

In order to reap the full potential of these catalytic reaction cascades, special care has to be taken that the catalysts do not inhibit or deactivate each other. We would here like to discuss a few examples out of our recent research that demonstrate the importance of immobilisation of either of the catalysts for their successful application in catalytic reaction cascades.

2 Immobilised chemo-catalysts combine well with enzymes

2.1 Enantioselective reduction and enzymatic hydrolysis

A classical application of a transition metal catalyst is the Nobel prize-winning enantioselective reduction of enamides. The Rh-DiPAMP-catalyst developed by Knowles was successfully applied on an industrial scale in the Monsanto L-DOPA process (Scheme 1).[11] The mild and selective reduction was, however, followed by a rather harsh hydrolytic step during which large amounts of waste were generated, thereby tarnishing the elegance of this synthesis. Replacing the acid-catalysed hydrolysis with a mild enzyme-catalysed cleavage of the protecting groups should significantly enhance this approach towards enantiopure amino acids. For the development of an efficient catalytic reaction cascade it is essential to find conditions that are suitable for both types of catalysts. In this case both reactions have to proceed in water, since this is a prerequisite for an enzymatic hydrolysis.[12]

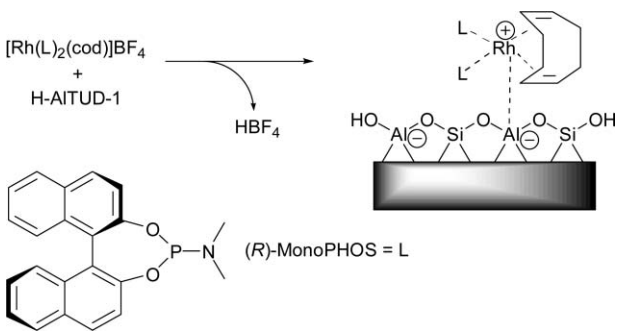
The problem that had to be solved was to find conditions under which the Rh-catalyst would work in water. At the same time the Rh-catalysts commonly employed for this type of reduction are toxic and very expensive. Therefore a straightforward separation and recycling of the Rh was a target in its own right. The solution to all of these challenges laid in the immobilisation of the Rh-catalyst. Different approaches can be utilised for this. Recently if was demonstrated that the electrostatic immobilisation is particularly efficient. For this purpose a carrier with a charge is utilised. The carrier can thus act as a counter ion to the transition metal catalyst, provided that the metal retains a charge throughout the catalytic cycle. With this methodology no ligand derivatisation is necessary and the immobilisation is an uncomplicated ion exchange reaction.[13]

For the planned application a new carrier material was developed. The mesoporous silicate TUD-1 with a three-dimensional sponge-like structure and a large surface area seemed ideal for the envisaged application. A straightforward addition of Al(III) isopropoxide to the synthesis mixture of TUD-1 yielded AlTUD-1. This new material not only retained the favourable characteristics of TUD-1 but more that 40% of the Al was coordinated tetrahedrally, bearing a negative charge. Several Rh(I) complexes were readily immobilised on this material *via* ion exchange (Scheme 2). AlTUD-1 immobilised Rh-DuPHOS, Rh-DiPAMP[14] and Rh-MonoPHOS[15] all performed well and could be recycled. A distinct influence of the solvent on the amount of metal leached was observed. However, no activity leached of the carrier, proving that the catalytic reduction was truly heterogeneous.

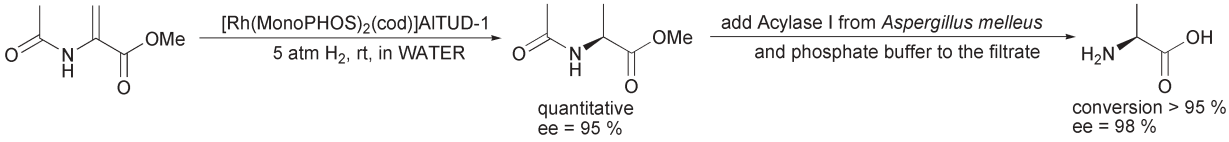
The immobilisation of Rh-MonoPHOS on AlTUD-1 significantly broadened the applicability of this catalyst. While the homogeneous catalyst works best in dichloromethane and is virtually inactive in water, the heterogenised catalyst displays its highest enantioselectivity in water. Moreover, virtually no Rh leaches (0.5%) when the immobilised catalyst is used in aqueous media. Thus the immobilised Rh-MonoPHOS fulfils all the criteria mentioned above: activity in water,[16] straightforward separation from the product and reusability.[15]

The second reaction in the cascade is the hydrolysis of the amide bond. In an extensive screening Acylase I from *Aspergillus melleus* displayed the highest activity for this reaction. Next to its activity its high enantioselectivity opened the opportunity for further improvements of the enantiopurity of the final product. In addition it cleaved the ester group of the starting material, too.[17]

The Rh-catalysed reduction and the Acylase I catalysed hydrolyses of both protection groups were performed as a cascade. Subsequent to the quantitative reduction the immobilised chemo-catalyst was filtered off to allow recycling of the Rh-MonoPHOS. Then the enzyme was added together with a phosphate buffer and the desired amino acid was obtained. Due to the enantioselectivity of the Acylase I its optical purity was even higher than that of the first chiral intermediate (Scheme 3). The overall reaction cascade comprises three catalytic steps that proceed under very mild conditions in an environmentally benign solvent with excellent yields and selectivities.[16,18]



Scheme 2 Straightforward immobilisation *via* ion exchange of Rh-MonoPHOS on the novel carrier material AlTUD-1.



Scheme 3 Chemo-enzymatic reaction cascade for the synthesis of enantiopure amino acids, comprising one enantioselective reduction and two enantioselective enzymatic hydrolysis reactions.

2.2 Chemical oxidation and enzymatic C–C bond formation

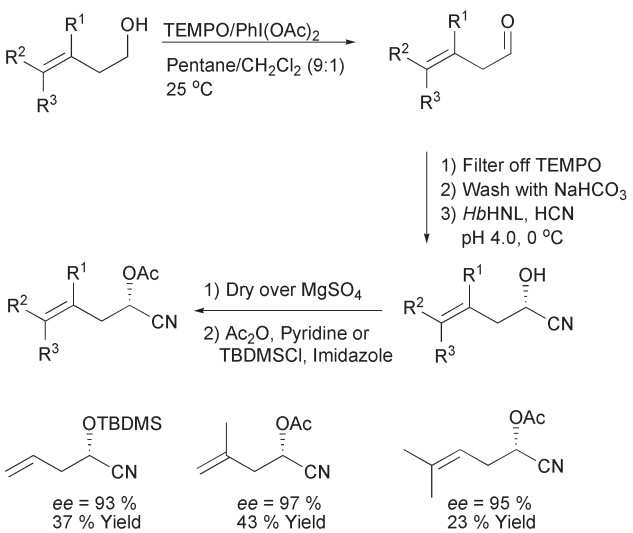
During a collaborative study with Dr Orru (Vrije Universiteit Amsterdam) towards a chemo-enzymatic *de novo* synthesis of non-natural nucleosides containing a 3′-deoxy ribose moiety, the optically pure (*S*)-γ,δ-unsaturated cyanohydrins in Scheme 4 were identified as key intermediates. A straightforward approach towards such intermediates would be the oxidation of γ,δ-unsaturated alcohols to their corresponding aldehydes followed by a C–C bond formation catalysed by the highly (*S*)-selective hydroxynitrile lyase from *Hevea brasiliensis* (*Hb*HNL).[9,12,19] However, the manipulation of the β,γ-unsaturated aldehydes is not uncomplicated. Their preparation is hampered by isomerisation into α,β-unsaturated aldehydes during work up, in particular under basic conditions. It was therefore chosen to perform the reaction sequence as a cascade using the reaction mixture from the oxidation reaction directly for the hydrocyanation reaction without isolating the aldehyde. Although *Hb*HNL works well under optimised conditions, it is very sensitive when applied outside this optimum. For a successful cascade, it was therefore essential that the oxidation proceeded not only without isomerisation of the product but also with reactants and waste products, which were harmless for the enzyme reaction.

As discussed above the oxidation reaction was performed with a chemical catalyst, since enzymatic oxidations are often cumbersome. The reagents of choice for the oxidation were catalytic amounts of TEMPO with $PhI(OAc)_2$ as the stoichiometric oxidant.[20] However, in order to couple it to the *Hb*HNL-reaction, some modifications had to be made. First of all, the reaction produces acetic acid, which is an efficient inhibitor of the enzyme. This was removed at the end of the oxidation, without isomerisation of the product, by simply washing with a saturated solution of $NaHCO_3$ at 0 °C. Since TEMPO was suspected to have a negative effect on the enzyme, it was immobilised ensuring an easy removal prior to the *Hb*HNL-catalysed step.[21] This immobilisation also allowed the TEMPO to be recycled at least once without any loss of activity. By exchanging the solvent from the normally used CH_2Cl_2, to a CH_2Cl_2–pentane (1:9) mixture, not only did the solvent become more suitable for the enzyme reaction, but both the conversion and the reaction time of the oxidation were improved dramatically. A complete conversion of the alcohol could be achieved within 1 h, most likely due to the removal of the polar solvent cage around the reagents.

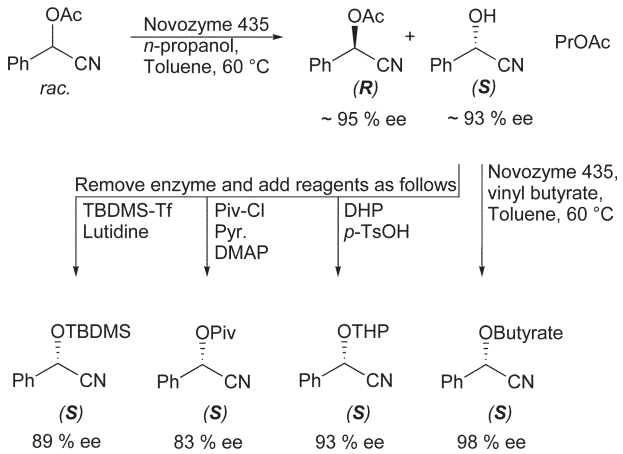
When the oxidation and the enzyme reaction, were coupled together, the whole cascade proceeded smoothly to the desired cyanohydrins, with excellent optical purities (Scheme 4). As the enzyme reaction is performed under mildly acidic conditions to prevent any chemical background reaction, nearly no isomerisation of the aldehyde was observed. When the reaction cascade was performed with homogeneous TEMPO the ee of the products were significantly lower (5–26% lower). This demonstrates the great importance of using immobilised TEMPO for this reaction and confirmed our earlier concerns about the compatibility of the oxidation catalyst and the enzyme. While conversions in the separate steps were excellent the isolated yields over all three steps, performed within one day, were moderate. As the reactions were performed on a 100 mg scale and the compounds involved in this reaction cascade are relatively polar and/or volatile and some loss/low yields could not be avoided.

Since the immobilisation of TEMPO was very successful, *Hb*HNL was immobilised in a sol–gel (similar to the carrier of TEMPO).[22] Although the encapsulated *Hb*HNL was active significant leaching was observed and therefore this enzyme preparation was not applied in the reaction cascade.

(*S*)-γ,δ-unsaturated cyanohydrins could be obtained with excellent optical purity in good yields by a chemo-enzymatic reaction cascade starting from γ,δ-unsaturated alcohols with virtually no isomerisation of the intermediate β,γ-unsaturated aldehyde.[23] For this cascade to proceed with excellent ee's, it was essential that the chemical catalyst is immobilised and removed prior to the enzymatic step, similar to the Rh-MonoPHOS-Acylase cascade.



Scheme 4 The three-step "one pot" cascade reaction from γ,δ-unsaturated alcohols to their corresponding protected (*S*)-γ,δ-unsaturated cyanohydrins.



Scheme 5 Kinetic resolution of mandelonitrile acetate and the protection of the formed (*S*)-cyanohydrin.

3 Carriers enable the use of enzymes in reaction cascades

3.1 Kinetic resolution and reprotection

In addition to HNLs, lipases have also successfully been used for the synthesis of enantiopure cyanohydrins. One attractive application is the kinetic resolution (KR) starting from acylated cyanohydrins (Scheme 5).[12,19,24]

The starting material can easily be prepared in a one-pot procedure from the corresponding aldehyde without use of the highly toxic HCN. Furthermore, the remaining enantiomer can, if desired, readily be racemised and resubmitted to the kinetic resolution, allowing for nearly quantitative yields of the product. Still, the resulting (*S*)-cyanohydrins are relatively unstable and racemise easily. The kinetic resolution should therefore ideally be coupled with a protection reaction, directly and without any elaborate workup. Moreover, an enzyme should be found that is not only enantioselective but also recyclable. To achieve this, a range of immobilised lipases were screened for this reaction, and the widely available (*S*)-selective† lipase B from *Candida antarctica* (CAL-B), immobilised on a macroporous acrylic resin (''Novozyme 435'') was found to be particularly enantioselective for the aromatic substrates, with $E > 100$.[25]

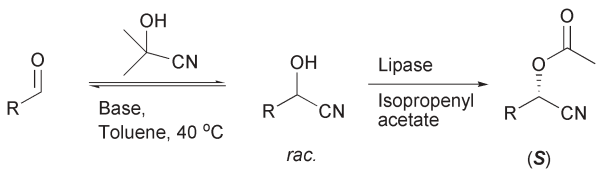
In order to recycle the enzyme at the end of this cascade, it is crucial that the enzyme is removed prior to any chemical protection reaction. Due to their size, the enzyme beads could easily be ''filtered off'' by simply transferring the liquid through a cannula to another reaction flask. Recycling experiments showed that the enzyme could be reused at least four times without any loss of enantioselectivity.[24]

After the straightforward removal of the enzyme, the (*S*)-cyanohydrins could readily be protected under basic conditions as TBDMS-ethers and pivaloates, and under acidic conditions as THP-ethers. The THP-ether had a slightly higher ee than the pivaloates and the TBDMS-ethers, probably due to the tendency of the cyanohydrins to racemise under basic conditions.

Protection under neutral conditions was realised by simply adding vinyl butyrate to the reaction mixture at the end of the KR, without prior removal of the enzyme. The enzyme then protected the (*S*)-cyanohydrin as its butyrate (Scheme 5). The optical purity of the resulting (*S*)-butyrates was increased compared to the (*S*)-cyanohydrins, due to the enantioselectivity of the enzyme.

All the protected (*S*)-cyanohydrins and the (*R*)-cyanohydrin acetates could then easily be separated by column chromatography‡ in both excellent yields and optical purities. The isolated yield of the (*R*)-acetates were generally >90% while the yield of the protected (*S*)-cyanohydrins were slightly lower (>80%), due to some decomposition of the intermediate cyanohydrin to its aldehyde.

Thus the enantiopure, protected cyanohydrins were made accessible *via* a cascade consisting of an immobilised lipase—catalysing the kinetic resolution—followed by the reprotection of the resulting (*S*)-cyanohydrins.[24]



Scheme 6 The enantioselective synthesis of cyanohydrin esters *via* a dynamic kinetic resolution.

3.2 Dynamic kinetic resolutions enable hydrolase-catalysed C–C bond formations

Although HNLs are excellent catalysts for the addition of HCN to aldehydes, yielding enantiopure cyanohydrins (2.2), they cannot be used in all cases. The range of accepted substrates is mainly limited to molecules of low complexity, and the sensitive nature of the enzymes complicate their use in dry organic solvents.

Since lipases in general have a wide substrate range and can be used in pure organic solvents, the lipase-catalysed dynamic kinetic resolution (DKR) of cyanohydrins is particularly interesting (Scheme 6). This catalytic cascade reaction was already described in 1991, and is the first example where a lipase is used in an enantioselective C–C bond formation.[10] However, in spite of its elegance, there are only few examples of its successful application.[26] This is mainly due to long reaction times, moderate enantioselectivities and the failure of this DKR when applied to aliphatic substrates.[10,27] A more active, enantioselective and readily available enzyme could therefore help increasing the attractiveness of this DKR. Encouraged by the results obtained with the immobilised

† *Candida antartica* lipase B in general follows Kazlauskas rule,[12] in the case of the cyanohydrins described here this means that it is (*S*)-selective. In other cases the same enzyme, still following Kazlauskas rule, can be (*R*)-selective.

‡ It was not possible to separate the (*S*)-THP-ethers from the corresponding (*R*)-acetates by column chromatography due to similar polarity of the molecules. However, by using cyanohydrin butyrates as starting compounds for the KR, this can easily be circumvented. When larger quantities of the (*R*)-cyanohydrin acetates and (*S*)-protected cyanohydrins are prepared the use of column chromatography might be replaced by distillation.

CAL-B (Novozyme 435, see chapter 3.1), we set out to explore its potential for the DKR.

This cascade of reactions combines a base-catalysed equilibrium between an aldehyde, acetone cyanohydrin and the resulting cyanohydrin of the aldehyde, with a lipase-catalysed acylation of one enantiomer of the racemic cyanohydrin. As the remaining enantiomer of the cyanohydrin is racemised by the base, theoretically 100% yield of the corresponding cyanohydrin acetate can be obtained.

There are also other advantages of this approach than the luring prospects of quantitative yields and high optical purity. While the traditional HNL approach is based on an equilibrium reaction where an excess of HCN is crucial for obtaining good yields, the DKR makes use of the cheap and relatively safe acetone cyanohydrin, which generates the HCN *in situ*. Furthermore, the last step of the DKR is a practically irreversible reaction, reducing the required amount of acetone cyanohydrin to merely 2 equivalents.

Relatively early in this work, it was found that the base-catalysed formation of the cyanohydrin, its racemisation and acylation all proceeded smoothly when performed separately, combined however, the reaction hardly gave more than a meagre 16% yield.[28] The problem was identified to be water bound to the carrier of the enzyme. During the reaction this water is readily released to the reaction media and used by the enzyme to hydrolyse the acylating agent, generating acetic acid. The acetic acid in turn neutralised the base, which lead to a full stop in the reaction. For each molecule of acetic acid that is neutralised, one molecule of water is liberated, which again can be used to produce more acetic acid until there is either no acylating agent left or until the entire base is neutralised. Thus the choice of carrier is essential to the success of the overall DKR.

Yet another difficulty could be identified when aliphatic substrates were used for the reaction. The yields were in line with what can be obtained from a kinetic resolution, indicating that the standard base for this reaction (OH^- conditioned Amberlite) is not strong enough to efficiently racemise the remaining enantiomer of the cyanohydrin.

Various approaches were explored to meet these two challenges. Obvious solutions to the water induced acidification such as adding more base or molecular sieves to the reaction did not yield the desired results. In contrast, an increased amount of base led to a base-catalysed polymerisation of HCN. This polymer turned out to be a highly efficient inhibitor of the lipase, putting a full stop of the reaction.

The possibility of replacing the traditionally used base with solid buffers (CAPSO pK_a 9.6, CAPS pK_a 10.4) was also investigated. It had previously been shown that solid buffers can be efficiently used to adjust the ionisation state of enzymes in organic media and to maintain it.[29] It was found that the buffers indeed did improve the results dramatically, both in respect to the water issue and the racemisation of the aliphatic cyanohydrin. However, since a relatively large amount of solid buffers (1–2 g of buffer/gram product) would be necessary for the reaction to proceed smoothly, other solutions were pursued.

To use NaCN as a base in the reaction turned out to be a straightforward solution for the aliphatic substrates. Not only was NaCN a strong enough base to efficiently racemise the aliphatic cyanohydrin, the reactions also proceeded to 100% conversion with a high ee for cyclohexanecarbaldehyde, implying that water is no problem in this case. The advantage of the cyanide salt is that it neutralises any acetic acid, yielding HCN and sodium acetate. In contrast to the water formed during the neutralisation of the amberlite, HCN does not take part in a destructive cycle but conveniently adds to the aldehyde yielding the racemic cyanohydrin.[30] When used in combination with an aromatic substrate, the yields were also excellent; however, the products were nearly racemic. The reason for this must be that the NaCN is strong enough as a base to catalyse the chemical acylation. Other cyanide salts were also probed ($Zn(CN)_2$ and CuCN) but they were not sufficiently basic to catalyse the reaction. Another solution was therefore necessary for the aromatic substrates.

The only difference between the reaction performed with Novozyme 435 and the few existing successful DKRs of cyanohydrins, except for the solvent and the enzyme itself, is the carrier of the enzyme. Previously, the various lipases have always been immobilised on a Celite, probably due to the effective and simple procedure. By simply immobilising the CAL-B on Celite R-633, both the yield and ee of mandelonitrile actetate was significantly increased and a nearly quantitative (97% yield) and enantioselective (98% ee) reaction was achieved.[31]

The reason for this difference is that Novozyme 435 is immobilised on a relatively hydrophobic carrier, and any water attached to this carrier will be liberally released to the reaction medium. In contrast to this, Celite is capable of binding water relatively tightly *via* hydrogen bridges, and is therefore not releasing any water into the reaction mixture. Indeed Celite has even been used to control water activities. The Celite-immobilised CAL-B was also used in combination with an aliphatic substrate and NaCN, but in this case water is less disturbing and thus Novozyme still proved to be the better solution.

A wide range of substrates was tested for the reaction, and in most cases both excellent yields and enantioselectivities could be obtained (Fig. 1). Compared to the first described DKR of cyanohydrins, the reaction time has been significantly shortened, and both the yields and enantioselectivities have been improved. The ee of aliphatic cyanohydrins was also improved in spite of the known poor selectivity of CAL-B towards straight chain aliphatic substrates.

Hence, the challenges presented by water and an insufficient racemisation of the intermediate cyanohydrin (in the case of aliphatic substrates) were solved based on the understanding of the influence of the carrier on the reaction. Using the readily available CAL-B with straightforward modifications of either the chemical catalyst or the carrier of the enzyme, excellent yields and enantioselectivities in the DKR of cyanohydrins starting from both aliphatic and aromatic aldehydes were achieved.[30–32]

4 Reductions and migrations

Due to their known pharmacological activity, *N*-acyl β amino alcohols are highly interesting structural motifs. Their facile

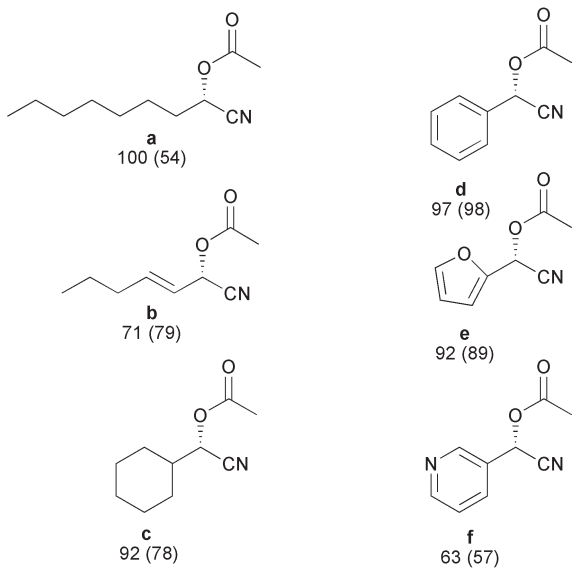
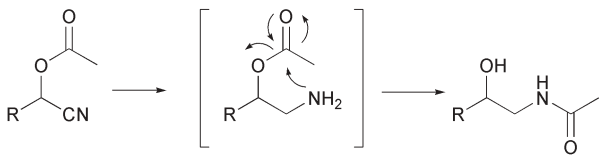


Fig. 1 Yield (*ee*) [%] after four days (two days for **a** and **b**). The yield of **c**, **e** and **f** are isolated yields.

conversion into β-secondary amino alcohols, an important class of compounds in the pharmaceutical and agrochemical industry makes them a valuable building block too. Their preparation starting from free cyanohydrins, normally consists of two steps, a reduction ($LiAlH_4$, BH_3 or catalytic hydrogenation under strongly acidic conditions)[19,33] followed by an acylation. As this procedure generates a relatively large amount of waste, and an intermediate work-up is necessary, a novel strategy was developed.

It was found that the hydrogenation of cyanohydrin esters was followed by a rapid intramolecular acyl migration to yield the *N*-acyl β-amino alcohols directly (Scheme 7). This one-pot two-step cascade reaction proceeds with a high atom efficiency under neutral conditions from readily available starting materials and is a significant improvement compared to the previous two-step procedure. Since the newly generated primary amines are rapidly acylated, the formation of secondary amines, a side reaction normally observed in the catalytic hydrogenation of nitriles under neutral conditions was also conveniently suppressed.

Since benzylic C–O bonds are readily cleaved by hydrogenation, the reaction was optimised separately for substrates containing a benzylic and a non-benzylic C–O bond. For the optimisation a design of experiment strategy was chosen.[34] This consisted of an initial small design (only around 7% of all possible combinations) where the results were used to drastically narrow down the parameter space for the second design. The conditions were further fine-tuned in a third design. By using this strategy only 70 reactions in total for each substrate



Scheme 7 Catalytic hydrogenation of acylated cyanohydrins.

type, from around 2000 possible combinations of the tested parameters (metal, support, solvent, temperature, reaction time, additives and pressure) were needed to find the optimum. As a result both time and chemicals could be saved.

For substrates with a non-benzylic C–O bond, the hydrogenation and the subsequent acyl migration proceeded smoothly using nickel on alumina in dioxane at 140 °C and 10 bar H_2 with water as an additive. Yields of up to 90% could be obtained, also when the acyl group was varied. In spite of the weak benzylic C–O bond, yields up to 50% could be obtained for this type of substrates using nickel on alumina in dioxane at 120 °C and 20 bar H_2.

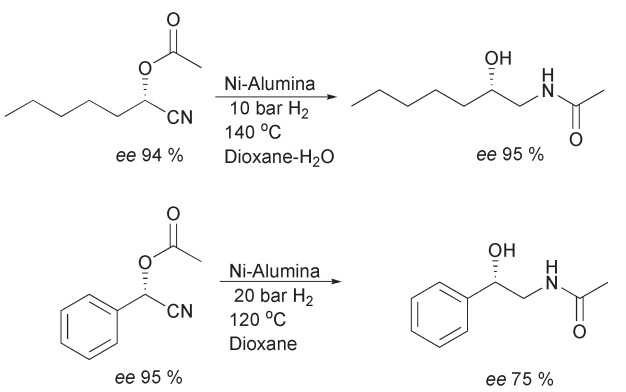
Chiral *N*-acyl β amino alcohols are a highly important group of compounds in organic chemistry. The applications vary from protected chiral building blocks to intermediate in the synthesis in pharmaceuticals such as denopamine.[35] With this objective, the reaction was also performed with chiral substrates (Scheme 8).

We were very pleased to see that the optical purity of the substrate without a benzylic C–O bond could be retained in the product after the cascade reaction. However for the substrate with a benzylic C–O bond, there was a small decrease in the ee during the reaction. This is probably due to racemisation of the substrate caused by the high reaction temperature or by basic side products formed in the reaction.

In short, a novel one step cascade reaction preparing chiral *N*-acyl β amino alcohols from acylated cyanohydrins was developed. A design of experiment strategy proved to be highly efficient in identifying the optimal reaction conditions. Although strictly speaking no catalytic cascade of reactions since only the first step is catalysed, the carrier of the catalyst plays a pivotal role. Out of a range of metal supports that were screened, many did not allow the desired reaction to take place.[36]

5 Conclusions

When we set out to develop the chemistry described above, we focussed on products and catalysts. However, during the course of our investigations it became more and more obvious that a parameter that organic chemists tend to neglect was the unifying factor between the very different reactions we were studying. Carriers and supports of catalysts are normally not



Scheme 8 Catalytic hydrogenation of enantiopure acylated cyanohydrins.

taken into consideration when planning synthetic strategies.[4] Often they are barely mentioned in synthesis.

When developing catalytic cascades, seemingly unimportant parameters become important. Carriers immobilise catalysts and thus allow keeping them separated (Schemes 3–5), avoiding inhibition and deactivation. Moreover, they enable efficient recycling of the often expensive and, in the case of the transition metals, toxic catalysts.

For the DKR the carrier of CAL-B has a very different additional function. The Celite R-633 obviously maintains low water activities in the reaction mixture. Only at such low water activities are efficient lipase-catalysed DKR's possible (Scheme 6, Fig. 1).

Next to these rather unexpected features of the carriers, the carriers can influence the catalyst that is immobilised on them. This is the case for the Ni-catalyst (Schemes 7 and 8). It performs best and most selectively when supported by alumina.

To summarise, carriers enable catalytic cascades, by ensuring compartmentalisation, by controlling the reaction conditions and by fine-tuning the catalyst. They often play a larger role than expected and should be taken into consideration when planning reaction cascades, chemo-enzymatic, enzymatic or purely chemical.

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