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Asymmetric one-pot reactions using heterogeneous chemical catalysis: recent steps towards sustainable processes

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The preparation of optically pure fine chemicals is among the most important and challenging tasks met by organic chemists. Recently, significant efforts have been focused on the development of green and sustainable procedures for the synthesis of these high value-added compounds. Asymmetric heterogeneous catalysis has provided efficient solutions to these challenges. The application of heterogeneous chiral catalysts in one-pot processes combines the advantages of use of these materials with time, material, and energy savings associated with cascade or sequential procedures. This review surveys these asymmetric one-pot reactions reported until July 2017, in which a heterogeneous chemical catalyst has been applied either as a single multifunctional catalyst or in combination with a second catalytically active material. These processes include one-pot procedures catalysed by carefully designed solids obtained by the immobilization of chiral metal complexes, by anchoring chiral organocatalysts, or by modifying catalytic surfaces with optically pure compounds, which may also incorporate uncatalyzed and homogeneously catalysed steps. Methods applying achiral heterogeneous catalysts in combination with soluble chiral chemical catalysts or biocatalysts are also presented. Sophisticated, finely tuned materials have been applied in most of these reactions, which have been discussed along with the main requirements necessary to perform these transformations in a one-pot manner.

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Introduction

Presently, the most important challenge in organic chemistry is to develop procedures having low environmental impact, which are able to produce target compounds in the desired quantities. Recent synthetic procedures have focused on green and sustainable alternatives for synthesizing complex organic compounds by innovative approaches. The widespread application of catalysis by metal complexes over the last few decades, the remarkable development of organocatalysis in this century, the introduction of alternative reaction media (water or supercritical fluids), the utilization of novel activation methods (ultrasound, microwave, and mechano-chemistry), and exploitation of the special properties of materials developed by material scientists (ordered micro- or mesoporous materials, layered materials, inorganic–organic hybrids, nanomaterials, and carbon allotropes, such as nanotubes or graphene) have contributed to the improvement of chemical processes, which tend to satisfy the increasingly strict environmental regulations.[1,2]

Most of the modern methods of preparing organic fine chemicals incorporate catalytic reactions as key synthetic steps. In the last few decades, development of novel catalysts or finding new catalytic applications for materials reported previously attracted significant attention.[3] The trends of replacing the widely applied soluble catalysts with insoluble, heterogeneous materials, were motivated by the simplicity of

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removal, regeneration and reuse of the latter.[4] Nowadays, sustainability is hardly imagined without applying heterogeneous catalysts, which also allow process intensification in flow systems, accompanied by space, time and energy savings.[5,6]

The increased demand for optically pure chiral intermediates of the pharmaceutical industry and the introduction of green and sustainable chemistry concepts in the preparation of high value-added fine chemicals have accelerated the development of asymmetric catalytic procedures.[7–16] Several types of chiral catalysts allowing high stereocontrol have been reported to date. Besides biocatalysts such as enzymes,[8,12] metal complexes bearing chiral ligands and organic molecules used as asymmetric organocatalysts have found numerous applications in organic synthesis. However, in many cases, the cumbersome and costly preparation of these catalysts have motivated studies aimed at preparing similarly efficient and selective heterogeneous catalytically active chiral solids.[17–19]

A simple method for obtaining chiral solid catalysts that were found to be surprisingly efficient in a limited number of reactions, is the surface modification of heterogeneous catalysts such as metals or metal oxides, by optically pure, preferably cheap, natural compounds.[17–24] In the asymmetric hydrogenation of certain unsaturated compounds, exceptionally high enantioselectivities were attained over chirally modified metal catalysts. However, widespread application of these catalysts in the fine chemical industry was hampered by their narrow substrate scope.

Another general approach to preparing chiral, catalytically active solid materials is the immobilization of efficient homogeneous catalysts, whether chiral complexes, organocatalysts or enzymes, on solid support by various methods.[18,19,25–31] The large variety of highly efficient chiral homogeneous catalysts warrants the possibility of developing solid catalysts for numerous applications. Furthermore, the selection of an appropriate anchoring method and choosing supports with special properties designed for specific purposes have often led to enhanced results, as compared to those obtained using the corresponding soluble catalytic species. These types of immobilized chiral catalysts usually possess all the favourable properties of the heterogeneous catalysts. Still, their application is obstructed by their tedious preparation procedures and by preserving some drawbacks of the corresponding homogeneous catalysts, which are often expensive materials; many of them are highly sensitive to manipulations and require high purity reaction components. However, oftentimes by appropriate material design, robust and stable chiral catalysts have been obtained, which allow preserved performances upon recycling, and the possibility of application in flow systems.[32–34]

Further increase in the sustainability of the catalytic reactions may result from carrying out several reactions in a single vessel, without isolation of the intermediate products in a so-called one-pot procedure.[35–38] One-pot reactions that allow two or more bond-forming transformations under the same conditions without intervention and with subsequent transformations occurring at the functionalities resulting from a previous step, are designated domino or cascade reactions.[39,40] Contrary to the stop-and-go methods, during these reactions, all components are introduced from the onset and only the purification of the final product is necessary, as shown in Fig. 1. Difficulties in designing cascade processes are attributable to requirements including the following: all reagents and catalysts needed in different steps must tolerate each other's presence; all reactions must occur under the same conditions; functional groups present in the molecules should participate only in the desired steps. However, due to their operational simplicity and enormous advantages provided by the material, energy, space and time savings, as compared with the classical stop-and-go methods, extensive efforts are devoted to the development of such synthetic procedures.[41–45]

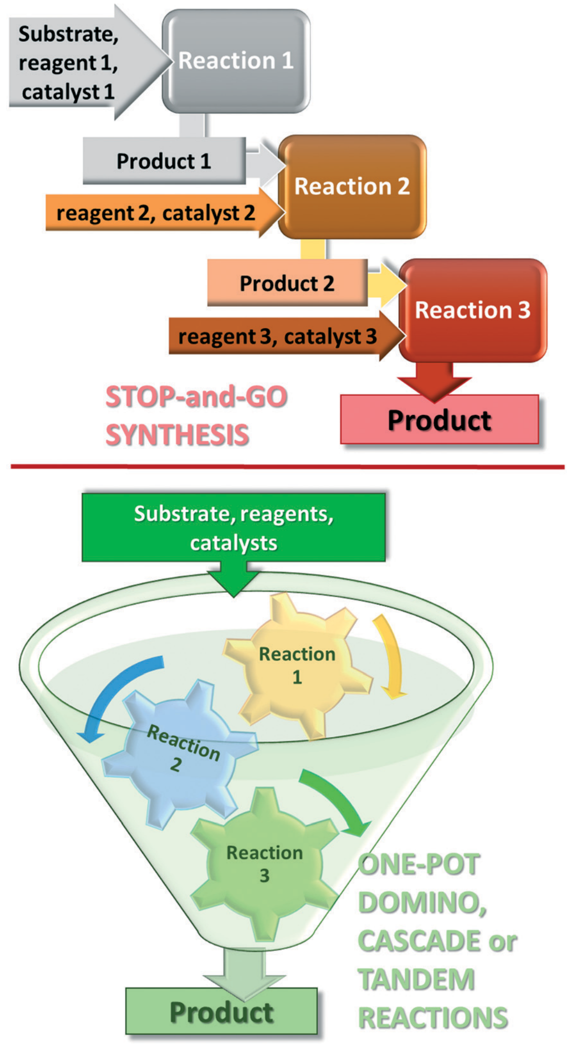


Fig. 1 Schemes of the stop-and-go and one-pot domino, cascade or tandem synthesis procedures.

During the last decade, the availability of a large variety of chiral catalysts[7–19] has been the driving force for the development of asymmetric catalytic one-pot procedures.[46–56] Such reactions could be applied in the synthesis of optically pure building blocks and active pharmaceuticals.[36–39] Enzymes, chiral metal complexes and organocatalysts, either as single catalysts or their various combinations with achiral or a second chiral catalyst, have been used in these reactions, allowing the preparation of complex organic molecules such as natural products and other bioactive compounds by significantly simplified procedures.[57–59]

Although extraordinary complexity may be easily achieved in these reactions, the recovery of the expensive chiral catalysts remain a major task. Accordingly, asymmetric catalytic one-pot reactions using recyclable heterogeneous catalysts have also been investigated. Among these were reactions catalysed by heterogeneous achiral materials in combination with chiral soluble catalysts and procedures in which the stereoselective step itself was promoted by a chiral solid catalyst and was mostly combined with another catalyst or with a spontaneous, uncatalysed reaction step. Nowadays, the number of reported asymmetric heterogeneous catalytic one-pot reactions utilizing chemical catalysis is growing rapidly. However, an overview of these reactions is still lacking. Some of these have been incorporated in monographs or reviews having broader scope, such as asymmetric reactions catalysed by transition-metal functionalized supports, domino or cascade reactions catalysed by heterogeneous catalysts[31,45,60–62] or recently, in surveys covering a narrower area or a different segment of such reactions, *i.e.* processes catalysed by combinations of enzymes and inorganic heterogeneous catalysts, by bio-nanocatalysts, or aminocatalysts combined with metals.[56,63,64]

The aim of the present review is to give a comprehensive survey of the asymmetric one-pot reactions in which heterogeneous chemical catalysts have been applied. Those procedures are included in which in a catalysed step stereoselective formation of at least one new chiral centre occurs. Reactions are classified according to the nature of the chiral catalyst used in the enantioselective step, *i.e.* homogeneous, heterogeneous and biocatalytic. Biocatalysts, especially enzymes, are among the most often used stereoselective catalysts,[8,12,39,65] which have also been applied in asymmetric one-pot processes,[66–68] often in combination with chemical catalysts.[39,63,64,69–71] The scope of the present review is limited to asymmetric one-pot processes utilizing heterogeneous chemical catalysis; accordingly, only those reactions will be included in which biocatalysts are used along with such materials. Dynamic kinetic resolutions (DKR) unite the kinetic resolution (KR) of racemic substrates, often catalysed by enzymes, with racemization of the unreacted enantiomers, and are therefore considered biocatalytic cyclic cascade reactions.[67] Although the racemization step may be carried out using homogeneous or heterogeneous chemical catalysts,[72–82] unless other heterogeneous catalytic steps are included in the process, these will be omitted, as only a part (ideally half) of the chiral compounds are involved in both steps. Procedures utilizing heterogeneous chiral chemical catalysts will be further divided according to the catalyst type, *i.e.* immobilized metal complexes, heterogeneous organocatalysts and chirally modified catalytic surfaces. The reaction pathways making possible these processes will be briefly discussed.

Before reviewing the asymmetric heterogeneous catalytic one-pot transformations, definitions of terms and classification of the one-pot processes is necessary. Without debate, one-pot reactions are defined as processes that allow more than one reaction to occur in a single flask, without isolation of the intermediate products. Introduction of reagents or catalysts between steps, or changes in the reaction conditions, may be necessary during these processes. Domino or cascade reactions are considered one-pot transformations in which all components, such as substrates, reagents, catalysts, auxiliaries, solvents *etc.*, are introduced in the system at the onset and the reaction conditions are not altered during the process. Accordingly, two or more bond forming transformations occur without any intervention.[40] In most of the catalytic cascade reactions reported recently, more than one catalyst or multifunctional catalysts are used. These reactions are defined as tandem catalytic processes: auto-tandem, assisted tandem (when a single catalyst is applied) or orthogonal catalytic processes (using more than one catalysts).[41] According to a different approach, domino or cascade reactions are those one-pot transformations in which the intermediates cannot be isolated and the individual steps cannot be performed separately. One-pot reactions performed sequentially and with intervention between steps were denoted as tandem reactions.[83] However, this latter definition diverges from the most often used terminology. Recently a novel classification of the catalytic one-pot reactions was proposed to suit better discoveries in this field.[84] The so-called tandem reactions were divided into cooperative and relay catalytic processes, whether the catalysts share the same catalytic cycles or not (Fig. 2). Relay catalysis was further divided into self-relay and orthogonal relay reactions, depending on the types and number of catalysts. Unlike sequential catalytic processes during which intervention between steps is necessary, all

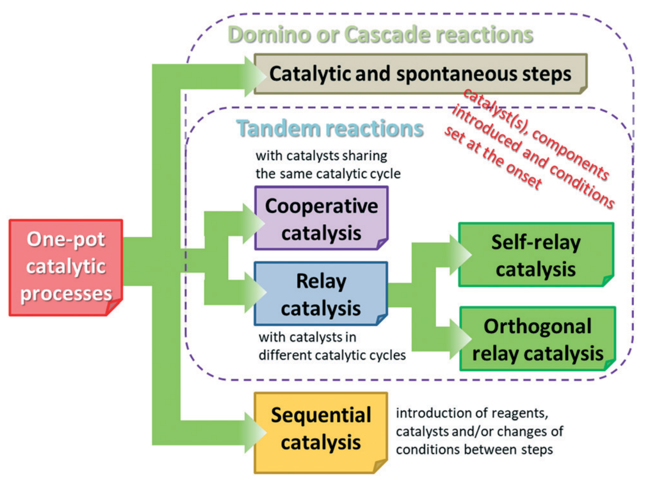


Fig. 2 Scheme of classification of the catalytic one-pot processes.

catalysts are present at the onset of the cooperative and relay catalytic procedures.[84]

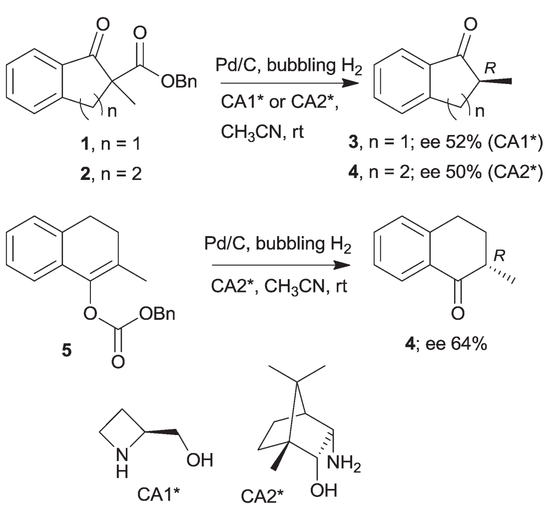
In spite of these classifications and denominations, often the general term "cascade reaction" is used for one-pot catalytic processes. In order to avoid confusion, in this review denominations met in the original reports are used, even if they are not in agreement with the above taxonomies. For clarity, intermediates that could not be or were not isolated are included in square brackets in schemes.

1. Heterogeneous catalytic one-pot reactions including homogeneous asymmetric steps

The last two decades of developments in organic chemistry resulted in the discovery of a large structural variety of highly efficient soluble chiral catalysts. Still, only few asymmetric catalytic one-pot reactions are known, which apply heterogeneous achiral solids combined with chiral soluble catalysts. A possible explanation of the scarcity in reports could be the often observed undesired interaction of the two types of catalysts leading to diminished performances of at least one of the active species, which compromises the formation of the target compounds. Besides, another, more practical reason is that the chiral catalysts are usually the more expensive, which should be recovered; thus the use of an achiral reusable heterogeneous catalysts is less attractive or important, than applying a chiral solid. Consequently, such reactions are by far less studied, as one would expect based on the vast number of efficient chiral homogeneous catalysts.

In their pioneering studies Hénin, Muzart and co-workers, described the hydrogenation of unsaturated benzyl carbonates or benzyl β-keto esters over Pd/C in the presence of chiral amino alcohols, which afforded optically enriched α-substituted ketones (Scheme 1).[85–87] In the early reports, 2-methyl-1-indanone (**3**) and 2-methyl-1-tetralone (**4**) were obtained in up to 52% and 50% enantiomeric excesses (ee) from the corresponding β-keto esters **1** or **2**,[86] whereas the benzyl carbonate **5** gave the optically enriched ketone **4** in 64% ee.[87] Several chiral diamines and amino alcohols were tested,[88,89] and the best results were obtained with (+)-*endo*-2-hydroxy-*endo*-3-aminobornane (Scheme 1, CA2*). Optimization of the reaction conditions using this chiral amine afforded **3** in up to 99% ee in the cascade reaction of **1**.[88] Later, the scope of the reaction was extended to various α-substituted-β-keto esters and enol carbonates. Representative substrate structures along with the best results obtained are summarized in Fig. 3.[88–95] In most of these reactions, high yields were reached accompanied by good ees (70 ± 5%). Prominent ee was reported only in the reaction of **1**.[88] It is noteworthy that with alterations in the structure of the substrate, the most efficient chiral amino alcohol was also varied, and thus in some reactions cinchona alkaloids CA4* or CA5* outperformed CA2* with respect to the attained ee. Therefore, the most efficient chiral base is also given next to the results (Fig. 3).

The heterogeneous Pd catalyst initiates the above cascade reactions through hydrogenolysis of the benzyl esters or carbonates. This step is followed by decarboxylation and



Scheme 1 Enantioselective cascade reactions of β-keto esters or benzyl carbonates initiated by Pd/C leading to optically enriched 2-alkyl ketones; Bn: benzyl.[85–88]

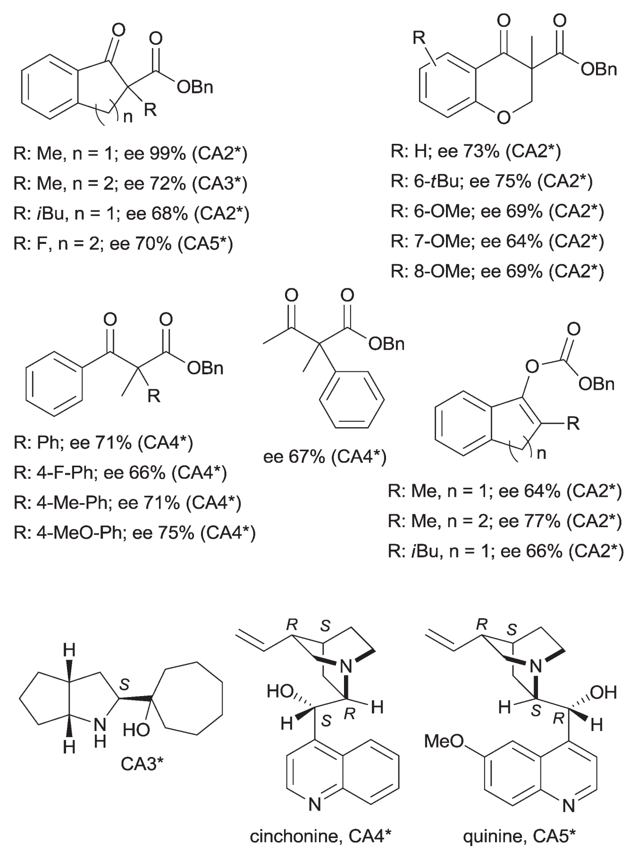
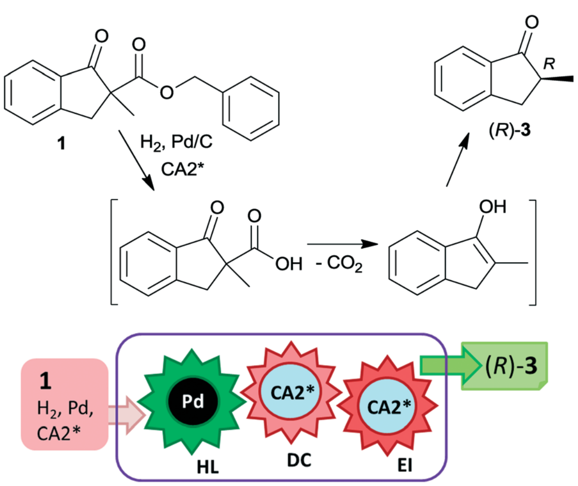


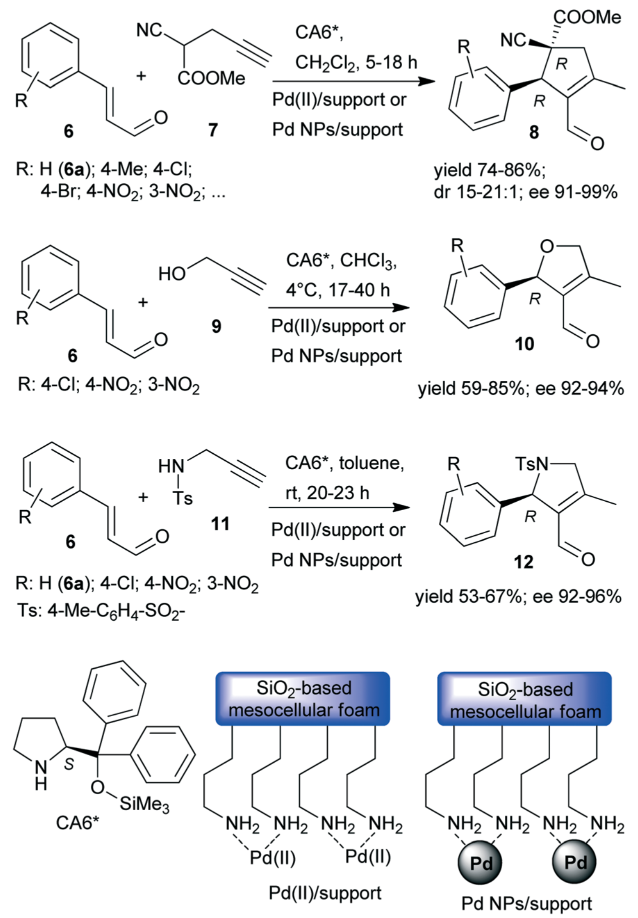
Fig. 3 Structure of benzyl β-keto esters and benzyl carbonates transformed in the Pd initiated heterogeneous enantioselective cascade reaction to α-substituted ketones and chiral amino alcohols used in these reactions.[88–93]

enantioselective protonation, with both steps possibly assisted by the chiral amine. Thus, the first step of the cascade takes place on the Pd surface, leading to the formation of the corresponding β-keto acids as was indicated by UV spectroscopy.[94] For a long time, it was uncertain whether the second and third steps occur in solution as organocatalysed processes or as a surface reaction over the Pd catalyst modified by the chiral amine.[22] Later, based on results obtained using cinchona alkaloids and other chiral amino alcohols of different adsorption strengths, it was suggested that the decarboxylation is catalysed by the chiral base in solution, followed by the stereoselective protonation also directed by the amino alcohol.[95] Kinetic studies of decarboxylation by NMR, IR and UV spectroscopy using cinchona alkaloids confirmed that following hydrogenolysis the dominant reaction route was catalysed by the chiral compound in the liquid phase as a homogeneous asymmetric organocatalytic reaction (Scheme 2).[96]

Recently, asymmetric cascade reactions using combinations of a soluble chiral organocatalyst and supported Pd catalysts were developed for the preparation of chiral five membered unsaturated cyclic compounds.[97] Good yields and high stereoselectivities were obtained in reactions of cinnamaldehyde derivatives (**6**) with propargylic C-, O- or N-nucleophiles (**7**, **9**, **11**), leading to the formation of cyclopentene, dihydrofuran or pyrroline derivatives (Scheme 3). Combinations of two catalysts were used in these reactions. One is a soluble pyrrolidine derivative chiral organocatalyst (CA6*) reported initially by Jørgensen and co-workers[98] and Hayashi and co-authors,[99] efficient in several organocatalysed reactions, including cascade reactions.[100–103] The second achiral heterogeneous catalyst was home-made, with either Pd(II) or Pd(0) nanoparticles (NPs) anchored on aminopropyl-functionalized silica-based mesocellular foam (the latter material being prepared by mild reduction of the former). Interestingly, the Pd NPs/support usually provided slightly better diastereomeric ratio (dr) and ee than the immobilized Pd complex Pd(II)/support. By recycling of the immobilized Pd(II) catalyst, improved activity and stereoselectivity were obtained, as a consequence of the adsorption of CA6* on the solid material, which increased the organocatalyst amount in the successive runs (additionally to the freshly added amount).



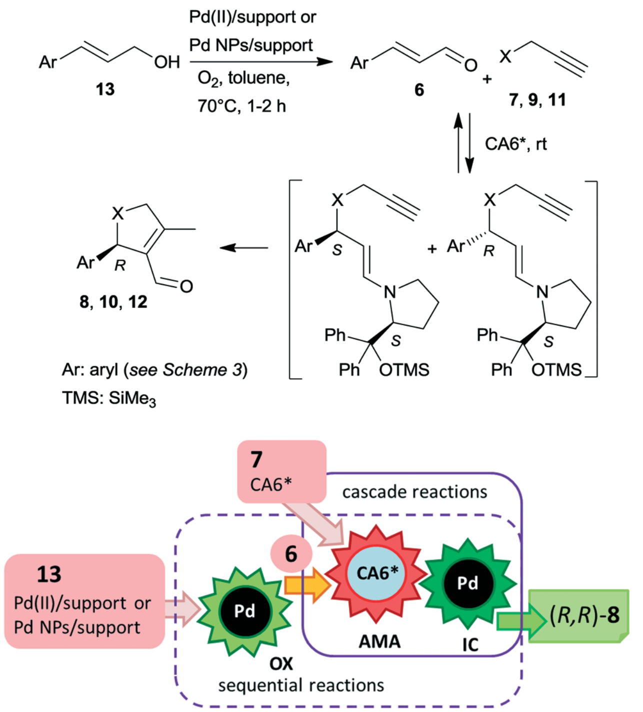
Scheme 2 Asymmetric catalytic cascade transformation of **1** using heterogeneous Pd catalyst and chiral amine organocatalyst; HL: hydrogenolysis, DC: decarboxylation and EI: enantioselective isomerization; the catalysts that promote the steps are given in the circles.



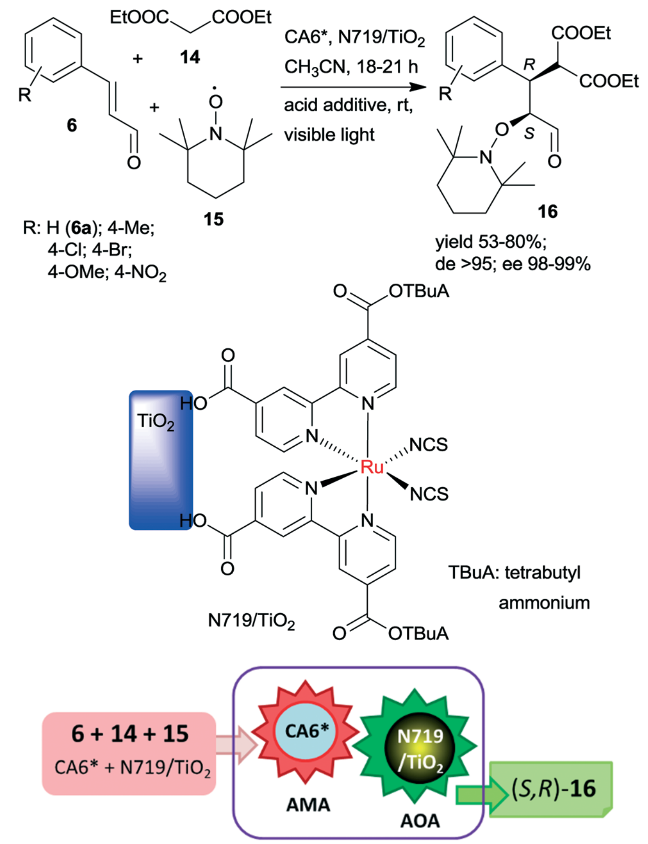
Scheme 3 Asymmetric cascade reactions of unsaturated aldehydes and nucleophiles bearing the propargylic group, catalysed by chiral amine and heterogeneous Pd catalysts.[97]

The cascade reaction included a homogeneous enantioselective organocatalysed Michael addition and a supported Pd(II) or Pd(0) NPs catalysed intramolecular carbocyclization, as shown in Scheme 4. The authors demonstrated that the second cyclization step proceeds *via* a heterogeneous pathway. Accordingly, the reaction is a heterogeneous variant of the earlier reported homogeneous one-pot dynamic kinetic asymmetric transformation.[104,105] The initial amine-catalysed reversible asymmetric Michael addition is followed by Pd catalysed intramolecular stereoselective irreversible cyclization of the two diastereomeric enamine intermediates. The different cyclization rates of the stereoisomers determined the stereochemical course of the reaction.

The scope of the above reaction was also extended to the preparation of saturated carbocyclic compounds by the



Scheme 4 Mechanism of the asymmetric cascade reaction of unsaturated aldehydes and alkyne nucleophiles using chiral organocatalyst CA6* and Pd catalyst coupled with sequential preparation of the aldehydes by oxidation (OX); AMA: asymmetric Michael addition, IC: intramolecular cyclization.



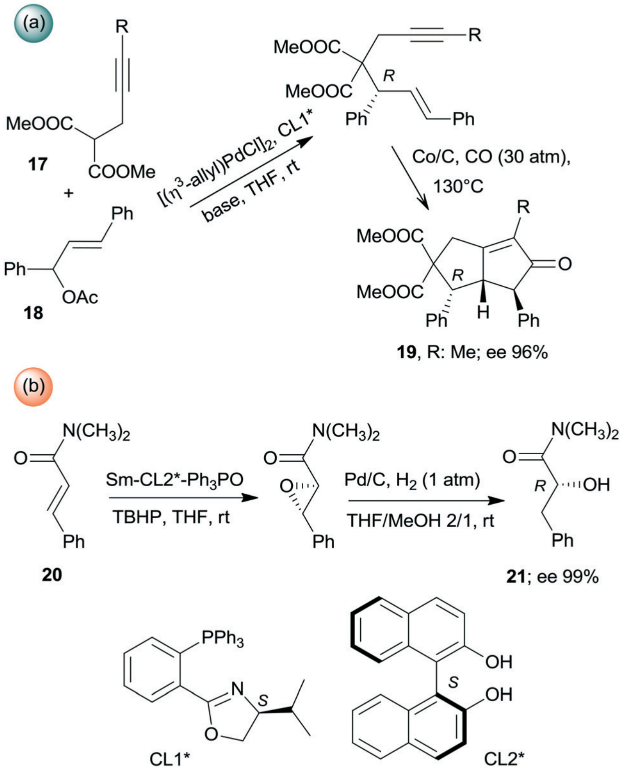
Scheme 5 Asymmetric tandem AMA and asymmetric oxamination (AOA) of unsaturated aldehydes using CA6* and heterogeneous photocatalyst N719/TiO_2.[112]

reaction of olefin nucleophiles containing leaving groups in allylic position.[106] Later, the cascade reaction was complemented by the *in situ* preparation of the α,β-unsaturated aldehyde in a one-pot manner by oxidation of the corresponding allylic alcohols (**13**) with O_2.[107–109] Although the supported Pd catalysed both the oxidation and the final carbocyclization steps, the reaction temperature was modified and **7** and CA6* was introduced following the oxidation of the allylic alcohol, leading to sequential one-pot reactions coupled with the above cascade process, as illustrated in Scheme 4. Heterogeneous catalysts prepared by immobilization of Pd(II) species over polyimine or azolinked porous polymer supports were also successfully used.[110,111]

The same chiral organocatalyst (CA6*) was also applied in the tandem asymmetric Michael addition, followed by the asymmetric photocatalytic oxamination process. In the latter visible light-induced step, a heterogeneous TiO_2-bound Ru photocatalyst (N719/TiO_2) was employed in order to increase the catalytic activity of the photoredox material.[112] By this unprecedented tandem iminium/heterogeneous photoinduced catalytic reaction, α,β-substituted aldehydes (**16**) were obtained in reactions of aromatic unsaturated aldehydes **6**, diethyl malonate (**14**) and 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (**15**) in good yields, high diastereomeric excesses (de) and excellent ees, as shown in Scheme 5. Recycling of the solid photocatalyst resulted in a gradual decrease in the yield of **16**. The role of the heterogeneous photocatalyst in this process was to generate the radical cation from the enamine of the Michael adduct, which reacts with **15** in the second step.

Besides the above cascade reactions, sequential one-pot transformations using combinations of homogeneous chiral and heterogeneous achiral chemical catalysts have also been described. Asymmetric allylic alkylation and the Pauson–Khand reaction sequence was catalysed by the successive addition of the homogeneous Pd complex formed with the chiral ligand CL1* and the Co/C heterogeneous catalyst (Scheme 6a). The second step of this one-pot reaction also required changes in the conditions, such as increase of the temperature and introduction of CO. Interestingly, the use of $Co_2(CO)_8$ for catalysing the second step was inefficient.[113] Similarly, during the one-pot asymmetric epoxidation followed by reductive ring opening of α,β-unsaturated amides (**20**), catalysed by chiral Sm-(*S*)-BINOL–$Ph_3P{=}O$ complex (BINOL: 1,1′-bi-2-naphthol) and Pd/C catalyst, the addition of the latter catalyst and introduction of H_2 and MeOH were necessary between the two steps (Scheme 6b).[114]

Interestingly, until now only the above discussed heterogeneous asymmetric catalytic cascade or sequential one-pot reactions have been reported with the stereoselective steps catalysed by soluble chiral catalysts. The most important advantage of using the heterogeneous catalysts, *i.e.* their easy



Scheme 6 Asymmetric one-pot sequential processes using achiral heterogeneous and soluble chiral catalysts.[113,114]

separation from the product, was the main reason for developing these systems. In one-pot reactions including the reductive step application of heterogeneous catalysts such as supported Pd was a convenient choice; thus, comparison with homogeneous catalysts was omitted. Still, the rarity of these one-pot reactions may be due to more efforts being dedicated to the recycling of the chiral catalysts and less elegance of methods in which a chiral catalyst is sacrificed, whereas the achiral heterogeneous catalyst, even if is a noble metal, is recovered and reused.

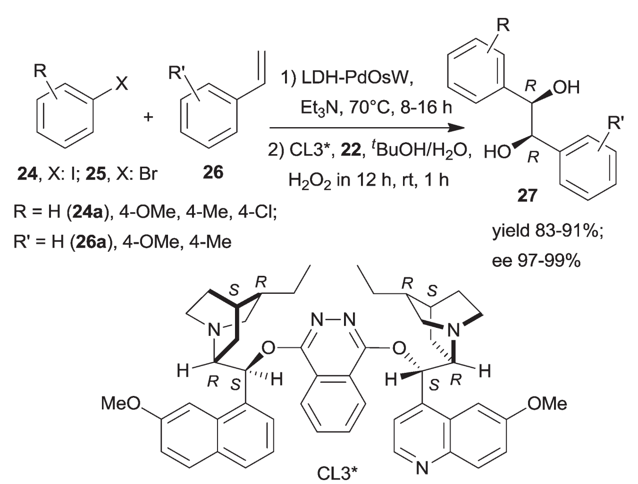
2. One-pot reactions including a heterogeneous catalytic asymmetric step

In contrast to the above reactions, much effort has been devoted lately to developing efficient one-pot processes using heterogeneous chiral catalysts. Chiral modification of catalytic solid surfaces would be the simplest approach to preparing such catalysts, however, the limited applicability of such systems has directed the attention of the researchers to using more arduously prepared homogeneous chiral catalysts anchored on solid supports. The latter, due to the large variety of available soluble chiral catalysts, solid supports and immobilization methods, may warrant efficient solutions to many challenges. However, the undesired interactions of reagents, catalysts needed in different steps and the often-necessary changes in reaction conditions have many times resulted in the development of sequential one-pot catalytic methods.

2.1. One-pot reactions with asymmetric steps catalysed by anchored chiral metal complexes

Widespread application of metal complexes formed with chiral ligands in asymmetric catalytic processes have made their immobilization over insoluble supports an attractive way to obtain efficient heterogeneous enantioselective catalysts.[26–29,31] However, in most instances, following immobilization, many of the unfavourable properties of the parent complexes were kept. Most importantly, their sensitivity to the impurities of the reactants and solvents and to the presence of other reagents and catalysts was the main obstacle to their application in one-pot reactions. Accordingly, only a few one-pot catalytic processes were reported using surface bonded chiral metal complexes, and part of these were applied in sequential procedures. With few exceptions, these materials were prepared by covalent bonding of the chiral ligand to insoluble supports followed by *ex* or *in situ* preparation of the anchored chiral complex employing an appropriate metal precursor.

2.1.1. Cascade reactions employing immobilized metal complexes. Choudary and co-workers reported the development of a trifunctional heterogeneous catalyst used in the Heck reaction and asymmetric dihydroxylation sequence.[115] $PdCl_4^{2-}$, OsO_4^{2-} and WO_4^{2-} were simultaneously exchanged in a layered double-hydroxide (LDH) anion-exchanger to obtain LDH-PdOsW catalyst, which allowed the use of H_2O_2 as the terminal oxidant. This catalyst also promoted the tandem oxidation of *N*-methylmorpholine (22) to the actual oxidant *N*-methylmorpholine *N*-oxide (23), which was consumed in the dihydroxylation of the olefin catalysed by the *in situ* formed chiral surface Os-complex (Scheme 7). The quinidine derived chiral ligand (CL3*), previously used in homogeneous dihydroxylations,[116,117] afforded vicinal diols in high yields



Scheme 7 Heterogeneous sequential Heck reaction and asymmetric dihydroxylation coupled with tandem generation and consumption of the oxidant.[115]

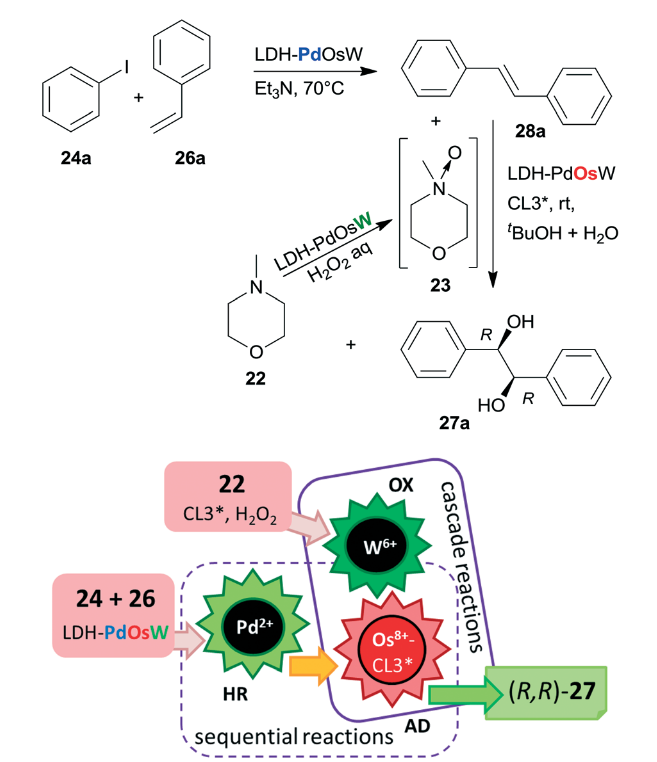
and excellent optical purities. Exceptionally, all catalytic species needed in both the sequential and the tandem catalytic transformations were immobilized on a single solid support. The catalyst could be reused five times efficiently, though the addition of chiral ligand during each run was necessary. It was suggested that the Os and W remained bonded to the support throughout the reaction, whereas Pd leached into solution and was redeposited on the LDH at the end of the process.[115]

Substituents on both the aryl halide **24** or **25** and the olefin **26** had only limited influence on results; moreover, acrylic esters also afforded optically pure diols. Steps of the reaction are illustrated in Scheme 8. The catalytic system was applied for the preparation of the dithiazem intermediate ethyl (2*R*,3*S*)-2,3-dihydroxy-3-(4-methoxyphenyl)propionate.[118] Other supports, such as nanocrystalline MgO or a quaternary ammonium cation functionalized resin were also successfully applied for preparing bifunctional catalysts, such as MgO–OsW, resin–OsW and MgO–PdOs, resin–PdOs. The former two were used in the oxidation-asymmetric dihydroxylation tandem process, whereas the latter two in the Heck reaction-asymmetric dihydroxylation sequence in combination with **23** or $K_3Fe(CN)_6$ co-oxidants used in over stoichiometric amounts.[119,120]

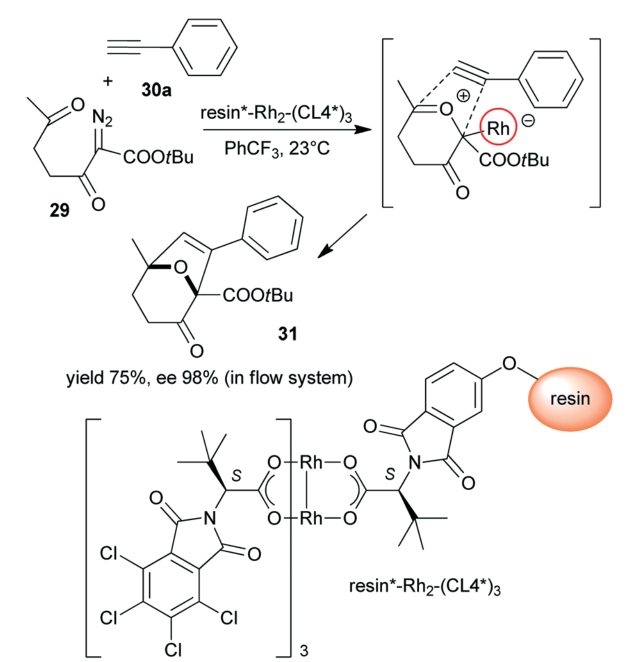
The same authors immobilized the ligand CL3* on SiO_2 surface by $-O_n(OMe)_mSi-(CH_2)_3-S-$ linker and used the chiral solid for the *in situ* preparation of the SiO_2–CL3*–OsO_4 complex. This material was efficient in the asymmetric dihydroxylation of olefins in a relay catalytic process, in which H_2O_2 was used as the terminal oxidant, and the oxidation of **22** to **23** was assisted by titanium silicalite heterogeneous catalyst.[121] Furthermore, deposition of $PdCl_2$ on unreacted $O_nSi-(CH_2)_3-SH$ surface groups of the functionalized support and reduction of the metal ions led to a catalyst containing both the anchored chiral ligand and Pd NPs. The material was used in the one-pot Heck reaction followed by the asymmetric dihydroxylation sequential process.[122]

Polymer supported chiral dirhodium(II)-complex [resin*–Rh_2–$(CL4*)_3$] was prepared from tetrakis[*N*-tetrachlorophthaloyl-(*S*)-*tert*-leucinate and *N*-phthaloyl-(*S*)-*tert*-leucine functional groups containing monomer copolymerized with achiral monomers (Scheme 9).[123] This heterogeneous Rh complex provided similar results to its soluble dirhodium counterpart in the tandem carbonyl ylide formation and intramolecular cycloaddition reaction of 2-diazo-3,6-diketo esters (**29**) with **26a** or phenylacetylene (**30a**). The reactions were highly stereocontrolled, both in batch and in flow systems.

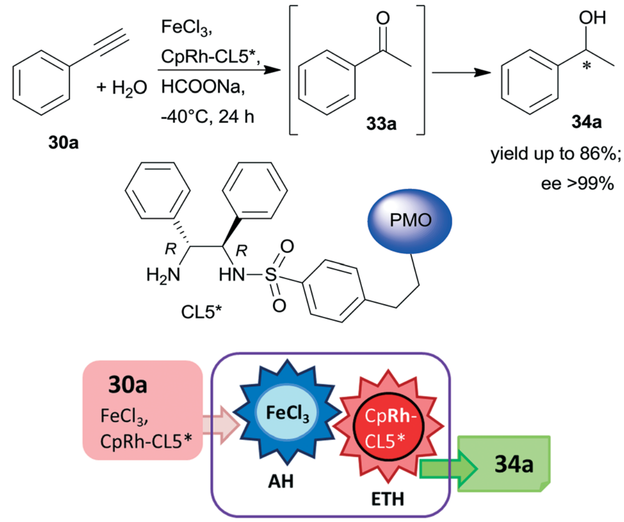
Periodic mesoporous organosilica (PMO) functionalized with (*R*,*R*)-1,2-diphenyl-1,2-ethylenediamine (*R*,*R*-**32**) through sulphonamide linker (CL5*) was used as a chiral insoluble ligand to immobilize a Rh complex formed from $(CpRhCl_2)_2$ precursor (Cp: pentamethylcyclopentadiene). This heterogeneous catalyst in combination with $FeCl_3$ catalysed the hydration of **30a** and the enantioselective transfer hydrogenation of the intermediate acetophenone (**33a**) in a cascade reaction providing similar results to the corresponding homogeneous Rh complex (Scheme 10).[124] The heterogeneous chiral



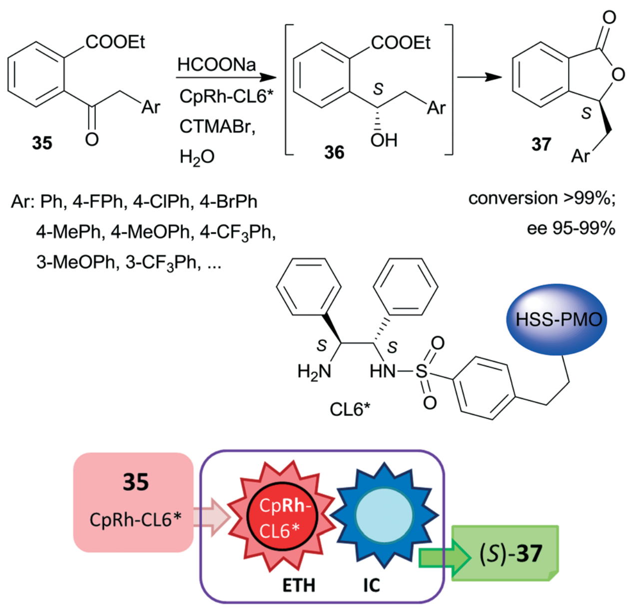
Scheme 8 Heck reaction and asymmetric dihydroxylation using **23**, obtained *in situ* from **22** over a trifunctional catalyst containing immobilized Os–CL3* chiral complex; HR: Heck reaction, AD: asymmetric dihydroxylation.



Scheme 9 Heterogeneous tandem carbonyl ylide formation and cycloaddition reactions using immobilized dirhodium complex bearing *tert*-leucine derived chiral ligand.[123]



Scheme 10 Preparation of chiral alcohol **34a** from **30a** by a heterogeneous catalytic cascade reaction using $FeCl_3$ and chiral Rh complex catalyst immobilized on PMO; AH: alkyne hydration, ETH: enantioselective transfer hydrogenation.[124]



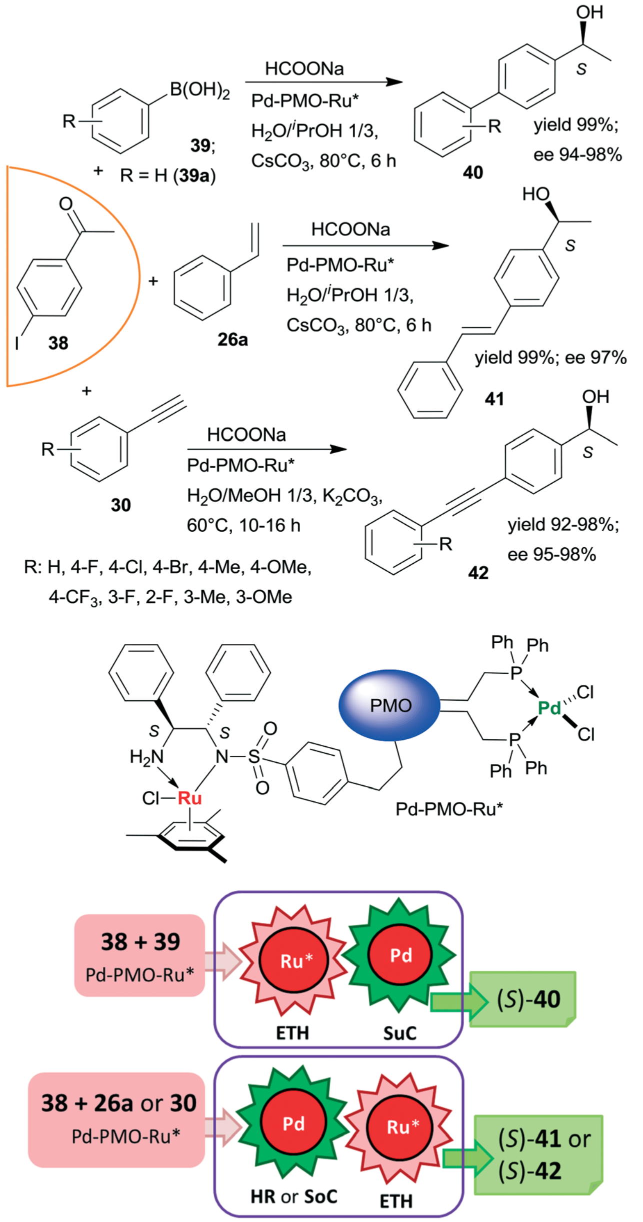
Scheme 11 Heterogeneous catalytic preparation of phthalides by tandem ETH and spontaneous intramolecular cyclization (IC) using HSS-PMO immobilized chiral Rh complex; CTMABr: cetyltrimethylammonium bromide.[125]

catalyst was recycled four times without significant loss in the activity or enantioselectivity.

Liu and co-workers, prepared hollow-shell-structured (HSS) PMO nanospheres-bonded *S*,*S*-**32** heterogeneous chiral ligand (CL6*), which was used for immobilization of Rh, Ir or Ru complexes.[125] These materials were applied as catalysts in the tandem enantioselective transfer hydrogenation and lactonization of 2-acylarylcarboxylates **35** to chiral phthalides **37** using HCOONa hydrogen donor and water as solvent. The best results were obtained with the immobilized Rh catalyst (Scheme 11). During this process, the heterogeneous catalytic asymmetric transfer hydrogenation step preceded the intramolecular spontaneous cyclization of the reduced chiral intermediates **36**. Remarkably, the solid catalyst was more active and enantioselective, than the corresponding soluble CpRh-*S*,*S*-Ts-**32** complex (Ts: *para*-toluenesulfonyl), which was explained by the high hydrophobicity of the hollow-shell-structured nanospheres and the increased activity of the confined, uniformly dispersed chiral Rh species. Similarly high enantioselectivities were obtained in this tandem reaction by using a silica-supported catalyst prepared by sequential grafting of *S*,*S*-**32** through benzenesulfonamide linker and acrylamide-acrylonitrile copolymer on SiO_2 NPs, followed by complexation using $(CpRhCl_2)_2$ precursor. The resulting surface-bonded thermoresponsive polymer formed a closed shell, which locked the catalytically active sites at low temperature (15 °C), whereas at 40 °C the polymer turned into an extended form, making the chiral complex accessible.[126] The above two heterogeneous catalysts were recycled without decrease in activity or enantioselectivity after 10 and 8 uses, respectively.

Heterogeneous bifunctional PMO-supported catalysts were obtained by co-condensation of appropriately functionalized Pd and Ru complexes and were used in tandem catalytic processes, such as in ETH-Suzuki coupling, in Heck reaction-ETH or in Sonogashira coupling-ETH transformations (Scheme 12).[127,128] The order of the steps in these one-pot cascade reactions was deduced based on the product distribution determined during the transformations, or in the case of the Heck reaction based on the enantiomeric ratios obtained with three iodine substituted acetophenone derivatives. All these processes afforded the corresponding chiral alcohols (**40**, **41**, **42**) in high yields and excellent enantioselectivities; moreover, the catalyst used in the ETH-Suzuki coupling kept its efficiency following 8 runs.[127] The excellent performances of these catalysts were attributed to the presence of site-isolated, uniformly distributed Pd and Ru catalytic species within a single mesoporous support.

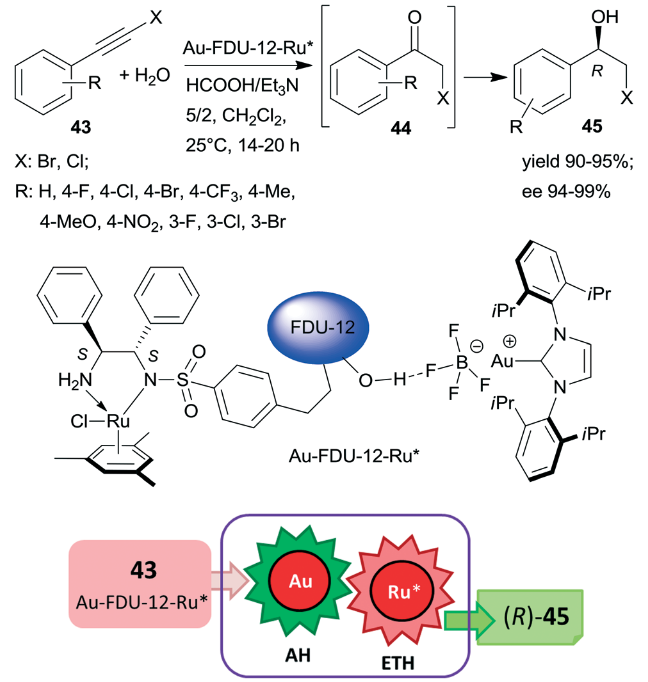
Large-pore mesoporous silica (FDU-12) was recently used as support for preparing chiral Ru and Au-carbene complexes containing bifunctional heterogeneous catalyst (Scheme 13). Initially, the chiral ligand functionalized mesoporous silica was synthetized using the appropriate *S*,*S*-**32** derivative, which by complexation with $(MesRuCl_2)_2$ (Mes: mesitylene) provided the anchored chiral Ru complex. Hydrogen bonding of Au(carbene)BF_4 complex to the silanol groups of this material resulted in the bifunctional catalyst Au-FDU-12-Ru*, which was highly efficient in the tandem AH-ETH process of haloalkynes **43** to chiral halohydrins **45** through haloketone intermediates **44**.[129] The high yields and enantioselectivities attained using a series of both bromo- and chloroalkynes proved the wide applicability of this catalytic material, which was reused several times without significant loss in its performance. Mass transport limitations were prevented by using mesoporous material with large pore size, as indicated by similar results obtained with this material as compared with



Scheme 12 Bimetallic catalyst promoted tandem **ETH** – C–C coupling reactions of iodine substituted acetophenone **38**; SuC: Suzuki coupling, SoC: Sonogashira coupling.[127,128]

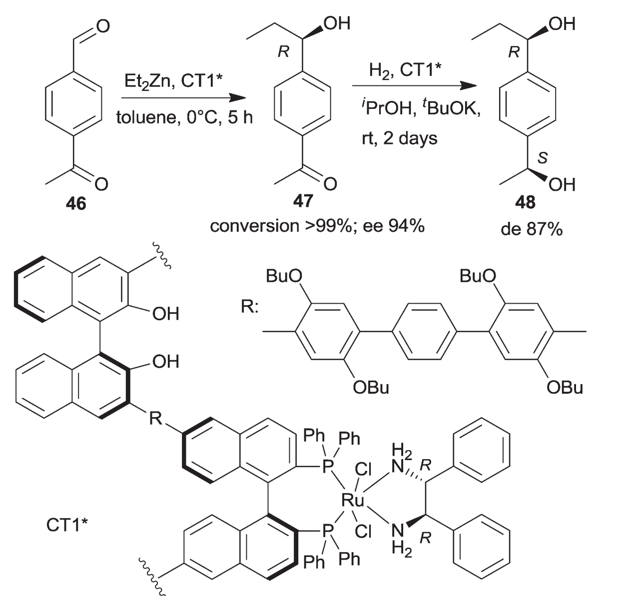
homogeneous counterparts applied as dual catalysts. Besides the uniformly distributed two metal complexes, the assistance of the surface silanol-functionalities also contributed to promoting this tandem reaction.[129]

2.1.2. Sequential one-pot reactions employing immobilized metal complexes. Besides the above presented cascade catalytic reactions using heterogeneous metal complexes, sequential one-pot asymmetric reactions promoted by these types of catalysts were also developed. An *R*-BINOL and *R*-BINAP (BINAP: 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) copolymer was used to immobilize the Ru-*R*,*R*-**32** complex (chiral catalyst CT1*, Scheme 14). This bifunctional material was efficient in the one-pot transformation of aromatic keto

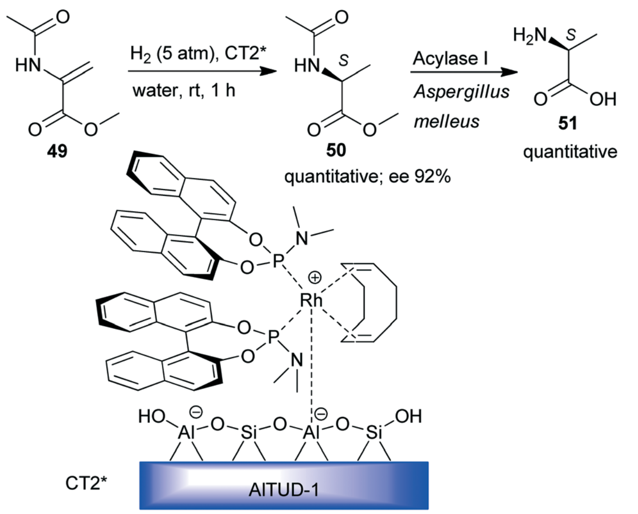


Scheme 13 Preparation of chiral halohydrins **45** from haloalkynes **43** by tandem catalysis using large-pore mesoporous silica (FDU-12) immobilized Au-carbene and chiral Ru complexes.[129]

aldehydes **46** to chiral diols **48** by sequential enantioselective Et_2Zn addition to the aldehyde functional group resulting in keto alcohol **47** followed by stereoselective hydrogenation of this intermediate. The BINOL units catalysed the first step of the sequence, whereas Ru-*R*,*R*-**32** complexed to the BINAP units catalysed the second step.[130]



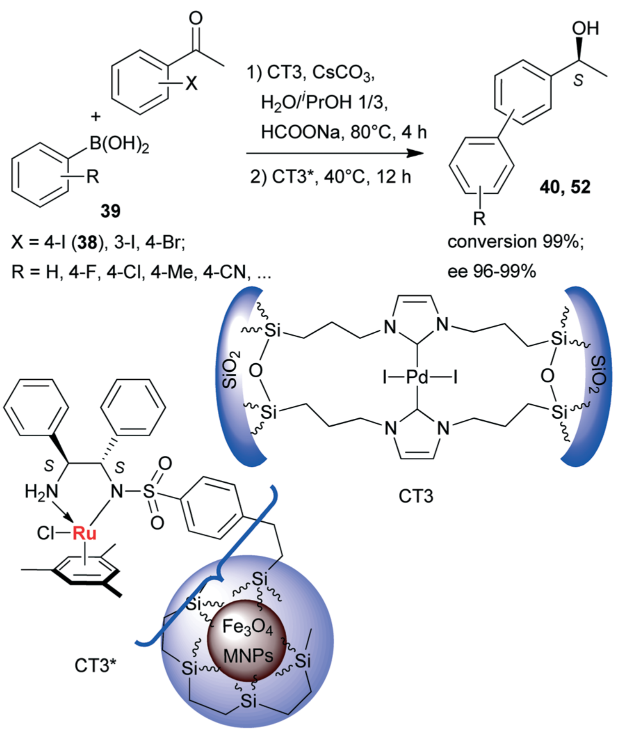
Scheme 14 Sequential enantioselective Et_2Zn addition – enantioselective hydrogenation by a chiral copolymer immobilized *R*,*R*-**32**-Ru-complex.[130]



Scheme 15 Sequential enantioselective hydrogenation – enzymatic hydrolysis using a chiral Rh complex anchored by ion-exchange on mesoporous aluminosilicate.[131]

Hydrogenation was the enantioselective step in a one-pot sequential preparation of L-alanine (**51**) starting from *N*-acetyl-dehydroalanine methyl ester **49** (Scheme 15).[131] A previously developed heterogeneous chiral Rh-(*S*)-BINOL complex immobilized by simple ion-exchange on mesoporous Brønsted acidic aluminosilicate (CT2*)[132,133] was used in the enantioselective hydrogenation of **49** to **50** under mild conditions and in water as the sole solvent. Thus, the enzymatic hydrolysis of the acetamido and ester groups could be carried out sequentially by the addition of an appropriate biocatalyst.

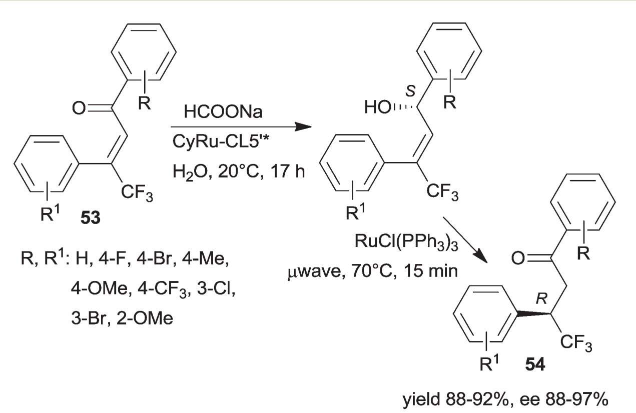
Sequential Suzuki couplings and enantioselective transfer hydrogenations were carried out by Liu and co-workers using a combination of two heterogeneous catalysts, one containing Pd immobilized on organic–inorganic hybrid silica (CT3), and the other carrying chiral Ru complexes formed within ethylene-coated Fe_3O_4 magnetic nanoparticles (MNPs) using surface bonded benzenesulfonamido-*S*,*S*-**32** as chiral ligand (CT3*).[134] The solvent, reactants and additives needed in both steps were introduced at the onset of the reactions, however, CT3* was added following the first step, when the reaction temperature was also decreased (Scheme 16). Close to complete conversion to biarylalcohols (**40**, **52**) and high ees were obtained using various halogenated acetophenones (**38**, and others) and arylboronic acids (**39**). The scope of this system was evidenced using other iodo- and bromo-arylketones, acetylboronic acids and their application in HR-ETR sequences. The MNPs eased the separation of the two heterogeneous catalysts; CT3 could be recovered by centrifugation following removal of CT3* by an external magnet. The catalysts maintained their activity even in their ninth use.



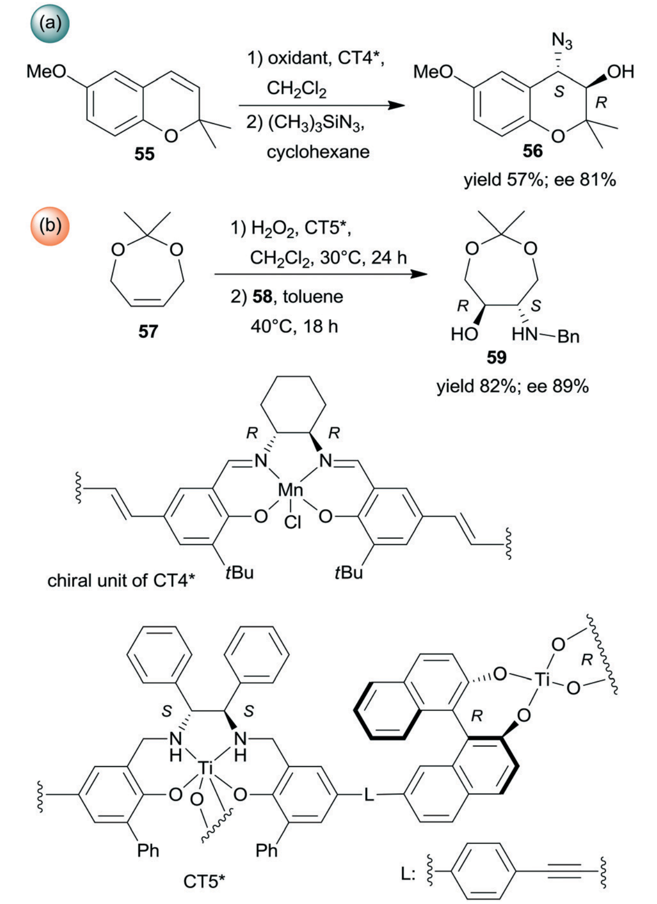
Scheme 16 Sequential SuC–ETH reactions catalysed by two heterogeneous catalysts containing anchored Pd and chiral Ru complexes.[134]

The same research group prepared a catalyst using CL5*-like PMO-supported ligand (CL5'*) and $(CyRuCl_2)_2$ precursor (Cy: *para*-cymene). This material was used in the sequential enantioselective transfer hydrogenation of β-trifluoromethyl-α,β-unsaturated ketones **53** in water at room temperature and isomerization catalysed by $RuCl(PPh_3)_3$ at 70 °C by microwave irradiation.[135] Several unsaturated ketones were transformed, obtaining the corresponding ketones **54** in high yields and excellent enantioselectivities (Scheme 17). The stability of the chiral heterogeneous catalyst was examined only in the ETH reaction, *i.e.* the first step of the sequence, thus, it is unknown whether following the second step, which was carried out under harsher conditions, the surface chiral sites were still preserved.

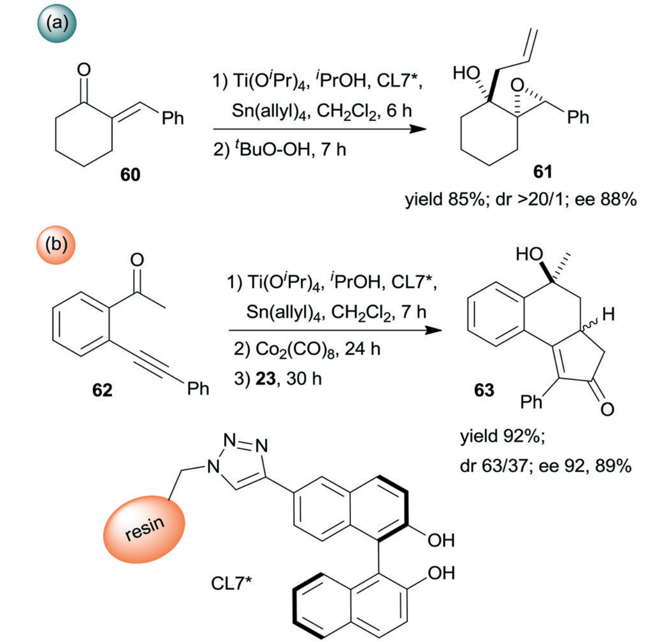
Sequential epoxidations of olefins followed by asymmetric opening of the rings using heterogenized chiral complexes were also developed. A metal–organic framework (MOF)



Scheme 17 Enantioselective preparation of β-trifluoromethyl ketones by sequential heterogeneous ETH and homogeneous catalytic asymmetric isomerization (AI).[135]



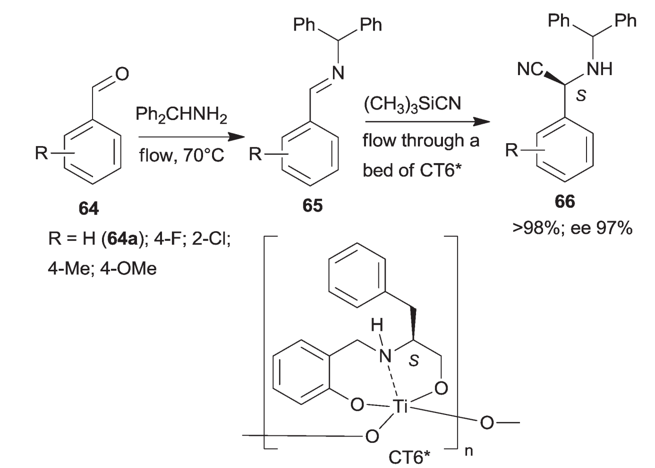
Scheme 18 Sequential processes combining asymmetric epoxidation and ring opening (a) or epoxidation and stereoselective ring opening (b).[136,137]



Scheme 19 Enantioselective allylation and epoxidation (a) and allylation and Pauson–Khand sequential reactions (b) using *in situ* formed resin immobilized titanium *R*-BINOLate complex.[138]

containing chiral Mn-Salen units (CT4*) was efficient in the preparation of α-hydroxyazide **56** from the unsaturated cyclic compound **55** (Scheme 18a). The asymmetric epoxidation catalysed by the chiral Mn unit was followed by ring opening catalysed by the Zn species found in the secondary building unit of the MOF, with preservation of the molecule chirality.[136] Chiral titanium metal–organic assemblies were prepared from BINOL/Salalen or BINOL/Salan heteroditopic ligands. These materials were used in the sequential epoxidation of a cyclic olefin **57** with H_2O_2, followed by the stereoselective ring-opening of the resulting *meso*-epoxide to hydroxylamine **59** using benzylamine (**58**) (Scheme 18b).[137] Among the most efficient chiral solids was the salan derived material CT5* shown in Scheme 18. Remarkably, in the latter reaction the use of the corresponding homogeneous catalysts either in a one-pot process or in a step-wise manner did not result in product formation or provide lower yield and enantioselectivity.[137]

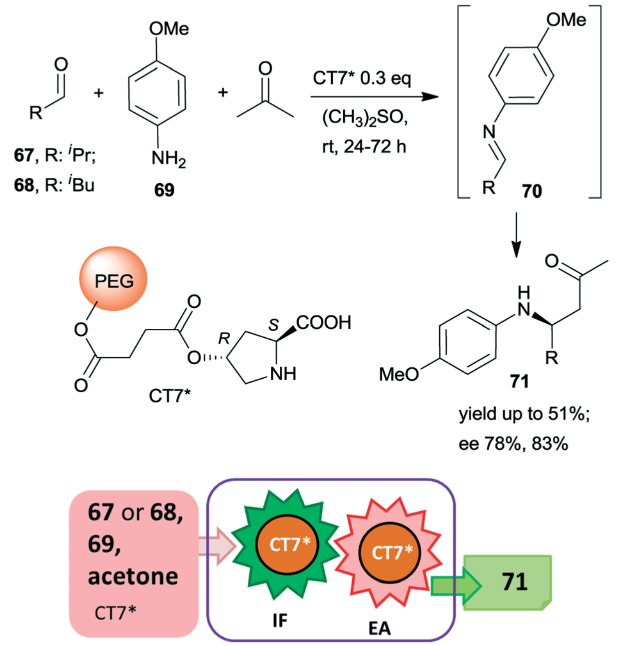
Epoxidation was the second step of a sequence initiated by asymmetric allylation of the unsaturated cyclic ketone **60** with *in situ* formed resin-supported titanium-*R*-BINOL complex using the anchored chiral ligand CL7* (Scheme 19a).[138] The same catalyst was also used in a one-pot sequential asymmetric allylation and enantioselective intramolecular Pauson–Khand reaction (Scheme 19b).[138] Recycling of the chiral solid catalyst following the first asymmetric allylation step required remetallation of the anchored ligand with $Ti(O^iPr)_4$, due to leaching of the titanium from the resin. Self-supported chiral titanium clusters were obtained by hydrolysis of chiral amino alcohol titanate complexes (CT6*, Scheme 20).[139] These materials were efficient in the preparation of α-aminonitriles (**66**) from benzaldehyde derivatives **64** by sequential imine formation with benzhydrylamine followed by asymmetric cyanation in a flow system. Recycling of the catalyst was examined in the cyanation of the **64a**



Scheme 20 Sequential imine formation and asymmetric cyanation catalysed by self-supported chiral titanium cluster CT6*.[139]

derived imine. The material kept its activity even in the 10th run, and the ee value remained constantly high.[139]

As the above presented examples showed, heterogenized chiral metal complexes proved their utility in asymmetric one-pot sequential and cascade reactions. Special care is required in designing such systems, due to possible deterioration of the catalytically active chiral sites of the heterogeneous catalysts in the presence of additives, reactants, other catalysts, or by harmful reaction conditions needed in other steps of these processes. However, as several examples indicated, it is possible to design such recyclable chiral materials for application in combination with homogeneous catalysts. Moreover, for application in some one-pot, especially cascade reactions, materials containing two distinct catalytic species immobilized on the same solid, were also reported. Due to site-isolation effects, these could outperform the corresponding soluble dual catalysts. Additionally, some examples were found in which the support was also involved in activation of the substrates. However, taking into account the sensitivity of most of the metal complexes, the development of such catalytic systems is a particularly difficult and demanding task, as illustrated by the limited number of the systems reported until now.



Scheme 21 Tricomponent asymmetric tandem Mannich-reaction using poly(ethylene glycol)-bonded chiral catalyst CT7*; IF: imine formation, EA: asymmetric addition.[153]

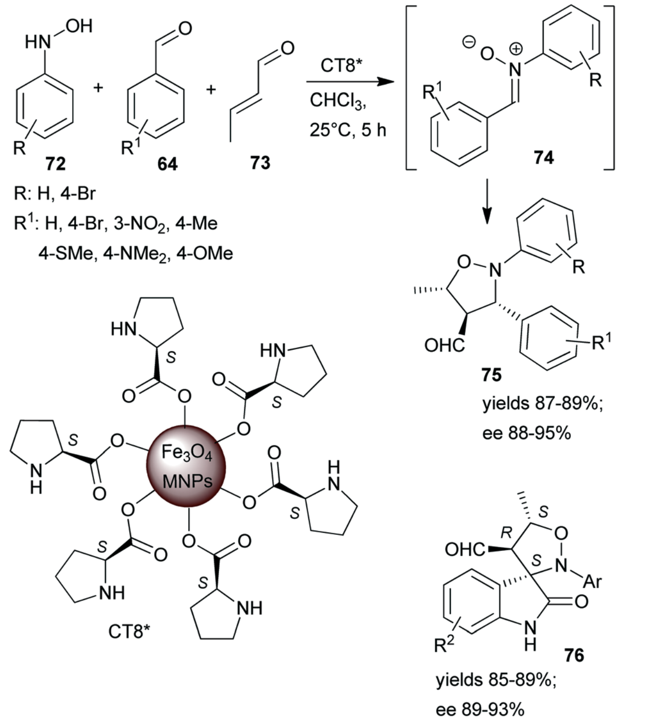
2.2. One-pot reactions using heterogenized chiral organocatalysts in the asymmetric step

Since the beginning of this century, the use of relatively simple chiral organic molecules as catalysts in the synthesis of optically pure products has become an increasingly attractive alternative to the reactions catalysed by metal complexes. The previously known asymmetric organocatalytic transformations,[140–143] have been complemented by reports demonstrating the versatility of these reactions,[144–147] leading to explosive growth in the application of such catalysts.[9,10,13–15] Although initially inexpensive, natural compounds or their easily prepared derivatives have been used as organocatalysts, which were usually less sensitive to the reaction conditions than the metal complexes; later, as the structure of the catalyst was tuned for defined applications, the complexity and value of the applied catalysts increased. Consequently, the recovery and reuse of these also became of paramount importance.

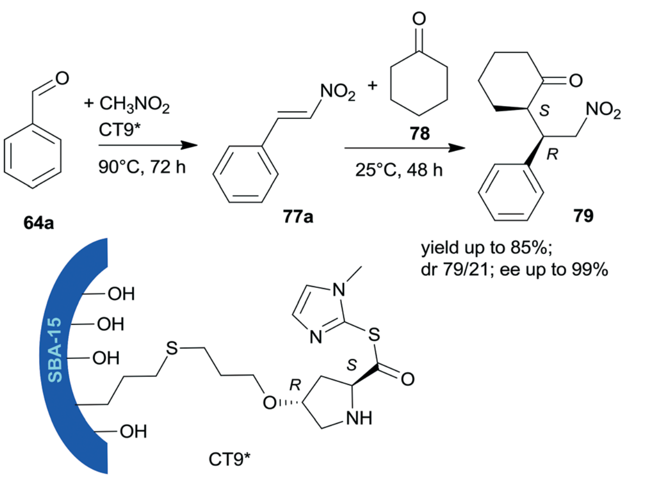
Accordingly, during the last fifteen years, the development of heterogeneous recyclable organocatalysts became a significant task.[16,32,148–152] Moreover, several efficient organocatalysts were able to catalyse various reactions or could tolerate the presence of other catalytic species. Thus, their application in one-pot reactions also evolved rapidly.[51–56] As a consequence, one-pot processes using heterogeneous organocatalyts, either in combination with soluble catalysts or using multifunctional catalytic materials became one of the preferred ways of increasing the sustainability of preparation of chiral fine chemicals. Due to the larger numbers of such materials, it was expedient to subdivide this section according to the type of immobilized organocatalyst.

2.2.1. One-pot reactions using anchored proline or proline derivatives. One of the first reports using heterogeneous chiral organic catalysts in one-pot reactions was published soon following the introduction of L-proline (L-Pro) as catalyst in the tricomponent Mannich-reaction.[147] Immobilization of *trans*-4-hydroxy-L-proline (L-Hyp) on poly(ethylene glycol) support through the 4-hydroxyl group provided a heterogeneous catalyst with both free amino and carboxylic acid groups (CT7*), which catalysed the enantioselective formation of β-amino ketones **71** from aldehydes, *para*-methoxyaniline (**69**) and acetone (Scheme 21).[153] Moderate yields and good enantioselectivities were obtained in reactions of isobutyraldehyde (**67**) and isovaleraldehyde (**68**). During this process, the *in situ* formation of the imines **70** may be catalysed by the acidic surface groups of CT7*, although this has not been evidenced in the study. Recycling of the supported organocatalyst was checked using preformed imine, indicating a decrease in the activity of the catalyst, while the ee was maintained.

One-pot tricomponent Mannich-reactions using catalysts prepared by anchoring L-Pro over Fe_3O_4 MNPs (CT8*) were also studied.[154] Although good yields and high *anti*/*syn* isomer ratios were obtained, the enantioselectivity values were not reported. The same catalyst was used in a tricomponent cascade reaction between *N*-arylhydroxylamines **72**, aromatic aldehydes **64** and crotonaldehyde (**73**), leading to isoxazolidines **75** by catalytic dipolar cycloaddition between the nitrone **74** and the iminium intermediate formed from the catalyst and **73** (Scheme 22).[155] High yields and ees were obtained. The scope of the reaction was extended using few isatin derivatives instead of **64**, leading to the formation of



Scheme 22 Tricomponent asymmetric cascade reactions catalysed by L-proline immobilized on the surface of Fe_3O_4 MNPs.[155]

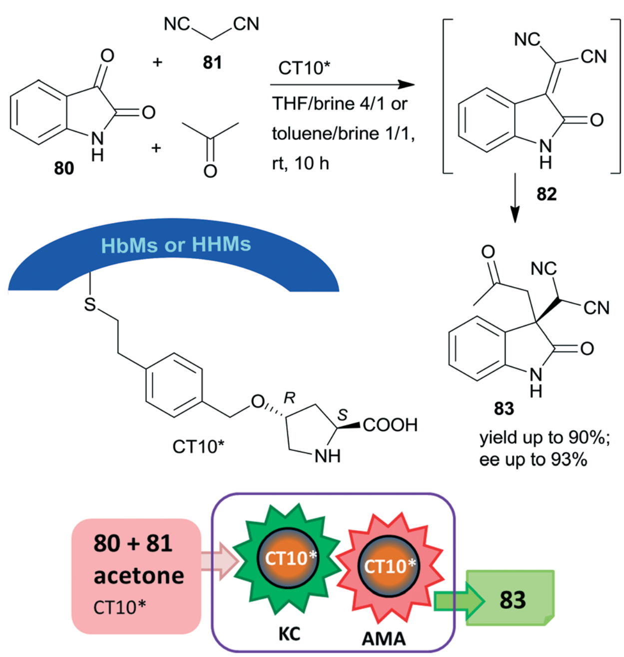


Scheme 23 Sequential one-pot nitroaldol reaction and **AMA** using SBA-15 mesoporous silica anchored L-Pro derivative.[156]

spiroisoxazolidines **76**, also in high yields and good optical purities. Easy recovery of the catalyst was facilitated by using MNPs as support and recycling four times showed no activity decrease.

Heterogeneous bifunctional catalysts were prepared by anchoring proline derivatives on SBA-15 mesoporous silica and were used in the one-pot sequential nitroaldol reaction followed by asymmetric Michael addition (Scheme 23).[156] The synergistic catalytic effect of the surface achiral hydroxyl groups and the immobilized chiral pyrrolidine moiety assured high yields and excellent enantioselectivities in the one-pot reaction of **64a**, nitromethane and cyclohexanone (**78**). The surface hydroxyl groups contributed to the activation of **64a** and nitromethane, and thus accelerated the first step of the one-pot reaction and played a role in the orientation of the intermediate **77a** in the second step. The sequential addition of reactants, *i.e.* introduction of **78** following the first step, and decrease of the reaction temperature to 25 °C was necessary in order to obtain good stereoselectivities in the second step. The best results were obtained using CT9* catalyst, containing L-Hyp thioester derivative bonded by the 4-hydroxyl group to SBA-15 functionalized with pendant mercaptopropyl surface groups. The corresponding proline derivative was not able to catalyse the Henry reaction, which showed the probable involvement of the surface achiral groups in this reaction. The CT9* catalyst was reused three times, with only slight decrease in the activity and stereoselectivities.

Later, the same research group prepared mesoporous silicas with either hydrophobic (HbMs) pores, hydrophilic pores or containing both hydrophobic and hydrophilic alternating blocks (HHMs) in the pore walls. These tailored supports were used to anchor L-Hyp, leading to materials containing surface immobilized L-Pro.[157] The heterogeneous organocatalysts were tested in the Knoevenagel condensation, followed by the asymmetric Michael addition cascade reaction of isatin (**80**), malononitrile (**81**) and acetone in biphasic organic-aqueous solvent mixtures (Scheme 24). The best results were achieved when the surface was either completely or partially hydrophobic (CT10*), attributed to the more effective organic–water interface developed in the channels of these materials, where the surface hydroxyl groups and/or the

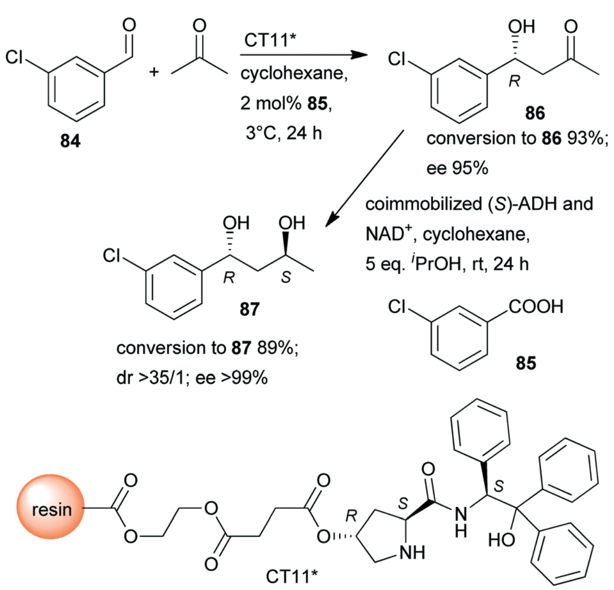


Scheme 24 Knoevenagel condensation (KC) and AMA cascade reaction catalysed by L-Pro grafted on hydrophobic and hydrophilic blocks containing mesoporous silica.[157]

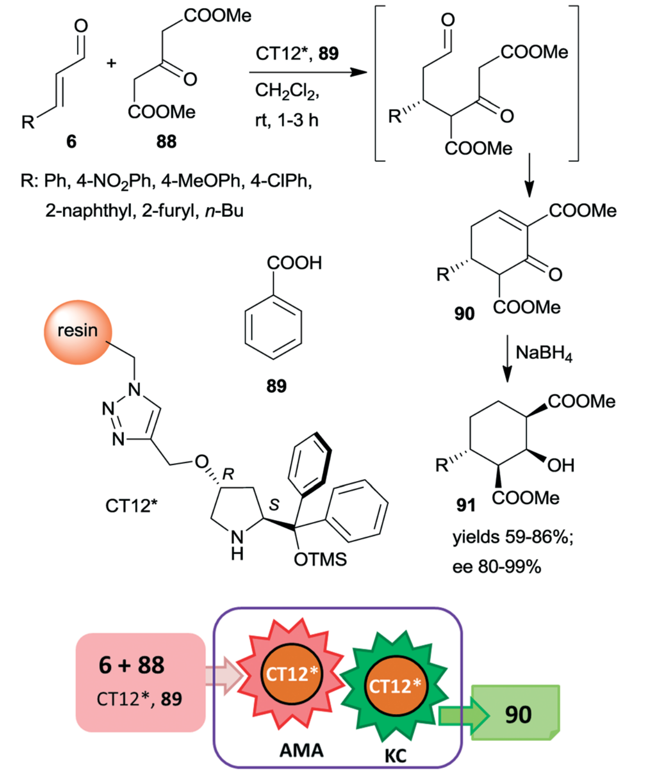
water molecules at the interface were also involved in the catalytic processes. The possibility of carrying out the two steps in cascade was ensured by the much faster condensation step as compared with the **AMA.** The catalyst having alternating surface pore properties (HHMs) was reused three times.

In a so-called "one-pot like" reaction, the initial asymmetric direct aldol addition of 3-chlorobenzaldehyde (**84**) and acetone was catalysed in high yield and excellent enantioselectivity[158] by a resin immobilized L-prolineamide derivative (CT11*) developed for this purpose (Scheme 25).[159] The subsequent reduction to chiral diol **87** was catalysed by alcohol dehydrogenase (ADH) immobilized on a super-adsorbent polymer together with its cofactor NAD^+. The process could be run in organic solvent, *i.e.* cyclohexane, which, following the removal of the volatile components such as acetone after the first step, allowed direct addition of the co-immobilized enzyme (*S*)-ADH and its cofactor and ^{i}PrOH co-substrate. Fortunately, neither the unreacted **84** nor **85**, or CT11* found in the system, showed inhibition in the biocatalytic step, and diol **87** was obtained in excellent overall yield and optical purity.[158] The stereochemical outcome of the second reduction step was fully controlled by the biocatalyst, overriding the influence of the chiral centre formed in the first step, which implies that all stereoisomers are selectively accessible by using appropriate catalysts.

2.2.2. One-pot reactions catalysed by other anchored pyrrolidine ring containing compounds. The pyrrolidine ether CA6* is one of the most efficient and often used organocatalysts, which may be prepared from natural L-Pro.[98–103] As a consequence, several methods to anchor CA6* to insoluble supports were disclosed, and application of these materials in one-pot reactions was also attempted.



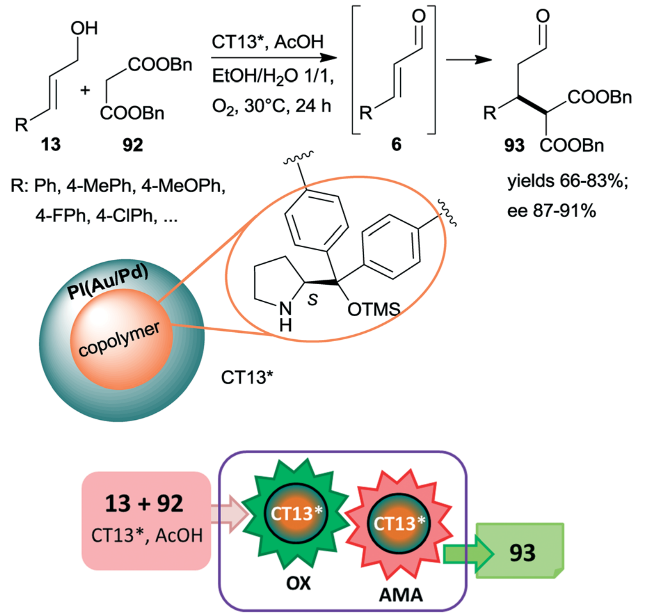
Scheme 25 Sequential one-pot asymmetric direct aldol addition and enzymatic reduction using immobilized chemical and biocatalysts.[158]



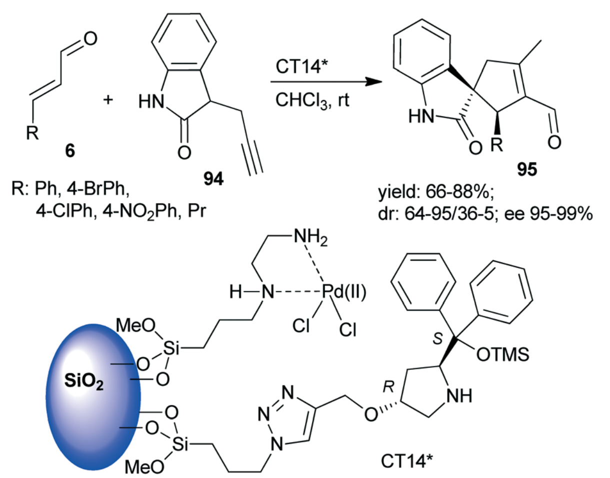
Scheme 26 AMA and KC cascade reactions catalysed by immobilized CA6*.[160]

This organocatalyst was bonded by azide-alkyne cycloaddition of the corresponding 4-propargyloxy derivative to Merrifield resin containing azidomethyl groups (CT12*).[160] The chiral polymer was used as catalyst in the asymmetric Michael addition followed by the Knoevenagel condensation domino reaction of unsaturated aldehydes **6** and dimethyl 3-oxoglutarate (**88**) (Scheme 26). These reactions resulted in the formation of cyclohex-2-en-1-ones **90** in good yields and excellent enantioselectivities. In a subsequent step, **90** was reduced to cyclohexane derivatives **91** containing four chiral centres, obtained as single enantiomers. The activity of the catalyst slightly decreased upon reuse, thus, increasingly longer reaction times were necessary during recycling. The solid catalyst charged in a fixed-bed reactor was also able to provide the cyclic compound **90** with similar enantioselectivity to that obtained in the batch reactor.

An ingeniously prepared heterogeneous layered bifunctional catalyst was reported by Kobayashi and co-workers.[161] A chiral copolymer containing immobilized CA6* was placed in the inner layer, whereas achiral polymer incarcerated Au/Pd alloy NPs constituted the outer shell of the catalyst beds (CT13*). This layering and separation of the active components assured the isolation of the catalytic sites and resulted in an active and enantioselective catalyst for the tandem catalytic aerobic oxidation of allylic alcohols **13**, followed by asymmetric Michael addition of dibenzyl malonate **92** to the resulting unsaturated aldehyde intermediates **6** (Scheme 27). When the metal alloy NPs were placed in the inner part and



Scheme 27 Cascade aerobic oxidation followed by **AMA** catalysed by bifunctional layered catalyst containing anchored CA6*; PI: polymer incarcerated.[161]

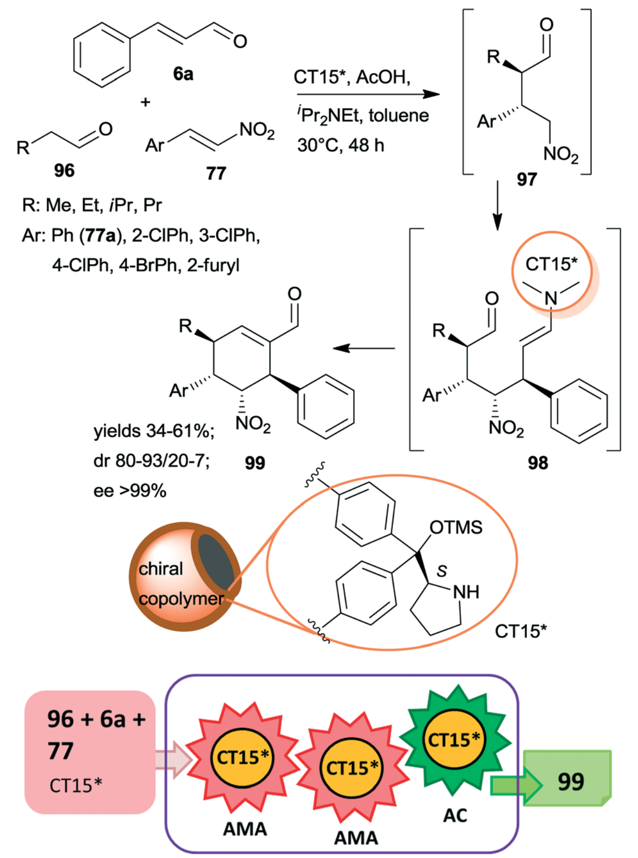


Scheme 28 The asymmetric cascade reaction of unsaturated aldehydes and alkyne nucleophiles using the heterogeneous catalyst CT14* (see Schemes 3 and 4).[162]

the chiral copolymer was in the outer layer of the composite, the tandem reaction did not proceed, showing the importance of the layering order of the two active phases. Moreover, recycling of CT13* was obstructed by deactivation as a consequence of transformation of the pyrrolidine secondary amino group.

A chiral heterogeneous catalyst containing both an achiral metal complex and CA6* immobilized on SiO_2 support (CT14*, Scheme 28) was developed by Córdova and co-workers[162] for heterogeneous synergistic catalysis of the asymmetric Michael addition and intramolecular carbocyclization cascade reaction described initially using soluble organocatalyst (see Scheme 3 (ref. 97)). Interestingly, this heterogeneous catalyst provided a slightly better enantiomeric ratio than was obtained in reaction with the homogeneous CA6*. The scope of the heterogeneous relay catalytic process was investigated using **7** or the oxindole derivative **94**,[162] the latter resulting in spirolactams **95** with various unsaturated aldehydes **6**.[108–110] However, recycling of the catalyst was not successful, due to deactivation of the surface bonded chiral amine as a consequence of the inhibition by the aldehyde or by the product.

Recently, multi-hollow organic microspheres containing anchored CA6* organocatalyst were prepared by solvent etching the poly(styrene/acrylic acid) core of microparticles having a chiral copolymer shell. This shell was obtained by copolymerization of acrylamide, styrene and CA6* derived monomer crosslinked with *para*-divinylbenzene and ethylene glycol dimethacrylate (CT15*).[163] The material was used in the tricomponent triple cascade process reported earlier,[101,164,165] which resulted in the formation of four chiral centres in a stereoselective manner in the first two asymmetric Michael additions (Scheme 29). The initial addition of the aliphatic aldehyde **96** to β-nitrostyrene derivatives **77** by enamine catalysis was followed by addition of the resulting intermediate **97** to the activated unsaturated aldehyde **6a** *via* iminium catalysis. Intramolecular cyclization of the enamine intermediate **98** by aldol condensation eventually led to the

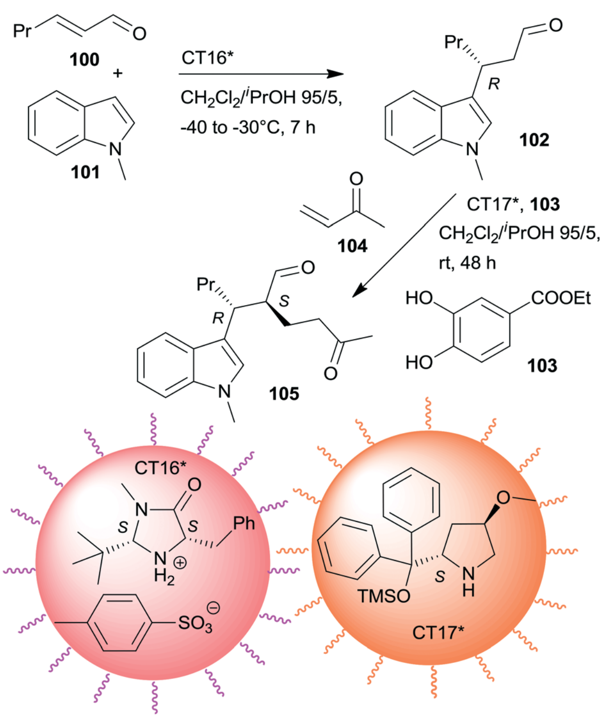


Scheme 29 Tricomponent asymmetric triple cascade reaction catalysed by multi-hollow copolymer microparticles containing immobilized CA6*; AC: aldol condensation.[163]

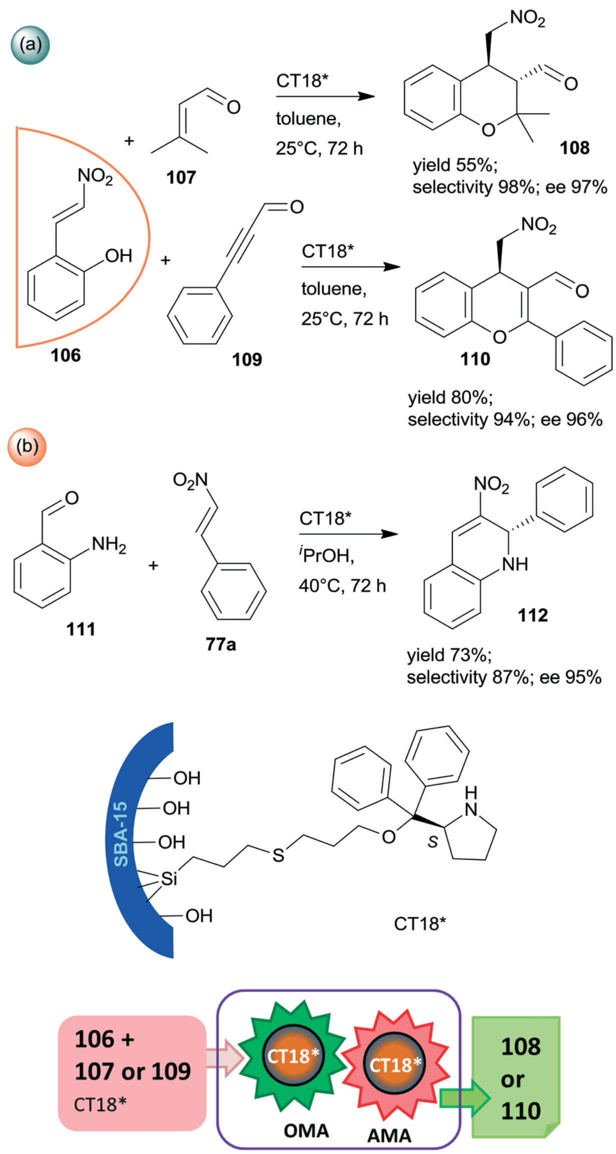
cyclohexene derivative **99**. Results obtained using the heterogeneous catalyst CT15* were similar to those reported using the homogeneous counterpart CA6*. The stereoselectivities were maintained following five uses of CT15*; however yields slightly decreased, which was ascribed to several reasons, among which the partial collapse of the hollow structure may have a significant contribution to this phenomenon.

Non-interpenetrating star polymers immobilized chiral organocatalysts were used in the sequential asymmetric Friedel–Crafts reaction taking place by iminium catalysis followed by asymmetric Michael addition through enamine catalysis.[166] The first step was catalysed by MacMillan's catalyst[167] bonded by ionic interactions to pendant benzenesulfonic acid groups of a star polymer (CT16*), whereas the second was with CA6* anchored on star polymer by copolymerization (CT17*). Activation of the Michael acceptor by hydrogen-bonding using **103** increased the yield. CT17*, **103** and the unsaturated ketone **104** were added to the system following the completion of the first step (Scheme 30). Application of star polymers assured the catalytic site isolation necessary in this sequential reaction; the use of either TsOH acid or CA6* instead of the corresponding chiral copolymers or using similar linear copolymers did not provide the desired product **105**.

Finally, a highly efficient example of chiral heterogeneous organocatalyst in which diphenyl prolinol was anchored by the hydroxyl group through ether bond and used in asymmetric cascade reactions was recently reported (CT18*).[168] Similar to the previous report from the same research group,[156]



Scheme 30 One-pot sequential asymmetric Friedel–Crafts reaction and **AMA** catalysed by chiral catalysts immobilized on non-interpenetrating star polymers.[166]

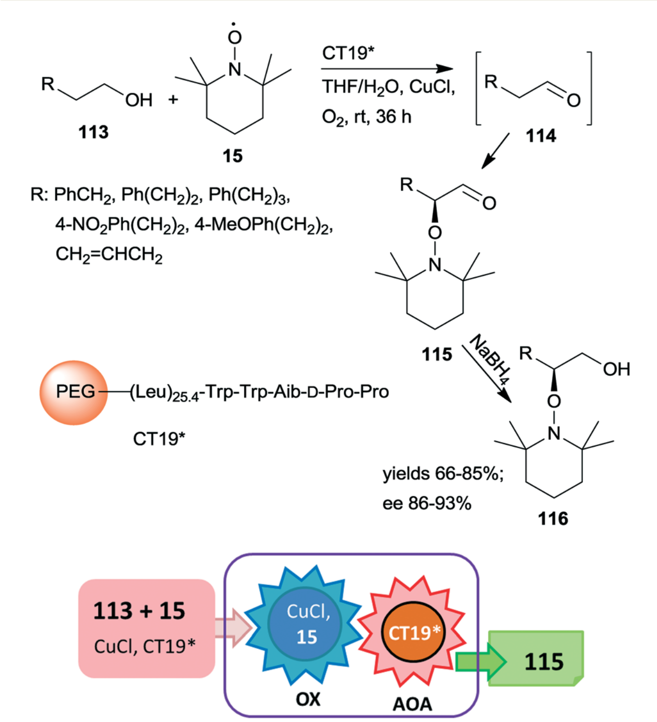


Scheme 31 Cascade oxa-Michael reaction (**OMA**) and **AMA** (a) and asymmetric aza-Michael reaction and nitro-aldol condensation (b) catalysed by SBA-15 anchored diphenyl prolinol.[168]

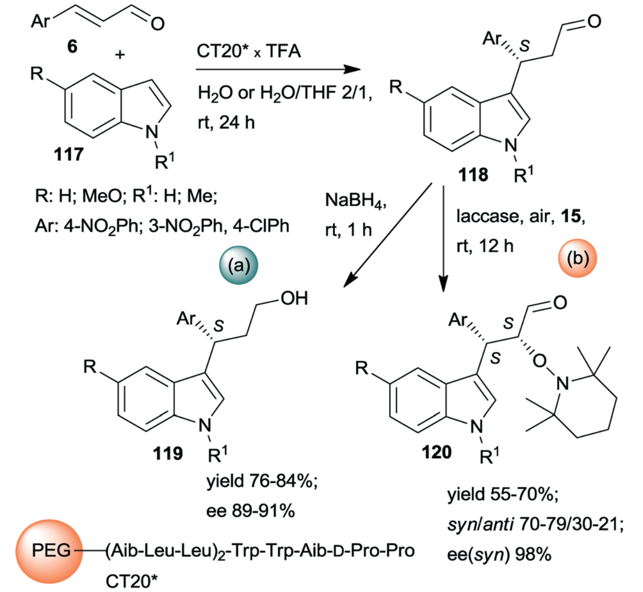
the use of SBA-15 mesoporous silica as support resulted in a synergistic catalytic effect of the surface acidic achiral hydroxyl groups and the immobilized chiral secondary amine moiety, complemented by a presumed geometrical constraint of the mesopores. These interactions were supposed to be responsible for the high yields and excellent enantioselectivities in the oxa-Michael reaction coupled with asymmetric Michael addition cascades of **106** with **107** or **109** (Scheme 31a). Catalyst CT18* was also successfully used in the asymmetric Michael addition and acetalization cascade of **106** and butanal (not shown); moreover, high enantioselectivity was obtained in the asymmetric aza-Michael addition followed by nitro-aldol condensation of **111** and **77a** leading to 1,2-dihydroquinoline derivative **112** (Scheme 31b). The activity of this heterogeneous organocatalyst and the resulting stereoselectivity hardly decreased following five uses in the oxa-Michael reaction and asymmetric Michael addition cascade.[168]

2.2.3. One-pot reactions catalysed by immobilized oligopeptides. Besides L-Pro, its simple derivatives and other chiral pyrrolidine ring containing compounds, oligopeptides, especially Pro terminated materials, were also applied as catalysts in the asymmetric synthesis of optically pure fine chemicals. The efficient oligopeptides were also used as immobilized heterogeneous catalysts. Contrary to other surface-bonded chiral organocatalysts, the anchored peptides may be prepared by solid phase peptide synthesis, and therefore the polymer-bonded variants are oftentimes obtained more easily, than the oligomers.

A polymer-supported oligopeptide catalyst (CT19*) was used as a heterogeneous organocatalyst in the tandem oxidation of primary alcohols **113** and asymmetric α-oxamination of the obtained aldehydes **114** with **15** and CuCl (Scheme 32).[169] The asymmetric oxamination reported a few years previous,[170] takes place by the enamine activation mechanism in homogeneous systems.[171] This oxamination was catalysed by the resin-supported oligopeptide CT19* catalyst using $FeCl_2$ and $NaNO_2$ in aqueous media under aerobic conditions.[172] The novel tandem reaction occurred under similar conditions, except that **15** used as reactant in the second step also served as oxidant in the Cu(I)/**15** catalysed and 1,1′-bipyridine additive assisted first homogeneous oxidation step of the process. Good yields and high enantioselectivities were reached, determined following an additional reduction of the cascade products **115** to alcohols **116**.[169] The immobilized peptide could be reused following the tandem reaction and similar results were obtained even in the seventh run.



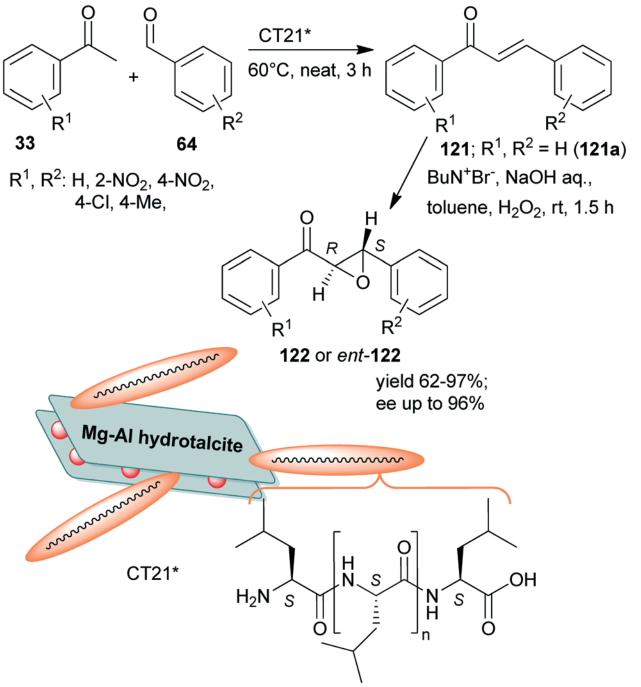
Scheme 32 Tandem oxidation and asymmetric oxamination catalysed by resin-supported oligopeptide organocatalyst; **AOA**: asymmetric oxamination.[169]



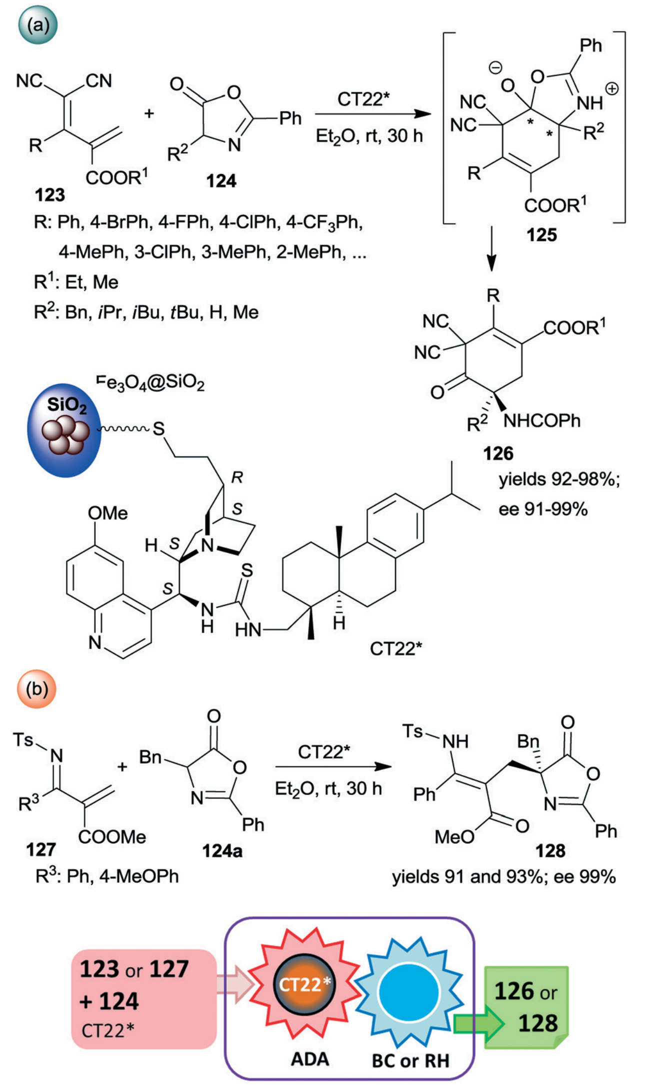
Scheme 33 One-pot sequential heterogeneous catalytic asymmetric Friedel–Crafts reaction followed by homogeneous reduction (a) or enzymatic AOA (b) using polymer-bonded oligopeptides; TFA: trifluoroacetic acid.[173,174]

Kudo and co-workers also developed one-pot sequential prodesses in which asymmetric Friedel–Crafts reactions between *N*-methylindole derivatives **117** and aromatic unsaturated aldehydes **6** were the first steps (Scheme 33).[173,174] Several supported oligopeptide catalysts were used, such as the previously developed CT19* (see Scheme 32). The best results were obtained using $(Leu–Leu–Aib)_2$ linker between the terminal penta-peptide and the polymer (CT20*) in water or a mixture of water and THF. The reaction sequences were continued either by one-pot reduction or by asymmetric α-oxamination of the resulting aldehydes **118** with **15**. The latter reaction was carried out in the presence of the oxidative enzyme laccase. In this sequence, the stereochemistry of the α-oxamination step was determined by the immobilized peptide, demonstrated by effects observed upon changing the configurations of the chiral amino acids in the terminal penta-peptide unit. Insufficient water in the solvent mixture inactivated the laccase, thus inhibiting the second peptide/enzyme-catalysed oxidation step.

Inspired by the Juliá–Colonna asymmetric epoxidation using polyamino acid catalysts,[175] poly-L-leucine was used as a recyclable organocatalyst in the second step of the sequential Claisen–Schmidt condensation, followed by an asymmetric epoxidation one-pot process, whereas the initial step was carried out using KOH aqueous solution.[176] The scope of the reaction was demonstrated using various benzaldehyde and acetophenone derivatives. The recycled chiral catalyst gave a slightly decreased yield and enantioselectivity in the tenth run. Recently, rehydrated hydrotalcite was used as a support



Scheme 34 Sequential one-pot Claisen–Schmidt condensation and asymmetric Juliá–Colonna epoxidation catalysed by hydrotalcite-supported poly-L-leucine; *ent*: enantiomer.[177]



Scheme 35 Inverse-electron-demand Diels–Alder reaction (ADA) and intramolecular C–O bond cleavage (BC) cascade catalysed by cinchona alkaloid derivative bonded on the surface of MNPs decorated SiO_2 (a) and the cascade occurring by reacting unsaturated N-Ts-imines followed by retro-hemiaminalization (RH) (b).[179]

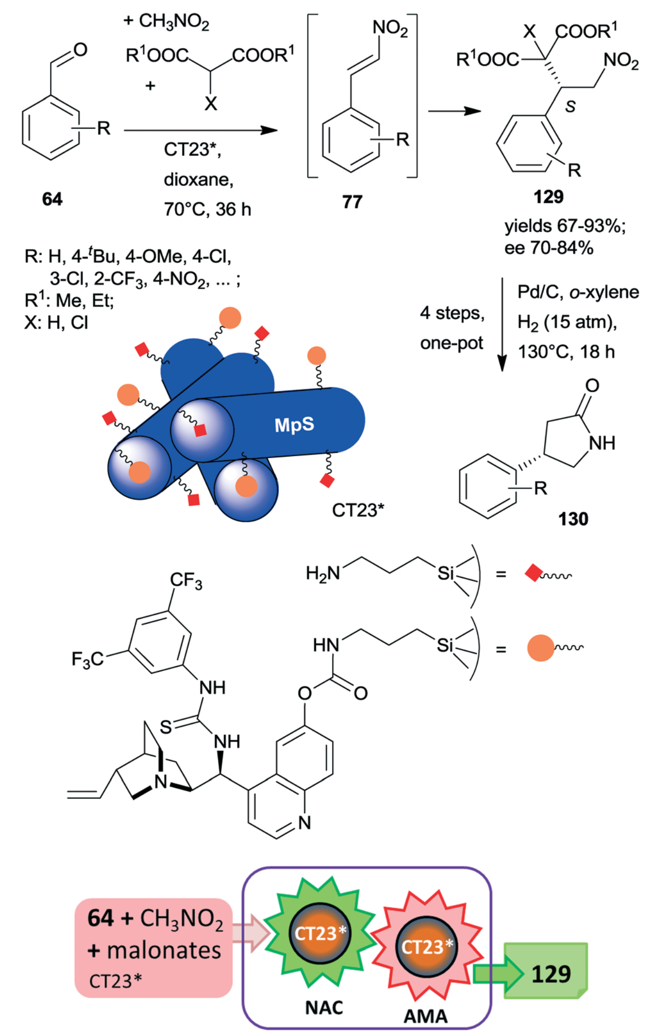
to immobilize poly-L-leucine by simple adsorption.[177] The resulting inorganic–organic hybrid material (CT21*) was applied as catalyst in the above sequential Claisen–Schmidt condensation – asymmetric Juliá–Colonna epoxidation one-pot process (Scheme 34). The first step catalysed by basic sites of the inorganic material proceeded most efficiently under neat conditions leading to the unsaturated ketones **121**, whereas between steps, toluene, NaOH, H_2O_2 and $Bu_4N^+Br^-$ were added. The catalyst was stable, providing high yields of **122** and slightly decreased ee during the fourth use. Interestingly, the *ortho*-nitro-substituted benzaldehyde gave the opposite enantiomer in excess (2*S*,3*R*), as compared with the unsubstituted or *para*-substituted derivatives (excess of 2*R*,3*S* enantiomer), attributed to the steric effect of the *ortho* substituent.[177]

2.2.4. One-pot reactions catalysed by immobilized cinchona alkaloid derivatives. A privileged class of organocatalysts are the natural cinchona alkaloids and their derivatives, which are highly efficient in several asymmetric reactions. During this century, a large number of derivatives have been prepared and applied in various transformations.[178] Although these organocatalysts were also anchored over solid supports,[19] the obtained heterogeneous catalytic materials were rarely applied in asymmetric one-pot reactions.

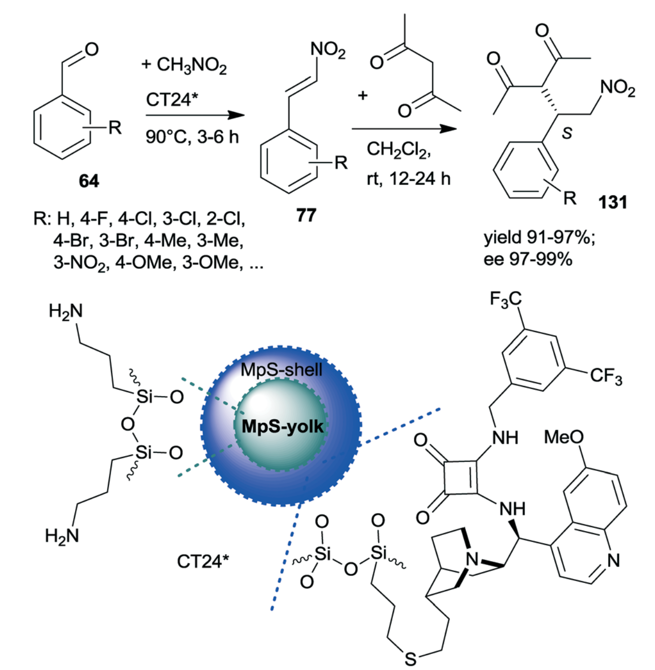
Among the first attempts, an *epi*-cinchona alkaloid thiourea derivative was immobilized on a carrier containing silica supported Fe_3O_4 MNPs.[179] This chiral solid (CT22*) was found efficient in asymmetric inverse-electron-demand Diels–Alder reactions in which the dienophiles were generated by the activation of azlactones **124** (Scheme 35). The resulting intermediates **125** underwent regioselective intramolecular C–O bond cleavage leading to chiral cyclohex-3-en-1-one derivatives **126** in high yields and excellent enantioselectivities (Scheme 35a). The second step of the cascade occurred spontaneously. The heterogeneous catalyst provided similar results to the corresponding homogeneous thiourea derivative. When **123** was replaced with unsaturated N-Ts imines **127**, the inverse-electron-demand Diels–Alder reaction was followed by retro-hemiaminalization, resulting in unsaturated amino acid precursors **128** in similarly high enantioselectivities, as obtained in the previous cascade (Scheme 35b).[179] It must be mentioned that the role of the MNPs is solely to ease the separation of the catalyst from the reaction mixture; moreover, using Fe_3O_4 as support led to poor activity and an almost racemic product, indicating the paramount role of the silica in anchoring the cinchona alkaloid. Recycling of CT22* resulted in a slight decrease in the yield and ee following ten uses.

At the same time, the preparation of a hybrid catalyst containing *epi*-cinchona alkaloid thiourea derivative and aminopropyl units incorporated in the structure of a mesoporous silica support (CT23*) was reported.[180] The multifunctional chiral material was obtained by co-condensation of tetramethylorthosilicate with the silylated cinchona alkaloid precursor prepared from quinine functionalized by carbamate groups. Due to partial hydrolysis of the carbamate moiety, the material also contained free aminopropyl pendant groups. This hybrid catalyst afforded high yields and good enantiomeric ratios in the tricomponent reaction of aldehydes, nitromethane and malonates *via* nitroaldol condensation and asymmetric Michael addition one-pot cascade (Scheme 36).[180] It must be noted that the generation of the primary amino groups by partial hydrolysis of the chiral precursor produced the surface sites necessary to catalyse the first step of the cascade reaction. The recovered catalyst was reused two times with a small decrease in its performance; however, the activity of the material decreased with further recycling. This heterogeneous asymmetric cascade procedure was later combined with an ulterior transformation of the products **129** through another one-pot domino process over Pd/C, incorporating the reduction of the nitro group, intramolecular cyclization, ester hydrolysis and decarboxylation reactions in order to prepare γ-aminobutyric acid derivatives **130**, which are pharmaceutically relevant chiral building blocks.[181] New chiral centres in the final product were not generated during this second domino reaction over Pd/C; however, the chirality of the intermediates **129** was preserved in the final products **130**.

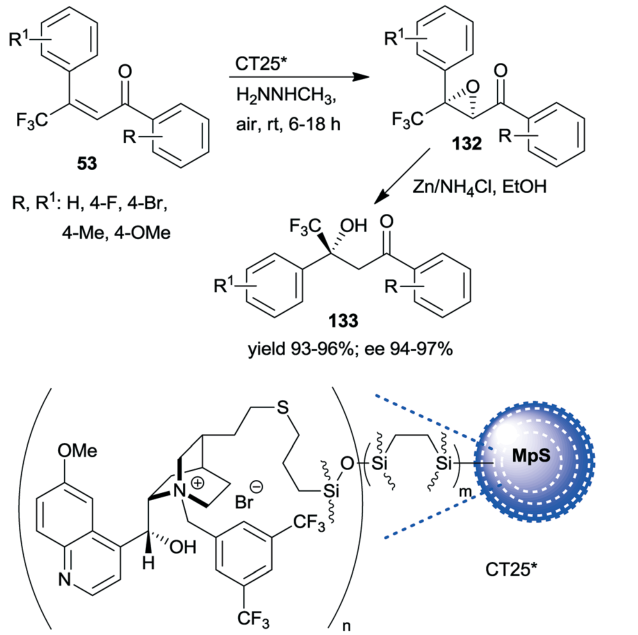
A similar one-pot reaction carried out sequentially was developed by Liu and co-workers using bifunctional yolk–shell structured mesoporous silica nanospheres (CT24*).[182] The nitroaldol reaction of **64** and nitromethane, affording **77**, was catalysed by the basic amino groups bonded to the yolk of the particles, whereas the asymmetric Michael addition of acetylacetone to **77** occurred in the mesoporous shell, where a cinchona-based squaramide derivative was anchored (Scheme 37). Products **131** were obtained in high yields and enantioselectivities using various substituted benzaldehydes; however, between the two steps, the addition of solvent, acetylacetone, and a change in the reaction temperature were necessary. It was shown that the cinchona squaramide hardly affected the first step of this sequential reaction, whereas the surface silanol groups accelerated it by contributing to the activation of the reactants, similar to what was suggested in the nitroaldol or oxa-Michael reactions followed by **AMA** one-pot



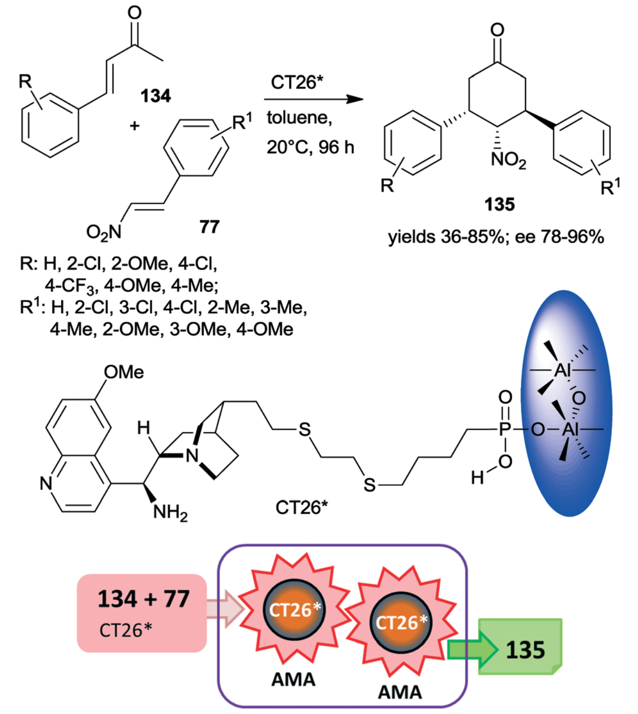
Scheme 36 One-pot cascade nitroaldol condensation (**NAC**) and **AMA** catalysed by the multifunctional chiral catalyst and transformation of the products in a consecutive one-pot four step reaction over Pd/C; MpS: mesoporous silica.[180,181]



Scheme 37 Sequential one-pot **NAC** and **AMA** using anchored cinchona alkaloid derivative and pendant primary amine containing catalyst.[182]



Scheme 38 One-pot sequential heterogeneous catalytic asymmetric epoxidation followed by homogeneous reductive ring opening.[183]



Scheme 39 Double AMA cascade reaction of unsaturated ketones and nitroolefins using *epi*-cinchona alkaloid derived chiral aluminum phosphonate.[184]

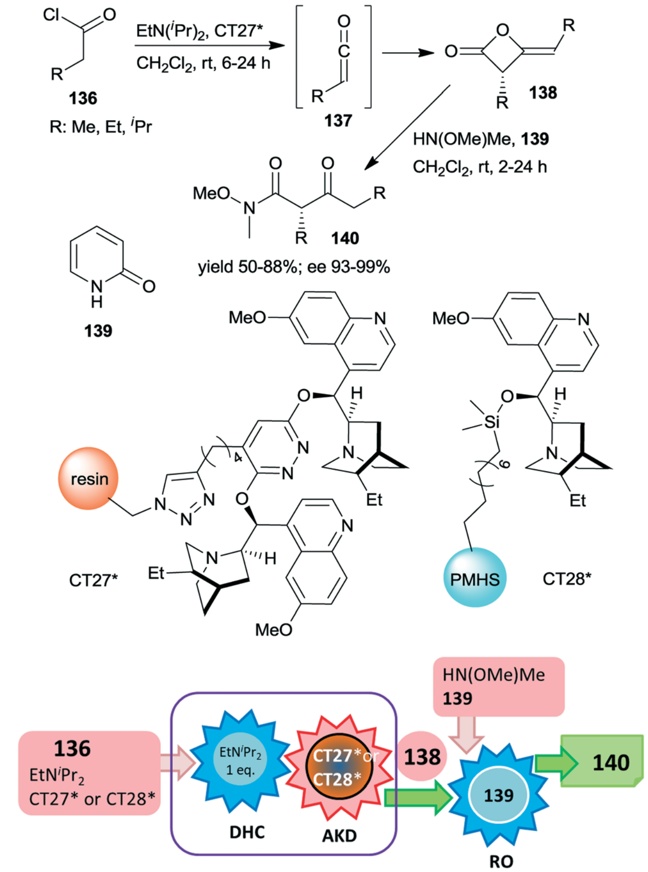
transformations catalysed by SBA-15 anchored chiral pyrrolidine derivatives (Schemes 23 and 31).[156,168] Recycling of the heterogeneous catalyst showed that the material was active in four consecutive runs. The same research group prepared mesostructured silica anchored *N*-(3,5-bistrifluoromethylbenzyl)quininium bromide (CT25*) and used this solid as the heterogeneous chiral catalyst in the asymmetric epoxidation of **53** to **132** (Scheme 38).[183] The addition of Zn/NH_4Cl and ethanol to the slurry afforded in sequential one-pot manner the corresponding β-hydroxy ketones **133** by reductive ring opening of the chiral intermediates in high yields and excellent ees. The reusability of the heterogeneous catalyst was examined in the first step of the sequential process, *i.e.* the epoxidation of the unsaturated ketones, leading to high yields and preserved ee values following seven recycling processes.

Very recently, chiral solid organocatalysts were prepared by direct precipitation of cinchona alkaloids derived phosphonic acids with sodium aluminate.[184] The materials containing 9-amino(9-deoxy)*epi*-quinine tethered aluminum phosphonates along with defective P–OH acid sites (CT26*) were used in the double asymmetric Michael addition cascade occurring between unsaturated ketones **134** and nitroolefins **77** through enamine and iminium catalysis (Scheme 39). The reaction afforded cyclohexanone derivatives **135** in good yields and diastereoselectivities and excellent enantiomeric purities. Compared with the corresponding functionalized cinchona derivative, the chiral solid material provided significantly increased yield and better diastereomeric ratio, explained by the acid strength of the free $-PO_3H_2$ groups. Furthermore, the amount and acidity of the P–OH defects of the solid material also had significant influence on the catalytic performance of the heterogeneous catalyst. The catalyst CT26* was recycled four times with only slight loss in its performance.[184]

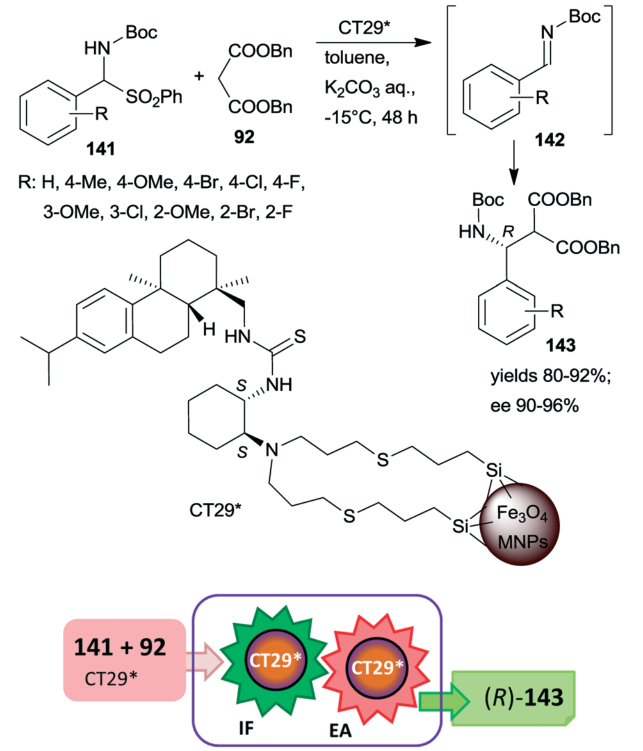
Heterogeneous asymmetric ketene dimerization was accomplished using cinchona alkaloid derivatives immobilized either on polystyrene resin or on cross-linked poly(methylhydrosiloxane) elastomeric films.[185,186] Ketenes **137** were generated *in situ* from acid chlorides **136** using EtN^iPr_2. The chiral dimers **138** were further transformed into the corresponding Weinreb amides **140** by ring opening with HN(OMe)Me using 2-pyridone **139** as a homogeneous catalyst.

The latter reaction was not carried out *via* a one-pot procedure, in order to prevent the contamination of the heterogeneous organocatalyst by reactants used in the final step. Thus, before the ring opening reaction, the heterogeneous catalyst was separated from the reaction mixture (Scheme 40). In these studies both polymer anchored (dihydro)quinidine dimers (CT27*)[185] or dihydroquinidine immobilized by functionalization of the C–OH group (CT28*)[186] were found to be similarly efficient to their homogeneous counterparts, both providing high enantioselectivities. The immobilized dimeric cinchona alkaloid CT27* was recycled 19 times with only small decreases in the yields and enantioselectivities in the final runs.

2.2.5. One-pot reactions catalysed by other immobilized chiral organocatalysts. Besides the above presented materials, other heterogenized chiral organocatalyst types were hardly tested in one-pot reactions. A tricomponent Mannich-type



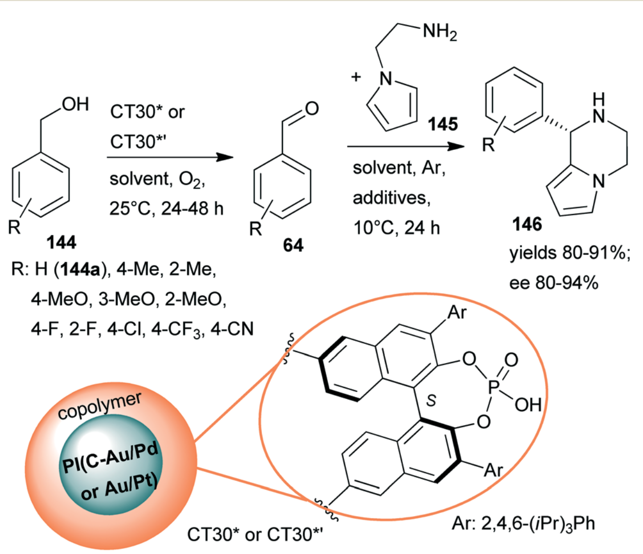
Scheme 40 One-pot acid chloride dehydrochlorination (**DHC**) and asymmetric ketene dimerization (**AKD**) using heterogeneous cinchona alkaloid catalyst followed by ring opening (**RO**) to Weinreb amides; PMHS: poly(methylhydrosiloxane).[185,186]



Scheme 41 Tandem **IF** and **EA** starting from Boc-protected α-amino sulfones catalysed by 1,2-cyclohexanediamine derived chiral catalyst anchored on MNPs.[187]

reaction was described, starting from racemic *N*-Boc (*N-tert*-butoxycarbonyl) protected α-amino sulfones **141** and **92** using optically pure 1,2-cyclohexanediamine-thiourea derivative bonded on the surface of Fe_3O_4 MNPs (CT29*).[187] In reactions of aromatic α-amino sulfones, high yields and enantioselectivities were obtained (Scheme 41). The easily separated chiral magnetic catalyst was recycled 14 times without a decrease in performance. The chiral products **143** were transformed in optically pure β-amino acids. Similar to the previously shown Mannich-reaction (Scheme 21),[153] the first step, *i.e.* the formation of the imines **142** from **141**, could also be catalysed by the solid material, however, no evidence was provided to support this pathway.

Continuing their efforts at designing bifunctional chiral heterogeneous catalysts for one-pot reactions (Scheme 27),[161] Kobayashi and co-workers prepared layered bifunctional catalysts that had an achiral polymer incarcerated carbon black-supported Au/Pd or Au/Pt NPs core and a copolymer shell containing chiral phosphoric acid units (CT30* or CT30*').[188] Previously, chiral phosphoric acids proved their efficiency in homogeneous asymmetric organocatalytic reactions.[189] The novel chiral materials were used in the sequential aerobic oxidation of benzyl alcohols **144** followed by organocatalytic asymmetric aza-Friedel–Crafts reaction of the aldehydes **64** and *N*-aminoethylpyrrole (**145**), leading to piperazine derivatives **146** (Scheme 42). Although the one-pot reaction did not proceed in a cascade manner, due to the deactivation of the NPs by the primary amine, sequential elaboration by addition of **145** and additives following the oxidation step provided the desired products in high yields and ees. Reverse



Scheme 42 Sequential oxidation – enantioselective aza-Friedel–Crafts reaction catalysed by bifunctional layered catalysts; PI: polymer incarcerated.[188]

placement of the metal alloy and organocatalyst in the layered material resulted in a similarly efficient catalyst as CT30*. Substituents on the phenyl ring of **144** had a significant effect on the results when Au/Pd NPs were applied, whereas the Au/Pt NPs were efficient catalysts even in the presence of electron withdrawing substituents. The catalysts could be reused, unlike CT13*, which was deactivated under the reaction conditions.[161]

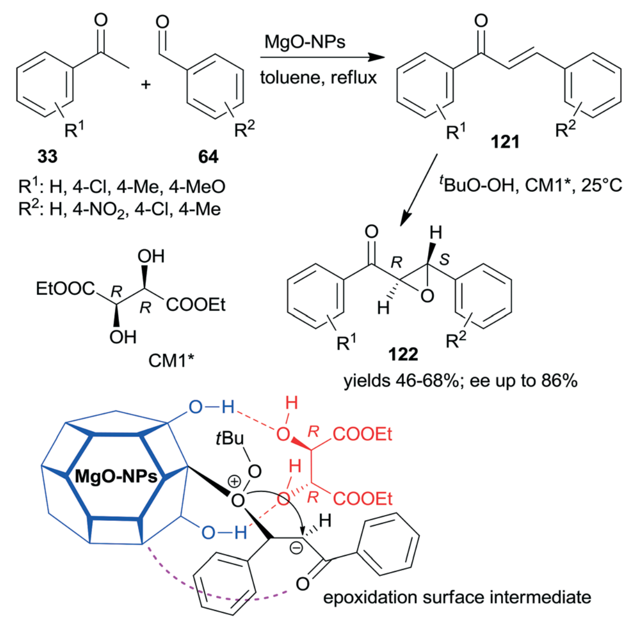
The relatively numerous examples of applications of heterogeneous chiral organocatalysts in cascade or sequential one-pot asymmetric processes, the majority being developed in the last decade, are due to the insensitive nature and ease of anchoring these catalytically highly efficient chiral compounds. Furthermore, the successful recycling of these heterogeneous catalysts has promoted their application in continuous-flow systems.[190,191] Sequential asymmetric reactions using immobilized reagents, chiral organocatalysts and scavengers placed in successive fixed-bed reactors provided the opportunity for the convenient preparation of optically pure fine chemicals. Similar to the one-pot reactions, during these processes, several purification steps may be eliminated; moreover, reactions occurring through sensitive, unstable, hazardous intermediates are easily carried out. Lectka and co-workers described an elegant early example using immobilized quinine catalyst. A chiral β-lactam was prepared from ketenes and iminoesters, both obtained in preceding columns.[192] The chiral product was purified in flow by passing through a final scavenger column for removing side-products. As the catalysts, reagents used in different steps are separated in space (in different columns) and due to the possibility of using scavenger columns between or following the reactors, there are no undesired interactions and consequently no unfavourable effects on the performance of the reaction components; thus, the products may be obtained in high quality. Despite these advantages, these reactions may not be considered one-pot reactions, and are accordingly out of the scope of the present review. Moreover, the development of such processes is still in its infancy, mostly due to the laborious design of the necessary experimental setups, making the one-pot batch methods more accessible for laboratory chemists.

The examples surveyed in the above subsection, in which heterogeneous chiral organocatalysts are applied in one-pot reactions have demonstrated the potential of using such catalysts for the convenient preparation of chiral fine chemicals. Although many of these solid catalysts were applied in combination with homogeneous catalysts, several materials were developed, which contain all the catalytic species immobilized on a single support, leading to isolation of the active sites needed in different steps. Accordingly, such catalysts could give improved results as compared with the homogeneous catalysts. In a few reactions, the support was also involved in the activation of one or more substrates or intermediates. Thus, the role of the heterogenization of the chiral organocatalysts is often not merely to facilitate the recovery and reuse of these materials, but also to improve the performances of the chiral catalysts. The known examples also show that the latter goals may be reached only by meticulous catalyst design.

2.3. Asymmetric one-pot reactions over chirally modified solid catalysts

A convenient method to obtain heterogeneous chiral catalysts is the modification of catalytic surfaces by optically pure compounds, the so-called chiral modifiers.[17–24] The chiral compounds used have no catalytic activity in the reaction and will have "solely" the role of directing the substrate on the catalyst surface. Usually, the simple adsorption of the chiral modifier is sufficient to reach appropriate results and often the addition of the modifier to the reaction slurry, *i.e.* the *in situ* modification, gives similar results to those obtained with catalyst premodified before introduction in the systems.

Most of the efficient chirally modified heterogeneous catalysts are supported metals, which are used in enantioselective hydrogenations of ketones and olefins.[20–24] However, metal oxides are also used as enantioselective catalysts following modification with chiral compounds.[193,194] Still, only one example of an asymmetric one-pot sequential reaction applying chirally modified metal oxide catalyst is known.[195] Nanocrystalline chirally modified MgO was used in the Claisen–Schmidt condensation and asymmetric epoxidation reaction sequence. The surface of the oxide nanoparticles was modified *in situ* with (+)-diethyl tartrate (CM1*) following the condensation step as illustrated in Scheme 43, when the oxidation agent was also introduced. The same sequence was also catalysed by preadsorbed poly-L-leucine on hydrotalcite



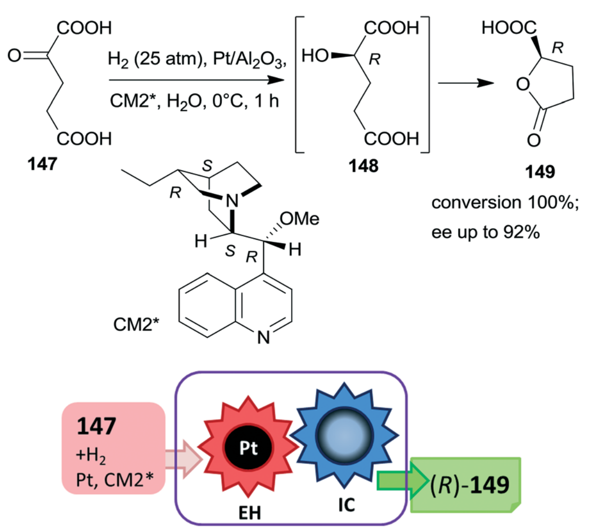
Scheme 43 Claisen–Schmidt condensation and asymmetric epoxidation one-pot sequential reaction catalysed by chirally modified nanocrystalline MgO and the suggested structure of the surface intermediate.[195]

CT21*, as shown previously (Scheme 34), where the oligopeptide was already present in the system in the first condensation step and was the active catalyst in the second asymmetric Juliá–Colonna epoxidation.[177] In contrast, CM1* has no catalytic activity, it was anchored on the surface of the MgO by hydrogen-bonding and controlled the direction of delivery of the nucleophilic oxygen of the surface-bonded peroxide (Mg–OO^{t}Bu) to the intermediates formed from the chalcone derivatives **121**, as shown by the structure in Scheme 43. In this one-pot sequential reaction, lower yields and enantioselectivities were obtained as compared to the use of CT21* or even with the two-pot method using the same MgO-NPs and CM1*. However, due to its simplicity and the catalyst recyclability, the procedure is an attractive way of preparing chiral ketoepoxides **122**.[195]

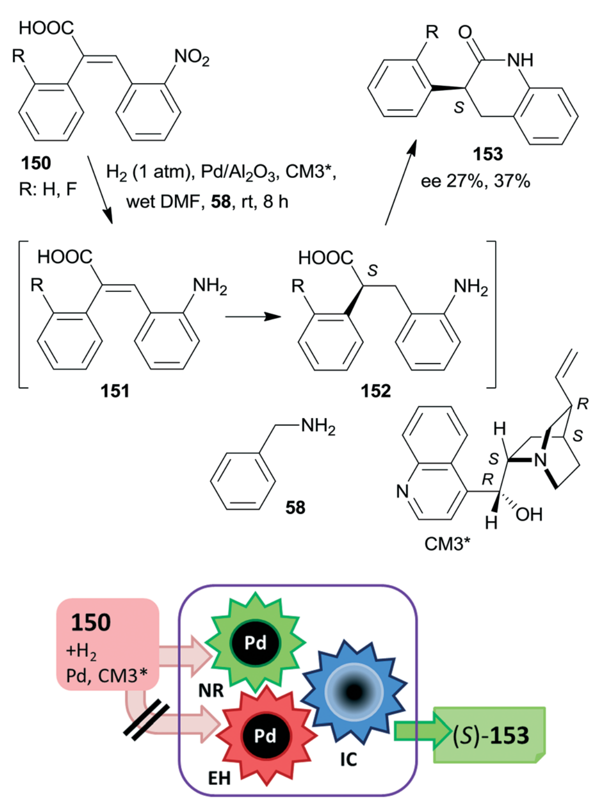
The use of heterogeneous chirally modified metal catalysts in enantioselective hydrogenations became extensively studied at the turn of this century. Among these, three catalytic systems were found to be highly efficient: the tartaric acid-modified Ni catalysts for the hydrogenation of β-keto esters and the Pt and Pd catalysts modified by cinchona alkaloids used in the enantioselective hydrogenation of α-keto esters and activated olefins, respectively.[20–24] However, the application of these catalysts in one-pot sequential or cascade reactions was retarded by the narrow substrate scope of these reactions and by the sensitive nature of the active chiral surfaces.

The first one-pot cascade reaction using a chirally modified metal catalyst exploited the facile cyclization of γ-hydroxycarboxylic acids to the corresponding chiral butyrolactones. Enantioselective hydrogenation of 2-oxoglutaric acid **147** over Pt/Al_2O_3 *in situ* modified by cinchona alkaloids gave 2-hydroxyglutaric acid **148** as the intermediate product, which by cyclization resulted in the formation of 5-oxotetrahydrofuran-2-carboxylic acid **149** (Scheme 44).[196] Hydrogenation in the same catalytic system of the diethyl ester of **147** also resulted in the chiral alcohol in up to 96% ee, however, the cyclization of the product needed a subsequent step using TsOH as catalyst.[197] The cascade reaction of the dicarboxylic acid **147** could be carried out in water; the best results, *i.e.* up to 92% ee at full conversion, were obtained at low temperature, under 25 atm H_2 pressure using dihydrocinchonidine methyl ether as modifier (CM2*). The second step of the cascade reaction may occur either on the catalyst surface or in the liquid phase, however, this was not investigated in the report.[196]

Cinchonidine (CM3*) was found to be the most efficient chiral surface modifier for the enantioselective hydrogenation of α,β-unsaturated carboxylic acids over supported Pd catalysts,[198] among which substituted (*E*)-2,3-diphenylpropenoic acids were hydrogenated in up to 96% ee.[199–201] During the hydrogenation of (*E*)-2,3-diphenylpropenoic acids bearing 2-nitro substituents on the 3-phenyl ring (**150**), the nitro group reduction, enantioselective hydrogenation and intramolecular amidation cascade took place, leading to 3-phenyl-3,4-dihydroquinolin-2(1*H*)-ones **153** (Scheme 45).[202] Although close to complete conversions of the acids to **153** were detected, the enantioselectivities were low due to the unfavourable effect of the substituents in the *ortho* position of the β-phenyl ring, similar to acids substituted with other groups in the same position.[199,201] It must be noted that the first two reductive steps of these reactions are competitive; however, both are necessary for the formation of the final



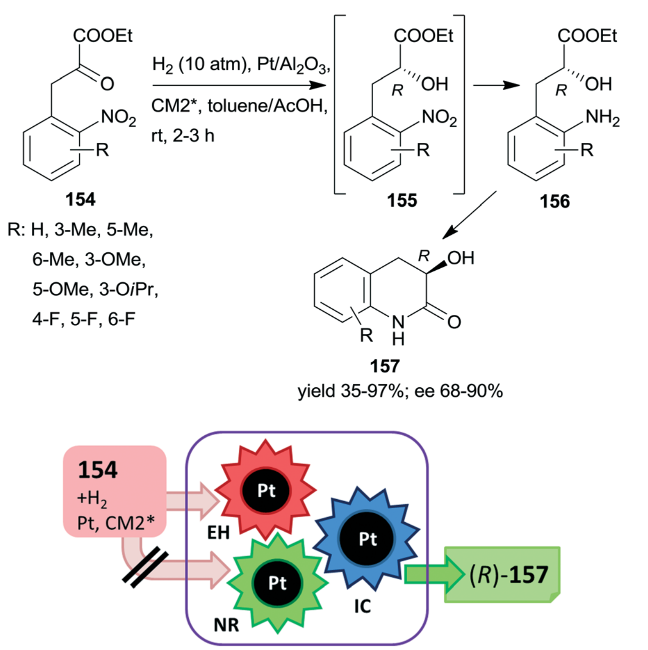
Scheme 44 Cascade enantioselective hydrogenation (**EH**) and intramolecular cyclization (**IC**) of 2-oxoglutaric acid using Pt catalyst modified by cinchona alkaloid CM2*.[196]



Scheme 45 Cascade nitro group reduction (**NR**), **EH** and **IC** over cinchonidine modified Pd catalyst.[202]

cyclic product. The order of these steps could be deduced from the high initial H_2 up-take rate characteristic of the nitro group reduction and confirmed by the ee values, which suggest the presence of electron donating groups (–NH_2) during the hydrogenation of the olefinic bond. There was no indication of whether the final step takes place on the catalyst surface or in solution; however lack of detection of the saturated intermediate **152** in the solution at any time may suggest the former pathway.

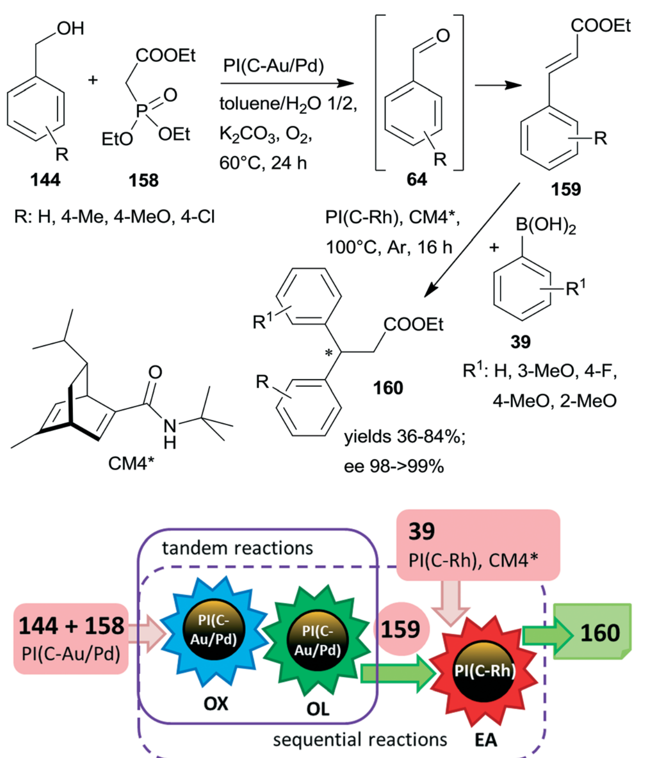
Aromatic nitro group reduction was also one of the steps of a one-pot cascade reaction developed recently over Pt catalyst modified by cinchona alkaloids.[203,204] The hydrogenation of 2-nitrophenylpyruvates **154** over chirally modified Pt catalysts resulted in the formation of optically enriched 3-hydroxy-3,4-dihydroquinolin-2(1*H*)-ones **157** (Scheme 46), instead of the indole-2-carboxylates usually formed *via* Reissert indole synthesis if other reduction methods are applied. Although in this cascade reaction the first two reductive steps are also competitive, the high yields of the quinolone derivatives **157** showed that the enantioselective hydrogenation accelerated by the presence of the chiral modifier preceded the reduction of the nitro group. The intermediate **156** bearing both hydroxyl and amino groups desorbed from the Pt surface and was further transformed following readsorption after consumption of the pyruvates **154**.[204] The highest ee values were obtained using CM2* as chiral modifier. Substituents on the phenyl ring of **154** had significant effects on both the yield and the ee by influencing the rate of the –NO_2 group reduction, and as a consequence the product distribution and by affecting the substrate-modifier interaction. Substituents next to the nitro group had beneficial influence on the quinolone selectivity.[203]



Scheme 46 Cascade **EH**, **NR** and **IC** of 2-nitrophenypyruvates over chirally modified supported Pt catalyst.[203,204]

It was demonstrated that the chiral modifier has multiple roles; besides inducing differentiation between the molecule enantiofaces by directing the adsorption of **154**, it accelerated the hydrogenation of the keto group, a feature characteristic to this catalytic system, and decelerated the reduction of the nitro group by occupying surface active sites. Moreover, it was shown that the presence of the nitro group also contributed to reaching good enantioselectivities by interacting with the adsorbed modifier; the absence of this group diminished the ee value. This heterogeneous cascade reaction was also carried out in a flow system using a Pt catalyst bed, however, the results obtained in batch system could not be equalled, especially as concerning the selectivity of the desired product **157**.[205] Results obtained in the flow system showed that instantaneous cyclization without desorption of the intermediate from the Pt surface also occurs at higher conversion.

The polymer incarcerated carbon black supported bimetallic Au/Pd NPs, *i.e.* PI(C-Au/Pd) used as the core of CT30* (Scheme 42) was applied in the oxidation followed by the Horner–Wadsworth–Emmons olefination tandem reaction to obtain α,β-unsaturated esters **159** (Scheme 47).[206] The tandem reaction was continued by a sequential asymmetric 1,4-addition of phenylboronic acid derivatives **39** to **159** using polymer incarcerated carbon black supported Rh Nps, *i.e.* PI(C-Rh), chirally modified with an optically pure diene CM4*. This three-step one-pot reaction afforded chiral β-branched esters **160** in moderate to good yields and



Scheme 47 Tandem **OX** and olefination (**OL**) followed by sequential one-pot enantioselective 1,4-addition (**EA**) over chirally modified Rh nanoparticles.[206]

outstanding enantioselectivities from various benzylalcohol derivatives and phenylboronic acids.

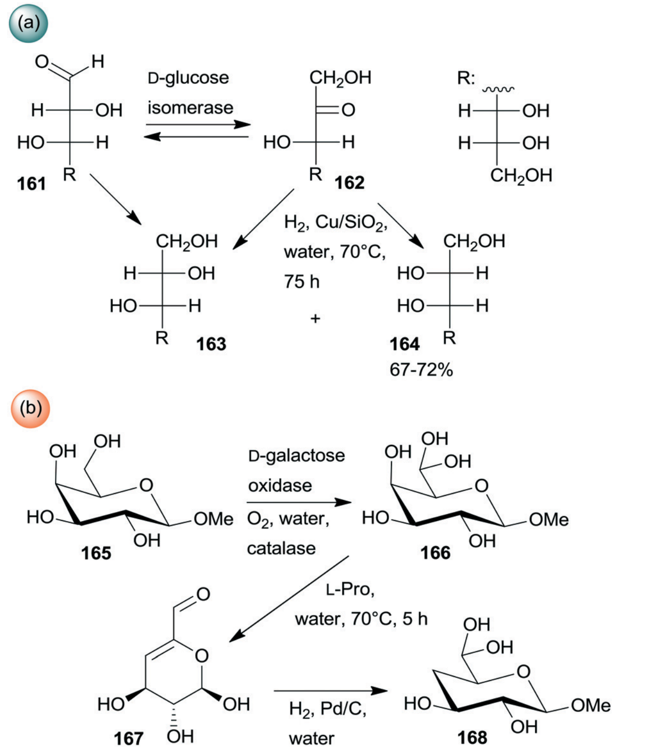
Chiral undecagold clusters bearing as ligand (*R*)- or (*S*)-(6,6′-dimethoxybiphenyl-2,2′-diyl)bis(diphenylphosphine) in combination with silver salts were used in tandem hydroarylation and cyclization reactions.[207] The Ag salt promoted the formation of larger Au NPs, as well as bimetallic gold complexes. Thus, during reaction, chiral surface modified Au was also formed, however, it was suggested that the complexes are the catalytically active species, which afford the target cyclopentane derivative in high yields and up to 44% ee. Utilization of the support chirality was attempted in the one-pot tricomponent aldehyde, alkyne, amine coupling. Deposition of Au NPs into channels of a chiral metal–organic framework prepared from L-lactic acid resulted in catalytically active material, without inducing significant enantioselectivities.[208] The latter two examples illustrated alternative approaches to preparing chiral catalytically active metal surfaces; however, these were less successful, as compared to the use of known enantioselective heterogeneous chirally modified catalysts.

In spite of the simplicity of obtaining and applying chirally modified metal catalysts in enantioselective reactions, the few examples of utilizing such materials in one-pot processes showed the difficulties in harmonizing the conditions and the tolerance of the components necessary in different steps of cascade or sequential reactions.

3. One-pot reactions including biocatalytic asymmetric step combined with heterogeneous chemical catalysis

Biocatalysis is still one of the most important ways to prepare optically pure fine chemicals.[12,65] The activities and stereoselectivities of enzymes are enviable. Attempts to reproduce these performances by chemical catalysts necessitate carefully designed catalytic materials. Complementing the substrate specificity of the enzymes with the broad applicability of chemical catalysts was the main driving force for developing one-pot processes combining the two types of catalysts.[69–71] In most of these processes applying such catalyst combinations, the stereoselective steps are biocatalysed, leaving the opportunity for choosing convenient heterogeneous chemical catalysts for the other steps. Exceptions to this strategy have already been presented in previous subsections (see Schemes 15, 25 and 33), in which anchored chiral chemical catalysts were applied along with enzymes. Although in **DKR**s enzymes are often used for the **KR** and heterogeneous chemical catalysts in the racemization steps,[73,75,77,79–82] these processes are beyond the scope of the present review, as indicated in the Introduction section.

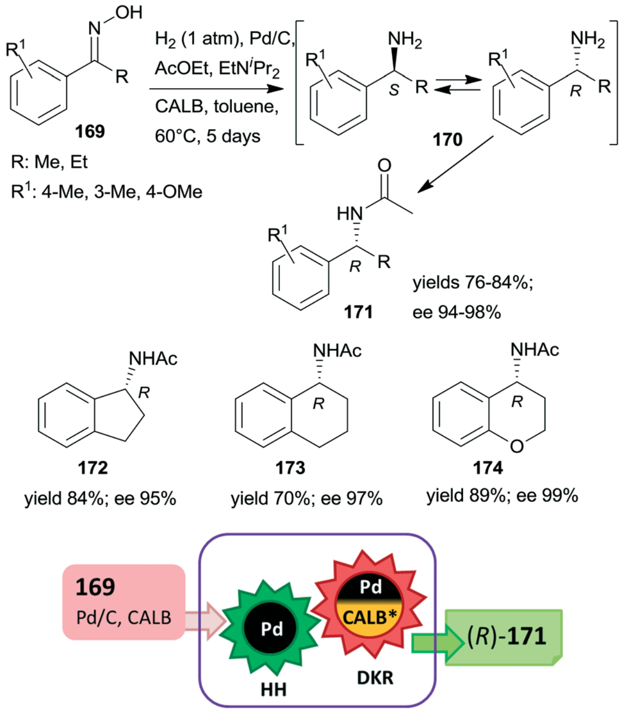
An early one-pot tandem process was developed by Van Bekkum and co-workers, who combined the enzymatic isomerisation of D-glucose (**161**) using immobilized glucose



Scheme 48 One-pot processes including enzymatic isomerization and heterogeneous catalytic hydrogenation (a); enzymatic oxidation, homogeneous catalytic dehydration and heterogeneous catalytic hydrogenation (b).[209–211]

isomerase with the heterogeneous catalytic hydrogenation of the **161** and D-fructose (**162**) mixture (invert sugar) to a mixture of D-glucitol (**163**) and D-mannitol (**164**).[209,210] Although the process may be considered a **DKR**, starting from pure **161** it was possible to reach high **164** selectivities using Cu/SiO_2 catalyst, suggesting that **161** is transformed in a biocatalytic and heterogeneous chemical catalytic cascade (Scheme 48a). Later, also in carbohydrate chemistry a sequential three-step one-pot process was developed for the transformation of methyl β-D-galactoside (**165**) to methyl 4-deoxy-6-aldehydo-β-D-glucoside hydrate **168**.[211] The one-pot process included a sequence of enzymatic oxidation, homogeneous catalytic dehydration and heterogeneous catalytic hydrogenation. Changes in reaction temperature and addition of catalysts was necessary between steps, which could be performed in water, warranting the success of the one-pot procedure (Scheme 48b). During the process, the only step in which a chiral centre was formed was the heterogeneous hydrogenation of the prochiral olefinic bond over Pd/C, and the stereoselectivity of this step was not induced by the catalyst. These sequential heterogeneous catalytic reactions were included in this survey as pioneering examples of using combinations of enzymatic and heterogeneous chemical catalytic steps in one-pot processes.

The one-pot combination of heterogeneous catalytic preparation of racemates with their successive **DKR** was initially described using Pd/C and lipase tandem catalysis.[212]

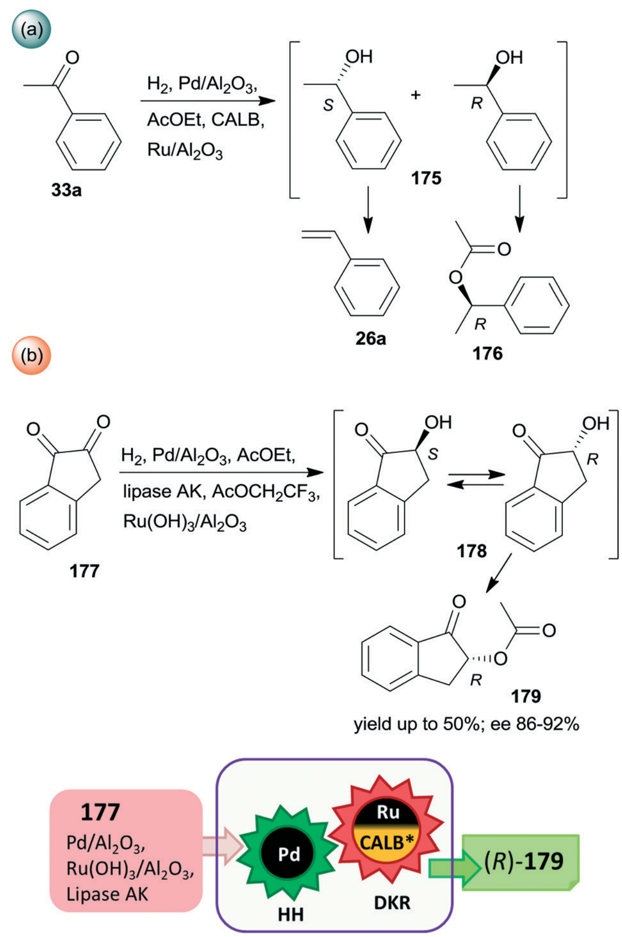


Scheme 49 One-pot transformation of prochiral ketoximes by heterogeneous catalytic hydrogenation (**HH**) and **DKR** using Pd/C and lipase B (CALB) catalysts.[212]

Prochiral ketoximes **169** were hydrogenated over Pd/C catalyst, followed by acetylation of the amine intermediate **170** with ethyl acetate using *Candida Antarctica* lipase B (CALB) immobilized on polyacrylamide polymer (commercially available as Novozym-435) in organic solvent, when the Pd also catalysed the racemization of the unreacted amine enantiomer. By **DKR** of the amines **170**, (*R*)-*N*-acetyl amines **171** were prepared in high yields and excellent enantioselectivities using various ketoximes, including carbocyclic and heterocyclic compounds (**172**–**174**) (Scheme 49). Notably, the Pd/C catalysed both the hydrogenation and the racemization reactions. Later, home-made Pd nanocatalyst, Pd/AlO(OH), was also applied in this cascade reaction using ethyl methoxyacetate in the acylation step, obtaining similar high yields and enantioselectivities in shorter reaction time (48 h).[213]

By a similar approach, prochiral ketones were transformed into acylated alcohols through chemo-enzymatic heterogeneous catalytic cascade reactions using supported Pd catalysts in the initial hydrogenation step.[214] These reactions, previously carried out using homogeneous hydrogenation catalysts,[215,216] were studied in more detail than the above presented one-pot reaction of ketoximes. In most of these studies, acetophenone **33a** was transformed into (*R*)-1-phenylethylacetate (**176**) by hydrogenation using supported Pd catalysts to produce racemic 1-phenylethanol (**175**) followed by acylation with ethyl acetate, applying the immobilized CALB (Novozym-435) catalyst.[214,217–221] In contrast to the one-pot reaction of ketoximes, in the transformation of **33a** it was shown that the Pd catalyst was not efficient in the racemization step. Although optically pure **176** was obtained, the selectivity of the product did not exceeded 50%. It was shown that the chiral product resulted from **KR** of racemic **175**, whereas the *S* alcohol enantiomer was consumed by side-reactions, such as dehydration to **26a**. Moreover, based on results obtained using different supports, it was concluded that by-products decreased the activity of both the metal and the enzyme.[214,217,218]

The sequential continuous-flow hydrogenation of **33a** over Pd/SiO_2–Al_2O_3 and **KR** of **175** by immobilized CALB or cross-linked enzyme aggregates was carried out in supercritical CO_2 using consecutive reactors.[219] Later, in order to catalyse the racemization of the unreacted (*S*)-**175**, supported Ru catalyst was also introduced in the batch system, which in the absence of Pd did not promote the hydrogenation of **33a**.[220] Promising results were obtained over Ru/Al_2O_3 (Scheme 50a).[220,221] The scope of the latter cascade reaction was extended on the transformation of 1,2-indanedione **177** using Pd/Al_2O_3, $Ru(OH)_3$/Al_2O_3 and lipase AK immobilized on celite as catalysts and trifluoroethyl acetate as acylation agent (Scheme 50b).[222] The evolution in time of the composition of the reaction mixture showed the **DKR** of *rac*-2-hydroxy-1-indanone **178** formed regioselectively by hydrogenation over Pd/Al_2O_3. The (*R*)-2-

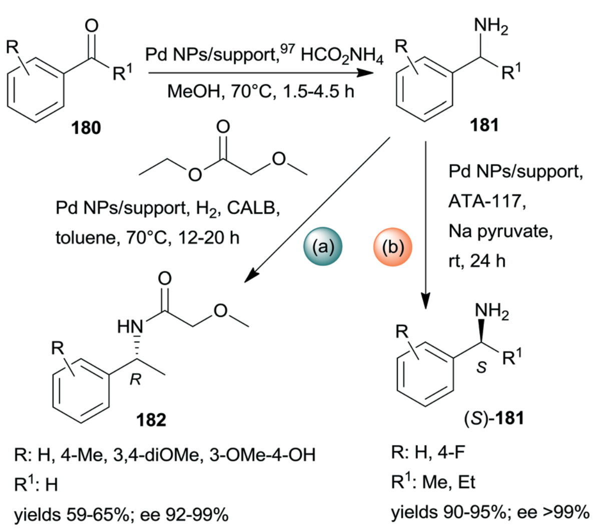


Scheme 50 Cascade reaction of prochiral ketones by **HH** and **KR** or **DKR** using supported Pd, Ru and immobilized lipase catalysts.[220–222]

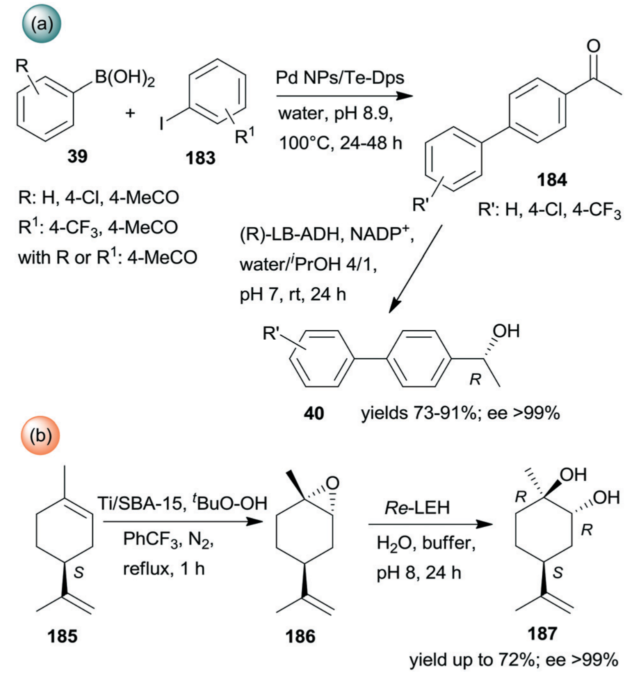
acetoxy-1-indanone **179** resulted in good enantiomeric purity (86–92% ee), however, only up to 50% yield was achieved.

Córdova and co-workers disclosed asymmetric one-pot heterogeneous metal – enzymatic relay catalytic processes using Pd NPs anchored on aminopropyl-functionalized mesocellular silica foam catalyst developed previously (Pd NPs/support,[97] Scheme 3).[223] Aromatic ketones **180** were transformed into racemic amines **181** by reductive amination using $HCOONH_4$ for the *in situ* generation of imines and also the hydrogen source in the reductive step catalysed by Pd. The enzymatic **KR** of the racemic amines followed this heterogeneous catalytic step by transformation of **181** into amides **182** using lipase (CALB, Novozym-435) catalyst and ethyl methoxyacetate as acylation agent. Changing the solvent between the two catalytic steps and introduction of additional Pd catalyst in the second reaction to decompose the excess $HCOONH_4$ hydrogen donor was necessary. However, it was found that under these conditions, no racemization of the amine occurred, and the corresponding amides were obtained in good optical purities, but low yields. In order to foster the racemization of the unreacted amine enantiomer, the second step was carried out under H_2 atmosphere, which promoted this reaction and allowed increased yields of the *R* amides (Scheme 51a). The reductive amination using the same Pd catalyst was also combined in a one-pot sequential process with enzymatic kinetic resolution of the amines **181**. Amine transaminase (ATA-117) and sodium pyruvate together with supported Pd catalyst afforded high yields and optically pure (*S*)-**181** in this catalytic relay process (Scheme 51b).[223]

Palladium NPs stabilized by thermostable protein (Pd NPs/Te-Dps; Dps: DNA binding protein from starved cells) was used in the one-pot sequential Suzuki–Miyaura cross-coupling and enzymatic enantioselective reduction of phenylboronic acid **39** and phenyl iodide **183** derivatives,



Scheme 51 Sequential one-pot catalytic transformations of prochiral ketones by reductive amination and consecutive **DKR** to amides or kinetic resolution of the amines using supported Pd and CALB or ATA catalysts.[223]



Scheme 52 Sequential one-pot Suzuki–Miyaura reaction followed by enzymatic enantioselective reduction (a) and stereoselective epoxidation followed by asymmetric enzymatic hydrolysis (b).[224,225]

with one of the substrates bearing the acetyl group in the *para* position. The acetyl biaryl intermediates **184** were reduced to chiral biaryl alcohols **40**.[224] The first step was carried out in water at 100 °C, whereas cooling the mixture to room temperature and addition of ^{i}PrOH, alcohol dehydrogenase [(*R*)-LB-ADH] and $NADP^+$ afforded the optically pure alcohols **40** in high yields after 24 h of stirring, as shown in Scheme 52a. However, attempts to recycle the heterogeneous Pd catalyst were unsuccessful; in the third use, no transformation was observed, which showed that Pd species were removed from the protein.

One-pot sequential preparation of a single (1*R*,2*R*,4*S*)-menthene-1,2-diol isomer **187** was possible by epoxidation of (−)-limonene **185** using Ti deposited on ordered or amorphous mesoporous silica (Ti/SBA-15 or Ti/SiO_2) catalysts and ^{t}BuO-OH as oxidant in $PhCF_3$ solvent followed by selective hydrolysis with recombinantly expressed *Rhodococcus erythropolis* (*Re*-LEH) enzyme in potassium phosphate buffer, as illustrated in Scheme 52b.[225] The enzyme tolerated the presence of the organic solvent; thus, after cooling the mixture to room temperature, the addition of the aqueous biocatalyst solution to the crude product was sufficient to cause the second hydrolysis step to proceed. Good yields were obtained following the two steps; moreover, starting from (+)-limonene, the opposite diol enantiomer, *ent*-**187**, could be obtained.

Finally, the few examples reported on the application of heterogeneous chemical catalyst and biocatalyst combinations in one-pot preparation of optically pure compounds indicated the difficulties met in employing the two catalyst

Table 1 Summary of the one-pot asymmetric reactions using heterogeneous chemical catalysts

Chiral catalyst type	Type of the one-pot reaction: Cascade	Sequential
1. Soluble chemical catalyst	3 systems	2 systems
2. Heterogeneous chemical catalyst		
2.1. Immobilized metal complexes	6 catalysts	9 catalysts
2.2. Anchored organocatalysts	15 catalysts	8 catalysts
2.3. Modified solid catalysts	3 catalysts	2 catalysts
3. Biocatalyst	2 systems	4 systems

types concomitantly, due to often met incompatibilities with the components needed in different steps. Such incompatibilities are mostly due to differences in the solvent nature and reaction temperature required in steps catalysed by these very dissimilar catalysts. Due to these dissimilarities, the research of one-pot processes applying these catalyst combinations is directed mainly toward sequential procedures. However, owing to the outstanding stereoselectivities reached in the biocatalytic reactions and the practical advantages of the heterogeneous catalysts, the development of novel one-pot cascade reactions unifying these catalyst types is expected.

Conclusions and outlook

Asymmetric one-pot processes, which include heterogeneous catalytic steps, are presently the most suitable for improving efficiency and sustainability, and decreasing the environmental impact of the methods designed to prepare chiral fine chemicals. These processes may compete or complement the frequently applied biocatalytic methods by uniting the advantages provided by handling heterogeneous catalysts with the benefits of avoiding the intermediate product isolation. In spite of these attractive features, asymmetric one-pot processes using heterogeneous chemical catalysts have rarely been reported until now, although a vast number of highly efficient chiral catalysts used in asymmetric homogeneous one-pot processes are known. This is explained by the often laborious immobilization of these catalysts, the sometimes maleficent presence of the support and by the frequently observed unfavourable effect of reaction components and conditions needed in different steps of one-pot processes.

Detailed surveys of the reported results obtained using heterogeneous chemical catalytic systems showed the dominance of the application of catalysts obtained by immobilizing chiral organocatalysts, mostly by covalent bonding on organic polymers or inorganic supports, as shown in Table 1 (the numbers refer to the developed catalysts and the applicability in different reactions is not included). More than twenty catalytic systems have been disclosed with chiral catalysts prepared from amino acid derivatives such as proline and its derivatives, amino alcohol derivatives such as the highly efficient diphenyl prolinol ethers, peptides, cinchona alkaloid derivatives and some other chiral organocatalysts. Obviously, the most efficient, easily available and least sensitive catalytic compounds were anchored for these purposes in these studies, which in many instances ensured cascade reactions, without intervention between steps. However, some processes had to be carried out in a sequential manner, due to incompatibilities of the reactants, catalysts, or owing to the necessity for changing the reaction conditions between steps. The most sophisticated materials designed were solid catalysts bearing more than one kind of catalytic species that are incompatible; however, by site-isolation or compartmentalization, they led to highly efficient, multifunctional catalysts.

Heterogenized chiral metal complexes were less frequently applied in asymmetric one-pot processes as the anchored organocatalysts (Table 1). In the earliest examples, materials containing the metals that were transformed into the chiral complexes *in situ* by the addition of the ligand were applied, covalent bonding of the ligands to support prevailed later on. Accordingly, the same or similar immobilization methods could be used for preparing anchored organocatalysts and metal complexes. These common procedures accelerated the research aimed at applying both anchored organocatalyst and metal complexes. Among the one-pot reactions developed using heterogenized chiral metal complexes, those carried out sequentially are more numerous, as compared with the cascade procedures, which is explained by the higher sensitivity of the metal complexes. However, examples of site-isolated materials using chiral metal complexes were also reported, similar to the anchored organocatalysts.

Although simple to prepare, chirally modified catalytically active surfaces were less frequently employed in one-pot reactions, due to the narrow substrate specificity of the few efficient chirally modified catalytic systems. Thus, only few examples of one-pot reactions are known to date, which use such chiral catalysts. Moreover, catalytic systems applying heterogeneous achiral catalysts in combination with soluble chiral catalysts or biocatalysts are also scarcely met in the literature, which is mostly due to the focus on chiral catalyst recycling in these processes.

This survey of the asymmetric heterogeneous catalytic one-pot reactions showed that during the last twenty years significant efforts were devoted to developing such catalytic systems, which culminated in the last few years. The several successful examples disclosed to date have demonstrated the preparative potential residing in such procedures. Undoubtedly, the multiple advantages of these methods will further accelerate the development of asymmetric one-pot reactions relying on the use of heterogeneous chemical catalysts.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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