Preface

Over the last decade the environmental setup has changed for synthetic organic chemists to a considerable degree. So far synthetic organic chemistry had focussed on methodology development which mainly deals with the development of new reactions as well as new reagents and catalysts. These ought to be able to perform preferentially highly selective (chemo-, regio- and stereoselective) synthetic transformations, often applied in the context of complex and highly functionalized molecules.

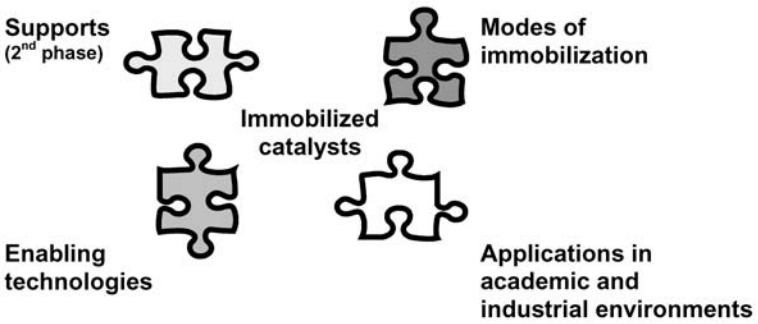
Except for the synthesis of peptides and oligonucleic acids, little attention has been spent on the question of how synthesis can be carried out in an environment of sophisticated technologies which includes improved hardware. While peptides and oligonucleotides are conveniently prepared by Merrifield's solid phase technique, solution phase synthesis of most other synthetic targets have not been substantially replaced by this solid phase approach. Without discussing this aspect in detail it is obvious that today a renaissance of sophisticated solution phase synthesis can be noted. Immobilization of reagents and particularly catalysts, an old concept indeed, recently returned back onto the stage and this is addressed in this volume of Topics in Current Chemistry in a broader sense.

The volume consists of eight chapters and is intended to introduce the reader to various aspects of immobilizing catalysts. Particular focus was spent on the concept that immobilization is only one out of many new enabling technologies introduced to organic synthesis and that the future of intelligent use of enabling technologies is associated with the clever and successful combination and integration of these techniques. As enabling techniques ionic liquids or perfluorinated solvents need to be listed, as well as the use of microwave assistance and continuous flow devices, and these aspects have been incorporated into this volume. In fact, immobilization of homogeneous catalysts not only requires detailed knowledge on the performance and properties of homogeneous catalysts. Successful applications of homogeneous catalysts in an heterogeneous environment must take the second phase and the mode of immobilization into account, often underscored by synthetic organic chemists.

Thus, this volume tries to tell a story. Definitely, it is not the only story to be told on immobilized catalysts. Our story starts with the phase to which the catalyst is attached to and further proceeds to the question of how homogeneous

catalysts can best be fixed to a second phase. From there the journey proceeds to actual synthetic applications of catalytic processes with particular focus on Pd-catalyzed transformations before two contributions will show how immobilized catalysts can conveniently be combined with other enabling technologies, namely microwave assistance and continuous flow reactors.

Finally, the breakthrough of new technologies can clearly be spotted when they have paved their way into industrial applications. Then such technologies are versatile and economical enough to create products or improve processes on larger scales. Little details on these aspects can be found in the literature, as chemical and pharmaceutical companies tend to be vague about the introduction of new concepts into process engineering. This volume covers two reports on immobilized catalysts in industrial settings. From these reports one can conclude that immobilized biocatalysts have reached the production lines already while solid phase attached chemical catalysts are still struggling through a jungle composed of lack of efficiency, leaching problems and finally recyclability of these catalytic systems as well as attitudes and closely defined perceptions among those who deal with process engineering. However, it is only a matter of time before immobilized catalysts will become a common tool outside the academic world.



Finally, I have to thank all contributing authors and colleagues who made this volume possible. It has been a great privilege and honour to assemble a magnificent crew of outstanding scientists who put a lot of effort into the production of state of the art manuscripts and who at the same time ideally held all deadlines set by the editor. Particular thanks are directed to Springer Verlag and Frau Marion Hertel as well as Frau Birgit Kollmar-Thoni who always gave support and encouragement when required.

Hannover, August 2004 Andreas Kirschning

Contents

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Polymeric Supports for the Immobilisation of Catalysts

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Abstract This chapter summarises the most frequently used polymeric supports for catalysis and highlights some recent developments in the field. Two classes of polymers, crosslinked solid phase supports and non-crosslinked soluble polymeric supports, are discussed with the focus on covalently attached catalysts. In addition, for soluble polymeric supports the different separation techniques are critically compared and evaluated for their application in catalysis.

Keywords Solid phase supports · Soluble polymeric supports · Hybrid supports · Dendrimers · Separation techniques · Homogeneous catalysis

Abbreviations

BET	Brunauer–Emmett–Teller adsorption isotherm
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
DB	Degree of branching
DCM	Dichloromethane
DMF	*N*,*N*-dimethylformamide
DVB	Divinylbenzene
GPC	Gel permeation chromatography
Leu	Leucine
MPEG	Monomethylated poly(ethylene glycol)
MWCO	Molecular weight cut-off
SEC	Size exclusion chromatography
PAMAM	Poly(amido amine)
PD	Polydispersity
PEG	Poly(ethylene glycol)
PEI	Poly(ethylene imine)
PPI	Poly(propylene imine)
PS	Polystyrene
ROMP	Ring opening metathesis polymerisation
TADDOL	$\alpha,\alpha,\alpha',\alpha'$-Tetraaryl-1,3-dioxolane-4,5-dimethanol
TLC	Thin layer chromatography

1 Introduction

Polymeric supports revolutionised organic synthesis and catalysis at the end of the twentieth century and became a major driving force for lab automation and modern separation techniques [1]. Investigations on polymer-supported catalysts have been ongoing for many decades [2–4] but it wasn't until the explosion of interest in the field of combinatorial chemistry that the subject became an area of intense research activity [5–8]. Also in the last decade, a rapidly increasing number of new polymeric supports, crosslinked (insoluble) [9–12] and non-crosslinked (soluble) polymers [13–17], have been published and used for polymer-supported catalysis. The reader should be aware of the fact that there is no polymeric support for general application in organic synthesis and catalysis. Every polymer has its drawbacks (e.g. chemical stability, polarity etc.) and hence can be used only within a certain range of reaction conditions.

In this chapter, we will describe the structure and the properties of the most frequently used polymeric supports as well as the effects of different spacer molecules (Fig. 1). Spacer molecules, as compared to linker or ligand molecules, are used to provide more accessible catalytic sites and to modify the properties of the polymer matrix (e.g. polarity, swelling characteristics). The two major classes of polymeric supports, solid and soluble polymers, will be discussed with respect to their application in catalysis. Detailed examples will be found in the chapters by Bergbreiter and Uozumi. This chapter will focus on cova-

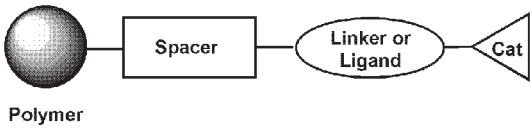


Fig. 1 General structure of a polymeric support for catalysis application

lently attached catalysts and will not cover immobilised enzymes, molecular imprinted polymers (MIPs) or inorganic supports [18, 19].

2 Polymeric Solid Phase Supports for Catalysts

2.1 Polystyrene-Based Resins

Functionalised polystyrenes are available as linear non-crosslinked and as crosslinked polymers. The latter ones, generally referred to as PS resins, are among the most commonly used solid supports for solid-phase organic synthesis and catalysis. Nowadays, numerous types of polystyrene resins are commercially available. They can be obtained in different sizes, loading capacities (amount of functionalisation) and different degrees of crosslinking. In addition resins with a large variety of different linker groups, reagents and catalysts have been commercialised over the last 5–10 years [20].

Macroporous and microporous polystyrene resins are typically prepared by suspension polymerisation [21, 22]. The basis of this process is the dispersion of an organic phase (constituted of a monomer, a radical initiator, a crosslinking agent and eventually a comonomer) into an aqueous phase [23, 24]. The size of the initial droplets is adjusted by emulsifying the organic phase under stirring in the presence of a polymeric surfactant, which governs the final size and the final size distribution of the beads after polymerisation [21, 22]. The different bead sizes are then separated by a multiple sieving process. Resin beads used for solid-phase synthesis and catalysis are spherical particles, typically in the range of 50 to 500 μm, which can be easily handled.

In order to obtain insoluble resins, a crosslinking agent has to be used for the synthesis of the beads by suspension polymerisation [9, 10, 22]. A crosslinking agent is generally a bi- or multifunctional molecule that can be incorporated in two or more growing chains during the polymerisation process, leading to interconnected chains. The most popular crosslinking agent, used in the presence of styrenic monomers, is divinylbenzene (DVB) but many other crosslinkers have also been used to obtain special effects (see below).

For chemists working with polymeric supports, it is of great importance to have a good knowledge of the internal structure and morphology of the mi-

crobeads, because they strongly influence the physical properties and as a consequence the reactivity of the functional sites. For example, if active sites are located in highly crosslinked microdomains, as can be the case in macroporous resins, they will remain inaccessible for reactions and the effective loading will be lower than the theoretical one [25].

Even in microporous resins, one can expect some heterogeneities due to the different reactivities of the monomers and crosslinking mixtures involved in the suspension polymerisation process [22, 26]. However, it has been demonstrated experimentally that the distribution of reactive sites is homogenous throughout the whole bead [27–30]. Based on geometrical considerations, one should also be aware of the fact that in microbeads with a diameter of 100 μm, 50% of the active sites are within the first 10 μm of the outer shell [27].

2.1.1
Macroporous Resins

Macroporous resins are generally highly (>5%, typically 20–25%) crosslinked polystyrene microbeads [9, 10, 21]. The term "macroporous" refers to their inner skeleton, which is made of a permanent porous structure even in the dry state (cf. Scheme 1c). Historically, functionalised macroporous resins have mainly been used for ion exchange and separation. Nowadays, many new applications, especially in the field of polymer-supported reagents [31, 32] and catalysts [5, 7], have been developed.

Macroporous resins are prepared by suspension polymerisation of monomers such as styrene, vinyl pyridine, acrylamide or glycidyl methacrylate with a porogen agent, such as a low boiling solvent (Scheme 1) [21, 33]. Thus, a mixture of monomer with eventually a comonomer and a crosslinking agent is copolymerised after dispersion in aqueous medium in the presence of the porogen, which remains within the beads during the polymerisation and acts as a template for the formation of the permanent internal porous structure of the final resin. After completion of the polymerisation the porogens are re-

Scheme 1a–c Synthesis and structure of macroporous resins. **a** Polymer network forming; **b** porogen phase acts as pore template; **c** dry macroporous resin with large interconnected pores. (*1*) Porogen and network start to phase separate; (*2*) porogen phase removed to yield pores (*hatched area*=crosslinked polymer, *dots*=porogen phase)

moved depending on their characteristics and a hard opaque bead with a rough surface remains. The opacity of the macroporous resins, as compared to the glassy appearance of the microporous beads, is due to their heterogeneous structure made of highly crosslinked polymeric microdomains and pores devoid of polymer.

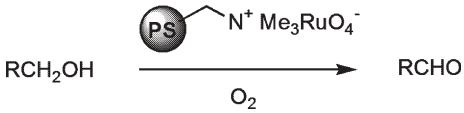
2.1.1.1 Structure and Physical Properties of Macroporous Resins

Due to their mode of preparation, macroporous microbeads are constituted on the one hand of a permanent macroporous internal structure and on the other hand of highly crosslinked areas (Scheme 1c). The porous areas are made of numerous interconnected cavities of different sizes leading to a large internal surface available for functionalisation, whereas the crosslinked areas provide the rigidity to such structures [22, 33]. This high internal surface area, typically ranging from 50 to 1,000 m^2/g (determined by N_2 BET), is accessible even in the dry state. In general, macroporous resins show very low swelling in organic solvents due to the very highly crosslinked areas. For that reason, macroporous beads remain unaffected by changes in the direct environment, even in the presence of "good" solvents. Another consequence is that the pores can accommodate a large variety of solvents including polar solvents as water and low molecular weight alcohols. Because of the pore size and the presence of channels interconnecting these cavities, solvents can diffuse rapidly in and out of these pores.

One drawback of these heterogeneous structures is the very low accessibility of the solvents and reagents to the very crosslinked areas, with the consequence of limited loading capacities with a typical range of 0.8 to 1.0 mmol g^{-1} [12]. However, some commercial ion-exchange resins, also used for immobilisation of organic reagents and catalysts, have loading capacities up to 4.5 mmol g^{-1} [32]. Generally, macroporous resins display lower reactivities than microporous swollen beads. In contrast to microporous resins, they show high resistance towards osmotic shock [22], but they can be brittle when not manipulated carefully [23].

2.1.1.2 Applications of Macroporous Resins in Catalysis

The most extensively used macroporous resins are polystyrene-based ion-exchange resins. They are made of poly(styrene-*co*-divinylbenzene) with subsequent modification to arylsulphonic acids, quaternary ammonium salts or other derivatives mainly located on the internal surface of the pores [33, 34]. This renders them accessible to numerous organic solvents including water and alcohols. Recently, these ion-exchange resins have had a revival for the immobilisation of ionic reagents [31, 32] in automated synthesis. Macroporous beads have also been used for the immobilisation of catalysts [5, 7]; however, leach-



Scheme 2 Perruthenate oxidation catalyst supported on an ion-exchange resin

ing may be problematic in some cases due to the weak ionic interaction. A powerful example is the polymer-supported perruthenate (Scheme 2) introduced by Ley et al., which converts primary alcohols in the presence of oxygen selectively to the corresponding aldehydes [35, 36].

2.1.2 Microporous Resins

Microporous beads are weakly crosslinked resins obtained by suspension polymerisation of styrene and divinylbenzene in the absence of any porogen agent. This process leads to the formation of a homogeneous network evidenced by a glassy and transparent appearance. The most commonly used supports for solid-phase organic synthesis and catalysis are styrene-divinylbenzene copolymers crosslinked with only 1–2% DVB. Many of their derivatives are commercially available [20].

The loading capacity is controlled by the yield of the electrophilic aromatic substitution. Typically loading values are between 0.2 and 4.0 mmol g^{-1}, and a loading capacity of 1.5 mmol g^{-1} (for the most commonly used Merrifield resins) [37] corresponds approximately to 20% substituted aromatic groups. Higher loading Merrifield resins (4 mmol g^{-1}) have also been used in organic synthesis [38]. However, the highest possible loading of 6.55 mmol g^{-1}, which corresponds to 100% chloromethylstyrene, would not be useful in practice [10].

2.1.2.1 Crosslinkers and their Effects on the Matrix Properties

For microporous resins the exact degree of crosslinking and the nature of the crosslinker are even more important than for macroporous resins, due to the severe effect on the swelling properties and matrix effects. The most common microporous resins are 1 to 2% crosslinked, but resins with less crosslinkage have also been studied [39]. They are mechanically weak and consequently easily subject to damage [9]. However, increased reaction rates have been observed for these more flexible polymer networks. It is important to keep in mind that the divinylbenzene used for crosslinking is usually a technical grade product with a composition that can vary from one batch to another and influence the properties of the beads. The consequences are variable amounts of crosslinking agents incorporated in resins depending on the different polymerisation

batches, which generally lead to relatively high error values (±0.5%) in the degree of crosslinking.

Alternative crosslinkers are ethylene glycol dimethacrylate (EGDMA), *N*,*N*-methylene bisacrylamide (MBA) and trimethylolpropane trimethacrylate (TRIM) and, more recently, novel crosslinkers have been introduced like 1,4-bis(vinylphenoxy)-butane [40] and bis(vinylphenoxy)-PEG [41, 42], which present the advantage of having a strong influence on the swelling properties due to the increased flexibility between the two crosslinking units and their compatibility with polar or even protic solvents. Crosslinkers with a higher degree of functional groups, and especially those with ligands incorporated, have also been used in solid-phase catalysis (Fig. 2).

Styryl-terminated Fréchet-type dendrimers have been introduced as novel polymer crosslinkers by Seebach et al. [43–45]. They are constituted of four to 16 peripheral styryl units attached to aryl end branches of dendritic TADDOL, BINOL or Salen ligands and were copolymerised with styrene by suspension polymerisation. The catalytic performance of the polymer-bound catalyst was identical to that of the homogeneous analogues; however, the supported catalysts could be used in many consecutive catalytic runs with only small loss in catalytic activity. A major drawback of fixing the catalytic unit in the core of the crosslinker is the poor loading capacity of the final polymer (0.13–0.20 mmol g^{-1}), especially when high amounts of catalysts (10–20 mol%) are needed.

2.1.2.2 Physical Properties of Microporous Resins

In contrast to macroporous resins, microporous beads have a low internal surface area in the dry state of less than 10 m^2/g (determined by N_2 BET) [22], due

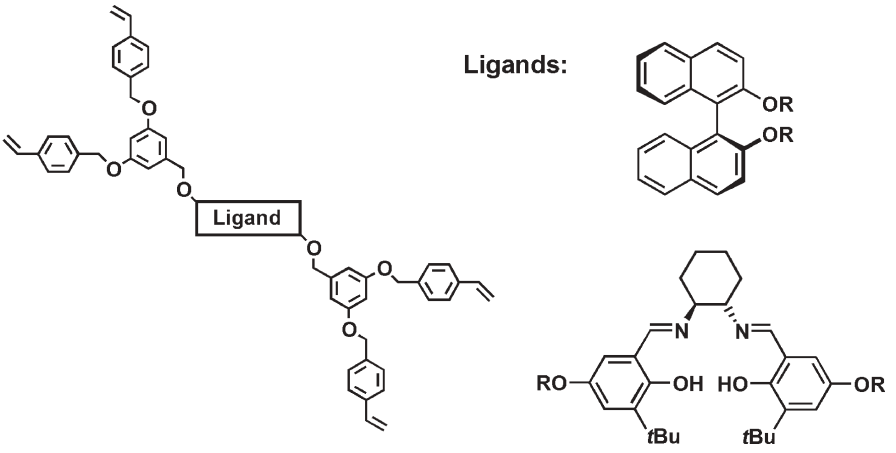


Fig. 2 Dendritic crosslinkers for the immobilisation of chiral ligands

to their more homogeneous structure that does not allow the diffusion of gases or "bad" solvents into the polymeric network. As polystyrene is hydrophobic and non-polar, swelling of microporous polystyrene resins will occur in non-protic solvents such as dioxane, dichoromethane, DMF, tetrahydrofuran or toluene, but *not* in polar protic solvents (e.g. water, alcohols) and apolar aprotic solvents (e.g. alkanes) [46]. The swelling of a resin not only depends on the nature of the solvent but also on the degree of crosslinking and the spacer molecules [39, 47]. It is indeed obvious that the percentage of swelling is inversely proportional to the crosslinker over monomer ratio. Thus, 1% DVB polystyrene swells four to six times its volume in dichloromethane, while in contrast 2% DVB polystyrene swells two to four times its volume in dichloromethane. The transformation of polystyrene microbeads by the grafting of spacer groups (cf. Fig. 1), such as PEGylation, can lead to dramatic changes in the swelling properties (see Sect. 2.2) [9, 10].

2.1.2.3 Mechanical and Chemical Stability of Microporous Resins

Care has to be taken when working with microporous resins in different solvents. Osmotic shock can occur, when a pre-swollen bead (in a good solvent) is introduced into a bad solvent. The beads start rapid shrinking under expulsion of the good solvent and are subjected to stress. This leads to mechanical damage or at least to non-negligible modifications of the structure [9]. Another problem that has to be encountered when conducting a reaction on swollen microporous resins is that they can break if agitation conditions are too vigorous, e.g. with a magnetic stirrer. Scanning electron microscopy studies revealed that most of the beads are broken as compared to the beads collected after a reaction conducted on a mechanical shaker [9]. The consequence for broken resin beads is the clogging of the filters used during their purification.

Concerning the chemical stability of polystyrene resins and their derivatives, it has been shown that they are relatively stable towards weak oxidants, strong bases and acids. In fact, reactions that are known to proceed on alkyl-substituted aromatic compounds, especially electrophilic substitutions, will also occur on crosslinked polystyrene [10]. Strong oxidants at elevated temperatures and electrophilic reagents should therefore be avoided [10, 23].

2.1.2.4 Application of Microporous Resins in Catalysis

Due to the easy handling of polystyrene microbeads a large number of recent reviews have appeared to highlight the tremendous developments in this area [3–8]. Some more detailed examples are presented in the chapter of Uozumi et al. Despite the great efforts made in this area, it should be noted that many catalytic reactions using transition metal catalysts in combination with solid phase supports often require larger amounts (1–100 mol%) of catalyst due to

deactivation of the active species as compared to the soluble systems [6, 8]. Also, leaching of the catalyst from the polymeric support can become a significant problem when monodentate ligands, such as triphenylphosphine, are used [6, 7].

2.2 Polystyrene Hybrid Supports

2.2.1 PEGylated Solid Phase Resins

Even if Merrifield resins and their derivatives are still the most commonly used resins for the synthesis of small molecules, one of their limitations is the poor swelling in polar protic solvents. For instance, Merrifield resins can not be applied in protic solvents, such as water or alcohols. This problem, however, can be overcome by designing "amphiphilic" resins made of a 1% crosslinked polystyrene matrix onto which poly(ethylene oxide) chains are grafted (Fig. 3) [48, 49]. Typically, their composition is 70 wt% of PEG grafts (average molecular weight of 3,000 g mol^{-1}) and 30 wt% of PS. Therefore, the loading of PEGylated resins (TentaGel, ArgoGel, NovaGel) is relatively low (loading values range from 0.15 to 0.60 mmol g^{-1}) as compared to the higher loading capacities that can be reached for Merrifield resins. PEGylated supports are far more polar than unmodified polystyrene resins and hence they swell in a broad range of solvents from apolar aprotic to polar protic solvents and even water [9, 10, 46].

PS-PEG hybrid resins opened many new possibilities for supported catalysts by allowing the use of protic solvents. Even on-bead screening is possible with these resins. A drawback of such PS-PEG hybrid resins for catalysis originates from the nature of the PEG polymer, which is hygroscopic. Hence the presence of large amounts of PEG (up to 70%) renders the beads more sticky and then more difficult to be completely liberated from water [22].

PEGylated resins, e.g. TentaGel, were originally developed to build up peptidic molecules [48, 50]. Recently, peptidic ligand libraries and their catalytic activities have been investigated by several groups [51]. In some cases severe effects of the PEG chain on the efficiency and selectivity of the peptidic catalyst have been observed. For example, Berkessel et al. screened several TentaGel-bound peptides for enantioselective epoxidations of unsaturated ketones and found a highly active pentapeptide (L-Leu)$_5$ on TentaGel-NH_2, which can form

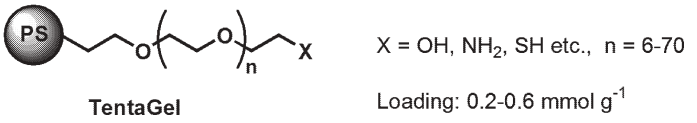


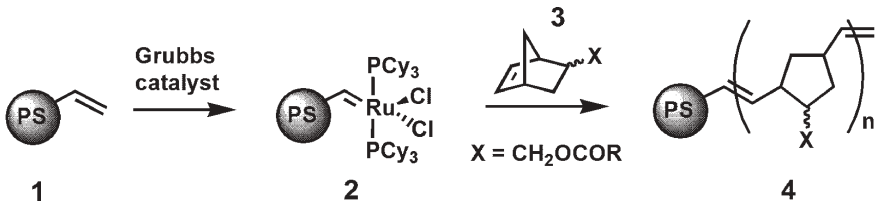
Fig. 3 Chemical structures of TentaGel resin and typical functional groups

a helical structure [52]. They also compared the catalytic performance of the TentaGel-bound peptides with (i) L-Leu oligomers bound to MeO-PEG-OH and (ii) free L-Leu oligomers. Interestingly, for the PEG-bound materials, the 5-mer already showed some enantioselectivity (>50% *ee*), whereas an onset of selectivity was found around the 10-mer in the case of the free L-Leu oligomers. This comparison of PEG-bound and TentaGel-bound peptides suggests that the attachment of the PEG peptide conjugates to a polystyrene matrix (i.e. peptide on TentaGel) further favours the helical arrangement and thereby enhances the selectivity.

2.2.2 High-loading Polystyrene Hybrid Supports

2.2.2.1 Polystyrene – Linear Polymer Hybrids

A general problem in solid-phase catalysis is the low loading capacities of the commonly used solid phase resins. Often, large quantities of resin are required in order to support substantial amounts of catalyst. Even though several linear graft polymers with high loading capacities (~3 mmol g^{-1}) have been prepared, e.g. ROMP-spheres **4** [53] and RASTA silanes [54], they have not yet been applied in catalysis. However, similar crosslinked ROMP-based polymers without a polystyrene backbone have been used as supports for catalysts [55]. Also, during the development of the ROMP-spheres an interesting catalytic intermediate **2** was used to build up the polymer chain by ring-opening metathesis polymerisation. This high-loading solid phase support uses cross metathesis between vinyl polystyrene beads **1** and norbornene derivatives. In a first step the immobilisation of the ruthenium catalyst (Grubbs catalyst) on vinyl polystyrene **1** can be achieved via insertion of ruthenium into the styryl double bond to form a carbene complex (Scheme 3). The PS-supported ruthenium alkylidene **2** shows good stability under normal atmospheric conditions when dried. Treatment of the PS-supported catalyst **2** with an excess of a norbornene derivative **3** yields a ROMP-based polymer **4**, the so-called ROMP-spheres (Scheme 3). The catalytic intermediate **2** was further developed to become an



Scheme 3 Cross metathesis of the supported Grubbs catalyst and a norbornene derivative to yield ROMP-gels **4**. The polymer-supported catalyst **2** has also been used for ring-closing metathesis

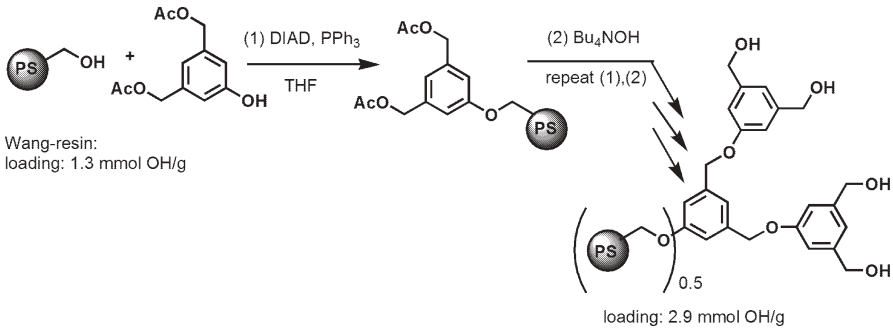
efficient PS-supported ruthenium catalyst for metathesis reactions [56]. The catalyst is believed to operate in a boomerang-type fashion for olefin metathesis. However, many other examples have been reported for solid-phase-supported metathesis catalysts [57].

2.2.2.2 Polystyrene – Dendrimer Hybrids

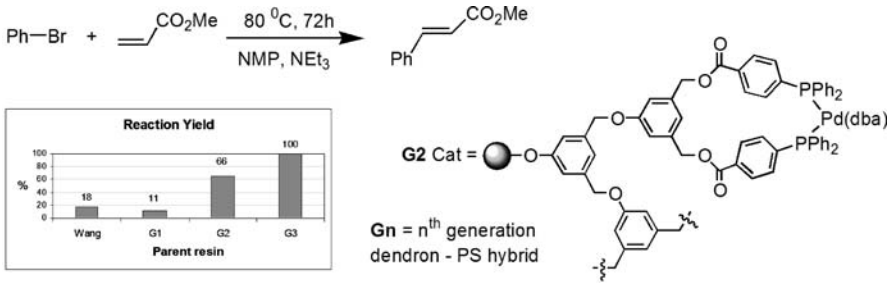
Another approach to high-loading resins are polystyrene–dendrimer hybrids [58–61]. Dendrimers are highly branched macromolecules built by a stepwise approach. The dendritic spacer molecules provide a rapid and efficient method to increase the loading capacity. For example, the use of a Fréchet-type aryl-ether dendronised solid support was reported by Bradley and coworkers (Scheme 4) [59]. These dendrons were introduced to find an alternative to PAMAM dendrimers, which form strong complexes with organometallic reagents and are thermally instable. The loading capacity of the solid support increased during the dendronisation from 0.82 mmol g^{-1} (0.44 nmol per bead) (starting resin hydroxymethylpolystyrene) to the sevenfold value of 2.9 mmol g^{-1} (3 nmol per bead) ([G3]-dendrons). A similar approach was also developed by Portnoy et al. who also investigated the catalytic properties of functional derivatives [62].

Functionalisation of these templates with phosphine ligands, followed by complexation with Co or Pd precursors, led to the demonstration of remarkable dendritic effects on the activity and selectivity of the catalytic systems in the Pauson–Khand [63] and Heck reactions (Scheme 5) [64]. The advantage of the weakly coordinating polyether dendritic backbone, as compared with the coordinating dendritic backbones (e.g. polyamide), was demonstrated for the Heck reaction [65].

Although the emerging characteristics of the dendritic supported catalysts hold promise for the improvement of immobilised catalytic systems, there is a serious problem impeding the investigation and development of such systems. The synthesis of dendritic molecules is a time- and effort-consuming process.



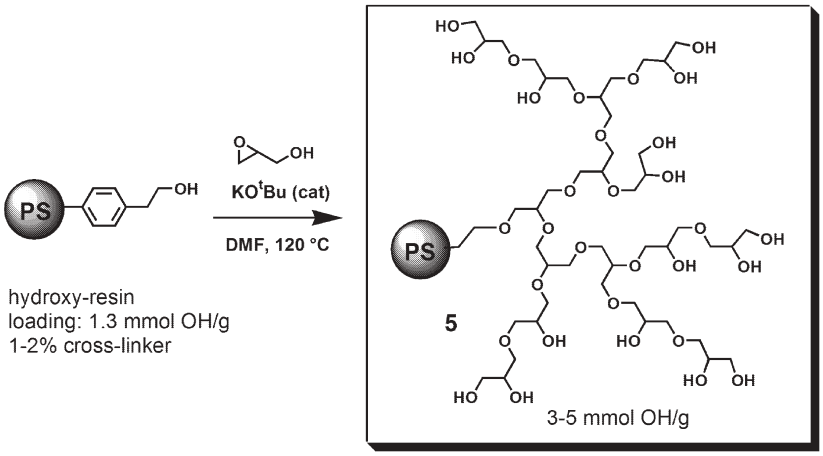
Scheme 4 Synthesis of high-loading PS-aryl ether dendrimer hybrid supports



Scheme 5 Remarkable dendritic effect in the Heck reaction using aryl ether dendrons on PS solid support

Preparation of dendrimers in solution via divergent or convergent routes proceeds through repetitive reaction sequences and is frequently complicated by incomplete conversion and difficult separation procedures [13]. Although the preparation of dendrons on solid supports (which usually proceeds along a divergent route) benefits from technical advantages characteristic of solid-phase synthesis, multistep synthesis on solid supports remains time-consuming and frequently results in partial decomposition of the support and reduced purity of the resin-bound species. A possible solution to this difficulty may be the replacement of dendritic units on supports by dendron-like hyperbranched oligomers.

Recently, Haag and coworkers reported on the synthesis of polystyrene beads dendronised with a hyperbranched polymer [66, 67]. The polystyrene–polyglycerol hybrid support **5** was obtained by grafting of a hyperbranched polyglycerol directly onto a Merrifield resin [67] or alternatively polymerising glycidol directly onto a polyhydroxylated crosslinked polystyrene



Scheme 6 One-step synthesis of high-loading DendriGel supports **5** by grafting glycidol onto hydroxy-PS resins

starter (Scheme 6) [66]. This support shows high loading capacities (3–5 mmol g^{-1}), good swelling properties (e.g. in DCM, DMF, MeOH, water) and is currently under investigation for catalytic applications.

Even though the solid-phase beads are heterogeneous, the reaction rate of catalytic reactions can be similarly high as compared to homogenous monomeric systems [68]. Arya and coworkers reported on the solid-phase synthesis of Rh-complexed PAMAM-diphosphonated dendrimers anchored onto polystyrene beads and pseudopeptide-based building blocks to form the dendritic skeleton [69, 70]. Again the formation of a rhodium complex with dendritic phosphine ligands was achieved. Different dendrimer generations were prepared and tested as catalysts for the hydroformylation reaction of several olefins. For the hydroformylation of styrene, the PS [G2] dendrimer showed complete conversions (>99%) and selectivities (94% branched isomer) higher than the first generation, and its activity did not decrease for up to five cycles. The origin of this increased reactivity might be due to the higher density of ligands on the outer shell and cooperative effects, and once again would be an example for a positive dendritic effect.

3
Soluble Polymeric Supports for the Immobilisation of Catalysts

3.1
General Aspects

For use in organic synthesis the most common solid phase supports show some disadvantages, such as heterogeneous reaction conditions and therefore unadvantageous kinetics, low loading capacities, an exacerbated analysis and problematic mechanical stability. Due to the heterogeneity of the support, access to the reactive site is often reduced and hence results in poor catalysis. Also the structural information regarding this type of reaction is limited: while the ability of the catalyst to be recycled is easily assessed in a test experiment, structural analysis of the precatalyst before as well as after recovery (at the end of the reaction) requires specialised techniques for insoluble polymers. In some cases these problems can be overcome using soluble polymeric supports, which have been proposed since the early seventies as an alternative to conventional solid phase supports [48].

Soluble supports feature homogeneous reaction conditions and enable the application of standard analytical techniques (TLC, IR, NMR, MALDI-TOF etc.) as well as the orthogonal use of insoluble reagents. One drawback of soluble supports is the fact that there is no generally practicable separation technique as for solid phase supports. Although several simple purification methods exist, it has to be carefully decided which one to employ, especially when automation and parallelisation are investigated. Several overviews of this class of supports, which have been used in organic synthesis and catalysis includ-

ing applicable separation techniques, have been published [9, 13, 14, 16, 17, 71–78].

The soluble polymeric supports presented in this chapter will be classified according to their topology, which strongly influences the physical properties of these materials. There are three major classes: (i) endgroup-functionalised linear polymers, (ii) linear polymers which contain a reactive group in every monomer unit and (iii) starpolymers and branched structures like hyperbranched polymers and dendrimers.

3.2 Separation Techniques

One of the major benefits of polymer-supported catalysis is the recovery and the reuse of immobilised catalysts, especially when dealing with chiral catalysts which can be extremely expensive [17]. Therefore effective separation methods are required [1]. However, one has to keep in mind that even the best separation technique can't overcome all the problems that can occur in polymer-supported catalysis. For example, metal leaching is one major problem associated with the use and the recycling of metal-based, polymer-supported catalytic systems and often the addition of fresh metal species to the recovered catalysts is

Table 1 Separation techniques for soluble polymeric supports

Parameter	Dialysis	Ultra-filtration	SEC	Precipitation/ filtration	Liquid-phase separation
Separation by	Hydro-dynamic volume	Hydro-dynamic volume	Hydro-dynamic volume	Solubility	Solubility
MW of polymer	>1000 g mol^{-1}	>1000 g mol^{-1}	–	>3000 g mol^{-1}	–
Typical sample volume	5 mL^{-1} L	1–100 mL	< 1 mL	1–100 mL	10 mL^{-1} L
Commer-cially available	Yes	Yes	Yes	–	–
Suitable for automation	Yes	Yes	Yes	No	Yes
Suitable for high through-put	No	Yes	Yes	No	Yes
Limitations	Only suitable for polymer isolation	–	–	Coprecipitation of impurities possible	Clear phase separation required

required [79]. Several comprehensive reviews dealing with separation techniques for soluble polymers can be found in the literature [1, 9, 13, 58, 72, 73, 78]. Soluble polymers can be separated from low molecular weight compounds in solution either by physicochemical properties or by size. Some different techniques and their restrictions are summarised in Table 1.

3.2.1 Separation by Physicochemical Properties

The most common protocol to separate soluble polymers from low molecular weight compounds is precipitation/filtration. This technique is frequently used in polymer chemistry and works particularly well if the polymer is crystalline and the glass transition temperature, T_g, is above ambient temperature [1]. For PEGs (poly(ethylene glycol)s) (soluble in water and most organic solvents; insoluble in hexane, diethyl ether, *tert*-butyl methyl ether, cold ethanol and isopropanol) and linear polystyrene (soluble in non-polar solvents, insoluble in methanol) this method has been widely applied [72]. The precipitation can be induced by adding a poor solvent to a solution of the support, by using polymers with temperature-dependent solubility (e.g. polyethylene oligomers, poly(alkene oxide), poly(*N*-alkylacrylamides)), or by using polymers which precipitate upon change of the ionic strength of the solution. Although disadvantages for multistep organic synthesis (trapping of low molecular weight compounds) can occur, it can be useful for the separation of a polymer-bound catalyst [1]. Also, conventional liquid–liquid extraction could be employed in some cases. The latter technique, of course, cannot be used generally since a complete difference in solution behaviour between the separated compounds is required. This requirement is met by water-soluble polymers; on the other hand, polymer-supported fluorous biphasic chemistry is an actual field of research. These two separation methods contain problems when they should be used in a parallel or even automated fashion. Another technique is the simple filtration of the mixture over functionalised silica gel. It is especially suitable to remove a polymeric reagent or catalyst and has been used in a parallel and automated way.

3.2.2 Separation by Hydrodynamic Volume (Size)

To perform a separation by size, the employed macromolecules should have medium molecular weights (5,000 to 10,000) and narrow molecular weight distributions (PD<2). Dialysis and ultrafiltration are membrane techniques [80] to separate high molecular weight compounds in solution from low molecular weight compounds in solution [81]. Both techniques make use of membranes (e.g. from benzoylated cellulose) with certain molecular weight cut-offs (MWCO, e.g. 1,000 g mol^{-1}, slight variation possible depending on the employed solvent). Molecules with a small hydrodynamic volume can pass this mem-

brane whereas molecules with a high hydrodynamic volume are held back. Currently, many different membranes of high chemical stability and compatibility with most organic solvents are commercially available.

In dialysis (Fig. 4), the mixture is placed in a dialysis tube consisting of the membrane. This tube is then put into a solvent where the small molecules (<MWCO) can diffuse while the big molecules (>MWCO) are retained. The surrounding solvent is changed several times manually or continuously recycled using an apparatus like that in Fig. 4 [1, 81]. In the latter, up to twelve large-scale reaction mixtures (up to 10 mmol supported ligand) can be purified simultaneously. However, full automation of this procedure is difficult. In addition, its use is unadvantageous for the purification of a reaction mixture after transformation of a low molecular weight species using a polymer-bound catalyst, since the desired compound would be diluted in a large volume of solvent. On the other hand, this technique could be a valuable tool in the course of the preparation of the supported ligands and catalysts [82].

Better suited for the separation of low molecular weight products from polymeric catalysts is ultrafiltration or nanofiltration [83, 84]. As there is no sharp distinction between these two types, only the term ultrafiltration is used for

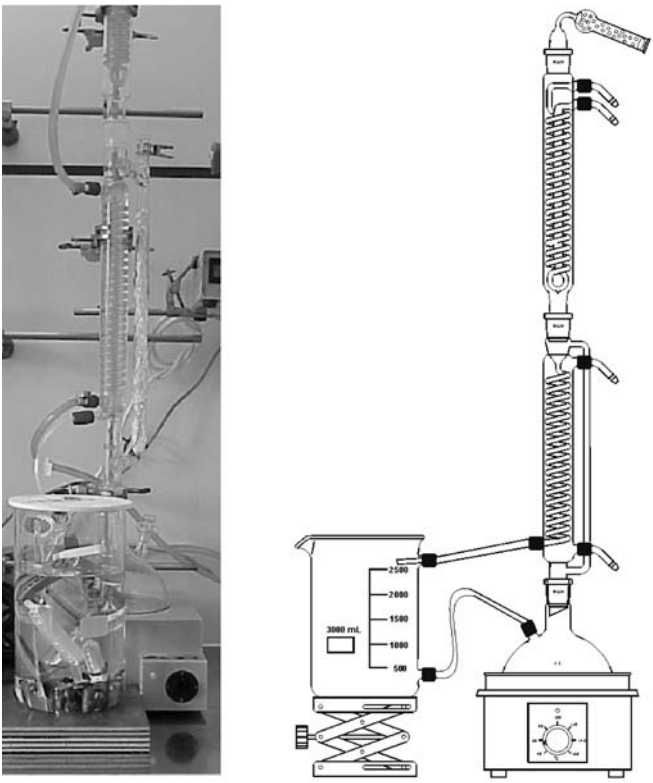


Fig. 4 Continuous dialysis apparatus for the parallel purification of up to twelve samples

both [85]. In a commercially available system (Fig. 5) [86], the mixture is placed in a cell which contains a membrane in its base [1]. Under gas (e.g. N_2) pressure (3–30 bar) and stirring the sample is pushed through the membrane. The low molecular weight compounds can be collected beyond the membrane whilst the polymeric species remain in the cell. This technique requires less time than dialysis (usually <6 h) and full automation of ultrafiltration is possible. Also some industrial setups for multi-kilogram purification have been realised.

Van Koten and coworkers examined the permeability of nanofiltration membranes (SelRO-MPF-60; MWCO 400 g mol^{-1}) using coloured metallodendrimers ([G0]–[G3]) of increasing molecular weight and size (≈0.6–1.0 nm) in CH_2Cl_2 [87]. The retention times were measured via UV-Vis spectroscopy ([G1]: $t_{1/2}$=108 h; [G2]: $t_{1/2}$=300 h; [G3]: $t_{1/2}$>60 days). In this way the authors showed that dendrimers do not have to be exceptionally large for successful retention. Subsequently they functionalised the support of choice with a catalytically active centre instead of the dye. Nanofiltration membrane-capped immersion vials were developed and used to compartmentalise homogeneous dendritic catalysts. These catalytic systems could be regenerated and stored for months without losing their activity.

The same principle has been used in so-called continuous membrane reactors [83, 85, 88–95]. In this case the membrane is used to retain a soluble polymer bound catalytic species. Low molecular weight substrates are transformed continuously in the reactor and ideally pure products can be collected beyond the membrane. This can lead to easy separation and an increase in the total turnover number of the catalyst [85]. However, these systems are very demanding on support and membrane, since for efficient use a retention of more than 99.9% has to be guaranteed. In addition, even the best membranes cannot prevent metal leaching.

In 1999 Brinkmann and Kragl reported on a dendrimer supported Pd-catalysed allylic substitution reaction performed in a continuous membrane reac-

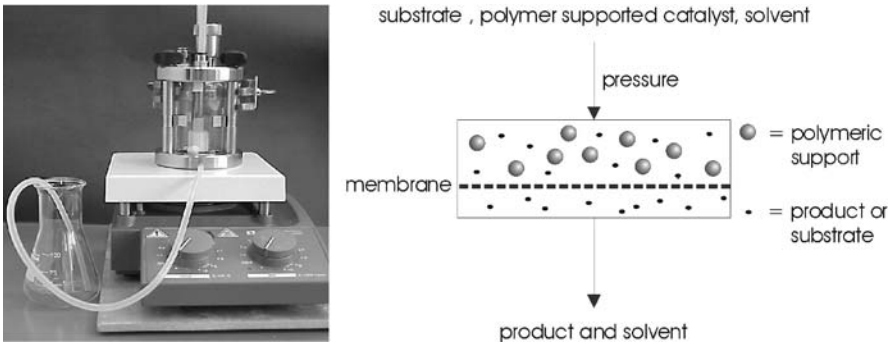


Fig. 5 Commercially available ultrafiltration apparatus for pressures up to 6 bar. On the *right*: the low molecular species accumulate together with the solvent in the Erlenmeyer flask, whereas the high molecular species are retained by the membrane. Via the tube on the upper side the cell can be set under pressure. On the *left*: schematic description

tor [85]. The authors examined the retention of the catalyst using two different ultrafiltration cells (SELRO MPF-50, Koch Membrane Systems, Düsseldorf, Germany; Nadir UF-PA-5, Hoechst Celanese, Wiesbaden-Biebrich, Germany). For the first membrane they observed a retention of 0.999, for the second 0.992. For a single filtration step this difference seems to be fairly low. For a continuously operated reactor, however, with a very large number of replacements of the reaction volume, which is equal to the number of residence times, even a small difference of 0.007 has a large impact. Consequently, the authors preferred the first membrane. The problem of metal leaching was also observed. However, for the continuous process using the dendritic catalyst, a sixfold increase of the turnover number was achieved compared to the batch reaction with a low molecular weight catalyst.

Reek and van Leeuwen showed that the catalyst stability is of crucial importance when reactions are performed in a continuous-flow membrane reactor [88]. Also important is the solvent dependence of the catalyst retention. The authors examined carbosilane dendrimer supported Pd-catalysed allylic substitution reactions. In contrast to the batch reaction, they observed rapid deactivation of the catalyst employed in a continuous allylic alkylation in THF. Since the retention of the dendrimer was high, they suggested that the deactivation was induced either by interactions with the membrane or by leaching of small inactive palladium species. In a control experiment pieces of membrane added to the batch reaction did not result in catalyst deactivation. Thus, one of the intermediate palladium complexes of the catalytic cycle was less strongly bound to the dendritic ligand. This way, inactive palladium species were transported out of the reactor. In allylic amination reactions in CH_2Cl_2 (retention 99.7%) they observed the same loss of activity. After performing control experiments, deactivation by reaction with the solvent as well as lower retention of the species of the catalytic cycle could be ruled out, and the authors concluded that deactivation was stimulated by the presence of the substrate allyl acetate. If they changed the spacer length between ligand and support from methylene to ethylene the catalyst was much more stable, and the formation of product was fairly constant during ten reactor volumes. In this way, the authors showed that small changes in the dendrimeric ligand had a large impact on the catalyst stability.

The required pressure for ultrafiltration can also be generated by centrifugation [1]. The separation time depends on the rotation speed of the centrifuge. However, due to the low solvent compatibility of the commercially available membrane ampoules this technique can only be employed conditionally.

In conclusion, membrane techniques still need much improvement. New membranes that are compatible with a variety of organic solvents and organometallic reagents are required to develop this area of supported catalysts to its full potential [84, 89].

Another possibility to separate molecules by size is size exclusion chromatography (SEC) or gel permeation chromatography (GPC) [1]. Here, the separation occurs on the basis of different hydrodynamic volumes. Large molecules cannot diffuse in the pores of the stationary phase as well as small molecules,

and therefore have lower retention times. These techniques can be performed on the analytical or preparative (typically up to 100 mg) scale. At present, due to the high cost of these serial devices, parallelisation is not possible.

3.3 Soluble Polymer Supported Catalysis

This chapter will only deal with catalytic systems covalently attached to the support. Dendrimer [96–101], hyperbranched polymer [102, 103], or other polymer [100] encapsulated catalysts, micellar catalysis [104] and non-covalently bound catalysts (via ionic [105, 106], fluorous, etc. intercations) are not being treated. Also catalysis with colloidal polymers [107, 108] and biocatalysts, such as enzymes and RNA, will not be reviewed here.

3.3.1 Comparisons of Different Polymeric Supports

Janda and coworkers compared salen catalysts bound to different soluble and insoluble polymeric supports as well as the low molecular weight analogue in asymmetric epoxidation reactions of olefins [68]. Poly(ethylene glycol) monomethyl ether and non-crosslinked polystyrene were used as soluble supports, while a gel-type polystyrene support (flexible crosslinker) and Merrifield resins (rigid crosslinker) served as insoluble supports. Since catalyst deactivation can occur caused by site–site interaction the authors expected that a poor loading support provided the best results. However, it has been shown that in low loading ranges (0.1–0.75 mmol g^{-1}, gel-type support) no dependence on *ee* values occurred. Furthermore, they expected that a soluble polymer-supported salen complex would be an effective catalyst since it is believed that non-binding interactions between the catalyst and approaching olefinic substrate are critical in determining enantioselectivity. Heterogenisation of the catalyst (or the substrate) can therefore result in diminished enantiomeric excess of the product. The soluble polymer-supported catalysts were recovered by precipitation and could be used twice before a decline in yield and enantioselectivity was observed. The catalyst attached to the gel-type support could be used for three cycles in some cases. The Merrifield-bound catalyst was found to lose activity with each use. In conclusion, the authors showed that the enantioselectivities derived from the soluble and gel-type polymeric catalysts were nearly equivalent to those for the commercial low molecular weight catalyst. However, the soluble polymer-supported catalyst could only be reused once.

3.3.2 Linear Soluble Polymers with Functionalised End-Groups or Initiator Moieties

Some selected examples of catalysis using linear soluble supports with functionalised end-groups or initiator moieties are summarised in Table 2. The most

Table 2 Selected examples for catalysis using linear endgroup-funtionalised polymeric supports or polymers with reactive groups containing initiator moieties

Linear endgroup-functionalised polymeric support/ligand	M_w (g mol^{-1})	Loading (mmol g^{-1})	Solubility	Applications	Purification	References
MPEG with $(DHQD)_2$-PHAL ligand			*t*-BuOH/H_2O[b], acetone/H_2O[b]	Sharpless dihydroxylation	Precipitation (diethyl ether)	[135]
MPEG	≈2,000 ≈3,400	(≈0.5)	CH_3CN	Phase-transfer catalysis	Precipitation	[136, 137]
PEG	≈4,000	(≈0.5)	DMF	Phase-transfer catalysis		[138]
MPEG with quaternary ammonium salt	≈5,000	≈0.2[a]	CH_2Cl_2[c]	Phase-transfer catalysis	Precipitation (r)	[79]
MPEG with salen ligand			CH_2Cl_2, THF, EtOAc, DMF	Asymmetric epoxidation	Precipitation (diethyl ether) (r)	[68]
MPEG with chiral imidazolidin-4-one	≈5,000[a]	≈0.2[a]	CH_3CN/H_2O[c]	Enantioselective Diels–Alder reactions	Precipitation (diethyl ether) (r)	[139]
MPEG with proline PEG with proline	≈5,000[a] ≈4,600[a]	≈0.2[a] ≈0.4[a]	DMF[c], DMSO[c], MeCN[c], CH_2Cl_2[c], toluene[c], acetone[c]	Enantioselective aldol and imino aldol condensations	Precipitation (diethyl ether) (r)	[140]
PEG with different Ru-complexes	≈3,400[a] ≈4,500[c]	≈0.6[a] ≈0.4[c]		Metathesis	Precipitation (diethyl ether) (r)	[71]
MPEG with Ru-porphyrin-complexes		≈0.06–0.14[c] (via ^{1}H-NMR)	CH_2Cl_2[c]	Alkene epoxidation Alkene cyclopropanation Cyclisation of α-diazo-carbonyl compounds Alkene aziridination	Precipitation (r) Precipitation (diethyl ether) Precipitation (diethyl ether)	[141]

[a] Support without ligand; [b] Naked dendritic ligand; [c] Final catalytic system; (r) = Reuse was investigated.

widely used soluble polymeric support in organic synthesis is monomethylated polyethylene glycol (typically MPEG 5,000), soluble in many organic solvents and easily precipitated in non-polar solvents (e.g. diethyl ether). Due to the linear topology of this polyether, it contains only one reactive functionality and hence exhibits a rather poor loading capacity (0.2 mmol g^{-1}) [13, 17]. However, it is commercially available in a wide range of molecular weights [68].

Benaglia and coworkers reported on the application of a PEG-supported phase-transfer catalyst [79]. They compared their system to the low molecular weight analogue, to pure PEG and to an analogue bound to an insoluble crosslinked polystyrene resin. The latter needed higher reaction temperatures and/or longer reaction times. In addition, solid-supported phase-transfer catalysts require a preliminary, long conditioning time (up to 15 h) to ensure bead swelling and optimum accessibility of substrate and reagent to the catalytic site. Finally, the high stirring rate necessary with solid-phase-supported catalysts resulted in extensive mechanical degradation of the polymer beads, which were difficult to recover by filtration.

Lamaty and coworkers used PEG-bound Ru catalysts for metathesis reactions [71]. In contrast to solid-phase-bound catalysts, the soluble polymeric support allowed for analysis which provided information on the recycling capacities of the catalyst: while the activity remained high, the return of the metal on the supported ligand was not total.

3.3.3
Soluble Polymeric Supports with Reactive Groups Along the Polymer Chain

In general, linear polymeric supports containing reactive groups on every monomeric unit have potentially high loading capacities. However, their polymer characteristics, such as solubility and chemical stability, as well as their materials properties are problematic in some cases for broad application in organic synthesis and catalysis [13]. Some selected examples of catalysis using linear soluble supports with reactive groups along the polymer chain are summarised in Table 3.

3.3.4
Starpolymers, Hyperbranched Polymers and Dendrimers as Supports for Catalysts

The disadvantages of linear polymers, such as limited solubility in many organic solvents, gel formation and problematic thermal behaviour (high melting points and T_g) in some cases can be overcome by the use of branched polymer architectures [13, 91]. An extreme in terms of tree-like branching are the perfectly branched dendrimers [109]. These well-defined macromolecules are soluble in many organic solvents (depending on their end functionalities) and possess a maximum capacity of easily accessible functional groups in their periphery.

Table 3 Selected examples for catalysis using polymeric supports which contain reactive groups on every monomeric unit

Linear polymeric support containing reactive groups on every monomeric unit/ligand	M_w (g mol^{-1})	Loading (mmol g^{-1})	Solubility	Applications	Purification	Ref.
Non-crosslinked polystyrene with salen ligand			CH_2Cl_2, THF, EtOAc, DMF	Asymmetric epoxidation	Precipitation (methanol) (r)	[68]
Non-crosslinked polystyrene with onium salt residues		0.5–3.8[a] 0.7–2.3[c]	DMF, DMSO, DMA, toluene, anisole, MeOH, MeCN, diglyme	Regioselective addition reaction of phenyl glycidyl ether with *S*-phenyl thioacetate		[142]
Non-crosslinked polystyrene copolymerised with a chiral phosphine ligand	14,765[b]			Pt-catalysed asymmetric hydroformylation of olefins	Precipitation (diethyl ether) (r)	[143]
Poly(acrylic acid) with Rh-phosphine complexes		≈1.04[b]	H_2O	Hydroformylation of olefins (gas phase and biphasic solution)	Phase separation (r)	[144]
Poly(ethylene imine) with Rh-phosphine complexes		≈0.84[b]	H_2O	Hydroformylation of olefins (gas phase and biphasic solution)	Phase separation	[144]
Copolymer of PEG, (*R*)-5,5′-diamino-BINAP, and terephthaloyl chloride		≈0.05[b]	H_2O[c], MeOH[c], ethylene glycol[c], EtOAc/H_2O[c]	Ru-catalysed asymmetric hydrogenation of α,β-unsaturated carboxylic acids (+)	Precipitation (ether)	[145]

Table 3 (continued)

Linear polymeric support containing reactive groups on every monomeric unit/ligand	M_w (g mol^{-1})	Loading (mmol g^{-1})	Solubility	Applications	Purification	Ref.
Polyethylene and polyethylene-block-poly(ethylene glycol) with ligand and CuBr	893[a] 905[a] 717[a] 465[a]	1.1[a] 1.1[a] 1.4[a] 2.2[a]	Toluene (high temp.), phenyl ether	Atom transfer radical polymerisation	Precipitation, centrifugation, decantation (r)	[146, 147]
Oxidised polyethylene with quaternised Jeffamine groups			Toluene, chlorobenzene, xylenes (temperature-dependent)	Phase-transfer catalysis	Filtration (r)	[148]
Amphiphilic polymer containing 4-(dialkylamino)pyridine groups			Methanol/H_2O	Solvolysis of p-nitrophenyl alkanoates		[149, 150]
Poly(N-vinyl-2-pyrrolidone)-supported $PdCl_2$/$2CuCl_2$			EtOH	Oxidative carbonylation of aniline (+)		[151]

[a] Support without ligand; [b] Naked dendritic ligand: [c] Final catalytic system; (±) Enhanced or decreased reactivity and/or selectivity compared to low molecular weight analogues; (r) = Reuse was investigated.

Dendrimeric catalysts ideally combine the advantages of both homogeneous and heterogeneous catalysts, namely the presence of a number of well-defined active sites like in conventional homogeneous catalysis as well as the possibility of simple separation and reuse [91, 110–112]. The relative proximity of terminal sites may be controlled by the nature and generation number of the dendrimer. In dendrimers of higher generations an extremely high local concentration of the catalyst exists (4M local catalyst concentration in a [G2]-carbosilane dendrimer with phosphane ligands) [91]. By varying the generations, at least in principle, a dendritic framework may be used to enforce and control cooperative interactions between catalyst units and therefore increase activity and/or selectivity [111]. This "positive dendritic effect" has been observed by several groups [111, 113–116]. But there are also examples where site–site interactions or steric crowding are believed to be responsible for catalyst deactivation ("negative dendritic effect"). In these cases it was expected that low loading polymers with isolated sites would provide better results in catalytic reactions [68, 89, 90, 117, 118].

The first proof of the existence of a negative dendritic effect was given by van Koten et al. in 2000 [90, 118]. His group examined the influence of generation as well as the linker nature and length on the catalytic activity of carbosilane dendrimer-supported Ni catalysts employed in the Kharasch reaction. The lower activity of higher generations with catalyst-crowded surfaces was attributed to site–site interactions with formation of inactive Ni^{II}/Ni^{III} complexes.

Ropartz and coworkers examined the regioselectivity of the hydroformylation reaction catalysed by Rh-containing dendrimers of different generations with diverse spacer moieties [114]. They showed that the appearance of a positive dendritic effect is not only generation-dependent but also depended on an exact spacer length and composition between the support and the ligand.

Despite the promising features of dendrimers concerning catalysis, the relatively high price and limited chemical stability of the commercially available poly(amidoamine) or polyamine dendrimers might well be the reason for their limited use as supports in organic synthesis [13, 119]. Several other dendrimers have been prepared and employed as supports for catalysts. However, the general drawback of any dendrimer is the tedious and expensive multistep preparation of higher generations (molecular weight exceeding 1,500 g mol^{-1}, which is the lower limit for membrane separation techniques) [13, 82]. For this reason, perfectly branched dendrimers have mainly been used as supports for valuable transition metal catalysts with ligands attached to the core and the shell of the macromolecule (*vide infra*) [13].

These problems might be overcome by using randomly branched polymer structures as supports [13, 82, 112]. In contrast to dendrimers, hyperbranched polymers are easily available in one reaction step. This allows the production of large quantities of material [82]. They contain dendritic, linear and terminal monomer units in their skeleton and hence can be considered as interme-

diates between linear polymers (degree of branching, DB=0%) and dendrimers (DB=100%) with an approximate DB between 40 and 60% [13]. In contrast to dendrimers, hyperbranched polymers [120] are polydisperse and the reactive sites will be distributed throughout the molecules, but it has been shown that in some cases the catalyst support properties of hyperbranched polymers are very similar to those of analogous dendrimers and thus, structural perfection is not always required [82, 112].

The potential loading capacity of these hyperbranched polymers is similarly high as for dendrimers (5–14 mmol g^{-1}) and some hyperbranched polymers are even commercially available [13, 121]. The use of these commercial materials as supports for organic synthesis, however, is limited due to the chemical stability of the respective polymer backbone (e.g. polyamines, polyesters) and the relatively broad molecular weight distributions (typically PD>2) [13]. Therefore, new hyperbranched species have been developed.

3.3.4.1
Hyperbranched Polymers as Supports for Catalysts

Some selected examples of hyperbranched polymer-supported catalysis are summarised in Table 4. Dendritic carbosilane structures are well suited for catalysis because they are relatively inert to common organometallic reagents and their structures can be easily modified. For example, Frey and van Koten reported on the synthesis of a hyperbranched carbosilane, its functionalisation with NCN moieties and the introduction of palladium(II) sites into the structure [82]. This catalyst was introduced in aldol reactions and showed similar activity as the low molecular analogue.

3.3.4.2
Dendrimers as Supports for Catalysts

Several comprehensive reviews dealing with dendrimers in homogeneous catalysis have been published recently [58, 83, 91, 112, 122]. Catalytically active sites can be introduced into the core (monovalent), the branches, or the shell (multivalent) of dendritic systems. Core-functionalised dendrimers have a very poor loading of catalyst and therefore catalysis with these supports will be much more expensive than with shell-functionalised dendritic structures. In addition, dendrimers themselves can act as catalysts.

The construction of a dendrimer around a catalytic core [122] can result in the steric protection of the catalytic site (prevention of aggregation and bimetallic catalyst deactivation) and is a means to finely tune the catalytic activity (e.g. increase via desolvation of the substrate on the way to the catalytic site or decrease via hindered access) and selectivity [123, 124]. The latter can be enhanced by the local environment defined by the dendrimer, especially when consisting of rigid branches. However, if the generation is too high the branches become sterically too demanding and the access of substrate is there-

Table 4 Selected examples for catalysis using branched polymeric supports

Branched support*/ ligand	M_w (g mol^{-1})	Loading (mmol g^{-1})	Solubility	Applications	Purification	Ref.
Star-shaped core with iron-sandwich units	2,987[c] 4,527[c]	2.0[c] 1.3[c]	H_2O (basic)	Electrochemical aqueous nitrate and nitrite reduction		[152]
Aryl ether dendrimer [G1] with concave pyridine endgroups	2,557[c] 3,863[c]	1.6[c] 1.6[c]		Selective acylations of primary, secondary and tertiary alcohols with diphenylketene	Nanofiltration	[153]
Aryl ether dendrimer [G0]–[G2] with Ru porphyrins (core)	1,627[c] [G0] 2,047[c] [G1] 3,451[c] [G1] 3,749[c] [G2] 6,847[c] [G2]	0.61[c] [G0] 0.49[c] [G1] 0.30[c] [G1] 0.27[c] [G2] 0.15[c] [G2]	Common organic solvents (CH_2Cl_2, acetone)	Epoxidation and cyclopropanation of alkenes	Precipitation, column chromatography	[129]
Aryl ether dendrimer [G1]–[G3] with BINOL ligand (core)	950[b] [G1] 1,821[b] [G2] 3,518[b] [G3]	1.1[b] [G1] 0.55[b] [G2] 0.28[b] [G3]	Toluene	Enantioselective addition of diethylzinc to benzaldehyde (–)	Precipitation (MeOH) (r)	[154]
BINOL with two aryl ether dendritic wedges [G1]–[G3]	922[b] [G1] 1,749[b] [G2] 3,447[b] [G3]	1.1[b] [G1] 0.57[b] [G2] 0.29[b] [G3]	CH_2Cl_2	Ti-catalysed allylation of aldehydes with allyl stannane		[155]
Aryl ether dendrimers [G3] with arylplatinum (II) pincer[156] site (core)	1,936[c]	0.52[c]	CH_2Cl_2	Kharasch addition of CCl_4 to methyl methacrylate (r)	Nanofiltration, compartmentalisation in a membrane-capped vial	[87]
Salen complexes with two dendritic aryl ether wedges [G1], [G2]	1,071[b] [G1] 1,169[b] [G1] 1,920[b] [G2] 2,018[b] [G2]	0.93[b] [G1] 0.86[b] [G1] 0.52[b] [G2] 0.50[b] [G2]	CH_2Cl_2	Mn-catalysed enantioselective epoxidations		[157]

Table 4 (continued)

Branched support*/ ligand	M_w (g mol^{-1})	Loading (mmol g^{-1})	Solubility	Applications	Purification	Ref.
TADDOL with four dendritic aryl ether wedges [G0]–[G4] (also with chiral branching units)	891[b] [G0] 1,740[b] [G1] 3,438[b] [G2] 3,719[b] [G2] 6,834[b] [G3] 13,626[b] [G4]	1.1[b] [G0] 0.57[b] [G1] 0.29[b] [G2] 0.27[b] [G2] 0.15[b] [G3] 0.073[b] [G4]	Toluene	Enantioselective addition of Et_2Zn to benzaldehyde (–)		[125]
Aryl ether dendrimer [G0]–[G3] with tertiary amine core	419[c] [G0] 1,019[c] [G1] 2,327[c] [G2] 4,871[c] [G3]	2.4[c] [G0] 0.98[c] [G1] 0.43[c] [G2] 0.21[c] [G3]	Nitroalkane	Nitroaldol (Henry) reaction (–)	Flash chromatography	[126]
Several dendritic pincer [156] complexes			CH_2Cl_2	Michael reaction (+)	Nanofiltration	[115]
Carbosilane (hyperbranched)	5,500[a]	13.1[a]	Et_2O[a], $CHCl_3$[a], CH_2Cl_2[c]	Aldol condensation	Dialysis[b,c]	[82]
Carbosilane dendrimer	2,769[c] [G0] 5,850[c] [G1] 8,532[c] [G2]	1.4[c] [G0] 1.4[c] [G1] 1.4[c] [G2]	Saturated hydrocarbon and arene solvents[c]	Own functionalisation of carbosilane dendrimers, hydrosilation of acetophenone		[158]
Carbosilane dendrimer [G0], [G1] with different Ru-complexes	2,921[c] [G0] 3,065[c] [G0] 6,153[c] [G1] 6,441[c] [G1]	1.4[c] [G0] 1.3[c] [G0] 1.3[c] [G1] 1.2[c] [G1]	CH_2Cl_2	Ring-opening metathesis polymerisation (ROMP) of starpolymers		[159, 160]

Table 4 (continued)

Branched support*/ ligand	M_w (g mol^{-1})	Loading (mmol g^{-1})	Solubility	Applications	Purification	Ref.
Carbosilane dendrimers [G0], [G1] with phosphanyl ligands and Pd-centers	1,956^{c} [G0] 4,517^{c} [G1]	2.0^{c} [G0] 1.8^{c} [G1]	CH_2Cl_2, THF	Hydrovinylation of styrene (–)		[117]
Carbosilane dendrimer with core ligand	8,567^{b}	0.12	THF	Pd-catalysed allylic alkylation		[161]
Carbosilane dendrimer [G0], [G1] with tripodal phosphane ligands with Rh-centrers	3,163^{b} [G0] 4,356^{c} [G0] 6,641^{b} [G1] 9,024^{c} [G1]	1.3^{b} [G0] 0.92^{c} [G0] 1.2^{b} [G1] 0.89^{c} [G1]	THF	Hydrogenation of alkenes	Removal of all low molecular weight compounds in vacuum (r)	[162]
Carbosilane dendrimer [G0], [G1] with chiral β-amino alcohols	1,445^{b} [G0] 4,558^{b} [G1]	2.8^{b} [G0] 2.6^{b} [G1]	Toluene	Enantioselective addition of dialkylzinc to aldehydes		[132]
Carbosilane dendrimer with Ti and Zr metallocene cores	706^{c} [G1] 776^{c} [G1] 952^{c} [G1] 1,022^{c} [G1] 1,656^{c} [G2] 1,699^{c} [G2]	1.4^{c} [G1] 1.3^{c} [G1] 1.1^{c} [G1] 0.98^{c} [G1] 0.60^{c} [G2] 0.59^{c} [G2]	Toluene	Ethylene polymerisation with MAO cocatalyst (–)		[163]
Carbosilane dendrimers [G0]–[G2] with phosphane groups	1,170^{b} [G0] 1,282^{b} [G0] 1,907^{b} [G0] 4,071^{b} [G1] 5,888^{b} [G1] 11,202^{b} [G2]	3.4^{b} [G0] 3.1^{b} [G0] 2.1^{b} [G0] 2.9^{b} [G0] 2.0^{b} [G1] 3.2^{b} [G2]	THF, CH_2Cl_2	Pd-catalysed allylic substitution	Nanofiltration, continuous-flow membrane reactor	[88]

Table 4 (continued)

Branched support*/ ligand	M_w (g mol^{-1})	Loading (mmol g^{-1})	Solubility	Applications	Purification	Ref.
Carbosilane dendrimers [G0]–[G2] with Ni-pincer[156] ligands	1,421[c] [G0] 3,155[c] [G1] 4,488[c] [G1] 5,689[c] [G1] 13,689[c] [G2]	2.8[c] [G0] 2.5[c] [G1] 2.7[c] [G1] 2.1[c] [G1] 2.6[c] [G2]	CH_2Cl_2	Kharasch reaction of CCl_4 with methyl methacrylate (–)	Membrane reactor	[89, 90, 118]
Carbosilane dendrimers [G0]–[G2] with aryl-amine units (cyclo-palladated)	Precursors with Pd: 1,788 [G0] 2,184 [G0] 3,833 [G1] 4,001 [G1] 5,709 [G1] 17,494 [G2]	Precursors with Pd: 2.2 [G0] 1.8 [G0] 2.1 [G1] 2.0 [G1] 2.1 [G1] 2.1 [G2]	CH_2Cl_2[c] (in the presence of the substrate)	Aldol condensation (–)		[164]
Polyhedral oligomeric silsesquioxane dendrimer [G1], [G2] with diphenyl-phosphine units and different spacers	4,297[b] [G1] 5,647[b] [G1] 4,174[b] [G1] 4,430[b] [G1] 4,654[b] [G1] 4,623[b] [G1]	3.6[b] [G1] 4.3[b] [G1] 3.8[b] [G1] 3.6[b] [G1] 3.4[b] [G1] 3.5[b] [G1]	Most non-polar organic solvents[b]	Regioselective rhodium-catalysed hydroformylation of alkenes (+)		[114, 165]
PAMAM [G0], [G1], [G2] with salen-ligand	2,629.4 [G0][b]	1.5 [G0][b]	THF[c]	Hydrolytic kinetic resolution of terminal epoxides (+)	Precipitation, SEC	[111]
PAMAM [G4] with Co(II) Schiff base complexes	14,196[a]	4.5[a]	H_2O, MeOH[c]	Hydrolysis of phosphate esters	Dialysis	[134]

Table 4 (continued)

Branched support*/ ligand	M_w (g mol^{-1})	Loading (mmol g^{-1})	Solubility	Applications	Purification	Ref.
PAMAM dendrimer [G3] with phosphine ligands and hydrophilic endgroups	8,692[b] 13,896[b] 9,063[b] 11,649[b]	1.0[b] 1.3[b] 0.44[b] 0.52[b]	H_2O	Rh-catalysed two-phase hydroformylation of alkenes	Two-phase catalysis	[166]
Oxazoline with one or two (chiral) polyester dendritic wedges [G1], [G2], [G4]	410[b] [G1] 706[b] [G1] 762[b] [G1] 1,411[b] [G1] 682[b] [G2] 2,413[b] [G4] 4,712[b] [G4]	2.4[b] [G1] 1.4[b] [G1] 1.3[b] [G1] 0.71[b] [G1] 1.5[b] [G2] 0.41[b] [G4] 0.21 [G4]	CH_2Cl_2	Pd-catalysed allylic alkylations (±)		[127]
Phosphorous-containing dendrimer [G3]	17,240,2[b]	1.4[b]	DMF[c], THF[c]	Stille-coupling (+) Knoevenagel-reaction (+) Michael-addition	Precipitation (r) Precipitation (r) Precipitation (r)	[113, 167]
Phosphorous-containing dendrimer [G3] (core)	5,159[b]	0.2[b]	THF[c]	Michael-addition	(r)	[113]
Organophosphine dendrimer with Rh(I) [G1]–[G4]	5,053[c] [G2]	2.0[c] [G2]	THF	Hydrogenation of decene	Extraction, recrystallisation (r)	[168]
Organophosphine dendrimers with Pd	2,168[b] 1,400[b]	6.9 P-atoms 10.7 P-atoms	DMF	Electrochemical reduction of CO_2 to CO		[169]

Table 4 (continued)

Branched support*/ ligand	M_w (g mol^{-1})	Loading (mmol g^{-1})	Solubility	Applications	Purification	Ref.
1,1′-binaphthalene-capped oligo(arylene)-based dendrimers [G0], [G1] with Al	1,518[b] [G0] 3,186[b] [G1]	2.0[b] [G0] 1.9[b] [G1]	CH_2Cl_2	Asymmetric Diels–Alder reactions (+)	Filtration through a pad of silica gel	[170]
Poly(propylene imine) [G3] (dimethylphosphinomethylated)	8,029[b]	2.0[b]	THF[c], DMF[c]	Heck-reaction, hydroformylation (+)	Precipitation (r)	[110]
Poly(propylene imine) [G3], [G4] (dimethylphosphinomethylated)	10,212[c] [G3] 16,199[c] [G4]	1.6[c] [G3] 2.0[c] [G4]	CH_2Cl_2	Pd-catalysed allylic substitution	Ultrafiltration, continuous membrane reactor	[85]
Poly(propylene imine) dendrimers [G0]–[G4] with chiral phosphine-ligands and Rh-centrers	1,158[b] [G0] 2,457[b] [G1] 5,054[b] [G2] 10,249[b] [G3] 20,637[b] [G4]	1.7[b] [G0] 1.6[b] [G1] 1.6[b] [G2] 1.6[b] [G3] 1.6[b] [G4]	CH_2Cl_2, MeOH	Asymmetric hydrogenation (–)		[130]
Poly(propylene imine) dendrimer			H_2O	Cu(II)-, Zn(II)-, Co(II)-hydrolysis of bis-(*p*-nitro-phenyl) phosphate		[171]
Cationic poly(propylene imine) dendrimers with poly(ethylene glycol) endgroups			H_2O	Decarboxylation		[108]

Table 4 (continued)

Branched support*/ ligand	M_w (g mol^{-1})	Loading (mmol g^{-1})	Solubility	Applications	Purification	Ref.
Hydroxyisophthalic acid-based dendrimers [G0]–[G2] with 1,3,5-benzene tricarboxylic acid, 1,3,5,7-adamantanetetra-carboxylic acid, or cyclo-phosphazene cores and chiral ferrocenyl diphos-phine groups	2,029 [G0] 2,111 [G0] 4,844[b] [G1] 6,491[b] [G1] 6,503[b] [G1] 8,298[a] [G1] 10,007[b] [G2] ≈13,000[b] [G2]	1.5[b] [G0] 1.4[b] [G0] 1.2[b] [G1] 1.2[b] [G1] 1.2[b] [G1] 1.4[a] [G1] 1.2[b] [G2] ≈1.2[b] [G2]	Et_2O,[b] THF,[b] CH_2Cl_2,[b] $CHCl_3$,[b] C_6H_6,[b] toluene,[b] MeOH[c]	Rh-catalysed asymmetric hydrogenation and hydro-boration, Pd-catalysed asym-metric allylic substitution (–)	Nanofiltration	[133, 172, 173]
Poly(phenylethyne) dendrimer with chiral ligand [G1], [G2]	910[c] [G1] 2,041[c] [G2]	3.3[c] [G1] 2.9[c] [G2]	Toluene[c]	Enantioselective addition of dialkylzincs to aldehydes	(r)	[131]
Dendritic cations [G0], [G1] with Ru_2S_3 or Rh_2S_3 branching units either in the core or in the arms with phosphine ligands	1,710[b] [G0] 1,717[b] [G0]	1.8[b] [G0] 1.7[b] [G0]	MeOH	Ru/Rh-catalysed carbonylation of methanol		[174]
Dendritic [G0] macro-cyclic Pd-complexes	2,569[c]	1.2[c]	CH_2Cl_2	Aldol condensation (+)		[116]
Dendritic [G0]–[G2] iron porphyrin complexes (core)	1,762[c] [G0] 4,235[c] [G1] 11,552[c] [G2]	0.57[c] [G0] 0.24[c] [G1] 0.086[c] [G2]	CH_2Cl_2	Epoxidation of olefins, oxida-tion of sulfides to sulfoxides (+)	Filtration over silica gel	[175]
Dendritic tris-based polyoxometalates	16,406[c] 21,226[c]	0.24[c] 0.19[c]	MeCN, toluene	Oxidation of tetrahydrothio-phene with *t*-BuOOH or H_2O_2	Precipitation (Et_2O) (r)	[176]

Table 4 (continued)

Branched support*/ ligand	M_w (g mol^{-1})	Loading (mmol g^{-1})	Solubility	Applications	Purification	Ref.
Dendritic phthalocyanines [G0], [G2] (core) based on Behera's amine	2,688[c] [G0] 19,067[c] [G2]	0.37[c] 0.052[c]	MeOH	Co-catalysed oxidation of 2-mercaptoethanol with O_2		[123]
Fe-porphyrin with four dendritic poly(phenylene) wedges [G1]–[G2.5]	1,671[b] [G1] 3,336[b] [G2] 3,578[b] [G2] 3,668[c] [G2.5]	0.60[b] [G1] 0.30[b] [G2] 0.28[b] [G2] 0.27[c] [G2.5]	THF, CH_2Cl_2	Shape-selective epoxidations of olefins with iodosylbenzene (–)		[124]
Thiazolio-cyclophanes (core) with four poly(etheramide) dendritic [G2] wedges bearing different surface groups	6,815[c] 11,572[c]	0.15[c] 0.086[c]	MeOH/H_2O	Oxidation of naphthalene-2-carbaldehyde in presence of a flavin derivative		[177]

* Core-functionalised dendrimers (monovalent) are marked with "core". All other supports are shell-functionalised (multivalent).
[a] Support without ligand.
[b] Naked dendritic ligand.
[c] Final catalytic system.
(±) Enhanced or decreased reactivity and/or selectivity compared to low molecular weight analogues.
(r) = Reuse was investigated.

fore hindered which results in reduced catalytic activity [124–127]. On the other hand, catalytic sites residing at the core (focal point) of the dendrimer (or dendritic wedge) can be used to change, for example, the solubility properties of the catalyst [116]. To date, the introduction of regio- or stereocontrol in a chemical reaction by using dendrimers with an interior isolated catalytic site has been difficult. In most cases, the molecular networks of the dendrimers studied have been too flexible and thus unable to impose distinct spatial constraints on the course of the reaction.

When the catalytic units are placed in a densely packed surface (of a higher generation dendrimer) they are easily accessible and can interfere with each other either increasing (*vide supra*: positive dendritic effect) or decreasing (*vide supra*: negative dendritic effect) catalytic activity.

A further question is whether the catalyst-containing end-groups of a dendrimer are indeed located at the surface of the support or are backfolded into the dendrimer's interior. Naidoo and coworkers performed computational investigations into the potential use of dendrimers as supports for organometallic catalysts [128]. They studied the structure and conformation of organic and organochromium poly(benzyl phenyl ether) dendrimers and showed that the metal carbonyl centres are available to participate in chemical reactions. The terminal groups of both the organic and organochromium dendrimers smaller than [G3] undergo significant backfolding and are capable of penetrating the dendrimer core region. However, in the organochromium case [>G3], the terminal groups do not penetrate the core region to the same extent as do the terminal groups in the organic dendrimers of similar generation. This is mainly due to molecular crowding. Both dendrimer types are compact structures. However, the terminal groups of the latter organochromium polymers are solvent accessible and hence spatially available to act as catalysts in chemical reactions.

In the following, we will give some examples for core- [122] and shell-functionalised dendrimers and dendrimers with chiral branching units for catalysis. Further selected examples can be found in Table 4. Che and coworkers reported that the number and generation of dendritic wedges on a central porphyrin catalyst strongly influence the chemoselectivity and diastereoselectivity of alkene epoxidation reactions [129]. The selectivities significantly increase with the generation number of the dendron or the number of the dendrons attached to the catalytic core.

Gade and coworkers examined the generation-dependent catalytic activity of [G0]–[G4] poly(propylene imine) dendrimers with immobilised diphosphine rhodium complexes in catalytic hydrogenation reactions [130]. The activity decreased in regular increments upon going from [G0] to [G4]. Also a decrease in selectivity of the systems from the second generation onwards has been observed. These reductions may be due to the reduced accessibility of metal centres in the higher generation dendrimers. Reduced accessibility through back-bending may be overcome by the use of a more rigid dendrimer core. Also the tertiary amine groups of the support backbone, which may

weakly coordinate to the metal centres, can reduce the performance of cationic rhodium complexes.

Sato and coworkers reported on addition reactions of diethylzinc to aldehydes. They used dendrimers with rigid backbones and therefore isolated catalytic centres [131] as well as dendrimers with flexible backbones, where the catalytic centres can interact [132]. They concluded that flexibility of the skeleton of the dendritic chiral catalyst enables high enantioselectivity.

Togni and Köllner reported on hydroxyisophthalic acid-based dendrimers with 1,3,5-benzenetricarboxylic acid or 1,3,5,7-adamantanetetracarboxylic acid cores and chiral ferrocenyl diphosphine groups [133]. They have shown via spectroscopic characterisation that the single ligand units are independent from one another. So they expected that the dendritic catalysts preserve the properties of the parent compound. They explored the catalytic activity and selectivity of the different supports in Rh-catalysed asymmetric hydrogenation and hydroboration and Pd-catalysed asymmetric allylic substitution reactions using also different spacer lengths. As expected, the dendrimers showed similar stereo- and regioselectivities and no trend in reaction rates depending on the dendrimer size.

Seebach and coworkers prepared TADDOLs with four dendritic wedges [125]. These wedges contained achiral or chiral branching units. The authors investigated the influence of the stereoconfiguration of the chiral branching units on the enantioselectivity of the Ti-TADDOLat-catalysed addition of diethylzinc to benzaldehyde. It was found that neither of the two enantiomeric branches of the dendrimers influenced the selectivity of the reaction significantly. Other groups reported analogous observations but also increased stereoselectivity was observed in some cases [127].

Reetz and coworkers transformed a now commercially available [G3] poly(propylene imine) (PPI) dendrimer via phosphinomethylation of the 16 amino end-groups to yield the dendritic chelate ligand **6** (Fig. 6) [110]. This multiple ligand can complex diverse transition metals (Pd(II), Pd(0), Ir(I), Rh(I), Ni(0)) with full or partial loading. The Pd(0) complex has been introduced in Heck reactions and could be completely removed by means of precipitation with diethyl ether. Recycling and reuse has been investigated. The authors observed a remarkable dendritic effect and an increased thermal stability of the complex as compared to the low molecular weight analogues. The Rh-containing dendritic catalyst has been employed in hydroformylation reactions.

Caminade and Majoral reacted phosphorus-containing dendrimers with various transition metal complexes (Fig. 7) [113]. Via phosphane, diphosphane, or P=N–P=S ligands, they were able to incorporate several metals (Pd, Pt, Rh, Au, Fe, W, Zr) either in the core or in the periphery of their dendrimers. The dendritic palladium and ruthenium complexes **7** have been introduced in Stille couplings, Knoevenagel condensations and diastereoselective Michael additions. A positive dendritic effect and high stability of dendritic Pd complexes has been observed. Separation occurred by precipitation with ether and reuse was reported.

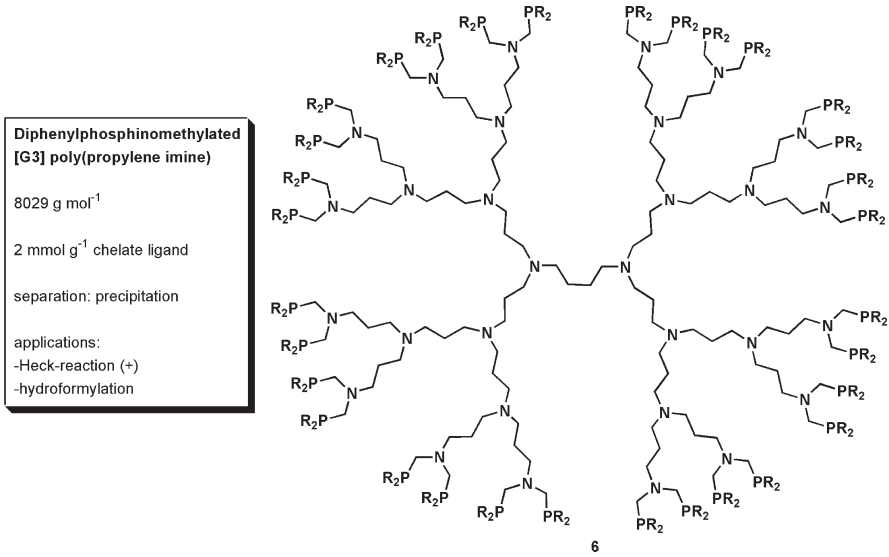


Fig. 6 Phosphine-terminated polyamine dendrimer

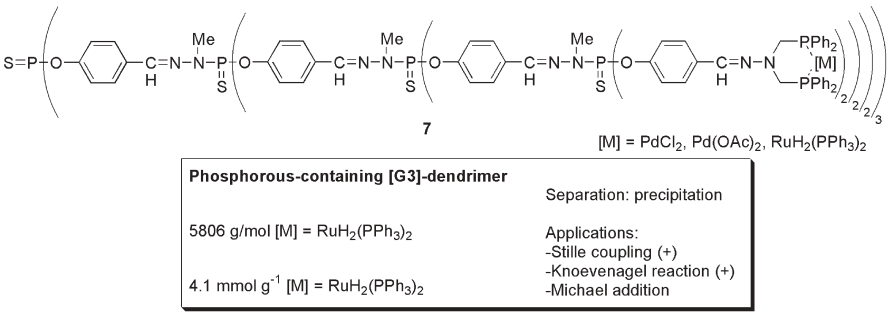


Fig. 7 Phosphorus dendrimers as multivalent ligands

Poly(amido amine) (PAMAM)-aided reactions should be carried out under mild conditions [134], since under harsh reaction conditions, due to the amide skeleton, a significant decomposition of the support can occur.

Margerum and coworkers compared PAMAM dendrimer and hyperbranched PEI-based Co complexes with different ligands for the catalytic hydrolysis of phosphate esters [134]. They concluded that the hydrophilic PAMAM structure is responsible for the reactivity differences observed between PEI- and PAMAM-based systems. Since the location of the Co(II) complexes is at the periphery of the dendrimer, this leads to more homogeneous and accessible catalytic sites compared to PEI. The random distribution of amine reactive sites could lead to many different microenvironments, which may lead to

inactive catalytic sites, to sites with different binding properties, or to sites with different metal aqua/hydroxo equilibria. However, with one substrate a decrease of activity occurred which the authors assign to less cooperativity between sites on PAMAM.

4 Conclusions

After more than ten years of intensive research on the preparation and the application of polymeric supports in catalysis, many new polymeric materials have been developed and evaluated. However, there is still no polymeric support for general application in catalysis. Every polymer has its drawbacks (e.g. chemical stability, polarity, loading capacity etc.). Therefore, a polymeric support has to be carefully selected for the synthetic problem to be solved. In solid-phase catalysis several new supports with better swelling properties in a wider range of organic solvents and higher loading capacities have been introduced. Among these are several new polystyrene hybrid resins, which offer a number of advantages in terms of swelling behaviour and flexibility (kinetics). Considering the loading capacity only dendritic hybrid resins have been employed advantageously. In some cases, remarkable positive dendritic effects have been observed, leading to higher activity and stability of the catalyst as well as higher yields of products when going to higher dendrimer generations. A possible solution to the tedious multistep grafting of dendrimers onto the solid phase may be the replacement of dendritic units on supports by dendron-like hyperbranched oligomers.

Soluble polymeric supports for catalysis, like solid supports, have had a similar growth over the past decade. In terms of stability, aliphatic polyethers, silanes and non-crosslinked polystyrene are among the most promising candidates. Dendritic and linear polyfunctional soluble polymers have by far the highest loading capacities and show great potential as supports for reagents and catalysts in synthesis due to their homogeneous reaction conditions. The use of these soluble polymers for parallel applications, however, requires further progress in automation of solution-phase separation techniques. Membrane reactors have been optimised over the past decade for many solution-phase processes using soluble polymeric catalysts. High-loading soluble polymeric supports are therefore believed to be promising candidates for industrial processes; however, the retention in membrane reactors still requires further improvement (up to 99.999%).

For both solid phase and soluble polymers metal leaching remains to be solved in some cases and more stable, generally applicable polymeric supports are required. For broad application, however, further development of more flexible, economically attractive, not over-specified catalyst systems is needed.

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Non-Covalently Solid-Phase Bound Catalysts for Organic Synthesis

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Abstract Catalysts immobilized on solid supports have become valuable tools for simplified product isolation and catalyst recycling. An alternative to covalent attachment to a solid support is to immobilize catalysts by non-covalent bonding through hydrogen bridges, or ionic, hydrophobic or fluorous interactions. Compared to covalent attachment, such non-covalent approaches increase the flexibility in the choice of the support material, reaction conditions and work-up strategies. Numerous catalytic reactions employing one of these non-covalent bonding strategies have meanwhile appeared in the literature.

Keywords Supported catalysts · Non-covalent immobilization · Heterogeneous catalysis

Abbreviations

acac	Acetylacetonate
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
bmim	1-Butyl-3-methylimidazolium
CPG	Controlled-pore glass
CTAB	Cetyltrimethylammonium bromide
DME	Dimethoxyethane
ee	Enantiomeric excess
FRPSG	Fluorous reversed-phase silica gel
LDH	Layered double hydroxide
NBD	Norbornadiene
o-Tol	*ortho*-Tolyl
OTPPTS	Triphenylphosphine trisulphonate oxide trisodium salt
RPSG	Reversed-phase silica gel
RT	Room temperature
SAPC	Supported aqueous-phase catalysis
TOF	Turnover frequency
TON	Turnover number
TPPMS	Triphenylphosphine monosulphonate monosodium salt
TPPTI	Triphenylphosphine trisulphonate tris(1-butyl-3-methyl-imidazolium) salt
TPPTS	Triphenylphosphine trisulphonate trisodium salt

1 Introduction

In recent years, supported catalysts have become valuable tools for the simplified separation and recovery of catalysts from reaction mixtures. Commonly, the catalysts are attached covalently to a solid support. This covalent attachment of catalysts may lead to a partial loss of efficacy due to the decreased mobility. Alternatively, catalysts can be immobilized by non-covalent bonding through hydrogen bridges, or ionic, hydrophobic or fluorous interactions. Compared to covalent attachments, such non-covalent approaches increase the flexibility in the choice of the support material, reaction conditions and work-up strategies.

Adsorption on silica gel surfaces or silica gels coated with water or thin layers of ionic liquids has been used to immobilize transition metal complexes by ionic interactions and hydrogen bonding. Reversed-phase silica gels were used to retain catalysts by hydrophobic interactions. Support of catalysts on fluorous reversed-phase silica gel by the solvophobic nature of perfluoroalkyl chains is a new and promising approach with potential in catalysis and combinatorial chemistry.

2
Catalyst Immobilization in Polar Liquid Films on Solid Phase

2.1
Supported Aqueous-Phase Catalysis

Supported aqueous-phase catalysis (SAPC) was introduced by Davis and coworkers in 1989 as a new type of heterogeneous catalysis [1]. The key feature of the concept is to immobilize a polar (e.g. water, ethylene glycol) catalyst in a thin layer of hydrophilic liquid that is supported on a solid hydrophilic material. The support is then used for catalysis in organic solvents immiscible with the hydrophilic film, thereby retaining the catalyst on the support. Silica and controlled-pore glass (CPG) are the supports of choice because they are hydrophilic and have a high surface area. As hydrophilic liquid phase, water and ethylene glycol are used because they are immiscible with most organic solvents. The catalysts used have to be hydrophilic. Therefore, commercially available metal precursors (e.g. $PdCl_2$) are mixed with water-soluble ligands (e.g. sulphonated phosphines).

There are two methods for SAPC. In the first method, the solid support is added to a solution of the catalyst precursor and the solvent is evaporated in vacuo. Thus, the surface of the support is covered with the metal complex. Immediately before the reaction, the desired amount of water is added to the support. The second method is the so-called self-assembly method. Here, all components necessary for the SAPC including the substrates and the organic solvent are placed in the reactor. During the reaction, the supported catalyst is formed in situ.

The reactions are proposed to take place at the water–organic interface, either in the pores or on the surface of the support, depending on the pore size and the amount of hydration (Fig. 1) [2–4]. After the reaction, the heterogeneous catalyst is easily separated from the product phase by filtration or decanting. After washing of the solid phase, the catalyst can be reused. A further advantage of SAPC is that it needs no covalent attachment to the solid support, and existing catalytic aqueous–organic biphasic systems can be transferred to SAPC. Because of the features mentioned above, the SAPC principle is of great importance for economic and ecological reasons. Meanwhile, many different applications using SAPC have appeared in the literature, which are summarized in the following sections in more detail. Recently, the principle of SAPC was extended to ionic liquid films on silica gel, in which polar catalysts were immobilized.

2.1.1
C–C Coupling Reactions

One of the most versatile methods for C–C bondformation is Pd-mediated C–C coupling. These reactions are widely used on the laboratory scale as well as in industrial processes.

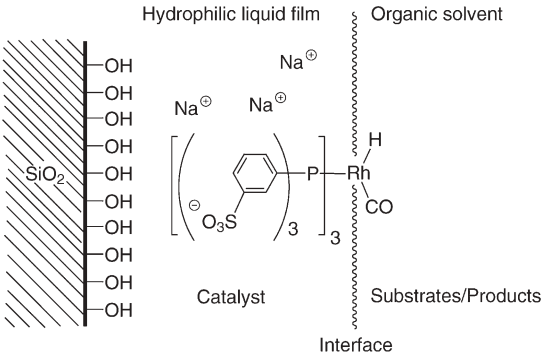
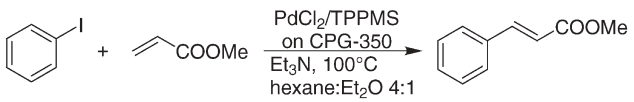


Fig. 1 Model for a SAPC catalyst

2.1.1.1 Heck Reaction

The Heck reaction of iodobenzene and methyl acrylate was successfully applied under SAPC conditions (Scheme 1) [5]. Prior to reaction, a small amount of ethylene glycol was added to the dried supported catalyst, thus forming the SAPC system. The employed ligands were the sodium and lithium salts of triphenylphosphine trisulphonate (TPPTS) and triphenylphosphine monosulphonate (TPPMS). Comparing the different ligands, it was observed that TPPTS retained the palladium better in the hydrophilic film but showed lower activity. On the other hand, the TPPMS/SAPC system was more active. However, more leaching of metal into the organic phase took place. Concerning the counter-ions, sodium turned out to be superior to lithium because its complex proved to be more actively associated with a decreased loss of palladium. From their results, the authors decided that Na-TPPMS was the best compromise between hydrophilicity, activity and leaching.

The activity of the catalyst increased linearly with the amount of supported palladium. The experiments revealed that more than 85% of the activity originated from palladium complexes dissolved in the organic phase, which indicated that the reaction proceeded predominantly homogeneously. However, most of the metal species were taken up again during the reaction. This observation was called temporary leaching. Only a small amount remained in solution after the end of the reaction. The leaching of the metal could be eliminated by adding 6.5 equivalents of TPPMS. When higher excesses of ligand were



Scheme 1 Heck reaction

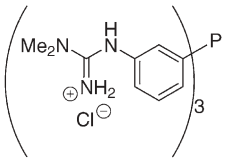
used, the activity decreased by a factor of 3. Recycling experiments of the Heck/SAPC system showed a significant decrease of the activity after the first run. At the same time, high amounts of oxidized phosphine ligands (OTPPMS) were observed. It was suggested that the OTPPMS rendered the palladium inactive.

Investigating the influence of the loading of the hydrophilic liquid phase, it was observed that maximum activity was obtained with a pore filling of 10%. That amount of hydrophilic phase corresponded to a theoretical film thickness of 16 Å. Molecular modelling of the Pd-TPPMS complex revealed that the average diameter of the complex was 11 Å, the largest diameter being 15 Å. Thus, a monolayer of catalyst on the support was assumed.

CPG material was used as support instead of silica gel for a Heck/SAPC system [6]. There, iodobenzene was coupled with different olefins. The dependencies of different substrates and different bases on the activity were examined. The system was active for several types of olefins. The reactivity of the aryl halides was comparable to that of the homogeneous catalysis. Iodides reacted easily, while bromobenzene was converted inefficiently. No reaction occurred using chlorobenzene. With Et_3N as base, the highest conversions were achieved. However, leaching of palladium was observed and an*E*/*Z* mixture of products was isolated. When the amine was replaced by KOAc, the Heck reaction gave selectively the *E*-isomer. No leaching was observed (detection limit approx. 0.1 ppm), but the conversion dropped to 80%. The catalytic system with KOAc as base was successfully used for five consecutive runs, with an overall TON of > 1,200. In all cases, conversion ranged from 70 to 80% and 100% selectivity of the *E*-isomer was achieved.

In addition, the Heck reaction of iodobenzene with butyl acrylate was studied in more detail [7]. In all experiments, butyl cinnamate was selectively produced. It was observed that the activity was only dependent on the palladium concentration in the hydrophilic liquid, but neither on the total amount of complex applied nor on the quantity of the liquid used. In recycling experiments, a short induction period occurred in the first runs. This was not observed in the following runs. Furthermore, repeated application of the catalyst resulted in an increased reaction rate. Other investigators observed a decrease of activity during the recycling experiments [5]. The authors explained their results with an accumulation of Et_3NHI during consecutive runs. It was assumed that the accumulated ammonium salt had the same promotion effect as tetrabutylammonium halide additives in Heck reactions (Jeffery conditions) [8].

Apart from palladium, nickel is also known to catalyse Heck vinylations [9–12]. A supported nickel catalyst was applied for the Heck reaction of iodobenzene with butyl acrylate [13]. The supported aqueous-phase catalysis performed almost as well as the analogous homogeneous catalyst $NiCl_2(PPh_3)_2$. Only the conversion was slightly lower. No leaching of metal into the product phase was observed (detection limit approx. 1 ppm). The immobilized catalyst was successfully recycled three times without observing loss of activity and selectivity.

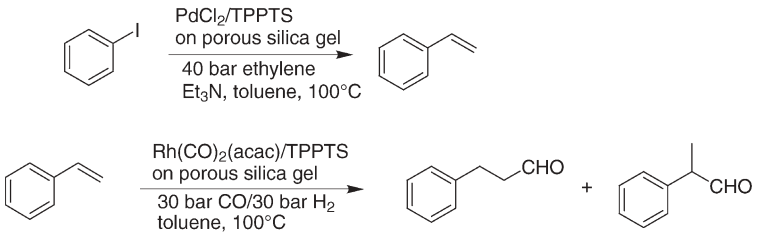


1

Fig. 2 Guanidinium phosphine

Besides sulphonated phosphines, guanidinium phosphines are also able to render metal complexes water-soluble. Their synthesis is straightforward in contrast to the harsh conditions required for sulphonation [14]. The guanidinium phosphine **1** (Fig. 2) was prepared in three high yielding steps [15]. Heck reactions afforded moderate to good yields (55–87%) combined with low palladium leaching (≤0.2%). Recycling experiments were successful. The coupling of iodobenzene and methyl acrylate was performed in four consecutive runs. In each run, the product was isolated in good yield (78–85%) and only a low palladium leaching was observed (≤0.2%).

Multifunctional catalytic systems reduce the number of steps for the synthesis of complex molecules. Until today, only a few reports are known of mixtures of homogeneous catalysts [16, 17]. Commonly, when different homogeneous catalysts are mixed, unfavourable interactions between the organometallic species occur, thus decreasing the activity of each catalyst. The concept of supported liquid-phase catalysis was used to overcome this problem [18]. Different immobilized catalysts were used in one pot without interfering with each other. A reaction sequence consisting of a Heck reaction and a hydroformylation was investigated (Scheme 2). First, ethylene was reacted with iodobenzene. Then, the resulting styrene was converted with CO/H_2. Besides the individual immobilized catalysts, the SAPC sample containing both complexes on the support was also reacted. In both cases, the yield of the Heck products was moderate. The mixed system, however, showed a better activity. The palladium complex seemed to gain from the presence of the rhodium complex. The latter instead showed a strong deterioration in its activity and *n*/*i* selectivity (cf. Table 1). When the individual catalysts were applied simultane-



Scheme 2 Heck reaction/hydroformylation reaction sequence

Table 1 Heck-Hydroformylation reaction sequence[a]

Entry	Catalyst	Heck reaction Yield (%)	Hydroformylation[b]		
			Yield (%) linear	Yield (%) branched	*n*:*i*
1	Pd-SAPC+Rh-SAPC	50.5	29.6	60.3	0.49
2	(Pd+Rh)-SAPC[c]	68.6	6.4	17.8	0.36

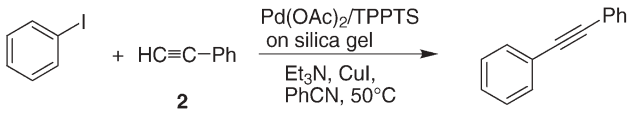
[a] For reaction conditions see Scheme 2.
[b] Yields are based on the amount of the Heck product formed.
[c] The catalyst was prepared from an ethylene glycol solution containing both Pd-TPPTS and Rh-TPPTS.

ously, the hydroformylation catalyst showed high activity but low selectivity. The*n*/*i* ratio was only 0.49, which does not match the selectivities obtained with other Rh-SAPC systems.

2.1.1.2 Sonogashira Reaction

The SAPC strategy was also applied to the Sonogashira reaction [19]. Therefore, $Pd(OAc)_2$ and TPPTS were immobilized on silica in a thin film of water. Two different ligand-to-metal ratios were investigated. On the one hand, five equivalents of phosphine are known to result in complete reduction of Pd(II) to Pd(0). On the other hand, two equivalents are usually recommended in the literature for standard Sonogashira couplings [20–22]. Both ratios were examined using the coupling of iodobenzene with phenylacetylene **2** in benzonitrile (Scheme 3). In recycling experiments, the system in which five equivalents of phosphine were employed showed constant activity over three runs, which then significantly dropped. With two equivalents of phosphine, only during the first run activity was retained. However, in both cases palladium leaching turned out to be high. After filtration of the solid phase the supernatant solutions were catalytically active towards newly added substrates.

Also for the Sonogashira couplings, catalytic system **1** was used as ligand. The reactions proceeded well, with yields from 58–87%. The leaching of palladium did not exceed 0.2%.



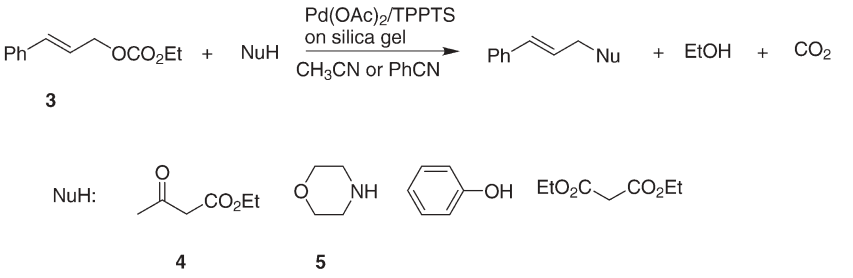
Scheme 3 Sonogashira reaction

2.1.1.3 Allylic Substitution Reaction

A different palladium-catalyzed reaction is allylic substitution. In this case, (*E*)-cinnamyl ethyl carbonate (**3**) and either ethyl acetoacetate (**4**) or morpholine (**5**) as nucleophiles were used as starting materials (Scheme 4) [23]. High activity was obtained when the catalyst was formed at 50 °C in solution. Under these conditions, complete reduction of Pd(II) to Pd(0) took place as judged by ^{31}P-NMR experiments. Comparing acetonitrile and benzonitrile as organic solvents, it was observed that the latter enhanced the activity of the SAPC due to its lower miscibility with water. Unlike acetonitrile, the reaction of **3** with **4** in benzonitrile proved to be superior to the analogous reaction in a homogeneous aqueous–biphasic process. In addition, it was observed that the more water-soluble substrate **5** gave improved yields under SAPC conditions.

Under optimized reaction conditions, the SAPC system showed higher activity, selectivity and stability of the catalyst compared to the homogeneous water/nitrile solvent system. Indeed, even phenol and dimethyl malonate, which were not converted under biphasic conditions, were successfully applied as nucleophiles [24].

Recycling experiments were performed to find the optimum conditions for a continuous flow process. Initially, the reactions were carried out in anhydrous benzonitrile. The reaction was terminated by filtration of the loaded support, which was then washed with benzonitrile and reused with a new batch of substrates. This procedure led to a dramatic loss of activity, for which the loss of palladium was not responsible but rather leaching of water into the organic phase. Thus, the mobility of the immobilized catalyst was reduced combined with a decrease of the activity. The use of benzonitrile/water (v/v=1/1) resulted in a constant level of activity. For a continuous flow experiment, a dry SAPC sample was prepared from $Pd(OAc)_2$ and five equivalents of TPPTS. The dry support was then placed into a reactor. The required amount of water was transferred from water-saturated benzonitrile. The test reaction was the transformation of cinnamyl ethyl carbonate with morpholine. The process achieved a TON of 2,200 and worked continuously for approx. 12 h without loss of activity.



Scheme 4 Allylic nucleophilic substitution

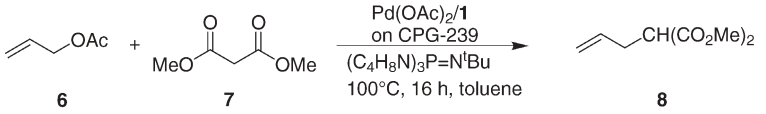
Alternatively, $Pd(OAc)_2$/TPPTS was immobilized on cellulose powder [25]. The new support was also tested in allylic substitution using **3** and **4** as starting materials (cf. Scheme 4). Cellulose-supported complexes were also dependent in their activity on the degree of hydration. Here, two maxima were observed. This was explained by the swelling properties of cellulose in water: the surface area increases by two orders of magnitude, thereby enhancing the surface accessibility and activity [26]. With 26 wt% water, the first maximum was reached. The second one was obtained when the amount of water was raised to 66 wt%. The increase of surface accessibility mentioned above was observed. Complete conversion occurred within 100 min with 66 wt%. With 26 wt%, only 60% conversion was obtained for the same reaction time.

The guanidinium phosphine **1** (cf. Fig. 2) was also successfully tested for allylic substitutions. The reaction of allyl acetate **6** and malonate **7** afforded coupling product **8** in 56% yield. The palladium leaching was determined to be about 0.3% (Scheme 5).

2.1.2 Hydrogenation

Although hydrogenation is a very important reaction in organic synthesis, there exist only a few examples using solid aqueous-phase catalysis. The feasibility of hydrogenations with a SAPC system using the Ru-BINAP derivative **9** (Fig. 3) was demonstrated [27]. Catalyst **9** dissolved in ethylene glycol was immobilized on CPG-240. Ethylene glycol was chosen because like water it is a highly polar, non-volatile liquid and immiscible with non-polar organic solvents. Unlike water, which initiates hydrolysis of theRu–chloride bond, thus leading to a lower enantioselectivity, it is inert towards ruthenium catalyst **9**. As is depicted in Scheme 6, the reduction of alkene **10** to naproxen proceeded at 24 °C with a 96% enantiomeric excess for both **9** immobilized on CPG-240 and homogeneous **9** inmethanol. Ruthenium leaching was below the detection limit of 32 ppb.

It was shown that catalyst **9**, dissolved in ethylene glycol, had negligible activity in the absence of CPG-240. When CPG-240 and the liquid phase containing the catalyst were loaded separately into the reactor along with substrate **10**, self-assembly took place and complete conversion was observed. Additionally, all the Ru had been immobilized after the reaction on the support. In essence, it was shown that the activity was dependent on the interfacial area between the two liquid phases.



Scheme 5 Allylic nucleophilic substitution

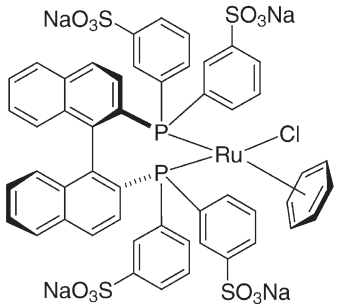


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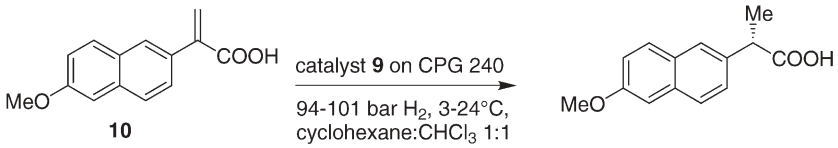
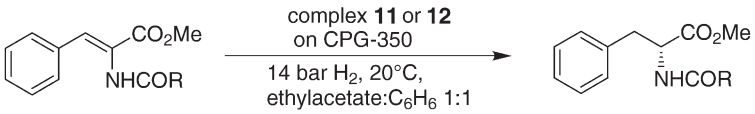
Fig. 3 Ru complex for hydrogenation



Scheme 6 Synthesis of naproxen

The catalysts **11** and **12** (Fig. 4) were used for the synthesis of phenylalanine derivatives (Scheme 7) [28]. Besides the SAPC system, both the homogeneous hydrogenation and the aqueous–biphasic system were investigated. The supported complex **11**, like the homogeneous analogue, showed poor performance as far asenantio selectivities are concerned. In contrast, the aqueous–biphasic catalyst performed at least moderately enantioselective. In this context enhanced selectivity was achieved with immobilized catalyst **12**. The increased ee values (from 16 to 55%) were obtained at the expense of an extended reaction time, which increased from 2 to 40 h.

A simultaneous hydrogenation of an aldehyde and an olefin was examined. The substrates for the hydrogenation protocol were 3-phenylpropionaldehyde **13** and *trans*-stilbene **14** (Scheme 8). A Ru-SAPC was used for theselective reduction of the aldehyde and additionally a Pd-SAPC for the olefin. The individual immobilized catalysts alone performed almost as well as their homogeneous counterparts as far as yields and selectivities for the functional



Scheme 7 Synthesis of protected phenylalanine

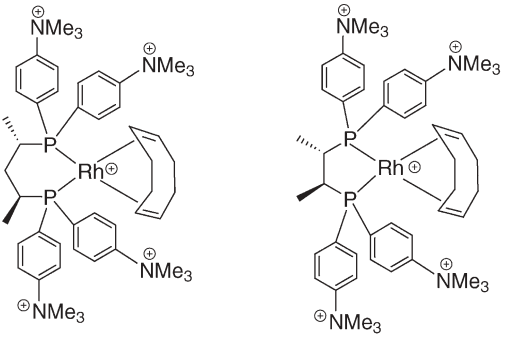
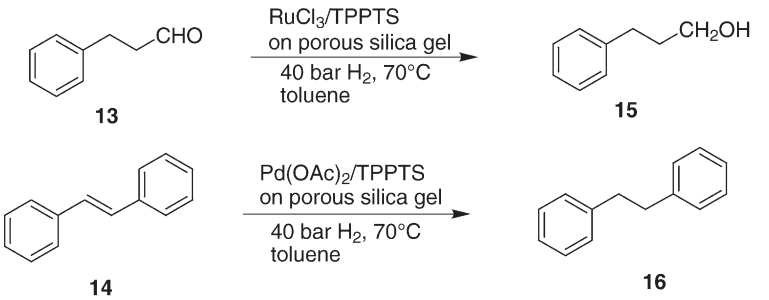


Fig. 4 Rh complexes for hydrogenation



Scheme 8 Simultaneous hydrogenation of an aldehyde and an olefin

groups are concerned. When both catalysts were supported simultaneously on silica gel, the result was the same when using both Ru-triphenylphosphine (TPP) and Pd-TPP in solution in one pot. The activity of the palladium was strongly suppressed while the yield of the alcohol**15** decreased only marginally. However, using the individual SAPC samples in one pot, both reductions worked well. The yield of **15** corresponded to that of the single reaction. The 64% yield of 1,2-diphenylethane **16** was not comparable to that of the single reaction (cf. Table 2). After the reaction, the catalysts were easily separated by filtration and were successfully recycled. In addition, no metal leaching was observed.

2.1.3 Hydroformylation

Hydroformylation is a very important industrial process. Olefins are converted to aldehydes, which can be further transformed into acids, alcohols or amines. The Ruhrchemie/Rhône-Poulenc hydroformylation process is an aqueous–organic biphasic process which uses an easily separable water-soluble rhodium

Table 2 Simultaneous hydrogenation of a mixture of 3-phenylpropionaldehyde and *trans*-stilbene[a]

Entry	Catalyst	Yield (%)	
		15	**16**
Homogeneous			
1	Ru-TPP	94.1	1.0
2	Pd-TPP	0.3	98.9
3	Ru-TPP+Pd-TPP	90.1	7.8
SAPC			
4	Ru-SAPC[b]	89.8	2.2
5	Pd-SAPC[b]	1.7	88.0
6	(Ru+Pd)-SAPC[c]	92.5	2.8
7	Ru-SAPC+Pd-SAPC	87.2	64.0
8	Ru-SAPC+Pd-SAPC[d]	84.4	76.6

[a] For reaction conditions refer to Scheme 8.
[b] Besides the SAPC sample, 0.5 g of silica containing 0.3 ml of water was added before the reaction was started.
[c] The catalyst was prepared from an aqueous solution containing both Ru-TPPTS and Pd-TPPTS.
[d] The catalysts for entry 7 were recycled.

complex [29]. However, this process is only useful for the smaller olefins because only they possess sufficient solubility in water. Higher olefins have to be hydroformylated in a homogeneous process, and the catalyst is separated subsequently by distillation, which may lead to its partial decomposition. In this case, SAPC offers a promising alternative. It was shown that by using SAPC no discrimination between water-soluble and water-insoluble olefins occurred [3].

Catalyst **17** was immobilized on non-porous fumed-silica nanoparticles as support for SAPC hydroformylation (Fig. 5) [30]. In aqueous solutions, the fumed silica possesses great adsorption capacity and the active sites on its surface form strong hydrogen bonds with water molecules [31]. This makes fumed silica an ideal support for solid aqueous-phase catalysis. Additionally, a porous granular silica was also used. The hydroformylation of 1-hexene was investigated and the results were compared with those of the aqueous–biphasic hydroformylation. In all cases, *n*-heptanal was produced with a selectivity of close to 100%. The activity of the fumed-silica SAPC was comparable to that of the biphasic catalytic system with cetyltrimethylammonium bromide as additive. But the loss of rhodium was one order of magnitude lower in the case of the fumed silica than that of the latter system. The lowest rhodium leaching was observed with the system using porous silica as support. Six different kinds of commercially available fumed silicas with different surface areas and particle sizes were compared concerning their catalytic performance in the hydro-

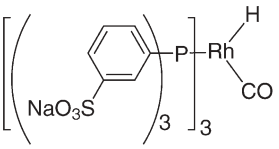


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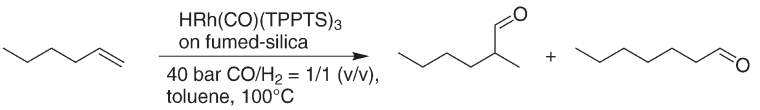
Fig. 5 Complex for hydroformylation



Scheme 9 Hydroformylation of 1-hexene

formylation of 1-hexene (Scheme 9). The prevailing trend was that the reaction rate and the selectivity towards the linear aldehyde increased with smaller particle size and higher surface area of the support.

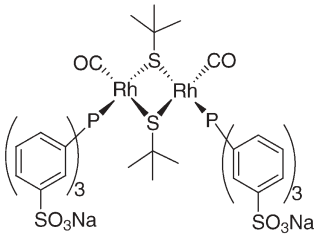
The water content of the support exhibited an interesting influence on the activity. With porous silica as support, the dependence of the activity on the water content showed a single maximum. On the other hand, fumed silica showed high activity over a wide range of hydration states. The highest conversions took place between 40 and 64 wt% water, almost independently of the ligand/rhodium ratio and the type of fumed silica used. The regioselectivity of the hydroformylation was not influenced significantly by varying the amount of water. With a molar olefin/rhodium ratio of 2,500, the highest reaction rates were obtained.

The influence of the triphenylphosphine trisulphonate trisodium salt (TPPTS)/metal ratio was low and conversion as well as the degree of regioselectivity remained almost constant. However, the reaction performance was dependent on the pressure applied. Lower pressure resulted in increased regioselectivity in favour of the linear aldehyde, but also in decreased reaction rate. The authors reasoned that coordination of the phosphine ligand to the metal was preferred over coordination by CO because of the lower CO concentration. Additionally, ^{31}P-NMR spectroscopy was carried out to examine the phosphine species on the support. After the preparation of the supported catalyst, three different signals were observed: free TPPTS, coordinated TPPTS and oxidized TPPTS (OTPPTS). The amount of OTPPTS increased during the reaction. Pretreatment of the silica with basic inorganic salts like Na_2CO_3 or Na_2HPO_4 suppressed the oxidation, which was in accordance with previous results [32]. In these studies, complex **17** was immobilized on a commercially available silica. In order to obtain a mobile complex, 40% D_2O was added. The first observation was that the amount of oxidized TPPTS of the SAPC sample was three times higher than in the case of complex **17** dissolved in D_2O. Due to the immobi-

lization, it also seemed that a new rhodium-TPPTS species was formed. This was indicated by a reduced rhodium-to-ligand ratio (changing from 1:3 to 1:2) and different peaks in the ^{31}P spectrum. This new species interacted strongly with the support as it was impossible to remove it by simple washing with D_2O. The new complex was assigned to be $[Rh(CO)(TPPTS)_2]_n$ (n=1,2). When the catalyst loading on the support was increased, the signals for the original complex **17** appeared. It was assumed that **17** reacted with the silica forming the new species, which then coated the surface of the support. When the whole surface was covered with the new complex, excess of **17** remained unchanged. It was assumed that the acidic property of the silica facilitated the oxidation of the basic TPPTS and therefore alteredcomplex **17**. Pretreatment of SiO_2 with Na_2CO_3 or TPPTS led to a reduced acidic environment on the support, so that no structural change occurred at all and **17** remained intact.

In a multifunctional process, a Rh/TPPTS system was applied besides a Pd/TPPTS system for a tandem Heck reaction/hydroformylation sequence in one pot (cf. Scheme 2). The results are described in more detail in Sect. 2.1.1.1.

A different complex **18** [33] was immobilized on silica for the hydroformylation of 1-octene (Fig. 6) [34]. The catalyst preparation was done using the self-assembly method. In an earlier paper, it had been demonstrated that catalyst **18** requires an excess of phosphine in order to suppress the formation of an inactive tetracarbonyl complex under CO pressure [35]. Hence, the SAPC system was first examined concerning the optimal phosphine-to-rhodium ratio. With a ratio of 6, the highest conversion was observed with about 80% in favour of the linear aldehyde. Addition of more phosphine caused two effects: (a) the selectivity for the linear product increased and (b) the degree of conversiondecreased. The reason for this result was seen in the enhanced competition between the ligand and the olefin for the coordination to the metal centre. But while the effect on the selectivity was low, the conversion dropped by about 20%. The major part of the study dealt with the influence of the hydration of the support on the catalytic performance. It was shown that the conversion increased considerably with total saturation of the silica pores, which corresponded to 16.5 wt%. Excess of water resulted in enough mobility of the catalyst on the surface. Hence, between 19 and 44 wt% the highest degree ofconversion was observed, the maximum being at 24 wt%. Above 44 wt%, the activity decreased again because the water, and subsequently the catalyst, was not sufficiently retained on the silica. In the range 19–44 wt%, *n*/*i* ratios from 3:1 to 8:1 were obtained. At this point the role of the pores inside the support was not clear. Thus, the influence of porous and non-porous supports was investigated. When non-porous glass beads were used, no catalytic activity was observed, only rhodium leaching into the organic phase took place. Having two silicas with different pore sizes, the dependence on the conversion couldbe demonstrated. Supports with large pores behaved according to the proposed mechanism [3]. The reaction took place inside the pores. Therefore, the maximum degree of conversion was seen before the total filling of the pores. When the pores were completely filled, the activity decreased, because the organic sol-



18

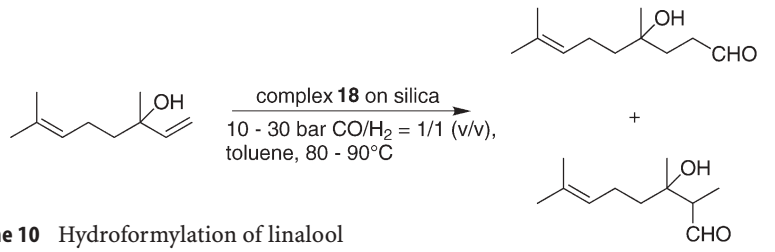
Fig. 6 Complex for hydroformylation

vent could not penetrate the pores and the contact between catalyst and substrate was diminished. The silica with smaller pores behaved differently. The pores served as a storage for TPPTS and the catalyst. The reaction occurredat the external surface of the support. Therefore, complete saturation of the pores was necessary for high conversion.

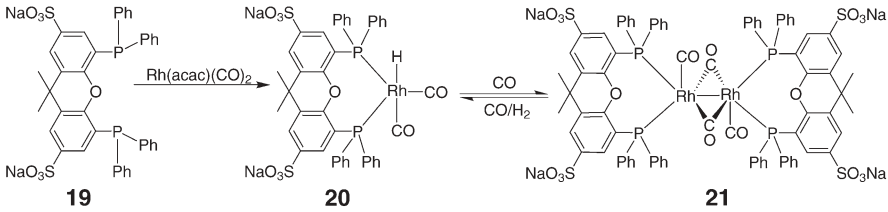
Catalyst **18** was then used to investigate the kinetics of the hydroformylation of linalool in toluene (Scheme 10) [36]. The reaction proceeded well with the aldehydes being the sole products. The selectivity in favour of the linear aldehyde was in the region of 70%.

The turnover frequencies measured at different temperatures were comparable to those found for hydroformylations using other strategies [1, 3, 33, 35]. To develop the kinetic model, the effects of the linalool and the catalyst concentration and of the total carbon monoxide and hydrogen pressure on the outcome of the hydroformylation were investigated. In all cases, the reaction rate was enhanced by a first-order dependence. The results were in good agreement with the calculated model. The activation energy was found to be 14.5 kcal mol^{-1}.

The metal precursor $Rh(acac)(CO)_2$ and **19** were loaded onto CPG-240 with a ligand-to-Rh ratio of 10:1 (Scheme 11) [37]. The in situ formed complex **20** was studied in hydroformylation experiments using 1-octene and compared with $Rh(TPPTS)_3$ on silica. Catalyst **20** was very selective in favour of linear aldehydes (*n*/*i*=40:1). Even after ten runs, the selectivity remainedhigh. With TPPTS as ligand, only a regioselectivity of *n*/*i* 3:1 was achieved. But the activity of complex **20** in toluene was poor (1 h^{-1}). It could be enhanced by about 15 times when neat 1-octene instead of toluene was applied (15 h^{-1}). Increasing the



Scheme 10 Hydroformylation of linalool



Scheme 11 Complex **20** and the reversible switch into its storage form

temperature from 80 to 100 °C further enhanced the activity (55 h^{-1}). A concentration effect concerning 1-octene was not observed in the case of catalyst **17**. But here an increased activity with rising temperature also occurred by the same factor. Complex **20** could not match the activity of **17** but had the advantage of higher regioselectivity and, furthermore, the reusability proved to be better. All runs showed no loss in activity, and no traces of metal were detected in the product phase (detection limit 1 ppm). Instead, the TPPTS system showed good performance only over three runs. In the fourth run, the activity decreased, the regioselectivity dropped and 50% of 1-octene was isomerized and not converted into aldehyde. Additionally, complex **20** could be stored for weeks by transforming it into the more stable dimeric complex **21** (Scheme 11). This was achieved by changing the atmosphere from a mixture of CO/H_2 to pure CO. Importantly, this process was reversible and the catalyst could afterwards be reused without loss of activity.

2.2 Supported Ionic Liquid Catalysis

Ionic liquids have attracted significant attention as alternative reaction media for catalysis in biphasic systems [38–42]. Because of their highly polar nature they are immiscible with many organic solvents. This forms the basis for biphasic reactions where the catalyst is present in the ionic liquid while the substrate stays in the organic phase.

A combination of the advantages of ionic liquids and heterogeneously supported materials was achieved by covering silica gel particles with a thin film of an ionic liquid [43]. This reduces the required amount of ionic media, which is beneficial from an economic and toxicological point of view. Both hydroformylation and hydrogenation reactions were investigated [43, 44].

2.2.1 Hydroformylation Reactions with an Ionic Liquid-Supported Catalyst

In the case of hydroformylation reactions, thesilica gel was modified with a monolayer of covalently attached ionic groups as depicted in Fig. 7, covering approximately 35% of the silica gel's hydroxyl groups. Treatment of this

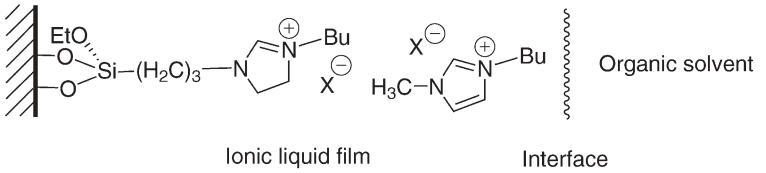


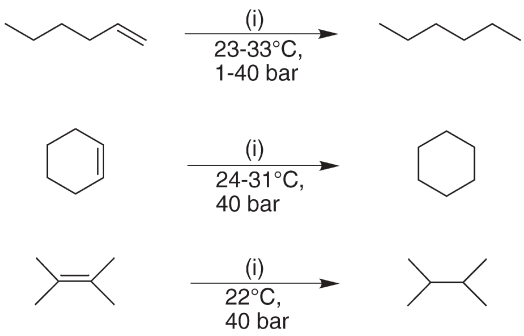
Fig. 7 Layer of ionic liquid supported on a modified silica gel

monolayer surface with a mixture of the rhodium catalyst precursor and ligands (TPPTS, TPPTI, ratio Rh:P 1:10) dissolved in acetonitrile and ionic liquid phase ([bmim][BF_4] or [bmim][PF_6], 25 wt% loading) followed by removal of thesolvent under reduced pressure yielded the immobilized multilayered supported catalyst as a free-flowing powder. The supported catalyst was tested in the hydroformylation of 1-hexene, where it performed reasonably well. The observed TOFs (TOF = turnover frequency) ranged from 56 to 65 min^{-1} (with different ligand-solvent combinations, yields from 33 to 46%), which is significantly higher than the observed TOFs with the biphasic non-supported systems (2.4 to 23 min^{-1}, yields from 11 to 70%). The enhanced activity was attributed to the general increase of interface area and the higher local concentration of catalyst at the interface. Compared to the homogeneous system, where a TOF of 400 min^{-1} (yield 95%) was observed, however, the activity was significantly lower. Nevertheless, the supported ionic liquid system is attractive due to its convenient product separation. Metal leaching ranged from 0.07 to 2.1%, which lies in the range of biphasic reactions. The clear advantage over the biphasic reactions is the decreased loss of expensive ionic liquid phase.

2.2.2 Hydrogenation Reactions with an Ionic Liquid Supported Catalyst

[Rh(NBD)(PPh_3)$_2$]PF_6 (NBD=norbornadiene) as a pre-catalyst was immobilized by treatment with acetone, [bmim][PF_6] and silica gel (untreated, without attached ionic liquid fragments). The obtained material was a free-flowing powder despite an ionic liquid loading of 25 wt%. The estimated thickness of the ionic liquid layer was 6 Å.

The supported catalyst was successfully employed using different substrates, depicted in Scheme 12. For the reduction of 1-hexene a TOF of 447 min^{-1} (99% yield, 30 °C, 600 psi) was observed for the supported catalyst, compared to 46 min^{-1} (29% yield, 50 °C, 600 psi) for the homogeneous system. This enhanced activity is supposedly due to the absence of a coordinating solvent that blocks coordination sites on the Rh, thus inhibiting the reaction significantly. Comparison with the biphasic reaction showed a TOF of 4 min^{-1} under similar conditions. This can be explained by the higher local concentration of catalyst in the case of the supported system. The catalyst activities for the hydro-



Scheme 12 Hydrogenation of olefins: (i) H_2, Rh catalyst in supported ionic liquid

genation of cyclohexene and 2,3-dimethylbutene were slightly reduced, due to the decreased accessibility of the double bond in these substrates.

Catalyst leaching was not observed and the same catalyst was used for 18 batch runs without significant loss of activity. Both hydroformylations and hydrogenations clearly showed that supported ionic liquid catalysis is a very useful and efficient principle.

3
Immobilization by Polar Interactions

3.1
Catalysts Bound by Hydrogen Bonding

3.1.1
Hydrogenation with Hydrogen Bonded Catalysts

In this and the following sections we describe the methods which do not need a hydrophilic solvent to retain the catalyst on the surface of the solid support. Utilization of hydrogen bonding for the non-covalent immobilization of Ru and Rh complexes on silica gel was investigated in detail [45–47]. The loading of the support was done without further covalent modification of the silica gel, and there was no need for a solvent film covering the support particles.

The investigated supported complexes **22** and **23**, outlined in Fig. 8, were used for hydrogenations of alkenes, nitriles and α,β-unsaturated ketones. Furthermore, **23** was used in the reduction of different heterocycles like benzothiophene, quinoline, indole, dibenzothiophene and acridine. The supported chiral Rh complexes, depicted in Fig. 9, were used for hydrogenation reactions with prochiral olefins.

The immobilization procedure consisted of dissolving the complexes in anhydrous dichloromethane and subsequent stirring with activated silica gel (ac-

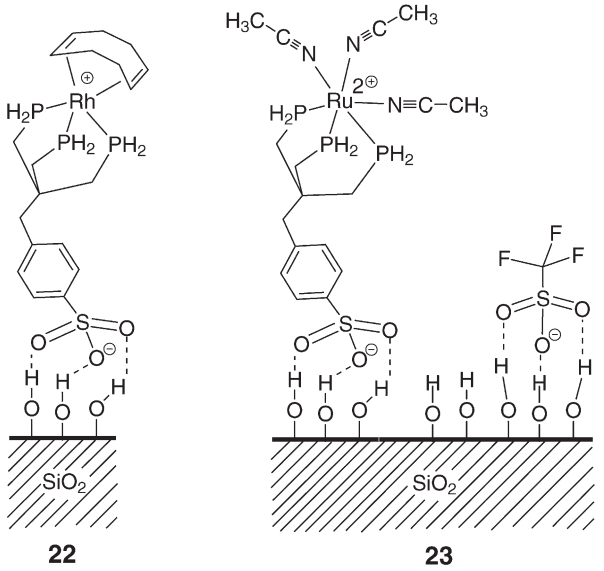


Fig. 8 Catalysts immobilized by hydrogen bonding on silica gel

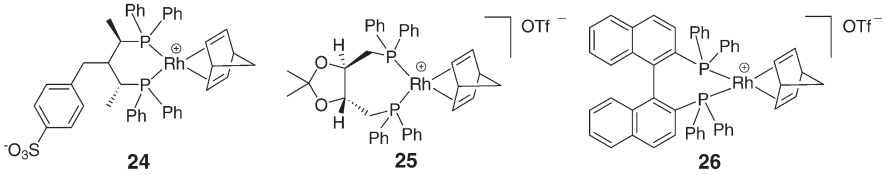
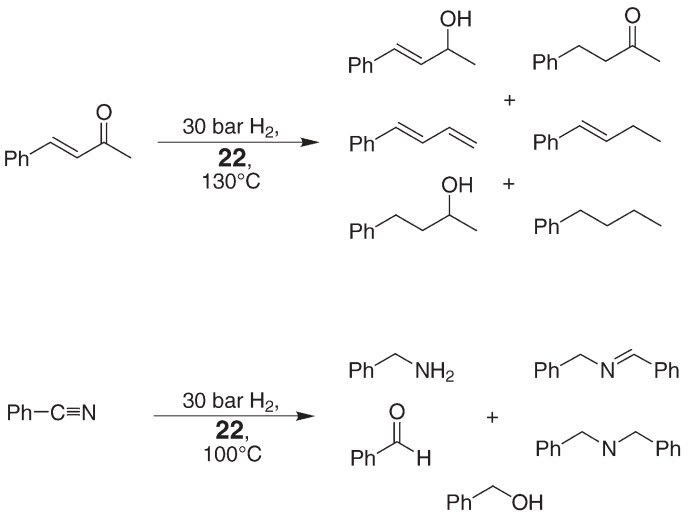


Fig. 9 Chiral Rh complexes

tivated by heating to 300 °C for several hours to remove physisorbed water). The progress of silica loading could be observed as the yellow colour of the solution faded and the silica gel turned increasingly yellow. After filtration the supported catalysts were obtained, with 2 wt% catalyst loading in the case of the non-chiral and 1 wt% in the case of the chiral complexes **24**, **25** and **26**.

The supported catalyst **22** was tested in the reduction of benzylideneacetone and benzonitrile (Scheme 13). Thus, the supported catalyst, the substrate and solvent*n*-octane were combined in the reaction vessel followed by charging with hydrogen (30 bar) and stirring at 130 °C. The reaction product was removed by filtration and the filtrate was analysed by GC.

In the case of benzylideneacetone, the conversion of 61% was significantly lower than with a biphasic aqueous–organic catalyst system (87% conversion) or the conventional homogeneous catalyst system (100% conversion). However, the observed selectivity in the case of catalyst **22** was 96%, i.e. almost selective reduction of the olefinic moiety took place whereas the carbonyl substructure



Scheme 13 Hydrogenation of an unsaturated ketone and a nitrile

remained nearlyuntouched. This is not observed when the biphasic (87% of the desired product) or the homogeneous catalyst (1% of the desired product) is used. In the case of the homogeneous catalyst both olefinic and carbonyl substructures were reduced.

With benzonitrile as substrate, catalyst **22** performed significantly better than the biphasic catalytic system. Both conversion (95%) and selectivity (92%) of the supported system were superior compared with the performance of the biphasic system (25% conversion, 65% selectivity), where the main product was not even the desired product. The best performance, however, was achieved with the homogeneouscatalyst, which reached 98% conversion and 100% selectivity. Nevertheless, the easy separation and reusability of the catalyst make the system **22** attractive for use in hydrogenation reactions.

As mentioned above, catalyst **23** was successfully applied to the hydrogenation of various heterocycles, where only the heterocycle was hydrogenated, whereas annulated aromatic systems remained untouched [48]. The reduction of prochiral olefins (Fig. 10) with the supported chiral catalysts gave generally

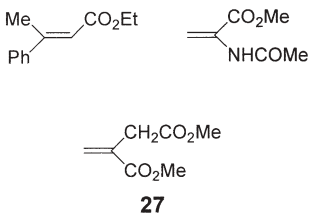


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Fig. 10 Prochiral olefins

nearly quantitative yields, but the enantioselectivity was mediocre, 53% in the best case using catalyst **24** and olefin **27**.

In the same manner mentioned above, [(*R*,*R*)-Me-(DuPHOS)Rh(COD)]OTf [Me-DuPHOS=1,2-bis(2,5-dimethylphosphacyclopentyl)ethane] **28** (Fig. 11) was immobilized via hydrogen bonding of the triflate [49]. The immobilized complex was found to exhibit high catalytic activity and selectivity for the hydrogenation of three prochiral α-enamide esters (Fig. 12). For example, hydrogenation of **29** in hexane at room temperature led to complete conversion (99%) with high enantioselectivity (99%). Reduction of the other two olefins **30** and **31** gave similar results. Those reactions were superior to homogeneous reactions in hexane, where comparable conversion could be observed but with significantly reduced enantioselectivity (from 85 to 87%). Only the homogeneous reduction in MeOH, which generated similar conversion and enantioselectivity, could rival the reaction utilizing the supported system in hexane. According to the authors, leaching of catalyst could not be observed and repeated application without loss of conversion orselectivity proved the reusability of the supported catalyst.

Another more recent publication reported the grafting of chiral Rh complexes on silica gel via hydrogen bonding [50]. Different chiral ligands (Fig. 13) were converted to Rh trifluoromethanesulphonate complexes and immobilized applying the same immobilization technique mentioned above, the anionic part tethered non-covalently to the surface of the silica particles. Those complexes were applied in the hydrogenation of (*E*)-α-phenylcinnamicacid to 2,3-diphenyl propanoic acid, carried out at 20 barH_2 and 40 °C. Conversion (up to 90%) and enantioselectivity (up to 97%) were generally higher than with the same ligands in homogeneous complexes (conversion up to 88%, ee up to 83%).

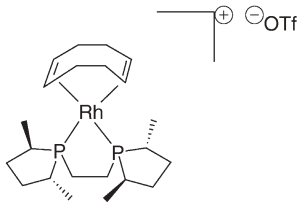

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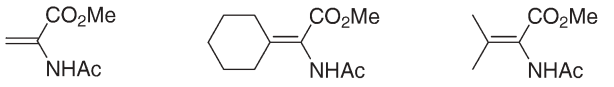
Fig. 11 Chiral hydrogenation catalyst



29 **30** **31**

Fig. 12 More prochiral olefins

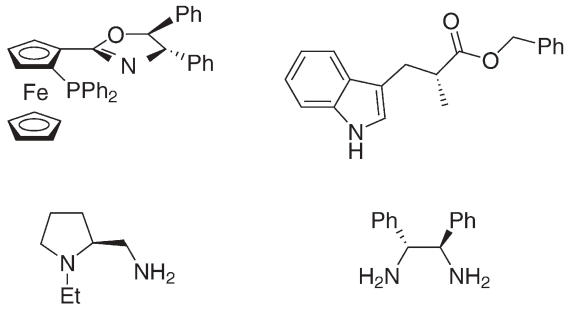


Fig. 13 Different chiral ligands

3.1.2 Epoxidation with a Supported Hydrogen-Bonded Catalyst

Besides hydrogenations, epoxidations with hydrogen-bonded catalysts were reported [51, 52]. Copper(I) pyrazolborates (Fig. 14) were immobilized on silicagel by dissolving the complexes in dichloro methane and subsequent stirring forseveral hours and filtration.

The air-labile complexes were supposed to interact with the support not only through classical hydrogen bonds but also through so-called non-classical hydrogen bonds. These non-classical hydrogen bonds, also called dihydrogen bonds, are similar to those recently found in BH_3NH_3 [53]. As proposed by Crabtree, these bonds must be interpreted as the interaction of the NH proton, or in this case, as the OH proton and the BH bond as a whole.

Epoxidation reactions with the immobilized catalysts **32** and **33** (Scheme 14) using oxoneas oxidant did not work as well as the homogeneous reactions, however. Whereas the homogeneous reaction provided styrene oxide in 60% (with catalyst **33**) and 70% (with catalyst **32**) yield (corresponding to the oxidant) with only a small amount of benzaldehyde by-product (<5%), the heterogeneous reaction provided mainly amixture of by-products and styrene. The

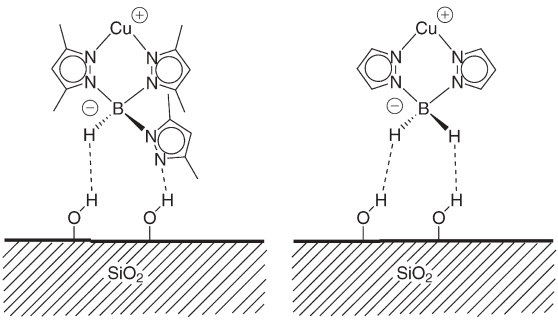
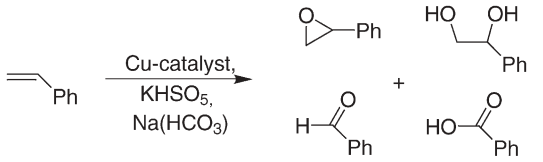
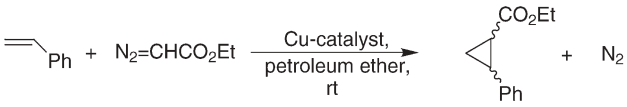


Fig. 14 Copper complexes bound to silica gel



Scheme 14 Epoxidation with oxone and a supported Cu catalyst



Scheme 15 Cyclopropanation with a supported Cu catalyst

main by-product, 1-phenylethanediol, generated by nucleophilic ring opening, is a consequence of the acidic nature of the solid support. If all by-products are taken into consideration, an overall yield of 57% (for **32**) and 68% (for **33**) was achieved, which is lower than under homogeneous oxidation conditions.

3.1.3
Cyclopropanations with a Supported Hydrogen-Bonded Catalyst

Apart from epoxidations, cyclopropanations were performed with the same immobilized catalysts mentioned above [54]. However, the performance of the catalytic system for cyclopropanations was significantly better than for epoxidations.

Cyclopropanation reactions were carried out with ethyl diazoacetate as carbene source and styrene, using petroleum ether as solvent (Scheme 15). After completion of the reaction, the mixture was filtered in order to separate catalyst and products. The heterogeneous system provided slightly higher yields (up to 90%) and similar lower diastereoselectivities compared to the homogeneous system.

To summarize the reactions above, the feasibility of immobilization via hydrogen bonding has been demonstrated, and the generally low leaching of catalyst, the relatively simple catalyst preparation and thehigh activity, and in some cases high selectivity, make this approach veryattractive. However, the choice of solvent is very important to avoid highercatalyst leaching. For example, most of the catalysts mentioned above arewashed off the solid support with alcohols like MeOH or EtOH, whereas thehydrogen bonding remains intact with dichloromethane.

3.2
Heck Reactions with Catalysts Immobilized by Ionic Interactions

Recently, the heterogenization of a water-soluble complex via an ion-exchange process was described [55]. As solid support, a layered double hydroxide (LDH)

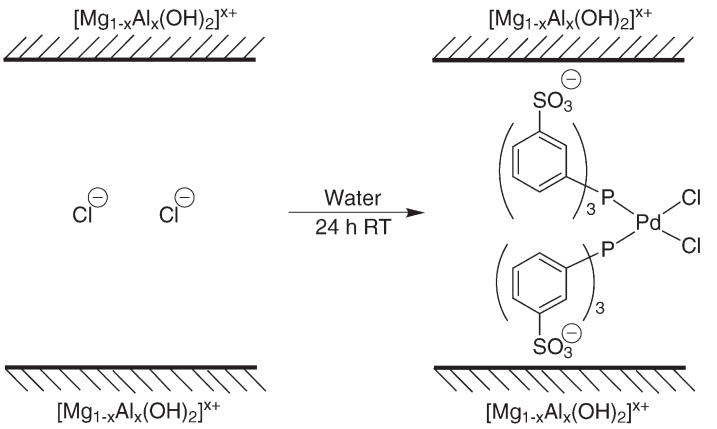


Fig. 15 Pd complex immobilized between thelayers of a double hydroxide by an ion exchange process

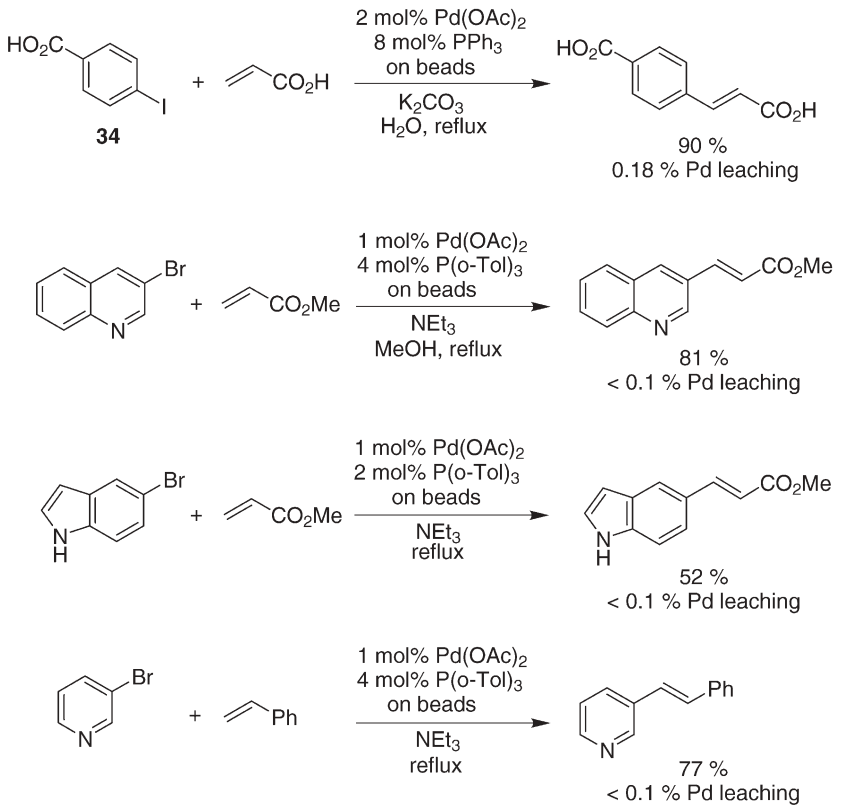
consisting of alternating cationic $[Mg_{1-x}Al_x(OH)_2]^{x+}$ and anionic $Cl^- \cdot nH_2O$ layers was employed. The complex $Pd(TPPTS)_2Cl_2$ was immobilized by stirring for 24 h in decarbonized water with the suspended solid support [56]. After filtration the resulting solid was washed and dried (Fig. 15).

The supported catalyst obtained was investigated in Heck arylation reactions, where the olefin, haloarene, supported catalyst, tributylamine and DMF were stirred at 120 °C under nitrogen. The supported catalyst performed very well, with excellent yields and high trans-selectivity. For example, the reaction of *p*-bromoanisole with styrene afforded the coupled product in 87% yield. This result is good, considering the use of a donor-substituted bromoarene, which generally do not perform well in Heck reactions. The observed leaching of total Pd was below 0.5%. The yields observed using this technique were generally higher than those using the homogeneous catalyst. This is supposedly due to some beneficial interactions of the LDH support during the catalytic cycle. The higher activity, low Pd leaching, reusability and easy catalyst separation make this immobilization process attractive.

4
Immobilization by Hydrophobic Interactions

4.1
C–C Couplings with Catalysts Immobilized on Reversed-Phase Solid Support

The use of hydrophobic interactions for the non-covalent immobilization of catalysts is another possible concept for attachment of catalysts. The concept is based on hydrophobic interactions between commercially available reversed-phase silica gel and a hydrophobic anchor attached to catalysts.



Scheme 16 Heck reactions with catalyst on reversed-phase silica gel

Utilizing this principle, Heck reactions were performed [57]. The silica gel was derivatized with a C_8H_{17}-trimethoxysilane to obtain the desired reversed phase properties, followed by treatment with palladium acetate and triphenylphosphine in cyclohexane. After removal of the solvent, an air-stable catalyst supported on reversed-phase silica gel (RPSG) was formed. This supported catalyst was employed with variable success in Heck C–C coupling reactions, as depicted in Scheme 16.

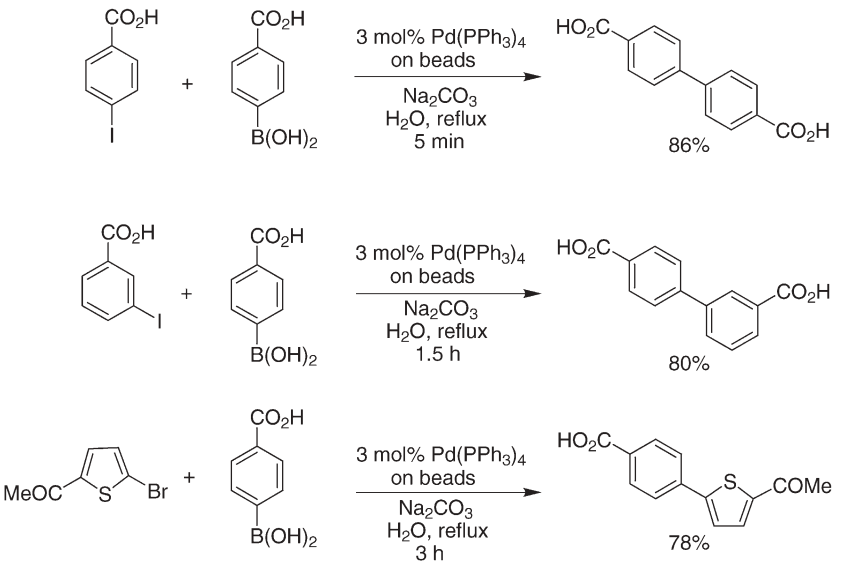
The leaching of total Pd was very low, ranging from 0.02 to 0.18%. For example, *p*-iodobenzoic acid (**34**), acrylic acid, supported catalyst (2 mol% Pd) and K_2CO_3 were dissolved in water and heated under reflux for 2 h. After filtration the coupled product could be isolated in 90% yield. The reactions were performed with different solvents, not only water, but also methanol, Et_3N and DMSO. Hence, there was no requirement to use water-soluble substrates. Another advantage of this reversed-phase silica gel method is that more polar substrates compared to the conventional homogeneous Heck reaction can be employed. In homogeneous Heck reactions polar substrates are difficult to

separate from metal contamination. Examples of polar substrates are the *N*-containing heterocycles (quinoline, indole and pyridine) shown in Scheme 16.

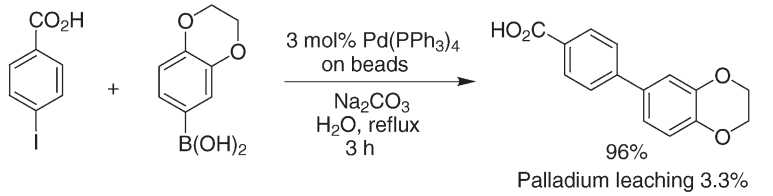
Later, the principle of hydrophobic catalyst immobilization was extended to Suzuki reactions [58]. Instead of P(*o*-Tol)$_3$ as a phosphine ligand, PPh_3 was used. Grafting of the catalyst onto RPSG followed the same procedure mentioned above. Several haloarenes were reacted with *p*-carboxyphenyl boronic acid in water under reflux (Scheme 17). The yields obtained were similar to those reached with homogeneous catalysts. Observed leaching was low, reaching from 0.06 to 0.63% of total palladium. If *p*-chlorobenzoic acid was used as a reactant, no coupling was observed. However, immobilization of other non-polar ligands should be possible. The presence of the glass beads seemed to have a beneficial influence on the rate of reaction. Thus, the reaction of *p*-iodobenzoic acid proceeded to completion within 5 min, while conventional $Pd(PPh_3)_4$ gave only 50% conversion after 7.5 h. This increased reaction rate was attributed to the large contact area between water and supported catalyst. The catalyst was recycled once and reused without any loss of activity.

Both Heck and Suzuki reactions proved the worth of hydrophobic immobilization, and in the latter case the higher reaction rate was an additional advantage. Beneficial, too, is the fact that conventional catalysts could be used without further modification, because there was no need to adjust the ligand solubility. A major drawback of this procedure, however, is the restriction in the choice of suitable reactants.

Since non-polar reactants are able to wash down the equally non-polar catalyst, the range of suitable reactants is limited to more or less polar substances.



Scheme 17 Suzuki reactions with catalyst on reversed-phase silica gel



Scheme 18 Suzuki reaction with less polar boronic acid

Scheme 18 depicts a Suzuki coupling with a non-polar boronic acid and catalyst leaching of 3.3% due to this reagent.

4.2 Immobilization on Fluorous Reversed-Phase Silica Gel

Ever since the initial report by Horváth and Rábai [59], fluorous biphasic systems have received much attention as a tool for the separation and recovery of reagents or catalysts. Accordingly, a number of reviews on his topic have appeared in the literature [60–65]. The concept is based on the temperature-dependent immiscibility of perfluorinated solvents and common organic solvents. Organic compounds are usually not soluble in perfluorinated solvents, but the solubility greatly increases when perfluoroalkyl chains, so-called perfluoro tags, are attached to the molecule (Fig. 16).

Accordingly, the partitioning coefficient between organic and fluorous solvents of a molecule depends on the presence of perfluoro tags. This has been employed in numerous separation strategies based on phase separation of organic and fluorous solvents [64, 65]. Perfluorinated solvents have the advantage that they are chemically inert and, thus, not flammable and of low toxicity. But besides their relatively high price, their major drawback is that they are potent greenhouse gases by virtue of their volatility, inertness, which causes long atmospheric lifetimes, and their strong IR absorption [66]. Thus, it would be highly desirable to omit perfluorinated solvents, while still making use of fluorous–fluorous interactions. In this context the thermomorphic behaviour of certain perfluoro-tagged compounds was employed [67, 68]. In a more general approach, fluorous reversed-phase silica gel (FRPSG) (**35**) (Fig. 17) has been utilized as a solid support for the non-covalent immobilization of perfluoro-tagged Pd catalysts [69]. As such it was applied to C–C couplings in organic solvents.

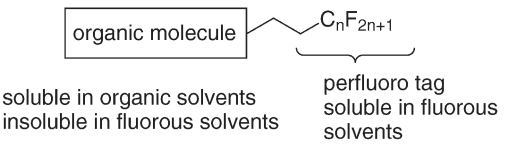


Fig. 16 Schematic representation of a perfluoro-tagged molecule

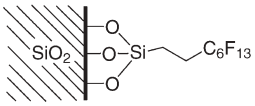


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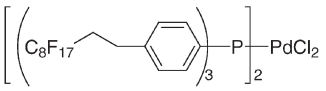
Fig. 17 Fluorous reversed-phase silica gel

For the immobilization of perfluoro-tagged bis(triphenylphosphine) Pd complexes **36**, **37**, **38** (Fig. 18), FRPSG **35** was shaken with a solution of the complex in a volatile solvent (e.g. diethyl ether) and the solvent was evaporated. The thus immobilized pre-catalyst is an air-stable, free-flowing powder. This, along with the dilution of the catalyst by FRPSG, facilitates the precise handling of small catalyst amounts, especially in parallel reactions. Typically, the FRPSG was loaded with 10 mg of complex per gram of FRPSG, which corresponds to 3 μmol/g. Suzuki couplings of phenylboronic acids with aryl bromides were carried out in biphasic mixtures of DME and aqueous Na_2CO_3 (Scheme 19).



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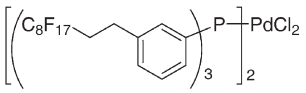

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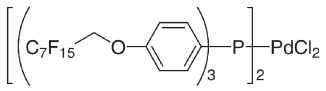

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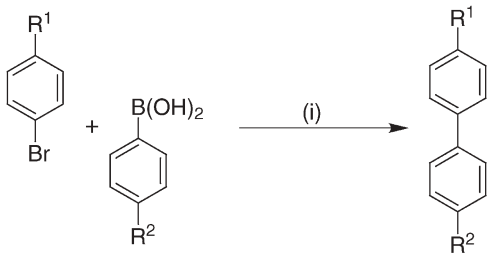
Fig. 18 Perfluoro-tagged Pd complexes

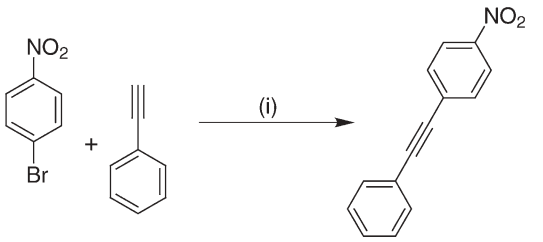


Scheme 19 Suzuki reaction with catalyst on FRPSG: (i) 0.1 mol% Pd, DME, 2 M aq. Na_2CO_3, 80 °C, 16 h

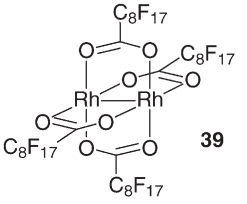
For the isolation of the product, the catalyst supported on FRPSG was filtered, washed with DME and water, and reused for further reactions. With catalyst loadings of 0.1 mol% yields were high for electron-deficient aryl bromides, and recycling of the catalyst was successful with very reactive substrates like *p*-bromonitrobenzene or *p*-bromobenzonitrile.

This catalyst immobilization on FRPSG was also employed in the Sonogashira coupling of *p*-nitrobromobenzene and phenylacetylene (Scheme 20). The same strategy was used for the immobilization of dirhodium(II) perfluorocarboxylates [70]. Rhodium complex **39** was adsorbed on FRPSG and used as catalyst for the alcoholysis of silanes (Scheme 21). In the solventless protocol, 0.1 mol% of supported catalyst was mixed with 1-octanol and triethylsilane, which led to complete conversion within 24 h. The catalyst could be recycled by simple filtration, with Rh leaching of 2.6%. Despite the small leaching, the activity was slightly reduced, which was attributed to slow catalyst decomposition.

The attempt to immobilize a perfluoro-tagged Co(III) salen complex **40** (Fig. 19) on FRPSG did not lead to active catalysts [71]. While complex **40** was active in solution as catalyst for the hydrolytic kinetic resolution of epoxides, the adsorbed complex was inactive. The authors attributed this to site-isolation on the solid support, which counteracts the proposed cooperative reaction mechanism [72, 73].



Scheme 20 Sonogashira reaction: (i) 2 mol% catalyst on FRPSG, CuI, *n*-Bu_2NH, DMF, 100 °C, 14 h



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Scheme 21 Alcoholysis of $HSiEt_3$

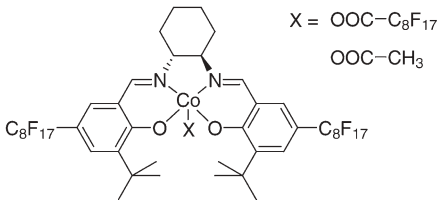

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Fig. 19 Perfluoro-tagged chiral Co-salen complex

The important feature of the immobilization on FRPSG is the selectivity of the interactions. The perfluoro-tagged catalyst exhibits a preference for the fluorous solid support in organic media as well as in aqueous media. Neither non-polar organic substances nor inorganic salts adhere appreciably to the FRPSG. This is a unique distinction between FRPSG on the one hand and reversed-phase materials or polar supports like silica gel on the other hand. Since it allows one to work with polar and non-polar liquid phases simultaneously, which is often necessary during work-up, immobilization on FRPSG will certainly see further application in the near future.

In combinatorial chemistry FRPSG can also be used as a solid support for organic synthesis. As a first example of this strategy, the synthesis of a library of 16 quinazoline-2,4-diones starting from perfluoro-tagged benzyl alcohol was described [74].

5 Conclusion

As detailed in this overview, the non-covalent attachment of catalysts on a solid support is an important additional technique for the separation and recovery of catalysts from reaction mixtures. Such non-covalent immobilization strategies bring together a number of advantages of solution-phase chemistry and solid-phase supported chemistry. The catalysts can be separated from reaction mixtures by simple filtration. The pre-catalysts can be prepared and characterized in solution. The underlying principle is partitioning between a solid phase or a supported liquid phase and a liquid reaction phase of different solvating power.

Silica gels and controlled-pore glass, which were covered with thin films of polar phases such as water, ethylene glycol or ionic liquids, were used as polar solid supports. These systems are limited to very polar, usually ionic catalysts and non-polar reaction media in order to prevent catalyst leaching. This in turn, can be limiting to the range of substrates. Existing catalytic processes in common liquid–liquid biphasic systems can be easily transferred to supported liquid-phase conditions. At the same time the interfacial area between the

phases can be increased dramatically. The support materials are inexpensive and readily available on the large scale. For supported aqueous and ethylene glycol films the liquid phase is very cheap, but a drawback is that the amount of liquid layer has to be carefully optimized for every process. For supported ionic liquids the liquid phase is very expensive, but the necessary amount is much lower as compared with the corresponding liquid–liquid biphasic system. Although it is conceivable that these strategies may find application in laboratory synthesis, the major part of research has been directed towards industrial processes.

Similarly, silica gel without a liquid film and clay-like materials have been used as polar solid phases for the attachment of catalysts by ionic interactions or hydrogen bonds. The main advantages and limitations are along the lines mentioned above for supported liquid phases.

Reversed-phase silica gel has been used to immobilize hydrophobic catalysts. This strategy is limited to polar solvents like H_2O, methanol, triethylamine or DMSO and to polar substrates and therefore it is complementary to immobilizations using polar supports.

These strategies have in common that they rely on a large difference in polarity of catalysts and substrates, where one component is very hydrophilic and the other very lipophilic. While such strategies can be successful for single reactions or smaller classes of substrates with similar solubility, it cannot be applied generally to substrates of differing polarity. An advantage is that the supports are often inexpensive and available in large quantities. Since optimization of every single reaction is necessary, these strategies are attractive mainly for industrial processes, while application on the laboratory scale will probably be limited to special cases.

Fluorous reversed-phase silica gel has been used as the support for perfluoro-tagged catalysts. The main advantage is the solvophobicity of perfluoroalkyl tags. They result in a selective partitioning onto the fluorous reversed-phase silica gel, while untagged components possess no affinity to the fluorous phase. As a consequence, polar as well as non-polar reaction media can be used, which makes this strategy applicable to a broader range of reaction and work-up conditions. It is conceivable to further adjust the reactivity by release from the support during the reaction and re-adsorption after a solvent switch. The main limitation is the necessity to modify both the solid support and the catalyst with perfluoroalkyl tags, but FRPSG and an increasing number of modified catalysts are becoming commercially available. This strategy will probably find use mainly in laboratory applications and it might also be applied to special processes of fine chemical production.

It remains to conclude that non-covalent catalyst immobilization is an interesting alternative to covalent attachment and this growing field will certainly influence catalytic processes.

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Recent Progress in Polymeric Palladium Catalysts for Organic Synthesis

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Abstract Recent progress in the design, preparation, and application of polymer-supported palladium complexes is reviewed. In particular, the preparation of various supported palladium-phosphine complexes used in a variety of carbon–carbon bond forming reactions such as the Heck reaction, the Suzuki–Miyaura coupling, and π-allylic substitution is discussed. Immobilization of the palladium complexes has often been achieved by anchoring phosphorus-based ligands on functionalized polymer supports via covalent bonding, and subsequent complexation of the anchored ligands with palladium precursors. Encapsulation of palladium catalysts in polymer supports and immobilized chiral palladium catalysts are also introduced. Heterogeneous catalytic asymmetric carbon–carbon bond forming reactions with high stereoselectivity have likewise been achieved using polymeric chiral palladium complexes.

Keywords Polymeric catalyst · Palladium catalysis · Immobilization · Asymmetric catalysis

Abbreviations

BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
Boxax	2,2′-Bis(oxazolyl)-1,1′-binaphthyl
cod	Cyclooctadiene
dba	Dibenzylideneacetone

DVB	Divinylbenzene
MAS	Magic angle spinning
MOP	2-Diphenylphosphino-2′-functionalized 1,1′-binaphthyls
PNIPAM	Poly(*N*-isopropylacrylamide)
PE Polyethylene	
PEG	Poly(ethylene glycol)
PAMAM	Polyaminoamide dendrimer
PS	Polystyrene
PS-PEG	Polystyrene-poly(ethylene glycol)
ROMP	Ring-opening metathesis polymerization
TMEDA	Tetramethylethylenediamine

1 Introduction

The development of catalytic fine organic transformations has emerged as one of the most exciting and challenging areas in modern synthetic chemistry. Homogeneous transition metal catalysts are widely used for a variety of organic transformations, and palladium complexes, in particular, have been recognized as the most powerful tool in the arsenal of synthetic organic chemists [1–3]. Nevertheless, immobilization of transition metal catalysts is presently undergoing very rapid growth [4–11]. Thus, catalytic processes with transition metal complexes are often hindered due to difficulties in recovering costly noble metals and ligands as well as in removing trace amounts of metal species from the resulting products, coproducts, and solvent waste. Immobilization of metal-based catalysts does meet both economical and green chemistry requirements and has proven effective in overcoming these problems. Another major driving force for the recent progress in the immobilization of synthetic catalysts is the rapid development of combinatorial chemistry [12, 13] where, owing to more efficient methods for compound purification, high-throughput synthesis of large numbers of organic molecules by solution-phase catalysis is becoming a useful methodology. One approach employs supported catalysts that can be readily removed by simple manipulation (e.g., filtration) from a solution-phase reaction mixture.

This manuscript will attempt to review the recent progress in palladium complex immobilization and the catalytic reactions with these immobilized complexes. In particular, polymer-based heterogenization of the corresponding homogeneous carbon–carbon bond forming reactions using palladium catalysts [14] will be discussed.

Several approaches to immobilize transition metal catalysts on polymer supports have been reported in the literature. The most representative ones are: (1) immobilization of ligands as well as ligand-metal complexes by covalent and/or coordination bonds; (2) adsorption of catalysts on the supports; (3) formation of ionic pairs between, for example, the surface of the support bearing anionic functional groups and cationic metal species; and (4) entrapment of catalysts

(metal complex, metal microcrystals) in the porous cavity of the support. The first approach has been widely investigated and has proven to be highly versatile. One of the major problems associated with bonding immobilization is the solid-phase preparation of the ligands and metal complexes, where the standard chromatographic monitoring methods and spectroscopic analysis (e.g., solution-phase NMR techniques) are not utilized. Recently, solid-phase organic synthesis and solid-phase NMR analysis have been rapidly gaining popularity as a means of solving these problems. The immobilized metal catalysts prepared by the second (adsorption) and third (ion-pair formation) approaches often suffer from leaching problems because the nonbonding immobilization mode must compete with the exchange with solvents, substrates, ionic substrates, ionic salts, etc. This review will cover the immobilization of palladium catalysts on polymeric solid supports by the bonding approach. Recent topics of encapsulation of palladium particles (microcrystals) as well as other immobilizations on polymeric supports will also be introduced in this article. The relatively mature heterogeneous hydrogenation will not be included here since many other review articles and books are already available. The design, preparation, and use of chiral palladium complexes inasymmetric catalysis will also be included.

2
Complexation of Palladium with Polymeric Ligands

The complexation of polymeric ligands with palladium precursors is the most popular protocol for the preparation of polymeric palladium catalysts. A number of polymeric palladium complexes, in particular palladium-phosphine complexes, have been designed and prepared to combine the advantages of both homogeneous and heterogeneous catalysts within one system. There are two main approaches to polymeric ligands, namely, polymerization of ligand monomers and introduction of ligand groups to the functionalized polymers. In this section, several recent representative examples for the preparation of polymer-supported palladium complexes with the polymeric ligands and their catalytic use in organic synthetic processes will be discussed.

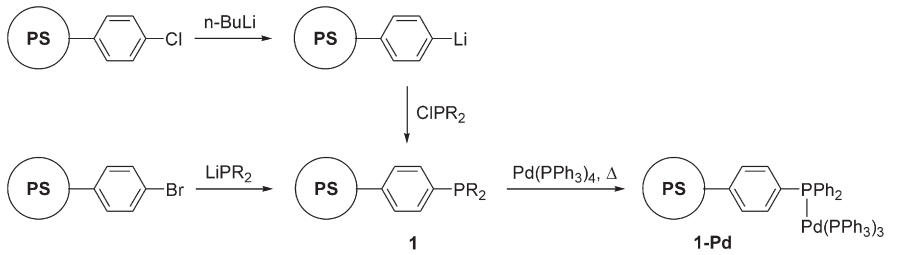
2.1
Polystyrene (PS)

Polystyrene is the most frequently used polymeric support for the immobilization of palladium complexes [15]. The PS resins are well developed in the field of solid-phase peptide synthesis. Therefore resins bearing various chemical functional groups, diameter size, loading value, degree of cross-linking, for example, are now commercially readily available to permit investigation of these variables on the catalytic property. The most widely used polystyrene in

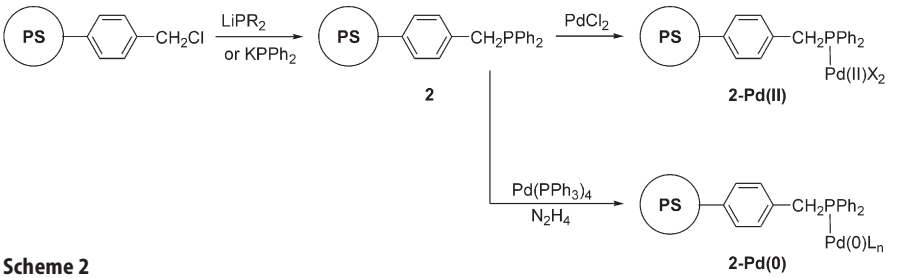
the preparation of supported phosphine ligands is a polystyrene crosslinked with 1–2% divinylbenzene (DVB) of 10–200 μm diameter.

The PS-supported phosphines have received much attention as polymeric ligands to coordinate with various transition metal species forming PS-supported metal-phosphine complexes. The PS-supported phosphines are known to complex with various transition metals, such as Pd, Co, Rh, Pt, etc. [15]. Standard procedures for the preparation of PS-supported phosphine ligands usually entail surface modification of commercially available polymer resins, for example, halogenated or chloromethylated PS resin (Scheme 1) [4, 8, 16]. Chloro(or bromo)polystyrene was lithiated with alkyllithium and then quenched with chlorodiphenylphosphine to give PS-PPh_2 (**1**). Direct nucleophilic substitution of bromopolystyrene with lithium or potassium phosphide was also employed to give the phosphinylated polystyrenes. PS-supported phosphines having various alkyl groups at the phosphorus atom were prepared by these methods. Pioneering work on the immobilization of palladium complexes was reported by Pittmann and coworkers as well as by Trost and coworkers [17, 18]. Thus, for example, PS-PPh_2-Pd$(PPh_3)_3$ (**1-Pd**) was prepared by mixing **1** and Pd$(PPh_3)_4$ and heating. Another very early example is based on palladium complexes of PS-supported benzyl(diphenyl)phosphine (PS-CH_2PPh_2, **2**) [19–23], in which the reaction of chloromethylated polystyrene with an excess of lithium diphenylphosphide gave the (diphenylphosphino)methylated polystyrene **2** in quantitative yield (Scheme 2). The palladium(0) complex **2**-**Pd**(**0**) was obtained by the treatment of **2** with Pd$(PPh_3)_4$. The reaction of **2** with $PdCl_2$ (or $PdCl_2$(cod)) gave the resin-bound palladium(II) complex **2**-**Pd**(**II**) which was readily converted to **2**-**Pd**(**0**) by reduction with hydrazine in the presence of PPh_3. The physical properties of the resin matrix and the loading value of the phosphine residue are dependent on the crosslinking value (DVB, %) and the yield of the chloromethylation step, respectively.

Diverse palladium-phosphine complexes have been prepared from this class of PS-phosphines, such as PS-PPh_2 (**1**), PS-CH_2PPh_2 (**2**), PS-P(*o*-tol)$_2$ (**3**), PS-P(*n*-Bu)$_2$ (**4**), PS-P(c-Hex)$_2$ (**5**) (Fig. 1) which are commercially available from a range of suppliers, and the parent palladium complexes, Pd$(PPh_3)_4$, $PdCl_2(PhCN)_2$, $PdCl_2(cod)_2$, PdCp(η^3-C_3H_5), Pd$(OAc)_2$, etc. The catalytic per-



Scheme 1



Scheme 2

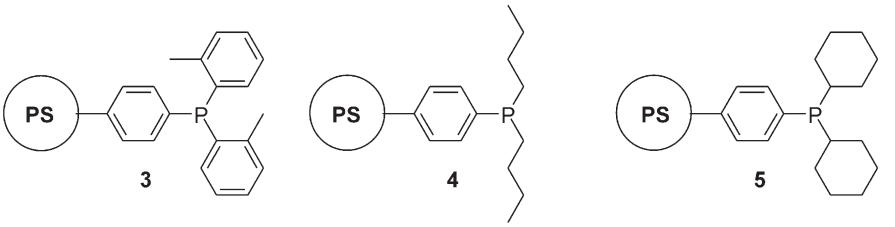


Fig. 1

formances of the resin-bound palladium-phosphine complexes have often been examined for π-allylic substitution [18, 24–26], the Heck reaction [22, 27–30], and the Suzuki–Miyaura coupling (Scheme 3) [31–33].

A plug-shaped solid support was prepared from high-density polyethylene cosintered with chloromethylated PS-DVB and was also converted to the "plug" bearing the diphenylphosphinomethyl PS-DVB moiety (Fig. 2)[1] [34]. The resulting white-colored phosphine plug was treated with $Pd(PPh_3)_4$ in refluxing benzene to give a black-colored palladium plug which showed good catalytic activity in the Suzuki–Miyaura coupling of aryl iodides with arylboronic acids. The catalyst plug was readily removed from the reaction mixture with tweezers [35].

The bisphosphines **6** and **8** bearing alkyl substituents on their phosphorus atoms were supported on PS resin by the nucleophilic substitution of the chloromethyl groups on the resin to give **7** and **9**, respectively (Scheme 4) [36, 37]. A palladium complex of **7** showed moderate catalytic activity to promote the Heck reaction of iodobenzene with methyl acrylate affording methyl cinnamate.

The biarylphosphines **10** also reacted with the chloromethylated PS resin under basic conditions to give the PS-supported biarylphosphines **11** and **12** (Scheme 5) [38]. The resin-bound biaryl(dialkyl)phosphines **11** and **12** were the ligands designed for use in the palladium-catalyzed amination and Suzuki–Miyaura coupling of aryl halides, especially those of aryl chlorides,

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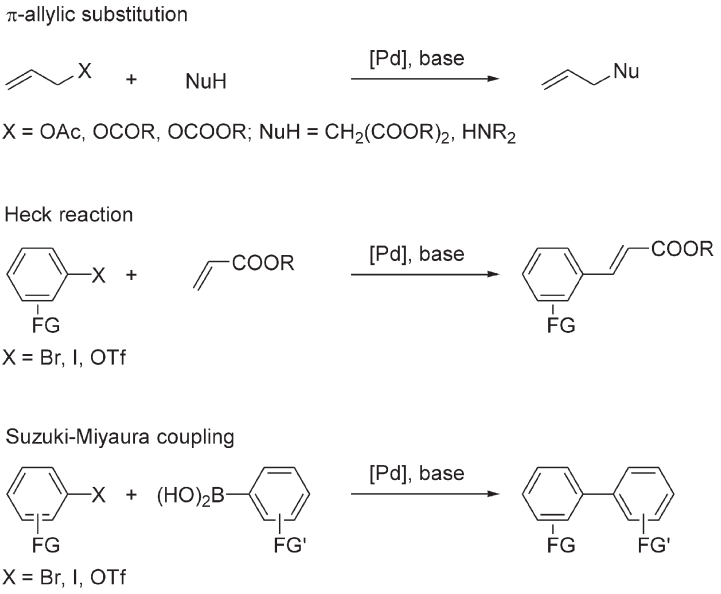


Scheme 3

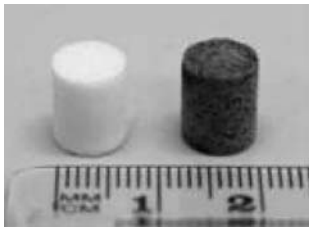
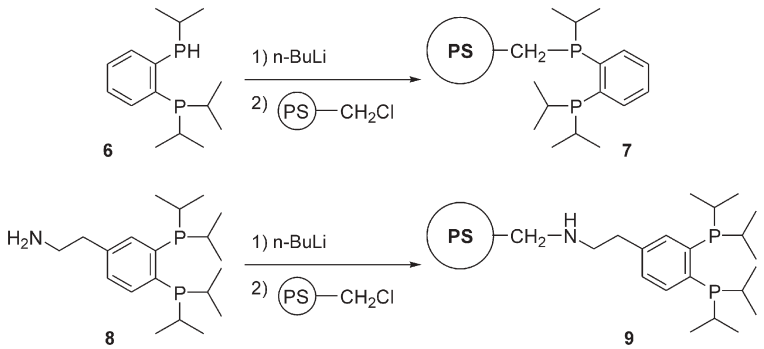
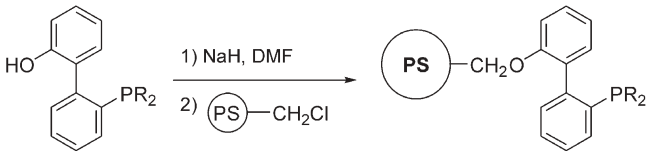


Fig. 2



Scheme 4



10

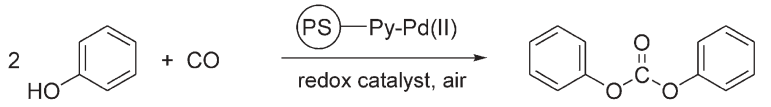
11: R = cyclo-Hex
12: R = $C(CH_3)_3$

Scheme 5

where the use of electron-rich phosphine ligands allowed for an increase in the scope of the aryl halide substrate [39, 40].

The PS resins having various pyridyl groups as coordination groups to palladium were prepared by introduction of the pyridyl carboxyl groups to the PS-CH_2X resins. The immobilized pyridyl group can coordinate with $PdCl_2(PhCN)_2$ at room temperature to give the corresponding palladium complexes [41]. Several examples (compounds **13**-**16**) are shown in Fig. 3. Since the sp^2 nitrogen-based ligands are relatively more stable than phosphines under oxidative reaction conditions, these resin-supported pyridyl-palladium complexes exhibited good catalytic activity in the oxidative carbonylation of phenols, as shown in Scheme 6.

Recently, palladium complexes of carbene ligands have been recognized as highly reactive catalysts for palladium-promoted reactions, in particular for the Heck reaction [42–44]. The polymer-supported palladium carbene complexes **18** and **19** were prepared by the nucleophilic substitution of the bromomethylated Wang resin with **17** under basic reaction conditions (Scheme 7) [45]. The catalytic activity of **18** and **19** was examined for the Heck reaction of aryl bromides with acrylates or styrene to exhibit high TONs up to 5,000. The polymer-supported palladium-carbene complexes are air-stable and recyclable.



Scheme 6

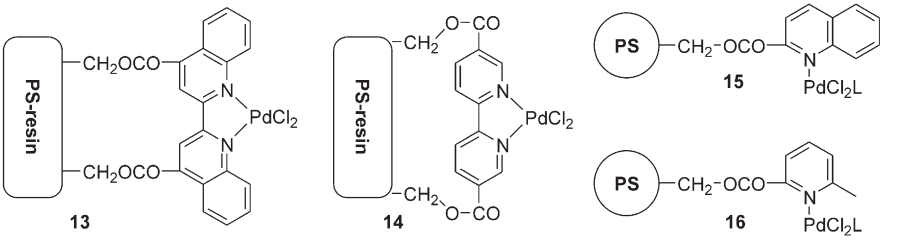
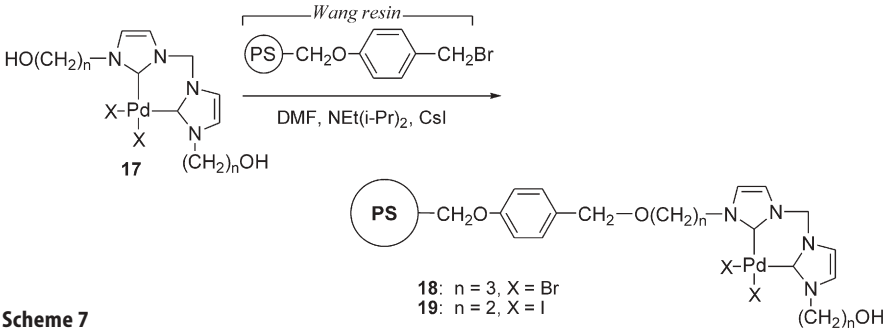


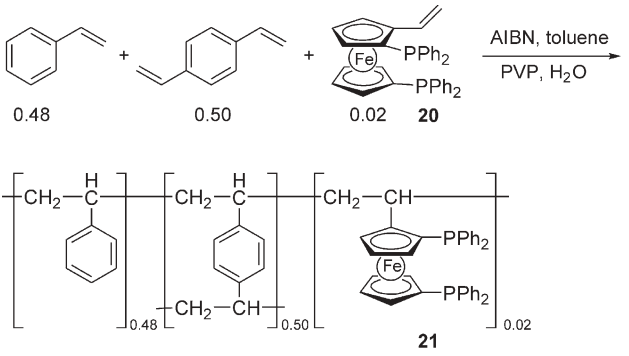
Fig. 3

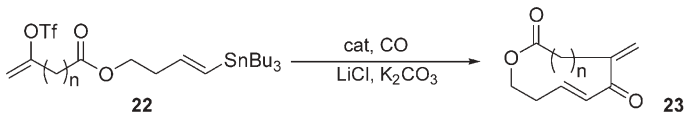


Scheme 7

Polymerization of ligand monomers is a useful tool for preparing polymer-supported ligands. The cross-linked polystyrene bound ferrocenyl bisphosphine ligand **21** was prepared by the copolymerization of styrene, divinylbenzene, and 1,1′-bis(diphenylphosphino)-2-vinylferrocene (**20**) (Scheme 8) [46]. The loading density of the catalyst on the support was readily controlled by the ratio of the monomers used.

Carbonylative intramolecular Stille coupling to form macrocyclic molecules was investigated with a palladium complex of the polymer-bound ferrocenyl phosphine **21**. One of the major problems encountered in the intramolecular



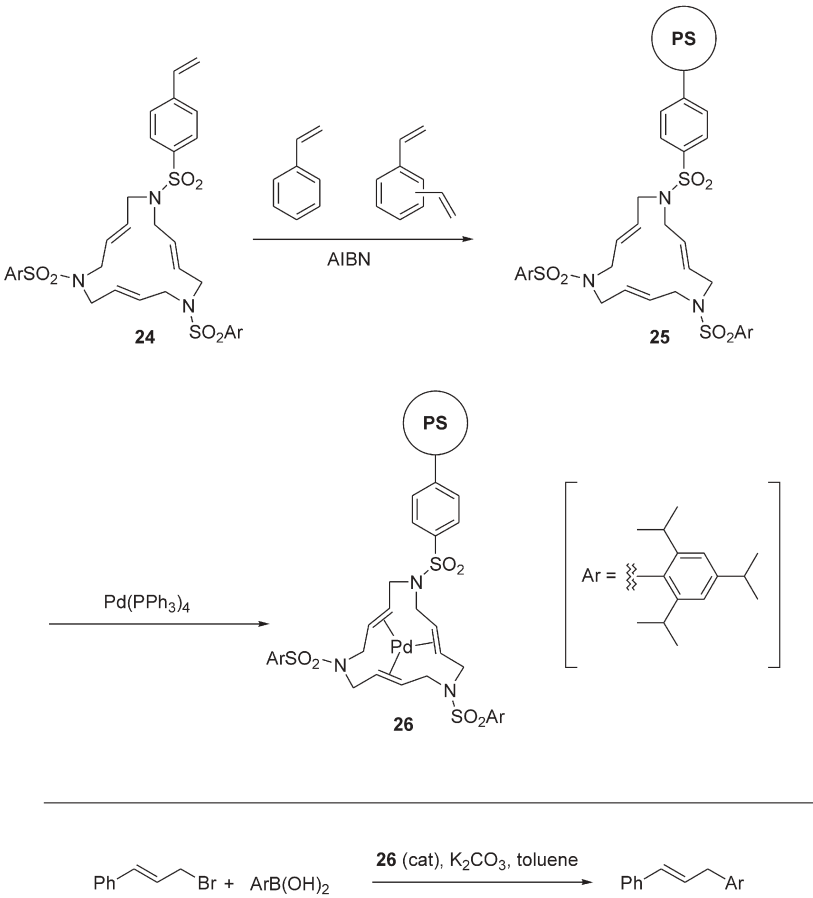


cat	n = 6	n = 7	n = 8
$Pd(PPh_3)_4$	—	59	60
$PdCl_2(dppf)$	60	55	—
$Pd(dba)_2$/**20**	78	76	70

Scheme 8

macrocyclization is the formation of linear oligomers via an intermolecular pathway. "Site isolation" of the catalytic sites on a polymer backbone has been achieved with relatively low loading density of the catalyst to suppress the intermolecular reactions. Thus, the ester **22** bearing an alkenylstannane and an alkenyl triflate gave high yields of the corresponding keto lactone **23** using the Pd(0)/**21** complex and LiCl under carbon monoxide atmosphere, whereas only moderate yields of the macrocycles were obtained under homogeneous conditions using $Pd(PPh_3)_4$ or $PdCl_2$(dppf).

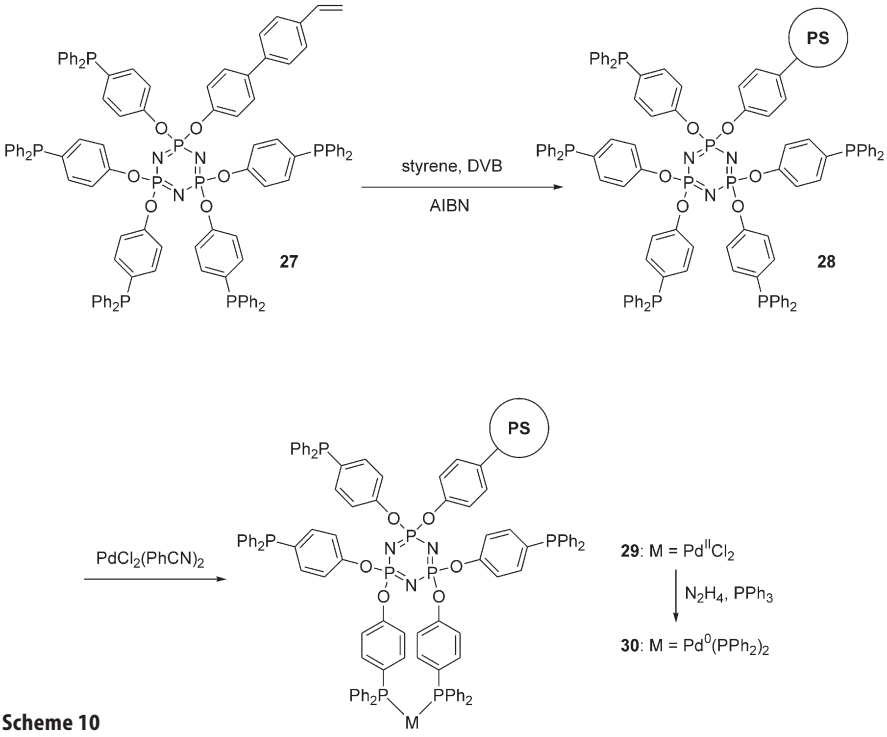
A novel triolefin ligand (*E*,*E*,*E*)-1,6,11-tris[(2,4,6-triisopropylphenyl)sulfonyl]-1,6,11-triazacyclopentadeca-3,8,13-triene was anchored to a polystyrene support [47] (Scheme 9). Thus, the 15-membered triene **24** bearing a styrene group underwent polymerization with styrene and DVB to afford the cross-linked PS-supported cyclic triene **25**. The supported macrocyclic triene **25** was treated with $Pd(PPh_3)_4$ to give the palladium complex **26**. The complex



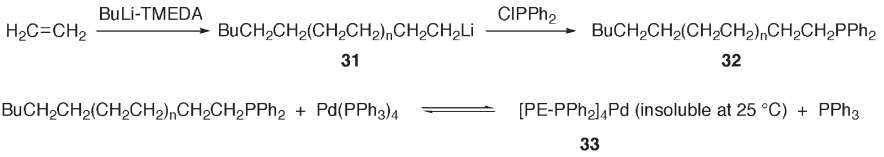
Scheme 9

26 catalyzed Suzuki–Miyaura couplings of aryl halides and arylboronic acids thus forming biaryls. Allylic arylation of a cinnamyl bromide via a π-allylpalladium intermediate was found to take place with a catalytic amount of the triene complex of palladium **26**.

An inorganic–organic hybrid polymer has been designed, prepared, and used as a novel solid support for the immobilization of phosphine ligands (Scheme 10) [48]. Thus, cyclophosphazene, an inorganic composite bearing triarylphosphine units and a styryl group (**27**), was exposed to DVB in the presence of AIBN to form a DVB-cross-linked polystyrene having a pendant cyclophosphazene **28**. The triphenylphosphines connected to the cyclophosphazene can coordinate to a palladium(II) precursor (e.g., $PdCl_2(PhCN)_2$) to give a PS-cyclophosphazene-phosphine-palladium(II) complex **29** which was readily reduced with hydrazine in the presence of PPh_3, forming a PS-cyclophosphazene-phosphine-palladium(0) complex. The catalytic activity and recyclability of **30** were examined for the Heck reaction of phenyl iodide with methyl acrylate and styrene.



Scheme 10



Scheme 11

2.2 Polyethylene (PE)

Polyethylene has also been used for immobilization of various late transition metal catalysts [49–51]. A phosphine ligand anchored on polyethylene support has been prepared simply by anionic living polymerization of ethylene with butyllithium-TMEDA followed by quenching of the resulting long-chained alkyllithium with $ClPPh_2$ to afford the phosphinated polyethylene **32** (Scheme 11) [52]. The polymeric phosphine ligand was treated with $Pd(PPh_3)_4$ at 100 °C in toluene. The reaction mixture then was cooled to precipitate the polyethylene-bound phosphine-palladium complex **33**. The polymeric palladium complex catalyzed, for example, π-allylic substitution of allyl esters with active methylene and nitrogen nucleophiles.

Polyethylene fiber having a triphenylphosphine group is commercially available, and various palladium complexes of the PE fiber phosphine have been prepared [53]. Representative examples **34**–**36** are shown in Fig. 4.

Recently, poly(acrylic acid)-grafted polyethylene has been developed by Bergbreiter et al. [54, 55]. Thus, the surface of commercially available PE powder was oxidized by treatment with chromic acid to give a polyethylene having a COOH group **37** (Scheme 12). The resulting PE-COOH **37** was activated with ClCOOEt and then reacted with a functional poly(*t*-butyl acrylate) oligomer (PTBA). After cleavage of the *t*-butyl esters of the PTBA moieties, the resulting COOH groups (compound **39**) were repeatedly subjected to this process to give hyperbranched poly(acrylic acid)-grafted polyethylene (PE-PAA, **40**). The COOH groups of PE-PAA **40** were condensed with $H_2N(CH_2)_3PPh_2$ to give PAA-PE-supported phosphine **41**. A palladium complex of PAA-PE-phosphine catalyzed the allylic substitution of allylic esters with amine nucleophiles at 25 °C and was readily recycled.

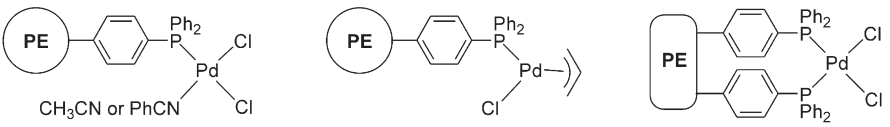
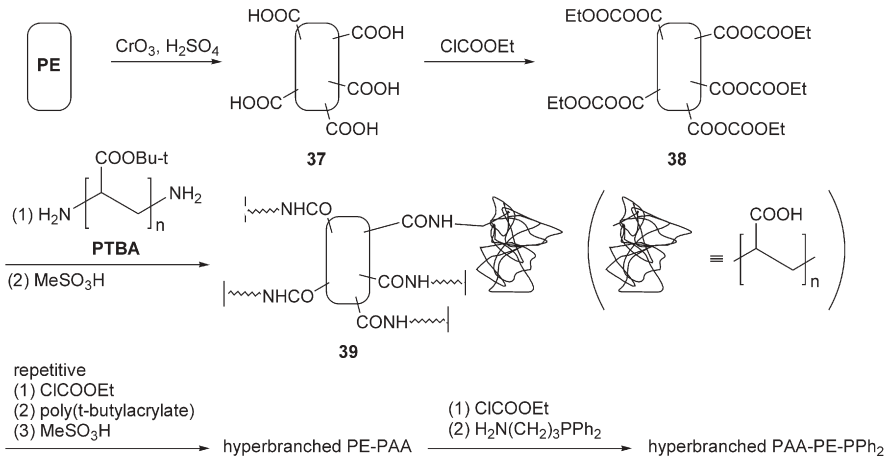


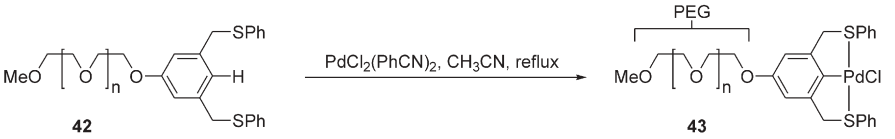
Fig. 4



Scheme 12

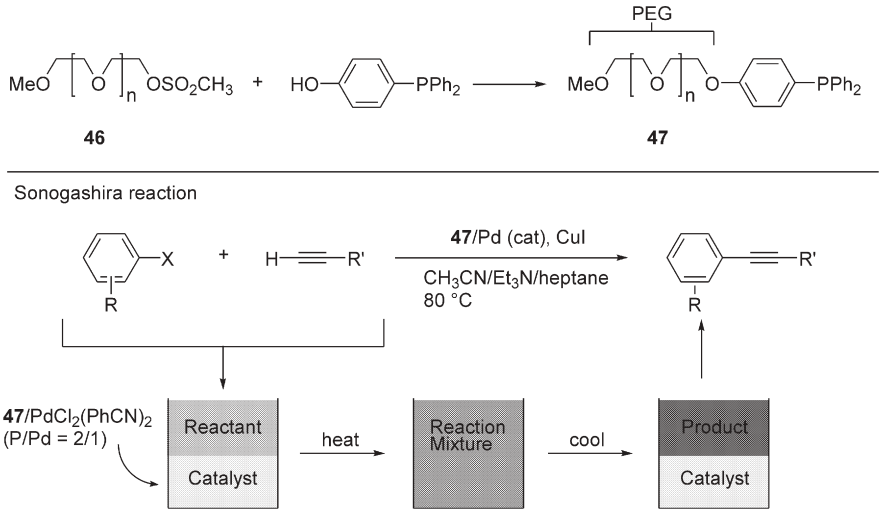
2.3 Poly(ethylene glycol) (PEG)

The linear polymer of ethylene oxide, the so-called poly(ethylene glycol), poly(ethylene oxide) (PEO), polyoxyethylene (POE), or polyoxirane, typically having a molecular weight ranging from 2,000 to 20,000, has been used in organic synthesis as a soluble polymer support. It can be dissolved in various organic solvents to perform solution-phase chemical protocols and can be solidified on demand by controlling the polarity of the medium. While homogeneous palladium-catalyzed organic transformations of PEG-supported organic substrates have been used routinely in parallel combinatorial synthesis [56–59], those with PEG-supported palladium-mediated catalysts have received only scattered attention [60, 61]. PEG-supported pincer palladium complexes having a SCS ligand system, developed by Bergbreiter, are one of the earliest examples of PEG-supported palladium catalysts [62, 63]. Thus, 1,3-bis(phenylthiomethyl)benzene **42** anchored on a MeOPEG resin at the 5-position reacted with $PdCl_2(PhCN)_2$ to give the PEG-supported SCS pincer palladium complex **43**. Condensation of a hemisuccinate of a similar pincer complex **44** with PEG-NH_2 was also examined to give the MeOPEG-$NHCOC_3H_6CONH$ pincer complex **45** (Scheme 13). The pincer palladium complexes have been developed as highly active catalysts for the Heck reaction under homogeneous conditions [44, 64–66], as is the case for the PEG-supported SCS pincer complexes. Thus, the PEG-supported SCS pincer complex **45** catalyzed a reaction of iodobenzene with styrene and methyl acrylate to give stilbene and methyl cinnamate in high yields, respectively. The supported complex **45** was readily recovered by lowering the polarity of the medium (for example by addition of ether) and reused.



Scheme 13

Though the PEG-supported triarylphosphines have been developed with a view toward using them in various phosphine-promoted reactions, such as in the Mitsunobu esterification [67], their use as phosphine ligands in palladium catalysis has only recently been reported [68]. Thus, monomethylated poly(ethylene glycol) with a mass of 2,000 Da ($MeOPEG_{2,000}$) was activated via mesylation and then reacted with 4-diphenylphosphinophenol to form $MeOPEG–O–C_6H_4–PPh_2$ (**47**). The MeOPEG-supported palladium complex generated in situ by mixing **47** and $PdCl_2(PhCN)_2$ (phosphine/palladium=2/1) exhibited high catalytic activity to promote the cross-coupling reaction of aryl halides with terminal alkynes forming arylalkynes, the so-called Sonogashira reaction [69]. It is worth noting that the ternary solvent mixture of CH_3CN/Et_3N/heptane used for the Sonogashira coupling reaction constructs a biphasic system at ambient temperature and a monophasic system above the critical mixing temperature to realize thermomorphic catalysis (Scheme 14). Thus, the coupling reaction was carried out under monophasic conditions at 80 °C, higher than the critical temperature, and the resulting reaction mixture was cooled to give the biphasic system (thermomorphic liquid/liquid separation). The desired coupling product was obtained from the upper layer of the

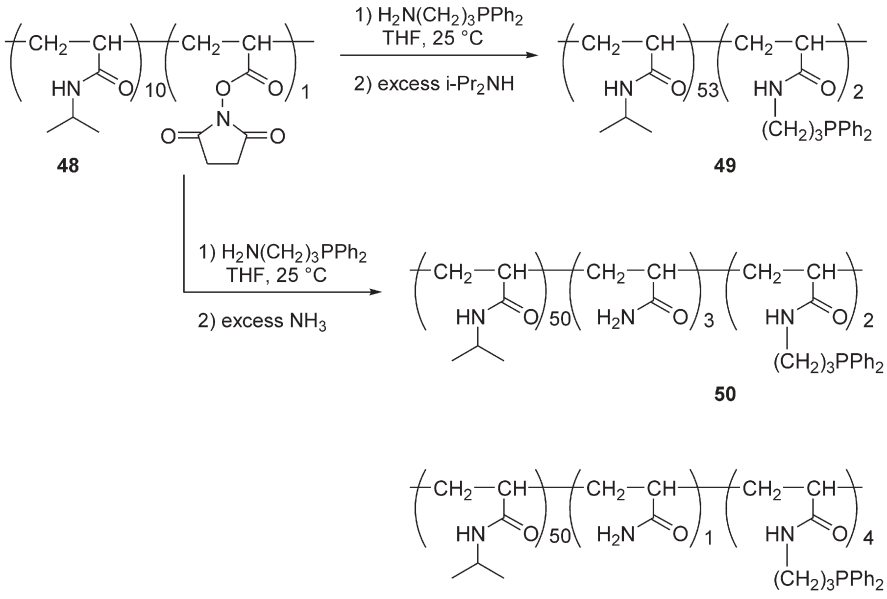


Scheme 14

biphasic system, and the lower layer containing the MeOPEG-supported palladium catalyst was taken to its second use without isolation of the complex. The more basic and sterically demanding phosphine ligand group, benzyl(diadamantyl)phosphine, anchored on the MeOPEG support has also been prepared to expand the tolerance of the leaving groups of aryl halides.

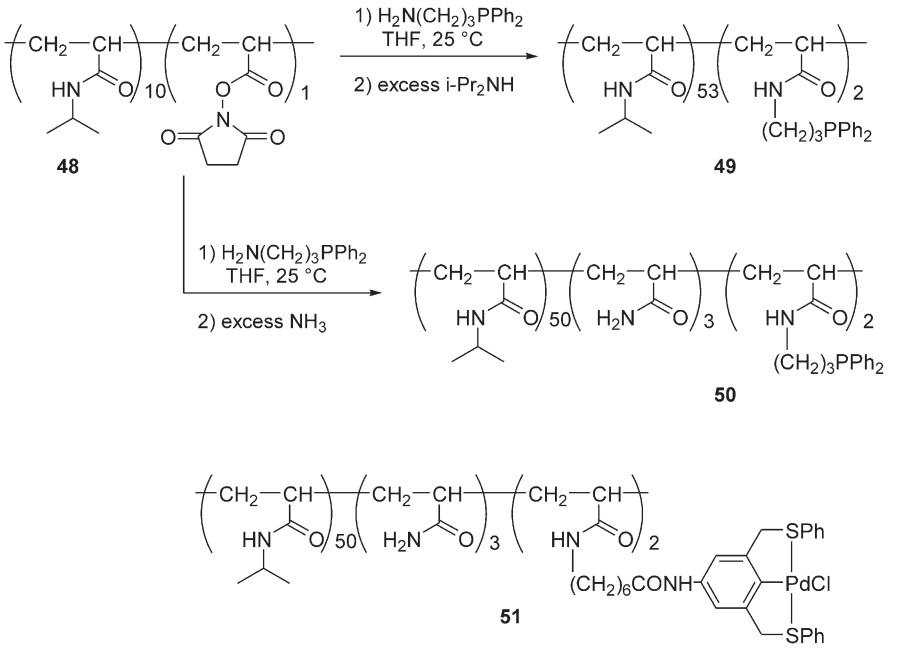
2.4 Poly(acrylate) Derivatives

Poly(acrylamide) and poly(acrylate) supports are also an important class of soluble solid phases for the immobilization of a variety of transition metal catalysts [63]. Various functional groups were incorporated into the polymer supports in a tailor-made fashion using various combinations of starting monomers. Thus, for example, the hydrophilic poly(*N*-isopropylacrylamide) (PNIPAM) support **48** was readily converted to the PNIPAM-supported phosphine ligands **49–51** (Fig. 5) [70–72], where the loading value of the ligand group can be controlled (Scheme 15). Similarly, the SCS pincer palladium complex was also attached to the PNIPAM support to give compound **52** [73]. Palladium and rhodium complexes of the PNIPAM phosphines **50** and **51** as well as the supported pincer **52** dissolve in polar solvents including water due to the hydrophilicity of the PNIPAM support. Thus, for example, the palladium complex of the PNIPAM phosphine, formed from the reaction of **49** or **50** with $Pd(dba)_2$, showed high catalytic activity both in organic solvents and in water to promote π-allylic substitution and the Sonogashira reaction.



48 **49** **50** **51**

Scheme 15



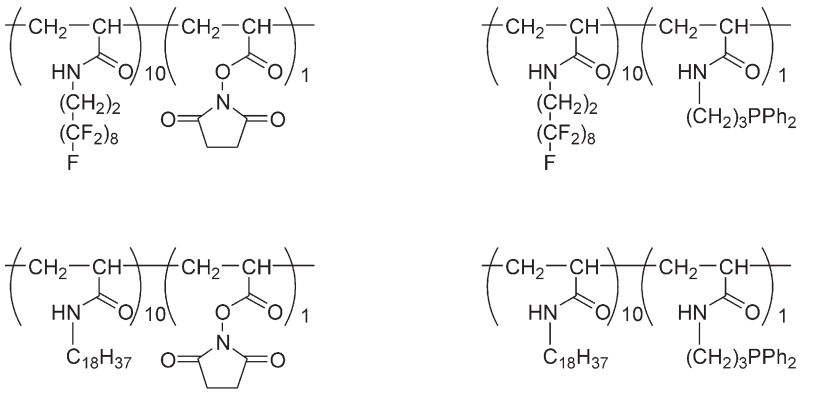
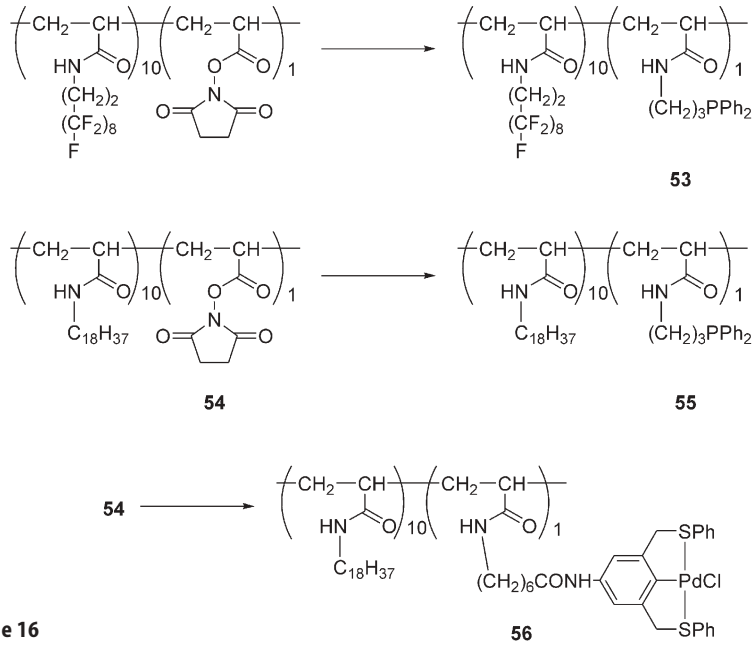


Fig. 5

The solubility of the PNIPAM-supported metal complexes is strongly affected by the alkyl substituents on PNIPAM. The supported phosphines **53** and **55** bound to fluoroalkyl-PNIPAM [74–76] and ODS-PNIPAM [73] showed good solubility in fluorous solvents and less polar organic solvents, respectively (Scheme 16).



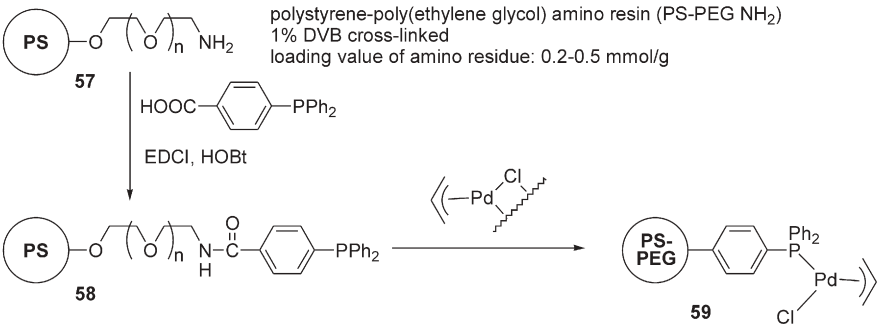
Scheme 16

Imidazolinyl rings were constructed on polyacrylonitrile (PAN) fiber by the reaction of the nitrile group of PAN and triethylenetetramine. The fiber-supported imidazoline can coordinate to palladium to give PAN fiber-supported palladium complexes. Though the exact structure of the PAN fiber-supported complex has not been clearly elucidated, the complex catalyzed the Heck reaction with high recyclability [77].

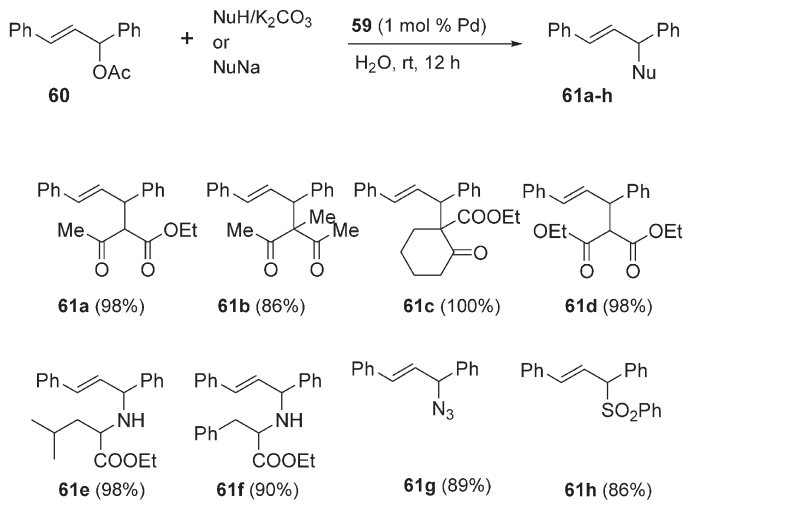
2.5 Grafting Polymers and Copolymers

Polystyrene-poly(ethylene glycol) graft copolymer (PS-PEG) resins [78–81], exhibiting a relatively uniform swelling property not only for various polar and less polar organic solvents but also for water, were developed as polymer supports for solid-phase peptide synthesis with the aim of using them under aqueous conditions [82–84]. PS-PEG resin-supported palladium catalysts were developed to achieve palladium catalysis in water under heterogeneous conditions where the advantages of both aqueous-switching and heterogeneous-switching of the homogeneous palladium catalysis were combined within one system [85]. Several types of PS-PEG resin [PS-DVB (1–2% cross-linked) having a long PEG chain (ca. 30–80 PEG units) as linkers to the terminal functional groups, such as NH_2, OH, Cl, etc.] are commercially available.

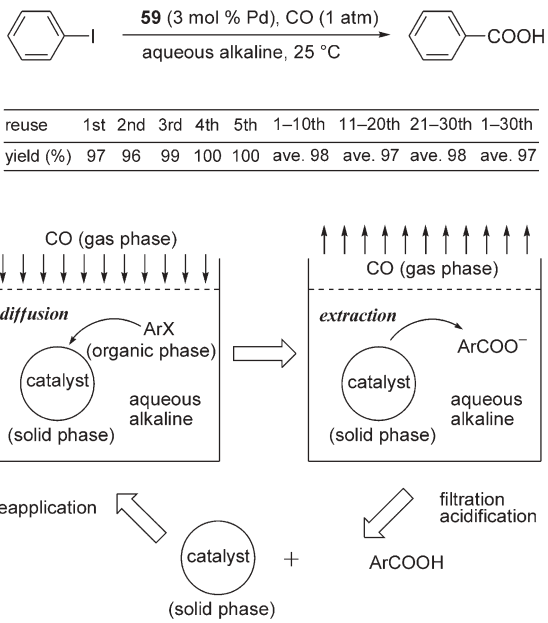
A PS-PEG resin-supported phosphine ligand **59** has been prepared simply via condensation of the PS-PEG NH_2 resin (**57**) and 4-(diphenylphosphino) benzoic acid. The PS-PEG triarylphosphine reacted smoothly with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ to quantitatively form a PS-PEG resin-supported palladium complex **59** (Scheme 17) [86, 87]. This polymeric palladium catalyst found widespread utility in palladium-catalyzed carbon–carbon bond forming reactions. Thus, π-allylic substitution of allylic esters [86, 87] with active methylene nucleophiles was achieved in aqueous K_2CO_3 at 25 °C to give excellent yields of the corresponding allylic substituted products where no organic cosolvent was required (Scheme 18). Sodium azide, sodium phenylsulfinate, and amino acids, which have not often been used as nucleophiles in π-allylic substitution due to their low solubility in organic solvents, have also successfully reacted with allyl esters in water to give allyl azide, allyl sulfone, and *N*-allylamino acids, respectively, under heterogeneous conditions.



Scheme 17



Scheme 18

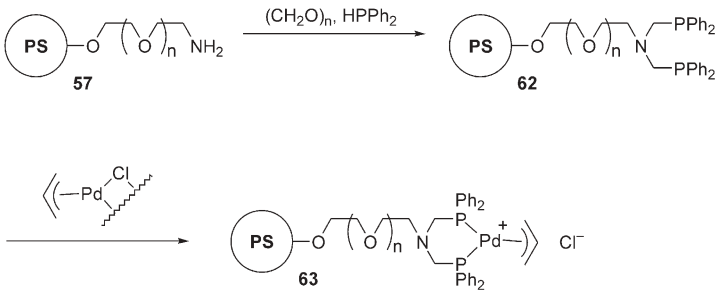


Scheme 19

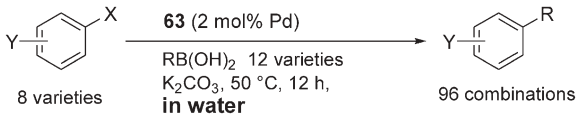
The catalytic utility of the PS-PEG resin-supported palladium complex has also been examined for insertion reactions, hydroxycarbonylation [88] and the Heck reaction [89]. Aryl halides underwent catalytic hydroxycarbonylation at room temperature in aqueous alkaline solution under atmospheric pressure of carbon monoxide in the presence of the polymeric catalyst **59** to give quantitative yields of benzoic acids. The hydroxycarbonylation is comprised of four phases, gas, solid, organic, and aqueous. By using this four-phase protocol, carbon monoxide (gas phase) and the starting halide (organic phase) should diffuse into the catalyst resin (solid phase) during the reaction, and the resulting carboxylic acid is immediately extracted with alkaline solution (aqueous phase). They are readily separated from each other and subsequent reapplication of the catalyst is made easy (Scheme 19). Thus, after the hydroxycarbonylation of iodobenzene, the recovered catalyst resin was subjected to the second series of the reaction to give a 96% yield of benzoic acid under otherwise similar reaction conditions. The chemical yield observed in *30 continuous runs* ranged from 94 to 100%, the average being 97%.

This simple protocol for the preparation of carboxylic acids was also successfully applied to carbonylation of alkenyl and aryl bromides under the same reaction conditions [88]. The reaction of aryl halides (including heteroaromatics, e.g., halothiophenes) with methyl acrylate, phenyl vinyl sulfone, cyclopentene, and dihydrofuran, proceeded smoothly in water using the same PS-PEG-supported catalyst to give the corresponding alkenylated aromatics in high yields [88, 89].

Cross-coupling reactions have also been examined in water using amphiphilic PS-PEG resin-supported palladium complexes. Palladium-catalyzed coupling of aryl halides with aryl(or alkenyl)boronic acids (the so-called Suzuki–Miyaura coupling) took place in aqueous alkaline solution in the presence of polymeric catalyst **59** at 25 °C to give the biaryls in excellent yields [90, 91]. The amphiphilic PS-PEG resin-supported N-anchored 2-aza-1,3-bis(diphenylphosphino)propane ligand (PS-PEG adppp) **62** was readily prepared from PS-PEG NH_2 resin [92]. Thus, the reaction of PS-PEG NH_2 with (diphenylphosphino)methanol (Ph_2PCH_2OH), generated in situ by mixing Ph_2PH and paraformaldehyde, gave the PS-PEG adppp **62**. This protocol to form the adppp moiety was originally used for the preparation of dendrimer-anchored adppp ligands [93, 94]. Treatment of PS-PEG adppp with $[PdCl(\eta^3\text{-}C_3H_5)]_2$ quantitatively afforded the polymeric coordinated chelation palladium-bisphosphine complex **63** (Scheme 20). Due to the chelating coordination of the adppp moiety, the polymeric catalyst was more stable under air, moisture, and thermal conditions. This complex exhibited wide functional group tolerance to achieve the combinatorial high-throughput Suzuki–Miyaura coupling. The coupling of eight aryl halides and 12 boronic acids gave a 96-membered biaryl library in water where the 96 library members were obtained in >97% purity without chromatographic purification (Scheme 21) [91].

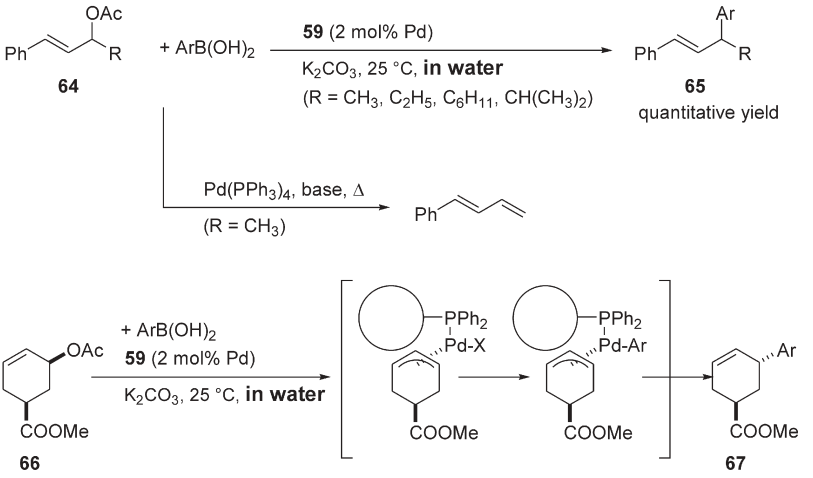


Scheme 20



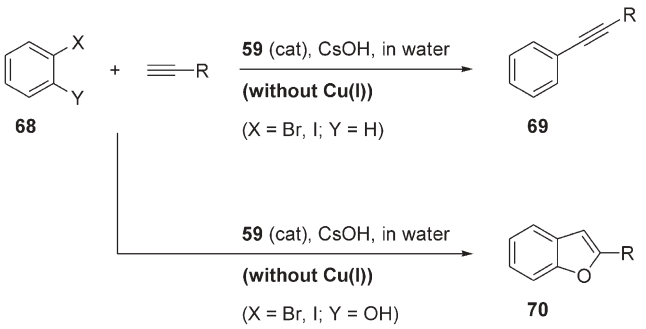
Scheme 21

Reactions of arylboronic acids with allyl esters have also been found to proceed smoothly in water to give allylic arylation products via a π-allylic intermediate with net inversion of configuration (Scheme 22) [90]. It was reported that the secondary allyl esters (alkyl vinyl carbinol esters) undergo β-hydrogen elimination of the π-allylpalladium intermediates forming conjugated dienes under the standard Suzuki–Miyaura coupling conditions due to the relatively lower reactivity of arylboronic acids.



Scheme 22

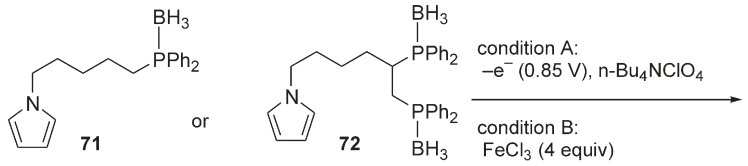
It was also found that the Sonogashira reaction [69] takes place under aqueous alkaline conditions in the presence of the PS-PEG-supported palladium complex **59** [95]. The combination of the resin catalyst **59**, cesium hydroxide [96], and water is essential to promote high yielding coupling of **69.** Using copper-free conditions, a one-step preparation of the benzofurans **70** was achieved in water via coupling of 2-iodophenol **68** (X=OH) and the terminal alkynes (Scheme 23).



Scheme 23

2.6 Other Polymeric Supports

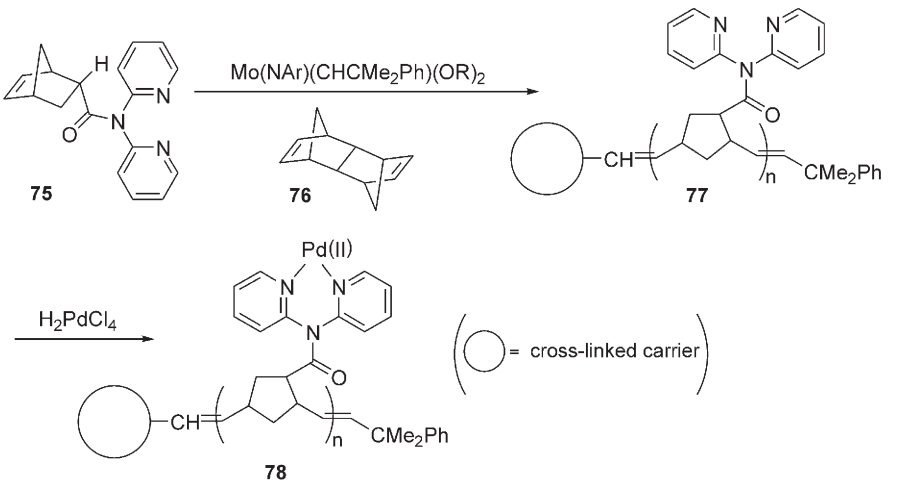
Polymerization of various monomers was performed with the ligands examined to synthesize a variety of polymeric ligands. The polypyrrole-bound mono- and bisphosphines **73** and **74** were prepared as their P-borane com-



Scheme 24

plexes from the corresponding monomers **71** and **72** via $FeCl_3$-induced or electrochemical polymerization conditions (Scheme 24) [97]. These phosphine-borane complexes reacted with palladium(II) without pre-decomplexation to give the polypyrrole-bound palladium(0)-phosphine complexes, where the borane on the phosphorus atom served as the reducing agent for palladium(II). The resulting immobilized polypyrrole palladium(0)-phosphine complexes catalyzed the Heck reaction and the π-allylic substitution of allyl acetates.

Ring-opening metathesis polymerization (ROMP) has been recognized as one of the most powerful methods for the preparation of polymer materials bearing high loadings of various functional groups [98–100]. The polymer supports prepared via the ROMP process (the so-called ROMPgels) have found utility for the immobilization of various catalysts including transition metal complexes [101]. The norbornene monomer **75** having a 2-endo-*N*,*N*-di(2-pyridyl)carbamide group underwent living polymerization using the Schrock catalyst (Scheme 25) [102, 103]. The resulting living polymer chains were cross-linked using 1,4,4a,5,8,8a-hexahydro-1,4,5,8-exo-endo-dimethanonaphthalene (**76**) to give the bispyridyl ligand **77**. Its palladium complex **78**, generated by treatment of **77** with H_2PdCl_4, catalyzed the Heck reaction of aryl bromides and even aryl chlorides. Thus, the reaction of chlorobenzene with styrene in the



Scheme 25

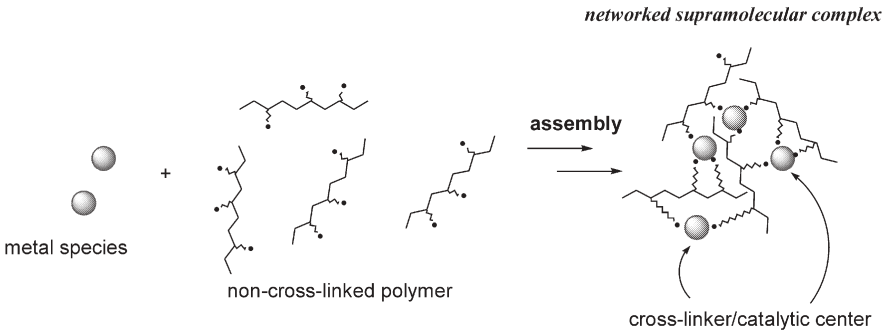
presence of 0.003 mol% of the palladium species **78** and tetrabutylammonium bromide in dimethylacetamide at 140 °C gave an 89% isolated yield of *trans*-stilbene where the TON observed reached 23,600.

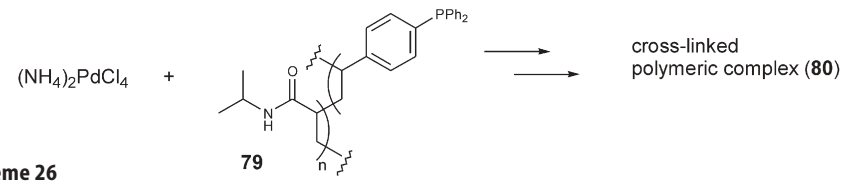
2.7 Metal-Directed Cross-Linkage of Polymeric Palladium Catalysts

Recently, metal-directed cross-linkage for the formation of cross-linked polymers in which the metal species or metal complexes have served as a cross-linker and simultaneously as a catalyst has been developed. The concept is shown in Scheme 26 [104–109].

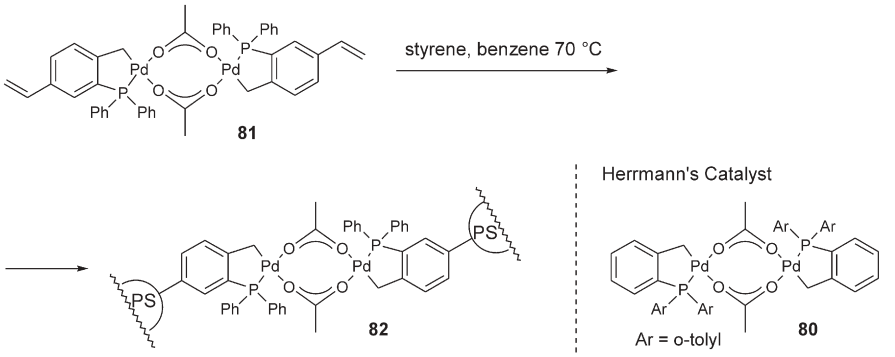
The non-cross-linked poly(acrylamide) **79** bearing the triarylphosphino groups was prepared from the acrylamide monomer and diphenyl(styryl) phosphine. The metal-directed self-assembly process between the non-cross-linked polymer ligand **79** and the palladium species afforded the networked supramolecular complex **80** [106, 109]. The complex catalyzed the Suzuki-Miyaura coupling [106, 109] and the same concept, a tungsten-based self-assembly complex, has also been developed for the catalytic oxidation process.

An acetate-bridged palladacycle dimer shown in Scheme 27 was developed by Herrmann and coworkers as the catalyst demonstrating significantly high efficiency for the Heck reaction, Suzuki–Miyaura coupling, and Sonogashira reaction [42–45, 110, 111]. The styryl analog of the Herrmann catalyst **81** was used as a monomer cross-linking polystyrene network to afford the PS-supported palladacycle catalyst **82**. The polymeric palladacycle **82** exhibited high





Scheme 26



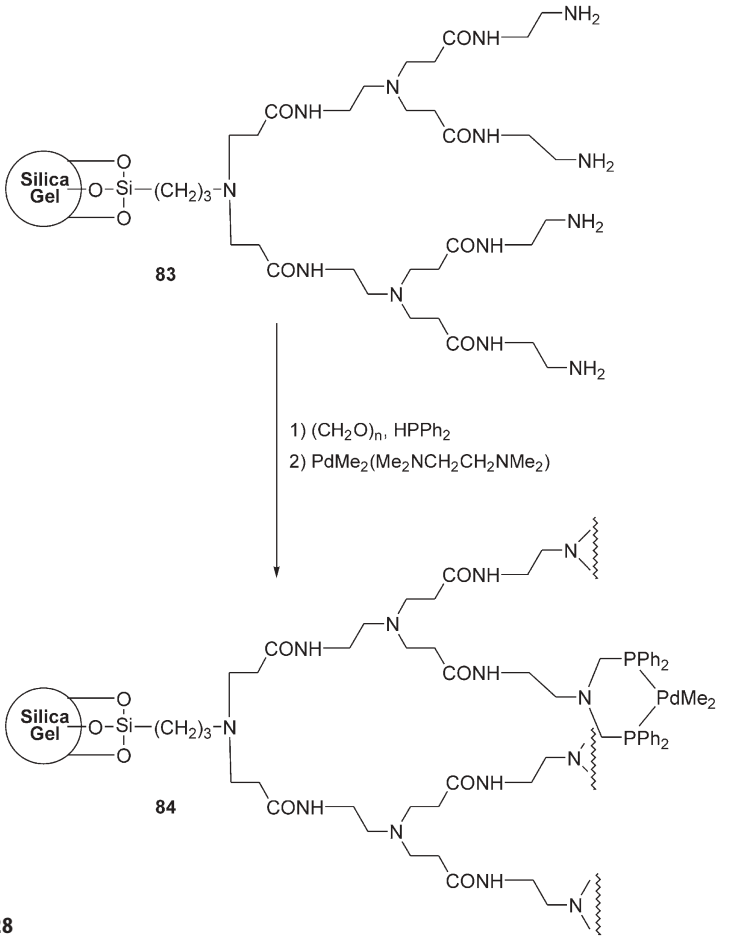
Scheme 27

catalytic activity and recyclability for the Heck reaction and the Suzuki-Miyaura coupling [112].

2.8 Dendrimers

Dendrimers have also been recognized as useful soluble supports for immobilization of ligands as well as palladium complexes. Thus, for example, (diphenylphosphino)methyl groups were introduced on the terminal nitrogen of polyaminoamide dendrimer (PAMAM) chains by treatment with diphenylphosphinomethanol generated in situ by mixing paraformaldehyde and diphenylphosphine to give the PAMAM-bound N-anchored 2-aza-1,3-bis(diphenylphosphino)propane (PAMAM-adppp) [93, 94]. The PAMAM-adppp can complex with palladium as well as group 9 metals to exhibit catalytic activity in various carbon–carbon bond forming reactions, such as π-allylic alkylation. PAMAM dendrimers of generation 0–4 on silica [113, 114] and carbosilane dendrimers [115] were also used as solid supports for immobilization of the adppp ligand. Treatment of the resulting dendrimer-bearing diphenylphosphino groups with $PdMe_2$(tmeda) gave the chelate complex **84** (Scheme 28) which showed good catalytic activity in the Heck reaction.

A dendritic spacer of poly(aryl benzyl ether) was used for incorporation of phosphine ligands onto a PS resin support [116, 117]. Thus, the condensation of 4-(diphenylphosphino)benzoic acid with Wang resin bearing poly(aryl benzyl ether) (generation 1–3) gave the PS-supported dendritic phosphine **86**. Treatment of the dendritic phosphine **86** with $Pd(dba)_2$ in THF afforded the bisphosphine-palladium complex **87** (Scheme 29) [118]. The PS-supported palladium complex exhibited a positive dendritic influence on the Heck reaction of bromobenzene with methyl acrylate.

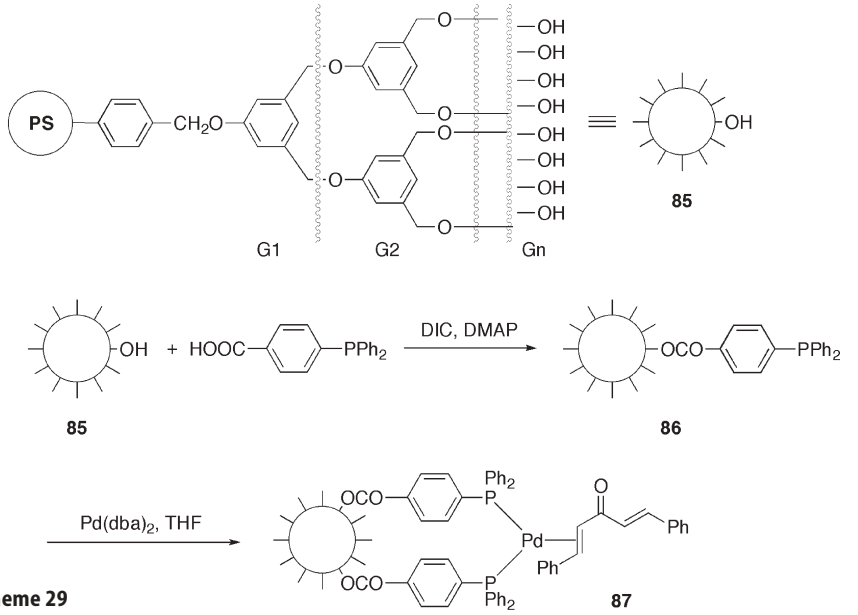


Scheme 28

3 Encapsulation and Related Protocols

Entrapment or intercalation of metal species in pores and cavities of solid supports has frequently been used for the immobilization of catalysts in inorganic materials such as zeolites, clays, charcoals, silicas, aluminas, and other solids. Though this review article focuses on the immobilization of palladium complexes on polymer supports via covalent and/or coordination bonds, recent novel approaches to polymer-supported palladium species (including palladium nanoparticles) via nonbonding immobilization, such as encapsulation and incarceration, are intriguing because of their high potential for utility. In this section, several representatives are introduced.

Polymer-microencapsulated scandium and osmium catalysts have recently been developed by Kobayashi and coworkers [119–121]. This protocol has been



Scheme 29

applied successfully to the preparation of the PS-encapsulated palladium complex MC[Pd(PPh_3)] [122]. Palladium catalysts microencapsulated in epoxide-containing copolymers (e.g., styrene/vinylbenzyl glycidyl ether/alcohol) underwent further "incarceration" via thermal cross-linking steps to form polymer-incarcerated palladium (PI-Pd) [123]. PI-Pd showed high catalytic activities in both hydrogenation and π-allylic substitution. Phosphorus MAS-NMR and XPS studies on PI-Pd revealed that it does not bear any phosphine ligands despite being prepared from $Pd(PPh_3)_4$.

An inorganic–organic hybrid catalyst was prepared by encapsulation of palladium-on-carbon (Pd/C) [124]. Thus, powdery Pd/C was introduced into the anionic polymerization step of poly(oxyethylene)-poly(propoxylene) (POEPOP) to afford the POEPOP-encapsulated Pd/C catalyst which exhibited uniform swelling properties in various solvents including water. POEPOP Pd/C showed good catalytic activity and recyclability in hydrogenation reactions.

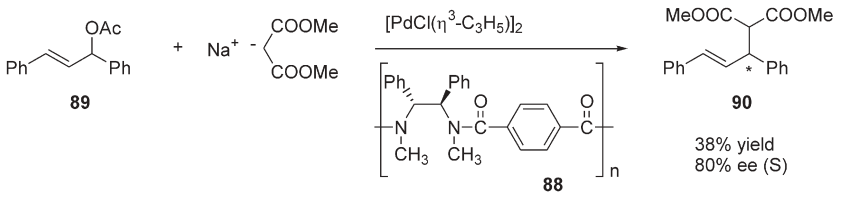
Polymer-stabilized palladium nanoparticles (or nanoclusters) [125–127] have recently received increasing attention in the field of synthetic organic chemistry [128, 129]. Thus, for example, the poly(*N*-vinyl-2-pyrrolidone) (PVP)-supported Pd particle catalyzed the Suzuki–Miyaura coupling in water [130]. Poly(amidoamine) (PAMAM) dendrimer-encapsulated palladium nanoparticles were designed and prepared to provide highly selective catalysts for hydrogenation of olefins [131–133]. Hyperbranched aromatic amides (aramids) and PS-DVB-methacryloylethylenesulfonic acid resin have also been

used as polymeric and dendrimeric supports, respectively, to entrap palladium nanoparticles [134–136]. The aramid-supported palladium particles showed catalytic activity in hydrogenation of unsaturated substrates. Palladium(II) acetate and palladium nanoparticles have been encapsulated in polyurea [137], and have found catalytic utility in synthetic transformations, such as the Suzuki–Miyaura coupling, the Heck reaction, carbonylation, and others [138, 139]. Palladium particles dispersed in amphiphilic PS-PEG resin exhibited good catalytic activity in aerobic alcohol oxidation in water where various alcohols were transformed to the corresponding carbonyl compounds under totally safe and green conditions [140].

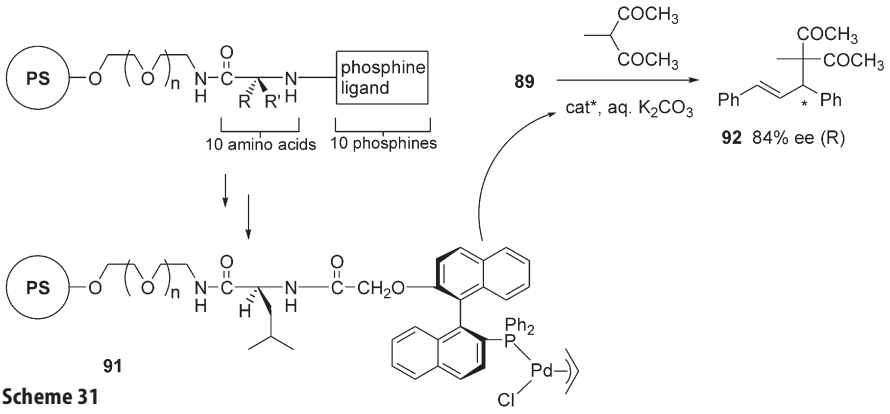
4
Asymmetric Catalysis

Development of catalytic asymmetric transformations has emerged as one of the most exciting and challenging subjects in the domain of modern synthetic chemistry [141, 142]. Homogeneous transition metal complexes with chiral ligands are currently recognized as the most versatile and powerful enantioselective catalysts. A number of chiral palladium complexes have been developed to achieve various homogeneous asymmetric processes with high stereoselectivity. Providing that the chiral ligands and/or the chiral palladium complexes are immobilized on polymer supports, the catalytic systems would represent almost ideal chiral catalysts [143]. Thus, the application of single enantiomers of chiral compounds has become very important in the pharmaceutical field as well as in agrochemical sciences. Therefore, the chiral compounds should be uncontaminated with metal species that would cause serious problems in biological activities. From a practical point of view, recycling of relatively expensive chiral ligands is also an important issue for consideration. The immobilization of chiral ligands and/or metal complexes would meet these requirements. However, relatively few successful polymeric chiral palladium complexes have appeared to date. In this section, several recent successful results in asymmetric catalysis with polymeric palladium complexes will be discussed.

Asymmetric allylic alkylation is the test-bed reaction with chiral palladium complexes under homogeneous as well as heterogeneous conditions. In 1995, a palladium complex of a chiral polyamide **88** was found to promote the asymmetric alkylation of 1,3-diphenylpropenyl acetate **89** with the sodium salt of dimethyl malonate, forming a moderate yield of the alkylated product **90** with 80% ee stereoselectivity (Scheme 30) [144]. A PS-PEG resin-supported MOP ligand **91** bearing an amino acid spacer was identified as a chiral ligand bringing about high stereoselectivity (up to 84% ee) in water in the π-allylic alkylation from a series of PS-PEG resin-supported MOP ligands prepared via a combinatorial approach (Scheme 31) [145]. Oxazoline-based chiral ligands were immobilized on PS and PS-PEG resin supports.



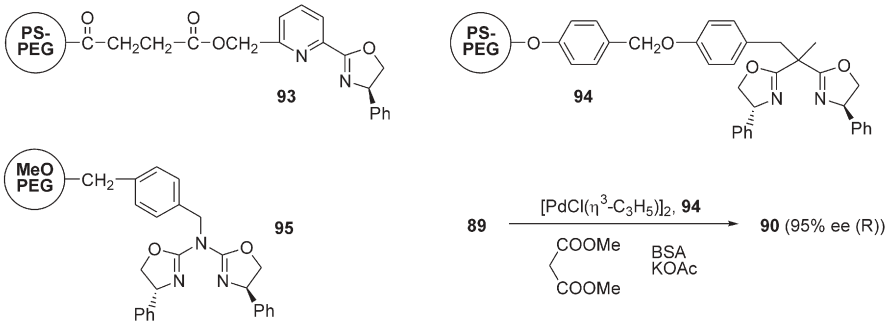
Scheme 30



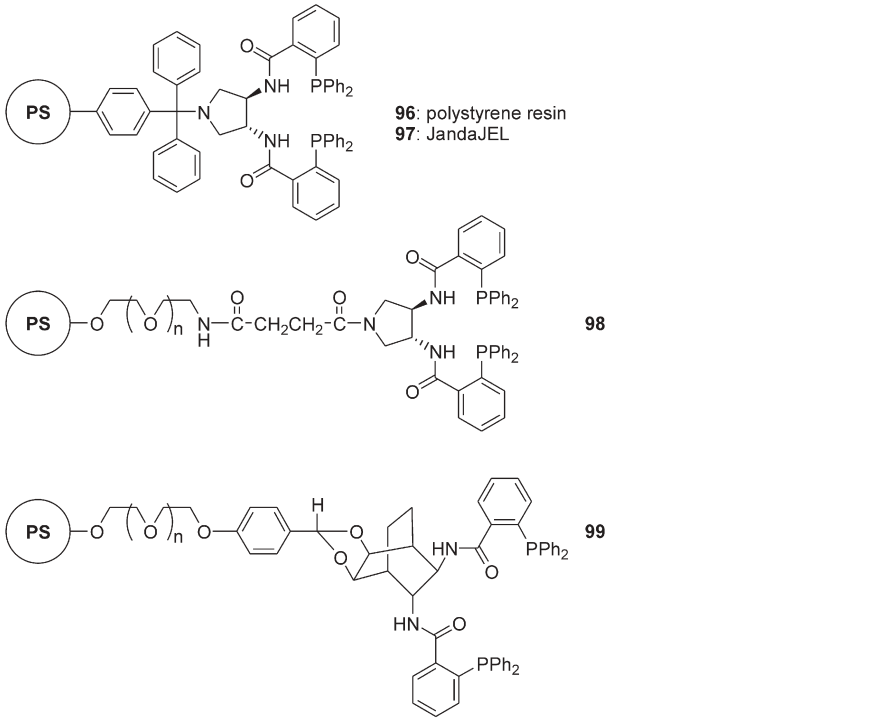
Scheme 31

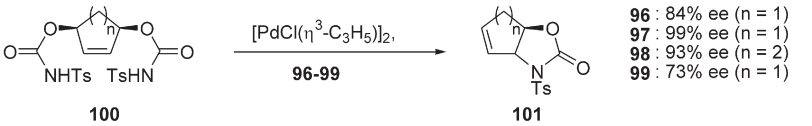
Pyridinooxazoline ligands are known to induce stereoselectivity in various homogeneous Rh-, Co-, and Cu-catalyzed reactions. Pyridinooxazoline was readily attached to the polymer supports to give the polymeric chiral ligand **93** whose palladium complexes were found to catalyze the π-allylic alkylation with up to 80% stereoselectivity [146]. The supported bis(oxazoline) ligands **94** and **95** were prepared on PS-PEG resin and PEG support (Scheme 32) [147, 148]. The PS-PEG-supported **94** was tested in the palladium-catalyzed π-allylic alkylation to show excellent stereoselectivity of up to 95% ee, though the catalytic activity of the palladium complex of **94** was low. Trost's bisphosphine ligand is known to catalyze π-allylic substitution with excellent stereoselectivity. Polymeric palladium complexes of Trost-type pyrrolidine-based ligands **96**, **97**, and **98** promoted the enantioposition-selective π-allylic substitution–carbamate cyclization of meso-**100** forming **101** [149–151], where the JandaJEL-supported complex **97** exhibited higher stereoselectivity (up to 99% ee) [149] than the PS- and PS-PEG-supported complexes **96** and **98** (Scheme 33) [150]. The Trost-type chiral bisphosphine ligand **99** bearing the bicyclo[2.2.2]octane backbone was also immobilized on the PS-PEG resin and its palladium complex showed moderate stereoselectivity in enantioposition-selective cyclization [150].

A chiral phosphine having an imidazoindole backbone was designed to attach to the polymer supports [152]. Imidazoindole phosphine **102** was readily



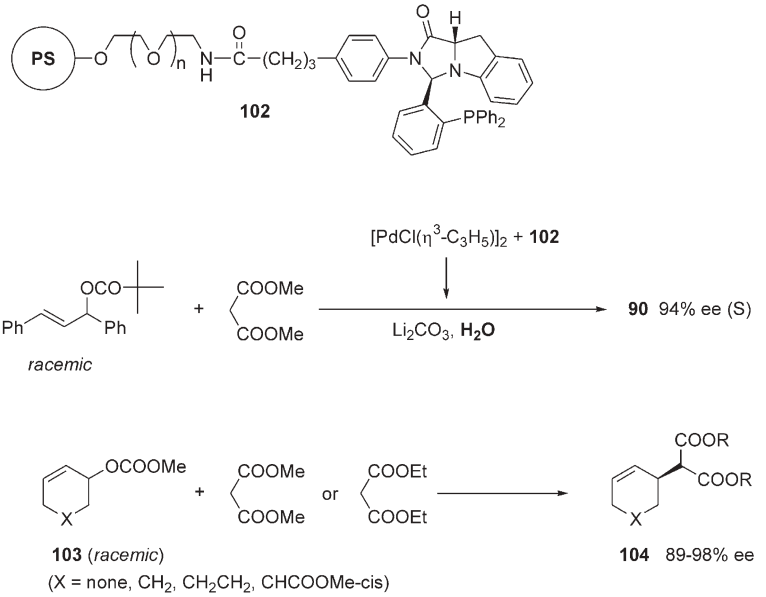
Scheme 32





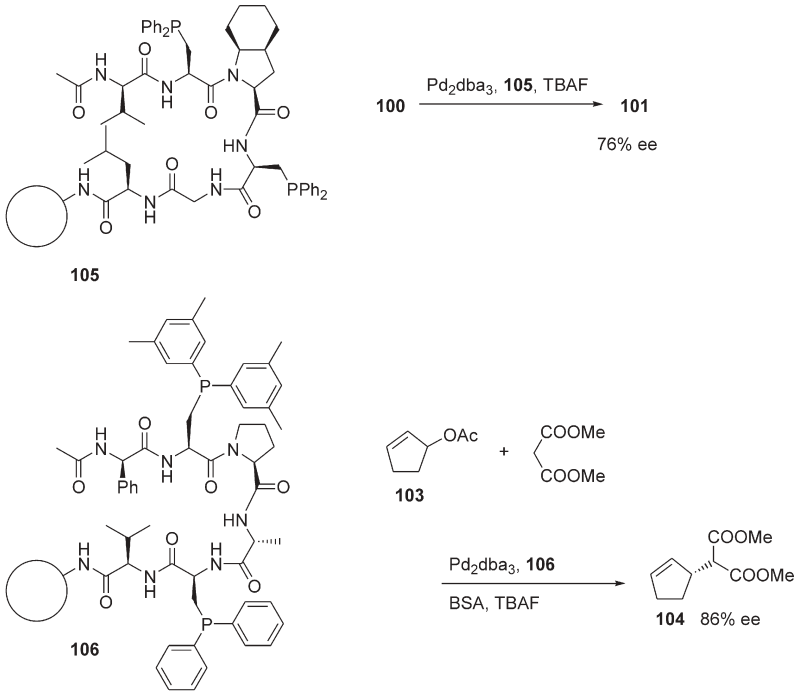
Scheme 33

prepared from aniline, indoline carboxylic acid, and 2-(diphenylphosphino) benzaldehyde and immobilized on PS-PEG amino resin [153]. The enantiocontrolling ability of the palladium complex of **102** was examined for π-allylic alkylation of both acyclic and cyclic alkenyl esters. In contrast to the vast amount of research on the asymmetric π-allylic substitution of acyclic esters (e.g., 1,3-diphenylpropenyl esters) with malonate nucleophiles, only scattered attention has been focused on cyclic substrates. The PS-PEG-supported **102**-Pd complex was found to promote the π-allylic alkylation smoothly in water due to the amphiphilic property of the PS-PEG support. Cyclopentenyl, cyclohexenyl, and cycloheptenyl carbonates underwent asymmetric π-allylic alkylation with malonates in aqueous Li_2CO_3 in the presence of the polymeric palladium complex of **102** to give the corresponding alkylated products with 90–98% enantioselectivity [153]. The stereoselectivity achieved with **102** is comparable to that of the best ligands known for this catalytic transformation using a homogeneous catalyst system (Scheme 34).



Scheme 34

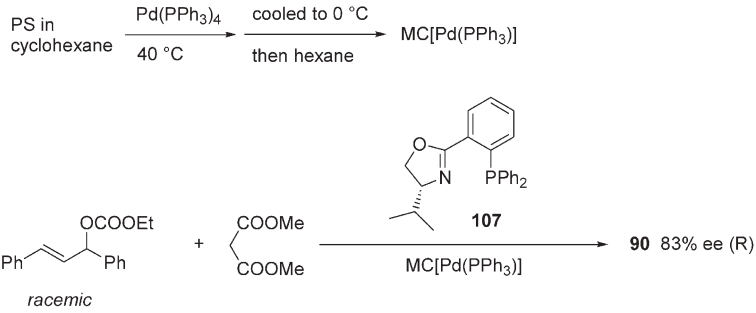
The peptide-based phosphine ligand **105** was identified from a polymer-supported phosphine library of 75 members [154]. Enantioposition-selective desymmetrization of the meso-cyclopentenediol derivative **100** was promoted by a palladium complex of **105** to afford the cyclic carbamate **101** with 76% ee. This result demonstrated that the combinatorial approach is effective in the lead-generation stage of stereoselective catalyst development [155, 156]. The resin-supported palladium complex of Ac-D-Phg-Pro-D-Val-Pps-D-Leu-NH resin **106**, which has also been developed through the combinatorial approach,



Scheme 35

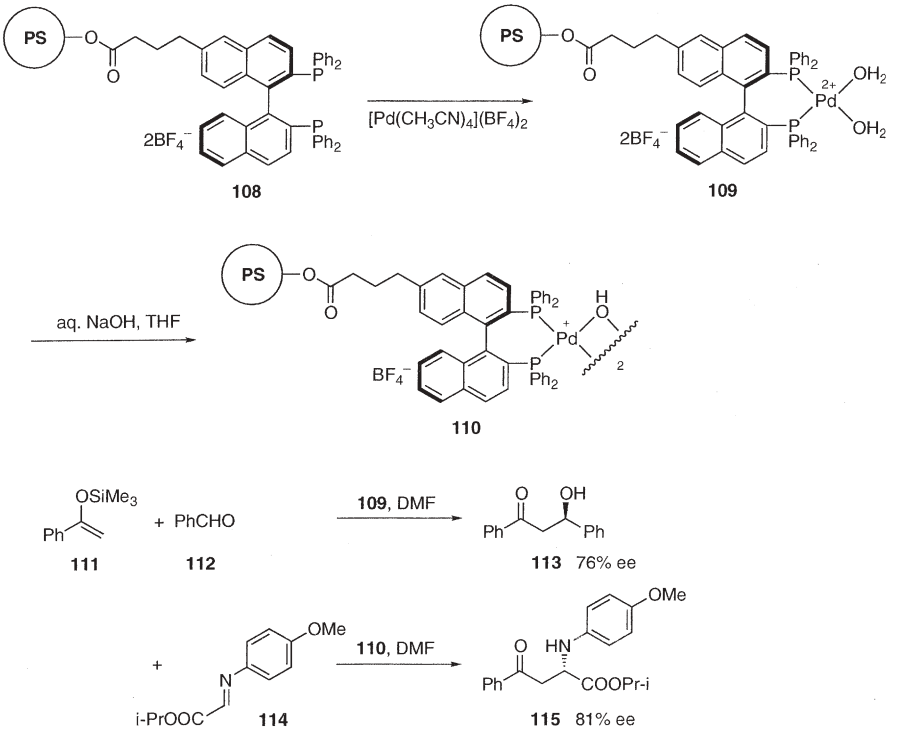
catalyzed the asymmetric allylic alkylation of cyclopentenyl acetate with dimethyl malonate to give 95% yield of the dimethyl cyclopentenylmalonate **104** with 86% stereoselectivity (Scheme 35) [157, 158]. The peptide-phosphine part was resynthesized in solution phase and applied to the asymmetric allylic alkylation under homogeneous conditions to provide up to 95% stereoselectivity.

Microencapsulated palladium (MC[Pd(PPh_3)]) was found to catalyze the allylic alkylation of 1,3-diphenylpropenyl ester with good stereoselectivity (up to 83%) in the presence of an external chiral ligand **107** (Scheme 36) [122].



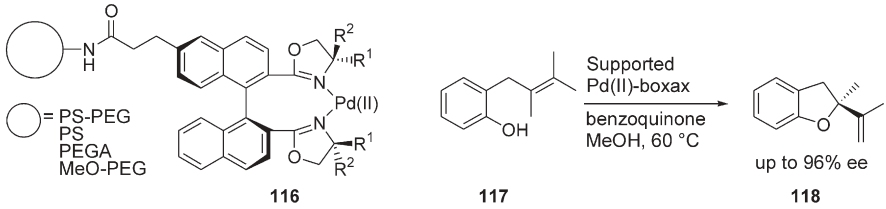
Scheme 36

It has been reported that dicationic diaqua palladium-BINAP complex and a binuclear μ-hydroxo palladium-BINAP complex catalyzed the asymmetric aldol reaction and Mannich-type reaction, respectively, with good enantioselectivity (Scheme 37) [159–162]. Heterogeneous switching of these asymmetric catalysts has been examined by using polystyrene resin-supported BINAP ligand. PS-supported BINAP **108** was originally prepared for heterogenization of ruthenium-catalyzed asymmetric hydrogenation [163]. The dicationic diaqua palladium complex **109** anchored to the PS-BINAP ligand was prepared and used in the palladium-catalyzed aldol condensation of the silyl vinyl ether **111** to give the aldol product **113** in 76% enantiomeric purity [164]. The dicationic diaqua palladium complex **109** was readily converted to the binuclear μ-hydroxo complex **110** by treatent with aqueous alkaline solution. The Mannich-type reaction of **111** and an imine **114** took place at room temperature in the presence of the supported complex **110** to give the adduct **115** with 81% stereoselectivity.



Scheme 37

Binaphthyl-bisoxazoline ligands (the so-called boxax) [165, 166] have also been immobilized on various polymer supports [167]. A palladium complex of polymeric boxax **116** catalyzed the Wacker-type cyclization [168, 169] of allylphenol **117** with up to 96% ee (Scheme 38) [170].



Scheme 38

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Applications of Catalysts on Soluble Supports

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Abstract The use of soluble polymers as supports for catalysts is discussed and reviewed. Strategies where immobilized catalysts on soluble polymers are used in a monophasic reaction, but where the immobilized catalyst is recovered as an insoluble polymer-supported species in a liquid/solid separation step, are discussed. Such strategies include temperature perturbation, pH perturbation, and solvent precipitation as a means of producing a solid/liquid mixture for separation after a homogeneous reaction. Strategies where immobilized catalysts on soluble polymers are used in a monophasic reaction, but where the immobilized catalyst is recovered in one phase of a biphasic liquid/liquid mixture, are also described. Examples where temperature perturbation or additive addition are used as a means of producing a solid/liquid mixture for separation after a homogeneous reaction are discussed. Finally, examples where soluble polymers are used as supports homogeneously or biphasically and separated from products by membrane filtration or biphasic extraction are described.

Keywords Soluble polymers · Thermomorphic · Biphasic catalysis · Latent biphasic catalysis · Separation

Abbreviations

BINOL	1,1′-Bi-2-naphthol
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
$BAr^F{}_4$	Tetrakis(3,5-bis(trifluoromethyl)phenyl)borate)
DVB	Divinylbenzene
DMA	*N*,*N*-dimethylacetamide
EO-PO-EO	Ethylene oxide-propylene oxide-ethylene oxide
LCST	Lower critical solution temperature
PDADMAC	Poly(diallyldimethylammonium chloride)
PE_{Olig}	Polyethylene oligomer
PEG	Poly(ethylene glycol)
PEGs	Poly(alkene oxide)s
PEO	Poly(ethylene oxide)
PIB	Polyisobutylene
PNHEAM	Poly(*N*-hydroxyethylacrylamide)
PNIPAM	Poly(*N*-isopropylacrylamide)
PNODAM	Poly(*N*-octadecylacrylamide)
PtBS	Poly(4-*tert*-butylstyrene)
ROMP	Ring-opening metathesis polymerization
TBME	*Tert*-butyl methyl ether
TOF	Turnover frequency
TONs	Turnover numbers

1 Introduction

This review discusses applications where soluble polymers behave as ligands or supports for catalysts. In this role, the polymer replaces a more conventional low molecular weight ligand, in most instances with the objective of making a catalyst more readily recyclable or reusable. The macromolecular ligand is supposed to mimic the chemistry of its low molecular weight analog.

The subject of soluble polymers as supports in catalysis has been discussed in a number of recent reviews [1–5]. These other reviews each focused on a particular polymer or groups of polymers or on some aspect of catalysis (e.g., organic catalysis or asymmetric synthesis) [2, 3, 6–8]. Soluble polymers' use as supports in synthesis has also been reviewed, but this topic is not covered below because in synthesis the polymer is used in a stoichiometric amount and is generally not recyclable [5, 9–11]. This review takes a general approach, focusing on soluble polymers used as catalyst supports. It discusses these supports within a context of the separation strategies that could be or were used to separate or recover the soluble polymer-bound catalyst from the products. This review emphasizes examples from the last few years where soluble polymers are used but includes, for completeness, earlier examples if a particular

strategy has not received as much recent attention. All sorts of soluble linear polymers ranging from nonpolar to polar species are included. However, species like enzymes, colloids, polymer micelles, or encapsulated catalysts are generally excluded even though the species involved may be macromolecular and soluble [12–20]. Various sorts of dendrimer-bound catalysts have also been extensively discussed in a series of recent reviews and only select examples of these polymer-supported catalysts are included in the discussions below [1, 3, 6, 21, 22].

Polymers as solids are ubiquitous in our modern society. They are some of the most common synthetic materials. Biologically derived macromolecules are also abundant. Whether it is a piece of wood, a natural fiber, or a lobster shell, nature uses solid organic macromolecular materials as key architectural material. This abundance of examples of synthetic and natural solid polymeric materials is mirrored in the prevalence with which insoluble cross-linked polymer supports are used in synthesis and catalysis [23–25]. However, while solid-phase synthesis and related catalysis chemistry most commonly employ cross-linked supports that resemble those originally used by Merrifield [26], the polymers found in nature are neither always insoluble nor always cross-linked. Indeed, soluble polymers are as common materials as their insoluble cross-linked analogs. Moreover, nature quite commonly uses soluble polymers as reagents and catalysts. Thus, it is a bit surprising that synthetic soluble polymers are so little used in chemistry as supports for reagents, substrates, and catalysts.

There are presumably a variety of reasons why soluble polymers are less often used as supports or ligands for catalysis. The most likely reason is that there is a perception that recovery of a soluble polymer is experimentally more difficult than recovery of an insoluble cross-linked polymer. This perception stems from the mistaken belief that a soluble polymer can only be isolated as a viscous, intractable gooey material. However, as is demonstrated in the examples below, this is not true. Indeed, many soluble polymers can be easily isolated as tractable solids. Moreover, even in cases where the soluble polymer is not a tractable solid or where a solid/liquid separation is deemed less desirable, soluble polymers can often be separated from low molecular weight products either on the basis of size (membrane filtration) or on the basis of their selective solubility in one phase of a biphasic mixture.

2 Separation Techniques

Organic reactions inevitably involve a separation step. While distillation, extraction, and filtration are the common procedures used with most compounds that are gaseous, liquid, or solid, liquid/liquid or liquid/solid separations are most common with macromolecules and are the techniques most used to recover soluble macromolecular ligands and catalysts. Liquid/solid separations (Fig. 1) are most commonly used. The actual separation step can involve either

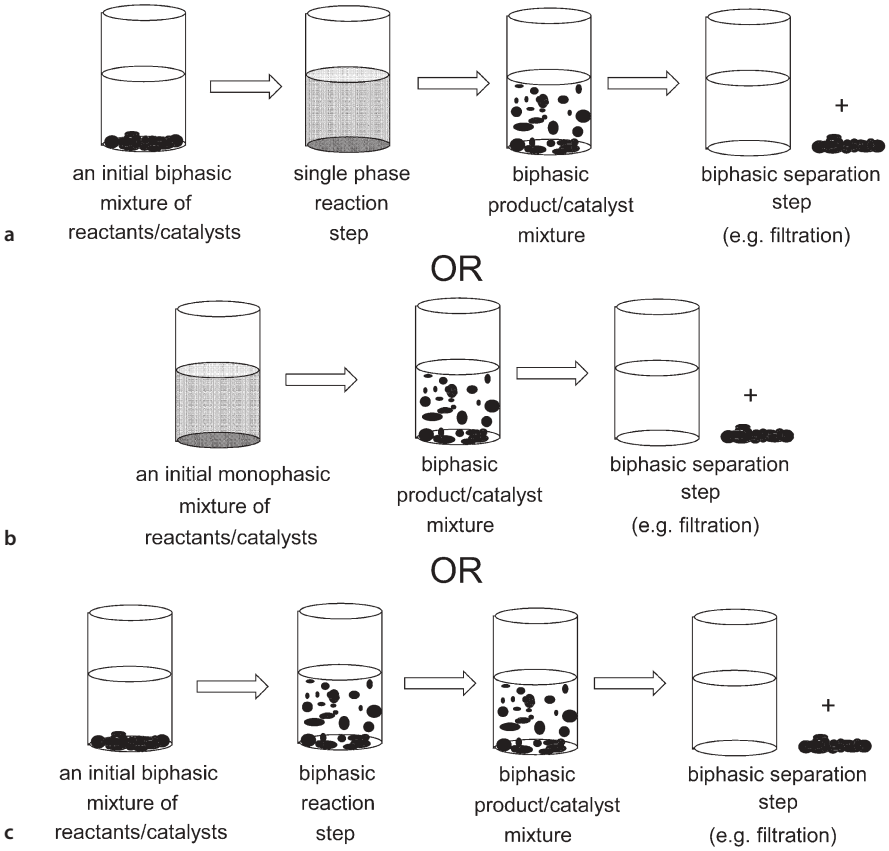


Fig. 1a–c Biphasic solid/liquid separations of a soluble polymer: **a** beginning with a biphasic mixture of reactants and polymeric catalyst but with an intermediate monophasic reaction mixture and a biphasic solid/liquid separation; **b** beginning with a monophasic mixture of reactants and polymeric catalyst, with an intermediate monophasic reaction mixture but with formation of a biphasic mixture of polymer and products that is separated; or **c** beginning with a biphasic mixture of reactants and polymeric catalyst that remains biphasic throughout the reaction and through the separation stage

filtration or centrifugation and decantation. This is the type of separation most commonly used with other cross-linked insoluble polymer-supported catalysts and reagents.

Soluble polymers also can be separated by liquid/liquid separations. These liquid/liquid separations can involve membrane filtrations that use to advantage the relative size differences of macromolecules and low molecular weight substrates. Alternatively, the physical size or the phase-selective solubility of macromolecules can be used to advantage, separating a solution of a macromolecule-bound ligand or catalyst from a low molecular weight product on the basis of size or phase-selective solubility (Fig. 2).

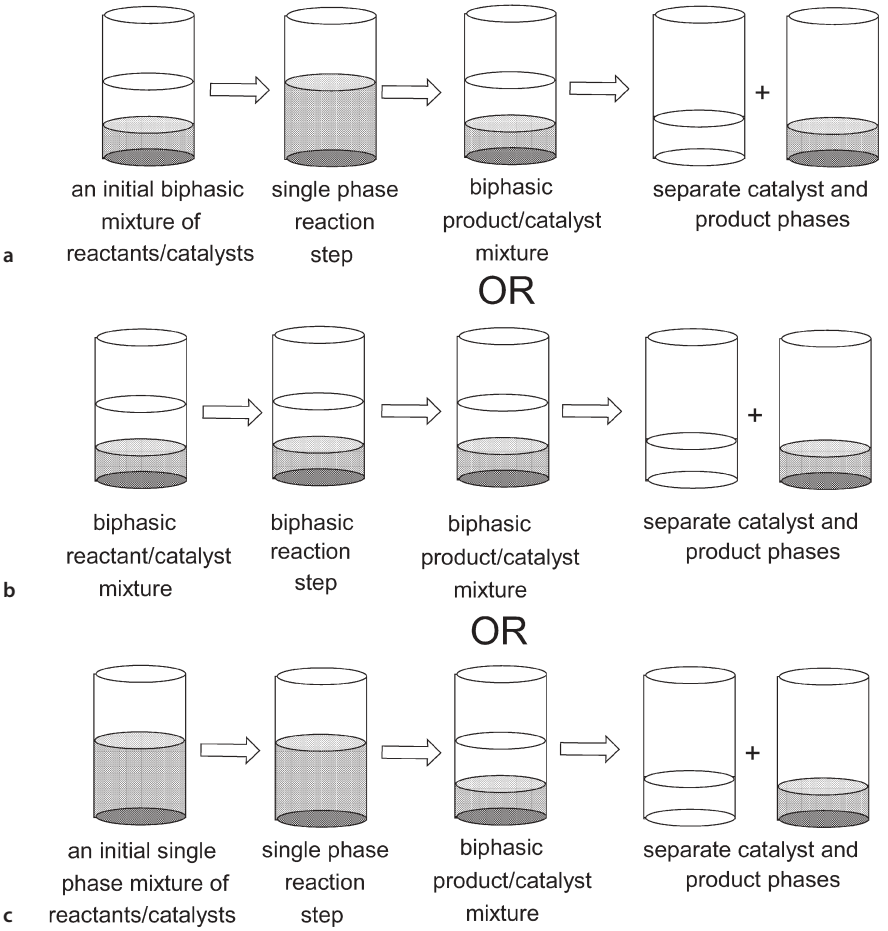


Fig. 2a–c Biphasic liquid/liquid separations of a soluble polymer: **a** beginning with a biphasic mixture of reactants and polymeric catalyst but with an intermediate monophasic reaction mixture and a biphasic liquid/liquid separation; **b** beginning with a biphasic mixture of reactants and polymeric catalyst, with an intermediate biphasic reaction mixture and with a biphasic mixture of polymer and products that is separated; or **c** beginning with a monophasic mixture of reactants and polymeric catalyst that remains monophasic throughout the reaction but is separated into a catalyst and product phase at the end of the reaction via a physical separation or by some chemical perturbation

In practice, the nuances within this manifold of separation strategies reflect the fact that a reaction basically has three stages – the initial stage of the reaction, the time during the reaction itself, and the end of the reaction. At each stage, a polymeric catalyst can be present either as a solid with a soluble reactant, as a cosolute with a reactant in a monophasic reaction, or in one of two liquid phases in a biphasic mixture. The review below discusses recent examples

of soluble polymeric catalysts that fit in with the various possible combinations of these separation/reaction motifs, focusing first on systems where the separation step involves a solid/liquid separation and second on systems where the separation step involves a liquid/liquid separation.

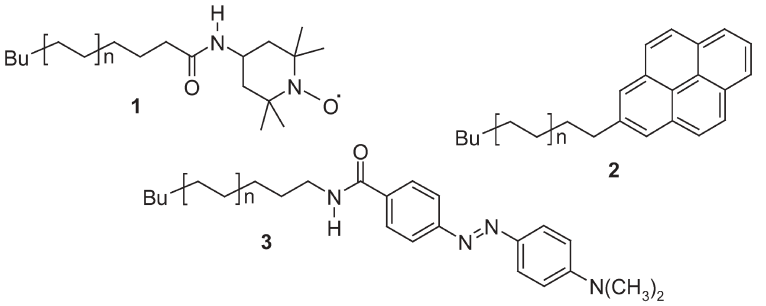
3
Solid/Liquid Separations (Fig. 1)

3.1
Biphasic/Monophasic/Biphasic Systems with Polymers that are Insoluble at the Separation Stage

Polyethylene is an example of a common polymer that is completely insoluble in all solvents cold but soluble hot in solvents like toluene, dibutyl ether, or dichlorobenzene. While such temperature effects on solubility might be considered ordinary, polymers like polyethylene are of interest as catalyst supports because these effects are seen even with oligomers whose molecular weight is quite low, e.g., 1,500 Da [27]. The cold/hot insolubility/solubility seen with these relatively small oligomers can be transferred to other functionalities that can in turn be used as ligands for catalysts so long as the ligand or catalyst that is being attached to the oligomer is not overly large relative to the underlying polymer [28]. Polyethylene in this regard is more useful than some other polymers in that this insolubility/solubility characteristic is seen with oligomers whose molecular weight is <10,000 Da with solutions containing 1 g of polymer per 10 mL of solvent. At these concentrations and with this molecular weight, solutions that are 10^{-2} M can be prepared. Most homogeneous catalysts are useful at concentrations of 10^{-3} M. Thus, oligomers with this loading and solubility are well within a practical range for use as catalysts.

To be useful in recovery, polymers that are soluble during a reaction but precipitate afterwards need to quantitatively precipitate. The extent of insolubility of these polyethylene oligomers meets this criterion based on separate studies with spectroscopically labeled polyethylene oligomers. Studies of polyethylene oligomers that contained nitroxyl spin labels as terminal groups (e.g., **1**) showed that an ethylene oligomer like **1** was soluble at 110 °C in toluene [29]. However, at 25 °C, ESR spectroscopy was unable to detect any soluble nitroxyl radicals indicating that essentially 100% of the oligomer **1** precipitates on cooling. This profound temperature-dependent insolubility has subsequently been confirmed in room temperature measurements that show complete insolubility for fluorescence- and visible spectroscopy-labeled polyethylene oligomers like **2** and **3**

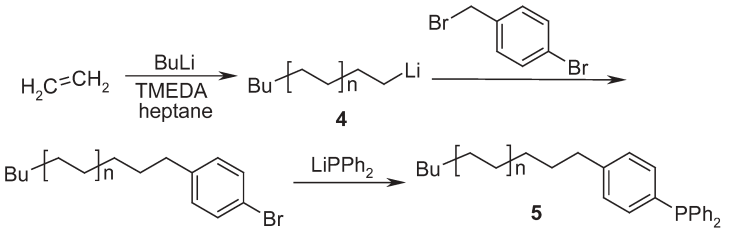
Solid/liquid separations of polymers like the polyethylene oligomers **1**–**3** from a solution are selective as well as quantitative. The linear oligomers that determine the solubility of the probes **1**–**3** and the ligands and catalysts discussed below do not entrain species other than polyethylene-like species. The



oligomers can, however, form intimate mixtures with other polyethylene-like species. Indeed, it can be experimentally advantageous to deliberately add a small amount of "virgin" high molecular weight polyethylene in a reaction to artificially increase the mass and to facilitate the handling of what would otherwise be a few tens of milligrams of a precipitate.

3.1.1 Polyethylene Oligomers as Catalyst Supports

Several groups have used the temperature-dependent solubility of polyethylene to advantage in catalysis. Typical examples of this are shown below. The oldest of these examples is work from our own group where ethylene was polymerized anionically to form a living oligomer (Eq. 1) [28]. Quenching the oligomericlithium reagent **4** formed in this process with electrophiles like chlorodiphenylphosphine produced the polyethyldiphenylphosphine ligand **6**. This reaction leads directly to apolymer-bound ligand. Other multistep syntheses like that shown in Eq. 1 were also successful in transforming end groups of polyethylene oligomers into ligands, and a widevariety of ligands have been subsequently attached to polyethylene oligomers asterminal groups. Examples of other ligands that employ a polyethylene oligomer have been prepared by various groups and are shown in Fig. 3 (**5** in Eq. 1) (**5**–**13**) [28, 32–42].While these species are usually used as ligands to prepare catalysts, species such as the polyethylene-bound benzo-15-crown-5 ligand **11** are useful as catalysts themselves [39]. The phosphines **5** and **6** too could presumably be useful as organic catalysts in their own right [43, 44].



(1)

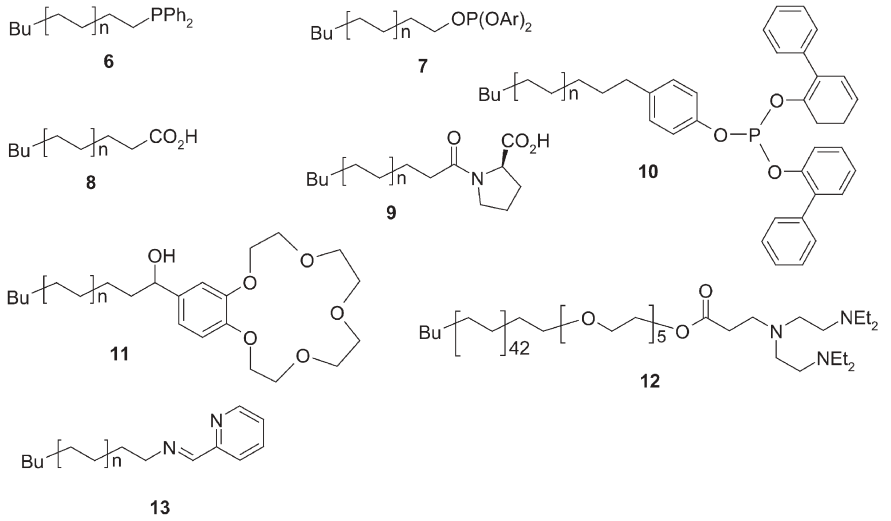
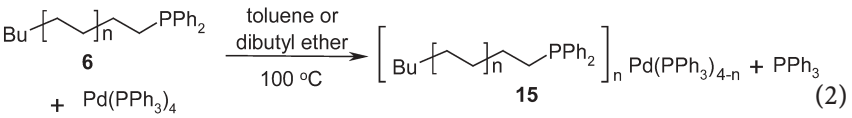


Fig. 3 Polyethylene oligomers with terminal ligands useful in catalysis: diphenylphosphinated polyethylene **6** [25]; polyethyldiarylphosphite **7** [30]; carboxylated polyethylene **8** [25, 31–33]; a chiral polyethylene carboxylate **9** [34]; polyethyltriarylphosphite **10** [35]; polyethylene-bound benzo-15-crown-5 **11** [36]; polyethylene-*b*-poly(ethylene glycol)-bound tetraethyl diethyleneamine **12** [38]; and polyethylene-bound pyridyl ligand **13** [39]

Given the structural diversity of the ligands that can be attached to polyethylene oligomers, it is not surprising that there is a similar diversity in the sorts of catalysts that have been supported on these materials. Selected examples of catalysts prepared using polyethylene ligands are shown in structures **14**–**26** in Fig. 4 [32–34, 38–40, 45–49]. While most of these catalysts contain transition metals, non-transition metal catalysts like polyethyldibutyltin chloride **14** or phase-transfer onium catalysts like **24** have also been prepared.

The use of phosphines like**5** or **6** as supports for Pd(0) allylic substitution or Rh(I) hydrogenation catalysts illustrates the way in which a polyethylene-bound ligand can be used to prepare catalysts that can be used homogeneously but recovered as solids. The polymeric Pd catalyst **15** ($[PE_{Olig}PPh_2]_4Pd$) was initially prepared by simply equilibrating a hot toluene or dibutyl ether solution of $(Ph_3P)_4Pd$ with PE_{Olig}-PPh_2 (**6**) (Eq. 2). The phosphine exchange reaction 2 which results would produce a mixture of Ph_3P- and PE_{Olig}-PPh_2-ligated Pd species. However, entropically >98% of the Pd will have at least one polyethyleneoligomer as a ligand. Since the polyethylene oligomers quantitatively pre-



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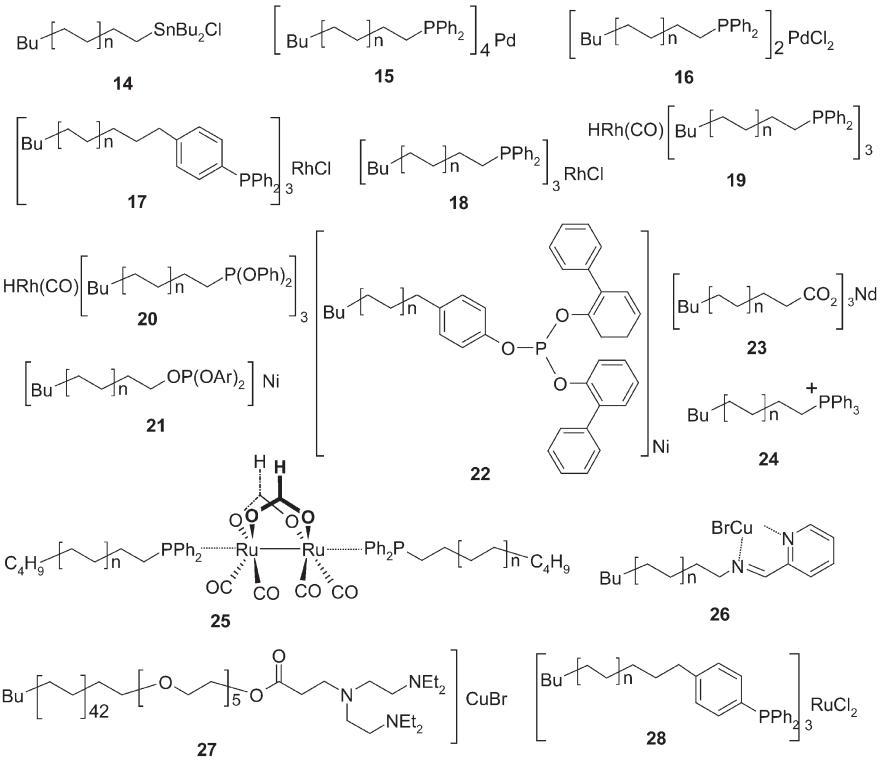
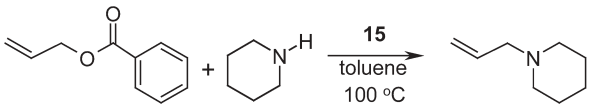


Fig. 4 Polyethylene-bound catalysts that dissolve hot in nonpolar solvents but precipitate on cooling: $PE_{Olig}SnBu_2Cl$ **14** [41]; $(PE_{Olig}PPh_2)_4Pd$ **15** [42, 43]; $(PE_{Olig}PPh_2)_2PdCl_2$ **16** [42, 43]; $PE_{Olig}C_6H_4PPh_2)_3RhCl$ **17** [29]; $(PE_{Olig}PPh_2)_3RhCl$ **18** [29]; $(PE_{Olig}PPh_2)_3RhH(CO)$ **19** [43]; $(PE_{Olig}P(OPh)_2)_3RhH(CO)$ **20** [30]; $PE_{Olig}P(OAr_2)Ni$ **21** [44]; $PE_{Olig}C_6H_4POP(OAr)_2Ni$ **22** [35]; $(PE_{Olig}CO_2)_3Nd$ **23** [31]; $PE_{Olig}PPh_3^+$ **24** [36]; $(PE_{Olig}PPh_2)_2Ru_2(CO)_4(HCO_2)_2$ **25** [37]; $(PE_{Olig}N{=}CHC_5H_4N)CuBr$ **26** [39]; $(PE_{Olig}NCH_2CH_2N(CH_2CH_2NEt_2))CuBr$ **27** [38]; and $(PE_{Olig}C_6H_4PPh_2)_3RuCl_2$ **28** [49]

cipitate on cooling and since the precipitated Pd species cannot equilibrate with Pd species in solution, cooling and precipitation entropically insures that >98% of the Pd is ligated by one or more PE_{Olig}-PPh_2 ligands and thatsequestration of Pd from the solution is quantitative [46, 50]. The resultingpolyethylene oligomer-ligated catalyst **15** was insoluble in all solvents at room temperature but did dissolve in toluene or dibutyl ether at 100 °C. As a solution, it was a competent catalyst for allylic substitution of allyl acetates by carbon and nitrogen nucleophiles (Eqs. 3 and 4). The catalyst **15** was used at 2 mol% levels success-



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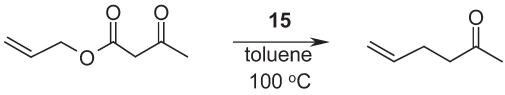
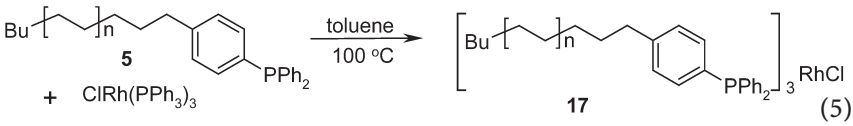


(4)

fully for up to ten cycles with quantitative yields of product. ICP analyses showed no detectable Pd in the filtrates. These analyses could have detected as little as 0.001% of the charged Pd.

Either **5** or **6** can be used to make an analog of Wilkinson's catalyst that is soluble hot in toluene but completely insoluble cold by exchange with a triphenylphosphine ligand as in Eq. 2 above or via the chlororhodium (ethylene dimer) (Eqs. 5 and 6, respectively). The catalyst **18** formed from the latter process was most reliably prepared and exhibited the same heat soluble/cold insoluble thermomorphic behavior exhibited by the phosphine ligand **6**. The catalyst **18** prepared from the phosphine **6** was nearly identical to $ClRh(PPh_3)_3$ in its reactivity in the hydrogenation of styrene or disubstituted alkenes. It is about 60% as active in the hydrogenation of terminal alkenes. Its activity is essentially the same as that of the alkyldiphenylphosphine-ligated Rh(I) complex $(C_{18}H_{37}PPh_2)_3RhCl$in 1-octene hydrogenation in *p*-xylene at 100 °C. The catalyst is stable to storage in air as a solid. Recycling experiments showed the catalyst could be used through as many as 20 cycles without significant activity loss. ICP analysis for Rh showed <0.1% of the charged Rh catalyst was lost in any given cycle. A three-phase test with a 2% DVB cross-linked polystyrene-bound alkene was used to show that the polymer-bound catalyst **18** "fresh" or "used" was still a homogeneous molecular catalyst [32, 51, 52].



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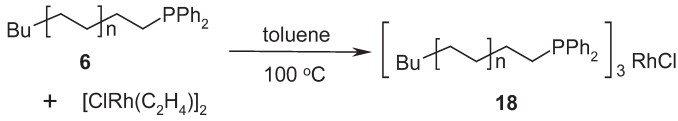


(6)

The thesis of the above work with **16** and of the work described with **18** (or with other polyethylene-bound catalysts or ligands usingspecies **5**–**26**) was that the reactivity of a terminal functional group, ligand, or catalyst on these polyethylene oligomers would be identical under homogeneous soluble conditions to the reactivity of an electronically similar low molecular weight catalyst. The polyethylene oligomer was supposed to only instill recoverable and reusable character into the catalyst and was not supposed to change the steric behavior of the catalyst or the catalyst's chemistry. The reactivity and recycling experiments show this is generally true. In addition, NMR spectroscopic studies com-

paring the T_1 values of **6** versus $C_{18}H_{37}PPh_2$ show that at 100 °C the phosphine ligands on these two alkanes have a very similar steric and electronic environment. Other similar NMR studies that compared phosphines on insoluble cross-linked polymers with low molecular weight phosphine ligands showed much larger differences in T_1 values.

While the PE_{Olig}-PPh_2 Rh(I) and Pd(0) **15–19** catalysts above exhibit a reactivity with low molecular weight substrates that is generally the same as that of catalysts with low molecular weight ligands, there are differences. Specifically, the catalysts on these polyethylene oligomers are generally not reactive or not very reactive when the polyethylene oligomer support is insoluble, because the catalyst is embedded in a nonswollen polyethylene matrix under those conditions and is diffusionally isolated from soluble substrates. These polyethylene-bound catalysts are also unreactive if the substrate is embedded in a different insoluble polymer matrix. It is known that soluble polymer-bound species generally can have lower reactivity within soluble supports [53], and these differences in reactivity are noticeable in reactions of solutions of these polyethylene oligomer-bound catalysts with macroscopic reactants. For example, in a three-phase test where **18** reduced a DVB-cross-linked alkene [32, 51, 52], there were marked differences in reactivity between **18** and $ClRh(PPh_3)_3$. These differences were ascribed to the diffusional restrictions **18** faced in reacting with the insoluble substrate. Even larger and more dramatic effects were seen when **18** was used in the presence of an insoluble cross-linked polarpoly(vinylpyridinium) salt resin [54]. As noted in Fig. 5, the catalyst **18** was stable even at 100 °C in the presence of a Cr(VI) species, because the Cr(VI) species which would have consumed either the Rh(I) or the phosphine ligand at a diffusionally limited rate was phase separated from **18.** A variety of one-pot sequences where multiple, otherwise incompatible, reagents are used in multiphase sys-

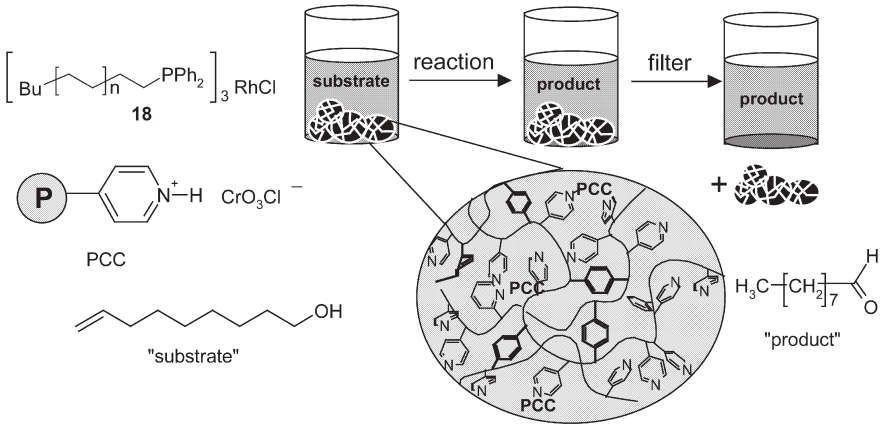
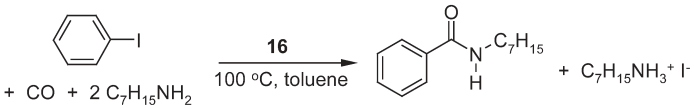


Fig. 5 A multistep oxidation/reduction reaction using the diffusional restrictions of a soluble and insoluble macromolecular species to insure strict phase isolation of two otherwise incompatible species

tems have beendescribed by others. However, these other systems typically involve two insoluble species [11, 55–60].

The Kharkhanov group at Moscow State University was another group to early on use polyethylene oligomers **6** or **7** with terminal diphenylphosphine or diphenylphosphite groups to prepare soluble, recoverable transition metal catalysts [33, 61, 62]. While the Moscow State University work involved several sorts of chemistry, their use of polyethylene oligomer-bound ligands to complex Pd(II) carbonylation and Rh(I) hydroformylation catalysts illustrates the general approaches they used. The catalysts they studied were used in aryl halide amidocarbonylation chemistry (Eq. 7) and in alkene hydro formylation (Eq. 8). The catalysts were recovered by cooling, precipitation, and filtration. The activity and selectivity of the oligomeric polyethyldiphenylphosphine-ligated catalysts this group studied were comparable to low molecular weight catalysts. For example, in iodobenzeneamidocarbonylation the catalyst **16** was about 60% as active as $Cl_2Pd(PPh_3)_2$. However, unlike $Cl_2Pd(PPh_3)_2$, the oligomeric catalyst $(PE_{Olig}PPh_2)_2PdCl_2$ could be reused for up to 12 cycles. In this chemistry, catalyst **16** was recycled by cooling and filtration. While this recycling was accompanied by some decrease in activity at the later cycles, this decrease in catalyst activity was attributed to inadvertent phosphine ligand oxidation, a phenomenon seen with other Pd catalysts. In accord with this suggestion, the authors noted that a catalyst mixture that was prepared using excess phosphine ligand **6** was slightly less active than the complex prepared with stoichiometric amounts of the oligomeric phosphine ligand, but that the resulting homogeneous catalyst mixture was more stable.



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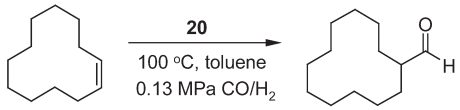
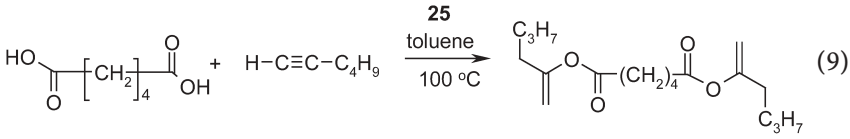


(8)

Hydroformylation catalysts are among the catalysts of most interest for recycling in industry because of the problems of separating catalysts from higher boiling products. Hydroformylation catalysts ligated by polyethylenediphenylphosphine ligands were described in studies of the Moscow State University group who used aPE_{Olig}-ligated Rh(I) catalyst in the hydroformylation of alkenes including 1-dodecene, cyclododecene, styrene, and 1,5-cyclooctadiene(cf. Eq. 8). While the hydroformylation of cyclododecene has no regiochemistry issues, regiochemistry is an issue in the hydroformylation of 1-dodecene. The ratio of linear to branched product in the 1-dodecene hydroformylation was sensitive to syngas pressure and to the presence of ex-

cess oligomeric ligand and was as high as 87%. Catalyst solutions containing excess phosphine ligand were again most stable and were recycled for at least ten times successfully using the precipitation/filtration protocol. Such recycling is successful because of the aforementioned insolubility of the polyethylene oligomer. Such recycling maintains the phosphine/Rh(I) ratio because both the excess ligand and catalyst are equally efficiently recovered on cooling.

Dixneuf reported using the ruthenium catalyst **25** in the synthesis of enol ethersfrom alkynes and carboxylic acids. Both formation of enol esters by Markovnikov addition of a carboxylic acid to a terminal alkyne (Eq. 9) and formation of dioxolanones (Eq. 10) was successful. In both cases the reactions were carried out homogeneously at 100 °C and the catalyst was recovered by cooling. Filtration led to recovery of the catalyst which was successfully recycled multiple times, as shown by experiments where a single 0.1 mmol sample of catalyst was used to prepare over 50 mmol of a mixture of enol esters using different carboxylic acids and different alkynes in a series of sequential reactions with different substrates and the same catalyst sample.



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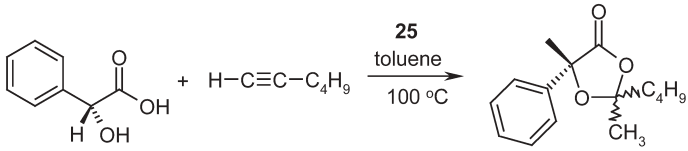
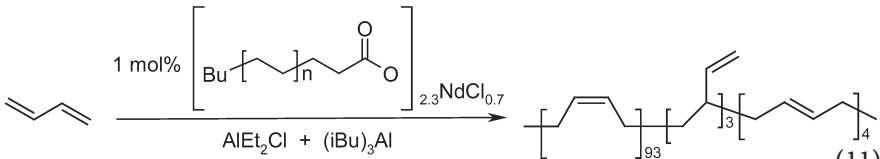


(10)

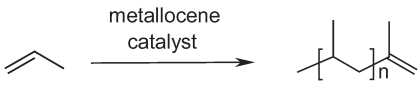
Polyethylene-supported catalysts that are initially insoluble but that become soluble on heating and are separated as insoluble materials on cooling are also used as catalysts in polymerization reactions. Infact, this was the first way a polyethylene-bound catalyst was used (Eq. 11) [34]. However, soluble polymers used in this manner appear to have several deficiencies. First, separation of the products from the catalyst may notalways be as simple as was the case with catalysts like **11** or **12** and low molecular weight products. For example, while a hot solution of a polyethylene-bound neodymium salt was successfully used in the stereoselective polymerization of butadiene to form high molecular weight (*Z*)-poly(1,4-butadiene), the product mixture after cooling was a thick, viscous sus-



(11)

pension of the precipitated polyethylene powder in a hydrocarbon/(*Z*)-poly-(1,4-butadiene) mixture. Separation by filtration or centrifugation was impractical and effective isolation of the insoluble catalyst from the soluble polymer product could only be effected by addition of significant amounts of additional toluene solvent – an undesirable step in green chemistry terms. Second, reactivity can be a problem. When Brittain used a polyethylene-bound Cu(I) species **26** as a catalyst in atom-transfer radical polymerization (ATRP) chemistry, he was able to effect the reaction but the product polymers were not as monodisperse as they were with a conventional low molecular weight catalyst [42, 63]. In a subsequent report, Shu showed that a similar ATRP catalyst **27** on a block copolymer prepared from a polyethylene oligomer and a short poly(ethylene oxide) group was significantly more effective, producing polystyrene products with excellent monodispersity. In addition to showing better reactivity than simpler polyethylene oligomers, Shu's work is also interesting as an example where a soluble diblock copolymer is used as a support. While copolymers including diblock copolymers are discussed elsewhere in this review, and while such block copolymers can be used to design new polymer supports with desirable solubility [64], most work with soluble polymers still uses homopolymers decorated withterminal functionality (e.g., **1**–**11** or **13**) or homopolymers (*vide infra*) that are modified such that <20% of the pendant groups are catalyst or ligand moieties [41, 64, 65].

Much of the work with polyethylene oligomers as catalyst supports described above dates from the 1990s. However, this area should receive more attention in the future since the necessary starting oligomers should be readily available now by a variety of newer procedures. For example, single-site alkene polymerization catalysts can be designed to produce a terminal vinyl group and to very simply and economically afford linear or otherwise structurally defined polyolefin oligomers whose terminal groups can be readily modified (Eq. 12) [66–68]. Metathesis can also be used to produce well-defined polyethylene derivatives with defined terminal functionality even with older generations of ROMP catalysts (Eq. 13), a process that is even easier with newer ruthenium catalysts [69, 70]. Anionic polymerization of methylene groups is also practical (Eq. 14) [27]. Finally, C–H functionalization of unfunctionalized polyolefins has been shown to produce functional groups at methyl termini of chains or branches (Eq. 15) [71]. At low loadings, such groups would notaffect



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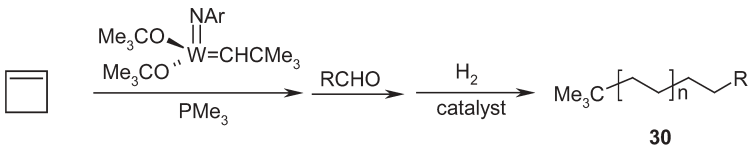

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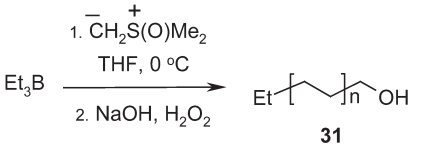

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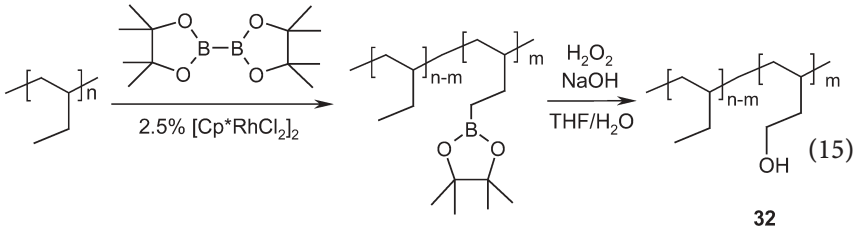


(15)

32

the solubility of the polyolefin and such polymers could be elaborated into ligands and catalysts using reported procedures [71–73].

While polyethylene oligomers' complete insolubility cold and solubility hot as a function of temperature provides a thermomorphic way to separate a catalyst and product, it should be noted that polymers are not the only vehicle for thermomorphic separations that involve a quantitative temperature-dependent solid/liquid separation. This is most evident in fluorous systems. For example, Gladysz has described several examples of fluorinated catalysts that are insoluble in organic solvents cold but soluble hot [74]. Qualitatively, these catalysts behave as if they were attached to a piece of Teflon that had temperature-variable solubility like the polyethylene oligomers above. Similar temperature-dependent solubility has been noted with other fluorous catalysts too [75–77].

3.2 Monophasic/Biphasic Systems with Polymers that are Insoluble at the Separation Stage but Initially Soluble

This is the most common motif for recovery of a polymer-bound catalyst in reactions where a solid/liquid separation is used with soluble polymer. However, while it is common to separate soluble polymers as solids at the end of a reaction, there are several conceptually different strategies that are used to induce polymer precipitation.

The methods to engender insolubility of a polymer can be divided into methods that require a substantial amount of solvent or those that require minimal or no solvent. The first method is solvent precipitation and is by far the most general way to induce polymer insolubility. Thermal precipitation is a second scheme used by a few groups. It is less common because it requires that the polymer have a lower critical solution behavior in a readily accessible temperature range. A third method would be to use a small amount of an additive to change the solvent properties and to induce insolubility of a polymer. A pH change would be an example of the latter strategy.

3.2.1 Solvent Precipitation

Solvent precipitation is the most common way to recover a soluble polymer-bound catalyst. It is a technique often used to isolate a soluble polymer after polymerization and depends on a specific polymer having poor solubility in a solvent in which the products are readily soluble. Several polymers are typically recovered as solids using this strategy. In this separation strategy, the solution of the polymer-immobilized catalyst, the product, and any unreacted starting materials, by-products, or reagents is poured into an excess of a second solvent – a solvent that is chosen because it is a "poor" solvent for the polymer. Assuming that the solvent mixture that results is no longer a solvent for the polymer that is the support for the catalyst, the polymer and the catalyst immobilized on it will precipitate. In order to be effective this strategy requires that the polymer quantitatively precipitates and the products remain in solution. Fortunately, this is typically the case.

3.2.1.1 Poly(alkene oxide)-Supported Catalysts

The most generally used soluble polymer in synthesis or catalysis is poly(ethylene glycol) (PEG) or poly(ethylene oxide) (PEO). While both terms refer to the same polymer, the PEO appellation is more commonly used for higher molecular weight material. This polymer is widely available in varying molecular weight ranges. Furthermore, because PEG is often used to prepare drug conjugates, PEG derivatives with many end groups are commercially sold. As the most common soluble polymer support, applications of PEG in synthesis and catalysis have been reviewed [5, 78–80]. In addition to PEG and PEO, other poly(alkene oxide)s such as poly(propylene oxide) or copolymers of poly(propylene oxide) with poly(ethylene oxide) can be used as supports for catalysts.

The sorts of poly(alkene oxide)s (PEGs) that are used as supports vary both in the structure of the polymer and in the structures of the end groups. The simplest species would be terminally functionalized species like **33–41** shown in Fig. 6. These ligands and their associated catalysts can be used as homogeneous species in much the same way as a low molecular weight ligand and catalyst. They can be characterized by solution-state NMR spectroscopy. They behave in many respects like a low molecular weight species so long as the solvent is a good solvent for the polymer. Overall, the underlying strategy is much like that used for the polyethylene oligomer-bound catalysts discussed above, except that more polar solvents that are appropriate for PEG-bound catalysts are used and an excess of a "bad" solvent is necessary at the separation step.

Both the polyethylene oligomers and the PEG oligomers used are typically modest in molecular weight (<10,000 Da, n<200 for structures **33–41**). This insures that catalyst concentrations will easily be 10^{-3} M. However, while poly-

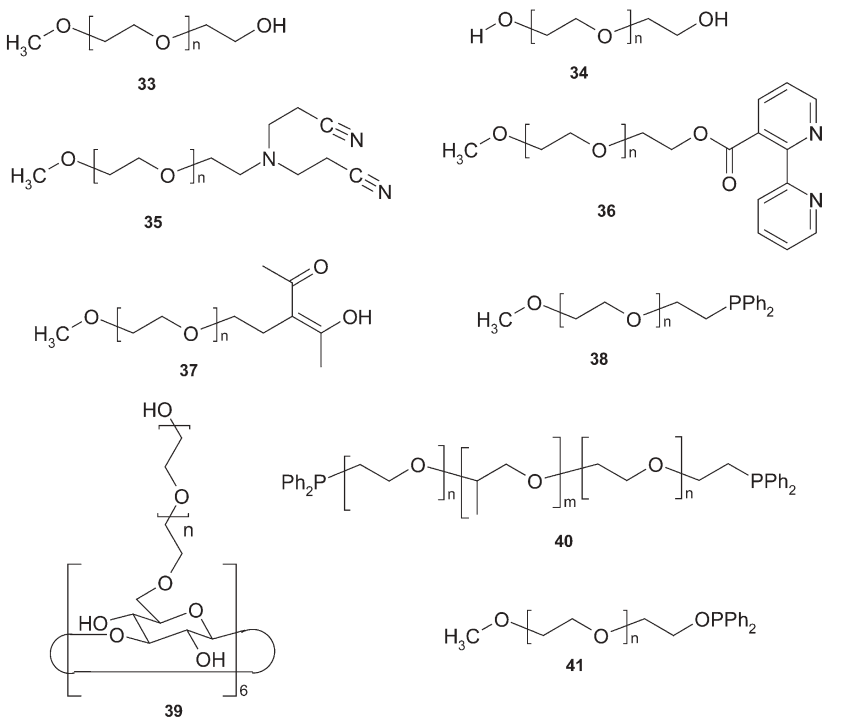
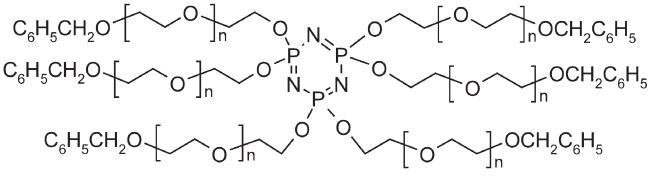


Fig. 6 Poly(alkene oxide)-based ligands for transition metal catalysts

ethylene oligomers have always been used as monofunctional derivatives, PEGs can be readily obtained with functionality at either end of the oligomer, increasing the capacity or loading of the support 2-fold. Further increases are also possible. Janda has described so-called stealth star PEG derivatives of phosphazene (**42**) that have 6-fold increases in capacity [81]. Such stealth star PEG derivatives have solubility and separability characteristics like those of PEG. Species like **42** have been further modified by debenzylation, mesylation, and ether formation with $HOC_6H_4PPh_2$ to form phosphines, though reports of catalysts on such polymers have not appeared. These star polymers like their simpler analogs **33** quantitatively precipitate from diethyl ether.

While PEG is a polyether, it has been used in various applications as a support for oxidation catalysts. One example of this is the PEG-bound ruthenium



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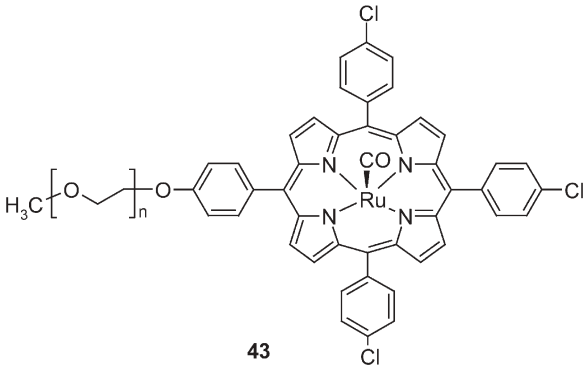
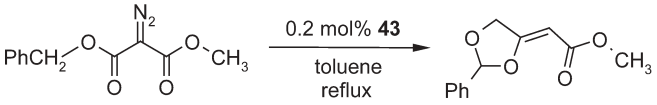


43

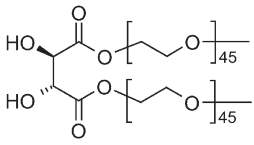
porphyrin **43** [82]. This ruthenium porphyrin derivative of PEG was prepared by reaction of the unsymmetrical monophenolate of the trichlorophenyl ruthenium porphyrin with a PEG mesylate. The formation of a covalent adduct was confirmed by UV-visible spectroscopy and by ^{1}H NMR spectroscopy. The loading of this material was 0.14 mmol of Ru/g of polymer. Subsequent reaction of 0.1 mol% of this PEG-immobilized Ru porphyrin with alkenes and 2,6-dichloropyridine N-oxide led to epoxide formation, typically in >90% yield, in reactions in CH_2Cl_2 at 40 °C over 40 h. Product turnovers of up to 9,180 moles of product/mole of catalyst were obtained in one example. Typical turnover numbers (TONs) were on the order of 900–1,000. Solvent precipitation, isolation of the catalyst, and recycling were successful through five cycles with only a slight decrease in activity.

The Ru-porphyrin catalyst immobilized on PEG was also useful in catalytic cyclopropanations, carbene insertion chemistry, and aziridination reactions. While the TONs in the aziridination reaction were only modest, catalyst **43** was substantially more efficient in the formation of (*Z*)-2-phenyl-4-(methoxycarbonylmethylene)-1,3-dioxolanes from *γ*-benzyloxy-*α*-diazo-*β*-keto methyl esters than the corresponding low molecular weight Ru-porphyrin (Eq. 16). Adding ether to the reaction mixture quantitatively precipitated the catalyst **43**, eliminating the need for column chromatography to separate the catalyst and reaction products.



92% (16)

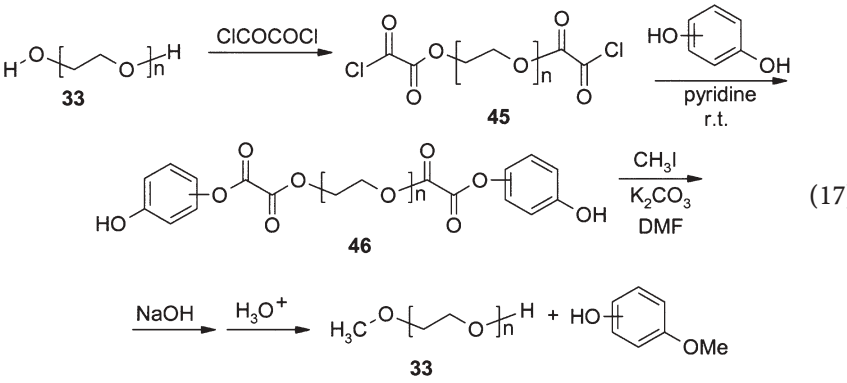
Epoxidations and dihydroxylations catalyzed by soluble PEG-bound catalysts are well-established reactions and this chemistry has been discussed in recent reviews [5, 83, 84]. In a recent report [85], tartrate esters **44** prepared with a PEG_{750} or PEG_{2000} were shown to be effective in the asymmetric epoxidation of (*E*)-hex-2-en-1-ol using $Ti(O(CH(CH_3)_2))_4$ and $(CH_3)_3COOH$ in CH_2Cl_2 at –20 °C. Yields of 85% were obtained with e.e. values of the epoxide of 93% – a



44

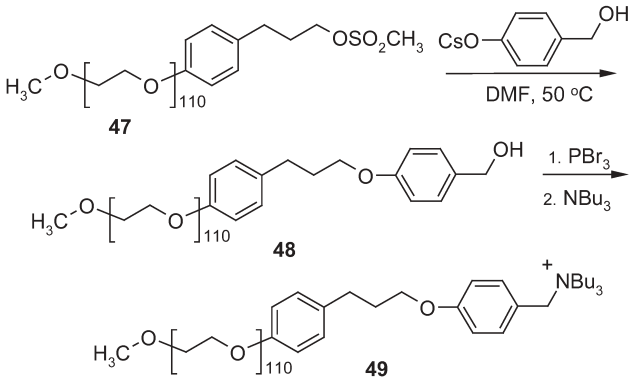
level of stereoselectivity that is comparable to that obtained with diethyl tartrate (94% e.e.) or dimethyl tartrate (>98%) under comparable conditions.

PEG itself is useful as a phase-transfer catalyst because it is an acyclic analog of a crown ether [86]. This property of PEG and its potential as a support for a substrate were combined in a recent synthesis of monoethers of hydroquinone and resorcinol [87]. In this chemistry (Eq. 17), a dihydroxyl PEG 4,000 (n=ca. 90) **33** was first allowed to react with an excess of oxalyl chloride. The resulting diacid chloride was then allowed to react with the hydroquinone or resorcinol to form a diester, which was easily isolated by solvent precipitation with diethyl ether. Subsequent treatment of this phenolic ester with an alkyl iodide in the presence of K_2CO_3 in DMF led to the PEG-bound monoether ester. In this reaction, the PEG acted both as a support and as a phase-transfer catalyst. Subsequent hydrolysis generated the monoether of the hydroquinone or resorcinol.



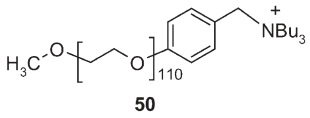
(17)

While PEGs can themselves serve as phase-transfer catalysts [86], onium salts are generally more effective as catalysts. Using the chemistry shown in Eq. 18, a methoxy-PEG_{5000} derivative **47** was first treated with the Cs salt of 4-hydroxybenzyl alcohol to form the alcohol **48**. Conversion of the alcohol to the bromide followed by reaction with tributylamine produced a quaternary ammonium salt **49**. This salt was as active as low molecular weight salts in typical phase-transfer catalyzed reactions like those of alkyl halides with KI, KCN, phenol, and pyrrole [88]. Yields were often in the >90% range. Reactions were typically carried out at <40 °C and could be performed either with water or without solvent. Control experiments showed that the ammonium group of **49** was necessary as the simple alcoholic PEG derivative **48** was much less effec-

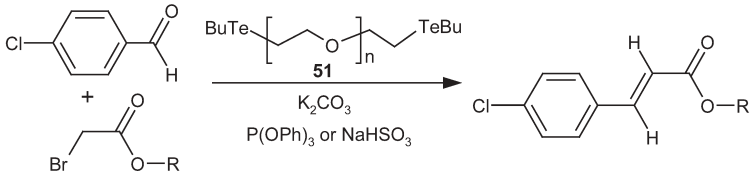


(18)

tive than **49**. Interestingly, the very similar species **50** which differed from **49** only in the spacer separating the ammonium salt from the PEG, was slightly less effective than **49**.

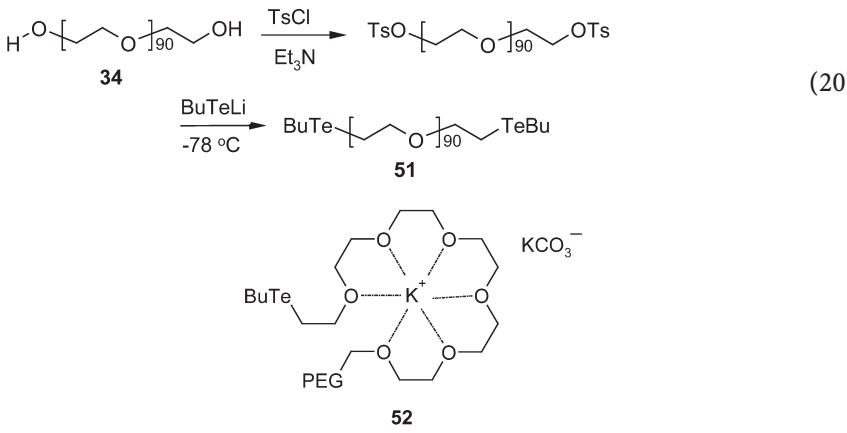


The phase transfer properties of PEG have also been used to advantage in the design of a catalytic Wittig-type olefination reaction (Eq. 19) [89]. In this reaction, a reducing agent like triphenyl phosphite or $NaHSO_3$ was required. The overall isolated yields of α,β-unsaturated esters from aryl and alkyl aldehydes in the reaction of the PEG-telluride **51** with α-bromoesters were typically in the 80% range. Only 2 mol% of the catalyst **51** was necessary and **51** was easily prepared from commercially available dihydroxylated PEG_{4000} using the chemistry shown in Eq. 20. Separate control experiments using crown ethers and Bu_2Te, or Bu_2Te alone in place of the PEG-telluride **51**, showed that the PEG group of **51** was important, possibly because of complexation of the K^+ of the K_2CO_3 by the PEG (cf. **52**) to make the KCO_3^- counterion more basic.



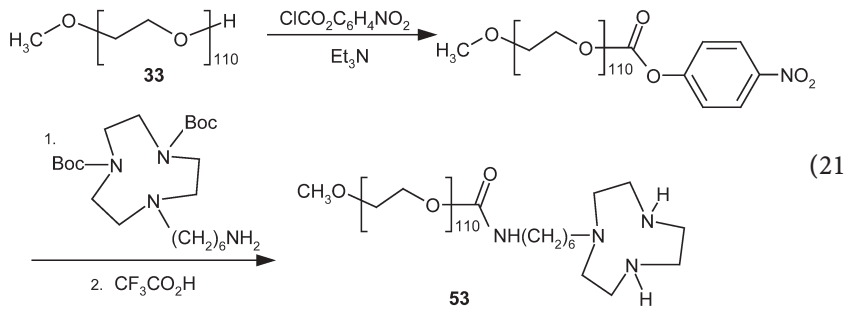
(19)

Monomethoxy poly(ethylene glycol) **33** has also been used to bind Cu(II) complexes known to be useful in hydrolysis of phosphodiesters [90]. Binding a Cu(II) complex to a PEG derivative was accomplished using the chemistry in Eq. 21. In this chemistry, the PEG-bound triazacyclononane was shown to be



(20)

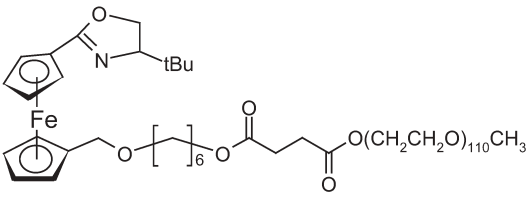
capable of binding Cu(II) based on the appearance of an absorption band at 620 nm. These experiments also showed that the stoichiometry of the complex was 1:1. Hydrolysis studies were carried out using bis(4-nitrophenyl)phosphate as a substrate. These studies showed that the PEG-bound Cu(II) complex **53** was about 3-fold more active than triazacyclononane-Cu(II) complexes alone. Recovery of the catalyst was effected by an extraction with CH_2Cl_2 followed by diethyl ether precipitation.



(21)

Chiral ligands for addition of diethylzinc or diphenylzinc to aldehydes have been studied by several groups with many sorts of polymer-supported catalysts [91]. The PEG-immobilized chiral ferrocenyl oxazoline **54** was very effective in promoting phenyl transfer from diphenylzinc to *p*-chlorobenzaldehyde [92, 93]. Average e.e. values through five cycles were 96% e.e. and the synthetic yields were also high using 10 mol% of **54** as a chiral catalyst. This work also compared this chiral ligand on a soluble polymer support versus the same ligand on an insoluble polymer support. The soluble polymer was much more effective. Addition of a 10-fold excess of diethyl ether was effective at precipitating **54** for recovery and reuse.

A feature of many polymer-supported reactions is the presence of a linker. A linker group is often introduced to minimize polymer–catalyst interactions.

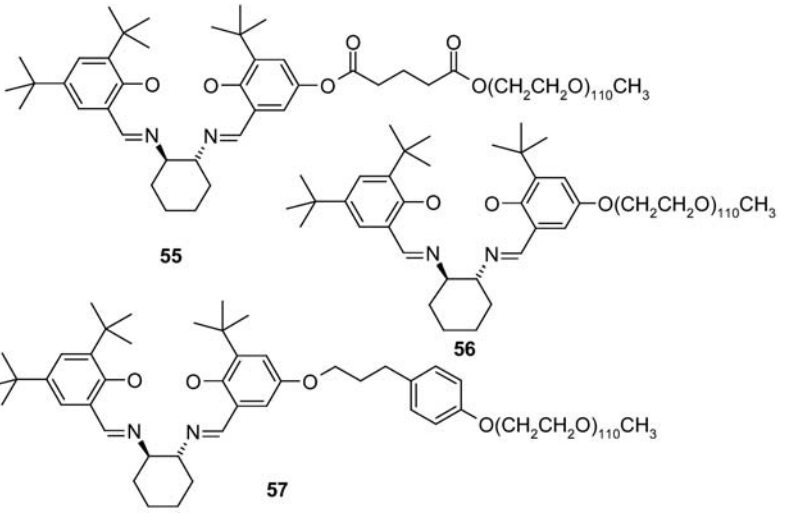


54

However, the linker group itself can affect reactivity as was shown in work with PEG-supported salen ligands **55–57**, where **55** was the most selective catalyst for the stereoselective addition of diethylzinc to aromatic aldehydes [94].

The utility of PEG for recycling of chiral bisoxazolines known to be effective in a variety of carbon–carbon bond forming reactions was reported by Cozzi [95]. In these reactions, PEG-supported bisoxazolines **58** and **59** were immobilized on a PEG and used with $CuOSO_3CF_3$ or $Cu(OSO_3CF_3)_2$ in Diels-Alder, cyclopropanation, and aldehyde-ene reactions. Stereoselectivities were higher than with similar bisoxazolines on insoluble polymer supports and were maintained in recycling studies.

Ruthenium metathesis catalysts have been the focus of much recent attention. Two recent papers describe efforts to recycle such catalysts. In the first of these reports, Yao described a PEG-bound version of a ruthenium catalyst de-



55

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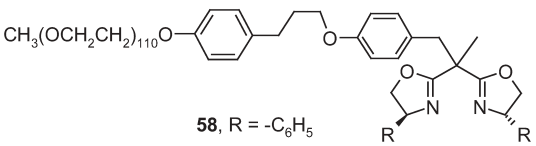
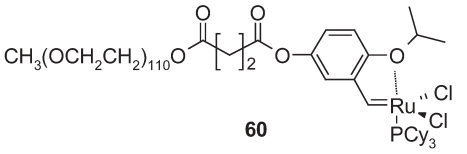


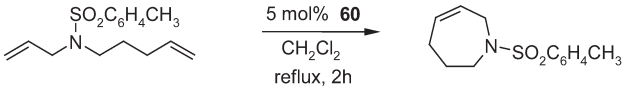
58, R = $-C_6H_5$

59, R = $-C(CH_3)_3$



60

veloped by Hoveyda [96, 97]. This catalyst (**60**) was reused in the ring-closing reaction in Eq. 22 through eight cycles with a slight (ca. 5–10%) decrease in reactivity. The PEG-immobilized ruthenium catalyst was recovered by diethyl ether precipitation and filtration.



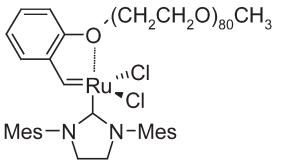
(22)

Lamaty reported the synthesis of several PEG-bound ruthenium catalysts similar to **60** [98]. The most active one was the catalyst **61** that used an *N*-heterocyclic carbene ligand in place of the tricyclohexylphosphine ligand in **60**. Some decrease in activity in reuse of **61** was noted. This work included extensive characterization data for **61** along with studies of ligand exchange of **61** and related species with low molecular weight Grubbs' catalysts.

Karakhanov's group has also been exploring poly(ethylene oxide)- and poly(alkene oxide)-copolymer-bound catalysts [99–102]. A notable aspect of this work is the design of polyethers like **39** that contain *β*-cyclodextrins and calyx[4]- and calyx[6]arenes. Such polyethers couple the molecular recognition associated with these macrocycles with the catalytic activity of acac, phosphine, dipyridyl, and catechol ligands. Metals complexed to such ligands have been used in reactions like hydroformylation, Wacker oxidations, and arene hydroxylation.

A variety of other PEG-based catalysts have been developed. Some recent examples not explicitly discussed above are shown in Fig. 7. These catalysts were prepared by reactions like those described above. The recovery and reuse of these catalysts generally follows the pattern described above where a poor solvent, most often diethyl ether, is used to precipitate the catalyst after a reaction.

Other polymers are also often recovered by solvent precipitation. Chief among these is polystyrene. Polystyrene was one of the first examples of a soluble polymer support. It is typically recovered by solvent precipitation much like PEG derivatives use solvents like methanol, diethyl ether, or acetonitrile.



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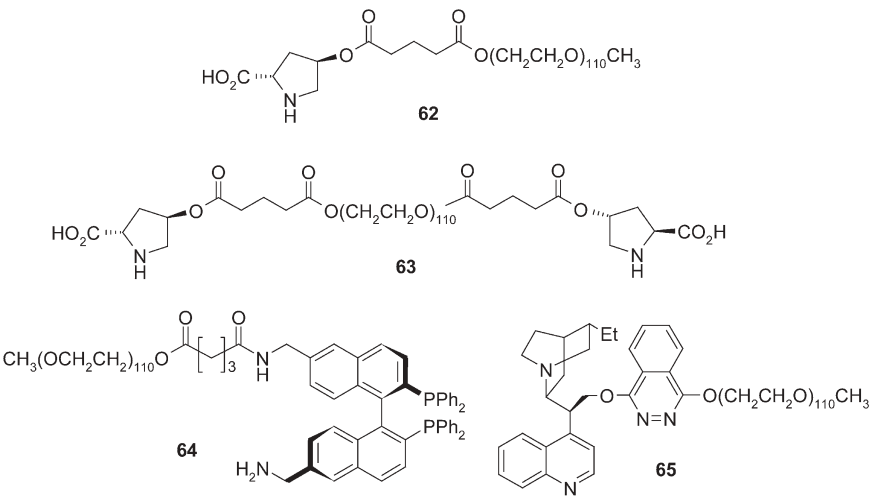
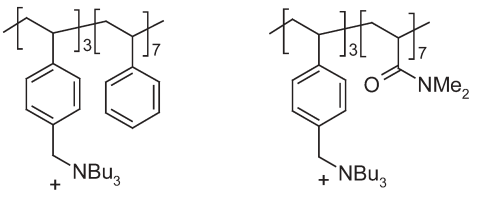
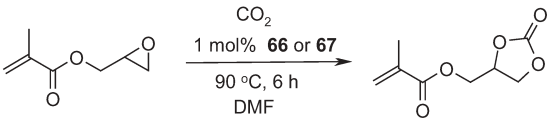


Fig. 7 Poly(ethylene glycol)-immobilized ligands: PEG_{5000}-supported proline (**62** or **63**) for aldol and iminoaldol reactions [186]; PEG_{5000}-supported BINAP **64** for Rh(I) and Ru(II) asymmetric hydrogenations [187]; and PEG_{5000}-supported alkaloid **65** for asymmetric dihydroxylation of olefins [188]

Soluble polystyrene supports differ from the terminally functionalized PEGs and polyethylene oligomers discussed above in that the catalyst moieties are attached to polystyrene via pendant groups, the loading of which can affect both the catalyst activity and separability. One example of a simple polystyrene-supported catalyst is the polystyrene copolymer-supported quaternary ammonium salts **66** and **67** [103]. These copolymers can be prepared with varying ratios of the styrene unit in the copolymer – the most active catalysts had 20–40 mol% of the vinylbenzylammonium groups in the copolymers. The utility of these catalysts was studied in a variety of solvents in the addition reaction of glycidyl methacrylate and carbon dioxide (Eq. 23). Polar solvents were most useful. The necessary polymer supports for preparation of catalysts **66** and **67** were prepared from chloromethylstyrene-styrene or chloromethylstyrene-*N*,*N*-dimethylacrylamide copolymers that were in turn prepared by radical polymerization of the styrene or acrylamide monomers. The catalysts were recycled up to four times with small (ca. 6%) decreases in activity – de-

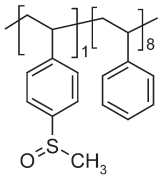




(23)

creases that were attributed to loss of the ammonium group from the polymeric catalysts under the reaction conditions used.

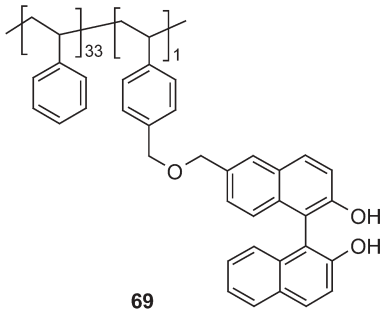
Soluble linear polystyrene can also be used to prepare recyclable sulfoxide reagents for Swern oxidations [104]. While the styrene copolymer sulfoxides **68** are not strictly catalysts, they are easily recycled by precipitation with cold methanol. Reoxidation of the sulfide with *t*-BuOOH reformed the starting polymeric sulfoxide **68**. While some decrease in yield was seen from cycle to cycle through four cycles, the products were not contaminated with polymer – an advantage in high throughput chemistry where separations need to be as simple as possible.



68

Immobilization of chiral ligands to effect asymmetric induction in alkylation of aromatic aldehydes by diorganozinc reagents promoted by PEG-immobilized ligands **54–57** can also be promoted by soluble polystyrene-bound species. A recent example of this is work where a polystyrene-bound BINOL was prepared [105]. This polymer **69** was used to form titanium-BINOLate and AlLibis(binaphthoxide) catalysts for Et_2Zn reaction with benzaldehyde and for asymmetric Michael additions of stabilized carbanions to cyclohexenone. While good stereoselectivities were obtained with these catalysts, the synthetic yields were modest.

Linear polystyrene was originally used as a soluble polymer support for transition metal catalysts in the 1960s [106, 107]. It continues to be used in this



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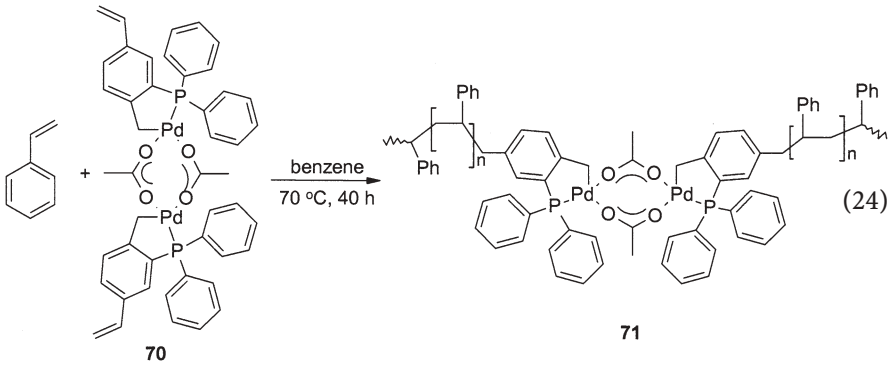
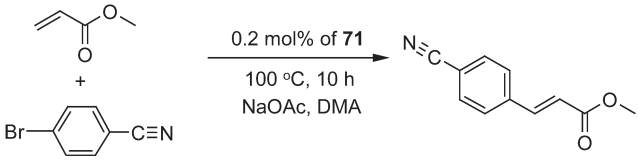


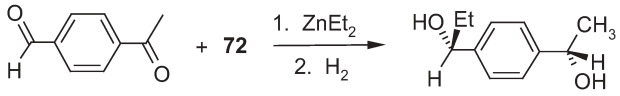
(24)

fashion. A recent report by Luo describes Pd chelates on polystyrene that are useful in Heck, Suzuki, and Sonogashira carbon–carbon bond forming reactions [108]. In this work, the soluble polystyrene-bound catalyst **71** was prepared directly using the dimeric Pd complex **70** as a monomer (Eq. 24). While ^{1}H NMR spectra of these materials is likely to be uninformative, the ^{31}P NMR spectra were useful and were used to characterize the catalyst **71** both before and after a reaction (Eq. 25). The catalysts were recycled by precipitation in diethyl ether or acetonitrile. Some decrease in yield of product occurred by the fourth cycle. While the origin of this decrease in yield was not described, the authors noted that the catalyst **71** was sensitive to water.



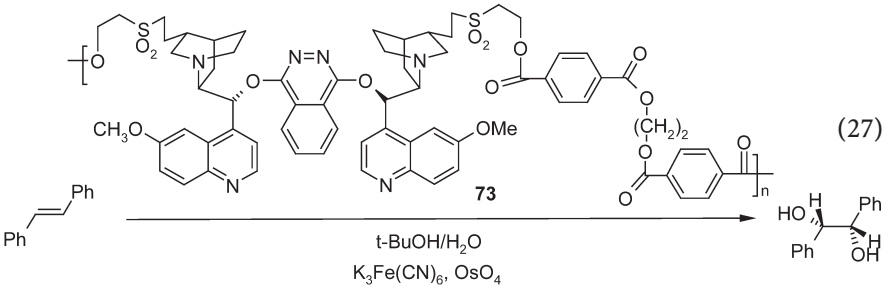
(25)

Solvent precipitation is widely used with polymers other than poly(ethylene glycol) and polystyrene too. For example, the chiral polymer copolymer catalyst **72** developed by Pu, containing both BINOL and BINAP groups in the polymer main chain, is recovered by precipitation in methanol after its use in a tandem asymmetric reaction where it catalyzes both the asymmetric addition of diethylzinc to an aromatic aldehyde and asymmetric hydrogenation of the aryl methyl ketone (Eq. 26) [109].



(26)

Another example of a chiral polymer that can be used in solution and recovered as a solid is the copolymer **73** [110]. This soluble block copolymer-supported ligand was very effective both in terms of synthetic yield and stereoselectivity in an asymmetric dihydroxylation of (*E*)-stilbene (Eq. 27) with an average synthetic yield of 84% and an average e.e. of 98% through five cycles.



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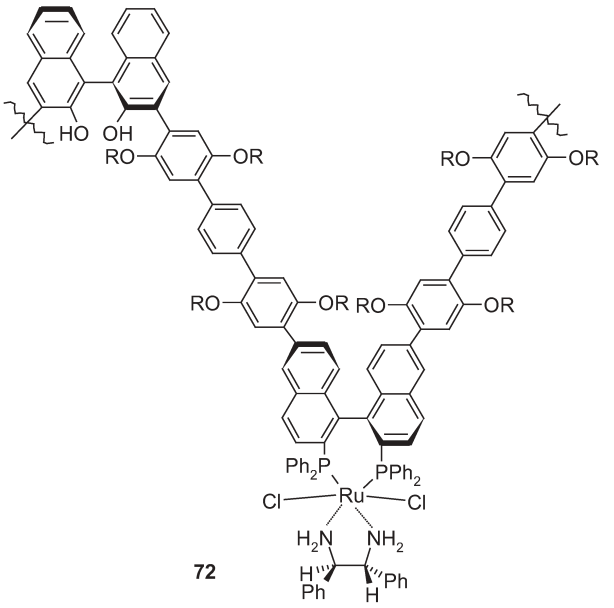
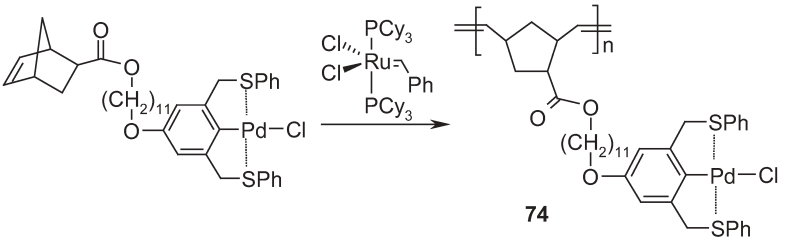


ROMP polymerization (Eq. 28) of norbornene esters containing SCS-Pd(II) pincer-type complexes useful in Heck, Suzuki, and Sonogashira couplings have been reported by Weck's group [111, 112]. The SCS-Pd(II) complexes in the polymer **74** prepared by this chemistry are competent catalysts in iodoarene couplings. The product polymer **74** is soluble and recoverable by precipitation using hexanes.



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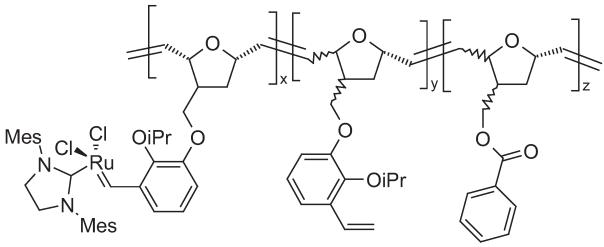
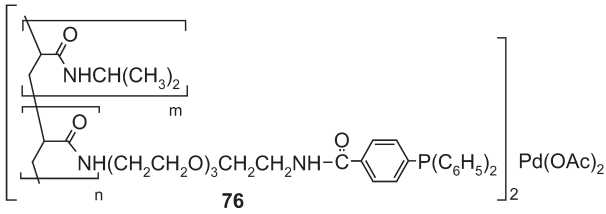


75 x:y:z = 1:9:30

Metathesis catalysts generally are of interest in synthesis and their recycling is a subject of continued interest because of their versatility and potential for use in fine chemical synthesis [113]. A very active recoverable catalyst that shows excellent activity in ring-opening metathesis and cross metathesis is the ROMP-based catalyst **75** developed by Blechert [114]. This catalyst is a "second"-generation ruthenium catalyst and as such is highly active in CH_2Cl_2 at 20 °C at 1 mol% catalyst loading. It is recoverable by precipitation with diethyl ether and the ruthenium content of the product solutions was analyzed by total reflection X-ray fluorescence. A maximum of 0.004% ruthenium was present and the authors suggest that this very low number may reflect the polymer serving both as an immobilization agent for the catalyst and as a sequestrant for any decomposed catalyst. This catalyst is also interesting as it is much more active and robust than the poly(ethylene oxide)-supported second-generation catalyst discussed earlier [98].

Precipitation from poor solvents is routinely used in purification of polymers and in many or most cases is part of the synthetic workup used in making the polymer-immobilized catalysts described throughout this review. Solvent precipitation is also sometimes used incidentally as a way to recover catalysts that are more commonly recovered in some other way. Examples of this are seen in the use of hexane to precipitate the poly(*N*-alkylacrylamide)-bound Pd-phosphine complexes **76** and **77** or the poly(*N*-*tert*-butylacrylamide)-bound sulfonic acid catalyst **78** [115–117], catalysts that are routinely recovered as solids by thermal precipitation (*vide infra*).

Dendrimers are very attractive macromolecules with potential applications as catalyst supports. They are attractive both because they are discrete molecular species versus a mixture of molecules with varying degrees of polymer-



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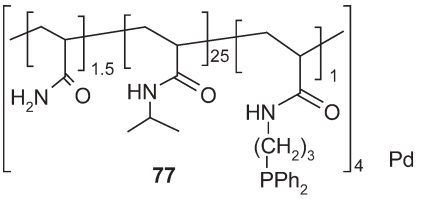

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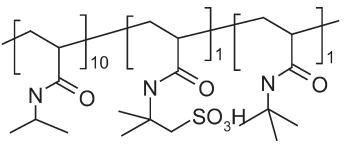
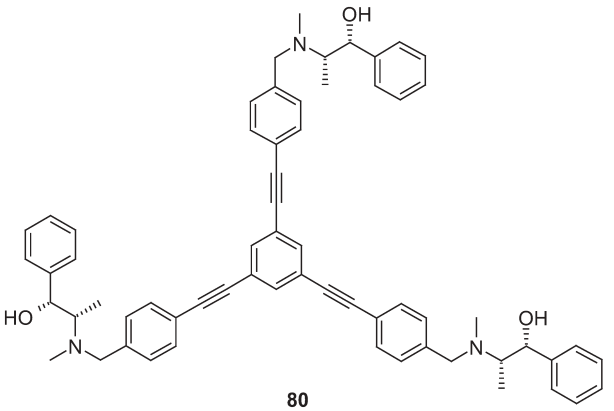


78

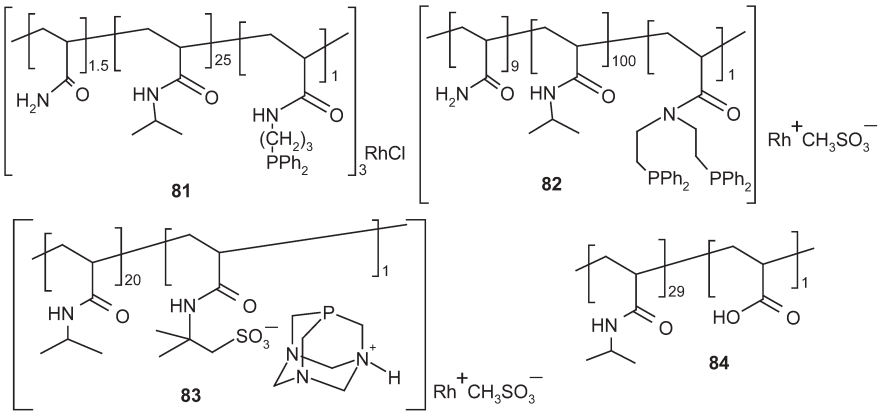
ization, as is the case for other linear polymers, and because they have higher loading than mono- or difunctional linear polymers [118]. Such materials can be recovered in varying ways including by solvent precipitation. Solvent precipitation has been used by Hu to recover higher molecular weight (1*R*,2*S*)-ephedrine-bearing dendronized polymers with poly(phenylene) backbones after the polymers were used to catalyze the asymmetric synthesis of 1-phenyl-1-propanol from benzaldehyde and Et_2Zn [91]. These polymers had M_w values of 141,100 Da. Simple solvent precipitation of these dendrimers avoided the chromatographic separations necessary with otherwise similar but smaller dendrimers like **80**.



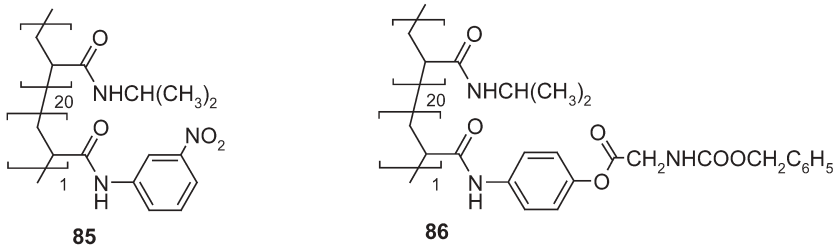
80

3.2.2 Thermal Precipitation by Heating

Thermal precipitation by cooling is the scheme chemists normally use in recrystallizations and is the "normal" behavior of small molecules. Macromolecules are different in that they can often be phase separated from solution by heating [119, 120]. Thermal precipitation by heating is a process that produces a solid polymer without addition of anything other than heat. It is the inverse of the process used with the polyethylene oligomers discussed above. This inverse temperature-dependent solubility of macromolecules is a phenomenon that is most simply ascribed to the unfavorable entropy of solvation of a macro-



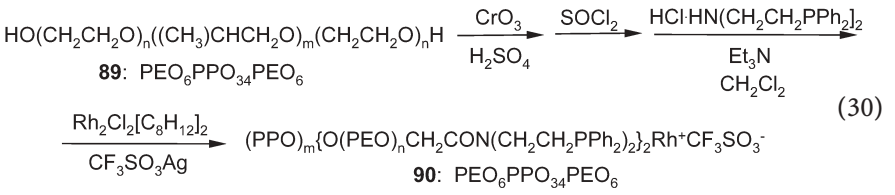
molecule [120]. This lower critical solution temperature (LCST) behavior is most commonly seen in accessible temperatureregions with polar polymers in strongly interacting solvents like water. It can also be seen in other systems though an LCST is sometimes only seen above the boiling point of the solvent. It has been used in catalysis with blockcopolymers prepared from ethylene oxide-propylene oxide-ethylene oxide (EO-PO-EO) and poly(*N*-alkylacrylamides) toprepare "smart" homogeneous catalysts like **76–78**, **81–84**, **88**, and **90** and smart substrates like **85** or **86** [116, 117, 121–123].



The triblock poly(alkene oxide)-supported catalysts **88** and **90** can be simply prepared using the same chemistry used earlier to prepare poly(ethylene oxide)-immobilized hydrogenation catalysts (Eqs. 29 and 30) [124]. Once prepared, these ligands and their Rh(I) complexes separate as oil-in-water emulsions from water at temperatures in the 0–50 °C range. The actual LCST depends on the substrate concentration and on the ratio of hydrophilic/hy-

$$\underset{\textbf{87}:\ PEO_{16}PPO_{59}PEO_{16}}{HO(CH_2CH_2O)_n((CH_3)CHCH_2O)_m(CH_2CH_2O)_nH} \xrightarrow[Et_3N,\ CH_2Cl_2]{MsCl} MsO(PEO)_n(PPO)_m(PEO)_nOMs \xrightarrow[THF]{LiP(C_6H_5)_2}$$

$$(C_6H_5)_2P(PEO)_n(PPO)_m(PEO)_nP(C_6H_5)_2 \xrightarrow[toluene]{Rh_2Cl_2[C_8H_{12}]_2} \underset{\textbf{88}:\ EO_{16}PO_{59}EO_{16}}{[(C_6H_5)_2P(PEO)_n(PPO)_m(PEO)_nP(C_6H_5)_2]_{1.5}RhCl} \quad (29)$$

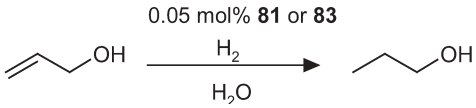


(30)

drophobic EO/PO groups in the block copolymers and is 86 and 32 °C for **87** and **89**, respectively, and between 0 and 25 °C for **88** and **90**. Since these poly(alkene oxide)-bound catalysts separate as oils, they cannot easily be isolated or recovered. However, their separation from aqueous solutions of substrates on heating does lead to smart behavior wherein a catalyst like **88** or **90** is inactive hot and active cold (anti-Arrhenius behavior).

Poly(*N*-alkylacrylamide)s like poly(*N*-isopropylacrylamide) (PNIPAM) are the polymers most used as smart thermoresponsive supports in catalysis. Such materials also can be recovered by thermal precipitation because they precipitate as solids that can be isolated by centrifugation or filtration. These polymers also have LCST behavior that is dependent on the hydrophilicity of the *N*-alkyl pendant groups of the polymer [125, 126]. Such effects can be engineered into the polymer by modifying functional groups on the polymer [127]. They can also be studied using high-throughput parallel analyses [126, 128].

PNIPAM-bound phosphines have been used to prepare catalysts like the Pd(II), Pd(0), Rh(I) transition metal catalysts **76**, **77**, and **81–83** [115–117]. Thesecatalysts can be used in carbon–carbon bond forming reactions like Heckreactions, Suzuki couplings, or Sonogashira couplings. After use as a catalystin reactions like Eqs. 31 or 32, the polymer-bound Pd or Rh catalyst can be recovered by heating if the reaction is carried out in water or by solvent precipitation in other solvents.



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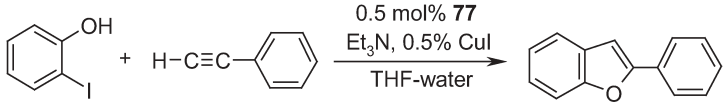
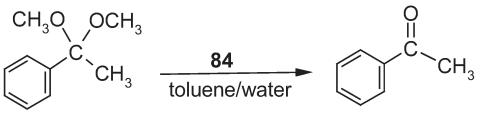


(32)

Acid catalysts **78** and **84** were both successfully used inacid-catalyzed acetal hydrolyses (Eqs. 33 and 34). However, the reactions did not always strictly turn "on" and "off" below and above the LCST of **78** and **84**. For example, when **84** was usedin a biphasic toluene/water mixture at 1 °C, hydrolysis of the acetal of acetophenone was about four times slower than at 24 °C. At 48 °C (above **84**'s LCST), the hydrolysis rate was ca. half the rate at 24 °C. In this case the reaction



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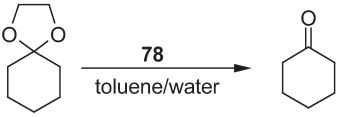
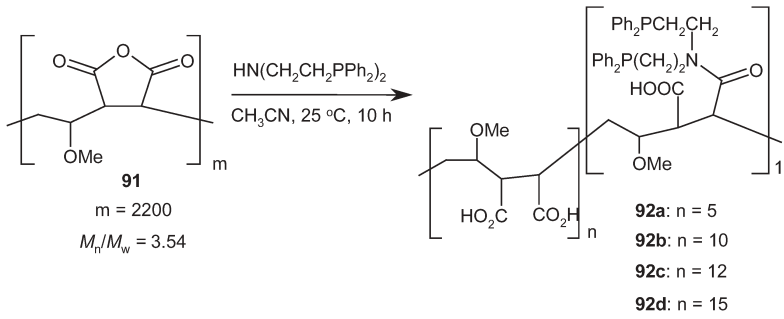


(34)

did not turn off, presumably because some of the acetal partitioned itself into the precipitated polymer phase. Such effects are not useful where the goal is a system that turns itself on and off but are, as noted by Davies, useful in the design of "hyper-Arrhenius" systems [129].

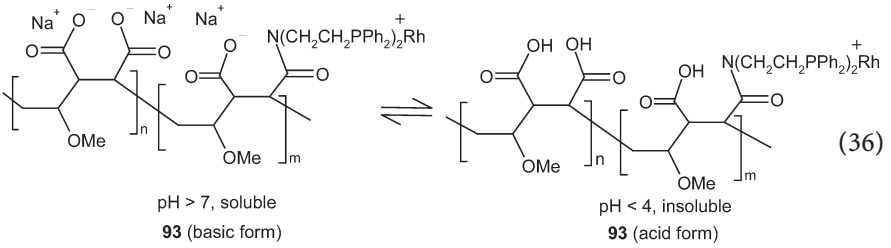
3.2.3 Precipitation by a pH Change

Polymers that contain basic or acidic groups can be used homogeneously and precipitated by a change in pH. Since only a small volume of acid or base is necessary to change a pH dramatically, pH precipitation is a way to change the solubility of a polymer that contains basic or acidic sites. Such a procedure has been used to advantage with a number of catalysts. For example, ligands formed by amidation of the maleic anhydride–methyl vinyl ether copolymer **91** can be prepared with variable loadings of amide and $-CO_2H$ groups by reaction of the anhydride copolymer with substoichiometric amounts of the secondary aminophosphine $HN(CH_2CH_2PPh_2)_2$ in CH_3CN (Eq. 35) [130]. This insoluble–CO_2H-rich polymeric ligand was soluble in water at a pH>7.5. A cationic Rh(I) catalyst **93** formed from a solution of this polymer **92** and 1 equiv of $[Rh(DOD)]^+CF_3SO_3^-$ proved to be a competent catalyst in the aqueous hydrogenation of water-soluble alkenes with turnover frequencies (TOFs) in hydrogenation of *N*-isopropyl acrylamide that were essentially the sameas those measured using a low molecular weight catalyst. Recovery of the catalyst **93** was



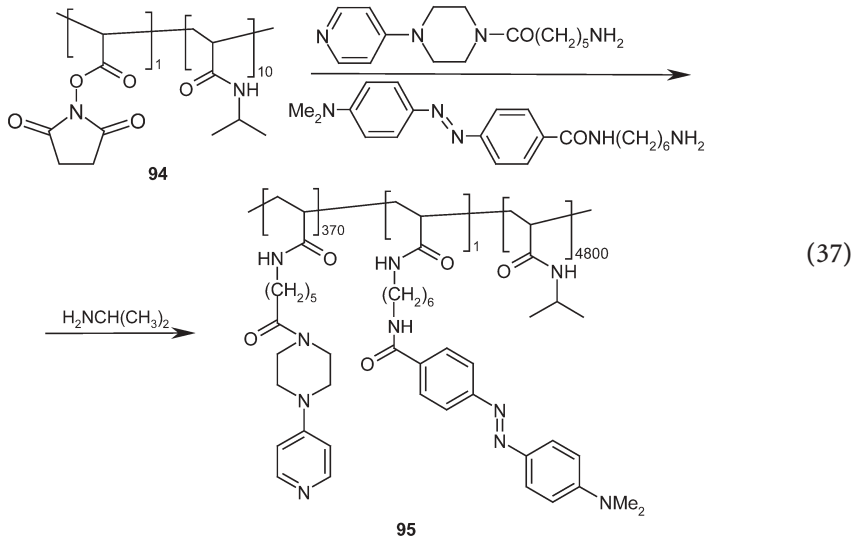
(35)

effected by simply changingthe pH to <7.5 by addition of CF_3SO_3H (Eq. 36). Addition of base converted the acid form of the catalyst into the basic form, redissolving the catalyst which was recycled without substantial loss of activity through three reaction cycles.



(36)

The basic nucleophilic poly(*N*-alkylacrylamide)-immobilized catalyst **95** was prepared from the active estercopolymer **94** according to the chemistry shown in Eq. 37 [131]. This polymercontained a ca. 8 mol% loading of an analog of *N*,*N*-dimethylaminopyridine, anucleophilic catalyst that others had immobilized on insoluble cross-linked resins previously. This soluble version was shown to be effective as a catalyst for acylation of hindered alcohols and phenols (Eqs. 38 and 39). This catalyst contained an azo dye as a marker, which facilitated analysis of the phase separation of the polymer-immobilized catalyst.



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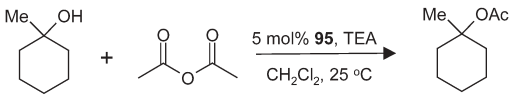
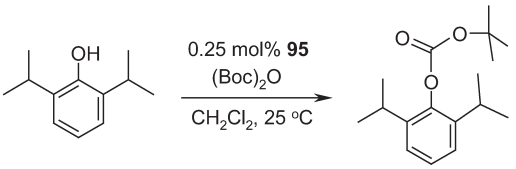


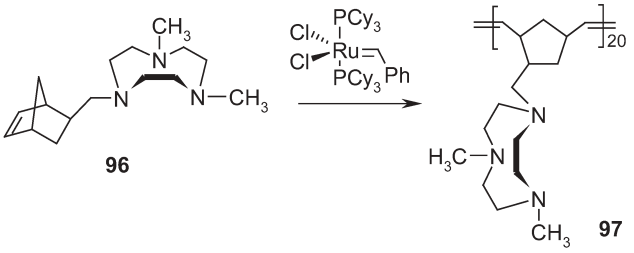
(38)



(39)

Based on visible spectroscopic analysis, **95** was soluble at pH values <10 but quantitatively precipitated above that pH. The pKa of this polymer was estimated to be 9.7.

A third example of a polymeric ligand with pH-sensitive solubility is **97**. This ligand was prepared by ring-opening metathesis polymerization of the 1,4,7-triazacyclononane-containing monomer **96** by the chemistry shown in Eq. 40 [132]. This polymer was capable of forming Mn(IV) complexes that oxidize alkenes and cycloalkanes with hydrogen peroxide. This basic polymer's solubility is affected by pH, as is the case with the other polymers **93** and **95** described above.



96 **97**

(40)

3.3 Biphasic/Biphasic/Biphasic Systems with Polymers that are Insoluble at the Separation Stage and Throughout the Reaction

Non-cross-linked polymers can be used in this way just as cross-linked polymers can. For example, we have used polyethylene supports with surface grafts to support Pd(0) catalysts [133, 134]. In these cases, the polymer-immobilized catalyst is used in exactly the same way as an insoluble polymer-bound catalyst. Such supported catalysts do require that the insoluble polymer be swollen or permeable to substrates or that the catalysts be within a solvent-permeable, thin immobilized graft. While this approach can be useful, it takes no advantage of the polymer's solubility. It is an approach that conceptually is no different than that used with insoluble inorganic supports or with polymers that are by design insoluble by virtue of cross-linking, and is an approach to catalyst immobilization that is not further discussed since this review is focused on polymer-immobilized catalysts that are used under solution-state conditions.

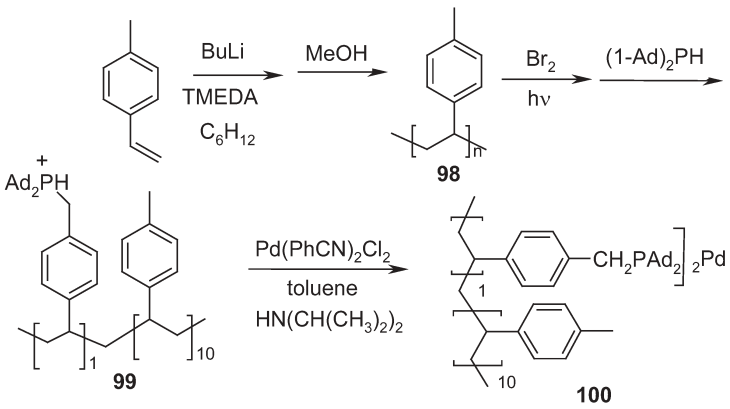
4
Liquid/Liquid Separations (Fig. 2)

Using soluble polymers under conditions where the products and polymer supports both remain in solution during the separation stage is a scheme that is uniquely applicable to soluble polymers. It is, for the most part, the scheme used in nature where enzyme catalysts are used and separation is based on size. To date, liquid/liquid separations remain a less common way of recovering soluble polymer-bound species. However, the earliest examples where soluble polymers were used in catalysis separated the solutions of soluble polymer-bound catalyst from the products with membranes [106, 107]. While solid/liquid separations (*vide infra*) still predominate, that situation may change as new separation strategies are invented and perfected or as new more durable and improved membranes are developed. Indeed, as can be seen from the discussion below, a variety of new and improved approaches have recently been developed where soluble polymer-bound catalysts are isolated as solutions.

4.1
Membrane Separations

The use of a solid or liquid membrane to separate products and reactants is most attractive as it lends itself to continuous operations. The main problems are the efficiency of the separation, the speed of the separation, and the durability of the membrane. Membrane separation was also one of the first ways linear soluble polymer-bound catalysts were separated from products. However, separation efficiencies in those first examples were not as high as present ones, as membrane technology has substantially improved over the past 35 years [135]. Thus, it is not surprising that many recent examples using membranes to recover polymer-bound catalysts and to separate them from products have been reported. This technique seems particularly apt for dendrimers because of their overall globular structure [136]. However, improved membranes can also be useful with linear soluble polymer-bound catalysts. A recent review summarizes much of this work [137].

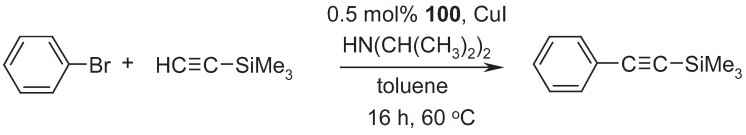
Plenio's group has recently described the use of nanofiltration to separate and recover poly(4-methylstyrene)-bound Pd(0) catalysts [138]. These soluble catalysts were prepared using the procedure shown in Eq. 41. The necessary poly(4-methylstyrene) support was prepared by the anionic polymerization of 4-methylstyrene. This chemistry produces relatively monodisperse polymers **98** with a polydispersity index of ca. 1.04. Samples with M_n values ranging from 5,000 to 35,000 were prepared. Since these polymerizations were quenched with methanol, there were no ligand or catalyst attachment sites on the polymer. This necessitated a polymer functionalization step. Suitable benzylic bromide groups were introduced onto this polymer by light-promoted bromination. Polymers with loadings of <15 mol% $-CH_2Br$ were prepared and phosphinated with diadamantylphosphine. This latter reaction produced the polystyryl-



(41)

diadamantylphosphonium salt **99** – a product that usefully precipitated from the xylene reaction mixture and which can be stored in air without any problem due to oxidation. Adding this salt to a toluene solution of $Pd(PhCN)_2Cl_2$ and a base formed the active Pd catalyst **100** in situ.

In catalytic Pd(0) reactions, this phosphonium salt was treated with a Pd(II) source, base, and substrates to form an active catalyst for Sonogashira, Suzuki, and Heck coupling chemistry (Eq. 42, Eq. 43, Eq. 44). The reactions used 0.5 mol% of the Pd catalyst, >99.9% of which was recovered based on Pd analysis of the filtrate of a nanofiltration using UV-visible and total reflection X-ray fluorescence analysis. The spectroscopic analyses reportedly could detect as little as 0.05% of the 0.01 mmol of starting Pd catalyst in the leachate. The membrane used in this chemistry was a solvent-resistant nanofiltration membrane consisting of a porous poly(acrylonitrile) layer and a dense surface layer of poly(dimethylsiloxane). This membrane worked through nine cycles in the



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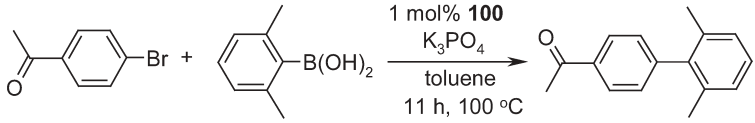
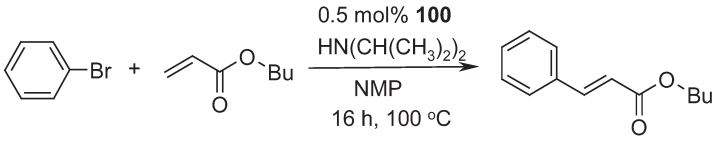


(43)



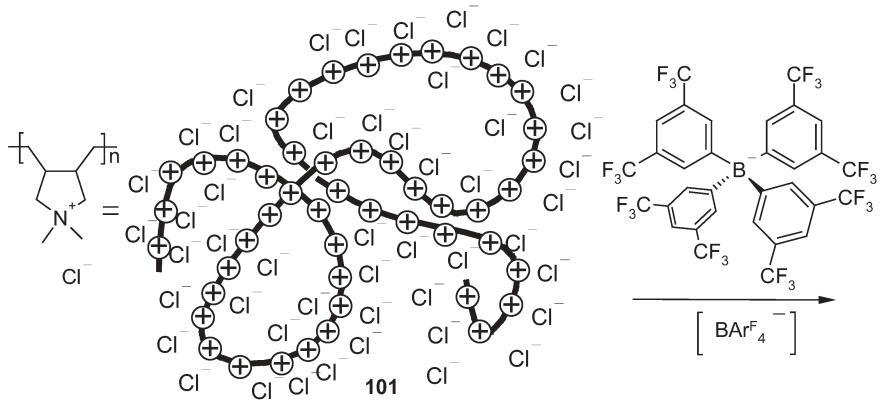
(44)

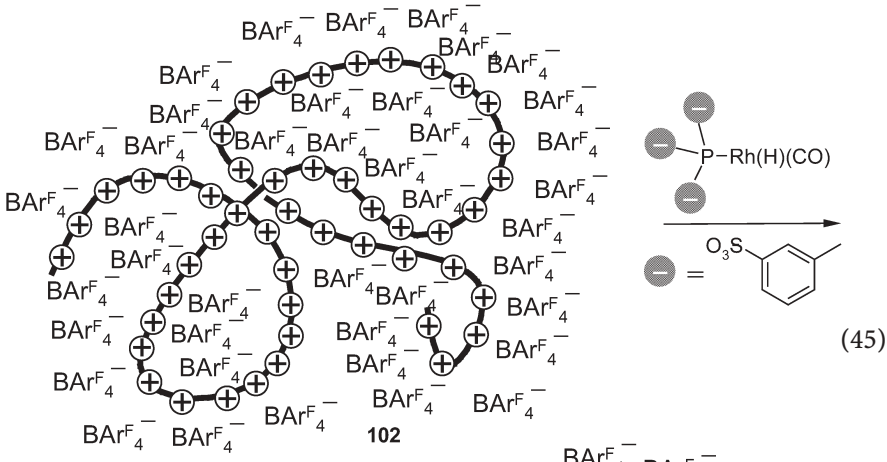
Sonogashira and Suzuki couplings that were effected in toluene, though the conversions in these reactions dropped from near quantitative values into the low 80% range after four to six cycles. The Heck reaction required more polar solvents like DMA. In these solvents the membrane degraded – a problem that could be alleviated only if the reaction mixture was diluted with a large amount of cyclohexane. The conversions in the Heck reaction also notably decreased after only a few cycles.

Ionic assembly of catalysts into macromolecular assemblies has also been successfully used to prepare Rh catalysts for hydroformylation [139]. This approach combined the known functionality of the low molecular weight sulfonated phosphine Rh complex with an ionic polymer – poly(diallyldimethylammonium chloride) (PDADMAC) (**101**). To prepare an enlarged active hydroformylation catalyst, the more reactive chloride anions of this polyelectrolyte were replaced with tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BAr^F_4) anions to produce the species **102** (Eq. 45). Exchange of some of the BAr^F_4 anions of the PDADMA-BAr^F_4 polyelectrolyte with the sulfonated phosphine-ligated Rh(I) complex produced a soluble catalyst **103**. Atomic-absorption spectroscopy showed 98% of the rhodium catalyst was recovered using a commercial polyethersulfone membrane with a 50-kDa molecular weight cutoff. The catalysts used in these cases were prepared from PDADMAC polymer with a M_w of 3×10^5 Da that had first been purified by membrane filtration (to remove ca. 5% of lower molecular weight polyelectrolyte).

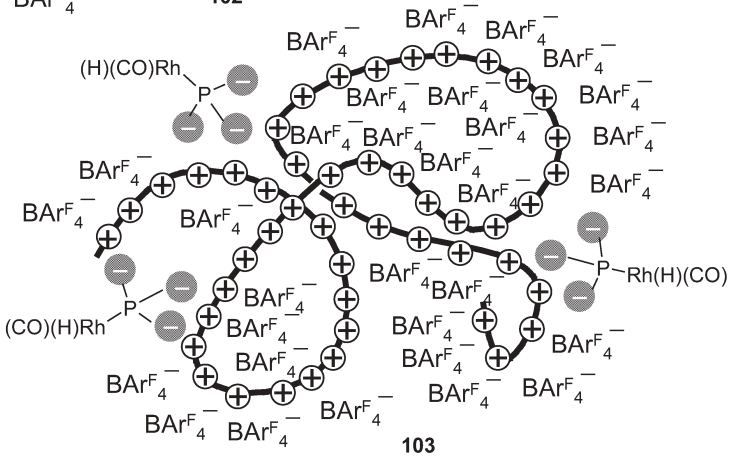
The idea of enlarging catalysts through formation of a linear polymer-immobilized species like **100** or a more complex assembly like the polyelectrolyte **103** can be extended to even larger species. Oehme has recently described the use of chiral hydrogenation catalysts that are part of polymer-surfactant complexes [140]. Several different polymeric surfactants were examined (**104–107**, Fig. 8). Some were naturally derived (e.g., sorbitan) and nonracemic. Others (e.g., the PNIPAM-based surfactant **107**) would have been racemic. There was no clear effect of the surfactant on the stereochemistry of the reaction. Enantioselectivities in the hydrogenation of (*Z*)-α-acetamidocinnamate (Eq. 46) were generally in the 75–90% e.e. range. Depending on the surfactant and membrane used there were practical issues that affect the practicality of the process. Typical problems included long filtration times and gradual fouling of the membrane – general issues for any filtration process. As was true in Plenio's work, it is clear that the nature of the materials used – the surfactant and membrane structure in this case – affects the permeability rates and reactivity of the catalyst. Such factors would be important in any industrially useful process.

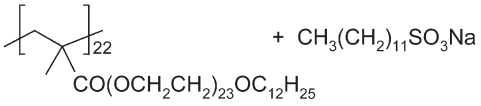
Bolm has used ring-opening metathesis to prepare a chiral catalyst library to evaluate proline-like ligands for Et_2Zn additions to aldehydes [141]. In the polymer below, the R* groups used were derived from hydroxyproline and were tested as chiral catalysts for the addition of Et_2Zn to aldehydes. In this example, shown in Eq. 47, the product macromolecular ligand **109** had a solubility that could be tuned by using mixtures of monomers, varying the R groups of the achiral monomer. Purification of the polymer was not explicitly


n
Cl
101
F3C
CF3
B
[BArF4]


BArF4
102
P–Rh(H)(CO)
O3S

(45)


(H)(CO)Rh
(CO)(H)Rh
P–Rh(H)(CO)
BArF4
103



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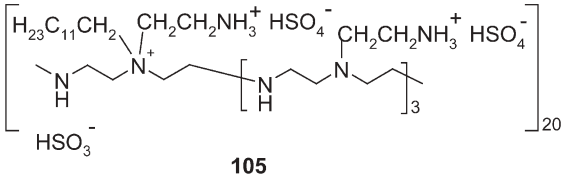

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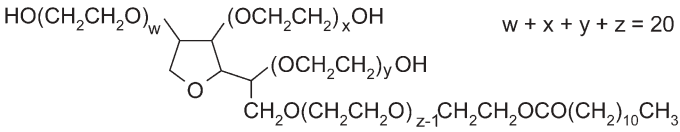

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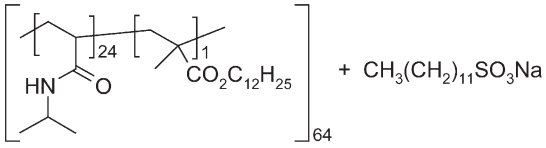
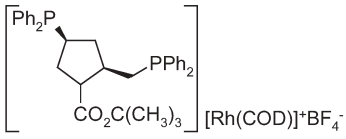
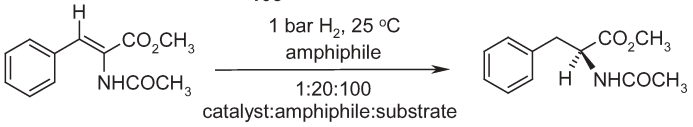


107

Fig. 8 Polymeric amphiphiles and polymericamphiphile complexes **104–107** that can be used to immobilize the cationic a symmetric hydrogenation catalyst **108** in a membrane reactor



108



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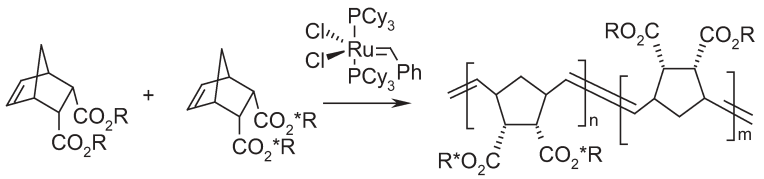


(47)

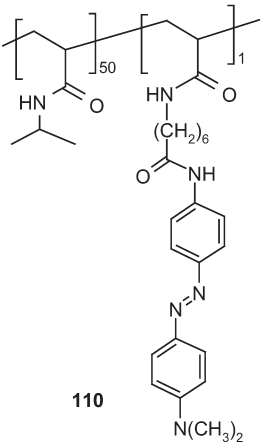
109

described as Bolm's focus was on preparation of a small library of catalysts to optimize enantioselectivity. However, it was noted that membrane filtration was a possible purification tool. Such a separation might be especially feasible with catalysts on these sorts of polymers since the ROMP polymerization can be tailored to control molecular weight and polydispersity, and can accommodate copolymers that can be designed both to facilitate catalysis and separation.

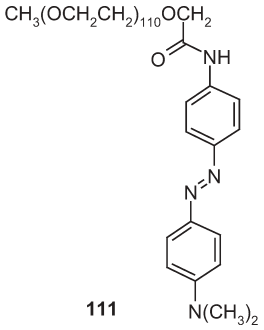
4.2 Thermomorphic Systems

The separation of catalysts and products in a liquid/liquid biphasic system is a scheme that has the advantage of demonstrated practicality. Aqueous biphasic catalysis is used in hydroformylation and biphasic separations are important parts of several other commercialized processes [86, 142, 143]. Recent reports using low molecular weight catalysts in aqueous biphasic systems, in fluorous systems, and in ionic liquids are indicative of the growing interest in this general area – chemistry that has been summarized in a number of recent reviews [8, 144–150].

Soluble polymers can be used in a variety of ways in liquid/liquid systems. An approach originally developed in our group concerned polar polymers in liquid/liquid systems whose miscibility changes with temperature. The first of these so-called thermomorphic liquid/liquid systems studied used polar polymers like poly(*N*-isopropylacrylamide) (PNIPAM) or poly(ethylene oxide) (PEO) [151]. Experiments using the dye-labeled PNIPAM (**110**) or PEO (**111**) where the dye served as a surrogate for a catalytic species, showed that these polymers had excellent (>500:1) phase-selective solubility in the polar phase of an equivolume thermomorphic mixture of heptane and 90% aqueous ethanol.

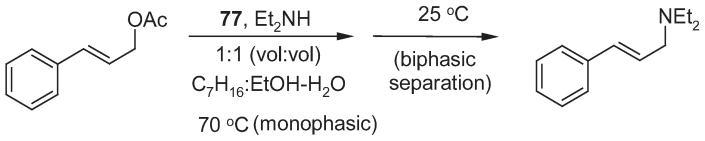


110



111

Since polymers like **110** or **111** are phase-selectively soluble in the polar phase of a polar/nonpolar biphasic mixture cold and still soluble when the solvent mixture is heated to miscibility, polymers like **77** or **81** can be used as recoverable, recyclable allylic substitution, Heck, or hydrogenation catalysts in Eq. 48, Eq. 49, or 50, respectively.



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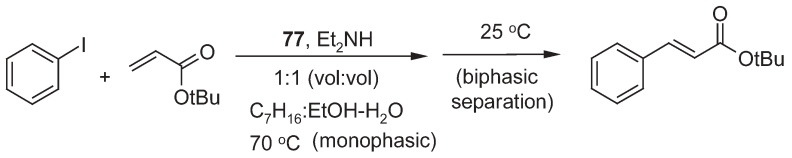

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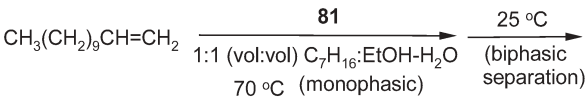
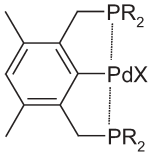


(50)

The change in activity of these catalysts with temperature and their recyclability is illustrated by the data for hydrogenation rates of 1-octadecene by **81** shown in Fig. 9. As shown in this figure, the rates of hydrogenation of 1-octadecene (Eq. 50) in each cycle at 70 °C with fresh batches of alkene substrate were the same. This shows that the catalyst **81** can be completely recovered in the ethanol-rich phase on cooling. After separating the heptane phase containing the product from the catalyst phase, the same rate was seen when fresh substrate in heptane was added and the solvent mixture reheated to miscibility. No hydrogenation occurred at 22 °C in the biphasic mixture.

While phosphine-ligated catalysts like **77** and **81** are effective in thermomorphic systems, the oxidation of phosphine ligands in the presence of transition metal compounds and especially in the presence of Pd(0) poses experimental and practical problems in recycling catalysts in batch reactions. Such issues can be handled with more rigorous inert atmosphere equipment. Alternatively, more stable catalysts can be used. In the case of Heck and Suzuki chemistry, very stable pincer-type catalysts are available. These include phosphine-ligated species like **112** and thioether-ligated species like **113** [152–154].



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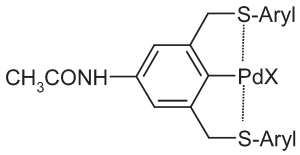

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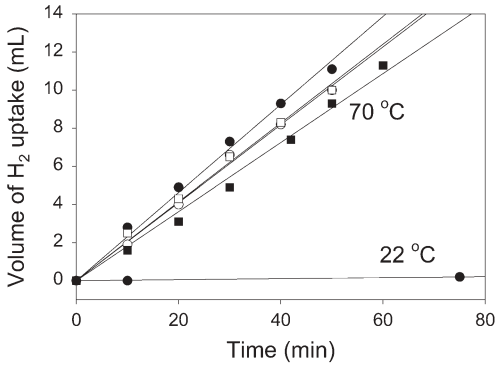
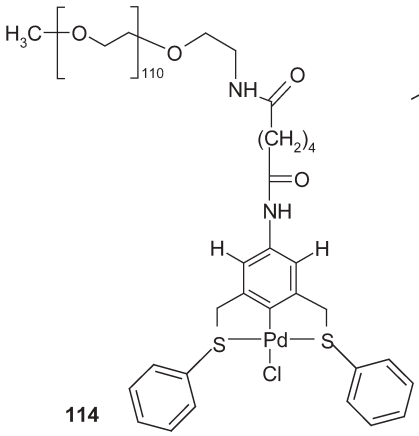


Fig. 9 Kinetic data for hydrogenation of 1-octadecene by catalyst **81** showing both theactivity of recycled material and the inactivity of the catalyst when the reaction mixture was biphasic; the rate of hydrogen uptake in various cycles for **81** reacting with 1-octadecene in variouscycles (cycle 1, *filled circle*; cycle 2, *empty circle*; cycle 3, *filled square*; cycle 4, *emptysquare*). In each cycle, catalyst **81** was separated by cooling a miscible hot solution of EtOH-H_2O and heptane, separating the ethanol/water and heptane phases after cooling, and then adding fresh heptane/1-octadecene to the original ethanol/water phase and reheating to miscibility (70 °C) to begin another cycle. A separate plot shows the inactivity of the catalyst in the immiscible biphasic system at 22 °C

Polymer-supported versions of the latter sort of SCS-Pd(II) catalysts (**114** and **115**) have been used with both PEG and PNIPAM supports in reactions like the Heck coupling of iodoarenes to alkenes (Eq. 51) and in Suzuki biaryl syntheses (Eq. 52) [155].

While recovery of a polymer-bound catalyst like **115** in a thermomorphic system is quantitative based on the absence of detectable Pd in the nonpolar phase, product yields can often be lowered in the first few cycles. This is illustrated by the data in Table 1 for Heck and Suzuki reactions like Eqs. 51 and 52



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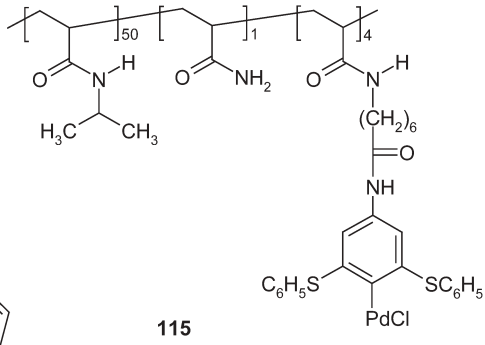
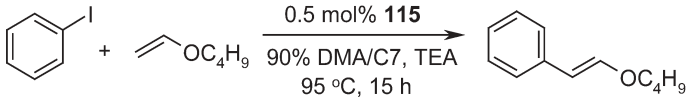


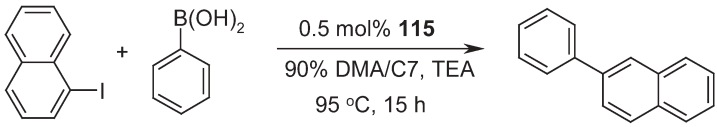
115

Table 1 Applications of Catalysts on Soluble Supports. Isolated yields of products from Heck and Suzuki couplings using various iodoarenes and various alkene and arylboronic acid substrates under thermomorphic conditions with the SCS-Pd(II) catalyst **115**

Iodoarene	Acceptor	Cycle 1 (%)	Cycle 2 (%)	Cycle 3 (%)	Cycle 4 (%)
Iodobenzene	*tert*-Butyl acrylate	71	89	99	99
Iodobenzene	Butyl vinyl ether	43	91	95	99
4-Iodotoluene	*tert*-Butyl acrylate	82	90	99	
1-Iodonaphthalene	*tert*-Butyl acrylate	64	99	99	
Iodobenzene	Phenylboronic acid	32	55	70	77
4-Iodotoluene	Phenylboronic acid	43	60	72	90
1-Iodonaphthalene	Phenylboronic acid	56	70	99	99



(51)

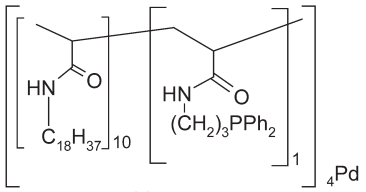


(52)

carried out with the SCS-Pd(II) catalyst **115**. These lower yields in early cycles in these liquid/liquid thermomorphic systems are a general phenomenon seen in other biphasic systems [156, 157]. These lower yields are not due to incomplete conversion of substrates, but are rather due to the partitioning of a portion of the product into both phases during the first few cycles. In the examples here, this involves some partitioning of the relatively nonpolar product into the polar phase. If, as is the case in Table 1, the product yields only reflect isolated product yields from the nonpolar phase, this loss of product makes the yield appear to be low. However, since the same catalyst phase is used in multiple cycles, the catalyst phase eventually is saturated with products. Thus, the yields in later cycles in Table 1 are near quantitative.

A problem with using thermomorphic systems whose catalysts reside in the polar phase in room-temperature biphasic mixtures of nonpolar and polar solvents is that a nonpolar solvent like heptane is not a good solvent for most polar organic products. Thus, the low yields seen in early cycles in the above chemistry can be even more problematic with compounds more polar than those listed in Table 1 when polar polymers are used in polar thermomorphic systems. Moreover, many of these reactions produce salt by-products and salts that accumulate in the polar phase. Such salt accumulation will eventually frustrate the miscibilization of solvents that facilitates a thermomorphic process. To avoid these problems, other nonpolar polymer supports have been developed.

The modifications that are necessary to change the phase-selective solubility of a poly(*N*-alkylacrylamide)-bound catalyst can be quite subtle [158]. Changing the alkyl group of such polymers from an *N*-pentyl to an *N*-octyl group changes the phase-selective solubility of a poly(*N*-alkylacrylamide) by a factor of $>10^5$ in a heptane/aqueous ethanol thermomorphic mixture. Thus, the use of lipophilic *N*-octadecyl groups in poly(*N*-octadecylacrylamide) (PNODAM) is more than sufficient to achieve a >10,000:1 phase-selective solubility for a PNODAM-bound catalyst in the heptane-rich phase of the resting biphasic state of a heptane/DMF or heptane/aqueous ethanol mixture. When such PNODAM polymers were prepared with an SCS-Pd(II) catalyst (**116**) (Eq. 53) or with a phosphine ligand (**117**) (Eq. 54) and a Rh(I) or Pd(0) catalyst (**118** and **119**, respectively), these lipophilic catalysts can be used through multiple cycles in Heck, Suzuki, hydrogenation, and allylic substitution chemistry (Eqs. 55–57) [151]. In such cases, reactions are carried out at elevated temperature (70 °C) and the separation and recovery of the catalysts are effected at 25 °C where the reaction mixture is biphasic and where the catalyst resides exclusively in the heptane-rich phase.



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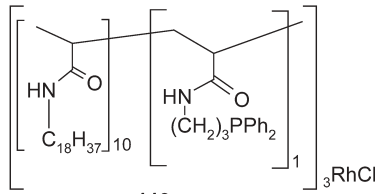

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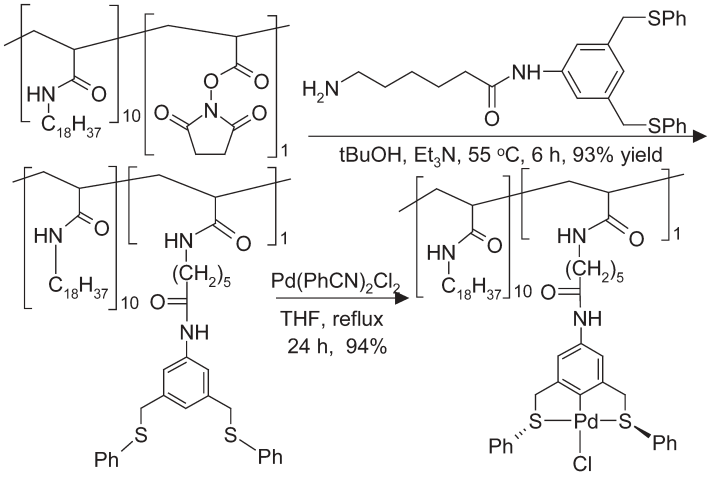

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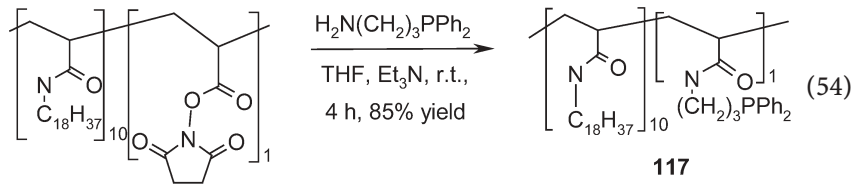

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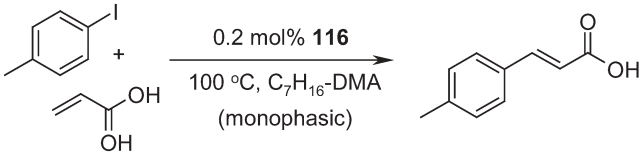

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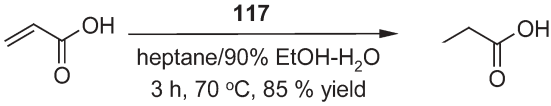

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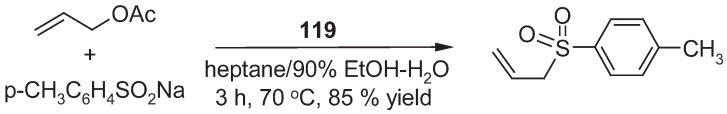
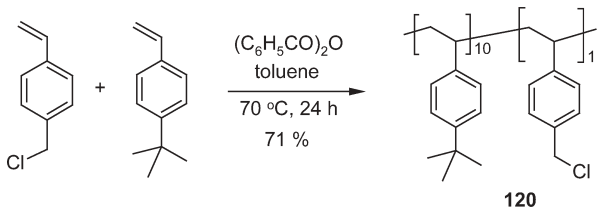


(57)

Linear polystyrene has been used to support catalysts, substrates, and reagents and is a nonpolar polymer that can also be phase-selectively separated into a nonpolar toluene phase in a toluene/aqueous ethanol mixture [5, 159, 160]. However, it is most commonly recovered by solvent precipitation.

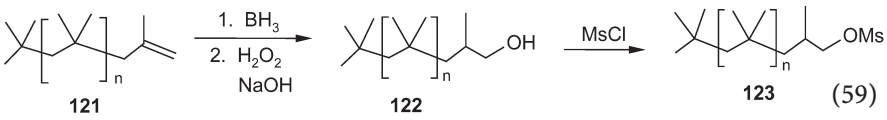
Poly(4-*tert*-butylstyrene) is an alternative to polystyrene that can be prepared by radical polymerization of a commercial monomer. While poly(4-*tert*-butylstyrene) (PtBS) has received limited attention as a component in block copolymers [64], PtBS homopolymers have not generally been used as supports, presumably because they offer no advantages in separation if separation involves solvent precipitation chemistry. PtBS' heptane solubility does make it useful in liquid/liquid biphasic separations. PtBS and other alkylated polystyrenes are otherwise similar to polystyrene and such heptane solubility under biphasic separation conditions is a general strategy for separation and recovery of species bound to these polystyrene-like polymers. A version of this polymer support suitable for catalyst immobilization (**120**) can be prepared by radical copolymerization with chloromethylstyrene as a comonomer (Eq. 58). This alkylated polystyrene is highly phase-selectively soluble in heptane when another polar phase like DMF or 90% aqueous ethanol is present, but is soluble in miscible mixtures of heptane with these polar solvents at 70 °C.

Terminally functionalized polyisobutylene (PIB) is commercially available with alkene terminal groups and is another soluble polymer that can be readily recovered using thermomorphic conditions [161]. The terminal alkene

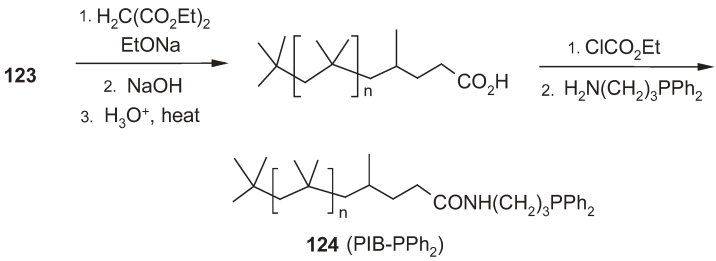


120 (58)

groups of this polymer can be modified using conventional organic syntheses (Eq. 59 and Eq. 60). As an M_n 1,000 or 2,000 species, it is much like poly(ethylene glycol) in that it can be characterized very readily by solution-state ^{1}H NMR spectroscopy. This is very useful as it means that one can readily follow the synthetic steps leading to ligands or catalysts. Solution-state NMR spectroscopy is generally useful with soluble polymer supports. However, with supports containing pendant groups, there is often considerable line broadening and there are interfering peaks due to the underlying polymer. PIB though, like poly(ethylene glycol), has a very simple ^{1}H NMR spectrum. Moreover, since most of the functionality of interest has a chemical shift >2.0 δ, and since terminally functionalized polymers have solution-state spectra with excellent resolution, ^{1}H NMR spectroscopy is particularly useful (cf. Fig. 10).



121 122 123 (59)



124 (PIB-PPh_2) (60)

Terminally functionalized PIB oligomers have been used in a thermomorphic heptane/*N*,*N*-dimethylacetamide mixture as supports for thermally stable SCS-Pd(II) Heck catalyst precursors. A PIB-supported SCS-Pd(II) Heck catalyst was prepared from the carboxyl-terminated PIB oligomer by the sequence of reactions shown in Eq. 61. The PIB-bound SCS-Pd(II) species **125** so ormed was then used to carry out Heck chemistry (Eq. 62). As was true for SCS-Pd(II) species on other polymers [154, 155, 162], this catalyst was only effective for aryl iodides or activated aryl bromides. However, the catalyst could be used through

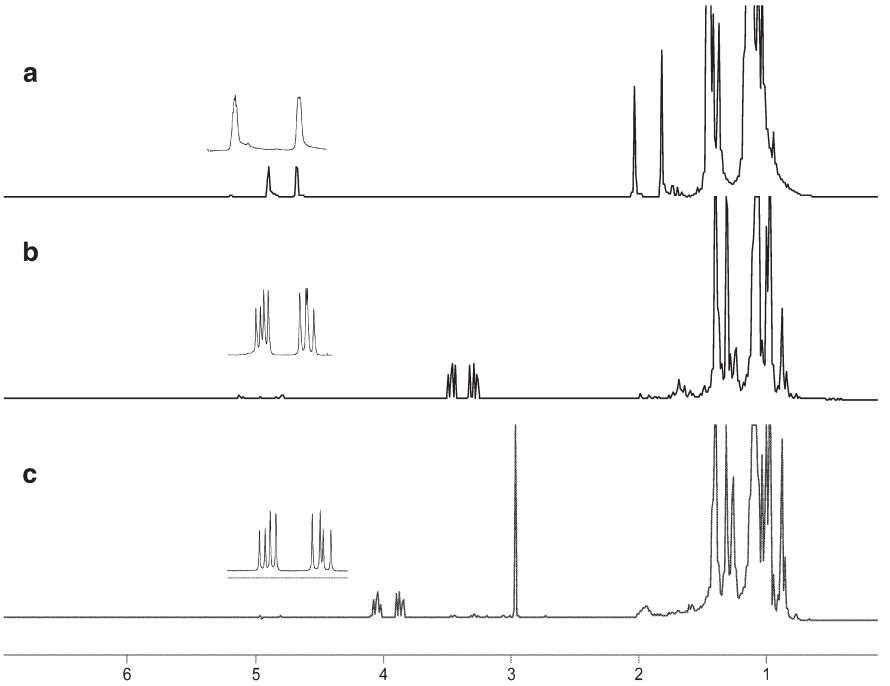
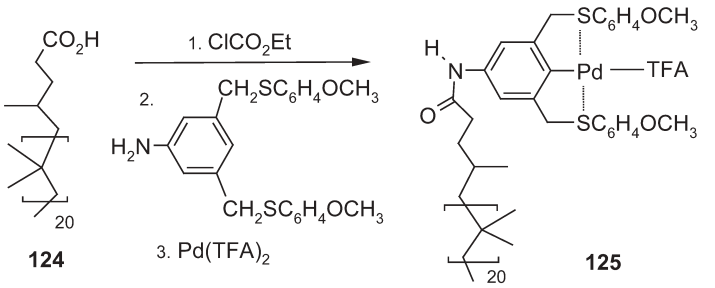


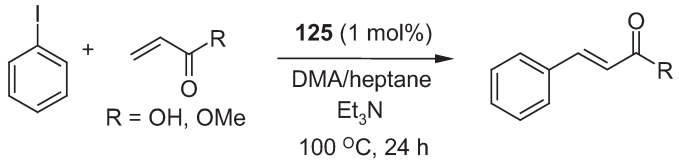
Fig. 10a–c ^{1}H NMR spectra of polyisobutylene oligomers: **a** avinyl-terminated oligomer (**121**) with two diastereotopic, resolved vinyl Hs; **b** a hydroxyl-terminated oligomer (**122**) with the terminal diastereotopic –C$\underline{H}_2$OH group resolved as a doublet of doublets; and **c** theme sylate-terminated oligomer (**123**) showing both the resolved and coupled terminal –C$\underline{H}_2$OSO$_2$CH$_3$ protons and the –CH$_3$ singlet of the –CH$_2$OSO$_2$C$\underline{H}_3$. The expansions overlaid on these spectra cover 0.4 δ in each case



(61)

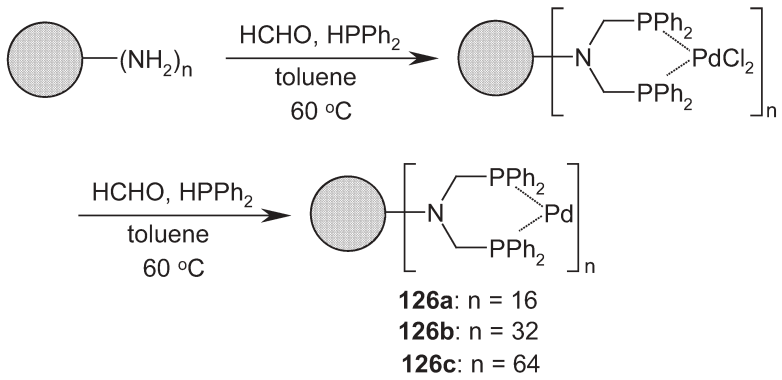
three cycles without any detectable loss of activity by cooling a reaction mixture to room temperature and separating the heptane-rich phase containing the PIB-bound catalyst from the polar phase containing the product. The products were isolated from the polar phase, purified by chromatography, and identified by ^{1}H and ^{13}C NMR spectroscopy. Recycling simply involved adding fresh sub-

strate(s) solution to the recovered heptane phase and reheating. In this way, iodobenzene was coupled to both acrylic acid and methyl acrylate to yield cinnamic acid and methyl cinnamate, respectively.



(62)

Dendrimers too can be used in thermomorphic systems. In a report describing dendrimer-bound Pd(0) catalysis [163], Kaneda compared the liquid/liquid thermomorphic separation scheme with more established membrane and solvent precipitation procedures. Starting with commercially available third-, fourth-, and fifth-generation poly(propylene imine) dendrimers, the primary amine groups at the periphery were converted into chelating phosphines. The resulting phosphines were in turn allowed to react with $Cl_2Pd(PhCN)_2$ to form Pd(II) complexes that were reduced by hydrazine in the presence of triphenylphosphine to form the Pd(0) catalyst **126** (Eq. 63). This catalyst was successfully used in the allylic amination shown in Eq. 64. In this example, solvent precipitation, membrane filtration, and thermomorphic liquid/liquid separation were all used to recycle **126**. The latter procedure proved to be simplest with the best recovery of active catalyst.



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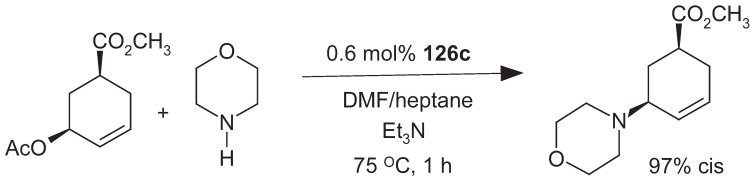
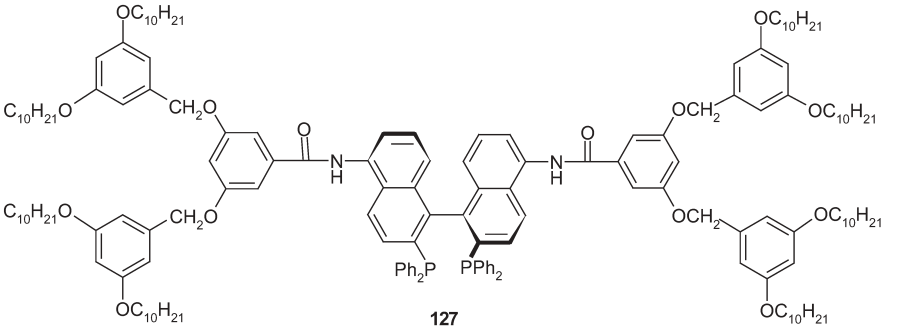


(64)

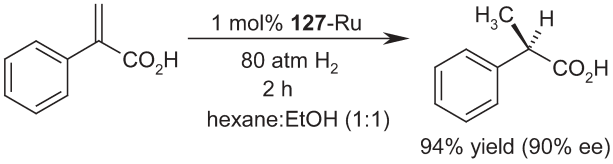
4.3
Latent Biphasic Systems

A latent biphasic system is a miscible solvent mixture that will become biphasic by the addition of a small amount of an additive. For example, a mixture of 10 mL of heptane, 9.2 mL of ethanol, and 0.8 mL of water would be miscible near room temperature. However, addition of a small amount (200 µL) of water or the addition of some salt would make this mixture biphasic. Such solvent mixtures that are at the cusp of immiscibility are useful as homogeneous media for catalysis and, after perturbation, as biphasic systems for separation. If a soluble polymer-immobilized catalyst is present that is by design phase-selectively soluble in one or the other phases of the biphasic mixture, it is possible to design recoverable reusable homogeneous catalysts with such latent biphasic systems.



127

The first reported example using macromolecule-supported catalysts in latent biphasic systems was work by Chan's group that employed a dendrimer-bound BINAP **127** that was used to form a chiral ruthenium hydrogenation catalyst [164]. The dendritic Ru-BINAP complex formed from the reaction of $[RuCl_2(benzene)_2]_2$ and **127** was successfully used in four cycles in the hydrogenation of 2-phenylacrylic acid (Eq. 65) in a 1:1 (vol/vol) ethanol/hexane mixture. Addition of 2.5 vol% water to this mixture produced a biphasic mixture where >99% of the dendritic catalyst was in the hexane phase. Addition of a fresh ethanolic substrate solution to this hexane phase produced another miscible solution of catalyst and substrate. The second and subsequent cycles of hydrogenation carried out in this manner led to consistent conversions of substrate with synthetic yields of >91% with e.e. values of 90%.



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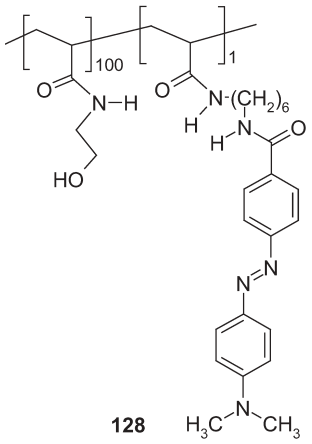
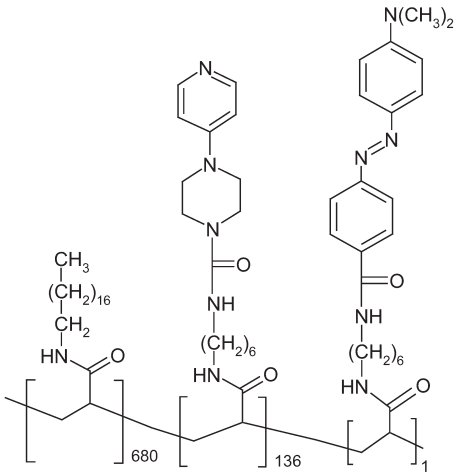


128

Our work on latent biphasic systems has focused on linear polymers [165]. Initially these studies focused on poly(*N*-alkylacrylamide)s like PNODAM because we had earlier shown that these lipophilic materials are very phase-selectively soluble in heptane [158, 165]. This initial work used the PNODAM-bound SCS-Pd catalyst **116** in a DMA–heptane mixture with iodobenzene and acrylic acid as substrates and triethylamine as a base. This catalyst mixture was initially homogeneous at 25 °C. On heating, Heck chemistry occurred to form cinnamic acid. Subsequent cooling of this reaction mixture formed a biphasic mixture even without addition of water because the reaction had formed some triethyl ammonium iodide, and this ammonium salt functioned as the perturbant.

While nonpolar poly(*N*-alkylacrylamide)s would be most suitable for catalyst isolation in a latent biphasic system comprised of polar/nonpolar solvents, polar polymers can be designed that quantitatively separate into the most polar phase of a polar/polar biphasic solvent mixture. Specifically, while both the dye-labeled poly(*N*-hydroxyethylacrylamide) **128** (PNHEAM) and PNIPAM **110** both dissolve in a 5:3:2 (vol:vol:vol) mixture of *tert*-butyl methyl ether (TBME), ethanol, and water, these polymers that contain dyes as surrogates for immobilized catalysts end up in different phases after 10 vol% of water is added to perturb this solvent mixture. The PNIPAM **110** ends up in the less polar TBME-rich phase after water perturbation of this latently biphasic mixture. In contrast, the more polar PNHEAM **128** ends up in the more polar water-rich phase.

A second example of latent biphasic catalysis used the polymer-bound trifunctional base catalyst **129** as a dimethylaminopyridine analog in acylation of 2,6-dialkylphenols by $(Boc)_2O$ in a 1:1 heptane–ethanol solvent mixture. After acylation of the phenol was complete, the addition of 10 vol% H_2O perturbed the system. The yields of product carbonate from Eq. 66 were 35, 66, 89, 99%, 99, and 99% through the first six cycles.



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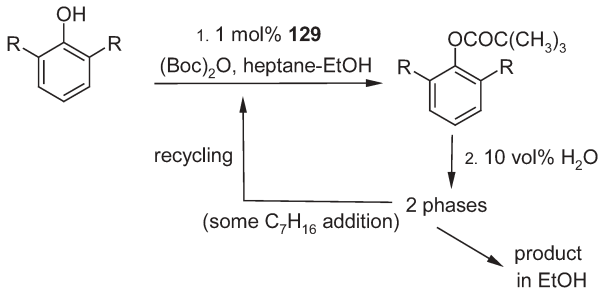
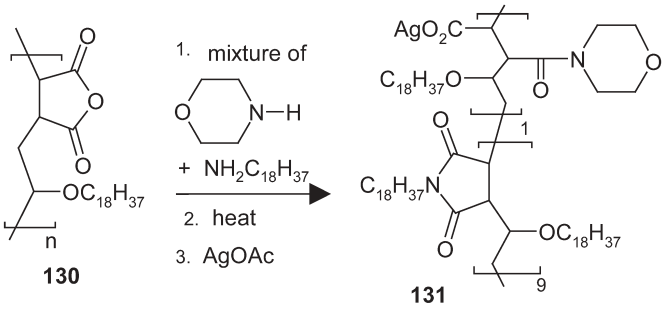


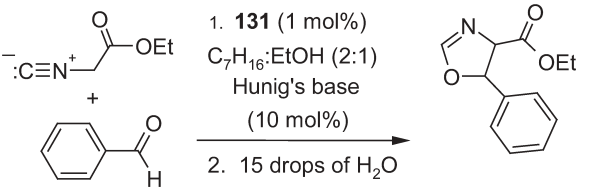
(66)

Any phase-selectively soluble polymer support should work in this latent biphasic strategy. A third example of a polymer that does this is the nonpolar polymeric Lewis acid catalyst **131**. This polymer was prepared from a copolymer **130** formed from octadecyl vinyl ether and maleic anhydride. Post-polymerization amidation of the anhydride groups of this copolymer with a 1:1 mixture of octadecylamine and morpholine followed by imidization produced this terpolymer that contained *N*-octadecylmaleimide and octadecylvinyl ether repeating units with a ca. 10% loading of $-CO_2H$ groups. Exchange of some of the protons of these remaining carboxylic acid groups with silver acetate produced the heptane-soluble polymeric Lewis acid **131** (Eq. 67).

This Ag(I) polymer **131** was found to be effective in catalyzing oxazoline formation from ethyl isocyanoacetate and benzaldehyde (Eq. 68) under latent biphasic conditions. Recycling **131** proved to be possible and involved addition of fresh EtOH, heptane, and fresh reagents to the recovered catalyst-containing heptane phase. Analysis of the polar phase showed <0.11% loss of Ag(I) per cycle – a loss that was attributed to anionic contaminants.



130 **131** (67)



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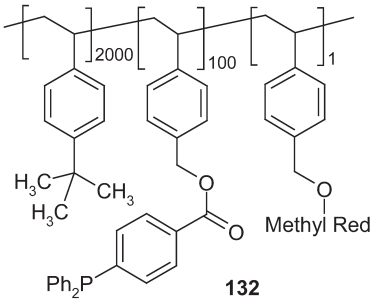
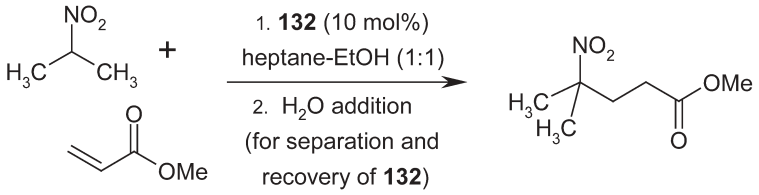


132

Poly(4-*tert*-butylstyrene) copolymers containing nucleophilic catalysts or ligands can be prepared by modification of **120** and are also useful in latent biphasic catalysis [166]. For example, a triarylphosphine can be attached to a PtBS (**132**) support and can be used to catalyze the Michael addition of 2-nitropropane to methyl acrylate (Eq. 69).

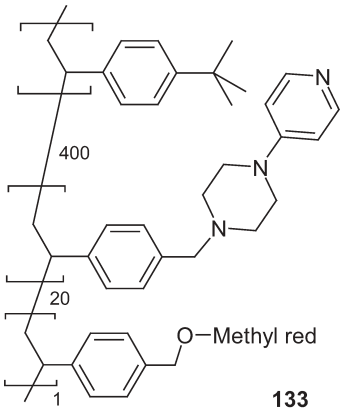
In this nucleophilic Michael reaction, the supported catalyst **132** was first dissolved in heptane. Then an equal volume of an ethanol solution of the substrates was added. The resultant reaction occurred in a homogeneous mixture



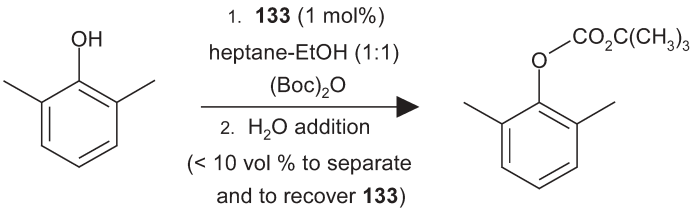
(69)

of ethanol and heptane. Unlike the thermomorphic systems discussed above, elevated temperature was not required to achieve miscibility since no water was present. After 24 h at 25 °C, a small amount (<10 vol%) of water was added to induce phase separation. The product was isolated from the ethanol phase. All the PtBS-bound catalyst was in the nonpolar heptane-rich phase, an observation that correlated with a simple visual inspection of color of the two phases of this latent biphasic system when the soluble PtBS support was labeled with a dye. Isolated yields of Michael addition product through the first five cycles were 31.5, 56.7, 69.0, 72.5, and 71.1%. The increase in yield with increasing cycle number is due to partitioning of some product into heptane in the early cycles, a phenomenon seen in other biphasic systems [166].

A second nucleophilic catalyst supported by PtBS is the polymer-bound dimethylaminopyridine analog that was also used in latent biphasic catalysis with the poly(*N*-alkylacrylamide) support **129** [131]. This example of a nucleophilic catalyst (**133**) was used to catalyze formation of a t-Boc derivative of 2,6-dimethylphenol (Eq. 70). In this case, the extent of recovery of the catalyst and the yields of product were directly comparable to those seen with thermomorphic systems. The isolated yield for the first five cycles of this reaction were 34.3, 60.9, 82.2, 94.6, and 99%. In this case we reused catalyst **133** through 20 cycles. Yields after the first few cycles were essentially quantitative (ca. 93% average for each of 20 cycles). Separation of the polymer from the aqueous ethanol phase was quantitative as judged by either visual observation or UV-visible spectroscopic analysis.

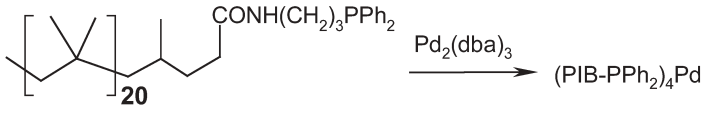


133



(70)

Terminally functionalized polyisobutylene oligomers are yet another example of a nonpolymer support useful in latent biphasic systems. In this example, the phosphine-functionalized polyisobutylene oligomer **125** was used to prepare a Pd(0) catalyst by simple exchange with Pd_2dba_3 (Eq. 71). This Pd(0) catalyst was not isolated but was prepared in situ as a species that was soluble in an equivolume mixture of heptane and ethanol. This polyisobutylene-bound Pd(0) catalyst was phase-selectively soluble in only the heptane phase after this mixture of solvents was perturbed by addition of water. This catalyst was successfully used in two reactions – allylic substitutions of allyl acetates by secondary amines (Eq. 72) and in Sonogashira couplings of iodobenzene and alkynes (Eq. 73). These catalysts could be used through three cycles without any detectable loss of activity by cooling a reaction mixture to room temperature and separating the heptane-rich phase containing the catalyst from the polar phase containing the product.



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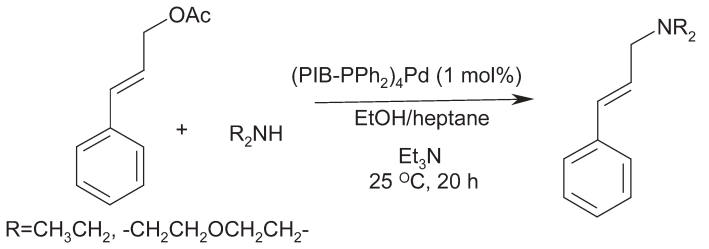

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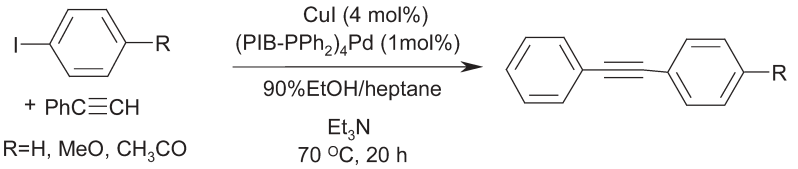


(73)

4.4 Always Biphasic Liquid/liquid Systems

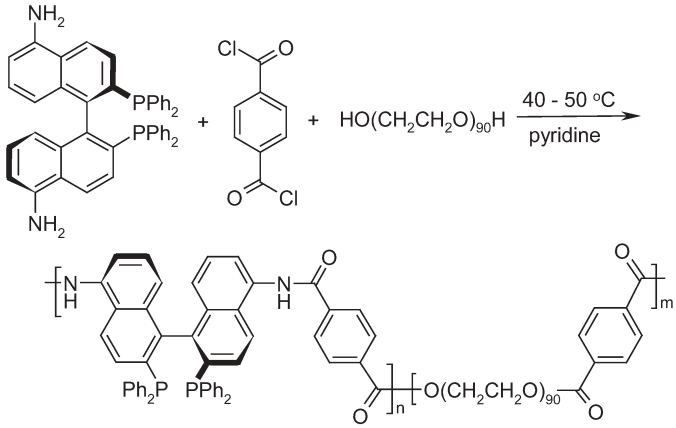
While mixed solvent systems that change from biphasic to monophasic and back again or that change from monophasic to biphasic at the end of the reaction to facilitate catalyst/product separation are newer and potentially interesting, liquid/liquid systems that are biphasic always are the only systems that have demonstrated commercial utility. Aqueous biphasic systems are the best

example of this and several recent reviews have included examples of both low molecular weight and polymeric catalysts [149, 167]. Fluorous biphasic and ionic liquid systems represent other examples of these systems – examples that have in the past few years generated increasing attention [145–148, 150, 168]. In these latter cases, fluorous or ionic ligands or catalysts are necessary to enforce phase segregation.

Polymers are a general alternative to low molecular weight ligands in always biphasic liquid/liquid systems. Just as the nonpolar or polar polymers above imparted phase-selective solubility to catalysts in thermomorphic systems, the appropriate polymer can impart aqueous or fluorous phase-selective solubility to a catalyst. Several recent examples illustrate this for aqueous, fluorous, and other biphasic catalysts.

Water-soluble polymers prepared from a hydrophilic polyester have been shown to be highly effective water-soluble polymer-supported catalysts for aqueous biphasic hydrogenations [169]. The necessary amphiphilic polyester **134** with a BINAP ligand in the main polymer chain was prepared according to Eq. 74 using terephthaloyl chloride, dihydroxy-PEG_{4000}, and a diaminated BINAP ligand. The resulting chiral polymeric phosphine was then used to form a Ru(BINAP)-type complex by reaction with $[Ru(cymene)Cl_2]_2$; this complex formed in situ and was used to hydrogenate the naproxen precursor shown in Eq. 75. The activity of this complex in naproxen synthesis in this biphasic system was higher than in pure ethyl acetate or in miscible methanol–water mixtures. This in situ formed catalyst was also more active than a low molecular weight Ru(4-NaO_3S-BINAP) catalyst in a similar asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)acrylic acid.

Fluorous biphasic systems typically require that the catalyst contain a fluorinated ligand to enforce fluorous-phase solubility on the catalyst. While such Teflon "ponytails" are most commonly perfluorinated alkyl groups, several groups have shown that fluorinated polymers are equally suitable fluorous-



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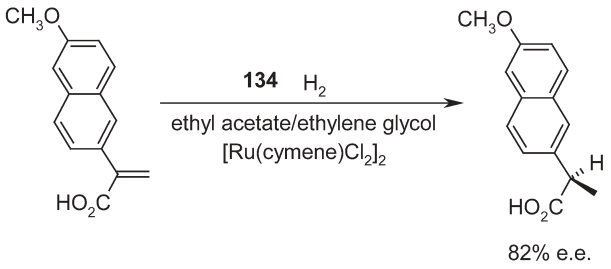


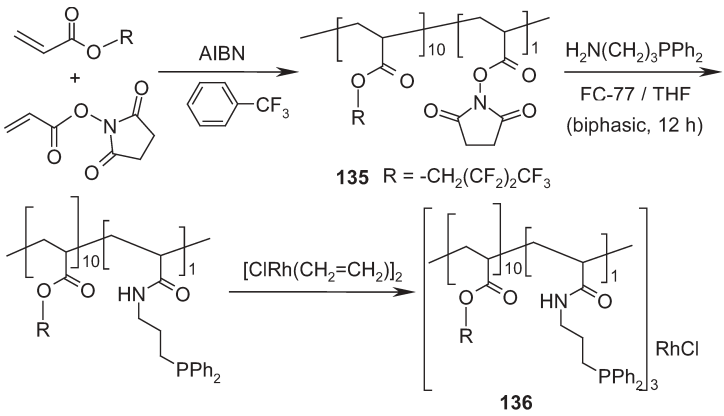
(75)

phase handles. Early work by our group showed that fluorinated polyacrylates such as **135** and their phosphinated derivatives **136** dissolve exclusively in a perfluorinated phase of a fluorous biphasic mixture [170]. Such fluorous-phase solubility is best achieved with pentadecafluorooctyl acrylates. Less fluorinated poly(heptafluorobutyl acrylate) was not as phase selectively soluble [171].

The Bergbreiter group was also the first to show that fluorinated acrylates were suitable as supports for fluorous ligands and catalysts [172]. Using the sequence of reactions shown in Eq. 76, a fluorinated polyacrylate Rh(I) hydrogenation catalyst **136** was prepared. The catalyst so formed had 0.013 mmol of Rh/g and three equivalents of phosphine/Rh.

The Rh(I) hydrogenation catalyst **136** had TOFs for 1-octene hydrogenation of 203 mmol of H_2/mmol of Rh/h, 78 mmol of H_2/mmol of Rh/h for cyclohexene, and 65 mmol of H_2/mmol of Rh/h for bicyclo[2.2.1]hept-2-ene. While this catalyst's hydrogenation activity was not exceptional, it was very recyclable. Using a Paar apparatus and simply decanting the organic phase away from the denser fluorous phase, the catalyst **136** was used successively in a series of hydrogenations of various substrates. Little or no cross contamination of products from one reaction to the next was seen. The overall TON for seven such cycles was 21,700 mmol of alkene hydrogenated/mmol of Rh.

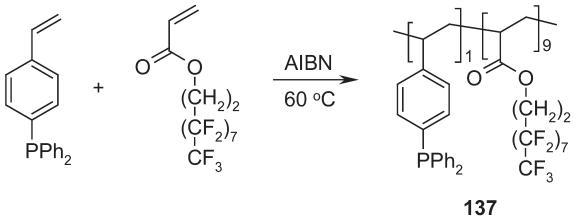
Fluoracrylate polymer-bound catalysts similar to **136** have also been used by the Akgerman and Fackler groups in supercritical CO_2 [173–175]. These cata-



(76)

lysts were prepared using a procedure like that in Eq. 76 that was developed by Frels [176].

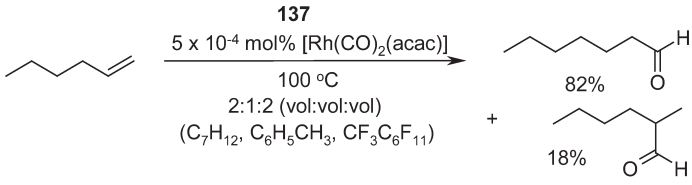
While the hydrogenation catalyst **136** was only used under biphasic conditions in a fluorous/organic mixture, thermomorphic conditions can also be used in fluorous biphasic systems. Indeed, Horvath's original report on fluorous phase catalysis emphasized this with a graphic picture of a fluorinated phthalocyanine dye that was fully biphasic at 25 °C and present as a single dark blue phase at 40 °C [177]. Nonetheless, while thermomorphic behavior was noted in Horvath's original report, most fluorous phase chemistry has used conditions that mimic aqueous biphasic catalysis with reactions that occur under two-phase conditions. An exception to that is work by Xiao [178], in which a copolymer of 4-diphenylphosphinostyrene and heptadecafluorononyl acrylate was prepared by radical polymerization in benzotrifluoride (Eq. 77). When $[Rh(CO)_2(acac)]$ was added to a mixture of this fluorinated phosphine-containing polymer **137**, hexane, toluene, and perfluoromethylcyclohexane, a Rh(I)



(77)

137

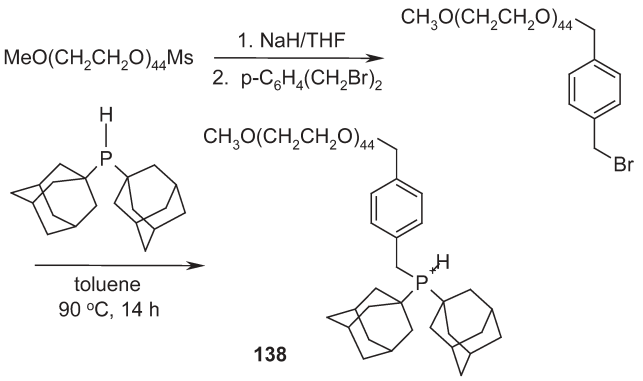
phosphine complex formed. Heating this biphasic mixture to 50 °C produced a miscible solution that separated on recooling. These thermomorphic conditions, obtained only if hexane were present, were used in the catalyst synthesis and in hydroformylations. In hydroformylations (e.g., Eq. 78), the catalyst formed in situ from $[Rh(CO)_2(acac)]$ and **137** was quite active. With a ratio of 1-hexene/Rh of 200,000/1, the in situ formed catalyst at 50 bar syngas afforded hydroformylation product with a 98% selectivity for aldehyde and a TON of 140,000. These catalysts were also recyclable, though leaching of the perfluoromethylcyclohexane into the organic phase did lead to some loss of Rh. Indeed, by the end of three runs, all the perfluorinated solvent had been lost.



(78)

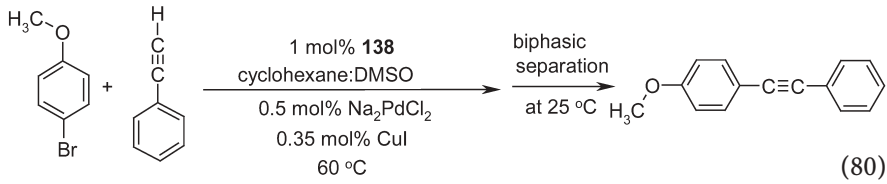
The Plenio group recently described the advantages of using simple PEG supports with sterically demanding phosphines in biphasic and thermomorphic systems. In their work, the best ligand was the diadamantylbenzylphosphine **138** (Eq. 79). They chose to use a 2,000-Da polymer because ^1H NMR

spectroscopic studies showed leaching of this size PEG into heptane from a polar solution (CH_3CN, DMSO) was negligible. This phosphine was used in situ to form a Pd(0) complex using $HN(CH(CH_3)_2)_2$ as a base and Na_2PdCl_4 as the Pd source. A variety of solvents were studied. In coupling reactions of alkynes like phenylacetylene, trimethylsilylacetylene, and 1-octyne with relatively unreactive aryl bromides like 4-bromoanisole or 2-bromotoluene, yields/cycle through five cycles of a coupling reaction like Eq. 80 averaged 90%. The actual reactions take place in partially or fully miscibilized mixtures of solvents (miscibility is, for example, affected by the accumulated presence of by-product salts). However, even partial miscibilization can significantly increase catalyst-substrate accessibility so this may not be a problem and other bases can be used to avoid formation of soluble salts [162, 179]. Retention of Pd in the DMSO phase of these DMSO/heptane mixtures at room temperature was >99.995% based on total reflection X-ray fluorescence.



(79)

Another alternative to PEG in biphasic catalysis is poly(4-methylstyrene). Plenio has described using the phosphinated polymer **99** to prepare a Pd catalyst **100** that is useful in nonpolar biphasic catalysis. Using this polymer good yields of Suzuki coupling products were obtained with aryl bromides and chlorides (cf. Eq. 81) [180]. These Suzuki reactions and Sonogashira couplings, like the Pd chemistry discussed above that used a polar polymer-tagged phosphine **138**, occur readily with 1–1.5 mol% Pd catalyst in cyclohexane–nitromethane or cyclohexane–DMSO mixtures. Yields through five cycles of isolated product typically average about 90% per cycle. Catalyst retention in the nonpolar cyclohexane layer using **100** was found to be >99.8% for these nonpolar biphasic catalysts.



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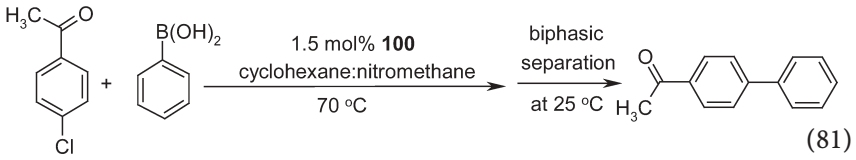
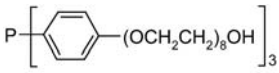


(81)

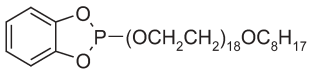
4.5 Thermoregulated Biphasic Catalysis

Thermoregulated biphasic catalysis is a version of biphasic catalysis that combines some of the features of aqueous biphasic catalysis and thermomorphic catalysis. In this scheme, a polymeric ligand like the poly(alkene oxide) ligands **139** is prepared [181–183]. Such ligands have phase-preferential solubility that is temperature dependent because the poly(alkene oxide) support exhibits LCST behavior. Thus, these polymeric ligands and the catalyst supported on them are soluble in polar aqueous phases cold. At higher temperatures, these polymers become less water soluble. In the presence of a second organic phase they transfer into the organic phase. If substrates are present in the organic phase, this increased concentration of catalyst in that phase facilitates catalysis.



139

Thermoregulated biphasic catalysis was first developed by Jin's group in Dalian, China. Their initial work focused on the aqueous/organic two-phase hydroformylation of alkenes using phosphine ligands like **139**. They also used the polyether-resorcinol-derived phosphite ligand like **140** in thermoregulated catalysis [184]. Catalysts formed with this ligand had good reactivity and good regioselectivity in the hydroformylation of styrene, forming ca. 85% branched aldehyde product in yields that were >99%. A recent report by Lemaire's group extended this work [185]. Lemaire's group prepared chiral polyether phosphite ligand **141**, a chiral version of the phosphite **140** prepared by Jin [182, 183, 185].



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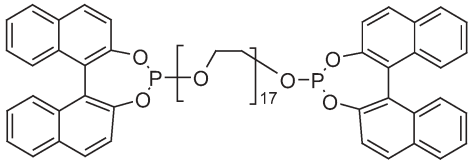

141

In Lemaire's work, BINOL was used in place of resorcinol to prepare chiral bis(diarylalkylphosphite) end groups on poly(ethylene glycol). When this ligand **141** was combined with $[Rh(cod)_2]BF_4$, a catalyst was obtained that exhibited thermoregulated behavior similar to that seen by Jin with other poly(alkene oxide)-bound Rh catalysts. However, while high conversions in hydroformylation were observed, the enantioselectivity for the hydroformylation of styrene by the Rh complex of this phosphite **141** was only modest (ca. 25% e.e.).

Acknowledgement We acknowledge our coworkers who contributed conceptually and practically to the results described in this chapter. We would also like to express our gratitude to the National Science Foundation, the Robert A. Welch Foundation and the Petroleum Research Fund who have funded our work at Texas A&M that has allowed us to explore and expand on the ways polymer can be used to facilitate catalysis.

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Microwave-Assisted Synthesis Involving Immobilized Catalysts

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Abstract The review highlights solid-phase/heterogeneous catalysts, supported, immobilized and/or impregnated on a variety of supports of inorganic and/or organic nature, applied in organic synthesis induced by microwave heating. The application of solid-phase catalysts in combination with microwave irradiation has been described encompassing different chemistries of interest. More importantly, the advantages and limitations of using such catalysts often in comparison with their homogeneous analogues have been discussed. The review also illustrates the diversity of organic transformations achieved by microwave heating.

Keywords Immobilized catalysts · Microwave heating · Organic supports · Inorganic supports

Abbreviations

Ac	Acetyl
Ac_2O	Acetic anhydride
Ar	Aryl
Bn	Benzyl
BSA	*N*,*O*-bis(trimethylsilyl)-acetamide
Cbz	Benzyl carbamate
dba	Dibenzylidene acetone
DMAP	4-(Dimethylamino)pyridine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
dppp	Bis(diphenylphosphino)propane
DMSO	Dimethyl sulphoxide
Et	Ethyl
h	Hour(s)
Hal	Halogen
HTS	High-throughput synthesis
LDH	Layered double hydroxide
Me	Methyl
min	Minute(s)
mol	Mole(s)
MTBE	Methyl *tert*-butyl ether
MW	Microwave
Pr	Propyl
i-Pr	Isopropyl
PS	Polymer-supported
RTIL	Room temperature ionic liquid
TEA	Triethylamine

1 Introduction

Over the past decade the use of microwaves has grown exponentially in chemical synthesis. Microwave conditions are applied in many types of chemical transformations and the area of organic synthesis has benefited significantly from this technique. In 1986, the seminal reports of Gedye [1] and Giguere [2] highlighted the use of domestic microwave ovens in organic synthesis with notable rate enhancements. Ever since, the use of microwaves has developed copiously to achieve many different types of organic synthesis. Several recent contributions [3] give a comprehensive account of the work achieved in this area so far and explain the underlying theory. Microwave conditions have been applied to most types of chemical transformations promoted by heat, largely due to the frequently observed acceleration in reaction rates, reduced reaction times and higher yields. The most rudimentary experiments in microwave-assisted organic synthesis were pioneered using domestic microwave ovens. However, these experiments did not feature a close monitoring of the temperature

and pressure developing in the reaction mixture and often resulted in explosion due to lack of robust reaction vessels and pressure control. Whilst the actual nature of the effect of microwaves remains a subject of intense debate [4], the heating under microwave conditions is explained by the wave–material interaction (dielectric and conduction losses) [5]. This methodology recently found scope in more advanced and sophisticated areas like combinatorial chemistry, medicinal chemistry and high-throughput parallel synthesis [6].

2
Scope and Limitations

The use of supported catalysts is growing rapidly in the area of organic synthesis, and also finds application in solution and solid-phase catalysis under microwave conditions. In this review, we have laid emphasis on giving an account of catalysts specifically immobilized and/or impregnated on an insoluble heterogeneous phase of an organic and/or inorganic nature in combination with microwaves. Any non-functionalized and/or unmodified inorganic supports such as clay, zeolites, silica, alumina and doped reagents, often recognized as acid or base catalysts, have not been included herein. The purpose of the review has been constrained to immobilized catalysts mainly in solution and solvent-free organic synthesis under microwave conditions and excludes discussion of their synthetic and preparative details that are found elsewhere. Use of immobilized catalysts in gas-phase reactions is also recognized; however, this does not become a highlight in our account and therefore only limited examples have been considered. In general, the classification of immobilized catalysts will follow two broad categories, viz. on an inorganic support including silica, alumina, carbon/graphite, glass and clay backbones and on an organic support, mostly based on a styrene–divinylbenzene cross-linked backbone.

3
Inorganic Supports and Immobilized Catalysts

Inorganic supports like silica, alumina, aluminosilicates, zeolites, montmorillonite, clays and carbon/graphite have been particularly useful in immobilizing reagents and/or catalysts [7]. Reagents and/or catalysts immobilized on such supports with generally good thermal and mechanical stability offer better dispersion of active sites and surface adsorption, leading to significant improvement in reactivity and often increased reaction selectivity with potential advantages in laboratory and manufacturing scale synthesis. These surfaces are effective as support material as a result of several factors including surface area, porosity and the crystalline or amorphous nature of the material [7]. The surfaces of most materials considered here are generally irregular with voids, pores and other surface imperfections. Particle size and shape contribute to the surface area of crystals or powders, as does the materials'

porosity (usually defined as surface imperfection). This character in a surface greatly influences its application as a support. The shape and size of a diffusing or dispersing substrate closely matches the support pore diameter. Larger surface areas ranging from ca. 100 m^2g^{-1} for some aluminas and crude clays to close to 1,000 m^2g^{-1} for some activated carbons are generally better suited for applications as supports.

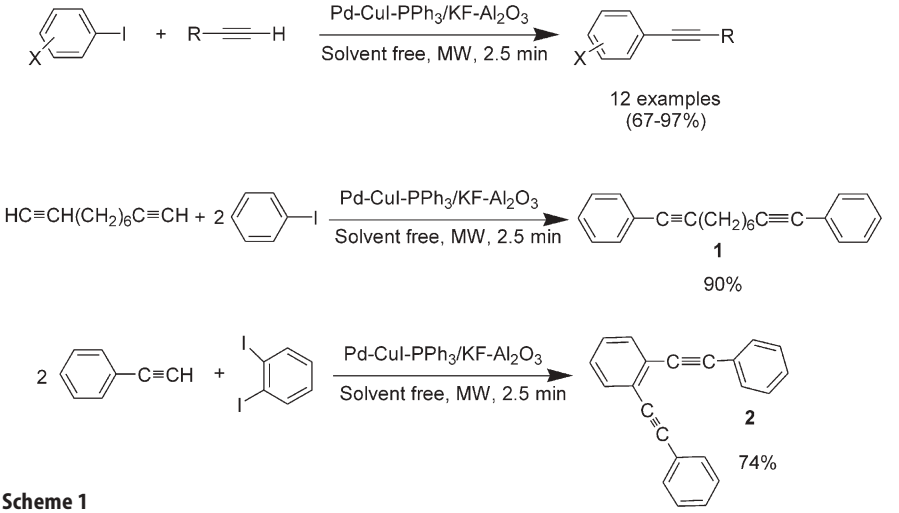
3.1 Catalyst Immobilization on Alumina

Alumina (Al_2O_3) is a particularly useful reagent in organic synthesis because it can be modified in a variety of ways which enhances its reactivity and can be utilized to solve some of the environmental problems associated with organic reagents [8]. Of particular interest is its application as a support for immobilizing catalysts/reagents in organic synthesis typically under solvent-free conditions.

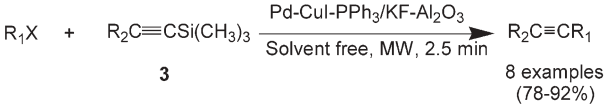
Reactions involving the coupling of terminal alkynes with aryl or alkenyl halides, also termed the Sonogashira coupling [9], are of significant importance in organic synthesis with numerous applications to natural product syntheses and the construction of complex antibiotics [10]. An easy recovery of the rather expensive palladium catalysts dissolved in the solvents during the reaction is always desirable. Microwave-accelerated solvent-free Sonogashira couplings have been studied with palladium powder doped on an alumina/potassium fluoride (KF/Al_2O_3) mixture in the presence of triphenylphosphine (PPh_3) and cuprous iodide (CuI) to provide high yields of the desired aryl alkynes. This solvent-free methodology is environmentally friendly and overcomes the usual problems of recyclability of solvent and catalysts found with soluble palladium reagents in organic solvents. Kabalka et al. have reported coupling reactions between a variety of aryl iodides, heteroaromatic iodides and vinyl iodides with terminal alkynes. In some cases, the bis-Sonogashira coupling products of type **1** and **2** were formed in excellent yields (see Scheme 1) [11]. However, aryl bromides and chlorides failed to show reactions. Studies on the substituent effects suggested that electron-donating groups on the aromatic ring enhanced the reaction and led to the desired product in excellent yields, whereas strong electron-withdrawing groups led to more moderate yields. More importantly, the solid-state catalytic system (Pd-CuI-PPh_3) had appreciable recyclability. The activity was reinstated by addition of potassium fluoride (KF) and triphenylphosphine (PPh_3) after a reaction and showed only minor decreases in reaction yields through seven repetitive cycles.

Couplings have also been afforded using trimethylsilyl derivatives of aryl terminal alkynes of type **3** in one-pot Sonogashira reactions in excellent yields (see Scheme 2) [11].

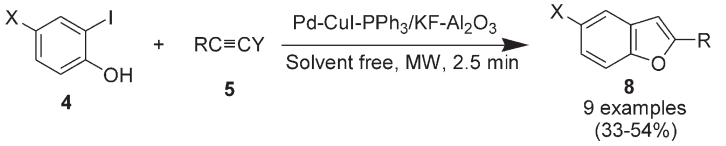
The microwave-assisted solvent-free Sonogashira coupling-cyclization of *o*-iodophenols **4** with terminal alkynes **5** and that of *o*-ethynylphenols **6** with organic iodides **7** to generate 2-substituted benzo[*b*]furans (**8** and **9**) has been



Scheme 1



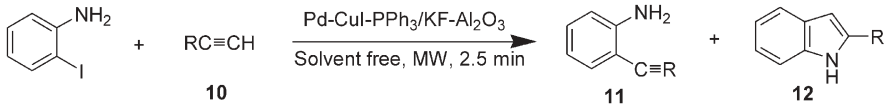
Scheme 2



Scheme 3

studied in the presence of the Pd-CuI-PPh_3 catalytic system doped on KF/Al_2O_3 (see Scheme 3) [11].

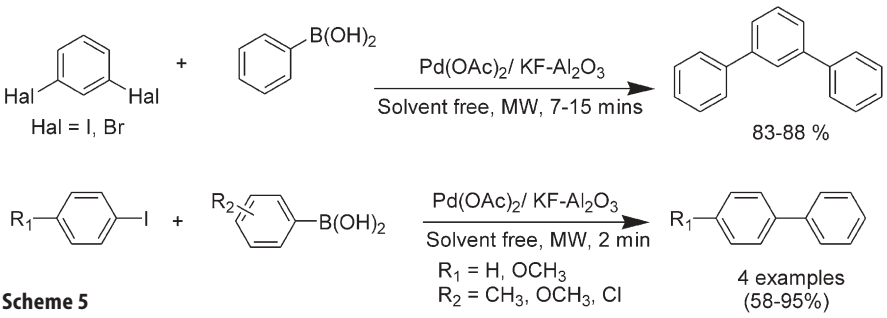
Similar types of coupling cyclizations were investigated in a microwave-assisted solvent-free synthesis of indoles catalysed by Pd-CuI-PPh_3 doped on KF-alumina (see Scheme 4) [11]. The reaction conditions influence the coupling reactions studied, and in the case of a 1:1 ratio of *o*-iodoaniline to alkynes of type



Scheme 4

10, only the desired coupling product **11** was obtained. The cyclized indole product **12**, along with the coupling product **11**, was obtained when the ratio was changed to 2:1. The percentage of indole formation could be improved by introducing additional Pd(II) to the reaction mixture, which paralleled the results obtained in solution. Interestingly, the indole product was generated exclusively when starting from *N*-(*o*-ethynylphenyl)methanesulphonamide.

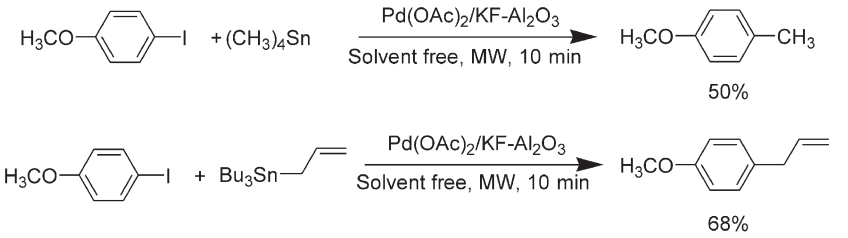
In related work, the synthesis of a range of conjugated polyaryls has been reported using a one-pot microwave-assisted Suzuki coupling utilizing $Pd(OAc)_2$ as catalyst on a KF-alumina surface [12]. The preparation of biaryls with this solvent-free method is superior to most of the classical methods with greater selectivity and generality of the reaction, including higher reaction yields and more rapid reaction times. Polyarylation of polyhaloaromatics with phenylboronic acid has been reported with 53–91% isolated yields in 7–20 min of microwave irradiation. Substrates with iodo and bromo substitutents have been reported to show comparable reactivity (see Scheme 5).



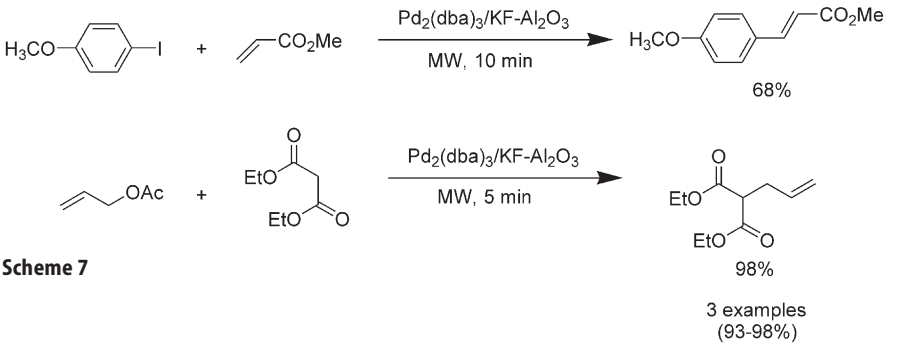
Scheme 5

Solvent-free Suzuki reactions have also been reported under monomode microwave irradiation using $Pd(OAc)_2$ catalyst on the surface of KF-Al_2O_3 (see Scheme 5) [13]. The catalyst had a good dispersion on the solid surface, which was obtained by grinding the Pd catalyst with KF-Al_2O_3. The transformations showed good yields of coupling products adsorbed on the support starting from aromatics and heteroaromatics with best results from iodides over bromides and chlorides.

With a similar catalytic system, microwave-assisted Stille reactions (see Scheme 6) have been studied with good yields [13]. The main advantage in this



Scheme 6

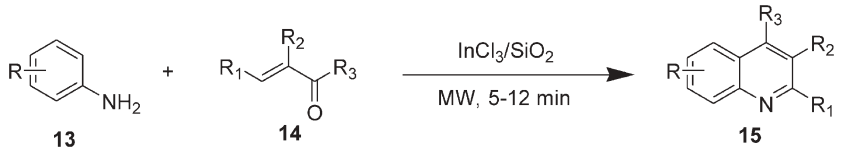


Scheme 7

methodology is that the organotin reagent remains adsorbed on the KF-Al_2O_3 support. Heck and Trost–Tsuji reactions (see Scheme 7) have been studied by dispersing a stable complex of palladium(0), [$Pd_2(dba)_3$], on the surface of KF-Al_2O_3 under solvent-free microwave conditions [13].

3.2
Catalyst Immobilization on Silica

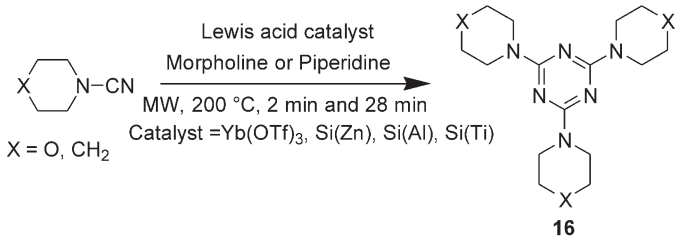
Like alumina, silica surfaces have equally been utilized for immobilization of catalysts/reagents. A microwave-assisted solvent-free synthesis of 4-alkylquinolines of type **15** using anilines **13** and alkyl vinyl ketones **14** has been achieved on the surface of silica gel, where the catalyst indium(III) chloride ($InCl_3$) is impregnated on silica gel (see Scheme 8) [14]. This procedure using $InCl_3$ on the silica gel surface smoothly leads to the initial imine formation which is otherwise sluggish in the presence of $InCl_3$ alone. More importantly, microwave ac-



Scheme 8

tivation is observed to be superior over conventional heating, which shows considerable polymerization of the vinyl ketones and reduced yields of the corresponding quinolines. Overall, the procedure under microwave conditions is claimed to provide operational simplicity, faster reaction, higher yields and a general applicability with a variety of possible substitution patterns.

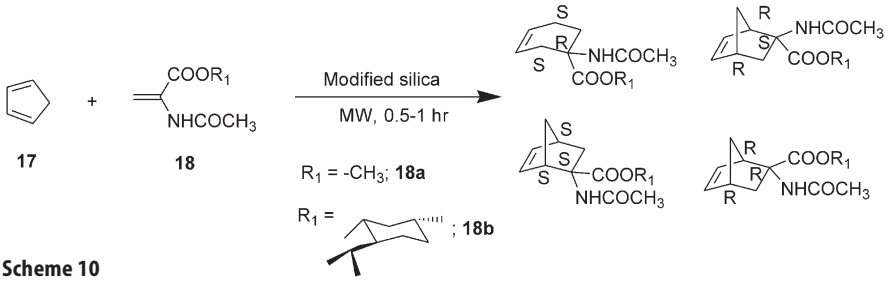
Catalysts such as $ZnCl_2$, $TiCl_4$ and Et_2AlCl supported on silica gel have shown great utility as Lewis acid catalysts. These systems have been applied as a green alternative to the use of lanthanide ions in the solvent-free cyclotrimerization of nitriles to afford 1,3,5-triazines under solvent-free microwave conditions (see Scheme 9). Synthesis of 1,3,5-triazines by cyclotrimerization of nitriles otherwise catalysed by acids, bases or activated magnesium requires harsh conditions and in most cases provided only moderate yields [15]. The utility of such immobilized heterogeneous catalysts is of interest since these can be stored and recovered after reaction without loss of catalytic activity. In general, silica gels modified with Lewis acids, especially with $ZnCl_2$, have been found to be effective and environmentally benign catalysts for the cyclotrimerization of aliphatic and aromatic nitriles to 1,3,5-triazines of type **16** [16]. Reactions under microwave conditions with variable power have favoured the best results in conjunction with short reaction times.



Scheme 9

Some of the catalysts immobilized on a heterogeneous phase also find interesting application in classical C–C bond forming Diels–Alder reactions. The cycloadducts of cyclopentadiene **17** and 2-acetamidoacrylates of type **18** could be easily converted to cycloaliphatic amino acids. Some of these amino acids bearing the norbornane skeleton display interesting biological properties and could also be obtained in enantiomerically pure form through Diels–Alder reaction of cyclopentadiene with chiral 2-acetamidoacrylates [17].

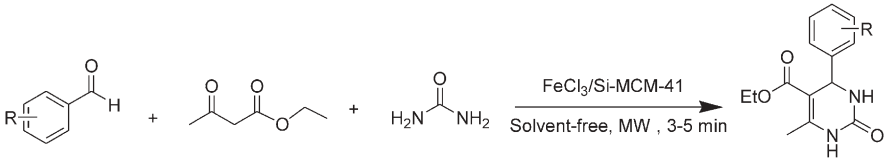
Cativiela et al. [18] reported on the microwave-assisted increased reaction rate and high selectivity in the cycloaddition of normally less reactive methyl and (–)-menthyl 2-acetamidoacrylates **18b** with cyclopentadiene **17** using supported Lewis acid catalysts (see Scheme 10). Microwave activation in this case shortened reaction times (0.5 to 1 h) in dry media conditions otherwise requiring long reaction times (24 h). Silica gel modified by treatment with $AlEt_2Cl$ or $TiCl_4$ catalysed the cycloaddition with best results in terms of retention of



Scheme 10

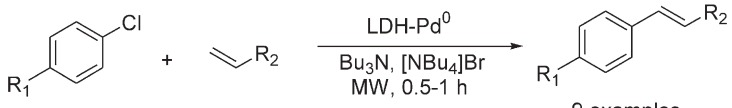
exo/*endo* selectivities found similar to reactions with homogeneous Lewis acids. However, it was noted that the selection of the input power was of great importance and depended on the type of catalyst. Also, silica modified with $AlEt_2Cl$ functioned as a more suitable catalyst over silica modified with $TiCl_4$, which only resulted in the decomposition of the dienophile at all input powers tested. Similarly, silica modified with $AlEt_2Cl$ catalysed the cycloaddition of cyclopentadiene **17** with (–)-menthyl 2-acetamidoacrylate **18b** as the dienophile under microwave activation, giving 92% conversion in 1 h as opposed to the homogeneous $TiCl_4$-catalysed reaction with better conversions only after 3 h and 72% conversion after 22 h using $AlCl_3$ as catalyst.

The microwave-assisted solvent-free preparation of dihydropyrimidinones via the Biginelli reaction has been studied with a Si-MCM-41-supported $FeCl_3$ catalyst and was shown to give better yields than other catalysts like montmorillonite K10 clay-supported $ZnCl_2$, $AlCl_3$, $GaCl_3$, $InCl_3$ and $FeCl_3$ individually (see Scheme 11) [19]. Biginelli synthesis with Si-MCM-41-supported $FeCl_3$ catalyst is of significant practical importance because the catalyst could be easily separated after reaction and reused with no significant leaching of $FeCl_3$. In addition, the catalyst bears a pore size large enough to allow diffusion of large molecules, allowing for short reaction times, particularly in the absence of any solvent. Other catalysts prepared over montmorillonite K10 clay and applied under microwave conditions in the Biginelli reaction gave the corresponding dihydropyrimidinones of type **19** in 65–79% isolated yields. This was still lower than the observed yields for similar reactions and applied conditions (microwave irradiation times ranging from 3 to 5 min) catalysed by $FeCl_3$ supported on Si-MCM-41 after first use (85%), second use (84%) and third use (84%).



Scheme 11

A novel layered double hydroxide (LDH)-supported nanopalladium catalyst (LDH-Pd^0) has been reported to exhibit superior activity in C–C coupling reactions over a range of supported catalysts, from acidic to weakly basic Pd/C, Pd/SiO_2, Pd/Al_2O_3 and resin-$PdCl_4^{2-}$ [20]. Under microwave conditions, this catalytic system exhibits higher activity and selectivity with excellent yields and high turnover frequencies in the Heck olefination of electron-poor and electron-rich chloroarenes in non-aqueous ionic liquids (NAIL) over the homogeneous $PdCl_2$ (see Scheme 12). The olefinations gave excellent yields with >99% *trans*-selectivity leading to *trans*-stilbenes. Under microwave irradiation the Heck olefinations were afforded in 0.5–1 h as opposed to 10–40 h by thermal heating. The reactivity of the chloroarenes in the coupling reaction, in the order of activated electron-poor chloroarenes>non-activated electron-neutral chloroarenes>eactivated electron-rich chloroarenes, correlates to the nucleophilicity of the aromatic ring. This recyclable heterogeneous catalytic system also dispenses with the need to use expensive and air-sensitive basic phosphines for palladium-catalyzed coupling reactions of chloroarenes. The Mg-Al layered double hydroxide support in the catalytic system not only stabilizes the nanopalladium particles but also provides adequate electron density to the anchored Pd^0 species to facilitate the oxidative addition of the deactivated electron-rich chloroarenes. This type of layered double hydroxide-supported nanopalladium catalytic system has also been applied in some Suzuki couplings, Sonogashira couplings and Stille-type couplings under conventional heating [20].



Scheme 12

Silica-based materials have been utilized as supports in slurry reactions under conventional as well as microwave conditions [21]. In this approach, norborn-2-ene surface-functionalized silica has been used to graft *N*,*N*-dipyrid-2-ylnorbor-2-ene-5-ylcarbamide monomer and then generate tentacles of poly-(*N*,*N*-dipyrid-2-ylnorbor-2-ene-5-ylcarbamide) by controlled polymerization (see Fig. 1). The catalyst generated by Pd loading has been used to catalyse microwave-assisted Heck reactions, mainly of iodoarenes with styrene with quantitative conversions. The supports could be easily removed by filtration [21]. More importantly, the use of microwaves in these cases has led to drastic reduction in reaction times, which is of particular interest for high-throughput synthesis (HTS). In these experiments, irrespective of the application, the leaching of Pd into the reaction mixture was only minor (<2.5%). These catalysts have been successfully applied in the coupling of selected aryl iodides and aryl bromides under various conditions including flow-through, cartridges and biphasic catalysis [21].

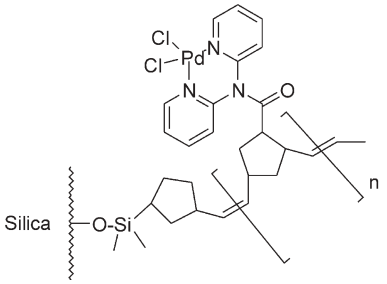
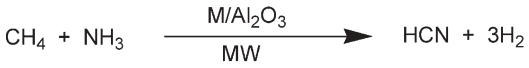


Fig. 1 Silica grafted support

3.3 Supported Catalysts for Gas-Phase Reactions

Heterogeneous gas-phase reactions are very important in industrial processes especially in petrochemicals and related fields. The reactions are generally performed in a continuous system with a fixed catalyst bed (exceptionally a fluidized bed) largely consisting of an inorganic backbone [22]. In these cases, microwave energy proves advantageous to induce catalytic reactions since it can heat the catalysts selectively to a temperature well above the bulk temperature of the reactants. More importantly, in the case of a catalyst bed, microwave energy heats the bed from the interior (*incore heating*) and not from the exterior, as seen in conventional methods. This improves the selectivity of a reaction by lowering the extent of side or consecutive reactions. This often helps retain the reactive products which could otherwise be destroyed/decomposed conventionally. Microwave heating also ascertains a homogeneous heating of the catalytic sites to the desired temperature for a particular chemistry prior to desorption of the reactants from its surface.

The transformation of methane to the higher hydrocarbons or oxygenated products is amongst the most studied catalytic gas-phase reactions and its simplification has been highly desirable. Wan et al. primarily studied catalytic gas-phase reactions induced by microwaves [23]. Pulsed microwave irradiation has been applied to study the reaction of methane in the absence of oxygen using a series of nickel catalysts [24]. Nickel supported on SiO_2 (Ni/SiO_2) produced 93% ethyne, which is better yielding over a standard Ni powder catalyst under similar irradiation conditions. Microwave irradiation has been reported to be comparatively efficient over conventional heating in the partial oxidation of methane to syngas over Ni and Co catalysts [25]. Nickel-based supported catalysts (Ni/ZrO_2, Ni/La_2O_3) showed higher reactivity and selectivity over supported Co catalysts (Co/ZrO_2, Co/La_2O_3). The microwave-induced catalytic conversion of NO to N_2 over Co-ZSM-5 zeolites in the presence of oxygen at 250–400 °C showed 70% conversion against no reaction observed under thermal runs. The activation of methane to form methyl radicals at relatively low reaction temperatures was reasoned for the high activity and selectivity of the reduction of NO by methane under microwave conditions.



M = Pt, Ru

Scheme 13

A pulsed microwave-induced small-scale production of HCN has been reported in the reaction of methane with ammonia (see Scheme 13) [26]. The process uses a series of Pt/Al_2O_3, Ru/Al_2O_3 and carbon-supported catalysts with conversions exceeding 90%.

Reports describe the microwave-assisted endothermic decomposition reaction of H_2S catalyzed by MoS_2 supported on γ-Al_2O_3 with much higher conversions as compared to conventional heating at identical temperatures [27]. A large dielectric loss difference between MoS_2 and γ-Al_2O_3 suggested that the MoS_2 particles may absorb microwave energy at a higher rate than the surrounding γ-Al_2O_3 particles, and that therefore a temperature gradient develops from the reaction surface to the gas phase. The H_2S conversions reported were higher than the theoretical equilibrium H_2S conversion, which was attributed to the higher reaction temperatures at some sites in the catalyst bed often referred to as "hot spots" [28]. More importantly, the conversion of H_2S with a mechanically mixed catalyst (30 wt% MoS_2+70 wt% γ-Al_2O_3) was noted to be higher than that obtained with the impregnated catalyst at the same temperature. Also, there was no significant difference observed in H_2S conversion when using a pre-heated (230 °C) reactant gas compared to the conversion without pre-heating, at bulk catalyst temperatures of either 600 or 700 °C.

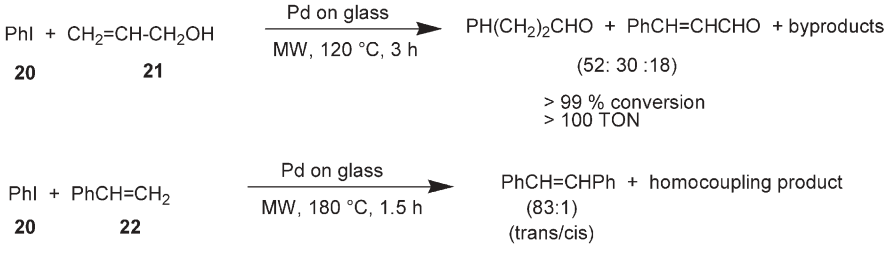
Microwave heating has been applied in the catalytic reforming of methane with carbon dioxide over some supported platinum catalysts [29]. In this case, the microwave conditions have generally shown higher product selectivity (H_2/CO) and conversions as opposed to conventional heating at the same measured temperature. This has once again been largely attributed to the formation of hot spots with higher temperatures than those measured in the bulk catalyst used. Platinum impregnated on CeO_2/γ-Al_2O_3 or La_2O_3/γ-Al_2O_3 has been applied as catalyst in these studies with CeO_2 and La_2O_3 used as promoters. The conversions of CO_2 and CH_4 over the catalyst Pt (8%)/CeO_2 (20%)/γ-Al_2O_3 were observed to increase with temperature. Higher conversions than the calculated equilibrium data were obtained under microwave conditions. The product selectivity in terms of H_2/CO ratio over Pt (8%)/CeO_2 (20%)/γ-Al_2O_3 catalyst increased when the temperature was raised, and typically under microwave conditions this was higher than the equilibrium value in the lower temperature range 450–600 °C. Interestingly, upon increasing the CO_2/CH_4 ratio, greater conversion of CH_4 was observed, however the CO_2 conversion decreased. Under microwave conditions, these were always higher than those obtained with conventional heating. Under microwave conditions, platinum loadings had no effect on CH_4 and CO_2 conversions and the highest conversion and H_2/CO ratio was shown by platinum supported on γ-Al_2O_3. Wan et al. [30] showed that carbon dioxide reacted over a supported metal catalyst in the presence of water

vapour yielding alcohols and other oxygenated species when the catalyst was irradiated with microwaves and the reaction proceeded at relatively low temperatures (220–350 °C). Several other examples in the development of industrial applications of microwave irradiation in catalytic processes have been documented [31].

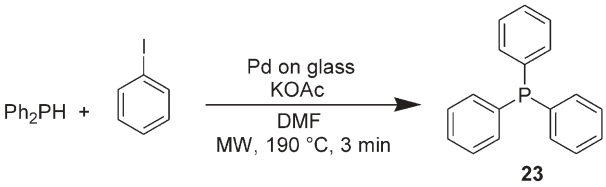
3.4 Catalysts Immobilized on Glass

Solution-phase organic coupling reactions in the presence of palladium catalysts are among the most heavily studied organic transformations [32]. Most of these reactions incorporate the susceptibility of the palladium catalysts to be poisoned, together with the disadvantage of making it necessary to involve relatively large amounts (1–5 mol%) for appreciable conversions. Organopalladium complexes in the form of homogeneous catalysts containing phosphine ligands provide alternatives to overcome these disadvantages; however, their separation and recovery after the reaction becomes difficult. Palladium metal on porous glass tubing as a catalyst has been investigated in reactions conducted continuously or batchwise. Under microwave conditions, in a pressure-tight batch reactor, the Heck coupling of iodobenzene **20** with allyl alcohol **21** and styrene **22** with reduced molar ratio of catalyst (0.02 mol% Pd) gave >99% conversions with regioselectivity [33], which was in agreement with previous findings (see Scheme 14) [34].

Palladium on porous glass also showed quantitative conversions for the coupling of phenylacetylene with iodobenzene and with 4-bromobenzaldehyde, and satisfactory results for coupling of phenylacetylene with 4-bromoacetophenone and 2-bromopyridine [33]. Interestingly, the coupling of 4-bromoacetophenone with phenylacetylene in dimethylacetamide (DMA) with NaOAc as the base and its reaction with hexyne previously failed with phosphapalladocycles, but proceeded when using palladium on porous glass as the catalyst [35]. Stadler et al. [36] reported a Pd-doped microwave process vial wherein Pd deposited on the inner glass surface has been applied as a catalyst in heterogeneous C–P couplings leading to triphenylphospines **23** under mi-



Scheme 14



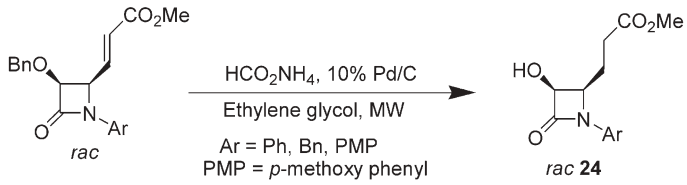
Scheme 15

crowave conditions. The catalytic activity under microwave heating is, however, reported to be somewhat lower (85% yield) than that using Pd on charcoal (98% yield) under identical reaction conditions (190 °C for 3 min). The vials with doped Pd could effectively be reused several times before significant loss of catalytic activity. In addition the necessity of catalyst filtration and additional reaction work up is eliminated (see Scheme 15).

3.5 Catalysts Immobilized on Carbon

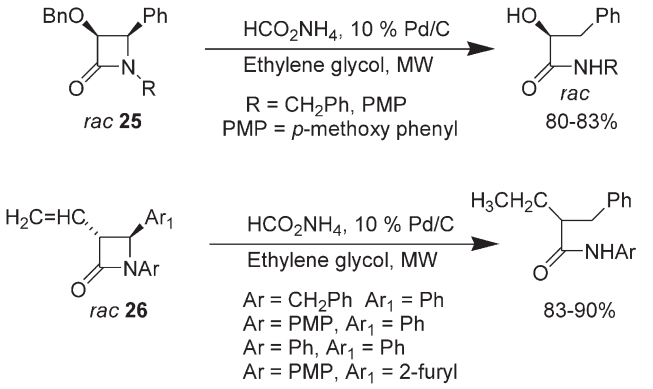
Carbon is inert in nature and bears a high surface area making it highly suitable as a support for catalysts. The surface characteristics and porosity of carbon could be easily tailored for different applications. Acid treatment is often applied to modify the surface chemistry of carbon for specific applications. Typically, active metal species are immobilized on carbon for application in catalysis.

Pd on carbon is a catalyst heavily employed in catalytic transfer hydrogenations. Microwave-assisted open-vessel reduction of double bonds and hydrogenolysis of several functional groups have been studied safely and rapidly using 10% Pd/C catalyst and ammonium formate as the hydrogen donor [37]. Microwave-assisted selective hydrogenolysis of only the *O*-benzyl (Bn) group while retaining the *N*-benzyl group, together with the reduction of the unsaturated ester to give a saturated side chain in a β-lactam (see Scheme 16), has been reported [37]. The authors involve a non-conventional experimental setup in Erlenmeyer flasks or beakers with loose covers under ambient pressure conditions using a high boiling point solvent such as ethylene glycol well below its conventional boiling point (110–130 °C), termed as MORE (microwave-induced



Scheme 16

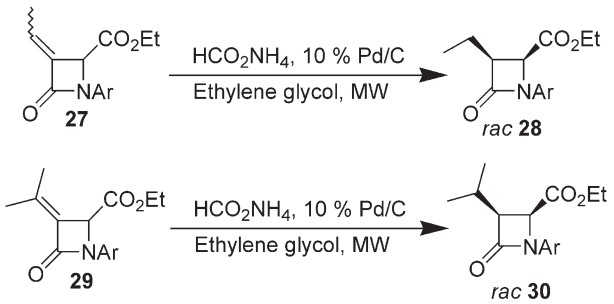
organic reaction enhancement) chemistry techniques. In a stereoselective preparation of β-lactam synthons like **24** using microwave-assisted catalytic transfer hydrogenation (CTH) conditions as above, unsaturation in a sugar moiety was successfully removed without disturbing the β-lactam ring. In addition, microwave-assisted 10% Pd/C-catalyzed transfer hydrogenolysis has been documented involving a rapid scission of 4-phenyl-2-azetidinones such as **25** and **26**. The hydrogenolysis conditions selectively deprotect the *O*-Bn group at C-3 to an OH group and all the alkenes are reduced to corresponding alkyl groups with high yields in a few minutes (see Scheme 17). Microwave-assisted reduction of phenylhydrazone has also been carried using 10% Pd/C in the presence of ammonium formate to give the corresponding amine in 4 min with 92% yield.



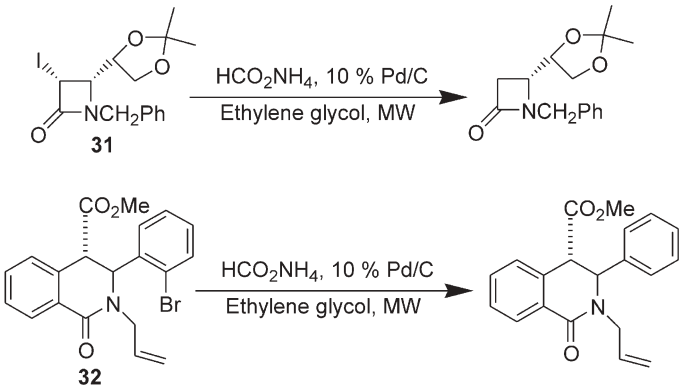
Scheme 17

In studies on carbapenem synthons, a series of monocyclic β-lactams of type **27** and **29** were generated with an exo-alkene group at C-3 [38]. The conjugated double bonds herein could be reduced easily under microwave-assisted CTH conditions with stereospecificity leading to only *cis* β-lactams of type **28** and **30**, which is highly desirable (see Scheme 18).

Pd/C-catalyzed transfer hydrogenations have also been applied for dehalogenation under microwave conditions [37] and the end products and time of



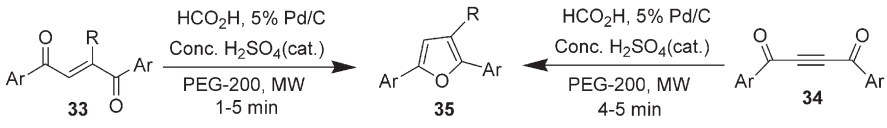
Scheme 18



Scheme 19

completion of the reaction were observed independent of the order of addition of the reactants, in contrast with a previous report [39]. Microwave-assisted dehalogenations on several *β*-lactams such as **31** and isoquinoline derivatives **32** have also been catalyzed by 10% Pd/C by transfer hydrogenation in a few minutes (see Scheme 19). Dehalogenations of 1-bromonaphthalene and 9-bromoanthracene have also been achieved [37].

Microwave-mediated transformations of 2-butene-1,4-diones **33** and 2-butyne-1,4-diones **34** to furan derivatives **35** have been studied [40]. Several di- and triaryl furan derivatives have been prepared in high yields from but-2-ene-1,4-diones/bu-2-yne-1,4-diones using formic acid in the presence of catalytic amounts of Pd on carbon (5%) in poly(ethylene glycol)-200 medium in a one-pot operation under microwave irradiation (1–5 min) (see Scheme 20). Microwave irradiation was applied using a domestic microwave oven, which proved advantageous over the conventional conditions affording high yields of furan derivatives in shorter reaction times (1–5 min). The synthesis activated under microwave conditions incorporates a combined procedure of the reduction of the starting enediones and their subsequent cyclization to the furan derivatives. Formic acid present in the reaction mixture at higher temperature decomposes to hydrogen and carbon dioxide and the hydrogen generated is utilized for metal-mediated hydrogenation of double or triple bonds. It also catalyses the dehydrative cyclization of the 1,4-diketones to the furan derivatives. In the case of furan synthesis from 2-ene-1,4-diones the nature of the sub-



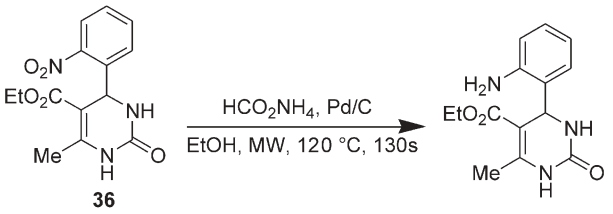
Scheme 20

stituents on the phenyl ring influenced the furan formation. The reductive dehydrative cyclization reaction on diketones bearing electron-withdrawing Cl and Br groups in the C-4 position readily (within 2 min of microwave irradiation) gave the furan derivatives. However, the reaction was sluggish with diketones bearing electron-donating groups like Me and OMe on the phenyl ring, yielding the double bond reduced product together with the furan derivatives. In these cases, the presence of catalytic amounts of concentrated sulphuric acid (5 mol%) in addition to the formic acid and palladium on carbon helped to lead the reaction to completion within 5 min of microwave irradiation furnishing the corresponding furans in excellent yields. It was argued that the reactivity of the hydrogenated diketones towards dehydrative cyclization is influenced by the substituents on the phenyl ring. And a stronger acid catalyst such as concentrated sulphuric acid possibly aided the protonation of the carbonyl oxygen prior to the cyclative dehydration step. A similar behaviour was observed in the case of the conversion of 2-yne-1,4-diones to furan derivatives. The reaction shows the possibility of scale-up and could be easily applied for the preparation of both 2,5-diaryl- and 2,3,5-triphenylfuran derivatives.

The microwave-assisted catalytic transfer hydrogenation of different homo- or heteronuclear organic compounds in room temperature ionic liquids (RTIL) as solvent has also been studied under microwave heating [41]. Based on the exceptionally high thermal stability and immiscibility with organic solvents, the ionic liquid (IL) *N*-butyl-*N*′-methylimidazolium hexafluorophosphate ($[BMIM]^+[PF_6]^-$) has been used as a solvent with 10% Pd/C catalyst in the presence of ammonium formate as the hydrogen donor for transfer hydrogenation of various organic substrates. Reduction of 4-nitrobenzoic acid methyl ester under microwave heating (7 min) gave 92% yield of 4-aminobenzoic acid methyl ester using the ionic liquid as the solvent. Similarly, 10% Pd/C reduction of methyl cinnamate under microwave heating with a final temperature of 150 °C over 70 min and 30 min cooling to 50 °C in ionic liquids gave quantitative yields of the corresponding α, β-saturated methyl cinnamate. Various functional groups (i.e. nitro, alkene, alkyne) have been cleanly reduced in ionic liquids under microwave irradiation [41] and conveniently isolated by simple liquid/liquid extraction with MTBE (methyl *tert*-butyl ether) in high yields and purity. In this study, the recyclability of the solvent/catalyst system has also been demonstrated wherein, after five repetitive catalytic cycles, a 40% loss in the catalytic activity could be observed which could always be reinstated by addition of the corresponding amount of the fresh catalyst.

Pd/C-catalyzed transfer hydrogenation conditions have also been applied in the microwave-assisted (120 °C for 2 min) reduction of a nitro substituent on a Biginelli scaffold **36** (see Scheme 21) [42].

Besson and co-workers have exploited microwave-assisted Pd/C-catalyzed transfer hydrogenation conditions in the multistep synthesis of some important thiazoloquinazolinone derivatives involving the reduction of a nitro substituent in several intermediate steps [43]. Herein, thermal reactions carried out under microwave conditions have greatly favoured in reducing the overall time

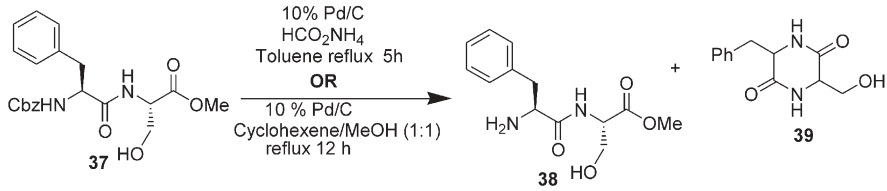


Scheme 21

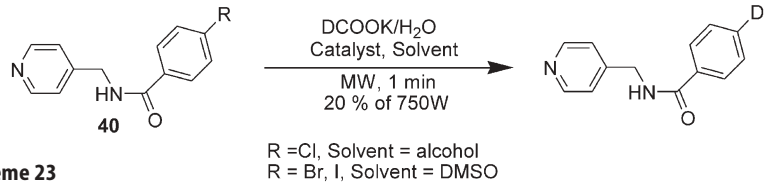
of the multistep synthesis. Microwave-induced catalytic transfer hydrogenation conditions involving Pd/C catalyst are also efficient in deprotection strategies, particularly with benzyl carbamate (Cbz) and benzyl (Bn) protecting groups. Amino groups protected as Cbz or Bn have been easily deprotected in a few minutes by microwave-assisted transfer hydrogenation with Pd/C in *i*-PrOH as the solvent and ammonium formate as the hydrogen donor.

Deprotection of a dipeptide such as **37** has been illustratively achieved following the so-called MORE techniques using Pd/C and ammonium formate in boiling toluene for 5 h or with cyclohexene in boiling MeOH for 12 h. In either case, deprotection was observed together with 20–40% diketopiperazine **38** (see Scheme 22) [44]. The scope of the microwave acceleration was explored with different substrates and the deprotected amine was afforded always in more than 90% yield. Some examples illustrate the selective hydrogenolysis of the Cbz group in the presence of allylic groups occurring together with hydrogenation of the double bond, and in the presence of *N*-Fmoc groups, the Cbz group was selectively removed (1 min irradiation). Also noteworthy was that the microwave-assisted deprotection in some cases was fully compatible with enantiomerically pure amino acids and peptides as no racemization was observed in the amines **38** upon deprotection (see ref. 44 for details).

The Pd/C-catalyzed rapid and specific deuterium labelling by microwave-enhanced dehalogenation of a number of *N*-picolyl-4-halogenbenzamides **40** using deuterated formates as deuterium donor has been studied (see Scheme 23) [45]. The percentage deuterium incorporated was always lower when using alcohol over the aprotic DMSO as the solvent. Both homogeneous [$Pd(OAc)_2$ and $RhCl_3$] and heterogeneous catalysts (Pd/C) were effective catalysts, however the latter showed a tendency of biphenyl by-product formation via palladium-mediated coupling. Typically, complete



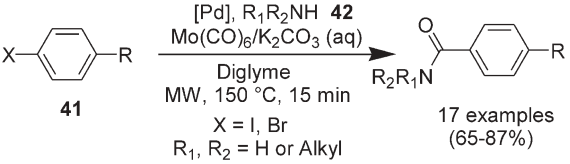
Scheme 22



Scheme 23

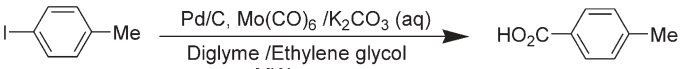
dehalogenation was observed within 1 min of microwave irradiation with chemical yields >90%.

A microwave-assisted fast and convenient route to palladium-catalyzed carbonylation reactions has been reported. The microwave-assisted amidation of aryl halides **41** was achieved utilizing in situ generated carbon monoxide from [$Mo(CO)_6$] (see Scheme 24) [46]. Aliphatic non-hindered primary amines **42** were observed to couple easily whereas hindered amines or amines with low nucleophilicity, e.g. anilines, afforded low yields and incomplete conversions. No difference in reactivity among electron-deficient, neutral or electron-rich aryl halides was found. In general, iodides could be coupled with solid Pd/C (or $Pd(OAc)_2$) as catalyst, while bromides required a homogeneous catalyst. Amidations were studied in a sealed microwave protocol at 150 °C for 15 min, which could also be performed in a classical oil bath without any loss of yield.



Scheme 24

By excluding the amine from the above procedure, a rapid tool for synthesizing the corresponding benzoic acid **43** was devised (see Scheme 25). Addition of ethylene glycol together with diglyme/K_2CO_3 mixture as a co-solvent resulted in competitive formation of the corresponding benzoic acid derivative [46]. The temperature and solvent used were responsible for the reproducibility of the carbonylations. $Mo(CO)_6$ was more suitable as an in situ source of carbon monoxide over $Cr(CO)_6$, which tends to sublime at the reaction temperatures (130–150 °C). A combination of diglyme and 4 M $K_2CO_{3(aq)}$ was the most suitable solvent system for carbonylation reactions and alternative solvents like DME or other non-polar solvents afforded precipitation of the solid molybde-



Scheme 25

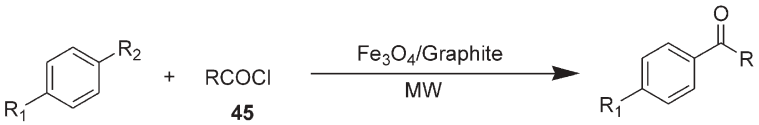
num metal on the glass wall of the reaction vessel, resulting in poor reproducibility due to a thermal breakdown of the Pyrex glass.

3.6 Catalysts on Graphite

Graphite has often been utilized as a support and with metal inclusions as a catalyst. A variety of substances could be intercalated between the carbon layers (GIC – graphite intercalated compounds) or dispersed on the graphite surface and used as reagents and/or as catalysts in numerous reactions [47]. The catalytic ability of graphite is driven by the metal content dispersed in the carbon lattice [48]. Two synthetic graphites (viz. Graphite X and Graphite Y) will be discussed in detail for their application in catalysis experiments. Importantly, graphite X has been analysed to contain more iron (0.41%) and aluminium (0.02%) than in graphite Y (Fe: 0.007%; Al: 0.002%) together with other elements (Ca, K, Si, Ti, V, Mn) at lower concentrations in both cases. Graphites combined with a variety of metals, termed "graphimets", are known for their catalytic activity [47]. The iron-graphite compound in the presence of Fe_3O_4 crystallites efficiently catalyses the acylation of anisole [48]. The iron content (5%) catalysing this reaction was much higher than that found in ordinary graphite X (0.41%). The benzoylation of anisole could not be achieved when using graphite Y alone as a catalyst, however graphite Y doped with Fe_3O_4 progressed but with lower yields.

Also, the graphite-supported acylation of toluene **44** (R_1=CH_3, R_2=H) and naphthalene **44** (R_1=H, R_2=C_4H_4) has been studied under the action of continuous or sequential microwaves (see Scheme 26) [48]. With non-volatile reactants the yields under classical heating and microwave heating were comparable. However, when using acylating agents **45** such as MeCOCl or *i*-PrCOCl and a sublimable reactant like naphthalene; the yield under microwave irradiation was higher.

A higher catalytic activity of graphite X over graphite Y probably depends on the iron (Fe_3O_4) impurity content and possibly also on iron sulphides or sulphates dispersed on the graphite support. It has also been suggested that $FeCl_3$ actually generated in situ by the reaction of the iron compounds with acid chloride and hydrogen chloride catalyses the acylation reaction. This has also been supported by an observation indicating that no acylation occurred in the ab-

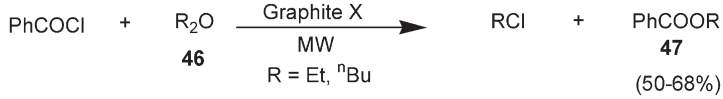


R_1 = CH_3, R_2 = H, R = Ph;
R_1 = OCH_3, R_2 = H, R = Ph, Me, ^{i}Pr
R_1 = H, R_2 = C_4H_4, R = Ph

Scheme 26

sence of a chlorinating agent, i.e. using acid anhydride as the acylating agent and iron oxide as the catalyst. Microwave-induced acylation using acid anhydride was effective only after addition of catalytic amounts of $FeCl_3$. The increased catalytic activity has been attributed to the strong interaction of the dispersed Fe_3O_4 impurity (on graphite) with microwaves and the presence of hot spots in the region of Fe_3O_4 crystallites.

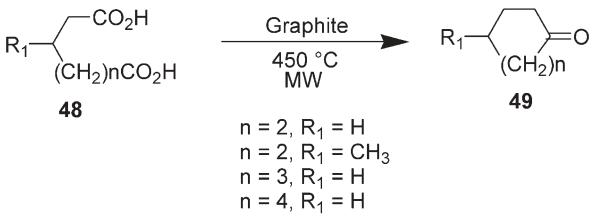
A solvent-free microwave-assisted cleavage of some dialkyl ethers **46** catalyzed by graphite X (Fe_3O_4 on graphite) has been achieved (see Scheme 27) [49]. With irradiation by microwaves up to 80% conversion and 62% isolated yield were obtained in ther case of *n*-butyl benzoate **47** (R=^{n}Bu). Due to the highly volatile nature of diethyl ether, the yield of ethyl benzoate was lower. These results suggested that the cleavage of more reactive ethers like *sec*- or *tert*-alkyl, benzylic or allylic groups could very well be possible in a similar manner. Similar to the earlier observation, it was proposed after a careful mechanistic study that the catalyst of the graphite-assisted acylative cleavage of ether was actually $FeCl_3$ generated in situ from the iron content (Fe_3O_4) dispersed on graphite.



Scheme 27

The catalytic cyclization of diacids **48** is of significant importance for producing cyclic ketones **49** [50]. This, however, also demands a temperature high enough to have a convenient reaction rate, but low enough to avoid vaporization of the diacid. The limiting temperature for adipic acid is 290–295 °C. However, in the presence of microwave energy over a graphite support a higher temperature could be reached rapidly and at the same time the vaporization could be delayed. In addition, graphimets could be substituted as catalysts over the conventionally applied magnetite catalyst (Fe_3O_4) for the decarboxylation of acids.

Graphite X and graphite Y have been applied in a sequential microwave- irradiation-promoted decarboxylation of adipic acid with a reaction temperature of 450 °C (see Scheme 28) [51]. Under microwave conditions, for example, graphite X with its higher iron dispersion/content showed a 90% yield of a cy-



Scheme 28

clopentanone **49** from adipic acid **48** (n=2, R_1=H). Besides, microwave conditions also revealed a shortening of the reaction times over the conventional heating at the same reaction temperature. On the other hand, graphite Y with comparatively lower iron content showed only 33% yield. When Fe_3O_4, which is a strong absorber of microwaves, was doped with graphite Y, its activity was improved leading to 51% conversion, almost as much as that of graphite X. Similarly, doping Fe_2O_3 and FeO catalysts with graphite Y showed increased activity in decarboxylations. However, other doped catalysts like Al_2O_3, Bi_2O_3 and KF were inactive. At this point it was also noted that the yield improvement is pronounced only in cases when the Fe_3O_4 catalyst was used in the presence of a graphite support. In the absence of the graphite support, the decarboxylation reaction catalyzed only with Fe_3O_4 showed a dramatic reduction in yields (10%) and the adipic acid could be recovered almost completely. The graphite support herein could adsorb the starting adipic acid and essentially allow the cyclization before its vaporization. This methodology also has potential in devising a large-scale process by using a continuous supply of diacid (as a solid or in the molten state) in a graphite bed.

4
Microwaves and Polymeric Material

The polymer material involved in the development of polymer (organic) support for immobilization of catalysts and/or reagents is generally a functionalized polystyrene/divinylbenzene copolymer. Cross-linking with divinylbenzene renders mechanical strength to the polymer support making it resistant against detrimental conditions like vigorous stirring. Chemical functionality is introduced onto the polymer support by physical adsorption or by chemical bonding. These cross-linked poly(styrene-co-divinylbenzene) resins (1 to 2% cross-linking) are stable with high loading capacity (>1 mmol/g), high swelling properties and are compatible with a variety of non-protic solvents. It is generally understood that introducing a reactive species on a polymer support leads to site isolation. By increasing the percentage of cross-linking, the polymer chain mobility can be restricted and subsequently the interaction of reactive sites on a polymer chain can be restrained. The supported substrate molecule acts as a flexible spacer group to facilitate interaction of reactive sites. This concept in terms of polymer-supported catalysts is advantageous, resolving the need for a higher catalyst loading capacity. And the reactivity is improved when the catalyst bearing reactive sites co-operatively acts upon a substrate molecule.

Microwave-assisted organic transformations using polymer-supported reagents and/or a catalyst has been given appreciable attention in the chemical community. Microwave heating involves rapid instantaneous heating in closed vessels, often together with high internal pressures and temperatures reaching well above the conventional boiling points of the solvents used. This

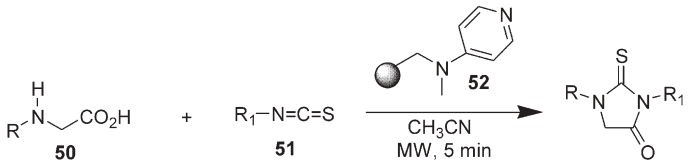
kind of flash heating is adapted to the overall stability of the commonly used polymer backbone and the supported species. On the contrary, conventional heating methods upon prolonged exposure to higher reaction temperatures often encounter degradation/decomposition of material. This feature of microwave heating together with the possibility of automating an entire synthetic process involving polymer-supported catalysts/reagents makes it popular. The frequently observed increased reaction rates under microwave irradiation could possibly be explained by the selective absorption of reactive sites on a polymeric material. Typically, considering metal-impregnated catalysts, the metal particles would heat preferentially over the polymer support [52]. Since microwave heating is influenced by the dielectric properties of the substrate, some temperature differences may arise when the absorption characteristic of the polymer support differs from that of the supported reagent and/or catalyst. In heterogeneous systems, the difference in the coupling ability of active sites and support together with the reaction media often leads to localized heating or development of hot spots.

Equally important is the interaction of a solvent with microwaves and its ability to diffuse into the polymer support for catalytic applications. Most functional groups on the polymer-supported system are within a polymer bead of diameter of about 100 μm and the reactants in the solution enter the beads and react in the gel phase. Under microwave heating, the migration of reactants is influenced by the different swelling factors of some polymers with polar monomer units [53]. This is rate determining and at times selectivity arises because a more bulky group diffuses more slowly to the reactive sites [54]. Above all, the considerations on the characteristics of polymeric material as supports for catalysts and/or reagents, the ease of separation after the reaction, recyclability and the possibility of reinstating catalytic activity post-reaction make their application increasingly popular.

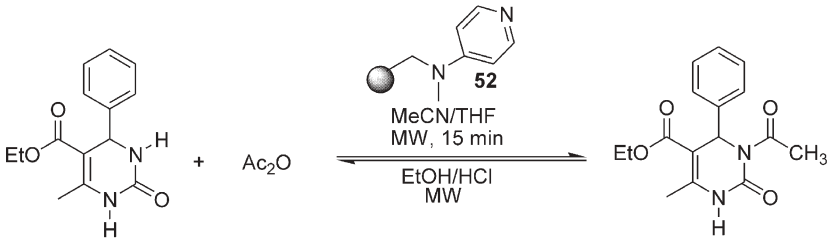
4.1 Polymer-Supported Catalysts

The microwave-assisted one-pot three-step synthesis of thiohydantoins has been studied together with a polymer-supported catalyst and/or reagent [55]. Cyclization of a number of *N*-substituted amino acids of type **50** and thioisocyanates **51** has given satisfactory yields within 5 min at 170 to 180 °C (see Scheme 29). Polymer-supported dimethylaminopyridine (PS-DMAP) **52** has been utilized as a supported base herein to catalyse the reaction; however, in most cases the yield was comparatively lower to the use of triethylamine (TEA). PS-DMAP also assisted in simplifying the purification.

Microwave-assisted selective protection of dihydropyrimidinones has also been afforded using PS-DMAP. The microwave-induced selective *N*3-acylation has been applied to a diversely substituted dihydropyrimidinone scaffold with 30–97% isolated yield within 10–20 min of microwave irradiation (see Scheme 30) [56].



Scheme 29

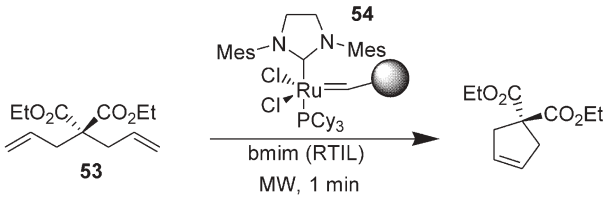


Scheme 30

Ring-closing metathesis is efficiently applied for the construction of small, medium and macrocyclic ring systems. Even so, microwave heating accelerates the ring-closing metathesis reactions in the presence of ruthenium-based catalysts. Kiddle and co-workers [57] have used polymer-supported Ru catalyst (vinyl polystyrene bound) **54** for model studies (see Scheme 31) on the ring-closing olefin metathesis of diethyl diallylmalonate **53** using a domestic microwave oven in room temperature ionic liquid (RTIL), and report its reactivity to be 2 orders of magnitude less (40% conversion) than that of the homogenous analogue (80–100% conversion).

A similar type of ring-closing metathesis has been studied together with reduced reaction times with microwave heating using a polymer-supported second-generation Grubbs catalyst [58]. The use of polymer-supported catalysts in combination with microwave heating demonstrates an easy approach to make small libraries of target compounds.

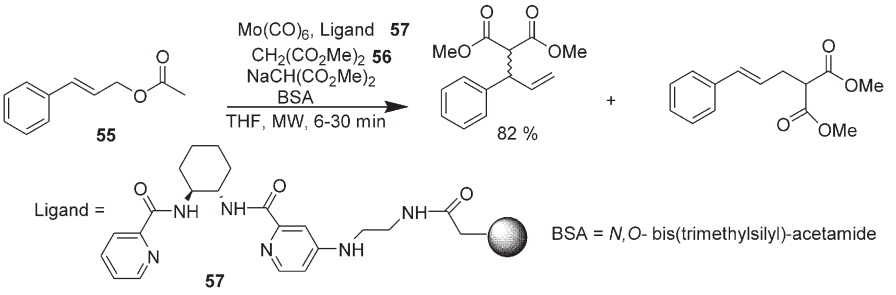
Immobilized catalysts have also been applied to prepare chiral compounds. Solid-supported chiral ligands together with suitable metal catalysts form the basis of asymmetric catalysis. Chiral ligands immobilized on a solid support provide the advantage of rapidly removing them post-reaction while retaining



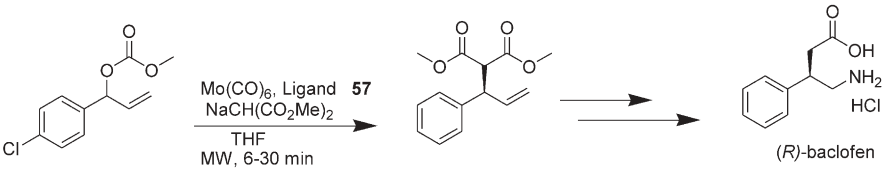
Scheme 31

their activity [59]. The microwave-assisted molybdenum-catalyzed allylic allylation has been studied using a recyclable polymer-supported pyridylamide (see Scheme 32) [60]. The catalytic reaction of 3-phenylprop-2-enyl methyl carbonate **55** with dimethyl malonate **56** using polymer-supported ligand **57** was slower because the insoluble resin-bound ligand renders a heterogeneous nature to the catalyst. However, when the reaction was conducted with double concentration of the reagents, no starting material could be detected after 30 min of microwave irradiation (160°C) and the product exhibited a branched-to-linear ratio of 35:1 and an enantiomeric excess of 97%. The ligand could be recycled and reused at least seven times with no significant change in the reaction outcome. A similar polymer-supported ligand has been used in the microwave-induced asymmetric allylic alkylation [60] as a key step in the enantioselective synthesis of (*R*)-baclofen, the racemic form of which is used as a muscle relaxant (antispasmodic). The (*R*)-enantiomer is pharmacologically important and a useful agonist of the $GABA_B$ (*γ*- aminobutyric acid) receptor [61]. The microwave-assisted asymmetric alkylation (see Scheme 33) using polymer-supported ligand and $Mo(CO)_6$ catalyst afforded the product in good yield but with lower enantioselectivity due to a memory effect [62]. However, the enantioselectivity was further improved to 89% when the reaction was microwave irradiated with toluene as the solvent. This was in agreement with a previous report [62] suggesting the minimization of the memory effect in toluene.

Studies on the controlled microwave-irradiated novel palladium-catalyzed reaction of a fluorous-tagged bidentate ligand (1,3-bis(diphenylphosphino) propane ligand, [F-dppp]) for regioselective Heck vinylations of enamides have

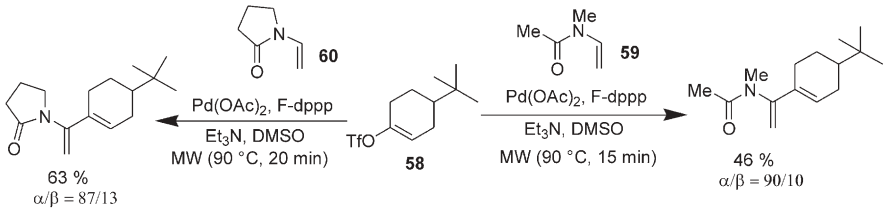


Scheme 32



Scheme 33

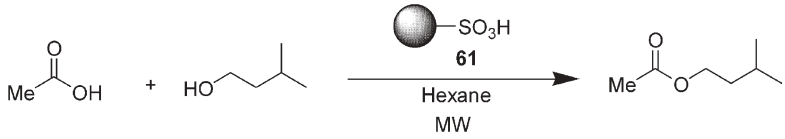
been performed [63]. The microwave-induced studies on vinyl triflate of type **58** have suggested that $Pd(OAc)_2$ catalyzed vinylation of enamides like **59** and **60** in the presence of F-dppp ligands (see Scheme 34) have rendered almost the same yields of Heck reaction products as with non-fluorous ligands, however the regioselectivity was slightly lower. Microwave heating herein showed higher reaction rates compared to the classical heating method. The obvious advantage viewed with the use of fluorous F-dppp ligands in the Heck vinylation is the simplified and rapid purification to completely remove the tagged phosphine ligand, palladium-complexed ligand and oxidized phosphine ligand by direct solid fluorous-phase separation before product isolation.



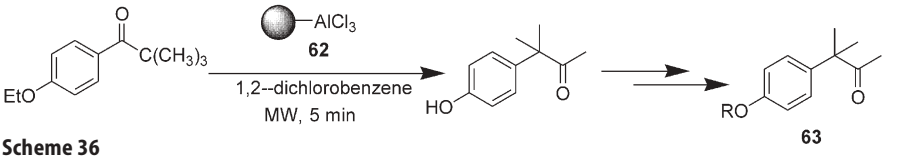
Scheme 34

Functionalized monolithic supports based on either organic or inorganic polymers have been useful for interactions/reactions with immobilized functionalities and the surrounding liquid phase. "Monoliths" comprise solid inorganic and/or organic materials with a defined porosity. Poly-(*N*,*N*-dipyrid-2-yl-7-oxanorborn-2-en-5-ylcarbamido.$PdCl_2$)-grafted monolith supports have also been used to catalyse Heck reactions [21]. The efficacy of monolithic supports (conventional heating) as compared to the silica-based support (under microwave heating) for catalysing Heck reactions (see also Sect. 3.2) has been reportedly low.

Microwave-assisted esterification by a heterogeneous acid catalyst has been studied in a low dielectric constant medium (see Scheme 35) [64]. A continuous-flow setup has been devised in the system and the heterogeneous acid catalyst (Amberlyst A15 sulphonic acid cation-exchange resin) **61** localized in a polyethylene active flow cell. Use of a low dielectric constant medium (hexane) ensured absorption of microwave radiation only to the reacting species. In this case, the findings suggest a comparable esterification reaction under both microwave and thermal conditions. Furthermore, the presence of water in the catalytic resin resulted in a reduction of the reaction rate irrespective of the type



Scheme 35



Scheme 36

of energy input. Also chemical reactions showed similar behaviour when thoroughly circulated regardless of the source of the energy.

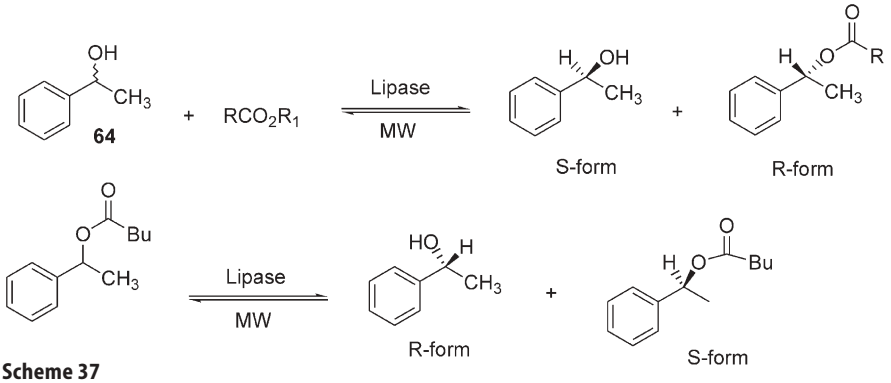
In an improved synthesis of 3-(4-alkoxyphenyl)-3-methylbutan-2-ones of type **63**, a microwave-induced ketone–ketone rearrangement has been described utilizing a polymer-supported $AlCl_3$ catalyst **62** (see Scheme 36) [65]. Anhydrous $AlCl_3$ immobilized by preparing a tightly bound complex with styrene-divinylbenzene copolymer serves as a mild Lewis acid catalyst [66]. Use of polymer-supported $AlCl_3$ herein has been suggested to circumvent the direct handling of corrosive $AlCl_3$ together with the advantage of smooth product yield in 3–5 min of microwave irradiation.

5
Catalysis with Supported Enzymes

Enzymes used as catalysts are usually applied in aqueous or organic solvents at reaction temperatures below 40 °C to maintain their activity. Consequently, such reactions are often extended for longer times. However, immobilizing enzymes on a solid support [67] renders them thermally stable and under these conditions, the catalysis could be operated with appreciable activity in the range 80–100 °C. Moreover, these could be utilized both under conventional and microwave heating under close temperature control.

Loupy and co-workers [68] have studied the effectiveness of microwave irradiation in increasing the enzymatic affinity and selectivity of supported lipases in esterification and transesterification reactions under dry media conditions (see Scheme 37). The esterification and transesterifications of racemic 1-phenylethanol **64** were studied in a temperature range of 70–100 °C. The lipases considered were the *Pseudomonas cepacia* lipase (LP) and *Candida Antarctica* lipase (SP-435). The initial rates and enantiomeric ratios *E* were significantly enhanced under microwave irradiation. Even so, in cases where classical conditions showed poor reaction, complete conversion could be achieved with increased reactivity under microwave conditions. This was largely attributed to the exclusion of the volatile by-products from the equilibrium. More importantly, the supported enzymes showed good stability and could be reused three more times in the reactions under study without loss of activity.

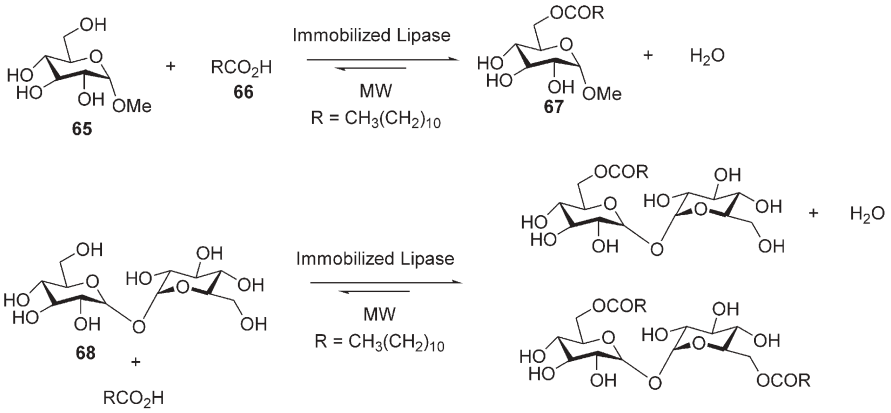
The immobilized *Candida Antarctica* lipase (Novozym 435)-catalyzed esterification of methyl α-D-glucopyranoside **65**, α-glucose and α,α-trehalose **68** with dodecanoic acid **66** has been studied under microwave irradiation (see



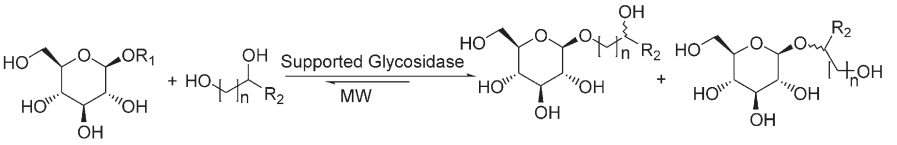
Scheme 37

Scheme 38) [69]. Regioselective esterification of methyl-α-D-glucopyranoside with complete conversion to methyl-6-*O*-dodecanoyl-α-D-glucopyranoside **67** was obtained under solvent-free microwave conditions (95–110 °C for 2–5 h) when only 55% conversion was observed under classical heating after 5 h. Furthermore, the supported lipase under study (Novozym 435) could be reused without loss of activity after several hours of heating in a microwave reactor at 95 °C and subsequent extraction of the products by washing with distilled water. Using this approach, various other sugars have been esterified with high regioselectivity, and enhanced reactivity has been claimed, largely attributed to improvement in the irreversibility of the reaction due to prompt exclusion of water by-product together with some specific (non-thermal effects) of microwaves including entropic effects [70]. Supported lipases such as Novozym SP-435 have also been applied in catalyzing transesterification under microwave conditions [71].

Microwave-assisted reversed hydrolysis and transglycosidation in dry media have been described using a glycosidase catalyst typically immobilized on



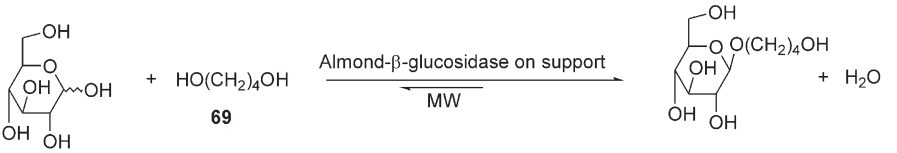
Scheme 38



Scheme 39

neutral alumina (see Scheme 39) [72]. Glycosidases are able to catalyse glycoside synthesis under conditions of low water/high alcohol concentration, in the presence of an appropriate glycoside donor (phenyl-, nitrophenyl-glycoside etc.). However, this involves the possibility of the hydrolysis of the donor and/or the product resulting in lower yields. Working under dry media conditions using neutral aluminium oxide as a mineral support, the biocatalyst for transglycosidation could be reused under microwave and classical heating. Thermostable enzymes like the crude homogenate of *Sulfolobus solfataricus* and recombinant *β*-glucosidase from *Pyrococcus furiosus* have been applied in transglycosylation reactions. Microwave irradiation when compared to classical heating generally resulted in complete conversion of transglycosidation products within 2–3 h while hydrolysis was lowered to 10% with optimal conditions at 95 °C under open vessel conditions. With controlled heating of the dry reaction mixture involving mineral support as opposed to organic solvents, the kinetics of glycosidations have been improved. Higher temperatures increase the solubility of many compounds as well as the diffusion rate and allow the removal of volatile products.

Dry condition microwave-induced glucosidations with 1,4-butanediol **69** catalyzed by almond-*β*-glucosidase on different supports have been studied (see Scheme 40) [73]. In dry media, Celite R-640 was observed to be best support for glycosidation. A rapid loss in the water influenced the conversions of glucosidations and microwave heating in some cases showed lower yields due to rapid loss of water, resulting in the irreversible loss of enzymatic activity. Amyloglucosidase is responsible for the in vivo starch digestion resulting in the breaking of all glycosidic bonds with release of D-glucose. Some thermophilic biocatalysts on mineral supports have been reported [72] to enhance reaction kinetics under microwave conditions. The hydrolysis of starch has been studied on a mineral support and with minimal amounts of water [73]. The hydrolysis could be accelerated under microwave conditions (60 °C) and 75% glucose was obtained within 5 min or 98% within 15 min.



Scheme 40

6 Conclusion

In conclusion, this review has highlighted various immobilized catalysts and their applications have been described in combination with microwaves. The review has discussed the attributes of different supports and their suitability in terms of immobilizing catalysts. The examples discussed herein have been taken from experimentations done on both domestic microwave ovens and dedicated microwave instruments. Microwave-induced catalysis of important chemical transformations such as C–C couplings, cycloadditions, metathesis and many other syntheses and processes appealing to a wider chemical community have been included. The review has illustratively provided the reader with an insight into the use of catalysts supported on inorganic as well as organic surfaces. The reader has seen an overview of the developments in the area of supported catalysts in combination with microwave heating.

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Applications of Immobilized Catalysts in Continuous Flow Processes

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Abstract As part of the dramatic changes associated with automation in pharmaceutical and agrochemical research laboratories, the search for new technologies has become a major topic in the chemical community. Commonly, high-throughput chemistry is still carried out in batches whereas flow-through processes are rather restricted to production processes, despite the fact that the latter concept allows facile automation, reproducibility, safety, and process reliability. Indeed, methods and technologies are missing that allow rapid transfer from the research level to process development. Continuous flow processes are considered as a universal lever to overcome these restrictions and only recently, joint efforts between synthetic and polymer chemists and chemical engineers have resulted in the first continuous flow devices and microreactors which allow rapid preparation of compounds with minimum workup. Importantly, more and more developments combine the use of immobilized reagents and catalysts with the concept of structured continuous flow reactors. Consequently, the present article focuses on this new research field, which is located at the interface of continuous flow processes and solid-phase-bound catalysts.

Keywords Catalysis · Reactors · Continuous flow processes · Automated synthesis · Monolithic materials · Polymers

Abbreviations

BMIM	1-Butyl-3-methylimidazolium
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
BTA	Bis(trifluoromethanesulfonimide)
CIM	Convective interaction media
CMR	Continuous microwave reactor
EMIM	1-Ethyl-3-methylimidazolium
GalK	Galactokinase
GalT	Galactose-1-phosphate uridylyl transferase
GalU	UDP-glucose pyrophosphorylase
HPLC	High-performance liquid chromatography
HWE	Horner–Wadsworth–Emmons olefination
NDK	Nucleotide diphosphate kinase
NDP	Nucleotide diphosphate
NMP	*N*-methylpyrrolidinone
PASSflow	Polymer-assisted solution-phase synthesis in the flow-through mode
PDMS	Polydimethylsiloxane
PLA	Polylactide
PPA	Inorganic pyrophosphatase
PpK	Polyphosphate kinase
PTFE	Polytetrafluoroethylene
$scCO_2$	Supercritical carbon dioxide
TADDOL	$\alpha,\alpha,\alpha',\alpha'$-Tetraaryl-1,3-dioxolane-4,5-dimethanol
TBAA	Tetrabutylammonium acetate
Tf	Trifluoromethylsulfonyl
TsDPEN	Tosyl-*N*,*N*′-diphenyl-1,2-ethanediamine
UDP	Uridine diphosphate
UMK	UMP kinase

1 Introduction

The art of organic synthesis has continuously flourished for many decades and great improvements in the fields of catalysis, asymmetric synthesis, combinatorial chemistry and others have been achieved lately. The explosion of improvements in synthetic chemistry is often unjustifiably underscored in public, because the changes are not visible but have taken place behind laboratory doors inside the flask. Indeed, the environment in which synthesis is conducted has not changed, as reactions are still typically performed batchwise in standardized glassware which has commonly been in use since Justus Liebig's time. As combinatorial chemistry started its triumphant progress in drug discovery a little more than 10 years ago [1] chemists learnt to deal with new "hardware" and "environments". Today combinatorial and parallel synthetic methods are a widely accepted tool in organic chemistry. However, despite this strong trend for automation in pharmaceutical research, high-throughput chemistry is still carried out in batches whereas flow-through

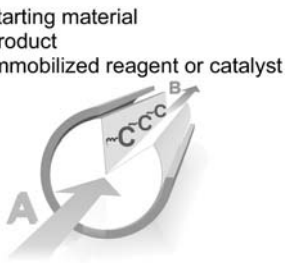


Fig. 1 A concept for a flow-through reactor containing immobilized reagents or catalysts

processes are rather restricted to production processes. Indeed, continuous processing is established as cost-effective in the commodity sector. This can be understood, because facile automation, reproducibility, safety, and process reliability and control due to constant reaction parameters (temperature, time, amount of reagents, solvent etc.) increased productivity, and improved quality and yields can be assured.

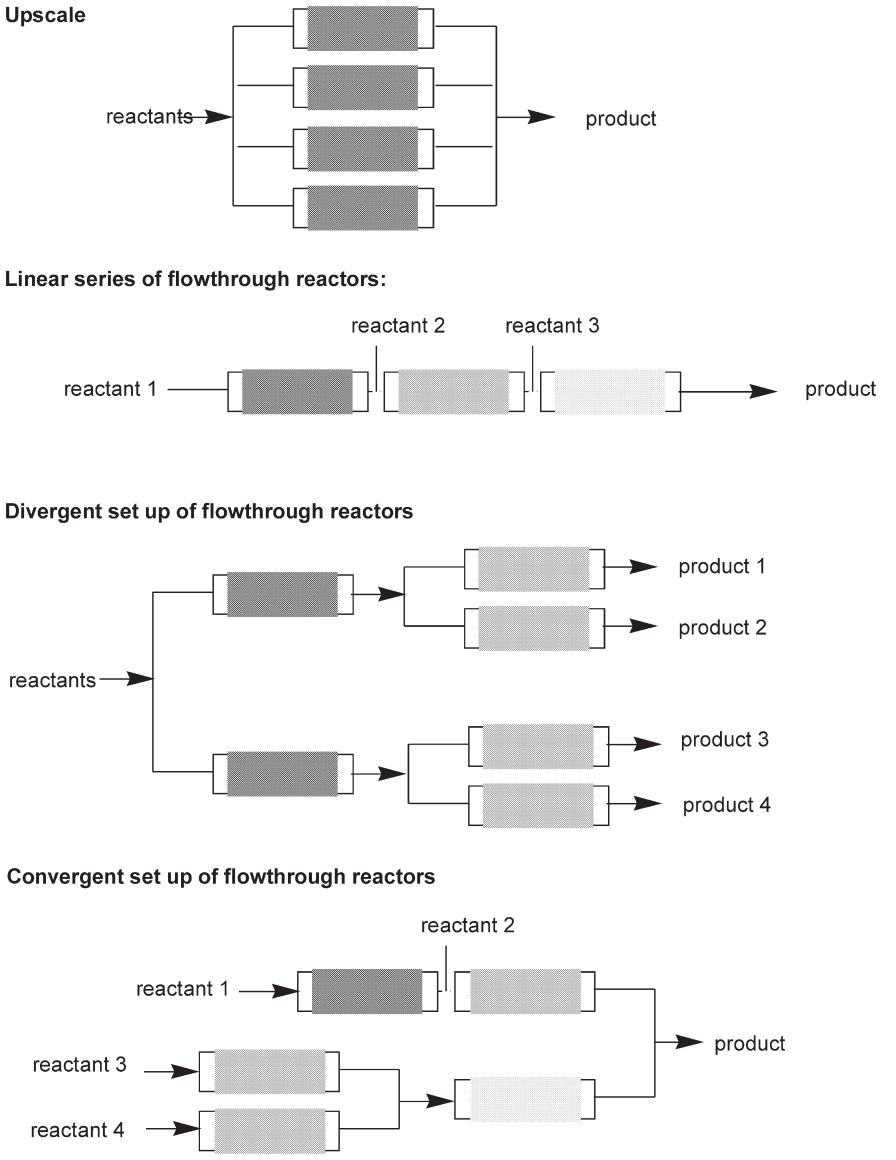
Advantageously, continuous flow processes can further be improved by techniques that originate from high-throughput chemistry laboratories as they can be combined with the use of immobilized reagents or catalysts, parallelizing fixed-bed reactors (Fig. 1) [2]. Purification of the product, recovery of the catalyst or regeneration of the reagent can easily be achieved under these circumstances. Ideally, the flow rates are slow enough to guarantee full conversion of the starting material and only the desired product(s) are gained at the end of the reaction. In fact, reaction and filtration operations are carried out simultaneously whereas in corresponding batch reactions both processes have to be performed separately. Simplified reaction workup is the result and in some cases only the evaporation of the solvent is needed as a single workup step.

Only recently, chemists in industry as well as in academia have begun to focus on the development of flow devices for laboratory use and hence for industrial applications by combining new chemical technologies with flow reactors [3]. These technologies include microwave assistance, the use of immobilized reagents and catalysts, and new fluids such as supercritical CO_2 and ionic liquids.

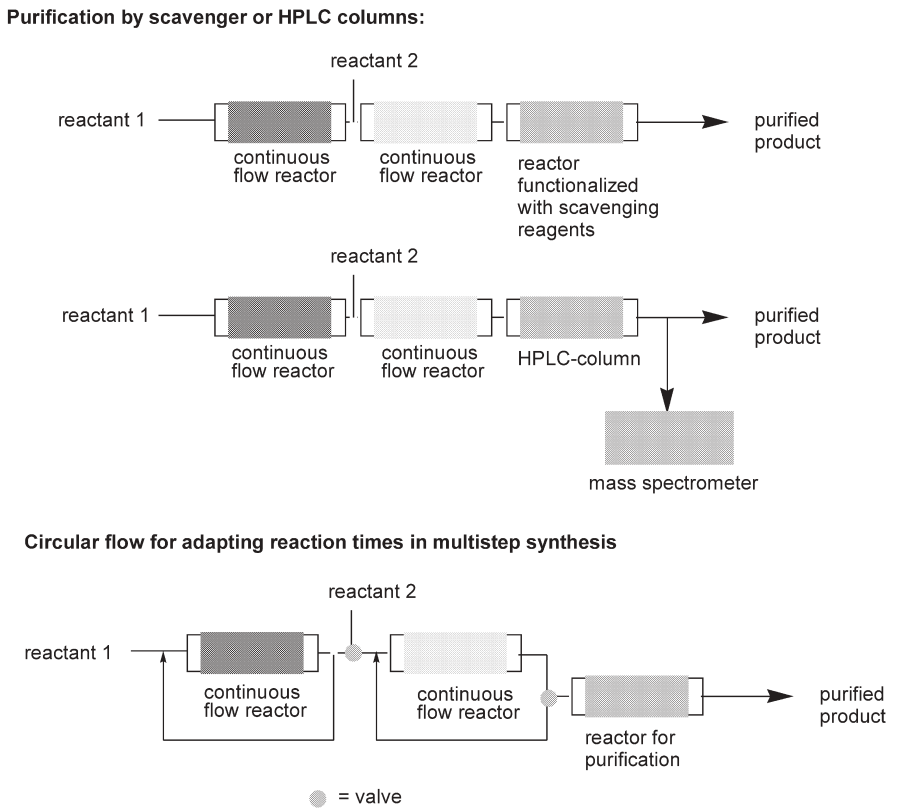
The present report gives a critical and up-to-date literature survey on these recent developments in continuous flow processes with particular emphasis on solid-phase catalysts. Although very important, this overview excludes the concept of microreactor technology which is based on microfluids. This technology holds great future potential but so far little attention has been paid to merging this technique with immobilization strategies for catalysts or reagents. In addition, industrial continuous processes are also excluded but the reader is referred to the chapters of this volume written by K.-U. Schöning for obtaining further information.

2
Concepts for Parallel and Multistep Synthesis in Continuous Flow Systems

The switch from a synthetic batch-mode protocol to a continuous flow process has various consequences. It opens opportunities which rarely can be achieved with similar simplicity when employing batch reactors. Scale-up can be con-



Scheme 1 Parallelization and multistep synthesis with flow-through reactors



Scheme 2 Coupled synthesis, purification, and analysis with flow systems

ducted by parallelization of reactors. By assembling a line of reactors multistep syntheses can be achieved with minimum or no purification in between two reaction steps. Divergent as well as convergent multistep syntheses, which either create compound libraries or complex target molecules, are also feasible with flow systems (Scheme 1). The concept can beneficially be extended by incorporating separation and analytical techniques into the flow system. This is particularly important if solid-phase-bound metal-based catalysts are employed which tend to undergo leaching. On a small scale this demand is easily achieved with HPLC equipment in conjunction with detector devices like mass spectrometers or diode-array detectors (Scheme 2).

However, a critical view on flow systems reveals that various difficulties have to be considered. The realization of reaction sequences by flow-through processes is hampered by (a) limitations in the maximum number of sequential reaction steps, (b) inert properties of all materials toward a large variety of different organic solvents, (c) the necessity to switch the solvent for selected reaction steps, (d) efficient regeneration of reaction columns, and (e) facilities to purify intermediates. In addition, the reaction times for transformation should

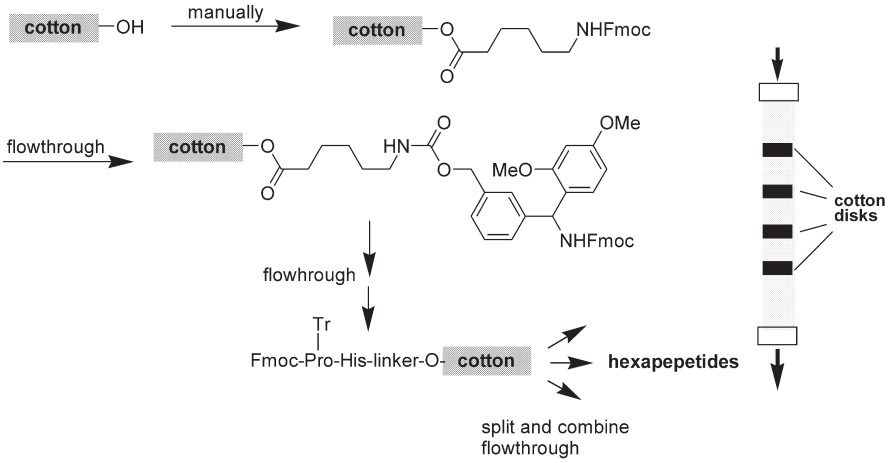
be similar in order to avoid complex valve techniques for controlling flow rates. If reaction times for complete conversion during a single run are too long, the flow of reactants will have to be led in a circular mode through the flow system until a valve directs the products into the next reactor system. It is obvious that the chemist dealing with flow systems will not only be confronted with chemical problems but will also have to consider technical aspects.

3
Solid-Phase-Assisted Continuous Flow Concepts

3.1
Early Solid-Phase Continuous Flow Concepts

Merrifield's research set the stage for solid-phase-assisted synthesis and thus had a strong impact on laboratory automation. The high repetitive character of coupling reactions and protecting groups and the small amounts of product required in peptide and oligonucleotide synthesis ideally fit the demands of automation. Not surprisingly the first synthesis machines were developed for the synthesis of these biomolecules. Commonly, peptide synthesis is exclusively associated with solid-phase protocols, but indeed it is forgotten that Merrifield originally envisaged a flow-through system for peptide synthesis, as can be read in his autobiography from 1993 [4]. It took another 20 years since the first publications by Merrifield until a reliable continuous flow protocol for peptides was at hand [5]. The intrinsic disadvantages (particularly swelling of the support) were overcome by polymerizing the support within the pores of a rigid macroporous matrix (also refer to Sect. 3.2 of this article and to the report by R. Haag in this volume). In a comparative study it was shown that peptides can be synthesized quicker and easier by a continuous flow approach [6], reducing the times for the whole process by a maximum factor of 10 [7]. Recently, Wikberg et al. [8] prepared a library of hexapeptides by means of continuous flow. They utilized a common peptide synthesizer which was altered with respect to the original concept of Frank and Doering [9]. The authors conducted the simultaneous multiple peptide synthesis on paper disks by a continuous flow approach (Scheme 3). This technique is based on labeled cotton disks as supporting material which were piled up in a column. These disks were manually premanipulated and preactivated for introduction of an Fmoc-protected linker. Advantage was taken from a split and pool strategy which was realized by means of individual labeling and spatial encoding of the disks and their assembly in the column.

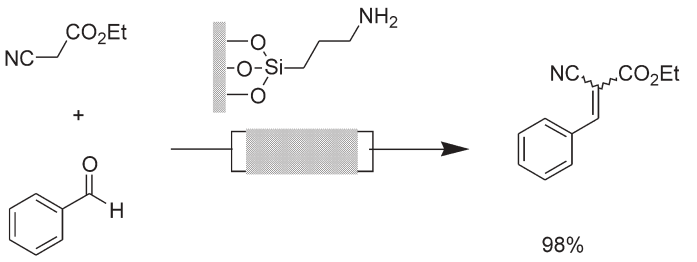
The authors noted that with a typical commercial continuous flow peptide synthesizer, it should be possible to accomplish six different amino acid couplings per day on 50 disks resulting in 300 peptide couplings per day. This rather classical but very straightforward and efficient approach combines the continuous flow technique with traditional solid-phase supported chemistry.



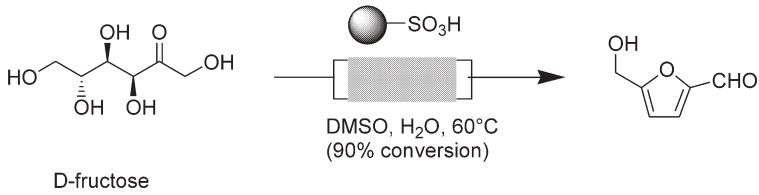
Scheme 3 Wikberg's continuous flow synthesis of peptides using cotton disks in a split and pool strategy

Besides this early example another application was reported in 1988 by Venturello and coworkers [10]. They disclosed the use of aminopropyl-functionalized silica gel as a suitable catalyst in Knoevenagel condensations under continuous flow conditions (Scheme 4). Good yields were obtained when aromatic aldehydes, cyclohexanone, and acetophenone were condensed with ethyl acetoacetate, ethyl cyanoacetate or malononitrile [11, 12]. The concept was based on a conventional column reactor which was equipped with a vertical double-jacket thermostat. The catalyst was introduced into the column while the reactants were placed on the top of the column. Toluene was passed through the column and the products were conveniently obtained by evaporation of the solvent.

Another early example of a continuous flow process was disclosed in 1980 by Nakamura and Morikawa [13]. It was demonstrated that recirculating an aqueous DMSO solution of fructose through a bed of strongly acidic exchange resin led to isomerization and dehydration, producing the corresponding furyl aldehyde (Scheme 5).



Scheme 4 Knoevenagel condensations in a flow-through reactor



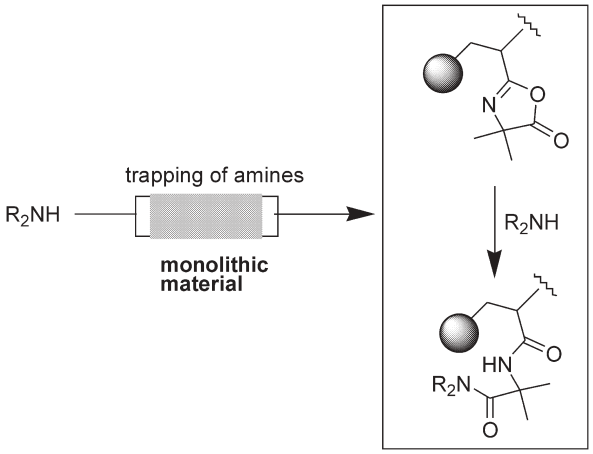
Scheme 5 Proton-mediated transformation of D-fructose into a furyl aldehyde

3.2 Why Monolithic Materials in Solid-Phase-Assisted Flow-Through Processes?

Continuous flow processes relying on functionalized solid phases are typically designed by adapting the reaction conditions to the equipment available. Commonly, reactors are equipped with randomly packed catalytic beds and thus have uncontrolled fluid dynamics, which is a disadvantage from a chemical reaction engineering standpoint. Thus, stagnation zones and hot-spot formation can occur as well as broad residence time distribution, low selectivity, and in essence low process efficiency. In this context structured beds, which are designed on a nanoscale up to the macrogeometry, can overcome these drawbacks. A monolith is regarded as the best structured material known. In a general sense it is defined as a block of structured material which consists of continuous substructures or regular or irregular channels [14]. To date, these materials have found wide use in the automobile industry as supports for catalysts. In addition, they most often have been used as separation media in various chromatographic modes [15, 16], in solid-phase extraction, and for the fabrication of thermally controlled valve- or gate-like devices. So far, inorganic materials based on silica gel or carbon with uniform mesopores and tunable microchannels have mainly been employed for these purposes.

Monolithic materials have a high void volume and a large geometric surface area. This guarantees a low pressure drop during the passage of a gas or a fluid. In addition, a large contact area of the reagent or the catalyst with the fluid is achieved [17]. Due to these advantages various groups recently designed new monolithic materials, most of them of a polymeric nature, which are adaptable in continuous flow reactors for synthesis. Three important concepts which can become part of a flow system are described in detail here:

1. Copolymerization of different monomers in the presence of porogens.
2. Preparation of diblock copolymers in which a well-defined cylindrical and degradable polymer is embedded inside the second polymer. After selective removal of the degradable polymer nanotubes are regenerated within the stable matrix.
3. Polymerization of a monolithic polymeric phase wedged inside the microchannel pore system of an inert support such as glass and other preformed inorganic materials.

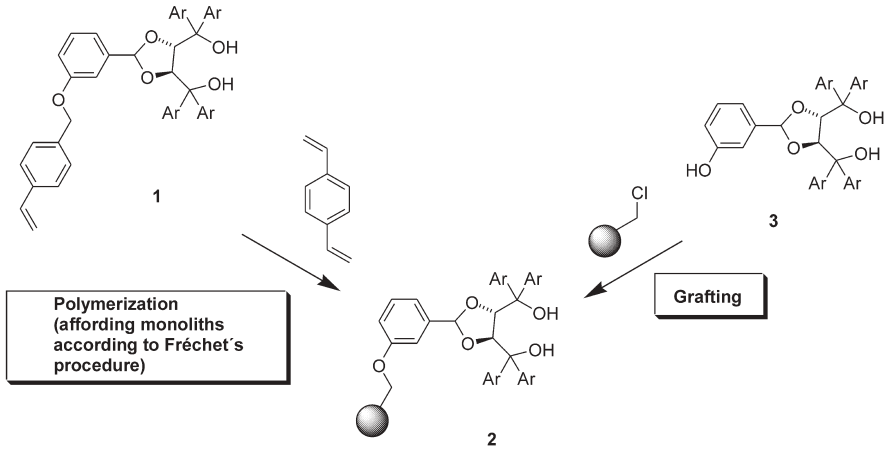


Scheme 6 Scavenging of amines with Fréchet's monoliths

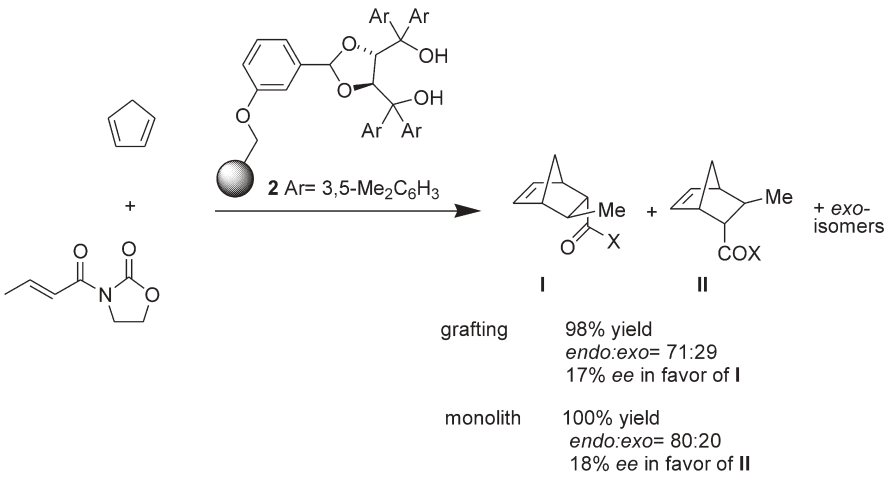
The first concept was developed and studied in detail by Fréchet, Svec, and Sherrington [18, 19]. These groups prepared monolithic porous polymers of virtually any shape within a column housing or mold by copolymerization of styrene, divinylbenzene, and poly(methyl acrylate) in the presence of a porogen without the necessity of using a suspending medium. The resulting rod can be used as a reactor or may be cut into disks. For example, this material was functionalized with an azlactone moiety which allows it to scavenge amines from solution as depicted in Scheme 6. The authors note that this monolithic porous structure shows superior properties to conventional beads because of improved diffusion rates. And in contrast to the direct copolymerization of reactive monomers grafting increases the accessibility of the reactive groups.

Based on Fréchet's work [20], Luis and coworkers [21] studied the influence of the mode of preparation of the polystyrene backbone functionalized with TADDOL ($\alpha,\alpha,\alpha',\alpha'$-tetraaryl-1,3-dioxolane-4,5-dimethanol) **2**. This immobilized ligand was loaded with titanium on the topicity of an asymmetric transformation. Here, the Diels–Alder reaction of cyclopentadiene with 3-crotonyl-1,3-oxazolidin-2-one was chosen as a model reaction. The TADDOL ligands were incorporated into the polymeric backbone either by polymerization using functionalized styrene derivative **1** or by grafting and coupling of phenol **2** to Merrifield-type resins (Scheme 7).

Although the diastereo- and enantioselectivities observed for this model reaction were poor, a remarkable observation was made by the authors (Scheme 8). The topicity of this process was reversed when changing from the grafted polymer (which equals soluble catalysts) to the monolithic material (prepared from **1**). At this point a rationale cannot be given but it is a clear indication that the nature of the matrix has an influence on the course of metal-catalyzed reactions.



Scheme 7 Preparation of monolithic and grafted materials functionalized with TADDOL ligands



Scheme 8 Applications of Ti-TADDOL catalysts **2** in Diels–Alder cycloadditions

Buchmeiser and coworkers [22] followed a transition metal-based approach for the generation of new monolithic materials. The continuous matrix was prepared within a glass column by ring-opening metathesis copolymerization of norbornene in the presence of a porogen. The "living" ruthenium carbene termini were treated in situ with norbornene which itself had been functionalized with a modified second-generation Grubbs catalyst. This procedure yielded a porous monolithic metathesis catalyst **4** (Fig. 2).

Convective interaction media (CIM) are supports which are related to Fréchet's monoliths. They are block polymers prepared by radical copolymerization of glycidyl methacrylate and ethylene dimethacrylate in the presence of

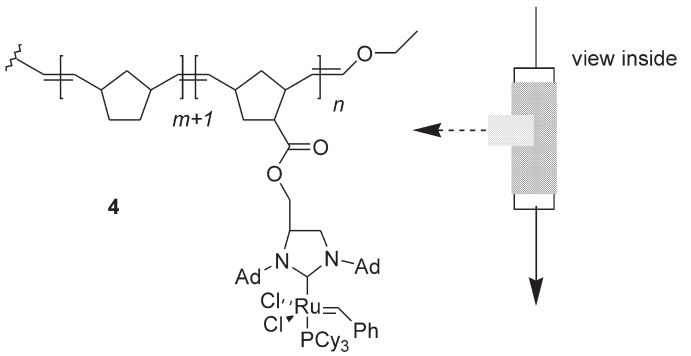


Fig. 2 Buchmeiser's concept of a monolithic Grubbs catalyst

a porogen [23]. The resulting materials are monolithic in nature, rigid, and macroporous and contain epoxy groups as functional groups. These additional functionalities can be activated for immobilization of various ligands. Utilization as chromatographic supports [24] and in biocatalysis [25] can be found in the literature. Thus, solid-phase peptide synthesis was performed on a glycidyl methacrylate-*co*-ethylene dimethacrylate monolithic column [26]. The resulting immobilized peptide (directed against human blood coagulation factor VIII) showed good properties as a peptide affinity chromatography matrix and did not adsorb proteins unspecifically.

The second concept for the generation of monolithic polymers is based on diblock copolymers which were prepared by Hillmyer and coworkers [27]. These copolymers contain oriented nanoscopic cylinders of the degradable polymer polylactide (PLA) which were embedded in polystyrene. The latter served as an inert thermoplastic matrix, while PLA could be selectively removed under well-defined conditions using sodium hydroxide in aqueous methanol. The resulting mesoporous monolithic polystyrene contains nanochannels with defined pore size. The major drawback of this material free of any cross-linker is associated with reduced mechanical and chemical stability.

The third solution to the design of monolithic matrices was developed by Kunz and Kirschning. The concept is based on the design of a novel type of monolithic block. It contains a chemically functionalized highly porous polymer/glass composite. This composite was prepared by precipitation polymerization of vinylbenzene or other monomers in the pore volume of highly porous glass rods. This procedure yields a polymeric matrix inside the rod [28, 29] which consists of small beads (1–5 μm diameter). Surprisingly, these minute beads are cross-linked with polymeric bridges (Fig. 3) yielding a monolithic phase with a high surface area. The porous glass system itself serves as an inert, inorganic support with defined shape. As will be shown later these materials can be functionalized and become part of a continuous flow reactor system.

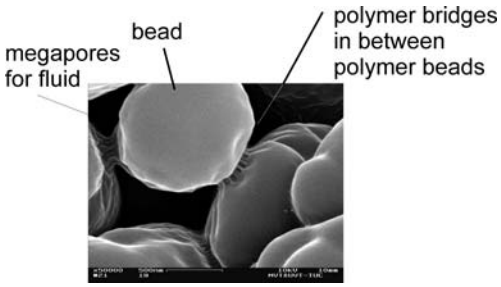


Fig. 3 REM view of the monolithic composite material

3.3 Recent Applications of Continuous Flow Processes with Solid-Phase-Attached Chemical Catalysts

As a result of the preliminary examples described in Sect. 3.1 and the quest for automation techniques in solution-phase synthesis, various examples of continuous flow processes appeared in the literature lately which utilized solid-phase-bound chemical catalysts. In a simple example, Yamamoto and coworkers studied the use of super Bronsted acids loaded on polystyrene beads **5** for use in a single-pass column system (Fig. 4) [30]. It was shown that these columns are suited for the acetylation of alcohols, acetalization of carbonyl compounds, Sakurai–Hosomi allylation reactions, and Mukaiyama aldol reactions.

In this context, however, asymmetric transformations with chiral metal complexes or enzymes are particularly important. The demand for enantiopure building blocks in the fine chemical and pharmaceutical industries is still hampered by simple asymmetric processes which can be scaled up, as well as by the stability, recyclability, and hence the price of most chiral catalysts (refer also to the chapter by K.-U. Schöning in this volume). Immobilization of effective and robust catalytic systems and their application in continuous flow reactors is regarded as a key for success in this field.

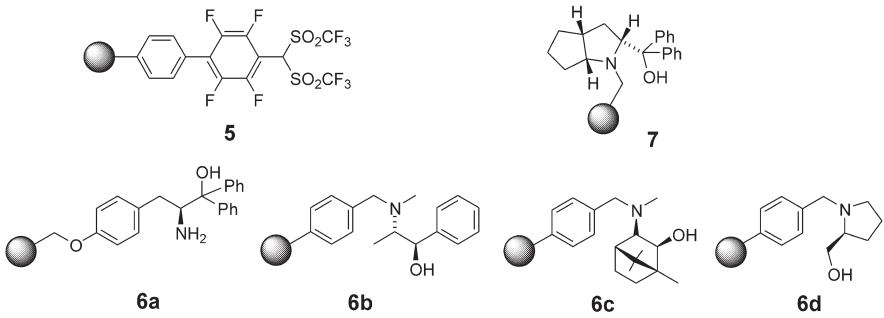


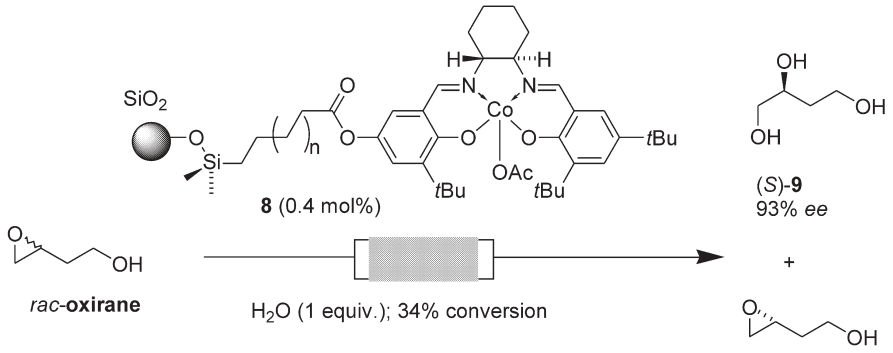
Fig. 4 Selected immobilized ligands and catalysts employed in flow systems

Indeed, by immobilization of optically active α- or β-amino alcohols on cross-linked polystyrenes as in **6a–d**, utilization of chiral borane complexes becomes feasible. These functionalized polymers were incorporated into simple columns and enantioselective reductions of aldehydes and ketones were performed. Thus, reduction of acetophenone with a borane complex prepared from **6d** yielded optically active (–)-1-phenyl-2-propanol in high optical yield (>99% *ee*) [31]. In addition, the flow system also served for continuous regeneration of the immobilized complex. Injection of borane and valerophenone into the column, which was loaded with polymer **6a**, was followed by collection of fractions every 30 min. The individual batches of collected 1-phenylpentanol were analyzed and the enantiomeric excess was determined to be 87, 93, and 91% for three batches [32].

Resin-bound amino alcohols also served to load diethyl zinc which then was employed in continuous flow additions to aromatic aldehydes [33]. Both diethyl zinc and *p*-chlorobenzaldehyde were added simultaneously at a slow rate under nitrogen into a cooled column loaded with functionalized polymer **6a**, which afforded 1-(*p*-chlorophenyl)-propanol with good enantiopurity (94% *ee*). The authors note that 58 mmol of the optically active alcohol were prepared in a continuous process by only employing 0.7 mmol of the immobilized catalyst. Similar results were reported for immobilized ephedrine, so it was concluded that continuous flow processes are often superior in efficiency and practicability compared to batch processes. In some cases, it was found that enantioselectivities were higher for convective flow processes than for the corresponding batch systems [34].

Luis, Martens and coworkers developed a closely related flow system [35] which was based on Fréchet-type polymeric monoliths (refer also to Sect. 3.2) [36]. They immobilized azabicyclo[3.3.0]octane-3-carboxylic acid **7** both by grafting and by polymerization (Fig. 4). The addition of diethyl zinc to benzaldehyde in a column was studied. It was found that the monolithic catalyst prepared by polymerization turned out to be superior (up to 99% *ee*) compared to the catalyst prepared by grafting (compare with Schemes 7 and 8). Differences in appropriate chiral cavities inside the polymer may be responsible for these results, the other factors being differences in reaction conditions and most probably the avoidance of diffusional problems in the monolithic catalyst at high flow rates.

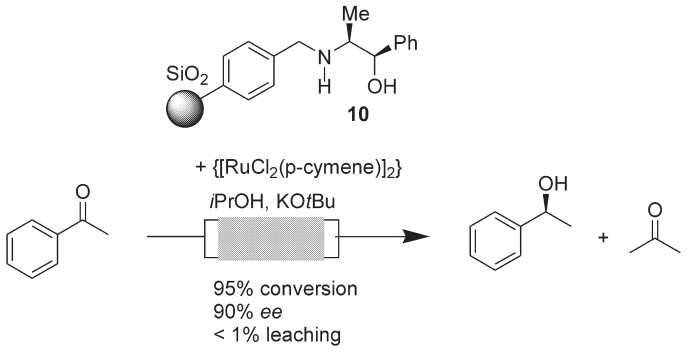
In pharmaceutical research and fine chemical synthesis, chiral salen-based catalysts are among the most appealing ones as they access a plethora of chiral intermediates starting from easily accessible epoxides. It was shown that they also work efficiently for large-scale synthesis. Jacobsen and coworkers [37] developed a synthetic protocol for the immobilization of salen complexes on polystyrene and silica resins by employing unsymmetrically substituted salen ligands **8** (Scheme 9). Flow-through applications were tested for easy catalyst recovery. The hydrolytic kinetic resolution of racemic 4-hydroxy-1-butene oxide was achieved in a HPLC column which was loaded with the catalyst and yielded triol **9** with high enantiomeric excess.



Scheme 9 Continuous flow and kinetic resolution

This example illustratively shows that inorganic materials are well suited for continuous flow processes in column-like reactors. Thus, covalently immobilized NH-benzyl-(1*R*,2*S*)-(–)-norephedrine **10** on silica inside a column was doped with ruthenium. This setup was used to carry out continuous asymmetric transfer hydrogenation reactions (Scheme 10) [38]. Remarkably, no catalyst deactivation occurred over a period of one week, which the authors ascribed to the successful site isolation of the catalyst on the support.

Kunz and Kirschning developed a chemically functionalized monolithic material which is based on a glass/polymer composite [28, 29] (refer to Sect. 3.1). This material is available in different shapes including rods, disks, and Raschig rings. The polymeric phase of this composite was chemically functionalized (e.g., substitution of the benzylic chlorine by trimethylamine or sulfonation). Rod-shaped objects were first embedded in a solvent-resistant and shrinkable PTFE tube. This was followed by encapsulation with a pressure-resistant fiber-reinforced epoxy resin housing with two standard HPLC fittings, which created



Scheme 10 Asymmetric transfer hydrogenation in the flow mode

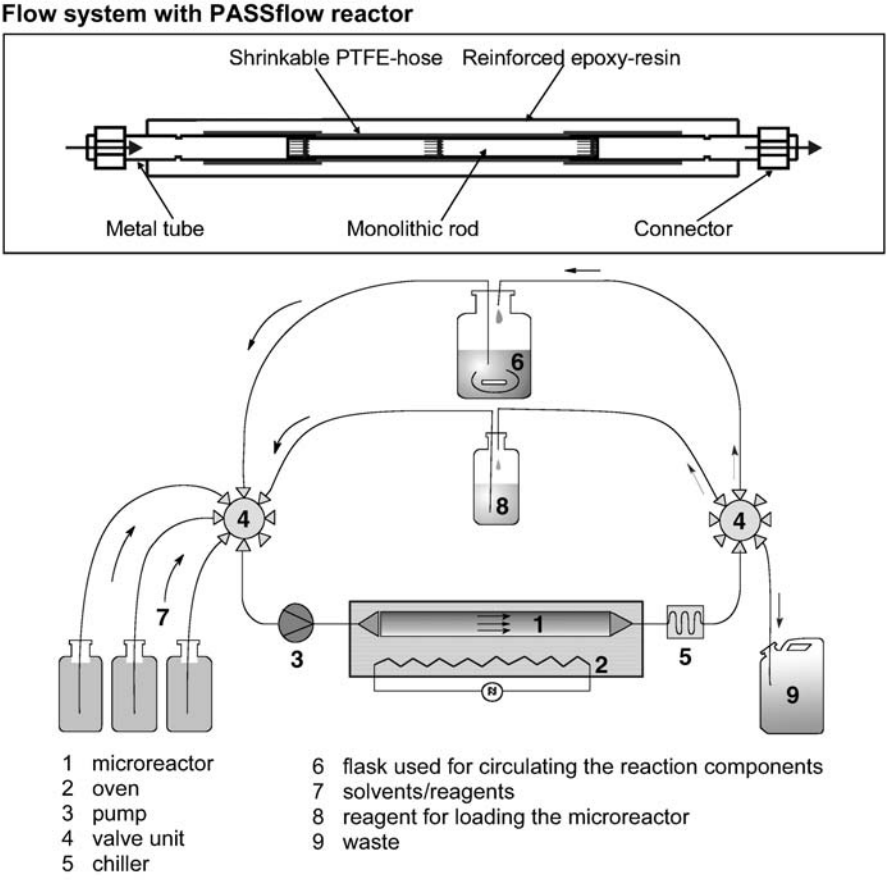
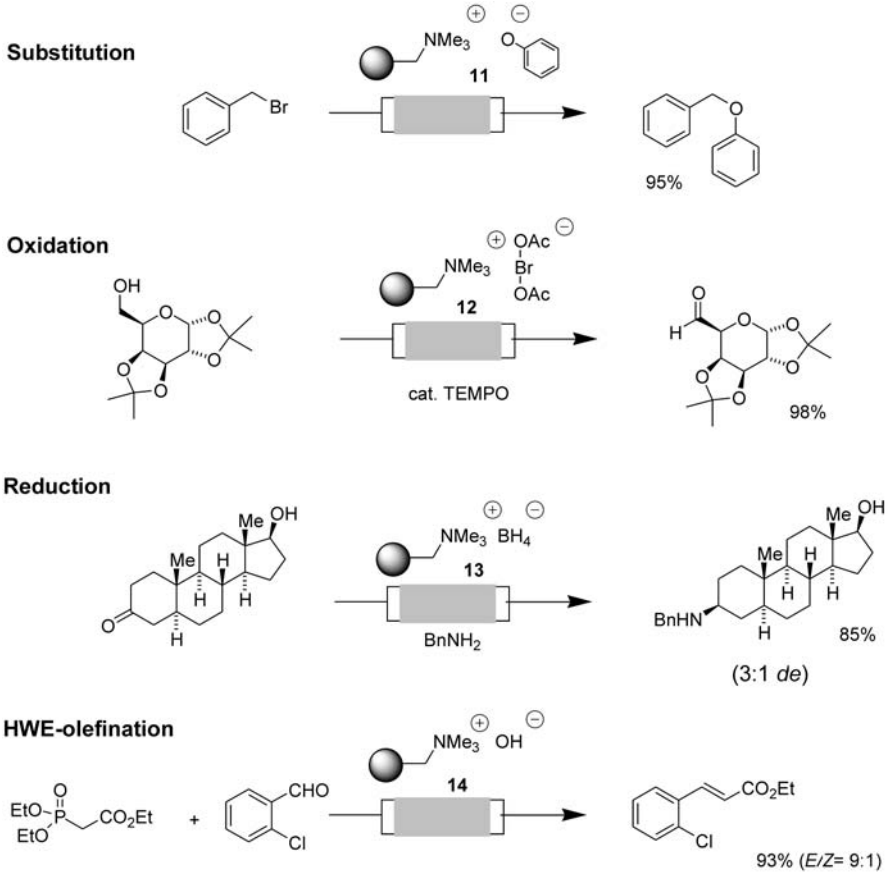


Fig. 5 Cross-sectional view through the PASSflow reactor (PTFE=polytetrafluoroethylene) and setup of the flow system

a microreactor, called a PASSflow reactor, as shown in Fig. 5. This PASSflow (Polymer-assisted solution-phase synthesis in the flow-through mode) system (reactor: about 110 mm in length, about 5 mm diameter) loaded with the strongly basic ion-exchange resin can be functionalized with various anions (about 10 to 20 mass% polymer). These anions are useful as stoichiometrically employed reagents or as catalysts. Initial studies were conducted with chemically functionalized continuous flow reactors **11**–**14** which served as immobilized reagents in basic transformations such as substitution, oxidation [39], reductive amination, and Horner–Wadsworth–Emmons (HWE) olefination (Scheme 11) [28, 40]. The reaction kinetics were too slow to operate the system in a single-pass operation. Instead, an external recycle loop was introduced which guaranteed complete transformation of the starting material, while by-products and excess of immobilized reagent such as bromide, phenolate, phos-



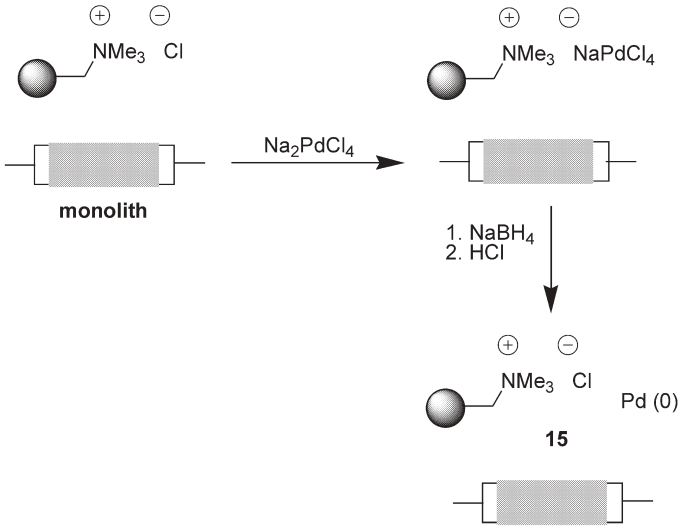
Scheme 11 PASSflow syntheses with stoichiometrically employed reagents

phonate, and others remained ionically bound to the polymeric phase. Finally, removal of solvents was typically the only further purification step.

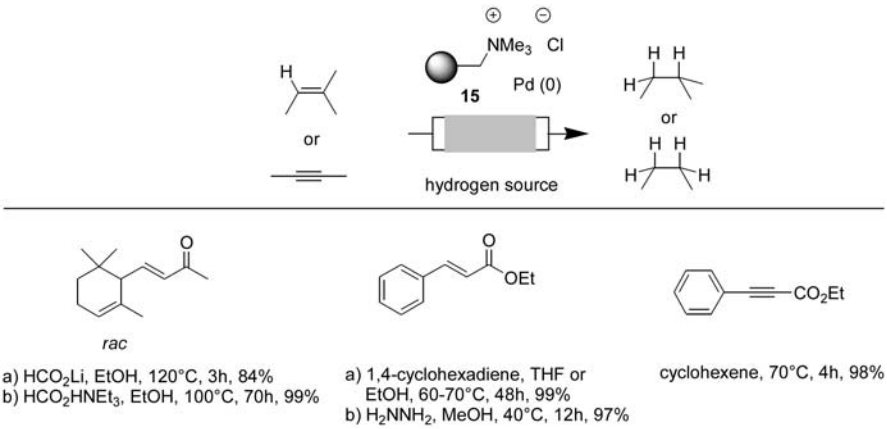
More importantly, catalytic transformations such as transfer hydrogenations, Suzuki cross-coupling reactions, the Heck reaction, and the Sonogashira reaction were routinely performed in these PASSflow reactors under continuous flow conditions (Schemes 12–15) [41].

For this purpose, nanodispersed palladium **15** was introduced into the composite material locating the Pd next to the polymer-bound ammonium cations. This was achieved after ionic attachment of Pd as palladate followed by reduction to Pd(0) and then pumping a solution of borohydride or hydrazine through the reactor (Scheme 12). Besides benzyl ether cleavage transfer hydrogenations were utilized for the reduction of alkenes, alkynes, and aromatic nitro groups (Scheme 13).

Using these palladium(0) particles, the activated aryl halide iodoacetophenone smoothly underwent coupling with *n*-butyl acrylate (Scheme 14) to yield

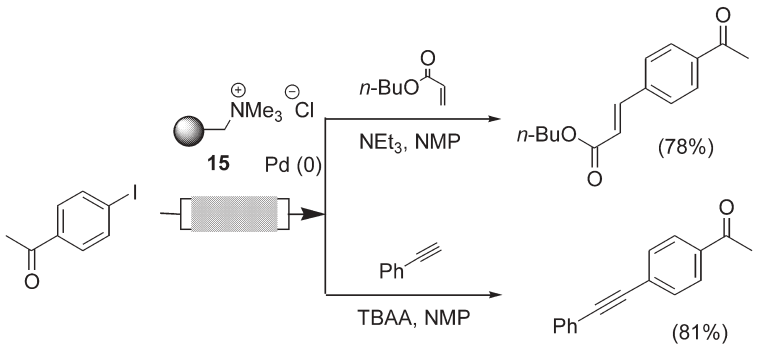


Scheme 12 Immobilization of palladium(0) particles onto the monolithic phase inside the microreactor



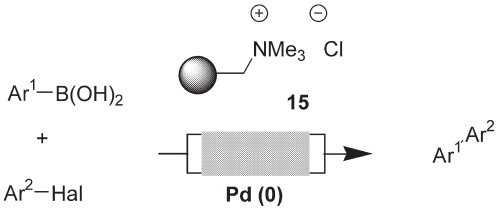
Scheme 13 Transfer hydrogenations of alkenes and alkynes in the flow-through mode using palladium(0) particles

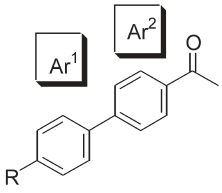
the *E*-configured alkene which was free of homocoupled by-products after aqueous workup. Additionally, the palladium(0) particles allowed the Sonogashira reaction of phenylacetylene and 4-iodoacetophenone to be performed, which led to complete consumption of the starting material and formation of the disubstituted alkyne with only negligible traces (<9%) of homocoupling product [42]. Here, it was important to find homogeneous reaction conditions without the use of CuI in order to avoid blocking of the irregular microchannels.

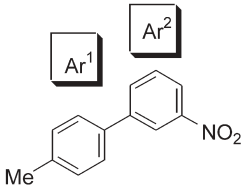


Scheme 14 Ligand-free palladium-catalyzed Heck and Sonogashira reactions in the PASSflow reactor (yields refer to purified products; *TBAA*=tetrabutylammonium acetate; *NMP*=*N*-methylpyrrolidinone)

Finally, the Suzuki–Miyaura reaction, which has become one of the most versatile and important reactions for the construction of C–C bonds, could be performed in a continuous flow process under ligand-free conditions [43]. The PASSflow reactor is suited for the coupling of 4-iodoacetophenone and other aryl halides with arylboronic acid to yield the corresponding diaryls within 3 h without formation of homocoupling by-products (Scheme 15). After collecting







1. Hal= I; R= H
   KOH, H_2O, DMF, 100°C, 3h, 99% (77%)
2. Hal= Br; R= H
   KOH, DMF, 100°C, 24h, 98% (72%)
3. Hal= I; R= Me
   KOH, DMF, 100°C, 7.5h, 98% (74%)

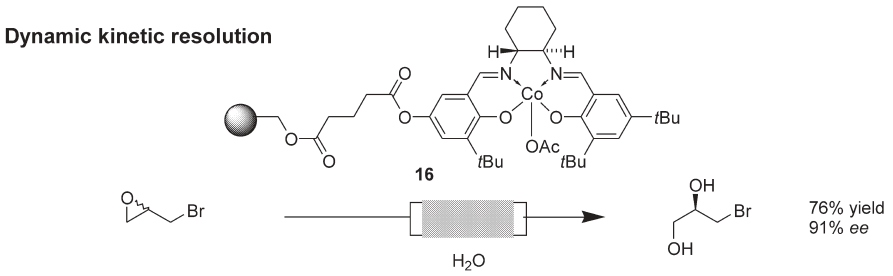
Hal= I; KOH, DMF, 100°C, 4.5h, 98% (76%)

Scheme 15 Ligand-free palladium-catalyzed Suzuki–Miyaura reactions in the PASSflow reactor (first percentage refers to degree of transformation; yields in parentheses refer to purified products)

the reaction solution, aqueous workup is necessary in order to remove the base and residual boronate. However, soluble palladium(0) catalysts like $Pd(PPh_3)_4$ often require complex chromatographic purification due to the phosphine ligands present.

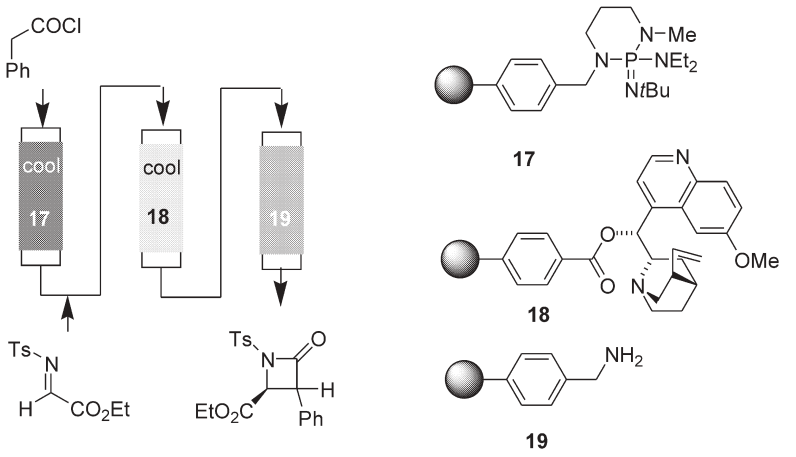
The first example of an asymmetric transformation in a PASSflow reactor was achieved with the known dynamic kinetic resolution of racemic bromohydrin in the presence of water and an unsymmetrical salen–cobalt complex **16** (Scheme 16; refer also to Scheme 9) [44]. This complex was bound to a Merrifield surface via a glutaric acid linker. The yield and the enantiopurity of the resulting 1,2-diol are similar to those reported for the solution phase [45]. However, workup and isolation of the product are highly simplified which makes this approach attractive for use in fine chemical synthesis of enantiomerically pure building blocks. In addition, the reactor was used in three consecutive runs. Reduced catalyst activity was observed during the fourth run, which increased during the following runs (see also the chapter by R. Haag in this volume).

Reaction rates for the flow-through processes were compared with analogous batch-mode reactions using the commercial resin IRA-900. In general, these rates were considerably higher when the reaction mixture was pumped through the irregular microchannels of the monolithic structured reactor. This clearly indicates that the monolithic and functionalized material guarantees a short diffusion path length for the soluble organic reactants and products and in addition enables good convective flow [46].



Scheme 16 Asymmetric transformation in continuous PASSflow synthesis

The power of column-like reactors for continuous flow processes lies in the possibility to sequentially link them up in order to carry out multistep syntheses in solution in one run (see also Schemes 1 and 2). Lectka and coworkers utilized conventional fritted and jacketed columns for this purpose. These columns were filled with conventional functionalized polymeric beads [47]. The continuous flow was forced by gravity. En route to β-lactams polymer beads functionalized with the Schwesinger base **17**, a cinchona alkaloid derivative **18** as a chiral catalyst, and a primary amine **19** were sequentially employed. They first guaranteed the generation of phenyl ketene from phenyl

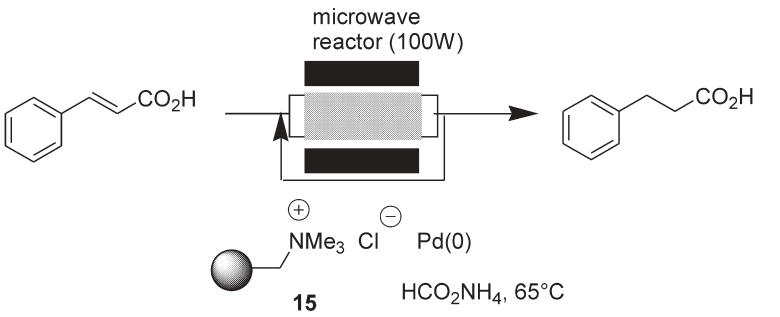


Scheme 17 Three-step preparation of β-lactams in continuous flow mode

acetyl chloride. Secondly they achieved the [2+2] cycloaddition in the presence of imine, and thirdly column **19** was responsible for scavenging traces of intermediate ketene and phenyl acetyl chloride (Scheme 17) [48]. The target β-lactam was isolated in 65% yield (91% *ee*).

Nevertheless, it is important to note that this single-pass concept is only feasible when fast reactions are chosen. This requirement is, however, not necessarily guaranteed when employing immobilized reagents and catalysts. And ideally each of the three reactions has to proceed at a similar rate.

First introduced by Giguere in 1986 [49], microwave-assisted synthesis has evolved as a versatile tool in organic chemistry. Particularly, in the drug discovery approach it has found widespread acceptance due to dramatic shortening of reaction times [50]. With the current microwave equipment, upscale of batch reactions in a microwave field is restricted to volumes well below one liter due to safety reasons (refer also to the chapter by Kappe and coworkers in this volume). However, reactions which are carried out in a continuous flow mode using immobilized reagents or catalysts may be an option to scale up reactions under microwave irradiation conditions. Hence, this concept was first tested for conventional solution-phase synthesis by Strauss and coworkers who developed a continuous microwave reactor (CMR) [51]. Microwave conditions are also successfully adapted to solid-phase synthesis [52], but until today continuous methods have been almost unknown. Only very recently the PASSflow approach was applied to microwave reactions under continuous flow conditions (Scheme 18) [53]. Thus, cinnamic acid was reduced under transfer hydrogenation conditions with nanodispersed Pd(0) as catalyst (refer also to Scheme 14). The transparent continuous flow reactor was incorporated into a microwave field, which allowed acceleration of the process. Indeed, after 5 min 97% of the hydrogenated product was formed and after 10 min only the product could be detected.



Scheme 18 Microwave-assisted continuous transfer hydrogenation with Pd(0) nanoparticles

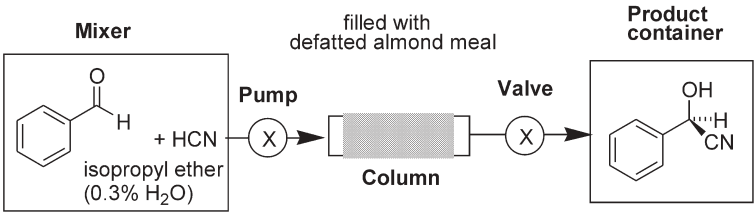
3.4 Continuous Flow Processes with Immobilized Biocatalysts

Continuous flow processes have traditionally been applied in enzyme-mediated transformations and many examples are presented in the article by K.-U. Schöning in this volume. In the present report, we selected two recent academic examples in order to demonstrate the feasibility of continuous flow processes in this context.

Enzymes which are commercially available in an immobilized form are easily applied to transformations in a continuous way using a tubular reaction vessel. The intrinsic advantages are simplified isolation of the enzymes from the reaction mixture, stability and reuse of the enzymes, and in some cases improved reaction kinetics [54]. Importantly, it was shown that scale-up is feasible in industrial environments, making preparation of intermediates for pharmaceuticals and fine chemicals possible on the ton scale.

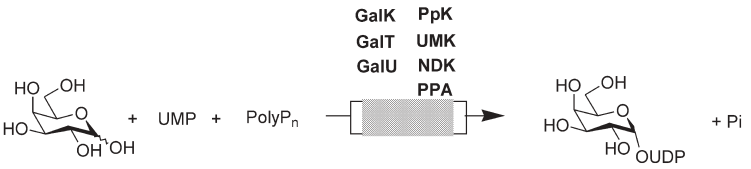
Based on this knowledge, a solution of aldehydes and HCN in isopropyl ether doped with water was pumped through columns filled with defatted almond meal (Scheme 19). The cyanohydrins were isolated in yields above 90% and stereochemical purity between 97 and >99% *ee* with high substrate/catalyst ratio [55]. An output of 3.653 g of product per liter of almond meal per day could be achieved and an equivalent to 66.7 mol/g pure enzyme was produced. Remarkably, the column retained its high catalytic activity after 2 mol of substrate had passed. The authors emphasize that no purification step was needed. The crude products could be used directly for further transformations. It was found that flow rates do have an influence on the yields and enantioselectivity of the process. The authors presented helping rules for calculating optimized flow rates for this particular process.

Wang and coworkers [56] reported a continuous flow process for the efficient and practical gram-scale synthesis of UDP-galactose from inexpensive starting materials. NDP-sugars are particularly valuable, because they are the necessary glycosyl donors in enzyme-mediated glycosidation reactions promoted by glycosyl transferases. These glycosidations are superior to chemical

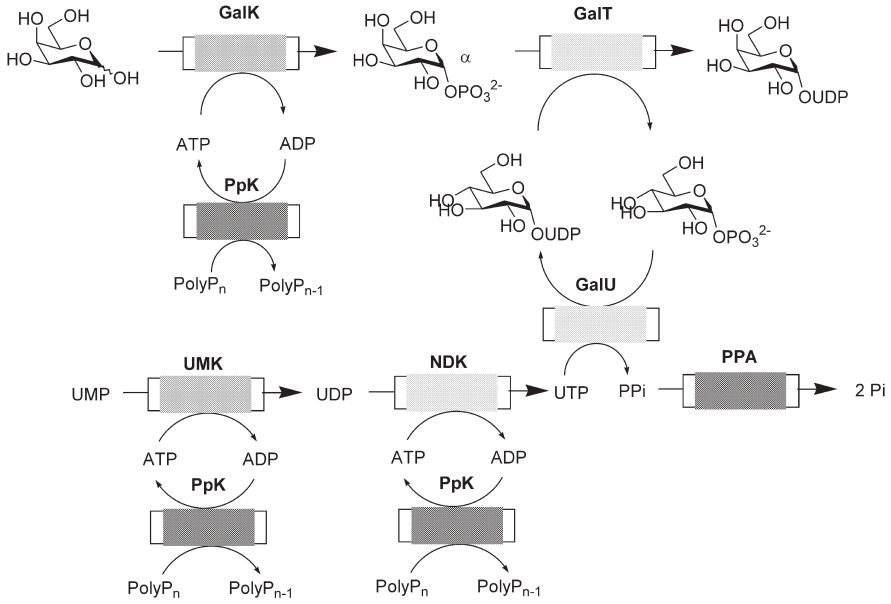


Scheme 19 Enzymatic cyanohydrin formation in a continuous flow process

Overall transformation



Individual steps and intermediates



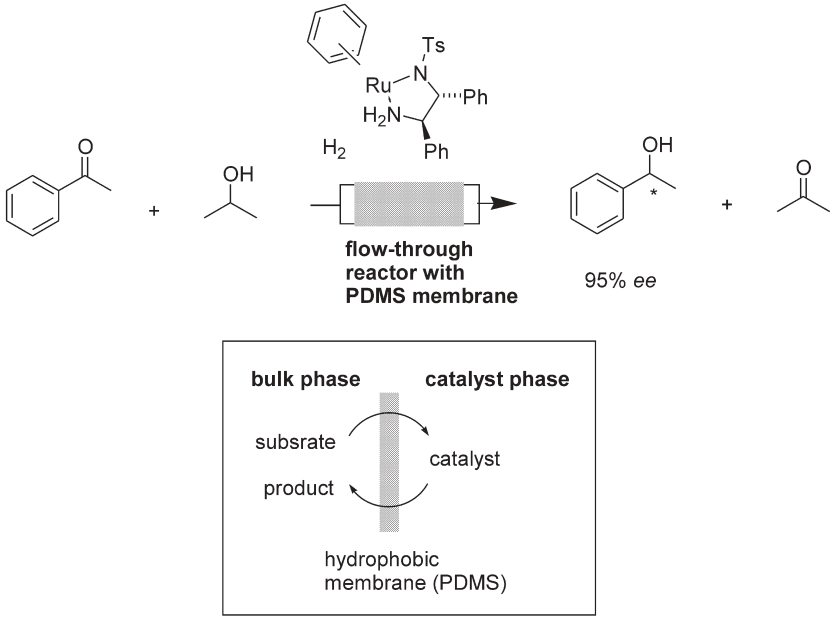
Scheme 20 Multistep enzymatic preparation of UDP-galactose in the flow-through mode. *GalK* (galactokinase; EC2.7.7.6), *GalT* (galactose-1-phosphate uridylyl transferase; EC2.7.7.12), *GalU* (UDP-glucose pyrophosphorylase; EC2.7.7.9), *PPA* (inorganic pyrophosphatase; EC3.6.1.1), *UMK* (UMP kinase; EC2.7.4.14), *NDK* (nucleotide diphosphate kinase; EC2.7.4.6), *PpK* (polyphosphate kinase; EC2.7.4.1)

methods because they are usually highly stereo- and regioselective so they do not require protected carbohydrates. The synthesis depicted in Scheme 20 was guided by a proposed biosynthetic pathway and has the potential to overcome the traditional bottleneck of enzyme-mediated glycosidations, namely the provision of sufficient amounts of NDP-sugars. Not less than seven overexpressed enzymes, each of them immobilized by histidine tags on nickel agarose beads, were employed (Scheme 20). The reaction mixture, which contained all starting materials, was continually circulated through a column loaded with enzyme-charged beads. Although the reactions proceeded with slower kinetics than in solution, the space-time yield of the on-column reaction was superior to that of the classical solution-phase approach. Importantly, the immobilized enzymes could be reused at least four times with only slight loss of activity.

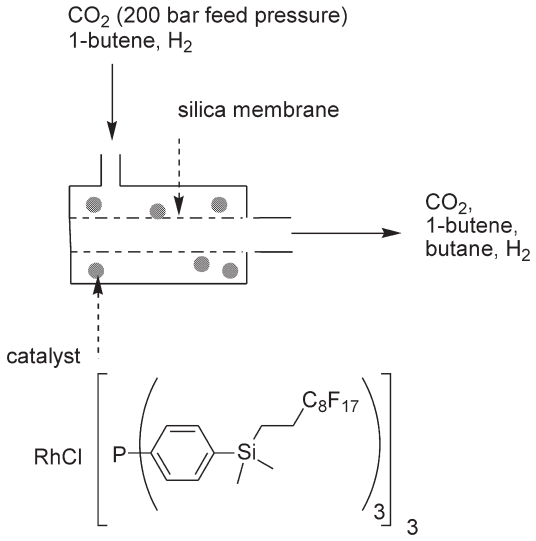
4
Alternative Immobilization Concepts for Continuous Flow Processes

The examples that are listed in Sect. 3 commonly focussed on solid-phase immobilization concepts for catalysts in flow-through reactors. There are alternative strategies to separate starting materials and products from the catalytic system. These are particularly associated with new solvent systems and fluids such as ionic liquids, perfluorinated solvents, and supercritical CO_2. In addition, continuous flow processes in conjunction with membrane technology are showing increasing potential, particularly in catalyst recovery. It can be considered as a special heterogenization method of soluble catalysts and reflects the fact that recycling of homogeneous transition metal catalysts is very expensive or even impossible [57, 58]. Catalysts are separated from the educts and products by a polydimethylsiloxane (PDMS) membrane prepared such that the catalyst is not able to pass the membrane (Scheme 21). In very recent publications the coupling of catalysis to dialysis was reported [59]. Homogeneous 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) or tosyl-*N*,*N*′-diphenyl-1,2-ethanediamine (TsDPEN) catalysts applied in transfer hydrogenations could be recovered efficiently and reused several times without loss of activity. Van Koten and coworkers applied homogeneous dodecakis (NCN-Pd^{II}) catalyst in a related nanofiltration membrane reactor under continuous reaction conditions [60]. This technique was exploited in the double Michael reaction between methyl vinyl ketone and ethyl-α-cyanoacetate. Due to its macromolecular dimensions, the catalyst is retained in the reactor (R=99.5%) during catalysis.

Supercritical solvents are completely miscible with gaseous reagents and therefore avoid possible diffusion limitation in gas–liquid reactions. An important aspect for employing homogeneous catalysts in $scCO_2$ is the solubility of the catalyst, which can be achieved by attaching perfluoroalkyl groups to the ligands. Broeke and coworkers developed a continuous reactor for homogeneous catalysis in $scCO_2$ which allowed an integrated catalyst separation (Scheme 22) [61]. Perfluoro-tagged Wilkinson catalyst served as soluble hy-



Scheme 21 Enantioselective reduction of acetophenone by dialysis-coupled catalysis

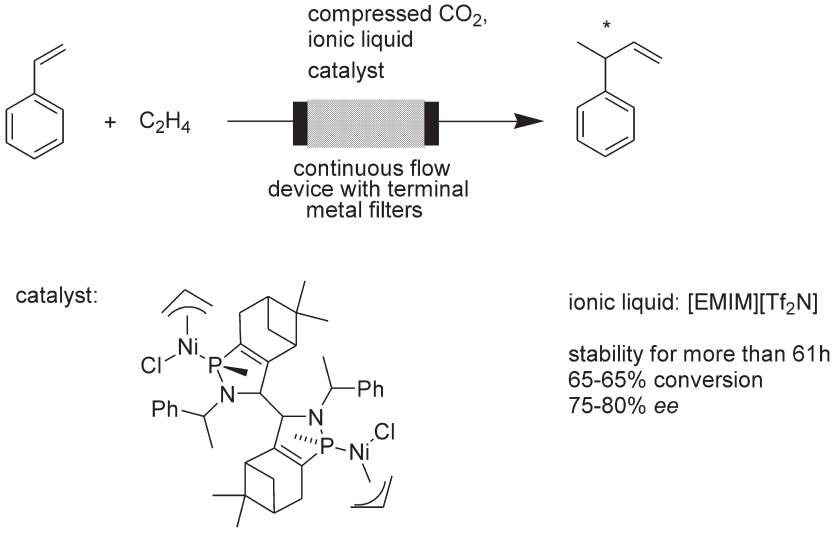


Scheme 22 Continuous flow reduction with $scCO_2$ as fluid and target-specific perfluorinated Wilkinson catalyst

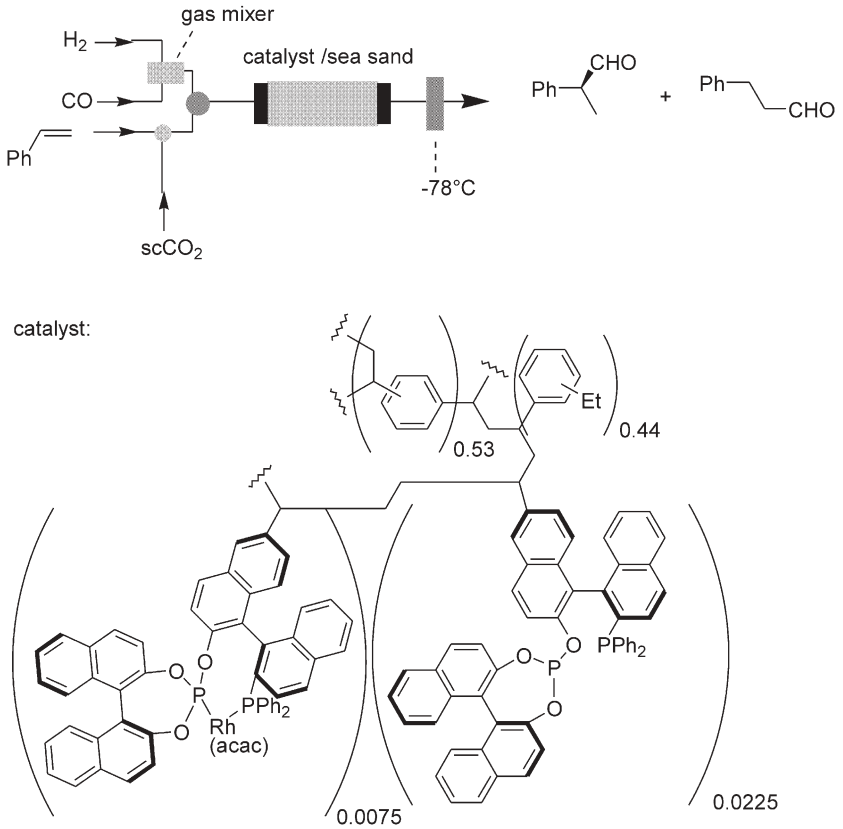
drogenation catalyst, which was located on one side of a microporous silica membrane (average pore size: 0.6 nm). The low cohesive energy density of the perfluoro tag allowed the required solubility of the catalyst in $scCO_2$. Simultaneously the increased size ensured effective retention of the catalyst in the membrane reactor. Both reactants and products can diffuse through the membrane. The authors note that this process may be highly relevant for the further development of clean chemical processes based on homogeneous catalysis carried out in high-density gases.

Leitner and Wasserscheid devised a continuous flow apparatus for homogeneous asymmetric hydrovinylation performed in a fluidic environment which consisted of an ionic liquid and compressed CO_2 [62]. Wilke's complex served as the catalyst and among various ionic liquids employed the cations 1-ethyl-3-methyl-imidazolium (EMIM) with a weakly coordinating anion such as the bis-triflic amide anion were found to be best suited for high rates of transformation, good regioselectivity, and good enantioselectivity (Scheme 23). It turned out that this system offers a versatile immobilization technique for homogeneous catalysis. The combination of nonvolatile ionic liquids with nonhazardous CO_2 allows product separation from the catalyst without exposing the catalyst to a variation of temperature, pressure, or substrate concentration. Advantageously, the compressed CO_2 greatly decreases the viscosity of the ionic catalyst solution, thereby facilitating mass transfer during the catalytic reaction. The authors point out that this system enables a reactor design that is similar to classical fixed-bed reactors [63].

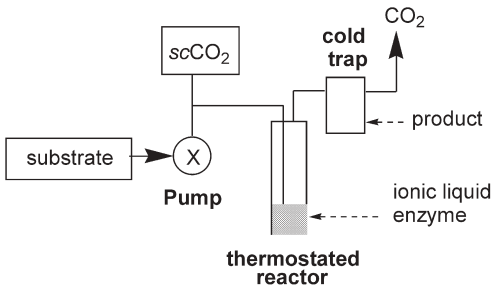
Nozaki and coworkers recently disclosed the use of (*R*,*S*)-BINAPHOS-Rh(I) catalyst that is covalently anchored to a highly cross-linked polystyrene in the



Scheme 23 Continuous asymmetric hydrovinylation with catalysts immobilized in an ionic liquid



Scheme 24 Continuous asymmetric hydroformylation using gases as reactants and fluids



Scheme 25 Enzymatic transformation using ionic liquids for immobilization of the enzyme and supercritical CO_2 as fluid

asymmetric hydroformylation of nonvolatile olefins such as styrene (Scheme 24) [64]. The reaction was performed in a supercritical CO_2-flow column reactor (120 atm) and yielded the isoaldehyde (74–81%) with high *ee* value (81–86%) at a high level of conversion (81–94%). The activity of the catalyst marginally decreased after seven runs.

Based on their work on supercritical CO_2 (see also Scheme 23), Reetz and Leitner introduced a technologically new and interesting continuous flow process for enzymatic reactions [65]. The group designed a protocol for enzymatic reactions, namely the lipase-catalyzed acylation (CAL B) of octan-1-ol by vinyl acetate in ionic liquids (1-butyl-3-methylimidazolium bis(trifluoromethanesulfonimide) [BMIM][BTA]) using supercritical CO_2 as the mobile phase (Scheme 25). The alcohol is pumped through the biphasic system and the products are obtained in solvent-free form in a cold trap. The enzyme/ionic liquid mixture can be recycled in batchwise or continuous flow operations.

5 Perspectives and Outlook

At the end of the last century the art of synthesis created the impression that every thinkable molecule can be prepared in a reasonable amount of time as long as enough manpower is available. This impression, however, denies the fact that many synthetic routes and chemical methods are far from being efficient in terms of ease of isolation and speed. This is particularly true when multistep sequences are envisaged. Moreover, despite the tremendous efforts in automation and the optimization of solid-phase-assisted synthesis, in the past 10 years there has been an overall deficiency in new chemical technologies. Continuous flow processes can be considered to be a significant breakthrough towards more efficient syntheses including multistep sequences.

But the time has come to include technological aspects in chemical research which are focussed on new ways of performing organic synthesis. The examples given in this overview are meant to lead the reader's attention to rethink classical synthetic environments and combine or merge new methodologies and technologies for creation of new synthesis platforms. Indeed, flow-through processes can already be combined with functionalized solid phases, ionic liquids, supercritical CO_2, and microwave irradiation. Nevertheless, the number of examples of continuous flow processes performed in the laboratory is only small today. But predictably a bright future can be expected for this approach. The time will soon come when many chemists will be able to carry out synthesis in continuous flow processes with standard laboratory equipment at reasonable prices. Whatever chemists require – synthesis of a few milligrams of a compound in drug discovery, the synthesis of building blocks on the multigram scale for parallel synthesis, the preparation of kilogram quantities for clinical research, or even the production of fine chemicals – continuous flow processes are a universal lever and a crucial link between differently scaled reactions.

There is a chance that continuous flow synthesis will see a similar development in chemical synthesis as was encountered in analytical chemistry when HPLC was introduced into the chemist's laboratory. In this context, microreactor technology and microfluid systems will also play an important role [66, 67].

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Immobilized Catalysts in Industrial Research and Application

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Abstract The present state of the art of the application of immobilized/heterogenized homogeneous catalysts in industrial research and production will be introduced. Special attention is drawn to catalysts which have been tested for the synthesis of chiral compounds. In a second part, commercially available immobilized catalyst systems will be presented, giving the reader an impression of what the favored directions of industrial development are and where future applications of such systems are most likely to occur.

Keywords Immobilized metal catalysts · Heterogenized homogeneous catalysts · Solid supported catalysts · Industrial catalysis · Commercially available immobilized catalysts

1 Introduction

1.1 Classification of Catalysts

Catalysts have been successfully used in the chemical industry for more than 100 years. The numerous catalysts known today can be categorized in various ways. One possibility is to classify them with regard to the state of aggregation in which they act (see Fig. 1) [1]. According to this categorization, catalysts can be divided into three groups: homogeneous catalysts, heterogeneous catalysts, and an intermediate group, to which biocatalysts and heterogenized homogeneous catalysts belong. The latter ones are also referred as "hybrid catalysts" [2, 3].

By far the most important catalytic systems are the heterogeneous catalysts, which find an extremely broad use in the chemical industry. Depending on their structure and method of production, they can be divided into bulk catalysts and supported catalysts. Bulk catalysts are mainly produced from cheap active components, and since the preferred method of production is precipitation, they are also known as precipitated catalysts [1]. Supported catalysts can be divided into impregnated catalysts and shell catalysts, the latter ones bearing the active part only on the surface. In particular, catalysts with expensive active components such as noble metals are employed as supported catalysts, and a widely used support is Al_2O_3. Catalytic processes that take place in a uniform gas or liquid phase belong to the field of homogeneous catalysis. Homogeneous catalysts are generally well-defined chemical compounds or (transition) metal complexes, which are molecularly dispersed in the reaction medium.

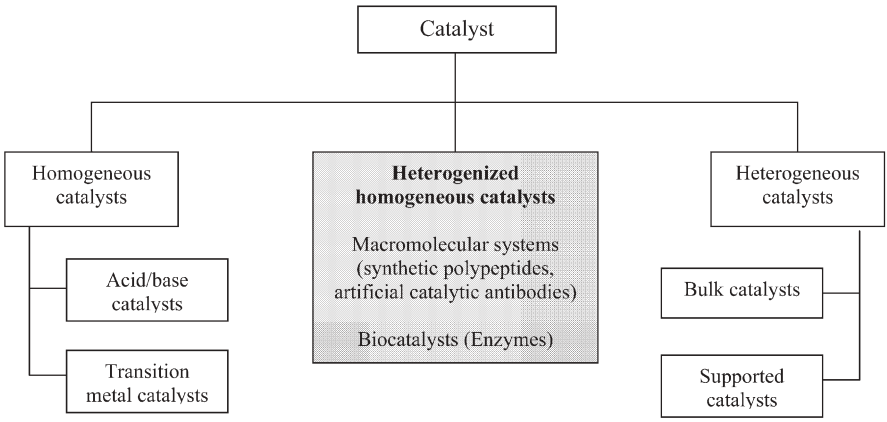


Fig. 1 Classification of catalysts

The investigation of the above mentioned class of hybrid catalysts has been driven by the vision of combining the positive aspects of a homogeneous catalyst (e.g., high activity, high selectivity, good reproducibility) with those of a heterogeneous catalyst (e.g., long lifetime and ease of separation) and represents an important field of catalysis research [4].

1.2 Immobilization Techniques

Since the late 1960s many approaches have been published by academia and industry to "heterogenize", "immobilize" or "anchor" a homogeneous catalyst [5–8]. In addition, many excellent reviews have emerged in recent years, which describe in detail the synthesis and (academic) use of polymer-supported catalysts [9–19] and catalysts on inorganic carriers [20–24], or both [4, 25–27] (Fig. 2). Covalent binding is by far the most frequently used strategy. It can be effected either by copolymerization of functionalized ligands with a suitable monomer, or by grafting functionalized ligands or metal complexes with reactive groups on to a preformed support.

Another common and simple immobilization technique of catalytically active metal complexes is ionic binding, which is particularly useful for cationic rhodium or palladium catalysts (*vide infra*). Various supports with ion-exchange capabilities can be used, including standard organic or inorganic ion-exchange resins, inorganic materials with polarized groups, and zeolites.

The advantage of immobilization by adsorption is the ease of preparation of the heterogenized catalyst by simple procedures, very often even without the need to previously functionalize the ligand. In this respect, immobilization by ionic binding can be seen as a special case of heterogenization via adsorption. An innovative modular method was developed by Augustine, who used heteropoly acids as anchoring agents to attach various metal complexes to different supports (see also Sect. 3.2) [28].

Using entrapment as a method for heterogenization, the size of the metal complex is more important than the specific adsorptive interaction. There are two different preparation strategies: One is based on building up catalysts in well-defined cages of porous supports. This approach is also called "ship in a bottle" [29]. The other approach is to build up a polymer network around a preformed catalyst.

Supported aqueous-phase catalysts (SAPC) can be seen as a special case of adsorption, whereby a water-soluble catalyst dissolved in a very polar solvent is adsorbed on a hydrophilic support forming a water film on the inner surface of the support [30, 31]. In the case of supported liquid-phase catalysis (SLPC), the water film on the inner surface is replaced by a solvent of low vapor pressure (e.g., phthalic acid esters) [2]. The reaction itself takes place in the supported liquid or at the interface of the supported liquid film, or in the gas phase or organic phase when dealing with SLPC or SAPC, respectively. The use of SLPC catalysts is generally restricted to the synthesis of low-boiling compounds.

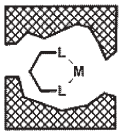
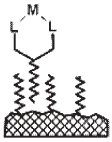
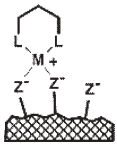
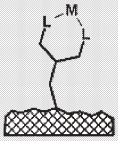
Technique	Comments / Problems
Biphasic Catalyst	Aqueous (Phase Transfer Catalyst) Non-aqueous
Supported Liquid-Phase Catalysts (SLPC)	Nonvolatile organic liquid in porous support
Supported Aqueous-Phase Catalysts (SAPC)	Water soluble catalyst in thin aqueous film on hydrophilic high surface area support
Catalyst anchored to support via physisorption or entrapment 	Strict control of porosity of support Problems with diffusion Restricted applicability
Catalyst anchored by adsorption 	Possible competition with solvents, substrates Restricted applicability
Catalyst anchored to support via ionic bonding 	Anionic or cationic Possible competition with ionic substrates, salts
Catalyst anchored to support via covalent bonding 	Polymeric organic matrix, inorganic matrices Broad applicability

Fig. 2 Immobilization techniques [7]

The long-known field of biphasic catalysis represents on the one hand liquid–liquid systems containing two immiscible liquids without any additional additive. On the other hand, there is the option of applying phase transfer catalysts to increase the mobility of a given catalyst or reactant into a favored phase.

Finally, to complete the field of heterogenization, it should be mentioned that the catalyst class of synthetic polypeptide derivatives and catalytic antibodies do not belong to the "classical" heterogenized catalysts as they do not have a known homogeneous counterpart. They are macromolecular systems

where activation and also stereocontrol are connected to supramolecular effects.

In order for the immobilized version of the homogeneous catalyst to be successful in an industrial chemical process, it must not negatively impact the economics of the process in view of its cost, activity, selectivity, and lifetime. According to Hagen [1] the ideal immobilized metal complex for industrial applications has not yet been found, as was shown by weighing up the advantages and disadvantages of different types of catalysts.

Advantages of immobilized catalysts:

- Separation and recovery of the catalyst from the product stream is straightforward (see also [32]).
- Multifunctional catalysts can be obtained in which more than one active component is bound to a carrier.
- Stabilization of highly reactive, coordinatively unsaturated species that cannot exist in solution.

Disadvantages:

- Insufficient stability of the immobilized homogeneous catalysts due to leaching of the metal and/or ligand.
- Problematic features of homogeneous catalysts, such as corrosion, catalyst recovery, and catalyst recycling, have so far not been overcome satisfactorily.
- Lower catalytic activity than with homogeneous catalyst due to:
- Poor accessibility of the active sites for the substrate
- Steric effects of the matrix
- Incompatibility of solvent and support (in particular polymers)
- Deactivation of the active center
- Inhomogeneity due to different linkages between support matrix and complex.

The driving force for the introduction of catalytic processes in the chemical industry is almost exclusively economic considerations. As mentioned before, the classical heterogeneous catalysts find widespread use, in particular for the synthesis of bulk and commodity chemicals. Homogeneous catalysis, especially in the field of asymmetric catalysis, has a considerably smaller significance for industrial production issues, although a large number of important processes have been developed (for an excellent compilation see [33]). The immobilization of catalysts may have advantages in given cases, but the reference and strongest competitor certainly always is the corresponding homogeneous system. The application of (heterogenized) homogeneous catalyst is more probable the higher the added value of a desired product is. Thus, these types of catalysts mainly find use in the pharmaceutical and agrochemical industries and to a lesser extent in the manufacture of specialty and bulk chemicals.

In this review, we mainly focus on the application or attempted application of heterogenized catalysts and catalytic polymers in the chemical industry. An-

other chapter will deal with the commercialization of such catalysts for industrial use or academia. It was specifically tried to show in which direction future developments may go. In order to provide a broad range of accessible information, many examples were taken from recent patent applications and from web publications, but unfortunately these sources often have the disadvantage of being less precise or even incomplete. To the careful reader it might seem as if important information is missing, but for those cases the information was simply not accessible.

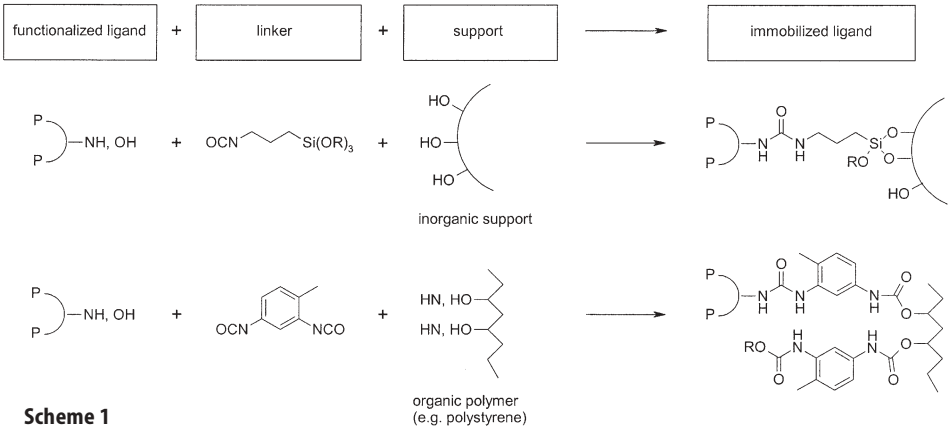
2
Use of Immobilized Catalysts in the Chemical Industry

In a very recent article, Cole-Hamilton described new approaches to catalyst separation, recovery, and recycling [32]. He states that, to his knowledge, only one commercial example of a homogeneous catalyst heterogenized on a solid support is presently in use, i.e., for the carbonylation of methanol. Chan et al., in their 2002 review on recoverable catalysts, came to the same conclusion [15]. These two statements are in full agreement with our experience. Although many publications and in particular patent applications show the potential interest of the chemical industry in this field, it was not possible to find more confirmed production processes. It will be seen from what follows that many attempts have been made to use and develop immobilized catalyst systems, but in all cases they suffered from missing economy. Nevertheless, we feel that it is important to demonstrate what has been tried so far.

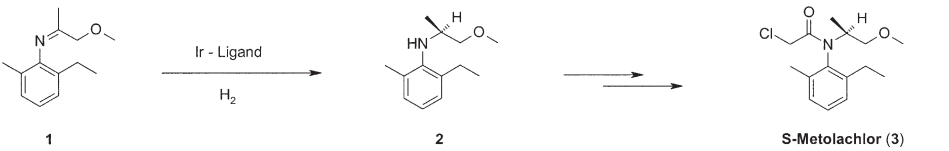
2.1
Hydrogenation Reactions

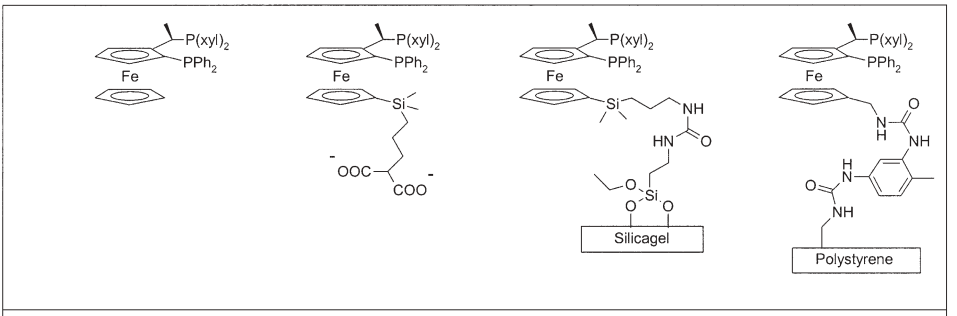
There have been attempts by several large companies to immobilize homogeneous hydrogenation catalysts – in general only with moderate success. Solvias AG is one of the organizations active in this field, and parts of the work can be tracked back to the former Ciba-Geigy AG and later Novartis Corporation. Here, it was tried to immobilize various diphosphine ligands bearing an additional hydroxy or amino functionality onto a solid support via commercial diisocyanate linkers [34–37]. The solid supports used were chosen from the group of inorganic supports (silica, aerosil) and organic polymeric structures, for instance aminomethylated polystyrene (Scheme 1). Best results in hydrogenation reactions were obtained with silica gel-supported catalysts, since this material does not change its properties during use in organic solvents. In many cases, the immobilized catalysts were at least as efficient as their homogeneous counterparts or were even superior with respect to catalytic activity and productivity.

During the search for a reasonable enantioselective synthesis route toward the herbicide metolachlor (**3**), it was tried to immobilize functionalized Josiphos ligands (Scheme 2) [38]. Silica gel- and polystyrene-bound versions



Scheme 1



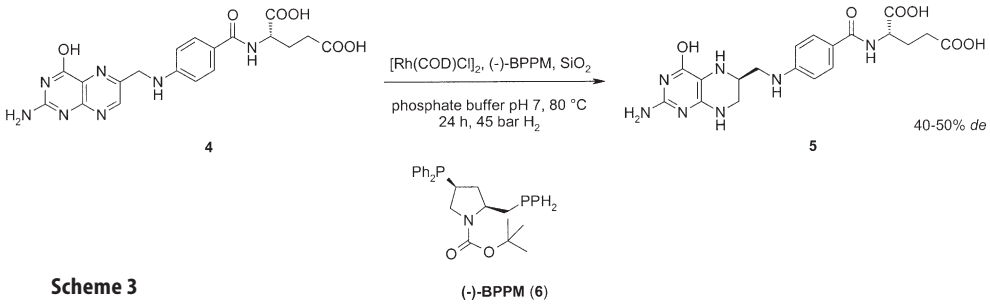


S/C	120 000	120 000	120 000	50 000
time	2.1 h	3 h	10 h	30 h
ee	80%	79%	78%	74%

Scheme 2

were synthesized but were found to be significantly less active than the corresponding extractable, soluble catalysts, and therefore it was decided to apply a non-immobilized catalyst in the production process. This was despite the fact that the silica-bound catalyst is holding the world record of 120,000 TON for an immobilized catalyst [39]. The scope and limitations of heterogeneous enantioselective catalysts have also been addressed by Blaser et al. in a similar context [40].

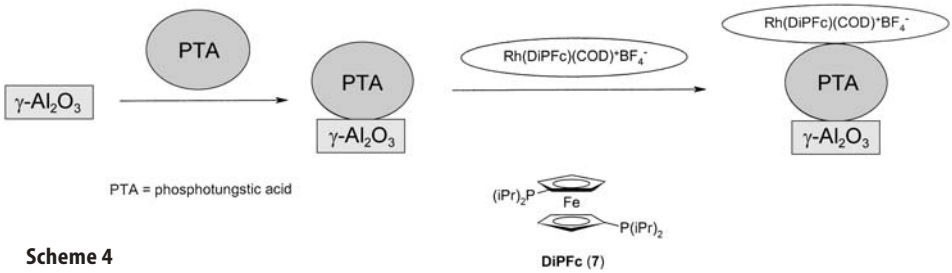
The use of an immobilized rhodium(I) complex for the diastereoselective hydrogenation of folic acid (**4**) to tetrahydrofolic acid (**5**) has been described



Scheme 3

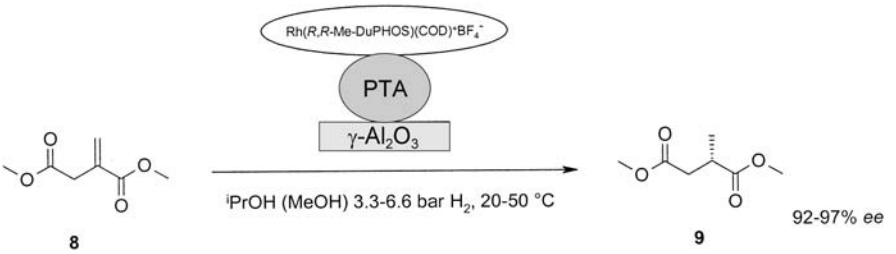
by BASF AG some years ago [41]. The optically active diphosphine (–)-BPPM (**6**) proved to be the most versatile ligand among many others tested and resulted in an active and recyclable catalyst after immobilization onto silica gel (Scheme 3). The hydrogenations were performed in aqueous buffer systems and resulted in high overall conversions but only moderate diastereoselectivities in the range of 40–60% *de*.

An immobilized ferrocene-based catalyst for efficient and selective aldehyde hydrogenation was published by Chirotech Technology [42]. The company used the Augustine technology (see Sect. 3.2) for the immobilization of different catalysts onto alumina and silica gel (Scheme 4). The prepared catalysts satisfied the following criteria: (1) the catalyst is easily and economically immobilized, (2) low metal leaching occurs during catalysis, (3) the immobilized catalyst displays high catalytic activity and efficiency for the desired transformation, (4) the immobilized catalyst operates under mild conditions (e.g., low temperatures and pressures), (5) the immobilized catalyst exhibits high levels of selectivity (e.g., chemoselectivity, stereoselectivity, etc.), (6) the immobilized catalyst exhibits broad tolerance of organic functionality (e.g., sulfur, alcohol, amine, etc.), (7) the immobilized catalyst precursor is robust (insensitive to air and moisture), and (8) the immobilized catalyst may be removed efficiently from the reaction mixture and recycled. The use of DiPFc (**7**) afforded an especially versatile catalyst, since it can also be used for the hydrogenation of functionalized alkenes and alkynes [43]. Worth mentioning is the fact that the catalyst was developed in a joint collaboration with Engelhard [44].



Scheme 4

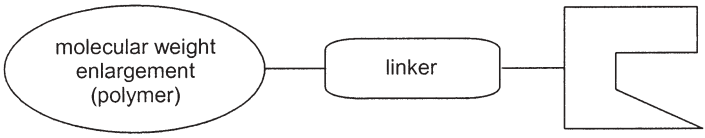
Engelhard also investigated the possibility of synthesizing immobilized chiral DuPHOS catalysts [44, 45]. Two different homogeneous catalyst precursor complexes, i.e., $[Rh(COD)_2]BF_4$ and $[Rh(COD)Cl]_2$, were immobilized on phosphotungstic acid-modified alumina to form γ-Al_2O_3/PTA/$Rh(COD)_2BF_4$ and γ-Al_2O_3/PTA/$[Rh(COD)Cl]_2$, respectively. These immobilized complexes have been modified with (*R*,*R*)-MeDuPHOS to form the immobilized chiral catalysts γ-Al_2O_3/PTA/Rh((*R*,*R*)-MeDuPHOS)(COD)BF_4 and γ-Al_2O_3/PTA/Rh((*R*,*R*)-MeDuPHOS)(COD)Cl, respectively. It could be shown that immobilization and subsequent modification by ligand exchange reactions of general precursor complexes is a powerful method to prepare chiral and achiral anchored rhodium catalysts. Enantioselective hydrogenation reactions performed on the substrate dimethyl itaconate (**8**, Scheme 5) showed that the activity and selectivity differences between the homogeneous DuPHOS catalysts and the immobilized versions became roughly comparable at elevated temperature and hydrogen pressure. Enantiomeric excesses were typically in the range of 95–97% *ee*, and it could be demonstrated that catalyst leaching can be minimized by optimization of the reaction parameters.



Scheme 5

Finally, it is worth mentioning that both ICI/Synetix and Degussa filed patent applications in the field of catalyst heterogenization. ICI/Synetix described catalytic systems which can be used for asymmetric hydrogenation reactions and which comprise chiral metal–ligand complexes immobilized on a mesoporous aluminosilicate [46]. Particularly suitable complexes possessed a cationic metal ion and a neutral mono- or bidentate ligand, and the catalyst was formed by ion exchange with the acidic sites of the support. Preferred complexes were rhodium(I) complexes of (*R*)-BINAP, (*R*)-Prophos, (*R*,*R*)-DuPHOS, and (*R*,*S*)-Josiphos. The catalysts were reusable and maintained their activity even after several runs, although the enantiomeric excess slightly decreased over the time.

Degussa developed a way to construct molecular weight-enlarged ligands and catalysts, which can be used in continuous asymmetric hydrogenation processes in membrane reactors [47]. This could be achieved by covalent bonding of modified catalyst systems via a linker to polymers such as polysiloxanes, polystyrenes, polyethers or polyacrylates, as exemplified in Scheme 6 (for further information see also the chapter of Haag in this volume).



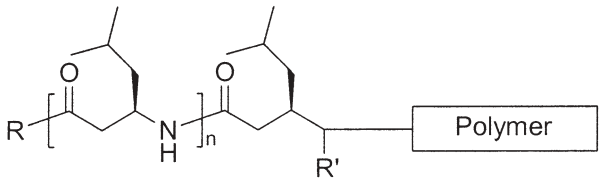
Scheme 6

2.2
Oxidation Reactions

The Juliá-Colonna asymmetric epoxidation using poly-L-leucine has been known for many years and should be referred as a special case of immobilized catalytic systems. The original method employed a system consisting of the insoluble catalyst (generally polyalanine or polyleucine), a solution of an enone in a water-immiscible organic solvent, and a basic aqueous layer containing H_2O_2 (known as the triphasic protocol) [48, 49]. In a collaboration of Degussa and Roberts et al., two protocols were reported that lead to greatly reduced reaction times and a significantly expanded substrate range. The first, referred to as the biphasic protocol, consists of the insoluble catalyst and a solution of the substrate and an anhydrous urea/H_2O_2 complex in THF/DBU [50]. The second, carried out in a homogeneous solvent mixture of water and DME, utilizes sodium percarbonate as both oxidant and base and is known as the percarbonate protocol [51]. All three protocols employ simple polyamino acids such as polyleucine or polyalanine as catalysts, typically with chain lengths of around 30 residues. However, in the case of the biphasic protocol it is also possible to utilize a form of the catalyst in which the insoluble polyamino acid is adsorbed onto silica (PaaSiCat) [52–54]. The advantages of the silica-supported polyamino acid catalyst are improved filtration properties, higher catalyst activity (allowing increased substrate loading), and improved catalyst recycling. In comparison, the filtration properties of the unsupported polyamino acid were unsuitable for large-scale work; even on the sub-gram scale filtration proved to be problematic due to the small particle size of the catalyst. For this reason the biphasic protocol, utilizing silica-supported polyleucine, was the method of choice for optimization.

A further approach toward polymeric epoxidation catalysts was also carried out by Degussa and Roberts et al. and is based on the use of poly-β-amino acids attached to resins (Scheme 7) [55]. Enantiomeric excesses as high as 70% *ee* were achieved at high conversion rates using this system. High optical purities could also be achieved by using polymer-bound (polyethylene glycol or styrene based) oligo-L-leucines, and epoxidations in membrane reactors were shown to be feasible [56].

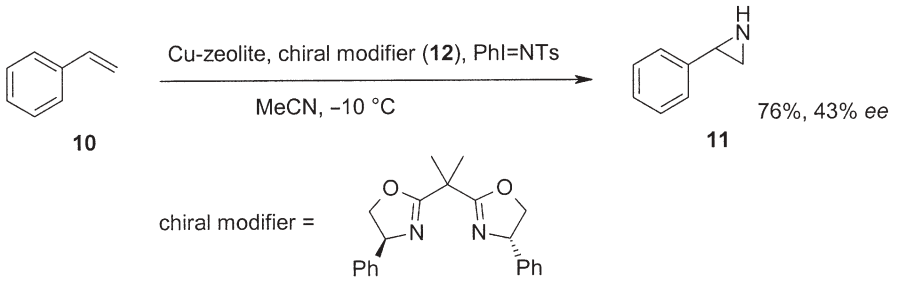
Bayer is another company which started activities in this particular field. The company describes in recent patent applications the epoxidation of α,β-unsaturated enones or -sulfones under optimized conditions. This is the ap-



Scheme 7

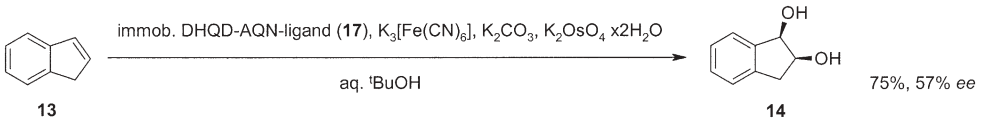
plication of a water-free biphasic system in the presence of a base and a phase-transfer catalyst and the use of non-preactivated homo-polyamino acids [57–59]. Bayer also describes a new procedure for the preparation of derivatized polyamino acids possessing a diaminopropane backbone with improved catalytic activity [60] (see also Sect. 3.4).

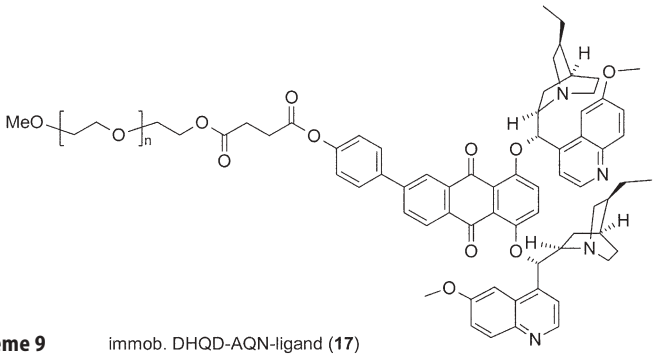
An approach toward the (asymmetric) aziridination of double bonds was published by ICI [61]. The company disclosed an acidic, copper-impregnated zeolitic material having a pore size large enough for the reactants to enter and for the aziridination product to leave the zeolite supercage. Asymmetric aziridinations may be conducted by treating the catalyst with a chiral modifier, e.g., the 4,4′-disubstituted bis(oxazoline) **12**, before contact with the nitrene donor (PhI=NTs). The aziridines could be isolated in moderate optical purity (30–40% *ee*), and Scheme 8 shows the exemplified transformation of styrene (**10**) to the corresponding aziridine **11**. Further details of this topic can be found in a research project, financially supported by Synetix [62].



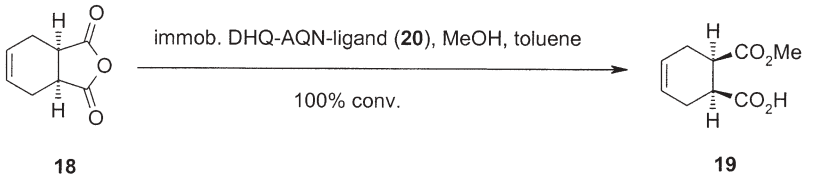
Scheme 8

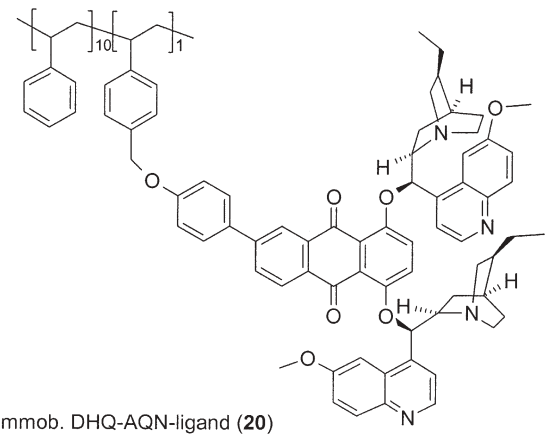
Molecular-weight-enlarged ligands and catalysts were also tested for dihydroxylation and aminohydroxylation reactions of unsaturated compounds by Degussa [63]. The invention comprises the use of optically active, homogeneous, soluble polymer-supported ligands containing chirality-inducing units such as dihydroquinidine or dihydroquinine groups. The polymer may be selected from the group of polyacrylate, polyvinylpyrrolidone, polysiloxanes, polybutadiene, polyisoprene, hydrocarbon polymers, PEG, PPG, polystyrene, or polyoxazoline, and the bulky catalyst can be used in membrane reactors. Typical reactions are exemplified in Scheme 9. The same catalyst systems can also





Scheme 9 immob. DHQD-AQN-ligand (**17**)





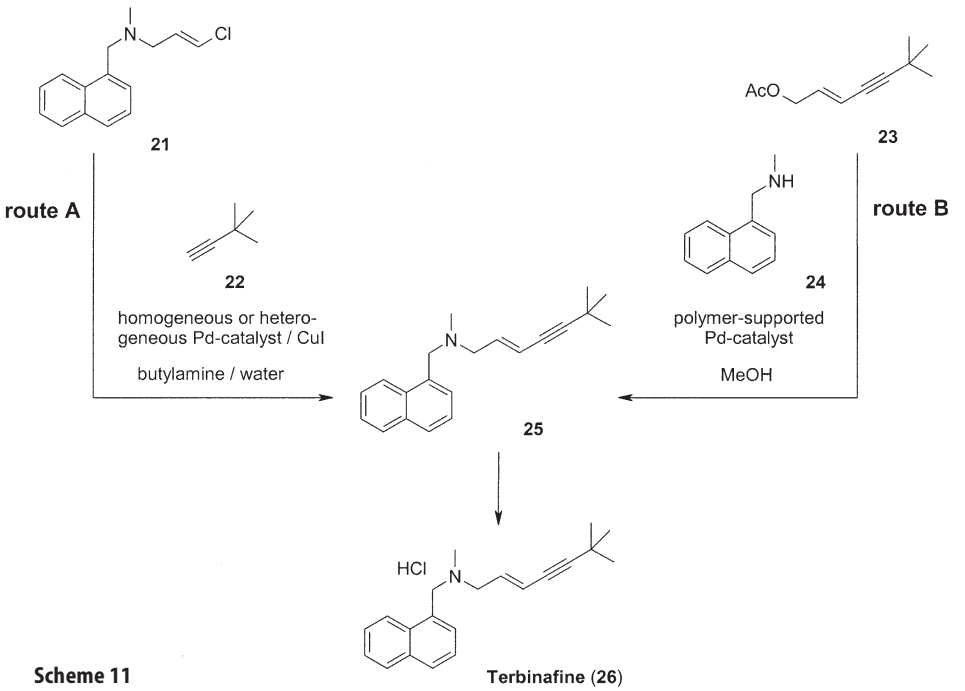
immob. DHQ-AQN-ligand (**20**)

Scheme 10

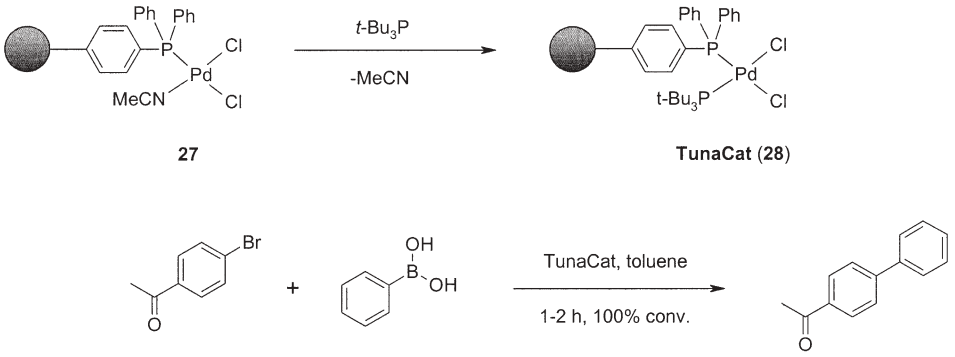
be used for the enantioselective opening of prochiral anhydrides (Scheme 10) [64].

2.3 Carbon–Carbon Coupling Reactions

A route selection for an industrial production process toward the antimycotic agent terbinafine (**26**) at the former Sandoz Pharma Ltd. comprised the comparison of homogeneous and heterogenized homogeneous palladium catalysts [65]. Possible routes toward **26** were either starting from vinyl chloride **21** and *tert*-butylacetylene **22** or from allyl acetate **23** and *N*-methylnaphthylamine **24** (Scheme 11). The palladium-catalyzed coupling of **21** and **22** following route A worked well with homogeneous catalysts; nevertheless, the immobilization of $Pd(PPh_3)_4$ was examined in order to achieve an easier catalyst separation. The same reaction in the presence of polystyrene-supported palladium catalyst gave terbinafine base **25** in 90% yield and with excellent stereoselectivity. However, the turnover rate of the reused catalyst dropped dramatically in the second and third runs, presumably due to a copper–palladium exchange. An alternative to this way was the coupling of allyl acetate **23** with amine **24** (route B). This reaction could be performed in a loop reactor, where the reaction solution was circulated over a bed of polymer-supported catalyst. The reaction proceeded smoothly in the presence of low catalyst concentrations but only led



Scheme 11 Terbinafine (**26**)



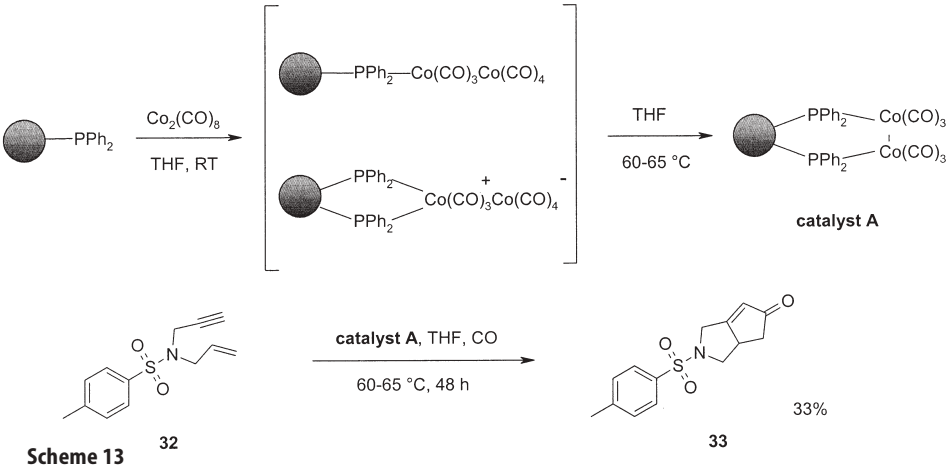
Scheme 12

to an *E*/*Z* ratio of 97:3. In addition, this route was considerably longer than route A. As a result, it was decided to establish a production process based on route A using a homogeneous catalyst system, which was superior with regard to economical considerations as well as selectivity.

FibreCat from Johnson Matthey, which will be described in detail in Sect. 3.1, proved to be a very effective catalyst for Suzuki coupling reactions [66]. A range of activated and deactivated aryl bromides were coupled in high yields in water/ethanol systems and in pure organic solvents. For more challenging systems, it was possible to tune the catalysts by adding tertiary phosphines (Scheme 12). These modified catalysts ("TunaCat", **28**) are air stable and were able to perform the Suzuki coupling at room temperature in the presence of potassium carbonate within a short time. A coupling reaction is exemplified in Scheme 12 by the reaction of aryl bromide **29** and boronic acid **30** to obtain the biphenyl derivative **31**. Palladium leaching was not observed in most solvents or solvent combinations.

AstraZeneca published the use of an immobilized transition metal carbonyl complex as a catalyst in the Pauson–Khand reaction [67]. This reaction is known to produce useful products but it also suffers from a number of drawbacks: dicobalt octacarbonyl and its analogs are volatile, toxic, and unstable due to loss of carbon monoxide and aerial oxidation. These drawbacks can be avoided by the use of an immobilized metal carbonyl complex (Scheme 13), which is safe and convenient to handle (see also [68]). It offers the additional advantages of being reusable after recovery from the reaction medium and the product becomes less contaminated with metal carbonyl remnants. The reaction was applicable to a wide range of substrates with the exception of tetrasubstituted alkenes. A typical reaction of enine **32** to the bicyclic enone **33** is depicted in Scheme 13.

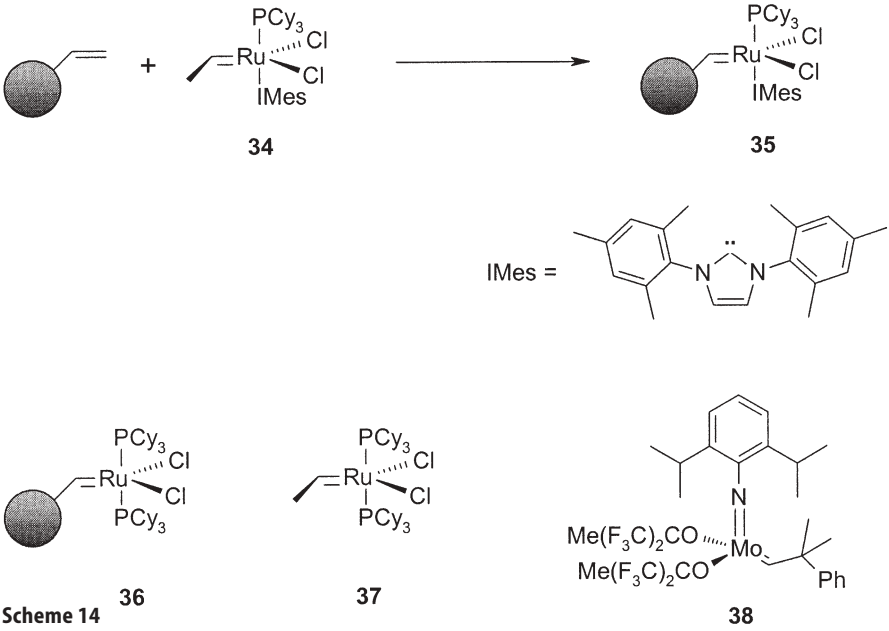
Another option for bond-forming reactions was mentioned by Degussa. It was considered to use known polymeric catalysts containing the amino acid proline [69] for enantioselective aldol or Mannich reactions in membrane reactors [70]. Concrete examples were unfortunately not published.



Scheme 13

Metathesis reactions are another important method to achieve C–C couplings. Quite a few companies showed interest in this topic, and only the former Glaxo Wellcome [71] and BASF [72] filed patent applications. Glaxo was involved in a collaboration with Barrett et al. to develop new recyclable polymer-supported metathesis catalysts. The commercially available Grubbs catalyst **37** has many advantages, as it is easy to handle and tolerates a wide range of functional groups. However, it is expensive, it cannot be recovered, and the reaction product is invariably contaminated with ruthenium compounds, thereby requiring purification by chromatography. As a consequence, Grubbs et al. tried to synthesize immobilized versions of this catalyst by attaching it to a solid support via diphosphine groups; however, these catalysts were found to be at least two orders of magnitude less active than the homogeneous catalyst [69]. To overcome this limitation, Barrett et al. developed polymer-supported catalysts where the catalyst is attached to the support via the ruthenium itself. This so-called boomerang catalyst (**36**, Scheme 14) operates by reversible release of the metallocarbene entity into the solution phase from the resin, and recapture by the support after the reaction ("boomerang effect"), but the reaction had to be run with rigorous exclusion of air [73]. To overcome this limitation, the second-generation catalyst **35** was developed, which showed improved activity and stability [74]. It was derived from the robust imidazolylidene-ruthenium complex **34** (independently described by Grubbs [75] and Nolan [76]) and has a comparable activity to the Schrock metallocarbene **38**. Although being significantly more active than **36**, it showed the tendency to lose this high activity between the third and fifth reuse.

Clearly, the field of immobilization of metathesis catalysts is dominated by academia and numerous publications can be found on this field – in particular from 1999 to the present [13, 18].

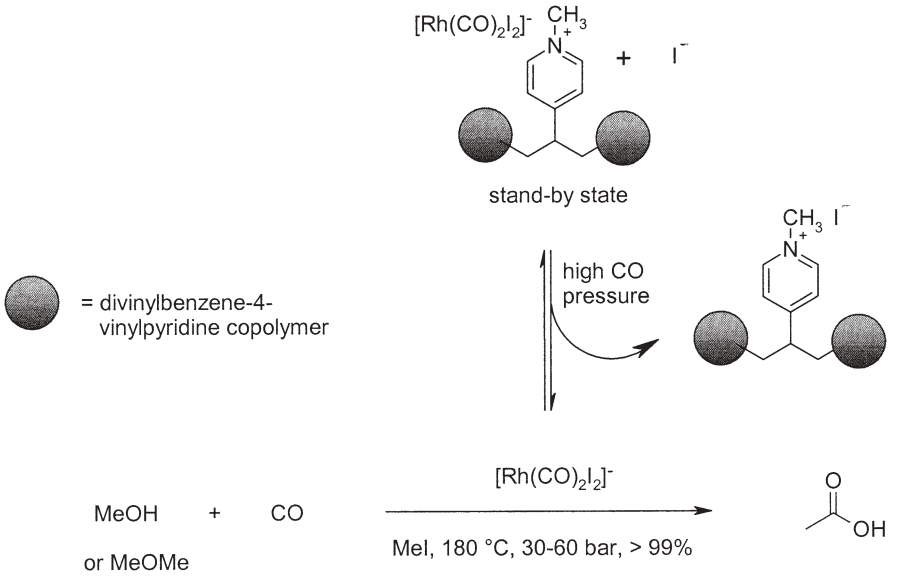


Scheme 14

2.4 Hydroformylation Reactions

Hydroformylations are a class of important reactions for large-scale chemical manufacturing [77]. A typical example is the commercial production of acetic acid via a low-pressure carbonylation of methanol in the presence of a homogeneous rhodium catalyst and a methyl iodide promoter. Some years ago, Chiyoda and UOP (Universal Oil Products) introduced the so-called Acetica process (Scheme 15). This novel technology is based on a heterogeneous rhodium catalyst in which the active rhodium complex is bound in the stand-by state to a poly(vinyl pyridine) resin (Reilex) by strong electrostatic interactions [78]. Under high CO pressure, the active anionic rhodium complex is partially released, although the equilibrium strongly favors the immobilized state. Compared to the former homogeneous processes, the new process leads to a higher acetic acid production rate, reduced by-product formation, and reduced rhodium losses. For the continuous process, an operational stability of more than 7,000 h has been reported without any catalyst deactivation [79]. Up to now, the Acetica process is the only production process which makes use of polymer-supported metal catalysts. A similar process has also been patented for the manufacture of acetic anhydride starting from methyl acetate [80].

Polymer-supported bis-phosphorus ligands were also disclosed by DuPont for use in hydroformylation reactions [81, 82]. Active catalysts were formed when the ligands were complexed with a catalytically active metal such as

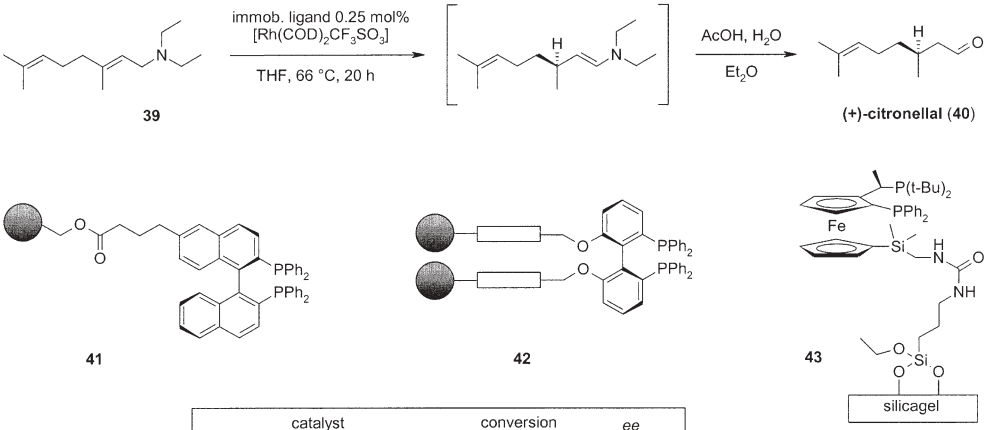


Scheme 15

rhodium. Another patent by the same company is also worth mentioning in this context, since it gives a good overview on the synthesis of polymer-anchored phosphorus ligands for catalysis [83, 84].

2.5 Isomerization of Olefins

The field of (alkane) isomerization has been thoroughly exploited by the petrochemical industry, resulting in many publications. The use of immobilized chiral catalysts, however, is still not common nowadays and was only described by Firmenich [85, 86]. They presented the first example of the use of a chiral diphosphino ligand, neither C_2-symmetric nor atropic, for the rhodium(I)-catalyzed preparation of citronellal **40** via isomerization of allylic amines or alcohols (Scheme 16). The catalyst systems used were polymer-anchored BINAP (**41**), TentaGel-supported MeO-bipheb derivatives (**42**), and silica gel- or polymer-supported Josiphos ligands (e.g., **43**). It was found that the use of immobilized or homogeneous systems led to a comparable optical purity of **40**, but the solid phase-bound catalysts exhibited a considerably lower activity. Moreover, the sense of induction depended on the support/linker used. The best performing supported ligand in terms of reactivity, selectivity, and recoverability was found to be **41**, which showed a turnover number of more than 14,400. Using this method it was possible to convert either (*E*)- or (*Z*)-allylic amines or the corresponding allylic alcohols into **40**. The principal reaction is shown in Scheme 16 using diethylgeranylamine **39** as one out of several examples.



catalyst	conversion	*ee*
41	100	98
homogeneous analogue	99	97
42	79	88
homogeneous analogue	100	97
43	81	96
homogeneous analogue	99	92

Scheme 16

2.6 Further Areas of High Industrial Involvement

Supported metallocene catalysts are an important field of research for the polymer industry and shall be mentioned here only briefly. Single-site olefin polymerization catalysts have been extensively investigated and are now achieving wide acceptance in the polyolefin industry. In order to achieve commercial significance, these soluble metallocene catalysts have to be immobilized on a carrier. The challenges of supporting these catalysts have been addressed in many creative ways and this topic has been taken up in an excellent review by Carnahan et al. [87]. This paper mainly describes anchoring techniques to silica, but these concepts may also be applied for other purposes.

Supported ionic liquid compositions are also a vivid field of research in which many companies tried to make their claims [88–90]. By immobilizing ionic liquids onto silica- or alumina-based carriers it is possible to obtain new Lewis acid catalysts with interesting characteristics. These are presently preferably used for alkylation and acylation reactions of aromatic compounds [91, 92] or isomerizations. Even the co-immobilization of ionic liquids with transition metal complexes [93] or Lewis acids [94] has been described, and it can be anticipated that this particular field offers many options for future catalyst development.

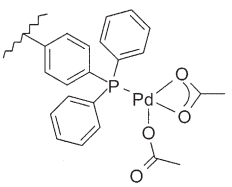
3
Immobilized Catalysts as Commercial Products

3.1
FibreCat

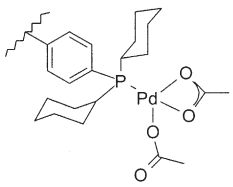
In 2000, Johnson Matthey agreed a phased acquisition of Oy Smoptech Ab, a Finnish start-up company that had developed novel advanced polymer fiber catalyst supports. The combination of Smoptech's polymer fiber technology with Johnson Matthey's expertise in precious metal catalysis delivers a new generation of catalysts, called FibreCat [95]. They are typical examples of catalysts covalently bound to a support. In contrast to traditional polymer supports, these fibers have good mechanical properties, good functional group accessibility, and they are easy to handle [95]. Up to now, four series of these catalysts are commercially available. The FibreCat 1000 series consists of palladium catalysts for coupling reactions, whereas the 2000 series covers rhodium catalysts for hydrogenation reactions. The 3000 series consists of oxidation catalysts, one ruthenium catalyst for selective oxidations and two osmium catalysts for dihydroxylations. The 4000 series includes one platinum catalyst for hydrosilylation reactions. Scheme 17 shows some representative examples of these catalysts.

The use and the advantages of these catalysts are described in several papers especially for palladium-catalyzed coupling reactions [66, 96, 97]. Levels of selectivity have been compared with those achievable with conventional homogeneous catalysts in a variety of reactions. In general the FibreCat versions show comparable activities to the non-anchored versions.

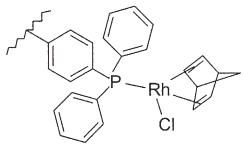
Smoptech's fiber technology has also given access to a vast range of functional polymer resins, which have been developed as precious metal scavengers called Smopex. A number of Smopex products are available for metal scav-



FibreCat™ 1001



FibreCat™ 1000-D7



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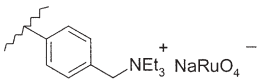

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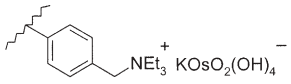


FibreCat™ 3000-D2

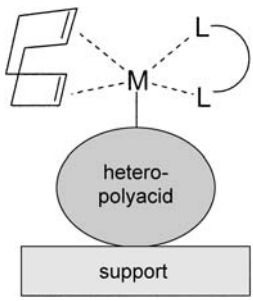
Scheme 17

enging from solutions, for instance Smopex-111, which is used for palladium recovery in coupling reactions. These fibers functionalized with diphenylphosphine groups were also reported as ligands for palladium coupling reactions [98].

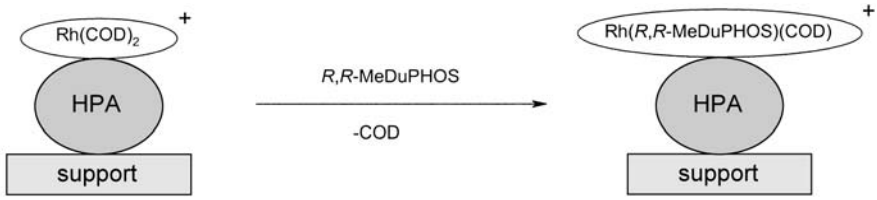
3.2
Augustine's "Magic Glue"

In the late 1990s, Augustine at the Center for Applied Catalysis developed a novel catalytic system comprised of a homogeneous complex anchored to a solid support. Heteropoly acid (HPA) served as the anchoring agent (Scheme 18) [99–101]. These catalysts have been found to be at least as active and selective as the homogeneous analogs and have been reused many times with no loss of activity or selectivity [28, 99, 102]. Catalyst leaching was not observed. Since the homogeneous catalyst is bound to the support via the metal atom of the complex, there is no need to modify the ligand attached to the complex. Because of this feature, these anchored species are particularly effective as heterogeneous enantioselective catalysts. This type of bonding was based on the published structures of the complexes formed by the interaction of Rh(COD) with a Keggin HPA [103]. The technique has been successfully used to prepare different anchored homogeneous catalysts based on both rhodium and ruthenium complexes. Materials such as alumina, carbon, silica, lanthana, and clay have all been used as supports. The HPAs, phosphotungstic acid (PTA), silicotungstic acid (STA), phosphomolybdic acid (PMA), and silicomolybdic acid (SMA) have all been used as anchoring agents with varying degrees of success, and PTA clearly seems to be the most useful anchoring agent (see also Scheme 4).

In a newsletter in 2000, Dow CMS announced it had joined forces with the Center for Applied Catalysis to speed the commercialization of solid-supported homogeneous chiral catalysts [104]. However, in the information given on the homepage of the Center for Applied Catalysis dated 2002, Johnson Matthey is marketing these catalysts [105]. Johnson Matthey, on the other hand, an-



Scheme 18



LigandNet™ $Rh(COD)_2BF_4$

Scheme 19

nounced in December 2001 a collaboration with the Center for Applied Catalysis with emphasis on the manufacture and commercialization of Augustine's catalysts [95]. But so far, no product has been commercialized.

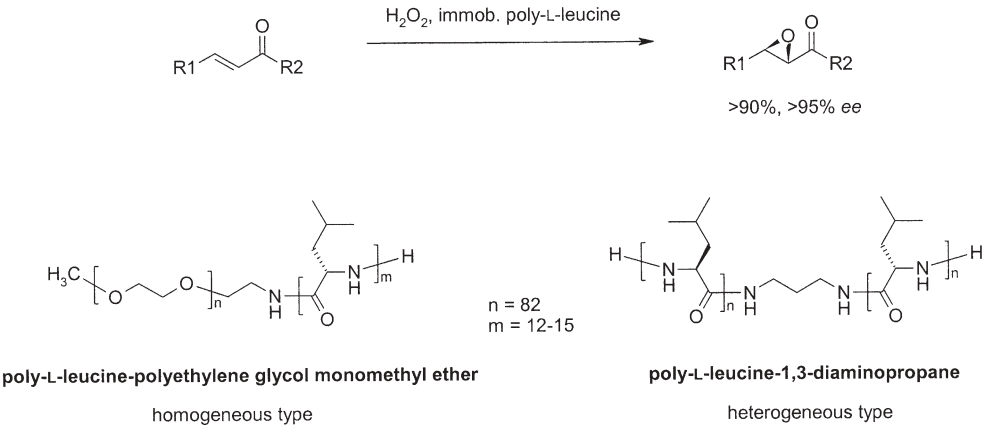
3.3 LigandNet

Engelhard is marketing an immobilized rhodium catalyst LigandNet $Rh(COD)_2BF_4$, based on the technology developed by Augustine [28, 99]. LigandNet $Rh(COD)_2BF_4$ is air stable and can be modified with the ligand of choice via a simple ligand-exchange reaction (Scheme 19). Immobilized Rh(*R*,*R*)-MeDuPHOS, prepared from LigandNet $Rh(COD)_2BF_4$ and (*R*,*R*)-MeDuPHOS, was for example used in the asymmetric hydrogenation of dimethyl itaconate [44, 45]. The activity and selectivity of the immobilized Rh(*R*,*R*)-MeDuPHOS catalyst are comparable to those of its homogeneous analog. The immobilized catalyst can be separated from the product mixture by simple filtration and was reused in subsequent reactions [106].

3.4 Polyleucine Catalysts

An exclusive collaboration with StylaCats Ltd. allows Lancaster, a Clariant Group Company, to offer new polyleucine-based catalysts for the asymmetric epoxidation of alkenes. Developed and patented by StylaCats, under the direction of Stan Roberts of the University of Liverpool, these reagents represent the first of an exciting series of new enzyme mimics [52]. The new reagents require no pretreatment and can operate under homogeneous or heterogeneous conditions according to the nature of the catalyst. Polyethylene glycol/polyleucine copolymers give homogeneous epoxidation catalysts suitable for adaptation to a continuous flow membrane reactor, while polyleucine with a 1,3-diaminopropane backbone serves as a heterogeneous-type catalyst (Scheme 20).

Both, poly-L-leucine and poly-D-leucine systems are readily available for research use. World patents are pending on commercial applications [52]. The catalysts are stable to air, light, heat, and moisture and they are active at low cat-



Scheme 20

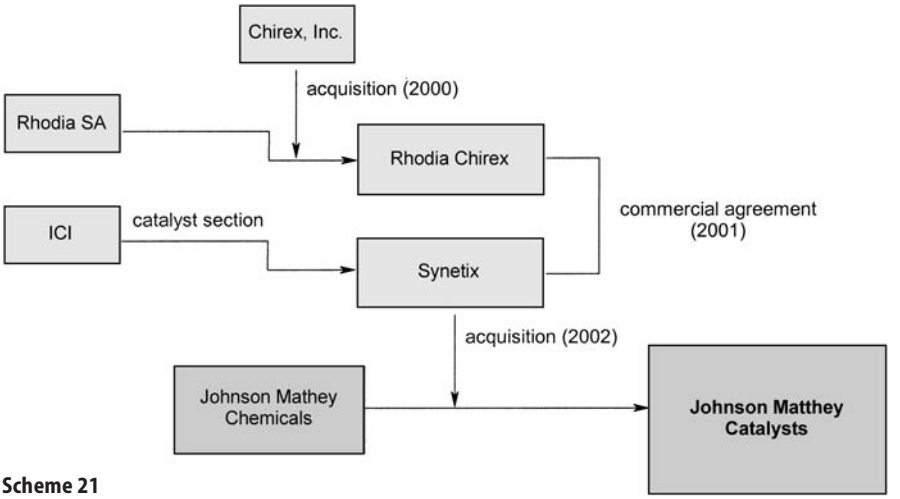
alyst loadings giving high conversion rates and excellent enantioselection. With these catalysts in hand, a wide range of functional chiral epoxides can be prepared from electron-poor alkenes according to the Juliá-Colonna protocol (see also Sect. 2.2).

3.5 Immobilized Co-Salen Catalysts

In June 2001 Rhodia ChiRex Inc. and Synetix announced the agreement of jointly developing and manufacturing immobilized catalysts for the production of pharmaceutical intermediates and fine chemical compounds. Synetix had formed Synetix Chiral Technologies (SCT) shortly before, which had successfully immobilized Rhodia ChiRex's proprietary Co-salen catalyst [107, 108], licensed from Harvard in 1996. It was also announced that Synetix will now manufacture commercial quantities of the newly immobilized catalyst for Rhodia ChiRex. Two years later, in June 2003, Johnson Matthey announced that, following the acquisition of Synetix from ICI in November 2002, JM Chemicals and Synetix are now brought together as the "process catalysts and technologies business" of Johnson Matthey and that these catalyst businesses will trade under the new brand name of Johnson Matthey Catalysts (Scheme 21).

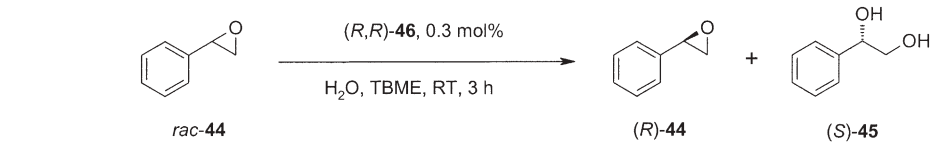
So far, neither Johnson Matthey nor RhodiaChirex are commercializing an immobilized Co-salen catalyst. RhodiaChirex, however, filed a patent application in 2002, in which they claim immobilized salen complexes and the preparation thereof [108]. Another very recent patent application describes the synthesis and use of Co-salen complexes immobilized on silica [108].

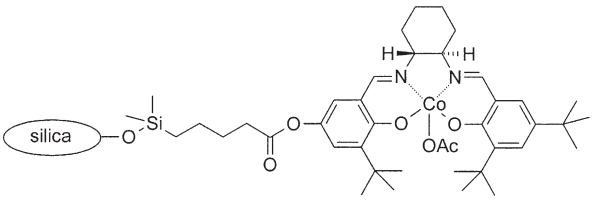
Co-salen complexes are used as catalysts for the hydrolytic kinetic resolution (HKR) of terminal epoxides originally developed by Jacobsen [109–113]. During the resolution, the catalyst adds water to one enantiomer of the epox-



Scheme 21

ide, and the absolute configuration of the product can be set by choosing the correct catalyst. The technology provides economic access to a wide range of C-3 synthons, as the HKR is effective for a wide range of terminal epoxides. The efficacy of an immobilized Co-salen complex in the HKR reaction was tested in the resolution of *rac*-styrene oxide (*rac*-**44**, Scheme 22) [113]. Using only 0.3 mol% catalyst **46**, the reaction proceeded close to completion of the reactive enantiomer of the starting material within 3 h, forming the diol (*S*)-**45** product in 96% *ee*. It was found that the turnover number of the immobilized catalyst was considerably higher compared to that of the soluble one [114], and it was also shown that the immobilized catalyst **46** was suitable for application in a continuous flow system [113].

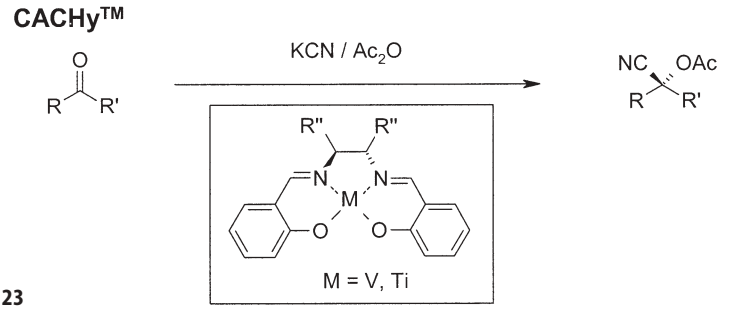




Scheme 22 (*R*,*R*)-**46**

3.6
Immobilized CACHy and CATHy

Avecia, a former part of the Zeneca Group, developed a range of cheap and highly active titanium- or vanadium-based salen catalysts called CACHy catalysts (Scheme 23). They are based on Jacobsen's salen technology, but they are much more reactive and can, for example, be used in concentrations as low as 0.1 mol% in the cyanation of aryl aldehydes. The catalysts show similar reactivity with alkyl aldehydes and ketones and are applicable to the synthesis of the commercially important mandelic acid derivatives.

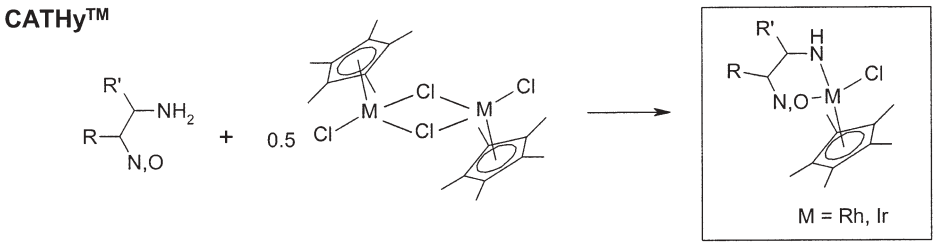


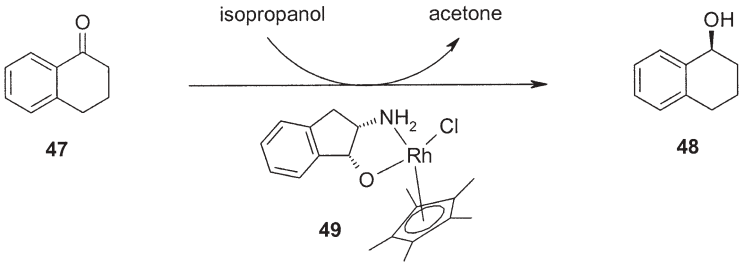
Scheme 23

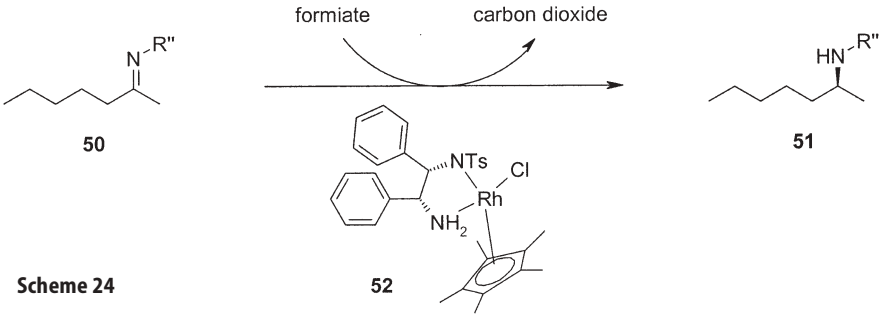
CATHy are highly efficient catalysts for the asymmetric transfer hydrogenation of a broad range of ketones and imines to chiral alcohols and amines. The catalysts are prepared *in situ* by combining a chiral bidentate ligand with a Rh(III) or Ir(III) metal complex containing a substituted cyclopentadienyl ligand (Scheme 24). CATHy catalyst kits consisting of three different ligands and two metal complex precursors are available from Strem. According to a C & EN report [107], Synetix has made progress in immobilizing both catalyst systems. However, no immobilized versions are commercially available so far.

3.7
EnCat

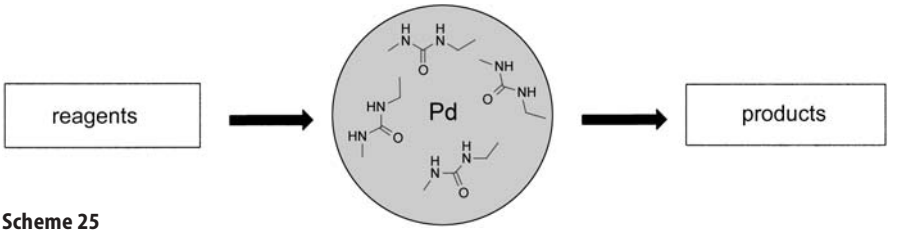
Avecia and Ley et al. co-developed a method to encapsulate palladium(0) in a polyurea framework and generated an immobilized catalyst, which is especially well suited for carbon–carbon cross-coupling reactions [107, 115]. With this EnCat immobilization technology, no additional ligands for metal stabilization are required, since they are supplied by the polymer itself (Scheme 25). Additional advantages of this technology are an extremely low palladium leaching and a simple catalyst recovery by filtration, which enables catalyst recycling. Moreover, the technique should be applicable to other metals as well [114]. Ley and coworkers are currently testing PdEnCat in transfer hydrogenation [116], hydrogenation [117], and cross-coupling reactions [118].







Scheme 24



Scheme 25

4 Summary

In this review we showed that the use of heterogenized catalysts for industrial production is still a rather unexplored field. Many homogeneous catalysts in use are reasonably active and also easy to separate, making recycling not a worthwhile effort. But immobilization cannot only be a considerable cost factor itself, it may also cause a deactivation of the catalyst or lead to an unintentional change of selectivity due to reduced accessibility of the active site. Section 2 in this article exemplified some attempts to improve relevant industrial reactions, but in no case could the performance of homogeneous catalysts be surpassed. The search for better performing and more reliable systems is therefore ongoing and a few companies have nevertheless recognized the potential of immobilized catalysts. Today, we have the situation that a sufficient number of potential supports and carriers, both organic and inorganic, are available, and the methods for immobilization are also in an advanced state. Some companies tried to position themselves either by building alliances with other companies or by collaborations with academia. These cooperations finally led to the marketing of catalyst systems as described in Section 3 of this paper. However, even these relatively advanced catalyst systems have not yet made their entrance into the field of industrial manufacture, but find occasional use in academic research. Compared to the field of biotransformation, where the use of immobilized biocatalytic systems has proved to be advantageous for many reactions, the area of heterogenized metal catalysts is far less advanced. However, the examples of biotransformations could be indicative to show in which direction this field might evolve in the future (see also the article "Immobilized Biocatalysts in Industrial Research and Production" in this volume).

5 Outlook

In contrast to the chemical industry, the research in academia on immobilized catalytic systems is done much more extensively and with a broader focus. Numerous publications do underline this statement, and the industry has recognized this potential for many years. An interesting survey among European companies active in the field of catalysis was conducted in 1998/1999 and clearly states that catalysis is a major and increasing contributor toward sustainable industrial production [119]. Hot topics in industrial catalysis are discussed, which are for the production of fine chemicals for instance:

- Ensuring high activity and selectivity in the immobilization of homogeneous catalysts and avoiding of leaching.
- Improved enantioselectivity; availability of cheaper chiral ligands and of enantioselective heterogeneous catalysts.

– High activity at low temperatures for the production of thermally unstable fine chemicals.

This summary not only shows the preferred direction and requirements of industrial research, it also reveals a high need for cooperation between industry and academia. Further interesting papers worth mentioning in this context are the "Catalysis and Biocatalysis Technologies 1998 White Paper" from the American Advanced Technology Program [120] and the "Technology Roadmap Catalysis" from the Dutch Ministry of Foreign Affairs [121].

Immobilization is and will be an important issue in the future. Much research has been focused on the use of simple insoluble polymeric systems as supports, but there have also been attempts to immobilize chiral catalysts via encapsulation. The chiral membrane reported by Vankelecom [122], and the microencapsulated chiral catalysts prepared by Kobayashi et al. [123] represent excellent examples of such variations. In addition, the immobilization of catalysts using thin films was reported [14].

With the development of structurally well-defined mesoporous molecular sieves and other silica-based carriers as chiral catalyst supports, it was possible to achieve high enantioselectivity and reactivity, and some were even higher than those of the homogeneous parent systems [22, 26]. The more recent developments of effective inorganic solid or organic and inorganic hybrid-supported chiral catalysts are important advancements in this area of research [4].

The use of soluble polymers or dendrimers as chiral catalyst supports is another interesting way for catalyst separation [13]. Behaving like a homogeneous catalyst during the reaction, the catalyst can easily be separated by precipitation at the end of the reaction. High catalytic activities were reported using this approach. In addition, even use in membrane reactors may be possible using the ball-shaped dendrimers.

Sol–gel-processed interphase catalysts are another contribution to the field of supported catalysis [124]. An interphase is defined as a region within a material in which stationary and mobile components penetrate each other on a molecular level. The stationary phase is composed of an inert matrix, a flexible spacer, and an active center, whereas the mobile phase consists of a solvent or a gaseous, liquid, or dissolved reactant. Therefore, an interphase is able to simulate homogeneous reaction conditions, and at the same time it has the advantage of a heterogeneous catalyst. Rigid but highly porous materials can as well serve as supporting matrix provided that sufficiently long spacers lead to a satisfactory mobility of the reactive centers.

Certainly, the use of heterogenized (homogeneous) catalysts is not the only important field of industrial catalyst research. There are many other possibilities, which enable the easy separation of catalysts after the reaction has been performed. Some present concepts with (potential) industrial applicability are the use of fluorous biphasic systems [125, 126], of ionic liquids [127–129] and ionic liquids in multiphasic reactions [130–132] and heterogeneous multifunctional reaction systems (simultaneous application of two or more sup-

ported liquid-phase organometallic catalysts) [133]. These methods are presently at the interface of research/application and may find their use on a commercial scale some day. The concept of supported aqueous-phase catalysis, which is the combination of solid-supported catalysis and biphasic catalysis, has already been demonstrated to be an attractive approach to chiral catalyst immobilization [30].

Finally, it can be expected that the number of methods will steadily increase in the future. And it will certainly remain a challenge to develop supported catalyst systems which at least equal their homogeneous counterparts with regard to activity and selectivity and which are sufficiently economic.

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Immobilized Biocatalysts in Industrial Research and Production

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Abstract The use of various immobilized biocatalysts in industrial research and production will be introduced. The applied catalysts span the range from isolated enzymes to microbial whole cells, and even examples of the use of plant cells and mammalian cells could be found. Approximately 65 processes have been reviewed in this article, roughly 50% of which are actual production processes in the chemical industry. The remaining 50% refer to biocatalytic transformations which were carried out at laboratory scale up to pilot scale. In this review special attention was drawn to the range of transformable substrates and the variety of different supports.

Keywords Biocatalysis · Immobilized enzymes · Immobilized biocatalyst · Biocatalytic process · Enzymes in production · Enzymatic manufacture

1 Introduction

This review intends to give a survey of the application and development of immobilized biocatalytic systems in the industrial environment. The authors focus on scientific data published or processes used from 1993 to 2003 with particular emphasis on developments during the last 5 years. It was tried to cover the whole range of biocatalytic systems which are either commercially available or under industrial development nowadays, and to give the reader an impression of what is of interest and where hurdles are to be noted from an industrial point of view. Thereby, emphasis was placed on demonstrating the variety and complexity of possible substrates and not only on the structures and characteristics of the supporting material. Embedded in this review are articles and books published in recent years as well as many examples from patent literature. It was tried to give as many reaction details as possible, but quite a lot of process-relevant data have never been published for obvious reasons. Biocatalytic reactions, even immobilized versions, can be found in almost any industrial area and enable the conversion of substrates in almost any volume range. The focus of this review was mainly put on the industrial research and production of fine chemicals for various applications, and neglected the huge application fields in the food processing industry, in water and air treatment, in textile and polymer chemistry, and in analytical applications (diagnostics).

Since the late 1960s immobilized biocatalysts have been extensively studied and used for the industrial production of important intermediates and products such as amino acids, sugars, lipids, acids, and pharmaceuticals [1–3]. A recent OECD report not only states that biocatalysts can and should be used in a wide range of industrial applications, but also identifies a need for reusable systems [4]. Improving the robustness of biocatalysts was also an important topic of a 1999 workshop of 50 leading scientific and industry experts in biocatalysis [5].

The industrial use of biocatalysts has been reviewed in many excellent papers from industrial and academic experts in recent years [6–20]. These publications clearly show that immobilized systems find only limited use in present bioprocesses. Straathof et al. recently investigated 134 industrial biotransformations and came to the conclusion that only 20 confirmed processes rely on immobilized biocatalysts [15]. This is due to the fact that immobilization can be a considerable cost factor and is frequently used in combination with less common continuous reactors. In addition, many transformations belong to the class of redox reactions and require a cofactor for the reaction to occur. Such processes can in many cases be realized perfectly under fermentative conditions by the use of living or resting cells [17, 21–25].

Table 1 Selection of solid supports for biocatalystimmobilization

	Organic	Inorganic
Covalent attached	Polyacrylamide, polystyrene (Tentagel), polyolefines	Porous glass
Adsorption	Cellulose, chitine (chitosan), nylon, polypropylene fibres, polymer nets and membranes, wood, lignine, ion-exchange resins, polyurethane foam, polyacrylamide	(Porous) glass, clay, bentonite, zeolithes, ceramics, mesoporous silica, metal oxides (Fe, Ti, Mg), metal phosphates, mineral powder
Entrapment	Agar, dextrane, alginate, carrageenan, collagen, polyacrylate, polysiloxane, polyvinylalcohol, polyethyleneglycol	Calcium phosphate gel

1.1 Why, What, and How to Immobilize?

Most biocatalysts are inherently unstable – operational stability is therefore of high importance for any bioprocess and is sometimes as important as the search for a suitable biocatalyst itself. Certainly, not only isolated enzymes may be immobilized, it is also common to support living or resting cells, which may stem from bacterial, fungal, and archaeal origin as well as from higher animals or plants [21, 23, 26, 27]. Many ways have been investigated to achieve additional stabilization of biocatalysts [28, 29]. The most obvious measures to prolong the lifetime are using an organic or inorganic solid support [3, 30–34], cross-linking of enzymes [35–37], solvent engineering techniques [38, 39], bioimprinting [40], or reactor design [41]. Additionally, with the amazing success of genetic manipulation techniques such as directed evolution, these new methods became irreplaceable tools for enzyme modification and stabilization [42–49]. The solid supports used today belong to the classes shown in Table 1 [50–53] and the methods for immobilization span the range from adsorption and covalent bonding to encapsulation and entrapment [50, 51].

A number of the above-mentioned carriers can be found in industrial applications – either due to the ease of immobilization or due to economic reasons. The following solid phases are worth mentioning in this context: Eupergit (oxirane acrylic beads, Röhm GmbH & Co. KG, Darmstadt, Germany) [54, 55], Accurel (polypropylene powder, Membrana GmbH, Obernburg, Germany), and Celite for enzymes as well as calcium alginate or agar for whole cells.

The potential advantages associated with the immobilization of biocatalyst are:

- Higher stability with regard to temperature, pH, and catalyst poisoning
- Repetitive use of biocatalysts
- Higher resistance to shear stress and contamination
- Higher activity by better availability of catalytic centers
- Ease of developing continuous processes
- Easy separation from reaction media (easier downstream processing)
- Fast reaction rate due to high catalyst concentration (for certain reactor types)

However, there are also disadvantages such as:

- The necessity of developing an immobilization process
- Additional cost caused by support and additional reagents
- The existence of mass transfer resistances (diffusion limitations)

It is important to emphasize that no single immobilization method is best for all enzymes or all applications of a given enzyme. Figure 1 gives an overview of known immobilization strategies. The choice of a certain procedure, an appropriate support, or even the best enzyme strongly depends on the chosen process and must be evaluated from case to case. The development of an immobilized version of an existing enzyme can therefore be laborious and may be too expensive in cases where the enzyme is highly active or particularly cheap.

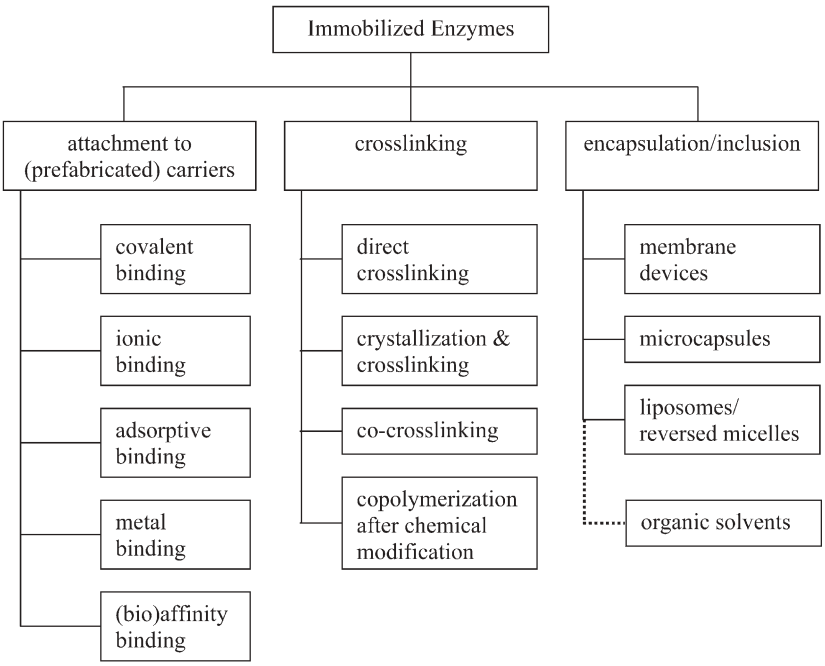


Fig. 1 Overview of immobilization methods [51]

1.2 Availability of Biocatalysts

Many biocatalysts used in industrial production processes are commercially available, some even in immobilized form, and are for instance provided by the following major enzyme suppliers (in alphabetical order): Amano Pharmaceutical (Japan), Biocatalysts (UK), Boehringer (Roche Diagnostics, Germany/Switzerland), Genencor (USA), Meito Sangyo (Japan), Nagase (Japan), and Novozymes (Denmark). Whole cell biocatalysts however, although available from several public stem collections all over the world, are frequently discovered and optimized by the industrial institutions themselves, since they are a rich source of proprietary knowledge.

According to the EC system of the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (IUBMB), the enzymes are classified in six main classes (Table 2), which in turn are divided into three orders of enzyme subclasses. This EC system was a guideline throughout this review and the use of a particular enzyme can be found in its class.

Clearly, most biocatalytic reactions for the production of fine chemicals are used to obtain enantiopure or enantioenriched compounds, and only a minor number of syntheses lead to products without chiral centers. More than 65 applications of immobilized enzymes or whole cells for industrial research and production have been treated in this review, and it can be stated that approximately 80% utilize the class of hydrolytic enzymes. This number reflects the ease of handling and the broad utility of these enzymes. The reported hydrolytic enzyme applications mainly involve lipases, whereas other hydrolases can only be found in fewer but nevertheless just as attractive cases. The broad field of asymmetric synthesis (e.g., asymmetric reduction/oxidation) is defi-

Table 2 EC-System

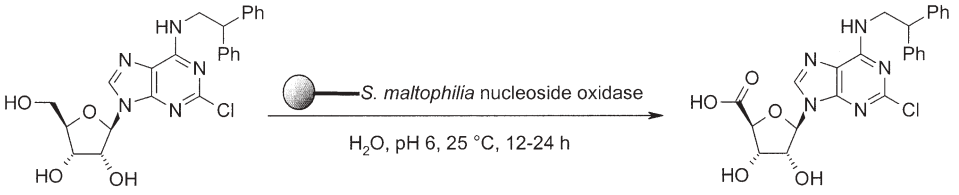
IUBMB enzyme class	Reactions catalyzed
EC 1 Oxidoreductases *Co-substrate required*	Reductions/oxidations at –CH–OH, –C=O, –C=C, etc.
EC 2 Transferases *No co-factors required*	Transfer of functional groups such as C_1, aldehyde, keto, acyl, glycosyl, etc.
EC 3 Hydrolases *No co-factors required*	Hydrolysis/condensations of esters, glycosides, nitriles, amides, halogenes, etc.
EC 4 Lyases *No co-factors required*	Additions/eliminations; cleavage of C–C, C–O, C–N-bonds
EC 5 Isomerases *No co-factors required*	Racemization, *cis-trans*-isomerization, epimerization
EC 6 Ligases *Co-substrate ATP required*	Formation of C–O, C–S, C–N, C–C-bonds

nitely underrepresented in this review. This is mainly due to the fact that most enzymes of this class require a cosubstrate for the reaction to occur and whole cells can be applied for this purpose in an economical and efficient way. Modern reactor design (e.g., enzyme membrane reactors and higher sophisticated apparatuses [56]) also eliminates the need for biocatalyst support in many cases.

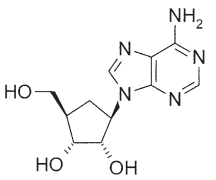
2
Application of Immobilized Biocatalysts in Industry

2.1
EC 1: Oxidoreductases

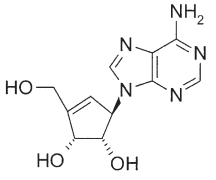
A nucleoside oxidase from *Stenotrophomonas maltophilia* (FERM BP-2252), which proved to possess broad substrate specificity for unnatural nucleosides, has been used to generate 5′-carboxylic acid derivatives of nucleoside analogs by Glaxo Wellcome [57]. Compound **2** (Scheme 1) was a key intermediate in the synthesis of novel compounds with broad anti-inflammatory properties. The chemical oxidation of alcohol **1** suffered from problems during scale-up due to the heterogeneous nature of the reaction and also required the use of protecting groups for the 2′/3′-hydroxyl groups. The oxidation with *S. maltophilia* oxidase was accomplished with crude lysate, but the enzyme was also immobilized on Eupergit-C with an efficiency of 20–40%. Problems encountered with the free enzyme – slow and insufficient conversion – could, however, even at bead concentrations of 40% (w/v), not be overcome with the modified enzyme. Nevertheless, the synthetic utility of the nucleoside oxidase could be exploited to produce also the 5′-carboxylates of several other purine analogs, including



1 2



Aristeromycin (**3**)



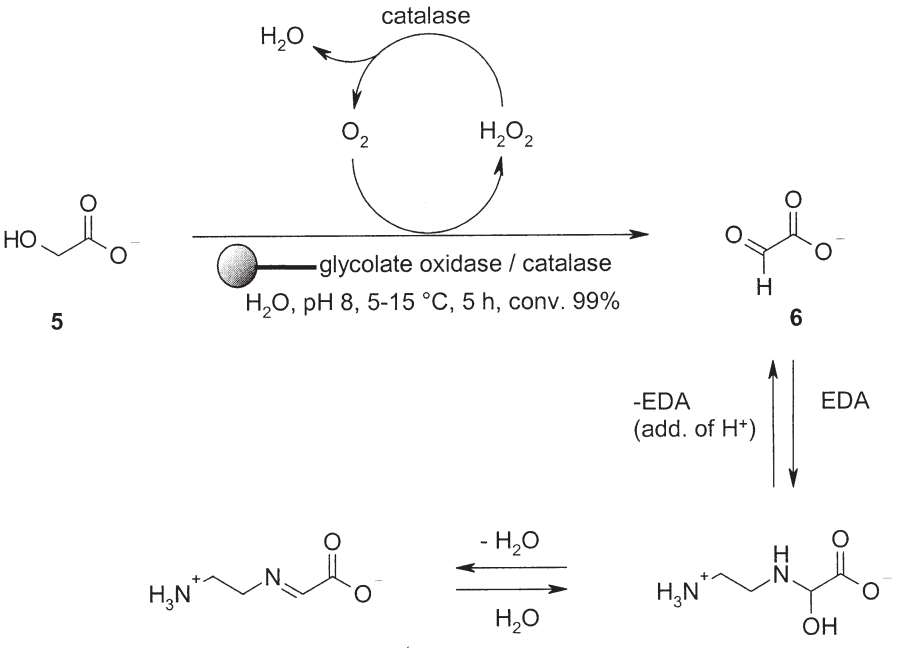
(-)-Neplanocin A (**4**)

Scheme 1

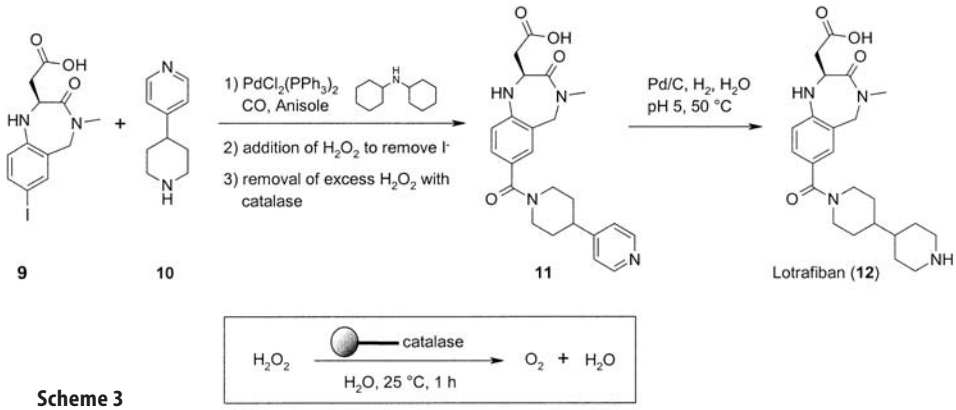
the compounds aristeromycin (**3**) and neplanocin A as substrates (**4**) on a preparative scale.

A highly selective enzymatic glyoxylic acid production method was developed by DuPont some years ago [58, 59]. Glycolic acid (**5**) could be oxidized with glycolate oxidase isolated from spinach to give glyoxylic acid (**6**), which further reacted with ethylenediamine to the corresponding hemiacetal **7** and finally imine **8** (Scheme 2). The combination of aldehyde scavenging and hydrogen peroxide destruction by the enzyme catalase prevented further enzymatic oxidation of **6** to oxalic acid and also its chemical oxidation to formate and carbonate. Glycolate oxidase and *Aspergillus niger* catalase were covalently bound to Eupergit C beads and the coimmobilization proved to have no negative impact on the specific activity. The supported enzymes exhibited good stability and attrition resistance, and the yield of glyoxylic acid at complete conversion was typically in the range of 98–99%. Recovery and reuse of the catalyst was possible and a total turnover number for glycolate oxidase of circa 1×10^7 was still reached after ten cycles.

An illustrative example of utilizing a supported enzyme as a tool for reaction optimization was published by GlaxoSmithKline [60]. During the development of a manufacturing process for a key compound to Lotrafiban (**12**) (see also Scheme 21), the need arose to efficiently destroy an excess of hydrogen peroxide (Scheme 3). The oxidant was used to remove iodide ions, which were a by-product of the aminocarbonylation of iodide **9** and amine **10**. This became



Scheme 2



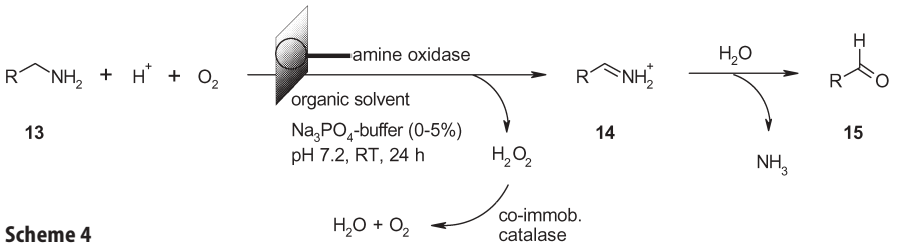
Scheme 3

necessary as iodide inhibited the catalytic hydrogenation of pyridine **11** to yield piperidine **12**. Hydrogen peroxide degrading catalase was found to be the best solution for this problem, and the most promising enzymes were identified from *Aspergillus niger* and *Corynebacterium glutamicum* – both available on a large scale. Due to efficiency reasons the catalase was immobilized on Eupergit C250L, a carrier suitable with regard to cost, enzyme activity, and stability. Up to nine cycles could be run without any loss of activity and it was assumed that on the manufacturing scale only 15 kg of enzyme would be required to produce 30 t of **12**.

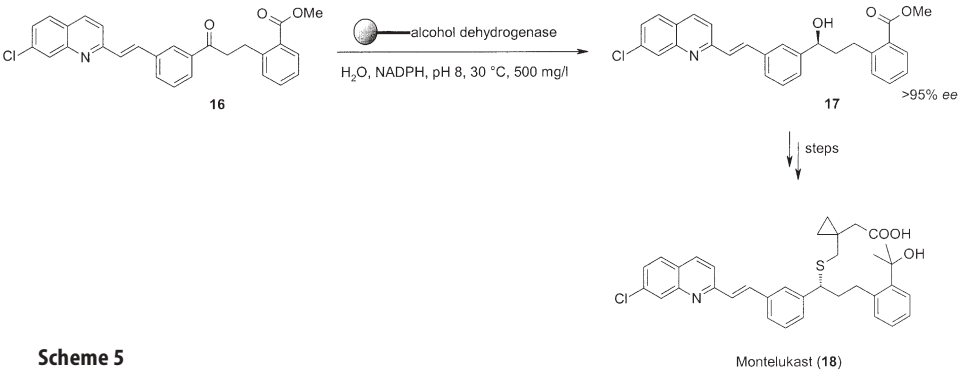
The destruction of hydrogen peroxide by catalase was also a research topic at Mitsubishi Gas Chemical Company [61]. Here, it was tried to encapsulate the enzyme in polymer microcapsules based on cross-linked polystyrene. The microencapsulated catalase showed improved thermostability and showed the same activity at 65 °C as the free catalase did at room temperature. A specific use of the immobilized enzyme was unfortunately not indicated.

The synthetic potential of amine oxidases was explored in different reaction systems by EnzyMed, a division of Albany Molecular Research [62]. Amine oxidases catalyze the oxidation of amines **13** to the corresponding Schiff bases **14**, which finally results in the formation of aldehydes **15**, ammonia, and hydrogen peroxide (Scheme 4). Enzyme immobilization on Celite was feasible and even coimmobilization with hydrogen peroxide destroying catalase could be achieved. The enzyme system was applied in a low water environment after preequilibration in a salt hydrate system and was found to tolerate a broad range of organic solvents. Although not published, the authors claim to have used the enzyme for a wide range of structurally diverse amines with conversions as high as 90%. The use of organic solvent-containing reaction systems thus presents a convenient method for oxidizing poorly water-soluble amines.

The Merck Research Laboratories described one of the rare approaches to use immobilized alcohol dehydrogenase (ADH) – in this case for the enantioselective reduction of ketone **16**, a key intermediate for the production of the



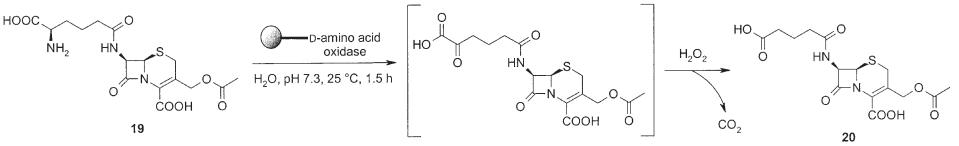
Scheme 4



Scheme 5

antiasthma drug Montelukast **18** (Scheme 5) [63]. *Microbacterium campoquemadoensis* (MB 5614) produces a NADPH-dependent reductase capable of reducing **16** to the corresponding (*S*)-alcohol **17**. The enzyme was purified, characterized, and subsequently immobilized on Eupergit beads, and the supported enzyme proved to have a similar activity to that of the free enzyme in two-phase solvent systems (DMSO, Hexane). Using the immobilized Ketoreductase, a volumetric productivity of 0.04 g $(ld)^{-1}$ was achieved at a substrate concentration of 0.5 gl^{-1}.

As long ago as the 1970s a first process for the enzymatic production of 7-aminocephalosporanic acid (7-ACA, **129**, see Scheme 40), an intermediate for semisynthetic penicillins and cephalosporins, was developed by Toyo Jozo Asahi Chemical [64]. In 1996, Hoechst Marion Roussel replaced an existing chemical process by an enzymatic one due to environmental considerations and was able to reduce the absolute costs of environmental protection by 90% per ton of 7-ACA. One of the two enzymatic steps comprises the oxidative deamination of amino acid **19** using an immobilized D-amino acid oxidoreductase from *Trigonopsis variabilis* (Scheme 6). The *β*-keto ester obtained *in situ* spontaneously undergoes decarboxylation in the presence of the by-product hydrogen peroxide, which results in the high yielding formation of glutaric acid derivative **20**. This process takes place in 10,000 l batch reactors with a capacity of 200 t/a. The reaction solution is directly transferred to another 10,000 l batch reactor (same annual capacity) where the next enzymatic reaction takes place (for continuation see Scheme 40).



Scheme 6

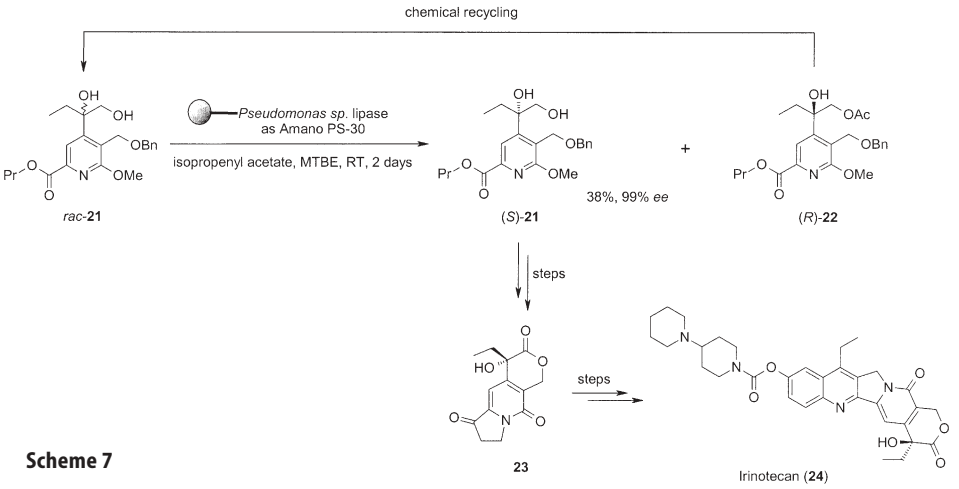
2.2 EC 2: Transferases

No examples of immobilized transferases for industrial applications could be found in the literature.

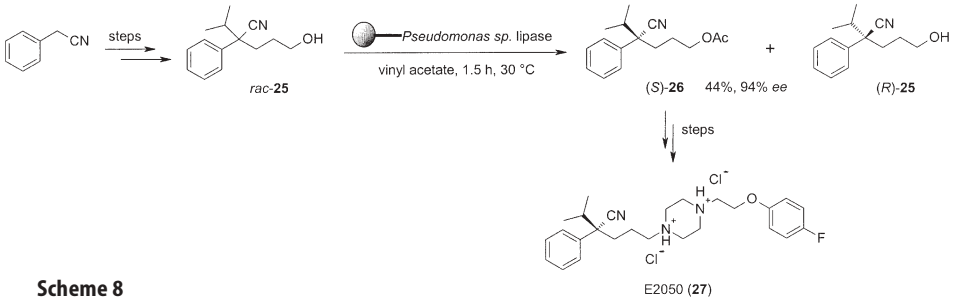
2.3 EC 3: Hydrolases

2.3.1 Use of Immobilized Lipase

Pharmacia & Upjohn developed a practical synthesis toward the anticancer agent Irinotecan (Camptosar, **24**), which involved an enzymatic resolution step to provide the strategic intermediate **23** (Scheme 7) [65, 66]. Lactone **23** could be produced by internal esterification of oxidized (*S*)-diol **21**, which in turn was obtained by biocatalytic resolution of *rac*-**21**. An asymmetric acetylation was achieved with isopropenyl acetate catalyzed by Amano PS-30 (*Pseudomonas cepacia*) lipase immobilized on Celite and could be driven to 60% conversion. (*S*)-**21** was isolated in 38% yield and with 99% optical purity, whereas the unwanted (*R*)-stereoisomer **22** was recycled in a three-step procedure. Changing the support to Celite 521 significantly increased the reaction rate, as did rais-



Scheme 7

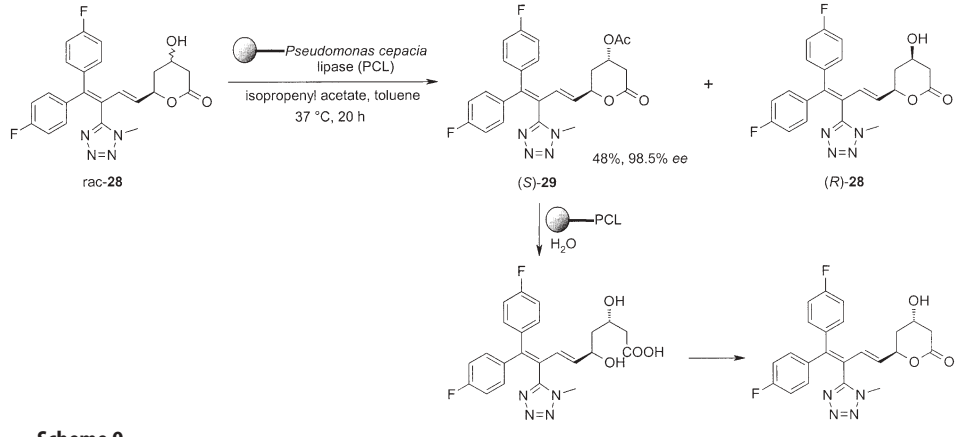


Scheme 8

ing the reaction temperature to 40–50 °C. The chemistry described was scaled up successfully to pilot scale and amounts of more than 35 kg of (*S*)-**21** were produced.

The neuron-selective calcium-channel blocker E2050 (**27**) was discovered by the Eisai Corporation during their research program toward novel neuroprotective agents (Scheme 8) [67]. The screening of different enzymes for the resolution of the racemic key intermediate *rac*-**25** by asymmetric acylation gave superior results with immobilized *Pseudomonas sp.* lipase (Wako Pure Chemical Industries). (*S*)-**26** was produced with high optical purity (94% *ee*), although the relevant stereogenic center is four carbon atoms away from the location where the enzymatic reaction takes place. Based on this result, **27** was accessible in reasonable quality in four chemical steps. Problems became apparent during the reuse of the enzyme, since a 90% drop of the initial activity was observed. This was presumably due to the release of acetaldehyde during the esterification in vinyl acetate, and a necessary optimization of the reaction conditions was the subject of further studies.

Pseudomonas cepacia (Amano PS-30) lipase immobilized on polypropylene beads was the key enzyme in a Bristol-Meyers Squibb process for the production of a HMG-CoA reductase inhibitor (Scheme 9) [68]. Racemic lactone *rac*-



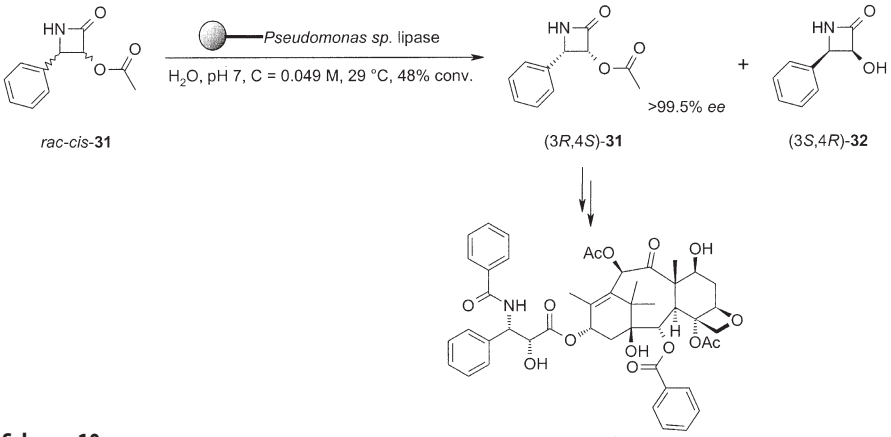
Scheme 9

28 was subjected to an enzymatic acetylation with isopropenyl acetate in a 9 mM solution in toluene to give the free alcohol **28** and the desired (*S*)-configured acetate **29** in 48% yield. Compound **29** could subsequently be hydrolyzed by the same enzyme in an aqueous/organic two-phase system to the hydroxy acid **30**, to finally give the active compound (*S*)-**28**. This enzymatic process takes place in a repetitive batch reactor with a volume of 640 l, resulting in conversions of approximately 2.5 kg per day, and the immobilized lipase can be reused five times.

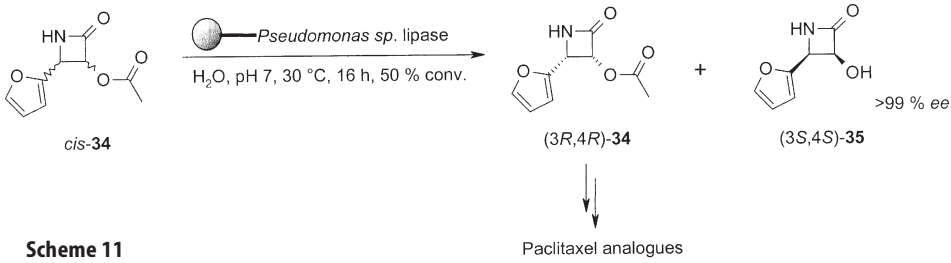
Another Bristol-Meyers Squibb process represents an enzymatic route for the production of side-chain precursors of Paclitaxel (**33**, Scheme 10) [69]. Racemic *cis*-azetidinone acetate (*rac*-**31**) is subjected to the hydrolytic treatment of *Pseudomonas cepacia* lipase (PCL), which is used in its immobilized form on polypropylene beads. Thus, (3*R*,4*S*)-acetate **31** can be obtained in high *ee* as well as the remaining alcohol **32**. The process takes place in 150 l reactors where 1.2 kg *rac*-**31**/batch can be resolved with a hydrolysis rate of 0.12 g/lh. Lowering the reaction temperature to 5 °C after full conversion causes (3*R*,4*S*)-**31** subsequently to crystallize. Due to the immobilization, the enzyme can be reused for at least ten cycles without any loss of activity, productivity, or optical purity of the product. Paclitaxel is finally accessible by further chemical steps.

Paclitaxel analogs bearing a side chain containing heterocyclic or cycloalkyl groups have also been shown to possess anticancer activity, and the enzymatic resolution of racemic mixtures of such intermediates has again been investigated at Bristol-Meyers Squibb [70]. Racemic *cis*-**34** could be stereoselectively hydrolyzed by *Pseudomonas cepacia* lipase (Amano PS-30) immobilized on Accurel and led to high optical purities of the desired (3*R*,4*R*)-enantiomer **34** (Scheme 11). Contrary to the use of the free enzyme, the immobilization reduced the required amount of biocatalyst by a factor of 10.

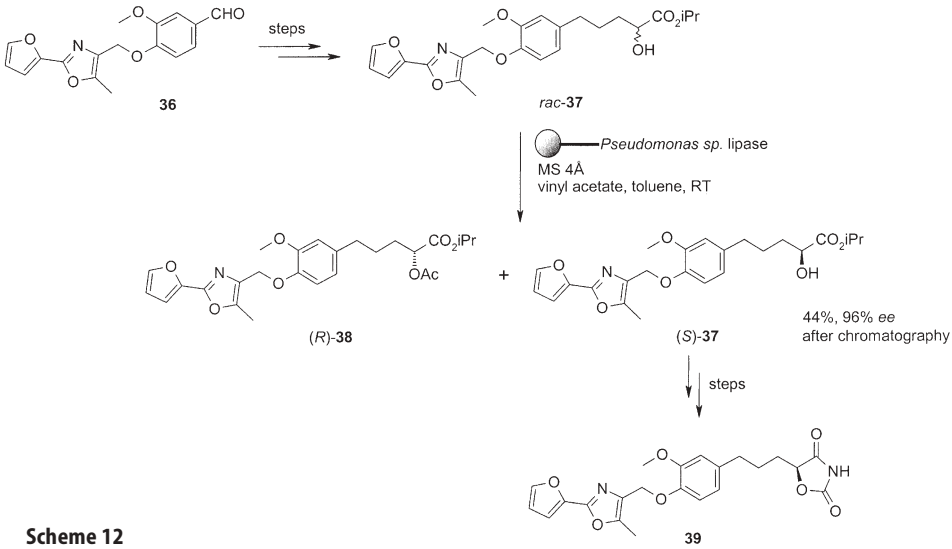
Scheme 12 shows the optical resolution of α-hydroxy ester *rac*-**37**, which was a key step in Takeda's synthesis of 2,4-oxazolidinedione **39** [71]. The compound



Scheme 10



Scheme 11

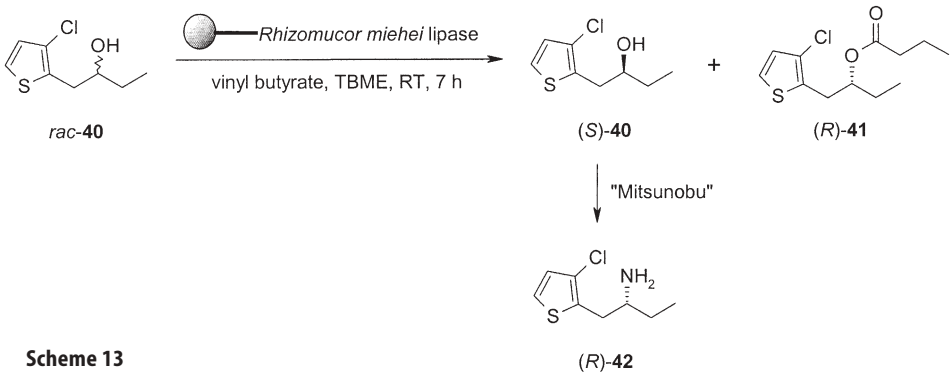


Scheme 12

shows antidiabetic (glucose- and lipid-lowering) activity and is one example of a group of related structures. Immobilized lipase from *Pseudomonas sp.* (LIP-301 – Toyobo Corporation) was found to be suitable for the asymmetric *O*-acylation, and the free alcohol (*S*)-**37** and the (*R*)-acetate **38** could be synthesized in gram amounts for activity screening assays.

The enzyme-catalyzed production of (*R*)-2-(2-aminobutyl)-3-chlorothiophene ((*R*)-**42**) was a research project at Zeneca a few years ago [72]. Compound **42** was an intermediate in the preparation of adenosine derivatives and Scheme 13 outlines the relevant enzymatic step. Racemic alcohol *rac*-**40** was treated with *Rhizomucor miehei* lipase immobilized on an ion-exchange resin (Lipozyme RM IM from Novozymes) in the presence of vinyl butyrate to yield the free (*S*)-alcohol **40** and the (*R*)-ester **41.** Alcohol **40** was subsequently converted into the strategic intermediate **42,** which found further use in the synthesis of antihypertension drugs.

The synthesis of chiral building block (*S*)-*tert*-leucine ((*S*)-**45**) was accomplished by Chiroscience via a hydrolase-catalyzed dynamic kinetic resolution

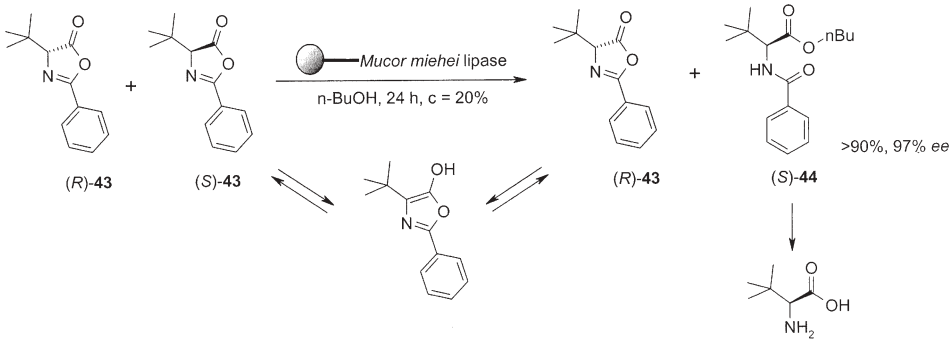


rac-**40** (*S*)-**40** (*R*)-**41** (*R*)-**42**

Scheme 13

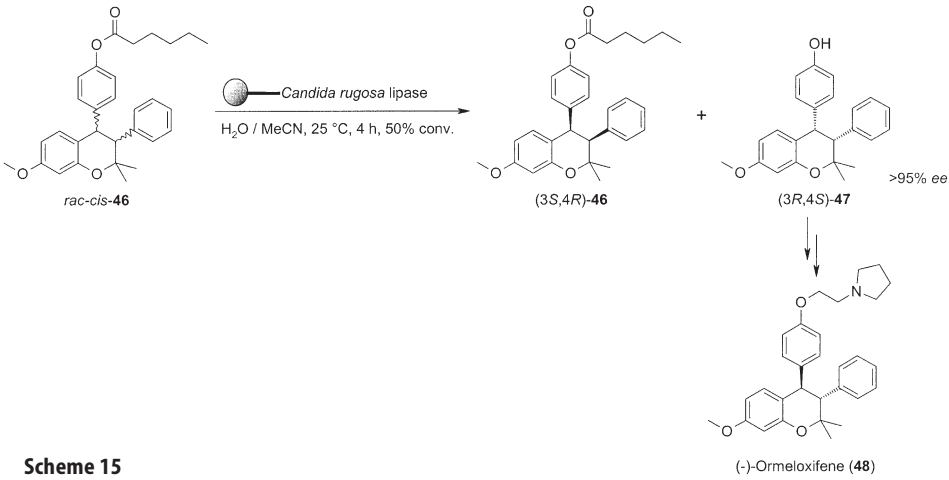
of azlactones (Scheme 14) [73]. This procedure is an alternative to the well-known Degussa process, which is carried out as a reductive amination of a prochiral keto acid with L-leucine-NAD oxidoreductase in an enzyme membrane reactor [7]. The Chiroscience process utilizes immobilized *Mucor miehei* lipase to open up the azlactones (*R*/*S*)-**43** in the presence of water-free *n*-butanol. *N*-protected butyl ester (*S*)-**44** is formed with high enantioselectivity, whereas (*R*)-**43** remains untouched. The latter easily racemizes, in particular in high substrate concentration (up to 20% of (*R*)-**43**), to furnish new (*S*)-**43**. Thus, (*S*)-**44** can be obtained in more than 90% overall yield and is converted to enantiopure (*S*)-**45** in a few additional steps.

Novo Nordisk showed in the synthesis of (–)-Ormeloxifene (**48**), a drug candidate for the treatment and prevention of osteoporosis, that the enzymatic asymmetric hydrolysis of potential intermediates can be carried out using *Candida rugosa* lipase (CRL) immobilized on Accurel (Scheme 15) [74]. Racemic *cis*-hexanoate *rac*-**46** was subjected to enzymatic hydrolysis in aqueous acetonitrile and gave the phenol *cis*-(3*R*,4*S*)-**47** in 95% *ee*. This transformation is a nice example to demonstrate that the enzyme can recognize and use remote stereocenters. The reaction was run on a 10 g scale, and it was even possible to recycle hexanoate (3*S*,4*R*)-**46**. Simple recovery of the immobilized enzyme by



(*R*)-**43** (*S*)-**43** (*R*)-**43** (*S*)-**44** (*S*)-**45**

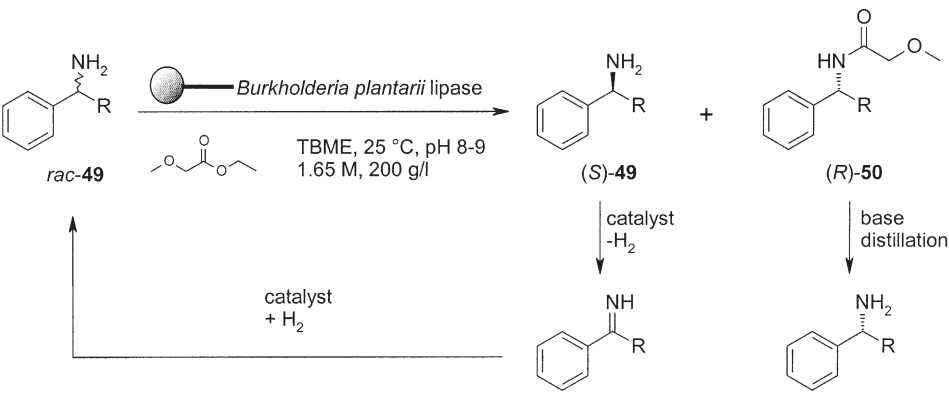
Scheme 14



Scheme 15

filtration allowed multiple recycling of the catalyst without significant loss of enzymatic activity.

Optically active amines are important intermediates and chiral auxiliaries in the technical synthesis of agrochemicals and pharmaceuticals. BASF, one of the world's leading producers of chiral amines, developed a process based on the enzymatic resolution of racemic amines **49** with *Burkholderia plantarii* lipase immobilized on polyacrylate (Scheme 16) [75, 76]. Methoxyacetic acid estars are particularly well suited for the stereospecific enzymatic differentiation, giving both the free amine (*S*)-**49** and the acylated product (*R*)-**50** in high *ee*. The reaction stops at 50% conversion and the selectivity factor was calculated to be as high as 500. A plug-flow or batch reactor can be used for the enzymatic reaction and the residence time is in the range of 5–7 h. The more important amine (*R*)-**49** can be liberated with the aid of base and is subsequently purified by distil-



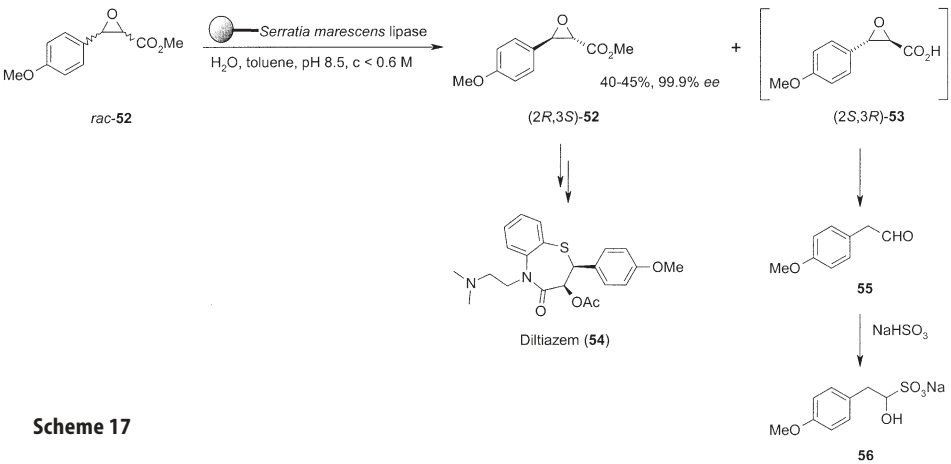
Scheme 16

lation, whereas the corresponding (*S*)-**49** is recycled by a dehydration/hydration procedure via imine **51**. A plant based on this process has been set up at the Ludwigshafen BASF site with a capacity of more than 1,000 t/a. The product range covers phenylalkyl amines, alkyl amines, and *O*-protected amino alcohols.

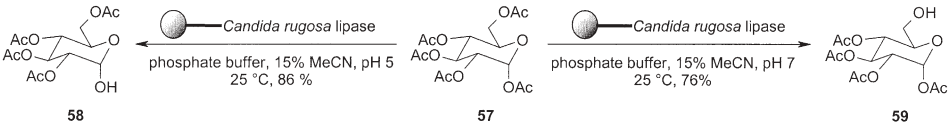
An enzymatic production process for Diltiazem (**54**), a coronary vasodilator and calcium channel blocker, was started in 1993 by Tanabe Seiyaku, Japan [7, 77]. The epoxide (2*R*,3*S*)-**52** is a key intermediate in this synthesis (Scheme 17) and can be produced via asymmetric hydrolysis of *rac*-**52** catalyzed by *Serratia marescens* lipase immobilized on spongy layers. The whole process takes place in a polyacrylonitrile hollow fiber membrane reactor and produces (2*R*,3*S*)-**52** in yields of 40–45%. The hydrolyzed product (2*S*,3*R*)-**53** is not stable under the prevailing reaction conditions and decarboxylates to aldehyde **55**, a strong enzyme deactivator. The aldehyde needs therefore to be removed, which is achieved by continuous filtration of its bisulfite adduct **56**. Using this enzymatic process it was possible to bring down the number of required steps en route to **54** from nine to five. This process is also carried out by other companies (e.g., DSM) with a worldwide annual production of 100 t.

The attachment and use of enzymes on hydrophilic supports covered with a dense layer of highly hydrophobic groups has been shown by Vita-Invest in recent years [78]. Various lipases were immobilized on Octyl-Sepharose CL-4B, and in certain cases an increase of activity of more than 100 times could be observed. The usefulness of these supported enzymes was demonstrated in first experiments by the regioselective hydrolysis of glucose pentaacetate (**57**) to glucose tetraacetate with *Candida rugosa* lipase (Scheme 18). The regioselectivity was found to be pH dependent, and the 2-*O*-deacylated derivative **58** could be obtained at pH 5, whereas the 6-*O*-deacylated product **59** was formed at pH 7.

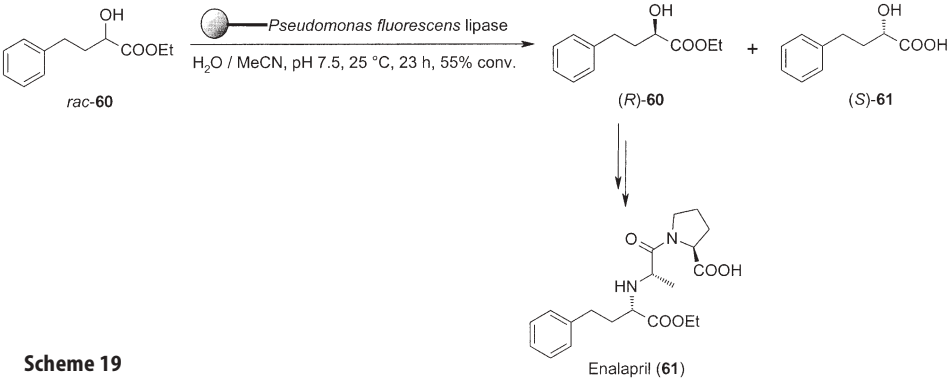
Using the same technique, the hydrolytic resolution of racemic *trans*-ethyl-2-hydroxy-4-phenylbutanoate (*rac*-**60**, Scheme 19), an important intermediate for the synthesis of antihypertension drugs such as Enalapril (**61**), could be accomplished [79]. The key compound (*R*)-**60** was obtained in reasonable yield and op-



Scheme 17



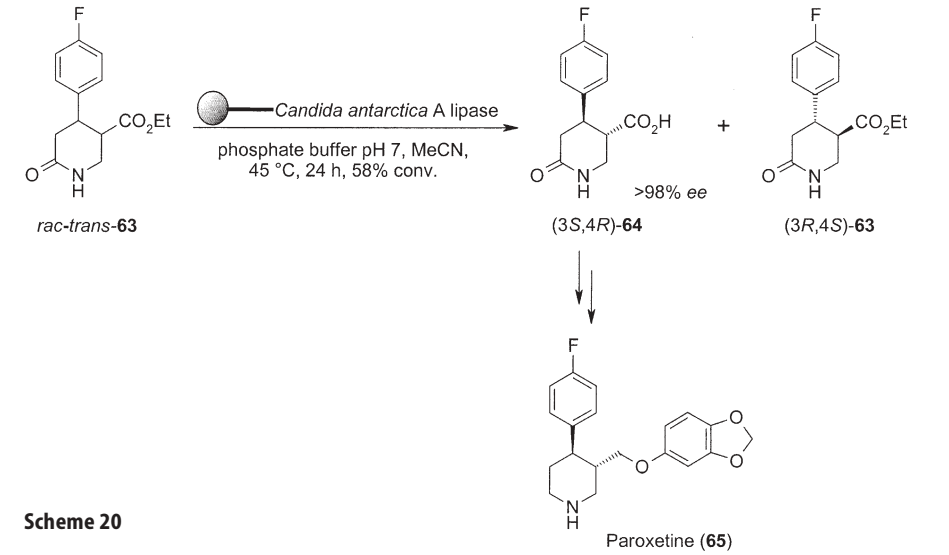
Scheme 18



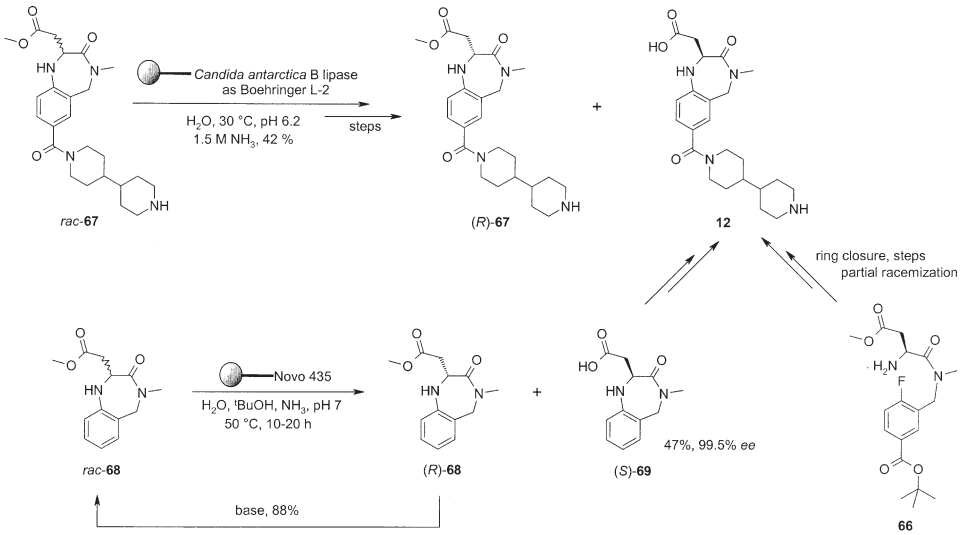
Scheme 19

tical purity through stereoselective ester hydrolysis with *Pseudomonas fluorescens* lipase. The remaining acid (*S*)-**61** could be recycled to obtain new *rac*-**60**.

Another Vita-Invest process was developed for the production of enantiopure 4-(4-fluorophenyl)-6-oxopiperidine-3-carboxylic acid ((3*S*,4*R*)-**64**), an intermediate suitable for the preparation of antidepressant Paroxetine (**65**, Scheme 20) [80]. Lipase from *Candida antarctica* A was found to catalyze the enantioselective hydrolysis of ester *rac-trans*-**63** best and worked especially well immobilized onto a polyethyleneimine/agar support. The enantiomerically



Scheme 20

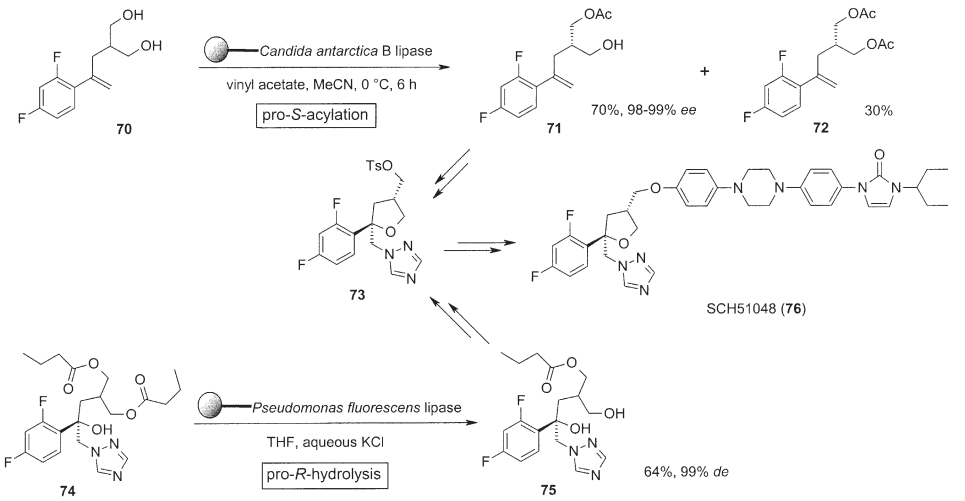


Scheme 21

pure acid (3*S*,4*R*)-**64** and the unhydrolyzed ester (3*R*,4*S*)-**63** were obtained under mild pH and temperature conditions and the acid was converted to **65** in a few chemical steps.

Lotrafiban (**12**), an orally active GPIIb/IIIa fibrinogen receptor antagonist, was designed by GlaxoSmithKline for the prevention of thrombotic events (Scheme 21) [81]. Problems with partial racemization during the intramolecular ring closure of fluoro amine **66** were the beginning of the development of a biocatalytic route toward **12.** It was decided to conduct an enzymatic resolution of *rac*-**67** to produce the optically pure drug. *Candida antarctica* B lipase (CAL-B) covalently bound to a macroporous cross-linked resin (Chirazyme L-2 C-1, supplied by Roche Molecular Biochemicals) proved to be ideal for this purpose. It was anticipated that at least 100 reuses of the resin should be possible using mild reaction conditions. And indeed, a few kilograms of supported enzyme were sufficient to produce several hundred kilograms of **12.** However, a major drawback of this route was the low overall yield because of the late-stage enzymatic resolution. Over the years a new route evolved, in which the biocatalytic step is carried out at an earlier stage. The new strategic intermediate *rac*-**68** could again best be resolved by CAL-B, now immobilized on a polyacrylate carrier (Novo 435 from Novozymes). The enzyme delivered superior results in terms of yield, time, and optical purity of acid (*S*)-**69** and could be reused many times. (*R*)-**68** was recycled to give new *rac*-**68** and the whole new process has been carried out in a pilot plant to prepare ~4 t of (*S*)-**69** [82, 83].

The enzymatic desymmetrization of prochiral 2-substitued-1,3-propanediols was a key step for the synthesis of antifungal compound SCH21048 (**76**) at Schering-Plough [84]. Two possible routes are shown in Scheme 22: the enzymatic differentiation of dibutyrate **74** and the selective acetylation of prochi-

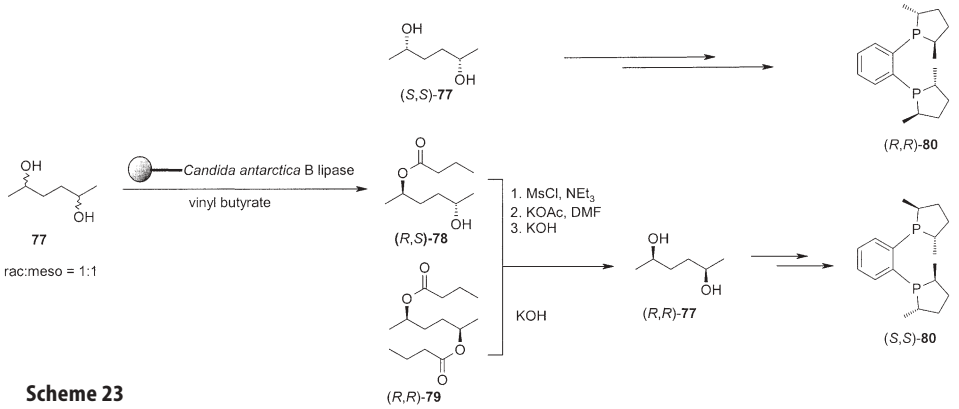


Scheme 22

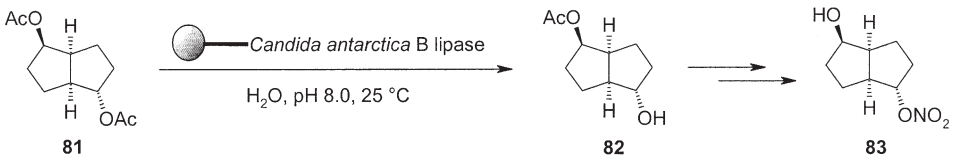
ral diol **70**, both leading to furan intermediate **73**. The selective pro-(*R*)-hydrolysis of **74** could be accomplished using immobilized *Pseudomonas sp*. lipase (Amano AK) in potassium chloride containing aqueous tetrahydrofuran. The monobutyrate **75** was obtained, essentially free of triol, in 64% yield and 99% *de*. However, a simpler and shorter process proved to be the acetylation of racemic diol **70**. Novo 435 clearly showed the best balance between an optimal optical purity of monoester **71** and its chemical yield, and it was observed that the *ee* increased over time at the expense of diol formation. 30-kg batches (150 l scale) were run under optimized process conditions and gave alcohol **71** in approximately 70% yield. Additional chemical steps via furan **73** led to the final compound **76**. The enzyme recyclability could also be demonstrated six times without major loss of activity [85].

The use of enzyme technology has also been exemplified in a Chirotech process for the synthesis of both enantiomers of the hydrogenation catalyst DuPHOS (**80**) [2, 86]. A hexanediol mixture consisting of 50% meso and 50% racemic diol **77** was acylated with the aid of immobilized CAL-B (Scheme 23). Only the (*R*)-configured alcohol was converted by the enzyme and led to the monobutyrate (*R*,*S*)-**78** and the bisbutyrate (*R*,*R*)-**79**. The unchanged (*S*,*S*)-diol **77** could be removed by extraction with water and was purified by crystallization from ethyl acetate, to reach an optical purity of 98% *ee* and 88% *de*. The mesylate of alcohol (*R*,*S*)-**78** could be inverted with potassium acetate, and saponification of this acetate and of compound (*R*,*R*)-**79** followed by a crystallization step provided the enantiopure diol (*R*,*R*)-**77** in 48% yield. Although this procedure was used to produce approximately 30 kg of DuPHOS, it has not been used further for commercial catalyst production.

Another application of immobilized CAL-B has been discovered by Roche scientists for the synthesis of isosorbide monoacetate (**82**, Scheme 24) [3]. In



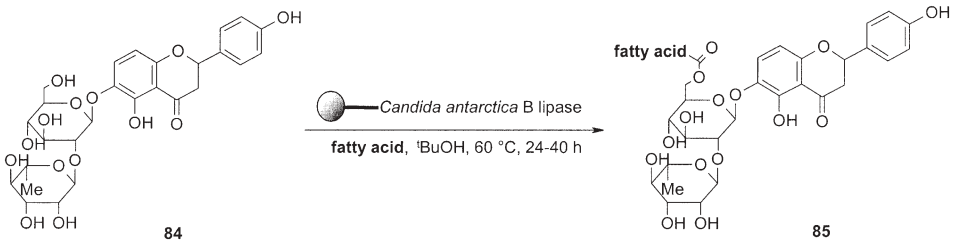
Scheme 23



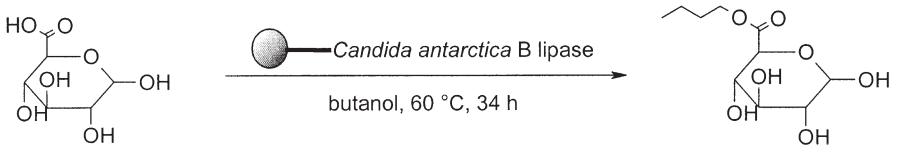
Scheme 24

this process, the diacetate **81** was hydrolyzed to the 2-acetate **82**, which can serve as a precursor for isosorbide-5-nitrate (**83**), a coronary vasodilator. Although this enzyme-based process is highly competitive compared to the chemical one, it has never been commercialized.

Immobilized CAL-B was also used by Henkel to synthesize fatty acid esters of flavone and isoflavone glycosides (Scheme 25) [87]. Compounds such as **84** are known to be oxygen radical scavengers as well as inhibitors of skin proteases and can therefore serve as antiaging agents. It was found that esterification with fatty acids improved the biological availability, and the new compounds were claimed to possess antiaging/antiwrinkling properties as well as an improved influence on collagen production. Despite the fact that these carbohydrate derivatives are not natural substrates of lipases, CAL-B was especially well suited for the syntheses of compounds **85** and showed a high selectivity toward the primary hydroxyl group in the esterification reaction. Henkel



Scheme 25



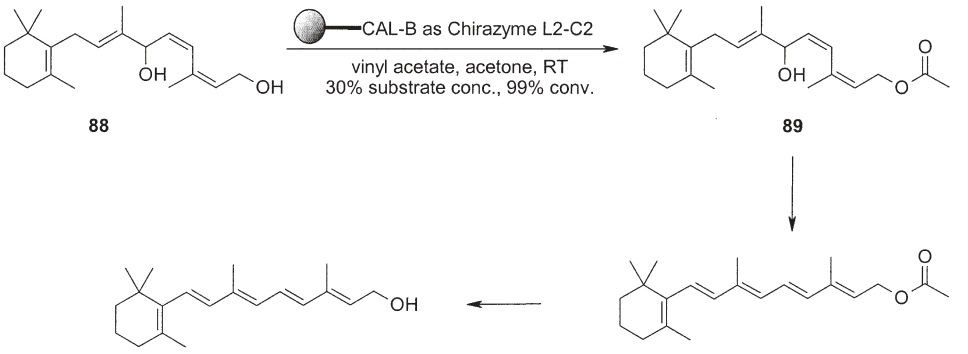
86 **87**

Scheme 26

has also claimed the use of CAL-B for the synthesis of other glycosidic esters recently [88].

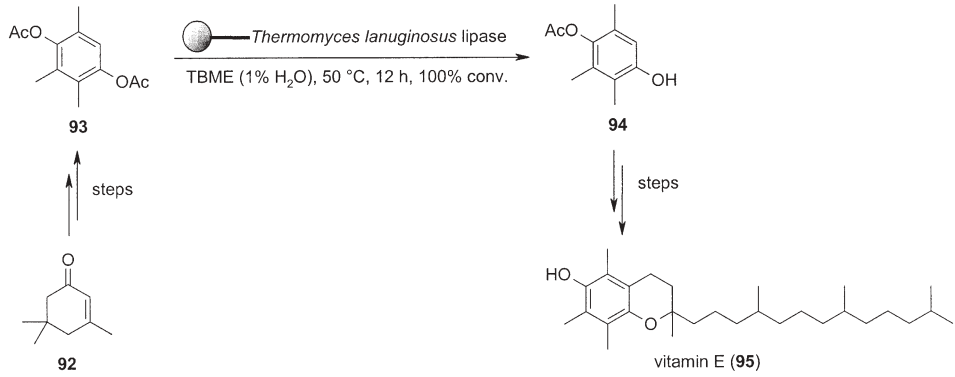
Similar transformations have also been published by Cognis [89], for instance the esterification of uronic acid **86** with various alcohols (e.g. butanol) catalyzed by immobilized CAL-B (Scheme 26). The esters such as **87** possess surface activity and may show antimicrobial activity and can therefore be used as (co)-surfactants, emulsifying agents, or antimicrobials in the home and personal care area.

Chirazyme L2-C2 (CAL-B) proved to be a very useful enzyme for the development of an acylation process for the large-scale production of vitamin A (retinol, **91**) at Roche (Scheme 27) [90, 91]. In the plant process of vitamin A, intermediate **88** is partially acylated and then subjected to acid-catalyzed dehydration and isomerization to yield the vitamin A ester **90** via acetate **89**. Contrary to the chemical acylation, an enzymatic approach allowed for a highly selective monoacylation of **88**, and Chirazyme L2-C2 showed a very high conversion rate at 30% (w/w) substrate concentration. A first continuous process on the laboratory scale was set up with a 15 ml fixed-bed reactor containing 5.0–8.0 g of immobilized biocatalyst; 4.9 kg of **89** was synthesized within 100 days in 99% yield and with 97% selectivity for the primary hydroxyl group. The laboratory process was implemented in a miniplant (120 g of biocatalyst), which could convert 1.4 kg of **88** into 1.6 kg **89** per day. After 74 days the conversion efficiency was still 99.4%. Further development of this transformation led to a modified process, which uses *Thermomyces lanuginosus* lipase immobilized on Accurel MP1001 for the continuous production of **89** [92].



88 **89** **90**

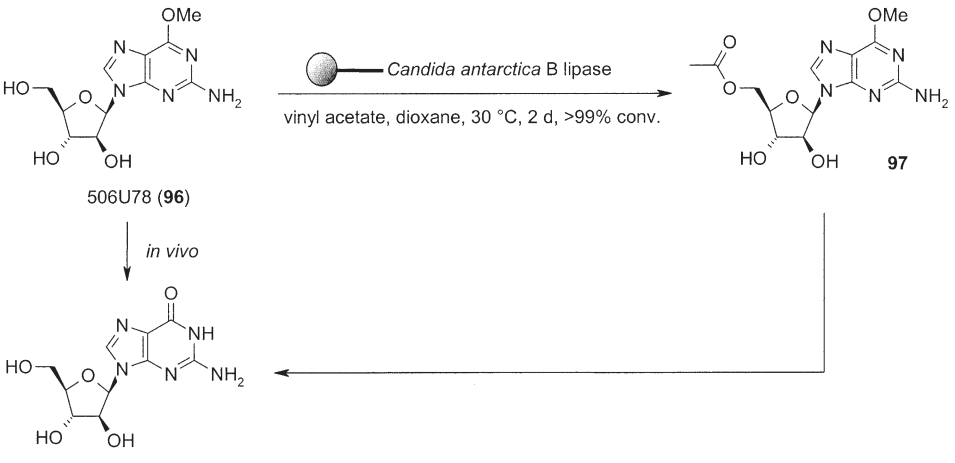
Scheme 27



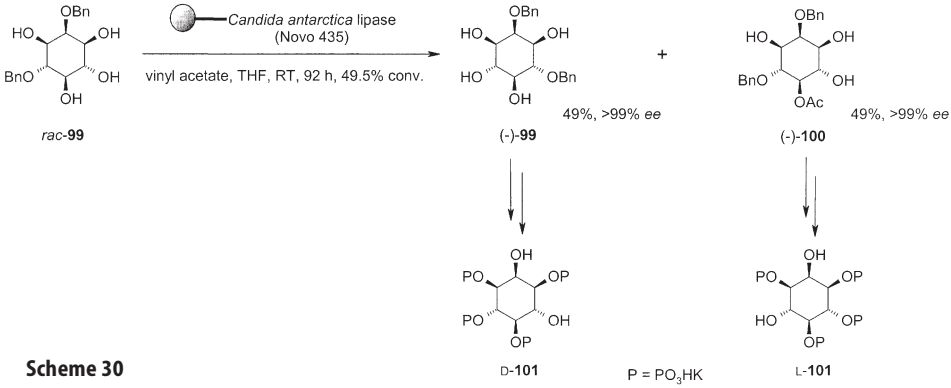
Scheme 28

(All-*rac*)-α-tocopherol (**95**) is the economically most valuable product of the vitamin E family. An innovative route by Roche scientists toward **95** started from monoacetate **94**, which is difficult to synthesize by standard chemical methods [93]. However, by using cheap isophorone (**92**), the diacetate **93** is easily available, and an enzymatic hydrolysis was again an elegant solution to get hold of **94** (Scheme 28). An enzyme screening revealed that *Thermomyces lanuginosus* lipase was highly active and selective in the partial hydrolysis of **93** and led to virtually quantitative conversion without concomitant hydrochinone production. Furthermore, immobilization on Accurel MP1001 increased the hydrolytic activity tenfold without affecting the high regioselectivity.

An interesting application of Novozyme 435 has been demonstrated by Glaxo Wellcome [2, 94] by using this enzyme for the acylation of the antileukaemic prodrug 506U78 (**96**, Scheme 29). It was already known that acetylation of purine **96** rendered the compound more soluble and bioavailable, and the 5′-monoacetate **97** was of particular interest for studies related to metabo-



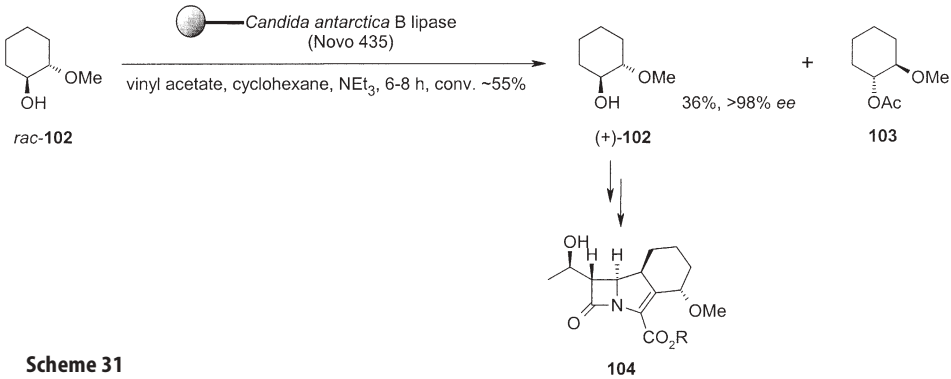
Scheme 29



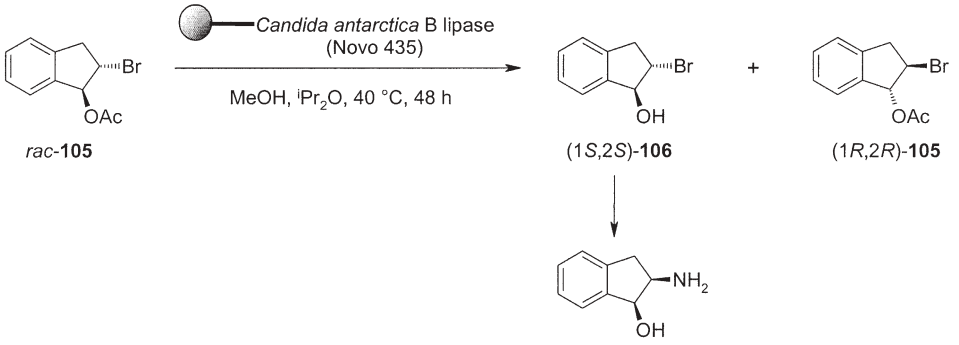
Scheme 30

lite **98**. Several enzymes were found to acylate **96** at the 5´-position, but most of them also formed by-products. Novo 435 clearly performed best, and it was found that concentrations could easily be increased to 50 g/l without compromising reactions rates. However, increasing the substrate concentration further to 100 g/l led to diminished conversion of 60–70%. The enzymatic transformation caused only a very low level of related impurities (<0.5%) giving virtually pure **97** after filtration of the enzyme beads.

Novozyme 435 has also been applied by a Novartis group for the synthesis of optically pure 2,6-di-*O*-benzoyl-*myo*-inositol ((–)-**99**) and its monoacetate (–)-**100**. These intermediates are precursors for the rare and expensive inositol phosphates D-**101** and L-**101** (Scheme 30) [95], compounds which are essential for a number of physiological processes in differentiated higher cells, e.g., the activation of thrombocytes in the blood clotting process or hormone signal transduction. The key intermediate *rac*-**99** could be prepared in four chemical steps, and the Novo 435-catalyzed asymmetric acetylation afforded monoacetate (–)-**100** besides unconverted inositol derivative (–)-**99** with optical purities of >99%, respectively. The subsequent chemical hydrolysis of (–)-**100** quantitatively yielded the antipode of (–)-**99**, and a phosphorylation,



Scheme 31



rac-**105** (1*S*,2*S*)-**106** (1*R*,2*R*)-**105**

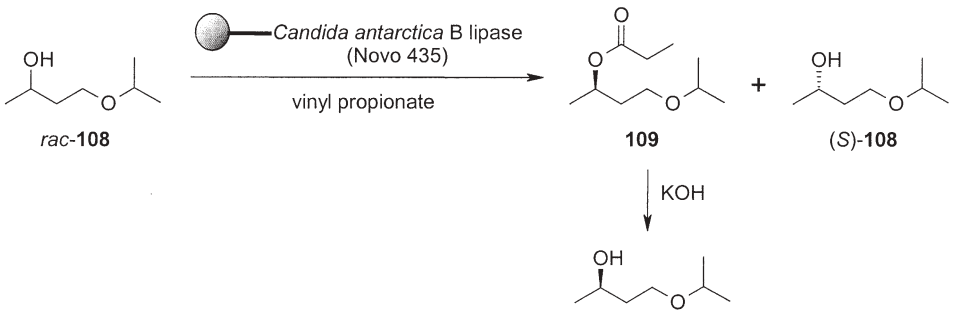
107

Scheme 32

oxidation, and deprotection sequence of both enantiomers finally furnished D-**101** and L-**101** in gram quantities.

An efficient procedure for the large-scale preparation of (1*S*,2*S*)-*trans*-2-methoxycyclohexanol ((+)-**102**), a key intermediate in the synthesis of a new class of tricyclic β-lactam antibiotics (**104**), has been developed by Glaxo Wellcome [96]. The key step of the synthesis was the enzyme-catalyzed resolution of *rac*-**102** with immobilized *Candida antarctica* B lipase (Scheme 31). Novo 435 was used for the asymmetric acylation of *rac*-**102** and provided direct access to the important alcohol (+)-**102** in good yield and high optical purity. The enzyme exhibited excellent stability and retained about half of its initial activity after nine cycles of use. This process is now operating on a manufacturing scale.

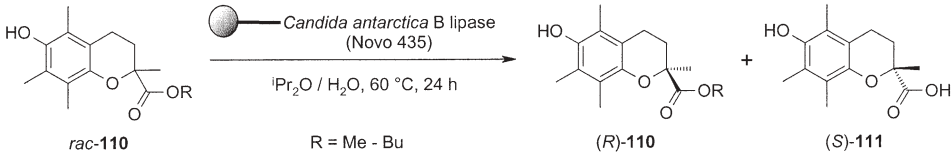
The manufacture of optically active *trans*-2-bromoindan-1-ol (**106**) and its esters starting from racemic *trans*-2-bromo-1-(acyloxy)indan (*rac*-**105**) has been conducted by Ichikawa Gosei Kagaku Co., Japan (Scheme 32) [97]. Compound **106** is a useful intermediate for the synthesis of *cis*-1-aminoindan-2-ol (**107**), which can be used for the preparation of anti-HIV drugs. An asymmetric hydrolysis of *rac*-**105** could be performed through enzyme-catalyzed acyl transfer onto methanol. Thus, alcohol **106** was produced by applying Novozyme 435 in diisopropyl ether/methanol in 45% yield besides acetate (1*R*,2*R*)-**105** in 52% yield.



rac-**108** **109** (*S*)-**108**

(*R*)-**108**

Scheme 33



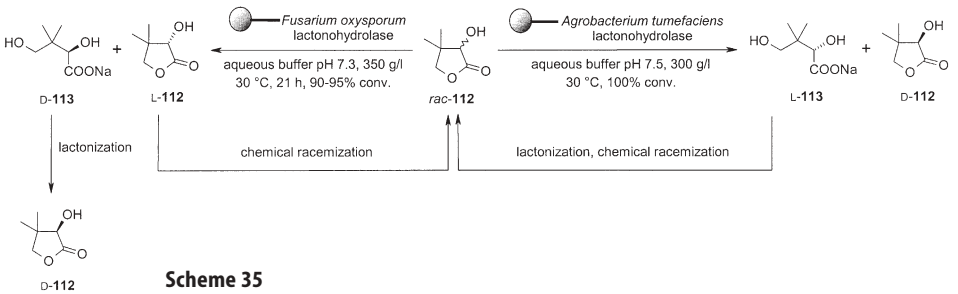
Scheme 34

Further uses of Novozyme 435 have been described in recent patent applications filed by the Mitsubishi Gas Chemical Company and comprise processes for the production of optically active secondary alcohols (Scheme 33) [98] and the manufacture of optically active chroman-2-carboxylic acids (Scheme 34) [99]. In the first case the resolution of racemic 4-isopropyloxy-2-butanol (*rac*-**108**) by Novo 435 was an important step toward (*R*)-(+)-4-(isopropyloxy)-2-butanol ((*R*)-**108**) via acetate **109**. Compound (*R*)-**108** can be used for the synthesis of liquid crystal materials.

In the second case, (*S*)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid ((*S*)-**111**), a useful intermediate for industrial chemicals, agrochemicals, and pharmaceuticals, could be manufactured by asymmetric hydrolysis of short-chain alkyl esters of *rac*-**110** with Novo 435 (Scheme 34). The methyl ester of *rac*-**110** could, for example, be hydrolyzed in a diisopropyl ether/water mixture at 60 °C within 24 h to give (*S*)-**111** with 98% *ee* in 27.5% yield.

2.3.2
Use of Lactonase

About 6,000 t of the animal feed additive calcium-D-pantothenate are produced annually via D-pantolactone (D-**112**) (Scheme 35, left side). D-Pantolactone itself is an important chiral intermediate for chemical synthesis and a chiral resolution agent for optically pure amines. Optically pure D-**112** is for instance produced by Fuji Chemical Industries by using the D-specific 1,4-lactone hydroxyacylhydrolase from *Fusarium oxysporum* [100–102], an enzyme that catalyzes the stereospecific hydrolysis of various kinds of lactones. Treatment of *rac*-**112** leads to an exclusive hydrolysis of D-**112**; the hydroxy acid D-**113** can be easily separated from the remaining lactone L-**112** and is subsequently chemically con-



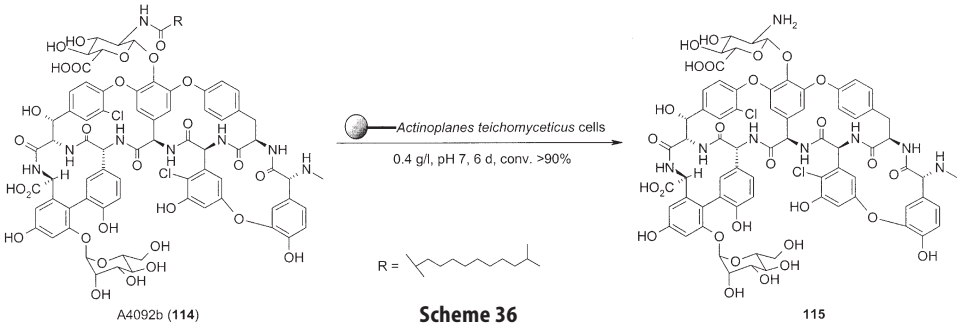
Scheme 35

verted to D-**112**. Using a repetitive racemization protocol for L-**112**, it is possible to reach overall conversions of D/L-**112** as high as 90–95%. This process takes place in a fixed bed reactor and uses whole cells immobilized in calcium alginate. As a result, the cells still retain about 60% of their initial activity after repeated use for 180 times. The enzymatic commercial production of D-pantolactone started in 1999 and the enzymatic manufacture clearly excels former chemical processes in view of economical and environmental aspects.

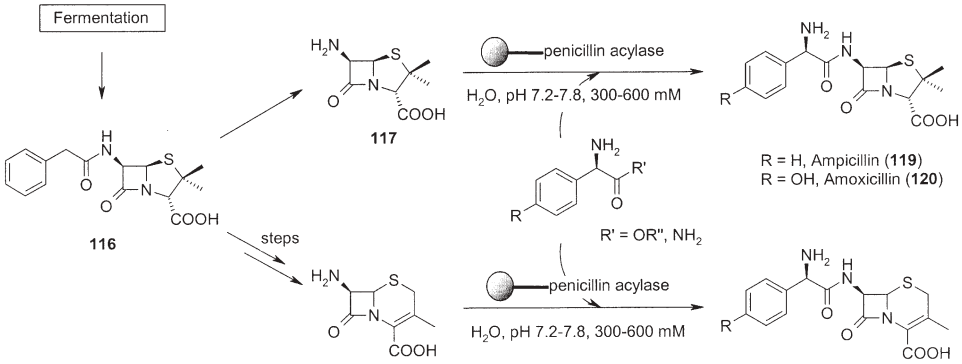
Contrary to the Fuji process, BASF described the characterization and cloning of an L-specific pantolactone hydrolase from *Agrobacterium tumefaciens* [103, 104]. This enzyme exclusively opens up the undesired lactone L-**112**, providing a more direct route to D-**112** (Scheme 35, right side). In addition, this new process is expected to be much more robust toward the competing spontaneous chemical hydrolysis, which could theoretically cause a diminished optical yield in the Fuji process. The enzymatic resolution of D/L-**112** in repeated batches with membrane filtration techniques provided D-**112** in 50% yield and with 90–95% *ee*. By immobilization onto Eupergit C it was possible to obtain a stable biocatalyst which was easy to use in repeated batch reactions.

2.3.3
Use of Amidase (Acylase) and Hydantoinase

One of the rare examples for the use of supported living cells for production issues was given by Biosearch Italia S.p.A. [105–108]. A member of the vancomycin family, antibiotic A40926 (**114**), can be produced via a fermentation process and appears as a mixture of different side chains attached to the glucuronic acid moiety (Scheme 36). Mycelium of *Actinoplanes teichomyceticus* (ATCC 31121) was coimmobilized with soybean meal (*in situ* nutrient supply) in calcium alginate beads and used to deacylate A40926. The action of the endoenzyme deacylase gives rise to the glycopeptide nucleus **115**, which can synthetically be modified to form new antibiotic analogs. Repeated-batch biotransformations (up to 300 l) could be successfully maintained for longer than 30 days (five cycles), although a significant decrease of the deacylation rate occurred. By applying this technique it was even possible to remove *tert*-butoxy-



A4092b (**114**) **Scheme 36** **115**

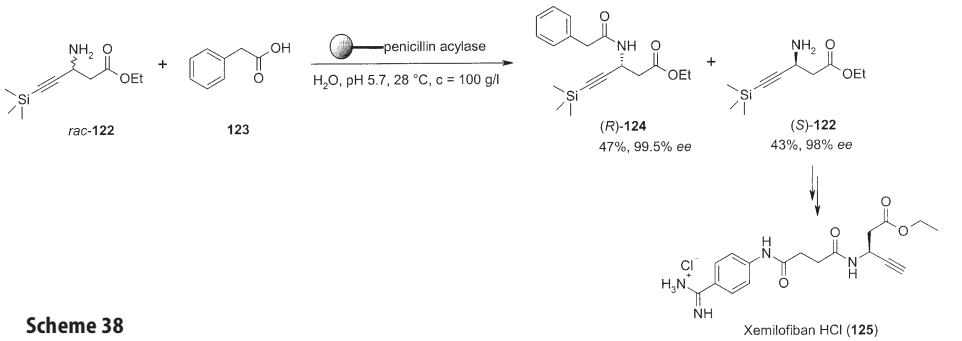


Scheme 37

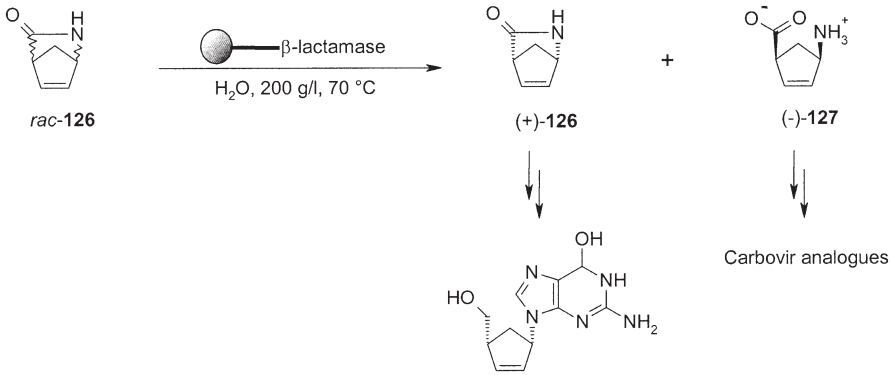
carbonyl protecting groups, which are often introduced to protect amino groups during chemical synthesis.

Chemferm is one of among several companies which apply penicillin acylase for the kinetically controlled industrial synthesis of semisynthetic antibiotics in aqueous environments (Scheme 37) [109–111]. Ampicillin (**119**) and amoxicillin (**120**) can be obtained by the enzyme-catalyzed condensation of 6-aminopenicillic acid (6-APA, **117**) with the amide or ester of D-(–)-4-hydroxyphenylglycine and D-(–)-phenylglycine, respectively. In a similar way, cephalexin (**121**) can be obtained by reaction of D-(–)-phenylglycine with 7-aminodesacetoxycephalosporanic acid (7-ADCA, **118**). Penicillin acylase from diverse microbial strains such as *E. coli*, *Klyveromyces citrophila*, and *Bacillus megabacterium* was successfully applied for this transformation and was used in its immobilized form based on a gelatin carrier. The immobilization allows an easy separation from the reaction medium and the reuse of the enzyme for at least 50 cycles. Impressive characteristics of this transformation are yields >90%, a selectivity of >95%, and an optical purity of >99% *ee*. The industrial manufacture takes place in repetitive batch reactors at many locations worldwide with an annual production volume of 2,000 t.

An enzymatic route toward a key intermediate for the production of pseudopeptide Xemilofiban (**125**), a platelet adhesion inhibitor, was recently in-



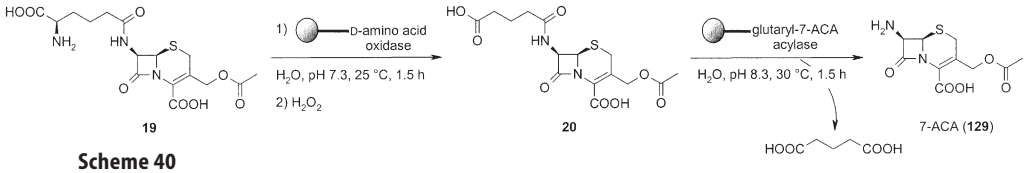
Scheme 38



Scheme 39

troduced by Searle [112] (and Pharmacia [113]). Due to low yields in the chemical resolution of racemic amine *rac*-**122**, an enzymatic approach based on the asymmetric acylation of *rac*-**122** with phenylacetic acid (**123**) catalyzed by penicillin amidohydrolase (penicillin G amidase, PGA) was developed (Scheme 38). After screening several commercial sources of immobilized enzyme, PGA-450 (Roche Diagnostics) was found to be highly efficient in terms of activity and stability. The undesired (*R*)-enantiomer could be obtained as its amide **124** in high yield and *ee*, and virtually untouched (*S*)-**122** could subsequently be converted into **125** in a few chemical steps. This process was scaled up to a 70 l scale and further investigations indicated that the enzyme was able to retain up to 50% of its initial activity for 20 to 25 cycles. Fortunately, the incremental cost contribution of the enzyme was assumed to be less than 5% after 15 cycles, making the enzymatic acylation approach economically acceptable.

A production process for the synthesis of carboxylic nucleoside precursors, which can be used for the manufacture of anti-HIV-1 agents such as carbovir (**128**) and analogs, has been developed by Chiroscience (Scheme 39) [114]. The process uses β-lactamhydrolase from *Aureobacterium sp.* immobilized on a glutaraldehyde-activated solid support for the optical resolution of lactam *rac*-**126**. The biotransformation is conducted as a batch reaction and an aqueous solution of *rac*-**126** is cycled through a fixed bed of immobilized enzyme. This setup guarantees that the enzyme can be used in a steady-state production for more than six months, limited only by the mechanical stability of the carrier. The reaction stops when (–)-**126** is completely hydrolyzed and a simple addition of acetone causes only the amino acid (–)-**127** to crystallize. The latter can be used



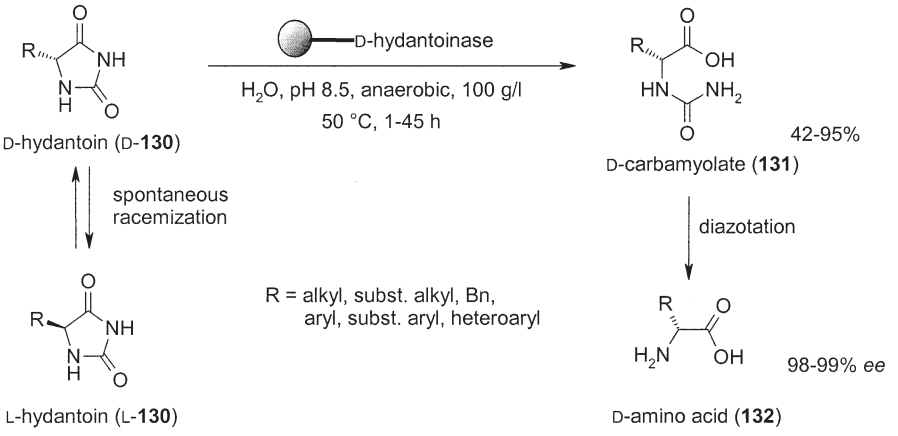
Scheme 40

for the synthesis of carbovir analogs, whereas (+)-**126** leads directly to carbovir in a few chemical steps.

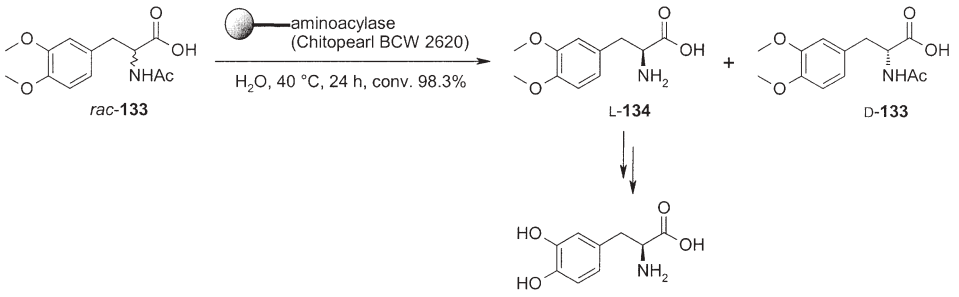
Scheme 40 describes the second part of the Hoechst Marion Roussel process of 7-ACA (**129**) manufacture – the first enzymatic transformation has already been described in Scheme 6. Glutaric acid derivative **20** is now subjected to treatment with immobilized *Pseudomonas sp.* ω-amidodicarboxylate amidohydrolase (recombinant in *Escherichia coli*). The enzyme catalyzes the chemo- and stereoselective hydrolysis of the amide and gives the free amine **129** in reasonable yield and optical purity. The whole process has also been established in several other companies, with minor modifications. Anbics, for example, is presently setting up a fermentation process with its subsidiary Bioferma Murcia in Spain for the production of 7-ACA. A typical isolated yield of 82% has been reported for **129**, which can be further optimized to >85% by applying techniques such as reversed osmosis on the production scale [115].

A process for the production of D-α-amino acids has been developed by Roche Diagnostics based on the enzyme D-hydantoinase [115]. The recombinant protein was covalently fixed onto a carrier and used for the synthesis of a broad range of natural and artificial D-amino acids (**132**, Scheme 41). Starting from racemic hydantoins D/L-**130**, the enzyme exclusively hydrolyzed D-**130** to **131**, and new D-**130** was internally produced by continuous *in situ* racemization of L-**130**. The process worked especially well with 5-(*p*-hydroxyphenyl)- and 6-phenylhydantoin, affording the corresponding amino acids **132** in high yield and optical purity. The number of reuse cycles until 50% of the initial enzyme activity was reached was calculated to be as high as ~200. Unfortunately, this process has never been used in the production of D-amino acids, as diazotation was found to be too noxious and complicated.

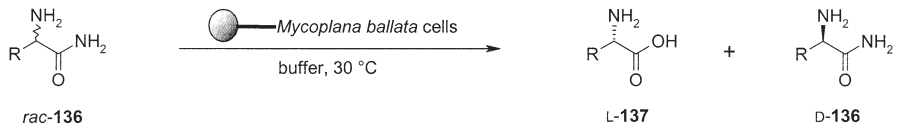
A process for the synthesis of L-veratrylglycine (**134**, Scheme 42), a useful intermediate in the synthesis of L-dopa (**135**), has been published by Sankyo [116]. The product is manufactured by asymmetric hydrolysis of racemic *N*-



Scheme 41



Scheme 42



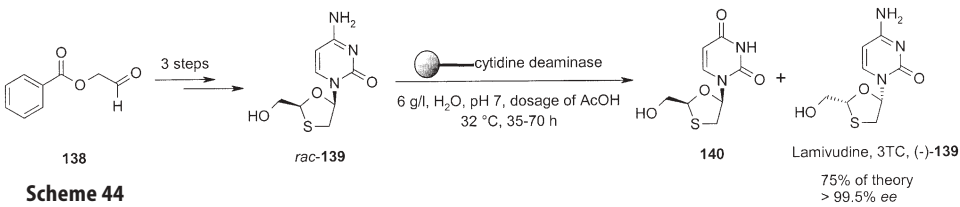
Scheme 43

acetyl-veratrylglycine (*rac*-**133**) with amidase immobilized on Chitopearl BCW 2620 (chitosan polymer). Contacting *rac*-**133** with the enzyme at 40 °C for 24 h led to a hydrolysis rate of 98.3%. Enzyme recovery and reuse in the same reaction still allowed a very good hydrolysis rate of 97.4% after 19 cycles.

The manufacture of optically active L-α-amino acids from racemic amino acid amides was shown by Mitsubishi Gas Chemical, Japan [117]. In this process different microorganisms were immobilized on polymers made from (meth)acrylic acid esters or urethane acrylates and applied for the stereoselective hydrolysis of racemic amides (Scheme 43). D/L-Leucinamide (*rac*-**136**), for example, can be hydrolyzed with *Mycoplana bullata* cells immobilized on polyethylene glycol dimethacrylate-*N*,*N*′-methylenebisacrylamide copolymer at 30 °C to produce L-leucine (L-**137**) over 3,000 h.

2.3.4 Use of Deaminase

An enzymatic production of enantiomerically pure (2′*R*-*cis*)-2′-deoxy-3′-thiacytidine (3TC, Lamivudine, (–)-**139**), a potent anti-HIV agent, has been devel-



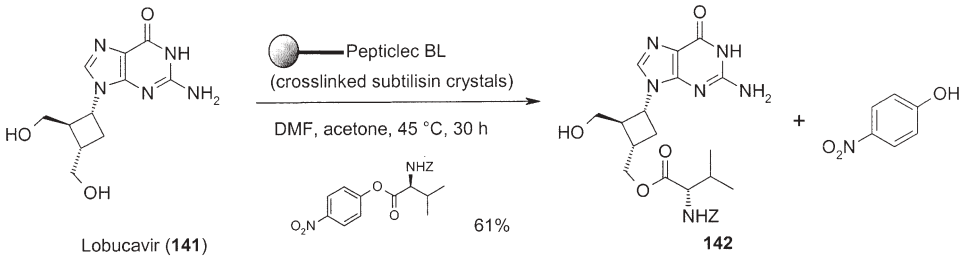
Scheme 44

oped by Glaxo Group Research Ltd. [118, 119]. 2′-Deoxy-3′-thiacytidine (*rac*-**139**), which can be obtained from aldehyde **138** in three steps, was resolved with the aid of cytidine deaminase from *Escherichia coli* (Scheme 44). The enzyme catalyzed the stereoselective deamination of (+)-**139**, providing the keto compound **140** and essentially enantiomerically pure (–)-**139**. Kilogram amounts of 3TC could be synthesized in a production process, using an optimized enzyme which was obtained by strain improvement, fermentation development, and finally by cloning and overexpression. The enzyme was immobilized on Eupergit C, which allowed its reuse for at least 15 cycles although the residence time increased from initially 35 h to more than 70 h. The enzyme showed no substrate inhibition up to 30 g/l of **100**, allowing high volumetric productivities. The process was finally intended to be scaled up to produce ton quantities of 3TC.

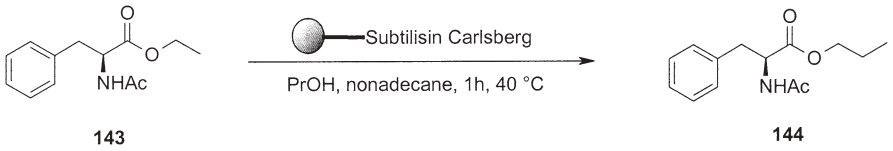
2.3.5 Use of Protease

The regioselective enzymatic aminoacylation of the cyclobutyl guanine nucleoside analog Lobucavir (**141**, Scheme 45) has been conducted by chemists at Bristol-Myers Squibb [120]. A prodrug form in which one of the two hydroxyl groups is coupled to valine was difficult to synthesize by classical chemistry but appeared to be accessible by an enzymatic approach. Attempts to perform a biocatalytic regioselective hydrolysis of the bis-valine ester proved to be unsuccessful, but the selective mono esterification with *Z*-protected valine *p*-nitrophenyl ester was possible using cross-linked enzyme crystals of the protease subtilisin (ChiroCLEC BL, Altus). Compound **142** could be obtained in 61% yield, and although the conversion rates dropped on the fourth and fifth reuse of the enzyme, the reaction could be scaled up successfully to give 4.5 kg of **142** from a 4.4 kg input of **141**. Further alternatives for the synthesis of **142** arose by the use of immobilized *Pseudomonas cepacia* lipase, which resulted in a yield of 84% on a small scale. Thus, PCL was finally the enzyme taken for development.

The use of an immobilized protease for transesterification reactions and the procedure for the immobilization have been described by FMC Corporation [121]. The company applied the protease subtilisin Carlsberg embedded into a dehydrated hydrocolloid polymer gel consisting of kappa-carageenan for the



Scheme 45



143 144

Scheme 46

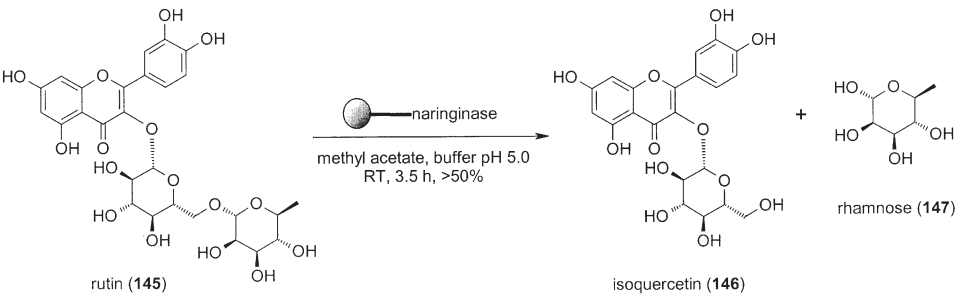
transesterification of amino acids such as *N*-acetyl-L-phenylalanine ethyl ester **143** to the corresponding propyl ester **144**, as indicated in Scheme 46.

2.3.6 Use of Glycosidase

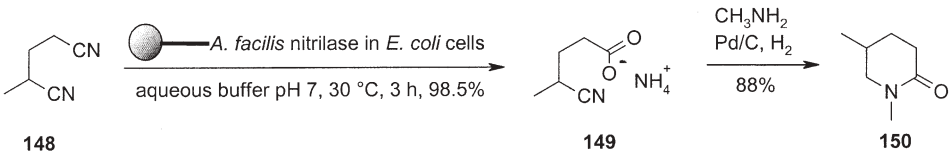
Merck has published a method for producing monoglycosidated flavonoids and the carbohydrate rhamnose (**147**) by enzymatic hydrolysis of rutinosides [122]. Naringinase (a mixture of rhamnosidase and beta-glucosidase) was immobilized on magnetic silica gel particles using the cross-linking agent 3-aminopropyltriethoxysilane. The immobilized enzyme was employed in a magnetic stirred tank bioreactor for the cleavage of rutin (**145**) to obtain its aglycone isoquercetin (**146**) and sugar **147** in reasonable yield (Scheme 47). Typically, **146** precipitated during the reaction. By applying a magnetic field to the suspension at the end of the reaction it was possible to separate the biocatalyst from the product and to enable its reuse. This inventive method reduces the costs for the enzymes, and simultaneously provides a high degree of automation associated with an optimized space/time yield.

2.3.7 Use of Nitrilase

DuPont developed a commercial process for the conversion of 2-methylglutaronitrile (MGN, **148**) to 4-cyanopentanoic acid ammonium salt (4-CPA, **149**, Scheme 48). Compound **149** is an intermediate for the synthesis of 1,5-dimethyl-2-piperidone (**150**), which is known as a precision cleaning solvent



Scheme 47



148 149 150

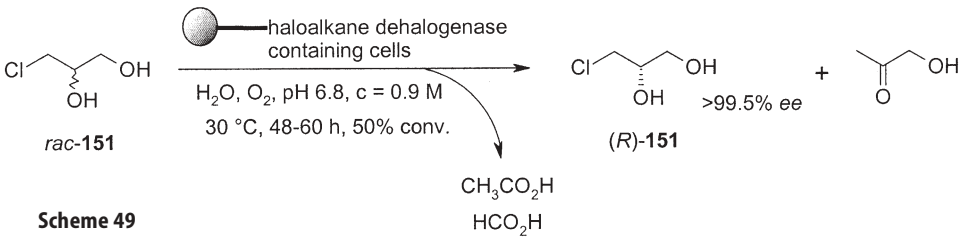
Scheme 48

(Xolvone) mainly for the electronics industry [123, 124]. The hydrolysis of **148** to 4-CPA was accomplished by using the nitrilase activity of *Acidovorax facilis* 72 W cells immobilized in alginate beads. The hydrolysis reaction yields only one of the two possible isomers with >98% selectivity at 100% conversion and produces only 1–2% 2-methylglutaric acid salt as by-product. The specific nitrilase activity was improved by expressing the corresponding gene in *E. coli*, followed by immobilization of the recombinant cells. The recombinant *E. coli* transformant proved to be an exceedingly robust catalyst with a significantly improved specific activity. The volumetric productivity of **149** was not only improved by a factor of 4, but the productivity of the new catalyst was also at least 3,500 g/g dry weight. In addition, the recovered catalyst activity after 195 cycles was found to be still 67% of the initial activity.

2.3.8 Use of Dehalogenase

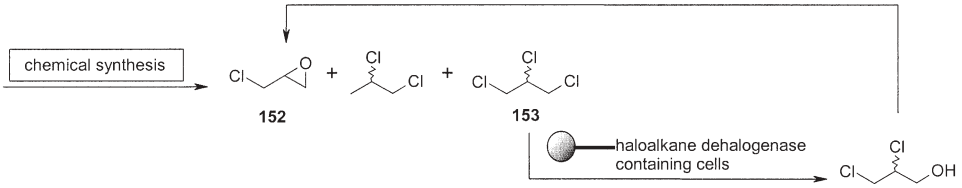
The synthesis of optically pure (*R*)-3-chloro-1,2-propanediol ((*R*)-**151**) started on a production scale at Daiso in 1994 (Scheme 49) [125–128]. *Rac*-**151** (produced from propylene) is treated with whole cells of *Alcaligenes species* or *Pseudomonas species,* which are able to selectively metabolize one enantiomer by using the enzyme haloalkane dehalogenase. The cells are immobilized in calcium alginate to achieve convenient handling and are used for the production of chiral diol (*R*)-**151** in 25,000 l batch reactors. The conversion of *rac*-**151** leads to (*R*)-**151** in high yield and high optical and chemical purity. (*R*)-**151** may be converted into two important optically active epoxides, epichlorohydrin and glycidol. Both have value as chiral synthons in various pharmaceutical and agrochemical applications.

The opportunity to increase the productivity of existing chemical processes [129] has been taken by Dow Chemical by developing a biocatalytic process



rac-**151** (*R*)-**151**

Scheme 49

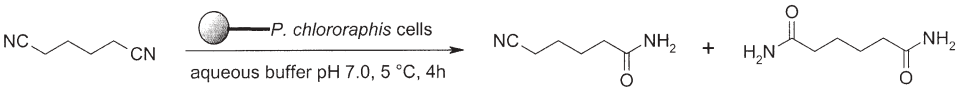


Scheme 50

also based on haloalkane dehalogenase [130]. Dow's halohydrin-based manufacture of the commodity chemicals propylene oxide and epichlorohydrin (**152**) also generates low-value coproducts (1,2-dichloropropane and 1,2,3-trichloropropane, **153**). The value of **153** can be recovered biocatalytically by chemoselective hydrolytic dehalogenation to obtain the resulting halohydrin **154** (Scheme 50). Compound **154** can be recycled to the process by transforming it into **152**, providing an improved overall yield and eliminating incineration costs. A continuous process was set up using a dehalogenase enzyme from *Rhodococcus sp*. ATCC 55388 recombinant in *E. coli*, which was immobilized onto a polyethyleneimine/alumina carrier [131]. Despite success with recombinant expression of the enzyme and optimization of the supported biocatalyst, the commercialization was challenged by inherent kinetic limitations of the enzyme. Thus, the subsequent goal was to improve the catalytic turnover rate and the biocatalyst lifetime in order to achieve an overall increase in productivity.

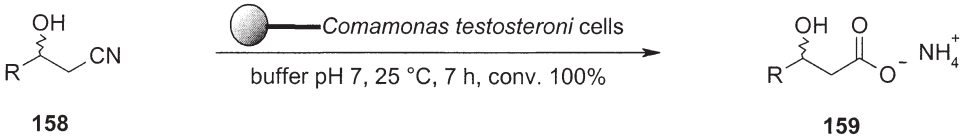
2.4
EC 4: Lyases

Nitrile hydrolyzing enzymes are particularly well suited for the high-volume production of amides (or acids), which has not only been shown by the well-known and impressive acrylamide production process developed by Nitto [7]. A biocatalytic process for the hydration of adiponitrile (**155**) to give 5-cyanovaleramide (5-CVAM, **156**), an intermediate for the production of herbicides, has been developed by DuPont (Scheme 51). The biocatalyst consists of *Pseudomonas chlororaphis* B23 microbial cells immobilized in calcium alginate beads. The nitrile hydratase-containing cells catalyze the conversion of **155** to amide **156** with high regioselectivity, thereby producing less than 5% of the by-product adipamide (**157**). An impressive 58 consecutive batch reactions with immobilized biocatalyst recycling were run to convert a total of 12.7 t of **155** to 5-CVAM. At 97% dinitrile conversion, the yield of the monoamide was 13.6 t,



155 **156** **157**

Scheme 51 93% <5%



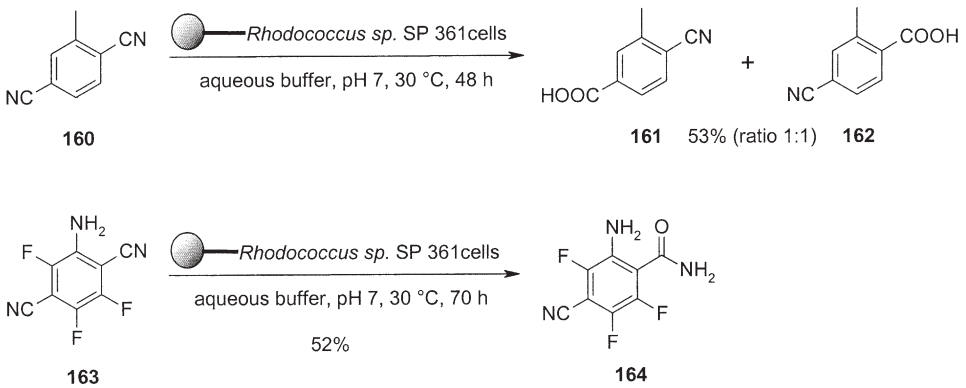
158 159

Scheme 52 R = H, Me, Et

and the total weight of **156** produced per weight of catalyst was 3,150 kg/kg (dry cell weight). This enzymatic process leads to higher conversion rates, produces more product per weight of catalyst, and generates significantly less waste than alternative chemical processes [132].

3-Hydroxyalkanoic acids are intermediates for the manufacture of linear or branched polyesters for fiber, film, molding, and coating applications. Again, researchers from DuPont developed a biocatalytic process, this time for the hydrolysis of 3-hydroxyalkanenitriles (**158**) to the corresponding 2-hydroxy acids (**159**), as shown in Scheme 52 [133]. More than 500 microbial strains with nitrile hydrolyzing activity were screened and it was found that cells having a combination of nitrile hydratase and amidase activity had a significantly higher specific activity for the transformation of **158** than microbial nitrilase catalysts. *Comamonas testosteroni* 22-1 cells immobilized in alginate reached conversions of 99–100% and showed superior enzyme stability and volumetric productivity. In a series of 85 consecutive batch reactions with biocatalyst recycling, the recovered nitrile hydratase and amidase activity decreased to 29 and 40%, respectively. However, the catalyst productivity was still high enough to produce 670 g **159**/g dry weight. This process is currently used to produce 100 kg quantities of 3-hydroxyvaleric acid.

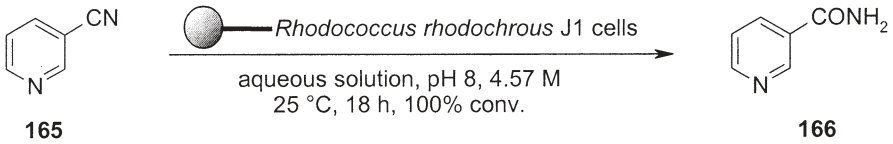
An older publication by the Zeneca Fine Chemicals Manufacturing Organization describes the use of immobilized whole cells of *Rhodococcus sp.* SP 361 for the hydrolysis of aromatic dinitriles (Scheme 53) [134]. It was found that fluorinated aromatic dinitriles (**163**) were regioselectively hydrolyzed by nitrile



160 161 53% (ratio 1:1) 162

163 164

Scheme 53



165 166

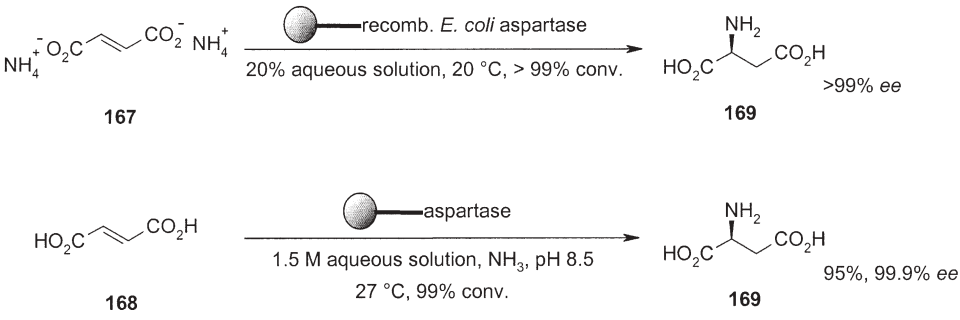
Scheme 54

hydratases to give the corresponding monoamides **164.** In contrast, the non-fluorinated nitriles (**160**) were converted with poor selectivity to the corresponding cyano acids **161/162,** most likely by the additional activity of amidases. Scheme 53 exemplifies two out of several experiments.

Lonza has started a high-volume manufacturing process (3,000 t scale) in recent years at its production site in China: the biocatalytic synthesis of nicotinamide (vitamin B3, **166**) starting from 3-cyanopyridine **165** (Scheme 54) [7, 135]. Nicotinamide is an essential component of enzymes catalyzing hydrogenation and dehydrogenation reactions in living organisms and is also used as a vitamin supplement for food and animal feed. The use of immobilized *Rhodococcus rhodochrous* J1 cells [136, 137] was found to outperform the alternative alkaline hydrolysis in terms of selectivity and yield – **166** can be produced in virtually 100% yield. The reaction conditions in Scheme 54 were taken from the original process published by a Japanese group due to the lack of precise data for the Lonza process, but they give a good clue of how the process may work [137].

The enzymatic production of diverse amino acids has been described by quite a lot of companies over the last 20–30 years and many processes are based on the use of lyases [138–141]. With regard to the use of immobilized biocatalysts only two new processes shall be introduced here: the production of L-aspartic acid (**169**) using an immobilized cell catalyst by Nippon Shokubai Kagaku Kogyo, Japan [142, 143] and the use of an immobilized enzyme by BioCatalytics [7] (both Scheme 55).

The Nippon process comprises the use of (L)-aspartase gene recombinant *Escherichia coli* cells. Prior to use the cells were mixed with cross-linked water-sol-



167 169

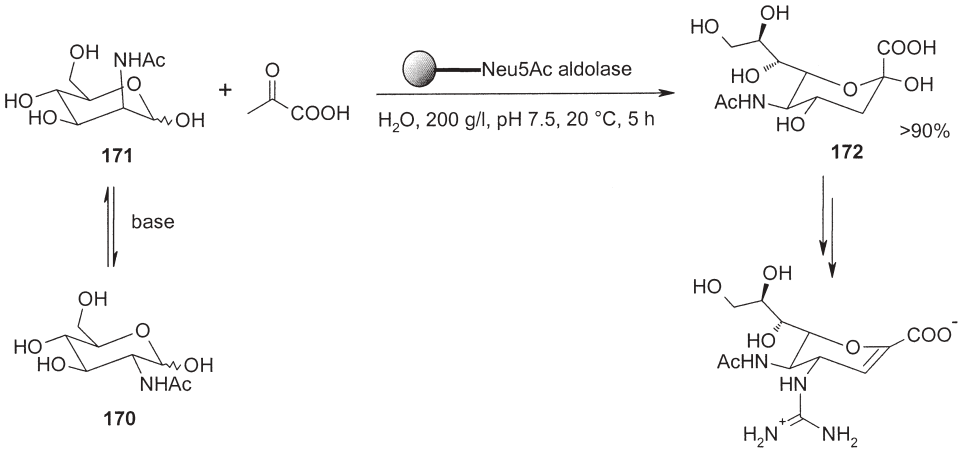
168 169

Scheme 55

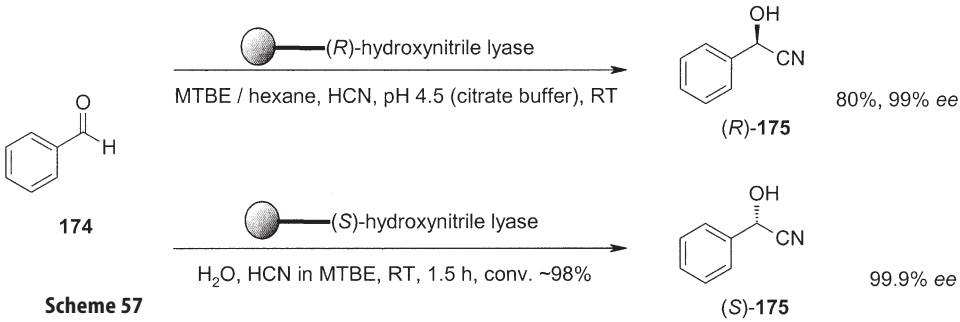
uble polymers and afterwards immobilized on the surface of the ion-exchange resin Amberlite IRA-96SB (C1 type, Organo Ltd.). A thin biocatalyst-containing gel layer formed on the resin surface and a 20% (w/w) ammonium fumarate (**167**) solution was passed over a column packed with these beads. The enzyme catalyzes the addition of ammonia to **167** and the conversions to **169** were as high as 99.7 mol% for up to 4 months. The reactivity of this immobilized biocatalyst was about 10–20 times higher than that of conventional methods. The addition of fumaric acid (**168**) is an important part of this efficient process, since it serves not only as new raw material but also as a precipitant for **169**.

The process by BioCatalytics is comparable in terms of starting material and product but favors the use of isolated, silica-supported, immobilized L-aspartase. This process was claimed to have a higher productivity than a comparable whole cell process and takes place in a plug flow reactor, which is fed with **168** and ammonia solution. The immobilized enzyme is stable and keeps half of its initial activity for approximately half a year. The high activity can best be described by the fact that a single kilogram of enzyme produces 10,000 to more than 100,000 kg of **169**, making it one of the most efficient biocatalytic processes known [144].

An efficient process for the production of *N*-acetylneuraminic acid (Neu5Ac, **172**) using *N*-acetylneuraminic acid aldolase was developed by the former Glaxo Wellcome [145]. Neu5Ac is a major representative of a particular class of amino sugars, the sialic acids, which play an important role in a wide range of biological recognition processes. It can be prepared using natural sources or by chemical means, but with the availability of recombinant aldolase (produced by *E. coli*) this became a favored route for the production of large amounts (Scheme 56). The enzymatic reaction requires expensive *N*-acetyl-D-mannosamine **171**, which needs to be produced by epimerization of the corresponding glucosamine (**170**). The Eupergit C-immobilized enzyme was able to catalyze the twofold addition of pyruvate to **171** (in a mixture of **170** and **171**)



Scheme 56



Scheme 57

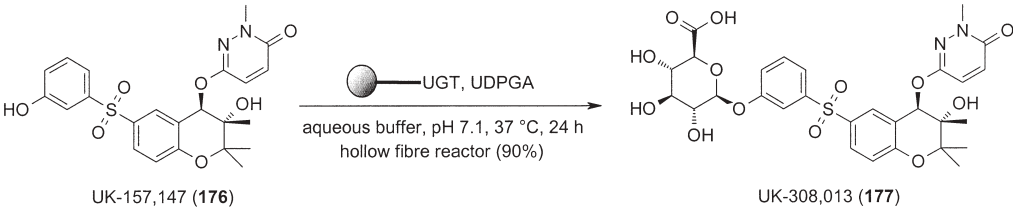
and produced **172** in very high yields. The immobilization allowed the reuse of the enzyme for at least nine cycles without significant loss of activity, and the process has been used to produce **172** in multiton quantities for the production of the anti-influenza drug Zanamivir (**173**).

One of the rare examples for the use of immobilized oxynitrilases has been published by Degussa [146]. The company investigated the asymmetric synthesis of (*R*)-cyanohydrins and used (*R*)-oxynitrilase, which had been cross-linked and subsequently polyvinyl alcohol-entrapped. The obtained immobilized lens-shaped biocatalysts were much more satisfying in terms of long-term stability and activity compared to the free enzyme and also showed less catalyst leaching than other enzyme supports. Moreover, the immobilization method is cheap, efficient, feasible on an industrial scale, and gives particles of defined size. The utility of these entrapped enzymes could be shown, as indicated in Scheme 57, in the synthesis of (*R*)-mandelonitrile ((*R*)-**175**) from aldehyde **174**. No catalyst deactivation was observed even after 20 cycles of reuse and yields as well as optical purities of (*R*)-**175** remained constant within normal limits.

Nippon Shokubai Kagaku Kogyo disclosed a complementary process for the synthesis of optically active cyanohydrins. (*S*)-hydroxynitrile lyase derived from plants like Euphorbiaceae, Gramineae, and Olacaceae could successfully be applied to synthesize 99.9% optically active (*S*)-mandelonitrile (*S*)-**175** [147]. The enzymes showed high absorption ratios when immobilized on porous inorganic material such as ceramics, silica, alumina, or silica/alumina zeolithes and were also used for the synthesis of other cyanohydrins.

2.5 EC 5: Transferases

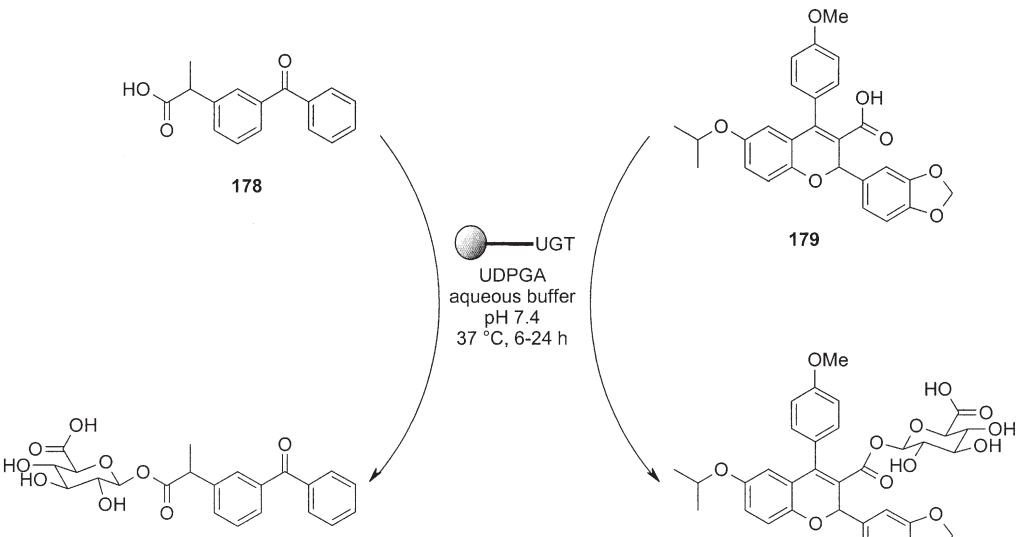
The synthesis of the glucuronide metabolite of potassium channel opener UK-157,147 (**176**) using immobilized uridine 5′-diphosphoglucuronyltransferase (UGT) has been demonstrated by Pfizer's Central Research group [148]. Compound **177** was required for metabolic studies, and it was decided to use the UGT-catalyzed addition of 5′-diphosphono-α-D-glucuronic acid (UDPGA) to



Scheme 58

the aglycone **176** (Scheme 58). The Pfizer group succeeded in immobilizing UGT containing dog liver microsomes in a hollow fiber reactor, which subsequently allowed the conversion of **176** to **177** in high yields on a small scale. This enzymatic technique was chosen because it is simple and easy to use and involves little direct intervention during the period of the reaction. Also, the eluent from the reactor contains very little protein contamination, allowing for an easy purification of the glucuronide metabolite.

Another use of immobilized dog liver microsomes was demonstrated by the Shionogi Research Laboratories [149]. The researchers used the cells, attached to phospholipid-coated octadecylsilica (ODS) particles, for the synthesis of acylglucuronides of ketoprofen (**178**) and of the nonpeptide endothelin receptor antagonist S-1255 (**179**, Scheme 59). Again, UDP-glucuronosyl transferase catalyzed the reaction of the acids **178** and **179** with UDPGA to the corresponding glucuronides **180** and **181**, respectively. The supported catalyst was readily prepared by stirring ODS particles with a solution containing the microsomes, and the productivity of these catalysts was approximately three times higher as compared to the free microsomes.



Scheme 59

2.6
EC 6: Ligases

No examples of immobilized ligases in industrial applications could be found in the literature.

3
Final Remarks and Outlook

This survey clearly shows that hydrolases, and in particular lipases, are among the most useful enzymes which can be found in the industrial production of chemical intermediates and products. The reasons are, on the one hand, the ease of isolation, the broad substrate specificity, and the fact that many hydrolases are commercially available – in many cases even in immobilized form. On the other hand these enzymes require no cosubstrates and are therefore easy to apply. Reactions can be conducted in aqueous or pure organic environments and some supported species can stand temperatures as high as 90 °C. *Candida antarctica* B and *Pseudomonas sp*. were by far the most used lipases for the synthesis of chiral compounds, whereas another important class, the nitrile hydrolyzing enzymes, are valuable for the production of high-volume commodity chemicals. The use of carriers prolongs the enzyme lifetime in many cases and allows processes to be run in a continuous fashion – saving precious time and material. The carriers themselves can be found among almost all kinds of materials, natural and unnatural, and it can be assumed that the number of available supports will steadily increase. In addition, the number of commercialized supports bearing reactive anchoring groups also rises, giving researchers a broad variety of options in their hands.

It can be anticipated that a lot of new processes are presently under development and have not been published yet. The introduction of difficult to handle enzymes into chemical manufacture must surely become easier with these new tools, especially in combination with the methods of nonnatural enzyme improvement.

The vast number of recently published articles concerning immobilization give the impression that this field has not been exhaustively exploited by far. Literature provides a huge number of new developments, some of which will probably be applied mainly in academia, for instance the use of ionic liquids [150, 151] and supercritical CO_2 [152]. Besides the use of biocatalysts in nonconventional media [153], it can be expected that new techniques based on bioencapsulation become more important for enzymes and whole cells [154, 155]. Entrap-immobilization [156], hydrophobic gels [157], cryogels [158], and hydrogels such as LentiKats [159] are only some keywords which should be mentioned in this context. In addition, the second generation of sol–gel-encapsulated lipases can deliver robust heterogeneous biocatalysts for long-term applications [160]. Other interesting research fields are dealing with biocat-

alytic composites [161] and smart polymers. The last-mentioned class is able to modify its structure upon external triggering such as temperature [162] or pH change [163], and combines the advantages of soluble and immobilized catalyst systems. Even photoresponsive polymer/enzyme systems have been described in a similar context [164]. A clever combination of these techniques should allow the production of tailored catalysts for a variety of industrial applications in future, and may result in an overall broader use and acceptance of the fascinating and versatile biocatalysts.

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Applications of Catalysts on Soluble Supports

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Author Index Volumes 201 – 242

Author Index Vols. 101–150 see Vol. 150
Author Index Vols. 151–200 see Vol. 200
Author Index Vols. 26–50 see Vol. 50
Author Index Vols. 51–100 see Vol. 100

The volume numbers are printed in italics

Subject Index