DOI: 10.1002/ejoc.201000319

Polymer-Supported Chiral Organocatalysts: Synthetic Strategies for the Road Towards Affordable Polymeric Immobilization

Tor E. Kristensen[a] **and Tore Hansen***[a]

Keywords: Organocatalysis / Immobilization / Asymmetric catalysis / Asymmetric synthesis / Biomimetic synthesis

In this microreview, we highlight the field of polymer-supported organocatalysis, especially immobilized enamine and iminium organocatalysts. We try to formalize the overall synthetic strategies for polymeric immobilization as spanning the area of two overlapping regions, from a copolymer strategy favoured by low-valued and small catalysts to a classical post-modification strategy favoured by valuable and/or large catalysts. Organocatalysis is particularly interesting as it is probably best described as being located in the transitional region, and we will trace the historic and factual origins for the unfortunate predispositions towards post-modification schemes. In addition, we try to identify affordable and useful syntheses of key organocatalyst immobilization intermediates, as well as polymer supports that are more compatible with a broader range of reaction solvent polarity, something of crucial importance in organocatalysis.

Introduction

At the time of writing of this review, organocatalysis is just about to enter its second decade after its rediscovery in 2000 through the now already legendary publications of List, Lerner, Barbas and MacMillan.[1] It can no longer be considered a new and immature field, but has proven itself as an established method (alongside the more traditional methods of bioenzymatic catalysis and transition metal catalysis) for conducting catalytic asymmetric synthesis. At the same time, it is also more than 40 years since the seminal work by R. Bruce Merrifield on solid-phase synthesis,[2] and more than 25 years since he received the Nobel prize for this work. As has happened on numerous occasions before, the discovery of new catalysts or reagents quickly converged with Merrifield's methodology for polymeric immobilization to create a subfield, namely the polymer-supported versions of the catalysts or reagents in question, and in the case of organocatalysis, the field of polymer-supported organocatalysts.[3]

However, it is important to keep in mind that the subsequent polymeric immobilization of reagents and catalysts, which in many instances must be considered as very low-valued substrates, was not the use for which this methodology was originally developed and intended. It was developed for the immobilization of peptides, which most often are to be considered as very high-valued substrates, and later into other high-valued substrates such as oligonucleo-

Tor Erik Kristensen was born in 1982, and raised just outside Oslo, Norway. He studied chemistry and chemical engineering at the Norwegian University of Science and Technology in Trondheim, and completed his Master's degree there in 2006. He is currently in the final phase of his PhD studies at the Department of Chemistry, University of Oslo, under the supervision of Associate Professor Tore Hansen and Professor Finn Knut Hansen. Tor Erik entertains a wide variety of interests within chemistry, especially within organic synthesis and polymer science. His current area of research is polymer-supported chiral organocatalysts.

Tore Hansen was born in 1969 in Trondheim, Norway. He obtained his PhD from State University of New York, Buffalo under the supervision of Professor Huw M. L. Davies working on the development of catalytic asymmetric intermolecular C–H insertion reactions. He was a post doctoral fellow in the laboratory of Professor Karl Anker Jørgensen in Århus, Denmark, working on asymmetric metal-catalyzed reactions and organocatalysis. After working in the medicinal chemistry department at H. Lundbeck A/S in Copenhagen, he started his independent research career as an Associate Professor at the University of Oslo in 2003. The research in his group is focused on carbenoid chemistry and immobilized organocatalysis.

---

[a] Department of Chemistry, University of Oslo,
P. O. Box 1033 Blindern, 0315 Oslo, Norway
Fax: +47-2285-5441
E-mail: tore.hansen@kjemi.uio.no

© 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

tides.[4] There it functions as a chemically inert scaffold to anchor these substrates onto under a long synthesis that had to withstand a wide variety of (often) rather harsh reaction conditions. This has important implications when the methodology is adapted unaltered for the immobilization of many catalysts and reagents, namely the cost-issue. Polymer-supported catalysts and reagents have been around for decades, but it still has a long way to go before it is a common tool for work on preparatory scale in the synthetic organic chemist's laboratory. As was so clearly remarked in the classical work on total synthesis by Nicolaou and Snyder: "Every synthetic technology, however, has a drawback. For solid-supported reagents, it is their cost. If one checks the prices of some resin-supported reagents in any commercial catalogue, one will find that they can be truly exorbitant.".[5] Although it is true that a recyclable catalyst remedies this situation somewhat as when compared to a reagent, the cost-issues are nevertheless the single most dictating constraint for the widespread utility of polymer-supported catalysts, and especially so for simple organocatalysts.

With the advent of organocatalysis, a new situation has established itself. Chiral organocatalysts traditionally operate via simplified enzyme-mimetic mechanisms, implicating mild reaction conditions and an improved leverage for the chemical inertness of the polymer matrix. In addition, as we will highlight more thoroughly later on, the polymer matrix seems to integrate itself as a more natural part of the overall catalytic system, influencing both catalyst activity and selectivity. However, unlike what traditionally has been the case, the polymer scaffold can now even enhance catalyst performance by providing a favourable microenvironment around the organocatalysts. We will start out by providing a short overview of the chemistry of polymer supports in general. As peptide synthesis have been the driving factor, these supports form the basis for post-modification schemes where substrates are anchored to prefabricated supports, but will also be useful in the analysis of bottom-up copolymerization strategies later on.

Polymer Resins for Polymeric Immobilization

The Polystyrene-Derived Resins

Solid-phase peptide synthesis (SPPS), as pioneered by Merrifield in the early 1960s,[2] has been the primary driving force for the development of new and improved polymer resins for organic synthesis. Numerous reviews are now available that comprehensively review the field of available polymer supports, both of the soluble and crosslinked types.[6] However, despite the vast literature, we will provide a summary here as the ideas from the field have permeated some of the work within polymer-supported organocatalysts. We start out with the crosslinked polystyrene (PS) supports and its modified derivatives.

After intensive research with several polymeric materials, Merrifield introduced the chloromethylated and divinylbenzene (DVB) crosslinked PS, known simply as the Merrifield resin (**1**).[2,6a] It has favorable swelling properties in typical nonpolar organic solvents such as THF, halogenated and aromatic hydrocarbons. As this was restrictive when difficult peptide sequences were prepared and when the methodology was transferred to immobilized reagents and catalysts, a number of improvements were introduced (Figure 1). The simplest approach is to introduce a longer and more flexible crosslinker to enhance swelling characteristics, and Toy and Janda introduced tetrahydrofuran-derived crosslinkers to give JandaJel™ (**2**), now a commercial product.[7] The crosslinker is prepared by alkylating short oligomeric ethylene glycols with 4-vinylbenzyl chloride.[7] A cheaper, but chemically less inert, alternative is to use inexpensive tetraethylene glycol diacrylate (TTEGDA) as crosslinker for PS (**3**).[8]

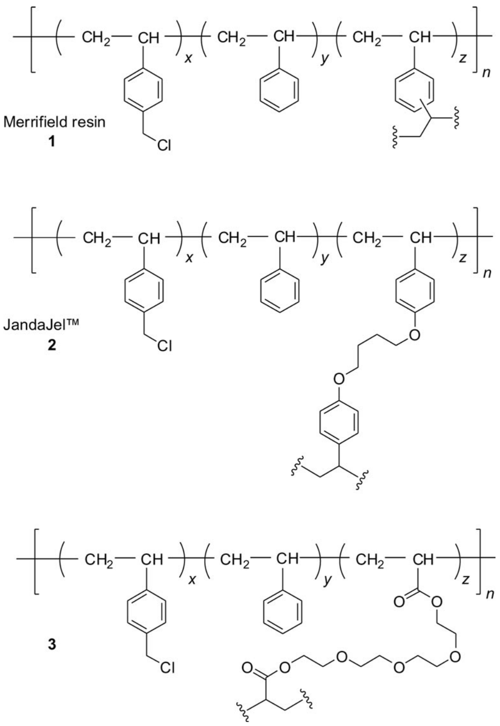


Figure 1. The Merrifield resin and derivatives with modified crosslinkers.

The other intuitive way to enhance the swelling characteristics of crosslinked PS is to incorporate elements that are more compatible with polar solvents. The traditional way of doing this is to incorporate the versatile polyethylene glycol (PEG) backbone (Figure 2). Already in 1982, PEG-derivatized and crosslinked PS was prepared through esterification,[9] but it was first in the mid 1980s that the first commercial PEG-PS resins were introduced,[10–11] known as PEG-PS[10] and TentaGel™ (**4**),[11] the last one now being a well-known commercial product. Both of them are PEG-grafted Merrifield resins, but while PEG-PS is prepared by attaching pre-fabricated and hetereobifunctional PEG derivatives onto aminomethylated Merrifield resin,[10b] the TentaGel™ resins are prepared through graft polymerization of ethylene oxide on Merrifield resin that has been derivatized with tetraethyleneglycol first.[11] HypoGel™ is a resin almost identical to TentaGel™, but with an extra methylene group connected to the benzylic position, thus avoiding the acidically more labile benzylic ether of the latter resin. NovaSyn™ is another PEG-grafted PS support analogous to TentaGel™.[10c]

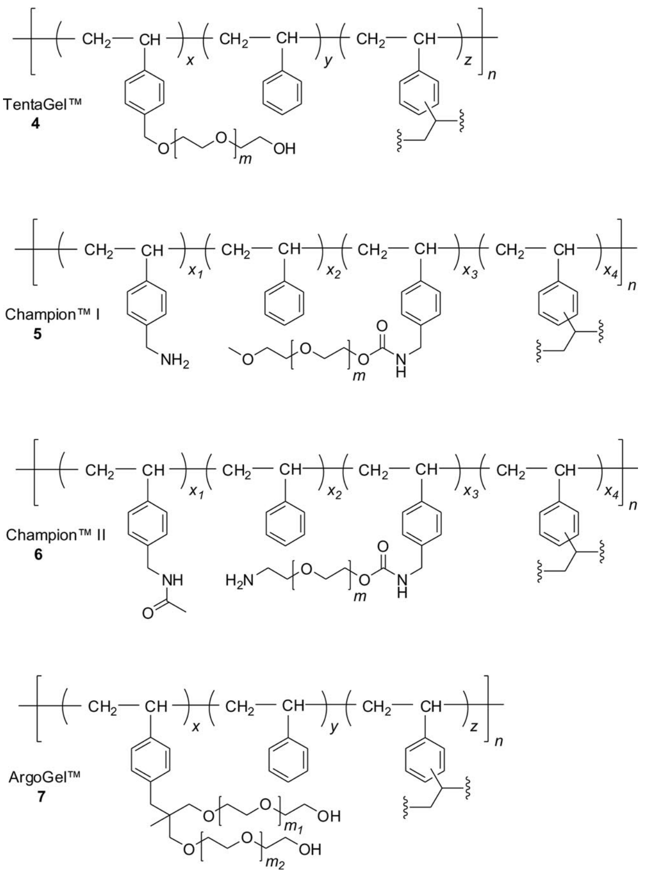


Figure 2. Typical examples of the PEG-PS family of polymer supports.

Towards the end of the 1990s, two further important resins of the same type were developed,[12–13] Champion I and II (**5** and **6**, NovaGel)[12] and ArgoGel™ (**7**).[13] The first of these is prepared through a rather lengthy synthesis where a standard PS resin is aminoalkylated and then coupled to hetereobifunctional PEG derivatives, usually followed by further modifications.[12] The ArgoGel™ family are important commercial products that are prepared by treating the Merrifield resin with methylmalonic ethyl ester in a nucleophilic substitution to give an immobilized branching point diester that is subsequently reduced to a diol, whereupon ethylene oxide is grafted by anionic polymerization.[13] In the same period, a quite elegant way of introducing a non-benzylic alcohol directly onto non-derivatized and crosslinked PS using propylene oxide and Lewis acid was reported.[14] The alcohol was then grafted with ethylene oxide by anionic polymerization to give a useful resin.[14] An interesting notion to keep in mind is the fact that, of the PEG-grafted crosslinked PS resins, the types that have received the most significant commercial success are prepared by grafting the PEG-chains through polymerization (e.g. TentaGel™, ArgoGel™) and not installment of prefabricated PEG.

The resins above all use crosslinked PS as a core for PEG-grafting. An alternative way of incorporating PEG into a PS matrix is to crosslink the resin with PEG (analogous as that for JandaJel™) instead of grafting it on afterwards. A useful comparison between such supports and the more conventional grafted support has been published,[15] and it showed that the PEG-crosslinked supports generally exhibited a larger degree of swelling.[15] Later on, we will return to this methodology, used by ourselves with an important modification, as it proved crucial to obtain useful supports for immobilized organocatalysts. All in all we can see that the traditional way of adapting a PS support to give useful swelling in a polar solvent usually involves a tedious modification, and subsequently a very costly product. However, some of the principles utilized and lessons learned can be integrated into a synthetic scheme that actually makes polymer-supported chiral organocatalysts more affordable.

The Acrylic Resins

Taking notice of the similarity between the main solvent for peptide synthesis (DMF) and the acrylamides, Atherton, Clive and Sheppard introduced a polyacrylamide support for peptide synthesis in the mid 1970s.[16] The support was prepared by inverse radical emulsion copolymerization of dimethylacrylamide, *N*,*N*′-bis(acryloyl)ethylenediamine and a functionalized mono-acryloylhexamethylenediamine in water/1,2-dichloroethane (**8**, Figure 3).[16] Although un-

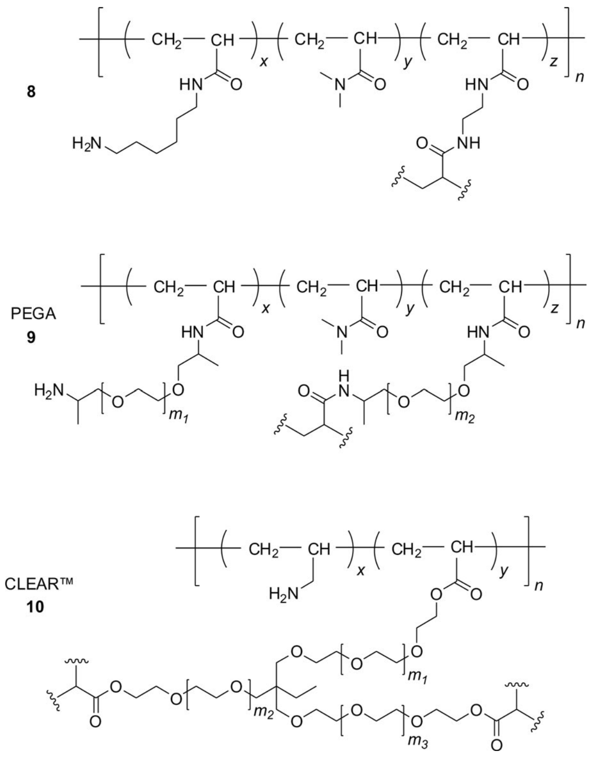


Figure 3. Typical examples of acrylic resins (depicted in one of several possible representative forms).

derappreciated when viewed from the standpoint of synthetic organic chemistry, the mode of preparation of the polymer supports,[17] and not only its constituents, play a vital role in its characteristics and should be used with benefit also for immobilized organocatalysts. For example, although less recognized, Letsinger and Kornet introduced a PS for solid-phase synthesis more or less simultaneously with Merrifield,[18] but not the nicely beaded suspension polymerized product that has become so popular, but a "popcorn"-type polymer that was prepared by a rather crude precipitation polymerization.[18]

As was the case for the PS supports, the incorporation of PEG chains into the polymer matrix was also a natural extension in the development of the polyacrylamide supports. In 1992, Meldal introduced the PEGA resin (**9**), a flow stable PEG–dimethylacrylamide resin useful for continuous flow solid-phase peptide synthesis.[19] Mono- and difunctionalized aminopropyl-PEG derivatives are readily available, and mono- or diacylation with acryloyl chloride gave acrylamides that were combined with dimethylacrylamide through either radical precipitation copolymerization or inverse radical suspension copolymerization in water/CCl_4/heptane.[19]

Probably the most innovative of the acrylic PEG resins is the CLEAR™ (Cross-Linked Ethoxylate Acrylate Resin, **10**) family of resins introduced in the mid 1990s and now important commercial products.[20] It was prepared by radical copolymerization of trimethylolpropane ethoxylate triacrylates with one or more of PEG-dimethacrylate, PEG ethyl ether methacrylate, trimethylolpropane trimethacrylate, allylamine and 2-aminoethyl methacrylate·HCl.[20] This was done either in bulk (followed by simply grinding up the polymer afterwards) or normal phase suspension mode to give the conventional beaded product.[20] The resin is in nature of being an ester-linked network chemically less robust than the acrylamide-based supports. CLEAR™ was, however, unique in the way that it went against the conventional wisdom of the field at the time since it is a fully crosslinked matrix (its main constituent being trifunctional acrylates), previously thought to be unfeasible in peptide synthesis since only a weakly crosslinked matrix was supposed to give the well-solvated gels necessary for reactions to take place. In fact, the notion that fully crosslinked resins can achieve excellent swelling characteristics was used by us later to make polymer supports for immobilized organocatalysts that operated in aqueous solvents, lower alcohols or MeCN.

In summary, we see that the acrylic resins introduce a wide variety of chemistry that can be incorporated into the polymeric backbone of a polymer-supported organocatalyst. In addition, it is important to keep in mind that given the fact that enamine/iminium organocatalysts are used under mild reaction conditions, a much wider assortment is useful for that purpose than for solid-phase peptide synthesis.

Other Crosslinked Resins and Soluble Linear Supports

Since all solid-phase peptide syntheses are based on anchoring substrates onto prefabricated polymer supports that had to withstand a wide variety of harsh reaction conditions (different protocols for peptide synthesis can have orthogonal sets of reaction conditions), research strived for ever-more chemical inertness. In addition, a high degree of crosslinking usually meant better mechanical stability and flexible ethereal type polymer chains meant more favorable and general swelling characteristics. This work converged to their natural conclusion through the development of resins such as the POEPS (polyoxyethylene–polystyrene),[21] POEPOP (polyoxyethylene–polyoxypropylene),[21] HYDRA (hydroxy- and amine-functionalized resin)[22] and EXPO[23] resins from the mid 1990s onwards, as well as probably reaching its zenith through the SPOCC (superpermeable organic combinatorial chemistry)[24] resin and ChemMatrix (NovaPEG).[25] POEPS is prepared by radical copolymerization of PEG that have been homo- or dialkylated with 4-vinylbenzyl chloride or 4-vinylphenylpropyl chloride, either as bulk or inverse suspension copolymerization.[21] POEPOP is prepared in analogy by mono- or dialkylating PEG with epichlorohydrin, followed by anionic polymerization (*t*BuOK-initiated).[21] SPOCC on the other side, is prepared by a novel cationic polymerization ($Et_2O{\cdot}BF_3$-initiated) of PEG-oxetane macromonomers dissolved in a MeCN solution that is dispersed in silicon oil to give the resin as spherical beads.[15,24] The ChemMatrix resins are prepared very much on the same technological platform by dialkylating PEG with ethyl 2-(bromomethyl)acrylates, followed by normal-phase radical suspension polymerization (with some subsequent post-modifications).[25b]

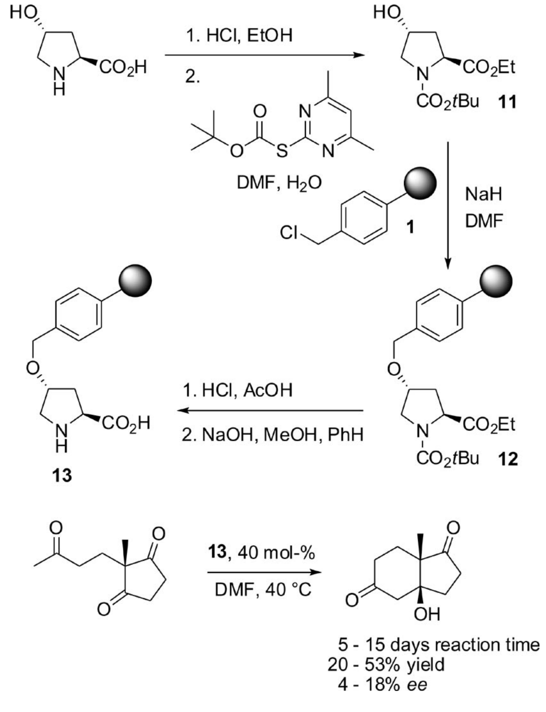
All in all, the latter developments in the preparation of polymer supports for peptide synthesis does not look to be of interest for polymer supported organocatalysis, both because of economic reasons (they are prohibitively expensive) and because their chemical inertness (they form virtually inert all-PEG networks) is an advantage that is probably uncalled for in organocatalysis. However, we wish to stress the fact that the synthetic methodologies can be of great use when planning for polymeric immobilization in general. This is a fact that seems to be underappreciated. As we believe cost-issues to be a neglected matter in polymeric immobilization, we will later analyse immobilized organocatalysis in a broader context, and we will trace the historic origins of the bias towards post-anchoring strategies for organocatalysts, funnelling research into a rather narrow path.

In addition to the crosslinked supports described above, it is of course also possible to anchor substrates to soluble polymers of the linear type to give homogeneously soluble systems that can be recovered after reaction by addition of non-solvents.[6d–6h] We will not describe these systems in more detail as they form a type of sub-class of the crosslinked systems with regard to polymer chemistry, and usually does not add new specific chemistry. At the outset, these systems have the benefit of giving homogeneous systems, but have the shortcoming of always requiring the addition of suitable non-solvents after reaction, sometimes giving rise to rather sticky precipitates unless catalyst loadings are made very small.

Polymer-Supported Proline

Pioneering Efforts

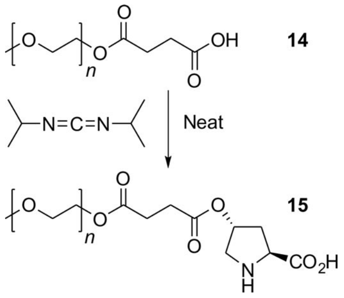
The revival of organocatalysis around the turn of the millennium in no way implied its birth. As is well-known, its historic origins go much further back.[26] A milestone was the Hajos–Parrish–Eder–Sauer–Wiechert reaction (asymmetric proline-catalyzed Robinson cyclization) reported in the early 1970s.[27] Already in 1985, a group of Japanese researchers reported the first type of polymer-supported proline, used for this very reaction (Scheme 1).[28] Although the catalytic efficiency and selectivity by today's standards of this supported proline must be perceived as mediocre,[28] it nevertheless bears a striking resemblance to the supports that about 20 years later would give the field of polymer-supported proline its breakthrough. As for most reports nowadays, the Merrifield resin and the proline derivative *trans*-4-hydroxy-L-proline was the starting point (Scheme 1). Protection of the hydroxyproline by esterification and carbamate protection gave protected derivative **11**, which was then directly anchored to the Merrifield resin (**1**) through an ether linkage. Subsequent deprotection gave polymer-supported proline **13** (Scheme 1).[28] A close derivative containing a methylene spacer was also prepared.[28] Unfortunately, the catalyst was rather ineffective in the asymmetric Robinson cyclization, but the authors used optical rotation for determination of enantiomeric excess, a procedure prone to inaccuracies as small amounts of pollutants can give highly distorted results. The poor selectivity is surprising, taking into consideration its close resemblance to polymer-supported prolines that 20 years later would prove so successful in the intermolecular aldol reactions.



Scheme 1. The first immobilization of proline.[28]

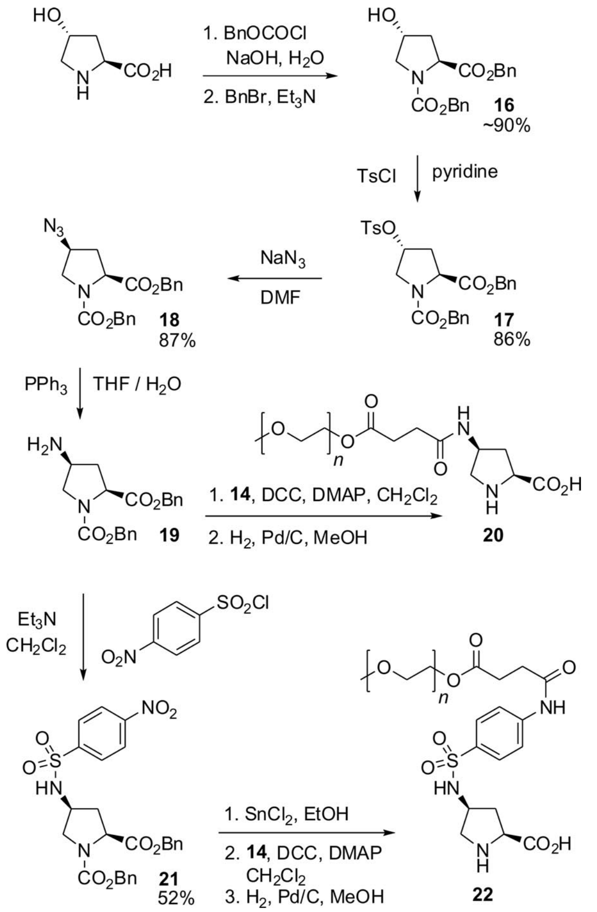
Proline Immobilization on Linear Polymers

Shortly after the revival of organocatalysis in 2000,[1] the first reports on immobilized proline since the Japanese 1985 disclosure surfaced in 2001–2003 from Italian researchers at the University of Milan, marking the starting point for the modern era of polymer-supported organocatalysis.[29] Unlike the crosslinked supports that would later dominate the field, the researchers used linear and homogenously soluble PEG as their support.[6d–6h,29] A very expedient immobilization of proline was reported where succinate modified MeOPEG (**14**) was directly linked to unprotected *trans*-4-hydroxy-L-proline in a rather brute fashion, using diisopropylcarbodiimide (DIC) under neat conditions for 20 h at 140 °C (Scheme 2).[29a] The MeOPEG-proline **15** was used in asymmetric intermolecular aldol reactions with acetone and aldehydes under classical conditions (DMF, DMSO) to give aldol products with moderate to good yields and enantioselectivities.[29a] In their subsequent full paper, the researchers also introduced a bifunctional PEG-proline.[29b] These PEG-prolines proved useful for intermolecular aldol reactions, Robinson cyclizations and Mannich reactions,[29b] but had very poor results in asymmetric Michael additions of cyclohexanone to nitrostyrene (10–60% yields, 15–35% *ee*).[29c]



Scheme 2. Proline immobilized on linear PEG.[29]

Although crosslinked polymer beads have later dominated the area of polymer-supported prolines, more recent disclosures have also highlighted the use of linear supports.[30] Chinese researchers developed more refined PEG-supported prolines **20** and **22** in 2007,[30a] and obtained good to excellent yields (up to 94%), but medium enantioselectivities (typically 30–60% *ee*) in asymmetric Michael additions of ketones to nitrostyrene.[30a] However, although interesting, their catalyst syntheses must be considered one of the most cumbersome reported to date,[30a] and is outlined in Scheme 3. The secondary alcohol of diprotected derivative **16** is converted to amine **19** through tosylation, displacement with azide and PPh$_3$ reduction. It is then linked to succinate-modified MeOPEG, either through direct amide linkage to give **20**, or through nosylation, reduction and finally peptide coupling to give **22**.[30a] In addition to being excessively long, this synthesis positioned the acid and amido functionality of proline in a presumably less favourable *cis* relationship.



Scheme 3. Proline immobilized on PEG via amide linkages.[30a]

In much the same manner, the preparation of linear polystyrene immobilized proline have been reported, using a key intermediate much like diprotected amine **19**.[30b,30c] The synthesis will not be detailed here as it provides little additional insight, but more interestingly, these linear PS-prolines gave reasonable yields, but excellent stereoselectivities in the asymmetric aldol reactions of cyclohexanone and substituted benzaldehydes at only 5 mol-% loading, both in DMF/water or only water.[30b,30c]

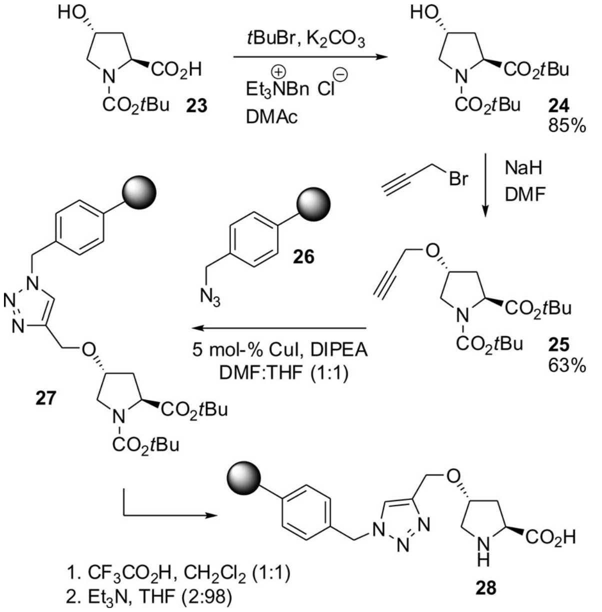
All in all, the use of linear PEG as support for proline seems less advantageous than the crosslinked resins for two reasons. Catalyst loadings are generally low (typically 0.2 mmol/g catalyst), and the performance seems poorer than the crosslinked catalysts. In addition, as is also the case for linear PS, crosslinked resins gives simplified workup by direct filtration, without the need for any addition of non-solvents. Linear supports also tend to give a much less favourable pattern in recycling with a more rapid loss of activity/selectivity.[30]

Proline Immobilization on Crosslinked Polymer Beads

The Post-Modification Strategy

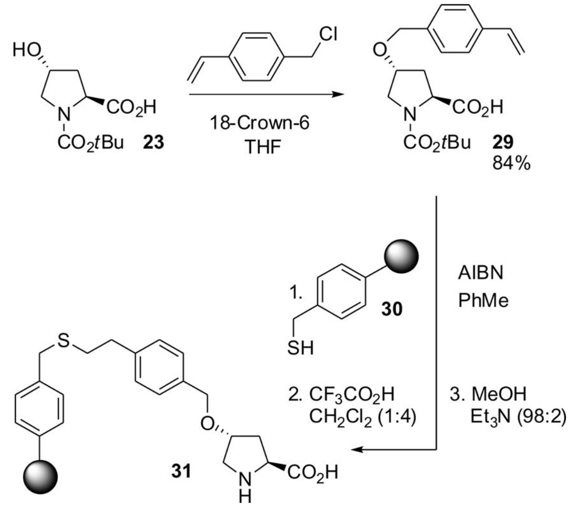
In 2006, a series of high-profiled publications on the use of amphiphilic proline derivatives for asymmetric aldol reactions in water caught widespread attention within the community of organocatalysis and synthetic organic chemistry in general.[31] Among them, simple derivatives of hydroxyproline where the secondary alcohol had been derivatized with either fatty acids or bulky silyl groups (e.g. *tert*-butyldiphenylsilyl) to give amphiphilic prolines, proved extraordinary effective in aldol reactions of cyclic ketones and substituted benzaldehydes. This was not just interesting in that typical solvents in which these reactions had typically been conducted (DMF, DMSO), and which had hampered the widespread use of these reactions on scale, now became obsolete, but probably even more so from the mechanistic point of view. A general and at times lively debate on the role of water in these aldol reactions quickly surfaced.[32] For an in-depth discussion of the role of water in stereoselective organocatalytic reactions, the reader should consult the recent review by Gruttadauria, Giacalone and Noto which details these matters in great detail.[3e]

For research within polymer-supported organocatalysis, these disclosures were to introduce the golden age of polymer-supported prolines in the way that the hydrophobic residues present in the amphiphilic proline derivatives could probably be successfully substituted with a hydrophobic resin. Off course, the archetypical Merrifield resin, the starting point for nearly all avenues of polymeric immobilization, was the natural choice. Shortly after the publications on amphiphilic prolines in 2006, the research group of Pericàs in Spain therefore introduced the PS-supported proline **28** (Scheme 4).[33a] Taking advantage of the Huisgen–Meldal–Sharpless reaction (the Cu^{I}-catalyzed cycloaddition of alkynes and azides),[34] these researchers prepared the alkyne-modified diprotected proline **25** and azide-modified PS resin **26** (by simply treating the Merrifield resin with NaN_3 in DMSO) and coupled them together. Subsequent deprotection gave the supported proline **28**.[33a]



Scheme 4. Immobilization of proline onto modified Merrifield resin through Cu^{I}-catalyzed azide–alkyne cycloaddition.[33a]

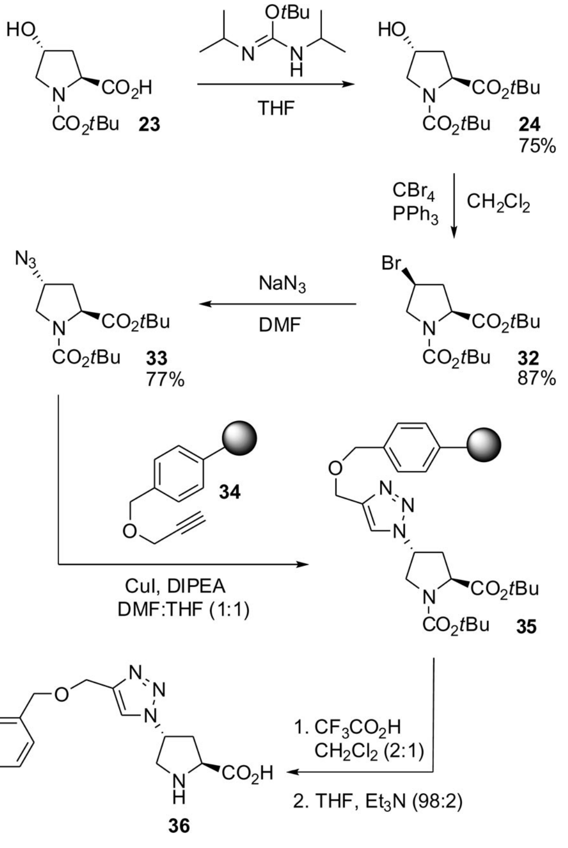
More or less simultaneously, the research group of Gruttadauria in Italy introduced another PS-supported proline (**31**).[35] In this case, a monoprotected hydroxyproline was alkylated with 4-vinylbenzyl chloride to give styrenic proline **29**. This was coupled to a mercapto-functionalized Merrifield resin (**30**) through a thiol–ene coupling (Scheme 5).[36] Subsequent deprotection gave supported proline **31**.[35]



Scheme 5. Immobilization of proline onto modified Merrifield resin through thiol–ene coupling.[35]

Both supported proline **28** and **31** proved very selective in the asymmetric aldol reaction of ketones and substituted benzaldehydes (typically a 95:5 or better diastereoselectivity and >95% *ee*), but with a rather sluggish reactivity (up to 50–100 h of reaction time).[33a,35a] Especially for proline **28**, DiMePEG ($M_w \approx 2000$) was added to enhance diffusion.[33a] Proline **28** shortly afterwards also proved successful in enantioselective aminoxylations of aldehydes and ketones.[33b]

These publications sparked off considerable interest, and the research group of Pericàs in Spain published several new polymer-supported prolines in early 2008.[33c] By far the most efficient of these, supported proline **36**, was prepared as described in Scheme 6.[37,33c] Commercially available Boc-protected hydroxyproline (**23**) was converted to diprotected hydroxyproline **24** with *O*-*tert*-butyl-*N*,*N*-diisopropylisourea in THF. Inversion of configuration at position 4 of proline **24** by treatment with CBr$_4$/PPh$_3$ gave *cis*-bromoproline **32**. Nucleophilic substitution of **32** with NaN$_3$ in DMF then gave another inversion of configuration to *trans*-azidoproline **33**. This azidoproline was coupled to a modified Merrifield resin **34** (prepared from Merrifield resin and propargyl alcohol/NaH) through azide–alkyne cycloaddition as for **28** (Scheme 6).[33c] This resin (**36**) has a very favourable swelling in the reaction mixture and showed enhanced reactivity in asymmetric aldol reactions of cyclic ketones and substituted benzaldehydes as compared to **28** or **31** (high yields in only 24 h, up to 97:3 *dr* and 99% *ee*).[33c] The most interesting property of supported catalyst **36** is the fact that it has excellent swelling properties in water, despite the hydrophobic nature of the styrene-matrix on which it is immobilized (this is not the case for the closely related catalyst **28**). Also of great interest, the authors also prepared a proline resin analogous to **13** (as was prepared by the Japanese research group in 1985) and two supported prolines analogous to **28**, but anchored via the same chemistry to either a PEG-grafted PS resin or a macroporous support (ArgoPore™). While the resin analogous to **13** gave a reasonable yield (40%) in the aldol reaction of cyclohexanone and benzaldehyde after 60 h, but poor enantioselectivity (40% *ee*), the use of PEG-grafted PS resin or macroporous ArgoPore™ gave only negligible conversions in the same reaction.[33c] This underlines the essential role of the polymer support in immobilized organocatalysts.



Scheme 6. Immobilization of proline onto modified Merrifield resin through Cu^I-catalyzed Huisgen cycloaddition.[37,33c]

The same research group has recently also reported the use of resins **28** and **36** in asymmetric Mannich reactions of aldehydes and ketones with *N*-(*p*-methoxyphenyl) ethyl glyoxylate imine, both in batch and continous-flow mode.[33d] At 20 mol-% in DMF at room temperature (in batch mode), resin **28** gave medium to excellent yields (40–95%) after 2–48 h reaction time and excellent stereoselectivities (87:13 to >97:3 *dr* and up to 99% *ee*). Also the resin **31** has been tried successfully in other reactions, both in α-selenenylation of aldehydes and in the Baylis–Hillmann reaction between methyl/ethyl vinyl ketone and substituted benzaldehydes (with imidazole as co-catalyst).[35a,35c] Gen-

© 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

erally, all these crosslinked PS resins described here are readily recycled with only small diminishments of catalytic activity.[33,35] In summary, both the catalytic performance and recycling of these crosslinked PS proline resins seems to be considerably better than those of the linear supports described earlier. Other polymer-supported prolines linked through C-4 of hydroxyproline have been reported, such as polymer-supported dendrons,[38] but do not seem do offer additional benefits. For more information on non-polymeric immobilizations of proline and proline derivatives (e.g. silica, ionic liquids etc.), the reader should consult the review by Gruttadauria, Giacalone and Noto.[3d] While immobilization of proline on PEG-containing resins has not attained the same success as the unmodified Merrifield resin, there are several reports on the immobilization of small proline-peptides that usually make use of the PEG-modified resins that we described earlier.[39] Especially the TentaGel™/NovaSyn™ (**4**) has been the most popular choice,[39b–39d,39f] but also standard Merrifield resin has been used successfully.[39e] The research group of Wennemers reported that they obtained the best results for their immobilized Pro-Pro-Asp-peptide in the aldol reaction of acetone and 4-nitrobenzaldehyde when PEGA (**9**) or TentaGel™ (**4**) were used (89–93 % yield and 75–79 % *ee* at 1 mol-% loading and 18 h reaction time).[39d] Use of PS or polyacrylamide gave lower yields and poorer selectivity (67–85 % yield and 52–64 % *ee*). They also reported that a higher catalyst loading was coupled with a lower catalyst reactivity.[39d] This is probably an indication that a larger degree of swelling is favourable, and that the strong symbiosis between the polymer backbone and organocatalyst is much more pronounced for proline than for proline-containing peptides.

Some Comments Regarding the Post-Modification Strategy

Before proceeding to an alternative strategy for preparation of polymer-supported proline, it may be informative to take a step back and offer a few clarifications regarding the overall synthetic strategies that have been described until this point. As should be clear, the post-modification strategy at first view has several attractive advantages. Numerous polymer supports are now commercially available, spanning a broad range of both solvent compatibilities and chemical inertness. At the present advanced state of synthesis, a substrate (either catalyst or reagent) can be fitted with appropriate linkers/handles and protecting groups and coupled to polymeric supports that have the right properties to endow the finished system with properties that suffice to solve a particular problem that its creators had in mind. Regrettably, it does little to solve the most important problem of all for polymer-supported substrates, namely its cost-issues. At hindsight, it is quite remarkable that a simple molecule like proline (or rather hydroxyproline since it is the natural starting point for immobilization) requires the synthetic machinery we have been describing here, something that is evident when taking an overall look at Schemes 3, 4, 5, and 6. Particularly, the need for going through doubly protected derivatives such as **16** and **24**, usually followed by several other steps using chromatographic purifications, confines chemistry to the sub-gram scale. As the preparations themselves are usually limited to supplementary information in publications, it can be difficult to grasp overall efficiencies.

The post-modification strategy was historically designed for solid-phase peptide substrates, that is, high-valued substrates. It has very rarely been adopted successfully for low-valued substrates (such as proline), it simply cannot accommodate such substrates in a cost-efficient manner. Even the simplest of functional resins, the Merrifield resin (**1**), was formerly prepared by post-modification of crosslinked PS, but is preferably prepared today by copolymerizing styrene and DVB with 4-vinylbenzyl chloride.

In literature reviews on proline-immobilization, comments such as: "Considering that the cost of proline (€ 97.00 for 100 g) is less than half that of *trans*-4-hydroxyproline (€ 225.00 for 100 g), it can be concluded that, even if the catalyst is generally used at high loadings (20–30 mol-%), the immobilization of proline through the hydroxy group is not economically convenient unless the supported catalyst could be recycled for a number of times".[3b] This quotation is probably representative for how work within the field of polymeric immobilization is traditionally conducted, but is certainly too simplistic or right-out erroneous. Firstly, the prices were quoted from a laboratory supplier and are more than an order of magnitude out of range of actual costs for these materials, providing no basis for comparative cost analysis. However, more importantly though, the quotation gives the mistaken impression that the major cost of polymeric immobilization of small catalysts like proline is somehow connected to starting materials (prolines), and not the overall costs. The overall costs are, however, actually costs of catalyst starting materials plus polymer support, as well as the cost of the chemistry that is needed to both protect and link the catalyst to the polymer support (including linkers etc.). Even a single step of preparative chromatography (costing around $ 1200 to $ 5000 per kg on scale),[40] and as we have seen there are usually multiple of those involved in classical proline immobilization by post-modification, would dwarf the cost of any proline starting materials. If more economically viable routes to polymeric immobilization are to be developed, it is not possible to disconnect the synthetic strategy in this manner, but only to take a holistic approach where any analysis are to be taken on the strategy in its entirety. The factual reasons for the bias towards post-modification schemes are certainly not as well rooted in a rational analysis as is perhaps appreciated, but are apparently more entrenched for historical reasons and through the unfortunate barriers that regrettably do exist between the different field of chemistry, in this case polymer chemistry and synthetic organic chemistry.

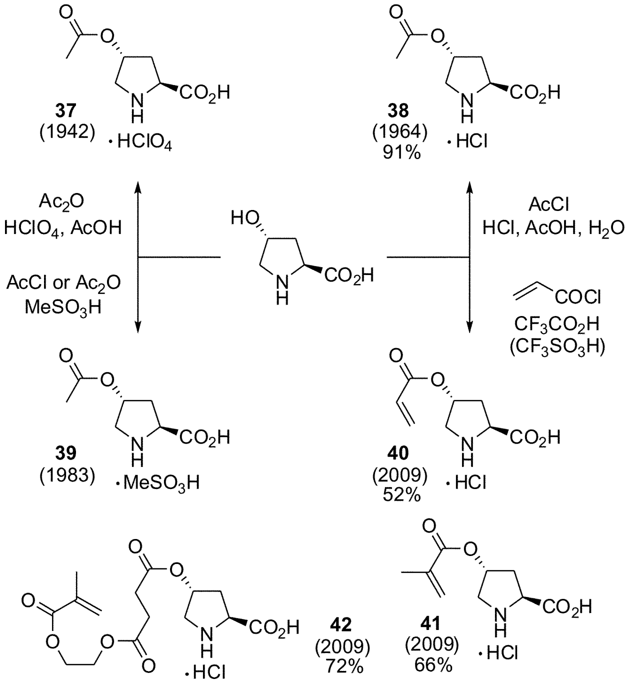
That said, the post-modification approach is the natural starting point for polymeric immobilization as it requires only sparse knowledge in polymer chemistry and rapidly can provide insight on the performance of immobilized catalysts/reagents. It will thus most certainly continue to be the cornerstone for polymeric immobilization in the time to come. Polymer-supported organocatalysts are probably in an especially interesting position as the (usually) modest complexity of organocatalysts spans an intermediate region from where a post-modification strategy is definitely preferred (complex catalysts) and into the region where the alternative approach (see below) is favoured, proline probably more naturally located in the latter.

Proline Immobilization on Crosslinked Polymer Beads

The Copolymerization Strategy

Taking the discussion above into consideration, we decided to undertake the polymeric immobilization of proline in a bottom-up fashion by first developing new synthetic machinery and then make acrylic proline-monomers that could be copolymerized to catalytic polymer beads.[41] In this way, we would have excellent control on catalyst loadings as these are now simply a matter of mixing monomers in the appropriate ratios. In addition, the swelling characteristics of the polymer beads can be varied by simply using comonomers of a suitable type.

In an attempt to circumvent the doubly protected derivatives of proline (e.g. **16** and **24**) that halted scalability in the post-modification approach, methodologies for directly activating the 4-hydroxy group of hydroxyproline were sought. We were surprised to see that fragmented knowledge existed in literature on the selective *O*-acylation of hydroxyproline, as direct preparation of *O*-acetylhydroxyproline salts (**37**–**39**, Scheme 7) have actually been known for decades.[42] In a remarkable paper from 1942, an exceptionally thorough study on the competition of *N*- vs. *O*-acetylation of hydroxyamino acids with Ac_2O in an anhydrous $HClO_4$/AcOH solution was reported.[42c] For hydroxyproline, an almost complete *O*-acetylation was obtained after 1 h while less than 10% *N*-acetylation had taken place. Moreover, the *N*-acetylated product (an amide) is easily separated from the *O*-acetylated product via its salts. In this manner, *O*-acetylhydroxyproline·HCl (**38**) was prepared in 1964 in a highly expedient manner by acetylation of hydroxyproline in a mixture of conc. aqueous HCl and AcOH (Scheme 7) and precipitation of product by addition of Et_2O, a vast improvement on previous procedures.[42a] This methodology is not transferrable to many other *O*-acyl derivatives,[41a] but the acylation procedure reported in 1983 by a Japanese research group (using a medium of $MeSO_3H$) can be adopted to several *O*-acyl derivatives.[42b] Surprisingly, this also includes several *O*-acyl derivatives of the amphiphilic type that were to prove so effective in asymmetric aldol reactions more than 20 years later, but still prepared in the standard inefficient manner through doubly protected hydroxyproline.[31] The use of $MeSO_3H$ for *O*-acylations is hampered by the impractical nature of the resulting oily (ionic liquid type) nature of the methanesulfonic salts.[41a,42b] We developed a more general *O*-acylation reaction for hydroxyproline on the basis of employing acyl chlorides in CF_3CO_2H, something of great practicality as the low affinity of CF_3CO_2H vs. HCl for amines makes the resulting crystalline amine hydrochlorides easily isolable by addition of Et_2O.[41a]

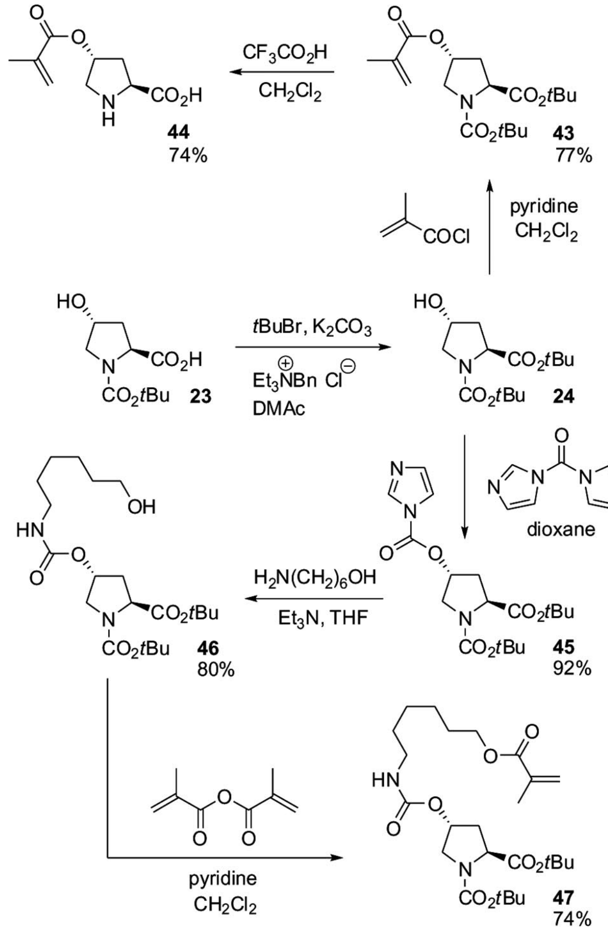


Scheme 7. Direct activation of hydroxyproline through acidic *O*-acylation.[41,42]

For polymer-supported proline, acidic acylation of hydroxyproline with readily available acryloyl, methacryloyl or 2-methacryloyloxyethylsuccinoyl chloride gave directly access to proline building blocks (**40**–**42**, Scheme 7) in only one step on multigram scale with no chromatography.[41a,41b] The sluggish reactivity of (meth)acryloyl chloride is manifested by the moderate yields for **40** and **41**. Traditionally, such building blocks from hydroxyamino acids have only been available through tedious syntheses using either copper or carbamate protection.[43] Shortly after and independently of ourselves, the research groups of Fernández-Mayoralas and Gallardo prepared analogous methacrylic derivatives, using the more traditional chemistry outlined in Scheme 8.[44] Both a small methacrylate (**44**), the free amino acid of our hydrochloride **41**, and aminohexanol-derived proline **47** were prepared. We found acrylic derivative **40** to be very unstable in free form,[41a,41b] presumably because of conjugate addition, so methacrylic esters are definitely preferred as building blocks for copolymerization strategies.

With derivatives such as **41**–**44** and **47** in hand, a very wide assortment of polymer-supported proline is now available through free radical polymerization. Unlike the post-modification approach, anything from completely full-loaded homopolymers (**48**–**50**) to normally loaded and

© 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 8. Preparation of proline methacrylates.[44]

crosslinked beaded polymer products are available (Figure 4).[41,44] Also, because of the chemical tolerance and experimental simplicity of suspension polymerization, these preparations are easily undertaken on >10 g scale and as such are much more scalable than the post-modification strategies.[41]

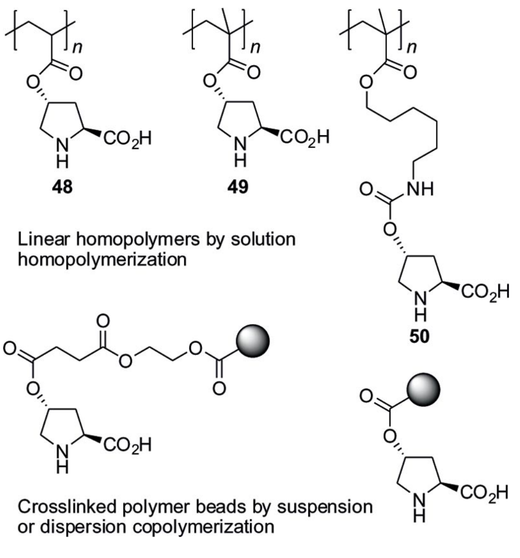
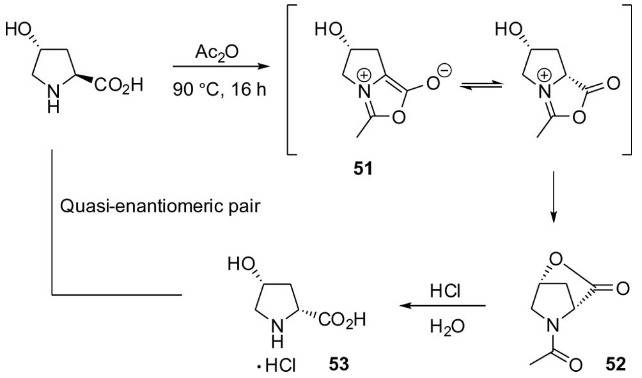


Figure 4. Polymerization of functional (meth)acrylates.[41,44]

For all polymeric immobilizations of proline, the use of *trans*-4-hydroxy-L-proline as starting material has the profound shortcoming in that its enantiomer is not readily available as it requires the inversion of two stereocenters.[45a,45c] However, the conversion to the diastereomer *cis*-4-hydroxy-D-proline is curiously facile (Scheme 9).[45] By simply heating the *trans*-hydroxyproline in neat acetic anhydride overnight, the ring-closed acyl intermediate **51** is formed.[45b] This is in equilibrium with a *trans*- and a *cis* derivative, the latter of which is trapped intramolecularly by the 4-hydroxy to give acetylated *cis*-lactone **52**. Deprotection and hydrolysis of **52** in aqueous HCl gives *cis*-4-hydroxy-D-proline hydrochloride **53**.[45b] We thought that it would be interesting to investigate the performance of such a *cis*-hydroxyproline on solid support as this simple preparation from *trans*-hydroxyproline gave us ample amounts of **53**, and the possibility of reaching products with the complementary stereoconfiguration.[41c]

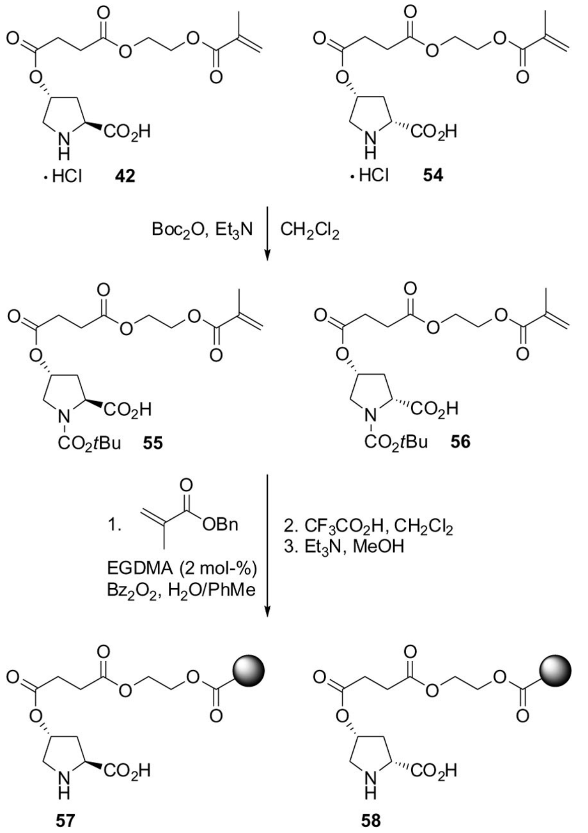


Scheme 9. The conversion of *trans*-4-hydroxy-L-proline into *cis*-4-hydroxy-D-proline hydrochloride.[45]

Completely analogously as for **42**, direct *O*-acylation of **53** with 2-methacryloyloxyethylsuccinoyl chloride gave functional methacrylate **54**. In order to make **42/54** more hydrophobic and useful in suspension polymerization, they were converted into their corresponding Boc derivatives **55/56**. Suspension copolymerization with benzyl methacrylate and ethyleneglycol dimethacrylate (EGDMA), followed by standard deprotection gave polymer-supported prolines **57/58** on large scale (20–50 g).[41b,41c] These catalysts form a quasi-enantiomeric pair and showed very good results in the intermolecular aldol reaction of substituted benzaldehydes and cyclohexanone, although *cis*-catalyst **58** generally shows a somewhat poorer selectivity (≈ 5–10% *ee* less) for most derivatives.[41c] We also prepared styrenic-acrylic copolymers in addition to the fully acrylic **57/58** with equally positive results, catalysts functional down to the 1 mol-% level of catalyst loading[41b] (Scheme 10).

We had very little success with the use of linear high-load homopolymers (**48–49**) in organocatalytic test reactions, but others have reported that homopolymers **49** and **50** provided good conversion (up to 80–100%) and medium to high enantioselectivity (up to 88% *ee*) in intermolecular aldol reactions of 4-nitrobenzaldehyde and 2,2-dimethyl-1,3-dioxan-5-one in DMF.[44] Homopolymer **50** showed better

© 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 10. Polymer-supported prolines by suspension copolymerization of functional methacrylates.[41b,41c]

conversion, but poorer selectivity than **49**.[44] For our acrylic polymer beads, the presence of a spacer seemed to have a surprisingly small effect on enantioselectivity, but slightly more on the diastereoselectivity.[41b] However, for proline supported on the styrenic Merrifield resin, the presence of a suitable linker seems much more vital.[33c]

In summary, it looks as the copolymerization strategy for polymeric immobilization of proline offers an advantageous scalability and versatility when compared to the post-modification strategy because of the tolerance and simplicity of free radical polymerization. In the post-modification scheme more complex chemistry usually has to be undertaken on the linker (between the catalyst and polymer support) for adjustment of the characteristics of the finished system (especially for swelling), while this can be more naturally accommodated in the copolymerization scheme by simply using appropriate comonomers. It would be very interesting to see in the future whether more refined techniques for radical polymerization, such as atom transfer radical polymerization (ATRP)[46] or reversible addition-fragmentation transfer (RAFT)[47] polymerization, will be used by researchers to prepare new polymeric architectures for organocatalytic systems that may show new and exciting reactivities and selectivities.[46–47] We ourselves have used dispersion copolymerization to directly copolymerize methacrylic ester hydrochloride **41** directly with benzyl methacrylate and EGDMA to give agglomerated microspheres (giving only two steps overall for the preparation of polymer-supported proline from hydroxyproline) that showed results very similar to our other acrylic organocatalysts from suspension polymerization.[41b] This is only one example on how a certain footing in polymer chemistry can dramatically shorten the overall preparation of polymer-supported organocatalysts.

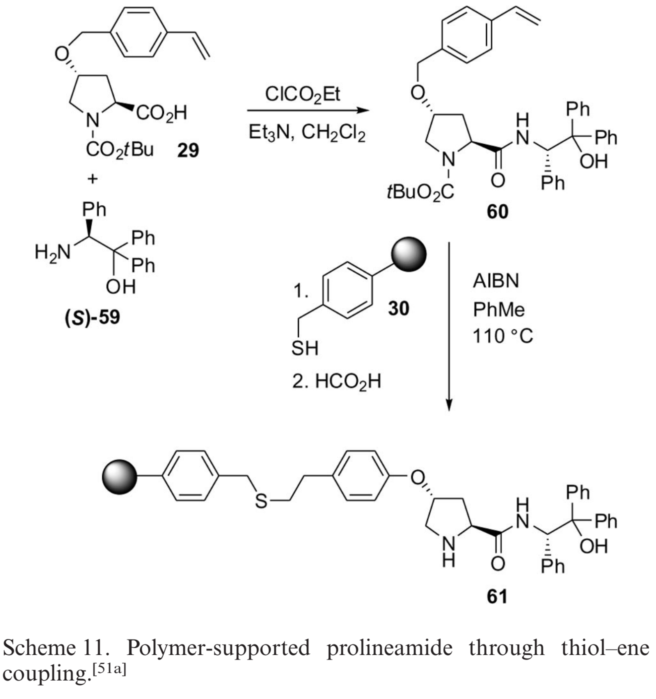
Polymer-Supported Prolineamides

Prolineamides as More Efficient Organocatalysts Than Proline

In the period of 2003–2005, a Chinese research group published a series of papers describing the use of simple prolineamides, prepared from proline and chiral β-amino alcohols, as highly efficient catalysts for the aldol reactions of substituted benzaldehydes and ketones.[48] These publications were to introduce a flood of publications in the years to come where prolineamides, small peptides and other related derivatives were proven effective in asymmetric organocatalytic aldol reactions.[49] In 2006, a research group in India introduced prolineamides of proline and chiral β-amino alcohols derived from readily available amino acids as especially effective catalysts for this transformation.[50] Originally, for these prolineamides, as was the case for those reported earlier,[48] the aldol reactions were undertaken in neat ketones as the reaction medium. However, in 2007, the use of the prolineamides (of proline and the diphenylamino alcohols derived from phenylglycine or leucine) in an aqueous reaction mixture gave aldol products in high yields and excellent enantioselectivities, even at only 0.5 mol-% of catalyst loading.[50b]

Polymer-Supported Prolineamides

Because of the excellent activities of the prolineamides in organocatalytic aldol reactions, they are definitely interest-



Scheme 11. Polymer-supported prolineamide through thiol–ene coupling.[51a]

ing targets for polymeric immobilization. While polymeric immobilization of proline probably functions more as a testing ground for immobilization strategies and methodologies than as a true candidate suitable for immobilization, the more valuable prolineamides are definitely more appropriate candidates. The most comprehensive and thorough studies on polymer supported prolineamides have been undertaken by the research group of Gruttadauria.[51] Using the protected styrene-derived proline **29**, used by the same researchers for preparation of polymer-supported proline (Scheme 5),[35] styrenic prolineamide **60** was coupled with (*S*)-diphenyl phenylglycinol via a mixed anhydride (Scheme 11).[51a]

Using the thiol-modified Merrifield resin **30**, a thiol–ene coupling (at a rather harsh 110 °C overnight) and subsequent deprotection gave polymer-supported prolineamide **61**. This is a powerful catalyst for asymmetric aldol reactions, and unlike polymer-supported proline, it can also provide excellent selectivity in aldol reactions of substituted benzaldehydes with water-soluble acetone.[51a] For aldol reactions with substituted benzaldehydes and acetone in water/$CHCl_3$, catalyst **61** gave high yields (quantitative for several derivatives) and excellent enantioselectivities (89–97% *ee*).[51a] In a second disclosure, the closely related prolineamide **62** (with the amino alcohol derived from leucine) was introduced in exactly the same manner (Figure 5).[51b] The recyclability of **62** was investigated very thoroughly, and it was discovered that treatment with formic acid could be used to regenerate the catalyst activity when this became diminished, this presumably because of the formation of imidazolidinones that subsequently became ring-opened when treated with formic acid.[51a–51b] In fact, using this treatment, polymer-supported prolineamide **62** was reused (with HCO_2H-regeneration) up to 22 times.[51b]

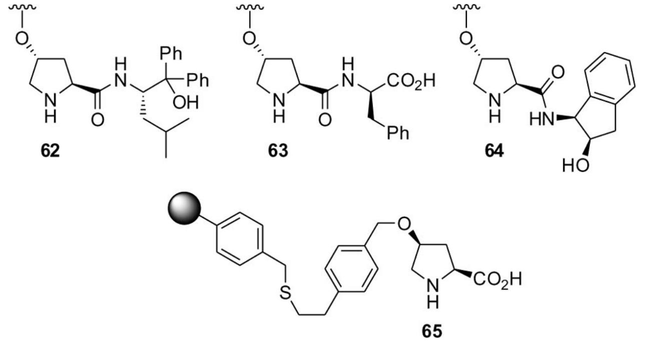
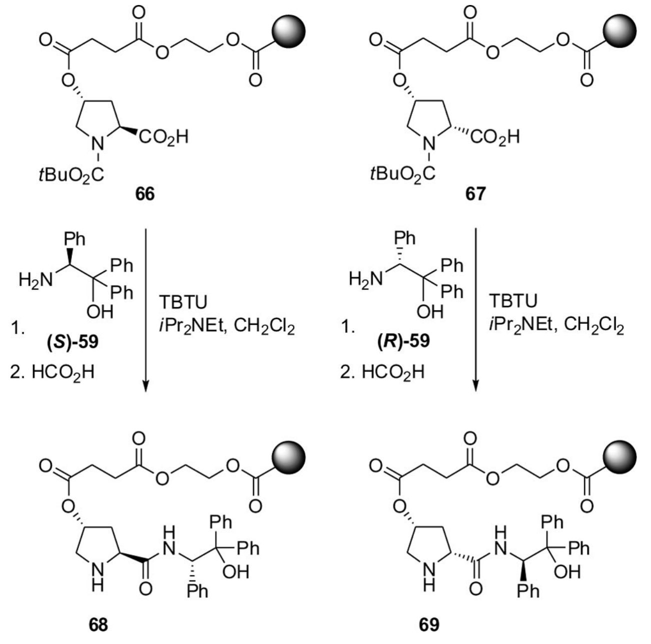


Figure 5. Polymer-supported prolineamides and *cis*-proline **64**.[51b–51c]

Shortly afterwards, the same research group prepared a whole range of polymer-supported dipeptides and prolineamides by the same thiol–ene coupling of styrenic derivatives onto the mercapto-functionalized Merrifield resin **30** and tested them in asymmetric aldol reactions.[51c] It was proven that polymer-supported prolineamides and dipeptides could indeed give better selectivities than unsupported catalysts, again underlining the fortunate symbiosis that can be achieved between an organocatalyst and the polymer scaffold.[51c] Especially immobilized catalysts **63** and **64** were thoroughly investigated.[51c] However, it is generally to be understood that a higher catalyst loading is necessary for polymer-supported catalysts than for free catalysts. Interestingly, the researchers reported the *cis*-hydroxyproline catalyst **65** in this paper, but unfortunately, no references or experimental details are provided for how it was prepared.[51c] As we have pointed out earlier, the inversion of configuration at C-4 in hydroxyproline is very laborious. It was reported that *cis*-catalyst **65** gave lower enantioselectivity than a *trans*-catalyst,[51c] very much in line with our own results for the quasi-enantiomeric catalyst pair **57/58**.[41c]

We also wanted to use our acrylic copolymerization strategy for immobilization of organocatalysts to prepare polymer-supported prolineamides.[41b–41c] However, unlike the previous disclosures, we wanted to prepare multigram quantities of both catalysts as well as products resulting from their use. As mentioned earlier, suspension copolymerization of proline methacrylates required Boc-protection to furnish monomers with an adequate degree of hydrophobicity. However, this meant that large amounts of acrylic polymer-supported Boc derivatives such as **66** and **67** (which gave prolines **57/58** when deprotected directly) were available. These could simply be peptide-coupled with the appropriate diphenyl phenylglycinol (*S*- or *R*-**59**) with a standard peptide coupling reagent (TBTU) to furnish multigram quantities of polymer-supported prolineamides **68/69** (Scheme 12). As was the case for the quasi-enantiomeric proline pair **57/58**, polymer-supported prolineamide **68** (derived from *trans*-hydroxyproline) gave somewhat better enantioselectivity (0–9% *ee* higher) in the asymmetric aldol reaction between substituted benzaldehydes and acetone in water than **69** (derived from *cis*-hydroxyproline), but



Scheme 12. Polymer-supported prolineamides by copolymerization followed by post-modification.[41c]

the selectivity was also nearly indistinguishable for some derivatives.[41c] On the other hand, our system has the advantage of offering access to both enantiomeric series of the aldol products, and the catalysts can be reused to prepare the aldol products on gram scale.[41c]

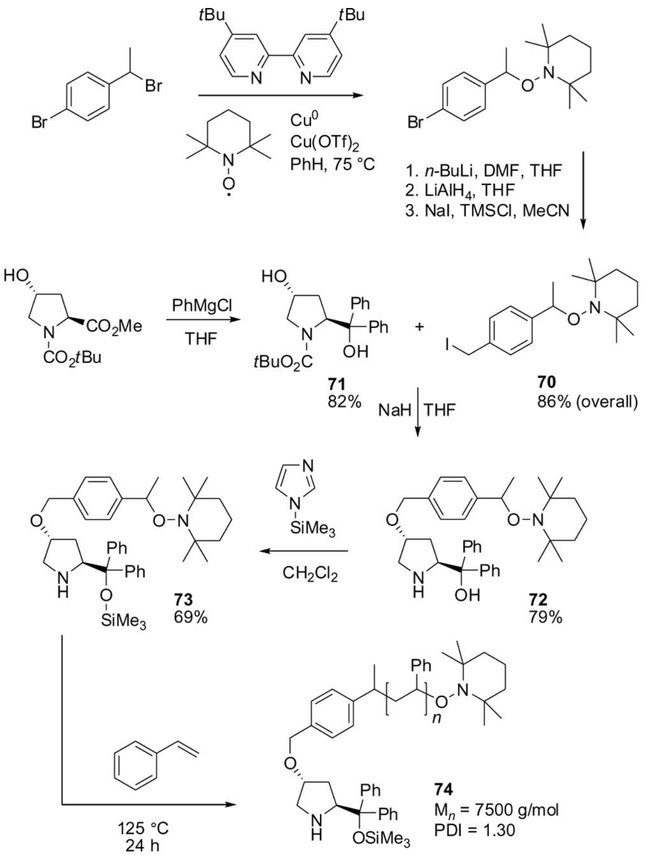
Polymer-Supported Diarylprolinols

Jørgensen–Hayashi Diarylprolinol Organocatalysts

In 2005, the research groups of Jørgensen in Denmark and Hayashi in Japan independently reported diarylprolinol silyl ethers as efficient organocatalysts for a range of transformations.[52–53] Among the organocatalysts, the Jørgensen/Hayashi diarylprolinols hold a special position because of its unique ability to undertake both enamine and iminium catalysis with excellent results, something which make them probably the most versatile and useful of all the organocatalysts, at least of the ones belonging to the enamine/iminium class.[3i] Unfortunately, and unlike the proline derivatives we have discussed until now and the MacMillan imidazolidinones which we will discuss later on, work on polymer-supported diarylprolinol silyl ethers has been very sparse until very recently.[54–57,41c] Indeed, reviews of immobilized organocatalysts have until now had no need for a separate chapter on these catalysts. This is surprising given the fact that this class of catalysts are probably the most promising candidates for polymeric immobilization as they are both relatively high-valued and are used at considerable catalyst loadings, often as high as 10–20 mol-%. However, they offer considerable challenges as compared to the prolines because these catalysts have a very different degree of hydrophobicity and many reactions using them are undertaken in solvent systems (MeOH, EtOH, MeCN etc.) that are relatively incompatible with the traditional styrene/DVB supports that dominate the field of polymeric immobilization. As such, the diarylprolinols are probably the class of organocatalysts that by now through developments the last couple of years has provided the most innovative procedures for polymeric immobilization of organocatalysts.

Polymer-Supported Diarylprolinol Silyl Ethers

As we will see, polymer-supported diarylprolinols have existed for some time because of the Corey-Bakshi-Shibata asymmetric reduction,[58] but polymer-supported diarylprolinol silyl ethers have emerged only recently.[54–57,41c] In 2008, a German research group reported the immobilization of diphenylprolinol TMS ether through a novel procedure wherein oligomeric styrene-prolinol conjugates were immobilized into polystyrene by electrospinning.[55] In this procedure, oligostyrene–prolinol conjugate **74** was prepared as shown in Scheme 13. Nitroxide **70**, prepared from readily available TEMPO, was coupled with protected hydroxyprolinol **71** through alkylation and subsequently silylated with TMS-imidazole to give nitroxide-prolinol **73**, an initiator for nitroxide-mediated polymerization (NMP).[47] Heating of **73** in neat styrene for 24 h gave oligostyrene–prolinol conjugate **74** with a high degree of monodispersity (Scheme 13).[55] This conjugate was then immobilized into high-molecular weight polystyrene by electrospinning, a method in which electrical charge is used to draw very fine fibers from a liquid.[59] Through electrospinning from a *N*,*N*′-dimethylacetamide solution of **74** and high-molecular weight polystyrene (M_n = 150 000 to 300 000 g/mol), fibers with a diameter of around 1.15 µm was prepared. These fibers were subsequently stabilized further by coating with a thin layer of poly-*p*-xylylene via chemical vapour deposition (CVD) starting from [2.2]paracyclophane as a precursor.[55] This fibrous catalyst system was benchmarked in an asymmetric Michael addition of dimethyl malonate to cinnamaldehyde in EtOH. The selectivity of these catalytic fibres was more or less identical to those of the monomeric catalyst used under exactly the same, although homogeneous, reaction conditions. Yet, the chemical yield was only 42%, compared to 84% for the monomeric catalyst.[55] However, it is important to keep in mind that this testing was undertaken at only 5 mol-% of catalyst loading, and a more favourable comparison could have emerged if testing was



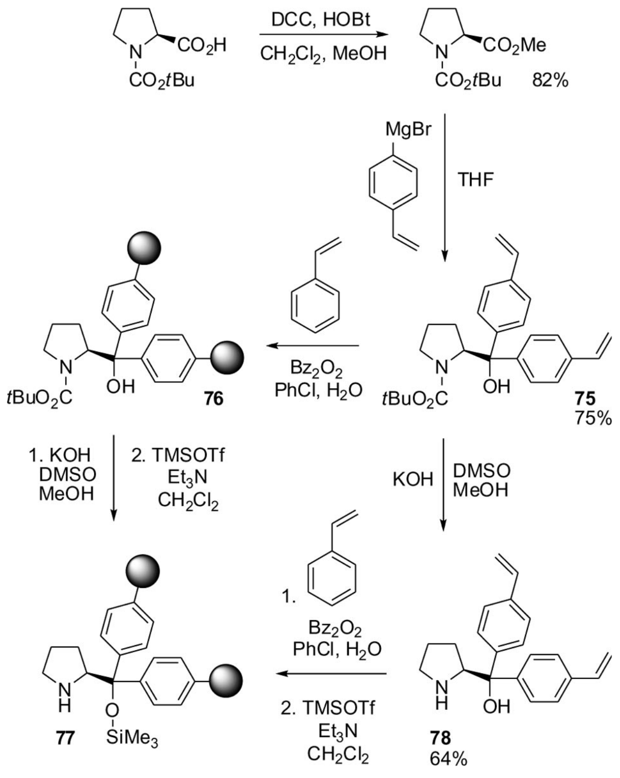
Scheme 13. Preparation of oligostyrene–prolinol conjugate via nitroxide-mediated radical polymerization.[55]

© 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

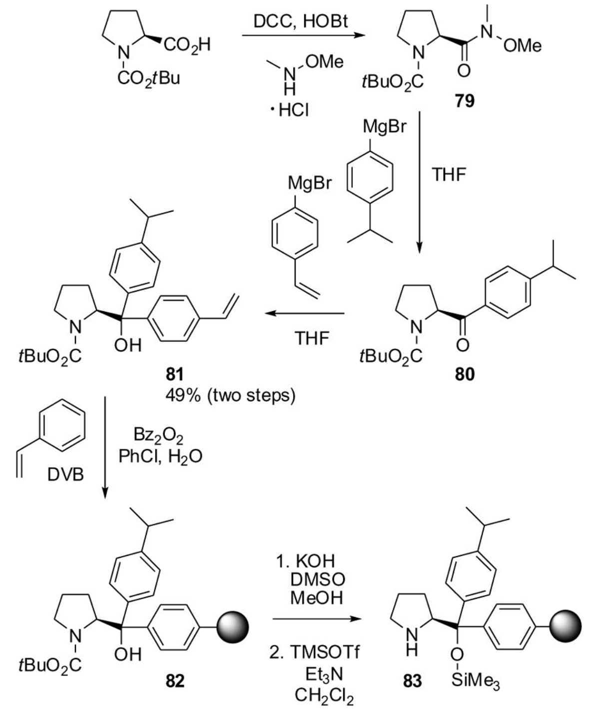
undertaken at the 10 mol-% level. The fibrous catalyst was recycled a total of 9 times, and the initial reactivity remained for the second run, giving a chemical yield of 42%, but then decreased and levelled off at about 25% of the initial activity. The authors were of the opinion that desilylation was not the cause of the deactivation and instead speculated that changes in the macrostructure of the fibrous system perhaps lead to a change of diffusion rates. Leaching of the catalytical prolinol conjugate **74** from the fibers was not detected.[55]

From the viewpoint of the overall synthetic strategy regarding the immobilization, the procedure going via nitroxide-mediated polymerization followed by electrospinning is highly interesting and innovative compared to standard post-modification. The same research group has in fact used the same approach for immobilization of proline, but the procedure will not be detailed further here as these fibres were not tested in catalytic reactions.[60] As we have pointed out earlier, methodologies for controlled radical polymerization, such as NMP, ATRP and RAFT, could achieve considerable importance in organic synthesis in the time to come.[46–47] Their lack of use within organic synthesis is probably, but unfortunately, a result of the invisible barriers existing between the different fields of chemistry. Although the overall synthetic strategy is strictly not a copolymerization Scheme as we have used the term earlier on, it clearly belongs to the same class of bottom-up philosophy for polymeric immobilization. In fact, the next report on polymer-supported diarylprolinol silyl ethers (also in 2008) was a bottom-up approach as well, this time by a research group in California using the more classical free-radical copolymerization of functional monomers together with comonomers (Scheme 14).[54,61]

Carbamate-protected proline methyl ester was prepared by carbodiimide-coupling of Boc-proline and methanol. Treatment of this ester with an excess of freshly prepared 4-vinylphenylmagnesium bromide gave protected diarylprolinol **75**. This distyrenic functional monomer was then used as the crosslinker in a suspension copolymerization together with styrene in $PhCl/H_2O$ to give polymer beads **76**. Deprotection and silylation then gave polymer-supported diarylprolinol silyl ether **77** (Scheme 14).[54,61] Interestingly, the researchers also reported the preparation of the same polymer beads by first deprotecting **75** to free amine **78** and then undertaking the suspension polymerization to give **77**. However, the yield for the polymerization of **78** was poor, only 29%.[61a] This probably has a natural explanation, as in view of our own work, the polymerization of free amines (as **78**) is incompatible with the use of benzoyl peroxide as free radical initiator, as was used by these researchers.



Scheme 14. Preparation of polymer-supported diarylprolinol by copolymerization of styrenic diarylprolinol crosslinker and styrene.[54,61]



Scheme 15. Preparation of polymer-supported diarylprolinol by copolymerization of styrenic diarylprolinol with styrene and DVB.[54,61]

In addition to the distyrenic derivative **75**, the same research group also reported the preparation of monostyrenic derivative **81** and its subsequent suspension copolymerization (Scheme 15).[54,61] Weinreb amide **79**, obtained from coupling of Boc-proline and *N*,*O*-dimethylhydroxylamine hydrochloride, was treated with 4-isopropylphenylmagnesium bromide to give ketone **80**, which upon addition of 4-vinylphenylmagnesium bromide yielded styrene **81**. Suspension copolymerization together with styrene and DVB (crosslinker essential since **81**, as opposed to **75**, is monostyrenic), followed by deprotection and silylation furnished

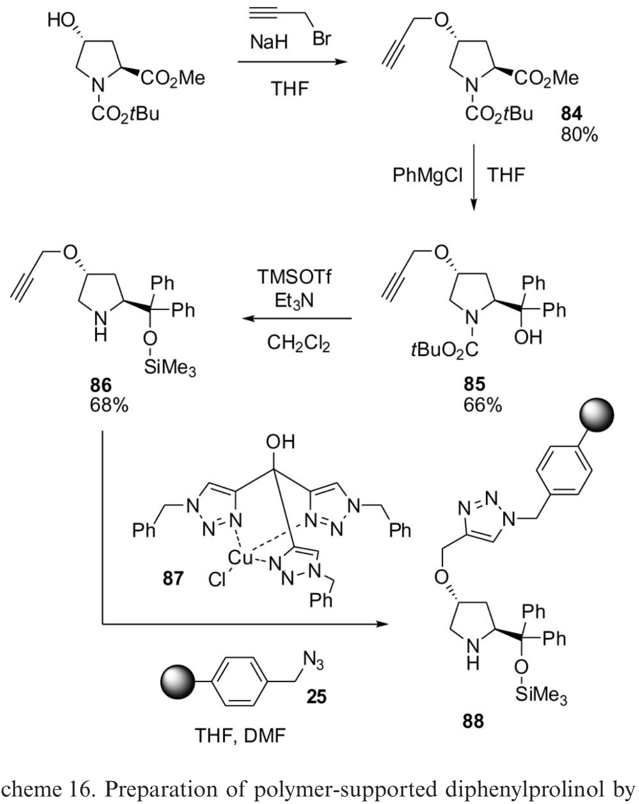
© 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

polymer beads **83**. It is imperative to note that the these immobilized diarylprolinols were originally developed for polymer-supported Corey–Bakshi–Shibata (CBS) asymmetric reduction catalysts nearly a decade ago,[61] and only the final silylation of the CBS catalysts into diarylprolinol silyl ethers **77** and **83** were new developments in their 2008 report.[54] In addition to the procedures outlined in Schemes 14 and 15, the researchers later introduced analogous procedures with 2-(trimethylsilyl)ethoxycarbonyl (Teoc) protected functional monomers.[61b]

For a supported CBS catalyst, the styrene-network is ideal because these reductions are normally carried out in THF. Conversely, for organocatalysis, this is a clear disadvantage as many reactions using diarylprolinol silyl ethers are often carried out in solvents like lower alcohols, aqueous systems and the like. As such, because of the limitations imposed by the use of a styrene-network, the researchers had to undertake organocatalytic reactions in typical swelling solvents for this type of polymers. Crosslink-bound catalyst **77** and pendant-bound catalyst **83** were tested in asymmetric epoxidations of cinnamaldehyde in a 50:50 CH_2Cl_2/EtOH- or THF/trimethyl orthoformate mixture, but only with poor conversions and selectivities that were inferior to those obtained using a monomeric catalyst.[54] On the other side, asymmetric Michael addition of aliphatic aldehydes to *trans*-β-nitrostyrene in benzene worked well, giving high chemical yields (more than 80%), diastereomeric ratios (up to 99:1) and enantioselectivities (up to 99% *ee*). Crosslink-bound catalyst **77** was found to be slightly better than pendant-bound catalyst **83**.

These converted CBS-catalysts were also tested in a three-component organocatalytic cascade, first reported by the research group of Enders.[62] In this triple cascade, a tetrasubstituted cyclohexene carbaldehyde with four stereogenic centers is prepared in one step from a cinnamaldehyde, nitrostyrene and aldehydes.[62] The catalytic cycle involves both enamine and iminium catalysis and is a testimony to the unique opportunities offered by the Jørgensen/Hayashi diarylprolinols. Remarkably, unlike the more trivial Michael addition of aldehydes to nitrostyrenes, the pendant-bound catalyst **83** was much more efficient in this cascade reaction than crosslink-bound catalyst **77**.[54] While **77** gave a modest 15% yield of product (using cinnamaldehyde, *trans*-β-nitrostyrene and propionaldehyde as the three components) with 89% *ee* after 7 days, catalyst **83** gave 45% yield and 99% *ee* after the same reaction time.[54] This compares to the 40% yield and >99% *ee* that can be obtained with the non-supported diphenylprolinol silyl ether, although now in only 24 h.[62a] The researchers speculated that crosslink-bound catalyst **77** is less effective because of the more constrained steric environment as when compared to pendant-bound catalyst **83**.[54] We believe this is a sensible conclusion and supported by our own report, which we will discuss more later on.[41c] Recycling of catalysts **77**/**83** worked poorly and with severe catalyst deactivation, even when catalysts were resilylated before use.[54]

As described, the first polymer-supported diarylprolinol silyl ethers were prepared in a bottom-up fashion, but very recently, the research group of Pericàs in Spain reported polymer-supported diphenylprolinol silyl ether prepared by a more conventional post-modification (Scheme 16).[56] Using analogous methodology as utilized for their proline-immobilization (see above),[33] carbamate-protected hydroxyproline methyl ester was alkylated with propargyl bromide to **84** and then converted into the diphenylprolinol **85** with PhMgCl. A combined silylation/deprotection then furnished the key catalyst precursor **86** in reasonable yield. This precursor was anchored to the azido-modified Merrifield resin **26** (described earlier) through the copper-catalyzed azide–alkyne cycloaddition to give polymer-supported catalyst **88**.[56] Interestingly, the cycloaddition using **86** is challenging because the free amine group of this catalyst precursor tend to deactivate copper catalysts. The issue was resolved by employing the tris(triazolyl)methanol–Cu^I complex **87**, developed recently by the same research group,[63] as cycloaddition catalyst (1 mol-% catalyst loading). Although the overall preparation is rather laborious because of the multiple chromatographic purifications necessary and the use of a specialized Cu^I catalyst, the advantage of using the azide–alkyne cycloaddition for immobilization relies in the fact that the resultant 1,2,3-triazolyl structural fragment has an unusually large dipole moment. This means that the linker where this structural element is included confers a very polar element to the system and plays a pivotal role in the overall character and hydrophobicity of the catalyst. A triazolyl-connected catalyst may therefore show more compatibility with polar solvents than would probably be expected at first hand.



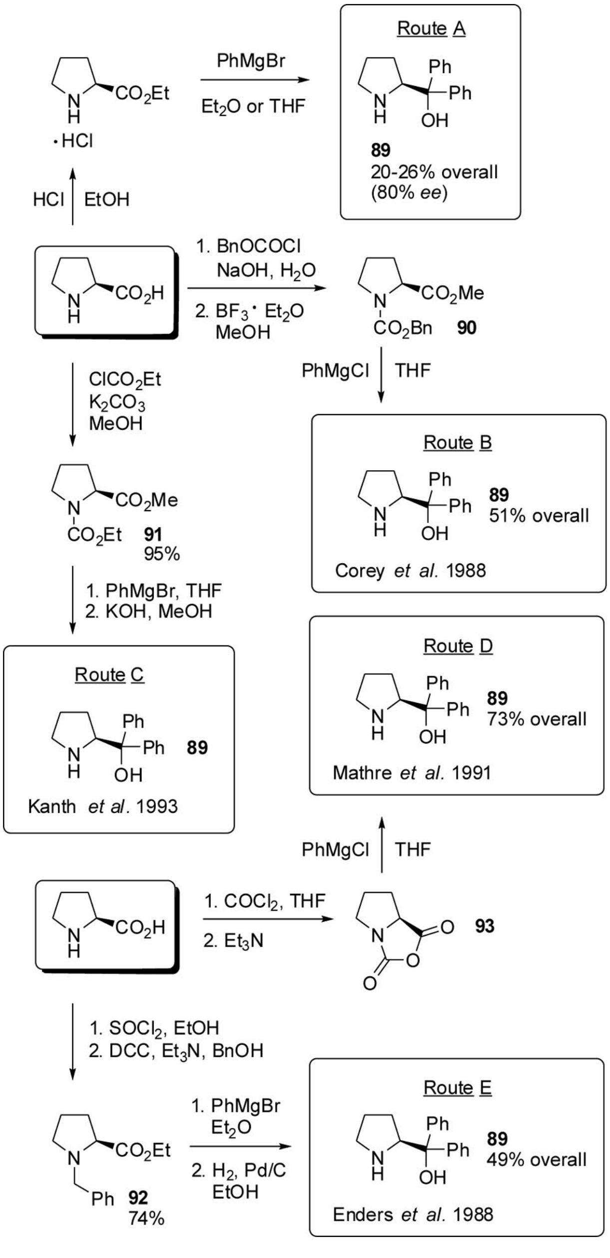
Scheme 16. Preparation of polymer-supported diphenylprolinol by post-modification of Merrifield resin.[56]

Polymer-supported catalyst **88** was benchmarked in the asymmetric Michael addition of aldehydes to nitrostyrenes.[56] It provided excellent results, comparable to the best homogeneous catalysts in the same process, with virtually quantitative yields and very high diastereo- and enantioselectivities. However, again, these reactions were carried out in CH_2Cl_2, a powerful swelling solvent for styrene/DVB networks. Reactions in water were possible only by using DiMePEG additive.[56] Most interesting was the remarkable and strong substrate selectivity for linear short chain aldehydes. Longer aldehydes were less successful and branching in the β-position of the aldehydes was deleterious for conversion, while α-branching completely obstructed the reaction. Ketones like acetone and cyclohexanone were completely unreactive.[56] In the presence of both short chain linear and branched aldehydes, catalyst **88** only catalyzed the Michael addition of the linear aldehydes. Since the rate of reaction was considerably slower, indicating the reversible formation of unproductive enamine intermediates, the researchers attributed the selectivity to the different reactivity of equilibrating enamine intermediates.[56] Hopefully, this catalyst will also be used for cascade reactions in the future, so as further insight can be gained and more direct comparisons can be made to the other polymer-supported diarylprolinol silyl ethers.

Unlike the reports preceding this work, recycling of polymer-supported catalyst **88** was successful as long as reconditioning was undertaken. Inactivated catalyst gained full recovery after a brief treatment with trimethylsilyl *N*,*N*-dimethylcarbamate in hexane/MeCN, something which clearly demonstrated that hydrolysis of the labile silyl ether could be the main pathway of deactivation for this class of organocatalysts.[56]

Simultaneously with the work described above, we were actively pursuing a synthetic route for large-scale preparation of polymer-supported Jørgensen–Hayashi catalysts.[41c] As our strict requirements for scalability ruled out chromatographic purifications and pressed the use of protective groups to an absolute minimum, none of the reported procedures seemed to us especially useful as a foundation that we could extend. As for proline, we believed the more comprehensive acrylics offered a more practical starting point than styrenics, and we planned to prepare polymeric systems more compatible with polar solvents.

For a start, it looked like preparation of the diphenylprolinol from proline or hydroxyproline was a key issue.[64–65] Because of the CBS-reduction in the late 1980s,[58] the efficient preparation of diphenylprolinol **89** suddenly became a hot research topic for academic and industrial research group alike (Routes A–E, Scheme 17).[64] It is not as clear-cut as probably imagined at first sight because the standard mode of preparation of diphenylamino alcohols from amino acids, the addition of phenyl-Grignard reagents to an alkyl ester of the appropriate amino acid, works extremely poorly for proline (Route A).[64a,64d] The original preparation by the research group of Corey (Route B), going through the carbamate-protected proline methyl ester **90**, works only moderately well and is rather laborious.[64b] Subsequently, a more expedient route (Route C) was developed by a research group in India where proline is diprotected directly in one-pot with ethyl chloroformate and K_2CO_3 in MeOH to **91**, which is then treated with PhMgBr and deprotected in KOH/MeOH to give diphenylprolinol **89**.[64c] This seems to be the preferred route to **89** in academic laboratories, but of more interest for us was the fact that it do seem to be the sole method (after 1933) that is reported for the preparation of the corresponding diphenylhydroxyprolinol,[65] obviously a key intermediate in the preparation of polymer-supported Jørgensen–Hayashi organocatalysts. This was therefore our starting point, but we found it to be unsuited for preparations on the >10 g scale. Two other large-scale routes to **89** (Routes D and E) are

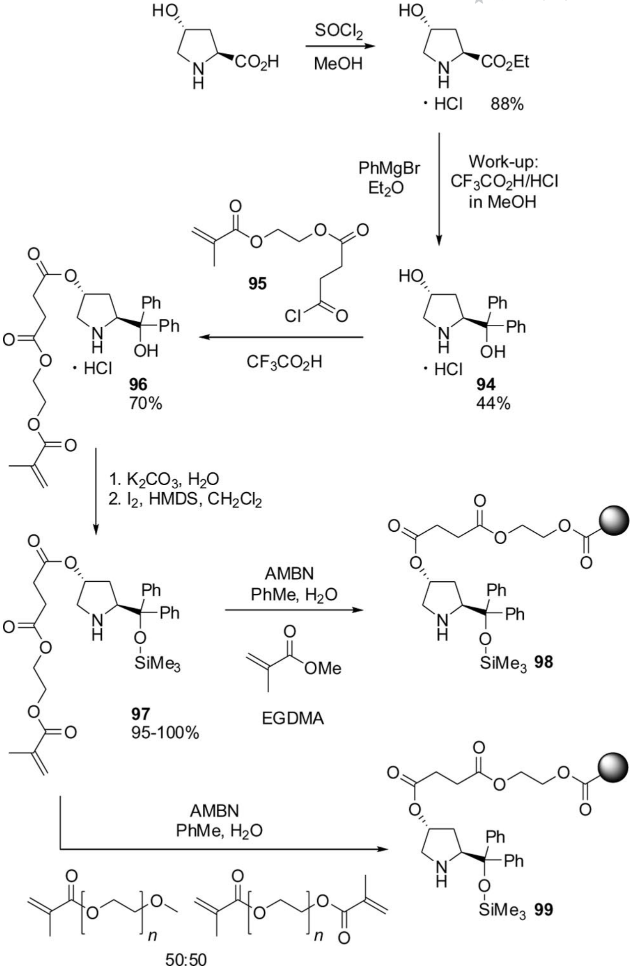


Scheme 17. The most important synthetic routes to diphenylprolinol.[64]

depicted in Scheme 17. A research group from Merck reported the preparation of proline-*N*-carboxanhydride **93** from L-proline and phosgene, followed by treatment with PhMgCl to give **89** in good overall yield.[64d] The toxic nature of phosgene makes this route unattractive. A more conventional route (Route E) going via *N*-benzylproline ethyl ester **92** is also possible, but not especially elegant or efficient.[64e] Some other, more specialized, routes have also been reported, but did not seem particularly useful,[64f–64g,58b] although one procedure using silyl-protected proline seemed quite novel.[64g]

After extensive investigations into diphenylprolinol chemistry, we reported the completely non-chromatographic and protective-group free synthesis of polymer-supported diphenylprolinol silyl ether shown in Scheme 18.[41c] We found out that the direct route to diphenylhydroxyprolinol (depicted as Route A in Scheme 17 for the equivalent proline derivative) was much more efficient for hydroxyproline than proline, as have actually been known since 1933,[64a] although that seem to have passed unnoticed. Among other things, the diphenylprolinol of hydroxyproline has superior crystallinity as compared to its proline analogue (as reflected in its melting point, which is approximately 100 degrees higher for the former).[64a] Direct treatment of hydroxyproline ethyl ester·HCl gave diphenylhydroxyprolinol·HCl **94** on large scale (>30 g) after a modified work-up.[41c] Even better, **94** could be selectively *O*-acylated, in the presence of the unprotected amine and tertiary alcohol, directly to crystalline methacrylate salt **96** on 30 g scale with the acid chloride of widely available 2-methacryloyloxyethylsuccinic acid (**95**). Silylation using the mild, but very powerful I_2/HMDS protocol gave functional acrylic monomer **97**.[41c]

Straightforward suspension copolymerization of **97** together with methyl methacrylate and EGDMA in H_2O/PhMe gave polymer-supported catalyst **98**. These standard microporous beads have swelling properties much in common with the standard styrene networks and are useful in THF, PhMe, CH_2Cl_2 and the like. To make beads compatible with MeOH, MeCN etc., we were inspired by the CLEAR-family[20] of resins (see above) which are fully crosslinked, but still show excellent swelling in a wide range of solvents. We wanted to make a PEG-based network by copolymerization of **98** with PEG-methacrylates. However, the combination of hydrophilic PEG derivatives (water-miscible) with the hydrophobic **97** in suspension polymerization would most likely prove difficult. After all, the PEG-based PEGA resin (described earlier) that was introduced by Meldal and co-workers in the early 1990s used inverse suspension polymerization,[19] incompatible with **97**. We were intrigued by the fact that the preparation of PEGA by inverse suspension polymerization gave only moderate yields in a polymerization reaction which would normally be expected to be virtually quantitative.[19] We believed this to be connected with the peculiar properties of PEG, which is fully water-miscible at room temperature, but that can precipitate above a certain cloud point as the PEG-chains become dehydrated. Therefore, we tried to suspension copolymerize a toluene solution of **97** together with a 50:50 mixture of PEG 400 methyl ether methacrylate and PEG 600 dimethacrylate in water, the idea being that also the PEG derivatives would partition favourably into PhMe at the polymerization temperature. Gratifyingly, a quantitative recovery of **99** as very practical polymer spheres resulted.[41c] These spheres showed the expected useful compatibility with the polar solvents we wanted.



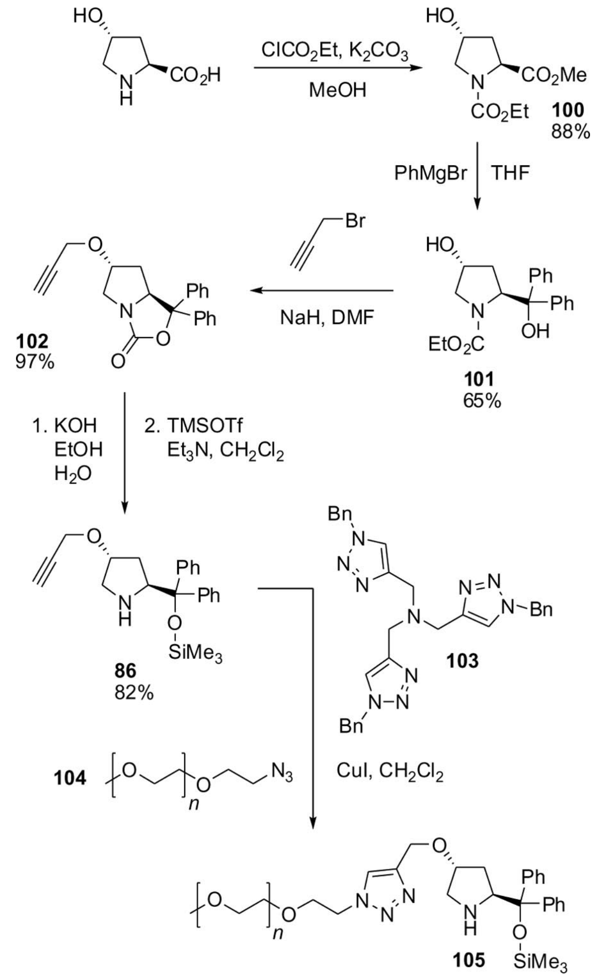
Scheme 18. Preparation of polymer-supported diphenylprolinol by acrylic copolymerization.[41c]

We tried catalysts **98** and **99** in the Enders cascade, using propionaldehyde, cinnamaldehyde and 2-chloro-β-nitrostyrene as the three components.[41c] Microporous beads **98**, in a well-expanded state in PhMe, provided the expected product in descent 32% yield (after 7 days) and excellent selectivity (>99% *ee*). On the other side, catalyst **99** in MeCN (a solvent we on beforehand had verified that worked nicely under homogeneous catalysis) gave no detectable yield of the final cascade product, but full conversion into the first Michael addition of propionaldehyde to the nitrostyrene that constitutes the first part of the overall catalytic cycle.[41c] These results compares usefully with the catalyst pair **77**/**83**, where only the less hindered pendant-bound catalyst **83** and not the more constrained crosslink-bound **77** provided useful quantities of cascade product.[54]

Early in 2010, a German research group reported a PEG-linked Jørgensen–Hayashi catalyst (Scheme 19).[57] The strategy is in essence very similar to that described for preparation of catalyst **88** earlier (Scheme 16). Propargyl derivative **86**, the same as that reported first by Pericàs and coworkers (Scheme 16),[56] was prepared in five steps from hydroxyproline. By using an analogous route to that of the classical route C in Scheme 17 (see our discussion above concerning routes to diarylprolinols),[64c] hydroxyproline was diprotected in one step to carbamate ester **100** and treated with PhMgBr to furnish protected diarylprolinol **101**. Alkylation of **101** with propargyl bromide gave **102**, which was subsequently deprotected through alkaline hydrolysis and silylated with TMS-triflate to the key intermediate **86**.[57] As discussed previously for this intermediate, a cycloaddition with azides is not straightforward as amines coordinate to and deactivate copper. The researchers used tris(benzyltriazolylmethyl)amine (**103**) together with CuI to successfully link intermediate **86** and azide-modified PEG derivative **104** through the copper-catalyzed azide–alkyne cycloaddition to give PEG-linked catalyst **105** (Scheme 19).[57] Importantly, it was reported that use of the Boc-protected methyl ester of hydroxyproline led to significant deterioration of the catalyst's optical purity.[57]

Catalyst **105** was tested in the asymmetric Michael addition of nitromethane to cinnamaldehydes in MeOH, giving excellent chemical yields and enantioselectivities, unchanged as compared to the homogeneous catalyst.[57] In fact, the resultant products could be isolated in pure form without the need for column chromatography. In recycling experiments, the selectivity of the catalysts remained virtually unchanged for five reaction cycles, but the product yields dropped significantly. Interestingly, the researchers did not attribute this loss of catalytic activity to desilylation, as is commonly done, but mainly to product inhibition of the catalyst. Stirring the catalyst with the cinnamaldehyde starting material (which then displaces product from the catalyst) did actually fully restore its initial activity, as well as release more product.[57] As experiments conducted by separate research groups seem to indicate that deactivated diarylprolinol silyl ether catalysts can be revived both through resilylation under one set of reaction conditions and through stirring with starting material under another,[56,57] most probably the exact reaction conditions prevailing in the organocatalytic transformation of use may affect the catalyst in different ways. An alternative explanation is that also reconditioning through resilylation actually has its effect by releasing product from the deactivated catalyst.

It is important to point out that catalyst **105**, in nature of being immobilized on linear PEG, is completely compatible with polar solvents such as MeOH. As mentioned, the use of linear polymers for polymeric immobilization is usually more cumbersome than using crosslinked beads as a separate precipitation step is required and some loss of catalyst is unavoidable. Nevertheless, unlike its use for immobilization of proline, the use of linear PEG is better suited for Jørgensen–Hayashi catalysts as it solves the important problem of making the hydrophobic silyl ether catalyst compatible with polar solvents. As described, our own systems combined the compatibility of PEG-systems with the practicality of crosslinked beads.[41c]



Scheme 19. Jørgensen–Hayashi catalyst supported on linear PEG.[57]

Future Developments for Polymer-Supported Jørgensen–Hayashi Organocatalysts

As we have alluded to previously in this chapter, the Jørgensen–Hayashi organocatalysts seem as particularly interesting candidates for polymeric immobilization. This is primarily not because they are relatively high-valued organocatalysts (at least compared to proline), but more because the polymeric backbone and linker do seem to have an especially large degree of influence on catalyst activity and selectivity. The reaction cavity as defined by the combination of catalyst, linker and polymer backbone seems to control catalyst activity/selectivity in an especially strong manner for this family of catalysts.

Taken together, the results reported until now do seem to imply that only relatively non-hindered diarylprolinol silyl ether catalysts are able to undertake the demanding

Enders-type cascade, but that most are able to undertake a standard Michael addition of simple aldehydes to nitrostyrene. However, as we have seen, also in the Michael addition to nitrostyrenes, a strong "enzyme-like" behaviour towards simple non-branched aldehydes has been observed, and the two phenomena are probably connected. We certainly anticipate that more exciting developments are to come in the near future for this class of organocatalysts.

As interest in non-silylated diarylprolinols as bifunctional organocatalysts are on the increase,[66] this might also widen the scope and utility of the polymer-supported diarylprolinols. Although other effective organocatalysts, a few even in polymer-supported versions, have been reported for some specific asymmetric Michael additions, they are less general than the Jørgensen–Hayashi catalysts and will not be detailed further.[67] Of the work that has taken place within the CBS-type chemistry over the years, a few reports have utilized catalyst precursors that have been linked through either position 4 of a diphenylhydroxyprolinol or the aryl residues on a diarylprolinol (such as for distyrene **78**) and as such may be used as a platform for future preparations of polymer-supported Jørgensen–Hayashi catalysts.[64g,68] These disclosures contains both strategies of the post-modification and bottom-up type.[64g,68] Since the reactions constraints in CBS reductions are so different from most organocatalytic reactions, and because none of them have been tested in organocatalytic transformations, they will not be detailed further. It is important to note that the styrene-networks of most of these reports can now be advantageously complemented by the richer acrylic chemistry because of the mild reaction conditions prevailing in organocatalysis.

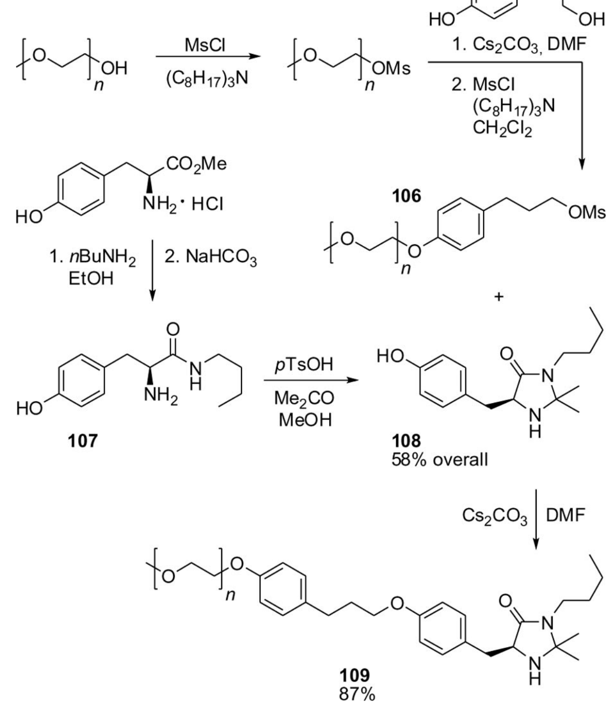
Polymer-Supported MacMillan Imidazolidinones

MacMillan Imidazolidinone Organocatalysts

Concurrently with the reports on the successful intermolecular proline-catalyzed aldol reactions reported by List, Lerner and Barbas in 2000, the research group of MacMillan published the use of chiral imidazolidinones as organocatalysts for asymmetric Diels–Alder reactions.[1b,69] In the years that have followed, this family of organocatalysts has enjoyed an ever-widening reaction scope.[3i] In addition to Diels–Alder reactions, imidazolidinone catalysis has been used for 1,3-dipolar cycloadditions, Friedel–Craft alkylations, α-halogenations, epoxidations etc.[3i] Although, as we will treat more fully later on, recycling of immobilized MacMillan imidazolidinones has usually been coupled to a rather nonsatisfactory drop in efficiency, immobilized imidazolidinones have nevertheless remained an active area of research.[70–75] Concepts developed in the pursuit of polymer-supported MacMillan imidazolidinones provide useful and additional insight as they are built on phenylalanine, and not the proline skeleton. Of more interest is probably the fact that many of the reactions employing MacMillan catalysts, as was the case for the Jørgensen–Hayashi catalysts, take place in solvents that can be challenging to accommodate within a classical immobilization scheme.

Polymer-Supported MacMillan Imidazolidinones

The first reports on polymer-supported MacMillan imidazolidinones surfaced in 2002.[70–71] The research group of Cozzi in Milan, who pioneered the use of PEG-supported proline during the same period,[29] reported the PEG-supported imidazolidinone **109** (Scheme 20).[70] As a starting point, PEG-mesylate **106**, which had been used in previous work by the same research group,[76] was prepared from PEG by mesylation, followed by substitution with 3-(4-hydroxyphenyl)-1-propanol and then another mesylation. Imidazolidinone **108** was prepared by treating L-tyrosine methyl ester·HCl with *n*-butylamine to give tyrosineamide **107**, which upon ring-closure with acetone in MeOH furnished **108**. Alkylation of the phenolic functionality of imidazolidinone **108** with PEG-mesylate **106** gave PEG-supported MacMillan catalyst **109**.[70] This linear PEG catalyst is compatible with a with range of solvents because of its favourable solubility profile and was tested in asymmetric Diels–Alder cycloaddition of acrolein and cyclohexadiene in MeCN/H_2O. Compared to the monomeric catalyst, in this case meaning either **108** or **108**-OMe, PEG catalyst **109** actually provided a better diastereoselectivity (94/6 for **109**·CF_3CO_2H compared to 92/8 for **108**-OMe·CF_3CO_2H) and enantioselectivity (92% *endo ee* vs. 84% *endo ee*). However, this is slightly lower selectivity than in the original report of MacMillan using (*S*)-5-benzyl-2,3,3-trimethyl-

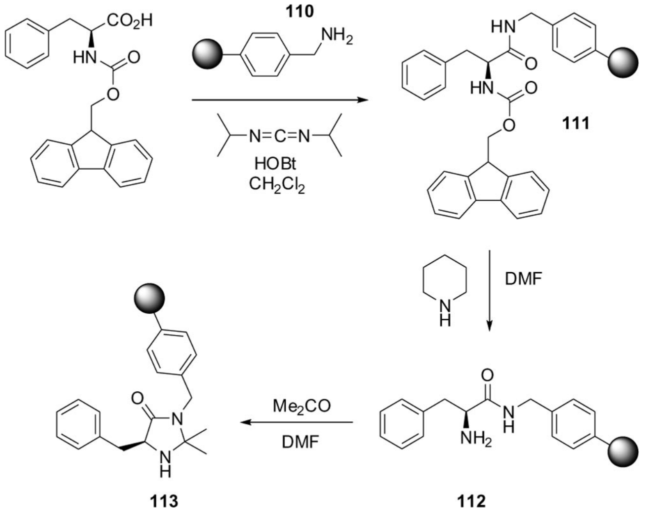


Scheme 20. Imidazolidinone supported on linear PEG.[70]

© 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

imidazolidin-4-one·HCl,[1b] and the chemical yields for supported catalyst **109** are generally lower than the monomeric catalysts and the reaction time was a considerable 40 h at 10 mol-% of catalyst loading.[70] Interestingly, recycling had only a modest effect on enantioselectivity, decreasing from 92% to 85% *ee* in the fourth cycle, but yields were lowered because of catalyst degradation. The catalyst was recovered in a modest 70–80% by evaporation of solvent and precipitation with Et_2O. In a later full paper by the same research group, catalyst **109** also proved successful in 1,3-dipolar cycloadditions, with the same pattern of reduced yields but with relatively preserved selectivity.[70b]

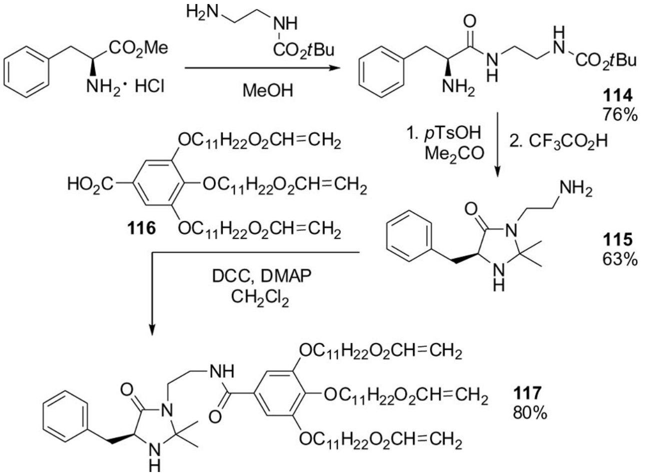
At the same time as the report on PEG-immobilized imidazolidinones appeared, Pihko and co-workers reported a JandaJel™-supported MacMillan imidazolidinone (Scheme 21).[71] The researchers chose amino-functionalized JandaJel™ **110** as their starting point because of the good compatibility with many solvents (see the previous section in this microreview on polymer supports). Using a novel polymer-supported assembly, *N*-Fmoc protected L-phenylalanine was coupled to resin **110** through a diimide-promoted coupling to supported amide **111**, which was subsequently deprotected to supported amide **112** with piperidine in DMF. Cyclization with 50% acetone in DMF then completed the synthesis of JandaJel™-supported imidazolidinone **113**.[71]



Scheme 21. Polymer-supported imidazolidinone by on-bead synthesis.[71]

Catalyst **113** was tested in asymmetric Diels-Alder cycloadditions of α,β-unsaturated aldehydes and dienes. The enantioselectivities were very good, equalling or even surpassing those obtained by solution phase catalysts, but chemical yields were generally no more than moderate. Using the catalyst from a previous run, easily obtained by simple filtration, gave results very close to fresh catalyst, but no more extensive recycling was apparently investigated. A silica-supported catalyst was also reported, but will not be detailed any further.[71]

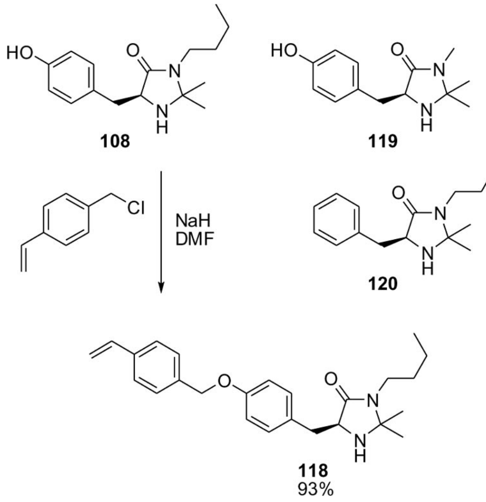
In 2005, a research group in USA developed a completely different immobilization approach for chiral imidazolidinones.[72] Using the synthetic sequence depicted in Scheme 22, an amphiphilic functional monomer for lyotropic liquid crystal (LLC) assembly was prepared. L-Phenylalanine methyl ester·HCl was treated with a monoprotected ethylenediamine to amide **114**, which was cyclised with acetone and deprotected to imidazolidinone **115**. The pendant primary amine was then coupled to 3,4,5-tris(11′-acryloyloxy-1-undecyloxy)benzoic acid (**116**), a known polymerizable LLC starting unit, to give **117**. When **117** is treated with acid in water, the protonated derivative (**117**·HX) induces an amphiphilic liquid crystal behaviour to give an unique nanoporous structure. This LLC assembly was then radically photo-crosslinked to a nanostructured solid catalyst. The phosphate, sulfate and tartrate of **117** showed the most interesting LLC behaviour.[72]



Scheme 22. Preparation of functional monomer for lyotropic liquid crystal assembly.[72]

In the organocatalytic Diels–Alder reaction of crotonaldehyde and cyclopentadiene in $MeCN/H_2O$, these LLC-derived catalysts (as its phosphate, sulfate and tartrate salts) showed a diastereo- and enantioselectivity nearly identical to the standard MacMillan catalyst (as its HCl salt), albeit with a lower overall reaction rate. The catalysts could be recovered and reused at least once, giving slightly reduced yields, but virtually identical selectivities.[72]

The immobilization of chiral imidazolidinones via functional monomers with LLC behaviour is not a polymeric immobilization in the traditional sense that we have used the term up to this point, but it does have the radical polymerization of unsaturated monomers as its foundation. In much the same manner, in 2006, a research group in Singapore reported a related approach to immobilized MacMillan imidazolidinones through polymer-coated mesocellular foams (MCF).[73] The mesocellular foams are mesoporous silicate materials with high surface area and tuneable cell-like pores that are prepared using oil-in-water microemulsion templated synthesis. The researchers prepared styrenic imidazolidinones as shown in Scheme 23.[73] Using the same tyrosine-derived imidazolidinone **108** as developed by Cozzi and co-workers some years earlier (together with the analogous derivative **119**), simple alkylation with vinylbenzyl chloride gave styrenic imidazolidinone **118**.[73]

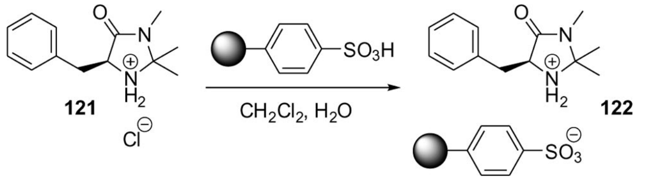


Scheme 23. Preparation of functional styrenic monomer for polymer-coating of mesocellular foams.[73]

Spherical MCF microparticles of 2–10 µm with a BET surface area of 504 m^2/g were used as the basis for the solid support. The MCF silanols were then pre-capped with TMS groups by reaction with excess HMDS at 80 °C. Styrenic imidazolidinone **118** (or the analogue prepared from **119**) together with styrene, DVB and AIBN were then wet-impregnated onto the MCF and polymerized by heating to give a uniform layer of polymer-supported catalyst onto the MCF framework.[73]

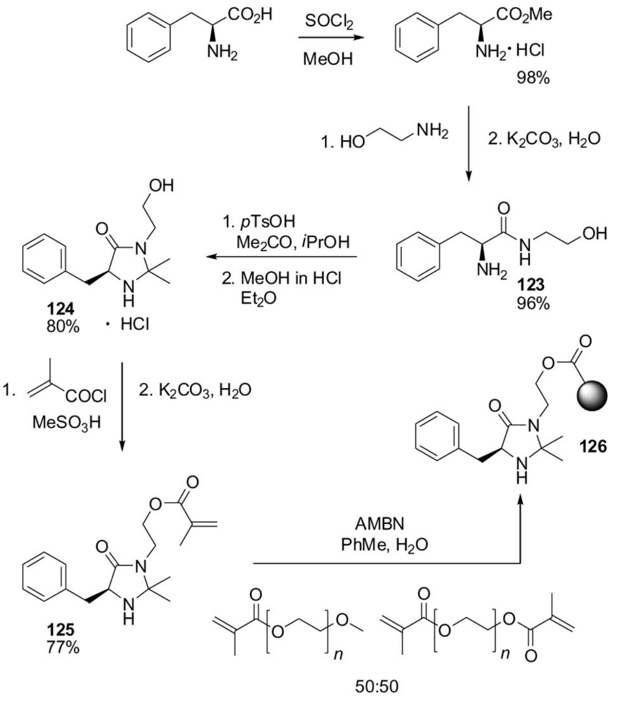
The polymer-coated MCF catalyst prepared from **119** was tested in the asymmetric Diels–Alder reaction of cinnamaldehyde and cyclopentadiene.[73] At only 5 mol-% (compared to 10 mol-% for **109** and 20 mol-% for **113**) of catalyst loading, it gave near quantitative yields (94%), considerably better than either PEG-based catalyst **109** or JandaJel™-supported catalyst **113**. The enantioselectivity was slightly lower though, but the catalyst could be recycled at least once without any appreciable loss of activity or selectivity.[73] In the same report, the direct anchoring of allylsilane imidazolidinones onto MCF was also described. As this is not a polymeric immobilization, it will not be described further, but it is important to mention that imidazolidinone **120** (Scheme 23) was reported. This building block would later be used by us to make a new polymer-supported imidazolidinone.

From 2006 until the present year, there were only minor developments on polymer-supported MacMillan catalysts.[74] In 2010, a Japanese research group reported a very simple route to a polymer-supported chiral imidazolidinone that involved a straightforward ion exchange reaction of the standard 1st generation MacMillan imidazolidinone **121** (as its HCl salt) with a standard sulfonated styrene/DVB polymer (Scheme 24).[75] The ion-bonded catalyst **122** was investigated in the asymmetric Diels–Alder reaction of cinnamaldehyde and cyclopentadiene. At 10 mol-% of catalyst loading, it provided slightly poorer enantioselectivity than the analogous solution phase catalysts, but full conversion and with the same diastereoselectivity. Again, this type of catalyst can be isolated and reused at least once with nearly unaffected results, but as is regretfully the case for most reports on supported MacMillan imidazolidinones, no more extensive testing on the recyclability is not reported. For catalyst **122**, both the hydrophilicity/hydrophobicity balance, as well as degree of crosslinking, are important for catalyst performance.[75]



Scheme 24. Preparation of polymer-supported MacMillan imidazolidinone via ion exchange reaction.[75]

We also very recently reported a polymer-supported version of the 1st generation MacMillan imidazolidinone within our acrylic copolymerization strategy for polymer-supported enamine/iminium organocatalysts (Scheme 25).[41c] As for our other polymeric immobilization procedures, we wanted to make all intermediates and finished catalysts on a preparative scale without resorting to chromatography. Unlike the majority of previous disclosures, we did not find tyrosine a very suitable substrate for large scale preparation of amides, as the phenolic functionality interfered to give rather messy syntheses that necessitated chromatographic purification at some point.[41c] Instead, we focused our attention on linkage via the amide



Scheme 25. Preparation of polymer-supported MacMillan imidazolidinone by acrylic copolymerization.[41c]

nitrogen and completely reworked the synthesis of imidazolidinone **120** (Scheme 23) from phenylalanine as the key building block (**124** in its HCl-form, Scheme 25). Treatment of L-phenylalanine methyl ester·HCl with ethanolamine under neat conditions, followed by selective extraction gave amide **123**. An azeotropic cyclization in acetone/*i*PrOH and crystallization of the product as its HCl salt in Et_2O furnished crystalline imidazolidinone **124** in an excellent overall yield on 60 g scale. As we have done in our syntheses of both immobilized proline and the Jørgensen–Hayashi catalysts, we directly and selectively acylated **124** (in $MeSO_3H$ this time) with methacryloyl chloride to acrylic imidazolidinone **125**. Using a normal suspension polymerization of **125** together with PEG-methacrylates in PhMe/H_2O (see our discussion under the section on the diarylprolinol catalysts), we obtained polymer-supported imidazolidinone **126** as practical spherical beads.[41c]

Because of the good compatibility of PEG networks with most solvents, catalyst **126** was fully operational in polar solvents, while at the same time retaining the practicality of the beaded crosslinked products. Asymmetric Diels–Alder reactions of 4-nitrocinnamaldehyde and cyclopentadiene catalyzed by **126**·HCl provided product selectivities only very slightly below the homogeneous phase catalyst **121**, but with the same chemical yield and this time on a gram scale. The catalyst **126**·CF_3CO_2H had a slightly diminished selectivity as compared to **126**·HCl, but was readily recycled once. However, in a third and fourth reaction cycle, the selectivities started to drop significantly, even though chemical yields remained high as long as the catalyst was replenished with acid cocatalyst.

In conclusion, it seems unlikely that the 1st generation MacMillan catalyst is very suitable for polymeric immobilization if only the standard justification for doing so, namely the recycling of catalyst, is used as the sole rationalization. However, as is the case for proline, the chiral imidazolidinones nonetheless remains a very useful testing ground for the development of new methodologies for polymeric immobilization. The development of synthetic machinery that can efficiently accommodate MacMillan catalysts in a cost-efficient manner, while at the same time remain compatible with a broad range of reaction solvents, can safely be expected to receive valued notice in the time to come.

That said, the polymeric immobilization of a few valuable enamine/iminium organocatalysts that to our best knowledge has not been reported, are eagerly awaited. One of them is the 5-benzyl-2-*tert*-butyl-3-methyl-4-imidazolidinones, probably the most useful of the MacMillan catalysts. In addition, the 3,5-bis(trifluoromethyl)phenyl analogues of the Jørgensen–Hayashi catalyst is certainly another. Probably the most advanced use of polymer-supported enamine/iminium organocatalysts reported to date was the 2008 disclosure of Fréchet and co-workers where asymmetric cascade reactions was catalyzed by two different organocatalysts (one diarylprolinol methyl ether catalyst and one MacMillan type catalyst) in the same reaction mixture by using soluble star polymers with highly branched non-interpenetrating catalytic cores.[77] The diarylprolinol catalyst was anchored covalently to styrene star polymers through a copolymerization strategy using a hydroxyproline-derived functional styrenic monomer, while the MacMillan catalyst was anchored by simple salt formation (much like that in Scheme 24) to a sulfonic acid star polymer.[77] Interestingly, in this advanced system, a post-modification strategy was then actually combined with a copolymerization strategy, showing how these two methods of synthetic strategy, forming the basis of this microreview, can be ingeniously combined to complement each other.

Final Conclusions

In this microreview, we have highlighted the field of polymer-supported chiral enamine and iminium organocatalysts, but primarily from the viewpoint of the synthetic strategies that have been utilized for their preparation, and not solely for their pattern of reactivity, as is more commonly done. The reason for doing this is not only that we want to emphasize the close relationship between the preparation of the supported catalyst and its actual catalytic properties, but also because we want to draw attention to the core problem for polymer-supported catalysts, namely the restrictive cost-issues. The idea that a substrate/reagent/catalyst can be anchored to a polymer matrix, and that useful chemistry can be undertaken (with results at least comparable to those obtained under homogeneous reaction conditions, given that a suitable resin is selected) is now nearly half a century old. By just continuing to link an ever-widening assortment of substrates, whether they are organocatalysts or not, onto the same limited variety of polymeric supports, will probably not take us especially far. It is true that organocatalysts offer new possibilities as the polymeric backbone do seem to integrate itself more naturally as part of the overall catalytic system. As such, a different selectivity than that of the homogeneous phase catalyst is frequently observed, and the analogy to enzymes and enzyme-like behaviour is frequently encountered. That said, the supposed selectivity is simply usually a preference for only the simplest of substrates and therefore probably not a true selectivity. In addition, as we have seen repeatedly in this microreview, the recurrent problem of an impeded catalyst activity when they are immobilized does definitely seem to continue into the foreseeable future.

We believe that research groups engaged within the area of catalyst immobilization (at least catalysts for use in organic synthesis) can roughly be divided into two main groups. The first group is mainly composed of synthetic organic chemists, most often engaging in lengthy syntheses of catalyst precursors (some of the latest disclosures operating at the <10 mg level for key intermediates),[78] anchoring them to a limited assortment of resins through a post-modification strategy, but undertaking extensive catalyst testing to underscore its value. The second group most often has a strong association to material science, regularly using the latest methodology for the creation of micro-, meso- and macroporous networks (all of which have proven useful in

© 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

organocatalysis), but often undertaking limited testing of their final products. The old mantra of interdisciplinary cooperation definitely comes to mind yet again!

As for the synthetic strategies available for polymeric immobilization, we think that in relation to usefulness and overall expenditure, it is natural to draw the following conclusions: For small and/or cheap substrates, a bottom-up strategy (usually a copolymerization strategy) is usually favoured. The incorporation of the substrate as the natural part of a macromolecular preparation that has to be undertaken anyway seems entirely natural. This is also at least in part due to the ruggedness and experimental simplicity of the free radical polymerization, the workhorse of polymer science. A copolymerization strategy is also useful if more than one catalyst is to be incorporated into the same support in a controlled manner, an issue that will probably be vital as cascade sequences become more widespread. On the other side, for large and/or high-valued substrates, a post-modification of premade polymer supports appear to be the strategy of choice as these substrates are simply not compliant with the preparation of the solid supports. Organocatalysts, in view of their simple to medium complexity and chemical robustness, are in our mind especially interesting as they to a certain extent start somewhere in the transitional area of these two overarching strategies (where no strategy can be conclusively assigned with certainty) and probably transcend well beyond it, particularly with time.

Alongside the enamine and iminium catalysts treated in this microreview, other valuable organocatalysts, such as the Cinchona-derived catalysts and the thioureas, have enjoyed a history of polymeric immobilization that stretches considerably further back in time, starting already in the 1970s for Cinchona catalysts.[79–80] Although not covered here, we believe the general trends that we have outlined can be used advantageously also for these systems.

Not only do we believe the field of polymer-supported organocatalysts will stay alive and vibrant in the years to come, but we think furthermore that it may also hold the promise to help the overall legitimacy of the field of polymer-supported substrates in general.

Acknowledgments

We kindly acknowledge the Norwegian Research Council and Birkeland Innovation (the Technology Transfer Office of the University of Oslo) for financial support for our work within polymer-supported organocatalysis, and Evonik Degussa GmbH for generously donating samples of amino acids.

---

[1] a) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; b) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.

[2] R. B. Merrifield, *J. Am. Chem. Soc.* **1963**, *85*, 2149–2154.

[3] For relevant reviews, see: a) M. Benaglia, A. Puglisi, F. Cozzi, *Chem. Rev.* **2003**, *103*, 3401–3429; b) F. Cozzi, *Adv. Synth. Catal.* **2006**, *348*, 1367–1390; c) B. Altava, I. Burguete, S. V. Luis, in: *The Power of Functional Resins in Organic Synthesis* (Eds.: J. Tulla-Puche, F. Albericio), Wiley-VCH, Weinheim, **2008**, pp. 247–308; d) M. Gruttadauria, F. Giacalone, R. Noto, *Chem. Soc. Rev.* **2008**, *37*, 1666–1688; e) M. Gruttadauria, F. Giacalone, R. Noto, *Adv. Synth. Catal.* **2009**, *351*, 33–57; f) A. F. Trindade, P. M. P. Gois, C. A. M. Afonso, *Chem. Rev.* **2009**, *109*, 418–514; g) J. M. Fraile, J. I. Garcia, J. A. Mayoral, *Chem. Rev.* **2009**, *109*, 360–417; h) D. E. Bergbreiter, J. Tian, C. Hongfa, *Chem. Rev.* **2009**, *109*, 530–582; i) *Chem. Rev.* **2007**, *107* (Issue 12), 5413–5883, special issue on organocatalysis.

[4] For an introduction, see: a) D. A. Stetsenko, in: *The Power of Functional Resins in Organic Synthesis* (Eds.: J. Tulla-Puche, F. Albericio), Wiley-VCH, Weinheim, **2008**, pp. 529–583. For oligonucleotide synthesis in general, see: b) C. B. Reese, *Org. Biomol. Chem.* **2005**, *3*, 3851–3868.

[5] K. C. Nicolaou, S. A. Snyder, *Classics in Total Synthesis II*, Wiley-VCH, Weinheim, **2003**, pp. 594.

[6] For an historical account, see: a) D. Hudson, *J. Comb. Chem.* **1999**, *1*, 333–360; b) D. Hudson, *J. Comb. Chem.* **1999**, *1*, 403–457. For a starting point and up-to-date comprehensive review of polymer supports for polymeric immobilization in general, see: c) J. Lu, P. H. Toy, *Chem. Rev.* **2009**, *109*, 815–838 and references cited therein. For soluble polymer supports, see also: d) D. J. Gravert, K. D. Janda, *Chem. Rev.* **1997**, *97*, 489–509; e) P. H. Toy, K. D. Janda, *Acc. Chem. Res.* **2000**, *33*, 546–554; f) T. J. Dickerson, N. N. Reed, K. D. Janda, *Chem. Rev.* **2002**, *102*, 3325–3344; g) D. E. Bergbreiter, *Chem. Rev.* **2002**, *102*, 3345–3384; h) D. E. Bergbreiter, J. Tian, C. Hongfa, *Chem. Rev.* **2009**, *109*, 530–582. For polystyrene in particular, see: i) C. A. McNamara, M. J. Dixon, M. Bradley, *Chem. Rev.* **2002**, *102*, 3275–3300. For ROMPgels, see: j) A. G. M. Barrett, B. T. Hopkins, J. Köbberling, *Chem. Rev.* **2002**, *102*, 3301–3324.

[7] P. H. Toy, K. D. Janda, *Tetrahedron Lett.* **1999**, *40*, 6329–6332.

[8] a) M. Renil, R. Nagaraj, V. N. R. Pillai, *Tetrahedron* **1994**, *50*, 6681–6688; b) M. Renil, V. N. R. Pillai, *J. Appl. Polym. Sci.* **1996**, *61*, 1585–1594.

[9] a) H. Becker, H. W. Lucas, J. Maul, V. N. R. Pillai, H. Anzinger, M. Mutter, *Makromol. Chem. Rapid Commun.* **1982**, *3*, 217–223; b) H. Hellermann, H. W. Lucas, J. Maul, V. N. R. Pillai, M. Mutter, *Makromol. Chem.* **1983**, *184*, 2603–2617.

[10] a) S. Zalipsky, F. Albericio, G. Barany, in: *Peptides: Structure and Functions, Proceedings of the Ninth American Peptide Symposium* (Eds.: C. M. Deber, V. J. Hruby, K. D. Kopple), Pierce, Rockford, Illinois, **1985**, pp. 257–260; b) S. Zalipksy, J. L. Chang, F. Albericio, G. Barany, *React. Polym.* **1994**, *22*, 243–258; c) S. A. Kates, B. F. McGuinnes, C. Blackburn, G. W. Griffin, N. A. Solé, G. Barany, F. Albericio, *Biopolymers* **1999**, *47*, 365–380.

[11] a) E. Bayer, B. Hemmasi, K. Albert, W. Rapp, M. Dengler, in: *Peptides: Structure and Function, Proceedings of the Eighth American Peptide Symposium* (Eds.: V. J. Hruby, D. H. Rich), Pierce, Rockford, Illinois, **1983**, pp. 87–90; b) W. Rapp, in: *Combinatorial Peptide and Nonpeptide Libraries, A Handbook* (Ed.: G. Jung), Wiley-VCH, Weinheim, **1996**, pp. 425–464.

[12] J. H. Adams, R. M. Cook, D. Hudson, V. Jammalamadaka, M. H. Lyttle, M. F. Songster, *J. Org. Chem.* **1998**, *63*, 3706–3716.

[13] O. W. Gooding, S. Baudart, T. L. Deegan, K. Heisler, J. W. Labadie, W. S. Newcomb, J. A. Porco, P. van Eikeren, *J. Comb. Chem.* **1999**, *1*, 113–122.

[14] B.-D. Park, H.-I. Lee, S.-J. Ryoo, Y.-S. Lee, *Tetrahedron Lett.* **1997**, *38*, 591–594.

[15] M. Grøtli, C. H. Gotfredsen, J. Rademann, J. Buchhardt, A. J. Clark, J. Ø. Duus, M. Meldal, *J. Comb. Chem.* **2000**, *2*, 108–119.

[16] a) E. Atherton, D. L. J. Clive, R. C. Sheppard, *J. Am. Chem. Soc.* **1975**, *97*, 6584–6585; b) E. Atherton, D. L. J. Clive, R. C. Sheppard, *J. Chem. Soc. Perkin Trans. 1* **1981**, 529–537.

[17] For a thorough distinction between suspension, emulsion and dispersion polymerization, see: R. Arshady, *Colloid Polym. Sci.* **1992**, *270*, 717–732.

© 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[18] R. Letsinger, L. Kornet, *J. Am. Chem. Soc.* **1963**, *85*, 3045–3046.

[19] a) M. Meldal, *Tetrahedron Lett.* **1992**, *33*, 3077–3080; b) M. Renil, M. Meldal, *Tetrahedron Lett.* **1995**, *36*, 4647–4650; c) F.-I. Auzanneau, M. Meldal, K. Bock, *J. Pept. Sci.* **1995**, *1*, 31–44.

[20] M. Kempe, G. Barany, *J. Am. Chem. Soc.* **1996**, *118*, 7083–7093.

[21] a) M. Renil, M. Meldal, *Tetrahedron Lett.* **1996**, *37*, 6185–6188; b) J. Buchardt, M. Meldal, *Tetrahedron Lett.* **1998**, *39*, 8695–8698.

[22] T. Groth, M. Grøtli, W. D. Lubell, L. P. Miranda, M. Meldal, *J. Chem. Soc. Perkin Trans. 1* **2000**, 4258–4264.

[23] C. W. Tornøe, M. Meldal, *Tetrahedron Lett.* **2002**, *43*, 6409–6411.

[24] a) J. Rademann, M. Grøtli, M. Meldal, K. Bock, *J. Am. Chem. Soc.* **1999**, *121*, 5459–5466; b) L. P. Miranda, W. D. Lubell, K. M. Halkes, T. Groth, M. Grøtli, J. Rademann, C. H. Gotfredsen, M. Meldal, *J. Comb. Chem.* **2002**, *4*, 523–529.

[25] a) F. García-Martín, M. Quintanar-Audelo, Y. García-Ramos, L. J. Cruz, C. Gravel, R. Furic, S. Côté, J. Tulla-Puche, F. Albericio, *J. Comb. Chem.* **2006**, *8*, 213–220; b) S. Côté (Inventor), WO2005/012277, **2005**. This patent application also contains very many useful patent references for the polymeric supports covered in this review.

[26] For a discussion, see: A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, **2005**, pp. 1–8. See also reference 69.

[27] a) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496–497; b) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615–1621.

[28] K. Kondo, T. Yamano, K. Takemoto, *Makromol. Chem.* **1985**, *186*, 1781–1785.

[29] a) M. Benaglia, G. Celentano, F. Cozzi, *Adv. Synth. Catal.* **2001**, *343*, 171–173; b) M. Benaglia, M. Cinquini, F. Cozzi, A. Puglisi, G. Celentano, *Adv. Synth. Catal.* **2002**, *344*, 533–542; c) M. Benaglia, M. Cinquini, F. Cozzi, A. Puglisi, G. Celentano, *J. Mol. Catal. A* **2003**, *204–205*, 157–163.

[30] a) L. Gu, Y. Wu, Y. Zhang, G. Zhao, *J. Mol. Catal. A* **2007**, *263*, 186–194; b) Y.-X. Liu, Y.-N. Sun, H.-H. Tan, W. Liu, J.-C. Tao, *Tetrahedron: Asymmetry* **2007**, *18*, 2649–2656; c) Y.-X. Liu, Y.-N. Sun, H.-H. Tan, J.-C. Tao, *Catal. Lett.* **2008**, *120*, 281–287.

[31] a) Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, M. Shoji, *Angew. Chem. Int. Ed.* **2006**, *45*, 958–961; b) Y. Hayashi, S. Aratake, T. Okano, J. Takahashi, T. Sumiya, M. Shoji, *Angew. Chem. Int. Ed.* **2006**, *45*, 5527–5529; c) N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 734–735. Numerous publications have followed later on.

[32] a) A. P. Brogan, T. J. Dickerson, K. D. Janda, *Angew. Chem. Int. Ed.* **2006**, *45*, 8100–8102; b) Y. Hayashi, *Angew. Chem. Int. Ed.* **2006**, *45*, 8103–8104; c) D. G. Blackmond, A. Armstrong, V. Coombe, A. Wells, *Angew. Chem. Int. Ed.* **2007**, *46*, 3798–3800; d) N. Zotova, A. Franzke, A. Armstrong, D. G. Blackmond, *J. Am. Chem. Soc.* **2007**, *129*, 15100–15101.

[33] a) D. Font, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2006**, *8*, 4653–4655; b) D. Font, A. Bastero, S. Sayalero, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2007**, *9*, 1943–1946; c) D. Font, S. Sayalero, A. Bastero, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2008**, *10*, 337–340; d) E. Alza, C. Rodríguez-Escrich, S. Sayalero, A. Bastero, M. A. Pericàs, *Chem. Eur. J.* **2009**, *15*, 10167–10172.

[34] a) R. Huisgen, *Angew. Chem.* **1963**, *75*, 604–637; b) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057–3064; c) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599. For a comprehensive review, see: d) M. Meldal, C. W. Tornøe, *Chem. Rev.* **2008**, *108*, 2952–3015.

[35] a) F. Giacalone, M. Gruttadauria, A. M. Marculescu, R. Noto, *Tetrahedron Lett.* **2007**, *48*, 255–259; b) M. Gruttadauria, F. Giacalone, A. M. Marculescu, P. L. Meo, S. Riela, R. Noto, *Eur. J. Org. Chem.* **2007**, 4688–4698; c) F. Giacalone, M. Gruttadauria, A. M. Marculescu, F. D'Anna, R. Noto, *Catal. Commun.* **2008**, *9*, 1477–1481.

[36] For recent reviews on the thiol–ene coupling, see: a) A. Dondoni, *Angew. Chem. Int. Ed.* **2008**, *47*, 8995–8997; b) C. E. Hoyle, C. N. Bowman, *Angew. Chem. Int. Ed.* **2010**, *49*, 1540–1573.

[37] Personal communication with the authors.

[38] a) T. Kehat, M. Portnoy, *Chem. Commun.* **2007**, 2823–2825; b) K. Goren, T. Kehat, M. Portnoy, *Adv. Synth. Catal.* **2009**, *351*, 59–65.

[39] a) G. Szöellősi, G. London, L. Baláspiri, C. Somlai, M. Bartók, *Chirality* **2003**, *15(Suppl.)*, S90–S96; b) M. R. M. Andreae, A. P. Davis, *Tetrahedron: Asymmetry* **2005**, *16*, 2487–2492; c) K. Akagawa, S. Sakamoto, K. Kudo, *Tetrahedron Lett.* **2005**, *46*, 8185–8187; d) J. D. Revell, D. Gantenbein, P. Krattiger, H. Wennemers, *Biopolymers* **2006**, *84*, 105–113; e) J. Yan, L. Wang, *Synthesis* **2008**, 2065–2072; f) R. D. Carpenter, J. C. Fettinger, K. S. Lam, M. J. Kurth, *Angew. Chem. Int. Ed.* **2008**, *47*, 6407–6410.

[40] Neal G. Anderson, in: *The art of drug synthesis* (Eds.: D. S. Johnson, J. J. Lie), Wiley, USA, **2007**, pp. 22.

[41] a) T. E. Kristensen, F. K. Hansen, T. Hansen, *Eur. J. Org. Chem.* **2009**, 387–395; b) T. E. Kristensen, K. Vestli, K. A. Fredriksen, F. K. Hansen, T. Hansen, *Org. Lett.* **2009**, *11*, 2968–2971; c) T. E. Kristensen, K. Vestli, M. G. Jakobsen, F. K. Hansen, T. Hansen, *J. Org. Chem.* **2010**, *75*, 1620–1629.

[42] a) M. Wilchek, A. Patchornik, *J. Org. Chem.* **1964**, *29*, 1629–1630; b) T. Kawasaki, T. Komai, *Polym. J.* **1983**, *15*, 743–751; c) W. Sakami, G. Toennies, *J. Biol. Chem.* **1942**, *144*, 203–217. This early publication was not referenced in our own paper (ref. 41a) as we have first become aware of it at a later time.

[43] For side-chain (meth)acrylic analogues of amino acids, see: a) H. Morawetz, E. J. Sammak, *J. Phys. Chem.* **1957**, *61*, 1357–1359; b) Société Pluripharm, FR 2035789, **1971**; c) K. Takahashi, K. Mimura, H. Tada (Inventors), Mitsubishi Rayon Co., JP 48090984, **1973**; d) D. Zbaida, I. Weissbuch, E. Shavit-Gati, L. Addadi, L. Leiserowitz, M. Lahav, *Reactive Polymers* **1987**, *6*, 241–253; e) K. Shiraishi, T. Ohnishi, K. Sugiyama, K. Okada, O. Matsuo, *Chem. Lett.* **1997**, 863–864; f) K. Shiraishi, T. Ohnishi, K. Sugiyama, *Macromol. Chem. Phys.* **1998**, *199*, 2023–2028; g) K. Shiraishi, M. Kohta, K. Sugiyama, *Chem. Lett.* **2004**, 646–647; h) S. Nagaoka, A. Shundo, T. Satoh, K. Nagira, R. Kishi, K. Ueno, K. Iio, H. Ihara, *Synth. Commun.* **2005**, *35*, 2529–2534. For more information on these types of derivatives, see ref. [41a].

[44] E. G. Doyagüez, F. Parra, G. Corrales, A. Fernández-Mayoralas, A. Gallardo, *Polymer* **2009**, *50*, 4438–4446.

[45] a) D. S. Robinson, J. P. Greenstein, *J. Biol. Chem.* **1952**, *195*, 383–387; b) P. Dalla Croce, C. La Rosa, *Tetrahedron: Asymmetry* **2002**, *13*, 197–201; c) G. L. Baker, S. J. Fritschel, J. R. Stille, J. K. Stille, *J. Org. Chem.* **1981**, *46*, 2954–2960.

[46] For a recent review on ATRP, see: K. Matyaszewski, N. V. Tsarevsky, *Nat. Chem.* **2009**, *1*, 276–288.

[47] For a useful treatment of both RAFT, ATRP, NMP and other methods for controlled radical polymerization, see: a) G. Moad, D. H. Solomon, *The Chemistry of Radical Polymerization*, 2nd ed., Elsevier, Amsterdam, **2006**. For reviews of NMP, see: b) C. J. Hawker, A. W. Bosman, E. Harth, *Chem. Rev.* **2001**, *101*, 3661–3688; c) A. Studer, T. Schulte, *Chem. Rec.* **2005**, *5*, 27–35; d) V. Sciannamea, R. Jérôme, C. Detrembleur, *Chem. Rev.* **2008**, *108*, 1104–1126. For reviews of RAFT, see: e) G. Moad, E. Rizzardo, S. H. Thang, *Aust. J. Chem.* **2005**, *58*, 379–410; f) G. Moad, E. Rizzardo, S. H. Thang, *Aust. J. Chem.* **2006**, *59*, 669–692; g) G. Moad, E. Rizzardo, S. H. Thang, *Aust. J. Chem.* **2009**, *62*, 1402–1472.

[48] a) Z. Tang, F. Jiang, L.-T. Yu, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, Y.-D. Wu, *J. Am. Chem. Soc.* **2003**, *125*, 5262–5263; b) Z. Tang, F. Jiang, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-

Z. Jiang, Y.-D. Wu, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5755–5760; c) Z. Tang, Z.-H. Yang, X.-H. Chen, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, *J. Am. Chem. Soc.* **2005**, *127*, 9286–9289.

[49] For a recent review of catalysts for organocatalytic aldol reactions, see: S. G. Zlotin, A. S. Kucherenko, I. P. Beletskaya, *Russ. Chem. Rev.* **2009**, *78*, 737–784.

[50] a) M. Raj, V. Maya, S. K. Ginotra, V. K. Singh, *Org. Lett.* **2006**, *8*, 4097–4099; b) V. Maya, M. Raj, V. K. Singh, *Org. Lett.* **2007**, *9*, 2593–2595; c) M. Raj, V. Maya, V. K. Singh, *J. Org. Chem.* **2009**, *74*, 4289–4297.

[51] a) M. Gruttadauria, F. Giacalone, A. M. Marculescu, R. Noto, *Adv. Synth. Catal.* **2008**, *350*, 1397–1405; b) M. Gruttadauria, F. Giacalone, A. M. Marculescu, A. M. P. Salvo, R. Noto, *ARKIVOC* **2009**, *8*, 5–15; c) M. Gruttadauria, A. M. P. Salvo, F. Giacalone, P. Agrigento, R. Noto, *Eur. J. Org. Chem.* **2009**, 5437–5444.

[52] a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 794–797; b) J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296–18304.

[53] Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212–4215.

[54] M. C. Varela, S. M. Dixon, K. S. Lam, N. E. Schore, *Tetrahedron* **2008**, *64*, 10087–10090.

[55] C. Röben, M. Stasiak, B. Janza, A. Greiner, J. H. Wendorff, A. Studer, *Synthesis* **2008**, 2163–2168.

[56] E. Alza, M. A. Pericàs, *Adv. Synth. Catal.* **2009**, *351*, 3051–3056.

[57] I. Mager, K. Zeitler, *Org. Lett.* **2010**, *12*, 1480–1483.

[58] a) E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553; b) E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen, V. K. Singh, *J. Am. Chem. Soc.* **1987**, *109*, 7925–7926.

[59] For a review on electrospinning, see: A. Greiner, J. H. Wendorff, *Angew. Chem. Int. Ed.* **2007**, *46*, 5670–5703.

[60] M. Stasiak, C. Röben, N. Rosenberger, F. Schleth, A. Studer, A. Greiner, J. H. Wendorff, *Polymer* **2007**, *48*, 5208–5218.

[61] a) M. D. Price, J. K. Sui, M. J. Kurth, N. E. Schore, *J. Org. Chem.* **2002**, *67*, 8086–8089; b) M. C. Varela, S. M. Dixon, M. D. Price, J. E. Merit, P. E. Berget, S. Shiraki, M. J. Kurth, N. E. Schore, *Tetrahedron* **2007**, *63*, 3334–3339.

[62] a) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861–863; b) D. Enders, M. R. M. Hüttl, G. Raabe, J. W. Bats, *Adv. Synth. Catal.* **2008**, *350*, 267–279; c) C. B. Shinisha, R. B. Sunoj, *Org. Biomol. Chem.* **2008**, *6*, 3921–3929. For a recent review of organocatalytic cascade reactions, see: d) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167–178.

[63] S. Özçubukçu, E. Ozkal, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2009**, *11*, 4680–4683.

[64] a) J. Kapfhammer, A. Matthes, *Hoppe-Seyler's Z. Physiol. Chem.* **1933**, *223*, 43–52; b) E. J. Corey, S. Shibata, R. K. Bakshi, *J. Org. Chem.* **1988**, *53*, 2861–2863; c) J. V. B. Kanth, M. Periasamy, *Tetrahedron* **1993**, *49*, 5127–5132; d) D. J. Mathre, T. K. Jones, L. C. Xavier, T. J. Blacklock, R. A. Reamer, J. J. Mohan, E. T. T. Jones, K. Hoogsteen, M. W. Baum, E. J. J. Grabowski, *J. Org. Chem.* **1991**, *56*, 751–762; e) D. Enders, H. Kipphardt, P. Gerdes, L. J. Breña-Valle, V. Bhushan, *Bull. Soc. Chim. Belg.* **1988**, *97*, 691–704; f) S. T. Kerrick, P. Beak, *J. Am. Chem. Soc.* **1991**, *113*, 9708–9710; g) S. Itsuno, K. Watanabe, T. Koizumi, K. Ito, *React. Polym.* **1995**, *24*, 219–227.

[65] a) H. Nakano, K. Takahashi, Y. Okuyama, C. Senoo, N. Tsugawa, Y. Suzuki, R. Fujita, K. Sasaki, C. Kabuto, *J. Org. Chem.* **2004**, *69*, 7092–7100; b) Y. Li, X. Liu, Y. Yang, G. Zhao, *J. Org. Chem.* **2007**, *72*, 288–291.

[66] A. Lattanzi, *Chem. Commun.* **2009**, 1452–1463.

[67] a) E. Alza, X. C. Cambeiro, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2007**, *9*, 3717–3720; b) T. Miao, L. Wang, *Tetrahedron Lett.* **2008**, *49*, 2173–2176; c) Y. Chuan, G. Chen, Y. Peng, *Tetrahedron Lett.* **2009**, *50*, 3054–3058.

[68] a) S. Itsuno, K. Kamahori, K. Watanabe, T. Koizumi, K. Ito, *Tetrahedron: Asymmetry* **1994**, *5*, 523–526; b) M. Felder, G. Giffels, C. Wandrey, *Tetrahedron: Asymmetry* **1997**, *8*, 1975–1977; c) S. Degni, C.-E. Wilén, R. Leino, *Org. Lett.* **2001**, *3*, 2551–2554; d) J. Wöltinger, A. S. Bommarius, K. Drauz, C. Wandrey, *Org. Process Res. Dev.* **2001**, *5*, 241–248; e) R. J. Kell, P. Hodge, P. Snedden, D. Watson, *Org. Biomol. Chem.* **2003**, *1*, 3238–3243.

[69] For historical accounts on the origins of organocatalysis, see: a) D. W. C. MacMillan, *Nature* **2008**, *455*, 304–308; b) C. F. Barbas III, *Angew. Chem. Int. Ed.* **2008**, *47*, 42–47; c) B. List, *Angew. Chem. Int. Ed.* **2010**, *49*, 1730–1734.

[70] a) M. Benaglia, G. Celentano, M. Cinquini, A. Puglisi, F. Cozzi, *Adv. Synth. Catal.* **2002**, *344*, 149–152; b) A. Puglisi, M. Benaglia, M. Cinquini, F. Cozzi, G. Celentano, *Eur. J. Org. Chem.* **2004**, 567–573.

[71] S. A. Selkälä, J. Tois, P. M. Pihko, A. M. P. Koskinen, *Adv. Synth. Catal.* **2002**, *344*, 941–945.

[72] C. S. Pecinovsky, G. D. Nicodemus, D. L. Gin, *Chem. Mater.* **2005**, *17*, 4889–4891.

[73] Y. Zhang, L. Zhao, S. S. Lee, J. Y. Ying, *Adv. Synth. Catal.* **2006**, *348*, 2027–2032.

[74] B. P. Mason, A. R. Bogdan, A. Goswami, D. T. McQuade, *Org. Lett.* **2007**, *9*, 3449–3451.

[75] N. Haraguchi, Y. Takemura, S. Itsuno, *Tetrahedron Lett.* **2010**, *51*, 1205–1208.

[76] R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, *Chem. Eur. J.* **2000**, *6*, 133–138.

[77] Y. Chi, S. T. Scroggins, J. M. J. Fréchet, *J. Am. Chem. Soc.* **2008**, *130*, 6322–6323.

[78] For this recent disclosure on the first polymer-supported chiral Brønsted acid organocatalysts, see: M. Rueping, E. Sugiono, A. Steck, T. Theissmann, *Adv. Synth. Catal.* **2010**, *352*, 281–287.

[79] For polymer-supported Cinchona derivatives, see: a) K. Yamauchi, M. Kinoshita, M. Imoto, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3186–3187; b) T. Yamashita, H. Yasueda, Y. Miyauchi, N. Nakamura, *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1532–1534; c) K. Hermann, H. Wynberg, *Helv. Chim. Acta* **1977**, *60*, 2208–2212; d) N. Kobayashi, K. Iwai, *J. Am. Chem. Soc.* **1978**, *100*, 7071–7072; e) N. Kobayashi, K. Iwai, *Tetrahedron Lett.* **1980**, *21*, 2167–2170; f) N. Kobayashi, K. Iwai, *J. Polym. Sci. Polym. Chem. Ed.* **1980**, *18*, 923–932; g) N. Kobayashi, K. Iwai, *Macromolecules* **1980**, *13*, 31–34; h) N. Kobayashi, K. Iwai, *Polym. J.* **1981**, *13*, 263–271; i) N. Kobayashi, K. Iwai, *Makromol. Chem. Rapid Commun.* **1981**, *2*, 105–108; j) N. Kobayashi, K. Iwai, *J. Polym. Sci. Polym. Chem. Ed.* **1982**, *20*, 85–90; k) P. Hodge, E. Khoshdel, J. Waterhouse, *J. Chem. Soc. Perkin Trans. 1* **1983**, 2205–2209; l) N. Kobayashi, *Brit. Polym. J.* **1984**, *16*, 205–211; m) P. Hodge, E. Khoshdel, J. Waterhouse, J. M. J. Fréchet, *J. Chem. Soc. Perkin Trans. 1* **1985**, 2327–2331; n) M. Inagaki, J. Hiratake, Y. Yamamoto, J. Oda, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4121–4126; o) A. Sera, K. Takagi, H. Katayama, H. Yamada, *J. Org. Chem.* **1988**, *53*, 1157–1161; p) L. Canali, C. E. Song, D. C. Sherrington, *Tetrahedron: Asymmetry* **1998**, *9*, 1029–1034; q) R. Alvarez, M.-A. Hourdin, C. Cavé, J. d'Angelo, P. Chaminade, *Tetrahedron Lett.* **1999**, *40*, 7091–7094; r) Z. Zhengpu, W. Yongmer, W. Zhen, P. Hodge, *React. Funct. Polym.* **1999**, *41*, 37–43; s) R. Chinchilla, P. Mazón, C. Nájera, *Tetrahedron: Asymmetry* **2000**, *11*, 3277–3281; t) A. M. Hafez, A. E. Taggi, T. Dudding, T. Lectka, *J. Am. Chem. Soc.* **2001**, *123*, 10853–10859; u) V. Athawale, N. Manjrekar, *Tetrahedron Lett.* **2001**, *42*, 4541–4543; v) B. Thierry, J.-C. Plaquevent, D. Cahard, *Tetrahedron: Asymmetry* **2001**, *12*, 983–986; w) B. Thierry, T. Perrard, C. Audouard, J.-C. Plaquevent, D. Cahard, *Synthesis* **2001**, 1742–1746; x) B. Thierry, J.-C. Plaquevent, D. Cahard, *Tetrahedron: Asymmetry* **2003**, *14*, 1671–1677; y) T. Danelli, R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, G. Tocco, *Tetrahedron: Asymmetry* **2003**, *14*, 461–467; z) S. H.

Youk, S. H. Oh, H. S. Rho, J. E. Lee, J. W. Lee, C. E. Song, *Chem. Commun.* **2009**, 2220–2222.

[80] For polymer-supported thioureas, see: a) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902; b) M. S. Sigman, P. Vachal, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2000**, *39*, 1279–1281.

Received: March 8, 2010
Published Online: May 7, 2010