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A General Approach for Preparation of Polymer-Supported Chiral Organocatalysts via Acrylic Copolymerization

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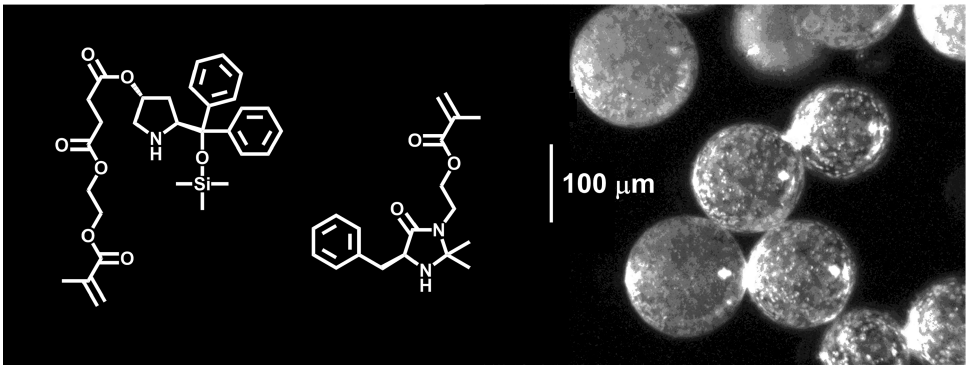

Polymer-supported chiral organocatalysts, as well as most other forms of immobilized catalysts, are traditionally prepared by a postmodification approach where modified catalyst precursors are anchored onto prefabricated polymer beads. Herein, we report an alternative and more scalable approach where polymer-supported chiral enamine and iminium organocatalysts are prepared in a bottom-up fashion where methacrylic functional monomers are prepared in an entirely nonchromatographic manner and subsequently copolymerized with suitable comonomers to give cross-linked polymer beads. All syntheses have been conducted on multigram scale for all intermediates and finished polymer products, and the catalysts have proven successful in reactions taking place in solvents spanning a wide range of solvent polarity. While polymer-supported proline and prolineamides generally demonstrated excellent results and recycling robustness in asymmetric aldol reactions of ketones and benzaldehydes, the simplest type of Jørgensen/Hayashi diarylprolinol TMS-ether showed excellent selectivity, but rather sluggish reactivity in the Enders-type asymmetric cascade. The polymer-supported version of the first-generation MacMillan imidazolidinone had a pattern of reactivity very similar to that of the monomeric catalyst, but is too unstable to allow recycling.

Introduction

Polymer-supported organocatalysts are valuable materials for conducting catalytic asymmetric transformations under simple and environmentally benign conditions.[1] Because organocatalysts typically operate via enzyme-mimetic strategies, a polymer scaffold can to a certain extent be considered to be a peptide-backbone substitute that can influence the selectivity of the catalysts, often in a highly beneficial manner.[1] In this way, organocatalysts hold promise for polymeric immobilization as the traditional benefits for catalyst immobilization (ease of separation, reuse of catalyst) are complemented with the additional benefit of a modulated reactivity that in some cases may prove valuable.[1] Unfortunately, widespread use of polymer-supported versions of any catalyst tends to be hampered by the considerable costs usually associated with such polymeric immobilization, as has also been the case for organocatalysis.

Traditionally, polymer-supported organocatalysts (as well as most other immobilized catalysts) are prepared by anchoring modified catalyst precursors onto prefabricated polymer supports, a strategy originally developed for

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solid-phase peptide synthesis in the 1960s and subsequently adopted for immobilization of reagents, scavengers, and catalysts.[2,3] However, it is important to keep in mind that this strategy was developed for the immobilization of high-value substrates (peptides) during a lengthy synthetic sequence that (often) involved rather harsh reaction conditions, and as such required inert polymer scaffolds.[2,3] On the other hand, many organocatalysts can be considered rather low value substrates, and they are in an especially fortunate position because the mild reaction conditions under which they operate make an especially broad range of polymeric materials useful for their immobilization. In such cases, it can make sense to undertake the polymeric immobilization in a bottom-up fashion where polymer products are prepared via a copolymerization strategy, implying that functional monomers are copolymerized with suitable comonomers in analogy to industrial procedures for preparation of more simple functionalized resins. The excellent chemical tolerance of free radical polymerization provides useful leverage for accommodation of a very broad range of functionalities in the catalyst monomers, and as such can be advantageously integrated into the overall synthetic sequence. As such, a traditional postmodification strategy can perhaps be considered a first-generation approach with high convenience, but low cost-efficiency, while a copolymerization strategy can be considered a second-generation approach in higher need of interdisciplinary research, but one that in the end achieves a better overall cost-efficiency and versatility. As a simple example, this is mirrored in the preparation of the Merrifield resin, which was previously prepared by postmodification (chloromethylation) of polystyrene beads, but is currently prepared by copolymerization of functional monomer (4-vinylbenzyl chloride) with comonomers (styrene/divinylbenzene).

Herein, we report the polymeric immobilization of prolines, prolineamides, the simplest Jørgensen/Hayashi diarylprolinol TMS-ether, and the first-generation MacMillan imidazolidinone through such a copolymerization strategy, the most generalized system for polymeric immobilization of chiral enamine/iminium organocatalysts reported to date. The procedures have an advantageous scalability, both through the use of only affordable feedstock acrylics and the avoidance of any chromatographic purification. In addition, control of catalyst loading is improved as compared to the traditional postmodification scheme, and the strategy can be easily adjusted for preparation of polymer supports useful for reactions taking place in both nonpolar as well as polar solvents like aqueous systems, lower alcohols, and MeCN, something of crucial importance within asymmetric organocatalysis.

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

(2) Merrifield, R. B. *J. Am. Chem. Soc*. **1963**, *85*, 2149.

(3) For an introduction to the use of functional resins in organic synthesis, see: *The Power of Functional Resins in Organic Synthesis*; Tulla-Puche, J., Albericio, F., Eds.; Wiley-VCH: Weinheim, Germany, 2008.

Results and Discussion

Polymer-Supported Prolines. The immobilization of proline within a postmodification scheme, using the hydroxyl group in position 4 of *trans*-4-hydroxy-L-proline and either linear polyethyleneglycol/polystyrene or cross-linked beaded polystyrene-based supports, has been disclosed on several occasions since 2001.[4,5] Especially hydroxyproline anchored by means of a linker onto the hydrophobic Merrifield resin via the Huisgen−Meldal−Sharpless cycloaddition or the thiol−ene coupling has proven to be a very efficient catalyst for the asymmetric aldol reactions of ketones and benzaldehydes, taking place under neat conditions with water as additive.[5b−h] These systems resemble and work in close parallel to the amphiphilic proline derivatives that for the first time proved the efficiency of proline under aqueous reaction conditions,[6] which can readily outperform proline itself.[5b−h] These cross-linked polymer systems also seem to offer an advantageous recyclability when compared to proline immobilized on linear supports (which are homogenously soluble in the reaction medium).[1d,4,5b−5h] The excellent performance of these systems prompted us to investigate the polymeric immobilization of proline in a more efficient manner, one that would retain the excellent performance, but that could be scaled up to work on preparatory scale.[7]

To avoid complicated synthetic procedures where doubly carbamate-protected hydroxyproline was involved, we developed the selective *O*-acylation of hydroxyproline in CF_3CO_2H, a quite general method for the direct preparation of *O*-acyl derivatives of hydroxyproline.[7a] This procedure was founded upon the fragmented knowledge that existed in the literature on acidic activation of hydroxyproline,[8] and has been reported by us earlier.[7a] With it, we could, in addition to preparing amphiphilic proline derivatives useful as catalysts by themselves, also prepare acrylic proline derivatives **2**−**4** (Scheme 1).[7] Together with the corresponding and more hydrophobic Boc-derivatives **5** and **6**

(4) For linear supports, see: (a) Benaglia, M.; Celentano, G.; Cozzi, F. *Adv. Synth. Catal*. **2001**, *343*, 171. (b) Benaglia, M.; Cinquini, M.; Cozzi, F.; Puglisi, A.; Celentano, G. *Adv. Synth. Catal*. **2002**, *344*, 533. (c) Benaglia, M.; Cinquini, M.; Cozzi, F.; Puglisi, A.; Celentano, G. *J. Mol. Catal. A* **2003**, *204*−*205*, 157. (d) Gu, L.; Wu, Y.; Zhang, Y.; Zhao, G. *J. Mol. Catal. A* **2007**, *263*, 186. (e) Liu, Y.-X.; Sun, Y.-N.; Tan, H.-H.; Liu, W.; Tao, J.-C. *Tetrahedron: Asymmetry* **2007**, *18*, 2649. (f) Liu, Y.-X.; Sun, Y.-N.; Tan, H.-H.; Tao, J.-C. *Catal. Lett*. **2008**, *120*, 281.

(5) For cross-linked supports, see: (a) Kondo, K.; Yamano, T.; Takemoto, K. *Makromol. Chem*. **1985**, *186*, 1781. (b) Font, D.; Jimeno, C.; Pericàs, M. A. *Org. Lett*. **2006**, *8*, 4653. (c) Font, D.; Bastero, A.; Sayalero, S.; Jimeno, C.; Pericàs, M. A. *Org. Lett*. **2007**, *9*, 1943. (d) Font, D.; Sayalero, S.; Bastero, A.; Jimeno, C.; Pericàs, M. A. *Org. Lett*. **2008**, *10*, 337. (e) Alza, E.; Rodríguez-Escrich, C.; Sayalero, S.; Bastero, A.; Pericàs, M. A. *Chem.—Eur. J*. **2009**, *15*, 10167. (f) Giacalone, F.; Gruttadauria, M.; Marculescu, A. M.; Noto, R. *Tetrahedron Lett*. **2007**, *48*, 255. (g) Gruttadauria, M.; Giacalone, F.; Marculescu, A. M.; Meo, P. L.; Riela, S.; Noto, R. *Eur. J. Org. Chem*. **2007**, 4688. (h) Giacalone, F.; Gruttadauria, M.; Marculescu, A. M.; D' Anna, F.; Noto, R. *Catal. Commun*. **2008**, *9*, 1477. (i) Kehat, T.; Portnoy, M. *Chem. Commun*. **2007**, 2823.

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

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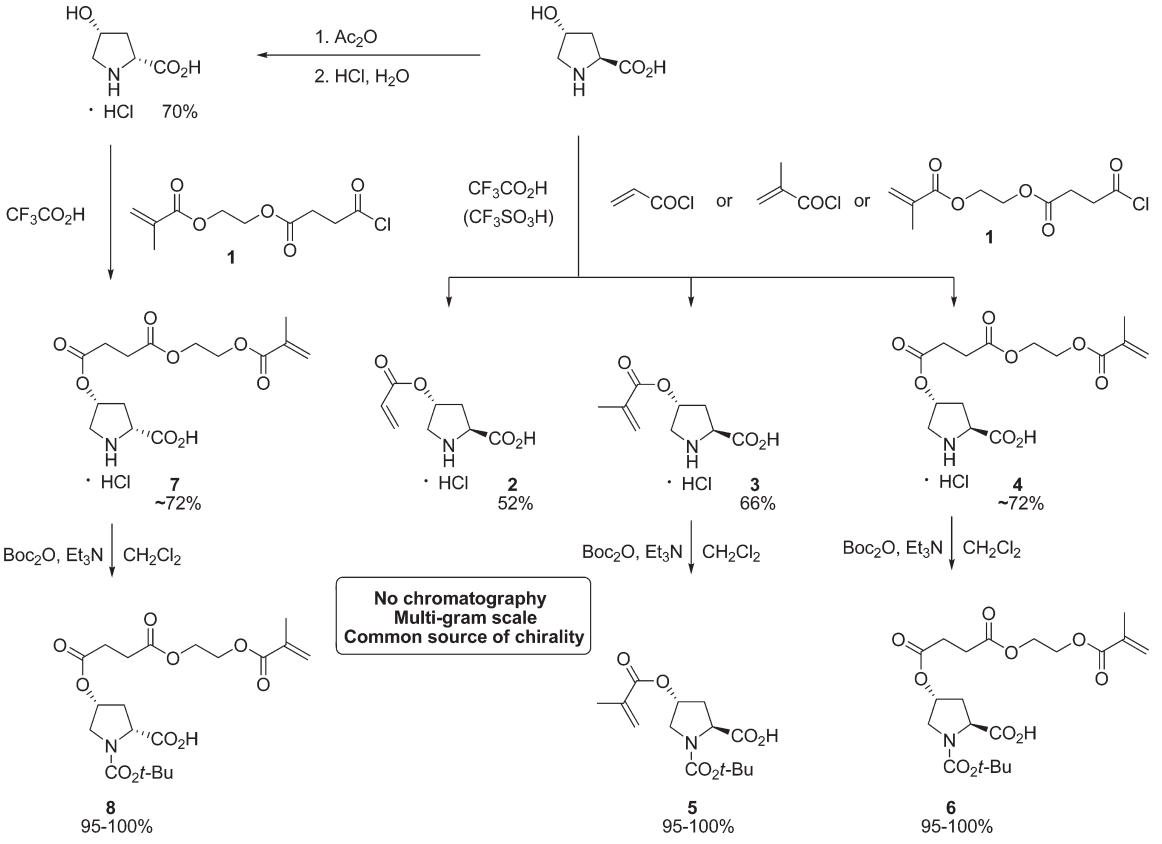
(8) (a) Sakami, W.; Toennies, G. *J. Biol. Chem*. **1942**, *144*, 203. (b) Wilchek, M.; Patchornik, A. *J. Org. Chem*. **1964**, *29*, 1629. (c) Kawasaki, T.; Komai, T. *Polymer J*. **1983**, *15*, 743.

SCHEME 1. Acrylic Proline Building Blocks for Copolymerization



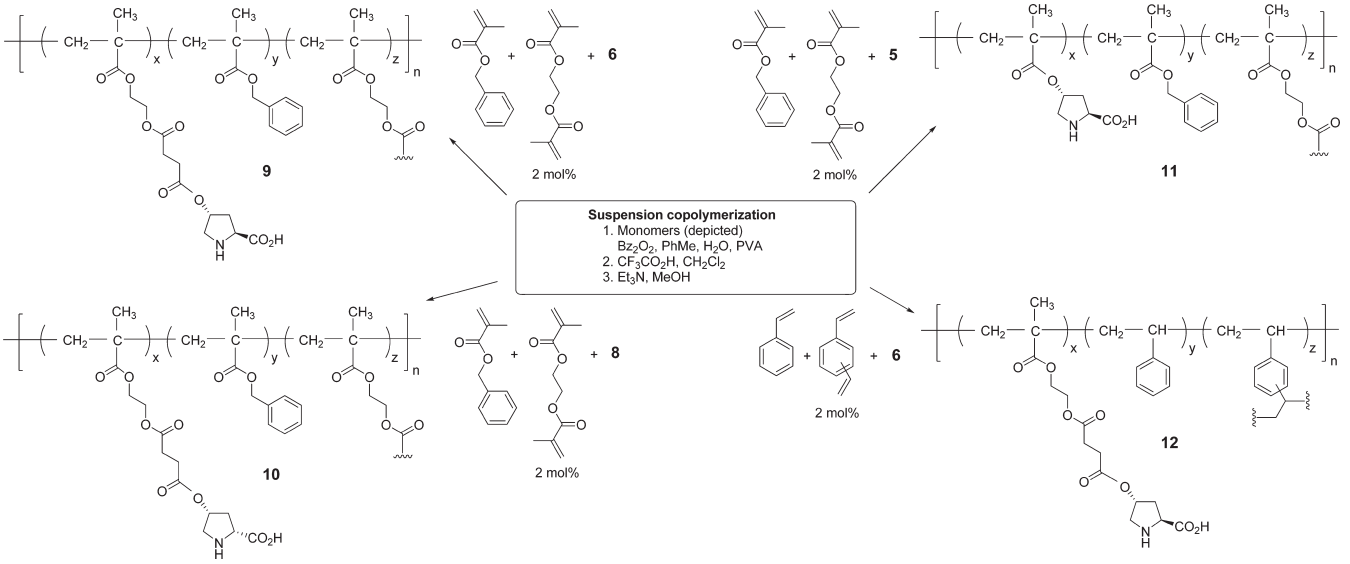
(Scheme 1), we now had available a set of building blocks on multigram scale on which to build our copolymerization strategy for immobilization of proline. Although hydroxyproline is a simple catalyst and subsequently not of prime interest for polymeric immobilization, it remains an extremely useful proving ground for the development of new immobilization strategies as its three basic functionalities are notoriously difficult to manage in a cost-efficient manner, usually requiring double carbamate protection.[4,5] As we have pointed out earlier, however, there exists an erroneous perception within academia that *trans*-4-hydroxy-L-proline is an expensive compound.[7a] In addition, the reported procedures for polymer-supported prolines have not disclosed methods for preparation of enantiomeric/diastereomeric catalysts for preparation of chiral products of the opposite stereochemistry, as the enantiomer of *trans*-4-hydroxy-L-proline is prohibitively expensive. Again, we resorted to the informative literature of hydroxyproline chemistry, and the conversion of *trans*-4-hydroxy-L-proline into the diastereomer *cis*-4-hydroxy-D-proline is curiously facile.[9] The secondary alcohol of hydroxyproline locks the carboxylic acid in a cis-relationship from a planar acyl-intermediate during treatment with Ac_2O.[9b] As such, *cis*-4-hydroxy-D-proline·HCl was available on >30 g scale, and as this was an equally useful starting point for our *O*-acylation, we later added proline building blocks **7** and **8** to our selection of monomers (Scheme 1).

Copolymerization of the acrylic proline building blocks gave access to polymer-supported prolines (Schemes 2 and 3), either through solution, suspension, or dispersion copolymerization.[10] As methacrylates are much less prone to decomposition by conjugate addition than acrylates (decomposing rapidly as unprotected amine), methacrylates are preferred as monomeric building blocks. Especially the traditional beaded products prepared by suspension polymerization seemed attractive because of the especially practical nature of the relatively large spherical polymer beads. Unfortunately, this mode of polymerization necessitates that the monomers do not have a considerable degree of water-solubility, which was not the case for amino acid hydrochlorides **2**−**4** (Scheme 1). We therefore suspension copolymerized Boc-derivatives **5**, **6**, and **8** in slightly alkaline water (containing polyvinyl alcohol stabilizer) together with either benzyl methacrylate and 2 mol % ethyleneglycol dimethacrylate (EGDMA) or styrene and 2 mol % divinylbenzene (DVB) to give polymer-supported prolines **9**−**12** after deprotection (Scheme 2). Therefore, the use of the Boc-protected derivatives within the copolymerization scheme served merely to endow the proline derivatives with the correct hydrophobicity for suspension polymerization, and not for chemical inertness (although its presence is crucial for post-modification into prolineamides, as we describe later). In fact, the free radical polymerization is one of the remarkably few reactions that can withstand the presence of reactive functionalities like unprotected carboxylic acids, alcohols, and many

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

(10) For a thorough distinction between suspension, emulsion, and dispersion polymerization, see: Arshady, R. *Colloid Polym. Sci.* **1992**, *270*, 717.

SCHEME 2. Polymer-Supported Prolines by Suspension Copolymerization

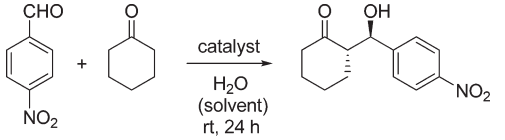


amines, something we wanted to use to our advantage. Of the worldwide production of synthetic polymers of nearly 40 kg per person per year (with sales of over $250 billion in the United States alone), about half is based on copolymers prepared by radical polymerization.[11] Still, its widespread use within synthesis in general remains limited.

In addition to the traditional beaded products, we also prepared a high-load linear polymer (**13**) by solution copolymerization.[7] We found this amphiphilic polymer to be of little use in organocatalysis because of its restricted solubility.[7b] Very recently, and independently of us, other researchers have also reported the preparation of such high-load linear polymers, and their properties now have been investigated more thoroughly.[12] Within the copolymerization scheme, it is also possible to prepare cross-linked copolymers containing proline on multigram scale without any resort to protecting groups at all. Using dispersion copolymerization,[10] we prepared a granulated cross-linked product (**14**) by copolymerizing proline methacrylate **3** with benzyl methacrylate and EGDMA from an initially homogeneous medium of a MeOH solution of monomers (the solution containing polyvinylpyrrolidone as stabilizer).[7b] Generally, dispersion polymerization gives microspheres in the size range of 1−10 μm,[10] but we lowered the amount of stabilizer to allow for a controlled agglomeration that furnished a granulated product that can be handled in the same manner as polymer spheres from suspension polymerization. However, although the dispersion mode of copolymerization allows for the combinations of monomers with near orthogonal solubility properties, the precipitation mechanism means that the polymer composition is no longer a more or less direct reflection of the monomeric composition, as is the case for suspension polymerization with its excellent control of catalyst loadings.

As reported by us earlier, we benchmarked polymer beads **9**, **11**, and **12** together with polymer granulate **14** in the typical aldol reaction of cyclohexanone and benzaldehydes (Table 1).[7b] All catalysts provided good results, with water as sole additive. This was surprising, as even supports that do not contain any form of linker (**11** and **14**) showed promising results (Table 1). The presence of a linker does seem to affect the *anti*:*syn* ratio to an appreciable extent (especially for **14** in a highly expanded state in $H_2O/CHCl_3$), but has little effect on enantioselectivity (97−99% ee in all cases). As for chemical yields, we found them to be more dependent on the ease of which we could retrieve the aldol product than on any observable difference of activity/conversion at 10 mol % catalyst loading. Of more interest was the fact that such acrylic polymer beads, in the form of acrylic−styrenic hybrid **12**, retained good activity and selectivity at only 1 mol % of catalyst loading, something that is very rare for proline.[13]

TABLE 1. Initial Screening of Polymeric Catalysts for Asymmetric Aldol Reactions



catalyst	*f* [mol %][a]	yield [%][b]	*anti*:*syn*[c]	ee [%][d]
11	10[e]	85	94:6	97
11	10[f]	67	91:9	98
12	10[e]	85	98:2	98
12	10[f]	91	96:4	98
12	5[e]	71	97:3	98
12	1[e]	85	97:3	98
9	10[e]	88	95:5	99
9	10[f]	83	99:1	98
14	10[e]	76	93:7	98
14	10[f]	65	88:12	98

[a] *f* = catalyst loading. [b] Isolated yield. [c] Determined by ^{1}H NMR of crude product. [d] Determined by chiral HPLC analysis. [e] In H_2O. [f] In $H_2O/CHCl_3$.

(11) Matyjaszewski, K.; Tsarevsky, N. V. *Nat. Chem.* **2009**, *1*, 276.
(12) Doyagüez, E. G.; Parra, F.; Corrales, G.; Fernández-Mayoralas, A. *Polymer* **2009**, *50*, 4438.
(13) For a discussion of loading issues of proline and prolineamides, see: Lombardo, M.; Easwar, S.; Pasi, F.; Trombini, C. *Adv. Synth. Catal.* **2009**, *351*, 276 and references cited therein.

SCHEME 3. Polymer-Supported Prolines by Solution and Dispersion Copolymerization

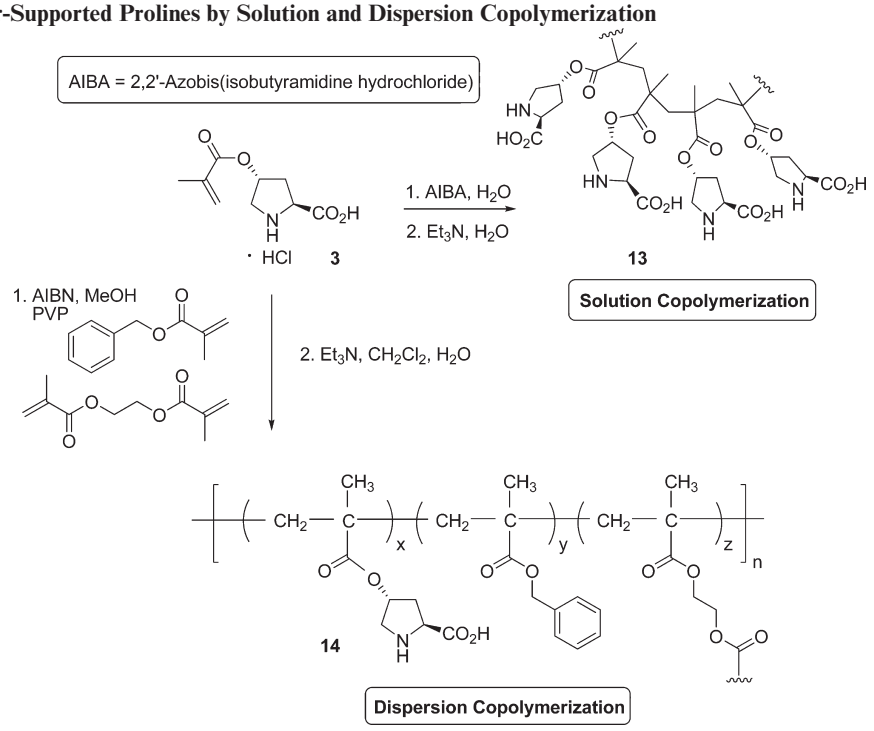
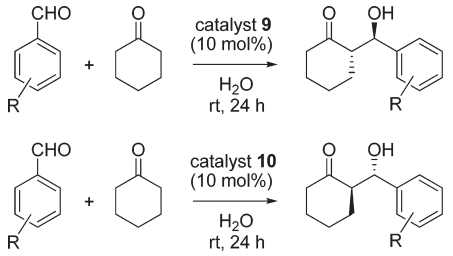


TABLE 2. Asymmetric Aldol Reactions in Water with Polymer-Supported Prolines 9 and 10



catalyst	R	yield [%][a]	*anti*:*syn*[b]	ee [%][c]
9	2-NO_2	63	97:3	89
10	2-NO_2	77	96:4	91
9	3-NO_2	81	95:5	95
10	3-NO_2	80	94:6	90
9	4-NO_2	88	95:5	99
10	4-NO_2	91	94:6	86
9	4-CF_3	72	97:3	98
10	4-CF_3	76	96:4	91
9	H	49	93:7	97
10	H	57	93:7	95
9	4-Br	66	95:5	99
10	4-Br	83	95:5	98
9	4-MeO	7	91:9	97
10	4-MeO	13	93:7	97
9	3,4-Cl	68	95:5	96
10	3,4-Cl	73	96:4	93

[a]Isolated yield. [b]Determined by ^{1}H NMR of crude product. [c]Determined by chiral HPLC analysis.

We investigated acrylic polymer-supported prolines **9** and **10** in aldol reactions of cyclohexanone with an assortment of substituted benzaldehydes (Table 2). Because catalysts **9** and **10** are C-2 epimeric, it would be interesting to see whether a trans- versus cis-relationship of the hydroxyproline would affect the catalyst selectivity. We were positively surprised to see that cis-catalyst **10** in general exhibited a selectivity that was only modestly lower than that of trans-catalyst **9**, and nearly identical for several derivatives (Table 2). To our knowledge, quasi-enantiomeric catalyst pair **9**/**10** (from a common source of chirality) is the first example of polymer-supported proline on hydroxyproline-basis that can be used for preparation of both enantiomeric series of a given product. As for other polymer-supported prolines, such acrylic supports are readily recyclable, and polymer support **12** was reused five times with unaffected results.[7b] This is consistent with other prolines immobilized on cross-linked supports.[5b−h]

Polymer-Supported Prolineamides. Amides of proline and certain amino alcohols are highly efficient catalysts for asymmetric aldol reactions, efficient even down to the 0.5 mol % level of catalyst loading.[14] Unlike proline, they also efficiently catalyze aldol reactions with the water-soluble acetone.[14] Gruttadauria and co-workers have investigated such prolineamides immobilized on Merrifield-resin in great detail.[15] We used the precursors for polymer-supported prolines **9** and **10** (before deprotection), and coupled them with diphenyl phenylglycinol **15** (*S*-**15** for **16** and *R*-**15** for **17**) through a standard peptide coupling to give prolineamides **16** and **17** (Scheme 4) after a mild Boc-deprotection with HCO_2H. As the starting material for **15** is synthetic phenylglycine, both enantiomers are nearly equally affordable.[16]

As we have shown earlier, while an analogous prolineamide to **16** (made from **12**) gave more than 90% ee and

(14) (a) Raj, M.; Maja, V.; Ginotra, S. K.; Singh, V. K. *Org. Lett.* **2006**, *8*, 4097. (b) Maya, V.; Raj, M.; Singh, V. K. *Org. Lett.* **2007**, *9*, 2593. (c) Raj, M.; Maja, V.; Singh, V. K. *J. Org. Chem.* **2009**, *74*, 4289.

(15) (a) Gruttadauria, M.; Giacalone, F.; Marculescu, A. M.; Noto, R. *Adv. Synth. Catal.* **2008**, *350*, 1397. (b) Gruttadauria, M.; Salvo, A. M. P.; Giacalone, F.; Agrigento, P.; Noto, R. *Eur. J. Org. Chem.* **2009**, 5437.

(16) Kristensen, T. E.; Vestli, K.; Hansen, F. K.; Hansen, T. *Eur. J. Org. Chem.* **2009**, 5185–5191.

SCHEME 4. Polymer-Supported Prolineamides

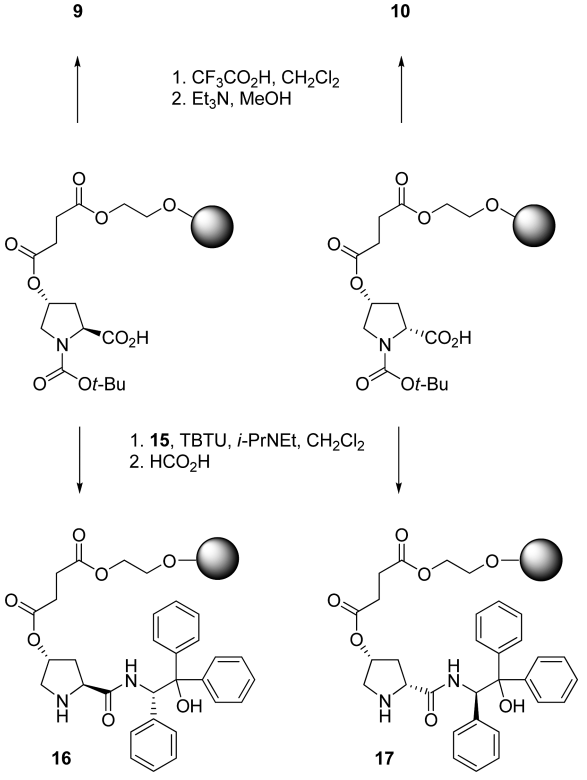
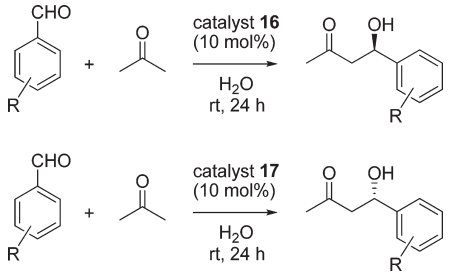


TABLE 3. Asymmetric Aldol Reactions in Water with Polymer-Supported Prolineamides 16 and 17

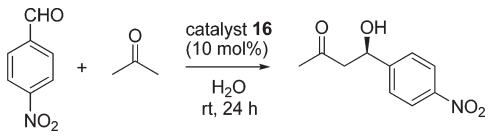


catalyst	R	yield [%][a]	ee [%][b]
16	2-NO_2	90	91
17	2-NO_2	88	82
16	3-NO_2	87	99
17	3-NO_2	88	99
16	4-NO_2	72	91
17	4-NO_2	82	85
16	4-CF_3	77	90
17	4-CF_3	82	86
16	H	29	91
17	H	47	86
16	4-Br	56	91
17	4-Br	79	83

[a]Isolated yield. [b]Determined by chiral HPLC analysis.

80−90% yield in the aldol reaction of 4-nitrobenzaldehyde and acetone, the same support in its proline form (**12**) only managed a mediocre ∼30% ee in very poor yields.[7b] As for supported prolines **9**/**10**, prolineamides **16**/**17** also form a quasienantiomeric pair, and we investigated the aldol reactions of acetone with substituted benzaldehydes catalyzed by **16**/**17** (Table 3). As for supported prolines **9** and **10**, the catalyst with a cis-relationship (**17**) generally gave somewhat lower enantioselectivity, but again, for some derivatives, the selectivity is more or less identical. We also investigated the recycling of prolineamide support **16** (Table 4), and it has an interesting pattern of activity where a slightly enhanced activity is seen after the first time usage. Nearly 3 g of aldol product (acetone/4-nitrobenzaldehyde) with a weighted average of 92% ee was prepared through five repetitive reaction cycles (Table 4). All in all, our synthesis of prolineamides combines our copolymerization strategy with a traditional postmodification. As for the postmodification, its strength is the reliance on only the most well-proven reaction of all in solid-phase synthesis, namely the peptide coupling, a reaction with an ever-widening scope on solid-phase.

TABLE 4. Recycling of Polymer-Supported Prolineamide



cycle	yield [%][a]	ee [%][b]
1	76	84
2	85	99
3	79	98
4	82	91
5	81	90

[a]Isolated yield. [b]Determined by chiral HPLC analysis.

Polymer-Supported Jørgensen/Hayashi Diarylprolinols. The Jørgensen/Hayashi diarylprolinols are arguably the most useful of all the organocatalysts because of their ability to undertake both enamine and iminium catalysis with excellent selectivities.[1i,17] In contrast to proline and prolineamides, work within supported silylated diarylprolinols is very sparse.[18] Again, unlike the hydrophilic proline, the usual methodology has met limited success with the diarylprolinols because of the much lower hydrophilicity of these catalysts.[18a−c] When bound to resins, proline can confer useful swelling properties in polar solvents upon hydrophobic supports such as polystyrene, although use of water with proline or prolineamide supports should be regarded as an additive more than a true solvent as other components dominate the reaction mixture. The diarylprolinols have important use in solvents like MeOH, EtOH, or MeCN, and a polystyrene network with diarylprolinols shows negligible swelling in such solvents, limiting reactions to take place mainly in solvents like PhMe, CH_2Cl_2, or $CHCl_3$.[18a] The main reason for this shortcoming is the fact that polymer-supported Jørgensen/Hayashi diarylprolinols reported until now are mainly silylated versions of polymer-supported Corey−Bakshi−Shibata (CBS) reduction catalysts,[19]

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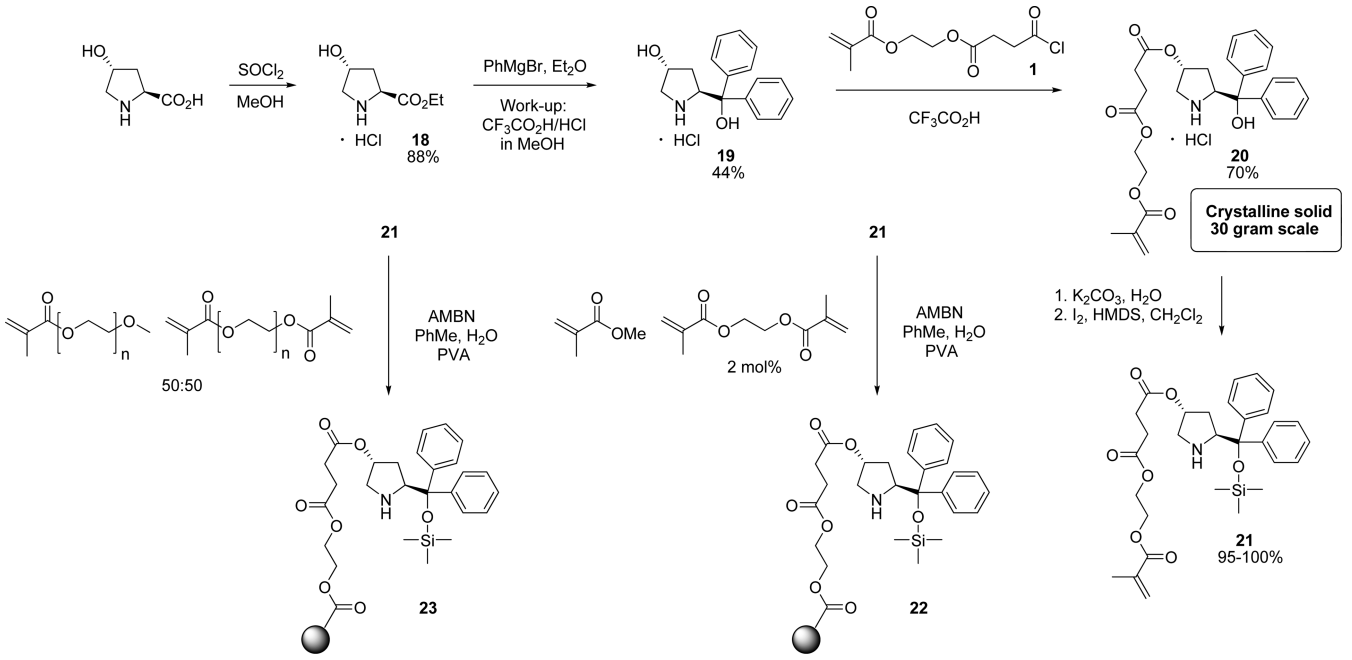
(18) (a) Varela, M. C.; Dixon, S. M.; Lam, K. S.; Schore, N. E. *Tetrahedron* **2008**, *64*, 10087. (b) Röben, C.; Stasiak, M.; Janza, B.; Greiner, A.; Wendorff, J. H.; Studer, A. *Synthesis* **2008**, 2163. (c) Alza, E.; Pericàs, M. A. *Adv. Synth. Catal.* **2009**, *351*, 3051. (d) Maltsev, O. V.; Kucherenko, A. S.; Zlotin, S. G. *Eur. J. Org. Chem.* **2009**, 5134.

(19) (a) Price, M. D.; Sui, J. K.; Kurth, M. J.; Schore, N. E. *J. Org. Chem.* **2002**, 8086. (b) Varela, M. C.; Dixon, S. M.; Price, M. D.; Merit, J. E.; Berget, P. E.; Shiraki, S.; Kurth, M. J.; Schore, N. E. *Tetrahedron* **2007**, *63*, 3334.

SCHEME 5. Polymer-Supported Jørgensen/Hayashi *O*-TMS Diphenylprolinol



a reaction with entirely different reaction constraints compared to most enamine/iminium organocatalytic reactions.

Because of the CBS reduction,[20] unusually large efforts, especially in the late 1980s and early 1990s, have gone into research directed toward efficient large-scale preparations of the simplest diphenylprolinol (α,α-diphenyl-2-pyrrolidinemethanol).[20−22] Despite its simple nature, its synthesis is challenging as the normal mode of preparation for such diphenylamino alcohols, the addition of PhMgBr to an alkyl ester hydrochloride of the corresponding amino acid, works poorly for proline (20−26% yield, ca. 80% ee).[21,22b] Of the methods developed over the years, probably the most important are the original preparation of Corey through the addition of PhMgCl to Cbz-protected proline methyl ester,[20a,c] addition of PhMgBr to proline-*N*-carboxyanhydride (prepared from proline and $COCl_2$),[22b] addition of PhMgBr to *N*-benzylproline ethyl ester followed by catalytic hydrogenolysis,[22a] addition of PhMgBr to the *N*-ethyl carbamate of proline methyl ester (conveniently prepared in only one step from proline and ethyl chloroformate in MeOH) followed by alkaline hydrolysis,[22d] enantioselective deprotonation of *N*-Boc-pyrrolidine with *s*-butyllithium/(−)-sparteine followed by reaction with benzophenone,[22c] addition of PhMgCl to methyl pyroglutamate followed by reduction with borane and resolution of the racemate with *O*-acetylmandelic acids,[20b] as well as some less well-known procedures such as addition of PhMgBr to silylprotected proline (from proline and HMDS/Me_3SiCl).[22e] Of special interest to us was the curious fact that for hydroxyproline, the likely starting point for immobilization of proline, the addition of PhMgBr to the ethyl carbamate of hydroxyproline methyl ester followed by alkaline hydrolysis, as reported for proline in 1993,[22d] seemed to be the only method in general use for preparation of the diphenylprolinol of hydroxyproline.[23] As we needed this material on the scale of tens of grams for our copolymerization approach, and as this was clearly not obtainable through the methods in use,[23] we instead turned our attention to the original disclosure from 1933.[21] In this work, addition of PhMgBr directly to hydroxyproline ethyl ester hydrochloride gave a yield of ca. 50%, a yield comparable to that of the standard method and superior to that for normal proline, a fact clearly not generally comprehended. We wanted to use the superior crystallinity of the hydroxyproline derivatives as compared to the proline derivatives, as for example the diphenylprolinol of hydroxyproline has a melting point approximately 100 deg higher than that of the poorly crystalline diphenylprolinol of proline.[21]

We prepared two types of acrylic polymer beads (**22** and **23**) with supported *O*-TMS-diphenylprolinol as shown in Scheme 5, one of them for use in nonpolar solvents (PhMe, CH_2Cl_2, etc.) and one for use in solvents such as lower alcohols and MeCN. As discussed in the previous section, treatment of the ethyl ester hydrochloride of *trans*-4-hydroxy-L-proline (**18**) directly with PhMgBr/Et_2O gave diphenylprolinol hydrochloride **19** after a novel workup with use of a CF_3CO_2H/HCl exchange. The diphenylprolinol of hydroxyproline, as opposed to that for proline, is a poorly soluble material requiring disproportionate amounts of solvents for extraction and recrystallization, which in our hands were found unworkable on larger scales. A method was therefore

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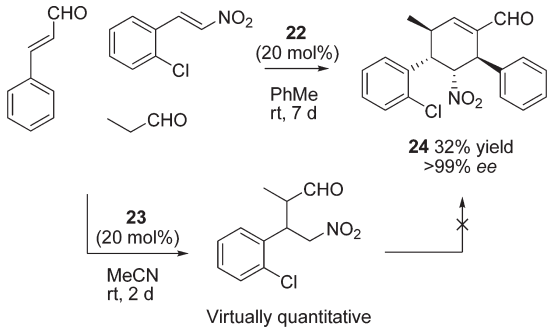
SCHEME 6. Asymmetric Cascade Reaction Catalyzed by Polymer-Supported Jørgensen/Hayashi *O*-TMS-Diarylprolinols 22 and 23



devised in which the product is brought into solution as its soluble CF_3CO_2H-salt and precipitated as its crystalline hydrochloride. Hydroxyprolinol **19**, as hydroxyproline, had the amino alcohol motif and as such was a substrate for our acidic *O*-acylation. Gratifyingly, selective *O*-acylation of **19** in CF_3CO_2H gave methacrylate **20** on a 30 g scale as a storage-stable crystalline solid in only three steps overall. Subsequent silylation with HMDS/I_2[24] gave Jørgensen/Hayashi methacrylate **21** in quantitative yield.

Standard suspension copolymerization with methyl methacrylate and 2 mol % of EGDMA gave microporous polymer beads **22**, useful for reactions in nonpolar solvents. In complete analogy, by substituting the methyl methacrylate/EGDMA with a 50:50 mixture of feedstock PEG 400 methyl ether methacrylate and PEG 600 dimethacrylate, we prepared polymer beads **23**, a swellable macroporous support extremely useful for reactions in lower alcohols, MeCN, or aqueous solvents. The classic way of utilizing PEG for immobilization is by anchoring the catalyst onto linear PEG to give a homogeneously soluble polymer that is subsequently precipitated after reaction by addition of a nonsolvent.[4a−d] However, we realized that PEG derivatives, which at room temperature can be completely miscible with water, can still be readily suspension polymerized in water because PEG derivatives have the unusual ability of being much less soluble in water at elevated temperatures and then partitioning favorably into toluene. Therefore, we found that use of PEG can be undertaken in the same practical bead form as for classical styrene supports by the use of PEG-methacrylates, in the practical sense a clear advantage when compared to linear PEG.

We used polymer supports **22** and **23** in the asymmetric Enders cascade-reaction,[25] an enamine and iminium organocatalytic triple cascade reaction forging a tetrasubstituted cyclohexene carbaldehyde with four stereogenic centers (Scheme 6).[25] We found an interesting reaction pattern for these polymer-supported versions when compared to the standard monomeric catalyst, as has also been observed by others.[18a] While polymeric Jørgensen/Hayashi prolinol **22** gave product **24** in decent 32% yield and superb selectivity, it required 7 days of reaction time. This compares usefully with the work of Varela et al.[18a] where an analogous product was obtained in 45% yield after 7 days with the best of their polymer-supported catalysts. In our case, the minor enantiomer was completely undetectable by chiral HPLC analysis. As the prolonged reaction time is probably much more than what can be reasonably explained through the more restricted rate of diffusion in a polymer network, it is definitely a sign of the challenges that are met when conducting more complicated reactions than the standard aldol reactions on solid phase. Interestingly, further investigations demonstrated the product of the first step of the cascade, the Michael adduct of propionaldehyde and nitrostyrene, to form rapidly and then accumulate. However, its further conversion into the final product (**24**) was very slow (see the Supporting Information for more details). Furthermore, in trials with the monomeric catalyst, we found the cascade to operate nicely in MeCN, something not mentioned in the original disclosures on this cascade.[25] Therefore, we tried out the organocatalytic cascade in MeCN with PEG-based support **23**. While the initial Michael-adduct formed rapidly, the conversion to final product was virtually nonexistent. In summary, it seemed like only the strongly swollen microporous network of **22** in PhMe was able to provide product **24** in appreciable quantities.

Polymer-Supported MacMillan Imidazolidinone. Since the pioneering disclosure by the research group of MacMillan in 2000,[26] there have been reported a few versions of polymer-supported MacMillan imidazolidinone.[27] Although its labile nature makes it a quite unattractive target for polymeric immobilization when based solely on recovery and reuse, it nevertheless presented useful challenges for a system of polymer-supported enamine/iminium organocatalysts that aimed to be general in its nature. In addition, as it typically operates in highly polar media, it is especially useful for the development of polymer networks that are operational in solvents as lower alcohols and MeCN. We therefore also developed a large-scale approach to the first-generation MacMillan imidazolidinone organocatalyst (Scheme 7). The traditional way of immobilizing the MacMillan imidazolidinone is by substituting phenylalanine with tyrosine,[27b−d] although linkage via the amide is also possible.[27d] None of the reported procedures using tyrosine had to our knowledge furnished building blocks in a robust nonchromatographic manner, and this was also the case in our hands because of the problematic phenolic functionality of tyrosine. Instead, we utilized the incorporation of ethanolamine instead of methylamine in the original MacMillan procedure, as the pendant alcohol together with the amine of phenylalanine would later on give an amino alcohol substrate (**25**) viable for selective *O*-acylation. Treatment of phenylalanine methyl ester hydrochloride with ethanolamine under neat conditions, followed by selective extraction of ethanolamine gave pure L-phenylalanylaminoethanol. A novel azeotropic ring-closure with acetone in

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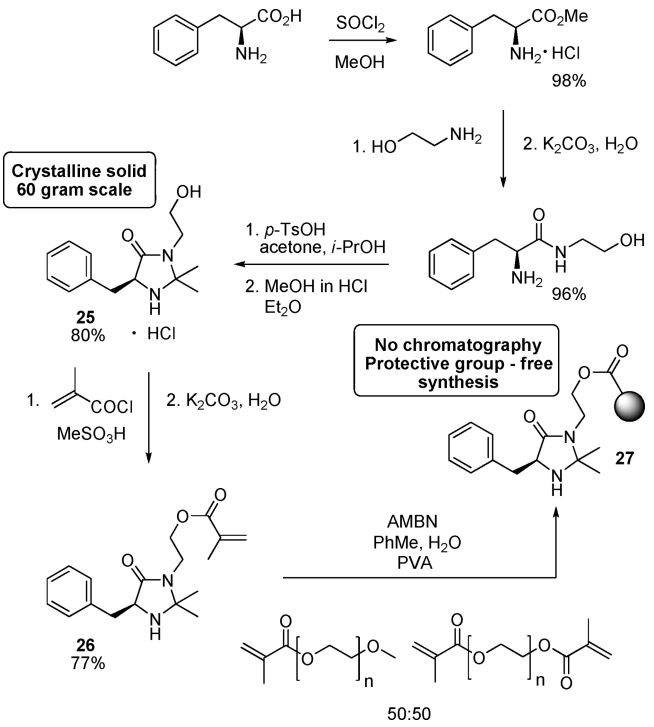
SCHEME 7. Polymer-Supported MacMillan Imidazolidinone



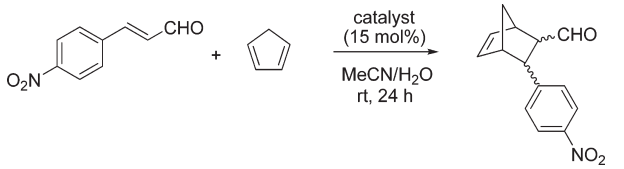
i-PrOH gave crystalline imidazolidinone **25** on a robust 60 g scale as a crystalline solid. Selective *O*-acylation with methacryloyl chloride in cheap $MeSO_3H$ (see the Supporting Information for more details) gave MacMillan methacrylate **26**. As for the Jørgensen/Hayashi diphenylprolinols, the entire sequence does not involve any protective groups or chromatographic purifications.

Suspension copolymerization of functional methacrylate **26** with a 50:50 mixture of feedstock PEG 400 methyl ether methacrylate and PEG 600 dimethacrylate gave (in the same manner as for preparation of Jørgensen/Hayashi support **23**) polymer beads **27**. These polymer beads were fully functional in aqueous MeCN, and we benchmarked them in a classical asymmetric Diels–Alder reaction of cyclopentadiene and 4-nitrocinnamaldehyde (Table 5). Supported MacMillan imidazolidinone **27** gave results (as its HCl-salt) only slightly inferior to those obtained with standard monomeric MacMillan imidazolidinone (**28**), slightly poorer in the form of its CF_3CO_2H-salt. However, as known from others, recycling of the MacMillan imidazolidinones is coupled to a rather rapid erosion of the catalyst selectivity,[27] even after just 2–3 reaction cycles (Table 5). It was nevertheless interesting to see that our copolymerization strategy could encompass a member of this important class of organocatalysts.

Conclusions

Work within polymer-supported organocatalysts, like most other forms of polymeric immobilization, tends to do little to overcome the most important limitation for the widespread utilization of polymer-supported reagents and catalysts, namely its restraining cost issues. For simple reagents and organocatalysts, overall expenditures are much more closely connected to the synthetic strategy of immobilization in its entirety than any cost of starting materials, as a superficial

TABLE 5. Asymmetric Diels–Alder Reactions with Polymer-Supported MacMillan Imidazolidinone



catalyst[a]	yield [%][b]	*exo*:*endo*[c]	*exo* ee [%][d]	*endo* ee [%][d]
28·**HCl**[e]	91	1.27:1	86	92
27·**HCl**[f]	92	1.29:1	85	89
27·**TFA**	86	1.23:1	75	81
27·**TFA**[g]	92	1.22:1	78	84
27·**TFA**[h]	73	1.26:1	54	62
27·**TFA**[i]	82	1.31:1	46	51

[a]All reactions undertaken at 1.5 mmol scale unless otherwise noted. [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]Determined by chiral HPLC analysis after reduction to the alcohol and conversion to the benzoyl ester. [e]**28** = (5*S*)-(−)-2,2,3-trimethyl-5-benzyl-4-imidazolidinone·HCl. [f]Gram scale (7.5 mmol). [g]Second cycle. [h]Third cycle. [i]Fourth cycle (replenished with CF_3CO_2H before use).

analysis might indicate. We therefore believe that for simple organocatalysts, a synthetic strategy conducted in a bottom-up fashion where functional monomers are copolymerized into finished beaded products can advantageously compete with most postmodification strategies. Because of the mild reaction conditions prevailing in organocatalytic transformations, the vast assortment of acrylics is probably a favorable alternative to the more limited styrenics. We have used the copolymerization strategy for the preparation of polymer-supported prolines, prolineamides, Jørgensen/Hayashi diphenylprolinols, and the first-generation MacMillan imidazolidinone. As some of these represent simple catalysts not very attractive for polymeric immobilization, they nevertheless pose interesting challenges in the developmental phase because they operate in reaction media that span a wide range of solvent polarity, and as such cannot be readily encompassed in a postmodification strategy by using a small number of specialized and prefabricated polymer supports. We have also undertaken a quite considerable investigation into hydroxyproline chemistry relevant for the development of efficient syntheses of useful intermediates in the preparation of polymer-supported enamine/iminium organocatalysts.

While the initial successes connected to the use of polymer-supported prolines in asymmetric aldol reactions hold promise for future work, more complicated transformations such as the demanding Enders cascade are probably indications of the challenges laying ahead for the preparation of polymer-supported organocatalysts spanning a more comprehensive range of transformations.

Experimental Section

The synthesis and characterization of the acrylic derivatives *O*-acryloyl-*trans*-4-hydroxy-L-proline hydrochloride (**2**), *O*-methacryloyl-*trans*-4-hydroxy-L-proline hydrochloride (**3**), and *O*-(2-methacryloyloxyethylsuccinoyl)-*trans*-4-hydroxy-L-proline hydrochloride (**4**) together with their corresponding Boc-derivatives (**5** and **6**) have been reported by us previously.[7] Polymer-supported prolines **9** and **11**–**14** have also been reported in a preliminary report.[7b]

General Procedure for the Asymmetric Aldol Reaction of Benzaldehydes with Cyclohexanone. Benzaldehyde derivative

(0.40 mmol) was dissolved in cyclohexanone (2.0 mmol), contained in a small vial (by gentle heating on a water bath if necessary). Water (0.14 mL) was added, followed by the polymer beads (**9** or **10**, 10 mol %). For noncrystalline benzaldehydes, the vial is charged with polymer beads first, followed by the benzaldehyde derivative and solvents/additives. The reaction was mixed gently with a closed capillary tube and then left without stirring for 24 h. The reaction mixture was diluted with EtOAc and transferred to a small folded paper filter. The polymer beads were washed with additional small quantities of EtOAc (20 mL in total for dilution and washing), and the filtrate was evaporated in vacuo to yield the crude product. Purification by flash column chromatography on silica gel with EtOAc/hexanes yielded the pure aldol product. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product, and the enantiomeric excess was determined by HPLC analysis of the purified product. All the aldol products are well-known compounds with spectroscopic data in accordance with literature.[28]

General Procedure for the Asymmetric Aldol Reaction of Benzaldehydes with Acetone. Benzaldehyde derivative (0.40 mmol) was dissolved in acetone (8.0 mmol), contained in a small vial. Water (0.14 mL) was added, followed by the polymer beads (**16** or **17**, 10 mol %). For noncrystalline benzaldehydes, the vial is charged with polymer beads first, followed by the benzaldehyde derivative and solvents/additives. The reaction was mixed gently with a closed capillary tube and then left without stirring for 24 h. The reaction mixture was diluted with EtOAc and transferred to a small folded paper filter. The polymer beads were washed with additional small quantities of EtOAc (20 mL in total for dilution and washing), and the filtrate was evaporated in vacuo to yield the crude product. Purification by flash column chromatography on silica gel with EtOAc/hexanes yielded the pure aldol product. The enantiomeric excess was determined by HPLC analysis of the purified product. All the aldol products are well-known compounds with spectroscopic data in accordance with literature.[29]

General Procedure for Asymmetric Cascade Reaction. A vial was charged with polymer beads (**22**, 20 mol %) and 2-chloro-β-nitrostyrene (1.00 mmol). Toluene (4.0 mL) was added together with a stirring bar, cinnamaldehyde (1.05 mmol), and propanal (1.20 mmol). The reaction mixture was stirred for approximately 2 h, in which time the polymer beads had swollen considerably, and further stirring was discontinued. The reaction mixture was then left at room temperature for the indicated time. The reaction mixture was transferred to a filter paper with a small amount of EtOAc. The vial and the polymer beads were washed several times with small amounts of EtOAc (50 mL in all for transfer and washing). The mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (0−20% EtOAc in hexanes) to give the product as a white solid. This is a well-known compound.[25a]

Asymmetric Diels−Alder Reactions of 4-Nitrocinnamaldehyde and Cyclopentadiene. A vial was charged with PEG-methacrylic polymer beads (**27**, 15 mol %) and 4-nitrocinnamaldehyde (1.5 mmol). A solvent mixture of MeCN and water (95:5, 1.50 mL) was added, followed shortly by CF_3CO_2H (~0.23 mmol) and freshly cracked cyclopentadiene (4.5 mmol). The mixture was stirred gently at room temperature for 24 h and then diluted with EtOAc and filtered. The polymer beads were washed with EtOAc (totally 25 mL for dilution and washing) in small portions. The organic phase was washed with brine (25 mL), dried over anhydrous $MgSO_4$, and evaporated in vacuo to give the crude product as a brown oil. The crude product was purified by loading onto a column of silica gel and eluting with *n*-pentane followed by 40% Et_2O in *n*-pentane. The *exo*/*endo* relationship was determined by ^{1}H NMR analysis. The enantiomeric excess was determined by HPLC analysis after reduction of the product to the corresponding alcohol with $NaBH_4$ and subsequent conversion to the benzoyl ester.[30] This is a well-known compound.[31]

Full experimental procedures and characterization for all new compounds and polymer-supported organocatalysts can be found together with supporting details (pictures, comments etc.) in the Supporting Information.

Acknowledgment. This work has been supported by Birkeland Innovasjon, the Technology Transfer Office of the University of Oslo. Hydroxyproline was generously donated by Evonik Degussa GmbH.

Supporting Information Available: Full experimental procedures, pictures, and spectroscopic properties for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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