ORGANIC LETTERS

2009
Vol. 11, No. 14
2968−2971

Synthesis of Acrylic Polymer Beads for Solid-Supported Proline-Derived Organocatalysts

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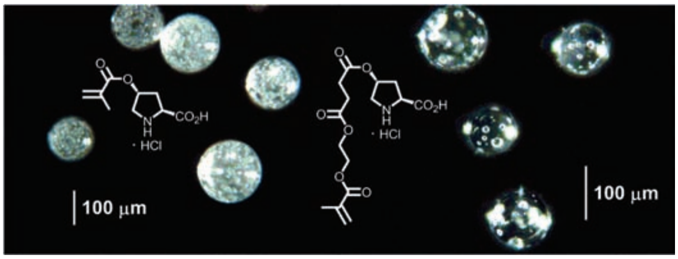
Received April 24, 2009

ABSTRACT



A completely non-chromatographic and highly large-scale adaptable synthesis of acrylic polymer beads containing proline and prolineamides has been developed. Novel monomeric proline (meth)acrylates are prepared from hydroxyproline in only one step. Free-radical copolymerization then gives solid-supported proline organocatalysts directly in as little as two steps overall, without using any prefabricated solid supports, by using either droplet or dispersion polymerization. These affordable acrylic beads have highly favorable and adjustable swelling characteristics and are excellent reusable catalysts for organocatalytic reactions.

Polymer solid-supported organocatalysts are potentially highly useful materials for conducting catalytic asymmetric synthetic transformations under especially simple, mild, and environmentally benign reaction conditions. Pioneering efforts within this field were undertaken in 1985,[1] but the widespread interest the field has received in recent times has primarily been the result of several important disclosures since the prosperous rebirth of organocatalysis nearly a decade ago.[2,3] Cozzi and co-workers introduced poly(ethylene glycol)-immobilized proline in 2001,[2a−d] and linear polystyrene was introduced a couple of years later.[2e−f] These polymers are homogenously soluble in the reaction medium and can be precipitated after the reaction by the addition of suitable non-solvent for the polymer. Especially good results have been obtained with the type of cross-linked polystyrene-anchored proline supports introduced by the groups of Pericàs and Gruttadauria, from 2006 onward.[2g,i−m] These solid-supported prolines can readily outperform monomeric ver-

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[1] Kondo, K.; Yamano, T.; Takemoto, K. *Makromol. Chem.* **1985**, *186*, 1781.

[2] (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*, 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. (g) Font, D.; Jimeno, C.; Pericás, M. A. *Org. Lett.* **2006**, *8*, 4653. (h) Kehat, T.; Portnoy, M. *Chem. Commun.* **2007**, 2823. (i) Giacalone, F.; Gruttadauria, M.; Marculescu, A. M.; Noto, R. *Tetrahedron Lett.* **2007**, *48*, 255. (j) Gruttadauria, M.; Giacalone, F.; Marculescu, A. M.; Meo, P. L.; Riela, S.; Noto, R. *Eur. J. Org. Chem.* **2007**, 4688. (k) Font, D.; Sayalero, S.; Bastero, A.; Jimeno, C.; Pericás, M. A. *Org. Lett.* **2007**, *9*, 1943. (l) Alsa, E.; Cambeiro, X. C.; Jimeno, C.; Pericás, M. A. *Org. Lett.* **2007**, *9*, 3717. (m) Font, D.; Sayalero, S.; Bastero, A.; Jimeno, C.; Pericás, M. A. *Org. Lett.* **2008**, *10*, 337.

[3] For reviews, see: (a) Gruttadauria, M.; Giacalone, F.; Noto, R. *Chem. Soc. Rev.* **2008**, *37*, 1666. (b) Gruttadauria, M.; Giacalone, F.; Noto, R. *Adv. Synth. Catal.* **2009**, *351*, 33. (c) Trindade, A. F.; Gois, P. M. P.; Afonso, C. A. M. *Chem. Rev.* **2009**, *109*, 418. For a recent comprehensive review of polymeric immobilization in general, see: (d) Lu, J.; Toy, P. H. *Chem. Rev.* **2009**, *109*, 815.

10.1021/ol901134v CCC: $40.75

sions of proline, creating additional incentives for the development of these solid-supported organocatalysts. In addition, these cross-linked beads have higher catalyst loadings and are of a much more practical nature than the earlier soluble polymers. Recently, Gruttadauria also introduced the more powerful immobilized prolineamide catalysts using the same methodology.[4]

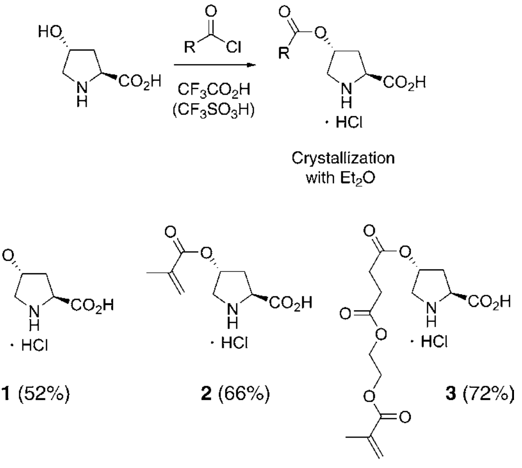
Given the excellent catalytic performance of such polymer solid-supported catalysts, new, more versatile, and affordable procedures for the preparation of such polymer beads that are useful for work on a preparative scale is of great interest. The traditional Merrifield approach, in which catalysts are simply anchored onto prefabricated solid supports by way of modified catalyst precursors and used within solid-supported organocatalysis, is well established but has certain profound limitations. During a multistep sequential preparation, the difficulty of monitoring reactions on cross-linked solid supports often requires several time-consuming and costly elemental analyses, and final catalyst loadings are somewhat unpredictable. Styrenic polymeric supports, now in use for more than 40 years,[5] are chemically very robust but have favorable swelling characteristics in a very limited variety of solvent systems because of the hydrocarbon nature of styrenes. More modern solid supports with better swelling properties, such as Tentagel, JandaJel, etc., still have styrene chemistry at their core but are very expensive. As such, the traditional direct anchoring of modified catalysts is more suited for high-valued substrates/catalysts used under harsh reaction conditions, rather than the cheap organocatalysts that are used under mild enzyme-mimetic reaction conditions.

We want to introduce a new "bottom-up" approach for solid-supported proline-derived organocatalysts, modular at the monomeric rather than the polymeric level, and founded on acrylic chemistry. Acrylic polymer chemistry spans everything from superabsorbent acrylate "Super Slurpers" to DuPont's exceptionally hydrophobic fluorinated Zonyl monomers, giving numerous possibilities for matching a preferred set of reaction conditions. The advent of organocatalysis means acrylic solid supports should be especially useful.

In our method, we have first introduced a new family of proline (meth)acrylates **1**−**3** (Scheme 1). These are prepared on large scale (10−40 g) in a one-step, non-chromatographic, and protecting-group-free procedure directly from inexpensive *trans*-4-hydroxy-L-proline,[6] using methodology developed recently in our group.[6] This circumvents the cumbersome double Boc/Cbz protection of hydroxyproline under alkaline acylations.[6]

Acrylate **1** and methacrylate **2** are prepared from acryloyl and methacryloyl chloride, respectively, while methacrylate **3** is prepared from commercially available 2-methacryloyloxyethylsuccinic acid. This latter, inexpensive, and convenient methacrylate, derived from the industrial hydroxyethylmethacrylate (HEMA) and succinic anhydride,[7] comprises a "complete package" of both a methacrylate, linker and functional handle. It is cleanly converted to the acyl halide by simple stirring in oxalyl chloride[7] or neat $SOCl_2$ and subsequent removal of the volatiles by evaporation in vacuo.

Scheme 1. Synthesis of Acrylic Building Blocks



Next, plentiful variants of solid-supported proline derivatives are now available through copolymerization. The free radical (co)polymerization of unsaturated monomers[8] is one of the most atom-economic, selective, functionally tolerant, and robust reactions available, tolerating free carboxylic acids, alcohols, most amines, water, and low degrees of chemical purities. Actually, it can, by analogy, be considered a click reaction, considering the fact that the thiol−ene click coupling is essentially a fully chain transferred free radical polymerization.[9] Both the traditional Huisgen-type azide/alkyne cycloaddition and the thiol−ene coupling are click reactions that Pericàs and Gruttadauria have used in the traditional postmodification approach to solid-supported proline derivatives.[2g,i−m] In our acrylic approach, such a versatile reaction completes both the solid support and the anchoring of the catalyst in the same step.

Two high-load linear polymers (**4** and **5**) were directly accessed by polymerization of **1** or **2**, respectively, in water with azobis(isobutyramidine) dihydrochloride (AIBA), a water-soluble azo-initiator (Scheme 2).[6]

These linear polymers are brittle and glassy materials (see Supporting Information for pictures). They present the highest loaded form of polymer-immobilized proline available but have limited solubilities. They are soluble in formamide, or in water in their cationic/anionic forms. These solvents gave poor results in aldol test reactions.

We then prepared traditional polymer beads, analogues to the traditional Merrifield resin, by suspension (droplet) copolymerization of proline methacrylates **2** and **3** with

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(4) Gruttadauria, M.; Giacalone, F.; Marculescu, A. M.; Noto, R. *Adv. Synth. Catal.* **2008**, *350*, 1397.

(5) (a) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149. (b) Merrifield, R. B. *Science* **1965**, *150*, 178.

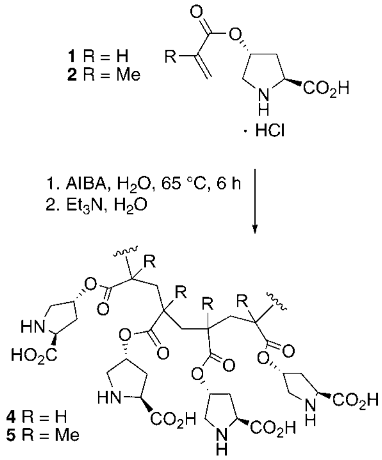
(6) Kristensen, T. E.; Hansen, F. K.; Hansen, T. *Eur. J. Org. Chem.* **2009**, 387.

(7) van Esch, J.; Schoonbeek, F.; de Loos, M.; Kooijman, H.; Spek, A. L.; Kellogg, R. M.; Feringa, B. L. *Chem.*−*Eur. J.* **1999**, *5*, 937.

(8) Moad, G.; Solomon, D. H. *The Chemistry of Radical Polymerization*, 2nd ed.; Elsevier: Amsterdam, Boston, 2006.

(9) Dondoni, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8995.

Scheme 2. High-Load Linear Proline Polymers

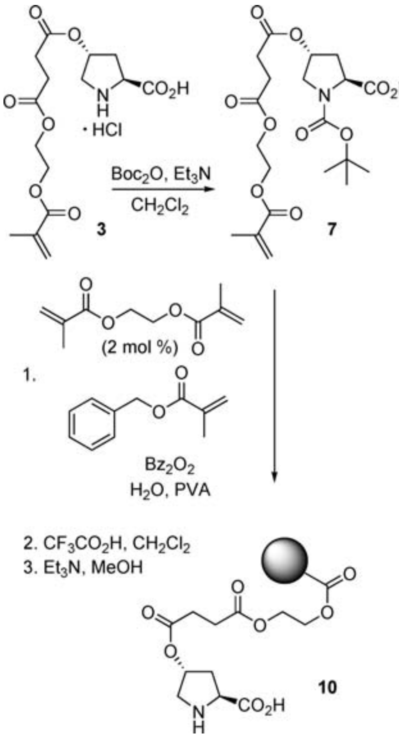


benzyl methacrylate or styrene, using the standard 2 mol % of crossbinder, either ethyleneglycol dimethacrylate (EGDMA) or divinylbenzene (DVB).[10] The benign experimental procedures involved in suspension polymerization are superb for large-scale preparations. Workup and purification are simple decantation, filtration, and Soxhlet extraction.

A monomer in suspension polymerization cannot have a very high degree of water solubility, so proline methacrylate **2** and **3** were carbamate protected to their equivalent Boc-derivatives **6** and **7**, respectively. Straightforward copolymerization with different comonomers then gave acrylic polymer beads **8**−**10**, as exemplified for polymer beads **10** in Scheme 3. The proline methacrylate **3** is protected to carbamate **7** and suspension copolymerized together with benzyl methacrylate and 2 mol % EGDMA (in water with polyvinyl alcohol (PVA) as suspension stabilizer) to fully methacrylic beads **10**, directly in one operation by using carbamate **7** directly in crude form.

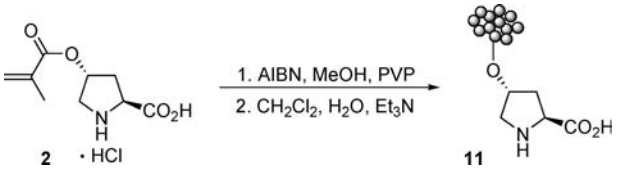
As for beads **10**, beads **8** are prepared in complete analogy by starting with proline methacrylate **2** (without a linker). Polymer beads **9** are equivalently prepared from proline methacrylate **3**, but this time using styrene with 2 mol % DVB instead of the methacrylic comonomers, giving a methacrylic/styrenic hybrid polymer bead. All beads were deprotected and purified by Soxhlet extraction before use, giving beautiful pearly polymer beads on >10 g scale with very little work and no chromatography (micrographs of all polymer beads are given in Supporting Information). The desired catalyst loading is conveniently attained by simply mixing the monomers in the appropriate ratios, in a more controllable manner than direct catalyst anchoring. In this work, we have simply used a catalyst methacrylate/comonomer ratio so as to give catalyst loadings in the typical 0.5−0.8 mmol/g range, very similar to the earlier work.[2g−m] The swelling properties of the resultant beads in water and lower alcohols (solvents that are difficult to use with traditional polystyrene supports) can easily be controlled by substituting some of the comonomer with *tert*-butyl methacrylate. During the CF_3CO_2H treatment, free carboxylic acids are liberated, giving a polymer that can, if needed, swell to a very high degree in water.

Scheme 3. Polymer Beads by Suspension Copolymerization



In our new approach, it is even possible to prepare solid-supported proline without using any protecting groups by using dispersion copolymerization, a form of stabilized precipitation polymerization (Scheme 4).[10,11]

Scheme 4. Agglomerated Polymer Microspheres by Dispersion Copolymerization



Proline methacrylate **2** is simply dissolved in MeOH together with benzyl methacrylate, EGDMA, AIBN, and polyvinylpyrrolidone (PVP) as stabilizer and stirred for 5 h to give a polymer granulate **11** that encompasses both a microporous and macroporous structure (see Supporting Information for pictures by reflection electron microscopy)

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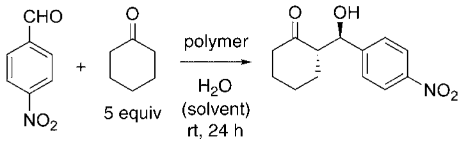
(10) For a thorough distinction between suspension, emulsion and dispersion polymerization, see: Arshady, R. *Colloid Polym. Sci.* **1992**, *270*, 717.

(11) For a review of polymer microspheres by dispersion polymerization, see: Jayachandran, K. N. N.; Chatterji, P. R. *J. Macromol. Sci. Polymer Rev.* **2001**, *C41*, 79.

on a >10 g scale. This makes solid-support proline available from hydroxyproline in only 2 steps overall, a far shorter route than by traditional anchoring.[2] This product is interestingly reminiscent of the popcorn polymers of Letsinger,[12] a pioneer of the field together with Merrifield in the early 1960s.[5] This dispersion method can combine very hydrophilic with very hydrophobic monomers directly, but catalyst incorporation during the precipitation is now no longer the near direct reflection of the monomeric composition, as in suspension polymerization.

We have benchmarked these polymeric supports in the typical aldol reaction of *p*-nitrobenzaldehyde with cyclohexanone (Table 1). Both fully methacrylic supports (**8**, **10**, **11**) and acrylic/styrenic hybrid **9** performed excellently, giving quantitative conversions and excellent enantioselectivities after 24 h in water. This was also the case for supports without any sort of linker (**8** and **11**), a result we found surprising given the very poor performance of such nonlinked proline on the Merrifield resin, showing the promising potential of such acrylic supports.[2m] The addition of $CHCl_3$, which naturally influences swelling of such styrenes and methacrylates quite strongly, influences enantioselectivities to a negligible extent but can give marked differences in the diastereomeric ratio, as seen especially for the very porous dispersion polymerized support **11**. The hybrid support **9**, the most extensively studied of our copolymer beads, was reused 5 times with unaffected results. These beads even performed nicely at 1 mol % loading with virtually unaffected results (however, with incomplete conversion), this being unusually rare for proline.[13]

Table 1. Benchmark Aldol Reaction Catalyzed by Suspension and Dispersion Copolymerized Supports

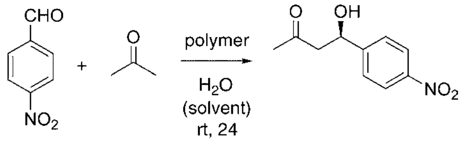


polymer	f [mol %][a]	yield [%][b]	*anti*:*syn*[c]	ee [%][d]
8	10[e]	85	94:6	97
8	10[f]	67	91:9	98
9	10[e]	85	98:2	98
9	10[f]	91	96:4	98
9	5[e]	71	97:3	98
9	1[e]	85	97:3	98
10	10[e]	88	95:5	99
10	10[f]	83	99:1	98
11	10[e]	76	93:7	98
11	10[f]	65	88:12	98

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

A solid-supported prolineamide catalyst, very powerful for aldol reactions with acetone (Table 2),[4] was directly available from the prolines through peptide coupling, again on a robust multigram scale, before deprotection (Scheme 5). By using (*S*)-diphenyl phenylglycinol (**13**), beads **9** gave prolineamide **12** after peptide coupling, the premium reaction for solid supports.

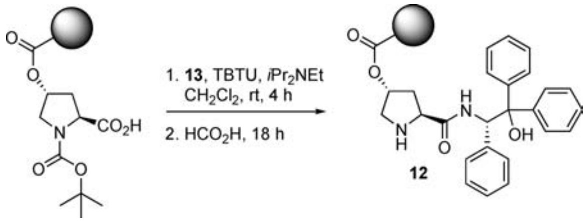
Table 2. Aldol Reaction Catalyzed by Proline Support **9** and Prolineamide Support **12**



polymer	f [mol %][a]	yield [%][b]	ee [%][c]
9	10[d]	29	27
9	10[e]	18	36
12	10[d]	82	90
12	10[e]	93	91

[a] f = catalyst loading. [b] Isolated yield. [c] Determined by HPLC. [d] In H_2O. [e] In $H_2O/CHCl_3$.

Scheme 5. Prolineamide Beads **12** from Beads **9**



As known from the work by Gruttadauria, supported prolineamide of type **12** readily outperformed supported proline in aldol reactions with acetone giving the products in high yields and enantioselectivities (Table 2),[4] a reaction in which immobilized proline gave only mediocre results (Table 2). In comparison to those previously reported, our acrylic/styrenic beads **12** were readily available on preparative scale and did not require addition of $CHCl_3$ for high-quality results.[4] Other prolineamides should be readily available by adopting the peptide coupling for other amines of interest.

In conclusion, we have shown how the introduction of acrylic chemistry gave immediate access to solid-supported proline and prolineamides on preparative scale in a system with abundant possibilities for adaption.

Acknowledgment. This work was supported by Birkeland Innovation, the Technology Transfer Office of the University of Oslo. *trans*-4-Hydroxy-L-proline was generously donated by Evonik Degussa GmbH.

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

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(12) Letsinger, R. L.; Kornet, M. J. *J. Am. Chem. Soc.* **1963**, *85*, 3045.

(13) For an extensive 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 therein.