Homogeneous Catalysis

DOI: 10.1002/ange.200502095

One-Pot Reaction Cascades Using Star Polymers with Core-Confined Catalysts**

Brett Helms, Steven J. Guillaudeu, Yu Xie, Meredith McMurdo, Craig J. Hawker, and Jean M. J. Fréchet**

An attractive feature of dendritic systems, and possibly other highly branched polymers, is their ability to encapsulate and isolate various functional groups within the interior of the molecule.[1] In many applications, from light harvesting to catalysis, the benefit derived from site isolation is typically the preservation of both the structure and activity of moieties that would normally be sensitive to quenching or deactivation if used as small molecules.[2] Site isolation as such has been used since the work of Patchornik and co-workers with so-called "wolf and lamb" reactions, in which otherwise incompatible reagents on large heterogeneous particulate solid supports were used in mixed-bed reactors to perform multiple steps of a reaction sequence.[3] More recent investigations of sol–gels with encapsulated opposing reagents have made the concept of "wolf and lamb" reactions emerge as a powerful tool to probe site-isolation effects in cross-linked solid materials.[4] To our knowledge, this concept has never been applied to soluble molecular reagents, such as star polymers, although their synthetic accessibility relative to dendrimers makes them attractive targets for practical applications. Herein, we report a one-pot reaction cascade performed with two different star polymers, each containing a different catalytic group confined in its core. To demonstrate the synthetic utility that site isolation affords, we have devised a "wolf and lamb" test, in which otherwise incompatible acid and base catalysts are employed to effect the overall transformation. Our results clearly show that encapsulation of both acidic and basic groups within highly branched, yet fully soluble, multiarm star polymers suppresses their mutual deactivation, thus allowing for a sequence of acid and base reactions to be performed in succession (Figure 1). Thus, the concept of "wolf and lamb"

---

[*] Prof. C. J. Hawker
Materials Research Laboratory
University of California
Santa Barbara, CA 93106 (USA)
Fax: (+1) 805-893-8797
E-mail: hawker@chem.ucsb.edu

B. Helms, S. J. Guillaudeu, Y. Xie, M. McMurdo, Prof. J. M. J. Fréchet
Department of Chemistry
University of California
Berkeley, CA 94720 (USA)
Fax: (+1) 510-643-3079
E-mail: frechet@berkeley.edu

[**] This work was funded through the National Science Foundation (NSF-DMR0317514) and the Department of Energy (DE-AC03-76SF00098). Dr. Jeffrey Pyun contributed to early exploratory work on this project.

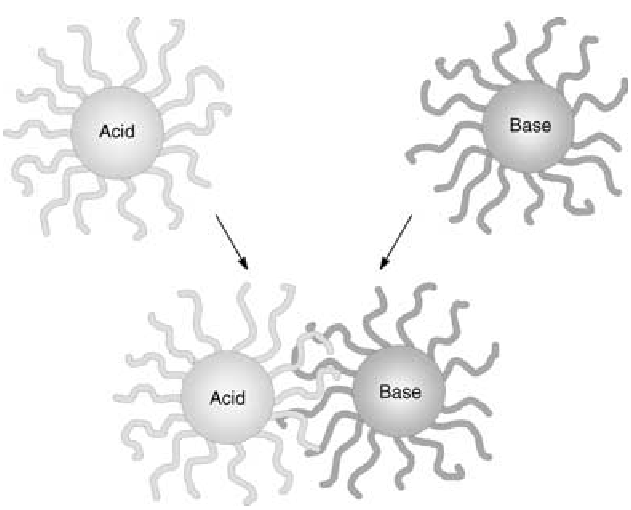


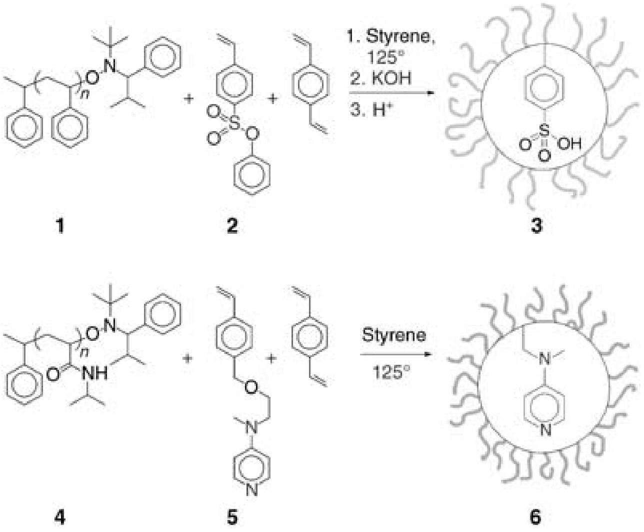
Figure 1. Acid- and base-containing star polymers with non-interpenetrating highly cross-linked cores.

reactions, previously limited to immiscible solid reagents, has now been demonstrated successfully with reactive moieties attached to well-defined and sterically restricted locations within soluble synthetic macromolecules that are comparable in size to many proteins.

The preparation of highly branched multiarm star polymers with a narrow polydispersity has been an active area in polymer science as these materials provide quick access to globular macromolecules that bear some crude resemblance to the more structurally perfect dendrimers. Although syntheses of dendrimers have been well documented, it is only recently that techniques have been put forth to prepare well-defined star polymers without resorting to living anionic methods.[5] We recently reported an "arm-first" approach based on nitroxide-mediated living free-radical polymerization.[6]

Star polymers that contain analogues of *para*-toluenesulfonic acid (PTSA) groups at the core were prepared by using the arm-first approach. A low-molecular-weight polystyrene macroinitiator **1** was prepared in bulk from an α-hydrido-alkoxyamine initiator and styrene at 125 °C (Scheme 1; size-exclusion chromatography (SEC) with THF: $M_n = 6250$, $M_w = 6730$, polydispersity index (PDI) = 1.07).[7] Star polymers were then obtained by using a 1:4:10 ratio of **1**, divinylbenzene (DVB), and a mixture of co-monomers (styrene and the functional monomer phenyl 4-styrenesulfonate (**2**) in 3:2 ratio). The phenylsulfonate esters were saponified with KOH in methanolic THF and then acidified to generate the active form of the catalyst. The star polymers **3** thus obtained were of high molecular weight (SEC with THF: $M_n = 66150$, $M_w = 78530$; multiangle laser light scattering (MALLS): $M_n = 221200$, $M_w = 260200$) and narrow polydispersity (PDI = 1.19). Further examination of the SEC traces of **1** and **3** indicates clean conversion to the macromolecule without any low-molecular-weight polymer contaminants (Figure 2a), which is critical to achieve catalyst isolation. Elemental analysis of the sulfur content of **3** revealed 0.45 mmoles of sulfonic acid groups per gram of polymer, or approximately 100 residues per star polymer. These values correspond to 3–4 acidic groups per arm for the 35–40-arm star polymer or 7–8 wt %.

Similarly, star polymer **6**, which contains amine moieties, was synthesized by the arm-first method from an *N*-isopropylacrylamide (NIPAAm) macroinitiator **4** (SEC with *N*,*N*-dimethylformamide (DMF): $M_n = 4450$, $M_w = 5890$, PDI = 1.32) and a styrene monomer **5** that contains a pendant 4-(dialkylamino)pyridine catalyst (Scheme 1). The same optimized ratio of 1:4:10 was used for the polymerization of **6** (SEC with DMF: $M_n = 59160$, $M_w = 110210$, PDI = 1.86; MALLS: $M_n = 526300$, $M_w = 640800$), with the co-monomer portion composed of styrene and **5** in a 1:1 ratio. Although the SEC data with DMF as the solvent (Figure 2b) indicate a less-controlled star polymerization and a higher molecular weight for **6** (approximately 100 arms per star) relative to **3**, we were satisfied with the absence of contamination by low-molecular-weight species and proceeded with the catalytic experiments. The catalyst loading for **6** was evaluated by using UV spectroscopy with 4-(dimethylamino)pyridine (DMAP) as the reference compound in $CHCl_3$ ($\lambda_{max} = 260$ nm), with subtraction of any background absorbance from the poly-NIPAAm-core-(PS-co-DVB) star polymer. An upper value of 0.63 mmoles of **5** per gram of polymer was measured which corresponds to approximately 350 catalytic groups per star polymer or 3 or 4 residues per arm. Therefore, the DMAP-



Scheme 1. Synthesis of star polymers that contain core-confined PTSA analogues or 4-(dialkylamino)pyridines.

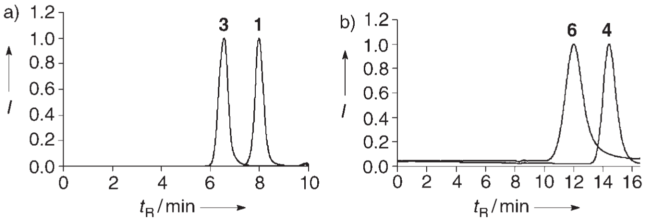
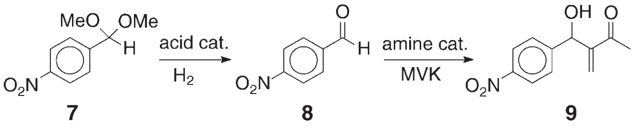


Figure 2. a) SEC traces with THF as the solvent for macroinitiator **1** and star polymer **3**; b) SEC traces with DMF as the solvent for macroinitiator **4** and star polymer **6**.

like residues constitute up to 5–7% of the weight in the polymer.

The chemical transformations targeted for this system were the acid-catalyzed deprotection of 4-nitrobenzaldehyde dimethyl acetal and the nucleophilic amine-catalyzed Baylis–Hillman reaction of 4-nitrobenzaldehyde with methyl vinyl ketone (MVK) (Scheme 2).[8] As control experiments, reactions were performed in the absence of any catalysts; with DMAP and PTSA; with non-polymer-bound DMAP and **3**; and with non-polymer-bound PTSA and **6** (Table 1).



Scheme 2. One-pot-reaction cascade involving sequential acid-catalyzed acetal hydrolysis followed by the amine-catalyzed Baylis–Hillman reaction.

Table 1: Catalytic results for the reaction cascade using acid and amine catalysts.

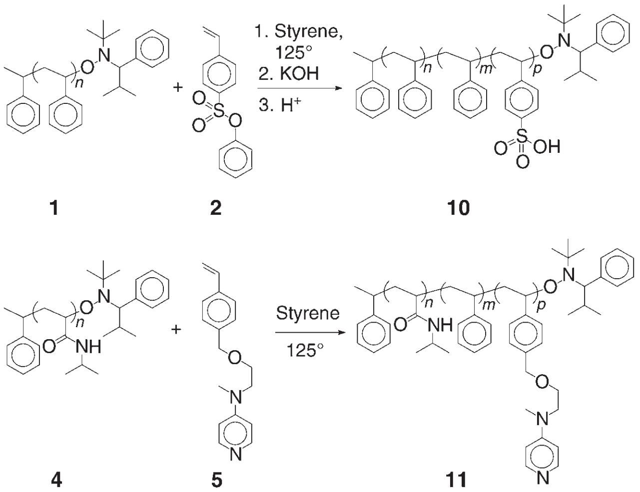
Entry	Acid catalyst[a]	Amine catalyst[a]	Yield of **8** [%][b]	Yield of **9** [%][b]
1	**3**	**6**	34	65
2	**3**	DMAP	9	0
3	PTSA	**6**	6	0
4	PTSA	DMAP	3	0
5	**3**	**11**	<1	0
6	**10**	**6**	<1	0
7	none	none	0	0

[a] Reaction conditions: 10 mol% acid and amine catalysts were used. $[\mathbf{7}]_0 = 0.50\,\text{M}$ in DMF with H_2O (1 equiv) and MVK (4 equiv). The reaction mixtures were heated at 70 °C in sealed vials for 36 h. [b] Yields are based on GC-MS measurements with decane as the internal standard. The values represent an average of three runs.

Complete hydrolysis of the acetal was observed over the course of a few hours when the reaction was performed with **3** and **6**, and at the end of the experiment 65% of the aldehyde had been converted into the Baylis–Hillman adduct. When either of the small-molecule catalysts DMAP or PTSA were added to **3** or **6**, respectively, only partial hydrolysis of the acetal was observed (Table 1, entries 2 and 3), which was also the case when PTSA and DMAP were added (entry 4). Finally, the acetal appears to be stable to hydrolysis when no catalysts are used (entry 7).

Given that a Baylis–Hillman adduct did not form in any of the entries except those in which both **3** and **6** were used, we reason that when the small molecules DMAP or PTSA are added to **3** and **6**, respectively, they can penetrate the cores of the star polymers and deactivate the acidic and basic groups through salt formation. The absence of reactivity for the resulting salt is confirmed by entry 4. The partial hydrolysis observed in entries 2 and 3 points to the difficulty of titrating the exact amount of catalyst in each internally cross-linked star polymer for a given reaction.

To examine further the site-isolation properties of these polymers, acid- or amine-containing diblock copolymers were synthesized from the same macroinitiators and functional monomers used in the preparation of **3** and **6** (Scheme 3). The acid-containing polymer **10** (SEC with THF: $M_n = 8170$, $M_w = 9090$, PDI = 1.11, 0.73 mmol of sulfur per gram polymer) and amine-containing polymer **11** (SEC with DMF: $M_n = 6980$, $M_w = 10\,050$, PDI = 1.44, 0.55 mmol of catalyst per gram polymer) were prepared to best resemble the star polymers in terms of composition but not architecture. When either of these diblock copolymer catalysts was used along with the complementary star polymer (namely, **3** with **11** or **10** with **6**, entries 5 and 6, respectively), the reaction cascade did not proceed. This result implies that the linear polymers can penetrate the corona of the star polymers with the same deleterious effects as either PTSA or DMAP, thus confirming our hypothesis that the catalysts must be confined to the sterically restricted core of the star polymers before the advantages of site isolation can be realized.



Scheme 3. Synthesis of diblock copolymers containing PTSA analogues or 4-(dialkylamino)pyridines.

Thus, we have shown that core-confined groups in these high-molecular-weight, yet fully soluble, star polymers appear to be site isolated as is observed with moieties at the core of dendrimers. As a result of this site isolation, sequential catalysis of a "wolf and lamb" two-step reaction using catalytic species that are normally incompatible with each other is possible. This ability to generate a pathway by which a cascade of reactions is enabled is reminiscent of biological systems in which a series of discrete reactions performed by different enzymes is used to create a wide range of chemical functionality and diversity through the combination of a few simple steps.

Experimental Section

3: The polymerization mixture containing polystyrene macroinitiator **1** (1.93 g, 0.355 mmol; SEC with THF: $M_n = 6247$, $M_w = 6728$, PDI = 1.07), DVB (336 mg, 1.42 mmol; 55 wt%), styrene (221 mg, 2.13 mmol), and phenyl 4-styrenesulfonate (**2**; 369 mg, 1.42 mmol) in DMF (7.28 g) was heated at 125 °C for 16 h. The reaction mixture was diluted with CH_2Cl_2 and precipitated on addition to *i*PrOH. Fractionation from benzene using methanol gave a solid, which was reprecipitated to give 2.54 g of the star polymer (89 %). The star polymer (250 mg, 1.25 µmol) was treated with KOH (250 mg, 4.45 mmol) in MeOH/THF (9:1) at 50 °C for 16 h, acidified with H_2SO_4, and precipitated on addition to *i*PrOH to give a white solid (215 mg, 87 %). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.5$–6.9 (br, Ar-H), 6.8–6.3 (br, Ar-H), 2.1–1.7 (br, -C(Ar)*H*-), 1.7–1.2 ppm (br, -CH_2-); IR (thin film): $\tilde{\nu} = 3600$–3200, 3081, 3059, 3025, 2924, 2850, 1942, 1873, 1804, 1746, 1730, 1713, 1687, 1600, 1584, 1492, 1452, 1413, 1372, 1217, 1179, 1155, 1126, 1069, 1030, 1006, 907, 834, 758, 699, 667 cm^{-1}; SEC with THF: $M_n = 66150$, $M_w = 78530$, PDI = 1.19; MALLS: $M_n = 221200$, $M_w = 260200$.

6: The polymerization mixture containing polyNIPAAm macroinitiator **4** (280 mg, 69.4 µmol; SEC with DMF: $M_n = 4453$, $M_w = 5888$, PDI = 1.32), DVB (66 mg, 0.279 mmol; 55 wt %), styrene (36 mg, 0.344 mmol), and 4-(dialkylamino)pyridine monomer **5** (93 mg, 0.345 mmol) in DMF (1.35 g) was heated at 125 °C for 16 h. The reaction mixture was diluted with CH_2Cl_2 and precipitated on addition to cold diethyl ether. Fractionation from acetone using hexanes gave the solid, which then reprecipitated to give 120 mg of the star polymer (33 %). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.3$–8.0 (br, Py-H; Py = pyridine), 7.1–6.2 (br, Ar-H, -N*H*-*i*Pr), 4.2–3.9 (br, -C*H*(Me)$_2$), 3.8–3.5 (br, N-C*H*$_2$-C*H*$_2$-O), 3.2–2.9 (br, N-CH_3), 2.5–2.3 (br, Ar-C*H*$_2$-O), 2.3–1.8 (br, -C(Ar)*H*-, -C(C=O)*H*-, -C*H*$_2$-), 1.8–1.5 (br, -CH_2-), 1.4–0.8 ppm (br, -CH(C*H*$_3$)$_2$); IR (thin film): $\tilde{\nu} = 2965$, 2928, 1664, 1608, 1598, 1529, 1453, 1384, 1366, 1211, 1171, 1129, 989, 910, 804, 763, 701 cm^{-1}; SEC with DMF: $M_n = 59160$, $M_w = 110210$, PDI = 1.86; MALLS: $M_n = 526300$, $M_w = 640800$.

Received: June 16, 2005

Keywords: amines · dendrimers · homogeneous catalysis · polymers · reaction cascades

---

[1] S. Hecht, J. M. J. Fréchet, *Angew. Chem.* **2001**, *113*, 76–94; *Angew. Chem. Int. Ed.* **2001**, *40*, 74–91.

[2] a) C. Müller, L. J. Ackerman, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.* **2004**, *126*, 14960–14963; b) L. F. Lee, A. Adronov, R. D. Schaller, J. M. J. Fréchet, R. J. Saykally, *J. Am. Chem. Soc.* **2003**, *125*, 536–540; c) E. M. Harth, S. Hecht, B. Helms, E. E. Malmström, J. M. J. Fréchet, C. J. Hawker, *J. Am. Chem. Soc.* **2002**, *124*, 3926–3938; d) D. Astruc, F. Chardac, *Chem. Rev.* **2001**, *101*, 2991–3023; e) R. M. Crooks, M. Zhao, L. Sun, V. Chechik, L. K. Yeung, *Acc. Chem. Res.* **2001**, *34*, 181–190; f) D.-L. Jiang, T. Aida, *Nature* **1997**, *388*, 454–456; g) P. Bhyrappa, J. K. Young, J. S. Moore, K. S. Suslick, *J. Am. Chem. Soc.* **1996**, *118*, 5708–5711.

[3] a) A. Patchornik, *Proc. IUPAC Macromol. Symp.* **1982**, *28*, 85; b) B. J. Cohen, M. A. Kraus, A. Patchornik, *J. Am. Chem. Soc.* **1981**, *103*, 7620–7629.

[4] a) F. Gelman, J. Blum, D. Avnir, *New J. Chem.* **2003**, *27*, 205–207; b) F. Gelman, J. Blum, D. Avnir, *Angew. Chem.* **2001**, *113*, 3759–3761; *Angew. Chem. Int. Ed.* **2001**, *40*, 3647–3649; c) F. Gelman, J. Blum, D. Avnir, *J. Am. Chem. Soc.* **2000**, *122*, 11999–12000.

[5] a) X. Hao, C. Nilsson, M. Jesberger, M. H. Stenzel, E. Malmström, T. P. Davis, E. Oestmark, C. Barner-Kowollik, *J. Polym. Sci. Part A* **2004**, *42*, 5877–5890; b) Y, Zhao, X. Shuai, C. Chen, F. Xi, *Macromolecules* **2004**, *37*, 8854–8862; c) M. Kamigaito, T. Ando, M. Sawamoto, *Chem. Rec.* **2004**, *4*, 159–175; d) V. Darcos, A. Dureault, D. Taton, Y. Gnanou, P. Marchand, A.-M. Caminade, J.-P. Majoral, M. Destarac, F. Leising, *Chem. Commun.* **2004**, *18*, 2110–2111; e) K. Matyjaszewski, P. J. Miller, J. Pyun, G. Kickelbick, S. Diamanti, *Macromolecules* **1999**, *32*, 6526–6535.

[6] a) A. W. Bosman, R. Vestberg, A. Heumann, J. M. J. Fréchet, C. J. Hawker, *J. Am. Chem. Soc.* **2003**, *125*, 715–728; b) A. W. Bosman, A. Heumann, G. Klaerner, D. Benoit, J. M. J. Fréchet, C. J. Hawker, *J. Am. Chem. Soc.* **2001**, *123*, 6461–6462.

[7] D. Benoit, V. Chaplinski, R. Braslau, C. J. Hawker, *J. Am. Chem. Soc.* **1999**, *121*, 3904–3920.

[8] a) D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811–891; b) J.-W. Huang, M. Shi, *Adv. Synth. Catal.* **2003**, *345*, 953–958.