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ARTICLE TYPE

Acid- and base-functionalized core-confined bottlebrush copolymers catalysts for one-pot cascade reactions

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We demonstrate a novel method that enables the core-confined bottlebrush copolymers (CCBCs) as catalysts support. Significantly, owing to the site-isolated effect, these CCBCs catalysts with the incompatible acidic para-toluenesulfonic acid (PTSA) and basic 4-

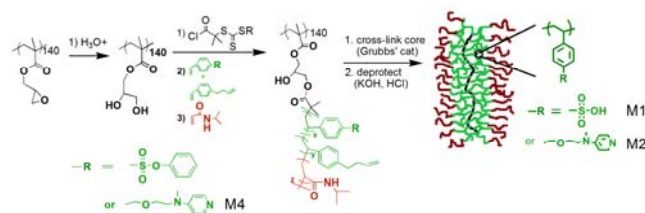
(dialkylamino)pyridine (DMAP) groups can conduct a simple two-step sequential reaction in one vessel.

In the past decade, many investigations have been focused on the development of green chemical processes and synthetic methods due to environment considerations.^{1,2} The capability to carry out multiple reactions in one flask plays an important role in the field of green chemistry because it decreases the number of work-ups and purifications, as well as the volume of solvent used. These reactions are often called cascade or domino reactions, which represents the development trend of modern organic synthesis due to the simplified process with low cost, less waste and product purification steps. A key problem for the cascade reactions is how to site-isolate catalysts or reagents from each other such that they do not come into contact and poison one another to avoid undesired interactions. Up to now, several catalyst site-isolation techniques have been developed by using solid supports or sol-gels to encapsulate opposite catalysts.³⁻¹³ More recently, soluble polymers with branched architectures, such as dendritic and hyperbranched polymers, have emerged as attractive nanoscale reactors for the encapsulation and isolation of various catalytic groups within the interior of the polymers.¹⁴⁻¹⁶ In particular, Frechet et al.¹⁷ reported the use of star polymers to combine the normally incompatible acid and base catalysts for one-pot cascade reactions. Although recent advancements in supramolecular chemistry, nanomaterial synthesis, and catalyst design have significantly improved our ability to construct incompatible multifunctional catalytic system, developing new and easy methods for site-isolating catalyst that can operate one-pot sequential reactions still retains a significant challenge.

Molecular bottlebrushes are single graft copolymer molecules with a well-defined cylindrical shape which is a result of the steric hindrance between the polymeric side chains forcing the backbone to adopt a nearly extended conformation.¹⁸⁻²⁴ Recently, considerable attention has been drawn to these macromolecules due to their potential for intramolecular nanoengineering, such as templates for inorganic nanoparticles or nanowires,²⁵⁻³¹ and for development of novel material properties, such as supersonic elastomers,^{32, 33} photonic crystals,³⁴⁻³⁸ molecular tensile

machines,³⁹ drug-loading vehicles,^{40, 41} organic nanotubes,⁴²⁻⁴⁴ other carbon nanostructures⁴⁵ and water-soluble organo-silica hybrid nanotubes.⁴⁶ Resembling dendritic, hyperbranched and star polymers, which contains multiple arms joined at a central core. Core-shell bottlebrush copolymers are composed of highly branched polymeric side chains emanating from a central backbone. Especially, the unique shape, easily controlled dimensions and versatile synthesis routes of molecular bottlebrushes render them useful as single-molecule manipulation to create site-isolated nano-objects. To date, there have been no reports for the precise introduction of catalytic functional groups into bottlebrush copolymers.

In this paper, we described a novel method that enables the CCBCs as catalysts support for one-pot cascade reactions. Owing to the site-isolated effect, these CCBCs catalysts with the incompatible acid and base groups can conduct a simple two-step sequential reaction in one vessel.



Scheme 1. Fabrication of core-confined bottlebrush copolymers supported catalysts

CCBCs containing acidic PTSA or basic DMAP catalysts confined in their core were successfully synthesized by a “graft-from” approach with the help of the reversible addition-fragmentation chain transfer polymerization (RAFT) and metathesis cross-linking reaction. The structure of the target bottlebrush copolymer precursor is shown in Scheme 1. First, poly(glycidyl methacrylate) (PGM) backbones with an average of 140 units were prepared by RAFT polymerization mediated by 2-cyanoprop-2-yl 4-cyanodithiobenzoate (CPD). The polymer had an extremely narrow molecular weight distributions (Mw/Mn < 1.1). Pendant epoxide groups of PGM were then hydrolyzed to provide diols, which served as initiators for S-1-Dodecyl-S'-(alpha, alpha'-dimethyl-alpha''acetic acid)trithiocarbonate (TC) RAFT modification. The successful outcome of the esterification was evident by the appearance of a new signal at 3.28 ppm

belonging to the methylene protons adjacent to the trithiocarbonate group (Fig. S1, ESI†). Based on the area integration analysis of the peak at 3.28 ppm (designated “e” in Fig. S1) and the methyl peak (around 0.90 ppm) from the main chain and RAFT end groups (designated “a” and “g” in Fig. S1), we can calculate the number of grafted RAFT groups. Under using an excess of RAFT agent acid chloride, an average of 63% of hydroxy units were successfully converted to RAFT groups. Then, the phenyl 4-vinylbenzenesulfonate (PVBS) or 4-N-(4-vinylbenzyl)oxyethyl-N-methylaminopyridine (VEMAP) as catalytic groups with cross-linkable 4-(3-butenyl)styrene (BS) groups were randomly grafted onto the PGM backbone by RAFT polymerization to form acid or base-containing bottlebrush copolymers. In order to improve the solubility and steric hindrance of the final CCBCs catalysts, a poly(N-isopropylamide) (PNIAAM) shell layer was introduced into the bottlebrush architecture to form core-shell structural precursor. Finally, the acid-containing bottlebrush copolymers were composed of the poly(PVBS/BS) core block with an average of 23 PVBS and 10 BS units and PNIAAM shell block with an average of 220 units confirmed by ¹H NMR spectroscopy analyses. Similarly, the base-containing bottlebrush copolymers contained the poly(GM-g-VEMAP\BS\St) core block with an average of 10 VEMAP and 4 BS and 4 St units and PNIAAM shell block with an average of

260 units (Fig. S2 and Fig. S3, ESI†). Every bottlebrush molecular contained approximately 4057 acidic groups (or 1764 basic groups) as measured by ¹H NMR analysis of the bottlebrush copolymer precursors. Size exclusion chromatography (SEC) traces of the acid or base-containing bottlebrush copolymers precursor exhibited monomodal molecular weight distributions trace with PDI = 1.17 and 1.10 respectively (Fig. S4 and Fig. S5, ESI†), which indicated efficient reinitiation and the formation of well-defined copolymers. According to previously reported method,³⁸ the pendant olefinic groups of the BS units were linked together by the cross-metathesis reaction to produce core-confined architecture in copolymers precursor. For the acid-containing bottlebrush copolymers, the phenylsulfonate esters can be deprotected with KOH solution and then acidified to produce acidic paratoluenesulfonic acid groups. The shape and size of the synthesized acid- and base-containing CCBCs were also characterized by transmission electron microscopy (TEM) (Fig. 1 and Fig. S6, ESI†). As we expected, clearly distinguishable of cylindrical nanorods with a length of 30±6 nm and a diameter of 8±2 nm can be observed.

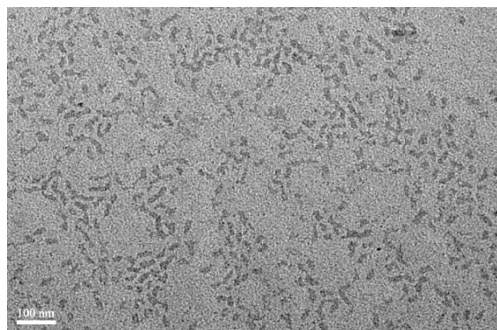
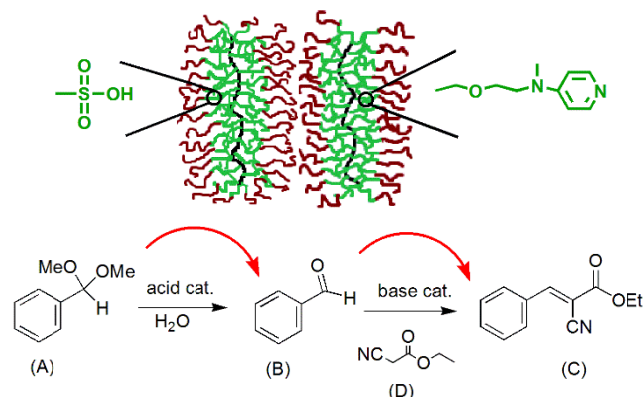


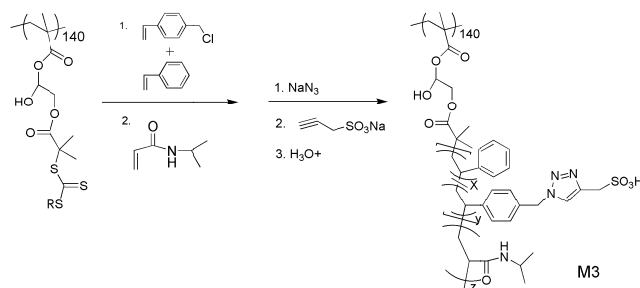
Fig.1 TEM characterization of acid-containing CCBCs.

Next, we explored the possibility of our materials as catalysts support for the one-pot cascade reactions. An acid-catalyzed acetal hydrolysis and the subsequent base-catalyzed Knoevenagel condensation were used as model reactions (Scheme 2). Reactions with either free acid or free base, and with uncross-linked bottlebrush copolymers catalysts were also performed as control experiments (Table 1).



Scheme 2 Illustration of core-confined bottlebrush copolymers supported catalysts for one-pot cascade reactions.

The results showed that a complete hydrolysis of the acetal to benzaldehyde and 87% yield of target product C were observed when the reaction was performed with M1 and M2. When the sequence is carried out only in the presence of small-molecule catalysts DMAP or PTSA with M1 or M2, only little hydrolysis of acetal and little yield of target product C is observed. As predicted, these small-molecular catalysts could freely diffuse into the core of the CCBCs and deactivate the acidic or basic groups through acid-base neutralization reactions. The deactivated CCBCs could no longer catalyze the reaction cascade. This acid-base neutralization-induced deactivation was also confirmed by mixing both DMAP and PTSA in the reaction solution (entry 4). Based on the above results, we conclude that CCBCs provides effective site-isolation, preventing mutual deactivation of incompatible core-bound catalytic groups.



Scheme 3 Synthesis of the acid-containing uncross-linked bottlebrush copolymers

The importance of cross-linking in the CCBCs was established by control experiments carried out with acid- or base-containing uncross-linked bottlebrush copolymers. Because the side chains in the bottlebrush copolymers will be cut off during the process

of phenylsulfonate esters deprotection. Therefore, an alternative procedure was offered to prepare the acid-containing uncross-linked bottlebrush copolymers with similar composition and architecture as shown in the Scheme 3. When the reaction cascade was carried out by using uncross-linked catalysts M3 and M4, only 5% yield of target product C was observed. Again, only 8% or 9% yield of target product C was observed when either of these uncross-linked catalysts M3 or M4 was used along with the complementary CCBCs M1 or M2 respectively. We reasoned that the uncross-linked bottlebrush copolymer can also penetrate the corona of the CCBCs with the same deactivation effects as either small-molecular PTSA or DMAP. Thus, the presence of cross-linking in the core layer of bottlebrush copolymers appears to be essential for producing site isolation effect for one-pot cascade reactions.

Table 1. Catalytic results for a one-pot reaction cascade using CCBCs acid and base catalysts.

Entry	Base catalyst ^[a]	Acid catalyst ^[a]	Conversion of A[%] ^[b]	Yield of C[%] ^[b]
1	M2	M1	100%	87%
2	DMAP	M1	5%	4%
3	M2	PTSA	7%	5%
4	DMAP	PTSA	0	0
5	M3	M1	9%	8%
6	M2	M4	10%	9%
7	M3	M4	6%	5%

[a] Reaction conditions: 10 mol% acid and base catalysts were used. The reaction mixtures were run for 48 h at 70°C in DMSO/H₂O (40:1), [D]=300mM, n(A):n(D) = 1:4. [b] Yields are based on GC-MS measurements.

Conclusions

In summary, we have developed a new system for preparing site-isolated catalysts based on the core-confined bottlebrush copolymers as support structure. By bound incompatible organic acid and base into the core-confined section of CCBCs, these acidic or basic groups can be effectively isolated and served as catalysts for a one-pot cascade reaction. We believe that this strategy can be further developed into a general pathway for other incompatible catalyst system, in which the efficiency of organic synthesis will improve significantly.

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Notes and references

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