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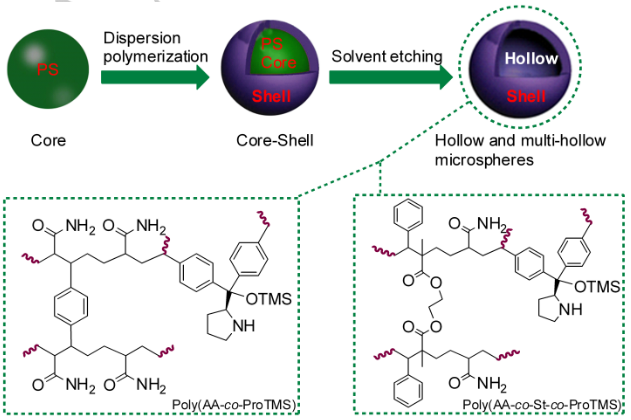
Novel functional hollow and multi-hollow organic microspheres: enhanced efficiency in heterogeneous asymmetric three-component/triple complex organocascade reaction

Fuqiang Dai[a], Zhiwei Zhao[a], Guangxin Xie[a], Dandan Feng[a] and Xuebing Ma*[a]

Abstract: The pioneered construction of monodisperse hollow and multi-hollow Jørgensen–Hayashi-functionalized microspheres with a well-defined spherical morphology, high surface area and large pore volume were developed by the first dispersion copolymerization of Jørgensen–Hayashi organocatalyst with acrylamide and styrene monomers cross-linked by *p*-divinylbenzene and ethylene glycol dimethacrylate respectively on the surface of poly(styrene/acrylic acid) (PS) microsphere to form the core-shelled structures, followed by the removal of PS core by etching in organic solvents. The as-prepared hollow and multi-hollow microspheres paved an exquisite strategy to achieve better mass transfer in complex heterogeneous asymmetric three-component/triple cascade reaction in good yields (31-61%) and excellent stereoselectivities (80:20–93:7 dr, >99 %ee).

Multi-component asymmetric organocatalytic cascade/domino reactions with the advantages of high atom-economy, reduced waste generation and synthetic efficiency have gained a great deal of interest over the last decade as an effective tool for the highly valuable construction of optically active complex molecular structures with multiple stereocenters relevant for pharmaceutical and natural products.[1] From the viewpoint of green chemistry, it is highly desirable for expensive organocatalyst to be recovered and reused to achieve the perspective of economical efficiency and sustainability in cascade/domino reactions by the immobilization of organocatalysts onto various supports such as polymers, inorganic silica and other metal oxides.[2] However, the ever-reported successful heterogenization of homogeneous star organocatalyst focused on relatively simple two-component/double cascade reactions. For more complicated three-component/triple cascade reaction, the harsher requirements appear to place many significant and somewhat differing demands on the characteristic of reaction environment, especially in heterogeneous catalytic phase. Unfortunately, the first heterogeneous three-component Michael/Michael/aldol condensation triple cascade reaction comprising a linear aldehyde, a nitroalkene and an *a, β*-unsaturated aldehyde, catalyzed by crosslinked or pendant-functionalized polystyrene[3] and acrylic polymer[4]-supported Jørgensen–Hayashi catalyst, afforded optically active tetra-substituted cyclohexene carbaldehydes with the disappointing catalytic results below 45% yield even for 7 days due to their intrinsic serious mass transfer limitations for the fast movement of guest molecules throughout the material.

The past two decades have witnessed the rapid growth of interest in hollow spheres owing to their outstanding features with a well-defined structure, high specific surface area, low density, abundant inner void, surface functionalization accessibility, permeability and good compatibilities.[5] Up to now, the tremendous efforts have been made in the fabrication of hollow-structured spheres with a controlled composition, tailored structure and unique properties *via* hard-templating, soft-templating and template-free methods.[6] In the field of catalysis, these hollow-structured spheres enhanced the catalytic activity and stability of catalyst owing to their protection against agglomeration and free access for reactants to active catalytic sites in heterogeneous catalysis,[7] such as metal catalysis,[8] photocatalysis,[9] acid catalysis [10] and organocatalysis.[11] Among them, silica was generally used as a backbone for constructing hollow-structured shell. In fact the compatibility of catalyst support with reactants played an important role in the mass transfer of reactants inside the inner matrix of heterogeneous catalyst. Therefore, in view of enhanceed mass transfer resulted from the good compatibility of hollow-structured organic shell, the development of functional hollow organic microsphere containing robust organocatalyst is imperative and highly desirable for successful heterogeneous multi-component asymmetric organocascade reactions. To the best of our knowledge, seldom was reported on the fabrication of hollow organic microspheres applied in the field of catalysis.



Scheme 1. The schematic illustration of the heterogeneous hollow Poly(AA-*co*-ProTMS) and multi-hollow Poly(AA-*co*-St-*co*-ProTMS) organocatalysts

In this communication, we reported the fabrication of a novel class of monodisperse functional hollow and multi-hollow organic microspheres bearing Jørgensen–Hayashi organocatalyst [(S)-*α*, *α*-Bis(4-vinylphenyl)prolinol trimethylsilyl ether, [12] ProTMS]. Based on hard-template-assisted method, the well-defined microspheres of ProTMS-functionalized hollow Poly(AA-*co*-ProTMS) and multi-hollow Poly(AA-*co*-St-*co*-ProTMS) were prepared *via* the first dispersion copolymerization of ProTMS with acrylamide (AA) or AA and styrene (St) cross-linked respectively by *p*-divinylbenzene (DVB) or ethylene glycol dimetha-

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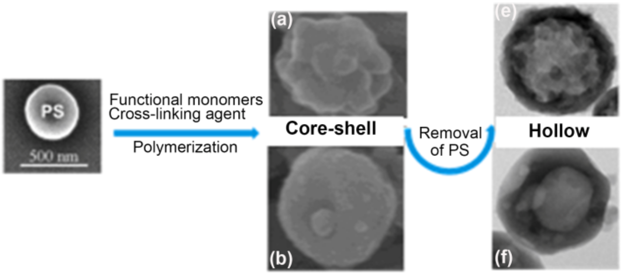
crylate (EGDMA) on the external surface of poly(styrene/ acrylic acid) (PS) microspheres to form the core-shelled structure, and then the further removal of PS core by etching in organic solvents (Scheme 1).



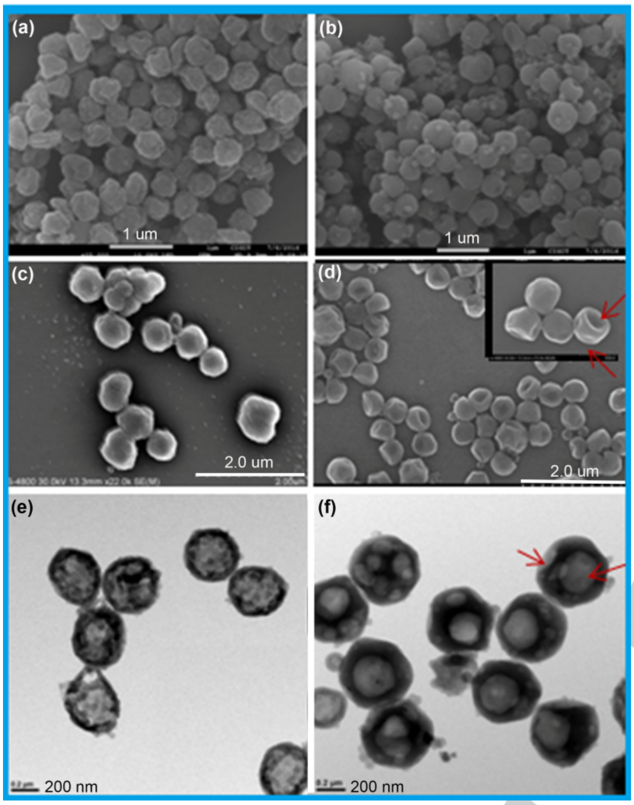


Figure 1. The SEM and TEM images of the core-shelled and hollow microspheres: SEM of PS@poly(AA-*co*-ProTMS) (a), SEM of PS@poly(AA-*co*-St-*co*-ProTMS) (b), SEM of hollow Poly(AA-*co*-ProTMS) (c), SEM of multi-hollow Poly(AA-*co*-St-*co*-ProTMS) (d), TEM of hollow Poly(AA-*co*-ProTMS) (e) and TEM of multi-hollow Poly(AA-*co*-St-*co*-ProTMS) (f).

The carboxyl-capping poly(styrene/acrylic acid) microspheres with the hexagonal and uniform size of 350–400 nm (Figure S1) were prepared by emulsifier-free copolymerizetion.[13] From the SEM images shown in Figure 1a, b, the shell thickness of core–shelled microspheres PS@poly(AA-*co*-St-*co*-ProTMS) and PS@poly(AA-*co*-ProTMS) was measured in the range of *ca.* 30–50 nm from the change of the diameter of particle in size, indicating the formation of uniform organic outermost shell. Due to the irregular aggregation of monomers and selective polymerization cross-linked respectively by DVB and EGDMA, it was observed that the core-shelled PS@poly(AA-*co*-ProTMS) and PS@poly (AA-*co*-St-*co*-ProTMS) exhibited the rough and highly smooth surface, respectively.[14] After the removal of PS and St-selfpolymerized-nanospheres (< 5 nm) by etching in DMF, the Poly(AA-*co*-St-*co*-ProTMS) microspheres with the multi-dimple-like concave (Figure 1d) and multi-hollow interiors (Figure 1f) were confirmed by SEM and TEM images. Similarly, using DVB as a cross-linker in the absence of monomer St, the well-defined hollow Poly(AA-*co*-ProTMS) (350–400 nm) with the THF-insoluble thin shell (25–40 nm) comprised of the copolymer of ProTMS with AA cross-linked by BVB was also constructed by the removal of PS core using THF as an etchant (Figure 1e). Moreover, in order to elucidate the enhanced catalytic efficiency promoted by mentioned-above hollow microspheres in multi-component/triple cascade reaction, the Poly(St-*co*-ProTMS) copolymer with the nanosphere-interlinked morphology (Figure S2) was also prepared as a control sample by the direct copolymerization of styrene and ProTMS in emulsive aqueous ethanol solution (*v/v* = 5:4) at 70 °C for 10 h.

The loading capacity of organocatalyst ProTMS in poly(St-*co*-ProTMS) was easily determined by elemental analysis to be 1.38 mmol g^{-1} on the basis of nitrogen content contained in ProTMS (1.93%). Owing to nitrogen-contained monomer AA, the gravimetric method by calcining the Poly(AA-*co*-ProTMS) and Poly(AA-*co*-St-*co*-ProTMS) samples at 1000 °C was used as a method to determine the loading capacities of ProTMS. Calculated from the mass of SiO_2 converted from organic silicon under oxygen atmosphere at high temperature, Poly(AA-*co*-ProTMS) and Poly (AA-*co*-St-*co*-ProTMS) possessed 0.57 mmol g^{-1} and 0.54 mmol g^{-1} of ProTMS organocatalyst, respectively. From N_2 adsorption-desorption isotherms (Table S2), the hollow Poly(AA-*co*-ProTMS) (112.8 m^2 g^{-1}, 0.487 cc g^{-1}) and multi-hollow Poly (AA-*co*-St-*co*-ProTMS) (138.8 m^2 g^{-1}, 0.558 cc g^{-1}) possessed the higher BET-specific surface areas and pore volumes than the core-shelled PS@poly(AA-*co*-ProTMS (56.1 m^2 g^{-1} and 0.198 cc g^{-1}) and PS@poly(AA-*co*-St-*co*-ProTMS) (73.4 m^2 g^{-1} and 0.278 cc g^{-1}), respectively. Unfortunately, the control sample Poly(St-*co*-ProTMS) copolymer afforded the lowest BET-specific surface area (13.1 m^2 g^{-1}) and pore volume (0.026 cc g^{-1}). Moreover, the pore size distributions (PSDs) (Figure S5, ESI†) displayed the porous shell of hollow Poly(AA-*co*-ProTMS) and multi-hollow Poly(AA-*co*-St-*co*-ProTMS), whose porous features were required especially for the diffusion and transport of reactants inside the active catalytic sites. It was noteworthy that the hollow Poly(AA-*co*-ProTMS) possessed the non-uniform microporous and mesoporous structures with the several peaks (0.7, 1.5, 1.9, 2.6, 4.8 and 8.0 nm) in the 0.5–10 nm range (Figure S5b, ESI†). Delightedly, using EGDMA as a cross-linking agent, the shell of the multi-hollow Poly(AA-*co*-St-*co*-ProTMS) exhibited the single microporous structure (1.4 nm) with a narrow porous distribution (Figure S5d, ESI†), which was different from the current hollow spheres with the quasi-nonporous or highly disordered porous shell.[15] Additionally, TGA showed that the multi-hollow Poly(AA-*co*-St-*co*-ProTMS) contained 11.8% of adsorbed hydration water from the mass loss below 150 °C. After the temperature reached above 200 °C, a sharp weight loss of organic moieties (82.8%) was observed (Figure S6, ESI†), which illustrated that the multi-hollow Poly(AA-*co*-St-*co*-ProTMS) only remained thermally stable below 200 °C.

In the proposed mechanism of three-component/triple Michael/Michael/aldol condensation cascade reaction, the three-step reaction begins with the first Michael addition of propionaldehyde enamine to nitrostyrene, further undergoes the second Michael addition to the iminium derivative of cinnamaldehyde, and then completes the intramolecular aldol cyclocondensation of the resulting enamine to produce optically active tetra-substituted cyclohexene carbaldehydes.[16] Here, the whole reaction process was monitored by HPLC. The peak area ratios (S_P/S_M) of the peak area (S_P) of final product (3S, 4S, 5R, 6R)-3-methyl-5-nitro-4, 6-diphenylcyclohex-1-ene carbaldehyde to that (S_M) of reactant *trans-β*-nitrostyrene plotted versus reaction time (0–48 h) were used as the parameters to evaluate the catalytic activities of the copolymeric Poly(St-*co*-ProTMS), core-shelled PS@ poly(AA-*co*-St-*co*-ProTMS) and multi-hollow Poly(AA-*co*-St-*co*-ProTMS).

From Figure 2, Poly(St-*co*-ProTMS) could not promote favourably the three-component triple cascade reaction only with S_P/S_M = 0.18 for 48 h due to its severe mass transfer limitation of the constrained steric environments resulted from the low surface area (13.1 m^2 g^{-1}) and pore volume (0.026 cc g^{-1}), although Poly (St-*co*-ProTMS) possessed the highest loading capacity of ProTMS organocatalyst (1.38 mmol g^{-1}). Indeed, the first Michael adduct of propylaldehyde to *trans-β*-nitrostyrene was isolated in good yield (86%) with 98 %ee, indicating that the first Michael adduct could be formed rapidly and then accumulated. However, the further Michael addition to the iminium derivative of cinnamaldehyde was sterically hindered for the final product (< 5% yield) owing to severe mass transfer limitation. By means of the package of ProTMS on the surface of PS microspheres, the core-shelled PS@poly(AA-*co*-St-*co*-ProTMS) with the significantly improved surface area (73.4 m^2 g^{-1}) and pore volume (0.278 cc g^{-1}), where most of active ProTMS were located on the external shell, exhibited the increased catalytic activity with S_P/S_M = 2.3 for 48 h due to the effective exposure of active ProTMS. Even so, the final product was isolated in only 12% yield. The similar yield (8%) for the core-shelled PS@poly(AA-*co*-ProTMS) was also obtained. For this process to succeed, the somewhat differing demands on the characteristics of catalytic environments should be required in this complex heterogeneous three-component/triple cascade reaction. To our delight, after the removal of PS core, the multi-hollow Poly(AA-*co*-St-*co*-ProTMS) with the highest surface area (138.8 m^2 g^{-1}) and pore volume (0.558 cc g^{-1}) in virtue of the most active catalytic sites showed the significantly enhanced catalytic activity with S_P/S_M = 10.3 for 48 h (Table S3, ESI†) and afforded the final product in 43% yield with the excellent stereoselectivity (89:11 *dr*, >99 %ee) similar as homogeneous ProTMS (46%, 89:11 *dr*, >99 %ee) (20 mol% of ProTMS in toluene at 30 °C for 48 h. Similarly, the hollow Poly(AA-*co*-ProTMS) (36%, 87:13 *dr*, 99 %ee) also displayed the more effective catalytic activity than its corresponding core-shelled PS@ poly(AA-*co*-ProTMS) (8%, 86:14 *dr*, 99 %ee) (Table S4, ESI†). Moreover, the further investigation of ever-reported MNPs Fe_3O_4 -supported ProTMS organocatalyst [12] gave the disappointed result (10% yield). On this basis, it was concluded that the multi-hollow and hollow-structured morphology significantly improved the pore volume and surface area of well-defined Poly(AA-*co*-ProTMS) and Poly(AA-*co*-St-*co*-ProTMS) microspheres, and eventually produced the more active and effective ProTMS, favoring the enhanced catalytic activity in the complex heterogeneous cascade reaction.

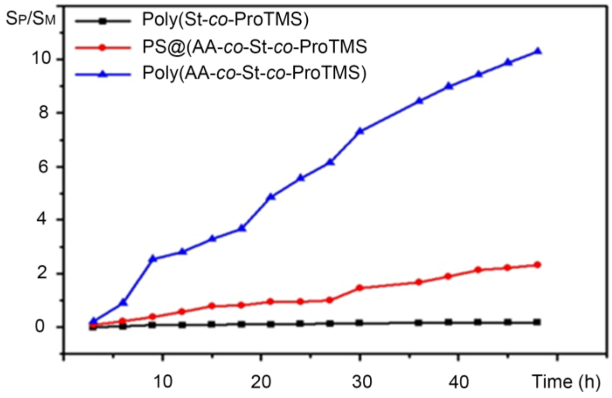
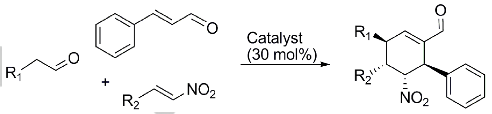


Figure 2. The peak area ratio profiles (S_P/S_M) of peak area (S_P) of the final product (3*S*, 4*S*, 5*R*, 6*R*)-3-methyl-5-nitro-4, 6-diphenylcyclohex-1-ene carbaldehyde to that (S_M) of *trans-β*-nitrostyrene plotted versus reaction times during whole reaction.

Table 1. Heterogeneous asymmetric three-component/triple organocascade promoted by hollow Poly(AA-*co*-St-*co*-ProTMS) and Poly(AA-*co*-ProTMS).[a]



Entry	R_1	R_2	Yield (%)[b]	Dr[c]	%ee[d]
1	Me	C_6H_5	61	91:9	>99
			55[e]	90:10	>99
2	Me	4-$MeOC_6H_5$	41	89:11	>99
			34[e]	89:11	>99
3	Et	C_6H_5	55	87:13	>99
			51[e]	87:13	>99
4	Me	Furyl	46	86:14	>99
			43[e]	85:15	>99
5	*i*-Pr	C_6H_5	45	80:20	>99
			40[e]	80:20	>99
6	Me	2-ClC_6H_5	45	91:9	>99
			41[e]	89:11	>99
7	Me	3-ClC_6H_5	40	90:10	>99
			39[e]	90:10	>99
8	Me	4-ClC_6H_5	35	89:11	>99
			34[e]	87:13	>99
9	Me	4-BrC_6H_5	34	93:7	>99
			31[e]	92:8	>99
10	*n*-Pr	C_6H_5	60	80:20	>99
			51[e]	80:20	>99
11	Et	3-ClC_6H_5	45	89:11	>99
			44[e]	89:11	>99
12	Et	2-ClC_6H_5	53	87:13	>99
			48[e]	85:15	>99

[a] Poly(AA-*co*-St-*co*-ProTMS) (110 mg, 30 mol%), *trans-β*-nitrostyrene (0.2 mmol, 1.00 eq.), cinnamaldehyde (0.21 mmol, 1.05 eq.), aliphatic aldehyde (0.24 mmol, 1.2 eq.), acetic acid (0.04 mmol) and DIPEA (0.06 mmol) in toluene (3 mL) at 30 °C for 48 h. [b] Yield of the isolated single, major diastereoisomer. [c] Determined by ^1H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis of isolated single, major diastereoisomer on a chiral phase. [e] Catalyzed by 30 mol% of poly(AA-*co*-ProTMS).

After the further optimization of catalytic conditions such as solvent, temperature and dosage of catalyst in heterogeneous Michael/Michael/aldol condensation cascade, the final product (3*S*, 4*S*, 5*R*, 6*R*)-3-methyl-5-nitro-4, 6-diphenylcyclohex-1-ene carbaldehyde in good yield (61%) with excellent stereoselectivity (89:11 dr, >99 %ee) were finally achieved with 30 mol% of multi-hollow Poly(AA-*co*-St-*co*-ProTMS) at 30 °C in toluene (3 mL) for 48 h. With the optimized conditions at hand, we set out to examine the scope of substrates promoted by multi-hollow Poly(AA-*co*-St-*co*-ProTMS). As shown in Table 1, not only the linear aldehydes but also branched aldehydes could afford optically active *tetra*-substituted cyclohexene carbaldehydes in the satisfactory yields (34–61%) with the high diasteroselectivities (80:20–93:7 *dr*) and excellent enantioselectivities (>99 %ee). Especially, the aromatic nitroalkenes bearing *o*-Cl substituent gave the higher yields than those bearing *m, p*-Cl substituents (Entries 6–8, 11, 12). Furthermore, the hollow Poly(AA-*co*-ProTMS) afforded the good diasteroselectivities (80:20–92:8 *dr*) and excellent enantioselectivities (>99 %ee), but slightly lower yields (31-55%) than multi-hollow Poly(AA-*co*-St-*co*-ProTMS). Unfortunately, like homogeneous ProTMS, the Poly(AA-*co*-St-*co*-ProTMS) and Poly(AA-*co*-ProTMS) microspheres catalyzed aliphatic nitroalkene to produce the trace product, even for 72 h. Additionally, it was worthwhile to note that the multi-hollow Poly(AA-*co*-St-*co*-ProTMS) afforded the similar catalytic performance as the homogeneous ProTMS.[16]

After the completion of cascade reaction, the microsphere Poly(AA-*co*-St-*co*-ProTMS) was recovered by centrifugation and directly reused in the next run after being washed with ethyl acetate (5 mL × 3). To our delight, the good diasteroselectivities (85–91:15–9) and constant excellent stereoselectity (99% ee) could be achieved in five consecutive cycles of Poly(AA-*co*-St-*co*-ProTMS). However, the isolated yields of final product gradually decreased from 61%, 58%, 54%, 49% to 48% in the fifth run, which was probably attributed to the several factors including the partially collapsed hollow structure (Figure S7, ESI†), irregular pore distribution (Figure S8, ESI†) and decreased surface area (32.1 m^2 g^{-1}), pore volume (0.203 cc g^{-1}) resulted from the adsorbed reactants and products.

In conclusion, the fabrication of monodisperse ProTMS-functionalized hollow and multi-hollow microspheres with the well-defined morphology, high specific surface area and large pore volume provided a strategy for solving catalytic efficiency of complex heterogeneous three-component/triple organocascade reaction through the dramatic increase in effective catalytic sites. We believe that the methodology of the enhanced catalytic efficiency by the hollow-structure for better mass transfer will benefit more extensive applications in other complex heterogeneous cascade reaction.

Experimental Section

Preparation of Poly(AA-*co*-ProTMS): A N$_2$-filled three-necked flask (100 mL) was charged with KI (6.0 mg, 0.035 mmol), K$_2$CO$_3$ (18.5 mg, 0.135 mmol), AA (143.0 mg, 2.0 mmol), aqueous poly(vinylalcohol) solution (PVA, 5 mL, 0.5 wt%) in turn and well-dissolved. Then, aqueous ethanol suspension (11 mL, *v/v* = 1/10) of carboxyl-capping PS (200 mg) containing PVA (0.5 wt%) was also added. After well-dispersed, the ethanol solution (2.0 mL) containing ProTMS (150.0 mg, 0.4 mmol) and *p*-divinylbenzene (DVB, 130.0 mg, 1.0 mmol) was injected and well-dispersed under sonication. Finally, the aqueous solution (2 mL) of potassium peroxydisulfate (40.0 mg, 0.15 mmol) was added by syringe. The resulting translucent emulsion was started by heating up to 70 °C and carried out for 20 h under N$_2$ atmosphere. The solid PS@poly(AA-*co*-ProTMS) was separated by centrifugation, washed with DI water (10 mL × 3) and ethanol (10 mL × 3). The obtained PS@poly(AA-*co*-ProTMS) was dispersed in THF (20 mL) under sonication for 5 min and separated by centrifugation. After treated three times in THF (20 mL), the primrose yellow solid was washed with DI water (10 mL × 3), ethanol (10 mL × 3) and dried under vacuum at 50 °C for 6 h to afford the hollow Poly(AA-*co*-ProTMS) (410.5 mg).

Preparation of Poly(AA-*co*-St-*co*-ProTMS): To a N$_2$ filled three-necked flask (250 mL) was successively added AA (213.5 mg, 3.0 mmol), aqueous ethanol suspension (11 mL, *v/v* = 1/10) of carboxyl-capping PS (250.0 mg) containing PVA (0.5 wt%) and aqueous PVA solution (55 mL, 0.5 wt% of PVA). After well-dispersed, the ethanol solution (3 mL) containing ethylene glycol dimethacrylate (EGDMA, 148.5 mg, 0.75 mmol), styrene (104.3 g, 1.0 mmol) and ProTMS (75.0 mg, 0.2 mmol) was added dropwise and well-dispersed under sonication for 30 min. The resulting translucent emulsion was heated to 80 °C and stirred for 24 h. The yellow solid PS@poly(AA-*co*-St-*co*-ProTMS) was separated by centrifugation and washed with DI water (10 mL × 3), ethanol (10 mL × 3). The obtained PS@poly(AA-*co*-St-*co*-Pro-TMS) was treated by DMF (20 mL) under sonication for 5 min to remove the core PS and then separated by centrifugation. After dealt with DMF (20 mL) three times, the primrose yellow solid was washed with ethanol (10 mL × 3) and dried under vacuum at 50 °C for 6 h to afford the hollow Poly(AA-*co*-St-*co*-ProTMS) (401.8 mg).

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Keywords: Heterogeneous catalysis • Organocatalysis• Hollow microsphere • Three-component/triple cascade reaction• Enhanced catalytic efficiency

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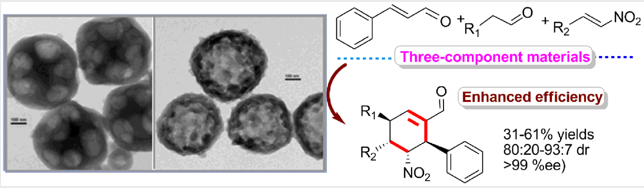

The monodisperse Jørgensen–Hayashi catalyst-functionalized multi-hollow and hollow microspheres with the well-defined spherical morphology and high surface area enhanced complex heterogeneous three-component asymmetric triple cascade reaction. The hollow microsphere exhibited the excellent stereoselectivity in the fifth reuse

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Novel functional hollow and multi-hollow organic microspheres: enhanced efficiency in heterogeneous asymmetric three-component/triple complex organocascade reaction