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One-Pot Multi-Component Asymmetric Cascade Reactions Catalyzed by Soluble Star Polymers with Highly Branched Non-Interpenetrating Catalytic Cores

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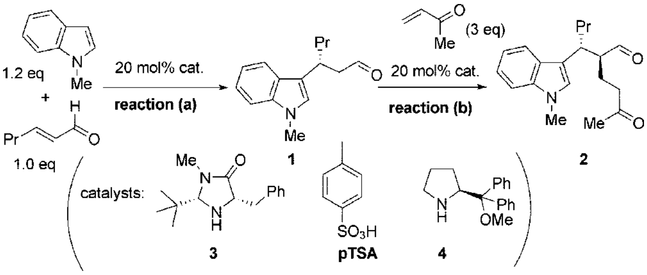
Living cells often concurrently make many complex molecules via multistep cascade reactions. For these multiple simultaneous enzymatic reactions to work well, one key concept nature adopts is “compartmentalization” or “site isolation”, through which incompatible substrates and enzymes are spatially separated to avoid undesired interactions.[1] Chemists have applied the principle of site isolation to catalysis by using solid supports[2] or sol−gels[3] to encapsulate opposite reagents.[4] In recent years, soluble dendritic and other hyperbranched polymers have emerged as attractive systems for the encapsulation and isolation of various functional groups within the interior of the polymers.[5] We have recently explored the use of *soluble* hyperbranched polymers to combine the normally incompatible acid and base catalysts in one pot for a simple two-step sequential reaction.[6] In this paper, we report the design of non-interpenetrating star polymer catalysts to combine iminium,[7] enamine,[8] and hydrogen-bond[9] catalysts in one pot for asymmetric reactions that generate cascade products with more than one chiral center. We also demonstrate that the proper combination of catalyst chirality allows straightforward access to all possible stereoisomers of the cascade products individually. To the best of our knowledge, our work represents the most sophisticated study on soluble polymers for site isolation asymmetric catalysis.

Previous research has established MacMillan imidazolidinone pairing with strong acid as optimal iminium ion catalyst[10] and proline-derived chiral pyrrolidine as excellent enamine catalyst.[11] In some cases, a single imidazolidinone or proline-derived pyrrolidine has also been used to mediate one-pot reactions involving both iminium and enamine catalysis. This approach has certain advantages, as it uses a single catalyst to mediate multiple catalytic cycles. However, the same amine catalyst is often *only* optimal for one catalytic cycle (poor for other cycles). Additionally, the use of a single asymmetric catalyst for one-pot multiple catalytic cycles can only give access to a limited set of diastereomer(s) of the cascade products. We aimed to develop a general system to combine *optimal* enamine and iminium catalysts in one pot for sophisticated multistep reactions. Our work began with careful investigation on an imidazolidinone-mediated nucleophilic addition of *N*-methyl indole to 2-hexenal to give **1** [iminium catalysis; reaction (a), Scheme 1] previously developed by MacMillan and co-workers[12] and a chiral pyrrolidine-catalyzed Michael addition of **1** to methyl vinyl ketone (MVK) [enamine catalysis; reaction (b), Scheme 1][8,13] using small molecule catalysts. Our results (see Supporting Information) showed that none of the three catalysts and cocatalysts (**3**, pTSA, and **4**) nor any of their combinations can mediate both reaction steps. In particular, the presence of strong acid pTSA (alone or paired with imidazolidinone **3**) diminished the ability of **4** to effect enamine catalysis. Consequently, a simple combination of these catalysts in one pot cannot mediate a cascade reaction involving both reactions (a) and (b).

Scheme 1. Study of Each Individual Reaction Step Using Small Molecule Catalysts



We therefore proposed to encapsulate analogues of pTSA or **4** in the core of a star polymer to give **5** and **7**, respectively (Figure 1). Star polymers **5** and **7** cannot penetrate each other’s core and therefore are expected to maintain their catalytic integrity. On the other hand, small molecule reagents and catalysts can freely diffuse to the core of the star polymers, allowing efficient catalysis to take place. For instance, small molecule imidazolidinone **3** can diffuse to the core of the acid star polymer **5** to form a desired salt **6**, which is an optimal iminium catalyst. Electrostatic attraction should retain **3** within the core of **5** during catalysis. Additionally, a hydrogen-bond donor catalyst (**8**, a much weaker acid than pTSA)[14] added to the one-pot reaction is expected to activate the relatively nonreactive Michael acceptor (MVK) in the enamine catalysis cycle.

To test our hypotheses, we synthesized star polymers with core-confined catalytic entities using the arm-first approach previously developed in the Hawker and Fréchet groups.[15] Acid star polymer **5** was prepared according to a known procedure.[6] Elemental analysis of the sulfur content of **5** revealed 0.60 to 0.67 mmols of sulfonic acid per gram of polymer. Similarly, amine star polymer **7** (SEC with THF: $M_n = 70\,014$, $M_w = 92\,151$, PDI = 1.32; MALLS: $M_w = 216\,900$) core-confined with chiral pyrrolidine was synthesized from polystyrene macroinitiator **9** (SEC with THF: $M_n = 6577$, $M_w = 7301$, PDI = 1.11), divinylbenzene cross-linker, and functional monomer **10** (Scheme 2).[16] ^{1}H NMR analysis of **7** indicated approximately 0.30 mmol amine catalyst per gram of polymer.[16]

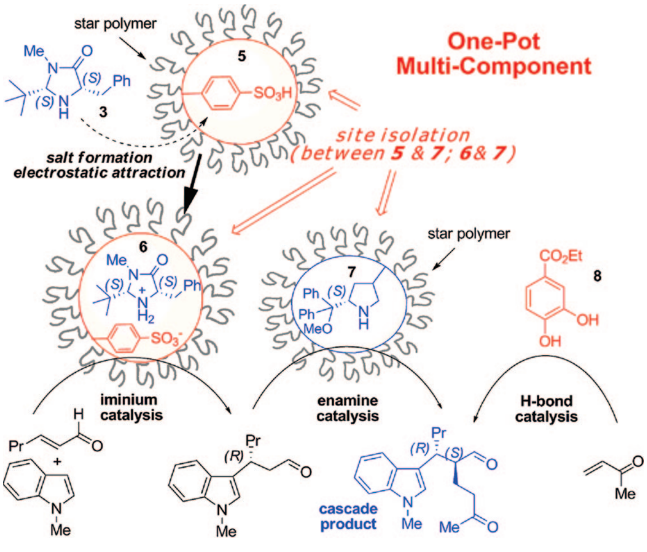


Figure 1. Illustration of our design: non-interpenetrating star polymers for one-pot cascade catalysis.

Scheme 2. Synthesis of Star Polymer

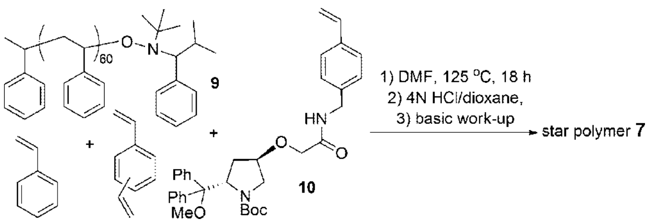
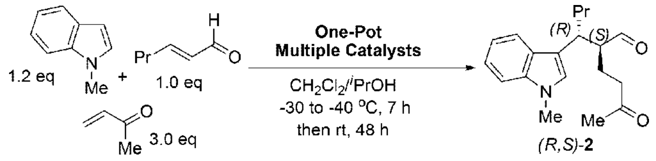


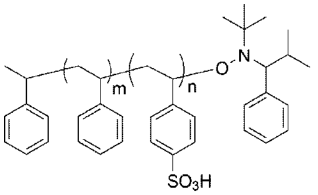
Table 1. One-Pot Multi-Catalyst Cascade Reactions



entry[a]	catalyst combination[b]		yield%[d] (**2**)	dr[d]	ee[e]
1	**3**, **5**, **7**	star polymers	33	100:7	n.d.[f]
2	**3**, **5**, **7**, **8**	star polymers	**89**	100:8	>99%
3	**3**, pTSA, **7**, **8**	controls[c]	0		
4	**3**, **5**, **4**, **8**	controls[c]	0		
5	**3**, pTSA, **4**, **8**	controls[c]	0		
6	**3**, **11**, **7**, **8**	controls[c]	4		
7	**3**, **5**, **12**, **8**	controls[c]	0		
8	(*R*,*R*)-**3**, **5**, **7**, **8**	star polymers	80	8:100 (*S*,*S*)-**2**	>99%

[a] See Supporting Information. [b] About 20 mol % (relative to 2-hexenal) of each catalyst (**8** is 100 mol %). [c] Star polymer catalyst was replaced by its small molecule or linear polymer analogue. [d] Sum of diastereomers; measured by ^{1}H NMR of the crude reaction mixture. [e] Determined by chiral phase HPLC after proper derivatization. [f] Not determined.

The catalytic activities of star polymers **5** and **7** were first evaluated separately. Polymer **5** showed a catalytic activity comparable to that of pTSA paired to imidazolidinone **3** for the iminium catalytic reaction (a) in Scheme 1. While the catalytic efficiency of unoptimized star **7** is somewhat lower than that of its corresponding small molecule analogues for enamine catalytic reaction (b) in Scheme 1, good catalytic turnover can still be obtained by extending the reaction time.[17]



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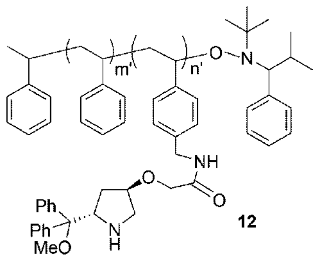

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We then employed the star polymer catalysts for the one-pot multiple-component cascade reaction shown in Table 1. In early experiments, the three catalyst components (**3**, **5**, **7**; ~ 20 mol % each, relative to 2-hexenal) and the three substrates (*N*-methyl indole, 2-hexenal, MVK) were mixed in one pot, and approximately 30% cascade product was observed after 5 days. Control experiments using small molecule catalysts (**3**, pTSA, and **4**) under the same conditions did not give any cascade product. Reaction condition optimization suggested that addition of **7** to the reaction mixture after the iminium catalytic cycle neared its completion gave better results (Table 1, entry 1).[18] The overall reaction efficiency was further enhanced when H-bonding catalyst **8** was used to activate MVK (100 mol % relative to 2-hexenal; Table 1, entry 2). This result showed that the widely studied hydrogen bonding catalysis could be combined in one pot with iminium and enamine catalysis to perform sophisticated tasks. Excellent yield (89%) and stereoselectivity (100:7 dr, >99% ee for the major diastereomer) of the cascade product can be achieved in 2 days when the non-interpenetrating star polymer catalysts are employed for the one-pot reaction. When acid star polymer **5** was replaced with pTSA, and/or amine star polymer **7** with **4**, no cascade product was observed (Table 1, entries 3−5). Additionally, replacing either of the star polymers (**5** and **7**) with their linear polymer analogues (**11** and **12**) resulted in little cascade product formation (Table 1, entries 6 and 7). These linear polymers were made to represent the chemical composition but not the architecture of the star polymers. The lack of cascade product formation likely arises from penetration of small molecule or linear polymer catalysts to the core of the star polymers. Finally, we demonstrated that individual access to all four possible stereoisomers of the cascade reactions can easily be achieved through a simple combination of catalyst chirality. For instance, when catalyst **3** is replaced with its enantiomer [(*R*,*R*)-**3**], a diastereomer of cascade product **2** can be obtained with excellent stereoselectivity (Table 1, entry 8).

In summary, we have demonstrated that proper site isolation with star polymers enables the combination of otherwise incompatible catalysts for sophisticated asymmetric cascade reactions. Our strategy may be extended to combine stereo-incompatible catalysts (i.e., catalysts that give opposite stereoselectivities) for one-pot cascade reactions.

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Supporting Information Available: Addtional experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Vriezema, D. M.; Garcia, P. M. L.; Oltra, N. S.; Hatzakis, N. S.; Kuiper, S. M.; Nolte, R. J. M.; Rowan, A. E.; Hest, J. C. M. V. *Angew. Chem., Int. Ed.* **2007**, *46*, 7378.
(2) (a) Zeidan, R. K.; Hwang, S.-J.; Davis, M. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 6332. (b) Motokura, K.; Fujita, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2005**, *127*, 9674.
(3) (a) Gelman, F.; Blum, J.; Avnir, D. *J. Am. Chem. Soc.* **2000**, *122*, 11999. (b) Avnir, D.; Coradin, T.; Lev, O.; Livage, J. *J. Mater. Chem.* **2006**, *16*, 1013.
(4) (a) Poe, S. L.; Kobaslija, M.; McQuade, D. T. *J. Am. Chem. Soc.* **2006**, *128*, 15586. (b) Phan, N. T. S.; Gill, C. S.; Nguyen, J. V.; Zhang, Z. J.; Jones, C. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 2209. (c) Voit, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4238. (d) Cohen, B. J.; Kraus, M. A.; Patchornik, A. *J. Am. Chem. Soc.* **1981**, *103*, 7620.
(5) Hecht, S.; Fréchet, J. M. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 74.
(6) Helms, B.; Guillaudeu, S. J.; Xie, Y.; McMurdo, M.; Hawker, C. J.; Fréchet, J. M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6384.
(7) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416.
(8) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.
(9) (a) Pihko, P. M. *Angew. Chem., Int. Ed* **2004**, *43*, 2062. (b) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520.
(10) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79.
(11) Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876.
(12) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172.
(13) Melchiorre, P.; Jorgensen, K. A. *J. Org. Chem.* **2003**, *68*, 4151.
(14) Peelen, T. J.; Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2005**, *127*, 11598.
(15) Bosman, A. W.; Heumann, A.; Klaerner, G.; Benoit, D.; Fréchet, J. M. J.; Hawker, C. J. *J. Am. Chem. Soc.* **2001**, *123*, 6461.
(16) See Supporting Information for details.
(17) The reaction rate with star polymer catalysts may be affected by mass transport, which can be influenced by solvent properties and reaction temperature.
(18) This is likely because **7** undergoes Michael addition to 2-hexenal (presumably reversibly), leading to partial consumption of **7**.

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