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Microcapsule Enabled Multicatalyst System

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One-pot multistep reactions are effective at reducing the waste and cost of a synthetic route because they decrease the number of work-ups and purifications, as well as the volume of solvent used.[1] These reactions are especially useful when multiple catalysts are used so that one traps an unstable intermediate formed by the other. Though a variety of these reactions have been reported, they are limited to a relatively small number of systems where the catalysts are compatible with each other.[1a,2] The work of Patchornik in 1981 demonstrated that this limitation can be overcome by immobilizing incompatible catalysts on solid supports.[3] Though this strategy has since been used to prevent catalyst interactions,[4] it often results in the loss of catalytic activity and in effect lowers efficiency.[5]

Recently, one-pot multicatalyst reactions have been facilitated by site-isolated catalysts that diverge from the traditional solid support paradigm.[6] These examples show how materials such as sol-gels and star-polymers render incompatible catalysts compatible. However, the reactions featured are relatively simple and yield the same result when run stepwise. In addition, such successful examples are few and not easily generalized for new catalysts. It is therefore desirable to develop other techniques to site-isolate catalysts for use in one-pot multicatalyst reactions.

We recently reported the successful encapsulation of a polymeric catalyst via interfacial polymerization of an oil-in-water emulsion.[7] We demonstrated that because of the unique microenvironment created by our isolation technique, our catalyst showed greater catalytic activity than a comparable solid-supported catalyst. In this Communication, we extend the scope of our technique by reporting a *microencapsulated amine catalyst* and demonstrate its utility by applying it to a tandem reaction sequence involving an otherwise incompatible Lewis acid catalyst (Figure 1). We also increase the complexity of such reactions by using the second catalyst to trap an intermediate from the first, forming a product that cannot be accessed when the reactions are performed sequentially.

A tandem amine−Lewis acid system was selected as a model because they are incompatible catalysts without site-isolation and because this two-catalyst system would be synthetically useful (vide infra). A brief screen of the literature suggested that we focus on nitroalkene formation as half of our tandem reaction sequence. This amine-catalyzed reaction often produces a mixture of nitroalkene and dinitro products, the latter being the result of a second addition of nitroalkane.[8] If we were able to prepare a site-isolated amine catalyst, we could trap the nitroalkene intermediate with a Lewis acid catalyst in order to direct it toward a second product rather than letting it reach the dinitro product. The Lewis acid we chose for this role is the nickel-based Michael catalyst (**2**) reported by Seidel and Evans to convert nitroalkenes to the corresponding Michael adduct in high yields.[9] By combining these two reactions in one pot, we hoped to achieve a higher yield of Michael adduct than we could if the reactions were run sequentially.

With the Lewis acid catalyst chosen, we assessed the necessity for developing an encapsulated amine catalyst[10] by screening a variety of commercially available amine-based catalysts for the

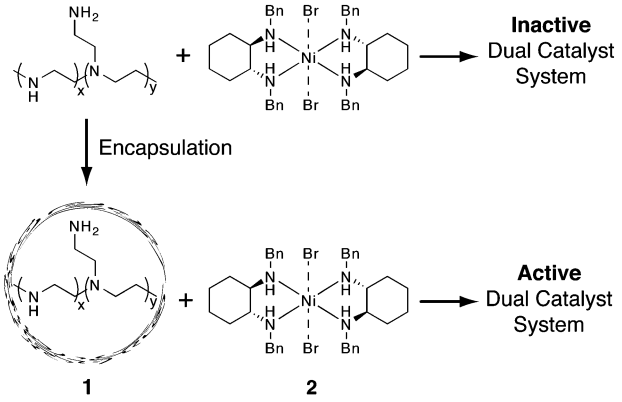

Figure 1. The site-isolation of two incompatible catalysts enables a tandem reaction. The two catalysts are microencapsulated PEI (**1**) and a nickel-based Michael addition catalyst (**2**).

reaction between benzaldehyde (**3**) and nitromethane. Small, soluble amines were found to catalyze the reaction, producing both *trans*-β-nitrostyrene (**4**) and 1,3-dinitro-2-phenyl-propane (**5**), but when used in tandem with **2** and dimethyl malonate (DMM), the two catalysts complexed and precipitated. On the other hand, amine catalysts attached to solid supports such as MCM-41 or polystyrene beads showed no activity toward nitroalkene formation under room-temperature conditions suitable for catalyst **2**. Rather, they required elevated temperatures between 60 and 90 °C to achieve nitroalkene formation.

We sought to encapsulate the polymeric amine poly(ethyleneimine) (PEI) to address the compatibility and activity problems we encountered with the commercially available catalysts. The catalyst was prepared by dispersing a methanolic PEI solution into a nonpolar cyclohexane phase with the help of a stabilizer. Upon emulsification, 2,4-tolylene diisocyanate (TDI) was added to the continuous phase to initiate cross-linking that occurs only at the interface of the emulsion droplets between TDI and PEI. After polymerization, microcapsules containing PEI chains were isolated for use in a reaction after drying.

We tested our new encapsulated (μcap) amine (**1**) as a catalyst for nitroalkene formation. In this experiment, the μcaps were swollen with methanol for 5 min before the remaining reagents were added. The reaction was performed at room temperature, and reaction progress was monitored by GC. Like the free amines, the μcap catalyst produces both **4** and **5** (Scheme 1). We currently propose that the retention of our catalyst's activity as compared to the traditionally solid-supported amines is due to the unique microenvironment that the capsules possess.[7] A second phenomenon we observed is that the PEI-capsule walls capture intermediate **4** in an irreversible Michael-type addition, resulting in lowered reaction yields.[11] A more detailed analysis of the μcaps is forthcoming.

The two undesired side reactions of **4** described above presented the opportunity to exploit a one-pot multistep reaction to its fullest

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Scheme 1. Single-Catalyst Dinitro Product Formation (Dashed) versus Double-Catalyst Michael Adduct Formation (Solid)

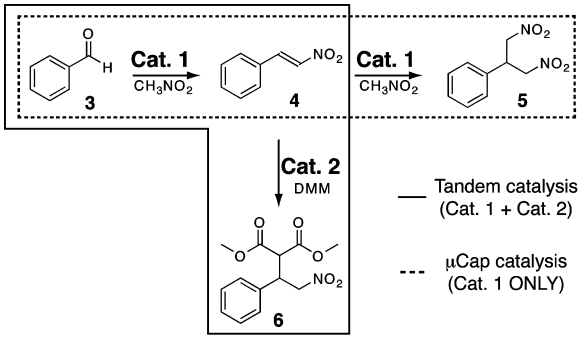

Table 1. Conversion of **3** and Yield of **6** after 24 h

catalyst system	conversion of 3 [%]	yield of 6 [%][a]
μcap amine (**1**) + Ni catalyst (**2**)	95	80.2
μcap amine (**1**) alone	67	2.1
Ni catalyst (**2**) alone	61	8.5
free PEI + Ni catalyst (**2**)	96	5.4

[a] Yields were determined by GC areas. For cases in which the product was isolated, isolated yields agree with GC yields.

potential: by adding a second catalyst to the system, we hoped to trap the transient nitroalkene intermediate and direct it toward the desired Michael adduct. The tandem reaction was carried out by first swelling the encapsulated amine catalyst in methanol for 5 min and then suspending it in toluene. The remaining catalyst and reagents were added, and reaction progress was monitored by GC. Initial formation of nitroalkene intermediate was followed by its conversion to the desired Michael adduct (**6**) rather than undesired **5** (Scheme 1). The Michael adduct was formed in 80% yield after 24 h. It should be noted that **6** *is not formed if only one of the catalysts is present or if the reactions are performed sequentially*, as it was demonstrated above that the first reaction alone resulted in two unproductive situations. This series of reactions is performed efficiently only when the catalysts are site-isolated and the reactions are run in one pot (Table 1).

As evidence for catalyst site-isolation, we investigated whether commercially available unencapsulated PEI could replace the encapsulated catalyst. We found that the two catalysts (PEI and **2**) produce the Michael adduct in only 5.4% yield (Table 1). On the basis of literature precedence, we suggest that free PEI strongly chelates Ni, making it inactive.[12] In addition, by monitoring UV−vis absorbance of **2** in the presence and in the absence of μcaps, we determined that the poisoning of **2** occurs only to a small extent (see Supporting Information). Finally, the rate of the Michael addition between **4** and dimethyl malonate by **2** was found to be enhanced rather than diminished by the presence of μcaps. We attribute this phenomenon to the activation of **4** by urea groups on the surface of the μcaps.[13] Furthermore, the yield of this reaction is the same as that of the control (no μcaps), suggesting that **2** is not degraded by the PEI and therefore that the Ni and the catalytic amines do not interact (see Supporting Information). We conclude based on these results that microencapsulation provides effective site-isolation, preventing catalyst fouling. Although the explicit reasons for site-isolation are currently being explored, the experimental evidence strongly suggests that the two catalysts do not interact.

We have demonstrated the potential for and subsequent development of an active, site-isolated amine catalyst. Our encapsulation method results in a catalytically active species that remains site-isolated during a one-pot multistep reaction, allowing it to be used in tandem with an otherwise incompatible catalyst. This example demonstrates the capabilities of tandem catalysis to trap and direct reaction intermediates efficiently. The Michael adduct formed by this reaction sequence can be used to access pharmaceutical agents such as baclofen, rolipram, and pregabalin, as well as other γ-amino acid analogs. The results of this catalyst system can likely be made general and applied to a variety of amine−Lewis acid tandem reactions as well as other incompatible catalyst systems. The efficiency of organic synthesis will improve significantly as both site-isolation techniques and tandem reactions are developed.

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Supporting Information Available: Experimental methods and catalyst preparation and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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