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Mechanism and Application of a Microcapsule Enabled Multicatalyst Reaction

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Abstract: In this paper, we describe the development and application of a multistep one-pot reaction that is made possible by the site isolation of two otherwise incompatible catalysts. We prepared a microencapsulated amine catalyst by interfacial polymerization and used it in conjunction with a nickel-based catalyst for the transformation of an aldehyde to a Michael adduct via a nitroalkene intermediate. The amine-catalyzed conversion of an aldehyde to a nitroalkene was found to proceed through an imine rather than a nitroalcohol. Kinetic studies indicated that the reaction is first order in both the nickel catalyst and the shell of the encapsulated amine catalyst. Furthermore, we provide evidence against interaction between amine and nickel catalysts and present kinetic data that demonstrates that there is a rate enhancement of the Michael addition due to the urea groups on the surface of the microencapsulated catalyst. We applied our one-pot reaction to the development of a new synthetic route for pregabalin that proceeds with an overall yield of 74%.

Introduction

Catalyst isolation techniques that enable one-pot multistep reactions hold great potential for increasing the efficiency of chemical synthesis. Performing multiple reactions simultaneously in a single reaction vessel offers possibilities for reduced waste and increased safety as well as manipulation of equilibria.[1] Although many site-isolated catalysts have been developed, the focus has been largely on catalyst recovery rather than on tandem catalysis. Indeed, since the pioneering work of Patchornik over 25 years ago[2] the sol−gel materials developed by Avnir and Blum have been the only catalyst supports used in the context of one-pot multistep catalysis until recently.[3] In the past few years, Fréchet et al. introduced a multicatalyst system that employed star polymers for catalyst isolation,[4] while Jones et al. showed that catalysts supported on polymer resins and magnetic particles could be used together while avoiding catalyst fouling.[5] In another approach Kaneda et al. immobilized two incompatible catalysts in mesoporous clays to achieve site isolation.[6] All of these examples demonstrate the effective separation of otherwise incompatible catalysts. Though each of these examples promises the possibility for application to more sophisticated systems, the full potential of multicatalyst systems will remain unrealized until applications to more complex molecules are demonstrated.

With this need in mind, we recently reported a microcapsule (μcap) enabled multicatalyst system that produces a synthetically useful product.[7] The reaction involves the amine-catalyzed transformation of an aldehyde to a nitroalkene followed by a transition-metal-catalyzed Michael addition in the same reaction vessel (Scheme 1). Typically, amine catalysts and nickel complexes are incompatible due to their tendency to chelate and render each other inactive.[7] However, microencapsulation of PEI forms catalyst **1**, which can successfully be used in tandem with the nickel-based catalyst **2** developed by the Evans group.[8]

Not only do these two reactions both form C−C bonds, but together they create a versatile synthetic building block. For instance, the nitroalkane can be converted into an amine via reduction or a carbonyl via the Nef reaction, while the ester groups can be transformed into a single carboxylate via hydrolysis−decarboxylation or a diol via reduction. Such subsequent reactions could provide access to a wide range of useful intermediates, such as those found en route to pharmaceuticals ranging from rolipram to baclofen to pregabalin (**3**, Scheme 2).

In this article, we show the generality of this reaction while providing mechanistic insight for our microencapsulated catalyst. We also discuss the application of this system to a pharmaceutically relevant problem: an efficient chemical synthesis of pregabalin.

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(2) Cohen, B. J.; Kraus, M. J.; Patchornik, A. *J. Am. Chem. Soc.* **1981**, *103*, 7620−7629.
(3) (a) Gelman, F.; Blum, J.; Avnir, D. *J. Am. Chem. Soc.* **2000**, *122*, 11999−12000. (b) Gelman, F.; Blum, J.; Avnir, D. *Angew. Chem., Int. Ed.* **2001**, *40*, 3647−3649. (c) Gelman, F.; Blum, J.; Avnir, D. *New J. Chem.* **2003**, *27*, 205−207.
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(5) Phan, N. T. S.; Gil, C. S.; Nguyen, J. V.; Zhang, Z. J.; Jones, C. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 2209−2212.
(6) Motokura, K.; Fujita, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2005**, *127*, 9674−9675.
(7) Poe, S. L.; Kobašlija, M.; McQuade, D. T. *J. Am. Chem. Soc.* **2006**, *128*, 15586−15587.
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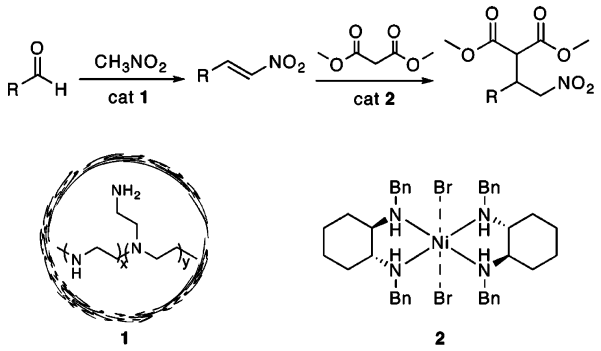
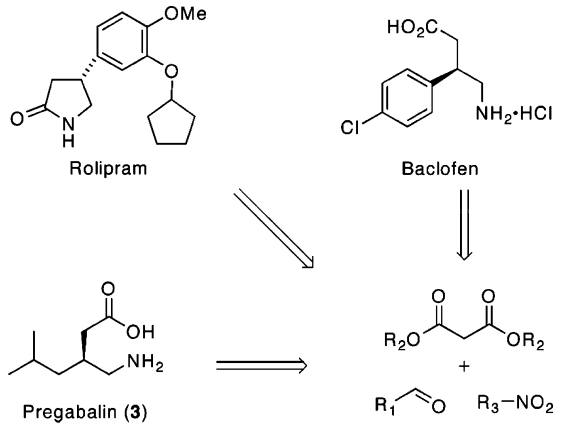
10.1021/ja071706x CCC: $37.00

Scheme 1 Transformation of an Aldehyde to a Nitroalkene and Subsequent Michael Addition of a Malonate Ester Can Be Performed in Tandem through the Use of Site-Isolated Catalysts[a]



[a] The two catalysts are microencapsulated PEI (**1**) and a nickel-based complex (**2**).

Scheme 2. Pharmaceutical Agents That Incorporate an Aldehyde, a Nitroalkane, and a Malonate Ester



Results and Discussion

Synthesis and Characterization of Microencapsulated Catalyst. Encapsulation of an amine-based Henry reaction catalyst was achieved via the interfacial polymerization of oil-in-oil emulsions, as described in our previous work. Poly(ethyleneimine) (PEI) was encapsulated by dispersing a methanolic PEI solution into a continuous cyclohexane phase. Upon emulsification, 2,4-tolylene diisocyanate (TDI) was added to initiate cross-linking at the emulsion interface, forming polyurea shells that contain free chains of PEI. The microcapsules crenate when dry and swell when placed in such solvents as methanol and DMF, suggesting a hollow capsule rather than a solid sphere (Figure 1).[9] Catalyst loading was determined to be 1.6 mmol/g[10] by acylation of the catalytic amines with trifluoroacetic anhydride followed by fluorine elemental analysis. Oxygen elemental analysis placed the upper limit on urea content of the μcap shells at 5.6 mmol/g (the upper limit assumes no water retention).

Activity and Mechanism of Microencapsulated Catalyst. To better understand the importance of μcap swelling, the reaction between benzaldehyde (**4**) and nitromethane was performed in a range of different solvents.[11] Swelling effects were separated from solvent effects by using both free and encapsulated PEI as catalysts for formation of *trans*-β-nitrostyrene (**5**) and 1,3-dinitro-2-phenyl-propane (**6**). Figure 2 shows benzaldehyde conversion after 6 h for each catalyst.

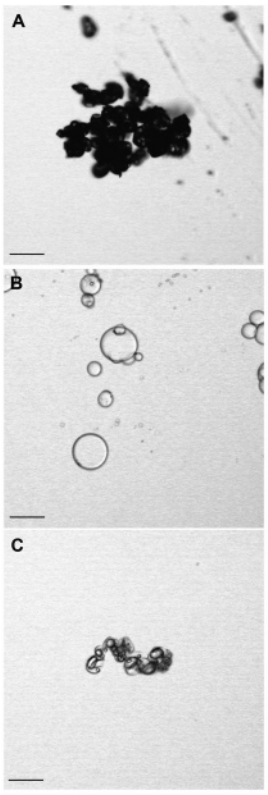
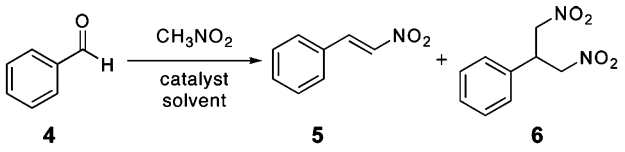


Figure 1. Optical micrographs of dry μcaps (a); μcaps in methanol, a swelling solvent (b); and μcaps in toluene, a nonswelling solvent (c). The scale bar is 30 μm.



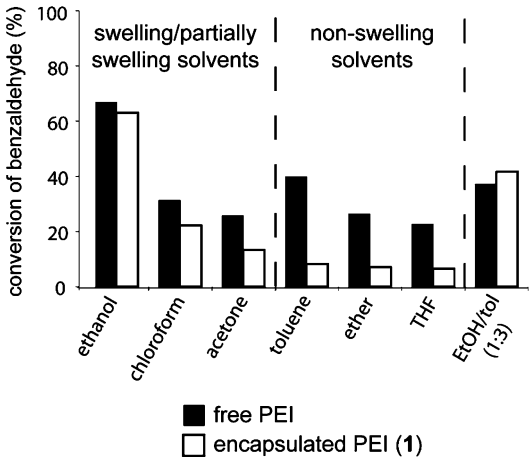


Figure 2. Conversion of benzaldehyde (**4**) after 6 h for the amine-catalyzed reaction between benzaldehyde and nitromethane. Catalysts for the reaction were free PEI (black bars, 4.6 mol %) and encapsulated PEI (white bars, 4.6 mol %).

The results for the reactions catalyzed by free PEI (black bars) are not affected by swelling or by the kinetic barrier introduced by the microcapsule shell and therefore indicate how effective

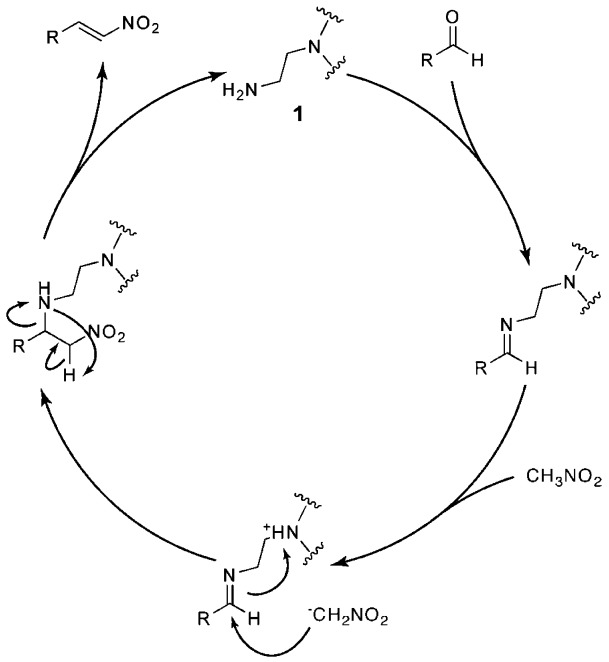
(9) For a detailed characterization of oil-in-oil microcapsules, see: Kobašlija, M.; McQuade, D. T. *Macromolecules* **2006**, *39*, 6371−6375.
(10) We define catalytic amines as the primary amines of PEI.
(11) See Supporting Information for full range of solvents.

each solvent is for this reaction. If the differences in conversion for the reactions catalyzed by encapsulated PEI (white bars) were based exclusively on solvent, we would expect the two cases to show the same trends. This is the case for both swelling and partially swelling solvents; for each catalyst conversions are high for ethanol, moderate for chloroform, and low for acetone. However, this is not true for nonswelling solvents. While the free PEI-catalyzed reactions revealed that toluene, ether, and THF were relatively good, moderate, and poor solvents, respectively, encapsulated PEI did not produce the same results. Despite the moderate conversion produced by free PEI in toluene, encapsulation resulted in an 80% decrease in catalytic activity in the same solvent. These results suggest that the solvent dependence of this reaction is 2-fold; not only must the solvent be favorable for the PEI-catalyzed reaction, but it also must be able to swell the microcapsules. Acetone swells the capsules but is a poor solvent for the reaction, while toluene is a good solvent for the reaction but is unable to swell the μcaps. Both of these cases result in poor conversions of benzaldehyde when encapsulated PEI is used as the catalyst. Only ethanol, a good solvent for the reaction that is also able to swell the capsules, is able to produce high conversions with both free and encapsulated PEI. Furthermore, in some cases catalytic activity is retained for capsules that are swollen in a swelling solvent and then placed in a bulk nonswelling solvent (Figure 2). We are currently pursuing the reasons for and implications of this phenomenon.[12]

With a better understanding of the conditions required for catalytic activity, we turned our attention to the mechanism of the μcap catalyst. Transformation of an aldehyde to a nitroalkene can occur via two different pathways. The first involves nitroalcohol formation through a traditional Henry reaction, which is then followed by elimination to form the double bond. The second proceeds through an imine intermediate rather than the nitroalcohol. This latter mechanism has been suggested for cases in which the catalyst contains both primary and tertiary amino groups as well as for solid supported catalysis.[13] Being that our catalyst exhibits both of these features, we predicted that μcap-enabled nitroalkene formation goes through an imine intermediate rather than the nitroalcohol. Indeed, when we followed the μcap-catalyzed condensation of benzaldehyde with nitromethane over time, we did not observe the nitroalcohol at any point in the reaction. However, the nitroalcohol was found to be present during the course of the one-pot reaction, possibly having been formed by the amine ligands of the nickel catalyst. This evidence precludes the possibility that elimination occurs as soon as the nitroalcohol is formed and suggests that the reaction might follow the latter route. To further support this hypothesis, when the nitroalcohol is placed in the presence of swollen μcaps, no nitroalkene formation is observed. The inability of the μcap catalyst to convert this potential intermediate to the final product provides further evidence against the nitroalcohol-elimination pathway. A proposed mechanism for μcap-catalyzed nitroalkene formation is shown in Scheme 3.

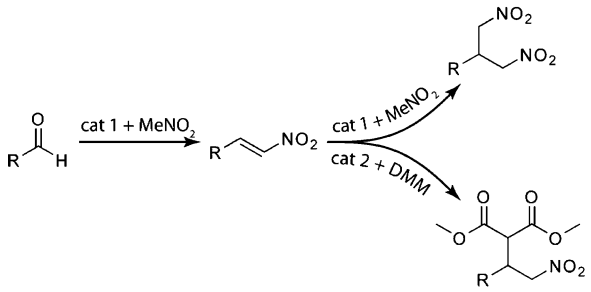
One-Pot Reaction. We reported that there is the possibility for the nitroalkene intermediate to either form the dinitro product or go through a Michael-type addition with the encapsulated PEI when subjected to the reaction discussed above. However, we have also shown that when the reaction is run in the presence of a second catalyst−reagent pair, this intermediate can be trapped and directed to a different reaction pathway (Scheme 4).

Scheme 3. Proposed Catalytic System of μcap-Catalyzed Nitroalkene Formation[a]



[a] Though the mechanism for nitroalkene formation and regeneration of the primary amine (left) is believed to occur intermolecularly, it is shown intramolecularly for clarity.

Scheme 4. Single-Catalyst Addition of Nitromethane (top) versus Double-Catalyst Addition of Dimethyl Malonate (DMM) (bottom)



Furthermore, because μcaps swollen in methanol retain their catalytic activity when placed in toluene, the reaction can be run in a mixture of two different solvents. This allows both the μcaps and the nickel catalyst to operate in their respective ideal solvents of methanol and toluene. To demonstrate the scope of this one-pot reaction, we performed this reaction with a variety of aromatic and aliphatic aldehydes. The results are shown in Table 1. It is evident that though the system tolerates both aromatic and aliphatic aldehydes, introduction of electron-withdrawing substituents on the aromatic substrates results in decreased yields. This effect is most pronounced in entries 6 and 7 for which the cyano- and nitro-substituted benzaldehydes yield minimal product formation. Assuming that the μcap-catalyzed step proceeds through an imine intermediate, this phenomemon can be rationalized by the observations of Santerre et al., who compared the rates of uncatalyzed imine formation

(12) Kobašlija et al. Unpublished results.
(13) (a) Tamura, R.; Sato, M.; Oda, D. *J. Org. Chem.* **1986**, *51*, 4368−4375. (b) Demicheli, G.; Maggi, R.; Mazzacani, A.; Righi, P.; Sartori, G.; Bigi, F. *Tetrahedron Lett.* **2001**, *42*, 2401−2403.

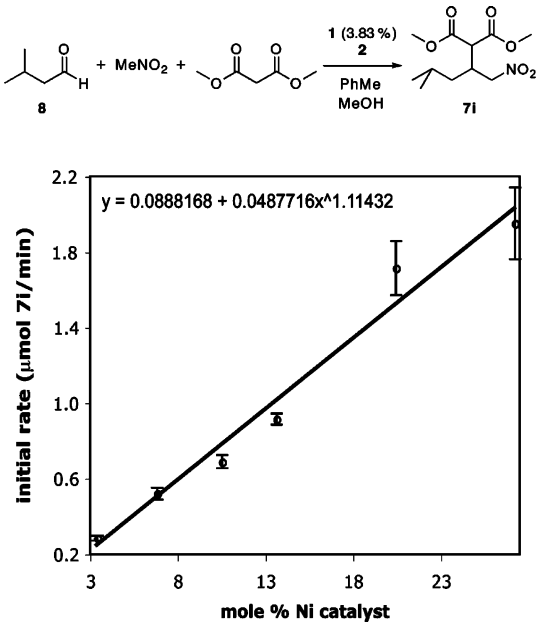
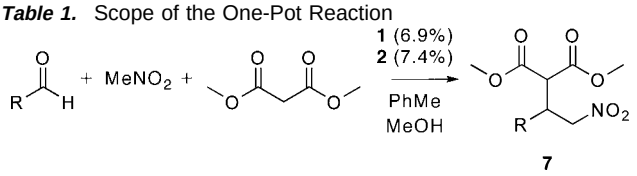


Figure 3. Kinetic studies on the tandem reaction of 3-methylbutyraldehyde, nitromethane, and dimethyl malonate.

Table 1. Scope of the One-Pot Reaction



entry	R	product	yield (%)
1	Ph	**7a**	80
2	4-Me-Ph	**7b**	94
3	4-MeO-Ph	**7c**	89
4	4-Br-Ph	**7d**	43
5	4-Cl-Ph	**7e**	48
6	4-CN-Ph	**7f**	<5
7	4-NO_2-Ph	**7g**	<5
8	$CH(Me)_2$	**7h**	71
9	$CH_2CH(Me)_2$	**7i**	65

between substituted benzaldehydes and aliphatic amines at room temperature.[14] It was found that the rate is maximal for unsubstituted benzaldehyde and steadily decreases as the substituents' σ values diverge in either direction on the Hammett plot. It is possible that the cyano and nitro substituents are too electron withdrawing to allow for any appreciable imine formation.

To gain information about the mechanism of the overall tandem reaction, we carried out kinetic studies to identify the rate-determining step. Changing the catalyst concentration in the reaction between 3-methylbutyraldehyde (**8**), nitromethane, and dimethyl malonate revealed that the reaction is first order in nickel catalyst **2** (Figure 3), indicating that the Michael addition of dimethyl malonate to the nitroalkene is the rate-determining step.

The kinetic data shown in Figure 3 reveal that the rate of the tandem reaction depends on the concentration of nickel catalyst **2** and consequently on the efficiency of site isolation. It is

(14) Santerre, G. M.; Hansrote, C. J.; Crowell, T. L. *J. Am. Chem. Soc.* **1958**, *80*, 1254−1257.

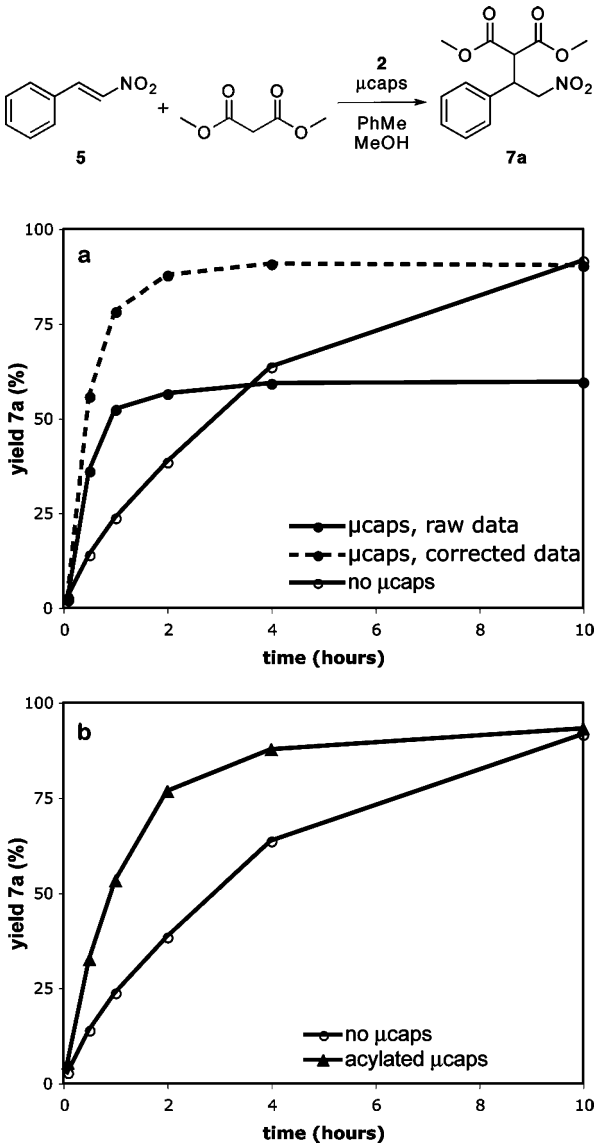


Figure 4. μcap-accelerated Michael addition between benzaldehyde (**4**) and dimethyl malonate in the presence of untreated μcaps (a) and in the presence of acylated μcaps (b).

therefore instructive to determine whether the rate-determining step is at all retarded by interaction between the two catalysts. We began our investigation by comparing the rates of the Michael addition in the absence and presence of the microencapsulated catalyst. One complicating factor, however, is that the catalytic amines within the μcaps irreversibly react with nitroalkenes, decreasing the amount of starting material available for reaction. Using the Michael addition between *trans*-β-nitrostyrene (**5**) and dimethyl malonate as a model, we approached this problem in two ways. The first approach was to "normalize" the data from the μcap-containing reaction in order to account for the loss of starting material (Figure 4a). Product yields were calculated using the formula (mol of **7a**)/(mol of **5** + mol of **7a**). It should be noted that these calculations correct only for decreased product formation due to nitroalkene−μcap interaction; any product suppression due to catalyst interaction should still be apparent. Both reactions attain an adjusted yield of 90% after 10 h, indicating that the presence of the μcaps does not depress the rate of the Michael addition. Indeed, they

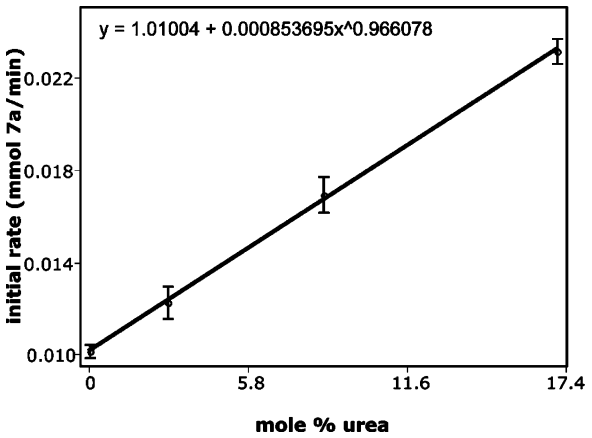


Figure 5. Order plot for the Michael addition between benzaldehyde (**4**) and dimethyl malonate in the presence of acylated μcaps. Rate is plotted as a function of nickel catalyst **2**. Mole % urea is based on oxygen content determined by elemental analysis.

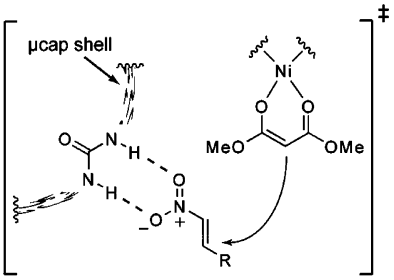


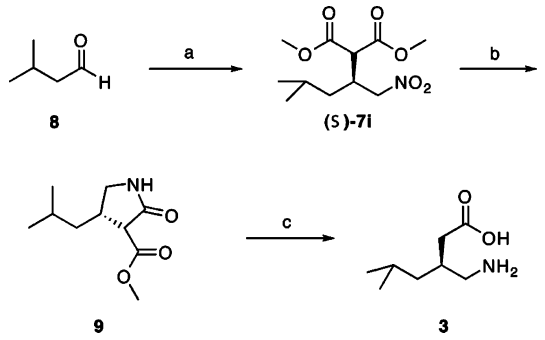
Figure 6. Proposed transition state for the tandem reaction.

instead appear to provide rate enhancement as the μcap-containing reaction reached its final yield after only 4 h.

To demonstrate that the apparent rate enhancement is not merely an artifact of data correction, we acylated the reactive amines in order to prevent their reaction with **5**. The data shown in Figure 4b confirms the rate enhancement in the presence of microcapsules. This result is consistent with previous studies reporting the acceleration of Michael additions by ureas and thioureas.[15] Since the capsule walls are composed of polyurea, it is not surprising that we observe the same phenomenon in our system. Upon further investigation into this rate enhancement this reaction proved to be first order in the concentration of urea groups (Figure 5). The proposed transition state for the tandem reaction is illustrated in Figure 6. This finding indicates that the presence of the urea-containing μcaps accelerates the Michael addition and ultimately the overall one-pot reaction. In addition, this rate enhancement does not appear to be accompanied by any degradation in yield, suggesting effective site isolation of the two catalysts.

Enantioselective Synthesis of Pregabalin. An attractive feature of our two-step one-pot reaction is that it not only incorporates an innovative technique for site-isolation but also produces synthetically useful products when an enantioselective version of **2** is used. The Michael adducts that are created are precursors to γ-amino acids, allowing access to γ-amino butyric acid (GABA) analogs. Pregabalin is one such analog that is approved for the treatment of both epilepsy and neuropathic pain. We imagined a synthesis of pregabalin where our two-catalyst system forms the pregabalin backbone efficiently and

Scheme 5. Synthesis of Pregabalin (**3**)[a]



[a] Reagents and conditions: (a) nitromethane, dimethyl malonate, **1**, **2**, toluene, methanol, room temperature, 48 h, 94%, 72% ee. (b) Raney Ni, H_2 (45 psi), EtOH, room temperature, 18 h, 96%. (c) 5 M HCl, 115 °C, 18 h, 95%, 72% ee.

enantioselectively. The desirability of performing these reactions in tandem rather than sequentially is evident when one considers the difficulty of isolating of the nitroalkene intermediate. An efficient nitroalkene-forming reaction between 3-methylbutyraldehyde (**8**) and nitromethane has only been reported once[16] and in our hands often yields a significant amount of byproducts. However, we demonstrated that with our one-pot reaction there is no need for nitroalkene isolation and the byproducts are avoided.

The total synthesis of pregabalin is depicted in Scheme 5. Using 3-methylbutyraldehyde (**8**) as the starting material and an enantioselective version of nickel catalyst **2**, the tandem reaction produced the corresponding Michael adduct (*S*)-**7i** in 94% yield and 72% ee. It should be noted that this tandem catalysis system efficiently suppressed the yield of the undesired dinitro byproduct to less than 5%. Overnight hydrogenation of (*S*)-**7i** with Raney Ni gave nearly quantitative conversion to the ring-closed product **9**. Subsequent acid hydrolysis and decarboxylation proceeded in 95% yield of the HCl salt of pregabalin (**3**), which retains an ee of 72%. It has been reported that enantiomeric enrichment of pregabalin can be achieved by recrystallization for cases in which the ee is at least 85% of the *S*-enantiomer.[17] Treatment of the 72% ee HCl salt with base followed by a single recrystallization from isopropyl alchol/water afforded a product with 91.5% ee. Our successful enrichment demonstrates the viability of obtaining an enantiomerically pure product without the need for a resolution step, which would bring the overall yield of this synthesis to 74% of enantiomerically pure material.

Conclusion

We developed and evaluated a two-step reaction that is capable of converting both aromatic and aliphatic aldehydes to their corresponding Michael adducts in a single reaction vessel. The two-catalyst system was made possible by microencapsulation of PEI in order to provide site isolation of two otherwise incompatible catalysts. Kinetic studies indicated that the presence of the microcapsule shell of catalyst **1** enhanced the rate of the reaction promoted by catalyst **2**. Therefore, the microcapsules not only make the reaction possible by providing catalyst site isolation, but they also serve a second function by

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(16) Kantam, M. L.; Sreekanth, P. *Catal. Lett.* **1999**, *57*, 227−231.

(17) Bao, J.; Beylin, V. G.; Greene, D.; Hoge, G. S.; Kissel, W.; Marlatt, M. E.; Pflum, D. A.; Wu, H.-P. U.S. Patent Application 2005/0228190 A1, 2005.

enhancing the rate-determining step. On the basis of our findings, we proposed mechanisms for each step that are consistent with previously published literature. Using this tandem reaction we achieved a three-step total synthesis of pregabalin in 74% overall yield, demonstrating the applicability of this system to creating synthetically interesting compounds. By obtaining a better understanding of this complex multicomponent system, we continue to make progress toward the development of similar tandem reactions.

Acknowledgment. We thank ARO (MAP-MURI), NSF (SENSORS), NSF (SGER), Nanobiotechnology Center, Tri-Institutional Program in Chemical Biology, and NYSTAR.

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

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