

## Heterogeneous Catalysis

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**Expanding the Utility of One-Pot Multistep Reaction Networks through Compartmentation and Recovery of the Catalyst\*\****Nam T. S. Phan, Christopher S. Gill, Joseph V. Nguyen, Z. John Zhang, and Christopher W. Jones\**

Living systems combine the use of highly specific catalysts coupled with compartmentation in different regions of the

[\*] Dr. N. T. S. Phan, C. S. Gill, Dr. J. V. Nguyen, Prof. C. W. Jones  
School of Chemical & Biomolecular Engineering  
Georgia Institute of Technology  
Atlanta, GA 30332 (USA)  
Fax: (+1) 404-894-2866  
E-mail: cjones@chbe.gatech.edu

Prof. Z. J. Zhang  
School of Chemistry and Biochemistry  
Georgia Institute of Technology  
Atlanta, GA 30332 (USA)

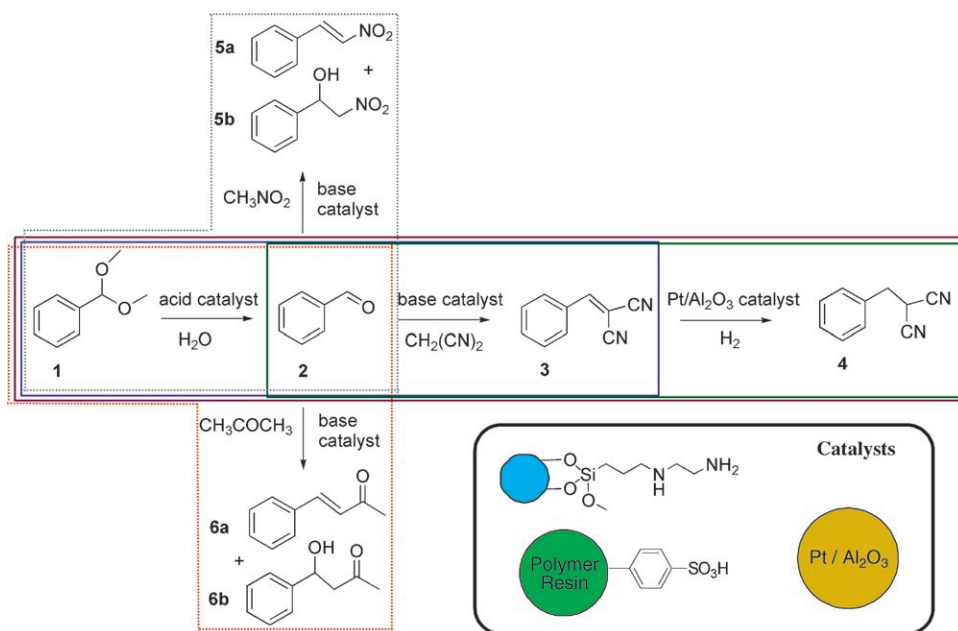
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cell to control multistep reaction networks, which are used to synthesize the complex organic molecules that cells need to survive.<sup>[1]</sup> Although there has been significant progress in mimicking nature's reaction cascade strategy over the past decades, the manipulation of sequential reactions using multiple catalysts in a single vessel is still relatively rare. Over the years, non-natural systems based on single- or multi-enzyme-mediated reaction sequences have been demonstrated, mimicking some aspects of nature's synthetic strategy.<sup>[2]</sup> Nonetheless, the vast majority of chemical syntheses are still conducted using the traditional paradigm of single catalytic reactions with homogeneous or heterogeneous chemical catalysts, followed by costly catalyst and/or product purification steps.<sup>[3]</sup> A primary reason is that controlling one-pot, multistep reactions using traditional homogeneous catalysts is rather difficult as, unlike for biocatalysts, interactions between soluble catalysts can cause deactivation. Many examples of complex reaction sequences or cascades do not use multiple catalysts, whereas in other cases combinations of homogeneous, heterogeneous, or enzyme catalysts in one pot were used to direct sequential reactions.<sup>[2,4,5]</sup> These cases represent carefully constructed systems that were optimized for one specific sequence. In such cases, standard workup procedures after the reaction most likely result in the used catalysts simply becoming a component of the reaction waste.<sup>[5]</sup> A critical aspect of living systems that thus far has not been effectively applied is the use of multiple combinations of catalysts sequentially.<sup>[6]</sup> An approach to achieve this within the chemical catalysis paradigm is to develop the ability to separate the multiple catalysts used in one-pot, multireaction cascades in essentially pure form, allowing reuse of the recovered catalysts in numerous other catalytic reactions, potentially in a combinatorial manner. Herein, we demonstrate this approach using a combination of catalysts recovered by magnetic,<sup>[7]</sup> gravimetric,<sup>[8]</sup> and membrane methods,<sup>[9-10]</sup> allowing excellent control of multistep reactions with recovery of each individual catalyst. In particular, the use of magnetically separable catalysts allows the creation of a variety of versatile catalysts that can be easily recovered without the need for specialized equipment. Furthermore, the recovered catalysts can be reused in different, subsequent multistep one-pot reactions. This is an unprecedented level of control over multistep, one-pot catalytic reactions.

This concept was demonstrated by combining base catalysts that are magnetically recoverable with acid catalysts that are recovered gravimetrically. Superparamagnetic spinel ferrite nanoparticles were prepared according to published procedures<sup>[11]</sup> and functionalized through silane chemistry with *N*-[3-(trimethoxysilyl)propyl]ethylenediamine to create surface base sites.<sup>[12]</sup> The basic nanoparticle solids were then used in conjunction with a sulfonic acid polymer resin in the tandem deacetalization–Knoevenagel reaction (see Supporting Information for experimental details and characterization of the catalyst). Both catalysts and all the reagents were added to a reaction vessel at time zero, and the contents were stirred for a prescribed period of time while the course of the reaction was monitored by GC. Complete conversion of **1** into **2** and **2** into **3** (Figure 1, blue box) was observed in just 30 minutes, with average turnover frequencies (TOF) of 3 h<sup>-1</sup>

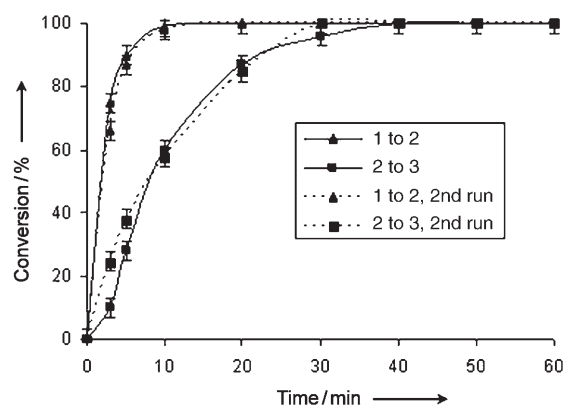


**Figure 1.** Multistep reaction networks controlled by the combination of different solid catalysts in a single vessel. See text for details.

for the acid resin catalyst and  $75 \text{ h}^{-1}$  for the basic magnetic catalyst. After reaction, the catalysts were separated by sonicating the reaction vessel and affixing a small permanent magnet externally to one wall of the vessel. The nonmagnetic resin catalyst was removed from the reaction vessel by decantation while the magnetic nanoparticle base catalyst was held stationary in the vessel by the magnet. Each catalyst was recovered in essentially pure form, as indicated by elemental analysis of the recovered catalysts. The amount of sulfur, an elemental tag for the resin catalyst, detected in the magnetic nanoparticle catalyst before and after reaction was essentially identical (0.07% S in the magnetic base catalysts before reaction and 0.05% S after reaction). The same is true of the amount of iron, an elemental tag for the magnetic catalyst, in the resin catalyst before and after reaction (0.01% Fe in the acid resin catalyst before reaction and 0.03% Fe after reaction). Reuse of the separated catalysts in the same reaction gave the same results with the same kinetic profile, indicating that no noticeable deactivation of the catalyst occurred upon combination of the two opposing catalysts (Figure 2).<sup>[13]</sup> Note also that each catalyst on its own was unable to promote the conversion of **1** into **3**, indicating that the tandem action of two catalysts was required to complete the sequence, as is often seen in biological systems (Table 1). These data, when combined with the results of elemental analysis, show that the catalysts can be recovered in pure form and that they can be subsequently reused without loss of performance. This is the first example of a multistep, one-pot reaction in which the catalysts can be recovered in pure form and used in later manipulations (see below).

To show the versatility of this method, the recovered magnetic nanoparticle catalyst was then effectively used in a second multistep, one-pot reaction (Figure 1, green box) in conjunction with a new solid catalyst, Pt/Al<sub>2</sub>O<sub>3</sub>. This tandem

Knoevenagel–hydrogenation reaction was carried out in one pot with all reagents and catalysts added at time zero. The reaction was started at atmospheric pressure, and after a period of time the pressure of the reaction was increased to 1000 psig (pounds per square inch gauge) H<sub>2</sub> to facilitate completion of the second reaction. In this case, **2** was converted into **3** using the basic catalyst and **3** was hydrogenated to **4** by the supported platinum, with both reactions going to completion. Similar results were also obtained when the one-pot reaction was pressurized to 1000 psig H<sub>2</sub> at time zero and maintained at this pressure throughout the course of the reaction (Table 1). As before, the individual catalysts were recovered through the magnetic separation process described above. The reaction sequence was then extended to three steps, again with catalyst recovery, with conversion of **1**



**Figure 2.** One-pot sequential reactions with acidic polymer resin and basic magnetic nanoparticle catalysts. Triangles and squares represent kinetic data for the reactions of **1**→**2** and **2**→**3**, respectively.<sup>[13]</sup> Broken lines show kinetic data for reactions with recycled catalysts.

into **4** (Figure 1, violet box) by adding the base catalysts supported on magnetic nanoparticles and the polymeric acid catalyst into the vessel along with the platinum catalyst enclosed in a membrane. In this case, all components were added to the reactor at time zero and the reaction was started at 1 atm total pressure. After 60 minutes, the hydrogen pressure was increased to 1000 psig to carry out the final step of the reaction. The overall yield of the final product **4** was 78% (Table 1); 100% yield of **4** was obtained in the absence of a membrane. This result indicated that some transport effects were slowing the final reaction when the membrane was used.

Stepwise control over the reaction sequence and the ability to continually reuse the original catalysts in multiple

**Table 1:** Results (% conversion) of catalytic reaction sequences carried out in one pot with multiple opposing catalysts.

Catalyst	Conv. [%]	Conv. [%]
Blue Sequence <b>1</b> → <b>2</b> → <b>3</b> <sup>[a]</sup>	<b>1</b> → <b>2</b>	<b>2</b> → <b>3</b>
solid acid and solid base	100	100
solid acid	100	0
solid base	0	0
solid acid and homogeneous base	0	0
solid base and homogeneous acid	0	0
homogeneous acid and base	0	0
Green Sequence <b>2</b> → <b>3</b> → <b>4</b> <sup>[a]</sup>	<b>2</b> → <b>3</b>	<b>3</b> → <b>4</b>
solid base and Pt/Al <sub>2</sub> O <sub>3</sub>	100	100
Violet Sequence <b>1</b> → <b>2</b> → <b>3</b> → <b>4</b> <sup>[a]</sup>	<b>1</b> → <b>3</b>	<b>3</b> → <b>4</b>
solid acid, solid base, and Pt/Al <sub>2</sub> O <sub>3</sub>	100	78 (100 <sup>[b]</sup> )
Gray Sequence <b>1</b> → <b>2</b> → <b>5a</b> + <b>5b</b> <sup>[a]</sup>	<b>1</b> → <b>2</b>	<b>2</b> → <b>5a</b> + <b>5b</b>
solid acid and solid base	100	100 (4:1 <b>5a/5b</b> )
Red Sequence <b>1</b> → <b>2</b> → <b>6a</b> + <b>6b</b> <sup>[a]</sup>	<b>1</b> → <b>2</b>	<b>2</b> → <b>6a</b> + <b>6b</b>
solid acid and solid base	100	82 (26:1 <b>6a/6b</b> )

[a] See Figure 1 for reaction sequences. [b] In the absence of a membrane. In this case, the Pt/Al<sub>2</sub>O<sub>3</sub> and the polymer resin were obtained after the reaction as a mixture, although the magnetic catalyst could be isolated.

reactions was demonstrated by the conversion of **1** to **2** to **5a** and **5b** (Figure 1, gray box) using the same acid and base catalysts. By adding the magnetic nanoparticles used in the first two reaction sequences (**1**→**2**→**3** and **2**→**3**→**4**) and the acidic resin used in the first reaction sequence (**1**→**2**→**3**) to new reagents in a single vessel, the synthesis of **5a** and **5b** was achieved with complete conversion of **1** into **5a** and **5b**. Note that this sequence represents the third use of a single sample of magnetic catalyst and the second use of a single sample of the acid catalyst. Similarly, products **6a** and **6b** were prepared in another one-pot reaction (Figure 1, red box) with excellent results.<sup>[14]</sup>

In summary, we have shown that excellent control of a reaction sequence using chemical catalysts can be achieved by 1) using combinations of a few versatile catalysts that can be used in a variety of reactions, with recovery of the catalyst in pure form after the reaction; 2) compartmentation of catalytic sites to allow for use of catalysts that would self-quit in homogeneous media;<sup>[5]</sup> and 3) regulation of the reaction pathway by manipulating the reaction conditions, including control of the catalysts and reagents that are present. The combination of magnetically and gravimetrically recoverable catalysts allowed the first successful application of opposing catalysts to multistep, one-pot catalytic reactions including the ability to steer the direction of the reaction at each step, all with recovery of each individual catalyst after use. The successful use of the recovered catalysts in combination with other catalysts in subsequent, unrelated reactions showed the versatility of this approach.<sup>[15]</sup> A library of magnetically and gravimetrically recoverable catalysts could thus be generated and used in a variety of one-pot multistep catalytic reactions,

and this methodology may be further expanded almost without limit through other means of catalyst separation, such as membrane encapsulation.<sup>[16]</sup>

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