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Organic Reaction Systems: Using Microcapsules and Microreactors to Perform Chemical Synthesis

ASHLEY R. LONGSTREET AND D. TYLER MCQUADE*
Department of Chemistry and Biochemistry, Florida State University, Tallahassee, Florida 32306, United States

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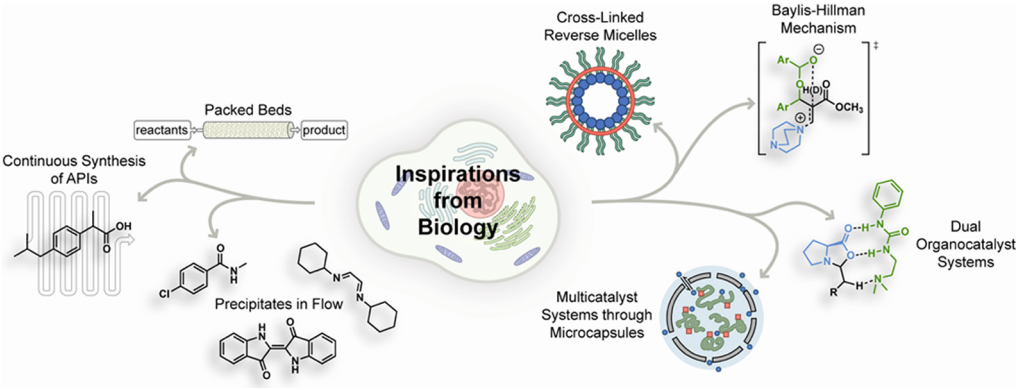

The appetite for complex organic molecules continues to increase worldwide, especially in rapidly developing countries such as China, India, and Brazil. At the same time, the cost of raw materials and solvent waste disposal is also growing, making sustainability an increasingly important factor in the production of synthetic life-saving/improving compounds. With these forces in mind, our group is driven by the principle that *how* we synthesize a molecule is as important as *which* molecule we choose to synthesize. We aim to define alternative strategies that will enable more efficient synthesis of complex molecules. Drawing our inspiration from nature, we attempt to mimic (1) the multicatalytic metabolic systems within cells using collections of nonenzyme catalysts in batch reactors and (2) the serial synthetic machinery of fatty acid/polyketide biosynthesis using microreactor systems. Whether we combine catalysts in batch to prepare an active pharmaceutical ingredient (API) or use microreactors to synthesize small or polymeric molecules, we strive to understand the mechanism of each reaction while also developing new methods and techniques.

This Account begins by examining our early efforts in the development of novel catalytic materials and characterization of catalytic systems and how these observations helped forge our current models for developing efficient synthetic routes. The Account progresses through a focused examination of design principles needed to develop multicatalyst systems using systems recently published by our group as examples. Our systems have been successfully applied to produce APIs as well as new synthetic methods. The multicatalyst section is then juxtaposed with our work in continuous flow multistep synthesis. Here, we discuss the design principles needed to create multistep continuous processes using examples from our recent efforts. Overall, this Account illustrates how multistep organic routes can be conceived and achieved using strategies and techniques that mimic biological systems.

1. Introduction

We theorize that one pathway to more sustainable chemical production is the creation of non-natural biosynthetic systems. Though biosynthetic systems are well-studied,[1,2] less attention has been devoted to the use of non-natural variants (sans cells) to synthesize organic molecules.[3] From a simplified view, cells produce compounds using two fundamentally distinct methods.

The first method uses collections of enzymes to couple sequences of reversible and irreversible reactions together (e.g., DNA biosynthesis, Scheme 1). Many anabolic pathways, including nucleic acid,[4] saccharide,[5] and terpine biosynthesis,[6] follow this rubric. The key here is that products from one step do not (or only minimally) inhibit the catalytic activity of another enzyme in the system because many reactions occur in the same vessel or compartment. Reagent compatibility is

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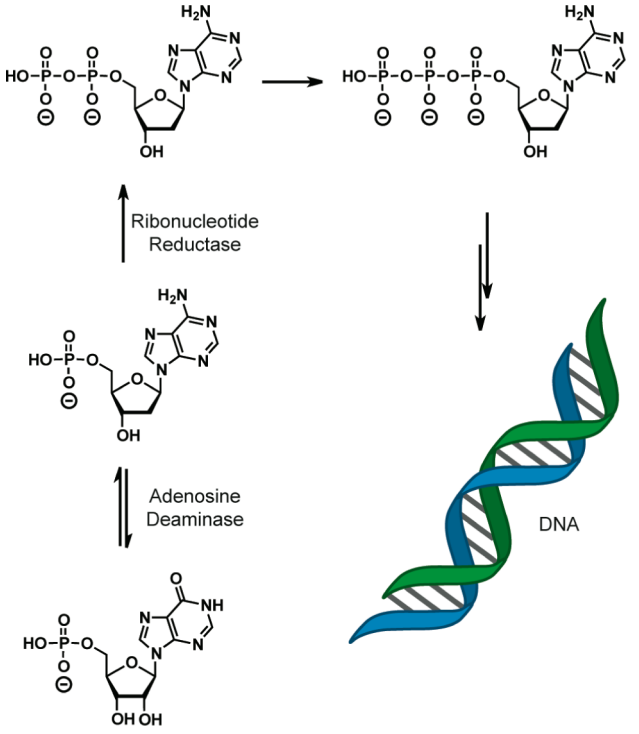
SCHEME 1. DNA Biosynthesis Is One Example of a Metabolic Process Achieved through a Multicatalyst System[7]



another critical consideration when oxidants/reductants or nucleophile/electrophile steps are coupled together. Biological systems have evolved cofactors to make these reagents compatible with each other.

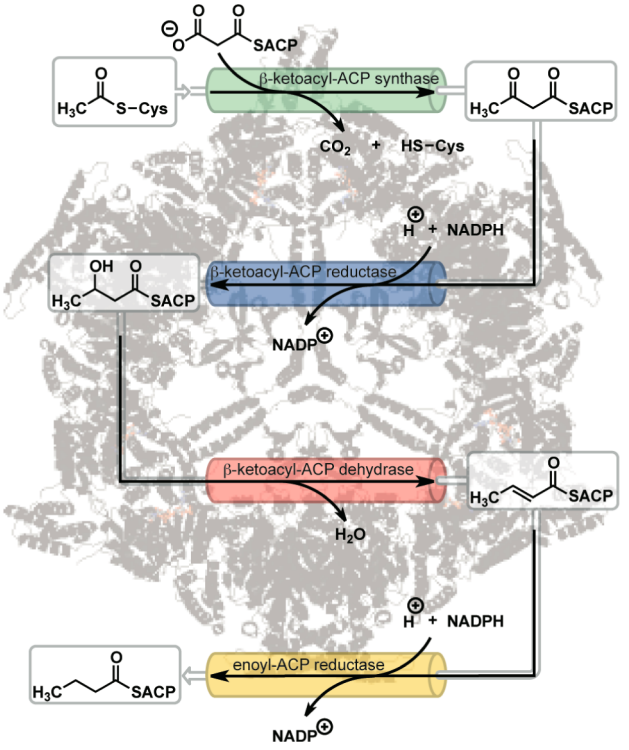
The other fundamental strategy employed by cellular anabolic processes is the linear combination of irreversible steps. The best characterized example is fatty acid biosynthesis (FAB), an oligomerization where each monomer unit is installed via an irreversible Claisen condensation often between malonyl CoA and acetyl CoA (Scheme 2, made irreversible via the loss of CO_2).[4] FAB and closely related cousin polyketide biosynthesis utilize enzymatic machines where intermediates are passed from catalytic site to site in series. Because each individual step (C–C bond formation, reduction, etc.) is irreversible, the catalytic sites and reagent delivery can be spatially separated.

We strive to mimic these fundamental metabolic strategies by synthesizing valuable compounds. Herein, we describe our successful creation of reversible and irreversible catalytic systems that conceptually mimic natural anabolic processes. We begin by summarizing the early observations that led to our more recent findings.

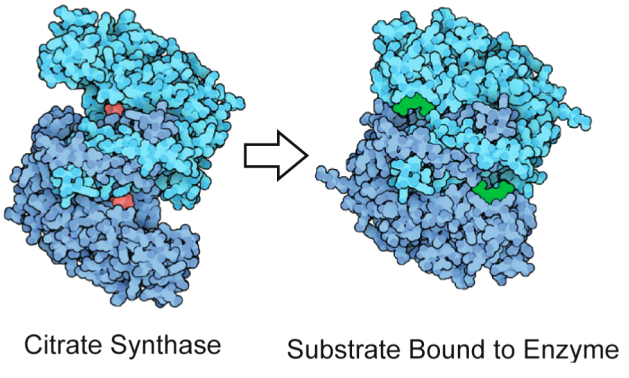
2. Early Observations

Cellular-based synthetic systems are complex collections of enzymes, cofactors and compartments. We began

SCHEME 2. Fatty Acid Biosynthesis (FAB), a Series of Irreversible Chemical Transformations Performed in a Spatial Order Defined by the Arrangement of the Multienzyme Complex[4,8]



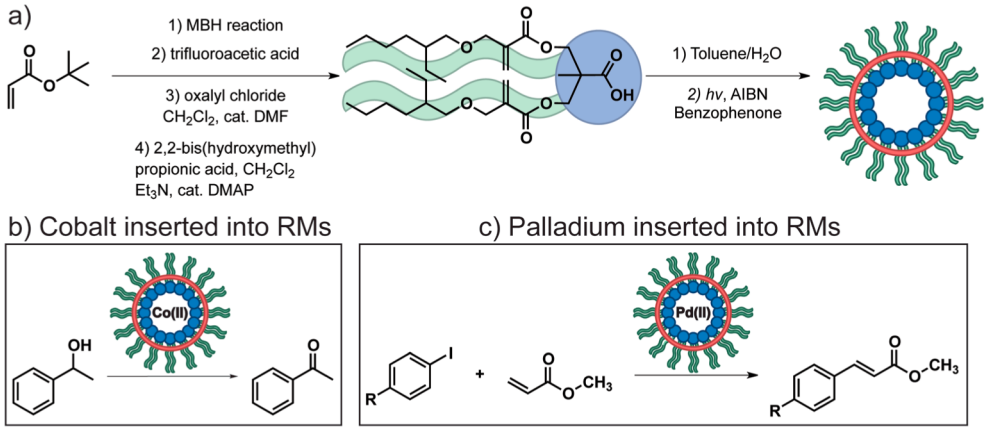
SCHEME 3. Simple View of an Enzyme Where Two Major themes (a macromolecular shell that both protects and organizes a catalytic core) Coexist[a]



[a]Here, citrate synthase changes conformation when bound to its substrate.[9]

mimicking these systems by creating non-natural enzyme-like catalysts. An enzyme can be simply viewed as a macromolecular structure where key functional groups are arranged in three dimensions around a catalytic core (Scheme 3). Clearly, noncatalytic enzyme components participate in protein–protein interactions and allosteric regulation, but less articulated is that the macromolecular shell protects the catalytic core from incompatible species.

SCHEME 4. The MBH Reaction Facilitates the Formation of a Cross-Linkable Monomer[a]



[a]Cross-linking and impregnation with metal atoms yield catalytic particles with a macromolecular shell that protects a catalytic core.

We predicted that cross-linked reverse micelles would approximate the size of an enzyme and mimic the catalytic core. Reverse micelles (RMs) are the result of dispersing an appropriate surfactant and a small amount of water into an organic phase. RMs are often nanometer-sized species where the surfactant headgroups interact with the water core and the hydrophobic tails interact with the organic phase. While RMs have the core–shell attributes we desired, they rapidly fuse and bud at room temperature and the contents of one are easily exchanged for those of another. For RMs to approximate enzymes, the surfactant shell must be cross-linked to prevent fusing and budding. Prior attempts to trap RMs using polymerization were known, but these seminal efforts did not prevent fusing and budding and the resulting polymer structures grew much larger than the progenitor RMs.[10] We predicted that the fusing and budding remained because former attempts did not produce a cross-linked matrix, and that RM forming surfactants where each tail of the surfactant contained a polymerizable group would yield a cross-linked shell. Using the Morita–Baylis–Hillman (MBH) reaction as a key step, we designed and synthesized a cross-linkable RM surfactant (Scheme 4).[11] We then demonstrated that these surfactants formed RMs and underwent radical-cross-linking to produce RMs that did not bud and fuse. Finally, we impregnated the RMs with Co(II) or Pd(II) salts and performed catalytic oxidations or cross-coupling reactions, respectively (Scheme 4).[11,12]

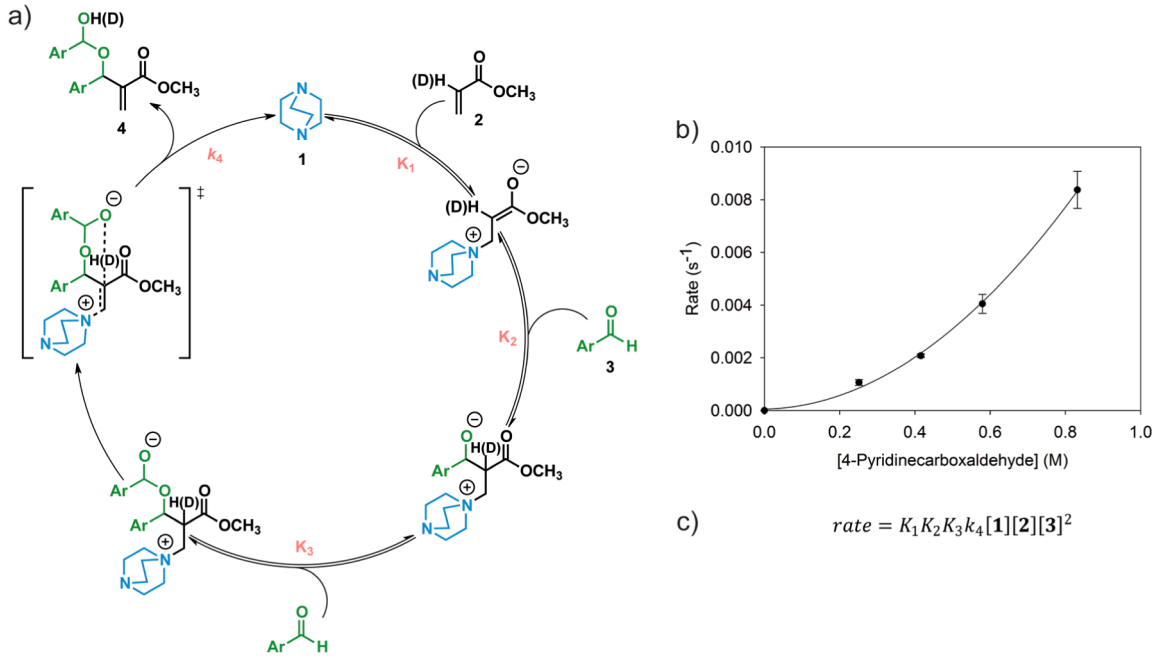
While our catalytic cross-linked RMs project taught us more about RMs, catalysis, and nanoparticles, the finicky MBH reaction made synthesis of the monomer difficult. At the time, we had two needs: (1) a higher yielding MBH reaction so we could synthesize gram quantities of the cross-linkable surfactant and (2) a deeper understanding of reaction kinetics to help drive creation of future multicatalyst systems. We thus studied the MBH reaction hoping to optimize the system and gain familiarity with reaction kinetics.[13,14] *The resulting research led directly to a major transformation of our group that over time reached far beyond the lessons gleaned from the MBH reaction itself.*

The MBH reaction, which combines an electron-deficient alkene and an aldehyde catalyzed by a Lewis base, has wide application, but the mechanism is different for different substrates.[15] Through kinetic isotope effect and rate data (Scheme 5), we demonstrated that MBH reactions with *acrylate substrates* exhibited second order kinetics (Scheme 5b) for the aldehyde substrate and that elimination of the Lewis base was rate limiting.[13,14]

Restated, this variation of the MBH reaction is catalyzed by both the Lewis base and one equivalent of aldehyde. To our delight, we stumbled on our first multicatalyst system. This observation that two simple catalysts (a Lewis base and aldehyde) could act together led us to recognize that multicatalyst systems abounded in the literature when one considers the combination of simple molecular catalysts together.[16] Learning that we were not alone in the catalyst systems universe helped us realize that success in the field required multicatalyst systems that perform novel chemistry.

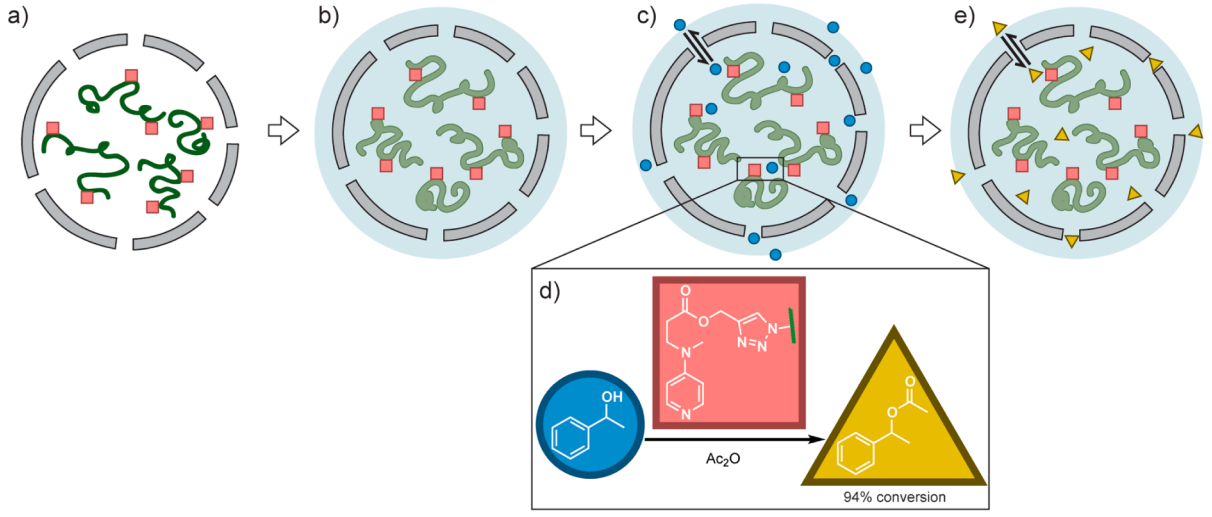
Struggles with the MBH reaction prompted us to examine other strategies for sequestering catalysts within a protective shell. Inspired by self-healing materials, we explored using microcapsules for encapsulating catalysts.[17] We were further buoyed by the body of work detailing preparation and characterization of microcapsules and by the work of Chang, who in the 1950s produced the first artificial cells.[18]

SCHEME 5. Summary of Our Morita–Baylis–Hillman Findings[a]



[a](a) A catalytic cycle that justifies the order in aldehyde we observed, (b) the second order rate data, and (c) the overall rate law. Reprinted (adapted) with permission from ref 14. Copyright 2004 American Chemical Society.

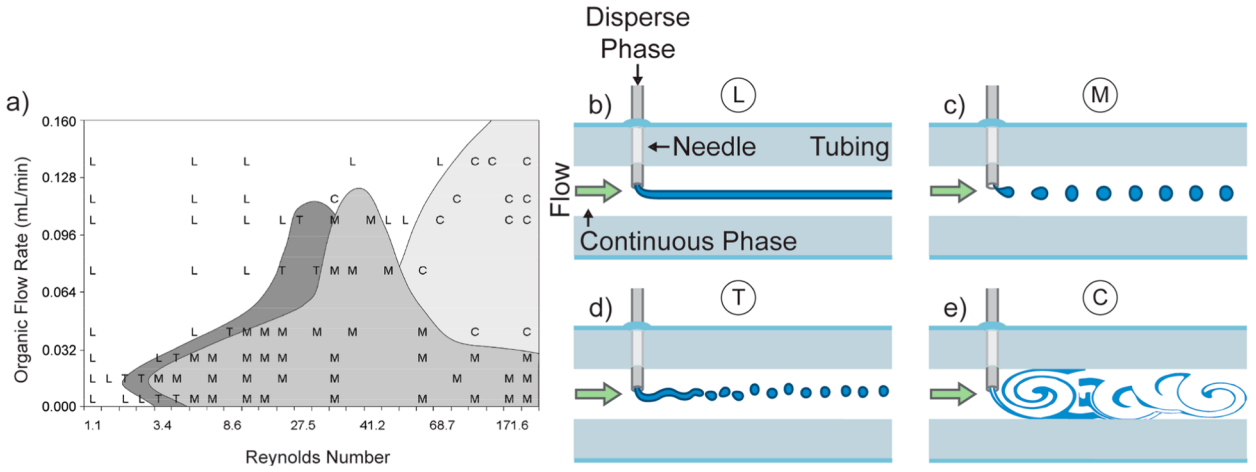
SCHEME 6. Catalytic Microcapsules[a]



[a](a) Reactive polymers trapped inside porous capsules. (b) The microcapsule is insoluble, while the catalytic polymer is soluble. (c) Substrates can enter the capsules while the polycatalysts cannot exit. (d) Reactions take place within the capsules, and product diffuses out.[24]

Unlike Chang and others who encapsulated enzymes, however, we sought to encapsulate organocatalysts and transition metal complexes. To this end, we created capsules containing reactive polymers.[19] This multimanuscript arc (Scheme 6) allowed us to (1) measure how encapsulated linear polymers self-diffuse within the capsules, (2) demonstrate that catalysts attached to these linear polymers did not diffuse out of the capsules but instead remained inside the capsules where catalytic activity approximating the small molecule versions was observed, (3) create capsules that could be functionalized on the shells and in the interior, (4) create capsules using novel emulsions such as formamide/cyclohexane, and (5) develop capsules where the polymers encapsulated would phase separate under certain conditions to yield capsules with different domains.[19–23] Finally, as discussed

SCHEME 7. Characterization of our Mesofluidic T-Junction Device[a]



[a](a) Diagram mapping the phases. (b) Representation of Laminar, (c) Monodisperse, (d) Transitional, and (e) Chaotic phases. Reprinted (adapted) with permission from ref 28. Copyright 2005 American Chemical Society.

in detail below, our microcapsule work enabled us to create a multicatalyst system that approximates a cellular system.

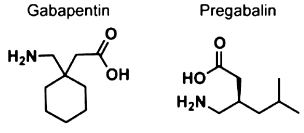
This last early observation was the spark that led us to the field of continuous (aka flow) chemistry. As we moved from RMs to microcapsules, we sought strategies to enable the production of monodisperse microcapsules (MMs). Though strategies for producing MMs have long been known,[25] no approach seemed right until we became familiar with the microfluidic community's monodisperse emulsion demonstrations.[26] Inspired to produce microcapsules this way, we prepared etched silicon-based microreactors.[27] The monodisperse emulsions were easily prepared, and we formed microcapsules using the emulsions as templates for interfacial polymerizations. The reactors were constantly ruined by clogging, making this method too costly to continue.

Fortunately, we realized that mesofluidic devices could be fabricated from simple tubing and connectors/needles.[28] Scheme 7 illustrates a tubing and needle T-junction device we created to produce capsules. The phase diagram (Scheme 7a) outlines the conditions yielding monodisperse capsules and different types of flow. We knew little about continuous chemistry[29] before this simple experiment, which opened up a whole new field to us. Specifically, this new set of tools provided a clear path for us to mimic FAB-type biosynthetic systems.

3. Coupling Catalytic Reactions: Reactions with Pre-equilibria

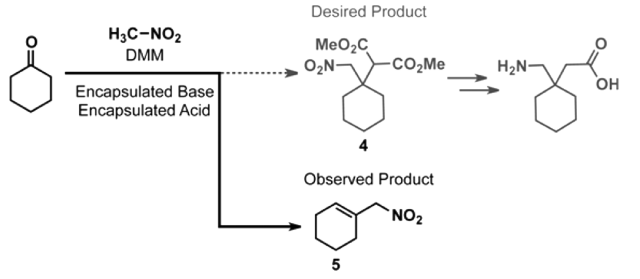
We spent our first five years importing and developing new approaches we believed essential for creating useful multicatalyst systems that could approximate cellular processes. We worked to design a two-step multicatalyst system where the first step produced an unstable intermediate trapped by a second step, restricting ourselves to valuable targets. Though other groups demonstrated landmark proof-of-concept cases, these examples did not provide a clear strategy for using multicatalyst systems in target-oriented synthesis.

3.1. Target Selection. Developing a rubric for target selection was harder than expected, as catalyst synthesis and system optimization were too time-consuming to produce "state of the art" natural products. We needed a high-value target with few steps, which led us to active pharmaceutical ingredients (APIs). Most modern APIs have at least one stereocenter and can be prepared in <6 steps, so we created structural lists based on the top 200 best-selling brand-name drugs.[30] Using these lists, we designed syntheses that might leverage microcapsule catalysts. The γ-aminobutyric acid analogues *gabapentin* and *pregabalin* caught our attention because both APIs are high volume. As discussed below, our study of APIs has been very productive and has stimulated a number of innovations within the group.



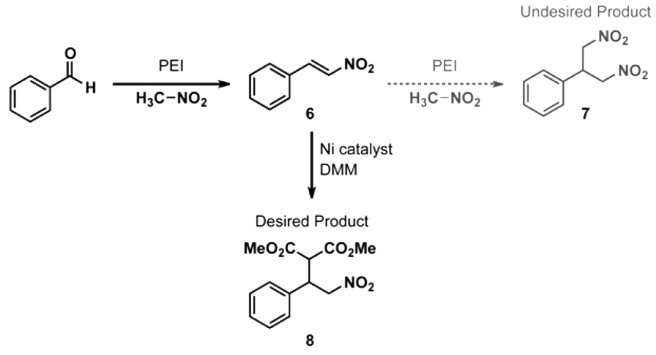
3.2. Route Design. Once we selected APIs as our target pool, we needed an approach to creating multiple catalyst system-based routes. Unlike normal synthetic design, we needed to (1) determine which steps would constitute the catalytic system, (2) consider reagent,

SCHEME 8. Failed Plan to Synthesize Gabapentin Where Competing Henry Reaction Followed by Elimination Resulted[a]



[a]Though many condition changes were made, we formed no desired product.

SCHEME 9. Microcapsules Enabled the Asymmetric Michael Addition to Occur Simultaneously after the Henry Reaction to Produce 8 (80.2%) by Avoiding the Undesired Dinitro-Substituted Product 7



substrate, and catalyst compatibility, (3) create systems where all inputs are provided at one time (thus avoiding sequential additions), and (4) showcase our microcapsule-catalyst aptitude by using incompatible catalysts.

3.3. Manifesting a Microcapsule-Based Multicatalyst System. We initially tried to synthesize gabapentin using a combination of acid and base catalysts.[31,32] We envisaged a tandem catalytic sequence where a Knoevenagel reaction was followed by a Michael addition. To our chagrin, the Henry-elimination reaction yielded an endocyclic alkene instead of the desired product (Scheme 8).

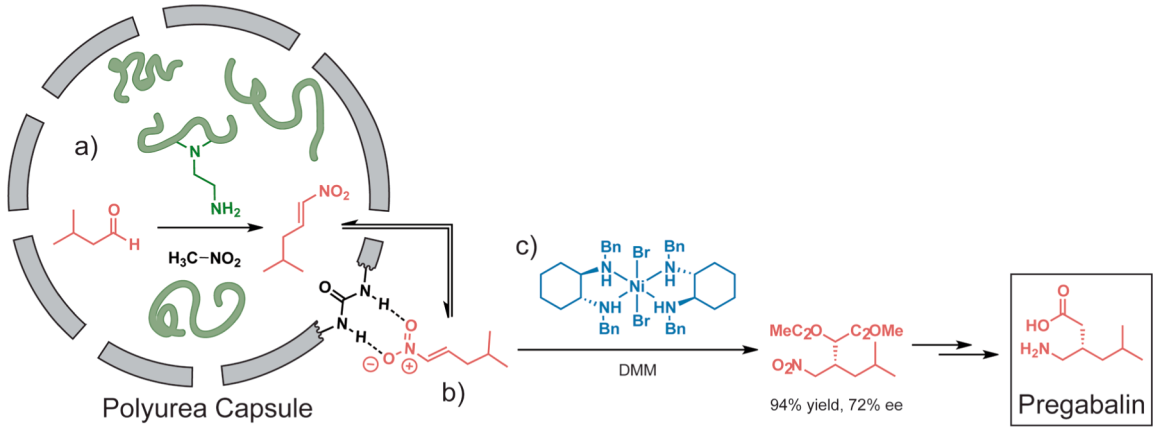
Recognizing the Henry-elimination reaction was fast, we designed a route to pregabalin that leveraged this.[33,34] We then identified catalysts to the nitroalkene and one to intercept the nitroalkene with an asymmetric Michael addition (Scheme 9). The Henry-elimination reaction is low yielding due to reversibility and multiple additions of nitromethane, making a multicatalyst system that intercepts the nitroalkene essential for high yields. A literature survey showed the most successful catalysts for the Henry elimination were amines, especially polyamines.[35] We also identified a number of promising catalysts for the asymmetric Michael addition including Evans's chiral nickel complex. Initial attempts to combine simple amine catalysts with the nickel complex yielded none of the desired product and produced colorful precipitates. *Devising a strategy to protect one catalyst from the other was a necessary condition for success.*

Simultaneous to our attempts at producing pregabalin, we were also synthesizing polyurea microcapsules using oil-in-oil emulsions.[20] In one case, capsules were produced via interfacial polymerization using polyethyeneimine (PEI) and a diisocyanate. These capsules had interiors rich in PEI and shells with hydrogen bonding sites (ureas), making them well-suited to prevent interaction between the polyamine and the nickel catalyst. This hypothesis proved valid, and the combination of the PEI-containing microcapsules and the nickel complex yielded the desired product in >80% yield (Scheme 10).[33] This was especially gratifying because using these catalysts independently yielded undesired products. Using only the PEI microcapsules, for example, provided the dinitro-product **7**.[33,34] In addition, the combination of unencapsulated PEI and the nickel catalyst yielded very little of the desired product.[33] This is a compelling demonstration of the potential multicatalyst systems might offer for altering chemical outcomes and producing functional group-dense products from simple starting materials.

Other fascinating details of this multicatalyst system included rate studies that showed the system to be first order in the nickel catalyst and that step 2 was rate-determining.[34] We also found that the reaction rate was dependent on the microcapsules.[34] After an extensive study, we determined that the ureas present in the shell of the PEI-microcapsules accelerated the nickel-catalyzed Michael addition.[34,36] We speculated that the urea might bind to the nitroalkene, thereby enhancing the rate. We later determined that simple bifunctional ureas (those with a urea proximal to a tertiary amine) are as effective as the microcapsules. We also demonstrated that this method could be used to produce pregabalin in an efficient three-step synthesis from commercially available starting materials.

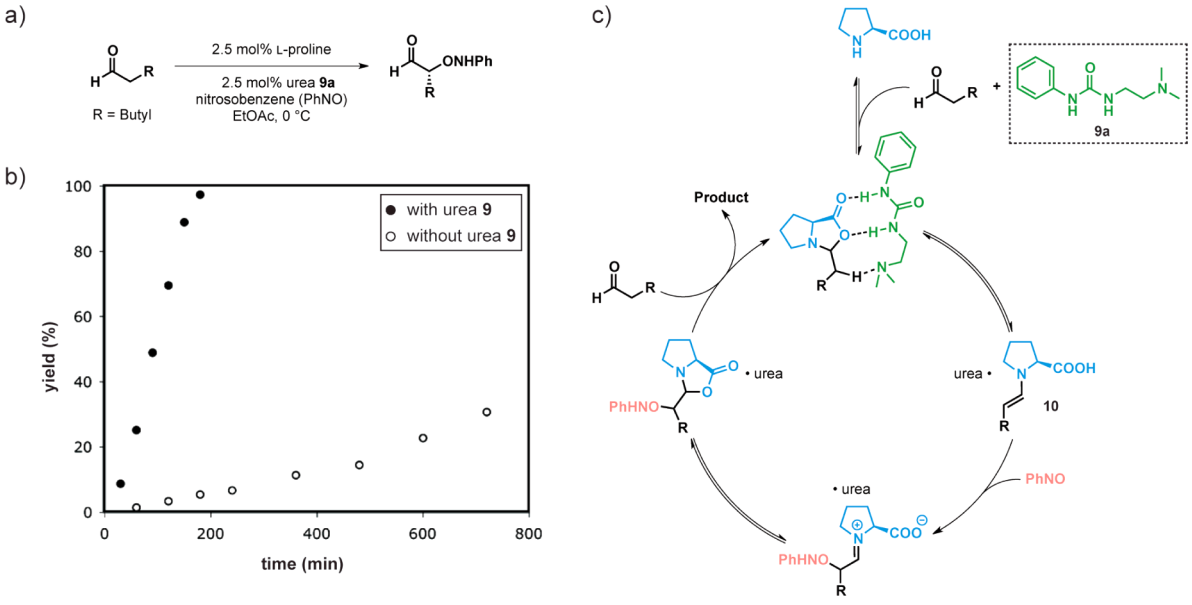
Excited by the observed urea cocatalysis, we tested the hypothesis that similar small molecule bifunctional ureas could accelerate other reactions. We speculated that addition of urea might enhance proline-catalyzed reactions because many of these reactions involve aldehydes, and

SCHEME 10[a]



[a]The PEI-microcapsule (a) enabled dual catalyst approach to pregabalin; the Henry-elimination product (b) is dependent on the capsules and urea sites and the michael addition is dependent on Evans's nickel catalyst (c) as indicated by high optical activity of the product.[36]

SCHEME 11. Summary of Our Proline/Urea-Catalyzed Aminoxylation[a]

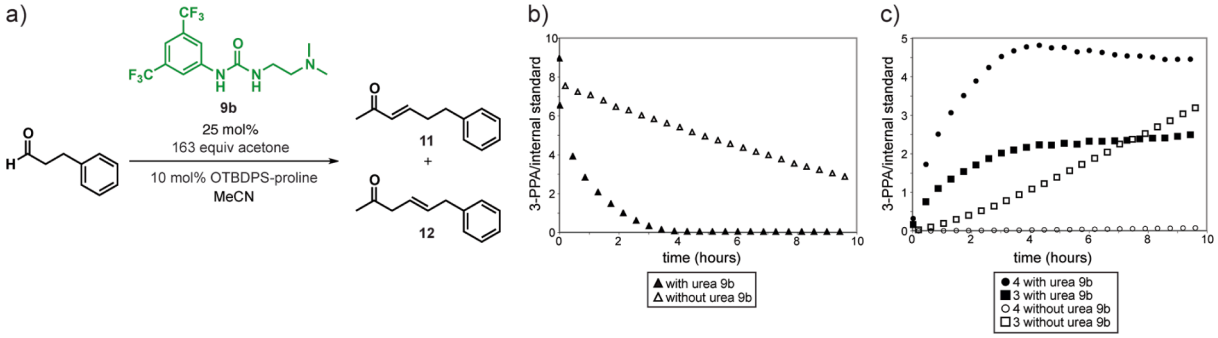


[a](a) An example reaction, (b) a demonstration of rate enhancement observed when proline/urea are combined compared to proline alone, and (c) the model developed. Reprinted (adapted) with permission from ref **42**. Copyright 2009 American Chemical Society.

carbonyl-urea interactions are well-established.[37,38] We tested our hypothesis by measuring the rate enhancement and product distribution changes the proline/urea mixtures had on aminoxylations and aldol reactions.

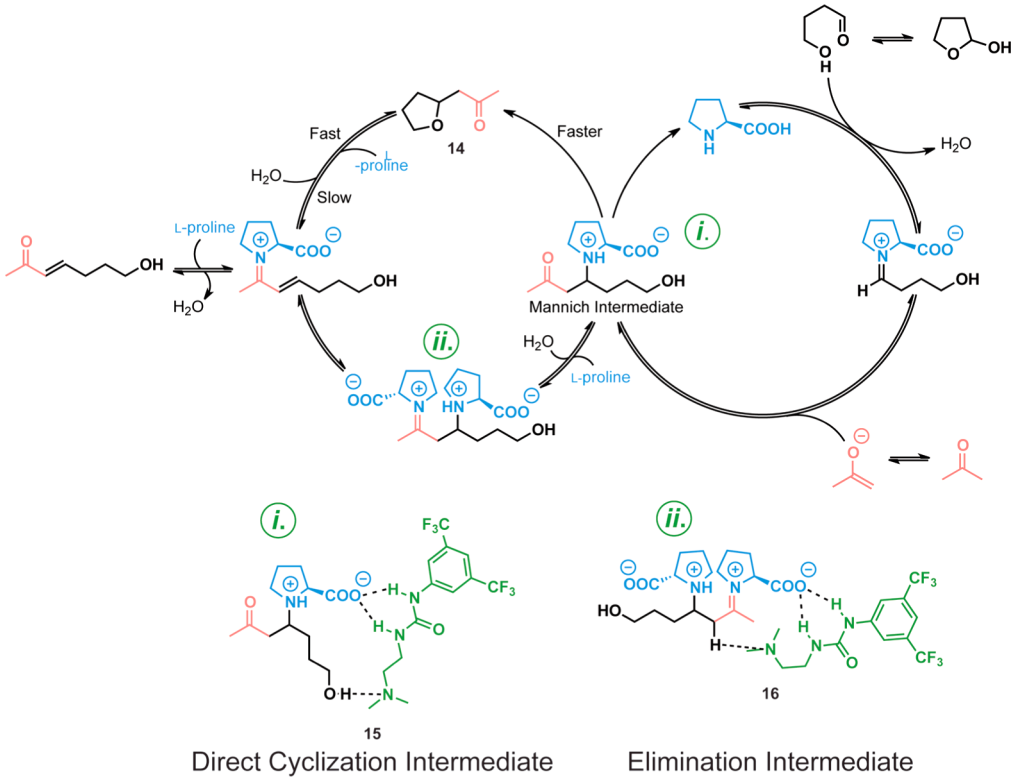
We selected the aminoxylation as an archetype for proline-catalyzed α-addition chemistry. Though aminoxylation reactions are fast, they often require undesirable solvents.[39−41] We found that proline/urea mixtures accelerated the α-aminoxylation 80-fold in solvents such as ethyl acetate.[42] We predicted the urea would participate in the activation of the nitrosobenzene electrophile, but were surprised the rate data indicated the urea facilitated the formation of the enamine (Scheme 11).[42] This model suggests that urea activation should be valid for proline-catalyzed reactions where an enamine is critical. We supported this hypothesis by demonstrating that the proline-catalyzed Mannich reaction is also accelerated by the addition of urea.[42] Though this example further supports our model that multicatalyst systems can improve organic synthesis, we pushed further to identify reactions where proline/urea mixtures provide products not formed when either catalyst is used independently.

SCHEME 12. Demonstration That Proline/Urea Mixtures Can Divert Product Outcomes[a]



[a](a) 3-Phenylpropanal (3-PPA) and acetone yield conjugated and non-conjugated products under proline/urea catalysis. (b,c) Illustration that rate and product distribution are strongly altered by addition of the urea cocatalyst. Reprinted (adapted) with permission from ref **43**. Copyright 2011 American Chemical Society.

SCHEME 13. Proposed Catalytic Cycle for the Proline/Urea-Catalyzed Synthesis of Substituted THF Derivatives[a]

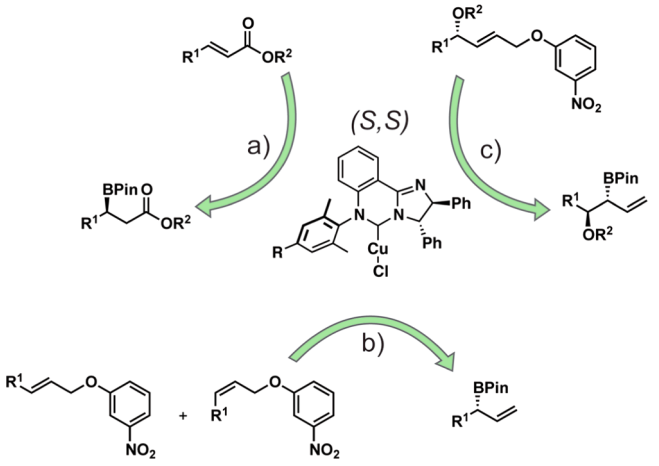


[a]Reprinted (adapted) with permission from ref **43**. Copyright 2011 American Chemical Society.

The proline/urea-catalyzed aldol reaction is an excellent example of how multicatalyst systems can divert reaction manifolds down paths unavailable to single catalyst systems (Scheme 12). The acetone and 3-phenylpropanal cross-aldol can form homoaldol (2 equiv of 3-phenylpropanal), cross-aldol, and the cross-aldol elimination product. When this reaction is catalyzed by a soluble proline derivative in acetonitrile, the only product observed is the conjugated elimination product (**11**).[43] When the soluble proline and urea are combined, the reaction rate increases significantly and the major product becomes the nonconjugated aldol/elimination product (**12**).[43] We speculated that this method could be applied to the synthesis of THF derivatives.

We predicted that THF derivatives would result when 2-hydroxytetrahydrofuran (2-HT) was used instead of a linear aldehyde. We were gratified to observe that no reaction was observed when proline was combined with 2-HT and a ketone, but the desired THF product resulted (**14**) when a bifunctional urea was added.[43] We also found that only proline derivatives with pendant carboxylic acids

SCHEME 14. Range of Reactions Catalyzed by a Novel Cu(I) Complex



provided sufficient catalysis.[43] Based on rate, substrate scope and catalyst structure data, we proposed that the catalytic cycle proceeds through two different manifolds where one manifold provides the THF product through a direct cyclization via the Mannich Intermediate and the other progresses through an elimination cyclization pathway (Scheme 13). Regardless of mechanism, this method is yet another interesting example of the altered paths through which multicatalyst systems can deviate.

4. The Future of Coupling Catalytic Reactions: Reactions with Pre-equilibria

As we progressed through the pregabalin multicatalyst to the proline/urea systems, we eventually recognized that combining catalysts developed by others offered less intellectual impact than combining novel catalysts of our own creation and thus began to produce transition metal catalysts alongside our microcapsule catalysts. Our most successful transition metal catalyst produced to date is a 6-*N*-heterocyclic (6-NHC)-copper(I) complex, the first rigid 6-NHC ligand shown to promote reactions with high stereoselectivity.[44−46] Family members of this complex exhibit excellent activity, enantio- and diastereoselectivity for both β-borylations and allylic substitutions (Scheme 14).[47,48] Now that we have demonstrated the veracity of our 6-NHC-Cu(I) complex, we aim to apply this catalyst to a novel multicatalyst system.

5. Coupling Catalytic Reactions: Sequential Irreversible Reactions in Flow

How a reaction is performed can profoundly impact its outcome. Organic chemistry is often conducted in batch mode, where the "how" of a reaction is defined by order of addition, temperature, solvents, concentration and gaseous

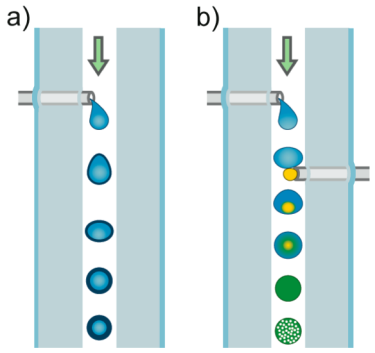
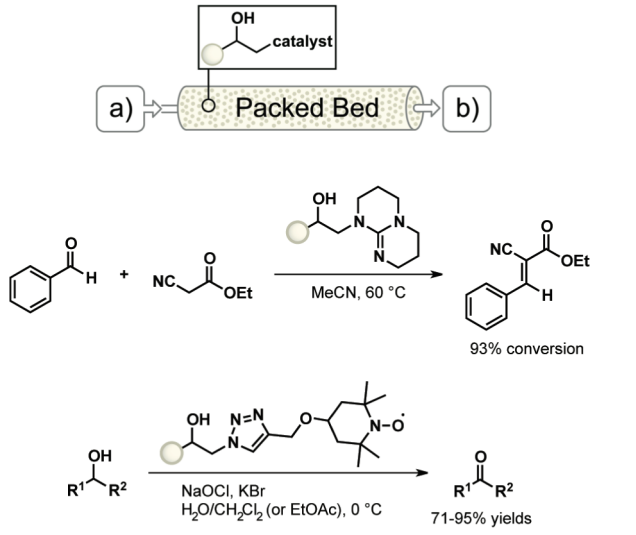


FIGURE 1. (a) Droplet formation and (b) collision of two droplets to form droplet reactors that produce solid products.

SCHEME 15[a]

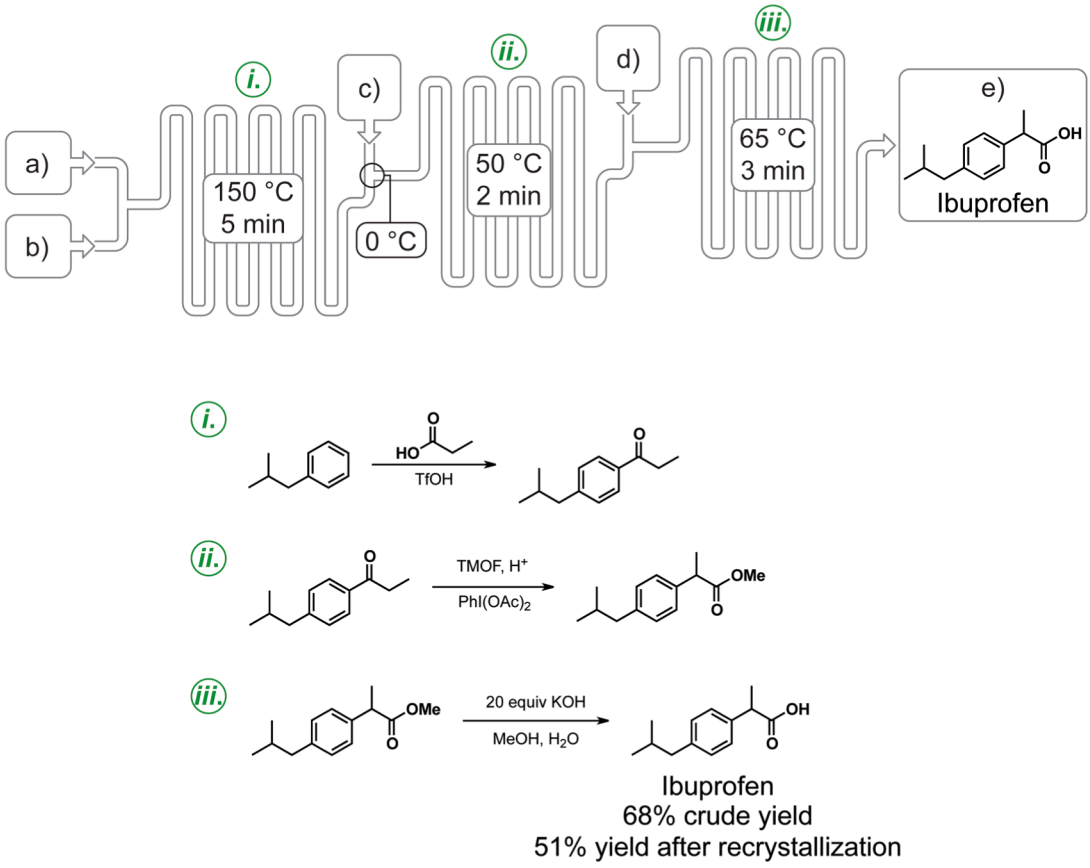


[a]Combining the concept of catalysts and solids in flow created a general approach to packed-bed flow reactors where (a) the solution of starting material is passed through the packed-bed to afford (b) the product.

environment. Alternatively, the "how" can also be a choice between batch or continuous conditions. As described above, a batch reactor is ideal when coupling reversible reactions to mimic anabolism. To mimic fatty acid biosynthesis (FAB), however, a continuous reaction modality is preferred because running reactions continuously allows serial reagent addition until the final product is realized. FAB is the quintessential example of a continuous system (Scheme 2).[4]

Over the past 20 years, first engineers and then chemists began miniaturizing reactors so that continuous chemistry could be achieved on small scale.[49−51] Early adopters praised microreactors for enabling rapid heat flow and mixing, which allowed reactions to be performed with greater control and safety.[50,52] Early devices contained small (<50 μm), square channels and often clogged if product or reactants contained even small amounts of particulate. This led most

SCHEME 16. Continuous Synthesis of Ibuprofen[a]



[a]A Friedel-Crafts acylation (i), a Favorskii rearrangement (ii), and a saponification (iii). Isobutylbenzene and propionic acid (a) were combined with triflic acid to perform reaction (i). A solultion of $PhI(OAc)_2$ and trimethylorthoformate in methanol (c) were introduced downstream to perform reaction (ii). Lastly, a solution of KOH was introduced to perform reaction (iii) to yield ibuprofen (e).

users to conclude that ideal continuous processes must be homogeneous.[53] Realizing we could make solids continuously without clogging by producing microcapsules via interfacial polymerization (Scheme 7), we began a program to understand and use solids in flow and to mimic irreversible biosynthesis using continuous strategies.

5.1. From Microcapsules to Synthesis of Precipitates in Flow. As described in Scheme 7, we demonstrated that droplets formed in a mesofluidic device could template formation of microcapsules.[27,28] By treating the droplets as micrometer-sized reactors, we speculated we could perform precipitate forming reactions within them.[26] A survey of microreactor reviews indicated this result would be significant.[53,54] Our hypothesis was that as droplets flowed coaxially through the channel, they would be protected from the reactor walls by the continuous phase and thus would not nucleate clogging. We selected *N*,*N*′-dicyclohexylethylenediimine, 4-chloro-*N*-methylbenzamide, and indigo as our synthetic targets because each requires a different continuous phase (hexanes, toluene, and mineral oil, respectively) and each product precipitates. For this proof-of-concept system, we created a dual droplet system where a reagent contained in one droplet would collide with a second droplet containing a second reagent (Figure 1). The continuous phase must be chosen wisely for two reasons: (1) the properties of the liquid affect fluid dynamics such as Reynolds number[28] and (2) the continuous phase must be immiscible with both the reagents and the product. The synthesis of indigo demonstrated that our coaxial hypothesis was valid because the indigo did not stain the walls of the tubing.[53]

5.2. Using Solids in Flow: Packed-Bed Catalytic Mesoreactors. Our natural next step was to combine catalytic microcapsules with continuous reactions. Though we initially hoped to achieve this result using our microencapsulated catalysts, we switched to Amberzyme-Oxirane (AO) resin due to mechanical and mass-transport reasons. This resin has large pores and thus high mass-transport. Using the AO resin, we realized a range of catalytic packed-bed microreactors including the supported TBD and TEMPO examples shown in Scheme 15.[55,56]

5.3. Mimicking Nature: A Completely Continuous API Synthesis. Our next progression in flow chemistry was to mimic fatty acid biosynthesis through the creation of completely continuous processes by linking reactions in series. Ley's group leveraged supported reagents and scavengers to realize their earliest multistep efforts.[57] We believed a further valuable contribution would be multistep syntheses that did not require these supported elements. We selected ibuprofen as our first target because the process has been optimized several times and we wanted to compare our new system to an optimized batch synthesis.[58]

We first performed a retrosynthetic analysis where we considered each step's reagents and solvents for compatibility with each downstream reaction. Based on our analysis, we predicted that a sequence of Friedel–Crafts acylation, 1,2-aryl migration, and saponification (Scheme 16) had the best chance of success. The final method we developed resulted in a crude yield of 68% (≈96% purity) and a yield of 51% (99% purity) after recrystallization.[59]

While the creation of continuous processes that do not require intermediate isolation or purification is still a young field, a number of demonstrations leading to valuable targets have emerged and the approach is being used for both process optimization and analoging within the context of medicinal chemistry.[60,61] We believe that a number of innovations are still needed to move this field forward: (1) new synthetic strategies that take reagent and byproduct compatibility into account; (2) reactions that yield few or unreactive byproduct; (3) a greater number of rapid (seconds to tens of minutes) catalytic reactions; and (4) simple continuous solvent exchange methods. Achieving these goals will allow for the production of active pharmaceutical agents with unparalleled efficiency, in turn better serving the needs of all those worldwide who might benefit from these medicines.

6. Conclusion

Over the past decade, the chemical industry has shifted to a more global workforce in pursuit of lower labor costs and weaker environmental regulations. At the same time, worldwide economic growth has raised the standard of living and expectations for a healthier environment for millions of people. We predict that the manner of production for current life-improving and life-saving molecules will soon become equally as important as the discovery of new molecules. Though most industrial and synthetic chemists are already concerned with efficiency, the field of chemical synthesis must incorporate even more innovative concepts, techniques, and intellectual strategies if it is to be made more sustainable in both economic and environmental terms. With these considerations in mind, the McQuade Group has explored strategies to mimic stepwise and continuous biosynthetic processes.

Our efforts to produce cross-linked reverse-micelle enzyme mimics led to our investigation of the MBH reaction. A deeper understanding of the multicatalyst nature of the MBH reaction resulted in an appreciation for simple multicatalyst systems. Microencapsulated catalysts led to our streamlined multicatalyst approach and then to the synthesis of γ-amino acid analogues (mimicking stepwise biosynthesis) and a recognition of the true power of flow chemistry. Our simple flow chemistry devices enabled us to mimic continuous serial biosynthesis as illustrated in the completely continuous synthesis of ibuprofen. Our future efforts are focused on using our recently developed 6-NHC-Cu(I) catalysts in both batch-based multicatalyst systems and continuous iterative syntheses of polyols. Nature produces billions of metric tons of biomass each year in environmentally sustainable ways. With the right tools and insights, chemists should one day be able to do the same.

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BIOGRAPHICAL INFORMATION

Ashley R. Longstreet was born in Livingston, New Jersey in 1988. She received her B.S. degree in biomedical science and chemistry at Lynchburg College in 2010 and is currently working toward her Ph.D. in organic chemistry at Florida State University under D. Tyler McQuade. Her work focuses on developing new flow chemistry methodologies and applying these methods towards total syntheses.

D. Tyler McQuade was born in Atlanta, Georgia in 1971. He received a degree in biology and chemistry from UC-Irvine and a Ph.D. in chemistry from UW-Madison under Professor Samuel Gellman. His education was completed by a NIH Fellowship at MIT with Professor Timothy Swager. He holds an Associate Professor position at FSU and a Group Leader position at the MPI for Colloids and Interfaces. Honors include the Dreyfus, 3M, Rohm and Haas, Beckman, and NYSTAR Young Investigator awards and the 2004 MIT Tech Review 100.

FOOTNOTES

*To whom correspondence should be addressed. E-mail: mcquade@chem.fsu.edu.
The authors declare no competing financial interest.

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